ADMET Conference

Translating research into clinical outcomes

7th - 8th July 2010
Crowne Plaza Hotel - St James, London, United Kingdom

Day One - 7th July 2010

8.30 Registration & Coffee

9.00 Chairman's Opening Remarks

Bernard Faller, Director of Metabolism & Pharmacokinetics / in-vitro ADME, **Novartis Pharmaceuticals**

9.05 ADME Optimisation in Early- and Late-Phase Drug Discovery
Integrating ADME into drug discovery in order to reduce the attrition rates

- Applicability domain and validity
- Decision points
- Preclinical strategies
- False positive rates

Gerhard Gross, Global Discipline Leader ADME, **AstraZeneca**

9.35 Targeting Drugs for the Brain
Innovative high-throughput method for early prediction of brain availability

- Fast and reliable prediction of brain disposition and free drug available in brain
- Classification of CNS versus non-CNS drugs based on rate and extent
- Prediction of CNS side-effects

Hinnerk Boriss, CEO, **Sovicell**

10.15 Morning Coffee

10.45 Probabilistic Model of Regioselectivity of Metabolism in Human Liver Microsomes

- A ligand-based model of regioselectivity, based on >850 structures
- Predicting probability to be a metabolism site for every atom in the molecule using separate models for different reactions
- Estimation of the reliability of prediction defining the model applicability domain
- Possibility to expand this applicability domain using in-house data

Pranas Japertas, Director of ADMET and PhysChem, **Advanced Chemistry Development**

11.25 Vinblastine Treated CaCo-2 Culture as a Drug Penetration Model
An added value model of drug penetration

- Characterisation of efflux transporters: function and importance
- Experimental approaches to identify P-gp substrates/inhibitors

- Comparison of cell culture models of drug penetration
- Establishment and characterisation of vinblastine treated Caco-2 culture
- Validation of the vinblastine treated Caco-2 penetration assay
- Practice of penetrability screening of new chemical entities in our preclinical research

Monika Vastag, Head of In vitro Metabolism Laboratory, **Gedeon Richter**

11.55 Integrating Predictive ADMET into Hit to Lead and Optimisation
Getting away from black & white by creating composite ADMET risk scores

- Hedging your bets by including ADMET diversity dimensions
- Balancing potential ADMET liability against potential potency, selectivity etc.
- Accommodating the inherent fuzziness of ADMET exclusion thresholds
- Managing interdependence among biological and physical properties

Robert Clark, Director of Life Sciences, **Simulations Plus**

12.35 Networking Lunch

1.35 Structure-based ADMET Studies
The challenges and the opportunities

- Metabolite prediction of CypP450 reactions
- Toxicity from Nuclear Receptors
- Understanding P-glycoprotein interactions
- Efforts towards predicting hERG liability

Frank Blaney, Director, **MemProt Consulting**

2.05 RAPIDD plus
An accelerated programme of integrated drug and biomarker development

- Addressing challenges of increasing time-to-market, cost and attrition
- Integrated drug and biomarker development in a pre-clinical setting

Denis Geffroy, Vice President Business Development, **Almac Group**

2.45 Building Hypotheses in Lead Selection and Optimisation
Linking in-silico, in-vitro and in-vivo data

- Translating PK parameters into MedChem actions
- When can one use rules derived from the analysis of generic drugs?
- Extracting information from the absence of correlation

Bernard Faller, Director of Metabolism & Pharmacokinetics / in-vitro ADME, **Novartis Pharmaceuticals**

3.15 Afternoon Tea

3.45 Supersaturation Effects in Solubility-Enhancing Excipients and Biorelevant Media

John Comer, Co-founder & Technical Director, **Sirius Analytical Instruments**

4.20 Prediction of DDI's Arising from Cytochrome P450 Inhibition

- Importance of understanding CYP inhibition
- Extrapolation of in vitro data to predict clinical interactions following CYP inhibition
- Factors influencing the extent of a DDI due to CYP inhibition

- Future Directions

Kuresh Youdim, Senior Principal Scientist, **Pfizer**

4.50 Developing a Mechanism-based PK/PD Model

- Influencing early phase development using preclinical models
- Connecting the PK with the pharmacology and pre-clinical efficacy of the compound
- Providing an improved rationale for selecting the dose rage for Phase I trials

Damien Cronier, Research Scientist, Global PK/PD, **Eli Lilly**

5.20 Drug Transporter Assays in Discovery

- Available assays
- How assays are used in the screening cascades
- Utilization of the data (case study)

Laurent Salphati, Scientist, **Genentech**

5.50 Chairman's Closing Remarks and Close of Day One

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8.30 Registration & Coffee

9.00 Chairman's Opening Remarks

Donna Dambach, Director, Investigative Safety Assessment, **Genentech**

9.10 The Utility and Application of TDI Screens in Early Discovery DMPK
In vitro TDI screens for in vivo DDI prediction and Reactive Metabolite potential

- Importance of front-loading TDI assays in Discovery
- In vitro - in vivo DDI extrapolation
- MBI data as a Reactive Metabolite early-warning flag

Richard Weaver, Associate Principal Scientist, **AstraZeneca**

9.45 System-dependent inhibition of cytochrome P450 (CYP) enzymes
Common misconceptions and errors

- When should cytochrome P450 (CYP) inhibition by drug candidates be evaluated in human hepatocytes and not just human liver microsomes or recombinant CYP enzymes?
- Rules to guide the selection of the appropriate test system to evaluate CYP inhibition
- Common errors associated with the processing of data from metabolism-dependent inhibition (MDI) studies that incorporate a dilution step.

- Why a dilution step - even with correct data processing - should be avoided in evaluating drug candidates MDI of CYP enzymes

Andrew Parkinson, Chief Scientific Officer, **XenoTech LLC**

10.25 Morning Coffee

10.55 Integrating Predictive Toxicology Model Development

- Data Management, Schema and Integrating Multiple Resources
- Predictive Toxicology Application-oriented Ontology Development
- Developing combined in silico in vitro Consensus Models
- Model Validation and Applicability Domain
- Incorporating Pharmacokinetics to Predict Exposure
- OpenTox Case Study Example

Barry Hardy, Director, Community of Practice & Research Activities and OpenTox Project Coordinator, **Douglas Connect**

11.30 Application of High Content Analysis for Predictive Cytotoxicity Testing & Preclinical Toxicity Biomarkers

- Criteria for effective cytotoxicity models
- Demonstration of predictive cytotoxicity screens and investigations of toxicity mechanisms
- Demonstration of toxicity in vivo using high content analysis of peripheral blood lymphocytes
- Application strategies for screening for toxicity, identification of mechanisms, and development of translational in vivo biomarkers of toxicity

Peter O'Brien, Veterinary Clinical Pathologist / Toxicologist, **University College Dublin**

12.05 Segregation of Genotoxic Compounds
Novel in vitro system approach with human HepG2 liver cell line

- Genotoxicity testing in the early phase of the drug development process
- Segregation of Genotoxicity scores from Salmonella, Yeast and HepG2 cells
    - HepG2 cells
      - analysis with toxicogenomics for global gene expression profiling of genotoxicants
      - validation of promoter based luciferase reporter assays with the promoters of RAD51C, and Cystatin A, and the responsive elements of p53 and Nrf2
      - in vitro micronuclei analysis with high content screening, the more traditional way
      - advantage of endogenous metabolism by phase I and II enzymes

Willem Schoonen, Senior Research Scientist, Toxicology & Drug Disposition, **MSD**

12.40 Networking Lunch

1.40 In Vitro and In Vivo Approaches for Assessing the Potential for Drug Induced Liver Injury
Tools and strategies to consider in characterising and investigating hepatotoxicity

- The line between overt toxicity, "outliers" and idiosyncratic toxicity
- In vitro-in vivo correlations-consideration of physiochemical and PK drivers of toxicity
- Assessing metabolism as the basis for toxicity
- Preclinical genomic assessments and their potential clinical application
- Clinical trial sampling-leveraging new, 'standard' endpoints

Donna Dambach, Director, Investigative Safety Assessment, **Genentech**

2.15 Emerging In Vitro Toxicity Assays and the Role of Stem Cells in Assessing Human Toxicology

- Microscale cell culture systems: novel approaches that mimic regulatory tests and allow for higher-throughput testing
- Current status of the development of human embryonic stem cell-derived tissue-specific cells and their applications

Claudia McGinnis, Group Head, In Vitro Toxicology, **Roche**

2.50 Mechanisms of Human (Hepato)Toxicity
Do we benefit from this knowledge?

- Business and science arguments for and against early investigation of mechanisms of toxicity
- Known mechanisms of human hepatotoxicity
- Assays available for prediction of specific mechanisms of toxicity:
- HCA, mitochondrial toxicity, phospholipidosis: validation
- Case studies: when and which assays are relevant?
- Path forward: new cell and tissue models

Katya Tsaioun, President, **Apredica**

3.30 Afternoon Tea

4.00 Metabolism-Based Drug Toxicity in Drug Development

- Case Study 1 - Assessing the value of reactive metabolite assays
- Looking to past failures - could we have predicted toxicity using modern in vitro tools?
- Determining the cause(s) of species differentiation in toxicity
- Case Study 2 - Exploring the value of "humanised" mice
- Looking to past failures - could we have predicted toxicity using modern in vivo tools?
- Translation to human toxicity prediction

Timothy Schulz-Utermoehl, Group Manager, In Vitro ADME, Clinical Pharmacology & DMPK, **AstraZeneca**

4.35 Evaluation of Microdosing Strategies Utilizing AMS and LC/MS-MS for ADME Studies in Drug Development
Case studies demonstrating the benefits of evaluating PK in early stage drug development

- Linear kinetics of test compounds across microdose/sub-pharmacological and pharmacological dose ranges
- Analytical tools to measure plasma concentrations over time to define kinetics at micro /sub pharmacological doses
- Review of the available information on microdosing approaches and usefulness of such studies

Punam Sandhu, Senior Investigator, **Merck**

5.10 Is There Too Much (Hot) Air in Genetic Toxicity Assessment?

- Does in vitro testing in atmospheric oxygen create misleading positive results?
- ICH S2 (R1) test guidelines update: what is the appropriate top testing dose?
- What is on the horizon for genotoxicity assessment? Maturing new technologies

Richard Walmsley, Professor of Genetics, **The University Of Manchester**

5.45 Chairman's Closing Remarks and Close of Day Two