课程大纲
COURSE SYLLABUS

1.	**课程代码/名称** **Course Code/Title**	蛋白质折叠错误与神经退行性疾病 Protein misfolding and neurodegenerative diseases
2.	**课程性质** **Compulsory/Elective**	专业选修课 / Elective
3.	**开课单位** **Offering Dept.**	医学院生化系/ Department of Biochemistry, School of Medicine
4.	**课程学分/学时** **Course Credit/Hours**	3/48
5.	**授课语言** **Teaching Language**	英文 / English
6.	**授课教师** **Instructor(s)**	苏明媛 / Ming-Yuan Su
7.	**开课学期** **Semester**	2022 秋 /2022 Autumn
8.	**是否面向本科生开放** **Open to undergraduates or not**	否 / No
9.	**先修要求** **Pre-requisites**	（如面向本科生开放，请注明区分内容。 If the course is open to undergraduates, please indicate the difference.）

10. 教学目标
Course Objectives

（如面向本科生开放，请注明区分内容。 If the course is open to undergraduates, please indicate the difference.）

This course aims to introduce students the information on protein properties, protein quality control systems, chaperone assisted folding and protein conformational diseases in neuron and beyond. In particular, the students will gain familiarity with principles of protein misfolding; protein misfolding diseases as well as current therapies.

The student can improve their abilities listed below:

- understand the fundamental properties of protein.
- describe protein folding kinetics and aggregate formation.
- understand and describe the biophysical and biochemical techniques to study protein folding and aggregates.
- be able to evaluate and interpret the scientific publications in the field.
- describe fibril structure and biophysical properties and become familiar with the relationship between protein misfolding and neurodegenerative as well as other diseases.
- become able to search, read, critically evaluate and discuss scientific literature related to protein misfolding and human diseases.

11. 教学方法
Teaching Methods

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Lecture, discussion and presentation.

12. 教学内容
Course Contents
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Section 1	**1. Fundamental properties of protein** In this section, we will cover the basic structure and function of proteins, including biochemical properties of amino acids, ribosomes structure and function, translation in eukaryotes and peptide bond formation. I will also teach co-translational and post-translational protein targeting and translocation.
Section 2	**2. Protein folding and three-dimensional structure** This section will introduce non-covalent interactions in proteins, including ionic interactions, hydrogen bonds, Van der Waals forces and hydrophobic interactions. I will introduce the concepts of the entropy and hydrophobic effect in protein folding, the energy landscape and folding funnel. We will discuss different levels of protein structures from primary to quaternary structures.
Section 3	**3. Molecular chaperones and catalysts of protein folding** In this section, we will learn molecular chaperones and catalysts of protein folding including Hsp60 family chaperonins encapsulate proteins in folding cages, Hsp70 chaperones maintain cellular proteostasis, Hsp90 chaperones stabilize proteins and molecular chaperones handle misfolded, intrinsically disordered and amyloidogenic proteins. We will also learn disulfide bond formation proteins, peptidyl-prolyl *cis/trans* isomerases and heat shock response.
Section 4	**4. Protein misfolding and aggregation** In this section, we will talk about protein misfolding caused by dominant-negative mutations, changes in environmental conditions (pH, ionic strength, temperature, and protein concentrations), error in post-translational modifications, increase degradation rate, oxidative stress and error in trafficking etc.
Section 5	**5. Technique in study protein folding and protein aggregation** This section will introduce different technique to study protein folding and protein aggregates, including single molecular biophysics (atomic force microscopy, optical tweezers, pulling forces), fluorescent dyes for protein aggregates detection, as well as the structural approaches and principles of cryoEM or cryoET etc.
Section 6	**6. Protein quality control system- autophagy** The section will introduce cellular mechanism of autophagy, a pathway to dispose misfolded and aggregated protein or damages organelles. We will cover the topics including formation of phagophore, substrate binding and autophagosome formation, current strategies for targeting autophagy for disease treatment. We will also talk about endoplasmic reticulum associated degradation and the unfolded protein response.
Section 7	**7. Protein quality control system-protease and ubiquitin proteasome systems** In this section, we will cover protein machinery that remove unfolded or aggregated proteins including Lon protease, ClpX protease and VCP/p97 protease etc. We will also introduce another important protein

		quality control pathway ubiquitin proteasome systems that aid protein degradation and turnover, and how the ubiquitination tagged protein are degraded by proteasome.
	Section 8	**8. Mid-term exam**
	Section 9	**9. Neuron, synapse and neurotransmission** In this section, we will cover the structure and function of neurons, the synapse and neurotransmission, ions channels.
	Section 10	**10. Alzheimer's disease (AD)** This section will cover neurodegenerative disease related to protein misfolding- Alzheimer's disease. We will talk about the pathogenesis for AD, APP processing and amyloid beta peptide, inflammation and tauopathies etc.
	Section 11	**11. Parkinson's disease (PD)** In this section, we will learn the structural characteristics of human alpha-synuclein, conformational behaviour of wild type and PD-related synucleins, their aggregations and mechanism of cell to cell spread.
	Section 12	**12. Huntington's disease and Prion disease** This section will talk about Huntington's disease and Prion disease, focusing on the structure of huntingtin protein, polyQ repeats and how does it misfold, oligomerize and aggregate. The student will also learn the prion biology and diseases, prion protein and structure, transmission and bovine spongiform encephalopathy etc.
	Section 13	**13. Amyotrophic lateral sclerosis and Frontotemporal degeneration (ALS/FTD)** In this section, we will cover the mutations in the SOD1 gene cause amyotrophic lateral sclerosis, the gain of toxic function by mutant SOD1, mutations in TDP-43 and FUS gene cause ALS/FTD, gain and loss of function of C9orf72 gene mutation in ALS/FTD, G4C2 repeats generate G-quadruplexes, repeated associated non-ATG (RAN) translation generates toxic proteins and RNAs.
	Section 14	**14. Cystic fibrosis, alpha-1 antitrypsin deficiency and cataract as protein-aggregation diseases** This section will introduce three different type of diseases caused by protein aggregation and their mechanism leads to diseases. Cystic fibrosis caused by mutations in the CFTR gene leading to misfolding and other defects, alpha-1 antitrypsin deficiency by point mutation leads to accumulation of misfolded secretory glycoprotein in the endoplasmic reticulum. Cataract caused by aggregation of crystallin protein.
	Section 15	**15. Diagnosis and therapeutic strategies targeting protein aggregates** In this section, the students will learn current and emerging strategies to ameliorate aggregation-associated degenerative disorders, with a focus on disease-modifying strategies that prevent the formation of and/or eliminate protein aggregates, such as antisense oligonucleotides (ASO), antibody mediated protein aggregate clearance, inhibition of Aβ levels by secretase inhibition.
	Section 16	**16. Final presentation** A list of scientific publications related to the topic of the course will be provided in the section 10 of the lectures. Each student will select one to

		present and discuss for 30 mins.

13. 课程考核
Course Assessment

（①考核形式 Form of examination；②.分数构成 grading policy；③如面向本科生开放，请注明区分内容。 If the course is open to undergraduates, please indicate the difference.）

1. 考核形式 Form of examination：本课采取期中考试和期末项目 PPT 展示的方式考核。
The form of examination will be mid-term exam and final presentation.

2. 分数构成 Grading policy
出席率/Attendance: 10%
期中考试/Mid-term exam: 40%
期末報告/Final presentation: 50%

14. 教材及其它参考资料
Textbook and Supplementary Readings

Textbook: Fundamentals of Neurodegeneration and Protein Misfolding Disorders
Author: Martin Beckerman
ISBN: 3-319-22117-5

Textbook: Molecular targets in protein misfolding and neurodegenerative disease
Author: Pierfausto Seneci
ISBN: 9780128001868

Scientific publications for reference:
1. Nature 2017 Jul 13;547(7662):185-190.
2. Nature 2020 Sep;585(7825):464-469.
3. Nature 2022 Mar 28. doi: 10.1038/s41586-022-04650-z.
4. Nature. 2022 Mar 28. doi: 10.1038/s41586-022-04670-9
5. Cell. 2022 Apr 14;185(8):1346-1355.e15.
6. Cell. 2022 Apr 14;185(8):1290-1292.