DRUG BIOTRANSFORMATION AND MOLECULAR MECHANISMS OF TOXICITY

**FALL SEMESTER 2014 3 CREDITS**

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Office hours M.O. James: P6-20, by appointment.

Prerequisites Recommended: Organic Chemistry (e.g. CHM 5224), undergraduate Biochemistry. If in doubt, seek instructor approval.

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| TIME & PLACE OF CLASS | Monday, Wednesday, Friday, 3-3:50 pm, room G201 (HPNP building), except for four dates listed below (G301A) |

**LEARNING OBJECTIVES.**

1. To predict, from the structure of a xenobiotic, the structures of its probable metabolites, including intermediates and final products.
2. To predict the enzymes (including isozymes where known) likely to be involved in the biotransformation of a xenobiotic and its primary metabolites.
3. To predict the transporter proteins likely to facilitate elimination of a xenobiotic or its metabolite
4. To understand and correctly use the terminology of the field.
5. To understand and be able to predict the effects of prototype inducers of xenobiotic biotransformation on enzymes present in liver and other organs.
6. To understand and be able to predict the effects of inhibitors of xenobiotic biotransformation with different mechanisms of inhibition.
7. To understand the role of route of administration on the fate of a xenobiotic or the action of a modulator of xenobiotic biotransformation, as well as on its transporter-mediated elimination.
8. To understand why some metabolites are chemically reactive, and therefore potentially toxic and to be able to predict the likelihood of formation of a reactive metabolite from a given xenobiotic.

**DESCRIPTION** : This course will employ a combination of lectures, student presentations and discussion of papers from the primary literature. In the **first** part of the course, the processes of xenobiotic absorption, distribution and elimination will be briefly reviewed, and the **major pathways of xenobiotic biotransformation** will be studied in detail from an enzymatic basis, including regulation of the enzymes and factors affecting metabolism or leading to higher or lower enzyme activity (e.g. age, sex, exposure to chemicals). Reference texts will be used along with recent review articles pertinent to each topic for in-depth study. In the **second** part of the course, concepts related to the role of metabolism in toxicity will be studied. Experimental design of drug metabolism studies will be discussed. Examples of metabolic activation of xenobiotics, including pharmaceutical agents, environmental pollutants and naturally occurring toxic chemicals will be discussed using original journal articles. Students will be expected to contribute to these examples.

**THERE IS NO REQUIRED TEXT:** The book listed below are available in Dr. James’ office or in the Health Center library, and may provide useful back-up to lectures:

**Cytochrome P450**, P. Ortiz de Montellano, ed., 3rd edition, Kluwer academic/ Plenum 2005

Other texts and original journal articles will be assigned, depending on the topic. There are various web pages related to drug metabolism. One site, with links to several relevant pages, is the website of the International Society for the Study of Xenobiotics at [www.issx.org](http://www.issx.org) under “resources”. A site at <http://medicine.iupui.edu/clinpharm/ddis/> lists drug interactions based on cytochrome P450. Students should check with Dr. James about the veracity of information on other web pages.

**LECTURE LIST,** with **approximate** timetable.

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| Date and classroom | Topic |
| Aug 25 room G201 | Introduction, Definitions, Overview of xenobiotic metabolism & route considerations |
| Aug 27 room G201 | Cytochrome P450: Reactions catalyzed, chemistry and mechanisms, role of NADPH-cytochrome P450 reductase |
| Aug 29 room G201 | Cytochrome P450: Multiplicity, nomenclature, pharmacogenetics |
| Sept 1 | No class, Labor Day |
| Sept 3 room G201 | Cytochrome P450: Regulation of expression |
| Sept 5 room G201 | No class, Dr. James out |
| Sept 8 room G201 | Cytochrome P450: Regulation of expression |
| Sept 10 room G201 | Cytochrome P450: Modulation by inhibitors and enhancers |
| Sept 12 room G201 | Cytochrome P450: Tissue distribution, purification, expressed CYP |
| Sept 15 room G201 | Flavin Monooxygenase |
| Sept 17 room G201 | Ester/amide hydrolases |
| Sept 19 room G201 | Epoxide hydrolase, microsomal and cytosolic |
| Sept 22 room G201 | UDP-glucuronosyltransferases and glucosyltransferase (UGTs): reactions |
| Sept 24 room G201 | UGTs: enzymology and regulation |
| Sept 26 room G201 | UGTs: inhibition |
| Sept 29 room G201 | Glutathione transferases (GSTs) |
| Oct 1 room G201 | GSTs |
| Oct 3 room G201 | GSTs and related pathways (cysteine ß-lyase) |
| Oct 6 | No class – Dr. James away |
| Oct 8 | No class – Dr. James away |
| Oct 10 room G201 | PAPS-sulfotransferases (SULTs) |
| Oct 13 room G201 | SULTs |
| Oct 15 room G201 | Acetylation |
| Oct 17 room G201 | Amino acid conjugation |
| Oct 20 | No class ISSX Meeting – Dr. James away |
| Oct 22 | No class ISSX Meeting – Dr. James away |
| Oct 24 room G201 | Chiral inversion of carboxylic acids; Fatty acid conjugation; Methylation |
| Oct 27 room G201 | Transporter proteins |
| Oct 29 room G201 | review session |
| Oct 31 room G201 | Exam (3-5pm) |
| Nov 3 room G201 | No class (AAPS is Nov 2-6) |
| Nov 5 room G301A | Metabolism and toxicity, general concepts |
| Nov 7 room G301A | Metabolic activation of constituents of pennyroyal oil |
| Nov 10 room G201 | Metabolic activation of drugs: acetaminophen and phenacetin |
| Nov 12 room G201 | Metabolic activation of drugs: acetaminophen and phenacetin |
| Nov 14 room G201 | Metabolic activation of drugs: valproate |
| Nov 17 room G201 | Metabolic activation of drugs: diclofenac |
| Nov 19 room G301A | Metabolic activation of halothane and chlorinated solvents |
| Nov 21 room G301A | Metabolic activation of ipomeanol |
| Nov 24 room G201 | Metabolic activation of polychlorinated biphenyls |
| Nov 26 | No class: Thanksgiving |
| Nov 28 | No class Thanksgiving |
| Dec 1 room G201 | Metabolic activation of pyrolysis products: polycyclic aromatic hydrocarbons |
| Dec 3 room G201 | Metabolic activation of pyrolysis products: iminoquinolines. Metabolic activation of arylamines |
| Dec 5 Room G201 | Presentations by students |
| Dec 8 HPNP G201 | Presentations by students |
| Dec 10 Room G201 | Review session for final exam |
| Dec xx Time TBA | Final Exam |
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GENERAL NOTES The written examinations will be short answer or essay type, including presentation of reaction schemes or pathways where appropriate, and will be based on the material presented. Previous exams will be available. The midterm exam will be 30% of the grade and the final exam will be 30% of the grade. Make-up exams are not usually given, but will be at the discretion of Dr. James, and the reason for non-attendance at the scheduled exam.

As well as exams, a term paper will contribute to the final grade. A paper on metabolic activation will be assigned to each student from a list of topics to be provided. Alternatively, the student can suggest a topic. Topics, and directions for the format of this paper will be given out in mid-September. The oral presentation of this paper in class will count for 10% of the grade, and the written paper for 30%.

As in any course at the University of Florida academic dishonesty and plagiarism will not be tolerated.