T-Cell Dependent Immunogenicity of Protein Therapeutics: Preclinical Assessment and Mitigation
L. P. Cousens 1, V. Jawa 2, M. Awwad 3, E. Wakshull 4, H. Kropshofer 5, W. Martin 1, A. S. De Groot 1
1 EpiVax, Inc., 2 Amgen Inc., 3 Merrimack Pharmaceuticals Inc., 4 Genentech, Inc., 5 Roche Glycart AG

Purpose
Adverse effects associated with immune responses to some biologic therapies have become a topic of some concern. While assessment of accurate product safety profile currently relies on the clinical immunogenicity data, drug developers are working to develop strategies to evaluate immune responses to protein therapeutics during both preclinical phases of development. Of the many factors that contribute to protein immunogenicity, T cell-dependent (Td) responses appear to play a critical role in the development of antibody responses to biologic therapeutics.

Methods
Focusing on the T cell contribution to immunogenicity, a range of methodologies to predict and measure Td immune responses to protein drugs are available. The advantages and limitations of these technologies will be discussed. Case studies will be presented to illustrate the importance of Td immunogenicity and the practical application of these methods. This analysis has led us to propose a framework for the prediction and measurement of Td immune responses as a critical component of risk assessment strategy.

Results
An evidence-based roadmap is proposed here (Figure 1) for identifying Td responses in protein therapeutics and step-wise assessment of immunogenicity by (i) sequence-driven assessment using in silico algorithms, (ii) in vitro assays, and (iii) in vivo models. Lastly, we introduce the emergence of methods for mitigating Td immunogenicity, such as de-immunization and tolerance induction.

Conclusion
A wide range of Td immunogenicity screening methods examining different aspects of the process by which a protein therapeutic may trigger an immune response are available. However, no single method has emerged as a definitive tool for determining whether or not a protein therapeutic will elicit a detrimental immune response in patients. Given the complexity of the immune system, a singular solution may not be realistic. Rather, the field is evolving to apply strategic combinations of multiple methods to most closely predict and mitigate immunogenicity risk. Td immunogenicity screening is a rapidly advancing science with implications in drug development, reducing risks to patients and costs to industry. As more preclinical immunogenicity testing is performed and clinical correlations become available, accuracy of preclinical immunogenicity screening methods and utility to industry are bound to improve.