

BIBB475 SYLLABUS: CELLULAR AND MOLECULAR MECHANISMS OF NEURODEGENERATIVE DISEASE

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Office hours: Tuesday and Thursday
4:00 – 5:00 by appointment

Course Description: This course will familiarize students with advances in our understanding of the clinical features and pathogenesis of a wide range of neurodegenerative diseases and disease processes. Students will analyze original research reports of proposed pathological processes that may represent steps in cell death pathways leading to the neuronal dysfunction and death seen in these diseases. Representative topics will include accumulation of misfolded and aberrant proteins, inflammatory response and release of neurotoxic cytokines, protein, protofibril formation, ubiquitin-proteasome system dysfunction, synaptic failure, excitotoxic insult, oxidative and nitrosative stress, mitochondrial injury and dysfunction, axonal and dendritic transport failure. Significant emphasis will be placed on the fast-expanding field exploring genetic contributions to neurodegenerative disease. Identification of genetic mutations pathogenic for familial neurodegenerative diseases has been a major driving force in neurodegenerative research and pointed researchers towards essential molecular process that may underlie these disorders. Strategies for therapeutic intervention in the management, prevention, and cure of neurodegenerative disease will be addressed.

Course Objectives: Upon completion of this course students will be able to:

- identify the presentation and clinical course of major classifications of neurodegenerative diseases.
- describe the disease-specific neuroanatomical regions of pathological insult
- discuss proposed hypotheses regarding common vs disease-specific pathological processes leading to the variable biochemical and molecular cascades of neuronal death.
- discuss past, current and future strategies for therapeutic intervention in the management, prevention, and cure of neurodegenerative disease.
- identify overarching questions and controversies guiding the direction of current and future research in this field
- acknowledge the challenges facing neuroscientists in elucidation of causative cellular and molecular mechanisms in the progressive events underlying neurodegeneration.
- critically evaluate reports of original research with regard to the rationale, hypothesis, research design, sources of error and variability, and significance of findings.
- share informed opinions about the cellular and molecular mechanisms of neurodegenerative diseases with peers and recognize constructive contributions of all participants in the discourse.
- work effectively with peers as part of a multidisciplinary team

Prerequisites: Successful completion of BIBB 109 or an equivalent is required for this course. The level of presentation of course material assumes that all students have mastered the content in the prerequisite courses. Texts used in these prerequisite courses will be most helpful for review and as additional resources for this course.

Course Format: The class will meet once a week for three hours. In addition to lectures and class discussions of assigned reading, learning activities will include weekly written assignments, small group work sessions, and group presentations.

Required Reading: The class readings are carefully selected from the vast literature available on topics related to the biological basis of psychiatric disorders. Assigned journal articles will be available either in the biomedical library or on-line via Penn Library e-journals. Students are encouraged to explore the scientific literature as they locate specific assigned articles.

Grading: There will be no formal exams in this seminar class. Semester grades will be decided based on performance in the following:

- ¼ **Class participation**
- ¼ **Weekly written assignments**
- ¼ **Group project and presentation**
- ¼ **Final (take-home essay ~10 pages)**

This grading scheme provides the opportunity for students to demonstrate mastery of course content in a variety of modalities including formal and informal oral and written assignments as well as interaction with peers in large and small group discussions, projects, and presentations. **Students who attend class and participate fully in relevant and collaborative ways in class discussions and activities will receive higher grades.** Grading is at the discretion of the faculty. Students may petition to have their grade re-evaluated by submitting a written rationale for the change of grade. The faculty will then have the option to increase, decrease or keep the grade the same.

Participation in Class Discussions: Participation in class discussions is required. Students who prepare for and participate fully in relevant and collaborative ways in class discussions and activities will receive higher grades. Most of the important questions about the pathophysiology and treatment of neuropsychiatric and neurodegenerative disorders do not have answers, thus, uncertainty and speculation will characterize our class discourse. Rigorous preparation of the weekly assignments will provide sufficient background for meaningful contribution to class discussions. If you are having trouble understanding a concept, please raise the issue in class. Chances are your classmates will have similar questions. If you are concerned that you do not understand the concepts, please schedule an appointment during my office hours prior to the class meeting so that you can be prepared to participate in class discussions.

Weekly Written Assignments: The 12 weekly written assignments are designed as extensions of the classroom learning experiences, as guidance for reading the scientific literature in a meaningful and efficient manner, and as preparation for class discussion. Rigorous preparation of these assignments will assure that you will be prepared to make significant contributions to the class discourse. As the neuroscience background varies greatly, the assignments should be used as a guide to pursue the assignment topics at your individual level of understanding. Weekly written assignments and class participation are graded separately.

Guidelines for Written Submissions

- All assignments must be “typed” / “word processed.”

- Documents must be formatted with appropriate styles including title, headings and subheadings.
- In all written and PowerPoint submissions, you must provide complete citations such that the reader has the necessary information to locate your primary sources.
- Documents must be submitted in a Word format that can be read on my Dell computer.
- Use a 12-point font and single space all written submissions.
- Include a running FOOTER on each page with Assignment #, Name, and Page Number in the following format:

475 # Jane Doe page 3/5

Replace the # with the appropriate assignment number.

- Submit electronically to lexowl@psych.upenn.edu with the following identifier in the subject line:

475 # last name first name.

Replace the # with the appropriate assignment number.

- Retain electronic copies of all assignments until final grades have been posted.
- Assignments must be received by midnight prior to class for which it is due.
- Late assignments, hardcopy or handwritten assignments will not be accepted; no exceptions.
- Please note that I will not acknowledge receipt of each and every submission; you must use your communication tools to verify that your submission was received by the intended recipient.

Group Projects: Students will work together to develop a presentation and homework assignment on a topic assigned by the faculty. The group project is an opportunity to demonstrate excellence in several areas: collaboration with peers; utilization of an array of scientific resources to discover the specifics of an unfamiliar topic; ability to organize information in a visual manner for presentation; and finally oral presentation skills.

Final Exam: The final exam will be a 10-page take-home research paper on a topic assigned by faculty. Students who have accumulated a grade of A on all written submissions, class discussions, and group projects will be exempt from the final exam.

Attendance: Regular attendance is essential; absences are discouraged. Contribution to class discussion is of paramount importance in this class. Neuroscience is a rapidly evolving and exciting field and class discussions will frequently cover topics that are hot off the presses. Regular attendance is essential for students to fully assimilate this material. Much of what we do in class cannot be obtained or replicated outside of class. Each student is expected to have completed and thought critically about the readings and assignments. You must come to class prepared to contribute to class discussions. Students who attend class regularly will receive higher grades. If circumstances - family or personal health issues, family celebrations or gatherings, deaths in the family, car accidents or dysfunction, work conflicts, or interviews for graduate/medical/vet/dental school - cause you to miss classes, I suggest that you withdraw from the course and resume in a semester when you can devote full participation to the course.

Collaboration: You are encouraged to develop knowledge and ideas from a large variety of resources throughout this course. Most scientists get valuable ideas and feedback from discussion with colleagues and collegial conversation is strongly encouraged on all assignments. In addition to discussions with your classmates, you should also contact authors of your papers and faculty members at this university or others involved in the research we are exploring.

Deadlines: Assignment deadlines are absolutely FIRM; assignments will not be accepted after the deadline. Sports, other academic commitments, work and social/volunteer activities are unacceptable excuses for late work or extension requests.

Backing Up: A computer crash is devastating but not an acceptable excuse for late submissions. Get in the habit of backing up your work regularly. You must retain electronic copies of all submitted work until after you have received your course grade for the semester. I strongly recommend that you have a foolproof back-up method for storing and retrieving your coursework.

MAC-PC Compatibility: All written submissions and group presentations must be accessible/readable on my Dell PC and the classroom computer. If you submit a file that cannot be read on my Dell PC or the classroom computer system and I have to send it back to you for reformatting, it will be considered late and all deadline penalties will apply. It is unacceptable to submit a powerpoint presentation that cannot be read in its entirety on a PC.

Citations: In all written and PowerPoint submissions you must provide complete citations so that the reader has the necessary information to locate your primary sources. Plagiarism is an academic violation with severe consequences. Please do not take risks with citation issues; consult faculty if you are uncertain when citations are necessary. The assigned scientific papers provide excellent examples of proper citation form. Select one form and use it consistently throughout the semester. In addition, the university provides tutorial services in writing research papers and you are encouraged to avail yourself of these resources if you are not comfortable with your skills in this area.

IMPORTANT NOTE: I will communicate with the class through Blackboard email. Communications may include changes or cancellations in class, office hours, meeting rooms or times, and/ or assignments. Please go into your personal profile in Blackboard and confirm that the email address listed is the email you will be reading on a daily basis. The class topics and reading assignments are subject to change with a weeks notice. These changes will be announced in class, posted on BB and confirmed by email.

LECTURE TOPICS AND RELATED READING

PART I MAJOR DISEASE CLASSIFICATIONS

Class #1

Lecture: Introduction, Overview, Historical Perspective

Reading for class discussion: Bossy-Wetzel, Schwarzenbacher, Lipton (2004) Molecular pathways to neurodegeneration. *Nature Medicine* S2-S9.

Class #2

Lecture: β -amyloid Hypothesis and Tauopathies

Reading for class discussion:

- Group 1: Wirths, Multhaup, Bayer (2004) A modified beta-amyloid hypothesis: intraneuronal accumulation of the beta amyloid peptide--the first step of a fatal cascade, *Journal of Neurochemistry* 91(3):513-520.
- Group 2: Lee, Goedert, Trojanowski (2001) Neurodegenerative tauopathies. *Annual Review Neuroscience* 24:1121-1159.

Class #3

Lecture: α -Synucleinopathies and Polyglutamine Repeat Diseases

Reading for discussion:

- Group 1: Gunawardena and Goldstein (2005) Polyglutamine diseases and transport problems: deadly traffic jams on neuronal highways. *Archives of Neurology* 62(1):46-51.
- Group 2: Everett and Wood (2004) Trinucleotide repeats and neurodegenerative disease. *Brain* 127(Pt 11):2385-2405.
- Group 3: Morfine, Pigino, and Bradley (2005) Polyglutamine expansion diseases: failing to deliver. *Trends in Molecular Medicine* 11(2):64-70.

Class #4

Lecture: Amyotrophic Lateral Sclerosis and Superoxide Dismutase; Creutzfeldt-Jakob and Prion Protein Diseases.

Reading for class discussion: Lindberg, Bystrom, Boknas, Anderson and Oliveberg (2005) Systematically perturbed folding patterns of amyotrophic lateral sclerosis (ALS)-associated SOD-1 mutants. *PNAS* 102(28):9745-9750.

PART II PROPOSED PATHOGENIC PROCESSES

Class #5

Lecture: Genetic Contributions to Neurodegenerative Disease

Reading for class discussion: Spire and Hannon (2005) Nature, nurture, and neurology: gene-environment interactions in neurodegenerative disease. *FEBS J* 272(10):2347-2361.

Class Activity: Cell Death Pathways

Class #6

Lecture: Axonal Transport Defects. Misfolding and Aggregation of Disease Proteins

Reading for class discussion: Roy, Zhang, M.-Y Lee, Trojanowski (2005) Axonal transport defects: a common theme in neurodegenerative diseases. *Acta Neuropathol* 109:5-13.

Class #7

Lecture: Oxidative Alterations. Mitochondrial Dysfunction

Reading for class discussion: Facheris, Beretta, and Ferrarese (2004) Peripheral markers of oxidative stress and excitotoxicity in neurodegenerative disorders: tools for diagnosis and therapy? *J Alzheimers Dis* 6(2):177-184.

PART III THERAPEUTIC APPROACHES – PAST, PRESENT, AND FUTURE

Class #8

Lecture: Current FDA-Approved Therapies; Future Strategies: The Ongoing Vaccine Story.

Reading for class discussion:

- Group 1: Forman, Trojanowski, M.-Y Lee (2004) Neurodegenerative diseases: A decade of discoveries pave the way for therapeutic breakthroughs. *Nature Medicine* 10:1055.
- Group 2: Bjarkam and Sorensen (2004) Therapeutic strategies for neurodegenerative disorders: emerging clues from Parkinson's disease. *Biological Psychiatry* 56(4):213-216.
- Group 3: RNA Interference Therapy. Harper, Staver, He, Eliason et al (2005) RNA interference improves motor and neuropathological abnormalities in HD mouse model. *PNAS* 102(16):5820-5825.

Classes #9, 10, 11, 12 Group Led Discussions

Lecture: Future Strategies – Stem Cells and Gene Therapy

Reading for class discussion:

- Group 1: Ruszynski, Thai, Pay, Salmon, Sang, Bakay, et al (2005) A Phase I clinical trial of nerve growth factor gene therapy for Alzheimer's disease. *Nature Medicine* 11(5): 551-556.
- Group 2: Lindvall, Kokaia, Martinez-Serrano (2004) Stem cell therapy for human neurodegenerative disorders-how to make it work. *Nature Medicine Suppl*:S42-50.
- Group 3: Mohapel and Brudin (2004) Harnessing endogenous stem cells to treat neurodegenerative disorders of the basal ganglia. *Parkinsonism Related Disorders* 10(5):259-264.
- Group 4: Mendez, Sanchez-Pernaute, Cooper, Vinuela, Ferrari, Bjorklund, Dagher, Isacson (2005) Cell type analysis of functional fetal dopamine cell suspension transplants in the striatum and substantia nigra of patients with Parkinson's Disease. *Brain* 128:1498-1510.

PART IV FUTURE DIRECTIONS AND CHALLENGES

Classes #12 & 13 Guest lectures, TBA

Lecture: Future Directions and Challenges; Questions and Controversies