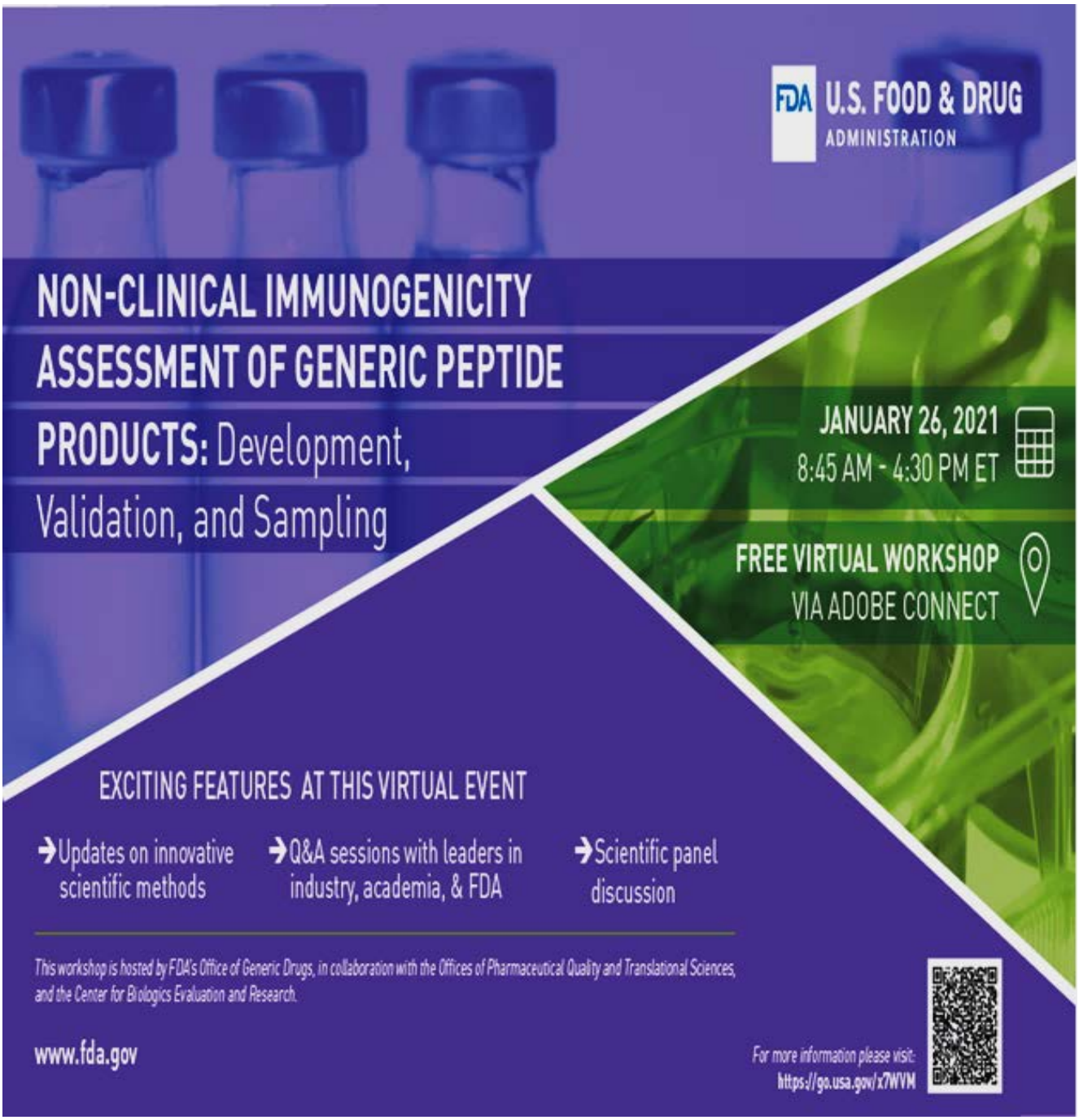
FDA U.S. FOOD & DRUG ADMINISTRATION
NON-CLINICAL IMMUNOGENICITY ASSESSMENT OF GENERIC PEPTIDE PRODUCTS: Development, Validation, and Sampling
JANUARY 26, 2021
8:45 AM - 4:30 PM ET
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Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

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Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Tuesday, January 26, 2021 | 8:45 AM – 4:30 PM (EST)
Meeting Link (Virtual only) –
https://collaboration.fda.gov/nonclinical012621overflow/

Agenda

Agenda Item	Title/Presenter	Time (EST)
Opening (15 mins)	**Welcome and opening remarks** Robert Lionberger, Ph.D., Director Office of Research and Standards/Office of Generic Drugs (OGD)/CDER/FDA	8:45 to 9:00 AM
Intro talk (15 mins)	**Introduction of immunogenicity risk assessment in generic peptide products** Eric Pang, Ph.D. OGD/CDER/FDA Daniela Verthelyi, M.D., Ph.D. Office of Pharmaceutical Quality (OPQ)/CDER/FDA	9:00 to 9:15 AM
Session 1: In silico methods to assess binding affinity to major histocompatibility complex (MHC): Method validation and MHC selection		
Introduction (10 mins)	Zuben Sauna, Ph.D. Division of Plasma Protein Therapies/Office of Tissues and Advanced Therapies/CBER/FDA	9:15 to 9:25 AM
Talk 1 (20 mins)	**MHC binding, eluted ligands and immunogenicity; benchmarking testing and predictions** Alessandro Sette, Ph.D. La Jolla Institute for Allergy and Immunology, USA	9:25 to 9:45 AM
Talk 2 (20 mins)	**The two-faced T cell epitope: predicting immunogenicity and tolerance** Anne S. De Groot, M.D. EpiVax, Inc., USA	9:45 to 10:05 AM
Panel Discussion for Session 1 (25 mins)		10:05 to 10:30 AM
Break (10 mins)		10:30 to 10:40 AM
Session 2: In vitro assays to monitor innate immune activation and inflammation: Technical challenges and best practices		
Introduction (15 mins)	Daniela Verthelyi, M.D., Ph.D. Office of Biologic Products/OPQ/CDER/FDA	10:40 to 10:55 AM

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Agenda Item	Title/Presenter	Time (EST)
Talk 3 (20 mins)	**In Vitro assessment of the innate immune responses to teriparatide using peripheral blood mononuclear cells** Marina A. Dobrovolskaia, Ph.D. Nanotechnology Characterization Laboratory, USA	10:55 to 11:15 AM
Talk 4 (20 mins)	**Whole blood cytokine release assays to assess the risk of innate immune activation to generic peptide products** Jeremy Fry, D.Phil. ProImmune Ltd., UK	11:15 to 11:35 AM
Panel Discussion for Session 2 (25 mins)		11:35 AM to 12:00 PM
Lunch Break (30 mins)		12:00 to 12:30 PM
Session 3: Assays monitoring antigen-specific T cell activation: Technical challenges and validations		
Introduction (10 mins)	Kristina Howard, D.V.M., Ph.D. Office of Clinical Pharmacology/Office of Translational Sciences/CDER/FDA	12:30 to 12:40 PM
Talk 5 (20 mins)	**Ex vivo immunogenicity assays – landscape and limitations** Campbell Bunce, Ph.D. Abzena, UK	12:40 to 1:00 PM
Talk 6 (20 mins)	**T cell immunogenicty assays: Time for harmonisation and standardisation** Sofie Pattijn ImmunXperts, Belgium	1:00 to 1:20 PM
Talk 7 (20 mins)	**Human PBMC-based assays for the immunogenicity risk assessment of therapeutic peptides** Noel Smith, Ph.D. Lonza, UK	1:20 to 1:40 PM
Panel Discussion for Session 3 (30 mins)		1:40-2:10 PM
Break (10 mins)		2:10-2:20 PM
Session 4: Using non-clinical data to assess immunogenicity risk		
Introduction (15 mins)	Amy S. Rosenberg, M.D. Office of Biotechnology Products/OPQ/CDER/FDA	2:20-2:35 PM
Talk 8 (20 mins)	**Using non-clinical data to assess immunogenicity risk: Are we there yet?** Valerie Quarmby, Ph.D., FAAPS Genentech, USA	2:35 to 2:55 PM

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Agenda Item	Title/Presenter	Time (EST)
Talk 9 (20 mins)	**Using preclinical risk assessment tools to identify and mitigate risks for therapeutic proteins and peptides** Vibha Jawa, Ph.D. Bristol Myers Squibb, USA	2:55 to 3:15 PM
Talk 10 (20 mins)	**Fit-for-purpose validation of an immunogenicity risk assessment in vitro assay** Sophie Tourdot, Ph.D. Pfizer, USA	3:15 to 3:35 PM
Talk 11 (20 mins)	**Systems immunology applied to the integration of non-clinical immunogenicity data** Timothy Hickling, D.Phil Roche, Switzerland	3:35 to 3:55 PM
Panel Discussion for Session 4 (30 mins)		3:55 to 4:25 PM
Closing (5 mins)	**Closing remarks** Steven Kozlowski, M.D., Director Office of Biotechnology Products/OPQ/CDER/FDA	4:25 to 4:30 PM

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Welcome to:

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Opening: **Welcome and opening remarks**

Speaker: Robert Lionberger, Ph.D. (FDA, USA)

Biography:

Dr. Robert Lionberger, Ph.D. serves as Director of the Office of Research and Standards (ORS) in the Office of Generic Drugs (OGD). Dr. Lionberger leads OGD's implementation of the GDUFA science and research commitments including internal research activities and external research grants and collaborations to ensure the therapeutic equivalence of generic drug products. ORS also provides pre-submission advice on complex generics through pre-ANDA meetings, product-specific guidance and controlled correspondence responses. He received his undergraduate degree from Stanford University in Chemical Engineering, and a PhD from Princeton University in Chemical Engineering. After his Ph.D., he conducted post-doctoral research in Australia in the Department of Mathematics and Statistics at the University of Melbourne. Prior to joining the FDA 17 years ago, he was an Assistant Professor of Chemical Engineering at the University of Michigan.

Introduction: **Introduction of immunogenicity risk assessment in generic peptide products**

Speakers: Eric Pang, Ph.D. and Daniela Verthelyi, M.D., Ph.D. (FDA, USA)

Biographies:

As a Senior Chemist in the Division of Therapeutic Performance in the Office of Research and Standards under the Office of Generic Drugs, Dr. Eric Pang is specialized in the analysis of peptide and large molecule drugs and is currently working on subjects related to immunogenicity. He is actively involved with the development of product-specific guidances of generic complex drug products, as well as managing several regulatory science projects related to generic complex drug substances and products. He has over nine years of experience in the Agency as a research chemist, a CMC reviewer, and a policy analyst. Dr. Pang received his PhD in Biochemistry from UCLA, and undergraduate degrees in Molecular Cell Biology and Legal Studies from UC Berkeley.

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Dr. Verthelyi received her MD from the University of Buenos Aires and a PhD in Immunology from the Virginia Tech, and then completed a fellowship training in Immunology at the Section in Retroviral Immunology in the Center for Biologics Evaluation and Research of the FDA before joining the Office of Biotechnology Products in CDER, FDA as a Principal Investigator. She currently heads the Laboratory of Innate Immunity and chairs CDER's newly formed Center for Excellence in Infectious Diseases and Inflammation. She directs a lab focused on developing tools to monitor and control innate immune and inflammatory responses including potential impurities in therapeutic products that may foster unwanted immune responses therapeutic proteins reducing their life-saving potential. In addition, she has chaired the FDA-NIH Immunology Interest Group, the NIH-FDA Cytokine Interest Group, and served on the Advisory Boards for the NIH Human Immunology Group. She has authored over 100 publications, holds several patents, and has received FDA's, CBER's, and CDER's "Excellence in Laboratory Sciences" awards, among other honors.

Session I:

In silico methods to assess binding affinity to MHC: Method validation and MHC selection

Introduction: **In silico methods to assess binding affinity to MHC: Method validation and MHC selection**

Speaker: Zuben Sauna, Ph.D. (FDA, USA)

Biography:

Zuben E. Sauna is a Principal Investigator and a CMC Reviewer at the U.S. Food and Drug Administration. His research interests lie in understanding the pharmacogenetic basis of the immune response to proteins used in therapeutic interventions as these affect efficacy and safety. His laboratory exploits a combination of computational, in vitro and ex vivo approaches to understand why some individuals and/or sub-populations develop immune responses while others do not. Work from his laboratory has been published in high impact journals such as Nature Biotechnology, Nature Medicine, Science, Science Translational Medicine and Nature Reviews Genetics. He received his Ph.D. from Poona University, India with subsequent training at the National Cancer Institute, Bethesda, USA.

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Title: **MHC binding, eluted ligands and immunogenicity; benchmarking testing and predictions**

Speaker: Alessandro Sette, Ph.D. (La Jolla Institute for Allergy and Immunology, USA)

Biography:

Dr. Alessandro Sette has devoted more than 35 years of study towards understanding the immune response, measuring immune activity, and developing disease intervention strategies against cancer, autoimmunity, allergy, and infectious diseases. The laboratory is defining in chemical terms the specific structures (epitopes) that the immune system recognizes and uses this knowledge to measure and understand immune responses. The Sette lab's approach uses epitopes as specific probes to define the immune signatures associated with productive/protective immunity versus deficient immunity/immunopathology. This research will improve understanding of how the body successfully battles infection, and conversely, how pathogens escape the immune system, causing the individual to succumb to disease. Because of the laboratory's success in its study of immune response, Sette and his team believe their research will lead to development of new therapeutic and prophylactic approaches to fighting infectious diseases. In this area, Dr. Sette's disease focus has shifted over the years from HIV, HBV and HCV to emerging diseases and diseases of potential biodefense concern to, most recently, diseases and pathogens relevant to worldwide global health, including SARS-CoV-2, Dengue, Zika, Chikungunya, malaria, M. tuberculosis, B. pertussis, and shingles. Furthermore, Dr. Sette's team has adapted the methods and techniques developed in the context of infectious disease to understand the T cell response to common allergens and to discover a cell component in Parkinson's Disease. Finally, Dr. Sette has overseen the design and curation efforts of the national Immune Epitope Database (IEDB), a freely available, widely used bioinformatics resource, since its inception in the early 2000s. The IEDB catalogs all epitopes for humans, non-human primates, rodents, and other vertebrates, from allergens, infectious diseases, autoantigens and transplants, and includes epitope prediction tools to accelerate immunology research around the world.

Abstract: A variety of tools are available to measure or predict immunogenicity. Predictions or measurement of which peptides are associated with HLA binding and/or eluted ligands is effective as a first step. Combining both methodologies (HLA binding and eluted ligands analysis) offers a limited but significant gain in prediction capacity. The field would benefit from increased objective benchmarkings of how well binding and in vitro immunogenicity predict not only in vivo immunogenicity but also ADA. In particular if ADA would be linked to specific HLA alleles, these allele specific ADA effects could be targeted by allele-specific strategies. However, in most cases the effects are not linked to a specific allele and therefore global predictions/analysis need to be performed on a general population level. We will discuss our work towards development and validation of such strategies based on human subject data.

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Title: **The two-faced T cell epitope: predicting immunogenicity and tolerance**

Speaker: Anne S. De Groot, M.D. (EpiVax, Inc., USA)

Biography:

Dr. Anne (Annie) Searls De Groot is a graduate of Smith College and University of Chicago, where she obtained her BA and MD, respectively. After medical school, she completed her residency in internal medicine at Tufts New England Medical Center, and then participated in a research fellowship in vaccinology at the NIH, and a second fellowship in infectious disease back at the New England Medical Center. Having become an Infectious Disease specialist and obtained her first NIH Grant, she joined the medical and research faculty at Brown University. She started EpiVax while still a faculty member at Brown and gradually shifted her effort from 20% corporate /80% academic to 20% academic and 80% corporate. She retains an active academic presence, most recently at University of Rhode Island, where she founded the Institute for Immunology and Informatics, and is currently professor and senior scientist at the University of Georgia, where she teaches and trains the next generation of vaccine researchers. Annie has served as Chief Executive Officer and Chief Scientific Officer of the biotech company EpiVax, which she cofounded with Bill Martin, COO/CIO, for the past 22 years. This company is privately held, employs approximately 30 high-level research scientists, and is a globally recognized immunoinformatics and vaccine design company. One of the company's more fundamental discoveries was that human pathogens use "human-like" sequences to camouflage themselves from immune response, and that removing these sequences from vaccines makes them more effective. The EpiVax team also discovered what are now known as "Tregitopes"—peptides that activate natural regulatory T cells. De Groot is the author of 200 publications and 46 patents, and has earned more than $35M in US federal funding. In addition to her research, Dr. De Groot continues to work to improve access to healthcare by volunteering evenings and weekends to direct the activities of Clinica Esperanza/Hope Clinic, which provides free medical care and preventive health services to uninsured adults living in Rhode Island. De Groot is also the founder and scientific director of the GAIA Vaccine Foundation, a nonprofit organization that aims to improve the health of women, children and families in Mali, West Africa.

Abstract: This presentation will highlight how to build better, more precise epitope prediction tools using matrices (EpiMatrix) and careful curation of input data. It will point out some of the flawed data that is published on line and contributes to errors in the development of prediction tools and will highlight some recent developments (such as the publication of the HLA ligand atlas) that facilitate epitope prediction. Dr Anne will also talk about how to select HLA supertypes for population-level analysis, use a 'cluster finder' (ClustiMer) to identify epitope-dense regions of proteins, and describe the use of individual matrices (iTEM) for predicting individual risk. This presentation will explain why the TCR face of the T cell epitope is taken into consideration when predicting tolerance, using our tools JanusMatrix and J-iTEM. She will provide a few case studies of peptides such at Teriparatide where we predicted and then validated the immunogenicity of the drug by taking these factors and others into consideration.

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Session II:

In vitro assays to monitor innate immune activation and inflammation: technical challenges and best practices

Introduction: **In vitro assays to monitor innate immune activation and inflammation: Technical challenges and best practices**

Speaker: Daniela Verthelyi, M.D., Ph.D. (FDA, USA)

Title: **In vitro assessment of the innate immune responses to teriparatide using peripheral blood mononuclear cells**

Speaker: Marina A. Dobrovolskaia, Ph.D. (Nanotechnology Characterization Laboratory (NCL), USA)

Biography:

Dr. Marina A. Dobrovolskaia is Laboratory Director of Operations and the Head of Immunology Section at the Nanotechnology Characterization Laboratory (NCL). In her role as the Director of Operations, Dr. Dobrovolskaia leads the NCL operations to provide preclinical nanoparticle characterization services to the nanotechnology research community, advance the translation of promising nanotechnology concepts from bench to the clinic, and contribute to the education of the next generation of scientists in the field of preclinical development of nanotechnology-based products, the activities emphasized in the NCL mission. She also directs the performance of Immunology, Client Relations and Administrative sections of the NCL. Closely integrated functioning of these sections plays a critical role in advancing the NCL's key strategic goals, and in supporting the missions of the Frederick National Laboratory for Cancer Research. In her role as the Head of the Immunology Section, Dr. Dobrovolskaia leads a team conducting preclinical studies to monitor nanoparticles' toxicity to the immune system both in vitro and in vivo using variety of immune function animal models. Prior to joining the NCL, Dr. Dobrovolskaia worked as a Research Scientist in a GLP laboratory at PPD Development, Inc. in Richmond, VA, where she was responsible for the design, development and validation of bioanalytical ligand-binding assays to support pharmacokinetic and toxicity studies in a variety of drug development projects. She received her M.S. degree from the Kazan State University in Russia; Ph.D. from the N.N. Blokhin Cancer Research Center of the Russian Academy of Medical Sciences in Moscow, Russia; and MBA from the Hood College in Frederick, MD. Since 2016, she is also a member of Project Management Institute and a certified Project Management Professional. Her research interests include immunology, toxicology, nanotechnology and bioanalytical methodology. Dr. Dobrovolskaia's list of publications and citations of the published work can be accessed via the following link https://scholar.google.com/citations?user=Biz76XAAAAAJ&hl=en

Abstract: Understanding a correlation (or a lack thereof) between the innate immune responses of healthy human blood cells and innate immunity modulating impurities (IIMIs) which may be present in synthetic peptide drug products is critical for supporting the review and approval processes of generic versions of these products. Our study involved a 16-plex panel that included type I interferon (IFNa), type II interferon (IFNg), type III interferon

(IFNl), interleukins (IL-1a, IL-1b, IL-2, IL-6, IL-8, IL-10, IL-12, IL-17), tumor necrosis factor alpha (TNFa), interferon-gamma inducible protein (IP-10), prostaglandin E2 (PGE2), macrophage inflammatory protein (MIP-1a), and monocyte chemoattractant protein (MCP-1). The study was performed using peripheral blood mononuclear cells (PBMC) isolated from 10 healthy donors. Teriparatide (TP) and ten IIMIs from various sources were tested, each at four concentrations; in addition, IIMIs were also incubated with cells in the presence of TP. The key findings included the following: 1) TP-mediated signature cytokine prostaglandin E2 (PGE2) was induced in a concentration-dependent manner; this effect was due to the formulation buffer (FB); 2) TP suppressed IIMI-mediated cytokine responses, and this effect was also mediated by the FB; 3) IIMIs induced a broad and often overlapping cytokine response consistent with the current knowledge of their cognate pattern recognition receptors and relevant signal transduction pathways; 4) two panels of three cytokines would provide at least one positive result for all 10 IIMIs and potentially could be used by users who do not have access to more than 3-plex cytokine detection panel: panel1 (IL-1a (or MIP-1a), IP-10, and IL-8) and panel 2 (IL-1a (or MIP-1a), MCP-1 and IL-8 (or IL-6). 5) due to the inter-individual variability in the magnitude of the cytokine response to individual IIMI, it is advisable to use a broad spectrum of cytokines for evaluating the PBMC model's sensitivity to individual IIMIs. In addition to the key findings, the presentation will discuss logistical considerations for conducting in vitro cytokine studies in PBMC derived from healthy human donors.

Title: **Whole blood cytokine release assays to assess the risk of innate immune activation to generic peptide products**

Speakers: Jeremy Fry, D.Phil. (ProImmune Ltd, UK)

Biography:

Dr. Jeremy Fry gained his DPhil. studying under Prof. Kathryn Wood at the Nuffield Department of Surgery at the University of Oxford developing MHC gene therapy strategies to induce immunological tolerance in transplant recipients. Following a post-doctoral position, Jeremy joined ProImmune to develop a new class of MHC class multimers, leading to the invention of the world-leading MHC Pentamer technology to monitor antigen-specific CD8+ T cells. Since 2001, he has been part of the senior leadership team at ProImmune focusing on developing and implementing innovative technologies to radically improve our understanding of both wanted and undesired immune responses.

Abstract: The deployment of fresh undiluted whole blood cytokine release assays to assess innate antigenicity of therapeutic proteins has proven to be a valuable tool in the risk assessment of unwanted immunogenicity. In this talk I will present our experience in the application of this assay to generic peptide products and their impurities and consider key study design challenges and considerations that should be addressed to ensure an optimum dataset.

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Session III:

Assays monitoring antigen-specific T cell activation: technical challenges and validations

Introduction: **Assays monitoring antigen-specific T cell activation: Technical challenges and validations**

Speakers: Kristina Howard, D.V.M., Ph.D. (FDA, USA)

Biography:

Dr. Kristina Howard received her D.V.M. from the Virginia-Maryland Regional College of Veterinary Medicine and her Doctorate in immunology from North Carolina State University. She joined the FDA in 2010 and is currently a principal investigator in the Division of Applied Regulatory Science, Office of Cliical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research of the United States Food and Drug Administration. Her research focuses on developing and improving *in vitro* and *in vivo* models to better predict the safety of small and large molecule drug products in humans. Her laboratory has been actively making bone marrow-liver-thymus (BLT) humanized mice and using them to evaluate biological and generic peptide drug products since 2012.

Title: **Ex vivo immunogenicity assays – landscape and limitations**

Speakers: Campbell Bunce, Ph.D. (Abzena, UK)

Biography:

Dr. Campbell Bunce is the Chief Scientific Officer at Abzena, a global Partner Research organisation supporting development of drugs and vaccines from discovery to GMP manufacture. His focus is in delivering high quality and tailored services to ensure a quick and de-risked route from drug concept and design to clinical testing. Campbell has been with Abzena for 5 years and beforehand spent 20 years working in the biotech sector for companies such as Cantab Pharmaceuticals, Piramed Pharma and immune Targeting Systems. He has led the development of many novel vaccine and therapeutic technologies targeting infectious disease, cancer, inflammatory and autoimmune disease, taking them through discovery and design stages to clinical evaluation. Campbell has a PhD in Immunology from the University of Manchester and has published numerous papers on immune mechanisms and novel drug development.

Abstract: There are several drivers of immunogenicity risk for drugs and the potential for them to induce an anti-drug immune response in patients. Numerous pre-clinical methods have been established to help inform potential risk and identify specific elements of drug product components that may be responsible for unwanted immunogenic effects. This short talk will present the landscape of currently used analytical platforms and discuss some of their limitations. It will also cover some case studies to illustrate their application and prompt discussion on their use to evaluate peptide-based drugs.

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Title: **T cell immunogenicity assays: Time for harmonisation and standardisation**

Speakers: Sofie Pattijn (ImmunXperts, Belgium)

Biography:

Dr. Sofie Pattijn (CTO and founder, ImmunXperts) has over 20 years of experience in the field of immunogenicity assessment (vaccines and biotherapeutics) and in vitro assay development with a focus on functional assays for immunogenicity, immune oncology and Cell and Gene Therapy products. She has extensive hands-on lab experience and has managed and coached several In Vitro teams over the last decade. From 2008 till 2013 she was Head of the In Vitro Immunogenicity group at AlgoNomics (Ghent, Belgium) and Lonza Applied Protein Services (Cambridge, UK). Prior to that, she worked at Innogenetics, Belgium for over 15 years.

Abstract: Early immunogenicity assessment can be performed using in vitro PBMC and DC-T cell assays. However, the use of in vitro assays comes with some challenges. Factors such as the quality and functionality of the primary cells can have a significant effect on the outcome and performance of these assays. Additionally, the availability of proficiency panels, specific guidelines and reference molecules could support the harmonisation and allow better comparison of data generated by different labs or providers.

Title: **Human PBMC-based assays for the immunogenicity risk assessment of therapeutic peptides**

Speaker: Noel Smith, Ph.D. (Lonza, UK)

Biography:

Dr. Noel Smith completed his Ph.D. and subsequent post-doctoral studies at the University of Cambridge in the field of metabolic disease. Noel joined Lonza in 2009 and was involved in the setup of the human primary cell-based assay platform and now Heads the Immunology group which develops assays to screen products for immunogenicity and immunotoxicity risk. The Lonza Cambridge site is focused on the development and provision of services to support the development of new biotherapeutic proteins and vaccines with a particular focus on immunogenicity, immunotoxicity, manufacturability and protein expression.

Abstract: Immunogenicity and Immunotoxicity are common challenges to address during drug development and can impact both the efficacy and safety of the drug. To assess these risks, a variety of tools can be applied during preclinical development. These include a range of different human primary cell assays to assess the innate and adaptive immune response to the drug as well as both target and off-target mediated immune reactions. This presentation will focus on how these tools can be applied during preclinical development to compare the adaptive immune response risk of generic peptide products compared to reference listed drugs.

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Session IV:

Using non-clinical data to assess immunogenicity risk

Introduction: Risk Assessment of immune responses to therapeutic proteins: Implications for therapeutic peptides and generic peptides

Speaker: Amy S. Rosenberg, M.D. (FDA, USA)

Biography:

A physician immunologist with extensive background in immunology and expertise in development and immunogenicity of therapeutic proteins and cellular products. Dr. Rosenberg have been involved in the regulation and approval of numerous FDA regulated products including hematopoietic stem cells and their selection devices, therapeutic proteins including monoclonal antibodies and fusion proteins, enzyme replacement therapies, immunomodulators including interleukins and interferons, hematologic and somatic cell growth factors, and combination device-biologics. She has extensive knowledge of product quality issues as well as the clinical aspects of experimental investigations and is a leading expert in the immunogenicity of therapeutic proteins and immune tolerance as a mitigation strategy. Dr. Rosenberg serves as FDA expert consultant to the National Institutes of Health's Immune Tolerance Network. She received an M.D. from the Albert Einstein College of Medicine and trained at NYU-Manhattan VA in Internal Medicine and Infectious Diseases. Post-doctoral work in Immunology was done in the Laboratory of Alfred Singer in the Experimental Immunology Branch of the NCI before joining the FDA.

Title: **Using non-clinical data to assess immunogenicity risk: Are we there yet?**

Speaker: Valerie Quarmby, Ph.D., FAAPS. (Genentech, USA)

Biography:

Dr. Valerie Quarmby is a Staff Scientist in Development Sciences at Genentech. Dr. Quarmby received her B.Sc. and Ph.D. from the University of London (UK). She was an NIH Fogarty International Postdoctoral Fellow at the National Institute of Environmental Health Sciences and did postdoctoral work in the Department of Pediatric Endocrinology at UNC-Chapel Hill. Dr. Quarmby worked in the field of clinical diagnostics prior to joining Genentech. Dr Quarmby has contributed to IND, BLA and related filings for many approved medicines at Genentech. She is past Chair of the American Association of Pharmaceutical Sciences (AAPS) "Therapeutic Product Immunogenicity Focus Group" and was a member of the 2010-2015 United States Pharmacopeia "Immunogenicity Testing Expert Panel". Dr. Quarmby has presented and published extensively in the areas of bioanalysis and biopharmaceutical development. In 2014, in recognition of her many contributions to the pharmaceutical industry, Dr. Quarmby was awarded AAPS Fellow Status.

Abstract: Every biotherapeutic has the potential to elicit unwanted immune responses, and these may compromise safety and efficacy. To minimize immunogenicity risk, biotherapeutics have

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

traditionally been designed to maximize "self" human sequence content. However, extensive engineering of candidate biotherapeutics is now possible and may be necessary to enhance best-in-class potential. Several in silico, in vitro and in vivo methods can be used during therapeutic lead selection and optimization to assess the likelihood that a biotherapeutic may be immunogenic. This talk will review non-clinical immunogenicity risk assessment systems in the context of biotherapeutic development.

Title: **Using preclinical risk assessment tools to identify and mitigate risks for therapeutic proteins and peptides**

Speaker: Vibha Jawa, Ph.D. (Bristol Myers Squibb, USA)

Biography:

Dr. Vibha Jawa is an Executive Director for Biotherapeutics Bioanalysis in Nonclinical Disposition and Bioanalysis (NDB) organization at Bristol Myers Squibb. In this role, Vibha is responsible for leading biotherapeutic and cell therapy bioanalytical (BA) function supporting PK and immunogenicity. She provides strategic and scientific oversight for BMS developmental portfolio. Prior to BMS, Vibha was at Merck for 4 years where she served as head of Predictive and Clinical Immunogenicity group and at Amgen for 14 years supporting Clinical Immunogenicity from Discovery to Development for biotherapeutics. Vibha brings more than 20+ years of experience in supporting biologics, vaccine development and gene therapy with contributions to multiple IND, BLA and MAA filings. Vibha is a recognized leader in the area of Bioanalysis and Immunogenicity with more than 50 peer reviewed publications and serves as a Reviewer and Editor for The AAPS Journal and J. Pharm Sci. She is an active member of American Association of Pharmaceutical Scientists (AAPS), American Association of Immunology (AAI), European Immunogenicity Platform (EIP) and Federation of Clinical Immunology Society (FOCIS). Within AAPS, she is actively involved as a Steering Committee member of the Therapeutic Protein Immunogenicity Focus Group (TPIFG) and is currently leading the Immunogenicity Risk Assessment and Mitigation Community as well as Industry Innovation and Quality (IQ) Consortium for Cell/Viral/Gene therapies. Outside of the work, Vibha enjoys volunteering as a board member for the state youth orchestra and mentoring high school students on STEM related research projects.

Abstract: Peptide based therapeutics can be potentially immunogenic like any other biologic like a recombinant protein or a monoclonal antibody. A preclinical risk assessment employing in silico and invitro risk assessment tools can help identify the potential liabilities and mitigate these risks by re-engineering, setting specifications on critical quality attributes and developing a bioanalytical strategy that could monitor immune responses in clinic. A robust preclinical strategy will rely on in silico algorithms that have been validated/supported by human in vitro assays and clinical trial derived samples to understand dosing and patient specific responses. A sound bioanalytical and clinical strategy would rely on a good understanding of the risks preclinically using qualified in vitro assays with use of relevant controls and cells to study the different phases of immune system.

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Title: **Fit-for-purpose validation of an immunogenicity risk assessment in vitro assay**

Speaker: Sophie Tourdot, Ph.D. (Pfizer, UK)

Biography:

Dr. Sophie Tourdot received her Ph.D. in T cell vaccine immunology from the University of Paris. Following her postdoctoral trainings at Imperial College London, she worked at the Pasteur Institute on HIV vaccine design then progressed to Stallergenes-Greer and ITS, where she led the Pre-clinical immunology teams. She then worked at the French National Research Institute for Health and Medical Research as Scientific Project Manager of the IMI-funded ABIRISK project, a consortium program focused on the analysis of underlying biological mechanisms, clinical relevance and prediction of unwanted immunogenicity of biopharmaceuticals. Sophie joined Pfizer's Biomedicine department in 2017 where she now leads the Immunogenicity Sciences group. Sophie acts as director of scientific affairs of the European Immunogenicity Platform.

Abstract: Therapeutic protein drugs have significantly improved the management of many severe and chronic diseases. A major obstacle to the success of such therapies is the ability of protein drugs to induce unwanted immunogenicity in a substantial number of patients. Anti-drug antibodies can alter pharmacokinetics and pharmacodynamics and lead to impaired efficacy and safety issues. In silico, in vitro, and in vivo tools have been developed to mitigate this immunogenicity risk during the molecular design phase of therapeutic proteins. Validation of key analytical and functional performance characteristics of in vitro immunogenicity risk assessment assays increases our confidence in utilizing them for screening and selecting therapeutic drugs candidates with the lowest immunogenicity risk. Here I will discuss the fit-for-purpose (FFP) validation of a dendritic cell (DC) activation assay performed to understand the impact of experimental variables on assay precision, develop a clear concise readout for DC activation results, establish a reliable response threshold to define a result as a positive DC activation response, and define in-study donor acceptance criteria and cohort size. FFP validation of this DC activation assay indicated that the assay is adequate to support its context of use, a preclinical immunogenicity risk management tool.

Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling

Title: **Systems immunology applied to the integration of non-clinical immunogenicity data**

Speaker: Timothy Hickling, D.Phil. (Roche, Switzerland)

Biography:

Dr. Timothy Hickling leads the Immunosafety group in Roche that includes responsibility for immunogenicity risk assessments and developing predictive methods for immune responses. Tim joined Roche in 2020 after leading Pfizer's Immunogenicity Sciences group, where he developed mathematical models of immune responses to vaccines and therapeutic proteins. He had previously obtained his Biochemistry degree and Immunology Doctorate from the University of Oxford, U.K. and was an Assistant Professor in Virology at the University of Nottingham, U.K.

Abstract: The immune system protects us from infection and malignancy and is by definition a complex series of biological interactions. The behavior of complex systems is difficult to predict. Using a combination of systems thinking and data-based evidence, we have built a mathematical model of the immune system with a purpose of predicting immune responses to biologics. A series of recognized inputs and known mechanisms of immunity are applied to derive outputs relevant for project decision making, including immunogenicity risk assessment. Models are generic, yet flexible, allowing inclusion of project specific parameters as inputs.

Closing: **Closing remarks**

Speaker: Steven Kozlowski, Ph.D. (FDA, USA)

Biography:

Dr. Steven Kozlowski is the Director of the Office of Biotechnology Products, Office of Pharmaceutical Quality, at the Center for Drugs Evaluation and Research (CDER), FDA. OBP is responsible for the quality assessment of monoclonal antibodies and most therapeutic proteins at CDER. OBP also provides expertise on immunologic responses to therapeutic proteins and performs mission related research. Dr. Kozlowski received his medical degree from Northwestern University and trained in Pediatrics at the University of Illinois. Prior to joining the FDA, Dr. Kozlowski worked as a staff fellow in the Molecular Biology Section of the Laboratory of Immunology, NIAID, NIH. Dr. Kozlowski joined the FDA in 1993 and he has been involved in all phases of the regulatory process, from pre-IND product development through inspections, licensing and post approval supplements. He is involved in ongoing policy development for biosimilars and advanced approaches for the manufacture of biopharmaceutical products.