GMP

Groupe *de* Métabolisme *et* Pharmacocinétique

36th GMP SYMPOSIUM

16th – 18th October 2024

Lyon - France

Espace de l'Ouest Lyonnais
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GMP
Groupe de Métabolisme et Pharmacocinétique

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Oral Communication

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Session 5: Methodologies and applications of therapeutic drug monitoring for treatment individualization

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S5.2 From therapeutic drug monitoring to model-informed precision dosing of anti-infective drugs

S5.3 Precision medicine in oncology: which role for therapeutic drug monitoring?

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One step aside: "Synthetic dreams" – how data and AI are re-inventing drug R&D

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Oral Communication

Day 3: 18th October 2024

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S7.2 Multimodal molecular imaging in Drug Discovery and Development

S7.3 Delivery of anti-cancer drugs using microbubble-assisted ultrasound in digestive oncology: from preclinical to clinical studies

S7.4 Clinical pharmacology considerations and model-informed drug development (MIDD) applied to Targeted Radiation Therapies (TRT)

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PROGRAM : detailed
Day 1 : 16th October 2024

09:30 – 12:30 **Workshops**

Feel the power of GPX in our upcoming workshop dedicated to special populations!

Join us for a 3-hour interactive session hosted by SimulationsPlus where you'll gain hands-on experience in various aspects of GPX. Learn how to include special physiologies in your model, with a focus on obesity. Discover how to optimize the physiology schedule to simulate changes in the fed state and long-term physiological changes like significant weight loss/gain over time.

DDIs in a changing regulatory landscape. What are the latest requirements and solutions?

Join us in 3-hour interactive session hosted by Certara going through regulatory gates, optimized strategies, solutions for complex DDIs and smart tools when you are managing DDI topics during the journey of drug development.

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PROGRAM

Day 1 : 16th October 2024

12:30 – 13:30 **Arrival and registration welcome coffee/tea**

13:30 – 13:40 **Welcome to 2024 GMP Symposium**

13:40 – 14:40 **Session 1**

Contribution of new in vitro models for DMPK prediction

Chairs: Madeleine Coimbra (Sanofi)**, Yannick Parmentier** (Servier)

In vitro tools are continuously being optimized for better performance. Their many benefits (increased accuracy and representativity to in vivo situation, decreased reliance on animal testing, high throughput capabilities, personalized medicine applications and safety assessment features) make them essential resources that the scientific community is working hard to perfect. Join this session to explore the potential of HepaSH and 3D models for DMPK prediction and expand your knowledge on this topic.

S1.1 Sylvie Klieber and Estelle Yau (Sanofi)
Organ-on-chip combined with in silico modeling as a promising tool for improved prediction of human pharmacokinetic
S1.2 Olivier Fardel (IRSET)
The use of HepaSH cells from humanized liver TK-NOG mice for drug detoxification and elimination studies

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14:40 – 15:40 Session 2

Transgenic models for DMPK

Chairs: Céline Amara (Sanofi)**, Olivier Petricoul** (Novartis)**, Sylvain Fouliard** (Servier)

Preclinical transgenic models have shown to be essential tools that improve the human translation of drug PK and/or PK/PD profile for clinical development. Humanized preclinical models of disease or humanized FcRn mice are of increasing usage, reducing uncertainty of prediction of exposure and drug effects in human, and also ultimately reducing the number of animal experiments to be run. This session will delve into the properties of these experimental models and the challenges that need to be tackled for them to deliver their full potential.

S2.1 Pauline Vachin (Sanofi)
Transgenic models from design to reality: challenges prior to use in R&D
S2.2 Michael Kiffe and Monika Gajewska (Novartis)
Humanized FcRn mouse model for evaluating PK and allometric scaling

15:40 – 16:10 Coffee break and poster session

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16:10 – 17:10 Session 3

Impact of gut microbiome on small molecules metabolism and integration of these parameters in drug discovery and development

Chairs: Priscilla Brun (Sanofi)**, Laurence Del Frari** (Pierre Fabre)

This session will present the reasons behind the under-consideration of the microbiome in pharma, the present limitations and progress of the microbiome tools (i -screen) , and the recommendation to integrate as early as possible the gut microbiome in the drug discovery and development process of small molecules;

S3.1 Patrick Jimonet (Medicen)
Integration of gut microbiome drug metabolism in drug discovery and development of small molecules
S3.2 Frank Schuren (TNO)
Microbiome mediated drug metabolism studies in the TNO i-screen model

17:10 – 18:10 Students poster blitz

We welcome student abstracts in the field of pharmacology (ADME, PK, PD, PBPK, DDI). All submitted abstracts will be reviewed by the selection committee and chosen to be part of a poster presentation and short-oral presentation. A "Best Student presentation" awards will be announced during the 2024 GMP Symposium

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Day 2 : 17th October 2024
Good Clinical PK practice

8:00 – 8:30 **Welcome coffee/tea**

8:30 – 9:30 **Key note speaker: Susan Cole**

Medicines for all: Pharmacokinetic models to support medicines use in special populations

Chair: Maxime Le Merdy (Simulations Plus), **Madani Rachid** (Sandoz), **Isabelle Deprez** (Certara)

09:30 – 10:00 **Coffee break and poster session**

10:00 – 12:00 **Session 4**

Special populations in drug development & clinical practice

Chairs: Carla Troisi (ESQlabs GmbH), **Fanny Gallais** (Pharmetheus), **Olivier Petricoul** (Novartis), **Madani Rachid** (Sandoz)

Special populations, including pediatrics and underrepresented subpopulations such as obese patients, require additional consideration with regard to clinical research. This session will present case studies and strategies for handling such populations both in drug development and clinical practice.

S4.1 Justin Hay (Certara)
From bench to crib: leveraging model-informed drug development and navigating regulatory considerations for paediatric drug development
S4.2 Johanna Eriksson (Pharmetheus)
Optimizing formulations for treatment of cryptococcal meningoencephalitis in sub-saharan HIV patients: insights from PBPK modeling
S4.3 Catherijne Knibbe (Leiden University, St. Antonius Hospital)
The importance of studying drug exposure in individuals with obesity during drug development: examples of antimicrobial and other agents
S4.4 Sandra Cvijic (University of Belgrade)
Empowering pharmacotherapy strategies for gastric bypass patients

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12:00 – 12:45 **GMP "Assemblée Générale"**

12:45 – 14:00 **Lunch & Posters**

14:00 – 15:30 **Session 5**

Methodologies and applications of therapeutic drug monitoring for treatment individualization

Chairs: Sarah Lobet (Calvagone)**, Carla Troisi** (ESQlabs GmbH)**, Alicja Puszkiel** (APHP)**, Etienne Chatelut** (Institut Universitaire du cancer)

This session explores developments in dose optimization and individualization across various medical disciplines. Presentations will cover optimizing antibiotics, personalized targeted therapies in oncology, and dose adaptation strategies in psychiatric pharmacotherapy.

S5.1 Romain Guilhaumou (CHU de Marseille)
Therapeutic drug monitoring and pharmacogenetics: applications in psychiatric disorders
S5.2 Sylvain Goutelle (CHU Lyon)
From therapeutic drug monitoring to model-informed precision dosing of anti-infective drugs
S5.3 Benoît Blanchet (Hôpital Cochin, Paris)
Precision medicine in oncology: which role for therapeutic drug monitoring?

15:30 – 16:00 **Coffee break and poster session**

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16:00 – 17:30 Session 6

Biomarker strategy for dose selection/optimization

Chairs: Loic Laplanche (Abbvie)**, Laurence Del Frari** (Pierre Fabre)**, Carla Troisi** (ESQlabs GmbH)

This session examines the utilization of biomarkers (ctDNA, cfDNA, phosphorylation of inhibition…) to enhance dose selection and optimization strategies across a spectrum of therapeutic areas and molecules - spanning from pre-clinical to clinical applications. Further explore the methodologies for biomarker measurements and gain a comprehensive understanding of the various modeling approaches (statistical analysis, machine learning, and non-linear mixed effects models) used in decision-making in clinical trials.

S6.1 Christine Bain (Active biomarkers)
How biomarkers contribute to driving the clinical development of DMTs in neurodegenerative diseases
S6.2 François Riglet (Servier)
Using target engagement biomarker for early decision-making in oncology
S6.3 Linh Nguyen-Phuong (Aix-Marseille University)
Computational modeling approaches for circulating cell-free DNA in oncology

17:30 – 18:30 One step aside

Synthetic dreams – How data and AI are re-inventing drug R&D

Chairs: Yannick Parmentier (Servier)**, Laurence Del Frari** (Pierre Fabre)

IIn this presentation, we will explore the current and potential roles of AI in drug R&D and how it redefines the way scientists integrate data generation with technological applications and wet-lab validation. We will deep-dive into the scientific implications, impacts on researchers, and the research process itself. A key question we will address is whether AI represents merely another tool or signifies a more profound shift in scientific inquiry.

Angeli Möller (Zühlke Group , Germany)

19:30 Gala dinner

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Day 3 : 18 th October 2024

8:30 – 9:00 Welcome coffee/tea

9:00 – 11:00 Session 7

Biodistribution : from technology to therapeutic support

Chairs: Yannick Parmentier (Servier)**, Olivier Nicolas** (Sanofi)**, Sarah Lobet** (Calvagone)

Reaching the right target tissue at the right time and effective concentration is the main objective of a therapeutic modality. Biodistribution studies explore either the best way to reach the target or where the modality, including potential metabolites and endogenous biomarkers stand over time. This session will give an overview of the new technologies including mass spectrometry imaging or ultrasound to tackle the biodistribution challenges..

S7.1 David Bonnel (Aliri Bioanalysis)
De-risking and accelerating drug development drograms: applications and integration of spatial bioanalysis and spatial biology at the site of action
S7.2 Michiel Vandenbosch (MI4, Maastricht University)
Multimodal molecular imaging in drug discovery and development
S7.3 Jean Michel Escoffre (Université de Tours)
Delivery of anti-cancer drugs using microbubble-assisted ultrasound in digestive oncology: from preclinical to clinical studies
S7.4 Amandine Manon (Certara)
Clinical pharmacology considerations and model-informed drug development (MIDD) applied to targeted radiation therapies (TRT)

11:00 – 11:30 Coffee break

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11:30 – 12:30 **Session 8**

New insights for biologics

Chairs: Loic Laplanche (Abbvie)**, Céline Amara** (Sanofi)**, Priscilla Brun** (Sanofi)

The diversity and importance of biologics create opportunities to apply innovative bioanalytics as well as modeling framework to measure, characterize and manage immunogenicity risks. This session will showcase such applications that should ultimately support the advancement of patient-centric care and enhance therapeutic benefit.

S8.1 Gianluca Selvaggio (Pharmetheus)
A quantitative systems pharmacology framework of immunogenicity to propose mitigation strategies after subcutaneous administration

S8.2 Stéphane Muccio (Sanofi)
Innovative hybrid LC-MS methods for the semi-quantification and isotyping of ADAs (Anti-Drug Antibodies) responsible for affecting the bioavailability and the activity of the biotherapeutic

12:30 – 12:45 **Master and PhD poster awards**

12:45 – 12:55 **Closing remarks**

12:55 – 14:00 **Farewell lunch**

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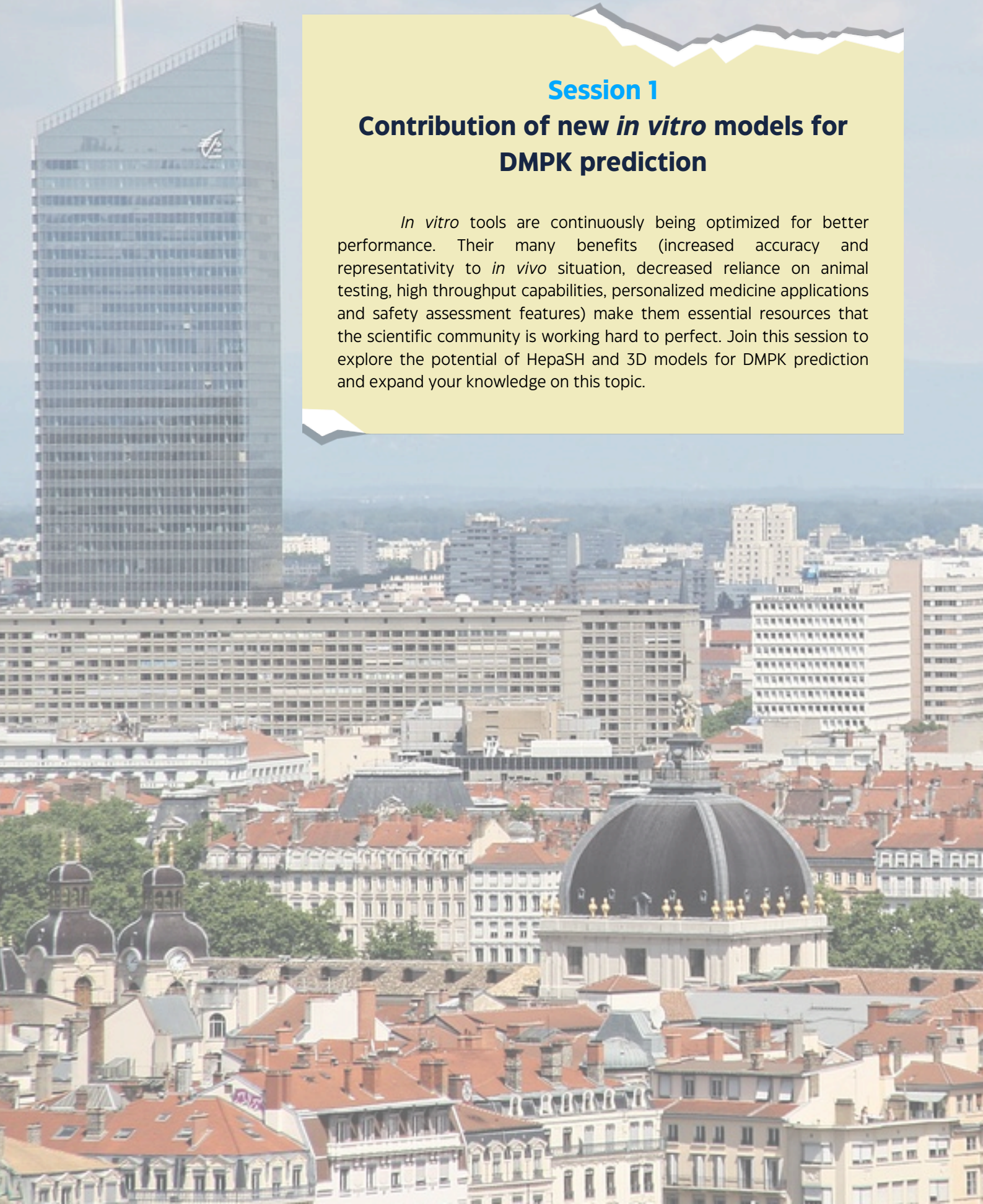
Session 1

Contribution of new *in vitro* models for DMPK prediction

In vitro tools are continuously being optimized for better performance. Their many benefits (increased accuracy and representativity to *in vivo* situation, decreased reliance on animal testing, high throughput capabilities, personalized medicine applications and safety assessment features) make them essential resources that the scientific community is working hard to perfect. Join this session to explore the potential of HepaSH and 3D models for DMPK prediction and expand your knowledge on this topic.



S 1-1. Organ-on-chip combined with in silico modeling as a promising tool for improved prediction of human pharmacokinetic

Sylvie Klieber PhD & Estelle Yau PhD
Sanofi, Vitry sur Seine, France.

Microphysiological systems (MPS), also known as organs-on-a-chip (OOC), represent promising tools for ADME (absorption, distribution, metabolism, and excretion) applications with the potential to capture the interaction of different tissues and to provide with improved in vitro and in vivo translation of drug efficacy and toxicity. Compared to conventional static in vitro 2D models, these systems include media flow to mimic blood circulation, promoting cell polarization and inducing a more mature cellular phenotype. For effective use of MPS, appropriate mathematical modeling of in vitro data is essential for predicting human pharmacokinetics to select the best drug candidate. Innovative MPS experimental data have been generated using CnBIO liver chip for a set of different clinical drugs and different biological donors to estimate hepatic clearance.

Combining these experimental data with appropriate mathematical modeling has demonstrated a significant improvement of the accuracy of human clearance prediction (within a 2-fold improvement), outperforming conventional approaches and demonstrating its translational predictivity.

Sylvie Klieber obtained her PhD in cell biology from the University of Montpellier. Sylvie Klieber is currently heading a Global In Vitro ADME team in DMPK at Sanofi and is located in Paris. Her group supports the optimization of drug discovery programs and she also has a broad experience in the characterization of pre-clinical and clinical candidates for the resolution of problems related to drug metabolism and DDI risk assessment. Her group is also working on developing and applying more physiologically relevant in vitro models based on 3D/MPS technologies, including Liverchips, spheroids or co-cultures to study drug disposition.

Estelle Yau is currently a PK/PD Modelling Scientist in DMPK at Sanofi, where she provides modeling support for research projects in different therapeutic areas. She has received her PharmD in 2017 from the University of Paris Descartes, France, and her PhD in pharmaceutical sciences in 2021 from the University of Manchester, UK. During her PhD in collaboration with Roche, Switzerland, she worked on simplifying physiologically based pharmacokinetic models for parameter optimization and translation from preclinical species to human.

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S 1-2. The use of HepaSH cells from humanized liver TK-NOG mice for drug detoxification and elimination studies

Pr Olivier Fardel
IRSET, Rennes, France

Human hepatocytes are currently the gold standard for *in vitro* studying interactions of drugs with hepatic drug metabolizing enzymes and drug transporters. These cells are notably useful for predicting hepatic drug clearance as well as potential drug-drug interactions. Primary human hepatocytes isolated from human liver donors however correspond to a rather limited and expensive resource. The development and validation of relevant and available surrogates to them is therefore a major issue. In this context, human hepatocytes isolated from humanized liver TK-NOG mice, called HepaSHTM cells, likely represent an interesting emerging alternative. Indeed, these cells, used fresh or cryopreserved, and as suspensions or cultures, exhibit notable expression of main hepatic drug metabolizing enzymes and drug transporters. They moreover retain regulatory pathways controlling expression of cytochromes P-450 and drug transporters and are thus potentially suitable for characterizing inducing effects of drugs. Main features of isolated and cultured HepaSH cells in terms of drug metabolizing enzyme and drug transporter expression and activity will be summarized. Some recent applications to pharmacological and toxicological studies of drugs or environmental pollutants will be detailed. Perspectives of the *in vitro* use of HepaSH cells in the metabolism, membrane transport and pharmacokinetics area will be finally drawn.

Olivier Fardel, PharmD, PhD, *is a professor of drug sciences at the Faculty of Pharmacy, University of Rennes, and responsible of the team 1 "Xenobiotics and barriers" at the Research Institute for Environmental and Occupational Health/INSERM unit 1085, at Rennes (France). His research studies focuses on interactions on membrane drug transporters with xenobiotics (drugs, chemical pollutants), with special emphasis on the consequences for pharmacokinetics/toxicokinetics, drug-drug interactions and drug or pollutant toxicity. Studies for characterizing and validating hepatic and extra-hepatic in vitro models for analyzing drug transporter expression, activity and regulation are also developed, Olivier Fardel is author or co-author of more than 200 papers in international peer-reviewed journals. His research work is funded by French or European public grants as well as by partnerships with pharmaceutical or biotechnological companies.*

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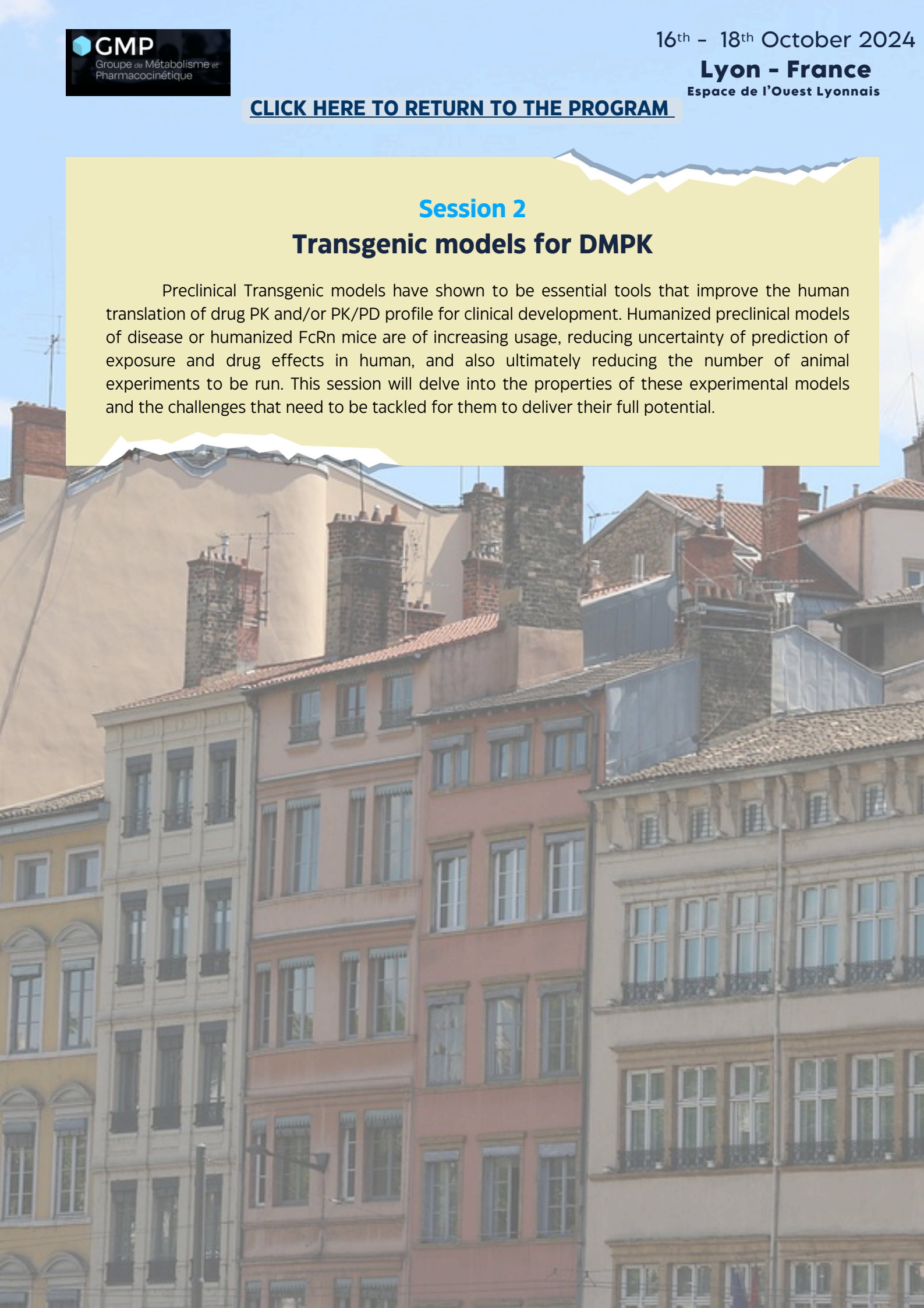
Session 2

Transgenic models for DMPK

Preclinical Transgenic models have shown to be essential tools that improve the human translation of drug PK and/or PK/PD profile for clinical development. Humanized preclinical models of disease or humanized FcRn mice are of increasing usage, reducing uncertainty of prediction of exposure and drug effects in human, and also ultimately reducing the number of animal experiments to be run. This session will delve into the properties of these experimental models and the challenges that need to be tackled for them to deliver their full potential.



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S2-1 : Transgenic models from design to reality: challenges prior to use in R&D

Pauline Vachin, PharmD. PhD
Principal Scientist in Transgenic In Vivo Models, Sanofi Montpellier, France

Transgenic models remain a tool of choice in R&D, not only to better understand the pathophysiology of certain diseases, but also to assess the potential of drug candidates. However, there may be differences between the theoretical design of the model and the effects observed in vivo. These issues, if not identified early in the project, can lead to biases in the evaluation of a therapeutic molecule. This presentation will give an overview of the problems we have identified and the methods we use (molecular biology, flow cytometry or histopathology, etc.) to confirm the suitability of a model for the needs of a project.

Pauline Vachin as part of a French PharmD-PhD course, completed a master's degree in genetics at Necker Hospital (Paris) before starting a thesis in immunology, which she defended in 2018. She joined a project in partnership with Inserm and a start-up company to develop an innovative treatment for rheumatoid arthritis. She joined Sanofi R&D at the end of 2022 to lead a team in charge of validating transgenic rodent models generated for the needs of different therapeutic areas using molecular biology and flow cytometry approaches.

S2-2 Humanized FcRn mouse model for evaluating PK and allometric scaling

Michael Kiffe, PhD & Monika Gajewska PhD
Novartis, Biomedical Research, Basel, Switzerland

Key element for the successful development of novel therapeutic antibodies is to fully understand their PK (and PD) behavior before performing toxicological and clinical studies. The long serum half-life of IgGs and drugs with Fc domains are due to their rescue and recycling by the neonatal Fc receptor (FcRn). Due to significant species differences between rodent and human FcRn reactivity, wild type rodent models are inadequate for studying variants with different half-life extension motifs and therefore mouse models have been established expressing human FcRn and lacking mouse FcRn protein by genetic engineering. The hFcRn mouse model shows comparable predictive performance compared to NHP in predicting human PK parameters through bodyweight-based allometric scaling, making it a valuable alternative for by-passing NHP studies in preclinical drug development. While Tg32 is mostly promoted for modeling human PK of therapeutic antibodies, our analysis shown that Tg276 hemi hFcRn mouse predicts PK parameters in human comparably well to Tg32 homo hFcRn mouse. Further investigation of this finding in a larger dataset is needed.

Michael Kiffe brings extensive expertise in drug development, with a career spanning nearly 30 years. He has experience in all stages of drug development, from early discovery to non-clinical and clinical development. Michael began his career at CIBA in 1995, after completing his PhD from the Technical University of Braunschweig in Germany. During his postdoctoral studies at Shimadzu Corporation in Kyoto, Japan, he focused on peptide synthesis and analytics. Later, Michael joined Novartis in the Discovery DMPK department as a PK and biotransformation expert for early projects. He quickly gained recognition and became a Disease Area representative for Oncology and Immunology.

Currently, Michael serves as the group lead for Pharmacokinetic Sciences Immunology at Novartis. In this role, he supports the discovery and development of both low molecular weight drugs and biologics across various stages of the development process.

Monika Gajewska holds a Master's degree in Chemical Engineering and Technology as well as a Ph.D. in Life Sciences. Her doctoral research at the Technical University of Munich focused on toxicokinetic and toxicodynamic modeling of repeated dose toxicity. The Ph.D. project was funded and conducted at the Institute for Health and Consumer Protection, Joint Research Centre, European Commission in Ispra, Italy. For the past decade, Monika has been employed at Novartis, working in the Modeling & Simulation/ Translational PK/PD group. In this role, she has provided support to projects spanning various therapeutic areas, including small molecules and biologics.

Her primary responsibilities include the application of PBPK (Physiologically-Based Pharmacokinetic), PK-PD (Pharmacokinetic-Pharmacodynamic), and QSP (Quantitative Systems Pharmacology) modeling techniques, as well as data analysis. Monika's expertise has been crucial in addressing project-specific questions, such as predicting safe and effective doses prior to First in Human (FiH) studies, population PK-PD modeling, disease modeling, absorption modeling, drug-drug interaction (DDI) modeling, evaluation of preclinical animal models (including FcRN mice models), and the development of in silico tools.

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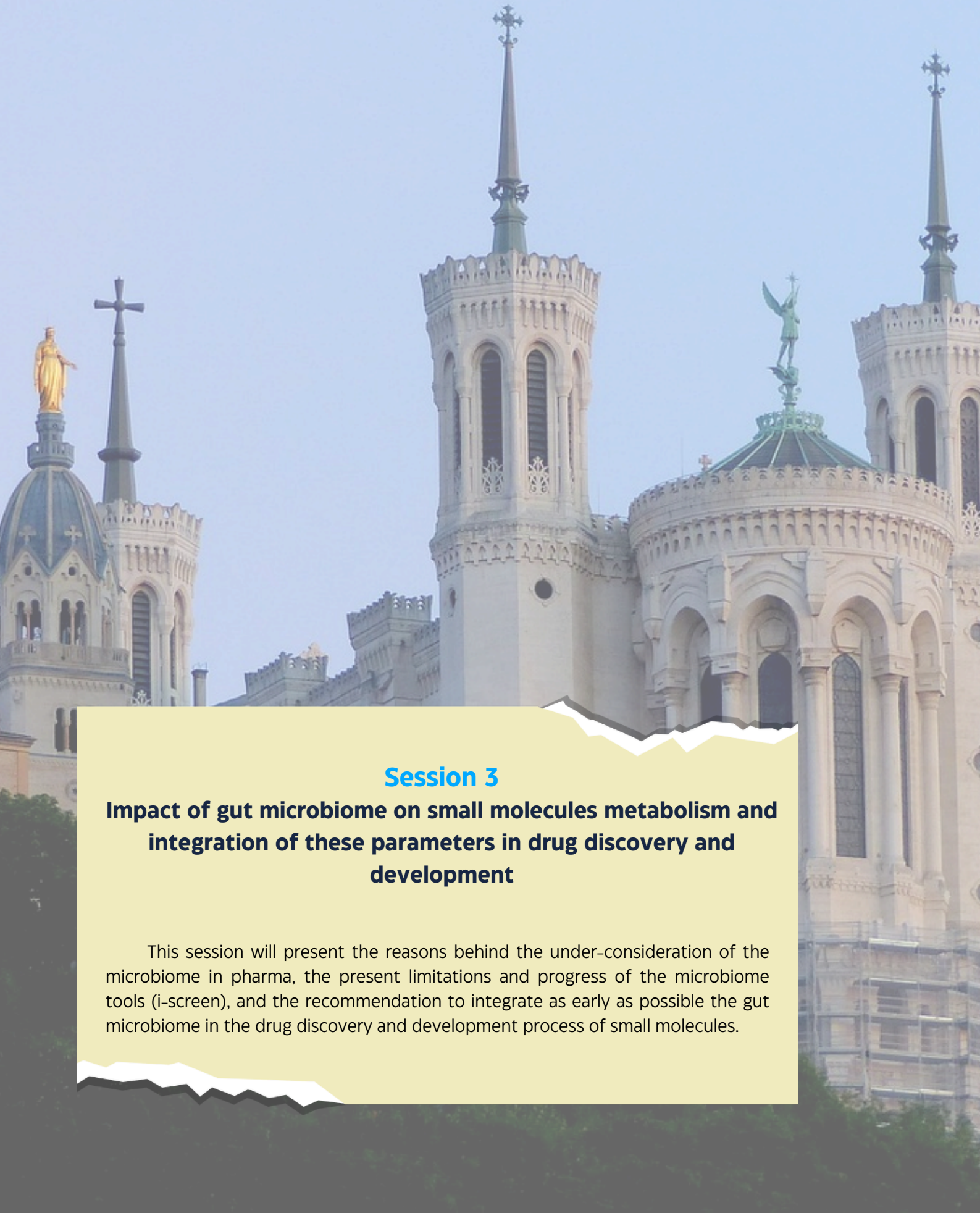

Session 3

Impact of gut microbiome on small molecules metabolism and integration of these parameters in drug discovery and development

This session will present the reasons behind the under-consideration of the microbiome in pharma, the present limitations and progress of the microbiome tools (i-screen), and the recommendation to integrate as early as possible the gut microbiome in the drug discovery and development process of small molecules.

S3-1 Integration of gut microbiome drug metabolism in drug discovery and development of small molecules

Patrick Jimonet, Céline Druart, Stéphanie Blanquet-Diot, Lilia Boucinha, Sephanie Kourula, Françoise Le Vacon, Sylvie Maubant, Sylvie Rabot, Tom Van de Wiele, Frank Schuren, Vincent Thomas, Bernard Walther and Michael Zimmermann, on behalf of the Medicen Microbiome Drug Metabolism Working Group

Medicen Paris Region, Paris, France

Human microbiomes, particularly in the gut, could have a major impact on the efficacy and the toxicity of drugs, as well as on the variability of individual response to treatment. However, gut microbial metabolism is often neglected in the drug discovery and development process. Medicen, a Paris-based human health innovation cluster, has gathered more than thirty international leading experts from pharma, academia, biotech, CROs and regulatory science to develop proposals to facilitate the integration of microbiome science into drug discovery and development. Seven subteams were formed to cover the complementary expertise areas of 1) pharma experience and case studies, 2) in silico microbiome- drug interaction, 3) in vitro microbial stability screening, 4) gut fermentation models, 5) animal models, 6) microbiome integration in clinical and regulatory aspects, and 7) microbiome ecosystems and models. Each expert team produced a state-of-the-art report of their respective field highlighting existing microbiome-related tools at every stage of drug discovery and development.

The presentation will underline the main conclusions from this analysis, the reasons behind the under-consideration of the microbiome in pharma, the present limitations and progress of the microbiome tools, and the recommendation from the group to integrate as early as possible the gut microbiome in the drug discovery and development process.

With a PhD in organic chemistry, **Patrick Jimonet** has over 30 years of experience in pharmaceutical research and business development. His various positions within Sanofi and predecessors have enabled him to lead therapeutic projects from biological target identification to clinical evaluation, to lead international transversal research projects, to identify external biological, chemical and technical innovations, to initiate new models of partnerships to strengthen pharma R&D. Patrick joined the Paris-based human health cluster Medicen in October 2019 as a volunteer for missions such as the microbiome initiative. An international working group, including 30+ members, was thus initiated with the objective to stimulate integration of the microbiome into drug discovery and development.

S3-2 Microbiome mediated drug metabolism studies in the TNO i-screen model

Dr Frank Schuren, S. Erpelink, E. van de Steeg
TNO Microbiology & Systems Biology, The Netherlands

The role of the gut microbiome in the metabolism of xenobiotics is increasingly recognized. It has been demonstrated that gut microbiota can directly metabolize xenobiotics into active, inactive or toxic metabolites, thereby influencing pharmacokinetics, efficacy and toxicity profiles of prescribed drugs. We have previously shown metabolism of selected drugs by pooled human microbiota (vd Steeg et al 2018). Here we will present multiple novel insights in the role of the microbiome towards drug metabolism including metabolism of human (liver) generated metabolites and their reversion to parent drug, individual variation in metabolism, possibilities to study small intestinal metabolism and quantitation of microbiome driven drug metabolism.

Frank Schuren received his PhD at Groningen University in 1987 on the molecular biological analysis of fungal development. After a postdoc in Groningen and at the ETH Zurich in Switzerland he joined TNO in 1996. At TNO he started the implementation of microarray technology in applied research which led to successful implementation in applied microbial research. These include novel diagnostic tools such as the Legionella chip and the analysis of complex microbial populations (such as the intestinal and vaginal microbiota). Furthermore Frank has extensive experience with different approaches for novel antimicrobial strategies. Currently Frank is senior scientist in the Microbiology team within TNO and actively involved in activities towards better understanding the role of the microbiome in human health and especially in innovative ways to modulate gut microbiome in order to improve human health, with a specific focus on dietary fibers and innovative approaches for dealing with individual variation as well as microbiome driven drug metabolism.

Key Note Speaker: Susan Cole

MHRA, Canary Wharf, London, UK

Medicines for all: Pharmacokinetic models to support medicines use in special populations

In order to ensure efficacy and safety for all, it is essential that medicines are developed for all appropriate populations and sub-populations. The same dose may not be suitable for all populations and a more personalised approach is of increasing interest. Deficiencies in the information to support certain sub-populations has become apparent over the last few decades. Regulators require information e.g. in different race, age, and disease groups at the time of authorisation of a new medicine. A drive globally to include children has resulted in an improvement in the availability of drugs for children, but there is still some way to go. Other populations of interest are pregnant women, breastfeeding women, the elderly and the obese. It is recognised that full efficacy and safety studies are not always possible in the population, but an extrapolation can be used based on pharmacokinetics (PK). Modelling is an important component of any extrapolation and often both population PK and physiologically based PK (PBPK) models will be used. In particular, physiologically based models allow in sillco predictions based on the compound's properties and the physiological changes known to occur in the population. Extensive analysis of models for children and more recently, pregnant and lactating women, has demonstrated the usefulness of the models but also uncertainties related to some of the gaps in knowledge. Currently, it is suggested that he use of PK.models can significantly reduce the Clinical studies required with only sparse confirmatory samples needed.

Susan Cole is an Expert Clinical Pharmacology Assessor and Head of the Clinical Pharmacology group, within the Innovative Medicines group at the UK Regulatory Agency (MHRA). Prior to joining the MHRA in 2012, Sue worked for 26 years at Pfizer in the UK in the field of Drug Metabolism and Pharmacokinetics. While in Industry Sue fulfilled a number of roles including Head of the preclinical Pharmacokinetics and Modelling group and as a Clinical Pharmacologist. Susan is a member of the ASCPT Regulatory and PKUK committees. She is also a member of a number of groups under the IQ consortium including: PBPK to inform modelling in paediatrics, and physiologically based modelling for biopharmaceutics.

Previously she was a member of the Pharmacokinetics, the Modelling and Simulation and the Scientific Advice, Working Parties at the European Medicines Agency and she worked on the guideline on Reporting PBPK modelling and simulation. Susan is the lead investigator on projects funded by the Gates Foundation to investigate models to support medicine use in pregnancy and RWD for contraceptives and she is the co-author on a number of publications on PBPK modelling including the use of PBPK models to support medicine use in pregnancy.

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Session 4

Special populations in drug development & clinical practice

Special populations, including pediatrics and underrepresented subpopulations such as obese patients, require additional consideration with regard to clinical research. This session will present case studies and strategies for handling such populations both in drug development and clinical practice.

S4-1 From bench to crib: leveraging model-informed drug development and navigating regulatory considerations for paediatric drug development

Justin Hay PhD, Senior Director
Certara, Radnor, PA, USA

Developing safe and effective medicines for children faces unique challenges due to ethical considerations and physiological differences across age groups. Traditional clinical trials can be limited by constraints on sample size and difficulty in recruiting specific paediatric populations. This presentation explores how Model-Informed Drug Development (MIDD) can optimise paediatric drug development strategies. MIDD integrates nonclinical data, clinical trial findings, and patient information to inform dose selection, predict drug behavior in children, and design efficient clinical trials. This presentation will discuss the regulatory landscape in Europe and the United States (US), highlighting key requirements for pediatric drug development plans (EU: PIP, US: iPSP) and the role of MIDD in fulfilling these requirements. The presentation will showcase how MIDD can contribute to extrapolation as well as a more efficient and informative approach to developing essential medications for children.

Justin Hay is a clinical pharmacologist with 25+ years' experience. He is a clinical pharmacology and regulatory expert at Certara and a core member of the Paediatric and Maternal Health Centre of Excellence and One Certara Oncology group. He was former EMA & MHRA Senior Assessor and Deputy Manager MHRA, UK prior to this he was Senior Clinical Scientist at the Centre for Human Drug Research (CHDR), Leiden, the Netherlands. He was conferred his PhD in Medicine (Pharmacology) from the University of Adelaide, Australia. He is the author of over 80 peer reviewed abstracts/manuscripts in the field of clinical pharmacology.
https://www.linkedin.com/in/drjustinhay/

S4-2 Optimizing formulations for treatment of cryptococcal meningoencephalitis in sub-Saharan HIV patients: insights from PBPK modeling

Johanna Eriksson, Ph.D,[1] Erik Sjögren, Ph.D,[1] Jean-Yves Gillon, Ph.D,[2] Vishal Goyal, Ph.D,[2] Vijay Satam Ph.D,[2] Stephen Robinson Ph.D,[2] Henri Caplain MD,[2] Isabela Ribeiro Ph.D,[2] Marylore Chenel Ph.D[1]

[1] Pharmetheus, Uppsala, Sweden

[2] Drugs for Neglected Diseases initiative (DNDi), Switzerlan

5-flucytosine (5FC) is used for the treatment of cryptococcal meningoencephalitis, which is a major cause of death for patients with advanced HIV in Sub-Saharan Africa. Currently, an immediate release (IR) tablet is dosed four times a day, with the risk of low adherence [1,2]; additionally, it is not well adapted for severely ill patients, who require administration by nasogastric tube. To address these issues, a sustained release (SR) pellet formulation was developed. A model-informed drug development (MIDD) strategy was implemented to inform decisions along the project [3]. In a first step, a PBPK model was developed to support the selection of SR formulations to be studied. From this first work, 3 SR formulation prototypes were selected to be tested for safety and plasma pharmacokinetics (PK) in fasted healthy participants (study 1), along with a commercial immediate-release (IR) tablet. To further support dosing and formulation selection in a subsequent clinical study (study 2: fed study in healthy participants) the PBPK model was updated with the PK data obtained in study 1. Based on these initial results and PBPK simulations of multiple dosing, the SR dosing regimen was adjusted to meet the exposure metrics for the IR formulation in healthy individuals. Further, the 5FC PBPK model was applied to simulate 5FC exposure in patients, including HIV-associated disease components (leaky intestine, damaged microvilli, diarrhea and severe malnutrition) for the IR and SR formulations, to assess the risk of switching from an IR to a SR formulation in terms of PK exposure.

The simulations indicate that the primary risk with regards to exposure stemmed from diarrhea induced by rapid gastrointestinal transit, resulting in a 10% lower ratio (SR/IR) for simulated exposure compared to healthy individuals. This discrepancy may be attributed to reduced absorption time in diarrheal patients, affecting the SR formulation more profoundly than the IR counterpart. In addition, the simulations suggests that severe malnutrition significantly affected the pharmacokinetics (PK) of both sustained-release (SR) and immediate-release (IR) formulations, leading to a median exposure increase (15-18%) and higher maximum concentration (Cmax) (13-15%), primarily due to decreased renal clearance in this population [4]. This impact remained consistent across both formulations, indicating that transitioning from IR to SR isn't inherently riskier for treating cryptococcal meningoencephalitis in severely malnourished patients.

Based on the PBPK simulations, the shift from an IR to an SR formulation for treating cryptococcal meningoencephalitis isn't expected to alter the exposure ratio (IR/SR) in the general patient population, except for those with fast transit diarrhea. However, for malnourished patients, the impact on exposure is significant but consistent across both formulations.

Johanna Eriksson received a Master of Science Degree in Pharmaceutical Sciences from Uppsala University, Sweden in 2015. In 2015 she started her Ph.D. studies at the Department of Pharmacy (now Department of Pharmaceutical Biosciences), Uppsala University, Sweden under the supervision of Hans Lennernäs and in collaboration with AstraZeneca, Gothenburg. The focus of the Ph.D. project was to increase the mechanistic understanding of pulmonary drug absorption. During her Ph.D. studies Johanna also worked as a teacher at the Master of Science in Pharmacy programme at Uppsala University, Sweden. Johanna Eriksson is an MIDD consultant at Pharmetheus since 2021.

S4-3 The importance of studying drug exposure in individuals with obesity during drug development: examples of antimicrobial and other agents

Catherijne A.J. Knibbe, PharmD PhD FCP, professor of Individualised Drug Treatment
St. Antonius Hospital, Dept of Clinical Pharmacy, Nieuwegein, The Netherlands
LACDR, Division of Pharmacology, Faculty of Science, Leiden University, The Netherland

Obesity is associated with many physiological changes. In contrast to other specific populations like patients with renal or hepatic impairment who are mainly at risk of overexposure of drugs, individuals with obesity who can be at risk of both under- and overexposure are not studied during drug development. From the available studies and evidence, prediction of obesity-related changes in pharmacokinetics is however hard, even when the primary pathway of elimination, logP or other characteristics are considered. Gaining knowledge on the influence of body weight on clearance during early phases of drug development through clinical studies will allow for optimisation of other phases of research, potentially increasing success rate of the drug, and can provide clinicians with vital information as soon as the drug reaches the market. In the presentation different examples on antimicrobial- and other agents are discussed.

Catherijne Knibbe is professor of Individualized Drug Treatment at the Leiden University, The Netherlands, and clinical pharmacologist-hospital pharmacist at the St Antonius Hospital Nieuwegein, the Netherlands. She leads the Quantitative Clinical Pharmacology group that aims to define how to adjust a drug dose in special patient populations such as (prematurely born) neonates or children, individuals with obesity or critically ill patients. Through combining the statistical power of the population approach with physiologically-based approaches, computer models are developed that can predict the efficacy and safety of drugs in each of these special patient populations. The studies of her group have led to in-depth insights on the influence of growth, maturation, organ function or obesity for many different drugs and populations.

She is a co-author of over 300 international peer-reviewed publications and contributions to books, has supervised 25 PhD students, is currently co-supervising 12 PhD students and 2 Post Docs, and. She is a frequently invited speaker on national and international conferences. She is a Fellow (FCP) of the American College of Clinical Pharmacology (ACCP) and serves on many (inter)national committees and boards.

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S4-4 PBBM modeling: empowering pharmacotherapy strategies for gastric bypass patients

Sandra Cvijic
Department of Pharmaceutical Technology and Cosmetology, University of Belgrade-Faculty of Pharmacy, Vojvode Stepe 450, Belgrade, Republic of Serbia

The prevalence of obesity has surged, with gastric bypass surgery emerging as a primary treatment for severe cases. However, bariatric patients often require pharmacological treatment for concomitant diseases, necessitating attention to oral drug dosing adjustments. Physiological changes post-bariatric surgery may significantly impact drug dissolution and absorption, challenging conventional dosing methods like tablet crushing or capsule opening. An alternative solution to tackle these challenges is physiologically based biopharmaceutical modeling (PBBM). This computer-based approach offers a personalized strategy for selecting appropriate pharmacotherapy for bariatric patients by accounting for drug-specific and physiological factors influencing drug absorption. The selected examples will demonstrate how PBBM predictions can be used in conjunction with in vitro data on drug properties to answer clinically relevant questions, such as selecting appropriate drug therapy in bariatric patients.

Sandra Cvijic (maiden name: Grbic) is a professor at the Department of Pharmaceutical Technology and Cosmetology, University in Belgrade-Faculty of Pharmacy, Serbia. She holds a PhD in Medical Sciences - Pharmacy (2011) and Specialization in Pharmaceutical Technology (2015) from the University of Belgrade-Faculty of Pharmacy. She has authored or co-authored more than 150 publications and presentations at national and international scientific meetings. She also held several seminars/workshops/training schools on physiologically-based pharmacokinetic/biopharmaceutics modeling. Her research interest has to do with biopharmaceutical characterization of drug substances/drug products, modeling and simulation of drug absorption and disposition, drug substances/products performance in specific populations, bioperformance dissolution testing, in vitro-in vivo correlation, formulation and characterization of oral and inhalation drugs

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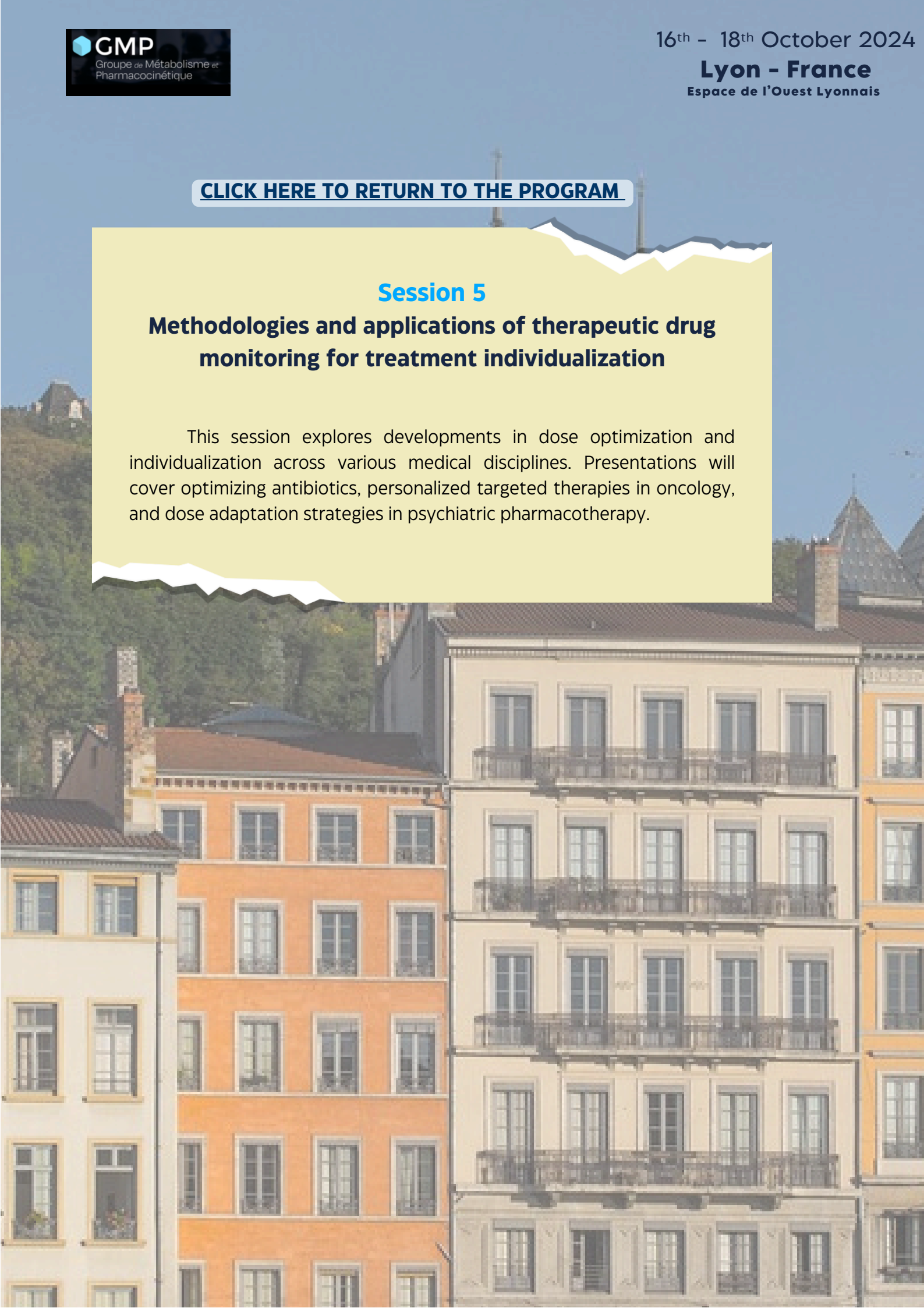
Session 5

Methodologies and applications of therapeutic drug monitoring for treatment individualization

This session explores developments in dose optimization and individualization across various medical disciplines. Presentations will cover optimizing antibiotics, personalized targeted therapies in oncology, and dose adaptation strategies in psychiatric pharmacotherapy.



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S5-1 Therapeutic drug monitoring and pharmacogenetics : applications in psychiatric disorders.

Romain Guilhaumou, PharmD, PhD, HDR
Aix Marseille University, APHM, INSERM, Service de Pharmacologie Clinique et Pharmacosurveillance, INS Institute Neuroscience Syst, Marseille, France

Despite the progress of treatments, psychiatric disorders are still associated with a chronic relapsing course and marked functional impairment in a substantial proportion of patients. The variability of treatment response for both efficacy and side effects is multifactorial. Non-pharmacological aspects, such as psychological and social implications, influence drug response but at the pharmacological level, drug response results from the interaction of genetic (e.g. drug-metabolizing enzymes, drug transporters, drug targets), personal (e.g. age, sex, disease states, treatment adherence) and environmental factors (e.g. smoking, diet, alcohol habits, drug-drug interactions) that produce interindividual differences in term of pharmacokinetics and pharmacodynamics. Moreover, non-adherence is linked to the pathology itself and also to adverse drug reactions. Because the development of new drugs is slow in psychiatric area, it is of paramount importance to use the currently available drugs as effectively as possible. An important aspect of effective use is dose personalization because, owing to interindividual differences in drug metabolism, the dose required to achieve optimal concentration varies substantially between patients. Two main tools are available for the optimization of psychotropic drugs exposure: Pharmacogenetics (PG) testing and Therapeutic Drug Monitoring (TDM).

PG testing can help reduce the uncertainty inherent in psychiatric pharmacotherapy by detecting genetic factors that predict clinical response and side effects, such as genetic variations that impact drug-metabolizing enzymes, drug transporters or drug targets. PG is the study of genetic differences in drug metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects.

TDM has a long standing history in clinical psychiatry and has been proved to be a reasonably adequate tool for the management of individual variability in psychotropic drug response. Non-response at therapeutic doses, uncertain drug adherence, suboptimal tolerability, or pharmacokinetic drug-drug interactions are typical indications for TDM. Additionally, TDM can be useful to educate patients and make them more aware of their treatment. Finally, TDM is likely to ensure a better tolerance and fewer side effects for antipsychotics drugs, while allowing a better efficacy.

To conclude, combined PG and TDM testing should improve acute and long-term treatment, prediction of therapeutic response, reduction of side effects, and monitoring of treatment compliance.

Romain Guilhaumou (PharmD, PhD, HDR), 41 yo, is Assistant Professor of Pharmacology at Aix-Marseille University and Hospital Practitioner in biological Pharmacology (Therapeutic Drug Monitoring and Pharmacogenetics). He is currently working in the Clinical Pharmacology & PharmacoSurveillance Department, Marseille University Hospital (APHM, Pr J. Micallef) and is member of the UMR AMU-INSERM 1106, Institut de Neuroscience des Systèmes, INS. His research activity is focus on personalization treatment in psychiatric disorders and on the development on a Virtual Brain Twin of schizophrenic patient (Virtual Brain Twin – for personalized treatment of psychiatric disorders).

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S5-2 From therapeutic drug monitoring to model-informed precision dosing of anti-infective drugs

Sylvain Goutelle, Pharm.D., Ph.D., Professor of Pharmacology
Hospices Civils de Lyon, GH Nord, Service de Pharmacie & Université Lyon 1, ISPB – Faculté de Pharmacie de Lyon et UMR CNRS 5558, Laboratoire de Biométrie et Biologie Evolutive

Anti-infective drugs have long been good candidates for Therapeutic Drug Monitoring (TDM) because of established concentration-response relationships, large inter-individual pharmacokinetic-pharmacodynamic (PK/PD) variability and relevance for acute care in special populations (e.g. critically ill patients, obese patients, children). However, traditional TDM has limitations, providing no clear guidance to the physicians on how to adjust the dosage regimen to achieve a target exposure.

Model-informed precision dosing (MIPD) can overcome those limitations by using PK models to interpret TDM results and compute maximally precise dosage regimens. In addition to PK, PD information (bacterial minimal inhibitory concentration – MIC - of the antibiotic) and clinical features (type of infection) can be used to individualize dosage regimens. We will present several examples of how MIPD can contribute to optimize efficacy and safety of anti-infective drugs and also to implement very personalized dosage regimens in situations of off-label drug use.

MIPD is a multidisciplinary approach and its development in hospital setting require progress in point-of-care microbiology, drug assay as well as PK programs and interfacing with electronic health record. A project in critical care will be presented as a motivating example.

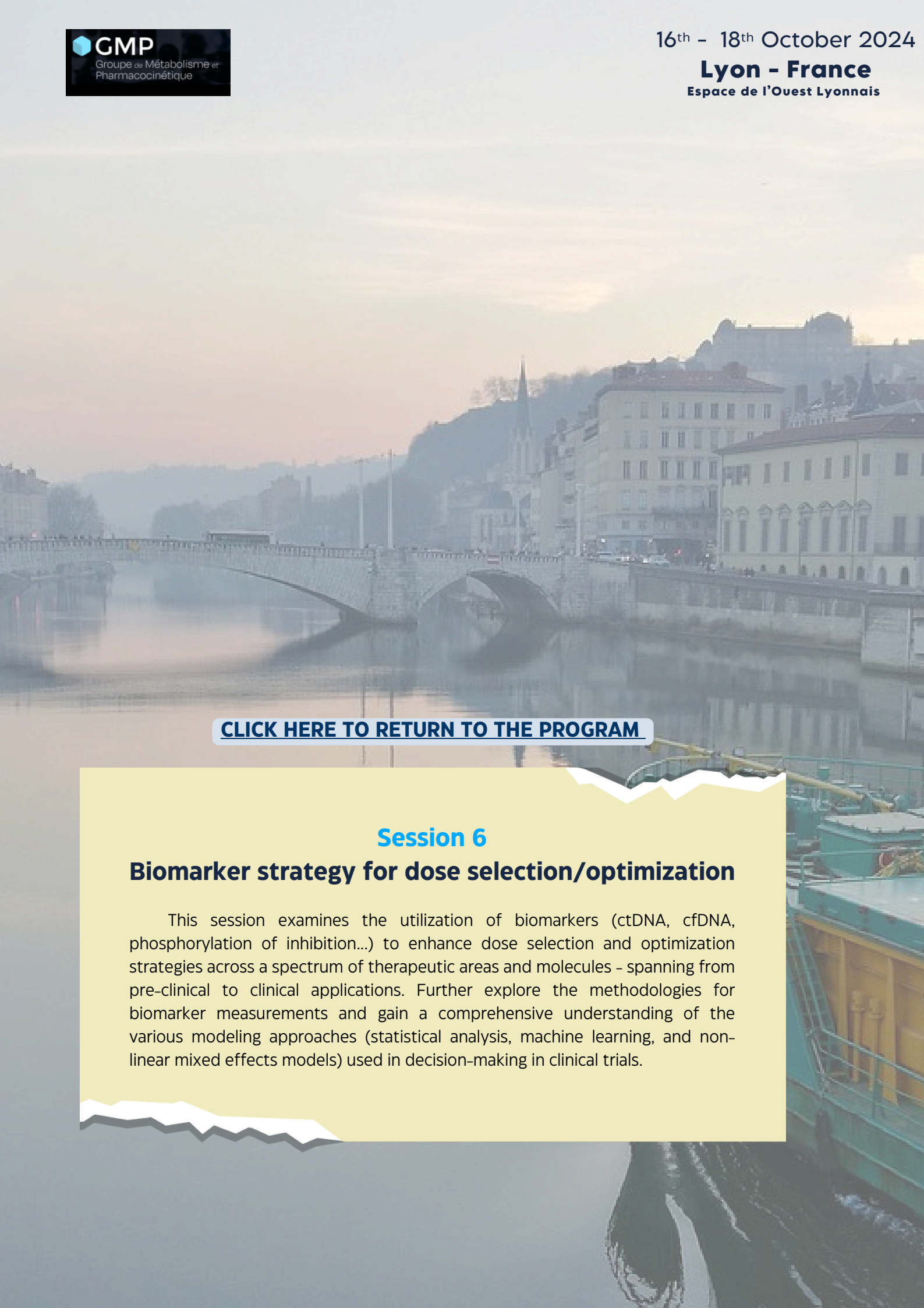
Sylvain GOUTELLE (PU-PH, Pharm.D., Ph.D.) is hospital pharmacist and professor of Pharmacology at the University Hospitals of Lyon, France. He is head of a hospital unit dedicated to model-informed precision dosing of drugs, mainly anti-infective agents.
His research activities within UMR CNRS 5558 (https://lbbe.univ-lyon1.fr/fr) focus on the development of PK/PD models for populations and individuals, with strong collaboration with critical care, infectious diseases and microbiology practitioners and researchers. He has contributed development and dissemination of nonparametric methods in population pharmacokinetics. He has also participated in the development of ddi-predictor, a web tool providing quantitative prediction of the impact of drug-drug interaction, gene polymorphism and cirrhosis on drug exposure (https://www.ddi-predictor.org/). He is member of CA-SFM (Comité de l'Antibiogramme de la Société Française de Microbiologie), the French national committee of antimicrobial susceptibility testing as a PK/PD expert.

S5-3 Precision medicine in oncology : which role for therapeutic drug monitoring?

Benoît Blanchet, Pharm.D., Ph.D
Assistance Publique Hôpitaux de Paris, Hôpital Cochin, Biologie du Médicament – Toxicologie, Institut du Cancer Paris CARPEM, Paris, France

Cancer treatment has undergone two paradigm shifts in the last decade with the emergence of oral targeted anticancer protein kinase inhibitors (PKIs) and immunotherapies. Therapeutic response to oral targeted anticancer PKIs is highly variable between patients, with insufficient efficacy in some of them and unacceptable adverse reactions in others. Therapeutic Drug Monitoring (TDM) is suitable for most of PKIs because of their large interindividual pharmacokinetic variability and their narrow therapeutic index. For immunotherapies such as anti-PD1and anti-PDL1, the exposure-response relationship is flat at the recommended doses, indicating a lack of TDM benefit to adjust the dosage regimen to achieve a therapeutic range. Nevertheless, reducing the dose intensity of anti-PD1and anti-PDL1 is currently a challenge to minimize patient toxicity, as well as to decrease the financial burden for healthcare systems. TDM could help physicians to individually adapt the dosing intervals of these immunotherapies, which could reduce the incidence of autoimmune adverse events and save money while maintaining efficacy. The presentation will focus on how TDM could be integrated into the precision medicine to optimize the therapeutic management of patients with cancer.

Benoit Blanchet (Pharm.D., Ph.D.) is a pharmacologist and head of the Oncopharmacology Unit at the Cochin Hospital (Paris). This unit is dedicated to the therapeutic drug monitoring of anticancer agents including small molecules and immunotherapies. Benoit Blanchet has worked on the characterization of the PK/PD relationship of oral protein kinase inhibitors in cancer patients treated for solid tumors, the optimization of the administration regimens of immunotherapies and the identification of circulating biomarkers to predict treatment response to kinase inhibitors or immunotherapies. He is a member of the GPCO (Groupe Pharmacologie Clinique Oncologique).



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Session 6

Biomarker strategy for dose selection/optimization

This session examines the utilization of biomarkers (ctDNA, cfDNA, phosphorylation of inhibition...) to enhance dose selection and optimization strategies across a spectrum of therapeutic areas and molecules - spanning from pre-clinical to clinical applications. Further explore the methodologies for biomarker measurements and gain a comprehensive understanding of the various modeling approaches (statistical analysis, machine learning, and non-linear mixed effects models) used in decision-making in clinical trials.

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S6-1 How biomarkers contribute to driving the clinical development of DMTs in neurodegenerative diseases

Christine Bain-Wendlinger, PhD,[1] Cécilia Estrella, PhD,[2] Aurélien Blondel, PharmD,[2] Audrey Pabiou,[1] Cendrine Josson,[1] Artin Karapet, MD,[2] Noelle Callizot, PhD[3] and Philippe Verwaerde, PhD.[2]
[1] KCAS Bio, LYON, FRANCE; [2] ALZPROTECT, LOOS, FRANCE; [3] NEUROSYS, GARDANNE

AZP2006 or Ezeprogind, developed by Alzprotect, proved, in preclinical models, to inhibit processes involved in neurodegeneration, such as tau aggregation, and neuroinflammation, and to modulate the production of Progranulin (PGRN), a neurotrophic factor that plays a key role in the development, survival and maintenance of neurons. When entering the lysosome, AZP2006 binds the Prosaposin-Progranulin complex, and thus stabilizes it. This complex is thought to play a key role in lysosome homeostasis and thus in the degradation of mis-folded proteins. In early clinical development, the molecule showed excellent safety upon a short-term exposure in healthy volunteers and was granted orphan drug designation by FDA and EMA, for the treatment of progressive supranuclear palsy (PSP), an atypical parkinsonism disorders characterized by intracerebral aggregation of the Tau protein.

The main objectives of this phase 2a clinical study were to confirm safety and determine the exposure-to-response (PK/PD) relationship over a 3 month-period of treatment in patients with PSP. In parallel with PGRN as a potential target engagement biomarker, a panel of biomarkers, including markers of neurodegeneration, proinflammatory and oxidative-stress mediators were measured in the plasma and cerebrospinal fluid (CSF) by KCAS Bio. After having evaluated the performance of selected commercially available kits, clinical samples were analyzed. Data showed that upon AZP2006 treatment, PGRN levels were increased in the plasma while not decreasing in the CSF, when compared to placebo. Among other biomarkers, only CSF Tau protein levels showed a significant decrease in the AZP2006 group. Lastly, although not significant, very promising trends in the slowing down of disease progression was observed in the treated groups.

Based on these encouraging results, establishing PGRN as a target engagement biomarker for AZP2006 in PSP, Alzprotect plans to initiate a randomized Phase 2b/3 proof of concept-controlled PROMISE-PSP trial, scheduled to commence in late 2024, and to expand in the coming years, its drug development to Parkinson's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis.

Immunologist by training, I have been working for years in the fields of immuno-oncology and persistent viral infections such as Chronic Hepatitis C at Biomérieux and Transgene. Before joining, in 2011, the company that was recently acquired by KCAS Bio, I was coordinating biomarker programs supporting the development of immunotherapeutic products in cancer and infectious diseases at Transgene.

As a senior scientific advisor at KCAS Bio, I am supporting the sales and operations team on scientific and technical aspects related to method development, validation and (pre)clinical sample analysis for pharmacokinetic, immunogenicity, and biomarker assays for biologics in immuno-oncology, infectious diseases, inflammatory and autoimmune syndromes.

I had also the pleasure of being a member of the GMP scientific committee from 2020 to 2023 and am currently a core member of the European Bioanalysis Forum (EBF) and EIP (European Immunogenicity Platform).

Session 6.2

S6-2 Using target engagement (TE) biomarker for early decision-making in oncology: establishment of Optimal Biological Dose (OBD) of a Bcl2 inhibitor through PK/PD Modeling of Bcl2-BIM Complex Disruption.

François Riglet, Samar Salem, Mathilde Romagnoli
Translational Medicine, Servier

S65487 is an intravenous potent and selective inhibitor of B-cell leukemia/lymphoma-2 (Bcl2), member of the Bcl2 family proteins with that regulate apoptosis. Bcl2 protein is overexpressed in cancer cells, resulting in tumor cell escape from apoptosis. The anti-apoptotic activity of Bcl2 is due to sequestration of pro-apoptotic BH3-only proteins, including BIM. Bcl2-BIM complex is disrupted by competitive binding with S65487, which triggers apoptosis through elevation in the levels of free BIM. Thereby, Bcl2-BIM complex disruption is a reliable target engagement (TE) biomarker to evaluate drug activity, directly related to S65487 mechanism of action.

S65487 was undergoing evaluation in two Phase I studies: as a single agent in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML), non-Hodgkin lymphoma, multiple myeloma or chronic lymphocytic leukemia [NCT03755154] and in combination with azacytidine (Aza) in newly diagnosed unfit patients with AML [NCT04742101]. Bcl2-BIM complex disruption was measured in patients' peripheral-blood mononuclear cells (PBMCs) collected before and after the S65487 infusion. Based on various preclinical studies, a threshold of 70% disruption from baseline, lasting for a minimum of 8 hours, was defined as the target to achieve in patients.

A simultaneous PK/PD modeling approach was performed to describe complex disruption after treatment with S65487.

A significant relationship was identified between the magnitude of Bcl2-BIM complex disruption and the plasma exposure of S65487 in monotherapy. Drug kinetics was described using a 3-compartment model with linear elimination and the best way to describe TE was a turnover inhibition model, highlighting S65487 mechanism of action preventing Bcl2-BIM complex formation. A study effect on IC50 was estimated with a four-fold lower IC50 in combination compared to monotherapy study. Based on this model, simulations were performed from this model for various dose levels, assessing magnitude and duration of effect, and the OBD was identified with a plateau effect in S65487-Aza combo study showing no benefit to increase the dose in combination.

François holds a PharmD from the University Paris Descartes, followed by a PhD thesis in Pharmacometrics during which time he worked in treatment individualization based on joint modeling approaches of longitudinal and survival data. As an extension of his thesis, he did a short post-doc in Translational Disease Modeling – Oncology team at Sanofi. François joint Servier Clinical Pharmacometrics team in 2022 to work on various Oncology projects.

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S6-3 Computational modeling approaches for circulating cell-free DNA in oncology

Linh Nguyen-Phuong
Aix-Marseille University

Many cancer patients undergoing immune-checkpoint inhibition (ICI) experience early progression (EP), defined as progression at the first imaging evaluation. Circulating cell-free DNA (cfDNA) fragmentation profiles, especially fragment size distribution, offer a promising non-invasive method for assessing treatment response independently of a specific molecular target, cancer type, and treatment. However, only few computational modeling studies investigated the underlying biological mechanisms of cfDNA dynamics during treatment monitoring.

The SChISM (Size CfDNA Immunotherapies Signature Monitoring) clinical study focuses on monitoring the plasmatic cfDNA size profile of the fragmentome in 139 advanced pan-cancer patients undergoing ICI treatment, to early manage therapeutic strategy before ICI-related progression or toxicity occurs. We performed statistical and survival biomarker analysis to predict EP and progression-free survival (PFS) using pre-treatment data. Plasmatic fragmentome-derived metrics, including concentration, size distribution of first and second peaks, and specific size ranges (p = 11 variables), were evaluated alongside standard clinical markers such as ECOG performance status, age, and pathology. The relative quantity of fragments over 1650 bp exhibited the highest discriminatory power for EP (median area under ROC curve on the test set = 0.7, 95% CI: 0.59-0.80). A lower relative quantity of these long fragments correlated with EP and shorter PFS in both the univariate and multivariate settings.

Following the development of empirical models capturing inter- and intra-patient variability in cfDNA metrics, a system of differential equations was constructed to individually describe cfDNA kinetics. Subsequently, a mechanistic model integrating cfDNA kinetics with longitudinal biological markers and tumor size imaging was developed to elucidate and comprehend the temporal dynamics of cfDNA quantitative profiles over time. Using population data, the model was calibrated within the nonlinear mixed effects statistical framework. Future perspective aims to employ machine learning models to predict EP, PFS or overall survival by integrating dynamic parameters with baseline variables.

Linh Nguyen Phuong is a PhD candidate with an academic background in applied mathematics and data science. She earned her bachelor's degree in Applied Mathematics and her master's degree in Data Science Applied to Biological Data from the University of Angers. In October 2022, she started her doctoral journey within the Inria-Inserm COMPO (COMPutational pharmacology and clinical Oncology) team of the Cancer Research Center of Marseille. Her research, co-supervised by Pr. Sébastien Salas and Dr. Sébastien Benzekry focuses on developing a mechanistic model of the evolution of cfDNA fragment sizes, aiming to predict early responses to immunotherapy.

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One Step Aside

"Synthetic Dreams" – How data and AI are re-inventing drug R&D.

Dr. Angeli Möller
Group Chief Health Officer and member of the Group Executive Committee at Zühlke Group

By 2022, there were 46,000 scientific publications on AI in biology and medicine, 158 AI-based pharmaceutical discovery programs, and 73 AI-derived compounds in pharmaceutical pipelines. From 2012 to 2022, over $116 billion was invested in AI for pharmaceutical R&D. Although AI in drug R&D is established, its clinical stage outcomes have yet to fully materialize. With the introduction of ChatGPT in November 2022, interest in AI has surged, transforming what seemed like science fiction into achievable possibilities. In this presentation, we will explore the current and potential roles of AI in drug R&D and how it redefines the way scientists integrate data generation with technological applications and wet-lab validation. We will deep-dive into the scientific implications, impacts on researchers, and the research process itself. A key question we will address is whether AI represents merely another tool or signifies a more profound shift in scientific inquiry.

Dr. Angeli is currently Group Chief Health Officer and member of the Group Executive Committee at Zühlke Group. She was also recently Managing Director at Sequoia Growth, where she consulted with and provided technical guidance to venture capital groups, government organizations, biotech, pharmaceutical and software companies. Prior to that she held various positions at Roche and Bayer; notably Head of Data and Integrations Generating Insights and Head of Pharma International Informatics at Roche and VP Head of Global Data Assets, Pharma Digital Transformation & IT at Bayer. She co-founded The Alliance for Artificial Intelligence in Healthcare, a global advocacy organisation that enables the advancement and use of AI in healthcare. Angeli is also a scientific advisory board member of Multiomic Health and a council member of UK's Science and Technology Facilities Council.

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Session 7

Biodistribution : from technology to therapeutic support

Reaching the right target tissue at the right time and effective concentration is the main objective of a therapeutic modality. Biodistribution studies explore either the best way to reach the target or where the modality, including potential metabolites and endogenous biomarkers stand over time. This session will give an overview of the new technologies including mass spectrometry imaging or ultrasound to tackle the biodistribution challenges.

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S7-1 De-risking and accelerating drug development programs: applications and integration of spatial bioanalysis and spatial biology at the site of action

David BONNEL, Mathieu GAUDIN & Corinne RAMOS
Aliri Bioanalysis, Parc Eurasanté, Lille, France

The complexity of tissue microenvironments has driven the development of numerous technologies in recent years, allowing for the analysis of molecular information at the cellular or histological scale. Today, it is possible to locate many classes of molecules (small drug molecules, lipids, metabolites, proteins, transcripts, etc.) as well as the phenotypes (cellular signatures) directly at the tissue level in order to confirm target exposure, study a mechanism of action, characterize lesions during toxicity studies, access the PK profiles of a developing molecule and its metabolites in all organs or identify some readout markers in translational research. This presentation will aim to provide a state of the art of applications in spatial bioanalysis combined with spatial biology in order to study the PK/PD directly at the site of action of developing molecules.

With two Ph.Ds. in Biology and Biochemistry from esteemed universities in France and Canada, **David BONNEL** has honed his expertise in biotechnology, biopharmaceuticals, R&D, and life sciences.

Currently serving as the Global Executive Director at Aliri (formerly ImaBiotech), he oversees site management, focusing on team dynamics, KPI optimization, revenue recognition, and cost-effectiveness, fostering significant growth. Since joining Aliri (CRO specialized in Bioanalysis, spatial-bioanalysis, spatial-Omics and spatial biology) in 2010, he has led over 1,000 preclinical and clinical studies with the scientific teams. He actively participates in the design of studies with partners, primarily pharmaceutical companies, bringing his expertise in molecular imaging for PK/PD investigations. Some of these studies have been published, resulting in over 25 scientific articles and several patents.

In addition to his corporate role, he contributes to the Board and the scientific review committee of the NHL Cluster, fostering collaborative research initiatives between private enterprises and academic institutions in the Hauts-de-France and broader French region.

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S7-2 MultiModal molecular imaging in drug discovery and development

Michiel Vandenbosch PhD

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In the dynamic field of drug discovery and development, a comprehensive understanding of drug absorption, distribution, metabolism, excretion and toxicity (ADMET) is crucial. Mass spectrometry imaging (MSI) has emerged as an indispensable analytical modality, increasingly deployed within the pharmaceutical industry. The Maastricht MultiModal Molecular imaging institute (M4i) is as an international renowned institute at the forefront of molecular imaging technologies. In this institute, MSI plays a central role. This advanced technique facilitates label-free detection of endogenous and exogenous molecules in thinly sectioned tissue samples, enabling the evaluation of the biodistribution of drug candidates, their metabolites, and potential alterations in lipidomic, proteomic, and metabolomic profiles. This presentation focuses on the qualitative and quantitative applications of MSI throughout the drug development process, spanning from target identification to clinical studies.

Upon completing his PhD in pharmaceutical sciences at KU Leuven, **Michiel Vandenbosch**, was driven to delve into various aspects of scientific research. This drive led him to embrace a fresh challenge in mass spectrometry imaging at M4i (Maastricht University). His post-doctoral work centered on lipodomics in Parkinson's disease. Presently, he leads the MassSpec CORE facility alongside his research group. In the CORE facility, M4i provides access to specialized mass spec equipment, services, and expertise that support various research projects across disciplines. His research group is dedicated to assessing novel therapeutics through a multi-omics approach utilizing mass spectrometry.

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S7-3 Delivery of anti-cancer drugs using microbubble-assisted ultrasound in digestive oncology: from preclinical to clinical studies

Jean Michel Escoffre
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The combination of microbubbles (MBs) and ultrasound (US) is an emerging method for the noninvasive and targeted enhancement of intratumor chemotherapeutic uptake. This method showed an increased local drug extravasation in tumor tissue while reducing the systemic adverse effects in various tumor models. I will focus on preclinical and clinical studies investigating the therapeutic efficacy and safety of this technology for the treatment of colorectal, pancreatic, and liver cancers. I will discussthe limitations of the current investigations and future perspectives. The therapeutic efficacy and the safety of delivery of standard chemotherapy regimen using MB-assisted US have been mainly demonstrated in subcutaneous models of digestive cancers. Although some clinical trials on pancreatic ductal carcinoma and hepatic metastases from various digestive cancers have shown promising results, successful evaluation of this method in terms of US settings, chemotherapeutic schemes, and MBs-related parameters will need to be addressed in more relevant preclinical models of digestive cancers, in small and large animals before fully and successfully translating this technology for clinic use. Ultimately, a clear evidence of the correlation between the enhanced intratumoral concentrations of therapeutics and the increased therapeutic response of tumors have to be provided in clinical trials.

Jean-Michel Escoffre is currently pursuing his research as Senior Researcher at the Institute of Imaging and Brain of the French Institute for Health and Medical Science (Inserm, University of Tours) in Tours, France. His main research interest lies in the fields of biodrug delivery using ultrasound-guided therapeutic ultrasound. He is expert in Diagnostic Tools, Therapies and Public Health for many national, European and international public and private agencies.

S7-4 Clinical pharmacology considerations and model-informed drug development (MIDD) applied to Targeted Radiation Therapies (TRT)

Amandine Manon,[1] PharmD, Senior Director Clinical Pharmacology;
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The field of the Targeted Radiation Therapies (TRT) or Radioligand Therapies (RLT) is quickly growing, and the regulatory landscape is also quickly evolving. This presentation will give an overview of the current requirements for the development and dose optimization of these drugs and show how Model-Informed Drug Development (MIDD) can help solving major development questions and streamlining TRT development:

• Quantitative Systems Pharmacology (QSP): Translating molecular features to predict drug properties, including biodistribution and therapeutic index.

• Pharmacometrics: Utilizing radiological/nuclear medicine imaging to predict biodistribution and absorbed doses per organ and tumor and correlate with clinical outcomes to guide dose optimization.

The TRT development is a nice example of how biodistribution/imaging data can support drug development and increase the probability of success.

Amandine Manon is a pharmacist by training (Paris XI University) and holds a Master's in Biopharmacy and Pharmacokinetics. Before joining Certara in 2020, she worked for more than 15 years in pharma industry in various clinical pharmacokinetics/ pharmacology positions. She started her career with junior positions at Pierre Fabre medicaments and Sanofi-Aventis before moving to a more senior position at Ethypharm. In this position, she was responsible for the biopharmacy and clinical pharmacokinetics development strategy of novel formulations. Later, she joined Ipsen as a Clinical Pharmacokinetics project manager where she was responsible for the DMPK and clinical PK strategy of compounds in development in various therapeutic areas (endocrinology, neurology, oncology).

She had then the opportunity to move internally at Ipsen to a Director position in Clinical Pharmacology with a special focus on translational medicine for oncology products. Of note, she was also seconded during 9 months in the Global Regulatory Affairs department at Ipsen to strengthen her regulatory knowledge. At Certara, she is now mainly focusing on oncology drug development and Project Optimus with a special expertise in radioligand therapies.

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Session 8

New insights for biologics

The diversity and importance of biologics create opportunities to apply innovative bioanalytics as well as modeling framework to measure, characterize and manage immunogenicity risks. This session will showcase such applications that should ultimately support the advancement of patient-centric care and enhance therapeutic benefit.

S8-1 A quantitative systems pharmacology framework of immunogenicity to propose mitigation strategies after subcutaneous administration.

Gianluca Selvaggio, Moriah Pellowe, Marylore Chenel, Erik Sjögren
Pharmetheus AB, Uppsala, Sweden

Therapeutic proteins (TPs) have the potential to induce an immune-mediated response (i.e. immunogenicity). Antidrug antibodies (ADAs) are an important readout to assess immunogenicity as they may affect the product's pharmacokinetic, pharmacodynamics efficacy and safety. Several factors play a role in the immunogenic response at different levels, such as product's characteristics (size, sequence, aggregation etc.), treatment's characteristics (route of administration, dosing regimen etc.) and patient's characteristics (genetic background).

We developed, a quantitative systems pharmacology platform that aims at providing a tool to support the development of new TPs via in-silico evaluation of their immunogenicity. A systemic immune response model has been implemented in MoBi (OSPSuite) to evaluate ADAs formation after intravenous (IV) administration and subsequently expanded with a physiologically based model for predictions of subcutaneous absorption (SC) of TPs which also includes a local immunogenic response. ADAs are generated in a T-cell dependent manner, where the concentration is driven by changes in immune cell differentiation and the memory cell pool, occurring both locally and systemically.

In particular, the framework can be used to address changes in route of administration as intravenous to subcutaneous (IV-to-SC) switch. TPs can also be analysed in terms of epitope properties (i.e. major histocompatibility complex (MHC)-II binding affinities) accounting for variations of the genetic background by generating virtual patients having different response strength (i.e. carrying different alleles for MHC-II).

Such *in silico* approach can be instrumental in exploring different strategies to minimize the immunogenic response either via modifying the route of administration or the regimen.

Dr Selvaggio is a Consultant at Pharmetheus. He obtained his MSc in Biomedical engineering from the University of Bologna (2010), and his PhD in Bioengineering from the New University of Lisbon (2016). Expertise includes mathematical modeling of biological processes in the quantitative systems pharmacology field in therapeutic areas such as oncology and immuno-inflammation. Previously Dr Selvaggio worked as Senior Modeler at the Fondazione Microsoft Research – University of Trento Centre for Computational and Systems Biology, where he also served as Project Leader. Joined Pharmetheus in 2023, actively working in client projects and supporting the development of the immunogenicity platform.

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S8-2 Innovative hybrid LC-MS methods for the semi-quantification and isotyping of ADAs (Anti-Drug Antibodies) responsible for affecting the bioavailability and the activity of the biotherapeutic.

Stéphane Muccio, Principal Scientist
Jérôme Vialaret, Project Manager [1]
Daniel Kramer, Global Scientific Advisor Immunogenicity [2]
Sandrine Descloux, Head of Physico-Chemical Bioanalysis Laboratory [3]
Olivier Fedeli, Local Head of Biomarkers and Clinical Bioanalyses Department [1]

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Anti-drug antibodies (ADAs) generated by biotherapeutics can impair the drug clearance, prevent the binding to its target or lead to hypersensitivity reactions, thereby affecting efficacy and safety. It is therefore essential to assess the immunogenicity of potential biotherapeutics, particularly in clinical development. LBA assays are the gold standard for ADA analysis due to their high sensitivity and throughput. However, LBA assays don't provide details on the isotypes produced and their relative abundance. As certain isotypes are known to be associated with ADA mediated adverse events, this information could be helpful to anticipate or better characterize the immunogenicity risk of biotherapeutics. A hybrid LC-MS strategy was developed for the detection of specific isotypes/subclasses of ADAs induced after administration of a biotherapeutic in a clinical trial. A first approach using the biotinylated drug to capture ADAs in human serum allowed the simultaneous semi-quantification of all IgG subclasses and the detection of ADAs of the IgM isotype in serum samples. The isotyping provided additional information for characterizing the immune response and contributed to a better understanding of the pharmacokinetic of the biotherapeutic. A second assay was developed to measure drug specific IgEs known to be potentially associated with hypersensitivity reactions and present at very low levels in serum. These innovative hybrid LCMS approaches could be applied to any new biotherapeutic.

I have worked in the pharmaceutical industry for over 20 years using mass spectrometry coupled to liquid chromatography to support the development of assays for the quantification of small and large molecules. Currently at Sanofi in the Biomarkers and Clinical Bioanalyses LCMS group in Montpellier, France, my focus is on the development and validation of large molecule assays. I develop hybrid LCMS methods to quantify protein drugs or biomarkers for clinical trials. Since 2019, I hold the position of scientific manager in the mass spectrometry bioanalytical laboratory of Sanofi Montpellier.

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Master 2 / PhD Posters

PB1 : Population pharmacokinetic study of Vancomycin in cerebrospinal fluid of patients with brain injuries and external ventricular drainage

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Background and objectives: Vancomycin is a key antibiotic used in the treatment of central nervous system (CNS) infections in Intensive Care Unit (ICU) patients with external ventricular drainage (EVD), particularly against multidrug-resistant Gram-positive pathogens like methicillin resistant Staphylococcus aureus (MRSA)[1]. Achieving therapeutic concentrations in the cerebrospinal fluid (CSF) is challenging due to vancomycin's poor CSF penetration[2]. The first objective of this study was to develop a population pharmacokinetic (PK) model describing vancomycin PK in both plasma and CSF of ICU patients with EVD and identify factors influencing the PK of the molecule. The second objective was to assess the efficacy and safety of different recommended dosing regimens.

Material and methods: A population PK model was developed using data from 33 patients with CNS infections and EVD. The patients received a loading dose (LD) of 15-20 mg/kg over 1 hour, followed by continuous infusions (CI) of 30-60 mg/kg/24h. CSF and plasma samples were collected for most patients (n=30) at steady state and after stopping the infusion, samples were also collected around the loading dose for some patients (n=3). Plasma vancomycin data were first modeled, then adjusted for protein binding (55%) to fit unbound CSF concentrations. In the final model parameters for both plasma and CSF data were simultaneously estimated. Monte Carlo simulations were conducted to determine the probability of target attainment (PTA) in CSF for different dosing regimens, including LD (15 and 20 mg/kg) followed by CI (30, 40 and 60 mg/kg) versus CI alone. The pharmacokinetic/pharmacodynamics (PK/PD) efficacy target in CSF was to maintain free drug concentrations above the minimum inhibitory concentration (MIC) throughout the dosing interval (fT>MIC=100). PTAs were calculated as the percentage of simulated patients who met this PK/PD target for MIC values of 0.5, 1 and 2 mg/L [3]. The risk of vancomycin toxicity was assessed for each dosing regimen tested by evaluating the probability of achieving a total plasma AUC over 24h (AUCplasma-24h) exceeding 600 mg*h/L [4,5].

Results: A two-compartment model (one for plasma and one for CSF) was identified as the most appropriate for describing vancomycin PK. Vancomycin exhibited a poor penetration into the CSF, with a median AUC ratio (fAUC48-72-CSF / fAUC48-72-plasma) of 0.24, which was characterized by a lower clearance from plasma to CSF (Qin = 0.0056 L/h) than from CSF to plasma (Qout = 0.015 L/h). CSF-to plasma albumin concentrations ratios showed a significant correlation with Qin suggesting that the degree of BBB damage influences vancomycin distribution in the CSF. Elimination rate of vancomycin from CSF via the EVD (QEVD) was not negligible, resulting in a decrease of CSF vancomycin exposure as QEVD increased. Simulations suggested that none of the dosing regimens tested would be appropriate for treating infections caused by pathogens with MIC > 1 mg/L. For an MIC of 0.5 mg/L, a LD followed by a CI of 30 mg/kg/day would be sufficient to

achieve PTA > 90%, whereas the dose should be increased to 60 mg/kg/day for an MIC of 1 mg/L. However, this latter recommended dosing regimen would result in AUCplasma-24h exceeding the toxicity threshold in 73.3% of cases. A reduced regimen of CI 40 mg/kg with LD could maintain CSF efficacy while lowering nephrotoxicity risk for patients with BBB dysfunction.

Conclusions: The findings confirmed the poor penetration of vancomycin into the CSF. A LD followed by CI of 60 mg/kg would be necessary to achieve CSF PK/PD target quickly and treat infections due to pathogens with MIC up to 1 mg/L. In patients with compromised BBB, reduced dosing regimens could still maintain therapeutic levels in the CSF while lowering the risk of nephrotoxicity.

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PB2: Vancomycin Population Pharmacokinetic Models: Uncovering Pharmacodynamic Divergence Amid Socio-Demographic Resemblance

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Background and objectives: Vancomycin is an antibiotic used for severe infections. To ensure microbiological efficacy, a ratio of AUC/MIC ≥ 400 is recommended[1]. However, there is significant interindividual variability in its pharmacokinetic parameters[2], necessitating therapeutic drug monitoring to adjust dosing regimens and ensure efficacy while avoiding toxicity. One of its adverse effects, frequently found in prolonged use (4 to 8 days of treatment), is nephrotoxicity (in more than 40% of treated patients[3]. Population pharmacokinetic (PopPK) models enable dose personalization, but the challenge lies in the choice of the model to use among the multitude of models in the literature.

Material and Methods: We compared 18 PopPK models created from populations with the same socio-demographic and clinico-biological characteristics. Simulations were performed for a 47 years old man, weighing 70 kg, with an albumin level of 35.5 g/L, a creatinine clearance of 100 ml/min, an eGFR of 106 ml/min/1.73m², and receiving an intravenous infusion of 1 gx2/day of vancomycin over 1h for 48 hours. Simulations of time-concentration profiles (using RStudio) revealed differences, leading us to determine the probability of achieving microbiological efficacy (AUC/MIC≥400) with each model.

Results: Depending on some models, a dose of 1gx2/day is required to ensure microbiological efficacy in over 90% of the population, while with the same dose other models do not exceed 10% of the population. To ensure that 90% of the patients are correctly exposed (AUC/CMI≥400), a dose of vancomycin ranging from 0.9gx2/day to 2.2gx2/day is necessary a priori depending on the chosen model.

Conclusion: These differences raise an issue in choosing a model for performing therapeutic drug monitoring using a PopPK model with or without Bayesian approach. Thus, it is fundamental to evaluate the impact of these differences on both efficacy/toxicity; if this impact is important, it is essential to understand the origin of a such variability.

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PB3: In vitro investigation of midazolam pharmacokinetics during therapeutic hypothermia

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The research was conducted as part of the I-PREDICT consortium and has received support from the FWO (grant number G0D0520N).

Background and objective: Perinatal asphyxia still causes significant morbidity and mortality. Therapeutic hypothermia is the only effective therapy for neonates with moderate to severe hypoxic-ischemic encephalopathy after perinatal asphyxia. However, there are still knowledge gaps about the short- and long-term effects of therapeutic hypothermia on the hepaticmetabolism of administered medicines[1-2]. This project aims to better understand the mechanisms of hypothermia on drug metabolism. As a first step, this poster details how to evaluate the short-term effects of hypothermia on the hepatic metabolism of midazolam in adulthuman liver microsomes and develop a valid protocol later applicable to neonatal liver microsomes.

Materiel and methods: Adult pooled human liver microsomes (150 donors) were incubated in 3 independent experiments (three replicates and one blank each) for 30 min at 33.5°C or 37.0°C with the clinically relevant drug, midazolam (MDZ; CYP3A4 substrate; 20 µM). Concentrations of midazolam and its metabolite, 1'-hydroxymidazolam (1-OH-MDZ), were analysed using HPLC with UV detection (LLOD 1 µM and 0.625 µM, respectively). An analysis of covariance was performed on the data to determine whether the MDZ concentration-time curves at 33.5°C and 37.0°C were

significantly different (P<.05). An unpaired t-test was performed to determine if there was a difference between 1-OH-MDZ formation at 33.5°C and 37.0°C (P<.05).

Results: The metabolic rate constant of MDZ was 0.0484 min-1 at 37.0°C and 0.032 min-1 at 33.5°C, representing a decrease of 33% at 33.5°C (P=1.39*10-5). The average concentration of 1-OH-MDZ formation throughout the experiment of 30 min was 14.8 µmol/mg microsomal protein at 37.0°C and 11.3 µmol/mg microsomal protein at 33.5°C, representing a decrease of 24% at 33.5°C (P=.010). Of the total amount of MDZ in µmol that disappeared, 58–71% was recovered per time point as the metabolite 1-OH-MDZ.

Conclusion: The data shows a significant short-term impact of this temperature decrease on CYP3A4 activity in pooled adult liver microsomes. As midazolam is an intermediate extraction ratio drug, this impact might be clinically relevant. The in vitro workflow presented in this poster in adult liver microsomes will then be applied to neonatal liver microsomes to evaluate the impact of temperature on neonatal hepatic metabolism. These in vitro data will later be incorporated into physiologically-based pharmacokinetic (PBPK) models to support the precision dosing of medication (e.g., MDZ) in neonates with perinatal asphyxia being treated with therapeutic hypothermia and to potentially adjust their medication doses.

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PB4: Inhalation Permeability Assessment: Tracing Propranolol Distribution

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Background and objectives: As an alternative to traditional experimental toxicology, the development of New Approach Methodologies (NAMs) for chemical evaluation is garnering increasing interest. These methodologies offer numerous advantages over traditional in vivo assays, including ethical benefits, cost and time efficiencies, enhanced mechanistic understanding, and reduced variability. Among these approaches, in vitro experiments are the most widely used tools, with the use of nominal concentrations to establish concentration-response relationships. However, these nominal doses often inaccurately represent actual exposure, as chemicals can partition into different compartments within the assay, such as serum components, plate plastic, and headspace. This frequently results in underdosing the cells, thereby reducing the free concentrations of chemicals to which the cells are exposed[1]. Although these in vitro models

provide useful information on permeability, they are limited by experimental conditions. In the context of pulmonary permeability assessment, an integrated approach combining in vitro and in silico techniques was employed to enhance understanding of xenobiotic distribution within the in vitro system, taking into account the multiple factors influencing chemical distribution.

Material and methods: Propranolol was selected as a reference compound for the validation of pulmonary cell permeability based on its high epithelial permeability. For the experimental assays, non-toxic concentrations were determined using the Lactate Dehydrogenase (LDH) assay and the PrestoBlue assay. Furthermore, non-specific binding to the polymer and the fraction evaporated were evaluated in an in vitro permeability system. Rapid Equilibrium Dialysis (RED) was employed to determine the free fraction in biological matrices including culture media and lysed lung cells. Two different concentrations (1 &10 µM) were evaluated in two distinct types of lung cells: Calu-3 and h-AELVI cells presenting bronchial and alveolar epithelium respectively. Tandem mass spectrometry (MS/MS) was employed for the analysis of samples exposed to Propranolol, utilizing a Thermo TSQ Vantage instrument. An updated mass balance model was developed by combining two existing models, the Virtual in vitro Distribution (VIVD) model[2] and Virtual Cell Based Assay (VCBA)[3] model to the pulmonary permeability case study.

Results: The actual fraction of propranolol to which cells were exposed in an in vitro system after 24 hours of propranolol exposure was higher when using Calu-3 cell culture medium compared to PBS buffer. The fraction of propranolol bound to the culture medium matrix for each cell type was comparable; however, the proportion of propranolol bound to the lysed h-AELVi cell matrix was greater than that bound to the lysed Calu-3 cell matrix at both concentrations employed. The experimental results were compared to the model simulations in both apical and basolateral media, as well as to the cell/tissue concentrations after exposure to the nominal concentration of propranolol.

Conclusions: The initial results highlight the importance of assessing the behavior of molecules within the entire experimental system. Moving forward, the prediction of the current model will undergo a rigorous comparison including in vitro and in vivo pulmonary permeability data and non specific binding to biological matrices data for a diverse array of chemicals.

Keywords: NAMs, in vitro assays, biokinetics, pulmonary absorption.

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PB5: Predicting the exposure of the human liver to bosentan by Physiologically-based pharmacokinetic modeling and simulation

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Background and objectives: Bosentan, an endothelin receptor agonist indicated for patients with pulmonary hypertension, has been reported to cause cholestatic liver injury[1]. Despite in vitro studies having identified several mechanisms underlying bosentan-induced cholestasis[2-3], it remains challenging to translate these results from in vitro to in vivo without knowing the clinical hepatic exposure to bosentan. To tackle this problem, a physiologically-based pharmacokinetic (PBPK) model of bosentan was developed and carefully calibrated to provide quantitative insights into clinical hepatic exposure to bosentan.

Material and methods: The PBPK model was built in PK-Sim® and MoBi® (Version 11 – Build 150; Open Systems Pharmacology Suite). The hepatic uptake through OATP1B1 and OATP1B3, as well as the metabolism via CYP2C9 and CYP3A4, were implemented with Michaelis-Menten kinetics. Bosentan-mediated induction of CYP3A4 and inhibition of OATP1B1 and OATP1B3 were also included. A first-order kinetics was used to cover the remaining minor metabolic pathways of bosentan. Enzymatic and transport kinetic data from in vitro studies were extrapolated considering the intersystem difference in protein abundance or activity and calibrated with clinical systemic exposure and mass-balance data in feces and urine. The predictive performance of the model was evaluated with the average fold errors (AFE) and absolute average fold errors (AAFE) of the area-under-the-curve (AUC).

The intrinsic hepatic clearance was calculated using the parameter estimates in the final model using Equation 1. The ratio (Kpuu,liver) between unbound liver concentration and unbound plasma concentration of bosentan was calculated using Equation 2.

$$CL_{int,h} = (CL_{act,up} + PS_{dif,inf}) \times \frac{CL_{int,met}}{PS_{dif,eff} + CL_{int,met}} \qquad \text{(Equation 1)}$$

$$Kp_{uu,liver} = \frac{C_{u,liver}}{C_{u,plasma}} \qquad \text{(Equation 2)}$$

Results: The developed PBPK model exhibited adequate accuracy and precision based on its AFE (1.023) and AAFE (1.168), with all the simulated studies having an AUC fold error within 0.5 – 2 and at least 80% within 0.75 – 1.33. In addition to the systemic exposure, the predicted amount and fraction of metabolites excreted to feces agreed with the observations. In the final model, the estimates of the calibrated enzyme and transporter kinetics were within 10 folds of the inputted values. Based on these estimates, the intrinsic hepatic clearance was approximately 190 µL·min-1·million cells-1, and the active hepatic uptake clearance was close to the reported value of 35.5 µL·min-1·million cells-1[4]. The simulated unbound liver concentrations were comparable to the unbound plasma concentrations, yielding a Kpuu,liver close to 1. Although the Kpuu,liver from our model was different from the reported values by Li et al., this could be attributed to different model structuresand model calibration strategies.

Conclusion: Overall, this bosentan PBPK model showed adequate and consistent predictive performance in systemic exposure and excretion, informing its capability to capture the key mechanisms related to hepatic uptake and metabolism.

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PB6: Population pharmacokinetics modelling in real-life abemaciclib-treated patients: A comparison of predictive performance of two published population PK models

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Background and objectives: Abemaciclib is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6), crucial enzymes in cell cycle regulation. Initially indicated for hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer, abemaciclib recently received marketing authorization for adjuvant treatment of HR+/HER2- early breast cancer with lymph node involvement and a high risk of relapse. Clinical studies have shown abemaciclib's efficacy in increasing progression-free survival and improving quality of life. However, careful monitoring is required to manage potential adverse effects such as neutropenia and gastrointestinal disorders. Studying the pharmacokinetic and pharmacodynamic relationships of abemaciclib in real life patients is essential to better understand its efficacy and tolerability in daily clinical practice and to propose targets for therapeutic drug monitoring (TDM). This study aimed to compare two population pharmacokinetic models published in the literature using real-life data from patients treated with abemaciclib.

Patients and methods: A retrospective study was conducted at Dijon's clinical cancer center. All patients starting abemaciclib treatment between April 2021 and December 2023 and followed at the center were included. As TDM of abemaciclib was routinely performed, plasma concentrations were available. Patient data and observations were collected from medical records. Two models from the literature describing the temporal evolution of abemaciclib blood concentrations were tested with our data to compare their predictive performance[1-2].Pharmacokinetic analyses were performed using Monolix® version 2024R1 (Lixoft SAS, Antony, France), applying a non-linear mixed-effects modeling approach with parameter values fixed to those estimated in the two previous studies. Model evaluation was based on graphical diagnostics (observed versus predicted population or individual concentrations, corrected predictive visual control (pcVPC), and plots of normalized prediction distribution error (NPDE) versus time or predicted population concentrations). Predictive performance was assessed by calculating mean prediction errors (MPE)

and mean absolute prediction errors (MAPE) to determine bias and imprecision.
Results: A total of 75 assays were available for 65 patients, with 10 patients having two assays. The mean concentration was 283 µg/L (±204), and the average sampling time after the last dose was 9 hours (±22 hours).
The first model, developed by Tate et al., is a linear one-compartment model with time- and dose dependent relative bioavailability (F_rel). The second, built by Chigutsa et al., is a bicompartmental parent-metabolites joint model incorporating intestinal and hepatic metabolism (including first-pass effect) using the well-stirred liver model. The parallel biphasic absorption model captured the slow and complex absorption process of abemaciclib.
Overall, both models showed acceptable goodness of fit, and no model misspecification could be observed. The pcVPCs of both models showed that the 10th, 50th, and 95th percentiles of observed abemaciclib concentrations lie within the 95% confidence interval of the predicted concentration. However, with the Chigutsa et al. model, the observed percentiles are closer to the predicted percentiles. The Tate et al. model showed MAPE and MPE values equal to 9% and -3%, respectively. While that of Chigutsa et al. showed MAPE and MPE values equal to 24% and 5%, respectively.
Conclusion: Both pharmacokinetic models accurately described the evolution of abemaciclib plasma concentrations in the study population. The Tate et al. model was developed with phase 1 data and hypothesizes a time and dose dependence on bioavailability based on data described in pre-clinical species. The Chigutsa et al. model, on the other hand, was developed with a large number of data from different studies including healthy subjects and cancer patients. A study with intravenous administrations of abemaciclib to determine absolute bioavailability was carried out. In particular, this study provided a better understanding of absorption processes. This model, with its complex metabolic mechanisms, may therefore offer a better understanding of drug absorption and distribution processes.

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PB7: Development of a PBPK model to predict monoclonal antibody pharmacokinetics and bioavailability following subcutaneous administration

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Background and objectives: Monoclonal antibodies (mAbs) are currently established components of oncology and immunology therapies, typically administered intravenously over extended treatment periods of several years[1]. To enhance patient convenience and improve quality of life, there is a growing interest in a less invasive, faster, and more flexible administration method,

typically the subcutaneous (SC) administration[2]. Nearly half of the approved mAbs by the Food and Drug Administration (FDA) in recent years involved SC administration[3], highlighting the growing importance of this route of administration[4]. Physiologically based pharmacokinetic (PBPK) models are useful approach during drug product development due to their ability to scale pharmacokinetic (PK) prediction between species and populations[5]. However, there is a current lack of a suitable model that adequately characterizes absorption after SC administration. The prediction of bioavailability following SC administration presents considerable challenges for therapeutic proteins like mAbs, primarily due to the limited predictive reliability of animal studies[6].

The aim of this study was to predict the PK of biologics (30 mAbs and 1 fusion protein). To achieve this, the generic PBPK model in PK-SIM, originally designed for mAbs administration via IV route, has been expanded. The extension incorporates the modeling and prediction of drug absorption and bioavailability after SC administration.

Material and methods: The open-source platform Open Systems Pharmacology Suite (OSPS) was used for model development with PK-Sim and MoBi[7]. A database containing in vitro drug properties and in vivo PK data of biologics (mainly mAbs) following IV and SC administration was compiled from the literature. Plasma concentrations vs time data of 31 drugs were digitized based on an intensive literature search. The IV plasma concentrations data for each drug were used to estimate the binding to FcRn receptor (FcRn Kd) and build a PBPK model for IV administration. The developed IV models were then expanded by a mechanistic model describing the SC compartment. Briefly, this model is composed by an injection site compartment and linked to the whole-body circulatory system through the SC administration site plasma flow and lymph flow. The top-level model structure for the injection site includes one depot compartment connected to 99 layers in series, representing the volume surrounding the depot. Based on the default PBPK model structure implemented in OSPS for biologics, each layer is composed of five sub-compartments representing: plasma, endosome, interstitial, lymphatic, and intracellular space. Additionally, it includes two compartments representing the local lymph node and the central collecting lymph duct. Model performances were evaluated by visual comparison of the simulated concentration-time profiles to the observed in vivo PK data and predictive errors for AUC and Cmax were also calculated.

The bioavailability was determined by calculating AUCSC/AUCIV (normalized by the dose) based on predictions derived from non-compartmental analysis (NCA). The bioavailability value obtained from prediction was compared to the reference bioavailability derived from observed data.

Results: PBPK models after IV administration were successfully established for all included drugs adopting the generic large molecule implementation in PK-Sim. These compound specific models described 90% of observed AUCs, across studies and doses, within a 0.80-1.25-fold difference. The SC PBPK model, informed by the estimated FcRn Kd, was able to successfully capture, within a 0.80-1.25-fold difference, observed AUC and Cmax for 60% of the database (18 mAbs), across studies and doses. Furthermore, the model achieved prediction accuracy within 0.50-2.00-fold range for most of the examined cases, 100% for Cmax and 94% for AUC.

Conclusion: The favorable predictive performance achieved by the implemented SC module confirm the potential of the physiologically based components in the OSPS platform, highlighting its usefulness as a valuable tool for enhancing PBPK modeling of mAbs administered SC.

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PB8: PK characterisation of S65487 and assesment of variability using pharmacometrics in healthy volunteers and patients with cancer

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Background and Objectives: S65487 is a BCL2 inhibitor in clinical development, with the aim of proposing a new effective treatment for patients with hematological malignancies, in particular acute myeloid leukemia (AML). Three clinical trials, including a microdose study on healthy volunteers[1] and phase I and I/II studies, have been carried out, with respectively 100 µg and from 25 to 1200 mg doses. The aim of this work is to characterize PK of S65487 on patients with cancer while integrating PK data generated during the microdose study in healthy volunteers and thus to characterize and find mechanistic explanations to the variability's sources between microdose and therapeutic doses.

Material and methods: Population Pharmacokinetic (pop PK) modeling is used to describe the time-course of drug concentration in each patient through the estimation of typical PK parameters (e.g. drug clearance, volume of distribution) and their associated variability. Data from 5 heathy volunteers were added to a PK model already developed by Servier teams. This model has been developed with data from patients in a phase I and I/II clinical trials, in where the drug is administered intravenously as monotherapy and in combination with azacitidine. Stochastic Approximation Expectation-Maximization (SAEM) algorithm is used to estimate population parameters of this model. Then, to compare microdose study and phase I and I/II studies, PK parameters estimates from each study has been performed to determine the information provided by the microdose study.

Results: Data from the microdose study have been added to the 3-compartment PK model, which describe with a good precision those low-concentration observations. It describes S65 concentrations as a function of time for each patient. Comparison of PK parameter estimates between the microdose study and phase I and I/II studies showed significant differences for clearance (CL) and volume of distribution in the central compartment (V1). Cl and V1 are on average respectively 3.5 times greater and 3.2 smaller in the microdose study and with less variability for both parameters.

In order to find sources of these variabilities, several hypotheses have been explored such asthe health condition of subjects and potential organ failure, in a first time. In a second time, we focused

on the CYP3A4 inhibition activity. In vitro studies have shown that S65 is a strong inhibitor, substrate of CYP3A4 and 70% metabolized by this enzyme. Hence the hypothesis that CYP3A4 inhibition activity is dependent on S65 concentration. In the microdose study, at very low concentration, CYP3A4 inhibition may be null or very low, resulting in a higher CL value than at high concentrations, where CYP3A4 activity would be inhibited and CL lower. This hypothesis can be verified by developing competitive inhibition and mechanism-based inhibition (MBI) models with an effect on CL[2-3]. Moreover, target-mediated drug disposition (TMDD) with its saturation of target at low doses, also present in small molecule, have been shown to be a possible source of non-linearity[4]. This hypothesis can also be an explanation in the difference of Cl estimates.

Conclusion: These pharmacometrics analyses will enable us to characterize the PK of the drug, investigate sources of variability, and participate in its development to support bringing it to patients.

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Poster 1: Cross-Species Population Pharmacokinetic Modeling of an Anti-Cancer Agent: Contributions to Human Dose Prediction

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Objectives: This inter-species analysis aims at providing comprehensive understanding of the pharmacokinetic (PK) disposition of a small anti-cancer molecule to support translational predictions.

Methods: Single and multiple dose PK studies were conducted after PO of drug X in mice, rats, beagle dogs, and cynomolgus monkeys. Administered doses vary from 3 mg/kg to 150 mg/kg. Based on all available preclinical PK data, a population PK (PopPK) analysis was conducted via nonlinear mixed effects modelling using NONMEM, V7.5. The First-Order Conditional Estimation with Interaction (FOCEI) method was used for the estimation process. Assessment of model adequacy and decisions about increasing model complexity were driven by the data and guided by goodness-of-fit criteria. An allometric scaling approach has been included in the pre-clinical model to check reliability to allow future prediction of PK parameters in humans.

Results: 1289 quantifiable concentrations from a total of 209 animals were used in the PopPK analysis. PK of drug X was adequately described by a 2-compartment model with linear elimination and first-order absorption. Inter-individual variability was estimated on all parameters. Residual variability was modeled using a proportional residual error and exponential model was used for the inter-individual variability. The estimated PK parameters (CV%) were absorption rate (Ka) of 1.21 h-1 (31.6%), apparent central clearance (CL/F) of 0.755 L/h (87.2%), apparent central volume of distribution (Vc/F) of 0.352L (14.8%), apparent inter-compartmental clearance (Q/F) of 0.939 L/h (72%), apparent peripheral volume of distribution (Vp/F) of 5.25 L (109%). Body weight was included on clearances and volumes as allometric scaling factors. These factors were estimated at 0.741 and 1.00 for clearances (including CL/F and Q/F) and volumes (including Vc/F and Vp/F), respectively.

Conclusions: The popPK model is able to characterize the PK of drug X by integrating the knowledge gathered from several preclinical studies in 4 different species. The allometric scaling approach appears to be relevant to predict initial dosing in humans. Subsequent simulations of different dosing regimens will be evaluated to support the next stages of development.

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Poster 2: Ceftobiprole in critically ill patients: proposal for new dose regimens

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Background and objectives : Ceftobiprole is a cephalosporin with broad-spectrum activity currently approved for the treatment of community-acquired pneumonia and hospital-acquired pneumonia. The recommended dosage regimen may not be sufficient to achieve a microbiological efficacy criterion in over 90% of critically ill patients.
Applying a modelling approach, our aim was to (i) evaluate if the dosage regimen proposed by the manufacturer ensures that a microbiological efficacy criterion is achieved in over 90% of patients; (ii) if not, to propose optimal dosage regimens for critically ill patients depending on their pathophysiological characteristics.
Material and methods : An extensive review was conducted to gather information from all published population pharmacokinetic models. Ceftobiprole concentrations were measured in 27 Intensive Care Unit (ICU) patients and compared against concentrations expected from population pharmacokinetic models through simulations. For this external evaluation, the multivariate exact discrepancy (MED) approach was used [1]. For each patient, the MED approach assessed the agreement between the model and the patient's observed concentrations. A major strength of this approach is to take into consideration the dependency between a patient's concentrations.
The model that best described the data was used to evaluate the dosage regimens proposed for ICU patients by evaluating the probability of reaching the pharmacokinetic/pharmacodynamic criterion (100%fT>4MIC) [2]. Additionally, this same model was employed to suggest dosage adjustments for these patients.
Results: Among the four models evaluated, only the Muller's model [3] allowed to describe the concentrations observed in the 27 patients. Hence, it was selected as the more suitable model for our population. Employing Muller's model[3], the evaluation of the dosage regimen shows that the manufacturer's dosage regimens do not enable the attainment of the PK/PD criterion in our ICU patients. Consequently, we proposed an abacus to ensure ceftobiprole's efficacy in at least 90% of patients.
Conclusions: The dosage regimen abacus developed using Muller's model [3] can be used to guide ceftobiprole dosing in critically ill patients, considering the patient's clinical and biological characteristics along with the bacteriological data. However, therapeutic drug monitoring remains essential at least once to confirm patient's exposure.

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Poster 3: Population PK/PD modelling to evaluate the effect of Ixodes ricinus-Contact Phase Inhibitor in patients with Spontaneous Intracerebral Haemorrhage

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Background and objectives: Ixodes ricinus-Contact Phase Inhibitor (Ir-CPI), also called BIOX-101, is a recombinant protein for the prevention of acute thrombo-inflammatory events, which does not increase the risk of bleeding. In addition to its anti-inflammatory effect on neutrophils, it acts specifically on the intrinsic coagulation pathway by inhibiting the activation of Factor XI (FXI) and Factor XII (FXII), which increases the activated partial thromboplastin time (aPTT). [1]
The objective of this work is to characterize plasma Ir-CPI concentrations-time profile following IV infusion and drug-induced pharmacodynamics (PD) effects (PKPD) in healthy volunteers to support further clinical development in patients with spontaneous intracerebral haemorrhage (ICH).
Material and methods: A First-in-Human (FIH) Phase I study, double-blind, placebo-controlled, single ascending dose of Ir CPI provided an initial assessment of the safety, tolerability, PK, and PD of Ir-CPI after 6-hour IV infusion to 32 healthy adult male volunteers.
The study included four groups of eight participants randomized to Ir-CPI doses of 1.5, 3, 6 and 9 mg/kg versus placebo (6-active: 2-placebo). Population PKPD (popPKPD) analyses were conducted via nonlinear mixed effects modeling using NONMEM, V7.5. The First-Order Conditional Estimation with Interaction (FOCEI) method was used during the estimation process of PK and PD parameters.
After determination of the population PK model, PKPD models for three parameters, namely, aPTTratio, percentage of inhibition of FXI and FXII procoagulant activities were developed.
Assessment of model adequacy and decisions about increasing model complexity were driven by the data and guided by goodness-of-fit criteria (visual inspection of diagnostic plots, plausibility and precision of parameter estimates, objective function value, visual predictive checks).
Results: 407 quantifiable Ir-CPI concentrations from 24 healthy male volunteers were obtained. Ir-CPI PK profiles were well described by a 2-compartment model with linear elimination. The population estimates (CV%) of the PopPK model were: Cl = 7.65 L.h-1 (15.1%); V1 = 39.2 L (21.3%); Q = 12.8 L.h-1 (16.0%); V2 = 178.0 L (14.5%). Inter-individual variability was estimated on all parameters. Body weight (WT) was included as a covariate on all PK parameters using allometric scaling with fixed exponents of 0.75 and 1 for clearances and volumes, respectively. Residual variability was

modeled using a proportional residual error and exponential model was used for the Inter-Individual Variability.
Drug effect represented by aPTT ratio, FXI and FXII inhibition percentage were best described by a simple Emax model with baseline, a simple Emax model and a sigmoid Emax model, respectively. The study included 321, 428 and 427 quantifiable PD data for aPTT Ratio, FXI(%) and FXII(%), respectively. A direct relationship was observed between PK and PD data. The population estimates (CV%) of aPTT Ratio, FXI(%) and FXII(%) were: Emax [aPTT]= 2.52 (16.9%); EC50 [aPTT] = 2000 ng/mL(37.7%); E0[aPTT] = 1, Emax [FXI%]= 61.6; EC50[FXI%] = 1070 ng/mL ; HC[FXI%] = 1.35 (27.7%), Emax[FXII%]= 80.6 ; EC50 [FXII%] = 846 ng/mL (21.7%); HC [FXII%] = 1.52. Additive error was considered for all PKPD models.
Conclusion: The popPK and the semi-mechanistic popPKPD models built on Phase I data provided good results in terms of goodness-of-fit plots and PKPD parameters with accurate estimates. Overall, no apparent bias in model predictions was observed and the models showed good predictive ability.
Although fitting reasonably well the observed PK data, the selected popPK model could not perfectly characterize the elimination process at higher exposure. [3] Model development will be further investigated at higher exposures with a larger sample size when Phase II data is available. Ultimately, the PKPD models will be reevaluated when further data is available.
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Poster 4: Predicting the pharmacodynamics of rosuvastatin in healthy, obese, and MASH subjects using a permeability-limited multi-compartment liver model

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Background and objectives: Statins, commonly prescribed for hyperlipidemia, are often used in patients with obesity and/or metabolic-dysfunction associated steatohepatitis (MASH). However, little is known about how MASH may affect statin disposition in hepatocytes, where their target, 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, is located. This study aimed to predict alterations in pharmacodynamic (PD) response at steady state following oral administration of rosuvastatin in Obese, Morbidly Obese, and MASH populations compared to a Healthy Volunteer population.
Material and methods: This study used a physiologically based pharmacokinetic (PBPK)/permeability-limited multi-compartment liver (PerMCL) framework, incorporating zonal transporter and drug-metabolizing enzyme data. Rosuvastatin is a substrate for OATP1B1, OATP1B3,

NTCP, and OATP2B1 with minimal hepatic metabolism [1]. In MASH, the total hepatic protein abundances of those transporters are decreased [2]. Furthermore, periportal OATP1B3 membrane-localized zonal abundance (OATP1B3MZA) is increased, while pericentral OATP1B1/1B3MZA are slightly decreased in MASH [3]. Systemic and hepatocellular concentrations of rosuvastatin were simulated in Healthy Volunteers (HV), Obese, Morbidly Obese, and MASH virtual populations using the Simcyp™ Simulator (Version 23). A previously published PD response model of rosuvastatin [4], which simulated mevalonic acid (MVA) exposure as an in vivo marker of HMG-CoA reductase activity, was updated to be driven by local (Zone 1-6) unbound hepatocellular rosuvastatin concentrations. An IC50 of 0.024 µM and Hill coefficient of 8 was optimised to recover the clinical data [5]. Steady-state plasma and zonal hepatocellular concentration-time profiles for each statin were simulated across virtual populations of 100 individuals aged 40-65 years.

Results: Simulated rosuvastatin Cmax,ss, AUCτ,ss, and Cmin,ss increased by ~100% in MASH compared to Healthy Volunteers. While minimal changes (<15%) in rosuvastatin unbound hepatocellular exposure in hepatic Zone 1 (periportal region) were predicted, Cmax,u,IW,ss and AUCτ,ss were simulated to decrease by 57% and 55%, respectively, in MASH relative to Healthy Volunteers in Zone 6 (pericentral region). These changes led to decreased efficacy (increased MVA AUCτ,ss) following 10 mg rosuvastatin administration for 14 days in Morbidly Obese and MASH populations compared to Healthy Volunteers. Exploratory simulations suggest that a 15 mg and 30 mg dose in MASH patients may be equivalent to a 10 mg and 20 mg dose, respectively, in Healthy Volunteers in terms of cholesterol-lowering efficacy.

Conclusions: The PD model predicted decreased rosuvastatin cholesterol-lowering efficacy in MASH compared to HV. Exploratory simulations suggest that this could potentially be compensated for by increasing the dose by 50%.

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Poster 5: Assessing Confidence in PBPK Models for Cosmetic Ingredients

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Background and objectives: The safety evaluation of cosmetic ingredients relies on non-animal testing methodologies. Physiologically Based Kinetic (PBK) modelling emerges as a robust tool for predicting systemic exposure, particularly in scenarios where in vivo pharmacokinetic (PK) data are scarce. This study aims to critically assess the application of PBK modelling for cosmetic ingredients, with a particular focus on the OECD Guidance Document No. 331 framework, which

delineates best practices for model development, validation, and reporting. The OECD guidance underscores the significance of PBK models in regulatory contexts, highlighting their potential to mitigate reliance on animal testing while ensuring that safety assessments are both scientifically rigorous and reliable.

Material and methods: This investigation entails a comprehensive analysis of the OECD Guidance Document No. 331 and the associated case studies. We explore various methodologies for establishing confidence in PBK models in the absence of in vivo/clinical data, concentrating on read across for validation of PBK predictions from a data rich chemical to a data poor chemical and the establishment of similarity criteria for chemical specific ADME parameters. We present a novel case study that exemplifies the application of the OECD guidance to a specific cosmetic ingredient, elucidating both the advantages and challenges encountered in this process. This approach aligns with the growing body of literature advocating for standardized methodologies in PBK modelling to enhance regulatory acceptance.

Results: Our analysis indicates that the stepwise approach recommended by the OECD guidance provides an initial framework for developing fit-for-purpose PBK models tailored to cosmetic ingredients, nonetheless, how to robustly validate these models requires further investigation. The case studies reviewed demonstrate that even in the absence of comprehensive in vivo data, meticulously constructed PBK models can yield valuable insights into the behaviour of cosmetic ingredients, provided chemicals similar in ADME could be found in the literature to serve as a validation reference. Our in-house case study (sunfilter ingredients homosalate, and its analogue octisalate) further corroborates this assertion, illustrating the model's efficacy in predicting key exposure parameters. The findings also reveal challenges associated with parameter uncertainty and the correctness of the assumptions made for model conceptualisation, thereby emphasizing the necessity for purposeful in vitro ADME profiling, as well as, sensitivity and uncertainty analyses, as highlighted in the existing literature.

Conclusions: The OECD guidance offers essential principles for the development and application of PBK models within the context of cosmetic ingredient safety assessments. While the case studies presented, including our own, illustrate the potential of this modelling approach, they also highlight the imperative for continuous refinement and adaptation based on specific ingredient characteristics and the data available. Future research should focus on addressing data-poor scenarios, enhancing parameter estimation methodologies, and standardizing approaches for uncertainty analysis to further bolster the applicability of PBK modelling in this domain.

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Poster 6: Physiologically-based systems modeling for new biologics modalities: A mechanistic approach to translate antibody drug conjugate design into FIH dosing predictions

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In the last decade, plenty of new treatment modalities have become available, enabled by advances in genetic engineering, biologics manufacturing (in particular hybridization technologies). Among those modalities antibody drug conjugates (ADCs) have become an important player in immuno-oncology nowadays. They combine the high target specificity of antibodies with high potencies of chemotherapies to become a “targeted missile”. Still, emergent pharmacologic properties (such as the impact of coupling chemistry, stability and biotransformation) and the intricate interplay between efficacy and toxicity have led to setbacks for several clinical programs. The large combinatorial space of biologics, small molecule payload and type of linkage calls for a systematic modeling approach, of which many properties (e.g., target expression, internalization, catabolism, small molecule distribution, etc.) can be predicted early in a program by feeding in in vitro/screening data into a quantitative systems pharmacology model (of which a number are published already)
In this contribution, we propose a whole-body translational approach to translate ADC design characteristic into FIH dosing predictions. We illustrate 10 typical model building steps implemented with an open source PBPK modeling framework for large and small molecules. The framework was developed using PK-Sim and MoBi (Open Systems Pharmacology Suite [1]). On the example of an in vivo xenograft experiment, we show how these steps contribute to understanding nonlinear PK properties, payload release and distribution and dose-dependent tumor growth inhibition profiles. We also provide an outlook on how integration of other pharmacodynamics and quantitative systems pharmacology models (e.g. myeloablation) could bridge the translational model with clinical development questions for new ADCs.

Reference:

[1] https://github.com/Open-Systems-Pharmacology

Poster 7: Physiologically-based systems modeling for new biologics modalities: Integrating molecule, indication and patient-specific aspects for bispecific T-cell engagers

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In the last decade, plenty of new treatment modalities have become available, enabled by advances in genetic engineering, biologics manufacturing (i.e. hybridization technologies). Among those modalities, bispecific antibodies (BsAbs), which recruit T cells to tumor sites (also termed T cell engagers, BiTEs or TCEs) have become an important player in immuno-oncology nowadays. Due to non-linearity, non-monotonicity and potential severe consequences of adverse reactions with these new modalities, a conservative FIH strategy and a dedicated dosing regimen is needed. This can be informed by comprehensive mathematical modeling which has become mature enough to support submissions for regulatory considerations.

Despite the availability of a few modeling platforms (some of them commercially available), there is still an unmet need to cover the wide variety of treatments (also considering other new modalities such as ADCs), the impact of disease state on the pharmacology as well as the numerous sources of between-patient variability that could be relevant under one common (modeling) umbrella.

In this contribution, we propose a modular approach to model new modalities, illustrated by an exploration of dosing strategies for a bispecific antibody. We integrated several modules into a physiologically based (PBPK) modeling framework (some of which are still under construction): target-mediated drug disposition, cellular kinetics, cytokine secretion and a detailed IL6 centric receptor binding. The aim of this work was to highlight the workflows for modelling 1) the kinetics for simple ternary complex formation in the target organ; and 2) the exploratory cytokine-signaling networks integrated with the model to support a CRS-predictive biomarker program.

With this modular concept and the upcoming release of the Open Systems Pharmacology Suite v12 [1], which allows for fully modular workflows, we give an outlook on a fully open-source modular platform using individual and fit-for-purpose composed models to support drug development of new biologics modalities.

Reference:

[1] https://github.com/Open-Systems-Pharmacolog

Poster 8: High-Throughput PBPK Framework in R using Open Systems Pharmacology Software

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Background and objectives: The increasing importance of Physiologically-Based Pharmacokinetic (PBPK) models in drug development and chemical risk assessment highlights the growing need to be able to run PBPK models very efficiently for a high number of compounds. Our goal is to

develop a robust framework in R that facilitates simulating a high number of PBPK models from in vitro and in silico compound data in an efficient manner using the open-source Open Systems Pharmacology (OSP) [1] software.

Materials and methods: Using open-source R packages from the OSP ecosystem: ospsuite, tlf, and ospsuite.parameteridentification, we developed a framework that allows efficient simulations of many compounds by leveraging the various packages capabilities.

Results: Using the capabilities of the open-source R packages from the OSP ecosystem, we developed a framework to predict in-vivo PK profile of many drugs or chemical compounds in an efficient manner. To this end we leveraged the possibility of reusing the same model structure (i.e. a single predefined .pkml file developed in PK-Sim or MoBi which can include various processes as needed). This predefined "generic" model can be used for multiple compounds and multiple study protocols can be created based on in-vitro and in-vivo data available. This generic model is then loaded and the simulation engine is initialized only once to reduce the associated cost of these steps. The various compounds can then be simulated in parallel by applying different parameter sets representing the various compound physico-chemical properties and additional in vitro data available. To achieve this one must define 1) a "generic" model structure .pkml, 2) define which parameters need to be varied across the compounds (physico-chemical properties, clearance values, administration protocols parameters, parameters allowing to turn on and off certain processes, ...). Additionally, this has been supplemented by the possibility of running parameter identification for each compound if in-vivo PK profile data is available.

Conclusion: Having an efficient HT-PBPK framework as many applications, it can be used with IVIVE during the initial stages of drug or chemical development where no or few in-vivo data are available to predict the associated PK-profiles (2). It can also be used retrospectively on large databases of compounds for which in-vivo PK data is available to systematically evaluate the effect of various methods, and structural model hypotheses that can be subject to discussion in the community. It can also be used to identify optimal IVIVE workflows for PBPK parametrization when no in-vivo data is available or to parametrize PBPK models of many compounds in an efficient manner when in-vivo PK data is available.

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Poster 9: User-friendly and Quality-Controlled PBPK/QSP M&S Framework in R for Regulatory Submissions using Open Systems Pharmacology Software

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Background and objectives: The increasing importance of Physiologically-Based Pharmacokinetic (PBPK) and Quantitative Systems Pharmacology (QSP) models for regulatory submissions in drug development requires user-friendly and quality-controlled tools and workflows. Our goal is to

develop a robust framework in R that facilitates PBPK/QSP modeling and simulation (M&S) projects using models developed with the open-source Open Systems Pharmacology (OSP) (1) softwares, promoting reproducibility, transparency, and automation in model development while minimizing error probability coming from maintaining complex R code.

Materials and methods: An open-source R package {esqlabsR} (2) has been developed that utilizes R packages from the OSP ecosystem: ospsuite, tlf, and ospsuite.parameteridentification. Additionally the Quarto framework is used for generation of Markdown/PDF reports, as well as a R Shiny package for the graphical user interface (GUI). All packages adhere to high transparency and quality control standards in software development and are available open-source.

Results: The framework offers a user-friendly workflow for working with models developed with PK-Sim and MoBi (as .pkml files). The key steps supported by the framework include:

1. Model development in PK-Sim and MoBi
2. Modification of species, individual characteristics, and populations in R
3. Configuration of simulation scenarios with species-, individual- and disease-specific parameters and application protocols
4. Performing sensitivity analysis
5. Running parameter identification routines
6. Generating markdown and PDF reports

The workflow is built around the definition of simulation scenarios from a single simulation file (as .pkml file) used as model structure. This approach ensures equal and up-to-date model structure for all scenarios and minimizes the risk of reporting results from an outdated model version. The scenarios are defined as a set of parameter values applied to the model structure, whereby different hierarchy levels of parametrization are available: i) global parametrization, ii) species-specific, iii) individual-specific, iv) population-specific, v) disease state and parametrization of vi) application protocol. The final parameter set is automatically reported by the generated simulation report, ensuring full transparency and reproducibility. The specified scenarios can be re-used in the subsequent steps while performing sensitivity analyses, parameter estimations, and generation of statistical and graphical results analyses. The configuration of the each workflow steps is done using Excel files, ensuring project reproducibility while minimizing coding errors, and facilitating its use by modelers with limited coding experience. Additionally a R Shiny application provides a convenient GUI for the execution of the entire workflow and automated generation of markdown report using report templates.

Conclusion: We present a novel R framework R that simplifies user interaction with PBPK/QSP models developed with OSP softwares. This framework prioritizes quality control and user friendliness, facilitating the creation of regulatory-compliant reports for pharmaceutical submissions. The {esqlabsR} package and the R Shiny application are freely available on GitHub, and users are encouraged to share feedback and participate in their development. In the future, more features and additional workflows will be supported by the framework, such as pre-defined workflows for drug-drug-interaction simulations, pediatric scaling, or high throughput PBPK modeling. The GUI R shiny application will be continuously developed to offer more model analyses functionalities and to allow generation of new model structure from pre-defined model blocks.

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Poster 10: A workflow for comparing drug candidates based on Probability of Pharmacological Success (PoPS)

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Background and Objectives: Probability of Pharmacological Success (PoPS) has been proposed as a framework for informing early stage drug-development decisions based on benefit and risk data currently available [1,2]. This poster introduces the concept of cumulative PoPS and a standardized workflow for efficient comparison of candidate drugs.

Methods: The template workflow was developed for RStudio and Quarto and applied to a hypothetical drug development example inspired by a real-life case study. The latter concerns a group of 3 dual-agonists (ABC001, ABC002 and ABC003), intended for treatment of neuropathic pain, with different binding characteristics including both full and partial agonism.

The workflow follows this structure:

Input data: An input data standard, and optional GUI for data entry, has been established to define PK and PD parameters (e.g. CL, EC50) as well as the specific criteria and ranges (e.g. NOAEL, target engagement). The designed structure allows to develop generic functions that handle any combination of assets and endpoints. The setup also offers flexibility with regards to inclusion of parameter uncertainty and between-subject variability for parameters.

Exposure-response: The user is prompted to define the exposure-response (ER) model in one dedicated chunk of the template. To support the creation of the required R list structure, instructions and examples are provided. The rest of the code is generic and doesn't require changes.

Simulated ER relationships are graphically represented in a grid format for each asset and endpoint. The figures aim to pedagogically illustrate the predicted ER relationships, including between-subject variability and uncertainty, in relation to target ranges.

Dose-exposure: The user is prompted to define the dose-exposure model. This section is generated the same way as the previous one, simulating exposure using sampled dose and parameter values from the input data.

Dose-response: Based on the input in the above sections, the predicted dose-response relationships for each asset and endpoint are simulated and graphically represented.

PoPS: At a given dose, the simulated response and exposure values are first compared with their respective targets and the proportion of individuals that meets each individual-level criterion is derived. Proportions are then evaluated against the population-level criteria (e.g. minimum fraction of subjects that should fulfil a specific criteria). From this, the probability to jointly meet all criteria (PoPS) is calculated for each dose level. The cumulative PoPS is computed additionally as the probability that a particular dose or any lower dose fulfils all the target criteria.

The section graphically represents the probability of individual target criteria fulfilment, PoPS and cumulative PoPS vs. dose in separate figures.

Results: The previously described PoPS concept has been extended to include assessment of cumulative PoPS across a dose range or for a limited selection of doses. This makes the concept more useful to prioritising between different assets.

For the neuropathic pain case study, the two assets ABC001 and ABC002 was found to have relatively similar maximum PoPS for their most likely therapeutic dose levels (48% vs 44%) outperforming ABC003 (28%). However, ABC001 demonstrated a clear benefit in terms of cumulative PoPS across a wider dose range (98% vs. 87% and 63%).

Conclusions: PoPS is an attractive framework for informing early-stage drug-development decisions. It can inform about the most likely successful therapeutic dose for a specific asset given multi endpoint success criteria. This work also demonstrates how calculation of cumulative PoPS across a dose range or for a limited selection of doses makes the concept more useful in prioritising between candidate drugs and selecting a dose-range of interest for further exploration (e.g. first-in-human study). The established standard workflow offers meaningful gains in terms of efficiency, quality control and accessibility.

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Poster 11: Development of QSP platform model for T Cell Engagers (TCE) predicting priming dose and CRS incidence of T Cell Engager (TCE) in Steap1 prostate cancer

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Background and objectives: CD3 bispecific antibodies are designed to bind both CD3 on T cells and tumor-associated antigens (TAAs) on cancer cells, triggering T cells to attack and eliminate the cancer cells. However, this activation can also lead to adverse effects, such as Cytokine Release Syndrome (CRS), even outside the tumor area. Research is focused on achieving the right therapeutic balance for these agents, combining experimental data with mechanistic modeling to better understand their effects in both tumor and normal tissues. Quantitative Systems Pharmacology (QSP) models are particularly useful in clarifying the drug's mechanism of action, highlighting how TAA receptor occupancy in tumors and on target off tumor tissues influences efficacy and the risk of side effects like CRS.

Material and Methods: In this study, a Quantitative Systems Pharmacology (QSP) platform model was created for a 2+1 STEAP1 x CD3 bispecific antibody targeting prostate cancer. The model builds on the framework developed by Hosseini et al. (2020) [1], which explored drug interactions with CD3 and tumor-associated antigens, focusing on the formation of dimers and trimers and the dynamics of T cells. The research emphasized the importance of target receptor occupancy in determining drug effectiveness and safety, offering insights for a 1+1 CD3 bispecific antibody in Non-Hodgkin's lymphoma. We extended this model to a 1+2 bivalent bispecific antibody specific to prostate cancer, aiming to optimize efficacy and devise a dose priming strategy to reduce CRS risk. To calibrate and validate the model, we utilized clinical data for Xaluritamig from public sources [2]. IL-6 was selected as the primary biomarker for toxicity due to its strong correlation with CRS events. Recently we showed a QSP model to recommend an alternate dosing regimen and incremental dose for Xaluritamig (a STEAP TDB for prostate cancer) at Page 2024.

Results: This QSP platform model was utilized to simulate various scenarios, reflecting its potential applications in early clinical development stages.

- To model trimer formation in tumor tissue (as a surrogate for efficacy) and normal tissue (as a surrogate for safety) across various doses of Xaluritamig.

- Suggest an initial dose and escalation strategy for Xaluritamig by calibrating the platform model to optimize trimer formation, aligning with pharmacokinetic/pharmacodynamic (PK/PD) characteristics and safety profiles from prior studies or clinical trials.
- Investigate dose priming strategies to reduce the risk of CRS and other adverse events.

Conclusions: The model can assess how antigen expression levels, binding affinities, and baseline T cell concentrations affect anti-tumor efficacy and CRS risk. This platform can be leveraged in early clinical development to guide dose priming strategies.

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Poster 12: A comprehensive multi-scale in silico approach for predicting antibody-drug conjugate clinical efficacy across oncological indications

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Background and objectives: Antibody-drug conjugates (ADCs) represent a major advancement in cancer treatment, improving precision in delivery of cytotoxic agents to tumor cells. To develop these innovative therapies effectively, it is crucial to understand and model a range of ADC characteristics, such as drug pharmacokinetics (PK), tumor growth inhibition dynamics, and the properties of payloads and linkers, as well as the bystander effect. However, despite the increasing number of clinical trials and in silico studies in targeted therapies, a significant gap persists in expanding findings from ADC research in one condition to another and accurately predicting patient outcomes.

Our approach aims to create an ADC platform to bridge the gap. Specifically, this study seeks to develop and implement a robust protocol that adapts an in silico model designed for breast cancer-utilizing multi-level data related to Trastuzumab deruxtecan (T-DXd) and the expression of human epidermal growth factor receptor 2 (Her2)- to generate predictive in silico results for dose-exposure response in gastric cancer. T-DXd is approved for both breast and gastric cancers, making the expansion of indications a primary area of interest, alongside other technical considerations such as data availability.

Material and Methods: (i) We started by selecting a published pharmacokinetic-pharmacodynamic (PK-PD) model [1] as our foundational model. This model already encompasses drug disposition at the cellular level, including antigen expression, drug-antigen interactions, internalization, and intracellular payload distribution. It also features a tumor drug distribution module, a tumor growth inhibition (TGI) module, and accounts for bystander killing based on the properties of the payload. (ii) We then extended this base model into a minimal physiologically based pharmacokinetic and quantitative systems pharmacology (mPBPK/QSP) model by adding a module to describe the systemic distribution of both the ADC and the drug. This expanded model was implemented in

SimBiology. (iii) The mPBPK/QSP model was calibrated using preclinical data [2] and clinical data (n=104, DESTINY trial [3]) from breast cancer patients treated with the approved ADC T-DXd. (iv) Using literature data, including antigen expression levels, we adapted the model's context of use to gastric cancer. (v) Finally, we assessed the model's predictions for patients diagnosed with gastric cancer who had been treated with T-DXd (n=44, DESTINY trial [3]).

Results: The original model developed for breast cancer, focusing on T-DXd, effectively captured the PK of both the payload and ADC in plasma and tumor tissues. This allowed for an accurate depiction of the responses observed in xenograft mice following ADC administration. The model was subsequently adapted for human use, where virtual clinical trial simulations successfully reflected the treatment response in metastatic breast cancer, specifically in terms of the best change in the sum of longest diameters (SLD) from baseline, while also considering variations in efficacy based on HER2 expression levels. Finally, the model was adapted for human gastric cancer, where it accurately predicted the efficacy of T-DXd, closely aligning with available clinical trial data.

Conclusions: In conclusion, this approach establishes a mPBPK/QSP framework that is valuable throughout various stages of ADC development. The use case demonstrates the potential of this in silico method to integrate diverse data sources and knowledge, enabling the prediction of ADC utcomes at the clinical stage. This platform shows promise for assisting in the selection of suitable patient populations or indications for ADC therapies.

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[3] Daiichi-Sankyo Presentation - ASCO, 2018

Poster 13: Prediction of a Claudin 18.2 targeted Antibody Drug Conjugate Pharmacokinetics in Cancer Patients Using PBPK Modeling and Simulation

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BACKGROUND: Antibody-drug conjugates (ADCs) are anticancer drugs where a monoclonal antibody, targeting specifically tumor cells, is linked to a toxophore which is released inside tumor cells, thus killing them without harming healthy cells[1]. Although physiologically-based pharmacokinetics (PBPK) modeling has become an important tool in drug development to mechanistically characterize drug exposure in different tissues[2], very few PBPK models have been developed for ADCs to date.

Methods: To capture ADC's pharmacokinetics (PK), we developed a human PBPK model in PK-Sim and MoBi[3] and compared it to three clinical studies for an anti-Claudin 18.2 ADC (SHR-A1904)

administered intravenously (IV) in 109 patients with gastric or pancreatic cancers (totaling in 908 and 824 plasma observations for ADC (whatever the drug antibody ratio) and deconjugated toxophore, respectively). First, we defined one PBPK model for each compound (ADC, toxophore, naked antibody), with input parameters either measured in vitro or predicted from the compound structure[4]. After integration of target-mediated drug disposition (TMDD), nonspecific catabolism and deconjugation of the toxophore in MoBi, a few unknown constants and parameters were fitted using a reference Chinese patient. The model was evaluated by visual inspection of predicted/observed plasma concentration-time profiles. PK parameters were considered inaccurate if the predicted error ratios were outside the two-fold error range (0.5-2)[5-6].

Results: While the first PK-Sim model captured the ADC concentration-time profile following IV administration of multiple escalating doses, additional clearance mechanisms such as TMDD and deconjugation elimination pathways were necessary to improve the fit of the ADC elimination phase. In MoBi, 3 and 4 parameters were optimized for the ADC and the toxophore, respectively. The data was adequately captured for those two compounds (Fig.), with predicted error ratio included in the two-fold range: Cmax of ADC (1.07-1.50) and toxophore (0.69-1.44) and all AUC0-504h (first administration), for ADC (0.59-0.98) and toxophore (0.82-1.38).

Conclusion: With several optimized parameters for TMDD and deconjugation elimination pathways, our model allowed an accurate prediction of the observed data in cancer patients for this anti-Claudin 18.2 ADC. This study paves the way for PBPK modeling of other ADCs currently in development.

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Poster 14: In-depth numerical model analysis tools to gain insight into model behavior of large-scale pharmacometric models

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Introduction: The development and application of pharmacometric models to describe and predict preclinical and clinical studies has become a routine exercise for an ever-growing community of pharmacometricians. However, in-depth analysis to gain insight into the developed models and the biological systems they represent is often lacking or minimal. The main tools applied to explore the applied models are individual simulations for smaller models and a (global) sensitivity analysis (SA) for larger (QSP or PBPK) models[1]. Occasionally, small (semi-)mechanistic models are thoroughly analyzed mathematically with tools such as a bifurcation analysis[2] or singular perturbation theory[3]. While this mathematical analysis provides a comprehensive insight, it requires a specific skillset and is often difficult to scale to large QSP or PBPK models and it is therefore not part of the standard pharmacometrics workflow. The current limitations in model analysis tools limits our understanding of the applied models. This decreases the efficiency of model development, the clarity of model communications and the quality/reproducibility of models, since model specification errors are more likely to pass undetected with a limited understanding of model behavior.

Objectives: In this study, we aim to bridge the gap between generic numerical high-level model analysis tools for large models and analytical in-depth model analysis tools for small models, by developing a numerical in-depth model analysis toolbox that can be applied to large models. [4]

Methods: The analysis toolbox presented here utilizes the standard SA spider plots as present in the esqlabsR package (v5.1.3) and the ospsuite package (v12.0.0) in R (v4.3.1). Simulation models were created using a whole-body PBPK (PK-Sim® v11.2) and extended in MoBi® (v11.2) to include TMDD or PD models.

Results: The starting point for this analysis was the first extension of a single local SA: a repeated local SA with the impact of a change in parameter value evaluated for the change in summary PK. The impact of parameter changes can be visualized by plotting the summary PK parameters versus the change in parameter values in a so-called spider plot. Here we developed a “repeated spider plot”, a first extension of a single spider plot, by repeating the same analysis for various combinations of two other parameters that define relevant scenarios. The next step towards a comprehensive understanding of model behavior was the normalization of the sensitivity for the sensitivity of the previous step in the causal change, which can be used to identify where the observed sensitivity originates. Finally, we applied the repeated spider plot to a modified model with continuous infusion in multiple compartments to identify rate-limiting steps and conditions as well as the compartment in steady-state. The developed analysis tools were applied to several whole-body PBPK model elements including a combined tissue TMDD-PBPK model and to a simple two-compartment model for comparison.

Conclusion: Our study demonstrates how variations on the local SA can provide a comprehensive insight into model behavior of large-scale mechanistic models, for which analytical model analysis is unfeasible. The studied examples demonstrate how these analysis tools can reveal rate-limiting steps and in which conditions the potential rate-limiting steps become relevant. The provided numerical analysis tools resolve the limited insight provided by other numerical tools like the global SA, while still being applicable to large-scale models.

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