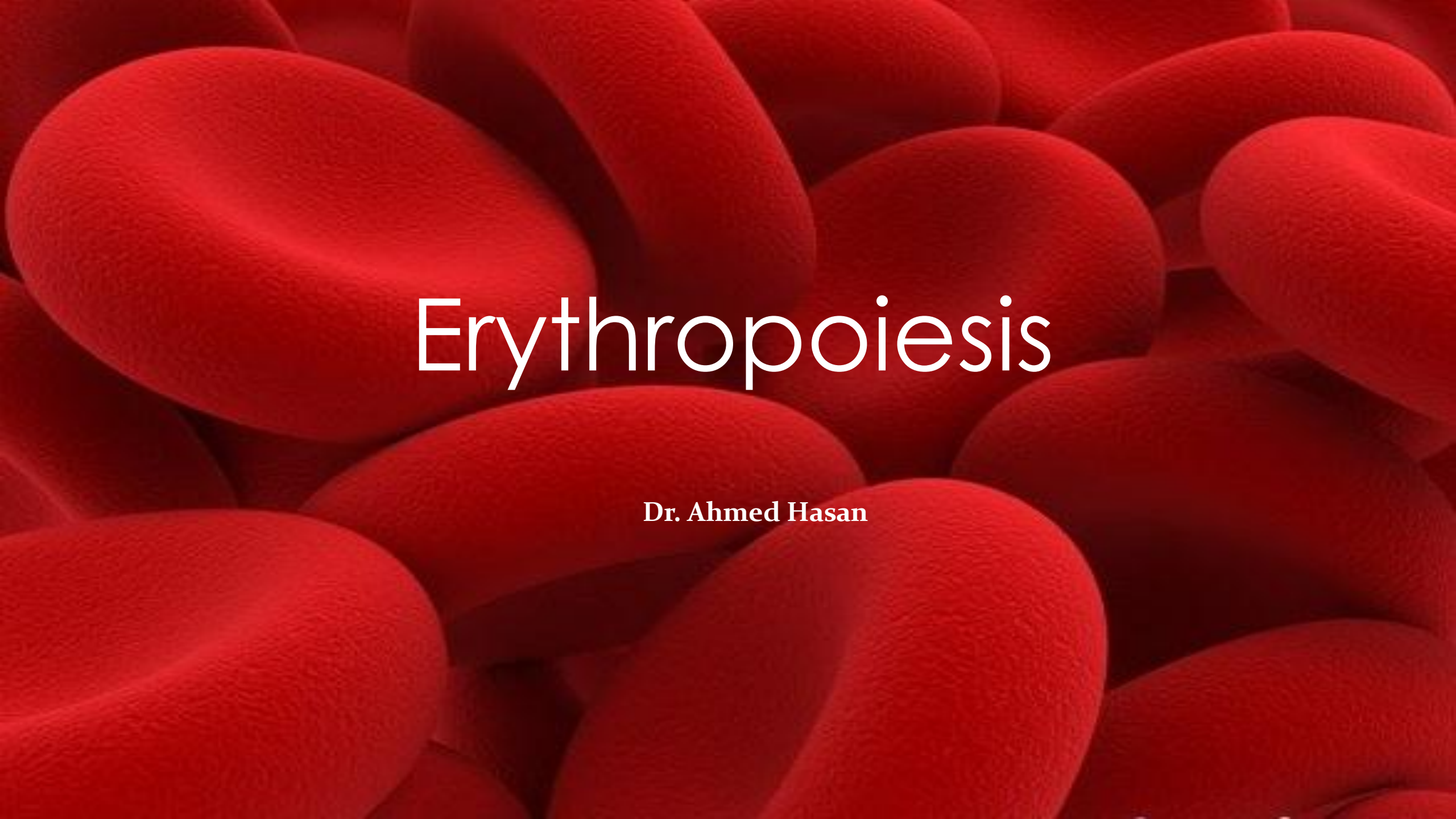


Erythropoiesis

Dr. Ahmed Hasan

Aim of the lecture

- Learning the site of erythropoiesis.
- Understanding the differentiation, development and regulation of RBC progenitors.
- Take a look on the characteristics of mature RBC and its fate.

<u>Question of the lecture:</u>

- Why just 20% of erythrocytes destructed intravascularly?

Site of erythropoiesis before birth

1. Mesoplastic stage: yolk sac produce nucleated RBC at 3rd week of gestation.
2. Hepatic stage: liver form RBC at 6th week of gestation.
3. Myeloid stage: bone marrow form RBC form 3rd month onwards.

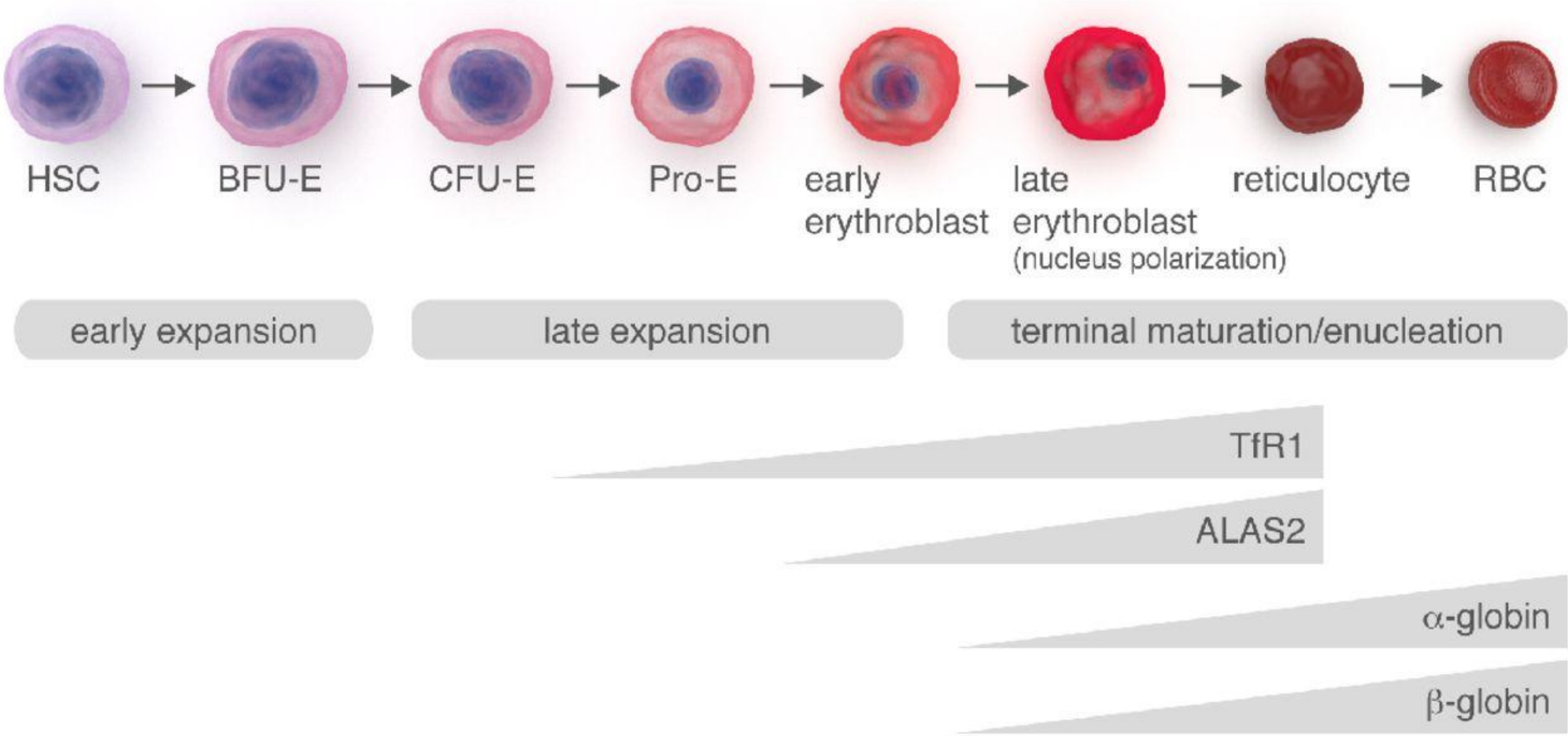
Site of erythropoiesis after birth

- RBC produced from bone marrow from all bones then at adult stage just some bone in the body will produce RBC.

Phases of Erythropoiesis

- commitment of pluripotent stem cell
- erythropoietin (Epo)-independent or early phase of erythropoiesis
- Epo-dependent or late phase of erythropoiesis

Stages of Erythropoiesis



Role of Bone Marrow environment

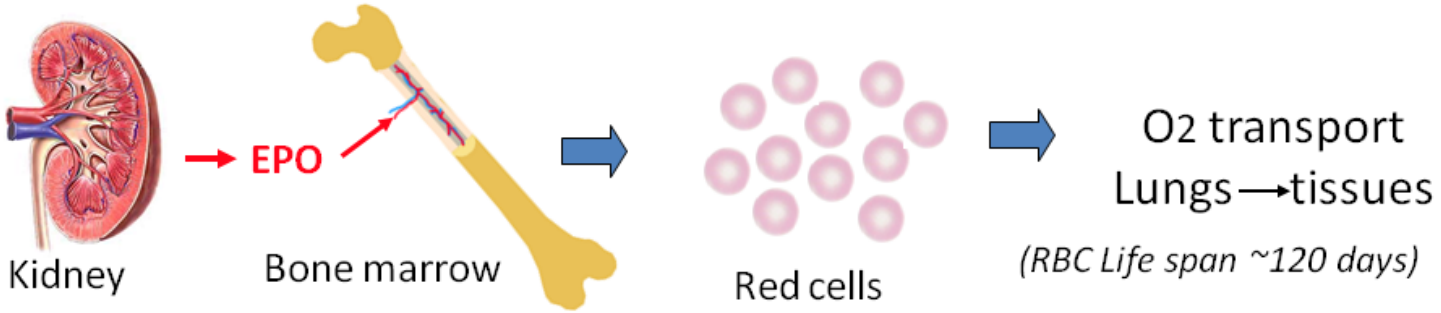
- Cell – cell interaction provide microenvironment for proliferation and differentiation of HSC.
- Extrinsic factors (soluble macromolecules), which interact on the cell surface receptors and initiate signaling pathways.

Role of erythropoietin in erythropoiesis

- The first phase of CFU-E differentiation is highly Epo dependent.
- Binding of Epo to Epo receptors (EpoRs) on the surface of erythroid progenitors triggers activation of multiple intracellular signal transduction pathways, including the Stat5 (Signal transducer and activator of transcription 5), Phosphoinositide -3 kinase/Akt, and Shc/Ras/Mitogen-Activated Kinase (MAPK) pathways.

Erythropoietin

Erythropoietin (EPO) is produced in the kidney, regulates the daily production of 200 billion red blood cells daily, and is inducible by low oxygen or hypoxia.



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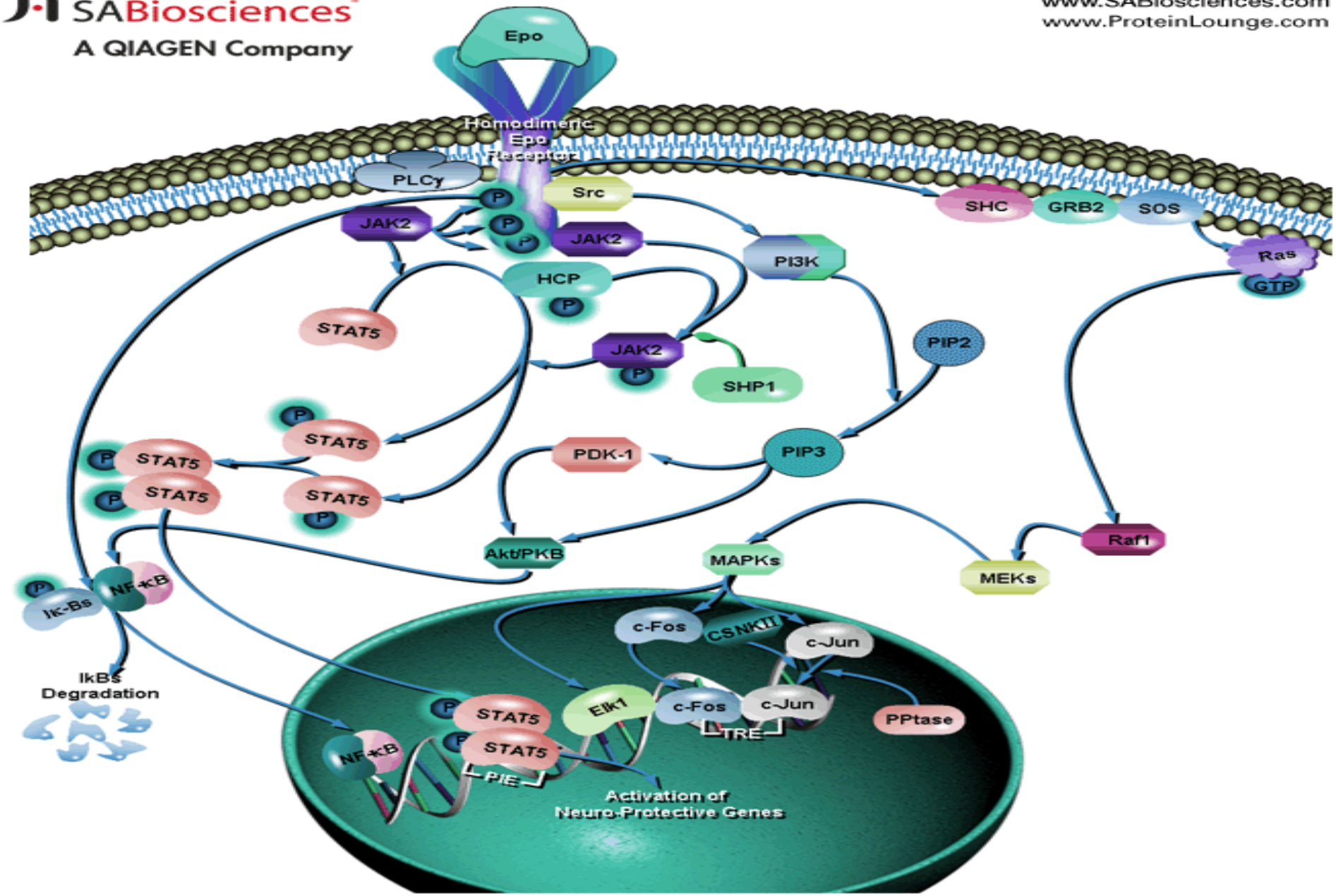
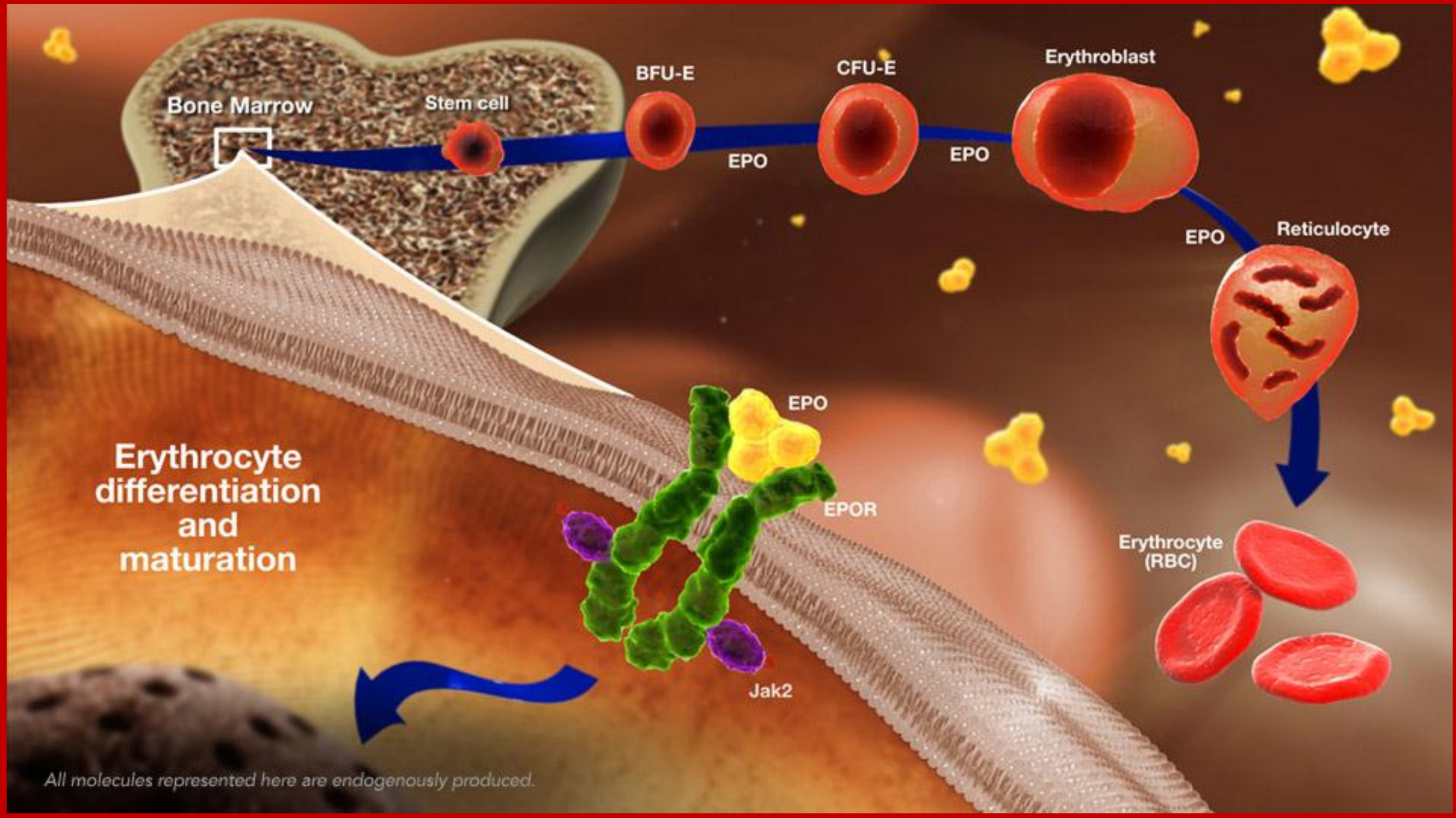



Bone Marrow
Stem cell
BFU-E
CFU-E
Erythroblast
EPO
EPO
EPO
Reticulocyte
EPO
EPOR
Jak2
Erythrocyte
(RBC)
Erythrocyte differentiation and maturation
All molecules represented here are endogenously produced.

Mature Erythrocyte

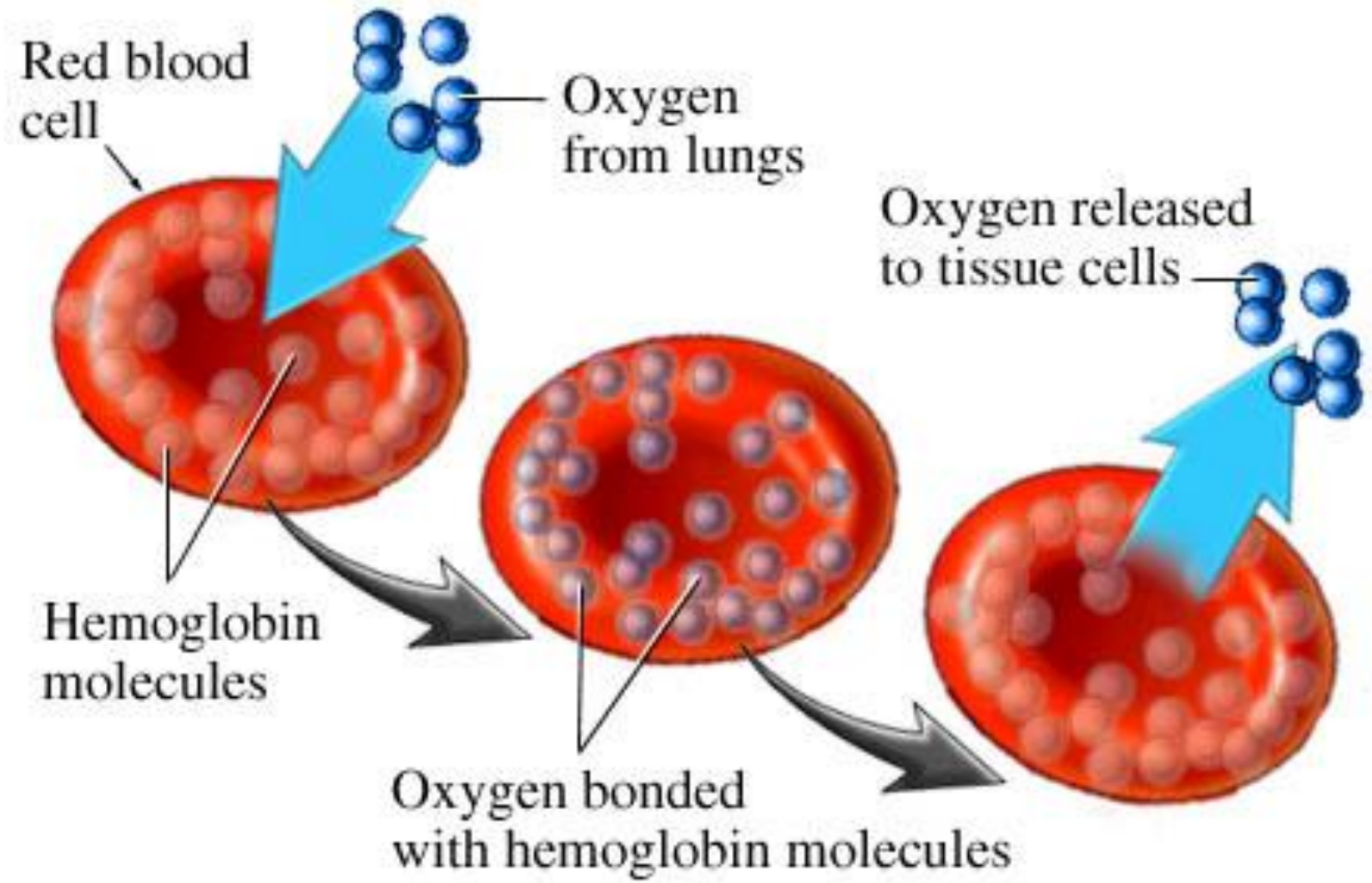
- Lacking a nucleus, mitochondria, or ribosomes, the red cell is unable to synthesize new protein, carry out the oxidative reactions associated with mitochondria, or undergo mitosis.
- More than 95% of the cytoplasmic protein is hemoglobin.
- The remainder includes those enzymes required for energy production and for the maintenance of hemoglobin in a functional reduced state.

Hemoglobin

- Vertebrate hemoglobin is a conjugated protein with a molecular weight near 64.5 kDa.
- In order to function as the primary medium of exchange of oxygen and carbon dioxide, hemoglobin must fulfill the four requirements:

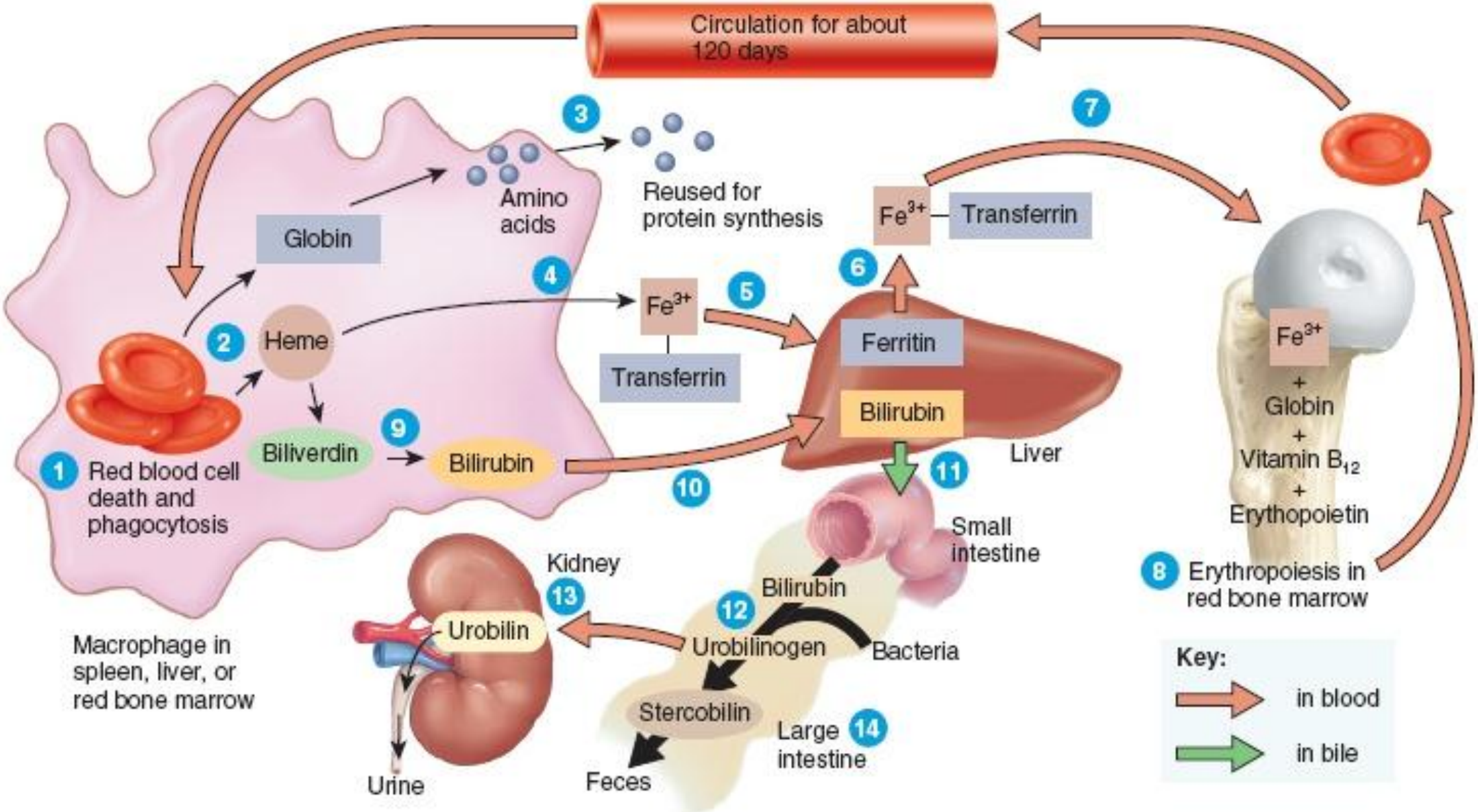
1. it must be capable of transporting a large quantity of oxygen.
2. it must be highly soluble.
3. it must take up and release oxygen at "appropriate pressures,"
4. it must also be a good buffer.

Gas Transportation



Cell Destruction

- Each day approximately 1% of the body's red cells (3×10^9 cells/kg) die and are replaced by reticulocytes.
- The explanations have included changes in red cell enzymes and energy depletion with age; alterations in calcium balance; changes in membrane surface charge; oxidative injury; development of autologous antibodies to membrane antigens; and changes in membrane phospholipid asymmetry.
- Under normal conditions, 80% to 90% of this normal erythrocyte destruction occurs without release of hemoglobin into plasma. Thus, most of the destructive process is considered to be *extravascular*, within macrophages of the spleen and, to a lesser extent, the liver and bone marrow.
- Approximately 10% to 20% of normal destruction is estimated to occur *intravascularly*.


Circulation for about 120 days
3
Amino acids
Reused for protein synthesis
7
Globin
4
Fe^{3+}
5
Fe^{3+} — Transferrin
6
2
Heme
Transferrin
Ferritin
Bilirubin
Liver
Fe^{3+} + Globin + Vitamin B_{12} + Erythopoietin
1
Red blood cell death and phagocytosis
Biliverdin
9
Bilirubin
10
11
Small intestine
8
Erythropoiesis in red bone marrow
Kidney
13
Urobilin
Bilirubin
12
Urobilinogen
Bacteria
Macrophage in spleen, liver, or red bone marrow
Stercobilin
Large intestine
14
Urine
Feces
Key:
in blood
in bile