APPLIED PHARMACEUTICAL ANALYSIS

WEBINAR

OCTOBER 12-16, 2020

SHORT COURSE: OCTOBER 19-20, 2020

2020 WORKSHOPS: Regulated Bioanalysis | Discovery Bioanalysis & New Technologies | Mechanistic ADME

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ORGANIZERS' WELCOME

Welcome to the 2020 Applied Pharmaceutical Analysis Conference.

Our organizers have gathered another excellent group of speakers for the annual APA 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 APA experience. Thank you for your participation.

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REGULATED BIOANALYSIS

Chair: Yongjun Xue, Celgene
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DISCOVERY BIOANALYSIS & NEW TECHNOLOGIES

Chair: Mark Qian, Takeda
Chair-Elect: Jonathan Josephs, Sanofi
Committee: Dieter Drexler, BMS; Hongying Gao, Innovo Bioanalysis LLC; Elizabeth Groeber, Charles River Laboratories; Christopher Kochansky, Merck; Violet Lee, Genentech; Katie Matys, PPD; Jing Tu, AbbVie; Liyu Yang, Vertex; Jenny Zhang, Gilead

MECHANISTIC ADME

Chair: Lisa Christopher, BMS
Chair-Elect: David Stresser, AbbVie
Committee: Eric Ballard, Takeda; Silvi Chacko, BMS; Nagendra Chemuturi, Takeda; James Driscoll, MyoKardia; Valerie Kramlinger, Novartis; Chandra Prakash, Agios Pharmaceuticals; Richard Voorman, RMLV Partners; Greg Walker, Pfizer; Cindy Xia, Takeda; Hongbin Yu, Boehringer-Ingelheim

APA 2020 CONFERENCE AGENDA

DAY 1: Monday, Oct. 12

Regulated Bioanalysis Workshop

SESSION I: FDA/Regulatory Session

Session Chairs: Fumin Li, PPD and Yongjun Xue, Celgene

11:00 - 11:10 AM **Conference/Workshop/Session I Introduction**
Fumin Li, PPD and Yongjun Xue, Celgene

11:10 - 11:35 AM **Importance of Bioanalysis in Drug Development**
Chongwoo Yu, FDA

11:35 - 11:40 AM **Q & A**

11:40 - 12:05 PM **Bioanalytical Issues Relevant in Drug Development**
Stanley Au, FDA

12:05 - 12:10 PM **Q & A**

12:10 - 12:40 PM **KEYNOTE:** ***The Role of Non-profits in Drug Discovery and Development***
Marc Rose, CHDI Foundation

12:40 - 12:45 PM **Q & A**

12:45 - 1:00 PM **Virtual Realities: Hosting Remote Audits (including the FDA) in a Post-COVID World**
David Schumacher, Alturas Analytics

1:00 - 1:30 PM **VENDOR PRESENTATION: Charles River Laboratories**
Fit-for-purpose Bioanalysis when Synthesis to NDA is 75 Days
Liam Moran, CRL

1:30 - 2:00 PM **BREAK**

SESSION II: Regulatory/Immunogenicity Risk Assessments and Integrated Summary of Immunogenicity

Session Chairs: Johanna Mora, BMS & Andre Iffland, Vertex

2:00 - 2:05 PM **Session Introduction**
Johanna Mora, BMS & Andre Iffland, Vertex

2:05 - 2:30 PM **Immunogenicity Risk Assessment to Inform Early Project Decision Making**
Bonnie Rup, Bonnie Rup Consulting LLC

2:30 - 2:35 PM **Q & A**

2:35 - 3:00 PM **Practicing Immunogenicity Risk Assessment on Published PEGylated and Multi-specific Biotherapeutics**
Joleen White, Bill & Melinda Gates Medical Research Institute

3:00 - 3:05 PM **Q & A**

3:05 - 3:25 PM **Panel Discussion**
David Schumacher, Alturas Analytics; Bonnie Rup, Bonnie Rup Consulting LLC, and Joleen White, Bill & Melinda Gates Medical Research Institute

3:25 - 3:45 PM **BREAK & POSTER PRESENTATION**

Discovery Bioanalysis & New Technologies Workshop

SESSION I: Microbiome/Microbiota

Session Chairs: Jenny Zhang, Gilead & Elizabeth Groeber, CRL

3:45 - 3:50 PM **Session Introduction**
Jenny Zhang, Gilead & Elizabeth Groeber, CRL

3:50 - 4:15 PM **Mapping Host-microbe Interactions with Mass Spectrometry**
Joshua Elias, CZ Biohub

4:15 - 4:20 PM **Q & A**

4:20 - 4:45 PM **Metabolomics Repository Scale Analysis Tools to Learn Microbial Metabolite-Disease Associations**
Pieter Dorrestein, UCSD

4:45 - 4:50 PM **Q & A**

DAY 2: Tuesday, Oct. 13 | Discovery Bioanalysis & New Technologies Workshop

SESSION II: New Technology and Platforms for Discovery BA

Session Chairs: Jing Tu, AbbVie & Katie Matys, PPD

11:00 - 11:10 AM **Conference/Workshop/Session I Introduction**
Mark Qian, Takeda; Jing Tu, AbbVie & Katie Matys, PPD

11:10 - 11:30 AM **Dynamic Monitoring of Tumors using Genomic Platforms**
Anup Madan, PPD

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

11:35 - 11:55 AM **Viral Gene Therapies: What's In It For DMPK**
Nagendra Chemuturi, Takeda

11:55 - 12:00 PM **Q & A**

12:00 - 12:30 PM **KEYNOTE: *The Triple Quadrupoe: Innovation, Serendipity, and Persistence***
Richard Yost, Univ. of Florida

12:30 - 12:35 PM **Q & A**

12:35 - 1:20 PM **BREAK AND POSTER PRESENTATION**

1:20 - 1:35 PM **VENDOR PRESENTATION: Frontage**
Highly Sensitive Hybridization ELISA Assay for Bioanalysis of Oligonucleotide-Based Drugs
Chenyi Pan, Frontage

1:35 - 1:40 PM **Q & A**

1:40 - 1:55 PM **VENDOR PRESENTATION: Hypha Discovery**
How to Secure Access to Difficult-to-Synthesize Metabolites for MIST Compliance: A One-Stop Multiple Tool Approach
Frank Scheffler, Hypha Discovery

1:55 - 2:00 PM **Q & A**

SESSION III: HRMS/HRMS Quan

Session Chairs: Violet Lee, Genentech & Jonathan Josephs, Sanofi

2:00 - 2:05 PM **Session Introduction**
Violet Lee, Genentech & Jonathan Josephs, Sanofi

2:05 - 2:25 PM **Affiity High Resolution Mass Spectrometry to Explore Translatability beteween In Vitro Stress vs In Vivo Biotransformation of Protein Therapeutics at High**
Phillip Chu, Genentech

2:25 - 2:30 PM **Q & A**

2:30 - 2:50 PM **High Resolution Mass Spectrometry and Nano-Flow Liquid Chromatography for Critical Reagent-Free Quantitation of Intact Peptides**
Barry Jones, Q2 Solutions

2:50 - 2:55 PM **Q & A**

2:55 - 3:15 PM **The Utility of HRMS in Quantitative Bioanalysis Labs**
Robert Sturm, Zoetis

3:15 - 3:20 PM **Q & A**

3:20 - 3:40 PM **BREAK**

Regulated Bioanalysis Workshop

SESSION III: Cell and Gene Therapy Bioanalysis in Regulated Environment

Session Chairs: Darshana Jani, Agenus Bio & Jakal Amin, CRL

3:40 - 3:45 PM **Session Introduction**
Darshana Jani, Agenus Bio & Jakal Amin, CRL

3:45 - 4:05 PM **Bioanalytical Strategies, Considerations and Solutions for Development of Stereopure Oligonucleotide Therapeutics**
Susovan Mohapatra, Wave Life Sciences

4:05 - 4:10 PM **Q & A**

4:10 - 4:30 PM **Talk Title TBA**
Timothy Mack, Celgene

4:30 - 4:35 PM **Q & A**

4:35 - 4:55 PM **Bioanalytical Strategies for RNA9 Therapeutic Development**
Guodong Zhang, Alnylam

4:55 - 5:00 PM **Q & A**

DAY 3: Wednesday, Oct. 14 | Mechanistic ADME Workshop

SESSION I: Current and Emerging Topics in Transporter and CYP Mediated Drug-Drug Interactions

Session Chairs: Eric Ballard, Takeda & David Stresser, AbbVie

11:00 - 11:10 AM **Conference/Workshop/Session I Introduction**
Eric Ballard, Takeda & David Stresser, AbbVie

11:10 - 11:30 AM **Complex DDI and Transporter/Metabolism Interplay: Insights from Extended CL Model**
Jashvant D. Unadkat, Univ. of Washington

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

11:35 - 11:55 AM **Flipping the Metabolic Switch from CYP3A4 to CYP1A1 in Smokers: Correlation between In Vitro and Clinical Data**
Aaron Teitelbaum, Boehringer Ingelheim

11:55 - 12:00 PM **Q & A**

12:00 - 12:05 PM **Plenary Speaker Introduction**

12:05 - 12:35 PM **KEYNOTE: *Predicting the Unpredictable: How the Innate Immune Response to Drugs Predicts Risk***
Jack Uetrecht, Univ. of Toronto

12:35 - 12:40 PM **Q & A**

12:40 - 1:25 PM **BREAK & POSTER PRESENTATION**

1:25 - 1:40 PM **MS VENDORS: Molecular Discovery**
Ismael Zamora, Lead Molecular Design

1:40 - 1:45 PM **Q & A**

SESSION II: Metabolism and Toxicology - Mechanistic Bioactivation

Session Chairs: James Driscoll, Myokardia & Silvi Chacko, BMS

1:45 - 1:50 PM **Session Introduction**
James Driscoll, Myokardia & Silvi Chacko, BMS

1:50 - 2:10 PM **Impact of Deuteration on Phase I and II Metabolism of Nevirapine and Nevirapine-Induced Hepatocyte Death**
Carley Heck, Pfizer

2:10 - 2:15 PM **Q & A**

2:15 - 2:35 PM **Mechanistic Insight into the Bioactivation of Bromfenac: The Role fo UGTs and CYPs**
James Driscoll, MyoKardia

2:35 - 2:40 PM **Q & A**

2:40 - 3:00 PM **BREAK**

Discovery Bioanalysis & New Technologies Workshop

SESSION IV: Gene and Cell Therapies

Session Chairs: Mark Qian, Takeda & Liyu Yang, Vertex

3:00 - 3:05 PM **Session Introduction**
Mark Qian, Takeda & Liyu Yang, Vertex

3:05 - 3:25 PM **Insights on Digital Droplet PCR based Cellular Kinetics and Biodistribution Assay Support for CAR-T Cell Therapy**
Hiroshi Sugimoto, Takeda

3:25 - 3:30 PM **Q & A**

3:30 - 3:50 PM **Bioanalytical Considerations for Gene Therapy**
Lina Loo, Vertex

3:50 - 3:55 PM **Q & A**

3:55 - 4:15 PM **Engineering Biology to Improve Diagnostics**
Brendan Manning, SherlockBio

4:15 - 4:20 PM **Q & A**

DAY 4: Thursday, Oct. 15 | Regulated Bioanalysis Workshop

SESSION IV: Studies in China/Chinese Bioanalytical Space/ Regulatory Environment

Session Chairs: Fumin Li, PPD; Ang Liu, BMS & Patrick Bennett, PPD

11:00 - 11:10 AM **Session Introduction**
Fumin Li, PPD & Ang Liu, BMS

11:10 - 11:30 AM **How to Work with Chinese CROs to Support NMPA Submission of BMS Assets**
Jim Shen, BMS

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

11:35 - 11:55 AM **Establishing a Western Styled Bioanalytical Lab in China: Lesson Learned and Future Perspective**
Min Meng, Denali Medpharma

11:55 - 12:00 PM **Q & A**

12:00 - 12:20 PM **Bioanalytical Method Transfer to Support NMPA and Global Study Fillings**
Song Zhao, Frontage Laboratories

12:20 - 12:25 PM **Q & A**

12:25 - 1:25 PM **BREAK**

1:25 - 1:55 PM **KEYNOTE: *Value of Diversity, Inclusion, and Equity in the Sciences***
Rigoberto Hernandez, John Hopkins Univ.

1:55 - 2:00 PM **Q & A**

SESSION V: When Bioanalytical Data were Critical to a Drug Product Submission Approval

Session Chairs: Lori Payne, Alturas Analytics & Jenifer Vija, CRL

2:00 - 2:05 PM **Session Introduction**
Lori Payne, Alturas Analytics & Jenifer Vija, CRL

2:05 - 2:20 PM **VENDOR PRESENTATION: Alturas Analytics**
Ready, Willing and Stable? Advice from the LC/MS Experts on Analysis of Unstable Compounds and Prodrugs
Chad Christianson, Alturas Analytics

2:20 - 2:45 PM **Immunogenicity Data and the Regulatory Landscape: Bioanalytical Lessons Learned from a Recent Biological Licensing Application Approval**
Jim Glick, Novartis

2:45 - 2:50 PM **Q & A**

2:50 - 3:15 PM **Overcoming ADA Interference by Using a Hybrid LC/MS>MS Method to Qyalify a Therapeutic Protein in Human Plasma**
Huiyu Zhou, Biomarin Pharmacetuical

3:15 - 3:20 PM **Q & A**

3:20 - 3:40 PM **BREAK**

Mechanistic ADME Workshop

SESSION III: Studies in Mechanistic Metabolism

Session Chairs: Valerie Kramlinger, Novartis & Greg Walker, Pfizer

3:40 - 3:45 PM **Session Introduction**
Valerie Kramlinger, Novartis & Greg Walker, Pfizer

3:45 - 4:05 PM **Aldehyde Oxidase and Species Specific Deuterium Isotope Effects**
Kevin Johnson, Genentech

4:05 - 4:10 PM **Q & A**

4:10 - 4:30 PM **N-Oxygenation of Oxycodone and Retro-reduction of Oxycodone N-Oxide**
John Cashman, Human Biomolecular Research Institute

4:30 - 4:35 PM **Q & A**

DAY 5: Friday, Oct. 16 | Mechanistic ADME Workshop

SESSION IV: ADME Challenges in Drug Approval Case Studies

Session Chairs: Lisa Christopher, BMS & Chandra Prakash, Agios

11:00 - 11:10 AM **Session Introduction**
Lisa Christopher, BMS & Chandra Prakash, Agios

11:10 - 11:30 AM **Challenges with Ozanimod Approval**
Sekhar Surapaneni, BMS

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

11:35 - 11:55 AM **ADME and Clinical Pharmacology of Avapritinib**
Sean Kim, Blueprint Medicines

11:55 - 12:00 PM **Q & A**

12:00 - 12:30 PM **VENDOR SHOWCASE:**
CRL, Alturas, Frontage, Hypha Discovey, Molecular Discovery

12:30 - 1:15 PM **BREAK**

Combined Workshops: Discovery BA & Mechanistic ADME

SESSION V: Emerging Technologies

Session Chairs: Richard Voorman, RMLV Partners; Hongbin Yu, Boehringer Ingelheim & Dieter Drexler, BMS

1:15 - 1:20 PM **Session Introduction**
Richard Voorman, RMLV Partners; Hongbin Yu, Boehringer Ingelheim & Dieter Drexler, BMS

1:20 - 1:40 PM **Use of Cell Based Off Target Screening in CART Programs**
Yen Ho, BMS

1:40 - 1:45 PM **Q & A**

1:45 - 2:05 PM **A Novel Matrix Insensitive Platform to Mesure Protein Kinetics**
Kalidip Choudhury, MagArray

2:05 - 2:10 PM **Q & A**

2:10 - 2:30 PM **Application of NGS in Cancer Screening and Early Detection using ctDNA**
Ming Chen, Yale School of Public Health

2:30 - 2:35 PM **Q & A**

APA 2020 SHORT COURSE AGENDA

Current Trends and Future Direction in the Development of Cell and Gene Therapies

Course Coordinators:
Cindy Xia, Takeda
Nagendra Chemuturi, Takeda
Johanna Mora, BMS

MONDAY, OCTOBER 19

1:00-2:00 pm
In Vivo Gene Therapy as a New Paradigm in Medicine: The Road to Today and Beyond
Guangping Gao, PhD
Horae Gene Therapy Center & Weibo Li Institute for Rare Diseases Research, University of Massachusetts Medical School

2:00-2:45 pm
Development of a Risk based Immunogenicity Strategy for Support of AAV based Gene Therapies in Clinic
Vibha Jawa, PhD
Director, Risk Assesment and Clinical Immunogenicity at Merck

2:45-3:30 pm
The Pharmacokinetics of AAV Gene Therapies – Biodistribution and Shedding
Mark Milton, PhD
Novartis Institutes for BioMedical Research

TUESDAY, OCTOBER 20

1:00-2:00 pm
Preclinical Assessment of Cell and Gene Therapy Products to Support an IND
Christopher Saeui, PhD
Cell and Gene Therapy Reviewer at FDA

2:00-2:45 pm
An Integrated Approach to Investigating CART Cell Immuno-biology, a Pharmacology Perspective
Piotr L. Pierog, PhD
Head of Cell Product Clinical Development, Cell Therapy Unit, Takeda Pharmaceuticals Inc.

2:45-3:30 pm
Considerations for the Bioanalysis of CARTs
Timothy Mack, PhD
Senior Principal Scientist at Celgene/BMS

APA ABSTRACTS

REGULATED BIOANALYSIS WORKSHOP

SESSION I: FDA/REGULATORY SESSION

Importance of Bioanalysis in Drug Development
Chongwoo Yu, FDA

Clinical pharmacology plays an important role in drug development, especially in determining the optimal dosage regimen. This involves the evaluation of the drug's pharmacokinetics and pharmacodynamics, food effect, drug interaction potential, bioanalysis, exposure-response relationship for safety and efficacy, and considerations when being used in specific populations.

Clinical Pharmacology data is pivotal in delivering drugs at the right dose, at the right time. Consequently, the reliability of that data is of considerable importance and bioanalysis is the firm foundation of the reliability of the data in drug development. Bioanalytical data and documentation from both method validation and clinical trials are critical elements supporting regulatory submissions such as new drug applications (NDAs) or biologics license application (BLAs).

Case examples will be presented to highlight the importance of bioanalysis in drug development to ensure the safe and effective use of drug products.

Virtual Realities: Hosting Remote Audits (including the FDA) in a Post-COVID World
David Schumacher, Alturas Analytics

As the COVID-19 pandemic spread across the USA in early 2020, many facilities had to reduce operations, preventing auditors from traveling to customer sites. Alturas Analytics developed processes to permit auditors to conduct their inspections remotely. Additionally, Alturas Analytics was one of the first companies to be inspected remotely by the FDA in April. This presentation will present tips for a simple and positive remote audits experience and describe the process employed by the FDA to successfully complete a remote regulatory inspection.

VENDOR PRESENTATION

Fit-for-Purpose Bioanalysis when Synthesis to NDA is 75 Days
Liam Moran, Charles River Laboratories

In November of 2016 a six-year-old patient was diagnosed with Batten disease by Boston Children's Hospital. Whole genome sequencing of the patient revealed that in addition to the known pathogenic mutation related to Batten disease, there was an additional mutation that was likely interfering with splicing in the gene MFSD8. Patient specific therapeutic candidates based on antisense oligo nucleotides (ASO) were prepared and screened by measuring the normal:mutant splicing ratio between exon 6 and exon 7 in the patients fibroblast cells. A lead candidate ("Milasen") was identified in October of 2017 and it was manufactured to scale for preclinical safety testing and patient treatment. The goal was to expedite FDA approval as the patient was experiencing rapid decline in late 2017. This would require extremely accelerated safety studies with accompanying bioanalysis. A fit for purpose safety strategy was proposed to the FDA that included two rat studies with exposure assessments in cerebral spinal fluid, spinal cord, brain, kidney and liver. The method for the spinal cord was validated while the methods for the other matrices were qualified by precision and accuracy testing. The LC-MS/MS methods featured a liquid-liquid extraction followed by a secondary clean-up with solid phase extraction. The curve range for the solid tissues was 5 – 5000 ng/mL and 50-25,000 ng/mL for the CSF. The methods were able to demonstrate exposure and biodistribution in the liver, kidney and multiple regionals of the spinal cord and brain. These data were used to set the clinical dose and, following a rolling IND approval process, the patient was cleared for treatment in late January 2018. Strategies for including safety testing and bioanalysis in accelerated development programs for n=1 patients will be discussed..

SESSION II: REGULATORY/IMMUNOGENICITY RISK ASSESSMENTS AND INTEGRATED SUMMARY OF IMMUNOGENICITY

Practicing Immunogenicity Risk Assessment on Published PEGylated and Multi-specific Biotherapeutics
Joleen White, Bill & Melinda Gates Medical Research Institute

While a prospective immunogenicity risk assessment is a key component of an overall integrated summary of immunogenicity,

health authorities are still not regularly receiving these with new applications for clinical research. Providing these assessments up front are an opportunity to share your scientific thinking and document your rationale for planned analyses – both analytical and statistical. This talk will focus on two case studies based on a combination of public data and author assumptions about what may have been available after preclinical studies. We'll walk through the primary risk factors that would be identified based on this information, and how that relates to a potential clinical development strategy. Please note that these do not represent the sponsors' original risk assessment and benefit from continued growth in the immunogenicity field since those preclinical studies were conducted.

SESSION IV: STUDIES IN CHINA/CHINESE BIOANALYTICAL SPACE/REGULATORY ENVIRONMENT

How to Work with Chinese CROs to Support NMPA Submission of BMS Assets

Jim Shen, BMS

Bioanalytical scientists are an integral part of the drug development team and responsible for following country specific regulatory guidance to support regulated bioanalytical (BA) work scope. China is a fastgrowing pharmaceutical market which typically requires specific clinical trials to be conducted in the country before an international company can submit application to market new products in China. At BMS, Bioanalytical scientists provide oversight on the generation of the regulated BA data and the subsequent health authority interactions including inspection. Our typical approach includes leveraging indigenous CROs in China with support from US based BMS BA outsourcing operations. In this presentation, we will use pertinent examples to delineate BMS's experiences in successfully supporting the filing of a number of new medicines in China. The presentation will discuss BMS BA interaction with National Medical Products Administration (NMPA) of China including initial inspection preparedness, onsite BA CRO audit, and in person consultation. In addition, we will discuss BMS BA's approaches on CRO/facility evaluations, remote monitoring at regular intervals, study data review & inspections, information technology connectivity with emphasis on overcoming cultural and communication barriers.

Establishing a Western Styled Bioanalytical Lab in China: Lesson Learned and Future Perspectives

Min Meng, Denali Medpharma

Because of sweeping new rules as part of NMPA's reform for the Chinese pharma industry and few independent and western experienced bioanalytical labs (BioA Lab) in China, Chongqing Denali Medpharma., was founded in 2017 by a group of US trained professionals. Although the analytical technologies used, the quality, performance principles and approaches applied are similar, the operation of the Chinese BioA Lab is very different in comparison with the western BioA Lab. The challenges are (1) Fast changing government regulations. These include very strict environment permitting, chemical and waste management, importing and exporting instruments and consumable materials, control of the blank biological matrices; (2) Language requirement. Such as managing a project for dual (NMPA and international) regulatory applications. (3) Cultural differences. The interaction between a US trained manager and the Chinese trained scientist, or the communication between the US study contact and the China trained Project Manager. (4) NMPA inspection and findings. The focus of the audit is following guidance as well as raw data scrutiny. (5) Regulatory guidance. NMPA requires Chinese BioA Lab following all applicable regulations (NMPA, EMA, US and ICH) and hold the highest standard if there are discrepancies. Overall, the operation of the BioA Lab is significantly more challenging in China than in the US. In this presentation, some valuable insights and experiences are shared during our effort of setting up a bioanalytical lab in China.

KEYNOTE PRESENTATION

Value of Diversity, Inclusion and Equity in the Sciences

Rigoberto Hernandez, John Hopkins Univ.

The Open Chemistry Collaborative in Diversity Equity (OXIDE) is aimed at institutional reform so as to lower inequitable barriers hindering the success of faculty from diverse groups. We implement the "top-down" hypothesis by asserting that academic middle managers—-namely, department heads and chairs—-held accountable for diversity and inclusion will make sustained and significant improvements in the representation and climate of their deportments. The collaborative itself is a partnership with the department heads of research-active chemistry departments, social scientists and other key stakeholders. The lowering of these barriers increases the likelihood that individuals already in the tenure pipeline will have equitable chances of success and thereby leads to changes in faculty demographics closer to those of the broader U.S. population. The creation of a more equitable climate is also expected to encourage more disadvantaged students

to enter academic careers in the chemical sciences. We will report on OXIDE's approaches to increase awareness of effective policies and practices that decrease inequitable barriers and improve the diversity climate in research-active chemistry departments. We will discuss how these findings can inform the intentional management of inclusive excellence in pharmaceutical departments in the academy or industry.

SESSION V: WHEN BIOANALYTICAL DATA WERE CRITICAL TO A DRUG PRODUCT SUBMISSION APPROVAL

VENDOR PRESENTATION

Ready, Willing, and Stable? Advice from the LC/MS Experts on Analysis of Unstable Compounds and Prodrugs
Chad Christianson, Alturas Analytics

In recent years, the prodrug approach has gained popularity in order to allow drugs to reach the chosen target and produce the desired pharmacological effect. Prodrugs are purpose designed to undergo fairly rapid enzymatic conversion in vivo to the active drug. This instability is beneficial for drug action, but has created analytical challenges for the bioanalytical scientist when trying to quantify low levels of unstable prodrug in biological samples. This presentation will discuss a variety of methods that we have used at Alturas Analytics, Inc. in order to overcome these challenges.

Immunogenicity Data and the Regulatory Landscape: Bioanalytical Lessons Learned from a Recent Biological Licensing Application Approval
Jim Glick, Novartis

The race to deliver new drug treatments to patients is simultaneously a sprint and marathon. Technical, logistical and regulatory hurdles ensure the path to success is long and winding. The talk will focus on discussing the challenges of bring a drug to market and will highlight key areas of consideration such as the management of teams, timelines and expectations.

Overcoming ADA Interference by using a Hybrid LC/MS/MS Method to Quantify a Therapeutic Protein in Human Plasma
Huiyu Zhou, BioMarin Pharmaceutical

Anti-drug antibody (ADA) interference can present a challenge to the development of a sensitive, accurate and reproducible ligand-binding assay for quantification of protein therapeutics. ADAs compete with the capture/detection antibody for target binding and can substantially impact the quantification of proteins that induce strong immune responses.

By combining acid dissociation, immunoaffinity capture and liquid chromatography-tandem mass spectrometry (LC/MS/MS) detection, we developed and validated a method to quantitate a therapeutic protein in human plasma. The ADA tolerance of this method was compared to that of an enzyme-linked immunosorbent assay (ELISA) and an electrochemiluminescence assay (ECLA) in a spike recovery experiment, which was performed on fifty-eight clinical samples selected based on ADA titers. The LC/MS/MS results of 94.8% (55 out of 58) of all samples were accurate within ±20.0%bias. In the subgroup of twenty-eight samples that had high titers for at least one ADA isotype, 89.3% (25 out of 28) of the LC/MS/MS results were accurate within ±20.0%bias while only 17.9% (5 out of 28) and 14.3% (4 out of 28) of ELISA and ECLA results were accurate within ±20.0%bias, respectively. Therefore, the hybrid LC/MS/MS method demonstrated an advantage in overcoming ADA interference for quantification of the therapeutic protein in clinical samples.

DISCOVERY BIOANALYSIS & NEW TECHNOLOGIES WORKSHOP

SESSION I: MICROBIOME/MICROBIOTA

Mapping Host-microbe Interactions with Mass Spectrometry
Joshua Elias, CZ Biohub

The intestinal microbiome profoundly influences immune responses within the gut, and can have far-reaching effects throughout the body. Complex, dynamic interactions between host, microbe and diet underlie these effects, but are only partially reflected by 16S and metagenomic sequencing which remain foundations of microbiome research. Towards building a more mechanistic understanding of how our resident microbes influence health and disease, we developed a "host-centric proteomics of stool" method which directly measures proteins secreted or shed into the gut in response to changing intestinal ecosystems. Where microbe sequencing data can correlate certain taxa with possible health effects, well-annotated host proteins more directly implicate specific host processes in health maintenance and disease. These kinds of pathway-level observations can be important for assessing health before the onset of symptoms, when interventions may be most effective. In this talk, I will review our efforts

to understand pre-symptomatic changes to host innate immune responses in a mouse model of multiple sclerosis, and an exploration of natural variation in self-reported healthy human subjects. I then describe our recent high-throughput strategy to make these kinds of measurements compatible with large, clinical-scale sample sets. Together, we believe this work represents an important step towards understanding the forces that shape the gut microbiome, and how it in turn can shift the balance between health and disease.

SESSION II:
NEW TECHNOLOGY AND PLATFORMS FOR DISCOVERY BA

KEYNOTE PRESENTATION

The Triple Quadrupole: Innovation, Serendipity and Persistence
Richard A. Yost, University of Florida

In this presentation I will provide a personal perspective on the conceptualization, development and demonstration of the analytical capabilities of the triple quadrupole mass spectrometer. And in that perspective, I will try to illustrate the roles of innovation, serendipity and persistence that are fundamental to scientific research.

The triple quadrupole mass spectrometer has become the most common mass spectrometer in the world today, with sales of over $1 billion per year. It is the gold standard for quantitative analysis in metabolomics, clinical analysis, drug discovery and development, and environmental analysis. Indeed, it is used today to screen millions of newborn babies every year for up to 100 inherited diseases, saving thousands of them from an early death. But when I proposed that instrument as the "ultimate computerized analytical instrument" as a new PhD student in Chris Enke's research group at Michigan State University in 1975, the NSF reviews were uniformly negative, with experts in the field unanimous that the proposed instrument would never work.

In the 40 years since, mass spectrometry has evolved from a niche research area, largely for fundamental chemistry studies, into a practical, widely available analytical technique. Indeed, one can hardly name a significant advancement in science that was not made possible by the inventions and development of new tools to see something or measure something, and that includes everything from litmus paper to giant telescopes on mountaintops. And common to these inventions and developments have been innovation, serendipity and persistence.

VENDOR PRESENTATION

Highly Sensitive Hybridization ELISA Assays for Bioanalysis of Oligonucleotide-Based Drugs
Chenyi Pan, Frontage

Oligonucleotide therapeutics have emerged as a promising therapeutic modality attracting a flock of biopharmaceutical companies in recent years. Advances in our understanding of human disease and the availability of the full human genome sequence have created numerous therapeutic applications for this class of drugs. This therapeutic modality consists of a diverse class of drugs, such as antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), microRNAs (miRNAs), antibody-ASO conjugates, aptamers, etc. To support the preclinical and clinical PK studies of oligonucleotide drugs, it is essential to develop a simple, specific and sensitive method for an accurate quantification of a drug in biological matrices. We have developed hybridization ELISA (HELISA) assays that provide sensitive quantification of oligonucleotides with a length of 16-30 nucleotides and various modifications, including ASOs, siRNAs, morpholinos (PMOs, PPMOs) and antibody-ASO conjugates, in various matrices, such as plasma, serum, cerebrospinal fluid and tissues. Based on their unique properties and the specific needs, we take different approaches for the bioanalysis of different oligonucleotide drugs, such as hybridization-ligation ELISA for ASOs, dual hybridization ELISA for siRNAs, nuclease-dependent hybridization ELISA for PPMOs and hybrid ELISA for antibody-ASO conjugates. These assays have advantages of low sample volume and no sample cleanup requirements, as well as a sensitivity of pg/mL, offering highly sensitive and efficient solutions for PK and biodistribution studies. We have validated or qualified HELISA assays in accordance with regulatory guidance on bioanalytical method validation (BMV) to support preclinical and clinical studies in drug development.

VENDOR PRESENTATION

How to Secure Access to Difficult-to-synthesize Metabolites for MIST Compliance: A One-stop Multiple Tool Approach
Frank Scheffler, Hypha Discovery Limited

Often several strategies are needed to access all key drug metabolites, especially where chemical synthesis is not straightforward. This talk will highlight through various case studies how a multi-method approach utilising microbial and liver tissue biotransformation, chemical synthesis, and recombinant enzymes can enable production of quantitative standards of most challenging metabolites for

regulatory studies, as analytical reference standards or for preclinical investigation and metabolite identification.

SESSION III: HRMS/HRMS QUAN

High Resolution Mass Spectrometry and Nano-Flow Liquid Chromatography for Critical Reagent-Free Quantitation of Intact Peptides

Barry Jones, Q2 Solutions

The prevalence of peptide therapeutics under development has driven the need for highly selective and sensitive bioanalytical solutions for measurement in biological matrices. However, immunoassay approaches for quantitation of peptide analytes are often challenged by limited specificity of antibodies against these targets.

The unique selectivity afforded by LC-MS makes this platform an attractive complement to LBA techniques. High resolution mass spectrometry – with or without fragmentation – achieves a level of selectivity above that afforded by conventional low-resolution MS approaches, which often translates to improved sensitivity by improvement in signal to noise ratio.

Nano-scale LC separation and ionization delivers the ultimate sensitivity where needed, and multidimensional chromatography with separation by molecule size further enables the robustness needed for high-throughput applications. Incorporation of size-exclusion chromatography (SEC) upstream of reversed phase separation can alleviate LC system pressure issues associated with intact circulating peptide quantification such that antibody-based purification is not needed to enable use of nano-LC. In this presentation, case studies are shown for a peptide therapeutic and biomarker using solid-phase extraction prior to online SEC, nano-LC, and HRMS detection to single digit pg/mL limits of quantitation. This allows highly sensitive, robust, high-throughput measurement without risk of capture bias and lengthy incubation times.

The Utility of HRMS in Quantitative Bioanalysis Labs

Robert Sturm, Zoetis

This presentation will review the role, technologies employed, and challenges traditional LCMS bioanalysis labs face when developing assays to support in-live studies. Tools to improve assay selectivity will be reviewed and the utility of HRMS in improving assay sensitivity through improved selectivity for small molecule and large molecule assays will be highlighted with three real world examples.

SESSION IV: GENE AND CELL THERAPIES

Insights on Digital Droplet PCR based Cellular Kinetics and Biodistribution Assay Support for CAR-T Cell Therapy

Hiroshi Sugimoto, Takeda

Characterizing the in vivo cellular kinetics and biodistribution of chimeric antigen receptor T (CAR-T) cells is critical for toxicity, non-clinical and clinical efficacy studies. To date, a standardized assay to characterize CAR-T cell distribution, expansion, contraction and persistence profile, does not exist. To overcome this limitation and to increase comparability amongst studies, we have established a universal protocol for analysis.

We established a duplexing ddPCR protocol for the CAR-T transgene and reference gene to normalize the input of genomic DNA prepared from mouse blood and tissue. High-throughput gDNA extraction enabled highly reproducible gDNA extraction while minimizing labor-intensive sample preparation. CAR-T cells were intravenously injected to female immunodeficient mice bearing human colorectal cancer model. Biomatrix samples were harvested to measure the cellular kinetics of CAR-T cells by ddPCR and flow cytometry.

The standard curves were linear throughout the calibration range with acceptable intra- and inter-day precision and accuracy. The gDNA recovery study which was performed by spiking in the exo-gene plasmid DNA or CAR-T cells revealed that the recovery ranged from 60–100% in blood and tissue homogenate. The unit conversion for cellular kinetics data between copy/µg gDNA and copy/µL blood both meets the current regulatory requirement and provides a better understanding of CAR-T cells expansion systemically, compared with flow cytometry-based data.

The cellular kinetics and biodistribution assay for CAR T-cell therapy by ddPCR was established including automated gDNA extraction. By incorporating the gDNA recovery study along with sample analysis, the standardization of reporting unit for cellular kinetics assay is feasible.

MECHANISTIC ADME WORKSHOP

SESSION I: CURRENT AND EMERGING TOPICS IN TRANSPORTER AND CYP MEDIATED DRUG-DRUG INTERACTIONS

Flipping the Metabolic Switch from CYP3A4 to CYP1A1 in Smokers: Correlation between In Vitro and Clinical Data

Aaron Teitelbaum, Boehringer Ingelheim

Pharmacokinetic data from a single rising oral dose study with BI-Z revealed lower plasma exposure of BI-Z in volunteers identified as active smokers. From initial in vitro reaction phenotyping experiments with BI-Z, CYP3A4 was identified as the predominant CYP isoform responsible for hepatic metabolism, while metabolism by CYP1A2, an enzyme inducible by cigarette smoke, was negligible. Additional reaction phenotyping experiments were conducted, where it was determined that CYP1A1, an extrahepatic enzyme also known to be inducible by cigarette smoke, contributes to the metabolism of BI-Z. To substantiate the role of CYP1A1 in facilitating BI-Z clearance in smokers, we conducted further mechanistic experiments using the Hepatopac™ model. Pivotal data from these in vitro experiments indicated that following induction of CYP1A with omeprazole, the clearance of BI-Z did not change during the co-administration of the CYP1A2 inhibitor furafylline. Furthermore, metabolite identification using plasma samples from smokers and non-smokers dosed with BI-Z, compared with data from in vitro metabolite identification studies, revealed that CYP3A4 and CYP1A1 produce distinct metabolites. Thus, based on a combination of in vitro and in vivo results, a metabolic switch occurs in volunteers administered BI-Z due to smoking. In non-smokers, the metabolic clearance of BI-Z occurs predominantly by CYP3A4, while in smokers, the metabolic clearance of BI-Z occurs via a combination of CYP3A4 and CYP1A1 due to induction of CYP1A1.

KEYNOTE PRESENTATION

Predicting the Unpredictable: How the Innate Immune Response to Drugs Predicts Risk

Jack Uetrecht, University of Toronto

Idiosyncratic drug reactions (IDRs) represent a significant source of patient morbidity and mortality. They also increase the risk of drug development. It will be difficult to reduce these risks without a better mechanistic understanding. There is compelling evidence that most IDRs are mediated by the adaptive immune system. The dominant response to drugs that can cause IDRs, especially in the liver, is immune tolerance, and we were able to unmask the ability of drugs to cause idiosyncratic drug-induced liver injury (IDILI) by impairing immune tolerance. This model can be used to test hypotheses such as the involvement of inhibition of the mitochondrial electron transport chain as a common cause of IDILI. Although the injury is mediated by the adaptive immune system, which requires a specific HLA/T cell receptor combination, an adaptive immune response requires an innate immune response to activate antigen presenting cells. The innate immune response does not require a specific HLA/T cell receptor to recognize drug-modified peptides; therefore, it should not be idiosyncratic. This means that it should be possible to study the innate immune response to drugs that cause IDRs in normal animals and in people who do not have a clinically evident IDR. We have found this to be true for clozapine and nevirapine. Both drugs produce a significant but clinically silent innate immune response in normal animals, and clozapine is known to produce an innate immune response in most patients who take the drug. Therefore, screening drugs for their ability to produce an innate immune response may be the most accurate way to predict the risk that a drug candidate will be associated with an unacceptable IDR risk.

SESSION III: STUDIES IN MECHANISTIC METABOLISM

Distinct Species Differences for Aldehyde Oxidase Metabolism and Observed Kinetic Isotope Effects In Vitro and In Vivo

Kevin Johnson, Genentech

Aldehyde oxidase (AO) metabolism has been of increasing important in drug discovery. This generally is the result of increasing incorporation of N-heterocyclic aromatic rings to optimize metabolic stability towards P450 metabolism. Species differences and in vitro-in vivo correlations (IVIVC) of AO metabolism are poorly understood, indicating an important issue to address for drug discovery. Here we present an N-heterocyclic compound which is cleared via aldehyde oxidase metabolism (in vitro and in vivo). The extent of AO-mediated oxidation varied between human, cyno, and rat in vitro systems. In addition, species-dependent inhibition patterns have been observed for typical AO inhibitors. We probed its metabolism in vitro by preparing deuterium labeled analogs as a strategy to modulate the metabolic clearance. We observed a range of observed kinetic isotope effects (KIE) for each species tested (human, cyno, and rat), which translated to similar species differences in vivo for cyno and rat.

N-Oxygenation of Oxycodone and Retro-reduction of Oxycodone N-Oxide

John Cashman, Human Biomolecular Research Institute

Oxycodone is used as a potent analgesic medication. Oxycodone is extensively metabolized. To fully describe its metabolism, the oxygenation of oxycodone to oxycodone N-oxide was investigated in hepatic preparations. The hypothesis tested was that oxycodone N-oxygenation was enzymatic and the amount of N-oxide detected was a consequence of both oxygenation and retro-reduction. Methods for testing the hypothesis included both in vitro and in vivo studies. Results indicated that oxycodone was N-oxygenated by the flavin-containing monooxygenase. Oxycodone N-oxide is chemically quite stable but in the presence of hepatic preparations and NADPH was retro-reduced to its parent compound, oxycodone. Subsequently, oxycodone was metabolized to other metabolites including noroxycodone, noroxymorphone and oxymorphone via cytochrome P-450. Retro-reduction of oxycodone N-oxide to oxycodone was facilitated by quinone reductase, aldehyde oxidase and hemoglobin but not to a great extent by cytochrome P-450 or the flavin-containing monooxygenase. To confirm the in vitro observations, oxycodone was administered to rats and humans. In good agreement with in vitro results, substantial oxycodone N-oxide was observed in urine after oxycodone administration to rats and humans. Administration of oxycodone N-oxide to rats showed substantial amount of recovered oxycodone N-oxide. In vivo, noroxycodone was formed as a major rat urinary metabolite from oxycodone N-oxide presumably after retro-reduction to oxycodone and oxidative N-demethylation. To a lesser extent, oxycodone, noroxymorphone and oxymorphone were observed as urinary metabolites.

SESSION IV:
ADME CHALLENGES IN DRUG APPROVAL CASE STUDIES

ADME and Clinical Pharmacology of Avapritinib

Sean Kim, Blueprint Medicines

Avapritinib is the first approved precision therapy for gastro-intestinal stromal tumor (GIST) and the only highly active treatment for PDGFRA exon 18 mutant GIST. In this presentation, we will discuss how the clinical pharmacology plan was constructed from preclinically characterized ADME properties of avapritinib and outcomes of selected clinical pharmacology studies.

COMBINED WORKSHOP:
DISCOVERY BA & MECHANISTIC ADME

SESSION V:
EMERGING TECHNOLOGIES

Use of Cell Based Off Target Screening in CART Programs

Yen Ho, BMS

For CAR T-cells, specificity is dependent on the targeting element of the CAR, usually a single chain variable fragment (scFv). Binding of the CAR scFv to proteins other than the desired target could cause CAR T-cell mediated off-target toxicity. Traditional tissue-based cross-reactivity studies used to identify potential off-target liabilities for biologics often cannot be performed for scFv-based test articles due to technical limitations with immunohistochemistry. An alternative technology for off-target binding assessment is the RetrogenixTM plasma membrane protein array. This array utilizes a proteomic-scale approach for identification of specific protein-protein interactions between the test article and human cells over-expressing individual human extracellular membrane proteins. The advantage compared to tissue cross-reactivity study is that it can identify specific potential off-target binding because it can cover over 75% of the human proteome.

A Novel Matrix Insensitive Platform to Mesure Protein Kinetics

Kalidip Choudhury, MagArray

Matrix effect is the Achilles heel of ligand binding assays, preventing the precise and reproducible measurement of molecular interaction. MagArray has developed an innovative platform that will drastically improve the way that ligand binding assays are carried out. By adapting a highly sensitive magneto-nanoparticle technology from the computer disk drive industry, theMagArray system allows for the accurate measurement of protein binding in a buffer insensitive manner with an elegant and easy to use system. We demonstrate that the MagArray platform can be used to probe protein-protein interactions and quantify proteins in biological fluids, that other platforms cannot. Lessons to drug discovery applications are derived.

APA BIOGRAPHIES

Stanley Au, FDA: Stanley is a Team Lead in in FDA's Office of Study Integrity and Surveillance (OSIS). Previously, he was a FDA clinical pharmacology reviewer with the antiviral products team. Before joining FDA in 2008, he worked in the pharmaceutical industry as a clinical pharmacology scientist. He received his Doctor of Pharmacy and Bachelors of Pharmacy degrees from the State University of New York at Buffalo's School of Pharmacy.

Ruben Ayala, FDA: Ruben is a Lead Pharmacologist in the Office of Study Integrity and Surveillance (OSIS) located in the Office of Translational Sciences (OTS), Center for Drug Evaluation and Research (CDER) at FDA. Before joining OSIS, Ruben was a reviewer in the Office of Clinical Pharmacology (OCP) at FDA. Prior to FDA, he held research positions in the industry including clinical pharmacology, DMPK and Protein Formulation Pharmaceutics.

John R. Cashman, PhD, Human BioMolecular Research Institute: Dr. Cashman, President and Founder, has more than 38 years of experience in biomedical research as a researcher, consultant, entrepreneur or administrator. In 1997, he founded the Human BioMolecular Research Institute, a non-profit research institute dedicated to conducting fundamental and applied research to address important human diseases. Previously, he was Senior Scientist at the Seattle Biomedical Research Institute and prior to that, he was Associate Director for the IGEN Research Institute in Seattle, Washington. In 1984, he was appointed Assistant Professor of Chemistry and Pharmaceutical Chemistry at the University of California, San Francisco. He completed a postdoctoral fellowship in the Department of Chemistry at Harvard University in Cambridge, Massachusetts with Professor E.J. Corey (1982-1984). In 1990, Professor Corey received the Nobel Prize. Dr. Cashman received his Masters and doctorate degrees in Medicinal Chemistry from the University of Kansas, Lawrence, Kansas (1982). Prior to graduate school, he obtained bachelor degrees in chemistry and biology at the College of Creative Studies, University of California, Santa Barbara (1977). Dr. Cashman was a University of California Presidents Undergraduate Researcher (1974-1976), received a Sigma Xi Undergraduate Research fellowship (1975), was a PEW Scholar Nominee at the University of California, San Francisco (1986), received a March of Dimes Basil O'Connor Research Award (1986), was appointed Technical Advisor, San Francisco Estuary Project (1990) and was elected Fellow of the American Association for the Advancement of Science in 1996. In 1991, Dr. Cashman was appointed to the Editorial Advisory Board, Chemical Research in Toxicology and in 1999 he was appointed to the Editorial Advisory Board of Current Drug Metabolism. Dr. Cashman is the author of over 230 research articles or book chapters and 16 patents in the area of drug discovery and evaluation. He is extensively consulted by biotechnology, pharmaceutical industry and government in various areas of human drug development, drug safety evaluation, medicinal chemistry, pharmacogenetics and biochemical toxicology. Dr. Cashman is on the Board of Directors of three biotechnology companies.

Nagendra Chemuturi, PhD, Takeda: Dr. Chemuturi received his Bachelor Degree in Pharmacy, with Distinction, from Kakatiya University in India. He then worked as a pharmaceutical sales representative before pursuing his Ph.D. at the University of Iowa. He was awarded the AAPS Graduate Symposium Award in 2005 for his dissertation work on the role of nasal drug transporters and metabolism in preferential nose-to-brain uptake of dopamine into brain. He started his career in the US at Vertex Pharmaceuticals in MA in 2005. Since then, he has worked at Alcon-Novartis and Seattle Genetics, and is currently with Takeda Pharmaceuticals. His experience lies in the fields of oncology and ophthalmology having served as DMPK lead on several small and large molecule projects. He is currently working on viral gene therapies including clinical aspects of viral gene therapies. He has given podium presentations at several scientific conferences, is active in IQ consortium, co-leading the MABEL working group, and has co-authored several articles and book chapters.

Kalidip "KC" Choudhury, PhD, MagArray: Dr. Choudhury is currently the VP/GM Life Sciences of MagArray, a Hitachi Technology funded company. He has more than 15 years of experience in commercializing new platforms and introducing new technologies to the market. KC carried out his graduate research on protein structure function relationship at CARB, University of Maryland and the molecular pathways of immune recognition at Stanford University.

Chad Christianson, Alturas Analytics: Chad has 20 years of related experience as an analytical scientist with over 16 years focused on bioanalysis at Alturas Analytics. This depth of experience in applied LC-MS/MS and GC-MS/MS, along with an education in chemical engineering provides the

backbone for productive and innovative science. Chad leads the biologics quantitation group at Alturas, applying novel techniques to a regulated, high-throughput production environment. As a Senior Principal Scientist Chad's primary focus is LC-MS/MS and GC-MS/MS method development, validation and sample analysis for small new chemical entities, biologics and antibody drug conjugate (ADC) programs in accordance with GLP guidelines. In addition, Chad leads a team of scientists as Study Director and Principal Investigator, providing technical oversight to clients across all therapeutic areas.

Philip Chu, Genentech: Phillip Chu is currently a scientific researcher in the department of Biochemical and Cellular Pharmacology at Genentech. His current research primarily involves analysis of protein therapeutics from complex biological matrices using mass spectrometry. He is interested in developing high throughput methods of bioanalysis and investigating the stability of protein therapeutics in vivo. He received his BS in Chemical Engineering from the University of British Columbia, and his MS in Biotechnology from Northwestern University (under supervision of Prof. Neil Kelleher).

Joshua Elias, PhD, CZ Biohub: Dr. Joshua Elias is a Cape Cod native who received his undergraduate degree from Cornell in Biology (1998), and his Ph.D. from Harvard Medical School in Cell Biology with Stephen Gygi (2006). Perhaps best-known for the ubiquitous "target-decoy" search strategy for controlling error in proteomics experiments, he has long been interested in bringing proteomics workflows in sync with the kinds of robust methods used in genomics and allied fields.

As a faculty member at Stanford University (2009-2019), Dr. Elias focused on solving three extraordinary challenges in proteomics: identifying disease-relevant antigens presented on MHC complexes; characterizing the biologically relevant proteins that mediate host-microbiome interactions, and improving methods for searching the vast sequence space these experiments encompass. As the Mass Spectrometry Platform Leader at the Chan Zuckerberg Biohub (2019-present), Dr. Elias and his team are continuing to define the range of antigens that underlie health and disease and how these antigens relate to our microbiomes. The technologies they are developing are broadly applicable, including methods to quantify the dynamic regulation of protein post-translational modifications and to identify novel post-translational modifications that have so far been hidden in the "dark matter" of biology — molecules invisible to genomic technologies and standard proteomic assays.

Jim Glick, Novartis: Jim Glick is an Associate Director in the Global Bioanalytics group of Translational Medicine's PK Sciences group within the Novartis Institutes for BioMedical Research. Over the past 7 years, he and his team have focused on both small and large molecule quantitative bioanalysis supporting projects from Discovery to the clinic. His group uses both ligand-binding and LC-MS based platforms to support challenging PK, TK and immunogenicity questions. Prior to joining Novartis, he was the Barnett Institutes' Core Mass Spectrometry facility Director at Northeastern University.

Rigoberto Hernandez, PhD, John Hopkins University: Dr. Rigoberto Hernandez is the Gompf Family Professor in the Department of Chemistry at the Johns Hopkins University as of July 2016, and remains as the Director of the Open Chemistry Collaborative in Diversity Equity (OXIDE) since 2011. Before Hopkins, he was a Professor in the School of Chemistry and Biochemistry at Georgia Tech, and Co-Director of the Center for Computational Molecular Science and Technology he co-founded. He was born in Havana, Cuba and is a U.S. Citizen by birthright. He holds a B.S.E. in Chemical Engineering and Mathematics from Princeton University (1989), and a Ph.D. in Chemistry from the University of California, Berkeley (1993). His research area can be broadly classified as the theoretical and computational chemistry of systems far from equilibrium. His current projects involve questions pertaining to the diffusion of mesogens in colloidal suspensions and liquid crystals, fundamental advances in transition state theory, design principles for sustainable nanotechnologies and the dynamics of protein folding and rearrangement, and the design of autonomous computing machines. This work is supported by the NSF through a single-investigator grant, the CCI Center for Sustainable Nanomaterials, and a collaborative HDR Big Idea grant. The OXIDE effort is presently supported by the Sloan Foundation.

Dr. Hernandez is the recipient of a National Science Foundation (NSF) CAREER Award (1997), Research Corporation Cottrell Scholar Award (1999), the Alfred P. Sloan Fellow Award (2000), a Humboldt Research Fellowship (2006-07), the ACS Award for Encouraging Disadvantaged Students into Careers

in the Chemical Sciences (2014), the CCR Diversity Award (2015), the RCSA Transformative Research and Exceptional Education (TREE) Award (2016), the Herty Medal (2017), the Stanley C. Israel Regional Award for Advancing Diversity in the Chemical Sciences (2018), and RCSA IMPACT Award (2020). He is a Fellow of the American Association for the Advancement of Science (AAAS, 2004), the American Chemical Society (ACS, 2010), the American Physical Society (APS, 2011), and the Royal Society of chemistry (FRSC, 2020). He was a Phi Beta Kappa Visiting Scholar in 2015-2016. He previously served as the as the District IV Director on the American Chemical Society Board of Directors (2014-2019). He currently serves on the Research Corporation SciaLog Selection Committee for Molecules Come to Life (2018-2021), the Sloan MPHD Advisory Committee, and the AAAS Committee on Opportunities in Science (COOS).

Yen Ho, BMS: Yen has over 15 years of scientific experience working in preclinical and nonclinical research and development, in both academia and pharmaceutical industry. She joined Juno Therapeutics in 2016, now Bristol Myers Squibb. In her current role in the Nonclinical Research and Development: Toxicology for Cell Therapy, she provides support and develop methods and tools to evaluate the nonclinical safety of CAR T-cell and TCR programs.

For CAR T-cells, specificity is dependent on the targeting element of the CAR, usually a single chain variable fragment (scFv). Binding of the CAR scFv to proteins other than the desired target could cause CAR T-cell mediated off-target toxicity. Traditional tissue-based cross-reactivity studies used to identify potential off-target liabilities for biologics often cannot be performed for scFv-based test articles due to technical limitations with immunohistochemistry. An alternative technology for off-target binding assessment is the RetrogenixTM plasma membrane protein array. This array utilizes a proteomic-scale approach for identification of specific protein-protein interactions between the test article and human cells over-expressing individual human extracellular membrane proteins. The advantage compared to tissue cross-reactivity study is that it can identify specific potential off-target binding because it can cover over 75% of the human proteome.

Kevin Johnson, PhD, Genentech: Dr. Johnson received his PhD in Chemistry from the University of Missouri (2014) in Kent Gates's lab studying DNA cross-links and small molecule DNA alkylators. From there he took on a Post-Doc position in Fred Guengerich's lab at Vanderbilt University focusing on DNA-peptide crosslinks and P450 metabolism. In 2017 Dr. Johnson joined the Biotransformation group in the DMPK department at Genentech. As an organic chemist by training, my primary responsibility involves supporting small molecule metabolite ID of in vitro, in vivo, and mechanistic studies for discovery programs. Additionally he works closely with chemists to solve metabolism problems, incorporating a variety of in silico tools to complement our work. Kevin has additional interests in bioactivation of compounds and incorporation of deuterium isotopes for investigating and solving metabolism issues.

Barry Jones, PhD, Q^2 Solutions: Dr. Barry Jones joined Q^2 Solutions (then Advion Biosciences) in 2007 and began the LC-MS Biologics Group in 2008. Research within the LC-MS biologics group at Q^2 Solutions is focused on targeted quantitative LC-MS analysis of endogenous biomolecules and large molecule biotherapeutics on triple quadrupole and orbitrap instruments. Dr. Jones is particularly interested in the application of hybrid Immunoaffinity-LC-MS/MS methods and High-Resolution Mass Spectrometry to high-throughput bioanalysis, as well as the scientific challenges and regulatory strategies for validation of LC-MS biomarker assays supporting drug development in a regulated environment.

Prior to joining Quintiles, Barry led the Mass Spectrometry Facility at Binghamton University, N.Y. using Q-TOF and MALDI mass spectrometry and nanoESI techniques in support of proteomic research. He earned his Ph.D. in Physical Chemistry at Binghamton University in 2006.

Sean Kim, PhD, Blueprint Medicines: Dr. Kim is Head, DMPK and Clinical Pharmacology at Blueprint Medicines in Cambridge, USA, where he is leading ADME, bioanalytical and clinical pharmacology functions to aid preclinical and clinical development of novel kinase inhibitors for oncology and rare diseases. Formerly, he was a group leader in Metabolism and Pharmacokinetics at Novartis Institute of Biomedical Research and before that, Senior Research Investigator in Metabolism and Pharmacokinetics at Bristol-Myers Squibb. Dr. Kim received his B.S. in biology from the Sogang University in Korea and Ph.D. in toxicology from Rutgers, The State University of New Jersey. He has represented DMPK function in multiple disease areas, including Oncology/IO, Ophthalmology, Neuroscience and Anti-infectives and led P450 induction lab. He has published over 25 peer-reviewed articles and two book chapters in the areas of carcinogenesis, P450 induction and human PK projection as well as discovery of new chemical entities.

Lina Loo, PhD, Vertex: Dr. Loo joined Vertex in early 2020 as a Director in the Bioanalytical Preclinical Development group at Vertex Cell and Gene Therapy. Her main responsibility includes design, development, and validation of bioanalytical assays to support AAV- based product for Gene therapy in non-clinical studies. Prior to this role, she was at Celgene/BMS with similar responsibilities to support biologic products and CAR-T programs, overseeing PK and Immunogenicity assays internally and externally. Dr. Loo previously served as a Senior Scientist at Merck in a GLP-compliant lab developing and validating immunogenicity assays including cell-based neutralizing assays to support multiple biologic products. She received her PhD degree in Chemistry from North Carolina state university and spent 3 years as a Postdoc researcher at Fox Chase Cancer Center.

Timothy Mack, PhD, Celgene: Dr. Mack performed his undergraduate studies at the University of Vermont where he majored in biochemistry and minored in chemistry. Following his time at UVM Tim spent five years at Schering Plough where he focused on the development and validation of bioanalytical assays for the quantification of recombinant protein therapeutics, as well as on the characterization of anti-drug antibodies. Tim then returned to an academic setting where earned a PhD in biochemistry from Rutgers University. The focus of his thesis was on the structural/functional characterization of bacterial signaling systems, his work provided an important biochemical perspective on the activation of the OmpR/PhoB subfamily of response regulators, the largest subfamily of response regulators. After completing his PhD he began working at ImClone Systems (acquired by Eli Lilly in 2008) where he spent 9 years working in a variety of different areas of preclinical drug development (early-phase compound screening/characterization, bioanalysis, PK/PD, toxicology, and translational) and was responsible for the nonclinical PK components of several INDs. In 2018 Tim moved to Celgene (acquired by BMS in 2019) where he currently manages bioanalytical studies supporting projects in all phases of development and is responsible for bioanalysis for CAR T therapeutics.

Susovan Mohapatra, PhD, Wave Life Sciences: Dr. Susovan Mohapatra is currently an Associate Director in the Department of Bioanalytical and Biomarker Development at Wave Life Sciences. Susovan received his Ph.D. in Pharmacology and Toxicology at Virginia Commonwealth University and continued his training in Bioanalytical chemistry at Massachusetts Institute of Technology as a postdoctoral fellow in the Bioengineering Department. He has over 10 years of experience in assay development focusing on nucleic acids. At Wave Life Sciences, Susovan leads a team to develop, validate and implement bioanalytical and biomarker assays on LC-MS and LBA platforms in preclinical and clinical settings to support development of oligonucleotide therapeutics.

Liam B. Moran, PhD, Charles River Laboratories: Dr. Moran is the Director, Bioanalytical Chemistry, for Charles River, assuming this role in October 2018, leading the science and business involved in the conduct, direction and execution of Bioanalytical Chemistry studies. He provides scientific direction, oversight and guidance to staff, and maintains and implements efficient processes and procedures to provide high quality standards of study design and timely reporting while contributing to new business development.

Prior to his current position, Liam was Associate Scientific Director, Bioanalytical Chemistry, November 2015 to October 2017, overseeing the scientific conduct of all projects/programs within the group, including oversight of the method development activities and discovery programs, leading strategic initiates for the purpose of growth in services, staff development, and promoting external scientific visibility, while also playing a key participant role in achieving revenue target goals and building and retaining sponsor relationships.

He began his career with Charles River, formerly WIL Research Labs, as a Senior Research Chemist, Bioanalytical Chemistry, from March 2014 to October 2014, before spending a year as Associate Director, Bioanalytical Chemistry, with AbbVie in North Chicago, IL from October 2014 to October 2015. Additional affiliations include Battelle, Columbus, OH, Senior Scientist, 2009 to 2014, Lexicon Pharmaceuticals, Houston, TX, Senior Group Leader, 2005 to 2009, Thermo Fisher, San Jose, CA, Application Chemist, 2000 to 2005, and ITT Research Institute, Chicago, IL, Research Chemist, 1998 to 2000.

Liam's education and certifications include PhD, Physical Chemistry, Michigan State University, East Lansing, MI, 1996, B.S., Chemistry, University of Illinois, Urbana-Champaign, IL, 1988.

Chenyi Pan, PhD, Frontage: Dr. Pan is an Associate Director of Biologics Services at Frontage Laboratories, Inc. He received his B.S. from Zhejiang University, China, and his Ph.D. in Biology from Georgia Institute of Technology. His Ph.D. research was focused on the epigenetic regulation of stem cells and cancer. Before joining Frontage in 2017, Dr. Pan worked as an NSF EBICS postdoctoral fellow in biomedical engineering at Georgia Tech, where he developed novel biosensor systems to monitor intracellular redox status during stem cell differentiation. At Frontage, Dr. Pan is leading the efforts in developing and validating bioanalytical assays for biomarkers, oligonucleotides, and gene and cell therapies. He has strong expertise in PK, immunogenicity, and biomarker assays based on various platforms, including ELISA, MSD electrochemiluminescence, Quanterix Simoa, Ella, flow cytometry, and qPCR. Being working in a GLP- and CLIA-regulated environment, he has been helping biopharmaceutical companies on preclinical and clinical drug development in various therapeutic areas.

Marc Rose, PhD, Gossamer Bio: Dr. Rose is currently the Head of DMPK at Gossamer Bio in San Diego, CA. But, as recently as August of this year, he was Director of DMPK at CHDI Management, Inc., a privately funded research foundation focused on finding a cure for Huntington's disease. At CHDI, Dr. Rose managed a diverse portfolio of research projects through CHDI's novel virtual model and so regularly interacted with contract research organizations. His research activities at CHDI included in vivo and in vitro preclinical characterization, human PK modeling, biomarker identification, GLP bioanalysis, and IND support.

Previously, Dr. Rose led a bioanalytical group in the PKDM department at Amgen Inc. (2004-2014), where he was responsible for the support of discovery, preclinical, toxicology, and clinical studies for small and large molecules. He also was responsible as a project representative on discovery teams across a range of therapeutic modalities, including small molecules, peptides, antibody conjugates, and antibodies. Before Amgen, Dr. Rose was a bioanalytical chemist in the Drug Metabolism Department at Merck Research Laboratories (1996-2003), where he focused primarily on supporting clinical testing, and he was an analytical scientist in the Pharmaceutics Department at Glaxo Inc. (1987-1991). Dr. Rose is a co-author of over 90 publications and presented abstracts in the areas of analytical chemistry, bioanalysis, and drug discovery. He received a B.S. in Chemistry from Pennsylvania State University (1987) and a Ph.D. in Pharmaceutical Chemistry from the University of Kansas (1996).

Bonita (Bonnie) Rup, PhD, Bonnie Rup Consulting LLC: Dr. Rup is a biopharmaceutical development consultant, providing expert advice on bioanalysis, immunogenicity risk assessment, and related regulatory strategy aspects of biopharmaceutical development.

Previously, she held positions of Research Fellow in Pfizer (Immunogenicity Discipline Lead), Assistant Vice President of Protein Bioanalytics in Wyeth; and various other positions directing development and application of immuno-ligand binding assay technologies for PK, immunogenicity and protein impurity analysis, and other aspects of biopharmaceutical development. During her career, she has been involved in multiple regulatory meetings and filings during preclinical, clinical development and marketing approval of biopharmaceutical products.

Bonnie is an active member of the American Association of Pharmaceutical Scientists (AAPS), and has been a member of European Immunogenicity Platform (EIP), European IMI ABIRISK consortium, and Biosafe; with these organizations, she has been a co-author for multiple publications related to monitoring immunogenicity and bioanalysis of therapeutic proteins.

Bonnie received her B.S. from University of Massachusetts, Amherst, Ph.D. from University of Texas, Austin, and conducted postdoctoral research at Duke University, NC and University of Rochester, NY.

Frank Scheffler, Hypha Discovery: Frank is Hypha's Head of Business Development and Global Collaboration, a role combining his academic background in bioscience and business built in London, Seoul and Hamburg. In his current role Frank has delivered talks at various scientific events including ACS and RSC conferences. In normal times he often visits the Boston and Cambridge area and enjoys discussing how Hypha's solutions for metabolite synthesis can support drug discovery projects.

David Schumacher, Alturas Analytics: Dave Schumacher, RQAP-GLP since 2004, is the QA Director for Alturas Analytics, Inc located in Moscow, Idaho. Dave graduated from University of Minnesota, Moorhead with a B.S. degree in Chemistry. After spending the first 17 years in environmental labs, he moved to a quality assurance role in various pharmaceutical companies including GLP and GMP. With over 20 years in Quality Assurance, Dave oversees the Alturas Analytics Quality Assurance program, offering risks assessments and solutions to staff and management.

Jim Shen, PhD, BMS: Dr. Jim Shen is a Senior Director and the Head of Regulated Bioanalysis Operations in Nonclinical Disposition and Bioanalysis department at Bristol-Myers Squibb. Jim received his B.S. in chemistry from the University of Arizona and his Ph.D. in analytical chemistry from the University of Texas at Austin under the direction of Professor Jennifer Brodbelt. Jim has held a number of leadership positions in the global life sciences industry, and is a senior leader with backgrounds and expertise in managing regulated bioanalytical operations, GLP complaint laboratories, and bioanalytical outsourcing processes. Jim's over twenty years of experience in the field included tenure-ships at leading pharmaceutical companies like Schering Plough and Merck. In his professional capacity, Jim has spoken widely in industry forums and led activities at organizations such as AAPS, ASMS, CPSA, EAS, and ACS. Jim is also a prolific writer, publishing extensively in various peer reviewed scientific journals.

Rob Sturm, Zoetis: Rob Sturm earned a B.S. in Chemistry and Biology from Aquinas College in Grand Rapids, MI before heading to University of Wisconsin-Madison for his graduate studies in chemistry. At UW-Madison, Rob worked under the mentorship of Professor Lingjun Li and developed targeted and discovery mass spectrometry based techniques for neuroproteomic and peptidomic applications. After graduate school, Rob joined Dr. Jack Henion at Advion Bioanalytical Services in Ithaca, NY as an industrial postdoc funded partially by Shire Pharmaceuticals. His postdoc work focused on the development of a dried plasma spot card for point of care sample collection, online dried plasma card extraction and LCMS analysis, and evaluation of HRMS instrumentation for quantitative bioanalysis applications. Following his postdoc, Rob accepted an assay development scientist role in the LCMS Biologics and Biomarkers Quantification group at Advion Bioanalytical Services (now Q Squared Solutions) and supported sponsor assay transfer and assay development employing multidimensional low-flow liquid chromatography and HRMS to enable highly sensitive and selective bioanalytical assay development for preclinical and clinical study support. Since 2016, Rob has been a member of Zoetis Animal Health's PDM group in Kalamazoo, MI and currently leads the discovery LCMS team that supports both small molecule and large molecule PK, TK, PD, and biomarker studies for both companion animal and livestock project teams.

Hiroshi Sugimoto, PhD, Takeda: Dr. Sugimoto is Senior Scientist and Group Leader in Global DMPK at Takeda Boston to lead the preclinical bioanalytical strategy and support for the Rare Disease Discovery Unit. He and his colleagues are currently focusing on nonclinical gene therapy assay support including immunocapture-LC/MS based biomarker assay, LBA-based transgene protein assay and digital droplet PCR-based viral genome and mRNA assay. Previously, he was serving as the DMPK representative for small molecule drug discovery stage in the oncology and neuroscience arena at Takeda Pharmaceutical Company in Japan. Dr. Sugimoto received his BS and MS in pharmaceutical science from the Kanazawa University and Ph.D. in pharmaceutical science from Shizuoka University in Japan with dissertation titled "Development of novel analytical methods for the determination of disease-related small molecule biomarkers by LC/MS/MS." He has contributed to multiple pharmaceutical research scientific communities including transporter-mediated drug interaction study, LC/MS-based quantitative biomarker and digital droplet PCR-based cellular kinetics assay.

Aaron M. Teitelbaum, PhD, Boehringer Ingelheim Pharmaceuticals: Dr. Teitelbaum is a Principal Scientist in the Drug Metabolism and Pharmacokinetics Department at Boehringer Ingelheim Pharmaceuticals. His main responsibility is to direct metabolite identification and biotransformation studies (both preclinical and clinical) in support of small molecule development programs. These studies mainly include metabolite profiling and structure elucidation from in vitro human hepatocyte incubations, preclinical 14C ADME, FIH SAD/MAD, and 14C human ADME studies. Dr. Teitelbaum's research interests include understanding chemical aspects of drug metabolism and bioactivation as well as biosynthesis of metabolites utilizing LC-SPE-NMR technologies. Prior to joining BI, Dr. Teitelbaum earned his Ph.D. in Medicinal Chemistry in 2012 from the University of Minnesota under the direction of Rory P. Remmel. Subsequently, he completed a post-doctoral fellowship at the University of Washington from 2012-2014 under the supervision of Profs. Allan Rettie and Rheem Totah. He then completed a second post-doctoral fellowship at Washington University in St. Louis from 2014-2016 under the guidance of Prof. Evan Kharasch.

Jack Uetrecht, PhD, University of Toronto: Dr. Uetrecht is Professor of Pharmacy and Medicine and held the Canada Research Chair in Adverse Drug Reactions from 2001 to 2015. He received his Ph.D. in organic chemistry at Cornell University in 1972, M.D. at Ohio State University in 1975, and did his medical residency at the University of Kansas Medical Center from 1975-1978. He completed his clinical pharmacology fellowship in 1981 at Vanderbilt University and then joined the faculty as an assistant professor. He moved to the University of Toronto in 1985 as an associate professor and was the associate dean of pharmacy from 1994 to 1998. He is a Fellow of the Canadian Academy of Health Sciences. He chaired the Gordon Conference on Drug Metabolism in 2002 and initiated and chaired a new Gordon Research Conference on Adverse Drug Reactions, the first of which was held in 2005. He was the chair of the organizing committee for the 2018 North American ISSX meeting. He received the Janssen-Ortho Research award in 2001, the Student's Administrative Council Undergraduate Teaching Award in 2005, and was voted Teacher of the Year by the 3rd year class in both 2007 and 2008. He received the Vos Award for Lifetime Career Achievement in Immunotoxicology from the Society of Toxicology in 2018 and the STC Gabriel Plaa Award of Distinction in 2019. He has over 170 research publications, 35 book chapters, and has published a book with Bill Trager on drug metabolism. His research is focused on the mechanisms of idiosyncratic drug reactions with an emphasis on reactive metabolites and immune mechanisms, and he consults for the pharmaceutical industry on problems with idiosyncratic drug reactions.

Jashvant (Jash) D. Unadkat, PhD, University of Washington: Dr. Unadkat is the Milo Gibaldi Endowed Professor in the School of Pharmacy at the University of Washington, Seattle. He received his Bachelors degree in Pharmacy (B. Pharm.) from the University of London (1977), his Ph.D. from the University of Manchester (1982; advisor Prof. Malcolm Rowland) and his postdoctoral training at the University of California at San Francisco (1982-85; advisor, the late Dr. Lewis Sheiner). Dr. Unadkat's research interests are focused on elucidating the mechanisms of transport and metabolism of HIV and related drugs. In particular his laboratory has been interested in metabolism and transport of drugs during pregnancy, and transport of drugs across the placental, hepatic, intestinal and blood-brain barrier. Dr. Unadkat has published more than 200 peer-reviewed research papers. He is a fellow of AAAS, AAPS, JSSX, and the founding co-chair (1999-2001) of the focus group of AAPS on Drug Transport and Uptake. Dr. Unadkat received the AAPS Research Achievement Award in 2012. Dr. Unadkat created and leads the UW Research Affiliates Program on Transporters (UWRAPT), a cooperative effort between the UW School of Pharmacy and pharmaceutical companies. He also leads UWPKDAP, a NIDA funded Program Project grant (P01) on drug disposition during pregnancy. Dr. Unadkat has been an Associate Editor for the Journal of Pharmaceutical Sciences, an Editor of AAPS Journal, and a member of the NIH Pharmacology study section (2000-3). Dr. Unadkat has organized or co-organized numerous national and international conferences on the role of transporters and pregnancy in disposition of drugs.

Joleen T. White, PhD, Gates MRI: Dr. White is Bioassay Development Lead and Bill & Melinda Gates Medical Research Institute (Gates MRI). In this role, she oversees all bioassay activities supporting primary and secondary objectives for two programs in the global health program: malaria and respiratory syncytial virus. The Gates MRI motto "Our bottom line: lives saved" resonates deeply for her, enabling her to pursue her passion of helping under-served patients in a full-time position.

Joleen earned a B.S. in Chemistry from Harvey Mudd College in 1997, and a Ph.D. in Biochemistry from The Scripps Research Institute in 2002. Prior to her position with Bill & Melinda Gates Medical Research Institute, she worked across bioanalytical, biomarker, and immunogenicity methodology and interpretation as Director and Global Head of NBE DMPK Project Support at EMD Serono, Principal Scientist at Biogen, Group Leader at Bristol-Myers Squibb, and Senior Scientist at BioMarin Pharmaceutical Inc.

Joleen is active in the international bioanalytical and immunogenicity community, including chairing or moderating 10 conferences and sessions, and representing Gates MRI and previous employers on working groups for both AAPS and the International IQ Consortium. She also supports data science initiatives working with PhUSE and CDISC.

Richard Yost, PhD, University of Florida: Dr. Yost is the University Professor and Head of Analytical Chemistry at the University of Florida. He is recognized internationally as a leader in the field of analytical chemistry, particularly tandem mass spectrometry (MS/MS). Dr. Yost received his BS degree in Chemistry in 1974 from the University of Arizona, having performed undergraduate research in chromatography with Professor Mike Burke

and his PhD degree in Analytical Chemistry in 1979 from Michigan State University, having performed graduate research with Professor Chris Enke. He then joined the faculty of the University of Florida.

Dr. Yost's professional activities have focused on research and teaching in analytical mass spectrometry, particularly tandem mass spectrometry (MS/MS). His group's research has reflected a unique balance between instrumentation development, fundamental studies, and applications in analytical chemistry. His group has led in the application of novel mass spectrometric methods and techniques to areas such as metabolomics, clinical, biomedical, pharmaceutical, environmental, petrochemical, and forensic chemistry. Dr. Yost has supervised the research of over 120 graduate students during the past 40 years, graduating almost 100 PhDs from his group. He has served as PI or Co-PI on grants and contracts totaling over $60M of funding. Research in the group has led to over 220 publications and 16 patents. He still loves teaching undergraduates and graduates in the classroom each semester. Dr. Yost recently completed terms on the Florida Board of Governors (Regents) and the University of Florida Board of Trustees. He is director of the Southeast Center for Integrated Metabolomics (SECIM) and of NIH's Metabolomics Consortium Coordinating Center (M3C). He is also a Professor of Pathology at both the University of Florida and the University of Utah/ARUP. His research has been recognized with the 1993 ASMS Award for Distinguished Contribution in Mass Spectrometry, the 2018 MSACL Award for Distinguished Contribution to Clinical Mass Spectrometry, and in 2019 was named the Florida Academy of Sciences Medalist and the CPSA Distinguished Analytical Scientist, was inducted into the Florida Inventor Hall of Fame, and was presented the National Distinguished Eagle Scout Award. Dr. Yost currently serves as the President of the American Society for Mass Spectrometry (ASMS).

Chongwoo Yu, PhD, FDA: Dr. Yu is a Master Clinical Pharmacology Reviewer in the Office of Clinical Pharmacology (OCP) at the U.S. Food and Drug Administration (FDA). Dr. Yu received his BS in Chemistry and MS in Physical Organic Chemistry from Hanyang University (Korea) and Dr. Yu earned his PhD in Analytical Chemistry with the focus on Drug Metabolism and Mass Spectrometry from the University of Illinois at Chicago (Chicago, IL).

Subsequently, Dr. Yu has worked in the Department of Pharmacokinetics, Dynamics, and Metabolism (PDM) at Pfizer (Ann Arbor, MI) and the Drug Metabolism and Pharmacokinetics (DMPK) Department at Schering-Plough (currently Merck; Kenilworth, NJ) for several years. At both organizations, Dr. Yu has been heavily involved in carrying out various types of drug metabolism, pharmacokinetics, and drug-drug interaction (DDI) studies using mass spectrometry.

Dr. Yu joined the Agency as a Clinical Pharmacology reviewer in 2007. Dr. Yu's work has been focused on the evaluation of reproductive, urologic, and endocrinology drug products. Dr. Yu served as a member of various FDA guidance working groups including the one for the *Bioanalytical Method Validation Guidance*. Dr. Yu currently serves as the chair of the FDA OCP Bioanalytical Research (BAR) Scientific Interest Group (SIG).

Ismael Zamora, PhD, Lead Molecular Design: Dr. Zamora is CEO of Lead Molecular Design, S.L and associated professor at POMPEU Fabra University in Barcelona. He got the PhD in 1998 in the organic synthesis of natural projects, after 1 year postdoc with Professor Gabriele Curciani at the University of Perugia, Italy working on modeling of ADME properties he joined AstraZeneca in Sweden at first as modeler for ADME properties inside of the DMPK department. He stayed at AstraZeneca for 3 years and contributed to the development of a global prediction system and to stablish the design groups between medicinal chemists, ADME scientists and modelers. In 2002, he found Lead Molecular Design, S.L. in Barcelona, the company has been dedicated to develop new applications in the field of Medicinal Chemistry/ADME/Design such MetaSite, Shop, MassMetaSite and WebMetabase in collaboration with Molecular Discover (distributor of the software developed). In 2010, Ismael Zamora received the Hansch award in QSAR and Modeling for the work done in the ADME area. Also, he has more than 60 articles and book chapters published in peer journals.

Guodong Zhang, PhD, Alnylam: Dr. Zhang is currently an Associate Director and Group Head at Alnylam. After he earned Ph.D. in the bioanalytical sciences from Dr. Bartlett's lab at the University of Georgia, he worked at Pfizer Groton site and Takeda/Shire in the regulated bioanalytical and biomarker area. Then, he joined Bioanalytical Sciences team at Alnylam in 2019. His team is focusing on bioanalytical support for PK, target tissue uptake, PD, and metabolite profiling of siRNA from pre-clinical to clinical programs in support of RNAi therapeutics.

Song Zhao, PhD, Frontage Laboratory: Dr. Zhao is currently the Director of Bioanalysis of Biologics at Frontage Laboratory in Shanghai. He oversees the overall laboratory activities of complex bioanalytical method development and/or specialty technologies projects to create new analytical methods for biologics, enhance existing methods, and transfer client-provided methods using multiple instrumentation techniques and multiple detection techniques. Mainly focused on the bioanalysis of biologics by hybrid LC-MS/MS technique. Dr. Zhao previously worked as Senior Research Scientist at PPD in Richmond, Virginia, where he mainly focused on the bioanalytical method development and validation for small molecules, biologics by hybrid LC-MS/MS, and biologics by ligand binding assay approach.

Dr. Zhao received his B.S. Medicinal Chemistry and M.S. Applied Chemistry from East China University of Science & Technology. He received his PhD in Bioorganic and Bio-analytical Chemistry from Virginia Polytechnic Institute and State University (Virginia Tech).

Development and Validation of RP-HPLC Method for Simultaneous Estimation of Ritonavir and Alpha Tocopherol in Nanoformulation

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Purpose:
Acquired immunodeficiency syndrome (AIDS), a life-threatening chronic condition in which the immune system of the body is affected mainly. Human immunodeficiency virus (HIV) is a lentivirus belongs to the family Retroviridae is a causative organism and attacks the lymphocytes with CD4 glycoprotein. Ritonavir is a drug used for the reatment of HIV, but having severe side effects and hepatotoxicity. The major side effect of this drug is hepatotoxicity. Ritonavir-induced hepatotoxicity is unknown, but increase in the oxidative stress levels is one of the typical indications seen. Alpha-tocopherol, a well known vitamin with a very good anti-oxidant properties. Hence, a nanoformulation that can encapsulate ritonavir and alpha-tocopherol would help in reducing the oxidative stress which helps to reduce the hepatotoxicity also. But there is no specific analytical method for the estimation of both the drugs in nanoformulation. Hence, in the present study an analytical HPLC method was developed and validated as per the ICH guidelines for the estimation of ritonavir and alpha-tocopherol in nanoformulations.

Methods:
The method was developed by using Inertsil ODS-3V C18 column (250 mm × 4.6 mm, 5 µm, 100 Å). The mobile phase used was acetonitrile, mathanol and orthophosphoric acid (with pH 3.0). The samples were detected at a wavelength of 242 and 290 nm for the quantification of ritonavir and alpha tocopherol, respectively. The developed method was validated for parameters such as system suitability, specificity and selectivity, linearity, precison, recovery and robusteness of the method.

Results:
The responses were found to be linear over a range of 300 ng/mL to 30 µg/mL with a correlation coefficient value of 1 and 0.9999 for ritonavir and alpha tocopherol, respectively. The method was found to be precise with intraday and interday precision values less than 1% and less than 2%, respectively for both ritonavir and alpha-tocopherol. The limit of detection and limit of quantification of ritonavir were found to be 37.92 and 114.91 ng/mL, respectively for ritonavir and 129.94 and 393.76 for alpha-tocopherol, which revealed the sensitivity of developed method. The mean recovery values for ritnovir were 105.04, 102.28 and 101.48% and for alpha-tocopherol 101.69, 97.23 and 97.29 for concentration levels 75, 100, and 125%, respectively. The method showed good robustness deliberate changes in various chromatographic conditions such as pH of the buffer, column oven temperature, wavelength, and injection volume. The validated method was successfully applied for the quantification of ritonavir and alpha tocopherol in prepared nanoformulations. The assay value was found to be more than 92.86 and 106.89% for ritonavir and alpha-tocopherol, respectively.

Conclusions:
The proposed method was sensitive, precise, and accurate hence can be used for the simultaneous quantitative analysis of ritonavir and alphatocopherol in the nanoformulations.

Assessing in vivo and in vitro Stability of a Pretargeted, Bioorthogonal Anti-sense Oligonucleotide using Click Chemistry Tools, a One-step SPE, and LC-MS/MS

Stanley Goldstein, Pei Li, Brendon Cook (Biogen, Cambridge, MA)

Purpose:
By exploiting the rapid inverse electron-demand Diels-Alder (IEDDA) reaction between trans-cyclooctene (TCO) and tetrazine (Tz), Biogen has used a TCO-modified antisense oligonucleotide (ASO) in a pretargeted imaging strategy to visualize the distribution of ASO in CNS tissue. However, TCO groups are known to convert to cis-cyclooctene (CCO), an isomer that does not react with Tz; in this vein, the in vivo stability of ASO-TCO is unknown. Due to the nature of cis-trans isomerism and the inherent challenges of ASO bioanalysis, LC separation is not practical in stability assessments. In this poster, we employ methyltetrazine dibenzocyclooctyne (MeTz-DBCO) as a clickable probe to tag ASO-TCO and distinguish it from ASO-CCO. Both the unreacted ASO-CCO and the reacted conjugate can be extracted from samples using a one-step SPE and analyzed via LC-MS/MS.

Methods:
ASO-TCO and ASO-TCO-MeTz-DBCO conjugates were evaluated for charge-state distribution with a precursor ion scan in a tuning-by-injection approach; the same approach was applied to optimize MRM parameters. The molar ratio of reactants was determined by titration. Completeness of the reaction was confirmed by comparing against removal of ASO-TCO from solution using magnetic bead immobilization. The SPE method was optimized across a range of wash and elution conditions using Phenomenex Clarity OTX plates. Extracted samples were separated on an AB Sciex ExionLC with a Phenomenex Clarity Oligo-MS column. Detection was carried out on an AB Sciex QTRAP 6500+. Data were processed using Analyst software.

Results:
Our work began with optimization of the LC-MS/MS conditions for separation and detection of ASO-TCO. The compound was injected onto an ion-pair reversed-phase system and analyzed for charge state distribution using a precursor ion scan of 94.9 Da, which represents the phosphorothioate backbone. The most abundant charge states were selected and selection of product ions provided MRMs, which were tuned-by-injection and gave robust signal concurrent with good specificity. The optimized SPE method required a more basic elution buffer than we had used historically, owing to the properties imparted by the TCO group. After adjusting the pH of the elution buffer, recovery increased from 2 – 7% to 28 – 35%. The completeness of the click reaction was tested by titration of ASO-TCO against increasing concentrations of MeTz-DBCO; the result was confirmed by a similar titration against MeTz immobilized to biotinylated magnetic beads. We found that a 10-fold molar excess of MeTz groups was sufficient to react with ASO-TCO in solution, and that approximately 30% of ASO related material in our standards was not reactable. This procedure was applied to samples from in vivo and in vitro studies to assess the stability of ASO-TCO in mouse brain, artificial CSF, FBS, and PBS. As expected, ASO-TCO had a shorter half-life than ASO-CCO under all test conditions. Notably, in PBS and artificial CSF, in which total ASO is stable, the disappearance of ASO-TCO aligned with appearance of ASO-CCO. In the brains of live mice, ASO-TCO and ASO-CCO had half-life values of 3.3 and 4.7 days, respectively.

Conclusions:
By modifying the pH of the SPE elution buffer, a TCO-modified ASO can be extracted from biological samples in one step. The eluent sample can then be reacted with an excess of MeTz-DBCO to form ASO-TCO-MeTz-DBCO conjugate while leaving ASO-CCO intact. The signal intensities of conjugate and ASO-CCO can be compared across time points to determine rate constants for ASO-TCO and ASO-CCO, allowing for a half-life calculation.

In vitro Assessment of Drug-drug and Herb-drug Interactions of Cannabis-based Medicinal Products with Anticoagulant Drugs

Andrea Treyer, Daniela E. Eigenmann, Matthias Hamburger

Purpose:
Determine the risk of CYP450-mediated interaction of cannabis extracts, tetrahydrocannabinol (THC, dronabinol) and cannabidiol (CBD) with coumarin-derived anticoagulants.

Methods:
Human liver microsomes were incubated with the commercially available medicinal products Sativex (based on an ethanolic Cannabis extract containing both THC and CBD) and dronabinol solution (pure THC solution in ethanol), and an ethanolic pure CBD solution prepared in-house. Inhibition curves were established over a wide range from nanomolar to micromolar concentrations. The substrates warfarin, acenocoumarol and phenprocoumon were added at concentrations approximating their reported Km. The formation of hydroxylated metabolites was followed using LC-MS/MS quantification. CYP2C9, CYP2D6 and CYP3A4/5 isoform specific inhibitors and substrates were used as controls.

Results:
The control experiments with CYP isoform-specific substrates indicated that both THC and CBD inhibit all three major enzyme isoforms at micromolar concentrations. THC was a stronger inhibitor than CBD for CYP2C9 and CYP2D6, whereas CBD was a stronger inhibitor for CYP3A4/5. The cannabis extract, normalized for its THC content, presented synergistic inhibitory effects. CYP-mediated interactions were observed with all three coumarin derivatives, but large differences could be observed between the three drugs. IC50 values of CBD and THC were 20- and 10-fold higher for acenocoumarol than for warfarin.

Conclusions:
This in vitro study is in line with previously reported case studies where interactions between e.g. warfarin and CBD were observed in the clinic. Generally, the observed IC50 values were close to the highest reported CBD and THC plasma concentrations after ingestion or inhalation of cannabis-based products, indicating that interactions are possible at high doses. However, reports of clinically achieved plasma concentrations are scarce and other factors, such as protein binding, will need to be taken into account to better assess the relevance of these in vitro findings for clinical settings.

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