Therapeutic Perspectives in Ineffective Erythropoiesis

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Imagine institute

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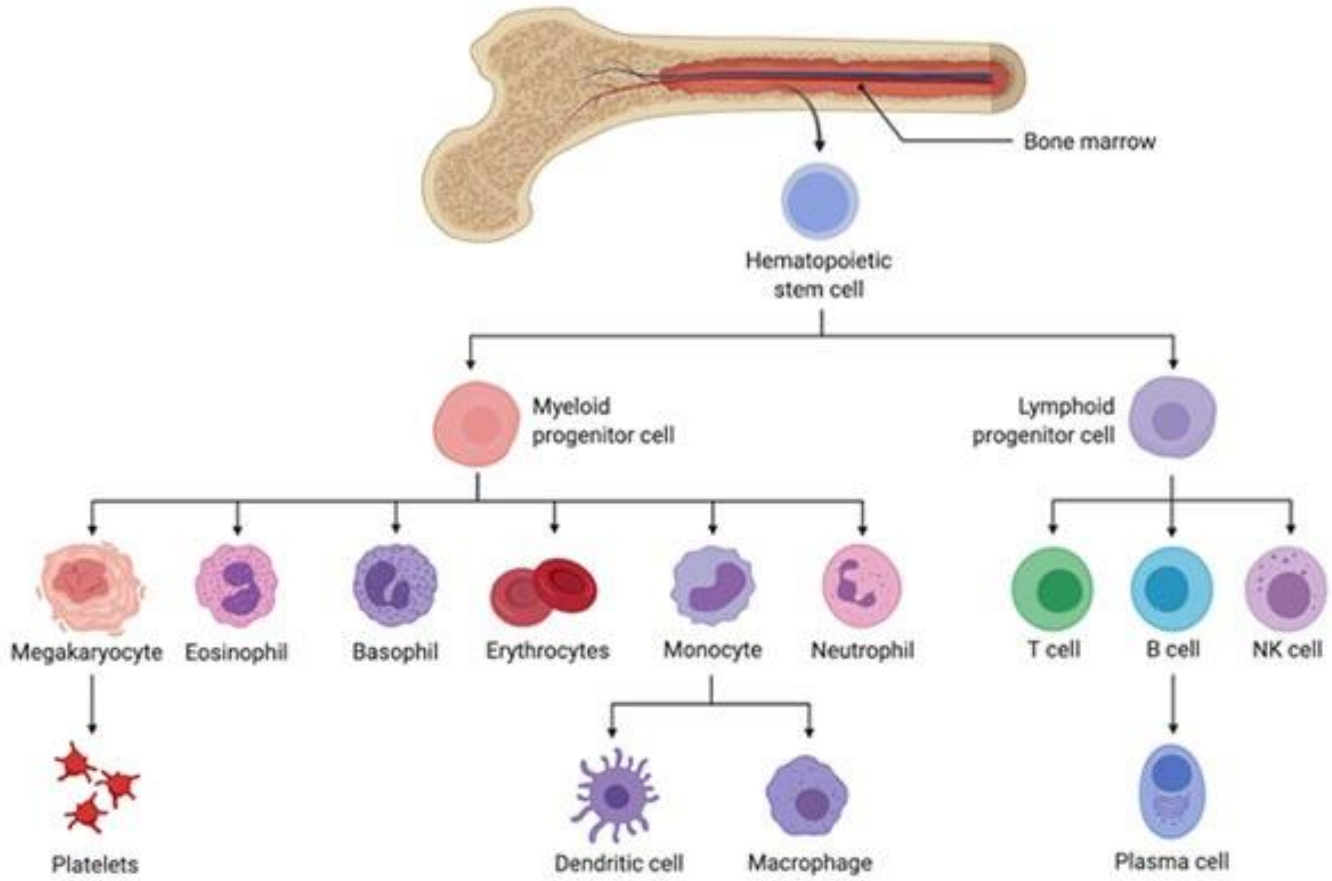
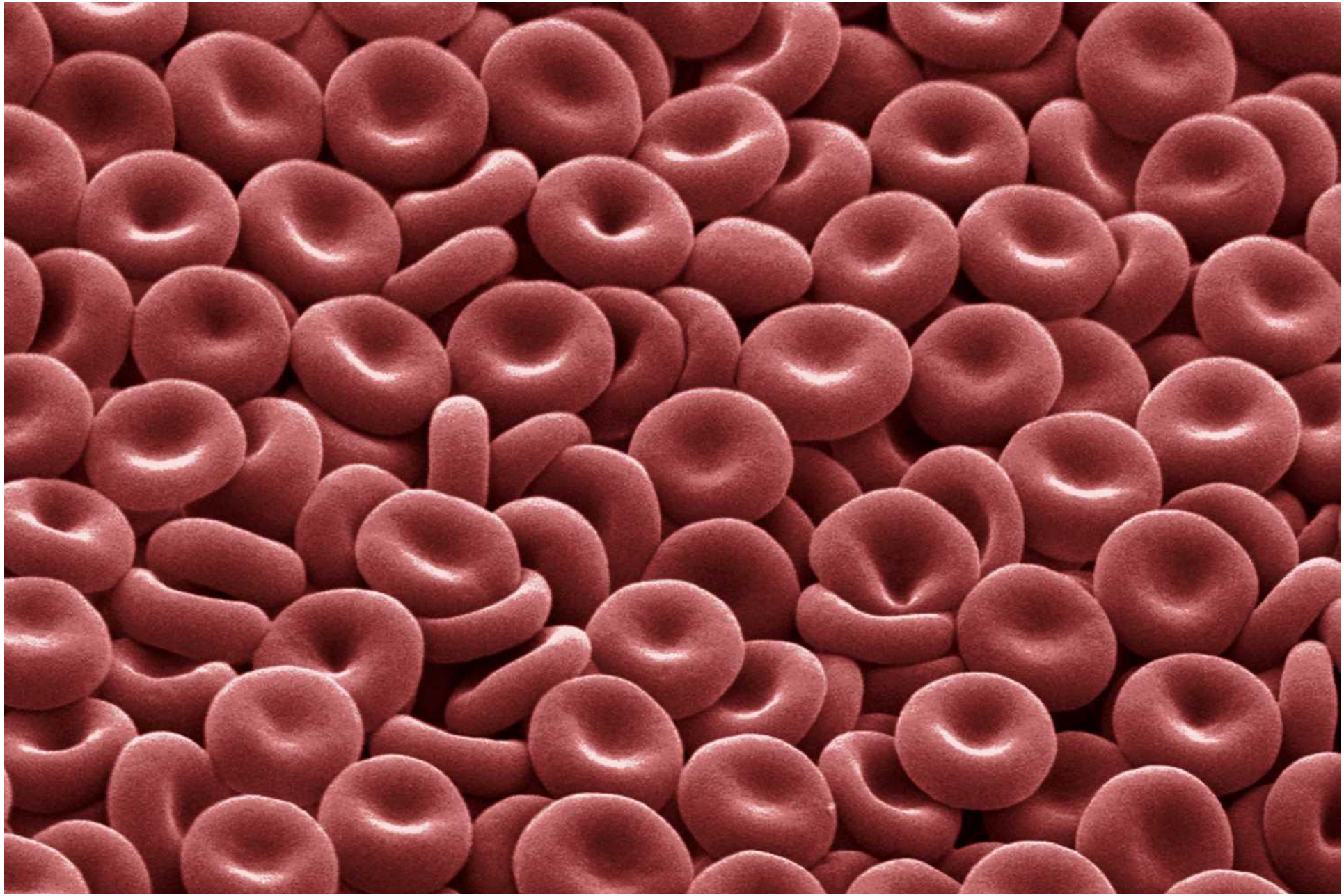
Conflicts of Interest

BMS research fund

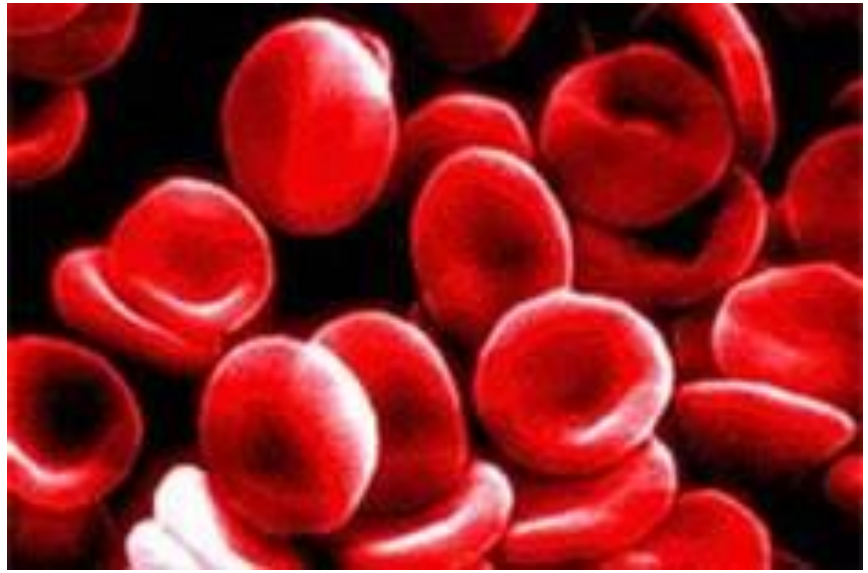
Bristol Myers Squibb

Hematopoiesis



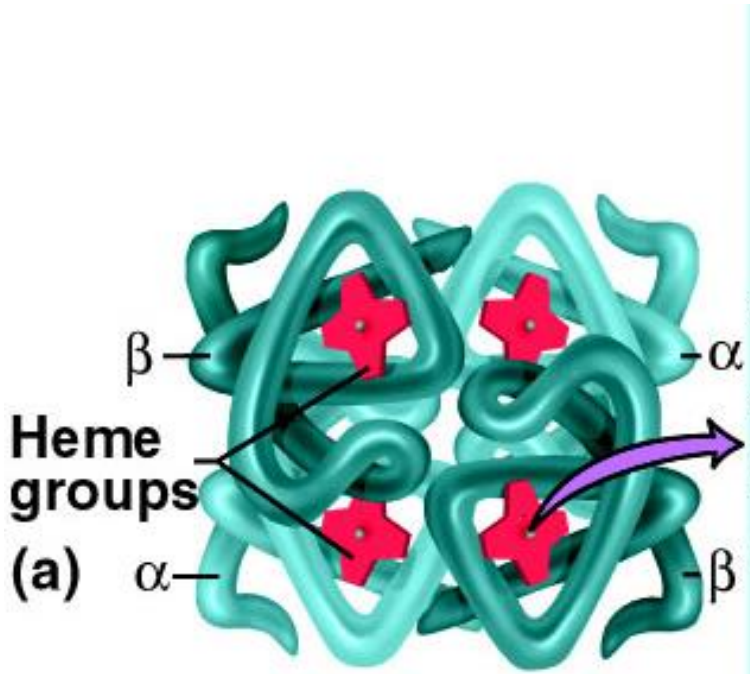


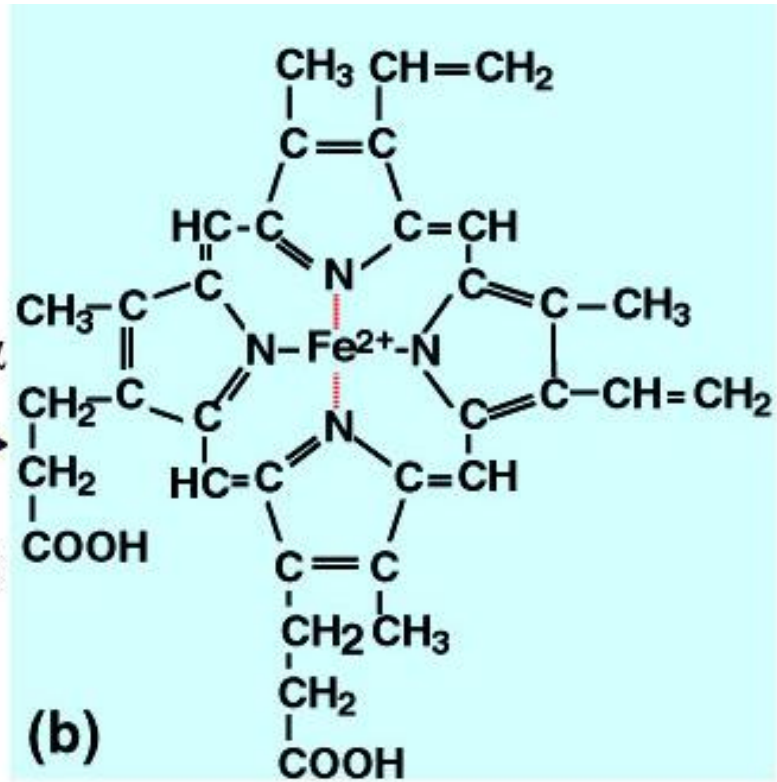
The Mature Erythrocyte I
(This is not your average cell)



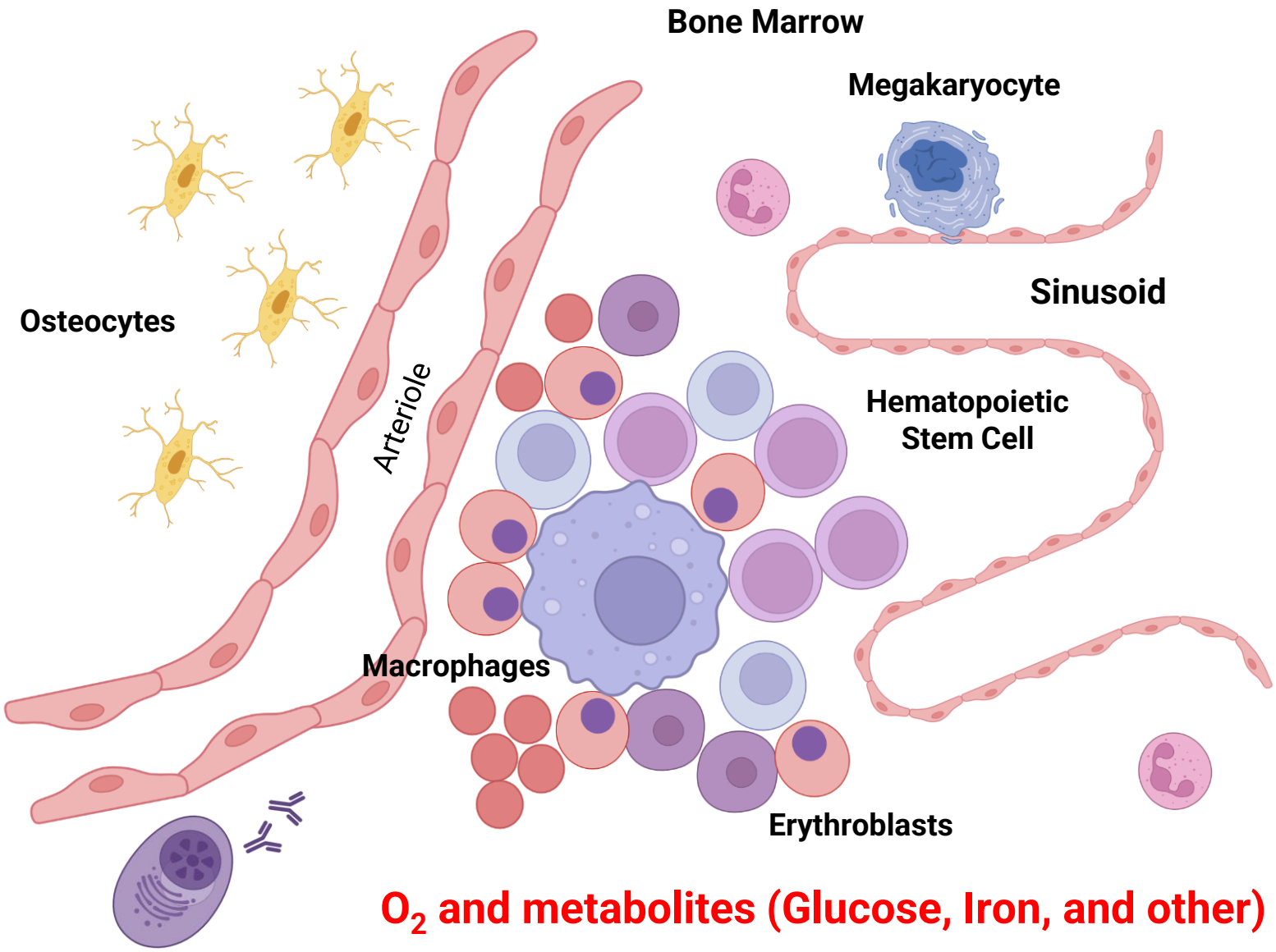
- One quarter of cells in human body are RBCs
- 2.4 million erythrocytes produced per second
- Develop in the bone marrow
- 7–8 microns in size (μm)
- Circulate for about 100–120 days
- Each cycle of circulation takes 20 seconds
- Erythrocyte components recycled by macrophages
- Must maintain slippery exterior
- Must maintain integrity in circulation

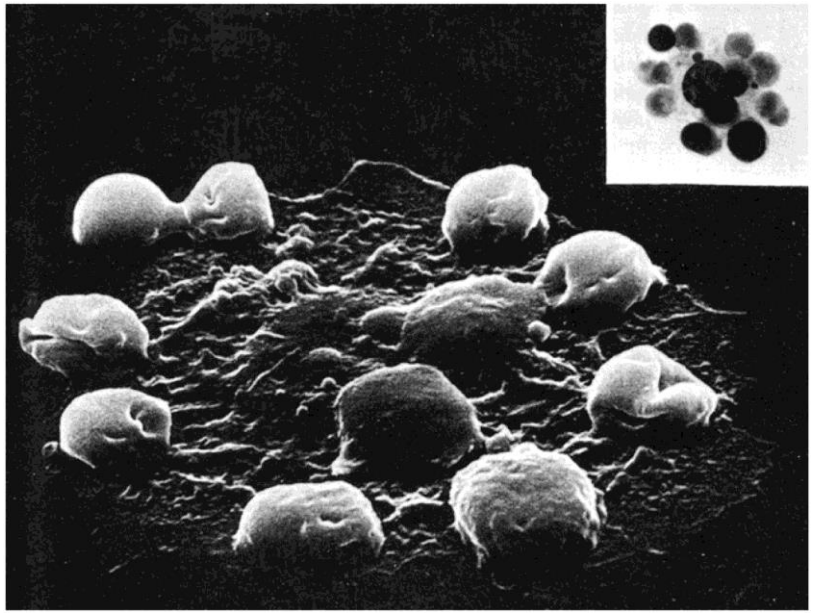
Hemoglobin


β
α
Heme
groups
(a)
α
β


CH3 CH=CH2
C=C
HC-C
C=CH
N
CH3-C
C
C
C-CH3
N-Fe2+-N
CH2-C
C
C
C-CH=CH2
N
CH2
HC=C
C=CH
COOH
C=C
CH2 CH3
CH2
COOH
(b)

Erythropoiesis occurs in the bone marrow niche





Erythroblastic islands
Marcel Bessis 1958

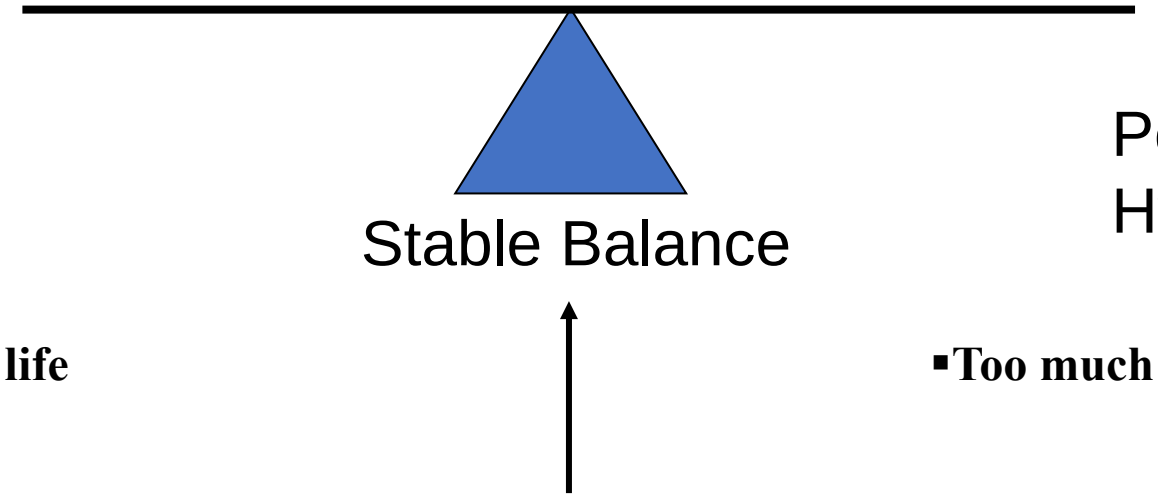
O_2 and metabolites (Glucose, Iron, and other)

Regulation of Erythropoiesis

Fine regulation of erythropoiesis is a matter of life and death

10^{11} erythrocytes /day

Iron, vitamines (B12, B9),
Hormones (T4, Androgens, IGF-1,..)



Anemia
Hypoxia

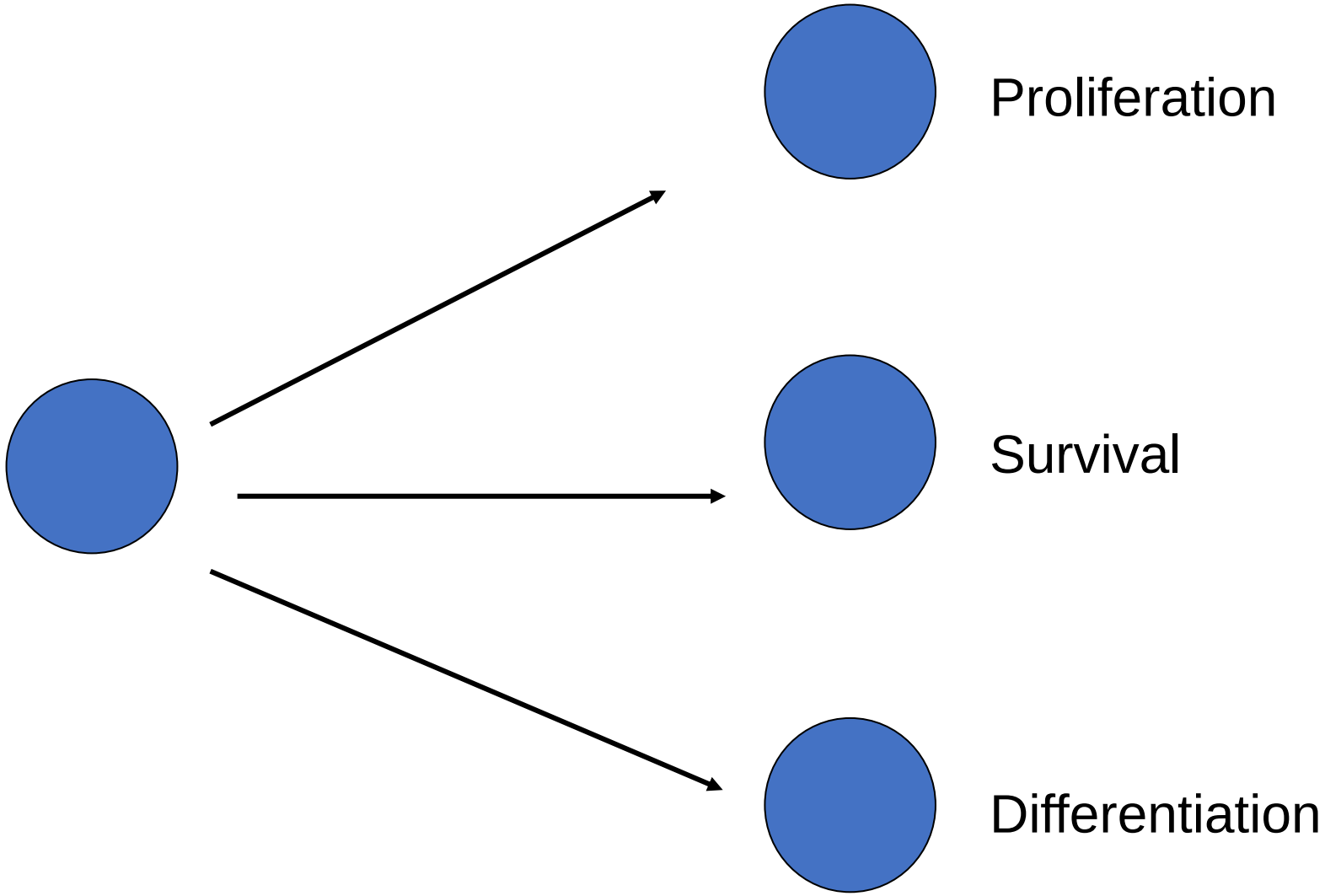
Stable Balance

Polycythemia
Hyperviscosity

- **No red cell = No life**
- **Too much red cells = No life**

Stroma
Cytokines +++, Others ?

ROLES OF CYTOKINES



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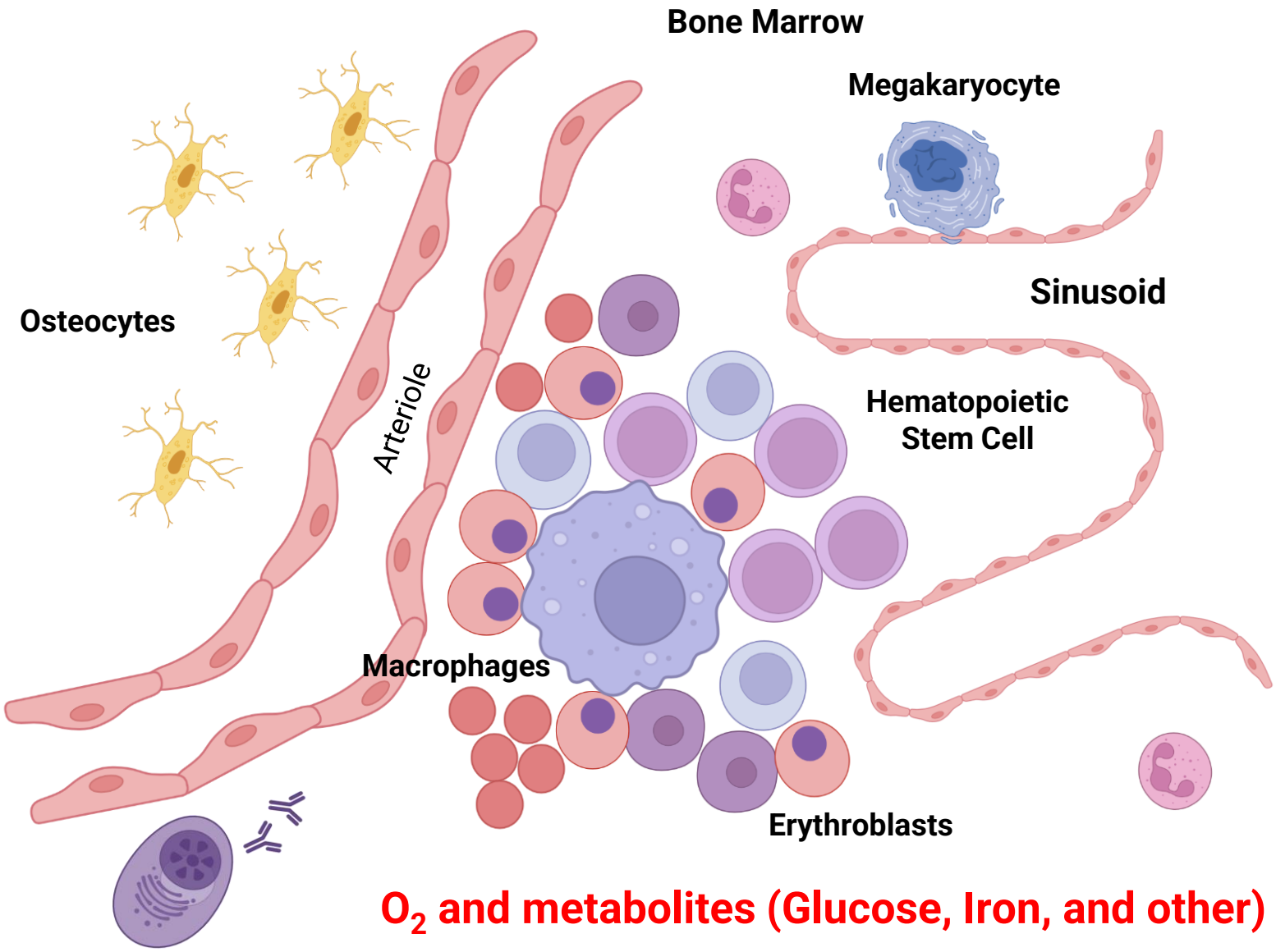

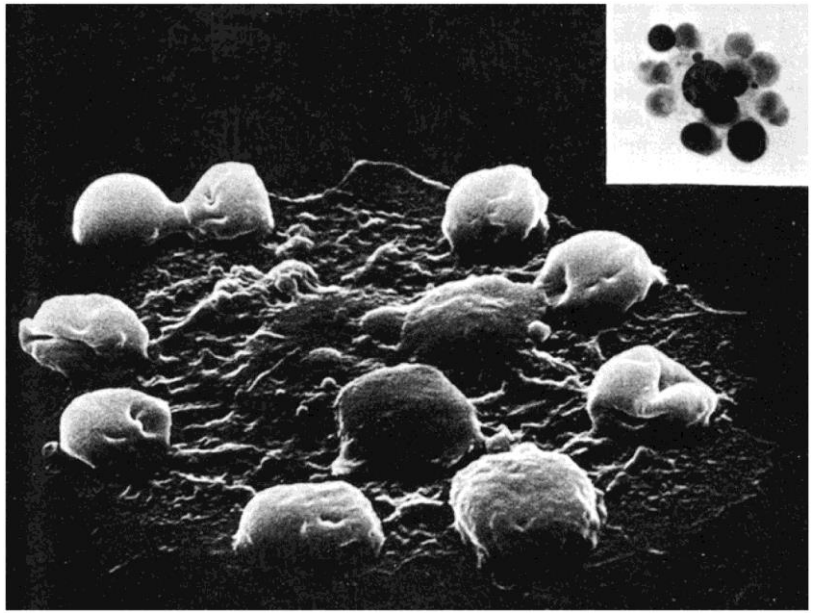

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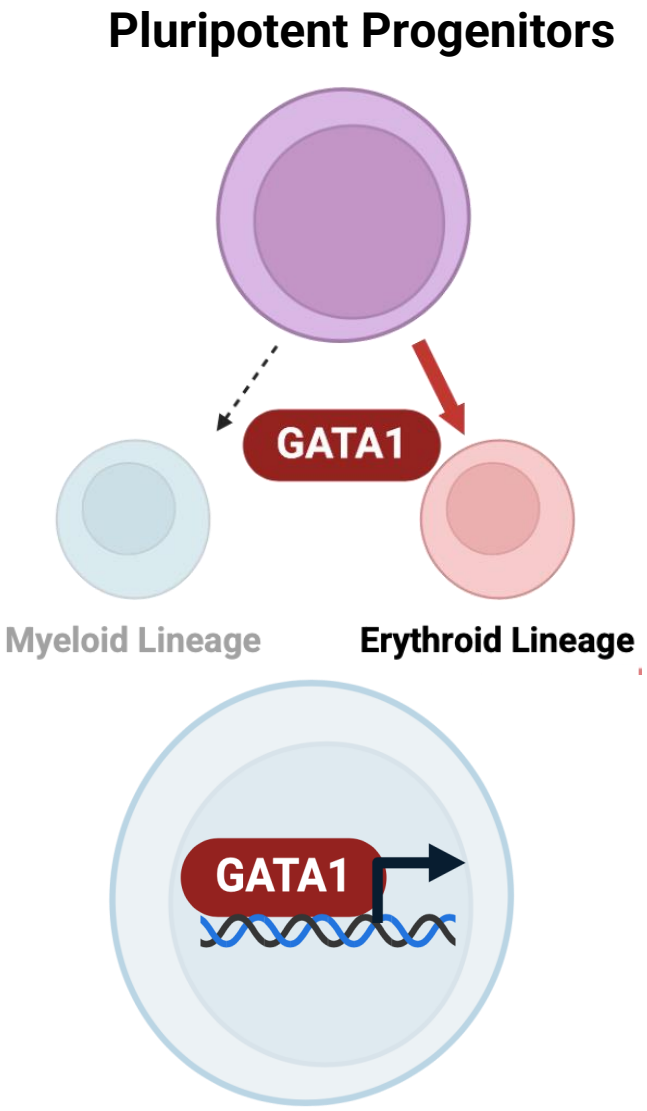
O_2 and metabolites (Glucose, Iron, and other)

GATA1: The master transcriptional factor regulator of erythropoiesis



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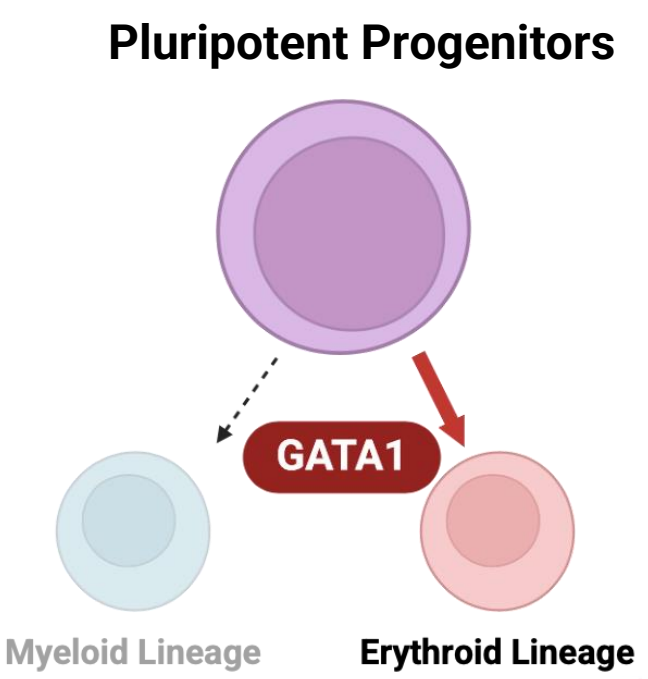
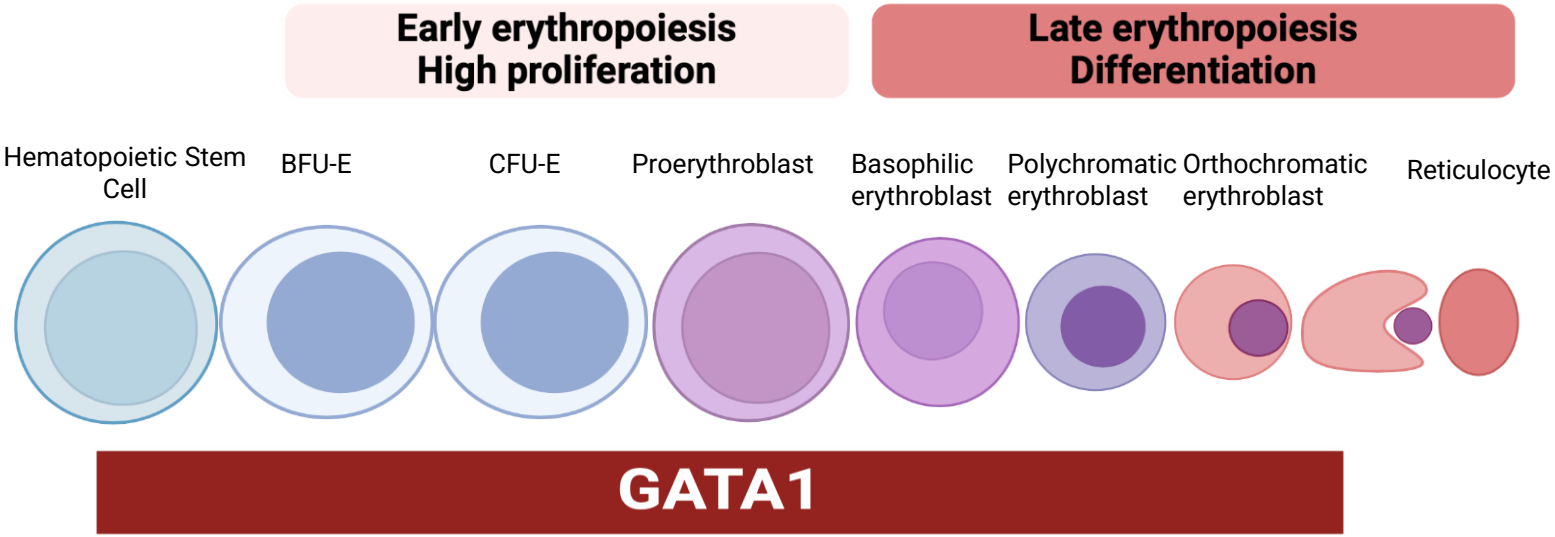
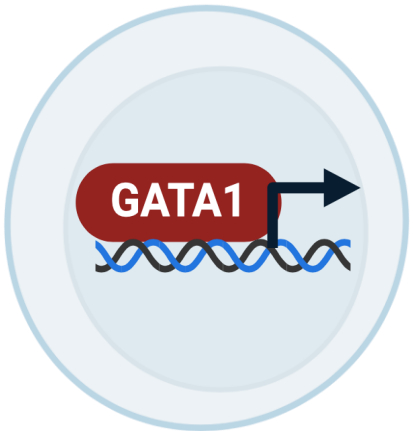
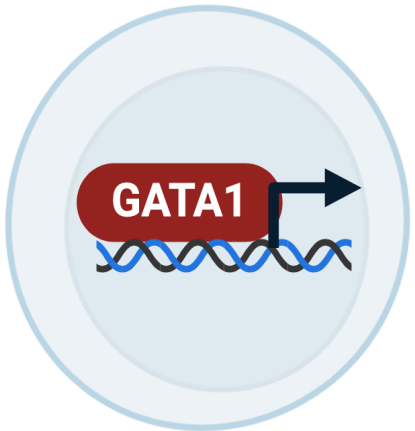






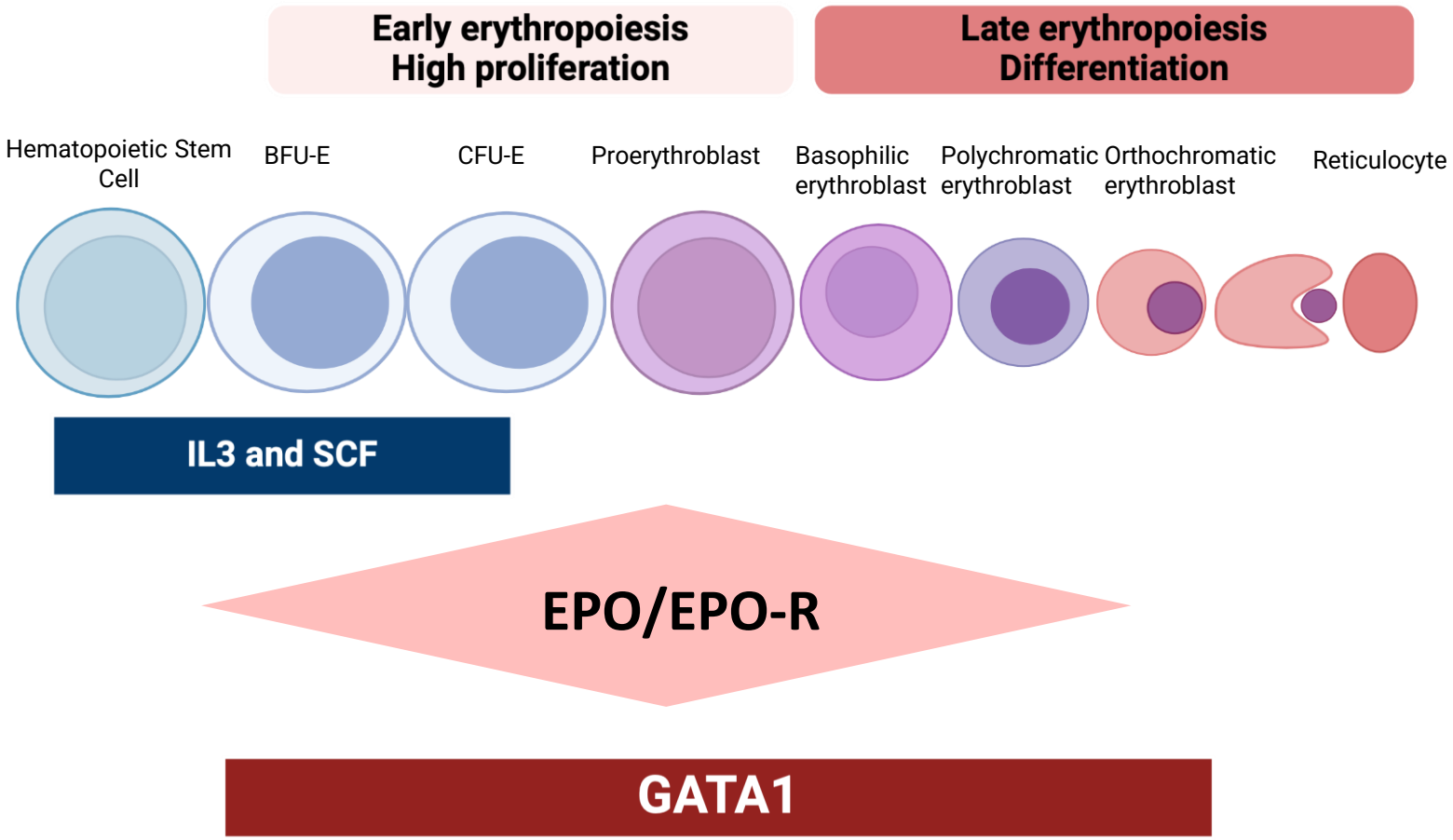
Erythroid Commitment



Erythroid Differentiation and Survival

Erythroid genes:
Hemoglobin, GPA, EPO-R, metabolism

EPO is the main regulator of erythropoiesis, allowing the GATA1 induced differentiation program



Bhoopalan SV et al. 2020

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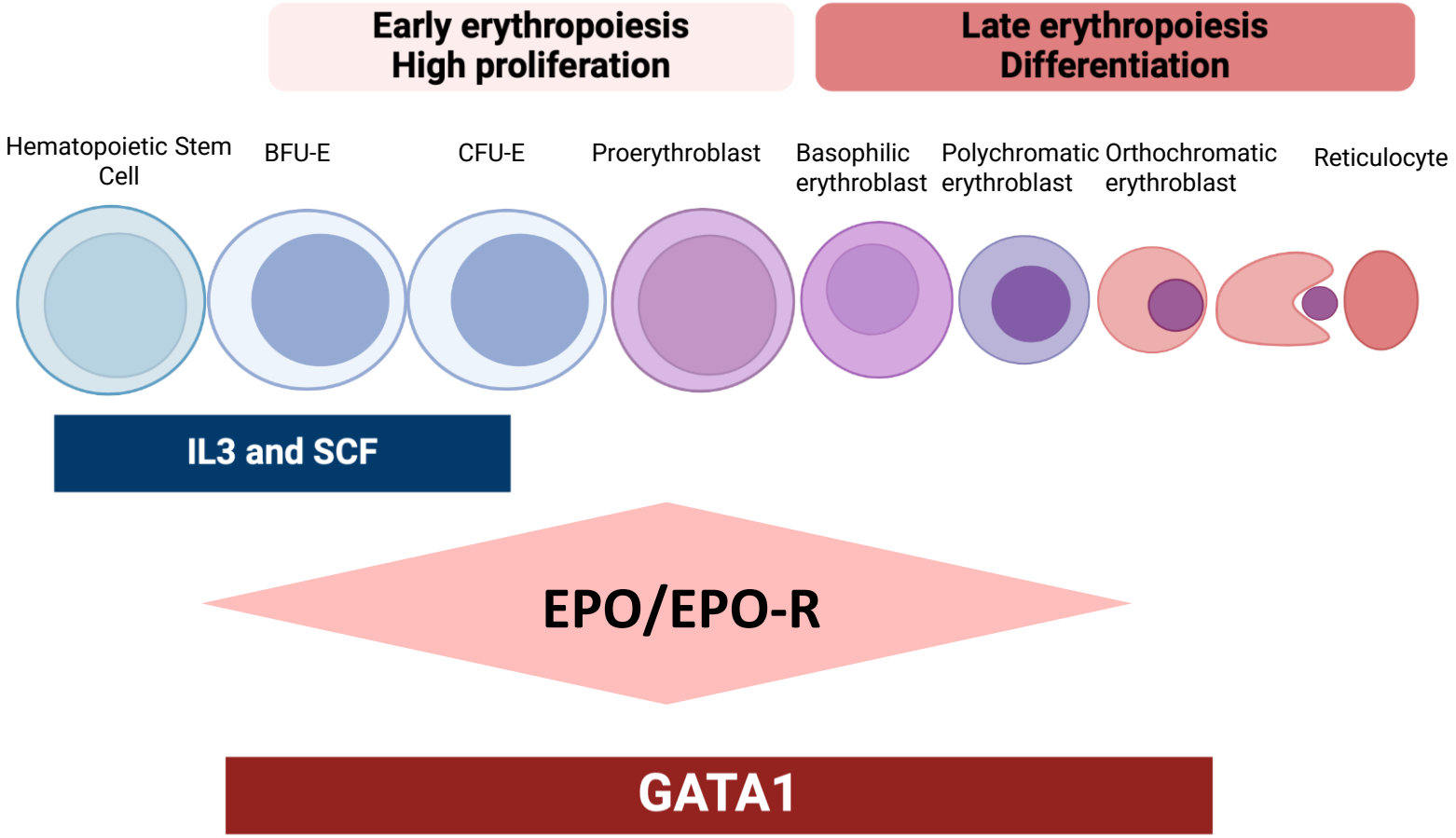
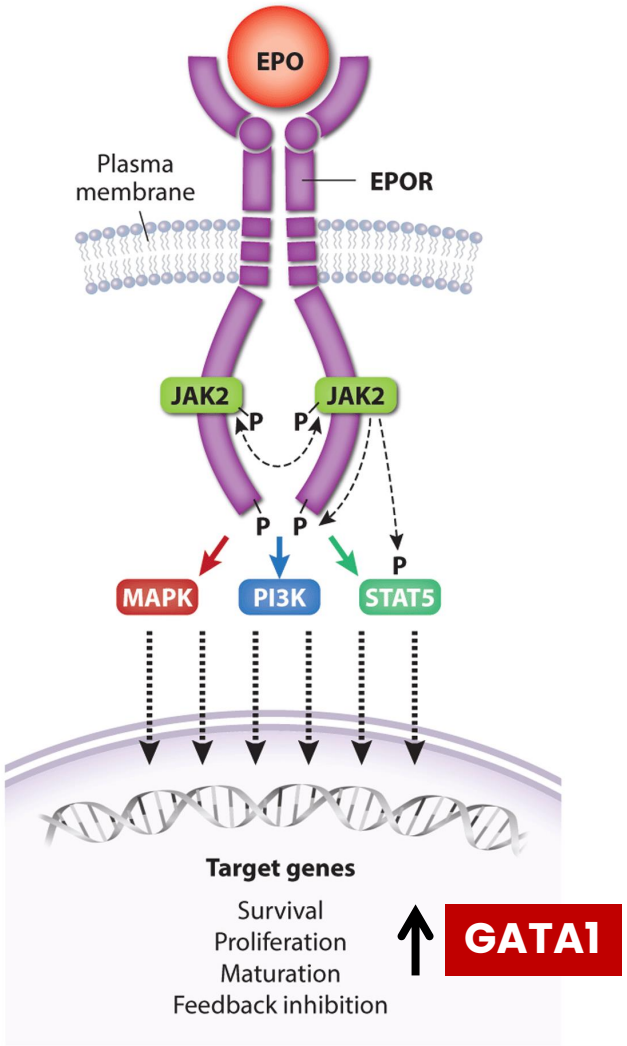
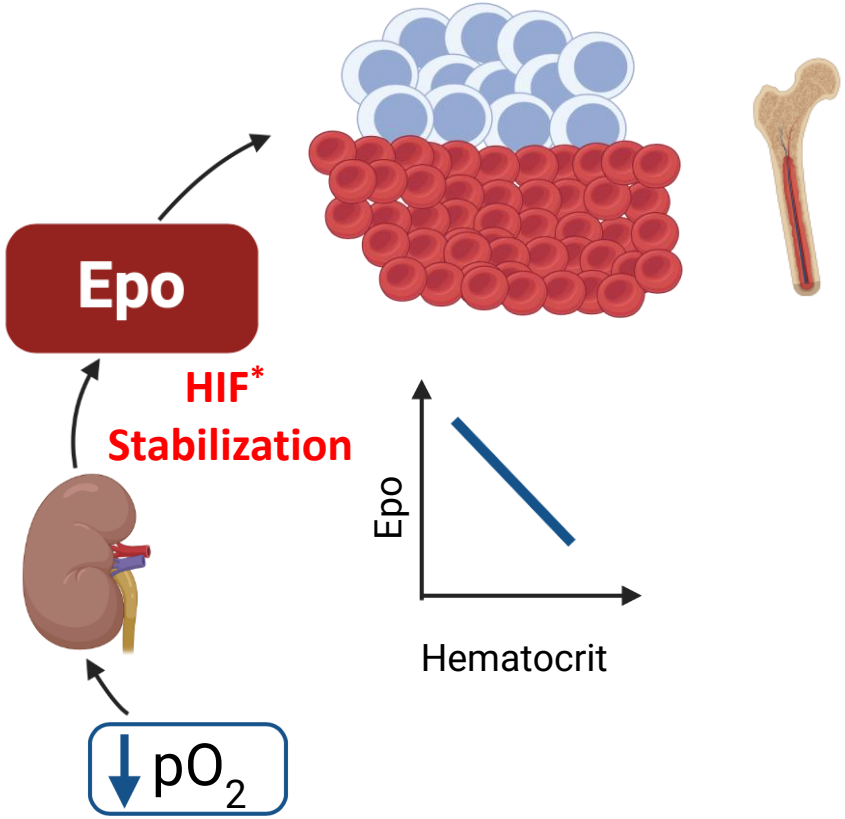
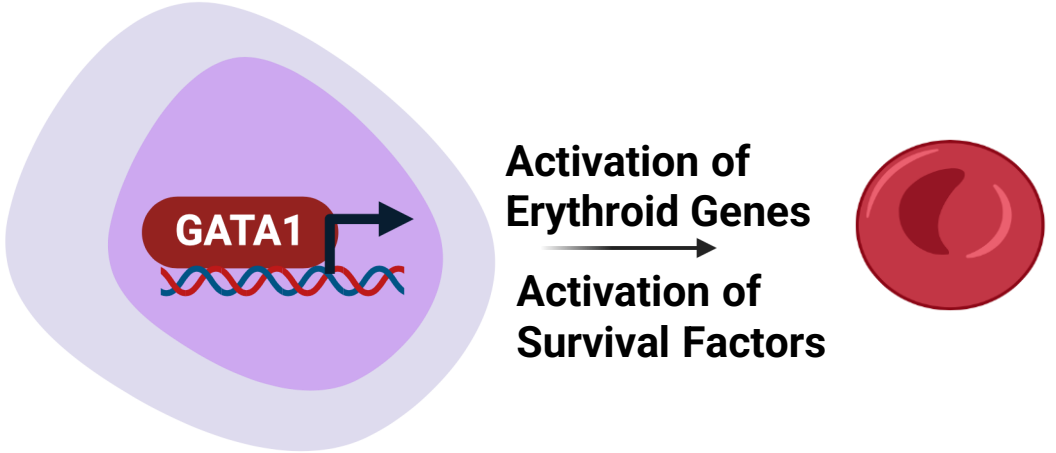




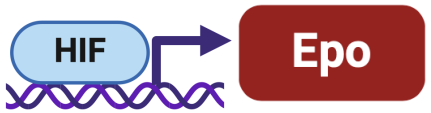
Bhoopalan SV et al. 2020

Model of erythropoiesis regulation : O_2 regulates EPO synthesis





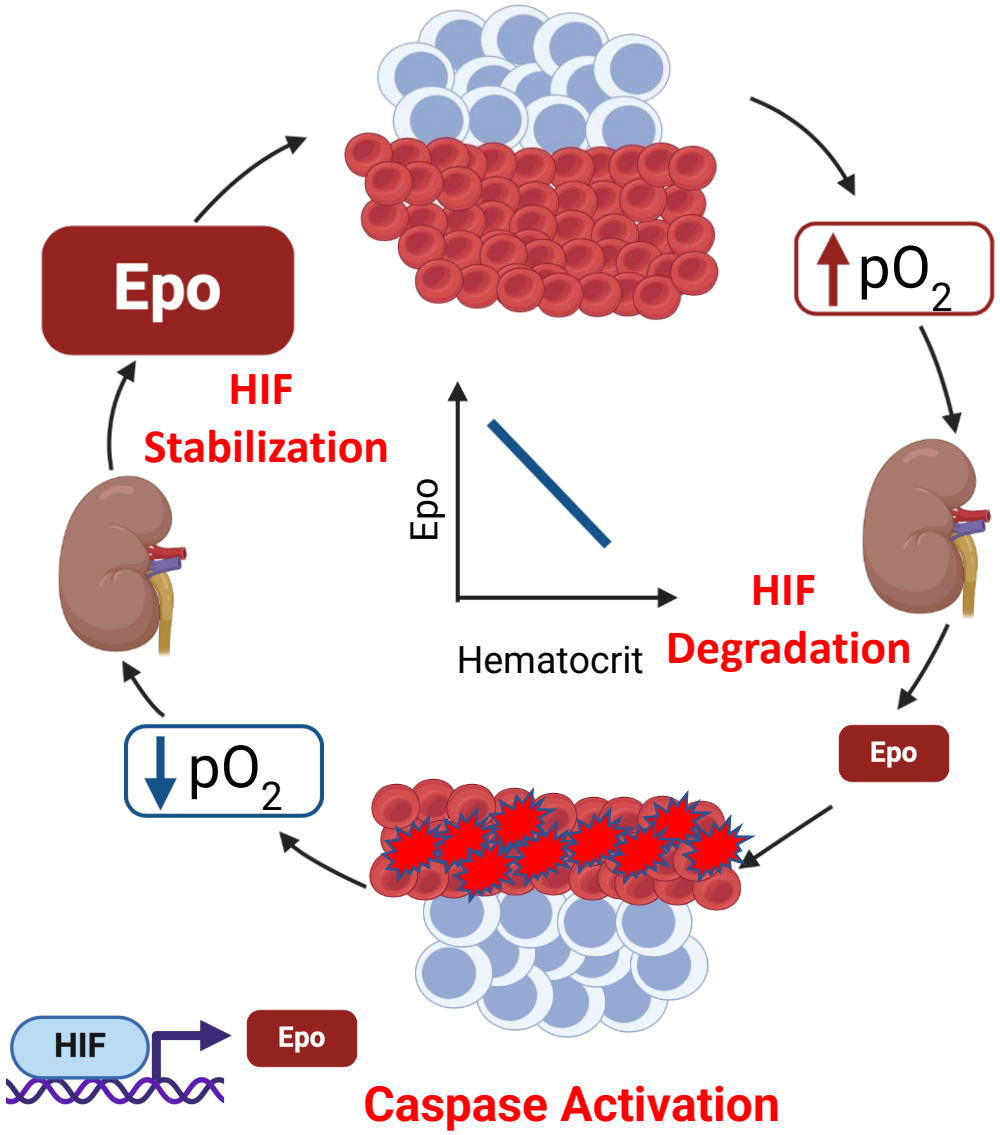
Differentiation of erythroid progenitors

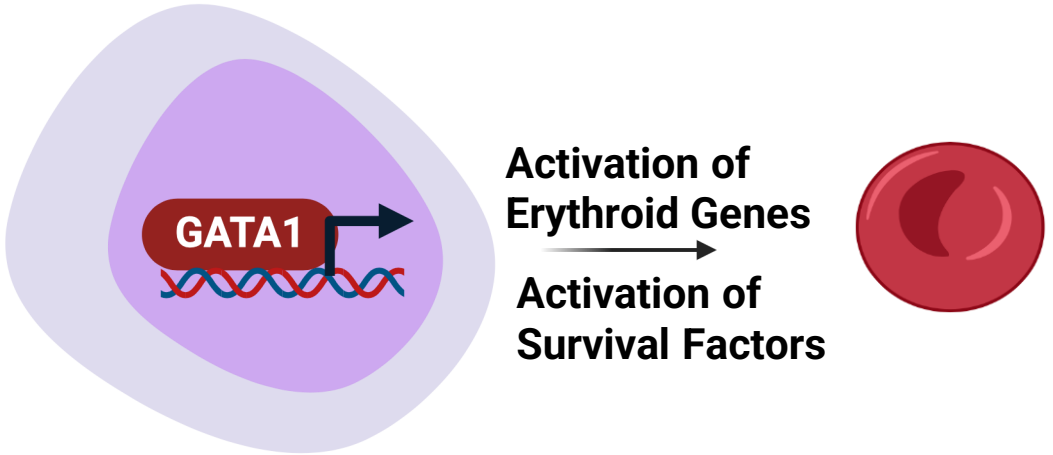


* HIF-Hypoxia inducible factor

Adapted from: Koury M and Bondurant M , Science 1990

Model of erythropoiesis regulation : Apoptosis as a key regulator





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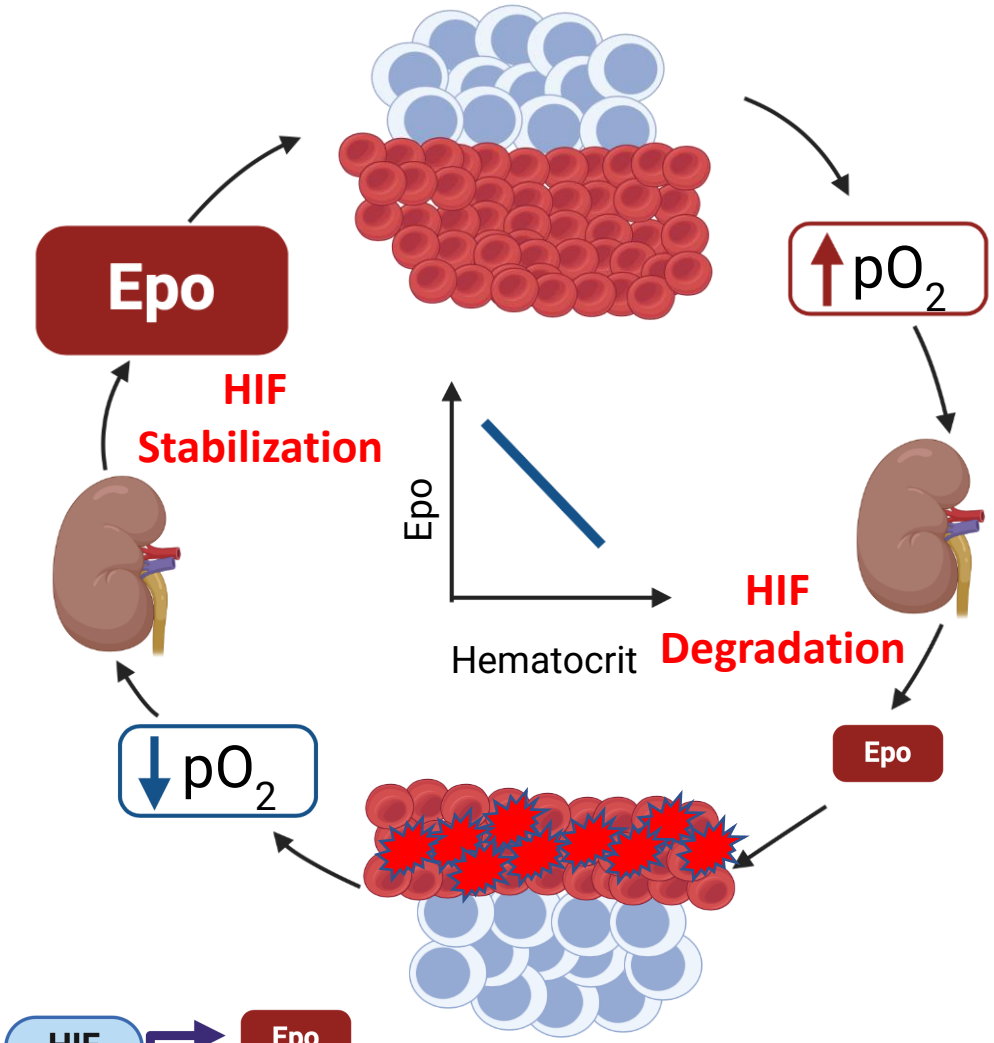
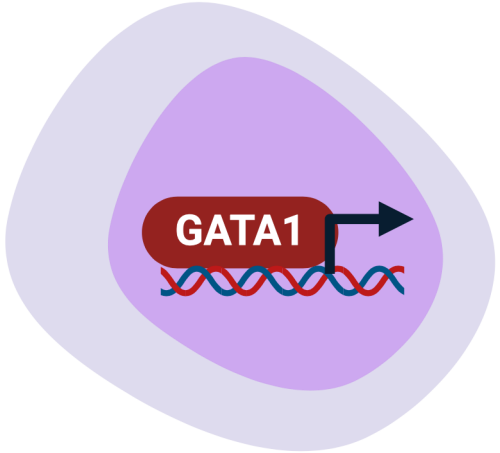
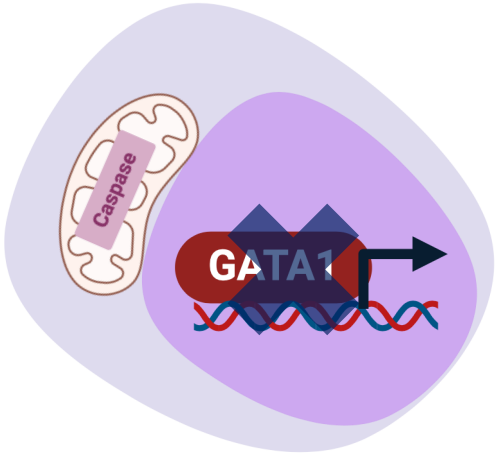




Activation of Erythroid Genes

Activation of Survival Factors

Differentiation of erythroid progenitors



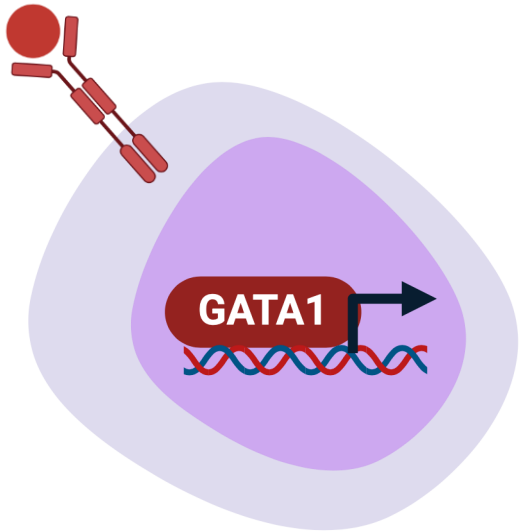
No differentiation

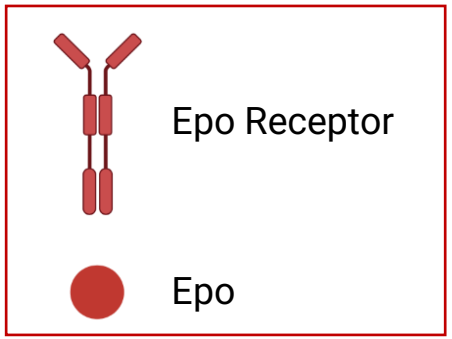
Apoptosis

Caspase Activation

Increased apoptosis of erythroid progenitors

Adapted from: Koury M and Bondurant M , Science 1990

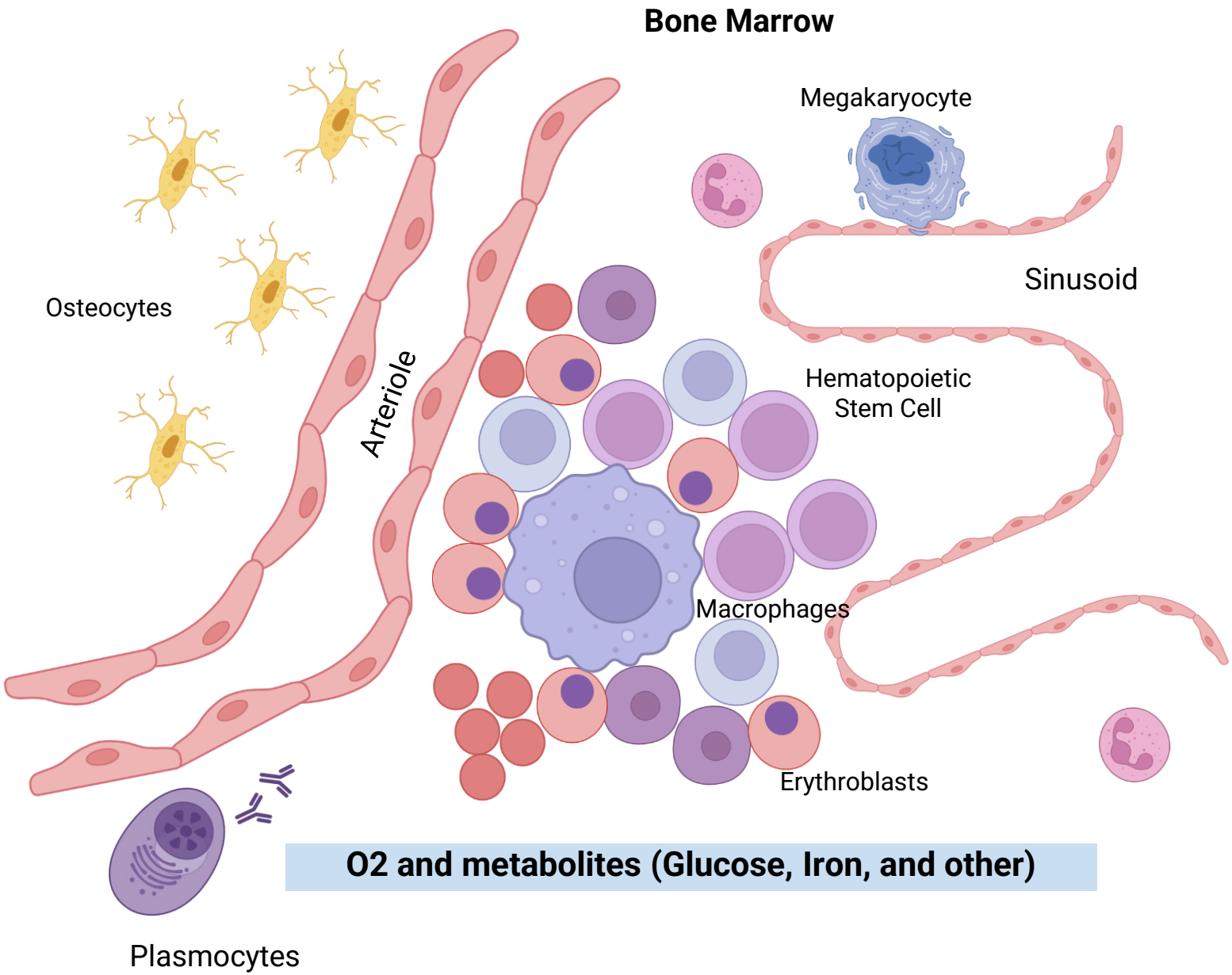




Differentiation of the erythroid lineage

What regulates sensitivity of erythroblasts to Epo?

What determine the sensitivity of progenitors to Epo in the BM niche?



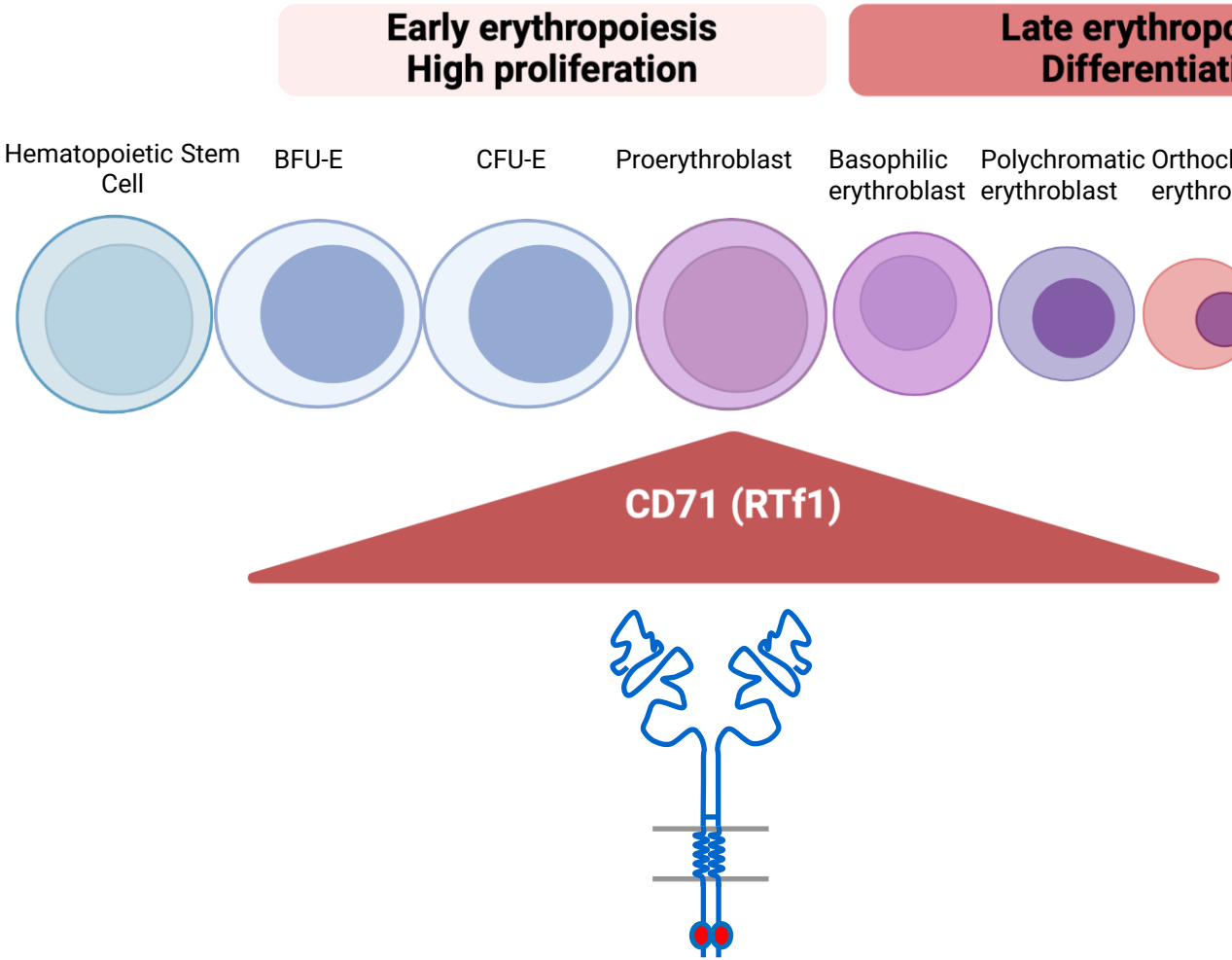
Oxygen is a key regulator in the bone marrow niche

$\downarrow pO_2$

HIF

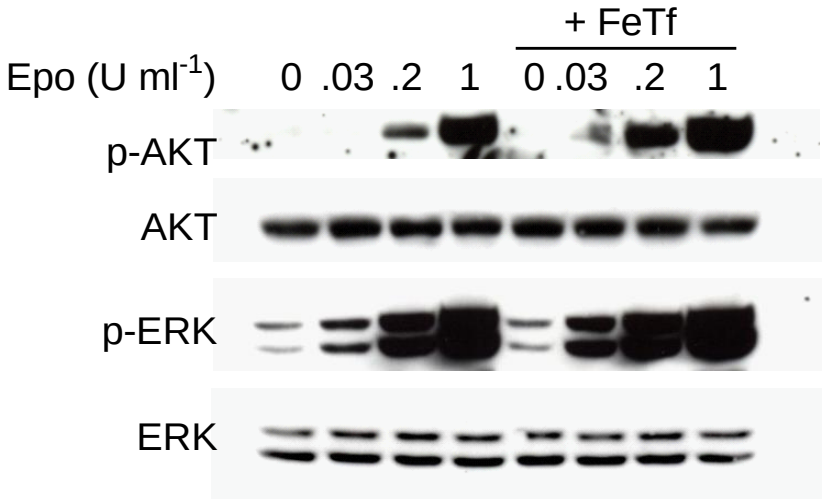
GLUT-1
EPO-R
Tf-R

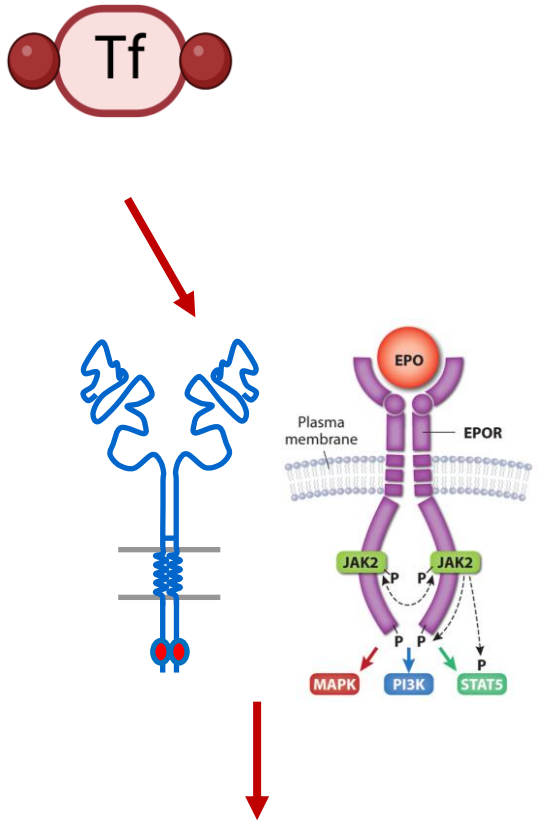
Transferin Receptor: A Key Regulator of Erythropoiesis



- **Cell Proliferation**
- **DNA Synthesis**
- **Mitochondrial Metabolism (ROS)**
- **Hemoglobin synthesis**

Transferrin Receptor activation synergizes with Epo signaling

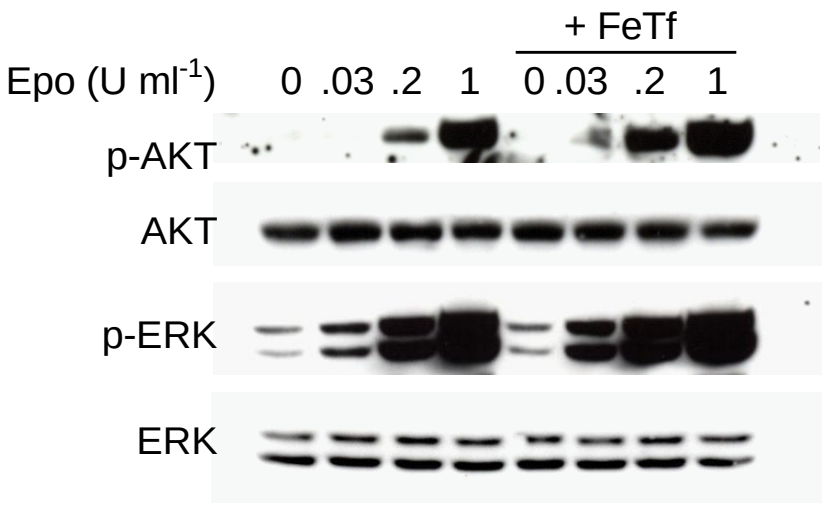


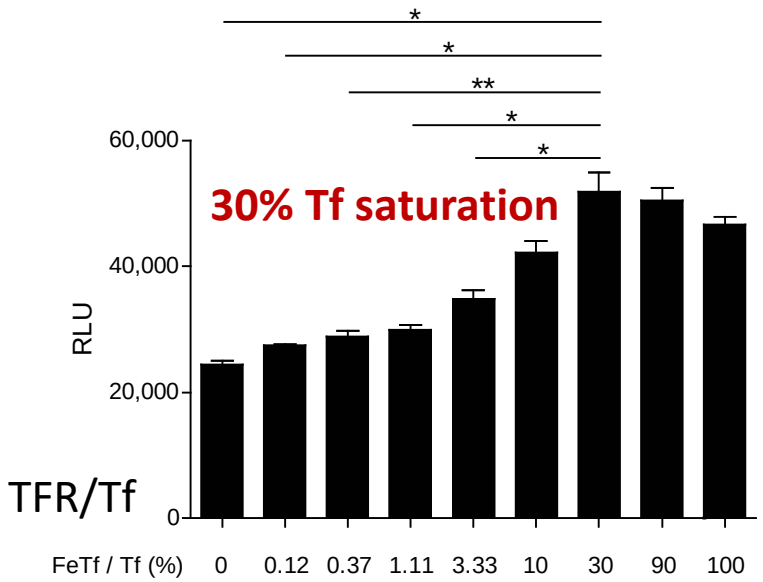


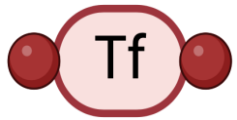
Signal Transduction
Synergy with Epo
MAPK and AKT

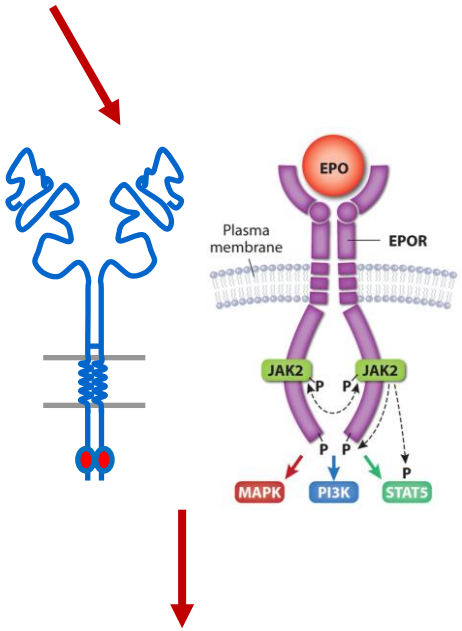
Dussiot et al Nature Medicine 2012

Transferin Receptor synergizes with Epo signaling









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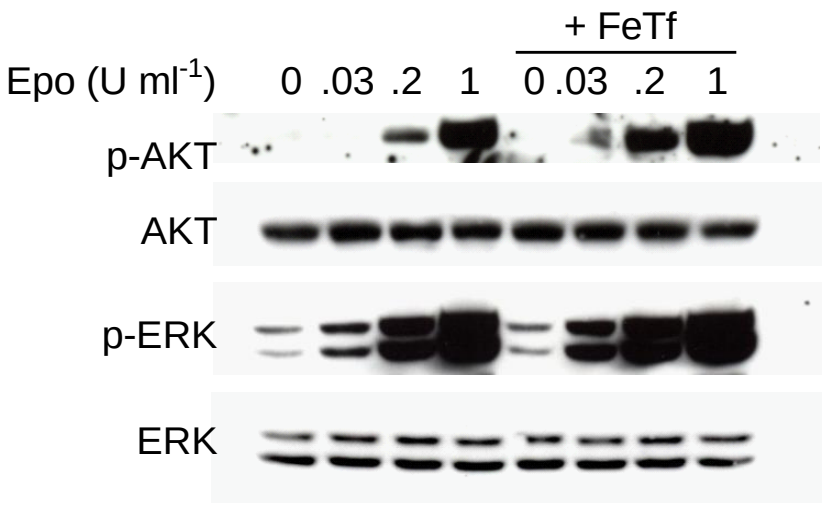

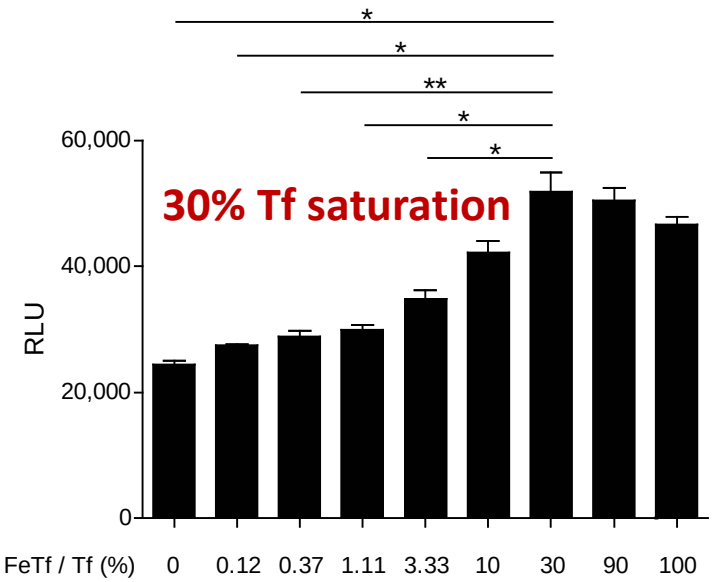

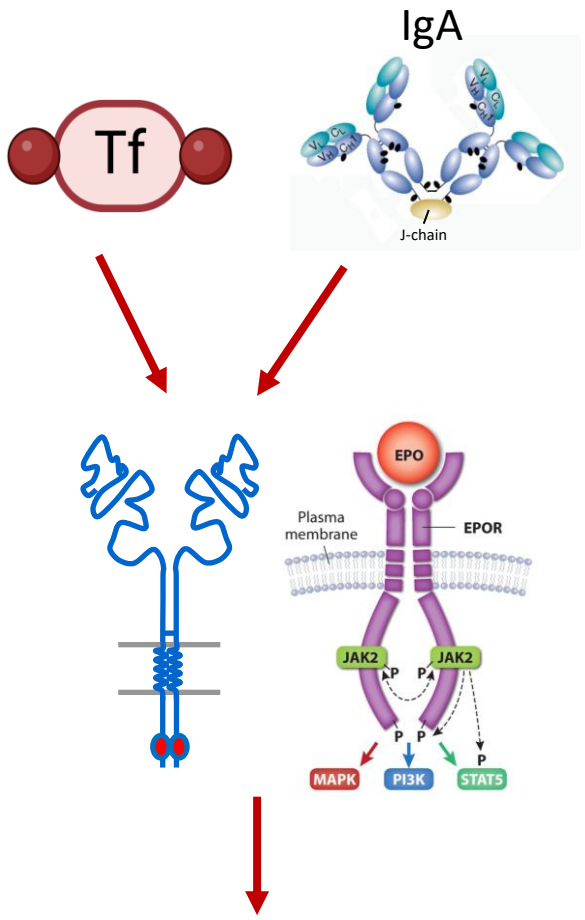

Signal Transduction
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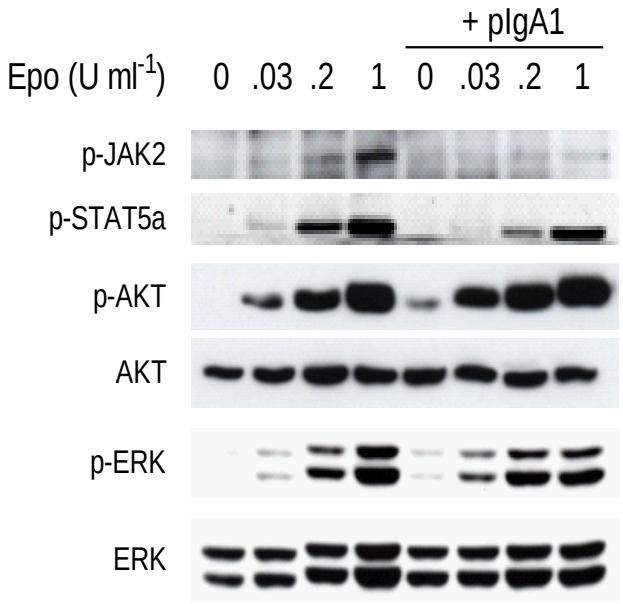

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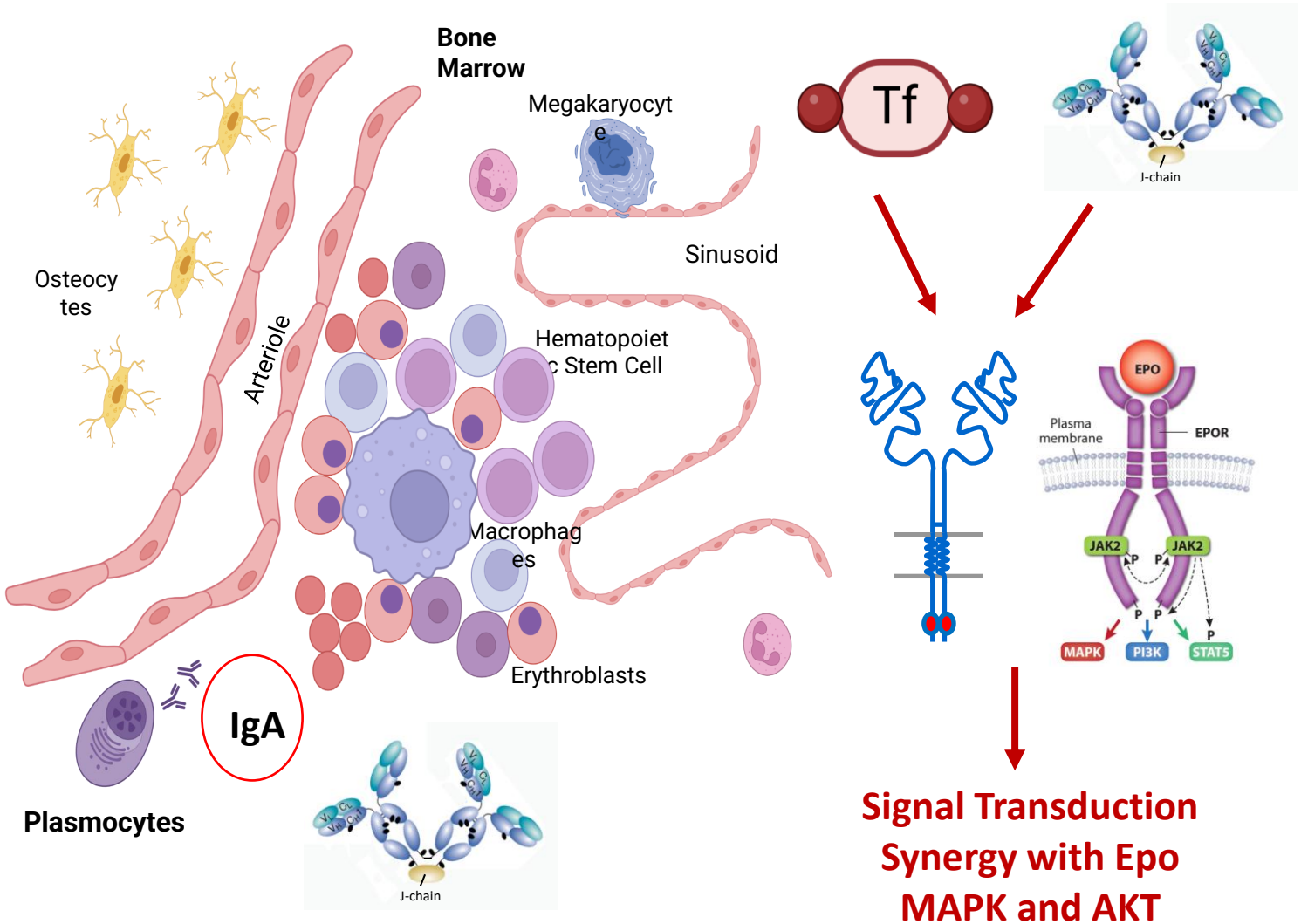
IgA binds and stimulation activation synergizes with Epo signaling



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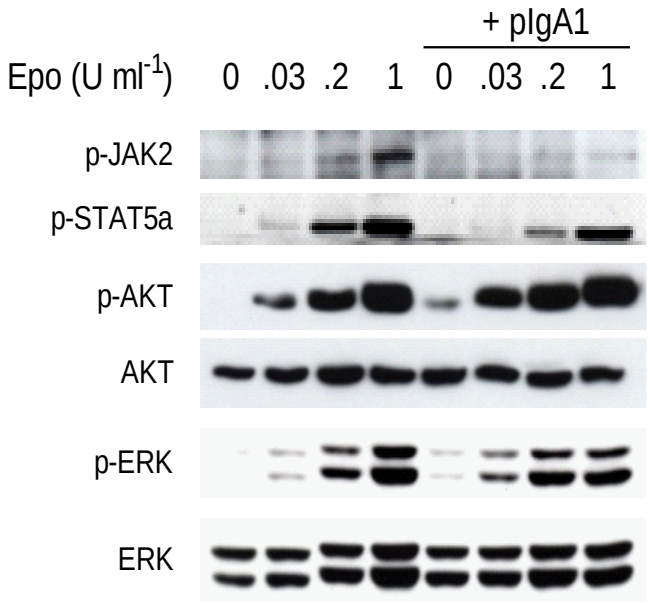

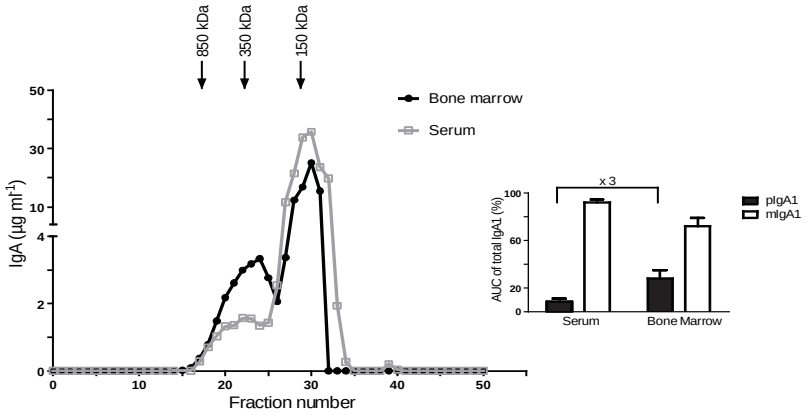

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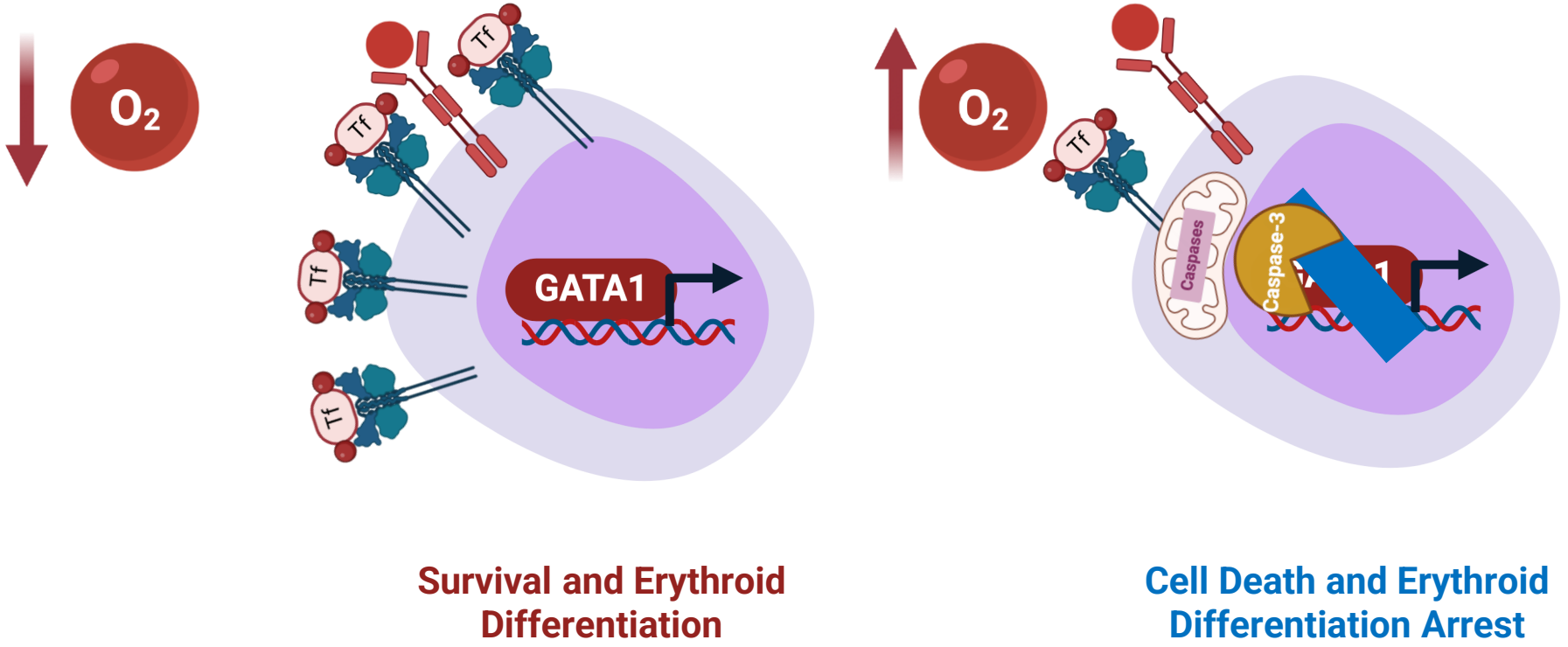
Transferrin Receptor Expression and Iron: Key Factors Underlying Erythroblast Sensitivity to Erythropoietin

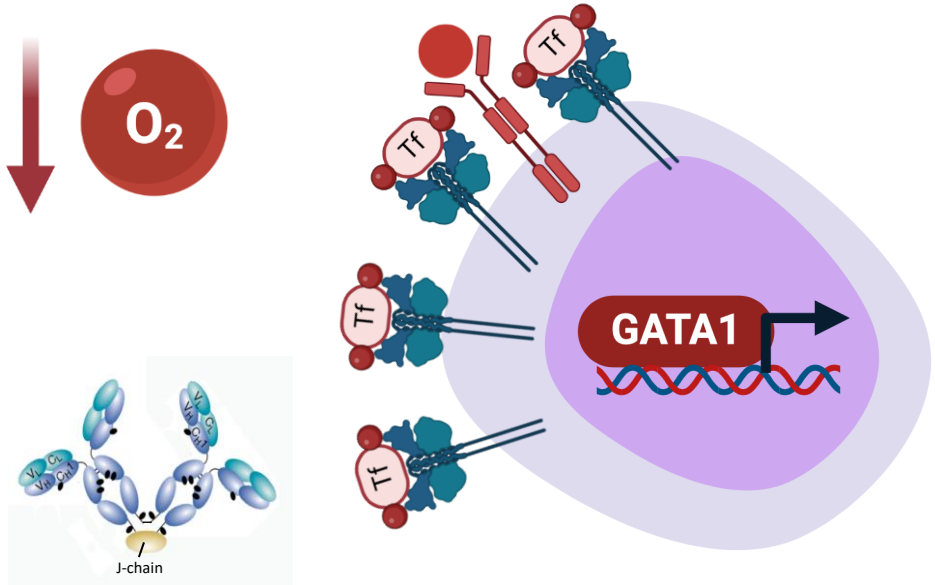


Survival and Erythroid Differentiation

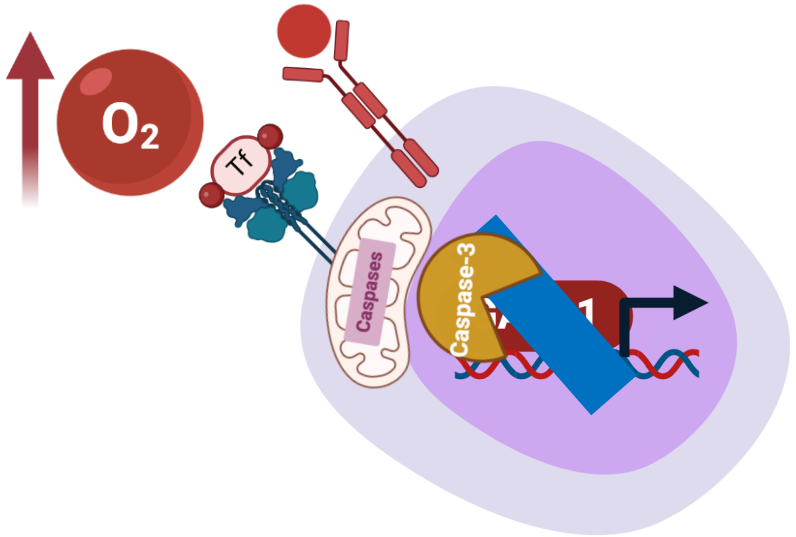
Cell Death and Erythroid Differentiation Arrest

Dussiot et al Nature Medicine 2012

Transferrin Receptor Expression and IgA: Key Factors Underlying Erythroblast Sensitivity to Erythropoietin



Survival and Erythroid Differentiation



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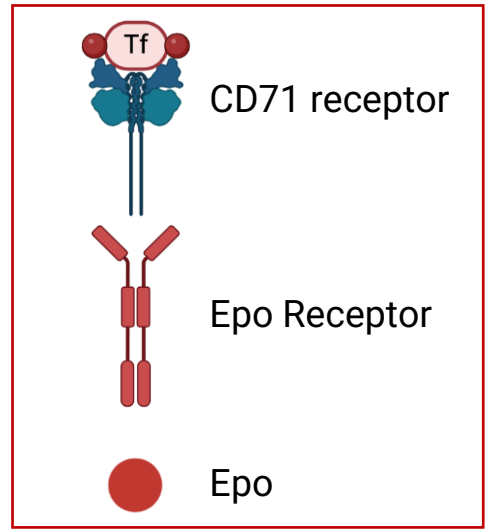

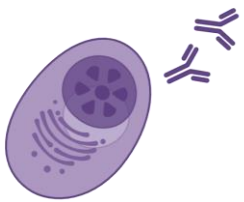

IgA

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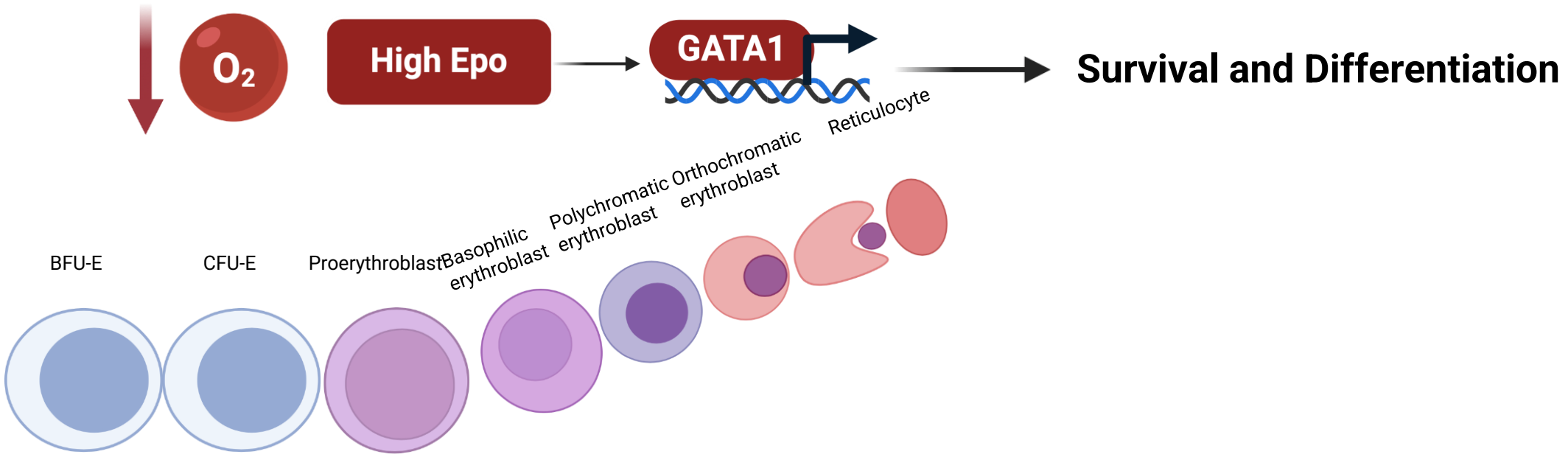
Caspase-3 is a key player in apoptosis of erythroid precursors



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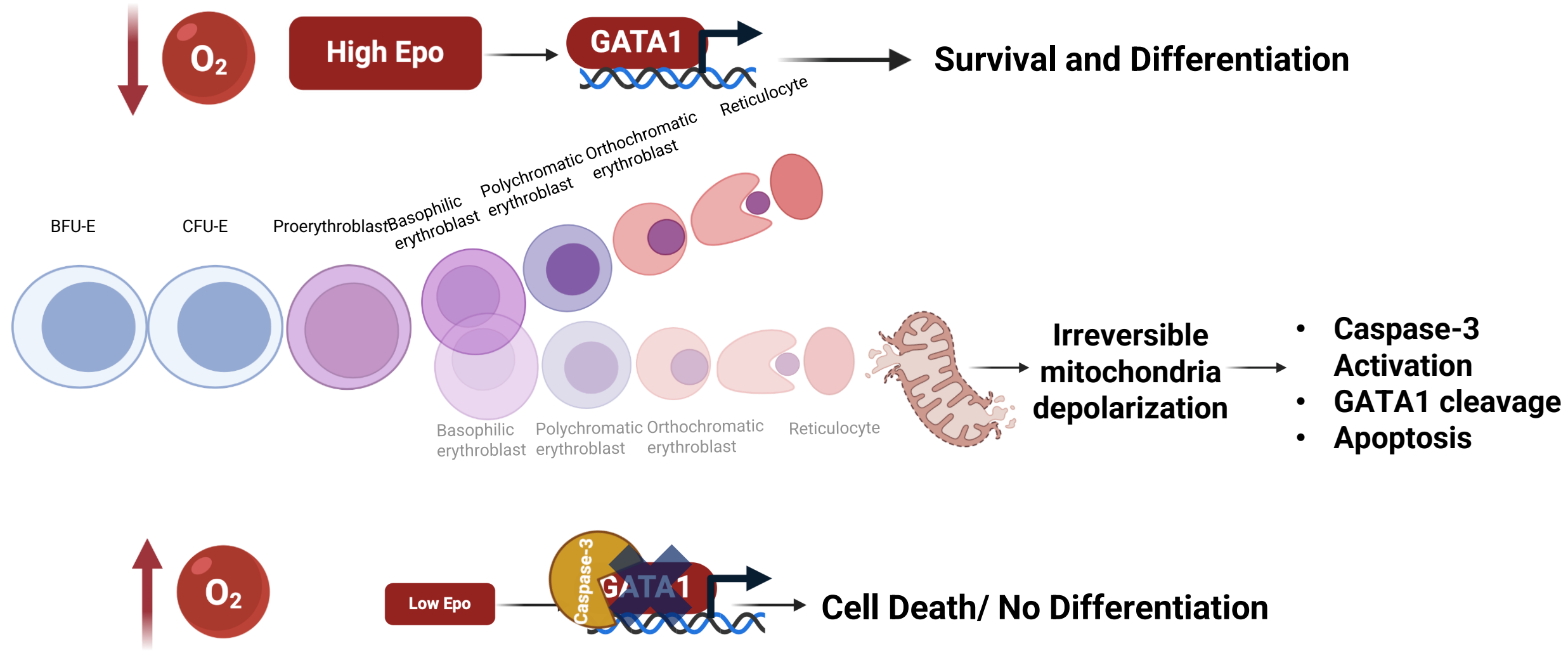
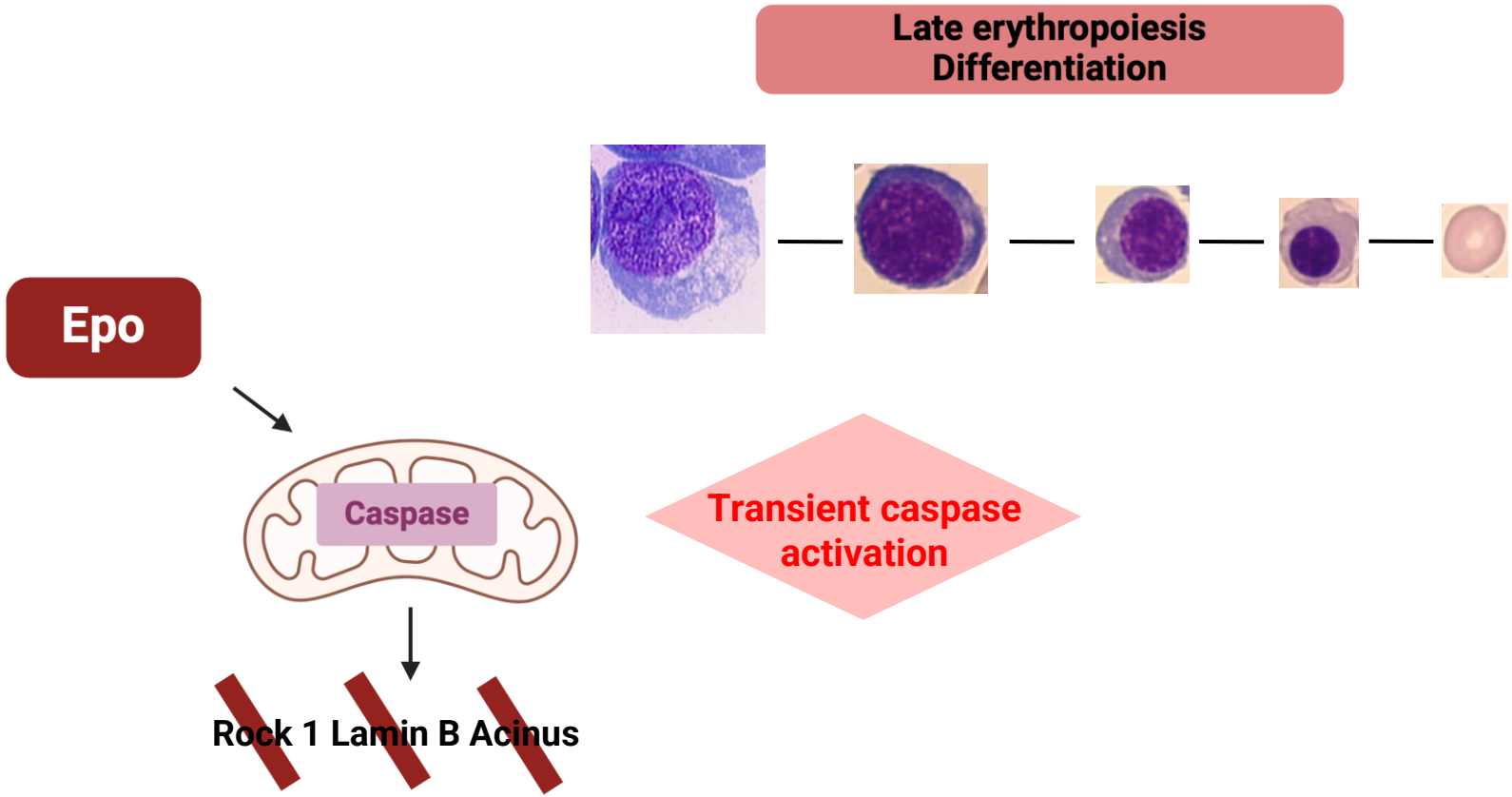


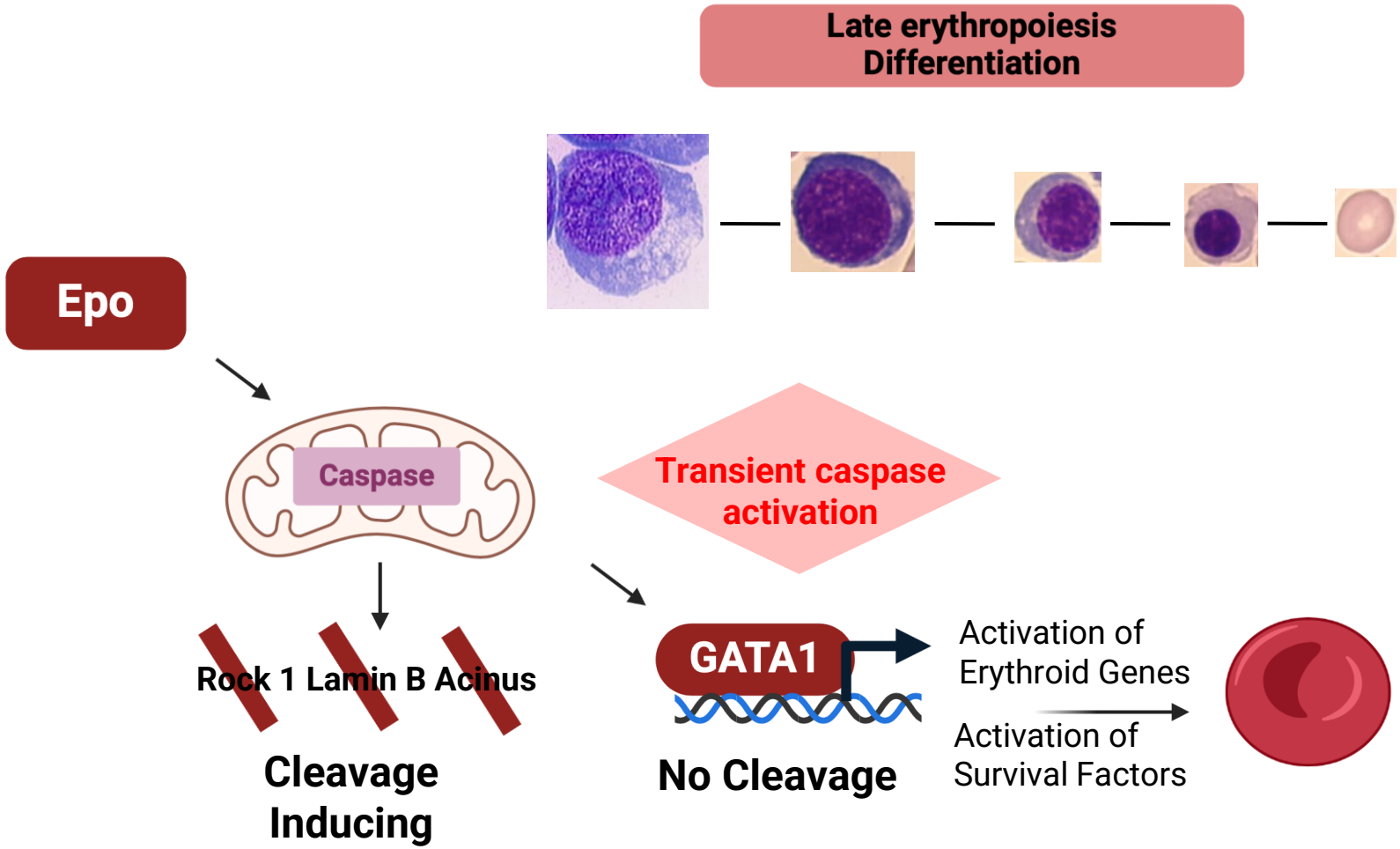
But transient caspase activation is required for terminal erythroid differentiation



Eric Solary

Zermati et al, J. Exp. Med. 2001

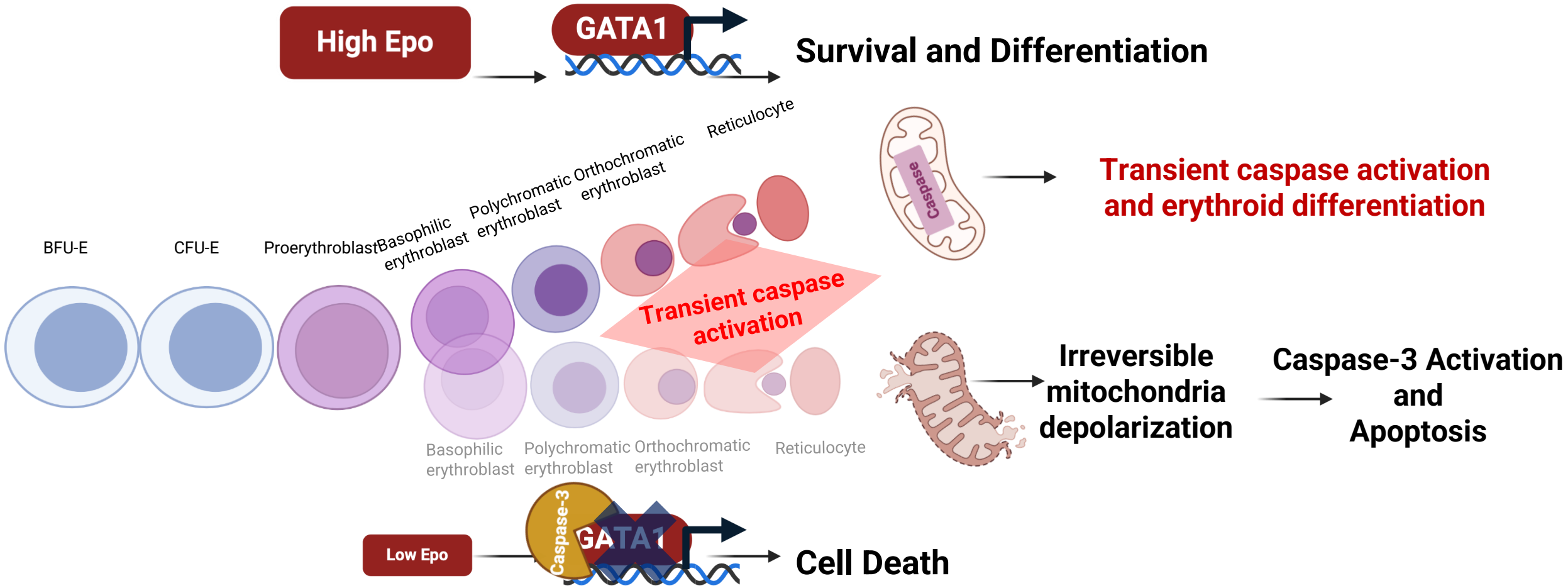
And GATA1 is not cleaved by Caspase-3 during erythroid differentiation



Eric Solary

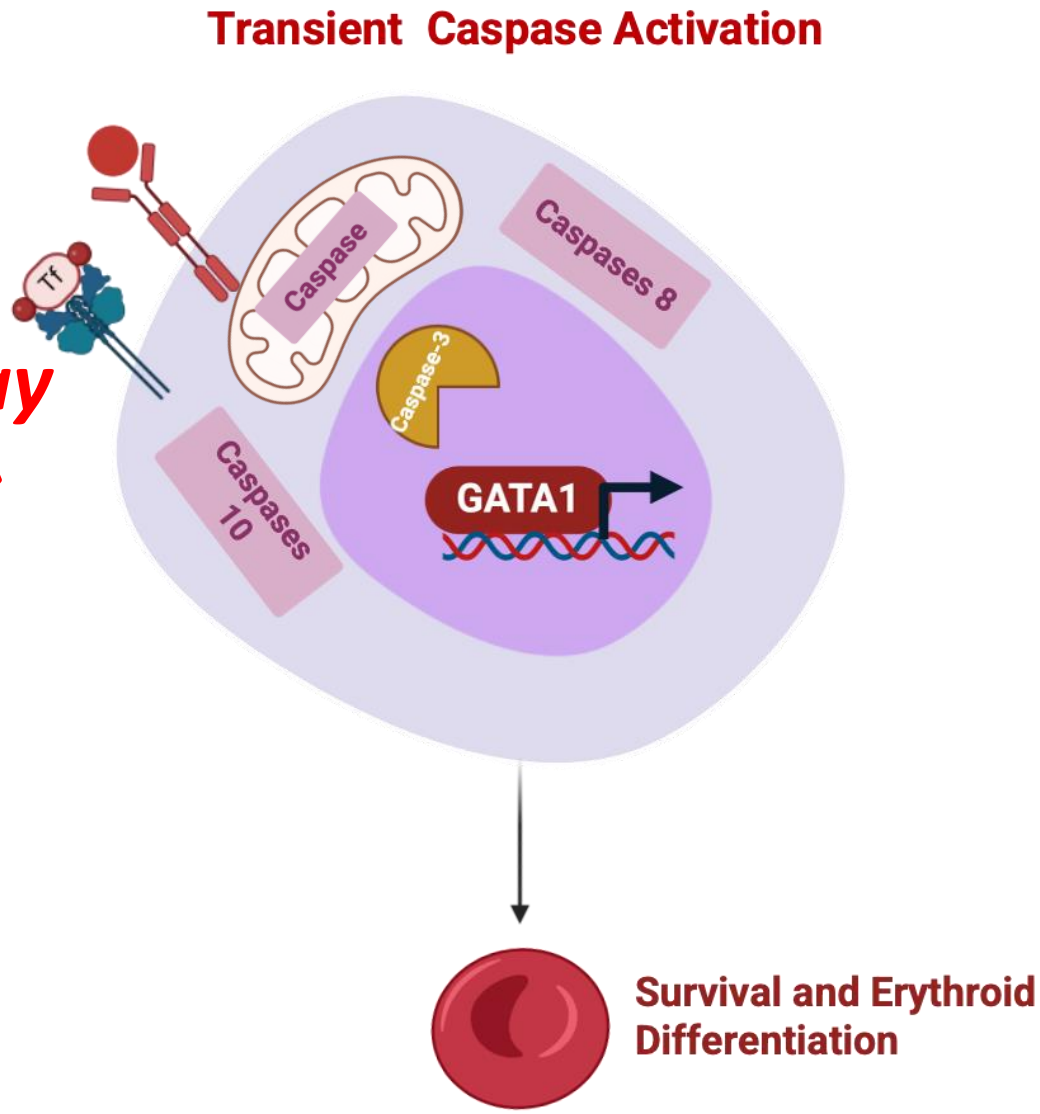
Zermati et al, J. Exp. Med. 2001

Caspase-3: A key player in terminal erythroid differentiation and apoptosis



Caspase 3 is critical both for differentiation and apoptosis

« Blocking this cell death process may prevent red blood cell generation »



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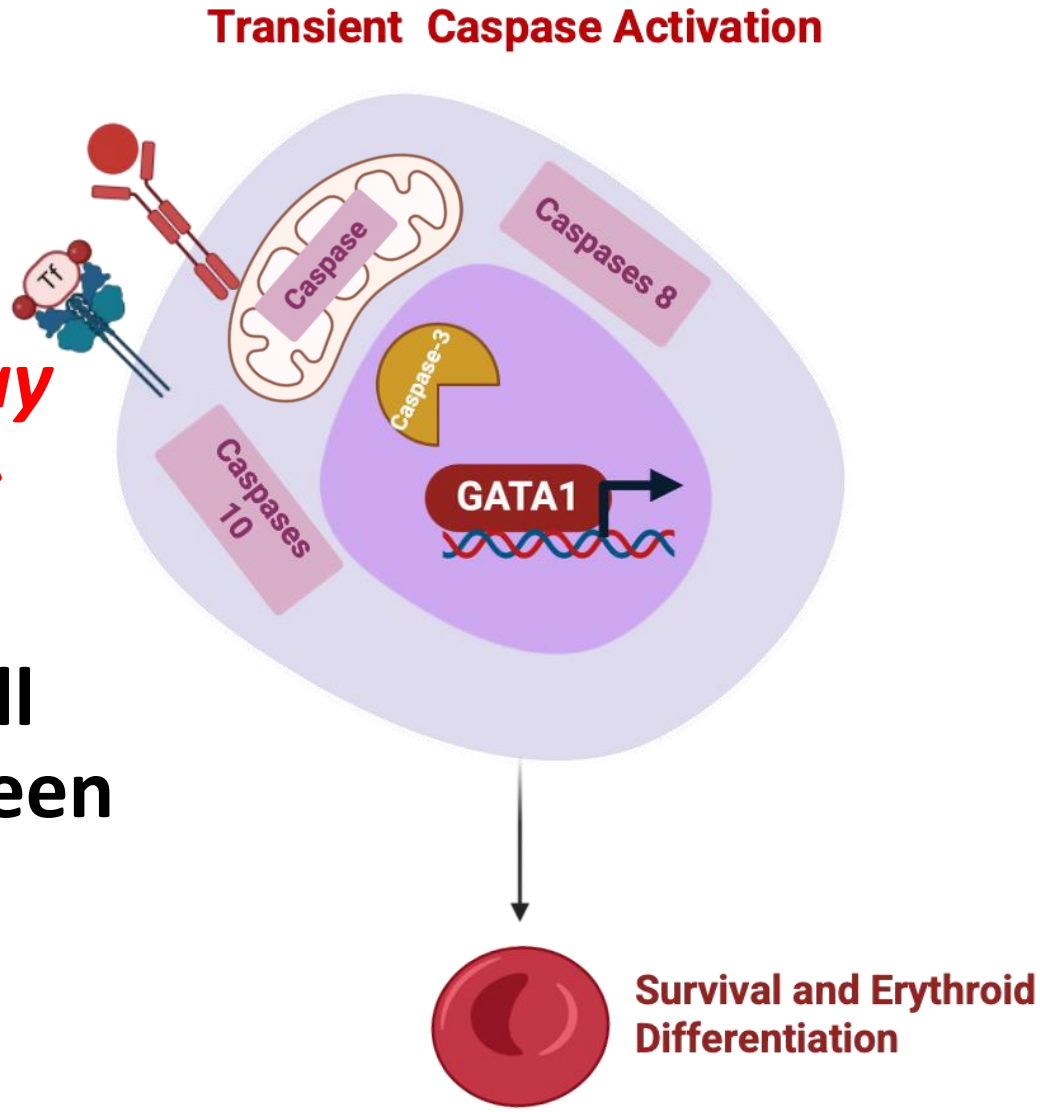
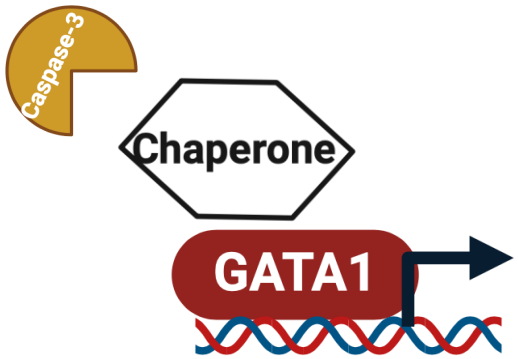


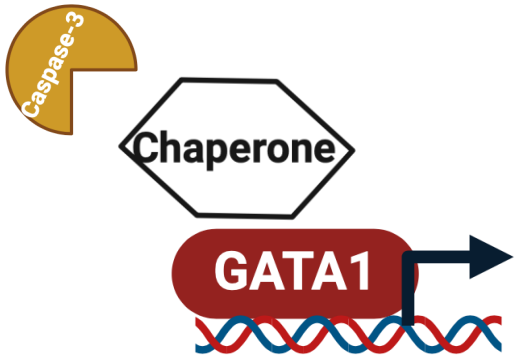
Cell differentiation is an abortive cell death program and the decision between death and differentiation is made downstream Caspase activation

How is GATA1 protected from cleavage downsteam of caspase 3 activation in the presence of Epo?

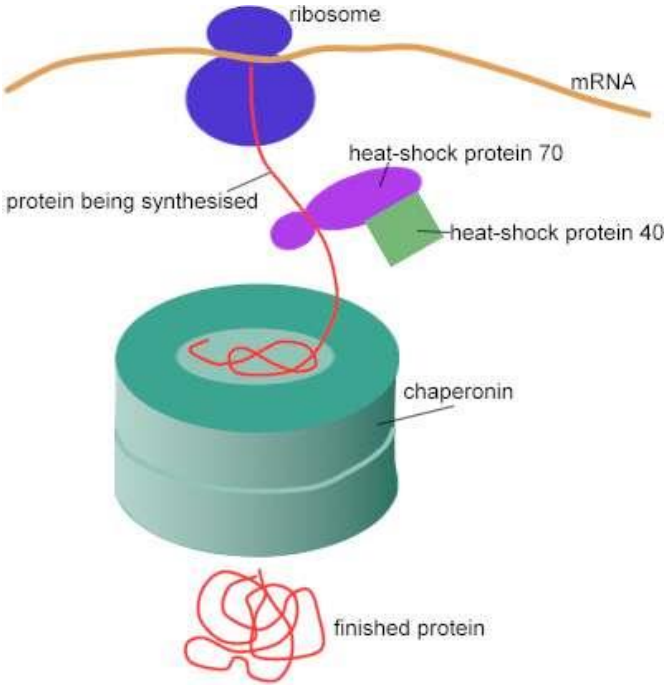
Role of chaperon proteins in cellular homeostasis



Role of chaperon proteins in cellular homeostasis



Heat Shock Protien 70 (HSP70)

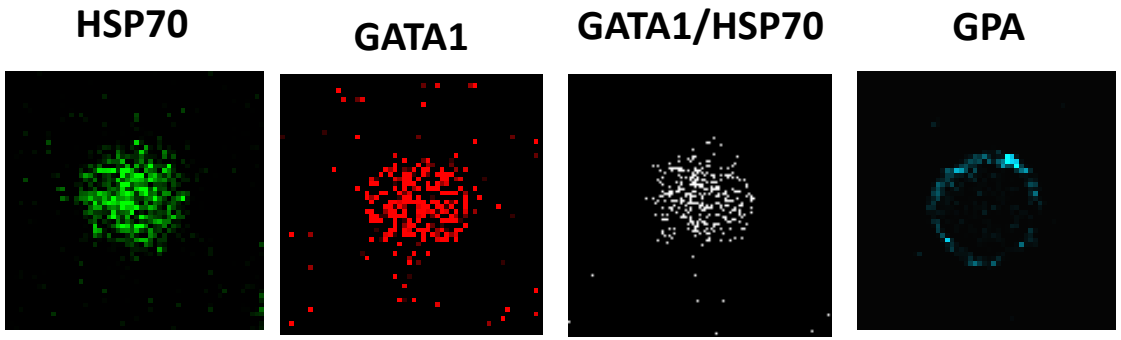


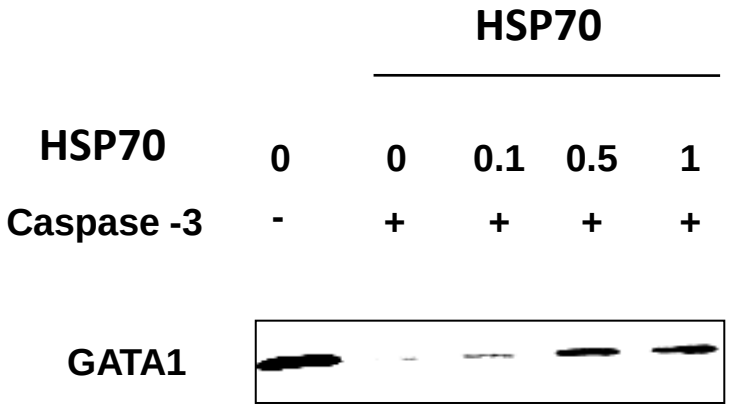
1. **Protein « folding »**
2. **Prevention of damaging aggregates**
3. **Disaggregation of aggretates**
4. **Protecting cancer cells from death by downstream caspase activation**

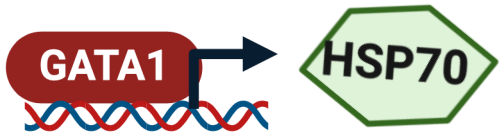
Is HSP70 the right candidate ?

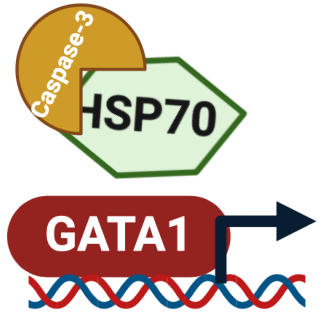
Carmen Garrido

HSP70 is constitutively expressed in bone marrow erythroid cells



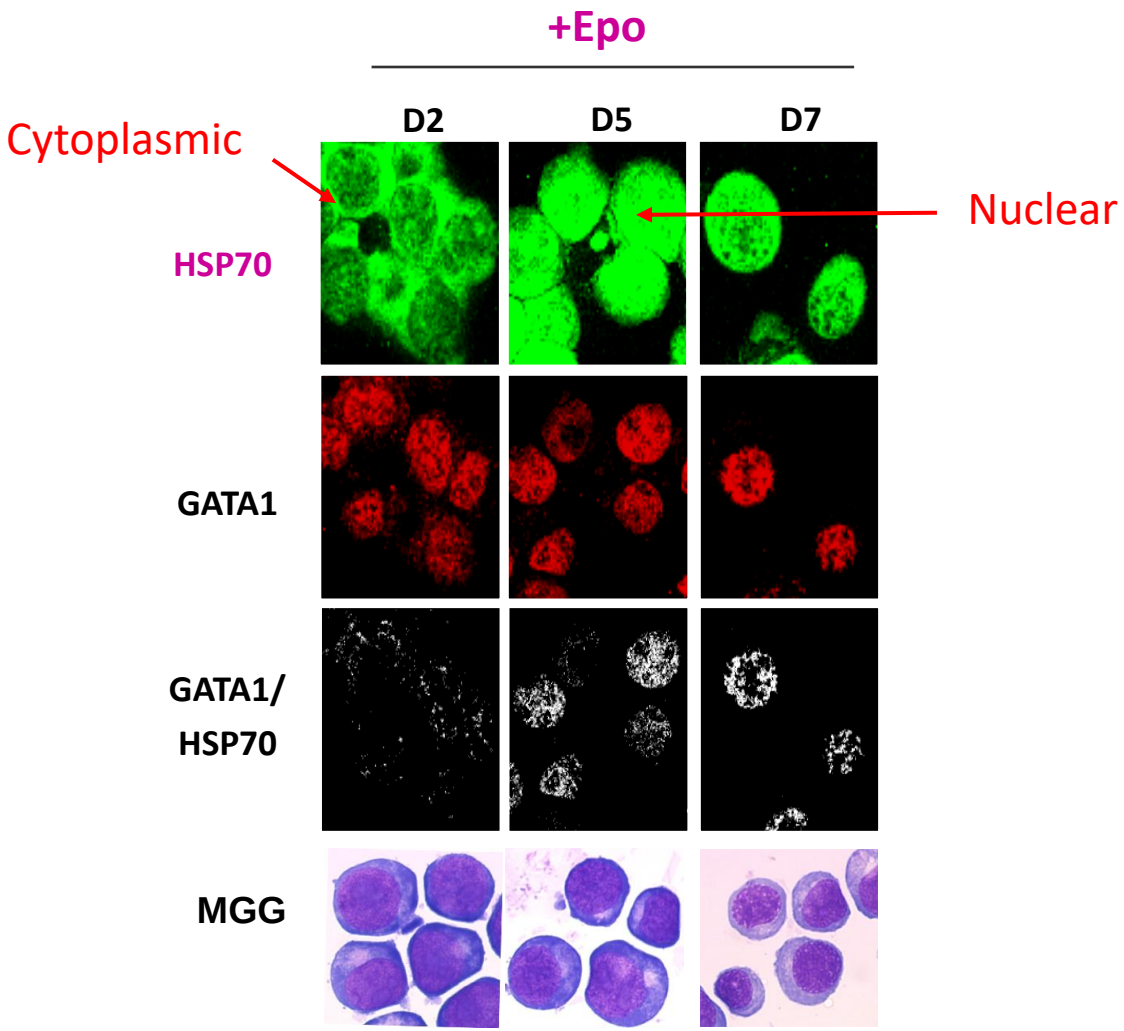


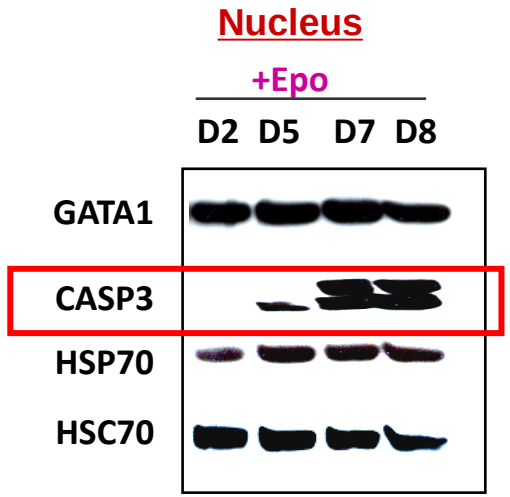




Ribeil, Zermati et al Nature 2007

HSP70 accumulates in the nucleus during erythroid differentiation, colocalizing with GATA1 at the time of caspase 3 activation





Ribeil, Zermati et al Nature 2007

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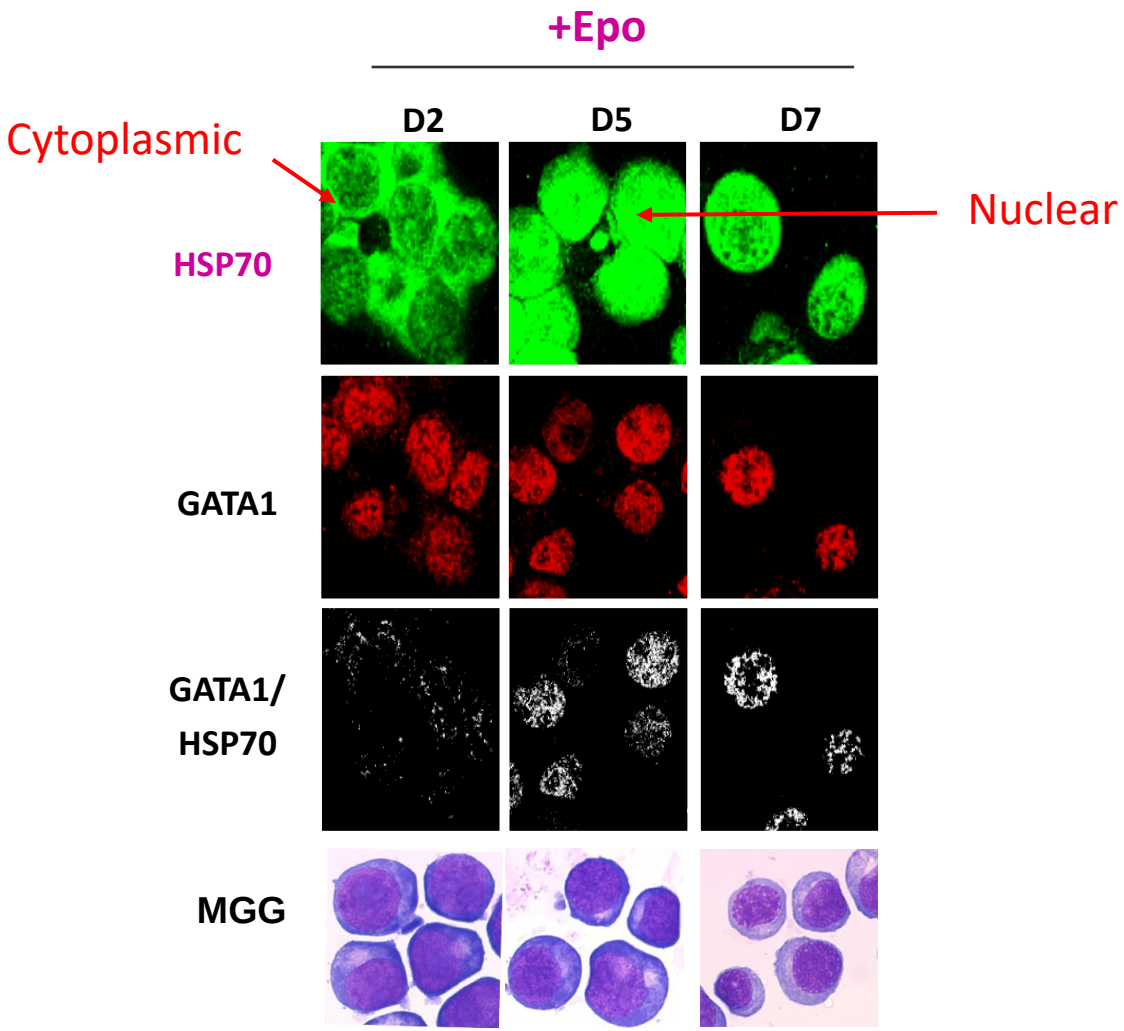
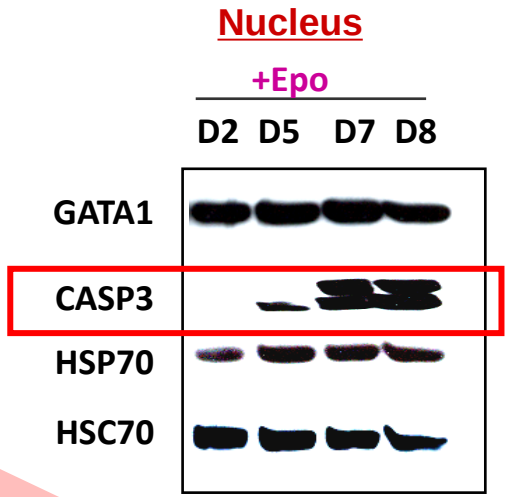
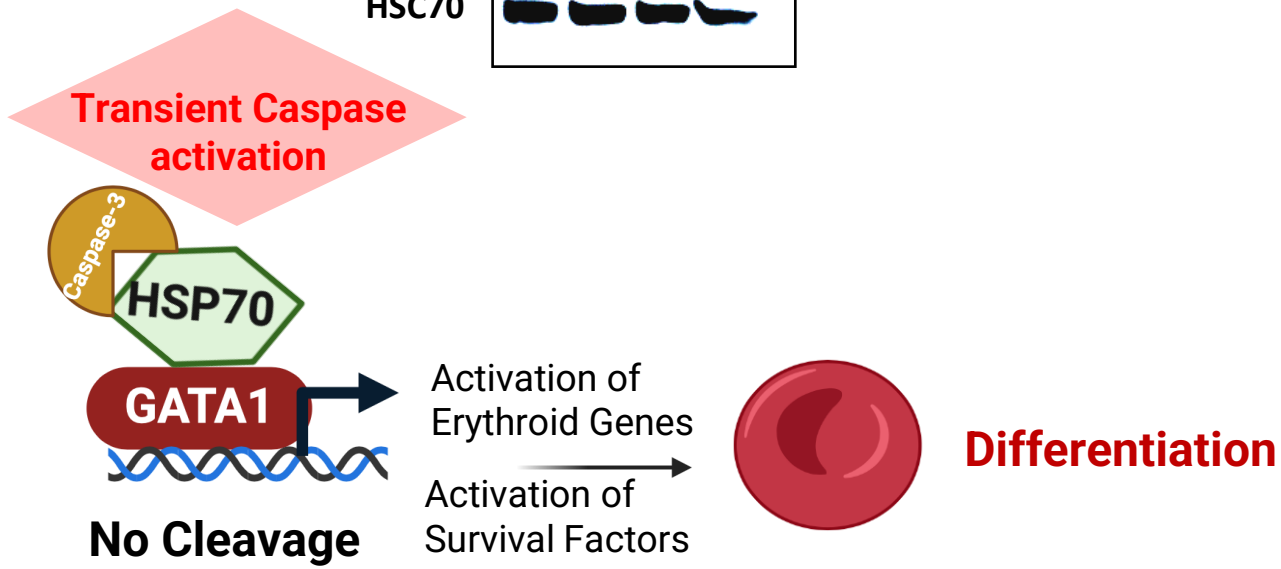


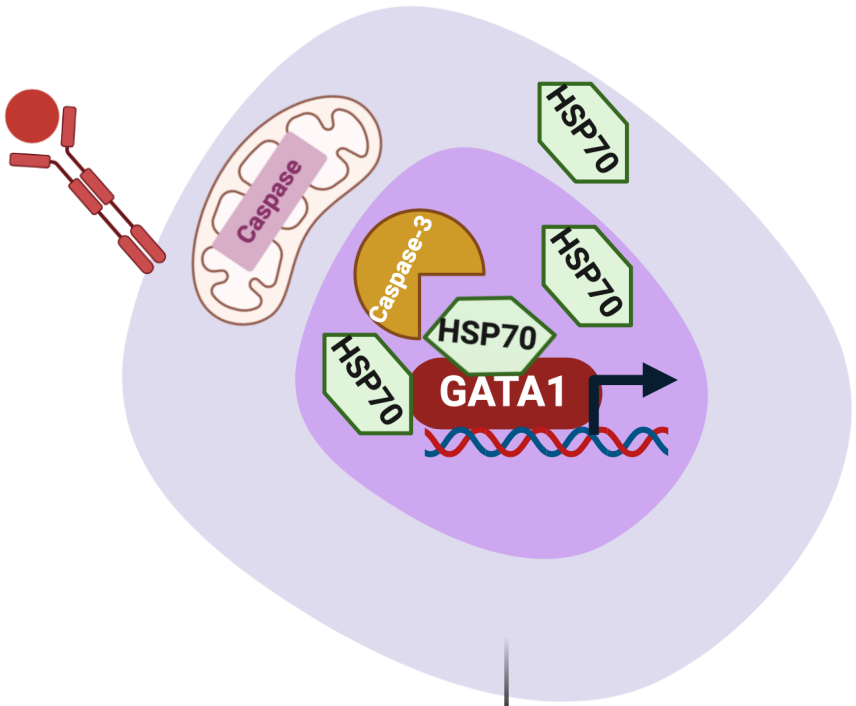




Ribeil, Zermati et al Nature 2007

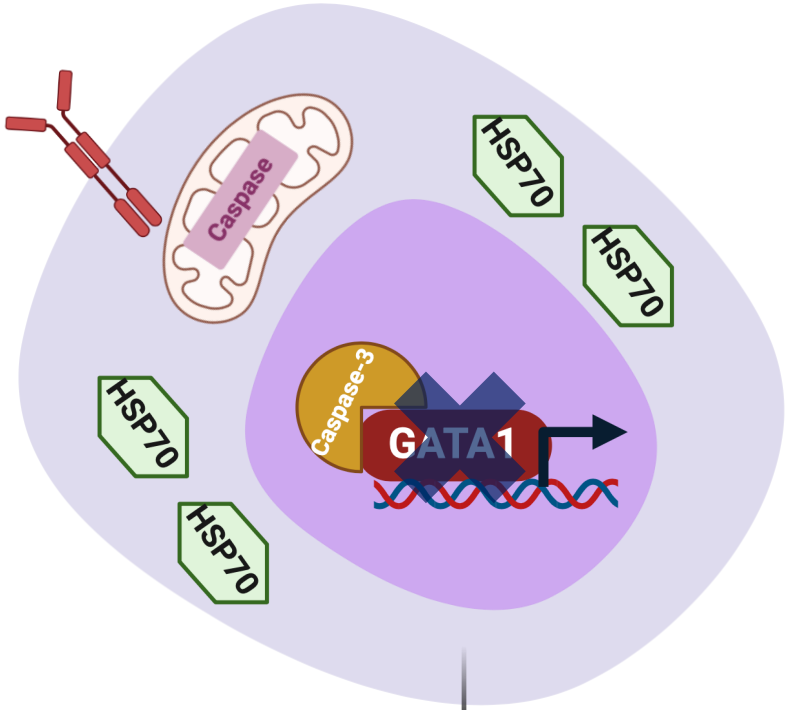
The fate of erythroblasts – between death and survival – depends on HSP70 nuclear localization

Transient Caspase Activation And HSP70 in the nucleus



Survival and Erythroid Differentiation

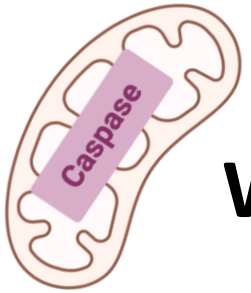
Irreversible Caspase Activation And HSP70 in the cytosol



Cell Death and Erythroid Differentiation Arrest

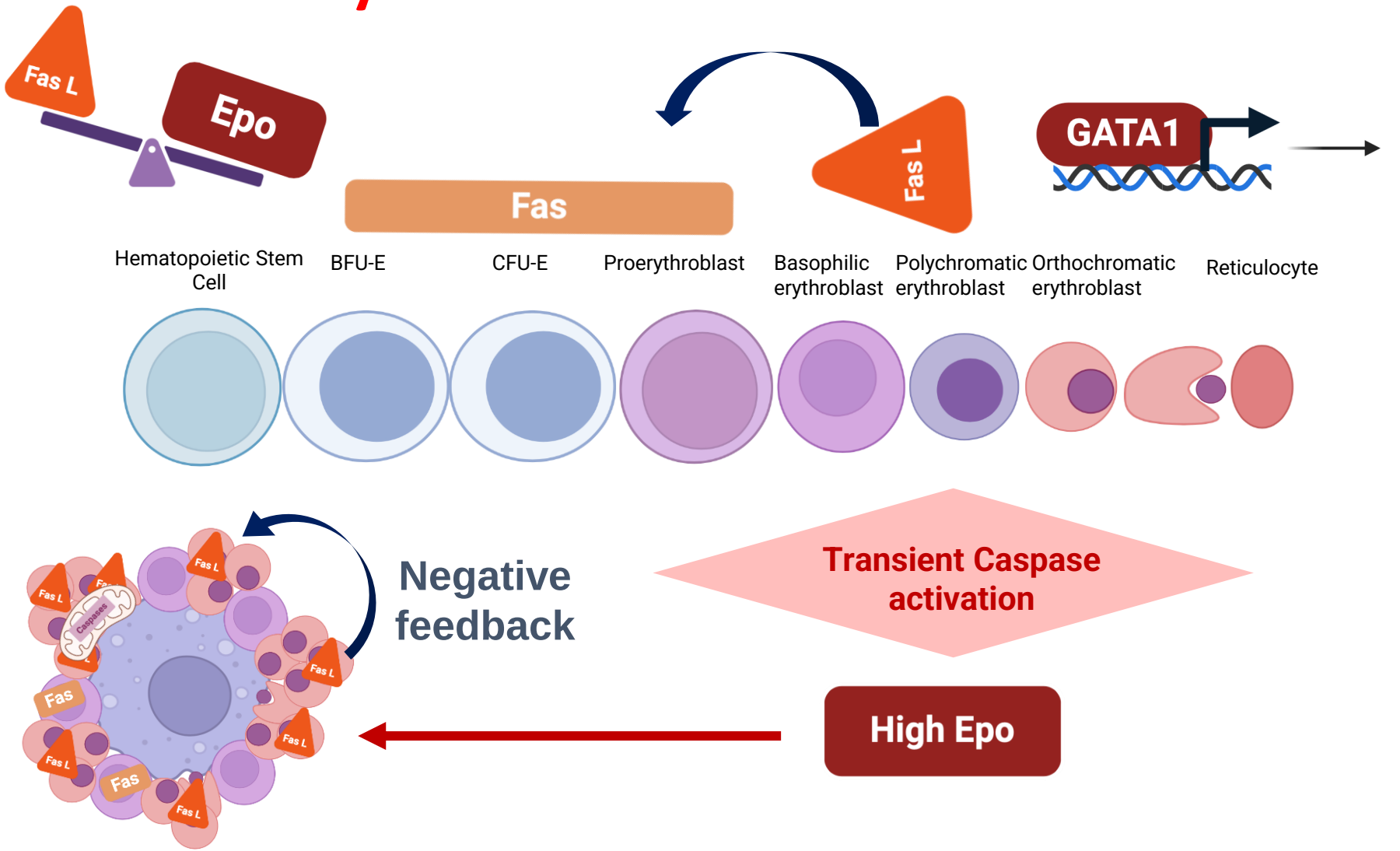
Ribeil JA et al, Nature 2007

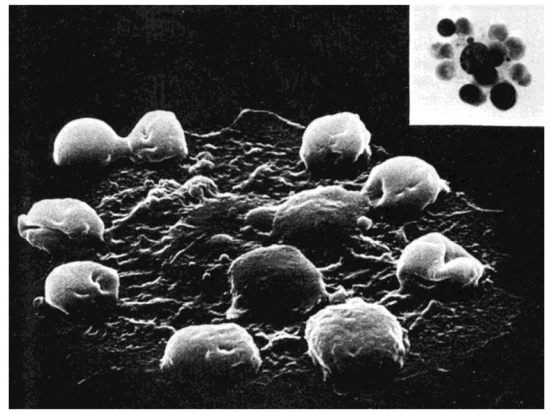
Guillem et al , Hematologica 2021



What is responsible for mitochondrial depolarization and caspase activation during erythroid differentiation?

Death receptor Fas and FasL interactions activate caspases during erythroid differentiation within the blood islands

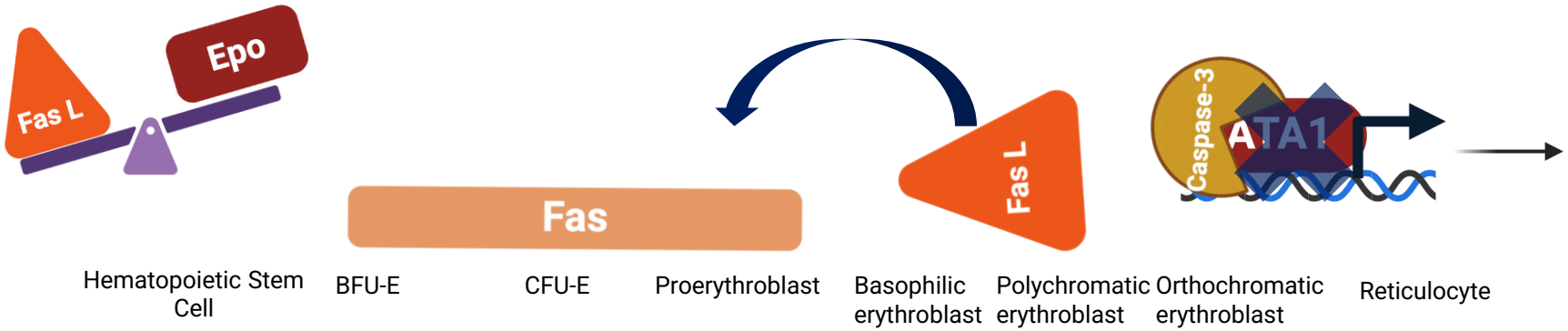


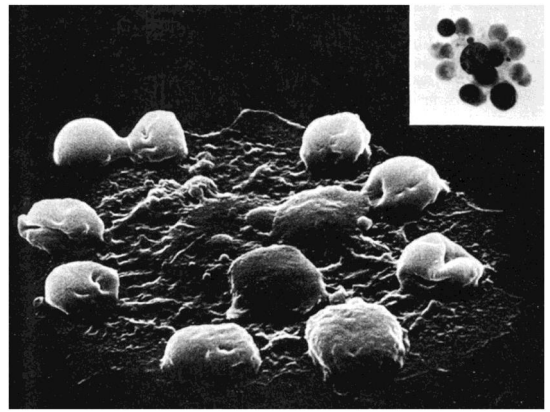


Erythroblastic islands
Marcel Bessis 1958

De Maria et al, Nature 1999

Fas and FasL interactions activate caspases during erythroid differentiation within the blood islands



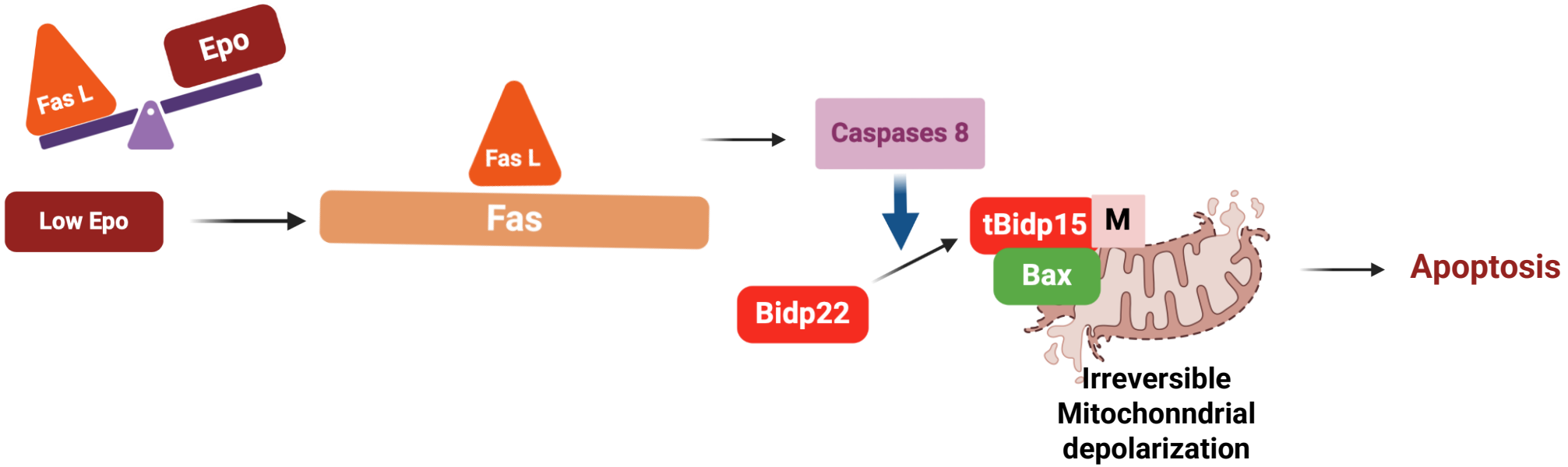


Erythroblastic islands
Marcel Bessis 1958

De Maria et al, Nature 1999

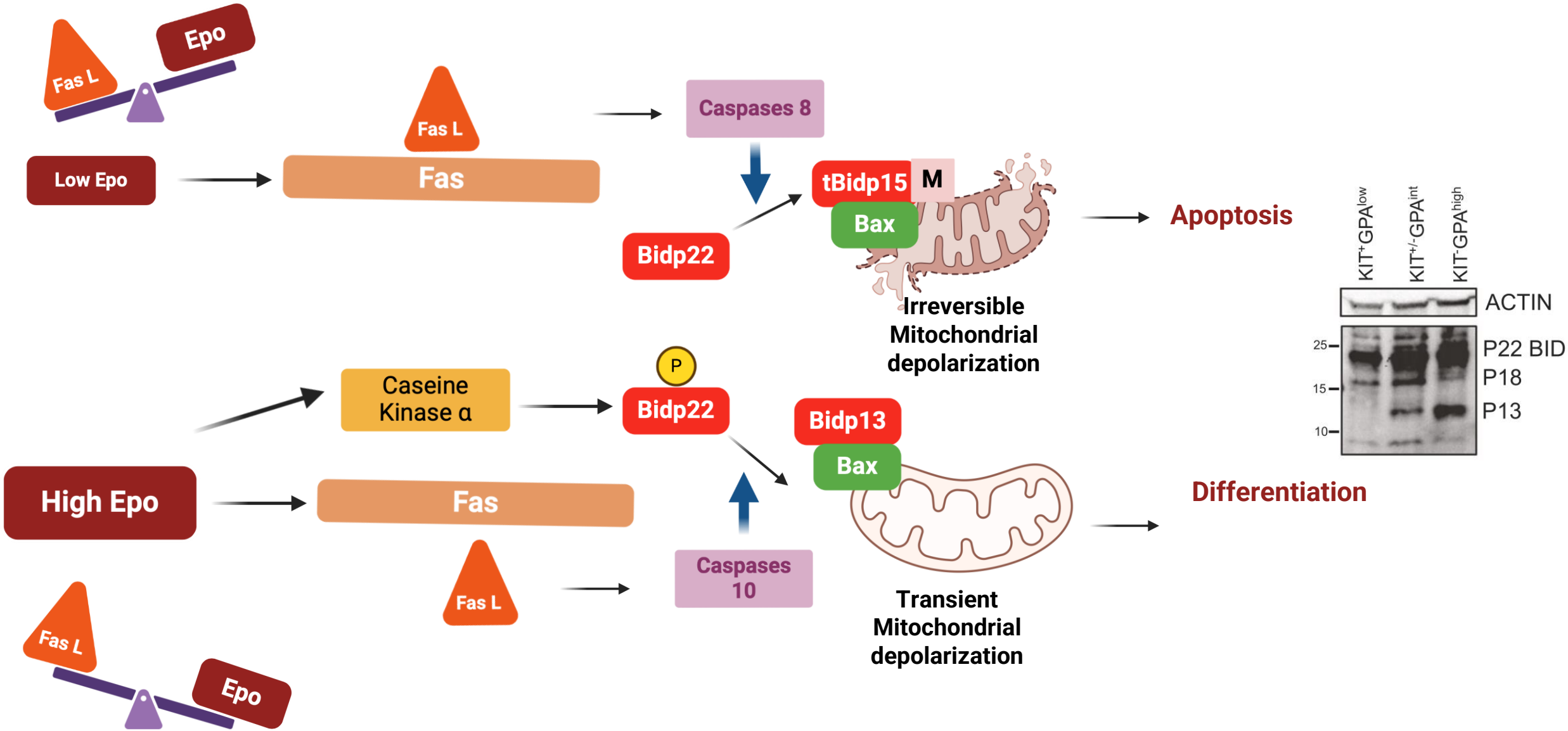
How does EPO control FAS-induced caspase activation?

Fas induced mitochondrial depolarization through Bid cleavage and Bax activation



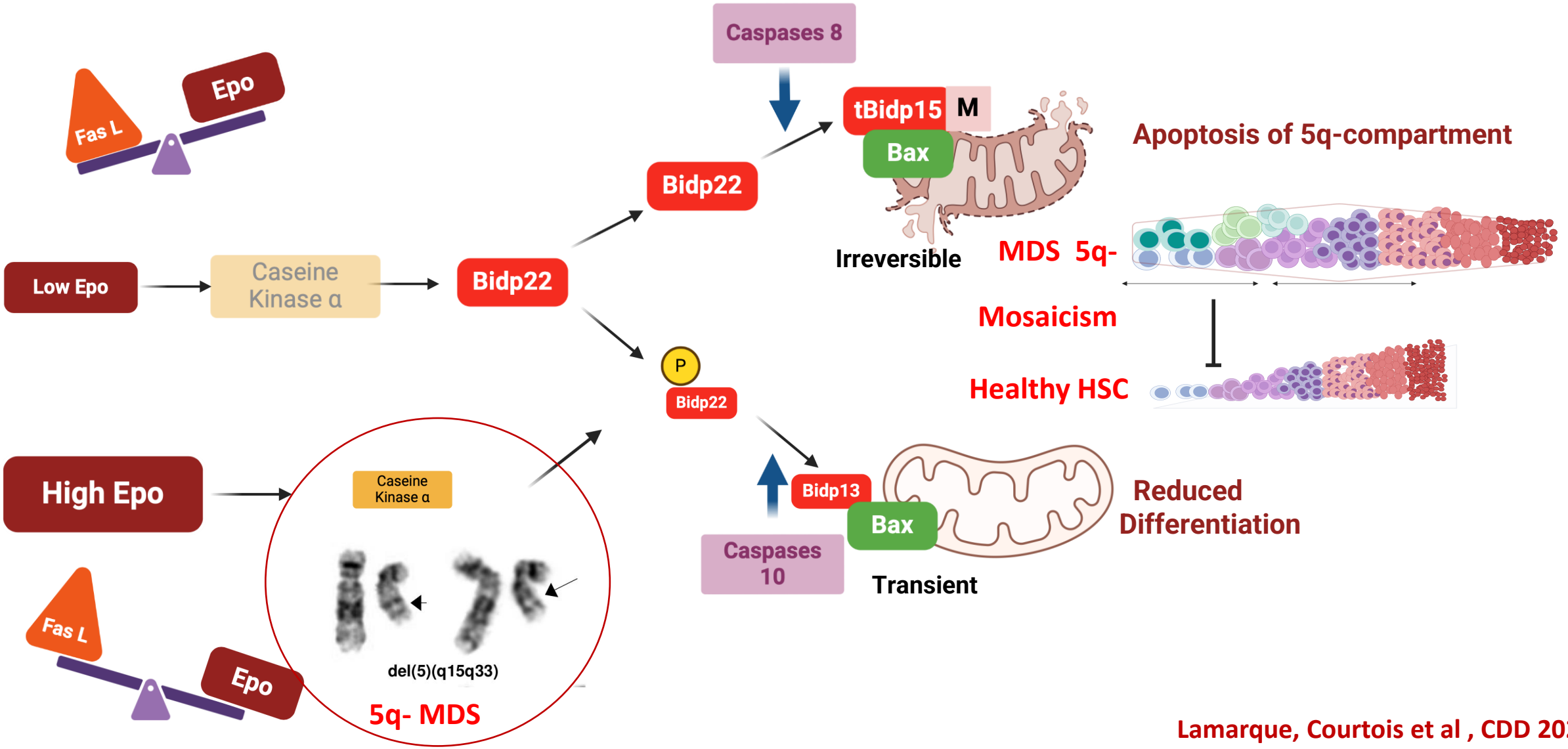
Lamarque, Courtois et al , CDD 2022

Epo modulates Bid cleavage both through induction of Caseine kinase and Caspase 10 activation



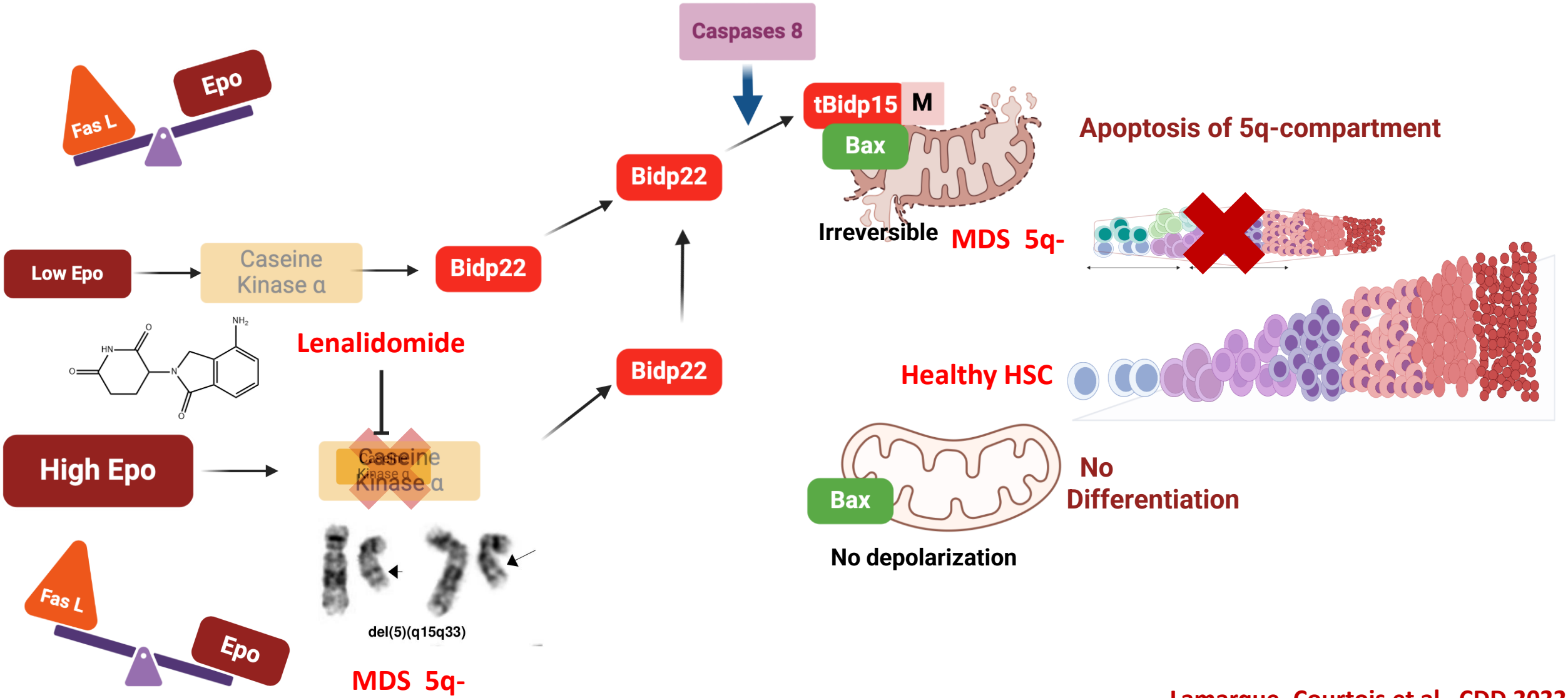
Lamarque, Courtois et al , CDD 2022

Epo modulates Bid cleavage through Caseine Kinase a expression and Caspase 10 activation : Implication in 5q-MDS

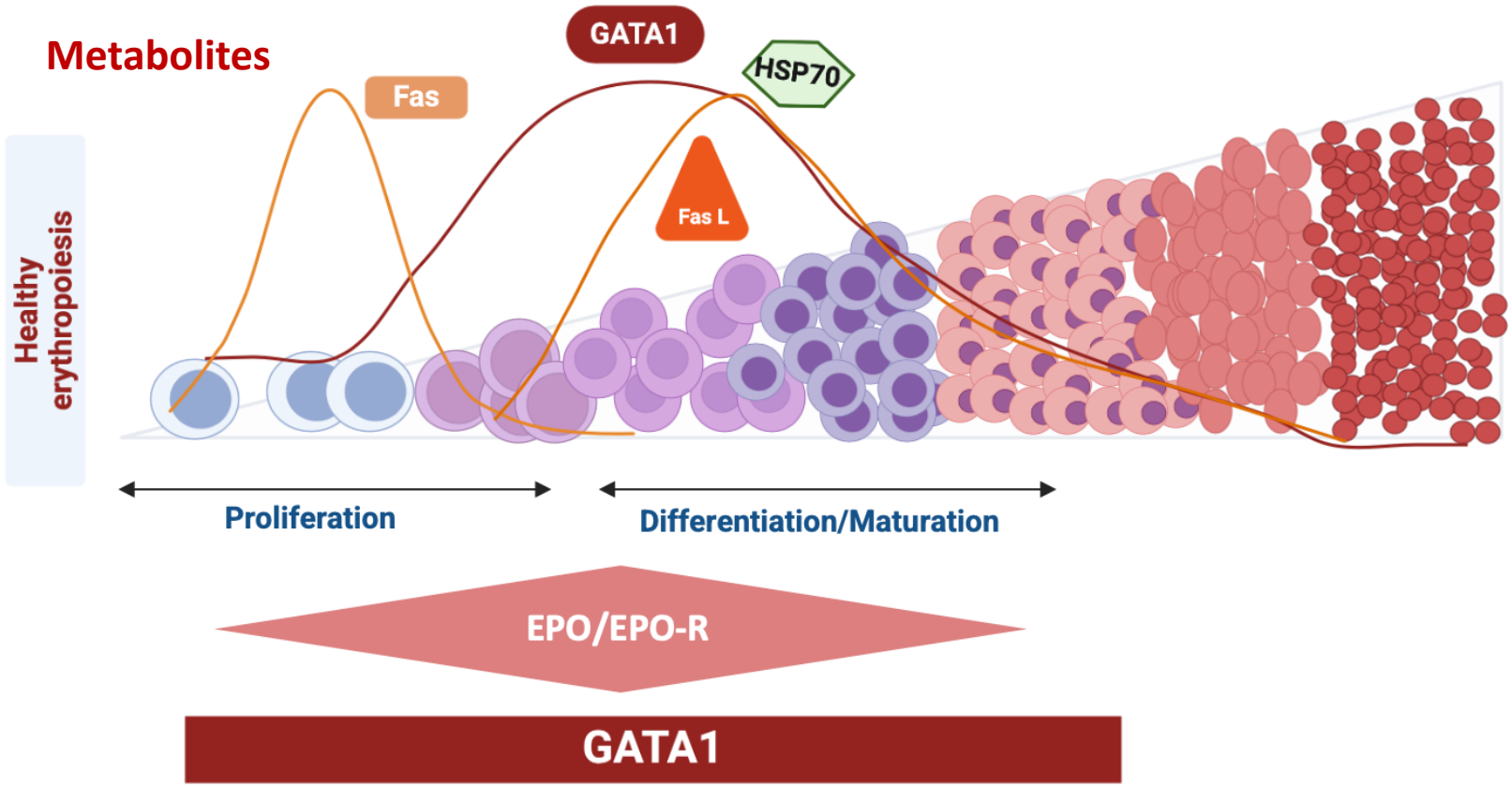


Lamarque, Courtois et al , CDD 2022

Epo modulates Bid cleavage through Caseine Kinase–α expression and Caspase 10 activation : Implication in 5q-MDS



Lamarque, Courtois et al , CDD 2022



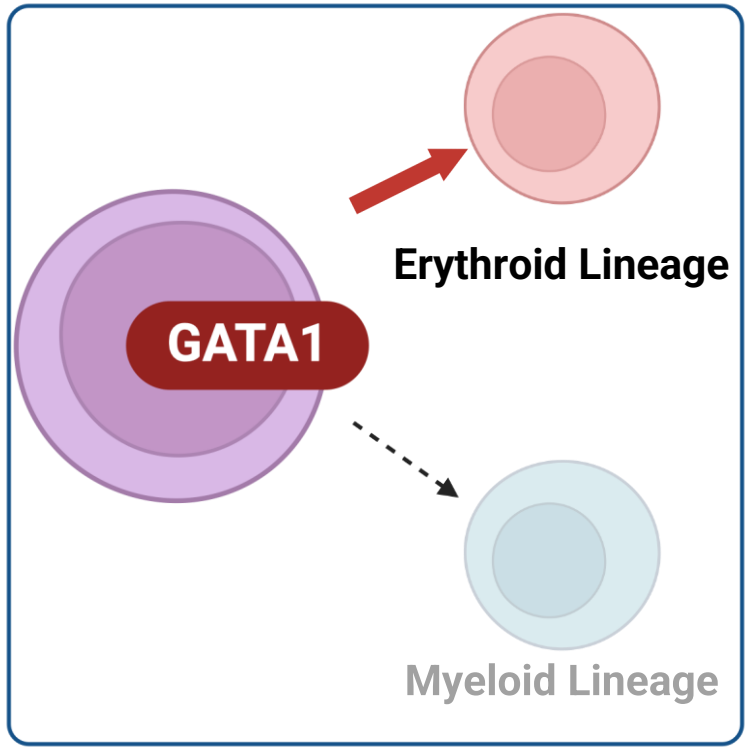
Abnormalities

– germline or somatic mutations/ environmental factors –

in this network may result in pathological erythropoiesis

Defects in Erythropoiesis

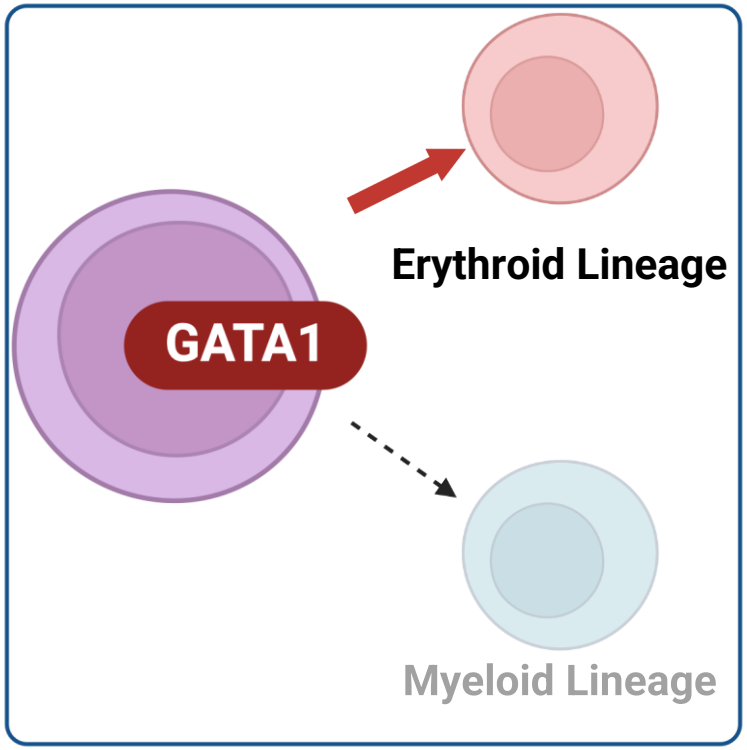
Defects in erythroid commitment



Genetic or environmental factors

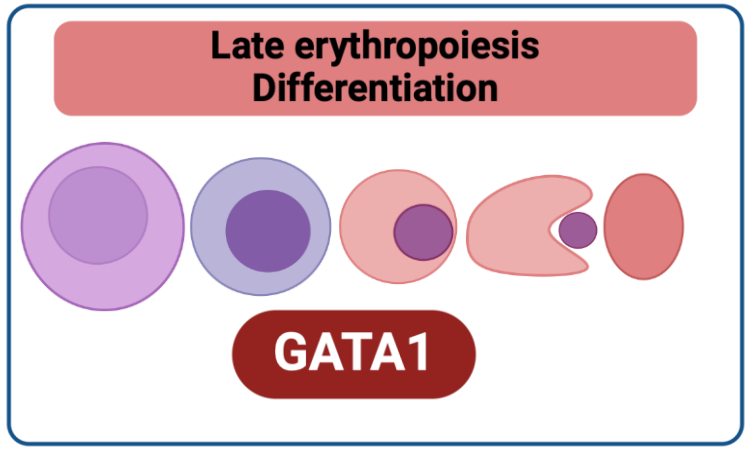
Defects in Erythropoiesis

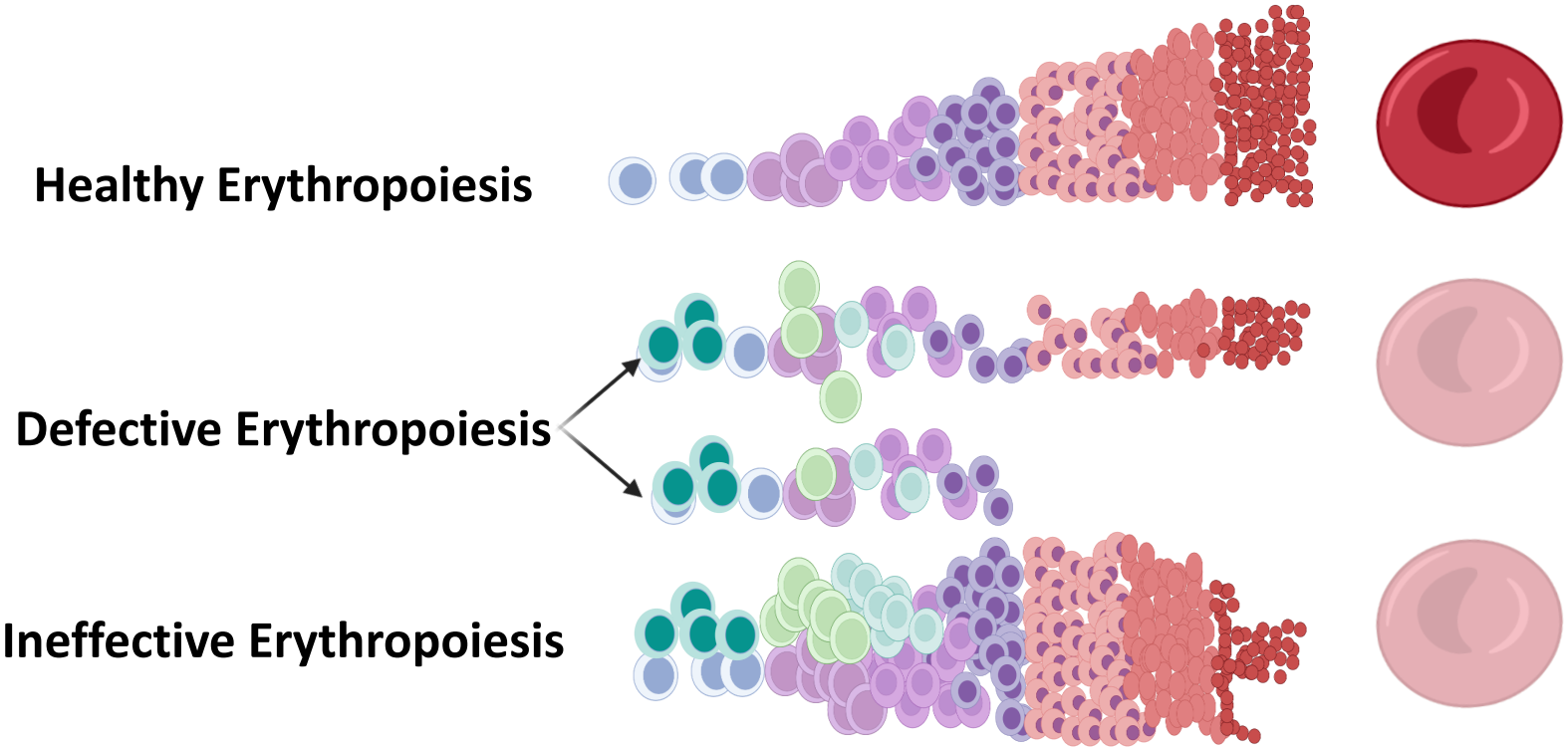
Defects in erythroid commitment



Genetic or environmental factors

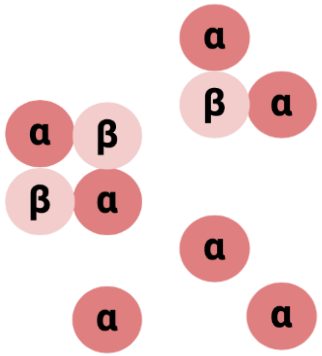
Defects in terminal erythroid differentiation



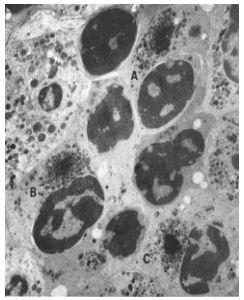


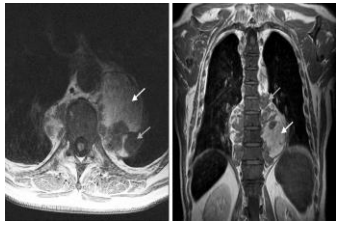
β-Thalassemia - Pathophysiology

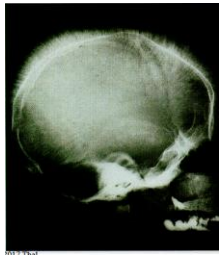
Free α chains



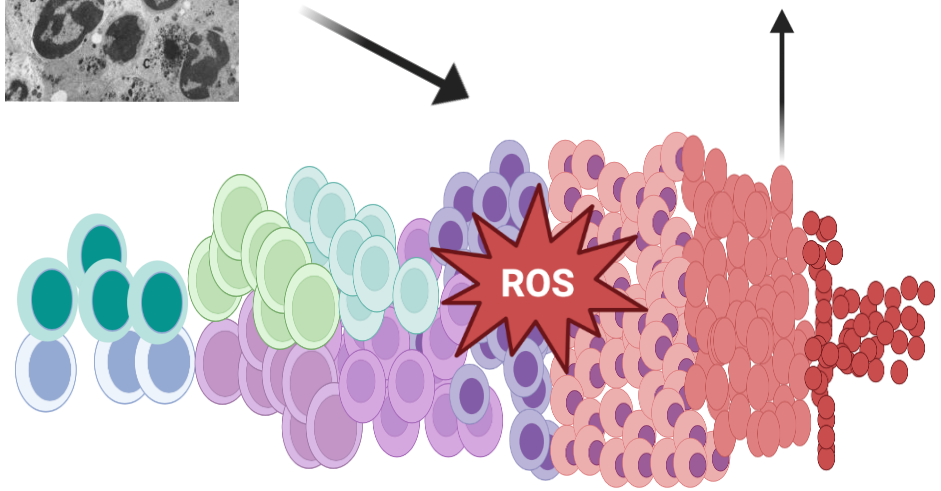
α aggregates







Bone Abnormalities
Extra-medullary erythropoiesis

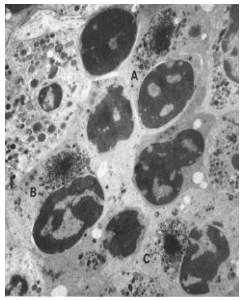


β-Thalassemia - Pathophysiology

Free α chains

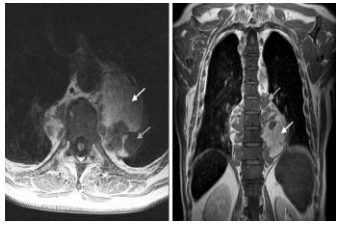
α α β α β α α α

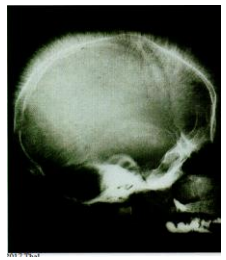
α aggregates



α α γ γ

Fetal Hemoglobin





Bone Abnormalities
Extra-medullary erythropoiesis

β Thalassemia Major - Transfusion Dependent (TDT)

Non-Transfusion Dependent Thalassemia (NTDT)

Hypothyroidism
Hypoparathyroidism

Silent cerebral ischemia

Cardiac siderosis left-sided heart failure

Pulmonary hypertension, right-sided heartfailure

Hepatic failure - viral hepatitis

Extramedullary hematopoiesis

Diabetes mellitus

Gallstones

Splenomegaly

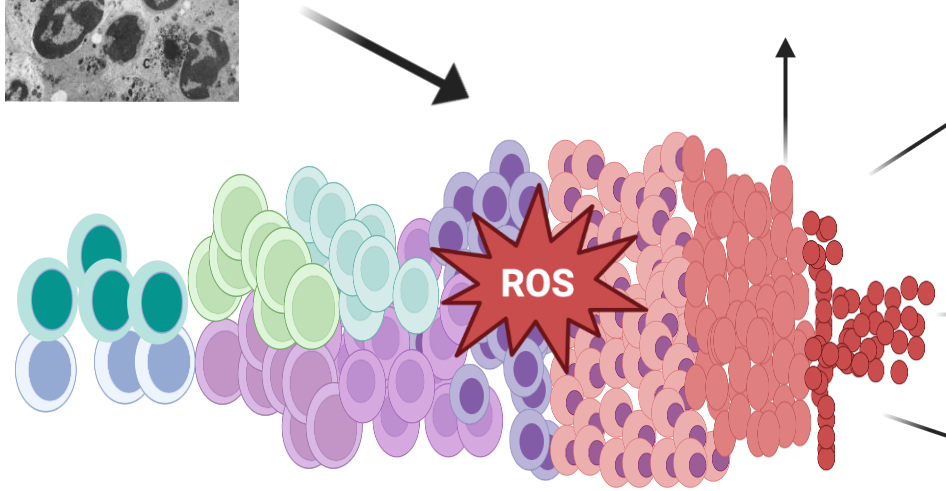
Hypogonadism

Osteoporosis

Leg ulcers

Osteoporosis

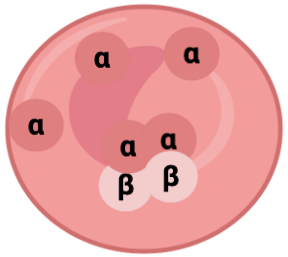
Venus thrombosis



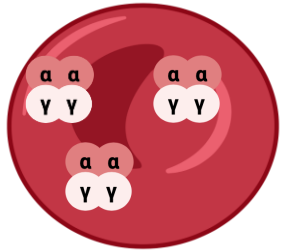
ERFE/hepcidin → Iron overload

Anemia

Other factors ?

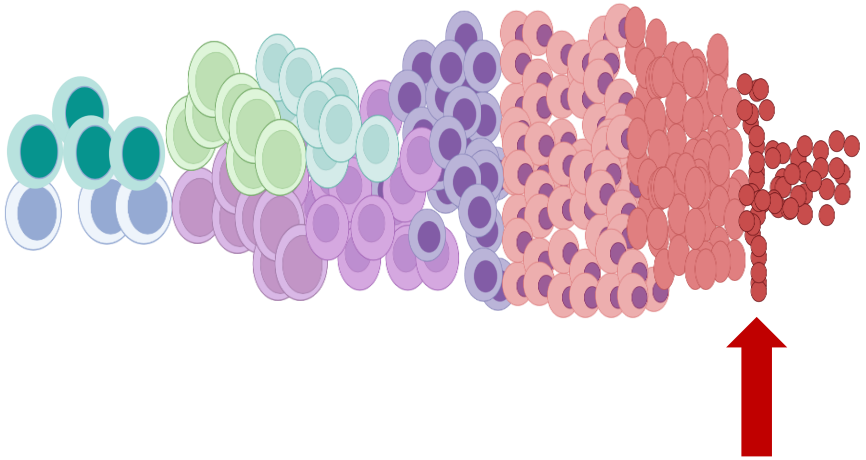


Abnormal red cells

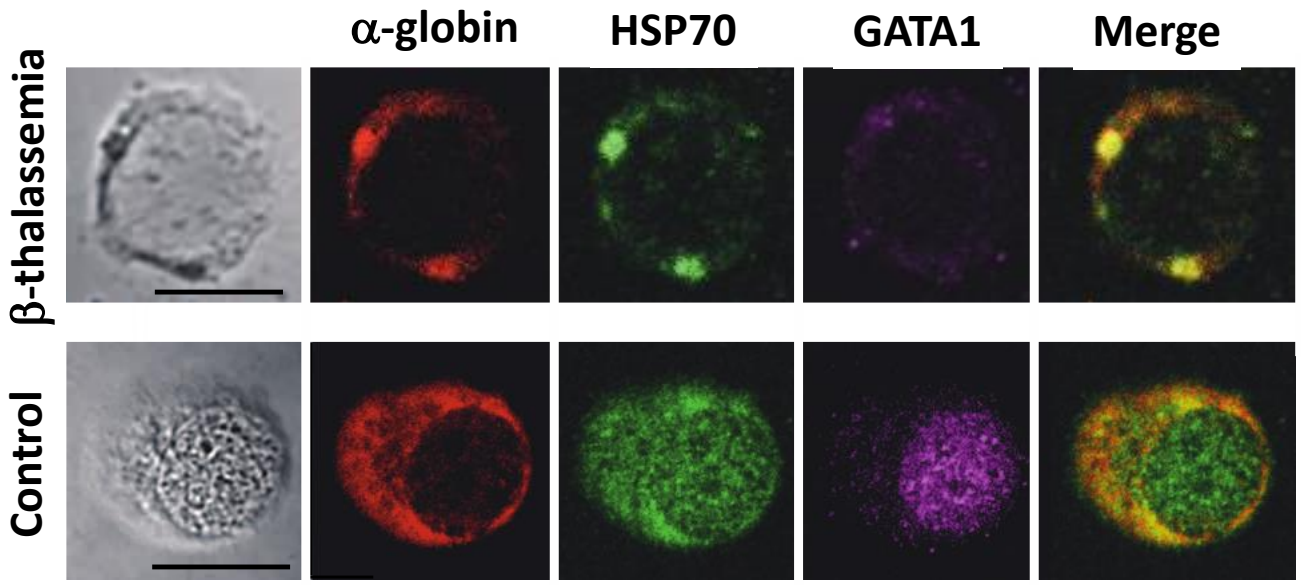


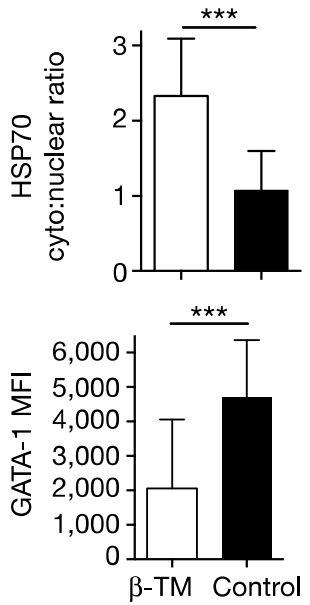
Healthy red cells

Why do mutations in the HBB gene results in defective late stage differentiation?



HSP70 is sequestered in the cytosol by alpha chain aggregates





Arlet JB et al, Nature 2012

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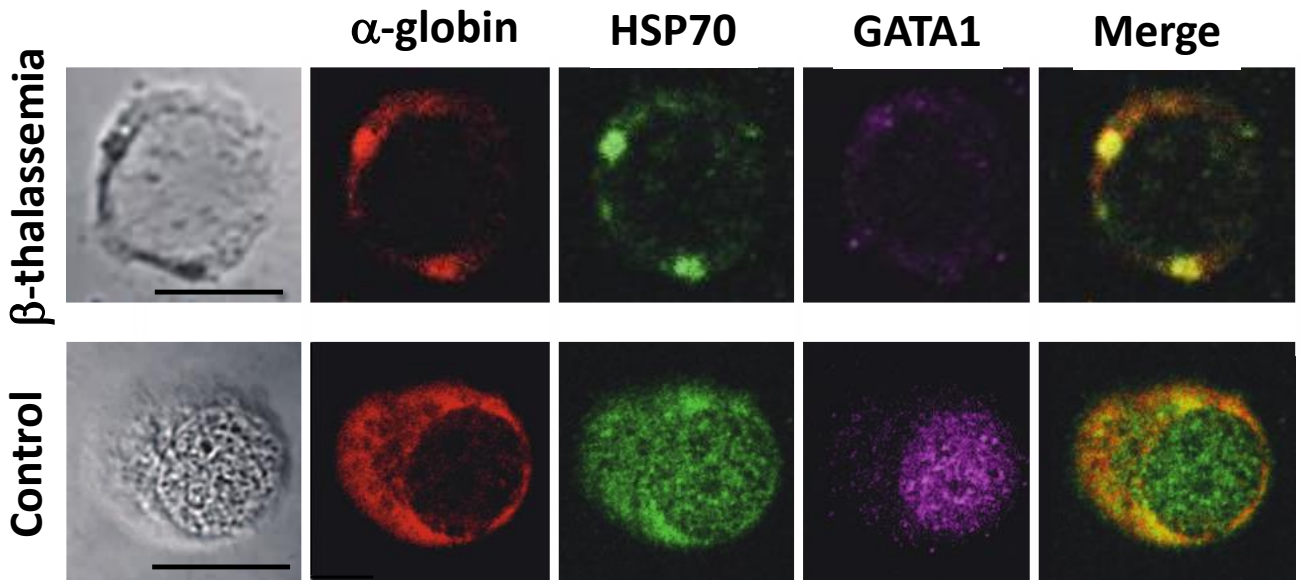
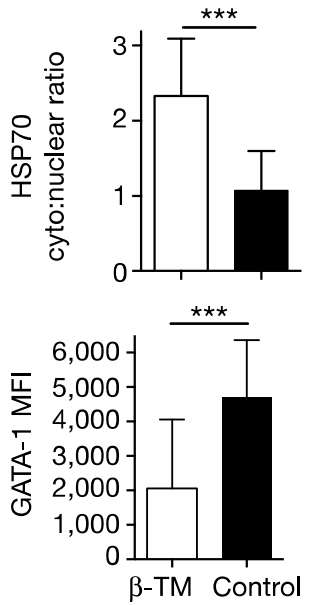
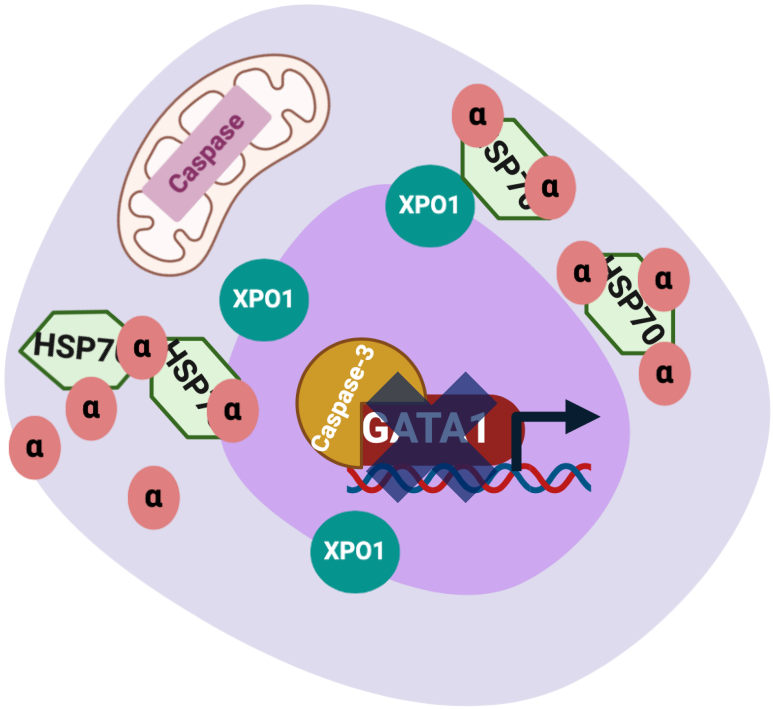




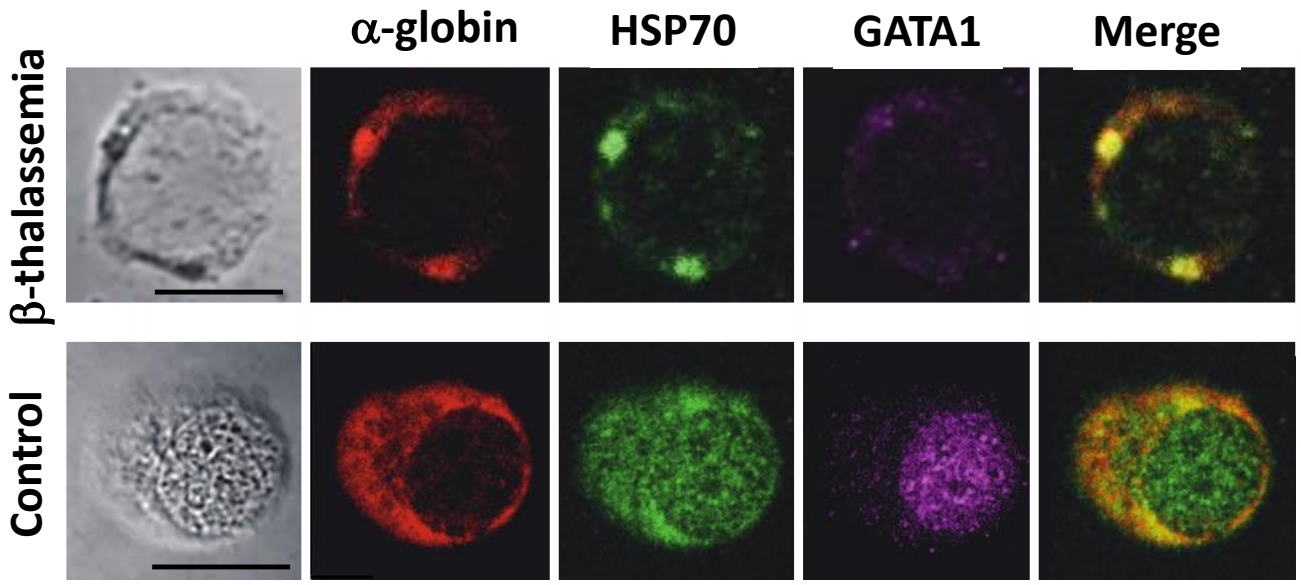


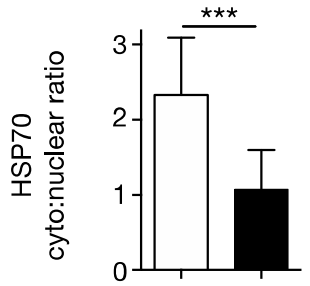
Cell Death and Erythroid Differentiation Arrest

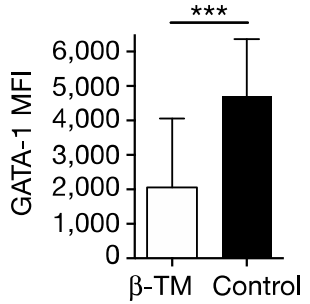
HSP70 sequestration decreases GATA1 Level

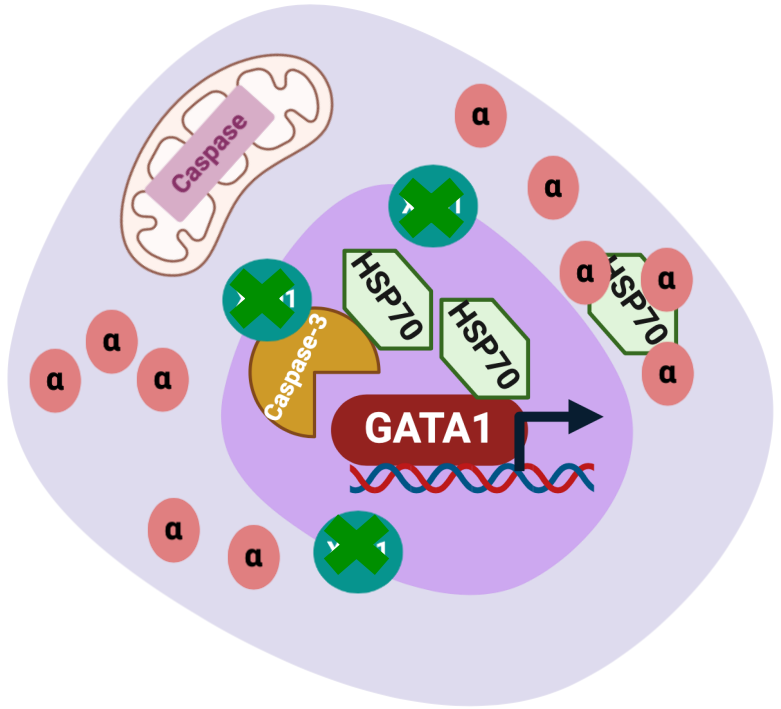
Arlet JB et al, Nature 2012

HSP70 is sequestered by alpha chain globin aggregates and may be a target of XPO-1 inhibitors

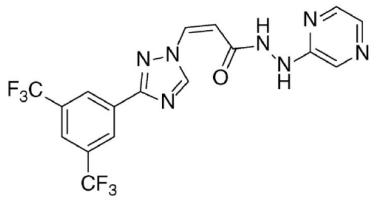


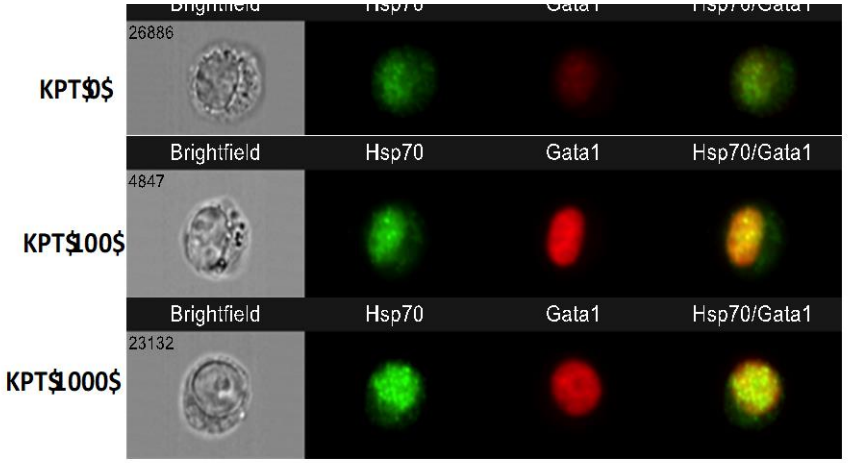






XPO1 Inhibitor

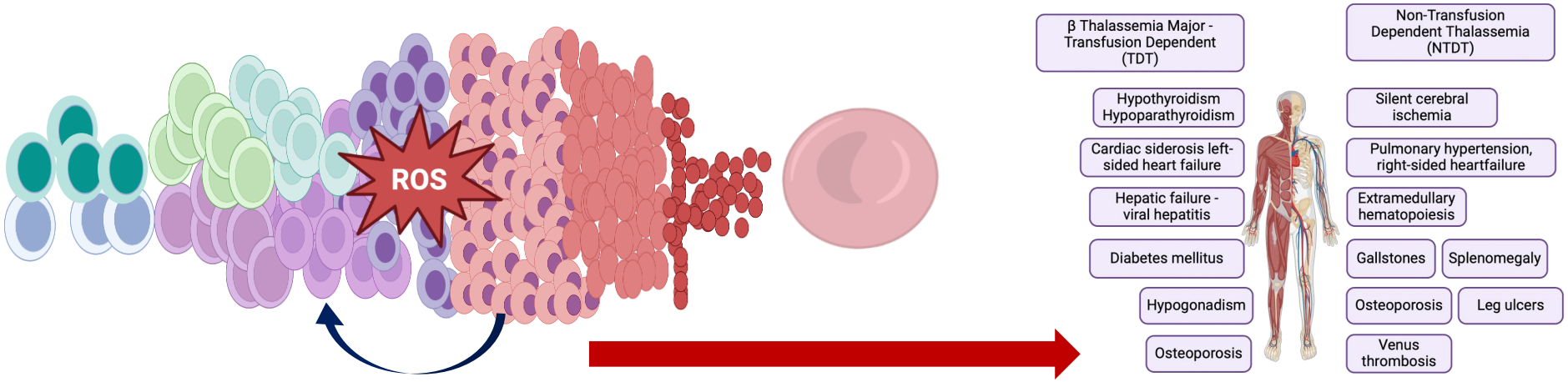




Survival and Erythroid Differentiation

Arlet JB et al, Nature 2012

Do thalassemic precursors express differentiation/ proliferation factors that can be therapeutically targeted?



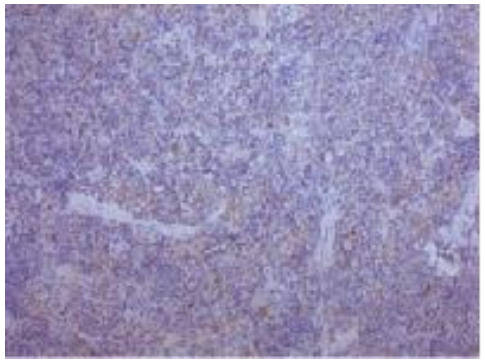
Secreted factors that could play a role in ineffective erythropoiesis and disease manifestations (bone, muscle, heart, endothelial cells) ?

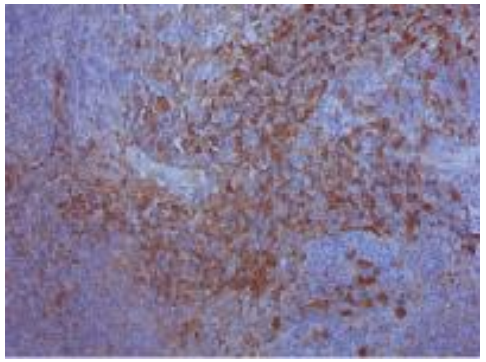
GDF-11 (TGF-β member family) expression is increased in β- Thalassemic mice and humans

Gdf11

Wild-type

Hbb th1/th1





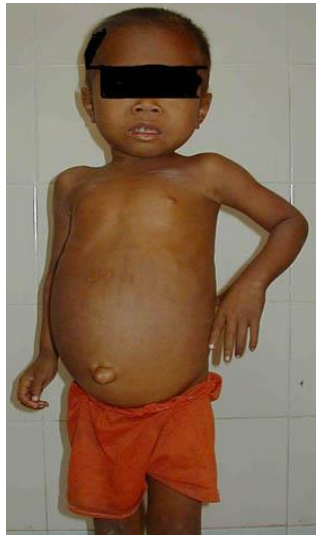
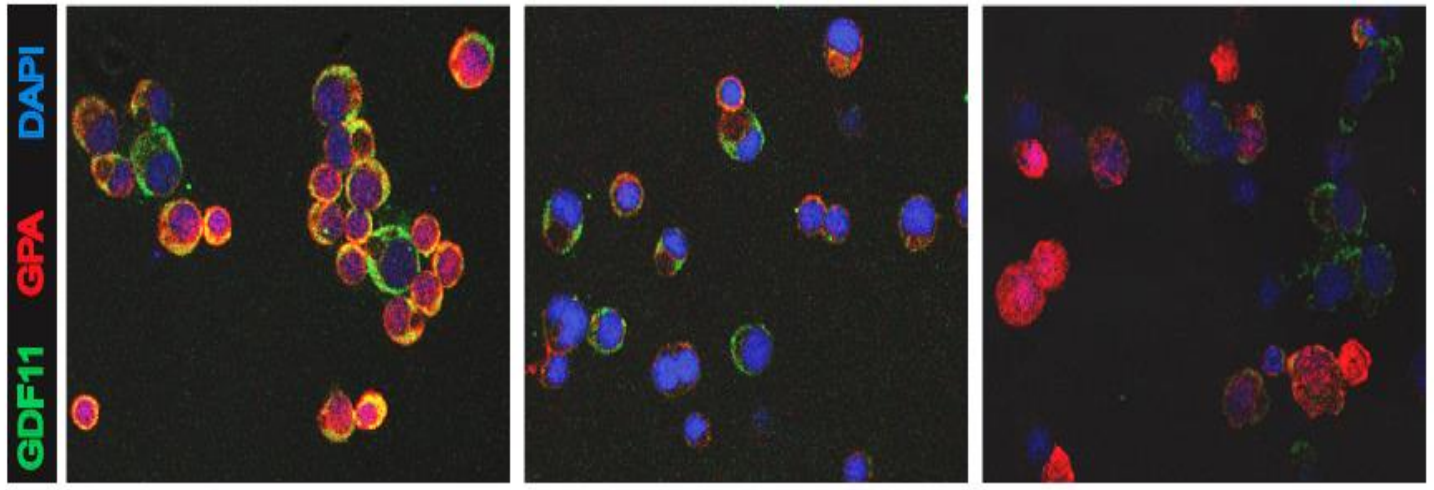


Photo used with consent

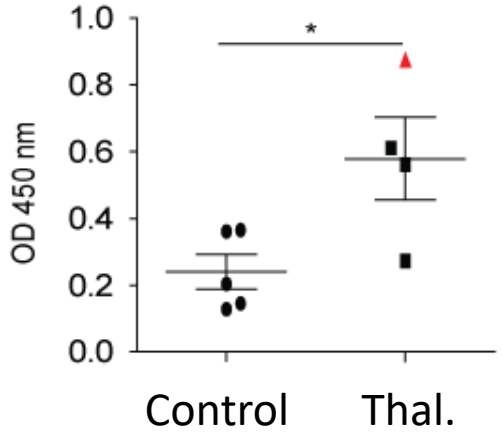
Thalassemia Major Patient 1

Thalassemia Major Patient 2

Cord blood (Control)

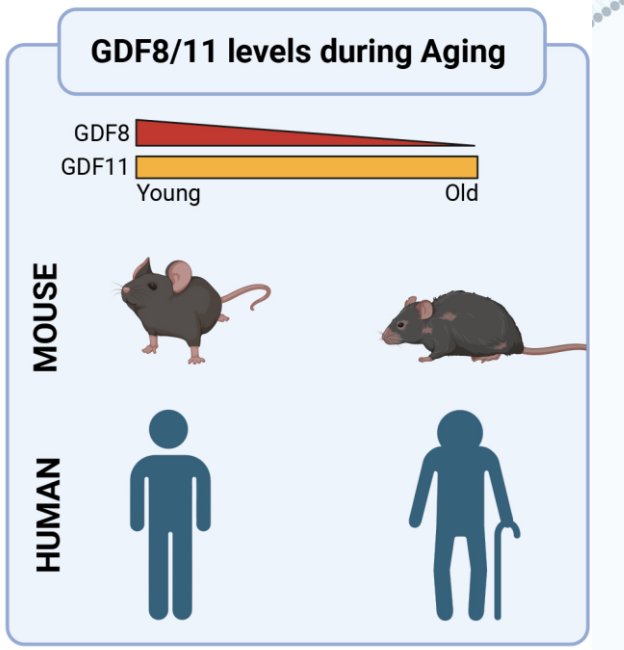


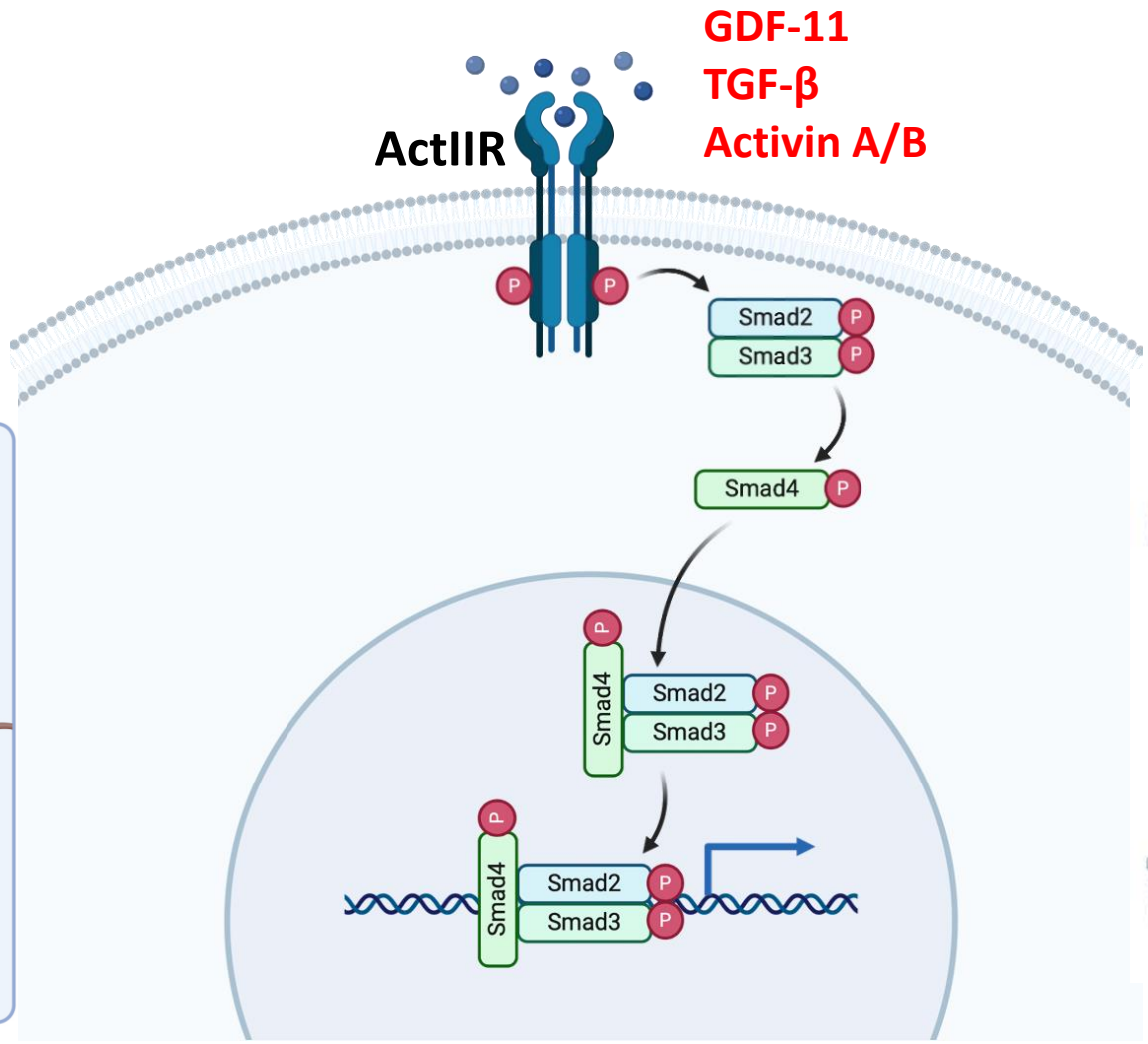
GDF-11

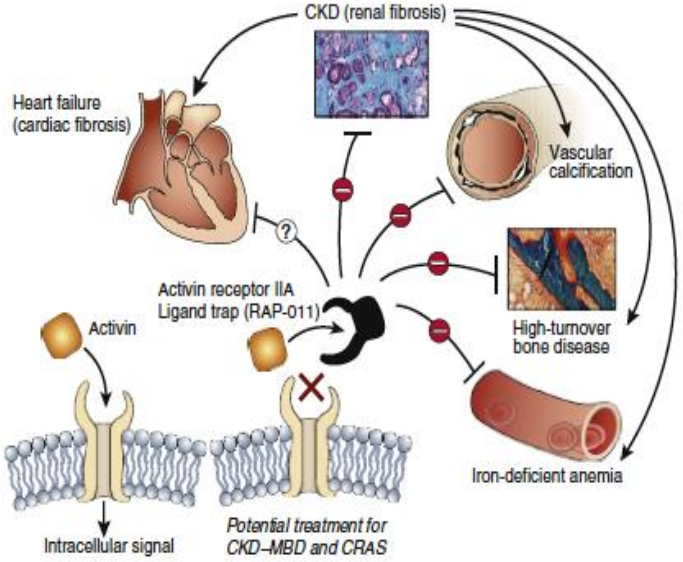


Dussiot M and Maciel TT et al, Nature Med 2014

GDF-11: A member of the TGF- β family of pleitropic cytokines



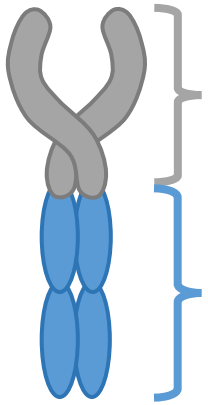




Adapted from: Agapova et al. Kidney International 2016

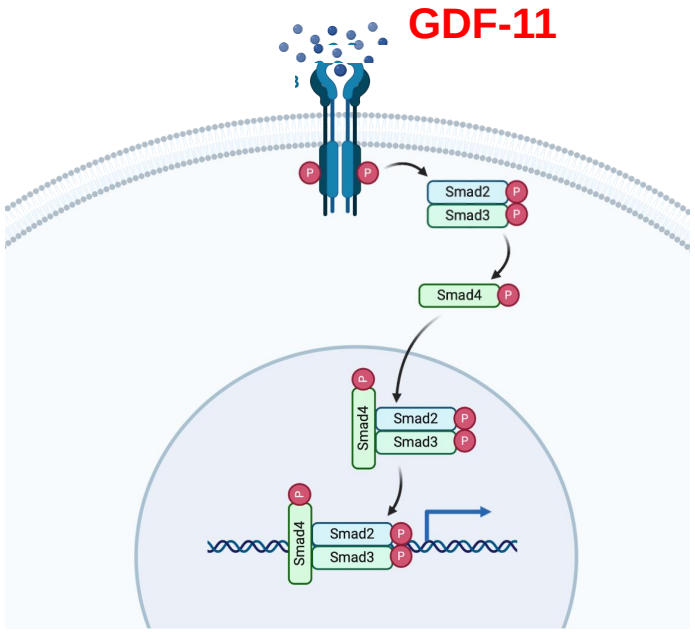
Luspatercept is a TRAP receptor of GDF-11

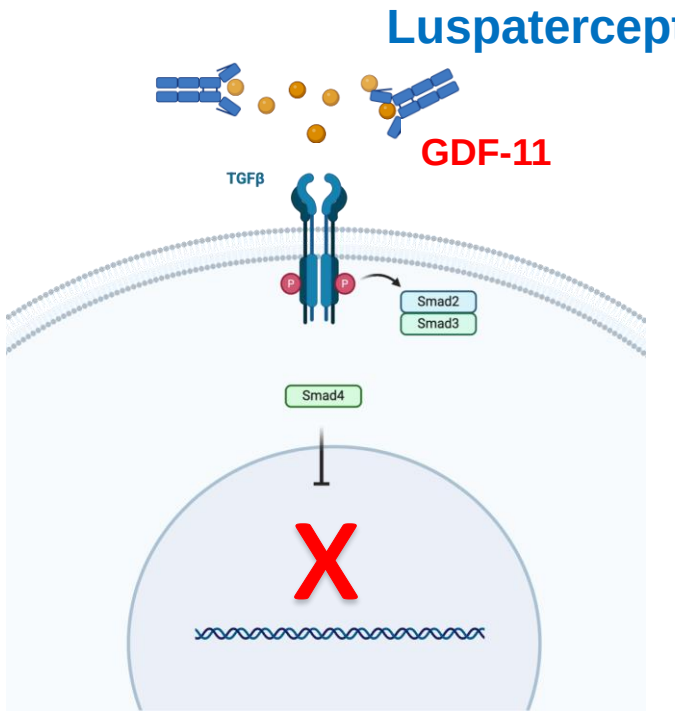
Luspatercept
ActRIIB / IgG1 Fc recombinant fusion protein



Modified extracellular domain of ActRIIB (GDF-8/11)

Human IgG1 Fc domain





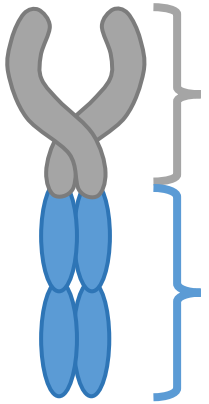
Can GDF-11 TRAP improve ineffective erythropoiesis ?

Dussiot M and Maciel TT et al, Nat Med 2014; Suragani et al Blood 2014

Luspatercept increases hemoglobin levels

Luspatercept

ActRIIB / IgG1 Fc recombinant fusion protein



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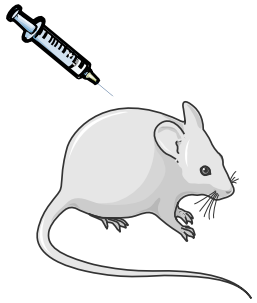
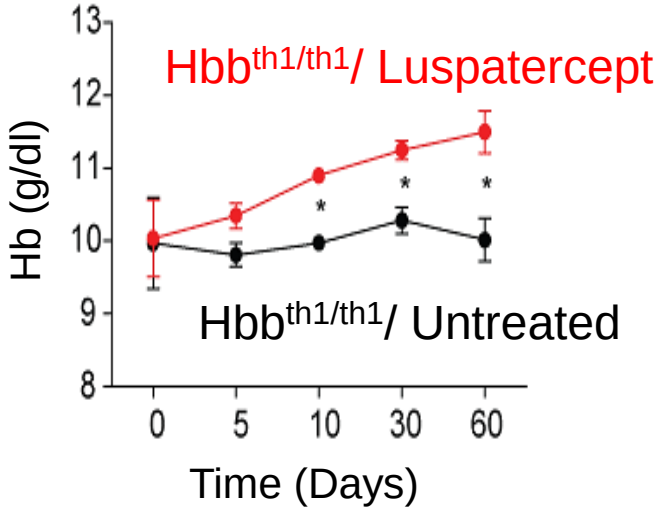
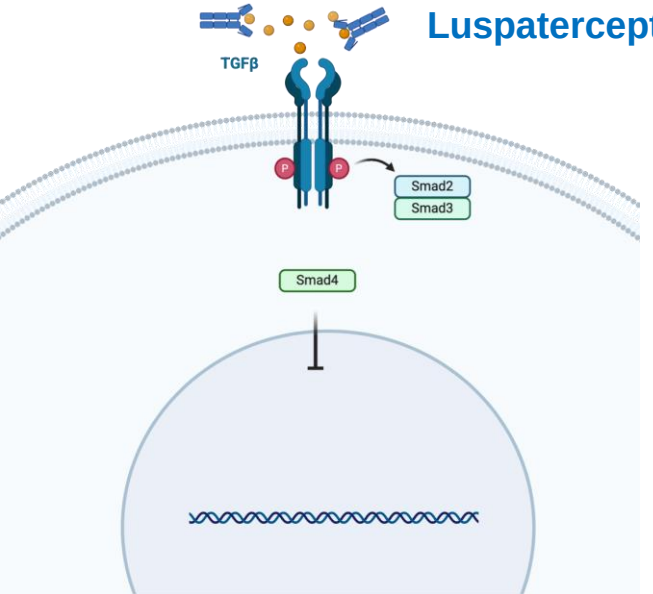
Human IgG1 Fc domain





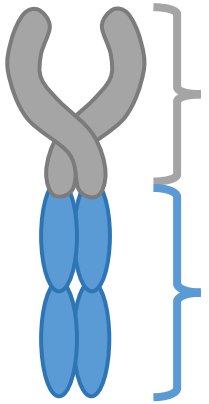


Dussiot M and Maciel TT et al, Nat Med 2014; Suragani et al Blood 2014

Luspatercept corrects ineffective erythropoiesis in a β-thalassemia mouse model ($Hbb^{th1/th1}$)

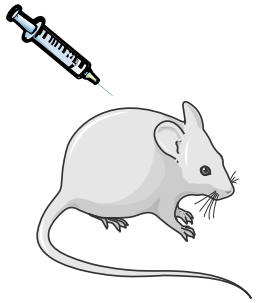
Luspatercept

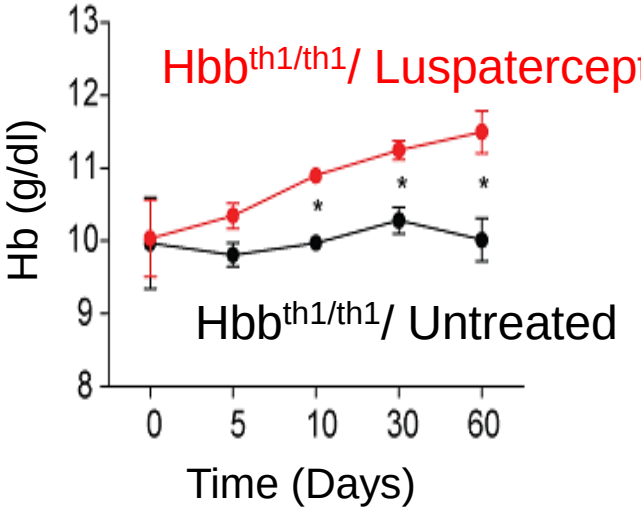
ActRIIB / IgG1 Fc recombinant fusion protein

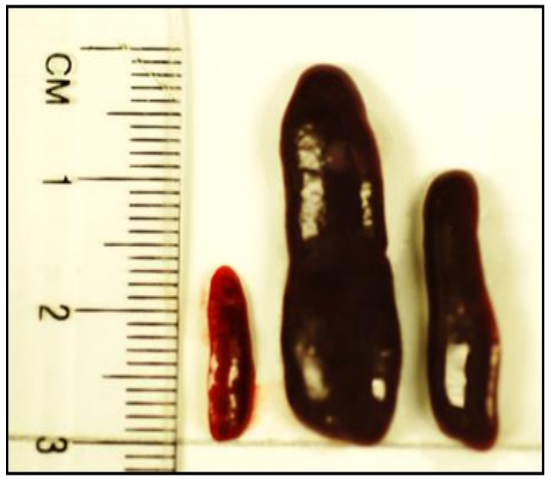


Modified extracellular domain of ActRIIB (GDF-8/11)

Human IgG1 Fc domain





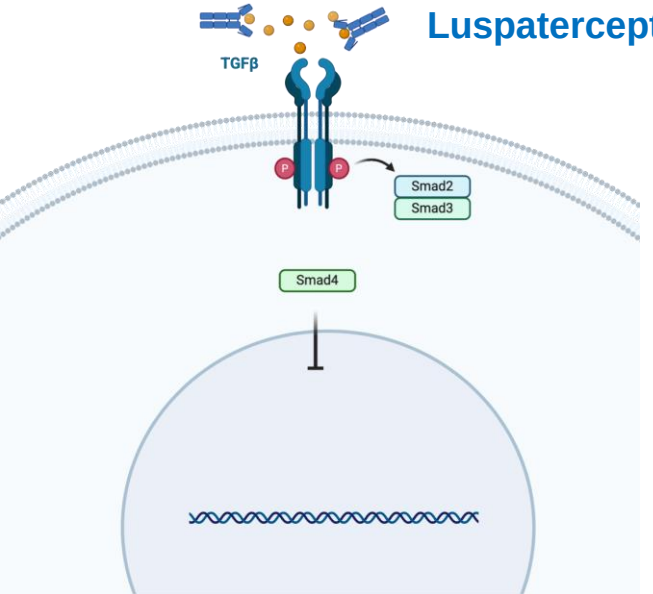


WT

$Hbb^{th1/th1}$/ Untreated

$Hbb^{th1/th1}$/ Luspatercept

Luspatercept



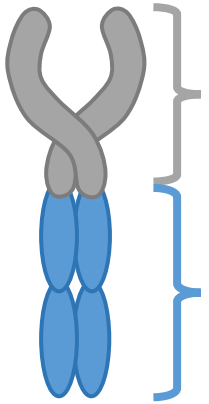
Luspatercept results in decreased splenomegaly in $Hbb^{th1/th1}$ mice

Dussiot M and Maciel TT et al, Nat Med 2014; Suragani et al Blood 2014

Luspatercept reduces co-morbidities in a β-thalassemia mouse model

Luspatercept

ActRIIB / IgG1 Fc recombinant fusion protein



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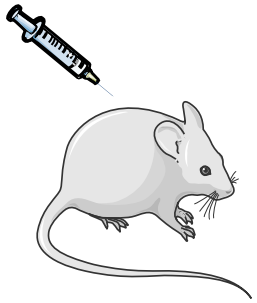
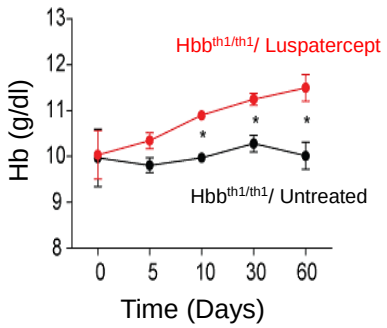
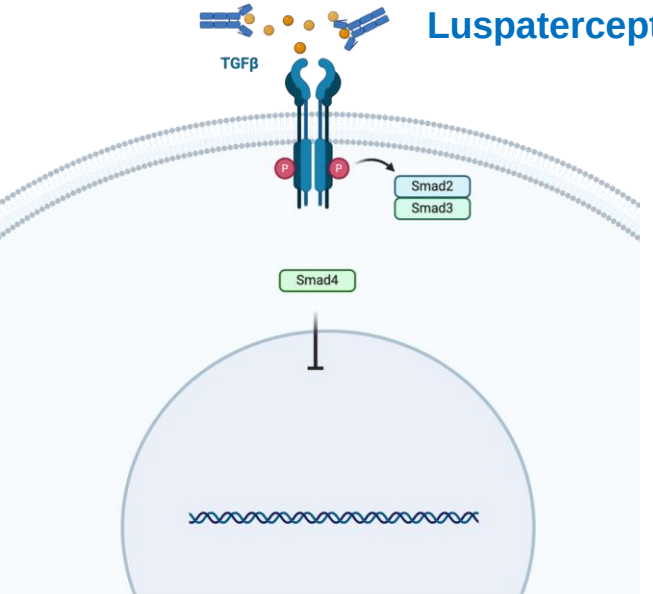
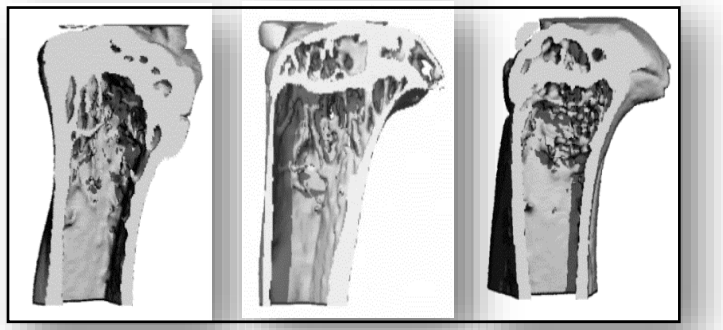
Human IgG1 Fc domain





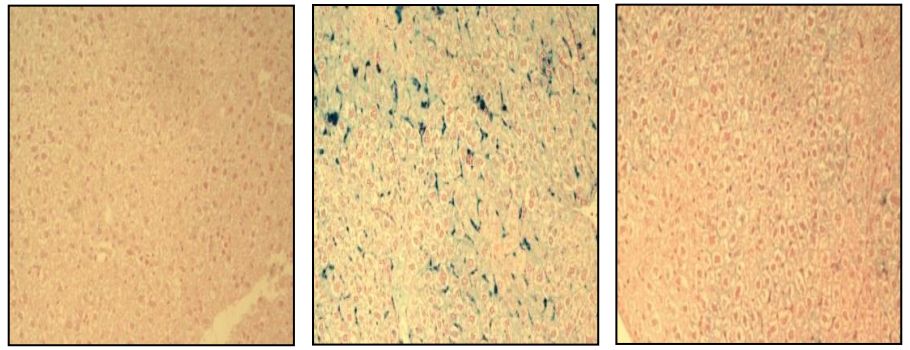


Improved Bone Mineral Density



WT | Hbb$^{th1/th1}$/ Untreated | Hbb$^{th1/th1}$/ Luspatercept

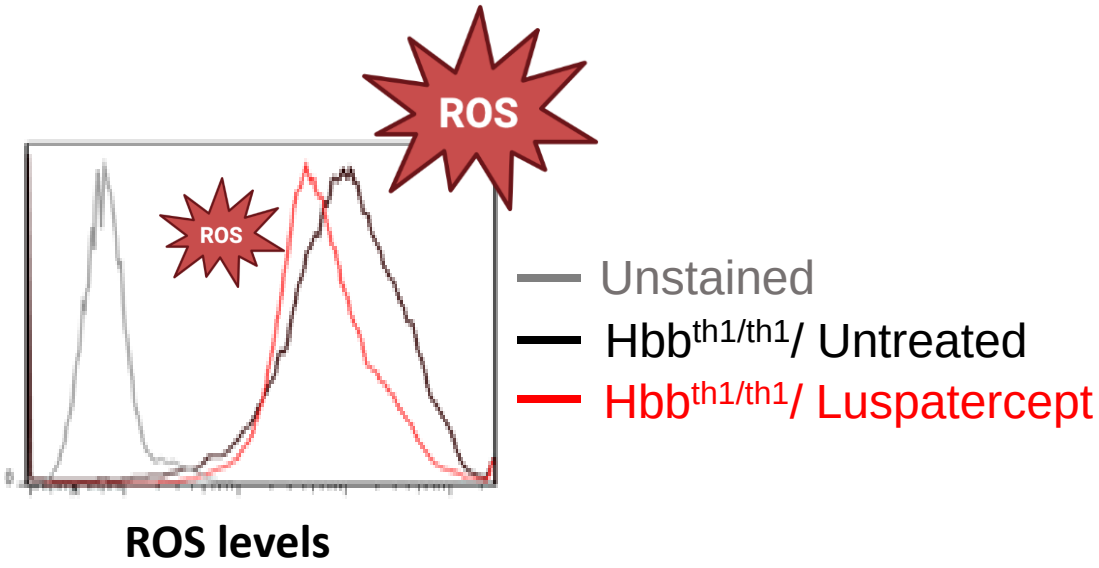
Decreased Liver Iron



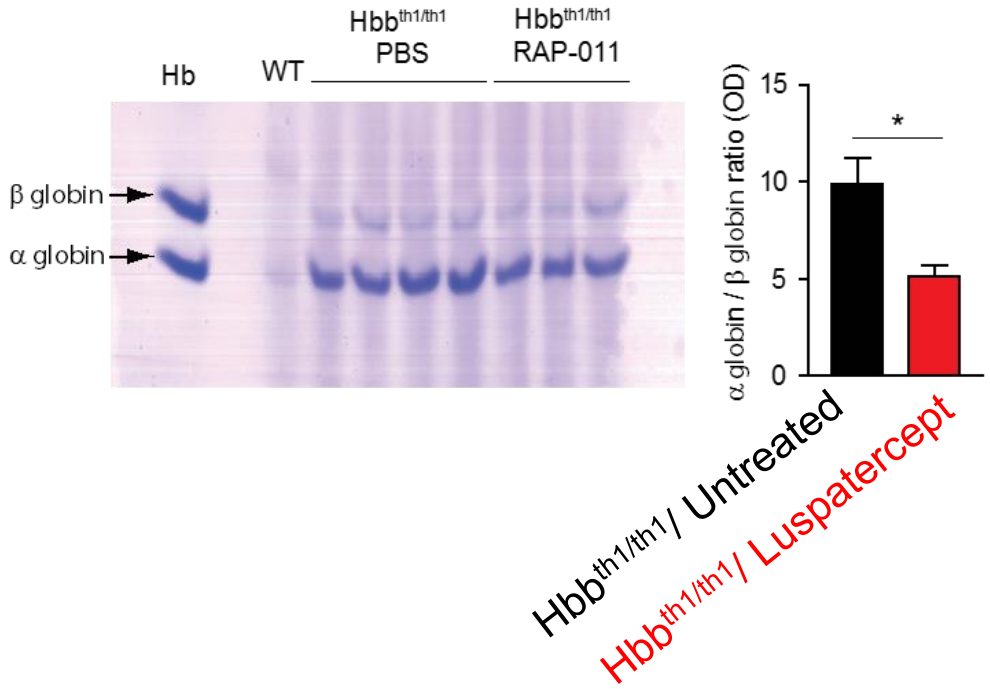
WT | Hbb$^{th1/th1}$/ Untreated | Hbb$^{th1/th1}$/ Luspatercept

Dussiot M and Maciel TT et al, Nat Med 2014; Suragani et al Blood 2014

Luspatercept reduces ROS generation, α-globin, hemoglobin precipitates in β-thalassemia

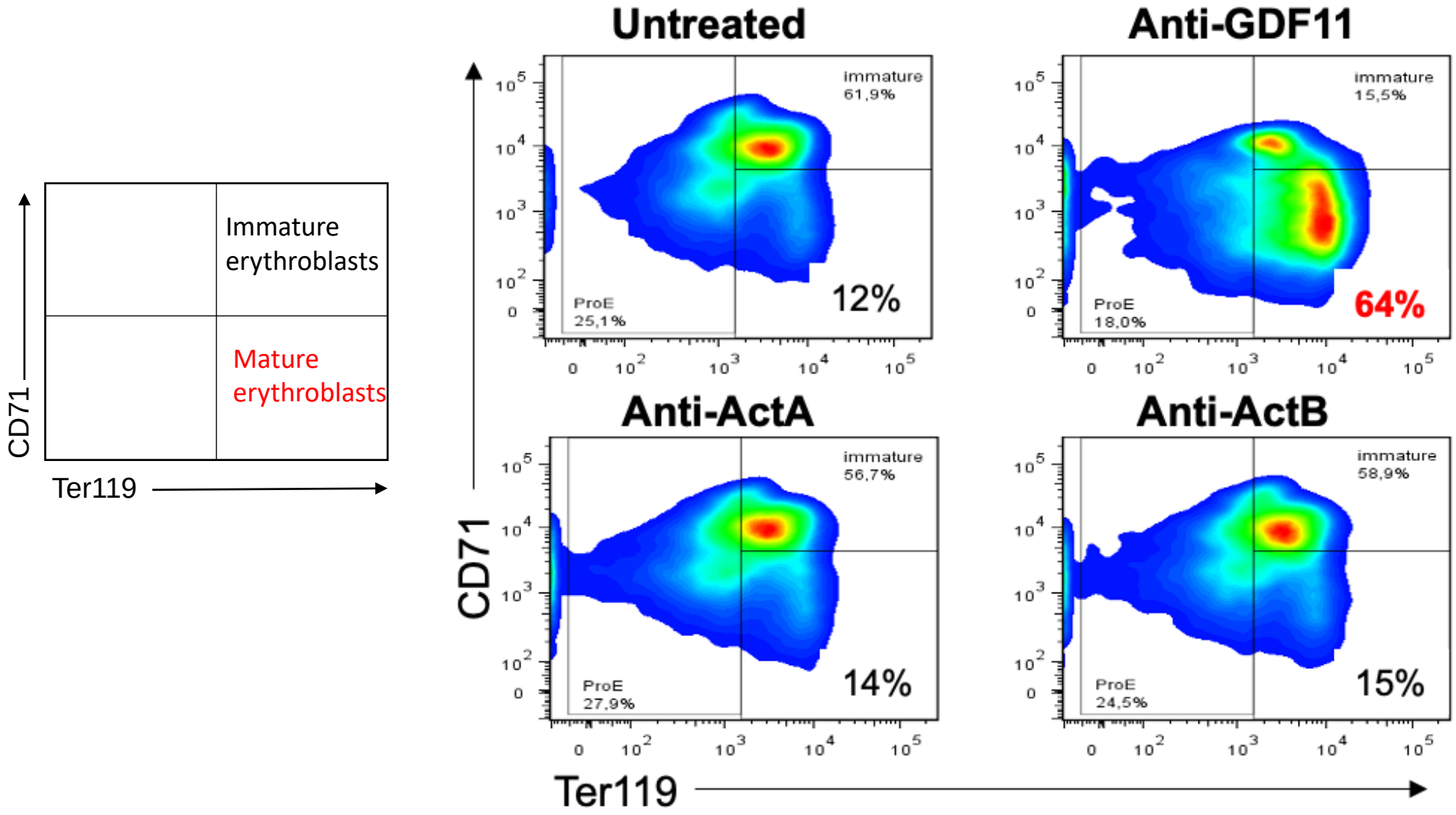


ROS levels



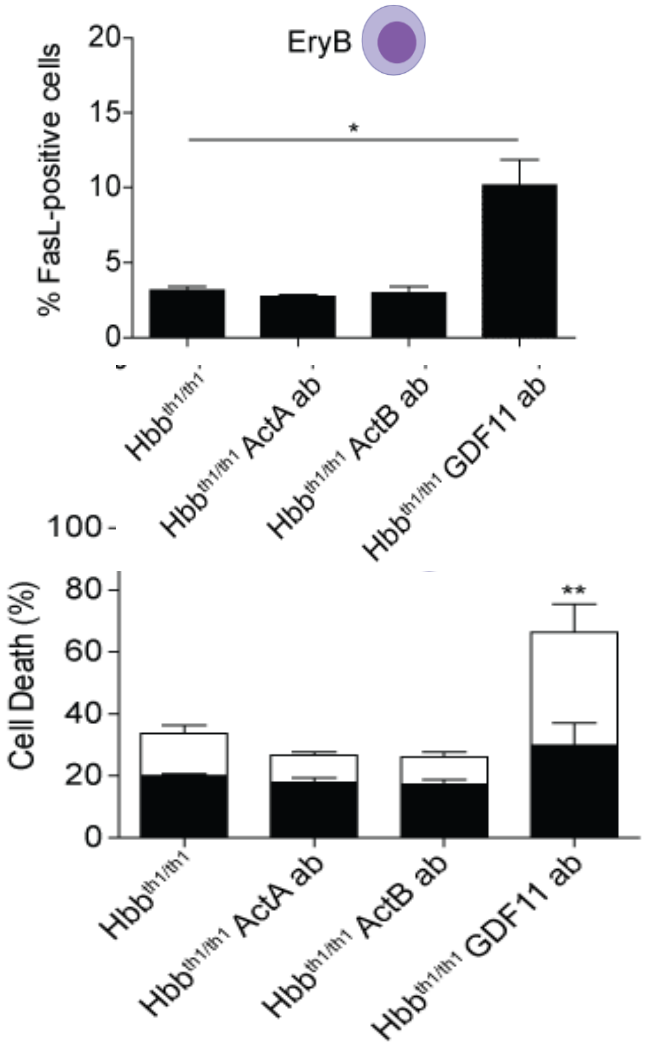
Dussiot M and Maciel TT et al Nature Medicine 2014

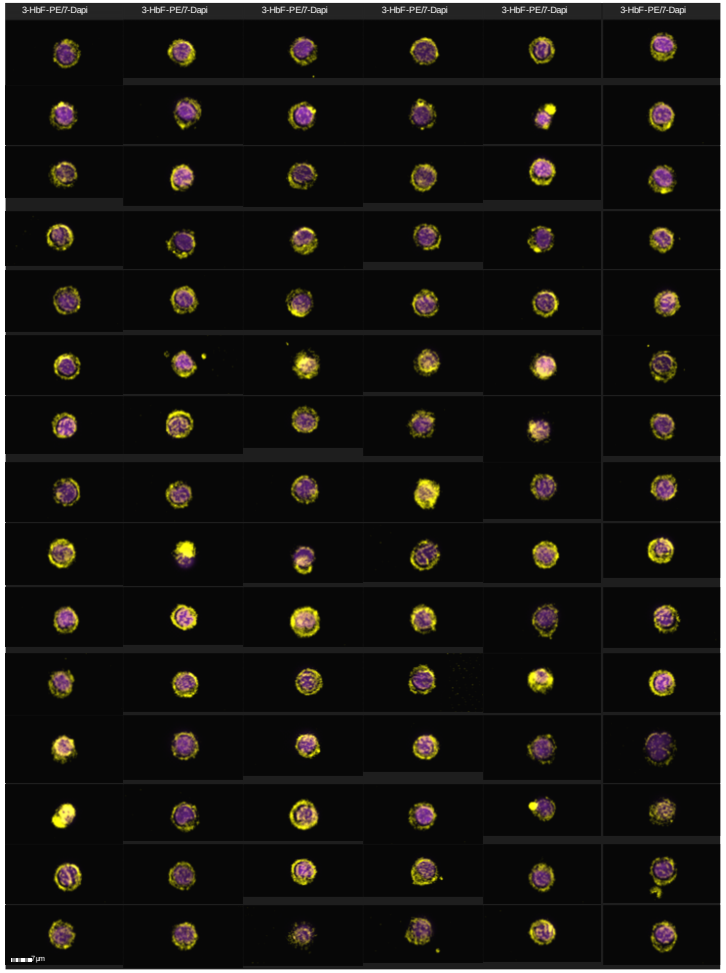
Luspatercept restoration of terminal erythroid differentiation occurs through GDF-11 trapping



Dussiot M and Maciel TT et al Nature Medicine 2014

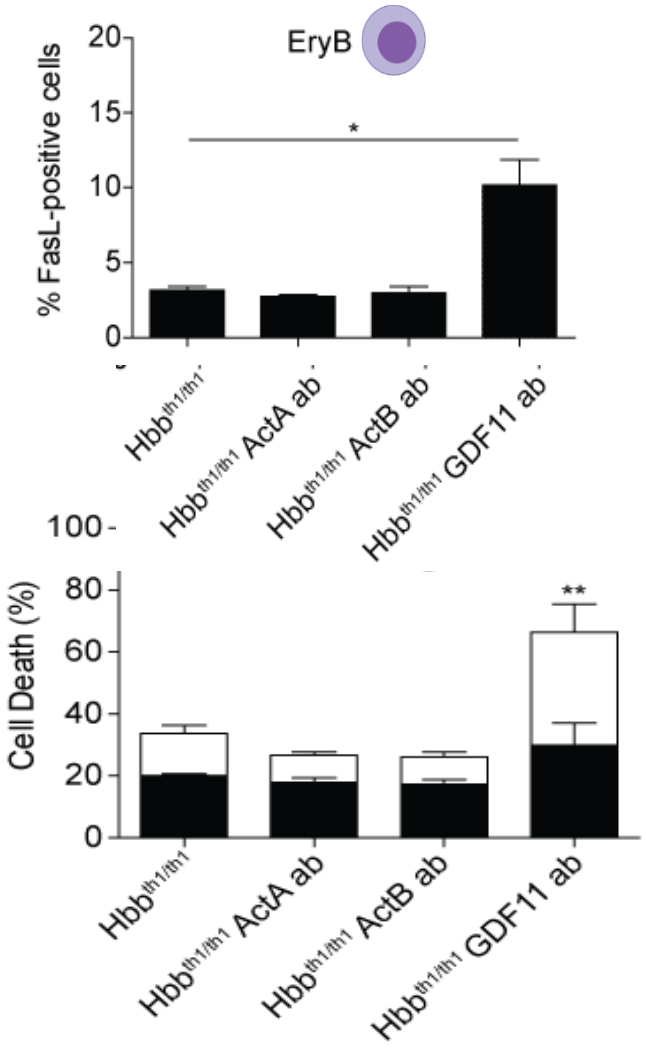
Luspatercept induces FAS-L and reduces ineffective erythropoiesis selecting « better » red cells with more HbF (human)

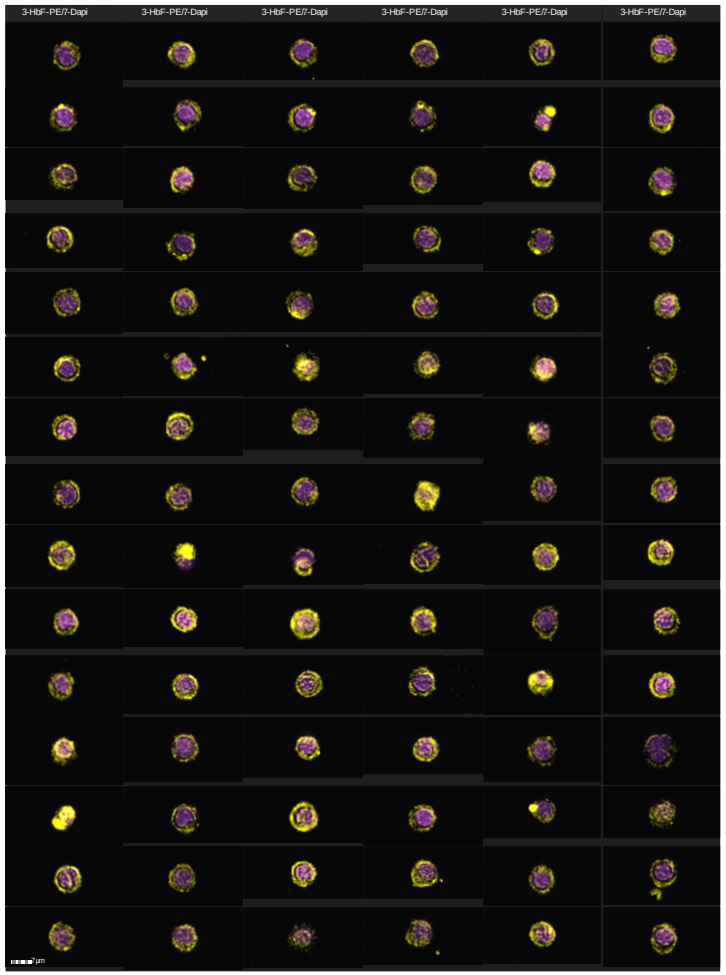




HbF (yellow) Nucleus (purple)

Luspatercept induces FAS-L and reduces ineffective erythropoiesis selecting « better » red cells with more HbF (human)





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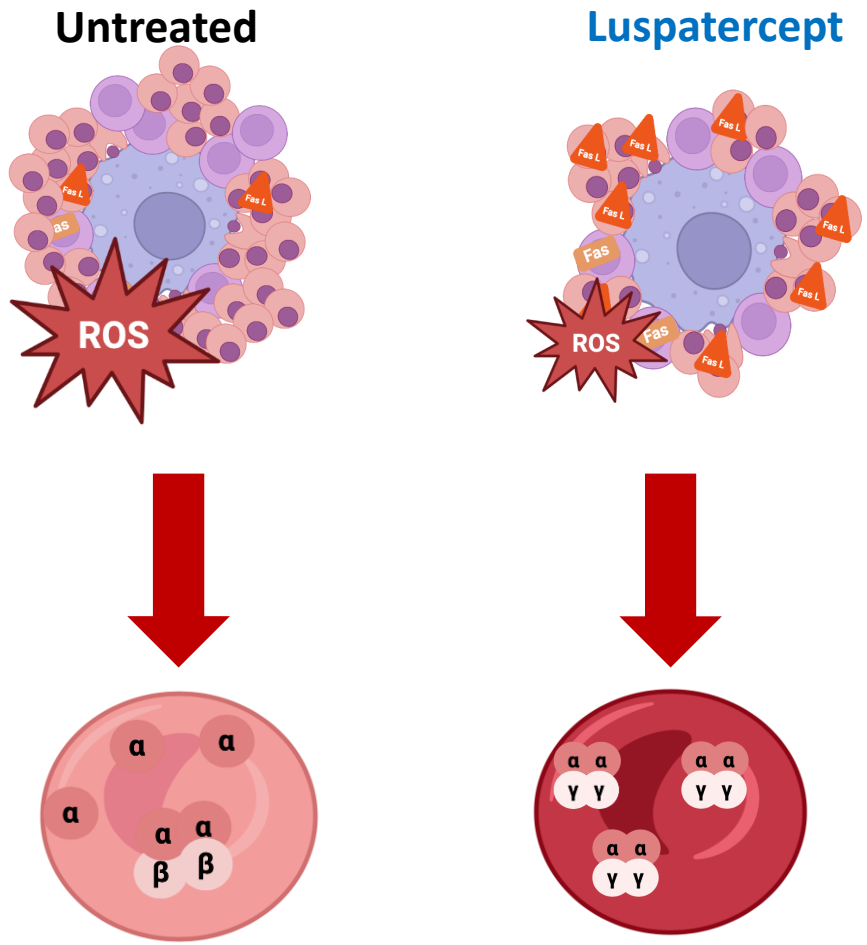
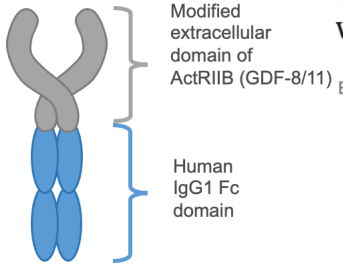


Luspatercept reduces blood transfusion needs in thalassemic patients and improves some manifestations of ineffective erythropoiesis

The NEW ENGLAND JOURNAL of MEDICINE

Luspatercept
ActRIIB / IgG1 Fc recombinant fusion protein

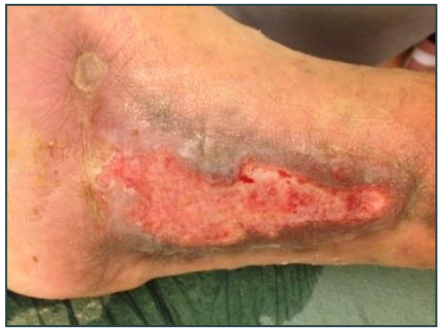


ORIGINAL ARTICLE

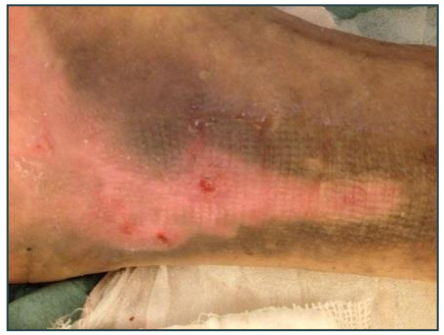
A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia

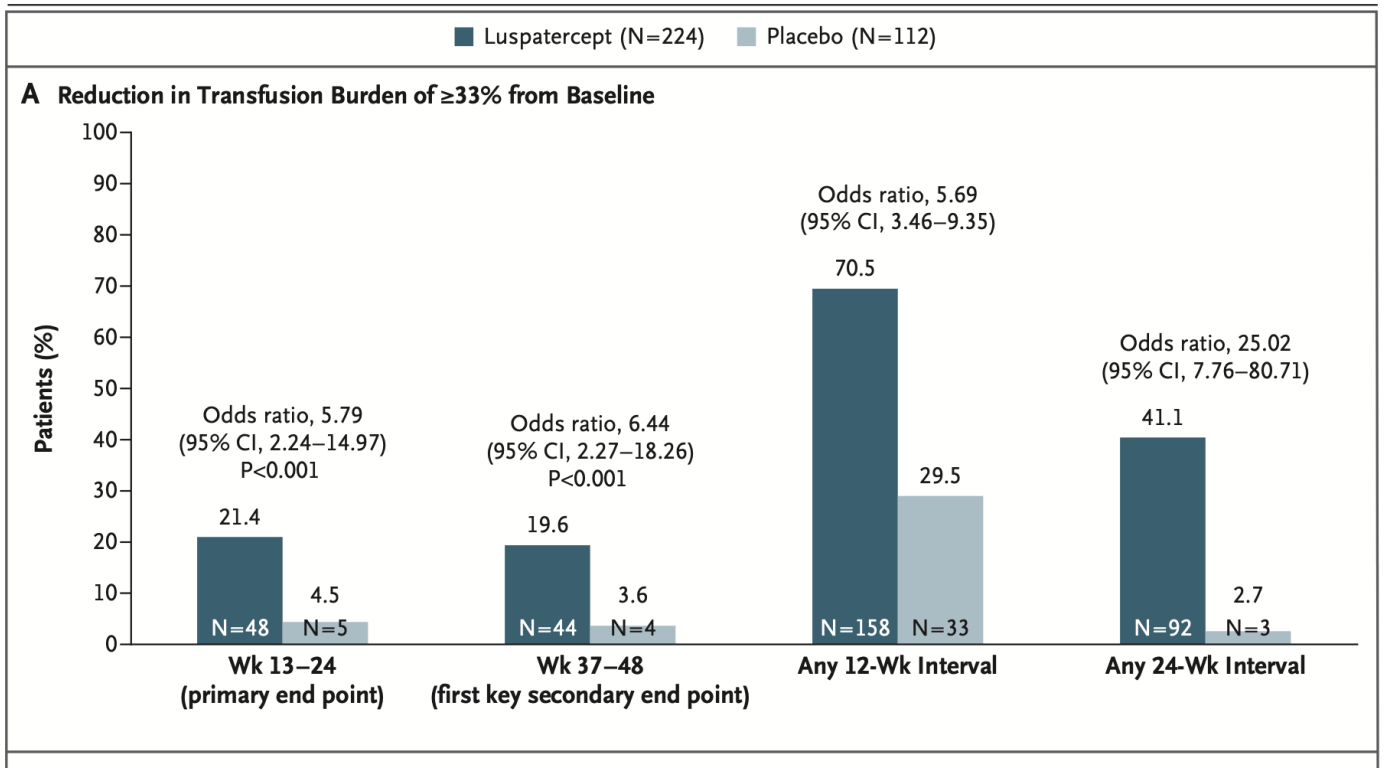
M.D. Cappellini, V. Viprakasit, A.T. Taher, P. Georgiev, K.H.M. Kuo, T. Coates, E. Voskaridou, H.-K. Liew, I. Pazgal-Kobrowski, G.L. Forni, S. Perrotta, A. Khelif, A. Lal, A. Kattamis, E. Vlachaki, R. Origa, Y. Aydinok, M. Bejaoui, P.J. Ho, L.-P. Chew, P.-C. Bee, S.-M. Lim, M.-Y. Lu, A. Tantiworawit, P. Ganeva, L. Gercheva, F. Shah, E.J. Neufeld, A. Thompson, A. Laadem, J.K. Shetty, J. Zou, J. Zhang, D. Miteva, T. Zinger, P.G. Linde, M.L. Sherman, O. Hermine, J. Porter, and A. Piga, for the BELIEVE Investigators*

Pre-Treatment



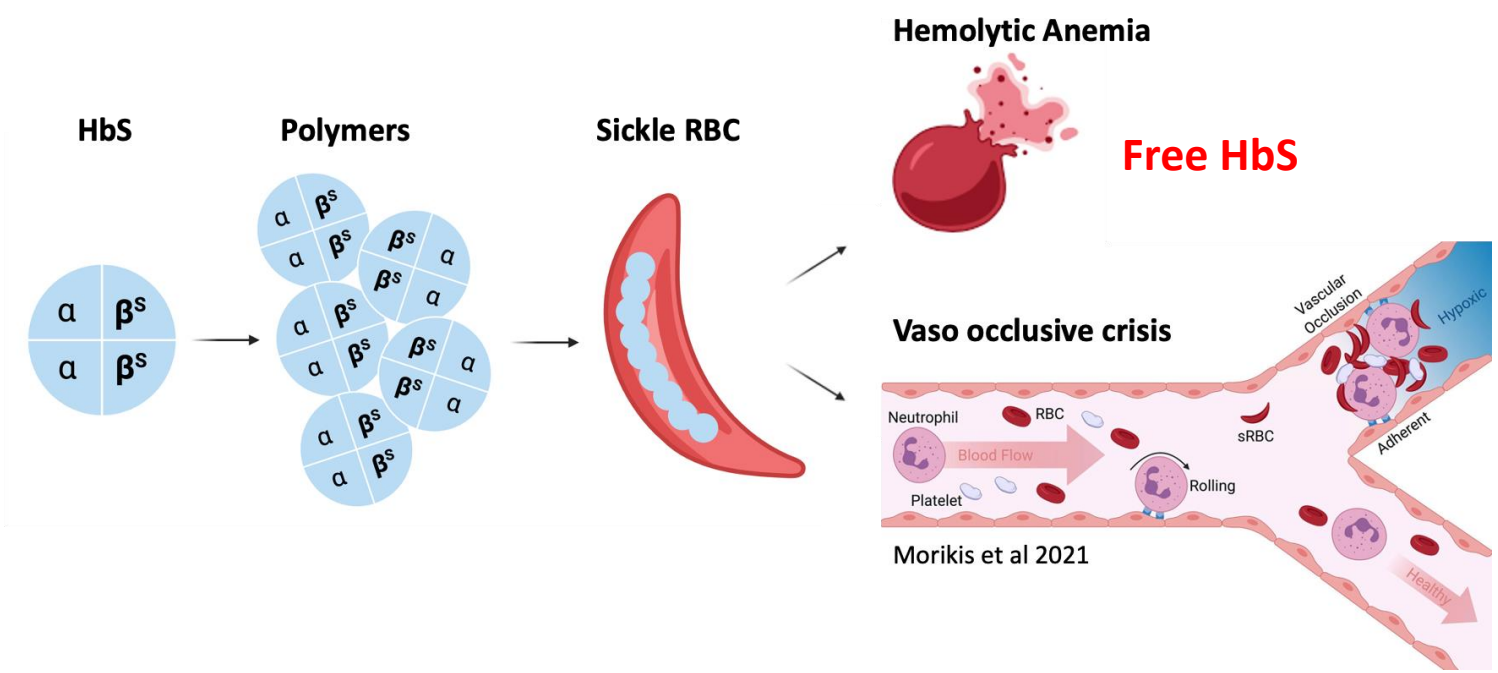
6 weeks Post-Treatment

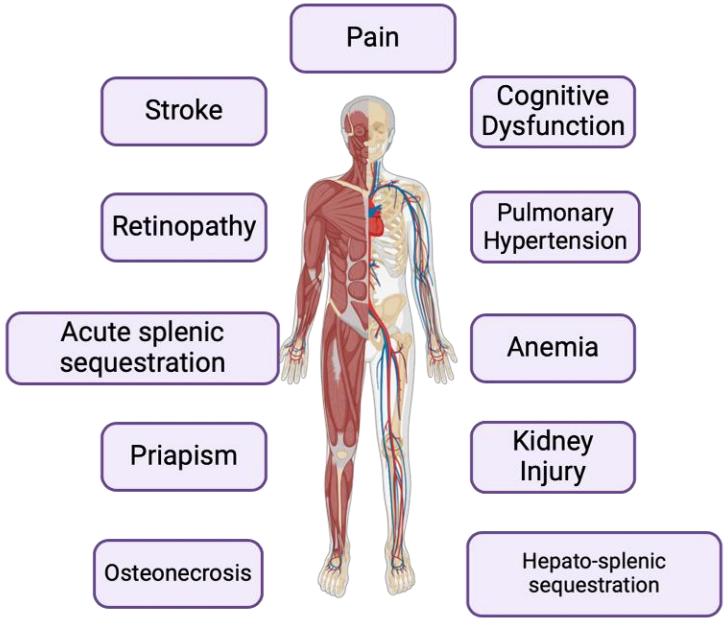




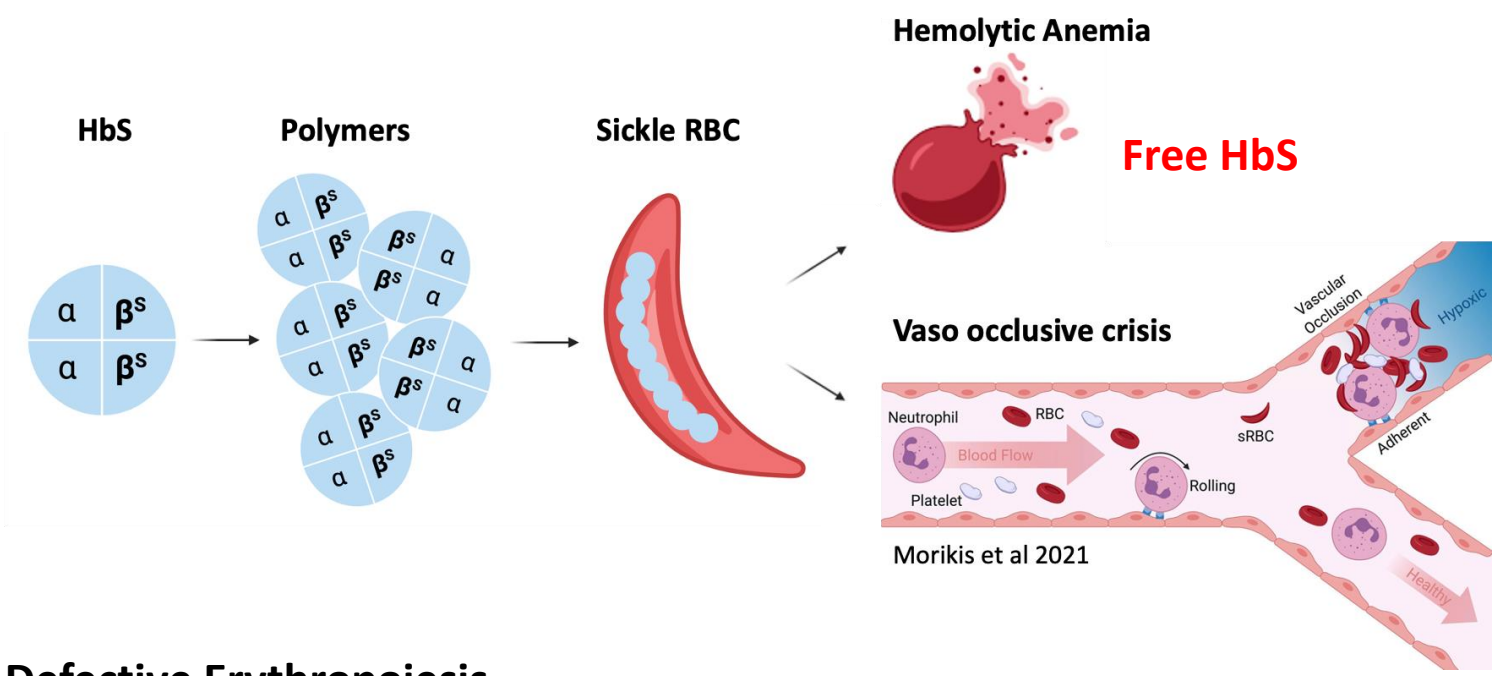
FDA and EMA approval for Transfusion-Dependent Beta-Thalassemia (2020)

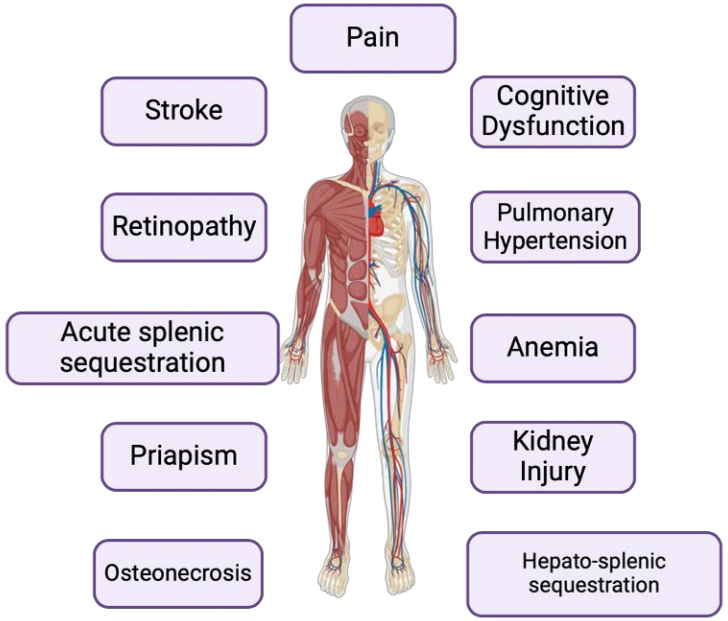
Sickle Cell Disease - Pathophysiology



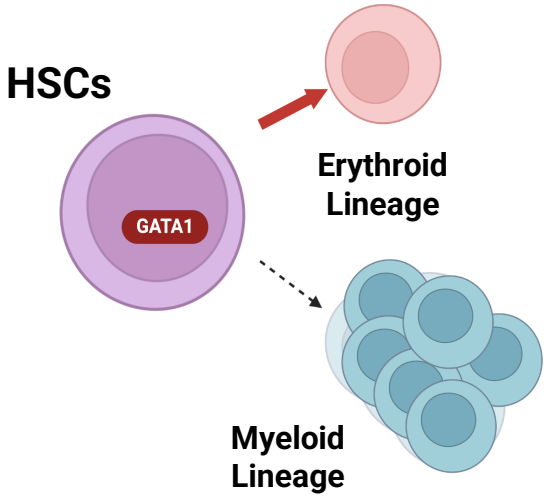


Sickle Cell Disease - Pathophysiology





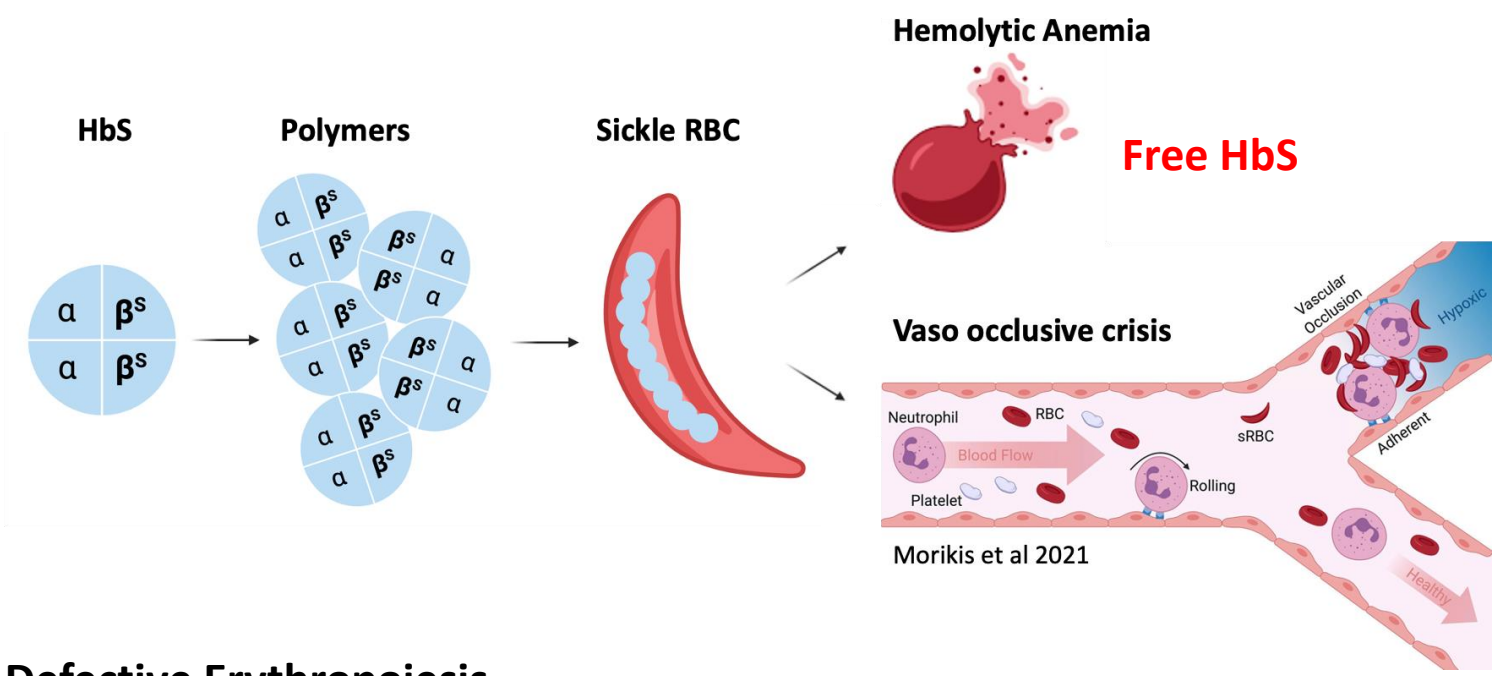
Defective Erythropoiesis

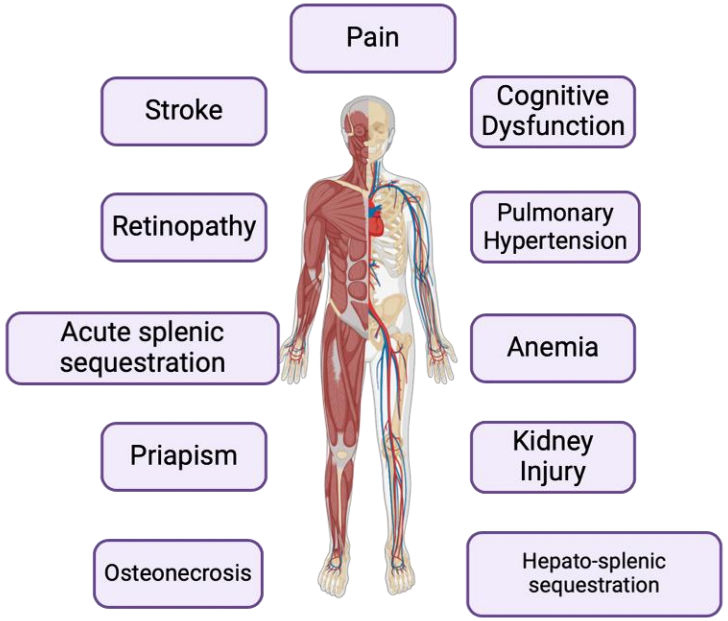


Skewing toward the myeloid lineage and increased inflammation

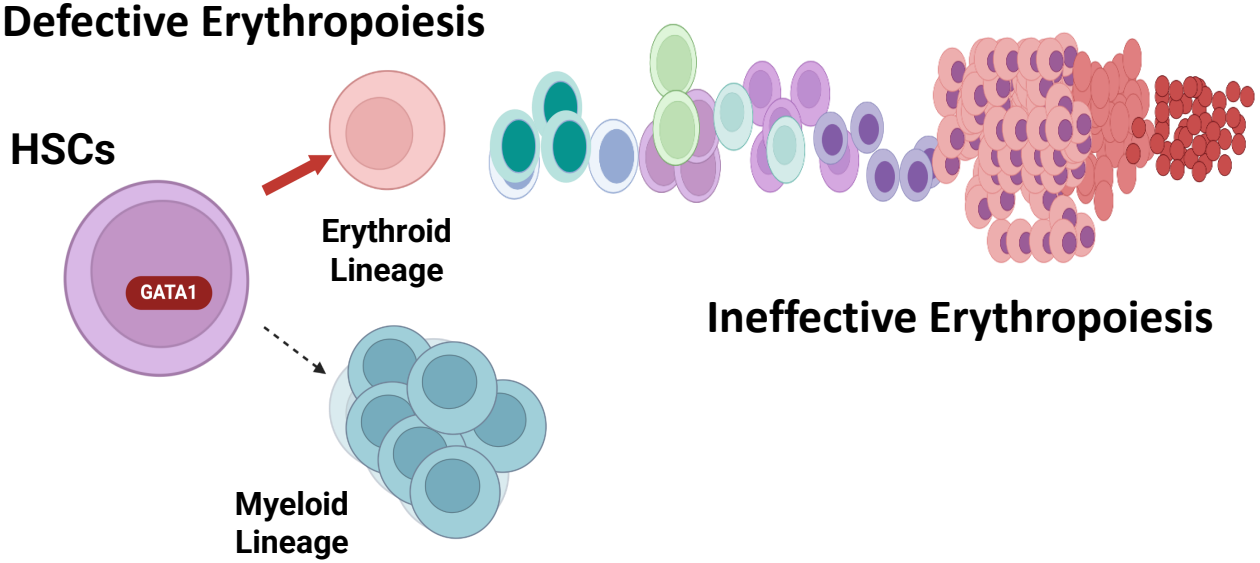
El Hoss et al , Hematologica 2024; and unpublished data

Sickle Cell Disease - Pathophysiology





Defective Erythropoiesis



Ineffective Erythropoiesis

Pathological Red Cells:

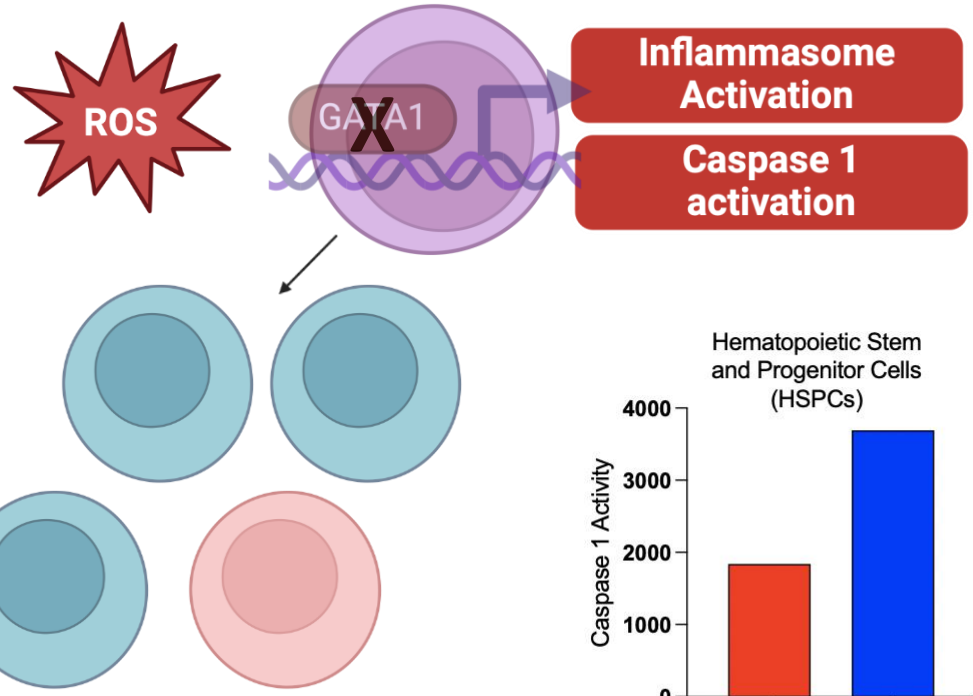
- Sickle Red Cells
- Abnormal adhesive properties
- Increase oxidative stress
- Enucleation defects

Skewing toward the myeloid lineage and increased inflammation

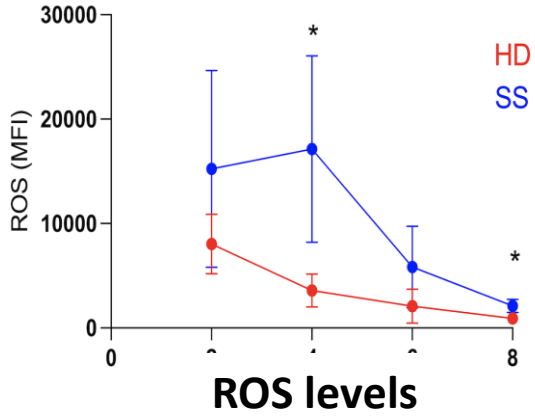
El Hoss et al , Hematologica 2024; and unpublished data

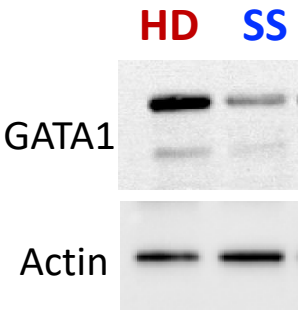
What is responsible for defective erythropoiesis in SCD?

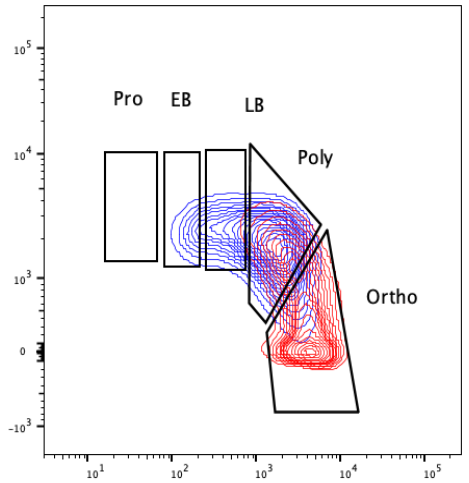
Caspase 1 is activated and cleaves GATA1 in early erythropoiesis



Skewing toward the Inflammatory Myeloid Lineage







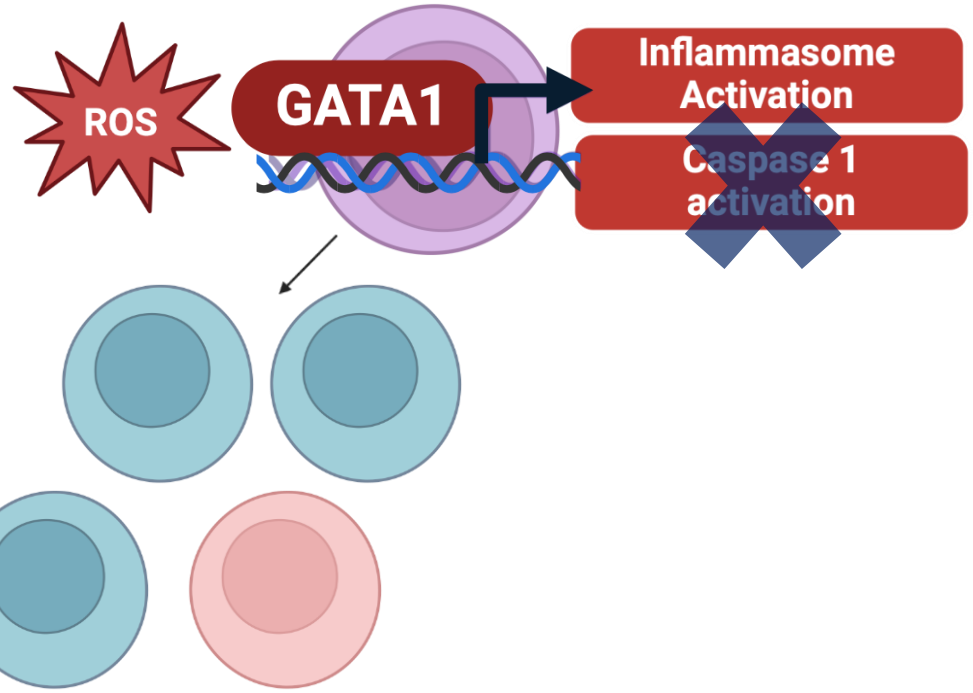
HD

SS

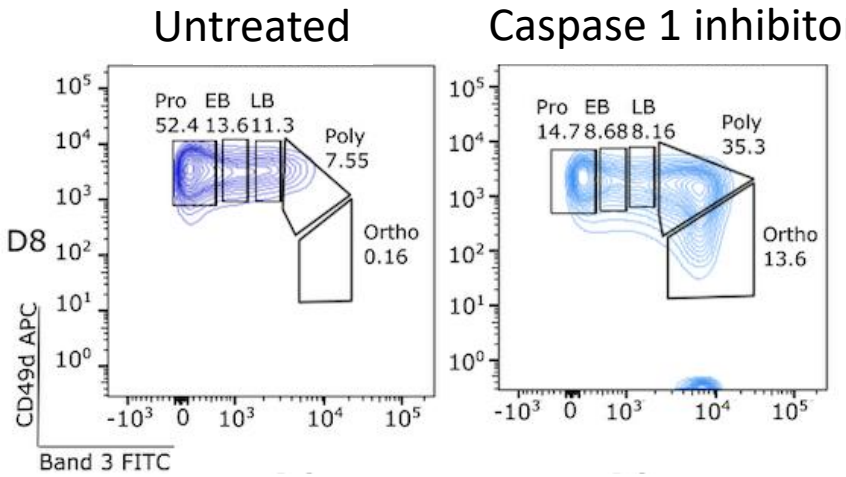
El Hoss et al unpublished data

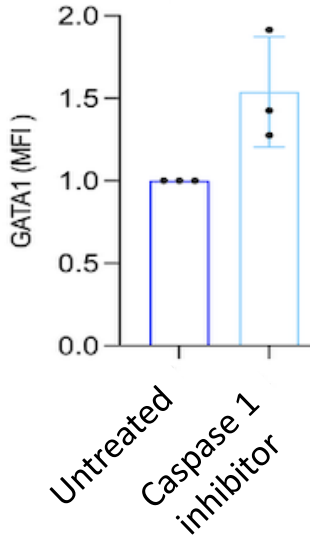
El Hoss et al , Hematologica 2024

Caspase 1 inhibition rescues erythropoiesis defects in SCD



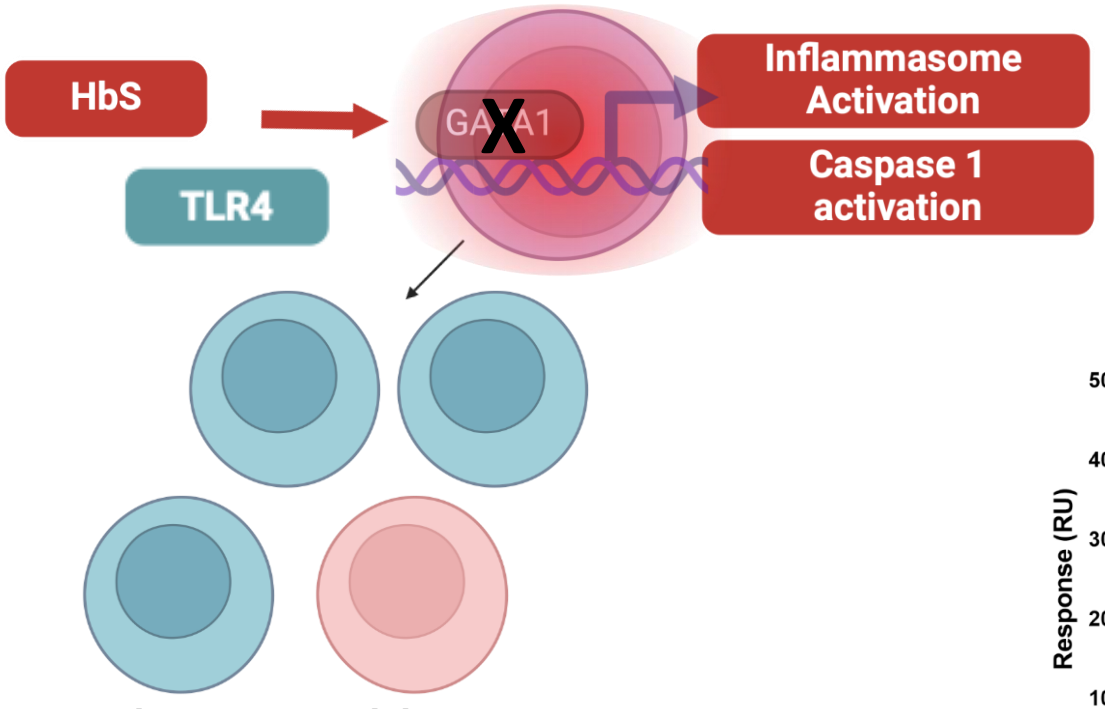
Skewing toward the Inflammatory Myeloid Lineage



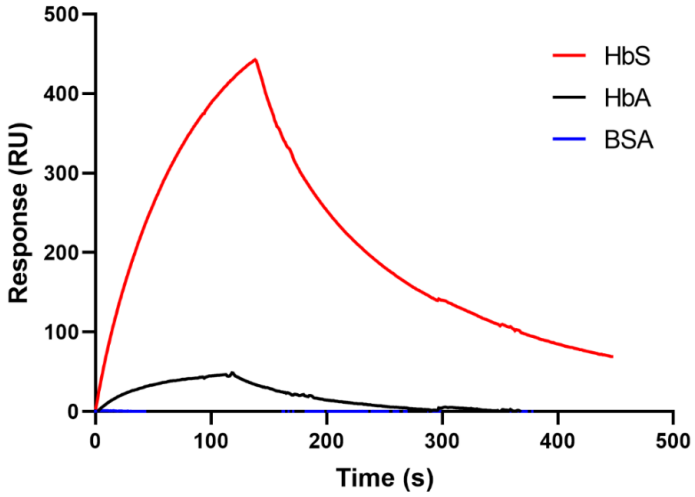


El Hoss et al , Hematologica 2024

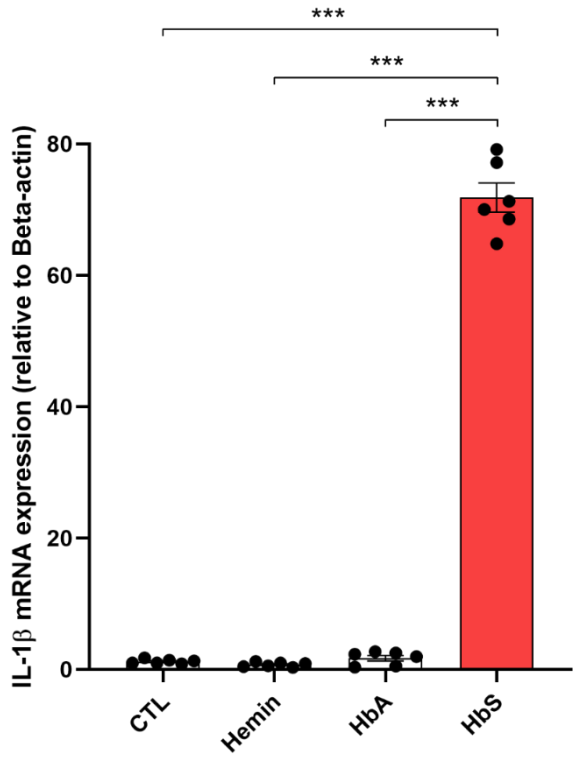
HbS/TLR4 interaction induced an inflammatory environment in SCD



Skewing toward the Inflammatory Myeloid Lineage



Binding HbS vs HbA to TLR4

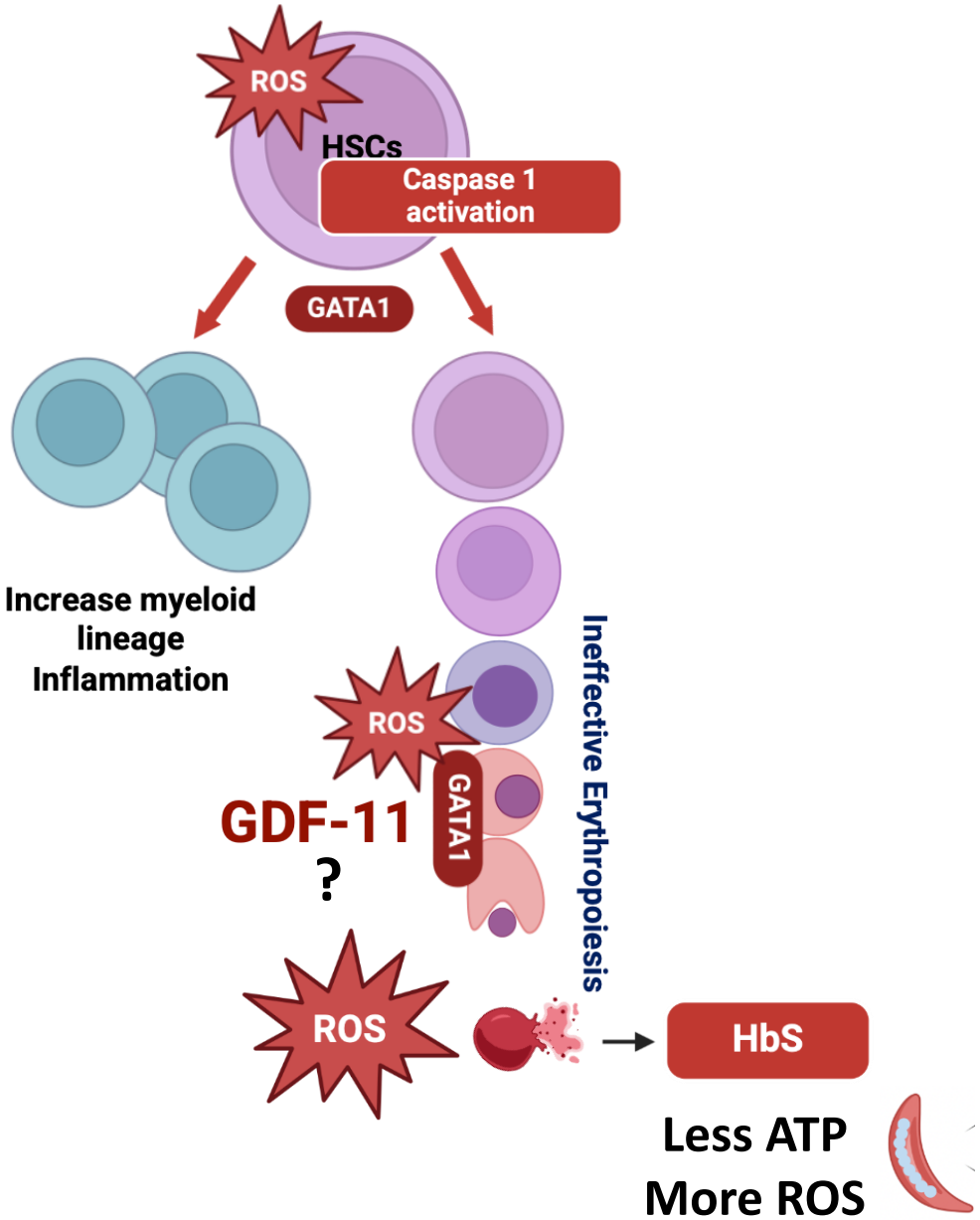


TLR4 activation by HbS vs HbA

Allali et al, Blood 2023

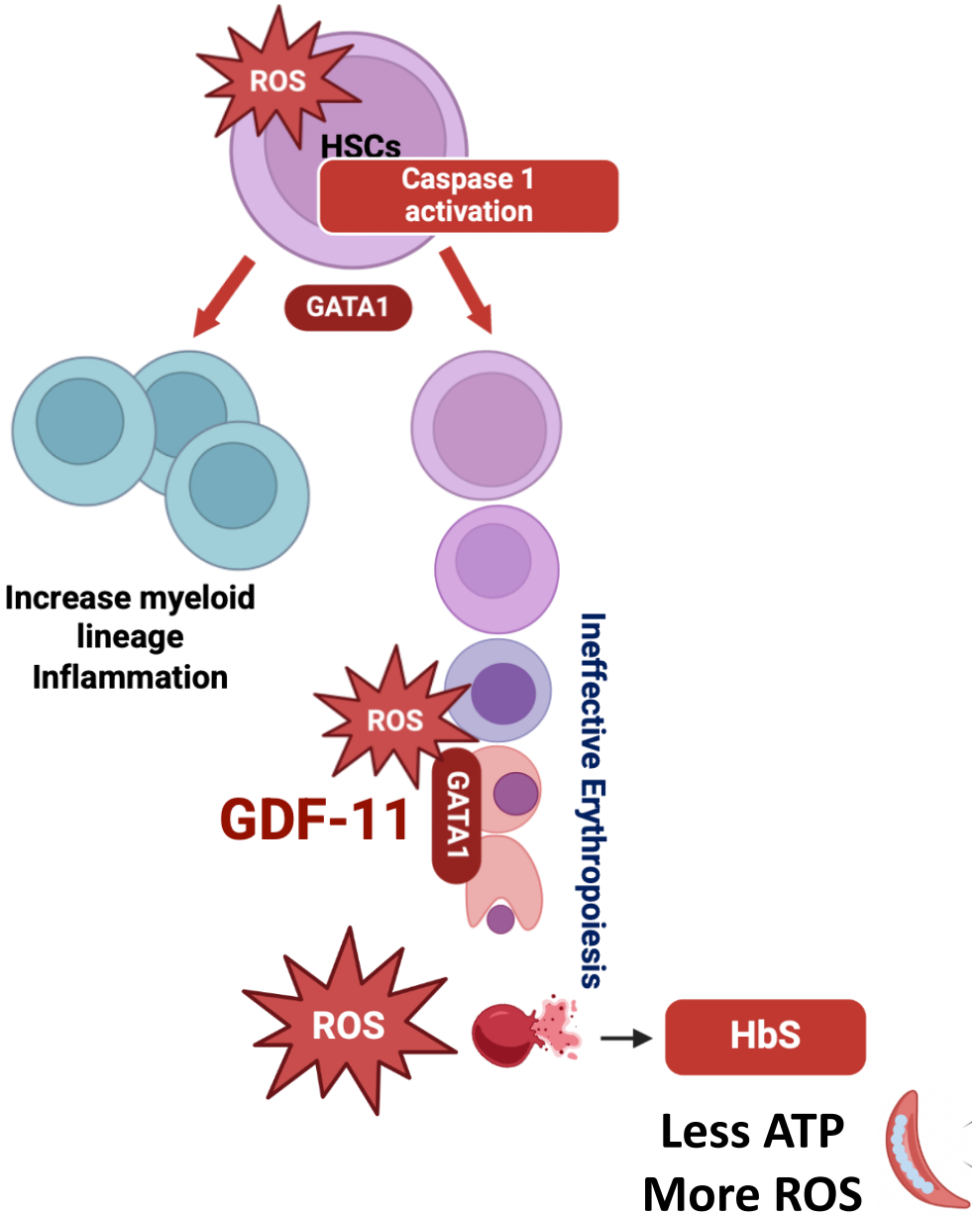
What explains the ineffective erythropoiesis in SCD?

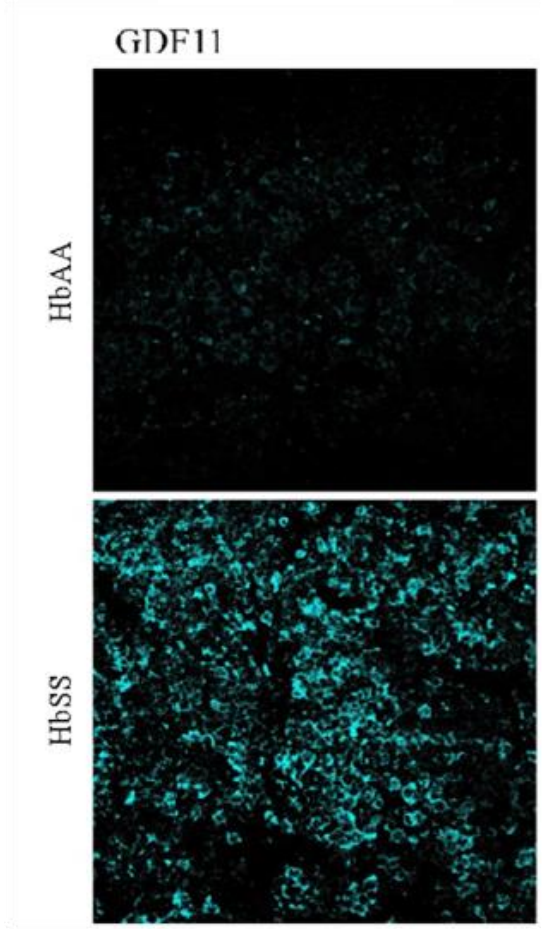
Is GDF-11 increased in SCD erythropoiesis?

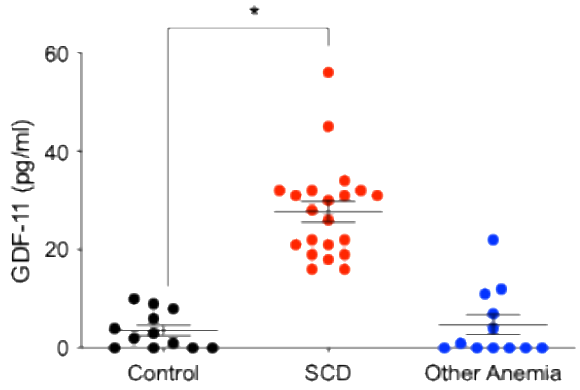


Trovati Maciel et al 2024 ASH Oral Abstract #621

GDF-11 is increased in SCD erythropoiesis





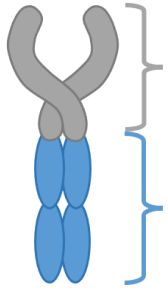


Trovati Maciel et al 2024 ASH Oral Abstract #621

Luspatercept rescues ineffective erythropoiesis in SCD and reduces sickling

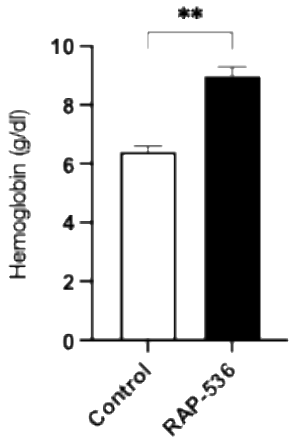
TOWNES SS Mice

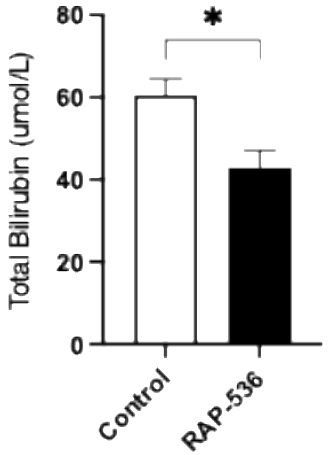
Luspatercept
ActRIIB / IgG1 Fc recombinant fusion protein

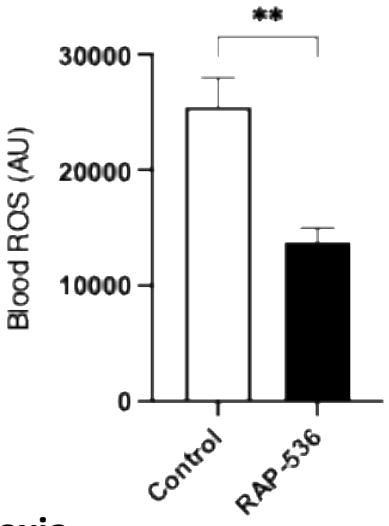


Modified extracellular domain of ActRIIB (GDF-8/11)

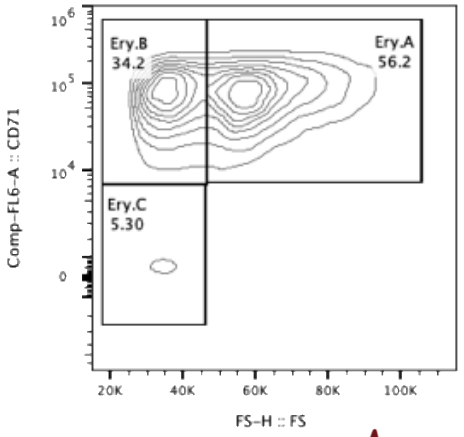
Human IgG1 Fc domain



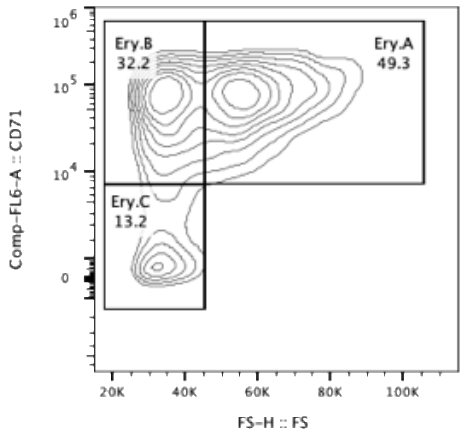




Control

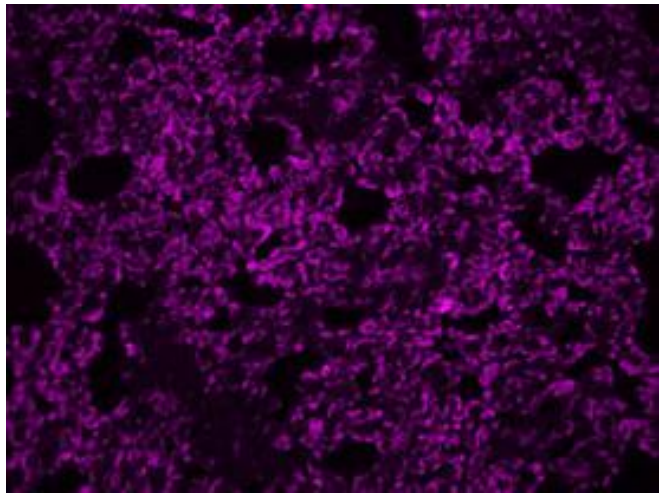


Luspatercept

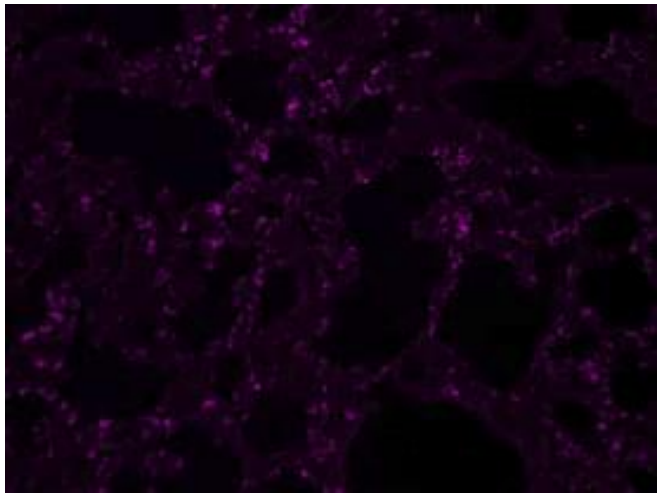


Lungs – Measurement of hypoxia inducded Vaso-occlusive crisis

Control



RAP-536



TER-119+ erythrocytes

Trovati Maciel et al 2024 ASH Oral Abstract #621

Could Luspatercept be utilized beyond hemoglobinopathies, in other conditions characterized with ineffective erythropoiesis?

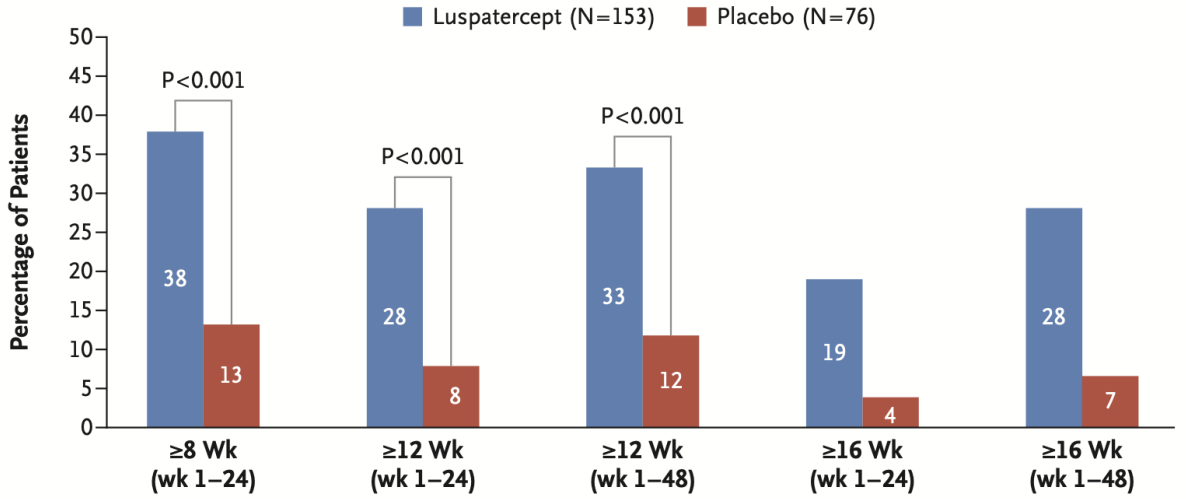
Luspatercept in myelodysplastic syndrome (MDS)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

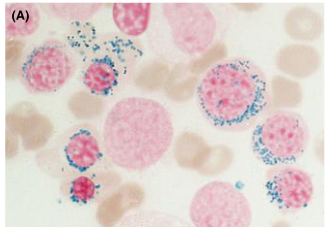
P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List



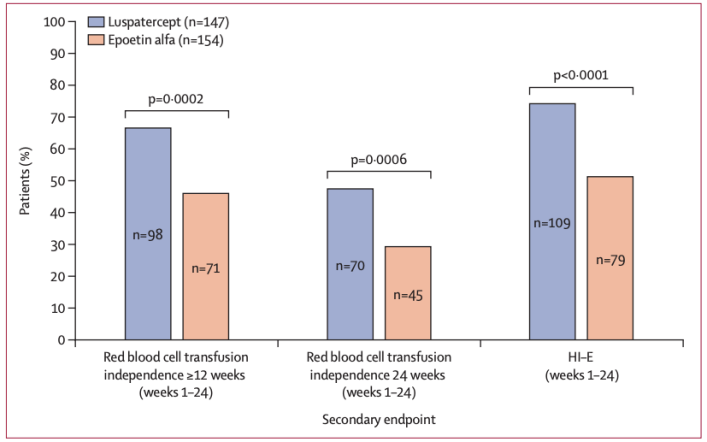
No. of Patients with Response (% [95% CI])					
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

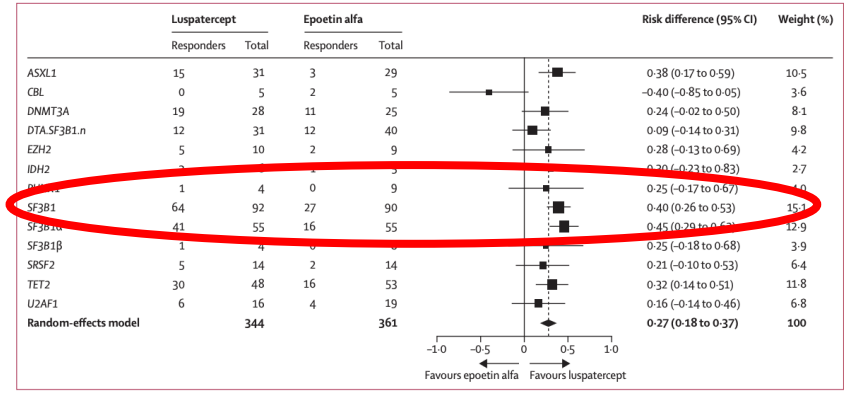
Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial

Uwe Platzbecker, Matteo Giovanni Della Porta*, Valeria Santini, Amer M Zeidan, Rami S Komrokji, Jake Shortt, David Valcarcel, Anna Jonasova, Sophie Dimicoli-Salazar, Ing Soo Tiong, Chien-Chin Lin, Jiahui Li, Jennie Zhang, Ana Carolina Giuseppi, Sandra Kreitz, Veronika Pozharskaya, Karen L Keeperman, Shelonitda Rose, Jeevan K Shetty, Sheida Hayati, Sadanand Vodala, Thomas Prebet, Andrius Degutys, Stefania Paolini, Thomas Cluzeau, Pierre Fenaux†, Guillermo Garcia-Manero†*

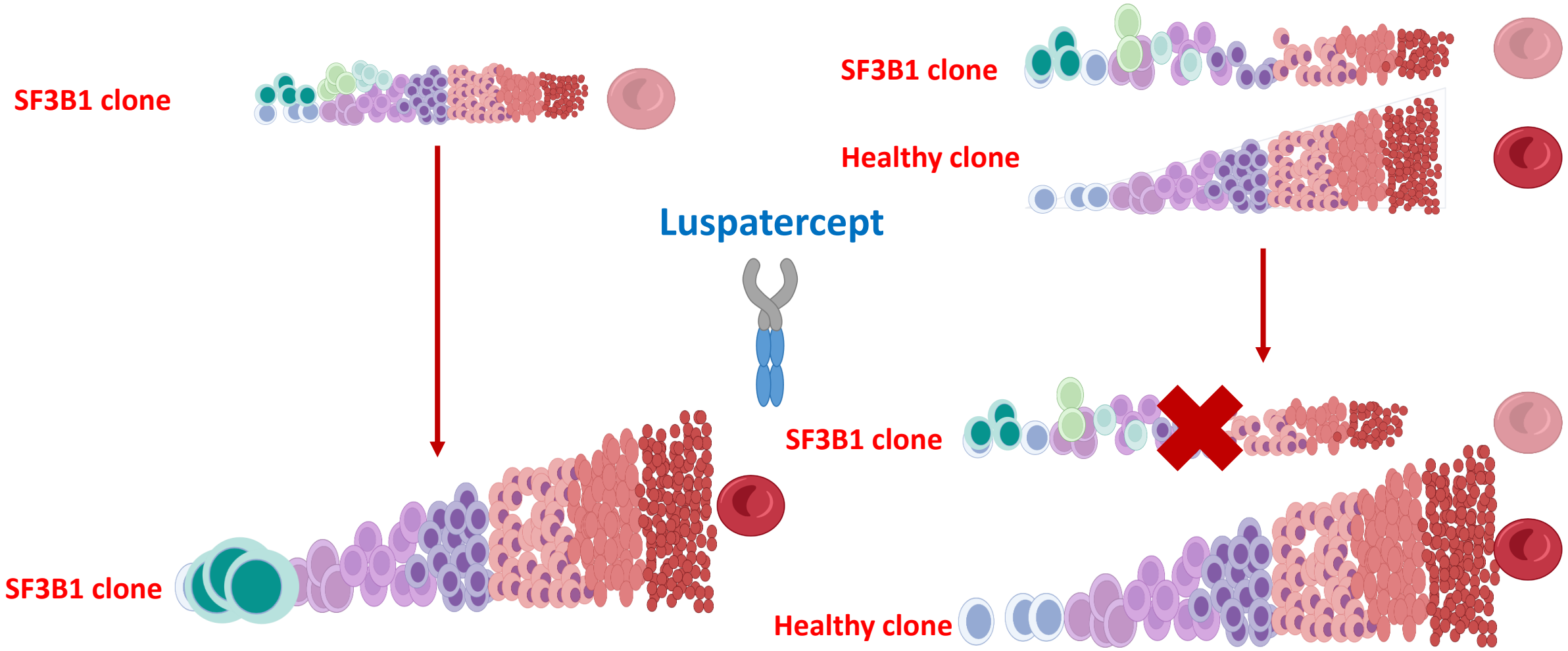


SF3B-1



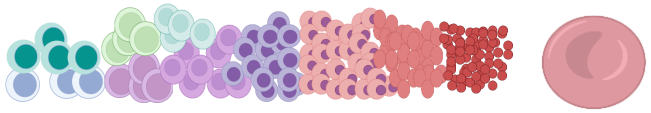


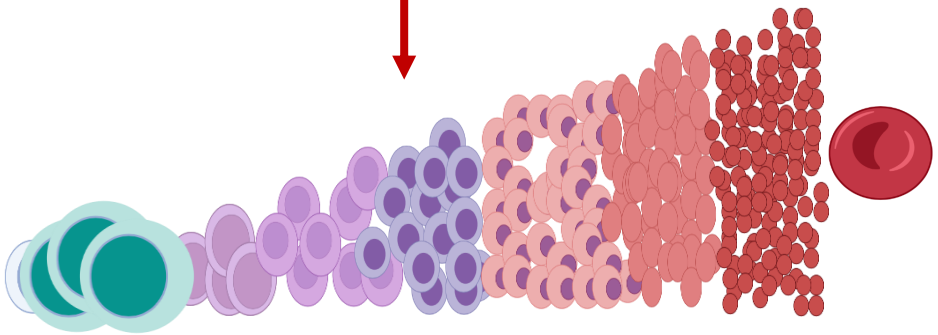
Mechanism of action: Increased differentiation vs extinction of SF3B1 clones and restoration of erythropoiesis



Mechanism of action:
Increased differentiation vs extinction of SF3B1 clones

SF3B1 clone





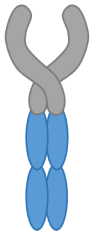
SF3B1 clone

No significant change in SF3B1 VAF
No clonal extinction

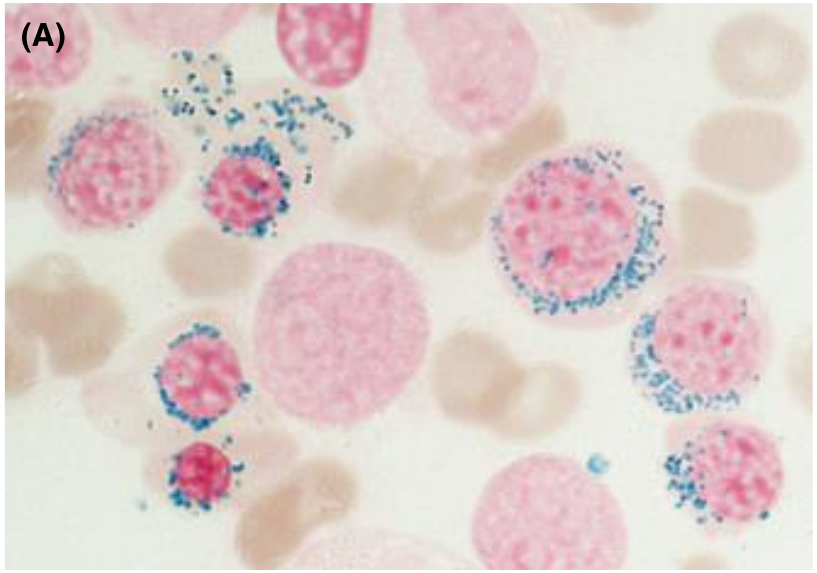
Luspatercept in congenital sideroblastic anemia?

Luspatercept corrects anemia in a patient with congenital sideroblastic anemia

Luspatercept

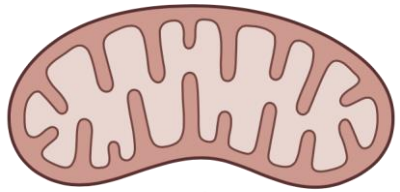


- Congenital sideroblastic anemia with PUS-1 deficiency
- 4g/dl Transfusion dependent
- Luspatercept 1mg/3wk
- Hemoglobin increased to 10-12g/dl (Transfusion independent for the last 18 months)
- Bone marrow aspiration no change from diagnosis (80% sideroblasts)

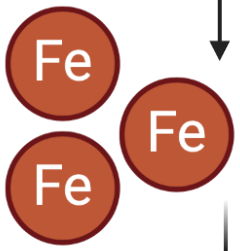


O Hermine, unpublished data

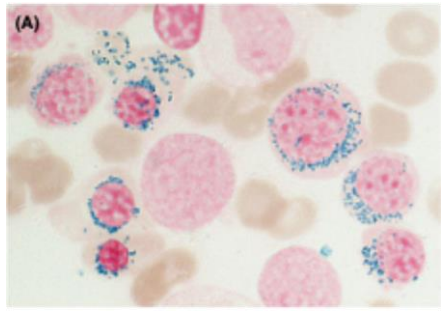
Acquired and congenital sideroblastic anemia : common mechanism ?



Genetic mutations
Germline or Somatic

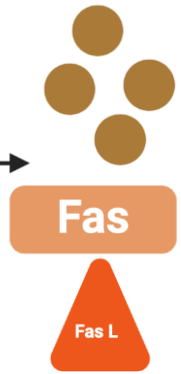


Iron
Accumulation



Increased
ROS

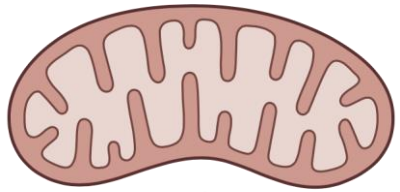
Increase in
GDF11



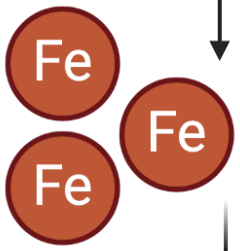
TGFβ
Family

Decrease in
Fas / FasL

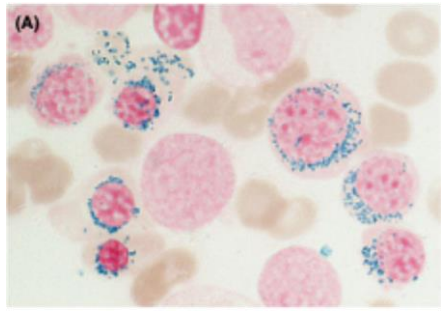
Acquired and congenital sideroblastic anemia : common mechanism ?



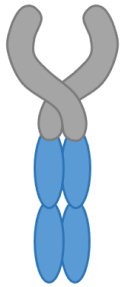
Genetic mutations
Germline or Somatic

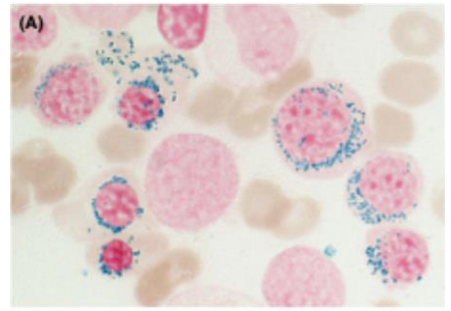


Iron
Accumulation



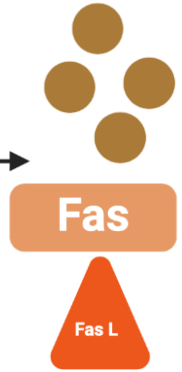
Luspatercept





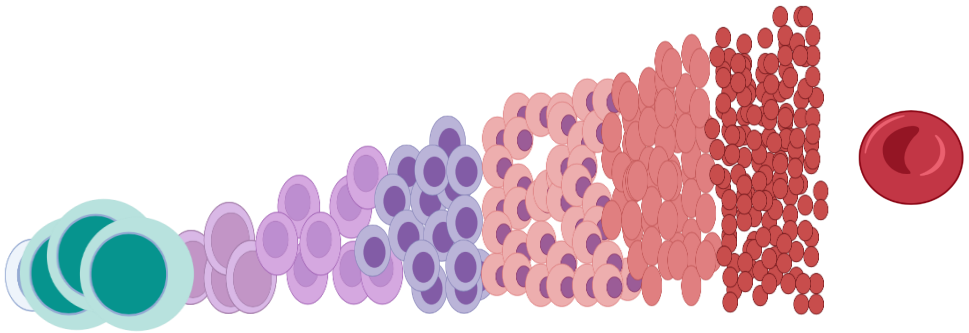
Decreased
ROS

Decrease
GDF11

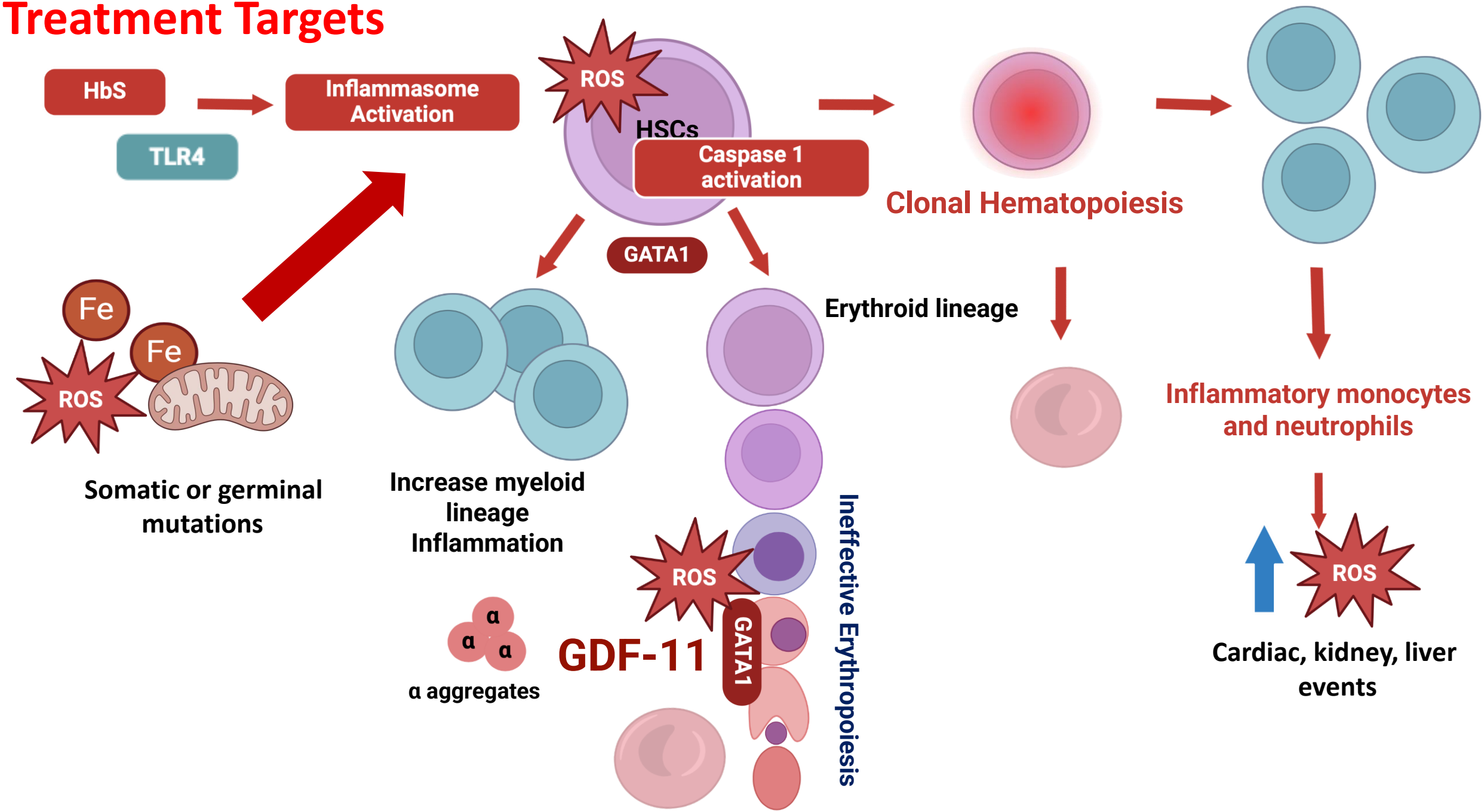


TGFβ
Family

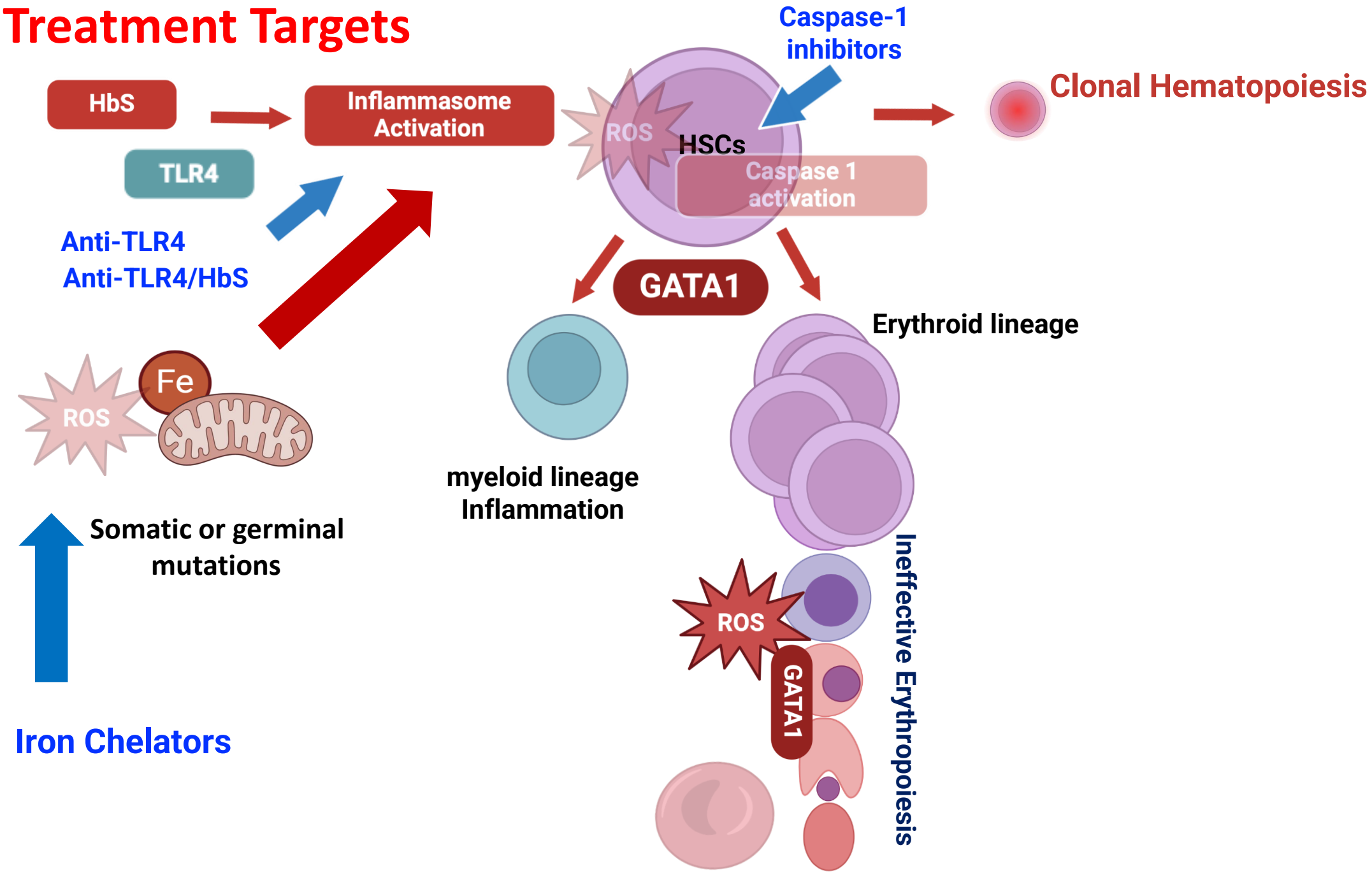
Decrease in
Fas / FasL



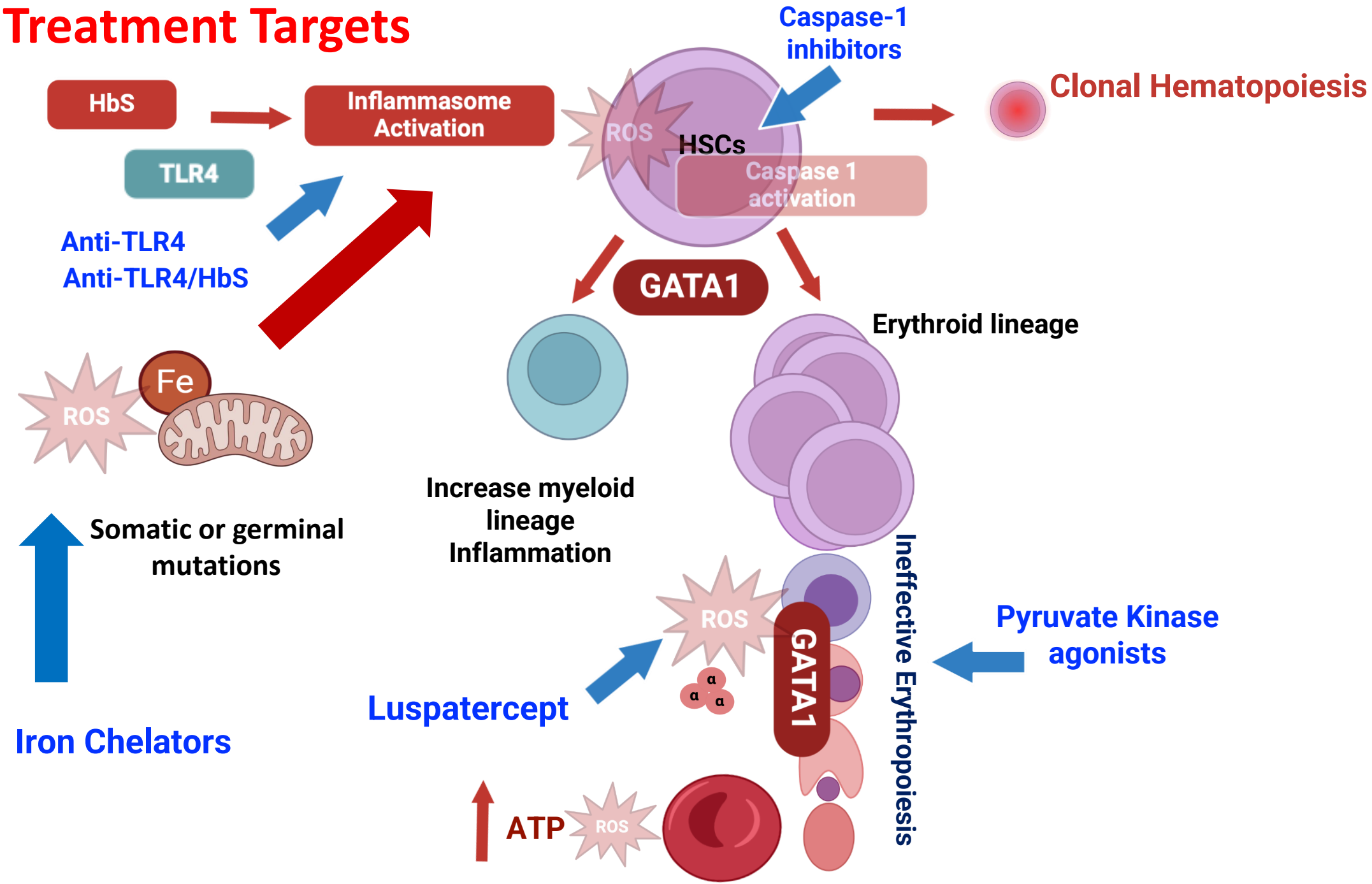
Treatment Targets



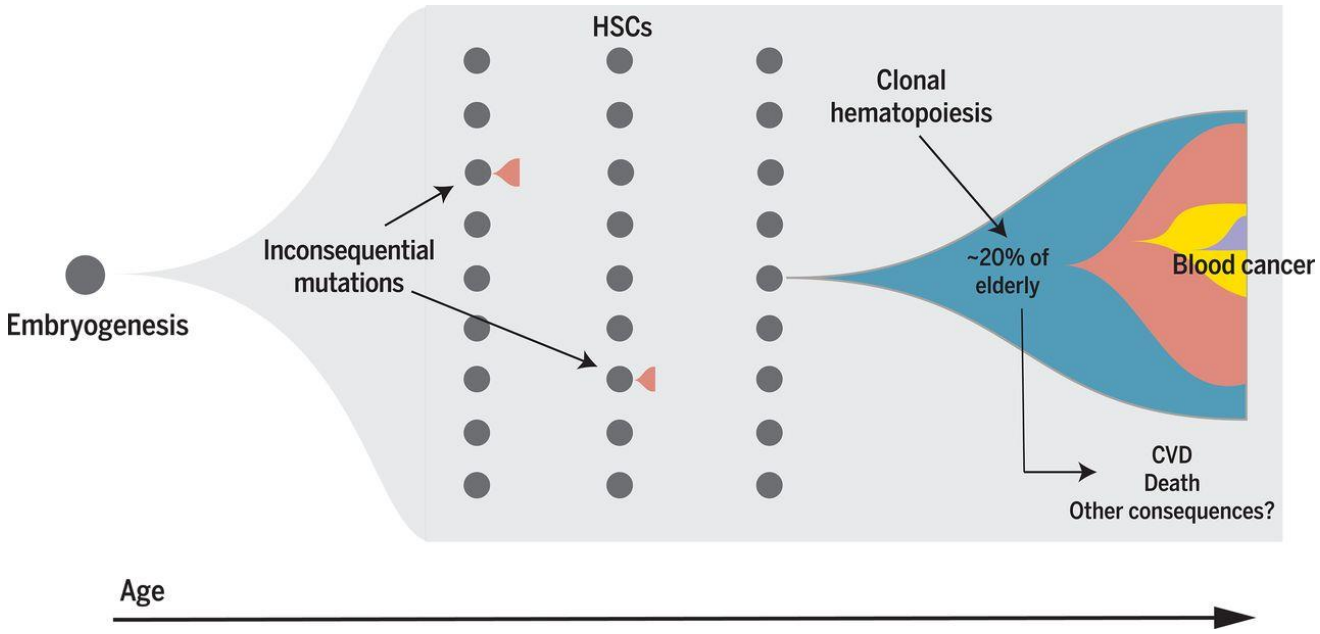
Treatment Targets

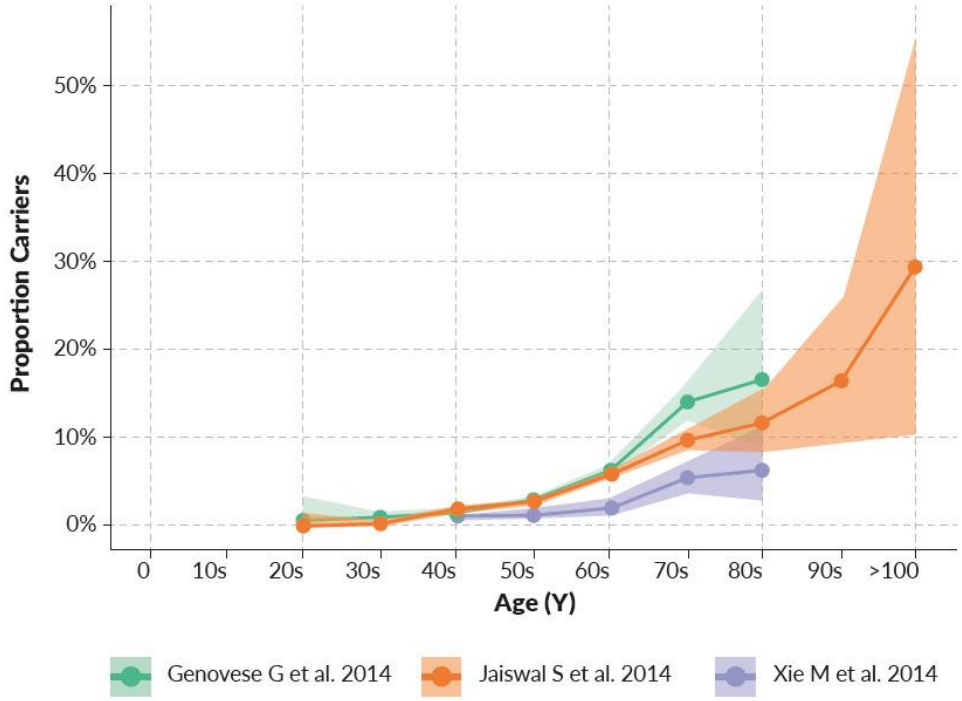


Treatment Targets

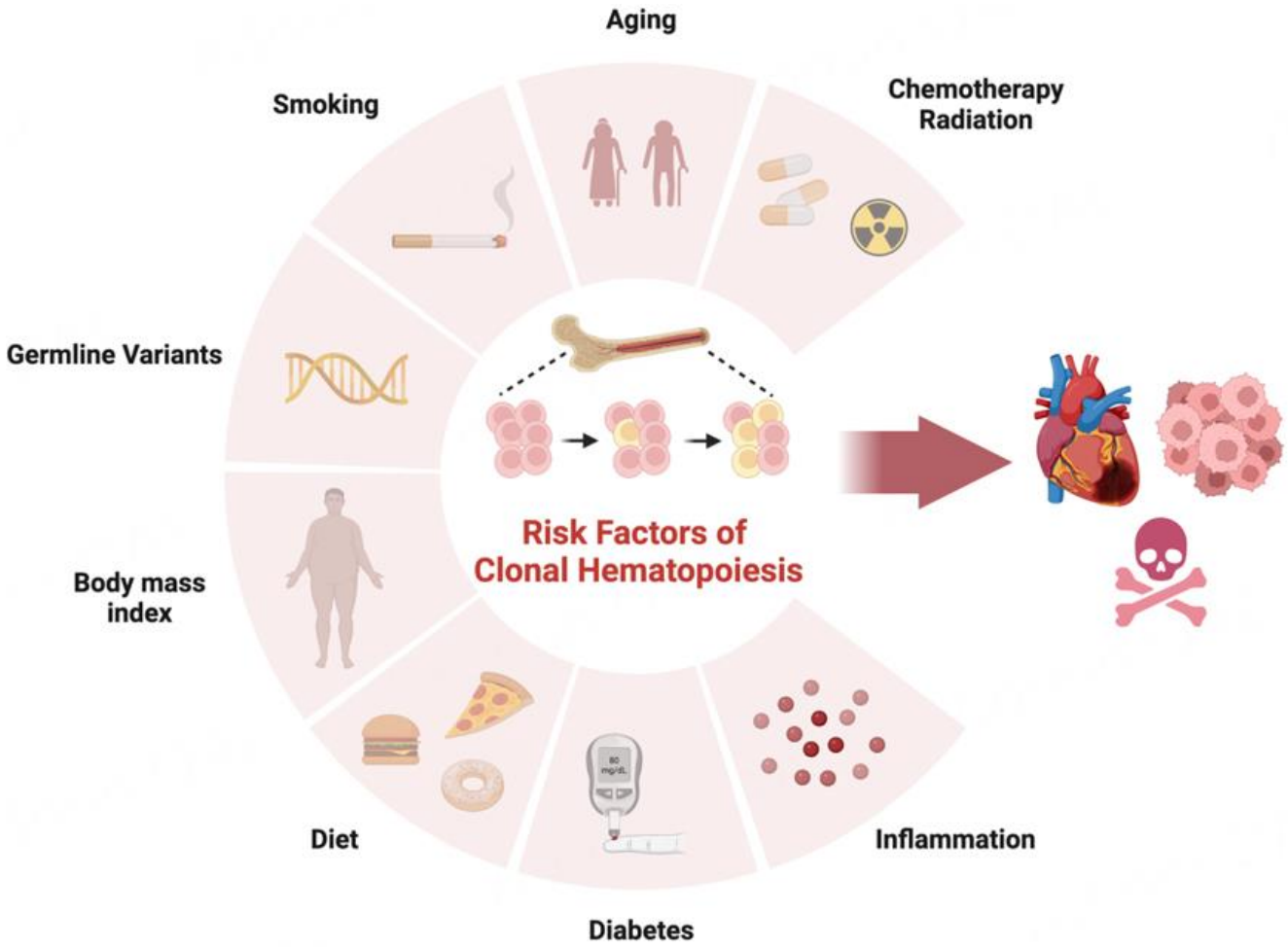


Clonal hematopoiesis

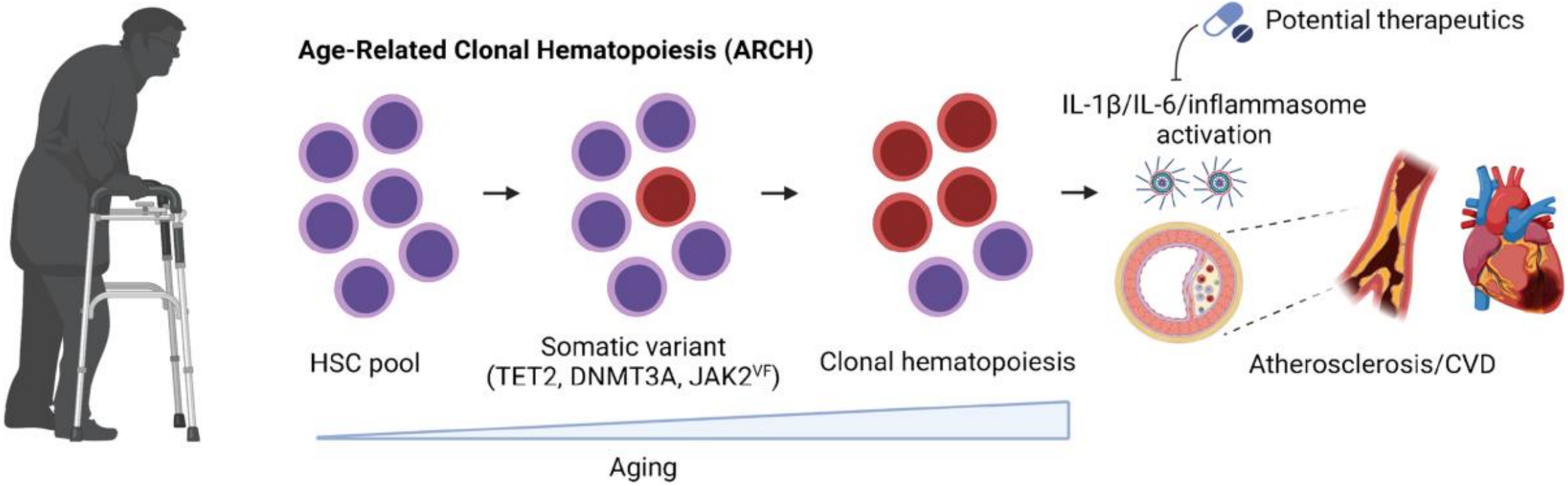




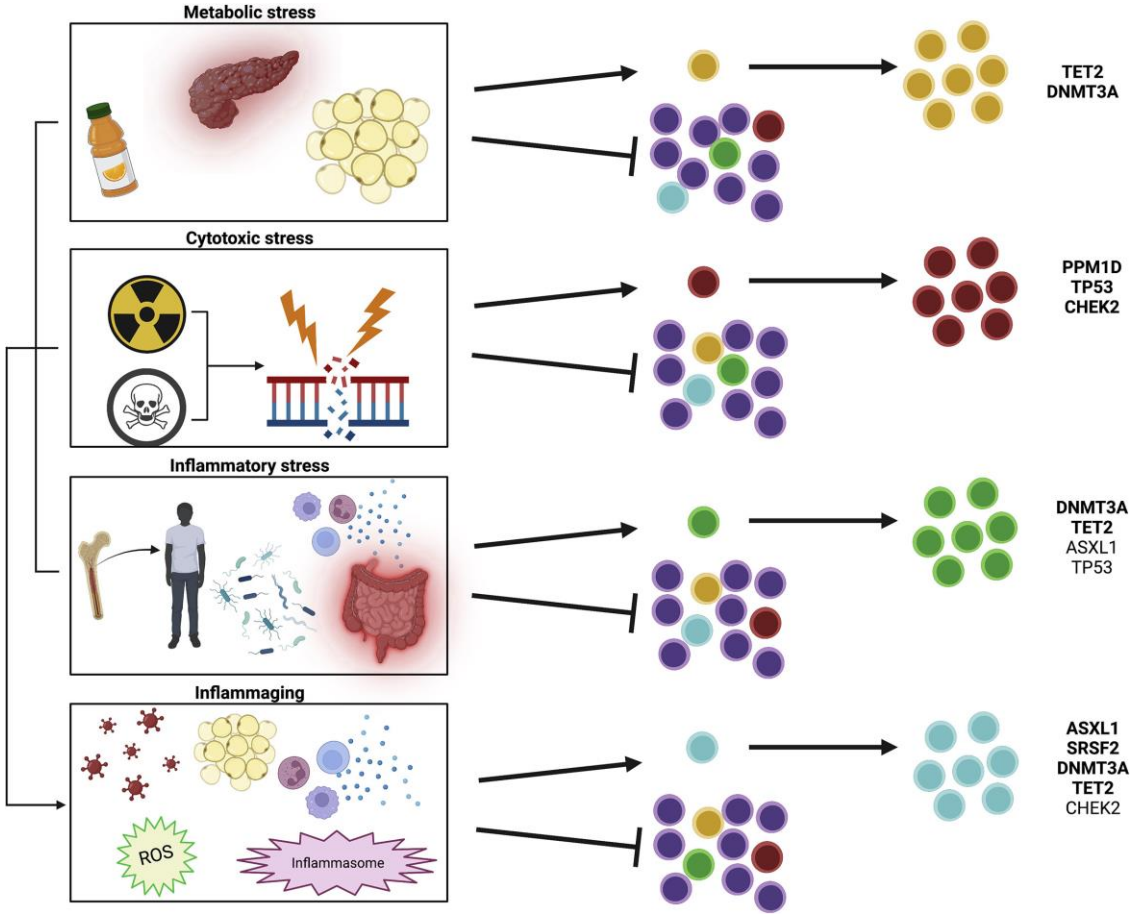
Clonal hematopoiesis : Risk factors

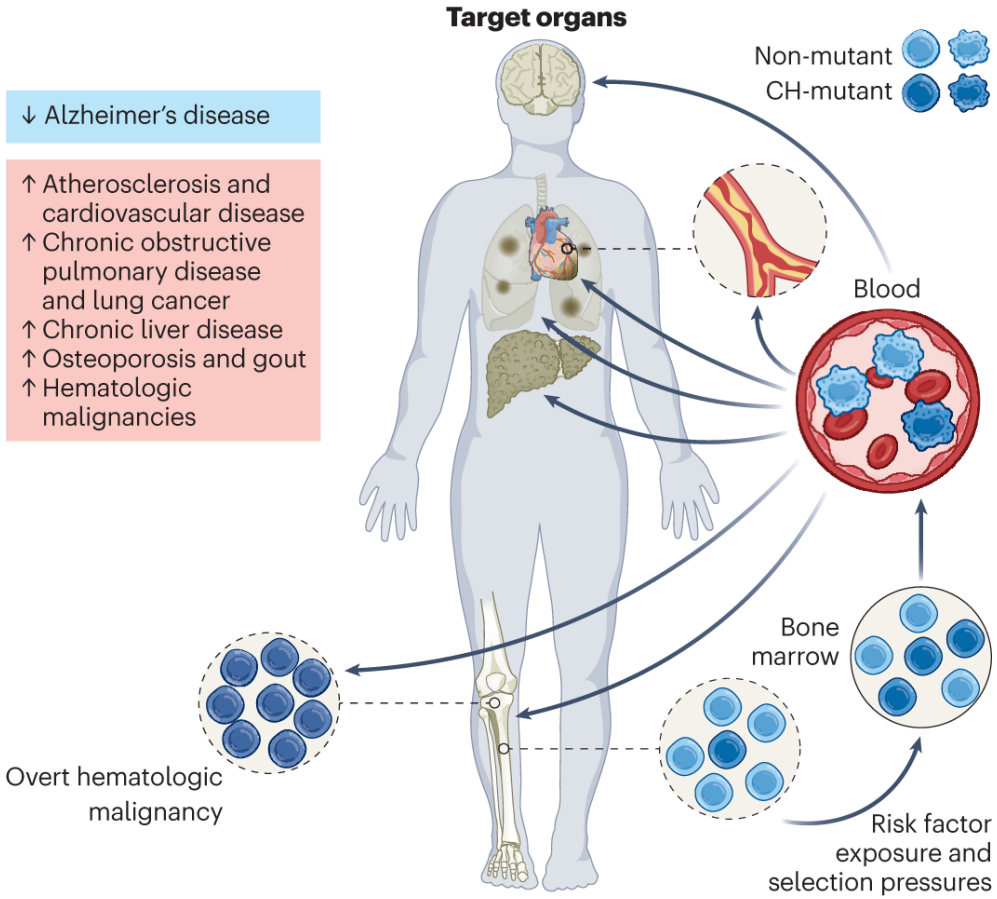


Age and Clonal hematopoiesis

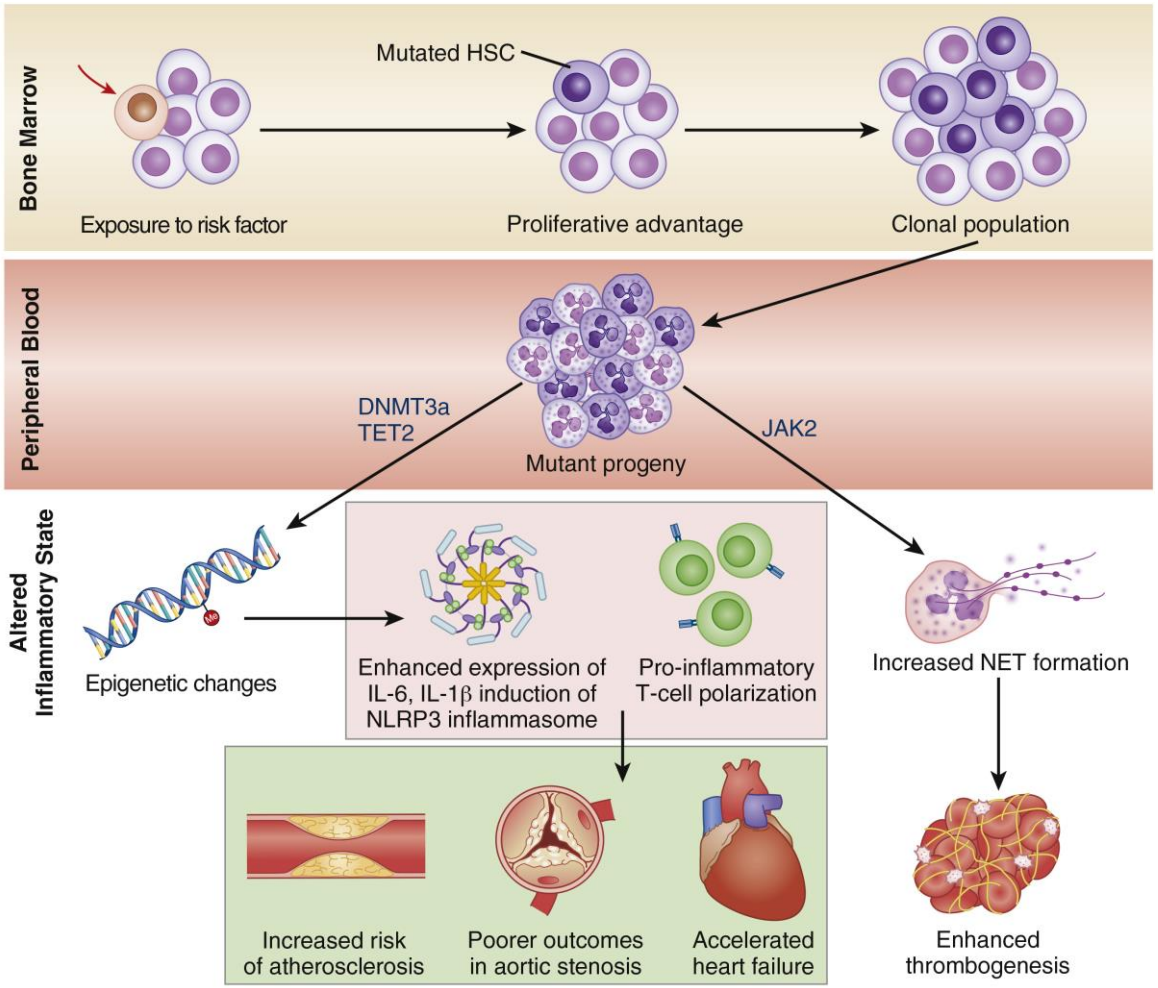


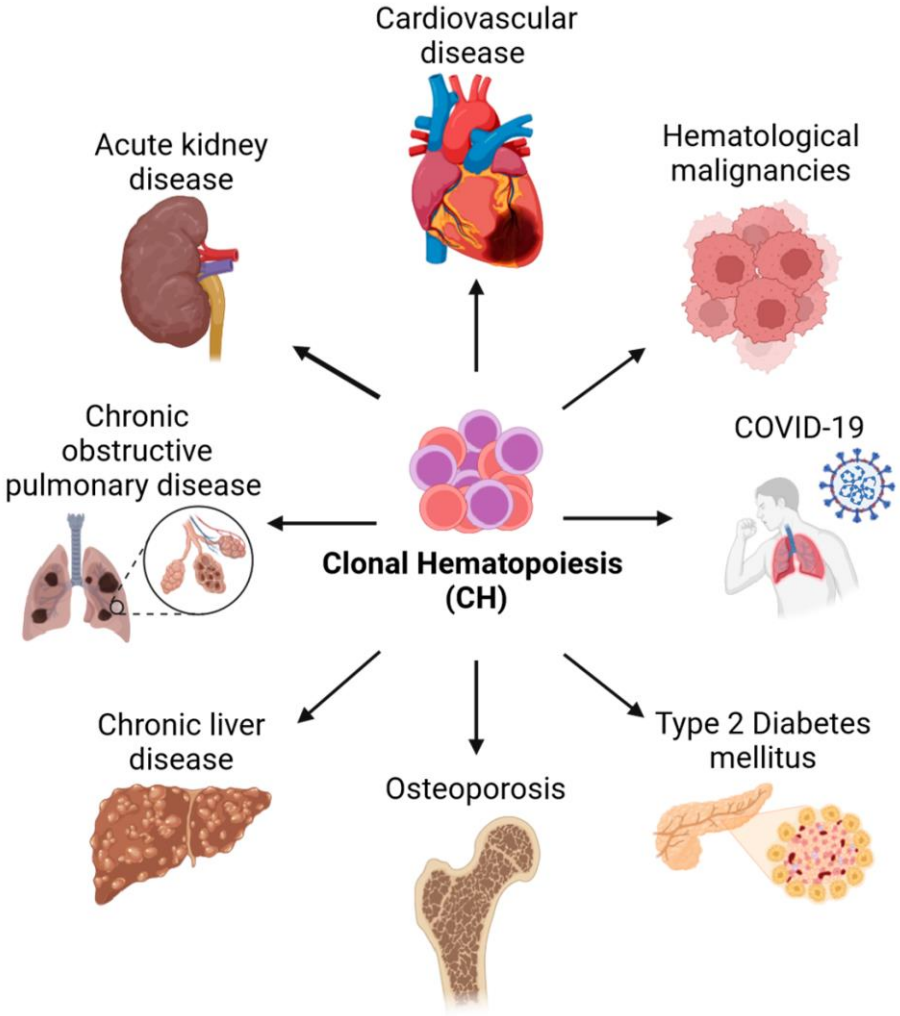
Clonal hematopoiesis : Mechanisms and consequences



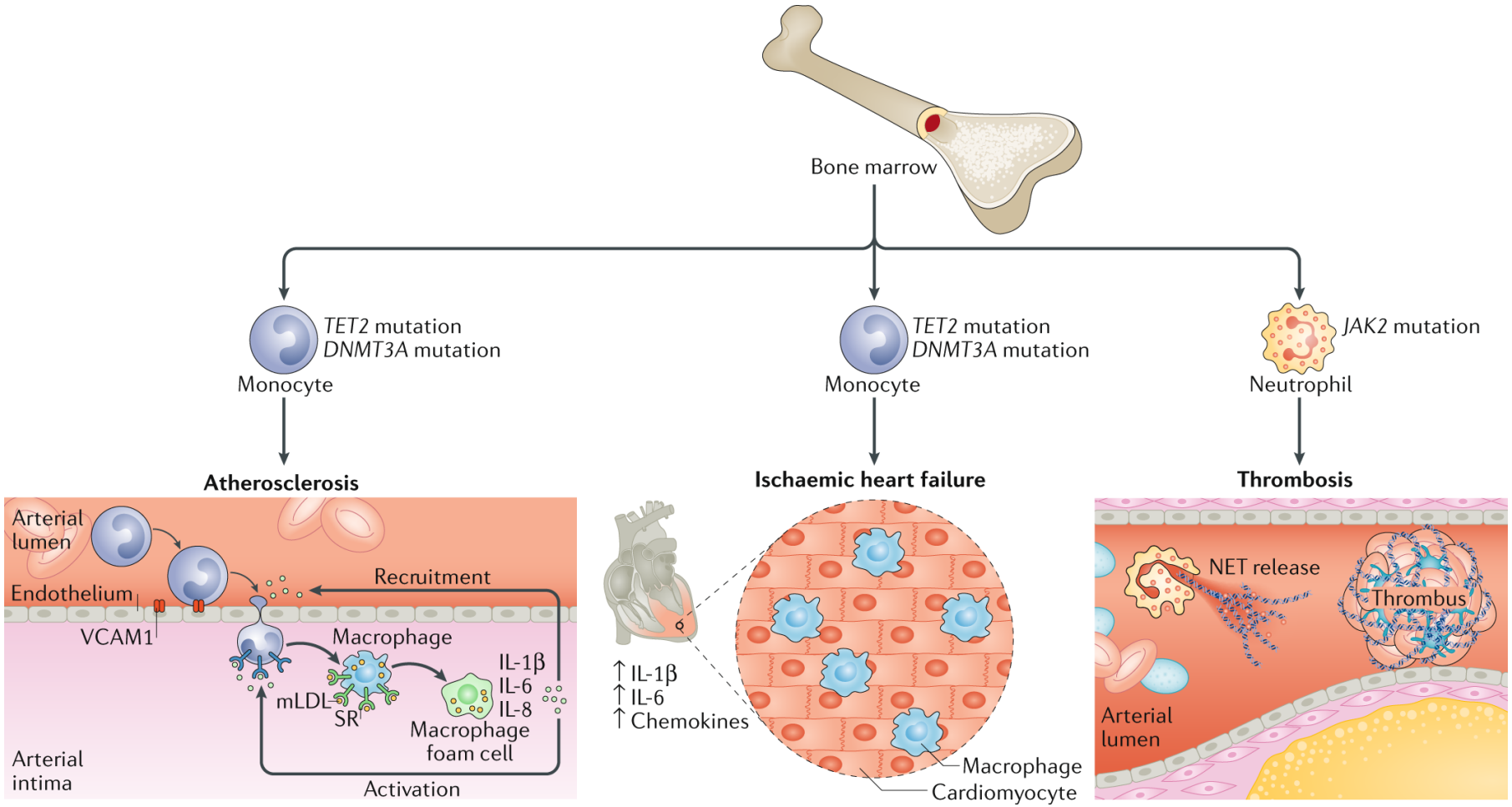


Clonal Hematopoiesis consequences

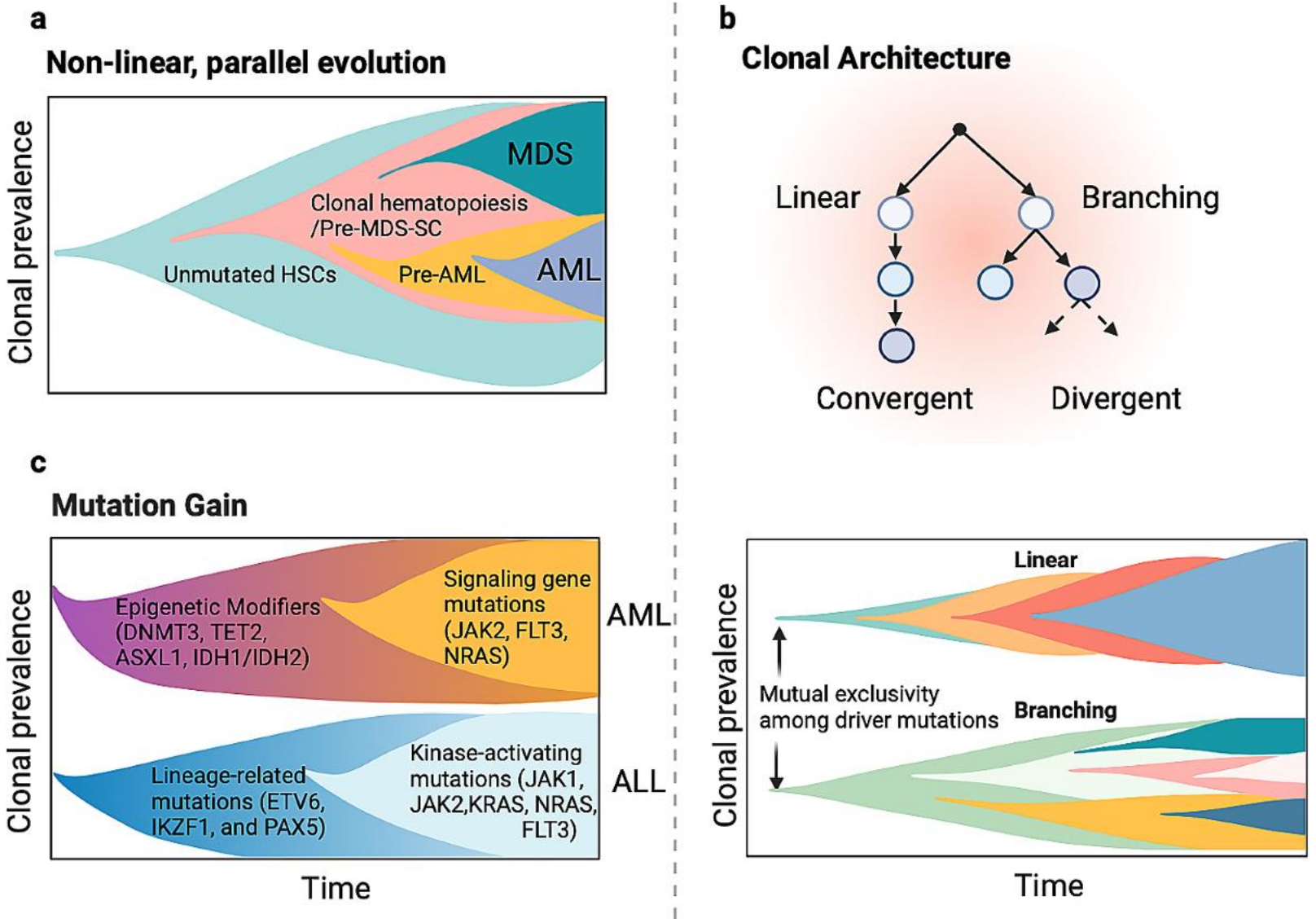




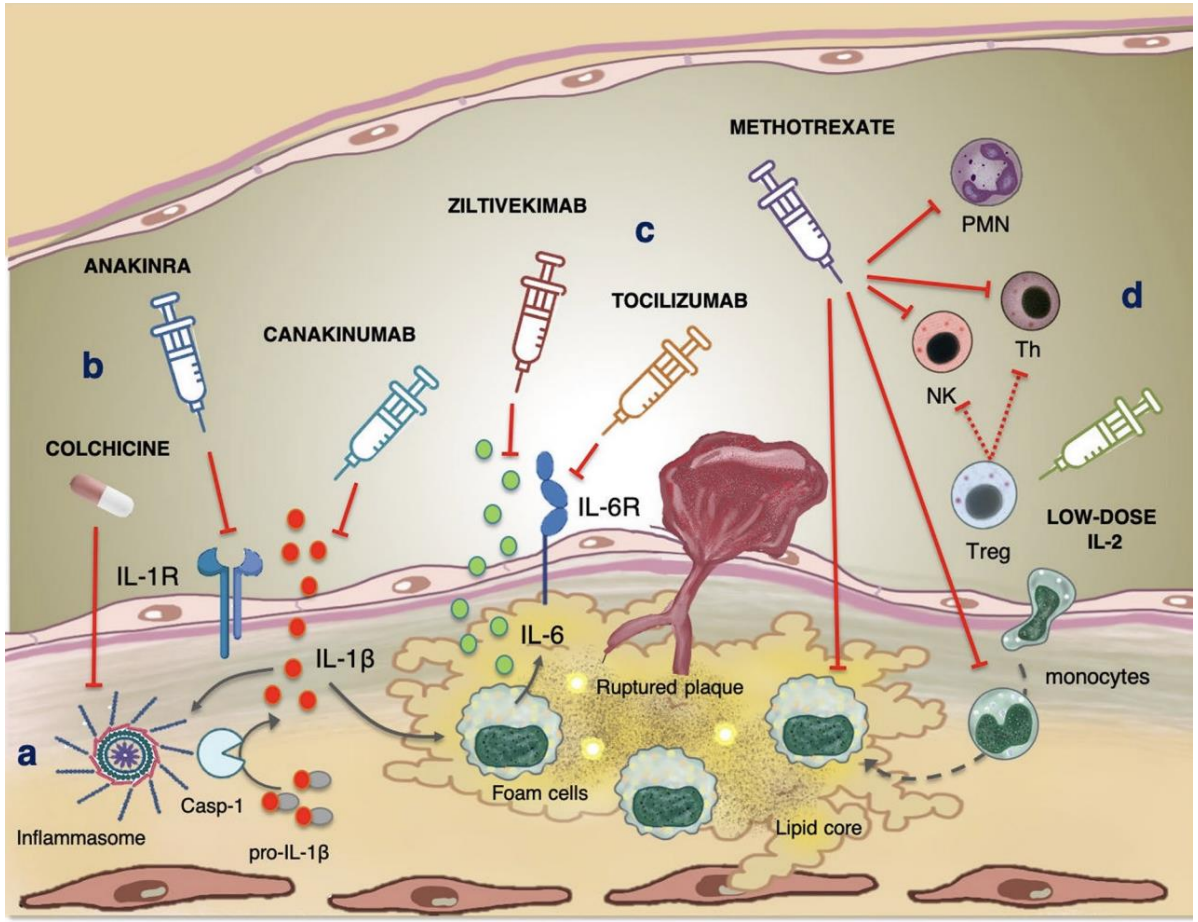
Mechanisms of cardiac diseases in clonal hematopoiesis



CHIP and leukemia



Clonal Hematopoiesis treatment



Relationship between chelation and clinical outcomes in lower-risk patients with myelodysplastic syndrome (MDS): Registry analysis at 5 years

Patient characteristics	Nonchelated n=328	Chelated n=271	Chelated ≥6 months n=202
Time to death, median (min/max) mo	**47.8** (43.4, 53.1)	**88.0** (78.4, 103.0) *P<0.0001	**100.0** (83.4, 118.2) *P<0.0001
Deaths (n), %	239 (72.9)	161 (59.4) *P=0.0005	115 (56.9) *P=0.0002
Median OS (mo) No CVC With CVC	 34.0 (n=42) 43.4 (n=286)	 69.3 (n=72) 67.7 (n=199) *P<0.0001	 79.3 (n=60) 72.6 (n=142) *P<0.0001
Median OS (mo) No EC With EC	 **38.5** (n=162) **44.6** (n=166)	 **67.1** (n=149) **75.0** (n=122) *P<0.0001	 **69.6** (n=114) **81.8** (n=88) *P<0.0001
Time to AML transformation from diagnosis, median (min, max) mo	46.4 (6.9, 82.5)	72.1 (16.4, 176.6) *P<0.0001	78.8 (16.4, 176.6) *P<0.0001
AML transformation, n (%)	**34** (10.4)	**17** (6.3)	**14** (6.9)

CVC, cardiovascular comorbidity; EC, endocrine comorbidity; CVA, cerebrovascular accident; GvHD, graft-vs-host disease *Versus nonchelated.

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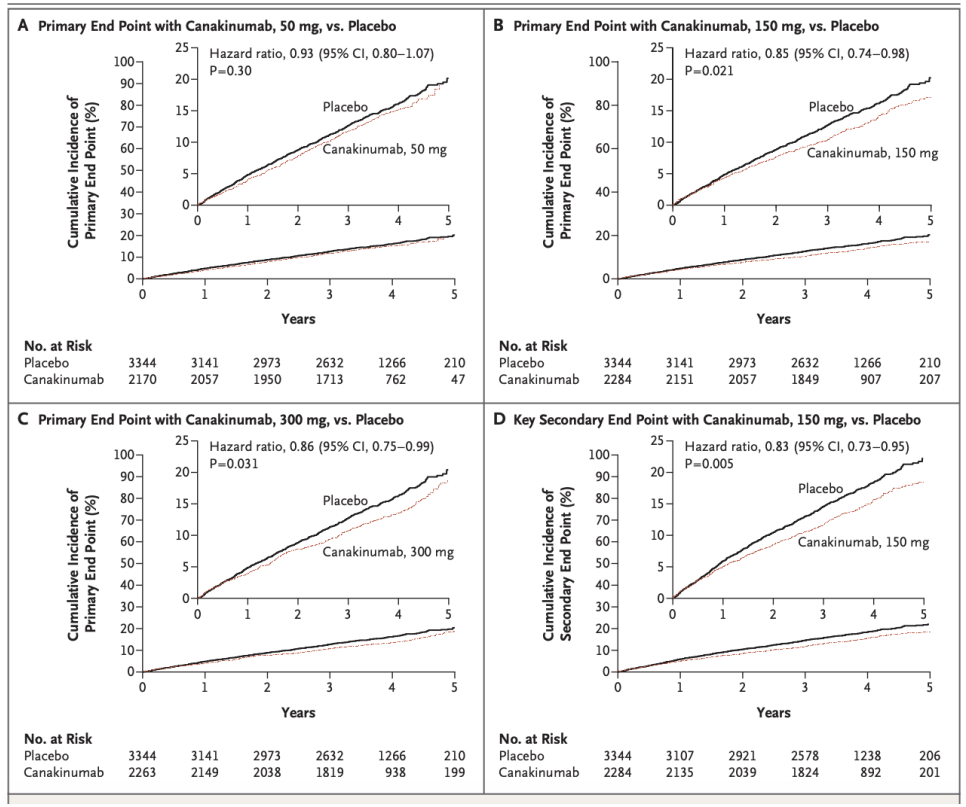
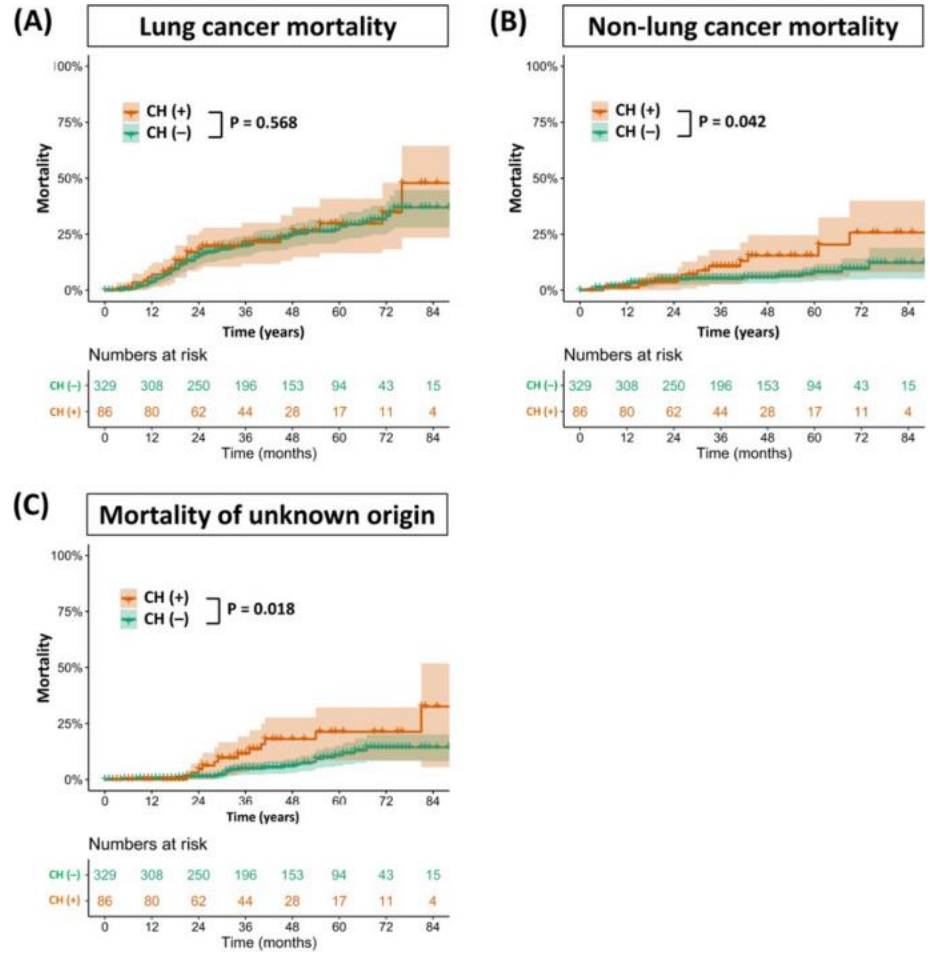
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

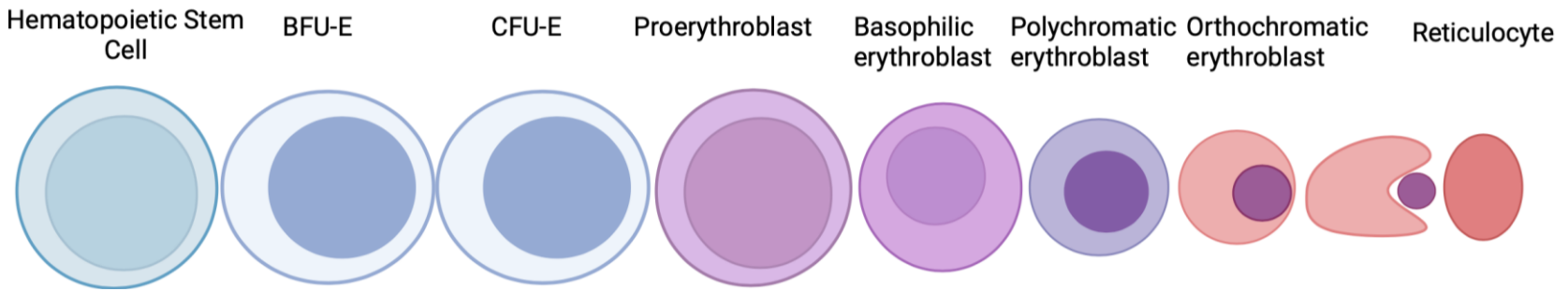




Total cancer mortality (n=196) was significantly lower icanakinumab group than in the placebo group (p=0·0007) (HR 0·23 [95% CI 0·10–0·54]; p=0·0002)

Conclusion

Erythropoiesis is a remarkable system:
A complex network regulates erythroblasts survival, proliferation, and differentiation to ensure constant oxygenation and optimal metabolism



Understanding ineffective erythropoiesis is essential for making informed treatment decisions in hematological disorders (benign and malignant) and may enhance our knowledge of basic science and disease pathophysiology beyond the field of hematology

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THANK YOU

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