“Therapeutics Discovery and Development”

general class information

This undergraduate class is a higher division lecture class within the Molecular Therapeutics emphasis of the MTx division in MCB.

It will meet three times per week for 1-hour lectures given by a faculty member of MTx. It will be supported by GSI-led discussion sessions once each week.

This class will provide **4 units** and it is a letter grade course.

MCELLBI 120 Therapeutics Discovery and Development
4 Units

COURSE OVERVIEW

This class is designed to introduce students to crucial concepts that underlie the discovery and development of therapeutic modalities. It will cover questions of target discovery and validation; basic properties of therapeutic modalities, such as small molecules, designer proteins, or genome engineering approaches; the design and execution of chemical screens; the medicinal chemistry, pharmacodynamics and -kinetics that is required for drug development; and the steps needed to introduce a new modality into the clinic. Lectures are based on a combination of textbook readings and primary literature and summarized through case studies that highlight critical aspects of drug discovery and development. Guest speakers from industry are invited to give first-hand accounts of important aspects of drug discovery and development.

PREREQUISITES

MCBC100A or MCB102 are prerequisites for this class. MCB140 can be taken concurrently with this class.

COURSE RESOURCES

Your most important resources are our textbook and the information and files listed on bcourses.

Text:
We will use Benjamin E. Blass, Basic Principles of Drug Discovery and Development, 2nd edition, as our textbook for this class.

https://www.amazon.com/dp/0128172142?psc=1&ref=ppx_yo2ov_dt_b_product_details

This class will also include required readings of primary literature and review articles that will be posted on bcourses.

Lecture Notes:
All lecture slides will be made available as pdfs prior to lectures and will remain on bcourses for the entire semester.

Office Hours:
Professor office hours will be on Zoom during the weeks they teach. There will be no office hours during the first week of class. A review class will be given by each professor in the RRR week before the final. GSI office hours will be determined ahead of class.

Class participation:
As many lectures build on material discussed in previous lectures, it is helpful to review lecture slides and prepare by reading the assigned literature ahead of each class. If anything is unclear, please do not hesitate to reach out to instructors or GSIs in office hours or at the end of class.

Please ask questions in person! Email is best for administrative purposes, not for questions on course content.

Letters of recommendation:
Any of the three instructors may be approached for letters of recommendation. We all are quite willing to provide a written evaluation for this purpose. So that we may prepare effective evaluations we ask that you follow the procedure outlined here. Be sure to attend at least 2 of the instructor's office hours. In addition, ask your discussion section GSI to write a brief note about your participation in section to the instructor. Sometime after the end of the course, request an interview with the instructor and bring a copy of your complete transcript, your CV and Personal Statement along with any recommendation forms that need to be filled in.

COURSE MECHANICS

Grading:
Grades for this class will be based on a combination of three midterm exams, one final exam, and two quizzes given by the GSI in their sections (20% each midterm, 30% final, 5% each quiz)

Midterms:
There will be three midterms given after each ~5 week block. Midterms will be on fixed dates. Makeup Midterms will only be given at the discretion of the instructors, upon sufficient advanced notice, and for extraordinary reasons. Professional or medical school interviews will not be sufficient reason for a makeup midterm exam.

Final:
There will be a final covering all sections of class.

Lecture participation:
Participation will impact overall grade, but can be achieved by asking questions during lecture, after lecture, or in office hours. Don't be shy to reach out to either professors or GSIs!

Accommodations for Students with Disabilities:
The purpose of academic accommodations is to ensure that all students have a fair chance at academic success. If you have Letters of Accommodations from the Disabled Students' Program or another authorized office, please share them with the professors as soon as possible, and we will work out the necessary arrangements. While individual circumstances can vary, requests for accommodations often fall into the categories listed on the Academic Calendar and Accommodations website (https://teaching.berkeley.edu/academic-calendar-and-student-accommodations-campus-policies-and-guidelines). The campus has well-developed processes in place for students to request accommodations, and you are encouraged to contact the relevant campus offices listed on the Academic Accomodations Hub (https://evcp.berkeley.edu/programs-resources/academic-accommodations-hub). These offices, some of which are confidential, can offer support, answer questions about your eligibility and rights, and request accommodations on your behalf, while maintaining your privacy.

Please inform us of any accommodations needed during the first two weeks of the course so that we can work out the necessary arrangements.

***Re-grading**:*
Regrades will be comprehensive for a full exam and requests should be limited to obvious mistakes in grading. In our experience, re-grades rarely result in an increased score, and may result in a lower overall score.

Academic Integrity and Cheating:
You are a member of an academic community at one of the world's leading research universities. You should keep in mind that as a member of the campus community, you are expected to demonstrate integrity in all academic endeavors and will be evaluated on your own merits. **The consequences of cheating and academic dishonesty—including a formal discipline file, possible loss of future internship, scholarship, or employment opportunities, and denial of admission to graduate school—are simply not worth it and may exceed student expectations.** For example, please be aware that, in addition to other consequences, any cheating found will result in loss of ability of the student to graduate with honors.
We know that most students are honest and do not cheat and our policy is designed to protect these students. **Thus, cheating of any type will not be tolerated**. UC Berkeley's cheating policy (http://bulletin.berkeley.edu/academic-policies/#studentconductappealstext) will be followed**.** Please note that although remote exams make it easier to cheat, they also make detection and documentation of cheating much easier. **If exams will have to be administered virtually, this will include safeguards to prevent cheating and measures to detect it.** Quizzes and midterms must be completed individually. Evidence that students have communicated information about these exams during or afterwards by any means will result in zeros for all parties involved and reporting to the Office of Student Conduct. If any other type of cheating is found, the student will automatically be assigned a zero for that test and the Office of Student Conduct will be notified. Our department has been proactive about detection of cheating and implementation of anti-cheating policies. As a result, hundreds of students have been referred to the Office of Student Conduct by MCB since the pandemic started.

Incompletes:
These requests are rarely granted and only for exceptional cases of prolonged illness or truly exceptional documented family emergencies, which extend over long periods of time. If an incomplete has been granted you can obtain an "I" Grade Report Form and instructions on their use MCB UG advising office.

Statement on Classroom Climate:
We are all responsible for creating a learning environment that is welcoming, inclusive, equitable, and respectful. We expect that professors, GSIs, and students all live up to this responsibility, even during vigorous debate or disagreement, and that we will intervene if exclusionary or harassing behavior occurs. If you feel that these expectations are not being met, you can consult your instructors or seek assistance from campus resources.

The classroom, lab, and workplace should be safe and inclusive environments for everyone. The Office for the Prevention of Harassment and Discrimination (OPHD) is responsible for ensuring the University provides an environment for faculty, staff and students that is free from discrimination and harassment on the basis of categories including race, color, national origin, age, sex, gender, gender identity, and sexual orientation. Questions or concerns? Call (510) 643-7985, email ask_ophd@berkeley.edu, or go to http://survivorsupport.berkeley.edu/Links_to_an external site.

LECTURE SCHEDULE

(please note that reading assignments have not been finalized and will be influenced by the faculty member teaching a class segment)

Lecture number	Lecture Title	Reading
1	Introduction into Drug Discovery and Development	Textbook p.11-14 "Drug discovery and development from 20,000 feet"
2	Target discovery – from GWAS studies to genetic screens	
3	Genetic target validation – the value of a knockout mouse	
4	**CASE STUDY: Statins and PSKC9**	
5	Properties of drug targets (tractability)	Textbook p. 156-176 "Classical targets in drug discovery"
6	Clinical context of drug targets	
7	R&D feasibility	
8	Assessing a competitive landscape	
9	**CASE STUDY: Covalent inhibitors of RAS** **Potential guest lecture: Ziyang Zhang (MTx faculty)**	Ostroem and Shokat, Direct small molecule inhibitors of KRas: from structural insights to mechanism-based design, *Nat. Rev. Drug Discovery* 2016
10	Chemical properties of small molecule drugs.	Textbook p.258-295 "SAR, pharmacophore"
11	From small molecules to induced proximity strategies: PROTACs	
12	Small molecule screening platforms (including DEL) **Potential guest lecture: Gwenn Hanson, CSO Nurix Therapeutics**	Textbook p. 186-199 "The language of screening: basic terms"
13	Review session – target identification, validation, small molecule targeting	
14	Differentiation of small molecules from antisense RNAs – properties and target space	
15	Comparison of small molecules and antibodies – the LYTAC approach	Carter and Rajpal, Designing antibodies as therapeutics, *Cell* 2022
16	When to use a small molecule and when an antibody? Considerations of drug development	
17	**CASE STUDY: targeting extracellular proteins** **Potential guest lecture: Jim Wells (Sunesis, UCSF)**	
18	Therapeutic modalities – designer proteins	
19	Therapeutic modalities – genome editing	Anzalone et al., Genome editing with CRISPR-Cas nucleases,

		base editors, transposases and prime editors, *Nat. Biotech.* 2020
20	Genome editing II - base editing	
21	CRISPR/Cas9 in diagnostics	
22	Genome editing – delivery methods	
23	**CASE STUDY: sickle cell anemia therapy** **Potential guest lecture: Jennifer Doudna (MTx faculty)**	Frangoul et al., CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia, *NEJM* 2022
24	Combined use of small molecules and gene editing: CarT/TILs	
25	**CASE STUDY: CarT in cancer (Nurix)**	
26	Review session: cell and genomic therapies	
27	Hit to lead development – medicinal chemistry and structure-based drug design	DeGoey et al., Beyond the Rule of 5: Lessons Learned from Abbvie's Drugs and Compound Collections, *J. Med. Chem.* 2019
28	Hit to lead development - AI	
29	PK/PD: absorption, distribution	Textbook: p. 309-362 "In vitro ADME and in vivo pharmacodynamics"
30	PK/PD: metabolism, excretion	
31	PK/PD: formulation	Textbook: p. 491-502 "Formulation"
32	**CASE STUDY: chemical chaperones/CFTR**	
33	Biomarkers	
34	IND	
35	Clinical trials	Textbook: p. 504-518 "Phase 1 clinical trials – phase 4 clinical trials"
36	Intellectual property	Textbook: p. 597-621 "Intellectual property and patents in drug discovery"
37	Drug failures: toxicology, resistance	Textbook p. 430-452 "Safety and toxicology"
38	Drug failures: mechanism (Biogen/Aduhelm)	
39	**CASE STUDY: From Thalidomide to PROTACs** **Potential guest lecture: Mary Matsikiela (former MCB postdoc), VP Neomorph**	
40	Review session: Hit to lead to clinic	