APPLIED PHARMACEUTICAL ANALYSIS

WEBINAR

OCTOBER 12-14, 2021

2021 WORKSHOPS: OCT 12 - Regulated Bioanalysis | OCT 13 - Discovery Bioanalysis & New Technologies | OCT 14 - Mechanistic ADME

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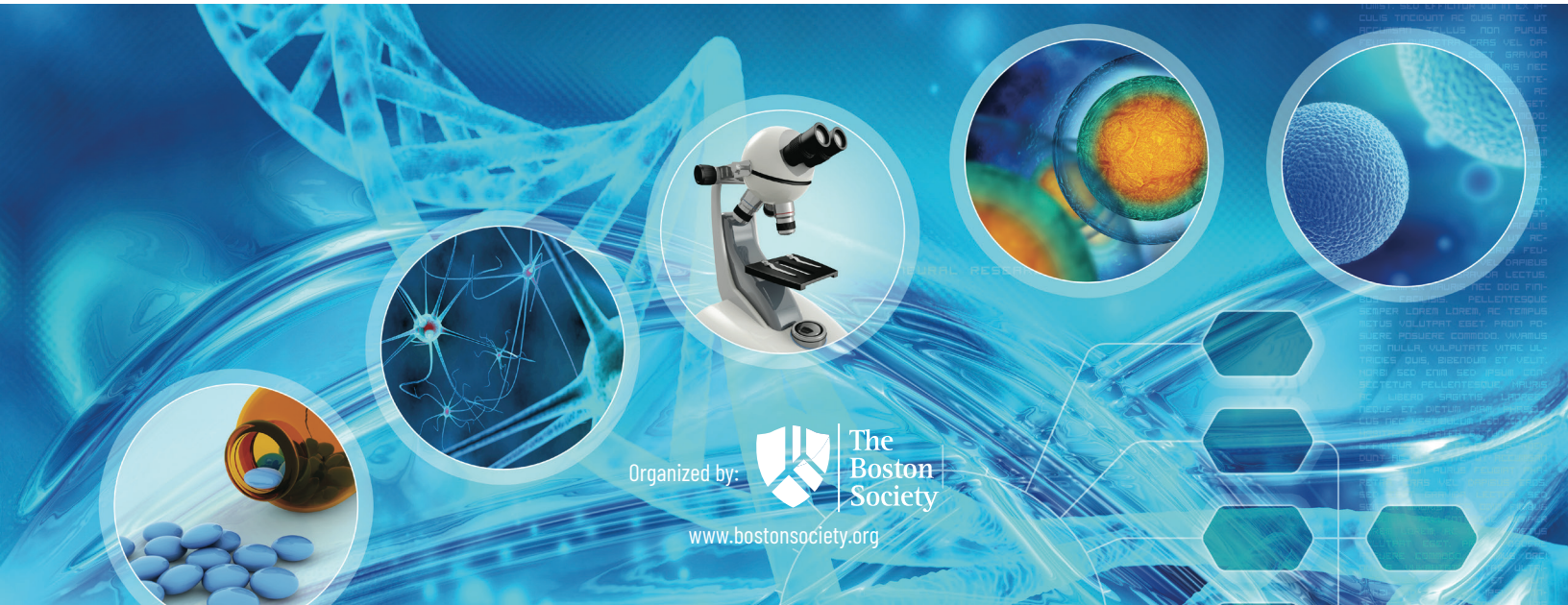

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ORGANIZERS' WELCOME

Welcome to the 2021 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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MECHANISTIC ADME

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APA 2021 CONFERENCE AGENDA

DAY 1: Tuesday, Oct. 12 | Regulated Bioanalysis Workshop

SESSION I: FDA/Regulatory Guidance

Session Chairs: Fumin Li, PPD; Ang Liu, BMS; Lori Payne, Alturas Analytics, and James Schiller, Merck

10:30 - 10:40 AM **Conference Opening & Session Introduction**

10:40 - 11:05 AM **Analytical Considerations for Biomarker Development and Qualification**
Abbas Bandukwala, FDA

11:05 - 11:10 AM **Q & A**

11:10 - 11:35 AM **Regulatory Considerations for Bioanalysis in Biosimilar Development**
Xiulian Du, FDA

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

11:40 - 12:05 PM **Bioanalytical Approaches to Support Individualized Dosing in Global Clinical Studies**
Julie Seroogy, BMS

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

12:10 - 12:55 PM **BREAK with Poster Presentations starting at 12:25**

12:55 - 1:20 PM **VENDOR PRESENTATION: Ultra-Sensitive Methods as a Means to Establish Levels for Key Biomarkers**
Photini Pitsikas, Charles River Laboratories

1:20 - 1:25 PM **Q & A**

1:25 - 1:40 PM **Bioanalytical Challenges: Developing a Rugged Chiral Assay for the Biomarker 2-hydroxyglutaric acid for Use in Routine Clinical Analysis of Plasma Samples from Oncology Studies**
Jennifer Zimmer, Alturas Analytics

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

1:45 - 2:05 PM **POSTER PRESENTATION**

2:05 - 2:25 PM **BREAK**

SESSION II: Recent Advances with Novel Modalities

Session Chairs: Darshana Jani, Agenus & Fumin Li, PPD

2:25 - 2:30 PM **Session Introduction**

2:30 - 2:55 PM **Bioanalytical Strategies for Advanced Modalities (Cell and Gene Therapies)**
Jim McNally, BioAgylitix

2:55 - 3:00 PM **Q & A**

3:00 - 3:25 PM **Bioanalysis ofTherapeutic Oligonucleotides using LC-MS and ELISA**
Noah Post, Ionis Pharmaceuticals

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

COVID 19 Vaccines and Therapeutics Development

Session Chair: Joseph Tweed, Cybrexa Therapeutics

3:30 - 3:35 PM **Plenary Speaker Introduction**
Joseph Tweed, Cybrexa Therapeutics

3:35 - 4:20 PM **KEYNOTE: *Building and Validating SARS-CoV-2 Analytical Assays During a Pandemic***
Jean-Claude Marshall, Moderna

4:20 - 4:30 PM **Q & A**

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

SESSION I: COVID 19 Vaccine, Diagnostics, and Treatment

Session Chairs: Jonathan Josephs, Genentech & Katie Matys, PPD

10:30 - 10:40 AM **Workshop Opening and Session Introduction**

10:40 - 11:00 AM **Disovery of SARS-CoV-2 Host-protein Targets for Antiviral Drug Repurposing**
Danielle Swaney, UCSF

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

11:05 - 11:35 AM **The Diagnostic Landscape of COVID-19: Overview of the various available diagnostics for COVID-19 (RT-PCR, POC, Ag, Ab, IL-6 etc)**
Allison McMullen & Allyson Kozak, Roche

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

11:40 - 12:05 PM **VENDOR PRESENTATION: Multiplexing LC-MS antibody PK method in support of COVID-19 Study**
Shengsheng Xu, Frontage

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

12:10 - 12:55 PM **BREAK with Poster Presentations starting at 12:25**

SESSION II: Lab of the Future

Session Chairs: Jonathan Josephs, Sanofi; Christopher Kochansky, Merck and Violet Lee, Genentech

12:55 - 1:00 PM **Session Introduction**

1:00 - 1:20 PM **Building Labs of the Future with Cloud Technology**
Lita Sands, AWS

1:20 - 1:25 PM **Q & A**

1:25 - 1:40 PM **TBA**
John Loughney, Merck

1:40 - 2:05 PM **TBA**
Patrick Bennett, PPD & Mark Arnold, LabCorp/Covance

2:05 - 2:25 PM **Round Table Discussion**

2:25 - 2:45 PM **BREAK**

2:45 - 3:00 PM **VENDOR PRESENTATION: Optimer Ligands to Enable Drug Discovery and Development**
David Bunka, Aptamer Group

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

3:05 - 3:25 PM **VENDOR PRESENTATION: New Flexible HRMS Platform for Improved Bioanalysis Sensitivity**
David Colquhoun, SCIEX

3:24 - 3:30 PM **Q & A**

SESSION III: Cell and Gene Therapies

Session Chairs: Elizabeth Groeber, Charles River Laboratories; Hiroshi Sugimoto, Takeda & Katie Matys, PPD

3:30 - 3:35 PM **Session Introduction**

3:35 - 3:55 PM **Role of Hybrid LC/MS in Cell and Gene Therapies: Prospective and Case Studies**
Dong Wei, Takeda

3:55 - 4:00 PM **Q & A**

4:00 - 4:20 PM **ddPCR Work Assay Development and Validation for Gene Therapy + Linkage Analysis and Multiplexing**
Andrew Melton, BioMarin

4:20 - 4:25 PM **Q & A**

4:25 - 4:45 PM **Bioanalytical Approaches in Support of Novel Biological Therapies**
Alex Kozhich, BMS

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

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

SESSION I: ADME Challenges with Degraders and other bRo5 Compounds

Session Chairs: David Stresser, AbbVie and Lisa Christopher, BMS

10:00 - 10:10 AM **Workshop Opening & Session Introduction**

10:10 - 10:30 AM **Optimizing Proteolysis - Targeting PROTAC for Oral Drug Delivery: A Drug Metabolism and PK Perspective**
Matthias Wittwer, Roche

10:30 - 10:35 AM **Q & A**

10:35 - 10:55 AM **Molecular Chameleonicity and Cell Permeability of Drugs and PROTACs in the bRo5 Space**
Jan Kihlberg, Uppsala University

10:55 - 11:00 AM **Q & A**

11:00 - 11:05 AM **Plenary Speaker Introduction**
David Stresser, AbbVie

11:05 - 11:35 AM **KEYNOTE: *Mining AbbVie's Global ADME Database for New Insights into Oral Absorption of bRo5 Drugs***
David Degoey, AbbVie

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

11:40 - 12:30 PM **BREAK & Poster Presentation**

12:30 - 12:45 PM **VENDOR PRESENTATION: Parallel Synthesis of Metabolites and Late-Stage Oxidized Derivatives of Lead Compounds - Dual Purpose Application of PolyCYPs Enzymes**
Julia Shanu-Wilson, Hypha Discovery

12:45 - 12:50 PM **Q & A**

12:50 - 1:10 PM **Can We Predict the Vss and Tissue Distribution of Targeted Protein Degraders using Mechanistic PBPK Models?**
Vaishali Dixit, Kymera Therapeutics

1:10 - 1:15 PM **Q & A**

1:15 - 1:35 PM **A Global Analysis of Models for Predicting Human Absorption QSAR, In vitro, and Pre clinical Models**
Edward Price, AbbVie

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

SESSION II: Mechanistic ADME and COVID

Session Chairs: Chandra Prakash, Agios Pharmaceuticals and Greg Walker, Pfizer

1:40 - 1:45 PM **Session and Plenary Speaker Introduction**

1:45 - 2:20 PM **KEYNOTE: *Why are Patients with COVID-19 at Risk for DDI, and What Can be Done to Minimize the Adverse Outcomes***
Sheldon Preskorn, MD, Department of Psychiatry and Behavioral Sciences, Wichita School of Medicine

2:20 - 2:25 PM **Q & A**

2:25 - 2:45 PM **Late-Stage Lead Diversification: Application to Inhibitors of SARS-CoV-2 Main Protease to Combat COVID-19**
Manjinder Lall, Pfizer

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

2:50 - 3:10 PM **BREAK**

SESSION III: Hot Topics

Session Chairs: Nagendra Chemuturi, Takeda and Silvi Chacko, BMS

3:10 - 3:15 PM **Session Introduction**

3:15 - 3:30 PM **Evaluation of Tissue Binding in Three Tissues across Five Species and Prediction of Volume of Distribution from Plasma Protein and Tissue Binding with an Existing Model**
Fabio Broccatelli, Genentech

3:30 - 3:35 PM **Q & A**

3:35 - 3:50 PM **Liquid Biopsy and its Application in Characterizing Individual Hepatic Drug Elimination Capacity**
Brahim Achour, University of Manchester

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

3:55 - 4:10 PM **What Is HLM-HHEP Disconnect Telling Us?**
Li Di, Pfizer

4:10 - 4:15 PM **Q & A**

4:15 - 4:30 PM **Developing Oligonucleotide Therapeutics, Considerations for DMPK Scientists**
Diane Ramsden, Takeda

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

APA ABSTRACTS

REGULATED BIOANALYSIS WORKSHOP

SESSION I: FDA/REGULATORY GUIDANCE

Analytical Considerations for Biomarker Development and Qualification
Abbas Bandukwala, FDA

The 21st Century Cures Act provided a regulatory framework for biomarker qualification as a drug development tool. This presentation will provide information on the CDER Biomarker Qualification Program (BQP) and the regulatory pathway to biomarker qualification. The presentation will discuss analytical considerations for these submissions which will be included in a future Biomarker Qualification Program Analytical Considerations Guidance Document.

Regulatory Considerations for Bioanalysis in Biosimilar Development
Xiulian Du, FDA

To support regulatory approval of biosimilar drugs, data are required to demonstrate that the biosimilar product is highly similar to the reference product, and there are no clinically meaningful differences between the biosimilar product and the reference product in terms of the safety, purity, and potency of the product. A pharmacokinetics (PK) study evaluating the similarity of systemic exposures is generally an important component of biosimilar programs. There are special considerations for the bioanalytical method used to evaluate PK similarity. As an example, the method performance bias between the biosimilar and reference products can affect the conclusion of PK similarity; therefore, the use of one method approach is proposed to minimize the impact of differences in method performance between biosimilar and reference products. Demonstrating method comparability is a practical step necessary to support the implementation of the one-method approach. This talk will provide an overview of the one method approach.

Bioanalytical Approaches to Support Individualized Dosing in Global Clinical Studies
Julie Seroogy, BMS

The role of pharmacokinetics in Phase 3 clinical studies is important depending on the program and therapeutic area. PK and exposure-response relationship characterization in the patient population of interest may be useful for better understanding the drug target range for efficacy and safety.

Therapeutic drug monitoring could be considered in the context of the Phase 3 study. Certain therapeutic areas like antibiotics, antiepileptics, and anticoagulants commonly employ TDM to individualize dosing/treatment or for safety monitoring. TDM may also be used for other therapeutic areas when real-time drug concentrations are needed for patient care.

The laboratory selection process and regulatory framework needed to support PK and TDM sample analyses in global clinical studies is important to ensure data quality for the study and regulatory submission. Typically, Good Clinical Laboratory Practices (GCLP) laboratories and/or CLIA certified laboratories are utilized, however a "fit-for-purpose" approach should be used in these decisions. While GCLP and CLIA are more similar than different, management at a GCLP lab must have appropriate quality standards and experience in place when the problem of GCLP and CLIA overlap arises.

This presentation will provide our experience where GCLP and CLIA assays have concurrent roles in global clinical studies. In the first case study, our experience converting a bioanalytical assay to a therapeutic drug monitoring assay for an FDA approved compound will be discussed. In the second case study, we will discuss our experience using a GCLP assay as the basis for a TDM assay during Phase 3 clinical studies. Lead time, resources, and development risks should be considered in the PK or TDM strategy and the laboratory selection process.

VENDOR PRESENTATION

Ultra-Sensitive Methods as a Means to Establish Baseline Levels for Key Biomarkers
Photini Pitsikas, Charles River Laboratories

According to the World Health Organization, Cardiovascular disease (CVD) is the number one cause of death globally. It is not surprising that several pharmaceutical companies are researching new treatments against CVD since such diseases can lead to acute myocardial infarction (AMI). It is also noteworthy that cTnI is a very effective

translational safety biomarker. As such, baseline concentration levels provide valuable safety assessment data. Therefore, it is critical to have immunoassays capable of measuring slight cTnI variations in different species.

Developing a Rugged Chiral Assay for the Biomarker 2-hydroxyglutaric acid for use in Routine Clinical Analysis of Plasma Samples from Oncology Studies

Jennifer Zimmer, Alturas Analytics

Investigators have shown that one enantiomer of hydroxyglutarate (D-2-HG) is abnormally accumulated in a variety of human cancers, such as glioblastoma, acute myeloid leukemia and cholangiocarcinoma. The isocitrate dehydrogenase (IDH) enzyme normally catalyzes the conversion of isocitrate to alpha-ketoglutarate (α-KG), but in these types of cancer, mutant IDH enzymes acquire an abnormal enzymatic activity which allows them to convert α-KG into D-2-HG. The measurement of D-2-HG levels can be used to monitor tumor burden and effectiveness of cancer treatments meant to inhibit mutant IDH.

We have developed and validated a chiral assay for D-2-HG that allows us to accurately quantify levels of this analyte from plasma samples. This assay employs a surrogate matrix in order to quantify absolute levels in the plasma samples. Because D-2-HG is a very small analyte, derivatization was required in order to separate the enantiomers as well as to increase ionization to achieve the desired lower limit of quantitation.

SESSION II: RECENT ADVANCES WITH NOVEL MODALITIES

Bioanalytical Strategies for Advanced Modalities (Cell and Gene Therapies)

Jim McNally, BioAgilytics

Novel biotherapeutics such as cell and gene therapy have unique challenges for bioanalysis. Pharmacokinetics and immunogenicity testing take on different forms and timing for implementation as compared to "standard" large molecule biotherapeutics. There are a number of different platforms and strategies utilized which will be discussed in this presentation. Emphasis on the unique aspects of bioanalysis with these therapies will be given. Since regulatory guidance is forthcoming in this space, the presentation will address where current guidance applies and common industry practices have been implemented.

Bioanalysis of therapeutic oligonucleotides using LC-MS and ELISA

Noah M. Post, Ionis Pharmaceuticals Inc.

While the pharmacokinetic (PK) properties of first- and second-generation antisense oligonucleotides (ASOs) are generally well understood, advances in medicinal chemistry have led to new modifications that have significantly altered ASO PK profiles. Understanding the PK of these new ASOs is critical to select an appropriate bioanalytical method to characterize them. A challenging aspect of this is that there are several orders of magnitude difference in concentrations between high accumulating tissues, such as kidney cortex and liver with concentrations in the µg/g range, and the trough plasma with concentrations in the 10's of ng/mL range or lower, which often necessitates the use of multiple assay methods, such as the ligand-binding methods and chromatographic methods. The different levels of sensitivity required for different assays means that each method must address the specific needs of each matrix. This presentation will discuss the challenges of using either a LBA or LCMS/MS method for ASO quantitation in the validated setting for both tissues and plasma. Additionally, while in many situations either method type may be used, a case study that needed both methods to fully characterize an ASOs PK is discussed, including addressing how to not duplicate GLP data.

DISCOVERY BIOANALYSIS & NEW TECHNOLOGIES WORKSHOP

SESSION I: COVID 19 VACCINE, DIAGNOSTICS, AND TREATMENT

Disovery of SARS-CoV-2 Host-protein Targets for Antiviral Drug Repurposing

Danielle Swaney, UCSF

Viruses hijack host proteins to promote viral replication and evade immune response. Here we have used proteomics approaches to identify hijacked host proteins, revealing numerous drugs in clinical trial or with FDA-approval that both target these hijacked proteins and inhibit SARS-CoV-2 infection in vitro.

The Diagnostic Landscape of COVID-19: Overview of the various available diagnostics for COVID-19

Allison McMullen & Allyson Kozak, Roche Diagnostics

This presentation will explore SARS-CoV-2 testing methodologies including molecular, antigen and serological approaches, as well as critical considerations when keeping up with this adaptable and ever-changing virus.

At the end of the session, the participants will be able to:

1. Recognize the challenges associated with designing diagnostic tests for SARS-CoV-2
2. Describe the differences between molecular, antigen and serology testing for SARS-CoV-2

VENDOR PRESENTATION

Multiplexing LC-MS/MS antibody PK method in support of COVID-19 Study

Shengsheng Xu, Frontage Laboratories, Inc.

Purpose

A multiplexing LC-MS/MS PK method was developed and validated to support preclinical study of a combo antibody therapy to treat SARS-CoV-2 infection. As SARS-CoV-2 continues to spread worldwide, it has already resulted in over 230 million cases and 4.7 million death. As one of the potential treatments of COVID-19, monoclonal antibody comb therapy is under development to treat SAR-CoV-2 infection by binding specifically to the receptor binding domain of the spike glycoprotein of the virus and blocking the viral entry into host cells. Comparing the traditional LBA PK assay, the multiplexing LC-MS/MS method will provide with the superior specificity and better efficiency to facilitate the process of drug development.

Method

The bottom-up approach was used for the antibody quantification using immunocapture LC-MS/MS method. Three surrogate peptides produced from trypsin/Glu-C co-digestion were selected to represent three monoclonal antibodies in the combo therapy. Anti-human IgG antibody was chosen to extract monoclonal antibodies from rat serum. To remove the interference compound from anti-human IgG antibody, a two-time acid wash (0.1 % TFA) was applied. This method was fully validated by following current FDA bioanalytical method validation guidance.

Results

The assay was validated with a quantitative range of 0.5 to 100 µg/mL per antibody. The accuracy (% bias) and precision (% CV) of QCs were within ± 25% for LLOQ and ± 20% for other concentration levels. The R2 of all calibration curves is above 0.98. No matrix effect was observed for this method. Recovery for mAb A, B, C at low, middle and high QC concentrations was around 62.7%, 93% and 27% respectively. The interconversion from each mAb to the other two mAbs was not observed in rat serum. Stability of those three mAbs was also evaluated to cover sample collection and handling.

Conclusions

A multiplexing LC-MS/MS method was developed and validated for the quantitation of three anti-SAR-CoV-2 monoclonal antibodies in rat serum. The method was demonstrated to be efficient, sensitive, robust and reliable.

SESSION II: LAB OF THE FUTURE

Building Labs of the Future with Cloud Technology

Lita Sands, AWS

Life sciences and biotech companies are balancing traditional "wet lab" environments while incorporating digital lab technology. Learn how cloud based analytics, artificial intelligence and machine learning (AI/ML) in the research lab can accelerate new discoveries while automating repetitive tasks; allowing scientists to free their time for value-add activities. Hear how leading organizations leverage AWS cloud services and solutions for data capture and storage, data sharing and collaboration, analytics, and AI/ML - accelerating their time to science while complying with industry regulations.

VENDOR PRESENTATION

Optimer® Binders to Enable Novel Analytical Targets and Techniques

David Bunka, Aptamer Group

Optimers are next-generation nucleic acid-based antibody mimetics engineered to enable research and development of new targets, new assays and new processes. Benefits include speed to discovery, wide target range, batch consistency, specificity and stability. Optimer binders are being employed in a range of analytical techniques to validate novel biomarkers, monitor novel targets, including small molecule drugs, and offer robust analysis of critical quality attributes. We have shown the potential of the Optimer platform to generate tailored binders to unlock targets and enable quality processes in pharmaceutical analysis.

VENDOR PRESENTATION

New Flexible HRMS Platform for Improved Bioanalysis Sensitivity
David Colquhoun, SCIEX

Though quantification of small molecules and therapeutic targets in matrices is typically performed using nominal mass instruments, some analytical methods are being transferred onto the high-resolution instruments to gain added selectivity. However, high-resolution mass spectrometers are still faced with critical challenges including reaching the desired sensitivity and linear dynamic range (LDR). In this presentation, a novel high-resolution QTOF mass spectrometer with greater MS/MS sampling efficiency was used for studies involving the quantitative analysis of small molecules and therapeutic targets in matrix.

SESSION III:
CELL AND GENE THERAPIES

Role of Hybrid LC/MS in Cell and Gene Therapies: Prospective and Case Studies
Dong Wei, Takeda

Cell and gene therapies are rapid growing modalities holding significant promise in many therapeutic areas such as oncology and rare diseases. Multiple bioanalytical platforms are implemented during the development of these novel modalities to evaluate PK/CK/PD, biodistribution, and immunogenicity. Hybrid LC/MS is emerged as a powerful tool in the measurement of transgene proteins and biomarkers such as target antigens, which is demonstrated in case studies.

MECHANISTIC ADME WORKSHOP

SESSION I:
ADME CHALLENGES WITH DEGRADERS AND OTHER bRo5 COMPOUNDS

Molecular Chameleonicity and Cell Permeability of Drugs and PROTACs in the bRo5 Space
Jan Kihlberg, Uppsala University

We have studied the conformations of orally absorbed drugs and PROTACs in the bRo5 space using NMR spectroscopy and analysis of crystal structures and found that they often behave as molecular chameleons. In an apolar, membrane-like environment they populate less polar and more compact conformational ensembles than in a polar environment such as water. As a result of the balance between rigidity and flexibility molecular chameleons combine aqueous solubility, cell permeability and target binding; properties that otherwise would have been mutually exclusive for compounds in the bRo5 space.

Predicting the conformations and properties of molecular chameleons is difficult, but classification models developed by machine learning show great promise for differentiation between compounds that have high or low cell permeability. Conformational sampling using molecular mechanics force fields appears useful for fairly rigid macrocycles, whereas more flexible compounds remain challenging. However, some general guidelines for design of molecular chameleons are beginning to emerge.

KEYNOTE PRESENTATION

Mining AbbVie's Global ADME Database for New Insights into Oral Absorption of bRo5 Drugs
David Degoey, AbbVie

Among the many challenges of drug discovery in beyond rule of five (bRo5) chemical space is a lack of correlation between in vitro ADME data and in vivo pharmacokinetic results. The discrepancy may arise from the challenging physicochemical properties, such as low solubility, for compounds in bRo5 chemical space compared to Ro5 compliant drugs for which most assays were developed. This results in a high reliance on in vivo testing for bRo5 drug discovery projects, along with inefficient triage of chemical series to identify the most promising ones. With a long history in antiviral and oncology protein-protein interaction inhibitor (PPI) discovery, AbbVie has a rich bRo5 data set for the evaluation of new physicochemical property descriptors and assays that might be part of a more effective drug discovery toolbox for medicinal chemists. New aspects of our ongoing analysis will be described.

VENDOR PRESENTATION

Parallel Synthesis of Metabolites and Late-Stage Oxidized Derivatives of Lead Compounds – Dual Purpose Application of PolyCYPs Enzymes
Julia Shanu-Wilson, Hypha Discovery

Hydroxylation has been identified as a key tactic to consider as part of a late-stage functionalization strategy to expand the medicinal chemistry toolbox (Boström et al., 2018).

The potential benefits of hydroxylation are multifold, including the ability to probe for beneficial polar interactions, enhance potency, selectivity and DMPK properties and to widen SAR. Approaching hydroxylation using a biocatalytic approach also offers a unique opportunity to identify and interrogate metabolites in parallel at a relatively early stage.

Hypha have developed a biocatalytic process for late-stage oxidation using a diverse set of cytochrome P450s – PolyCYPs® – recombinant enzymes cloned from Hypha's actinomycete bacteria and expressed in E.coli. Due to the wide range of organic molecules that PolyCYPs are able to oxidise, they are ideal catalysts for generation of multiple oxidised derivatives in parallel, whilst simultaneously exploring the possibility of active metabolites.

To expedite this process, called PolarExplorer, series of lead compounds are rapidly screened against a set of PolyCYPs enzymes to determine their susceptibility to late-stage oxidation. Compounds, for which usable conversions to oxidised products are observed, can then be prioritised for scale-up reactions to generate sufficient material for pharmacological testing and subsequent structural identification of active derivatives by cryoprobe NMR. This poster presentation will exemplify this process using a series of client compounds.

SESSION II: MECHANISTIC ADME AND COVID

A Global Analysis of Models for Predicting Human Absorption: QSAR, In vitro, and Pre-clinical Models

Edward Price, AbbVie

Models intended to predict intestinal absorption are an essential part of the drug development process. Although many models exist for capturing intestinal absorption, many questions still exist around the applicability of these models to drug types like "beyond rule of 5" (bRo5) and low absorption compounds. This presents a challenge as current models have not been rigorously tested to understand intestinal absorption. Here, we assembled a large, structurally diverse dataset of ~1000 compounds with known in vitro, preclinical, and human permeability and/or absorption data. In silico (quantitative structure–activity relationship), in vitro (Caco-2), and in vivo (rat) models were statistically evaluated for predictive performance against this human intestinal absorption dataset. We expect this evaluation to serve as a resource for DMPK scientists and medicinal/computational chemists to increase their understanding of permeability and absorption model utility and applications for academia and industry.

KEYNOTE PRESENTATION

Why Are Patients With COVID-19 at Risk for Drug-Drug Interactions and What Can be Done to Minimize the Adverse Outcomes

Sheldon Preskorn, Wichita School of Medicine

COVID-19 can range from a mild to a life-threatening illness. Individuals with the more serious forms of this illness are also at an increased risk for experiencing drug-drug interactions which can further complicated their outcomes. This presentation will provide information to healthcare professionals and the general public with information about drug-drug interactions (DDIs) and why DDIs are important to consider in those at serious risk of illness with COVID-19 to reduce the likelihood of adverse outcomes. It will cover the following points:

1) Multiple medication use is common and can be complex as documented by pharmacoepidemiological studies.
2) Patients at high risk for serious illness from COVID-19 are also at high risk for DDIs.
3) How to conceptualize DDIs?
4) How DDIs can present clinically.
5) Methods for preventing or mitigating DDIs.
6) Tools that can be used to avoid unintended and high risk DDIs including the University of Liverpool drug interaction checker

Late-Stage Lead Diversification: Application to Inhibitors of SARS-CoV-2 Main Protease to Combat COVID-19

Manjinder Lall, Pfizer

An experimental approach is described for late-stage lead diversification (LSLD) of inhibitors of SARS-CoV-2 main protease. The approach subjects lead molecules to P450 biotransformations and chemical transformations, generating a variety of new products for structure–activity relationships. A key feature of the strategy is the many ways by which C–H bond activation can be exploited to explore chemical space through incorporating -OH, -F or -CF3 groups. Another advantage to the approach is the utilization of microcryoprobe nuclear magnetic resonance (NMR) spectroscopy, which permits the use of low amounts of starting materials (1–5 µmol). Consequently, the method delivers multiple analogues from a single lead with known structure and concentration for in vitro pharmacology, permeability

and metabolic stability screening. Application of this approach resulted in the discovery of potent COVID-19 inhibitors with improved physicochemical properties.

SESSION III: HOT TOPICS

Evaluation of Tissue Binding in Three Tissues across Five Species and Prediction of Volume of Distribution from Plasma Protein and Tissue Binding with an Existing Model

Fabio Broccatelli, Genentech

The process of small molecule lead discovery towards the identification of a clinical candidate involves the optimization of the multi-parameter function defining therapeutic dose.

When the PKPD driver for efficacy is time over potency threshold, the optimization of drug in vivo half-life (hence VDss and CL) becomes an important objective.

While physiologically relevant and accurate models for VDss predictions from in vitro and physiochemical data are routinely incorporated in the late stage dose projection, their early adoption of the model might be limited by the reliance on experimental in vitro parameters that are not readily available for most new chemical entities.

In this work we explore, validate and expand a recent model proposed by Nagar and Korzekwa that utilizes routine in vitro binding assays to predict VDss. The usefulness of this model will be contextualized in the early compound optimization process.

Liquid Biopsy and its Application in Characterizing Individual Hepatic Drug Elimination Capacity

Brahim Achour, University of Manchester

Tailoring drug dosage regimens according to a patient's characteristics and specific needs, or so-called precision dosing, has recently been reinvigorated by the availability of novel technologies for characterising patients and wider acceptance of simulated drug trials. The concept is most useful for dosing drugs with a narrow therapeutic index and for patients from special populations or those prone to polypharmacy. In these cases, refined dosing is essential in order to improve therapeutic response and lower the risk of toxicity. The bottleneck for wider application of model-informed precision dosing (MIPD) has been the lack of approaches capable of generating individual 'system' data relevant to the patient's drug elimination capacity, such as the abundance of hepatic enzymes and transporters. The recent development of liquid biopsy technology, as a less invasive alternative to tissue biopsy, opened new avenues for MIPD.

This talk introduces the audience to the technique but focuses on the practical application of liquid biopsy with modelling and simulation in the area of drug dose individualization. The applications of such approach include effective clinical trial design in the drug development sphere and replacing the prevailing 'trial-and-error' approach to dosing in the clinic with model-informed decision making.

What Is HLM-HHEP Disconnect Telling Us?

Li Di, Pfizer

HLM (human liver microsomes) and HHEP (human hepatocytes) are both commonly used in drug discovery to measure intrinsic clearance and inhibition parameters of drug candidates. HLM and HHEP disconnects provide mechanistic insights on metabolic pathways and the rate-limiting step. When HHEP clearance is faster than HLM, non-CYP enzymes (e.g., AO, reductases) may be involved in metabolism. When metabolic rate is greater than permeability rate across the cell membrane, permeability becomes rate-limiting, resulting in HLM clearance higher than HHEP. P-gp efflux transport has minimal effect on HLM-HHEP disconnect for both clearance and inhibition. When HLM clearance is greater than HHEP, HLM is more predictive of human in vivo hepatic clearance than HHEP, suggesting in vivo passive intrinsic clearance is higher than in vitro. Poor passive permeability can also cause IC50 disconnect between HLM and HHEP leading to more potent IC50 in HLM. Prediction accuracy of drug-drug interactions is model dependent, when using in vitro inhibition potency from HLM or HHEP.

APA BIOGRAPHIES

Brahim Achour, University of Manchester: Brahim Achour is a research fellow at the Centre for Applied Pharmacokinetic Research (CAPKR), the University of Manchester, overseeing projects in the areas of liquid biopsy, precision dosing and proteomics. Dr Achour has co-authored more than 40 articles (H-index 19), as well as several patents as co-inventor of a novel liquid biopsy test. Brahim has extensive experience in multi-'omics' with specific expertise in quantitative proteomics and transcriptomics applied to the investigation of drug metabolism and transport. Along with experimental work, Brahim has teaching and consultancy responsibilities for external and affiliated companies and institutions in relation to the use of systems data in PBPK and liquid biopsy applications.

Mark Arnold, PhD, Labcorp: Dr. Arnold is Director of Science in Scientific Affairs for Labcorp Drug Development. In that role, he collaboratively develops the bioanalytical scientific and regulatory strategy to meet current and future client needs for ligand-binding, PCR, cell-based and LC-MS/MS assays to quantify drugs and metabolites, antidrug antibodies and biomarkers in animal and clinical biological samples to support pharmacokinetic and pharmacodynamic assessments. Mark was previously Executive Director of the Bioanalytical Sciences Department of the Bristol-Myers Squibb Co. He received a B.S. in biology from Indiana University of Pennsylvania and Ph.D. in pharmacology from the University of Pittsburgh. For more than 35 years, Dr. Arnold has been involved in the field of bioanalysis, including the review and interpretation of regulations and guidance as they apply to the evolving field of bioanalysis. He was co-chair of both the AAPS Crystal City V and VI Workshops on the 'FDA Draft Revised Guidance on Bioanalytical Method Validation' and 'Biomarkers', respectively. He is actively involved the Land O'Lakes Bioanalytical Conference, American Association of Pharmaceutical Scientists (AAPS, 2021 Scientific Program Chair for PharmSci360) and is an AAPS Fellow (2014). Dr. Arnold has over 100 peer-reviewed publications, and numerous invited podium presentations.

Abbas Bandukwala, FDA: Abbas Bandukwala graduated from Vanderbilt University as a Biomedical Engineer. He then served 5 years as a United States Naval Officer. He completed his Master's degree in chemical engineering from University of Maryland. He joined the FDA in 2009 in the Center of Devices and Radiological Health (CDRH), and reviewed pre-market applications for light based devices. In 2017, he moved from CDRH and became part of the Center Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP).

Patrick Bennett, PPD: Patrick Bennett is the Vice President PPD Laboratories Strategy and Development. He has over 35 years of experience in the industry. Patrick joined PPD in 2013 to establish the PPD Biomarker Laboratory. He is current involved in oversight of the new PPD Lab in Suzhou, China, Cell and Gene Therapy strategy, Decentralized Clinical Trials and external partnerships, mergers and acquisitions. Previously, Patrick was the global strategic marketing director for pharma/biopharma life sciences mass spectrometry at Thermo Fisher Scientific, Vice President of business development and Executive Director of Labs at Tandem Labs. He was also Sr. Lab Director at Advion (currently Q2 solutions) and a Research Scientist at BMS.

Patrick completed his B.S. Degree in Toxicology and M.S. Degree in Pharmacology at St. John's University and a Master of Business Administration in Marketing from Syracuse University.

Fabio Broccatelli, PhD, Genentech: Dr. Fabio Broccatelli received his PhD in computational chemistry from the University of Perugia working in Gabriele Cruciani's lab. His doctoral work focused on utilizing computational chemistry and machine learning to predict ADME properties. During his PostDoc at the Institute of Cancer Research London, he contributed to the discovery of the MPS-1 inhibitor BOS-172722 (currently in the clinics).

Dr. Broccatelli is a Principal Scientist at Genentech where he leads a group of scientists specializing in AI, PBPK and large trend analysis IVIVc. He leads several small molecule research wide initiative focused on AI, and supports therapeutic projects both as DMPK and computational chemistry team lead.

Dr. Broccatelli was awarded with the 2013 AAPS Manuscript Award, has published over 25 peer reviewed articles, patents and book chapters.

Dr. Broccatelli initiated and served as led for a cross-industry IQ working group including 17 pharmaceutical companies with the goal of influencing decision making through in silico ADME modeling.

David Bunka, PhD, Aptamer Group: David holds a Ph.D. in Molecular Biology and has spent over 20 years developing nucleic acid aptamers against a wide variety of targets, including small molecules (antibiotics, food contaminants, chemotherapeutics), disease associated proteins, several cancer associated cell-lines, viruses and tissue biopsies. This has been facilitated through the use of high throughput automated aptamer selection methods. David has built up a solid international reputation in the field and has authored several peer reviewed research articles, invited review articles and a book chapter on aptamer based therapeutics. He has also given many guest seminars covering aptamer-based applications, at top universities and international conferences.

David Colquhoun, PhD, SCIEX: David is the Biologics Workflows Specialist for SCIEX in the Mid-Atlantic. He has worked at SCIEX for over 5 years. David received his Ph.D. in Environmental Health Engineering from the Johns Hopkins Bloomberg School of Public Health, where he focused on the Public Health application of mass spectrometry for protein biomarkers. David held various roles at Johns Hopkins University School of Medicine prior to moving into industry. He currently lives in Westminster, MD.

David DeGoey, PhD, AbbVie: Dr. DeGoey is a Research Fellow at AbbVie. He received a B.S. degree in Chemistry from the University of Wisconsin Madison and earned a Ph.D. in Chemistry from Harvard University. He joined Abbott (now AbbVie) in 1995 where he has spent a large portion of his career in infectious diseases research working on the discovery of drugs in beyond rule of five chemical space to treat fungal, bacterial, and viral diseases, including HIV and hepatitis C. He co-led the medicinal chemistry team that discovered AbbVie's HCV NS5A inhibitors that are now approved for use in combination with other direct acting antivirals. He is currently part of the Centralized Medicinal Chemistry team at AbbVie, where he is responsible for lead optimization for projects across therapeutic areas.

Li Di, PhD, Pfizer: Dr. Li Di has over 25 years of experience in the pharmaceutical industry including Pfizer, Wyeth and Syntex. She is currently a research fellow at Pfizer Worldwide Research and Development, Groton, CT. Her research interests include the areas of drug metabolism, pharmacokinetics, drug-drug interactions, absorption, transporters, and blood–brain barrier. She has over 160 publications including two books and presented over 95 invited lectures. She is a recipient of the Thomas Alva Edison Patent Award, the New Jersey Association for Biomedical Research Outstanding Woman in Science Award, the Wyeth President's Award and Peer Award for Excellence.

Vaishali Dixit, PhD, Kymera: Dr. Dixit is currently Director of DMPK at Kymera Therapeutics where she leads the Modeling and Simulation function. She received Ph.D at University of Florida in Dr. Margaret James lab where she worked on environmental toxins and their metabolites in drinking water and the impact on fish. She did her post-doctoral fellowship at the University of Washington in the labs of Jash Unadkat and Nina Isoherranen with emphasis on DDI. After post-doctoral training she worked at Vertex pharmaceuticals for 8 years and Eisai Inc for 4 years where she worked in infectious disease and oncology therapeutic areas enabling programs through discovery and early clinical development. Her areas of emphasis and expertise are PK/PD and PBPK modeling.

Xiulian Du, PhD, FDA: Dr. Xiulian Du is a senior science advisor in the office of clinical pharmacology of center of drug evaluation and research at FDA (OCP/CDER/FDA) and is responsible for reviewing bioanalytical methods for biologics. Prior to joining at FDA, she had worked at Regeneron Pharmaceutical for 7 years and 9 months where she led the bioassay group for bioanalytical method development and validation to support multiple biologics drug commercialization/filings. Before Regeneron, she worked at NIH Vaccine Research Center for 9 months and Neogenix Oncology Inc for 3 years. Her research focused on biologics drug discovery and development, including biologics drug characterization, safety evaluation, and bioanalytical method development.

Dr. Du received her Ph.D. degree from the School of Pharmacy of Peking University and completed postdocs training in biomedical research at the Medical School of the University of Pennsylvania.

Jan Kihlberg, Uppsala University: Jan Kihlberg holds a chair in Organic Chemistry at Uppsala University, Sweden since 2013. Before moving to Uppsala he spent ten years at AstraZeneca R&D in Gothenburg, first as Director of Medicinal Chemistry and then as Director of Competitive Intelligence and Business Foresight Analysis. Prior to that he was Professor in Organic Chemistry at Umeå University during 1996-2003, after leaving Lund University where he established his independent research group in 1991. Professor Kihlbergs main research interests is to understand what properties convey cell permeability, aqueous solubility and target binding to drugs and PROTACs in the beyond rule of 5 chemical space and to translate this knowledge into guidelines for design. He is also involved in synthesis of macrocycles as ligands for difficult-to-drug targets, and of glycopeptides and peptides for use in diagnostics and treatments for rheumatoid arthritis. He has published 165 peer reviewed articles, 16 research reviews and four book chapters.

Allyson Kozak, PhD, Roche: Dr. Allyson Kozak is a field-based Scientific Liaison at Roche Diagnostics for core lab and point of care, whose primary objectives include delivering critical scientific exchange in support of healthcare professionals and aligning internal medical, commercial and support stakeholders. She has a wide-range of scientific expertise, from education and communication development, to laboratory management with a focus on core lab chemistry, special chemistry, toxicology and critical care. In her current role, she serves in an educational, scientific expertise role, responding to scientific inquiries and guiding clinical studies. Prior to Roche Dr. Kozak was Laboratory Medical Director for MetroHealth in Cleveland, Ohio, overseeing chemistry, special chemistry, critical care and toxicology testing and Assistant Professor at Case Western Reserve University School of Medicine.

She is a board certified clinical chemist and received her PhD in analytical chemistry and an MBA in finance from Ohio University, as well as a bachelor's degree in chemistry from the College of Wooster.

Alex Kozhich, PhD, BMS: Dr. Kozhich has over 20 years of experience in the pharmaceutical industry. For the past 11 years Alex has worked at Bristol Myers Squibb, in the Nonclinical Disposition and Bioanalysis department, and currently is a Scientific Direcor with the responsibility of providing exploratory bioanalytical support to large molecule discovery and development projects. Previously, Alex was early discovery scientist at MedImmune and also worked at a couple of smaller diagnostic companies. He has authored over 100 papers and/or poster presentations as primary or co-author and presented at scientific conferences across the United States, and his research interests include bioanalytical methods for biomolecules, peptide and protein biochemistry and immunology. Alex received his Ph.D. in Organic Chemistry from Shemyakin Institute of Bioorganic Chemistry and completed postdoctoral training in immunology at National Institutes of Health.

Manjinder Lall, PhD, Pfizer: Dr. Manj Lall was born in London, England and grew up in Calgary, Canada. He moved to the United States in 2000 and became a US citizen in 2011. Manj is a Senior Principal Scientist at Pfizer located in Groton, CT and has worked at Pfizer for 19 years in various lines (medicinal chemistry, process chemistry and ADME Sciences). He received his BS degree in Chemistry from the University of Calgary and Ph.D. in organic chemistry at the University of Alberta, in Canada. Manj completed postdoctoral studies at The Scripps Research Institute located in La Jolla, CA. Manj has been a member of the American Chemical Society for 25 years and serves as a committee member for the ACS Green Chemistry Institute Pharmaceutical Roundtable.

Jean-Claude Marshall, MSc, PhD, Moderna: Dr. Marshall currently serves as the head of Clinical Biomarkers for Moderna where his group oversees all clinical biomarker work across Moderna's therapeutic pipeline. Previously he was the head of the regulated Clinical Biomarker Laboratories at Pfizer. He previously led the Clinical Genetics and Biospecimens group for Pfizer, and prior to that headed the CLIA certified Pharmacogenomics lab. Prior to joining Pfizer he served as the laboratory manager for a CLIA certified sequencing laboratory in Baltimore. Jean-Claude's academic research was in pre-clinical drug and biomarker discovery in metastatic breast cancer at the NCI and uveal melanoma during his PhD at McGill University.

Allison R. McMullen, PhD, D(ABMM), Roche Diagnostics: Dr. Allison McMullen joined Roche Diagnostics in 2020 and is currently a Scientific Partner for Molecular Diagnostics. She earned her Ph.D. in Experimental Pathology/Virology at the University of Texas Medical Branch where she studied the molecular epidemiology and viral evolution of West Nile Virus. Dr. McMullen then went on to complete a postdoctoral research fellowship studying HPV at the Centers for Disease Control and Prevention (Chronic Viral Disease Branch), after which point she served as an ASM/CPEP Fellow in Clinical Microbiology at Washington University School of Medicine. Before joining Roche, Allison was the Medical Director of Microbiology and Immunology at Augusta University Medical Center and an Associate Professor in the department of Pathology at Medical College of Georgia.

Jim McNally, PhD, BioAgilytix: Dr. McNally has an extensive background in bioanalytical assay development and program leadership spanning nearly 20 years working in the pharmaceutical and biotechnology industry. Prior to joining BioAgilytix, Dr. McNally was Executive Director at CRISPR Therapeutics, where he led a team of scientists to develop a portfolio of assays to support development of gene-based therapeutic candidates throughout their lifecycle. He has also previously held roles at Genzyme, Pfizer, EMD Serono, and Shire which have given him broad experience in the development of large molecule, gene therapy, and cell therapy biotherapeutics. He previously served as Global Program Lead for a number of cell and gene therapy assets while leading teams developing assays to support the bioanalysis of these programs. He has a special interest in the immunogenicity of biotherapeutics and leads an industry-wide working group to address this issue. A key part of his role at BioAgilytix is advising on emerging scientific developments and providing scientific and regulatory guidance. Dr. McNally obtained his B.S. in Biology from Mississippi State University, his Ph.D. Viral Immunology from Louisiana State University School of Medicine in Shreveport, and his Post-Doc in Viral Immunology from University of Massachusetts Medical School.

Photini Pitsikas, PhD, Charles River: Dr. Photini Pitsikas is a Principal Scientist in the biomarkers group at Charles River in Montreal. She has been with Charles River for over 7 years, and currently leads the group responsible for the development of new immunoassay methods, which cover several therapeutic areas supporting pre-clinical and clinical studies for safety assessment. Photini also worked as a scientist in the Research and Development departments at ChondroGene, Luminex Molecular Diagnostics and Alexion from 2005 to 2013. Prior to working in industry Photini received her PhD in Cell and Molecular Biology from Concordia University in 2002, and was a postdoctoral fellow at McMaster University in the biology department from 2002 to 2005.

Noah Post, Ionis: Noah Post is an Assistant Director in the Bioanalytical group at Ionis. He is responsible for the development of LCMS/MS bioanalytical methods for the quantitative measurement of antisense oligonucleotides (ASOs) and transferring those methods to contract labs. His current research focuses on the SAR of ASO metabolism, including developing improved methods to identify the metabolites. Noah has fifteen years of experience as a bioanalytical scientist, the last twelve of which were at Ionis where most of his research has been on ASOs. Prior to that he was at Neurocrine Biosciences and Arena Pharmaceuticals where he worked on a wide variety of projects including solid form chemistry (DSC, Karl Fisher, polymorph studies, x ray powder diffraction, etc.), drug-drug interaction studies, small molecule PK via LCMS/MS, sample automation, and various molecular biology techniques ranging from LBAs to pull-downs to RT-PCR. Noah earned his B.S. in Biochemistry from the University of California at Santa Cruz and his M.S. in Cellular and Molecular Biology from San Diego State University.

Sheldon Preskorn, PhD, Wichita School of Medicine: Dr. Preskorn is an academic medical doctor, psychiatrist, clinical researcher, neuropsychopharmacologist, and educator. His 40+ medical career can be divided about 60:40 between research and patient care/medical education:

His research has included both basic and clinical studies principally in drug development. He has worked for over 140 pharmaceutical, biotechnology, device and diagnostic companies to help bring their products to the market including every antidepressant and antipsychotic medication marketed in the US over a 25-year period. He has published over 500 medical papers, books, and book chapters and has been cited in the medical literature over 16,000 times (the top 1% in molecular biology and clinical medicine is 1229 and 1390, respectively). He has also been a consultant to the Food and Drug Administration, the European Medicines Agency, the US Veterans Administration, and the National Institutes of Health.

The patient care/medical education aspect of his career has covered inpatient, outpatient, emergency room, and consultation-liaison. He has been invited to lecture on 6 out of 7 continent, in 55 countries, and at most medical schools in the US and throughout the world.

Edward Price, PhD, AbbVie: Dr. Edward Price is a Senior Scientist in the Drug Metabolism and Pharmacokinetics (DMPK) team at AbbVie. Here, he provides computational modeling support across various project teams in drug Discovery and Development. Edward earned his Ph.D. in chemistry from the NanoScience Technology Center at the University of Central Florida in 2019 where he focused on developing new in vitro cell-based methods and modeling approaches to predict nanoparticle and biologic disposition in pre-clinical species. While pursuing his Ph.D., Edward also worked at a small contract research organization (CRO) where he provided support and custom physiologically-based pharmacokinetic (PBPK) model development for various pharmaceutical companies, government agencies, and private organizations. Apart from work, Edward also enjoys outdoor activities like fishing, playing tennis, and spending time with family. He also manages to stay busy through cooking recipes he finds online and watching Netflix documentaries.

Diane Ramsden, Takeda: Diane Ramsden is an Associate Scientific Director in global DMPK within Takeda. She is currently responsible for representing drug metabolism and pharmacokinetics (DMPK) on program teams. Prior to joining Takeda she spent two years at Alnylam, the industry leader in harnessing RNA interference, and 16 years at Boehringer Ingelheim where she served as a DMPK project representative and hepatocyte lab head. Her research interests include the application of in vitro and in vivo models towards developing a mechanistic understanding of the disposition of novel therapeutics.

Lita Sands, AWS: Lita is the Worldwide Head of Life Sciences Business Development for AWS. In this role, she works with business leaders to accelerate transformation goals across the value chain through advanced cloud-based capabilities to drive better outcomes for patients, caregivers and healthcare providers. Lita has led large-scale transformation initiatives for pharmaceutical companies such as Novartis, Pfizer and Pharmacia. In her most recent client role as Chief Digital Officer for Novartis Pharma, she led the creation of the US and Global Multi-Channel and Digital capabilities, building solutions for customer facing teams around the globe, introducing the first digital patient applications for primary care, and driving employee upskilling and operational change management. Lita is a member of the inaugural MM&M Top 40 Healthcare Transformers, a member of Clinical Trial Transformation Initiative (CTTI) tech advisory board, and a founding member of Digital Medicine Society DiME.

Julie Seroogy, PhD, Bristol Myers Squibb: Ms. Seroogy joined MyoKardia/BMS in June 2020 as Senior Director of clinical pharmacokinetics and is currently in the Nonclinical Disposition and Bioanalysis department in the role of regulated bioanalysis.

Prior to BMS, she was head of DMPK at DiCE Molecules for 2 years and at Achaogen for 6 years contributing to the DMPK and clinical pharmacology efforts which advanced ZEMDRI™ (plazomicin) and its complementary diagnostic immunoassay through clinical trials and FDA approval.

Ms. Seroogy spent 6 years as a Director of Research at PharmacoFore heading the analytical, bioanalytical and DMPK functions. She was previously at Theravance and COR Therapeutics in the bioanalytical and pharmacokinetic departments and contributed to the development of VIBATIV® (telavancin) and INTEGRILIN® (eptifibatide). She holds a B.S. in Zoology from Arizona State University

Julia Shanu-Wilson, PhD, Hypha: Julia earned her degree and PhD in biochemistry from Imperial College London. Her PhD focussed on the discovery of microbial alkaloids using radiolabelled probes.

Following a post doc in New Zealand on the biosynthesis of indole diterpenoids, Julia joined the pharmaceutical industry as a Research Scientist, becoming a Programme Discovery Leader for Cubist Pharmaceuticals (subsequently bought by Merck). She was responsible for the team discovering new natural product derived anti-bacterial drugs, and was part of the cross-continent team responsible for bringing daptomycin to the market. Julia joined Hypha, a company specialising in drug metabolites in 2013, and is on the Management Team.

Danielle Swaney, PhD, UCSF: Dr. Swaney's lab is focused on using proteomics to enable biological discoveries. During her PhD training at the University of Wisconsin she developed novel approaches to study phosphorylation signaling and leveraged these approaches during her postdoctoral training at the University of Washington to enable high-throughput characterization of crosstalk between phosphorylation and ubiquitin signaling.

Now at UCSF, Dr. Swaney's lab has been focused on the discovery of protein-protein interactions and phosphorylation signaling that regulate diseases, including SARS-CoV-2.

Dong Wei, PhD, Takeda: Dr. Wei has over 20 years of experience in bioanalysis and biomarker research. Currently as an Associate Director at Takeda, he is leading a team in developing novel LC/MS and LBA assays to support the company's Oncology Programs, including small molecules, biologics, ADCs, Gene and Cell Therapies. He received a bachelor's degree in Chemistry e from Fudan University, and a Ph.D. in Analytical Chemistry from University of Maryland, Baltimore County.

Shengsheng Xu, PhD, Frontage Laboratories: DDr. Shengsheng Xu obtained his bachelor's degree in Wuhan University, China. He completed a Ph.D. degree in Chemistry from University of Massachusetts-Amherst. Dr. Xu's graduate research focused on development of novel linkers to enable the conjugation of antiviral medicines with potential protein carriers to achieve targeted drug delivery. LC-MS based techniques have been utilized in his projects to characterize the protein drug conjugates, including intact mass analysis (i.e. determination of drug to protein ratio) and peptide mapping (i.e. mapping conjugation sites and possible post-translation modifications).

Dr. Xu started his bioanalytical career after he graduated from University of Massachusetts-Amherst and joined Frontage Laboratories, Inc. as Senior Scientist I in 2017. He was promoted to group leader in 2021. Dr. Xu's current research mainly focus on development of LC-MS based methods to support quantitation of large molecule therapeutics (e.g. monoclonal antibody, antibody-drug conjugate and Fc fusion proteins) and biomarkers (e.g. proteins and glycosaminoglycan) in biological matrices. He is experienced with development of multiplexing LC-MS/MS methods including 3-in-1 combo antibody assay, 2-in-1 ADC assay (total antibody and conjugated payload) and 3-in-1 Fc fusion protein assay (target domain, block domain and Fc domain). In addition, he is familiar with development of top-down/middle-down methods to quantitate proteins at intact level or subunit level.

Jennifer Zimmer, PhD, Alturas Analytics: Dr. Jennifer Zimmer is the Laboratory Director at Alturas Analytics, Inc. and has been working in the field of bioanalysis for over 20 years. She received her B.A. degree in English and Zoology from the University of Idaho and her Ph.D. in Pharmacology from the University of Colorado Health Sciences Center, working in Dr. Robert Murphy's laboratory on the leukotriene lipid mediator pathway. Her post-doctoral experience in Dr. Richard Smith's laboratory focused on using metabolomics to elucidate disease pathways and to discover novel biomarker targets. Dr. Zimmer is responsible for the overall operation of the Alturas Analytics laboratory. She has experience with FTICR, TOF, ion trap and quadrupole instrumentation. She has utilized these instruments for quantitation as well as structure elucidation using HPLC-MS/MS and HPLC-MSn. She oversees the scientific staff and ensures that client deliverables are met while working laterally with the Alturas Analytics, Inc. QAU in order to maintain laboratory compliance with all procedures and regulations. Dr. Zimmer is an active participant the Global CRO Council (GCC) and a member of the American Society for Mass Spectrometry.

POSTER ABSTRACTS

Investigation of In-vivo Biotransformations of an Antibody-Drug Conjugate in Clinical and Preclinical Studies

Helen Davis, Suk Hyung, Surinder Kaur, Ola Saad

Purpose:
Antibody-drug conjugates (ADCs) undergo biotransformations in circulation and characterization of the structural changes is important to elucidate the mechanisms of ADC catabolism, and their potential impact on safety and efficacy. Biotransfonmations are often assessed by affinity capture LC-MS analysis of the intact protein. Here, we comprehensively characterized at both intact and subunit levels to study the structural modifications of an AOC in vivo. Biotransformations were examined across species in preclinical and clinical samples, all owing us to see possible differences between clinical and preclinical individuals.

Methods:
Samples containing ADC were subjected to immunoaffinity capture with biotinylated extracellular domain protein on streptavidin-coated magnetic beads. This is followed by treatment with IdeS protease or papain on-bead to yield $F(ab')_2$ (-100 kDa) fragments or F(ab) (-50 KDa) respectively. Capillary LC-MS was perfonmed on a Q-Exactlve mass spectromeler (Thenmo Fisher, Waltham, MA, USA) coupled with a Waters nanoACOUITY UPLC system (Waters, MIiford, MA, USA). Mass spectra were analyzed using Thermo Protein Deconvolution software (4.0).

Results:
Drug-to-antibody ratio (DAR) analysis of clinical samples from a multi-dose study were used to show the payload deconjugation over time from the ADC up to day 141. Similar in vivo stability was observed across 5 patients at different dose levels. The degree of DAR change over time was also found to be comparable in clinical patient samples to that seen preclinically with cynomolgus monkeys using both IdeS or papain sample processing. Further examination of the data shows that the major biotransfonmation pathways include payload loss due to disulfide exchange leading to fonmation of adducts between engineered cysteine and endogenous cysteine as well as glycation. This observation was consistently seen from analysis at the structural level of $F(ab')_{2'}$ Fab and light chain.

Conclusions:
ADC biotransformations in both preclinical and clinical in vivo samples were analyzed and used to assess the translatability of DAR stability across species. For this ADC the deconjugation stabili ty was similar in clinical and preclinical individuals over time. This approach has the potential to serve as a powerful tool to predict the in vivo stability of ADCs in the clinic. Further detailed assessment of the in vivo biotransfonmations observed at the peptide-level is underway and could potentially strengthen correlations made across species in regards to efficacy and safety.

Enhanced selectivity and sensitivity for peptide quantification in a complex matrix using high-resolution LC-MS/MS workflow

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Introduction:
Given the increased focus on producing new protein and peptide therapeutics, there is a resulting demand for highly sensitive and robust quantitative bioanalytical techniques to ensure proper testing for their safety and efficacy. Bioanalysis of peptide therapeutics is often faced with analytical challenges such as inadequate sensitivity and complexity of the matrix resulting in poor selectivity. High-resolution accurate mass spectrometry (HRAMS) has been increasingly adopted in bioanalytical workflows as it provides high selectivity with narrow mass extraction windows. As part of this work, evaluation of enhanced duty cycle by a novel ion beam to time-of-flight (TOF) pulser efficiency was performed. The new quantitative enhancements was evaluated for peptide quantification in a complex biological matrix.S.

Methods:
Digested universal proteomics standard (Sigma Aldrich, 48 human proteins) was spiked into rat plasma and serially diluted to generate a calibration curve. Samples were denatured using N-octyl-glucoside followed by reduction using dithiothreitol, and alkylation using iodoacetamide. Protease digestion was performed using Trypsin/Lys-C at 37 ºC overnight, at an enzyme:protein ratio of 1:25. Digestion was stopped using formic acid. Supernatant was subjected to LC-MS/MS analysis where chromatographic separation was achieved using a Phenomenex Kinetex C18 column on a ExionLC system. Samples were analyzed using a novel QTOF mass spectrometer (ZenoTOF 7600 system, SCIEX).

Preliminary Data:
Analysis of peptides was performed using scheduled MRMHR where a narrow mass window was used for the product ion profile.

Area in brackets is optional: [Previous analysis on a triple quadrupole mass spectrometer showed poor selectivity of some target peptides (076070_EGVVGAVEK, P02144_VEADIPGHGQEVLIR, and P41159_VTGLDFIPGLHPILTLSK) compared with the surrounding matrix components. Therefore, quantification of those peptides were highly challenging. However, with the higher resolution of a TOF MS/MS system, enhanced selectivity was achieved for 076070_EGVVGAVEK, P02144_VEADIPGHGQEVLIR, and P41159_VTGLDFIPGLHPILTLSK versus matrix components. Greater selectivity enabled better quantitative performance where lower limit of quantitation (LLOQ) of 18.43 ng/mL, 7.16 ng/mL, 6.78 ng/mL were achieved for 076070_EGVVGAVEK, P02144_VEADIPGHGQEVLIR, and P41159_VTGLDFIPGLHPILTLSK, respectively. In addition, the enhancement of duty cycle improved overall sensitivity for peptide quantification. Strong linearity was achieved for all peptides with r2>0.98. Accuracy at LLOQ was within 80%-120% with precision <15%, demonstrating high reproducibility of peptide quantification.

Since a full MS/MS profile was generated for each peptide precursor, summation of fragment ion XICs was examined for further sensitivity improvements. Summation of multiple high abundant fragment ions for P02787_DYELLC[CAM]LDGTR (y6, y7, y8, and b3) and P08263_FLQPGSPR (y5, y6) achieved a 3-fold improvement in LLOQ. The final LLOQs were 31.57 ng/mL and 3.75 ng/mL for P02787_DYELLC[CAM]LDGTR and P08263_FLQPGSPR, respectively. Excellent linearity was achieved and accuracy was within 85%-115% (LLOQ, 80%-120%) and overall precision was <14%, demonstrating high reproducibility of the assay.]

Overall, significantly better S/Ns were observed for quantification using fragment ions when compared with single MS quantification. However, peptides that exhibited low-noise using single MS were easily quantified in comparison with peptides with poor S/N. Exceptional accuracy and precision was achieved with single MS peptide quantification where overall precision was <12%. This demonstrated excellent reproducibility for intact peptide quantification.

Quantitative results demonstrate a highly accurate, selective, and sensitive assay for quantification of peptide therapeutics in complex matrices with both single MS and MS/MS.

Novel Aspect:
Highly sensitive and selective quantification of peptides in a complex matrix using a novel TOFMS/MS workflow.

Multiple approaches for routine early stage bioanalytical quantification

Rolf Kern, SCIEX, Redwood City, California

MRMHR methods, which closely parallel triple quadrupole MRM methods, will generally be the most sensitive approach for routine quantification of small molecule pharmaceuticals. But one distinct advantage of quadrupole time-of-flight systems is the flexibility to generate good quantitative data using different types of methods. Here quantitative data will be shown for two model small molecule compounds, in protein precipitated rat plasma, using generic sample prep and chromatography to mimic the routine nature of an early stage discovery bioanalytical laboratory, where scientists may not always have the time to optimize conditions for each new molecule that requires analysis. In addition to MRMHR, sensitivity and linearity are shown and discussed for some alternative mass spectrometry methods; including TOF MS, Zeno SIM, and Zeno EAD MRMHR, to show how the flexibility of the platform can be used to approach quantification should different workflow needs arise.

Optimer-enabled Biosensors

Banushan Balansethupathy – Aptamer Group, UK

Optimer binders are oligonucleotide based antibody mimetics. We developed highly selective for the antibiotic moxifloxacin, with limited cross-reactivity to the homologous ciprofloxacin and levofloxacin. Sensitive antibiotic detection over the clinical concentration range was achieved with the use of the moxifloxacin-specific Optimer-based rapid biosensing diagnostic platform. The Optimer-functionalised biosensor showed highly selective target binding in a complex human serum matrix. Optimer binders to a variety of biomarkers can be utilized in this platform for the development of novel rapid diagnostic assays for clinical use.

ABOUT OUR SPONSORS

Alturas Analytics is a GLP compliant bioanalytical CRO specializing in method development, validation, and sample analysis by LC-MS/MS and GC-MS/MS supporting early discovery through late phase clinical trials. In addition to providing PK support services to pharmaceutical companies worldwide, Alturas maintains an intensive research effort of applying new technologies leading to scientific advancement for high-throughput bioanalysis. The success of Alturas is built on developing long term collaborations with clients by delivering personalized, bioanalytical results on time with the highest level of integrity.

Aptamer Group is the developer of custom affinity tools for the life science industry through its proprietary Optimer platform.

Optimer ligands are nucleic acid-based affinity ligands that can be used as an antibody alternative to offer novel solutions and improvements to current processes across the therapeutic, diagnostic, bioprocessing and research sectors. The Optimer platform consists of three parallel processes optimized for target type to enable scientists with the best affinity ligand for small molecules, proteins or cell targets.

Offering rapid development in just weeks, full platform compatibility and tuneable binding kinetics to ensure desired end-use performance, Optimer ligands are enabling new insights and new molecules to progress life science for better healthcare for all.

Biomere is a global, nonclinical contract research organization (CRO) with locations on the east and west coast, as well as multiple locations in China (JOINN). In support of studies placed in China, we employ knowledgeable U.S. client liaisons to navigate Chinese study programs. Seamless, timely communication and process management support creates ease in placing studies globally. In addition to our rapidly growing ocular research program and gene therapy expertise, we support many areas of preclinical research. Visit the "CRO Expertise" area of our website at Biomere.com to review our capabilities and resources. Our globality, personal approach and our drive to expedite research timelines, makes us ideally suited to support our clients' needs.

Charles River Quality, scientific integrity, cost-effectiveness, and regulatory compliance are essential considerations when selecting an outsourcing partner. Charles River is adept at balancing these key values within the most stringent timelines to deliver comprehensive laboratory services from early screening through preclinical and clinical support. Whether clients choose to outsource the entirety of their laboratory work or are looking to supplement their own in-house capabilities, our global facilities provide the full-service resources to meet their requirements.

Frontage is a CRO providing integrated, scientifically-driven research, analytical and product development services throughout the drug discovery and development process to enable biopharmaceutical companies to achieve their drug development goals. We offer our clients comprehensive services in analytical testing and formulation development, drug metabolism and pharmacokinetics (DMPK), bioanalysis, preclinical safety and toxicology and early phase clinical studies.

Hypha Discovery is a specialist CRO supporting pharmaceutical and agrochemical companies worldwide through the production of metabolites and late-stage derivatives of drugs and agrochemicals in discovery and development. Hypha are experts in the scalable synthesis, purification and identification of drug metabolites and oxidised derivatives of lead compounds, and also possess a wealth of experience in the production, purification and structure elucidation of natural products.

SCIEX As therapeutics continually evolve to become more complex, you need new ways to simplify your method development, accelerate your workflows to get fast, accurate results – every time. SCIEX has a long-standing record of providing innovative mass spectrometry-based solutions to make you more productive and successful. SCIEX offers you a comprehensive portfolio of instruments and software that simplifies analytical workflows. Data is easier to interpret, and analyses are easier to perform. SCIEX solutions are used worldwide to advance therapeutic development and enable scientists to confidently submit their data to regulatory bodies.

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