令和８年度春季（第Ⅱ期）　九州大学大学院薬学府
創薬科学専攻　博士後期課程 一般選抜 入学試験問題

2026 Spring Semester
Entrance Examination Questions – Doctoral Program
Department of Medicinal Sciences
Graduate School of Pharmaceutical Sciences, Kyushu University

専門科目 Subject	生理学 Physiology
受験番号 Examinee's Number	K－１

【注意事項】

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４．表紙を除いて問題紙２枚，解答紙２枚をセットにしていますので，試験開始後に必ず確認し，落丁，乱丁，印刷の不鮮明な箇所があったときは，挙手して試験監督に申し出てください。
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生理学（Physiology）

１．以下の文章を読んで設問に答えなさい。

Read the following passage and answer the questions below.

(a) Adaptations of the pathways of energy production and energy utilization to the functional needs of different muscle types can be understood by examining the behavior of two long-eared European mammals, the rabbit and the hare. The rabbits live in burrows from which they venture only a short distance in search of food and adventure; to escape predators they rely on a rapid sprint to safety so that survival depends on their ability to accelerate quickly and run rapidly for short distances. Although excellent sprinters, rabbits are poor distance runners, tiring quickly if they cannot reach their burrow. Many species of hare, on the other hand, have no burrow but range widely in their habitat. These hares are excellent distance runners, relying on their staying power to escape pursuers – indeed the coursing of hares has been known since antiquity.

Early in the 20th century, it became clear to scientists – although this information had long been known to hunters and cooks – that the back and leg muscles of rabbits and hares differ in color; those in the rabbit are pale pink, almost white, whereas the back and leg muscles of the hare are deep red. Similar relationships between muscle color and function are found in other vertebrate species: “①” muscle is generally found where the need is for short bursts of intense activity, and “②” muscle where activity is sustained. In common culinary experience the chicken breast, which powers wings that are used only briefly, is ③ meat, whereas the dark meat of the chicken leg is obtained from muscles that are used for more continuous activity, such as walking around a barnyard. In birds capable of sustained flight, unlike the chicken, the breast muscles are ④, whereas the muscles of a snake, which strikes, and a frog, which hops are ⑤.

（出典（Source）：Physiology of the Heart 5th Edition by Arnold M Katz）

（１）下線(a)にある rabbit と hare それぞれの筋肉について、形態・機能・代謝の違いを説明しなさい。

Describe the differences in morphology, function, and metabolism between the muscles of the rabbit and those of the hare mentioned in the underlined section (a).

（２）①～⑤に入る色を答えなさい。

Identify the colors that should be inserted into blanks ① through ⑤.

（次のページへ続く）(Continue to the next page)

（３）骨格筋の赤身成分の分子実体とその役割について答えなさい。
Describe the molecular basis of the red coloration in skeletal muscle and explain its physiological role.

（４）哺乳類の心筋と骨格筋の類似点・相違点を説明しなさい。
Explain the similarities and differences between mammalian cardiac muscle and skeletal muscle.

（５）ヒトの骨格筋の形態と運動機能、健康寿命との関係について考察しなさい。
Discuss the relationship between the morphology and motor function of human skeletal muscle and healthy life expectancy.

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解答例：

（１）ウサギ：白筋（速筋、Type2a/2b)、嫌気的代謝（Mit 数↓)、毛細血管↓（血液供給量少ない)、疲労早い
野ウサギ：赤筋（遅筋、Type1)、好気的代謝（Mit 数↑）毛細血管↑（血液供給量多い)、疲労遅い

（２）① white, ② red, ③ white, ④ red, ⑤ white

（３）ミオグロビン　ヘム鉄を含み、酸素の貯蔵に寄与する。

（４）類似点：赤筋と似た性質（ミオグロビン、ミトコンドリア多い）を持つ
相違点：白筋を持たない。不随意運動（特殊（ペースメーカー）心筋を有する)。

（５）白筋と赤筋が入り混じった骨格筋を持ち、多様性に富む。短距離ランナーは白筋が発達しているのに対し、長距離ランナーでは赤筋の発達が多い。赤筋を多く持つ人は脂肪燃焼能が高く、転倒しにくい。白筋は加齢に伴い減少するため、運動による白筋の維持が重要と考えられている。

出題意図：

循環系、とりわけ筋組織・細胞の生理に関する基礎知識と理解度を問う。

英文で出題することで、博士後期課程で必要となる英語読解力もあわせて問う。

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2026 Spring Semester
Entrance Examination Questions – Doctoral Program
Department of Medicinal Sciences
Graduate School of Pharmaceutical Sciences, Kyushu University

専門科目 Subject	蛋白質創薬学 Protein Drug Discovery
受験番号 Examinee's Number	K－２

【注意事項】

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創薬科学専攻博士後期課程　一般選抜　入学試験問題
蛋白質創薬学（**Protein Drug Discovery**）

1. What are hot-spot residues? Explain their importance in protein-protein interactions. In addition, indicate up to three characteristics of protein-protein interfaces.

2. Explain the key equations describing the Gibbs free energy in terms of (i) the equilibrium constant and (ii) as a function of energetic terms at constant pressure. Describe a technology to determine the energetic terms of a binding reaction.

3. Explain the differences between “key-and-lock” and “induced fit” binding mechanisms.

4. Explain “protein domain”.

5. Explain the four levels of protein structure.

6. Explain the driving force of protein folding in aqueous solutions.

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蛋白質創薬学（**Protein Drug Discovery**）

PURPOSE

This exam evaluates the knowledge of the applicant about general as well as specific concepts of protein science that are useful for advanced research within the field of protein drug discovery in Pharmaceutical Sciences.

1. What are hot-spot residues? Explain their importance in protein-protein interactions. In addition, indicate up to three characteristics of protein-protein interfaces.

   - The protein-protein interface contains hot spots of binding affinity, which dominate the interaction. If the binding free energy of the complex were distributed evenly among all of the residues at the interface, we would expect to see a small reduction in the binding free energy resulting from mutation to Alanine. In reality, however, the mutation of certain residues to alanine reduces the binding energy substantially, by more than 2 kcal•mol–1, whereas mutating most of the residues at the interface individually to alanine does not cause a significant change in binding free-energy. The residues that have a disproportionate effect on the affinity are termed “hot spots”. As explained immediately above, mutation to Alanine reveals which residues are hot spots.

   Herein we also indicate some of the characteristics of protein-protein interfaces:
   - There are two major classes of protein–protein interactions. In one class of interactions, the surfaces of two folded protein domains make extensive contact with each other. The second class of interactions are mediated by specialized peptide recognition domains. Herein we will focus primarily on the first type.
   - Protein-protein interactions exhibit a wide range of dissociation constants, ranging from micromolar at the weaker end to nanomolar or even picomolar at the higher end.
   - Protein–protein interfaces usually have a small hydrophobic core. There is an increased likelihood of finding aromatic and hydrophobic sidechains at

interfaces. A typical protein–protein interface has a small core of hydrophobic sidechains surrounded by several polar residues.

- A typical protein–protein interface buries at least about 600 Å2 of surface area on each protein. Although this number is generally much greater, it seems that the minimum buried area indicated above indicates the minimum contact leading to stable interaction.

- Water molecules form hydrogen-bonded networks at protein–protein interfaces. A number of ordered water molecules (interfacial waters) help to improve the packing at the protein-protein interface, and increase the specificity of the complex.

- Residues that do not contribute to binding affinity may be important for specificity, suggesting that many protein-protein interfaces may be engineering to increase their affinity by up to several hundred-fold.

- The desolvation of polar groups at interfaces makes a large contribution to the free energy of binding. The favorable interactions at a protein–protein interface may be insufficient to overcome the energetic penalty of desolvating charged and polar groups. Thus, although hydrogen bond and ionic interactions at an interface may appear favorable, the cost of desolvating polar groups can disfavor the formation of protein–protein interfaces.

2. Explain the key equations describing the Gibbs free energy in terms of (i) the equilibrium constant and (ii) as a function of energetic terms at constant pressure. Describe a technology to determine the energetic terms of a binding reaction.

$\Delta G = RT \ln K_D$ and $\Delta G = \Delta H - T\Delta S$

Isothermal titration calorimetry is particularly useful for the analysis of the thermodynamics of binding interactions because it provides a way to obtain the dissociation constant, KD (and free energy), the standard enthalpy and entropy changes upon binding, and the stoichiometry. Titration calorimetry relies on direct measurement of the heat released upon binding of a ligand (for example

a drug) to a receptor (for example a protein). The measurement of heat released is carried out at a constant temperature while adding the ligand to the protein drop by drop. The value of the dissociation constant (K_D) is obtained indirectly, by analyzing the manner in which the amount of heat released during the titration of ligand into the protein changes with ligand concentration. The enthalpy is directly obtained from the calorimetric measurement, since the property detected by the instrument is heat. And the entropy is obtained from the equation that correlates free energy (ΔG or K_D) with enthalpy and entropy. The stoichiometry is obtained from the molar ratio ligand/protein at midpoint saturation.

3. Explain the differences between “key-and-lock” and “induced fit” binding mechanisms.

The biggest difference between the two models explaining the binding mechanism between an enzyme and a substrate (or a protein and a ligand) lies in the "flexibility" of the enzyme (specifically, its active site) prior to binding.

“Lock and Key” Model

This model assumes that the active site of the enzyme already possesses a rigid shape that perfectly matches the substrate. Just as only a specific key (substrate) fits exactly into a specific keyhole (enzyme), this model posits that the three-dimensional structure of the enzyme does not change before or after binding (i.e., it is a rigid body).

"Induced Fit" Model

This model proposes that the enzyme's active site is flexible. As the substrate approaches and binds, it induces a conformational change in the enzyme's three-dimensional structure, allowing it to achieve a perfect fit with the substrate. Just as a glove (enzyme) changes shape to accommodate a hand (substrate) being inserted, this model considers the enzyme's structure to change during the binding process (i.e., it is dynamic).

4. Explain “protein domain”.

   Domains are compact structures that can, in principle, be inserted into different proteins without affecting their internal structure. Each of the component domains of a protein can be grouped with similar domains in other proteins. Protein domains retain the essential character of their chain fold, even though genetic variation and natural selection lead to changes in amino acid sequence.

   There are families of proteins that have very similar three-dimensional architectures, but which differ considerably in their amino acid sequences. This is illustrated by comparing the structures of human myoglobin and hemoglobin to those of very distantly related members of the globin family. The polypeptide chains of all these proteins adopts the globin fold, despite the large differences in their sequence. Only truly critical residues necessary for the activity of the protein are conserved.

5. Explain the four levels of protein structure.

   Primary Structure: The primary structure of a protein is the linear sequence of amino acids.
   Secondary Structure: Secondary structure refers to the localized folding into repeating structures, such as α-helix and β-sheet, both of which are stabilized by hydrogen bonds.
   Tertiary Structure: Tertiary structure is the overall three-dimensional shape of a single polypeptide chain. It is generally the active form of proteins.
   Quaternary Structure: Quaternary structure happens when a protein is composed of two or more chains (subunits) such as in hemoglobin. Not all proteins have a quaternary structure.

6. Explain the driving force of protein folding in aqueous solutions.

   The folding of water-soluble proteins is primarily driven by the hydrophobic

effect. To avoid water, the unfolded polypeptide chain collapses, packing its water-repelling side chains inward to form a compact hydrophobic core. At the same time, secondary structures like alpha-helices and beta-sheets form to establish the protein's specific three-dimensional architecture. This process can occur spontaneously, with the final shape dictated entirely by the protein's amino acid sequence. According to the thermodynamic hypothesis, a protein's functional (native) structure represents a low free-energy state in an aqueous environment, no matter how complex the fold.

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2026 Spring Semester
Entrance Examination Questions – Doctoral Program
Department of Medicinal Sciences
Graduate School of Pharmaceutical Sciences, Kyushu University

専門科目 Subject	細胞生物薬学 Pharmaceutical Cell Biology
受験番号 Examinee's Number	K－３

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細胞生物薬学（**Pharmaceutical Cell Biology**）

1. 薬物代謝に関する下記の事項を説明しなさい。
Explain briefly the following subjects related to drug metabolism.

（１）シトクロム P450 に電子を供給する物質（補酵素）と供給酵素
Substance (= Co-factor) donating electrons to cytochrome P450 and the enzyme involved in this process

（２）薬物の代謝的活性化とその例
Metabolic activation of drugs and its examples

（３）薬物代謝第二相反応に関与する酵素
Enzymes involved in the phase II drug metabolism

（４）2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)によるシトクロム P450 1A1 (CYP1A1)の誘導機構
Induction mechanism of CYP1A1 by TCDD

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細胞生物薬学　（ **Pharmaceutical Cell Biology**　）（解答例）

1. 薬物代謝に関する下記の事項を説明しなさい。
Explain briefly the following subjects related to drug metabolism.

(1) シトクロム P450 に電子を供給する物質（補酵素）と供給酵素
補酵素：NADPH
供給酵素：NADPH-シトクロム P450 還元酵素
この反応では、２電子が供給される。２電子目の供給にはシトクロム b5 が関与する場合もある。

(2) 薬物の代謝的活性化とその例
Metabolic activation of drugs and its example
薬物は一般に代謝されるとその薬理作用を失うことが多いが、代謝によって逆に母化合物よりも薬理作用が強くなったり、毒性が強くなる場合、代謝活性化という。例えば、アセトアミノフェンが N 水酸化されて反応性の高いキノンイミン体となり生体高分子に結合し、肝細胞壊死を引き起こすこと。モルヒネが 6 位でグルクロン酸抱合され、モルヒネよりも遥かに鎮痛作用の強いモルヒネ 6-グルクロニドになること。

(3) 薬物代謝第二相反応に関与する酵素
グルクロン酸抱合　UDP-グルクロン酸転移酵素
硫酸抱合　硫酸転移酵素
グルタチオン抱合　グルタチオン *S* 転移酵素

(4) 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) によるシトクロム P450 1A1 (CYP1A1)の誘導機構
Induction mechanism of CYP1A1 by TCDD
TCDD は、細胞質にある芳香族炭化水素受容体 (AHR)に結合し、HSP90 が外れて核内に移行し、AHR-nuclear translocator (Arnt)とヘテロダイマーを形成するとともに、CYP1A1 の 5'上流域にある xenobiotic responsive element (XRE)と呼ばれる配列に結合して、転写が促進され CYP1A1 mRNA が増える。その結果、CYP1A1 が増える。