BIPN 194 Advanced Topics in Modern Biology:
Molecular Basis of Neurodegeneration
Winter 2018,

Class Meeting Time: Friday 10:00AM-11:20AM
Location: York Hall 3010

Professor Susan L. Ackerman
Email: sackerman@ucsd.edu Note: please include "BIPN194" in the subject line of emails concerning this class. If your email requires an elaborate reply, please see me before or after class, or during my office hours.

Office Hours: Mondays 3-4PM, and by appointment; Pacific Hall 1123A. Note, that there will not be normal office hours on Jan 15 and Feb 19 due to the official holiday, but I can meet by appointment those weeks. Additionally, each presentation group will meet with me on Tuesday of the week they are presenting a paper in class. Members of the group must coordinate their schedules and then a representative should coordinate with me to find a time we can meet.

Course Website: There will be a TritonED site for the course (tritoned.ucsd.edu). Student accounts will be added on the first day of class. **Announcements, updates, postings, required reading material and grades will be communicated on the course website using TritonED.**

Course Overview: Neurodegenerative disorders are common, particularly in the aging population. Genetic analysis demonstrates that these disorders likely have divergent causes. Furthermore, the majority of the prevalent disorders are sporadic with unknown causes. The goal of this course is to provide basic knowledge on neurodegenerative disorders and to discuss cutting-edge research on the molecular and cellular causes of neuron loss in these disorders.

Course Format: The first lecture will be instructor taught. All other course meetings will be student-led discussions of primary research literature. All meetings will be very interactive, with all students participating in discussions of the presentation. **Expect to spend at least four hours/week on the assigned reading and summary preparation, and 10+ hours the week you are presenting a paper.**

Prerequisites: Upper division knowledge of genetics, cell biology, molecular biology, and neurobiology is assumed. BICD 100 (Genetics), BIMM 100 (Molecular Biology), BICD 110 (Cell Biology), and BIPN 140 (Cellular Neurobiology) are strongly recommended.

Course materials: PDFs of the required readings will be posted on the course website. In addition, other papers will be recommended to give additional background on concepts covered in the required reading. There is no course textbook, but textbooks from other courses may help with general background.

Evaluation: There is no final exam. Your grade will be determined by:

1. Your performance during your groups' presentation.
2. Your attendance and participation in class.
3. Your summaries of papers being presented each week. These are due at the beginning of class. Please turn in a hard copy of your summary at the beginning of class and post your summary on the class website (as a Word doc) by 9AM on the day of class. **Late papers will not be accepted, nor will papers be accepted by email**.
4. Your final report (two single-spaced pages, Word doc) due on Friday March 19 at 10AM in Pacific Hall 1123A, AND on the website).

All four components will be count equally towards your grade. There is no final exam. ***Because of the discussion basis and the limited meetings of this course, missing one class (including the first one) will cap your grade at a 'B' and missing two classes will cap your grade at a 'C'.***

ASSIGNMENTS AND GRADING

Attendance and Participation. Attendance is mandatory. Documented medical or family emergencies will be accepted as excuses for missing the class. Students will be expected to participate in the discussion of assigned papers during the class and to ask questions during the presentation. Arriving late may impact your participation grade.

Weekly assignments. You are required to read the assigned paper and write a one page (maximum), single spaced document on the assigned paper, except on the day you are presenting. For your summary you should address:

1. What is the overall question being asked?
2. Why is this question important?
3. What are the strengths and weaknesses of the methodology used to test these hypotheses?
4. What conclusions did the authors arrive at from their experiments?
5. What part of the paper did you find the least convincing or the most confusing? Why?
6. What are the next experiments that follow from the author's findings in the paper?
7. What are the implications for these findings in the field of neurodegeneration?
8. What are two questions you have about the paper?

Presentations: Each group will have 40 minutes for the presentation and 15-20 minutes for questions and discussion. Each group member will have equal presentation time and should be prepared to answer questions and engage the class in discussions. It is the expectation that each group will clearly present the question/concept being tested in the paper, the approaches by which the question was tested, and the significance of the paper. You will need to look up any background or terminology that you are not familiar with so that you can explain it to the class.

Group meetings for the presentation. Each group of presenters needs to exchange contact information (phone numbers and email information) and arrange meetings to discuss the overall presentation and how the sections will be divided among group members. These meetings are essential. I will also meet with the entire group on Tuesday to discuss the presentation and help with questions. This is a mandatory meeting that will help with your presentation. Each group member should be prepared for this meeting and have read the paper and prepared 4-5 slides. After our meeting, the group may wish to meet again to tweak the presentation.

The group's entire presentation needs to be on one computer in one file (i.e., powerpoint, keynote, or a format agreed upon by the entire group) and the presentation needs to be backed up on a memory stick. The presentation needs to be uploaded onto the website by 9 AM on the Friday that you give your presentation. *The presenting group must arrive 10 minutes early to set up. You are responsible for bringing an adaptor to connect the presentation computer to the VGA projector.* If you don't have one they can be checked out from Geisel Library through the Tech Lending Program.

Background/Introduction: In this part of the presentation you need to describe the biological question that the authors were asking. You will need to provide the necessary background for the paper so that your audience can understand the importance of the authors' question.

Results: Here you need to logically present the experimental results. How did the authors address their question? Explain the tools and methodology that the authors use to address the question. What are the specific conclusions from their results? I recommend that each group member present one or two figures each. Most figures in papers have multiple panels. Many papers have supplementary figures that support the main figure and these are required reading for the paper. You will need to decide which of the panels in a figure to present and if any supplemental figures should be presented. For each figure you should explain what is being tested and why. Most figures have one or two main conclusions, be sure you are clear about these and can explain these two the class. Experiments require proper controls, also make sure you understand why the given controls were used. Discuss reservations, if any, about the data.

Conclusions and implications: Overall what are the findings of this paper? Does the data support the conclusions? What are the next steps that follow from these experiments? How do the data impact the field?

Nonpresenters: You are expected to read every paper before coming to class and be prepared to discuss and ask questions. During class you are expected to participate in discussion and ask questions. *At the end of each class you will write a short, constructive evaluation of the presentation, except on the day you are presenting.* These evaluations need to address how the presentation helped clarify the paper and your questions, what aspects of the presentation were particularly good, and how the presentation could have been improved. Note these evaluations need to be

constructive. They are an important part of your participation grade and will be shared with the presenters. These are due on the Friday by 9AM the week following the presentation and are to be uploaded on Triton Ed in a Word doc file.

Technology Etiquette: Please refrain from engaging in personal internet or communications during class and ensure that your cell phones and tablets are turned off. If you have a compelling reason that such devices remain on, please talk to me before class.

Academic Integrity: Academic dishonesty will not be tolerated. According to UCSD policy, academic dishonesty includes:

- Completing assignments for another student or allowing another student to complete an assignment for you
- Copying another student's work or allowing another student to copy your work
- Incorporating plagiarized material into assignments.

All instances of academic dishonesty will be reported to the Academic Integrity Office. Students will receive a final grade of 'F' if academic dishonesty is confirmed and other disciplinary actions deemed appropriate by the Academic Integrity Office.

COURSE SCHEDULE

January 12: *Introduction and organization of the course- Prof. Ackerman*

January 19: Human genetics and neurodegeneration

*Discussion paper***:** DeJesus-Hernandez et al., Expanded GGGGCC hexanucleotide Repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. (2011) *Neuron* 72:245-256.

Background reading: Weishaupt, Hyman, and Dikic, Common Molecular Pathways in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia (2016) *Trends Mol Med*. 22:769-783.

Haeusler, Donnelly, Rothstein. The expanding biology of the C9orf72 nucleotide repeat expansion in neurodegenerative disease. *Nat Rev Neurosci.* (2016) 17:383-95.

January 26*:* Novel mechanisms of proteinopathies

Discussion paper: Lee et al., Editing-defective tRNA synthetase causes protein misfolding and neurodegeneration. (2006) *Nature* 443:50-55

Background reading: Kumar et.al. Protein aggregation and neurodegenerative diseases: From theory to therapy. *Eur J. Med Chem.* (2016) 124:1105-1120.

Hipp et al., Proteostasis impairment in protein-misfolding and –aggregation diseases. *Trends Cell Biol.* (2014) 24:506-14.

February 2: Prion-like spreading of misfolded proteins in neurodegeneration

Discussion paper: de Calignon et al., Propagation of Tau Pathology in a Model of Early Alzheimer's Disease. (2012) Neuron 73:685-697.

Background reading: Aguzzi and Lakkaraju. Cell biology of prions and prionoids: A status report. (2016). *Trends Cell Biol.* 26:40-51.

Li and Gotz. Tau-based therapies in neurodegeneration: Opportunities and challenges. (2017). *Nat Rev Drug Discov*. 16:863-883.

February 9: Phase-separation and neurodegeneration

Discussion paper: Mackenzie et al., TIA1 Mutations in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia promote Phase Separation and Alter Stress Granule Dynamics. (2017) *Neuron* 95:808-816.

Background reading: Alberti, Hyman. Are aberrant phase transitions a driver of cellular aging? (2016) *Bioessays* 38:959-68.

Aguzzi and Altmeyer. Phase Separation: Linking Cellular Compartmentalization to Disease. (2016) 26:547-558.

February 16: Non-canonical mRNA translation and neurodegeneration

Discussion paper: Sellier et al., Translation of expanded cGG repeats into FMRpolyG is pathogenic and may contribute to Fragile X Tremor Ataxia Syndrome. (2017) *Neuron* 93:331-347.

Background reading: Kapur, Monaghan, Ackerman. Regulation of mRNA translation in neurons- A matter of life and death. (2017). 96:616-637.

Kong, Zhao, Xu, Jin, Jin. Fragile X-Associated Tremor/Ataxia Syndrome: From molecular pathogenesis to development of therapeutics. (2017). Front Cell Neurosci. 11:1-11.

February 23: Mitochondrial Dysfunction and neurodegeneration

Discussion paper: Wang et al., PINK1 and Parkin target Miro for phosphorylation and degradation to Arrest Mitochondrial Motility (2011) *Cell 147:893-906.*

Background reading: McWilliams and Muqit, PINK1 and Parkin: Emerging themes in mitochondrial homeostasis. (2017). *Curr Opin Cell Biol* 45:83-91.

Srivastava, The mitochondrial basis of aging and age-related disorders. (2017) *Genes* 19:8.

March 2: Glia, Reactive Oxygen Species and Neurodegeneration

Discussion paper: Liu, L., et al., The Glia-Neuron Lactate Shuttle and Elevated ROS Promote Lipid Synthesis in Neurons and Lipid Droplet Accumulation in Glia via APEO/D. (2017) Cell Metabolism 26:719-737.

Background reading: Sofroniew and Vinters, Astrocytes: biology and pathology. Acta Neuropathol. (2010) 119:7-35.

Angelova and Abramov. Role of mitochondrial ROS in the brain: from physiology to neurodegeneration. (2018). FEBS Lett. Epub ahead of print.

March 9: Treatment of dominant neurodegenerative diseases with antisense Oligonucleotides

Discussion paper: Kordasiewicz et al. Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. (2012) *Neuron* 74:1031-44.

*Background reading***:** Evers, Toonen, Roon-Mom, Antisense oligonucleotides in therapy for neurodegenerative disorders. (2015). 90-103.

March 16: No class. Final paper due by 10 AM.