“Therapeutic Modalities” – Overview

This graduate level class is targeting graduate students within their first year in MCB. It is offered by the new Molecular Therapeutics (MTx) division in MCB.

It will meet twice per week for 90-minute lectures given by a faculty member of MTx. There will be no GSI-led discussion sessions or office hours. Classes will devote a significant segment to presentations by students. Each student will need to take part in **three** team presentations about papers chosen by the teaching faculty and submit **three** short “News & Views” articles about papers of their own choice.

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

“Therapeutic Modalities” - Syllabus

COURSE OVERVIEW

This class is designed to introduce graduate students to a range of therapeutic modalities that are in development or use. It will focus on small molecules, genomic therapies (including genome editing), and biologics. This class will present different applications of small molecules, RNA or DNA therapeutics, and biologics and discuss both advantages and challenges in their clinical use.

In addition to providing a firm foundation in the basic science leading to a modality’s discovery and development, this class will present relevant case studies and introduce students to fundamental questions in modern translational science:

* what was the original path towards a new therapeutic modality?
* what are a modality’s most frequent chances and shortcomings in the clinic?
* did a new medicine spur the development of next generation therapeutics?
  development?
* which diseases are not covered by currently available modalities?

Lectures are based on research papers that highlight the basics of a modality and critical aspects of its discovery and development, and where available, on papers describing the clinical track record of a modality. As part of each class, students will form teams to present concepts or case studies to their peers. When possible, guest speakers from academia or industry are invited to give first-hand accounts of important aspects of therapeutics discovery and development.

PREREQUISITES

For MCB students, MCB200 is a prerequisite for this class. Students outside of MCB should check with the head instructor whether they have the required background to follow this class most productively.

COURSE RESOURCES

Text:
All reading material (i.e. primary research papers and reviews) will be listed on bcourses. There is no textbook for this class.

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

Class participation:
Students are required to prepare by reading the assigned literature ahead of each class. If anything is unclear, please do not hesitate to reach out to the instructors 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.

Class presentations:
Each student in class will work in a team of typically three students to present a recent primary research paper within the topics of this class. This will be done in each 5-week block of class (i.e. three team presentations per semester). Teams will be formed and assigned to papers selected by the teaching faculty member in the first lecture of each 5-week block. A presentation typically takes ~20 minutes and is followed by a 5-10 minute discussion with the class. Each student on the team is expected to take responsibility for a part of the presentation.

Written assignments:
After each five-week block, students will compose a short "News and Views" article (one page, single spaced) about a recent primary research paper (published in a journal or on BiorXiv). Thus, there will be three papers that need to be submitted. The students choose their paper of interest. The format of their article should include a brief discussion of background, the major experiment and finding, and an outlook, all justifying why they selected their particular paper for this discussion.

COURSE MECHANICS

Grading:
Grades for this class will be based on the required presentation (40%), written assignments (40%), and participation (20%). There will be no midterms or finals. Students won't be able to make up missed work after the deadline unless they have a clear justification for an exception.

Lecture participation:
Participation can be achieved by asking questions during lecture, after lecture, or in office hours. Don't be shy to reach out to your professors!

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.

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

Lecture number	Lecture Title	Reading
1	Introduction into Therapeutic Modalities	
2	Small molecules – discovery by different screening modalities (high throughput, fragments, DEL, AI)	Sunkari et al., High-power screening (HPS) empowered by DNA-encoded libraries, *Trends Pharm.* 2022
3	Small molecules – target identification after small molecule discovery **CASE STUDY: Tacrolimus, Rapamycin**	Doench JG, Am I ready for CRISPR? A user's guide to genetic screens, *Nat. Rev. Gen.* 2018
4	Small molecules – overview: medicinal chemistry (from hit to lead to IND to clinical trials)	Hughes JP et al., Principles of early drug discovery, *Brit. Journ. Pharm.* 2010
5	Small molecules – overview: pharmacodynamics and pharmacokinetics	
6	Small molecules – from cellular toxins to targeted kinase inhibitors **CASE STUDY: Gleevec and 2nd generation SRC inhibitors**	
7	Small molecules – covalent inhibition **CASE STUDY: Ibrutinib, RAS^{G12C} inhibitors, Paxlovid**	Ostrem and Shokat: Direct small-molecule inhibitors of KRAS: from structural insights to mechanism-based design, *Nat. Rev. Drug. Disc.* 2016
8	Small molecules – induced proximity **CASE STUDY: PROTACs**	Bekes et al., PROTAC targeted protein degraders: the past is prologue, *Nat. Rev. Drug Disc.* 2022
9	Small molecules – chemical chaperones **CASE STUDY: LUMACAFTOR (CFTR)**	
10	Small molecules - combination therapy **CASE STUDY: HIV? Cancer?**	Huang et al., Synthetic lethality as an engine for cancer drug discovery, *Nat. Rev. Drug Disc.* 2020
11	Genomic therapies, part 1: nucleic acids targeting RNA, splicing modulation **CASE STUDY: Nusinersen (SMA)**	
12	Nucleic acids targeting RNA continued – lessons from antisense oligos against Huntington's Disease **CASE STUDY: Tomimersen (HD)**	Tabrizi et al., Potential disease-modifying therapies for Huntington's Disease: lessons learned and future opportunities, *Lancet Neurol.* 2022
13	Genomic therapies, part 2: DNA as medicine (classical gene therapy) **CASE STUDIES: Zolgensma, Luxturna**	

14	Gene therapy continued: hard lessons in retroviral gene therapy again X-SCID	
15	Genomic therapies, part 3: editing ex vivo **CASE STUDY: HbF elevation**	Anzalone et al., Genome editing with CRISPR-Cas nucleases, base editors, transposases and prime editors, *Nat. Biotech.* 2020
16	Editing ex vivo: cell therapy **CASE STUDY: CarT**	
17	Genomic therapies, part 4: editing in vivo **CASE STUDY: Intellia TTR (amyloidosis)**	Nishiga et al., The use of new CRISPR tools in cardiovascular research and medicine, *Nat. Rev. Cardio.* 2022
18	Editing in vivo continued: beyond the liver, epiediting	
19	Genomic therapies 2023: from disease to target to modality – principles and challenges	
20	Biologics – intro: from proteins to antibodies to cells	
21	Biologics – designer proteins **CASE STUDY: IL20 variants?**	Cao et al., Design of protein-binding proteins from the target structure alone, *Nature* 2022
22	Biologics – monoclonal and bispecific antibodies **CASE STUDY: SARS-CoV2**	Ma et al. (2021). Bispecific antibodies: from research to clinical application. Front. Immunol. 12: 626616.
23	Biologics – antibodies in oncology **CASE STUDY: Trastuzumab (Her2 antibody)**	Carter and Rajpal, Designing antibodies as therapeutics, *Cell* 2022
24	Biologics – vaccine development and use **CASE STUDY: HPV vaccine**	
25	Biologics – mRNA vaccines **CASE STUDY: Covid vaccines**	Barbier et al., The clinical progress of mRNA vaccines and immunotherapies, *Nat. Biotech.* 2022
26	Biologics – TILs	
27	Biologics – Cell replacement therapy, regenerative medicine, organ-on-a-chip	Wolf et al., Biomanufacturing human tissues via organ building blocks, *Cell Stem Cell* 2022
28	Biologics – challenges on the path to the clinic	