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ORGANIZER’S WELCOME

Welcome to the 2017 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.

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APT 2017 CONFERENCE AGENDA

MONDAY, MAY 15

12:00 - 1:00  Registration

1:00 - 1:10  Conference Opening and Plenary Lecture Introduction
Padma Narayanan, Ionis Pharmaceuticals

1:10 - 1:55  **Plenary Talk:** 21st Century Cardio-Oncology: Identifying Cardiac Safety Signals in the Era of Precision Medicine
Javid Moslehi, Vanderbilt University Medical Center

DISCOVERY WORKSHOP
SESSION I: Immuno-Oncology
*Chairs:* Christine Karbowski, Amgen and Zoe Zhong, Genentech

1:55 - 2:00  Session Intro

2:00 - 2:30  Preclinical Investigation of the Mechanism-of-Action and Associated Challenges of Agonistic Anti-GITR Antibody Therapy
Amy Beebe, Merck

2:30 - 3:00  Dispelling the Myth that NHPs are not Sensitive to Immune Modulation
Oliver Thomas, Amgen

3:00 - 3:20  Break

3:20 - 3:50  CAR T Cell Design, Activity and Safety: Looking Back and Looking Forward
Rafael Ponce, Juno Therapeutics

3:50 - 4:20  Combinations in Immuno-Oncology: A Pharmacology Perspective
Marcia Belvin, Genentech

4:20 - 5:00  Round Table Discussion: Discovery & Development Hot Topics in Toxicology

5:00 - 6:30  Poster Session and Reception
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TUESDAY, MAY 16

8:00 - 9:00     Breakfast

SESSION II: Translation from Preclinical to Clinical
Chairs: Eric Bloome, AbbVie & Jonathan Heyen, Pfizer

9:00 - 9:05     Session Introduction

9:05 - 9:35     The Hunt for Novel Cardio-Oncology Biomarkers in Rodents
                Michelle Hemkens, Pfizer

9:35 - 10:05    Assessing Doxorubicin Related Heart Failure in the
                Cynomolgus Monkey – a Repeat-Dose Safety Pharmacology Study
                Mike Engwall, Amgen

10:05 - 10:35   Clinical Translation of Non-Clinical Gastrointestinal Effects
                Scott Mittelstadt, AbbVie

10:35 - 10:55   Break

SESSION III: Understanding and Minimizing Off-Target Toxicity
Chairs: Dolo Diaz, Denali Therapeutics & Dylan Hartley, Array Biopharma

10:55 - 11:00   Session Introduction

11:00 - 11:30   CNS Liability Screening During Drug Discovery
                 Research & Development: Challenges & Perspectives
                 Ying-Ying Zhou, Merck

11:30 - 12:00   Leveraging In Vitro Assays to Elucidate Off-Target Toxicities Observed with Novel Therapeutics
                 Nianyu (Jason) Li, Merck

12:00 - 12:30   A Mechanism of Hepatotoxicity for High Affinity Antisense Oligonucleotides
                 Sebastien Burel, Ionis Pharmaceuticals

12:30 - 1:50    Lunch

1:50 - 2:20     Vendor Talk:
                 Human iPSC-Derived Cardiomyocytes, Glutamatergic Neurons, and Hepatocytes;
                 Cells and Solutions to Improve Toxicity Testing Relevance and Predictivity
                 Blake Anson, Cellular Dynamics
DEVELOPMENT TOXICOLOGY WORKSHOP

2:20 - 2:30  Introduction to Development Workshop and Plenary Lecture Introduction

2:30 - 3:15  Plenary Talk: She Blinded Me With (Junk) Science! Scams, Shams, and Hoaxes in Medical Toxicology
Cyrus Rangan, California Poison Control System/Children’s Hospital LA

SESSION IV: Oncology Development - ADC’s
Chairs: Jorg Blumel, Genentech and Lise Loberg, AbbVie

3:15 - 3:20  Session Introduction

3:20 - 3:50  Strategies for Assessing and Qualifying Linker/Payload-Related Impurities in ADCs
Matthew Holdren, Genentech

3:50 - 4:20  Challenges and Approaches in the Early Stages of ADC Development using THIOMAB™ Technology to Improve Safety
Chris Frantz, Genentech

4:20 - 4:40  Break

4:40 - 5:05  On-Target Toxicity with ADCs: Species-Specific Toxicity and Preclinical to Clinical Translation
Anu Connor, Novartis

5:05 - 5:30  Induced On-Target Toxicity with a Novel ADC
Emily Meseck, Novartis

WEDNESDAY, MAY 17

8:00 - 9:00  Breakfast

DEVELOPMENT TOXICOLOGY WORKSHOP
SESSION V: NOAEL
Chairs: Brian Vuillemenot, Genentech and Vito Sasseville, Novartis

9:00 - 9:05  Session Introduction

9:05 - 9:35  The No-Observed-Adverse-Effect-Level in Drug Safety Evaluations: Use, Issues, and Definition(s)
Jeff Engelhardt, Ionis

9:35 - 10:05  Regulatory Perspective on the use and Interpretation of the NOAEL in Nonclinical Studies
Peyton Myers, FDA

10:05 - 10:25  Break
10:25 - 10:55  NOAEL Case Examples
Lise Loberg, AbbVie

10:55 - 11:25  Setting No-Observed-Adverse-Effect-Levels (NOAELs) for Immunomodulatory Drugs
Mark Vogel, Pfizer

11:25 - 12:25  Lunch

SESSION VI: Speed Session - Brief Updates
Chairs: Lauren Mihalcik, Amgen and Paul Cornwell, Eli Lilly

12:25 - 12:30  Session Introduction

12:30 - 12:50  TranSENDance - Genentech’s Ongoing Journey To SEND Implementation
Nidhi Singh Jindal, Genentech

12:50 - 1:10  Bial Trial Updates: FAAH Science
Tony Ndifor, Johnson & Johnson

1:10 - 1:30  BIAL Trial Update: Implications for FIH Clinical Trials
Graeme Moffat, Amgen

1:30 - 1:50  Elimination of Rat Carcinogenicity Studies –
An Update on the ICHS1 Revision Working Group
Ian Pyrah, Seattle Genetics

1:50 - 1:55  Closing Remarks
ABSTRACTS

PLENARY

21st Century Cardio-Oncology: Identifying Cardiac Safety Signals in the Era of Precision Medicine
Javid Moslehi, Vanderbilt University

Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high-grade, immune-related adverse events can occur, particularly with combination immunotherapy. We report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myositis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T-cell and macrophage infiltrates. Selective clonal T-cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab, which suggests that our patients were having a rare, potentially fatal, T-cell–driven drug reaction. (Funded by Vanderbilt–Ingram Cancer Center Ambassadors and others.)

Discovery Workshop

SESSION I

Dispelling the Myth that NHPs are not Sensitive to Immune Modulation
Oliver Thomas, Amgen

Harnessing the power of the immune system with novel cancer immuno-therapeutics presents new less-known safety aspects to the benefit/risk profile. Unique safety aspects of using new immune-oncological therapy include an understanding and managing acute cytokine release. This talk will provide an overview of the pre-clinical experience Amgen has gained with its BiTE® technology in terms of indicators of immune modulation including cytokine release: what does the release profile look like in cynomolgus monkeys; what other findings are associated with it in a tox study; what factors play a role in release (eg target expression profile); how can release be managed.

CAR T Cell Design, Activity and Safety: Looking Back and Looking Forward
Rafael Ponce, Juno Therapeutics

Engineered T cell products represent a new class of therapeutic encompassing attributes of cell therapy and gene therapy to provide novel functionality to the T cell. Among these products are chimeric antigen receptor (CAR) T cells, which express a novel cell surface protein with a ligand-binding domain, transmembrane domain, and intracellular signaling domain. Although these cells have shown impressive clinical activity, predominantly in CD19-related hematologic malignancies, a range of toxicities are associated with these therapeutics, with cytokine release and neurological toxicities as major clinical adverse effects. The emerging clinical efficacy and safety information is informing our understanding of attributes of the vector design, dosing, and patient that underlie safety-related risks. This talk will summarize this emerging experience and our efforts to improve our understanding of the mechanisms underlying the observed adverse effects.

Combinations in Immuno-Oncology: A Pharmacology Perspective
Marcia Belvin, Genentech

Immune checkpoint inhibitors such as anti-PD1 and anti-PDL1 have shown efficacy across a broad range of tumor types and are gaining approval in an increasing number of indications. The broad use of these agents, however, opens up an almost unlimited number of potential combination regimens that are designed to improve the breadth or depth of responses. Preclinical approaches designed to validate potential combination agents and inform the prioritization and clinical use of these agents require a major investment of time and resources.

There are many questions to be addressed when considering potential combinations with immune checkpoint inhibitors. Are there different immune subtypes among cancers? What are the general drivers of immune suppression in these subtypes? How can we identify druggable targets that would be predicted to modulate these immunosuppressive mechanisms? Which preclinical models can we develop
and test to validate these combinations? Which preclinical endpoints are most translatable to the clinic? These and other questions are what guide our preclinical studies with the ultimate goal of identifying and validating the most promising combination approaches to test in the clinic.

**SESSION II**

**The Hunt for Novel Cardio-Oncology Biomarkers in Rodents**
Michelle Hemkens, Pfizer

With the increasing number of people surviving cancer, patients and doctors are becoming equally focused on the quality of life in survivorship as they are on fighting cancer. Consequently, cardio-oncology has emerged as a new clinical discipline with focus on both the stratification of patients at risk and therapies that pose a cardiovascular risk, eg molecularly targeted therapies including tyrosine kinase inhibitors (TKI). Therefore, nonclinical research should strive not only to detect preclinical drug-induced changes in cardiac structure or function, but also to understand the relevance of these cardiotoxic effects to humans. As is typical for new disciplines, there is an unmet need for early and predictive tools to identify both of these factors. Currently, preclinical assessment of cardiovascular toxicity consists of repeat-dose in vivo toxicity studies focused primarily on histopathological endpoints; additional measures, such as cardiac function and biomarkers of cardiac injury, are not routinely assessed in these studies. Furthermore, analysis of these studies suggests that using young and healthy, drug-naïve animals do not adequately translate the TKI-induced cardiomyopathy phenotype; therefore, new nonclinical models are needed to address this gap. The developed model would ideally be used to assess the preclinical cardiotoxicity of proposed oncology therapies, but may also have utility in assessing cardioprotective therapies for use in cardio-oncology.

Data will be shown and discussed from a new model for studying cardio-oncology nonclinically that includes myocardial transcriptional signatures, strain echocardiography imaging, and pharmacologic (dobutamine) stress challenge. In general, rats with radiotelemetry were treated with vehicle, low dose doxorubicin (2 mg/kg/week IP) for 1 month, or sorafenib (10 mg/kg/day) for 21 days. Cardiac structure and function at rest and during stress were assessed using strain echocardiography in concert with a weekly dobutamine infusion. Circulating blood biomarkers of cardiac toxicity (eg, NTproBNP, NTproANP, cTropin, and miR-208) were collected weekly and at necropsy. At the end of the study, samples of cardiac tissue were taken from the ventricular apex and were submitted for transcriptional profiling along with standard histopathology. These data as well as recent publications give high confidence in developing a rodent model predictive of drug-induced cardiomyopathy.

**Assessing Doxorubicin Related Heart Failure in the Cynomolgus Monkey – A Repeat-Dose Safety Pharmacology Study**
Mike Engwall, Amgen

Doxorubicin related heart failure has been recognized as a serious treatment risk since the 1970s. The underlying mechanism for this risk is still a topic of debate. An emerging concern with CardioOncology has shown how difficult it can be to predict how long term function can affect cardiac function. This presentation will describe a repeat-dose study with doxorubicin in a non-human primate model to characterize the onset of left ventricular dysfunction (LVD) using invasive and non-invasive methods. Animals were treated with doses that were targeted and adjusted to minimize morbidity related to bone marrow depression. Telemetry instrumentation allowed regular hemodynamic assessment, and were augmented by cardiac imaging by echocardiography. Animals exhibited LVD following 6-8 weeks of dosing, which deteriorated into heart failure with continued dosing out to 4 months. This study demonstrated the utility of and associated challenges related to measuring cardiovascular parameters in a repeat-dose study.

**Clinical Translation of Non-Clinical Gastrointestinal Effects**
Scott Mittelstadt, AbbVie

Gastrointestinal (GI) responses to drugs, such as diarrhea, constipation, and emesis are some of the most frequently reported adverse effects in the clinical development of new chemical entities. Although, most of the time these effects are not considered life threatening and are monitorable, they can have an impact on the development and commercial success of new drugs. Therefore, many of the recommendations required from preclinical safety will be business decisions assessing the potential translation of observed effects to the clinic. Pharmaceutical scientists need to assess the importance of the findings and the type of preclinical GI
assays to be conducted within their own companies to help make these decisions. This presentation will focus on the advantages and disadvantages of different preclinical GI models and will discuss potential strategies that can be implemented to reduce the risk of unexpected clinical effects on the gastrointestinal system.

SESSION III

CNS Liability Screening During Drug Discovery Research & Development: Challenges & Perspectives
Ying-Ying Zhou, Genentech

Approximately 25% of attrition and adverse-effect-reactions (AERs) of drugs in clinical development are due to CNS toxicity. Numerous gaps in the assessment of neurotoxicity risk liability remain due to the complexity of the CNS, the lack of sensitivity, quantitative nature of histopathological approaches, spatial restrictions, invasive nature of sampling methods (CSF, CNS/PNS tissues), interspecies differences, lack of full understanding of predictive, translational CNS fluid-based biomarkers from preclinical safety/toxicology to clinical. The standard first-tier preclinical CNS safety assessment approach (i.e., standard FOB, etc.) as well as second-tier exploratory assays (e.g., EEG, PTZ) will be reviewed. Preclinical case studies using rodent hippocampal brain slice models as well as, rodents & non-rodents EEG monitoring for seizure liability detection will be presented. New qualitative and quantitative technologies including high-/mid-throughput screening MEA platforms using human/non-human stem cell neuronal cultures, brain slice cultures, 3D organ-on-a chip associating new biomaterials/tissue scaffolds, MRI/PET-imaging techniques, isolated human viable organs and the rapid expansion of genomic and proteomic tools are emerging. They may provide encouraging perspectives for screening, monitoring of potential mechanism(s) of off-target neurotoxicity, and for better predictivity of potentially delayed, deleterious CNS AERs resulting from long-term administration and therefore, unexpected high exposure or receptor/target occupancy.

Leveraging In Vitro Assays to Elucidate Off-Target Toxicities Observed with Novel Therapeutics
Nianyu (Jason) Li, Merck

Off-target effects have been recognized as one of the main contributors for drug-induced toxicity. To minimize this risk, new modalities with potentially less off-target effects have been pursued by the pharmaceutical industry. For instance, monoclonal antibody therapeutics are typically regarded to have high target specificity; however, emerging evidence suggest that potential off-target toxicity can still occur. Two case studies will be presented as examples of preclinical toxicities attributed to off-target activity. The first case study focuses on elucidating the mechanism of unexpected acute thrombocytopenia observed in cynomolgus monkey administered a therapeutic monoclonal antibody (mAb-Y). Importantly, other mAbs with similar biological activity against the intended target did not have the thrombocytopenia liabilities in vitro and in vivo, suggesting that the platelet effects of mAb-Y in cynomolgus monkeys likely occurred through an off-target mechanism. The use of various in vitro assays led to the understanding that the mechanism of mAb-Y induced thrombocytopenia was associated with antibody-induced monocyte phagocytosis of platelets. In the second case study, a novel therapeutic candidate (compound X) caused severe clinical signs at pharmacological doses in rodents, including acute mortality. These signs were consistent with an anaphylactic-like response, and were later confirmed to be associated with elevations in plasma histamine. In vitro studies demonstrated that sub-structural aspects of compound X induced an IgE-independent mast cell degranulation via an off-target mechanism. Together these case studies provide examples of approaches that could be used to elucidate underlying mechanisms of toxicity and guide optimization of drugs in discovery to minimize the potential for in vivo off-target toxicity.

A Mechanism of Hepatotoxicity for High Affinity Antisense Oligonucleotides
Sebastien A. Burel, Ionis Pharmaceuticals

High affinity antisense oligonucleotides (ASOs) containing bicyclic modifications (BNA) such as locked nucleic acid (LNA) or constrained ethyl (cEt) designed to induce target RNA cleavage have been shown to have enhanced potency along with a higher propensity to cause hepatotoxicity. In order to unravel the mechanism of this hepatotoxicity, We analyzed transcriptional profiles from the livers of mice treated with a panel of highly efficacious hepatotoxic or non-hepatotoxic LNA ASOs. The liver of mice treated with non-hepatotoxic LNA ASOs displayed highly selective on-target transcript knockdown, while the levels of many unintended transcripts were reduced in mice treated with hepatoxic LNA ASOs. We noted that this transcriptional signature was concurrent
with on-target RNA reduction and preceded transaminitis. Surprisingly, mRNA transcripts commonly reduced by toxic LNA ASOs were not strongly associated with any particular biological process, cellular component or functional group, rather they tended to have much longer pre-mRNA transcripts. We also demonstrate that the off-target RNA knockdown and hepatotoxicity was dependent on RNase H1. This suggests that for a certain set of BNA ASOs, hepatotoxicity can occur as a result of unintended off-target RNase H1 dependent RNA degradation.

**VENDOR PRESENTATION**

**Human iPSC-derived Cardiomyocytes, Glutamatergic Neurons, and Hepatocytes; Cells and Solutions to Improve Toxicity Testing Relevance and Predictivity**

Blake Anson, Cellular Dynamics

A model's utility is predicated on recapitulation and meaningful interrogation of native human biology. Tissue specific cells, differentiated from human induced pluripotent stem cells (iPSCs), enable access to human biology very early in drug discovery and development. Furthermore, multiple procedures exist for deploying these cells in predictive phenotypic screens and mechanistic investigations in low to high throughput formats. This talk will highlight recent advances exemplifying the utility of iCell® cardiomyocytes, glutamatergic neurons, and hepatocytes for drug discovery and toxicity testing. Specifically covering solutions with cardiomyocytes in pro-arrhythmia and contractility assessments, glutamatergic neurons in detecting excitotoxic and seizurogenic liabilities, and hepatocyte culture techniques for prolonged in-vitro culture, increased cell functionality, and enhanced CYP activity. Together these models provide in-vitro systems that closely align with relevant in-vivo biology and expedite more precise toxicity testing.

**Development Workshop**

**SESSION IV**

**Strategies for Assessing and Qualifying Linker/Payload-Related Impurities in ADC**

Matthew Holdren, Genentech

Currently implemented guidance documents from the International Council for Harmonisation (ICH) regarding the assessment of drug substance and DNA reactive (mutagenic) impurities (ICH Q3A and M7, respectively) provide an excellent framework for evaluating and controlling small molecule impurities in new chemical entities. As emerging classes of biopharmaceuticals utilize conjugational chemistry to specifically target cytotoxic drugs (Antibody-Drug Conjugates) or to maximize biologic activity (multimeric pegylated proteins), guidance on how to assess the safety of small molecule impurities in these biopharmaceuticals is needed. This presentation will propose an approach to assessing small molecule impurities in biopharmaceuticals and provide relevant case studies for discussion.

Challenges and Approaches in the Early Stages of ADC Development using THIOMABTM Antibody Technology to Improve Safety

Christopher Frantz, Genentech

Antibody drug conjugates (ADCs) are a unique class of drugs made up of a cytotoxic molecules conjugated with a linker to an antibody that is designed to target specific antigens. Currently the majority of ADCs are being developed for the treatment of serious, life threatening cancers. For cancer treatment, the potential to utilize the antigen-selectivity of mAbs to deliver toxic agents has been considered a mechanism to decrease the nonspecific toxicity induced by many chemotherapeutics to improve the overall therapeutic index. The successes of the two currently approved ADCs, Brentuximab Vedotin (Adcetris®) and Ado-Trastuzumab Emtansine (Kadcyla®) has driven an expansion of the ADC field to the point where there are now more than 40 ADCs in clinical trials and an even greater number in earlier stages of development within the pipelines of many biopharmaceutical companies. The small molecule toxins conjugated to antibodies have proven to be a considerable challenge to the identification and development of new ADCs. While ADCs are often described as targeted therapies with guided missile like properties, they can frequently cause off target toxicities, with only a small percentage actually reaching the intended target, while much of the administered dose results in undesired toxicities. Here we describe the use of THIOMABTM antibody technology to improve the safety of ADCs.

Conducting a series of early nonclinical safety studies provides an understanding of not only the toxicities associated with the
molecules toxicity, but also helps with an early determination of risk benefit profile. For the conduct of these studies one must consider the types and timing of toxicology studies, species, study duration, and what additional tests or assays will contribute to the overall safety assessment.

In addition, it is important to understand how target selection as well as modifications of an ADCs properties can impact safety and efficacy. By more fully understanding the mechanism of the cytotoxic payloads action, as well as effects of drug-antibody ratio (DAR), linker chemistry, and conjugation allows for better optimization. By applying the THIOMABT antibody technology for conjugation we have been able to increase the nonclinical safety and efficacy profiles of ADC molecules.

**On-Target Toxicity with ADCs: Species-Specific Toxicity and Preclinical to Clinical Translation**
Anu Connor, Novartis

Safety profiles with antibody drug conjugate therapies are driven, for the most part, by off target toxicity due to the cytotoxic component of the ADC. However, there are instances where target mediated toxicity can be appreciated. Two case examples of on-target toxicity will be reviewed. In the first example, on-target toxicity was noted in the rat but not cynomolgus monkey. In the second case example, the cynomolgus monkey was not predictive of clinical adverse events that were consistent with target-mediated toxicity.

**Induced On-target Toxicity with a Novel ADC**
Emily Meseck, Novartis

An antibody directed against a cell surface receptor conjugated with a controlled drug antibody ratio to an internal proprietary cytotoxic payload was tested by intravenous administration in Cynomolgus monkeys. Following two 6 mg/kg doses, acute renal failure occurred due to an on-target toxicity in the kidney. An isotype, non-binding antibody conjugated with the same payload resulted in dose limiting but less severe toxicity in the kidney. In addition, profound microscopic changes were observed in the cornea with the cell surface target ADC, although the target was not known to be expressed in normal corneal epithelium. Payload-related single cell necrosis in the corneal epithelium was hypothesized to have induced target molecule expression, resulting in subsequent, on-target effects in this tissue, including erosion, ulceration and atrophy. Further molecular localization work demonstrated that expression of the target was induced in corneal epithelium in Cynomolgus monkeys given either the isotype or target ADC.

**SESSION V**

**The No-Observed-Adverse-Effect-Level in Drug Safety Evaluations: Use, Issues, and Definition(s)**
Jeffery A. Engelhardt, Ionis Pharmaceuticals

The no-observed-adverse-effect-level (NOAEL) is a necessary part of the non-clinical risk assessment that continues to receive broad discussion on interpretation. Determining the NOAEL is rather simple when one decides how to conclude whether a given finding is adverse or not. However, criteria that influence interpretation of an adverse effect has been the subject of several review papers over the past decade. Each iteration better refines the definition of adverse but there remains room for interpretation and professional judgement that affects the NOAEL. This talk will take an in-depth look at the various interpretations of an adverse finding in a toxicity study and how best to apply these definitions to declare a NOAEL for use in a risk assessment. The obvious bias of being one of the multitude of authors on this topic will invariably come through.

**Regulatory Perspective on the use and Interpretation of the NOAEL in Nonclinical Studies**
Peyton Myers, FDA

A NOAEL is a common tool that is utilized as a benchmark during risk assessment in drug development. The NOAEL is based on findings in the toxicology studies that support drug development. Although the NOAEL is primarily used for FIH (first in human) dose calculations, it can also inform other risk assessments in the life cycle of drug development. Many factors may come into play when deciding a NOAEL, including the definition of “adverse” for a particular finding. Due to the varying definitions as to what may be considered adverse among toxicologists, there may be varying interpretations of the same findings for a NOAEL. In this presentation, Dr. Myers will discuss the decision making process for NOAEL calculations for FIH dosing. Furthermore, he will discuss the varying interpretations for adverse findings as it relates to determining a NOAEL. He will also discuss general concepts that may help minimize confusion during the weight of evidence review by regulatory staff. Lastly, he will discuss development pathways that may be pursued if NOAEL interpretation disagreements cannot be resolved.
Setting No-Observed-Adverse-Effect-Levels (NOAELs) for Immunomodulatory Drugs
Mark Vogel, Pfizer

When assessed in standard nonclinical general toxicity studies, immunomodulatory drugs intended to treat autoimmune diseases can have immunosuppressive effects on endpoints such as circulating leukocyte counts, spleen and thymus weights, or histologic cellularity of lymphoid organs or bone marrow. Depending on the mechanisms of action, it is not uncommon that one or more of these parameters may be affected (usually decreased) at “therapeutic” concentrations of the test article. Rather than a clear threshold, there is often a monotonic decrease across dose groups. In these circumstances it can be difficult to set unambiguous cut-offs for what is considered “adverse” as opposed to intended pharmacological effect, which complicates the designation of a NOAEL. Furthermore, it is difficult to relate specific changes in immune system parameters to infection risk in nonclinical studies. Independent of systemic exposure and changes in immune system parameters, the incidence of infections observed in nonclinical toxicity studies can vary from study to study depending on specific test facility, animal husbandry, source of animals, etc. The translation of changes in immune system endpoints or infection incidence in nonclinical studies to human infection risk is even more complex. Infection risk for a therapeutic agent in patients depends not only on some intrinsic degree of immunosuppression but also on multiple extrinsic factors such as: age, co-morbidities (eg, diabetes), concomitant treatments (eg, steroids, methotrexate), underlying disease severity, geographic location, etc. This presentation describes case studies of three Pfizer immunomodulator compounds (a Janus kinase inhibitor, a glucocorticoid agonist, and a p38 kinase inhibitor) that illustrate these issues. Based on these considerations, our current practice is to assess changes in immune system endpoints as “adverse” within a nonclinical toxicity study only if they are associated with clinical or histologic evidence of infection, or decreases in immune function (eg, T-cell dependent antigen response, TDAR). Nevertheless, any noteworthy test-article-related decreases in immune system endpoints such as circulating leukocyte counts, spleen and thymus weights, or histologic cellularity of lymphoid organs or bone marrow are considered evidence of potential infection risk in humans, and noted in regulatory documents such as Investigator Brochures and informed consent documents.

SESSION VI

TranSENDance - Genentech’s Ongoing Journey To SEND Implementation
Nidhi Jindal, Genentech

In recent years, Pre-Clinical industry has heard about the FDA Mandate where Non clinical Studies that start on and after Dec 2016 and are a part of NDA/BLA (Dec 2016) and INDs (Dec 2017) must be electronically submitted to the agency in the standard format FDA has recommended. This standard is called SEND (Standard for Exchange of Nonclinical Data)

IT professionals in every Pre Clinical support organization are keen on providing a technology as well as business solution to enable scientists to generate datasets in SEND format. Besides being in compliance with FDA mandate SEND presents an opportunity to enhance knowledge management by pulling all safety data in a standard format in a single repository.

The presentation will discuss Genentech’s very rewarding journey to be SEND ready, the challenges we have overcome and the contributions made by Genentech to the SEND community across the globe.

Bial Trial Updates: FAAH Science
Tony Ndifor, Johnson & Johnson

BIA 10-2474 is a fatty acid amide hydrolase (FAAH) inhibitor that was being developed by BIAL-Portela Portugal for a range of indications. It entered Phase I trials at the French CRO, Biotrial, in 2015. During the multiple ascending dose phase of the study, 5 of 6 subjects receiving study drug developed severe neurological symptoms leading to death of one of the subjects. Following extensive investigations by the French regulatory bodies, it was concluded that the toxicity was directly related to BIA 10-2474 although the mechanism remains elusive. The presentation will offer an overview of the FAAH target, characterization of the compound, the clinical trials, and outcome of the regulatory investigations into the cause of the accident.

BIAL Trial Update: Implications for FIH Clinical Trials
Graeme J Moffat, Amgen

In response to the events that occurred in the Phase 1 clinical trial for BIA 10-2474, the European Medicine Agency
(EMA) are revising their “Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products” (EMEA/CHMP/SWP/28367/07). This guideline was first introduced in 2007 in response to the Tegenero clinical trial tragedy. A draft revision to the guideline was released for public comment in November 2016 followed by a workshop (which included industry representatives) held in London in March 2017. It is expected that the revised guideline will be finalized in the summer of 2017. The key elements of the guideline revision together with the topics discussed at the March 2017 workshop will be presented.

Elimination of Rat Carcinogenicity Studies – An Update on the ICHS1 Revision Working Group
Ian TG Pyrah, Seattle Genetics

Conduct of lifetime carcinogenicity studies in rat and mouse have been a regulatory requirement for most pharmaceuticals for decades. These studies use large numbers of animals and significant resource, and many rodent carcinogens are not considered to be relevant to human carcinogenesis and are available as marketed drugs. In 2010, a publication by Reddy et al. reviewed data from 80 compounds which had been studied in rat chronic toxicity and rat carcinogenicity studies. The outcome of the rat carcinogenicity study was predicted by pre-neoplastic lesions in the rat chronic toxicity study in a majority of cases. The assessment was extended and predictive algorithm was refined by Sistare et al. in 2011. Following corroboration of the findings American, European, and Japanese regulatory bodies, an International Conference on Harmonization (ICH) S1 expert working group (EWG) was commissioned 2012 to evaluate the potential to replace the rat carcinogenicity assay. This group devised a mechanism for a prospective assessment of the predictive algorithm, in which industry provided a Carcinogenicity Assessment Document (CAD) prior to completion of the carcinogenicity study which predicted the outcome. The CAD was assessed by regulators, and feedback made available. Ultimately, the ICH S1 EWG will evaluate the success of the predictions and decide whether the algorithm could be used in place of a rat carcinogenicity study. The rate of submission of CADs has been less than expected, causing a delay to the anticipated completion of the assessment. This talk will provide an update on the progress to date of the ICH S1 EWG.
BIOGRAPHIES

Amy Beebe, Ph.D., Merck Dr. Beebe received her Ph.D. degree in Microbiology from the University of California, Davis. She holds a B.S. degree in Biology from the University of California, San Diego. She joined DNAX Research Institute in 1994 as a post-doctoral fellow in the laboratory of Dr. Robert Coffman, where she studied the genetic basis of CD4+ Th1 vs. Th2 differentiation. She has since held various positions in Biologics Discovery at Schering-Plough and then Merck Research Laboratory, and is currently a Senior Principal Scientist in Discovery Biology, Immuno-Oncology. Amy's focus has been on using animal models to understand the mechanism of action of biologic candidates and leading teams in the translation of basic research findings into early development.

Marcia Belvin, Ph.D., Genentech Dr. Belvin is Associate Director of the Department of Cancer Immunology at Genentech. The Cancer Immunology Department provides research support for immuno-oncology efforts at Genentech, and is responsible for both basic science discovery as well as support of pipeline projects. Part of her role is to partner closely with the clinical teams to provide scientific support to immune-oncology development efforts. Marcia joined Genentech in 2004 where she worked in the Cancer Signaling Department prior to joining the Cancer Immunology Department in 2013. She is an author on over 40 peer-reviewed papers and reviews.

Eric Blomme, Ph.D., AbbVie Dr. Blomme is Vice President, Global Preclinical Safety at Abbvie Inc. Eric has held several positions at Abbott/AbbVie, including Director Investigative Toxicology and Pathology and Director Integrated Pharmacology and Project Leader in Discovery Advanced Technologies. Prior to joining AbbVie, he worked at Pharmacia and Searle.

Eric attended the University of Lyon, McGill University, Cornell University and The Ohio State University and received his Doctor in Veterinary Medicine and PhD. Eric is Diplomate of the American Board of Veterinary Pathologists and current President of the Great Lake Chapter of the American Society of Pharmacology and Experimental Therapeutics. He has published over 70 peer-reviewed manuscripts, multiple editorials, several book chapters, and a book.

Jorg Blumel, Ph.D., Genentech Dr. Blumel currently holds a position as Head Development Toxicology within Safety Assessment at Genentech, South San Francisco, CA. In this role, he oversees the group of toxicology project team leads who is accountable for the regulatory strategies and nonclinical toxicity assessment of Genentech’s biotherapeutics and small molecule development portfolio spanning from clinical candidate selection/ early development up to post-marketing support. In addition, he is leading the Product Quality and Occupational Toxicology group at Genentech. This group is responsible for providing health-based assessments in support of technical development functions. Dr. Blumel joined Genentech in September 2014. Prior to Genentech, he held a position as Director Toxicology at MedImmune, the biologics division of AstraZeneca in Gaithersburg, MD, and headed the Nonclinical Safety / Drug Metabolism department at Merz Pharmaceuticals GmbH, Germany. Dr. Blumel is a board certified toxicologist and has more than 15 years of experience in nonclinical safety / nonclinical drug development for biotherapeutics and small molecules. He has a research background in immunotoxicology and received his PhD in 2000 from the University of Dusseldorf, Germany.

Sebastien Burel, Ph.D., Ionis Pharmaceuticals Dr. Burel is currently Director of Toxicology at Ionis Pharmaceuticals, Inc. where he is leading efforts to characterize mechanisms of oligonucleotide mediated inflammation and systemic toxicity and translating those into safety screening models. Other responsibilities include serving as a representative on several drug development project teams. Design, implementation, interpretation, and reporting of GLP toxicology and pharmacokinetic studies necessary to support Regulatory approvals. Dr. Burel rejoined Ionis (Formerly Isis Pharmaceuticals) in 2007 after he served as a senior scientist in the department of toxicology where he oversaw the toxicogenomic program aimed at early identification of hepatotoxic compounds at Neurocrine Biosciences Inc. from 2005 - 2007. From 2002 – 2004, He did his first stint at Isis Pharmaceuticals where he pursued a post-doc in the department of toxicology under Art Levin. He received a Ph.D. in Oncology and Hematology from the Paterson Institute for Cancer Research in Manchester, UK in 1999, studying the use of hematopoietic
cell line for the assessment of in vitro myelotoxicity.

**Anu Connor, Ph.D., Novartis** Dr. Connor is a board certified toxicologist, graduating from Northeastern University with a PhD in Biomedical Sciences with a specialization in Toxicology. After graduation, she joined Sepracor in Marlborough MA as a toxicologist developing CNS small molecules. She then moved to the west coast and spent several years in the Bay Area at Genentech as a scientist and pharmacology subteam leader in the biotherapeutics group. She has been working on ADC development since 2008 at broad range of companies, spanning from start up to large pharma. She currently works at Novartis as a Safety Assessment Expert in the Preclinical Safety Group and is responsible for the oversight and strategic development of the Antibody Conjugate portfolio.

**Paul Cornwell, Ph.D., Eli Lilly** Dr. Cornwell is a Principal Research Scientist in Nonclinical Safety Assessment at Eli Lilly and Company. Prior to joining Lilly, Paul was a research scientist at the former Rosetta Inpharmatics LLC, a wholly owned subsidiary of Merck & Co. Inc. Paul received his bachelor's degree from Wabash College and a Ph.D. in pharmacology from Indiana University. After his graduate work, he completed a postdoctoral fellowship at the former CIIT Centers for Health Research in Research Triangle Park, NC. Paul is currently the Chair-Elect for the Development Toxicology Workshop portion of the APT organizing committee, is currently a member of the Society of Toxicology, and is a Diplomate of the American Board of Toxicology. He has a significant amount of experience in the development of small and large molecule pharmaceuticals.

**Dolo Diaz, Ph.D., Denali Therapeutics** Dr. Diaz is currently the Head of Safety Assessment at Denali Therapeutics. Previously Dr. Diaz was the Head of Small Molecule Discovery Toxicology at Genentech, where for nine years she led compound optimization and safety strategies for the small molecule discovery portfolio across therapeutic areas. Before that, Dr. Diaz worked at CEREP Inc. for four years, where she established and headed the In-vitro Toxicology group. Dolo received her PhD in Toxicology from the University of Washington, followed by post-doctoral work at the Fred Hutchinson Cancer Research Center in Seattle. Dolo has authored/co-authored more than 30 peer-reviewed publications in the field of Toxicology and she is a Diplomate of the American Board of Toxicology.

**Heather Dowty, Ph.D., Pfizer** Dr. Dowty is currently an Associate Research Fellow and Drug Safety Team Lead in Drug Safety Research and Development at Pfizer in Andover, MA. Heather enjoys her portfolio role as a project team representative responsible for assessment of target safety liabilities, developing the nonclinical safety strategy for individual project teams from discovery through development, and supporting due diligence efforts for potential in-license programs. She has held previous roles in management of the General Toxicology Discipline, leading a team of In Vivo Study Scientists, Study Directors, and Project Team representatives to design, conduct and report in vivo exploratory toxicity studies in support of Pfizer’s research portfolio. She initially supported the Pfizer DSRD site in Saint Louis, MO and later was selected to lead the successful buildup and implementation of the General Toxicology Laboratory in Massachusetts. She received a BS in Pharmacology and Toxicology from the University of Wisconsin-Madison School of Pharmacy and a PhD in Toxicology at the Kettering Laboratories, Department of Environmental Health, University of Cincinnati. Heather began her career in toxicology as a Scientist in the Drug Safety Assessment Department at Procter & Gamble Pharmaceuticals gaining increased experience and responsibilities as a Study Director, Team representative, and PhRMA Genetic Toxicology working group member. She attained board certification from the American Board of Toxicology and is a Full Member of SOT and ACT.

**Jeff Engelhardt, Ph.D., Ionis Pharmaceuticals** Dr. Engelhardt received his undergraduate degree from the University of Illinois at Urbana and a MS in microbiology from the University of Notre Dame. He received his DVM degree and PhD in Veterinary Pathology from Purdue University where he was an NIEHS Post-Doctoral Fellow in chemical pathology. After completing his residency and PhD, he joined Eli Lilly and Company in 1988 as a toxicologic pathologist and rose thru various assignments to Preclinical Expert for the company until 2004 when he left to join Amgen as Executive Director of Pathology responsible for safety studies with monoclonal antibodies, peptides and proteins. He left Amgen in 2009 and had various roles in consulting and CRO pathology until 2013 when he joined Ionis Pharmaceuticals as Vice President of Pathology and Nonclinical Drug Development. He is currently involved with safety evaluation of antisense oligonucleotides. Dr. Engelhardt is a Diplomate of the American College of
Veterinary Pathology, a Fellow in the International Academy of Toxicologic Pathology, a member of the STP Vascular Injury Working Group for Biotherapeutics and Antisense Oligonucleotides, the ESTP Expert Panel on Adversity of Lysosomal Accumulation, and a member of the DIA Oligonucleotide Safety Working Group. He has published more than 60 articles and book chapters and given numerous oral presentations in the areas of toxicology, pathology and comparative medicine.

**Mike Engwall, DVM, Ph.D., DSP, Amgen** Dr. Engwall is currently at Amgen in the Integrated Discovery and Safety Pharmacology group within Toxicology Sciences at Amgen located in Thousand Oaks, California. Prior to that, he was in the Safety Pharmacology group within Drug Safety Evaluation at Pfizer in Groton, CT.

Dr. Engwall did his graduate and veterinary training at Iowa State University and post-doctoral work at the University of Wisconsin in Madison.

Dr. Engwall has over 20 years of experience in the pharmaceutical industry the majority of which has been in the area of cardiovascular hazard identification and risk assessment. He has been an active member of the Safety Pharmacology Society going back to when it was known as the General Pharmacology Interest Group and is currently on the SPS Board of Directors.

**Jonathan Heyen, Pfizer** Jonathan (Jon) Heyen is currently a senior principal scientist working in the Portfolio Support Department at Pfizer La Jolla. Jon completed his undergraduate and graduate degrees at the University of Illinois-Champaign Urbana. Jon joined the Searle Company in St. Louis Missouri where he worked in the Cardiovascular Discovery Group. Within this group Jon investigated the role of the immune system in various cardiovascular diseases and the potential for new therapies. At the completion of the Pharmacia/Pfizer merger in 2003, Jon relocated to La Jolla California and joined Pfizer Drug Safety Research & Development. Jon has had various roles within this department including as cardiovascular lead within safety pharmacology, study director within general toxicology and drug safety team lead. Jon’s current role is supporting the oncology portfolio from idea to loss of exclusivity for multiple oncology projects. He is an active member of several ILSI/HESI initiatives, APT, SOT and SPS.

**Matthew Holdren, Ph.D., Genentech** Dr. Holdren is a board certified toxicologist with over 10 years of experience designing and conducting nonclinical safety programs supporting the development of novel biologics and small molecules across diverse therapeutic areas. In addition to his toxicology expertise, Dr. Holdren has a broad scientific background that includes conducting impurity assessments, establishing animal models of human disease, and bioanalytical assay development. In his current role at Genentech, Dr. Holdren serves as a therapeutic area lead (infectious disease), pharmacology sub-team leader, and project toxicologist for small and large molecule programs.

Dr. Holdren earned a B.S. in Microbiology and a Ph.D. in Experimental Pathology from the University of Washington in Seattle. Prior to Genentech he has worked at multiple biopharmaceutical companies including Bristol-Myers Squibb and ZymoGenetics.

**Nidhi Jindal, Genentech** Nidhi Jindal is the Safety Assessment IT Manager at Genentech. Prior to joining Genentech, she was a senior Business Analyst at Merck in NJ/PA area supporting Safety and DMPK scientists for their IT needs. Nidhi received her Masters from the Department of Biosciences and Biotechnology from Indian Institute of Technology (IIT) Roorkee, formerly called as University of Roorkee. Nidhi is currently an active member of CDISC SEND Core team, PhUse and BioIT World. She has a significant amount of experience in the development, implementation and support of IT capabilities for Pre Clinical organizations in big Pharma and Biotech companies namely legacy Schering Plough, Merck, Genentech etc.

**Christine Karbowski, Ph.D., Amgen** Dr. Karbowski is a Senior Scientist in Comparative Biology and Safety Sciences at Amgen, Inc. She is a member of the Society of Toxicology, an organizing committee member for APT since 2014, and a previous member of the American Association for Cancer Research and the Environmental Mutagen Society. Dr. Karbowski received her B.A. in Molecular and Cell Biology and her Ph.D. in Molecular Toxicology, both from U.C. Berkeley. Her research has focused on applying ‘Omics technologies such as transcriptomics, proteomics, and metabolomics for hazard identification in preclinical toxicity studies. During her 8 years at Amgen, Dr. Karbowski has served as a subject matter expert utilizing gene expression and
genetic data for understanding potential target based liabilities as well as provided guidance for development of internal databases to query and visualize such data. Currently Dr. Karbowski serves as a project team representative for discovery and early stage programs across both large and small molecule modalities.

**Jason (Nianyu) Li, Ph.D., Merck** Dr. Li is a Principal Scientist in Merck Safe Assessment department. His research focus is to understand roles of immune signaling pathways in drug-induced toxicity. He develops in vitro/ex vivo assays as well as animal models in support of toxicological issue resolution and mechanistic studies for the development of large and small molecules. Before joining Merck, he was a member of Amgen Immunotoxicity and Discovery Toxicology group. Before his industrial career, he obtained his PhD from Purdue University Cytochemistry Laboratories under the guidance of Dr. J Paul Robinson and has a postdoc from the Department of Immunology at St. Jude Children’s Research Hospital where he worked under the guidance of Dr. Dario Vignali.

**Lise Loberg, Ph.D., AbbVie** Dr. Loberg has over 15 years’ experience as a toxicologist and project manager in the biopharmaceutical industry. Dr. Loberg supports preclinical safety evaluation of compounds in development, from lead selection to late-stage clinical trials and marketed drugs. She has experience with large molecule biotechnologies and small molecule drugs ranging across several therapeutic areas including neuroscience, oncology and renal disease. Dr. Loberg is a Diplomate of the American Board of Toxicology and has earned the Project Management Professional (PMP) certification. She served as Treasurer (2011-2013) and Councilor (2010-2011) for the Midwest Regional Chapter of SOT and has been on the planning committee for Applied Pharmaceutical Toxicology meetings in 2012-2016. Dr. Loberg is an employee at AbbVie, Inc., previously Abbott Laboratories, where she has worked in Preclinical Safety at three research & development sites (Ludwigshafen, Germany; Redwood City, California; and Lake County, Illinois) and three years in Drug Development Project Management. Prior to AbbVie/Abbott, Dr. Loberg supervised a Molecular Toxicology laboratory at IIT Research Institute (1996-1999). Dr. Loberg earned her Ph.D. in Toxicology at the University of Cincinnati (1996) and her B.S. in Psychology/Neuroscience at John Carroll University.

**Emily Meseck, Ph.D., Novartis** Dr. Meseck is a Director in the Project Pathology Group in Preclinical Safety at the Novartis Institutes for Biomedical Research in East Hanover NJ. Formerly, she was Associate Director of Pathology Sciences at Covance Laboratories and before that a Principal Scientist in Drug Safety Research and Development at Pfizer (formerly Wyeth Research). Dr. Meseck is a Diplomate of the American College of Veterinary Pathologists and the American Board of Toxicology (ABT), a member of the Society of Toxicology as well as the Society of Toxicologic Pathology, where she is actively involved as a member of the Global Executive Steering Committee for INHAND, the 2016 and 2017 Scientific Symposium Planning Committees, the CE subcommittee, the ACVP/STP Coalition Board of Governors and a Science and Regulatory Policy Committee Working Group on histopathology severity grading. Dr. Meseck received her DVM and anatomic pathology residency training from Cornell University College of Veterinary Medicine.

**Lauren Mihalcik, Ph.D., Amgen** Dr. Mihalcik is a Senior Scientist in Comparative Biology and Safety Sciences at Amgen. She received her B.S.E. in chemical engineering at Princeton University and her Ph.D. in Pharmacology from the University of Virginia, where she studied the molecular pharmacology and physiologic regulation of adenosine receptors in collaboration with medicinal chemists to discover potent and selective agonists which were advanced to clinical trials. Subsequently, she was the in-house pharmacologist for the NINDS Anticonvulsant Screening Program. In 2007 she joined the FDA as a Pharm/Tox reviewer in the Division of Metabolic and Endocrine Products within the Office of New Drugs in CDER. In this role, she evaluated the nonclinical data associated with 90+ INDs and NDAs for projects targeting diabetes, obesity, cachexia, and other metabolic and endocrine diseases. She served as CDER’s subject matter expert on the Standard for Exchange of Nonclinical Data (SEND) and drove the collaboration with external stakeholders on development of the standard and internal implementation. In 2015 she joined Amgen at their South San Francisco site where she serves as a project team representative, creating and implementing nonclinical safety strategies for both small and large molecule projects from discovery through post-marketing. Dr. Mihalcik is a member of the Society of Toxicology, the American College of Toxicology, and the American Society for Pharmacology and Experimental Therapeutics.
Graeme Moffat, Ph.D., Amgen  Dr. Moffat is an Executive Director, Preclinical at Amgen Inc, located in Thousand Oaks, CA. Since joining Amgen in 2007, Dr Moffat has served as the Toxicology Site Head at Amgen’s Seattle facility and led the nonclinical team supporting the marketing authorization of Amgen’s PCSK9 inhibitor, Repatha. Within Amgen’s Comparative Biology and Safety Sciences (CBSS) department, Dr Moffat currently leads a cross-site team of scientific experts responsible for the non-clinical safety strategy for programs spanning every stage of the pipeline, from discovery to post-marketing. He also serves as the CBSS strategic point of contact with many key partners in late stage development, including Global Regulatory, Clinical Development and Patient Safety. Dr Moffat holds accountability for all Amgen nonclinical Developmental and Reproductive Toxicology (DART) activities as well as those related to developing optimal nonclinical strategies to support pediatric drug development across the Amgen portfolio. Externally, Dr Moffat co-chairs the ILSI HESI DART Technical Committee and represents Amgen on the EFPIA Preclinical Development Expert Group.

Prior to joining Amgen, Dr Moffat spent 12 years at Syngenta (formerly AstraZeneca) in the UK where he held several positions of increasing responsibility including the Head of Developmental and Reproductive Toxicology. Dr Moffat received his PhD in the fields of molecular biology and immunology from the University of Glasgow, Scotland and was a Postdoctoral Fellow at Scripps Clinic, La Jolla CA and the Imperial Cancer Research Fund Biomedical Research Centre in Dundee, Scotland. Dr Moffat has served on numerous external scientific committees and has published over 30 peer-reviewed research articles.

Javid Moslehi, Ph.D., Vanderbilt School of Medicine  Dr. Moslehi is an Assistant Professor of Medicine and the Director of the Cardio-Oncology Program at Vanderbilt School of Medicine. He graduated from Johns Hopkins University and University of Connecticut School of Medicine. He then completed an internal medicine residency at Johns Hopkins Hospital. Following the completion of clinical cardiology fellowship at the Brigham and Women's Hospital and Harvard Medical School, he started a basic science post-doctoral fellowship at the Dana-Farber Cancer Institute focusing on the role of angiogenesis (formation of new blood vessels) in heart disease. In 2009, he founded the Cardio-Oncology program at Brigham and Women’s Hospital/Dana-Farber Cancer Institute and Harvard Medical School with a clinic and research program focused on the cardiovascular care for cancer patients and cancer survivors. Dr. Moslehi is an expert clinician on the management of cardiac complications associated with radiation and both novel and traditional chemotherapies. His clinic and research program is focused on the mechanisms of toxicities associated with novel targeted therapies and how this knowledge can be modulated to understand human cardiovascular biology.

Peyton Myers, Ph.D., FDA  Dr. Laine Peyton Myers is a Senior Pharmacology/Toxicology drug reviewer for antiviral products at the US Food and Drug Administration. Dr. Myers received his PhD in immunotoxicology from LSU Health Sciences Center in 2003 and was a postdoctoral fellow at NIOSH from 2003-2006. He joined the US FDA as a Pharm/Tox drug reviewer in 2006 and has experience in multiple divisions, including: antivirals, oncology, and reproductive/bone products. Dr. Myers has served on multiple US FDA Pharm/Tox subcommittees and is the current chair of the CDER Immunotoxicology subcommittee. He also serves in several professional Societies and is the President of the Immunotoxicology Specialty Section in the Society of Toxicology. Dr. Myers has helped organize multiple scientific sessions at various professional societies including SOT, DIA, and ACT. He is currently one of the Agency experts on the “animal rule” products at the FDA with a specialty in antiviral products. Outside of his professional duties, Dr. Myers is on the FDA and HHS Diversity Councils in the federal government.

Padma Narayanan, Ph.D., Ionis Pharmaceuticals  Dr. Narayanan received a BVSc (DVM equivalent) degree (1986) from College of Veterinary & Animal Sciences, Kerala, India; a Masters’ in Veterinary Surgery (1988), Madras Veterinary College, Tamil Nadu, India, and a Ph.D (1995) in Immunopharmacology from School of Veterinary Medicine, Purdue University, West Lafayette, IN. He utilized analytical cytology tools, flow and image cytometry, to gain insights into mechanisms of neutrophil and endothelial pathophysiology on exposure to pro-oxidants and environmental toxins during his graduate training at Purdue University Cytometry Laboratories, West Lafayette, IN. He broadened the scope of this investigation during his post-doctoral fellowship (1995-1997) at Los Alamos National Laboratories, Los Alamos, NM, to understand the role of oxidative stress in radiation-induced DNA damage, cell cycle regulation, silicosis and chronic beryllium disease. Padma later joined SmithKline Beecham (SB), Philadelphia, PA (1997) to establish an analytical cytology core facility in Safety Assessment to support non-
GLP and GLP toxicology studies for both large and small molecules. During his tenure at SB and later GlaxoSmithKline, Padma integrated cytometric technologies and cellular pathophysiological endpoints for identification and characterization of drug-induced pharmacologic/toxicologic responses at various stages of development. In addition, he was instrumental in designing investigative toxicology studies, general and genetic toxicology, and safety pharmacology studies in support of research and development compounds. Padma joined Amgen, Inc. in 2006 to establish an Investigative Toxicology group in Seattle and was Director of Cell Signaling and ImmunoToxicology Group in Discovery Toxicology, until 2014. In this role at Amgen, Padma provided advice, strategic planning, study design, and effective management of issue resolution and predictive toxicology efforts to support selection and timely development of proteins, monoclonal antibodies, and small molecules. Padma is currently (Executive Director-Toxicology, Ionis Pharmaceuticals, Carlsbad, CA) involved in both Experimental Pathology/Toxicology as well as development of antisense platform for neurodegenerative diseases.

**Rafael Ponce, Ph.D., Juno Therapeutics** Dr. Ponce is Sr. Director of Preclinical Development at Juno Therapeutics (Seattle, WA). Prior to this position he was a Scientific Director in the Comparative Biology and Safety Assessment group at Amgen (Seattle, WA), and Director of Preclinical Safety Assessment at ZymoGenetics, Inc. (Seattle, Washington). He has previously worked as a research toxicologist at SNBL USA and the University of Washington, and as a toxicologist for the Alaska Department of Health and Social Services. Dr. Ponce is an Affiliate Associate Professor in the Department of Environmental and Occupational Health Sciences, University of Washington and is a Diplomate of the American Board of Toxicology.

**Stephanie Powlin, Ph.D., DABT, Takeda Pharmaceuticals** Dr. Powlin is a board certified toxicologist with 19 years of experience in the pharmaceutical industry. She received her PhD from the University of Rochester in 1997 and conducted a postdoctoral fellowship with Jon Cook at E. I. DuPont de Nemours, Haskell Laboratory. She joined Bristol-Myers Squibb in 1998 where she held various roles as a study director/monitor, project representative, principal scientist, and group leader. Following BMS, Stephanie worked for 4 years at Bausch and Lomb on ophthalmic pharmaceuticals and medical devices, then joined Takeda Pharmaceuticals in 2014 as an Associate Scientific Fellow. She has worked in several different therapeutic areas, but has focused primarily on oncology compounds, contributing to every stage of drug development (from pre-IND to NDA), and was most recently responsible for the nonclinical content of the successful approvals for Ninlaro®. Stephanie is a member of the Society of Toxicology and a Diplomate of the American Board of Toxicology.

**Ian Pyrah, Ph.D., Seattle Genetics** Dr. Pyrah is Vice President of Non-Clinical Sciences at Seattle Genetics, Inc. Formerly he was Preclinical Executive Director at Amgen Inc. Dr. Pyrah is a Fellow of the Royal College of Pathologists and a Member of the Royal College of Veterinary Surgeons. He is a past president of the British Society of Toxicological Pathology. He has represented the pharmaceutical industry as an expert in the revisions of the International Conference of Harmonization regulations S1 (Rodent Carcinogenicity Studies for Human Pharmaceuticals) and S9 (Nonclinical Evaluations for Anticancer Pharmaceuticals). He is a member of a number of professional societies including Society of Toxicology, Society of Toxicologic Pathologists, and DRUSAFE. Dr. Pyrah received his veterinary degree and PhD in veterinary pathology from the University of Edinburgh. He also has graduated MBA from both UCLA and the National University of Singapore. He has presented and published widely on pathology, mechanisms of toxicity, and drug safety evaluation.

**Michael Santostefano, Ph.D., Merck** Dr. Santostefano received a B.S. degree in Biochemistry from the Univ. of Scranton, and a Ph.D. in Toxicology from Texas A&M University. After post-doctoral work at the Univ. of North Carolina, Michael joined GlaxoWellcome, Inc. as a senior toxicologist and held various roles as a study director/monitor, head of toxicology, project representative, and research investigator until his departure from GlaxoSmithKline in Oct, 2006. From 2006-2014, Michael worked as a principal scientist at Amgen and provided advice, strategic planning, study design, and effective management of discovery and development toxicology programs/projects to support the development of biologics and small molecules. In 2014, he joined Merck Research Laboratories in Boston and is currently the therapeutic area leader in preclinical safety assessment supporting the Business Development and Licensing organization and is responsible for working with potential partners in conducting the due diligence reviews of in-licensing candidates and facilitating transfer of information for out-licensing candidates. He also serves as a compound leader for a phase 3 asset in the immunology portfolio. In addition, he has provided oversight for regulatory submissions.
to international and national regulatory agencies while at Amgen, GSK, and Merck. His academic and pharmaceutical career has generated over 35 peer-reviewed manuscripts in the field of mechanistic toxicology. Michael is a Diplomate of the American Board of Toxicology and a member of the Drug Information Association (DIA), American College of Toxicology (ACT), and the Society of Toxicology (SOT), including chapters in North Carolina, the Pacific Northwest, and the Northeast. He also serves on the editorial advisory board for Toxicology and Applied Pharmacology and has served as a symposium organizer/chairperson for many scientific organizations. He serves on the membership committee for ACT and was previously the vice president of the North Carolina Chapter of the SOT. In addition to his position at Merck, he is currently working on a master’s degree in Regulatory Sciences at the Univ. of Southern California with anticipated graduation in spring of 2017.

Oliver Thomas, Amgen
Oliver Thomas is a project toxicologist in the department of Comparative Biology & Safety Sciences at Amgen and is based in Munich, Germany. For the last 8 years he has worked on Amgen’s Bispecific T cell Engager (BiTE®) technology in the field of cancer immunotherapy. He received his BSc in Zoology from the University of Nottingham, UK in 1992 and performed post-graduate work on the ecology of tephritid galling flies. He was inducted into the world of toxicology as a Study Director at CROs in the UK and France before joining a series of biotechnology companies in Munich culminating in joining Micromet GmbH, which was acquired by Amgen for its BiTE® platform. He was one of the toxicologists involved in the development of blincyto®, the first approved BiTE® used in the treatment of acute lymphoblastic leukaemia, and currently supports a number of BiTE® IND-directed programs in addition to BiTE® in early clinical development.

Mark Vogel, Ph.D., Pfizer
Dr. Vogel is a Pfizer Senior Director in Drug Safety Research - Development (DSRD) in Cambridge, MA. Since 2007, he has been a Therapeutic Area Lead, supporting the Inflammation - Immunology Research Unit. Mark manages the design and implementation of nonclinical safety strategies for this therapeutic area from target identification through loss of profitability. Drug Safety Team Leads on project teams report to Mark via direct or matrix relationships. Previously, Mark contributed to several therapeutic areas across the portfolio in the DSRD line responsible for nonclinical safety assessments, dossiers, impurity assessments, and various other regulatory documents. He headed the Safety Assessment group in Ann Arbor from 2004-2006, and also served as toxicology line representative on drug development and in-licensing teams.

Before joining then Pharmacia - Upjohn in 1999, Mark was a Pharmacology - Toxicology reviewer in the FDA Division of Pulmonary - Allergy Drug Products, and a Research Investigator at Hoffmann-LaRoche, where he supervised cardiovascular drug discovery and safety pharmacology studies, and developed small animal models of asthma, anaphylaxis, and bronchial hyperreactivity. He began his research career as a postdoctoral fellow and then faculty member (Assistant and Associate Professor) of the Boston University School of Medicine. His research involved myocardial ischemia and infarction, diastolic heart failure, cardiac hypertrophy, diabetic cardiomyopathy, and hemoglobin-based blood substitutes. Mark earned his BA in Biology from Temple University, and PhD in Pharmacology from the University of Michigan.

Brian Vuillemenot, Ph.D., Genentech
Dr. Vuillemenot is a pharmacology/toxicology scientist with twelve years of experience in nonclinical development of biological and small molecule therapeutics. His specialties include development of animal models of disease and direct administration of molecules to the lung and CNS. Brian received his Ph.D. from Tulane University in Molecular and Cellular Biology investigating the pathogenesis of interstitial lung disease. He conducted his postdoctoral fellowship at Lovelace Respiratory Research Institute on the role of epigenetics in lung cancer. Brian began his career in the biopharmaceutical industry in 2005 at Nektar Therapeutics as a scientist involved with exploratory safety assessment of inhalable insulins and other molecules for lung administration. Brian joined Anesiva in 2007 where he developed in vivo pharmacology models to test therapies for pain. From 2008 to 2014, Brian was employed at BioMarin Pharmaceutical Inc., where he served as a core team member and lead nonclinical scientist on programs developing therapies for orphan diseases. Brian is currently employed as a toxicologist in the department of Safety Assessment at Genentech. Brian is a member of the Society of Toxicology and American College of Toxicology and a Diplomate of the American Board of Toxicology.
**Zoe Zhong, Ph.D., Genentech** Dr. Zhong is a Senior Scientist and head of Small Molecule Discovery Toxicology in the Safety Assessment Department at Genentech where she oversees lead optimization and safety assessment strategies for the small molecule discovery portfolio across therapeutic areas. Zoe began her career in the pharmaceutical industry at Roche Palo Alto in 2002, where she conducted research in the discovery of novel therapeutic targets for genitourinary and pain diseases. Zoe has contributed to numerous INDs and IBs, and authored/co-authored 22 peer-reviewed papers, review articles and patents in the field of pharmacology and toxicology. Zoe earned her PhD in Pharmacology from the School of pharmacy, University of London in 1997. She completed postdoctoral studies at University College London and Wellcome Research Fellowship training at Kings College London. Zoe is a Diplomate of the American Board of Toxicology, and a member of the Society of Toxicology (SOT) and several specialty sections.
Development of Artificial Alveolar Model for Pharmaceutical Toxicity Applications

A. Arefin 1,2, J-H. Huang, PhD 3, P. Nath, PhD 4, Ishak Omar 2, D. Platts, PhD 4, R. Iyer, PhD 5 and J. F. Harris, PhD 2

1Nanoscience and Microsystems Department, University of New Mexico, Albuquerque, NM
2Bioscience Division, Los Alamos National Laboratory, Los Alamos, NM
3National Tsing Hua University, Hsinchu, Taiwan
4Applied modern physics Division, Los Alamos National Laboratory, Los Alamos, NM
5Systems Analysis and Surveillance Division, Los Alamos National Laboratory, Los Alamos, NM

Purpose

Approximately 7% of the world's mortality is caused by respiratory diseases. This can be attributed to the fact that it can take more than 10 years for a drug to be developed, put through clinical trials, and then finally be approved for prescription use. Some of the major impediments in studying respiratory diseases and the development of drugs to treat these conditions, is the lack of a reliable in vitro lung disease model. Because alveoli is a target for several drugs, an in vitro alveolar model can be a platform for both designing drugs and studying lung diseases. The model should allow for gas exchange, growth of two primary alveolar epithelial cells (Alveolar type I (ATI) and Alveolar type I (ATII) (1)), extracellular matrix production, and have similar mechanical properties to alveoli, creating an environment conducive to normal metabolic activity and cellular responses. The existing micro-physiological human alveolar models do not support sustained growth of primary alveolar populations at an air-liquid interface with mechanical stimuli (2), which is essential for the simulation of alveolar functionality. Here we address these limitations by designing a flexible porous polymeric membrane that allows for an air-liquid interface and cyclic mechanical stretch. Further, we established the growth of relevant primary alveolar mixed cell populations that mimic the physiology and functionality of the alveoli.

Methods

To create a physiologically relevant alveolar wall, we constructed a thin and stretchable Polyurethane (PU) membrane using spin coating technique, and an efficient microfabrication and lamination technique (3) to consistently handle and integrate these delicate membranes into microfluidic devices. We characterized for their elastic properties for mechanical stretch application and biocompatibility for cell culture. Next, we cultured Human primary alveolar epithelial cells on the membrane to investigate some of the key proteins that are produced by these cells by immunostaining and gene expression assays. In order to culture these cells at air-to-liquid interface setup, we micromachined arrays of holes on the PU membrane using femtosecond laser.

Results

We report a 15 µm thick polyurethane membranes which imitate the alveolar wall. The elastic modulus of the membrane was 13 MPa and was intact after applying 10 kPa pressure cyclic stress for two weeks. Next, we cultured Human Small Airway Epithelial Cells (HSAECs) on the PU membrane and two hallmark proteins: Surfactant protein C and Surfactant protein A were identified. Preliminary data suggests that AQP5 stained cells constitute almost 40% of the total cells and 12% of the total cells were stained with SFTPC. To facilitate air-liquid interface to the cells, approximately 10 µm sized pores were drilled on the PU membrane. Membrane's elastic modulus was measured after machining pores onto it and no significant change was observed. The porosity and culture conditions are under optimization to sustain cells' functionality under mechanical stimuli. Finally, lung toxic drugs will be tested to validate the functionality of the artificial alveolar model.

Conclusions

The in vitro model for artificial alveolus closely mimics the micro physiology of human alveolus and we predict this platform can be advantageous for rapid pharmaceutical toxicity testing applications.

References

Mechanistic Classification of Toxicants Using Differential Impedance-Based Real Time Cytotoxicity Profiles in Primary Human Hepatocytes

Michael J. Liguori, Tatiana Sharapova, Bruce LeRoy, and Eric A.G. Blomme
Investigative Toxicology and Pathology, AbbVie, Inc. North Chicago, Illinois, United States

Purpose
Impedance-based real time cytolethality profiling has become an important lead optimization toxicology tool in pharmaceutical discovery. This technique offers the advantage of continuous, non-destructive monitoring of changes in electrical impedance (reported as cellular index or CI) that correlates to alterations in cell health, morphology, and proliferation of adherent primary cells as well as cell lines. In this study, we used a panel of reference toxicants representing several distinct mechanisms of hepatotoxicity and evaluated their impact on CI profiles of cultured primary human hepatocytes (PHH). The mechanisms of action included: apoptosis (staurosporine; ceramide c2), cytoskeletal disruption (phalloidin; colchicine), mitochondrial inhibition (antimycin A; carbonylcyanide-p-trifluoromethoxyphenylhydrazone (FCCP)), plasma membrane perforation (Triton X-100), and general cellular detachment (trypsin digestion).

Methods
PHH donor to donor variability (n= 6 donors) was assessed using chlorpromazine, which acts through two cytotoxicity mechanisms: oxidative stress via quinoneimine formation and changes in mitochondrial membrane potential. Cryopreserved PHH were thawed and cultivated using conventional conditions in Williams E-based media. Cells were treated with eight concentrations of each toxicant or vehicle (0.1 to 0.5% DMSO) in electrode coated 96-well plates and monitored with an xCELLigence real-time cell analyzer (Acea Biosciences) for up to 3 days.

Results
Treatment of PHH with surfactant (Triton X-100) or trypsin resulted in an immediate decline of normalized cellular index (NCI). Mitochondrial function inhibitors caused a rapid decrease of NCI at doses as low as 1.6 and 3.1 µM. Staurosporine and ceramide treatment (apoptosis inducers) decreased NCI (IC50 =1 to 6 µM), but over an extended time (>10 h) compared to the mitochondrial toxicants. Interestingly, exposure to cytoskeletal disruptors led to a gradual increase in NCI over 3 days, plausibly due to subtle alterations in cell shape. There was a high degree of inter-individual variability in response to chlorpromazine treatment suggesting that cryopreserved PHH should be characterized using a positive control before an impedance-based compound evaluation.

Conclusions
Altogether, these results are useful to understand differences in impedance profiles based on compound toxicity mechanisms and can be compared to profiles from related liver-derived primary cells and cell lines.

All authors are employees of AbbVie. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.
A lead optimization strategy to establish in vitro to in vivo correlation of off-target mast cell activation and tolerated Cmax exposure

Dong Lee1, Trung Nguyen1, Nicole Valle1, Savita Ubhayakar2, Xiaorong Liang2, Yuan Chen2, Christopher Heise3, Michael Koehler4
Departments of 1Safety Assessment, 2DMPK, 3Biochemical Cell Pharmacology & 4Medicinal Chemistry
Genentech Inc., South San Francisco, CA 94080

Purpose:
Drug-induced anaphylaxis-like responses have been observed shortly after dosing with certain classes of small molecule compounds in preclinical and clinical studies. These types of compounds are commonly described as cationic amphiphilic class of molecules that possess physical chemical attributes of positive charge and both hydrophilic and lipophilic properties. Examples of such compounds include the neuropeptide Substance P and the antibiotics vancomycin and polymyxin. In many cases, this off-target acute toxicity has limited higher doses from moving forward into repeat-dose safety studies due to reaching a tolerated Cmax ceiling. Structure-activity relationships within a given chemical series have not been fully explored in relation to this particular secondary pharmacology. We set out to develop and validate an in vitro assay that could function to: 1) triage compounds with lower acute toxicity risk; and 2) provide SAR value for the discovery toxicology strategy.

Methods:
Previous studies have found an association with this drug-induced acute toxicity to the mechanistic action of histamine released from mast cell degranulation in an IgE-independent fashion. In this study, we describe a tractable method to explore and characterize the potential of novel compounds in a small molecule antibiotic drug discovery program to induce histamine release from rodent mast cells in vitro. Primary rat mast cells were sourced using peritoneal lavage. Culture and assay conditions were optimized to detect histamine release from compound treated mast cells in a dose-dependent manner.

Results:
The mast cell data was used to rank order compounds based on the safety risk of histamine release. Low and high risk compounds were cherry-picked and taken forward into rat dose-up tolerability studies. The results show in vitro to in vivo correlation, with mast cell histamine potencies being predictive of the relative tolerated Cmax exposure in rat.

Conclusions:
This method was used to move forward compounds of desired potency and pharmacokinetic properties that demonstrated the potential for higher safety margins for acute histamine toxicity into repeat dose safety studies. The methodology outlined provides an impactful compound safety de-risking strategy that is amenable to the lead optimization process in a small molecule discovery program and incorporates the 3Rs principle for animal use in research.
Evaluation of Circulating miR-122 as an Exploratory Biomarker of Liver Injury in Humans

Hiro Irimagawa1, Jennifer Vogt1, Min Tseng1, Daniel Sheinson2, Yuda Zhu2, Kathila S Rajapaksa1, and William R Proctor1

1Safety Assessment, Genentech, Inc., South San Francisco, CA
2Nonclinical Biostatistics, Genentech, Inc., South San Francisco, CA

Purpose:
The liver-specific miRNA, miR-122, appears to be a promising biomarker of hepatocellular injury, supported by pre-clinical and clinical studies in the context of drug-induced liver injury, viral hepatitis, and autoimmune hepatitis. Based on this, we set out to explore the performance of miR-122 to evaluate its utility to monitor liver function in a clinical setting.

Method:
A qRT-PCR based assay to detect miR-122 and 80 other miRNAs in circulation was developed and qualified based on a fit-for-purpose approach for exploratory biomarkers. miRNAs were detected in human serum utilizing commercially available reagents and kits with minor modifications to original protocols. Assay linearity, dynamic range, precision, and accuracy were assessed accordingly. Circulating levels of miR-122 were measured in serum from single-donation normal human volunteers (N=91), patients from clinical trials (N=36, 556 samples), and multiple-donation normal human volunteers (N=24). Relative expression of miR-122 was determined based on normalizing its expression levels to the sample average among several endogenous miRNAs selected from the larger panel using an adaptive algorithm. A 95% reference interval of miR-122 relative expression in serum was calculated using single-donation normal human volunteer data.

Results:
The 95% reference interval calculated from single-donation normal human volunteer data showed high miR-122 inter-subject variability of 175-fold dynamic range. In clinical trial samples, patients with reported severe hepatic adverse events had elevated expression of miR-122 in serum, although for some of these patients the increased miR-122 expression levels fell within the 95% reference interval. We then assessed the performance of miR-122 within a patient to determine the extent of intra-patient variability and its contribution to the movement of this miRNA. Accordingly, miR-122 levels in serum within a patient varied 3- to greater than 2000-fold from baseline (e.g. patient screening) levels, however most samples again fell within the 95% reference interval. These findings support that there was high intra-patient variability in relative expression of miR-122 in serum, in addition to high inter-patient variability across a population. From the longitudinal study with normal human volunteers, we were able to confirm that inter and intra-subject variability both contribute 50% to the total variability of miR-122 expression in humans.

Conclusion:
miR-122 is unlikely to be a useful prospective biomarker of liver injury in humans at present time due to the observed high inter- and intra-subject variability. Further characterization of intra-subject variability, continued assessment of specificity and sensitivity to identify liver injury, and additional investigation of the effects disease and other co-morbidities have on circulating levels of miR-122 are needed before clinical use is considered.
Setting a NOAEL in the midst of ADA-related safety findings

Kathila Rajapaksa, Gopinath Palanisamy, Matthew Holdren, Dimitry Danilenko, Paula Katavolos, Carolina Chou, Joey Bravo, Amy Oldendorp
Department of Safety Assessment, Genentech Inc. South San Francisco, USA

Purpose:
Anti-drug antibodies (ADA) are frequently observed in nonclinical programs with monoclonal antibody therapeutics. Development of ADA in toxicology studies can lead to loss of exposure and/or safety findings which can confound study interpretation and NOAEL determination. With novel antibody constructs currently being explored it is increasingly important to identify and distinguish ADA-related findings vs. on-target effects.

Methods:
Here we discuss 3 antibody therapeutics where ADA formation impacted safety interpretation in IND-enabling repeat dose toxicology studies in cynomolgus monkeys.

Results:
One animal in each of the 3 programs was found dead or euthanized moribund at the low or mid-dose levels with clinical, macroscopic, and clinical and pathologic findings consistent with anaphylaxis–like reactions. Other ADA-related findings across studies and doses included vasculitis (2/3 mAbs), perivascular mononuclear cell infiltration (1/3 mAbs) and clinical pathology findings consistent with an acute phase inflammatory response (all 3 mAbs).

Conclusions:
Findings such as these have been reported in the literature to be related to ADA. All animals with aforementioned safety findings were ADA positive and had decreased exposure, which led us to believe that these findings were related to an immune response to a humanized antibody in nonhuman primates and not a direct pharmacologic or toxicologic effect. Although immunogenicity-related findings were adverse, they were not considered representative of either the pharmacologic or toxicologic effects; therefore, the NOAEL for each mAb was considered to be the high-dose tested. This interpretation of the NOAEL, lack of clinical translatability of ADA responses from toxicology studies, along with careful clinical monitoring for potential anaphylaxis reactions was accepted by regulatory authorities and Phase 1 studies are currently underway.
3D tumor/stroma co-culture spheroid models for immuno-oncology applications

Irina Agarkova1, Tamara Tanos1, Francesca ChiavarO1, Sumeer Dhar1, Lei He2, Sue Grepper2, Patrick Guye1, Jens Kelm1

1InSphero AG, Schlieren, Switzerland
2InSphero Inc., Brunswick, ME USA

Purpose:
Recent advances in immuno-oncology therapy development have exhibited spectacular successes as well as enormous risks. Engineered complex human 3D tumor models are key for managing these risks in vitro, accelerating the development of therapies as well as reducing the likelihood of adverse outcomes in clinical trials. Scalability, uniformity, and affordability are crucial for any commercially viable engineered tissues intended for use in screening protocols. However, these requirements have proven difficult to meet, or come with severe limitations in the utility of the model, when produced using existing tumor/stroma co-culture methods.

Methods & Results:
Here we present a platform for generating in a scalable fashion, large numbers of uniform human 3D tumor/stroma co-culture spheroids. This platform reflects the complex interaction of tumor cells and stroma and enables a rapid screening of compounds in organotypic human settings. By treating these tumor/stroma spheroids with PBMCs and co-stimulatory antibodies, we assess infiltration and killing of tumor cells within the 3D co-cultures.

Conclusions:
This platform enables a highly efficient assessment of cell killing and immune response in human 3D tissues, paving the way to mitigate risks and streamline the development of next-generation oncology therapies.
MEA-Based Toxicity Screening in Networks of Glutamatergic iPSC-derived Neurons

Maryam Trabrizizad, Mathew Brock
Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080

Purpose:
The lack of translational in vitro assays for CNS effects may lead to costly advancement through development of compounds that eventually show in vivo or clinical safety issues such as seizure. Measurement of network-level electrical “phenotypes” in cultures of primary neurons by multielectrode array (MEA) has been validated for assessment of functional effect of environmental neurotoxins, and recent improvement in throughput and automation have made this approach an increasingly viable safety screening option for drug development. The inherent multi-site, non-invasive nature of recording can reveal acute and chronic effects of compounds on spontaneous action potentials, as well as effects on coordinated electrical activity in synaptic networks, and previous studies have show broad sensitivity to pro-convulsive compound classes. In the present study, we test the utility of recently-commercialized excitatory induced pluripotent stem cell (iPSC) derived neurons cultured on MEAs for functional CNS toxicity screening.

Methods:
Human iPSC-derived neurons of primarily glutamatergic subtype (Cellular Dynamics GlutaNeurons) were thawed and seeded in PEI/laminin-coated 48-well MEA plates (Axion Biosystems) at 120K neurons/electrode grid, with or without co-cultured human SC-derived astrocytes. Spontaneous field potentials were measured and recorded under atmospheric (5% CO2) and temperature (37oC) control with a Maestro MEA system and Axis software (Axion Biosystems).

Results:
Spontaneous action potentials in GlutaNeurons were evident within a few days of plating, and increased rapidly such that virtually all electrodes showed robust spiking, clustered into well-defined bursts, by day four. Between one and two weeks post-plating, bursting became synchronized across electrodes in a well, a pattern that persisted for at least 5 weeks. Exclusion of astrocytes did not prevent this electrical maturation process. Bursts were sensitive in indices of frequency, duration, regularity, and/or electrode cross-correlation to known pro-convulsant compounds such as activators of voltage gated sodium (NaV) channels (veratridine), GABA receptor antagonists (bicuculline, picrotoxin), and nicotinic cholinergic agonists (carbachol). Sensitivity of synchronous bursting to other compounds classes such as GABA receptor agonists (GABA), selective antagonists of NMDA (APV) and AMPA (NBQX) receptors, and NaV blockers (tetrodotoxin) further demonstrate the rich pharmacological sensitivity of this assay.

Conclusions:
The scalability, longevity in culture, broad pharmacological sensitivity, and potential translatability to clinical effects on humans makes the described approach promising for further development as a predictive in vitro CNS neurotoxicity assay.
Identifying mechanisms of drug-induced thrombocytopenia

Nicholas Corr, Aaron Fullerton, Karin Staflin
Genentech, Safety Assessment, 1 DNA Way, South San Francisco, CA, 94080

Purpose:
Thrombocytopenia, a potentially life-threatening disorder characterized by insufficient platelet counts, is a common adverse event and dose-limiting toxicity associated with many chemotherapy regimens. Methods for identifying and understanding this risk during drug development include in vivo studies, which may not translate to human, paired with the gold-standard in vitro human megakaryocyte colony-forming unit (MK-CFU) assay. The low-throughput, labor-intensive MK-CFU assay has changed little since the 1960’s when it was conceived, and fails to quantify drug effect on the most clinically relevant endpoint: platelet production. In an effort to create a better in vitro human assay, we developed a robust high throughput multiparametric flow-cytometry-based system with clinically-relevant readouts including drug effect on platelet production.

Methods:
Freshly-isolated bone marrow-derived CD34+ cells were differentiated into multinucleated, proplatelet and platelet-producing megakaryocytes (MK) over the course of 12 days in a 96-well serum-free format. Compound effect was assessed by flow cytometry on day 6 and 12. Model endpoints were further validated by fluorescent microscopy and CellTiter-Glo ATP assay.

Results:
Assay endpoints include drug effect on percent viability, progenitors/mL, early MKs/mL, mature MKs/mL, and platelets/mL. Using these endpoints, we report findings from an example compound set with diverse mechanisms of toxicity that result in clinical thrombocytopenia.

Conclusions:
This newly developed hematopoietic toxicity assay relies on multiparametric flow cytometry to simultaneously identify thrombocytopenia risk while also informing on mechanism of toxicity. In addition to the data provided by the MK-CFU assay, our method resolves drug effect on overall viability, early progenitor cells, MK maturation, and platelet production. Together, these endpoints prove useful for elucidating mechanisms of toxicities which we demonstrate here translate to clinical thrombocytopenia in a variety of ways. Understanding these mechanisms better informs drug development, and has the potential to provide useful information for design of pre-clinical and clinical dosing paradigms to help mitigate risk.
Using Biopharmaceutics Drug Disposition Classification System (BDDCS) Classification to Evaluate the DILI Causative Potential of bile salt export pump (BSEP) Inhibition

Rosa Chan and Leslie Z. Benet
Schools of Pharmacy and Medicine
University of California, San Francisco

Purpose:
Drug-induced liver injury (DILI) is a leading cause of drug failure in clinical trials and a major reason for drug withdrawals from the market. The present study examined the clinical impact of the BDDCS in evaluating the severity of DILI warning in drug labels approved by the FDA, the withdrawal status due to adverse drug reactions (ADRs), and the role of BSEP inhibition.

Methods:
FDA drug labels for 182 registered drugs were assessed for their BSEP inhibition. Next, the distribution of BSEP inhibition in each FDA hepatic liability category, DILI severity assignment, and BDDCS class were evaluated, as was, the correlation of all sources of FDA hepatic liability and BDDCS Class. Results were analyzed using chi-square tests for trend in proportions.

Results:
When BSEP inhibition data were correlated with FDA drug labels of registered drugs, we observed no discernible pattern between BSEP inhibition and DILI severity assessment categories (p = NS). Yet, when FDA hepatic adverse reactions were correlated with BDDCS Class a highly significant result (p <0.05). Our results show that the majority of BSEP inhibitors are BDDCS Class 2 drugs (84.6%, n=33/39), with concomitant decreases in the percentages of BDDCS class 1 and 3 drugs as BSEP inhibition increases.

Conclusions:
It appears that an apparent correlation of BSEP inhibitors with DILI is not related to the BSEP inhibition process, but due to the fact that the great majority of BSEP inhibitors are BDDCS Class 2 compounds, which are highly correlated with DILI independent of the BSEP process.
Utilization of the ExVive Human Liver Tissue Model to Assess Drug-Induced Liver Injury across a Diverse Set of Chemical Classes

Candace Crogan-Grundy, Timothy R. Smith, Ryan C. Smith, Thomas J. Murphy, Rhiannon N. Hardwick, Deborah G. Nguyen
Organovo, 6275 Nancy Ridge Drive, San Diego, CA 92121

Abstract:
One of the key challenges in the drug development process continues to be the early identification of compounds with adverse and potentially dose-limiting liver toxicity. Traditionally hepatotoxicity prediction has relied on two-dimensional hepatocyte monolayers, sandwich culture assays and non-human animal models. These systems often lack the cellular complexity required to model tissue-level outcomes of toxicity or are limited in their ability to accurately reflect in vivo human biology. In this study, drug-induced liver injury (DILI) was assessed in 3D-bioprinted human liver tissues comprised of primary hepatocytes, hepatic stellate cells, and endothelial cells.

(ExVive™Human Liver Tissues) treated with known high and low DILI risk compounds. Tissue response to compounds was evaluated using a range of biochemical, cytokine secretion, gene expression and histologic analyses. The high DILI risk compounds tolcapone, benzbromarone, danazol and tamoxifen were evaluated using a 28 day dosing regimen and compared to safer compounds entacapone, phentolamine, betahistine and chloramphenicol. Tissues treated with the known toxicants exhibited evidence of toxicity in at least two assays. A comparison of the clinically related compounds tolcapone and entacapone at concentrations of 1x, 3x and 10x Cmax revealed clear differences in their impact on the bioprinted tissues; tolcapone resulted in a dose dependent decrease in tissue viability at 10x Cmax while entacapone resulted in no significant changes in viability. Significant reductions in albumin secretion were seen at 3x Cmax with tolcapone treatment, vs. 10x Cmax with entacapone. Treatment of the 3D liver tissues with 5x and 20x Cmax concentrations of benzbromarone for 28 days resulted in decreased tissue viability with the highest concentration along with time and dose dependent decreases in albumin production beginning at treatment day 7 with the 5x and 20x Cmax concentrations. Histologic assessment of these tissues revealed significant loss of tissue and disruption of cellular cohesion at the 20x Cmax dose. These results suggest 3D bioprinted liver tissues are well suited to differentiate high risk from low risk DILI compounds and utilize both biochemical and histologic endpoints to assess multiple mechanisms of DILI in vitro, providing a comprehensive means of examining tissue injury.
Characterizing Compound-induced Renal Toxicity Using a 3D Bioprinted Tissue Model of the Human Kidney Proximal Tubule

J. William Higgins, Timothy R. Smith, Shelby M. King, Elizabeth Paffenroth, Thomas J. Murphy, Casey Fairbairn, Alice E. Chen, and Deborah G. Nguyen
Organovo, 6275 Nancy Ridge Drive, San Diego, CA 92121

Abstract: Due to its exposure to high concentrations of xenobiotics, the kidney proximal tubule (PT) is the primary site of nephrotoxicity which results in late-stage attrition during drug development. We have developed a 3D bioprinted, fully human in vitro model of the proximal tubulointerstitial interface to enable more accurate prediction of tissue level clinical outcomes. We challenged this model with a diverse set of known renal toxicants and assessed their impact using biochemical and histologic endpoints. Treatment of 3D PT tissues with the chemotherapeutic agent, cisplatin, induced dose and time-dependent loss of tissue viability and epithelial function over the 14 day time-course evaluated. Temporal evaluation of the soluble biomarker lactate dehydrogenase (LDH) showed that treatment with increasing concentrations of cisplatin resulted in an early and significant spike in secreted LDH. Histologic assessment of the tissues showed primarily epithelial cell-specific effects at the 2.5 µM and 5 µM doses, while additional toxicity in the interstitium was observed at the 10 µM dose. Co-treatment of the tissues with 5 µM Cisplatin and the OCT2 inhibitor cimetidine (1mM) attenuated the cisplatin-induced epithelial toxicity. To broaden the scope of nephrotoxicants evaluated, 3D PT tissues were treated with the antifungal, amphotericin B, and antibiotic, gentamicin. Amphotericin B induced a dose-dependent decrease in epithelial function without a corresponding decrease in overall tissue metabolic activity, while gentamicin treatment resulted in decreases in both epithelial function and tissue metabolic activity. LDH release indicated a rapid response of the tissues to even low concentrations of amphotericin B. Histologic assessment of amphotericin B-treated tissues demonstrated a flattening of the epithelial cells with no observable impact on the other cells within the tissue. As fibrosis is a common downstream effect of drug-induced injury, we extended model characterization to include evaluation of tubulointerstitial fibrosis upon exposure to Transforming Growth Factor β (TGFβ), a key mediator of the fibrotic response in vivo. Treatment of 3D PT tissues with TGFβ showed no significant global tissue toxicity as measured by resazurin metabolism but increased extracellular matrix deposition and interstitial thickening in a concentration-dependent fashion. In addition, a significant induction of fibrotic response markers were observed in TGFβ-treated tissues. Collectively, these results suggest that bioprinted kidney tissues are well-suited to assess multiple mechanisms of nephrotoxicity in vitro including fibrosis, using biochemical, transcriptional and histologic endpoints to comprehensively examine the mechanistic progression of tissue injury.
Advances in Human Induced Pluripotent Stem Cell Derived Cardiomyocytes: Maintaining Validated Responses and Enabling Relevant Toxicity Testing

Blake D. Anson, Tromondae K. Feaster, Brian Jarecki, Arne Thompson

Purpose:
The combined efforts of academic, pharmaceutical, and regulatory scientists in the large-scale Comprehensive In-Vitro Proarrhythmia assay (CiPA), Japan iPS Cardiac Safety Assessment (JiCSA), and Consortium for Safety Assessment using Human iPS Cells (CSAHi) consortia demonstrates the prominent role of human induced pluripotent stem cell (hiPSC)-cardiomyocytes across all sectors of research. As hiPSC-cardiomyocytes continue to evolve, it is imperative to understand their performance in relation to previously validated models and versions.

Methods:
This study used the CiPA compound collection and the multi-electrode array (MEA) platform to evaluate the responses of two generations of commercially available hiPSC-derived cardiomyocytes, iCell Cardiomyocytes2 and iCell Cardiomyocytes.

Results:
Baseline data demonstrated stable beating rates for both iCell Cardiomyocytes2 and iCell Cardiomyocytes. The single channel blocking compounds mexilitine, nifedipine, E-4031, and JNJ-303 and the multi-channel blocking compounds flecainide, moxifloxacin, quinidine, and ranolazine produced quantifiable effects on cellular electrophysiology that were comparable across both cell types and culture conditions.

Conclusions:
The concordance of the data indicate that despite negligible changes in beat rate, iCell Cardiomyocytes and iCell Cardiomyocytes2 respond similarly in chemical space and thus bridging studies should be sufficient for adopting new product iterations.
3D and 2D in vitro Models of Xenobiotic-Induced Hepatotoxicity using iCell Hepatocytes 2.0

Michael Hancock, Tromondae K. Feaster, Coby Carlson, Natsuyo Aoyama, David A. Mann, and Blake D. Anson

Purpose:
Hepatotoxicity is a leading cause of drug withdrawal from the market, and current preclinical models are not sufficiently predictive of drug effects in humans. Causes of hepatotoxicity include intrinsic toxic effects and the enzymatic production of toxic metabolites. Development of more predictive in vitro model systems to identify hepatotoxicity early in drug development is critical for decision making and to avoid Drug Induced Liver Injury in the clinic. Moreover, batch to batch and donor inconsistencies in primary human hepatocytes, as well as lack of maintained metabolic function have resulted in conflicting reports and poor predicticity.

Methods:
Here, we set out to demonstrate the functional utility of iCell Hepatocytes 2.0 (HC 2.0) to assess acute and chronic drug-induced hepatotoxicity. Human induced pluripotent stem cell (iPSC)-derived hepatocytes (iCell® Hepatocytes 2.0) exhibit high purity and sustained biologically relevant functions help to address some of the needs of hepatotoxicity assessment.

Results:
We evaluated HC 2.0 responses to a set of known hepatotoxins (i.e. amiodarone, acetaminophen, troglitazone, nefazadone, chlorpromazine, and FCCP) across a number of cell death readouts highlighting their capacity for mechanistic toxicity studies. In addition, the prolonged viability also enables chronic dosing in vitro affording the potential to detect the effects of slow to form metabolites and also perform analyses at physiologically relevant concentrations over protracted exposure periods. The short term high concentration sensitivities observed were comparable to those seen with primary human hepatocytes. However, effects seen over 48 hr and 7 day dosing are illustrative of the potential of HC 2.0 for predictive in vivo/in vitro toxicity correlation. With the ability to routinely access patient specific genotypes and also culture in 3D spheroids and in co-culture with other hepatic stellate cells HC 2.0 provide a biologically relevant human model system for investigating hepatotoxicity in preclinical drug development.

Conclusions:
These data illustrate how human-based iCell products offer an excellent model system for assessing compound effects in human-derived hepatocytes. In total, iPSC technology enables a reliable and predictive model systems not previously attainable, and provides new solutions, tools, and opportunities for more predictive toxicity testing.
Evaluating Networked Activity as an Integrated Assay for Seizurogenic Assessment Using Stem Cell Derived Glutamatergic Neurons

Kwi Hye Kim, Coby Carlson, Christian Kannemeier, Tromondae K Feaster, Brad Swanson, Blake Anson and Kile Mangan

Purpose:
Some ‘regular’ prescription medications are known to display seizurogenic potential and these adverse events can be mis-diagnosed as epilepsy. Therefore it is crucial to test for seizurogenic potential during drug development. Central to this need is the requirement for human material and the potential utility of human induced pluripotent stem cell (iPSC) technology. Here we present human iPSC-derived excitatory neuronal populations (e.g. iCell GlutaNeurons) that develop and display network-level coordinated spontaneous activity in vitro as evidenced by synchronized bursts captured and measured via MEA. This technology provides a unique means to assess and alter if necessary, early in the drug discovery process the propensity for compound-mediate modulation of neuronal electrical activity.

Methods:
Excitatory human neurons (iCell Glutaneurons) were derived using induced pluripotent stem cell technology. Spontaneous electrical activity, including synchronized bursting, was measured via micro-electrode array (MEA) technology before and after reference compound application.

Results:
Excitatory populations of iPSC-derived cortical neurons (i.e., iCell GlutaNeurons) develop and display network-level coordinated neuronal activity in vitro, evident by synchronized bursts captured and measured via MEA. Assay optimization dictates best practice timelines for ‘seizurogenic potential’ screening occurs between DIV20-23, post-thaw. Excitatory pharmacology that displays concentration-dependent seizurogenic-effects include picrotoxin [0.3-100 µM], GABAzine [1-100 µM], bicuculline [4-400 µM], pentylenetetrazol [7 µM-2 mM], 4-aminopyridine [1.6-50 µM], and kainic acid [0.4-300 µM]. Activity metrics displaying concentration-dependent changes with pharmacology include: mean firing rate, ‘single-channel’ burst rate, intensity and duration, ‘network-level’ burst rate, intensity and duration, and synchrony measures.

Conclusions:
These data establish human iPSC-derived GlutaNeurons as a reliable and predictive model. The presented data illustrate and couple the “seizure-in-a-dish” technology, previously limited to rodent-only investigation, with human iPSC-derived neurons to create an unprecedented investigatory space for assessing seizurogenic risk potential.
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INSPHERO sets the standard for in vitro testing of novel drugs, providing a suite of highly physiologically relevant 3D InSight™ Microtissues and Services which increase efficiency in drug discovery and safety testing. InSphero patent-pending technologies and methods enable large-scale, reproducible production of scaffold-free 3D microtissues driven solely by cellular self-assembly. The company specializes in delivering assay-ready and custom 3D models derived from liver, pancreas, and tumor tissues, to provide unrivalled biological insight into liver toxicology, metabolic diseases (e.g., diabetes and liver diseases), and oncology (with a focus on immuno-oncology).

Headquartered in the United States in Cambridge, Massachusetts, the NIBR research network includes a major research center in Basel, Switzerland, and additional centers in East Hanover, New Jersey, USA; Emeryville, California, USA; La Jolla, California, USA; Siena, Italy; Horsham, England; Singapore; and Shanghai, China.

ORGANOVO designs dynamic, multicellular, and fully-human 3D bioprinted tissues that closely model native architecture and biological function. With the NovoGen Bioprinter® Platform, the company develops tissues for use in applications spanning preclinical safety testing, disease modeling, ADME, and therapeutic areas. The ExVive™ Human Liver and Kidney Tissues are commercially available through its NovoView™ Preclinical Service Offering and custom tissues are accessible through strategic partnerships. ExVive™ 3D Bioprinted Tissues allow mechanistic insights into phenotypes that progress over
time and that require multiple cell types in a specific spatial organization, reflecting the true complexity of human tissue biology. By giving researchers the opportunity to evaluate drug candidates on functional human tissue, Organovo is bridging the gap between preclinical testing and clinical trials.

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REACHBIO RESEARCH LABS is a life sciences CRO company based out of Seattle, WA USA. We provide primary cell biology based contract research services and products to the drug development and life science research communities worldwide. With expertise encompassing many aspects of primary cell biology and a special focus on blood and bone marrow primary cell systems, we work with customers and clients involved in basic research through multiple areas of pre-clinical and clinical drug development. Our products and services help address our client and customers’ interests in a wide spectrum of areas that include hematology, immunology, toxicology, hematological diseases, immuno-oncology and much more.
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