May 17-19, 2018, Niagara Falls, NY

3-DAY WORKSHOP ON MONOCLONAL ANTIBODY PHARMACOKINETICS & PHARMACODYNAMICS

Concepts, Applications, & Case Studies

University at Buffalo
School of Pharmacy and Pharmaceutical Sciences

BMSR Biomedical Simulations Resource
bmsr.usc.edu

COURSE OUTLINE

This workshop has been designed to provide a detailed discussion of issues relevant to the pharmacokinetic / pharmacodynamic (PK/PD) modeling of antibody drugs, and to provide a series of "hands-on" case studies describing the development and application of mathematical models to simulate and characterize antibody PK/PD. Lectures will address primary determinants of antibody pharmacokinetics (PK) and pharmacodynamics (PD), the design and implementation of pre-clinical investigations of antibody PK/PD, and state-of-the-art mathematical models to characterize and predict antibody PK and PD. Case studies, featuring use of the ADAPT program, will include application of models for antibody-ligand binding and disposition, target-mediated disposition, and physiologically-based pharmacokinetic modeling. Special emphasis is placed on discussion of the role of FcRn on the absorption, distribution, and elimination of antibodies, on the mathematical modeling of target-mediated antibody disposition, and on physiologically-based modeling of antibody pharmacokinetics. The workshop content is provided as a combination of formal lectures and informal review sessions.

Subjects that will be presented include:

Determinants of antibody pharmacokinetics and pharmacodynamics: mechanisms of antibody elimination, the role of convection in the kinetics of antibody distribution, the role of FcRn in antibody absorption, distribution, and elimination

Interspecies Scaling of Antibody PK: considerations and examples involving the use of allometric methods to scale protein pharmacokinetics from pre-clinical models to humans

Drug-drug interactions: mechanistic considerations and examples for drug-drug interactions involving monoclonal antibodies, including consideration of antibodies as perpetrators and as victims of DDI

Target-Mediated Antibody Disposition: modeling, implications for interspecies scaling, implications for First-in-Human studies

Modeling of bimolecular antibody-ligand interaction

Physiologically-based pharmacokinetic modeling: Incorporation of FcRn-mediated antibody transport in PBPK models, incorporation of target-mediated disposition, use of PBPK and preclinical data to predict antibody disposition in humans

COURSE DIRECTION

Joseph P. Balthasar, PhD. Dr. Balthasar is Professor of Pharmaceutical Sciences at the University at Buffalo, State University of New York and Director of the Center for Protein Therapeutics. His PK/PD modeling interests and capabilities include the development and preclinical evaluation of anti-toxin immunotherapies, the development and preclinical evaluation of anti-cancer immunotherapies (including immunoconjugate immunotherapies), and the development and preclinical evaluation of novel immunotherapies for humoral autoimmune conditions.

David Z. D'Argenio, PhD is Professor of Biomedical Engineering at the University of Southern California and holder of the Chonette Chair of Biomedical Technology. He is a Fellow of the American Institute for Engineering in Medicine and Biology, American Association of Pharmaceutical Sciences, International Society of Pharmacometrics, and a past member of the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. Since 1985 he has served as co-director of the Biomedical and Simulations Resource (BMSR) at USC, which develops, applies and disseminates advanced modeling methods for studying biological systems, where he has also led the development of the ADAPT software for PK/PD modeling and analysis.

Donald E. Mager, PharmD, PhD is Professor of Pharmaceutical Sciences at the University at Buffalo, State University of New York. He was also a Visiting Professor at the University Paris Descartes (Jan. 2007-2013). He currently serves on the Clinical Pharmacology Advisory Committee to the FDA, and as an Associate or Consulting Editor at CPT:Pharmacometrics & Systems Pharmacology, J. of Pharmacology & Experimental Therapeutics, and Pharmacology, Research & Perspectives. His research involves identifying molecular and physiological factors that control the pharmacological properties of drugs, with a focus on anti-cancer and immunomodulatory agents.

Dhaval K. Shah, PhD is Assistant Professor of Pharmaceutical Sciences at the University at Buffalo, State University of New York. His research focuses on understanding the determinants for the ADME of protein therapeutics. He is involved in the development of a platform PBPK model for biologics that can characterize and predict the pharmacokinetics of diverse protein therapeutics in several preclinical species and human. Dr. Shah also directs the discovery, development and clinical translation of novel protein therapeutics like antibody-drug conjugates and bi-specific molecules in his laboratory. His research is supported by NIH & pharmaceutical industry.

AGENDA

Day 1

08:45-09:00	**Introductions**
09:00-11:00	**Introduction to Antibody Pharmacokinetics (Balthasar)** • Introduction to antibodies (isotypes, polyclonal vs. monoclonal, humanization, etc.) • Mechanistic determinants of antibody absorption, distribution, and elimination (contrasting with determinants of small-molecule ADME) • Comments on the mathematical modeling of antibody PK • Recent research relating to the role of FcR and mAb PK
11:00-11:15	Break
11:15-11:40	**Analytical Assays for Antibodies: Implications for PK/PD Analyses (Balthasar)** • Discussion of major types of analytical assays for monoclonal antibodies (ELISA, RIA, LC MS/MS, SPR, "direct" labeling) • Examples / case-studies
11:40-12:00	**Immunogenicity and Macromolecule PK/PD (Shah)** • Factors associated with immunogenicity • Identification of host "anti-drug" antibodies • PK modeling
12:00-1:00	Lunch
1:00-1:30	**Use of PK/PD Studies to Support Comparability Assessments of Therapeutic Proteins (Balthasar)**
1:30-2:15	**Interspecies Scaling of Antibody PK & PD (Balthasar)** • General review of interspecies scaling • Considerations for scaling antibody pharmacokinetics • Examples / case-studies
02:15-03:30	**Mathematical Modeling of Target-Mediated Disposition of Monoclonal Antibodies (Balthasar)** • Introduction to TMD of Mab with examples • Review of mathematical models that have been applied to characterize Mab TMD • Comparison of model performance; discussion of implications for predicting Mab PK/PD
03:30-03:45	Break
3:45 - 4:15	**Biologics and Drug-Drug Interactions (Balthasar)** • Mechanisms • Examples / case-studies
4:15-05:00	**Review Module #1: Design & Analysis of a Preclinical Investigation of Antibody PK (Balthasar)** • Study objectives • Consideration for study design • Assay considerations • Initial evaluation of data (Additional studies needed?) • Initial characterization of ADME (NCA vs. modeling) • Evaluation of NCA results

Day 2

09:00-10:00	**Mathematical Modeling of Bimolecular Antibody-Antigen Interaction and ADC PKPD (Shah)** • Review of binding kinetics (Law of Mass Action, equilibrium vs. non-equilibrium binding) • Mathematical modeling of antibody binding: Examples from antibodies used for immunotoxicotherapy • Introduction to mechanistic modeling of ADC PKPD
10:00-11:00	**Physiologically-Based PK Modeling of Mab (Balthasar)** • Review of PBPK models • Application of PBPK models applied to Mab • Discussion of major features of PBPK models for Mab & discussion of associated physiology (convection, restriction coefficients, sites of catabolism, "two-pore formalism", incorporation of specific binding, incorporation of FcRn)
11:00-11:15	Break
11:15-12:00	**Review Module #2: Design & Analysis of a Preclinical Investigation of Antibody PK (Part 2, Balthasar)** • Development of mechanistic mathematical models
12:00-01:00	Lunch
1:00-02:00	**Application of PK/PD Theory to Guide the Discovery and Development of New Immunotherapies (Balthasar)**
2:00-3:15	**Background: Modeling with ADAPT (D'Argenio)**
3:15-3:30	**Break**
3:30-4:15	**Review Module #3: Prediction of the Influence of Shed Antigen on the Distribution of Mab in Solid Tumors (Balthasar)** • Model building exercise • Simulations
4:15 – 5:00	**Review Module #4 (Balthasar)** • Discussion questions and review

Day 3

9:00 – 9:45	**Case Study: Target Mediated Drug Disposition (Mager)**
9:45 – 10:15	**Case Study: Antibody-Ligand Interaction and Disposition (Balthasar)**
10:15 – 10:30	**Break**
10:30 – 11:15	**Case Study: Physiologically-Based Pharmacokinetic Modeling for mAb (Balthasar)**
11:15 – 12:00	**Case Study: PKPD for Antibody Drug Conjugates (Shah)**
12:00 – 1:00	**Lunch**
1:00 – 1:45	**Modeling Bispecific mAb PKPD (Shah)**
1:45 – 2:30	**Case Study: Denosumab PKPD (Mager)**
2:30 – 2:45	**Break**
2:45 – 3:30	**Estimation Principles & Challenges for Biologics (D'Argenio)**
3:30 – 4:15	**Case Study: Non-depleting Anti-CD4 mAb (D'Argenio)**
4:15	**Discussion / Adjourn**

REGISTRATION INFORMATION

Course location: The course will be held at The Conference Center Niagara Falls, 101 Old Falls Street, Niagara Falls, NY 14303. USA. Phone: (716) 278-2100. Fax: (716) 278-0008. The Center is 28 min from Buffalo International Airport. Website: http://www.ccnfny.com

Hotel location: *Sheraton at the Falls*, 300 Third St., Niagara Falls, NY 14303. USA. Phone: (716) 285-3361. The price is $124/night single/double occupancy (triple/quadruple add $10 per person). *Hotel Deadline: April 16th, 2018.*

*W*ebsite: https://www.starwoodmeeting.com/Book/Pharmacokinetic2018

Fee: Individual fee: $2500. This includes course documentation, continental breakfasts, mid-session refreshments, lunches and opening dinner. Up to 5 graduate students may enroll at a fee of $1200 (registered MS and PhD). US Government rate: $1900 (FDA and NIH employees only).

Registration: Online registration will begin September 1st, 2017. The course is limited to the capacity of 30 participants. Confirmation email of registration will be returned upon successful registration at the following website: http://pharmacy.buffalo.edu/ under Quick Links.

Cancellations: Cancellations with a full refund may be made until March 13, 2018. No refund is possible on cancellations received after this date. Substitutions may be made at any time.

Payment: Mastercard, Visa, American Express, and Discover card payments will be accepted only at the following website: http://pharmacy.buffalo.edu/ under Quick Links. Contact course secretary: Suzette Mis, (716) 645-4831; mis@buffalo.edu, if you need further assistance.