M254A Section 4: 'Omics' approaches to understand transcription, translation, and protein degradation

Faculty: Keriann Backus & James Wohlschlegel

Course Schedule:	Student meeting	Mon	11:30 am – 1:30 pm
	Faculty-Student class	Tue	10:00 am – 12:00 pm
	Student meeting	Thu	11:30 am – 1:30 pm
	Faculty-Student class	Fri	10:00 am – 12:00 pm

Final Exam: ***Due Nov 6 at 5 pm***

Zoom link for the Faculty-Student meetings, including the first student meeting:

https://uclahs.zoom.us/j/98215559654?pwd=dk1MQUxMYmozeUJjMGhUMVhpQWNIUT09

Password: 2TG2Wc

Course Description: The MBIDP wants all of our graduate students to develop scientific thinking skills while working toward their Ph.D. We believe these skills are integral for your success in any scientific career. The 254 series is designed to strengthen your scientific thinking skills through practice and with guidance from faculty.

Topic Description: This course focuses on research articles that demonstrate how technological advances can drive the characterization of complex biochemical systems. We will discuss methods that include genome and protein engineering, mass spectrometry, chemical biology, and next-generation sequencing and how they can be used to gain insight into the function and regulation of transcription, translation, and protein degradation pathways**.** This section emphasizes self-driven learning based on primary literature.

Learning Outcomes: At the end of this module, we anticipate that you will become proficient in the following areas:

1. Identify and articulate the hypotheses being tested in primary research papers.
2. Develop and practice self-led discovery and curation of background info (literature searches).
3. Correlate the data and methods presented in a primary research paper with the authors' hypotheses and conclusions.
4. Evaluate the soundness of scientific arguments and conclusions presented in primary research papers.
5. Outline the logical flow of primary research papers and develop a generalized conception of logical scientific argumentation.
6. Correlate primary research findings with a larger body of work in the literature.
7. Devise, plan, and propose 'next step' experiments that could follow on from primary research papers.
8. Construct logical arguments, based on inductive reasoning, related to primary research papers.
9. Increase level of comfort, and skills in making presentations and discussing scientific concepts.

Our Commitment to Inclusivity: We will work with you to create a learning environment that is inclusive and promotes learning. We expect you to generate a peer learning environment where everyone is included and all opinions and thoughts are welcome. The MBIDP is committed to making our community an inclusive environment where all scientists can succeed and achieve their goals. We encourage you to discuss with each other how your environment can be inclusive and to hold each other accountable for maintaining it. Concerns about inclusivity may also be discussed with us, with the 254 Overall Organizers: Dr. Kathrin Plath (kplath@mednet.ucla.edu) and/or Dr. Siobhan Braybrook (siobhanb@ucla.edu), or the MBIDP Director Dr. Hillary Coller (hcoller@ucla.edu).

UCLA's Office for Equity, Diversity, and Inclusion provides resources, events, and information about current initiatives at UCLA to support equality for all members of the UCLA community. We hope that you will communicate with us if you experience anything in this course that does not support an inclusive environment, and you can also report any incidents you may witness or experience on campus to the Office of Equity, Diversity, and Inclusion on their website.

Course Structure: There will be nine paired meetings (student-only and faculty-student sessions) where different topics will be discussed. Seven of these meetings will involve the discussion of a primary research article. The other three meetings will focus on how to develop specific aims for a research proposal. Guidelines for these meetings are provided below.

Guidelines for Research Article Meetings: Students are required to meet together as a group before each faculty-led meeting. In these student sessions, we expect you to work together to understand the background material, experimental approaches, results and conclusions for the paper. Remember that you are a team! Leverage each other's expertise and knowledge during your discussions.

In addition to any other relevant topics, we would recommend thinking about and discussing the following questions in the student sessions:

- What was the main question being addressed in the selected research paper? For methods-centric papers, what is the key gap that the method is addressing?
- What were the relevant and important findings that led up to this paper?
  - How does the technique compare to established methods?
- For each Figure/Section
  - What were the hypotheses being tested?
  - What experiments (and methods) were used to test the hypotheses? Were they appropriate?
  - Are there different approaches that you can think of?
  - What were the conclusions for each Figure/Section? Are they supported by the results presented?
  - What do you think of the statistics used?
- What were the overall conclusions from the paper and how do they address the initial question?
- What is a follow-up question that you have based on this paper?
  - What hypotheses would you propose to test?
  - How could you go about testing them?

For each faculty session, a student will be assigned to "lead" the meeting. The leader has two primary responsibilities. First, the leader is responsible for preparing a slide deck that will be used to guide the faculty-led discussion and should include figures and tables from research article. The slides will be prepared in consultation with the faculty and may include additional slides provided by the faculty. Second, the leader is responsible for presenting a brief introduction of the

research article to be discussed. This presentation should be no more than 15-20 min and should include 1) introduction / background for the research article being discussed, 2) an overview of the main question being addressed and why that question is important to the field, and 3) a brief outline of the results and conclusions and their impact on the field. The leader-led overview will be followed by a round table discussion in which we discuss different aspects of the article in greater depth. This section of the discussion will be led primarily by the faculty and typically involves asking students to describe or interpret specific experiments in the article. Importantly, every student in the course will be responsible having a general understanding of the entire article (not just the leader) and expected to actively participate in the discussion.

Guidelines for Proposal Writing Meetings: In addition to discussing primary research articles, a significant portion of the course will focus on how to identify and design research aims in the context of a research proposal. This component of the course will be accomplished through a variety of assignments and include three faculty-led discussions. One faculty-led meeting will focus on the analysis / discussion of separate aims pages taken from a set of NIH grant applications. This will be followed by students submitting and research topic to us, followed by writing a specific aims page of their own over the following weeks that will be discussed with faculty who will provide individualized feedback. Based on the faculty feedback, students will revise the specific aims of the proposal and prepare a short presentation in which they will describe the proposed experimental plan to the class. These presentations will take place during the last two scheduled meetings of course. Additional details regarding the proposal writing component of the course will be discussed at the first class meeting.

How Your Learning Will Be Assessed (Grading Policy): Our 254 Course Grading Policy does not have an enforced grade distribution or curve. This encourages a collaborative learning environment, instead of a competitive one, which we believe models the best aspects of the scientific process. The distribution below delineates the letter-to-percentage ranges used in all 254s.

A: 90 - 100%
B: 80 - 89.9%
C: 70 - 79.9%
D: 60 - 69.9%
F: 0 - 59.9%

Grading Rubric

Participation in Discussion: 40%
- *Discussion leader presentation: 15%*
- *General participation: 25%*

Proposal Writing Component: 30%
- *Specific Aims page: 15%*
- *Specific Aims presentation: 15%*

Final Exam: 30%

Grading Breakdown:

Participating in Discussions: Participation will be evaluated based on the aspects below. Each will be scored during each student/instructor meeting. These will be used for mid-course feedback to students.

Attendance. You must attend Student & Instructor and Student-only meetings consistently and arrive on time. Legitimate absences (e.g. physical illness, mental health, bereavement) can be made up by providing written answers to assigned questions (provided on CCLE or upon request). Please notify us or a fellow student (student-only meetings) if you are going to miss a meeting so discussions are not held in waiting. Please discuss with us if there is a reason why you will need to be consistently late (e.g. from the past includes cross-campus travel).

Discussion Leader Presentation. The student leader for each article is responsible for providing a concise presentation to begin each discussion class. The goal of this presentation is to provide a concise overview of the paper and should include 1) background information to describe the current state of knowledge of the field, 2) the research question being addressed and its underlying scientific premise, 3) a brief summary of the articles' findings and 4) a discussion of the overall impact of the paper to the field.

Communication. You should be able to succinctly and accurately describe experiments and explain figures. Practice, in your student-only sessions, identifying and articulating the hypotheses being tested, the methods used, the results shown, and your interpretation of the results.

Critical skills. You should be able to provide critical insight into the methodological soundness and significance of experiments, as they relate to the hypotheses being tested and the overall question being addressed. Develop and practice these skills together in your student-only sessions.

Synthesis and Forward Thinking. You should engage fully with the papers and provide insights into the experimental implications and unanswered questions that present to you, as an individual.

Inclusive Group Behavior. You should engage respectfully with each other in all meetings. This doesn't mean you can't disagree or challenge each other's thinking, but it does mean we all have to remember that everyone comes from a different place of experience and learning. We are together to get it right, not to be right.

Feedback: In the third week (midcourse), the following feedback mechanism will be utilized to allow everyone to enhance their learning.

Peer Feedback. We will encourage you to reflect as a group on how your student sessions are working well and where you could work together to make them even better, and to present your intentions at the next student/instructor meeting.

Instructor Feedback to you. We will provide you with concrete feedback with respect to your class performance and provide constructive criticism for where improvements can be made. Feedback will be delivered in an individual meeting with one of us.

Student Feedback to Instructors. You will be encouraged to provide feedback to us, as instructors, on what is working well and where we could improve. We will summarize and reflect on your feedback and present concrete steps that will be taken to address concerns.

The Final: Exams are meant to show yourself and us what you've learned with respect to the course Learning Outcomes. As such, the final exam will be an assignment based on a paper that will be assigned at the last class meeting. Each final will be evaluated independently by the two instructors and a consensus score will be given and contribute 30% to your final course grade. The format will be a critical analysis of the assigned paper. Additional details regarding the format, organization, and expectations of this critique will be provided in class.

Dates and Primary Papers

Oct. 5/6: CRISPR-Cas9
Transcriptome-wide off-target RNA editing induced by CRISPR-guided DNA base editors. Grünewald J, Zhou R, Garcia SP, Iyer S, Lareau CA, Aryee MJ, Joung JK. Nature. 2019 569(7756):433-437. doi: 10.1038/s41586-019-1161-z.

Oct. 8/9: Ferroptosis/HTS
The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, Roberts MA,Tong B, Maimone TJ, Zoncu R, Bassik MC, Nomura DK, Dixon SJ, Olzmann JA. Nature. 2019 Nov;575(7784):688-692. doi: 10.1038/s41586-019-1705-2. Epub 2019 Oct 21. PMID:31634900; PMCID: PMC6883167.

Oct. 12/13:
Discussion of Specific Aims Pages

Oct. 15/16: Unnatural Amino Acid Incorporation
Designer membraneless organelles enable codon reassignment of selected mRNAs in eukaryot es. Reinkemeier CD, Girona GE, Lemke EA. Science. 2019 Mar 29;363(6434). pii: eaaw2644. doi: 10.1126/science.aaw2644. PMID:30923194
Deadline to submit research topic

Oct. 19/20: APEX
1: Fazal FM, Han S, Parker KR, Kaewsapsak P, Xu J, Boettiger AN, Chang HY, Ting AY. Atlas of Subcellular RNA Localization Revealed by APEX-Seq. *Cell*. 2019 Jun 14. pii: S0092-8674(19)30555-0. doi: 10.1016/j.cell.2019.05.027. PubMed PMID: 31230715.

Oct. 22/23: Crosslinking Mass Spec
A Single α Helix Drives Extensive Remodeling of the Proteasome Lid and Completion of Regulatory Particle Assembly. Tomko RJ Jr, Taylor DW, Chen ZA, Wang HW, Rappsilber J, Hochstrasser M. Cell. 2015 Oct 8;163(2):432-44. doi: 10.1016/j.cell.2015.09.022. PMID:26451487
Deadline to submit specific aims page to us

Oct. 26/27: PROTACs
1.0 Winter GE, Buckley DL, Paulk J, et al. Phthalimide conjugation as a strategy for in vivo target protein degradation. Science. 2015;348(6241):1376–1381. doi:10.1126/science.aab1433

2.0 Donovan KA, An J, Nowak RP, Yuan JC, Fink EC, Berry BC, Ebert BL, Fischer ES. Thalidomide promotes degradation of SALL4, a transcription factor implicated in Duane Radial Ray syndrome. Elife. 2018 Aug 1;7:e38430. doi: 10.7554/eLife.38430. PMID: 30067223; PMCID: PMC6156078.

Oct. 29/30:
Student Presentation of Specific Aims

Nov. 2/3:
Student Presentation of Specific Aims

Nov. 5/6:
Final Exam Due Nov 6 at 5 pm