

PHG 513: Basic Concepts in Pharmacogenetics and Toxicogenomics

Winter Quarter, 2012

Tuesday and Thursday 9:00 – 10:20 AM, RR-134

(3 credits)

Course Coordinators:

Dave Eaton, Ph.D.

Professor

Environ. Occup. Health Sci., Box 354695

Office: 4225 Roosevelt Way, NE, Rm 205

Phone: 685-3785; Fax: 685-4696

e-mail: deaton@u.washington.edu

Office hours: by appointment

Ken Thummel, Ph.D.

Professor and Chair

Pharmaceutics, Box 357610

Office: H272N Magnuson HSB

Phone: 543-0819; Fax: 543-3204

e-mail: thummel@u.washington.edu

Teaching Assistant:

Sara I. Crumb

Public Health Genetics

Office hours: by appointment

e-mail: sicrumb@uw.edu

Prerequisites: Biochem 442 or Genetics 372 or equivalent, or instructor permission.

Course Description: This course will draw from multiple disciplines to provide a general understanding of molecular approaches to genotyping, as well as the understanding of genotype/phenotype relationships and gene-environment interactions as determinants of disease susceptibility. Instruction will cover the application of array technologies for the identification of low penetrance disease susceptibility genes and the identification of potential gene targets for novel pharmacotherapeutic treatments of disease. It will also examine the molecular basis for interindividual differences in drug/xenobiotic disposition and application of that information for individualized drug treatment regimens and disease prevention strategies.

Learning Objectives: At the end of this course students should be able to:

1. explain the various technologies used to identify genetic polymorphisms, with particular emphasis on genes of pharmacological and environmental relevance.
2. be able to identify and understand the conceptual basis behind basic methodologies used to identify genetic variability in human DNA samples
3. explain the significance of genetic polymorphisms in the development, progression, and treatment of human disease.
4. appreciate the public health importance of genetic variability in specific multigene families of enzymes involved in metabolism of drugs and non-drug chemicals in the environment
5. describe the connection between environmental exposures, genetic polymorphisms, and risk for diseases of public health importance.
6. understand the role of genetic polymorphisms as determinants of adverse drug reactions and pharmacological efficacy.
7. read critically original scientific literature relating to 'gene-environment interactions'
8. have the technical background necessary to appreciate the ethical, legal and social implications that arise out of pharmaco- and toxicogenomic research.
9. write professionally about one area of 'gene-environment' interaction with public health importance
10. integrate basic concepts of ethics into arguments for and against genotyping of populations for 'environmental susceptibility' genes.

Grading

The course will include 3 exams (multiple choice / short answer) over materials covered in class and assigned readings that will count for 75% of your grade (25% for each of 3 exams). The remaining 25% of your grade will be based on your class term paper. An average numeric score of 80 will be approximately equal to a grade point score of 3.0, a score of 90 will be a 3.5 and average scores of 95 and above will be 4.0.

Readings

Textbook: We recommend that students use the textbook, "Gene-Environment Interactions: Fundamentals of Ecogenetics (LG Costa and DL Eaton, Editors, Wiley Press, 2006) for selected background reading, although it is not required. Some reading assignments will be from this textbook, although some additional background or supplemental reading may be provided. For students who feel that their background in basic molecular biology and genetics requires updating, we recommend any basic textbook in molecular genetics or medical genetics. A good text is: Strachan and Read's "Human Molecular Genetics," 2003 (\$60 used paperback), or *Human Genetics and Society* (2008) by Ronnee Yashon and Michael Cummings.

Hard copies of lecture notes will generally not be provided on the day of the lecture in class. Powerpoint and pdf files of the lecture notes can be accessed on-line, through the course website. An exception will be made when the lecture is not available at least 24 hr prior to the start of class.

Term Paper

You will be asked to choose a particular disease that has both a genetic and an environmental component to it, and write a brief paper (12-15 pages, double spaced) describing what is known about the etiology of the disease. In the paper, you should cover:

1. the fundamental biology of the disease, including which genes are involved
2. identify candidate genes that might act as susceptibility genes, and discuss their function
3. review the basic epidemiology of the disease that has led to discoveries that genetic factors are involved
4. identify and discuss any environmental factors that have been implicated in the etiology of the disease; environmental factors are defined in their broadest terms, and include diet, viruses and other microbiological factors, occupation, lifestyle factors, etc.
5. identify and discuss at least one "ELSI" problem – real or potential, that has surfaced in your study of the disease.
6. include all appropriate references

Possible diseases for discussion include, but are not limited to:

Parkinson's Disease	Diabetes
Amyotrophic Lateral Sclerosis (ALS: Lou Geherig's Disease)	Alcoholism
Alzheimer's Disease	Certain birth defects that may have a genetic component
Cancer, any kind, especially:	Heart disease
Colon Cancer	Lung diseases such as asthma, COPD, pulmonary fibrosis, etc.
Breast Cancer	Just about any other chronic disease that is not purely genetic
Brain Cancers (several forms)	Genetically determined adverse drug responses
Malignant Melanoma	
Leukemia	

LECTURE SCHEDULE, WINTER QUARTER, 2012

Date	Topic	Lecturer	Book[@]
Jan. 3	Introduction: genes, environment and disease	Eaton	Chp. 1 & 2
Jan. 5	Technological approaches to understanding genotype-phenotype relationships I – DNA analysis	Eaton	Chp. 3
Jan. 10	Technological approaches to understanding genotype-phenotype relationships II – RNA analysis	Eaton	Chp. 3
Jan. 12	Technological approaches to understanding genotype-phenotype relationships III – Proteomics and metabolomics analyses	Thummel	handout
Jan. 17	Applications of GWAS and Next Generation sequencing technologies	Eaton	handout
Jan. 19	Epigenetics	Eaton	Chp 6; handout
Jan. 24	EXAM 1 (from Jan 3 – Jan 19)		
Jan. 26	Polymorphisms and enzyme kinetics	Thummel	Chp. 7 handout
Jan. 31	Pharmacogenetics and individualized therapies - I (CYPs 2D6, 2C9, 2C19, PON1)	Thummel	Chp. 7 handout
Feb. 2	Pharmacogenetics and individualized therapies – II (CYPs 2C9, 1A1 &2, 2E1, FMO3, ALDH2)	Thummel	Chp. 7
Feb 7	Pharmacogenetics and individualized therapies – III (VKORC1, HLA, G-protein coupled receptors)	Thummel	Chp 11
Feb 9	Toxicogenomics -1 (CYPs 3A5, 1A1 &2, 2E1, FMO3, ALDH2)	Eaton	Chap 7
Feb. 14	Toxicogenomics - 2 (UGTs, SLTs, Transporters)	Thummel	Chp. 8
Feb. 16	Toxicogenomics - 3 (GSTs, mEH, NQ01)	Eaton	Chp. 8, 9
Feb. 21	Polymorphisms in DNA repair	Eaton	Chp. 10
Feb. 23	EXAM 2 (from Jan 26 – Feb. 16)		
Feb. 28	Pharmacogenomics and Drug development	Thummel	handout
March 1	ELSI related to Pharmaco- and Toxicogenomics	Wylie Burke	Chp. 21-23 and handout
March 6	ELSI related to Pharmaco- and Toxicogenomics	Wylie Burke	handout
March 8	G x E interactions and ALL	Thummel	handout
Final Week	EXAM 3 (from Feb. 21 – Mar 8); Term paper – due 4 PM, Friday March 16		

[@]Textbook: Costa, LG and Eaton DL. *Gene-Environment Interactions: Fundamentals of Ecogenetics*, Wiley Press, 2006. (Check Amazon.com for resale priced books)

NOTE: *Lecture notes will be on the web page at least 24 hours before class if available. If they are not posted by that time, hard copies will be provided on the day of the lecture in class. Any additional readings will be listed on the website if links are available.*

Guest Lecturers:

PHG 513: Basic Concepts in Pharmacogenetics and Toxicogenomics-- Winter 2012

Ed Kelly, Research Assistant Professor, Department of Pharmaceutics, UW;
edkelly@u.washington.edu

Yvonne Lin, Assistant Professor, Department of Pharmaceutics, UW;
yvonlin@u.washington.edu

Mark Rieder, Research Associate Professor, Department of Genome Sciences, UW;
mrieder@u.washington.edu

Wylie Burke, Professor and Chair, Department of Bioethics & Humanities, UW;
wburke@u.washington.edu

Karen Edwards, Associate Professor, Department of Epidemiology, UW;
keddy@u.washington.edu

Students with disabilities: To request academic accommodations due to a disability, please contact Disability Resources for Students, 448 Schmitz Hall, 206-543-8924 (V/TTY). If you have a letter from Disability Resources for Students indicating that you have a disability that requires academic accommodations, please present the letter to me so we can discuss the accommodations you might need in this class.