

20.201 Mechanisms of Drug Action

Introduction 4 Sept 2013

Instructors

Prof. Peter Dedon

Prof. Steven Tannenbaum

Dr. Mark Murcko

Dr. Charles Knutson

Guest lecturers

Dr. Bernard Fermini, Pfizer

Dr. Keith Hoffmaster, Novartis

Dr. Tess Schmalbach, Schmalbach LLC

Dr. Alex Wood, Novartis & MIT

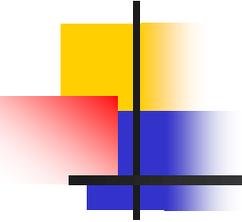
Dr. Teresa Wright, Shire Pharm.

Teaching Assistants

MIT Graduate Students

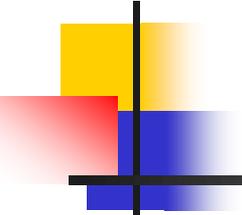
Monday and Wednesday 1:30-3:00 pm

Friday 1:30-2:30 pm



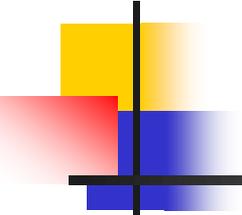
Learning Objectives

- Develop an understanding of the scientific basis for drug development, drug mechanisms, drug disposition and drug safety
- Develop an appreciation for the role of pharmacokinetics, drug metabolism and drug interactions in the mechanisms of drug action
- Understand the balance between environment and pharmacogenetics in the toxicity and therapeutic outcome associated with a drug
- Understand factors that lead to success and failure in drug development



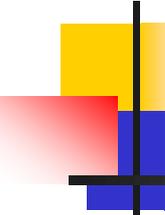
Steps in drug development

1. Identify a "target" in a disease
 - ~ receptor, enzyme, mRNA
2. Utilize cell lines with disease phenotypes
3. Identify one or more drug candidates
4. Test drug candidates in
 - ~ cells, tissues, animals
5. Test drug candidates in humans
6. Apply to FDA for approval as a drug



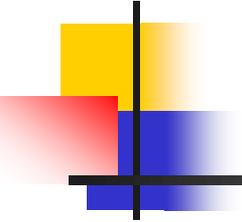
Selection of a drug target is only step #1

- Discovering new drug targets
 - ~ Example: screening 10^6 -compound libraries
 - ~ finding a new drug target is important...
 - ~ ...but only one part of drug development
- A drug candidate becomes a drug when the FDA is convinced that a candidate has been
 - ~ proven safe
 - ~ proven effective
- Concepts relevant to the safety and efficacy of a drug are as important as concepts of drug targets



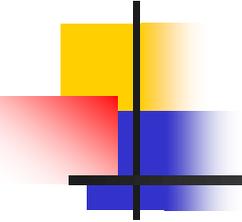
New/Old Approach is to Test Phenotypes

- Phenotypic screening (aka classical pharmacology) has been historically used in drug discovery. While technological developments have made the prevalence of target-based screening more popular, statistical analysis shows that a disproportionate number of first-in-class drugs with novel mechanisms of action come from phenotypic screening.



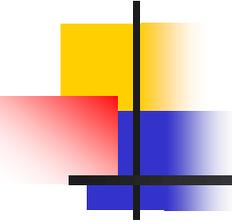
What will you get out of 20.201?

- Framework for understanding "drugs"
- Fundamental concepts of drug development and pharmacology
- Learn the language of the pharmaceutical and biotechnology industries
- Application areas for modern biological engineering, chemistry, biology
- Opportunities to meet scientists from drug companies



What is "drug action"

- The mechanism of action of a drug is not just limited to its interaction with one specific target and the response that ensues
- This is “pharmacodynamics”: the study of how a drug acts on a living organism, including the pharmacologic response and the duration and magnitude of response observed relative to the concentration of the drug at an active site in the organism.
- We will use the term "drug action" broadly to encompass:
 - ~ drug actions that lead to toxicity
 - ~ features of uptake, distribution and metabolism that alter or limit a drug's action ("pharmacokinetics"; ADME)



Mechanisms of drug action involve every aspect of a drug's fate

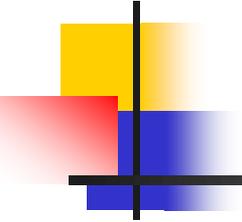
- An often under-appreciated facet of a drug's mechanism of action is its “pharmacokinetics”
- “Pharmacokinetics” (how/how much gets to the target) and “pharmacodynamics” (what it does at the target) are the foundations of drug action
- Pharmacokinetics, in its broadest definition, involves:

A ~ Uptake = absorption

D ~ Distribution

M ~ Metabolism

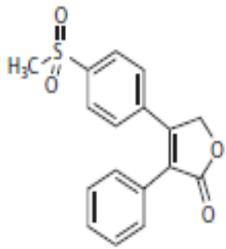
E ~ Elimination



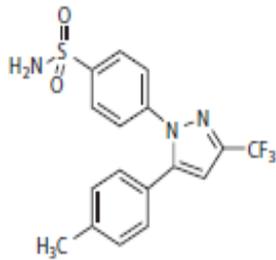
Drug Safety

- Toxicology
 - Drug causes or induces chemical/biological damage to cells and organs
 - Drug has off-target effects
- Lack of Efficacy
 - Drug doesn't have therapeutic effect

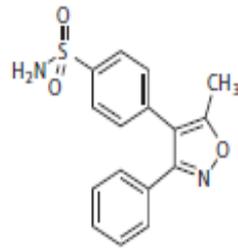
Pharmacophores & Toxicophores



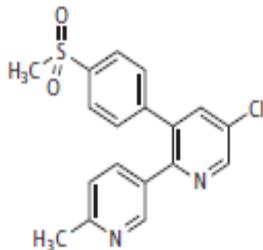
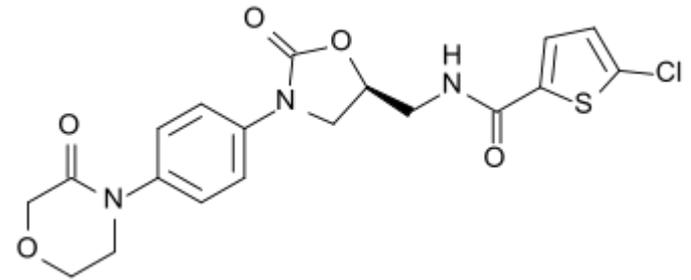
Rofecoxib



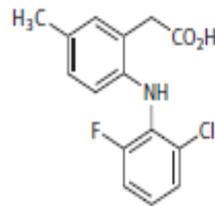
Celecoxib



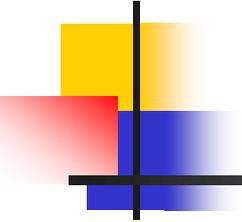
Valdecoxib



Etoricoxib

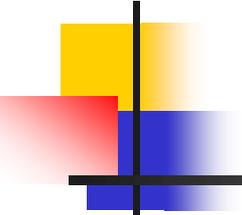


Lumiracoxib



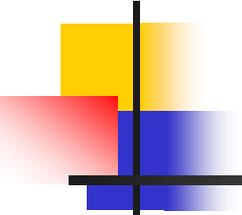
Topics covered in 20.201

- Mechanisms of action of drugs and drug classes
- Role of drug structure and drug transport proteins in uptake and distribution
- Kinetics of drug behavior in the human body
- Metabolism:
 - ~ chemical alterations of drugs
 - ~ generation of toxic metabolites
 - ~ metabolic activation of drugs
- Drug interactions leading to toxicity
- Drug-receptor interactions
- The role of pharmacogenetics in drug actions



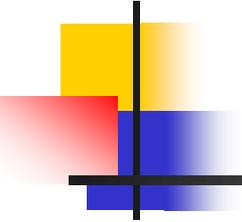
Our approach

- All sessions address a drug and its mechanism/use
- All sessions use specific examples of drugs and drug literature to illustrate the fundamentals of drug development, ADME, toxicity and pharmacodynamics
- Some sessions develop fundamental concepts in didactic format (i.e., straight lectures)
- Some sessions involve discussion of literature
- Many lectures use case study format to illustrate fundamental concepts
- Heavy emphasis on critical analysis of the primary literature



Why so Many Drugs?

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Statins
- Antacids
- Blood pressure



Grading Policy

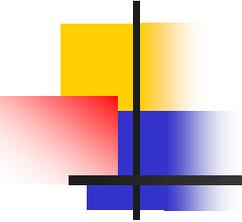
Percentage contributions to final grade:

30% Quiz mid-term

30% Case study project

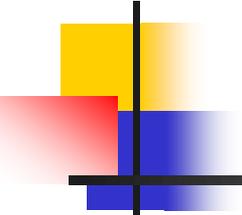
20% Evidence of reading assigned papers

20% Homework assignments



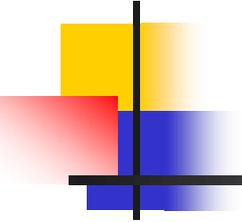
"Recitations"

- Lecture and problem set review offered Fridays from 1:30-2:30
- Several sessions will involve quiz review, discussion of projects and tutoring as needed



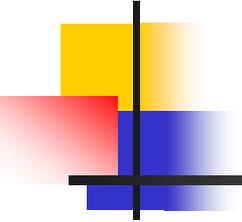
Homework assignments and readings

- Homework assignments cover:
 - ~ Problem sets relevant to lecture material
 - ~ Problem sets associated with the reading
- Readings
 - ~ Book chapters
 - ~ Review papers
 - ~ Papers from the primary literature
- Assignments available on course website
- Homework due as noted in class



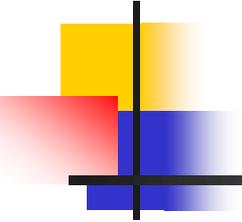
Quiz

- There will be one take-home quiz at approximately mid-term
- The quiz will cover application of fundamentals presented in the first series of lectures
- There is no final examination
There is an individual project due at end of term



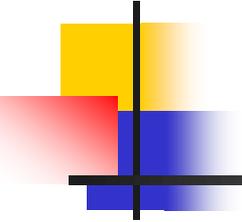
Critical analysis of the literature

- The class emphasizes the primary literature of drug mechanisms and toxicity
- Students are responsible for thoroughly reading each paper and should be prepared to make brief summary presentations of various facets of the paper:
 - (1) What is the hypothesis driving the work? What is the point of the paper? Is this an important question?
 - (2) What is the experimental plan here?
 - (3) Are the methods chosen appropriate for testing the hypothesis?
 - (4) Are the results substantive and credible? Statistical analyses performed properly?
 - (5) Are the conclusions justified by the results?



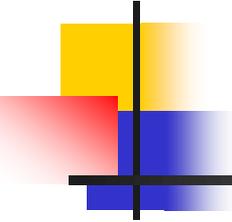
Required Text

- "Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy," by David E. Golan *et al.*, Lippincott Williams and Wilkins, 3rd Edition, 2012
- Best bet? Amazon.com for pricing?
- Available at Harvard Medical COOP:
333 Longwood Avenue
Boston, MA 02115
(617)499-3300
Store Hours: M-F 9-6; Sa 11-5



Other recommended Texts

- 7th edition of "Casarett and Doull's Toxicology, the Basic Science of Poisons, ed. Curtis Klassen, McGraw-Hill, NY, 2007
- *Other pharmacology text:* "The Pharmacologic Basis of Therapeutics" by Gilman, Rall, Nies and Taylor; Pergamon Press
- **Physiology texts:**
 - ~ "A Textbook of Medical Physiology" by Arthur Guyton (W.B. Saunders)
 - ~ "Human Physiology: The Mechanisms of Body Function" by Vander, Sherman, and Luciano
- **Histology texts:**
 - ~ "Basic Histology" by Junqueira, Carneiro, and Kelley; Appleton/Lange
 - ~ "A Textbook of Histology" by Bloom and Fawcet



The Chemistry/Biochemistry You Need to Know or Learn

Structures and Functional Groups

- carboxylic acids
- aromatic molecules/heterocycles
- amides
- aldehydes
- thiols (sulfhydryls)
- ketones
- esters
- epoxides

Nucleophiles/electrophiles

Bonding

- covalent bonds
- ionic bonds
- hydrogen bonding
- coordinate covalent bonds
- van der Waal's interactions

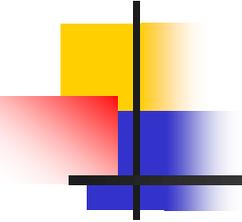
Reduction/oxidation

Thermodynamics and Equilibria

Acid/base chemistry

Reaction kinetics and mechanisms:

- zero-, first- and second-order reaction kinetics
- S_N1 and S_N2 nucleophilic substitution mechanisms
- Michael acceptors



The Chemistry/Biochemistry You Need to Know or Learn

Enzymes

- kinetics
- cofactors: NAD⁺/NADH; FAD/FADH; FMN; acetyl CoA; UDP-glucuronic acid; ATP; GTP; cAMP; cGMP; PAPS (3' =phosphoadenosine-5' -phosphosulfate); s-adenosylmethionine (SAM); glutathione

Lipids

- membrane structure
- types: fatty acids; triglycerides; cholesterol; phospholipids

Mitochondrial structure and function

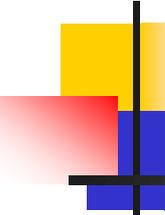
Metabolism and ATP generation

DNA structure

- bases, nucleosides, nucleotides
- primary, secondary structure

Proteins/peptides

- amino acid structure and side chain chemistry
- peptide bonds - glutathione



Other Sources of Information

- Google and Google Scholar
- Pubmed
- Wikipedia
- FDA website
- <http://canreviews.aacrjournals.org/>
- <https://diln.dcri.duke.edu/> (drug liver injury)
- NCTR
- <http://www.livertox.nih.gov/index.html>
- CDER
- Nature Reviews Drug Discovery

MIT OpenCourseWare
<http://ocw.mit.edu>

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