Course Syllabus – TRBIO 450

Course Information

Course Number: TRBIO 450 WI22
Course Name: Drug Discovery and Development
Term: WI 2022
Start Date: 01/03/2022
End Date: 03/25/2022
Credits: 3.0

Meeting Days / Times

Mondays and Wednesdays, 11:30am-1:00pm PT / 2:30-4:00pm ET
(See Calendar in Canvas for the most up-to-date schedule.)

Locations

CA Campus: Graduate Dining Room (Hazen Theory Building)
FL Campus: C304
Online via Zoom

Course Managers

Role	Last Name	First Name	Email Address
Instructor	Scampavia	Louis	scampl@scripps.edu
Instructor	Spicer	Timothy	spicert@scripps.edu
TA	Garabedian	Brett	bgarabedian@scripps.edu
TA	Massey	Lynee	lynee@scripps.edu

Course Description

Drug discovery is the process by which new candidate medications are ascertained and this course will review the processes through which potential new therapeutics are identified. This includes the description of the roles played by a wide-range of scientific disciplines, including biology, chemistry, in vitro/in vivo pharmacology, drug metabolism, pharmacokinetics, and ADME/Tox; all needed in the early drug discovery process. This course will survey the complexity of the drug discovery pipeline path involving a dynamic interaction between academia, industry, patent law and regulatory compliance needed to advance new medicines toward clinical trials. A discussion of methods/technologies used as well as historical case studies will provide an overview into biomedical investigational techniques, pharmacological studies and the medicinal chemistry development that is needed to drive the translational drug discovery process.

Modern drug discovery concepts will be reviewed including:

- Target ID
- Target Validation
- Assay Development
- Screening technologies
- Hit to Lead (H2L)
- Lead Identification
- Lead Optimization
- Candidate Selection
- Pre-clinical
- Clinical

Concepts in pharmacology will be reviewed including:

- DPMK: Drug Metabolism and Pharmacokinetics
- ADME-Tox: Absorption, distribution, metabolism, excretion and toxicity
- Dose Response Relationships and Therapeutic window

The multidisciplinary approach of drug discovery and development will be reviewed including the role of:

- Biomedical Investigators
- Pharmacologists
- Medicinal Chemists
- Safety Assessment

Screening and Design will be covered including:

- Natural products and small molecule screening
- Biologics
- High Throughput Screening (HTS)
- Virtual *in silico* screening
- Fragment-based screening
- Combinatorial library screening (i.e. DEL: DNA Encoded Libraries)

Program Learning Outcomes

By the end of the program, students will have accomplished these objectives:
PLO1: Original Research – graduate students are expected to develop the skills critical for generating high-quality research output. This would include absorbing, recalling, and contextualizing scientific knowledge, evaluating scientific information and data, creating testable hypotheses and investigating hypotheses, mastering scientific tools and techniques, displaying ethical behavior, and receiving and giving feedback.
PLO2: Communication – graduate students are expected to demonstrate the oral, written, and media skills to effectively communicate the impact of a study or a body of work to the greater scientific community and to the public at large using a number of methods.
PLO3: Critical Thinking – graduate students are expected to develop a self-directed process to analyze information, form opinions or judgments, and use this process to improve the quality of their scientific thoughts, navigate problems, and make informed decisions.
PLO4: Intellectual Curiosity – graduate students are expected to acquire the capacity to build their intellectual curiosity and demonstrate problem solving approaches that serve their professional growth and ability to impact a field.
PLO5: Career and Professional Development – graduate students are expected to develop a variety of transferable skillsets throughout their graduate experience, including management and leadership, inclusiveness, resilience, scientific rigor, collaboration, accountability, time management, teamwork, networking, and career planning.

Course Learning Outcomes

Upon completion of this course students will be able to:
CLO1: Demonstrate knowledge of the process through which potential new therapeutics are identified.
CLO2: Demonstrate an understanding of important drug discoveries.
CLO3: Demonstrate an understanding of pharmacology concepts including: DMPK, ADME/ TOX , dose response and therapeutic window relationships.
CLO4: Demonstrate knowledge of modern drug discovery techniques and methodologies.
CLO5: Demonstrate understanding of the complex multidisciplinary approach required to develop drugs.
CLO6: Understand and identify approaches to screening and design.
CLO7: Present advanced knowledge in order to demonstrate understanding of drug discovery and development.

Background Preparation (Prerequisites)

Exposure to one or more of the following courses is helpful, but not required:

- Molecular Biology
- Cell Biology
- Medicinal Chemistry

Course Materials

Required reading will be generated by selecting current journal articles from instructors that exemplify the subject matter of each lecture.

Useful to Consult: Sittampalam, editor (2019). *Assay Guidance Manual*.
Useful to Consult: Online publication from Eli Lilly & Company and the National Center for Advancing Translational Sciences. Bookshelf ID: NBK53196PMID: 22553861.
https://www.ncbi.nlm.nih.gov/books/NBK53196/

Expectations and Logistics

It takes over 10 years and $1 billion to develop a new medicine. This course will explore the concepts behind the drug discovery process and will describe some of the key concepts involved in early stage drug discovery drawing on examples from current pharmaceuticals. The course will start with a brief historical overview of drug discovery. We will then explore the process of selecting a disease and a biological target. Discussion on how advances in biology have transformed our thinking about drug targets. There will then be a general consideration of the different classes of drug targets, with a particular focus on G protein coupled-receptors (GPCRs) and Kinases. We will also explore the different classes of drugs designed to interact with these drug targets and explain the mechanisms of their biological activity. We will discuss the properties required of a drug and show how chemists discover the starting points for drug development, highlighting the importance of protein biochemistry, structural biology and synthetic organic chemistry.

Modern drug discovery utilizes a screening cascade consisting of a range of assays designed to probe whether a given compound meets different aspects of the drug profile. We will explore these different assays; the distinction between a research tool compound and a molecule that can be developed into a drug will be explained. This will introduce topics such as toxicity, metabolism, and clearance. One of the major ways to initiate a drug discovery project is to carry out a screen of small molecules against the drug target. This process often referred to as HTS, will be outlined. The strengths and weaknesses of this approach will be explored briefly. The concepts of chemical space and molecular diversity will be outlined.

There will then be an outline description of the later stages of the drug discovery process, Intellectual property, Regulatory bodies etc. What is involved in clinical trials? How long do they take?

Attendance Statement

Students are expected to attend all classes. Students who are unable to attend class must seek permission for an excused absence from the course director or teaching assistant. Unapproved absences or late attendance for three or more classes may result in a lower grade or an "incomplete" for the course. If a student has to miss a class, he or she should arrange to get notes from a fellow student and is strongly encouraged to meet with the teaching assistant to obtain the missed material.

Scientific and Professional Ethics

The work you do in this course must be your own. Feel free to build on, react to, criticize, and analyze the ideas of others but, when you do, make it known whose ideas you are working with. You must explicitly acknowledge when your work builds on someone else's ideas, including ideas of classmates, professors, and authors you read. If you ever have questions about drawing the line between others' work and your own, ask the course professor who will give you clear guidance. Exams must be completed independently. Any collaboration on answers to exams, unless expressly permitted, may result in an automatic failing grade and possible expulsion from the Graduate Program.

Technology Requirements and Support

For issues related to Canvas, please contact the Graduate Office by email at: gradprgm@scripps.edu or by phone at: 858-784-8469.

Course Grading

Grading is in accordance with the academic policies of the Skaggs Graduate School. The breakdown of grading is as follows:

- Participation**:** 10%
- Assignments/critiques**:** 40%
- Midterm Exam**:** 25%
- Final Exam**:** 25%

Letter Grade	Percent	GPA	Description
A	93-100	4.00	Outstanding achievement. Student performance demonstrates full command of the course subject matter and evinces a high level of originality and/or creativity that far surpasses course expectations.
A-	90-92	3.67	Excellent achievement. Student performance demonstrates thorough knowledge of the course subject matter and exceeds course expectations by completing all requirements in a superior manner.
B+	87-89	3.33	Very good work. Student performance demonstrates above-average comprehension of the course subject matter and exceeds course expectations on all tasks as defined in the course syllabus. There is notable insight and originality.
B	83-86	3.00	Satisfactory work. Student performance meets designated course expectations and demonstrates understanding of the course subject matter at an acceptable level.

B-	80-82	2.67	Marginal work. Student performance demonstrates incomplete understanding of course subject matter. There is limited perception and originality.
C+	77-79	2.33	Unsatisfactory work. Student performance demonstrates incomplete and inadequate understanding of course subject matter. There is severely limited or no perception or originality. Course will not count toward degree.
C	73-76	2.00	Unsatisfactory work. Student performance demonstrates incomplete and inadequate understanding of course subject matter. There is severely limited or no perception or originality. Course will not count toward degree.
P	73-100	0.00	Satisfactory work. Student performance demonstrated complete and adequate understanding of course subject matter. Course will count toward degree.
F	0-72	0.00	Unacceptable work/Failure. Student performance is unacceptably low level of knowledge and understanding of course subject matter. Course will not count toward degree. Student may continue in program only with permission of the Dean.
I		0.00	Incomplete is assigned when work is of passing quality but is incomplete for a pre-approved reason. Once an incomplete grade is assigned, it remains on student's permanent record until a grade is awarded.
W		0.00	Withdrew from the course with Dean's permission beyond the second week of the term.

- All courses will be recorded and maintained in the student's permanent academic record; only courses that apply towards the degree will appear on the academic transcript. Non-credit or audited courses will not appear on the transcript.
- 4 core courses taken for a letter grade (pass = B- or higher for a core course)
- 2 elective courses taken pass/fail (pass = A, B, C for an elective)

Because students are encouraged to take electives outside their area of expertise, a "C" letter grade is passing.

Course Schedule:

Date	Details
Mon Jan 3, 2022	Introduction and Overview to Drug Discovery (Scampavia)
Wed Jan 5, 2022	Modern Drug Discovery Techniques (Spicer)
Mon Jan 10, 2022	Assay Development (Spicer)
	Assignment-1 (AD)
Wed Jan 12, 2022	HTS Chemistry (Scampavia)
Mon Jan 17, 2022	No Class (Martin Luther King Jr. Day)
	Assignment-2 (DB mining)
Wed Jan 19, 2022	Screen, validation and characterization of small molecules against HIV (Valente)
Mon Jan 24, 2022	Biologics in Drug Discovery (Huang)
Wed Jan 26, 2022	Drug metabolism and pharmacokinetics (DMPK) Part 1 (Cameron)
Mon Jan 31, 2022	Evaluation of ADME/Tox Drug Properties in Drug Development Part 2 (Cameron)
	Assignment-3 (DMPK)
Wed Feb 2, 2022	Medicinal Chemistry-I: Drug Design Basics (Bannister)
Mon Feb 7, 2022	Medicinal Chemistry-II: Guiding Principles, Strategies and Case Study (Bannister)
	Assignment-4 (MedChem)
Wed Feb 9, 2022	Midterm Exam
Mon Feb 14, 2022	Cure for Cancer – Drug Discovery Challenges and Opportunities (Janiszewska)
Wed Feb 16, 2022	Cure for Cancer – Journal Club (Janiszewska)
Mon Feb 21, 2022	No Class (President's Day)
	Assignment-5 (Cancer)
Wed Feb 23, 2022	Key Concepts in Pharmacology (Stahl)
Mon Feb 28, 2022	Exploiting non-traditional GPCR (Martemyanov)
Wed Mar 2, 2022	Drug discovery case study from HTS to clinical trials (Niswender)
Fri Mar 4, 2022	Assignment-6 (GPCR)
Mon Mar 7, 2022	RTK inhibitors (Haley)
Wed Mar 9, 2022	Brain cell-centric phenotypic screening (Rumbaugh)
Mon Mar 14, 2022	Physiologically relevant assay development for allosteric drug targets (Nettles)
	Assignment-7 (Neuron)
Wed Mar 16, 2022	Target ID, Validation and Drug Discovery (Parker)
	Assignment-8 (Due Mar-21)
Mon Mar 21, 2022	Biophysical Methods in Drug Discovery (Kojetin)
	Assignment-8 (Target-ID)
Wed Mar 23, 2022	Final Exam