BIPN 194/BGGN284 Advanced Topics in Modern Biology:
Molecular Basis of Neurodegeneration
Winter 2022

Class Meeting Time: Thursdays 12:30PM-1:50PM
Location: University Center (U301), Room 122

Professor Susan L. Ackerman
*Email***:** sackerman@health.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, Pacific Hall 1123A. Note that there will not be normal office hours January 17th and February 21th due to the official holidays, 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 Canvas site for the course (canvas.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 Canvas.**

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 and all students expected to participate in discussions during 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 preparation and performance during your groups' presentation.
2. Your attendance and participation in class.
3. Your summaries of papers being presented each week. These are due before 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 noon 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 March 10 at noon 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', unless excused. Come to class!***

BGGN284 students. The course requirements are the same for you with the exception that your final report is four pages with more details on significance and future directions.

ASSIGNMENTS AND GRADING

Grading Scale.

A+ 98-100%	C+ 77-79%
A 93-97%	C 73-77%
A- 90-92%	C- 70-72%
B+ 88-89%	D+ 68-69%
B 83-87%	D 63-67%
B- 80-82%	D- 60-62%
	F Below 60%

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 were the specific hypotheses and how did the authors test them?
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 is the next question that follows from the author's findings in the paper?
7. What are two questions you have about the paper?

Presentations: Each group will have 50 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. Recommended papers for background reading are listed on the website.

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 slides. After our meeting, the group will likely wish to meet again to tweak the presentation.

Presentation details: 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. I don't recommend presenting in a Google Drive format- it can run very slowly. The presentation needs to be uploaded onto the website by noon on the Thursday 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 divide up the figures according to the amount of information in them. 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 (usually there are some that should be presented for clarification and/or justification of the conclusions). 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 to 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. These evaluations need to be constructive and are an important part of your participation grade. Your comments will be shared with the presenters. These are due on the Thursday by noon each week following the presentation and are to be uploaded on Canvas in a Word doc file.

Final Paper: Find a paper that you would recommend for the class next year, which will have the same emphasis. Write a two-page, single spaced paper (references should be on a separate page) on why you chose this paper. Begin by stating the question that the authors are addressing. Include background on what was known regarding this question prior to this paper. Describe the experiments that were done in order that they occur in the paper. Include the method used for each experiment and the conclusion from that particular experiment. Elaborate on the overall conclusion(s) of the paper and how it influenced, or will influence, future studies. Finally, on a separate page, write a paragraph on the paper you most enjoyed this quarter and why. In addition to uploading onto Canvas, please bring a hard copy of your paper by my office (Pacific Hall 1123A). In addition to your paper, upload the PDF (and supplemental material) of the paper you are evaluating. Note that I am happy to take a look at the paper you are thinking of writing on to evaluate whether it is appropriate for this assignment, if you email it to me at least two weeks before it is due. ***BGGN284 students*.** The format of your final paper is slightly different. Your paper will be as above, except that in addition to 2 pages on the paper you have chosen, you will need to include more background (a full page) and significance of the paper and a full page on potential and/or actual follow up experiments/papers.

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 person 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 6: *Introduction and organization of the course - Prof. Ackerman*

January 13: 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 20: 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.

January 27: Glia and neurodegeneration

Discussion paper: Bussian et al., Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. (2018). *Nature* 562:578-582.

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

Cohen and Torres, Astrocyte senescence: Evidence and significance. Aging Cell. (2019) e12937.

February 3: APOE4 and Alzheimer's Disease

Discussion paper: Wang et al., Selective removal of astrocytic APOE4 strongly protects against tau-mediated neurodegeneration and decreases synaptic phagocytosis by microglia. (2021) Neuron 109:1657-1674.

Background reading: Fernandez et al., *The* Role of APOE4 in Disrupting the Homeostatic Functions of Astrocytes and Microglia in Aging and Alzheimer's Disease. (2019) Front Aging Neurosci. 11:1-18.

Sankowski et al., Evaluating microglial phenotypes using single-cell technologies. (2021) Trends Neurosci.

February 10: 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 17: 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: Banez-Coronel and Ranum, Repeat-asstociated non-AUG (RNA) translation: insights from pathology. (2019). Lab Invest. 99:929-42.

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 24: 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 3: Treatment of neurodegenerative diseases with antisense oligonucleotides

Discussion paper: Hua et al. Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model. (2010) *Genes and Development 24:* 1634-44.

*Background reading***:**
Groen et al. Advances in therapy for spinal muscular atrophy: promises and challenges. (2018) Nat. Rev. Neurol. 14:214-24.

Goyal and Narayanaswami. Making sense of antisense oligonucleotides: A narrative review. (2018) *Muscle Nerve* 57:356-370.

March 10: No class. Final paper due by noon. Please upload onto Canvas and bring a hard copy by my office (Pacific Hall 1123A).