Drug Metabolism MOPH 810
Fall 2009
Classes: 80 minute class twice a week
Course Director: Dhiren R. Thakker
Eshelman School of Pharmacy, UNC-Chapel Hill

The course is taught by a team of UNC faculty and industry scientists

Goal/Purpose/Scope

The course has been designed to provide the students an understanding of

(i) chemical changes associated with metabolic transformations
(ii) major classes of drug metabolizing enzymes and pharmacogenetics of these enzymes
(iii) the role of transporters in affecting drug metabolism and drug clearance
(iv) the techniques used to study drug metabolism and drug disposition – e.g. cell and molecular biology, chromatography, mass spectrometry, NMR spectroscopy, and radioisotope studies
(v) clinical implications of drug metabolism, including metabolic detoxification and activation as well as metabolism-based drug interactions
(vi) implications of metabolism in the design and development of safe and efficacious therapeutic agents
Drug Metabolism MOPH 810 - Course Syllabus

Fall 2009

Catalog course description:
Metabolic transformations and metabolic enzymes, contemporary techniques in drug metabolism, and clinical relevance of metabolic processes in the design and development of safe and efficacious drugs are discussed.

Prerequisites: Course Director's permission

Credit hours: 3

Tuesdays / Thursdays – 10:30 AM to 12:00 noon

Exams: Two Mid-term and a Final (students will be bound by the UNC honor code)

Course Material:
There will be no text-book for the course. Required reading material will be posted as electronic reserve material. Additional suggested reading material will be in the form of literature references. Handout material will be posted before each class.

Faculty: Dhiren Thakker (Course Director)
    UNC (and adjunct) faculty members
    Scientists from pharmaceutical companies
**Goal/Purpose/Scope**

The Proposed course in Drug Metabolism has been designed to provide the students an understanding of (i) the key role played by metabolic processes in the design and development of safe and efficacious therapeutic agents, (ii) the relevant metabolic transformations and the enzymes (enzymology) responsible for these transformations, and (iii) the contemporary techniques in cell and molecular biology, chromatography, mass spectrometry, and spectroscopy used to study metabolic processes and the role of specific metabolic enzymes in the metabolism of drug molecules.

<table>
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<tr>
<th>Lecture</th>
<th>Topics</th>
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| 1.      | Introduction to Drug metabolism  
*Historical Perspective and General Principles*  
*Drug metabolism as a mechanism for clearance of therapeutic agents; pharmacokinetic concepts, metabolic clearance, its role in the total clearance of drug molecules, Stereochemistry in Drug Metabolism- general concepts, role in drug metabolism and pharmacokinetics, regulatory issues. Role of drug metabolism in the design and development of safe and efficacious therapeutic agents, regulatory issues* |
| 2-5.    | Chemistry of Metabolic Reactions  
*Oxidation*  
*Reduction*  
*Hydrolysis*  
*Conjugation* |
| 6.      | Biochemistry of Cytochrome P450  
*Classification*  
*Isozymes*  
*Multipliclity and Substrate Specificity*  
*Localizaiton*  
*Variability* |
| 7-8.    | Induction of Drug Metabolizing Enzymes  
*Mechanisms*  
in *vitro models to asses induction*  
*Clinical considerations/implications* |
| 9.      | Intestinal Oxidative Metabolism  
*Intestinal cytochrome P450 enzymes*  
*Role of intestinal cytochrome P450 enzymes in drug-drug interactions* |
10. Phase I (non-P450) Enzymes
   Oxidative
   Reductive
   Hydrolytic

11. Mid-term Exam 1

12. Inhibition of Drug Metabolizing Enzymes
   Mechanisms
   In vitro assessment
   Clinical considerations/implications

13. Phase II Enzymes
   Introduction
   Glutathione Transferases
   Reaction and substrates
   Physiological considerations
   Expression and Regulation
   Species and strain differences

14. Glucuronosyl transferases and sulfotransferases:
   Classification
   Reactions and classes of substrates
   Physiological considerations and cofactors
   Expression and regulation
   Species and strain differences

15. In Vitro Model Systems for Transport
   In vitro techniques to study drug transport
   Transport models to elucidate and predict transporter-based drug interactions

16-17. Hepatobiliary and Renal Disposition – Hepatic and Renal Transport
   First Pass Effect
   Mechanisms
   Hepatic and renal clearance
   Classes of drugs excreted
   Pharmacological factors influencing biliary excretion of xenobiotics:
   Methods for examining biliary and renal excretion
   Enterohepatic recirculation and actors that influence enterohepatic cycling
   Transporter-based hepatic and renal toxicity
18. Intestinal Transport and Transporters
   - Intestinal transport mechanisms
   - Absorptive and Barrier properties of intestinal epithelium
   - Absorptive and Secretory transporters
   - Uptake and efflux transporters
   - Transporter-based drug-drug interactions

19. Mid-term Exam 2

20-22. Analytical Techniques for Studying Drug Metabolism
   - NMR
   - LC/MS
   - Stable isotopes
   - Radioisotopes

23-24. Metabolism-based Drug Toxicity
   - Mechanisms of toxicity - reactive metabolites
   - Genotoxicity
   - In vitro systems to assess toxicity
   - Drug- and metabolite-induced hepatotoxicity
   - Implications in drug discovery/development

25-27. Pharmacogenomics of Drug Metabolizing Enzymes and Transporters
   - Basic Concepts,
   - Pharmacogenomics of Drug Metabolizing Enzymes and Transporters
   - Case studies and clinical implications
   - Regulatory impact

28. Integration of Drug Metabolism/pharmacokinetic Function in Drug Discovery and Development
   - Review of the DM/PK function within pharmaceutical R & D
   - DM/PK studies in drug discovery and development
   - Case histories

29. Review and Key Learnings from the course

30. Final Exam