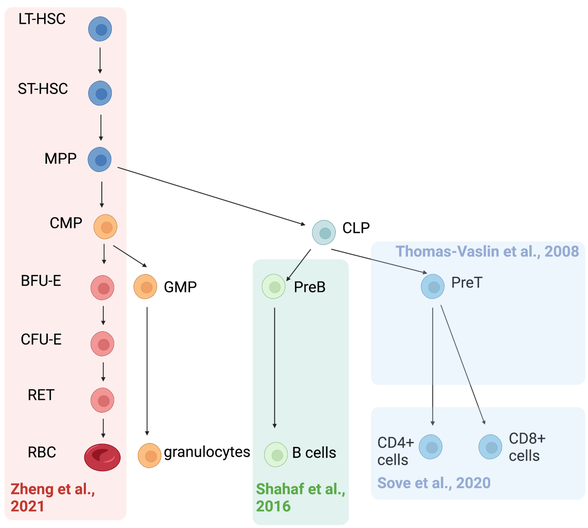
A multi-organ integrated QSP model for hematopoietic stem cell differentiation to predict the immune cell reconstitution in ex-vivo gene therapy

Yuezhe Li[1], Eric Jordie[1], Tim Knab[1]

[1]*Metrum Research Group*

Abstract

The differentiation of mammalian hematopoietic stem cells (HSCs) is complex and multi-scale, providing an opportunity for mathematical modeling and simulation to aid in mechanistic understanding and ultimately inform drug development efforts. Historically, mathematical models have been developed that were focused on the development of a subset of cells, but mathematical models that encompass the overall cellular system's complexity are rarely available. Here, we develop an integrated quantitative systems pharmacology (QSP) model that characterizes multi-organ recapitulation of HSC differentiation by integrating literature models and adding novel features. The result is a more comprehensive representation of mammalian hematopoietic stem cell development. We demonstrate our integrated model can accurately capture the reconstitution of RBCs, B cells, and T cells following HSC transplant in mice. Moreover, the humanized model successfully predicted the reconstitution of granulocytes and lymphocytes in patients with adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID) who underwent ex-vivo gene therapy.



Methods

We developed an integrated model that depicts the differentiation of hematopoietic stem cells (HSCs) into erythrocytes, lymphocytes, and granulocytes. The model was built incrementally by incorporating novel physiological-based features from literature while integrating published models:

- human HSC differentiation into red blood cells (RBCs) [1]
- mouse B cell development [2]
- mouse T cell development [3]
- human naive T cell dynamics model [4]

The model was developed in 4 steps:

- Implement an existing human HSC -> RBC differentiation model in [1]
- Scale the HSC -> RBC differentiation model from human to mouse
- Integrate T cells development model from [3], B cells development model from [2], and HSC -> granulocyte differentiation model into the mouse differentiation model
- Scale the integrated mouse HSC differentiation model to human.

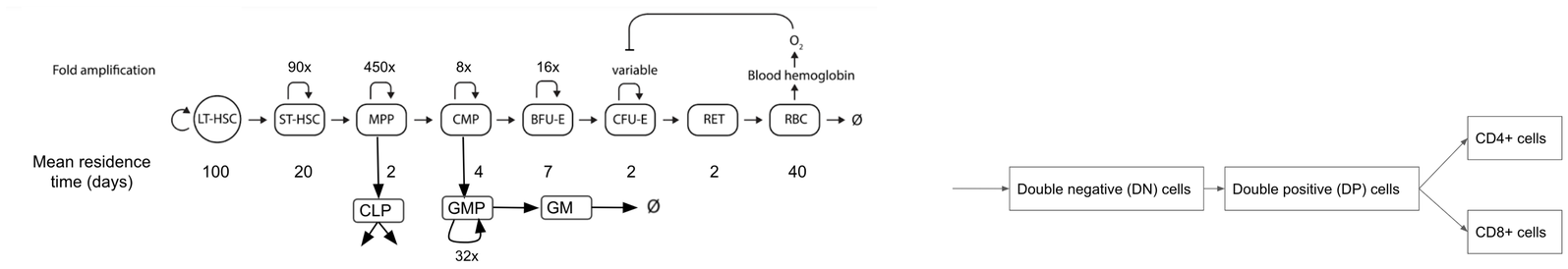
Further parameter tunings were carried out using steady state data (e.g. blood cell count) in mouse and in human. The integrated models for mouse and human were validated using cell reconstitution in peripheral blood after stem cell transplant/ ex-vivo gene therapy.

References

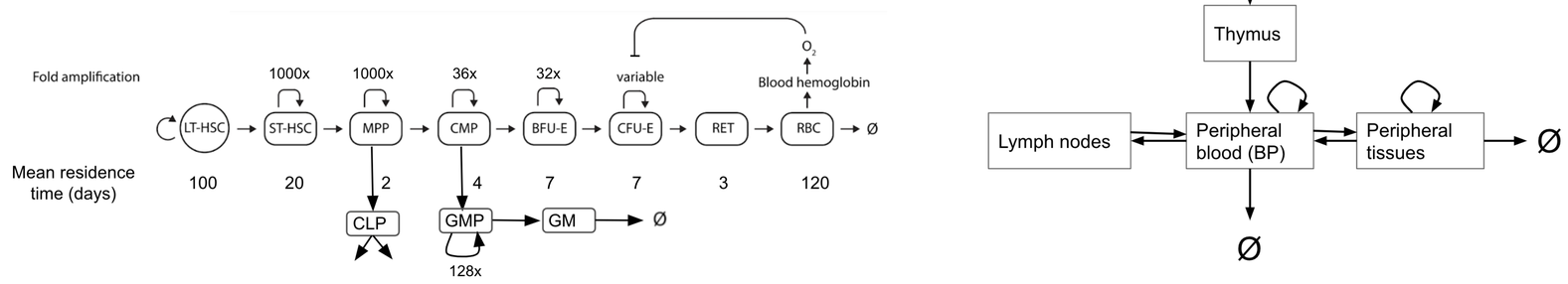
[1] Zheng, Bo, et al. "A systems pharmacology model for gene therapy in sickle cell disease." CPT: Pharmacometrics & Systems Pharmacology 10.7 (2021): 696-708. [2] Shahaf, Gitit, et al. "B cell development in the bone marrow is regulated by homeostatic feedback exerted by mature B cells." Frontiers in immunology 7 (2016): 77. [3] Thomas-Vaslin, Veronique, et al. "Comprehensive assessment and mathematical modeling of T cell population dynamics and homeostasis." The Journal of Immunology 180.4 (2008): 2240-2250. [4] Sové, Richard J., et al. "QSP-IO: a quantitative systems pharmacology toolbox for mechanistic multiscale modeling for Immuno-oncology applications." CPT: pharmacometrics & systems pharmacology 9.9 (2020): 484-497.

Results

The integrated HSC differentiation model for mouse can be summarized by the figure follow. Briefly, ...



The integrated HSC differentiation model for human can be summarized by the figure follow. Briefly, ...



Conclusion

Our work has resulted in a more comprehensive representation of mammalian hematopoietic stem cell development than previous partial efforts. Our integrated model is based on physiological understanding and validated with both mouse and human data. The models are implemented in both R and Julia, and the code will be available on GitHub. We believe this integrated model provides a versatile platform for predicting cell reconstitution after HSC transplant or ex-vivo gene therapy.