APPLIED PHARMACEUTICAL TOXICOLOGY

May 10-12, 2022

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APPLIED PHARMACEUTICAL TOXICOLOGY

ORGANIZERS' WELCOME

Welcome to the 2022 Applied Pharmaceutical Toxicology Conference.

Our organizers have gathered another excellent group of speakers for the annual APT conference. The program is arranged to incorporate extensive audience participation and discussion. We encourage attendees to take full advantage of the opportunity to engage in discussion in order to receive the maximum benefit from the APT experience. Thank you for your participation.

ORGANIZING COMMITTEES

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Chair: John Maher, Theravance Biopharma

DISCOVERY Toxicology Workshop Organizers

Chair: John Maher, Theravance Biopharma

Committee:
Darcey Clark, Merck
Lijin Feng, Amgen
Jodi Goodwin, Takeda
Jonathan Heyen, Pfizer
Bruce Leroy, AbbVie
Prathap Kumar Mahalingaiah, AbbVie
Jairo Nunes, Novartis
Rama Pai, Merck
Yoav Timsit, Blueprint Medicines
Zoe Zhong, Genentech

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Betty Pettersen, Pfizer
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Lise Loberg, AbbVie
Florence Lorget, Sparing Vision
Eunice Musvasva, Roche
Michael Santostefano, Merck
Nardos Tassew, Genentech
Caren Villano, Boehringer Ingelheim

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APPLIED PHARMACEUTICAL TOXICOLOGY

APT 2022 CONFERENCE AGENDA

TUESDAY, MAY 10
DISCOVERY TOXICOLOGY WORKSHOP

8:00 - 9:00 **Registration**

9:00 - 9:05 **Conference Opening**
Jonathan Maher, Theravance Biopharma

9:05 - 9:10 **Plenary Speaker Introduction**
Jonathan Heyen, Pfizer

9:10 - 9:55 PLENARY LECTURE:
Entering a New Era of Pharmaceuticals – Opportunities for mRNA Beyond COVID Vaccines
Claudia Lindemann, BioNTech

SESSION I: Nontraditional Therapeutic Modalities
Chairs: Jodi Goodwin, Takeda & Jairo Nunes, Novartis

9:55 - 10:00 **Session Introduction**

10:00 - 10:30 **Non-Clinical Safety Challenges when Developing Targeted Protein Degraders**
Will Proctor, Kymera

10:30 - 11:00 **Nonclinical Safety of GalNAc-conjugated ASOs**
Jessica Grieves, Ionis Pharmaceuticals

11:00 - 11:20 **Break**

11:20 - 11:50 VENDOR PRESENTATION:
Human Hepatic Organoids for Predictive Toxicology
Nathan Moerke, Stemcell Technologies

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11:50 - 12:20 **Safety of mRNA Lipid Nano Particle-Based Vaccines**
Eric Jacquinet, Moderna

12:20 - 12:45 **Panel Discussion**

12:45 - 2:00 **Lunch**

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SESSION II: Species Selection Paradigms for Large Molecules & New Modalities

Chairs: Prathap Kumar Mahalingaiah, AbbVie & Yoav Timsit, Blueprint Medicines

2:00 - 2:05 **Session Introduction**

2:05 - 2:35 **Species Selection and Preclinical Development of Immune Cell Engagers and Cell-based Therapies**
Richard Peterson, AbbVie

2:35 - 3:05 **Preclinical Safety Evaluation of mRNA Cancer Vaccine**
Binu Philip, Moderna

3:05 - 3:35 **Degrader Species Selection and Potential Off Target Screening**
Lisa Marroquin, Pfizer

3:35 - 3:55 **Panel Discussion**

3:55 - 4:55 **Reception**

WEDNESDAY, MAY 11

8:00 - 9:00 **Registration**

DISCOVERY TOXICOLOGY WORKSHOP

SESSION III: General Case Studies in Investigative and Discovery Toxicology

Chairs: Darcey Clark, Merck & Jonathan Maher, Theravance Biopharma

9:00 - 9:05 **Session Introduction**

9:05 - 9:30 **Toxicology Screening Strategy for CNS-Penetrant Therapeutics: Key"Watch Outs" in Discovery Stage**
Mark Jimenez-Canet, Denali Therapeutics

9:30 - 9:55 **Early Investigative Safety Assessment for TCR T Cell Therapy Products**
Elizabeth Mutter-Rottmayer, Genentech

9:55 - 10:20 **Leveraging Competitor Safety Information to Investigate Clinical Toxicities of New Modalities**
Matt Wagoner, Takeda

10:20 - 10:45 **Application of Human Lung Alveolus MPS Model in Investigating Mechanism of ADC-Induced Lung Toxicity**
Prathap Kumar Mahalingaiah, AbbVie

10:45 - 11:05 **Break**

DEVELOPMENT TOXICOLOGY WORKSHOP

11:05 - 11:15 **Workshop Introduction**
Joe Cichocki, Vertex

SESSION IV: Nonhuman Primates (NHP) Shortage

Chairs: Caren Villano, Boehringer Ingelheim & Eunice Musvasva, Roche

11:15 - 11:20 **Session Introduction**

11:20 - 11:55 **Significance of Country of Origin in Cynomolgus Macaques**
Dale Cooper, Charles River

11:55 - 12:25 **Alternatives to the NHP: FDA Guidance and Past Practice**
Ronald Wange, FDA

12:25 - 1:25 **Lunch**

1:25 - 1:55 **'A New Age' for Reduction of NHP Use in Drug Development**
Danuta Herzyk, Merck

1:55 - 2:20 VENDOR PRESENTATION:
The Future of Non-Human Primates Preclinical Research in the U.S.
Alain Stricker-Krongard, Envol Biomedical

envol BIOMEDICAL

2:20 -2:40 **Panel Discussion**

2:40 - 3:00 **Break**

SESSION V: Capsids, and Transgenes, and Double-Strand Breaks, "Oh My!": Development of Gene Therapy/Editing Products

Chairs: Joe Cichocki, Vertex, Michael Santostefano, Merck & Marjorie Peraza, Pfizer

3:00 - 3:05 **Session Introduction**

3:05 - 3:35 **Nonclinical Safety Considerations for Gene Therapy Products**
Jeff Moffit, Biotech in Stealth Mode

3:35 - 4:05 **Strategies for Nonclinical Development of Genome Editing Products**
Kathleen Meyer, Sangamo Therapeutics

4:05 - 4:35 **Developing Gene Therapy Products Incorporating Human Genome Editing: FDA/CBER Considerations for Preclinical Studies**
Sandhya Sanduja, FDA

4:35 -4:55 **Panel Discussion**
4:55 - 5:55 **Reception**

THURSDAY, MAY 12

8:30 - 9:30 **Registration**

DEVELOPMENT TOXICOLOGY WORKSHOP

SESSION VI: Updates on Global Recommendations and ICH Guidances

Chairs: Heather Dowty, Pfizer, Lise Loberg, AbbVie & Edward Dere, Genentech

9:30 - 9:35 **Session Introduction**

9:35 - 10:00 **ICH S5 and S11 – From Principles to a Project Plan (Pharma)**
Susan Laffan, GSK

10:00 - 10:25 **CH S5 and S11 – From Principles to Practice (CRO)**
Pragati Coder, Charles River Laboratories

10:25 - 10:35 **Q & A**

10:35 - 11:00 **Science-based Approach to Harmonize Contraception Recommendations in Clinical Trials & Pharmaceutical Labels**
Kary Thompson, Janssen/J&J

11:00 - 11:05 **Q & A**

11:05 - 11:30 **E141/S7B Q&A – Overview & Implementation from a "User Perspective"**
Chris Regan, Merck

11:30 - 11:35 **Q & A**

11:35 - 11:40 **Conference Closing**
Edward Dere, Genentech

ABSTRACTS

DISCOVERY TOXICOLOGY WORKSHOP

SESSION I

Nonclinical Safety Challenges When Developing Targeted Protein Degraders

William Proctor, Kymera Therapeutics

Targeted protein degradation (TPD) is an emerging and transformational modality for selectively degrading proteins involved in disease pathogenesis including those previously considered undruggable. Small molecule degraders act by selectively degrading proteins of interest (POI) by bringing the POI into proximity of an E3-ligase leading to ubiquitination and subsequent degradation via the ubiquitin proteosome system. Most commonly this targeted ubiquitination is achieved via heterobifunctional molecules that contain a ligand for the POI, a linker region, and an E3 ligase binding region that forms a stable ternary complex between the POI, TPD molecule, and E3 ligase. Degraders have been demonstrated to be very potent and selective, with durable and prolonged activity in preclinical studies and more recently in clinical trials. Due to potential species differences in the POI and E3 ligase expression, homology and/or, function, degraders present unique challenges when considering selection of nonclinical species for toxicology studies as well as assessing off-target pharmacology. In addition, heterobifunctional degraders often exist in a different chemical space than traditional small molecules and as a result present certain challenges for oral absorption, tissue distribution, and solubility. This presentation will focus on nonclinical development considerations for degraders across different therapeutic areas and will highlight both unique aspects for nonclinical safety assessment as well as the promise of this exciting and emerging modality.

Nonclinical Safety of GalNAc-conjugated Antisense Oligonucleotides

Jessica Grieves, Ionis Pharmaceuticals

Antisense technology held much promise when it was first described over 30 years ago and there are currently several marketed products in the antisense oligonucleotide (ASO) class with many more in development. The success of the field has not come without challenges, however. Limited productive uptake by target cells and narrow therapeutic margins, have been particularly difficult to address. Recent major advances in ASO chemistry, conjugation strategies, and local delivery have improved potency and uptake as well as the safety profile. Conjugation of ASOs to N-acetylgalactosamine (GalNAc), for example, has allowed for specific targeting to hepatocytes which, in combination with more potent chemistry, has led to drastic decreases in the efficacious dose and an improved safety profile. In this talk, the nonclinical safety profile of GalNAc-conjugated compared to unconjugated antisense oligonucleotides (ASOs) will be discussed. The future directions of ASO conjugation will also be highlighted.

VENDOR PRESENTATION

Human Hepatic Organoids for Predictive Toxicology

Nathan Moerke, Stemcell Technologies

Drug induced liver toxicity (DILI) is a major source of failure during preclinical and clinical drug development, as well as a significant cause of post-marketing drug withdrawals. The establishment of robust in vitro screening assays for hepatotoxicity at an early stage of development is critical for de-risking candidate drugs and mitigating the risk of late-stage failure. Human hepatic organoids provide a physiologically relevant model system for safety screening as they are proliferative, retain key features of liver cells, and recapitulate donor heterogeneity. The HepatiCult™ Organoid Kit (Human) provides a complete workflow for the culture of liver organoids including organoid establishment, expansion, and differentiation for downstream applications. In order to establish organoid lines, material isolated from normal human liver tissue can be seeded in the HepatiCult™ Organoid Initiation Medium to yield proliferative hepatic organoids. Organoids thus established can then be expanded in HepatiCult™ Organoid Growth Medium (OGM) and differentiated in HepatiCult™ Organoid Differentiation Medium (ODM). A hepatotoxicity screening assay has been developed using an ATP-based readout with either proliferative or mature organoids, maintained in OGM or ODM respectively. This assay has been used to screen known hepatotoxic compounds and produces responses consistent with their known liver toxicity in vivo. Mature hepatic organoids show greater sensitivity in the assay than HepG2 cells, primary human hepatocytes (PHH), and proliferative organoids. The results demonstrate the utility of hepatic organoids generated using the HepatiCult™ Organoid Kit (Human) for preclinical safety screening.

Safety of mRNA Lipid Nano Particle-based Vaccines

Eric Jacquinet, Moderna

The rapid development of vaccines against SARS-CoV-2, the virus responsible for the 'coronavirus disease 2019' (COVID-19) pandemic, exemplifies the power of mRNA technologies for vaccine development. The first human clinical trials of a COVID-19 vaccine were initiated within 4 months of the publication of the SARS-CoV-2 sequence using lipid nano-particle (LNP)-encapsulated mRNA-based vaccines engineered to encode the SARS-CoV-2 S ("Spike") protein in its pre-fusion conformation. Antibodies against S protein epitopes can neutralize the virus. The advantages of the RNA modality are in its versatility (antigen sequences can be swapped into the constructs easily), ease of manufacturing (in vitro transcription from a DNA template), and general safety. mRNA vaccines are non-infectious and non-integrating and because the mRNA is degraded by the host within cytosol quickly, both the mRNA and antigen expression are transient. As this type of vaccine is using the same cargo (LNP) to deliver the load (mRNA), the safety profile of the different vaccines become very predictable and allow a platform-based approach and a reduced development period.

SESSION II

Species Selection and Preclinical Development of Immune Cell Engagers and Cell-Based Therapies

Richard A. Peterson, AbbVie

Novel large molecule formats and cell-based modalities that target neoplastic cells in the tumor microenvironment with cytotoxic inflammatory cells (i.e., lymphocytes or NK cells) provide challenges in selection of toxicology species for regulatory studies. Frequently new modalities either have a single relevant species or lack a relevant toxicology species altogether. This presentation will provide a short overview of immune cell engagers and cell-based therapies, guidance for and examples of species selection with these modalities, discussion of the value of surrogate models/constructs, as well as a discussion of the impact of species selection for these agents on preclinical safety assessment and by extension the clinical starting dose.

Degrader Species Selection and Potential Off-target Screening

Lisa Marroquin, Pfizer

PROTACs are chimeric molecules that recruit E3 ubiquitin ligase to a protein of interest (POI) leading to protein degradation. PROTACs present a promising approach for crossing many hurdles of traditional small molecule drug discovery. Species selection is more crucial for degraders than small molecules because differences can arise from not only sequence homology of the E3 ligase and/or the POI, but also ternary complex formation. An unspecified [Target]-1/2 degrader with >100-fold selectivity for Target-1 over Target-2 in human cell lines is under development for oncology indications. This compound was advanced to exploratory toxicity studies in mice and unexpected toxicities in the hematopoietic system and liver were observed. To gain a mechanistic understanding of the findings, in vitro assays in primary bone marrow and primary hepatocytes were performed in cells isolated from multiple species. Surprisingly, we observed that in mouse hepatocytes Target-1/2 selectivity was lost and the in vitro mouse cultures were more susceptible to cytotoxicity from this CRBN-based degrader. Interestingly, when the target binder was paired with VHL, selectivity was not lost in mouse. In addition, we observed substantially less degradation efficacy and cytotoxicity in mouse hepatocytes and bone marrow cells when compared with corresponding cells from human, monkey, rat, and dog. Species differences observed here are not explained by target or ligase expression. Several possible mechanisms including species differences in intracellular concentration or efficiency of ternary complex formation are currently under evaluation. Our results indicate that the in vitro cross-species protein degradation efficiency and cytotoxicity profiles are sensitive to species differences, and these are not necessarily predicted by human-based in vitro assays alone. We therefore aim to evaluate species differences in cellular activities of PROTACs in our in vitro cross-species safety cell panel and off target proteomics screening.

SESSION III

Toxicology Screening Strategy for CNS-Penetrant Therapeutics: Key"Watch Outs" in Discovery Stage

Mark Canet, Denali Therapeutics

Neurodegenerative diseases remain one of the largest unmet medical needs of our time. The discovery of novel therapeutics that cross the blood brain barrier (BBB) and into the central nervous system (CNS) is critical for the treatment of these diseases;

however, optimizing physiochemical properties of small molecules to enhance BBB penetration creates challenges in identifying drug candidates with favorable pharmacokinetic and safety profiles. This presentation will review some important considerations for discovery toxicologists when designing a nonclinical toxicology plan for CNS-penetrant drug candidates. A case study will also be presented highlighting some of the challenges and lessons learned in this therapeutic area.

Early Investigative Safety Assessment for TCR T Cell Therapy Products

Elizabeth Mutter-Rottmayer, Genentech

Adoptive cell therapies have been a long-standing approach for cancer treatment, following recognition that the immune system's intrinsic ability to identify and eliminate aberrant cells could be exploited for targeting cancer. Advances in precision gene editing technologies have greatly expanded cellular immunotherapies and now comprise a variety of approaches including engineered T cell receptor (TCR) therapy, which involves ex-vivo modification of T lymphocytes to incorporate cancer antigen-targeting TCRs. TCR-engineered T cells can recognize specific HLA-presented peptides from intracellular proteins, expanding the target repertoire over chimeric antigen receptor (CAR) T cell therapies which are limited to cell surface epitopes. Key safety concerns for modified TCR T cells include: off-target toxicities (i.e. cross-reactive epitopes), alloreactivity, and genotoxicity related to the editing machinery (i.e. off-target editing). Additional target-specific concerns may include on-target/off-tumor toxicity (i.e. for targets upregulated in cancer but expressed in normal tissues) and near-target toxicity (i.e. reactivity to the wildtype versus mutant antigen targets). Given the HLA-restriction of the target antigen, in vivo models are not relevant for toxicity evaluation and the nonclinical safety package is limited to in vitro analyses. Key safety assessments used to de-risk modified T cell products will be reviewed.

Application of Human Lung Alveolus MPS Model in Investigating Mechanism of ADC-Induced Lung Toxicity

Prathap Kumar Mahalingaiah, AbbVie

Drug induced lung toxicity may pose significant challenge in preclinical drug development due to seriousness of its implications and difficulty in understanding its mechanisms to de-risk early in development. In this presentation, I will provide an update on our attempt to use traditional 2D as well as more advanced complex lung alveolus models (such as Micro physiological systems) to investigate potential mechanism of Antibody Drug conjugate (ADC)-induced lung toxicity observed in preclinical tox species. This presentation also includes information on key advantages as well as challenges in use of Lung MPS model in investigative toxicology studies.

DEVELOPMENT TOXICOLOGY WORKSHOP

SESSION IV

Significance of Country of Origin in Cynomolgus Macaques

Dale M. Cooper, Charles River Laboratories

The supply of macaque nonhuman primates for research has waxed and waned over time. The rhesus macaque (Macaca mulatta) was the first species to be used extensively in the development of pharmaceuticals. The supply for the rhesus from India was discontinued, so other sources needed to be identified. While China has exported the rhesus macaque, the supply was inadequate to meet industry needs. The cynomolgus or long-tailed macaque (Macaca fascicularis) began to replace the rhesus in the area of safety evaluation beginning in the 1980s. One advantage to the cynomolgus is its wide distribution throughout mainland Southeast Asia, Indonesia, the Philippines and the island of Mauritius, which ensured a robust supply. However, this wide distribution has also meant that as populations evolved in isolated geographies, the genetics of local populations have become distinct. The evolutionary origins of these different populations of cynomolgus macaques are reflected in some defined differences in the genetic and phenotypic background data that are available for animals from suppliers in different countries. There are few important genetic or phenotypic differences in animals from various Southeastern Asian mainland sources such as China, Cambodia, and Vietnam. Animals from Indonesia are distinct from the mainland animals but these two populations are more similar to one another than either are to the more isolated Philippine population. Animals from Mauritius appear to have originated in Indonesia and are similar in many respects to their source population, but present with some unique genetic and phenotypic differences due to their lower allelic heterozygosity. Understanding the differences among populations is very important due to the current challenges with nonhuman primate supply, as it can be difficult to ensure that the same source of animals will be available throughout the development cycle of a pharmaceutical program. Additional research on population differences and their impact on drug metabolism and safety are needed.

Alternatives to the NHP: FDA Guidance and Past Practice
Ronald Wange, FDA

Ron's presentation will focus on FDA's use of alternatives to the expanded pre- and postnatal development (ePPND) study in nonhuman primates (NHPs) for assessing the risks of biotherapeutic proteins to embryofetal and postnatal development. The first portion of the presentation will summarize the support that exists in current guidance for the use, where scientifically appropriate, of alternative in vivo approaches, as well as the use of weight-of-evidence (WOE) analyses for assessing developmental toxicity risk. In the second portion of the talk, an analysis will be presented on the sources of nonclinical data that have been used to inform section 8.1 of the labels for biologics approved by CDER over the last several years. The talk will conclude with a presentation of the guidance on "Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic," which was issued as final guidance earlier this year under FDA's COVID-19 health emergency authority.

'A New Age' for Reduction of NHP Use in Drug Development
Danuta Herzyk, Merck

The growth in development of therapeutic biologics, vaccines and novel modalities has led to a steady increase in use of non-human primates (NHP) within the pharmaceutical industry. The SARS-CoV-2 pandemic has significantly reduced the availability of NHP for biomedical research prompting biopharma industry and regulatory authorities to address the issue and examine opportunities to minimize NHP use in nonclinical safety evaluations of pharmaceutical molecules. This talk will focus on providing examples of replacing NHPs with rodent surrogate system or other non-rodent species, reducing the use of NHP by modifying study design or using a weight of evidence approach in toxicology programs.

VENDOR PRESENTATION

The Future of Non-Human Primates Preclinical Research in the U.S.
Dr. Alain Stricker-Krongrad, Envol Biomedical

As a US company with a global presence, Envol Biomedical has established itself as an innovator in contract research with a clear vision of the future of non-human primate research in the Continental US. That vision has driven us to implement a different outsourcing paradigm in our interaction with our pharmaceutical and biotech partners and has been integral to the development of our US Center of Expertise in non-human primate research. Moreover, the strength of our vision has been underlined by our ability to withstand the pandemic while maintaining a large (and expanding) population of naïve, bio-naïve and non-naïve non-human primates in the US. Our presentation will describe what steps were taken to re-engineer the standard outsourcing model and alleviate the issues research companies have experienced when conducting studies in non-human primates. In addition, we will describe what we believe the future of non-human primate research will be in the US, and what role we can play to ensure the availability of one of the most relevant translational preclinical model.

SESSION V

Nonclinical Safety Considerations for Gene Therapy Products
Jeff Moffit, Biotech in Stealth Mode

The nonclinical safety assessments for gene therapies are evolving, leveraging over 20 years of experimental and clinical experience. Despite the growing experience with these therapeutics, there are no approved harmonized global regulatory documents for developing gene therapies with only the ICH S12 guidance on nonclinical biodistribution currently under discussion. Several health authorities have issued guidance over the last 15 years on the nonclinical safety aspects for gene therapy products, but many of the recommendations are limited to high level concepts on nonclinical safety aspects or altogether silent on key topics. Historically, this approach was appropriately vague given our relatively small dataset of nonclinical experience, where a comprehensive and detailed regulatory guidance approach was unlikely to be appropriate to address all scenarios. However, harmonization of key considerations and assumptions can provide a consistent basis for developing the appropriate nonclinical safety development plans for individual programs, reducing uncertainty across regulatory regions and unnecessary animal use. Several key areas of nonclinical safety testing are nearing maturation for a harmonized approach including species selection, certain aspects of study design, study duration, and unintended genomic integration risks. Furthermore, several emerging topics are unaddressed in current regulatory guidance for gene therapy products, which will become key areas of differentiation for the next generation of therapeutics. These topics include redosing, juvenile/pediatric safety, and reproductive/developmental safety testing, where

relevant experience from other modalities can be applied. This presentation provides an overview of the current nonclinical safety regulatory landscape, summarizes typical nonclinical safety study designs, highlights areas of uncertainty, and discusses emerging topics that warrant consideration.

Strategies for Nonclinical Assessment of Genome Editing Products

Kathleen Meyer, Sangamo Therapeutics

Genome editing offers great promise for correction of genetic diseases due to the ability to inactivate genes, correct mutated genes or insert genes into specific regions of the genome. These novel advanced therapeutics include ZFNs, TALENs, MegaTALs, and CRISPR/Cas platforms focused on different cell targets (in vivo or ex vivo) and delivery methods. Assessing the nonclinical safety profile of these medicines prior to First-in-Human studies and during clinical development requires blending traditional toxicology expertise with new set of bioinformatic and molecular tools to assess mechanisms of action and impact of editing at the genome level. A case-by-case assessment if most often needed. This presentation will discuss nonclinical considerations for safety assessment of novel genomic medicines delivered to target cells.

Developing Gene Therapy Products Incorporating Human Genome Editing: FDA/CBER Considerations for Preclinical Studies

Sandhya Sanduja, FDA

Efforts in the development of investigational gene therapy products incorporating human genome editing (GE) for the treatment of human diseases have increased exponentially over recent years. While the potential benefits of this approach are conceptually apparent, the risks associated with these products following administration in patients are not as well understood. Thus, the transition of these products to clinical trials requires comprehensive characterization of product risks and how they can be potentially mitigated. This presentation will provide a general overview of the recent draft GE guidance and the existing regulatory framework to guide preclinical assessment of activity and potential risks of GE products to enable administration in early-phase clinical trials.

SESSION VI

ICH S5 and S11 – From Principles to a Project Plan (Pharma)

Susan Laffan, GSK

ICH S5 and S11 – From Principles to Practice (CRO)

Pragati Coder, Charles River Laboratories

Both Drs. Laffan and Coder will cover recent updates to ICH S5 guidelines and the new ICH S11 guidelines. The speakers will discuss the underlying principles and practical considerations of designing and conducting DART and juvenile animal studies (JAS). For DART studies, the focus will be on overall study strategy, including study type and species selection, and timing. For juvenile toxicity studies, the focus will be on using a weight of evidence approach to deciding whether a juvenile animal study is warranted. As there is no set default study design for a JAS, the speakers will highlight considerations to help inform study design decisions customized to each pediatric development plan.

Science-based Approach to Harmonize Contraception Recommendations in Clinical Trials & Pharmaceutical Labels

Kary Thompson, J&J

This presentation is an EFPIA-PDEG topic group consensus on a data-driven approach to harmonized contraception recommendations for clinical trial protocols and product labeling. There is no international agreement in pharmaceutical clinical trial protocols or product labeling on when/if female and/or male contraception is warranted and for how long after the last dose. This absence of consensus has resulted in different recommendations among regions. For most pharmaceuticals, contraception recommendations are generally based exclusively on nonclinical data and/or mechanism. For clinical trials, contraception is the default position and is typically maintained for females throughout clinical development, whereas appropriate information can justify removing male contraception. Conversely, contraception is only recommended in product labeling when warranted. A base case rationale is proposed for whether or not female and/or male contraception is warranted, using available genotoxicity and developmental toxicity data. Contraception is generally warranted for both male and female subjects treated with mutagenic pharmaceuticals. We propose that contraception is not typically warranted when the margin is 10-fold or greater between clinical exposure at the maximum recommended human dose and exposure at the established no-observed-adverse-effect-level (NOAEL) for purely aneugenic pharmaceuticals and for pharmaceuticals that induce fetal malformations or embryo-fetal lethality. Other factors are discussed, including methods of contraception, pregnancy testing,

drug clearance, options for managing the absence of a developmental toxicity NOAEL, drug-drug interactions, radiopharmaceuticals, and other drug modalities. Overall, we present a data-driven rationale that can serve as a basis for consistent contraception recommendations in clinical trials and in product labeling across regions.

E141/S7B Q&A – Overview & Implementation from a "User Perspective"

Chris Regan, Merck

The S7B and E14 ICH guidances were adopted over 15 years ago to limit the incidence of life-threatening ventricular arrhythmias that had been observed unexpectedly for certain marketed drugs and that subsequently resulted in their withdrawal. Despite E14 and S7B's effectiveness in reducing the development of compounds with QT prolongation dependent arrhythmia risk, there is room for refinement. Specifically, that a well-defined preclinical:clinical integrated QT risk assessment strategy would reduce the number of clinical thorough QT (TQT) studies through increases opportunity to submit a TQT waiver. To this end, the recently completed Stage 1 E14/S7B questions and answers focused on workflows to enable an integrated preclinical:early clinical QT assessments for compounds that are inactive on hERG in vitro and do not demonstrate QT prolongation in vivo (preclinical double negative) to expand TQT waiver opportunities. This talk will provide a brief background and a user's perspective on the interpretation and implementation of the stage 1 E14/S7B Q&As.

SPEAKER BIOGRAPHIES

Mark Canet, PhD, Denali Therapeutics Dr. Canet is a project toxicologist at Denali Therapeutics where he functions as nonclinical safety lead on project teams supporting the development of large and small molecule therapeutics for the treatment of neurodegenerative diseases. An Arizona native, Mark attended the University of Arizona where he received a BS degree in molecular and cellular biology and PhD degree in pharmacology and toxicology. His PhD dissertation work focused on how liver disease may alter the pharmacological and toxicological fate of drugs through the disruption of drug transporter function. Mark currently resides in the Bay Area with his wife Dani and their 9 year-old Bernese mountain dog, Panda. In his spare time he enjoys hiking, cycling, and learning how to cook amazing cuisines across the world!

Prägati Coder, PhD, DABT, Charles River Laboratories Dr. Coder is a Senior Director of Developmental and Reproductive Toxicology (DART) at Charles River Laboratories and holds scientific oversight and management responsibilities for the Ashland, OH (formerly WIL Research) and Mattawan, MI (formerly MPI Research) sites. In her role, she directs the DART study management teams, serves as a study director, and routinely provides consultation to clients on scientific issues, data interpretation, and program development on DART, neurotoxicity, endocrine and juvenile toxicity programs. Prior to her current role, Pragati served as the DART Discipline Leader at Battelle Columbus. She received her PhD from the Indian Institute of Technology-Bombay and did her postdoctoral work in Male Reproductive Toxicology at the College of Pharmacy, University of Texas at Austin. Pragati became a Diplomate of the American Board of Toxicology in 2008. She is a well-recognized face in the DART community, and an active member of the HESI-DART Technical Committee, Middle Atlantic Reproduction and Teratology Association (MARTA), Society of Toxicology and the Society for Birth Defects Research and Prevention (formerly Teratology Society). Pragati is currently serving a 3-year term on the BDR-P council and her 6th year as an officer of the Reproductive and Developmental Toxicology Specialty Section for SOT.

Dale M. Cooper, DVM, Charles River Laboratories Dr. Dale M. Cooper is the Attending Veterinarian and Senior Director of the Office of Animal Care at Charles River Laboratories- Mattawan. He studied veterinary medicine at the University of Wisconsin. He was employed in private veterinary practice for 3 years and then trained in Laboratory Animal Medicine at the University of Minnesota and received a Master of Science degree in Clinical Laboratory Science-Microbiology. He is a Diplomate of the American College of Laboratory Animal Medicine. He has been employed in academia, the pharmaceutical industry, animal models production, and contract research. He has 18 peer-reviewed publications, 3 book chapters, and nearly 40 abstracts and presentations on topics including laboratory animal models, husbandry, compliance, microbiology, surgical asepsis, analgesia, and animal diet safety.

Jessica Grieves, DVM, PhD, DACVP, Ionis Pharmaceuticals Jessica is a Toxicologic Pathologist and Toxicologist at Ionis Pharmaceuticals where she focuses on the nonclinical safety of ASOs intended for CNS, cardiac, renal, metabolic, liver, pulmonary, and ophthalmology indications. Prior to joining Ionis, Jessica was part of the Takeda nonclinical safety team where she worked on a diverse array of projects that utilized a variety of modalities including small molecules, nanoparticles, enzymes, and biotherapeutics.

Danuta Herzyk, PhD, Merck Dr. Herzyk has 30 years of experience in development of biologics, vaccines and small molecules while working at GlaxoSmithKline and Merck.

Dr. Herzyk earned her MS degree in Pharmaceutical Sciences and PhD in Clinical Immunology and Biochemistry from the Medical University of Wroclaw (pronounced Vrotzlav), Poland. She emigrated to USA in 1985 after applying for a postdoctoral position

in the Department of Microbiology and Immunology at the Ohio State University, following by a research associate position in the Department of Pulmonary and Critical Care Medicine at OSU. In 1992, she moved from academia to pharmaceutical industry and became a Director of Immunologic Toxicology Laboratory in Nonclinical Safety Assessment at GSK. After joining Merck in 2007, her work has been focused on the preclinical development and safety assessment of oncology and immunology therapeutics, including approved medicines such as KEYTRUDA®, ILUMYATM and WELIREGTM.

Dr. Herzyk is author or co-author of 60 peer-reviewed articles and co-editor of two books, "Immunotoxicology Strategies for Pharmaceutical Safety Assessment" and "Nonclinical Development of Novel Biologics, Biosimilars, Vaccines and Specialty Biologics". She served on BioSafe Leadership Committee and had multiple roles in Immunotoxicology Specialty Section (ITSS) and BioTechnology Specialty Section (BTSS) of the Society of Toxicology.

Eric Jacquinet, PhD, Moderna After graduating from Veterinary School in Belgium, Dr. Jacquinet spent 7 years at the University of Liege in the Pathology department. His time was distributed between the necropsy floor, research, teaching, and biopsies. Additionally, he also spent 3 years in the Pulmonary Department at the University of Utah, where he described TPMRSS2 leading to his PhD.

After defending its thesis, he moved to CRL Montreal to embrace a career in toxicological pathology. He held few different positions within the industry, he as now working for Moderna as Senior Director of Pathology.

Susan Laffan, PhD, GSK Dr. Laffan is currently a head of the Investigative Safety group at GlaxoSmithKline, she has over 19 years of pharmaceutical industry experience. Susan is the nonclinical chair of GSK's pediatric network providing advice to project teams on their pediatric development plans. Dr. Laffan represented PhRMA on the ICH S11 Working Group. She is an expert in reproductive and developmental toxicology and has been directly involved on development teams supporting the nonclinical safety assessment of compounds from discovery through post marketing. Susan earned a PhD in toxicology from the University of North Carolina at Chapel Hill, conducting her dissertation at the USEPA, Research Triangle Park, NC. In addition to being a member of the Society of Toxicology, she is also a member of BDRP, and the HESI DART Technical Committee

Claudia Lindemann, PhD, BioNTech Dr. Lindemann completed her PhD training at the Jenner Institute at University of Oxford. Since 2018 she has been employed by BioNTech in Germany in positions of increasing scope and responsibility. She oversees integrated nonclinical strategies for platforms of RNA therapeutics and specific product candidates from concept to market. And is responsible for generating and reviewing safety assessment reports and documentation for internal decision making, as well as regulatory submissions to health authorities and approval processes in all phases of drug development. She is currently an associate director of nonclinical safety.

Prathap Kumar Mahalingaiah, DVM, PhD, Abbvie Prathap is a veterinarian by training with specialization in veterinary pathology and board-certification in toxicology (DABT and ERT) with 10 years of working experience in CRO and pharmaceutical industry. He is currently working as a Principal Scientist in Investigative Toxicology and Pathology group at Abbvie. In this role, Prathap is leading molecular toxicology group and is responsible for designing and conducting in vitro and in vivo investigative toxicology studies to understand mechanisms of toxicity. His group is also actively involved in evaluating and implementing advanced complex invitro models including Micro physiological systems (MPS) in preclinical safety evaluation. He is representing Abbvie in multiple external scientific consortium and working groups. Prathap has published several original research papers as well as review papers in peer reviewed journals and authored/co-authored 3 book chapters.

Lisa Marroquin, MS, Pfizer Lisa Marroquin is a Senior Scientist within Drug Safety Research & Development at Pfizer in Groton, CT where she is part of the Investigative Toxicology team. She earned a bachelor's degree from the University of California San Diego, and a master's degree from the San Diego State University. She joined Pfizer is 2003 where she provides strategic guidance on the validation of in vitro safety assays for multiple modalities, including protein degraders. In addition, Lisa has led multiple cross-functional teams in support of target and mechanistic safety de-risking. She has co-authored 15 peer-reviewed publications with over 1700 citations. In her current position she manages experimental design and provides scientific expertise for the early safety screening programs.

Kathleen E. Meyer, MPH, PhD, DAB, Sangamo Therapeutics Dr. Kathleen Meyer is Vice President of Nonclinical Development at Sangamo Therapeutics and leads nonclinical strategy and development of Sangamo's zinc finger (ZF) -based gene editing and gene regulation, cell and AAV-based gene therapy therapeutic candidates. Dr. Meyer oversees pharmacology/toxicology, bioanalytical sciences, nonclinical operations, and nonclinical project management groups supporting early research and clinical development programs. She has over 25 years of industry experience in nonclinical safety evaluation and guiding development of ZF nuclease-based gene editing, ZF-transcription factor gene regulation, gene and cell therapy, small molecule, monoclonal antibody, enzyme replacement, and botulinum toxin programs. Prior to joining Sangamo, she worked at BioMarin Pharmaceutical Inc. where she guided small molecule and biologic drug candidates through the nonclinical development process supporting clinical trials and marketing authorization for rare diseases and metabolic disorders. She led the nonclinical safety, pharmacokinetics and bioanalytical sciences group at XOMA LLC focusing on development of monoclonal antibodies for inflammatory and oncology disorders, as well as small molecule programs. Prior to this, she worked at Elan Pharmaceuticals developing therapeutic candidates and approved products for neurology indications. Before joining industry, she worked as a post-doctoral fellow evaluating non-viral methods of gene delivery at the University of California, San Francisco. Dr. Meyer received an A.B. in Physiology, a Master's degree in Public Health specializing in Toxicology and Epidemiology, and her Ph.D. in Environmental Health Science/Toxicology from the University of California, Berkeley. Dr. Meyer is a Diplomat of the American Board of Toxicology. She is a member of the Society of Toxicology, American College of Toxicology and American Society of Gene and Cell Therapy.

Nathan Moerke, PhD, Stemcell Technologies Dr Moerke holds a B.Sc. in Biochemistry from the University of Minnesota, and a Ph.D. in Biological Chemistry and Molecular Pharmacology from Harvard University. Previously he worked in the areas of cancer pharmacology at Harvard Medical School, and neuroscience drug development at Denali Therapeutics. Nathan is a scientist in the Contract Assay Services group at STEMCELL Technologies.

Jeff Moffit, Biotech in Stealth Mode Jeff Moffit has 15 years of pharmaceutical and biotech industry experience as a board-certified toxicologist, having worked in all phases of drug development and on several marketed products. He has experience across a wide range of therapeutic areas and orphan indications using small molecules, biologics, RNAi, viral and non-viral gene therapy, and cell editing modalities. Presently, Jeff is Vice President and Head of Nonclinical Development at a Biotech in Stealth Mode. Formerly, he served in leadership positions at Generation Bio, Bioverativ, Alnylam, and FORUM Pharmaceuticals, starting his career as a project toxicologist at Boehringer Ingelheim. He currently holds Adjunct Assistant Professorships at the Alpert Medical School of Brown University and the University of Rhode Island.

Liz Mutter-Rottmayer, PhD, Genentech Dr Mutter-Rottmayer received her B.S. (UC Davis) and her PhD in Toxicology from UNC Chapel Hill, studying mechanisms of genotoxicity and DNA repair. She completed a drug development postdoc at Roivant Sciences before being hired on full time at their sister company Axovant, a clinical stage gene therapy company working on novel treatments for neurological and neuromuscular diseases. After returning to the West Coast Liz joined Sangamo Therapeutics where she worked on pharm/tox and nonclinical development strategies for AAV-delivered gene replacement, regulation and editing technologies. She joined Genentech's Safety Assessment team in late 2020 and currently supports nonclinical safety of

multiple modalities across development stages.

Richard A. Peterson II, DVM, PhD, Diplomate ACVP, Abbvie Dr. Peterson II received his BS in Zoology in 1986, DVM magna cum laude in 1998 and PhD in Veterinary Biosciences in 2003, all from the Ohio State University. He became an ACVP Diplomate in 2003. His PhD thesis work was performed in the Department of Veterinary Biosciences at the Ohio State University in the laboratory of Kathryn A. Eaton DVM, PhD, DACVP, where he focused on mouse models of Helicobacter pylori-associated gastritis and neoplasia. Rich has been in the field of toxicologic pathology for 18 years both at GlaxoSmithKline (2004-15; Director, Investigative Pathology; Head, Investigative Pathology Laboratory, and Project Representative) and AbbVie (2015-22; Research Fellow, Director Global Pathology, and Project Representative), working in both regulatory and investigative pathology. He is an author on over 32 peer-reviewed journal articles, three book chapters, and numerous posters/abstracts and platform presentations. Rich has been an STP member since 2004, and has served as STP Secretary-Treasurer (2016-2020), Scientific Program Planning Committee (SPPC) chair for the 2012 STP Symposium: Mechanisms of Toxicity (Boston, MA; 2009-12), co-chair/chair of the Annual Symposium Committee (ASC; 2012-14), chair of the Joint Education-Based Committee (JEBC; 2014-16), and a member of the Poster Sub-committee of the ASC (2014-16). In addition to STP activities, Rich has been the chair/co-chair of the 2008-14 Research Triangle Park Rodent Pathology Courses (i.e., covering topics such as: immune system, hepatobiliary, urinary, and endocrine pathology), and has represented GSK and AbbVie on multiple PSTC, IQ, and HESI consortia working groups (e.g., HESI Targeted Protein Degrader Safety Committee, PSTC Hepatobiliary Working Group, and the IQ PreFIH Attrition Working Group). Rich has interests in immune system, hepatobiliary, endocrine, ultrastructural, and investigative pathology.

Binu Philip, PhD, Moderna Dr. Philip is a board certified toxicologist and is currently working as a Scientific Director and Research Area Lead for Oncology programs at Moderna. Dr. Philip attended University of Madras, India where he received a MS and PhD in Toxicology. He has more than a decade of experience working in major pharmaceutical companies as a project toxicologist and therapeutic area lead for oncology programs. Prior to joining Moderna, he worked at Abbvie and BMS as a project toxicologist across various therapeutic areas and modalities. He has contributed to several successful IND/CTA filings. Dr. Philip is author/co-author of several peer-reviewed articles and book chapters. He is an active member of SOT since 2004.

William Proctor, PhD, DABT, Kymera Therapeutics Dr Proctor is a Senior Director in the Pre-Clinical Safety group at Kymera Therapeutics, a clinical stage biotechnology company focusing on discovering and developing targeted protein degraders. Prior to joining Kymera in November of 2021, Will served as the Senior Director of Predictive Toxicology at Genentech, where he oversaw the Investigative Toxicology Laboratory, Complex In Vitro Systems Laboratory, and non-clinical safety support for the Small-Molecule Drug Discovery (SMDD) organization. Will earned his BS in Chemistry from Trinity College and PhD in Pharmaceutical Sciences from the University of North Carolina at Chapel Hill in the laboratory of Dr. Dhiren Thakker with a focus on drug transport and pharmacokinetics. He then performed postdoctoral training at the National Institutes of Health in the laboratory of Dr. Lance Pohl, with research centered on immune mechanisms of drug-induced liver injury (DILI). Will is a board-certified toxicologist and organizational leader with 10 years of pharmaceutical industry experience in non-clinical safety and drug discovery.

Christopher Regan, PhD, DSP, Merck A scientific leader with over 20 years of pharmaceutical research experience across Discovery Research, Safety Pharmacology, and Preclinical Development, Dr. Regan collaborates within internal discovery teams, internal/external blended alliances, and licensing teams to shape integrated safety pharmacology risk assessment plans. His current responsibilities include leadership of a team of in vivo scientists responsible or investigative and regulatory-enabling preclinical cardiovascular, respiratory, and neurobehavioral in vivo safety risk assessment models. The overall goal of these efforts is to utilize a blend of standard and fit for purpose solutions to deliver clinically translatable markers of safety in both the

exploratory and regulated space for teams throughout the drug development continuum. As a Safety Pharmacology Society member and Diplomate in Safety Pharmacology (DSP), he has participated broadly to help shape the scientific content and direction of the society through positions on programming, best practices, and abstract review committees. Overall, Dr. Regan and his collaborators have authored 46 publications in peer-reviewed journals and one book chapter.

Sandhya Sanduja, PhD, FDA Dr Sanduja is currently a Team Leader in the Office of Tissue and Advanced Therapies (OTAT) in CBER, FDA. She leads the pharmacology/Toxicology review process for advanced biologics including cell and gene therapies (CGTs) through all phases and drug development and licensure. Sandhya serves on several committees and working groups, within FDA and externally, to guide regulatory framework of CGTs. Prior to joining the FDA, she was a postdoctoral fellow at the Whitehead Institute of MIT where she investigated signaling pathways in cancer. Sandhya received her Ph.D. in Biological Sciences from University of South Carolina, Columbia. During her research tenure, she has authored several high-impact publications and has received research grants from various foundations.

Alain Stricker-Krongrad, PhD, Envol Biomedical, LLC Dr Stricker-Krongrad has over 30 years of international experience in pharmacology and preclinical research, both in pharmaceutical and contract (CRO) organizations.

He is currently the CEO of Envol Biomedical, LLC, the U.S. Center of Excellence in Non-human Primates Research. He previously served as the Chief Scientific Officer of Sinclair Research and Charles River Laboratories where he advanced key science-based programs and helped foster science-related initiatives and capabilities. Alain has managed pharmacokinetics, efficacy, and safety departments for multiple disease indications within Charles River Laboratories, Millennium Pharmaceuticals in the U.S., and Novartis Headquarters and Ciba-Geigy in Switzerland. Alain received his License, Master and Ph.D. degrees from the University of Nancy, France. He conducted his doctoral and post-doctoral research on preclinical and clinical drug evaluation at the National Institute of Scientific and Medical Research (INSERM) for which he has received two international awards for distinguished research. Alain has published more than 70 peer-reviewed articles and brings a wealth of expertise in preclinical and early clinical drug efficacy and safety evaluation.

Kary Thompson, PhD, Janssen Dr Thompson is Global Head of Study Toxicology at Janssen where she oversees general, reproductive, and juvenile toxicology studies and a team of study toxicologists. Previously, she was the Director of DART and a project toxicologist at Bristol-Myers Squibb Company. Kary received her PhD at the University of Arizona, and completed a postdoctoral fellowship at the U.S. EPA in the Reproductive Toxicology Division, looking at the utility of sperm RNA as a biomarker of testis toxicity. Kary is the co-chair of the HESI DART technical committee, and previously served as President of the Reproductive & Developmental Toxicology Specialty Section of SOT. She holds an adjunct faculty position at Rutgers, where she teaches and serves on graduate student dissertation committees.

Matt Wagoner, PhD, Takeda Pharmaceuticals Wagoner leads the Global Investigatory Toxicology team at Takeda Pharmaceuticals, where their team applies complex in vitro models and in silico approaches as predictive and mechanistic tools to help make safer medicines. Before Takeda, Matt led the mRNA safety strategy for AstraZeneca Pharmaceuticals, and worked to develop and deploy in vitro and in vivo models in support of oncology and cardiovascular drug discovery projects.

In the academic arena, Matt co-taught a drug discovery course at Simmons College in Boston. He received his PhD in Molecular and Cellular Pharmacology from the University of Wisconsin-Madison and bachelors in biochemistry from the University of Illinois Urbana Champaign.

In lieu of hobbies, Matt has four kids and a debilitating addiction to home improvement projects.

Ronald Wange, PhD, FDA Dr Wange is an Associate Director for Pharmacology and Toxicology within the Office of New Drugs in the Center for Drug Evaluation and Research at FDA and has over 15 years of experience reviewing small-molecule drugs, biologics and oligonucleotide-based therapeutics. He has a BS in Biochemistry from the University of California and a Ph.D. in Pharmacology from Vanderbilt University. Ron served as the FDA Topic Lead for the most recent revision of ICH S5 (R3), which provides guidance to industry on how to appropriately assess developmental and reproductive toxicity of human pharmaceuticals. He was also the lead author on FDA's 2022 guidance for industry on "Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising from the COVID-19 Pandemic."

POSTER ABSTRACTS

Identifying Seizures with MEA: Complementary Human and Rat Neuronal models enhance predictivity

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Predicting the seizurogenic and neurotoxic potential of test compounds using microelectrode array (MEA) platforms is an important tool for in vitro neurotoxicity screening. Much of the early work for this model involved isolated rat cortical neuron cultures. Responses to known seizurogenic and neurotoxic pharmacological agents targeting many different receptors have been robust and consistent using the rat cortical model. There are, however, certain targets that have not responded definitively or reliably, such as muscarinic receptor agonists. An alternative screening model using human iPSC-derived glutamatergic neurons co-cultured with human iPSC-derived astrocytes (FCDI) demonstrates a highly active and organized neural network that is also effective in identifying compounds with CNS liabilities. In most cases, this model overlaps with the rat cortical model in the successful identification of seizurogenic and neurotoxic compounds. Furthermore, the human model has also demonstrated the ability to identify chemical agents targeting the muscarinic receptor, which is not definitively identified in rat cortical neuron models. However, the human model fails to identify GABAA antagonists definitively, which is consistently identified by the rat cortical model. With further evaluation and comparison of each of these models and their predictive abilities, it was determined that the response patterns observed for both models are often complementary and when used together provide a robust and accurate in vitro model for predicting CNS liabilities.

High throughout RNA-seq profiling of 3D liver organoids to predict Drug Induced Liver Injury (DILI)

Paul Walker, Monday Ogese, Ruediger Fritsch, Alicia Rosell-Hidalgo, You Feng, Rene Rex, Maiara Severo Witte, Timur Samatov, Ryan Barton, Emma Shardlow, Stephen Madden, Christopher Strock
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Drug-induced organ toxicity remains a major reason for drug attrition and a major concern in the development of new drugs. It is estimated that 90% of drugs fail during clinical development; therefore, there is a pressing need for improved predictive methods during the early stages of drug discovery. A variety of in vitro liver models, such as organotypic three-dimensional (3D) microtissues combined with High-Content Imaging (HCI), have been developed in an effort to de-risk DILI in earlier drug discovery. Enhanced mechanistic understanding of off-target cellular effects can be gained by combining the most predictive and physiologically relevant in vitro models with analysis of the cellular transcriptome. Transcriptomics has been shown to play an important role in determining differentially expressed genes (DEGs), mechanisms of action and induced cell stress pathways associated with drug exposure. Utilising the 3D liver models HepaRG spheroids and primary human hepatocyte liver microtissues (hLiMTs), a 128-reference drug library with and without clinical DILI-associated compounds and 90 compounds with defined mechanisms of action have been profiled. High throughput RNA-sequencing (RNA-seq) in 384-well format was performed across an eight-point dose response range at a 7-day repeat dose time-point. The transcription profiles obtained allowed grouping of DILI positive and negative compounds into functional clusters by PCA (principal component analysis) and t-distributed stochastic neighbour embedding (t-SNE) analysis. DEGs in a dose-dependent manner were observed for DILI compounds and was shown to be mechanism and DILI rank dependent. Using the whole genome transcriptomic data a machine-Learning model was developed to perform DILI risk assessment. DILI compounds were assigned a DILI risk probability score identifying DILI compounds with an 80.6-89.6% sensitivity and 81.3-84.4% specificity across the two organoid models. In addition, specific gene signatures and community analysis was associated with individual mechanisms of action, illustrating the improved mechanistic insight and DILI risk assessment obtained by this approach. In summary, predictive toxicogenomics (TGx) combined with organotypic liver models can be used to profile novel chemical entities to determine DILI risk, providing insight in to the potential mode of action implicated in the drug's toxicity.

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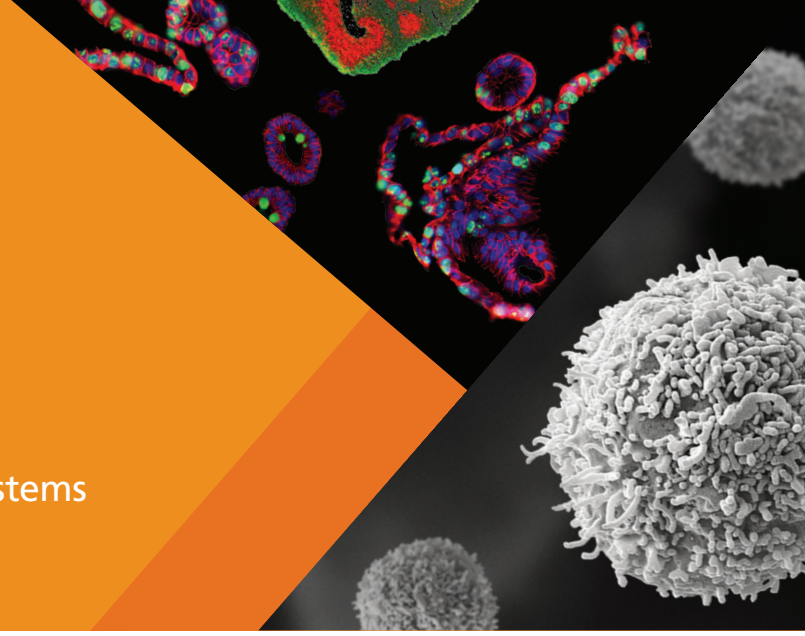

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