

Mathematical Modeling Of Human Megakaryopoiesis *Ex-Vivo*

Javad Hatami¹, Cláudia L. da Silva¹, Frederico C. Ferreira¹, Adélia Sequeira²
(javad.hatami@ist.utl.pt)

¹IBB-Institute for Biotechnology and Bioscience, Instituto Superior Técnico (IST),
Universidade de Lisboa, Portugal

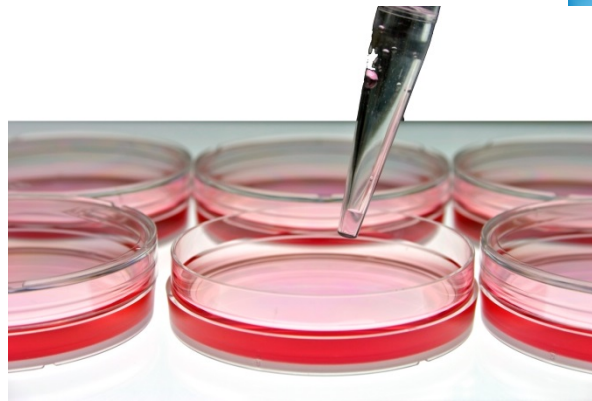
²Department of Mathematics and CEMAT-IST, Universidade de Lisboa, Portugal

5 Dec. 2014

Aim

To Find The Governing Equations And A Mathematical Description Of Hematopoietic Stem Cell (HSC) Expansion, Megakaryocyte Differentiation And Platelet Generation

- *In vitro*
- *Ex-vivo*

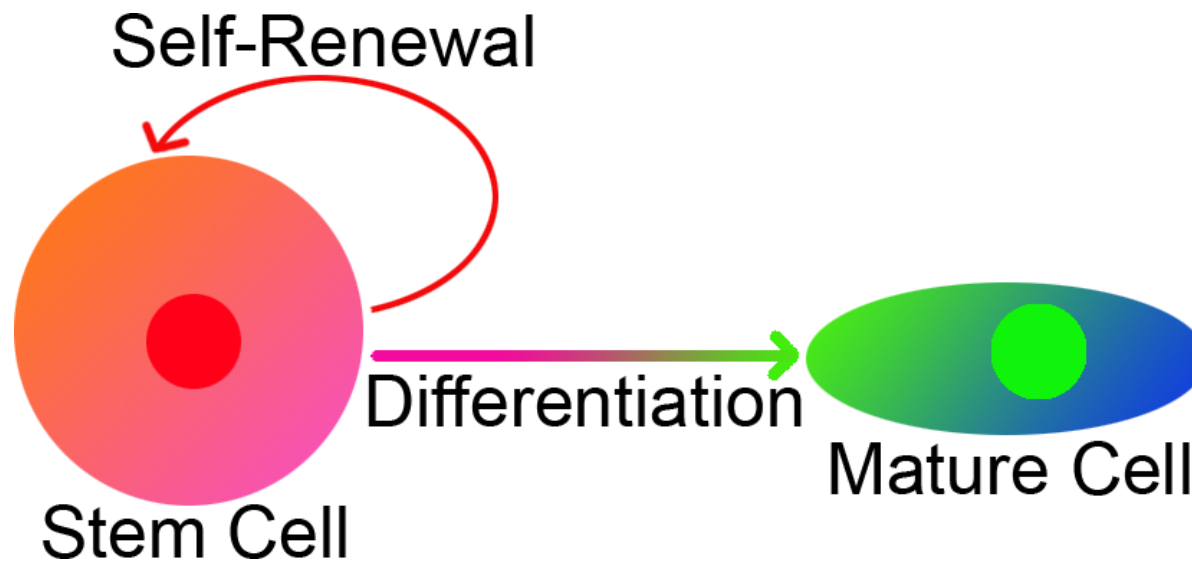


- *In vivo*

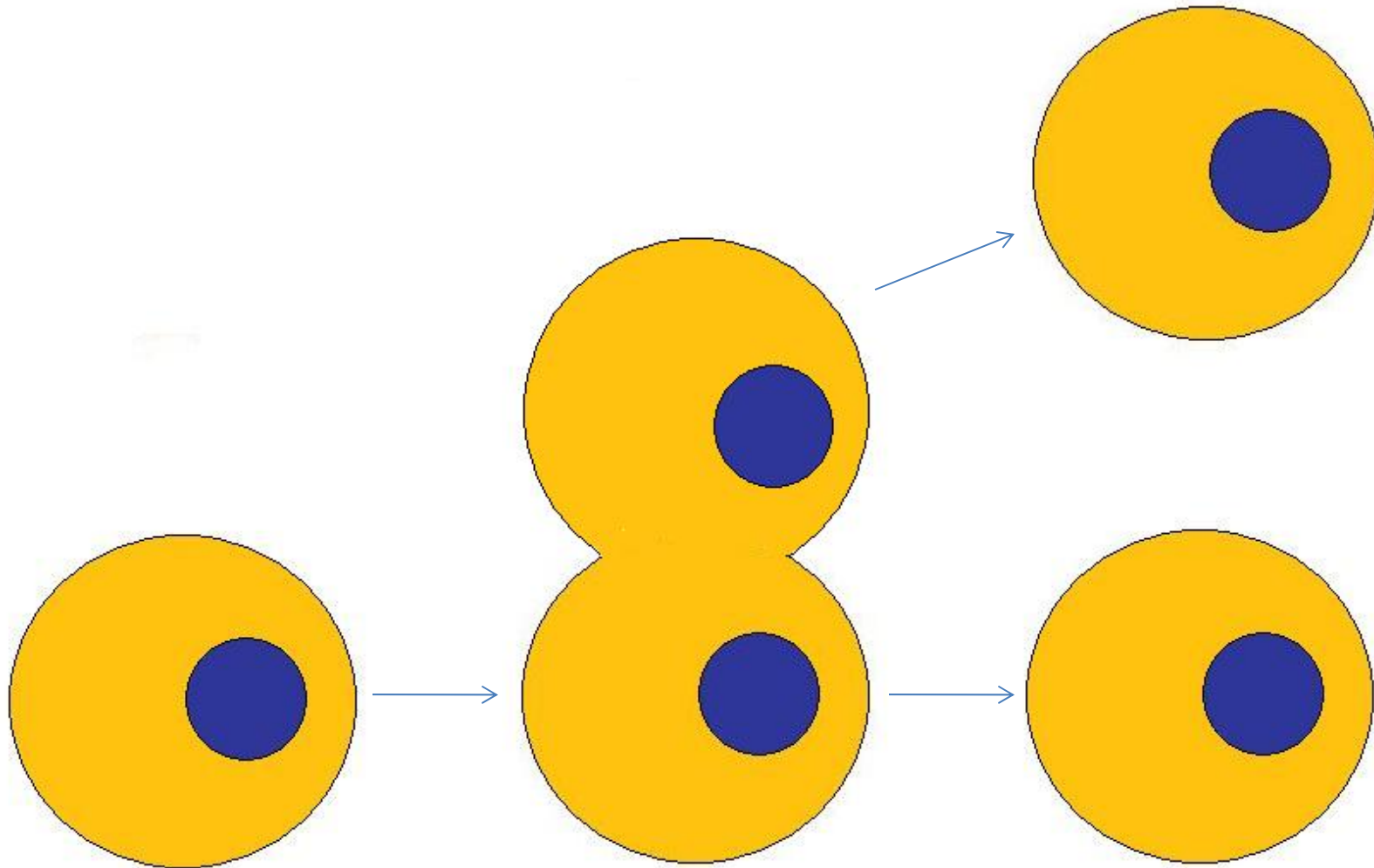


Stem Cell

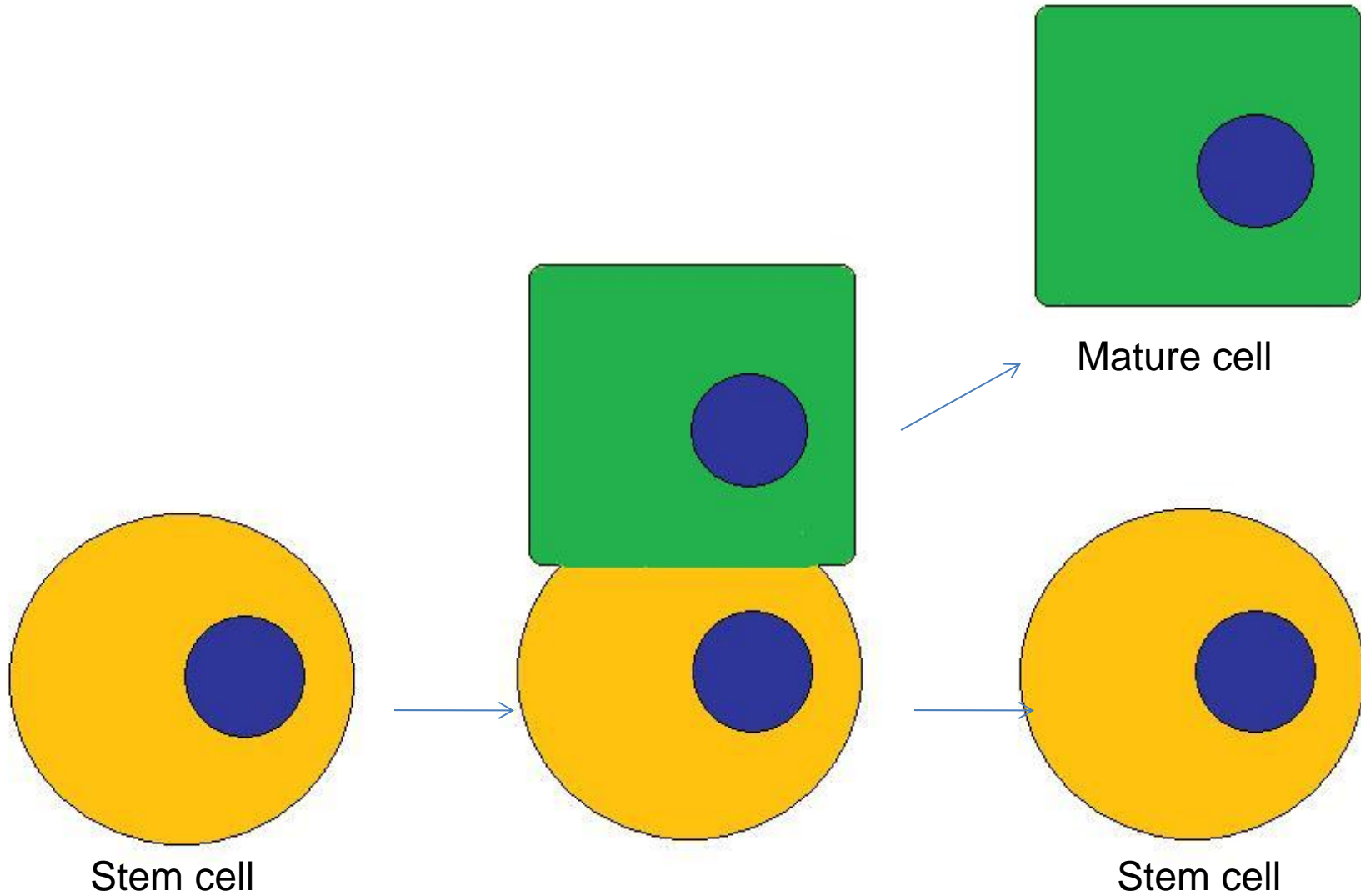
- Undifferentiated/unspecialized biological cells
 - Long-term self renewal
 - Ability to differentiate into different mature cells



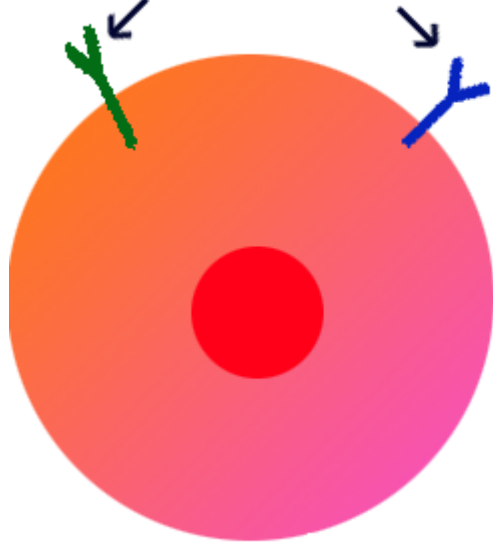
Self-Renewal (Expansion/Proliferation)



Differentiation



Cell Markers

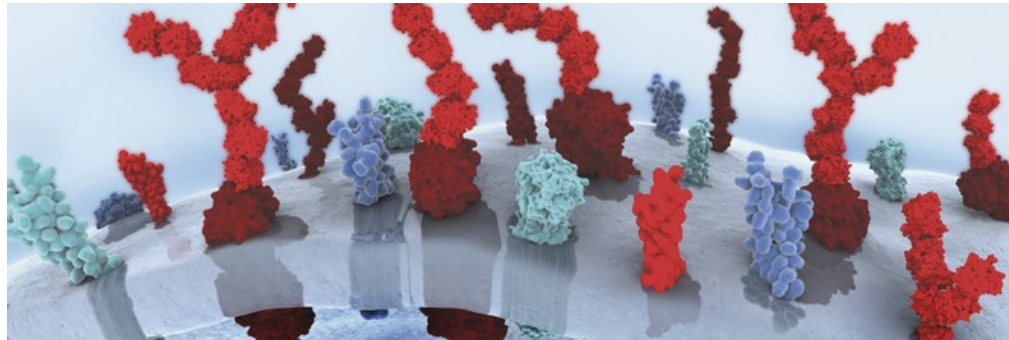


Cell

CD34⁺ (HSC)

CD41⁺ (Mk)

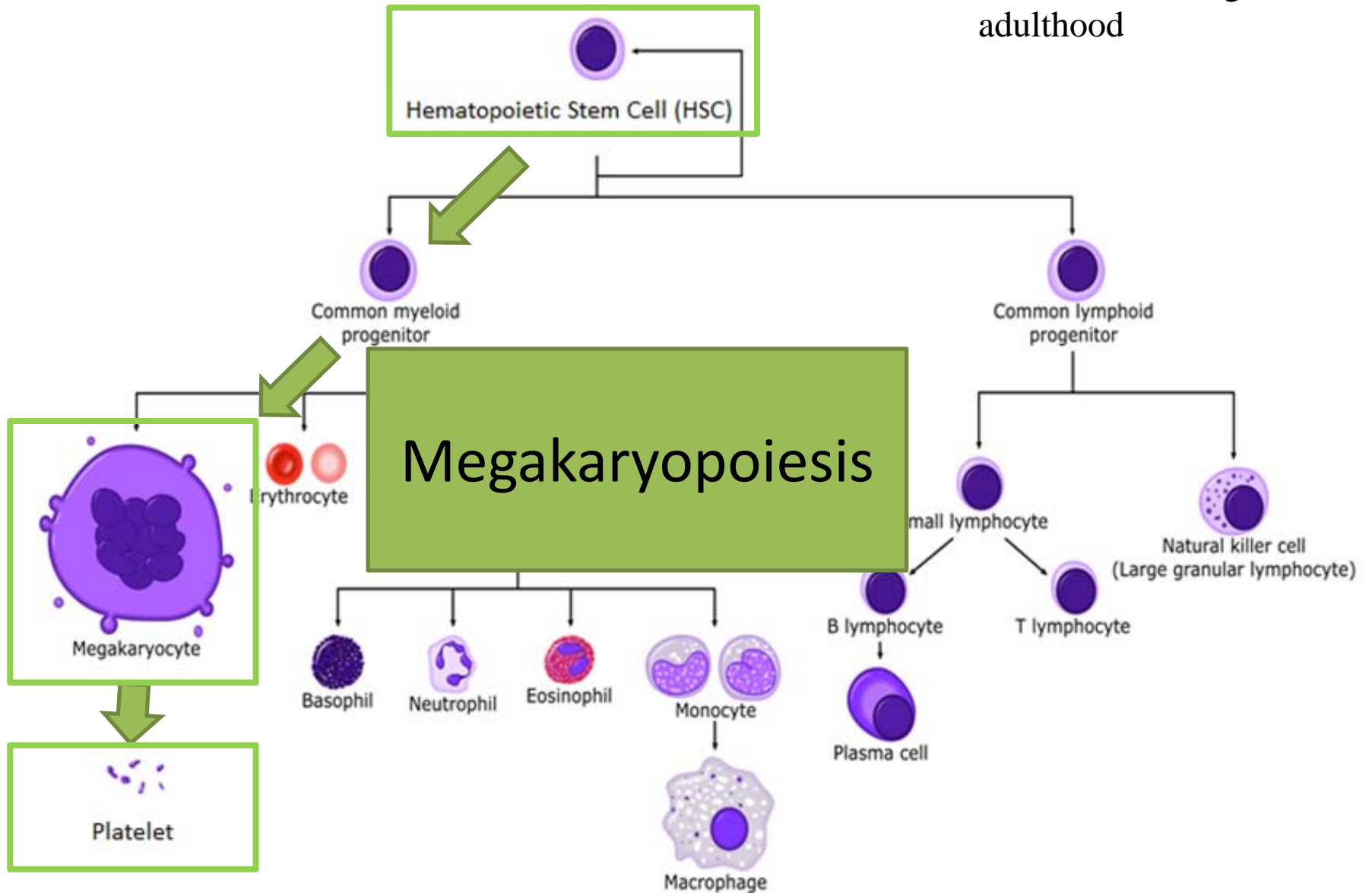
CD42b⁺ (Platelet/Mature Mk)



Flow Cytometry
(Phenotypic characterization)

Hematopoiesis:

Development of mature blood cells throughout adulthood



Platelet Functions/Clinical Importance

- **Platelet Function:**
 - Homeostasis & Thrombosis
 - Inflammation
 - Maintenance & regulation of vascular tone
 - Host defense
- **Clinical Importance:**
 - Platelet transfusions
 - Cancer Chemotherapy (leukemia,..)
 - Heart Surgery
 - Severe Thrombocytopenia
 - Platelet dysfunction
 - Platelet-derived growth factor

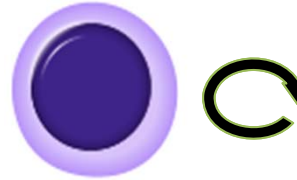


2 milion donated
Platelet transfue annually
in USA=> 31% wasted

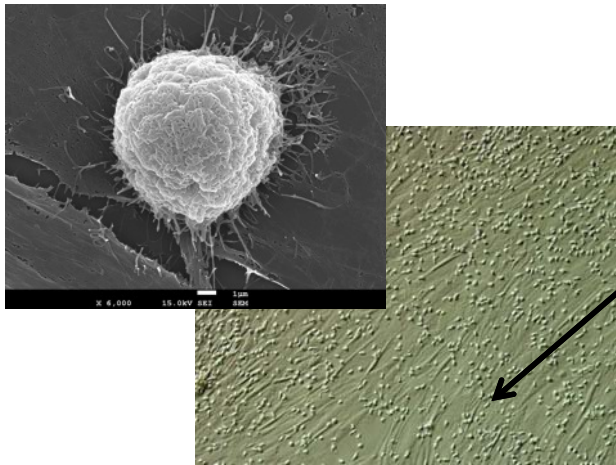
Experimental Set-up



Co-Culture System for HSC Expansion

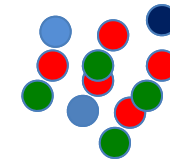


**Hematopoietic Stem Cell
(CD34⁺)**



Feeder Layer:

Derived from human Bone
Marrow Mesenchymal Stem cell
(BM MSC)

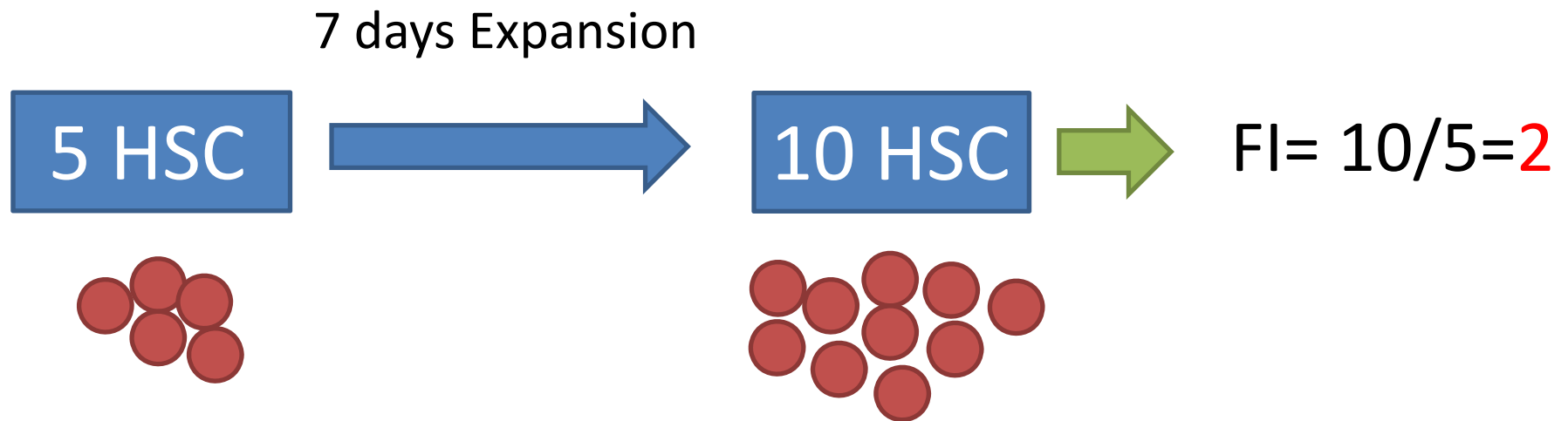


Cytokine (Z9):

Stem Cell Factor (SCF)
Fms-related tyrosine kinase 3 (Flt-3)
Thrombopoietin (TPO)
Basic Fibroblast Growth Factor (bFGF)
QBSF (serum free medium)

da Silva, CL. *et al.*, *Exp Hematol.* 2005;33(7):828-835.
Goncalves, R. *et al.*, *Exp Hematol.* 2006;34(10):1353-1359.
da Silva, CL, *et al.*, *J Tissue Eng Regen Med*, 2010 (4) 144-158

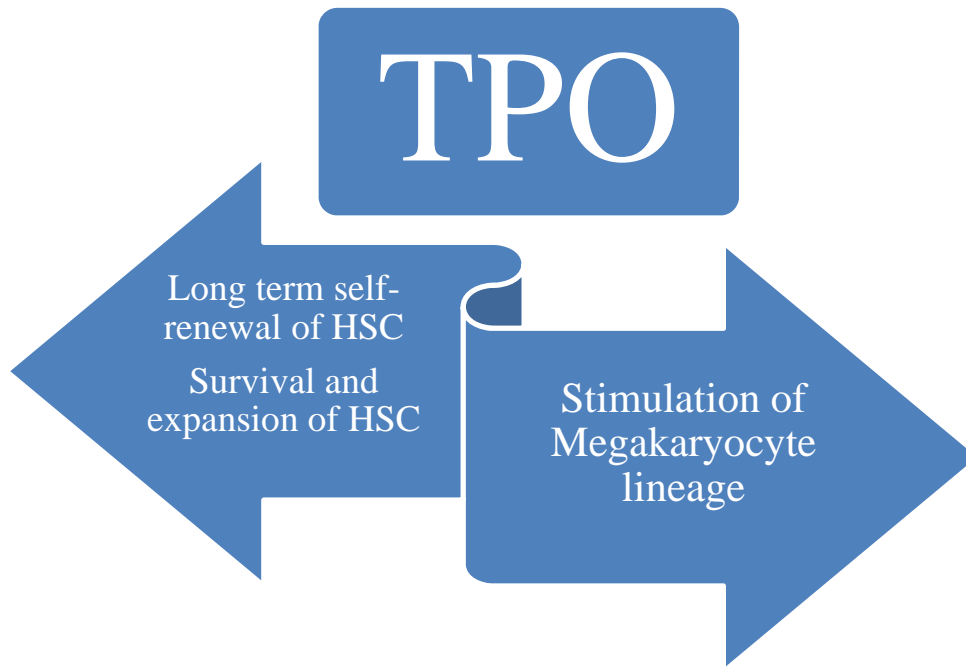
Andrade, PZ. *et al.*, *Mol. Biosystems* 2010 (6) 1207-15



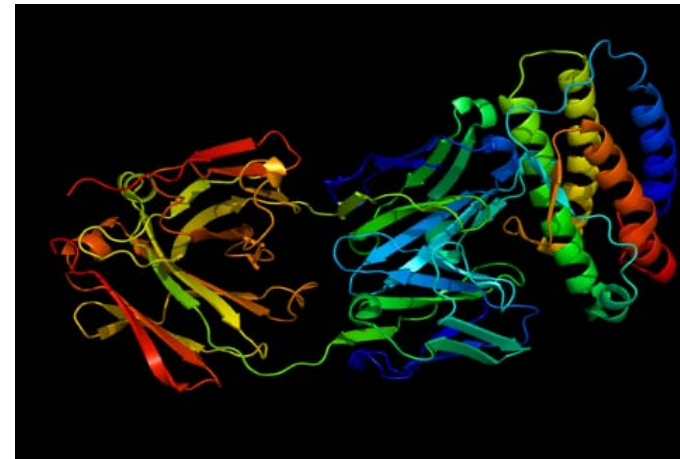
$$\text{Fold Increase(FI), CD34}^+ = \frac{\text{Number CD34}^+, \text{Day } \underline{X}}{\text{input Number of CD34}^+}$$

Thrombopoietin (TPO) in Expansion ?

Andrade et al., *Mol. Biosystems* 2010 (6) 1207-15



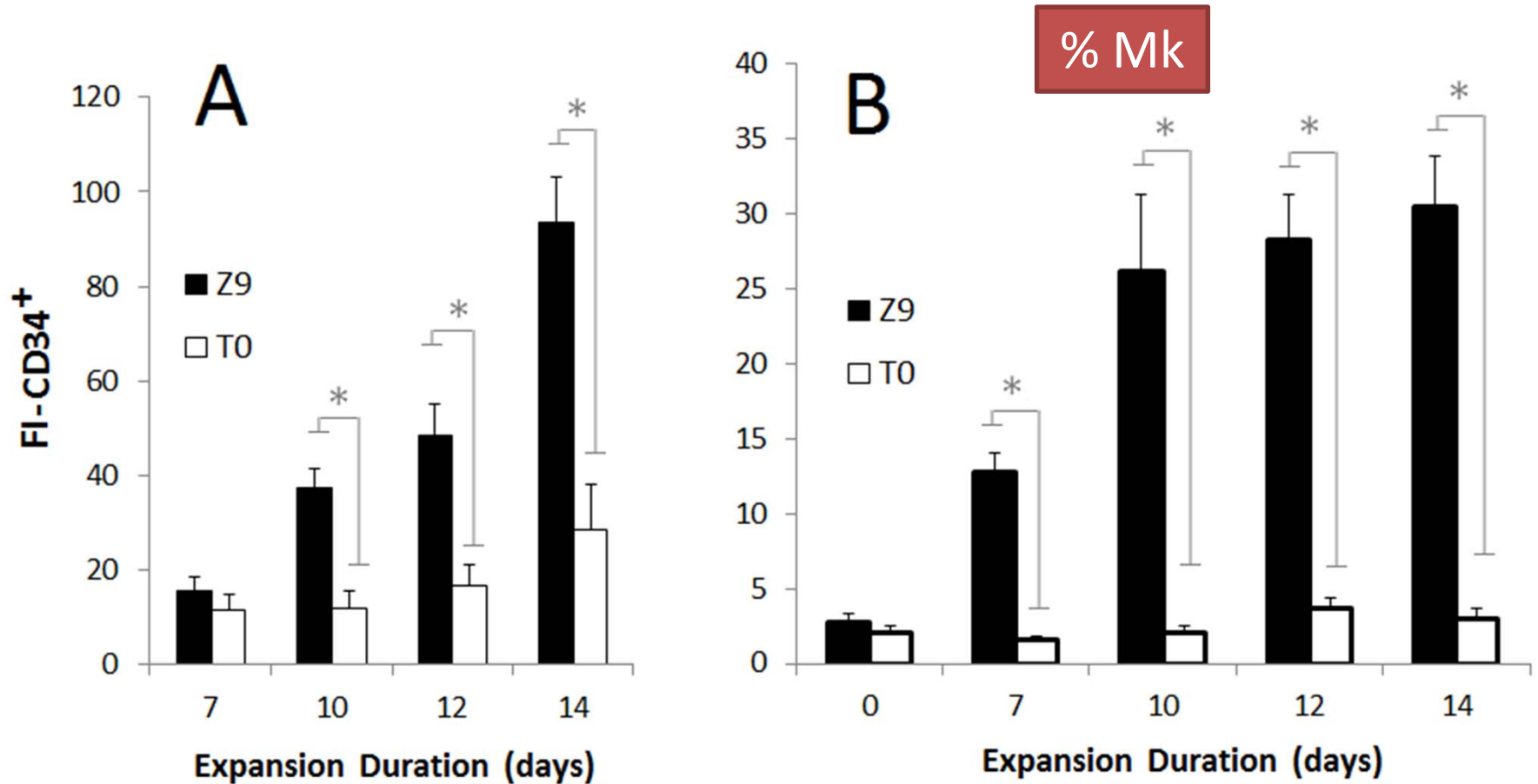
	Z9, ng/mL	T0, ng/mL
TPO	50	0
SCF	60	60
FLt3	55	75
b-FGF	5	5



produced in Liver, BM & Kidney
Regulation of Platelet production

	Z9, ng/mL	T0, ng/mL
TPO	50	0

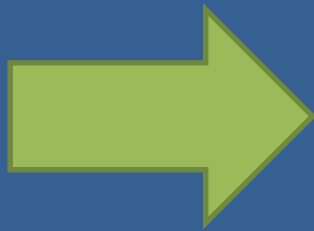
HSC Expansion: Z9 vs. T0



Result: Ave ± SEM
*: p<0.05

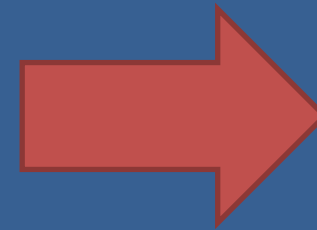
Mathematical Modeling

$u(t)$: Cell inflow
[number of cells/time]



$x(t)$: Cell population
 $\alpha \cdot x(t)$: Cell production and
destruction

$y(t)$: Cell outflow
[number of cells/time]



$$\frac{dx(t)}{dt} = u(t) + \alpha \cdot x(t) - y(t)$$
$$x(0) = x_0$$

Conclusion

- Efficient *Ex-vivo* Protocol (Cytokines & Culture Medium) For HSC Expansion ($eh \uparrow$ And $Kh \downarrow$)
- Critical Role Of TPO For Megakaryopoiesis ($em \uparrow$ And $Dp \uparrow$)
- Mathematical Description Of Megakaryopoiesis
- Quantitative Approach To Advance For Stem /Mature Cells Manipulation For Cell Therapy And Regenerative Medicine application

Acknowledgments

- Prof. Frederico Ferreira (IBB-IST)
- Prof. Claudia Lobato da Silva (IBB-IST)
- Prof. Adélia Sequeira (CEMAT, IST)
- Dr. Antonio Matos (Curry Cabral Hospital, Lisbon)
- All Colleagues in IBB-SCBL and CEMAT-IST



Mathematical and Computational Modeling of Human Physiology: PHYSIOMATH

