A multi-model strategy in R to address cytopenia

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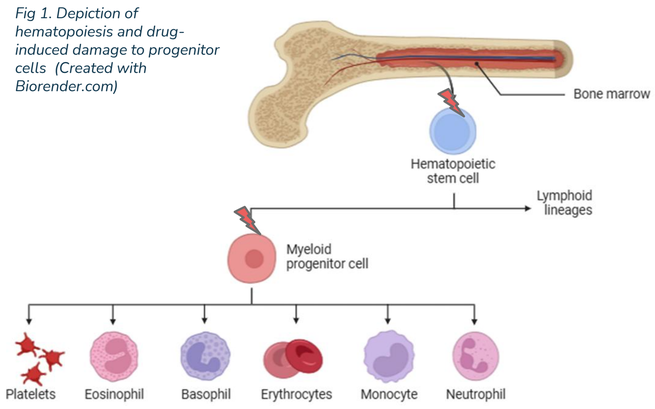
INTRODUCTION

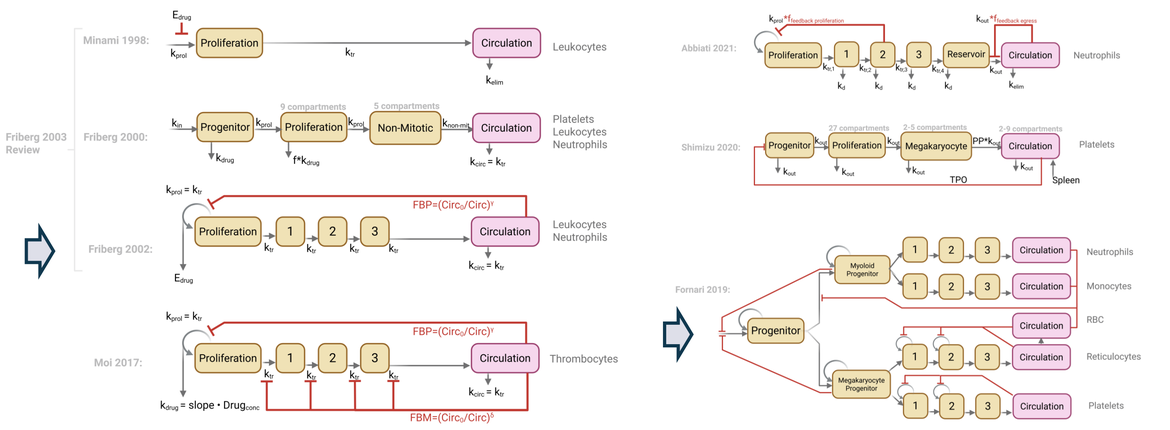
Hematological toxicity is a frequent and dose-dependent adverse event of chemotherapeutic regimens and other oncology drugs [1]. The consequential drop in cell count occurs also for other modalities, albeit with often idiosyncratic behavior (Fig 1). Predicting these adverse effects is a challenge due to multiple factors that need to predispose individuals simultaneously.

Fig 1. Depiction of hematopoiesis and drug-induced damage to progenitor cells (Created with Biorender.com)



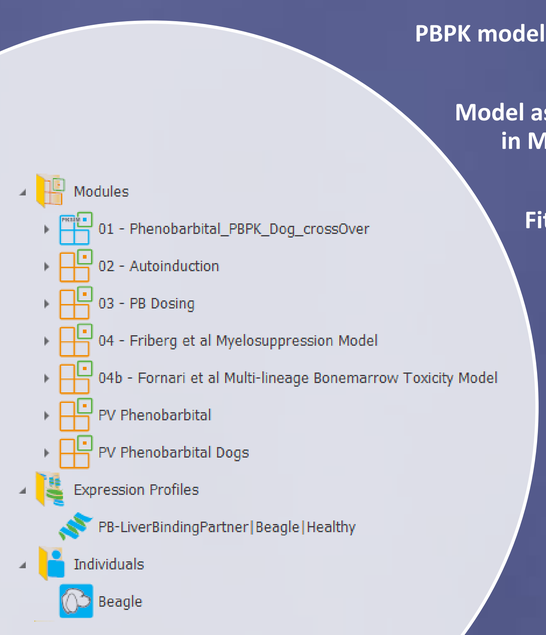
Preclinical toxicity studies often do not have sufficient sample size to observe overt idiosyncratic toxicity. Thus, new computational approaches are needed to leverage subthreshold preclinical data.

Phenobarbital (phenobarbitone) is a first-generation antiepileptic barbiturate. Its use has been associated with adverse effects caused by either dose-dependent (predictable) or idiosyncratic reactions such as cytopenias [2]. We therefore investigate data obtained in a PK/tolerability study for their potential use to predict idiosyncratic cytopenias.



Different empirical, semi-mechanistic and more mechanistic models are being used currently in various platforms for cytopenia analysis and predictive modeling [3-7]. Better toolchain integration and cross-platform operability has the potential to explore evidence more coherently. We therefore make use of an R-based multi-model ecosystem for the assessment of cytopenia in preclinical safety.

METHODS



Elements from an OSP – R based ecosystem to build, qualify, run and analyze and report PBPK-QSP simulations

Available phenobarbital multiple dosing pharmacokinetics and tolerability data was on a veterinary-specific product given over an 80 days time period in 8 healthy dogs [8]. The phenobarbital PBPK model was originally created for rats and humans based on physico-chemical properties and PK data [9-10]. It incorporates intestinal absorption, a binding partner in liver, as well as renal and hepatic clearance [refs, unpublished inhouse work). The model was translated to dogs by adding dog-specific physiology (Species: Beagle), unbound fraction in plasma and an adapted hepatic clearance rate in PK-Sim 12.1 [11]. An autoinduction of the clearance was added in MoBi 12.1 to adequately describe the long-term PK in dogs.

The semi-mechanistic myeloablation model from Friberg et al and the multi-lineage model from Fornari et al. [7] were re-implemented according to the published equations and parameters in MoBi. To drive the effect, the `Organism|Bone|Interstitial` concentration was used to mimic bone marrow exposure. Both models are implemented as modules.

Dosing regimens as in the PK/tolerability study and resembling a chronic use regimen (BID) were set up in PK-Sim and then used in MoBi as modules.

For the reproduction of rare canine phenobarbital induced cytopenia, the fitted parameters (shown for semimechanistic myeloablation model below) have been expanded into a multivariate lognormal distribution in R and 400 individuals sampled.

Virtual Twin Parameter Table – Varying Parameters Only

	Parameter_Name	Units	Dog1	Dog2	Dog3	Dog4	Dog5	Dog6	Dog7	Dog8
1	Specific clearance	1/min	2.80e-03	3.50e-03	0.003	2.5e-03	2.5e-03	3.5e-03	3.5e-03	2.50e-03
3	Emax	NA	1.20e+00	1.20e+00	1.000	1.0e+00	1.5e+00	1.2e+00	1.2e+00	2.00e+00
5	SLOPU	µmol/l	1.00e+03	5.00e+02	600.000	3.0e+03	1.2e+03	1.1e+03	1.0e+03	1.00e+03
6	MTT	h	9.00e+01	9.00e+01	120.000	9.0e+01	7.5e+01	9.0e+01	1.2e+02	7.50e+01
7	CIRC0	1/µl	6.72e+03	8.97e+03	5510.000	6.5e+03	8.2e+03	7.5e+03	5.0e+03	6.24e+03

Specific clearance: hepatic clearance rate constant, Emax: Autoinduction maximum effect (EC50 not fitted), SLOPU: Drug sensitivity of effect on progenitor proliferation, MTT = mean transit time from progenitor to circulating neutrophil
CIRC0 = baseline circulating neutrophil count

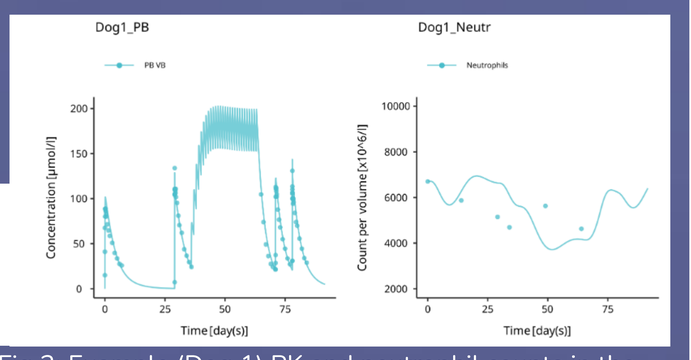


Fig 2: Example (Dog 1) PK and neutrophil counts in the study versus simulated PK/PD

RESULTS AND DISCUSSION

The overall weak effects of phenobarbital on individual dog lab markers can be covered with the current parametrization of the model even though quantitative fits are impeded by fluctuations (see **Fig. 2**). Drug sensitivity parameters are thus a conservative "worst case scenario" estimate.

The known idiosyncratic bone marrow damage leading to cytopenia can be recapitulated in the Vpop approach (**Fig. 3**, given that parameter distributions are sampled sufficiently at the extremities) informed by the individual fits. This workflow allows for translating sub-threshold behavior from few individuals into a population prediction (e.g. if population fit is unfeasible). Also, follow up mechanistic studies can be informed by through parameter covariance structure analysis (Fig. 3)

Through coupling of the myeloablation model with a whole-body PBPK model, exposure differences between different dog breeds (morphometrics) can be captured, and predictive exposure predictions (based on in vitro data) can be integrated (not shown).

Use the extended model to perform mechanistic exploratory investigations towards the mechanism of bone marrow toxicity. An indirect damage mechanism (**Fig 4**, as implemented in the Fornari et al. module) can only partially reproduce observed (reversible) cytopenia kinetics of blood cell counts, while at the same time, experimental mechanistic insight into this toxicity is very limited, but stepwise test of hypotheses in the structural model can give insight into their plausibility.

Further investigations on phenobarbital and induced bone marrow toxicity could focus on obtaining markers for inflammation, liver or other organ-bone marrow cross-talk or better characterize effects on bone marrow samples ex-vivo.

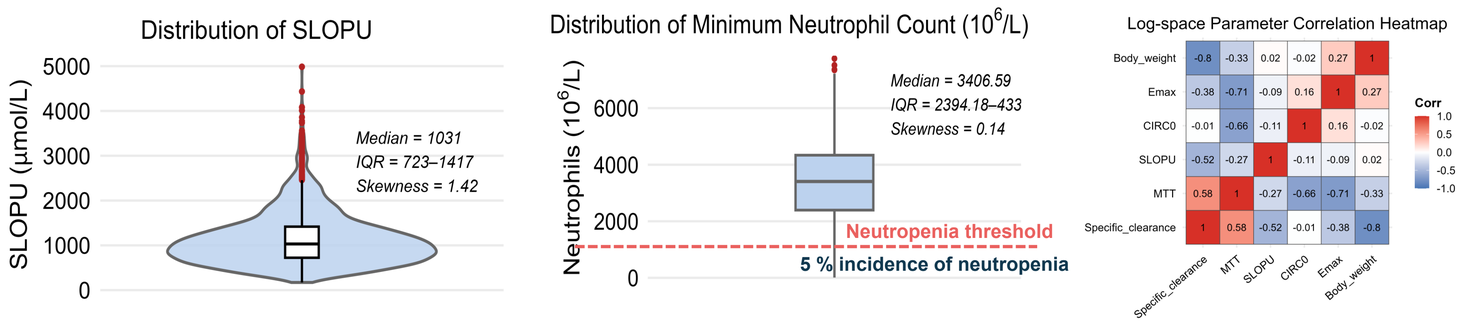
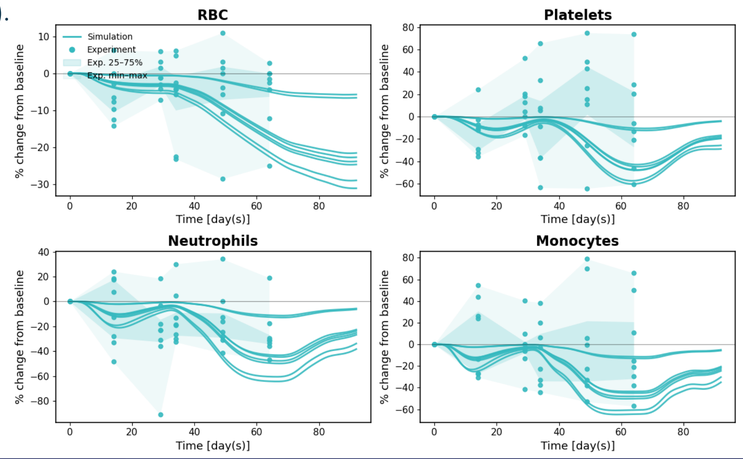


Fig 3: Estimated parameter marginal distribution of SLOPU (other parameters not shown) and corresponding minimal neutrophil count distribution matching 5 % neutropenia incidence in line with idiosyncratic adversity. Right: Correlation analysis, within the multivariate parameter distribution inferred from individual fits. Clearance-MTT: Dogs with faster clearance also have longer maturation times. Emax-MTT: Higher autoinduction Emax tends to appear in dogs with shorter MTT. MTT-CIRC0: High baseline counts tend to have faster cell turnover. Correlation analysis may guide further risk-stratifying biomarker analysis (e.g. liver – bone marrow axis).

Fig 4: Simulated (solid line) and experimental (dots) time courses (simulated with multi-lineage model, for individual dogs) for red blood cells (RBC), platelets, neutrophils, and monocytes percent change from baseline over time (days). The shaded turquoise band represents the minimum–maximum range of experimental measurements across all dogs. The model applies and indirect (e.g. inflammation) damage to a progenitor common to all lineages. Simulations are plausibly lying within the overall temporal trends of RBCs and neutrophils, while the experimental data for platelets and monocytes seem to feature mainly fluctuations.



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Modeling Scaling Coding

Supporting the open-source development of:
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