**BIPN 194/BGGN284 Advanced Topics in Modern Biology:**
**Molecular Basis of Neurodegeneration**
**Winter 2024**

**Class Meeting Time: Thursdays 2:00PM-3:20PM**
**Location: York 3010**

*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***:** Thursdays, after class. Additionally, each presentation person/group will meet with me on Tuesday of the week they are presenting a paper in class.

*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, most 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 three hours/week on the assigned reading, 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 presentation.
2. Your evaluation of the weekly presentation.

3. Your attendance and participation in class. This includes submission of a question on the **Results** section of the assigned paper. This is to be submitted by 1 PM on Wednesday, before class. Late questions will not be accepted, nor will questions be accepted by email.
4. Your final presentation.

*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 you will submit a final report on the paper your group is presenting. Your final report (two single-spaced pages, Word doc) due on March 21 at noon, on the website).

## 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. Part of your participation grade will be the submission of a question on the Results section of the assigned paper. These questions will be shared with the group that is presenting and therefore must be submitted on Canvas by 1 PM on the Wednesday before class.

**Weekly assignments.** You are required to read the assigned paper before class. To aid in your digestion of the paper, I suggest you think about the following points.

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? What conclusions did the authors arrive at from their experiments? Discuss these items in the order that they are presented in the figures.
4. What is the next question that follows from the author's findings in the paper?

5. What are two questions (e.g., things you didn't understand) you have about the Results section of the paper? Submit one of these as your question on the paper. The other (or both!) can be asked during class.

**Presentations:**
**Main presentation:** Each presentation will take 50 minutes and 15-20 minutes for questions and discussion. I will share questions from the class with the presenter(s) the afternoon before. Be prepared to answer questions and engage the class in discussions. It is the expectation that each person 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 (very useful for the introduction and future directions) are listed on the website.

*Preparatory meetings for the presentation:* If more than one person is presenting, the 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 presenter(s) on Tuesday to discuss the presentation and help with questions. This is a mandatory meeting that will help with your presentation. Each presenter 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 and practice.

*Presentation details:* The 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 an adaptor 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 and explain why the given controls were used. As they arise during the paper, discuss techniques that haven't been presented yet in class. 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 constructive evaluation of the presentation (up to one page), 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. Note that there are no evaluations for the final presentations.

**Final Presentation:** This presentation will demonstrate your synthesis of the paper you presented earlier with additional research that has occurred in this area. You need to work with members of your group (if applicable) that furthers the concept presented in the first paper you presented. Your paper to present should be chosen from *Neuron*, *Nature Neuroscience*, *Nature Cell Biology*, *Cell*, *Molecular Cell, Science or Nature*. Realize that there are other journals that *Cell*, *Science*, and *Nature* publish, papers from these other journals are not appropriate for the final presentation. This presentation will be much shorter than your first one (8 minutes total), you will be able to present many fewer slides starting with one to remind the class of the concept they learned during your earlier presentation and max, one slide per figure highlighting the conclusion of the figure. Some figures may need left out of the presentation. Because each group needs a chance to present, these presentations will be timed and stopped at 8 minutes, so practice prior to the presentation is crucial.

***BGGN284 students*-final paper.** You will write a two-page, single spaced paper (references should be on a separate page) on the paper that your group is discussing. 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 the order that they occur in the paper. Include the method used for each experiment and the conclusion from that experiment. Elaborate on the overall conclusion(s) of the paper and how it influenced, or will influence, future studies.

**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.
- Do your own work and do not rely on using ChatGPT.

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

### January 18: 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 25: 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 1: 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 8: 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 15: 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 22: 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 29: 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 7: 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 14: Final Presentations.** For BGGN 284 students, the final paper is due **March 21**st due by noon. Please upload onto Canvas.