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S-001

An Adaptive Bayesian Method for the Development of Individualized Anemia Management Protocols in End-Stage Renal Disease Patients

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Objectives: Anemia is a common complication in end-stage renal disease (ESRD). Anemia management protocols (AMPs) are still controversial and not accounting for intersubject/intrasubject variability in maintaining a narrow hemoglobin (HGB) target, 10 – 12 g/dL. We applied an adaptive Bayesian method to predict HGB responses to recombinant human erythropoietin (rHuEPO) in ESRD patients for the development of individualized AMPs.

Methods: Two data sets were used in this study. Data A included 22 patients receiving subcutaneously (SC) maintenance doses of rHuEPO over 85 days. Number of HGB concentrations per subject varied from 3 to 12 (median = 5). Data B included 24 patients treated similarly with rHuEPO. HGB concentrations were collected 5 times (2-week intervals over 8 weeks). A population Bayesian pharmacodynamic (PD) model was fitted to data A utilizing an established model and its parameters as priors [1]. The model contained 5 transit compartments describing red blood cell (RBC) life span (T_{RBC}). HGB concentrations were proportional to RBC counts in all compartments. Model parameters included S_{max} (maximum stimulation), SC_{50} (drug potency), and T_{RBC}. rHuEPO concentrations used to stimulate HGB responses were simulated from a validated population pharmacokinetic (PK) model for healthy subjects [2]. The posterior distributions of the population parameters were used as priors to fit the same PD model to each subject in data B individually. At step 1, the individual model was fitted using 3 HGB observations to predict the 4th and 5th observations. At step 2, the model was adaptively updated with the 4th observation to predict the 5th observation. The study utilized RStan with PKPD library Torsten in RStudio [3].

Results: The estimates of population parameters were: T_{RBC}: 62 days (41 – 111), median (95% credible interval, CrI); S_{max}: 0.00791 g/dL/h (0.00461 – 0.0121); SC_{50}: 3.74 mIU/mL (1.68 – 8.02). At step 1, HGB concentrations were well predicted within 95% CrIs in 15/24 subjects for the 4th observations and in 16/24 subjects for the 5th

observations. At step 2, the 5th observations in 16/24 subjects were predicted within 95% CrIs. Compared with step 1, the 5th observations in 14/24 were predicted more accurately after the model was adaptively updated at step 2.

Conclusions: The Bayesian PKPD model reasonably predicted HGB concentrations 2 weeks in advance in individual patients. Prediction accuracy was increased by incorporating new HGB information. We demonstrated that an adaptive Bayesian method can be used to develop individualized AMPs in ESRD patients. This approach leveraged prior knowledge of population model parameters to inform individual models in analyzing sparse clinical data. Intersubject/intrasubject variability was addressed by modeling data individually and adaptively.

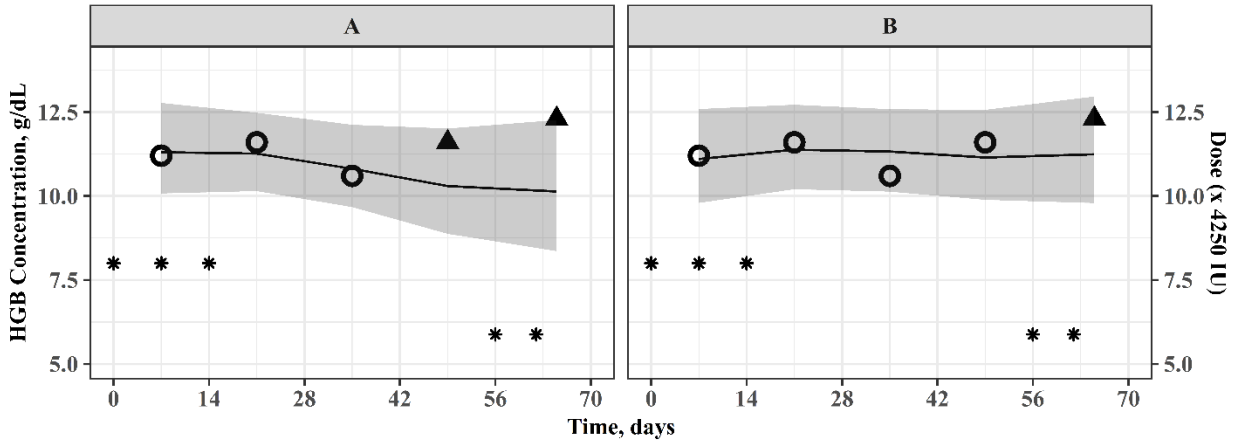

Figure 1: Goodness of fit and model predictions of HGB concentrations for a representative patient. Circles are observations used for model fitting, triangles are observations to be predicted, stars are rHuEPO doses, lines are median predictions, shaded bands are 95% credible intervals. At step 1 **(A)** the 4th observation was predicted well, but the 5th observation prediction was less accurate. At step 2 **(B)** the model was updated adaptively with the 4th observation resulting in a more accurate prediction of the 5th observation and a narrower 95% credible interval.

References: Wu et al. Journal of Clinical Pharmacology, 2015. 55(10): 1157-1166.
Olsson-Gisleskog et al. Clin Pharmacokinet, 2007. 46(2): 159-173.
Torsten Manual: https://github.com/metrumresearchgroup/Torsten/blob/master/example-models/torstenManual.pdf

S-002

Towards EMA Qualification of Islet Auto-Antibodies as a Model-Based Clinical Trial Enrichment Platform for Type-1 Diabetes Prevention Studies

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Objectives: Currently, there are no therapies to prevent or delay the onset of Type-1 Diabetes (T1D). It is widely accepted that three distinct Islet auto-antibodies (AAs) termed GAD65, IAA, and IA-2A, are biomarkers associated with T1D risk, where presence of multiple increases risk. The objective of this work is to highlight the progress of utilizing patient-level data from two T1D observational studies to develop a survival model for predicting T1D diagnosis based on AA numbers and other patient features for the purposes of generating strategies to optimize clinical trial design. The work is intended to be submitted to EMA for qualification of the model-based biomarker on behalf of the T1D consortium founded by the Critical Path Institute.

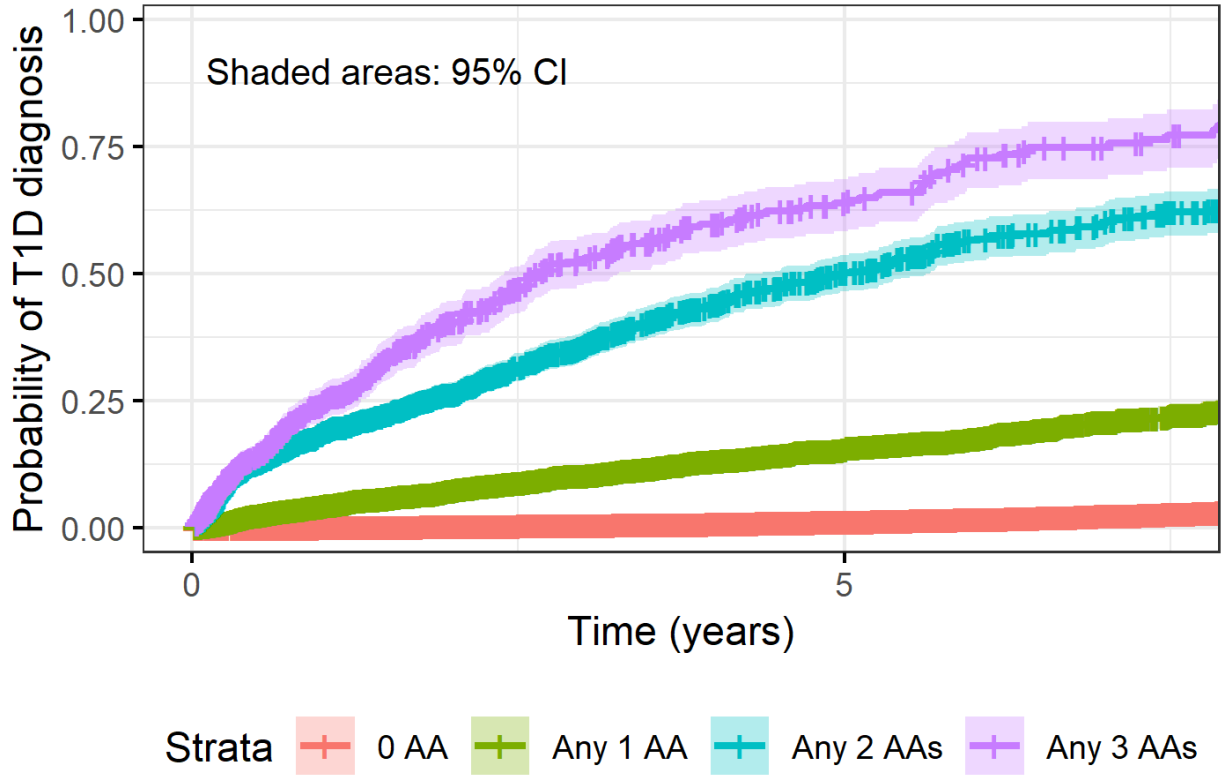
Methods: Patient-level data from the TN01 and TEDDY studies was acquired, curated, and aggregated to conduct preliminary analyses (51,932 individuals). A subset of data containing 2,395 individuals and corresponding covariates predictive of T1D were selected, which included the number and type of two or more AAs, blood glucose measurements at 0 (fasting) and 2 hours (after consuming a sugar rich liquid), HbA1c measurements (3 month time history metric is abnormal glucose), HLA subtypes (genetic risk factors), and patient demographics (age, sex, and

first-degree relative T1D status). A semi-parametric Cox proportional hazards (PH) model was used to quantify the effect of baseline covariates on the time to T1D diagnosis.

Results: A survival analysis was used to quantify risk associated with different numbers of baseline AAs using the larger dataset (**Figure 1**). Results indicate clear dependence of T1D onset associated with different numbers of baseline AAs. The concordance index for the PH model was 0.829 (SE = 0.008). Significant hazard ratios were indicated for IA2A, 2-hour blood glucose measurement, and baseline age with values (95% CI) of 2.14 (1.75-2.6), 2,77 (2.56-3.00), and 0.79 (0.73-0.86) respectively.

Conclusions: Regulatory endorsement of biomarkers for unmet medical needs is a critical component to provide confidence for drug developers to use these tools. Further, the practical adoption of these tools by drug developers requires model-based approaches to best leverage both the biomarker and relevant patient features together to best optimize clinical trials design.

Figure 1: Incidence curves for the time-varying probability to T1D diagnosis stratified by the number of baseline AAs



S-003

Development of a population pharmacokinetic model for recombinant factor IX and its use in determining limited sampling strategies for pediatric patients

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Objectives: IXINITY is a recombinant factor IX (rFIX) product used in the treatment of hemophilia B. A clinical trial to evaluate IXINITY pharmacokinetics (PK) in pediatric patients (<12 years old) will begin in August 2019 (NCT03855280). Outcome measures including half-life will be estimated following a sampling schedule based on the European Medicines Agency recommendations and consisting of five samples at predose (Pre), 0.25-0.5, 4-6, 24-26, and 46-50 hours post-infusion. However, participating centres may be reluctant or unable to collect this many samples from younger patients due to pediatric sample volume limitations. We aimed to leverage adult and pediatric PK data from other rFIX products and adult data from IXINITY to develop a population PK model relevant for all ages. The model was then used to perform a limited sampling analysis (LSA) to determine if any sampling times can be omitted without compromising the accuracy of the parameter estimates when assessed using Bayesian forecasting.

Methods: The modelling dataset for three brands of standard half-life rFIX was assembled via the Web Accessible Population Pharmacokinetic Service – Hemophilia (WAPPS-Hemo) from both clinical trials and routine practice (21% pediatric data; lowest age = 2.5 months). The model was developed and evaluated according to a previously published data analysis plan [3]. An LSA was performed to determine acceptable sampling strategies for pediatric populations ($n = 1000$) of age two, five, and eleven. The designs tested for the LSA are subsets of the aforementioned schedule. The Bayesian predictions of PK parameters from each sparse sampling design were then compared to those obtained from a rich (10+ samples) design.

Results: The results of the LSA were similar for all ages and are summarized in Figure 1, and indicate that the 48 hour sample is the most critical for the accurate estimation of half-life. If only three samples can be obtained, the Pre-6-48h and 0.5-6-48h designs performed the best, with median errors below 10% on all PK parameters and trough levels; on the other hand, the Pre-0.5-6h design accurately estimated central volume, but resulted in high errors on most outcomes of interest. Several two-sample designs also performed well (median half-life error <10%), most notably the 0.5-48h strategy.

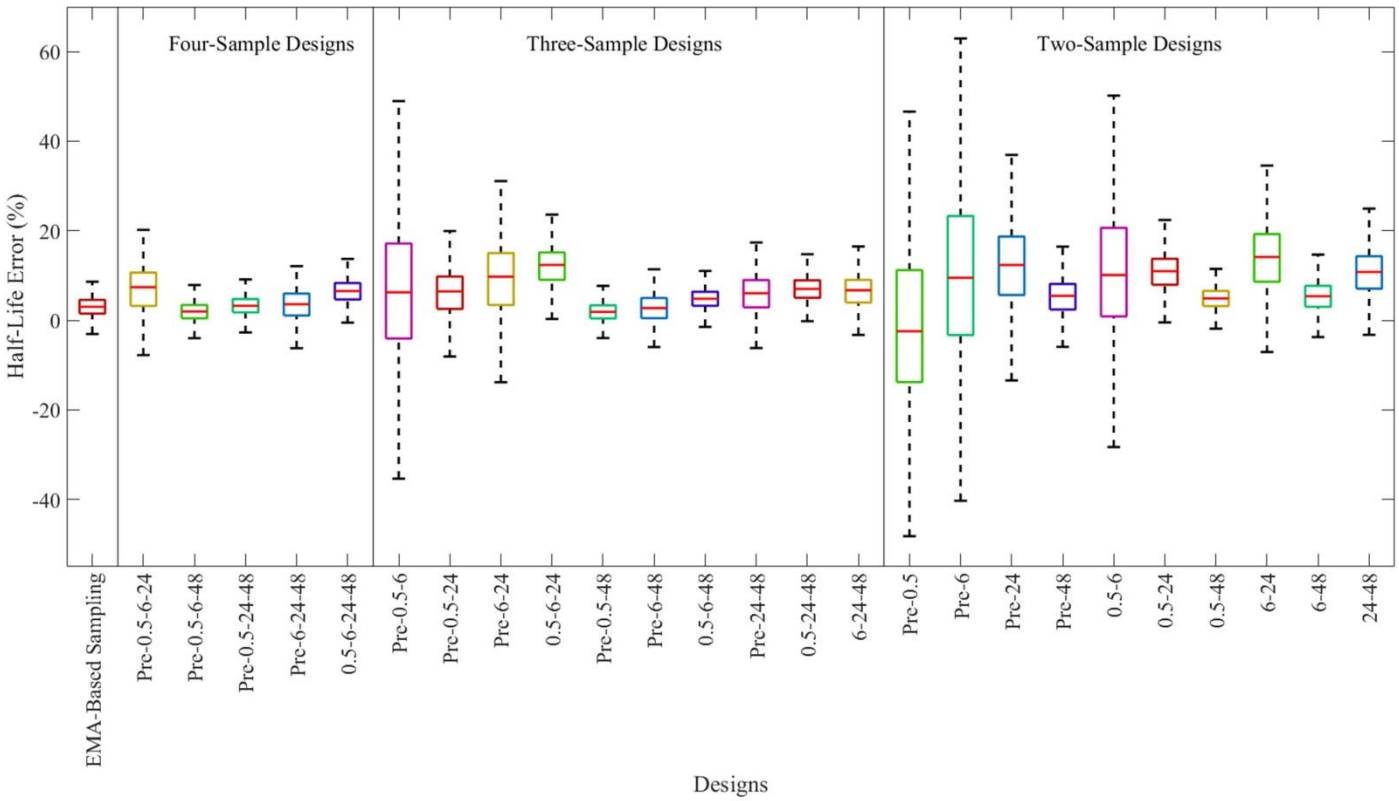

Figure 1. Error on half-life estimates from limited sampling strategies in 1000 virtual 5-year-olds

Conclusions: Leveraging pediatric data collected through the WAPPS-Hemo network, we developed a generic rFIX model. The LSA suggests that a subset of two or three of the five recommended sample times can be used to obtain accurate estimates of PK parameters in pediatric patients, provided one of the two later points is retained.

References: [1] Preijers et al. *J Thromb Haemost.* 2017;15(9):1737-1746. [2] Brekkan et al. *J Thromb Haemost.* 2016; 14(4):724-732. [3] McEneny-King et al. *JMIR Res Protoc*. 2016; 5(4):e232.

S-004

Selection of Fixed Dose 350 mg Every 3 Weeks (Q3W) Cemiplimab (Anti–PD-1) in Patients with Advanced Malignancies based on Population Pharmacokinetics (PopPK) Modeling

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Objectives: A PopPK model was developed to characterize the pharmacokinetics of cemiplimab and identify clinically relevant sources of variability in patients with a wide range of solid tumors. Results from PopPK simulations were used to select a fixed dose Q3W regimen that generates similar cemiplimab exposure as a body weight adjusted 3 mg/kg Q2W regimen.

Methods: PopPK analysis was based on combined data sets from Phase 1 and 2 studies of cemiplimab (NCT02383212 and NCT02760498), comprised of 505 patients with solid tumors. Majority of the samples (10,263/10,935=94%) were collected from patients who received body weight adjusted doses of cemiplimab (1, 3, 10 mg/kg Q2W and 3 mg/kg Q3W); the remainder received a fixed dose regimen (200 mg Q2W), the only fixed dose tested prior to model development.

The PopPK model was developed in three stages, resulting in a base model, a full covariate model, and a final covariate model. Significant sources of variability in cemiplimab exposure were identified by covariate analysis. Modeling and simulations of cemiplimab exposure with different dosing regimens were conducted for dose selection. Simulated concentration-time profiles and the corresponding exposure metrics were used to support the selection of a fixed dose Q3W regimen in patients with advanced malignancies.

Results: A two-compartment model with zero-order IV infusion and first-order elimination well describe the pharmacokinetics of cemiplimab. The within dosing interval half-life (post-hoc mean) of cemiplimab at steady-state in patients with solid tumors is 19.2 days and the total volume of distribution is 5.20 L, similar to the findings for typical monoclonal antibodies. The final covariate analysis show that baseline body weight, serum albumin level, and IgG level are the most significant covariates impacting the exposure of cemiplimab, without clinically relevance. Simulations and post-hoc estimates of cemiplimab exposure with a fixed dose of 350 mg Q3W in patients with advanced malignancies showed similar cemiplimab exposure and inter-patient variability in exposure compared with a body weight adjusted dose of 3 mg/kg Q2W.

Conclusions: The results from PopPK modeling and simulations support the use of a 350 mg Q3W fixed dose regimen, with similar cemiplimab exposure to a body weight adjusted 3 mg/kg Q2W regimen, in patients with advanced malignancies.

S-005

Survival of the Fittest: Using a Genetic Algorithm to Find Improved Combination-Dosing Strategies against Carbapenem-resistant *Acinetobacter baumannii* in Critically Ill Patients

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Laboratory for Antimicrobial Pharmacodynamics, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, Buffalo, New York[1], New York State Center for Excellence in Life Sciences and Bioinformatics, Buffalo, New York[2] College of Pharmacy, California Northstate University, Elk Grove, California[3]

Objectives: Recently, the WHO has listed carbapenem-resistant *A. baumannii* as the 'Number 1 Priority' pathogen for research, as it can have carbapenem resistance rates as high as 60%. Consequently, clinicians often turn to empiric, non-optimized combinations. The objective of this study was to generate then model *in vitro* data of meropenem and polymyxin B (PMB) in combination against *A. baumannii*, then use these data to inform a genetic algorithm (GA) search for optimal dosing strategies.

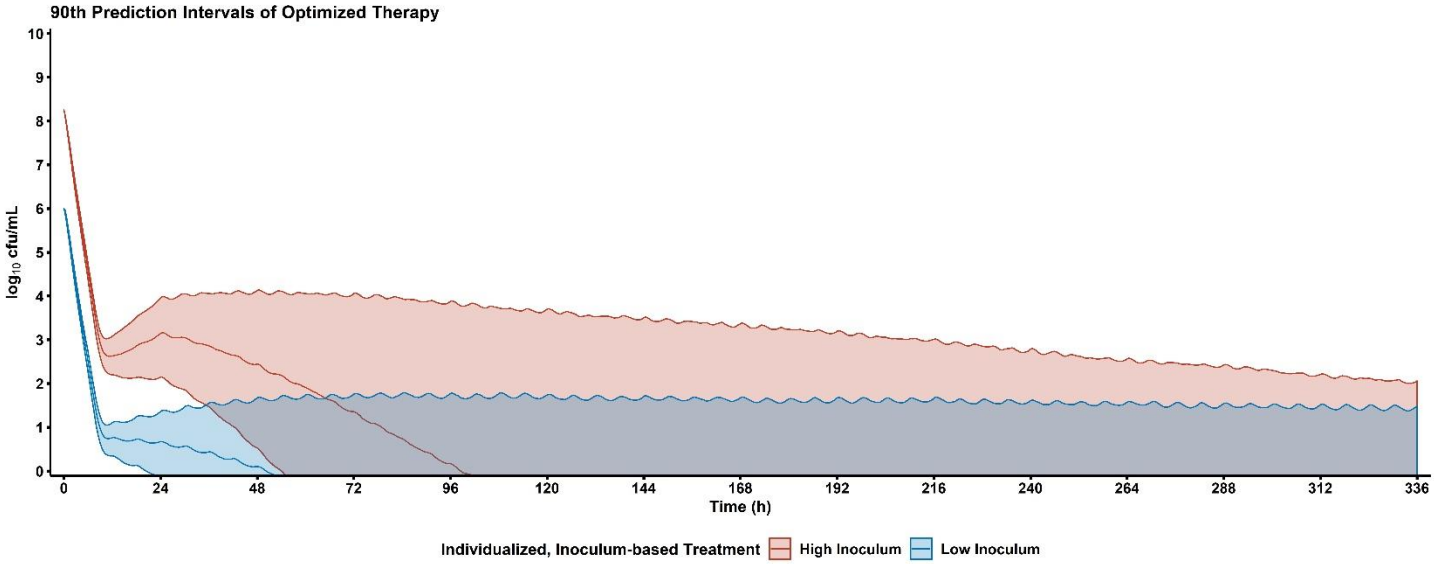
Methods: *A. baumannii* (N16870; $MIC_{meropenem}$ = 16mg/L [R], MIC_{PMB} = 0.5mg/L [S]) was studied *in vitro* using a dynamic hollow fiber infection model (HFIM) over 14 days at a high starting inoculum (10^8 cfu/mL). Meropenem was given to replicate the time-course of human PK as 4g 3hPI Q8H alone and in combination with PMB, which was given as a dose-escalated 'front-loading' regimen (0 h dose was approximately 2.3-fold higher than maintenance dosing) administered Q12H. The PMB dosing levels were selected to produce $fC_{ss,avg}$ = 0.75, 1.50, 2.50, 5.00, and 10.0 mg/L. A mechanism-based model (MBM) was then developed to describe total counts from these data and previously published HFIM data using S-ADAPT. Published PopPK data in critically ill patients was used to inform Monte Carlo simulations of the MBM. A GA was implemented to search for optimal dose, infusion time, dosing interval, and loading dose for both drugs given simultaneously guided by an objective function calculated using the 90th prediction interval of bacterial killing.

Results: Monotherapy for both drugs failed, showing bacterial growth to 10^{10} cfu/mL by 24 h. In combination, PMB $fC_{ss,avg} \geq 5.00$ mg/L achieved bacterial eradication (0 cfu/mL). The MBM described the data well, showing that the PMB-susceptible subpopulations had a much lower threshold for synergy (0.927mg/L) than the PMB-resistant subpopulations (3.40 mg/L). The GA had a strong preference for meropenem regimens that improved the %T>MIC: longer infusion times and shorter dosing intervals. For a high 10^8 cfu/mL inoculum, the GA found that 90% of simulated subjects experienced microbiologic cure using meropenem 19.6 g/day 2hPI Q5H + PMB 5.27mg/kg/day 2hPI Q6H (where the 0h Mero and PMB doses are 'front-loaded' with 80.5% and 42.2% of the daily dose,

respectively). The dose of meropenem and PMB decreased to 18.3 g/day and 4.84 mg/kg/day, respectively, in the case of a 10^6 cfu/mL inoculum.

Conclusions: Strategic use of robust *in vitro* data, described by a MBM, can be used to generate rational, optimized combination drug regimens of meropenem + PMB against *A. baumannii* using a genetic algorithm. These methods aid in providing more data-informed decisions on dosing of multiple drugs simultaneously.

References: Lenhard et al., J Antimicrob Chemother. 2017 Jan;72(1):153-165 Sandri et al., Clin Infect Dis. 2013 Aug;57(4):524-31 Mattioli et al., Eur J Clin Pharmacol. 2016 Jul;72(7):839-48



S-006

Population Pharmacokinetic Modeling of Gentamicin in Pediatrics

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Objectives: High variability and unpredictability of gentamicin's pharmacokinetics (PK) in pediatric populations still exist after decades of usage, which reinforces the value of individualized dosing. A prior model is needed for performing Bayesian forecasting with repeated therapeutic drug monitoring (TDM) measurements to inform individualized dosing. The primary objective of this work was to characterize the pharmacokinetics of gentamicin across the whole pediatric age spectrum from premature neonates to young adults with a single model by identifying significant clinical predictors.

Methods: A nonlinear mixed-effect population PK model was developed with retrospective TDM data. A total of 6459 drug concentration measurements from 3370 hospitalized patients were collected for model building (n=2357) and evaluation (n=1013). The results of the modeling were compared between Phoenix NLME and PuMaS, a Julia based modeling and simulation platform.

Results: In agreement with previously reported models, a two-compartment model with first-order elimination best described the drug PK. Final parameter estimates were consistent with prior reports. Patient-specific factors significantly impacting gentamicin clearance (CL) included fat-free mass, postmenstrual age, and serum creatinine (SCr). Based on our model, the deviation of the individual SCr from the age-dependent expected mean SCr value (SCrM) can result in a 40% lower CL in a patient with renal impairment than that in a patient with normal kidney

function, with SCrM:SCr ratios between 0.16 and 3.2 fold in this study. Consistent with the known age-dependent changes of the proportion of extracellular water in bodyweight, the inclusion of the impact of extracellular water maturation on volume of the central compartment (V_1) was found to improve the model fitting significantly. The covariate model was able to estimate gentamicin CL and V_1 with good precision in pediatric patients spanning a wide range of ages (1-day to 19-year-old). In comparison with other previously published models, external evaluation suggested the developed model was the least biased and inaccurate. The results were compared between Phoenix and PuMaS and they matched.

Conclusions: The model described in this study presents the first population PK model for gentamicin in the whole pediatric age spectrum ranging from 1-day-old newborns to 19-year-old young adults. The model was developed by physiologically plausible covariate parameterization informed by principles of allometric scaling, GFR maturation described by PMA, and standardization for the age expected SCr measurement. The developed model is capable of providing prior information for all pediatric age groups, with good agreement with the adults' results, and used for initial dose individualization and adaptive dose adjustment of gentamicin in pediatric patients to improve the achievement of exposure targets. These results will be used to inform individualized initial dosing strategies for gentamicin in pediatric patients and provide a prior PK model for Bayesian updating and forecasting as individual clinical observations become available.

S-007

Optimal cytarabine and lenograstim schedules for acute myeloid leukemia using a population pharmacokinetic-pharmacodynamic model

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Objectives: We developed a population pharmacokinetic-pharmacodynamic (PK/PD) model describing the dynamics of white blood cells (WBC) of acute myeloid leukemia (AML) patients treated with cytotoxic cytarabine (Ara-C) and support of lenograstim (G-CSF, granulocyte-colony stimulating factor) during consolidation therapy. Further, we derived optimal treatment schedules from (robust) optimization problems considering terms in the objective function for disease progression, healthiness of the patient and therapy costs.

Methods: The second priority consolidation arm of the AMLSG 12-09 study [1] was provided by the Department of Internal Medicine III, University Hospital Ulm, Ulm, Germany and used for model development, validation and calibration. We linked and extended the myelosuppression model considering endogenous G-CSF [2] with a PK model for Ara-C [3] and lenograstim [4].
To obtain a clinical impact from mathematically optimized treatment schedules, cytokine-dependent leukemic cells were incorporated to the PK/PD model via a two-compartment model [5]. The interaction between WBCs and leukemic cells occurs through competition for G-CSF. The PK/PD model was fitted to WBC and leukemic cell count measurements using nonlinear mixed-effects modeling (NONMEM 7.4). Then, we apply a computational approach for treatment schedule optimization to the novel PK/PD model [6]. For one exemplary patient the first two CCs were used for model personalization. The treatment schedule of the third CC was optimized and compared to the actual CC.

Results: The WBC concentration-time data were best described by the extended myelosuppression model considering a parametrized secondary PD effect of Ara-C on the proliferation speed. Regarding the obtained optimal treatment schedules, the optimization suggests two consecutive CCs with a reduced Ara-C dosage and daily lenograstim administrations leading to higher nadir values.

Conclusion: We present a PK/PD model for predicting leukopenia during consolidation therapy of AML patients. In a case study we demonstrate a computational approach minimizing the number of leukemic cells thereby reducing clinically important adverse events like leukopenia.

References: [1] Schlenk, R. F., et al., Randomized phase-II trial evaluating induction therapy with idarubicin and etoposide plus sequential or concurrent azacitidine and maintenance therapy with azacitidine, Leukemia, 2019. [2] Quartino A. L., et al., Characterization of endogenous G-CSF and the inverse correlation to chemotherapy-induced neutropenia in patients with breast cancer using population modeling, Pharmaceutical research, 2014. [3] Jost F., et al., Mathematical Models for cytarabine-derived myelosuppression in acute myeloid leukaemia, PLOS ONE (submitted 5.9.2018). [4] Hayashi N., et al., Pharmacokinetic and pharmacodynamic analysis of subcutaneous recombinant human granulocyte colony stimulating factor (lenograstim) administration, The Journal of Clinical Pharmacology, 1999. [5] Stiehl T., et al., Mathematical modeling of the impact of cytokine response of acute myeloid leukemia cells on patient prognosis, Scientific reports, 2018. [6] Jost F., et al., A feedback optimal control algorithm with optimal measurement time points, Processes, 2017.

S-008

Application of the Optimal Design Approach to improve Therapeutic Drug Monitoring of Busulfan in Children receiving Hematopoietic stem cell transplantation (HSCT).

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Objectives: Busulfan is the most commonly used agent in Hematopoietic stem cell transplantation (HSCT) conditioning regimes, given alone or in combination. Considerable inter-patient variability exists in the effectiveness and toxicity of busulfan-containing conditioning regimens. Therefore, personalizing Busulfan doses improves the clinical outcomes, and it is clinically accepted due to a narrow therapeutic window. The **objective** of this study was to find a design that minimizes the uncertainty of population parameters used for busulfan dose prediction.

Methods: Data on 72 patients receiving Busulfan prior an HSCT (7 months-18 years, 5.1–47.0 Kg), suffering from immunodeficiencies or malignant diseases, was used to build a 2-compartment pharmacokinetic (PK) model of the drug. Busulfan (1-2 mg/Kg) was administered intravenously in a 2 or 3-hour infusion for four days prior HSCT, either every day, twice daily or every 6 hours. Blood samples to determine busulfan concentration in plasma were obtained prior the first administration, and 5, 10 and 30 minutes, 1, 2 and 4 hours after the end of the infusion. Once the PK model was built, a distribution of the population parameters was used in the optimization as prior information. The software PopED was used to perform optimal design of the sampling schedule. The covariates included in the PK model were taken into account in the optimization exercise (weight affecting the dose and the all the PK model parameters and age, affecting clearance).

Results: The optimized design considered the three different administration schedules of busulfan, so there is only one protocol of sampling extraction independently from busulfan administration schedule. The optimized sample times that rendered best performance than the protocol times were: 15 minutes after the administration of the drug, and 5 minutes, 35 minutes, 1 hour and 45 minutes after the end of the infusion, and the last sample right after the next administration. Therefore, the new design represents a 16.6 % reduction (n=1) in sampling demanding with respect the current protocol. The efficiency of the optimized design with respect to the protocol was calculated to be 2.84, indicating significantly better performance of optimized design.
The expected Residual Standard Errors (RSE%) of the parameters under the optimal designs were compared to the RSE% of the protocol, showing a reduction from 1 to 27% RSE in the parameters. In addition, prediction performance of the optimized design was evaluated, obtaining similar parameter precision compared to the protocol (maximum bias <10 %).

Conclusions: An optimized sample times design for monitoring busulfan in pediatric patients under HSCT was developed. The evaluation of the reduced design suggests better performance than the original protocol, even reducing the samples per patient. We firmly believe that this work is of potential implementation in the clinical setting, improving patient care.

S-009

"Novel user-friendly applications for dose individualization of sunitinib and imatinib"

Authors: **Jonathan Chauvin, Geraldine Ayral, Pauline Traynard**

Affiliations: **Lixoft**

Objectives: Therapeutic drug monitoring (TMD) and dose individualization can contribute to increased benefits for patients by augmenting the efficacy and/or decreasing the risk of toxicity. TMD is especially interesting for drugs exhibiting a highly variable exposure between patients and a small therapeutic window. Target therapeutic windows are usually defined for the steady state through concentration of repeated dosing regimens and a single drug concentration measurement is made.

While dose individualization has been more and more advocated over the years, the lack of dedicated, user-friendly and reliable decision-support software hampers its use on a large scale in hospital care. We present dose-recommendation tools for two TKIs (sunitinib and imatinib) where clear relationships between exposure and treatment outcome have been established and the associated retrospective results on TMD hospital data.

Methods: The dose adaptation procedure is divided in two steps. We first determine the pharmacokinetic parameters of the patient, integrate the information from a population model and the drug concentration measurement(s) to calculate the conditional probability distribution of the individual parameters. Secondly, we use these parameters to perform simulations of alternative doses taking the operational constraints (such as available tablet doses) into account. The dose most likely to reach the target is selected.
This procedure has been implemented within two applications: one for sunitinib and one for imatinib in collaboration with hospital clinical pharmacologists.

Results: The interface is meant to be usable by non-modelers such as clinicians. The interface allows entering the current treatment, the last dose information. The application returns a dose recommendation as well as the drug concentration profile (and its uncertainty) with the current dose and with the proposed dose. A report is generated automatically and saved to an audit trail local data base.
To evaluate in advance the proportion of the patients that would benefit from sunitinib dose individualization, we have applied our dose-recommendation application to the TMD (without adaptation) data base of the Cochin Hospital (Paris, France). The data base records around 900 PK measures for 233 cancer patients. For only 16% of the patients the application recommended to maintain the standard dose, while for 67% the recommended dose was below the standard and for the remaining 17% above.

Conclusions: The developed dose-recommendation applications permit to use all available information in a rigorous mathematical framework to suggest the dose most likely to reach the therapeutic target. In addition, estimating the individual parameters gives more flexibility not requiring the measurement being at the trough.
The retrospective study on past sunitinib data shows the need for TMD and dose adaptation. In addition, the dose adaptation is expected to reduce the overall cost of the treatment as the average recommended dose is smaller than the standard dose.

S-010

Population Pharmacokinetics of Sarilumab in Japanese and Non-Japanese Patients with Rheumatoid Arthritis

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Objectives: To develop and validate a population pharmacokinetic (PopPK) model of sarilumab, a human monoclonal antibody blocking the interleukin (IL)-6α receptor, in Japanese and Non-Japanese patients with rheumatoid arthritis (RA), to determine sources of pharmacokinetic variability, and to identify covariates that are potential sources of variability in exposure.

Methods: A PopPK model was developed from sarilumab serum concentration data pooled across eight Phase 1, one Phase 2, and seven Phase 3 studies (including NCT01328522, NCT01850680, NCT02097524, NCT02017639, NCT02404558, NCT01061736, NCT01768572, NCT02057250, NCT02121210, NCT01709578, NCT02293902, NCT02373202), resulting in a final dataset of 12088 observations from 2,453 patients (76% Caucasian, 16% Asian including 285 Japanese, 3% Black and 5% other race) with RA. Leveraging the prior PopPK analyses and knowledge gained from cross-study comparisons, evaluation of covariates focused on demographic characteristics (including race, and Japanese vs non-Japanese), renal function, anti-drug antibody (ADA) and baseline disease activity. Potential covariates were identified according to a forward-addition, backward-deletion strategy. Validation of the final PopPK model was performed using bootstrapping and visual predictive checks.

Results: The pharmacokinetics of sarilumab were adequately described by a 2-compartment, target-mediated drug disposition model with parallel linear and non-linear (ie Michaelis-Menten) elimination and first order absorption. Body weight, ADA-status, albumin, sex, creatinine clearance and baseline C-reactive protein were statistically significant covariates influencing sarilumab pharmacokinetics. Sarilumab exposure increased with a lower body weight (analysis range 31.5 kg–183 kg). Compared with a typical 70 kg patient, with sarilumab at 150 mg q2w subcutaneously (SC) and 200 mg q2w SC, respectively, $AUC_{0\text{-}14}$ increased by 32% and 25% for a 59 kg patient and decreased by 23% and 20% for an 82 kg patient. Other statistically significant covariates were not considered to be clinically relevant. Race and Japanese vs non-Japanese had no statistically significant effect on the pharmacokinetics of sarilumab in the presence of the other covariates. A post hoc graphical inspection after repeated dosing suggested little or no impact of baseline Disease Activity Score 28-CRP or prior use of biologics on sarilumab exposure.

Conclusions: PopPK analysis indicated the absence of differences in the pharmacokinetics of sarilumab between Japanese and non-Japanese patients, aside from differences in body weight, which is the main intrinsic covariate in pharmacokinetics. No adjustment in sarilumab dose is required for body weight, or any other demographic characteristics assessed.

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Acknowledgements: Sanofi and Regeneron provided study funding and medical writing support (Sarah Feeny, Adelphi Communications). **Disclosures:** Christine Xu, Yoshihisa Shitara and Vanaja Kanamaluru are employees of Sanofi and Anne Paccaly is an employee of Regeneron Pharmaceuticals, Inc. All authors may hold stock and/or stock options in their company.

S-011

QT/TdP Risk Screen: a web-based tool for the early identification and real time assessment of drug-induced proarrhythmic and torsade de pointes safety risk

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Objectives: While it is well recognized that early identification of drug-induced proarrhythmic safety risks is crucial to drug development for ethical, animal sparing and costs reduction considerations[1], the availability of easily accessible, user-friendly tools for real time assessments of the proarrhythmic potential of chemical compounds has been lacking. The novel Tx index[2], implemented in the new web-based QT/TdP Risk Screen tool, was applied to a dataset of 84 compounds.

Methods: The tool is based on 206,766 cellular simulations of compound-induced effects on Action Potential Duration (APD) in isolated endocardial, midmyocardial, and epicardial cells and on 7,072 tissue simulations on QT prolongation in a virtual tissue[3]. Simulations were performed by blocking the slow and the fast components of the delayed rectifier current (I_{Ks} and I_{Kr}, respectively) and the L-type calcium current (I_{CaL}) at different levels. Based on these simulations, the Tx index was defined as the ratio of drug concentration leading to a 10% prolongation of the APD or QT over the maximum effective free therapeutic plasma concentration. A dataset of 44 non-torsadogenic and 40 torsadogenic drug compounds was used to validate the performance of the tool. The tool is available on the InSilicoTrials.com cloud-based platform built on the Microsoft Azure cloud environment, in compliance with the highest standards of security and privacy.

Results: The classification of the 84 compounds resulted in an accuracy ranging between 87% and 88% for the four Tx index values ($Tx\text{-}APD_{endo}$, $Tx\text{-}APD_{mid}$, $Tx\text{-}APD_{epi}$ and Tx-QT). Receiver operating characteristic (ROC) curves were constructed on the four estimated Tx values for each compound in the dataset to enable the identification of torsadogenic potential cut-off values. These were identified as 8, 8, and 6.4 for $Tx\text{-}APD_{endo}$, $Tx\text{-}APD_{mid}$, $Tx\text{-}APD_{epi}$ and as 9.2 for Tx-QT, respectively. Each risk assessment required only a few seconds per compound.

Conclusions: The web-based, user-friendly QT/TdP Risk Screen tool enabled a highly accurate classification of 84 known drug compounds paving the way to a potential break-through in *in silico* proarrhythmic risk assessment.

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S-012

Continuous learning in model-informed precision dosing: case study in pediatric dosing of vancomycin

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Background: Model-informed precision dosing (MIPD) has the potential to optimize drug dosing for many narrow therapeutic window drugs.[1-3] However, naively applying literature models into a new population often introduces significant bias and/or imprecision.[4,5] Developing new models for each new patient population requires considerable time and efforts, delaying potential optimal treatment of patients using MIPD. We have previously proposed a "Continuous Learning" strategy [4,6], in which an initial model is implemented at the point of care, then trained and updated continuously as new routinely collected TDM data becomes available.

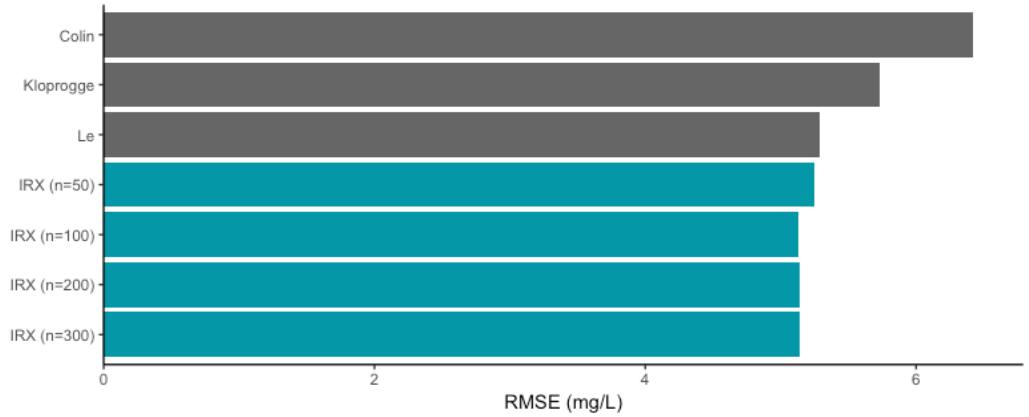
Objectives: Evaluate the potential improvement in predictive performance of CL applied to MIPD vancomycin dosing in a pediatric population.

Method: Models were trained and tested on de-identified patient data collected on the InsightRX platform during routine care of pediatric patients (1 month – 20 years of age) treated with vancomycin at a single US hospital. A popPK model was defined with a pre-specified model structure (serum creatinine and age affecting clearance, and allometric scaling of clearance and volume parameters). The data supported only estimation of 1-compartment models. This model was then trained on test datasets of varying sizes (n = 50, 100, 200, 300 patients), while predictive performance was evaluated in a hold-out dataset of n=322 patients. Predictive performance, defined as the ability of the tool to predict the next vancomycin trough level for the patient given all data available prior to the collected level, was compared to that of three previously published parametric population PK (popPK) models for

vancomycin built on data from a general pediatric population [7-9]. Computation was automated using NONMEM FOCEI and PsN proseval.

Results: CL improved predictive precision by 1-20% compared to the three literature models: RMSE for the CL models was 5.1-5.3 mg/L while RMSE for literature models was 5.3-6.4 mg/L.

Conclusion: As demonstrated previously for vancomycin dosing in adults [10], CL allows for better predictive performance compared to models from literature, even at low sample sizes. The benefit of training the model on increasingly larger datasets appears limited in this study, but might allow further optimization of model structure, or conditioning on more specific subpopulations. Further studies are ongoing to investigate the benefits of CL in other drugs and populations.



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S-013

Multiscale Quantitative Systems Pharmacology modeling to enable personalized treatment of congenital Long QT syndrome

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Objectives: Mutations in the SCN5A gene, which encodes the primary cardiac Na^+ channel (Nav1.5), can cause arrhythmic disorders such as Type 3 Long QT Syndrome (LQT3). In a pediatric patient with a novel missense mutation in SCN5A (Q1475P), the anticonvulsant drug phenytoin surprisingly proved to be more effective than the conventional anti-arrhythmic drug mexiletine at controlling the patient's arrhythmias. We sought to uncover: (1) what defects in gating at the molecular level could account for electrophysiological recordings; (2) what modified cellular properties could explain the patient's LQT3 phenotype; and (3) what molecular changes are induced by phenytoin that are able to restore normal cardiac rhythm.

Methods: Electrophysiology experiments, performed in HEK293 cells, demonstrated that, compared with Wild Type (WT) Nav1.5 channels, Q1475P channels exhibited: (1) a positive shift in the activation curve; (2) a positive shift in the inactivation curve; (3) faster inactivation; and (4) faster recovery from inactivation. Simulations attempted to recapitulate these results through population-based mathematical modeling of ion channel gating. Parameter randomization in a Markov model of Nav1.5 gating generated a large (n=10,000) population of channel variants, that was filtered to match WT and Q1475P channel behaviors. This approach produced subpopulations of channel variants describing the gating of either genotype and allowed us to simulate their response to phenytoin and

mexiletine. The maximal conductance for Nav1.5 channels was adjusted according to the experimental finding that the trafficking defects introduced by the mutation can be corrected by mexiletine but not by phenytoin.

Results: The analysis suggested that the channel gating steps most likely to be affected by the mutation include transitions from: (1) open to closed, (2) inactivated to closed; and (3) closed to inactivated state. When simulated Nav1.5 channels were incorporated into a model of the human ventricular action potential, Q1475P channels were more likely than WT channels to produce arrhythmogenic early afterdepolarizations (EADs) due to increased late Na^+ current that led to prolonged action potential duration (APD). Phenytoin and mexiletine partially recovered the defective Nav1.5 channels, correcting the voltage dependence of inactivation while leaving unaltered the activation kinetics. Cellular AP simulations showed that Q1475P channels treated with phenytoin led to smaller late Na^+ current and shorter APD than Q1475P channels treated with mexiletine, preventing the occurrence of EADs. This allowed us to speculate that phenytoin was more effective than mexiletine in treating this patient because it partially restored the kinetics properties of the defective channels without altering their trafficking.

Conclusions: The results provide important insight into this patient's LQT3 phenotype and demonstrate how population-based modeling can generate mechanistic hypotheses about: (1) alterations in ion channel gating that result from mutations; and (2) differential efficacy of drugs in the treatment of cardiac channelopathies.

S-014

Combining Systems Pharmacology Modeling with Machine Learning Techniques to Identify Sub-Populations at Risk of Drug-Induced Arrhythmias

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Objectives: When assessing whether to prescribe a drug that has potential arrhythmogenic side effects, the common assessment is based on the electrocardiographic QT interval, wherein an individual with a prolonged QT would not be prescribed the medication. Although this trait predicts susceptibility, there remains a percentage of patients who still succumb to an arrhythmia with a normal QT, or at the cellular level a normal action potential duration (APD). We sought to improve this imperfect assessment by combining systems pharmacology models with machine learning to unmask hidden features and provide greater insight needed to distinguish between arrhythmia-prone and resistant patients.

Methods: We used a systems pharmacology model that describes the electrophysiology of ventricular myocytes to generate a large heterogeneous population of cells (APs) by varying parameters within the model that control ionic channel magnitude, gating time constants, and voltage dependent shifts of gating. We then examined the effect of applying various arrhythmogenic triggers (block of hERG K^+ channel, increased L-type Ca^{2+} channel, hypokalemia, and increased inward current) on the population and split the cells into two groups (low and high risk) based on susceptibility. Thereafter, we trained multiple machine learning algorithms (support vector machine, random forest, logistic regression, and neural network) on features pertaining to the shape of the pre-perturbed AP and the outcome of the applied trigger.

Results: We found that APD predicted susceptibility to hERG block with only a ~57% accuracy, thus confirming the limitation of solely relying on APD (or QT interval) to predict risk. Moreover, we found that incorporating additional features (besides APD) that describe the shapes of the AP and the calcium transient improves prediction accuracy to ~73%. To better this prediction, we also determined additional experimental procedures that when added to the machine learning algorithms along with the waveform features, improves performance to ~87%. Furthermore, we tested this same approach on additional triggers and found that accuracy changed based on the perturbation. Machine learning poorly predicted arrhythmic risk to hypokalemia with only a 69% accuracy, but proficiently determined risk to increased inward current with a 91% accuracy.

Conclusions: Overall, our computational pipeline unveils a new set of predictors that can differentiate a high from a low risk patient. Moreover, this provides an automated approach to screen for patient susceptibility to drug-induced arrhythmias and represents a path towards improving the decision-making process when prescribing proarrhythmic therapies.

S-015

Aging does not impact the magnitude of drug-drug interactions – a proof of concept study usingphysiologically-based pharmacokinetic modelling

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Objectives: Aging is characterized by physiological changes which have an impact on drug pharmacokinetics [1], however, only a limited number of drug-drug interactions (DDIs) have been studied in the elderly. The aim of this proof of concept study was to investigate the impact of aging on DDI magnitudes through physiologically based pharmacokinetic (PBPK) modelling

Methods: A whole-body PBPK model constructed in Matlab® 2017a was used [2] considering age-related physiological changes [3]. Two DDIs involving midazolam were studied: I) in combination with clarithromycin and II) with rifampicin. Simulations were firstly carried out in young adults (20-40 years), before predicting drug disposition in the elderly (66-80 years) without modifying drug parameters. Simulations were compared to clinically observed data for both drug combinations to ensure correct predictions [4-6]. DDI magnitudes were predicted across adulthood (20-99 years) in 100 virtual individuals (50% women) in 16 age groups and the area under the curve (AUC) ratio was normalized to the youngest investigated age group (20-24 years).

Results: Simulated concentration-time profiles and predicted DDI magnitudes were within 1.5-fold of clinically observed data [4-6] for both drug combinations and age groups (Table 1). The PBPK model suggested no change in DDI magnitudes with advanced age for both investigated drug combinations.

Conclusions: Aging neither alters inhibition (clarithromycin) nor induction (rifampicin) of midazolam. Age-related physiological changes impact victim drugs and inhibitors/inducers to the same extent thereby leading to unchanged DDI magnitudes. Thus, prediction of the PBPK model suggest a similar management of DDIs in the elderly compared to young adults.

Table 1:
Table 1: Observed vs. predicted DDI magnitudes [4-6].

		young adults	elderly adults
Midazolam + Clarithromycin	observed	7.50 ± 5.50	7.54 ± 6.77
	predicted	6.77 ± 6.39	7.11 ± 6.98
Midazolam + Rifampicin	observed	0.10 ± 0.09	0.10 ± 0.09
	predicted	0.09 ± 0.07	0.08 ± 0.06

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S-016

Application of physiologically based pharmacokinetic (PBPK) modeling to predict fetal exposure to dolutegravir

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Objectives: Physiologic changes associated with pregnancy have a large impact on drug disposition, which may lead to subtherapeutic or toxic exposures.[1] The goal of this study was to build a maternal-fetal PBPK model to predict the fetal exposure to the HIV integrase inhibitor dolutegravir (DTG) at delivery.[1]

Methods: PBPK models were built in the Open Systems Pharmacology Software Suite version 7.3 (www.open-systems-pharmacology.org). The maternal-fetal PBPK model structure was developed in MoBi and exported to PK-Sim for population simulations. Placental transfer was parameterized based on information obtained from scaling equations available in the literature.[1,2] The predictive performance of the PBPK models was evaluated via comparison with *in vivo* data collected from HIV-infected pregnant women receiving DTG as part of clinical care. Maternal plasma samples were collected at delivery, with the range of gestational age at delivery of 35 to 42 weeks, along with infant cord blood sample.

Results: For DTG, the estimated diffusion was 0.43 L/min and the estimated placental partition coefficient was 0.4. A sensitivity analysis indicated that the fraction unbound is a critically important parameter for umbilical cord concentration prediction. The parameters were applied to the DTG maternal-fetal PBPK model and the DTG concentrations in the umbilical cord were adequately predicted (see Figure 1). Seventeen out of 20 maternal samples fell within the 2-fold error range of the prediction, and 13/20 maternal samples fell within the 1.5-fold error of the prediction. Eighteen out 20 cord samples fell within the 2-fold error range of the prediction and 15/20 cord samples fell within the 1.5-fold error of prediction.

Conclusions: These results increase the confidence in applying PBPK models to predict maternal and fetal drug exposure. Data on protein binding of DTG in both the mother and fetus are needed to increase the confidence in the underlying induction of the main clearance pathway as well as to improve predictions of umbilical cord exposure. Improved maternal-fetal PBPK models may streamline and accelerate the performance of pharmacokinetic studies for drugs in pregnant women.

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Figure 1: DTG predicted maternal-fetal PK vs observed data. Blue line= cord blood geometric mean prediction; Blue shaded area= 5-95% percentile range; Blue circles= cord blood observed data; Green line= maternal geometric mean prediction; Green shaded area= 5-95% percentile range; Green circles= maternal observed data.

S-017

An Exemplar of Model-Informed Drug Discovery and Development towards Discovering Promising Combination Therapies for Mycobacterium tuberculosis

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Objectives: Tuberculosis (TB) is one of the top 10 causes of death worldwide, causing an estimated 1.6 million deaths in 2017[1]. Discovering promising combination therapies for TB are needed in order to combat antimicrobial resistance as well as to shorten the therapy duration. Due to a huge number of possible drug combinations, a model-informed strategy will help to accelerate the discovery. The objective of this research was to inform experimental trial design of studies to investigate effects of two combination therapies of 1) bedaquiline (BDQ) with pretomanid (PMD) and 2) clofazimine (CFZ) with PMD against *Mycobacterium tuberculosis* (*M. tuberculosis*) in Log-, Acid-, and Nonreplicating-Persister (NRP)-metabolic phases through mathematical modeling approach.

Methods: *M. tuberculosis* bacterial counts were obtained in duplicate from the combination regimens for each metabolic phase through *in vitro* checkerboard assay. The use of the Greco model[2] allows us to characterize the effect (bacterial killing) of the different concentrations of the drugs in combination in a quantitative manner by evaluating the interaction parameter α and its confidence interval (CI). Synergy was declared if α had a positive value and the lower bound of the 95% CI does not cross zero. The interaction was antagonistic if α was negative and the upper bound does not cross zero. If the 95% CI of α contains zero, then additivity is declared for the effect of the drug combination. Model parameters were estimated in ADAPT 5 using either maximum likelihood or weighted least squares estimation methods. R (version 3.5.1) was used for data management and Mathematica (version 11.3) was used for creating 3-dimensional goodness-of-fit plots.

Results: The combination of BDQ and PMD showed additive effects against *M. tuberculosis* in all three metabolic phases. The combination of CFZ and PMD showed additive effects with a trend towards synergy in both Acid- and NRP-metabolic phases while it showed additive effects in Log-metabolic phase. The 3-dimensional diagnostic plots using the final parameter estimates suggest that the model was able to capture the observed checkerboard data reasonably well. The presence of mosaic surfaces suggests the existence of less-susceptible bacterial clones, which cannot be conclusively evaluated with the Greco model on the basis of checkerboard data.

Conclusions: The analyzed combination therapies were identified as promising options to promote *M. tuberculosis* bacterial killing in Log-, Acid-, and NRP-metabolic phases. Thus, these drug combinations will be further evaluated for resistance suppression in an *in vitro* hollow fiber infection model and in animal models. This study provides an exemplar for model-informed drug discovery and development towards discovering promising combination therapies for *M. tuberculosis*.

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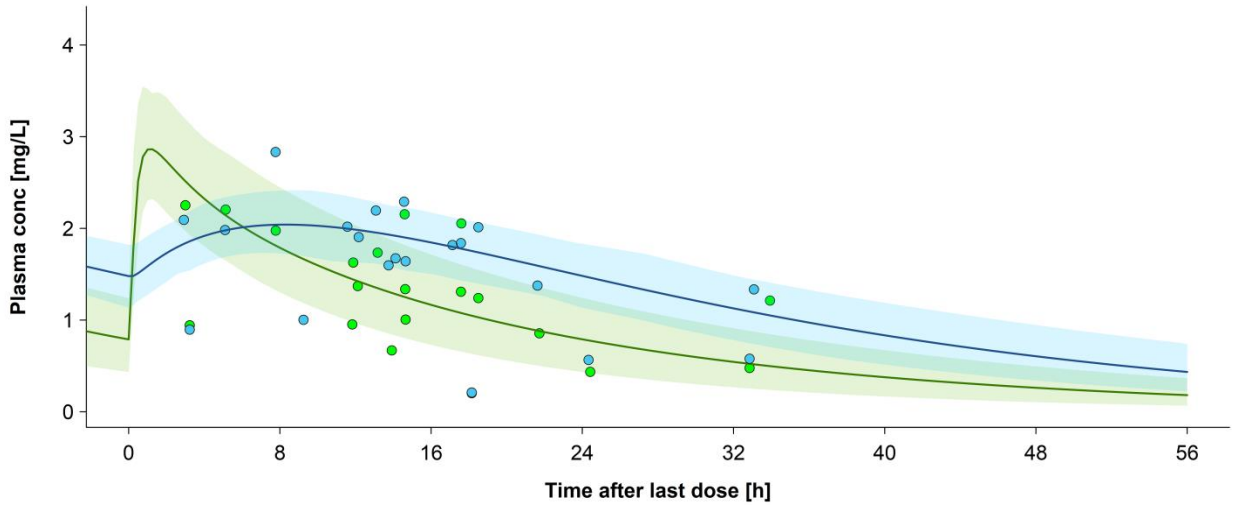

S-018

A Quantitative Model-Based Framework to Optimize Clinical Outcomes in Neonatal Opioid Withdrawal Syndrome using Real World Data

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Background and Objectives: Neonatal opioid withdrawal syndrome (NOWS) is a drug withdrawal syndrome that neonates exposed to opioids *in-utero* may experience after birth. At least 75% of these neonates require pharmacotherapy for treatment, with morphine being most commonly used [1]. Currently, the morphine starting dose and dosing adjustments are often empiric or stepwise in nature with significant heterogeneity potentially leading to a longer hospital stay and increasing the economic burden. The aim of the study is to use a quantitative, model-based, real world data-driven approach to optimize morphine dosing in neonates with NOWS to improve clinical outcomes such as reducing time on treatment thereby reducing length of hospital stay.

Methods: Longitudinal morphine dose and clinical response (Modified Finnegan Score (MFS)) data along with maternal and infant baseline factors were collected using a retrospective cohort design from the electronic medical records of infants with NOWS (N=189, Observations≈100000) admitted to the University of Maryland Medical Center (UMMC)- Neonatal Intensive Care Unit (NICU) from 2013 to 2017. A dynamic linear mixed effects (DLME) [2] model which enables the current response to be regressed on the previous response, fixed effects, and random effects, was used to develop the relationship between MFS and morphine dose adjusting for baseline risk factors. An independent error covariance structure was assumed to be normally distributed. Model evaluation was performed using a simulation-based approach, utilizing the UMMC morphine dosing protocol, and comparing the observed and model predicted clinically meaningful metrics such as time on treatment.

Results: Prenatal methadone exposure, poly-substance drugs, the race of the neonate, previous MFS response and previous morphine dose were significant predictors of the current MFS response. Autocorrelations of previous two observed MFS with current observed MFS were ρ_1=0.72 and ρ_2 =0.25 respectively, indicating positive correlations between consecutive MFS responses. On an average, for 100 microgram increase in the morphine dose, the MFS decreased by 0.5 units. The model evaluation showed that observed time on treatment and model predicted time on treatment (median: 11.0 vs 9.8 days) was not significantly different (p = 0.28).

Conclusion: A model-based framework is developed to describe the MFS–morphine dose relationship using real world data. Further improvements to the DLME model is underway to develop an adaptive, individualized morphine dosing strategy for infants with NOWS that could lead to better clinical outcomes.

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S-019

Development and Evaluation of Methods for Early Relapse Detection in Multiple Myeloma Patients Treated with Bortezomib

Authors: Yunqi Zhao, Guanyu Wang, Luke Edwards, Neeraj Gupta, Godwin Yung, Antonio Palumbo, Richard Labotka, Arijit Chakravarty, Dean Bottino

Objectives: Current treatment guidelines recommend waiting for IMWG progression criteria to be met before proceeding to the next line of therapy (Rajkumar et al, Blood 2011;117, NCCN Guidelines – Multiple Myeloma V2.2019 – Nov 16, 2019 NCCN.org). Assuming relapsed disease is more difficult to treat than disease that is still in remission, a tool that can accurately anticipate relapse 3-6 months before it occurs would be valuable for patient care.

Methods: Using dosing and serum M-protein time course data from 130 patients from the COMMPASS observational study (NCT01454297-IA9), we developed an individualized adaptive mathematical model of myeloma induction and relapse in patients taking any combination of bortezomib, lenalidomide, and dexamethasone. We tested the accuracy of this adaptive model to anticipate serum M-protein relapse 3-6 months in advance in a separate 'validation' set of 130 COMMPASS patients. For comparison, we also tested the ability of the M-protein 'velocity' calculated over the two most recent assessments to predict relapse over the same time window. We derived receiver operating characteristic (ROC) curves for both predictors to compare their sensitivity and specificity for relapse detection. The prespecified goal for using either tool in clinical practice was 80% sensitivity and specificity.

Results: ROC analysis showed that, at the target true positive rate (TPR) of 80%, the adaptive model-based method has a false positive rate (FPR) of 36%, while the M-protein velocity method has a FPR of 91%. At a FPR of 20%, however, the TPR of the adaptive method was 50% while the TPR for the M-protein velocity was slightly higher at ~61%.

Conclusion: While they were both better than random guessing, neither the current version of the adaptive model-based tool nor the M-protein velocity method could achieve the prespecified criteria of 80% sensitivity and specificity in predicting M-protein relapse 3-6 months in advance. ROC analysis suggests the two approaches have complementary operating characteristics. We hope to augment the model-based tool with Bayesian priors informed by baseline disease markers as well as incorporating minimal residual disease data as available.