平成３１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）第２次募集
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．答案紙には、「**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

Prior to the clinical phases of testing, safety, efficacy and pharmacokinetic profiles of lead compounds are evaluated in animal studies. These tests are primarily performed in rodents, such as mouse and rats. In order to reduce the number of animal experiments, computational models that predict the outcome of these studies and thus aid in prioritization of preclinical candidates are heavily needed. However, although computational models for human off-target interactions with decent quality are available, they cannot easily be transferred to rodents due to lack of respective data. In this study, we assess the transferability of human P-glycoprotein (P-gp) activity data for development of in silico models to predict in vivo effects in rats and mouse using a structure-based approach. P-gp is an ATP-dependent efflux transporter that transports xenobiotic compounds such as toxins and drugs out of cells and has a broad substrate and inhibitor specificity. Being mostly expressed at barriers, it influences the bioavailability of drugs and thus contributes also to toxicity. Comparison of the binding site interaction profiles of human, rat and mouse P-gp derived from docking studies with a set of common inhibitors suggests that the inhibitors share potentially similar binding modes. These findings encourage the use of in vitro human P-gp data for predicting in vivo effects in rodents and thus contributes to the 3Rs (Replace, Reduce and Refine) of animal experiments.

出典: Jain S *et al.* (2018) *Eur J Pharm Sci.* 122, 134-143.
（一部改変）

注）rodents：齧歯類、P-glycoprotein (P-gp)：P 糖蛋白質、in silico：コンピューターによる、xenobiotic：生体異物の

問題 2　次の英文を全文和訳せよ

The clinical availability of small molecule inhibitors specifically targeting mutated BRAF marked a significant breakthrough in melanoma therapy. Despite a dramatic anti-tumor activity and improved patient survival, rapidly emerging resistance, however, greatly limits the clinical benefit. The majority of the already described resistance mechanisms involve a reactivation of the MAPK signaling pathway. The p90 ribosomal S6 kinase (RSK), a downstream effector of the MAPK signaling cascade, has been reported to enhance survival of melanoma cells in response to chemotherapy. Here, we can show that RSK activity is significantly increased in human melanoma cells with acquired resistance to the BRAFV600E/K inhibitor vemurafenib. Interestingly, inhibition of RSK signaling markedly impairs the viability of vemurafenib resistant melanoma cells and is effective both in two-dimensional and in three-dimensional culture systems, especially in a chronic, long-term application. The effect of RSK inhibition can be partly replicated by downregulation of the well-known RSK target, Y-box binding protein 1 (YB-1). Intriguingly, RSK inhibition also retains its efficacy in melanoma cells with combined resistance to vemurafenib and the MEK inhibitor trametinib. These data suggest that active RSK signaling might be an attractive novel therapeutic target in melanoma with acquired resistance to MAPK pathway inhibitors.

出典：Kosnopfel C *et al.* (2017) *Oncotarget* 8, 35761-35775
（一部改変）

注) BRAF（※キナーゼの一種）、melanoma：メラノーマ（※悪性黒色腫という種類のがん）、MAPK：MAP キナーゼ、p90 ribosomal S6 kinase：p90 リボソーム S6 キナーゼ、signaling cascade：シグナル伝達カスケード、BRAFV600E/K: BARFV600E/K 変異体（※活性型 BRAF 変異体）、vemurafenib：ベムラフェニブ、　Y-box binding protein 1：Y-box 結合タンパク質 1、MEK（※キナーゼの一種）、trametinib：トラメチニブ

問題 3　次の英文を全文和訳せよ

Mammalian tissues are fueled by circulating nutrients, including glucose, amino acids, and various intermediary metabolites. Under aerobic conditions, glucose is generally assumed to be burned fully by tissues via the tricarboxylic acid cycle (TCA cycle) to carbon dioxide. Alternatively, glucose can be catabolized anaerobically via glycolysis to lactate, which is itself also a potential nutrient for tissues and tumours. The quantitative relevance of circulating lactate or other metabolic intermediates as fuels remains unclear. Here we systematically examine the fluxes of circulating metabolites in mice and find that lactate can be a primary source of carbon for the TCA cycle and thus of energy. Intravenous infusions of ^{13}C-labelled nutrients reveal that, on a molar basis, the circulatory turnover flux of lactate is the highest of all metabolites and exceeds that of glucose by 1.1-fold in fed mice and 2.5-fold in fasting mice; lactate is made primarily from glucose but also from other sources. In both fed and fasted mice, ^{13}C-lactate extensively labels TCA cycle intermediates in all tissues. Quantitative analysis reveals that during the fasted state, the contribution of glucose to tissue TCA metabolism is primarily indirect (via circulating lactate) in all tissues except the brain. Thus, glycolysis and the TCA cycle are uncoupled at the level of lactate, which is a primary circulating TCA substrate in most tissues and tumours.

出典: Hui S, *et al.* (2017) *Nature* 551, 115-118（一部改変）

問題 4　次の英文を全文和訳せよ

Loss-of-function mutations in dual oxidase (DUOX) 2 are the most common genetic variants found in congenital hypothyroidism (CH), and similar mutations have been recently reported in few very-early-onset inflammatory bowel disease (IBD) patients without CH. If DUOX2 variants indeed increase susceptibility for IBD, the enrichment of DUOX2 mutation carriers among CH patients should be reflected in higher risk for developing IBD. Using a database containing health insurance claims data for over 230 million patients in the United States, 42,922 subjects with CH were identified based on strict inclusion criteria using diagnostic codes. For subgroup analysis, CH patients with pharmacy records were stratified as transient or permanent CH based on the absence or presence of levothyroxine treatment, respectively. Patients were matched to an equal-sized, age- and gender-matched non-CH group. Compared to controls, CH patients had a 73% higher overall IBD prevalence. The CH-associated relative risk was higher for indeterminate or ulcerative colitis than Crohn's disease. Patients with transient CH had higher odds for IBD than those with permanent CH. We conclude that patients with CH are at an increased risk of developing IBD. The risk was highest for patients with transient CH, for which partial defects in the DUOX2 system are a particularly common finding.

出典: Grasberger H *et al.* (2018) *Sci Rep.* 8(1), 10158.
（一部改変）

注）variants：変異、congenital hypothyroidism (CH)：先天性甲状腺機能低下症、inflammatory bowel disease (IBD)：炎症性腸疾患、levothyroxine：レボチロキシン、relative risk　：相対リスク、ulcerative colitis　：潰瘍性大腸炎、Crohn's disease：クローン病

問題５　次の英文を全文和訳せよ

Multiple clinical, demographic, and genetic factors affect the pharmacokinetics of tacrolimus in children. It can take weeks to reach the target tacrolimus concentration. The objectives of this study were to determine the pharmacokinetics of tacrolimus immediately after kidney transplantation and to find relevant parameters for dose individualization using a population pharmacokinetic analysis. A total of 722 blood samples were collected from 46 children treated with tacrolimus over the first 6 weeks after renal transplantation. Non-linear mixed-effects modeling (NONMEM®) was used to develop a population pharmacokinetic model and perform a covariate analysis. Simulations were performed to determine the optimal starting dose and to develop dosing guidelines. The data were accurately described by a two-compartment model with allometric scaling for body weight. Mean tacrolimus apparent clearance was 50.5 L/h, with an inter-patient variability of 25%. Higher bodyweight, lower estimated glomerular filtration rate, and higher hematocrit levels resulted in lower total tacrolimus clearance. Cytochrome P450 3A5 expressers and recipients who received a kidney from a deceased donor had a significantly higher tacrolimus clearance. In total, these covariates explained 41% of the variability in clearance. From the significant covariates, the cytochrome P450 3A5 genotype, bodyweight, and donor type were useful to adjust the starting dose to reach the target concentration. Dosing guidelines range from 0.27 to 1.33 mg/kg/day.

出典：Louise M. et al. (2018) *Clin. Pharmacokinet.* 57, 475-489（一部改変）

注）demographic：人口統計学的、allometric scaling：アロメトリック（相対成長）スケーリング