

## Predictive Immunogenicity for Better Clinical Outcomes

### FDA – CERSI Collaborative Workshop

Food and Drug Administration (FDA) – White Oak campus – Building 31 Conference Center

10903 New Hampshire Avenue, Silver Spring, MD 20993

October 3 and 4, 2018

Wednesday, October 3 (Day 1): 8:30 a.m. – 5:00 p.m. (Registration begins at 7:30 am)

Thursday, October 4 (Day 2): 8:30 a.m. – 5:00 p.m. (Registration begins at 7:30 am)

## Agenda

### DAY 1 – October 3, 2018

8:30 AM to 8:45 AM	Welcome and about the FDA-CERSI partnership	JHU CERSI: G. Caleb Alexander, MD, MS, Johns Hopkins Bloomberg School of Public Health, Center for Drug Safety and Effectiveness; Program Director, Johns Hopkins University CERSI  UMD CERSI: James E. Polli, PhD, Professor and Ralph F. Shangraw /Noxell Endowed Chair in Industrial Pharmacy and Pharmaceutics, University of Maryland School of Pharmacy, Baltimore, MD
8:45 AM to 9:00 AM	Opening remarks from FDA's Center for Drug Evaluation and Research	Dr. Patrizia Cavazzoni, MD, Deputy Director, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)
9:00 AM to 9:15 AM	Opening remarks from FDA's Center for Biologics Evaluation and Research	Carolyn Wilson, PhD, Associate Director for Research, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA)
<b>SESSION 1: Advances in understanding the biology of T- &amp; B-cell responses as it applies to the immunogenicity of therapeutic proteins</b>		
Moderator: Amit Golding, MD, PhD, Staff Clinician and CDA Awardee, Baltimore VA/VAMHCS Assistant Professor, University of Maryland School of Medicine, Department of Medicine, Division of Rheumatology and Clinical Immunology, Baltimore, MD		
<i>The session will provide an overview of recent advances in immunology that could be pertinent to understanding and predicting the immunogenicity-risk of therapeutic proteins.</i>		
9:15 AM to 9:20 AM	Introduction to Session	Amit Golding
9:20 AM to 10:00 AM	Interplay of Cells involved in Therapeutic Agent Immunogenicity	Robert G. Hamilton, PhD, D.ABMLI, F.AAAAI, Professor of Medicine and Pathology, Johns Hopkins University School of Medicine, and Director, Johns Hopkins Dermatology, Allergy and Clinical Immunology Reference Laboratory,

		Johns Hopkins University School of Medicine, Baltimore, MD
<b>COFFEE BREAK 10:00 AM to 10:25 AM</b>		
<b>SESSION 2: New analytical techniques and improvements in existing technologies to predict immune response to therapeutic proteins</b>		
Moderator: Daniela Verthelyi, MD, PhD, Chief, Laboratory of Immunology, Office of Biotechnology Products - BDRR-III, OPQ/CDER/ FDA		
<i>The session will discuss the non-clinical tools for assessing immunogenicity risk at the early stages of drug development and the adoption of these tools by industry. A final talk will summarize the findings of the ABIRISK consortium that evaluated the predictive performance of a diverse set of in silico, in vitro and ex vivo methods.</i>		
10:25 AM to 10:30 AM	Introduction to Session	Daniela Verthelyi
10:30 AM to 11:00 AM	MHC binding and immunogenicity of eluted ligands - benchmarking and predictions	Alessandro Sette, Dr. Biol. Sci., Professor, Head and Member, La Jolla Institute for Allergy and Immunology, La Jolla, CA
11:00 AM to 11:30 AM	Use of risk assessment tools during preclinical development to drive a clinical immunogenicity strategy	Vibha Jawa, PhD, Director, Predictive and Clinical Immunogenicity Pharmacokinetics, Pharmacometrics and Drug Modeling Group, Merck and Co. USA
11:30 AM to 12:00 PM	The ABIRISK integrated approach to identify and evaluate predictive markers of immunogenicity	Sophie Tourdot, PhD, Immunogenicity Senior Principal Scientist, BioMedicine Design, Pfizer Inc.
<b>LUNCH BREAK 12:00 PM to 1:10 PM</b>		
<b>SESSION 3: The human cost and the economic burden: How immunogenicity affects patients and the economic burden on the healthcare system</b>		
Moderator: Frank F. Weichold, MD, PhD, Director, Critical Path and Regulatory Science Initiatives, Office of Regulatory Science and Innovation, Office of the Chief Scientist, Office of the Commissioner, FDA		
<i>In this session an economist and a patient discuss the costs associated with the immunogenicity. These include the costs to the patient and the healthcare systems as well as those borne by industry following drug attrition due to immunogenicity.</i>		
1:10 PM to 1:15 PM	Introduction to Session	Frank F. Weichold
1:15 PM to 1:45 PM	Immunogenicity economic impacts from gene therapy development to biosimilar markets: inconvenient biology truths for all	Mark Trusheim, MS, Strategic Director NEWDIGS, MIT Center for Biomedical Innovation Visiting Scientist, MIT Sloan School of Management

1:45 PM to 2:15 PM	A patient-centered approach to understanding the burden of inhibitors	Mark W. Skinner, JD President and CEO, Institute for Policy Advancement Ltd
<b>SESSION 4: Mathematical models that can integrate seemingly disparate measurements related to immunogenicity</b>		
Moderator: Million A. Tegenge, RPh, PhD, Pharmacologist, Analytics and Benefit-Risk Assessment Team, Office of Biostatistics & Epidemiology, CBER/FDA		
<i>The session will introduce an industry led coalition to develop mathematical models for immunogenicity and the potential use of systems biology approaches in understanding the immune responses to therapeutic proteins.</i>		
2:15 PM to 2:20 PM	Introduction to Session	Million A. Tegenge
2:20 PM to 2:50 PM	The development of an Immunogenicity Simulator through a quantitative systems pharmacology consortium approach	Piet H. van der Graaf, PharmD, PhD, Certara QSP, United Kingdom  Andrzej M. Kierzek, PhD, Certara QSP, United Kingdom
2:50 PM to 3:20 PM	Do differences make a difference: human immune responsiveness and single-cell variations	John Tsang, PhD, Chief, Systems Genomics and Bioinformatics Unit, LISB; Co-Director, Center for Human Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD
<b>BREAK 3:20 PM to 3:40 PM</b>		
<b>SESSION 5: PANEL DISCUSSION WITH DAY 1 SPEAKERS</b>		
Moderator: Zuben E. Sauna, PhD, Research Biologist/Principal Investigator, Office of Tissues and Advanced Therapies (OTAT), Center for Biologics Evaluation and Research (CBER)		
3:40 PM TO 4:45 PM	<b>EXPERT PANEL:</b> Dan Sikkema, Robert Hamilton, Alessandro Sette, Vibha Jawa, Sophie Tourdot, Mark Trusheim, Mark Skinner, Piet van der Graff, John Tsang	
4:45 PM TO 5:00 PM	Summary of day 1 and close	Zuben E. Sauna, PhD, Research Biologist/Principal Investigator, Office of Tissues and Advanced Therapies (OTAT), Center for Biologics Evaluation and Research (CBER)
5:00 PM	<b>END OF DAY 1</b>	

**DAY 2 – October 4, 2018**

8:30 AM to 8:35 AM

Welcome and housekeeping

**SESSION 6: Big data and immunogenicity: How “omics” workflows can be used to generate and analyze large data sets as they relate to immunogenicity**

Moderator: Joseph McGill, MS - Applied Statistics, ORISE Fellow, FDA/OMPT/CBER/OTAT/DPPT/HB

*Technologies and workflows that have been developed in the last few years permit the characterization of T-cell receptors-, antibody- and MHC-associated peptidome-repertoires. The session will introduce these technologies and the interrogation of the large data sets in the context of the immunogenicity of protein therapeutics.*

8:35 AM to 8:40 AM

Introduction to Session

Joseph McGill

8:40 AM to 9:10 AM

Tonsil organoid cultures as a model system to study human adaptive immune responses *in vitro*

Mark M. Davis, PhD, Director, Stanford Institute for Immunity, Transplantation and Infection; Investigator, Howard Hughes Medical Institute; and The Burt and Marion Avery Family Professor of Immunology; Professor, Department of Microbiology and Immunology; and Co-Director, Parker Institute for Cancer Immunotherapy, Stanford University, Stanford, CA

9:10 AM to 9:40 AM

Massively parallel screening of natively paired human antibody repertoires for antibody response analysis

Brandon J. DeKosky, Assistant Professor, The University of Kansas, Lawrence, KS

9:40 AM to 10:10 AM

Lessons Learned from the MHC II Immunopeptidome

Laura Santambrogio, MD, PhD, Professor of Pathology, Immunology and Microbiology, Albert Einstein College of Medicine, New York, NY

**BREAK 10:10 AM to 10:25 AM****SESSION 7: Identification and application of biomarkers for predicting immunogenicity**

Moderator: João A. Pedras-Vasconcelos, MSc, PhD, Product Quality and Immunogenicity Senior Staff Fellow, FDA/CDER/OBP/DBRR3

*The session will discuss the application of in silico, in vitro and ex vivo tools that measure individual steps in the immune response to therapeutic proteins into clinically relevant biomarkers.*

10:25 AM to 10:30 AM

Introduction to Session

Joao Pedras-Vasconcelos

10:30 AM to 11:00 AM	De-risking Protein Therapeutics: Should You Delete that T cell Epitope or Keep it? And Why.	Annie De Groot, MD, Chief Executive Officer, EpiVax, Inc., Professor and Director, Institute for Immunology and Informatics, University of Rhode Island
11:00 AM to 11:30 AM	Amplitude and peptide-specificity of CD4 T-cell response to therapeutic antibodies in healthy donors and in patients	Bernard Maillere, PhD, Head, laboratory of immunochemistry of the cellular immune response, Commissariat à l'Energie Atomique (CEA) Versailles, University Paris-Saclay, France

### SESSION 8: UPDATE NHLBI STATE OF THE SCIENCE WORKSHOP: INHIBITORS IN HEMOPHILIA

Moderator: Basil Golding, MD, Director, DPPT, OTAT/CBER/FDA

*In May 2018, the National Heart Lung Blood Institute (NHLBI) sponsored a workshop to generate a national blueprint for future research to address the problem of immunogenicity in hemophilia. This session will provide a summary of the key take-aways from this workshop.*

11:30 AM to 11:35 AM	Introduction to Session	Basil Golding
11:35 AM to 12:05 PM	Factor VIII Inhibitors: Generating a National Blueprint for Future Research	Donna DiMichele, MD, Deputy Director, National Heart, Lung, and Blood Institute (NHLBI), Division of Blood Diseases and Resources (DBDR), National Institutes of Health (NIH), Bethesda, MD

### LUNCH BREAK 12:05 PM to 1:05 PM

### SESSION 9: The Holy Grail: Deimmunizing protein therapeutics

Moderator: Amy S. Rosenberg, MD, Supervisory Medical Officer and Director, Division of Biologics Review and Research 3, Office of Biotechnology Products, CDER, FDA

*This session will present the scope of the problem (e.g. deimmunizing one or a few neo-sequences in an engineered human protein is a very different challenge than the wholesale deimmunization of a bacterial protein); the broad approaches for deimmunization of a protein and; present a case study, the deimmunization of a cancer immunotoxin.*

1:05 PM to 1:10 PM	Introduction to Session	Amy Rosenberg
1:10 PM to 1:40 PM	Recombinant Immunotoxins: Efficacy and Immunogenicity	Ira Pastan, MD, NIH Distinguished Investigator, National Cancer Institute, National Institutes of Health, Bethesda, MD
1:40 PM to 2:10 PM	Computationally-driven deimmunization of therapeutic proteins	Chris Bailey-Kellogg, PhD, CTO, Stealth Biologics, LLC

		Professor of Computer Science, Dartmouth, Hanover, NH
2:10 PM to 2:40 PM	Toward <i>de novo</i> design of immune silent protein and peptide therapeutics	Lance J. Stewart, PhD, MBA, Chief Strategy and Operations Officer, Institute for Protein Design, University of Washington, Seattle, WA
<b>BREAK 2:40 PM to 3:00 PM</b>		
<b>SESSION 10: PANEL DISCUSSION WITH DAY 2 SPEAKERS</b>		
3:00 PM to 4:45 PM	EXPERT PANEL: Mark Davis, Brandon DeKosky, Laura Santambrogio, Anne DeGroot, Bernard Maillere, Ira Pastan, Chris Bailey-Kellogg, Lance Stewart, Donna DiMichele	
<b>CLOSING</b>		
4:45 PM to 4:55 PM	Closing remarks	Amy S. Rosenberg, MD, Supervisory Medical Officer and Director, Division of Biologics Review and Research 3, Office of Biotechnology Products, CDER, FDA
4:55 PM to 5:00 PM	Acknowledgements & Wrap-up Declaring the workshop closed	Zuben E. Sauna, PhD, Research Biologist/Principal Investigator, Office of Tissues and Advanced Therapies (OTAT), Center for Biologics Evaluation and Research (CBER)