



A mechanism-based PK/PD model for iron-regulated hematopoietic stem and progenitor cells commitment towards erythroid and megakaryocyte lineages

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Introduction

- Iron deficiency causes anemia: ↓hemoglobin (HGB), ↓red blood cells (RBC)
- Iron deficiency is also associated with elevated ↑ platelet counts (PLT)
- In our preliminary *in vitro* study, it has been demonstrated that **systemic iron availability regulates hematopoietic stem and progenitor cells (HSPCs) commitment towards erythroid and megakaryocyte lineages (Fig. 1).**

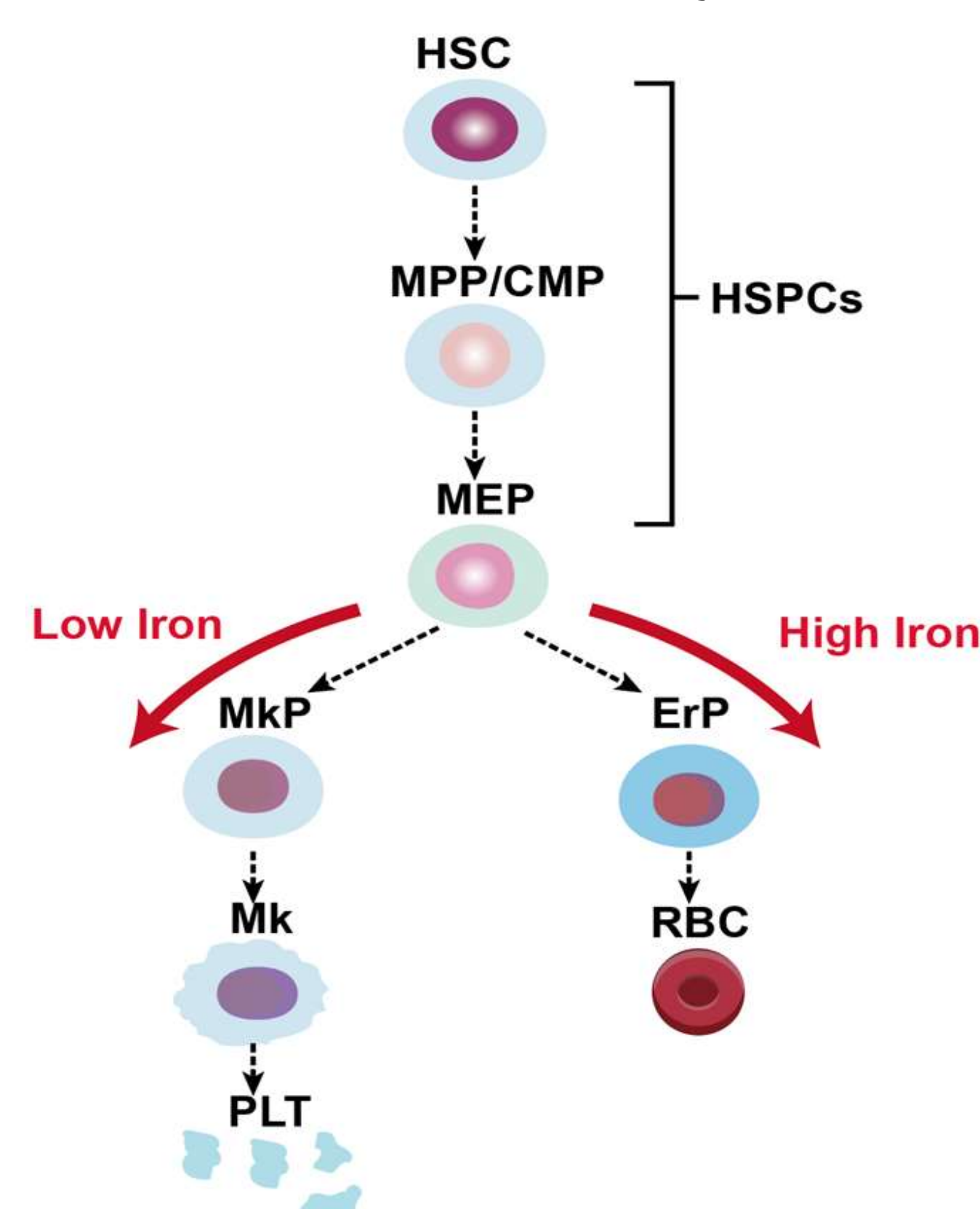


Fig. 1. The effect of iron on HSPCs commitment into erythroid and megakaryocyte lineages.

HSC, hematopoietic stem cell; HSPCs, hematopoietic stem and progenitor cells; MPP, multi-potent progenitor; CMP, common myeloid progenitor; MEP, megakaryocyte-erythroid progenitor; MkP, megakaryocyte progenitor; ErP, erythroid progenitor; RBC, red blood cell; Mk, megakaryocyte; PLT, platelets.

Objectives

- To investigate the effect of iron on erythropoiesis and thrombopoiesis in an *in vivo* study using rats with iron-deficiency anemia (IDA);
- To develop a mechanism-based pharmacokinetic/pharmacodynamic (PK/PD) model to quantify the effect of iron on HSPCs differentiation towards erythroid and megakaryocyte lineages.

Methods

- A PK/PD study of ferric carboxymaltose (FCM) was conducted in IDA rats

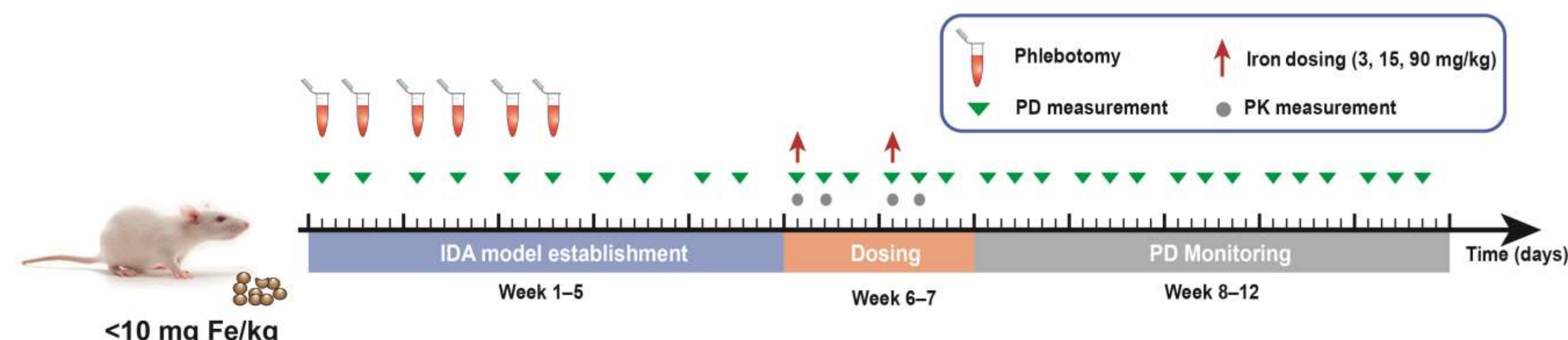


Fig 2. Study design of the *in vivo* study

- The pharmacokinetic profile of serum iron was described by a two-compartment model with linear elimination. A transit compartment model based on ordinary differential equations was applied to describe the effect of iron on erythropoiesis and thrombopoiesis.^[1-3]

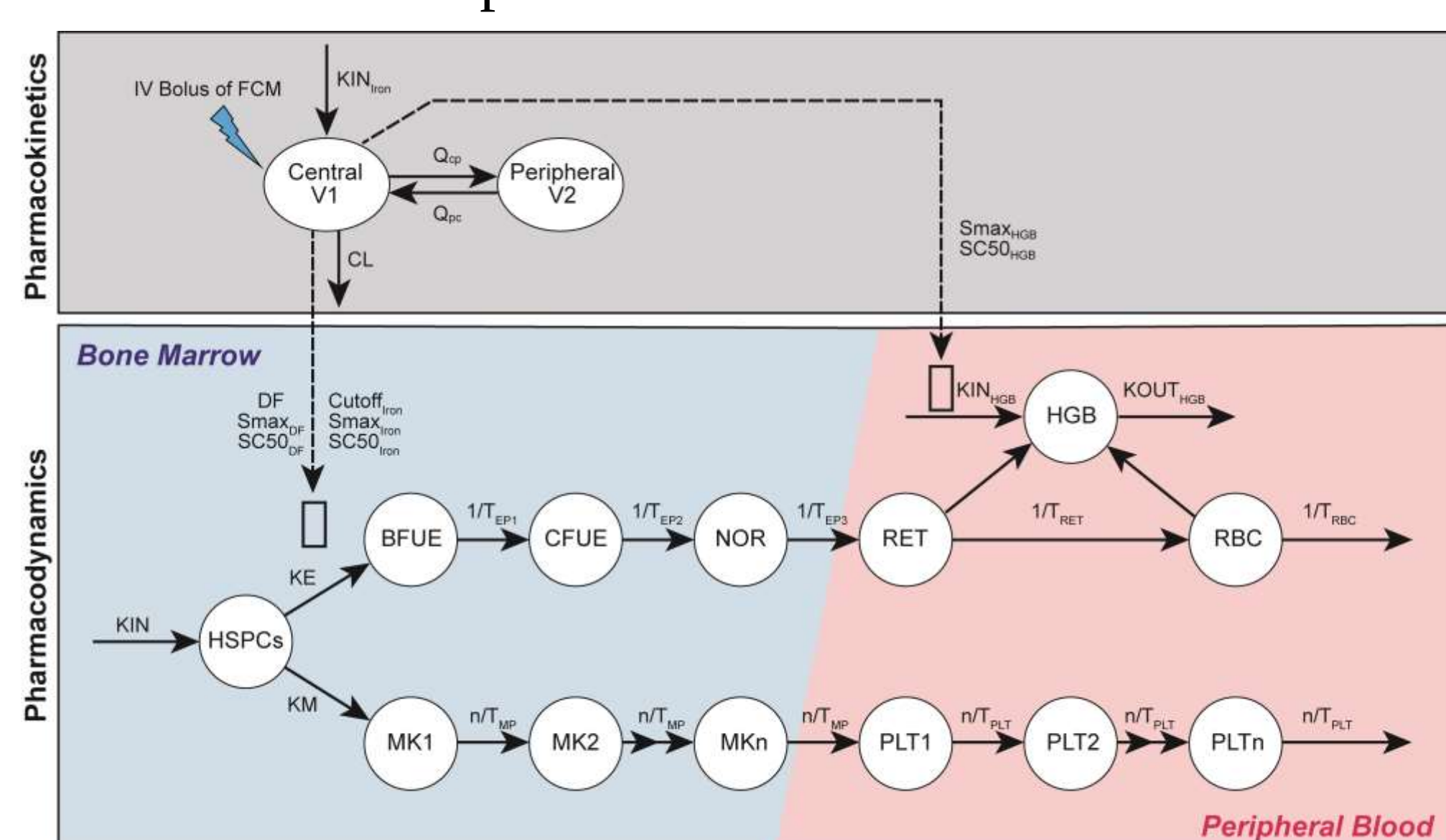


Fig 3. Schematic representation of the mechanism-based PK/PD model. HSPCs, hematopoietic stem and progenitor cells; BFUE: burst-forming unit-erythroid; CFUE: colony-forming unit-erythroid; NOR, normoblast; RET: reticulocyte; RBCs: red blood cells; HGB: hemoglobin; MK: megakaryocyte; PLT, platelet. (For PK model, the combination of sparse samplings (5 min and 48 h each dosing) in this study and intensive sampling in one literature^[4] was used for model development).

References & Acknowledgement

[1] ACS Pharmacol Transl Sci. 2023; 6(12): 1884-97.4. [2] J Pharmacol Exp Ther. 2022; 382(1): 31-43. [3] J Pharmacokinet Pharmacodyn. 2011; 38(1): 143-62. [4] Eur J Pharm Biopharm. 2022;174:56-76.

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Results

- Iron supplementation led to a dose-dependent increase in HGB levels.
- With the progression of iron deficiency, continuous decline of RBC counts and elevated PLT counts were observed in IDA rats.
- Iron supplementation resulted in increased RBCs and reversed the upward trend of PLT levels.

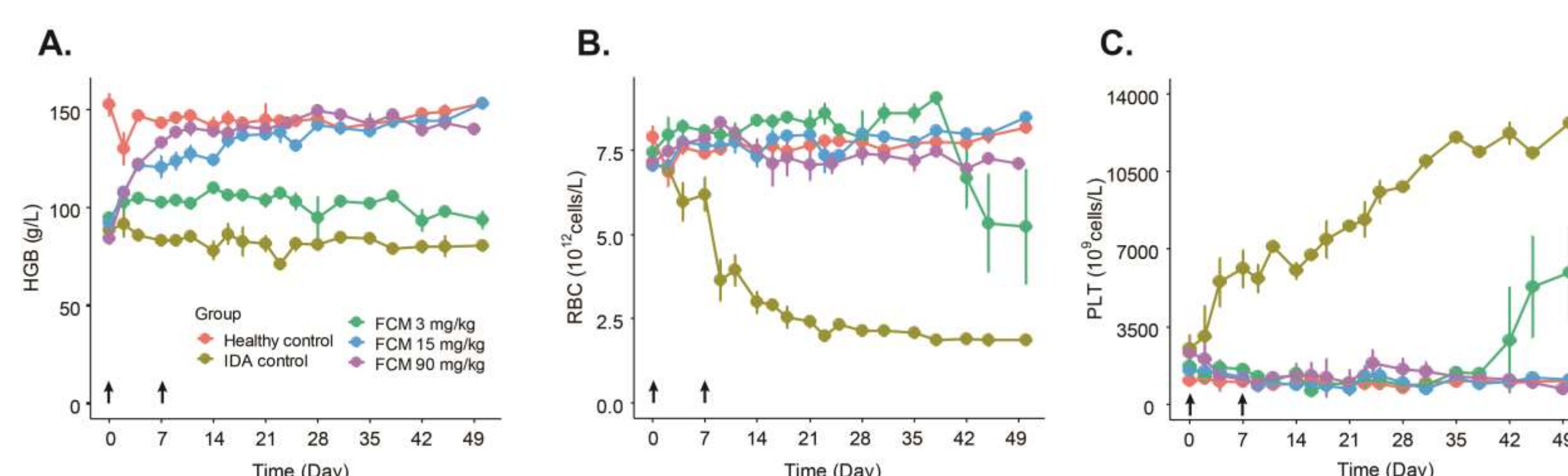


Fig. 4. Hematological parameters versus time after first dosing of FCM. Data were expressed as mean±SE, n = 3 in each group.

Table 1. Parameter estimates obtained from the PK model of IV iron

Parameter (Units)	Definition	Estimate	RSE (%)
CL (L/h/kg)	Clearance of iron	0.0001*	/
V1 (L/kg)	Volume of distribution of iron in central compartment	2.52	9.5
KIN _{iron} (mg/h/kg)	Input rate of iron	0.000197	6.7
V2 (L/kg)	Volume of distribution of iron in peripheral compartment	0.687	31.4
Qcp (L/h/kg)	Distribution rate from central to peripheral compartment	0.264	9.4
Qpc (L/h/kg)	Distribution rate from peripheral to central compartment	0.00132	22.4
σ _{prop}	Proportional residual error	0.231	8.8

*Considering there was no regulated mechanism for the excretion of iron, clearance was fixed to a very small number.

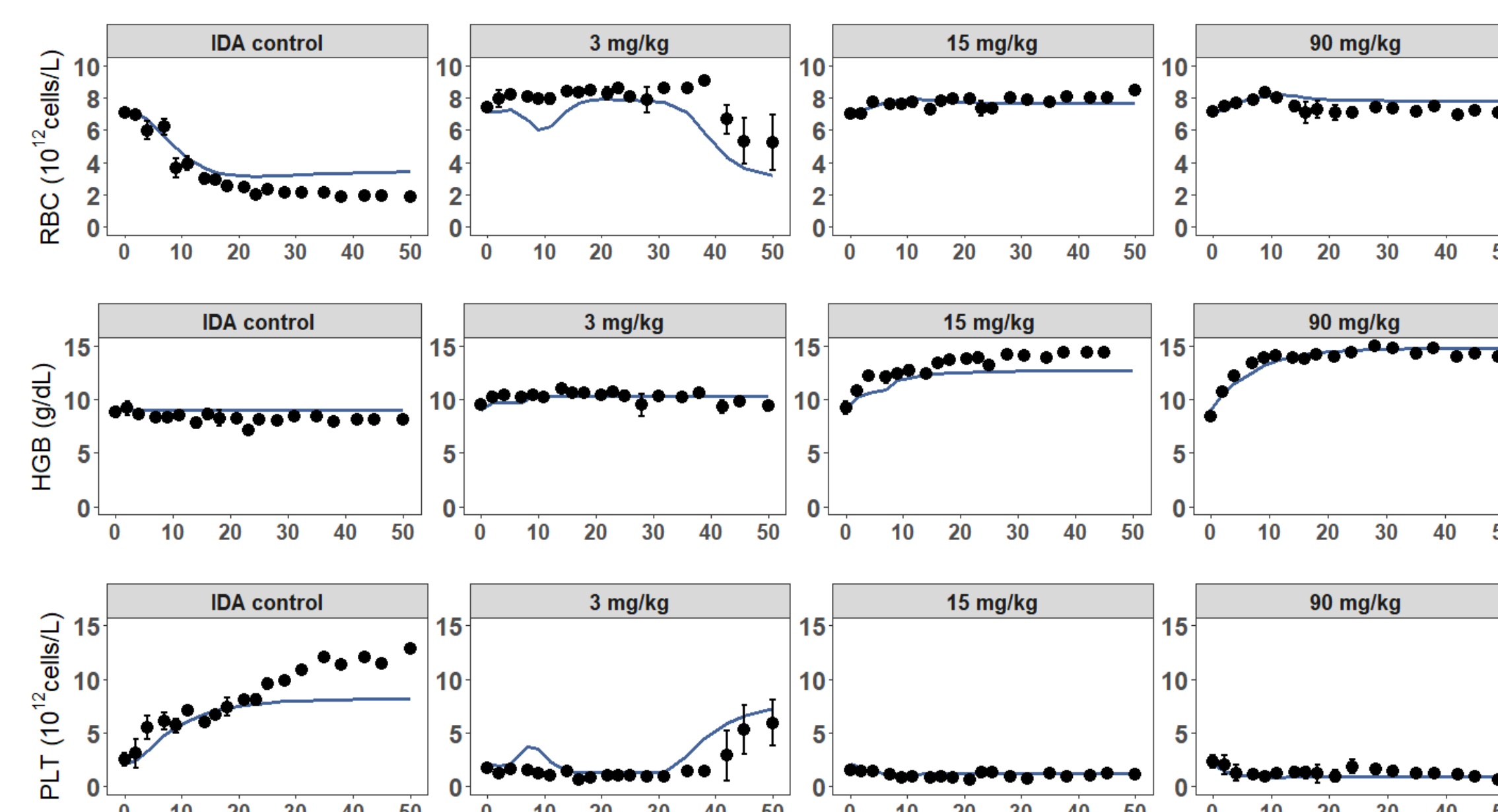


Fig 5. The observed (black dots) and model predicted (blue lines) RBC, HGB and PLT count in different treatment groups

Table 2. Parameter estimates obtained from the PD model

Parameters	Definition	Units	Estimate	%RSE
T _{ERT}	Mean residence time for reticulocytes	h	39.92	16.27
T _{RBC}	Mean residence time for RBCs	h	161.8	14.06
RBC ₀	Baseline of RBC counts	×10 ¹² cells/L	7.141	5.245
DF	Disease progression factor on HSPCs differentiation	/	0.8748	4.942
Smax _{iron}	Maximal stimulus of iron on HSPCs differentiation into BFU-E	/	12.63	32.24
SC50 _{iron}	SC50 of stimulus of iron on HSPCs differentiation	μg/dL	3.144	38.93
Smax _{HGB}	Maximal stimulus of iron on K _{in} of HGB (K _{IN_{HGB}})	/	0.7236	25.3
SC50 _{HGB}	SC50 of stimulus of iron on K _{in} of HGB	μg/dL	16.24	37.73
HGB ₀	Baseline HGB concentration	g/dL	8.985	4.936
T _{MP}	Mean lifespan of megakaryocyte precursor cells	h	3.491	38.5
T _{PLT}	Mean lifespan of platelets	h	85.7	18.79
PLT ₀	Baseline platelets count in blood	×10 ¹² cells/L	2.117	18.67
KE	First-order rate constant for differentiation of HSPCs into BFU-E	×10 ⁻⁴ /h	166.5	16.22
Cutoff _{iron}	Cutoff of iron concentration change from baseline to stimulate HSPCs differentiation into BFU-E	μg/dL	4.284	16.72
SC50 _{DF}	SC50 of IV iron on correction of disease progression	μg/dL	2062	7
σ _{prop-RBC}	Proportional residual error of RBC	/	0.292	7.127
σ _{add-HBG}	Additive residual error of HGB	/	0.790	5.106
σ _{prop-PLT}	Proportional residual error of platelets	/	0.584	6.802

Conclusions

- The effect of iron on HSPCs differentiation towards erythroid and megakaryocyte lineages *in vivo* was successfully characterized by a mechanism-based PK/PD model.
- We emphasize the importance of not only HGB and RBC but also PLT count as crucial biomarkers in iron therapy.
- The developed PK-PD model provides valuable mechanistic insights into iron-regulated HSPCs commitment towards erythroid and megakaryocyte lineages and holds promise as a useful tool for dose optimization of IV iron agents in management of anemia.

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