



CONVEGNO FISiM

Firenze, CSF Montedomini - "Il Fuligno"

24-25 ottobre 2024

GRUPPO DI LAVORO **MDS e metabolismo ferro/ROS** **Coordinatore Federica Pilo**

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Rossella Stella

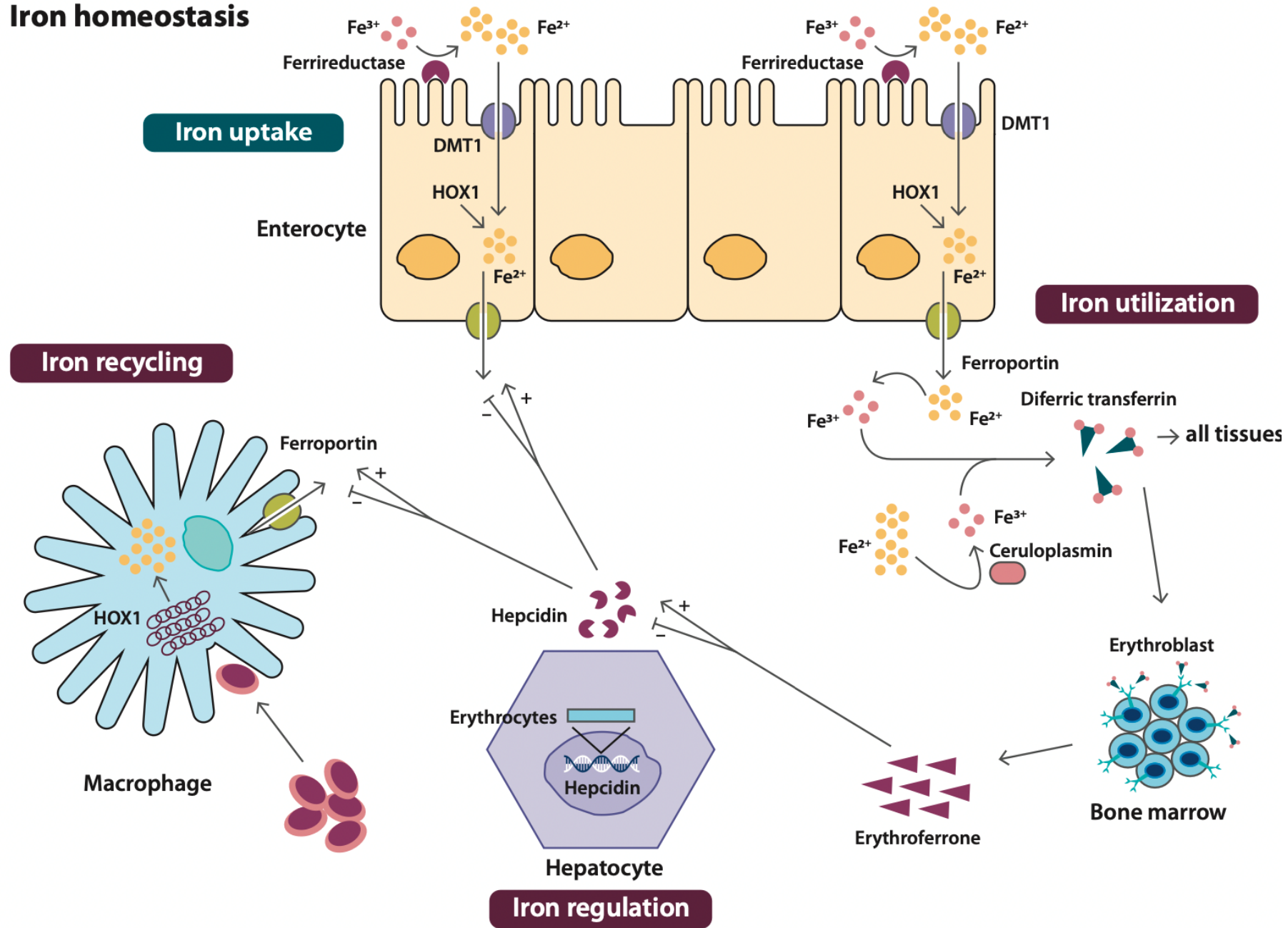
Federico Itri

Daniele Grimaldi

AGENDA

- **LINK IRON-ERYTHROPOIESIS**
rationale and study proposal
- **LINK ROS-HEMOPOIESIS**
rationale and study proposal

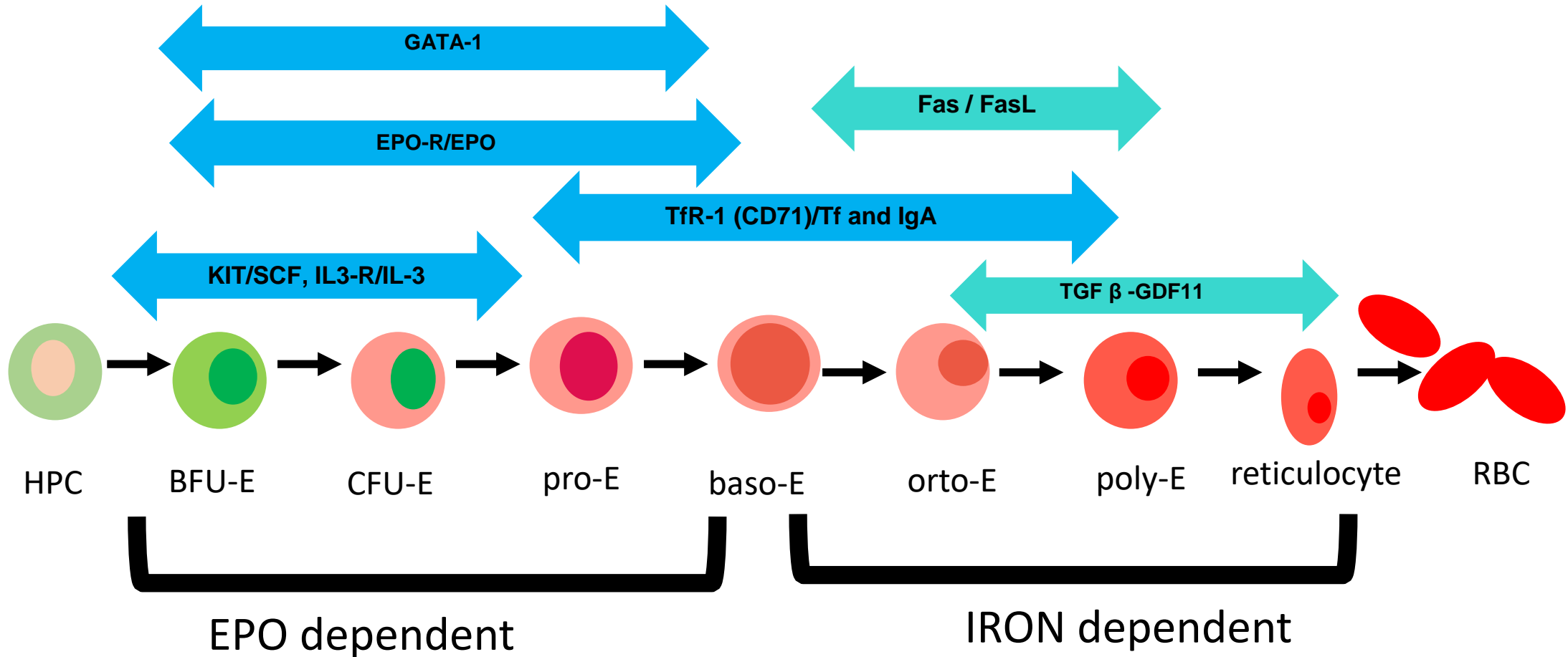
Iron homeostasis



Mechanisms of efficacy erythropoiesis

Positive growth factors for multipotent and early erythropoietic progenitor cells

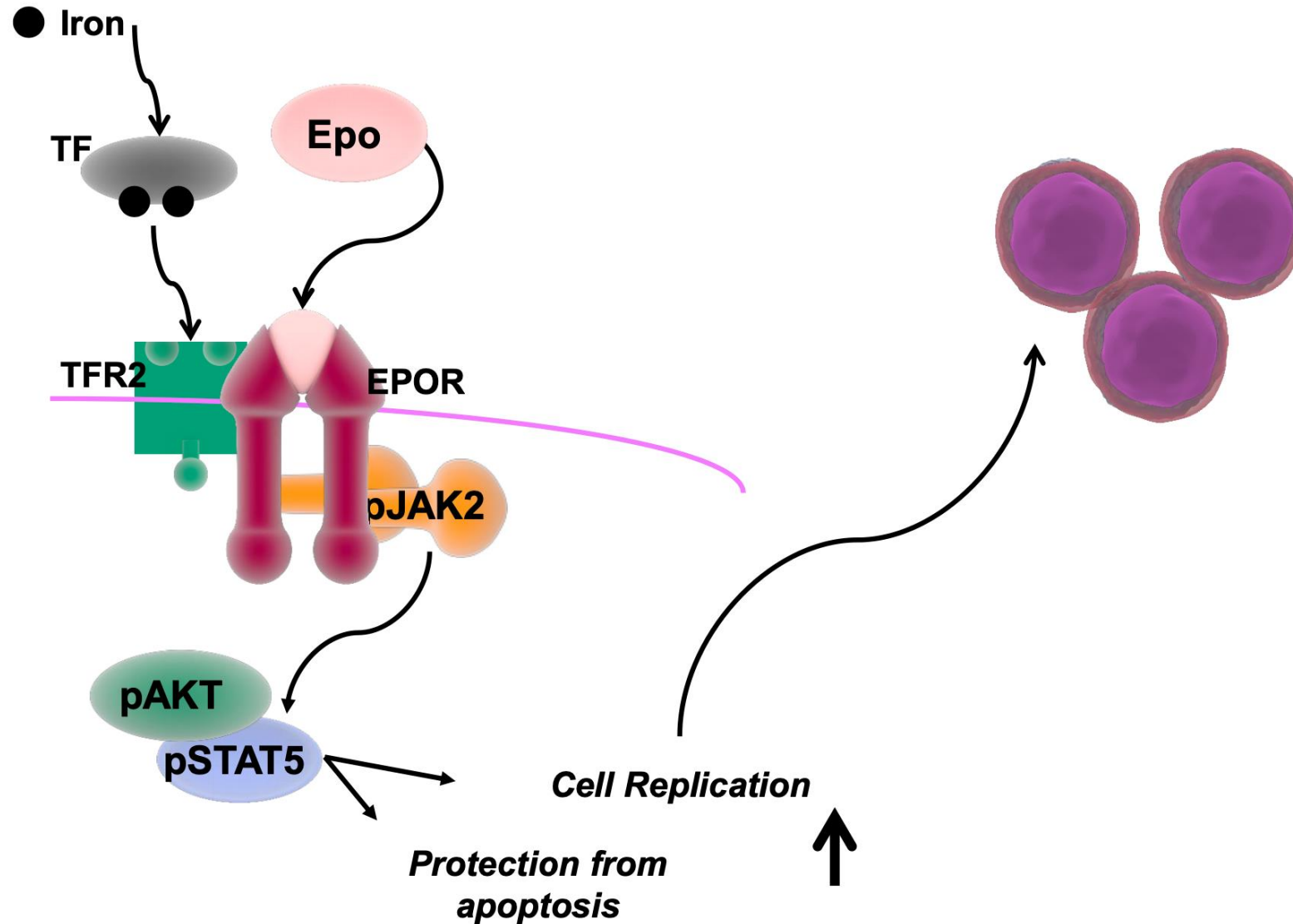
Negative growth regulators of erythropoietic progenitor cells



Early-stage erythropoiesis:
Proliferation of progenitor cells

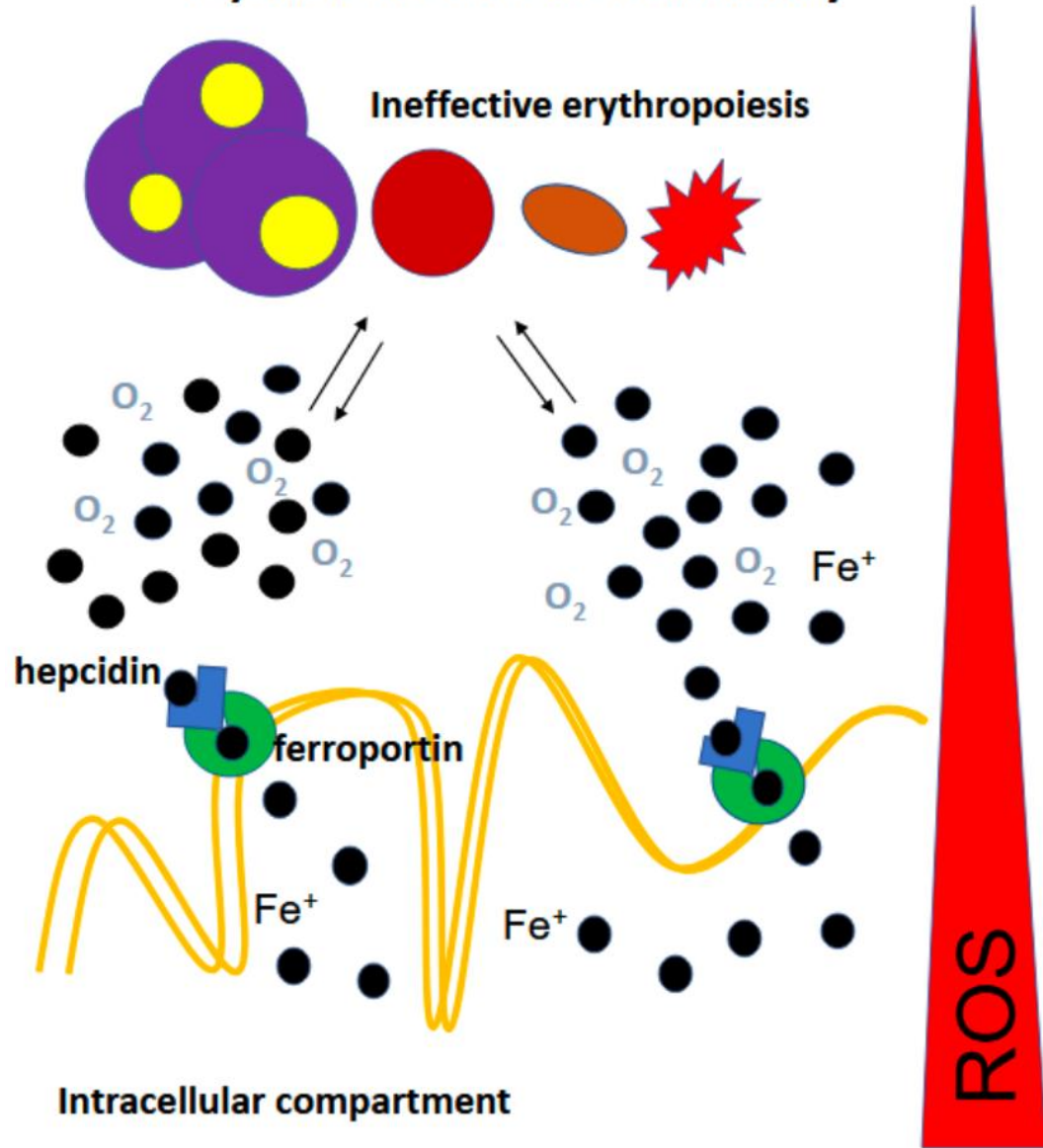
Late-stage erythropoiesis: Differentiation of erythroblasts and maturation of precursor cells to RBCs

Normal Erythropoiesis

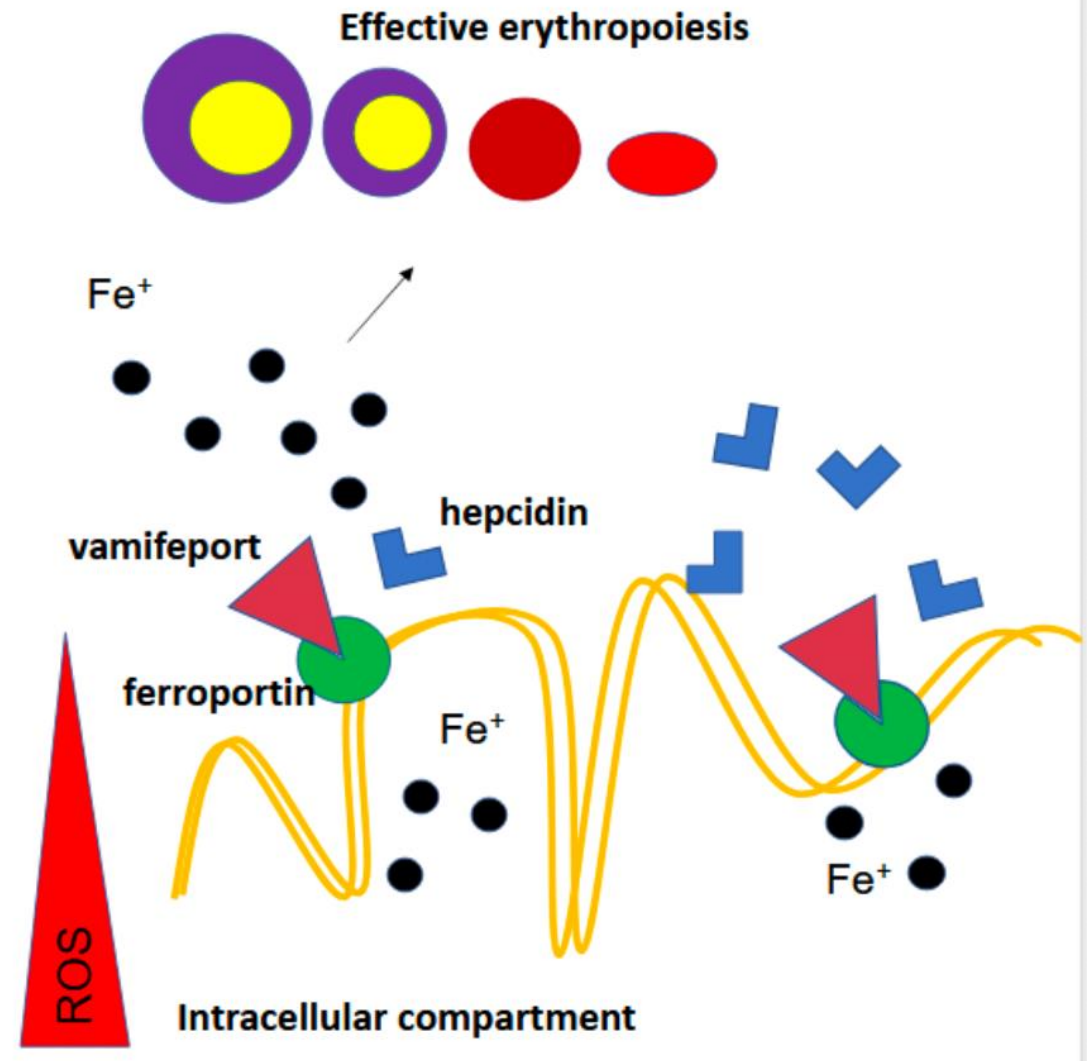


Mechanism	Target and/or drug	Disease											
		NTDBT	NTDAT	TDBT	TDAT	PV	CDA-II	DBA	MDS	IRIDA	Myel.	CKD	
+	Modulate erythropoiesis	SMAD pathways/Reblozyl (luspatercept)	+	+	+	-	-	+	?	+	+	+	+
+	Improve EPO sensitivity	Erythroid TFR2	+	+	+	+	-	+	?	+	?	?	+
	Reduction of splenomegaly	JAK2 inhibitors	-	-	+	+	+	-	-	-	-	-	-
	Improve red cell quality/Pyruvate kinase inducer	Pyruvate kinase/Pyrukynd (mitapivat)	+	+	+	-	-	?	?	?	-	-	-
	Inhibition of autophagy	mTORC1/rapamycin or similar	+	-	+	-	-	-	-	-	-	-	-
	Decrease iron absorption Hepcidin mimetics	Ferroportin/Rusfertide (PTG-300)	+	+	+	+	+	+	+	+	-	-	-
+	Decrease iron absorption Hepcidin inducers	TMPRSS6 mRNA/TMPRSS6-ASO	+	+	+	+	+	+	+	+	-	-	-
+	Decrease iron absorption Ferroportin inhibitors	Ferroportin/Vamifeport (VIT-2763)	+	+	+	+	+	+	+	+	-	-	-
	Decrease iron absorption ERFE inhibitors	ERFE	+	+	+	+	-	+	-	-	-	-	-
	Decrease TF saturation	TF	+	+	+	-	-	?	-	-	-	-	-
	Modulate heme synthesis	Glycine transporter 1 inhibitor/bitopertin	-	-	-	-	+	-	+	-	-	-	-
	Increase iron absorption	Hemojuvelin/DISC-0974	-	-	-	-	-	-	-	-	+	+	+
	Increase iron absorption	ALK2/momelotinib/LJ000328	-	-	-	-	-	-	-	-	+	+	+
	Increase TF saturation	Deferiprone	+	+	+	+	-	?	?	?	+	-	+

A) Increased iron availability



B) Restricted iron availability



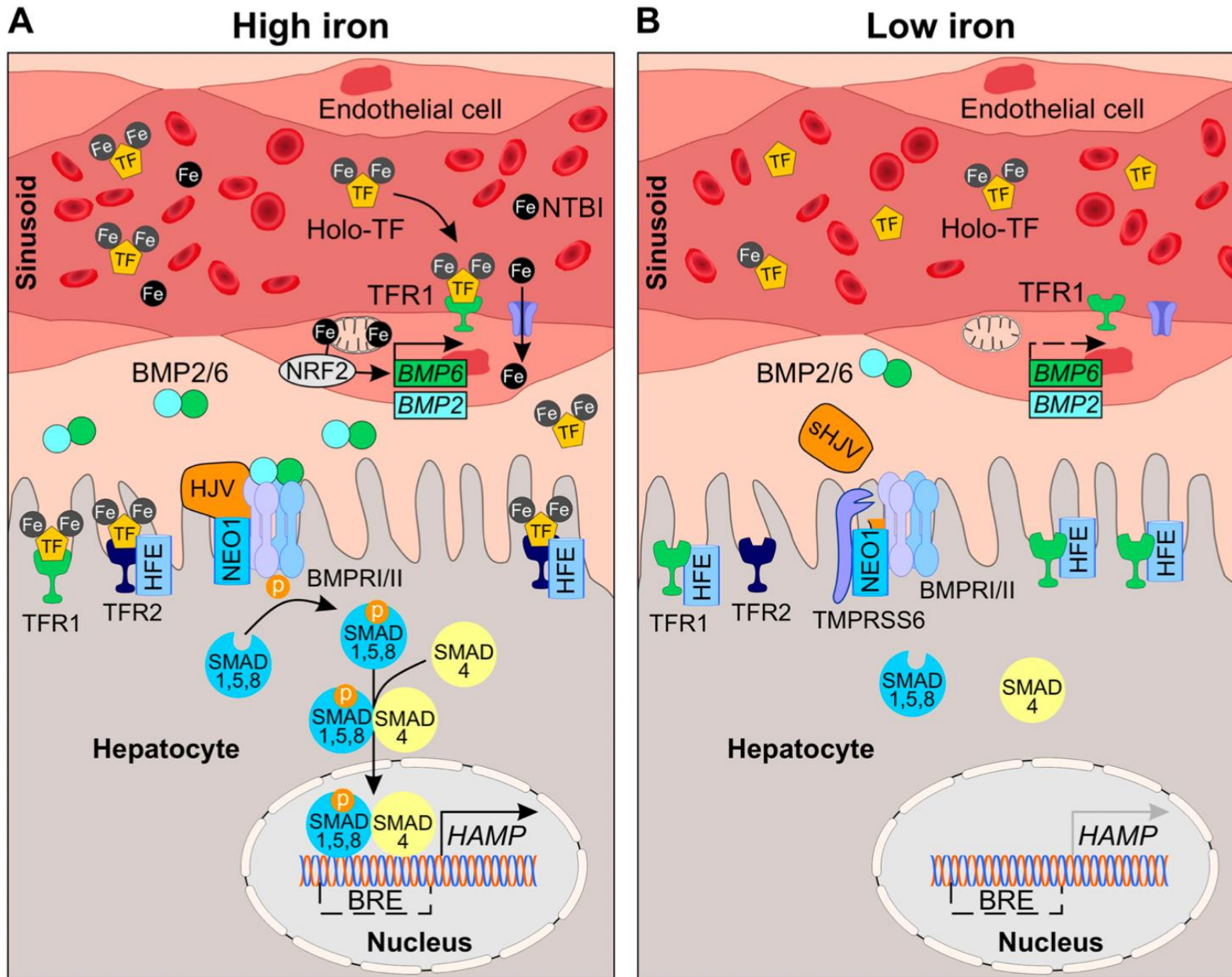


COMBINING IRON RESTRICTION AND ERYTHROID MATURATION AGENTS HAS A SUPERIOR THERAPEUTIC EFFECT IN MDS

ANTYPIUK Ada ¹, VANCE S.zebulon ¹, SHARMA Richa ¹, DÜRRENBARGER Franz ², MANOLOVA Vania ², VINCHI Francesca ¹

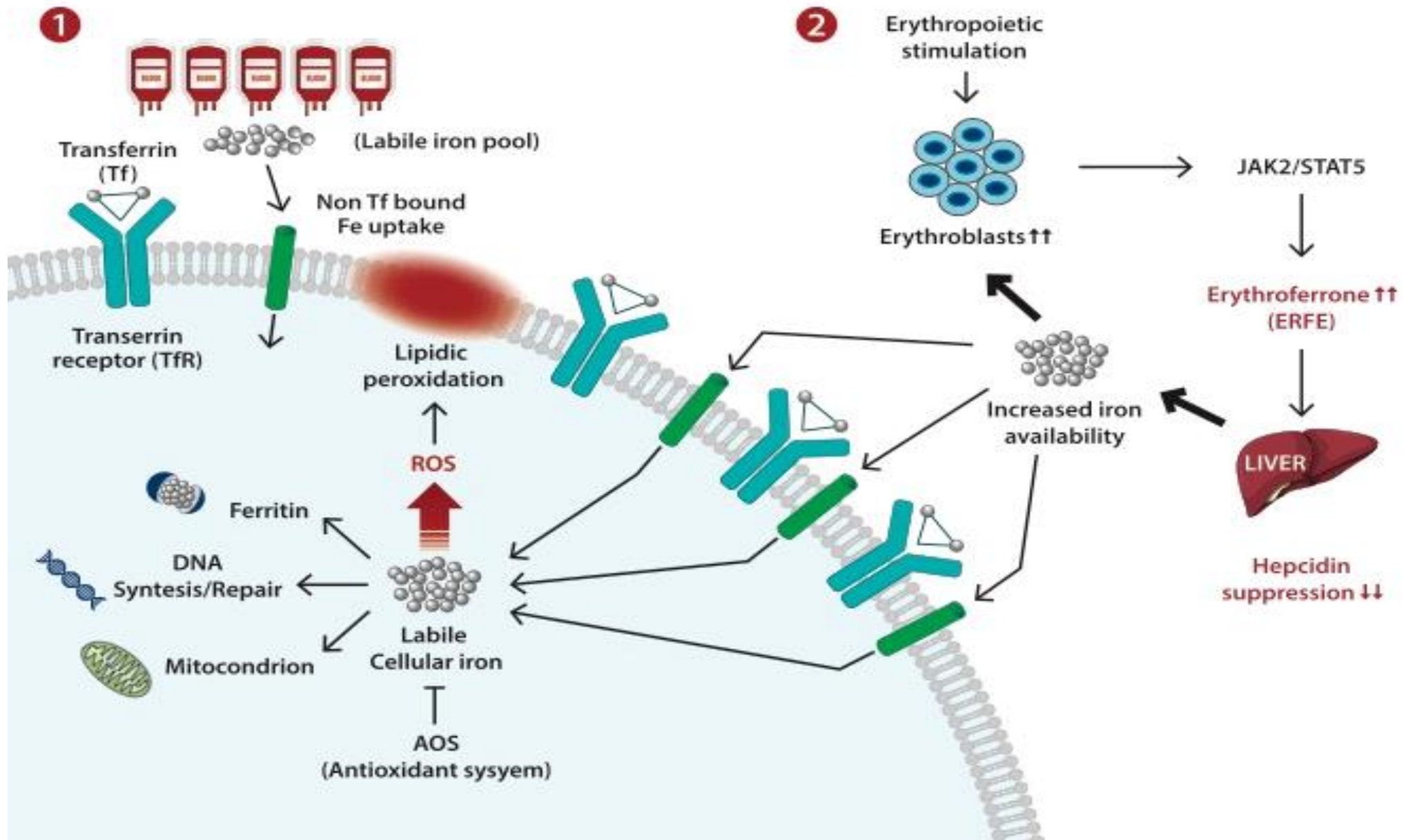
¹ New York Blood Center, New York , United States; ² CSL Vifor, St.Gallen, Switzerland

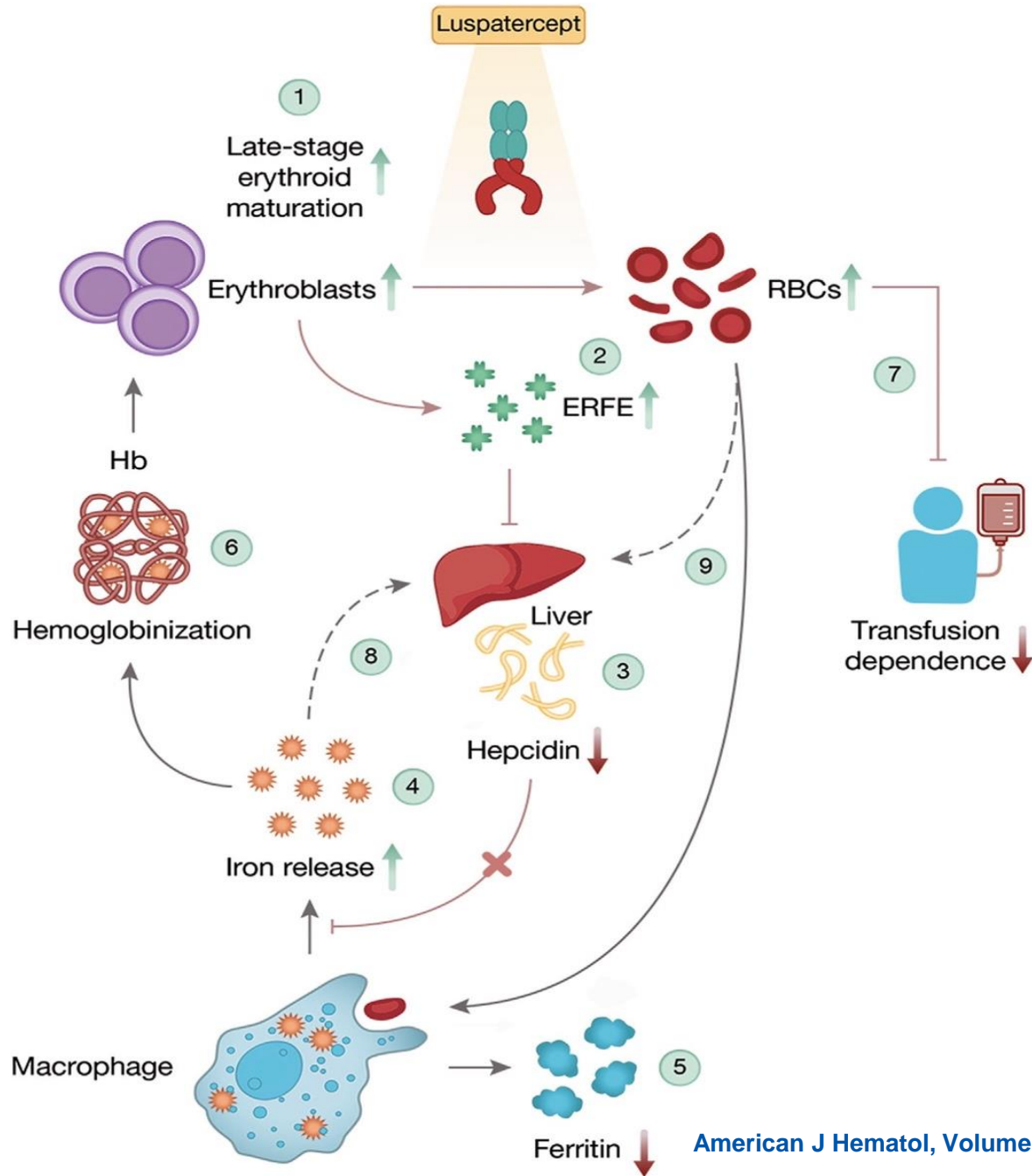
- Overall, these data prove that combo therapies aimed at restricting iron and boosting erythroid maturation have superior effects in improving MDS pathophysiology, providing pre-clinical evidence for their application, and suggest they may offer more effective strategies for MDS treatment.
- The HSPC pool and DNA damage were significantly ameliorated by vamifeport as single or combined treatment. Importantly, vamifeport, but not luspatercept, significantly attenuated myeloid expansion and myeloblasts in the MDS bone marrow, suggesting disease-modifying activity for this drug and revealing a major role of the iron status in myeloid skewing.



SLN 124 is a gene «silencing» therapy target **TMPRSS6** che agisce inibendo l'epcidina, il risultato è l'aumentata produzione di hepcidina che porta ad una restrizione di ferro che migliora l'eritropoiesi

Phase Ib for MDS (NCT04718844) and II for Thal and SCD Ongoing





- Decreased transfusion with luspatercept in patients with TDT was associated with increased erythropoietic markers and decreasing hepcidin..
- LIC increased in patients with intact spleens, consistent with iron redistribution given the hepcidin reduction.
- Thus, erythropoietic and hepcidin changes with luspatercept in TDT lower transfusion dependency and may redistribute iron from macrophages to hepatocytes, necessitating the use of concomitant chelator cover for effective iron management.

TITOLO PROPOSTA DI STUDIO:

EVALUATION OF THE ROLE OF THE ASSOCIATION DEFERASIROX- LUSPATERCEPT IN THE LONG-TERM RESPONSE IN LOW-INTERMEDIATE RISK MDS?

Studio osservazionale retrospettivo, multicentrico non interventistico

Obiettivi Primario:

Esplorare il ruolo dell'associazione Luspatercept-Deferasirox in termini di risposta a lungo termine e risposta ritardata rispetto alla scheda tecnica

Obiettivo secondario:

Raccolta eventi avversi cardiaci ed epatici

TITOLO PROPOSTA DI STUDIO:

EVALUATION OF IRON HOMEOSTASIS CHANGING DURING LUSPATERCEPT TREATMENT IN LOW-INTERMEDIATE RISK MDS?

Studio osservazionale prospettico, multicentrico non interventistico

Obiettivi Primari:

Valutare la redistribuzione del ferro durante la terapia con Luspatercept (tramite saturazione della transferrina, marcatori di emolisi ed MRI T2*)

Obiettivo secondario:

Personalizzare la ferrochelazione in base alla redistribuzione del ferro e non in base alla riduzione della Ferritina durante la terapia con Luspatercept

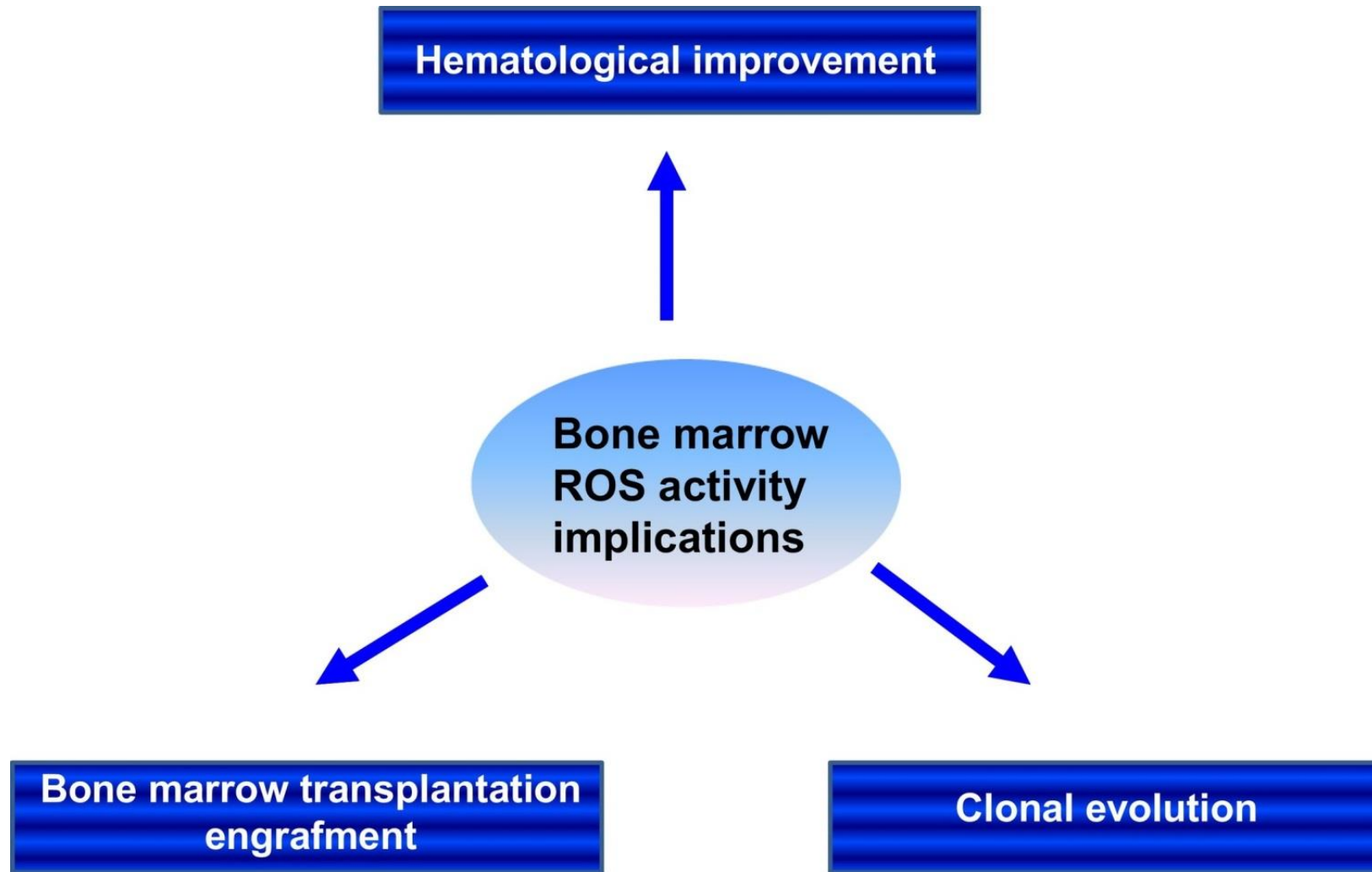
Raccolta eventi avversi cardiac ed epatici

Requisito di adesione dei Centri: disponibilità per MRI T2*

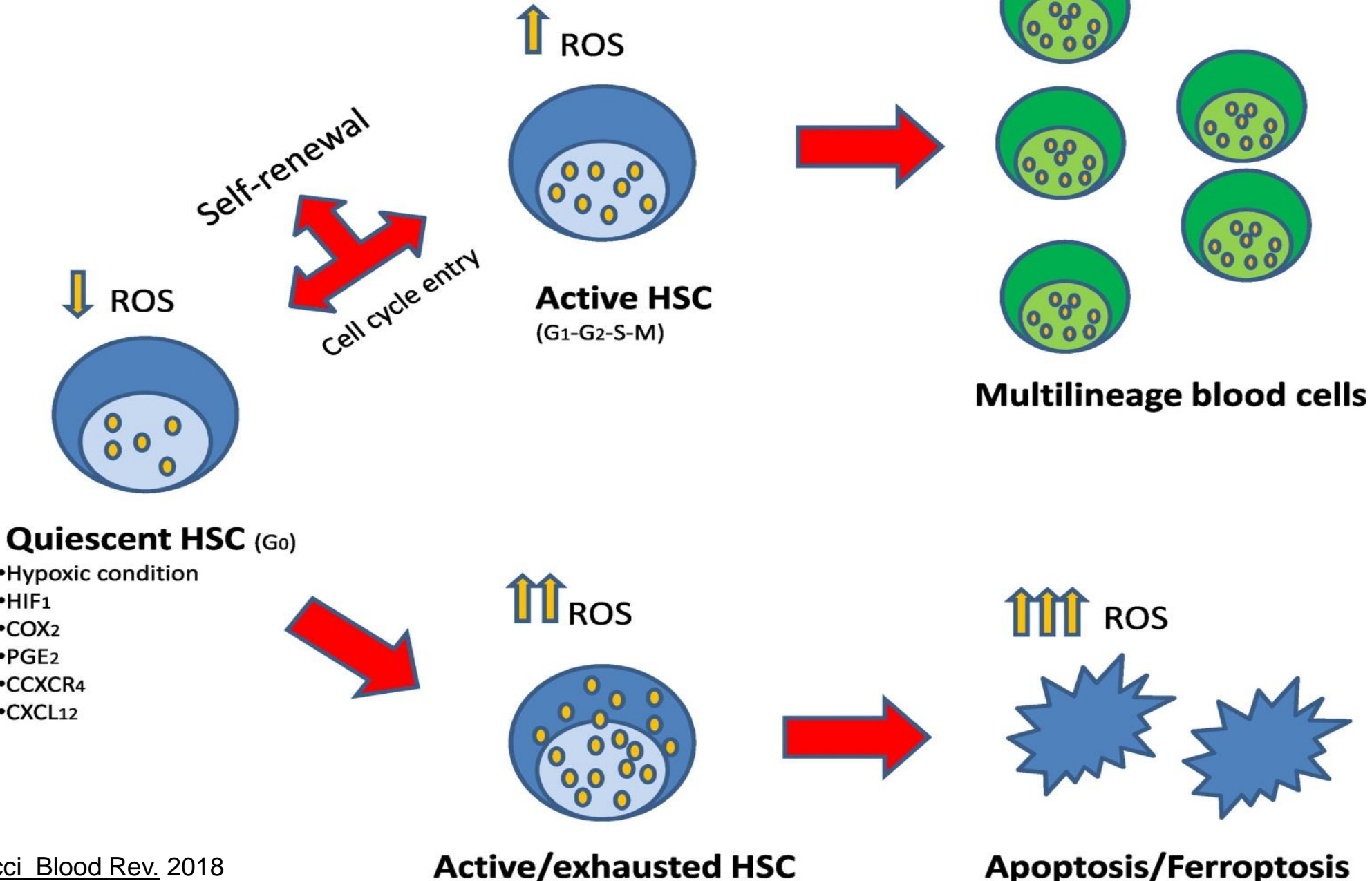
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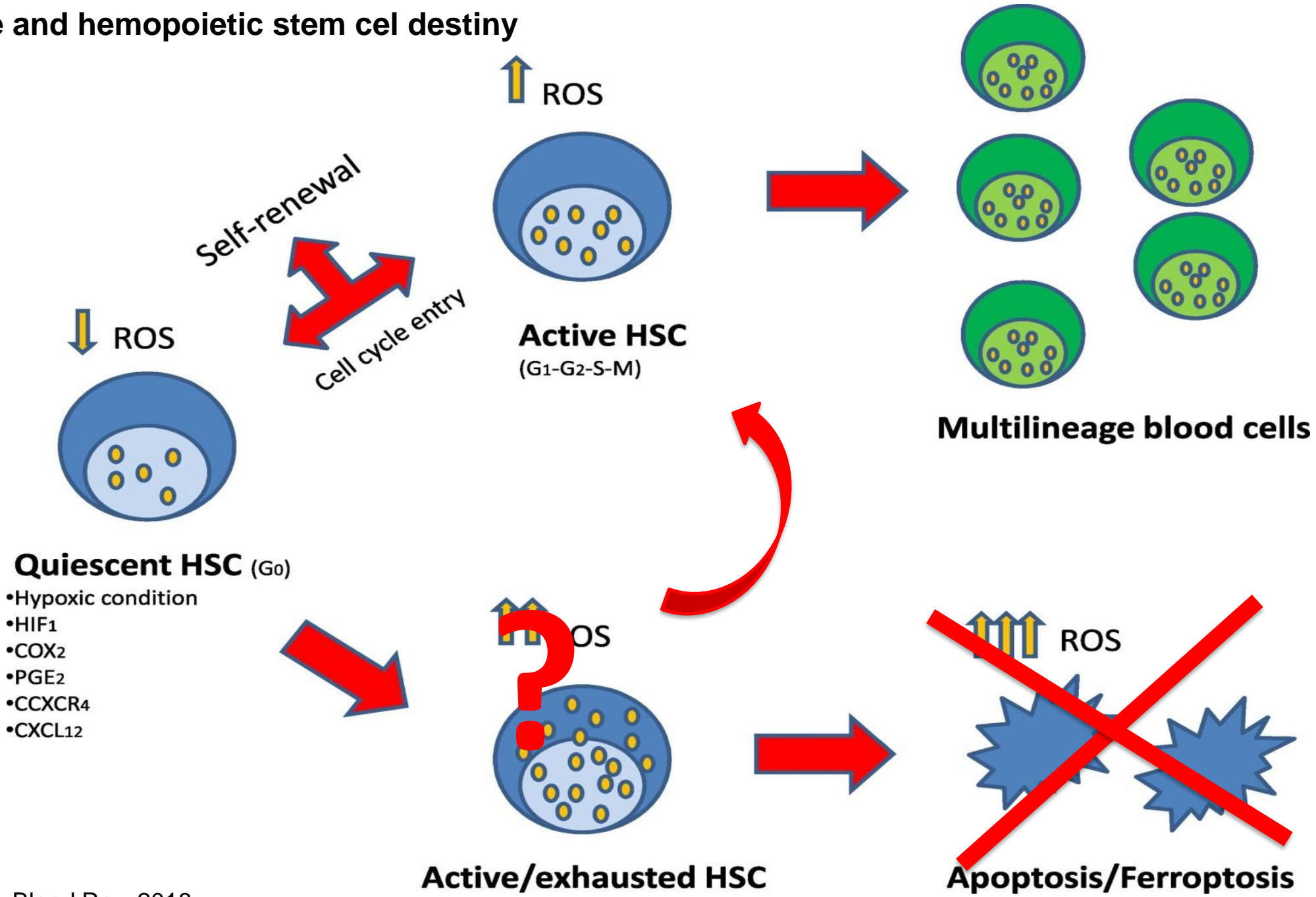
Process in which ROS activity could be involved



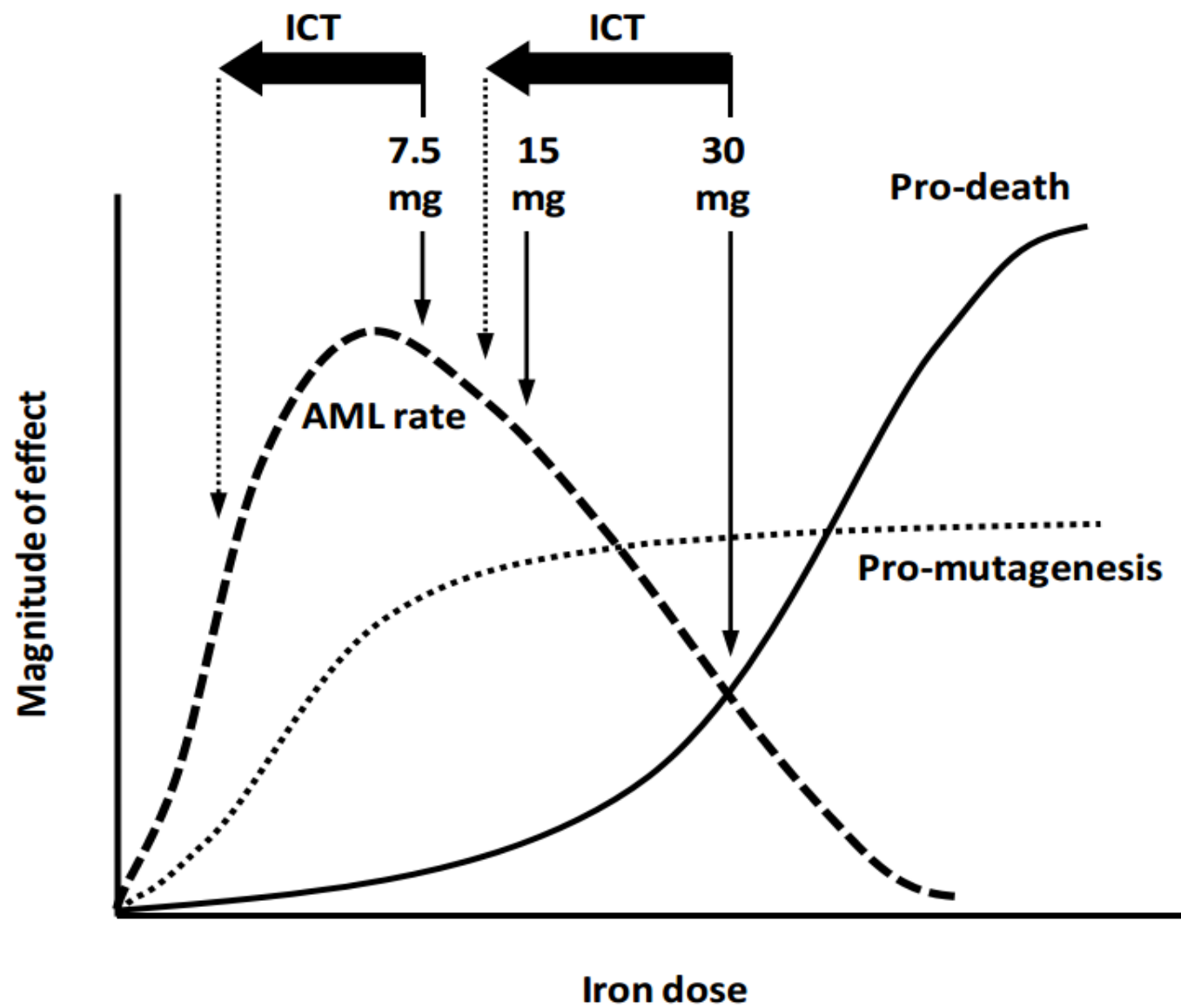
ROS balance and hemopoietic stem cell destiny



ROS balance and hemopoietic stem cell destiny



Proposed pro-death and pro-mutagenic influences of iron loading and ICT on the rate of AML

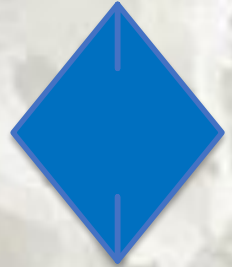


Proposed pro-death and pro-mutagenic influences of iron loading and ICT on the rate of AML

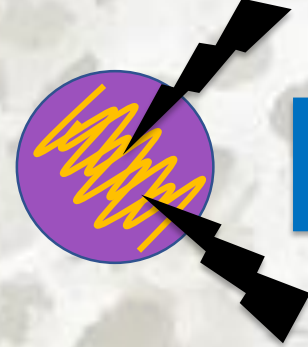
ROS



Quiescent
HSC



Efficient
HSC

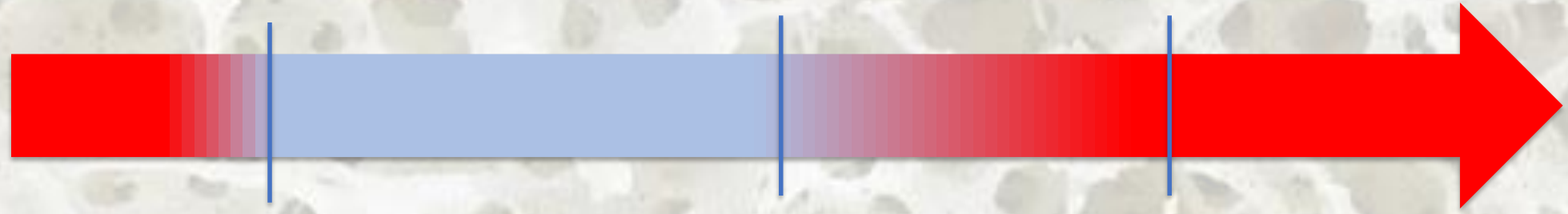


Exhausted
HSC



Ferropoptosis

DFX/NAC
dosage



???

???

New prospective: personalized iron chelation therapy

PRESENT	FUTURE
<ul style="list-style-type: none">• ferritin, transferrin saturation• blood transfusion intake,• MRI	<ul style="list-style-type: none">• NTBI, LPI/LCI ,• ROS (peroxides, superoxide, peroxides/superoxide ratio)• Reduced glutathione (GSH)• Lipid peroxidases (MDA)• Hpcidin, GDF 11 e 15• Erythroferrone,• 8-OHdG and OGG1 activity

Unusual parameters as ROS may be considered to detect the real iron tissue damage; connected to single patient niche damage and personalized iron chelation therapy

TITOLO PROPOSTA DI STUDIO:

CORRELAZIONE TRA STRESS OSSIDATIVO, EMOPOIESI E PROGRESSIONE LEUCEMICA NEI PAZIENTI LOW-INTERMEDIATE RISK MDS?

Studio sperimentale prospettico, multicentrico non interventistico

Obiettivo primario:

Esplorare il ruolo dei ROS nella patogenesi dell'evoluzione clonale e nella funzionalità delle cellule staminali e dei progenitori mieloidi, correlare il valore dei ROS alla progression leucemica e all'NGS

Obiettivi secondario:

Verificare in vitro l'efficacia del NAC e della Vit E nel migliorare la funzionatià della cellula staminale correlate allo stress ossidativo e correlarlo ai markers del ferro

Requisito di adesione dei Centri: **disponibilità del laboratorio del Centro per confronto su riproducibilità della metodica misurazione ROS. Non è possibile centralizzare**

**Thanks for your
very kind attention**



Iron-ROS-translational team

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