PHA6133 [Translational Clinical Pharmacology]
[Spring 2019 and every 2 years thereafter]
3 Credit Hours

Course Purpose:

The objective of this course is to provide Ph.D. students with an in-depth understanding of experimental, basic and advanced modeling & simulation methodologies and their application to optimize patient dosing and rationally develop drugs.

This course will provide participants the skill set to design pre-clinical experiments and modeling approaches for successful translation to clinical drug development (Phase I), and to rationally select dosage regimens and endpoint(s) for Phase II and III clinical trials. This translational drug development approach supports the rational development of optimal dosing strategies, including novel combination therapies, and achieving target goals most precisely in patients. The concepts and principles in this course are applicable to any therapeutic area.

Maximum enrollment: 30

Course Faculty and Office Hours

(See **Appendix A** for Who to Contact)

COURSE DIRECTOR: Jürgen B. Bulitta, PhD, Associate Professor
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Office Hours: Tuesday, 3-4 PM

Teaching assistants: Dr. Dhruvitkumar Sutaria (Orlando) and Dr. Sagar Bachhav (Gainesville)
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Course-Level Objectives

Upon completion of this course, students will be able to understand and apply the concepts and principles of translational drug development, pharmacometric modeling and simulations, and optimal individualized patient dosing. Specifically:

1. Understand the concepts and principles of an integrated experimental and modeling strategy for quantitative data analysis to move translational drug development programs forward.
2. Understand and apply the benefits of population modeling methodology for optimal patient dosing, analyzing datasets with between subject variability, and translational pharmacology.
3. Apply basic and advanced models to translate from *in vitro* and animal models to human clinical trial and to optimize patient dosing; familiarity with the 'critical questions in industry'.
4. Judge the pros and cons of different data analytical approaches for translational pharmacology, including population modeling via contemporary estimation algorithms.
5. Understand the types of datasets and experimental designs required to support translational modeling.
6. Become proficient in creating and handling datasets for mechanistic modeling & simulation analyses; understand principles and best practices of bioinformatics (including mining of large datasets).
7. Understand the assumptions and limitations of empiric and mechanistic models.
8. Gain advanced knowledge in selected disease areas and therapeutic dosing strategies.
9. Write and debug robust and clean modeling and simulation code for empiric and mechanistic models in relevant (population) estimation and simulation software packages.
10. Obtain pharmacological and disease expertise to understand antimicrobial, antiviral and cancer chemotherapy in the context of drug development.

Pre-Requisite or Co-Requisite Knowledge and Skills

Pre-requisite for participation in the Clinical Translational Pharmacology course is an introductory course on pharmacokinetic or pharmacodynamic principles which has been successfully completed; such as course:
PHA5132: Principles of Drug Therapy Individualization

Equivalent courses from other universities will be considered. Documentation of the course content (including contact hours) should be provided. The final decision about equivalency will be taken by the course director.

Co-Requisites: None

Course Outline

Contact hours: 45 (total)

- ✓ Module 1: Course Introduction
- ✓ Modules 2: General Concepts and Principles
- ✓ Modules 3-4: Basic Modeling and Study Design
- ✓ Modules 5-6: Empiric & Mechanistic Models for Translational Analyses
- ✓ Modules 7-10: Population Modeling
- ✓ Modules 11: Population Modeling Software
- ✓ Modules 12: Achieving Patient Target Goals Most Precisely
- ✓ Modules 13-14: Translational Drug Development in Action

Week	Date	Instructor	Topic/Learning Activities	Contact Hours	Reading
Week 1	1/9/19	Bulitta	**COURSE INTRODUCTION (M1)** Introduction & Objectives Importance of quantitative drug development and optimal dosing	1.5	[1], for background reading ('refresher') [14-16]
Week 1	1/11/19	Bulitta	**GENERAL CONCEPTS AND PRINCIPLES (M2)** Concepts and Principles of Translational Drug Development and Optimal Patient Dosing Strategies, including concepts and applications of - Pre-clinical to clinical translation, - Accounting for differences in body size, body composition and disease state	1.5	[2]
Week 2	1/16/19	Bulitta	**BASIC MODELING AND STUDY DESIGN (M3-4)** Basic modeling & estimation approaches and their assumptions – *Part I* Homework assignment 1 *(non-graded)*	1.5	[3], Chapter on Modeling Strategies
	1/18/19		Basic modeling & estimation approaches and their assumptions – *Part II*	1.5	
Week 3	1/23/19		Experimental design principles and datasets for translational pharmacology	1.5	
	1/25/19		Dataset generation & handling; Introduction to bioinformatics; Principles and practices of data mining	1.5	[4]
			Hands-on Session 1: Discussion of modeling and estimation approaches		
			Online/Individual Study: Homework assignment 2 **Select term paper 1 for each student**		
Week 4	1/30/19	Bulitta	**EMPIRIC & MECHANISTIC MODELS FOR TRANSLATIONAL PHARMACOLOGY (M5-6)** Basic pharmacokinetic / pharmaco-dynamic (PK/PD) models	1.5	[5]
	2/1/19	Bulitta	Hands-on Session 2: Dataset generation for PK and PK/PD case studies	1.5	
Week 5	2/6/19	Bihorel	Mechanistic PK/PD models	1.5	
	2/8/19	Bulitta	Applying models for translational pharmacology; translation from *in vitro* via animal to predict human studies	1.5	
Week 6	2/13/19	Bulitta / Bihorel	Translational modeling – part 2 Approaches to model drug combinations	1.5	[6]

Week	Date	Instructor	Topic/Learning Activities	Contact Hours	Reading
Week 6	2/15/19	Bulitta	**Presentation of term paper 1**, including a discussion of the strengths and weaknesses of the respective paper	1.5	
Week 7	2/20/19	Bulitta	**Selection of term paper 2 for each student**		
			POPULATION MODELING, M7-10		
Week 7	2/20/19	Bulitta	Concepts & Principles of Population Modeling & Monte Carlo simulations	1.5	[7]
	2/22/19	Bulitta	Clean Coding of Population Models in S-ADAPT and Diagnostic plots	1.5	[8]
Week 8	2/27/19	Bihorel	Empiric population PK & PK/PD modeling in ADAPT5	1.5	[9]
	3/1/19	Bulitta	Population PK modeling in S-ADAPT Hands-on Session 3 (diagnostic plots) Homework assignment 3	1.5	
			Week 9 = spring break (Mar 4-8)	1.5	
Week 10	3/13/19	Bulitta	Population PK/PD in NONMEM and S-ADAPT	1.5	[10]
	3/15/19	Bulitta	Empiric & mechanistic population PK/PD modeling in S-ADAPT		
Week 11	3/20/19	Bulitta	Hands-on Session 4 (PK/PD models)	1.5	[11]
	3/22/19	Bulitta	Population estimation algorithms (maximum likelihood) and Population PK models in NONMEM Homework assignment 4	1.5	

Week	Date	Instructor	Topic/Learning Activities	Contact Hours	Reading
Week 12	3/27/19	Bulitta	**POPULATION MODELING SOFTWARE (M11)** 1) Modeling Approaches and Software 2) Translational PK/PD from *in vitro* and animal models to humans 3) Immediate and delayed drug effects 4) Advanced aspects of combination modeling	1.5 1.5	
	3/29/19	Bulitta	Population Modeling Concepts, Applications and useful Tricks		
Week 13	4/3/19	Bulitta	**ACHIEVING PATIENT TARGET GOALS MOST PRECISELY (M12)** Nonlinear-mixed effects modeling: When and how to use which Algorithm Bayesian Approaches to population modeling Homework assignment 5	1.5	[12]
	4/5/19	Jiao, Tao, Bulitta	Population PK modeling of parent and metabolite data in plasma and urine Cellular penetration modeling	1.5	
Week 14	4/10/19	Bulitta	**Presentation & discussion of term paper 2**	**3.0**	
Week 14	4/12/19	Brown	**TRANSLATIONAL DRUG DEVELOPMENT IN ACTION (M13-14)** Translational Drug Development in Action – Experimental approaches – **Antivirals**	1.5	[13]
Week 15	4/17/19	Neely	Nonparametric population PK/Pmetrics Achieving Patient Target Goals Most Precisely in real patients via BestDose	1.5	
	4/19/19	Drusano	Why mathematical modeling is our friend – time to deal with real "bugs" Homework review	**1.0** 0.5	
Week 16	4/24/19	Louie	Translational Drug Development in Action – Experimental approaches – **Antibiotics**	1.5	
		Bulitta	**Final exam (Modules 1-14) – Take home**		
			Total Instructor Contact Hours	**45**	

Textbooks

The following reading materials are referenced in the Table above. The last three books in the list are intended for general background reading on general pharmacokinetics, physiological & pharmacological concepts, compartment models, and their assumptions, if students need to refresh their background on these topics.

1. Bulitta JB, Holford NHG (13 June, 2008). An Introductory Guide to Non-Compartmental Analysis. In: Wiley Encyclopedia of Clinical Trials, (Ralph B. D'Agostino, Lisa Sullivan, Joseph Massaro, eds.) Hoboken: John Wiley & Sons, Inc. dx.doi.org/10.1002/9780471462422.eoct340
2. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol 2004; 2: 289-300.
3. Gabrielsson J, Weiner D. Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts & Applications; Chapter Modeling Strategies, Swedish Pharmaceutical Press; 4 edition, 2007, ISBN-13 978 91 9765 100 4.
4. Bauer RJ, Guzy S, Ng C. A survey of population analysis methods and software for complex pharmacokinetic and pharmacodynamic models with examples. AAPS J. 2007; 9: E60-83.
5. Al-Sallami HS, Pavan Kumar VV, Landersdorfer CB, Bulitta JB, Duffull SB. The time course of drug effects. Pharm Stat 2009; 8:176-85. PMID: 19626596
6. Landersdorfer CB, Ly NS, Xu H, Tsuji BT, Bulitta JB. Quantifying subpopulation synergy for antibiotic combinations via mechanism-based modeling and a sequential dosing design. Antimicrob Agents Chemother. 2013; 57: 2343-51.
7. Bulitta JB, Holford NHG (14 March, 2008). Population Pharmacokinetic and Pharmacodynamic Methods. In: Wiley Encyclopedia of Clinical Trials, (Ralph B. D'Agostino, Lisa Sullivan, Joseph Massaro, eds.) Hoboken: John Wiley & Sons, Inc. dx.doi.org/10.1002/9780471462422.eoct338
8. Bulitta JB, Bingölbali A, Shin BS, Landersdorfer CB. Development of a new pre- and post-processing tool (SADAPT-TRAN) for nonlinear mixed-effects modeling in S-ADAPT. AAPS Journal 2011; 13:201-11; DOI: http://dx.doi.org/10.1208/s12248-011-9257-x . PMID: 21369876
9. Schmidt S, Derendorf H. Applied Pharmacometrics. Springer 2014 edition, 2014, ISBN-13 978-1493913039.
10. Tsuji BT, Okusanya OO, Bulitta JB, Forrest A, Bhavnani SM, Fernandez PB, Ambrose PG. Application of pharmacokinetic-pharmacodynamic modeling and the justification of a novel fusidic acid dosing regimen: raising Lazarus from the dead. Clin Infect Dis 2011; 52:S513-9. PMID: 21546628
11. Yadav R, Landersdorfer CB, Nation RL, Boyce JD, Bulitta JB. Novel approach to optimising synergistic carbapenem plus aminoglycoside combinations against carbapenem-resistant *Acinetobacter baumannii.* Antimicrob Agents Chemother. 2015; 59:2286-98. PMID: 25645842
12. Neely MN, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, Lodise TP. Are vancomycin trough concentrations adequate for optimal dosing? Antimicrob Agents Chemother. 2014; 58:309-16.
13. Bulitta JB, Landersdorfer CB, Forrest A, Brown SV, Neely MN, Tsuji BT, Louie A. Relevance of Pharmacokinetic and Pharmacodynamic Modelling to Clinical Care of Critically Ill Patients. Current Pharmaceut Biotechnol 2011; 12:2044-61. PMID: 21554212
14. Birkett D. Pocket Guide: Pharmacokinetics Made Easy. McGraw-Hill Education / Australia; 2 edition, 2009. ISBN-13: 978-0070285279.
15. Rowland M and Tozer TN. Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications. LWW; Fourth edition, 2010, ISBN-13: 978-0781750097.
16. Gibaldi M, Perrier D. Pharmacokinetics – Drugs and the Pharmaceutical Sciences. Marcel Dekker, 2nd Edition, 1982, ISBN-13 978-0824710422.

Student Evaluation & Grading

Students will be evaluated along the year through quizzes, homeworks, examinations in the classroom, and term papers and oral presentations.

Evaluation Methods and how grades are determined

Assessment Item	Grade Percentage
Homework / software assignments	30%
Term paper 1 and oral presentation	20%
Term paper 2 and oral presentation	20%
Exam	30%
Total	**100%**

Grading Scale

> 92.5%	A
89.5-92.4%	A-
86.5-89.4%	B+
82.5-86.4%	B
79.5-82.4%	B-
76.5-79.4%	C+
72.5-76.4%	C
69.5-72.4%	C-
66.5-69.4%	D+
62.5-66.4%	D
59.5-62.4%	D-
< 59.4%	E

Rounding of grades: Final course grade will only be rounded up if the decimal is 0.5 or higher. The above scale depicts this policy.

Class Attendance Policy

Class attendance is mandatory for all classes. Student attendance may be excused by Dr. Bulitta in the following situations: documented illness, family emergencies, religious holidays, and other reasons of serious nature. Conflict with work schedules is an unexcused absence.

Requests for excused absences MUST be made by an email prior to the scheduled session. The student is responsible for follow up.

To: Academic Coordinator and Campus Course Facilitator
CC: Course director and your specific campus director
Subject: PHA 6XXX – Excused Absence request

Dear Prof. Jürgen Bulitta,
Professionally and politely request an excused absence.
Explain the nature of conflict and rationale for receiving an excused absence.
Thank the faculty member for their consideration of your special request.
Salutation,

Juergen Bulitta and last 4 digits of UF-ID #: 5991, and College of Pharmacy (Orlando campus), University of Florida.

Failing to follow this policy will render the absence not excusable. A request for an "excused absence" does not guarantee acceptance. No precedence can be drawn from any courses in the College of Pharmacy or any other college within University of Florida.

Makeup assignment(s) will be made for any excused absence(s) and must be submitted ***within one-week of the missed session(s)***. If the situation leads to missing multiple class sessions and makeup becomes difficult, the student and Course Director will meet with the Associate Dean of Student Affairs to explore options such as a remediation plan or course withdrawal. Class attendance requires full engagement of activities and discussions.

The following are unacceptable during class: 1) read non-course related materials that are either in hard-copy or web-based, 2) study for other courses, 3) use a laptop for activities that are not course-related. Class participation will be reduced in such situations.

Please refer to the **University Attendance Policy** (including the **Religious Holidays** policy) at https://catalog.ufl.edu/ugrad/current/regulations/info/attendance.aspx

Additional Policy Specific to This Course: Quiz/Exam Policy

1. Students must arrive and be seated promptly to be eligible to take the exam. Students who arrive late for the exam will not be allowed to start the exam if they are more than 30 minutes late or if another student has left the room after seeing the exam.
2. No talking or other disruptive behavior during the distribution or taking of the exam.
3. During quizzes/RATs, all students must quietly wait until the quiz/RAT ends. Students may not leave the room until the quiz/RAT ends.
4. Nonessential materials are NOT allowed at the student's desk during examination periods. Please leave all nonessential materials outside of or in the front of the examination room.

5. Other exam rules may be instituted during the progression of the course.
6. Once the exam commences, students may not leave the room without first turning in or electronically submitting the exam. Once the exam is turned in or submitted, the examination period for the student is considered complete and the student must leave the examination room. If there is urgent need to use the restroom, the Proctor will provide guidance.

Failure to follow exam rules may be considered as evidence of academic dishonesty.

Make-up Quiz/Exam Policy

Makeup exams are given only under special circumstances. If the student is unable to take a scheduled examination, the Academic Coordinator must be notified before the examination. In addition, a written letter of explanation, requesting that the absence from the exam be excused, must be presented before the exam or immediately afterwards. An excused absence is allowable when: 1) the student is hospitalized and/or has been advised by a licensed medical practitioner or hospital not to attend the exam, or 2) if there is a documented death of an immediate family member as defined by UF policy. All excused absences will be considered on an individual basis by the Academic Coordinator. For unusual situations (e.g., wedding that was planned before admission), the faculty member will communicate with student affairs.

The makeup exam must be taken ***within one-week of the missed exam***. In extenuating circumstances (e.g., hospitalization, faculty availability), the instructor may arrange an alternate deadline for the exam.

The student may contact the Academic Leader to obtain details about why points were deducted. The student has two weeks following the return of the Exam to clarify any questions and appeal any possible grading errors. Any appeals on the final examination must be made in writing and submitted to your facilitator. **When an appeal is made to re-grade an Exam, the entire Exam will be reevaluated and scored.**

Additional Policy Specific to this Course: none

Academic Integrity Policy

Students are expected to act in accordance with the University of Florida policy on academic integrity (http://www.dso.ufl.edu/sccr/honorcodes/honorcode.php). This Honor Code specifies a number of behaviors that are in violation of this code and the possible sanctions. Furthermore, you are obliged to report any condition that facilitates academic misconduct to appropriate personnel. If you have any questions or concerns, please consult the Course Director. Students are also expected to abide by the UF Honor Code.

The following is the UF Honor Pledge: *We, the members of the University of Florida community, pledge*

to hold ourselves and our peers to the highest standards of honesty and integrity by abiding by the Honor Code.

On all work submitted for credit by students at the University of Florida, the following pledge is either required or implied: *"On my honor, I have neither given nor received unauthorized aid in doing this assignment."*

How to Request Learning Accommodations

Students with disabilities are strongly encouraged to register with Disabled Student Services in the Office for Student Services (P202 Peabody Hall) and it is recommended this to be accomplished prior to starting the course.

- Students requesting classroom accommodation must first register with the Dean of Students Office. The Dean of Students Office will provide documentation to the student who must then provide this documentation to the Instructor when requesting accommodation.
- Please visit the following URL for more information: http://www.dso.ufl.edu/drc

Please note that you must arrange for accommodations in advance; grades cannot be retroactively changed

Faculty and Course Evaluations

Students are expected to provide feedback on the quality of instruction in every course based on 10 criteria. These evaluations are conducted online at https://evaluations.ufl.edu . Evaluations are typically open around mid-semester and need to be completed by the established deadline. Summary results of these assessments are available to students at https://evaluations.ufl.edu .