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Author: Ivan Maillard, M.D., Ph.D., 2009

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HEMATOPOIESIS

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UM Medical School

Winter, 2011

HEMATOPOIESIS

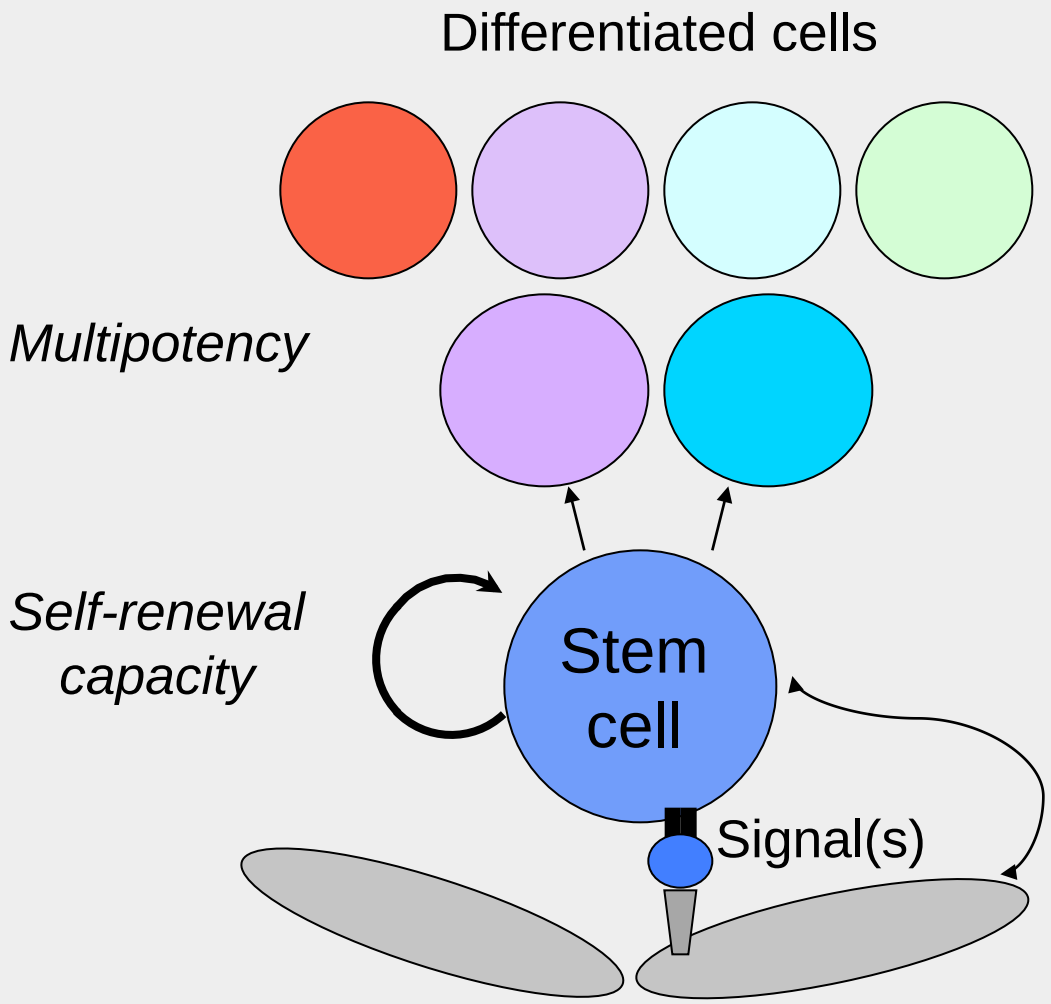
- **Topics of the course:**

  - **Location of hematopoiesis during embryogenesis and in the adult**
  - **Origins and properties of the hematopoietic stem cell**
  - **Assessment of hematopoietic precursors**
  - **Relationship of the stem cell to all classes of blood cells**
  - **Development of lymphocytes**
  - **Development of the erythroid, granulocytic, and megakaryocyte lineages**
  - **Differences in hemoglobin during development**

What is Hematopoiesis?

- **Development of the cells of the blood system and of their supporting structures**
  - **Elements of the hematopoietic system**
    - **Blood cellular elements: erythrocytes, megakaryocytes-platelets, white blood cells**
    - **Proteins**
    - **Stroma that supports blood development**
  - **Characterized by a regulated balance of progenitor self-renewal and commitment to differentiate**
  - **Organized as a hierarchy**

Hematopoietic Hierarchy



Why understand the details?

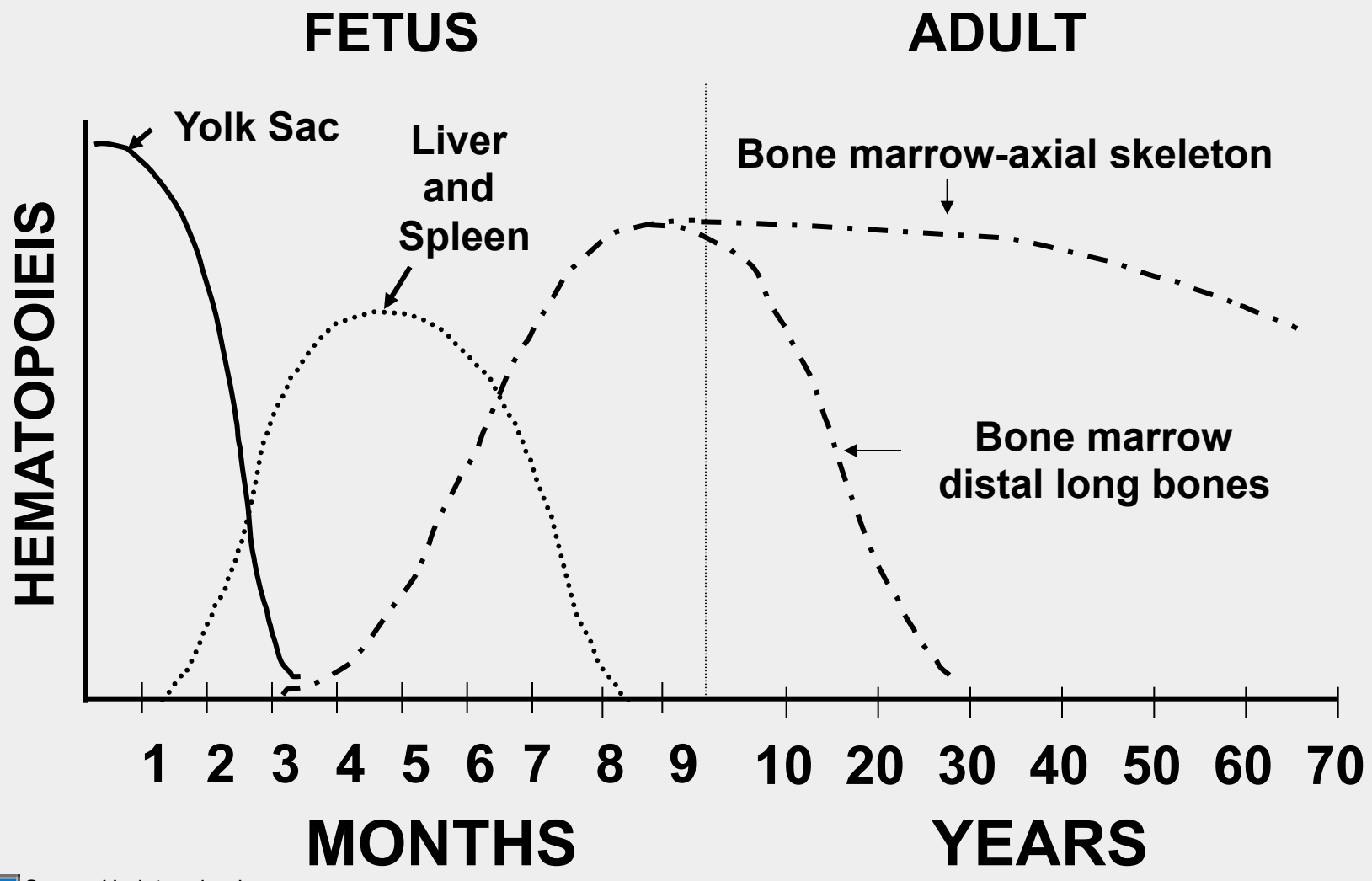
- **Narrow homeostasis of blood cell numbers**
  - If not actively maintained, hematopoietic failure
  - For example: 2 x 10^6 new red cells produced every second!
- **Hematopoietic response essential in many clinical situations**
  - Infection, wound healing
  - Hemorrhage
  - Chemotherapy, bone marrow transplantation
  - …
- **Dysregulation of the hematopoietic program in hematological maligancies**
  - Leukemia, lymphoma, multiple myeloma

Origins of Hematopoiesis

- **Primitive Hematopoiesis**
  - Transient, primitive program
  - Begins in early embryogenesis
  - First 8 weeks: cells arise in the embryonic yolk sac

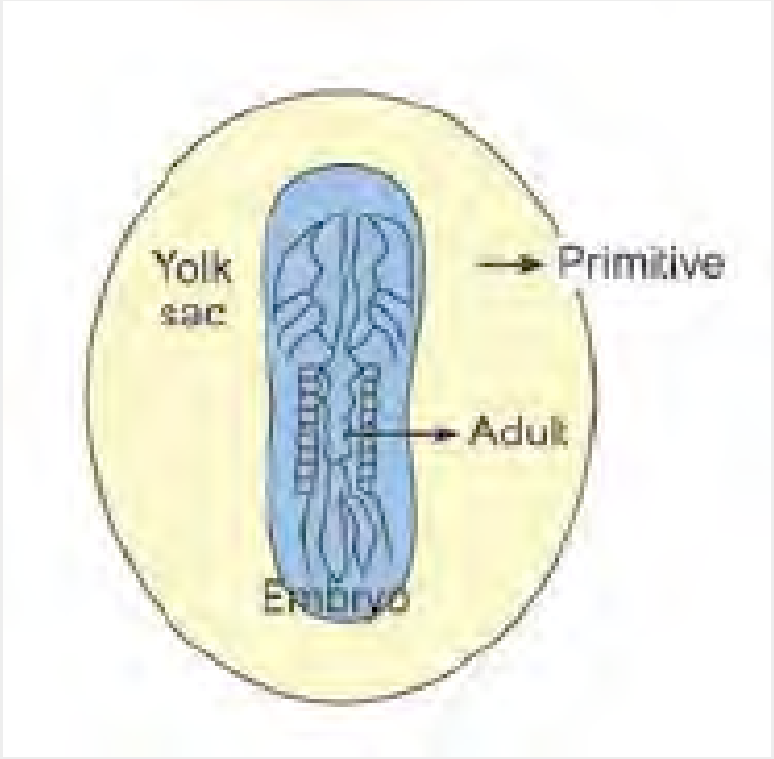
- **Definitive Hematopoiesis**
  - What we see in the adult
  - Begins during fetal life in association with vascular structures (fetal aorta, placenta)
  - Expands in the fetal liver and spleen
  - In the late fetus the bone marrow becomes the main site of hematopoiesis

Shifting Sites of Human Hematopoiesis



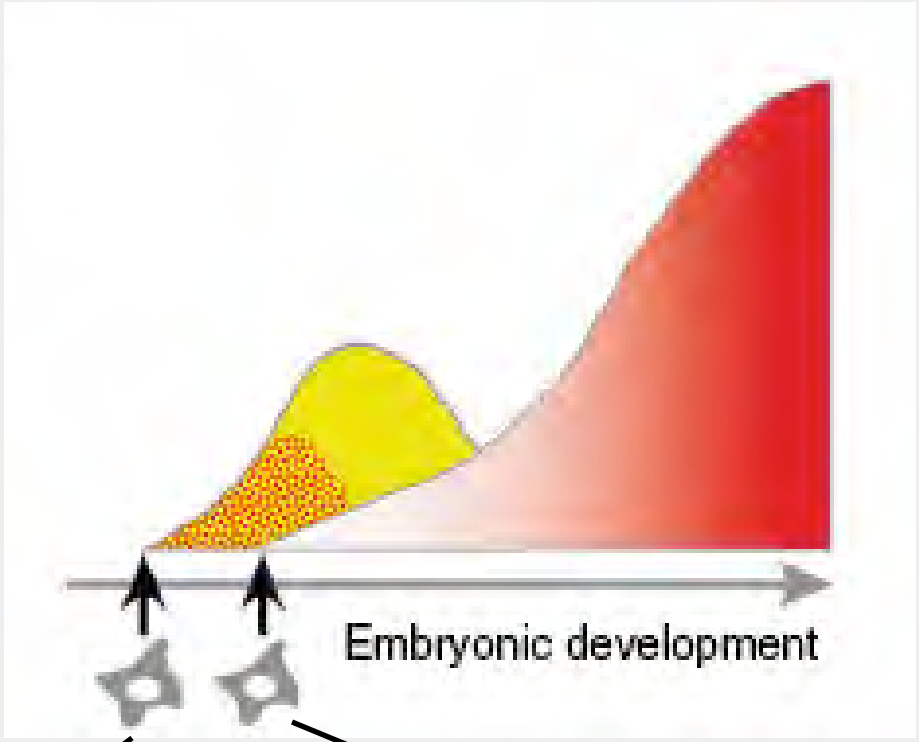
Primitive and definitive hematopoiesis

Avian chimeras



Dieterlen-Lièvre, 1975

Mouse, Human

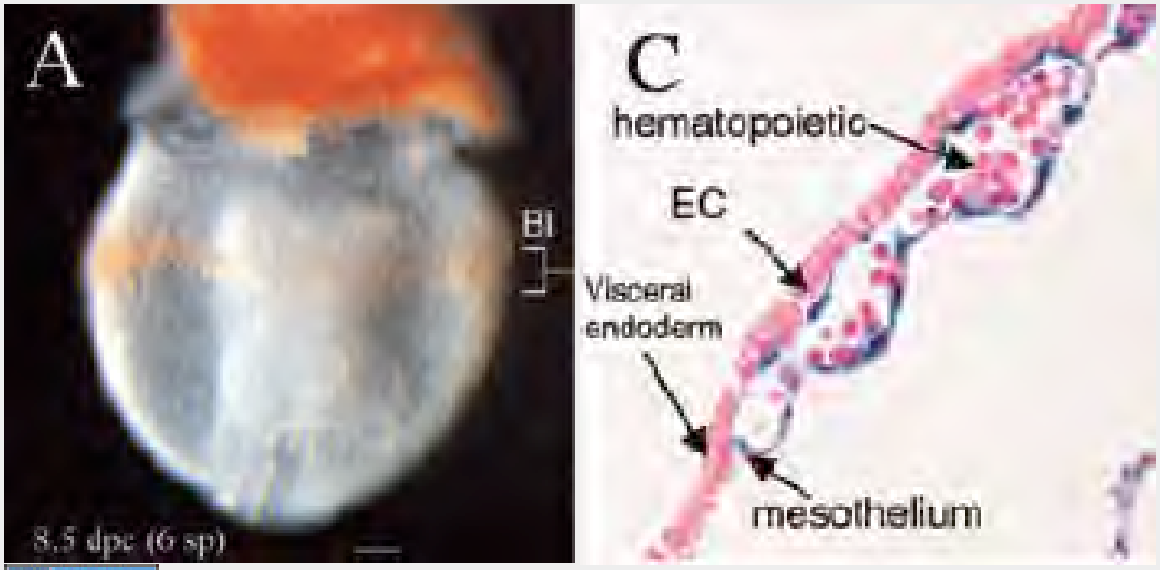


Primitive Hematopoiesis

Definitive Hematopoiesis

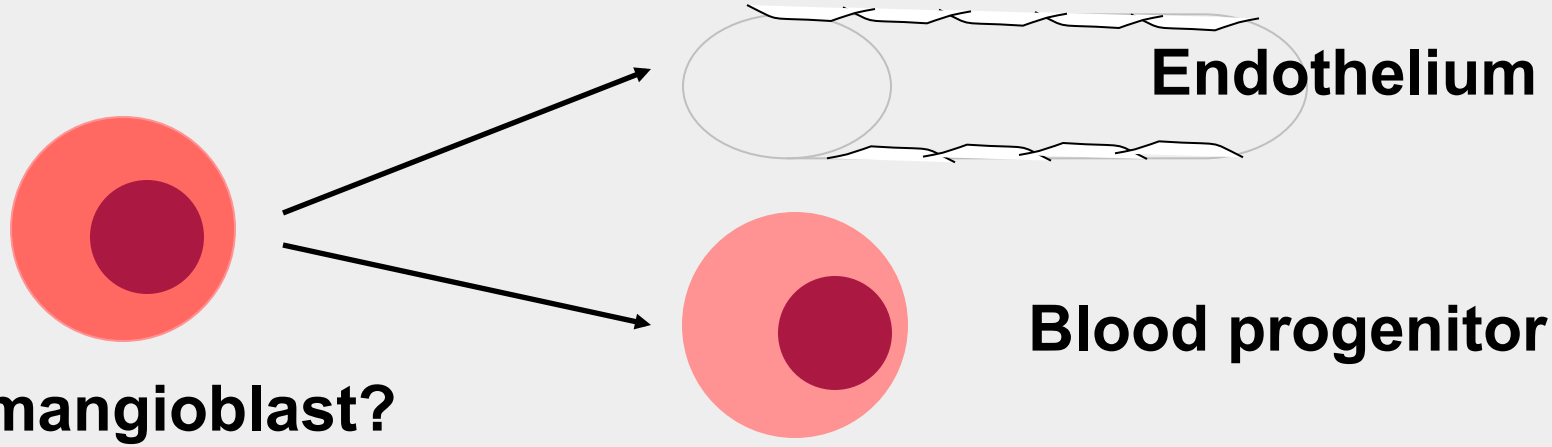
 Dieterlen-Lièvre, 1975

Primitive Hematopoiesis



PD-INEL Ema and Rossant, 2003

Yolk sac



PD-INEL I. Maillard

Early observations

PD-EXP

Florence Sabin (1871-1953)

PRELIMINARY NOTE ON THE DIFFERENTIATION OF ANGIOBLASTS AND THE METHOD BY WHICH THEY PRODUCE BLOOD-VESSELS, BLOOD-PLASMA AND RED BLOOD-CELLS AS SEEN IN THE LIVING CHICK

FLORENCE R. SABIN

Anatomical Laboratory, Johns Hopkins University

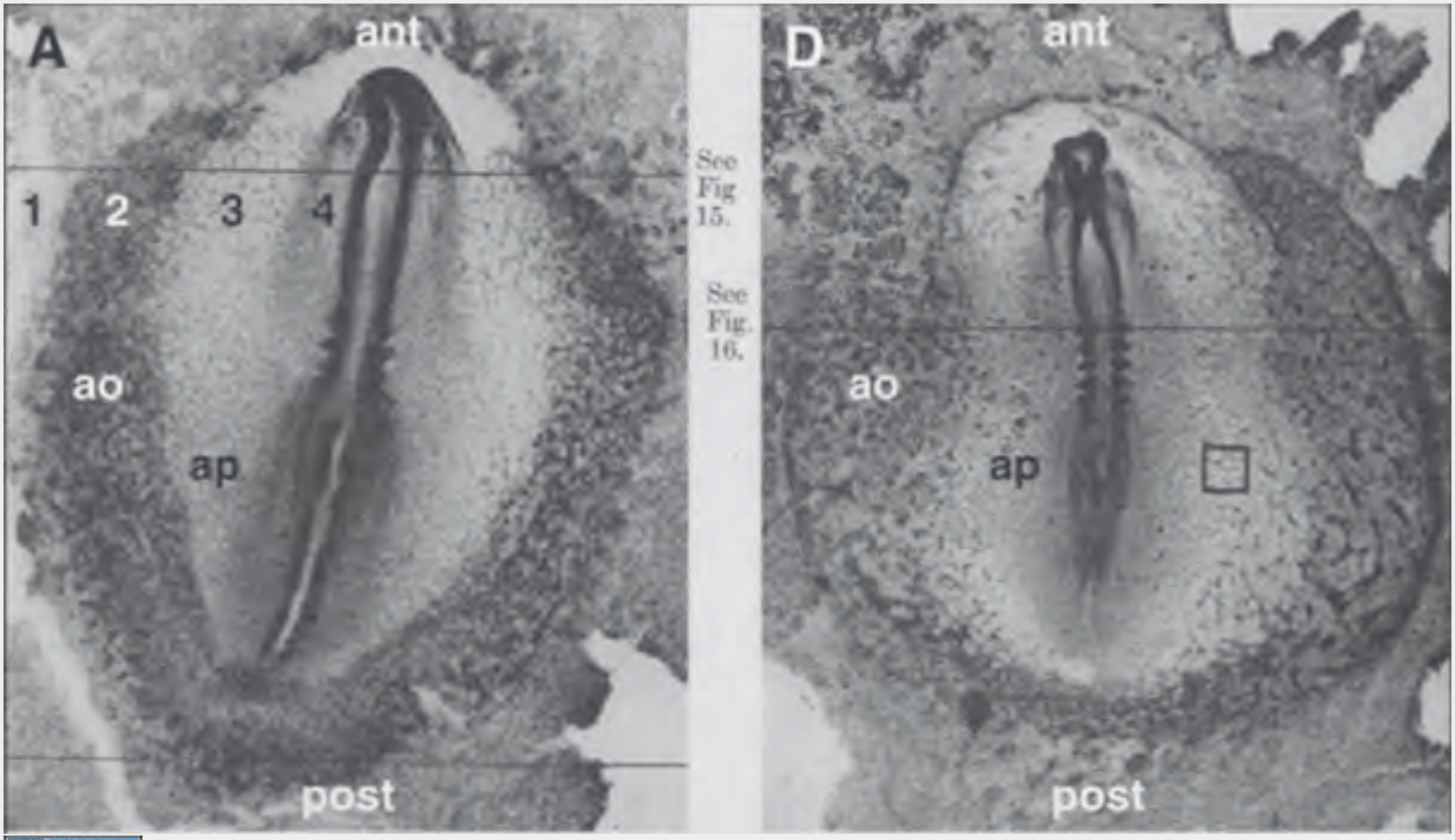
PD-EXP

Anatomical Record (1917)

The question of the origin of the vascular system can be solved by the method of studying the living blastoderm of the chick in hanging-drop preparations.

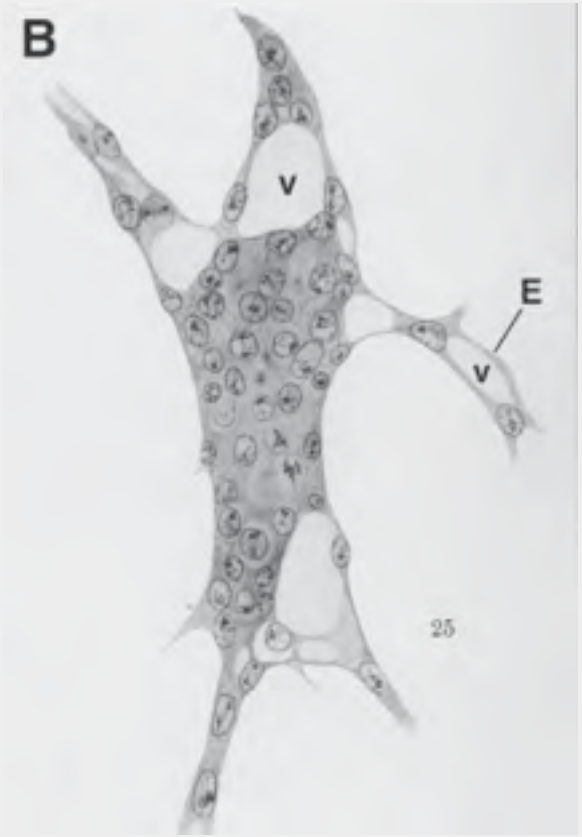
PD-EXP

Morphology of the chick blastoderm



PD-EXP Sabin (1920)

Angioblastic cords in the chick blastoderm

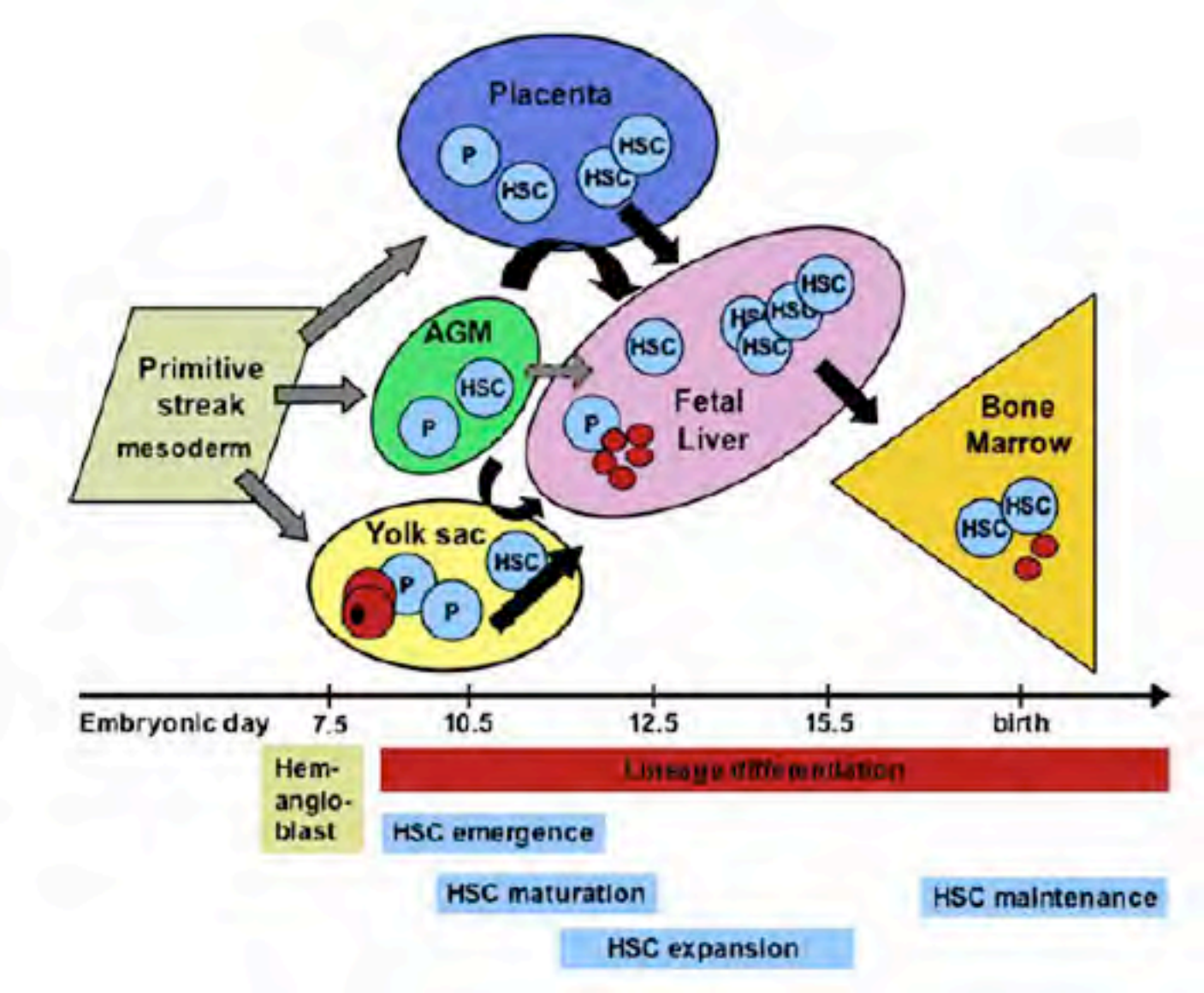


Lumenization and endothelial morphology

“Blood islands”

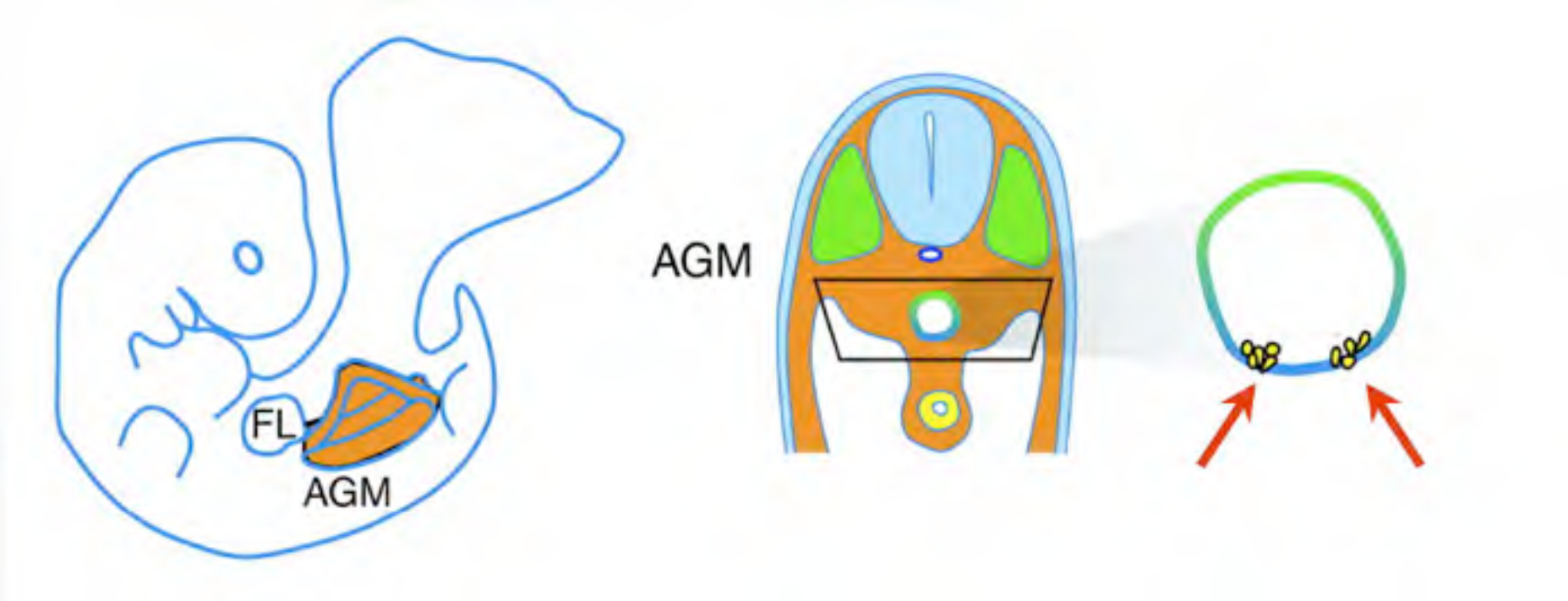
PD-EXP Sabin (1920)

Sites of Hematopoiesis



PD-INEL Mikkola and Orkin, 2005

Emergence of definitive hematopoietic stem cells



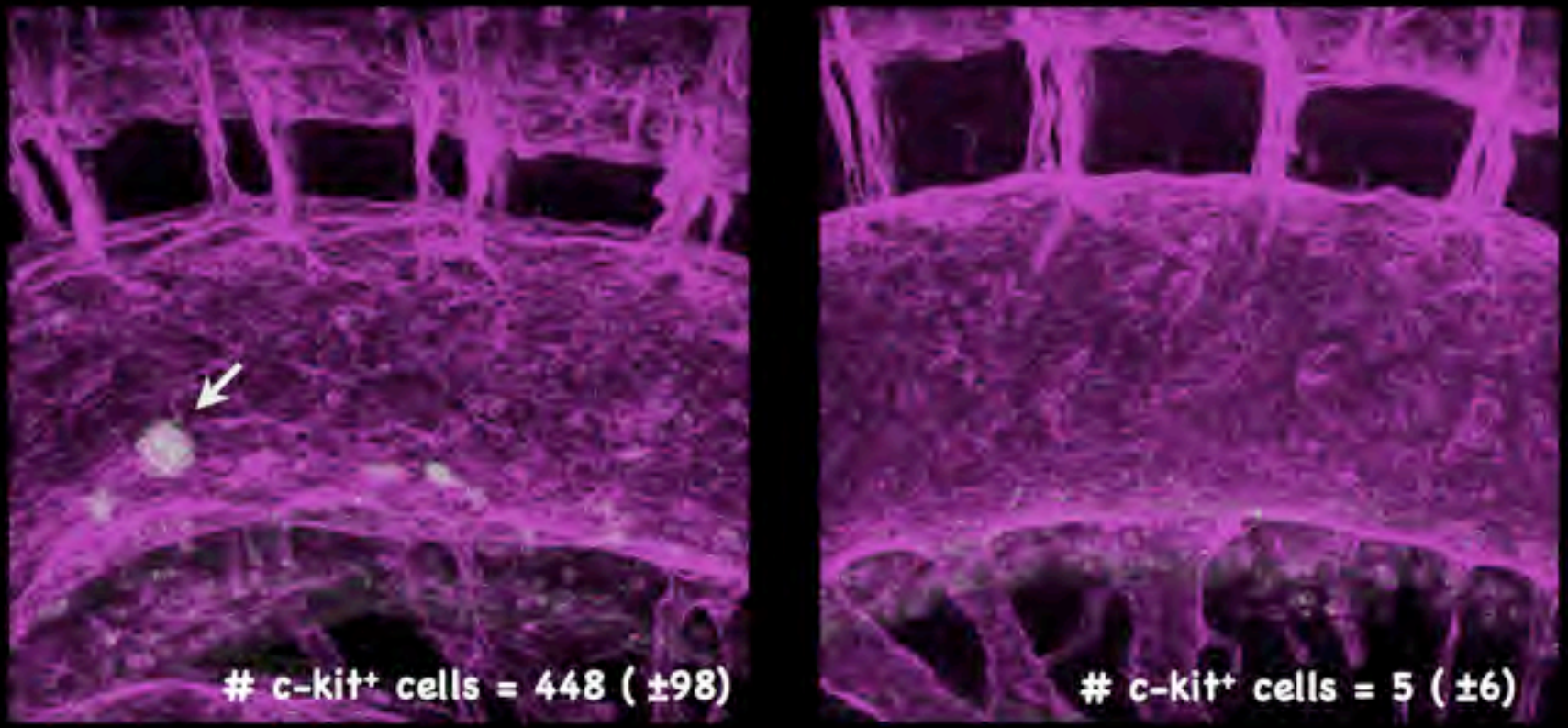
PD-INEL I. Maillard

AGM: aorta, gonad, mesonephros

Runx1 excision in endothelial cells eliminates intra-arterial clusters

$Runx1^{f/+}$

$Runx1^{f/f}$; Tg(VEC-Cre)



Yokomizo, Dzierzak and Speck, 2009

PECAM-1 c-Kit

Essential Properties of Definitive Hematopoietic Stem Cells

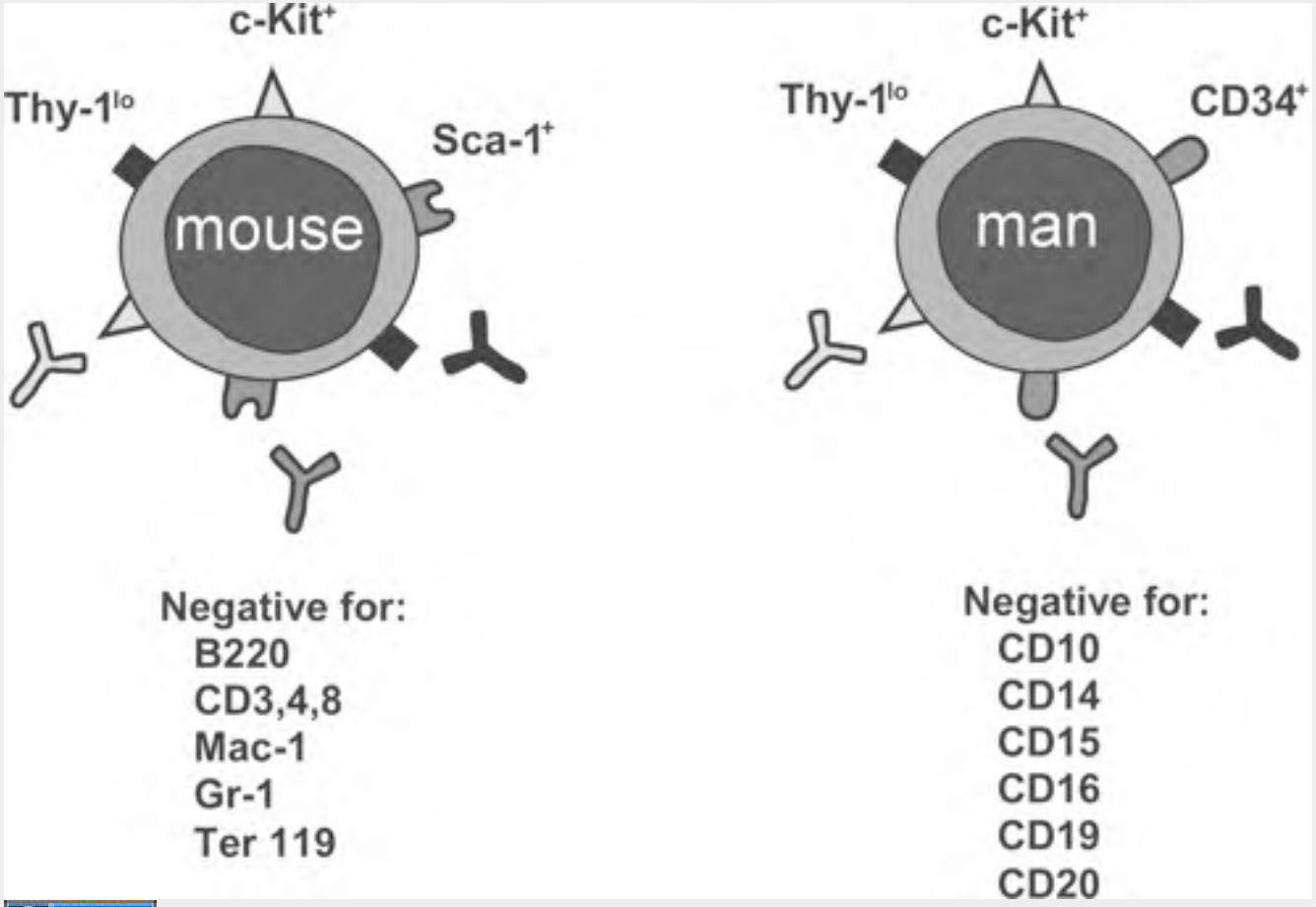
Hematopoietic Stem Cell:

- **Extensive self-renewal**
- **Quiescence (in steady-state conditions)**
- **Multipotency**
  - **Broad differentiation capacity - maintains all different classes of blood cells and lymphocytes**

→

- **Numbers are low**
- **Cannot be detected by the naked eye in the bone marrow**
- **Prospective identification relies on cell surface markers**
- **In humans, the stem cell has not been as clearly defined as in the mouse**

Hematopoietic Stem Cell Phenotype



Best defined somatic stem cell!

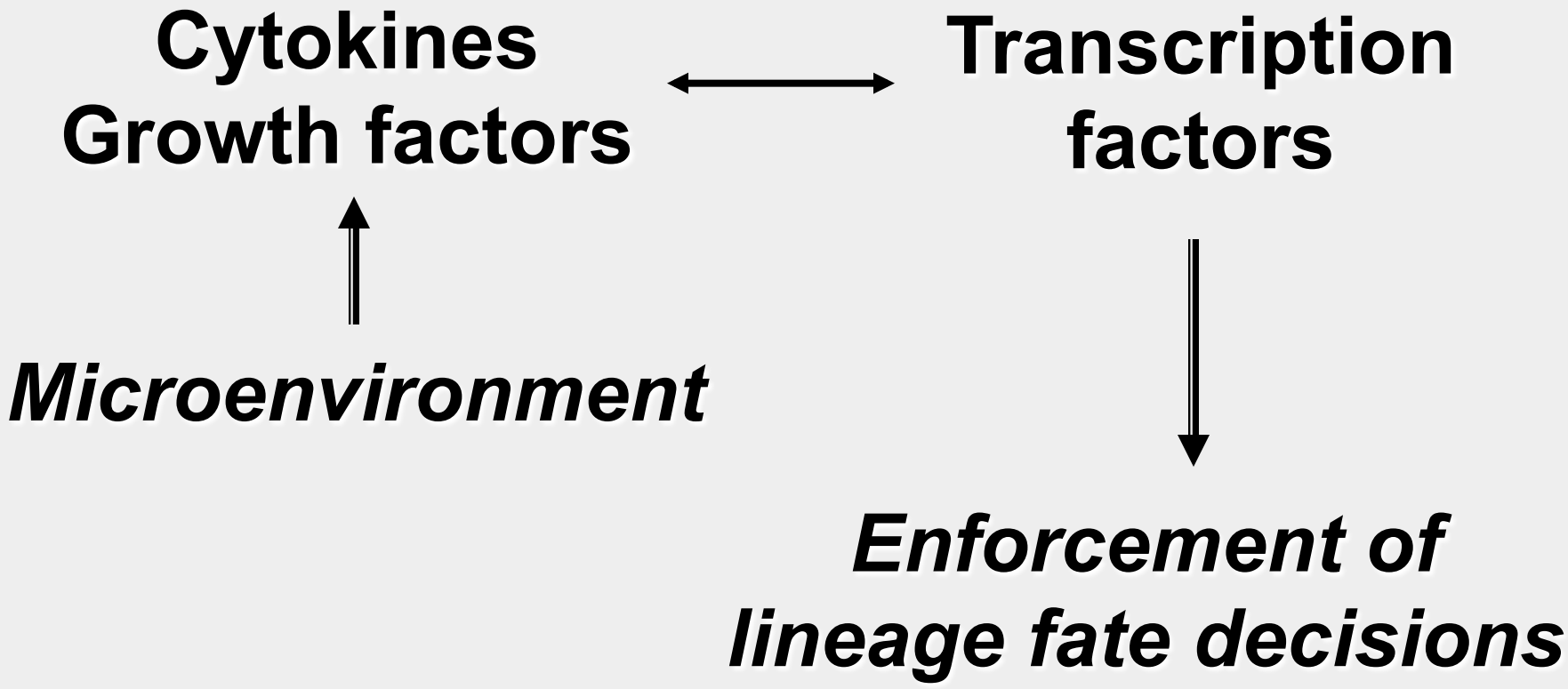
Weissman and collaborators
Kiel and Morrison (CD150+, CD48-)

How can we study hematopoietic stem and progenitor cells?

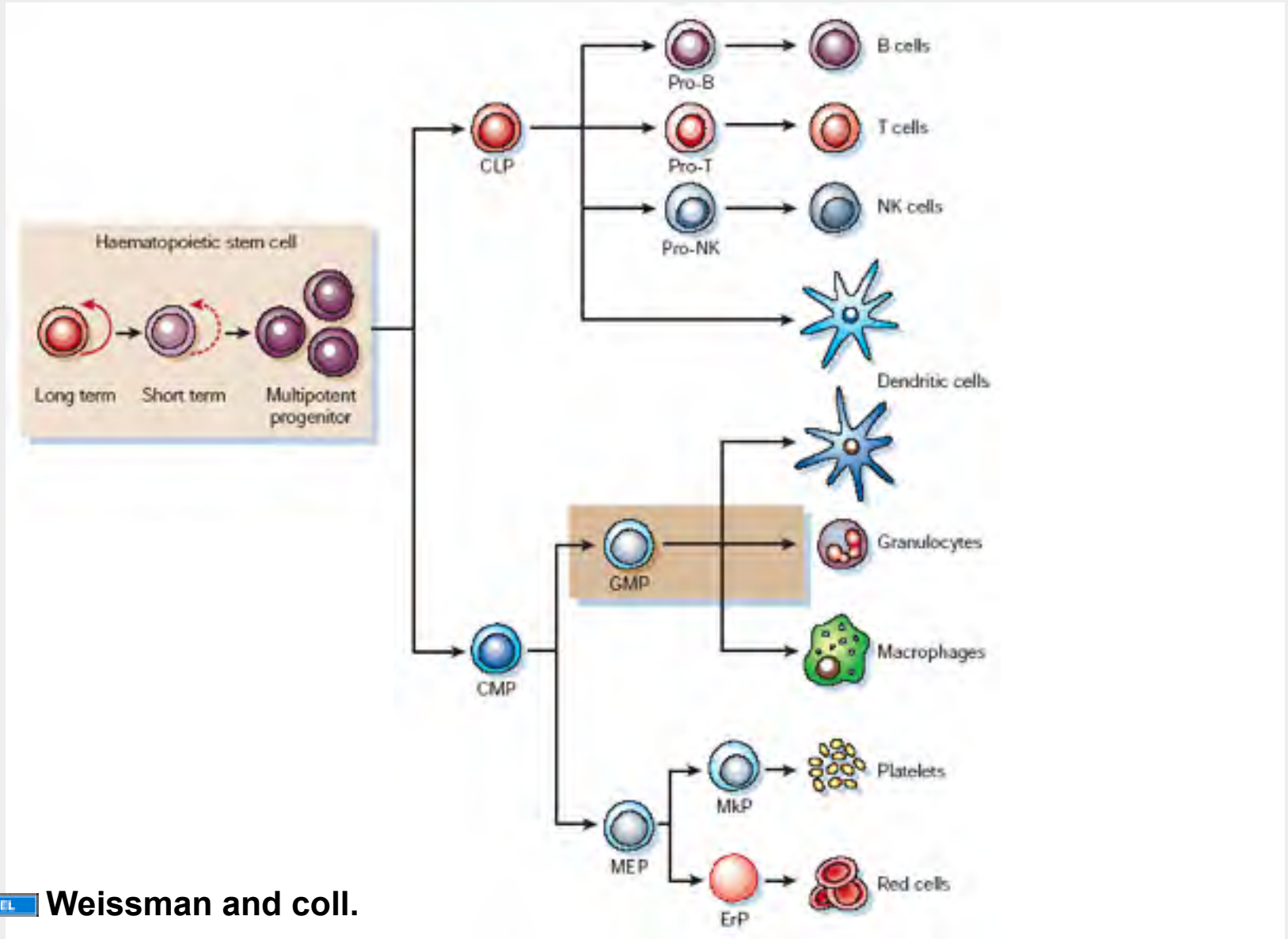
- **Transplantation models**
  - Donor cells into mice whose blood cells have been destroyed
  - Can determine the developmental potential of a given population of blood progenitors
  - One single hematopoietic stem cell can repopulate all the blood cell lineages!

- **Cell culture techniques**
  - BFU –Burst forming units
    - Proliferate
    - Not able to establish all cell lineages
  - CFU-Colony forming units
    - Later cell than the burst forming unit
    - Can repopulate a cell lineage but more restricted that the BFU

What directs hematopoietic stem cell differentiation to specific blood lineages?

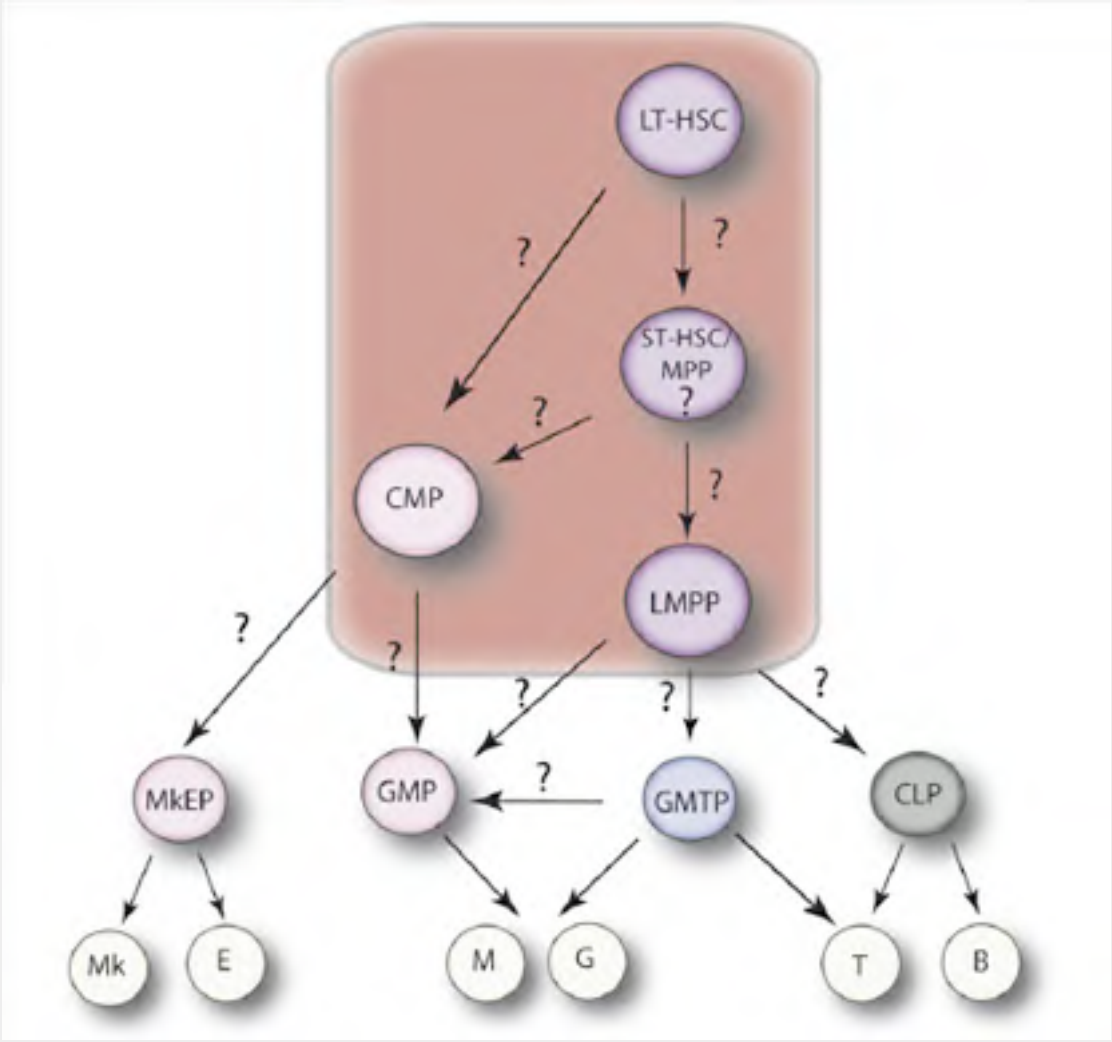


Hematopoietic differentiation
Classical Model



Weissman and coll.

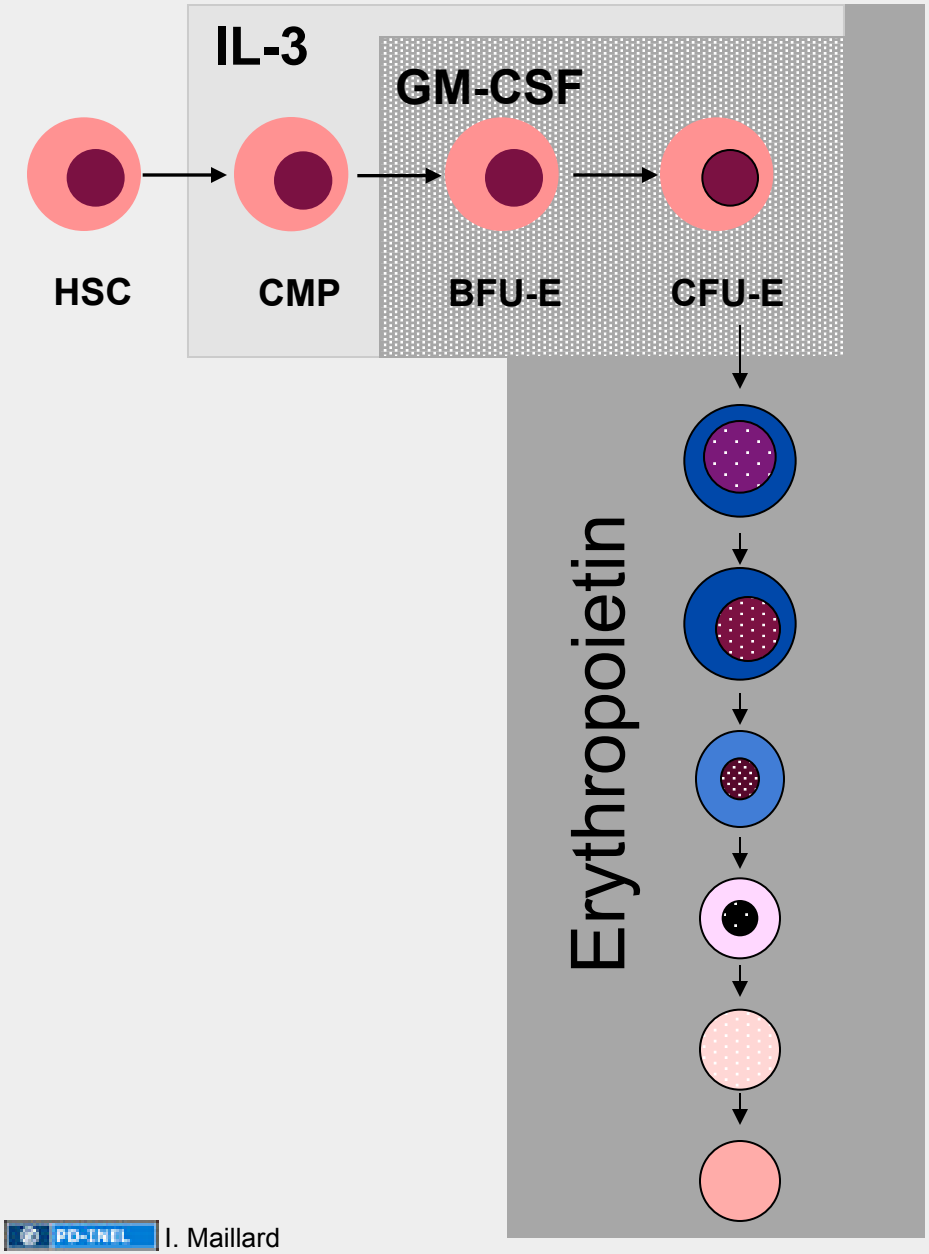
Hematopoietic Stem Cell Differentiation
An Evolving Model

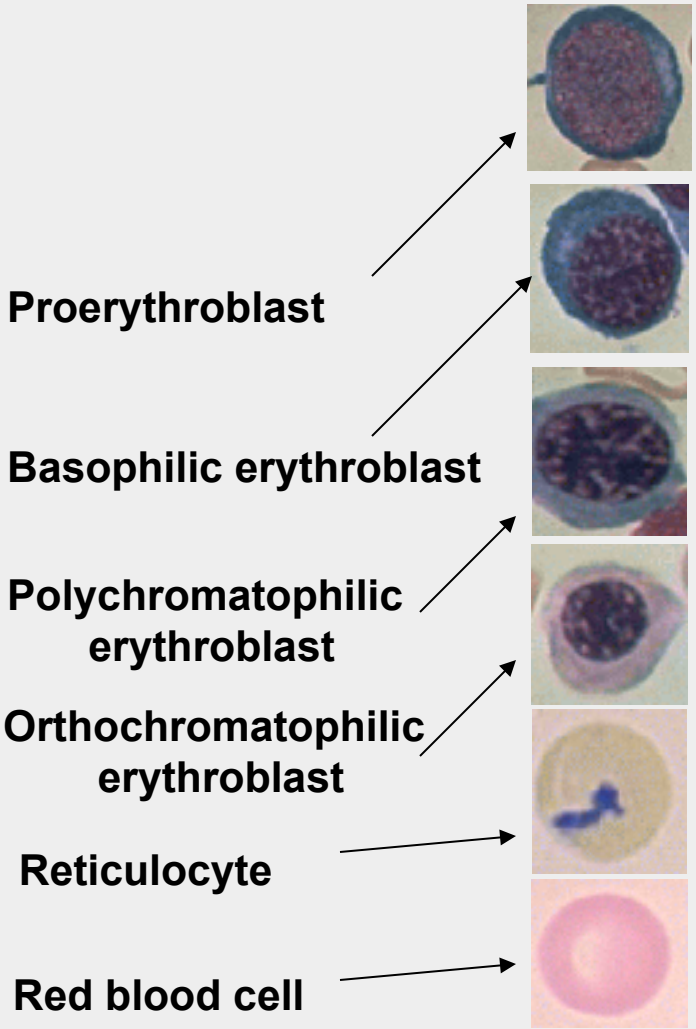


Erythropoiesis

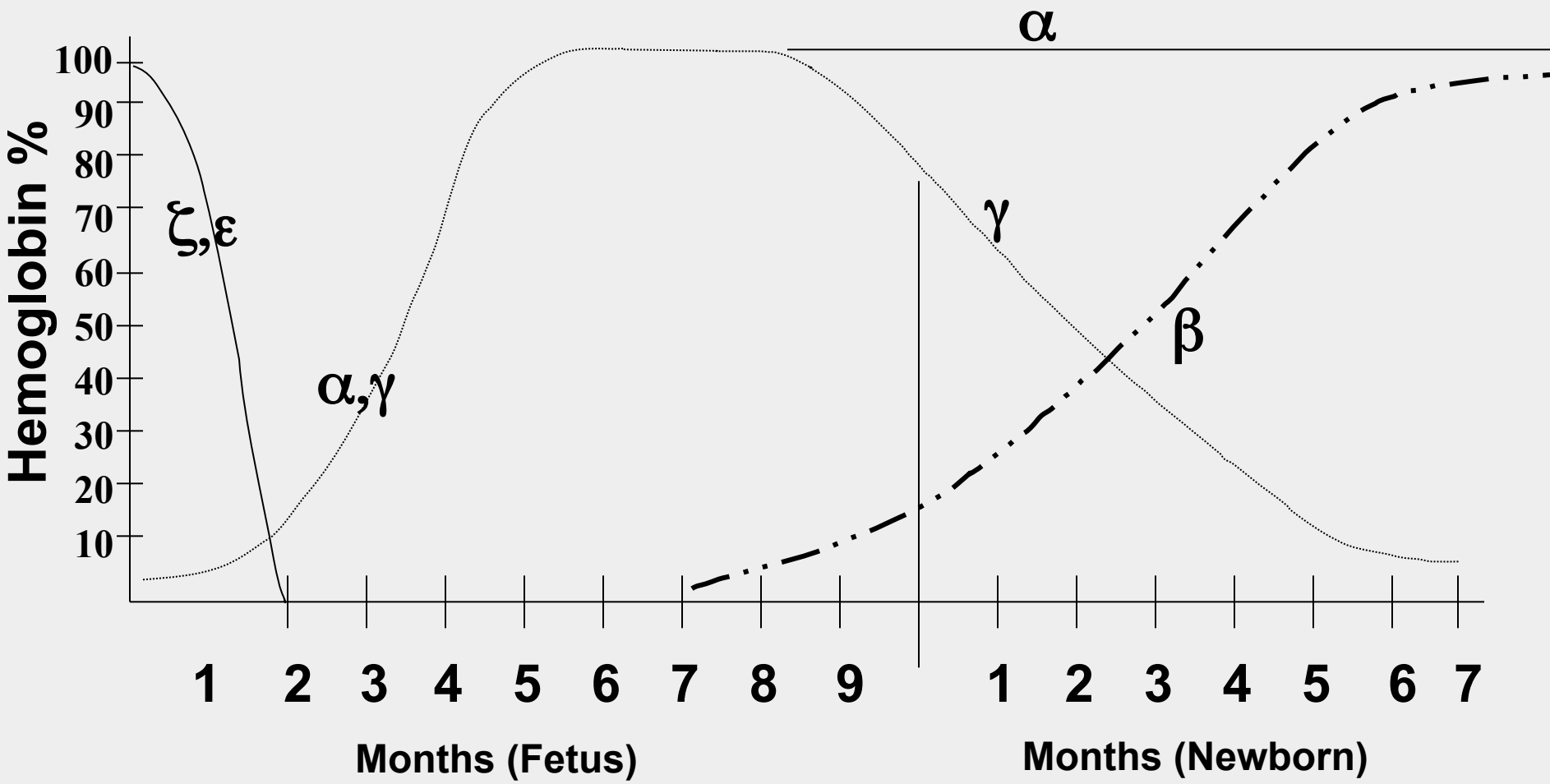
- Development of red blood cells
- Maintains a constant mass of red blood cells
- Major component is hemoglobin
  - Three elements are required for synthesis:
    - Globin protein chains
    - Protoporphyrin
    - Incorporation of iron
- Morphologic characterization of different stages of red blood cell development is tightly coupled to hemoglobin synthesis

ERYTHROPOIESIS





Hemoglobin Synthesis



1-2 months
Gower-1 $\zeta_2\varepsilon_2$
Gower-2 $\alpha_2\varepsilon_2$
Portland $\zeta_2\gamma_2$

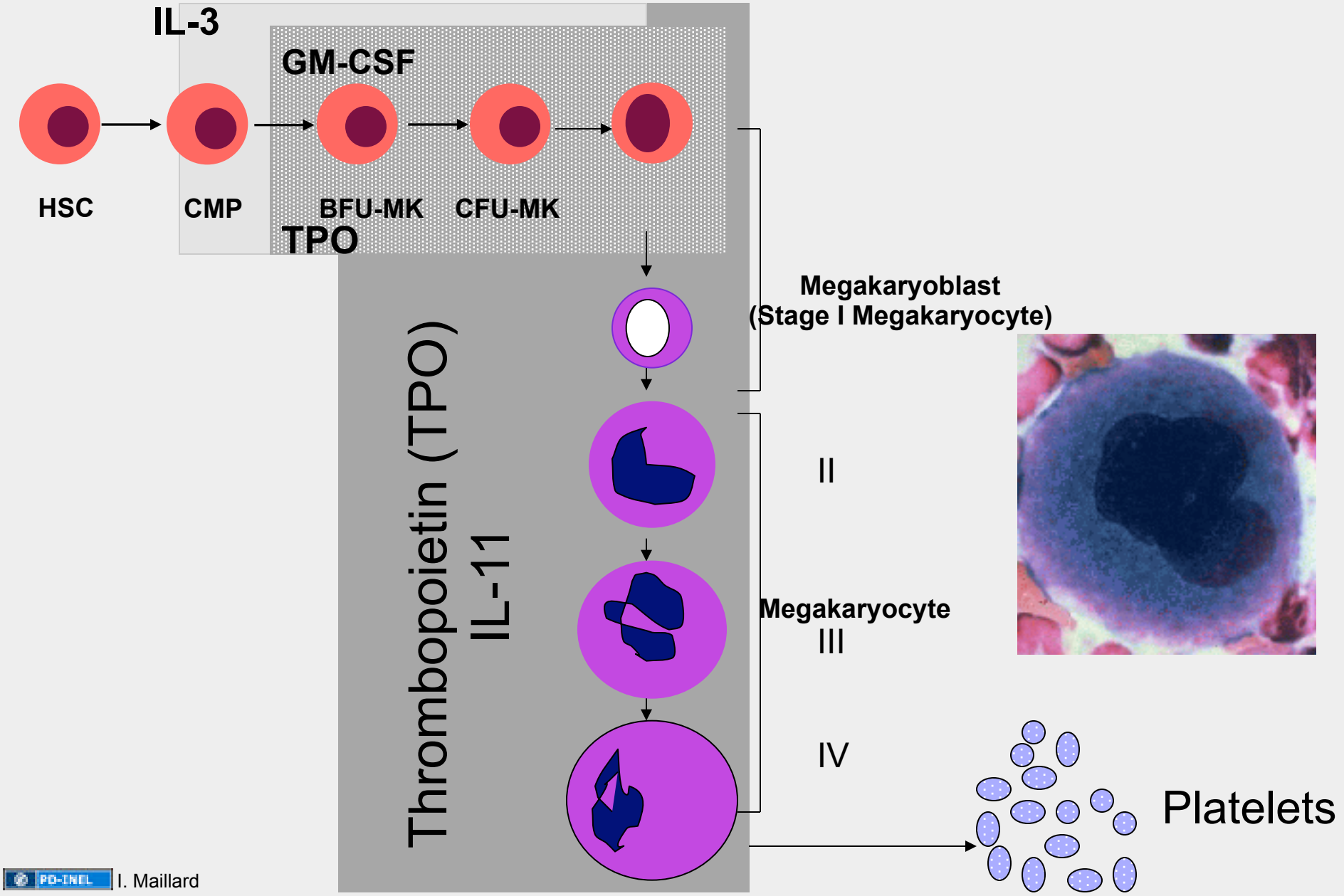
2-10 months
Hemoglobin F
$(\alpha_2\gamma_2)$
$\alpha_2\beta_2$ begins to appear

Birth
$\alpha_2\beta_2$ appears
Hemoglobin F diminishes

Megakaryopoiesis

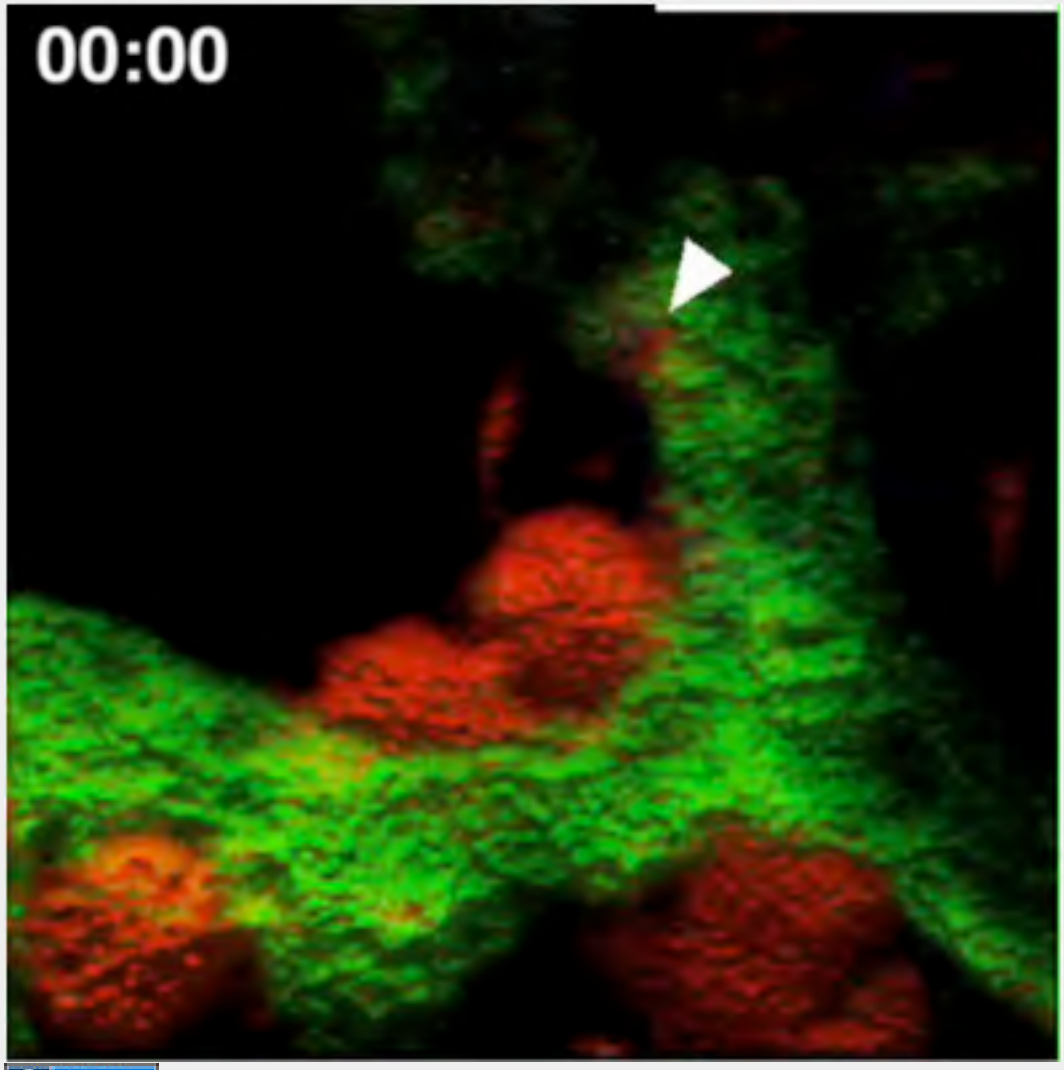
- Generation of platelets that are critical for hemostasis
  - Small anucleate cells
- Development characterized by endomitosis
  - Nucleus divides but cytoplasm does not
- Single polyploid nucleus and increased cytoplasmic volume
  - Cytoplasm becomes demarcated at the end stage of megakaryopoiesis
  - Platelets are shed from mature megakaryocyte and leave behind nucleus

MEGAKARYOPOIESIS



 I. Maillard

Platelet release by megacaryocytes

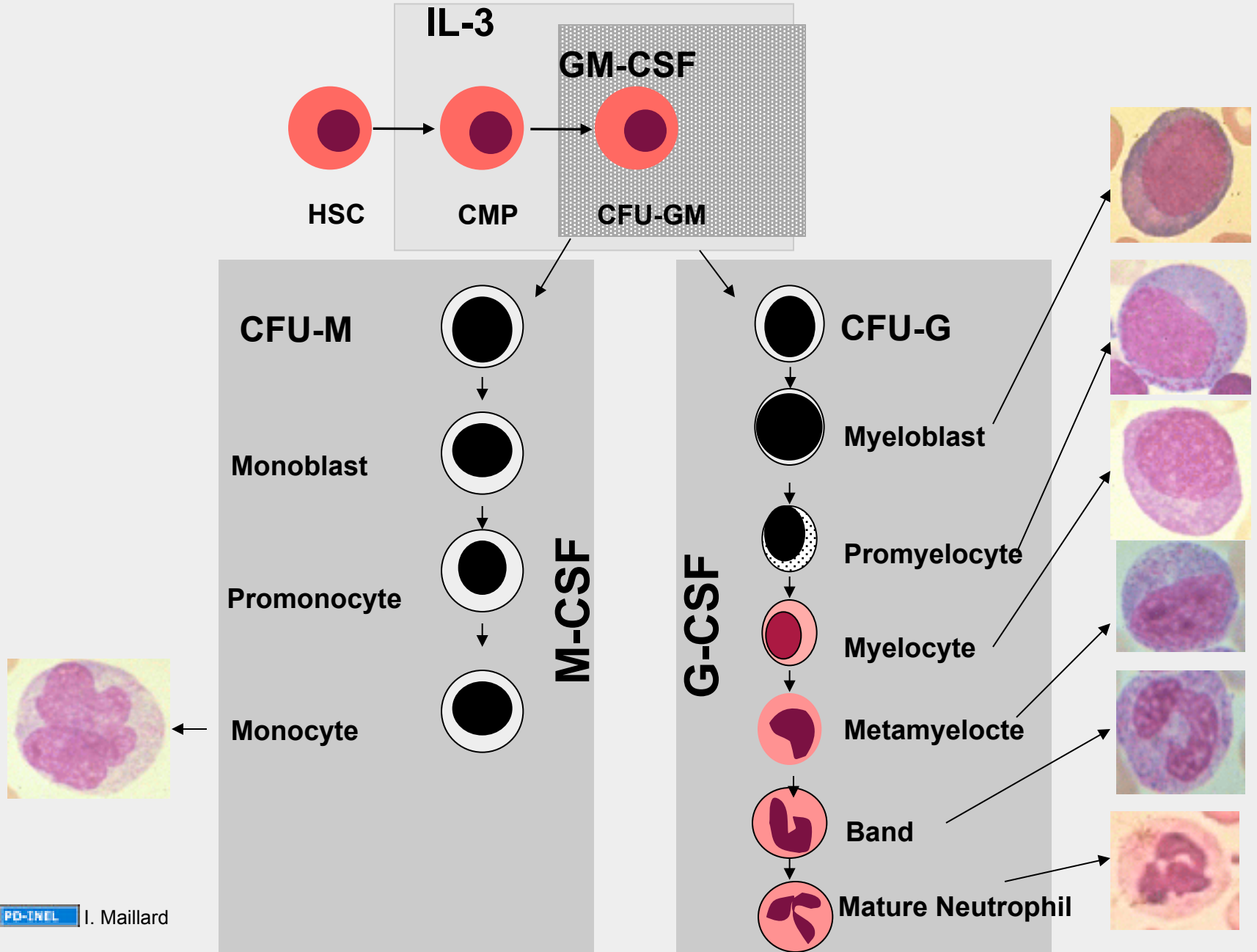


PD-INEL Junt et al., *Science* 2007

Monopoiesis and Granulopoiesis

- Derived from a common progenitor cell (GMP)
- Cells of the monocyte series differentiate into tissue macrophages
- Granulopoiesis involves the generation of cells that have prominent granules: neutrophils, eosinophils and basophils
- Can be enhanced therapeutically
  - G-CSF, GM-CSF…
- Mast cells that have basophilic granules are derived from the HSC and develop in tissues

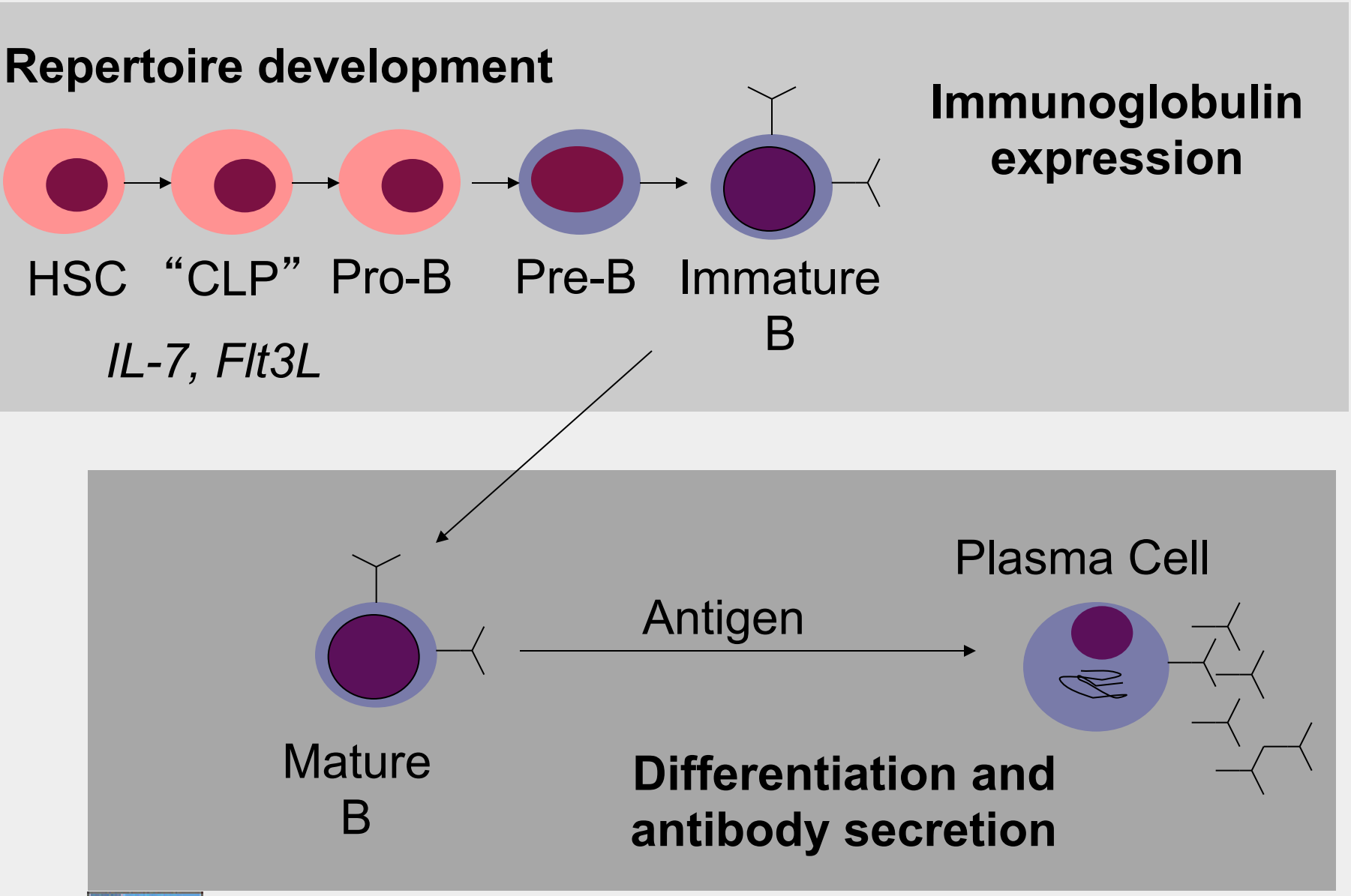
MONOCYTE AND NEUTROPHIL DEVELOPMENT



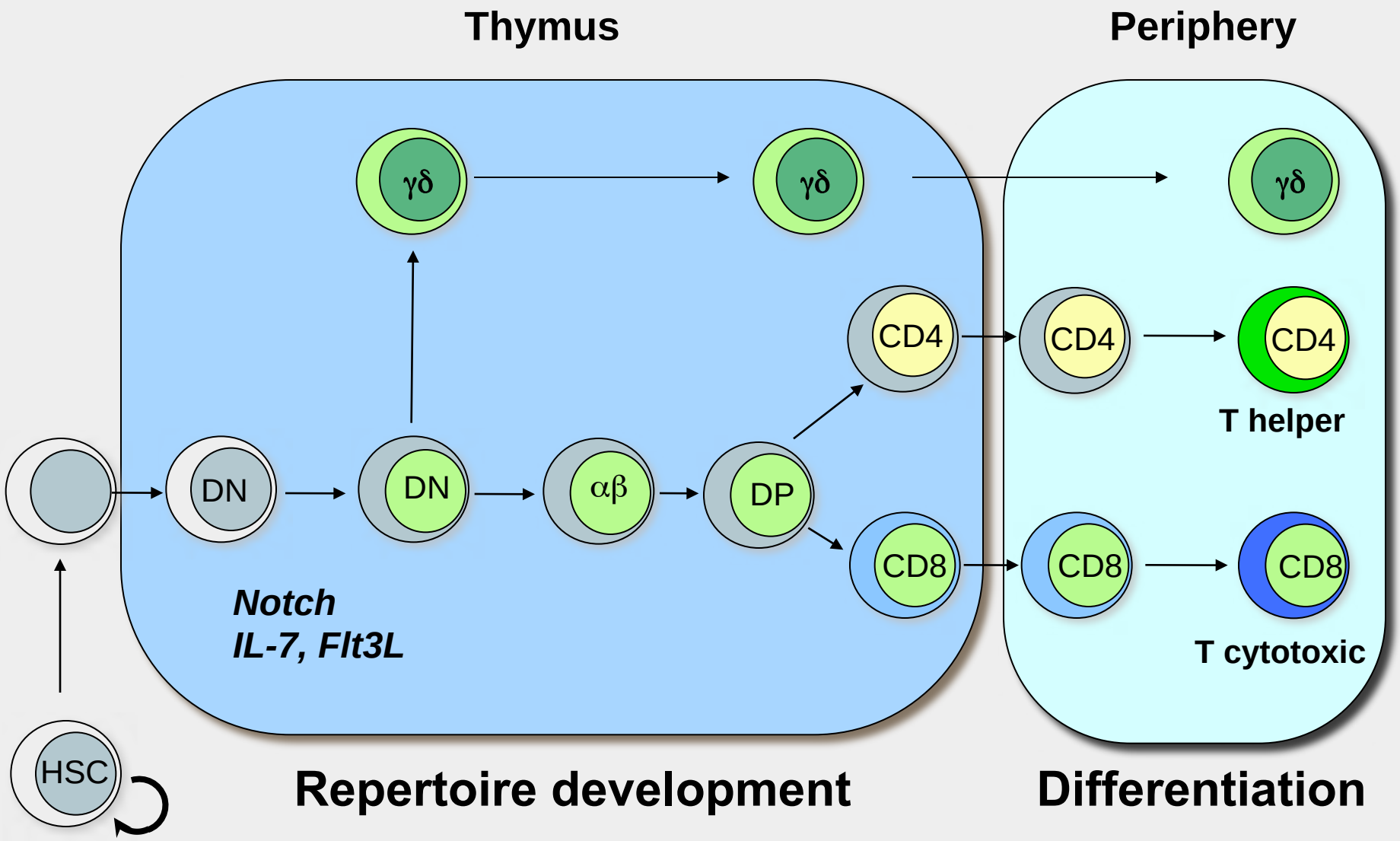
Lymphopoiesis

- Lymphocytes are derived from primitive bone marrow progenitors that activate a “lymphoid” program
  - e.g. immune receptor gene rearrangement (T and B cells)
- Sites of lymphoid development
  - T cells: thymus
  - B, NK cells: bone marrow
- Morphologically similar, but identification with antibodies directed against proteins on the cell surface and flow cytometry
- Heterogeneous populations
  - Function
  - Life span
  - Surface structures
  - Circulation in peripheral organs (spleen, lymph nodes, others)

B CELL DEVELOPMENT



T CELL DEVELOPMENT



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Slide 9: Source Undetermined
Slide 10: Dieterlen-Lièvre, 1975
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