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## JUNE 11, 2025

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**ADMESCOPE** is a European CRO with a comprehensive offering of in vitro ADME-tox and in vivo DMPK assays from early screening assays to regulatory-compliant IND-enabling studies. Core competencies include in vitro metabolism including met ID and profiling, DDI, fast-track PK screens and quantitative bioanalysis. We work with small molecules and other modalities including proteins, peptides, ADCs, ASOs and more. All protocols and reports can be tailored to your needs. Admescope is part of the Symeres family offering fully integrated drug discovery and development services from early hit-finding through to scale-up and CMC.

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**CYPROTEX** Founded in 1999, 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 offers comprehensive drug discovery and development solutions, guiding projects from target identification to the clinic.

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**DISCOVERY LIFE SCIENCES** is a global leader in biospecimens and specialty lab services, enabling the discovery and development of groundbreaking therapeutics and diagnostics. Our Gentest® solutions bring together subject experts in ADME-Tox and hepatocyte cell culture, offering a comprehensive portfolio of innovative, high-quality in vitro ADME-Tox products and services. Discovery is a commitment to providing consistent communication, scientific guidance, and relevant data, enabling IND submissions and helping our clients move drug candidates forward toward the goal of improving patient lives. For more information, visit www.dls.com.

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**EMIT IMAGING** is the pioneer in Cryo-Fluorescence Tomography (CFT), offering our state-of-the-art preclinical imaging system, Xerra™ and comprehensive CFT fee-for-service research to global scientific community. CFT is an ex vivo, volumetric tissue imaging technique that provides enhanced monitoring of the biodistribution of fluorescently labeled molecules or the expression of fluorescent reporter proteins with high resolution and high sensitivity. Anatomical and molecular images are co-registered, enabling unparalleled localization insights for drugs, delivery vehicles, proteins, and other biochemical processes in whole animals and tissues. EMIT Imaging is headquartered and conducts research services out of its Natick, MA office. Engineering and manufacturing are based out of the Owings Mills, MD production facility.

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**JOINN / BIOMERE** is a preclinical contract research organization (CRO) located in Worcester, MA. Biomere's core expertise includes ADME and DMPK studies of different drug modalities in large and small animal models. Biomere is AAALAC accredited, OLAW Assured, DEA Licensed, and USDA Registered. Our mission is to offer a personal approach that combines early discovery and PK/PD studies using a range of pharmacology models.

JOINN Laboratories (China) acquired Biomere in 2019 and this union supports extended GLP lab offerings and the option to significantly decrease your expenditure by placing your study in China. JOINN Laboratories is a trusted research partner and is the largest GLP preclinical CRO in China with facilities in Suzhou, Beijing, Wuzhou, Chongqing and Guangzhou. JOINN Laboratories is AAALAC accredited, US FDA GLP inspected, NMPA GLP certified, OECD GLP certified, PMDA GLP inspected, MFDS GLP inspected and CNAS/ILAC-MRA certified.

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**LIFENET HEALTH LIFESCIENCES** is a leader in all-human research solutions that accelerate discovery. Our unwavering commitment to honoring the donor gift leads to unsurpassed quality and human-relevance, including the largest selection of comprehensively characterized liver cells and tissue in the industry. We offer prospective recovery of biospecimens for research, including livers, brains, skin, and intestines. Our pioneering hepatic in vitro systems provide relevant, reliable new options for alternative methods to animal testing. We also offer a range of cytotoxicity services and unparalleled scientific support.

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**MEDICILON** is a leading CRO company that provides comprehensive drug R&D services on a global scale. From drug discovery, pharmaceutical research to preclinical research, Medicilon has supported more than 2000 client R&D programs worldwide resulting in 520 IND filings. With proven scientific excellence and FDA-aligned methodologies, we help biotech and pharmaceutical innovators fast-track their path from discovery to IND success.

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# ORGANIZERS' WELCOME

**Welcome to the 2025 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

### PRESIDING OFFICERS

Conference Chair:
Seema Chauhan Kumar, Flagship Pioneering
Conference Chair Elect:
Joseph Tillotson, Pfizer

### COMMITTEE MEMBERS

Dallas Bednarczyk, Novartis
Ruchia Duggal, Merck
Maria Fitzgerald, Ipsen
Vinayak Hosagrahara, Enveda
Pei Li, Vertex
Steven Louie, Medicilon
Mukesh Lulla, Biogen
Mitesh Patel, Novartis
Chris Rowbottom, Moderna
Zhiying Wang, BMS

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# NE-ADME 2025 CONFERENCE AGENDA

## WEDNESDAY, JUNE 11

| | |
|---|---|
| 7:30 - 8:30 AM | **Registration & Breakfast** |
| 8:30 - 8:40 AM | **Conference Opening and Plenary Lecture Introduction**<br>Seema Kumar, Pioneering Medicines |
| 8:40 - 9:20 AM | PLENARY: ***Blood-Brain-Barrier Assembloids For Modeling Therapeutic Delivery to Brain Tumors***<br>Choi-Fong Cho, Harvard University |
| 9:20 - 9:30 AM | Sponsor Presentation:<br>***Applications of Cryopreserved Plateable Mouse Hepatocytes in Drug Metabolism and Gene Regulation Discovery Studies***<br>Erik Willems, Discovery Life Sciences |
| 9:30 - 9:35 AM | **Speaker Introduction**<br>Steven Louie, Medicilon |
| 9:35 - 10:05 AM | ***Disposition of Novel Brain-Penetrant Therapeutics***<br>Cinthia Pastuskovas, Denali Therapeutics |
| 10:05 - 10:30 AM | Break |
| 10:30 - 10:35 AM | **Speaker Introduction**<br>Dallas Bednarczyk, Novartis |
| 10:35 - 11:05 AM | ***Predicting Oral Absorption, Intestinal Availability, CYP3A4 Induction and Transporter-Mediated Drug-Drug Interactions Using Human Primary Intestinal 3D Model (EpiIntestinal™)***<br>Paresh Chothe, AstraZeneca |
| 11:05 - 11:10 AM | **Speaker Introduction**<br>Vinayak Hosagrahara, Enveda |
| 11:10 - 11:40 AM | ***Highlights From the Final ICH M12 Guideline "Drug Interaction Studies" - What's Changed and Considerations for Your IND Programs***<br>Brian Ogilvie, BioIVT |
| 11:40 - 11:45 AM | **Speaker Introduction**<br>Pei Li, Vertex |
| 11:45 - 12:10 PM | Sponsor Presentation:<br>***Cryo-Fluorescence Tomography: Transformative 3D Imaging to Monitor Drug PK/PD***<br>Matt Silva, EMIT Imaging |
| 12:10 - 1:20 PM | Lunch |

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1:20 - 1:25 AM **Speaker Introduction**
Maria Fitzgerald, Ipsen

1:25 - 1:35 PM **Sponsor Presentation:**
***Advancing siRNA from Discovery Target to Preclinical Candidate***
Qingcong Lin, Medicilon

1:35 - 1:40 PM **Speaker Introduction**
Seema Kumar, Flagship Pioneering

1:40 - 2:10 PM ***AI/ML for Model-Informed Precision Medicine***
Nadia Terranova, Merck KGaA, Germany (EMD Serono, US)

2:10 - 2:15 PM **Speaker Introduction**
Chris Rowbottom, Moderna

2:15 - 2:45 PM ***Immunogenicity Risk Assessment Strategies Across Modalities: Regulatory-Driven Approaches for Clinical Development***
Jason DelCarpini, Moderna Therapeutics

2:45 - 3:10 PM Break

3:10 - 3:15 PM **Speaker Introduction**
Ruchia Duggal, Merck

3:15 - 3:45 PM ***Strategies and Approaches for Modeling and Prediction of Large Molecule Drug-Drug Interactions***
Jaydeep Yadav, Merck

3:45 - 3:50 PM **Speaker Introduction**
Joseph Tillotson, Pfizer

3:50 - 4:20 PM ***DMPK-on-a-Chip: Developing an Organ-Linked MPS System to Inform Human Pharmacokinetics***
James Gosset, Pfizer

4:20 - 4:25 PM **Speaker Introduction**
Dallas Bednarczyk, Novartis

4:25 - 4:55 PM ***Harnessing in vitro and Bioanalytical Data for Quantitative Systems Pharmacology (QSP) Modeling of Antibody-Drug Conjugates***
Eshita Khera, Novartis

4:55 - 5:00 PM **Closing Remarks**
Joseph Tillotson, Pfizer

5:00 - 6:00 PM **Reception**

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# ABSTRACTS

## PLENARY

### *Blood-Brain-Barrier Assembloids For Modeling Therapeutic Delivery to Brain Tumors*

Choi-Fong Cho, Harvard University

The inability of most therapeutics to cross the blood–brain barrier (BBB) is a major roadblock to effective treatment of diseases in the central nervous system (CNS). The BBB is comprised of the neurovascular unit (NVU), which includes brain endothelial cells (BEC), brain pericytes and astrocytic end-feet. This specialized microvasculature system has high expression of complex tight junctions that restrict paracellular permeability, efflux pumps, and specific transporters than peripheral vessels to regulate molecular trafficking between the blood and brain. Challenges: In vitro BBB models play critical roles for use in screening and prioritizing CNS drug candidates prior to in vivo studies. However, BECs tend to rapidly dedifferentiate and lose their BBB characteristics when they are grown as monolayer in cultures, resulting in the lack of expression of key BBB modulators and leaky paracellular barrier function. The mid-throughput 2D transwell BBB model is widely accessible, though it is associated with several limitations including barrier leakiness and loss of BBB marker expression. 3D microfluidic BBB systems have been developed to better simulate the BBB morphology, though these devices have limited throughput and require either purchase of a commercially available device or construction of one, making them relatively inaccessible to many laboratories. In vivo rodent models continue to face challenges in the field with interspecies differences, costs and throughput.

Recently, we have described a high-throughput, versatile and robust 3D human BBB organoid model. These miniature organoids are formed through the self-assembly of NVU cells in co-culture into a highly organized structure, where a layer of BEC encases the organoid, forming an intact 'barrier' between the inner organoid and its environment. Direct cell-cell interaction of BEC with other NVU cell types is known to be critical for the induction and maintenance of BBB properties in culture. Indeed, we show that the surface of the organoids recapitulates key BBB features, such as tight junctions, functional drug efflux pumps, and the MFSD2A transcytosis inhibitor. We have also adapted this platform to model brain tumors such as GBM, known as the 'blood-tumor-barrier (BTB) organoids', demonstrating GBM cells in the organoids exhibit enhanced clinical features as seen in GBM patient tissues compared to the traditionally used GBM monocultures. We demonstrate the organoids' effectiveness in predicting therapeutic delivery across the BBB in vivo, as well as drug efficacy for treating GBM. The organoids can be rapidly established within 3 days, and several thousands of the organoids can be simultaneously formed at a given time to expediate therapeutic assessment to mitigate failure risk at a later state of drug development.

## SPONSOR TALK

### *Applications of Cryopreserved Plateable Mouse Hepatocytes in Drug Metabolism and Gene Regulation Discovery Studies*

Erik Willems, Discovery Life Sciences

Inter-species and inter-individual differences from genetic as well as from environmental factors play a decisive role in determining the pharmacokinetic properties of a drug in a drug development campaign. In vitro testing in predictive non-human models allows affordable prioritization of large compound libraries toward lead compound verification for efficacy or safety in a selected animal model. The mouse is a valuable animal model for drug metabolism studies and efficacy testing of newer drug modalities for liver disease such as oligonucleotides. However, in vitro options have been limited due to challenges with maintaining mouse hepatocytes in culture for extended periods of time. We have made great progress in deriving high quality plateable cryopreserved mouse hepatocytes and we will share our progress with these hepatocytes both for the assessment of cytochrome P450 isoform induction as well as their use in validating efficacy of small interfering RNAs.

### *Disposition of Novel Brain-Penetrant Therapeutics*
Cinthia V. Pastuskovas, Denali Therapeutics

Delivery of biotherapeutics across the blood-brain barrier (BBB) has been a challenge when treating Central Nervous System (CNS) diseases. The use of protein-based therapies to treat neurodegenerative diseases has been limited by the minimum brain exposure following systemic administration. Only 0.01-0.1% of peripheral antibody concentrations reach the CNS and the brain associated antibody is largely confined to blood-CSF barrier.

All macromolecules are effectively restricted from reaching the brain in therapeutically relevant concentrations by physical and biochemical barriers, most notably the BBB.

To facilitate brain delivery, therapeutic recombinant enzymes or proteins have been fused to a TransportVehicle (TV) platform consisting of an Fc domain engineered to bind highly expressed proteins on brain endothelial cells that are capable of receptor-mediated-transcytosis such as the transferrin receptor(TfR)and CD98 heavy chain(CD98hc). The modularity of the TV platform enables multiple modalities, and when the TV is fused to Fabs the resulting Antibody TransportVehicle (ATV) is designed to deliver antibodies in bivalent or bispecific format to the brain. Herein, we demonstrate differentiated ATV systemic pharmacokinetics, brain uptake kinetics, and CNS biodistribution based on TV binding to TfR or CD98hc in a transgenic mouse model. This study is part of a comprehensive characterization aimed at enabling platform selection tailored for the treatment of distinct CNS disorders.

### *Predicting Oral Absorption, Intestinal Availability, CYP3A4 Induction and Transporter-mediated Drug-Drug Interactions Using Human Primary Intestinal 3D Model (EpiIntestinal™)*
Paresh Chothe, AstraZeneca

Successful prediction of the oral absorption of drugs in humans is critical in early drug development. Caco-2 cell line is commonly used for predicting oral absorption and evaluating efflux transporter liability, despite some physiological differences compared to human. Recently, complex in vitro models including 3D tissue cultures such as human intestinal organoid and microphysiological systems are emerging to provide more accurate predictions of oral drug absorption. To this end, we have comprehensively evaluated EpiIntestinalTM, a human primary intestinal 3D model, in accurately predicting oral absorption (Fa), intestinal availability (Fg), CYP3A4 induction and DDIs. The model presents clinically relevant expression of a key drug metabolizing enzymes, transporters, and a nuclear receptor, PXR. PBPK modeling, using EpiIntestinal™ permeability data, accurately predicted the Cmax of digoxin, and dabigatran etexilate (P-gp substrates). The model was also explored to predict intestinal Fg by PBPK modeling incorporating intrinsic clearance and permeability of CYP3A4/5 substrates drugs. Combining induction parameters of rifampicin from EpiIntestinalTM with those from the TruVivo (all-human hepatic model) into PBPK modeling accurately captured DDI effect on midazolam. The model was also investigated in predicting P-gp and BCRP-mediated DDIS using 2 clinical case studies of vepdegestrant (ARV-471) as a precipitant.

### *Highlights From the Final ICH M12 Guideline "Drug Interaction Studies" - What's Changed and Considerations for Your IND Programs*
Brian Ogilvie, BioIVT

The ICH M12 Guideline was finalized on May 21st, 2024, after extensive review of industry and other comments. The Guideline is the culmination of the extensive work by the Expert Working Group. The Expert Working Group was formed in 2018 and is a committee of experts charged with harmonizing member regulatory agencies' guidelines to create a single guideline that will be used across all member countries. The new Guideline replaces the corresponding drug interaction guidance documents from the US FDA, EMA, and PMDA, among others.

This presentation will offer perspectives on changes from the draft ICH M12 and differences between in vitro drug-drug interaction guidance from the relevant US FDA, EMA and PMDA guidance documents, as well as how to plan drug development strategies to meet the expectations of the final ICH M12 Guideline.

Key concepts covered in this webinar will include:

- An overview of changes to the in vitro sections from the

draft to the final ICH M12 Guideline
- A comparison of the in vitro sections of the final ICH M12 Guideline with previous guidance from FDA, EMA and PMDA
- A comparison of the equations and cutoff values highlighting changes from the draft version
- A comparison of in vitro experimental details highlighting changes from the draft version
- Impacts of finalization of the ICH M12 on in vitro DDI study design and interpretation

## SPONSOR TALK

### *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 biochemical processes is essential in preclinical research and drug discovery. However, current methods for assessing whole animals are limited by throughput, require complex tissue collection and processing, and are restricted to standard tissues that may not fully reflect drug disposition.

Cryo-Fluorescence Tomography (CFT) is a volumetric imaging technology that delivers high-resolution, high-sensitivity fluorescence and molecular images of whole animals or tissues. CFT has multiplexing capabilities, seamlessly integrates into existing laboratory workflows, and complements histopathological analysis by providing sub-organ localization of drug products, proteins, and biomarkers.

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

## SPONSOR TALK

### *Advancing siRNA from Discovery Target to Preclinical Candidate*

Qingcong Lin, Medicilon

The field of small interfering RNA (siRNA)-based therapeutics is rapidly evolving as biotech companies continue to develop novel targets to treating various diseases. The advancement and clinical application of siRNA technology, a post-transcriptional gene silencing method that targets and degrades mRNA. siRNAs, synthetic RNA molecules, bind to specific complementary mRNAs, leading to their degradation and silencing of gene expression. siRNA therapy offers advantages over other approaches like infrequent administration and improved patient adherence. Technological advancements, including chemical modifications and delivery systems, have improved siRNA bioavailability and stability, leading to the approval of several siRNA-based drugs for liver-directed therapies (e.g., Patisiran, givosiran, lumasiran, inclisiran). While promising, ongoing challenges remain in targeting organs beyond the liver and reaching special sites like the brain highlighting their potential as a novel approach for treating various diseases. We present our approach to supporting client siRNA preclinical candidate development from discovery to IND-filing, including the challenges of siRNA design, delivery, and the emergence of approved and investigational siRNA drugs.

### *AI/ML for Model-Informed Precision Medicine*

Nadia Terranova, Merck KGaA, Germany (EMD Serono, US)

This talk will explore how advanced data analytics, particularly Artificial Intelligence (AI) and Machine Learning (ML), can enhance model-informed drug development and precision medicine. Through concrete use cases, we will illustrate the added value of integrating AI/ML into drug-disease modeling and discuss emerging opportunities fueled by the increasing availability of high-dimensional and multimodal data, novel biomarkers, and digital real-world data.

### *Immunogenicity Risk Assessment Strategies Across Modalities: Regulatory-Driven Approaches for Clinical Development*

Jason DelCarpini, Moderna Therapeutics

Effective immunogenicity risk assessment is essential for the successful clinical development of both established and novel therapeutic modalities. This presentation will outline a structured, modality-agnostic approach to immunogenicity risk assessment that incorporates data from preclinical studies alongside other key factors to inform clinical strategy.

Critical inputs—including molecular design features, platform history, mechanism of action, patient population, route of administration, and preclinical findings related to immune activation or tolerability—will be discussed in the context of identifying both the likelihood and potential clinical consequences of an immune response. These elements form the foundation for determining the appropriate depth of immunogenicity monitoring and shaping the overall bioanalytical plan.

The presentation will also review current regulatory expectations and guidances (FDA, EMA, ICH) that influence how immunogenicity risk assessments are conducted and communicated. Attendees will gain practical insights into building scientifically justified, regulatorily aligned immunogenicity strategies to support diverse therapeutic programs across their development lifecycle.

### *Strategies and Approaches for Modeling and Prediction of Large Molecule Drug-Drug Interactions*

Jaydeep Yadav, Merck

Antibody drug conjugates (ADCs) are increasingly being used for treating cancer. ADCs are designed with two main components: a cytotoxic drug (payload) and a monoclonal antibody (mAb) with a linker to connect both. The cytotoxic drug is the potent payload that targets and kills cancer cells, while the monoclonal antibody provides specificity. The cytotoxic payloads, after release, are assumed to behave like traditional small molecules. There is a potential that DDIs can occur if the clearance pathways for payload are modulated. Moreover, payload itself can cause modulation of cytochrome P450. DDI assessment and translational strategies involve multiple approaches, including PBPK modeling. The talk will describe the modeling strategy used for predicting ADC payload DDIs, both as a victim and as a perpetrator. A semi-empirical approach was adopted which was used to predict DDIs mediated by the unconjugated payload. This approach was first validated using published literature clinical ADC PK and DDI data before applying it to an internal ADC program.

### *DMPK-on-a-Chip: Developing an Organ-Linked MPS System to Inform Human Pharmacokinetics*

James Gosset, Pfizer

In early drug design, there are significant efforts towards characterization of the ADME (absorption, distribution, metabolism, and excretion) properties of potential drug candidates using both in vitro and preclinical in vivo systems. We use these data to predict human pharmacokinetics (PK) and drug-drug interactions (DDI) enabling the selection of drug candidates for clinical development in human.

Over recent years, substantial investment of government and venture capital funding have produced novel technologies of more intact systems that can represent human organ physiology. These include cell culture systems that go beyond single cell type monolayer cultures (e.g., organoids, co-cultures in 2D and 3D formats) and human tissue chips, aka microphysiological systems (MPS) can replicate several organ systems (e.g., liver, gut, kidney).

While human MPS chips are primarily used in basic research, such technologies have limited utility in pharmacokinetic applications because the flow-through fluidic design, chip material, and small media / tissue volumes do not support drug quantification.

For this unmet need, in partnership with Javelin Biotech we designed single- and multi-tissue chips for pharmacokinetics applications. These chips are recirculating milli-fluidic chips made of low non-specific binding thermoplastic material. The milli-fluidic chips accommodate larger tissue and media than microfluidic chips to enable multiple media sampling for kinetic data. The recirculatory perfusion system dramatically extends drug-tissue retention time

allowing low-clearance and low-permeability drug studies. We characterized each tissue (liver, kidney (proximal tubule) and skeletal muscle) functionality for 21+ days with single- and multi-tissue chips and demonstrated physiologically relevant levels of enzyme and transporter activity in order to conduct pharmacokinetic studies.

A diverse set of small molecule drugs from all extended clearance classification system (ECCS) classes with various clearance mechanisms was evaluated on single- and multi-tissue chips. We quantified on-chip pharmacokinetic parameters, such as hepatic metabolism, uptake and disposition, tubular secretion and reabsorption, and muscle disposition. These on-chip pharmacokinetic parameters were then successfully scaled to clinical parameters for IV drugs: hepatic clearance, renal clearance, and volume of distribution. The predicted PK parameters showed high correlation to clinical parameters.

The vision is to employ this platform in the early development of drug discovery, where dramatic reduction in the required API, offer an alternative to, and hopefully a replacement of, pharmacokinetic studies in laboratory animals for the purposes of understanding drug disposition in an intact mammal as a surrogate for human.

### *Harnessing in vitro and Bioanalytical Data for Quantitative Systems Pharmacology (QSP) Modeling of Antibody-Drug Conjugates*

Eshita Khera, Novartis

Over 90% of clinical ADCs use pan-cytotoxic payloads, but there is emerging interest in selectively-targeted payloads such as protein inhibitors and degraders. However, designing ADCs with non-traditional payloads is even more complex than cytotoxic ADCs, and challenging to optimize empirically. The proposed talk will highlight some new guiding principles for designing non-traditional ADCs, guided by vignettes of integrated lab-to-model workflows powered by Quantitative Systems Pharmacology.

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# SPEAKER BIOGRAPHIES

**CHOI-FONG CHO, PhD,** Harvard Medical School Dr. Cho is an Assistant Professor in the Department of Neurosurgery at the Brigham and Women's Hospital (BWH), Harvard Medical School. She is also an Affiliate at the Massachusetts Institute of Technology (MIT), and the Dana Farber Cancer Institute. She received her PhD in Medical Biophysics at Western University in Canada, which was fully supported by national and provincial scholarships. She later completed her post-doctoral fellowship in Neuro-oncology at BWH, where her fellowship was funded by the Canadian Institute of Health Research. She was promoted to an Instructor within the Neurosurgery Department in 2017, and then an Assistant Professor in 2019. The Cho lab focuses on developing organoid platforms to model the blood-brain-barrier and blood-tumor-barrier in culture to facilitate the development of novel anti-brain cancer drugs with improved delivery into the brain.

**PARESH CHOTHE, PhD,** AstraZeneca Dr. Chothe is an Associate Principal Scientist in the Drug Metabolism and Pharmacokinetics department at AstraZeneca, Waltham MA where represents DMPK function on early drug discovery programs in Oncology. Additionally, he leads drug disposition efforts especially on drug transporters for small molecules in Oncology. His research interest involves drug transporters in ADME, DDI risk predictions, novel in vitro/ in vivo platforms in improving human PK predictions including oral absorption and hepatic clearance. Paresh received his PhD in Biomedical Sciences from Augusta University, Augusta, GA in 2010. Later, he worked as a Post-Doctoral Fellow at University of Maryland, Baltimore. Prior to joining AZ, Paresh held positions in DMPK at Vertex Pharmaceuticals (Boston, MA) (2015-2020) and Takeda Pharmaceuticals (Cambridge, MA) (2020-2022). Overall, he has 10 years of experience driving innovative research in ADME in pharmaceutical industry. He has published over 40 publications (including original research, reviews and book chapters) in the peer-reviewed journals and several presentations in the scientific conferences.

**JASON DELCARPINI, PhD,** Moderna With over 20 years in the pharmaceutical and biotech industries, Jason DelCarpini is a leader in bioanalytical science, specializing in pharmacokinetics, pharmacodynamics, and immunogenicity for innovative therapies, including mRNA-LNP, protein, gene, and cell-based treatments. As Director of Bioanalytics at Moderna, he develops and oversees clinical and preclinical bioanalytical strategies, ensuring regulatory compliance and advancing GLP/GCLP-regulated processes.

Jason has played key roles in founding and managing bioanalytical laboratories, with a focus on continuous improvement, adopting new technologies, and implementing digital workflows to enhance efficiency and compliance. An active contributor to the bioanalytical community, he regularly participates in industry seminars, publications, and working groups to advance knowledge and standards across the field.

**JAMES GOSSET, BSC,** Pfizer Mr. Gosset is a project representative within the department of Pharmacokinetics, Dynamics and Metabolism at Pfizer. He represents DMPK and translational research in small and large molecule projects providing strategic direction to project teams from idea to registration across multiple therapeutic areas. For over 25 years, he has been responsible for characterizing and optimizing the pharmacokinetic properties of small and large molecule drugs. James is particularly interested in DMPK predictive sciences and microphysiological systems for ADME endpoints with research publications in these areas. He has (co-)authored more than 25 peer-reviewed manuscripts and book chapters.

**ESHITA KHERA, PhD,** Novartis Dr. Khera is Principal Scientist II in the Modeling & Simulation group of PK Sciences at Novartis. She develops mechanistically driven computational models to capture the complex PK/PD of biologics across several disease indications, with a lead focus on antibody-drug conjugates and immune-cell engaging antibodies. Eshita earned her PhD in Chemical Engineering at the University of Michigan where she developed an integrated in vitro, in vivo, and predictive in silico

platform to understand ADC distribution, including bystander effects, in solid tumors. She also holds an MSE in Chemical Engineering and MS in Biomedical Engineering from the University of Michigan, and a BE in Biotechnology from VTU, India.

**QINGCONG LIN, PhD,** Medicilon Dr. Qingcong Lin holds a Ph.D. in Molecular Biology from the Albert Einstein College of Medicine of Yeshiva University. He has served as the Director of the Gene Modification Laboratory at Harvard-Partners Center for Genetics and Genomics (HPCGG). He has also published 24 papers in prestigious international journals such as MCB, JBC and holds multiple invention patents.

Before joining Medicilon, Dr. Lin held positions such as Senior Scientist II, Principal Research Scientist I & II, and Director of Molecular Genetics Laboratory at Wyeth Research; Principal Research Scientist II and Group Leader at Pfizer Research; Senior VP of Biology and Antibody R&D at Shenogen Pharma Group; and SVP of Beijing Biocytogen, CEO of Biocytogen Boston Corp.

**BRIAN OGILVIE, PhD,** BioIVT Dr. Ogilvie is Vice President of Scientific Consulting at BioIVT, a global company that provides biological specimens and research services for drug discovery and development. Brian obtained his Ph.D. in toxicology from the University of Kansas Medical Center, and B.A. in molecular biology from William Jewell College. He joined XenoTech in 1997 (acquired by BioIVT in 2022). Brian is an author or coauthor on over 50 scientific posters, peer-reviewed publications or book chapters on the topics of drug metabolism, transport and drug-drug interactions, and has been an invited speaker at various drug metabolism and toxicology conferences. As Vice President of Scientific Consulting, he provides senior level scientific and regulatory consultation to drug companies.

**CINTHIA PASTUSKOVAS, PhD,** Denali Therapeutics Dr. Pastuskovas earned her PhD in Neuroscience from the University of Córdoba, Argentina and moved to the U.S. for a postdoctoral position at the University of Iowa. Following her academic experience, she joined Genentech, where she specialized in the ADME characterization of novel biotherapeutics, including antibody-drug conjugates and bispecifics. After 13 years at Genentech, Cinthia transitioned to Amgen and later Merck, expanding her expertise to include a new generation of "Bispecific T-Cell Engager (BiTE)" and immunocytokines. Currently, at Denali Therapeutics, she leads efforts to advance a portfolio of blood-brain barrier-penetrant TV biotherapeutics, providing scientific contributions in pharmacokinetics, drug disposition and biodistribution, and translational pharmacology/pharmacodynamics.

**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.

**NADIA TERRANOVA, PhD, EMBA,** Merck Dr. Terranova is a Biomedical engineer by training with a PhD in Bioengineering and Bioinformatics and EPFL Executive MBA in Innovation and Technology, currently serving as the Head of Advanced Data Analytics in Quantitative Pharmacology at Merck KGaA, Darmstadt (EMD Serono, US). Dr. Terranova's contributions to the scientific community and to Merck's R&D organization range from impactful model-informed drug development, applications of advanced Machine Learning techniques to complex and multivariable drug development problems to entrepreneurial initiatives, data and digital innovation.

Dr. Terranova is the leading author of several papers in selected journals and in international conference proceedings, and serving on editorial boards for CPT and JPKPD journals as well as the Chair of the ASCPT Pharmacometrics & Pharmacokinetics Steering Committee.

**ERIK WILLEMS, PhD,** Discovery Life Sciences Dr. Willems was trained as a stem cell biologist in Brussels, Belgium. As a postdoc he then developed expertise in the use of pluripotent stem cells in high throughput screening assays for understanding basic biology, disease, and toxicity of cardiomyocytes at the Sanford Burnham Prebys Medical Discovery Institute in San Diego, California. Pursuing his passion for the development and application of biotechnology tools, Erik joined and subsequently led a team focused on customer driven projects at Thermo Fisher Scientific in Carlsbad, California, focusing on cell model generation and application in drug discovery and drug safety testing workflows. Continuing his desire to enable customers and their drug development efforts, Erik recently transitioned to Discovery Life Sciences where he is currently responsible for new product development and service offerings in the preclinical ADME space.

**JAYDEEP YADAV, PhD,** Merck Dr. Yadav is an Associate principal Scientist in the Department of Pharmacokinetics, Dynamics, Metabolism and Bioanalytics (PDMB), at Merck, Boston. Before joining Merck, he worked at Amgen, Department of PKDM from 2018 to 2020 where he worked on establishing in-vitro TDI assays and was a part of modeling groups in different programs. Jaydeep obtained his Ph.D. in Pharmacokinetics and Drug metabolism at Temple University in 2018.

Jaydeep's research areas include drug-drug interaction, time-dependent inhibition, drug metabolism, PK-PD modeling, PBPK modeling. Jaydeep has co-authored several peer-reviewed research and review articles and wrote a book chapter in 'Enzyme Kinetics in Drug Metabolism: Fundamentals and Applications'. Jaydeep is a past Chair of the AAPS student chapter. Jaydeep is a steering committee member of the ISSX, modeling and simulation group and part of the member organizing committee for ISSX 2026.

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# POSTER ABSTRACT

## DEVELOPMENT AND CHARACTERIZATION OF REPLIGUT® SYSTEM TO MODEL HUMAN DRUG PERMEABILITY, EFFLUX, AND METABOLISM

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Reliable prediction of human drug absorption and metabolism remains a cornerstone of preclinical development. While Caco-2 and Ussing chamber systems are widely used to assess permeability and transporter-mediated drug disposition, both have significant limitations: Caco-2 cells lack cell-type diversity and native expression levels of key enzymes and transporters, while Ussing chambers rely on scarce and variable human tissue samples and offer limited throughput.

To address these limitations, we characterized the RepliGut® Planar system, a primary human intestinal epithelial model derived from region-specific intestinal stem cells for capacity to more accurately represent the human in vivo intestine. RepliGut Planar recapitulates a physiologically relevant monolayer with tight junction integrity, native transporter and enzyme expression, and support for high-throughput workflows.

Transcriptomic analyses revealed 6- to 200-fold enrichment in expression of key ADME-relevant genes including ABCB1 (P-gp), ABCG2 (BCRP), CYP3A4 and CYP3A5, compared to Caco-2 cells. Whereas compared to native jejunum intestinal tissue, RepliGut monolayers expressed equivalent CYP3A5 and BCRP mRNA and 50% of CYP3A4 mRNA expression. RepliGut® Planar demonstrated functional efflux activity for both P-gp and BCRP, including response to inhibition. RepliGut® Planar was also capable of metabolizing CYP3A4 and UGT substrates. In head-to-head studies with Ussing chambers, RepliGut® Planar recapitulated expected passive permeability, bidirectional transport, and efflux ratios across multiple compounds, with higher reproducibility and scalability.

These results support RepliGut® Planar as a robust, human-derived in vitro model for intestinal ADME studies, offering improved physiological relevance, broader functional readouts, and better scalability than legacy systems. This platform may aid in more predictive evaluation of drug permeability, transporter interactions, and intestinal metabolism in early drug development.

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