令和７年度春季　九州大学大学院薬学府
修士課程　外国人ＡＯ選抜　入学試験問題

2025 Spring Semester
Entrance Examination Questions – Master's Program
AO Selection for International Students
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	W－１～W－２

【注意事項】

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３．解答紙には，必ず氏名及び受験番号を記入してください。
４．表紙を除いて問題紙１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。
５．日本語又は英語で解答してください。

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修士課程　外国人 AO 選抜　入学試験問題
蛋白質創薬学（**Protein Drug Discovery**）

PURPOSE

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

1. Describe van der Waals interactions, ionic (electrostatic) interactions, and hydrogen bonds.

van der Waals interactions: When two neutral atoms (that is, atoms with no net electrical charge) approach each other closely, they attract each other. This attraction is due to an induced dipole effect. This attractive force is called van der Waals attraction. Despite the attraction that brings atoms together, electron repulsion prevents atoms from getting much closer to each other.

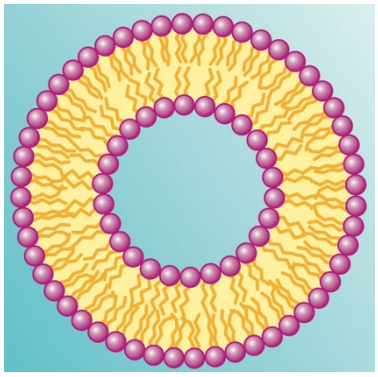
Ionic interactions: When two oppositely charged groups are close to each other, the interaction is called an ion pair or a salt bridge. Two opposite charges attract each other more strongly as they come closer. When the atoms get very close, electronic repulsions appear. The stabilization energy is much greater, and the attractive force makes the optimal distance smaller for an ion pair than for a van der Waals interaction. Water and ions can weaken electrostatic interactions, reducing their strength.

Hydrogen bonds: When a hydrogen is covalently bonded to a more electronegative atom (for example, nitrogen or oxygen), the hydrogen has a partial positive charge. If the hydrogen is close to an electronegative atom (for example, oxygen or nitrogen) then a favorable dipole–dipole interaction can result, which is called the hydrogen bond. The atom bearing the hydrogen is called the hydrogen-bond donor and the atom that interacts closely with the hydrogen is called the hydrogen-bond acceptor. Hydrogen bonds are common in biomolecules, such as DNA or proteins.

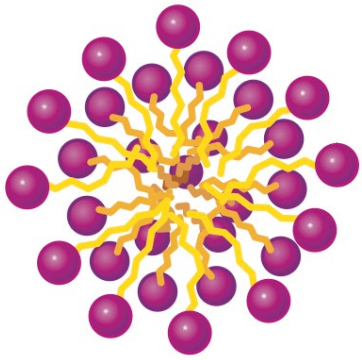
2. Describe the differences between micelles and membranes (bilayers). Draw a scheme of a typical micelle and a typical membrane.

Micelles and bilayers are both structures formed by the self-assembly of amphipathic molecules in an aqueous environment, yet they show significant differences.

- Molecular Arrangement and Shape: Micelles are spherical structures composed of a single layer of amphipathic molecules. Bilayers, in contrast, are composed of two layers of amphipathic molecules arranged in a sheet-like structure, such as in a liposome or a cell membrane.
- Composition: Micelles are generally formed by molecules with a single hydrophobic tail (conical or wedge-like shape lipids). Bilayers are typically formed by phospholipids, which have two hydrophobic tails. The more cylindrical shape of these double-tailed lipids allows them to pack together more efficiently as bilayers.
- Size: Micelles are relatively small, with diameters typically ranging from 3 to 15 nanometers. Bilayers form much larger structures. For instance, the plasma membrane of a cell is a continuous bilayer that can extend over the entire surface of the cell.
- Primary Function: Micelles primarily function in the solubilization and transport of hydrophobic substances. Bilayers are the fundamental structural component of cell membranes.



Bilayer



Micelle

3. Describe the effects of glycosylation in proteins. What is the difference between N- and O- glycosylation?

Glycans on proteins play important roles both inside and outside cells. For example, cell–cell interactions are often mediated through glycan–protein interactions. One way in which glycosylation can improve the efficacy of a protein is to protect it against degradation by protease enzymes. The presence of glycan can also stabilize the folded state of a protein, further protecting against degradation. Glycosylation is also important for the trafficking of proteins inside cells. Cell surface glycans can interact with proteins on other cells, establishing stable connections between cells. Cell-surface glycoproteins can also be recognized by antibodies in the immune system. For example, glycans present on red blood cells defi ne the “blood groups” A, B, AB, and O.

Difference between N- and O- glycosylation: The glycan can be linked to the sidechain amide of an asparagine (Asn) residue, which is referred to as N-linked glycosylation. Alternatively, in O-linked glycosylation, the glycan is linked to the sidechain hydroxyl of a serine (Ser) or threonine (Thr) residue.

4. Briefly explain the four levels of protein structure. What is the driving force for protein folding in water?

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.

The hydrophobic effect (and not hydrogen-bond formation) is the dominant factor that drives the folding of protein molecules in water.

5. Explain the concept of protein domain. What is the relationship between protein structure and conservation of amino-acids during evolution

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.

6. Describe the role of water molecules in drug binding.

Small molecules, whether they are natural ligands or inhibitors, lose a considerable amount of entropy when they bind to proteins, and this serves as a substantial barrier to binding. Nevertheless, the process of binding many protein–ligand interactions have a net favorable entropy change, which is a consequence of the release of water molecules from hydrophobic groups on the ligand or from the protein. Although hydrogen bonding is a very important determinant of specificity in molecular recognition, it often does not contribute substantially to the net free-energy change.

This is because water molecules form strong hydrogen bonds with polar groups on the ligand and the protein, and so the free energy gained upon complex formation represents a balance between the energy of hydrogen bonding in the complex and the hydrogen bonds to water that are broken when the intermolecular interface is formed.

7. What are the main characteristics of protein-protein interfaces?

- Protein–protein interfaces usually have a small hydrophobic core.
- A typical protein–protein interface buries at least about 600 $Å^2$ of surface area on each protein.
- Water molecules form hydrogen-bonded networks at protein–protein interfaces.
- Contains hot spots of binding affinity, which dominate the interaction.
- Residues that do not contribute to binding affinity may be important for specificity.
- The desolvation of polar groups at interfaces makes a large contribution to the free energy of binding.
- Contains many types of interactions.

8. Describe the general process of protein folding for a globular protein.

The folding of water-soluble proteins is driven by the hydrophobic effect. The unfolded polypeptide chain collapses and becomes compact so as to exclude hydrophobic sidechains from water, creating a hydrophobic core. The formation of secondary structural elements (α helices and β sheets) helps give the protein a defined three-dimensional shape. All of this can occur spontaneously, with the final structure determined by the amino acid sequence of the protein (thermodynamic hypothesis). In small globular proteins folding is generally a thermodynamically reversible process. The folding of some proteins involves the formation of transiently stable intermediates. The process of protein folding can be described as funneled movement on a multidimensional free-energy landscape.

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受験番号 Examinee's Number	W－３

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創薬ケミカルバイオロジー（**Medicinal Chemistry & Chemical Biology**）

出題意図：
薬学研究全般に用いられる様々な機器分析に関する測定原理や、それらのケミカルバイオロジー研究の応用についての理解度を問う.

１．　分光分析に関する以下の事項について説明しなさい。説明には、図を用いてもよい。
Explain the following terms in spectrophotometric analyses. You may use figures to explain things if necessary.

（１）紫外可視吸光光度法におけるモル吸光係数
Molar extinction coefficient in UV-visible absorption spectrometry

吸光度 A は以下のように定義される。
$A = \log10(I_0/I) = \varepsilon c\ell$
I_0：入射光、I ： 透過光、 ε ：モル吸光係数、c：物質濃度、ℓ：セルの曹長

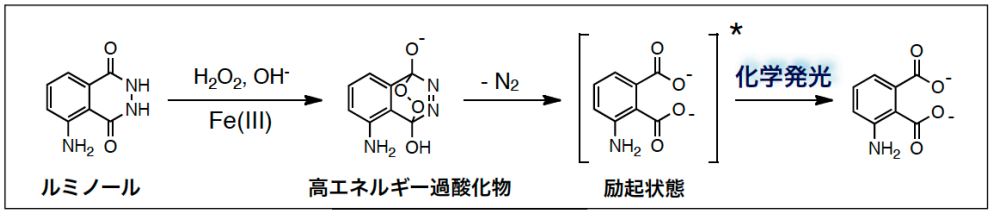
この時、モル吸光係数は、測定対象の物質１mol/l を溶解させた溶液のある波長における吸光度として定義される。

（２）蛍光発光における振動緩和と項間交差
Vibrational relaxation and intersystem crossing in fluorescence emission

光吸収によって基底状態から励起状態に励起された電子は、分子内の他の振動モードに余剰エネルギーを分配したり、溶媒分子に余剰振動エネルギーを奪われて高振動状態からゼロ点振動レベルまで落ちるこれを振動緩和と呼ぶ. 光励起後に励起一重項状態から励起三重項状態の高振動レベルに等エネルギー的に乗り移る現象を項間交差と呼ぶ。

（３）ルミノールの化学発光機構
Mechanism of chemiluminescence of luminol

化学発光の反応機構は以下のとおりである. 鉄イオンを触媒として高エネルギーの過酸化物が生じる。この過酸化物が分解する際に化学発光が生じる。



（４）核磁気共鳴(NMR)におけるラジオ波吸収の機構

Mechanism of radio wave absorption in nuclear magnetic resonance (NMR)

静磁場 Bo 中におかれた原子核のエネルギー順位は核スピン量子数を I として 2I＋１の状態に分裂する。例えば水素原子の場合、I＝1/2 であるため２つのエネルギー状態に分裂する。これをゼーマン分裂と呼ぶ。二つの状態のエネルギー差ΔE と同じエネルギーを有するラジオ波を照射すると吸収が起こり、低エネルギー状態から高エネルギー状態への遷移が誘起される。この現象を核磁気共鳴と呼ぶ。

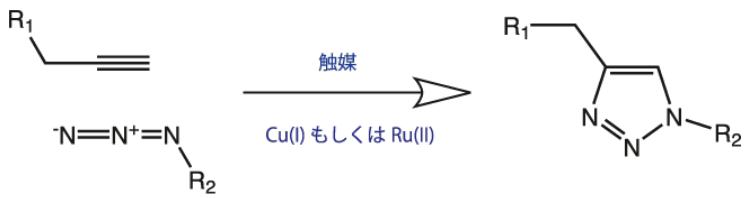
2. クリック反応のタンパク質解析への応用について、以下の問いに答えなさい。

Answer the following questions about the application of click reaction to protein analysis.

（１）クリック反応の例を一つ挙げ、その生体直交性について反応機構を記述して説明せよ。

Give an example of click reaction and explain its bio-orthogonality by describing the reaction mechanism.

最も代表的なクリック反応は、アジドとアルキンの銅触媒による[3 +2]付加環化反応でありトリアゾールを生じる。反応様式は以下のとおりである。本反応は反応性の生体分子が存在してもアジドとアルキンの間で選択的な反応が進む生体直行性を持つ。



（２）クリック反応のタンパク質解析への応用例を一つ挙げて、その有用性を説明せよ。

Give an example of the application of click reaction to protein analysis and explain its usefulness.

細胞中のタンパク質を反応性プローブでラベル化する場合、反応性プローブにアルキンを導入しておく。ラベル化後にアジドを有する蛍光色素とクリック反応させてゲル電気泳動を行う。さらに泳動後にゲル蛍光イメージャーで検出することで、反応性プローブが細胞中のどのタンパク質とどのくらい選択的に反応したかについての情報を容易に得ることができる。