平成 31 年度鹿児島大学医学部医学科

第 2 年次前期学士編入学試験

# 学力試験　II

平成 30 年　6 月 16 日　午前 11 時 30 分～午後 1 時

**注　意　事　項**

1. 試験開始の合図があるまで、この問題を開いてはいけません。

2. この問題は全部で **8** ページあります。
   落丁、乱丁または印刷不鮮明の箇所があれば、手をあげて監督者に知らせなさい。

3. 受験番号は、必ず **5** 枚の解答用紙のそれぞれに記入しなさい。

4. **5** 枚の解答用紙が渡されますが、第 1 問解答用紙には第 1 問について、第 2 問解答用紙には第 2 問について、第 3 問解答用紙には第 3 問について解答しなさい。

5. 解答は、必ず解答用紙の指定された箇所に記入しなさい。記入箇所を誤った解答については、その解答に限り無効とします。

6. 解答用紙は、持ち帰ってはいけません。

7. 英数字は解答欄の 1 マスに複数文字記入してもよい。
   例）

| RNA | ポ | リ | メ |
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| 100 | 名 | が | 参 |
|---|---|---|---|

**第１問.** 次の文章を読み、下記の問題に答えなさい。

Galactosemia is one of the most common metabolic diseases identified by newborn screening (NBS) in the United States. Classic galactosemia (CG) results from profound loss of galactose-1-P uridylyltransferase (GALT), the second enzyme in the highly conserved Leloir Pathway of galactose metabolism (Fig. 1). Affected infants can appear normal at birth but following exposure to high levels of galactose from lactose in breast milk or milk-based formula experience a rapid and devastating decline that can progress in days from vomiting, diarrhea and jaundice to hepatomegaly, failure to thrive, E. coli sepsis and neonatal death. The early detection and rapid restriction of dietary galactose enabled by NBS for galactosemia prevents or resolves the acute and potentially lethal symptoms of CG. However, by school age most patients experience one or more of a constellation of long-term complications that include: speech, cognitive and behavioral difficulties in at least half of all patients; tremor and/or other movement problems in close to 40% of patients; growth delay in many children; low bone mineral density in many children and adults; and primary or premature ovarian insufficiency in >80% of girls and young women. Life-long dietary restriction of galactose remains the only accepted treatment for patients with CG. However, a literature trail extending back more than 30 years documents that this treatment fails to prevent the long-term complications experienced by most patients. The mechanisms underlying acute and long-term outcomes in CG remain unclear, limiting prognosis and hampering efforts at improved intervention.

A number of intriguing hypotheses have been proposed to explain the acute and long-term pathophysiology of classic galactosemia. Many have focused on Gal-1P, a substrate of GALT that accumulates to high levels in the red blood cells (RBCs) and tissues of affected infants, especially following milk exposure. However, repeated studies asking whether either acute neonatal or chronic childhood RBC Gal-1P levels are associated with more severe long-term outcomes among patients have failed to demonstrate a correlation.

Studies from yeast, mice, and flies have also directly or indirectly addressed the role of Gal-1P as a candidate mediator of outcomes in GALT deficiency, and with the exception of yeast, have failed to demonstrate a causal relationship. In yeast, loss of galactokinase (GALK) relieves the galactose-dependent growth restriction otherwise seen for GALT-null cells cultured in non-fermentable media. However, a GALT-null mouse model created in the 1990s by Leslie and colleagues failed to demonstrate any relevant acute or long-term outcomes despite accumulation of high Gal-1P levels following exposure to galactose. A new GALT-null mouse, reported in 2014 by Lai and colleagues, demonstrated only subtle defects despite exposure to extraordinarily high levels of dietary galactose.

Galactose, galactitol, and galactonate also accumulate in patients with CG and have been proposed as candidate mediators of disease. However, until recently these other metabolites were generally discounted because they also accumulate in patients with GALK deficiency, an extremely rare condition in many populations that was long considered benign except for galactose-dependent cataracts. In 2011, that assumption was upended, however, by a report describing the outcomes of 18 patients with GALK deficiency identified by NBS in Germany. Of the 16 patients in this cohort evaluated for cognitive function, 31% were found to be intellectually disabled. Of note, these patients experienced accumulation of galactose and other metabolites such as galactitol but did not accumulate Gal-1P. Whether the negative cognitive outcomes in these patients reflected only their GALK-deficiency could not be conclusively proved, but they did associate with continued dietary galactose exposure and did not associate with known consanguinity in the families.

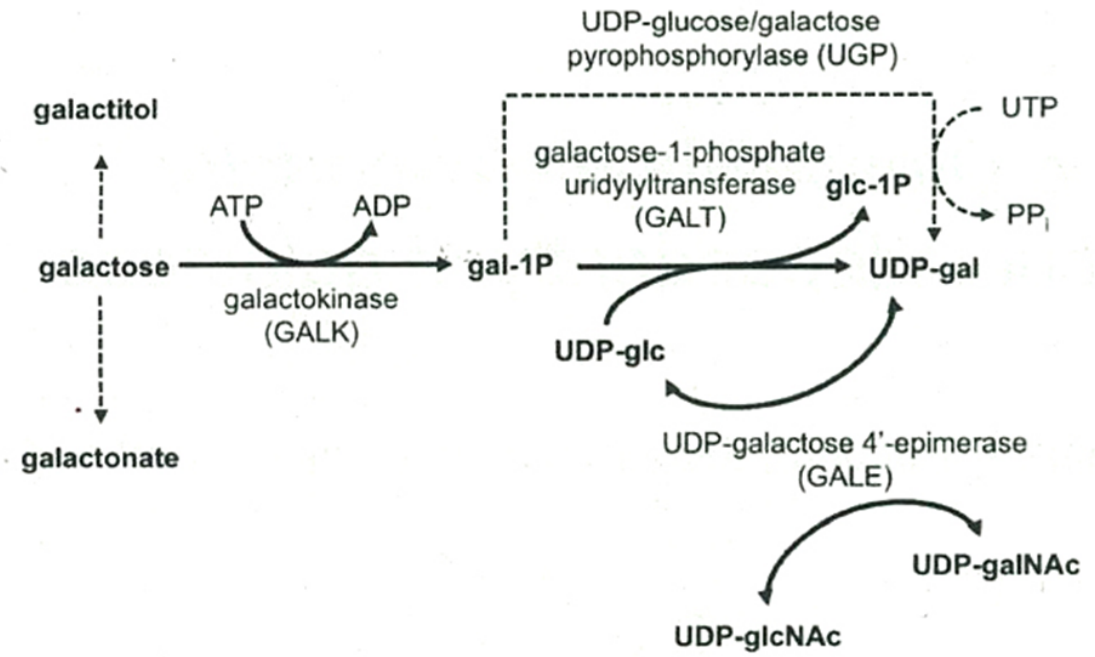


**Fig. 1. The Leloir pathway of galactose metabolism.** In organisms ranging from bacteria to humans, galactose is metabolized by the sequential action of three enzymes: galactokinase (GALK), galactose-1-phosphate uridylyltransferase (GALT) and UDP-galactose 4′-epimerase (GALE). The dashed line indicates the UDP-glucose/galactose pyrophosphorylase-dependent bypass pathway around missing GALT.

（出典”Acute and long-term outcomes in a Drosophila melanogaster model of classic galactosemia occur independently of galactose1-phosphate accumulation.” *Disease Models & Mechanisms* ; 9, 1375-1382, 2016 より抜粋、一部改変）

単語ノート

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|---|---|
| diarrhea | 下痢 |
| hepatomegaly | 肝腫大 |
| complication | 合併症 |
| ovarian | 卵巣の |
| prognosis | 予後、治療後の経過予想 |
| pathophysiology | 病態生理学 |
| substrate | 基質 |
| mediator | 仲介者 |
| Galactosemia | ガラクトース血症 |
| jaundice | 黄疸 |
| sepsis | 敗血症 |
| cataract | 白内障 |
| tremor | 振戦（手の震え） |
| cohort | 集団 |
| galactonate | ガラクトン酸（ガラクトースの代謝物の一つ） |

問題 1．下線で示した“this treatment”の最近明らかになった問題点を、“this treatment”の内容が分かるように説明しなさい。（120 字以内）

問題２．ガラクトース血症において、Gal-1P（ガラクトース 1 リン酸）が、病態発症に関与していると長く考えられてきた。そのことを支持する理由を 2 つ、支持しない理由を 3 つ、本文の内容に即して、説明しなさい。（それぞれ、50 字以内）

**第２問.** 次の文章を読み、下記の問題に答えなさい。

Tailoring treatment to the individual patient has revolutionized cancer therapy, but personalized medicine has yet to make much headway in the treatment of cardiovascular disease. With emerging insight into disease mechanisms and new treatment options, the time is now ripe for the cardiovascular field to adopt a more personalized approach to therapy.

Research on cardiovascular genetics has had some spectacular successes in uncovering new therapeutic targets—for example, the finding that people with inactivating mutations in the gene encoding the trafficking protein PCSK9 are at a much lower risk for heart attacks led to the development of antibody therapy targeting this protein. However, when it comes to personalizing treatment for cardiovascular disease on the basis of an individual patient's genetic makeup or biomarker data, there are currently only a handful of options where such an approach has proven to be clinically useful.

Prominent examples of cardiovascular drugs for which patient response is affected by gene polymorphisms include warfarin and clopidogrel, used to prevent blood clotting. For warfarin, the correct dose for a patient is determined in part from assessment of polymorphisms in the genes encoding the molecular target of the drug, VKORC1, and an enzyme that inactivates the drug, CYP2C9. In the case of clopidogrel, a variant in the gene encoding an enzyme needed for its bioactivation, CYP2C19, influences the drug's efficacy. Genetic variation also affects the response to drugs used to modify lipid levels and thereby reduce atherosclerosis and the risk of myocardial infarction. For instance, a genetic polymorphism affecting the transporter SLCO1B1 is a risk factor for myopathy, a serious side effect of statins. Another example is the drug dalcetrapib, designed to raise the level of high-density lipoproteins through inhibition of cholesteryl ester transfer protein (CETP). Although dalcetrapib and other CETP inhibitors have had a disappointing track record in clinical trials, retrospective analysis indicates that dalcetrapib may be more beneficial in individuals with a specific polymorphism in the gene encoding adenylate cyclase 9, and a clinical trial is underway to test this hypothesis more stringently.

As a blood-based biomarker, the level of C-reactive protein (CRP), which reflects an individual's inflammatory status, is emerging as an important parameter for predicting the efficacy of treatments used to prevent myocardial infarction. Statins were originally designed to lower the level of low-density lipoproteins,

but they also have anti-inflammatory effects, which may explain part of their benefit. In support of this idea, statins have shown efficacy in patients with a normal level of low-density lipoprotein but a high level of CRP. Taking this concept one step further, a recent clinical trial with an antibody blocking the inflammatory cytokine IL-1β showed that a more targeted anti-inflammatory agent can prevent cardiac events in individuals with high blood CRP levels. The efficacy of the antibody, canakinumab, correlated with its ability to reduce blood CRP levels, suggesting that only patients with high CRP levels are likely to benefit from this treatment.

The success of canakinumab might also open the door to a different type of strategy for patient stratification based on a recently discovered connection between inflammation and blood cell aging. As people age, mutations occur in hematopoietic stem cells, leading to the accumulation of mutant blood cells. This condition, called clonal hematopoiesis, is a risk factor for both leukemia and heart disease. Recent research indicates that the increase in cardiovascular risk may be due to elevated inflammatory activity of the mutant blood cells, including increased production of IL-1β. Indeed, heightened inflammation arising from clonal hematopoiesis may in part explain why age is such a strong risk factor for heart disease. According to this line of thinking, patients with high levels of clonal hematopoiesis—as detected by mutational profiling of blood cells—may be more likely to benefit from treatment with anti-inflammatory agents.

Another emerging area of research with the potential to lead to personalized treatment is the influence of the gut microbiome on the cardiovascular system. For example, specific types of bacteria in the gut use particular dietary constituents to generate compounds that can promote atherosclerosis or thrombosis. Profiling an individual's microbiome could conceivably guide treatment choice, particularly if microbiome-targeted treatments can be developed.

The development of new blood biomarkers—beyond lipoprotein and CRP levels—may also shake up the status quo and uncover new avenues for personalizing therapy. Notably, recent evidence suggests that high levels of ceramides—a type of lipid—in blood may be associated with an increased risk for cardiac events. This finding could spur efforts to test whether treatments designed to lower ceramide levels would benefit such individuals.

Drug development for cardiovascular disease is extremely challenging—clinical trials typically require large numbers of patients followed over long periods of time, and the tolerance for adverse side effects is very low. These obstacles have slowed down the pace of new drug development, as other areas of biomedicine have seemed more tractable. However, the recent emergence of new insights into how cardiovascular disease develops and the identification of new therapeutic targets may help to reinvigorate the field, providing a wider variety of treatment options that can be tailored to the individual patient.

（出典："Taking personalized medicine to heart" *Nature Medicine* **24**: 113, 2018）

単語ノート

| | |
|---|---|
| cardiovascular disease | 心血管系疾患 |
| therapeutic | 治療の |
| polymorphism | 多型 |

| | |
|---|---|
| warfarin | ワーファリン |
| clopidogrel | クロピドグレル |
| atherosclerosis | 粥状硬化症 |
| myocardial infarction | 心筋梗塞 |
| myopathy | ミオパチー（筋疾患） |
| lipoprotein | リポ蛋白 |
| cholesteryl ester transfer protein | コレステロールエステル転移蛋白質 |
| dalcetrapib | ダルセトラピブ |
| adenylate cyclase | アデニル酸シクラーゼ |
| stringently | 厳格に |
| C-reactive protein | C-反応性蛋白質 |
| statins | スタチン系薬剤 |
| canakinumab | カナキヌマブ |
| stratification | 階層化 |
| hematopoietic stem cell | 造血幹細胞 |
| gut microbiome | 腸内細菌叢 |
| status quo | 現状 |
| reinvigorate | 再び活気づける |

問題 1. Personalized medicine とはどのような概念か？本文の内容に即して 150 字以内で具体的に説明しなさい。

問題 2. Personalized medicine が心血管系疾患の治療にも応用可能であることを支持する具体的な証拠を本文の内容に即して 3 つ挙げ、それぞれ 75 字以内で説明しなさい。

問題 3. 心血管系疾患の薬剤開発で personalized medicine がなされるために必要なことを、本文の内容に即して 100 字以内で説明しなさい。

**第 3 問.** 次の文章を読み、下記の問題に答えなさい。

The enzyme telomerase maintains the length of specialized repetitive structures called telomeres, which are found at the ends of chromosomes. When they become damaged or shortened, telomeres can stop cells from dividing. Most cells in adult humans have very low or undetectable levels of telomerase and relatively short telomeres, and therefore have a limited ability to replicate. However, elevated telomerase levels are seen in various animal and human stem cells that must retain their replicative capacity for self-renewal. Telomerase defects are associated with tissue scarring (fibrosis) in the livers of both mice and humans, but which cells in the liver express telomerase, and whether they act as stem cells, has been unclear. In a paper in Nature, Lin *et al*. characterize this cell population in mice.

First, the authors identified telomerase-expressing cells in the mouse liver and tracked descendent cells. The group genetically engineered mice to contain a modified version of the gene *Tert*, which encodes a subunit of telomerase. When the mice are treated with a drug, this alteration causes cells expressing *Tert* to be indelibly labelled by a fluorescent protein. Once the genetically modified cells are triggered in this way, they and all their descendants produce the fluorescent protein, even if the cells no longer express *Tert* itself.

Lin *et al*. found that 3–5% of hepatocytes, the most prevalent type of cell in the liver, fluoresce in response to drug treatment. The authors confirmed, by quantitation of messenger RNA levels, that these cells express *Tert*. Next, they examined the livers of adult mice one year after drug treatment. The initially labelled cells (dubbed $Tert^{High}$) had given rise to clusters of descendants dispersed throughout the liver's lobes, making up about 30% of the liver's total mass. Adult hepatocytes die and are replaced infrequently, so the increase in labelled cells over long periods indicates that the $Tert^{High}$ hepatocytes contribute to the gradual renewal of the liver under normal conditions.

A key question is whether the $Tert^{High}$ hepatocytes are a stable, self-renewing population. Alternatively, *Tert* could be expressed in certain cells for a period of time, then shut off in those hepatocytes and expressed in others. In support of the former case, when Lin *et al*. triggered fluorescent-protein labelling three times over a ten-week period, they found that the numbers of labelled hepatocytes were comparable to those for a single trigger. Next, they showed that 75% of labelled hepatocytes expressed high levels of *Tert* mRNA when they were examined a month after a single drug treatment, whereas only 18% did so after a year, indicating that, as the population gradually expands, $Tert^{High}$ cells not only self-renew but also give rise to progeny that do not express *Tert* ($Tert^{Low}$). Finally, the researchers demonstrated that $Tert^{High}$ hepatocytes proliferate more than $Tert^{Low}$ cells, whereas $Tert^{Low}$ cells exhibit higher expression of genes relating to metabolism and biosynthesis than do $Tert^{High}$ cells.

Taking these data together, the authors suggest that $Tert^{High}$ hepatocytes behave like stem cells. But before concluding that the $Tert^{High}$ cells are bona fide stem cells for the liver, it will be necessary to determine whether the $Tert^{High}$ population becomes exhausted or remains at similar levels in older mice (because hepatocytes are still renewed in ageing mice), and whether $Tert^{Low}$ cells convert to $Tert^{High}$ over longer periods than those used here (which would indicate that this population is not acting as stem cells). It will also be interesting to determine the processes by which cells transition from $Tert^{High}$ to $Tert^{Low}$, and how this change relates to homeostatic control of liver mass.

Importantly, stem cells typically reside in a special tissue compartment, or niche, that supports their regenerative capacity. Yet the $Tert^{High}$ cells are dispersed throughout the liver. This dispersal of $Tert^{High}$ cells is interesting because hepatocytes reside in different zones in each lobe of the liver, and earlier studies implicated one zone or another as being more relevant to liver regeneration. By contrast, Lin *et al*. provide evidence for a 'distributed model' for hepatocyte renewal. The research indicates that, although the $Tert^{High}$ hepatocytes possess features of stem cells, those features are not of a conventional type.

In the past three years, one regenerative hepatocyte population near the central vein has attracted particular attention. The population responds to venous signals to self-renew during homeostasis, producing progeny that migrate outwards from the central zone. Lin *et al.* found a few $Tert^{High}$ hepatocytes in the central zone in healthy livers, but these cells did not reside close enough to the central vein to respond to its signals. However, when the authors damaged the central-vein zone, $Tert^{High}$ descendants appeared there and responded to venous signals. Moreover, after damage to the liver tissue in another region, around the portal vein, hepatocytes descended from $Tert^{High}$ cells appeared abundantly in the periportal and mid-lobular zones, and the researchers found that ablation of $Tert^{High}$ hepatocytes impaired this regenerative response, leading to liver fibrosis. Taking the above findings together with those of other studies of liver injury, it seems that various types of hepatocyte (as well as cells from the bile duct) can regenerate the mouse liver under a range of damage conditions.

（出典：Kenneth S. Zaret　"The telomerase enzyme and liver renewal", Nature **556**, 181-182 2018 より抜粋、一部改変）

単語ノート

| | |
|---|---|
| telomerase | テロメラーゼ（テロメア伸長酵素） |
| telomere | テロメア（真核生物の染色体末端を保護する構造） |
| replicative | 再生の |
| scarring | 瘢痕形成 |
| fibrosis | 線維化 |
| subunit | サブユニット、小単位 |
| indelible | 消えない |
| hepatocyte | 肝細胞、肝実質細胞 |
| dub | 授ける、新しくつける |
| disperse | 分散させる |
| bona fide | 真実に、本当に |
| niche | ニッチ、適所 |
| venous | 静脈の |
| periportal | 肝小葉の門脈付近 |
| mid-lobular | 肝小葉中間付近 |
| ablation | 除去、切除 |
| bile duct | 胆管 |

問題 1.　Lin らの実験方法を 140 字以内で説明しなさい。

問題 2.　Lin らの実験で得られた結果を 4 つ選び、それぞれ 100 字以内で説明しなさい。