

## Personalized Itinerary Planner and Abstract Book

SOT 2008  
March 15 - 20, 2008

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Saturday, March 15, 2008

*You have nothing scheduled for this day*

Sunday, March 16, 2008

*You have nothing scheduled for this day*

Monday, March 17, 2008

*You have nothing scheduled for this day*

Tuesday, March 18, 2008

Time	Session Info
7:30 AM-8:50 AM, 618 (CC), <b>Breaking the Log-Jam: Public-Private Partnerships as a Way to Discover and Advance Biomarkers of Drug-Induced Toxicity</b>	
7:30-8:50 AM	<b>631. Breaking The Log-Jam: Public-Private Partnerships As A Way To Discover And Advance Biomarkers Of Drug-Induced Toxicity</b> <u>W.B. Mattes</u> ; F. Pfannkuch; J. Vidal; F.M. Goodsaid
9:00 AM-11:45 AM, 6C (CC), <b>Accelerating Discoveries in Toxicology Through -Omics Research</b>	
9:00 AM-11:45 AM	<b>675. APPLICATION OF A SYSTEMS TOXICOLOGY APPROACH TO INVESTIGATE TROGLITAZONE HEPATOTOXICITY IN THE RAT</b> <u>E. Troesken</u> ; A. Gruhler; E. Boitier; J. Marchandeanu; K. Arnold; B. Bidlingmaier; A. Brandenburg; M. Kurz; A. Pfenninger; J. Schnieders; I. Stammberger; M. Stolte; A. Amberg
11:25-11:45 AM	<b>676. Integrated transcriptomic and proteomic evaluation of gentamicin nephrotoxicity in rats</b> <u>E. Com</u> ; E. Boitier; J. Marchandeanu; M. Courcol; J. Leonard; M. Duchesne; B. Genet; S. Schroeder; M. Wendt; J. Gautier
1:30 PM-4:15 PM, 602 (CC), <b>Novel Biomarkers of Drug-Induced Toxicity: Outcomes of Predtox and the Predictive Safety Testing Consortium</b>	
3:00-3:20 PM	<b>1269. -Omics in hepatotoxicity prediction</b> <u>A. Mally</u>
3:20-3:40 PM	<b>1270. An Integrated -Omics Approach Towards a Better Understanding of Drug-Induced Nephrotoxicity and Useful Biomarkers</b> <u>F. Staedtler</u>

Wednesday, March 19, 2008

*You have nothing scheduled for this day*

Thursday, March 20, 2008

*You have nothing scheduled for this day*

Final ID: 631

## Breaking The Log-Jam: Public-Private Partnerships As A Way To Discover And Advance Biomarkers Of Drug-Induced Toxicity

*W. B. Mattes*<sup>1</sup>; *F. Pfannkuch*<sup>2</sup>; *J. Vidal*<sup>3</sup>; *F. M. Goodsaid*<sup>4</sup>;

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**Abstract Body:** The drug-development process entails an interaction between the industrial (private) sector and public regulatory agencies. Likewise, changing this process through the use of innovative new safety tests also requires an interaction between the public and private sectors. Two unique and parallel efforts are the Innovative Medicines Initiative and the Predictive Safety Testing Consortium. The former, under the auspices of the European Union, brings together academics and companies in a combined effort to discover and qualify new -omics-based markers of toxicity. The latter, under the direction of the non-profit Critical Path Institute, brings together companies to comprehensively qualify new safety biomarkers for both non-clinical and clinical applications. Both efforts directly involve members of the regulatory agencies so that the processes are not just transparent to regulatory agencies, but result in assays that are accepted by the general scientific, industrial and regulatory communities. This Roundtable will provide an overview of these processes with particular attention to the interaction between scientific approaches and regulatory input, and allow discussion of how these partnerships achieve their goals.

Final ID: 675

## APPLICATION OF A SYSTEMS TOXICOLOGY APPROACH TO INVESTIGATE TROGLITAZONE

### HEPATOTOXICITY IN THE RAT

*E. Troesken*<sup>1</sup>; *A. Gruhler*<sup>2</sup>; *E. Boitier*<sup>1</sup>; *J. Marchandeu*<sup>1</sup>; *K. Arnold*<sup>3</sup>; *B. Bidlingmaier*<sup>1</sup>; *A. Brandenburg*<sup>4</sup>; *M. Kurz*<sup>1</sup>; *A. Pfenninger*<sup>1</sup>; *J. Schnieders*<sup>1</sup>; *I. Stammberger*<sup>1</sup>; *M. Stolte*<sup>1</sup>; *A. Amberg*<sup>1</sup>;

1. Sanofi-Aventis, Hattersheim, Germany.
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3. Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany.
4. Genedata AG, Basel, Switzerland.

**Abstract Body:** Troglitazone (TGZ), a PPAR- $\gamma$  agonist oral antidiabetic agent, was withdrawn from the market due to severe idiosyncratic hepatocellular toxicity in man. In the scope of the Innomed PredTox project, TGZ was tested as a model hepatotoxic compound using an integrated approach combining genomics, proteomics and metabonomics, along with conventional toxicology evaluation. TGZ was administered orally to male Wistar rats (n=5) at doses of 0, 200 or 1500 mg/kg/day for 1, 3 and 14 days. After a 14-day administration increased liver weights and a mild centrilobular hypertrophy at 1500 mg/kg/day were observed in all five animals. Gene expression analysis revealed a strong impact of high doses of TGZ on the liver transcriptome, peaking on Day 2 and decreasing with longer treatment duration. Functional analysis mainly indicated the pharmacological action of TGZ, namely induction of lipogenesis, inhibition of glucose production/utilization, activation of glycogenesis and repression of the inflammatory response. TGZ also presented PPAR- $\alpha$  activity at high doses: enhanced fatty acid  $\beta$ -oxidation, tightly coupled to induction of Krebs cycle and ketogenesis. Detoxifying enzymes were also induced, most likely underlying the centrilobular hypertrophy observed microscopically. Functional annotation of the 80 modulated proteins identified by 2D-DIGE confirmed the mobilization of lipid metabolism and glycolysis inhibition. Induction of mitochondrial and protein metabolisms, and a cellular stress response were also observed. Urine NMR analysis revealed an initial up-regulation of fatty acid metabolites. Trimethylamin-N-oxide, a chemical chaperone linked to protein metabolism, and betaine were up-regulated in a time-dependent manner. Integration the three "omics" approaches allowed the identification of the most relevant pathways involved in the toxicity of TGZ.

Final ID: 676

### Integrated transcriptomic and proteomic evaluation of gentamicin nephrotoxicity in rats

*E. Com*<sup>1</sup>; *E. Boitier*<sup>1</sup>; *J. Marchandea*<sup>1</sup>; *M. Courcol*<sup>1</sup>; *J. Leonard*<sup>1</sup>; *M. Duchesne*<sup>2</sup>; *B. Genet*<sup>2</sup>; *S. Schroeder*<sup>3</sup>; *M. Wendt*<sup>4</sup>; *J. Gautier*<sup>1</sup>;

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**Abstract Body:** Gentamicin is an aminoglycoside antibiotic, which induces renal tubular necrosis in rats. In the context of the InnoMed PredTox project ([www.innomed-predtox.com](http://www.innomed-predtox.com)), transcriptomic and proteomic studies were performed to provide new insights into the molecular mechanisms of gentamicin-induced nephrotoxicity. Male Wistar rats (n=5 per group) were treated with 25 and 75 mg/kg/day subcutaneously for 1, 3 and 14 days. Gene expression changes in kidney and blood were assessed using Affymetrix RAE230plus microarrays and protein modulations were evaluated by two dimensional difference gel electrophoresis (2D-DIGE) technology followed by mass spectrometry identification. Analysis of genomic data indicated a strong treatment-related gene expression modulation in kidney and blood at the high dose after 14 days of treatment, with the regulation of 463 (303 up and 160 down) and 3246 (923 up and 2323 down) genes respectively. The modulated genes were involved in the activation of the p38 MAPK cascade, NF- $\kappa$ B pathway, inflammation, apoptosis, protein metabolism, cell proliferation and T-cell activation. It is noteworthy that the top up-regulated gene in kidney was the nephrotoxicity biomarker KIM-1. The proteomic study showed an up-regulation of 49 proteins and a down-regulation of 57 proteins in kidney with 75 mg/kg/day after 14 days of treatment. Proteomic results were suggestive of a mitochondrial dysfunction with impairment of cellular energy production, an induction of oxidative stress, an effect on protein biosynthesis and on cellular assembly and organization. Transcriptomic and proteomic data turned out to be complementary and their integration gave a more comprehensive insight into the putative mode of nephrotoxicity of gentamicin that was in accordance with the tubular necrosis/regeneration observed in histopathology.

Final ID: 1269

**-Omics in hepatotoxicity prediction**

A. Mally<sup>1</sup>;

1. Department of Toxicology, University of Wuerzburg, Wuerzburg, Germany.

**Abstract Body:** The attrition rate of drug candidates due to late-breaking findings in preclinical safety studies is high. Improved prediction of drug toxicity and understanding of key mechanisms of toxicity through incorporation of new concepts and technologies may aid regulatory decision making and decrease the cost of drug development. To achieve these goals, the PredTox project, a collaborative effort by 15 pharmaceutical companies, 2 SMEs and 3 universities was initiated to assess the value of combining -omics technologies with conventional toxicology methods for improved prediction of toxicity and to identify novel biomarkers of (nephro-) and hepatotoxicity. Comprehensive data sets were collected from in vivo experiments in which rats were treated with the model compound troglitazone or one of 12 proprietary compounds that previously failed during drug development partly due to toxic effects in the liver. Liver, kidney, blood and urine were analyzed by a combination of -omics techniques, including toxicogenomics(Affymetrix), toxicoproteomics and metabolic profiling. Clinical chemistry and histopathology were assessed to provide phenotypic anchoring. Data sets were entered into an integrated database for in-depth cross-platform and cross-study data analysis. Hypertrophy, hepatocellular necrosis and biliary cell hyperplasia/necrosis were the most frequent histopathological alterations observed. For most compounds, treated animals were separated from control animals in a dose-dependent manner by principal component analysis. In several cases, -omics technologies were able to identify changes indicative of a toxic response before alterations were detected by conventional endpoints, suggesting that -omics technologies may contribute to improved prediction of hepatotoxicity and biomarker identification. Observations regarding synergies between technologies for improved MOA/MOT investigations will be presented.

The contribution of all members of the PredTox Consortium ([www.innomed-predtox.com](http://www.innomed-predtox.com)) is gratefully acknowledged. The InnoMed Project is supported by partial funding by the Sixth Research Framework Program of the European Union (LSHB-CT-2005-518170).

Final ID: 1270

## An Integrated –Omics Approach Towards a Better Understanding of Drug-Induced Nephrotoxicity and Useful Biomarkers

*F. Staedtler*<sup>1</sup>;

1. Biomarker Development, Novartis Pharma AG, Basel, Switzerland.

**Abstract Body:** In order to increase early attrition in preclinical pharmaceutical drug development, the new omics technologies have been assessed by investigational toxicologists and technology experts. The InnoMed PredTox consortium with participation of 3 academic institutions, 2 technology vendors and 15 major pharmaceutical companies, has focused on a systematic and integrated -omics approach assessed against conventional toxicology assessment in the rat. The goal was to obtain better insight into drug-induced organ toxicity and to confirm and detect early molecular biomarkers of organ toxicity. As a unique feature, the consortium members have selected 14 proprietary compounds, troglitazone that had been withdrawn from the market, and a reference nephrotoxicant, gentamycin. The drug development program of the proprietary compounds was abandoned for toxicity reasons at different development stages. The presentation will summarize and discuss the results obtained so far by the InnoMed PredTox consortium with particular emphasis on nephrotoxicity and potential ways forward towards a further validation and useful application of the results including the candidate biomarkers.