平成29年度
北海道大学大学院生命科学院
臨床薬学専攻（博士課程）入学試験問題

英　語

○受験に関する注意事項

１．試験時間　9:00～10:00

２．解答用紙には、「**受験科目：(問題番号)**」及び「**受験番号**」を必ず記入すること。

３．出題は、問題１から問題５までの計５問である。そのうち**２問を選択し**，選択した問題番号については，必ず所定の箇所（受験科目欄）に記入すること。

４．**１問１枚の解答用紙**を用いること。同じ問題の解答を複数の解答用紙に書いてはならない。解答は用紙の裏面も使用しても差し支えないが、上部を綴じるので**下部を上にして書くこと**。

５．解答用紙は２枚ある。

６．草案紙は２枚ある。草案紙は回収しない。

問題１　次の英文を全文和訳せよ

The suppression of hepatic cytochrome P450 (P450) expression during inflammatory and infectious diseases and the relief of this suppression by successful disease treatment have been previously demonstrated to impact drug disposition. In the present study we used the human hepatoma cell line (HepaRG) and cryopreserved primary human hepatocytes to investigate the effects of various inflammatory stimuli on P450 levels with the aim of further characterizing HepaRG cells as a useful surrogate for primary hepatocytes. In this study, HepaRG cells were exposed to bacterial lipopolysaccharide (LPS), interleukin-6 (IL-6), and interleukin-18 (IL-18) for 48 or 72 hours. The effects on CYP1A2, CYP2B6, and CYP3A4 mRNA and catalytic activity were measured. Cryopreserved pooled hepatocytes were also exposed to IL-6 or IL-18 for 48 hours, and the effects on CYP1A2, CYP2B6, and CYP3A4 mRNA levels were measured. The exposure of HepaRG cells to IL-6 and LPS resulted in suppression of CYP1A2, CYP2B6, and CYP3A4 mRNA levels as well as their catalytic activities. However, no suppression of P450 activities or mRNA levels was observed after exposure to IL-18. Similar results on CYP1A2, CYP2B6, and CYP3A4 mRNA levels were observed with primary hepatocytes. The present study indicates that different proinflammatory mediators influence the expression of P450 differentially and that HepaRG cells may be used as an alternative to human hepatocytes for studies on cytokine-mediated suppression of drug-metabolizing enzymes.

出典：Rubin K *et al.* (2015) *Drug Metab Dispos.* 43, 119-125 （一部改変）

注）proinflammatory cytokines：炎症性サイトカイン、bacterial lipopolysaccharide：細菌性リポ多糖

問題 2　次の英文を全文和訳せよ

Despite preventive education, the combined consumption of alcohol and caffeine (particularly from "energy drinks") continues to rise. Physiologic perturbations by separate intake of ethanol and caffeine have been widely documented. However, the biologic actions of the alcohol-caffeine combination and their underlying subcellular mechanisms have been scarcely studied. Using intravital microscopy on a closed-cranial window and isolated, pressurized vessels, we investigated the in vivo and in vitro action of ethanol-caffeine mixtures on cerebral arteries from rats and mice, widely recognized models to address cerebrovascular pathophysiology and pharmacology. Caffeine at concentrations found in human circulation after ingestion of one to two cups of coffee (10 μM) antagonized the endothelium independent constriction of cerebral arteries evoked by ethanol concentrations found in blood during moderate-heavy alcohol intoxication (40–70 mM). Caffeine antagonism against alcohol was similar whether evaluated in vivo or in vitro, suggesting independence of systemic factors and drug metabolism, but required a functional endothelium. Moreover, caffeine protection against alcohol increased nitric oxide (NO•) levels over those found in the presence of ethanol alone, disappeared upon blocking NO• synthase, and could not be detected in pressurized cerebral arteries from endothelial nitric-oxide synthase knockout ($eNOS^{-/-}$) mice. Finally, incubation of de-endothelialized cerebral arteries with the NO• donor sodium nitroprusside (10 μM) fully restored the protective effect of caffeine.

出典：Chang J *et al.* (2016) *J Pharmacol Exp Ther.* 356, 106–115

注）intravital: 生体内の、closed-cranial window: 閉鎖頭窓法（実験動物の頭蓋をガラスで置換する実験手法）、NO•：NO ラジカル

問題 3　次の英文を全文和訳せよ

Olaparib is an oral inhibitor of poly (ADP-ribose) polymerase (PARP) proteins that play a key role in DNA repair and genomic stability. Olaparib is indicated for use in treating certain patients with advanced, recurrent ovarian cancer who have mutations of the breast cancer 1 gene (*BRCA1*) or breast cancer 2 gene (*BRCA2*). In patients with *BRCA*-mutated cancers, olaparib blocks vital PARP-mediated tumor cell DNA repair mechanisms, leading to "synthetic lethality" and selective tumor cell death. In Phase II clinical trials including patients with platinum-sensitive, platinum-resistant, and platinum-refractory ovarian cancers, olaparib significantly improved progression-free survival, with similar rates of response reported in patients with *BRCA1*- and *BRCA2*-mutated disease. Olaparib is generally well tolerated; the most commonly reported adverse events in clinical trials were mild nausea, fatigue, vomiting, and diarrhea. Severe anemia and severe fatigue can occur in association with olaparib treatment. Concurrent administration of olaparib and strong or moderate inducers or inhibitors of cytochrome P-450 isozyme 3A should be avoided, as use of those agents may alter plasma concentrations of olaparib. In conclusion, Olaparib is a novel PARP inhibitor that is efficacious and well tolerated in patients with *BRCA*-mutated advanced ovarian cancers.

出典: Munroe M, Kolesar J. (2016) *Am J Health Syst Pharm.* 73, 1037-1041
(一部改変)

注）olaparib：オラパリブ、synthetic lethality：合成致死性（遺伝子変異により不活性化した遺伝子とパートナーの関係で機能を補助する遺伝子が存在する場合があり、このパートナーの遺伝子を阻害すると細胞が致死する現象)、platinum：プラチナ製剤、progression-free survival：無増悪生存率、nausea：吐き気、fatigue：疲労、vomiting：嘔吐、diarrhea：下痢、anemia：貧血

問題 4　次の英文を全文和訳せよ

Purpose of this study is to develop a stable micellar formulation of vitamin K for oral delivery, because the commercial and clinically used formulation of vitamin K destabilizes at gastric pH resulting in low bioavailability of this vitamin in neonates with cholestasis. Mixed micelles composed of EPC, DSPE-PEG 2000 and glycocholic acid, with and without vitamin K, were prepared by a film hydration method. The influence of pH on the stability of the micelles was analyzed by dynamic light scattering (DLS). The critical micelle concentration (CMC) was determined by fluorescence spectroscopy using pyrene and the morphology was evaluated by transmission electron microscopy. Caco-2 cells were used to study the cytocompatibilty. Mixed micelles with mean diameters from 7.1 to 11.0 nm and a narrow size distribution were obtained. Commercial product formed aggregated particles at gastric pH, which was avoided through steric stabilization by introducing PEG. Transmission electron microscopy showed that mixed micelles had a spherical size (diameter of around 10 nm) with a narrow size distribution in agreement with the DLS results. The loading capacities for vitamin K of mixed micelles with varying molar fractions of DSPE-PEG and EPC (from 0/100 to 50/50 (mol/mol)) were 10.8–5.0 w%. The mixed micelles showed good cytocompatibility at concentrations of glycocholic acid between 0.12 and 1.20 mM.

出典: Feilong S *et al.* (2016) *Pharm Res.* 33, 2168-2179　(一部改変)

注) cholestasis : 胆汁うっ滞、film hydration method : フィルム水和法、dynamic light scattering : 動的光散乱、cytocompatibilty : 細胞適合性

Abbreviations
EPC; Egg phosphatidylcholine, DSPE-PEG 2000; 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N- [methoxy(polyethyleneglycol)-2000],
PEG; polyethyleneglycol

問題5　次の英文を全文和訳せよ

Cellular senescence, a stress-induced irreversible growth arrest often characterized by expression of $p16^{Ink4a}$ (encoded by the *Ink4a/Arf* locus, also known as *Cdkn2a*) and a distinctive secretory phenotype, prevents the proliferation of preneoplastic cells and has beneficial roles in tissue remodelling during embryogenesis and wound healing. Senescent cells accumulate in various tissues and organs over time, and have been speculated to have a role in ageing. To explore the physiological relevance and consequences of naturally occurring senescent cells, here we use a previously established transgene, *INK-ATTAC*, to induce apoptosis in $p16^{Ink4a}$-expressing cells of wild-type mice by injection of AP20187 twice a week starting at one year of age. We show that compared to vehicle alone, AP20187 treatment extended median lifespan in both male and female mice of two distinct genetic backgrounds. The clearance of $p16^{Ink4a}$-positive cells delayed tumorigenesis and attenuated age-related deterioration of several organs without apparent side effects, including kidney, heart and fat, where clearance preserved the functionality of glomeruli, cardio-protective K_{ATP} channels and adipocytes, respectively. Thus, $p16^{Ink4a}$-positive cells that accumulate during adulthood negatively influence lifespan and promote age-dependent changes in several organs, and their therapeutic removal may be an attractive approach to extend healthy lifespan.

出典: Baker DJ *et al.* (2016) *Nature* 530, 184–189

注）senescence：老化、secretory phenotype：分泌表現形（老化細胞において炎症性サイトカインなどの炎症関連遺伝子の発現が亢進する現象）、transgene：トランスジーン（導入遺伝子）、 *INK-ATTAC*：$p16^{Ink4a}$陽性細胞選択的にアポトーシスを誘導するように設計されたFK506結合蛋白-caspase 8融合蛋白遺伝子、AP20187： ATTAC蛋白を2量体化させてアポトーシスを誘導する薬剤、K_{ATP} channels：ATP感受性K^+チャネル