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JUNE 13, 2024

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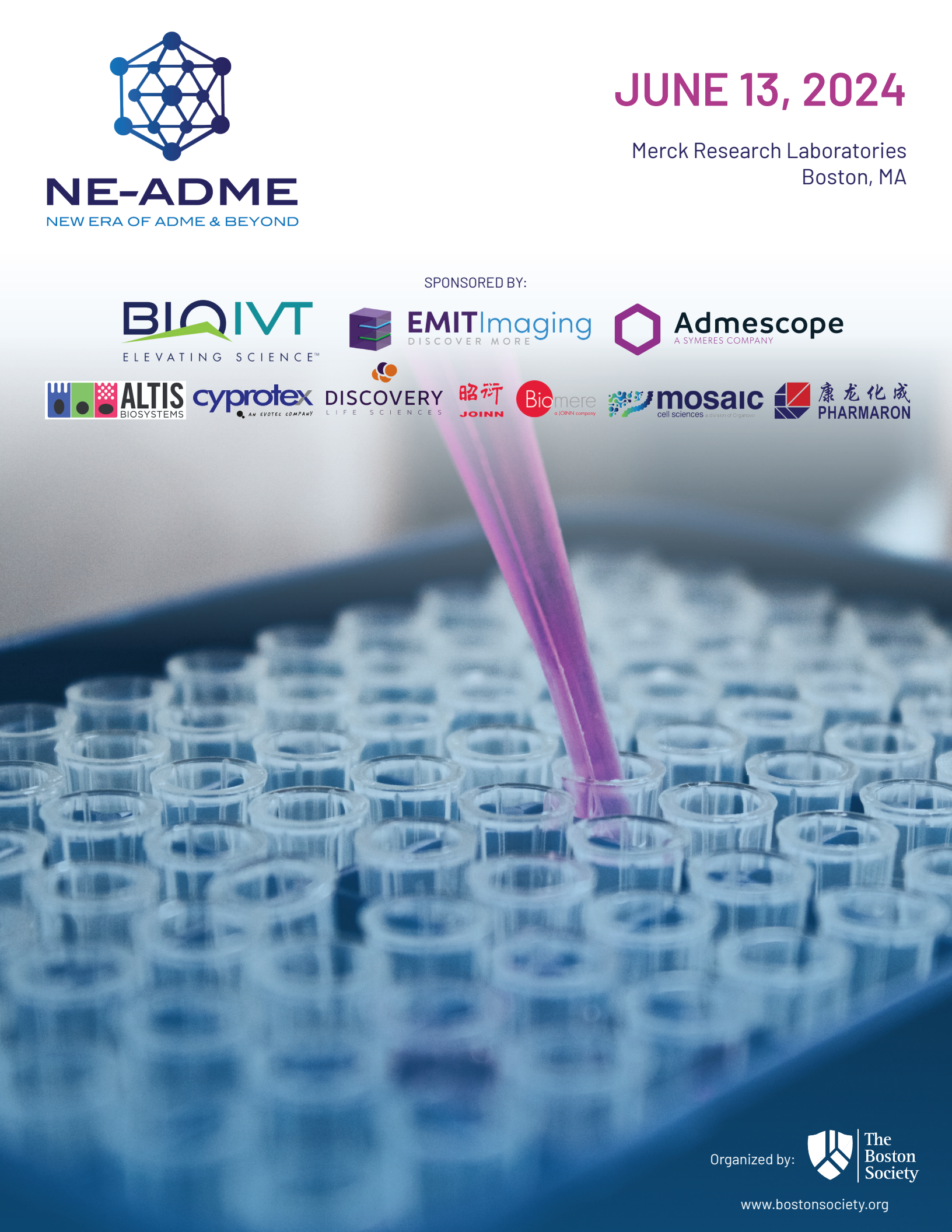

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Admescope
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ADMESCOPE is a preclinical contract research organization (CRO) providing tailor-made ADME-Tox (Absorption, Distribution, Metabolism, Excretion and Toxicity) services for drug discovery and development companies. Our unique expertise lies in drug metabolism, drug interactions, pharmacokinetics and quantitative bioanalysis, where we stand out with our innovative approach combined with the latest technology. Our services are available for all drug modalities, e.g., small molecules, peptides, oligonucleotides, antibodies and ADCs.

Since 2020, Admescope has been a part of Symeres, with the ability to provide medicinal chemistry and integrated drug discovery & development services with over 500 scientists based in Europe and the US.

ALTIS BIOSYSTEMS

ALTIS BIOSYSTEMS INC. is a leader in human cell-based model systems for pre-clinical drug development. The company offers both kits and assay services for utilizing a series of in vitro, stem cell derived intestinal cell models called RepliGut® Systems. RepliGut®Systems consist of human donor stem cells isolated from multiple regions of the intestine and include key cell types in the gastrointestinal epithelium. RepliGut® Models can be used for compound screening, disease modeling, toxicity, efficacy, and basic research studies to ultimately improve patient outcomes and advance our understanding of human biology.

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BIOIVT enables smarter science and accelerates medical breakthroughs by delivering high-quality personalized biospecimen solutions and research services to life science and diagnostic industries. Recognized as an industry leader, we specialize in control and disease state samples including human and animal tissues or preparations, cell and gene therapy products, blood, and other biofluids, as well as ADME contract research services from standalone bioanalytical support through tiered in vitro studies with submission-ready reports to customized consulting.

By combining our technical expertise, exceptional customer service, and unmatched access to biological specimens, BioIVT serves the research community as a trusted partner in ELEVATING SCIENCE®.

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CYPROTEX Founded in 1999, Cyprotex (www.cyprotex.com) has grown to become an industry leader in in vitro and in silico ADME-Tox. The company, with sites in the UK and USA, was acquired by Evotec (www.evotec.com) in 2016. The Evotec Group offer expert support from early discovery through to clinical development.

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DISCOVERY LIFE SCIENCES accelerates the discovery and development of new therapies and diagnostics by providing biopharma and diagnostic companies with the highest quality biospecimens, in vitro preclinical products, and cell & gene therapy starting materials coupled with specialty lab services that are grounded in science and offered at scale to support large scale clinical trials.

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EMIT IMAGING is the leading manufacturer of Cryo-Fluorescence Tomography (CFT) systems and provider of CFT fee-for-service research to pharma, biotech, and academia globally. CFT is a transformative 3D imaging modality that was created to better visualize on- and off-target drug distribution and protein expression (PK/PD) in whole animals at high resolution and sensitivity. EMIT designed and manufactured our flagship product, XerraTM, a fully automated preclinical imaging platform, and launched the first-generation production system in 2019. In 2023, EMIT launched CFT services to the global research community. EMIT developed CFT and Xerra to help researchers discover more from valuable preclinical experiments, complementing existing experimental paradigms and imaging workflows. CFT applications span drug discovery and delivery, oncology and immunotherapy, gene and cell therapy, neuroscience, and beyond. The company is based in Boston, MA, and Baltimore, MD.

JOINN / BIOMERE (A JOINN COMPANY) facilitates the individual needs of each of our partners across the globe in making drug development more efficient because to us, it's personal. We constitute a global, nonclinical contract research organization (CRO) with locations on the East and West Coast, as well as multiple locations in China (JOINN). Our International Liaison Team seamlessly navigates studies placed in China creating access to model abundance, expedient study-start times, GLP laboratories and an impressive resume of scientific talent. JOINN is the largest CRO in China and offers budget friendly study costs.

Globality, a personal approach and our drive to expedite research timelines, makes us ideally suited to support our clients' needs.

MOSAIC CELL SCIENCES a division of Organovo, provides high-quality primary human hepatic and intestinal cells from healthy and diseased donors, offering scientists the capability to recreate physiologically relevant parameters in their in vitro models. With over 45 years of combined experience, our world leading experts in liver isolation strive to advance our partners' research and discovery programs into the clinic. Interrogating the heterogeneity of the human population in predictive systems strengthens their translational impact, regardless of the complexity of the model. Furthermore, our team of experts can help you choose the human cell starting materials with the characterization profile that best meet your project requirements.

PHARMARON is a global life science service provider that offers a broad spectrum of research, development and manufacturing service capabilities throughout the entire drug discovery, preclinical and clinical development process across multiple therapeutic modalities, including small molecules, biologics and CGT products.

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ORGANIZERS' WELCOME

Welcome to the 2024 NE-ADME Conference.

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

ORGANIZING COMMITTEE

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Mitesh Patel, Novartis
Conference Chair Elect:
Seema Chauhan Kumar, Pioneering Medicines

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Chris Rowbottom, Moderna
Joseph Tillotson, Pfizer
Jun Zhang, BMS

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NE-ADME 2024 CONFERENCE AGENDA

THURSDAY, JUNE 13

7:30 - 8:30 AM **Registration**

8:30 - 8:40 AM **Conference Opening and Plenary Lecture Introduction**
Mitesh Patel, Novartis

8:40 - 9:20 AM PLENARY: ***ECCS Class 3A: Interaction of Gabapentin and Its Analogues with Transporters - A Love-Hate Relationship***
Ayman El-Kattan, IFM Therapeutics

SESSION I: Complex Models to Support Drug Development
Chairs: Mitesh Patel, Novartis & Ruchia Duggal, Merck

9:20 - 9:25 AM **Session Introduction**

9:25 - 9:55 AM ***Utilizing Ex Vivo Liver Slice Models for Preclinical Evaluation of LNP-Based mRNA Delivery***
Hema Muralidharan, Moderna

9:55 - 10:25 AM ***Liver MPS Model Comparison for Clearance IVIVC***
Birk Poller, Novartis, Basel

10:25 - 10:55 AM ***Overcoming Limitations of Caco-2 Cells for ADME Using Adult Human Crypt-Derived Planar Intestinal Epithelium Cultures***
Ben Scruggs, Altis Biosystems

10:55 - 11:15 AM Break

11:15 - 11:20 AM **Plenary Lecture Introduction**
Vinayak Hosagrahara, Nimbus Therapeutics

11:20 - 12:00 PM PLENARY: ***ADMET In The Age of AI***
Daniel Price, Nimbus Therapeutics

12:00 - 12:25 PM ***Fatty Liver Disease Modeling In a Micropatterned Primary Hepatocyte Co-culture (HEPATOPAC): Applications In Drug Development & Screening***
Karissa Cottier, BioIVT

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12:25 - 1:35 PM Lunch

1:35 - 1:45 PM ***Cryo-Fluorescence Tomography: Transformative 3D Imaging to Monitor Drug PK/PD***
Matt Silva, EMIT Imaging

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SESSION II: PK/PD for New Modalities

Chairs: Steven Louie, Moderna & Dallas Bednarczyk, Novartis

1:45 - 1:50 PM **Session Introduction**

1:50 - 2:20 PM ***Use of PK/PD Modeling to Understand the Potential and Pitfalls of New Modalities- Picking the Winners from the Losers***
Alison Betts, Takeda

2:20 - 2:50 PM ***Dynamical Modeling of Protein Degradation to Improve Compound Selection in Drug Discovery***
TK Phung, Novartis

2:50 - 3:20 PM ***Pharmacokinetics and Distribution of Lipid Nanoparticles***
Christopher Rowbottom, Moderna

3:20 - 3:40 PM Break

SESSION III: Advanced Tools to Support Drug Discovery & Development

Chairs: Joseph Tillotson, Pfizer & Seema Chauhan Kumar, Pioneering Medicines

3:40 - 3:45 PM **Session Introduction**

3:45 - 4:15 PM ***Measurement of Target Exposure and Binding with Positron Emission Tomography (PET) Imaging in Drug Research and Development***
Laigao Chen, Pfizer

4:15 - 4:45 PM ***Early Drug-Induced Liver Injury Risk Screening: "Free," as Good as it Gets***
Jonathan Jackson, Pfizer

4:45 - 4:50 PM **Closing Remarks**
Seema Chauhan Kumar, Pioneering Medicines

4:50 - 5:50 PM **Reception**

ABSTRACTS

PLENARY

ECCS Class 3A: Interaction fo Gabapentin and its Analogues with Transporters - A Love-Hate Relationship

Ayman El-Kattan, IFM Therapeutics

The extended clearance classification system (ECCS) was first reported in the literature in 2016, and since then its utility and use has expanded in the field of drug development. This presentation will focus on ECCS class 3A compounds, specifically gabapentin and its analogues, and the work that was done at various research institutions to understand the disposition of these molecules. Discussions will include the impact of system L transporters on gabapentin and pregabalin oral absorption, and the less-than-proportional increase in exposure noted with gabapentin oral dose increase. Also, we will shed light on the role of system L transporters in the distribution of Gabapentin, and detail how these transporters can be successfully used to affect the half-life of Gabapentin analogs and ensure once-daily dosing by increasing drug renal reabsorption and reducing active intestinal secretion mediated by renal transporters.

SESSION I

Utilizing Ex Vivo Liver Slice Models for Preclinical Evaluation of LNP-Based mRNA Delivery

Hema Muralidharan, Moderna

The ex vivo liver slice model stands at the forefront of translational research, adeptly filling the void between traditional in vitro assays and whole-organism studies by preserving the liver's intricate structure and cellular heterogeneity. Leveraging this model, we explored the translational potential for understanding the dynamics of LNP-mRNA-1944, an mRNA therapy that encodes a monoclonal antibody targeting Chikungunya virus (CHKV). In a Phase 1 clinical study (1), mRNA-1944 was evaluated in healthy volunteers to assess safety, tolerability, and the PK and PD of both the CHKV-24 immunoglobulin and the ionizable amino lipid carrier. The ex vivo liver slice model successfully recapitulated the in vivo behavior of mRNA-1944 LNPs, reflecting cellular uptake and protein expression, and producing gene and protein expression signatures akin to patient-derived samples. To continue building confidence in the translatability of the model and help us gain deeper insights into the mechanism of liver-targeted drug delivery, we plan to expand and develop a predictive framework based on this model using physiological-based pharmacokinetic modeling. These results underscore the ex vivo liver slice model's effectiveness as a predictive platform for the preclinical assessment of LNP-mediated drug delivery, indicating a potential translational bridge to clinical application.

Comparison of Long-Term Liver Models for the Prediction of Human Clearance

Birk Poller, Novartis

Predicting the systemic clearance of drug candidates is an essential part of estimating human pharmacokinetics in pre-clinical drug development. In vitro models are routinely used to evaluate the metabolic stability and to establish in vitro-in vivo correlations (IVIVC) for hepatic clearance. However, for compounds that are slowly metabolized it has remained challenging to measure clearance reliably. Emerging long-term liver models, that grow hepatocytes in co-culture with fibroblasts or as spheroids, enable longer incubation times and higher turnover of test compounds. The present study evaluated a recently developed multi-spheroid system and a co-culture model of hepatocyte and fibroblasts for the clearance assessment of low turnover compounds. While suspended hepatocytes did not allow measuring the clearance for most of the tested compound, both long-term culture models provided improved clearance IVIVC. Hepatocyte spheroid and co-culture models demonstrated comparable performance and provided systemic clearance predictions within three-fold to that observed in clinics (~80% of tested compounds). Our findings support the value of hepatocyte co-culture or spheroid models for the prediction of human clearance.

Overcoming Limitations of Caco-2 Cells for ADME using Adult Human Crypt-Derived Planar Intestinal Epithelium Cultures

Ben Scruggs, Altis Biosystems

The gastrointestinal (GI) tract is the primary route through which orally administered drugs enter the bloodstream. Understanding how drugs traverse this intricate barrier is fundamental to predicting their behavior in the body. The intestinal epithelium, the lining of the GI tract, plays a central role in this process. It acts as a selective gatekeeper, regulating the absorption and transport of drugs into the bloodstream. This barrier is composed of absorptive enterocytes that express various transporters for influx and efflux on both the apical and basolateral surfaces of the cell layer. Additionally, the intestinal epithelium contains phase I and II metabolism enzymes, particularly in the jejunum, which can significantly impact drug bioavailability and result in drug-drug interactions.

While cancer-derived Caco-2 cells offer a convenient and readily available model for characterizing contribution of intestinal epithelial cells to ADME of important orally administered drugs, they have several well-known limitations. First, these cells are derived from a colon cancer tissue, which inherently introduces genetic and phenotypic alterations. This can result in an inaccurate representation of normal intestinal epithelial cells and their functions. Additionally, cancer-derived Caco-2 cells have been extensively subcultured, leading to the loss of some key characteristics of primary cells. As such, Caco-2 cells are known to express genes and proteins consistent with both small and large intestine which have fundamentally different physiological functions. These limitations can significantly impact the reliability and relevance of findings related to metabolism and transport.

To overcome some of the limitations associated with Caco-2 cells, an adult human jejunum crypt-derived planar intestinal epithelium culture has been developed. Resident stem-cells isolated from intestinal crypts can undergo proliferation and subsequent differentiation that includes the absorptive enterocytes, as well as goblet cells and enteroendocrine cells creating an epithelium that is more representative of the in vivo tissue. This presentation will show how the model, termed RepliGut® Planar, was established and will show characterization of the reproducibility and robustness. Gene expression analysis was undertaken to characterize the baseline expression of metabolism and transporter genes in comparison to Caco-2 cells and in response to classic gene expression inducers 3-MC, CITCO, Calcitriol, and Rifampin. We will show results from clinical benchmarking passive permeability of 24 clinically relevant drugs. Finally, we describe characterization of metabolism in a microphysiological system containing both intestinal epithelium and liver cells.

PLENARY

ADMET in the Age of AI

Daniel Price, Nimbus Therapeutics

It is not hyperbolic to say that we are currently amidst a technological revolution in artificial intelligence/machine learning (AI/ML). Although innovation is occurring most rapidly in other domains, it is clear that there is both the fast injection of hype and a slower, albeit steady, trickle down of technology to the pharmaceutical domain. Despite the hype, the accurate prediction of ADMET (absorption, distribution, metabolism, excretion, toxicity) properties has been identified by many groups as an appropriate opportunity for modern ML to meaningfully bias molecular design and synthetic priority to ultimately reduce time to development candidate, though the fair assessment of the real-world impact of these technologies has been challenging for a number of reasons. This talk will discuss some realistic evaluations of the impact of modern ML specifically in the realm of ADMET, offer some strategies for companies to participate in this transformation even with modest data assets, highlight how predictive modeling can further accelerate programs by flexing the DMTA cycle, and argue for an expanded role of the DMPK expert in this brave new world.

Fatty Liver Disease Modeling in a Micropatterned Primary Hepatocyte Co-Culture (HEPATOPAC): Applications in Drug Development and Screening

Karissa Cottier, BioIVT

Development of new therapeutics for metabolic dysfunction–associated fatty liver disease (MAFLD) therapeutics is vital to combat its rising prevalence. Effective high-throughput in vitro models are an important aspect facilitating this drug discovery. In these studies a micropatterned hepatocyte co-culture (MPCC) was used to model liver steatosis. The MPCC model (HEPATOPAC) is comprised of hepatocytes and 3T3-J2 mouse stromal cells plated onto a patterned standard well plate, Here, high content imaging (HCI) analysis was used to assess lipid content in cultures, facilitating much faster data acquisition and analysis compared to manual imaging methods. Treatment of MPCC with free fatty acids (FFA), high glucose and fructose (HGF), or a combination of both induces hepatic steatosis and fatty liver related gene expression changes. In these studies, the utility of this model to assess lipid reduction or potentiation by small molecule and siRNA-based targets was demonstrated. Together, these data demonstrate that MPCC is an easy to use, long-term functional in vitro model of MAFLD having utility for compound screening, drug toxicity evaluation, and assessment of gene regulation.

Cryo-Fluorescence Tomography: Transformative 3D Imaging to Monitor Drug PK/PD

Matt Silva, EMIT Imaging

Accurate whole-body visualization of on- and off-target drug biodistribution, protein expression, and other biochemical processes is essential in preclinical research. However, current methods for analysis at large volume scales are limited by throughput or their ability to provide complete data.

3D Cryo-Fluorescence Tomography (CFT) addresses these gaps in current imaging workflows with high resolution, high sensitivity fluorescence and anatomical images. CFT has multiplexing capabilities, seamlessly integrates and extends in vivo imaging workflows, and complements microscopic analysis by providing improved sub-organ localization of drug products, proteins, and biomarkers. In this presentation, we will cover the fundamentals of CFT imaging via EMIT Imaging's XerraTM system and review key applications for this exciting technology.

Key Topics Include:

- Introduction to Cryo-Fluorescence Tomography (CFT)
- Overview of capabilities of the EMIT Imaging Xerra system
- Applications of CFT for the visualization of drug biodistribution

SESSION II

Use of PK/PD Modeling to Understand the Potential and Pitfalls of New Modalities: Picking the Winners from theLosers

Alison Betts, Takeda

The biopharma industry is undergoing a revolution in new therapeutic drug modalities, which are competing with traditional drugs in terms of both R&D resources and commercial sales. Traditional drug platforms such as small-molecule therapies and monoclonal antibodies are now established in the healthcare industry; new modalities that have emerged in the past 20 years include complex biologics, gene and cell therapies, and RNA drugs. Some of these modalities offer unprecedented new opportunities for delivering transformative medicines to patients. However, others are experiencing high failure rates in the clinic, or pose tremendous manufacturing or commercialization challenges. How do we determine which modality is appropriate for a specific target, mechanism or disease? How do we pick the winners from the losers? Can we do this in an efficient manner so as not to further impede the speed of the drug development process?

Mechanism based PK/PD and quantitative systems pharmacology models are useful tools for understanding complex mechanisms of drug action, increasing productivity, and enhancing decision making. These models can be used to link the exposure of drugs (or a combination of drugs) and the modulation of pharmacological targets, physiological pathways and disease systems. As such they can provide a quantitative framework to investigate optimal therapeutic formats, and to understand the quantitative relationship

between drug properties, such as valency, affinity, half-life, and dose, to help direct lead selection and optimization strategies. Upon selection of the lead molecules, the models can be used for preclinical to clinical translation, to optimize clinical dosing regimens and to address precision medicine questions.

In this presentation, the PK/PD considerations for a variety of new drug modalities will be considered including: bispecific antibodies, ADCs, oligonucleotides and cell therapies. Key variables in the pathway to success will be discussed including biodistribution to the site of action, biomarkers of target modulation and efficacy, and predictions of efficacious dose vs. safety. Through a selection of case studies, the use of modeling and simulation to successfully guide drug discovery and development of different drug modalities will be shown.

Dynamical Modeling of Protein Degradation to Improve Compound Selection in Drug Discovery

TK Phung, Novartis

Protein degradation via PROTACs (proteolysis targeting chimeras) or molecular glue degraders is an attractive new therapeutic approach. It provides a way to intervene on targets that were previously considered "undruggable", or more difficult to inhibit, for example proteins without a clear catalytic pocket. Additionally, for any target, degradation can provide a pharmacodynamic advantage over inhibition, particularly if the turnover of the target protein is slow, leading to the degradation of the target outlasting the presence of the drug. This in turns can lead to potential advantages with respect to dosing, side effects or possible resistance. During a drug discovery effort for a degrader, we can seek to optimize many compound characteristics: the pharmacokinetic properties of compounds, their binding kinetics to the target and/or to the ligase that will tag it for degradation, etc., but where are the sweet spots for different targets? To answer this question and better understand how to translate in vitro and in vivo observations of protein degradation to predict degradation in the clinical setting, we built multi-scale dynamical systems models of different modes of protein degradation. Using judiciously chosen and justifiable assumptions, we arrived at a simplified model that best captures current data. Our model analyses provide contextualized solutions to ranking compounds and predicting outcomes in relevant clinical scenarios.

Pharmacokinetics and Distribution of Lipid Nanoparticles

Christopher Rowbottom, Moderna

Lipid nanoparticle (LNP) encapsulated mRNA therapeutics are complex assemblages of naturally occurring and xenobiotic chemical components. The lipid components that encapsulate the therapeutic RNA drive the distribution and subsequent productive mRNA delivery to cells as well as being critical to stabilizing the mRNA and protecting it from in vivo degradation. The work described here provides a brief overview of the mechanisms for LNP uptake and transfection of the desired protein(s) followed by a deeper dive into a clinical molecule. A case study of mRNA-3927 for the treatment of Propionic Acidemia will be discussed, including the FIH modeling strategy based upon preclinical pharmacokinetics of Lipid 5, mRNA, expressed protein and translational biomarkers. In addition, although statistically limited, the preliminary clinical data suggests dose-dependent increases in systemic exposure of mRNA-3927 and correlative reduction in key disease-relevant biomarkers.

SESSION III

Measurement of Target Exposure and Binding with Positron Emission Tomography (PET) Imaging in Drug Research and Development

Laigao Chen, Pfizer

Positron emission tomography (PET) imaging is a powerful tool that can be used to measure target exposure and binding in drug discovery and development processes. PET imaging involves the administration of a radioactive tracer molecule, which is designed to specifically bind to a target of interest, such as a receptor, enzyme, or other biomolecule. By detecting the emission of positrons from the radioactive tracer, PET imaging can provide quantitative information about the distribution and concentration of the tracer within the body, and consequently, the target exposure and binding of the drug candidate. PET imaging can be utilized in drug

discovery and development for lead compound evaluation, drug candidate optimization as well as dose selection for clinical trials.

PET imaging offers several advantages over fluid/tissue-based biomarkers in drug discovery and development, including the ability to visualize and assess target engagement in living systems non-invasively, the potential to study drug distribution and kinetics in whole body, and the capability to obtain quantitative data on the relationship between the target occupancy and plasma exposure. However, it is important to note that PET imaging requires a rigorous process to develop suitable radiotracers for clinical use, including target level determination, lead identification and selection, radio-chemistry method development, in vivo preclinical evaluation, radiation dosimetry and acute toxicology assessment and testing in human subjects. In addition, multiple factors need to be considered when interpretating the PET data such as tracer metabolism, non-specific binding, and the optimal compartmental modeling methods.

Early Drug-Induced Liver Injury Risk Screening: "Free," as Good as it Gets

Jonathan Jackson, Pfizer

For all the promise of and need for clinical drug-induced liver injury (DILI) risk screening systems, demonstrating the predictive value of these systems versus readily available physicochemical properties and inherent dosing information has not been thoroughly evaluated. Therefore, we utilized a systematic approach to evaluate the predictive value of in vitro safety assays including bile salt export pump transporter inhibition and cytotoxicity in HepG2 and transformed human liver epithelial along with physicochemical properties. We also evaluated the predictive value of in vitro ADME assays including hepatic partition coefficient (Kp) and its unbound counterpart because they provide insight on hepatic accumulation potential. The datasets comprised of 569 marketed drugs with FDA DILIrank annotation (most vs less/none), dose and physicochemical information, 384 drugs with Kp and plasma protein binding data, and 279 drugs with safety assay data. For each dataset and combination of input parameters, we developed random forest machine learning models and measured model performance using the receiver operator characteristic area under the curve (ROC AUC). The median ROC AUC across the various data and parameters sets ranged from 0.67 to 0.77 with little evidence of additive predictivity when including safety or ADME assay data. Subsequent machine learning models consistently demonstrated daily dose, fraction sp3 or ionization, and cLogP/D inputs produced the best, simplest model for predicting clinical DILI risk with an ROC AUC of 0.75.

This systematic framework should be used for future assay predictive value assessments and highlights the need for continued improvements to clinical DILI risk annotation.

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SPEAKER BIOGRAPHIES

ALISON BETTS, PHD, Takeda Dr. Betts brings an extensive 29-year background in the industry, specializing in DMPK, PK/PD, and QSP modeling and simulation. Her career commenced at Pfizer in the UK in 1994 within the Drug Metabolism department, spanning 25 years and covering three distinct Pfizer sites: Sandwich UK, Groton, CT, and Cambridge MA. During this tenure, she contributed significantly to the discovery and development of various drug modalities across therapeutic areas. Notably, in her final 10 years at Pfizer, Alison led the modeling and simulation group for the Oncology research unit, playing a crucial role in initiatives such as the relaunch of Mylotarg, the approval of Inotuzumab, and the discovery of the BCMA-CD3 bispecific mAb.

In 2019, after a quarter-century at Pfizer, Alison transitioned to the role of Vice President of Scientific Collaborations at Applied BioMath. While here she also served as the Principal Investigator for an NIH SBIR Grant aimed at building a platform QSP model for ADCs (ADC Workbench), focusing on predicting efficacy and toxicity to enhance the therapeutic index.

Fast forward to 2023, Alison took on the role of Global Head of DMPK & Modeling at Takeda. In this capacity, she oversees scientists across three global sites (Boston, San Diego & Japan), supporting a multi-modality portfolio across three therapeutic areas – Oncology, GI, and Neuroscience.

Throughout her diverse career, Alison has published 31 manuscripts and presented at 40 conferences. Her educational background includes a Ph.D. in Systems Pharmacology from the University of Leiden, the Netherlands, and a B.Sc. in Biochemistry from the University of St Andrews, UK.

LAIGAO CHEN, PHD, Pfizer Dr. Chen is currently a Director in the PET/Molecular Imaging Group of Pfizer Research and Development. He has more than 20 years of pharmaceutical industry experience in applying Positron Emission Tomography (PET) and other imaging technologies in both pre-clinical and clinical phases of drug research and development. He has contributed to the discovery and development of >10 novel PET ligands across multiple therapeutic areas. Laigao obtained his bachelor's and master's degrees on Biomedical Engineering from Shanghai JiaoTong University, China; and Ph.D. on Medial Physics from Purdue University at West Lafayette, Indiana.

KARISSA COTTIER, PHD, BioIVT Dr. Cottier is a Senior Scientist, at BioIVT. Dr. Cottier earned her PhD in medical pharmacology at University of Arizona where she focused on drug delivery in migraine headache model. In her post-doctoral fellowship at Johns Hopkins University Karissa utilized molecular and histology-based assays in an in vitro model to study cerebral malaria. In 2019 Karissa joined the BioIVT Research and Development team in Baltimore Maryland, where she has worked on several projects including application development in the HEPATOPAC and HEPATOMUNE models.

AYMAN EL-KATTAN, IFM Therapeutics Ayman is the president of EPA Consulting Services Inc., He specializes in expert consulting services focused on preclinical drug Absorption, Distribution, Metabolism, and Elimination Pharmacokinetics (ADME-PK). Ayman optimizes physicochemical properties to refine ADME challenges and identify viable chemical leads for progression from drug discovery to preclinical stages. Leveraging advanced predictive modeling techniques, Ayman accurately projects human PK parameters and drug-drug interaction potential, crafting regulatory-compliant reports for effective communication with authorities.

In 2000, Ayman began his career at Pfizer as a Senior Scientist in Pharmacokinetics, Dynamics and Metabolism Department. He contributed to the progress of several drug discovery projects to preclinical and clinical development for the treatment of central nervous system, cardiovascular and inflammation diseases. Ayman joined then IFM Therapeutics as a DMPK Head,

where his contribution enabled IFM to identify 2 clinical candidates that were purchased by Novartis and for the treatment of inflammation diseases.

Ayman is an active member of the American Association of Pharmaceutical Scientists (AAPS) and serve on the committee of the Drug Transporter community. With over 75 speaking engagements at national and international conferences, Ayman published over 90 papers in peer-reviewed journals and book chapters. He also authored a book titled "Oral Bioavailability Assessment: Basics and Strategies for Drug Discovery and Development" published by Wiley.

JONATHAN P. JACKSON, PHD, Pfizer Dr. Jackson, a board-certified toxicologist (DABT), holds a PhD in Molecular and Cellular Toxicology from North Carolina State University, working with the NIEHS under Drs. Goldstein and Negishi. Joining Pfizer in June 2019, he serves as the DSRD Discovery and Investigative Tox DILI subject matter expert. With 17 years in biotech and biopharmaceutical industries, he specializes in ADME-Tox, focusing on drug metabolism, transport, and molecular toxicology. Dr. Jackson's expertise includes hepatic and intestinal in vitro models, particularly in drug-induced liver injury (DILI) and metabolic diseases. He has also explored drug-drug interactions, cell signaling, and gene regulation mechanisms to elucidate hepatic safety concerns.

HEMA MURALIDHARAN, Moderna Hema Muralidharan is a dedicated scientist within the translational biology group at Moderna Therapeutics, where her work is driven by her fervance for elucidating the translatable parameters critical for the success of Lipid Nanoparticle (LNP) drug delivery systems. At the forefront of her current research is the development of microphysical and ex vivo systems designed to unravel the mechanistic underpinnings of LNP efficacy. Before her tenure at Moderna, Muralidharan honed her expertise in early target discovery and cellular disease modeling, with a particular focus on neuroscience and neuroimmunology. Her true passion lies in the meticulous dissection of biological mechanisms and their application to advance cellular models that faithfully recapitulate human biology.

T.K. PHUNG, PHD, Novartis Dr. Phung is a Principal Scientist in Pharmacokinetic Sciences (PKS) Modeling & Simulation at Novartis Biomedical Research. Previously, he was a postdoctoral researcher at the Harvard School of Public Health studying airway epithelial biology and developing automated image analysis tools. He earned a Ph.D. in biomedical engineering at the University of Virginia in 2020 with his dissertation work building patient-specific, multiscale computational models for cardiac therapies. T.K. joined Novartis in 2022, where he provides translational modeling support for across drug modalities including targeted protein degraders for oncology.

BIRK POLLER, PHD, Novartis Dr. Poller works in the Pharmacokinetic Sciences department at Novartis, where he leads the In Vitro ADME labs at the Basel (Switzerland) site. The In Vitro ADME team characterizes drug candidates in vitro by measuring metabolic stability, protein binding, permeability and drug interactions in discovery and development stages. In addition, Birk Poller serves as ADME and DDI expert in cross-functional project teams throughout the translational drug development phases.

Before joining Novartis in 2010, Birk obtained his PhD from the University of Basel, Switzerland and he conducted postdoctoral research at the Netherlands Cancer Institute in Amsterdam.

DANIEL PRICE, PHD, Nimbus Therapeutics Dr. Price is Vice President of Computational Chemistry & Structural Biology at Nimbus Therapeutics, where he leads a team of internal and external scientists focused on delivering breakthrough medicines through structure-based design. In recent years, he and his team have been focused on complementing physics- and simulation-based potency prediction with the accurate modeling of ADMET endpoints using modern machine learning methodologies, and have built a cloud-based MLOps platform to help deliver on these ambitions. Before joining Nimbus, he spent 16 years at GlaxoSmithKline, where he led a team of computational chemists and data scientists across diverse areas of structure- and

ligand-based drug design, high-content screening analytics, predictive modeling, and cross-functional research informatics. Dr. Price received his undergraduate degree in chemical engineering from University of Colorado at Boulder and his Ph.D. in Molecular Biophysics & Biochemistry from Yale University with Prof. Bill Jorgensen, and was an NIH postdoctoral fellow with Prof. Charlie Brooks III at The Scripps Research Institute.

CHRISTOPHER ROWBOTTOM, Moderna Christopher Rowbottom is a Scientific Director of Drug Metabolism and Pharmacokinetics (DMPK) at Moderna TX. With a Bachelor of Science degree from Michigan State University, Christopher has amassed over 18 years of experience in the pharmaceutical industry.

In his current role at Moderna, Christopher serves as a DMPK project representative, contributing to a range of preclinical and clinical programs in a range of therapeutic areas including infectious diseases, immuno-oncology, and rare diseases. Prior to joining Moderna, he spent 5 years at Biogen and 10 years at Eisai, where he played a pivotal role in small molecule drug discovery, with a focus on in vitro drug-drug interactions (DDI) involving CYP P450 enzymes and drug transporters.

At the conference, Christopher will be sharing his expertise on the pharmacokinetics of lipid nanoparticles, offering valuable insights into this cutting-edge area of research.

BEN SCRUGGS, PHD, Altis Biosystems Dr. Scruggs is CEO of Altis Biosystems. Ben earned his PhD from Washington University in St. Louis in 2012 and holds a BE in biomedical engineering from Vanderbilt University. He completed postdoctoral training in the Epigenetics and Stem Cell Biology Laboratory at NIH/NIEHS. He is an experienced leader in the biotechnology industry and has been involved with building transformative healthcare companies in a wide range of areas, including inflammation, oncology, neurodegeneration, ophthalmology, cell therapy, and gene therapy.

MATT SILVA, PHD, EMIT Imaging Dr. Silva is the CEO of EMIT Imaging, the leader in Cryo-Fluorescence Tomography (CFT) imaging. Previously, he served as CEO of Invicro, a global imaging CRO and led the strategic vision and mission to support the drug discovery and development community with diverse imaging services spanning preclinical and clinical applications. Prior to Invicro, he led imaging biomarker groups at Vertex, Amgen, Millennium and Takeda Pharmaceuticals. Matt holds a Ph.D. in Biomedical Engineering from Worcester Polytechnic Institute.

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POSTER ABSTRACTS

HIGH THROUGHPUT AND FULLY AUTOMATED SAMPLE PREPARATION FOR QUANTITATIVE BIOANALYSIS USING LC/MS/MS

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Bioanalytical functions in the pharmaceutical industry face continuous pressure to shorten development timelines and minimize sample volumes requirements. The automation of bioanalysis samples in 384 well plates offer several known benefits, including reduced samples volume, increased throughput, improved accuracy/precision, and lower material cost. We employed the Bravo automated liquid handling platform to carry out the preparation of calibration curves, quality control (QC) and extraction of pharmacokinetic samples. The study included 16 different compounds, for which a 12-points calibration curve was generated. Additionally, four sets of QCs samples at high, mid, low, and lower limit of quantification (LLOQ) levels were analyzed in duplicate. Dextromethorphan, bupropion, imipramine, propranolol, ketoconazole, atenolol, raloxifene, doxepin, haloperidol, piroxicam, warfarin, tolbutamide, verapamil, sulindac, ranitidine and difelikefalin were selected as model analyst. Sample extraction using protein precipitation with acetonitrile was optimized to extract analytes from human plasma with maximum recovery. To a 10 µL of samples, 90 µL of acetonitrile containing an internal standard was added to precipitate the proteins in the sample. The chromatographic separation was performed on an Acquity UPLC HSS T3 (2.1 X 30 mm, 1.8 mM) column, maintained at 50°C with chromatographic run of 1 min. The LC-MS/MS system consisted of a Sciex 6500 mass spectrometer coupled with a Shimadzu NexeraX2 UPLC with electrospray ionization in the positive mode was used in detection. The method was validated according to the FDA guidelines on bioanalytical method validation over concentration ranges. The assay was linear over a range of 3.9 – 4000 ng/mL. The inter-day/intra-day precision and accuracy was within ±15%, when the QC samples were prepared in pooled human plasma. No matrix effect or significant carryover were observed. We successfully carried out high throughput and automation of bioanalysis for 16 different compounds in 384 wells, which greatly improves efficiency/productivity, eliminates human error, and enhances overall quality in bioanalysis.

Utilizing Long-term Culture in Human Liver Tissue Chip Platform to Predict Clinical PK Parameters

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PURPOSE

Metabolic clearance is one of the most critical parameters in ADME assays that guides human dose projection, making it crucial in the preclinical drug development pipeline. Primary human hepatocytes are considered to be the gold standards for metabolism-based studies, however, as traditional 2D cultures, they lose their metabolic function over time. Human tissue chip, or MPS, is an emerging technology that combines human cells and biomaterials leading to improved physiological relevance and stable metabolic activity in-vitro. However certain limitations of such technologies still exist including high non-specific binding, small media volumes for biochemical assays, and evaporation during long term incubations limiting their use for long term PK studies with multiple kinetic timepoints. Here, (i) we developed a novel millifluidic system preserving long-term metabolic activity of multiple PHH donors (ii) evaluated its physiological relevance by conducting long term PK studies (iii) conducted in-vitro DDI studies assessing PK changes for victim drugs in the presence of known CYP inducer, perpetrator.

METHODS

Millifluidic liver tissue chip (LTC) was evaluated with three different PHH donors assessing their functional (tissue morphology, albumin, and urea release) and metabolic activity of major CYPs (CYP3A4, 2C9, 2C19, 1A2, 2D6) for >15 days. We further evaluated the system with 16 small molecule drugs from all ECCS classes to estimate human clearance comparing it with the clinical data. Long-term PK based DDI studies were also conducted using victim drugs, midazolam and alprazolam, having high and low human hepatic clearance respectively, in the presence of perpetrator drug, rifampicin.

RESULTS

LTC sustained multiple PHH donors' functional and metabolic activity for 15+ days allowing for long term PK studies which was evaluated using multiple drugs of low, medium, and high in-vivo human hepatic clearance, showing high in vitro in vivo correlation (IVIVC) with physiologically based pharmacokinetic (PBPK) modeling. Long term PK based DDI studies provided clinically comparable results for midazolam victim study showing a decrease in AUC of substrate depletion curve by 43% leading to a 2-fold increase in intrinsic clearance for the rifampicin induced liver MPS compared to vehicle control. Primary metabolite of midazolam, 1-OH midazolam, profile also showed an increased production after rifampicin induction. The alprazolam victim study with rifampicin led to a 22% reduction in AUC of substrate depletion curve with a 2.6-fold increase in intrinsic clearance.

CONCLUSION

Thus, we addressed the current challenges in conducting long term PK studies by validating the LTC for maintaining functionality with multiple PHH donors, assessing its usability for hepatic clearance predictions and DDI studies, with a potential to provide physiologically relevant data for first in-human dose.

CYP46A1 Inhibition and Activation: An In Vitro High Throughput Screening Assay To Assess Possible Drug Interactions Using FDA Approved Chemical Library

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Cytochrome P450 46A1 (CYP46A1) is involved in the metabolism of cholesterol to 24-hydroxy cholesterol in the brain. It is mainly expressed in the brain and to a lesser extent in the endocrine tissues and retina. This enzyme's inhibition and activation has been studied for therapeutic potential. CYP46A1 has not been extensively studied for drug interactions and evaluating this may provide insight to avoid any potential adverse reactions. Here, we performed rapid and automated high throughput in vitro screening in a 384 well plate format with 2321 FDA approved drugs to identify any potential inhibitors or activators. Testosterone is known to be metabolized by CYP46A1 and is used as a probe substrate for reliability of initial screening for inhibition or activation of cassetted compound library due to short LC-MS/MS run time compared to cholesterol. Based on the cassetted analysis results, individual compounds were then tested with both testosterone and cholesterol as probe substrates. The control inhibitor, soticlestat, in both testosterone and cholesterol assay showed inhibition of 99% and 97% respectively. Based on the cassette testing results, 242 compounds were tested individually for inhibition or activation of CYP46A1 using both testosterone and cholesterol. The individual testing resulted in identifying 15 inhibitors and 12 activators affecting both testosterone and cholesterol. Cassetting was proven reliable to screen the compounds for the activation or inhibition of CYP46A1. To demonstrate the efficacy of this screen, we identified clotrimazole as an inhibitor of CYP46A1 which agrees with the previous literature. The compound library tested identified other azole's like bifonazole, luliconazole, fenticonazole, tioconazole, and atipamezole inhibiting CYP46A1. Anesthesia or sedation compounds such as dexmedetomidine, detomidine, medetomidine and etomidate also inhibited CYP46A1. Additional drugs increased the activity of CYP46A1. Examples of these are cetirizine, ketotifen, quercetin, flupirtine, linifanib and levothyroxine. The present work provides a reliable approach for effectively screening CYP46A1 as well as assessing possible drug interactions.

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