Pharmacogenomics
PHA 6449 – Section 13AG
Departments of Pharmacotherapy and Translational Research
Center for Pharmacogenomics, University of Florida
Credits: 2 hours

Spring 2016

Course Syllabus

COURSE DESCRIPTION: Pharmacogenomics is the study of how an individual's genetics influences responses to drugs. This course will focus on pharmacogenetics and pharmacogenomics research design, including utilization of key knowledge from the human genome, HapMap and 1000 genomes projects, genomic, transcriptomic, and metabolomics approaches, other considerations in design of human pharmacogenomics investigations, and approaches to defining functional effects of pharmacogenetic candidates. This course will use the framework of pharmacogenomics to lay the foundation for understanding other types of omic and pharmaco-omic study designs and analyses. The course will use a combination of lectures, discussions of assigned literature, projects and student-led presentations. This course is intended as a graduate course with a maximum of 12 students.

Pre-requisites: 1 semester of statistics (PHC 6052/6053 or similar) OR PCB 5065 (Advanced Genetics) (preferably both) OR instructor approval.

Learning Objectives: The goal of this course is to provide students with the knowledge and skills to undertake pharmacogenomics or pharmaco-'omic' research. The students will learn the basics of designing a pharmacogenomics study using genomic, transcriptomic and metabolomics approaches. The students will also gain hands-on experience of how to apply for access to publically available data and how to perform a pharmacogenomics GWAS analysis using real data. The focus on GWAS analyses will provide studies with a skill set that may be applied to many other types of 'omic' data.

CLASS PERIOD/ROOM:	2 hours per week – Mondays 3:00 -5:00 PM; HSC MSB Room P4-20 **Except Tuesday Jan 5, and Tuesday Jan 19th 3:00-5:00 PM; P4-20
COURSE COORDINATOR:	**Yan Gong, Ph.D. (gong@cop.ufl.edu)**
CO-COORDINATOR:	**Caitrin McDonough, Ph.D. (cmcdonough@cop.ufl.edu)**
FACULTY:	**Larisa Cavallari, Pharm.D. (LCavallari@cop.ufl.edu)** **Reggie Frye, Pharm.D.,Ph.D (frye@cop.ufl.edu)** **Julio Duarte, Pharm.D., Ph.D. (juliod@cop.ufl.edu)** **Vishal Lamba, PhD (vlamba@cop.ufl.edu)**
INVITED SPEAKER:	**Michael Pacanowski, PharmD** (Michael.Pacanowski@fda.hhs.gov)

TEXT: There is no required text. The instructor will provide the required readings.

GRADING AND EXAMS:

The course grade will be determined as follows:

- Written report of pharmacogenomics study/oral presentation 25%/5%
- Association analysis written report/oral presentation 15%/5%
- Association analysis follow-up written report/oral presentation 15%/5%
- Final oral exam 10%
- Class participation/completion of required readings 20%

Grades will be assigned as follows:	90-100:	A
	87-89	B+
	83-86	B
	80-82	B-
	77-79	C+
	73-76	C
	70-72	C-
	60-69	D
	< 60	E

ACCOMMODATIONS FOR STUDENTS WITH DISABILITIES: Students requesting classroom accommodation must first register with the Dean of Students Office. This office will provide documentation to the student who must then provide this documentation to the Instructor when requesting accommodation.

ACADEMIC HONESTY: As a result of completing the registration form at the University of Florida, every student has signed the following statement: "I understand that the University of Florida expects its students to be honest in all their academic work. I agree to adhere to this commitment to academic honesty and understand that my failure to comply with this commitment may result in disciplinary action up to and including expulsion from the University." It is understood that by registering for this course, you will abide by the academic policies of the University.

Plagiarism: Plagiarism is defined as the practice of taking someone else's work or ideas and passing them off as one's own. Plagiarism is not tolerated at the University of Florida or in this class. All written assignments will be examined for originality using iTheniticate software, to ensure the work represents each students own words, and that proper citation is used. If a written assignment is found to be plagiarized (e.g. large portions of the work are directly copied from another source), the incident will be reported to the University, and procedures outlined by the students' graduate program will be followed.

STUDENT ASSIGNMENTS

Projects/papers/presentations:

Note: All written reports are due at the start of class on the oral presentation days.

Pharmacogenomics project. For this project, you will be expected to find a publically available dataset with genome-wide SNP data (GWAS data), and drug information (NIH dbGaP is the recommended source, and will be covered in class). You will select your primary drug response phenotype from the phenotypes available in the study you are working with. You will select additional phenotypes that you would want to include as covariates in your analysis. You will identify the sample size, genetic information available (or other 'omic information available), your study design, the limitations in your study design that arise from using a publically available dataset, which was not necessarily collected with pharmacogenomic questions in mind, and ways that you plan to overcome these limitations. You will use the provided modified template for a dbGaP proposal for the written report, and you should include appropriate references. The oral presentation should be 8-9 minutes summarizing your written dbGaP proposal. You may also use other 'omics data available within dbGaP, or other 'omic data from similar databases (with instructor approval) to complete this assignment. The question, hypothesis and phenotype still must be pharmaco – omic based.

Association analysis project – Part 1. To gain experience with pharmaco-omic analyses and the types of large datasets these analyses use, you will conduct a pharmacogenomic GWAS analysis. You will be given data from the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR)-2 study for association analysis. It is expected that you will each be given directly typed or imputed data from either the whole genome, or part of the genome, and will be given the relevant covariates and drug response phenotype data (likely glucose change after chlorthalidone treatment). To conduct this analysis, you will need to learn PLINK software at the website: http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml or a similar analysis tool. Additionally, you will need a

HPC account (http://www.hpc.ufl.edu/help/account-request/), you should list your graduate advisor as the faculty member.

You will then summarize in both an oral and written report your analysis approach and statistically-strongest findings, including typical graphical representations of your findings. Your oral presentation should be 8-9 minutes.

Association analysis project – Part 2. The second part of your association analysis project will be to 1) describe the 3 strongest biological candidates/regions from your analysis, identifying the genes that make the region strong and why, 2) describe the LD in the top regions, and whether your top SNPs, or any LD/tag SNPs, are putative functional SNPs, and 3) summarize what you would consider your strongest 5 SNPs, based on all of the above, to move forward to replication in an independent cohort. You will submit these 5 SNPs to Dr. Gong or Dr. McDonough by April 6th for an attempt at replication in PEAR1, and will receive back the p-values, and effect, and will perform meta-analysis on your top 5 signals in METAL. Again, this will be summarized in a written and oral presentation. The oral presentation should be ~10 minutes long.

**Project requirements may change slightly depending on the students' knowledge level

Note: Prior offerings of this course have resulted in publication of the course project with all the participating students included as coauthors:
McDonough CW, Gillis NK, Alsultan A, Chang SW, Kawaguchi-Suzuki M, Lang JE, Shahin MH, Buford TW, El Rouby NM, Sá AC, Langaee TY, Gums JG, Chapman AB, Cooper-DeHoff RM, Turner ST, Gong Y, Johnson JA. Atenolol Induced HDL-C Change in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) Study. PLoS One. 2013 Oct 7;8(10):e76984. PubMed PMID: 24116192.

McDonough CW, El Rouby NM, Magvanjav O, Sa ACC, Dave C, Kawaguchi-Suzuki M, Mei W, Shen Y, Singh R, Solayman M, Tucker AN, Bailey KR, Boerwinkle E, Chapman AB, Turner ST, Cooper-DeHoff RM, Gong Y, Johnson JA. Genetic Variants Influencing Plasma Renin Activity in Hypertensive Patients from the Pharmacogenomics Evaluation of Antihypertensive Responses (PEAR) Study. *To be submitted Spring 2016.*

Conrado DJ, Gonzalez D, Gong Y, Shahin MH, Lobmeyer M, Cooper-DeHoff RM, Boerwinkle E, Turner ST, Chapman AB, Gums GG, Johnson JA. Genetic Predictors of Heart Rate Response to beta-blockers in the Pharmacogenomics Evaluation of Antihypertensive Responses (PEAR) Studies. *To be submitted Spring 2016.*

Final oral examination. Following your association analysis (Part 2) presentation, you will be asked questions related to this assignment, but will also be asked questions that will serve as your final oral examination (i.e. questions can derive from anywhere in the course).

Required Readings. Students are expected to complete all required readings PRIOR to class, and a portion of their grade will be based on class participation and their ability to discuss the required readings.

Attendance. Attendance to all class sessions, and to all other students' oral presentations is expected. If you need to miss a class session, you need to make ADVANCED arrangements with the course coordinators. All unexcused absences will receive a 'zero' for that week's participation grade.

Course and instructor evaluations. Course and instructor evaluations are essential elements to assessing the quality of the course and instructions and it is expected that all students will require these evaluations.

Late assignments. Assignments turned in late will receive a penalty:
1 hr to 24 hrs late: 20% deduction
25 hrs to 48 hrs late: 50% deduction
Assignments will not be accepted past 48 hrs, and the student will receive a zero.

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Course Schedule 2016

Week	Topic	Instructor
Jan 5 *TUESDAY*	Course introduction and Overview of pharmacogenetics and pharmacogenomics Study designs in pharmacogenetics and phenotype selection and Identifying biological candidate genes.	Gong
Jan 11	Linkage disequilibrium, HapMap, 1000 Genomes & ENCODE; Controlling for population structure in genetic association analyses	McDonough
Jan 19 *TUESDAY*	Introduction to 1st project, and NCBI dbGaP TagSNPs, pfSNPs, and other web tools and databases	McDonough
Jan 25	Genome-wide association studies in pharmacogenomics (discussions)	Gong & McDonough
Feb 1	Association analysis: GWAS and meta-analysis; Intro to 2nd project Computer hands-on training: PLINK	Gong McDonough
Feb 8	Computer hands-on training: Genomic QC with PLINK Association analysis: Meta-analysis	McDonough Gong
Feb 15	Student presentations of dbGaP pharmacogenomics study	All
Feb 22	Analysis Q&A	Gong & McDonough
Feb 29	**Spring Break**	
Mar 7	Application of Transcriptome and RNAseq in PGx Epigenetics and pharmacogenomics, DNA methylation analysis	Sá Lamba
Mar 14	Next-generation sequencing; Whole genome sequencing, Whole Exome sequencing (discussions)	Duarte
Mar 21	Genetic association analysis presentations	All
Mar 28	Application of Metabolomics in Pharmacogenomics	Frye
Apr 4	Integrated analysis of multiple ‘omics data	Gong
Apr 11	Pharmacogenomics: Regulatory Issues Pharmacogenomics: Translation to Practice	Pacanowski Cavallari
Apr 18 (Classes End 4/23)	Association analysis hits: strongest candidates presentations AND final oral exam	All 3 hours