崇城大学ＤＤＳ研究所紀要

第 4 巻 2020 年

SOJO UNIVERSITY

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DDS 研究所紀要発刊に寄せて

DDS 研究所所長　山﨑　啓之

崇城大学 DDS 研究所が開設され、はやくも 10 年目を迎えます。本研究所は、「次世代型 DDS 製剤の開発評価研究拠点を形成する研究プロジェクト」が文部科学省の平成 22 年私立大学戦略的研究基盤形成事業に採択され、その中核をなす研究所として設置されました。これまで、DDS 研究の課題である、ターゲティング製剤や放出制御製剤化等において多くの研究成果を上げ、それらを国際的学術誌に公表するとともに、国際学会等で発表して来ました。また、DDS 研究所所属の教員の指導の下では、博士課程在籍の大学院生が優れた研究業績を上げていることや、この中から毎年博士取得者が誕生しており、当初の目的としておりました、大学院薬学研究科での教育活動への DDS 研究所の有効活用も軌道に乗ってきたように思います。

近年、創薬の対象は低分子医薬からペプチド、タンパク質、抗体、核酸などバイオ医薬の開発へと急速にパラダイムシフトしており、これら精密に設計開発された薬物の治療効果を最大化させるうえで DDS の利用は不可欠となっています。最近話題となっている COVID-19 に対する mRNA ワクチンの開発でも、DDS 分野で汎用されている脂質ナノ粒子が mRNA の生体内環境での安定性確保を目的に利用されています。DDS 研究所では、①DDS 機能性素材探索グループ、②DDS 設計、評価グループ、③代替医療マテリアル開発・評価グループから構成される研究組織に、生体分子の構造や機能、精密合成化学や天然物化学、分子レベルでの薬効・生理活性の評価、サプリメントや医療用マテリアルの設計・臨床評価に精通した若手研究者と経験豊かな研究者が参画し、将来の医療の発展に貢献する DDS 研究を推進しております。DDS 研究所では、変化する医療ニーズや創薬動向を的確に捉えながら、研究所の総合力を活かし、社会に貢献できるような夢の DDS 製剤の開発を目指し今後も鋭意努力する所存です。

今後とも、本研究所発展のため、従前にも増して温かいご支援、ご鞭撻を賜りますよう宜しくお願い申し上げます。

研究グループと研究テーマ

DDS 研究所所長　　山﨑　啓之
DDS 研究所副所長　池田　剛

１．DDS 機能性素材探索グループ

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平山　文俊　　環状オリゴ糖シクロデキストリンの医薬への応用
山﨑　啓之　　血清タンパク質の構造・機能の解析と医薬への応用
井本　修平　　B 型肝炎治療薬を目指したヌクレオシド・ヌクレオチドの合成
　　塩基配列特異的な化学修飾能を持つオリゴヌクレオチドの合成
庵原　大輔　　シクロデキストリンを利用した薬物、炭素材料および高分子増粘剤の
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２．DDS 設計、評価グループ

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下野　和実　　薬物トランスポーターを利用した薬物動態制御
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武知　進士　　糖尿病合併症における糖化反応物の作用機序の解明
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　　酵素機能の創製
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門脇　大介	医薬品の抗酸化作用解析を基盤とした腎疾患治療への応用
瀬尾　量	サプリメントおよびジェネリック医薬品の品質評価
横溝　和美	ヘルペス性疾患に対する治療薬の開発
内田　友二	SLRP family 分子による自然免疫調節機構の解明

論 文 抄 録

Abstract of published papers

2019 年 10 月 1 日～2020 年 9 月 1 日発表分

1. DDS 機能性素材探索グループ

Drosera tokaiensis **extract containing multiple phenolic compounds inhibits the formation of advanced glycation end-products**

Tominaga Yuki（東海大学）
Sugawa Hikari（東海大学）
Hirabayashi Keita（東海大学）
Ikeda Tsuyoshi（崇城大学）
Hoshi, Yoshikazu（東海大学）
Nagai Ryoji（東海大学）

Arch. Biochem. Biophy., Vol.693 pp. 108586
2020（令和 2 年）
DOI: 10.1016/j.abb.2020.108586

The accumulation of advanced glycation end-products (AGEs) correlates with aging and accompanies the onset of age-related diseases, such as diabetes and arteriosclerosis. Therefore, a daily intake of natural compds. that inhibit the prodn. of AGEs may be beneficial in preventing these diseases. In this study, we evaluated the inhibitory effects of 14 natural crude exts., including those of *Drosera* species, which possess anti-inflammatory activity, on the formation of AGEs, such as N^{ω}-(carboxymethyl)arginine (CMA) and N^{ε}-(carboxymethyl)lysine (CML). Crude exts. of *Drosera* inhibited the formation of CMA and CML by incubation on gelatin with ribose more effectively than with other exts., so active compds. that prevent AGE formation were purified from *Drosera tokaiensis*, which is endemic to Japan. Several compds. were purified from *D. tokaiensis exts*. using HPLC and identified by NMR anal. These compds. included ellagic acid, 3,3'-di-O-methylellagic acid 4'-glucoside, myricitrine, and quercimelin. Furthermore, all compds. showed a significantly higher inhibitory effect on CMA and CML formations than aminoguanidine. Specifically, ellagic acid and myricitrine had the highest inhibitory effects of the compds. tested. However, not all compds. showed inhibition of CMA formation in a mixt. of gelatin and glyoxal (GO). These results suggest that the compds. in *D. tokaiensis* inhibit CMA and CML formations via the antioxidative activity of phenolic compds., rather than GO trapping action. This study provides the first evidence that *D. tokaiensis* inhibits CMA and CML formations and that phenolic compds. such as ellagic acid and myricitrine play an important role as

active components of *D. tokaiensis* exts.

（池田　剛）

Flavonoid compounds contained in Epimedii herba inhibit tumor progression by suppressing STAT3 activation in the tumor microenvironment

Pan Chen（熊本大学）
Fujiwara Yukio（熊本大学）
Horlad Hasita（熊本大学）
Shiraishi Daisuke（熊本大学）
Iriki Toyohisa（熊本大学）
Tsubok Jyunko（熊本大学）
Ikeda Tsuyoshi（崇城大学）
Komohara Yoshihiro（熊本大学）
Frontiers in Pharmacology, Vol.11, p. 262
2020（令和 2 年）
DOI: 10.3389/fphar.2020.00262

M2-like tumor-assocd. macrophages (TAMs) in the tumor tissues promote tumor progression by various mechanisms and represent possible targets of antitumor therapy. In the present study, we tested whether compds. from Epimedii Herba inhibit macrophage polarization to the M2/protumorigenic phenotype and prevent tumor progression, using human monocyte-derived macrophages (HMDMs) and an animal sarcoma model. Four Epimedii Herba-derived flavonoid compds., namely, limonianin, epimedokoreanin B, icaritin, and desmethylicaritin, inhibited CD163 expression and interleukin (IL)-10 prodn., which are known M2 markers, suggesting that these compds. inhibit M2 polarization. Among these compds., epimedokoreanin B and limonianin suppressed STAT3 activation in HMDMs. Notably, epimedokoreanin B also suppressed cell proliferation by blocking STAT3 activation in Saos-2 human sarcoma and LM8 mouse sarcoma cell lines. Furthermore, oral administration of epimedokoreanin B inhibited tumor growth in an LM8 tumor-bearing murine model. These results indicate that Epimedii Herba and Epimedii Herba-derived compds., such as epimedokoreanin B, may be potentially new agents that can be used for the treatment and prevention of various malignant tumors. They may also be promising compds. for targeting the tumor microenvironment by inhibiting M2 polarization of the TAMs.

（池田　剛）

A new steroidal glycoside from the fruits of *Solanum myriacanthum*

Ono Masateru（東海大学）
Shimode Mizuki（東海大学）
Tsutsumi Shuhei（東海大学）
Yasuda Shin（東海大学）
Okawa Masafumi（福岡大学）
Kinjo Junei（福岡大学）
Okawa Masafumi（福岡大学）
Miyashita hiroyuki（崇城大学）
Ikeda Tsuyoshi（崇城大学）
Yoshimitsu Hitoshi（崇城大学）
Nohara Toshihiro（崇城大学）
Nat. Prod. Res., Vol.34, online
2020（令和 2 年）
DOI: 10.1080/14786419.2020.1781117

A new cholestane-type steroidal glycoside, solamyriaside A (**1**), was isolated from the fruits of *Solanum myriacanthum* Dunal (Solanaceae), along with two known steroidal glycosides, namely, solaviaside A (**2**) and aculeatiside A (**3**), and three known steroidal alkaloid glycosides, namely, solamargine (**4**), khasianine (**5**) and solasonine (**6**), which were isolated for the first time from this plant. Based on spectroscopic data as well as chemical evidence, **1** was determined to be 3-*O*-α-L-rhamnopyranosyl-(1→2)-*O*-[α-L-rhamnopyranosyl-(1→4)]-ß-D-glucopyranosyl-22*R*,25*R*-cholest-5-ene-3ß,16α,22,26-tetraol 26-O-ß-D-glucopyranoside. The cytotoxic activity of **1**–**6** against HL-60 human promyelocytic leukaemia cells was examined. Compounds **4**–**6** showed cytotoxic activity. Among them, **4** exhibited the strongest activity with an IC50 value of 4.64 ± 0.17 μM, similar to the activity of cisplatin, a positive control.

（宮下裕幸、池田　剛、吉満　斉）

Preparation and Evaluation of Fullerene Based Nanomedicine

庵原 大輔（崇城大学）
YAKUGAKU ZASSHI, Vol.139, pp.1539-1546
2019（令和元年）
DOI: 10.1248/yakushi.19-00172

In this review, we focus on the development of hydrophilic C_{60} nanoparticles, the

surface of which is covered by cyclodextrin (CD), and then evaluate its biological activities. C_{60}/CD nanoparticles were stable under physiological conditions, and even under much harsher conditions. The nanoparticles generate reactive oxygen species (ROS) under visible light irradiation. Efficient photodynamic therapy against tumor growth was achieved by the intravenous injection of C_{60}/CD nanoparticles to tumor bearing mice, followed by photoirradiation. In addition, $C_{60}(OH)_{10}$, which is regarded as a potential candidate for use in scavenging ROS, was also prepared in the form of water soluble nanoparticles. $C_{60}(OH)_{10}$/CD nanoparticles protect the liver from injury by the suppression of oxidative stress occurring in the mitochondria. C_{60}-based nanoparticles represent a potentially promising material for use in the treatment of cancer and oxidative stress-related diseases, and are promising as well in terms of extensive biological applications.

（庵原大輔）

Efficient Anticancer Drug Delivery for Pancreatic Cancer Treatment Utilizing Supramolecular Polyethylene-Glycosylated Bromelain

T. Higashi（熊本大学）
T. Kogo（熊本大学）
N. Sato（熊本大学）
T. Hirotsu（熊本大学）
S. Misumi（熊本大学）
H. Nakamura（崇城大学）
D. Iohara（崇城大学）
R. Onodera（崇城大学）
K. Motoyama（熊本大学）
H. Arima（熊本大学）

ACS Appl. Bio Mater., Vol.3, pp.3005-3014
2020（令和 2 年）
DOI: 10. 1021/acsabm.0c00070

Pancreatic cancer is one of the most difficult cancers to treat largely because of the inability of anticancer drugs to penetrate into the cancer tissue as the result of the dense extracellular matrix (ECM). On the other hand, bromelain is known to degrade the ECM in cancerous tissue. However, the half-life of bromelain in blood is short, leading to its low accumulation in tissues. Recently, we developed a reversible poly(ethylene glycol) (PEG) modification technology that is able to improve blood retention of proteins without

loss of activity and termed it “Self-assembly PEGylation Retaining Activity (SPRA)” technology. Here, we prepared reversible PEGylated bromelain using SPRA technology (SPRA-bromelain) possessing high activity, long blood retention, and high tumor accumulation and evaluated its potential as a drug delivery system for pancreatic cancer.

（中村 秀明、庵原 大輔）

Pharmacokinetic Properties of Orally Administered 4'-Cyano-2'-deoxyguanosine, a Novel Nucleoside Analog Inhibitor of the Hepatitis B Virus, in Viral Liver Injury Model Rats

Hashimoto M（崇城大学）
Taguchi K（慶応義塾大学）
Imoto S （崇城大学）
Yamasaki K （崇城大学）
Mitsuya H（国立国際医療センター・熊本大学・NIH）
Otagiri M（崇城大学）

Biol Pharm Bull., Vol.43(9), pp.1426-1429
2020（令和 2 年）
DOI: 10.1248/bpb.b20-00372

A nucleoside analog, 4'-cyano-2'-deoxyguanosine (CdG), which was developed as an inhibitor of the chronic hepatitis B virus (HBV), exhibited a superior antiviral activity against both wild-type and drugs-resistant HBV to marketed nucleoside analogs. In addition to previous pharmacokinetic studies of CdG in healthy rats, this study reports on an evaluation of the pharmacokinetic characteristics of CdG in a rat model of viral liver injury (VLI) induced by treatment with concanavalin A. Following an intravenous administration of CdG at a dose of 1 mg/kg, the plasma concentration profile of CdG in VLI model rats was found to be similar to that of healthy rats with no significant difference in kinetic parameters. However, when CdG was orally administered at a dose of 1 mg/kg, the maximum blood concentration was much lower in VLI model rats than in healthy rats. Interestingly, the amount of residual food in the stomachs in VLI model rats was significantly larger than that in healthy rats, indicating that the adsorption of CdG in the gastrointestinal tract was inhibited in the presence of food as well as other marketed nucleoside analogs. As observed in healthy rats, CdG was largely distributed to the liver compared to the kidney in the VLI model. These results suggest that liver pathology has only a minor effect on the pharmacokinetic properties of CdG, but the influence of food on CdG absorption needs to be considered.

（山﨑　啓之）

Characterization of Bovine Lactoferrin Nanoparticle Prepared by Desolvation Technique

Taguchi K（慶応義塾大学）
Chuang VTG（Monash University Malaysia）
Hashimoto M（崇城大学）
Nakayama M（崇城大学）
Sakuragi M（崇城大学）
Enoki Y（慶応義塾大学）
Nishi K（崇城大学）
Matsumoto K（慶応義塾大学）
Seo H（崇城大学）
Otagiri M（崇城大学）
Yamasaki K（崇城大学）
Chem Pharm Bull (Tokyo)., VOL. 68(8), pp.766-772.
DOI: 10.1248/cpb.c20-00222.

Lactoferrin (Lf) nanoparticles have been developed as a carrier of drugs and gene. Two main methods, desolvation technique and emulsification method, for preparation of protein nanoparticles have been reported so far, but most of the previous reports of Lf nanoparticles preparation are limited to emulsification method. In this study, we investigated the optimal conditions by desolvation technique for the preparation of glutaraldehyde-crosslinked bovine Lf (bLf) nanoparticles within the size range of 100-200 nm, and evaluated their properties as a carrier for oral and intravenous drug delivery. The experimental results of dynamic light scattering and Transmission Electron Microscope suggested that glutaraldehyde-crosslinked bLf nanoparticles with 150 nm in size could be produced by addition of 2-propanol as the desolvating solvent into the bLf solution adjusted to pH 6, followed by crosslinking with glutaraldehyde. These cross-linked bLf nanoparticles were found to be compatible to blood components and resistant against rapid degradation by pepsin. Thus, cross-linked bLf nanoparticles prepared by desolvation technique can be applied as a drug carrier for intravenous administration and oral delivery.

（山﨑　啓之、小田切　優樹）

Characterization of the interaction of daptomycin with site II on human serum albumin

Yamasaki K（崇城大学）
Sakurama K（崇城大学）
Nishi K（崇城大学）
Watanabe H（熊本大学）
Maruyama T（熊本大学）
Seo H（崇城大学）
Otagir M（崇城大学）
Taguchi K（慶応義塾大学）
J Pharm Sci., VOL.109(9), pp.2919-2924
2020（令和 2 年）
DOI.org/10.1016/j.xphs.2020.06.011

Daptomycin, a cyclic lipopeptide antibiotic, is clinically used for the treatment of infections caused by Gram-positive bacteria, including the methicillin-resistant *Staphylococcus aureus* and the vancomycin-resistant Enterococci. While daptomycin shows high plasma protein binding (90-93%), our knowledge of the binding process is not extensive. To address this issue in more detail, we characterized the binding of daptomycin to plasma proteins and the findings indicate that the association constant for the binding of daptomycin to human serum albumin (HSA) is much higher than that for α1-acid glycoprotein, another plasma protein. Daptomycin was also found to bind to a single site on HSA, which was identified as site II. The findings also suggest that the n-decanoyl moiety of daptomycin penetrates into the hydrophobic pocket of site II and that this acyl moiety interacts with Tyr411 at the entrance to site II. Due to this selective interaction with site II, daptomycin binding was significantly inhibited by drugs (ibuprofen or diazepam) and endogenous compounds (uremic toxins or fatty acids) which also strongly bind to site II. In diseased states, such an inhibition in the binding could result in the pharmacokinetics and therapeutic action of daptomycin being substantially altered.

（山﨑　啓之）

Effects of Oxidation of Human Serum Albumin on the Binding of Aripiprazole

Sakurama K（崇城大学）
Nishi K（崇城大学）

Chuang VTG（Manash University Malaysia）
Hashimoto M（崇城大学）
Yamasaki K（崇城大学）
Otagiri M（崇城大学）
Biol Pharm Bull. 2020;43(6):1023-1026
2020（令和 2 年）
DOI: 10.1248/bpb.b20-00205.

Aripiprazole (ARP) is one of antipsychotics and binds to human serum albumin (HSA) with a high affinity. In this study, we investigated the binding characteristics of ARP to oxidized HSA as observed in chronic disease conditions. Oxidized HSAs were prepared using chloramine-T (CT-HSA) or metal-catalyzed oxidation system (MCO-HSA) in vitro, respectively. An increase in the carbonyl content was confirmed in oxidized HSAs. From the results of circular dichroism (CD) and tryptophan fluorescence spectra, no significant structural change of oxidized HSAs was observed. These results indicate that prepared HSAs are mildly oxidized and well reflects the status of HSA during chronic diseases. However, oxidized HSAs were observed to have a significant decrease in binding to ARP. The results of the induced CD spectrum suggested that ARP bound to oxidized HSAs with a similar orientation. These results suggest that oxidation of HSA during chronic disease state significantly affected the microenvironment of the binding site for ARP and binding capacity of HSA to ARP.

（山﨑　啓之）

Serum Albumin, Lipid and Drug Binding

Nishi K（崇城大学）
Yamasaki K（崇城大学）
Otagiri M（崇城大学）
Subcell Biochem., VOL.94, pp.383-397
DOI: 10.1007/978-3-030-41769-7_15

Albumin is widely conserved from vertebrates to invertebrates, and nature of mammalian albumins permit them to bind various endogenous ligands and drugs in the blood. It is known that at least two major ligand binding sites are present on the albumin molecule, which are referred to as Site I and Site II. These binding sites are thought to be almost completely conserved among mammals, even though the degree of binding to these sites are different depending on the physical and chemical properties of drugs and differences in the microenvironment in the binding pockets. In addition, the binding sites

for medium and long-chain fatty acids are also well conserved among mammals, and it is considered that there are at least seven binding sites, including Site I and Site II. These bindings properties of albumin in the blood are also widely known to be important for transporting drugs and fatty acids to various tissues. It can therefore be concluded that albumin is one of the most important serum proteins for various ligands, and information on human albumin can be very useful in predicting the ligand binding properties of the albumin of other vertebrates.

（山﨑　啓之）

A Safety Evaluation Study in Mice Revealed that Albumin Dimer is Safe for Medical and Pharmaceutical Applications

Hashimoto M（崇城大学）
Chuang VTG（Manash University Malaysia）
Ishima Y（徳島大学）
Ikeda M（徳島大学）
Maruyama T（熊本大学）
Yamasaki K（崇城大学）
Taguchi K（慶応義塾大学）
Otagiri M（崇城大学）
BPB Reports. VOL.3, pp.87-91
2020（令和 2 年）

Human serum albumin (HSA) dimer, where two molecules of HSA are genetically fused with a linker of 10 amino acid, has superior blood retention property, compared with HSA monomer. Moreover, HSA dimer derivative, s-nitrosated HSA dimer, functions as an enhanced permeability and retention effects enhancer. HSA dimer has gained considerable attention as drug delivery system carrier based on its prominent function. However, for the HSA dimer to be used clinically, the safety profile of the HSA dimer is required in order to exclude any potential toxicity or unwanted effects. Thus, the present study was undertaken to investigate the occurance of tissue damage and serologic changes due to repeated administration of HSA dimer (66.5 mg/kg) to mice every 3 d for 56 d, as part of a basic consideration on safety evaluation. The evaluation on survival, behavior and body weight indicate that HSA dimer has no effect on physical growth and physiological functions. Hematological tests suggest that HSA dimer has no direct influence on hemocytes, such as hemolysis and platelet aggregation. Moreover, plasma clinical chemistry and histological examinations indicate that the HSA dimer has no

deleterious effect on liver and renal functions. The results obtained here indicate HSA dimer is safe and should be useful for medical and pharmaceutical applications.

（山﨑　啓之）

Cell uptake and anti-tumor effect of liposomes containing encapsulated paclitaxel-bound albumin against breast cancer cells in 2D and 3D cultured models

Okamoto Y（崇城大学）
Taguchi K（慶応義塾大学）
Imoto S（崇城大学）
Giam Chuang VT（Manash University Malaysia）
Yamasaki K（崇城大学）
Otagiri M（崇城大学）
J Drug Deliv Sci Tech., Volume 55, 101381
2019（令和元年）
DOI.org/10.1016/j.jddst.2019.101381

Paclitaxel (PTX), a water insoluble anticancer drug, was incorporated into the inner aqueous core of a liposome without the aid of an organic co-solvent, via non-covalent binding with bovine serum albumin (BSA) to form a PTX-BSA liposome. In the present study, PTX-BSA-liposomes are shown to have potent effects on human-derived breast cancer cell lines, MCF-7 cells and MDA-MB-231 cells, in 2D monolayer cultured cells and 3D multicellular tumor spheroids. The results of cellular uptake studies in 2D monolayer cultured cells clearly showed that the fluorescence derived from dansyl-l-asparagine (DNSA), a model encapsulated drug, and Cy5-cholesterol (a model membrane) of DNSA-BSA-liposome were observed inside the cells. Along with cell uptake, the PTX-BSA-liposomes exhibited a concentration-dependent cytotoxicity against MCF-7 and MDA-MB-231 cells but the IC50 value of the PTX-BSA-liposomes was higher than that of free PTX and nab-PTX (albumin-bound PTX nanoparticle). On the other hand, PTX-BSA-liposome, as in the cases of free PTX and nab-PTX, inhibited cell growth in both 3D MCF-7 and MDA-MB-231 tumor spheroids, indicating that PTX-BSA-liposomes penetrated into the tumor spheroid. These results suggest that PTX-BSA-liposomes are an organic solvent free PTX formulation that would have potent anti-proliferative effects against breast cancer.

（山﨑　啓之）

２．DDS 設計、評価グループ

Use of Hemoglobin for Delivering Exogenous Carbon Monoxide in Medicinal Applications

Taguchi K（慶応義塾大学）
Maruyama T（熊本大学）
Otagiri M（崇城大学）
Curr Med Chem., Vol.27(18), pp.2949-2963
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Carbon Monoxide (CO), at low concentrations, can have a variety of positive effects on the body including anti-apoptosis, anti-inflammatory, anti-oxidative and anti-proliferative effects. Although CO has great potential for use as a potent medical bioactive gas, for it to exist in the body in stable form, it must be associated with a carrier. Hemoglobin (Hb) represents a promising material for use as a CO carrier because most of the total CO in the body is stored associated with Hb in red blood cells (RBC). Attempts have been made to develop an Hb-based CO carrying system using RBC and Hb-based artificial oxygen carriers. Some of these have been reported to be safe and to have therapeutic value as a CO donor in preclinical and clinical studies. In the present review, we overview the potential of RBC and Hb-based artificial oxygen carriers as CO carriers based on the currently available literature evidence for their use in pharmaceutical therapy against intractable disorders.

（小田切優樹）

Identification of a novel long-acting 4'-modified nucleoside reverse transcriptase inhibitor against HBV.

Higashi-Kuwata N（国立国際医療研究センター）
Hayashi S（名古屋市立大学）

Kumamoto H（日本薬科大学）
Ogata-Aoki H（国立国際医療研究センター）
Das D（アメリカ国立がん研究所）
Venzon D（アメリカ国立がん研究所）
Hattori SI（国立国際医療研究センター）
Bulut H（アメリカ国立がん研究所）
Hashimoto M（崇城大学）
Otagiri M（崇城大学）
Takamune N（熊本大学）
Kishimoto N（熊本大学）
Davis D（アメリカ国立がん研究所）
Misumi S（熊本大学）
Kakuni M（株式会社フェニックスバイオ）
Tanaka Y（熊本大学）
Mitsuya H（熊本大学）
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Background & aim: While certain nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are efficacious in treating HBV infection, their effects are yet to be optimized and the emergence of NRTI-resistant HBVs remains to be a challenging issue since life-long medication is needed, making it crucial to develop agents that more profoundly suppress wild-type and drug-resistant HBVs and have a long-acting feature for patients' greater quality of life.
Methods:(1S,3S,5S,E)-3-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2-(fluoromethylene)-5-hydroxy-1-(hydroxymethyl)cyclopentane-1-carbonitrile (E-CFCP) was newly synthesized. E-CFCP's in vitro anti-HBV activity was evaluated. In vivo anti-HBV activity was examined using HBV-infected human-liver-chimeric mice (PXB-mice). E-CFCP's long-acting features and E-CFCP-triphosphate's interactions with HBV-reverse transcriptase (HBV-RT) were examined.
Results: E-CFCP potently blocked HBVWTD1 production (IC50qPCR_cell=1.8 nM) in HepG2.2.15 cells and HBVWTC2 (IC50SB_cell=0.7 nM), ETV-resistant HBVETV-RL180M/S202G/M204V (IC50SB_cell=77.5 nM), and ADV-resistant HBVADV-RA181T/N236T production (IC50SB_cell=14.1 nM) in Huh7 cells. E-CFCP profoundly inhibited intracellular HBV-DNA production down to below detection limit, but ETV and TAF failed to do so. E-CFCP also showed less toxicity than ETV and TAF. E-CFCP better

penetrated hepatocytes and was better tri-phosphorylated and E-CFCP-triphosphate intracellularly persisted longer compared to ETV-triphosphate. Once-daily peroral E-CFCP administration over 2 weeks (0.02~0.2 mg/kg/day) reduced HBVWTC2-viremia by 2-3 logs in PXB-mice without significant toxicities and the reduction persisted over 1-3 weeks following treatment cessation, suggesting once-weekly dosing capabilities. E-CFCP also reduced HBVETV-RL180M/S202G/M204V-viremia by 2 logs over 2 weeks, while ETV completely failed HBVETV-RL180M/S202G/M204V-viremia reduction. None of E-CFCP-treated mice had significant adverse changes. Van der Waals interactions of E-CFCP's 4'-cyano and polar interactions of the fluorine with HBV-RT are important for E-CFCP's anti-HBV potency and that both 4'-cyano and fluorine help retain E-CFCP-triphosphate's interactions of HBVETV-RL180M/S202G/M204V-RT.
Conclusion: E-CFCP represents the first reported potential long-acting NRTI potent against HBVs.

（小田切優樹）

Drug Delivery System for Refractory Cancer Therapy via an Endogenous Albumin Transport System.

Ishima Y（徳島大学）
Maruyama T（熊本大学）
Otagiri M（崇城大学）
Ishida T（徳島大学）
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A unique phenomenon in solid tumors, the enhanced permeability and retention (EPR) effect is now well known in the development of macromolecular anticancer therapy. However, cancers with low vascular permeability have posed a challenge for these EPR based therapeutic systems. An intrinsic vascular modulator, such as nitric oxide (NO), could augment the endogenous EPR effect. However, the most important aim has been to construct an effective NO delivery system for cancer. Since it is well known that human serum albumin is one of the most important endogenous NO transport proteins in human circulation, for more than a decade we have demonstrated that S-nitrosated human serum albumin dimer (SNO-HSA-Dimer) becomes an enhancer of the EPR effect. Here, we summarize the enhanced effect of SNO-HSA-Dimer on the anticancer effect of macromolecular anticancer drugs such as PEGylated liposomal doxorubicin (Doxil®). In

C26-bearing mice with highly permeable vasculature, SNO-HSA-Dimer is able to increase more 3-fold the tumor accumulation of these anticancer drugs, thereby tripling their anticancer effects. Interestingly, the tumor accumulation of Doxil® in B16-bearing mice, which are characterized by a low permeable vasculature, increased more than 6-fold in the presence of SNO-HSA-Dimer, and the improved accumulation of Doxil® led to both increased survival and decreased tumor volume. These results strongly suggest that the more cancer is refractory, the more the SNO-HSA-Dimer could enhance the EPR effect via an endogenous albumin transport (EAT) system. Accordingly, we conclude that the EAT system is promising as a drug delivery system (DDS) strategy for refractory cancer therapy.

（小田切優樹）

Hepatic cytochrome P450 profiles in hemorrhagic shock model rats after transfusion with stored red blood cells

Tokuno M（崇城大学）
Taguchi K（慶応義塾大学）
Yamasaki K（崇城大学）
Otagiri M（崇城大学）
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Red cell transfusions, which deteriorate in quality during storage, triggers several negative biological responses. However, little is known regarding the effects of stored red cell transfusion on cytochrome P450 (P450) profiles. To clarify this issue, we investigated hepatic P450 profiles in hemorrhagic shock model rats after resuscitation with stored packed red cells (PRC). The pharmacokinetics data for P450-metabolizing substrates showed that the clearance of substrates for Cyp1A2 and Cyp3A2 in the stored PRC resuscitation group were decreased compared to sham group. The protein expression, metabolic activity and mRNA expression of the P450 isoforms in the stored PRC resuscitation group were lower than the corresponding values for the sham group. However, these changes would be expected to have weak effects on the in vivo pharmacokinetics of the concomitant drugs based on the criteria stated in the guideline on drug interactions. In contrast, the results of these P450 profiles in the stored PRC and fresh PRC resuscitation group exhibited a similar trend. These results suggest that the stored PRC transfusion has an influence on the hepatic P450 profiles, but is of little

clinical significance, not by the deterioration of the quality of red cells but pathophysiological alterations following the hemorrhage and transfusion.

（山﨑　啓之、小田切　優樹）

Assessing cytochrome P450-based drug-drug interactions with Hemoglobin-vesicles, an artificial red blood cell preparation, in healthy rats

Tokuno M（崇城大学）
Taguchi K（慶応義塾大学）
Sakai H（奈良医科大学）
Ohtsuki S（熊本大学）
Yamasaki K（崇城大学）
Otagiri M（崇城大学）

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Hemoglobin-vesicles (Hb-V), hemoglobin encapsulated within a liposome, were developed as an artificial red blood cell (RBC). When Hb-V becomes clinically available in the future, patients would presumably be co-administered with one or more drugs. Since drug-drug interactions can cause serious adverse effects and impede overall curative effects, evidence regarding the risk associated with drug-drug interactions between Hb-V and such simultaneously administered drugs is needed. Therefore, we report on cytochrome P450 (CYP)-based drug interactions with Hb-V in healthy rats. At 1 day after the saline, Hb-V or packed RBC (PRBC) administration, the blood retention of CYP-metabolizing drugs (caffeine, chlorzoxazone, tolbutamide and midazolam) were moderately prolonged in the case of the Hb-V group, but not the PRBC group, compared to saline group. The results of a proteome analysis revealed that the Hb-V administration had only negligible effects on the protein expression of CYPs in the liver. Hb-V administration, however, clearly suppressed the CYP metabolic activity of the four target CYP isoforms compared with the saline and PRBC group. However, these alterations were nearly recovered at 7 day after the Hb-V administration. Taken together, these results suggest that the administration of Hb-V slightly and transiently affects the CYP-based metabolism of the above drugs.

（山﨑　啓之、小田切　優樹）

Evaluation of cytochrome P450-based drug metabolism in hemorrhagic shock rats that were transfused with native and an artificial red blood cell preparation, Hemoglobin-vesicles.

Tokuno M（崇城大学）
Taguchi K（慶応義塾大学）
Sakai H（奈良医科大学）
Ohtsuki S（熊本大学）
Yamasaki K（崇城大学）
Otagiri M（崇城大学）

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Hemoglobin-vesicles (Hb-V) are being developed as red blood cell (RBC) substitutes. In this study, we report on quantitative and qualitative alterations of hepatic cytochrome P450 (CYPs) and the pharmacokinetics of CYP-metabolizing drugs, with a focus on four CYP isoforms (CYP1A2, CYP2C11, CYP2E1 and CYP3A2), after Hb-V resuscitation from a massive hemorrhage. The results of proteome analysis and western blot data indicate that resuscitation with both Hb-V and packed RBC (PRBC) resulted in a decrease in the protein levels of CYPs. Along with a decrease in the protein expression of CYPs, pharmacokinetic studies showed that the elimination of CYP-metabolizing drugs was prolonged in the Hb-V and PRBC resuscitation groups. It is also noteworthy that the CYP-metabolizing drugs in the Hb-V resuscitation group was retained for a longer period compared to the PRBC resuscitation group, and this is attributed to the CYP isoforms having a lower metabolic activity in the Hb-V resuscitation group than that for the PRBC resuscitation group. These findings suggest that resuscitation with Hb-V after a massive hemorrhage has a slight but not clinically significant effect on drug metabolism via CYPs in the liver due to decreased protein levels and the metabolic activity with respect to the CYPs.

（山﨑　啓之、小田切　優樹）

A method to induce hen egg lysozyme-specific humoral immune tolerance in mice by pre-exposition with the protein's oligomers.

Ohkuri T（崇城大学）
Yuge N（九州大学）
Sato K（九州大学）
Ueda T（九州大学）

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During treatment with protein therapeutics, such as monoclonal antibodies, the development of anti-drug antibodies is a serious side-effect of modern pharmacology. Anti-drug antibodies are produced as the number and exposure to therapeutic proteins increase. In this context, less immunogenic responses could diminish these noxious effects. Biophysical characterization of antigens, that is size, chemical composition, physical form, and degrability, are known to influence the outcome of immune responses. Here, using chemical modification, we have prepared oligomers of hen egg lysozyme (HEL), 3- to 5-mer, as a typical antigen in immunology and evaluated the efficacy as a tolerogen in HEL-specific antibody responses. Our results clearly demonstrated that pre-exposed the HEL-oligomers into mice effectively suppressed HEL-specific IgG responses regardless of the cross-linking mode. Therefore, the oligomerization is a method to induce tolerogenicity of proteins and may emerge as a promising strategy to control the production of undesirable anti-protein drug antibodies.

（大栗誉敏）

C-Terminal Cysteine PEGylation of Adalimumab Fab with an Engineered Interchain SS Bond

Nakamura H（崇城大学）
Anraku M（崇城大学）
Oda-Ueda N（崇城大学）
Ueda T（九州大学）
Ohkuri T（崇城大学）
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Conjugation with polyethylene glycol (PEG) is performed to increase serum half-life of the Fab for clinical applications. However, current designs for recombinant Fab only allow PEGylation at the interchain SS bond (disulfide bond) at the C-terminal end of the heavy chain and light chain of the Fab, which the decrease of thermostability occurred by partial reduction of the interchain SS bond. An adalimumab Fab mutant with a novel interchain SS bond (CH_1：C177-CL：C160) and one cysteine at the C-terminal end (mutSS Fab_{SH}) was designed to maintain Fab thermostability and for site-specific

PEGylation. MutSS Fab$_{SH}$ was expressed in *Pichia pastoris* and purified mutSS Fab$_{SH}$ was conjugated with 20-kDa PEG targeted at the free cysteine. Based on enzyme-linked immunosorbent assay (ELISA), PEGylation did not affect the binding capacity of the mutSS Fab$_{SH}$. To confirm the influence of PEGylation on the pharmacokinetic behavior of the Fab, PEGylated mutSS Fab$_{SH}$ was administered to rats via tail vein injection. Analysis of the mean serum concentration of the PEGylated mutSS Fab$_{SH}$ versus time through ELISA indicated an increase in half-life compared to that of non-PEGylated wild-type Fab. Consequently, we have successfully demonstrated that a Fab mutant with a novel interchain SS bond and one free cysteine at the C-terminal end can be PEGylated without changes in functionality. This design can potentially be used as a platform for modification of other recombinant Fabs.

（大栗誉敏）

Crystal structure of the complex of the interaction domains of *Escherichia coli* DnaB helicase and DnaC helicase loader: structural basis implying a distortion-accumulation mechanism for the DnaB ring opening caused by DnaC binding.

Nagata K（東京大学）
Okada A（東京大学）
Ohtsuka J（東京大学）
Ohkuri T（崇城大学）
Akama Y（九州大学）
Sakiyama Y（九州大学）
Miyazaki E（九州大学）
Horita S（東京大学）
Katayama T（九州大学）
Ueda T（九州大学）
Tanokura M（東京大学）

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Loading the bacterial replicative helicase DnaB onto DNA requires a specific loader protein, DnaC/DnaI, which creates the loading-competent state by opening the DnaB hexameric ring. To understand the molecular mechanism by which DnaC/DnaI opens the DnaB ring, we solved 3.1-Å co-crystal structure of the interaction domains of

Escherichia coli DnaB-DnaC. The structure reveals that one N-terminal domain (NTD) of DnaC interacts with both the linker helix of a DnaB molecule and the C-terminal domain (CTD) of the adjacent DnaB molecule by forming a three α-helix bundle, which fixes the relative orientation of the two adjacent DnaB CTDs. The importance of the intermolecular interface in the crystal structure was supported by the mutational data of DnaB and DnaC. Based on the crystal structure and other available information on DnaB-DnaC structures, we constructed a molecular model of the hexameric DnaB CTDs bound by six DnaC NTDs. This model suggested that the binding of a DnaC would cause a distortion in the hexameric ring of DnaB. This distortion of the DnaB ring might accumulate by the binding of up to six DnaC molecules, resulting in the DnaB ring to open.

（大栗誉敏）

Transport of 2,4-dichloro phenoxyacetic acid by human Na+-coupled monocar-boxylate transporter 1 (hSMCT1, SLC5A8)

Sugio, K.（東邦大学）
Inoda, D.（東邦大学）
Masuda, M.（東邦大学）
Azumaya, I.（東邦大学）
Sasaki, S.（東邦大学）
Shimono, K.（崇城大学）
Ganapathy, V.（テキサス工科大学）
Miyauchi, S.（東邦大学）
Drug Metab. Pharmacokinet., Vol.34(1),pp.95-103
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Using X. laevis oocyte expression system, we inves-tigated whether human Na+-coupled monocarboxylate transporter1 (SLC5A8, hSMCT1) is involved in 2,4-dichlorophenoxyacetate (2,4-D) uptake by the renal tubular epithelial cells. 2,4-D is a herbicide that causes nephrotoxicity. Heterologous expression of hSMCT1 in X. laevis oocytes conferred the ability to take up 2,4-D; the induced uptake process was Na+-dependent and electrogenic. The Na+-dependent uptake of 2,4-D was inhibited not only by known hSMCT1 substrates, but also by many structural an-alogs of 2,4-D. The currents induced by 2,4-D, 4-chlorophenoxyacetate (4-CPA) and 2-methyl-4-chlorophenoxyacetate (MCPA) were saturable: the rank order of the maximal induced

current and the affinity for hSMCT1 was 2,4-D > 4-CPA > MCPA. The relationship between the structures of the derivatives and their transport activity implied specific structural features in a compound for recognition as a sub-strate by hSMCT1. Furthermore, we have demon-strated using purified rabbit renal brush-border membrane vesicles that 2,4-D potently inhibited the Na+-dependent uptake of pyroglutamate, a typical substrate for Smct1, and that 2,4-D uptake process was Na+-dependent, saturable and inhibitable by a potent blocker, ibuprofen. We conclude that hSMCT1 is involved partially in the renal reabsorption of 2,4-D and its derivatives and their nephrotoxicity.

（下野和実）

β-Naphthoflavone, an exogenous ligand of aryl hydrocarbon receptor, disrupts zinc homeostasis in human hepatoma HepG2 cells

Takumi Ishida（崇城大学）
Shinji Takechi（崇城大学）
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Recent studies have demonstrated a relationship between the disruption of zinc homeostasis and the onset of diseases. However, little is known about the factors that disrupt zinc homeostasis. Here, we investigated the effects of ß-naphthoflavone, an exogenous ligand of aryl hydrocarbon receptor (AHR), on intracellular zinc levels. Human hepatoma HepG2 cells were treated with ß-naphthoflavone for 3 days, and intracellular labile and total zinc levels were assessed through flow cytometry and inductively coupled plasma atom emission spectroscopy, respectively. The mRNA levels of zinc transporters were determined by real-time PCR. Treatment of cells with ß-naphthoflavone induced a decrease in intra- cellular labile zinc in a dose-dependent manner, with significantly decreased levels observed at 1 μM compared with controls. Additionally, intracellular total zinc levels demonstrated a decreasing trend with 10 μM ß-naphthoflavone. Zinc pyrithione recovered the decrease in intracellular labile zinc levels induced by ß-naphthoflavone, while zinc sulfate had no effect. Moreover, significant decreases in the mRNA levels of zinc transporters ZnT10 and ZIP5 were observed in response to 10 μM ß-naphthoflavone. These results demonstrated that ß-naphthoflavone has the potential to disrupt zinc homeostasis in hepatocytes. Although the underlying mechanism remains to be determined, suppression of zinc transporter

transcription through AHR activation may be involved in the ß-naphthoflavone-induced disruption of intracellular zinc levels.

（石田卓巳、武知進士）

The effect of dihydropyrazines on lipopolysaccharide-stimulated human hepatoma HepG2 cells via regulating the TLR4-MyD88-mediated NF-κB signaling pathways

Madoka Esaki（崇城大学）
Takumi Ishida（崇城大学）
Yuu Miyauch（崇城大学）
Shinji Takechi（崇城大学）
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Dihydropyrazines (DHPs), including 3-hydro-2,2,5,6-tetramethylpyrazine (DHP-3), are glycation products that are spontaneously generated in vivo and ingested via food. DHPs generate various radicals and reactive oxygen species (ROS), which can induce the expression of several antioxidant genes in HepG2 cells. However, detailed information on DHP-response pathways remains elusive. To address this issue, we investigated the effects of DHP-3 on the nuclear factor-κB (NF-κB) pathway, a ROS-sensitive signaling pathway. In lipopolysaccharide-stimulated (LPS-stimulated) HepG2 cells, DHP-3 decreased phosphorylation levels of inhibitor of NF-κB (IκB) and NF-κB p65, and nuclear translocation of NF-κB p65. In addition, DHP-3 reduced the expression of Toll-like receptor 4 (TLR4) and the adaptor protein myeloid differentiation primary response gene 88 (MyD88). Moreover, DHP-3 suppressed the mRNA expression of tumor necrosis factor-alpha (TNFα), and interleukin-1 beta (IL-1ß). Taken together, these results suggest that DHP-3 acts as a negative regulator of the TLR4-MyD88-mediated NF-κB signaling pathway.

（石田卓巳、宮内優、武知進士）

In vivo ESR imaging of redox status in mice after X-ray irradiation, measured by acyl-protected hydroxylamine probe, ACP

Keita Saito（Frederick National Laboratory for Cancer Research）
Shoko Okazaki（崇城大学）

Yoko Tachibana（崇城大学）
Kazunori Anzai（日本薬科大学）
Toshihiko Ozawa（日本薬科大学）
Keizo Takeshita（崇城大学）
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More detailed investigations on the *in vivo* redox status are needed to elucidate the mechanisms contributing to
damage caused by ionizing radiation. In the present study, the *in vivo* redox status of mice was examined using *in vivo* electron spin resonance (ESR) imaging after an intraperitoneal injection of 1-acetoxy-3-carbamoyl-2,2,5,5- tetramethylpyrrolidine (ACP) as a probe. ACP is easily hydrolyzed to its hydroxylamine form in the mouse body, and the interconversion between hydroxylamine and the corresponding nitroxyl radical reflects the biological redox status. Liver damage, based on changes in liver weight and plasma aspartate aminotransferase levels, was detected in mice 4 days after X-ray irradiation at 7.5 Gy. ESR imaging showed that the signal intensity of the nitroxyl radical was high at the liver area in both damaged and healthy mice after administration of ACP. Whereas the signal decayed at the liver area for healthy mouse, the decay was negligible in damaged mice. Unlike healthy mouse, signal in the chest for damaged mouse increased with time. The distribution of the sum of hydroxylamine and the nitroxyl radical was similar in damaged and healthy mice. X-ray irradiation slightly lowered the reduction activity of the liver microsomal fraction for the nitroxyl radical. Thiobarbituric acid reactive substances in the liver were higher in damaged mice than in healthy mice; however, no significant differences were noted in reduced glutathione. The present results indicate that the redox status of mice exposed to X-ray irradiation is more oxidative than that in healthy mice.

（岡崎祥子・竹下 啓蔵）

Differences in pharmacokinetic behaviors of two lipophilic 3 - substituted 2,2,5,5 - tetramethylpyrrolidine - *N* - oxyl radicals, in vivo probes to assess the redox status in the brain using magnetic resonance techniques

Keizo Takeshita（崇城大学）
Hana Okazaki（崇城大学）
Megumi Tsukamoto（崇城大学）

Shoko Okazaki（崇城大学）
Magn. Reson. Med., in press
DOI: 10.1002/ mrm.28499

Purpose: The pharmacokinetics of 3-methoxycarbonyl- and 3-hydroxymethyl- 2,2,5,5-tetramethylpyrrolidine-N-oxyl radicals (MCP and HMP, respectively), magnetic resonance probes to assess the brain redox status, were examined in healthy mouse brains.

Methods: The time course of the concentration of the radical form of the probe in the brain was examined by signal enhancements on T1-weighted MR image after an intravenous injection. The distribution of the total probe (sum of radical and reduced forms) was investigated using brain homogenates.

Results: MCP distributed to the brain more than HMP. MCP exhibited biphasic decay with fast and slow components, whereas HMP exhibited monophasic decay with a similar rate constant to the slow component of MCP. Similar profiles were observed in various regions of the brain. The total probe for MCP exhibited mono- phasic decay at a similar rate constant to the slow component of the radical form; however, the initial content of the total probe was similar to its radical form. For HMP, decay of the total probe coincided with that of the radical form.

Conclusion: The decay of MCP needs to consider the reduction of the probe in and its elimination from the brain, while the decay of HMP may mainly result from its elimination from the brain.

（岡崎祥子・竹下 啓蔵）

３．代替医療マテリアル開発、評価グループ

Processing grapefruit juice with γ-cyclodextrin attenuates its inhibitory effect on cytochrome P450 3A activity.

Yamasaki K（崇城大学）
Iohara D（崇城大学）
Oyama Y（崇城大学）

Nishizaki N（崇城大学）
Kawazu S（崇城大学）
Nishi K（崇城大学）
Kadowaki D（崇城大学）
Taguchi K（崇城大学）
Anraku M（崇城大学）
Otagiri M（崇城大学）
Seo H（崇城大学）
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Objectives: Grapefruit (*Citrus paradisi*) juice enhances the oral bioavailability of drugs that are metabolized by intestinal cytochrome P450 3A4 (CYP3A4). Patients are advised to avoid drinking grapefruit juice to prevent this drug-grapefruit juice interaction. The aim of this study was to investigate whether processing grapefruit juice with cyclodextrins (CDs) would result in preventing or inhibiting this interaction.

Methods: Grapefruit juice and the major furanocoumarins found in grapefruit, bergamottin (BG) and 6', 7'-dihydroxy bergamottin (DHBG) were mixed with α, ß and γCDs. The effects of these processed juice samples and furanocoumarins on CYP3A activity were compared with the corresponding values for unprocessed juices and furanocoumarins. Interactions between CDs and these furanocoumarins were also investigated by phase solubility and 1 H NMR studies.

Key findings: The inhibition of CYP3A by grapefruit juice was significantly attenuated by processing particularly with γCD. Similar attenuation effects by γCD were observed in the cases of BG and DHBG. Furthermore, BG and DHBG were suggested to be strongly encapsulated in the cavity of γCD.

Conclusion: The encapsulation of BG and DHBG by γCD and the resulting attenuation of the inhibition of CYP3A activity by grapefruit juice may be applicable to juice processing for preventing drug-grapefruit juice interactions.

（門脇大介、瀬尾量、山﨑啓之、庵原大輔）

Toxicological Property of Acetaminophen: The Dark Side of a Safe Antipyretic/Analgesic Drug?

Ishitsuka Y（熊本大学）
Kondo Y（熊本大学）

Kadowaki D（崇城大学）
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Acetaminophen (paracetamol, N-acetyl-p-aminophenol; APAP) is the most popular analgesic/antipyretic agent in the world. APAP has been regarded as a safer drug compared with non-steroidal anti-inflammatory drugs (NSAIDs) particularly in terms of lower risks of renal dysfunction, gastrointestinal injury, and asthma/bronchospasm induction, even in high-risk patients such as the elderly, children, and pregnant women. On the other hand, the recent increasing use of APAP has raised concerns about its toxicity. In this article, we review recent pharmacological and toxicological findings about APAP from basic, clinical, and epidemiological studies, including spontaneous drug adverse events reporting system, especially focusing on drug-induced asthma and pre-and post-natal closure of ductus arteriosus. Hepatotoxicity is the greatest fault of APAP and the most frequent cause of drug-induced acute liver failure in Western countries. However, its precise mechanism remains unclear and no effective cure beyond N-acetylcysteine has been developed. Recent animal and cellular studies have demonstrated that some cellular events, such as c-jun N-terminal kinase (JNK) pathway activation, endoplasmic reticulum (ER) stress, and mitochondrial oxidative stress may play important roles in the development of hepatitis. Herein, the molecular mechanisms of APAP hepatotoxicity are summarized. We also discuss the not-so-familiar "dark side" of APAP as an otherwise safe analgesic/antipyretic drug.

（門脇大介）

Comparative Study of Constipation Exacerbation by Potassium Binders Using a Loperamide-Induced Constipation Model.

Narita Y（熊本大学）
Fukumoto Y（熊本大学）
Fukunaga M（熊本大学）
Kondo Y（熊本大学）
Ishitsuka Y（熊本大学）
Jono H（熊本大学）
Irie T（熊本大学）
Saito H（熊本大学）
Kadowaki D（崇城大学）

Hirata S（熊本大学）
Int J Mol Sci. Vol. 21(7), 2491.
2020（令和 2 年）
DOI: doi: 10.3390/ijms21072491

BACKGROUND: Constipation is frequently observed in patients with chronic kidney disease (CKD). Lactulose is expected to improve the intestinal environment by stimulating bowel movements as a disaccharide laxative and prebiotic. We studied the effect of lactulose on renal function in adenine-induced CKD rats and monitored uremic toxins and gut microbiota. METHODS: Wistar/ST male rats (10-week-old) were fed 0.75% adenine-containing diet for 3 weeks to induce CKD. Then, they were divided into three groups and fed as follows: control, normal diet; and 3.0- and 7.5-Lac, 3.0% and 7.5% lactulose-containing diets, respectively, for 4 weeks. Normal diet group was fed normal diet for 7 weeks. The rats were observed for parameters including renal function, uremic toxins, and gut microbiota. RESULTS: The control group showed significantly higher serum creatinine (sCr) and blood urea nitrogen (BUN) 3 weeks after adenine feeding than at baseline, with a 8.5-fold increase in serum indoxyl sulfate (IS). After switching to 4 weeks of normal diet following adenine feeding, the sCr and BUN in control group remained high with a further increase in serum IS. In addition, tubulointerstitial fibrosis area was increased in control group. On the other hand, 3.0- and 7.5-Lac groups improved sCr and BUN levels, and suppressed tubulointerstitial fibrosis, suggesting preventing of CKD progression by lactulose. Lac groups also lowered level of serum IS and proportions of gut microbiota producing IS precursor. CONCLUSION: Lactulose modifies gut microbiota and ameliorates CKD progression by suppressing uremic toxin production.

（門脇大介）

In vivo evaluation of drug dialyzability in a rat model of hemodialysis.

Fukunaga M（熊本大学）
Kadowaki D（崇城大学）
Mori M（熊本大学）
Murakami M（熊本大学）
Hagiwara S（熊本大学）
Narita Y（熊本大学）
Saruwatari J（熊本大学）
Tanaka R（大分大学病院）

Watanabe H（熊本大学）
Yamasaki K（崇城大学）
Taguchi K（慶応大学）
Ito H（大分大学病院）
Maruyama T（熊本大学）
Otagiri M（崇城大学）
Hirata S（熊本大学）
PLoS One. 15(6), e0233925.
2020（令和 2 年）
DOI: 10.1371/journal.pone.0233925.

It is important to calculate the drug removal by hemodialysis (HD) for drug dosing regimens in HD patients. However, there are limited and inconsistent information about the dialyzability of drugs by HD. Therefore, the aim of our study is to evaluate drug removal by utilizing a rat model of HD (HD rat) and to extrapolate this result to the drug removal rate in HD patients. HD rats received bilateral nephrectomy and HD for 2 h. The dialysis removal of 6 drugs was evaluated in HD rats. Dialysis efficiency, plasma protein binding rate (PBR) and distribution volume (Vd) of drugs were also measured. Furthermore, we examined the correlation between the dialyzability of drug in HD rats and humans and constructed the prediction formula of the drug dialyzability in HD patients. The clearance of urea and creatinine and normalized dialysis dose in HD rats were 0.83 ± 0.07 mL/min, 0.70 ± 0.08 mL/min, and 0.13 ± 0.06, respectively. The drug dialyzability in HD rats was similar to reported clinical data except for doripenem. A higher correlation was observed between drug dialyzability in reported clinical data and HD rats which were adjusted for PBR ($r2 = 0.936$; $p < 0.001$) compared to unadjusted ($r2 = 0.812$; $p = 0.009$). Therefore, we constructed the prediction formula of the drug dialyzability in HD patients by utilizing the HD rat model and PBR. This study is useful for evaluating the dialyzability of high-risk drugs in a clinical setting and might provide appropriate preclinical dialyzability data for new drug.

（門脇大介）

Investigation of methods for more accurate estimation of kidney function in people with high muscle mass.

Ichigi M（熊本大学）
Nakatani S（熊本大学）
Murakami M（熊本大学）

Harada Y（熊本大学）
Utsumi S（熊本大学）
Ogata M（熊本大学）
Maehara Y（島田病院）
Ikeda H（島田病院）
Shimada H（島田病院）
Fukunaga M（熊本大学）
Narita Y（熊本大学）
Saruwatari J（熊本大学）
Kondo Y（熊本大学）
Ishitsuka Y（熊本大学）
Irie T（熊本大学）
Kadowaki D（崇城大学）
Hirata S（熊本大学）
Clin Nephrol. Vol. 94(2), pp. 86-96
2020（令和 2 年）
DOI: 10.5414/CN110074.
Serum creatinine (SCr) levels depend on muscle mass and are therefore elevated in people with high muscle mass, potentially leading to underestimation of kidney function in this population. Although recent therapeutic guidelines have shown measurement of serum cystatin C (ScysC) to be useful, this method has not been validated in people with high muscle mass. We conducted this study to investigate methods for more accurately estimating kidney function in people with high muscle mass. Linear regression analysis was used to assess the correlation of endogenous creatinine clearance (24-hour CLcr) and 24-hour CLcr × 0.715 (i.e., modified glomerular filtration rate (GFR)); with estimated kidney function from SCr and ScysC in 15 healthy young adult men with high muscle mass. A significant but weak positive correlation was observed between 24-hour CLcr and estimated CLcr by the Cockcroft and Gault formula (CG CLcr; R2 = 0.371, p = 0.016). The estimated GFR calculated from ScysC (eGFRcys) was significantly higher than CLcr × 0.715, but the two were not correlated (R2 = 0.125, p = 0.197). However, when CG CLcr and eGFRcr were adjusted by muscle mass parameters, the correlation between measured and estimated values improved. Further improvement was seen when participants with a fat mass greater than 25% were excluded (R2 = 0.623, p = 0.004; R2 = 0.510, p = 0.014; n = 11 for both). The results of our study suggest that currently used formulas for estimating kidney function, including eGFRcys, may not be appropriate for people with high muscle mass, but use of muscle mass parameters may improve

predictivity.

（門脇大介）

循環器科入院患者における医師と薬剤師の協働による処方適正化の取り組みの成果分析

西村 文宏（熊本中央病院）
牛島 智子（熊本中央病院）
野田 勝生（熊本中央病院）
門脇 大介（崇城大学）
宮村 重幸（崇城大学）

日本老年薬学会雑誌, Vol.3(1), pp.9-14
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Objective: The aim of this study was to estimate medical economic costs associated with optimizing drugs brought to a cardiology hospital for inpatients with the help of pharmacists and doctors. Methods: We optimized drugs brought to the hospital, compared patient backgrounds, and estimated medical economic costs. Results: Medicine expenditure was 34.36 yen per day per patient post drug optimization with the help of pharmacists and doctors. Estimated glomerular filtration rates were significantly lower and patient ages and the number of prescriptions optimized were significantly higher in patients who regularly used 10 or more drugs than in those who used fewer than 10 drugs.Conclusion: A drug cost reduction effect is expected with the collaboration between doctors and pharmacists, and with prescription optimization of drugs brought to a hospital.

（門脇大介）

Effects of surface-deacetylated chitin nanofibers on non-alcoholic steatohepatitis model rats and their gut microbiota

M. Goto（崇城大学）
D. Iohara（崇城大学）
A. Michihara（福山大学）
S. Ifuku（鳥取大学）
K. Azuma（鳥取大学）
D. Kadowaki（崇城大学）
T. Maruyama（熊本大学）
M. Otagiri（崇城大学）

F. Hirayama（崇城大学）
M. Anraku（崇城大学）
Int. J. Biol. Macromol., Vol.164, pp.659-666
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DOI: 10. 1016/j.ijbiomac.2020.07.184

Nonalcoholic steatohepatitis (NASH), a more advanced form of nonalcoholic fatty liver disease (NAFLD), is associated with increased cardiovascular and liver-related mortality. We investigated the hepatic protective and antioxidant effects of surface-deacetylated chitin nanofibers (SDACNFs) that were administered to SHRSP5/Dmcr rats for 8 weeks. The administration of SDACNFs (80 mg/kg/day) resulted in a significant decrease in hepatic injury, oxidative stress, compared with the non-treatment. The SDACNFs also caused a reduction in the population of harmful members of the Morganella and Prevotella genus, and increased the abundance of the Blautia genus, a useful bacterium in gut microbiota. We therefore conclude that SDACNF exerts anti-hepatic and antioxidative effects not only by adsorbing lipid substances but also by reforming the community of intestinal microflora in the intestinal tract.

（庵原 大輔、門脇 大介、安楽 誠）

In vitro transdermal permeation of isosorbide dinitrate in the absence and presence of 2-hydroxypropyl-β-cyclodextrin:solutions and suspensions

K. Zao（熊本大学）
T. Ishiguro（崇城大学）
D. Iohara（崇城大学）
M. Anraku（崇城大学）
H. Seo（崇城大学）
T. Irie（熊本大学）
K. Uekama（崇城大学）
F. Hirayama（崇城大学）
J. Incl. Phenom. Macrocycl. Chem., Vol.96, pp.137-143
2020（令和 2 年）
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Interactions of a vasodilator, isosorbide dinitrate (ISDN), with the parent α-, β- and γ-cyclodextrins (α-, β- and γ-CDs) and 2-hydroxypropyl-α- and -β- and γ-CDs (HP-α- and -β- and -γ-CDs) and the dissolution properties of ISDN/β-CD complexes were investigated. The effects of HP-β-CD on the in vitro transdermal permeation of the drug in the forms

of solutions and suspensions were also investigated using skin from hairless mice. The size dependent guest–host interactions of CDs were clearly reflected in the stoichiometry of the complexes, i.e. ISDN interacted with two α-CD molecules (which have small cavities) to form a 1:2 (guest:host) complex, while ß-CD formed a 1:1 complex. Meanwhile, the large γ-CD cavity included two ISDN molecules to form a 2:1 complex. The permeation of ISDN in the presence of HP-ß-CD in solutions and in suspensions was slightly increased, when oleic acid or linoleic acid were added to the suspension. These results suggest that HP-ß-CD complexation has a positive effect on the percutaneous permeation of ISDN when the drug is in the form of a suspension, while the effect is negative when a solution is involved.

（石黒 貴子、瀬尾 量、庵原 大輔、安楽 誠）

Morphometric analysis of paramylon particles produced by *Euglena gracilis* EOD-1 using FIB/SEM tomography

M. Anraku（崇城大学）
D. Iohara（崇城大学）
H. Takada（コベルコ科研）
T. Awane（コベルコ科研）
J. Kawashima（神鋼環境ソリューション）
M. Takahashi（神鋼環境ソリューション）
F. Hirayama（崇城大学）
Chem. Pharm. Bull., Vol.68 (1), pp.100-102
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Euglena gracilis EOD-1, a microalgal strain, produces large quantities of paramylon, a class of polymers known as ß-1,3-glucans and has been reported to function as a dietary fiber and to improve the metabolic syndrome including obesity. However, despite its importance, the morphometric analysis of paramylon has not been conducted so far. In this study, we attempted to observe the detailed three-dimensional structure of paramylon by focused ion beam/scanning electron microscopy (FIB/SEM).

（庵原 大輔、安楽 誠）

A Thermoresponsive Hydrophobically Modified Hydroxypropylmethyl Cellulose/Cyclodextrin Injectable Hydrogel for the Sustained Release of

Drugs

M. Okubo（崇城大学）
D. Iohara（崇城大学）
M. Anraku（崇城大学）
T. Higashi（熊本大学）
K. Uekama（崇城大学）
F. Hirayama（崇城大学）
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The objective of this study was to develop a thermoresponsive injectable hydrogel for the sustained release of drugs by taking advantage of host-guest interactions between a hydrophobically modified hydroxypropylmethyl cellulose (HM-HPMC) and cyclodextrin (CD). A thermoresponsive injectable hydrogel was prepared by simply adding CDs to HM-HPMC hydrogel. The HM-HPMC hydrogel was converted into a sol with a low viscosity through host-guest interactions with CDs. A thermoresponsive injectable hydrogel was successfully constructed from the highly viscous HM-HPMC and β-CD, and the resulting formulation functioned as a sustained release carrier for drugs.

（庵原 大輔、安楽 誠）

Anti-proliferative Activities of Some Bivalent Symmetrical 5-Substituted Hydantoin Derivatives towards Human Brain Glioma U251 Cells (U251) and Human Carcinoma Cells (KB3-1)

Makoto Furutachi（福岡大学）
Kaori Ota（福岡大学）
Fumiko Fujisaki（福岡大学）
Ryuji Ikeda（福岡大学）
Naoki Yoshikawa（福岡大学）
Tsubasa Yokota（福岡大学）
Yasuo Takeda（福岡大学）
Kazumi Yokomizo（崇城大学）
Jian-Rong Zhou（崇城大学）
Nobuhiro Kashige（福岡大学）
Fumio Miake（福岡大学）
Kunihiro Sumoto（福岡大学）

Biol. Pharm. Bull., Vol.42(11),pp.1953-1956
2019（令和 1 年）
DOI: 10.1248/bpb.b19-00486

Novel bivalent twin-drug type hydantoin derivatives were evaluated in vitro using a human brain glioma cell line (U251) and a human carcinoma cell line (KB3-1). Among the 5-substituted hydantoin derivatives (1a-b and 2a-d) examined in this study, bivalent symmetrical 5-substituted hydantoin derivative 1b showed the highest anti-proliferative activity towards both U251 and KB3-1 cells. The values of anti-proliferative activity (IC50) of this hydantoin derivative against the two cell lines (U251 and KB3-1) were 0.46 and 5.21 μM, respectively. The anti-proliferative activity of all of the compounds except for compounds 2a and 2d against U251 cells was higher than that of cisplatin. Bivalent symmetrical compound 1b had a biphenylmethane linker in the molecule. All of the tested bivalent hydantoin derivatives showed higher activity against U251 cells than against KB3-1 cells. For twin-drug type hydantoin derivatives 2a-d, which have a linear methylene linker in the molecules, it was found that methylene linker length in these molecules have an effect on the anti-proliferative activity against U251 and KB3-1 cells.

（横溝　和美、周　建融）

Some Hybrid Linker Mode C2-Symmetrical 1,3,5-Triazine Derivatives and Their Biological Evaluation

Nobuko Mibu（福岡大学）
Makoto Furutachi（福岡大学）
Yusuke Inoue（福岡大学）
Yuka Fujita（福岡大学）
Yumemi Matsumoto（福岡大学）
Yuki Kawano（福岡大学）
Syoko Tomonaga（福岡大学）
Junko Matsuyama（福岡大学）
Kanae Yamada（福岡大学）
Ryo Sato（福岡大学）
Kazumi Yokomizo（崇城大学）
Jian-Rong Zhou（崇城大学）
Shunsuke Shimomura（福岡大学）
Kaori Ota（福岡大学）
Kunihiro Sumoto（福岡大学）

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We report the preparation of some new C2-symmetrical multivalent hybrid-type molecules having a methylene linker group and 1,3,5-triazine (TAZ) recognition moieties in the molecule and we also report the results of biological evaluation of their anti-herpes simplex virus type 1 (anti-HSV-1) activity and cytotoxic activity against Vero cells. All mid-size C2-symmetrical multivalent hybrid-type molecules (3a-2, 3a-4, 3b-2, 3b-3, 3b-4) showed considerably high levels of anti-HSV-1 activity (EC50 = 7.6 ~ 95.6 μM) with low levels of cytotoxicity (CC50 > 200 μM) against Vero cells. Among the tested compounds, the hybrid-type C2-symmetrical multivalent molecule (3a-4) seems to be an interesting new lead in the search for new hybrid-type multivalent mid-size antiviral compounds.

（横溝　和美、周　建融）

研 究 発 表

Presentation records

2019 年 10 月 1 日～2020 年 9 月 1 日発表分

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高塚絢巳 池田　剛 平山　悟 泉福英信 成澤直規 中尾龍馬	日大院・生資科 崇城大学･薬 感染研・細菌第一 感染研・細菌第一 日大院・生資科 感染研・細菌第一	抹茶による *Porphyromonas gingivalis* に対する阻害活性のメカニズム	第61回歯科基礎医学会学術大会	2019.10
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庵原 大輔 赤星 裕紀 安楽 誠 上釜 兼人	崇城大学 崇城大学 崇城大学 崇城大学	疎水化ヒドロキシプロピルメチルセルロース/シクロデキストリンヒドロゲルの薬物担体としての有用性評	第 69 回高分子学会年次大会（福岡）	2020.5

平山 文俊	崇城大学	価		
安楽　誠 水飼 康之 前崎 祐二 川野 和男 足立 知基 岡崎 祥子 竹下 啓蔵 庵原 大輔 平山 文俊	崇城大学 日本化薬フード 日本化薬フード 日本化薬フード 崇城大学 崇城大学 崇城大学 崇城大学 崇城大学	分散性の向上した造粒キトサン錠の崩壊性評価	第 34 回日本キチン・キトサン学会大会	2020.8
後藤 美和 庵原 大輔 道原 明宏 伊福 伸介 東　和生 小田切 優樹 平山 文俊 安楽 誠	崇城大学 崇城大学 福山大学 鳥取大学 鳥取大学 崇城大学 崇城大学 崇城大学	非アルコール性脂肪肝炎（NASH）モデルラットに対する表面脱アセチル化キチンナノファイバーの腸内細菌叢への影響及び肝保護効果	第 34 回日本キチン・キトサン学会大会	2020.8
山崎 啓之 小山 陽子 西崎 成美 河津 誠太郎 庵原 大輔 田口 和明 門脇 大介 小田切 優樹 瀬尾 量	崇城大学 崇城大学 崇城大学 崇城大学 崇城大学 慶応義塾大学 崇城大学 崇城大学 崇城大学	グレープフルーツの CYP3A 活性阻害におよぼすシクロデキストリン処理の影響	第 29 回日本医療薬学会年会（福岡国際会議場他／福岡）	2019.11
有働 なぎ子 西 弘二 櫻間 啓基 小橋川 敬博 森岡 弘志 橋本 麻衣 井本 修平 山﨑 啓之 小田切 優樹	崇城大学 崇城大学 崇城大学 熊本大学 熊本大学 崇城大学 崇城大学 崇城大学 崇城大学	アリピプラゾールのヒト α1-酸性糖タンパク質への結合特性評価	第 36 回日本薬学会九州支部大会（長崎大学／長崎）	2019.11
櫻間 啓基 西 弘二 橋本 麻衣 瀬尾 量 小田切 優樹 山﨑 啓之	崇城大学 崇城大学 崇城大学 崇城大学 崇城大学 崇城大学	アリピプラゾールのヒト血清アルブミンへの結合に及ぼす病態時各種変動因子の影響	第 36 回日本薬学会九州支部大会（長崎大学／長崎）	2019.11
橋本　麻衣 田口　和明 山﨑　啓之 井本　修平 満屋　裕明 小田切　優樹	崇城大学 慶応義塾大学 崇城大学 崇城大学 熊本大学・国立国際医療研究センター 崇城大学	健常ラット及び病態モデルラットにおける B 型肝炎ウイルスに対する候補薬である 4'-CN-2'-deoxyguanosine の薬物動態学的評価	日本薬物動態学会第 34 年会（つくば国際会議場／つくば）	2019.12
山崎 啓之 田口 和明 西 弘二	崇城大学 慶応義塾大学 崇城大学	アルブミンとの混合噴霧乾燥によるプラジカンテル粒子の調製と溶出性・経口吸	日本薬学会第 140 年会	2020.3

小田切 優樹 瀬尾 量	崇城大学 崇城大学	収性評価		
別府 拓豪 西 弘二 井本 修平 小田切 優樹 山崎 啓之	崇城大学 崇城大学 崇城大学 崇城大学 崇城大学	ヒト膵がん細胞に対するニトロ化フェニル酪酸の細胞死誘導効果	日本薬学会第 140 年会	2020.3
田口 和明 橋本 麻衣 中山 真雪 榎木 裕紀 西 弘二 松元 一明 瀬尾 量 小田切 優樹 山崎 啓之	慶応義塾大学 崇城大学 崇城大学 慶応義塾大学 崇城大学 慶応義塾大学 崇城大学 崇城大学 崇城大学	脱溶媒法によるラクトフェリンナノ粒子に与える調製パラメーターの影響	日本薬学会第 140 年会	2020.3
橋本 麻衣 田口 和明 井本 修平 山崎 啓之 満屋 裕明 小田切 優樹	崇城大学 慶応義塾大学 崇城大学 崇城大学 熊本大学 崇城大学	B 型肝炎ウイルス新規治療候補薬の腎障害モデルラットにおける体内動態解析	日本薬学会第 140 年会	2020.3
月川 健士 井本 修平 山崎 啓之 堤 敏彦 横山 祥子 小田切 優樹	九州保健福祉大学 崇城大学 崇城大学 九州保健福祉大学 九州保健福祉大学 崇城大学	酸性環境応答性を有するアルブミン結合型高分子化抗がん剤の設計と評価	日本薬学会第 140 年会	2020.3
中村　仁美 大栗　誉敏 服部　正策 上田　直子	崇城大学 崇城大学 東大医科研 崇城大学	ハブ毒筋壊死因子に対するモノクローナル抗体の中和作用と抗体フラグメント Fab の調製	日本薬学会第 140 年会（京都）	2020.3
佐々木将太郎 菅野美生 日改祐太 石川龍 杉尾和昭 増田雅行 下野和実 宮内正二	東邦大学 東邦大学 東邦大学 東邦大学 東邦大学 東邦大学 崇城大学 東邦大学	ニコチン酸によるオリゴペプチド輸送担体 PEPT1 の機能調節	第 41 回生体膜と薬物の相互作用シンポジウム（習志野、千葉）	2019.10
大森明子 佐々木将太郎 下野和実 宮内正二	東邦大学 東邦大学 崇城大学 東邦大学	熱力学的解析手法を用いた H^+/オリゴペプチドトランスポーター(YdgR)の有する多様な基質認識機構の解明	第 41 回生体膜と薬物の相互作用シンポジウム（習志野、千葉）	2019.10
下野和実 宮本秀一 宮内正二	崇城大学 崇城大学 東邦大学	大腸菌多剤排出トランスポーターEmrE の基質結合における水分子の役割	第 41 回生体膜と薬物の相互作用シンポジウム（習志野、千葉）	2019.10
杉尾和昭 府川和樹 増田雅行 佐々木将太郎 下野和実	東邦大学 東邦大学 東邦大学 東邦大学 崇城大学	SMCT1 の多彩な基質認識機構と腎再吸収機構における役割	第 41 回生体膜と薬物の相互作用シンポジウム（習志野、千葉）	2019.10

宮内正二	東邦大学			
Masayuki Masuda Kazuaki Sugio Shotaro Sasaki Kazumi Shimono Ryoji Konishi Ikuko Tsukamoto Seiji Miyauchi	Toho University Toho University Toho University Sojo University Kagawa University Kagawa University Toho University	Human concentrative nucleoside transporter 3 (hCNT3, SLC28A3) has versatile ability to transport nucleoside analogues, acyclovir and ganciclovir	AAPS2019 PharmSci360 (San Antonio, Texas, USA)	2019.11
下野和実 宮本秀一	崇城大学 崇城大学	分子動力学法による多剤排出トランスポーターEmrEの基質結合における水分子の動的解析	日本薬学会第 140 年会	2020.3
宮本秀一 下野和実	崇城大学 崇城大学	ICT を活用した物理化学の反転授業による学習効果の大幅改善	ICT 利用による教育改善研究発表会（東京）	2020.8
岡崎祥子 宮瀬のぞみ 有田瑠名 山田瑠依 竹下啓蔵	崇城大学 崇城大学 崇城大学 崇城大学 崇城大学	紫外線照射によりケトプロフェンが惹起するリポソーム膜障害の検出	第 58 回電子スピンサイエンス学会年会（川崎）	2019.11
岡崎祥子 宮瀬のぞみ 平尾誠 有田瑠名 山田瑠依 竹下啓蔵	崇城大学 崇城大学 崇城大学 崇城大学 崇城大学 崇城大学	紫外線照射下のケトプロフェンが惹起したラジカル反応によるリポソーム膜の障害	日本薬学会第 140 年会	2020.3
江﨑　円香 石田　卓巳 武知　進士	崇城大学 崇城大学 崇城大学	糖化産物曝露に伴う HepG2 細胞の TLR4 経路への影響	第 36 回日本薬学会九州支部大会	2019.11
蒲池　可紗 江﨑　円香 鹿志毛　信広 石田　卓巳 武知　進士	崇城大学 崇城大学 福岡大学 崇城大学 崇城大学	Dihydropyrazine 修飾タンパク質の解析	第 36 回日本薬学会九州支部大会	2019.11
宋　穎霞 李　任時 武田　知起 小野村　優子 古賀　貴之 石田　卓巳 武知　進士 田中　嘉孝 石井　祐次	九州大学 九州大学 九州大学 九州大学 九州大学 崇城大学 崇城大学 九州大学 九州大学	セレン結合性タンパク質 1 (SelenBP1) の脂質代謝における役割: SelenBP1 欠損マウスを用いた検討	第 36 回日本薬学会九州支部大会	2019.11

江﨑　円香 伊藤　俊治 吉田　雅紀 石田　卓巳 武知　進士	崇城大学 関西医療大学 長浜バイオ大学 崇城大学 崇城大学	糖化産物曝露に伴うHepG2 細胞の炎症性サイトカイン産生能抑制における TLR4 の関与	第 42 回日本分子生物学会年会	2019.12
江﨑　円香 石田　卓巳 武知　進士	崇城大学 崇城大学 崇城大学	糖化産物中間体 Dihydropyrazine による NF-κB signaling を介した影響	日本薬学会第 140 年会	2020.3
蒲池　可紗 江﨑　円香 鹿志毛　信広 石田　卓巳 武知　進士	崇城大学 崇城大学 福岡大学 崇城大学 崇城大学	Dihydropyrazine によるタンパク質修飾	日本薬学会第 140 年会	2020.3
江﨑　円香 伊藤　俊治 吉田　雅紀 宮内　優 石田　卓巳 武知　進士	崇城大学 関西医療大学 長浜バイオ大学 崇城大学 国際医療福祉大学 崇城大学	糖化産物ジヒドロピラジン類が有する抗炎症作用	フォーラム 2020 衛生薬学・環境トキシコロジー	2020.9
宮内　優 木村　茜 藤本　景子 廣田　有子 武知　進士 Mackenzie Peter 石井　祐次 田中　嘉孝	崇城大学 九州大学 九州大学 九州大学 崇城大学 Flinders University 九州大学 九州大学	新たな薬物代謝酵素発現系の構築：遺伝子改変バキュロウイルスを用いた哺乳動物細胞への遺伝子導入	フォーラム 2020 衛生薬学・環境トキシコロジー	2020.9
Masaki Fukunaga Akemi Uchida Miyu Sueyoshi Hitoshi Maeda Yuki Narita Hiroshi Watanabe Toru Maruyama Hakaru Seo Sumio Hirata Daisuke Kadowaki	熊本大学 崇城大学 熊本大学 熊本大学 熊本大学 熊本大学 熊本大学 崇城大学 熊本大学 崇城大学	The antioxidant activity of neurotropin contributes to the kidney protective effect	ASN KIDNEY WEEK 2019	2019.11
末吉 美優 丸山 徹 門脇 大介	熊本大学 熊本大学 崇城大学	腸腎連関をターゲットとした CKD 新規治療戦略	第13回日本腎臓病薬物療法学会 学術集会・総会 2019	2019.11
福永 雅樹 内田 朱美 末吉 美優 前田 仁志	熊本大学 崇城大学 熊本大学 熊本大学	ノイロトロピンの抗酸化作用及び腎保護効果への寄与	第13回日本腎臓病薬物療法学会 学術集会・総会 2019	2019.11

成田 勇樹 渡邊 博志 丸山 徹 瀬尾 量 平田 純生 門脇 大介	熊本大学 熊本大学 熊本大学 崇城大学 熊本大学 崇城大学			
村上 鞠奈 一木 美里 中谷 咲良 浦田 元樹 成田 勇樹 近藤 悠希 石塚 洋一 入江 徹美 門脇 大介 平田 純生	熊本大学 熊本大学 熊本大学 大野記念病院 熊本大学 熊本大学 熊本大学 熊本大学 崇城大学 熊本大学	薬物動態及び物性パラメータを用いた透析除去率予測についての検討	第13回日本腎臓病薬物療法学会 学術集会・総会2019	2019.11
大塚 勝二 原田 俊和 石川 実穂 小原 大輔 山本 達郎 村上 洋嗣 西 一彦 山田 麻美 久間 粧子 奥野 豊 門脇 大介	熊本大学病院 熊本大学病院 熊本大学病院 熊本大学病院 熊本大学病院 熊本大学病院 熊本大学病院 熊本大学病院 熊本大学病院 熊本大学病院 崇城大学	当院におけるメトトレキサート中毒による急性腎不全に対し血液浄化療法の施行経験	第13回日本腎臓病薬物療法学会 学術集会・総会2019	2019.11
中谷 咲良 前田 圭介 赤木 純児 一木 美里 村上 鞠奈 福永 雅樹 成田 勇樹 近藤 悠希 石塚 洋一 入江 徹美 門脇 大介 平田 純生	熊本大学 愛知医科大学病院 玉名地域保健医療センター 熊本大学 熊本大学 熊本大学 熊本大学 熊本大学 熊本大学 熊本大学 崇城大学 熊本大学	サルコペニア高齢者における筋肉量を使用した腎機能推算式補正の検討	第13回日本腎臓病薬物療法学会 学術集会・総会2019	2019.11
一木 美里 中谷 咲良 村上 鞠奈 緒方 美樹 前原 優一 池田 拡行 嶋田 英敬 成田 勇樹 猿渡 淳二 門脇 大介 平田 純生	熊本大学 熊本大学 熊本大学 嶋田病院 嶋田病院 嶋田病院 嶋田病院 熊本大学 熊本大学 崇城大学 熊本大学	筋肉質な人におけるより正確な腎機能予測法の検討	第13回日本腎臓病薬物療法学会 学術集会・総会2019	2019.11

長谷川 浩三 松本 拓也 西 竜二郎 緒方 真紀子 浦野 一貴 門脇 大介 宮村 重幸	のぞみ薬局 のぞみ薬局 のぞみ薬局 のぞみ薬局 のぞみ薬局 崇城大学 崇城大学	CKD 患者への医薬品適正使用を目的とした薬局間トレーシングレポートの活用	第13回日本腎臓病薬物療法学会 学術集会・総会 2019	2019.11
門脇 大介 福永 雅樹 内田 朱美 末吉 美優 前田 仁志 成田 勇樹 渡邊 博志 丸山 徹 平田 純生 瀬尾 量	崇城大学 熊本大学 崇城大学 熊本大学 熊本大学 熊本大学 熊本大学 熊本大学 熊本大学 崇城大学	ノイロトロピンの抗酸化作用及びHIF1αを介した腎保護効果	日本薬剤学会第 35 年会	2020.5
末吉 美優 福永 雅樹 中島 淳志 田中 雅久 村瀬 貴代 成田 勇樹 平田 純生 前田 仁志 渡邊 博志 瀬尾 量 丸山 徹 門脇 大介	熊本大学 熊本大学 三和化学研究所 三和化学研究所 三和化学研究所 熊本大学 熊本大学 熊本大学 熊本大学 崇城大学 熊本大学 崇城大学	腸腎連関をターゲットとしたラクツロースの腎不全に対する効果	日本薬剤学会第 35 年会	2020.5
横溝 和美 周 建融 國香 清	崇城大学 崇城大学 昭和学院短期大学	枸杞子を主とした健康飲料の終末糖化産物蓄積に及ぼす影響	第26回未病システム学会（名古屋）	2019.10
周 建融 貝原 健太 金納 成哲 野原 稔弘 横溝 和美	崇城大学 崇城大学 崇城大学 崇城大学 崇城大学	マウス樹状細胞成熟化に及ぼすトマト成熟果実サポニンの影響	第26回未病システム学会（名古屋）	2019.10
橋本 知佳 森 晋央 周 建融 横溝 和美	崇城大学 崇城大学 崇城大学 崇城大学	緑膿菌のバイオフィルム形成とクロルヘキシジン耐性に及ぼすアミノ酸の影響	日本薬学会第 140 年会（京都）	2020.3
流矢 敦 釘本 聖也 山口 賢也 木村 亮太 佐藤 桃子 松本 優太 周 建融 方 軍 横溝 和美	崇城大学 崇城大学 崇城大学 崇城大学 崇城大学 崇城大学 崇城大学 崇城大学 崇城大学	動脈硬化モデルマウスにおける枸杞子を主とした健康食品の効果	日本薬学会第 140 年会（京都）	2020.3

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