Apotekarsocieteten
Swedish Pharmaceutical Society

17th Symposium on Pharmacokinetics and Drug Metabolism

12-13 November 2024

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17th Symposium on Pharmacokinetics and Drug Metabolism

12-13 November 2024

Program

Tuesday 12th November	
11.30 – 12.00	Registration
12.00 – 13.00	Lunch
13.00 – 13.10	Opening and introduction of meeting Suzanne Iverson Hemberg, Toxicology Knowledge Team Sweden, Rasmus Jansson Löfmark, AstraZeneca
13.10 – 14.40	**Session 1: Biotransformation and impact of drug metabolites** Chairs: Johanna Haglund, MetaSafe, Johan Bylund, CTC, Clinical Trial Consultants **Speakers:** *13.10 – 13.40* • **"Unusual" Biotransformation Reactions of Drugs and Drug Candidates**, Emre Isin, Servier *13.40 – 14.10* • **Drug metabolism in drug discovery-PK, PD and safety aspects**, Carl Petersson, Merck Healthcare *14.10 – 14.40* • **Structural elucidation of conjugation drug metabolites by utilizing novel electron-activated dissociation (EAD)**, Ferran Sánchez, SCIEX
14.40 – 15.20	**Break & coffee**
15.20 – 17.00	**Session 2: Drug Transporter considerations across drug modalities** Chairs: Anna Nordmark, Nordmark ClinPharm consulting, Rasmus Jansson-Löfmark, AstraZeneca **Speakers:** *15.20-15.45* • **Drug transporters and large molecules**, Pär Matsson, Gothenburg University *15.45-16.10* • **Antibody Brain Exposure and Distribution Using Passive or Active Transport Mechanisms to Target Brain Diseases**, Sofia Gustafsson, BioArctic *16.10-16.35* • **Translational aspects of oxycodone brain delivery via the proton-coupled organic cation (H+/OC) antiporter system: the journey from cells to pigs.** Irena Loryan,Translational Pharmacokinetics/Pharmacodynamics group, Dep of Pharmacy Uppsala University *16.35-17.00* • **Use of endogenous biomarkers for evaluating transporter-mediated DDIs (tDDI) – Case studies from AstraZeneca**, Vijender Panduga, AstraZeneca
17.00 – 17.15	Break
17.15 – 18.00	**Candlelight lecture: At the Intersection of Science and Entrepreneurship – My CRO journey** Chair: Rasmus Jansson-Löfmark, AstraZeneca **Speaker:** Bengt Dahlström, PhD, Associate Professor Bengt Dahlström is Associate Professor in Pharmacokinetics and Drug Therapy from Uppsala University, Sweden and has published over 50 scientific papers in this area. He is an expert in pharmacokinetics, drug research and development with over 40 years' experience from leading positions in Pharmaceutical companies and CROs. He is co-founder of leading Clinical Research Organizations: CTC AB, PMC AB, MiniDoc AB and AB Biopharmacon.
18.00 – 18.45	**Poster session** with refreshments Chair: Alan Faraj, Novo Nordisk
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Wednesday 13th November	
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09.00-09.25	• **PBPK simulations in special populations. Are we ready for prime time?** Eva Berglund, Certara Drug Development Services
09.25-09.50	• **Clinical Pharmacology considerations for development of Sogroya (somapacitan) for rare pediatric growth disorders**, Rasmus Juul Kildemoes, Clinical Pharmacology RD&AT, Novo Nordisk
09.50-10.15	• **Model-informed development of Mim8 – a novel bispecific antibody for the treatment of haemophilia A**, Mads Kreilgaard, Pharmacometrics, Novo Nordisk
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10.45 – 12.15	**Session 4: Bridging strategies for drug-device products** Chairs: Markus Fridén, AstraZeneca, Mia Lundblad, Novo Nordisk **Speakers:**
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11.15-11.45	• **Improved bioequivalence assessment through model-informed and model-based strategies**, Xiaomei Chen, Uppsala University
11.45-12.15	• **Biopharmaceutical Evaluation of the Subcutaneous Administration**, Marta Venczel, Sanofi
12.15 – 13.15	Lunch
13.15 – 13.45	**Rosenön Award** Chair: Suzanne Iverson, Toxicology Knowledge Team Sweden **Award winner:** Luna Prieto Garcia, AstraZeneca
13.45 – 14.45	**Session 5: Pharmacokinetics-Pharmacodynamics of drug combination therapies** Chairs: Markus Fridén, AstraZeneca, Angelica Quartino, AstraZeneca **Speakers:**
13.45-14.15	• **Development of a pre-clinical model-based drug regimen platform for antibiotics within a European perspective**, Ulrika Simonsson, Uppsala University
14.15-14.45	• **Using Translational PKPD to narrow down the parameter space to explore dose and schedule in the clinic of anti-cancer agents,** Owen Jones, AstraZenca
14.45 – 15.00	Closure of meeting

Poster Abstracts

P1 Serum-free Caco-2 cultures for reliable drug permeability studies

Moamin Alkakaei*, Lazaros Primpas, Evgeniya Mickols, Maria Karlgren
* Department of Pharmacy, Uppsala University, Uppsala, Sweden. moamin.alkakaei@farmaci.uu.se

Aim:
To determine whether Caco-2 cells, commonly used for modeling the intestinal barrier and drug permeability, can maintain their functional and structural integrity under serum-free culture conditions.

Methods:
Caco-2 cells were cultured following established protocols and subsequently transitioned to serum-free culture conditions (Hubatsch et al., 2007, Rafnsdóttir et al., 2023). The growth rate, cellular morphology, and permeability were then assessed through a series of standardized assays. We examined whether the cells maintained their ability to form tight monolayers and transport drugs both passively and actively, using low permeable integrity markers, as well as breast cancer resistance protein (BCRP) and multi-drug resistance protein 1 (MDR1) substrates. Further, global proteomics was performed to compare the global proteomes and to identify and quantify the expression levels of proteins associated with cellular function, drug transport, and tight junction integrity.

Results and discussion:
Caco-2 cells cultured under serum-free conditions demonstrated a well-structured tight monolayer comparable to those cultured in conventional fetal bovine serum (FBS) based media. Permeability assays using membrane integrity markers like Lucifer yellow and FITC-dextran showed apparent permeability values well below $1x10^{-6}$ cm/s for both conditions, confirming intact membrane integrity. Further, actively transported compounds like dantrolene (BCRP substrate) and ritonavir (MDR1 substrate) showed higher efflux ratios in serum-free cultured Caco-2 cells compared to those cultured in conventional media, suggesting that serum-free conditions did not negatively impact active transport. These results are consistent with global proteomics data showing only minor differences in the global proteome between cultures. Interestingly, no significant difference in tight junction protein expression levels were observed, while protein expression levels of e.g., MDR1 (2.3-fold) and BCRP (5.1-fold) were significantly higher in serum-free Caco-2 cultures.

Conclusions:
Our findings suggest that serum-free medium provides a viable alternative to FBS-based media for culturing Caco-2 cells, maintaining cell morphology, membrane integrity, and drug transport function. By avoiding the batch-to-batch variability associated with FBS, this approach potentially enhances reproducibility while simultaniously complying to the replace, reduce and refine (3Rs) principles in scientific research.

References:

Hubatsch, I., Ragnarsson, E., & Artursson, P. 2007. Determination of drug permeability and prediction of drug absorption in Caco-2 monolayers. Nature Protocols, 2(9), 2111–2119.

Rafnsdóttir, Ó.B, Weber, T., & Oredsson, S., et al., 2023. A new animal product-free defined medium for 2D and 3D culturing of normal and cancer cells to study cell proliferation and migration as well as dose response to chemical treatment. Toxicol. Rep. 10, 509–520.

P2 Pharmacokinetic modelling of long-acting subcutaneously injectable depot drug delivery system for sustained release of peptides

Mikael Boberg*, Monika Sundqvist, Sashi Gopaul, Johanna Laru and Bin Yang

DMPK, Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden, mikael.boberg@astrazeneca.com

Aim: The aim of this work was to describe the in vivo pharmacokinetics of a peptide drug in a series of long-acting injectable depot drug delivery systems based on 1) peptide fiber structures, 2) low molecular weight poly lactic-co-glycolic acid (LWPLGA) depot or 3) peptide fiber structures inside LWPLGA depot administered subcutaneously to rats using a pharmacokinetic modelling and simulation approach.

Methods: Pharmacokinetic modelling was done using Phoenix 8.4 (Certara, USA) to describe the in vivo absorption and pharmacokinetics of a peptide in the rat. In total three long-acting injectable depot drug delivery systems were modelled: 1) peptide fiber structures, 2) LWPLGA depot or 3) peptide fiber structures inside LWPLGA depot with pharmacokinetic data from the rat. Various types of pharmacokinetic models describing the extended in vivo release with, e.g., models including first-order absorption rate constant (K_a) with and without lag time or transit compartment models with parallel routes of absorption from the dosing compartment were assessed.

Results and discussion: The in vivo plasma pharmacokinetics after subcutaneous administration of peptide were best described by a two-compartment pharmacokinetic model. A transit compartment model described the extended drug release followed by K_a from the absorption compartment. The estimated bioavailability after subcutaneous dosing were 20%, 12% and 3% for peptide fiber structures, LWPLGA depot or peptide fiber structures inside LWPLGA depot, respectively. The K_a and transit compartment rates were estimated to 0.19 h^{-1} and 0.019 h^{-1} for peptide fiber structures, 0.057 h^{-1} and 0.0054 h^{-1} for LWPLGA formulations and 0.016 h^{-1} and 0.0037 h^{-1} for peptide fiber structures in LWPLGA depot. Overall, in vivo rat data demonstrated that peptide fibers extended the plasma exposure in the rat over two weeks with $t_{1/2}$ up to 35 h. The $t_{1/2}$ was further extended for peptide fibers inside a LWPLGA depot as $t_{1/2}$ was extended to approx. 100 h, consistent with a more promising long term release formulation profile.

Conclusions: The pharmacokinetic modelling and simulation approach gave estimates of pharmacokinetic parameters for a series of long-acting injectable depot drug delivery systems for peptide drugs. The structure of the pharmacokinetic model could be applied to describe other extended releases for similar drug delivery systems and could potentially guide decision-making regarding, for instance, what formulations to investigate and dose-selection in future in vivo studies for extended $t_{1/2}$ of peptides.

P3 Pharmacokinetic and pharmacodynamic (PK/PD) assessment of novel small molecule GLP-1R agonist AZD5004 in obese non-human primates

Boianelli A[1], Wallenius K[2], Pemberton J[3], Clemmensen N[3], Collén A[4], Baker D[2], Wang W[5], Van Zuydam NR[5], Jansson-Löfmark R[1], Lindmark B[1]

[1]DMPK, eCVRM, [2]Bioscience Metabolism, eCVRM, [3]Pharmaceutical Sciences, [4]Project leaders, eCVRM, [5]Discovery Sciences, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

Aim: AZD5004 is an oral small molecule (sm) glucagon like peptide-1 receptor agonist (GLP-1 RA) being developed for treatment of T2D and obesity. The specific aim of this study was to define the exposure levels of AZD5004 needed to potentiate glucose stimulated insulin secretion (GSIS) in obese, insulin resistant non-human primates (NHPs). This model has been shown to accurately predict the clinically efficacious exposures needed to achieve body weight lowering and HbA1c reductions for several sm GLP-1 RA competitors.

Methods: Twenty-two, male NHPs with a glucose disposal rate (Kg) below 2% and body weight >8kg were included in this study. AZD5004 was evaluated at 6 doses (5, 15, 33, 100, 160 and 330 µg/kg) over two i.v. glucose tolerance test (ivGTT) rounds separated by two weeks. Following placebo or GLP-1 RA administration, the animals received an i.v. glucose bolus (0.5 g/kg). Repeated blood samples were collected over 60 min for analysis of compound, glucose, and insulin concentrations. Total exposure was measure at 10 and 60 minutes. An Emax response model was applied to estimate the in vivo potency of AZD5004 based on insulin area under the curve (AUC) and average exposure corrected for plasma protein binding.

Results and discussion: AZD5004 potentiated GSIS at the four highest doses 33, 100, 160 and 330 µg/kg with the AUC change from baseline: 29998 ± 9221, 45067 ± 9406, 44721 ± 8586 and 37209 ± 10553 µU/mL*min, respectively, $P \leq 0.05$). The increased insulin AUCs in these four treatment groups were accompanied by increased glucose disposal rate (Kg % change from baseline: 0.31 ± 0.03, 0.52 ± 0.04, 0.52 ± 0.03, and 0.45 ± 0.04 % for the four doses, respectively, $P \leq 0.0001$). From PK/PD modelling of the insulin AUC and exposure data, an in vivo potency EC_{50}=22 pM was calculated. The PK/PD analysis also showed that low exposures (51-500 pM) drive the maximum insulin response.

Conclusions: In response to the ivGTT, AZD5004 showed a dose-dependent increase in the insulin AUC, and Kg in obese, dysmetabolic NHPs. PK/PD assessment of the ivGTT data suggests that AZD5004 has a good preclinical potency thus supporting further development.

P4 Towards predictive *in vitro* assays for *in vivo* peptide metabolism

Isabella Bonner Karlsson*, Anja Ekdahl, Anushka Neeraj Sharma, Dina Al Halibi, Ulrik Jurva
Drug Metabolism and Pharmacokinetics (DMPK), Research and Early Development Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; isabella.bonnerkarlsson@astrazeneca.com

Aim: Bioactive peptides are promising therapeutic agents due to their specificity in targeting diseases, yet their clinical utility is often hindered by their short plasma half-lives (Akbarian 2022). Improved understanding of biotransformation of peptides, leading to their degradation, could be used to develop peptides with longer half-life and thus improved clinical success (Yao 2018). This study aimed to elucidate the biotransformation pathways of bioactive peptides using *in vitro* models of hepatocytes and kidney S9 fractions from human and rat, addressing the need for reliable *in vitro* systems in assessing the metabolic stability and identifying metabolites of therapeutic peptides.

Methods: Metabolism of publicly available peptides with reported human *in vivo* metabolic patterns was investigated in hepatocytes and kidney S9 fractions from human and rat. Liquid chromatography-high resolution mass spectrometry and tandem-mass spectrometry were used for sample analysis. WebMetaBase/ONIRO (Mass Analytica) was used to process the data. The software utilized a database of common Phase I and II metabolic transitions to identify both expected and potential unexpected metabolites within a specified mass defect filtering region. The identification process relied on the accurate mass of the molecular ion and the observed fragmentation patterns, including both fragments matching the parent compound and predicted b and y fragments. Generated metabolic profiles were compared with *in vivo* data from literature sources.

Results and discussion: The study revealed strong correlations between *in vitro*-generated metabolite profiles and human *in vivo* data for several peptides, indicating that the combined information from *in vitro* assessment of metabolism in hepatocytes and kidney S9 fractions reflect *in vivo* metabolic pathways. However, exceptions were observed, highlighting the complexity of peptide metabolism.

Conclusion: These findings suggest that assessments using liver and kidney models can aid in predicting peptide metabolic pathways relevant to *in vivo* conditions, thus providing valuable insights for early drug discovery stages.

References:

Akbarian M., Khani A., Eghbalpour S., Uversky V.N., 2022. Bioactive Peptides: Synthesis, Sources, Applications, and Proposed Mechanisms of Action. Int. J. Mol. Sci. 23, 1445.

Yao J.F., Yang H., Zhao Y.Z., Xue M., 2018. Metabolism of Peptide Drugs and Strategies to Improve their Metabolic Stability. Curr. Drug Metab. 19, 892-901.

P5 Translational Aspects of Oxycodone Brain Delivery via the Proton-Coupled Organic Cation (H^+/OC) Antiporter in Rats and Pigs

Frida Bällgren*, Tilda Bergfast, Aghavni Ginosyan, Jessica Mahajan, Miklós Lipcsey, Margareta Hammarlund-Udenaes, Stina Syvänen and Irena Loryan
Biomedicinskt Centrum, Husargatan 3, 751 23 Uppsala, frida.ballgren@farmaci.uu.se

Oxycodone has been shown to undergo active uptake at the blood-brain barrier (BBB) in rats, with an unbound brain-to-blood partition coefficient ($K_{p,uu,brain}$) of 3[1], linked to the proton-coupled organic cation (H^+/OC) antiporter. However, the extent of brain uptake and preservation of the antiporter system in higher species remains unclear. Species differences in other BBB transporters such as P-glycoprotein have previously been reported[2]. Also, previously observed sex differences in oxycodone pharmacokinetics (PK) and pharmacodynamics (PD), in humans[3] and rats[4], suggest a potential role of antiporter. **Aim:** Evaluate the inter-species translation and sex differences in oxycodone transport at the BBB. **Methods:** Microdialysis was used to obtain unbound oxycodone concentrations in brain interstitial fluid (ISF) and the bloodstream in Sprague-Dawley rats and Swedish landrace pigs of both sexes. Oxycodone-D3 was used as a calibrator for probe recovery. Oxycodone was administered intravenously with infusion rates selected to achieve clinically relevant plasma concentrations. Samples were analyzed by UPLC-MS/MS. **Results and discussion:** Active uptake of oxycodone was present at the BBB in both species, with a $K_{p,uu,brain}$ of 2.5±0.7 (n=6) in pigs and 4.4±1.0 (n=17) in rats. The extent of brain delivery was lower in pigs than in rats (p=0.0002). There was no sex difference in $K_{p,uu,brain}$ with values of 4.2±1.2 (n=7) in female and 4.6±0.9 (n=10) in male rats (p=0.77), and 2.5±0.8 (n=4) in female and 2.5 and 2.3 (n=2) in male pigs. Our findings suggest active uptake of oxycodone at the BBB with species-related variability in the antiporter function and/or expression level. Previously reported sex differences in oxycodone PK/PD cannot be explained by differences in extent of BBB transport. **Conclusions:** Our findings support the hypothesis of a preserved antiporter system across species, highlighting its potential as a target for enhanced brain drug delivery.

References: [1]Boström E, Simonsson US, Hammarlund-Udenaes M, 2006. In vivo blood-brain barrier transport of oxycodone in the rat: indications for active influx and implications for pharmacokinetics/pharmacodynamics. Drug Metab Dispos. 34,1624-31.[2]Syvänen S, Lindhe O, Palner M, Kornum BR, Rahman O, Långström B, et al., 2009. Species differences in blood-brain barrier transport of three positron emission tomography radioligands with emphasis on P-glycoprotein transport. Drug Metab Dispos. 37, 635-43. [3]Kaiko RF, Benziger DP, Fitzmartin RD, Burke BE, Reder RF, Goldenheim PD, 1996. Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. Clin Pharmacol Ther. 59, 52–61. [4]Chan S, Edwards SR, Wyse BD, Smith MT, 2008. Sex diferences in the pharmacokinetics, oxidative metabolism and oral bioavailability of oxycodone in the Sprague-Dawley rat. Clin Exp Pharmacol Physiol. 35, 295–302.

P6

CombiCTx: Screening diffusion gradients of anti-cancer drug combinations

Christina Stelzl[1, 2], Ada Lerma-Clavero[1], Selina Camenisch [1, 2], Benoit Simon[1, 2], Olle Eriksson[1, 2], Oliver Degerstedt[3], Hans Lennernäs[3], Femke Heindryckx[1], Johan Kreuger[1, 2] and Paul O'Callaghan[1, 2*]

*Presenting author: paul.ocallaghan@mcb.uu.se
[1]Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden
[2]The Science for Life Laboratory, Uppsala University, Uppsala, Sweden
[3]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Aim: To develop a novel combinatorial chemotherapeutic (CTx) drug screening assay, CombiCTx.

Methods: We reconfigured a device developed for antibiotic interaction testing (Fatsis-Kavalopoulos et al., 2020), as an anti-cancer drug screening assay. The CombiCTx device consists of three hydrogel reservoirs in which anti-cancer drugs of interest are loaded. The device is inserted into a cell culture dish containing hydrogel-covered cancer cells. Cells are exposed to dynamic concentration gradients of anti-cancer drugs that form across the entire assay area. To visualise these gradients, we imaged doxorubicin diffusion from CombiCTx reservoirs. An imaging protocol to quantify MDA-MB-231 breast cancer cell death along diffusion gradients of staurosporine was established, and was applied to study the combined effect of the chemotherapeutics navitoclax and gemcitabine on cancer cell death (Jaaks et al., 2022).

Results and discussion: Time-lapse microscopy of doxorubicin fluorescence revealed that overlapping dynamic gradients were successfully formed between CombiCTx drug reservoirs, and the proposed imaging protocol permitted quantification of cancer cell death along staurosporine diffusion gradients. Limited effects of drug synergies were observed for the navitoclax and gemcitabine combinations, which was in part attributed to limited navitoclax diffusion.

Conclusions: The CombiCTx assay permits screening of effective chemotherapeutic combinations along dynamic gradients within 3D hydrogels, which can be selected to mimic extracellular matrices (ECM) of interest. CombiCTx incorporates the 3D reality of the ECM and reveals how differences in drug diffusion properties may impact the effect of drug combinations. This in combination with classic 2D cell assays can provide valuable additional information about potential drug synergies.

References:

Fatsis-Kavalopoulos, N., Roemhild, R., Tang, P.-C., Kreuger, J., Andersson, D.I., 2020. CombiANT: Antibiotic interaction testing made easy. PLOS Biology 18, e3000856.
Jaaks, P., Coker, E.A., Vis, D.J., Edwards, O., Carpenter, E.F., et al., 2022. Effective drug combinations in breast, colon and pancreatic cancer cells. Nature 603, 166-173.

P7 The dose-dependent plasma exposure in rat in vivo of two proteolysis targeting chimeras (PROTACs)

Janis Niessen, Hans Lennernäs, Mikael Hedeland, Markus Sjöblom, Ilse Dubbelboer, Thomas Borchardt[a], Mirko Koziolek[b], Anura Indulkar[a], David Dahlgren*

*Department of Pharmaceutical Bioscience, Translational Drug Discovery and Development, Uppsala University, david.dahlgren@uu.se. [a]AbbVie Inc., North Chicago, IL, USA. [b]AbbVie Deutschland GmbH & Co. Ludwigshafen, Germany

Aim: PROTACs exhibit a unique and promising pharmacology (1). However, this comes with molecular properties exceeding the 'drug-like' Ro5 chemical space, which often limits oral absorption due to solubility/dissolution and/or permeability limitations (2). This study aimed to investigate the dose-dependent intestinal absorption and bioavailability in rat of two model PROTACS, ARV-110 (812 Da, LogP 3.6) and ARV-471 (724 Da, LogP 5.9).

Methods: Intestinal absorption/bioavailability of the two PROTACs was determined from plasma drug exposure during 6 h (AUC_{6h}) after iv dosing, compared to after an intra-duodenal administration at doses of 0.04, 0.2, and 1 mg/kg for ARV110, and 0.2, 1.0, 2.5, and 5 mg/kg for ARV-471. The particle size was also determined for both PROTACs at all doses using dynamic light (DLS) scattering. The PROTACs were formulated with 10% DMSO + 90% Phosphate buffer:0.05% TPGS.

Results and discussion: The AUC_{6h} of ARV110 increased from 4.3 to 23.8 ng/mL*h when the dose increased from 0.04 to 0.2 mg/kg, while no difference in exposure was observed between the 0.2 and 1.0 mg/kg doses. For ARV471 on the other hand, the AUC_{6h} increased almost linearly with all doses, from 18.5 ng/mL*h at 0.2 mg/kg to 285.8 ng/mL*h at 2.5 mg/kg. It was evident from the DLS measurements that the increase in particle size with dose for both drugs only affected the bioavailability of ARV-110, suggesting that precipitates for ARV-110 has a lower tendency to redissolve than for ARV-471. Formulation development for these two PROTACs should therefore focus on different approaches, where dissolution enhancing technologies may be more successful for ARV-110, while permeation enhancers may be a more suitable for ARV-471.

Conclusion: The intestinal absorption in rat of ARV-110 seems to be solubility/dissolution rate limiting while ARV-471 seems to be permeability rate limiting.

References:

(1) M. Békés, D. R. Langley, and C. M. Crews, 2022. PROTAC targeted protein degraders: the past is prologue. *Nature Reviews Drug Discovery*, vol. 21, no. 3. 181–200.

(2) Scott D. Edmondson, Bin Yang, Charlene Fallan, 2019. Proteolysis targeting chimeras (PROTACs) in 'beyond rule-of-five' chemical space: Recent progress and future challenges. *Bioorganic & Medicinal Chemistry Letters*, vol 29, issue 13, 1555-1564.

P8 Gastrointestinal transit times and accompanying hormone changes in healthy volunteers

Ilse R. Dubbelboer*[1], Dominic-Luc Webb[2], Hans Lennernäs[1], Per M. Hellström[2]
* ilse.dubbelboer@uu.se
[1] Department of Pharmaceutical Biosciences, Uppsala University
[2] Department of Medical Sciences, Uppsala University, Sweden

Aim: A large proportion of the global population is affected by disturbances of gastric, intestinal and colonic motor and sensory functions, such as gastroparesis, functional dyspepsia, diabetes, and/or obesity (*Al-Saffar A et al 2029*). This severely impacts and impairs quality of life and causes profound health-care costs *(Andreasson et al., 2021; International Working Group for Disorders of Gastrointestinal Motility and Function et al., 2018*). Baseline *in vivo* data on the healthy gut is essential to understand disease in an affected population. In addition, it is key to better understand how oral drug delivery should be optimized.

Methods: Healthy adults ingested a 260 kcal mixed meal followed by wireless motility gastrointestinal (GI) capsule (WMC) tests, which records luminal pH, temperature and pressure (*Diaz Tartera et al., 2017*). Blood samples were collected up to 4 hours post meal, to determine endocrinological profiles of metabolic and gut hormones. Food intake was permitted again 6 hours after the first meal.

Results and discussion: Regional transit data were obtained for gastric emptying time (GET), small (SBTT) and large bowel (LBTT), and whole gut transit time (WGTT). These transit times varied greatly in this healthy population. Endocrinological profiles of ten metabolic and gut hormones were analysed. A clear food effect was noticeable for GIP, GLP-1, glucose, glucagon, and insulin, despite the high variability.

Conclusions: Data will be further analysed with other methods such as machine learning, for enhanced understanding of patterns in and relations between the data of these healthy individuals.

References:

Andreasson, A., et al, 2021. An Increasing Incidence of Upper Gastrointestinal Disorders Over 23 Years: A Prospective Population-Based Study in Sweden. Am. J. Gastroenterol. 116, 210–213. https://doi.org/10.14309/ajg.0000000000000972

Diaz Tartera, H.O., et al, 2017. Validation of SmartPill ® wireless motility capsule for gastrointestinal transit time: Intra-subject variability, software accuracy and comparison with video capsule endoscopy. Neurogastroenterol. Motil. 29, 1–9. https://doi.org/10.1111/nmo.13107

International Working Group for Disorders of Gastrointestinal Motility and Function, 2018. Advances in the diagnosis and classification of gastric and intestinal motility disorders. Nat. Rev. Gastroenterol. Hepatol. 15, 291–308. https://doi.org/10.1038/nrgastro.2018.7

Al-Saffar A, Lennernäs H, Hellström PM. Gastroparesis, metoclopramide, and tardive dyskinesia: Risk revisited. Neurogastroenterol Motil. 2019 Nov;31(11):e13617. doi: 10.1111/nmo.13617. Epub 2019 May 2. PMID: 31050085.

Model-based meta-analysis to support dose selection and clinical trial design of ANGPTL3 reducing drugs

Authors: Helena Edlund[1], Theresa Crockett[2], Angelica Quartino[1].

1. Clinical Pharmacology & Quantitative Pharmacology CVRM, Clinical Pharmacology and Safety Sciences, AstraZeneca R&D, Gothenburg, Sweden. 2. Clinical Pharmacology & Quantitative Pharmacology CVRM, Clinical Pharmacology and Safety Sciences, AstraZeneca R&D, Gaithersburg, USA.

Aim: ANGPTL3, a protein predominantly produced by hepatocytes, inhibits lipoprotein lipase and endothelial lipase, and thus influence lipoprotein metabolism. Understanding the reduction of ANGPTL3 and its relationship to downstream lipid biomarkers is crucial in evaluating its potential as a therapeutic target for dyslipidaemia. This analysis aimed to assess the impact of ANGPTL3 targeting oligonucleotides on the reduction of ANGPTL3 protein in plasma and establish its relationship to downstream lipid biomarkers (TG, LDL-C and ApoB).

Methods: A model-based meta-analysis (MBMA) was performed on publicly available clinical data from trials involving ANGPTL3 targeting oligonucleotides [1-9]. A K-PD model [10] was developed to describe ANGPTL3 concentrations, and these parameters were then used to drive the response of the downstream biomarkers TG and LDL-C. ApoB levels were estimated from model-predicted TG and LDL-C concentrations using a previously established formula [11]. The developed models were then used in clinical trial simulations to compare results across treatments and study populations, representing healthy subjects, mixed dyslipidaemia, severe hypertriglyceridemia (HTG), and homozygous familiar hypercholesteremia (HoFH).

Results and Discussion: The developed models effectively captured the longitudinal response in ANGPTL3 and its impact on TG, LDL-C, and ApoB. The placebo response was negligible across all variables. Although patient population influenced baseline ANGPTL3 concentration, the response to ANGPTL3 reduction was consistent across populations. Dose-response curves for ANGPTL3 reduction were similar across treatments and approached a plateau at reductions beyond 75%. The downstream biomarker response varied depending on the patient population, with higher baseline concentrations leading to larger reductions at the same ANGPTL3 reduction. However, all populations approached normal biomarker concentrations at maximal ANGPTL3 reduction (~90%; ~15 ng/mL).

Conclusions: This comprehensive MBMA effectively characterizes the longitudinal ANGPTL3, TG, LDL-C, and ApoB data, providing insights across dose levels, study populations, and study phases. The enhanced understanding will be instrumental to optimize dose selection and clinical trial designs as well as accelerate the development of novel ANGPTL3 therapies in various dyslipidaemia indications.

References:

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P10 Impact of paclitaxel formulations on its transport across CNS and PNS barriers: link to chemotherapy-induced peripheral neuropathy development

Milda Girdenytė[1,2,*], Yang Hu[1,3], Aghavni Ginosyan[1], Margareta Hammarlund-Udenaes[1] and Irena Loryan[1]

[1] Translational Pharmacokinetics/Pharmacodynamics Group, Department of Pharmacy, Faculty of Pharmacy, Uppsala University, Box 580, SE-751 23, Uppsala, Sweden

[2] Pharmacy and Pharmacology Center, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, M.K. Čiurlionio, Str. 21/27, LT-03101 Vilnius, Lithuania

[3] Current affiliation: Non-clinical Safety & DMPK, BioNTech SE, Mainz, Germany

*** Corresponding author: milda.girdenyte@farmaci.uu.se (Milda Girdenytė)**

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse event observed in patients receiving paclitaxel formulated in polyethylated castor oil with ethanol (CreEL-PTX), in albumin-bound nanoparticles (nab-PTX) or in XR17 micelles (micellar-PTX). Clinical studies and meta-analysis suggest a higher incidence rate of CIPN in nab- and micellar-PTX treatment groups than CreEL-PTX. Hence, this study aimed to examine the formulation impact on paclitaxel's distribution to CIPN-sites in the central nervous (CNS; brain, spinal cord) and peripheral nervous (PNS; sciatic nerve, dorsal root ganglia (DRG)) systems as well as skeletal muscle, by evaluating the extent of transport across blood-tissue barriers using the unbound drug partition coefficient, $K_{p,uu,tissue}$.

Methods: *In vivo* studies were performed as 4-hour infusions of 4 mg/kg CreEL-PTX (N=8), 4 mg/kg nab-PTX (n=7) or 1 mg/kg micellar-PTX (n=6) rats. At the end of infusion plasma and terminal samples of CNS, PNS tissues, and skeletal muscle were collected and analyzed using UPLC-MS/MS. $K_{p,uu,tissue}$ were calculated using the CMA-CIPN, i.e., Combinatory Mapping Approach for CIPN with correction of plasma protein binding and tissue uptake (1). Data are presented as mean ± SD.

Results: Total paclitaxel plasma concentrations at steady-state were 369 ± 124 ng/mL, 83 ± 17 ng/mL and 43 ± 22 ng/mL in the CreEL-PTX, nab-PTX and micellar-PTX groups, respectively. The extent of paclitaxel distribution was lowest across the CNS barriers, with mean $K_{p,uu,Br}$ of 0.006 and $K_{p,uu,SC}$ of 0.004, compared to the PNS barriers with mean $K_{p,uu,SN}$ of 0.89 and $K_{p,uu,DRG}$ of 0.27, all determined in the CreEL-PTX group. At least a 2-fold significantly higher extent of paclitaxel distribution across all investigated barriers was observed after nab- and micellar-PTX compared to CreEL-PTX, while the net flux of unbound paclitaxel across all barriers was similar between nab- and micellar-PTX.

Conclusion: Our preclinical study shows that nab- and micellar-PTX formulations have significantly higher unbound tissue-to-plasma concentration ratios than CreEL-PTX in all investigated tissues, which could be influenced by the excipients present in the formulations. This might explain higher incidence rates of CIPN in patients receiving nab-PTX and micellar-PTX formulations.

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P11 17th Symposium on Pharmacokinetics and Drug Metabolism
Abstract- Oral: Pharmacokinetic and pharmacodynamic considerations in rare disease and special populations

Title: Leveraging Pharmacometrics and Natural History Studies to Enhance Trial-Readiness in Rare Diseases: The case of rare and ultra-rare neurodegenerative cerebellar ataxias

Authors: Alzahra Hamdan (1), Niels Hendrickx (2), Andrew C. Hooker (1), Xiaomei Chen (1), Emmanuelle Comets (2,3), Andreas Traschütz (4,5), Rebecca Schüle (4,6), ARCA Study Group, EVIDENCE-RND consortium, France Mentré (2), Matthis Synofzik (4,5), Mats O. Karlsson (1)

Institutions: (1) Pharmacometrics Research Group, Department of Pharmacy, Uppsala University, Uppsala, Sweden (2) Université Paris Cité, IAME, Inserm, F-75018, Paris, France (3) Univ Rennes, Inserm, EHESP, Irset - UMR_S 1085, 35000, Rennes, France (4) Department of Neurodegenerative Diseases, Center for Neurology and Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany (5) German Center for Neurodegenerative Diseases (DZNE) Tübingen, 72076 Tübingen, Germany (6) Division of Neurodegenerative Diseases, Department of Neurology, Heidelberg University Hospital, Germany

Background and objectives: Degenerative cerebellar ataxias is a heterogenous group of rare and ultra-rare genetic diseases that mainly affect the cerebellum and its associated tracts (1). While disease-modifying therapies are now on the horizon targeting an increasing number of genetic ataxias (2), a reliable Clinical Outcome Assessment (COA) as well as robust trial designs and analysis methods are lacking. The Scale for the Assessment and Rating of Ataxia (SARA) is by far the most widely used COA for assessing the severity and progression of cerebellar ataxias (3). To better inform ataxia trials, we applied pharmacometric methods and Item Response Theory (IRT) methodology; an important tool that is increasingly used to assess clinical outcome assessments data on the item level (4), to (i) evaluate the adequacy of SARA and its items for assessing the underlying ataxia severity, and (ii) to evaluate the natural history progression of several genetic ataxias.

Methods: A unidimensional IRT model was built to analyze SARA items data taken from the Autosomal Recessive Cerebellar Ataxias (ARCA) registry database (5), which comprises 990 patients with a total of 1932 visits (1 to 9 visits/patient), and mostly from a total of 115 defined genetic diagnoses. Item characteristic functions were used to model the relationship between the probability of a particular item response and the underlying individual's latent variable; *i.e.,* ataxia severity. Such functions allow to capture the properties of SARA items, and their informativeness in assessing the ataxia severity. A longitudinal component was then added to the IRT model to assess the natural history progression of the overall ARCA cohort as well as the 10 most common genotypes. Clinical trial simulations were performed to evaluate the impact of different design factors and analysis scenarios on sample sizes needed to detect treatment effects in two ARCA subpopulations as showcases; the Autosomal-Recessive Spastic Ataxia Charlevoix Saguenay (ARSACS) and Polymerase Gamma (POLG) ataxia.

Results and discussion: A unidimensional IRT model was successfully established, indicating that SARA capture one single latent variable representing the ataxia severity. All items had high discrimination as well as high informativeness indicating the ability of SARA to distinguish between patients with different disease status and the adequacy of all items. The longitudinal IRT models were able to describe the changes in the latent variable as a function of time since ataxia onset for both the overall ARCA cohort and the 10 most common genotypes. The progression rates varied between high in POLG and very low in COQ8A gene-related ataxia (~0.98 and 0.003, respectively, SARA points/year at SARA=20). 32 parallel, placebo-controlled (1:1) clinical trial scenarios were simulated for each genotype; the ARSACS and POLG with different trial durations (2- and 5-years), inclusion criteria (0-10, 10-20, 20-30, and 0-30 ataxia duration) and hypothetical treatment effects (0%, 30%, 50% and

100%). Smaller sample sizes were needed in case of faster progression (POLG vs. ARSACS), longer trials (7-10 folds larger with 2-year vs. 5-year) and larger drug effects (~3-5 folds larger with 50% vs. 100% inhibition). Among various analysis methods (including linear and 4-parameters logistic total score models, and IRT-informed total score model) the longitudinal IRT model had the largest power with a well-controlled type I error. Other analysis models had inflated type I error due to model misspecifications.

Conclusions: The established Pharmacometric IRT framework provides an evidence of the adequacy of SARA as a COA for ataxia, and allows for an efficient utilization of natural history data to define the disease progression of genetic ataxias. This will ultimately facilitate planning for treatment trials (design and analysis) in rare and ultra-rare genetic ataxias.

Acknowledgment: This work was supported by the European Joint Programme on Rare Diseases (EJP RD) Joint Transnational Call 2019 for the EJP RD WP20 Innovation Statistics consortium “EVIDENCE-RND”. Moreover, work in this project was supported by the Clinician Scientist programme "PRECISE.net" funded by the Else Kröner-Fresenius-Stiftung. This work was also financially supported by the Swedish Research Council Grant 2018-03317 (to M.O.K.). The computations of models were enabled by resources provided by the National Academic Infrastructure for Supercomputing in Sweden (NAISS) and the Swedish National Infrastructure for Computing (SNIC) at UPPMAX, partially funded by the Swedish Research Council through grant agreements no. 2022-06725 and no. 2018-05973.

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P12 Cross-Species Comparison of In-Vitro Metabolite Profiles in Fresh Whole Blood: Methodological Insights and Challenges

Myriam Hislen*, Lucia Kovac, Marie Wiik
OT Chemistry, Virdings allé 32 b, 75329 Uppsala; myriam.hislen@recipharm.com

Aim:

In-vitro metabolism studies are crucial for understanding drug candidate processing across species, informing safety and efficacy. This study compared the metabolism of Compound 1 in fresh whole blood from mouse, rabbit, dog, and human. Metabolites were characterized via LC-MS based on molecular formula, revealing key inter-species differences in metabolite formation.

Methods:

Blank blood from mouse, rabbit, dog, and human was spiked with Compound 1, after a 30-minute equilibration at 37°C. Samples were collected at 0, 30 min, 1, 3, and 6 hours, precipitated with 0.1% FA in ACN, and centrifuged. Supernatants were analysed using UPLC-MS/MS. Chromatographic analysis was performed on an Agilent 1290 HPLC with an ACE 3 AQ column (3 µm, 2.1 x 150 mm) using a gradient of 0-95% methanol over 20 minutes. Mass spectrometry was conducted on an Agilent 6550 Q-ToF in ESI+ mode, with a mass range of 100-1700 Da and data processed in Agilent Mass Hunter.

Results and discussion:

Whole blood in-vitro models face challenges due to limited enzyme diversity, focusing mainly on circulating metabolites rather than those formed in complex systems like liver microsomes. For Compound 1, which is intravenously administered and primarily metabolized in the blood, in-vitro models provide qualitative insights but may not fully mirror in-vivo outcomes. According to FDA guidance, these models are essential for identifying metabolites missing in animals potentially selected for toxicology studies, emphasizing the need for inter-species comparisons in drug development.

Species-specific differences were noted: certain metabolites were absent in mouse but present in others, while some were more abundant in mouse and rabbit. Compound 1 remained stable in dog and human but degraded rapidly in mouse and rabbit, with dog and human showing the most similar profiles.

Conclusions:

Significant inter-species variability in metabolite profiles underscores the importance of species-specific metabolic studies to improve the predictability of human pharmacokinetics. Insights from these comparisons can guide species selection in preclinical studies, enhancing safety and efficacy evaluations of drug candidates in humans.

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P13 Animal product-free culture conditions for 3D primary human hepatocyte spheroids improve long-term viability and CYP dependent drug metabolism

Evgeniya Mickols[1*], Lazaros Primpas[1], Stina Oredsson[2], Maria Karlgren[1]
[1]*Department of Pharmacy, Uppsala University, Uppsala, Sweden*
[2] *Lund University Cancer Centre, Lund, Sweden*
Department of Pharmacy, Uppsala University, Box580, 75123 Uppsala, evgeniya.mickols@farmaci.uu.se

Aim

3D cultures of primary human hepatocytes (3D PHH) are successfully used to reduce and replace the use of animal experiments in biomedical research. Yet, the initial formation of 3D PHH is highly dependent on the supplementation with fetal bovine serum (FBS). The use of FBS does not adhere to the Replacement, Refinement, and Reduction (3Rs) of animal experiments. In addition, the molecular composition of FBS and its´ effects on cultured cells are poorly understood and FBS is also prone to batch-to-batch variation and risk for immunogenic effects. Here, we aim to fully replace FBS with animal-free substitutes for 3D PHH cultures.

Method

We combined a previously developed animal-free FBS substitute developed by Rafnsdóttir et al. with the normological chemically defined culture medium developed in our laboratory for 3D PHH cultures. (Handin et al., 2021; Rafnsdóttir et al., 2023) 3D PHH were cultured for three weeks and the culture performance was assessed using morphological scoring, viability and CYP metabolism measurements, as well as global proteomics analysis.

Results and discussion

Morphological and viability evaluations demonstrated that 3D PHH formed in serum-free medium are as good as regular FBS-formed *in vitro* models, and sometimes even supersede the FBS-formed spheroids, with regard to the viability and functional performance of cytochromes P450s. Global proteomics analysis detected no significant change in the 3D PHH proteome fingerprint upon the transition to a fully serum-free culture protocol. In addition, we demonstrate stable expression of drug-metabolizing enzymes and transporters mentioned in IHC M12 guidelines.

Conclusion

Here, we exemplify how a fully chemically defined and 3R-compliant cell culture medium simplifies the interpretation of research results. We hope our study will contribute to more informed and eventually more harmonized protocols for 3D PHH cultures, as well as pave the way to serum-free primary human cultures.

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P14 Revealing the intracellular concentration of nucleic-acid based therapeutics using NanoSIMS

Michael Kurczy

Drug Metabolism and Pharmacokinetics, Research and Early Development, Cardiovascular, Renal and Metabolism CVRM, BioPharmaceuticals R&D, AstraZeneca, 43183 Gothenburg, Sweden

Aim: We set out to establish a robust NanoSIMS approach to quantify drug molecules in intracellular compartments following endocytosis, and to relate these concentrations to functional gene knockdown in in-vitro models, with the goal to understand the relationship between incubation concentration, intracellular drug uptake and knock-down.

Methods: Using well characterized models and standards it is possible to extract a concentration from the subcellular environment using NanoSIMS. We took a material research approach to deconstruct the typical biological sample for NanoSIMS. From this first principle we determined the relationship between the concentration of a ^{13}C labeled compound and the signal measured using the NanoSIMS. We validated this relationship using the well characterized dopamine containing secretory vesicles from PC12 cells finding good agreement when we compared our results to measurements done *in vitro*.

Results and discussion: The sensitivity of ^{13}C labeling was found to have limited use for nucleic acid-based therapeutics and thus we expanded the system to other labeling strategies, (^{34}S, & Iodine) which required the development of novel calibration standards. The availability of multiple labels additionally offered the opportunity to track more than one moiety simultaneously. The Iodine labeling strategy was validated using ^{13}C labeled amiodarone, where the concentration found using the Iodine standard was confirmed by the concentration measured using the ^{13}C method. Similarly, the ^{34}S method was validated against iodine-labelled drugs, using antisense oligonucleotides measured in human hepatocytes. Applying the obtained calibration standards, different ^{34}S- or iodine labelled ON-drugs have been quantified in subcellular structures of human hepatocytes, and the results show that the intracellular concentration is decoupled from the *in vitro* incubation concentration.

Conclusions: We have shown that we can measure the absolute concentration of nucleic acid-based therapeutics in what is generally considered to be the endosomal space. In this field there is a consensus the essentially all (~99%) of the nucleic acid-based therapeutic that enters the cell is trapped in the endosomal space, thus this amount of material is fundamental to the interpretation of downstream events such as endosomal escape and gene silencing. Gene silencing *in vitro* is measured with respect to incubation concentration. This value is fundamentally decoupled from cellular uptake therefore does not provide mechanistic insight. We propose that the intracellular concentration is a key parameter which needs to be considered when the efficacy of a nucleic acid-therapeutic being evaluated. It will serve to remove the ambiguity that arises from the convoluted relationship between exposure and cellular uptake.

Pharmacokinetics, pharmacodynamics and safety of tezepelumab in children with asthma

Anna Lundahl,[1] Jonathan Grigg,[2] Gillian Hunter,[3] Beata Pawlikowska,[4] Cecil Chen,[5] Jacob Leander,[1] Michael Levin,[6] Atul Gupta,[7] James Paton,[8] Katharine C Pike,[9] Lubna Abuqayyas,[10] Mickel Latchman[11] and Stephanie L Roseti[12]

[1]Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Gothenburg, Sweden; [2]Centre for Genomics and Child Health, Blizard Institute, Queen Mary University of London, London, UK; [3]Biometrics, Late-stage Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK; [4]Late-stage Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Warsaw, Poland; [5]Clinical Pharmacology and Safety Sciences, BioPharmaceuticals R&D, AstraZeneca, South San Francisco, CA, USA; [6]Division of Paediatric Allergology, University of Cape Town, Cape Town, South Africa; [7]Department of Paediatric Respiratory Medicine, King's College Hospital, London, UK; [8]School of Medicine, College of Medical, Veterinary & Life Sciences, University of Glasgow, Glasgow, UK; [9]Department of Paediatric Respiratory Medicine, Bristol Royal Hospital for Children, Bristol, UK; [10]Clinical Pharmacology, Modeling and Simulation, Amgen, Cambridge, MA, USA; [11]Global Medicine Development, Study Management and Operations, AstraZeneca, Mississauga, ON, Canada; [12]Late-stage Development, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA

Presenting author: Anna Lundahl

Character limit: 1809 / 1810 (**including** characters and spaces in the abstract title and **277 characters** for the figure)

Figure/table: 1/1

Background: Tezepelumab is approved for the treatment of patients aged ≥12 years with severe asthma.

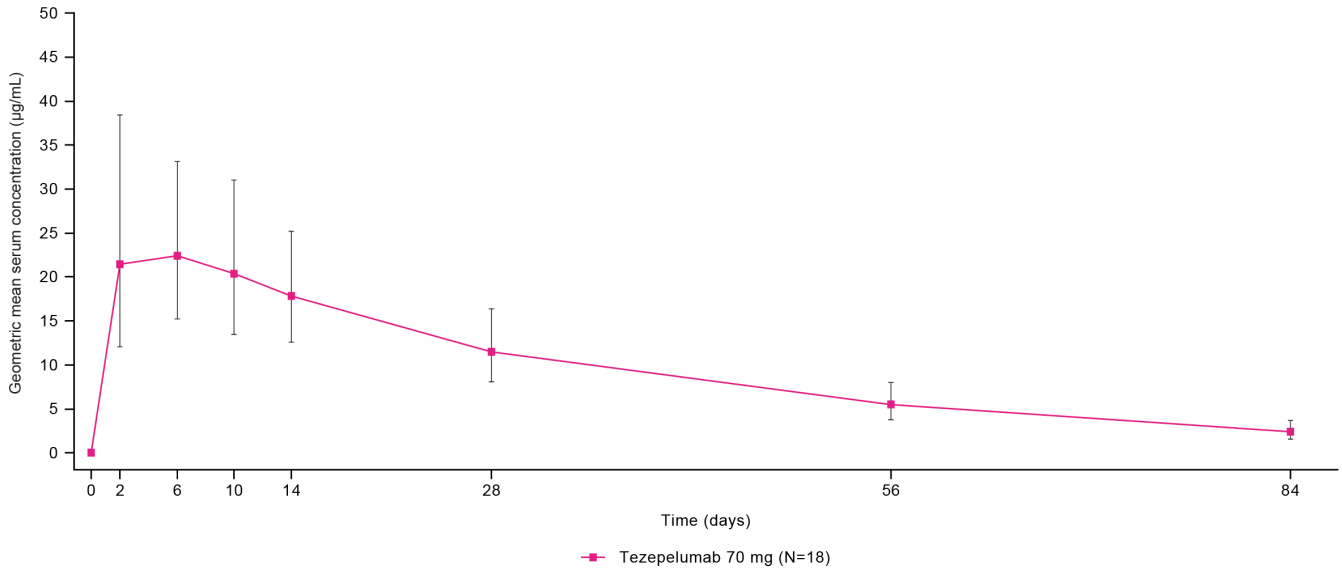
Objective: TRAILHEAD (NCT04673630) evaluated the pharmacokinetics (PK), pharmacodynamics (PD) and safety of tezepelumab in children with asthma.

Methods: TRAILHEAD was a phase 1, multicentre, open-label study in children (5–11 years) with mild, moderate or severe asthma requiring daily controller medication use. PK (primary outcome), PD (exploratory outcome) and safety were evaluated for up to 85 days after a single subcutaneous dose of tezepelumab 70 mg.

Results: Of 23 children enrolled, 18 received treatment and completed the study (median age, 8 years; 61% male). Max geometric mean serum concentration of tezepelumab (24.6 µg/mL) was observed at a median time of 3.5 days post dose, followed by exponential decline with a mean terminal half-life of 25.7 days (**Figure**). Mean area under the concentration–time curve was 974 µg*day/mL. Changes in biomarkers from baseline (blood eosinophil count, serum total IgE and FeNO) reflected the expected PD effects of tezepelumab. Seven patients (39%) reported adverse events; all were mild or moderate intensity and considered by the investigator to be unrelated to treatment.

Conclusion: The PK, PD and safety after a single 70 mg dose of tezepelumab in children were as expected from previous studies in other age groups, supporting further development of tezepelumab for children with asthma.

Figure. Geometric mean serum concentration of tezepelumab over time



The vertical lines represent the geometric mean / gSD and the geometric mean * gSD.
Geometric mean / gSD: $\exp(\text{mean}[\log_{\text{PK concentration}}]) / \exp(\text{std}[\log_{\text{PK concentration}}])$.
Geometric mean * gSD: $\exp(\text{mean}[\log_{\text{PK concentration}}]) * \exp(\text{std}[\log_{\text{PK concentration}}])$.
exp, natural exponential function; gSD, geometric standard deviation; PK, pharmacokinetic; std, standard deviation.

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Disclosures

Anna Lundahl, Gillian Hunter, Beata Pawlikowska, Cecil Chen, Jacob Leander, Mickel Latchman and Stephanie L Roseti are employees of AstraZeneca and may own stock or stock options in AstraZeneca. Jonathan Grigg has received speaker/advisory board fees from AstraZeneca, OM Pharma, Omron and Sanofi; and has received grants from Mariomed and OM Pharma. Michael Levin has received speaker/advisory board fees from Abbvie, Bayer, Cipla, ECN, Glenmark Pharmaceuticals, Organon, Pharmadynamics and Sanofi; and has received grants from AstraZeneca, Novartis and Sanofi. Atul Gupta has received consultancy fees for Aerogen, AstraZeneca, Boehringer Ingelheim Ltd, GSK and Novartis. James Paton has no disclosures. Katharine C Pike has received speaker/advisory board

fees from Adherium, Novartis and Sanofi; and has received grants from AstraZeneca. Lubna Abuqayyas is an employee of Amgen and may own stock in Amgen.

This abstract was previously presented at the European Respiratory Society (ERS) Congress, 7–11 September 2024, Vienna, Austria.

P16 Exploring the discrepancies between clinical trials and real-world data: a small-cell lung cancer time-to-event study

Authors: Luca Marzano*, Adam S. Darwich, Asaf Dan, Salomon Tendler, Rolf Lewensohn, Luigi De Petris, Jayanth Raghothama, Sebastiaan Meijer
Contact: KTH Royal Institute of Technology, Hälsovägen 11C, Huddinge, lmarzano@kth.se

Aim: we designed an approach that aims to explore how real-world data (RWD) could inform clinical trial (RCT) design by systematically accounting for the known differences in population samples (randomisation) and operation (protocols and clinical practice) [1].
Methods: the approach was tested using three Phase III (n=872) and three Phase I-II (n=124) RCTs control arms shared on Project Data Sphere platform [2] and a Swedish RWD cohort of patients treated at Karolinska University Hospital in Stockholm [3] (n=228) on survival of extensive-disease small cell lung cancer patients receiving platinum etoposide chemotherapy (n=1,224). The randomisation was simulated by sampling patients from the RWD and the examined RCT to create the surrogated control arm. Then, the hazard ratios (HR) for OS and PFS between real-world and clinical trials cohorts were computed. The HR reference was the RWD cohort. The analysis was carried out accounting for eight selection criteria (S) and six operations and study protocol factors (O) [1]. The main techniques used during the analysis to create the scenarios were: sub-cohort stratification, logistic propensity score [4], and patients synthetic generation using the SMOTENC machine learning algorithm [5].
Results and discussion: the discrepancy between real-world and clinical trial data potentially depends on differences in both patient populations and operational conditions (e.g., frequency of assessments, and censoring), for which further investigation is required.
Conclusions: Designing a comprehensive and systematic approach to investigate how selection criteria and operations are impacting on the measurements of outcome would allow us to estimate the trade-off between internal validity and generalizability of clinical trials.

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P17 Target discovery for the ADPKD repurposing candidates birinapant, bardoxolone methyl and salicylic acid

Alina Meyer*, Paraskevi Sotiropoulou, André Mateus, Daniel Dietrich, Per Artursson

*Department of Pharmacy, Uppsala University, Uppsala, Sweden;
alina.meyer@farmaci.uu.se

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a chronic, progressive hereditary disease characterized primarily by fluid-filled cysts in the kidneys and caused by mutations in the polycystin-1 or -2 gene. The treatment is currently limited to a single approved drug worldwide. In the search for additional drugs, drug repurposing offers an alternative approach in which clinically validated drugs with established pharmacokinetic and safety profiles are used for new indications.

Aim: Here, we aimed to validate known and identify novel targets of the ADPKD repurposing candidates birinapant, bardoxolone methyl and salicylic acid.

Methods: 2D-thermal proteome profiling (2D-TPP) was used to investigate protein-drug interactions across the whole cellular proteome. To mimic *in vivo* conditions, whole cell experiments were performed under physiological oxygen tension in the renal proximal tubular epithelial cell line RPTEC/TERT1.

Results and discussion: Our results confirmed the expected modes of action (MoA) for each of the three repurposing candidates. All candidates exerted shared effects on mRNA translation, monocarboxylate transport, and mitochondrial nucleotide transport and energy metabolism. In addition, focal adhesion kinase (PTK2) and the glucosidase GANAB were identified as novel targets of salicylic acid. The inhibition of PTK2, an activator of the proliferative PI3K/Akt/mTOR pathway, by salicylic acid was confirmed in a kinase assay. CETSA-Western blot confirmed that salicylic acid thermally destabilizes the glucosidase GANAB, an ADPKD-causing gene involved in polycystin maturation and trafficking. The Seahorse ATP rate assay confirmed an increase in oxidative phosphorylation by all three repurposing candidates. Finally, we corrected the observed dose-dependent changes in thermal stability with the measured unbound drug concentrations at the target site, defined as the intracellular bioavailability of the drug.

Conclusions: Our findings highlight the utility of 2DTPP for evaluation of drug target engagement of repurposing candidates, enabling complex MoA validation and target discovery. The newly identified targets of salicylic acid may not only shed light on its anti-proliferative effects in ADPKD but also provide insights for treatment of other diseases.

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P18 Global proteomics for routine assessment of *in vitro* 3D liver models used for drug development

Evgeniya Mickols[1*], Niklas Handin[1], Alina Meyer[1], Stefania Koutsilieri[2], Chen Xing[2], Volker Lauschke[2], Per Artursson[1], Maria Karlgren[1]

[1]*Department of Pharmacy, Uppsala University, Uppsala, Sweden*

[2]*Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden*

Department of Pharmacy, Uppsala University, Box580, 75123 Uppsala, evgeniya.mickols@farmaci.uu.se

Aim

3D spheroids of primary human hepatocytes (3D PHH) are gaining importance as a model for mechanistic liver homeostasis studies and *in vitro to in vivo* extrapolation (IVIVE) in drug discovery. However, existing 3D PHH culture protocols and phenotypical screening approaches need further refinements and standardization. Here we aim to improve the physiological relevance and drug development applicability of the 3D PHH cultures and to evaluate currently existing approaches to phenotypical assessment of these cultures.

Method

The 3D PHH were cultured for three weeks in ultra-low attachment 96 or 384-well plates. Culture conditions such as cell culture medium and culture plate selection were evaluated by light microscopy, viability screening, and functional performance along with gene and protein expression analysis. Applicability for the drug development studies was demonstrated by metabolic enzymes and transporter activity. Available global proteomics workflows were assessed to further improve the translatability of their results of phenotypical screening in 3D PHH.

Results and discussion

We demonstrate that cell culture media with fasting glucose and insulin levels gave spheroids with phenotypes closest to freshly isolated PHH. (Handin et al., 2021) In addition, we evaluated available cell-culture plates for these organotypic ex vivo cultures and demonstrated that cell-culture plastic has a direct influence on the culture performance and phenotype. (Xing et al., 2024) We show that 3D PHH remain viable and metabolically active for weeks in culture. Moreover, we exemplify the applicability of these cultures in drug discovery by performing transporter studies and CYP activity assays. (Handin et al., 2021; Mickols et al., 2024) Lastly, we evaluated various global proteomics workflows used for phenotypic assessment of 3D PHH and concluded that experimental workflow has a direct influence on biological conclusions. (Koutsilieri et al., 2024)

Conclusion

Our results provide a protocol for culture of healthy and physiologically relevant 3D PHH with maintained function, a prerequisite for studies of hepatocyte homeostasis and more reproducible hepatocyte research. We anticipate our study will further advance 3D PHH in drug-development pipelines.

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P19 Are your drug metabolites safety tested?

Relative method, challenges and solutions

Hitesh V. Motwani*, Anders Lindgren, Virginia Aimetta, Ivan Vachinski and Johanna Haglund
MetaSafe Sweden AB, SE-151 36 Södertälje, Sweden
*Hitesh.Motwani@metasafe.se

Background: For the toxicological assessment of metabolites of candidate drugs there are published guidelines[1,2] referred to as Metabolites in Safety Testing (MIST). MetaSafe utilises these guidelines and has further optimised the approach internally, with scientists within MetaSafe being part of this development ever since the guidance was released. Using a liquid chromatography-high resolution mass spectrometry (LC-HRMS) based method, we perform MIST with a relative method without requiring reference standards or absolute quantification for all metabolites. This allows possibilities to identify issues related in qualifying adequate exposure without synthesising reference compounds or developing bioanalytical methods for each metabolite.

Aim: To highlight potential scenarios leading to specific challenges in the exposure comparison of metabolites, and to propose pragmatic solutions in resolving them.

Experimental: In the relative method, direct exposure comparison is performed between plasma samples from repeated doses studies in the human and preclinical safety species. Time-proportionate AUC (area under concentration time curve) pools, representing mean plasma concentrations, are created for each species and dose group. Each AUC-pooled plasma is matrix-matched with blank plasma from other remaining species, prepared by protein precipitation, and analysed using LC-HRMS. The human AUC pools are evaluated to establish the metabolite profile (Met-ID), and human metabolites are identified in all species' plasma pools, and exposure levels compared between humans and the safety species.

Exposure comparison approach and challenges: The normalised MS peak areas reflect the mean plasma concentration of each metabolite at steady state of the parent. This data is used to establish exposure ratios of each human metabolite between human and safety species, servicing as a basis for the evaluation of adequate exposure in safety species without needing absolute metabolite levels. Challenges in exposure comparison may arise due to: i. insufficient plasma volumes for AUC pools; ii. ion suppression affecting peak areas due to matrix-matching; and iii. issues interpreting exposure ratios, including ESI-adduct formation and in-source fragmentation. This work outlines these challenges and proposes practical solutions for improving exposure comparison.

Conclusions: Exposure comparison using the relative method on repeated-dose samples is key to MIST evaluation for identifying disproportionate or unique human metabolites. Each drug and development process are unique, presenting challenges in metabolite safety assessment. However, certain approaches and principles can help address these challenges and meet regulatory guidelines for qualifying metabolite exposure in safety evaluation of new drugs.

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P20 Investigating the role of intestinal mucus as a barrier for oral delivery of macromolecules and permeation enhancers

Benyamin Naranjani[1,2,*], Marco Tjakra[1,2], Christel A S Bergström[1,2], Patrick D Sinko[1], Shakhawath Hossain[1], Per Larsson[1,2]
[1]Department of Pharmacy, Uppsala Biomedical Center, Uppsala University, 751 23 Uppsala, Sweden.
[2]Swedish Drug Delivery Center (SweDeliver), Uppsala University, 751 23 Uppsala, Sweden.
Address correspondence to: Benyamin Naranjani,. Email: benyamin.naranjani@farmaci.uu.se

Introduction: Oral delivery of macromolecules (MMs) faces significant challenges due to the gastrointestinal (GI) tract's protective mechanisms [1]. Permeation enhancers (PEs) like sodium caprate (C10) have demonstrated potential in improving MM absorption by temporarily increasing permeability [2]. Intestinal motility also plays a crucial role in drug transport, influencing residence time and mixing efficiency. Peristalsis propels drug formulations forward, while segmentation enhances mixing, both of which affect the absorption process. However, mucus can hinder absorption by acting as a barrier, limiting drug diffusion to the epithelial surface. This study explores how intestinal motility patterns and mucus properties influence MM and PE transport.

Aim: To investigate how intestinal motility patterns and mucus properties influence the transport and absorption of macromolecules (MMs) and permeation enhancers (PEs).

Methods: A computational model was employed to simulate the transport of insulin, used as a model MM, and sodium caprate (C_{10}), used as a PE. The model incorporated the effects of intestinal motility patterns, including peristalsis and segmentation, as well as varying mucus thicknesses (30 µm, 100 µm, 200 µm). The finite element method using COMSOL Multiphysics was used to solve the conjugated fluid flow and concentration variables.

Results and Discussion: Our findings indicate that mucus thickness significantly affects the transport dynamics of both MMs and PEs. In segmentation, thicker mucus was found to decrease transport towards the mucus interface, resulting in limited drug diffusion and reduced absorption. In contrast, peristalsis increased transport towards the mucus interface, enhancing the contact between drug formulations and the epithelial surface, thereby improving absorption. The interplay between motility type and mucus thickness was crucial in determining the efficiency of MM and PE transport, highlighting the importance of considering these factors in the design of oral delivery systems.

Conclusions: The combined effects of motility patterns and mucus properties significantly influence the absorption of macromolecules and permeation enhancers. Although the immediate impact of mucus on hydrodynamics might be small, over time, variations in mucus thickness can alter the fraction of absorbed macromolecules by an order of magnitude. Segmental motility, in particular, was found to be more susceptible to changes in mucus properties compared to peristalsis.

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P21 The contribution of P-gp of the rat intestinal permeability and bioavailability of two model proteolysis targeting chimeras (PROTACs)

Janis Niessen*, Hans Lennernäs, Mikael Hedeland, Markus Sjöblom, Ilse Dubbelboer, Thomas Borchardt[a], Mirko Koziolek[b], Anura Indulkar[a], David Dahlgren

*Department of Pharmaceutical Bioscience, Translational Drug Discovery and Development, Uppsala University, janis.niessen@uu.se. [a]AbbVie Inc., North Chicago, IL, USA. [b]AbbVie Deutschland GmbH & Co. Ludwigshafen, Germany

Aim: PROTACs exhibit a unique and promising pharmacology (1). However, this comes with molecular properties exceeding the 'drug-like' Ro5 chemical space, which often limits oral absorption (2). This study aimed to investigate the contribution of P-gp efflux on the rat intestinal permeability and bioavailability of two model PROTACS, ARV-110 (812 Da, LogP 3.6) and ARV-471 (724 Da, LogP 5.9).

Methods: Intestinal permeability of the two PROTACs was determined directly from luminal disappearance using single-pass intestinal perfusion (SPIP), with and without the P-gp/CYP3A4 inhibitor, ketoconazole. Intestinal absorption/bioavailability was determined from plasma drug exposure during 6 h after iv dosing, and compared to after an intra-duodenal dosing with without ketoconazole or the P-gp selective inhibitor, encequidar.

Results and discussion: ARV-110 had a moderate permeability (0.62×10^{-4} cm/s) and ARV-471 a low permeability (0.23×10^{-4} cm/s). There were clear P-gp effects on both PROTACs during SPIP, where P-gp inhibition resulted in a 1.6-fold increase in permeability for ARV-110 and a 2.3-fold increase for ARV-471. This resulted in corresponding increase in bioavailability for both PROTACs after dosing with ketoconazole or encequidar. The minor difference in plasma exposure of the ARVs after dosing with ketoconazole or encequidar suggests that the increased bioavailability was a result of P-gp inhibition, with only a minor contribution of gut-wall and hepatic extraction via CYP3A4.

Conclusion: It is suggested that P-gp reduces the intestinal permeability and bioavailability of ARV-110 and ARV-471 in rat.

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P22 Concentration Guided Dosing Duel: Defining True Dose Personalization

Zvonimir Petric

Department of Pharmacological Sciences, Research Institute for Medicines, Faculty of Pharmacy, University of Lisbon, Portugal; petric.zvonimir@gmail.com

Aim: The aim is to compare Target Concentration Approach (TCA) dosing versus Therapeutic Window Approach (TWA) dosing in the context of using a monoclonal antibody (MAb) for inflammatory bowel disease (IBD), recognizing that post-hoc analysis identified a trough concentration of at least 4 mg/L by week 16 as the PK endpoint for early interception of IBD progression in a patient of interest.

Background: MAb is administered as a starting i.v. dose of 5 mg/kg every 8 weeks. Time-varying inflammatory burden, immunological makeup and patient characteristics (i.e., covariates) influence drug PK and subsequent drug effects. Therefore, if inappropriate response is not managed early, treatment failure will occur [1]. TWA dosing uses a therapeutic window which assumes any concentration within this range is acceptable [2]. TCA uses a single concentration aiming to achieve optimal therapeutic effects. This target concentration (TC) is a key part of the TCA dosing [3,4]. In the first scenario, after patient stratification based on covariates and determination of the trough therapeutic window, TWA assumes that any trough concentration within the range of 2 to 6 mg/L is effective. No clinician intervention is expected if the starting dose yields a trough concentration within this range by week 8. In the second scenario, TCA assumes a single trough concentration of 5 mg/L and may require clinician intervention if the starting dose does not achieve this TC by week 8.

Methods: The popPK model was implemented in MonolixSuite, and individual PK profiles were simulated by Markov-Chain Monte Carlo sampling from a conditional distribution [5]. For TWA, the starting dose and the second dose were kept the same, since the observed trough concentration was not outside of the trough therapeutic window. For TCA the dose was adjusted to reach the TC based on a Bayesian estimate of clearance. The probability of target attainment was calculated from the distribution of trough concentrations predicted at week 16 within the therapeutic window for TWA dosing or within an acceptable range of 80-125% around the TC for TCA dosing.

Results and Discussion: Target attainment was 100% for TWA and 98% for TCA dosing. With TWA, maintaining the same dose—justified by its resulting trough concentration within the range—is unlikely to be beneficial, as the PK endpoint was not met. In contrast, TCA based on PKPD principles met the PK endpoint and is inferred to be beneficial.

Conclusion: TWA dosing largely ignores the relationship between drug concentration and effect. To improve clinical outcomes, the use of TCA dosing is encouraged, as it provides an individualized dose that is expected to be optimally effective. Blind and passive reliance on the trough therapeutic window risks IBD progression.

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P23 Novel oral PORCN inhibitor does not alter the PK of nintedanib, an approved therapy for idiopathic pulmonary fibrosis

Susanne Prothon[1](*), Ann Aurell Holmberg[2], Pradeep Sharma[3], Joachim Almquist[1], Sandra Grañana Castillo[4], Szilárd Nemes[5], Richard Baldry[3], Maciej Sosnowski[6], Karin Enarsson Ringqvist[7], Xiao-Hong Zhou[8], Engin Liathdale[9], Caroline A. Owen[10], Bernadette Gochuico[10], Gunilla Wall[11], David Steel[12], Ellinor Hornberg[13]

[1]Clinical Pharmacology & Quantitative Pharmacology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[2]Early R&I DMPK, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[3]Clinical Pharmacology & Quantitative Pharmacology, BioPharmaceuticals R&D, AstraZeneca, Cambridge, United Kingdom

[4]Clinical Pharmacology & Quantitative Pharmacology, BioPharmaceuticals R&D, AstraZeneca, Barcelona, Spain

[5]BioPharma Early Biometrics and Statistical Innovation, Data Science & AI, BioPharmaceuticals R&D, AstraZeneca, Sweden

[6]Early Phase Clinical Operations, Respiratory and Immunology (RI), BioPharmaceuticals R&D, AstraZeneca, Warsaw, Poland

[7]Early Phase Clinical Operations, Respiratory and Immunology (RI), BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[8]Patient Safety Biopharma, Chief Medical Office, Oncology R&D, AstraZeneca, Gothenburg, Sweden.

[9]Early Clinical Development, Research and Early Development, Respiratory and Immunology (RI), BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[10]Early Clinical Development, Research and Early Development, Respiratory and Immunology (RI), BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, US

[11]Early Phase Clinical Operations, Respiratory and Immunology (RI), BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[12]Parexel Early Phase Clinical Unit, Northwick Park Hospital, London, United Kingdom

[13] Projects, Research and Early Development, Respiratory and Immunology (R&I), BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

Astrazeneca R&D, Pepparedsleden 1, 431 83 Mölndal. susanne.prothon@astrazeneca.com

AZD5055 is a novel oral inhibitor of the enzyme porcupine, being investigated for IPF. AZD5055 is an inhibitor of the transporter permeability glycoprotein (P-gp) *in vitro*. Applying regulatory guidance basic models flagged a risk of drug-drug interaction (DDI) with P-gp substrate drugs in the intestine following oral dosing. Nintedanib is an approved oral therapy, widely used in IPF patients, and a known P-gp substrate with a narrow therapeutic index.[1, 2]

Aim:

The main objective was to identify and quantify a potential clinical pharmacokinetic DDI between AZD5055 and nintedanib at therapeutically relevant doses.

Methods:

In an open three-way cross-over study (NCT05644600), using single doses in a fasted state, 18 healthy volunteers received nintedanib alone or nintedanib + AZD5055 (35 mg) or nintedanib + AZD5055 (10 mg) in a randomized order, separated by a 3-day wash-out. The nintedanib dose was 100 mg. We measured nintedanib and AZD5055 plasma concentrations up to 48 hours after dose and computed the area under the concentration–time curve (AUC) and maximum concentration (Cmax).

Results and discussion:

Adjusted geometric mean ratios (with/without 35 mg AZD5055) were 102% and 111% for nintedanib AUC and Cmax, respectively. For both parameters, the 90% confidence intervals included 100%, suggesting similar exposure for administration alone and when co-administered. A similar effect on nintedanib PK was seen for the 10 mg AZD5055 dose. The AZD5055 PK profile was as observed in previous clinical studies. Both treatments were well tolerated.

Conclusion:

These data indicate there is no relevant pharmacokinetic DDI between AZD5055 and nintedanib, when co-administered in healthy volunteers.

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P24 Targeting loss of heterozygosity in cancer

Natallia Rameika[1*], Ioanna Tsiara[2], Xionang Zhang[1], Veronica Rendo[1], Snehangshu Kundu[1], Mario S.P. Correia[2], Ivaylo Stoimenov[1], Daniel Globisch[2], and Tobias Sjöblom[1]

[1]*Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden*
[2]*Department of Chemistry - BMC, Uppsala University, Uppsala, Sweden*
natallia.rameika@igp.uu.se

Aim: The Arylamine-*N*-acetyltransferase-2 (*NAT2*) locus on 8p22 is subject to loss of heterozygosity in ~20% of colorectal cancers (CRC) (1). Collateral *NAT2* loss in CRC leading to reduced NAT2 activity increases sensitivity to the cytotoxic compound 6-(4-aminophenyl)-*N*-(3,4,5-trimethoxyphenyl)pyrazin-2-amine (2). Here we aimed to systematically assess if metabolism of cytotoxic drugs by NAT2 occurs, and identify anticancer agents whose effects depend on NAT2 activity.

Methods: Previously established cell modes (2), expressing *NAT2*-slow or NAT2-rapid variant alleles and empty vector control in RKO CRC cells were used for drug screening. A set of 147 FDA approved clinically used cytotoxic drugs was used. MTT resazurin-based cell viability assessment of the difference in viability between cells lines with different NAT2 activity was performed with further validation in DLD1 cell model. Hit compounds were evaluated in LC/MS acetylation assay with recombinant NAT2 enzyme.

Results and Discussion: Among 147 drugs we found doxorubicin, daunorubicin, epirubicin, valrubicin, teniposide, afatinib, carmustine, vincristine, panobinostat, and vorinostat to have increased toxicity to cancer cells with high NAT2 activity. Additionally, we report NAT2-mediated acetylation of idarubicin, daunorubicin, doxorubicin, vorinostat, and CUDC-101.

Conclusions: These findings have implications for pharmacogenomics and cancer precision medicine using conventional chemotherapeutic drugs, as improving their efficacy and safety may affect more than 4 million cancer patients worldwide that receive these drugs as standard of care.

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P25 AZD8630 –Model informed dose selection for novel inhaled anti-TSLP Fab in Phase1 delivering positive POM

Waqas Muhammad Sadiq[1], Sara Asimus[1], Jason Cooper[2], Davinder Dosanjh[3], Xiao-Hong Zhou[4], Hitesh Pandya[3], Michael Cushion [3], Valmira Podrimcaku[5], Jane Parnes[6], Lubna Abuqayyas[6], Nestor Molfino[6], Sarah Doffman[3]

[1]Clinical Pharmacology and Quantitative Pharmacology, BioPharmaceuticals R&D, AstraZeneca, Sweden; [2] Biometrics and Statistical Innovation, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK; [3]Clinical Development, Early Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK; [4]Patient Safety Biopharma, Chief Medical Office, Oncology R&D, AstraZeneca, Gothenburg, Sweden, [5]Regulatory Affairs, Respiratory and Immunology, BioPharmaceuticals R&D, AstraZeneca, Sweden; [6]Amgen Inc., Thousand Oaks, CA, USA

AZD8630/AMG 104 is an inhaled fragment antibody targeting anti-thymic stromal lymphopoietin (TSLP) developed to treat asthma. This Phase1 study (NCT05110976) aimed to characterize safety, tolerability, pharmacokinetics (PK) and immunogenicity of AZD8630/AMG 104 in healthy volunteers and patients with asthma.

The study consisted of two parts; part A was conducted in healthy volunteers including global, Chinese and Japanese cohorts consisting of single and multiple inhaled and IV dosing of AZD8630/AMG 104. Part B was a randomized, double-blind, placebo-controlled design evaluating multiple dose levels of AZD8630/AMG 104 in patients with moderate-to-severe asthma. Participants in Part B received placebo or active drug once daily for 28 days. FeNO was used as POM biomarker. In patients change from baseline in FeNO versus placebo was analyzed using a mixed model for repeat measurements. A similar approach was adopted for the analysis of exploratory endpoints in lung function (Forced Expiratory Volume in 1 Second; FEV1) and symptom control (Asthma Control Questionnaire; ACQ-6).

Following inhalation, AZD8630/AMG 104 was steadily absorbed with a median Tmax observed at 5-10 hours. The systemic exposure of AZD8630/AMG 104 increased in a dose-proportional manner. Mean terminal half-life was 21-37 hours across cohorts. No differences were observed in PK due to ethnicity. Accumulation was 2- to 3-fold in serum at steady state. The incidence of anti-drug antibodies (ADA) was low; three individuals (2.4% of those dosed) developed treatment-emergent ADA during the study. Overall, AZD8630/AMG 104 was well tolerated and no safety concerns were raised. There was a statistically significant reduction in FeNO in those treated with high dose AZD8630/AMG 104 (23% reduction vs placebo, one-sided p value 0.037). This reduction was evident from 7 days and sustained to the end of the treatment period (28 days).

AZD8630/AMG 104 displayed dose proportional PK characteristics in the dose range studied and a half-life suitable for once-daily dosing. The addition of QD inhaled AZD8630/AMG 104 significantly reduced airway inflammation in patients with poorly controlled asthma on medium-high dose ICS/LABA and elevated baseline FeNO. These results support further development of AZD8630/AMG 104 inhaled anti-TSLP. Together with low rates of immunogenicity following 4-weeks of dosing this data supports the ongoing development of AZD8630/AMG 104 as a first-in-class inhaled biologic treatment option for asthma patients.

P26 3D human liver spheroids for metabolism studies of low-turnover compounds

Friederike A. Sandbaumhüter[1*], Anna-Pia Palmgren[1], Katarina Rubin[1], Dennis Hekman[2], Charlotta Vedin-Nilsson[2]

[1] Drug Metabolism and Pharmacokinetics, Research and Early Development, Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

[2] Drug Metabolism and Pharmacokinetics, Early Research and Development Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

*friederikeandrea.sandbaumhuter@astrazeneca.com

Aim

To predict drug metabolism and associated drug-drug interaction (DDI) liabilities hepatocyte based in vitro systems are routinely used in drug discovery. Three-dimensional liver spheroids that can maintain hepatocyte function over several days enable the study of low-turnover compounds. Here, we aimed to set up an assay that can provide information on drug intrinsic clearance, metabolite formation and involved enzymes from a single test system.

Methods

Cryopreserved human hepatocytes were seeded into micro-cavity Corning®Elplasia® 96-well plates with 79 micro-cavities per well. For the formation of spheroids they were cultured for 6 days with a medium change on day 3. At day 7 various substrates (1 µM each) were added separately and incubated with and without inhibitor (3 µM ketoconazole or 10 µM furafylline). To ensure effective inhibitor levels the inhibitors were re-dosed every 24 h. The metabolic reactions were stopped by adding a mixture of acetonitrile and methanol (1:1 *v/v*) after 0, 8, 24, 48, 72 and 96 h. After centrifugation the supernatant was analyzed by using liquid chromatography coupled to tandem mass spectrometry. The parent compound was quantified, formed metabolites were identified and the fractional intrinsic clearance ($frCl_{int}$) as well as inhibition of metabolite formation (IMF) were calculated.

Results and discussion

Metabolite formation mediated by several cytochrome P450 isoformes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5), UDP-glycosyltransferases, flavin-containing mono oxygenase and aldehyde oxidase was observed. Among the detected metabolites were both phase I and phase II metabolites. Substrate concentrations and metabolic profiles were determined in absence and presence of inhibitors (ketoconazole for CYP3A4 inhibition and furafylline for CYP1A2 inhibition). By evaluating the effect on the individual metabolic reactions the consequences of inhibition and the contribution of the inhibited enzymes could be estimated and described by the calculation of $frCl_{int}$ and IMF.

Conclusions

For the characterization of metabolic stable compounds we developed a flexible assay based on human hepatocyte spheroids with multiple ADME readouts. Over 96 h the kinetic profiles of the parent compounds and their metabolites can be followed. With the possibility to add enzyme specific inhibitors the victim DDI risks can be assessed.

P27 A Generative Pre-trained Transformer for Time-Course and Dose-Response Predictions

Mikael Sunnåker* and Angelica Quartino
mikael.sunnaker1@astrazeneca.com, angelica.quartino1@astrazeneca.com
AstraZeneca AB, Pepparedsleden 1, 431 83 Mölndal

Objectives: Neural networks (NNs) constitute a class of artificial intelligence methods inspired by the human brain to teach computers to process data. Generative pre-trained transformers (GPTs), which constitute a particular type of NNs, have recently increased in popularity due to impactful implementations of chat bots, such as ChatGPT, but have also been explored for analysis of time series [1].

Although NNs have been used for PK/PD predictions (e.g., neuralODEs [2]), we are not aware of any direct applications of GPTs in this domain. The objectives of this work are to investigate the applicability of GPTs for (1) simulation of dose regimens over time, (2) simulation of dose-response relationships, and (3) to investigate what type of data is required for GPTs to perform well.

Methods: We implemented a GPT following the approach described in [3,4], which uses the open-source neural network library Keras (TensorFlow) in Python. The input architecture is defined such that vectors of the training data, including time after the first- and last dose and the dose amount, are used to train the GPT.

Our GPT-implementation is applied to data that has been simulated from a one compartment PK model connected to an indirect dose-response model [5]. The simulated dataset describes the PD response to four consecutive doses with a dosing interval of 24 time units and including the subsequent return to baseline period. The performance of the GPT is then evaluated for its ability to predict unobserved time points as well as new dosing regimens (3 and 7 doses) by RSME (between average simulations and predictions) and visual inspection. We also investigate the performance of the GPT when the attention mechanism is removed.

Results: We first show that for sufficiently informative data, the implemented GPT can well describe the training dataset (4 doses), but also make realistic predictions of new dosing regimens (3 doses and 7 doses) over time including the return to baseline period. It is also shown that the self-attention mechanism contributes to the separation of temporal effects (e.g. resulting in improved predictions of the 7 doses regimen), which gives GPTs an advantage to alternative NN implementations for PD predictions.

Conclusions: We show that GPTs, when successfully implemented and trained on informative PD data, can be used for realistic simulations of PD time-courses and dose-response relationships.

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P28 Human 3D intestinal organoids as tools for the prediction of intestinal drug influx and efflux

Foteini Tzioufa*, Merve Ceylan, Jens Eriksson, Mikael E. Sellin, Madlen Hubert, Per Artursson

Address: Department of Pharmacy, Uppsala University, Husargatan 3, 75123 Uppsala, Sweden. E-mail: foteini.tzioufa@farmaci.uu.se

Aim: To evaluate human intestinal organoids (IOs) derived from jejunal tissue as models for predicting drug absorption, by assessing their barrier integrity and the activity of influx and efflux transporters.
Methods: Healthy jejunal crypt-derived IOs were initially grown in Matrigel™ in standard basal-out polarity (BO). IOs were differentiated in suspension to apical-out (AO) polarity (matrigel-free) or BO polarity (7.5% Matrigel) for 6 days (Co et al., 2019). Functional studies were performed to evaluate IO barrier properties as wells as influx and efflux potential. For barrier integrity, AO and BO IOs were incubated in suspension with hydrophilic marker lucifer yellow (LY). Dye accumulation was monitored over time using time-resolved fluorescence microscopy. Influx was assessed by measuring the activity of fatty acid transport protein 4 (FATP4) using the fluorescent substrate C1-BODIPY-C12, while efflux was studied using rhodamine 123 (Rho123), a substrate of P-glycoprotein (P-gp), which is an intestinal membrane efflux pump (Mizutani et al., 2012).
Results and discussion: IOs were successfully developed and grown in two configurations: AO with an exposed lumen, and BO with a contained lumen, in suspension culture. The human intestinal epithelium is expected to maintain an intact physical barrier. A LY-based assay was performed, showing that the marker did not diffuse paracellularly in either AO or BO IOs, confirming barrier integrity. In AO IOs, the fatty acid fluorescent analogue C1-BODIPY-C12 was taken up through apically located FATP4 transporters and accumulated in lipid droplets, demonstrating FATP4 functionality. In BO IOs, Rho123 accumulated in the lumen, indicating functional apical P-glycoprotein (P-gp) transporters.
Conclusions: Our results show that both AO and BO IOs form an intact epithelial barrier and exhibit active influx (FATP4) and efflux (P-gp) transporters, making them promising models for studying drug absorption.

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Lecturer Abstracts

L1 "Unusual" Biotransformation Reactions of Drugs and Drug Candidates

Emre M. Isin

Servier, Drug Metabolism and Pharmacokinetics Department, Translational Medicine, Servier Research and Development Institute in Paris-Saclay, Gif-sur-Yvette, France;
Emre.Isin@servier.com

Understanding the biotransformation pathways is key in assessing the efficacy and safety of drugs in humans and has been an important focus area in pharmaceutical industry as well as academia. Although our collective knowledge on biotransformation pathways has increased substantially over the years, accurately predicting the metabolic fate of drugs in humans remains a challenge and we continue to come across "unusual" metabolites/metabolic pathways during the drug discovery and development programs. In this presentation, a selection of some of these "unusual" observations reported recently in the literature will be discussed together with the proposed mechanisms.

L2 Drug metabolism in drug discovery -PK, PD and safety aspects

17th Symposium on Pharmacokinetics and Drug Metabolism

Carl Petersson, Scientific Director DMPK

Merck Healthcare, Darmstadt, Germany

The study of metabolism of small molecules has been an integrated part of the drug discovery process since decades. The impact of drug metabolism on optimization of pharmacokinetics will be covered in the presentation by concrete examples of different biotransformation mechanism demonstrating how attenuation of metabolic rates may be guided by identification of metabolites. The utility of drug metabolism studies to optimize safety aspects will be covered in a similar fashion. Strategies to identify metabolites with pharmacological activity will also be covered as well as the strength and weaknesses of available technologies to study metabolism in drug discovery.

L3 Structural elucidation of conjugation drug metabolites by utilizing novel electron-activated dissociation (EAD)

Ferran Sánchez *, Tom Ruane, Joshua Woolliscroft, Jose Jimenez, Mats Garmer,
ferran.sanchez@sciex.com
SCIEX UK, Alderley Park, Suite 21F18, 21 Mereside, Macclesfield SK10 4TG, United Kingdom

CID is the fragmentation approach widely used in LC-MS/MS qualification and quantitation of drugs and their metabolites. Conjugation metabolites are found to have multiple binding potentials to parent drugs. It is a great challenge to locate the binding sites by CID due to the information lost by highly selective cleavage at these sites. Novel electron-activated dissociation (EAD) is a recently developed technology on a SCIEX QTOF system. It produces varied fragmentation patterns generating additional or different fragments than CID. Here we demonstrate how these fragments can be crucial to locating the metabolic modification sites, especially for conjugations.

A series of drug compounds was incubated with rat liver microsome in the presence of NADPH, UDPGA and GSH at 37°C for 60 minutes. After incubation, the reaction was terminated by adding acetonitrile. After centrifugation the supernatants were evaporated under vacuum and injected into a UHPLC system coupled with a SCIEX ZenoTOF 7600 system and an HHS column (1.7 µm, 50 x 2.1 mm). After LC-HRMS full scans on the drugs and metabolites, EAD and CID fragmentations were conducted for MS/MS spectra.

Metabolite profiling identified several conjugation metabolites, including glucuronides and GSH adducts by characteristic mass shifts on the molecular ions. After optimization, both EAD and CID were employed to compare the characteristics of fragmentation. EAD showed the potential to fragment the molecular ions more extensively than CID. Most importantly, the EAD-specific fragments included the ones created by breaking the relatively stable bonds on the parent drug motifs but keeping the relatively weak conjugation bond intact. By this means, EAD significantly assisted identification of the conjugation binding sites. Moreover, a few cases demonstrated that EAD had the capability to generate different fragmentation patterns than CID producing unique fragments complementary to CID in metabolite profiling studies, enhancing the structure elucidation of conjugation drug metabolites.

L4 Drug transporters and large molecules

Pär Matsson, Sahlgrenska Academy, University of Gothenburg

The majority of drugs in current development pipelines are directed at intracellular targets, and must cross multiple lipid membrane-delimited cellular barriers to elicit their pharmacologic effects. With the increasing size of many modern therapeutic modalities – from beyond rule-of-5 ‘small’ molecules such as macrocycles and targeted protein degraders (PROTACs, etc), to oligonucleotide therapeutics and intracellularly targeted antibody therapeutics – the balance among the mechanisms involved in cellular drug transport is shifted. In this presentation, limits of molecular size for traditional drug transporters from the solute carrier (SLC) and ATP binding cassette (ABC) transporter superfamilies are discussed, as are the transport routes dominating in the cellular uptake of larger molecules in emerging therapeutic modalities.

L5 Antibody Brain Exposure and Distribution Using Passive or Active Transport Mechanisms to Target Brain Diseases

Sofia Gustafsson, BioArctic

Central nervous system (CNS) disorders affect individuals across all ages, with diseases like Alzheimer's and Parkinson's disease becoming increasingly prevalent in the aging population. A significant challenge in treating these diseases is the blood-brain barrier (BBB), a dynamic interface between the blood and the brain restricting especially the entry of large biotherapeutic molecules into the brain.

Although antibodies targeting CNS diseases are under development or have even reached the market, their penetrance into the brain is low, necessitating high doses to achieve desirable clinical effects. Enhanced brain uptake, as well as faster and wider brain distribution of therapeutic antibodies could potentially result in more efficient treatments. Hence, maximizing the therapeutic potential of these antibodies. Increased brain exposure would further support a lowering of doses. This in turn could impact overall treatment costs and minimize potential side effects associated with higher dosing and importantly lead to improved treatment of patients.

Advancements in protein engineering have led to the development of bispecific antibodies that not only bind to their therapeutic target but also interact with receptors such as the transferrin receptor (TfR), enabling receptor-mediated transcytosis (RMT) across the BBB. This approach will be exemplified by the BrainTransporter™ technology, which leverages TfR's natural role in iron delivery to overcome the restrictive nature of the BBB. This allows therapeutic agents to efficiently navigate into the brain using the vast brain capillary network, unlike regular IgGs, which are proposed to enter the brain passively in part through the cerebrospinal fluid and ventricular route.

Ongoing research aims to identify key features for optimal brain delivery at the BBB, with factors like valency and affinity towards TfR appearing crucial in tailoring brain uptake, possibly requiring fine tuning for different disease indications or site of action. Preclinical and clinical studies also demonstrate that the combination of BBB transport technologies with therapeutic antibodies represents a significant progression in the development of efficient treatment of CNS disorders.

L6 Translational aspects of oxycodone brain delivery via the proton-coupled organic cation (H+/OC) antiporter system: the journey from cells to pigs

Frida Bällgren[1], Aghavni Ginosyan[1], Miklós Lipcsey[2], Birger Brodin[3], Margareta Hammarlund-Udenaes[1], Stina Syvänen[4], Irena Loryan[1*]

[1]Translational Pharmacokinetics/Pharmacodynamics group (tPKPD), Department of Pharmacy, Uppsala University, Sweden
[2]Anaesthesiology and Intensive Care, Department of Surgical Sciences, Uppsala University, Sweden
[3]CNS Drug Delivery and Barrier Modelling group (CNSBM), Department of Pharmacy, University of Copenhagen, Denmark
[4]Molecular Geriatrics, Department of Public Health and Caring Sciences, Uppsala University, Rudbecklaboratoriet, Sweden

* presenter

Oxycodone, a widely used opioid analgesic, was previously discovered to undergo active transport across the blood-brain barrier in rats, with an unbound brain-to-blood partition coefficient ($K_{p,uu,brain}$) of 3. Along with other marketed drugs, its active uptake has been associated with the proton-coupled organic cation (H^+/OC) antiporter system. Despite the long history of the clinical use of oxycodone, the extent of brain delivery and the preservation of the active uptake system in higher species, including humans, remains uncertain. Confirmation of the presence of the antiporter system at the human blood-brain barrier would have significant implications for CNS drug development, highlighting its potential as a target for enhanced brain drug delivery.

The proposed presentation will cover a systematic investigation of oxycodone disposition in the CNS based on data from:

- Brain microdialysis studies conducted in Sprague-Dawley rats of both sexes in healthy and endotoxemia conditions
- Brain microdialysis in Swedish landrace pigs of both sexes in healthy and endotoxemia conditions
- Comparison of the extent of oxycodone delivery across the blood-brain and blood-CSF barriers will be provided along with a discussion on the usage of CSF as a surrogate of brain interstitial fluid.
- Studies of oxycodone uptake and transport in various in vitro models of the blood-brain barrier with critical thoughts on their translational value.
- The potential role of the proton-coupled organic cation (H^+/OC) antiporter system in the development of various forms of neurotoxicity will be discussed.

In conclusion, remaining challenges with the validation of this antiporter system as a potential brain drug delivery target will be presented.

L7 Presentation title: Use of endogenous biomarkers for evaluating transporter-mediated DDIs (tDDI) – Case studies from AstraZeneca.

Presenter: Vijender Panduga, Clinical Pharmacology Scientist, Clinical Pharmacology and Quantitative Pharmacology, AstraZeneca, Sweden

Drug-drug interactions (DDI) involving inhibition of transporters e.g., hepatic OATP1B1/3, intestinal BCRP, renal OCT2, MATE1, and MATE2K could increase the plasma exposure of transporter substrates such as statins or metformin, and thus may lead to adverse effects. Hence, in vitro transporter inhibition data (e.g., IC_{50}, half-maximal inhibitory concentration) is routinely measured for molecules to evaluate transporter mediated DDI (tDDI) risk based on regulatory agency recommended static approaches. However, in vitro based DDI assessments tend to give higher false positive predictions, leading to unnecessary clinical DDI studies. Moreover, tDDIs typically involve multiple pathways e.g., inhibition of OATP1B1/3 and BCRP transporters, and difficult to interpret, leading to additional DDI studies to understand the impact on individual pathways.

Quantifying changes in endogenous biomarkers of transporters from early clinical studies could help assessing transporter inhibition and in delineating complex DDI mechanisms. Examples of endogenous biomarkers include coproporphyrin-I (CP-I), 4-pyridoxic acid (4-PA) and N-methyl nicotinamide (NMN) for OATP1B1/3, OAT1/3 and OCT2/MATE1/MATE2K transporters, respectively. The current presentation is aimed to share how these biomarker-informed tDDI strategy is being implemented in AstraZeneca's clinical programmes and the impact of such strategy using AZD1 and AZD2 clinical programmes as an example.

In vitro data indicated DDI risk for AZD1 with BCRP, OATP1B1/3, and OAT1/3 substrates. As per the biomarker-informed tDDI strategy, plasma CP-I and 4-PA measurements were included in the early clinical studies of AZD1. No change in plasma exposure of CP-I and 4-PA in the presence of AZD1 ruled out OATP1B1/3 and OAT1/3 inhibition, respectively. These data supported including OATP1B1/3 and OAT1/3 transporter substrates in the AZD1 Ph2 programme. For AZD2, static assessments flagged DDI risk with BCRP and OATP1B1/3 transporter substrates. In a clinical DDI study, AZD2 Ph1 formulation significantly increased the plasma exposure of rosuvastatin (RSV), which is an FDA recommended substrate of both BCRP and OATP1B1/3 transporters. However, CP-I levels from this study suggested only a weak OATP1B1/3 inhibition for AZD2, thus helping to delineate the contribution of AZD2's OATP1B vs. BCRP inhibition for the observed increases in RSV. Also, CP-I levels from the subsequent studies with AZD2 Ph2 formulation supported validating AZD2 PBPK model for predicting DDI with OATP1B1/3 substrates and translating DDI risk from Ph1 formulation to the Ph2 formulation.

Thus, implementation of endogenous biomarker-based DDI strategy facilitate improved DDI risk assessment vs. based on in vitro data alone and provide powerful clinical data for PBPK model-based transporter DDI predictions and reduce unnecessary restriction on comedications in Ph2 programmes.

L8 Physiologically based pharmacokinetic modelling and simulation in perinatal populations: opportunities, challenges and case examples

Lecturer: Pieter Annaert

Affiliations:

(1) KU Leuven Department of Pharmaceutical and Pharmacological Sciences
(2) BioNotus

Physiologically-based pharmacokinetics (PBPK) approaches continue to evolve as unique in silico modelling and simulation (M&S) tools for predicting pharmacokinetics in specific populations. Accurate simulations however require high resolution input data in terms of relevant pathophysiology of the target populations. In addition, quantitative knowledge on the underlying compound-specific disposition mechanisms is crucial. Well designed experiments in standardized preclinical ADME tools can generate such information, subsequently requiring proper translation/scaling into the PBPK model. Furthermore, clinical data, preferably obtained in independent studies with various populations, are needed for subsequent model evaluation. It follows that a succesful PBPK modelling workflow requires multidisciplinary discussions between preclinical researchers, PBPK modellers and clinicians.

This presentation will illustrate PBPK M&S worflows and outcomes with two case studies: (i) dose finding for sildenafil during pregnancy for fetal treatment of congenital diaphragmatic hernia; (ii) predicting secretion of maternal medication in human breastmilk, including estimation of infant exposure (contribution of IMI ConcePTION). Both case studies will inform recommendations for future efforts in the field of PBPK-based simulations in perinatal populations.

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L9 PBPK simulations in special populations. Are we ready for prime time?

Speaker

Eva Gil Berglund*, PhD

Senior Director in Clinical Pharmacology and Regulatory Strategy, Certara Drug Development Support, Oss, The Netherlands

eva.berglund@certara.com

Aim:
In this talk, the current status of PBPK simulations of PK in special populations will be covered. Can PKPB simulations replace conventional studies? Can the analysis support a sparse dataset? PBPK has established use in pediatric dose predictions enabling generation of efficacy and safety in children. Here a sparse dataset can also be reinformed with virtual populations. For patients with hepatic or renal impairment, as well as other populations for which an altered PK is expected, a combined MIDD approach is proposed for these populations, predicting exposures using PBPK, confirming using popPK and E-R. This approach allows safety and efficacy information to be generated in these populations, going beyond the single-dose PK study usually present for labelling support. In cases where the conventional single dose study is performed, steady state exposures can be simulated where needed. Combination treatment can be addressed as well as DDIs.

L10

Clinical Pharmacology considerations for development of somapacitan for rare paediatric growth disorders.

Rasmus Juul Kildemoes

Introduction: Somapacitan is a once weekly long-acting growth hormone (GH) approved for treatment of GH deficiency (GHD) in children and adults, and in development for other rare growth indications in children. In children with GHD somapacitan increases growth velocity primarily via pharmacodynamic (PD) marker Insulin like-growth factor-I (IGF-I). This presentation aims to outline the clinical pharmacology considerations during development of somapacitan in children, including trial designs and pharmacokinetic (PK) and PD sampling, dose selection rationales and comparison to daily GH and PK/PD characterization.

Methods: Full PK and PD profiles of somapacitan were collected and characterized in phase 1 after single and multiple doses adults (healthy and with GHD, doses ranging 0.01 mg/kg to 0.32 mg/kg/week) and after single doses (0.02-0.16 mg/kg) in 24 children with GHD. In children with GHD, phase 2 was conducted in 59 patients investigating 0.04-0.16 mg/kg/week somapacitan compared to daily GH and phase 3 compared 0.16 mg/kg/week to daily GH in 200 children. In both phase 2 and 3 sparse PK/PD sampling was implemented to characterize peak, average and trough PK. A separate phase 2 was conducted in 62 children born short for gestational age (SGA) at 0.16-0.24 mg/kg/week, and phase 3 is currently ongoing. Across studies population PK/PD and exposure-response modelling was used to bridge across studies, select doses relative to comparator daily GH and guide trial designs to maximize information in the relative few patients available in these rare indications.

Results: Across studies somapacitan was found to display non-linear pharmacokinetics consistent with a dual absorption pathway and target mediated saturable elimination. In all investigated indications somapacitan was able to provide a weekly IGF-I response with a peak around day 2 and an average matching approximately day 4 after dose. Exposure-response to growth velocity was demonstrated in both phase 2 and 3 in children with GHD and in phase 2 in SGA (phase 3 ongoing). The trial designs, PK/PD sampling and modelling strategy was successful in guiding dose selection across phases and allowed dose setting and initiation of a successful phase 2 in SGA.

Conclusion: The development of somapacitan in rare paediatric growth disorders demonstrated the value of a robust clinical pharmacology and PK/PD modelling approach in dose selection and bridging across indications.

L11 Model-informed development of Mim8 - a novel bispecific antibody for the treatment of haemophilia A

Author: Mads Kreilgaard (1)*, Mads Bjelke (1), Paula Persson (1)

Institution: (1) Novo Nordisk A/S, Denmark, *email: mdkd@novonordisk.com

Aim: Mim8 is a novel, next-generation fully human monoclonal bispecific antibody in Phase 3 clinical development for subcutaneous treatment of haemophilia A (Lentz et al.; Persson et al.). Mim8 acts as a mimetic of activated FVIII by bridging activated coagulation factor IX and coagulation factor X on the surface of activated platelets. Assisted by model-informed drug development strategy, clinical development has been frontloaded to reduce time from first human dose to initiation of pivotal phase 3 in less than two years, including introduction of a novel tiered weight range treatment paradigm in haemophilia.

Methods: Prior to clinical data, a cynomolgus monkey Mim8 PK model was scaled to humans by allometric methods. Furthermore, two PKPD prediction models were developed: a) peak thrombin generation (biomarker for haemostasis) for Mim8 and emicizumab (Shima et al.); b) Repeated time-to-event model of treated bleeds in haemophilia patients (primary endpoint in pivotal phase 3).
Clinical PK and PKPD models were developed from Mim8 phase 1/2 studies, (Lentz et al.; Persson et al.). Iterative study simulations were performed to support phase 3 dose and weight-band selection in adult/adolescent and paediatric populations to ensure safety exposure cap as identified in FRONTIER1 and high reduction in relative bleed risk were covered for all extremes in the tiered weight range groups across QW, Q2W and QM dosing intervals.

Results and discussion: The popPK of Mim8 were best described with a structural 2-comp model with the baseline body weight (BW) included as allometric exponents on systemic PK parameters and drug product strength as covariate on relative bioavailability. The peak thrombin PKPD profiles for Mim8 and emicizumab were best described by a common sigmoidal Emax model with drug as covariate on all structural parameters. Mim8 was shown to generate equivalent peak thrombin response as emicizumab with 15-fold lower plasma concentration and have a 7% higher Emax compared to emicizumab. Treated bleeds were adequately captured by a repeated time-to-event model with constant baseline hazard and estimated Mim8 IC_{50} of 0.07 µg/mL on bleed risk in alignment with expectation from the peak thrombin biomarker.
The clinical PKPD models were used to define dosing regimens for the phase 3 studies in patients from 5-140 kg BW with QW, Q2W and QM dosing frequencies using a one-time loading dose followed by a maintenance dose in three weight ranges from <15, 15-<45 and >=45 kg. Study simulations ensured the average exposure cap was not exceeded and supported >97% relative reduction in bleed risk across all BW.

Conclusion: The model-informed drug development of Mim8 was shown to adequately design a novel treatment paradigm for patients living with haemophilia by utilising tiered dosing in phase 3 studies, and to enable early decision making and regulatory guidance to accelerate drug development.

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L12 Ambition Zero Carbon: Accelerating adoption of Next Generation Propellant inhalation sprays by linking propellant and aerosol physics to predicted lung efficacy

Duy Nguyen & Michael Williams, AstraZeneca

No abstract available

L13 Improved bioequivalence assessment through model-based and model-informed strategies

Xiaomei Chen, Mats O. Karlsson, Andrew C. Hooker,
Pharmacometrics Group, Department of Pharmacy, Uppsala University

We have developed a model-based method for bioequivalence (BE) evaluation. Unlike traditional non-compartmental analysis (NCA), this method is capable of handling sparse data and supporting alternative BE study designs, offering greater flexibility with higher statistical power. A challenge in applying the model-integrated BE method is identifying an appropriate population pharmacokinetic (popPK) model for the analysis. In some cases, popPK models for the reference product are either unavailable or not identifiable based on BE data. To solve the above problems, we have investigated strategies such as model averaging for model-based BE approaches. Another challenge is the potential inflated type I error, for which we applied and compared three methods to estimate parameter uncertainty. Among the explored methods, the sampling importance of resampling showed controlled type I error through simulation studies in the scenarios of sparse sampling. The developed model-based BE analysis makes it possible to evaluate the bioequivalence of long-acting injectables (LAI) based on a shorter study design than a standard steady-state crossover BE study. An alternative strategy for LAIs BE evaluation is model-informed BE analysis, in which the existing popPK model is not used in the process of BE evaluation but to inform the development of a modified NCA-based BE method.

L14 Biopharmaceutical Evaluation of the Subcutaneous Administration

Marta Venczel, Sanofi

No abstract available

L15 Development of a pre-clinical model-based drug regimen platform for antibiotics within a European perspective

Ulrika Simonsson, Department of Pharmaceutical Biosciences, Uppsala University, Sweden

The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to improve health by speeding up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need. IMI facilitates collaboration between the key players involved in healthcare research, including universities, the pharmaceutical and other industries, small and medium-sized enterprises (SMEs), patient organizations, and medicines regulators. It is a partnership between the European Union (represented by the European Commission) and the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations).

Tuberculosis is the leading cause of death by an infectious disease worldwide. According to the World Health Organization (WHO), an estimated 10 million people became ill with tuberculosis in 2018, and 1.6 million died. Europe has a critical patient situation, mainly due to high resistance to existing antibiotics. Until now, the development of new drugs has been slow and their incorporation into tuberculosis treatment regimens conducted in a sequential manner. Standard tuberculosis treatment is based on a combination regimen of four drugs that were all developed over 60 years ago. Treatment lasts for at least six months and, in the case of resistance to the standard drugs, can be as long as two years. The current drugs are inefficient by today's standards and a new, faster-acting and safer treatment is required to reduce the length of therapy and to overcome the menace of drug-resistant strains.

The European consortia ERA4TB (era4tb.org), funded by IMI, started in 2020 and will last seven years, at the end of which, the consortium expects to have developed at least two or more new combination regimens with treatment-shortening potential ready for Phase II clinical evaluation. The partners intend to maintain the ERA4TB platform active beyond the project official duration.

Assessment of pharmacodynamic drug interactions is a cornerstone of the development of combination drug therapies for tuberculosis. In addition, a crucial step for accelerating tuberculosis drug development is bridging the gap between preclinical and clinical trials.

L16 Combinations in cancer treatment: Using Translational PKPD to narrow down the parameter space to explore dose, sequence & schedule

Owen Jones, AstraZeneca

Combining two or more drugs is an important therapeutic approach for the treatment of many cancers. Combinations provide an opportunity to enhance the effectiveness of the treatment, overcome resistance mechanisms, or broaden the number of patients that see benefit. The last few years has seen a considerable increase in the proportion of clinical trials involving combination approaches, however, the success rate of these trials is very low. The reasons for this low success rate include the challenge in finding the optimal way in which to dose the combination that ensures tolerability, whilst retaining the desired efficacy. The variables for how to dose a compound to a patient include the size of the dose, the frequency of the dose (schedule) and the order in which the therapies are delivered (sequence). To fully explore these options in the clinic can be prohibitive and therefore, it is desirable to be able to use non-clinical data and Translational PKPD modelling to prioritise the options to test clinically. Using three case studies, this talk will present the case for the use of non-clinical data and Translational PKPD modelling to narrow down the options around dose, schedule and sequence, to input into more focussed clinical trial designs.

List of Participants

First name	Last name	Organisation	City
Virginia	Aimetta	MetaSafe Sweden	Södertälje
Moamin	Alkakaei	Uppsala universitet	Uppsala
Mounier	Almett	AstraZeneca	Mölndal
Anita	Andersson	RegSmart Life Science	Uppsala
Pieter	Annaert	KU Leuven	Leuven
Johan	Areberg	Lundbeck	Valby
Sara	Asimus	AstraZeneca	Mölndal
Michael	Baldwin	Novo Nordisk	Søborg
Jens	Barthel	Federal Office of Consumer Protection and Food Safety	Berlin
Eva	Berglund	Certara	Uppsala
Mikael	Boberg	AstraZeneca	Mölndal
Alessandro	Boianelli	AstraZeneca	Mölndal
Britta	Bonn	Ribocure Pharmaceuticals	Mölndal
Isabella	Bonner Karlsson	AstraZeneca	Mölndal
Olof	Breuer	Karolinska University Hospital	Huddinge
Johan	Bylund	CTC Clinical Trial Consultants	Uppsala
Frida	Bällgren	Uppsala University	Uppsala
Paul	Callaghan	Uppsala University	Uppsala
Brooke	Carlson	AstraZeneca	Mölndal
Simon	Carter	Astrazeneca	Mölndal
Fang-Ching	Chao	Astrazeneca	Mölndal
Xiaomei	Chen	Uppsala University	Uppsala
David	Dahlgren	Uppsala University	Uppsala
Bengt	Dahlström	CTC Clinical Trial Consultants	Uppsala
Maria	de Frumiere	AstraZeneca	Mölndal
Paul	Dickinson	Seda Pharmaceutical Development Services	Stockport
Ilse	Dubbelboer		Uppsala
Emma	Eckernäs	Pharmetheus	Uppsala
Helena	Edlund	AstraZeneca	Mölndal
Hans	Ericsson	Astrazeneca	Mölndal
Ulf	Eriksson	UGE PK Consulting	Kungsbacka
Alan	Faraj	Novo Nordisk	Uppsala
Erika	Fredriksson	Läkemedelsverket	Uppsala
Markus	Fridén	AstraZeneca	Mölndal
Aghavni	Ginosyan	Uppsala University	Uppsala
Milda	Girdenyte	Uppsala University	Uppsala
Sofia	Gustafsson	BioArctic	Stockholm
Johanna	Haglund	MetaSafe Sweden	Södertälje
Alzahra	Hamdan	Uppsala University	Uppsala
Margareta	Hammarlund-Udenaes		Uppsala
Lene	Hansen	H. Lundbeck A/S	Valby
Lisa	Helgeson	Irlab	Göteborg
Irene	Hernandez Lozano	Novo Nordisk	Søborg
Myriam	Hislen	Recipharm OT Chemistry	Stockholm
Madlen	Hubert	Uppsala University	Uppsala
Gunilla	Huledal	Clinical Optime AB	Solna
Darina	Hynes	BioIVT	Kansas City
Emre	Isin	Servier	Vaugrigneuse
Suzanne	Iverson Hemberg	Toxicology Knowledge Team Sweden	Södertälje
Rasmus	Jansson Löfmark	AstraZeneca	Mölndal
Owen	Jones	AstraZeneca	Mölndal
Karl-Gustav	Jostell	qParmetra LLC Ciconia Clinical Consulting	Uppsala
Imola	Juhasz	BioIVT	Szeged
Rasmus	Juul Kildemoes	Novo Nordisk	Bagsvaerd
Maria	Karlgren	Uppsala university	Uppsala
Jasia	King	AstraZeneca	Mölndal
Therese	Knubbe	Integrative Research Laboratories Sweden	Göteborg
Mads	Kreilgaard	Novo Nordisk	Bagsvaerd
Michael	Kurczy	AstraZeneca	Mölndal
Eva	Lamm Bergström	AstraZeneca	Mölndal
Jacob	Leander	AstraZeneca	Mölndal

Rory	Leisegang	Novo Nordisk	Bagsvaerd
Hans	Lennernas	Uppsala University	Uppsala
Elsa	Lilienberg	SDS Life Science	Uppsala
Elin	Lindhagen	Läkemedelsverket	Uppsala
Irena	Loryan	Uppsala University	Uppsala
Anna	Lundahl	AstraZeneca	Mölndal
Mia	Lundblad	Novo Nordisk	Malmö
Boel	Löfberg	Integrative Research Laboratories Sweden	Göteborg
Lakshmi Mohan Vamsi	Madgula	Sai Life Science Limited	Macclesfield
Luca	Marzano		Stockholm
Pär	Matsson	Göteborgs Universitet	Göteborg
Veena	Mechanda Madappa	Sai Life Science Limited	Macclesfield
Johanna	Melin	AstraZeneca	Mölndal
Alina	Meyer	Uppsala University	Uppsala
Evgeniya	Mickols	Uppsala University	Uppsala
Nicolai Rytter	Mortensen		Søborg
Hitesh	Motwani	MetaSafe Sweden	Södertälje
Victorine	Muse	Novo Nordisk	Bagsvaerd
Judi	Møss	Novo Nordisk	Bagsvaerd
Benyamin	Naranjani	Uppsala University	Uppsala
Yomna	Nassar	Novo Nordisk	Søborg
Duy	Nguyen	AstraZeneca	Mölndal
Janis	Niessen	Uppsala University	Uppsala
Anna	Nordmark	Nordmark ClinPharm Consulting	Huddinge
Vijender	Panduga	AstraZeneca	Mölndal
David	Pekar	Lablytica Life Science	Uppsala
Sofia	Pekkari	Red Glead Discovery	Lund
Paula	Persson	Novo Nordisk	Bagsvaerd
Carl	Petersson	Merck	Darmstadt
Zvonimir	Petric		Mölndal
Henrik	Podéus Derelöv	Linköping University	Linköping
Susanne	Prothon	AstraZeneca	Mölndal
Angelica	Quartino	AstraZeneca	Mölndal
Natallia	Rameika	Uppsala University	Uppsala
Sonja	Rapp	BioNTech SE	Mainz
Joana	Rebouta	AstraZeneca	Mölndal
Vanessa	Rees	Novo Nordisk	Bagsvaerd
Carl	Roos	Novo Nordisk	Bagsvaerd
Staffan	Rosenborg	Karolinska University Hospital	Huddinge
Muhammad Waqas	Sadiq	AstraZeneca	Mölndal
Ferran	Sanchez	Sciex	Madrid
Friederike	Sandbaumhüter	AstraZeneca	Mölndal
Anna	Sandholm	TKT Sweden	Södertälje
Frank	Scheffler	Hypha Discovery Limited	Abingdon
Ulrika	Simonsson	Uppsala University	Uppsala
Fianne	Sips	InSilico Trials Technologies	Trieste
Erik	Sjögren	Pharmetheus	Uppsala
Carl	Stenbratt	AstraZeneca	Mölndal
Marie	Strimfors	AstraZeneca	Mölndal
Nicolas	Sundqvist	Linköping University	Linköping
Mikael	Sunnåker	AstraZeneca	Mölndal
Carolina	Säll	Novo Nordisk	Bagsvaerd
Foteini	Tzioufa	Uppsala University	Uppsala
Johannes	Törnell		Västra Frölunda
Irès	van der Zwaan	AstraZeneca	Mölndal
Márta	Venczel	Sanofi	Frankfurt am Main
Pete	Webborn	PJHW Consultancy	Macclesfield
Patrick	Wehrli	AstraZeneca	Mölndal
Erik	Westrin		Uppsala
Michael	Williams	AstraZeneca	Mölndal
Joshua Charles	Woolliscroft	SCIEX	Alderley Park
Ulrika	Wählby Hamrén	AstraZeneca	Mölndal

Organizing Committee

Johanna Haglund, MetaSafe
Suzanne Iverson Hemberg, Toxicology Knowledge Team Sweden
Rasmus Jansson Löfmark, AstraZeneca i

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