Biology 466 (BIOL466): Molecular Genetics of Neurological Disease

Fall 2015

Description: This course will focus on the molecular basis of neurological diseases, exploring in detail key papers that cover topics including defining the disease genes, to development of animal models that provide mechanistic insight, and seminal findings that reveal molecular understanding. Diseases covered will include neurological diseases of great focus today such as Alzheimer's, Fragile-X and autism, dementia, motor neuron degeneration, and microsatellite repeat expansion disorders. The course will provide a perspective from initial molecular determination through to current status. Students will gain an understanding of how the molecular basis of a disease is discovered (from classical genetics to modern genomics), and how such diseases can be modeled in simple genetic systems for mechanistic insight.

Time: TTh 1:30-3:00PM.

Prerequisites: BIOL221 (required); BIOL251 and BIOL421 (recommended).

Class Procedure: The hour and one half class periods will consist of lectures, discussions of one or more seminal research papers with in-class discussion. There will be numerous in-class activity sessions covering the approaches and design of experimentation to molecularly define, understand and model a disease. Preparation prior to the lectures will include reading of material on the topic, or preparation for in-class activities.

Location: Goddard Lab 100

Instructor: Dr. Nancy Bonini (306A Leidy Laboratory, appointments by request); email: nbonini@sas.upenn.edu

Textbook: No official textbook. Materials including papers to read prior to class, lecture notes, and papers discussed in class and activities will be distributed on the Canvas courseware site (https://canvas.upenn.edu), accessible with your PennKey.

Grading: Grade will be based on in-class participation (25%), and three papers stemming from in-class activities (50%), and the final assignment (25%).

Background and Lecture Reading: Reading materials will be made available for each lecture for download on the course website. The reading is comprised of research papers and reviews, which must be read PRIOR to the class session. The class sessions will consist of both overview lectures and working through the research papers figure by figure.

Course Syllabus

Date	Topic
Th, Aug 27	Introduction to the course & medical genetics: Overview of approaches to the genetic basis of neurological disease, including refresher on terminology, techniques and anatomy
Tu, Sept 1	Alzheimer's disease 1: What is Alzheimer's & cloning of the first familial mutation
Th, Sept 3	AD2: Cloning of the second familial Alzheimer's gene and how functional insight came from model organisms
Tu, Sept 8	AD3: The tangles in Alzheimer's tissue & the first mouse model
Th, Sept 10	***AD In-class activity & assignment: an APP protective mutation***
Tu, Sept 15	Huntington's disease 1: The disease and cloning of the gene
Th, Sept 17	HD2: Modelling the phenotype in a mouse & mechanistic insight
Tu, Sept 22	HD3: Reversibility
Th, Sept 24	HD4: Protein Context (assign Ordway paper here, plus activity paper)
Tu, Sept 29	***HD In-class activity & assignment: Knocking down the disease gene***
Th, Oct 1	Fragile X Syndrome 1: Cloning FMR & discovery of the genetic mechanism of disease Papers: Hogan (bkgd); Yu et al., 1991; also do Fu et al., Sherman paradox.
Tu, Oct 6	FXS 2: Mouse and fly models, and their predictions
Tu, Oct 13	FXS 3: 1 gene, multiple diseases—fragile X associated ataxia and tremor (FXTAS)
Th, Oct 15	FXS 4: Reversing neurological disease
Tu, Oct 20	Amyotrophic Lateral Sclerosis 1: SOD1 is mutated & the nature of the mutations
Th, Oct 22	ALS 2: Non-autonomy of the disease—glia kill the neurons
Tu, Oct 27	ALS 3: Entirely new insight from RNA binding proteins—TDP-43
Th, Oct 29	ALS 4: Mutations in TDP-43 & FUS
Tu, Nov 3	ALS5: Discovery of the most common mutation in ALS—c9orf72
Th, Nov 5	***ALS In class activity & assignment: "non-coding" RNAs make proteins too***
Tu, Nov 10	Cloning now 1: Nextgen sequencing and its application to defining human disease genes
Th, Nov 12	Cloning 2: X-linked mental retardation by nextgen approaches & de novo mutations
Tu, Nov 17	Prion 1: What is a prion disease?
Th, Nov 19	Prion 2: Spreading of amyloid disease proteins within the brain
Tu, Nov 24	The missing heritability: Finding causes of LOAD (late onset Alzheimer's disease).
Tu, Dec 1	Modeling neurological disease in simple genetic systems: —The extraordinary approach of a simple system
Th, Dec 3	***In-class activity & final assignment: Is it the nerves or not?***
Tu, Dec 8	Wrap up session: summary overview of the course & new directions/hot areas