

**Principles of Drug Design**  
**16:663:502 (3 credits – graduate students)**  
**30:715:452 (3 credits – Pharmacy students)**

**Spring 2010**  
**Time: F 3:00 - 6:00 pm**  
**Place: Pharmacy 007**

**Course Description:**

The *Principles of Drug Design* course aims to provide students with an understanding of the process of drug discovery and development from the identification of novel drug targets to the introduction of new drugs into clinical practice. It covers the basic principles of how new drugs are discovered with emphasis on lead identification, lead optimization, classification and kinetics of molecules targeting enzymes and receptors, prodrug design and applications, as well as structure-based drug design methods. Recent advances in the use of computational and combinatorial chemistry in drug design will also be presented. The course is further enhanced with invited lectures on recent developments and applications of drug design principles in the pharmaceutical industry.

**Course Instructors/Invited Speakers:**

- Dr. Longqin Hu (Course coordinator)
- Dr. David Kimball
- Dr. John Kerrigan (CINJ)
- Dr. Qun Sun (Discovery ChemScience)
  
- Dr. Zhoupeng Zhang (Merck)
- Dr. David Floyd (Rutgers, Pharmacopeia, BMS)
- Dr. Ashwinikumar Gavai (BMS)
- Dr. Louis Lombardo (Roche)
- Dr. Robert Borzilleri (BMS)
- Dr. Christopher Molloy (Interim Provost and Professor, Rutgers)

**Course Material:**

Handouts, Class Lectures, Seminars, and Computational Labs

**Course Website:**

<http://medchem.rutgers.edu/drugdesign/>  
<https://sakai.rutgers.edu/portal/site/76f26a9b-9c3d-4917-bb69-01fd2402c572>

**Examinations:**

Term paper and project, and two exams

**Grading:**

Term paper on a drug target with 5 drug design principles	<b>20%</b>
Computational project(s)	<b>20%</b>
Exam 1 on approaches to drug discovery (analog design), enzymes, receptors, prodrugs, and seminars	<b>30%</b>
Exam 2 on computational, combinatorial chemistry, and seminars	<b>30%</b>
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Total	<b>100%</b>

16:663:502 and 30:715:452  
***Principles of Drug Design***  
Instructor and course coordinator: Longqin Hu

***Tentative Course Outline***

I.	Introduction to The Drug Discovery/Development (Hu)	1 lecture	BMC Chp 2 p1-36 and Chp 9 p251-300
	A. Drug Discovery		
	B.. Drug Development		
	C.. Source of Drugs		
	D. Structural effects on drug action		
II.	Approaches to New Drug Discovery (Hu)	2 lectures	BMC Chp 19 p783-802 MCP Chp 13-14 p189-225
	A. Drugs Derived from Natural Products		
	B. Existing Drugs as a Source for New Drug Discovery		
	C. Using Disease Models as Screens for New Drug Leads		
	D. Physiological Mechanisms: the Modern “Rational Approach” to Drug Design		
	E: Approaches to Lead Optimization		
	1. Bioisosteric replacement		
	2. Conformation restriction		
	a. Increase selectivity		
	b. Increase affinity		
	3. Pharmacophore		
	4. Molecular dissection		
	5. Metabolic stabilization		
III.	Enzymes as Targets of Drug Design (Kimball)	2 lectures	BMC Chp 18 p733-782
	A. Enzyme kinetics (Kimball)		
	B. Enzyme inhibition and activation (Kimball)		
	C. Approaches to the Rational Design of Enzyme Inhibitors (Kimball)		

IV. Receptors as Targets of Drug Design (Kimball)	2 lectures	BMC Chp 11 p349-397
<ul style="list-style-type: none"> <li>A. Receptor Theory</li> <li>B. Receptor Complexes and Allosteric Modulators</li> <li>C. Second and Third Messenger Systems</li> <li>D. Molecular Biology of Receptors</li> <li>F. Receptor Models and Nomenclature</li> <li>G. Receptor Binding Assays</li> <li>H. Lead Compound Discovery of Receptor agonists and antagonists</li> </ul>		
V. Prodrug Design and Applications (Hu)	2 lectures	
<ul style="list-style-type: none"> <li>A. Definition</li> <li>B. Applications</li> <li>C. Prodrug Design Considerations</li> <li>D. Prodrug Forms of Various Functional Groups               <ul style="list-style-type: none"> <li>1. Ester prodrugs of compounds containing <math>-COOH</math> or <math>-OH</math></li> <li>2. Prodrugs of compounds containing amides, imides, and other acidic NH</li> <li>3. Prodrugs of Amines</li> <li>4. Prodrugs for compounds containing carbonyl groups</li> </ul> </li> <li>E. Drug release and activation mechanisms               <ul style="list-style-type: none"> <li>1. Simple one-step activation</li> <li>2. Cascade release/activation systems</li> </ul> </li> <li>F. Prodrugs and intellectual property rights – two court cases</li> </ul>		
VI. Computer-Aided Drug Design (Kerrigan)	7 lectures + lab sessions	
<ul style="list-style-type: none"> <li>A. Docking and virtual screening</li> <li>B. Molecular Dynamics and binding free energy methods</li> </ul>		
VII. Combinatorial Chemistry and Microwave Chemistry	4 lectures	CC Chp 3. p51-97 Chp 7. p177-198 Chp 14. p399-411
<ul style="list-style-type: none"> <li>A. Introduction: Concepts and Terms (Dr. Qun Sun)</li> <li>B. Solid-phase Strategies</li> <li>C. Solution Phase Strategies</li> <li>D. Microwave Chemistry</li> </ul>		

## VIII. Seminars (Hu)

7 lectures

- 1) Dr. Zhoupeng Zhang from Merck to give 1 lecture on “**Metabolite ID and Profiling in Drug Design**” – confirmed for February 15
- 2) Dr. David Floyd from Rutgers Chemistry Department and former Executive Vice President of Discovery and Chief Scientific Officer at Pharmacoepia and vice president of Discovery Research at Bristol-Myers Squibb to give 1 lecture on the “**Discovery of New Antimalarial Agents**” – confirmed for February 20
- 3) Dr. Ashvinkumar Gavai from BMS to give 1 lecture on “**Androgen Receptor (AR) Antagonists**” – confirmed for February 22
- 4) Dr. Lou Lombardo from Roche to give 1 lectures on the “**Case Studies on Kinase Inhibitors**” – confirmed for March 5
- 5) Dr. Robert Borzilleri from BMS to give 1 lecture on “**Discovery of Ixabepilone**” – confirmed for March 7
- 6) Dean Chris Molloy to give 1 lecture on “**Drug Discovery and Development Process**” – confirmed for April 25

### Reference Textbooks:

- Kerns, E.H.; Di, L. *Drug-Like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*, Academic Press, Oxford, **2008**
- BMC – *Burger’s Medicinal Chemistry and Drug Discovery*, 5th Edition, Vol. 1. Principles and Practice, edited by M. E. Wolff, John Wiley & Sons: New York, **1995**.
- PMC – *Principles of Medicinal Chemistry*, 4th Edition, edited by W.O. Foye, T.L. Lemke, and D. A. Williams, Williams and Wilkins: Philadelphia, **1995**.
- MCPP – *Medicinal Chemistry: Principles and Practice*, edited by F.D. King, Royal Society of Chemistry: Cambridge, **1994**.
- CC – *A Practical Guide to Combinatorial Chemistry*, edited by A. W. Czarnik and S. H. DeWitt, American Chemical Society: Washington DC, **1997**.