Principles of Drug Design

**Course Number (16:663:502 for graduate students;
30:715:452 for PharmD students)**

Credit Hours: 3
Spring 2026

Course Coordinator:

Longqin Hu, Ph.D., Professor, Medicinal Chemistry, (848) 445-5291, longhu@pharmacy.rutgers.edu, PH 314, Office Hours: *By appt*.

Course Faculty:

Longqin Hu, Ph.D., Professor, Medicinal Chemistry, (848) 445-5291, longhu@pharmacy.rutgers.edu, PH 314, Office Hours: *By appt*.

Robert Palmere, Ph.D., Senior Scientist, Office of Advanced Research Computing, (848) 445-5233, rdp135@oarc.rutgers.edu, Office Hours: *By appt*.

Youyi Peng, Ph.D., Aizyvia Biotech LLC and Tonix Pharmaceuticals, pengcin@gmail.com, Office Hours: *By appt*.

List of Invited Speakers (tentative)
Dr. Nickolas Meanwell (formerly, Bristol-Myers Squibb)
Dr. Lou Lombardo and Dr. Zhicai Shi (Janssen, JNJ)
Dr. Dimitris Agrafiotis (Arsenal Capital)
Dr. Alaric Dyckman (Bristol-Myers Squibb)
Dr. Scott Watterson (Bristol-Myers Squibb)
Dr. Jennifer Hickey (Merck)
Dr. Ray Bakhtiar (formerly, Novartis, Merck, Teva, Organon & Co.)
Dr. Zhoupeng Zhang (Bristol-Myers Squibb)

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 Meeting Time(s) and Location(s):
PH 288, Tuesday, Thursday, 4:10 PM - 5:30 PM

Program-Level Educational Outcomes and Course Learning Objectives:

Domain	Sub-Domain # Name	One Word Descriptor	Outcome Description	*Bloom's Taxonomy Level
Knowledge	2.1.a Scientific thinking	Learner	The graduate is able to seek, analyze, integrate, and apply foundational knowledge of medications and pharmacy practice (biomedical; pharmaceutical; social, behavioral, and administrative; and clinical sciences; drug classes; and digital health).	3
Skills	2.1.b Problem solving process	Problem-Solver	The graduate is able to use problem solving and critical thinking skills, along with an innovative mindset, to address challenges and to promote positive change.	3

Course Learning Objectives:
At the conclusion of this course, learners will be able to:

1. Describe the overall process of drug discovery and development, including the major stages from target identification to clinical introduction.
2. Explain the fundamental principles of enzyme and receptor kinetics as they relate to drug action and classification (e.g., agonists, antagonists, inhibitors).
3. Define and differentiate the key steps of lead identification and lead optimization within a drug discovery project.
4. Identify the rationale and application of prodrugs in overcoming challenges related to drug delivery and bioavailability.
5. Apply the principles of structure-based drug design (SBDD) to critically analyze and predict the binding interactions of small molecules with a specific therapeutic target.
6. Evaluate the role of physicochemical properties (e.g., solubility, lipophilicity, pKa) in determining a compound's Drug-Likeness and ADME (Absorption, Distribution, Metabolism, Excretion) profile.
7. Analyze how computational chemistry methods (e.g., docking, virtual screening) and combinatorial chemistry techniques are integrated to accelerate the identification and optimization of drug leads.
8. Propose and justify modifications to a lead compound's structure to improve its potency, selectivity, or pharmacokinetic profile (Lead Optimization).
9. Discuss and critically evaluate recent advances and real-world case studies in drug design, including the current application of these principles within the pharmaceutical industry.
10. Formulate a preliminary strategy for a drug discovery project, integrating knowledge of target validation, lead generation methods, and optimization techniques for a novel drug target.

Methods of Instruction:

- Canvas will be used as the Learning Management System for this course.
- Classroom lectures and invited seminars
- Hands-on tutorials using CADD software – Molecular Operating Environment (MOE)

Tentative Class 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. Dr. Nick Meanwell (Formerly, BMS), “Applications of Bioisosteres in Drug Design”
2. Dr. Nick Meanwell (Formerly, BMS), “Applications of Fluorines in Drug Design”
3. Dr. Lou Lombardo and Dr. Zhicai Shi (JNJ), “Innovative Chemistry Capabilities in Current Drug Discovery Paradigm”
4. Dr. Dimitris Agrafiotis (Arsenal Capital), “Application of AI in Drug Discovery”
5. Dr. Alaric Dyckman (BMS), “Discovery of afimetoran, a small molecule dual antagonist of toll-like receptor 7 and 8 (TLR7/8) for the treatment of lupus”
6. Dr. Scott Watterson (BMS), “Multiple Shots on Goal: Dual Approaches to the Design of Inhibitors of Bruton’s Tyrosine Kinase (BTK) that Advanced into Clinical Studies”
7. Dr. Jennifer Hickey (Merck), “Cyclic peptides for trapping IL-1β”

8. Dr. Ray Bakhtiar (formerly, Novartis, Merck, Teva, Organon & Co.), "Monoclonal, antibody drug conjugates & peptide therapeutics"
9. Dr. Zhoupeng Zhang (BMS), "Metabolic ID and Profiling in Drug Design"

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**.

Attendance and Participation Policy

Students are expected to attend all lectures and invited seminars; if you expect to miss one or more lectures, please use the University absence reporting website ***https://sims.rutgers.edu/ssra/*** to indicate the date and reason for your absence. An email is automatically sent to the faculty coordinator.

Assessment and Grading:

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

Assessment Mapping Table

Assessment	**Mapping COs**	**ACPE Appendix 1**	***Bloom's Levels**
Exam	2.1.a 2.1.b	Medicinal Chemistry, Biochemistry, Pharmacology, Toxicology, Clinical Pharmacokinetics, Health Information Retrieval and Evaluation, Pharmacotherapy	3
Term paper or minireview	2.1.a 2.1.b	Medicinal Chemistry, Biochemistry, Pharmacology, Toxicology, Clinical Pharmacokinetics, Health Information Retrieval and Evaluation, Pharmacotherapy	3
CADD project	2.1.a 2.1.b	Medicinal Chemistry, Biochemistry, Pharmacology, Toxicology, Clinical Pharmacokinetics, Health Information Retrieval and Evaluation, Pharmacotherapy	3

Grading Policy:

Term paper on a drug target with 5 drug design principles or a Minireview article for potential publication 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%**

Grading Scale:

A = 89.5-100 (4.0)
B+ = 84.5-89.4 (3.5)
B = 79.5-84.4 (3.0)
C+ = 74.5-79.4 (2.5)
C = 69.5-74.4 (2.0)
D = 59.5-69.4 (1.0)
F = 0-59.4 (0.0)

AI Policy:
For assignments such as the term paper, minireview, or CADD project report, AI tools are permitted solely for language refinement (e.g., grammar and style checks). Under no circumstances should generative AI be used to compose the substantive, intellectual content of the work, and all use of AI-generated text requires careful proofing and verification for accuracy and academic integrity.

Accessibility:
Rutgers University is committed to the creation of an inclusive and safe learning environment for all students and welcomes students with disabilities into all the University's educational programs. The Office of Disability Services (ODS) is responsible for the determination of appropriate accommodations for students.

Once a student has completed the ODS process (registration, initial appointment, and submitted documentation) and reasonable accommodations are determined a Letter of Accommodation (LOA) can be requested and will be sent to the student and instructor. This should be done as early in the semester as possible as accommodations are not retroactive, and a discussion should occur about how the accommodations will be implemented.

More information can be found at https://ods.rutgers.edu/.
To begin this process, please complete the registration form (https://webapps.rutgers.edu/student-ods/forms/registration).
You can contact ODS at 848-202-3111 or via email at dsoffice@echo.rutgers.edu for any questions.

Academic Integrity Policy:
Graduate students and Pharmacy students are subject to the University academic integrity policy, which is provided to new students at orientation and is also available online from https://academicintegrity.rutgers.edu at:
https://academicintegrity.rutgers.edu/sites/default/files/pdfs/current.pdf
This policy was updated in the summer of 2020.

Ernest Mario School of Pharmacy have also established an ad hoc committee on academic integrity. The committee has membership from both the faculty and student body. Given the serious nature of the work health care workers provide, academic integrity and honesty are of the utmost importance in pharmacy school. The faculty of the Ernest Mario School of Pharmacy approved the following statements for both students and faculty which were developed by the committee in conjunction with student leadership.

In the new policy, violations of academic integrity are generally divided into three categories: Level 1, Level 2, and Level 3.

- Level 1 violations may occur as a result of inexperience or lack of malicious intent by the person committing the violation.
- Level 2 violations include misconduct of a more serious character or misconduct that affects a major, significant, or essential portion of work done to meet course requirements. These violations demonstrate premeditation or may have posed harm to others. The student alleged to have committed the violation may have one or more previous violations.
- Level 3 violations represent the most serious breaches of conduct. They may involve a serious violation of a professional code of conduct; may include extreme cases of dishonesty and maliciousness or violations of law; and/or are likely to cause direct harm to others.

The procedures for adjudicating alleged violations of academic integrity are different for Level 1, Level 2, and Level 3 violations. Students are referred to the full policy at the link above for examples of violations and potential sanctions. When a student is accused of one or more Level 3 violations that include alleged violations of law or a professional code of conduct, or when it is reasonable to believe that the student is likely to cause direct harm to others, they may be removed from a course, clinical, or internship setting on an interim basis, with the approval of the dean of the school.

The profession of pharmacy is one that demands adherence to a set of ethical principles. These high ideals are necessary to ensure the quality of care extended to patients. Students at Ernest Mario School of Pharmacy are responsible for upholding the principles of the Policy on Academic Integrity for Undergraduate and Graduate Students. At the Rutgers School of Graduate Studies and Ernest Mario School of Pharmacy all students are held accountable for their actions. Each student should review the entire Academic Integrity Policy as well as the Student Code of Conduct.

The following are some general examples of the responsibilities of students:

- To understand the definition of scholastic dishonesty.
- To understand the instructions for each assignment, quiz, or examination.

- To refrain from committing any acts of scholastic dishonesty.
- To take appropriate action when acts of scholastic dishonesty are observed.
- To understand the importance of confidentiality in pharmacy practice and the ramifications of breaching patient trust.
- To engage in appropriate classroom and laboratory conduct.

As noted, this list serves only as an example. The entire Academic Integrity Policy should be reviewed, downloaded and printed from the link above. It is the student's responsibility to review the entire policy for more specific information regarding specific infractions and penalties. Violations of any of these principles will result in prosecution by Rutgers School of Graduate Studies, Ernest Mario School of Pharmacy, and the Student Judicial Affairs department. Being students enrolled in a school of health professions, severe penalties may be levied which may include expulsion from the School of Graduate Studies or Ernest Mario School of Pharmacy as well as from the entire Rutgers University

Class recordings:
Students seeking to record a lecture must obtain prior authorization from the lecturer.