the evolutionary dynamics of hematopoiesis
(in health & disease)

Jorge M. Pacheco
atpgroup

http://dl.dropbox.com/u/6053055/SP2016-1-of-5.pdf

ICTP SAIFR International Centre for Theoretical Physics South American Institute for Fundamental Research
unesp UNIVERSIDADE ESTADUAL PAULISTA "JÚLIO DE MESQUITA FILHO"

layout

mon – 12:00 – 13:15 : quantifying HSC in adult mammals

tues – 11:15 – 12:30 : ontogenic growth & HSC in humans

wed – 11:15 – 12:30 : from HSC to circulating blood :

the *standard model* of hematopoiesis (SM)

thu – 11:15 – 12:30 : disease in hematopoiesis

fri – 11:15 – 12:30 : extensions & challenges of the SM

layout

monday – 12:00 – 13:15

- hematopoiesis : facts & fiction
- quantifying hematopoiesis : many questions, few answers
- hematopoietic stem cells (HSC)
- quantifying HSC in adult mammals : allometry & HSC scaling

why quantifying hematopoiesis

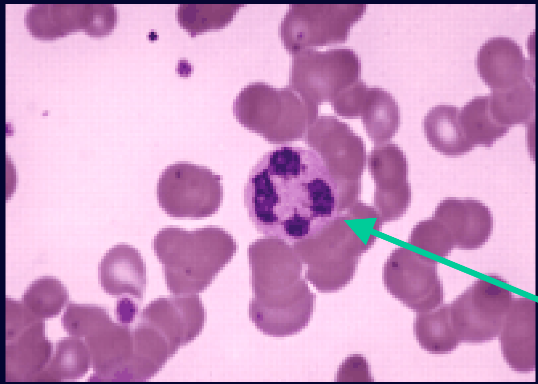
landmarks in hematology

oldest discipline in Medicine

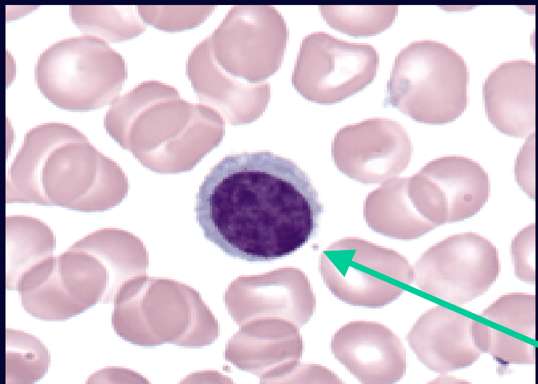
1628	concept of circulation was 1st introduced
1662	1st IV injection in humans
1667	1st blood transfusion (lamb → human)
1770	W. Heuson identifies leucocytes (father of Hemtology)
1818	1st blood transfusion (human → human)
1901	blood groups are identified
1908	stem-cell concept was first conceived
1936	1st blood bank in the USA
1962	1st factor to treat coagulation disorders in hemophilic
1963	blood cell self-renewal is first identified in mice
1968	1st bone-marrow transplantation
1971	war on cancer was declared
1972	stem-cell concept is first established in human blood
2010 …	are we winning the war on cancer ?

diversity in hematopoiesis

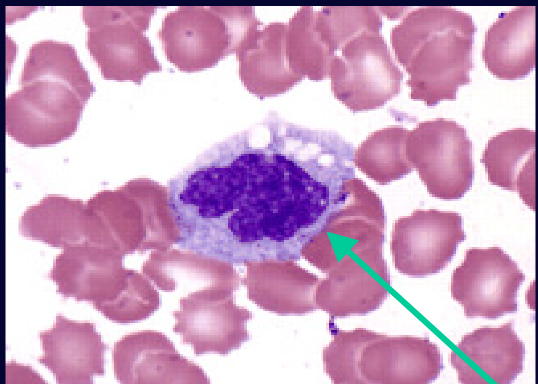
(formation & development of different types of blood cells)



neutrophils



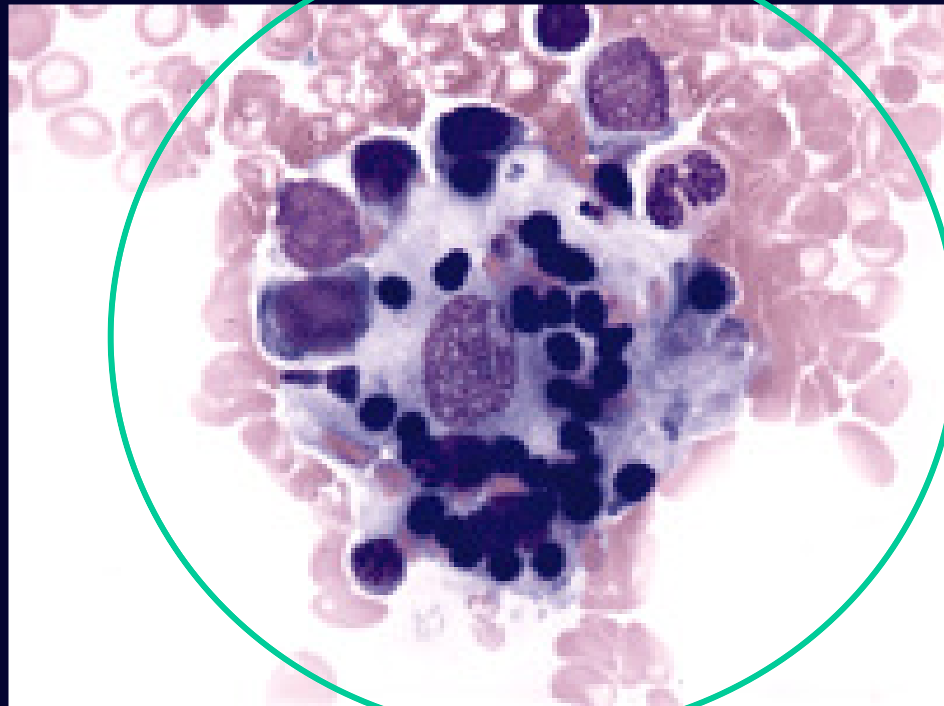
lymphocytes



monocytes

(*leucocytes*)

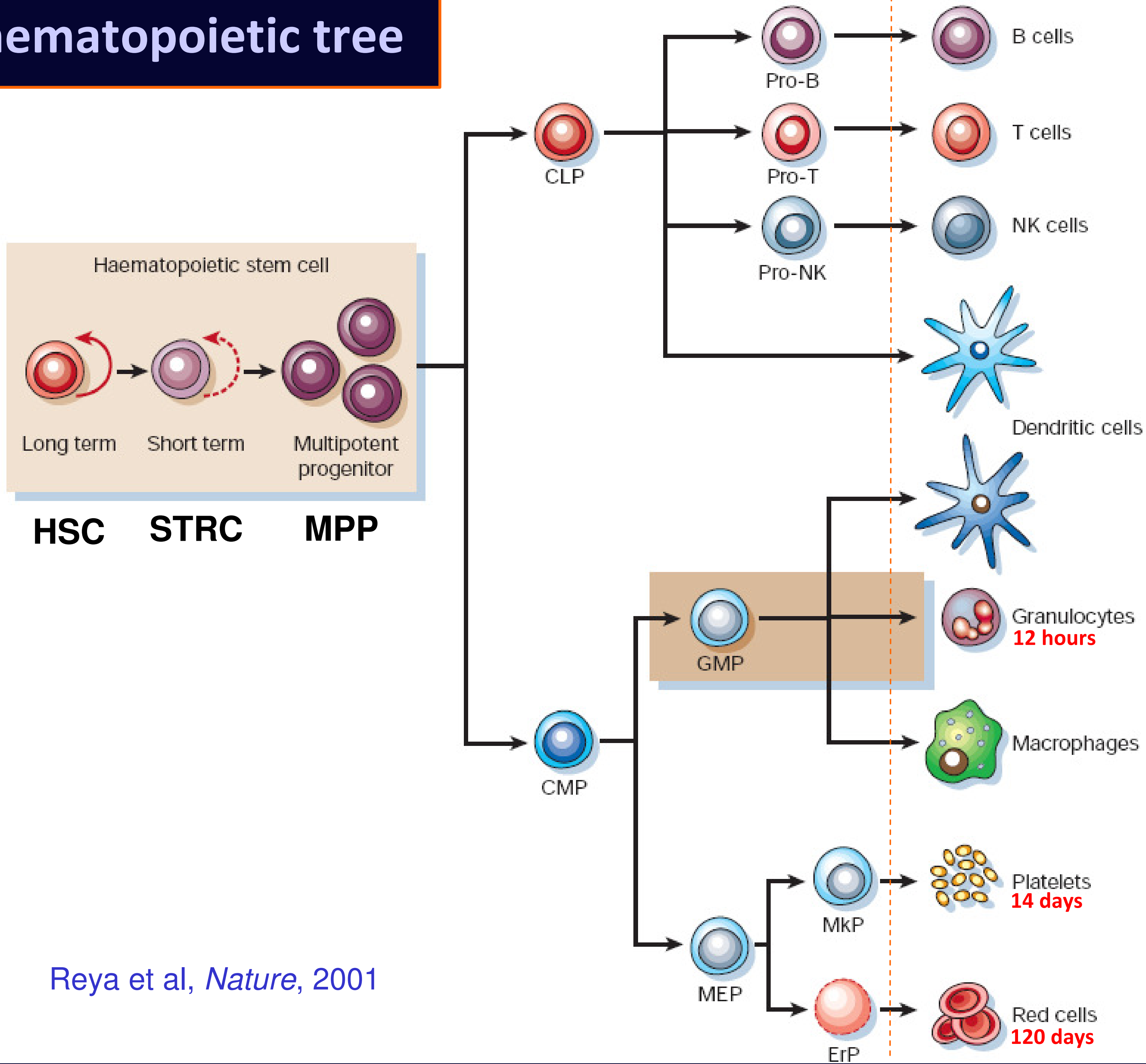
bone marrow



red blood cell formation

one single origin:
hematopoietic stem cells

the hematopoietic tree

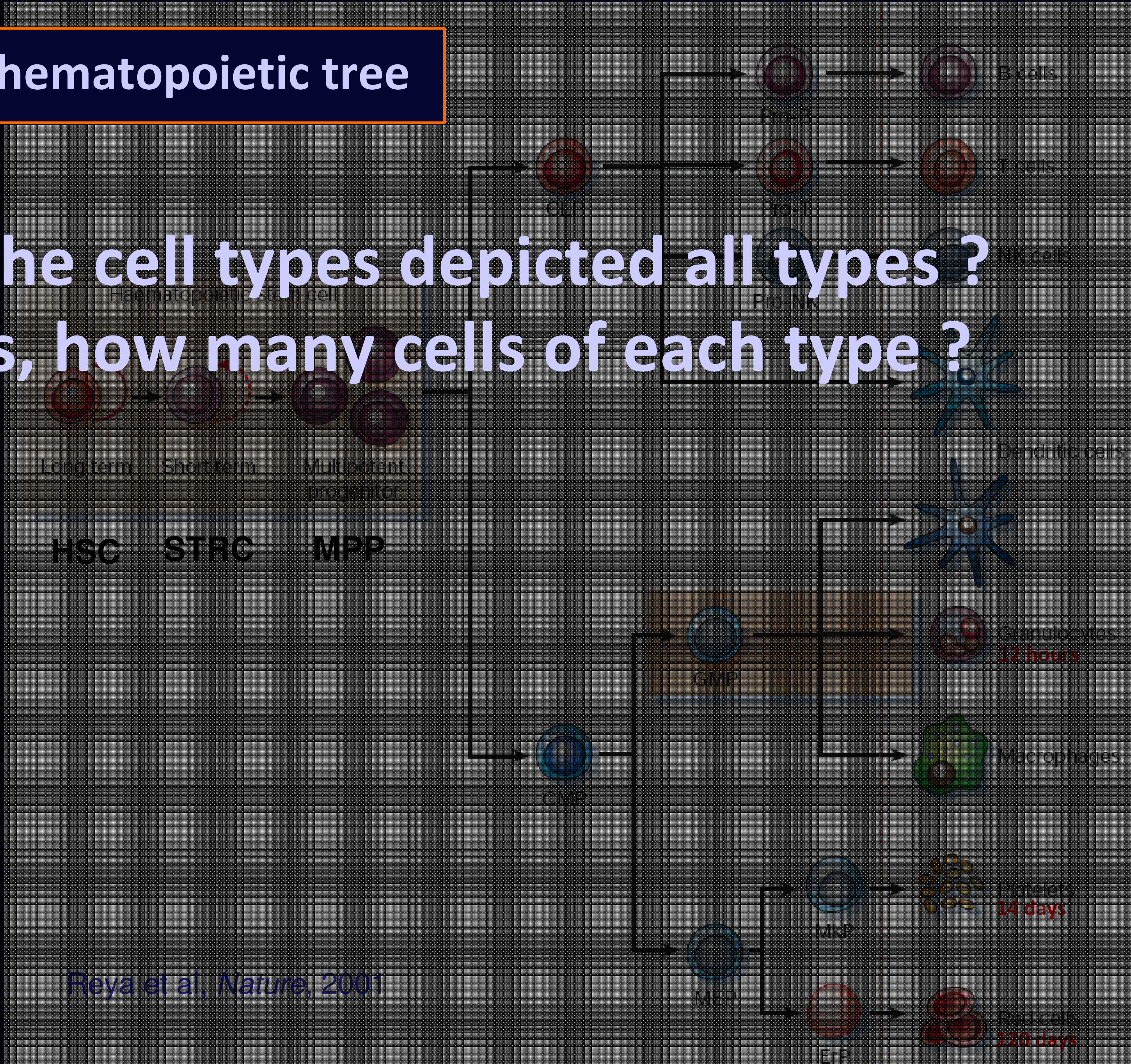


Reya et al, *Nature*, 2001

the hematopoietic tree

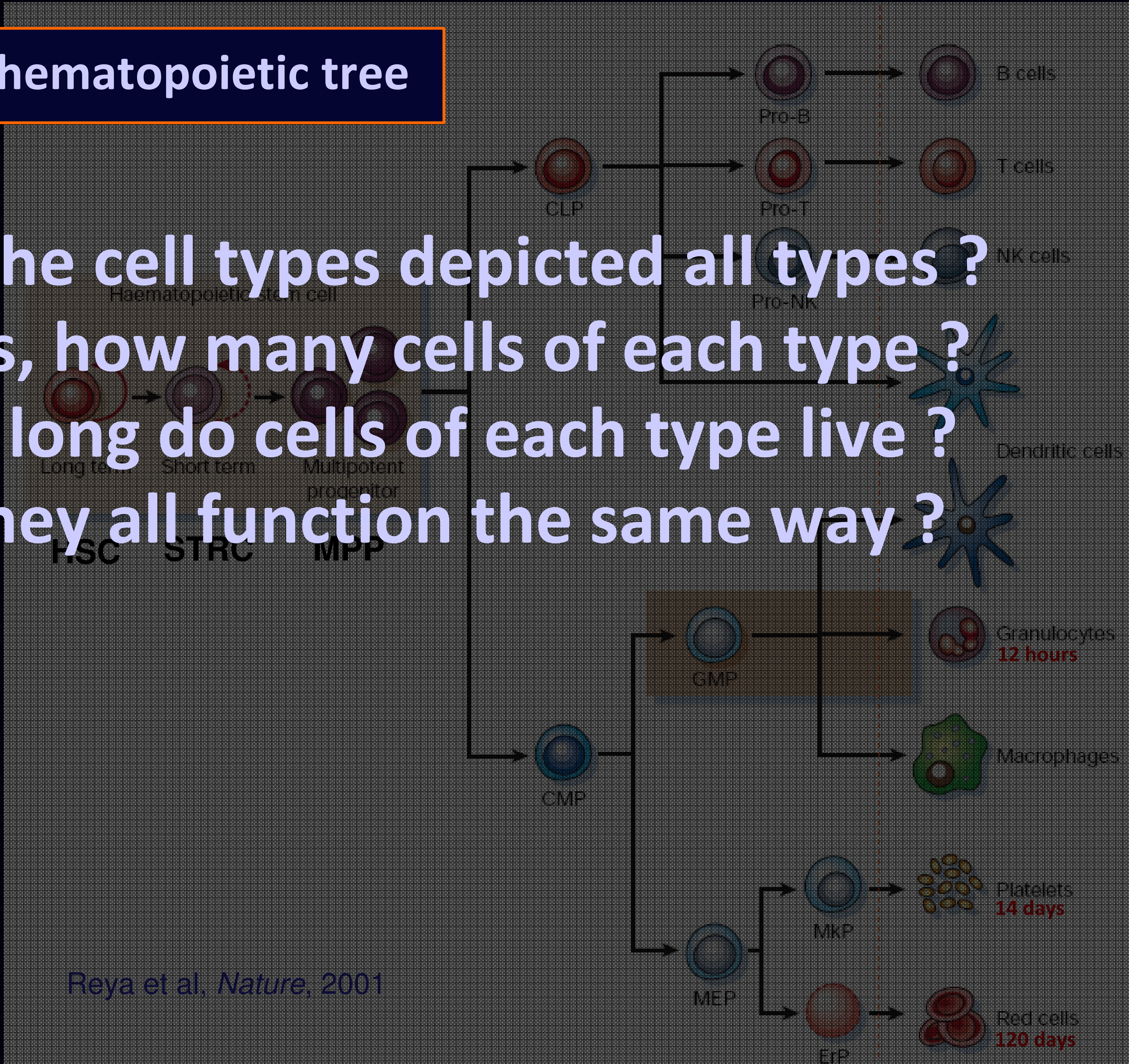
are the cell types depicted all types ?

if yes, how many cells of each type ?



Reya et al, *Nature*, 2001

the hematopoietic tree



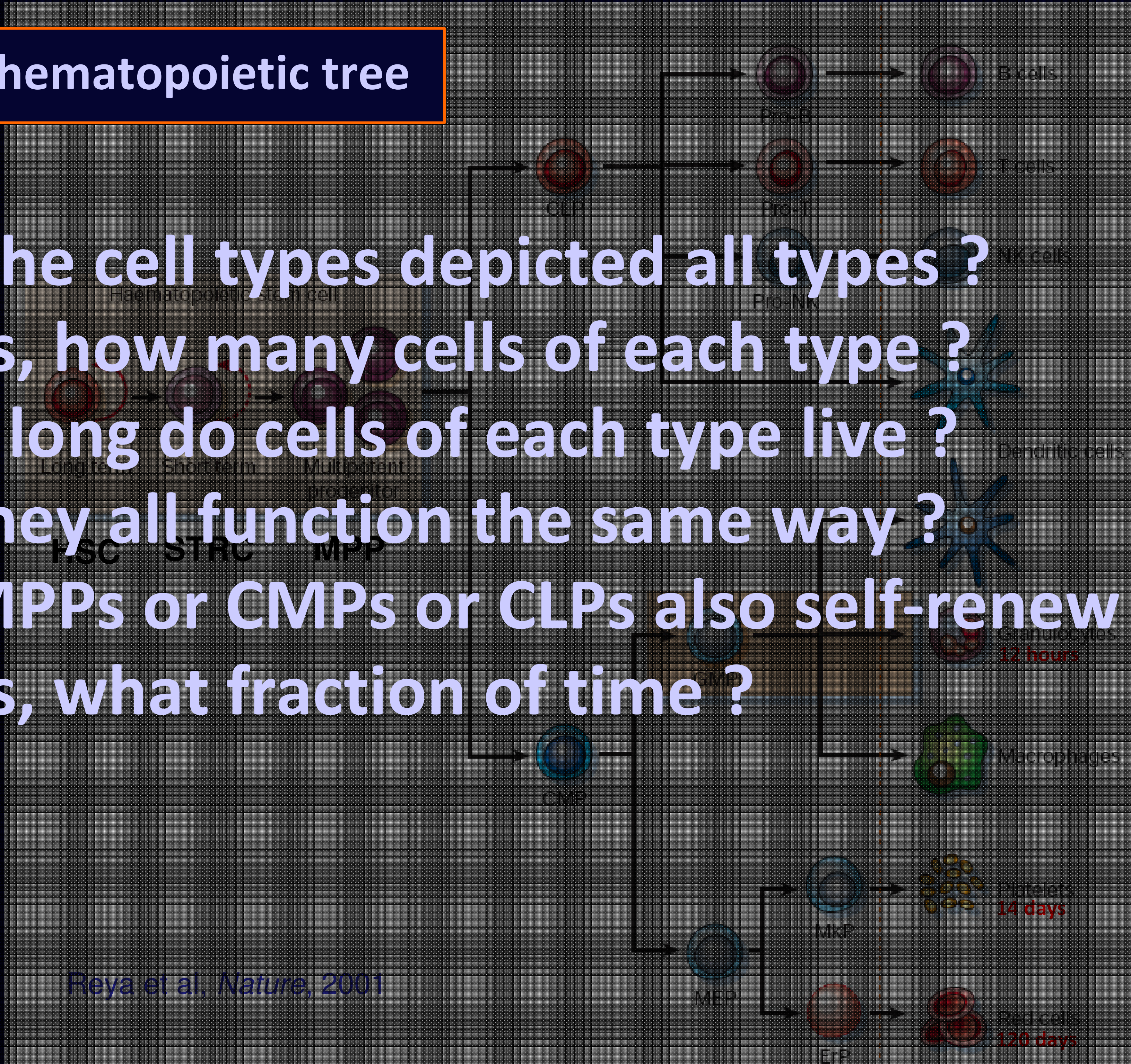
are the cell types depicted all types ?

if yes, how many cells of each type ?

how long do cells of each type live ?

do they all function the same way ?

the hematopoietic tree



are the cell types depicted all types ?

if yes, how many cells of each type ?

how long do cells of each type live ?

do they all function the same way ?

do MPPs or CMPs or CLPs also self-renew ?

if yes, what fraction of time ?

Reya et al, *Nature*, 2001

the hematopoietic tree

are the cell types depicted all types ?

if yes, how many cells of each type ?

how long do cells of each type live ?

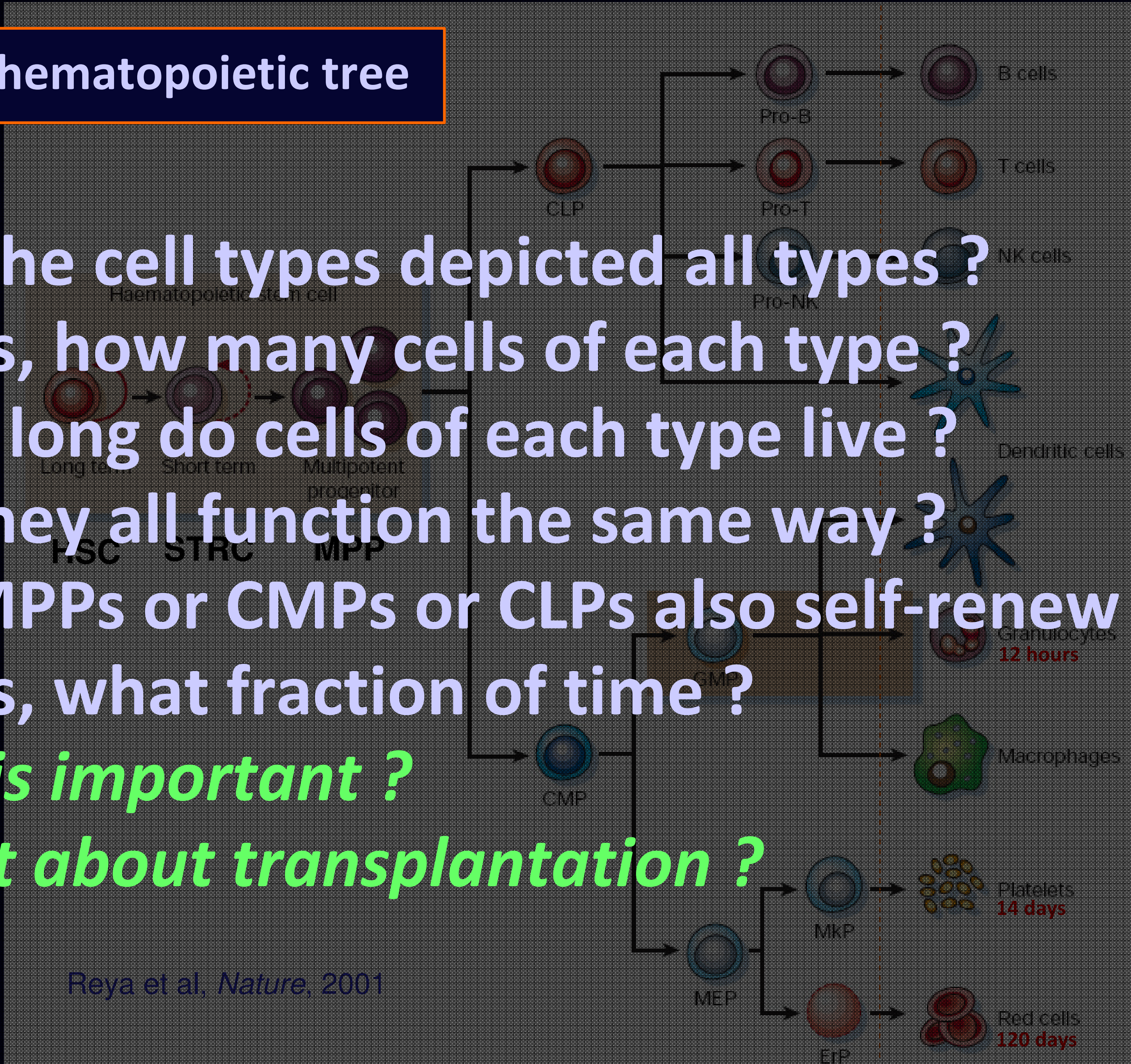
do they all function the same way ?

do MPPs or CMPs or CLPs also self-renew ?

if yes, what fraction of time ?

is this important ?

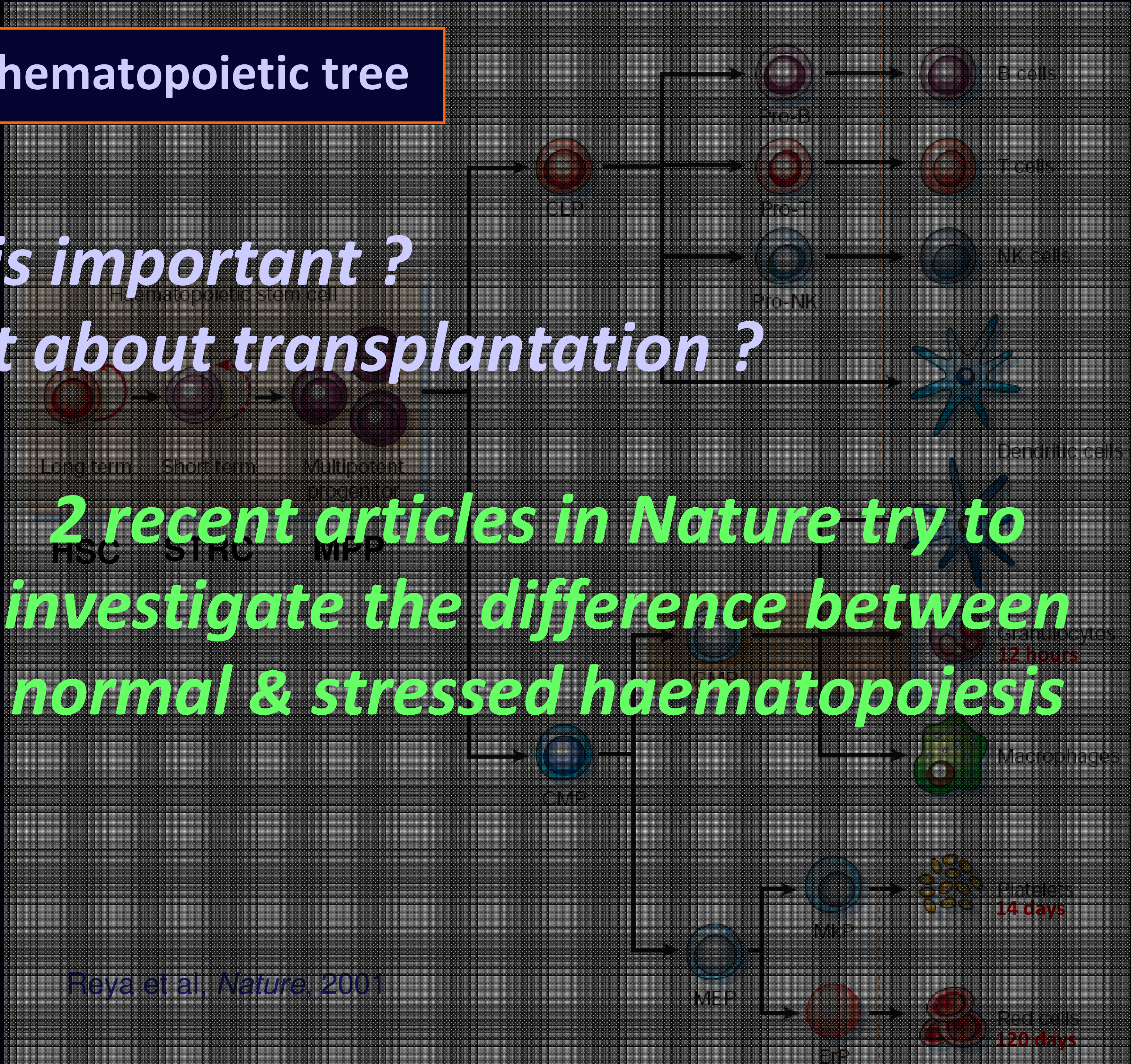
what about transplantation ?



the hematopoietic tree

is this important ?
what about transplantation ?

2 recent articles in Nature try to investigate the difference between normal & stressed haematopoiesis

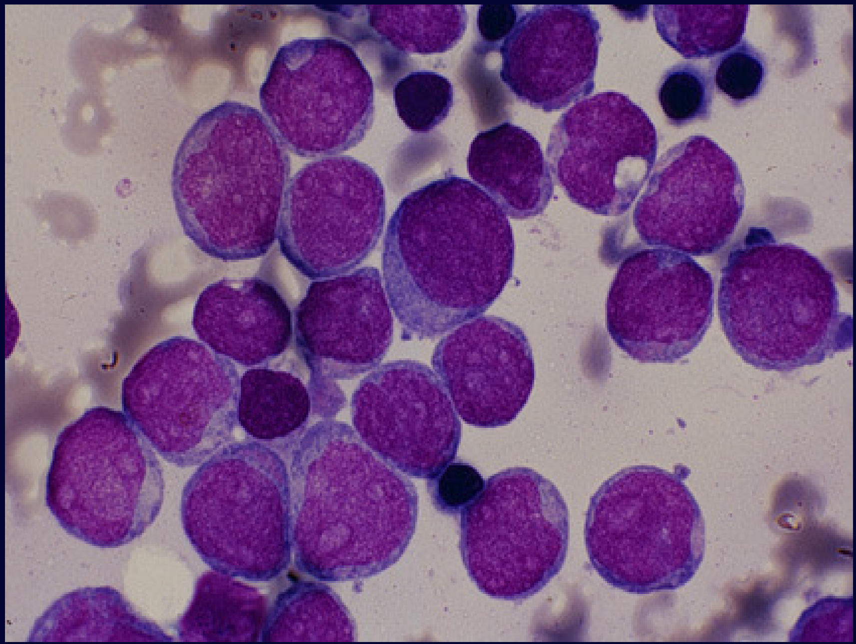


Reya et al, *Nature*, 2001

bone marrow “normal”

diversity

bone marrow “neoplasic”



uniformity

(blasts)

Cyclic Neutropenia (CN)

features

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation 42 (2009) 330-338
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

- **rare congenital disorder in hematopoiesis**
- → **oscillations of neutrophil count**
- **it happens in humans ; it happens in dogs**

Cyclic Neutropenia (CN)

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation 42 (2009) 330-338
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

features

- rare congenital disorder in hematopoiesis
- → oscillations of neutrophil count
- it happens in humans ; it happens in dogs
- is it the same disease ? is the biology the same ?

Cyclic Neutropenia (CN)

features

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation 42 (2009) 330-338
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

- rare congenital disorder in hematopoiesis
- → oscillations of neutrophil count
- it happens in humans ; it happens in dogs
- is it the same disease ? is the biology the same ?
- how do we know ? where do we look ? which cell type(s) ?

Cyclic Neutropenia (CN)

features

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation 42 (2009) 330-338
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

- rare congenital disorder in hematopoiesis
- → oscillations of neutrophil count
- it happens in humans ; it happens in dogs
- is it the same disease ? is the biology the same ?
- how do we know ? where do we look ? which cell type(s) ?
- does it happen in mice ? (experimentally: *no . . .*)

Cyclic Neutropenia (CN)

features

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation 42 (2009) 330-338
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

- rare congenital disorder in hematopoiesis
- → oscillations of neutrophil count
- it happens in humans ; it happens in dogs
- is it the same disease ? is the biology the same ?
- how do we know ? where do we look ? which cell type(s) ?
- does it happen in mice ? (experimentally: *no . . .*)
- is the mouse a good model for Humans ?

Cyclic Neutropenia (CN)

features

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation 42 (2009) 330-338
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

- rare congenital disorder in hematopoiesis
- → oscillations of neutrophil count
- it happens in humans ; it happens in dogs
- is it the same disease ? is the biology the same ?
- how do we know ? where do we look ? which cell type(s) ?
- does it happen in mice ? (experimentally: *no . . .*)
- is the mouse a good model for Humans ?
- if not, have we been wasting our time ?

Cyclic Neutropenia (CN)

features

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation 42 (2009) 330-338
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

- rare congenital disorder in hematopoiesis
- → oscillations of neutrophil count
- it happens in humans ; it happens in dogs
- is it the same disease ? is the biology the same ?
- how do we know ? where do we look ? which cell type(s) ?
- does it happen in mice ? (experimentally: *no . . .*)
- is the mouse a good model for Humans ?
- if not, have we been wasting our time ?
- *and* money ? a mouse LAB costs 20 M€ to setup . . .

Paroxysmal Nocturnal Hemoglobinuria (PNH)

what is known :

- rare disease & a true stem-cell disorder since it originates in the PIG-A gene of a HSC
- rate of PIG-A gene mutation is normal
- often BMF is later observed

Paroxysmal Nocturnal Hemoglobinuria (PNH)

what is known :

- rare disease & a true stem-cell disorder since it originates in the PIG-A gene of a HSC
- rate of PIG-A gene mutation is normal
- often BMF is later observed

present explanations regarding disease development :

- a 2nd mutation leads to a fitness advantage of PNH cells → disease expansion
- *relative fitness advantage* of PNH cells due to an imunne attack to normal HSC → disease expansion

Paroxysmal Nocturnal Hemoglobinuria (PNH)

what is known :

- rare disease & a true stem-cell disorder since it originates in the PIG-A gene of a HSC
- rate of PIG-A gene mutation is normal
- often BMF is later observed

present explanations regarding disease development :

- a 2nd mutation leads to a fitness advantage of PNH cells → disease expansion
- *relative fitness advantage* of PNH cells due to an imunne attack to normal HSC → disease expansion

does this make any sense at all ? how do we know ? where do we look ?

Chronic Myeloid Leukemia (CML)

what is known :

- Hematopoietic stem cell disorder
- Initial event: Philadelphia chromosome
- ? HSC are enough to drive chronic phase ?
- clonal expansion and myeloproliferation
- stem cell derived but progenitor cell driven
- *abl*-kinase inhibitors very effective

Chronic Myeloid Leukemia (CML)

what is known :

- Hematopoietic stem cell disorder
- Initial event: Philadelphia chromosome
- ? HSC are enough to drive chronic phase ?
- clonal expansion and myeloproliferation
- stem cell derived but progenitor cell driven
- *abl*-kinase inhibitors very effective

how long does it take to develop ?

Chronic Myeloid Leukemia (CML)

what is known :

- **Hematopoietic stem cell disorder**
- **Initial event: Philadelphia chromosome**
- **? HSC are enough to drive chronic phase ?**
- **clonal expansion and myeloproliferation**
- **stem cell derived but progenitor cell driven**
- ***abl*-kinase inhibitors very effective**

how long does it take to develop ?
how does it progress from HSC to the peripheral blood ?

Chronic Myeloid Leukemia (CML)

what is known :

- Hematopoietic stem cell disorder
- Initial event: Philadelphia chromosome
- ? HSC are enough to drive chronic phase ?
- clonal expansion and myeloproliferation
- stem cell derived but progenitor cell driven
- *abl*-kinase inhibitors very effective

how long does it take to develop ?
how does it progress from HSC to the peripheral blood ?
how & when to best treat it ?

Chronic Myeloid Leukemia (CML)

what is known :

- **Hematopoietic stem cell disorder**
- **Initial event: Philadelphia chromosome**
- **? HSC are enough to drive chronic phase ?**
- **clonal expansion and myeloproliferation**
- **stem cell derived but progenitor cell driven**
- ***abl*-kinase inhibitors very effective**

how long does it take to develop ?
how does it progress from HSC to the peripheral blood ?
how & when to best treat it ?
why are ABL-KINASE inhibitors effective ?

Chronic Myeloid Leukemia (CML)

what is known :

- **Hematopoietic stem cell disorder**
- **Initial event: Philadelphia chromosome**
- **? HSC are enough to drive chronic phase ?**
- **clonal expansion and myeloproliferation**
- **stem cell derived but progenitor cell driven**
- ***abl*-kinase inhibitors very effective**

how long does it take to develop ?
how does it progress from HSC to the peripheral blood ?
how & when to best treat it ?
why are ABL-KINASE inhibitors effective ?
how to fight resistance mutations ?

Chronic Myeloid Leukemia (CML)

what is known :

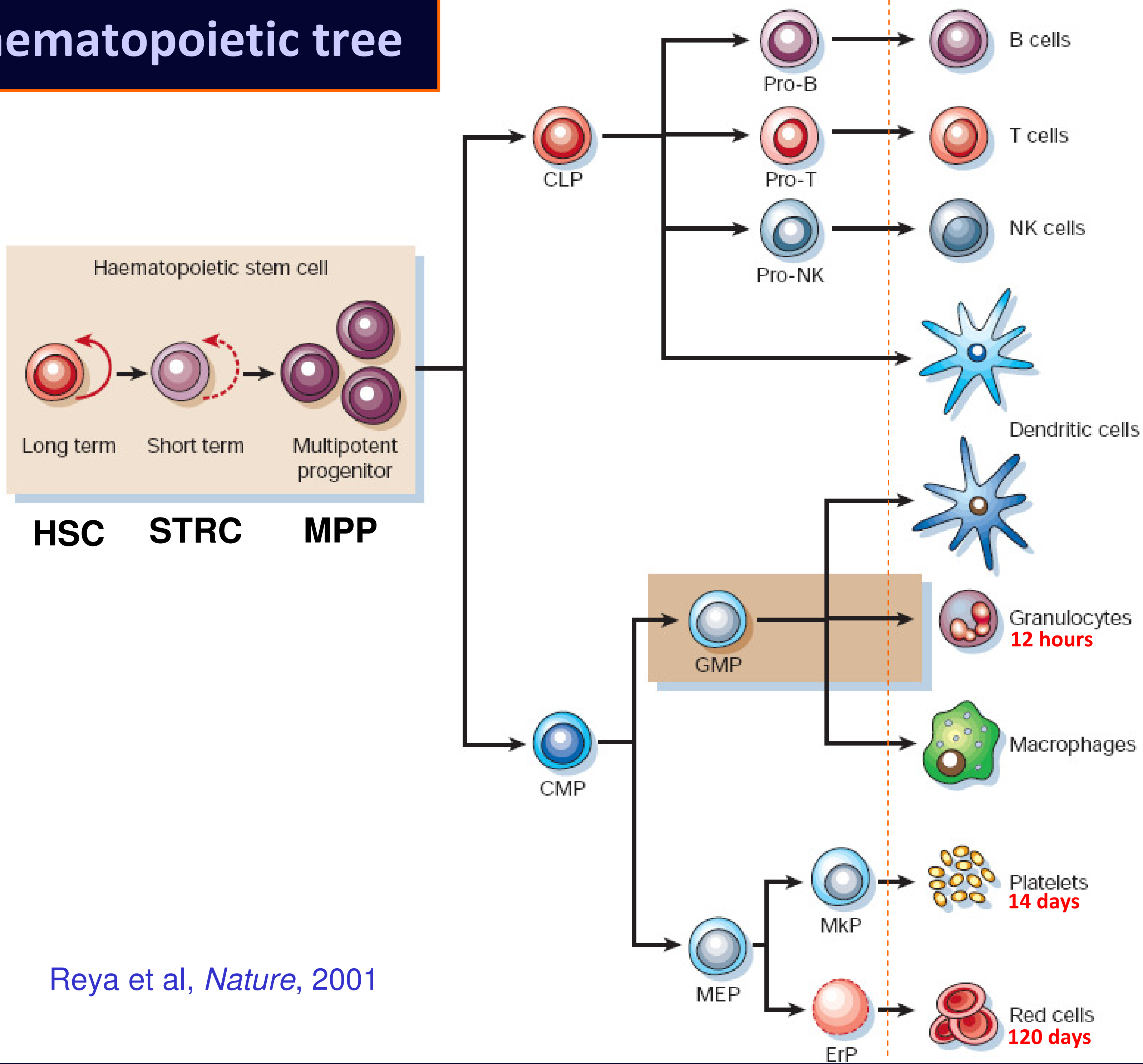
- Hematopoietic stem cell disorder
- Initial event: Philadelphia chromosome
- ? HSC are enough to drive chronic phase ?
- clonal expansion and myeloproliferation
- stem cell derived but progenitor cell driven
- *abl*-kinase inhibitors very effective

how long does it take to develop ?
how does it progress from HSC to the peripheral blood ?
how & when to best treat it ?
why are ABL-KINASE inhibitors effective ?
how to fight resistance mutations ?

no idea…

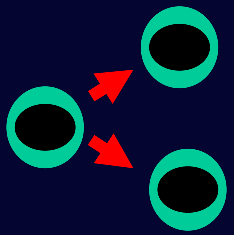
building a math model of hematopoiesis

the hematopoietic tree



Reya et al, *Nature*, 2001

hematopoietic stem cells (HSC)

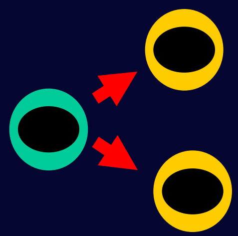


self-renewal **:**

for how long ?

(Hayflick hypothesis,

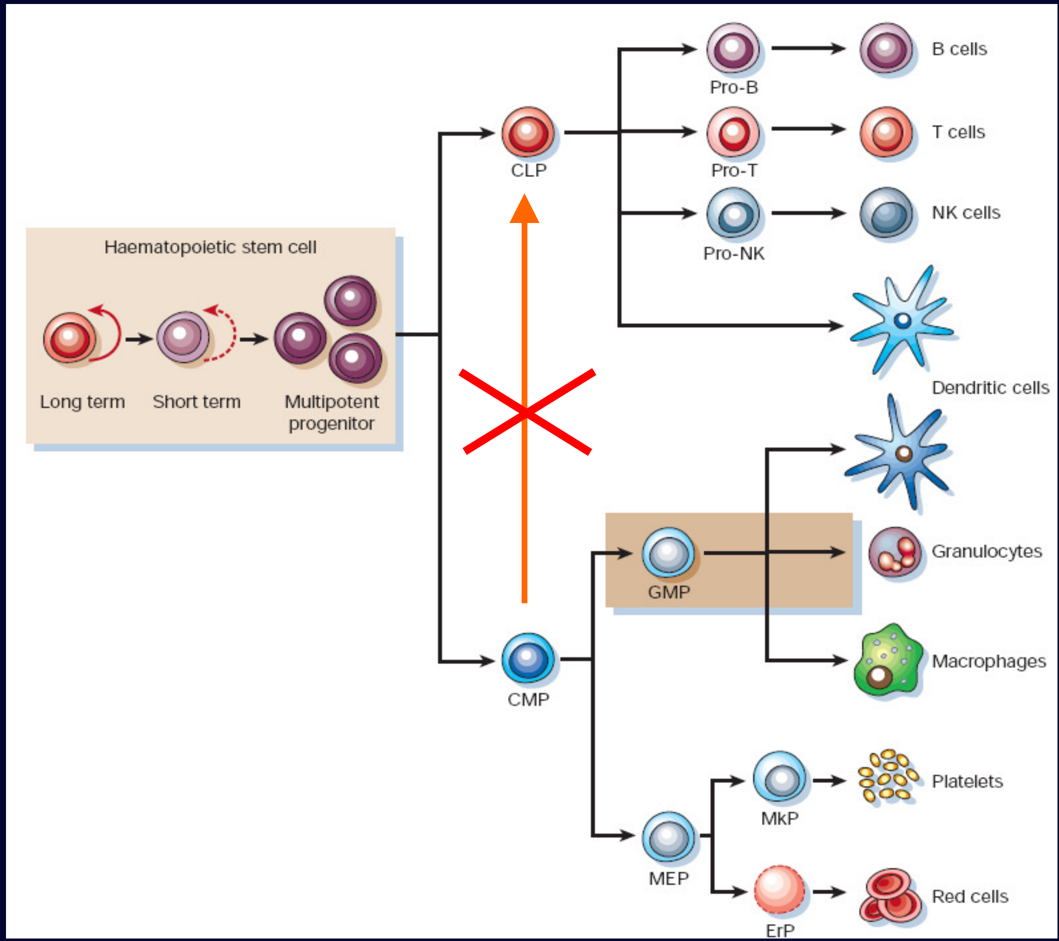
telomere shortening)



differentiation **:**

capacity to differentiate

into all other types of blood cells



stemness is a matter of degree – you have to stand at the root of the hematopoietic tree

characteristics of HSC

- ***never been directly observed*** **(their elusiveness reminds the *electron*)**
- ***existence & abundance inferred mostly from experiments of*** **reconstitution of bone marrow (via transplant) or by use of gene markers (*no marker which uniquely identifies HSC . . .*)**

characteristics of HSC

- *never been directly observed* (their elusiveness reminds the *electron*)
- *existence & abundance inferred mostly from experiments of* reconstitution of bone marrow (via transplant) or by use of gene markers (*no marker which uniquely identifies HSC . . .*)

transplant :

- *destruction of bone marrow (chemo-t…, radio-t…)*
- *infusion of marrow cells (including HSC) (from another mouse genetically identical)*
- *reconstitution of bone marrow (≈ 2 phase process)*
  - fast : induced by “progenitor” cells
  - slow : stabilization – HSC (≈1 year in humans . . .)

properties of HSC

- *slow rate of replication (~ once / year)*

- *contribute to hematopoiesis for long periods of time*
  (perhaps the entire lifespan of the animal ?)

- *statistical model of HSC data collected from different mammals led authors to propose that the total number of HSC is conserved in mamals.*

- *contribution to hematopoiesis occurs in "niches",* which set the "*right*" micro-environment

- *stochastic behaviour ? if stochastic, how and with which consequences ?*

problems of HSC

- *bone marrow failure*

hereditary (dyskeratosis congenita, Diamond-Blackfan anemia)

acquired (paroxysmal nocturnal hemoglobinuria, PNH)

- *Neoplasias*

myeloid (chronic myeloid leukemia, CML)

(therapy: tyrosine kinase inhibitors :

imatinib, dasatinib, nilotinib)

lymphoid

HSC: many questions, few (scattered) answers

- *how many HSC ?*
- *how long do they live ?*
- *how often do they replicate ?*
- *what's their dynamics of replication ?*
- *how to characterize the hematopoietic tree ?*
- *how to understand disease in this context ?*

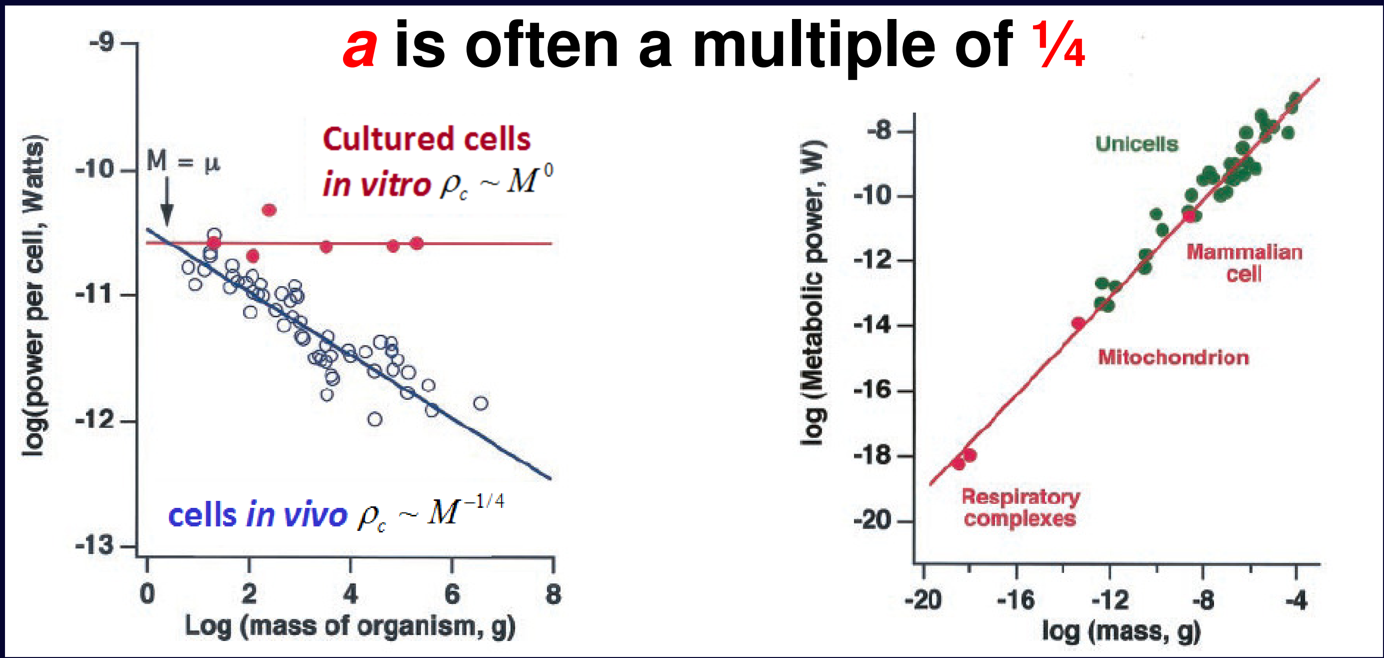
HSC scaling in mammals

Dingli & Pacheco, *PLoS ONE*, 2006

cell metabolic rates

similarly to metabolic rate and many other energy related quantities in biology, also **hematopoiesis** should obey **allometric scaling relations**, reflecting common underlying organizational principles in, e.g., mammals:

allometry : scaling relations of type $Y = Y_0 M^a$ (M=mass)

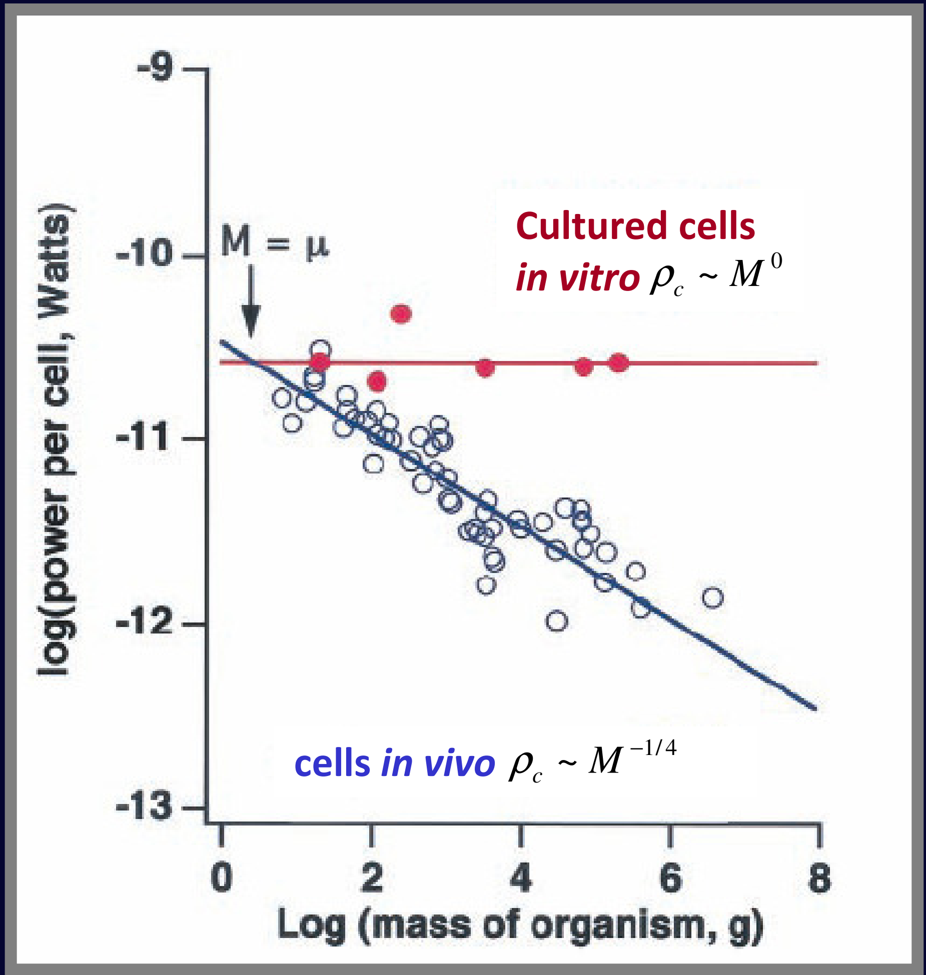


$Log(Y) = Log(Y_0) + a\, Log(M)$

West et al. PNAS (2002)

organism cell requirements

different animals have different blood requirements !



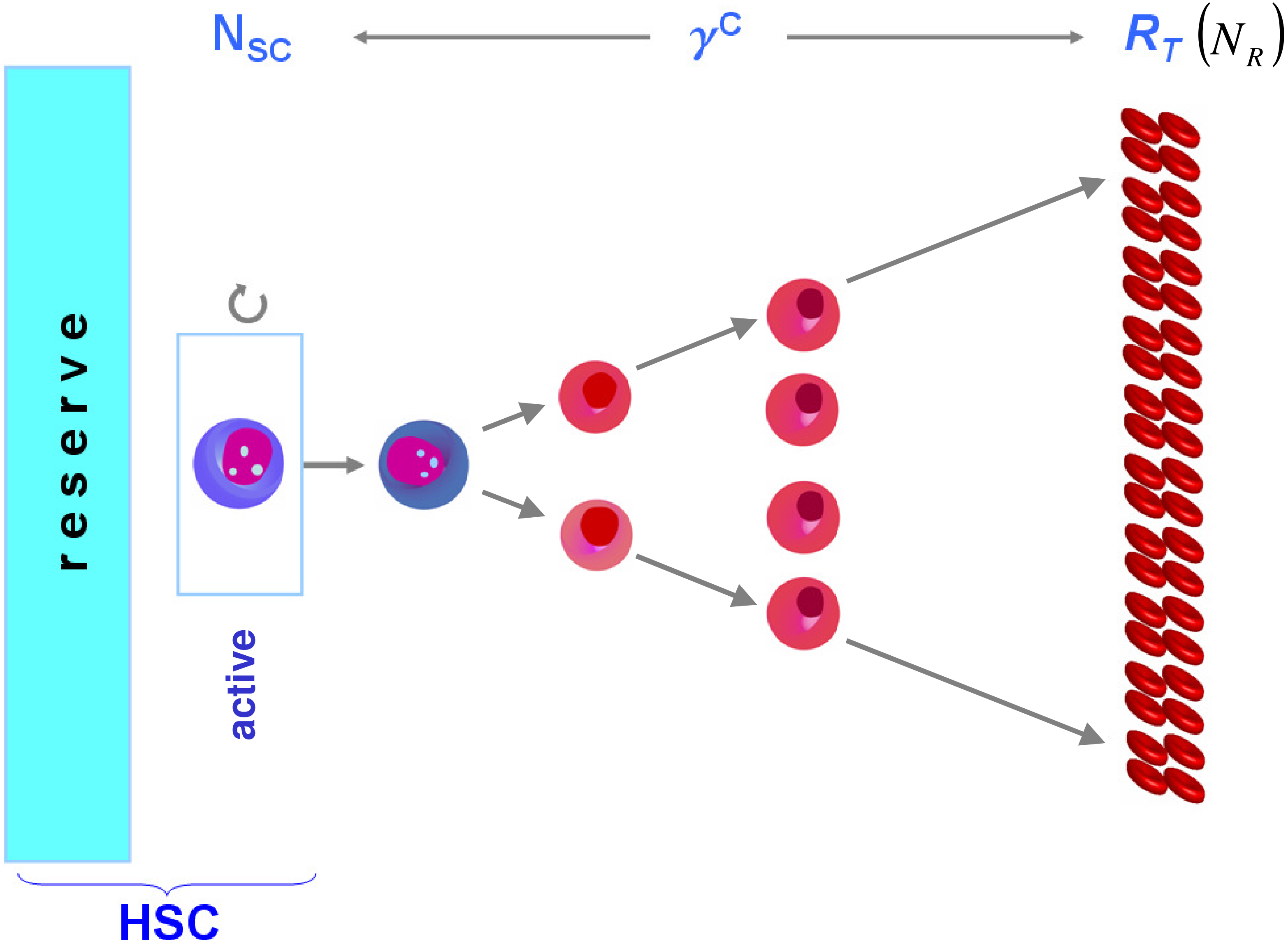
$\text{Log(Y)} = \text{Log}(Y_0) + a\ \text{Log(M)}$

rate of blood production in the bone-marrow :

mouse (2 years) ≈ cat (1 week) ≈ man (1 day)

a scaling model of HSCs - 1

we assume all mammals have the same hematopoietic tree structure . . .



Dingli & Pacheco, *PLoS ONE*, 2006

. . . data recently available supports this hypothesis

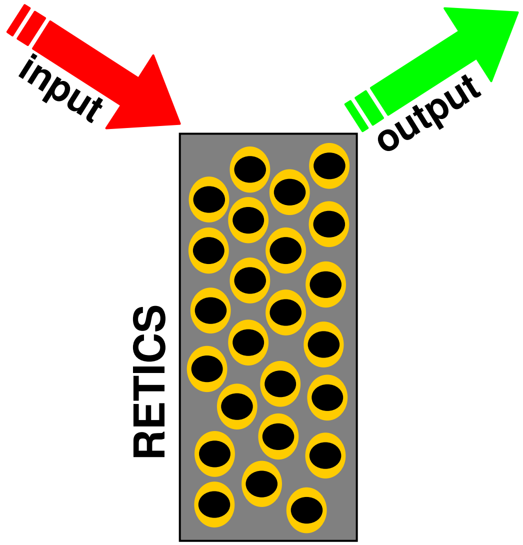
a scaling model of HSCs - 2

number of reticulocytes : N_R

specific metabolic rate : $\rho_c \sim M^{-1/4}$

retics maturation time : $\tau \sim \rho_c^{-1}$

$\sim N_{SC} \cdot \gamma^C \cdot \rho_c$



$N_R \tau^{-1} \sim N_R \cdot \rho_c$

$$N_{SC} \sim N_R$$

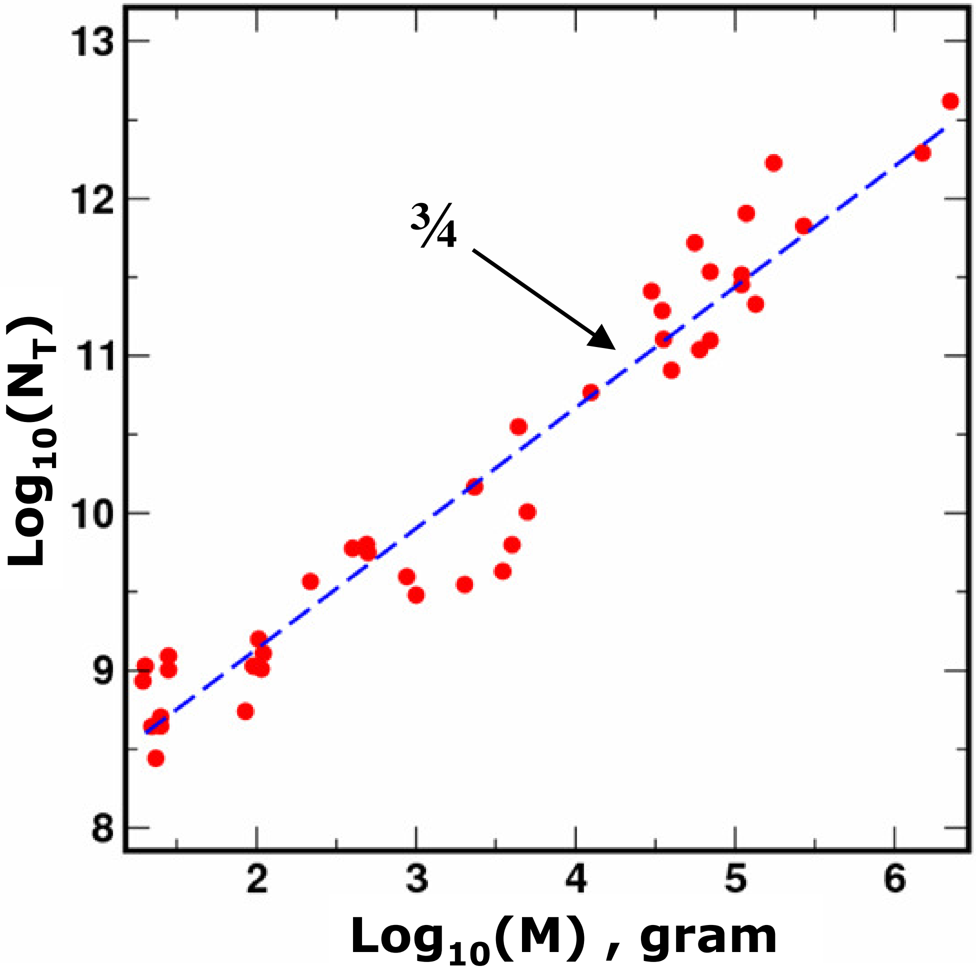
normal physiology

$\leftrightarrow$

dynamical balance

input rate = *output* rate

a scaling model of HSCs - 3



$$N_{SC} \sim M^{3/4}$$

Dingli & Pacheco, *PLoS ONE*, 2006

$$N_{SC} = N_0 M^{3/4}$$

a scaling model of HSCs - 4

use experimental estimates for cats for calibration (fix N_0):

under normal conditions, ≥ 40 ! (*Abkowitz et al, Blood, 2002*)

what	model predictions ×	experimental data
HSC in humans *cat = 40*	385	~400 *(Buescher et al, J Clin Invest, 1985)*
rate HSC division *cat post-TRX = 8 week^{-1}*	60 week $^{-1}$	~ 52-104 week $^{-1}$ *(Rufer, et al, J Exp Med, 1999)*
human post-transplant *cat = 13*	111	~ 116 *(Nash et al, Blood, 1988)*
mouse	1	1 *(Abkowitz et al, PNAS , 1995)*
rate macaques	23 week^{-1}	23 week^{-1} *(Shepherd et al, Blood , 2007)*
rate baboons	36 week^{-1}	36 week^{-1} *(Shepherd et al, Blood , 2007)*

Dingli & Pacheco, *PLoS ONE*, 2006