

# Prediction of Drug-Induced Hematotoxicity by an Integrated Clinical-Experimental-Computational Human Hematopoiesis Systems Toxicology Model

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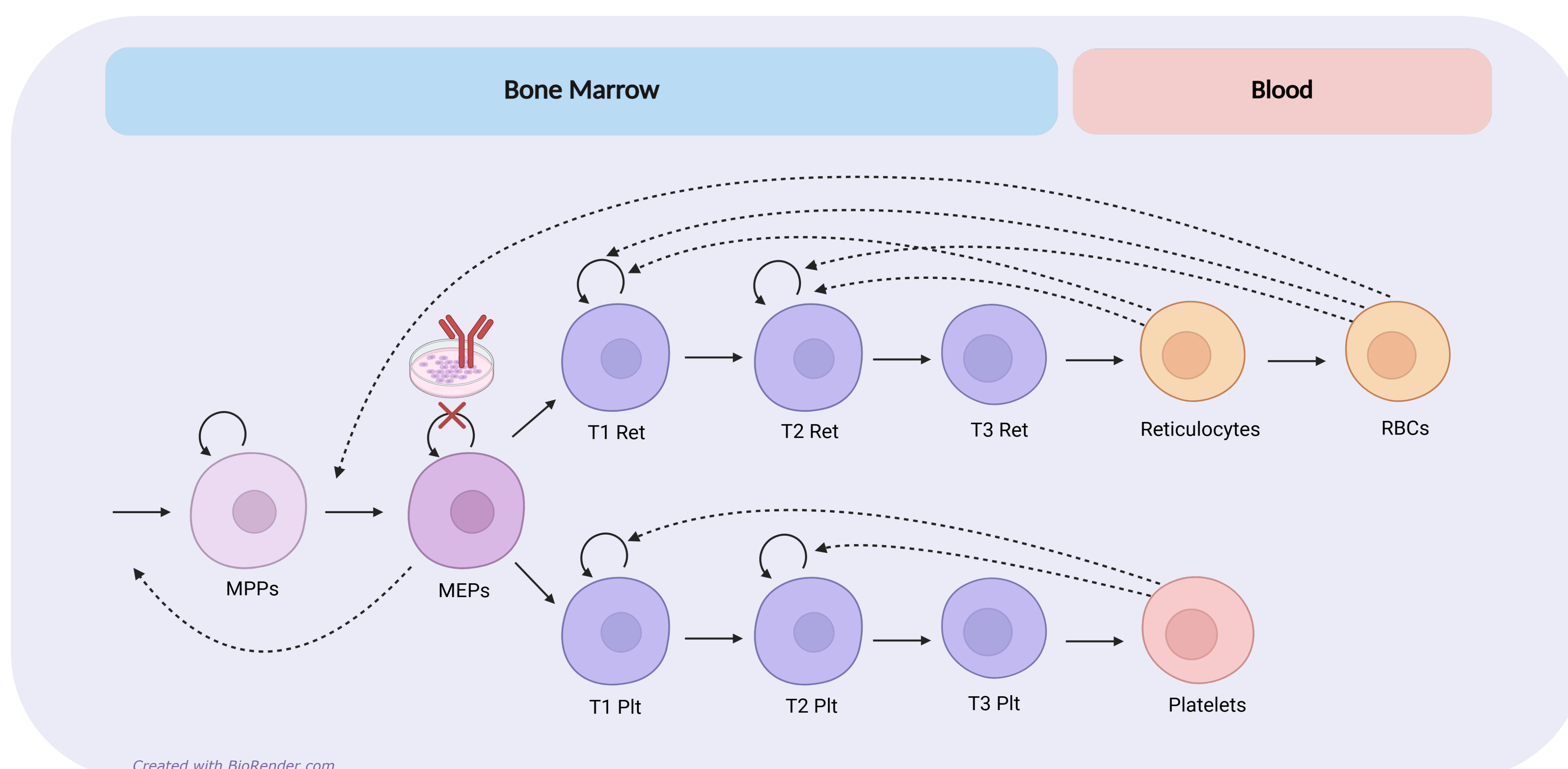
## Background

- New Biological Entities (NBE), such as antibody-based biologics, have revolutionized the treatment of many neoplastic and inflammatory diseases over the last years. However, pharmacology of the NBE might also alter normal physiology of non-intended target cells or organs.
- One frequent secondary target organ for NBEs targeting the immune system is the bone marrow, which maintains the homeostasis and lineage of peripheral blood cells such as red blood cells (RBCs) and platelets.
- Understanding how the hematopoietic system is affected is crucial to assess and predict the potential for hematotoxicity such as anemia or thrombocytopenia caused by NBE.

## In Silico Assessment of the Altered Human Hematopoietic System

- The hematologic system is regulated by complex biological processes, involving multiple progenitor cells, pathways, and anatomical compartments which are difficult to recapitulate with static *in vitro* assays.
- We adapted a mathematical model of human hematopoiesis by linking it with drug-related *in vitro* accessible parameters including drug potency and tissue exposure to permit exposure-related predictions and simulations of the modulated hematopoietic system.
- To facilitate hematotoxic risk assessment of our preclinical candidate molecules relative to a benchmark, we studied their effect on RBCs and platelets in comparison to an antibody in clinical development with known effects on the hematopoietic system.

## In Vitro Informed Human Hematopoiesis Systems Toxicology Model



### Clinical data & assumptions

1. Clinical data of the comparator showed no changes in blood parameters for a dose of 100mg Q2W (12 weeks), whereas some patients showed anemia and thrombocytopenia for a dose of 300mg Q2W (12 weeks).
2. The PK of the benchmark molecule was used to model the PK of the preclinical molecules.
3. The potency\* of the molecules was used to reflect the concentration-dependent perturbation of the baseline hematopoietic system by inhibition of MEP cell proliferation.

Visualization of the mathematical model for the human hematopoietic system (Fornari et al. CPT Pharmacometrics Syst. Pharmacol. 2019).

MPPs = Multi-Potent Progenitors; MEPs = Megakaryocyte-Erythrocyte Progenitors; Ret = Reticulocytes; Plt = Platelets; T1,2,3 = Transit compartments  
Thanks to P. Trairatphisan and F. Jost (both Sanofi) for helping with model implementation.

\*Potency data from a TF-1 hematopoietic cell proliferation assay performed at Sanofi (not shown)

## Clinical Observations vs. Simulations for the Comparator

## Comparative Study of the Proprietary Preclinical Molecules



| Compound   | Potency IC50 [mg] | Simulated Mean maxRBC [%] |       |       |       |       |
|------------|-------------------|---------------------------|-------|-------|-------|-------|
|            |                   | 50mg                      | 100mg | 150mg | 200mg | 300mg |
| Molecule 1 | 0.10530           | [Green bar]               |       |       |       |       |
| Molecule 2 | 0.08598           |                           |       |       |       |       |
| Molecule 3 | 0.04464           |                           |       |       |       |       |
| Molecule 4 | 0.03647           |                           |       |       |       |       |
| Molecule 5 | 0.03410           |                           |       |       |       |       |
| Comparator | 0.02203           | [Yellow bar]              |       |       |       |       |
| Molecule 6 | 0.01279           | [Red bar]                 |       |       |       |       |

Assumption: Q2W (12 weeks)

Color-coding based on clinical observations of the comparator:

- **green** no changes in RBC parameters
- **yellow** not evaluated in the study
- **red** relevant changes in RBC parameters (anemia: 17%)

This clinical-computational correspondence was used to assess simulated RBC reduction.

**Interpretation:** A subset of molecules and maximal tolerated doses could be identified as less prone to clinical occurrence of anemia as compared to the benchmark.

## Conclusions

1. A potency-based modeling and simulation approach can be used to rank-order and benchmark preclinical molecules according to their risk of hematotoxicology.
2. The *in vitro* informed model framework is not tailored to a specific modality and can cover potentially adverse effects of different targeted receptors.
3. This *in silico* study could help to optimize the selection of potentially safer molecules in early research.



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