

Chemistry 765
Molecular Mechanisms of Human Disease
Fall 2019

Instructor:

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Course time: Tues/Thur, 5:30-6:45 pm in HH-218. Attendance is mandatory since the course has significant emphasis on discussion, in-class tutorials, and active learning.

Office hours:

E-mail me to make an appointment. I am happy to make an appointment with you, but please note I do not take walk-ins.

Textbooks:

No textbooks are required for this course. Instead, mandatory reading is in the form of scientific literature provided in PDF format through blackboard.

Other course materials:

We will be using Blackboard. You also need to download Pymol on your laptop. If you do not have a laptop, this is ok as you can use a computer lab for assignments and look on with a neighbor for in class tutorials. I will provide a laptop for class presentations.

Course details:

This class is capped at 20 students (historically we have opened this class up to 25 students). This is a graduate-level course, *but advanced Chemistry and Biology major undergraduates may enroll provided they meet the prerequisites and are comfortable reading primary scientific literature. Having had research experience is also beneficial.* In order to enroll in 600-700 level graduate level courses, an undergraduate senior must have completed a minimum of 90 units, with a GPA of 3.0 or better in their last 60 units.

Prerequisites – General Biochemistry CHEM 560 or CHEM 365, and CHEM 232 and 432 (or equivalent at previous institutions).

Course description – Students will probe the implications of altered enzymes from the catalytic and structural perspective to the physiological manifestations in the patient to understand the molecular mechanisms of cancer and HIV. We will study how diseases are therapeutically targeted and the mechanisms of drug resistance, explore the process of drug development from design to FDA approval, understand basic principles of pharmacology and kinetics, and navigate the science/business/ethics/promise of drug companies and therapeutics. Students will have extensive opportunity to explore the mechanistic features of disease, highlighting research techniques discussed in this class and in their own labs. Finally, students will research local biotech companies of interest to them through the lens of preparing for a job interview and/or considering financial investment. This course emphasizes active learning, critical discussion, hands-on tutorials, student-led learning, oral presentations, and career development/job preparation. Students interested in biotechnology, biochemistry, pharmacology, medicinal chemistry, pharmacology, enzymology, cancer biology, structural biology, drug regulatory processes, patent law, and/or bioethics will enjoy this course.

Learning objectives:

- 1) To think critically and argue/defend a point.
- 2) To critically read and evaluate primary scientific literature.
- 3) To examine the functional effects altered protein folding and/or activity can have and interpret the downstream consequences.
- 4) To use research tools like cBioPortal (<http://www.cbioportal.org/>), PDB (<http://www.rcsb.org/pdb/home/home.do>), Pymol (<https://www.pymol.org/>), and Pubmed (<https://www.ncbi.nlm.nih.gov/pubmed/>), and to understand theoretically and practically how important experimental methods like stopped-flow spectroscopy, rapid quench, computer-aided drug design, X-ray crystallography, and mass spectrometry can solve mechanistic problems.
- 5) To explain the basic features and challenges of drug design.
- 6) To design hypothesis-driven experiments to address questions in their own research.
- 7) To evaluate and orally present current research findings and challenges.
- 8) To have the tools to evaluate the biological functions at work in health and disease.
- 9) To help society in evaluating and disseminating accurate scientific information, and explore ethical issues in medicine and drug design.
- 10) To pose and answer important questions needed to prepare for a career or investing in biotech.

Resources available to students - The lectures and scientific articles are the primary resources for this course. Slides used in lectures will be posted in Blackboard. Make an appointment with the professor to ask questions about material you find confusing.

Participation – This includes active participation in in-class discussions, evaluating peers on their oral presentations, asking questions during lecture and student presentations, and attendance.

Assignments – More details will be provided in class. Assignments are due by the end of the day (11:59 pm) via email (csohl@sdsu.edu) by the assigned deadline. I will take assignments up to four days late, but I will take off 10 percentage points each day it is late. I will not accept assignments after four days, no exceptions.

Take home assignment: “Assessing FDA-approved drugs through the lens of a medicinal chemist”: You will select one active-site-binding, small molecule drug approved by the FDA in the previous year that has both typical “drug-like” features, and features that would fail Lipinski’s Rule of 5. Based on the molecular target and natural substrate, you will hypothesize how the drug interacts with the target. Undergraduates and graduate students will turn in this assignment.

Literature reading assignments: Of the assigned papers, graduate students will select THREE to perform a review. I strongly encourage you to read all the assigned papers. Please email me (csohl@sdsu.edu) a typed version of the form provided by the end of the day (11:59 pm) one day after the paper was assigned. This is to help you to distill complicated concepts down to a few key points. I will not accept literature reviews late – you instead simply need to pick a different paper. Undergraduate students taking this course will select TWO of the assigned papers to perform a literature review. One additional literature review can be submitted worth up to 2 percentage points.

Presentation #1: “Mechanisms of oncoproteins and tumor suppressors in cancer.” You will use Pubmed, cBioPortal, PDB, and Pymol to explore an assigned oncogene or tumor suppressor implicated in cancer. You will describe the molecular and physiological mechanisms of the protein and describe attempts to target it. You will teach the class about the structural and functional features of the protein, drug-like features of therapeutic interventions, challenges and consequences in targeting attempts, and any mechanisms of resistance to therapy. Your presentation slides are due on a specific date to me regardless of presentation order so that everyone will have the same deadline and cannot alter their talk after hearing others’

presentations. Undergraduate and graduate students will give a presentation.

Presentation #2: “Biotech startup due diligence: preparing for a job/investing in industry.”

You will research extensively one local (San Diego area) biotech start-up company of interest to you, reporting on their history/origin story, science, financing, and management/culture/compensation. You will also formulate three interview questions you’d ask as a potential interviewee, and advise the class whether we should invest in the company if/when it is publicly traded. Your presentation slides are due on a specific date to me regardless of presentation order so that everyone will have the same deadline and cannot alter their talk after hearing others’ presentations. Undergraduate and graduate students will give a presentation.

Grading –

Take home assignment: “Assessing FDA-approved drugs through the lens of a medicinal chemist”: 100 points

Literature reviews: 50 points total

Presentation #1: 100 points (75 points from professor evaluation of individual, 25 points from audience evaluation (average))

Presentation #2: 100 points (75 points from professor evaluation of individual, 25 points from audience evaluation (average))

Class participation: 100 points (participating in class discussion, judging and asking questions after student presentations). A percentage of effort-to-date will be shown on blackboard to prevent end-of-year surprises and encourage improvement.

Total points: 450

Grading scale – The course may be curved at my discretion using Z score values and standard deviations.

A = ≥ 92.5%

A- = 89.5-92.4%

B+ = 87.5-89.4%

B = 82.5-87.4%

B- = 79.5-82.4%

C+ = 77.5-79.4%

C = 72.5-77.4%

C- = 69.5-72.4%

D+ = 67.5-69.4%

D = 62.5-67.4%

D- = 59.5-62.4%

F < 59.4%

Expectations - I expect you to:

- 1) Attend lectures and actively participate in learning.
- 2) Help provide a positive and safe space for learning. This includes showing respect to your peers and me by not using cell phones, laptops, or other technology, or disrupting others by websurfing.
- 3) Make an appointment with me if you are needing help in the course.

Attendance and absences – Class attendance is mandatory. If you have a medical or other emergency that prevents you from completing an assignment on time, I need a note from your physician to allow you to turn in an assignment late. Otherwise you will lose points as described. If you have a conflict that requires you to present your individual presentation on a particular day, plan to fill out the doodle pool immediately after it opens to ensure you get your needed time/date. There are no make-ups for presentations.

Students with Disabilities - The University is committed to providing reasonable academic accommodation to students with disabilities. If you require accommodation, contact the Student Disability Services Office (or visit http://go.sdsu.edu/student_affairs/sds/) at (619) 594-6473. The instructor cannot provide any accommodations without prior consent of Student Disability Services.

Religious Observances - By the end of the first week of classes, students should notify me of any planned absences for religious observances. The student and I will work together to reasonably accommodate students who have notified in advance of absences for religious observances.

Statement on Cheating and Plagiarism – Basically, don't cheat, no exceptions! The University adheres to a strict [policy regarding cheating and plagiarism](http://studentaffairs.sdsu.edu/srr/conduct1.html) (<http://studentaffairs.sdsu.edu/srr/conduct1.html>). If you cheat, you will receive an F for the course, and you will be referred to the University for disciplinary measures. If you have questions on plagiarism, consult the [policy](http://www.sa.sdsu.edu/srr/conduct1.html) (<http://www.sa.sdsu.edu/srr/conduct1.html>). If you feel overwhelmed, make an appointment with the professor. Appreciate how cheating can ruin your bright future.

Syllabus is Subject to Change - This syllabus and schedule are subject to change. If you are absent from class, it is your responsibility to check on announcements made while absent.

The following schedule provides the topics, required readings, and important dates.

Date	Topic	Reading assignment	Assignments, due dates
8/27 #1	<u>Part I: Cancer</u> Brief cancer history, hallmarks of cancer		
8/29 #2	<u>Part I: Cancer</u> Cancer progression	Hanahan <i>Cell</i> 2011	Oncoproteins assigned for presentation #1
9/3 #3	<u>Part I: Cancer</u> Cancer metabolism: zoom out		
9/5 #4	<u>Part I: Cancer</u> Cancer metabolism: zoom in	Badur <i>Cell Rep</i> 2018	
9/10 #5	<u>Part I: Cancer</u> Methods of fighting cancer		
9/12 #6	<u>Part I: Cancer</u> Kinases: structure, function, druggability; x-ray crystallography	Müller <i>Nat Chem Bio</i> 2015	
9/17 #7	<u>Part I: Cancer</u> Case studies: Gleevec and erlotinib in kinase inhibition, TCGA/cbioportal	Paez <i>Science</i> 2004	Bring your laptop to class!
9/19 #8	<u>Part I: Cancer</u> Tutorial – using Pymol		Bring your laptop to class!
9/23: Email your slides to Dr. Sohl by 12pm; she will randomly assign a presentation order and assemble slides into a single powerpoint			
9/24	<u>Part II: In-class presentations:</u> Oncogenes and tumor suppressors		<i>Plan to stay late ~10 min</i>
9/26	<u>Part II: In-class presentations:</u> Oncogenes and tumor suppressors		<i>Plan to stay late ~10 min</i>
10/1	<u>Part II: In-class presentations:</u> Oncogenes and tumor suppressors		<i>Plan to stay late ~10 min</i>
10/3	<u>Part II: In-class presentations:</u> Oncogenes and tumor suppressors		<i>Plan to stay late ~10 min</i>
10/8	<u>Part II: In-class presentations:</u> Oncogenes and tumor suppressors		<i>Plan to stay late ~10 min</i>

10/10 #9	<u>Part III: Drug design and ethics</u> PK/PD, ADME basics	Vitaku <i>J Med Chem</i> 2014	
10/15 #10	<u>Part III: Drug design and ethics</u> SAR, features of a successful drug	Murcko <i>J Med Chem</i> 2018	Random assignment of case study group; read required reading by class on 10/17
10/17 #11	<u>Part III: Drug design and ethics</u> Patent law case study: BRCA	Required reading: your team's material, all group material, and ppt slides	Ensure you have read your assignment before coming to class!
10/22 #12	<u>Part III: Drug design and ethics</u> Ethics in clinical trials: the story of Vioxx	Ross <i>JAMA</i> 2008	
10/24 #13	<u>Part III: Drug design and ethics</u> Understanding and researching a drug company	Kneller <i>Nat Rev Drug Discov</i> 2010	Select your startup company for presentation #2
10/29 #14	<u>Part III: Drug design and ethics</u> Ethical minefield of oncology drug pricing	Scannell <i>Nat Rev Drug Disc</i> 2012	
10/31 #15	<u>Part III: Drug design and ethics</u> Superstars of year: neatest stories from this year's FDA approvals		
11/5 #16	<u>Part IV: Kinetics and HIV</u> Primer on basic kinetics and inhibition	Pollard <i>Mol Biol Cell</i> 2013 (problem set not necessary)	
11/7 #17	<u>Part IV: Kinetics and HIV</u> Primer on kinetics and inhibition, cont.		
11/12 #18	<u>Part IV: Kinetics and HIV</u> K_d , IC_{50} , K_i and other measurements		
11/14 #19	<u>Part IV: Kinetics and HIV</u> HIV infection, RT inhibition, resistance		
11/19 #20	<u>Part IV: Kinetics and HIV</u> Pre-steady-state kinetics: rapid chemical quench, stopped-flow spectroscopy	Kellinger <i>Proc Natl Acad Sci</i> 2010	
11/21	<u>No class today</u>		Take-home assignment due by the end of the day!
11/25: Email your slides to Dr. Sohl by 12pm; students will be presenting in reverse order from presentation 1, and she will combine slides into a single powerpoint			
11/26	<u>Part V: In-class presentations</u> Industry due diligence		
11/28	No class, Happy Thanksgiving!		
12/3	<u>Part V: In-class presentations</u> Industry due diligence		
12/5	<u>Part V: In-class presentations</u> Industry due diligence		
12/10	<u>Part V: In-class presentations</u> Industry due diligence		
12/16, 3:30- 5:30pm	<u>Part V: In-class presentations</u> Industry due diligence (Final exam day; use as extra time for presentations)		