M254B: Mechanical Forces in Cell Biology

Faculty: Alison F. Frand (AFrand@mednet.ucla.edu) & Julia J. Mack (JMack@mednet.ucla.edu)

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

Final Exam: ***Due December 15 @ 5 pm***

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

https://zoom.us/j/5537762319?pwd=dUFEZWlvWThKUkdiYkJoYVNBb1gwdz09

Meeting ID: 553 776 2319
Passcode: 4DvvLJ

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 uses a self-driven learning approach to strengthen scientific thinking skills through group discussion, faculty guidance and practice.

Topic Description: This section focuses on molecular mechanisms by which cells sense and respond to physical forces that directly influence the specification of cell fates, the development of three-dimensional organs and the progression of human diseases including cancers and cardiovascular pathologies. We will discuss research publications exploring the role of mechanotransduction in guiding protein-protein interactions, gene transcription, cytoskeletal organization, cell shape and motility to uncover how physical forces regulate key biological processes at the molecular, cellular and tissue levels.

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. Develop and practice self-led discovery and curation of background info (literature searches).
2. Correlate the data and methods presented in a primary research paper with the authors' hypotheses and conclusions.
3. Evaluate the soundness of scientific arguments and conclusions presented in primary research papers.
4. Outline the logical flow of primary research papers and develop a generalized conception of logical scientific argumentation.
5. Correlate primary research findings with a larger body of work in the literature.
6. Devise, plan and propose 'next step' experiments that could follow on from primary research papers.
7. Construct logical arguments, based on inductive reasoning, related to primary research papers.
8. 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) focused on the discussion of a primary research article. Guidelines for these meetings are provided below.

Guidelines for Research Article Meetings: Students are required to meet together as a group before each student/faculty 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 recommend thinking about and discussing the following questions in the student sessions:

- What was the main question being addressed in the selected research paper?
- What were the relevant and important findings that led up to this paper?
- 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?
    - 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 "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 discussion and should include figures and tables from research article. 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.

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: 70%
- *Discussion leader presentation: 20%*
- *General participation: 50%*

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.

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 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/faculty 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 Papers

November 9/10: Cues from the microenvironment
Matrix elasticity directs stem cell lineage specification.
Engler, A.J., Sen, S., Sweeney, H.L. & Discher D.E. *Cell* 126, 677-689 (2006).
https://doi.org/10.1016/j.cell.2006.06.044

Commentary: Even-Ram, S. *et al.* Matrix Control of Stem Cell Fate. *Cell* 126, 645-7 (2006).
https://doi.org/10.1016/j.cell.2006.08.008

November 12/13: Mechanotransduction
Role of YAP/TAZ in mechanotransduction.
Dupont, S., Morsut, L., Aragona, M. *et al. Nature* 474, 179-183 (2011).
https://doi.org/10.1038/nature10137

Commentary: Halder, G. *et al.* Transduction of mechanical and cytoskeletal cues by YAP and TAZ. *Nat Rev Mol Cell Biol*. 13, 591-600 (2012).
https://doi.org/10.1038/nrm3416

November 16/17: Focal adhesions as mechano-transceivers
Measuring mechanical tension across vinculin reveals regulation of focal adhesion dynamics.
Grashoff, C., Hoffmann, B.D., Brenner, M.D. *et al. Nature* 466, 263-266 (2010).
https://doi.org/10.1038/nature09198

Commentary: Doyle, A.D. & Yamada, K.M. Cell biology: Sensing tension. *Nature* 466, 192-3 (2010).
https://doi.org/10.1038/466192a

November 19/20: Integrin signaling
Matrix crosslinking forces tumor progression by enhancing integrin signaling.
Levental, K.R., Yu, H., Kass, L. *et al. Cell* 139, 891-906 (2009).
https://doi.org/10.1016/j.cell.2009.10.027

Commentary: Ng, M.R. & Brugge, J.S. A stiff blow from the stroma: collagen crosslinking drives tumor progression. *Cancer Cell* 6, 455-57 (2009).
https://doi.org/10.1016/j.ccr.2009.11.013

November 23/24: Endothelial response to shear stress
A mechanosensory complex that mediates the endothelial cell response to fluid shear stress.
Tzima, E., Irani-Tehrani, M., Kiosses, W. *et al. Nature* 437, 426–431 (2005).
https://doi.org/10.1038/nature03952

November 30/December 1: Shear force sensation
The guidance receptor plexin D1 is a mechanosensor in endothelial cells.
Mehta, V., Pang, K.-L., Rozbesky, D. *et al. Nature* 578, 290-295 (2020).
https://doi.org/10.1038/s41586-020-1979-4

Commentary: Fernández-Ruiz, I. Plexin D1 is a mechanosensor that regulates the site-specific distribution of atherosclerosis. *Nat Rev Cardiol* 17, 199 (2020).
https://doi.org/10.1038/s41569-020-0355-2

December 3/4: Mechanosensation in vascular disease
Integrin-YAP/TAZ-JNK cascade mediates atheroprotective effect of unidirectional shear flow.
Wang, L., Luo, J., Li, B. *et al. Nature* 540, 579–582 (2016).
https://doi.org/10.1038/nature20602

Commentary: Mohri, Z., Hernandez, A.D.R. & Krams, R. The emerging role of YAP/TAZ in mechanotransduction. *J Thorac Dis* 9, 507-509 (2017).

December 7/8: Mechanosensitive calcium signaling
TRPV4-mediated calcium signaling in mesenchymal stem cells regulates aligned collagen matrix formation and vinculin tension.
Gilchrist, C.L., Leddy, H.A., Kaye, L. *et al. PNAS* 116, 1992-1997 (2019).
https://doi.org/10.1073/pnas.1811095116

December 10/11: Tissue morphogenesis
Keratins and plakin family cytolinker proteins control the length of epithelial microridge protrusions.
Inaba, Y., Chauhan V., van Loon, A.P. *et al. eLife* 9:e58149 (2020).
https://doi.org/10.7554/eLife.58149

December 14/15: Paper to be assigned
Final Exam Due December 15 at 5 pm