Science at Sunrise: Clin Pharm for Biologics 101: Key differences from small molecules

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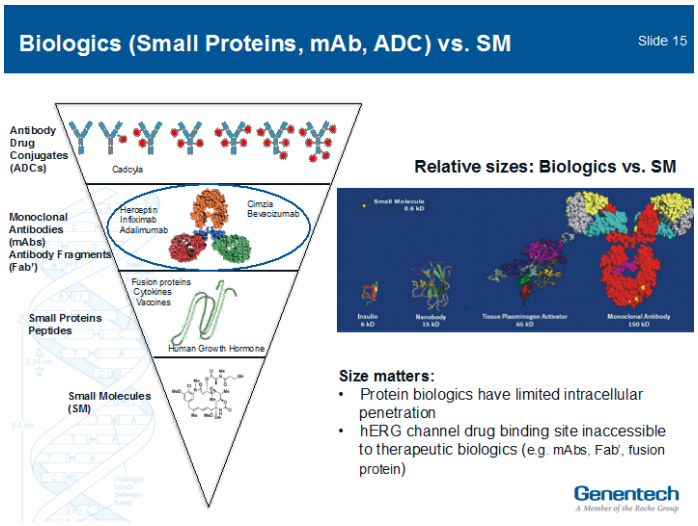
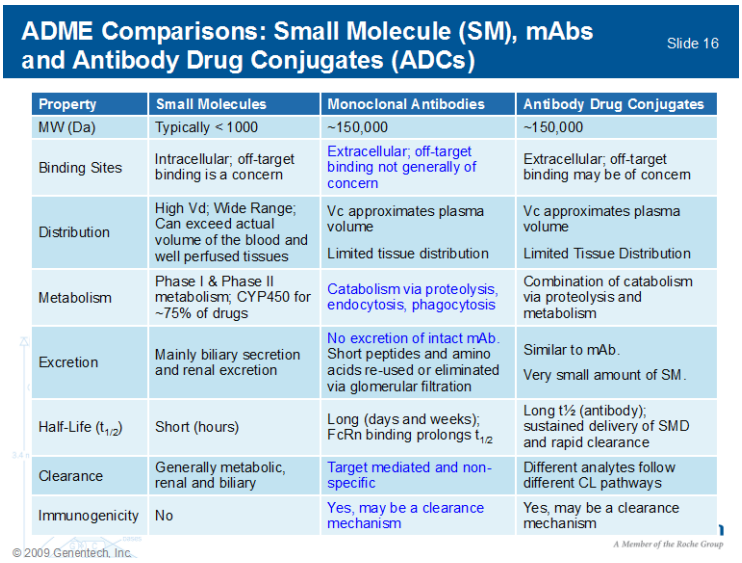
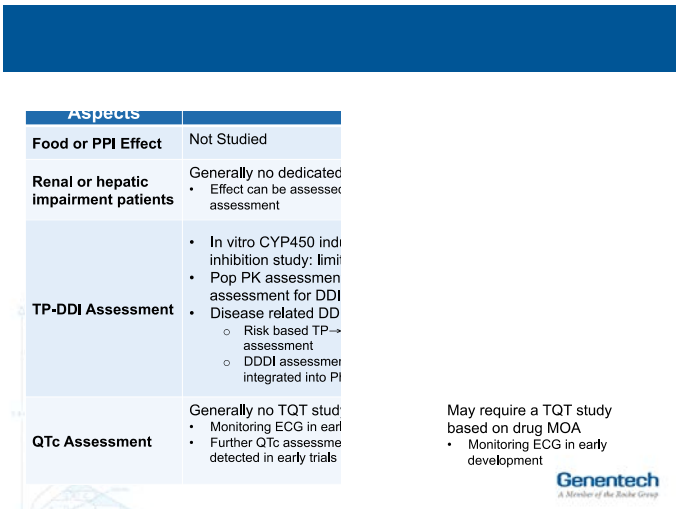
Scientific importance/background: Biological drugs are playing an ever increasing role in the treatment of a range of diseases. In 2012, 7 of the top 10 best selling "drugs" were actually biologics. Although biologics have traditionally been used for hormone or cytokine replacement (eg rHuEPO, Factor VIIa, insulin) and treatment of cancers (eg trastuzumab, bevacizumab) and inflammatory conditions (eg anti-TNFs), they are now being developed in areas that traditionally have been the domain of small molecules (eg pain disorders, cholesterol-lowering). Therefore, there is a high likelihood that a clinical pharmacologist will be called upon to provide support to a biologics program. At times, it is not possible to conduct traditional healthy volunteer clinical pharmacology studies to complete the information package necessary for informing prescribing physicians and regulators. The clinical pharmacologist has to develop novel ways to assess the risks and develop plans to collect information from patient studies. This session, while not fully inclusive, aims to highlight the key areas of differences for a biologic, compared to a small molecule, to help demystify this exciting area of drug development, including the regulatory expectations.





Slides courtesy of Meina Tang

1. **What clinical pharmacology aspects are "simpler" with a biologic?**
Meina Tang PhD, Genentech Inc



Key reference:

D Lu, ,S. Sahasranaman, Y Zhang & S Girish: Strategies to address drug interaction potential for antibody-drug conjugates in clinical development. ***Bioanalysis*** (2013) 5(9), 1115–1130

Morgan ET **CPT** 2009; 85(4): Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics.

2. What clinical pharmacology aspects are "more complex" with a biologic?
Indranil Bhattacharya PhD, Pfizer Ltd

Summary: What Clinical Pharmacology Aspects are 'Complicated' for Biologics

Clin Pharm Aspects	Therapeutic Proteins
TMDD, PK/PD characterization	❑ Good understanding of biology/target ▪ Homogeneity of target ▪ Membrane vs. circulating ▪ Slow vs. fast turnover ❑ Correct assays for TP and target ▪ Free ▪ Total ❑ TMDD model approximation based on biological considerations
Immunogenicity	❑ Understand perceived risks ▪ Biologic specific ▪ Patient specific ❑ Appropriate assays ▪ Anti-drug antibodies ▪ Neutralizing antibodies ❑ Sampling strategy -consider TP washout ❑ Harmonized reporting of results ❑ Impact on PK/PD/safety/efficacy parameters

Key references:

Approximations of the target-mediated drug disposition model and identifiability of model parameters. L Gibiansky, E Gibiansky, T Kakkur and P Ma. *J Pharmacokin Pharmacodyn* (2008) 35:573 – 591

Challenda and approaches for the development of safer immunomodulatory biologics. JG Sathish, S Swaminathan et al. *Nature* (2013) 12: 306 -324

Therapeutic monoclonal antibody concentration monitoring: free or total? B Kuang, L King, HF Wang. Bioanalysis (2010) 2(6): 1125 - 1140

3. What are the regulatory expectations for dose selection of biologics?
Hong Zhao, Ph.D., Food and Drug Administration

Speaker will cover regulatory expectations regarding dose selection, with an emphasis on dose selection for registration trials. Key questions to be addressed include:

- How are clinical trial doses selected for biologics?
- What are the problems with traditional clinical trial dose selection for biologics?
- How to optimize clinical trial dose selection?
- What are regulatory recommendations for clinical trial selection for biologics?

Key references:

Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials, Diane D. Wang, Shuzhong Zhang, Hong Zhao, Angela Y. Men and Kourosh Parivar, *J Clin Pharmacol* July 2009, 49 (9):1012

Fixed Dosing Versus Body Size–Based Dosing of Therapeutic Peptides and Proteins in Adults, Shuzhong Zhang, Rong Shi, Chunze Li, Kourosh Parivar, and Diane D. Wang, *J Clin Pharmacol* 0091270010388648, first published on January 13, 2011 as doi:10.1177/0091270010388648

The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making, Jun Yang, Hong Zhao, Christine Garnett, Atiqur Rahman, Jogarao V. Gobburu, William Pierce, Genevieve Schechter, Jeffery Summers, Patricia Keegan, Brian Booth and Yaning Wang; J Clin Pharmacol published online 1 May 2012, this article can be found at: DOI: 10.1177/0091270012445206