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

Spring 2014
Time: M, W 5:00 - 6:20 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. Vlad Kholodovych (RBHS Info. Serv. & Tech., High Performance Computing)
- Dr. Qun Sun (Discovery ChemScience)
- Dr. Zhoupeng Zhang (Merck)
- Dr. Ed LaVoie (Rutgers Med Chem)
- Dr. Ashwinikumar Gavai (BMS)
- Dr. Gretchen Schroeder (BMS)
- Dr. Joel Freundlich (Rutgers New Jersey Medical School)
- Dr. Chris Molloy (Senior Vice President, Rutgers)
- Dr. Ray Bakhtiar (Teva Pharmaceuticals)
- Dr. Sam Chackalamannil (Rutgers Med Chem)

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:
<table>
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<tr>
<th>Grade Description</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Term paper on a drug target with 5 drug design principles</td>
<td>20%</td>
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<tr>
<td>Computational project(s)</td>
<td>20%</td>
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<tr>
<td>Exam 1 on approaches to drug discovery (analog design), enzymes, receptors, prodrugs, and seminars</td>
<td>30%</td>
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<tr>
<td>Exam 2 on computational, combinatorial chemistry, and seminars</td>
<td>30%</td>
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<td>Total</td>
<td>100%</td>
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# 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  
MCPP  
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 (Hu)  
2 lectures  
BMC  
Chp 18 p733-782  
PMC  
Chp 8 283-306  

- A. Enzyme kinetics  
- B. Enzyme inhibition and activation  
- C. Approaches to the Rational Design of Enzyme Inhibitors
**IV. Receptors as Targets of Drug Design (Hu)**

- **A.** Receptor Theory
- **B.** Receptor Complexes and Allosteric Modulators
- **C.** Second and Third Messenger Systems
- **D.** Molecular Biology of Receptors
- **F.** Receptor Models and Nomenclature
- **G.** Receptor Binding Assays
- **H.** Lead Compound Discovery of Receptor agonists and antagonists

2 lectures

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<thead>
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<th>Source</th>
<th>Pages</th>
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<tbody>
<tr>
<td>BMC Chp 11</td>
<td>p349-397</td>
</tr>
<tr>
<td>PMC Chp 7</td>
<td>263-282</td>
</tr>
</tbody>
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**V. Prodrug Design and Applications (Hu)**

- **A.** Definition
- **B.** Applications
- **C.** Prodrug Design Considerations
- **D.** Prodrug Forms of Various Functional Groups
  1. Ester prodrugs of compounds containing –COOH or –OH
  2. Prodrugs of compounds containing amides, imides, and other acidic NH
  3. Prodrugs of Amines
  4. Prodrugs for compounds containing carbonyl groups
- **E.** Drug release and activation mechanisms
  1. Simple one-step activation
  2. Cascade release/activation systems
- **F.** Prodrugs and intellectual property rights – two court cases

2 lectures

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**VI. Computer-Aided Drug Design (Vlad Kholodovych)**

- **A.** Docking and virtual screening
- **B.** Molecular Dynamics and binding free energy methods

7 lectures + lab sessions

**VII. Combinatorial Chemistry**

- **A.** Introduction: Concepts and Terms (Dr. Qun Sun)
- **B.** Solid-phase Strategies
- **C.** Solution Phase Strategies

4 lectures

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<tr>
<td>CC Chp 3</td>
<td>p51-97</td>
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<td>Chp 7</td>
<td>p177-198</td>
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<td>Chp 14</td>
<td>p399-411</td>
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<table>
<thead>
<tr>
<th>Seminar</th>
<th>Title</th>
<th>Speaker/Institution</th>
<th>Time</th>
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<tr>
<td>1.</td>
<td><strong>Metabolic ID and Profiling in Drug Design</strong></td>
<td>Dr. Zhoupeng Zhang (Merck Research Laboratory)</td>
<td>5:00 - 6:20 pm</td>
<td>PH-007</td>
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<td>Monday, March 3, 2014</td>
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<td>2.</td>
<td><strong>Design and Discovery of Novel Topoisomerase Inhibitors</strong></td>
<td>Dr. Ed LaVoie, Rutgers Med Chem</td>
<td>5:00 - 6:20 pm</td>
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<td>Wednesday, March 5, 2014</td>
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<td>3.</td>
<td><strong>Discovery of Novel Androgen Receptor Antagonists for Prostate Cancer</strong></td>
<td>Dr. Ashvinkumar Gavai (Bristol-Myers Squibb)</td>
<td>5:00 - 6:20 pm</td>
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<td>4.</td>
<td><strong>Discovery of Tyrosine Kinase Inhibitors for Oncology Indications</strong></td>
<td>Dr. Gretchen Schroeder (Bristol-Myers Squibb)</td>
<td>5:00 - 6:20 pm</td>
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<td>5.</td>
<td><strong>TB Drug Discovery</strong></td>
<td>Dr. Joel Freundlich (Rutgers New Jersey Medical School)</td>
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<td>6.</td>
<td><strong>Antibody-Drug Conjugates</strong></td>
<td>Dr. Ray Bakhtiar (Teva Pharmaceuticals)</td>
<td>5:00 - 6:20 pm</td>
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<td>7.</td>
<td><strong>Discovery of Vorapaxar - A New Antiplatelet Agent</strong></td>
<td>Dr. Sam Chackalamannil, Rutgers Med Chem</td>
<td>5:00 - 6:20 pm</td>
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<td>8.</td>
<td><strong>Drug Discovery Overview</strong></td>
<td>Dr. Chris Molloy, Senior Vice President, Rutgers</td>
<td>5:00 - 6:20 pm</td>
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**Reference Textbooks:**