Chemistry 765
Molecular Mechanisms of Human Disease
Fall 2017

Instructor:
Dr. Christal Sohl, Ph.D.
Department of Chemistry and Biochemistry
Office: CSL 328
Phone: 619-594-2053
Email: csohl@mail.sdsu.edu

Course time: Mondays and Wednesdays, 5:30-6:45 pm in GMCS 327. Attendance is mandatory since the course has significant emphasis on in-class tutorials, active learning, and discussion.

Office hours:
E-mail 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.

Other course materials:
We will be using Blackboard. You also need to download Pymol and Kintek Explorer on your laptop. If you do not have a laptop, this is ok. You will need to use a computer lab for assignments.

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 and are very comfortable reading primary scientific literature.

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.

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 cBioPortal (http://www.cbioportal.org/), PDB (http://www.rcsb.org/pdb/home/home.do), Pymol (https://www.pymol.org/), and KinTek Explorer (https://kintekcorp.com/software/), and to understand theoretically and practically how important experimental methods like stopped-flow spectroscopy, rapid quench, computer-aided drug design, X-ray crystallography, mass spectrometry, and CRISPR-Cas9 can solve mechanistic
4) To explain the basic 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. 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, contributing meaningfully (i.e. evidence of critical thinking) on each paper in blackboard discussions, asking questions during lecture and student presentations, and attendance.

Assignments – More details will be provided in class. All assignments are due by the end of the day (11:59 pm) via email (csohl@mail.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.

Assignment 1, “Exploring kinase structure and function”: You will use cBioPortal, PDB, and Pymol to explore a kinase implicated in cancer. You will assess the consequences of altered function and describe attempts to target the protein.
Assignment 2, “Assessing FDA-approved drugs through the lens of a medicinal chemist”: You will select active-site-binding drugs currently approved by the FDA this year that have 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.

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) one day after the paper was assigned. This is to help you to distill complicated concepts down to a few key points. I will accept literature reviews up to four days late, but you will lose 5 percentage points each day it is late. I will not accept lit reviews after four days, no exceptions. Undergraduate students taking this course will select 4 of the assigned papers and perform literature reviews for these only.

Individual Presentation: You will choose an enzyme that has been successfully targeted therapeutically for a disease of your choice. It is ok to have more than one presentation on the same disease. You will teach the class about the structural and physiological features of the target, drug-like features of your inhibitor, consequences of inhibition, and any mechanisms of resistance.

Grading –
Assignment 1 “Identify and explore enzyme mutations”: 150 points
Assignment 2 “Assessing FDA-approved drugs through the lens of a medicinal chemist”: 150 points
Literature reading: 150 points
Presentation (individual): 150 points (100 points from professor evaluation of individual, 50 points from audience evaluation (average))
Total points: 600

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%
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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 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, 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.

<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
<th>Reading assignment</th>
<th>Assignments, due dates</th>
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<tbody>
<tr>
<td>8/28</td>
<td>#1</td>
<td>Part I: Cancer</td>
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<td>Brief cancer history, hallmarks of cancer</td>
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<tr>
<td>8/30</td>
<td>#2</td>
<td>Part I: Cancer</td>
<td>Hanahan <em>Cell</em> 2011</td>
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<td>Cancer progression</td>
<td>Kinases randomly assigned for HW 1</td>
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<tr>
<td>9/4</td>
<td>#3</td>
<td><em>Happy Labor Day! No Class!</em></td>
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<td>Date</td>
<td>Week</td>
<td>Topic</td>
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| 9/6  | #4   | Part I: Cancer  
The role of altered metabolism in cancer |
| 9/11 | #5   | Part I: Cancer  
Tools to understand and target altered metabolism in cancer  
Robert *NEJM* 2014 |
| 9/13 | #6   | Part I: Cancer  
Methods of fighting cancer |
| 9/18 | #7   | Part I: Cancer  
Kinases: structure, function, druggability; x-ray crystallography |
| 9/20 | #8   | Part I: Cancer  
Case studies: Gleevec and erlotinib in kinase inhibition, TCGA/cbioportal  
Müller *Nat Chem Bio* 2015 |
| 9/25 | #8, cont. | Part I: Cancer  
Tutorial – using Pymol  
Bring your laptop to class! |
| 9/27 | #9   | Part I: Cancer  
Pymol tutorial, cont.  
Bring your laptop to class! |
| 10/2 | #10  | Part II: Kinetics and drug design  
PK/PD, ADME basics  
Vitaku *J Med Chem* 2014 |
| 10/4 | #11  | Part II: Kinetics and drug design  
SAR, features of a successful drug |
| 10/9 | #12  | Part II: Kinetics and drug design  
In silico drug design and optimization, CADD  
Ross *JAMA* 2008 |
| 10/11 | #13  | Part II: Kinetics and drug design  
Ethics in clinical trials: the story of Vioxx |
| 10/16 | #14  | Part II: Kinetics and drug design  
Ethical minefield of oncology drug pricing  
Assignment 1 due by the end of the day! |
| 10/18 | #15  | Part II: Kinetics and drug design  
Superstars of 2017: neatest stories from this year’s FDA approvals  
Pollard *Mol Biol Cell* 2013 |
| 10/23 | #16  | Part II: Kinetics and drug design  
Primer on basic kinetics and inhibition |
| 10/25 | #17  | Part II: Kinetics and drug design  
Primer on kinetics and inhibition, cont |
| 10/30 | #18  | Part II: Kinetics and drug design  
Kd, IC50, Ki and other measurements |
| 11/1 | #19  | Part III: Reverse transcriptase and HIV  
HIV infection, RT inhibition, resistance |
| 11/6 | #20  | Part III: Reverse transcriptase and HIV  
Pre-steady-state kinetics: rapid chemical quench, stopped-flow spectroscopy |
| 11/8 | #21  | Part III: Reverse transcriptase and HIV  
Tutorial: Global fitting  
Liao *Nat Comm* 2014  
Bring your laptop to class! |
| 11/13 | #22  | Part III: Reverse transcriptase and HIV  
CRISPR/Cas9 as potential therapy |
| 11/15 | #23  | Part V: Prion diseases  
Survey of protein aggregate diseases |
| 11/20 | #24  | Part V: Prion diseases  
Proteomics and metabolomics: the  
Doussineau *Angewandte* 2016  
Assignment 2 due by the end of the day! |
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<tr>
<th>Date</th>
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<tbody>
<tr>
<td>11/22</td>
<td><strong>Happy Thanksgiving! No Class!</strong></td>
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<tr>
<td>11/27</td>
<td>Part V: Prion diseases</td>
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<td>Understanding prion diseases with mass spectrometry, including HDX</td>
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<td>11/29</td>
<td>Part VI: Exploring molecular targets</td>
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<td>Class presentations</td>
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<td>12/4</td>
<td>Part VI: Exploring molecular targets</td>
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