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

Spring 2022
Time: T, Th 5:40 - 7:00 pm
Place: Pharmacy 288

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 Objectives:

Students completing the *Principles of Drug Design* course will be expected to demonstrate the following abilities-based outcomes (ABOs):

1. Develop and demonstrate depth and breadth of knowledge in biomedical, pharmaceutical, social/administrative/behavioral, and clinical sciences. (1.1.1)
2. Integrate knowledge from foundational sciences to explain how specific drugs or drug classes work and evaluate their potential value in individuals and populations. (1.1.2)
3. Apply knowledge in foundational sciences to solve therapeutic problems. (1.1.3)
4. Critically analyze scientific literature related to drugs and disease to enhance clinical decision making. (1.1.4)
5. Identify and critically analyze emerging theories, information, and technologies that may impact patient-centered and population based care. (1.1.5)

Course Instructors/Invited Speakers:

- Dr. Longqin Hu (Course coordinator)
- Dr. Vlad Kholodovych (Rutgers Office of Advanced Research Computing)
- Dr. Youyi Peng (Rutgers Cancer Institute of New Jersey)

- Dr. Nickolas Meanwell (BMS)
- Dr. Zhoupeng Zhang (Merck)
- Dr. Sam Chackalamannil (Rutgers Med Chem)
- Dr. Ashwinikumar Gavai (BMS)
- Dr. Ed LaVoie (Rutgers Med Chem)
- Dr. Ray Bakhtiar (Organon & Co.)
- Dr. Zhicai Shi (Janssen, JNJ)
- Dr. Blair Wood (Merck)

Course Material: Handouts, Class Lectures, Seminars, and Computational Labs

Course Website: https://pharmacy.rutgers.edu/med-chem-principles-of-drug-design/
https://rutgers.instructure.com/courses/168542

Examinations: Term paper or a Minireview, CADD project report, and one exam

Grading:

Term paper on a drug target with 5 drug design principles or a Minireview article to be published in *Med. Chem. Res.*	**20%**
Exam on approaches to drug discovery (analog design), enzymes, receptors, prodrugs, and combinatorial Chemistry	**40%**
Computational project	**35%**
Class/Seminar attendance and participation	**5%**
Total	**100%**

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Principles of Drug Design

Instructor and course coordinator: Longqin Hu

Tentative Course Outline

I. Introduction to The Drug Discovery/Development (Hu) 1 lecture

- 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

- A. Drugs Derived from Natural Products
- B. Existing Drugs as a Source for New Drug Discovery
- C. Screening for New Drug Leads
- D. Modern "Rational Approach" to Drug Design
- E: Approaches to Lead Optimization
  1. Bioisosteric replacement (Nick Meanwell, BMS)
  2. Conformation restriction
     a. Increase selectivity
     b. Increase affinity
     c. Pharmacophore
     d. Molecular dissection
     e. Metabolic stabilization
  3. Homolgation of alkyl chain(s) or alteration of chain branching, design of aromatic ring position isomers, and alteration of ring size
  4. Alteration of stereochemistry, or design of geometric isomers or stereo isomers
  5. Design of fragments of the lead molecule that contain the pharmacophoric group
  6. Alteration of interatomic distances within the pharmacophoric group or in other parts of the molecule

III. Enzymes as Targets of Drug Design (Hu) 2 lectures

- A. Enzyme kinetics – a brief review
- B. Enzyme inhibition and activation
- C. Approaches to the Rational Design of Enzyme Inhibitors

IV. Receptors as Targets of Drug Design (Hu) 1 lectures

- 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

V. Prodrug Design and Applications (Hu)	2 lectures

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

VI. Combinatorial Chemistry	1 lecture

A. Introduction: Concepts and Terms
B. Solid-phase Strategies
C. Solution Phase Strategies

VII. Computer-Aided Drug Design (Vlad Kholodovych and Youyi Peng)	8 lectures + lab sessions

A. Docking and virtual screening

B. Molecular Dynamics and binding free energy methods

C. Ligand-based design strategies

VIII. Seminars (Hu)	9 lectures

1. **Applications of Bioisosteres in Drug Design**
   Dr. Nick Meanwell (Bristol-Myers Squibb), 5:40 - 7:00 pm, PH-288, Tuesday, Jan. 25, 2022
   https://rutgers.webex.com/rutgers/j.php?MTID=me075a325d434bf506add7b2722a4eaea

2. **Applications of Fluorines in Drug Design**
   Dr. Nick Meanwell (Bristol-Myers Squibb), 5:40 - 7:00 pm, PH-288, Tuesday, Feb. 22, 2022

3. **Metabolic ID and Profiling in Drug Design**
   Dr. Zhoupeng Zhang (Merck Research Laboratory), 5:40 - 7:00 pm, PH-288, Thursday, Feb. 24, 2022

4. **Discovery of Vorapaxar - A New Antiplatelet Agent**
   Dr. Sam Chackalamannil (Rutgers Med Chem, formerly Merck), 5:40 - 7:00 pm, PH-288, Tuesday, Mar. 1, 2022

5. **Design and Discovery of FtsZ-Targeting Compounds as Novel Antibiotics**
   Dr. Ed LaVoie (Rutgers Med Chem), 5:40 - 7:00 pm, PH-288, Thursday, Mar. 3, 2022

6. **Innovative Chemistry Capabilities in Current Drug Discovery Paradigm**
   Dr. Zhicai Shi (Janssen Pharmaceuticals, Johnson & Johnson), 5:40 - 7:00 pm, PH-288, Tuesday, Mar. 8, 2022

7. **Discovery of an NLRP3 Agonist as an Immune-Oncology Agent**
   Dr. Ashvinkumar Gavai (Bristol-Myers Squibb), 5:40 - 7:00 pm, PH-288, Tuesday, Apr. 19, 2022

8. **Discovery of MK-0616, a Novel Orally Active Tricyclic Peptide PCSK9 Inhibitor to Lower LDL Cholesterol**
   Dr. Blair Wood (Merck Research Laboratory), 5:40 - 7:00 pm, PH-288, Thursday, Apr. 21, 2022

9. **Monoclonal, Antibody Drug Conjugates & Peptide Therapeutics**
   Dr. Ray Bakhtiar (Organon & Co.), 5:40 - 7:00 pm, PH-288, Tuesday, Apr. 26, 2022

10. **Discovery of Small Molecule Direct Inhibitors of Keap1-Nrf2 Protein-Protein Interactions**
    Dr. Longqin Hu (Rutgers Med Chem), 5:40 - 7:00 pm, PH-288, Thursday, Apr. 28, 2022

Reference Textbooks:

- Kerns, E.H.; Di, L. Drug-Like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization, 2nd Edition, Academic Press, Oxford, **2016**
- Burger's Medicinal Chemistry and Drug Discovery, 7th Edition, Vol. 1. Methods in Drug Discovery, edited by D. Abraham and D. Rotella, John Wiley & Sons: New York, **2010.**
- Foye's Principles of Medicinal Chemistry, 8th Edition, edited by V. F. Roche, S.W. Zito, T.L. Lemke, and D. A. Wolters Kluwer: Philadelphia, **2019**.