BIPN 194/BGGN284 Advanced Topics in Modern Biology:
Molecular Basis of Neurodegeneration
Winter 2021

Class Meeting Time: Thursdays 2:00PM-3:20PM
Location: Online – The zoom link for each class is on Canvas (under Syllabus).

Professor Susan L. Ackerman
Email: sackerman@health.ucsd.edu Note: please include "BIPN194 or BGGN248" 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, via Zoom. Note that there will not be normal office hours January 18th and February 15th due to the official holidays, but I can meet by appointment those weeks. **The Zoom link for office hours is on Canvas under the syllabus.** 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 must coordinate with me by Friday to find a time we can meet. If you are in the group for the next week, please stay on Zoom after class the week before to coordinate with me.

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 performance during your groups' presentation.
2. Your attendance and participation in class.
3. Your summaries of the research papers being presented each week. These are due by 1PM on the day of class. All assignments should be completed and uploaded as a Word document to Canvas. **Late papers will not be accepted, nor will papers be accepted by email**.
4. Your final report (two single-spaced pages, Word doc as above) due on March 11 at 2PM).

All four components will be count equally towards your grade. There is no final exam. ***Because of the discussion aspect of the class and the limited meetings, 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'.***

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 to receive full credit for participation. 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 is the next research question that follows from the author's findings in the paper (in your opinion)?
6. What are two questions you have about the paper? These can be about a technique being used, why a certain experiment was done, confusion on interpreting data etc.

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. 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 presentation 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. Note that while the presentation should be cohesive, each group member will receive an individual grade that is reflective of their part in the project.

Presentation details: The group's entire presentation needs to shared by one computer in one file (i.e., PowerPoint, Keynote, or a format agreed upon by the entire group). Please make sure that other members of the group have the final presentation, in case of a technical problem. The presentation needs to be uploaded onto the website by 1PM on the Thursday that you give your presentation. *The presenting group should be on Zoom promptly to ensure that share screen options are working. All class members should have their video on during class. If this is a problem for you, I need to know why* (*via email*) *prior to class.*

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 the figures in the paper are split up between group members. 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. Please have your camera on so that the presenters can interact with you and vice versa. If this is not possible, please email me to explain. *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 may be shared with the presenters. These are due on the Thursday by 1pm the 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. Please upload the Word docs on Canvas. In addition to your paper, upload the PDF (and supplemental material) of the paper you are evaluating. ***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 other 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 7: *Introduction and organization of the course - Prof. Ackerman*

January 14: 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. (2016) *Nat Rev Neurosci.* 17:383-95.

January 21*:* Novel mechanisms of proteinopathies

Discussion paper: Vo et al., 2018. ANKRD16 prevents neuron loss caused by an editing defective tRNA synthetase. (2018). *Nature* 557-510-515

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

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

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

January 28: 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 4: 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) *Trends Cell Biol* 26:547-558.

February 11: 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). *Neuron* 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 18: 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. (2010) *Acta Neuropathol*. 119:7-35.

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

Pajvani et al, Fat apoptosis through targeted activation of caspase 8: a new mouse model of inducible and reversible lipoatrophy. (2005) *Nature Med* 11:797-803.

February 25: 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***:** Levin. Treating disease at the RNA level with oligonucleotides. (2019) *N Engl J Med*. 380:57-70.

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

March 4: Reprogramming non-neuronal cells to replace dead neurons

Discussion paper: Reversing a model of Parkinson's Disease with in situ converted nigral neurons

Background reading: Barker, Götz, Parmar. New approaches for brain repair-from rescue to reprogramming (2018) *Nature* 557: 329-334.

Zhu and Roth. DREADD: A chemogenetic GPCR Signaling Platform (2014) Inter. J. of Neuropsychopharmacology Doi:10.1093/ijnp/pyu007 pp.1-6.

Zhou et al. Glia-to Neuron Conversion by CRISPR-CasRX Alleviates Symptoms of Neurological Disease in Mice (2020) Cell 181, 590-603.

March 11: No class. Final paper due by 1PM. Please upload your Word Doc in Canvas.