Dresden University of Technology

Ingmar Glauche

From binary switches to continuous landscapes:

Challenges in modeling hematopoietic stem cell dynamics and clonal progression

22.February.2026

Mephistopheles: Blut ist ein ganz besondrer Saft.

Mephistopheles: Blood is a very special juice.

Johann Wolfgang von Goethe, Faust 1

Stem cell behaviour

Development 110, 1001–1020 (1990)
Printed in Great Britain © The Company of Biologists Limited 1990

Stem cells: attributes, cycles, spirals, pitfalls and uncertainties

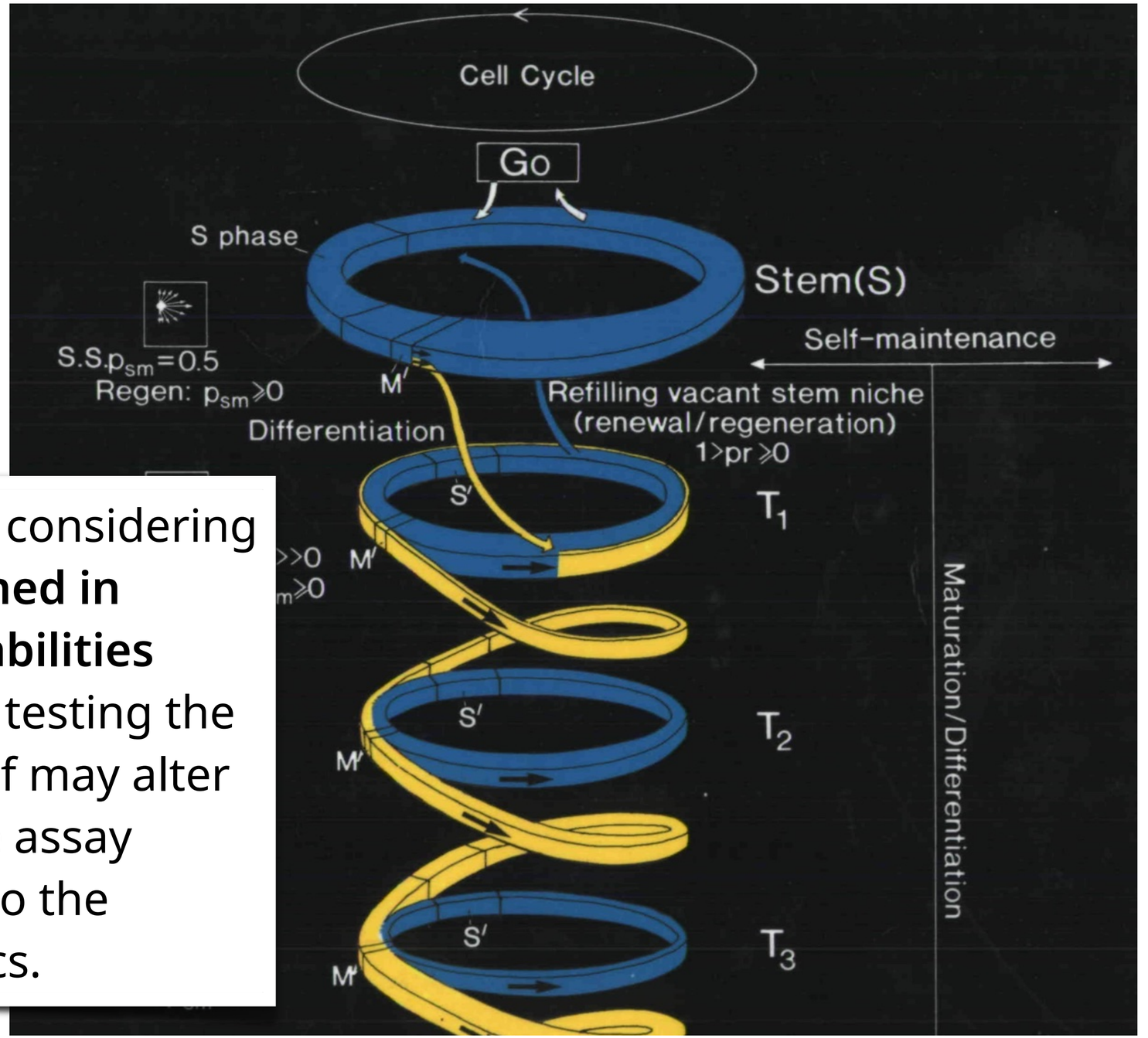
Lessons for and from the Crypt

C. S. POTTEN[1,*] and M. LOEFFLER[2]

[1]*CRC Department of Epithelial Cell Biology, Paterson Institute for Cancer Research, Christie Hospital & Holt Radium Institute, Manchester M20 9BX, UK*
[2]*Department of Biometry, Medizinische Universitaetsklinik, LFI-02, Joseph-Stelzmann Strasse 9, D5000 Koeln 41, West Germany*

* Author for correspondence

One of the major difficulties in considering stem cells is that they are **defined in terms of their functional capabilities** which can only be assessed by testing the abilities of the cells, which itself may alter their characteristics during the assay procedure: a situation similar to the **uncertainty principle** in physics.



HSCs: self-renewal and multipotency

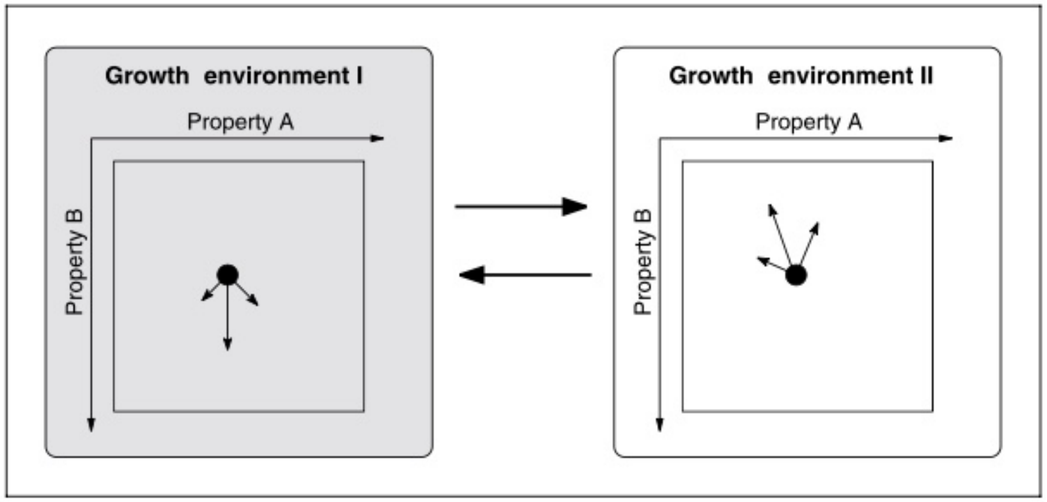
Cells Tissues Organs

Cells Tissues Organs 2002;171:8–26

Tissue Stem Cells: Definition, Plasticity, Heterogeneity, Self-Organization and Models – A Conceptual Approach

Markus Loeffler Ingo Roeder

Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany



Amended Definition of Tissue Stem Cells

Stem cells of a particular tissue are:

(S1) a potentially heterogeneous population of functionally undifferentiated cells, capable of:

(S2) homing to an appropriate growth environment;

(S3) proliferation;

(S4) production of a large number of differentiated progeny;

(S5) self-renewing or self-maintaining their population;

(S6) regenerating the functional tissue after injury with

(S7) flexibility and reversibility in the use of these options.

HSCs: self-renewal and multipotency

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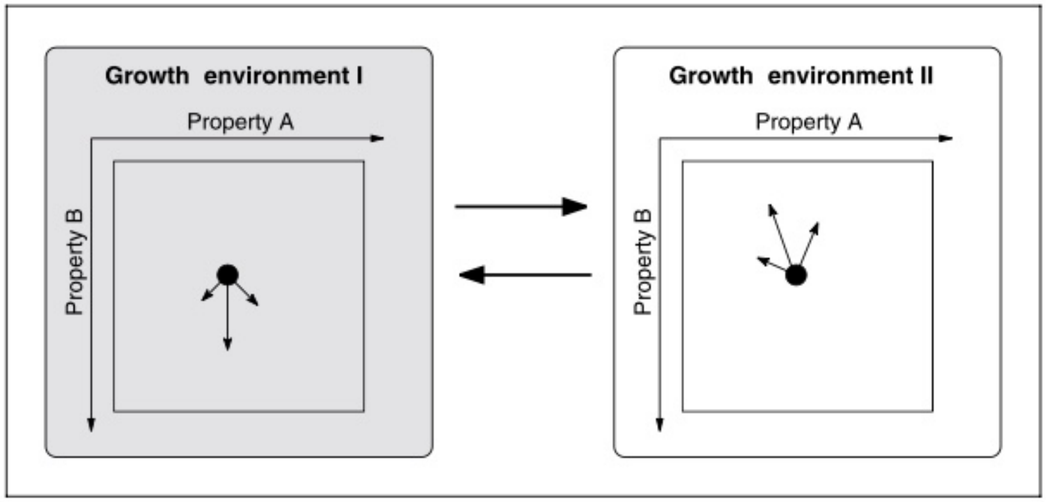
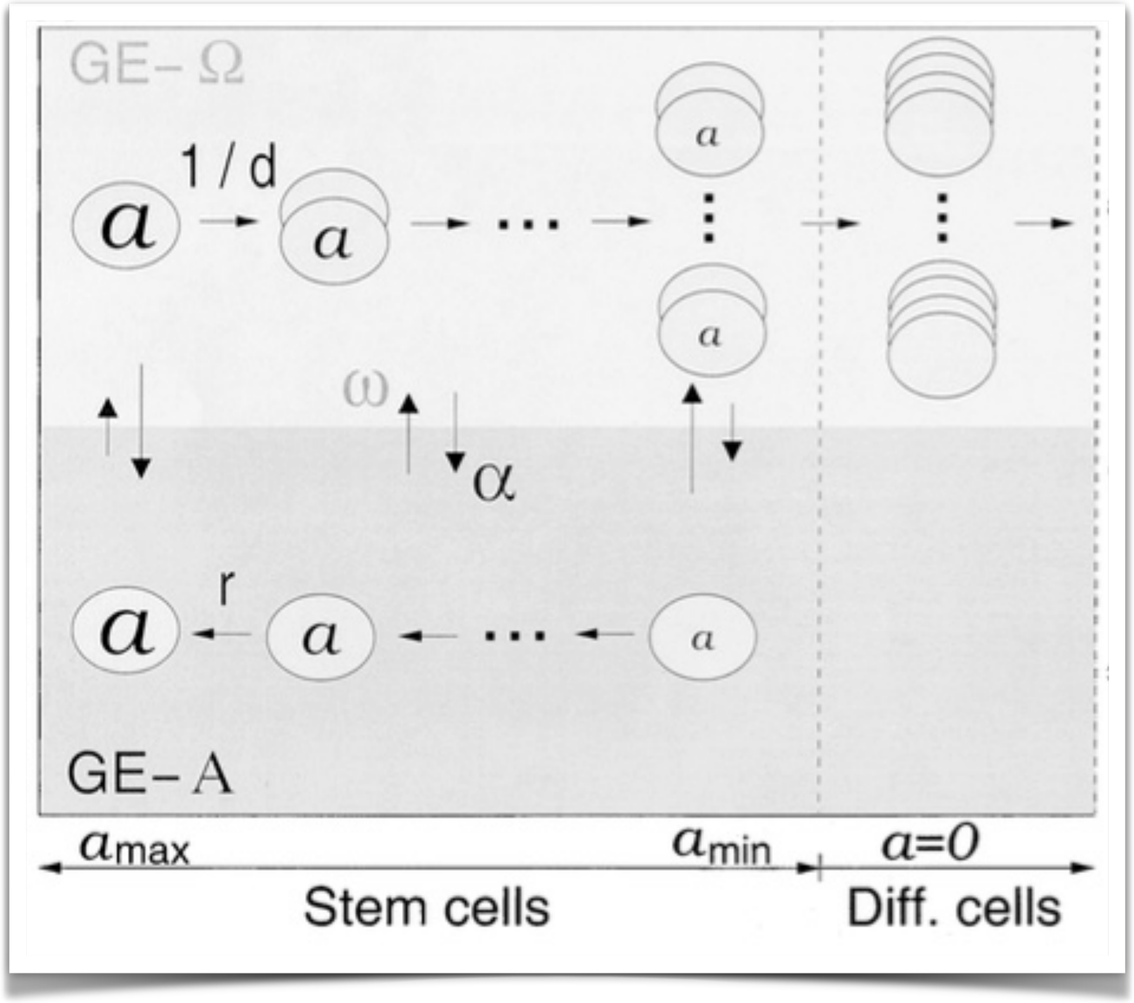


agent-based model

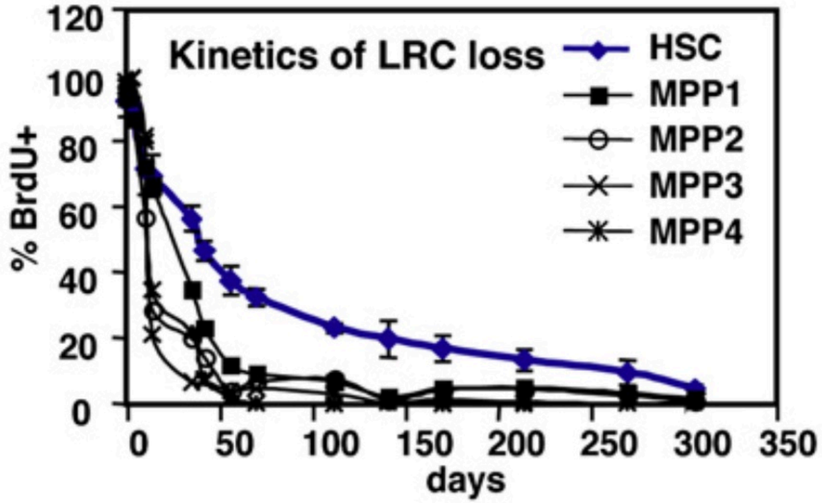


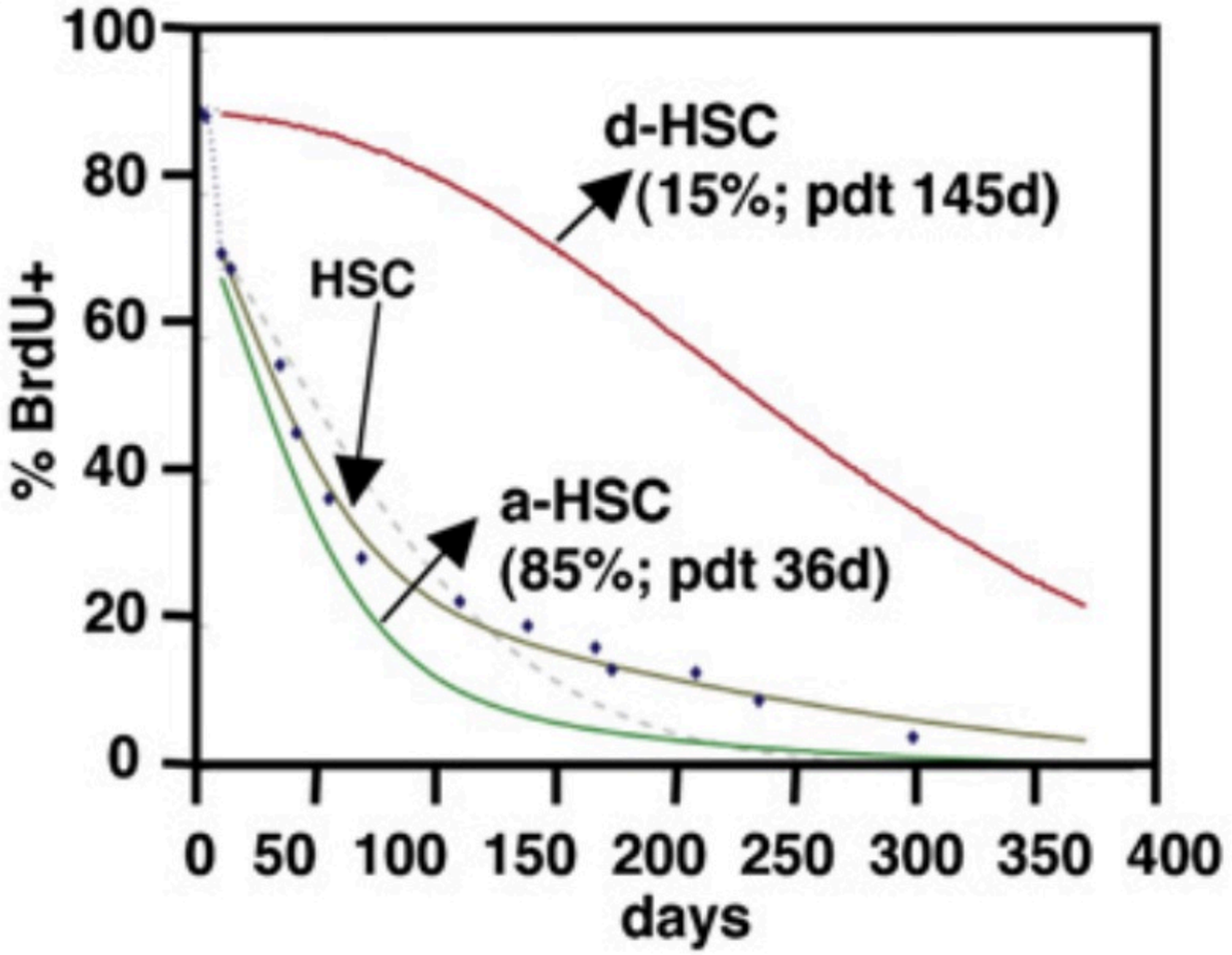
HSCs: reversible activation

Cell

Hematopoietic Stem Cells Reversibly Switch from Dormancy to Self-Renewal during Homeostasis and Repair

Anne Wilson,[3] Elisa Laurenti,[1,8] Gabriela Oser,[1,8] Richard C. van der Wath,[4,8] William Blanco-Bose,[1,8] Maike Jaworski,[1] Sandra Offner,[1] Cyrille F. Dunant,[6] Leonid Eshkind,[5] Ernesto Bockamp,[5] Pietro Lió,[4] H. Robson MacDonald,[3] and Andreas Trumpp[1,2,7,*]





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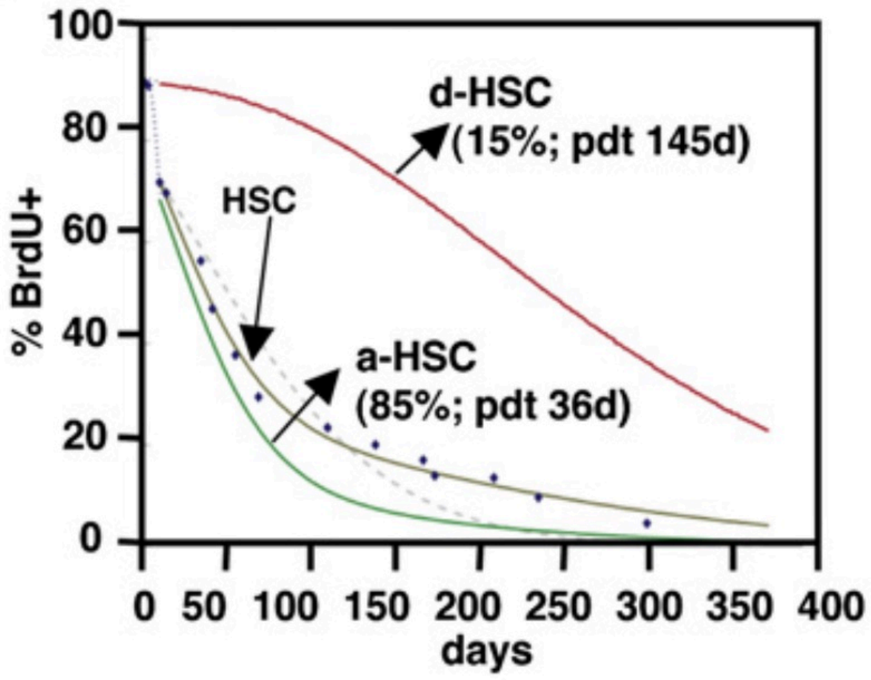
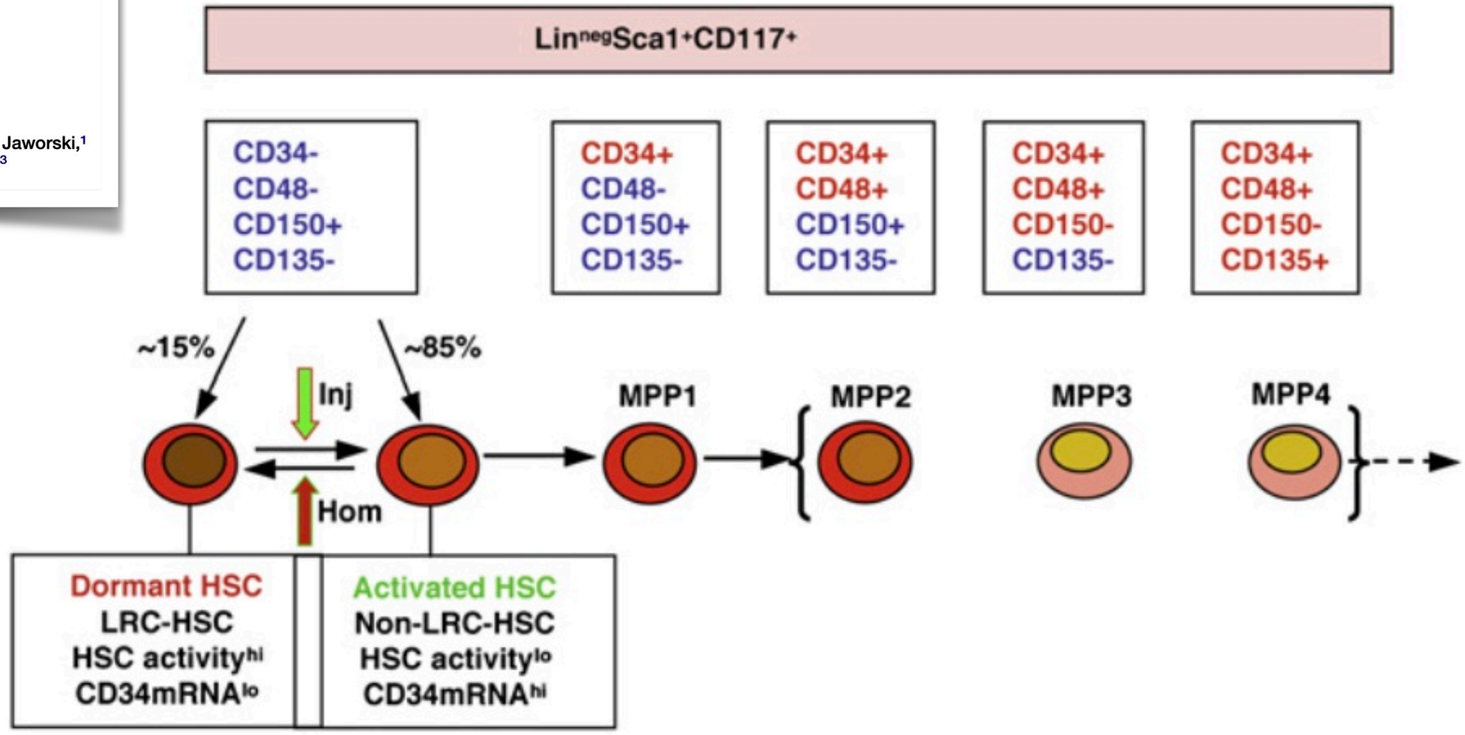




HSCs: modeling reversibility

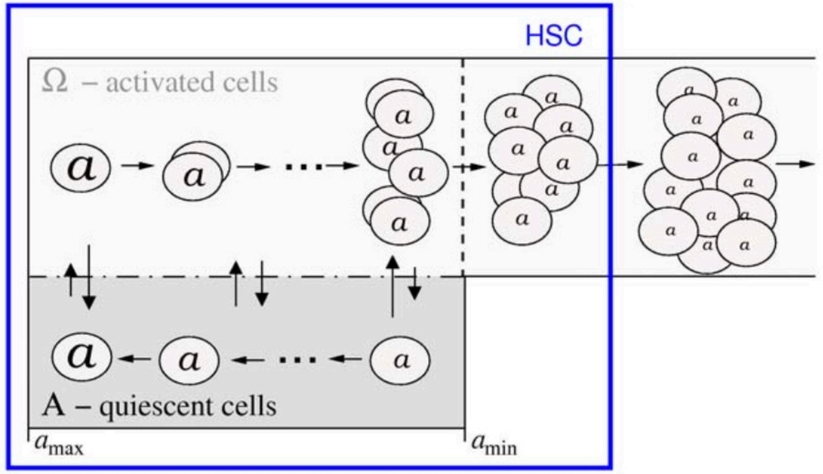
OPEN ACCESS Freely available online

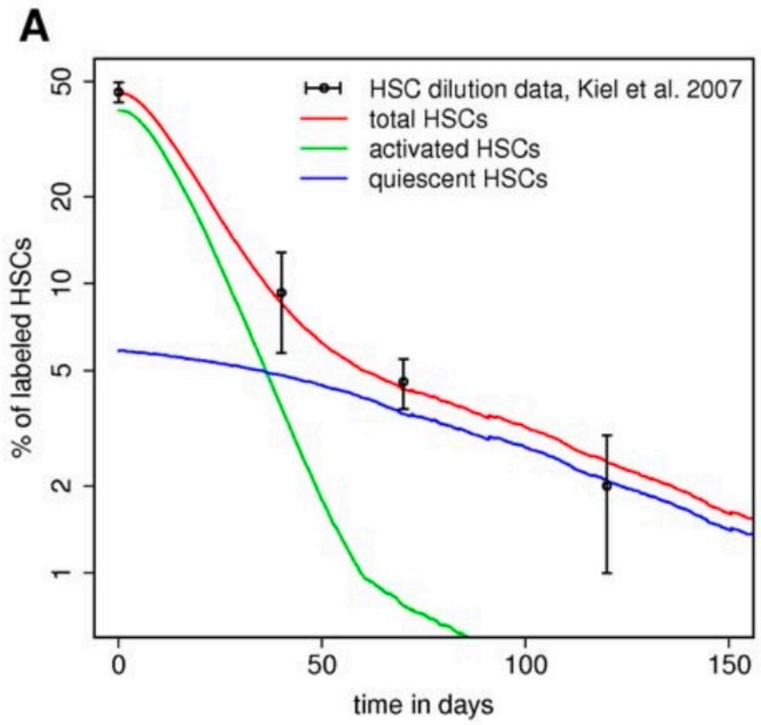
PLOS COMPUTATIONAL BIOLOGY

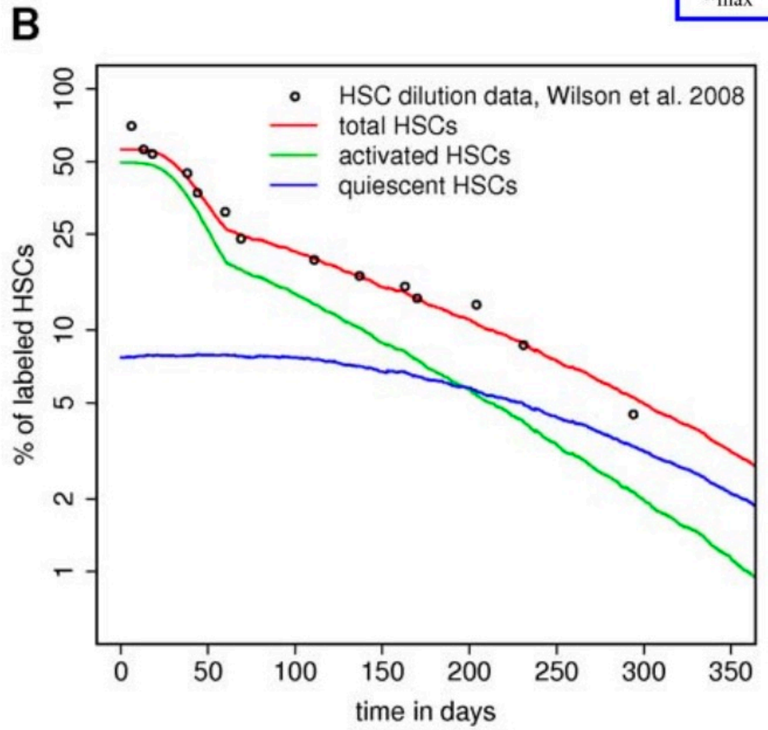
Stem Cell Proliferation and Quiescence—Two Sides of the Same Coin

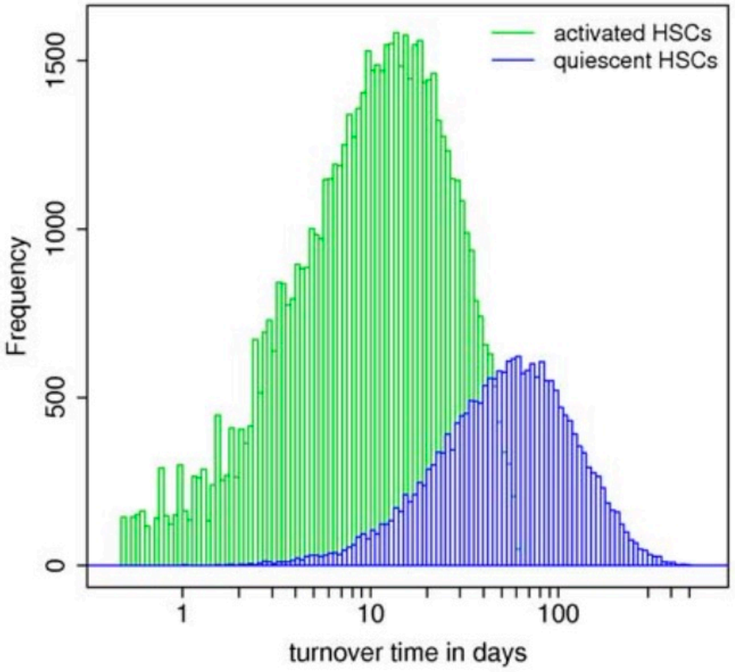
Ingmar Glauche[1]*, Kateri Moore[2], Lars Thielecke[1], Katrin Horn[1], Markus Loeffler[1], Ingo Roeder[1,3]

1 Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany, **2** Department of Gene and Cell Medicine, Mount Sinai School of Medicine, New York, New York, United States of America, **3** Department of Computing, Goldsmiths, University of London, London, United Kingdom

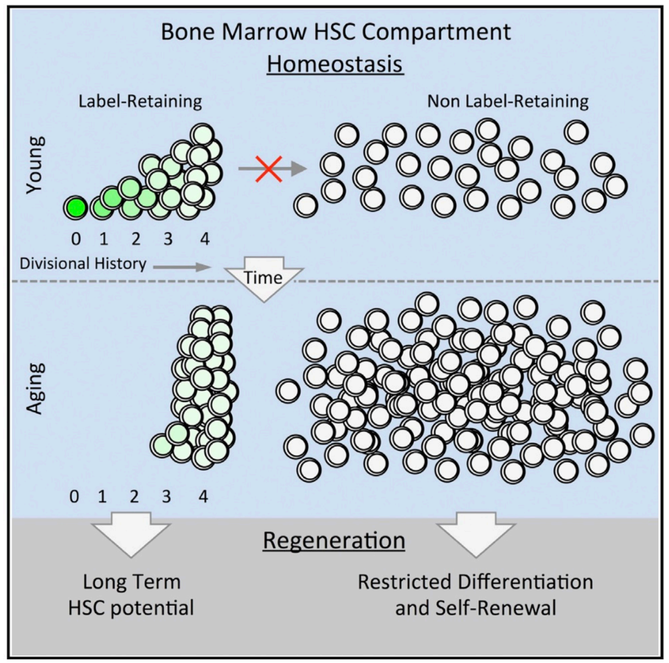


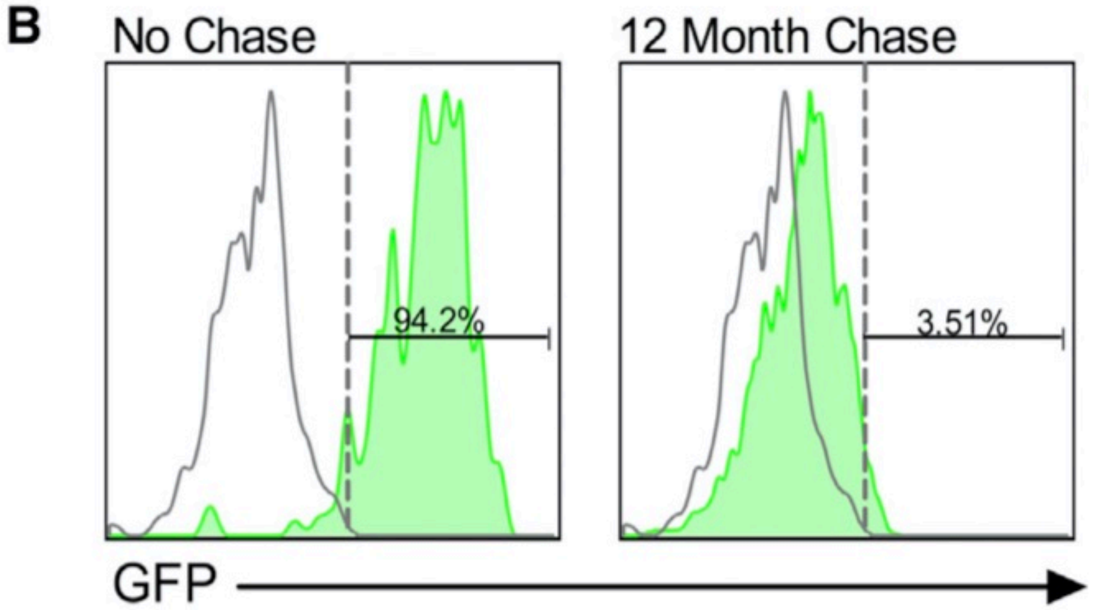


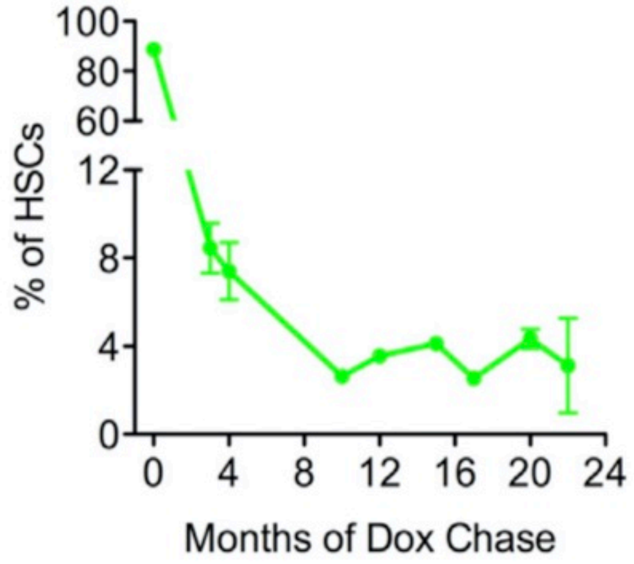




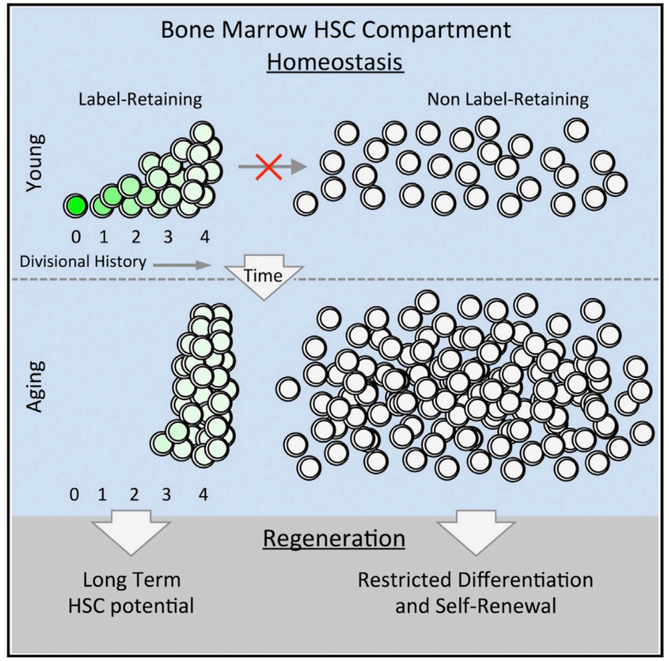
HSCs: understanding dormancy

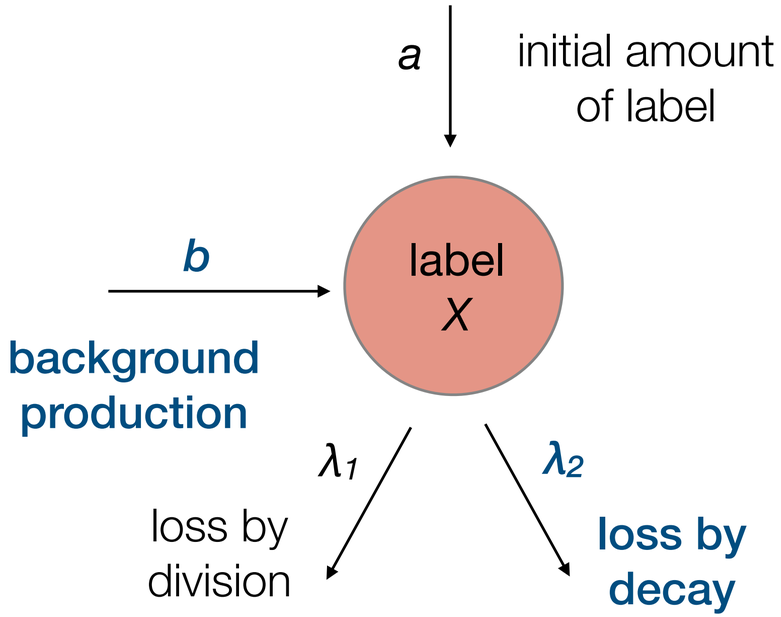






HSCs: understanding dormancy





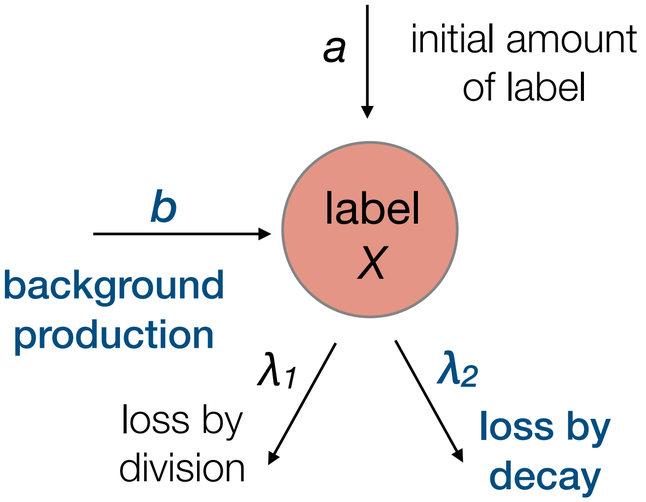
HSCs: understanding dormancy

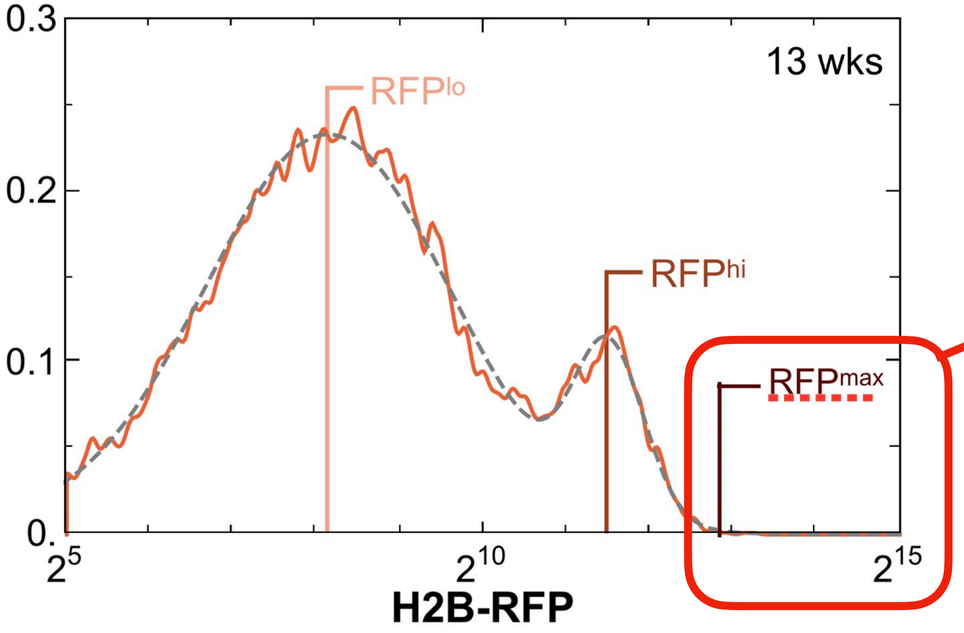
JEM Journal of Experimental Medicine

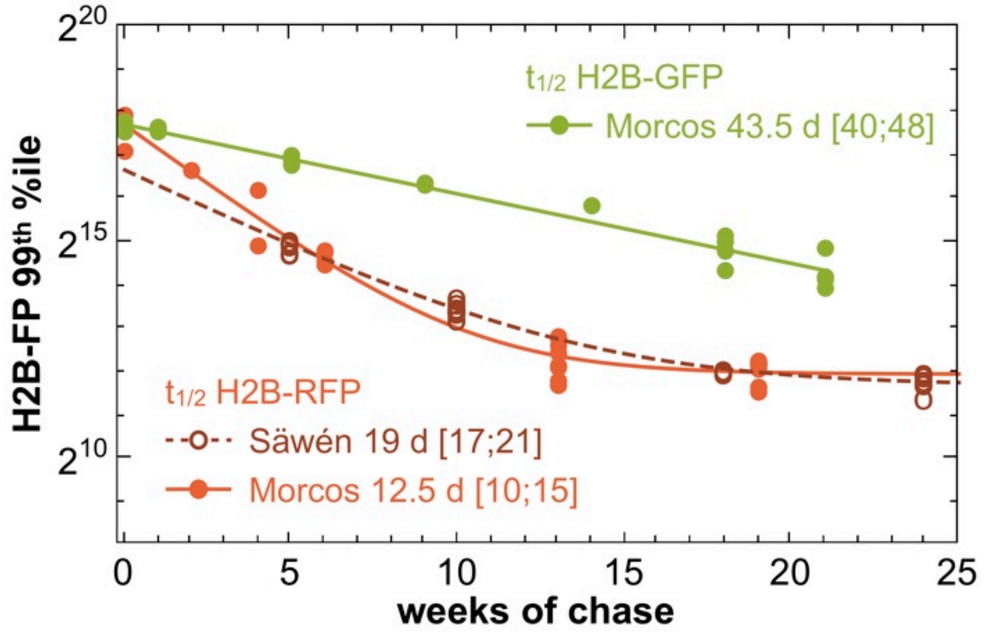
ARTICLE

Continuous mitotic activity of primitive hematopoietic stem cells in adult mice

Mina N.F. Morcos[1], Thomas Zerjatke[2], Ingmar Glauche[2], Clara M. Munz[1], Yan Ge[1], Andreas Petzold[3], Susanne Reinhardt[3], Andreas Dahl[3], Natasha S. Anstee[4], Ruzhica Bogeska[4], Michael D. Milsom[4], Petter Säwén[5], Haixia Wan[5], David Bryder[5,6], Axel Roers[1], and Alexander Gerbaulet[1]



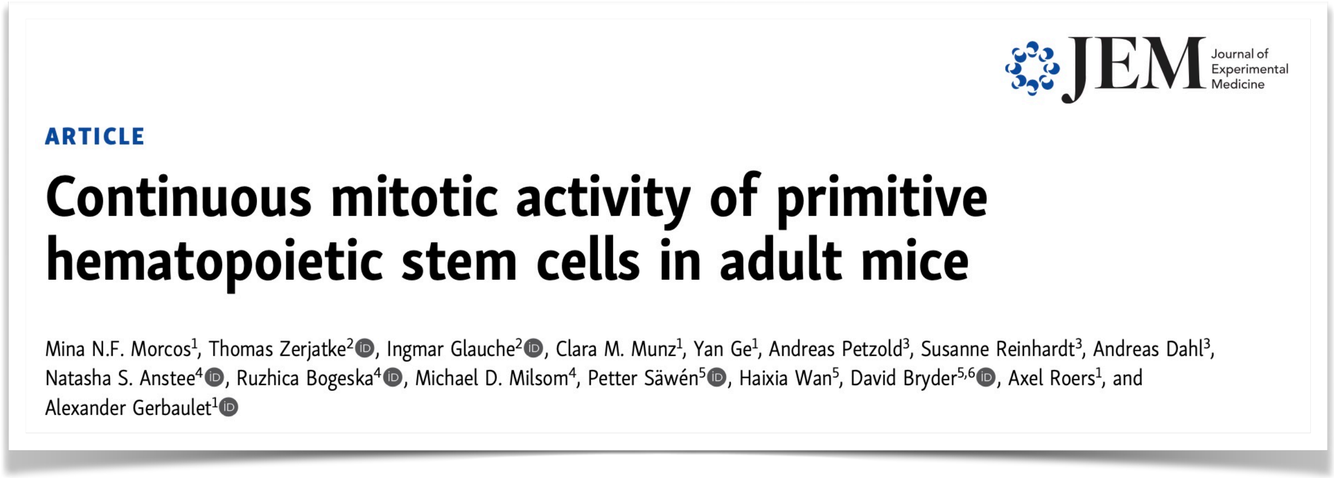


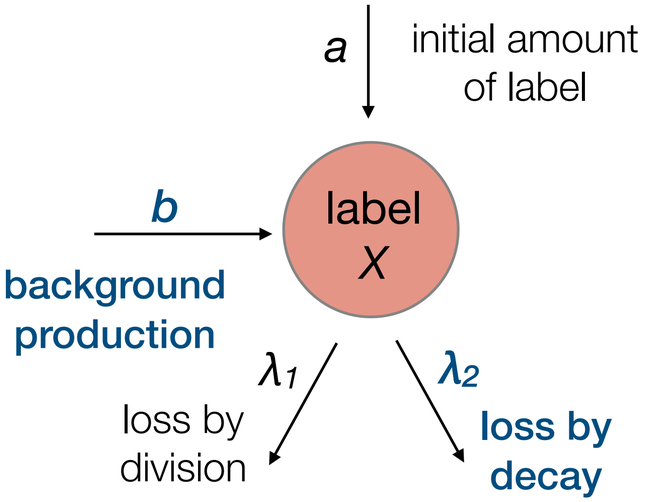


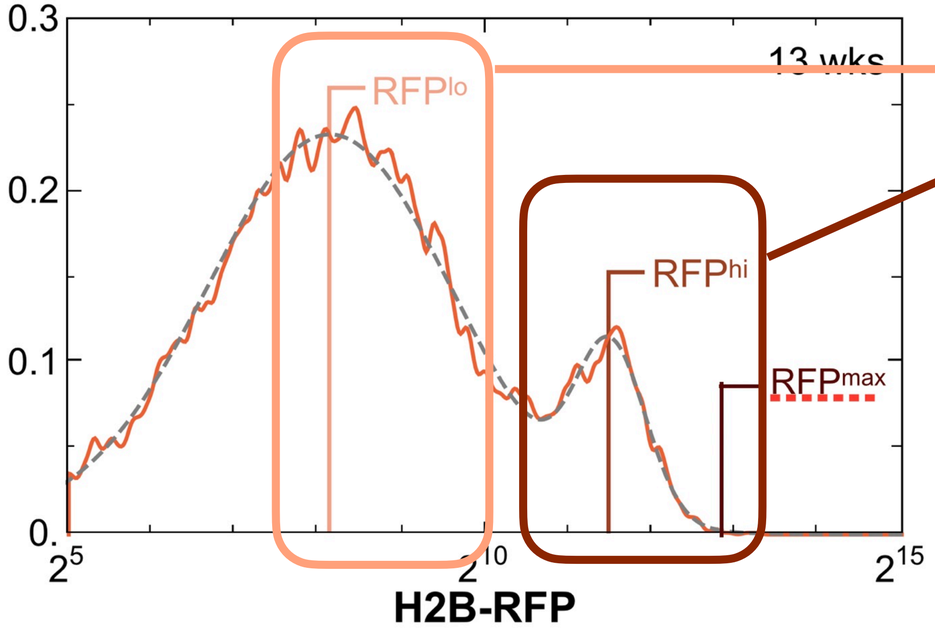
-> **estimated loss by decay:**

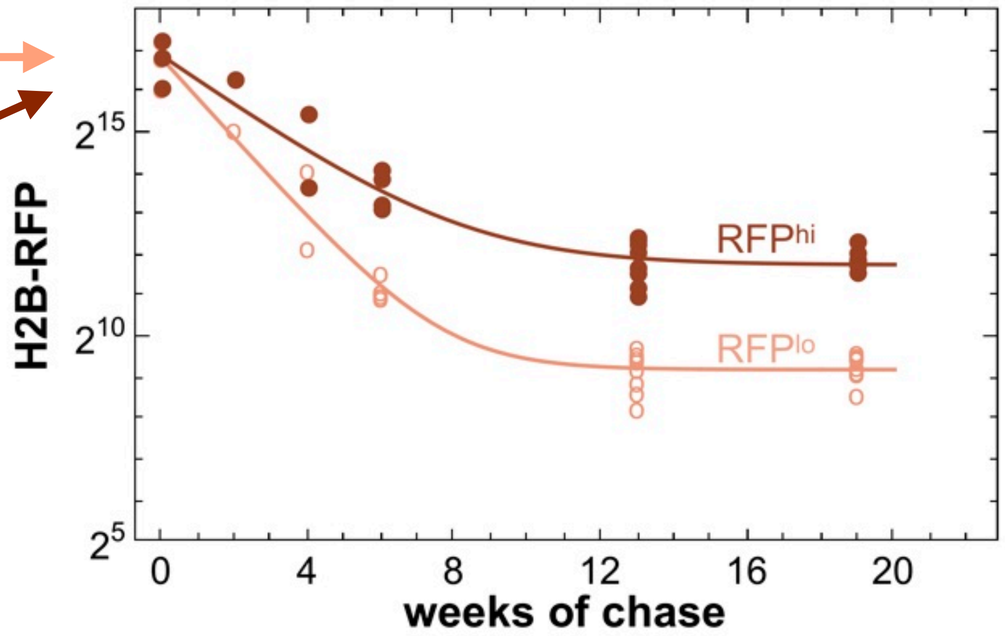
12.5 days for RFP (6 weeks for GFP)

HSCs: understanding dormancy









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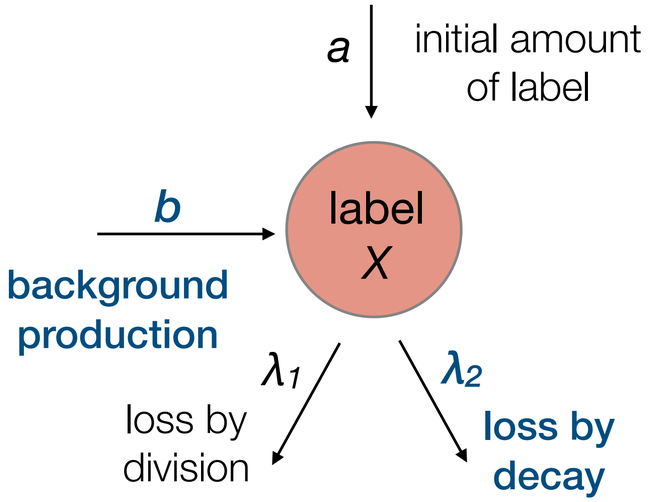
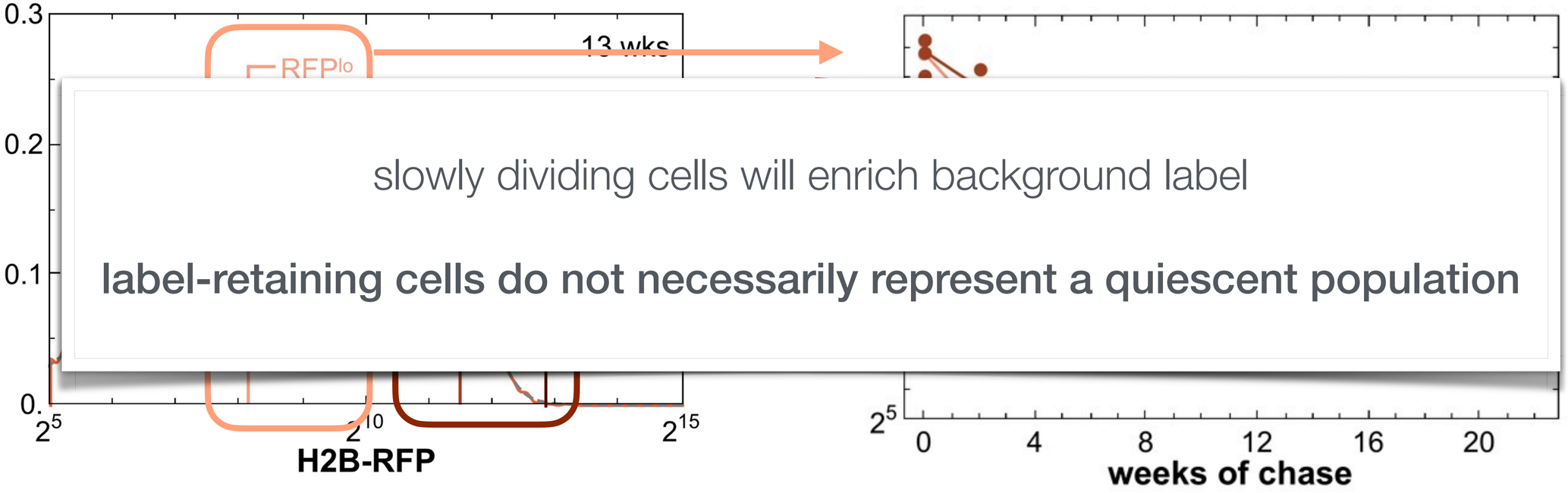




slowly dividing cells will enrich background label

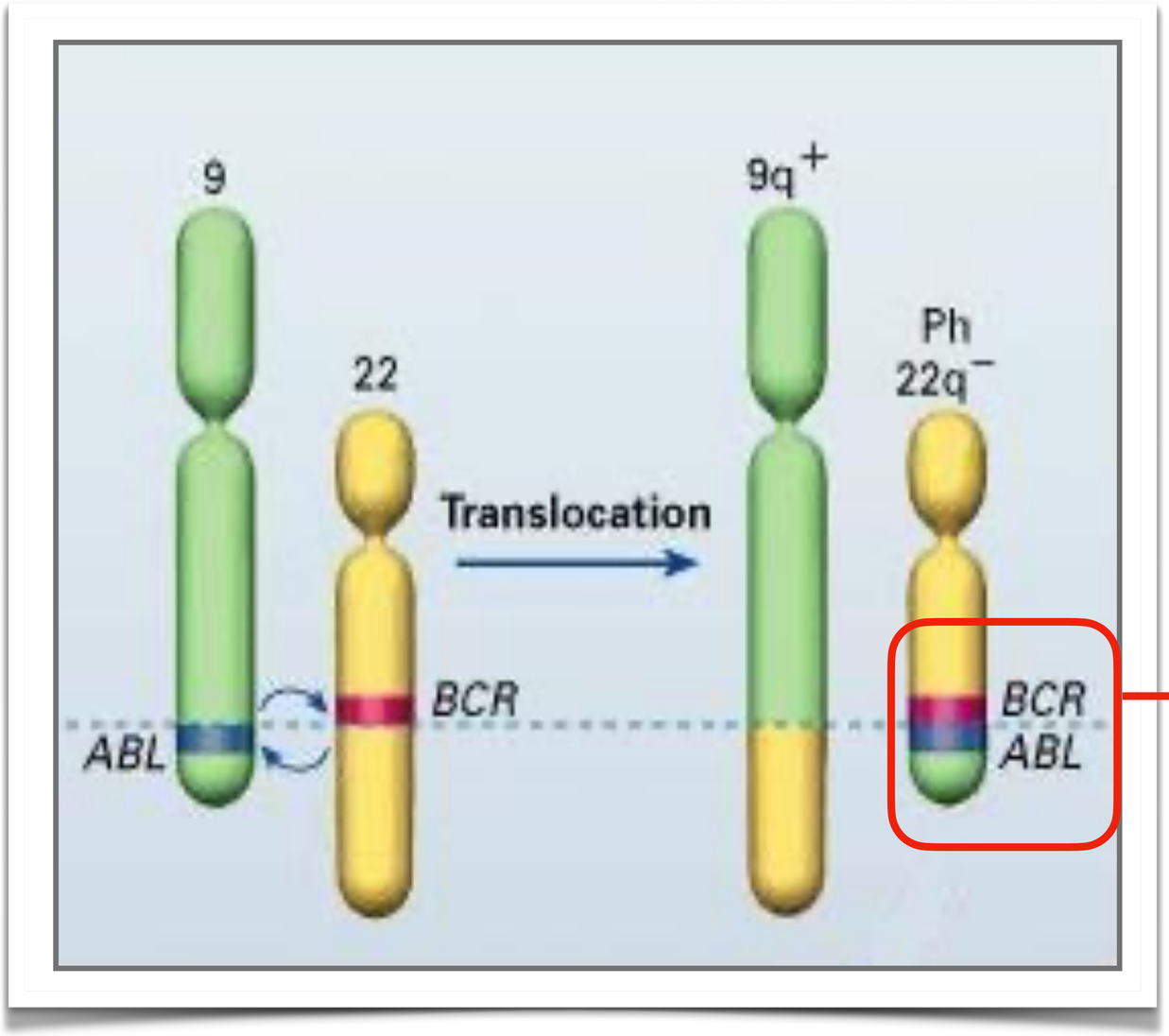
label-retaining cells do not necessarily represent a quiescent population

-> estimated division times:

2 weeks for proliferating cells

15 weeks for dormant cells

Leukemia treatment response



Chronic Myeloid Leukemia (CML)

enhanced production of differentiated BCR-ABL⁺ myeloid cells

displacement of normal hematopoiesis

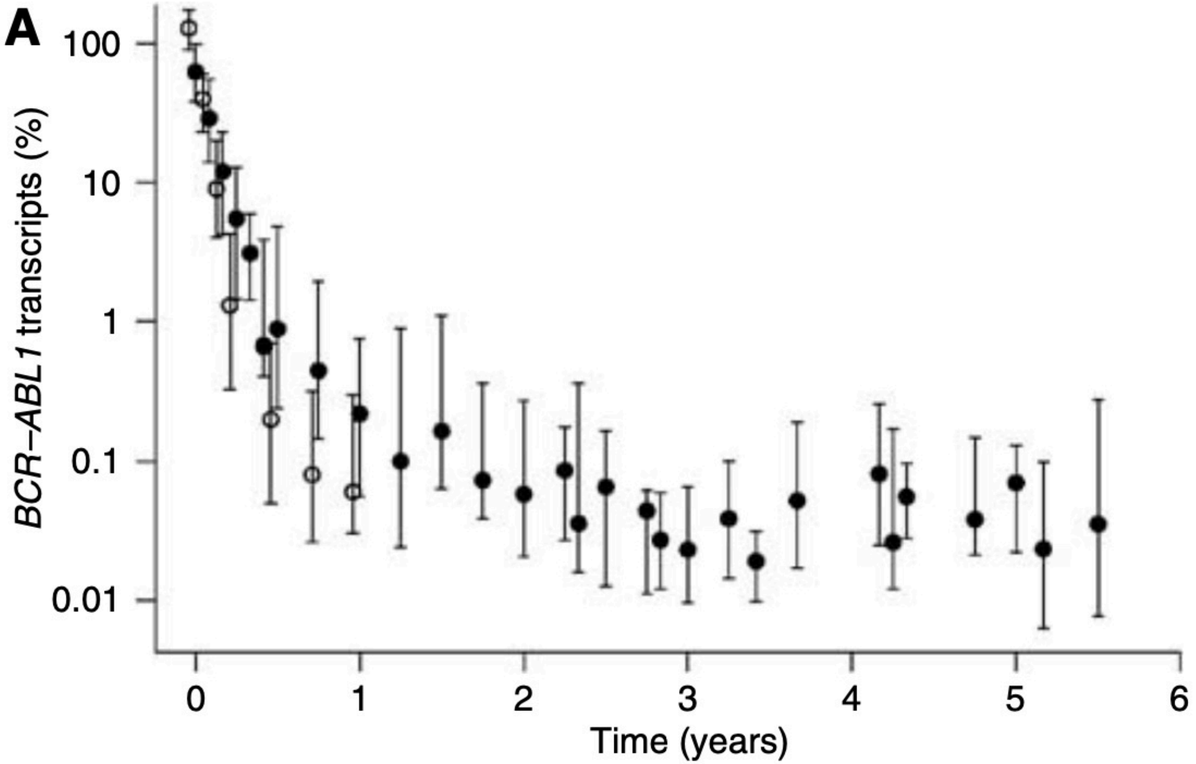
transit into (mostly lethal) blast crisis

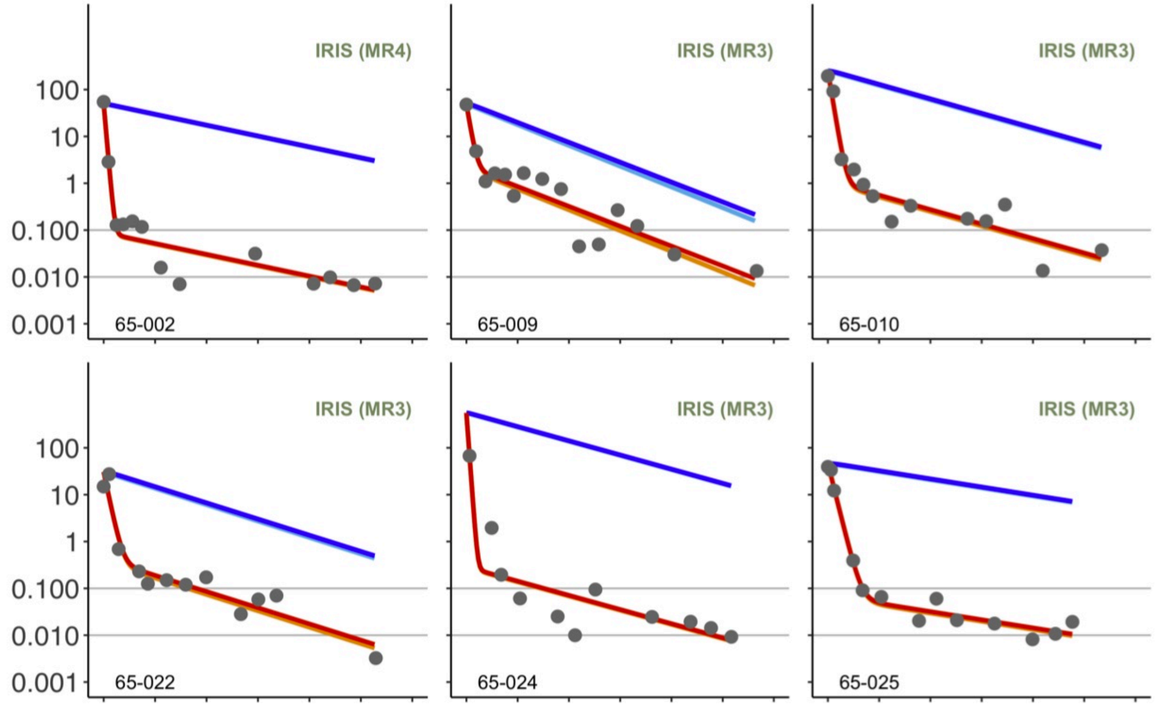
Unique

Measurable

Targetable

Leukemia treatment response

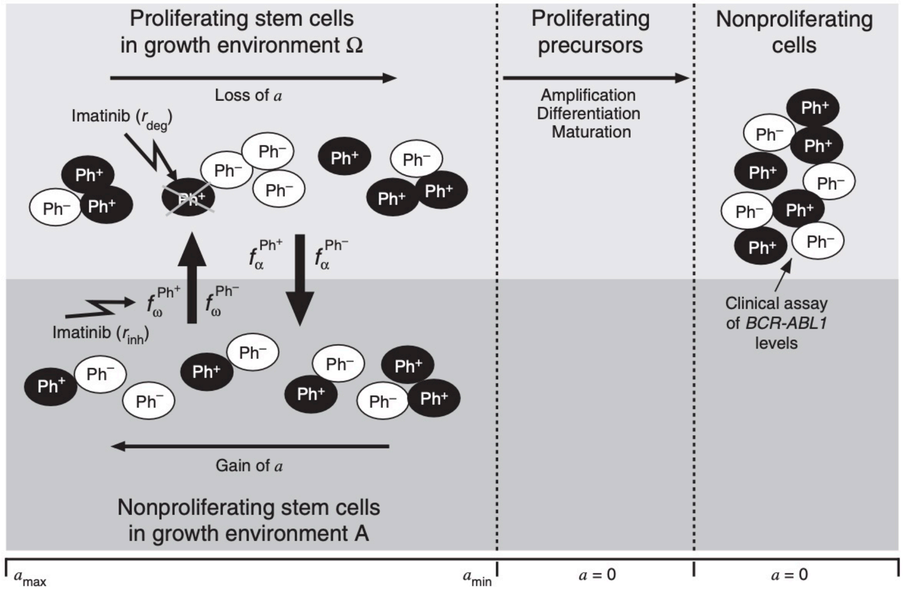


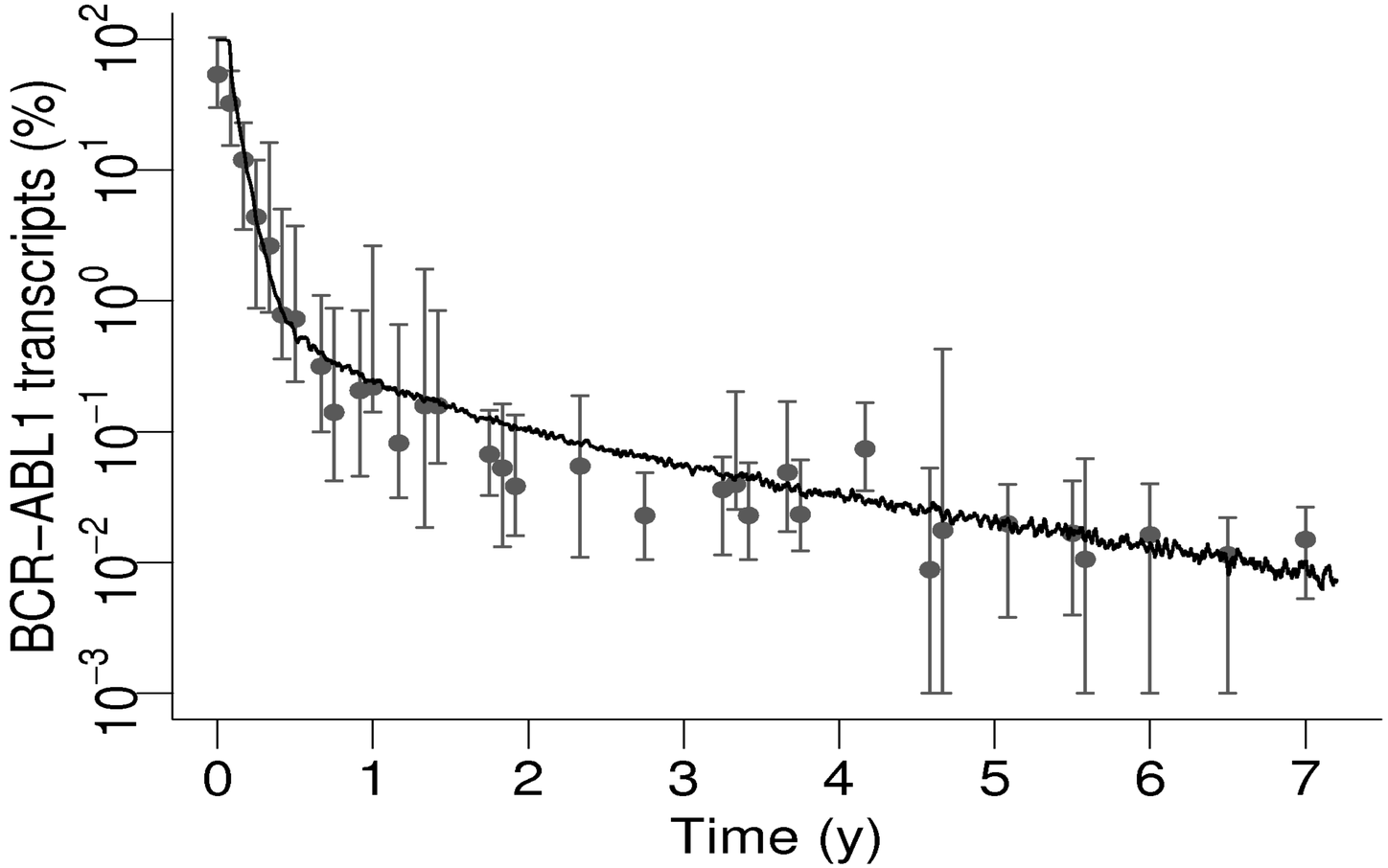


biphasic response pattern

Leukemia treatment response

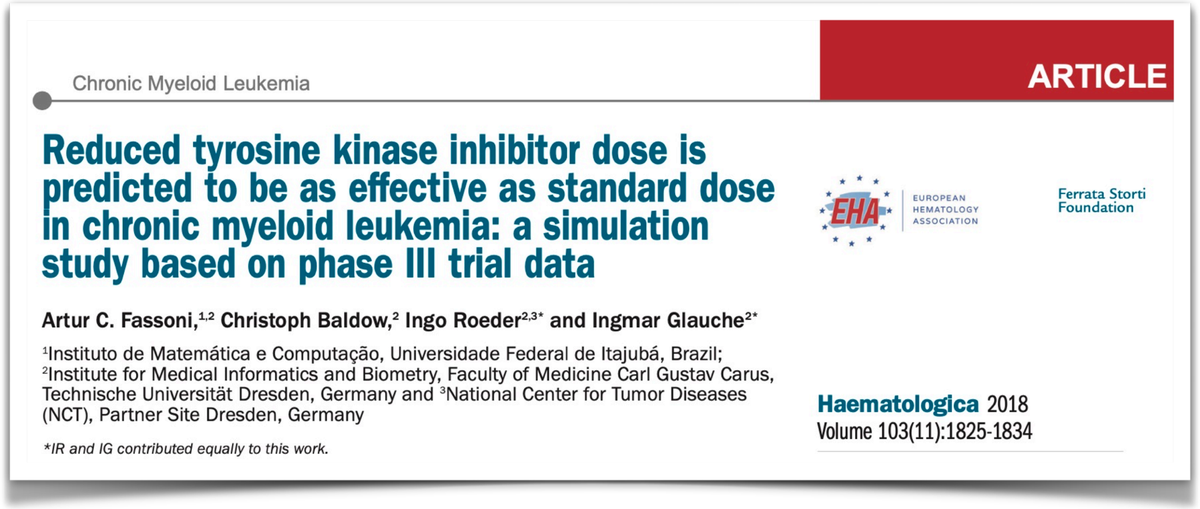
biphasic response pattern





Roeder at al., Nat Med, 2006

Leukemia treatment response



Chronic Myeloid Leukemia

ARTICLE

Reduced tyrosine kinase inhibitor dose is predicted to be as effective as standard dose in chronic myeloid leukemia: a simulation study based on phase III trial data

EUROPEAN HEMATOLOGY ASSOCIATION

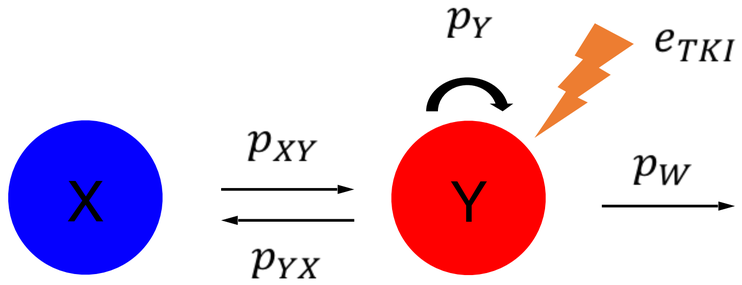
Ferrata Storti Foundation

Artur C. Fassoni,[1,2] Christoph Baldow,[2] Ingo Roeder[2,3*] and Ingmar Glauche[2*]

[1]Instituto de Matemática e Computação, Universidade Federal de Itajubá, Brazil; [2]Institute for Medical Informatics and Biometry, Faculty of Medicine Carl Gustav Carus, Technische Universität Dresden, Germany and [3]National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany

*IR and IG contributed equally to this work.

Haematologica 2018
Volume 103(11):1825-1834



quiescent leukemic stem cells

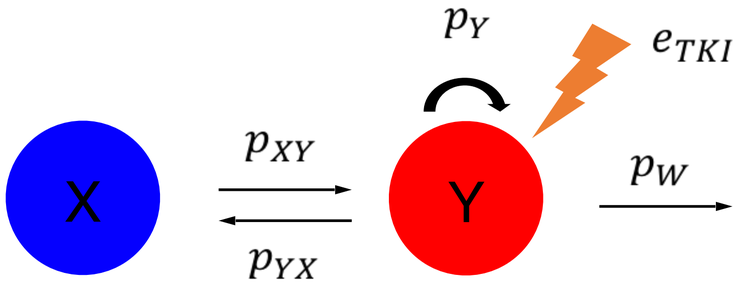
proliferating leukemic stem cells

translation into a mathematical formulation:

$$\frac{dX}{dt} = -p_{XY}X + p_{YX}Y$$

$$\frac{dY}{dt} = p_{XY}X - p_{YX}Y + p_Y Y - e_{TKI}Y$$

Leukemia treatment response



quiescent leukemic stem cells

proliferating leukemic stem cells

$$\frac{dX}{dt} = -p_{XY}X + p_{YX}Y$$

$$\frac{dY}{dt} = p_{XY}X - p_{YX}Y + p_Y Y - e_{TKI}Y$$

$$\frac{d}{dt}\begin{bmatrix} X \\ Y \end{bmatrix} = \begin{bmatrix} p_{XY} & -p_{YX} - q \\ -p_{XY} & p_{YX} \end{bmatrix}\begin{bmatrix} X \\ Y \end{bmatrix}$$

with effective toxicity

$$q = e_{TKI} - p_Y$$

Yielding the following solution

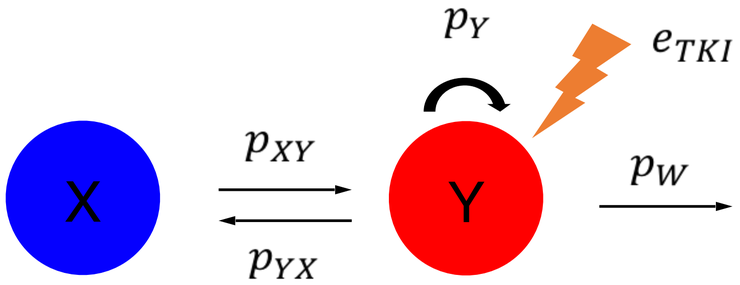
$$Y(t) = Y_0\left(C_1 e^{\lambda_1 t} + C_2 e^{\lambda_2 t}\right) \text{ and } X(t) = Y_0\left(C_3 e^{\lambda_1 t} + C_4 e^{\lambda_2 t}\right)$$

With eigenvalues

$$\lambda_1 = \frac{1}{2}\left(-p_{XY} - p_{YX} - q - \sqrt{(p_{XY} + p_{YX} + q)^2 - 4p_{XY}q}\right)$$

$$\lambda_2 = \frac{1}{2}\left(-p_{XY} - p_{YX} - q + \sqrt{(p_{XY} + p_{YX} + q)^2 - 4p_{XY}q}\right)$$

Leukemia treatment response



quiescent leukemic stem cells

proliferating leukemic stem cells

$$\frac{dX}{dt} = -p_{XY}X + p_{YX}Y$$

$$\frac{dY}{dt} = p_{XY}X - p_{YX}Y + p_Y Y - e_{TKI}Y$$

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with effective toxicity

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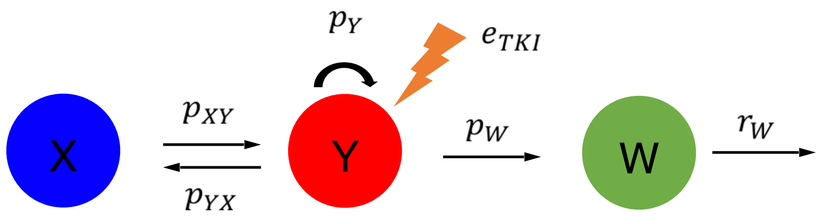
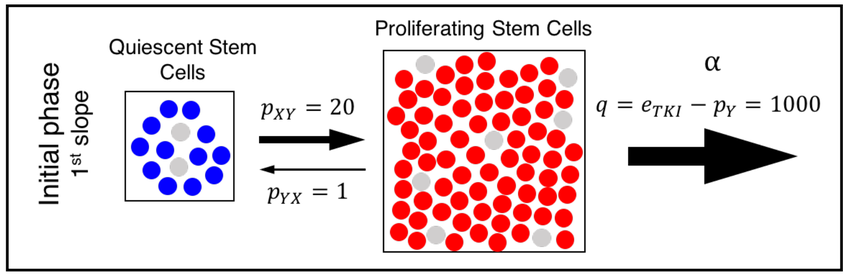
With eigenvalues

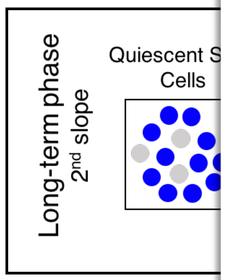
$$\lambda_1 = -q\left(1 + \varepsilon_1\varepsilon_2 + \varepsilon_1 O(\varepsilon_2^2)\right) = -q\left(1 + O(\varepsilon_3)\right)$$

$$\lambda_2 = -p_{XY}\left(1 - \varepsilon_1\varepsilon_2 + \varepsilon_1 O(\varepsilon_2^2)\right) = -p_{XY}\left(1 + O(\varepsilon_3)\right)$$

Leukemia treatment response

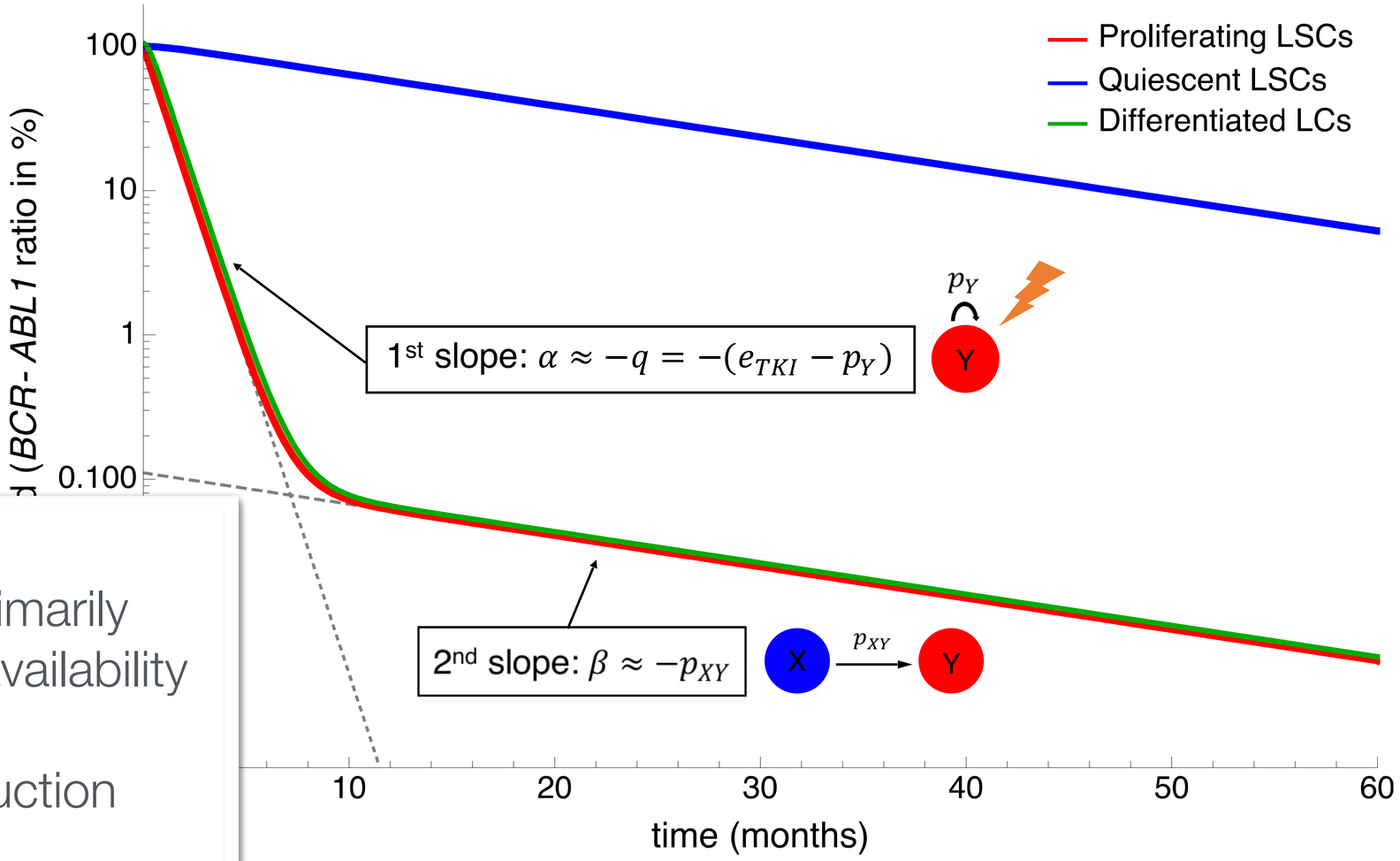






second slope is not primarily determined by the drug availability

potential for dose reduction



HSC heterogeneity

LETTER

doi:10.1038/nature14242

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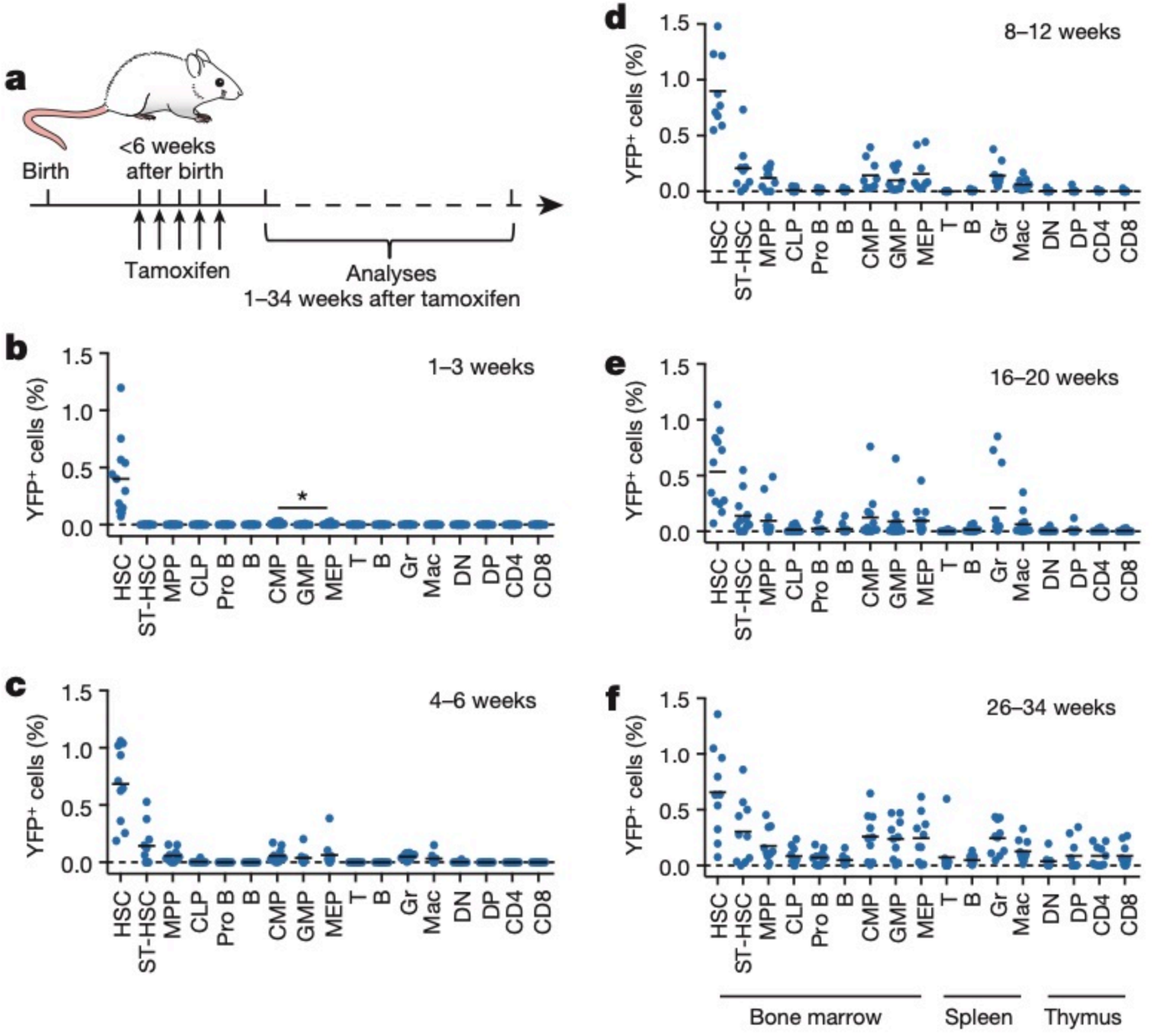
Katrin Busch[1], Kay Klapproth[1]*, Melania Barile[2]*, Michael Flossdorf[2]*, Tim Holland-Letz[3], Susan M. Schlenner[4,5], Michael Reth[6,7], Thomas Höfer[2] & Hans-Reimer Rodewald[1]



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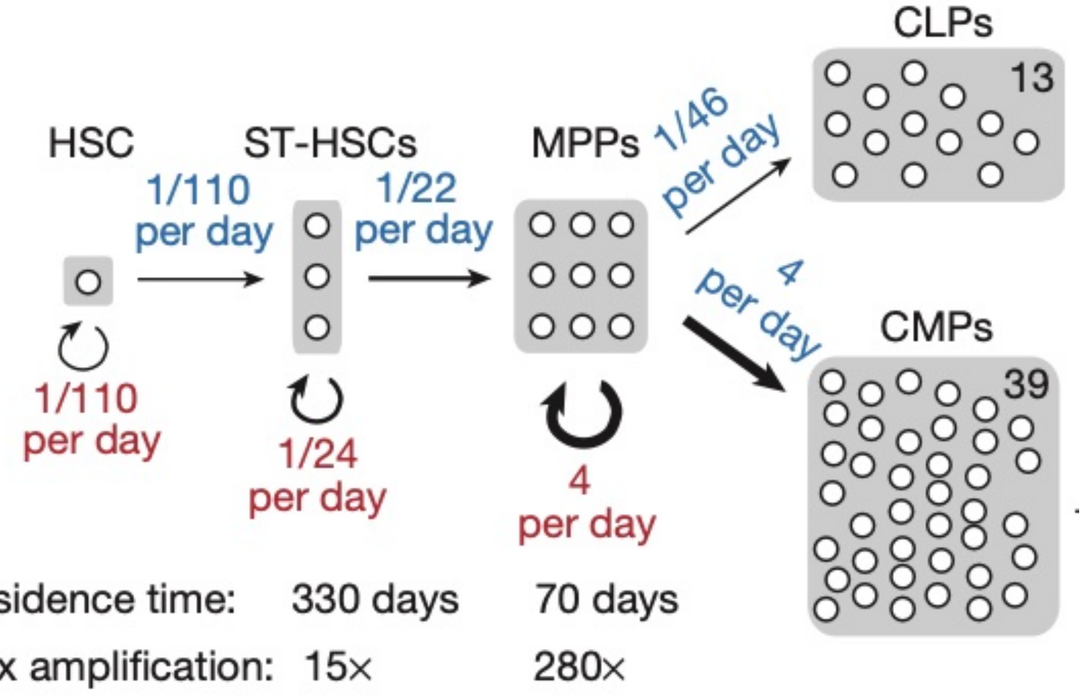

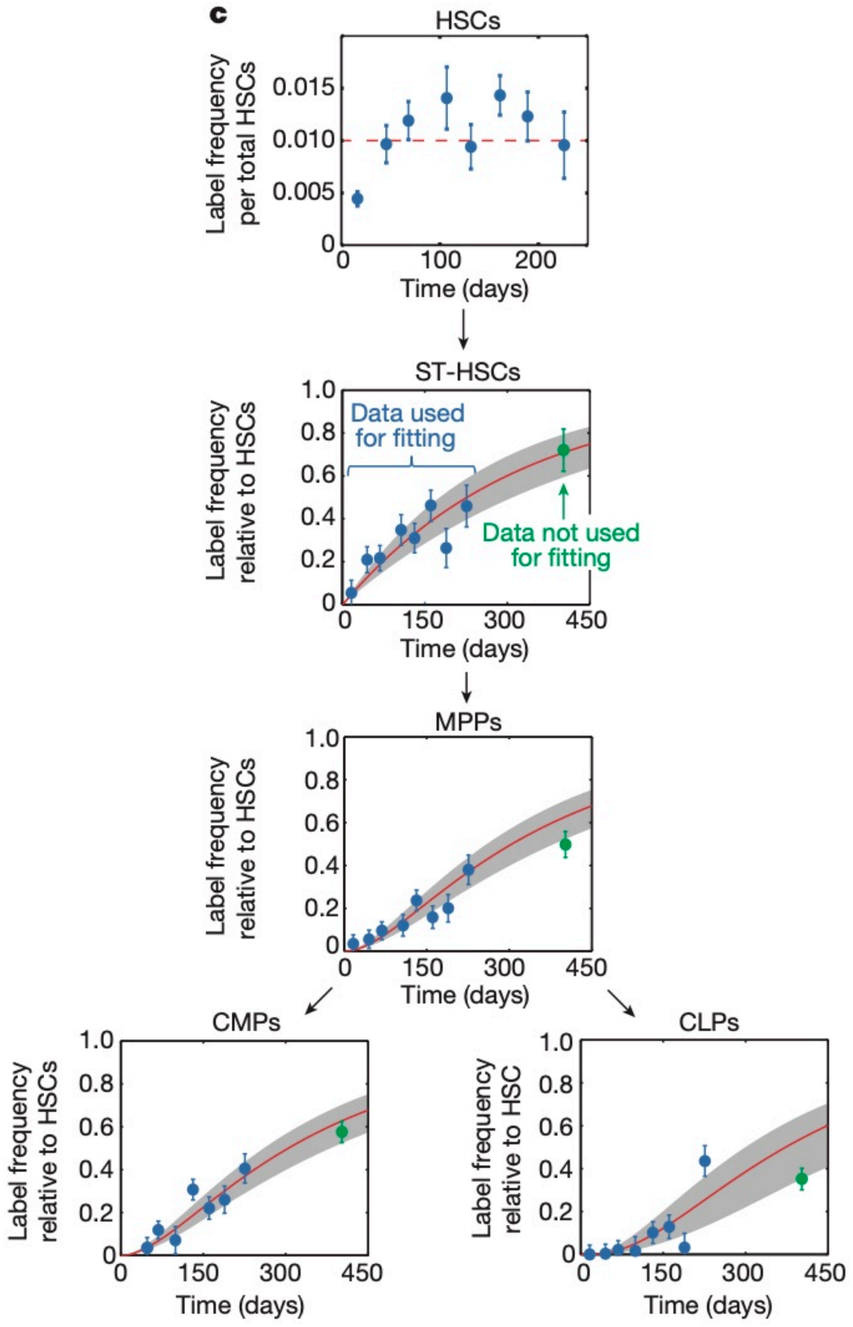

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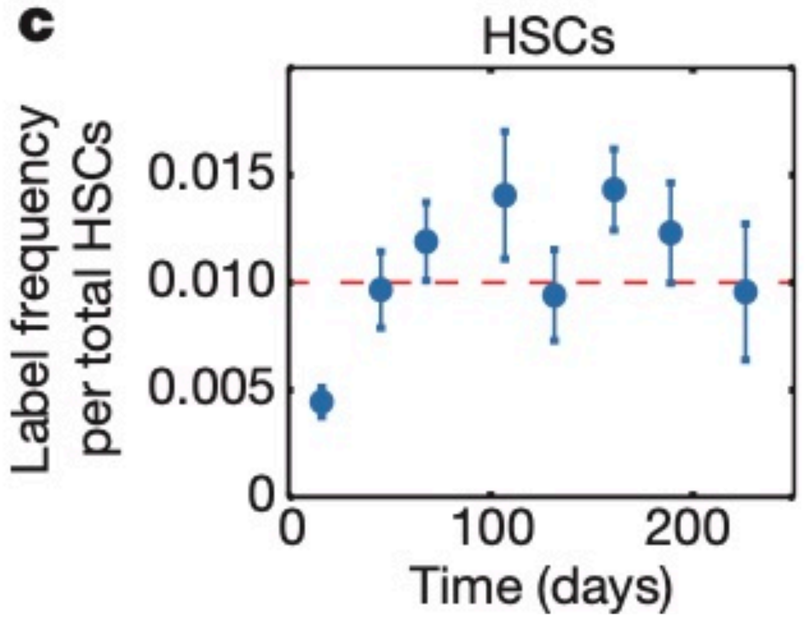
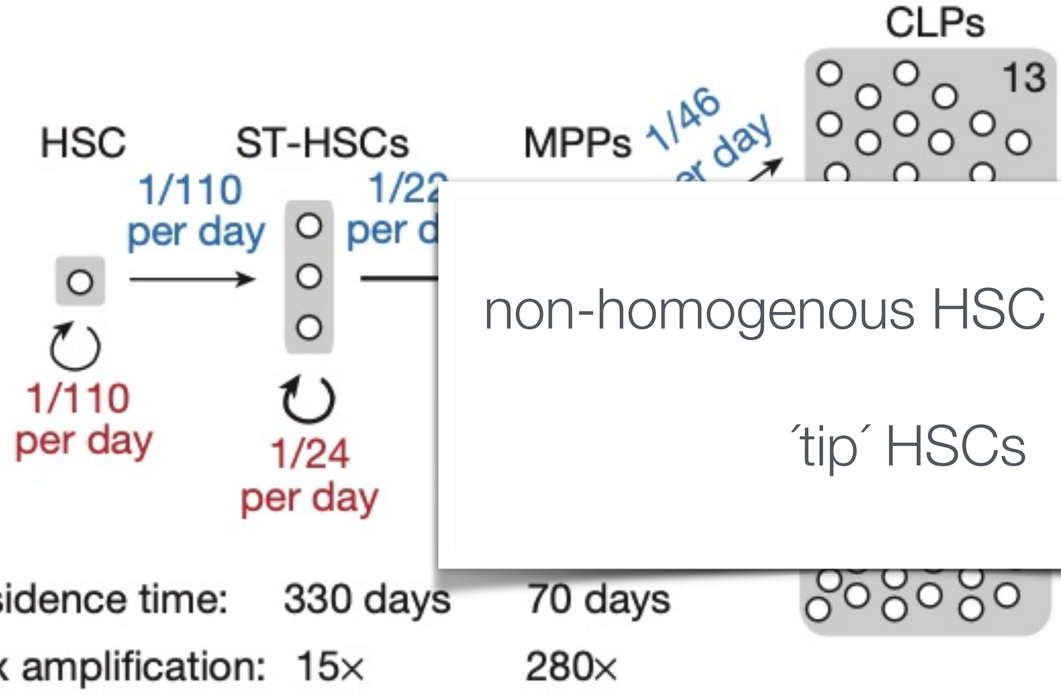
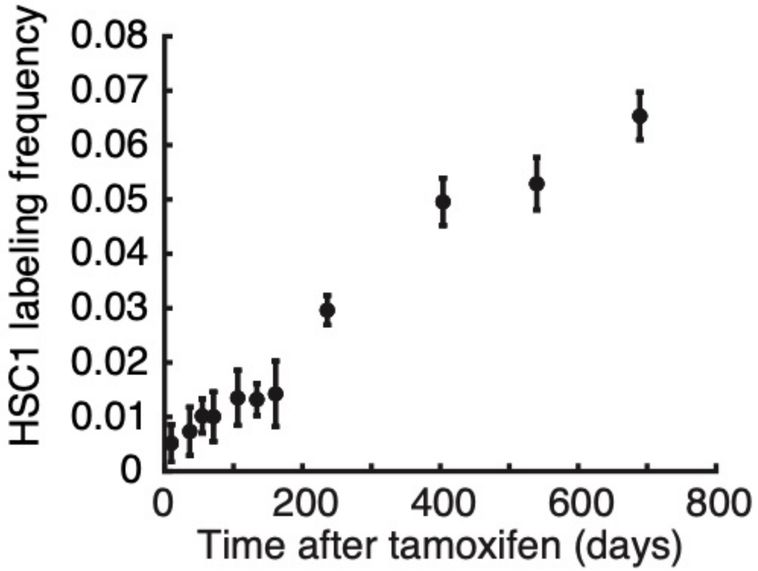




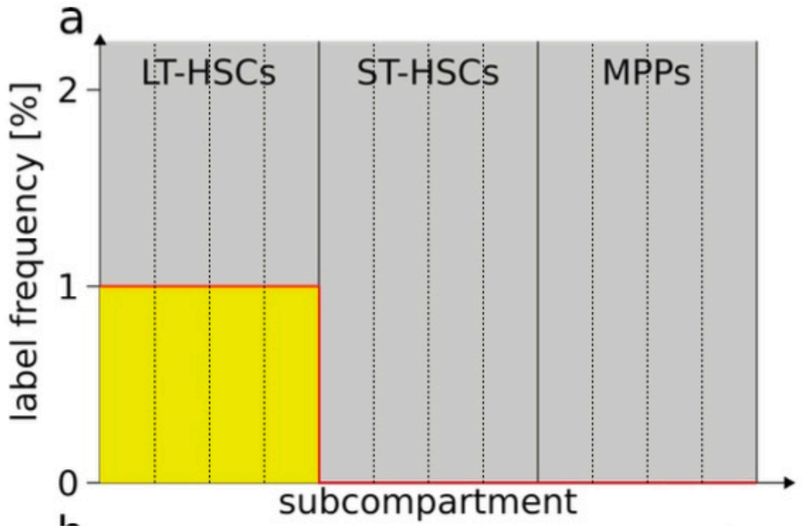
non-homogenous HSC population:

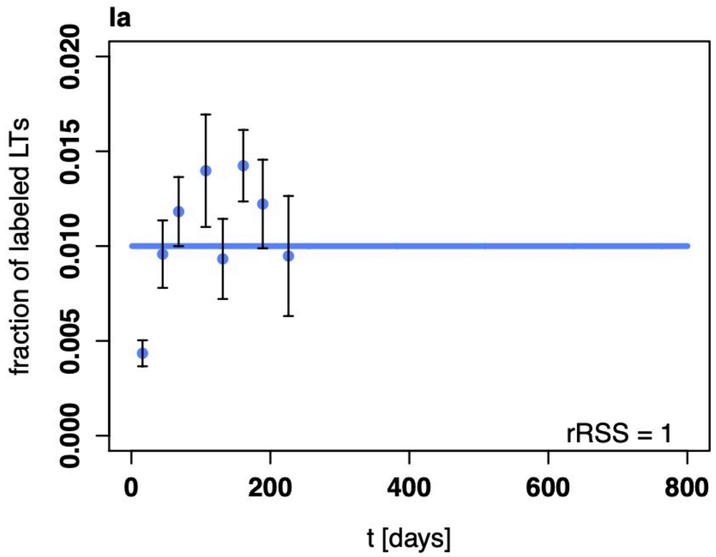
´tip´ HSCs

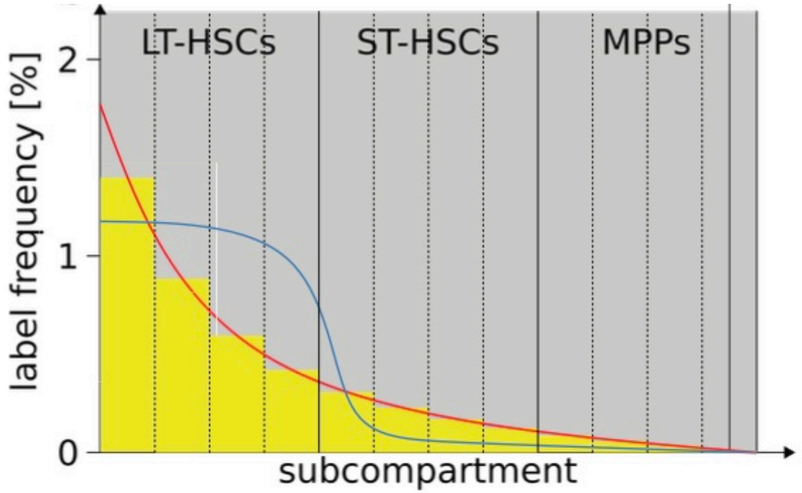


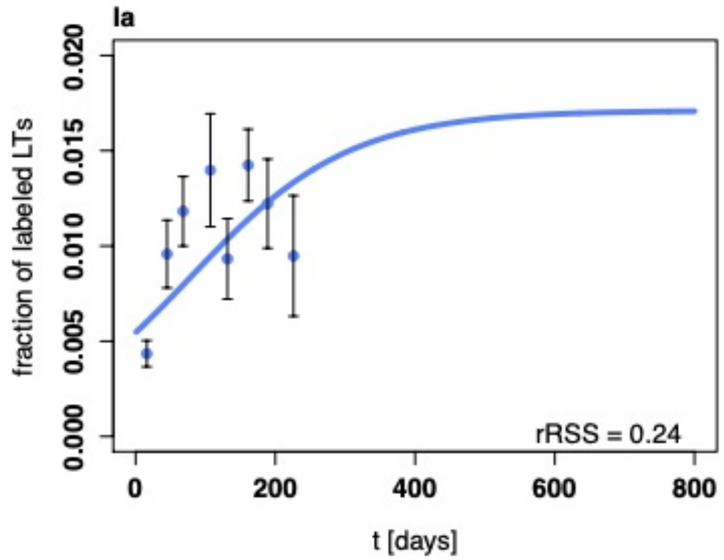
Barile et al., bioRxiv, 2020

HSC heterogeneity









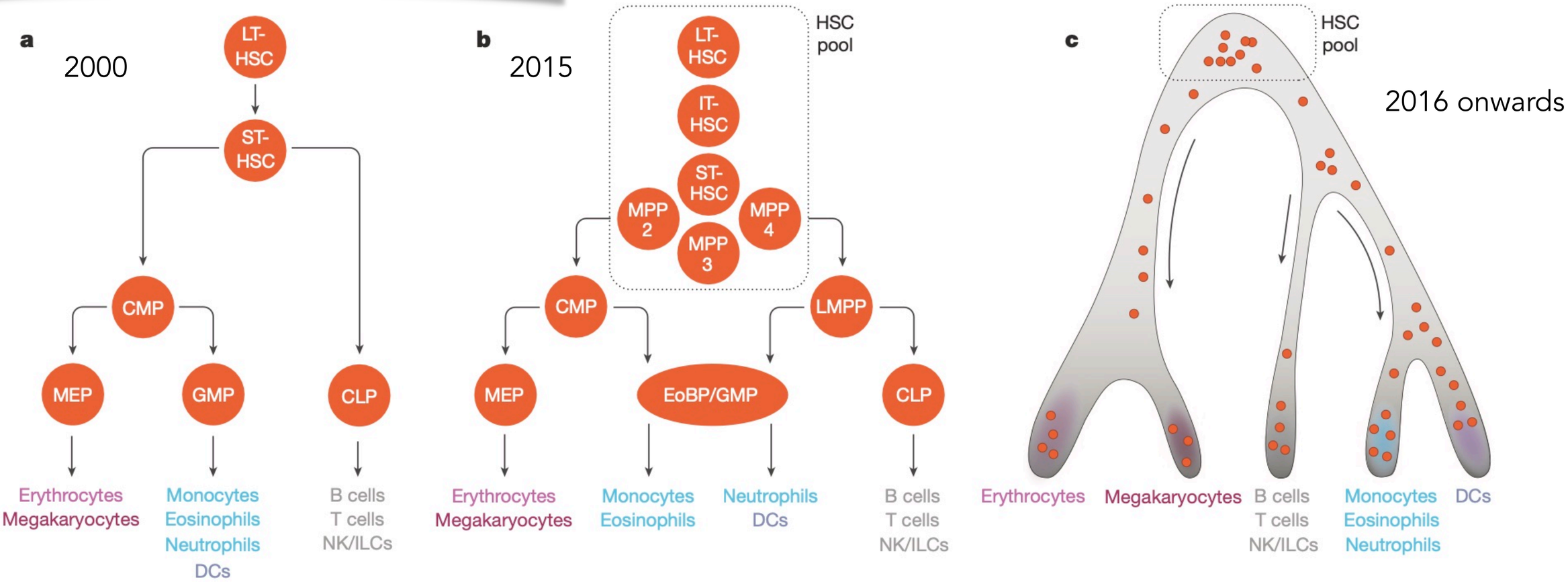
HSC heterogeneity

REVIEW

doi:10.1038/nature25022

From haematopoietic stem cells to complex differentiation landscapes

Elisa Laurenti[1] & Berthold Göttgens[1]

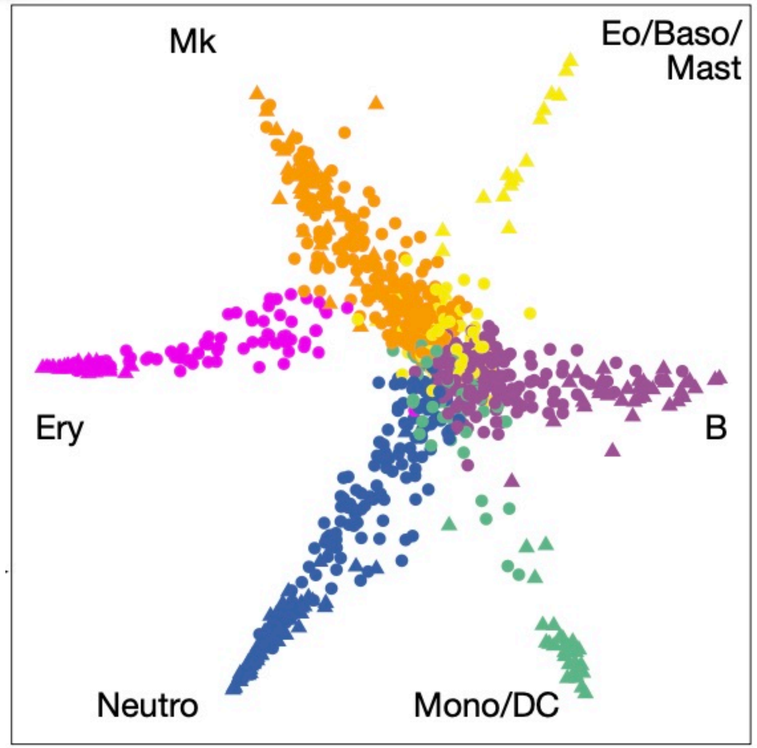


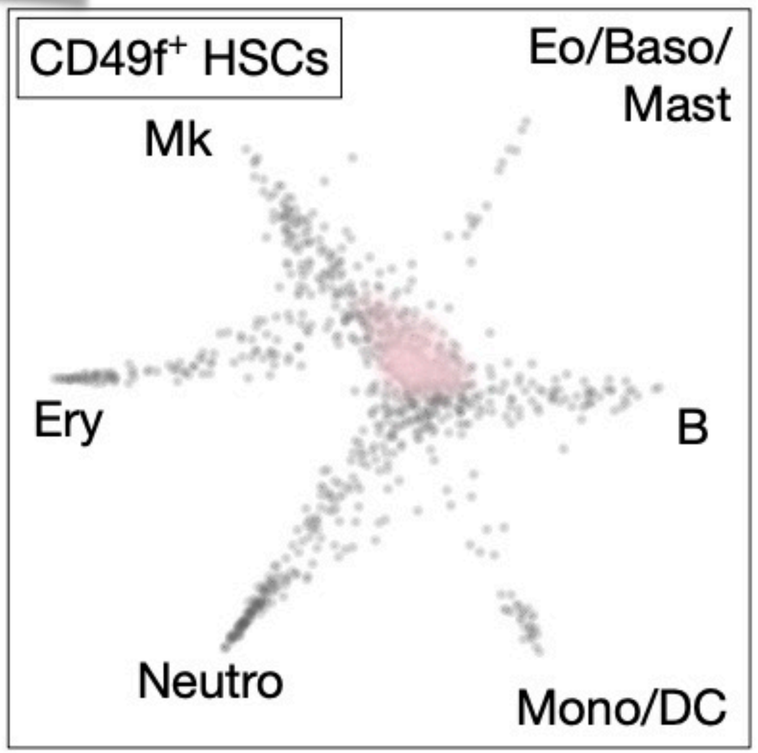
HSC heterogeneity

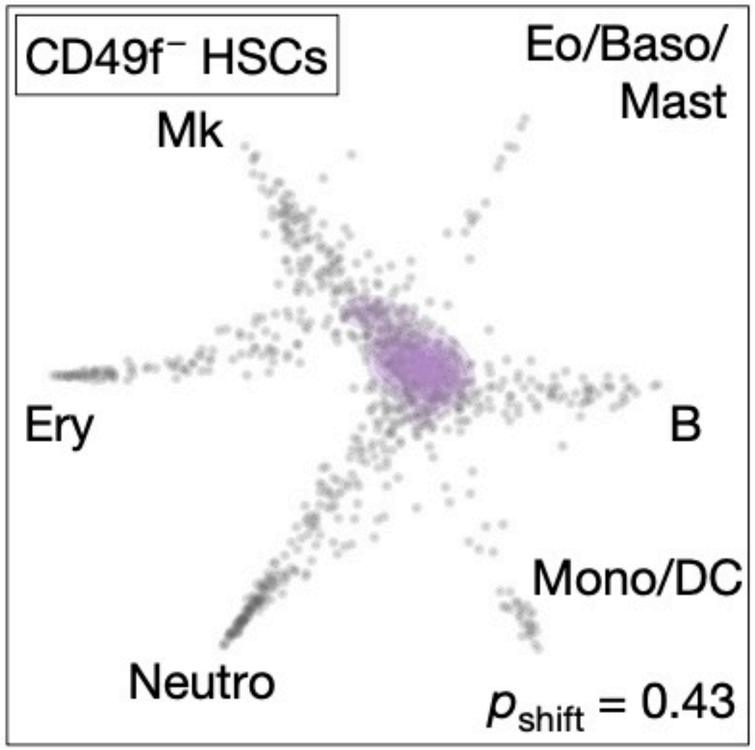
nature
cell biology

Human haematopoietic stem cell lineage commitment is a continuous process

Lars Velten[1,10], Simon F. Haas[2,3,4,10], Simon Raffel[2,4,5,10], Sandra Blaszkiewicz[2,3], Saiful Islam[6], Bianca P. Hennig[1], Christoph Hirche[2,3], Christoph Lutz[5], Eike C. Buss[5], Daniel Nowak[7], Tobias Boch[7], Wolf-Karsten Hofmann[7], Anthony D. Ho[5], Wolfgang Huber[1], Andreas Trumpp[2,4,8,11,12], Marieke A. G. Essers[2,3,11,12] and Lars M. Steinmetz[1,6,9,11,12]







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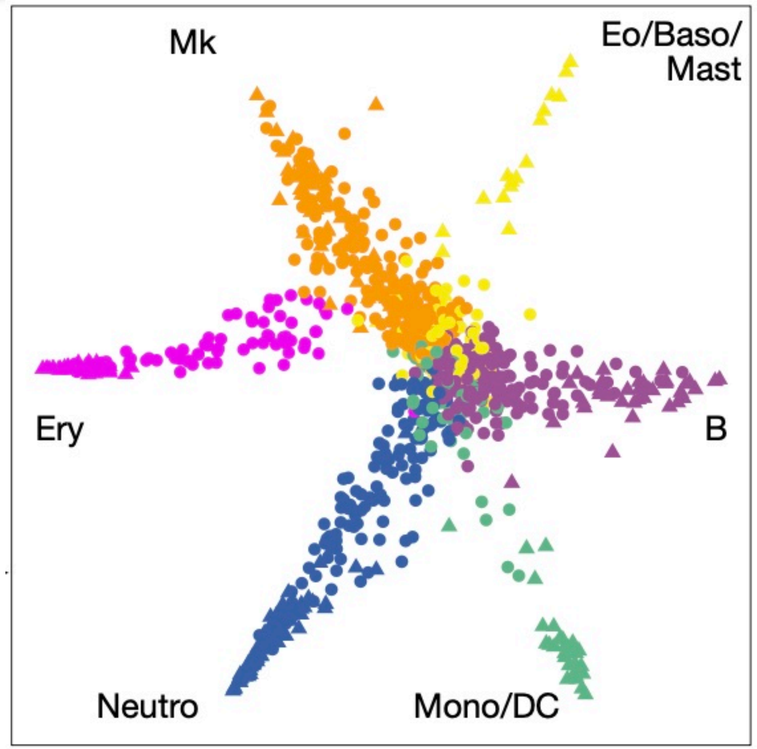

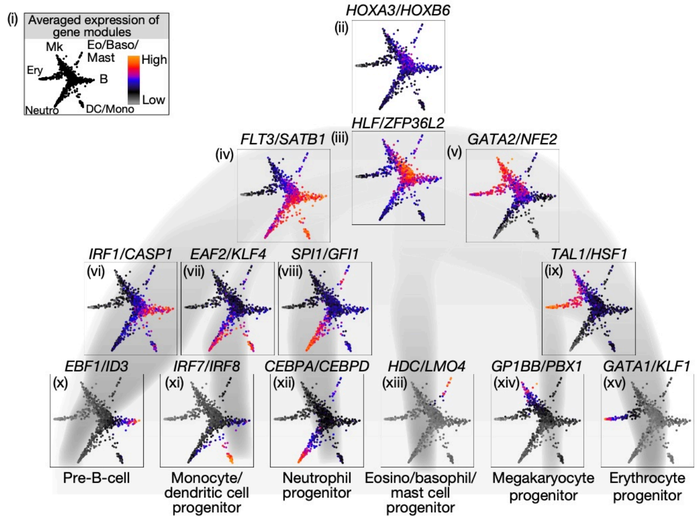

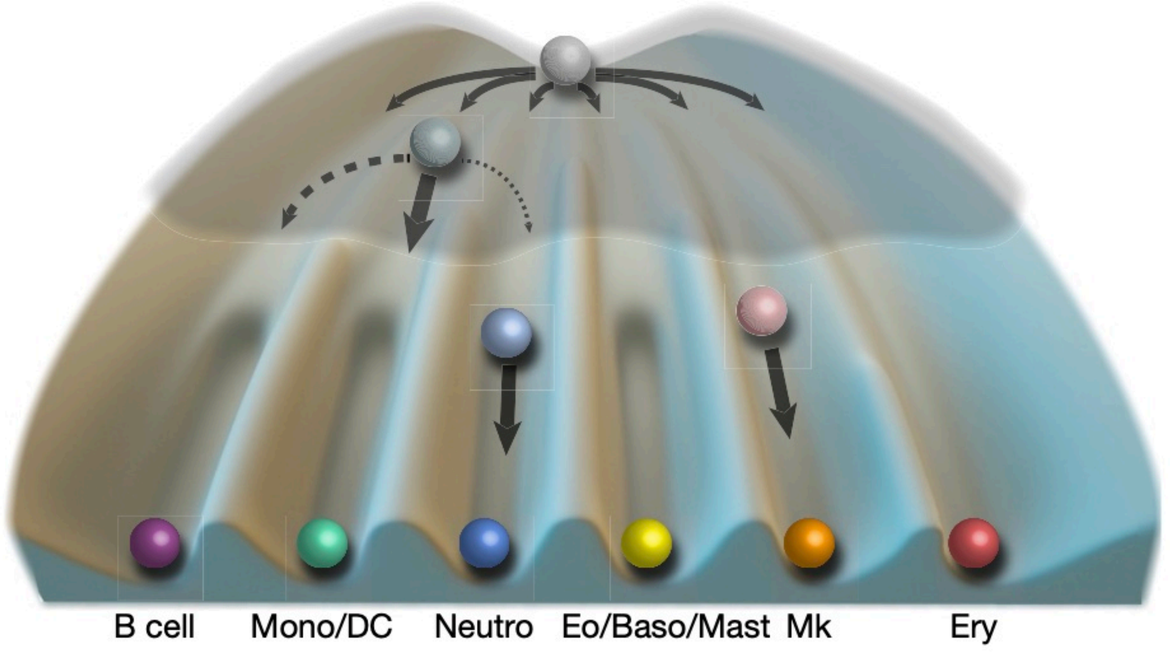

Dresden University of Technology

Summary

It is an open conceptual and formal question **whether quiescence and activation in HSCs are truly two distinct and discrete states, or whether they are better understood as two extremes along a continuous spectrum of functional activity**. The continuous concept can incorporate further aspects of functional and phenotypic heterogeneity and confers a dynamic perspective on stem cells.

HSC heterogeneity is a feature not a mistake.