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Second Annual

Immunogenicity Summit 2010

October 19-21, 2010

Loews Philadelphia Hotel ■ Philadelphia, Pennsylvania

PART ONE:
Immunogenicity Assessment and Clinical Relevance
October 19-20

PART TWO:
Immunogenicity Prediction and Control
October 20-21

PRE-CONFERENCE SHORT COURSES
October 18

1: Technical Advice on Assay Development, Validation and Sample Analysis

2: Development of Cell-Based Neutralizing Antibody Assays

Course Leaders

Arno Kromminga, Ph.D., Professor & CEO, Immunology, IPM Biotech

Lakshmi Amaravardi, Ph.D., Director, Pre-clinical & Clinical Development, Biogen Idec, Inc.

Shobha Purushothama, Ph.D., Scientist, Bioanalytical R&D, Pfizer, Inc.

KEYNOTE PRESENTATIONS

Developing a Risk-Based Approach to Immunogenicity Assessment

Steven J. Swanson, Ph.D., Executive Director, Clinical Immunology, Amgen, Inc.

Visible and Subvisible Aggregates: Assessing their Potential Impact on Immunogenicity

Jack A. Ragheb, M.D., Ph.D., Principal Investigator, Laboratory of Immunology, Division of Therapeutic Proteins, Office of Biological Products, CDER, FDA

Update on the Biosafe White Paper for Pre-Clinical Immunogenicity

Lakshmi Amaravardi, Ph.D., Director, Pre-clinical & Clinical Development, Biogen Idec, Inc.

Immune Tolerance Mechanisms: Animal Models and Approaches

David W. Scott, Ph.D., Vice Chair for Research, Uniformed Services, University of Health Sciences, Bethesda

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Pre-Conference Short Courses*

MONDAY, OCTOBER 18

Instructors for both courses:

Lakshmi Amaravardi, Ph.D., Director, Pre-Clinical & Clinical Development, Biogen Idec, Inc.

Arno Kromminga, Ph.D., CEO, Immunology, IPM BIOTECH

Shobha Purushothama, Ph.D., Scientist, Bioanalytical R&D, Pfizer, Inc.

SC 1: TECHNICAL ADVICE ON ASSAY DEVELOPMENT, VALIDATION AND SAMPLE ANALYSIS

8:00 – 9:00 am Registration

9:00 – 12:30 pm Short Course

This interactive session will enable attendees to work out an immunogenicity pre-clinical and clinical testing protocol for their particular therapeutic protein. Recent advances will be presented and areas of difficulty will be addressed. Attendees are encouraged to contribute with their own experiences and to bring questions for discussion.

The following topics will be covered:

- Immunology behind immunogenicity
- Immunogenicity concerns for different types of product
- Assay methodologies
- Critical issues in assay validation
- Challenges to anticipate
- Application step to discuss sample analysis and any relevant issues

SC 2: DEVELOPMENT OF CELL-BASED NEUTRALIZING ANTIBODY ASSAYS

12:30 – 1:30 pm Registration

1:30 – 5:00 Short Course

Neutralizing antibodies not only affect efficacy of the therapeutic but also pose the danger of cross-reacting antibodies and ensuing adverse reactions. This interactive session is designed to enable attendees to work out how to design, develop and validate their assays for neutralizing antibodies, and to interpret the results. Attendees are encouraged to contribute with their own experiences and to bring questions for discussion.

The following topics will be covered:

- Strategy for design, development and validation of neutralizing antibody assays
- Challenges to anticipate
- Interpretation of results
- Emerging trends in the development of neutralizing antibody assays
- Clinical implementation of established neutralizing antibody assays
- Regulatory guidance and guidelines

**Separate Registration Required*

Cambridge Healthtech Institute's Second Annual

Immunogenicity Summit 2010

October 19-21

Following inaugural success, we present our *Second Annual Immunogenicity Summit:* A case study-rich event covering advances in immunogenicity assays and their application to pre-clinical and clinical development. Also includes risk assessment, regulatory and white paper guidance, factors causing immunogenicity and means of predicting and controlling it. Excellent networking and discussion opportunities.

Keynote Speakers

Steven J. Swanson, Ph.D., Executive Director, Clinical Immunology, Amgen, Inc.

Jack A. Ragheb, M.D., Ph.D., Principal Investigator, Laboratory of Immunology, Division of Therapeutic Proteins, Office of Biological Products, CDER, FDA

Lakshmi Amaravardi, Ph.D., Director, Pre-clinical & Clinical Development, Biogen Idec, Inc.

David W. Scott, Ph.D., Vice Chair for Research, Uniformed Services, University of Health Sciences, Bethesda

Featured Presentations

Matthew Baker, Ph.D., Chief Scientific Officer, R&D, Antitope Ltd.

Deborah Finco, Ph.D., Senior Principal Scientist, Immunotoxicology, Pfizer, Inc.

Valerie Quarmby, Ph.D., Principal Scientist & Director, BioAnalytical Technologies & Strategies, Genentech, Inc.

Wytske Kingma, M.D., S.V.P., Global Medical Affairs, Genzyme Corp.

Stephen Lee, Ph.D., Associate Professor, Biomedical Engineering, Ohio State University

Distinguished Faculty List

Margot O'Toole, Ph.D., Director, Translational Medicine, Pfizer, Inc.

Donald Bennett, Ph.D., Director, Biostatistics, Biogen Idec, Inc.

Satish K. Singh, Ph.D., Research Fellow, Biotherapeutics Pharmaceutical Sciences, Pfizer, Inc.

Michele Fiscella, Ph.D., Associate Director, Clinical Immunology, Human Genome Sciences

Patrick Liu, Ph.D., Associate Director, Development Sciences Management, Genentech, Inc.

Joao A. Pedras-Vasconcelos, Ph.D., Visiting Associate, Therapeutic Proteins CBER, FDA

Sebastian Spindeldreher, Ph.D., Deputy Head, Bioanalytics, Novartis Pharma A.G.

Kay-Gunner Stubenrauch, Ph.D., Senior Scientist, Pharma Research, Bioanalytics, Roche Diagnostics

Masanori Onda, M.D., Ph.D., Laboratory of Molecular Biology, NCI/NIH

Josefin-Beate (Josi) Holz, Ph.D., Chief Medical Officer, Drug Development, Ablynx nv

Frank J. Carr, Ph.D., Director, Biologics Research, Antitope Ltd.

Arno Kromminga, Ph.D., CEO, Immunology, IPM BIOTECH

Katherine A. High, M.D., Investigator, Howard Hughes Medical Institute; William H. Bennett Professor of Pediatrics, University of Pennsylvania School of Medicine; Director, Center for Cellular and Molecular Therapeutics, The Children's Hospital of Philadelphia

Jaya Goyal, Ph.D., Principal Investigator, Clinical Science and Technology, Biogen Idec, Inc.

David W. Scott, Ph.D., Professor of Surgery and of Microbiology and Immunology, University of Maryland School of Medicine

Eric D. Foehr, Ph.D., Director, Bioanalytical R&D, Biomarin Pharmaceuticals, Inc.

Philippe Stas, M.B.A., Head, Applied Protein Services, Lonza Biologics; Head, Algonomics NV

Matthew Seefeldt, Ph.D.,Vice President, Research, BaroFold, Inc.

Christoph Giese, Ph.D., Director, Probiogen GmbH

Mikael Sørud, M.Sc., Director, Regulatory Affairs, Novo Nordisk A/S

Bernard Maillere, Ph.D., Head, Immunochemistry, Institute of Biology and Technologies, CEA

Ralf Hess, Ph.D., Principal Consultant, Early Stage Drug Development, Parexel

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PART ONE: Immunogenicity Assessment and Clinical Relevance

TUESDAY, OCTOBER 19

7:30 am Registration & Morning Coffee

UPDATE ON WHITE PAPERS & CURRENT CONCERNS

8:30 Chairperson's Opening Remarks

Valerie Quarmby, Ph.D., Principal Scientist & Director, BioAnalytical Technologies & Strategies, Genentech, Inc.

KEYNOTE PRESENTATION

8:35 Update on the Biosafe White Paper for Pre-Clinical Immunogenicity: Differences between Immunogenicity Evaluation in Non-Clinical vs. Clinical Studies

Lakshmi Amaravardi, Ph.D., Director, Preclinical & Clinical Development, Biogen Idec, Inc.

This presentation will outline the current status, ongoing challenges and potential future directions of the Biosafe White Paper regarding preclinical Immunogenicity evaluation. It will present effect of Immunogenicity on toxicology, study design considerations, timing of sample collection and analysis considerations, immunogenicity assay challenges in supporting nonclinical studies, and finally data interpretation. A decision tree for conducting immunogenicity evaluation in non-clinical studies and future directions will also be discussed.

UPDATE ON APPROACHES TO IMMUNOGENICITY ASSAYS

9:05 Strategy for Dealing with Drug Interference

Michele Fiscella, Ph.D., Associate Director, Clinical Immunology, Human Genome Sciences

We have developed a protein therapeutic that combines the efficacy of interferon alfa with the half-life of serum albumin. The novelty of the product combined with the certainty of unmatched interference generated many challenges. The approach to assess overall immunogenicity and the development of an assay with acceptable sensitivity will be discussed.

9:35 Experiences with Fluorometric and Electrochemiluminescence Based Blocking/Neutralizing Assays during the Clinical Development of a Biotherapeutic

Jaya Goyal, Ph.D., Principal Investigator, Clinical Science and Technology, Biogen Idec, Inc.

This case study highlights that during the course of clinical development; careful consideration of study population, dose levels and anticipated levels of circulating drug is required prior to the selection of assay configuration. Membrane based Delfia® fluorometric assay that provides ease of use may potentially be used for the detection of antibodies in a healthy volunteer study but in studies with autoimmune disease population, cell based ECL assay format that provides better matrix tolerance may be more appropriate.

10:05 Immunogenicity Assays: A Single Step in the Right Direction

Sponsored by Quotient Bioresearch

Nicola Gaskell, Client Manager, Bioanalytical Sciences, Quotient Bioresearch

10:35 Networking Coffee Break, Poster and Exhibit Viewing

11:15 Detection of Neutralizing Activity Using Cell-Based RNA Expression Assay

Margot O'Toole, Ph.D., Director, Translational Medicine, Pfizer, Inc.

Ex vivo treatment of human and monkey blood with recombinant human IL-21 (rhuIL21) induced IL2RA gene expression, and this response was inhibited in the presence of anti-human IL21R antibody. We evaluated correlations between the pharmacodynamic (PD) activity of, and anti-product antibody responses to, two anti-human IL21R antagonistic antibodies. Reflecting *in vivo* PD activity, the *ex vivo* rhIL21-dependent response was inhibited in blood from monkeys dosed IV with anti-IL21R, and inhibition correlated with pharmacokinetics. In monkeys that developed neutralizing ADA, however, anti-IL21R had no effect on their *ex vivo* response to rhIL21, providing a reliable cell based assay for neutralizing activity.

INTERPRETING THE DATA

11:45 Inducing Tolerance to Statisticians: Cutpoint Determination Made Easier with Statistics

Donald Bennett, Ph.D., Director, Biostatistics, Biogen Idec, Inc.

This presentation will demonstrate the advantage of tolerating statistician's requests when defining a cutpoint for an immunogenicity assay. We will compare statistical methods of cutpoint determination with immunogenicity data examples to help you evaluate which method to use for your assays. The goal is a better understanding of the statistical options for cutpoint determination, targeting false positive rates, and the data needed to get a good cutpoint estimate. Ultimately a statistically well defined immunogenicity assay cutpoint will save you and your company time and money.

12:15 pm Strategies for Identification and Characterization of ADAs Using MSD

Sponsored by MSD Meso Scale Discovery

David Sloan, Ph.D., Meso Scale Discovery

The MESO SCALE DISCOVERY® (MSD) platform offers significant advantages for the rapid development and robust implementation of immunogenicity assays in preclinical and clinical settings to detect and characterize antibodies produced in response to biological therapeutics. High sensitivity, broad dynamic range and tolerance to free drug, along with reduced matrix effects and a simplified workflow renders the platform ideally suited to address the challenges of immunogenicity assays. MSD® also provides solutions for NAb (neutralizing antibody) assays. Nab assays on the MSD platform can range from monitoring changes in receptor phosphorylation status or modulation of intracellular markers, to quantification of secreted proteins such as cytokines, to characterization and measuring cell surface receptors directly on the surface of whole cells. In this talk, strategies for optimization of screening immunogenicity assays will be discussed, and the applicability of the multiplexing capabilities of the MSD platform to isotype ADAs will be presented.

12:45 Luncheon Presentation or Lunch on Your Own

(Opportunity available, please contact Ilana Quigley, Iquigley@healthtech.com)

CASE STUDIES: PRE-CLINICAL IMMUNOGENICITY ASSESSMENT

2:15 Chairperson's Remarks

Michele Fiscella, Ph.D., Associate Director, Clinical Immunology, Human Genome Sciences

FEATURED PRESENTATION

2:20 Studies in Immunotoxicology in Animals

Deborah Finco, Ph.D., Senior Principal Scientist, Immunotoxicology, Pfizer, Inc.

Administration of human monoclonal therapeutic antibodies administered to species commonly used in toxicology studies generally elicits an anti-drug antibody (ADA) response in some animals. The generation of ADA may impact drug exposure and/or result in other immune mediated toxicological findings. This case study present a unique hepatic toxicity associated with intravenous administration of a human monoclonal antibody to rats in a 13-week study. Similar findings were not observed in the subcutaneous arm of the rat study or in the IV or SC arms of a cynomolgus

monkey study. The findings and possible mechanistic reason(s) for the findings will be discussed.

2:50 Risk Assessment and Monitoring of Antibody Responses to Biopharmaceuticals: BioMarin Case Studies

Eric D. Foehr, Ph.D., Director, Bioanalytical R&D, Biomarin Pharmaceuticals, Inc.

The following topics will be covered and discussed: evaluating immunogenicity in animal models of enzyme replacement therapeutics; review of a successful tolerance regimen in a canine model; the role of pre-existing antibodies in immune response to enzyme therapeutics; case studies of the impact of immunogenicity on safety, PK, and PD.

3:20 Optimizing a Suite of PK-PD-IG Assays for Assessment of Immunogenicity Illustrated by Case Studies

Sebastian Spindeldreher, Ph.D., Deputy Head, Bioanalytics, Novartis Biologics

Immunogenicity to a monoclonal antibody (mAb) often affects clearance of the mAb itself and/or binding to the target ligand. In addition, analytical methods which characterize either drug exposure or target binding are often affected by the presence of anti-drug antibodies and/or mAb-ligand complexes. Consequently, additional information regarding immunogenicity and the ability to neutralize target binding can be obtained from an understanding of the assay characteristics for both PK and PD assays. An integrated approach which combines information from a suite of appropriate PK-PD and IG assays can obviate the need for assays designed to characterize the neutralizing ability of anti-drug antibodies.

3:50 Networking Refreshment Break, Poster and Exhibit Viewing

MOVING FROM PRE-CLINICAL TO CLINICAL

FEATURED PRESENTATION

4:30 Informative Immunogenicity Assessment Strategies for Clinical Trials

Valerie Quarmby, Ph.D., Principal Scientist & Director, BioAnalytical Technologies & Strategies, Genentech, Inc.

In order to assess the immunogenic potential of biotherapeutics, appropriate methods must be developed for the detection and characterization of ATA responses. These methods must then be deployed in a systematic manner in well designed clinical studies, so that clinical events can be correlated with laboratory test results. This talk will discuss methods and strategies that are used in the acquisition of immunogenicity data from clinical trials. The talk will also review case studies showing the importance of interpreting ATA results in the context of safety, efficacy, pharmacokinetic and pharmacodynamic aspects of protein therapeutics.

5:00 Interpretation of Pre-Clinical Immunogenicity Results and How they Correlate with the Clinical Outcome

Kay-Gunnar Stubenrauch, Ph.D., Senior Scientist, Pharma Research, Bioanalytics, Roche Diagnostics

The immunogenicity of novel biologics is frequently screened for by use of a bridging ELISA. However, the ELISA is considered to be limited in the detection of low-affinity or IgG4 subtype anti-drug antibodies (ADAs). This case study will report on the experience with a clinical safety event-driven immunogenicity testing strategy for a novel biologic in comparison to conventional two-tiered immunogenicity testing. The correlation of ELISA-based ADA screening results with the incidence of clinical ADA events will be discussed in the light of the consistency of the results of the bioanalytical testing battery. The relevance of a safety event-driven testing strategy to reduce the risk of false-negative ELISA results will be examined.

5:30 Break-Out Sessions

Break out sessions are interactive moderated discussions on topics of interest to investigators in the field of Immunogenicity. Problems are discussed and solutions are shared.

6:30 Networking Reception in the Exhibit Hall

7:30 End of Day One of Immunogenicity Assessment and Clinical Relevance

WEDNESDAY, OCTOBER 20

MOVING FROM PRE-CLINICAL TO CLINICAL

7:30-8:15 am Sponsored Breakfast Presentations Available

(Please contact Ilana Quigley, iquigley@healthtech.com)

8:30 am Chairperson's Remarks

Margot O'Toole, Ph.D., Director, Translational Medicine, Pfizer, Inc.

8:35 Immunogenicity Monitoring of Nanobodies®: Translation of Pre-Clinical Data into Clinical Development

Josefin-Beate (Josi) Holz, Ph.D., Chief Medical Officer, Drug Development, Ablynx NV

Ablynx develops antibody-derived therapeutic Nanobodies for the use in patients affected by diseases such as cardiovascular, bone and inflammation. Currently there are 4 llama-derived Nanobodies in clinical development and data will be presented on assessment of pre-clinical and clinical immunogenic potential and translation of immunogenicity assays from bench to bedside. The talk will address challenges of immunogenicity assay development, preclinical versus clinical outcome, and risk assessment.

9:05 Assessment of Immunogenicity and Relevance to Clinical Observations

Matthew Baker, Ph.D., Chief Scientific Officer, R&D, Antitope Ltd.

New technologies are evolving aimed at pre-clinical prediction of immunogenicity in patients with the main focus being on detection of CD4+ T cell epitopes and analysis of immunogenicity in animal models. Validation of these pre-clinical technologies has either been through comparison of the MHC restriction or T cell responses in the laboratory vs. the clinic, or through comparison of immunogenicity in the laboratory vs. the clinic. Data from laboratory studies will be shown in order to determine the relevance of various preclinical technologies to clinical observations of immunogenicity including studies with *in silico, ex vivo* and animal model technologies.

CLINICAL CASE STUDIES

9:35 Measurement and Clinical Impact of IgE Anti-Drug Antibodies

Arno Kromminga, Ph.D., CEO, Immunology, IPM BIOTECH

There has been an increasing concern about the possibility and risk of IgE mediated type I hyper-reactivities, particularly due to novel host systems such as plants or yeast. In addition, the route of administration may increase the risk of IgE ADA formation. The detection of IgE ADA is technically challenging due to the (un)-availability of appropriate positive controls and low circulating levels (ng/ml) of IgE.

10:05 Validation of a Neutralizing Antibody (NAB) Elisa Based on Enzymatic Protein Functional Activity in Human Serum

Sponsored by Intertek

Dominique Gouty, Ph.D., Scientific Director, Intertek-ALTA Immunochemistry

The clinical effect of patient immune responses to therapeutic proteins has ranged from no effect at all to extremely harmful effects to patient health depending on the therapeutic drug. For some therapeutics, such as replacement proteins, validation of a neutralization assay may be required at the clinical stage. In this presentation, we will describe the validation of an ELISA-based assay of serum enzymatic protein functional activity that has been adapted to detect the presence of NAB. We will highlight the unique challenges of setting an IC50 cutpoint, determining the stability, linearity, and sensitivity for this assay.

10:20 Clinically Relevant Immunogenicity Testing of Biologicals – Hypersensitivity Risks and IgE Measurement

Sponsored by Phadia Setting the Standard

Jörgen Dahlström, Ph.D., Scientific Director, Immune Response Diagnostics, Phadia, Sweden

The dramatic increase in the use of recombinant monoclonal antibodies and other biopharmaceuticals in the treatment of cancers and autoimmune diseases such as inflammatory bowel disease and rheumatoid arthritis has resulted in increased reporting of hypersensitivity reactions including anaphylaxis. This talk will cover the clinical benefits of measuring IgE antibodies to biologicals. Further, the value of quantification of antibody responses to biologicals in clinical situations will be discussed.

10:35 Networking Coffee Break, Poster and Exhibit Viewing

FEATURED PRESENTATION

11:10 Immunological Aspects of Enzyme Replacement Therapy

Speaker to be Announced

A presentation of the safety profile of enzyme replacement therapy including anaphylactic reactions, infusion associated reactions and immune-mediated reactions. Immune tolerance induction trials in Pompe patients treated with alglucosidase alfa will be described.

11:40 Immune Responses to Vector and Transgene Product in AAV-Mediated Gene Therapy

Katherine A. High, M.D., Investigator, Howard Hughes Medical Institute; William H. Bennett Professor of Pediatrics, University of Pennsylvania School of Medicine; Director, Center for Cellular and Molecular Therapeutics, The Children's Hospital of Philadelphia

Recombinant adeno-associated viral vectors (AAV) have been successfully used in gene transfer for genetic disease. However, studies in healthy donors have shown antigen-specific memory CD8+ T cells to AAV capsid in a substantial portion of the human population. A clear understanding of capsid antigen processing and presentation, and of T cell responses to AAV, will be key to optimal application of the vector. In addition, immune responses to the transgene product itself may limit the success of gene transfer in the setting of genetic disease. Risk factors for these immune responses will also be discussed.

12:10 pm Luncheon Presentation or Lunch on Your Own

(Opportunity available, please contact Ilana Quigley, iquigley@healthtech.com)

Combined Sessions: Parts One and Two

INTERACTION WITH THE EXPERTS ON REGULATORY CONCERNS AND RISK

WEDNESDAY, OCTOBER 20

12:30 pm Registration for Part Two

1:30 Chairperson's Remarks

Steven J. Swanson, Ph.D., Executive Director, Clinical Immunology, Amgen, Inc.

KEYNOTE PRESENTATIONS

1:35 Developing a Risk-Based Approach to Immunogenicity Assessment

Steven J. Swanson, Ph.D., Executive Director, Clinical Immunology, Amgen, Inc.

When developing a strategy to determine the immunogenicity of a therapeutic protein it is important to consider the likelihood of mounting an immune response and the clinical consequences of an immune response. Understanding the answers to these important questions can allow a determination of how comprehensive the immunogenicity testing to support the therapeutic protein should be. This presentation will focus on ways to understand risk and how to fit an assessment strategy to best match that risk.

2:05 Visible and Subvisible Aggregates: New Pre-Clinical Models for Assessing their Potential Impact on Immunogenicity

Jack A. Ragheb, M.D., Ph.D., Principal Investigator, Laboratory of Immunology, Division of Therapeutic Proteins, Office of Biological Products, CDER, FDA

Our understanding of how protein aggregate attributes such as size, and external factors such as dose, route, and patient characteristics contribute to immunogenicity is very limited. This talk will focus on visible and subvisible protein aggregates, how they may interact with the immune system, the potential impact these particles could have on a product's safety and efficacy profile, the factors affecting this risk, and recent efforts to evaluate and control the associated risk.

2:35 Immunogenicity of Protein Therapeutics: An Updated Regulatory Perspective

João A. Pedras-Vasconcelos PhD Visiting Associate DTP-OBP-CDER-FDA

Immunogenicity is a significant safety and efficacy concern for protein therapeutics. This talk will provide an update on the new FDA immunogenicity guidance document for biological therapeutics including: FDA expectations regarding the submission of assay development and validation data; clinical assessment of immunogenicity; managing immunogenicity and immunogenicity studies as part of comparability exercises. Common pitfalls in submissions will be discussed.

3:05 Challenges and Successes of Measuring Antigen-Specific T cell Responses

Sponsored by C.T.L. Cellular Technology Ltd.

Magdalena Tary-Lehmann, M.D., Ph.D., Chief Scientific Officer, Cellular Technology Ltd

Assessing immunogenicity is a challenge as an increasing number of new drugs and vaccines aim to elicit a response from the cellular components (e.g. T cells) of the immune system. Therefore, monitoring antigen-specific T cells and their effector functions is crucial for the understanding of the efficacy of specific immune therapies. ELISPOT assays have recently emerged as a primary tool for monitoring antigen-specific, low frequency measurements of cellular immunity, recording two cardinal features of cell-mediated immunity: the clonal sizes and the cytokine effector class which will be discussed during the presentation.

3:20 Networking Refreshment Break, Poster and Exhibit Viewing

4:00 Health Authority Expectations for Immunogenicity Data Required for Second Generation Manufacturing Changes for Insulin Products

Mikael Sørud, M.Sc., Director, Regulatory Affairs, Novo Nordisk A/S

Novo Nordisk has specialised in insulin manufacture for almost 90 years. Over the last decade a couple of second generation manufacturing processes for insulin human and insulin analogues have been developed and submitted to health authorities world wide. Pre-submission consultations on the requirements for immunogenicity studies have been conducted with several authorities, including EMA, FDA, TGA, SFDA, PMDA and BGTD with very different outcomes. Differences in regulations and specific requirements will be discussed as well as recommendation on how to approach different authorities with a global strategy.

4:30 Discussion

5:00 End of Part One

5:15 Break-Out Sessions for Part Two attendees

6:00– 7:00 Networking Reception for Part Two Attendees

PART TWO: Immunogenicity Prediction and Control

THURSDAY, OCTOBER 21

FACTORS AFFECTING IMMUNOGENICTY

8:30am Chairperson's Remarks

Matthew Baker, Ph.D., Chief Scientific Officer, R&D, Antitope Ltd.

8:35 High Pressure Dissociation of Aggregate Structure and Resulting Decreased Immunogenicity

Matthew Seefeldt, Ph.D., Vice President, Research, BaroFold, Inc.

Studies have identified the causal relationship of the presence of small levels of aggregates in protein-based therapeutics to the development of immunogenicity toward native proteins after repeated dose administration. BaroFold's novel, proprietary, high pressure refolding technology is effective for the reversal of aggregates present in commercial drug formulations and is scaleable in the GMP setting. We have demonstrated proof-of-principle on commercial growth hormone formulations, decreasing the immunogenicity of Nordiflex and IFN-beta-1b formulations in murine models. This talk will summarize the lessons that we have learned in the context of aggregate size, structure, content and immunogenicity.

9:05 Impact of Product Related Factors (CMC factors) on Immunogenicity

Satish K. Singh, Ph.D., Research Fellow, Biotherapeutics Pharmaceutical Sciences, Pfizer, Inc.

Several factors influence the generation of an immune response including patient characteristics, disease state and the therapy itself. Product-related factors such as the molecule design, the expression system, post translational modifications, impurities, contaminants, formulation and excipients, container/closure as well as degradation products are also implicated. The talk will critically examine the available data for the impact of these latter factors on clinical immunogenicity. Deconvolution of the clinical impact of product attributes from patient susceptibility is not readily feasible.

9:35 Quantification of Pre-Existing CD4 T Lymphocytes Specific to Therapeutic Proteins as a Tool of Evaluation of Immunogenicity Potential

Bernard Maillere, Ph.D., Head, Immunochemistry, Institute of Biology and Technologies, CEA

We have quantified the number of pre-existing CD4 T lymphocytes specific to murine, chimeric, humanized and human therapeutic antibodies in the blood of healthy individuals. Irrespective of the humanization levels, the number of antibody-specific CD4 T lymphocytes was in good concordance with their known immunogenicity. We also successfully applied this approach to human erythropoietin and provide a possible explanation for the immune response that was observed for certain batches of recombinant EPO.

10:05 Sponsored Presentation
(Opportunity available, please contact Ilana Quigley, iquigley@healthtech.com)

10:35 Networking Coffee Break, Poster and Exhibit Viewing

IMMUNE TOLERANCE STUDIES

KEYNOTE PRESENTATION

11:10 Immune Tolerance Mechanisms: Animal Models and Approaches

David W. Scott, Ph.D., Vice Chair for Research, Uniformed Services, University of Health Sciences, Bethesda

This presentation will focus on the parameters for immunogenicity of biotherapeutics and how an understanding of tolerance mechanisms can be used to control undesirable immune responses. The nature of the multiple factors impacting on immunogenicity and approaches to control them will be discussed. Novel and classical approaches to induce tolerance will be reviewed together with their advantages and disadvantages. The uses of IgG chimeric fusion proteins and gene therapy, for example, have provided additional insights for tolerance mechanisms. Moreover, this has led to a focus on regulatory T cells in this and other models. These studies have an impact on the design of protein therapeutics for reduced immunogenicity and adverse events.

11:40 To be Announced

12:10 pm Sponsored Presentation
(Opportunity available, please contact Ilana Quigley, iquigley@healthtech.com)

12:25 Luncheon Presentation or Lunch on Your Own
(Opportunity available, please contact Ilana Quigley, iquigley@healthtech.com)

APPLICATION OF PREDICTIVE METHODS TO SELECT NON-IMMUNOGENIC PROTEINS

2:00 Chairperson's Remarks

David W. Scott, Ph.D., Professor of Surgery and of Microbiology and Immunology, University of Maryland School of Medicine

2:05 A Human Lymphoid Organ Model (HuALN) For Predictive Testing of Immunogenicity, Immunotoxicity and Immune Functions *in vitro*

Christoph Giese, Ph.D., Director, Cell and Tissue Services, ProBioGen AG

Human tissue based models which emulate immune organ function are conceived to bridge the gap in testing immune functionality, immunotoxicity and predictive immunogenicity between early lead optimization and the pre-clinical development stage. The model of the Human Artificial Lymph Node (HuALN) is designed to investigate induced immune responses *in vitro*. The 3D organoid model can be used for long-term culture and repeated dosing. Cytokine release, antibody secretion, cellular functionality and tissue formation are monitored.

2:35 *In Silico* Prediction of Immunogenicity: Sense and Non-Sense

Philippe Stas, M.B.A., Head, Applied Protein Services, Lonza Biologics; Head, Algonomics NV

Different methods and algorithms exist for the prediction of CD4+ T-cell epitopes. As these epitopes are a requirement for a sustained immunogenicity, selection of protein therapeutics based on their relative epitope content has been applied for over 2 decades. This presentation focuses on the use of *in silico* methods for lead selection, and how they complement the *in vitro* strategies for immunogenicity assessment. In specific cases, antibody engineering techniques can be used to reduce or avoid immunogenicity of the drug. Selected case studies are presented to explore the clinical relevance of predictive methods in biotherapeutic development.

FEATURED PRESENTATION

3:05 Generation of Therapeutic Proteins Against Inflammatory Disease and Cancer Targets with a Low Risk of Clinical Immunogenicity

Frank J. Carr, Ph.D., Director, Biologics Research, Antitope Ltd.

CD4+ T cell epitopes in the variable region sequences of therapeutic proteins have been identified by *ex vivo* T cell epitope mapping. The

number and potency of T cell epitopes correlated with the immunogenicity (frequency of anti-therapeutic responses) of these proteins in the clinic. Furthermore, the presence of aggregated antibody induced more frequent *ex vivo* T cell responses. Data will be presented that provides evidence linking the presence of T cell epitopes in the sequences of therapeutic proteins with immunogenicity observed in patients as well as how proteins can be engineered to avoid T cell epitopes.

3:35 Networking Refreshment Break, Poster and Exhibit Viewing

4:00 Reducing the Immunogenicity of the Pseudomonas Exotoxin-Based Immunotoxins by Modification of B Cell Epitopes

Masanori Onda, M.D., Ph.D., Laboratory of Molecular Biology, NCI/NIH

Our approach to de-immunize our immunotoxin is to identify the B cell epitopes and to modify them by mutagenesis. The mutated new immunotoxin was fully active and of extremely low immunogenicity. This approach can also be applicable for other protein therapeutics.

FEATURED PRESENTATION

4:30 Design Space Available for Non-immunogenic Proteins

Stephen Lee, Ph.D., Associate Professor, Biomedical Engineering, Ohio State University

My group has derived an algorithm which explicitly identifies literally all possible variants of any protein that lack binding motifs for preselected class I or class II haplotypes, based on set theory. It is useful in vaccine or non-immunogenic protein design. The number of possible epitope-free variants can be immense (>10^10 in many cases). Along with data from deep protein mutagenesis experiments, this suggests identification of non-immunogenic protein sequences should be possible today, though discovery of the subset of biofunctional variants will involve laborious, deep mutagenesis, and non immunogenic proteins may be very different in sequence from their parents.

5:00 End of Part Two

HOTEL and TRAVEL INFORMATION

Loews Philadelphia Hotel
1200 Market Street
Philadelphia, PA 19107
Phone: 215-627-1200
Fax: 215-231-7305
Discounted Room Rate: $179 s/d
Discounted Room Rate Cut-off Date: September 19, 2010

To reserve your accommodation, call the hotel directly, and to receive your discounted room rate, identify yourself as a Cambridge Healthtech Institute conference attendee. Reservations made after the cut-off date or after the group room block has been filled (whichever comes first) will be accepted on a space-and-rate-availability basis. Rooms are limited, so please book early.

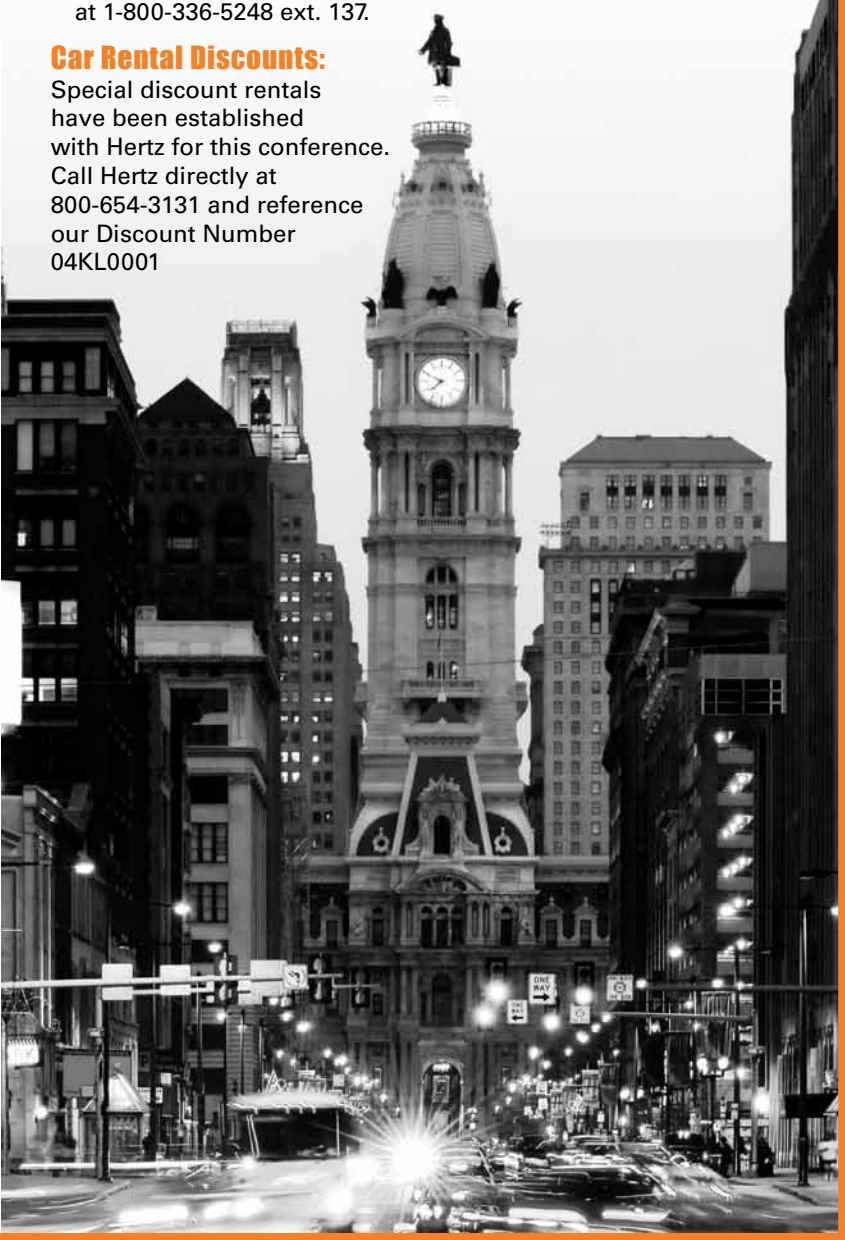
Flight Discounts:

To receive a 5% or greater discount on all American Airline flights please use one of the following methods:

- Call 1-800-433-1790 (authorization code A48H0AP).
- Go online at www.aa.com (enter A48H0AP in promotion discount box).
- Contact our designated travel agent, Wendy Levine, at 1-800-336-5248 ext. 137.

Car Rental Discounts:

Special discount rentals have been established with Hertz for this conference. Call Hertz directly at 800-654-3131 and reference our Discount Number 04KL0001



SPONSORSHIP and EXHIBIT INFORMATION

Showcase your company's expertise, brand your solutions and develop revenue opportunities with qualified decision-makers by becoming an Exhibitor or Sponsor!

Sponsored Presentation Opportunities
Speak to a captive audience about your latest product or service for 15 or 30 minutes as part of the conference program, ensuring your audience is seated and ready to listen.

Breakfast or Luncheon Presentations- Invite session delegates to enjoy breakfast or lunch on your company's behalf while you give a 30-minute presentation. Your presentation is concluded with 15 minutes of Q&A, allowing you to interact with your customer base.

Invitation Only Networking Receptions - CHI will invite delegates that you select to a private reception at the host hotel. Cocktails and hors d'oeuvre's will be served in a setting conducive to networking. These receptions are available on a first-come, first served basis.

Additional Networking & Promotional Opportunities

- Refreshment Breaks
- Exhibit Hall Reception
- Tote Bags
- Tote Bag Insert
- Conference Padfolios
- Attendee Coffee Mugs
- Badge Lanyards and more!

Exhibitor Information
The exhibit hall presents an excellent opportunity to network with prominent scientists and executives who attend the event to learn about cutting edge research and technologies in their field. Exhibiting will allow your company to meet hard to reach prospects face to face, and pave the way for future sales.

We can CUSTOMIZE any opportunity to meet your current MARKETING OBJECTIVES and BUDGET.

To find out more about our comprehensive sponsorship and exhibit packages, please contact:

Ilana Quigley
Manager, Business Development
781-972-5457
iguigley@healthtech.com

Cambridge Healthtech Institute's Second Annual

Immunogenicity Summit 2010

October 19-21, 2010 • Loews Philadelphia Hotel • Philadelphia, Pennsylvania

REGISTRATION INFORMATION

Key Code 1027F

❑ Mr. ❑ Ms. ❑ Mrs. ❑ Dr. ❑ Prof.

Name _____

Job Title _____ Div./Dept. _____

Company _____

Address _____

City/State/Postal Code _____

Country _____

Telephone _____

How would you prefer to receive notices from CHI? Email: ❑Yes ❑No Fax: ❑Yes ❑No

Email* _____ Fax _____

*Email is not a mandatory field. However, by excluding your email you will not receive notification about online access to pre-conference presenter materials, conference updates, networking opportunities and requested eNewsletters.

PRICING

PRE-CONFERENCE SHORT COURSES - OCTOBER 18	Commercial	Academic, Government, Hospital-affiliated
1 Short Course	❑ $695	❑ $395
2 Short Courses	❑ $995	❑ $695

Please select the short course(s) you would like to attend:

❑ SC1: Technical Advice on Assay Development, Validation and Sample Analysis

❑ SC2: Development of Cell-Based Neutralizing Antibody Assays

SUMMIT PRICING - OCTOBER 19-21 **BEST VALUE**		
Advance Registration Deadline until September 17, 2010	❑ $1995	❑ $945
Registrations after September 17, 2010 and on-site	❑ $2195	❑ $995
INDIVIDUAL CONFERENCE PRICING		
Advance Registration Deadline until September 17, 2010	❑ $1445	❑ $775
Registrations after September 17, 2010 and on-site	❑ $1645	❑ $875

Please select which part you will be attending:

❑ Part 1: Immunogenicity Assessment and Clinical Relevance (October 19-20)

❑ Part 2: Immunogenicity Prediction and Control (October 20-21)

POSTER DISCOUNT	❑ $50 off	❑ $50 off

☛ **REGISTER 3 - 4th IS FREE**

Individuals must register for the same conference or conference combination and submit completed registration form together for discount to apply. Please reproduce this registration form as needed.

GROUP DISCOUNTS AVAILABLE! Special rates are available for multiple attendees from the same organization. For more information on group discounts contact **David Cunningham at 781-972-5472**

❑ I cannot attend but would like to purchase the Immunogenicity Summit conference CD for $350 (plus shipping). Massachusetts delivery will include 6.25% sales tax.

❑ Please send information on exhibiting and opportunities to present workshops.

PAYMENT INFORMATION

❑ Enclosed is a check or money order payable to Cambridge Healthtech Institute, drawn on a U.S. bank, in U.S. currency.

❑ Invoice me, but reserve my space with credit card information listed below.

Invoices unpaid two weeks prior to conference will be billed to credit card at full registration rate. Invoices must be paid in full and checks received by the deadline date to retain registration discount. If you plan to register on site, please check with CHI beforehand for space availibility.

❑ Please charge: ❑ AMEX (15 digits) ❑ Visa (13-16 digits) ❑ MasterCard (16 digits)

Card # _____

Cardholder _____

Signature _____

Cardholder's Address (if different from above) _____

City/State/Postal Code _____

Country _____

Please refer to the Registration Code below:

HOW TO REGISTER:

Online:
ImmunogenicitySummit.com

Email:
reg@healthtech.com

Phone: 781-972-5400

Fax: 781-972-5425

Yes! I would like to receive a FREE eNewsletter subscription to:

CAMBRIDGE HEALTHTECH MEDIA GROUP
chimediagroup.com

❑ Weekly Update
The latest industry news, commentary and highlights from Bio•IT World

❑ eCliniqua
Innovative management in clinical trials

CHI Insight Pharma Reports
A series of diverse reports designed to keep life science professionals informed of the salient trends in pharmaceutical technology, business, clinical development, and therapeutic disease markets. For a detailed list of reports, visit InsightPharmaReports.com, or contact Rose LaRaia at rlaraia@healthtech.com, 781-972-5444.

Barnett Educational Services
Barnett is a recognized leader in clinical education, training, and reference guides for life science professionals involved in the drug development process. For more information, visit www.barnettinternational.com.

Present a Poster and Save $50!

Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions.

To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by **September 22, 2010**. Register online, or by phone, fax or mail. Indicate that you would like to present a poster and you will receive abstract submission instructions via email.

I am interested in presenting a poster at

❑ **Immunogenicity Summit**

Title _____

_____

_____

Additional Registration Details

Each registration includes all conference sessions, posters and exhibits, food functions, and a copy of the conference proceedings link.

Register 3 - 4th is Free! Individuals must register for the same conference or conference combination and submit completed registration forms together for discount to apply. Please reproduce this registration form as needed.

Group Discounts are Available! Special rates are available for multiple attendees from the same organization. For more information on group discounts contact David Cunningham at 781-972-5472

Handicapped Equal Access
In accordance with the ADA, Cambridge Healthtech Institute is pleased to arrange special accommodations for attendees with special needs. All requests for such assistance must be submitted in writing to CHI at least 30 days prior to the start of the meeting.

Substitution/Cancellation Policy
In the event that you need to cancel a registration, you may:

- Transfer your registration to a colleague within your organization.
- Credit your registration to another Cambridge Healthtech Institute program.
- Request a refund minus a $100 processing fee per conference.
- Request a refund minus the cost ($350) of ordering a copy of the CD.

NOTE: Cancellations will only be accepted up to two weeks prior to the conference. Program and speakers are subject to change.
Video and or audio recording of any kind is prohibited onsite at all CHI events.

Cambridge Healthtech Institute
250 First Avenue, Suite 300, Needham, Massachusetts 02494
T: 781-972-5400 or toll-free in the U.S. 888-999-6288
F: 781-972-5425 • www.healthtech.com