

BCHB 522 Drug Targets and Drug Design (DTDD) Spring 2008**1 credit Monday 5:00– 7:00 pm PCS LA2****1/14, 1/28, 2/4, 2/11, 2/25, 3/10, 3/24, 3/31****Course Directors: Dr. Jack Chirikjian, Sharon Helling****Instructor: Dr. Lee Eiden, NIH**

The objective of this course is to furnish students with a comprehensive background in the history of pharmacology and therapeutics leading to the current theory and practice of drug design and the basic pharmacology, biochemistry, molecular biology and bioinformatic concepts that drive it. The course includes lectures on the future of drug design and discovery in the 'post-genomic' era including a survey of structural bioinformatics, combinatorial drug design, and bioinformatic analysis of cell signaling underlying physiological and pathophysiological processes such as inflammation in arthritis, cell transformation in cancer, and hormone and neurotransmitter action in diabetes, obesity, and mental illness. Students should take from the course an understanding of fundamental biological and biotechnological concepts required to assess current and future approaches to drug discovery along the pathway from basic biomedical research to identification of cellular and molecular mechanisms of disease, drug targets, and rational design and high throughput screening of drug candidates.

There will be a mid-term exam (for Spring 2009).

Drug Targets and Drug Design (DTDD)--course mechanics.

- DTDD will be presented in six two hour sessions, covering twelve core concepts, followed by a review session and an examination.
- all subject matter will be available in pdf format; usually 50-60 items plus an assigned reading for each session except for the first one (five outside readings in all).
- subject matter distilled to selected readings and about 100 powerpoint items one week prior to review session

Objectives of DTDD

- provide a survey of the intellectual history of the drug discovery and development process up to the present time (~20%)
- outline basic principles of pharmacology, pharmaceutical science and medicinal chemistry required to understand the drug discovery and development process in operation (~20%)
- describe the current interface between drug development, chemi- and bioinformatics, and biotechnology, and how it is likely to evolve in the coming decades (~60%)

Core Concept 1. History of pharmacology and pharmaceuticals provides a basis for modern drug discovery and design.

- materia medica, purgatives and poisons, plant alkaloids and other natural products
- the pharmacopeiae
- antique and medieval bioinformatics--drug discovery, recordation, tests and standardization

-concepts of drug discovery, development, and design including serendipity, proof of concept, target validation, lead compounds, ‘druggability’

Core Concept 2. Differential toxicity as a basis for drug design

-Ehrlich’s magic bullet
 -antibiotics
 -chemotherapeutics
 -whole-organism genome and metabolic pathway mapping and antiparasitic and antiviral drug design
 -the holy grail of drug selectivity, and the holier grail of drug specificity
 -two approaches to peptic ulcer; omeprazole and proton pumping; antibiotics and helicobacter pylorii—the Barry Marshall story

Core Concept 3: All Drugs Have Receptors

-concept of drug receptors, from Arrhenius to Kosterlitz
 -receptor-based high-throughput drug screening
 -G-protein coupled receptors (GPCRs) as drug targets
 -enzyme inhibitors as drug targets. Angiotensin inhibitors, protein kinase inhibitors—Gleevec (STI-571) for chronic myelogenous leukemia (inhibits abl and c-kit); Iressa (ZD 1839) and Tarceva (erlotinib); EGFR Y-kinase inhibitors for treating lung cancer.

Core Concept 4. Structure-Activity Relationships (SAR)

-SAR is a cornerstone of drug design
 -ligand and receptor modification
 -ligand mimickry and ligand agonist/antagonist identification
 -new concepts in ligand-receptor interaction: spiegelmers, aptamers
 -finding drug receptors outside of active sites and binding pockets

Core Concept 5. Drug screening

-relies in many cases on “focusing serendipity”
 -molecular cloning and target-based drug screening
 -the historical antecedents of high-throughput screening
 -combinatorial chemistry and drug discovery
 -recent case histories of structure-based rational drug design

Core Concept 6. Drug design: Part I. Systems-based targets and drug design

-drug design by target group approach: kinases
 -pharmacophores and structural bioinformatics
 -limitations and potential of data mining and bioinformatics in the 21st century
 -drug design and the ‘omes’—the genome, the transcriptome, the proteome, the kinome
 -genomics/proteomics interaction-the GSK kinome approach.

Core Concept 6 (cont). Drug design: Part II. Better drugs for validated targets; validation of new targets

- immunosuppressants
- 100 years of aspirin: second-generation drug mechanisms, second generation therapeutics, learning from bumps in the road
- examples of new targets and how they are validated.

Core Concept 7. Combinatorics, signal transduction, and new rules for drug specificity

- cellular responses activated by multiple pathways
- convergence and divergence in phosphoprotein signaling in mammalian cells

Core Concept 8. Genomics, proteomics and expression profiling in drug design

- microarray/proteomics-based profiling to create new kinds of drugs
- redefining pharmacological specificity from the one to the many
- relationship between biomarkers and drug targets
- meta-targets in drug discovery

Core Concept 9. Pharmacogenetics, pharmacokinetics, and pharmacotoxicology-partners in drug therapy

- ADME
- pharmacogenetics makes good drugs work better: responder profiles and drug action
- pharmacokinetics and bioavailability,
- toxicology, tolerated dosage, testing and product liability

Core Concept 10. High-throughput drug screening.

The role of high-throughput drug screening at multiple points in the drug discovery/development process will be discussed, and the concept of the *drug development pipeline* laid out.

- high throughput assays
- programs to develop drug classes (the GSK Kinase Inhibitor Approach)
- the random, the rational, and the future of drug design-identifying bottlenecks in 'high-throughput everything'

Core Concept 11. The Critical Pathway to drug development, from targets to design to hits to leads to drugs.

- construction and re-modeling of the 'drug development pipeline'
- current ideas on improving the 'hits to leads' ratio in drug design
- drug development from Phase I to Phase III

Core Concept 12. Drug Hunting, Trapping, and Development-some real-world accounts of how making drugs is an opportunistic enterprise.

-mapping drug discovery territories; some detailed accounts of real-world drug development case histories from Joseph Moskal, Falk Institute (peptide-based prototype drug development); Jeffrey Wiseman (metadevelopment—tools for drug design based on free energy calculations for drug binding); Christian Felder, Eli Lilly (the biological surround and development of drug classes for Alzheimer’s disease); Yoel Kloog, Tel Aviv University (Ras inhibitors as anti-cancer drugs); Alcino Silva, UCLA (statins for treatment of CNS manifestations of neurofibromatosis); Michael Iadarola, NIH (resiniferatoxin for treatment of intractable pain).

Review

Final exam to be scheduled by Dr. Chirikjian

Multiple choice exam-50 questions.