Chemistry 763
Cellular Regulation: Molecular Mechanisms of Human Disease
Spring 2017

Instructor:
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Course time: Tuesdays and Thursdays, 2-3:15 pm in EBA 444. Some class periods will be meeting in GMCS 245 computer lab (see schedule below). Attendance is mandatory since the course has significant emphasis on in-class tutorials, active learning, and discussion.

Office hours:
3:30-4:30 pm. Thurs., or e-mail to make an appointment.

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

Other course materials:
We will be using Blackboard. We will be using the CHEM department computer lab extensively both for in class work and for your assignments. These computers will have Pymol, MOE, and Kintek Explorer pre-loaded.

Course details:
This class is capped at 20 students. This is a graduate-level course, but advanced Chemistry and Biology major undergraduates may enroll provided they meet the prerequisites.

Prerequisites – General Biochemistry CHEM 560 or CHEM 365, and CHEM 232 and 432

Course description – We will explore the biochemical basis of diseases, focusing primarily on cancer, HIV, and prion-related disorders, and the research tools laboratories use to understand the molecular mechanisms of disease. Students will probe the implications of altered proteins from the catalytic or structural effect to the physiological manifestations in the patient. How diseases are therapeutically targeted and the mechanisms of the development of resistance to these drugs will also be addressed. Students will have extensive opportunity to explore the mechanistic features of diseases they find interesting, and to explore how the presented experimental methods can enrich their own research. This course emphasizes active learning, student-guided and student-led learning, and critical discussion. While this is a graduate level course, advanced undergraduate students may also take this course provided prerequisites are met.

Learning objectives:

1) To critically read and evaluate primary scientific literature.
2) To examine the functional effects altered protein folding and/or activity can have and interpret the downstream consequences.
3) To use research tools like The Cancer Genome Atlas (TCGA), PDB, Pymol, MOE, and kinetic fitting software; and to understand theoretically and practically how important experimental methods like stopped-flow spectroscopy, rapid quench, X-ray crystallography, mass spectrometry, and CRISPR-Cas9 can solve mechanistic problems.

4) To explain the basic, biochemically-focused features and challenges of drug design.
5) To design hypothesis-driven experiments to address questions in their own research.
6) To evaluate orally current research findings and challenges.
7) To have the tools to evaluate the biological functions at work in health and disease.
8) To help society in evaluating and disseminating accurate scientific information.

Resources available to students - The lectures and scientific articles are the primary resources for this course. Most slides used in lectures will be posted in Blackboard. Make use of office hours to ask questions about material you find confusing.

Participation – This includes active participation in in-class discussions, contributing meaningfully (i.e. evidence of critical thinking) on each paper in blackboard discussions, asking questions during lecture and student presentations, and attendance. Points will be updated during the semester so you have regular feedback of your performance.

Movie nights – Movie nights are an opportunity to watch a film exploring different perspective on diseases we're learning about in class. They are fully optional, and not attending will not affect your ability to complete any graded material in any way. Locations are on campus, TBD.

Assignments – More details will be provided in class.
Assignment 1: You will use cBioPortal, PDB, and Pymol to explore an enzyme mutation in a kinase likely implicated in cancer. You will use the primary literature to assess the likely driver or passenger status of this mutation, and propose three experiments to further explore the mutation.
Assignment 2: You will select 2 active-site-binding drugs currently approved by the FDA that have both typical "drug-like" features, and features that would fail Lipinksi's Rule of 5. Based on the molecular target and natural substrate, you will hypothesize how the drug interacts with the target.

Literature reading – For each assigned paper, you will email me (csohl@mail.sdsu.edu) a typed version of the form provided in class by the end of the day (11:59 pm) the paper was assigned. This is to help you focus your reading and distill complicated concepts down to a few key points.

Presentations – More details will be provided in class.
Presentation 1: You will develop a hands-on Pymol-based tutorial on an NNRTI targeting HIV reverse transcriptase. You will teach the class about the molecular interactions and resistance by guiding them through your active learning tutorial, and describe the pre-steady-state kinetics associated with incorporation.
Presentation 2: You will find an enzyme that has successfully targeted therapeutically for a disease of your choice. You will teach the class about the structural and molecular features of the target and the physiological implications.

Grading –
Assignment 1: 150 points
Assignment 2: 200 points
Assignment 3: 200 points
Literature reading: 200 points
Presentation 1 (group): 150 points (100 points from professor evaluation of individual, 25 points from audience evaluation of group (average), 25 points from fellow group member evaluation (average))
Presentation 2 (individual): 250 points (200 points from professor evaluation, 50 points from audience evaluation (average))
Total points: 1150

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) Read the assigned material before coming to class in order to participate in class discussion. You may find you need to re-read the material after class.
2) Attend lectures and actively participate in learning.
3) Help provide a positive and safe space for learning. This includes showing respect to your peers and I, and not using cell phones or disrupting others by websurfing.
4) Seek help during office hours as needed.

Attendance and absences – Class attendance is mandatory. If you are going to miss a class day and have a valid excuse, I need to know at least 1 week in advance (with the exception of documented medical or other emergencies to be assessed at my discretion). Come and see me AND email me so I have written record of this. You are required to provide a written excuse from the Office of Student Life. Late assignments will not be accepted.

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 second week of classes, students should notify the instructors of any planned absences for religious observances. The student and instructor will work together to reasonably accommodate students who have notified in advance of planned 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). 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). If you feel overwhelmed, come to office hours. 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
1/19 #1	Part I: Kinases and cancer Brief cancer history, hallmarks of cancer	Hanahan *Cell* 2000; Hanahan *Cell* 2011	
1/24 #2	Part I: Kinases and cancer Cancer progression	Al-Hajj *PNAS* 2003	
Wed 1/25, 7 pm: OPTIONAL movie night -- Cancer: The Emperor of All Maladies (2 h) GMCS 325			
1/26 #3	Part I: Kinases and cancer Primer on cancer therapies	Robert *NEJM* 2014	Assignment 1 assigned
1/31 #4	Part I: Kinases and cancer Kinases, EGFR mutations, therapy and resistance, X-ray crystallography	Schwaederle *Mol Can Ther* 2015	
2/2 #5	Part I: Kinases and cancer Tutorial – using Pymol to explore structure, TCGA/cbioportal	Yun *Canc Cell* 2007	***Note: class meeting in computer lab!***
2/7 #6	Part I: Kinases and cancer Guest Lecturer: Prof. Jeff Gustafson Selectivity filters in kinase drug design	Müller *Nat Chem Bio* 2015	
2/9 #7	Part II: Drug design PK/PD, ADME basics, HTS	Vitaku *J Med Chem* 2014	Assignment 1 due at the beginning of class
2/14 #8	Part II: Drug design SAR, features of a successful drug	Leeson *Nat Rev Drug Disc* 2007	Assignment 2 assigned
2/16 #9	Part II: Drug design Guest Lecturer: Prof. David Hecht MOE/Molecular docking	Hecht *Curr Comp Aided Drug Des* 2009	***Note: class meeting in GMCS 245 computer lab!***
2/21 #10	Part II: Drug design Primer on basic kinetics and inhibition	Pollard *Mol Biol Cell* 2013	
2/23 #11	Part II: Drug design K_d, IC_{50}, K_i and other measurements	Fallahi-Sichani *Nat Chem Biol* 2013	
2/28 #12	Part III: Reverse transcriptase and HIV HIV infection, RT inhibition, resistance	Ray *Antiv Chem Chemo* 2003	
Tues 2/28, 7 pm: OPTIONAL movie night – And the Band Played On (141 min) GMCS 325			
3/2 #13	Part III: Reverse transcriptase and HIV Pre-steady-state kinetics: rapid chemical quench, stopped-flow spectroscopy	Kellinger *PNAS* 2010	Part IV groups assigned
3/7	Class not formally meeting; take the opportunity to work on group presentations	Das *Prog Biophys* 2004	Email me your chosen NNRTI and PDB code by 5pm (no duplicates!)
3/9	Class not formally meeting; take the opportunity to work on group presentations	Chatterjee *Bioorg Med Chem* 2014	Email your PDB code to the class so all can download files
3/14 #14	Part III: Reverse transcriptase and HIV Tutorial: Global fitting	Singh *JBC* 2012	***Note: class meeting in GMCS 245 computer lab!*** Part IV groups assigned
3/16	Part IV: Exploring molecular targets Class presentations	TCGA *Nature* 2008	***Note: class meeting in GMCS 245 computer lab!***
3/21	Part IV: Exploring molecular targets Class presentations	Hu *J Med Chem* 2014	***Note: class meeting in GMCS 245 computer lab!***

3/23	Part IV: Exploring molecular targets Class presentations	Liao, Nat Comm 2015 (you will help present on this!)	***Note: class meeting in GMCS 245 computer lab!*** Assignment 2 due at the beginning of class
3/28	Spring Break		
3/30	Spring Break		
4/4 #15	Part III: Reverse transcriptase and HIV cont. CRISPR/Cas9 as potential therapy	Wang *Cell Rep* 2016	
4/6 #16	Part V: Prion diseases Survey of protein aggregate diseases	Stöhr *Proc Natl Acad Sci* 2008	
4/11 #17	Part V: Prion diseases Mass spectrometry, proteomics, metabolomics	Shi *Mol Cell Prot* 2015	
4/13 #18	Part V: Prion diseases Understanding prion diseases with mass spectrometry, including HDX	Graham *J Prot Res* 2016	
Thurs 4/13, 7 pm: OPTIONAL movie night – Double feature – Kuru: The Science and The Sorcery and Dying to Sleep (1.5 h total) GMCS 325			
4/18	Part VI: Exploring molecular targets Class presentations	Lovering *J Med Chem* 2009	
4/20	Part VI: Exploring molecular targets Class presentations	Anderson *Methods* 2010	
4/25	Part VI: Exploring molecular targets Class presentations	Turski *Mol Canc Thera* 2016	
4/27	Part VI: Exploring molecular targets Class presentations	Schwaederle *Mol Canc Thera* 2016	
5/2	Part VI: Exploring molecular targets Class presentations	Doussineau *Angewandte* 2016	
5/4	Part VI: Exploring molecular targets Class presentations	Macarron *Nat Rev Drug Disc* 2011	