**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.

| **Lecture** | **Topics** |
|---|---|
| 1. | Introduction to Drug metabolism<br>*Historical Perspective and General Principles*<br>*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<br>*Oxidation*<br>*Reduction*<br>*Hydrolysis*<br>*Conjugation* |
| 6. | Biochemistry of Cytochrome P450<br>*Classification*<br>*Isozymes*<br>*Multipllicity and Substrate Specificity*<br>*Localizaiton*<br>*Variability* |
| 7-8. | Induction of Drug Metabolizing Enzymes<br>*Mechanisms*<br>*in vitro models to asses induction*<br>*Clinical considerations/implications* |
| 9. | Intestinal Oxidative Metabolism<br>*Intestinal cytochrome P450 enzymes*<br>*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*

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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