Model-based Solutions to Complexities in Developing Drugs Exhibiting Target-Mediated Drug Disposition (TMDD)

Co-Chairs

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Description

Target-mediated drug disposition (TMDD) is now a well-recognized phenomenon for many biological therapeutics in which drug-binding to the pharmacological target influences its own pharmacokinetics [1]. Although conceptual and physiological models of TMDD for monoclonal antibodies and antibody-drug conjugates are available [2-4], challenges remain in the development and utilization of TMDD models at physiological sites of action [5], with integration in quantitative systems pharmacology models, and for regulatory decision-making purposes. This session is intended to highlight these specific challenges and to provide examples of innovative techniques and approaches used to overcome these obstacles as part of translational PK-PD models to support scale-up of monoclonal antibodies from animals to patient populations during clinical development and for biosimilar product development.

References:

- Ryman JT, Meibohm B. Pharmacokinetics of Monoclonal Antibodies. CPT Pharmacometrics Syst Pharmacol. 2017 6:576-88.
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- Dua P, Hawkins E, van der Graaf PH. A Tutorial on Target-Mediated Drug Disposition (TMDD) Models. CPT Pharmacometrics Syst Pharmacol. 2015 4:324-37
- Chen X, Jiang X, Jusko WJ, Zhou H, Wang W. Minimal physiologically-based pharmacokinetic (mPBPK) model for a monoclonal antibody against interleukin-6 in mice with collagen-induced arthritis. J Pharmacokinet Pharmacodyn. 2016 43:291-304.

Learning Objectives

1. To identify the challenges associated with the development of drugs that exhibit TMDD.
2. To describe potential model-based approaches to characterizing TMDD at tissue sites of action.

3. To describe approaches for combining TMDD and QSP models to construct mechanistic models of drug action for streamlining drug development.
4. To describe simulation-based approaches for exploring study designs for assessing the biosimilarity of drugs that exhibit TMDD.

Session Speakers and Presentations

Christopher M. Rubino - Translational PK-PD model with TMDD in lung to support clinical development of a monocolonal antibody combination product to neutralize S. aureus toxins in patients with lung infections

This talk will highlight a preclinical translational PK-PD model developed in non-infected rabbits and rabbits intranasally challenged with S. aureus to quantitatively characterize TMDD at the site of action in the lung, and then to translate the effect to hospitalized patients who have or are at risk of developing S. aureus pneumonia.

Jin Y. Jin - Translational pharmacokinetics and pharmacodynamics of lampalizumab administered intravitreally to monkeys and patients with geographic atrophy (GA).

This talk will feature mathematical models of lampalizumab pharmacokinetics in ocular tissues and systemic circulation in monkeys and patients with GA. The final models predict target occupancy in ocular tissues and can be used to guide dosing regimen selection for future clinical trials.

John M. Burke - Integrating TMDD and QSP models to accelerate the development of biological immunotherapy

This talk will describe the development and application of a coupled TMDD and QSP model to guide the development of antibody-based immunotherapy targeting PD-1 and TIM-3 receptors. The final model provided new insights into the biological system and is useful for identifying lead compound(s) and accelerating their development.

Scott Van Wart - Challenges and potential opportunities to better predict bioequivalence and switchability for biologics exhibiting TMDD

This talk will discuss study design related considerations and other challenges associated with establishing bioequivalence and switchability for biologics which display TMDD. A case study using a clinical trial R Shiny simulation tool will also be discussed as a multi-disciplinary example of integrating PK modeling, study design characteristics, selection of blood collection times for PK and anti-drug antibody formation, and formal statistical testing procedures to develop a biosimilar.