

Towards a Translational QSP Modeling Approach to Predict Bone Marrow Toxicity



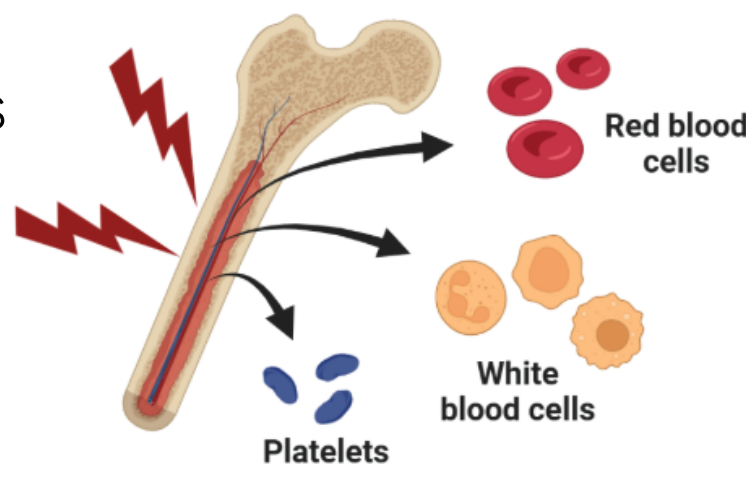
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Background

Bone marrow function can be impaired by certain drugs, especially anti-cancer therapies, leading to dose-limiting **cytopenias** such as anemia, neutropenia, and thrombocytopenia.

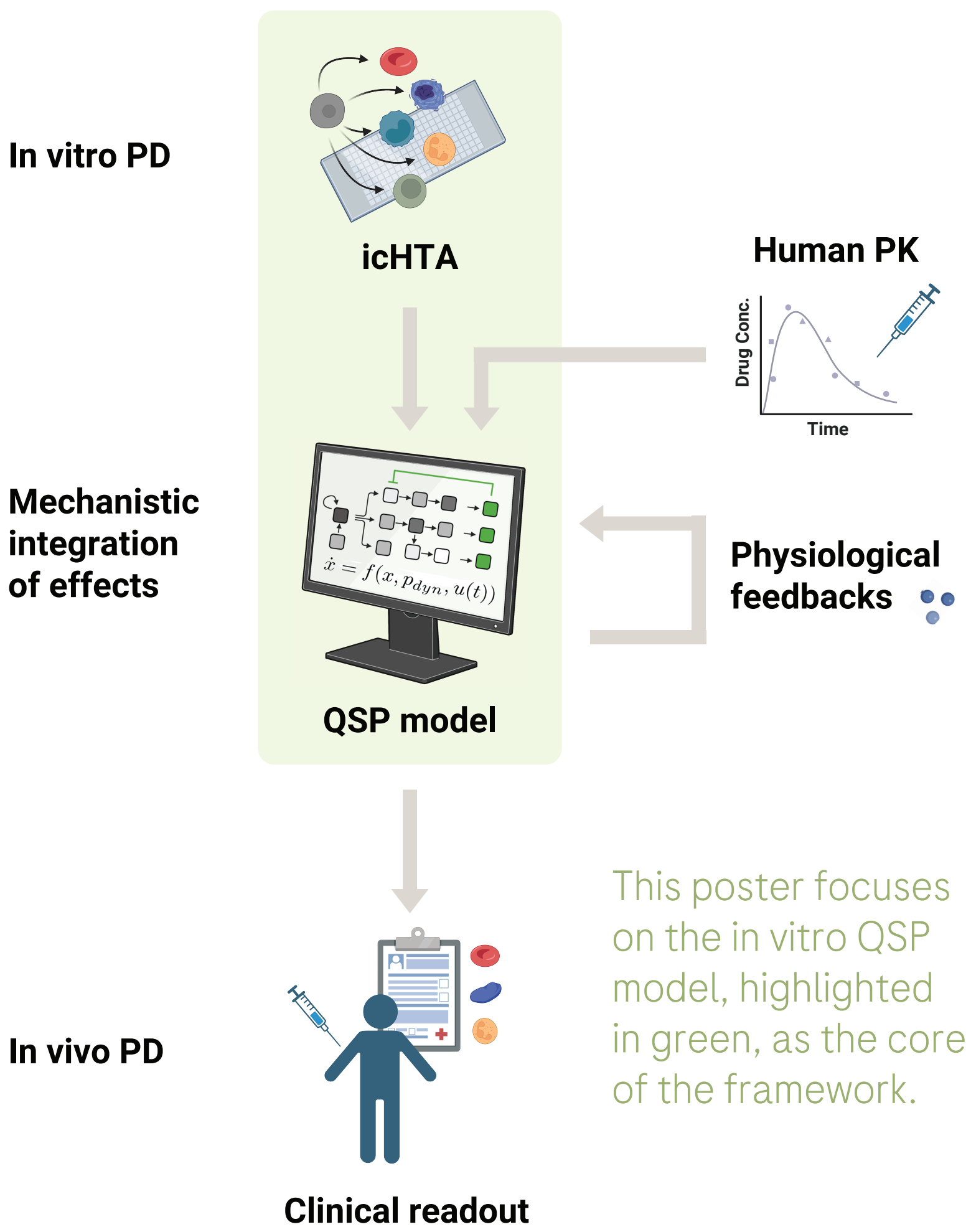
Current preclinical approaches including animal models, recurrently **lack clinical translatability** and raise ethical concerns [1,2].



We propose a **translational in vitro-in silico approach** to improve early prediction of clinical drug-induced myelosuppression across multiple hematopoietic lineages.

Objective

A framework to translate insights from in vitro assay data to clinical effects:



Our translational quantitative systems pharmacology (QSP) model aims at **simulating drug-induced myelosuppression** and predict clinical blood count changes by integrating

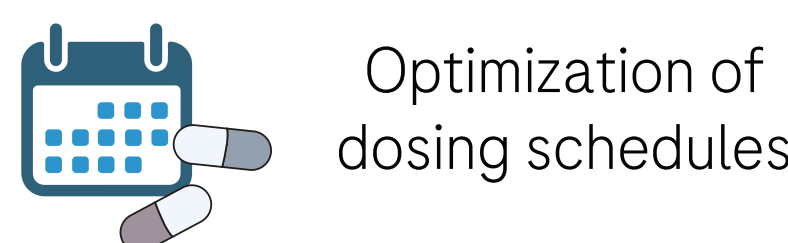
- in vitro **pharmacodynamic** (PD) responses from an immunocompetent hematotoxicity assay (icHTA)
- human **pharmacokinetic** (PK) profiles
- in vivo cytokine-mediated **feedback mechanisms** such as via EPO, TPO, and G-CSF
- **mechanistic knowledge** on the hematopoiesis process.

Conclusion & Next Steps

The presented in vitro-in silico approach **captures multilineage baseline hematopoiesis and PD effects**. It forms the basis of the translational framework for the prediction of clinical hematotoxicity risk.



In a next step, Pharmacokinetics and in vivo feedback mechanisms via EPO, TPO and G-CSF are integrated with the final aim to guide **therapeutic strategies optimization** to mitigate myelosuppression in patients.



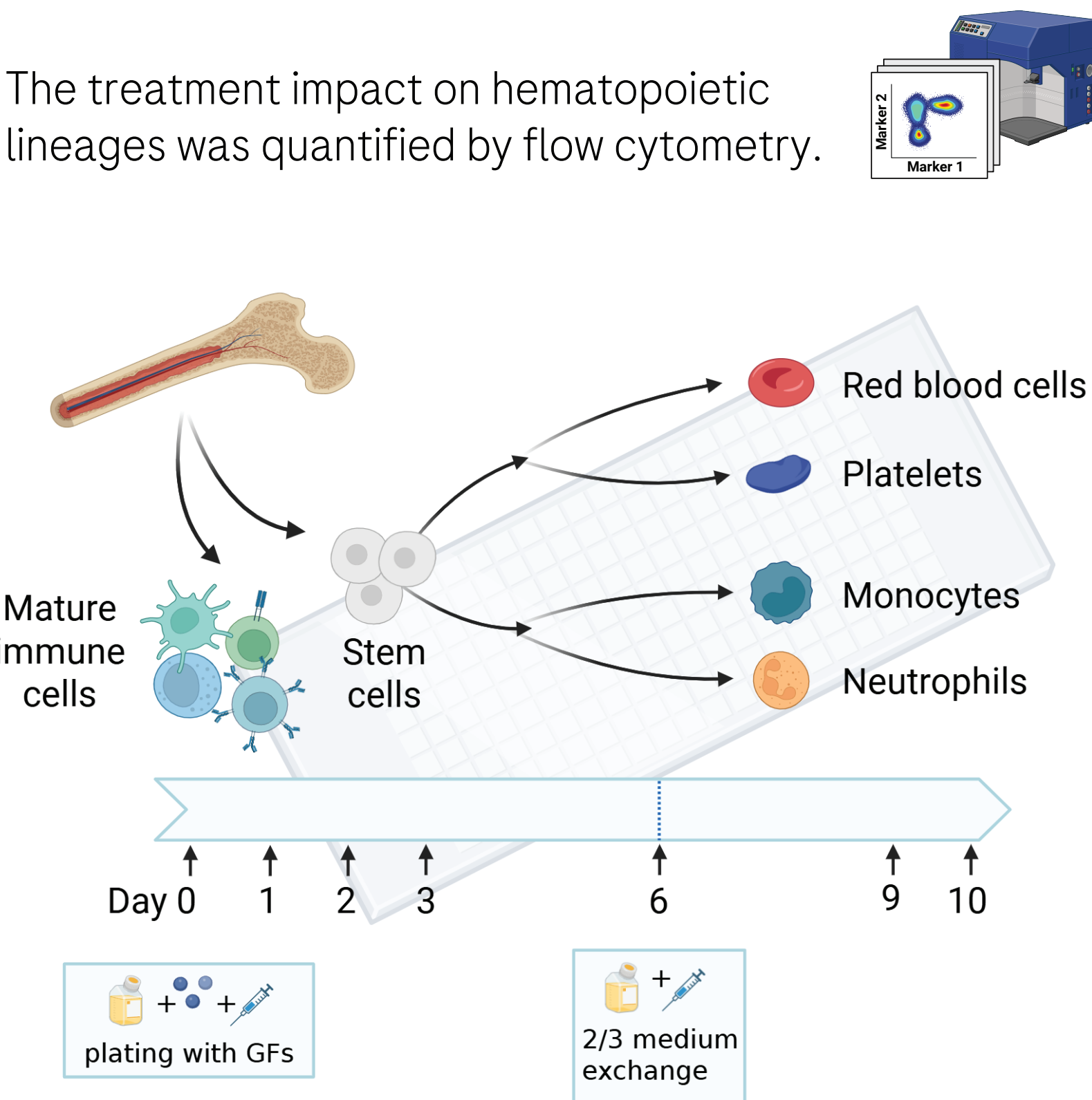
Methods

Immunocompetent Hematotoxicity Assay

The experimental setup

The differentiation of healthy human mononuclear bone marrow cells into hematopoietic lineages was induced in an autologous immunocompetent context. Compounds of interest were titrated in the assay to maintain continuous drug exposure.

The treatment impact on hematopoietic lineages was quantified by flow cytometry.

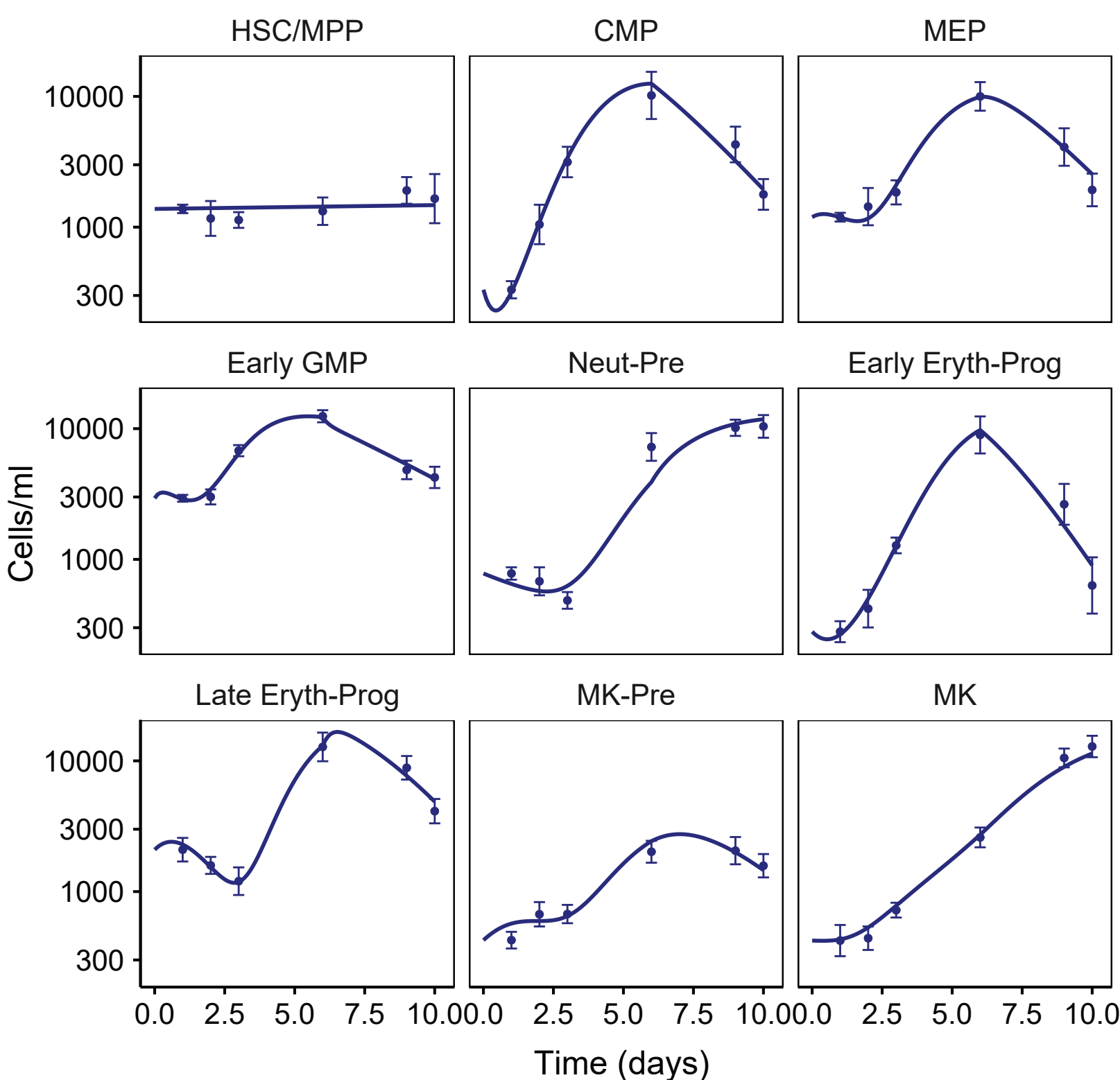


Experimental setup. Cells derived from four donors were plated before the start of the experiment in replicates, a mixture of growth factors (GFs) was added along with the compound of interest. After six days, 2/3 of the medium was exchanged with fresh drug, but without new GFs to favor differentiation over proliferation in this second phase of the experiment. Measurements were taken at indicated days.

Results - Part 1

Baseline hematopoiesis

We identified three characteristic profiles across hematopoietic lineages in the absence of drug treatment: (1) **transient peaks** typical of progenitors, (2) **sigmoidal increases** reflecting accumulation of mature cells, and (3) **stable dynamics**, consistent with homeostatic maintenance and minimal turnover.



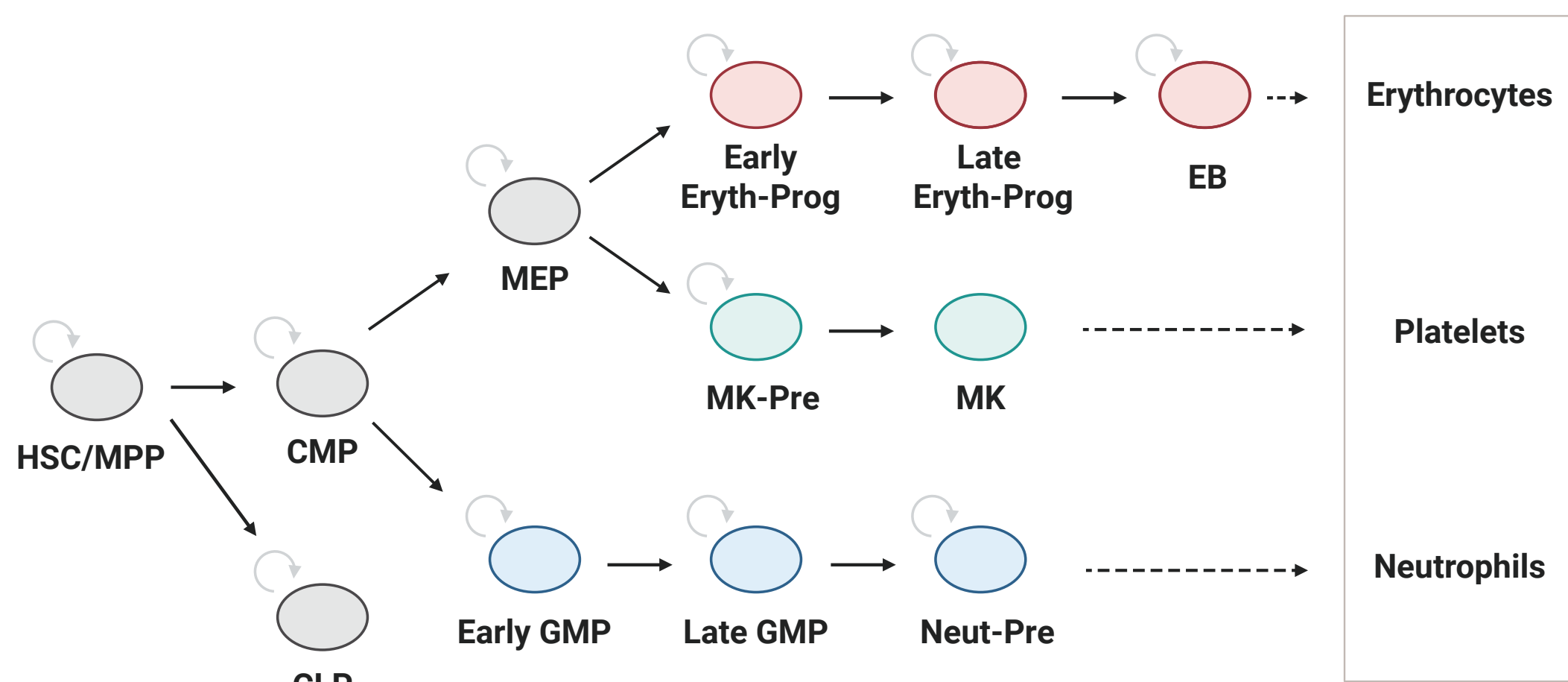
Baseline data with model fits. The model successfully reproduces multilineage hematopoiesis kinetics over the ten-day period. Dots with error bars represent the mean and standard deviation of 6-12 replicates of the same donor. Lines indicate the calibrated model trajectory.

Quantitative Systems Pharmacology Model

Mechanistic understanding of baseline hematopoiesis and PD effects

The in vitro QSP model describes the hematopoiesis in the bone marrow and the mechanistic effects of drugs on the different hematopoietic cell populations. It is based on the previously published model by Wilson et al. [3].

Model reactions were encoded as **ordinary differential equations** and parameters values were estimated using the maximum likelihood method.



Model schematic. All cell subsets indicated by circles were observed and used for model calibration. Straight arrows represent differentiation, circular arrows indicate proliferation, and all cells undergo death (not shown). *HSC* - hematopoietic stem cell; *MPP* - multipotent progenitor; *CMP* - common myeloid progenitor; *CLP* - common lymphoid progenitor; *MEP* - megakaryocyte/erythroid progenitor; *EB* - erythroblast; *MK* - megakaryocyte; *GMP* - granulocyte/macrophage progenitor; *Pre* - precursor.

Proliferation of cell subsets x was modeled as logarithmic growth dependent on (1) cytokine availability and (2) drug concentrations:

$$k_{\text{growth},x} = k_{\text{growth},0}(x) \cdot f(\text{cytokine}) \cdot g(\text{drug})$$

Cytokine modulation function

$$f(\text{cytokine}) = \exp \left(\beta_{\text{cytokine},x} \cdot \left(\frac{[\text{cytokine}]}{[\text{cytokine}]_{\text{ref}}} - 1 \right) \right)$$

Drug inhibition function

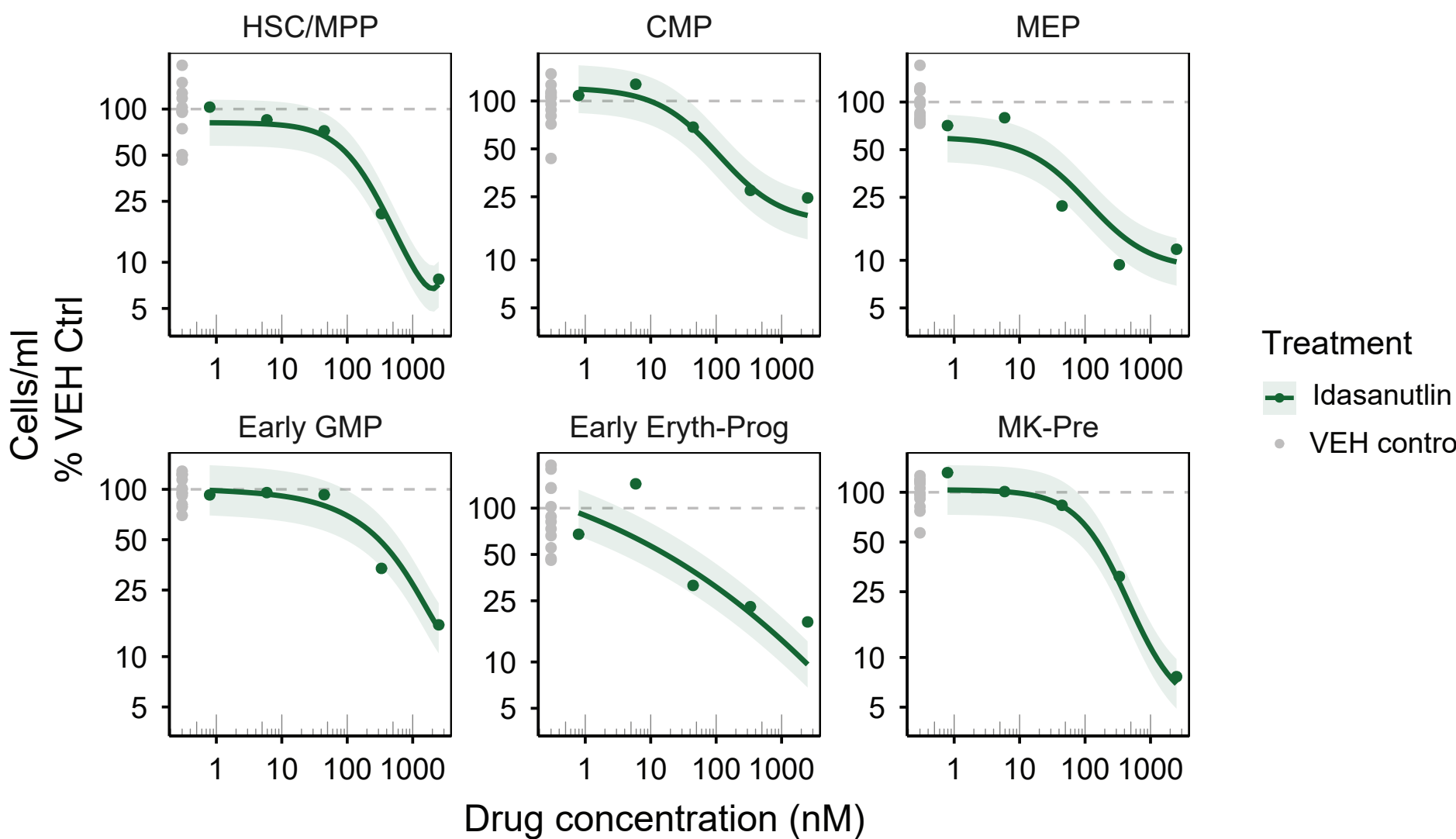
$$g(\text{drug}) = 1 - \frac{I_{\text{max},x} \cdot [\text{drug}]^{\alpha_x}}{IC50_x^{\alpha_x} + [\text{drug}]^{\alpha_x}}$$

For this purpose, **cytokine** was introduced, as a latent state variable with first-order elimination, to reflect medium exchange with concentration reduced to one-third at day 6.

Results - Part 2

Pharmacodynamic effects

Below, the **effect of idasanutlin** on the hematopoietic system is shown. This compound is known block the cell cycle by mdm2 inhibition and is thus implemented to act as an inhibitor of cell proliferation (see methods).



Concentration response data after 10 days with model fits. The model successfully reproduces the concentration-dependent effect of idasanutlin on the hematopoietic lineages. Measurements are displayed as dots and trajectories of the model fit are indicated as solid lines along with shaded error bands corresponding to one standard deviation.

References

- [1] Wendler and Wehling (2010) The translatability of animal models for clinical development: biomarkers and disease models. *Curr. Opin. Pharmacol.* 10(5): 601-606.
- [2] Worp et al. (2010) Can animal models of disease reliably inform human studies? *PLOS Medicine.* 7(3): 1549-1676.
- [3] Wilson et al. (2020) An in vitro quantitative systems pharmacology approach for deconvolving mechanisms of drug-induced, multilineage cytopenias; *PLoS Comput Biol.* 16(7): e1007620.