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Cambridge Healthtech Institute's Fourth Annual PRECLINICAL DEVELOPMENT

How Can We Improve Prediction of Clinical Safety?



March 26-28, 2008 • Moscone North Convention Center • San Francisco, CA

KEYNOTE SPEAKERS:



Improving R&D Productivity Through Better Preclinical Decision Making and Science

B. Michael Silber, Ph.D., Chief, Drug Discovery R & D, Adjunct Professor of Neurology and Biopharmaceutical Sciences, Institute for Neurodegenerative Diseases, University of California San Francisco



Toxicity Testing in the 21st Century: Opportunities for Pharmaceutical Risk Assessment

Daniel Krewski, Ph.D., MHA, Professor and Director, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa

HIGHLIGHTED PRESENTATIONS:



From Publication to Practice: Interlaboratory Validation of Microarray and QPCR-based Signatures for Predicting Carcinogenicity in the Rat

Mark Fielden, Ph.D., DABT, Discovery and Investigative Safety, Non-Clinical Drug Safety, Roche Palo Alto LLC



Mechanistic Cardiac Modeling: Concepts and Utility in Drug Development

Anna Georgieva, Ph.D., Associate Director, Modeling & Simulation, and Ruben Bibas, Ph.D., Biology Modeler, Modeling & Simulation, Novartis Inc.



Challenges of Doxercalciferol, a Prodrug of a Potent Vitamin D Hormone

Joyce Knutson, Ph.D., Senior Scientific Director, Genzyme Corporation



Defining and Finding Relevant Animal Models: The Evolution of "Relevant" During Development

Nancy Wehner, Ph.D., Senior Director, Non-clinical Safety Evaluation, Elan Pharmaceuticals



Predicting the Undesirable Pharmacodynamic Effects of Small Molecules on Physiological Function: From the Brain to the Heart

Vivek Kadambi, Ph.D., Director of Drug Safety Evaluation, Millennium Pharmaceuticals, Inc.



Predicting Cardiac Toxicity with Adjuvant Trastuzumab Therapy

Ellie Guardino, M.D., Ph.D., Assistant Professor of Medicine, Breast Oncology, Stanford University



Imaging Biomarkers in Early Clinical Development of Novel Therapeutic Agents

Jeffrey L. Evelhoch, Ph.D., Executive Director, Medical Sciences, Imaging, Amgen Inc.

SESSIONS:

- Advances in Toxicity Testing and Prediction
- Case Studies: Successes and Failures in Preclinical Development
- Toxicity Pathways
- Finding the Relevant Model for Toxicity Testing
- Choosing an Imaging Modality

TUESDAY MARCH 25 • PRE-CONFERENCE SHORT COURSES

(SC5) IMMUNOLOGICAL BIOMARKERS: "HOW TO" AND THREE CASE STUDIES

(SC8) MODELS FOR EVALUATING DRUG-DRUG INTERACTION POTENTIAL IN PRECLINICAL DEVELOPMENT

Hot Topics This Year

- Interlaboratory Validation of Signatures for Predicting Carcinogenicity
- Mechanistic Cardiac Modeling and Utility in Drug Development
- Defining and Finding Relevant Animal Models
- Advances in Liver Toxicity Testing
- Predicting Cytokine Storms from *in Vitro* Cell Based Models
- Translating Safety from Animals to FIH Studies of Biologics

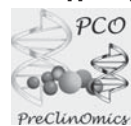
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7:00am Registration (Open until 5:30pm)

PLENARY KEYNOTE SESSION

8:00 Plenary Keynote Introduction



Harry Glorikian, Managing Partner, Scientia Advisors

8:15 Diagnosing the Disease: Disruptive Innovation in Healthcare



Clayton M. Christensen, DBA, Robert and Jane Cizik Professor of Business Administration, Harvard Business School

In the absence of the ability to precisely define a disease, the care of patients is best undertaken by highly skilled professionals, whose intuition is based on deep experience. This describes the history of health care, and we call this the practice of intuitive medicine. Molecular biology holds the promise of transforming medical practice into a new phase that we call precision medicine. It promises to dramatically reduce cost and increase the predictable effectiveness of therapy.

9:45 Coffee Break

10:15am - 1:15pm Morning Pre-Conference Short Course*

Recommended Short Course*

(SC5) IMMUNOLOGICAL BIOMARKERS: "HOW TO" AND THREE CASE STUDIES

Moderator: Eric Wakshull, Ph.D., Senior Scientist/Group Leader, Development Sciences, Genentech Inc.

10:15 HLA and T Cell Response as Biomarkers Linked to the Immunogenicity of Protein Therapeutics

Annie De Groot, M.D., Chief Executive Officer, EpiVax, Inc. and Brown University

Immunogenicity elicited by protein therapeutics can cause serious side effects in humans. We affirm that immunogenicity can be predicted and patients who are at increased risk of developing adverse immune responses can be identified using immunoinformatics tools. We have used EpiMatrix, an in-silico epitope-mapping tool, and iTEM, an "individualized T cell epitope measure" to determine whether protein therapeutics will elicit an immune response. In a recent published case, we identified promiscuous epitopes ("EpiBars") in the C-terminal region of a recombinant fusion protein (FPX) consisting of two identical, biologically active, peptides attached to human Fc fragment. On administration of FPX in 76 healthy human subjects, 37% developed antibodies after a single injection. A memory T-cell response against the carboxy-terminus of the peptide was both predicted and observed. Promiscuity of the predicted T-cell epitope(s) was confirmed by representation of all common HLA-alleles in antibody positive subjects. And finally, as predicted by iTEM (individualized T cell epitope measure), HLA-haplotype DRB1*0701/1501 was associated with the highest T-cell and antibody response.

10:45 Case Study of GDNF: Characterizing the Immune Response Against Protein Therapeutics

Michael Moxness, Ph.D., Principal Scientist Clinical Immunology, Amgen
A case study of GDNF will be used to demonstrate a risk-based strategy for designing assays to detect antibodies against protein therapeutics. Methods to characterize isotype, subclass and neutralizing activity will be discussed. The role of non-clinical studies, T-cell epitopes, and pre-existing antibodies will also be examined in the context of clinical development.

11:15 Break

11:45 Case Study of DR 0701: Genome-Wide Pharmacogenetic Investigation of a Hepatic Adverse Event Without Clinical Signs of Immunopathology Suggests a Underlying Immune Pathogenesis

Karin Cederbrandt, Ph.D., Molecular Toxicology, AstraZeneca
One of the major goals of pharmacogenetics is to elucidate mechanisms and identify patients at increased risk of adverse events (AEs). To date, however, there have been only a few successful examples of this type of approach. In this paper, we describe a retrospective casecontrol pharmacogenetic study of an AE of unknown mechanism, characterized by elevated levels of serum alanine aminotransferase (ALAT) during long-term treatment with the oral direct thrombin inhibitor ximelagatran. The study was based on 74 cases and 130 treated controls and included both a genome-wide tag single nucleotide polymorphism and large-scale candidate gene analysis. A strong genetic association between elevated ALAT and the MHC alleles DRB1*07 and DQA1*02 was discovered and replicated, suggesting a possible immune pathogenesis. Consistent with this hypothesis, immunological studies suggest that ximelagatran may have the ability to act as a contact sensitizer, and hence be able to stimulate an adaptive immune response.

*Separate Registration Required

12:15 Case Study

Assessing Immunogenicity in an Emerging Biological Class, Adnectins

Eric Furfine, Ph.D., Senior Vice President, Research & Preclinical Development, Adnexus, a Bristol-Myers Squibb R&D Company
Adnexus is leading the advancement of Adnectins, a novel, proprietary class of targeted biologics that are derived from a well-characterized, high-concentration, plasma protein, human fibronectin. Adnectin-based products offer various potential advantages as compared to traditional protein therapeutics, including speed of discovery, ease of manufacturing, and multi-functionality. Angiocept (CT-322) is an inhibitor of VEGFR-2, and is the first Adnectin in clinical trials. Angiocept has a low-risk immunogenicity profile based on clinical data to date. In addition, Adnexus has identified an early-stage, potent Adnectin that blocks an important cancer target with low immunogenic potential using a combination of our PROfusion discovery engine and EpiVax in silico technology. Results of these programs will be discussed as case examples of how one can successfully manage or improve immunogenicity risks within a new biologics class.

12:45 Panel Discussion with Q&A

*Separate Registration Required

1:15 Lunch on Your Own

2:30 - 5:30 Afternoon Pre-Conference Short Course*

Recommended Short Course*

(SC8) MODELS FOR EVALUATING DRUG-DRUG INTERACTION POTENTIAL IN PRECLINICAL DEVELOPMENT

This course will cover:

- An overview of drug-drug interactions from the clinical perspective, withdrawn drugs and the overall impact on development
- CYP inhibition and induction methods and *in vitro/in vivo* correlations
- Transporter models and *in vitro/in vivo* correlations

More Short Courses:

- (SC1) BIOMARKERS ARE US: INTERACTIVE SHORT COURSE ON HOW BIOMARKERS WILL IMPACT THE FIELD OF ONCOLOGY
- (SC2) THE CHALLENGE OF THE BLOOD-BRAIN BARRIER: A MEDICINAL CHEMISTRY PERSPECTIVE
- (SC3) ADMET CASE STUDIES FROM A MEDICINAL CHEMISTRY PERSPECTIVE
- (SC4) THE EPIGENETIC STEM CELL SIGNATURE
- (SC6) CIRCULATING TUMOR CELLS
- (SC7) CANCER STEM CELLS
- (SC10) NAVIGATING THROUGH INDIAN REGULATORY TERRA INCOGNITA: A HANDS-ON WORKSHOP

*Separate Registration Required

7:00am Registration (Open until 5:30pm)

PLENARY KEYNOTE SESSION

8:00 Plenary Keynote Introduction



Edward G. Heidig, Chief Deputy Director, Department of Managed Health Care

8:10 Risk Diagnosis for Disease Prevention



C. Thomas Caskey, M.D., F.A.C.P., Director and Chief Executive Officer, Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center

There are an increasing number of presymptomatic diagnostic options which include: genetic, imaging, and analyte technology. Examples of linking a specific diagnostic to a therapeutic decision and FDA approval have fueled the activity for personalized medicine. It must be appreciated that diagnostic capacity emerges far more rapidly than an approved safe therapeutic. Thus the personalized medicine goal has a bottle neck for broad utility. A strategy of studying approved drugs for maximal efficacy is realistic and reasonable toward that goal since it is estimated that many approved drugs are effective in less than 50% of patients. These approaches will be discussed.

8:55 Disruption of the Pharmaceutical Industry: Moving from Products to Solutions



Elizabeth L. Bewley, MBA, Vice President, Strategic Planning, Johnson & Johnson Health Care Systems Inc.

The pharmaceutical industry is bracing itself for a period of unprecedented challenges. This new era for our industry is being brought on by the confluence of several environmental factors, both internal and external to the industry, including: 1) non-sustainable increases in healthcare expenditures, 2) spiraling costs and decreasing productivity of R&D, 3) reimbursement driven by medical and economic outcomes, and 4) the proliferation and redistribution of healthcare outcomes information. Although all of these factors threaten to disrupt our industry, it is the evolving transparency in healthcare outcomes information that represents the most unsettling threat to our current business model, as well as the largest opportunity to transform our industry. For this transformation to take place, it is imperative that we change from an industry in which the sole mission is to provide products to one that provides broader, cost-effective solutions to areas of major healthcare needs.

9:40 Grand Opening Refreshment Break in the Exhibit Hall

OPENING SESSION: KEYNOTE PRESENTATIONS

(Combined with Trends in Drug Safety)

11:00 Chairperson's Remarks

William B. Mattes, Ph.D., DABT, Director of Toxicology, The Critical Path Institute (invited)

11:10 Improving R&D Productivity Through Better Preclinical Decision Making and Science



B. Michael Silber, Ph.D., Chief, Drug Discovery R & D, Adjunct Professor of Neurology and Biopharmaceutical Sciences, Institute for Neurodegenerative Diseases, University of California San Francisco

An analysis of significant contributors to overall productivity, as measured by getting a new medicine to registration, regulatory approval and launch, yielded some interesting findings. These contributors have been known and described by many investigators and apply to pharmaceutical R & D in general. The major contributors to attrition and survival include the confidence in rationale (CIR) and confidence in the safety (CIS) for the target, and CIR and CIS for the compound, impacting on success in each of the phases of discovery and development. Development strategies often assume success and build in significant front-loading and cost, but don't take into account the probability of success at each stage of the R & D process. A model created that looks at ways to improve overall productivity suggests that significant increases are possible, in principle, if flexible strategies to development are adopted early as opposed to a one size fits all strategy. This includes appropriate preclinical development strategies dependent on the early Phase I plans in the clinic. A simulator-based model to R & D was developed that suggests significant increases in productivity can be achieved without increases in budget. Discussion will focus on what these analyses suggest, with a focus on alternative strategies and plans. It will focus on developing the alternative preclinical packages at the appropriate time to perform hypothesis testing and proof of concept.

11:55 Toxicity Testing in the 21st Century: Opportunities for Pharmaceutical Risk Assessment



Daniel Krewski, Ph.D., MHA, Professor and Director, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa

Current approaches to toxicity testing of environmental agents rely primarily on a complex array of studies that evaluate adverse effects in intact animals at high doses. Anticipating the opportunities that will be provided by recent scientific advances in cell and molecular biology, genomics, high-throughput robotics, bioinformatics, computational systems biology, and other disciplines, the National Research Council's Committee on Toxicity Testing and Assessment of Environmental Agents developed a long-range vision for toxicity testing and a strategic plan for implementing that vision. This vision was designed to (i) develop a more robust scientific basis for assessing adverse health effects of environmental agents, (ii) provide broad coverage of chemicals, chemical mixtures, outcomes, and life stages, and (iii) reduce the cost and time of toxicity testing. In addition, the process envisioned would greatly reduce the numbers of animals used in toxicity testing. The main elements of the vision will be outlined in detail, and the potential applications of the vision to assessing the potential risks of pharmaceutical products examined.

12:40pm Technology Spotlight (Sponsorship Available)

1:10 Walk & Talk Luncheon in the Exhibit Hall

ADVANCES IN TOXICITY TESTING AND PREDICTION

(Combined with Trends in Drug Safety)

2:15 Chairperson's Remarks

Joy Cavagnaro, Ph.D., DABT, RAC, President, Access BIO

2:20 Overview



William B. Mattes, Ph.D., DABT, Director of Toxicology, The Critical Path Institute

2:40 From Publication to Practice: Interlaboratory Validation of Microarray and QPCR-based Signatures for Predicting Carcinogenicity in the Rat



Mark Fielden, Ph.D., DABT, Discovery and Investigative Safety, Non-Clinical Drug Safety, Roche Palo Alto LLC

Interlaboratory evaluation of putative biomarkers is essential for their validation prior to use, however, the majority of efforts to date are limited to single publications and/or analytical platforms, thus limiting their general applicability. Based on hepatic changes in gene expression, the Carcinogenicity Working Group of the Critical Path Institute has validated biomarkers of non-genotoxic carcinogens across companies and are

working towards developing a QPCR-based platform for larger deployment and tier 2 validation. It is anticipated that the interlaboratory validation and widely accessible platform will provide industry with a valuable tool to evaluate the potential for molecules to induce tumors in the rat, thus providing essential information for early human risk assessment and assist in compound prioritization and selection.

3:00 Mechanistic Cardiac Modeling: Concepts and Utility in Drug Development



Anna Georgieva, Ph.D., Associate Director, Modeling & Simulation, and Ruben Bibas, Ph.D., Biology Modeler, Modeling & Simulation, Novartis Inc.

Blockade of the delayed rectifier potassium channel current, I(Kr), has been associated with drug-induced QT prolongation in the electrocardiogram and life-threatening cardiac arrhythmias. However, it is increasingly clear that compound-induced interactions with multiple cardiac ion channels may significantly affect QT prolongation that would result from inhibition of only I(Kr). A complete experimental pre-clinical assessment of the pro-arrhythmic potential of all drug candidates may not be feasible due to multi-factorial processes that are also time-dependent and highly non-linear. Here, we present an example of a systems-based integrative modeling approach to characterizing risk carried by pharmaceutical compounds based on limited pre-clinical data.

3:20 Advances in Liver Toxicity Testing: What's on the Horizon?



Holly L. Jordan, DVM, PhD, Dipl. ACVP, Director of Clinical Pathology, Safety Assessment, GlaxoSmithKline

Current approaches to evaluation of liver injury in drug safety testing rely extensively on histopathologic and clinicopathologic assessment in preclinical species. These standard elements successfully predict the potential for hepatotoxicity in the clinical setting in only about half of the cases. Through comprehensive, collaborative efforts, such as the Hepatotoxicity Working Group in the Predictive Safety Testing Consortium of the Critical Path Institute, a number of novel preclinical and clinical biomarkers of liver injury have been proposed and are currently under evaluation worldwide. These candidate predictive markers are designed to address general hepatotoxicity or in some cases, very specific types of liver injury. Modalities under investigation encompass a variety of technologies, including new and/or modified serum enzyme assays and gene expression panels with an emphasis on non-invasive or minimally invasive testing that can be applied to preclinical species and humans.

3:40 SDAR: Spectrometric Data Activity Relationship Modeling



Dan Bazuta Ph.D., Research Chemist, National Center for Toxicological Research, FDA

A brief introduction to a class of novel and highly accurate modeling methods capable of predicting chemical and biological properties for substances based on chemical spectral information. This includes chemical reactivity, biological activity, and toxicity. The presentation will include a discussion regarding the fundamental concepts behind the principle, several examples of published SDAR models, and advancements to the original technique that increase predictive accuracy.

3:55 Modeling and Assaying Dioxin-Like Biological Effects for Both Dioxin-Like and Certain Non-Dioxin-Like Compounds



Jon Wilkes, Ph.D., Research Chemist, National Center for Toxicological Research, FDA

Quantitative spectrometric data-activity relationship (QSDAR) models were used to correlate ¹³C NMR data to World Health Organization Toxic Equivalency Factors (TEFs) of the 29 polychlorinated dioxin-like compounds (PCDDs, PCDFs, or PCBs) for which non-zero TEFs have been defined. The best QSDAR models predicted TEFs of 0.037 and 0.004, respectively, for 1,3,7,8-tetrachlorodibenzo- π -dioxin (TCDD) and 1,2,3,4,7-pentachlorodibenzo- π -dioxin (PeCDD), both of which are among the 390 congeners for which zero value TEFs are assumed. A QSDAR model of Relative Potency (REP) values estimated the corresponding values as 0.115 and 0.020. Both models indicated that these two congeners are likely to exhibit significant dioxin-like toxicity. We used a luciferase gene expression *in vitro* assay based on mouse liver cells to determine experimental REPs of 0.027 and 0.013, respectively, for 1,3,7,8-TCDD and 1,2,3,4,7-PeCDD. The corresponding QSDAR-estimated and gene-expression assayed values were in close agreement with the predicted values demonstrating that SDAR prediction followed by a relatively inexpensive *in vitro* assay could be used to nominate a few candidates among hundreds for expensive *in vivo* evaluation.

4:20 Reception in the Exhibit Hall (Sponsorship Available)

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5:00 - 6:00pm Break-out Discussions in the Exhibit Hall

Carcinogenicity Biomarkers

Moderator: Mark Fielden, Ph.D., DABT, Discovery and Investigative Safety, Non-Clinical Drug Safety, Roche Palo Alto LLC

- What degree of validation and performance is necessary for carcinogenicity biomarkers to impact drug development?
- What other tumor types beyond liver would benefit from predictive carcinogenicity biomarkers?
- What other technologies or approaches may be more predictive or provide other advantages over genomic biomarkers?
- What do genomic assays provide above and beyond existing assays?

Liver Toxicity Biomarkers

Moderator: Holly L. Jordan, DVM, Ph.D., Dipl. ACVP, Director of Clinical Pathology, Safety Assessment, GlaxoSmithKline

- What the advantages and disadvantages of current preclinical hepatotoxicity biomarkers?
- What are the most relevant gaps in assessing liver injury during drug development?
- What type of data are necessary to support implementation of a new liver injury marker?

Translation of Preclinical Safety Biomarkers to the Clinic

Moderator: William B. Mattes, Ph.D., DABT, Director of Toxicology, The Critical Path Institute

- What makes a truly translational safety biomarker?
- What data do you need to support Phase 1 studies vs. data to support standard of care?
- Ethical considerations

Finding the Relevant Model for Toxicity Testing of Biopharmaceuticals

Moderator: Mary Haak-Frendscho, Ph.D., Vice President, Preclinical Research & Development, XOMA (US) LLC

- Paying attention to preclinical data
- Finding the right toxicity, disease, and activity models
- Predicting cytokine storms from preclinical data, focus on target specific activity
- Regulatory consequences from the TeGenero Case Study, reinventing toxicity testing for Antibodies
- Screening for target-mediated adverse events

provides for the clinical development of GMX1777 will be discussed.

10:00 Technology Spotlight

Digital Toxicologic Pathology in Preclinical Contract Research: The Importance to Pharmaceutical and Biotech Partners

Sponsored by  aperio

Steven J. Potts, Ph.D., MBA, Director, Biopharma, Aperio Technologies

Digital toxicologic pathology is a new technology that will transform preclinical pathology. Whole slide images and searchable databases allow pathologists to annotate and review slides remotely, search across preclinical studies, discuss abnormal cases with CRO partners and specialists, conduct peer reviews remotely, standardize scoring, and measure protein expression in tissues. In this talk I will discuss the transition of preclinical pathology from glass slides, and what preclinical pharmaceutical executives should know as the industry moves closer to digital slides.

10:30 Poster Competition & Refreshment Break in the Exhibit Hall

11:30 Discovery and Development of AMD3100 as a Stem Cell Mobilizer



Ron T. MacFarland, Ph.D., Senior Director, Pharmacology and Toxicology, Anormed Pharmaceuticals

AMD3100 is a small molecule inhibitor of the chemokine receptor CXCR4 and blocks binding of its cognate ligand SDF-1. AMD3100 was originally discovered in an antiviral drug screening program, and its initial development directed towards use in the treatment of HIV infection. Transient increases in white blood cell counts observed in humans following AMD3100 administration, combined with an understanding of the role of the SDF-1/CXCR4 axis in blood cell homing and maturation in the bone marrow prompted investigation and subsequent development of AMD3100 for use as a stem cell mobilizing agent.

12:00pm The Importance of Integrating Disciplines to Increase the Probability of Successful Drug Development

Cindy Berman, Ph.D., Independent Consultant

The importance of understanding cross-species pharmacological responsiveness will be presented in several case studies of small molecules. The need to understand pharmacological specificity to minimize toxicity related to non-specific effects will be discussed. Potential PK differences between normals and disease condition (*in vitro*, animal, or human) will be considered, as will the importance of understanding whether the receptor is up or down regulated in the disease condition. Potential "tox" differences between normals and patients and the advantages and disadvantages testing for toxicity in a model that reflects the clinical population will be discussed.

Thursday, March 27

CASE STUDIES: SUCCESSES AND FAILURES IN PRECLINICAL DEVELOPMENT (Combined with Trends in Drug Safety)

8:20am Chairperson's Remarks



Judith K. Marquis, Ph.D., Group Vice President, Pharmacology & Preclinical Development, Genzyme Corp.

8:30 Challenges of Doxercalciferol, a Prodrug of a Potent Vitamin D Hormone



Joyce Knutson, Ph.D., Senior Scientific Director, Genzyme Corporation

Doxercalciferol is a potent compound (therapeutic dose in micrograms), that is inactive until metabolized in the liver to an active form (circulating concentration pg/mL) that is also an endogenous compound. Bioanalytical challenges were compounded by species differences in sensitivity and gender differences in metabolism. Anticipation and proactive actions to overcome these preclinical challenges resulted in the successful development of doxercalciferol for treating dialysis patients for secondary hyperparathyroidism.

9:00 Predicting the Undesirable Pharmacodynamic Effects of Small Molecules on Physiological Function: From the Brain to the Heart



Vivek Kadambi, Ph.D., Director of Drug Safety Evaluation, Millennium Pharmaceuticals, Inc.

This presentation will focus on two case studies which have shown a good correlation between the effects observed in nonclinical studies and in humans. Case study 1 will focus on the CNS effects relating to sedation and somnolence. Case study 2 will focus on the electrophysiologic effects on the cardiac conduction system.

9:30 GMX1777 Case Study: Using Metabolomics to Determine the Mechanism of Action of an Anti-Cancer Compound



Anne Roulston, Ph.D., Group Leader, Cancer Biology, Gemin X Biotechnologies Inc., Canada

GMX1777 is a soluble prodrug of the pharmacologically active compound GMX1778. Initiation of Phase I clinical trials began in patients with refractory solid tumors and lymphomas. We have since discovered that GMX1778 functions by inhibiting nicotinamide phosphoribosyl transferase (NAMPT), an enzyme involved in nicotinamide adenine dinucleotide (oxidized) (NAD+) biosynthesis. The approach used to identify the key mechanism of action of GMX1778 and the new opportunities this information

LUNCHEON TECHNOLOGY WORKSHOP

12:30 Presentation I

Application of Global Biochemical Profiling in Pharmaceutical Discovery and Development

Sponsored by  METABOLON

Don Rose, Ph.D., VP Marketing, Metabolon, Inc.

Global biochemical profiling, sometimes referred to as metabolomics, analyzes a broad spectrum of biochemicals and metabolites in a biological sample and looks for biochemical perturbations due to the action of drug or the effect of disease. This presentation will review several case studies from pre-clinical discovery and development where this approach was used to elucidate the drug mechanism of action as well as identify early-stage biochemical markers indicative of drug toxicity.

1:00 Presentation (Sponsorship Available)

TOXICITY PATHWAYS

(Shared session with Pathway Analysis, Trends in Drug Safety and Cancer Molecular Markers)

1:45 Chairperson's Remarks

Eric A. G. Blomme, D.V.M., Ph.D., Diplomate A.C.V.P., Project Leader, Abbott Laboratories

1:50 Integration of Novel Technologies in Discovery and Early Development Toxicology



Eric A. G. Blomme, D.V.M., Ph.D., Diplomate A.C.V.P., Project Leader, Abbott Laboratories

Toxicity represents an important cause of failure in the late stages of discovery and preclinical development. Therefore, early identification of the toxic liabilities of experimental compounds represents one of the most promising alternatives to decrease overall R&D costs. In this presentation, we will review our current Discovery toxicology strategy that leverages several new methodologies in an effort to characterize the toxicologic profile of compounds at early stages. Using specific examples, we will illustrate how this approach can be successfully implemented in a discovery or preclinical organization.

2:20 A Lead Optimization and Early Development Toxicology

Barbara Davis, V.M.D., Ph.D., Associate Director Toxicology & Pathology, Millennium Pharmaceuticals, Inc.

Discovery stage and early nonclinical development toxicology studies in the oncology therapeutic area present unique challenges in predicting for success in the clinic, relative to adverse effects. The attrition rate in oncology development is over 90%, often because of toxicity. Frequently, what is termed failed efficacy is actually a consequence of lack of tumor specificity for the therapeutic target. The challenge to the discovery & early development stage toxicologist is amplified for novel targets in oncology. A strategy to avoid progressing molecules with chemical structure based adverse effects while refining the understanding of the tumor specificity and the PK/PD/toxicity relationships across species, specific to novel oncology therapeutic candidates, will be the focus of this presentation.

2:50 Predictive Value of *in Vitro* Safety Studies



Willi Suter, Ph.D., Unit Head, Genetic Toxicology and Safety Pharmacology, SP&A, Novartis Pharma AG

The predictivity of *in vitro* methods and their importance for decision-making in drug development is shown for four important areas of pharmaceutical safety evaluations, i.e. genetic toxicology, safety pharmacology, phototoxicity and organ toxicity. A comprehensive analysis of the predictivity of genetic toxicity tests for rodent carcinogenicity revealed a major problem with the specificity of the *in vitro* mammalian cell assays, which indicates the risk that efficacious drug candidates might have been dropped because of false positive *in vitro* results. Therefore, data from *in vitro* studies, including the recently introduced hERG channel inhibition test to predict QT interval prolongation and from the *in vitro* 3T3 NRU phototoxicity test to predict phototoxicity should be used with great care for decision-making. *In vitro* organ toxicity models provide important mechanistic information. The information obtained from *in vitro* models has significantly improved the safety of patients in clinical studies, since there is much more data available early in the development process.

**3:20 Plenary Keynote Speaker
Ice Bound - A Doctor's Incredible Battle for Survival at the South Pole**

Dr. Jerri Nielsen, MD.

In the coldest and most isolated place on earth, Dr. Jerri Nielsen, author of Ice Bound, found the courage to survive. As sole doctor on a 12-month scientific expedition, she diagnosed her own breast cancer. The Antarctic winter made leaving impossibility, thereby forcing Dr. Nielsen and her teammates to use their skills and resourcefulness to treat her illness. This is an incredible story of one women's courage and survival.

4:00 Ice Cream Refreshment Break in the Exhibit Hall with BEST OF SHOW AWARDS

4:45 Strategies for Early Toxicity Testing with Focus on Genotoxicity Evaluations



Michael J. Schlosser, Ph.D., D.A.B.T., President and Founder of Midwest BioResearch (MBR)

There is a wide array of new screening tools available to toxicologists, but the use of a particular screen must be decided carefully to optimize the success of a drug program. Although rapid throughput genetic toxicity screens that require minimal amounts of compound are available during lead optimization, their value for predicting regulatory outcome is dependent on the specific screen chosen. Screens that mimic the ICH genotoxicity testing battery are best at predicting IND success and will need to keep pace with possible changes in ICH guidelines to maintain predictive value. Regulatory-based genotoxicity screening technologies are also useful in supporting the safety of metabolites, impurities and degradation products when only minimal amounts of these materials are available. Several examples of regulatory-based genotoxicity screening strategies, including SAR techniques, will be presented.

5:15 Speaker to Be Determined

5:45 End of Day

FINDING THE RELEVANT MODEL FOR TOXICITY TESTING OF BIOPHARMACEUTICALS LESSONS LEARNED FROM TEGENERO
(Combined with Trends in Drug Safety)

8:30am Chairperson's Remarks

Mary Haak-Frendscho, Ph.D., Vice President, Preclinical Research & Development, XOMA (US) LLC

8:35 Defining and Finding Relevant Animal Models: The Evolution of "Relevant" During Development



Nancy Wehner, Ph.D., Senior Director, Non-clinical Safety Evaluation, Elan Pharmaceuticals

Defining and finding relevant animal models for biopharmaceutical toxicity testing is a major challenge for drug development due to the generally limited species reactivity of these compounds. This challenge can be greatly heightened when specific safety concerns exist that can't be easily tested due to this limited reactivity or when clinical events reveal issues that were not identified preclinically in the chosen "relevant" species. These circumstances can and should lead to a reevaluation of the animal models being used and a willingness to examine/utilize less traditional models and methodologies when appropriate. This talk will examine this evolution of relevance through case studies.

9:05 Predicting Cardiac Toxicity with Adjuvant Trastuzumab Therapy



Ellie Guardino, M.D., Ph.D., Assistant Professor of Medicine, Breast Oncology, Stanford University

Trastuzumab, a monoclonal antibody, has been incorporated into the adjuvant treatment of HER2-positive breast cancer. I will discuss cardiotoxicity found in the major adjuvant trastuzumab trials reported to date including NSABP B-31, NCCTG N9831, HERA, Breast Cancer International Research Group (BCIRG) trial 0069 and the Finland Herceptin (FinHER) trial. Attempts at reducing the risk of cardiotoxicity and selecting appropriate patients for treatment will be discussed.

9:35 Translating Safety from Animals to FIH Studies of Biologics: Science or Art?



Lauren E. Black, Ph.D., Senior Scientific Advisor, Navigators, Preclinical Services, Charles River Laboratories

After TGN1412, IL-12, and thrombopoietin, does the future for biologics seem insecure? Do biologics have to be a perfect "magic bullet" to be a successful therapeutic advance? No, long term clinical experience with monoclonal antibodies show how risk and benefit can be balanced. But we have to acknowledge that sometimes, startling things can happen when protein drugs enter human trials - why can't we prevent every risk? Why aren't animals always perfect models of human response? As regulators and large pharma push for complete risk prevention, the biologics community can only fight for risk mitigation. The answer is not "more [animals] is better". To move forward in these times, we have to use every muscle - our interdisciplinary experts, new technologies and history- to craft unique approaches for each biologic IND. There are simple steps that we can take to mitigate risks that are couched in traditional science - like the ancient quote from Paracelsus, "the dose makes the poison." The FDA "Starting Doses" guidance hold some little-known clues and is discussed by one of it's authors. The last page lists the factors which lead to larger safety margins - among them is a hint that if you can't ferret out the dose/response relationship, all bet's are off (read: "kill the drug"). But if you can, the Pharmacologically Active Dose can be used as a conservative index for FIH dosing, a method which is very pertinent to biologics and other receptor-targeted drugs. This dose extrapolation index can offer a moderate dose estimate approach that will appease reviewers without either caving to paranoia or ignoring the frailties in pre-clinical testing.

10:05 Technology Spotlight (Sponsorship Available)

10:20 Coffee Break in the Foyer

11:00 Development of an *in Vitro* Cytokine Release Assay and its Predictive Value



Jing Min, Ph.D., Principal Scientist, Biotherapeutics, Pfizer

In light of the tragic FIH clinic outcome of TGN1412, a predictive cytokine release assay would be beneficial for the early safety assessment of any future immunomodulators. Using a synthesized anti-CD28 superagonist mAb as a positive control a human PBMC-based *in vitro* cytokine release assay has been developed. The predictive value of the assay has been further assessed with various control antibodies.

11:30 The Early Development of Raptiva® (efalizumab) for Plaque Psoriasis



Kathleen Meyer, Ph.D., Director of Toxicology, XOMA (US) LLC

The early nonclinical safety evaluation and clinical development of Raptiva® (efalizumab) will be discussed, focusing on the predictive value of animal studies to the clinical situation. Raptiva is an immunosuppressive recombinant humanized IgG1 kappa isotype monoclonal antibody that binds a human CD11a, thus reducing T cell activation, adhesion and migration. Raptiva is indicated for the treatment of adult patients with chronic moderate to severe plaque psoriasis.

12:00pm Luncheon Workshop (Sponsorship Available) or Lunch on Your Own

CHOOSING AN IMAGING MODALITY FOR BOTH INTERNAL DECISION MAKING AND REGULATORY APPROVAL

(Shared session with Translational Medicine)

1:00 Chairperson's Remarks



Kohkan Shamsi, M.D., Ph.D., President & CEO, Acunova Life Sciences Inc. and Director, Symbiotic Pharma Research

1:05 Imaging Biomarkers in Early Clinical Development of Novel Therapeutic Agents



Jeffrey L. Evelhoch, Ph.D., Executive Director, Medical Sciences, Imaging, Amgen Inc.

Over the past decade, biomarkers (objectively measured indicators of a biological/pathobiological process or pharmacologic response to treatment) have been recognized as a critical element to improve predictability and efficiency in the process of developing more effective, more affordable, and safer therapeutics for patients. In the early clinical development of novel therapeutics, biomarkers can provide information critical to internal decision-making (i.e., establish presence of target, evaluate biological/clinical activity, dose selection for later phase trials, stratify study populations, conduct interim analysis of efficacy and/or safety). Imaging is a powerful biomarker that can provide information about genetic, biochemical, physiological and anatomic processes in many diseases including multiple sclerosis, cancer, arthritis, atherosclerosis, Alzheimer's disease, and others. This talk will explain how imaging is used as a biomarker and give several examples of how it can impact decision-making in early clinical development.

1:35 Imaging in Phase II/III Clinical Development



Haren Rupani, M.D., FACR, FACNP, Global Head, Oncology Imaging, Novartis Pharmaceuticals Corporation

- Standard or Validated Imaging Modalities
- RECIST and McDonald Criteria
- Role of Exploratory Imaging in Phase II/III

2:05 Imaging as a Biomarker in Oncology Drug Trials and Improving Cancer Patient Care



Gary Kelloff, M.D., Advisor, Cancer Imaging Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute

New promising imaging tools for measuring biomarkers have also been developed and are based on direct visualization by microscopy, nanotechnologies, and direct and remote imaging. Definitions and classifications of these biomarkers for use in oncology drug development are presented, as are activities of the NCI/FDA Interagency Oncology Task Force; opportunities under the Oncologic Biomarker Qualification Initiative (OBQI) and Biomarkers Consortium for establishing public/private partnerships; and validation/qualification studies of imaging-based biomarkers.

2:35 The Promises and Realities of Imaging as a Translational Biomarker in Drug Development



Timothy J. McCarthy, Ph.D., Senior Director and Head of Imaging, Translational and Molecular Medicine, Pfizer Global R&D

- Overview of the use of non-invasive imaging in drug development
- Identification of issues around translational imaging
- Opportunities for future technical innovations

3:05 Close of Conference

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- Track 6: Clinical Trials Asia
- Track 7: Preclinical Development**
- Track 8: Translational Medicine
- Track 9: Cytokine-Based Therapeutics
- Track 10: Cancer Molecular Markers
- Track 11: Trends in Drug Safety

Yes, I will attend Clayton Christensen's Keynote presentation (March 25)

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