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. Jian Shen (Sanofi-Aventis)
- Dr. Qun Sun (Discovery ChemScience)
- Dr. Louis Lombardo (Bristol Myers Squibb)
- Dr. David Floyd (Rutgers, Pharmacopeia, BMS)
- Dr. Zhoupeng Zhang (Merck)
- Dr. Ray Bakhtiar (Merck)
- Dean Christopher Molloy

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 20%
Computational project(s) 20%
Exam 1 on approaches to drug discovery (analog design), enzymes, receptors, prodrugs, and seminars 30%
Exam 2 on computational, combinatorial chemistry, and seminars 30%

Total 100%
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
   1. Definition of Drug Discovery
   2. Stages of drug discovery
   3. Strategic Issues in drug discovery

B. Drug Development
   1. Chemistry
   2. Preclinical Studies
   3. Transition from Preclinical to Clinical
   4. Planning the Drug Development Process
   5. Clinical Research

C. Source of Drugs
   1. Drugs from Natural Sources (Natural Products)
      a. Plants
      b. Animals
      c. Microorganisms (Fungi, Bacteria)
   2. Drugs from Organic Synthesis

D. Structural effects on drug action
   1. Sequence of events after drug administration
   2. Physico-chemical properties that are related to drug action
   3. Structurally Non-Specific Drugs
   4. Structurally Specific Drugs
   5. Role and types of chemical bonding involved in drug-target interactions
   6. Steric factors and pharmacological activity
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

A. Enzyme kinetics (Hu)  
   1. The Michaelis-Mention Equation  
   2. Steady state of an enzyme-catalyzed reaction  
   3. Validity of the Steady-state assumption  
   4. Graphs of the Michaelis-Mention Equation  
   5. Practical aspects of kinetic studies  
B. Enzyme inhibition and activation (Hu)  
   1. Reversible and irreversible inhibition  
   2. Linear inhibition  
   3. Plotting inhibition results  
   4. Inhibition by a competing substrate  
   5. Enzyme activation  
C. Approaches to the Rational Design of Enzyme Inhibitors (Hu)  
   1. Transition state analogues  
   2. Mechanism-based inhibitors  
   3. Affinity labels
IV. Receptors as Targets of Drug Design (Hu)  2 lectures

A. Receptor Theory
B. Receptor Complexes and Allosteric Modulators
C. Second and Third Messenger Systems
D. Molecular Biology of Receptors
E. Receptor Models and Nomenclature
F. Receptor Binding Assays
G. Lead Compound Discovery of Receptor agonists and antagonists
   1. Natural Product Sources
   2. Pharmacophore-based Ligand Libraries
   3. Diversity-based ligand libraries
   4. High-throughput screening

V. Prodrug Design and Applications (Hu)  2 lectures

A. Definition
B. Applications
   1. Increasing lipophilicity to increase systemic bioavailability
   2. Sustained release prodrug systems
   3. Improving gastrointestinal tolerance
   4. Improving taste
   5. Diminishing gastrointestinal absorption
   6. Increasing water solubility
   7. Tissue targeting and activation at the site of action
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
VI. Computer-Aided Drug Design (Dr. Jian Shen)  
2 lectures + 2 lab sessions (3 hrs each over a 4 week period)

A. Lead Optimization and Computer-Aided Drug Design
1. Overview of Ligand-Based and Structure-Based Design
2. Review of Protein Structures
   - Primary Structure
   - Secondary Structure
   - Tertiary Structure
   - Quaternary Structure
3. Viewing Tools and Graphics Tools
   - Rasmol (http://www.umass.edu/microbio/rasmol/)
   - DeepView (http://ca.expasy.org/spdbv/)
   - VMD (http://www.ks.uiuc.edu/Research/vmd/)
   - Molscript (http://www.avatar.se/molscript/)
   - Raster3D (http://skuld.bmsc.washington.edu/raster3d/)

B. Homology Modeling
1. Similarity Searching and Sequence Alignment
   - Multiple Sequence Alignments using ClustalW and ClustalX (http://www.ebi.ac.uk/Tools/clustalw/ and http://portal.litbio.org/Registered/Option/clustalx.html)
2. Homology Modeling Programs
   - Modeller (Sali’s popular model builder) - http://www.salilab.org/modeller/ (Tutorial at http://www.salilab.org/modeller/tutorial/)

C. Introduction to Force Fields and Modeling
1. Introduction to Force Fields
2. Building small molecules
3. Building small peptides/nucleic acids

D. Molecular Dynamics
1. Energy minimization (theory and applications)
2. Molecular Dynamics
   - Theory
   - Applications using AMBER and CHARMM force fields
3. Monte Carlo techniques (theory and applications).
E. Docking
   1. Simulated Annealing
      • Autodock (http://autodock.scripps.edu/)
   2. Genetic Algorithms
      • Autodock (http://autodock.scripps.edu/)
      • FlexX
      • Gold
   3. Other Methods
      • Tabu
      • DOCK (spheres vs grids)
      • FTDOCK (Docking small/medium sized polypeptides to proteins)
   4. Scoring Methods
      • Simple Interaction Energies
      • GB/SA scoring (implicit solvation)
      • CScore (consensus scoring algorithms)

F. Project tutorials in the computer lab

VII. Combinatorial Chemistry and Microwave Chemistry
     4 lectures
     CC Chp 3. p51-97
     Chp 7. p177-198
     Chp 14. p399-411

A. Introduction: Concepts and Terms (Dr. Qun Sun)
B. Solid-phase Strategies
   1. General Strategies and Concepts
   2. Specific Implementation Issues
      a. Solid support
      b. Anchoring chemistry
      c. Coupling chemistry
      d. Protection schemes
      e. Analytical methods
C. Solution Phase Strategies
D. Microwave Chemistry
VIII. Seminars (Hu)  

<table>
<thead>
<tr>
<th>Lecture Details</th>
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<tbody>
<tr>
<td>1) Dr. Lou Lombardo from BMS to give 2 lectures on the “<strong>Discovery of Dasatinib and Brivanib</strong>” – confirmed for February 26, 3:00 – 6:00 pm</td>
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<td>2) Dr. David Floyd from Rutgers Chemistry Department and former Executive Vice President of Discovery and Chief Scientific Officer at Pharmacopeia and vice president of Discovery Research at Bristol-Myers Squibb to give 1 lecture on the “<strong>Drug Design for Multiple Actions</strong>” – confirmed for March 5, 3:00 – 4:20 pm</td>
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<td>3) Dr. Zhoupeng Zhang from Merck to give 1 lecture on “<strong>Metabolite ID and Profiling in Drug Design</strong>” – confirmed for April 2, 4:40 – 6 pm</td>
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<tr>
<td>4) Dr. Ray Bakhtiar from Merck to give 2 lectures on “<strong>Biologics including siRNA, Mab, and Peptides</strong>” – confirmed for April 23, 3:00 – 6 pm</td>
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<tr>
<td>5) Dean Chris Molloy to give 1 lecture on “<strong>Drug Discovery and Development Process</strong>” – confirmed for April 30</td>
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Reference Textbooks:

## Principles of Drug Design - Spring 2010

**Week 1**
- **T 19-Jan**: L1-2 - Intro/Drug Discovery & Development (Hu)
- **W 20-Jan**: L11-12 - Discovery Dasatinib & Brivanib (Lou Lombardo, BMS)

**Week 2**
- **T 26-Jan**: L1-2 - Intro/Drug Discovery & Development (Hu)
- **W 27-Jan**: L13 - Drug Design for Multiple Actions - 3 pm (Jian Shen, Sanofi-Aventis)

**Week 3**
- **M 1-Feb**: L25 - Microwave Chemistry
- **T 2-Feb**: L26-27 - Combinatorial Chemistry

**Week 4**
- **M 8-Feb**: L28 - Drug Discovery and Development

**Week 5**
- **W 15-Feb**: L19-20 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 6**
- **M 22-Feb**: L14 - Metabolite ID and Profiling (4:40 pm) (Zhoupeng Zhang, Merck)

**Week 7**
- **W 26-Feb**: L15-16 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 8**
- **M 1-Mar**: L17-18 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 9**
- **W 3-Mar**: L19-20 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 10**
- **M 11-Mar**: L20-21 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 11**
- **W 17-Mar**: L22-23 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 12**
- **M 24-Mar**: L23-24 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 13**
- **W 30-Mar**: L24-25 - Discovery Dasatinib & Brivanib (Lou Lombardo, BMS)

**Week 14**
- **M 6-Apr**: L25 - Microwave Chemistry (Jian Shen, Sanofi-Aventis)

**Week 15**
- **W 13-Apr**: L26-27 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 16**
- **M 20-Apr**: L28 - Drug Discovery and Development (Jian Shen, Sanofi-Aventis)

**Week 17**
- **W 27-Apr**: L19-20 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 18**
- **M 3-May**: L21-22 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 19**
- **W 10-May**: L22-23 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 20**
- **M 17-May**: L23-24 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 21**
- **W 24-May**: L24-25 - Discovery Dasatinib & Brivanib (Lou Lombardo, BMS)

**Week 22**
- **M 31-May**: L25 - Microwave Chemistry (Jian Shen, Sanofi-Aventis)

**Week 23**
- **W 7-Jun**: L26-27 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 24**
- **M 14-Jun**: L28 - Drug Discovery and Development (Jian Shen, Sanofi-Aventis)

**Week 25**
- **W 21-Jun**: L19-20 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 26**
- **M 28-Jun**: L21-22 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 27**
- **W 5-Jul**: L22-23 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 28**
- **M 12-Jul**: L23-24 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 29**
- **W 19-Jul**: L24-25 - Discovery Dasatinib & Brivanib (Lou Lombardo, BMS)

**Week 30**
- **M 26-Jul**: L25 - Microwave Chemistry (Jian Shen, Sanofi-Aventis)

**Week 31**
- **W 2Jul**: L26-27 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 32**
- **M 9-Jul**: L28 - Drug Discovery and Development (Jian Shen, Sanofi-Aventis)

**Week 33**
- **W 16-Jul**: L19-20 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 34**
- **M 23-Jul**: L21-22 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 35**
- **W 30-Jul**: L22-23 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 36**
- **M 6-Aug**: L23-24 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 37**
- **W 13-Aug**: L24-25 - Discovery Dasatinib & Brivanib (Lou Lombardo, BMS)

**Week 38**
- **M 20-Aug**: L25 - Microwave Chemistry (Jian Shen, Sanofi-Aventis)

**Week 39**
- **W 27-Aug**: L26-27 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 40**
- **M 3Sep**: L28 - Drug Discovery and Development (Jian Shen, Sanofi-Aventis)

**Week 41**
- **W 10-Sep**: L19-20 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 42**
- **M 17-Sep**: L21-22 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 43**
- **W 24-Sep**: L22-23 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 44**
- **M 1-Oct**: L23-24 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 45**
- **W 8-Oct**: L24-25 - Discovery Dasatinib & Brivanib (Lou Lombardo, BMS)

**Week 46**
- **M 15-Oct**: L25 - Microwave Chemistry (Jian Shen, Sanofi-Aventis)

**Week 47**
- **W 22-Oct**: L26-27 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 48**
- **M 29-Oct**: L28 - Drug Discovery and Development (Jian Shen, Sanofi-Aventis)

**Week 49**
- **W 5-Nov**: L19-20 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 50**
- **M 12-Nov**: L21-22 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 51**
- **W 19-Nov**: L22-23 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Week 52**
- **M 26-Nov**: L23-24 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 53**
- **W 3-Dec**: L24-25 - Discovery Dasatinib & Brivanib (Lou Lombardo, BMS)

**Week 54**
- **M 10-Dec**: L25 - Microwave Chemistry (Jian Shen, Sanofi-Aventis)

**Week 55**
- **W 17-Dec**: L26-27 - Combinatorial Chemistry (David Floyd, Rutgers Chemistry)

**Week 56**
- **M 24-Dec**: L28 - Drug Discovery and Development (Jian Shen, Sanofi-Aventis)

**Week 57**
- **W 31-Dec**: L19-20 - Computer Assisted DD (2-5 pm) (Jian Shen, Sanofi-Aventis)

**Final Exam**