

BIBB475: Syllabus

Cellular and Molecular Mechanisms of Neurodegenerative Disease

Faculty: Nedra Lexow, Ph.D.
Email: nedralexow@comcast.net
Office telephone number: 610 212 2664
Office hours: Monday and Wednesday 3:00 – 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, including Alzheimer's disease and other dementias, prion diseases, Parkinson's disease and atypical parkinsonisms, neurodegenerative ataxias, motor neuron diseases, degenerative diseases with chorea, iron and copper disorders, and mitochondrial diseases. Students will analyze original research reports on a range of proposed pathological cellular processes that may represent steps in cell death pathways leading to neuron loss seen in these diseases. Representative topics will include accumulation of aberrant proteins, inflammatory response and release of neurotoxic cytokines, protein misfolding, 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, as 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.

Prerequisites:

Successful completion of an introductory neuroscience course.

Texts:

Selected chapters from:

The Neuropathology of Dementia

Edited by Margaret Esiri, Virginia M.-Y Lee, and John Q. Trojanowski

July 2004

Neurodegenerative Diseases

Edited by Beal, Lang and Ludolph

June 2005

Molecular Mechanisms of Neurodegenerative Disorders

Edited By Marie Francois Chesselet

Neurodegeneration 2004, Nature Medicine supplement to Volume 10. A collaborative supplement of review articles and perspectives published by Nature Medicine and Nature Reviews.

Articles from the scientific literature. See outline below for reading list. All assigned journal articles are available either in the biomedical library or on-line via Penn Library e-journals.

Additional Resource:

<http://www.alzforum.org/>

Course Objectives:

Upon completion of this course students will be able to:

- identify the presentation and clinical course of major classifications of neurodegenerative diseases.
- 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.

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 small group work sessions as well as individual and group presentations.

Evaluation:

Class Participation	20 points
Midterm Paper (5-7 pages)	20 points
Group Presentation	20 points
Final Research paper (10-20 pages)	20 points
Neuroanatomy exam	20 points

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

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: Morfini, 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 #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

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.

Class #9

Lecture: Future Strategies: The Ongoing Vaccine Story.

Reading for class discussion: 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.

Class #10

Lecture: Future Strategies – Stem Cells and Gene Therapy

Reading for class discussion:

- Group 1: Ruzynsk, 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.

Class #11

Lecture: Future Directions and Challenges; Questions and Controversies

Classes #12 and 13 Group Presentations of recent research on pathogenic processes.