

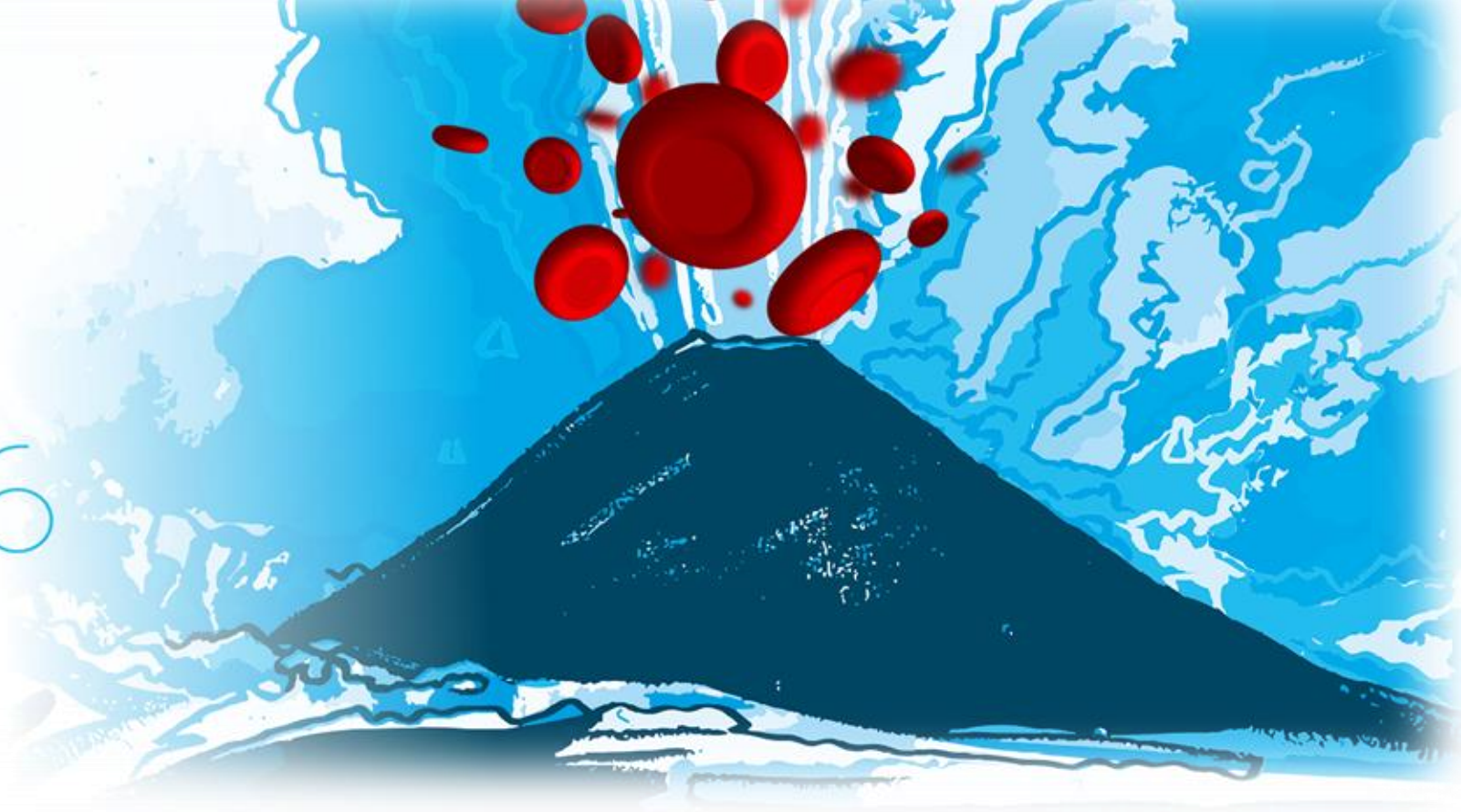
Meeting del CLUB DEL

Globulo Rosso 2026

NAPOLI

28-29 SETTEMBRE 2026

Complesso dei SS. Marcellino e Festo



Metabolismo del ferro nelle sindromi da eritropoiesi inefficace

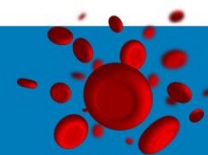
Antonella Nai, PhD

Group Leader, Regulation of Iron Metabolism Unit

San Raffaele Scientific Institute, Milan, Italy

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other



The multiple life of iron

Iron and erythropoiesis exert a reciprocal regulation

~ 60%

ution

Fe

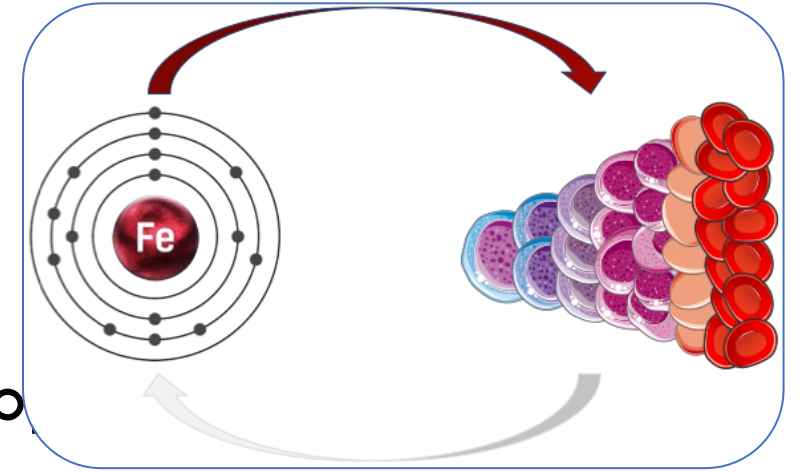
Fe

Total iron ~4g

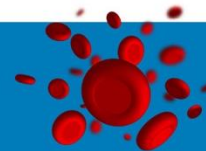
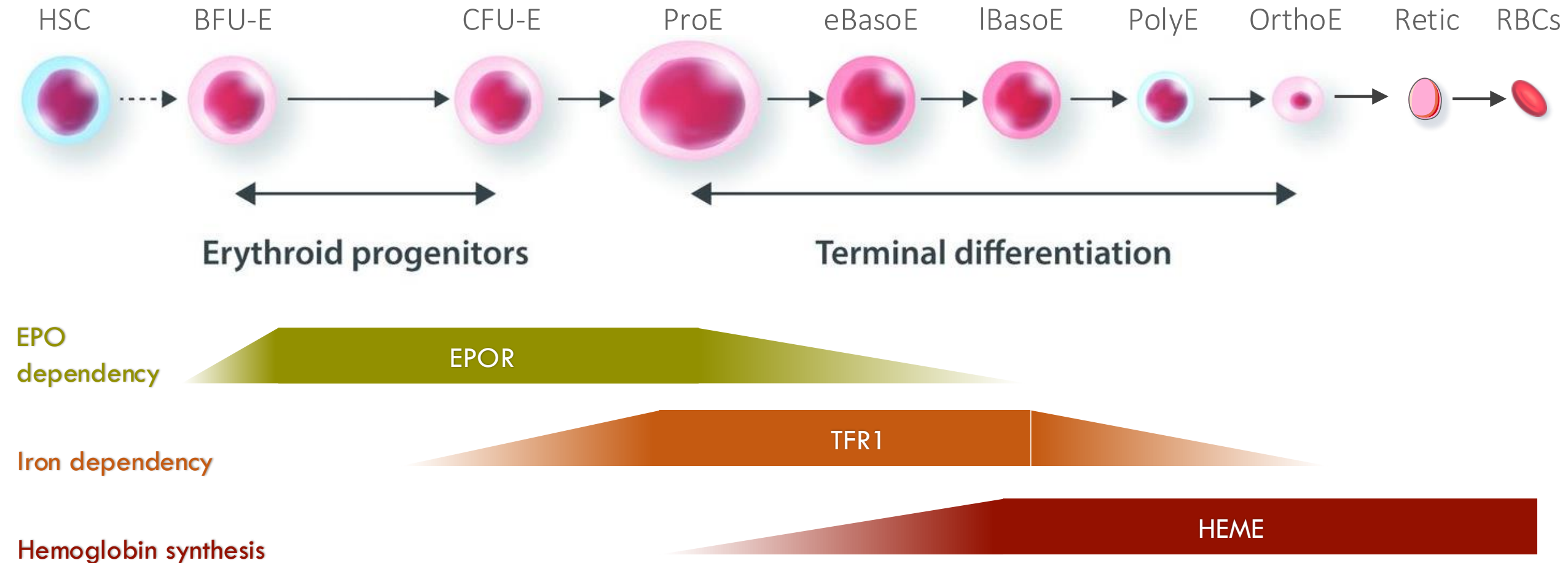
Uwitonze AM et al., *Front. Nutr.* 2023

Outline of the presentation

- ✓ Iron uptake and utilization by erythroid cells
- ✓ Regulation of systemic iron homeostasis from erythro
- ✓ Modulation of iron homeostasis for the amelioration of ineffective erythropoiesis

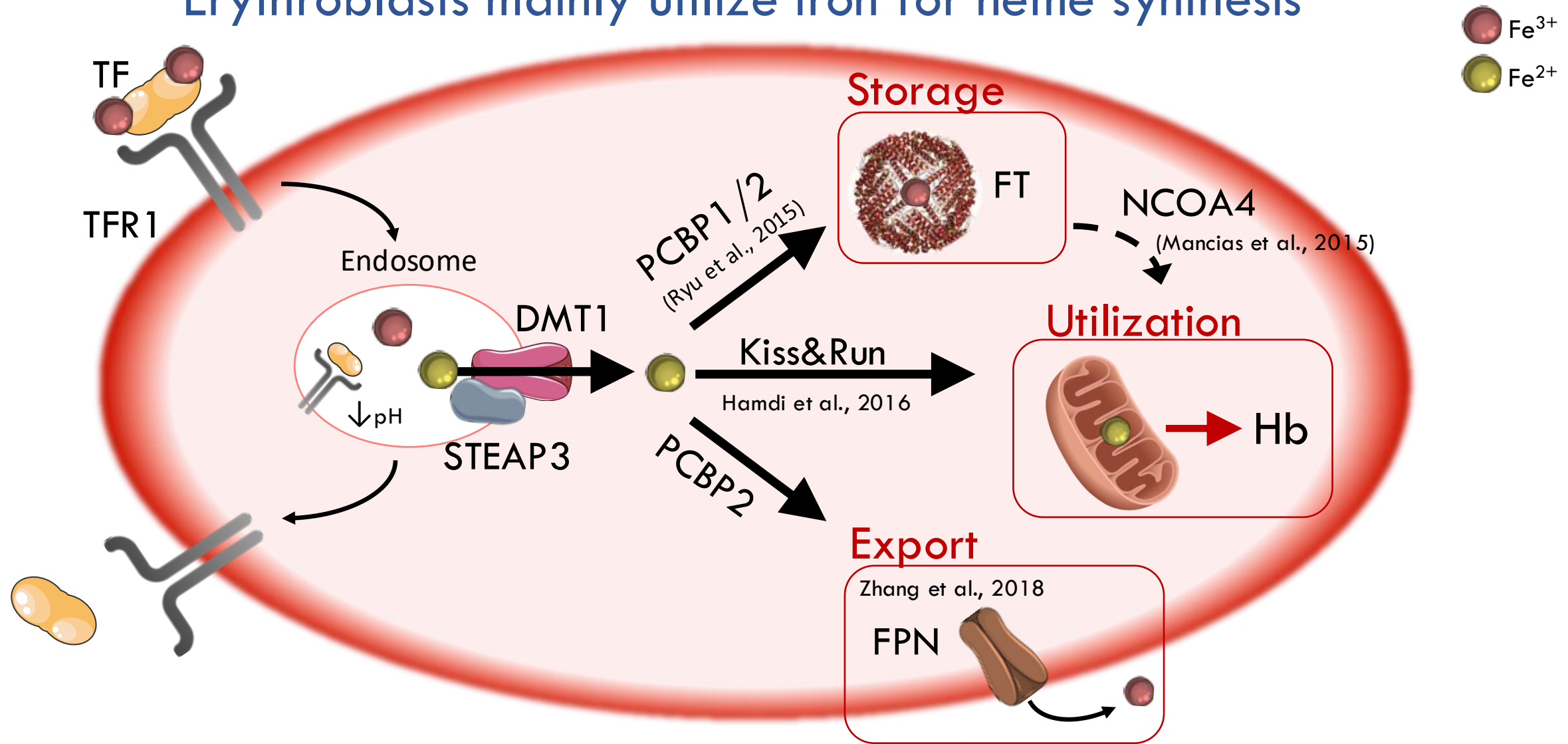


Terminal erythropoiesis is strongly iron-dependent

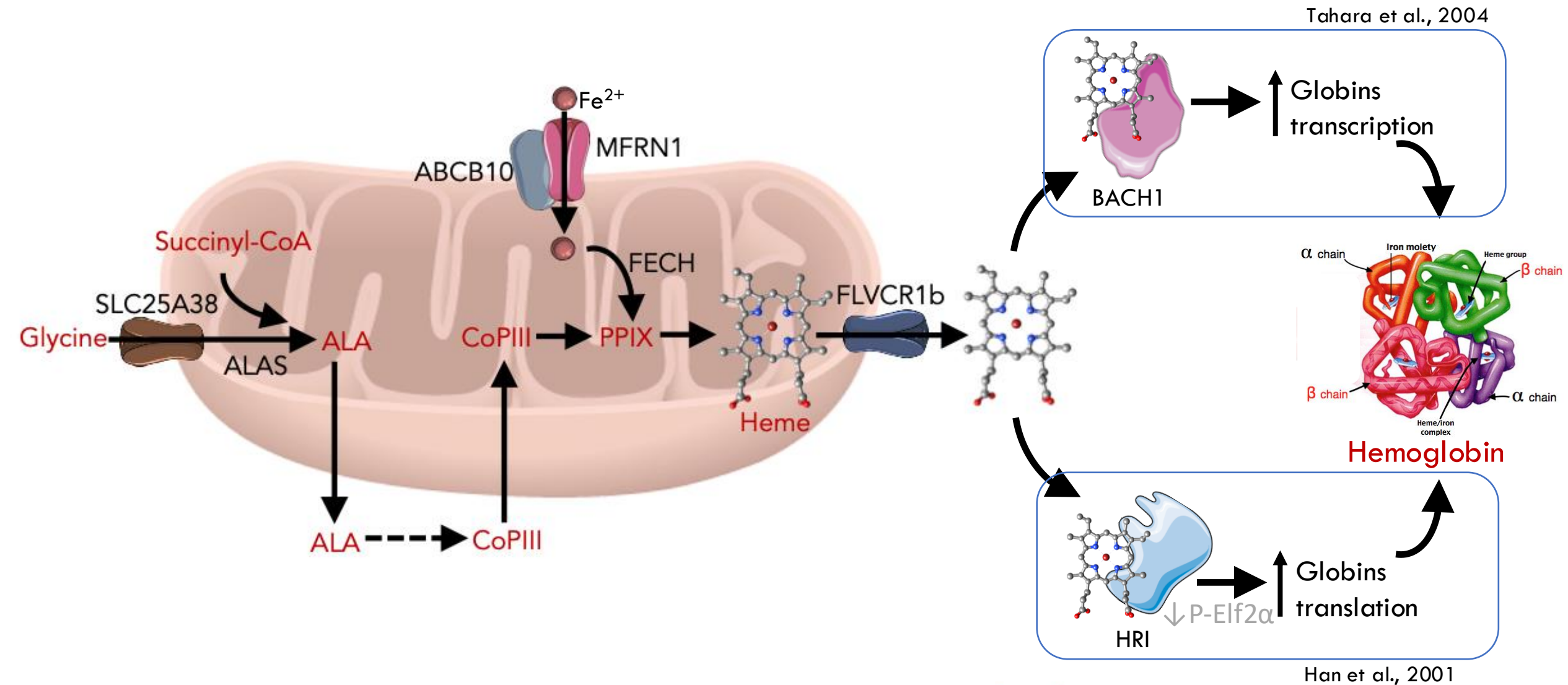


Erythroblasts uptake iron via Transferrin Receptor 1

Erythroblasts mainly utilize iron for heme synthesis



Hemoglobin synthesis



Iron-dependent erythroid disorders

Low iron availability

➤ CAUSES:

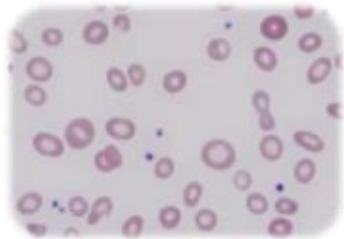
- Systemic iron deficiency
- Deficiency of TFR1, DMT1, PCBP1, NCOA4

➤ CONSEQUENCES:

- ↓ Heme and Hb synthesis
- ↓ EPO synthesis (IRP1-mediated inhibition of HIF2 α translation)



Microcytic Hypochromic Anemia



Mitochondrial iron accumulation

➤ CAUSES:

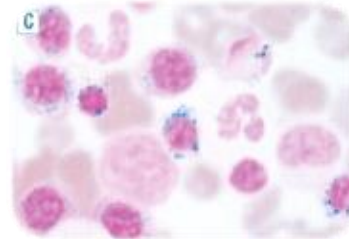
- Low glycine uptake
- Deficiency of the heme/Fe-S cluster biosynthetic pathways

➤ CONSEQUENCES:

- ↓ Heme and Hb synthesis
- Ineffective erythropoiesis (↑ stress and apoptosis of erythroblasts)



Congenital Sideroblastic Anemia



Cellular iron accumulation

➤ CAUSES:

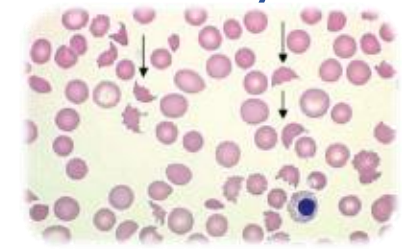
- Defective globin synthesis (i.e. thalassemias)
- FPN deficiency

➤ CONSEQUENCES:

- Heme excess, but ↓ Hb (thal)
- Ineffective erythropoiesis
- ↑ stress of mature RBCs

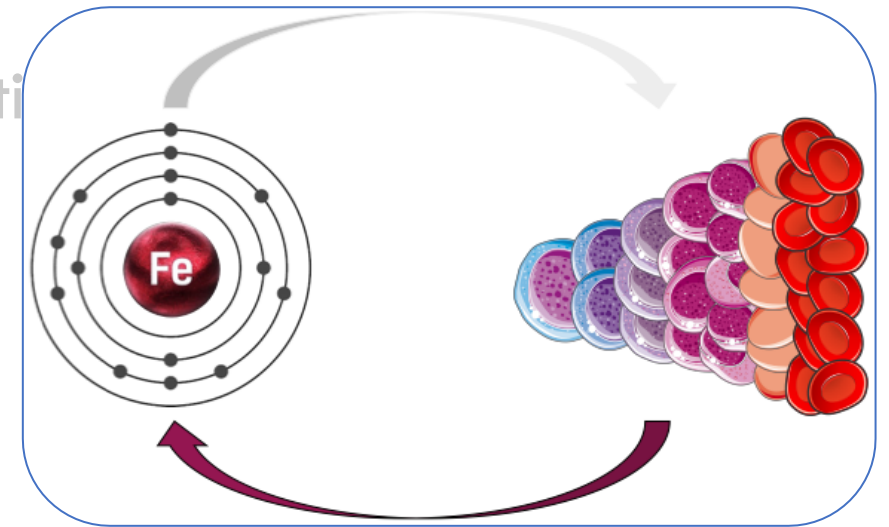


Hemolysis

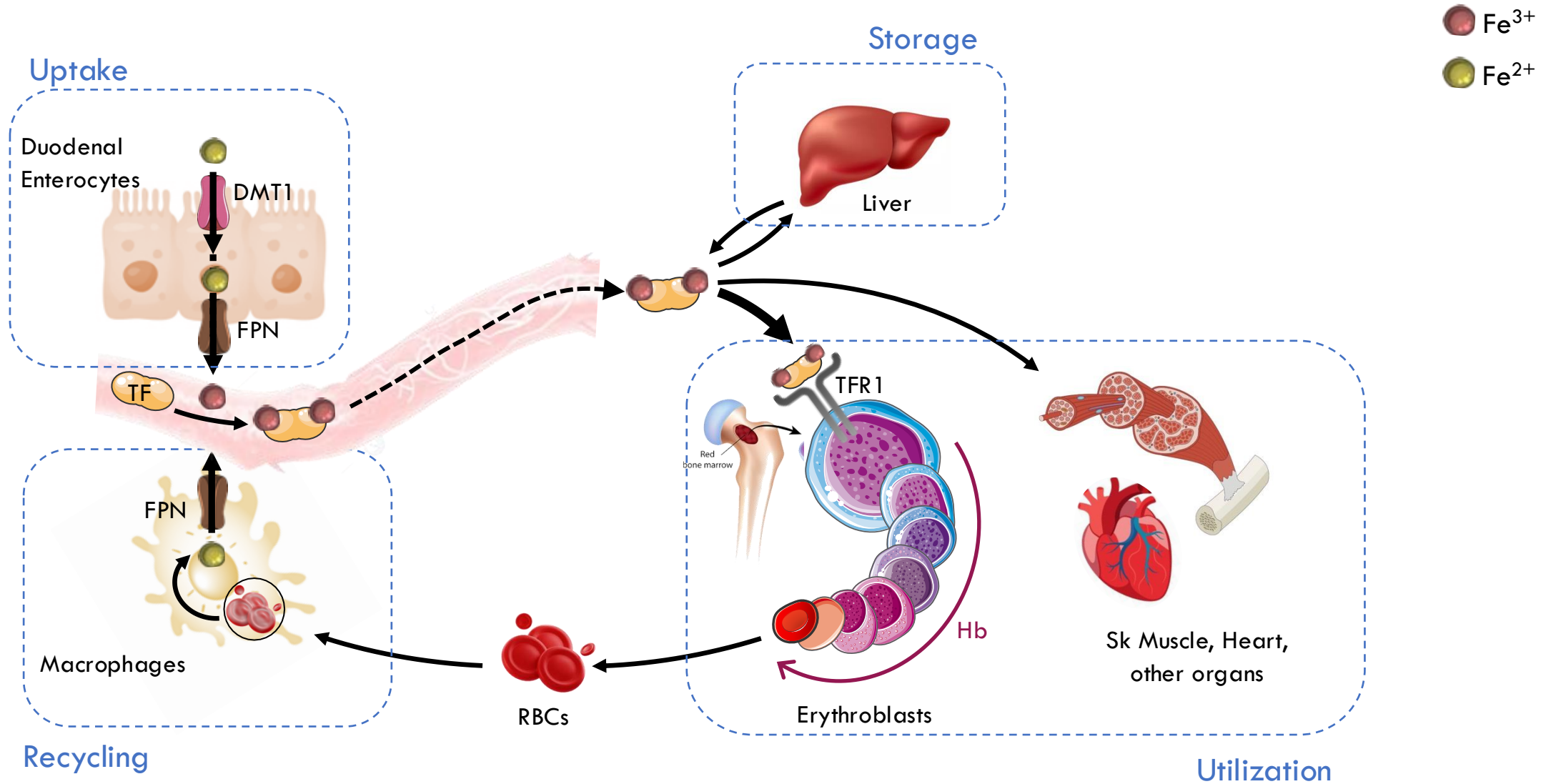


Outline of the presentation

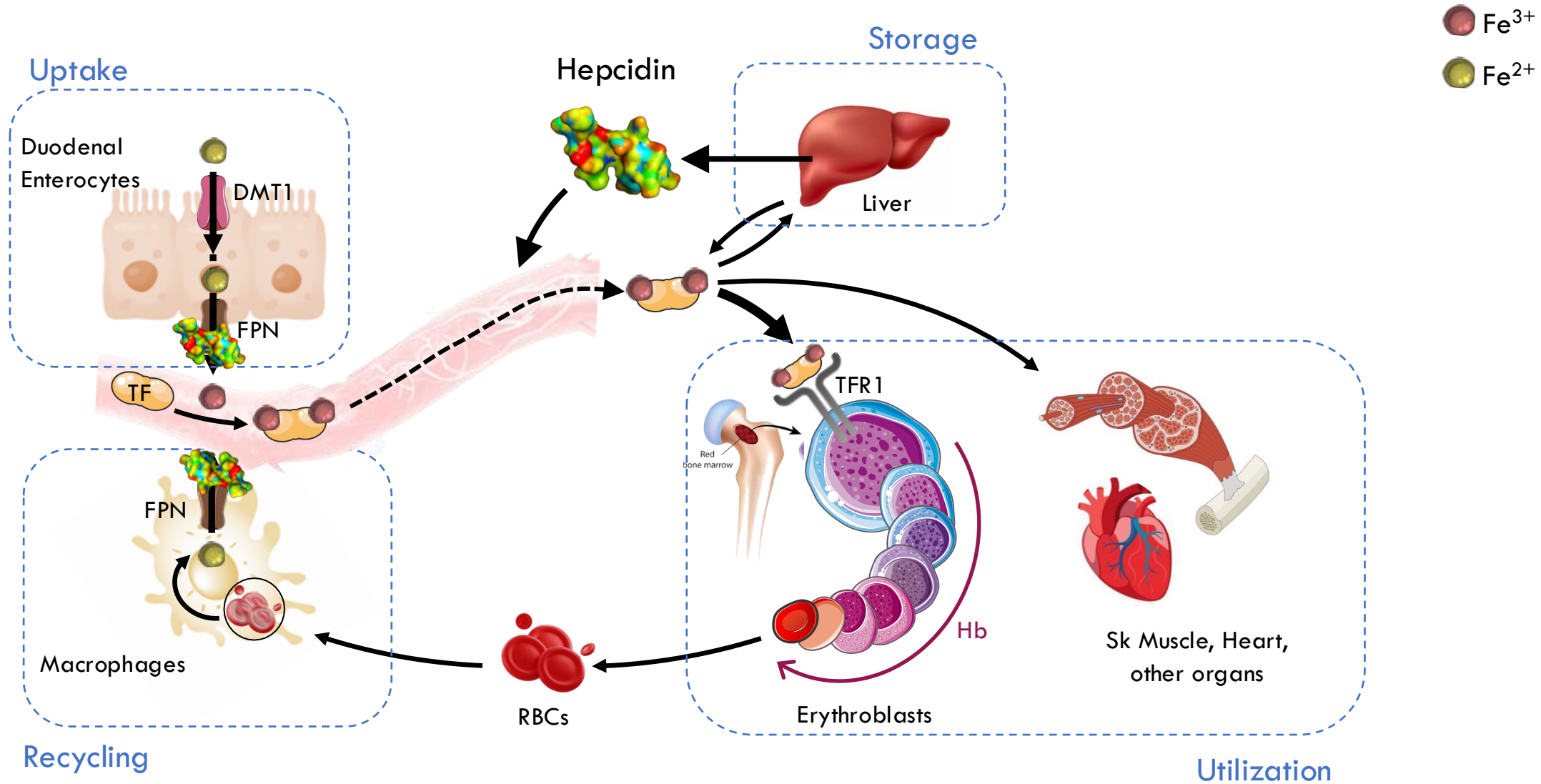
- ✓ Iron uptake and utilization by erythroid cells
- ✓ Regulation of systemic iron homeostasis from erythropoiesis
- ✓ Modulation of iron homeostasis for the amelioration of erythropoiesis



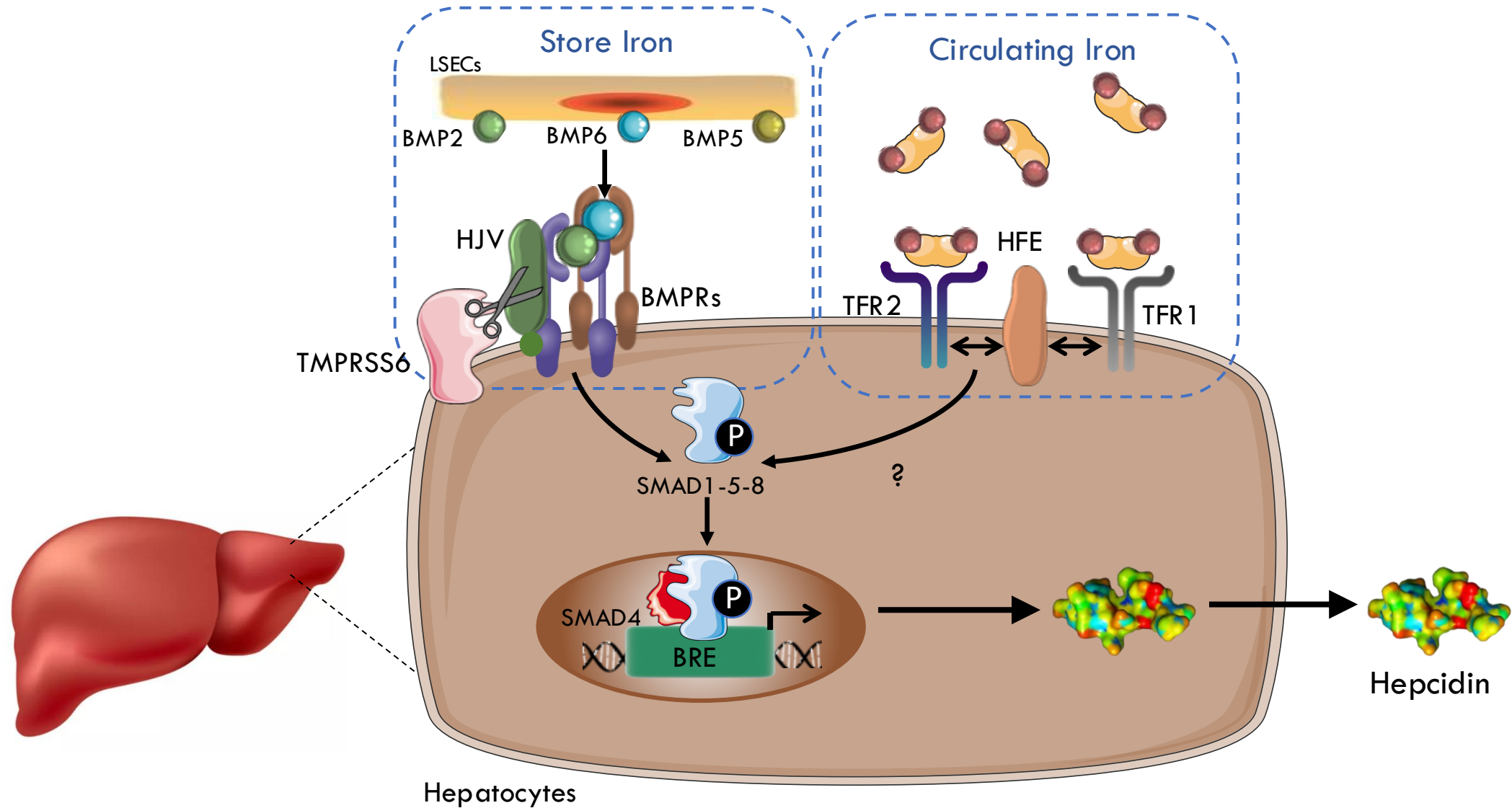
Systemic iron homeostasis



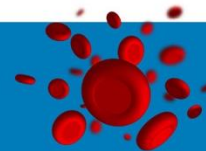
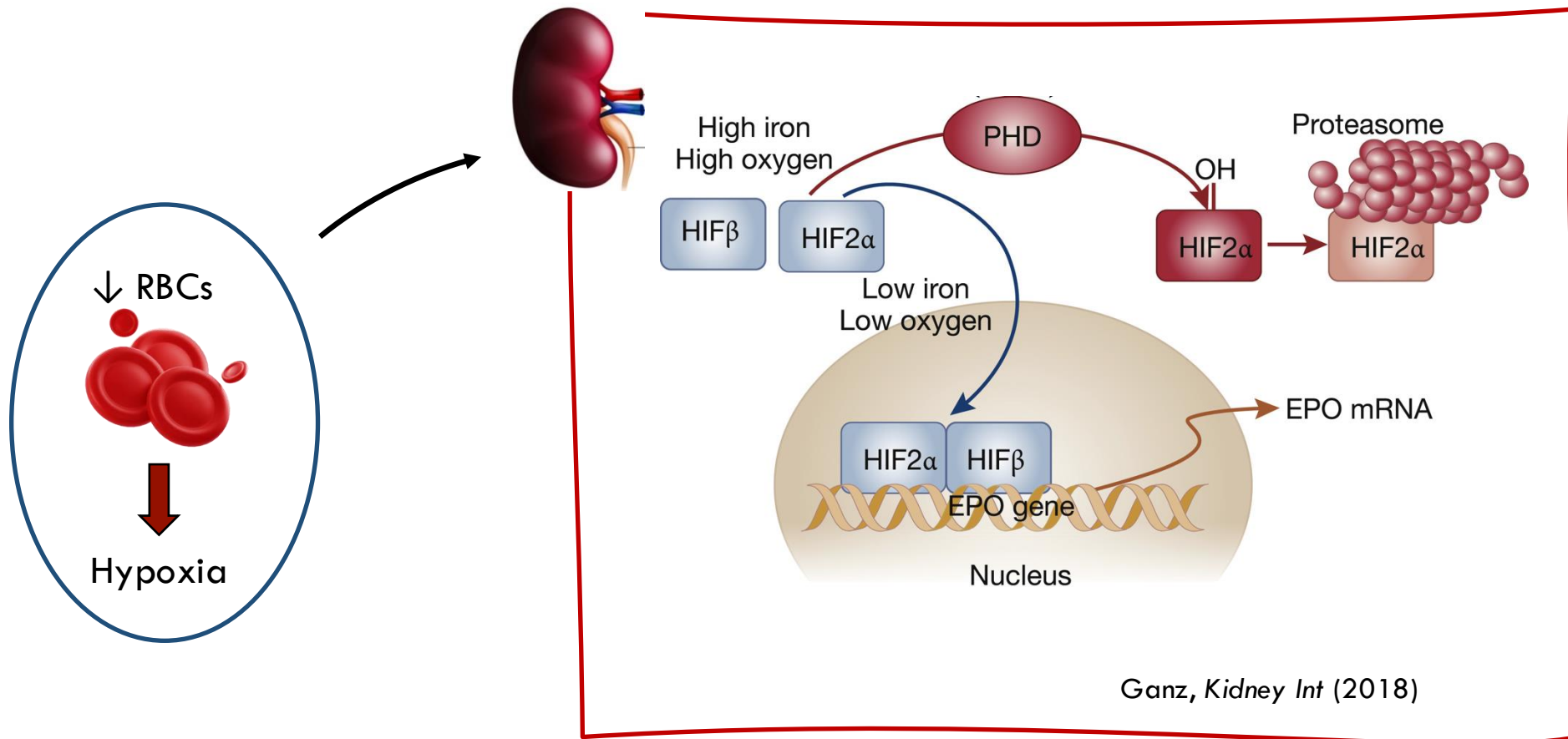
Systemic iron homeostasis



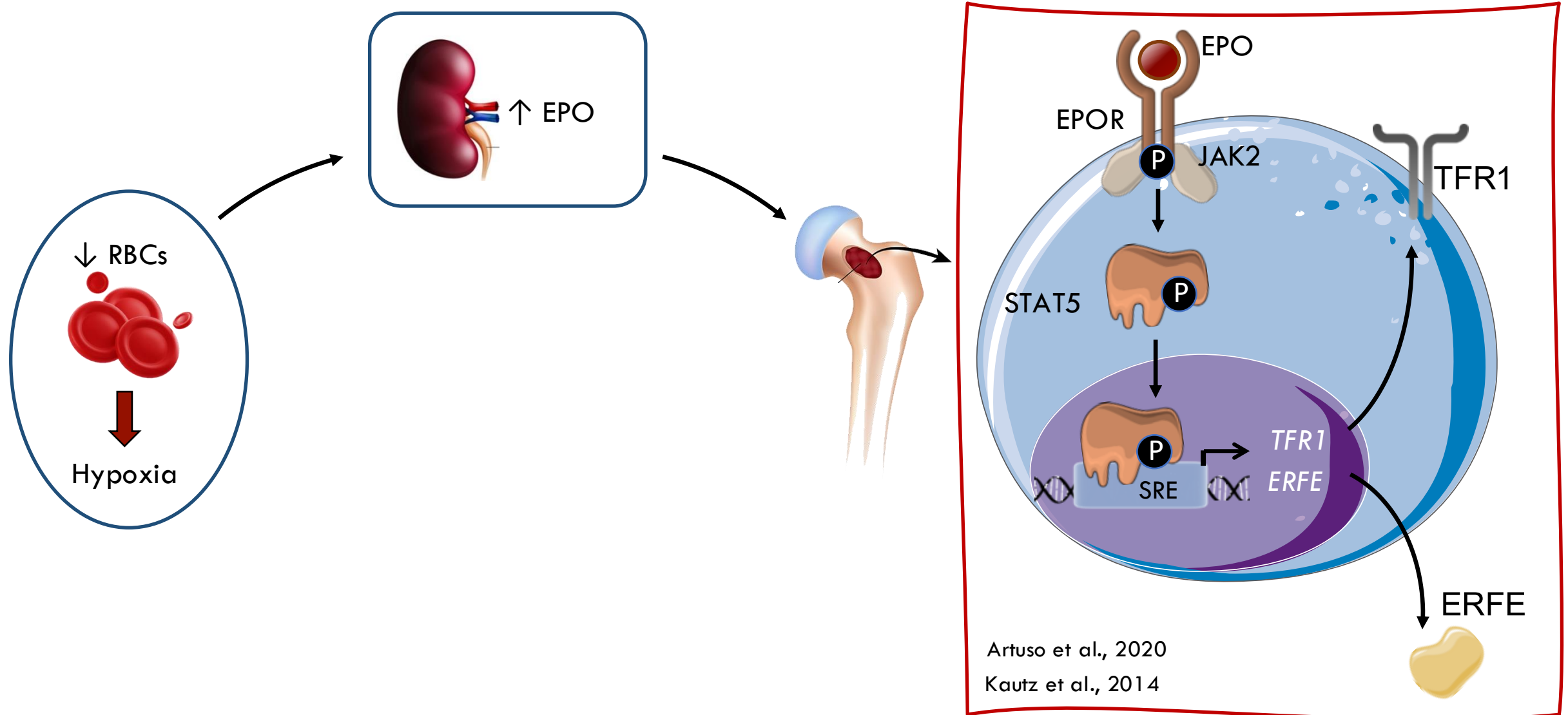
Hepcidin regulation by iron



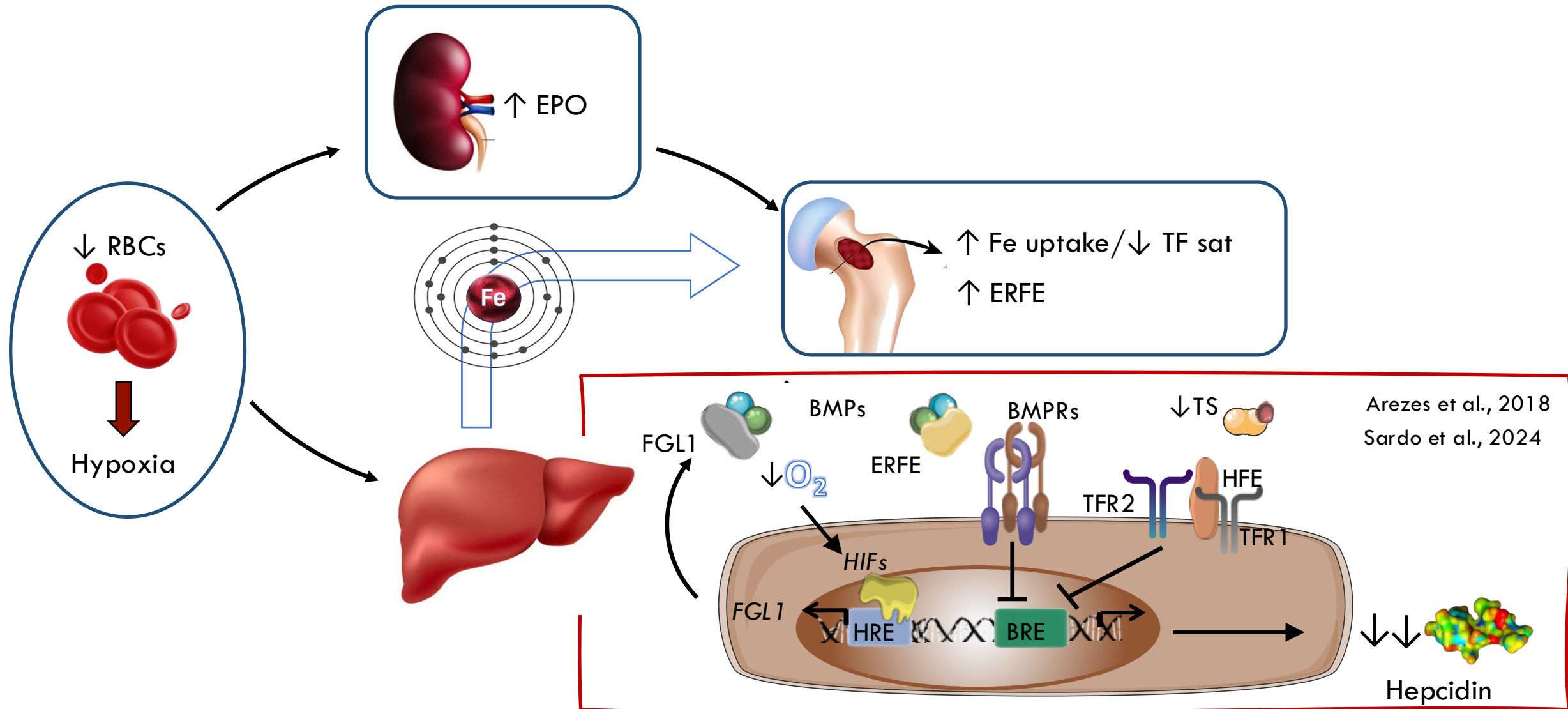
Erythropoiesis-mediated regulation of iron homeostasis



Erythropoiesis-mediated regulation of iron homeostasis



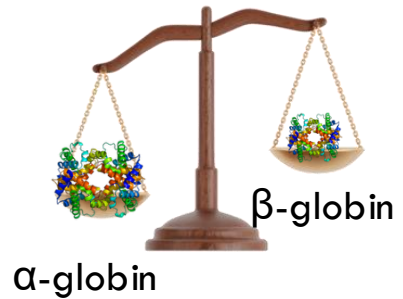
Erythropoiesis-mediated regulation of iron homeostasis



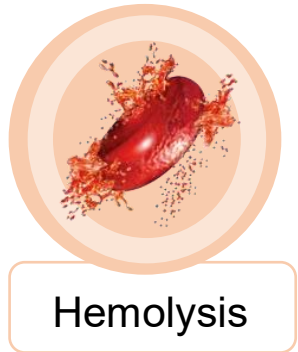
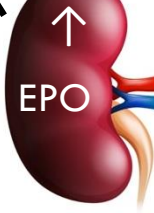
Ineffective erythropoiesis causes secondary iron-overload

β -thalassemia

Impaired HSCs
fitness



Anemia



SF3B1-mutated MDS

➤ ERFE^{VPFQ} variant

Bondu et al., 2019

↑ ERFE

↑ FGL1

↓ Hepcidin

↑ Iron

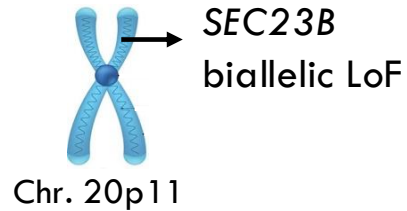
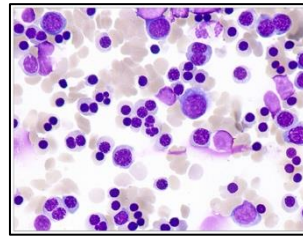
Fe

NTBI

Transfusions

Disease-specific drivers of systemic iron dysregulation

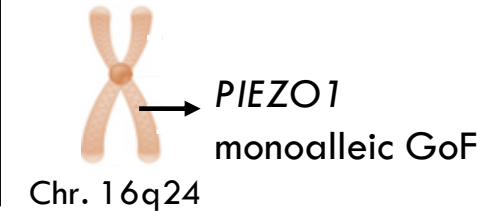
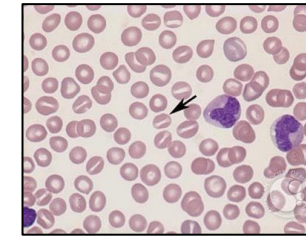
Congenital Dyserythropoietic Anemia II (CDA II)



- High ERFE because of the *ERFE-A260S* variant (12.5% of high risk patients)
- *SEC23B* LoF in hepatic cells affects the glycosylation pathway

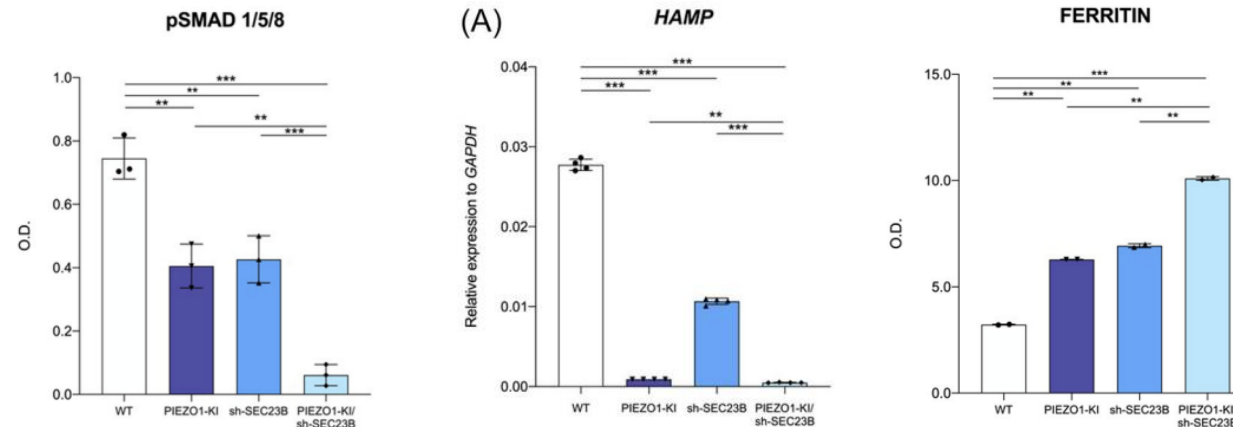


Dehydrated Hereditary Stomatocytosis I (DHSI)



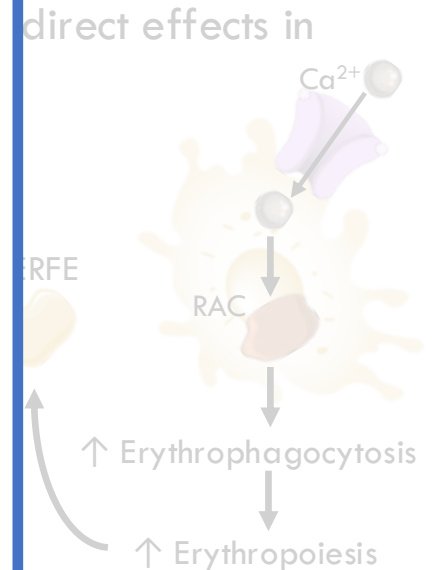
- Iron-overload is independent from erythroid defects

Dual inheritance of *SEC23B* and *PIEZO1* mutations has additive detrimental effects on iron homeostasis



Nostroso et al., 2026

Rosato et al., 2022

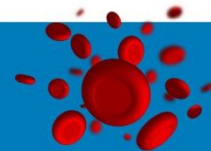


Ma et al., 2019

Andolfo et al., 2020; Rosato et al., 2024

Outline of the presentation

- ✓ Iron uptake and utilization by erythroid cells
- ✓ Regulation of systemic iron homeostasis from erythropoiesis
- ✓ **Modulation of iron homeostasis for the amelioration of ineffective erythropoiesis**



Modulating iron homeostasis to ameliorate IE

IRON DEFICIENCY/ RESTRICTION

Aim



Reduce iron availability acting on systemic iron homeostasis



Experimental Proof



- ✓ Iron-deficient diet
- ✓ Hepcidin overexpressing mice

Gargenhi et al., 2010



Tools

- ✓ Iron chelators
- ✓ Hepcidin analogues
- ✓ Hepcidin inducers



REDUCE ERYTHROID IRON UPTAKE

Aim



Reduce iron availability limiting erythroid iron uptake



Experimental Proof



- ✓ *Tfr1* haploinsufficient mice
- ✓ Transferrin treatment

Li et al., 2010 & 2017



Tools

- ✓ Transferrin
- ✓ Erythroid TFR1 antagonists



DECREASE ERYTHROID IRON SENSING

Aim



Reduce iron sensing to reshape erythroid EPO sensitivity



Experimental Proof



- ✓ *Tfr2*^{BMKO} mice
- ✓ TFC-blocked overexpressing mice

Artuso et al., 2018; Guerra et al. 2021



Tools

- ✓ Erythroid TFR2 antagonists
- ✓ Mutated monoFe TF



LIMIT ERYTHROID HEME UPTAKE

Aim



Reduce heme uptake to limit toxicity



Experimental Proof



- ✓ *Hrg1* haploinsufficient mice

Belot et al., 2026



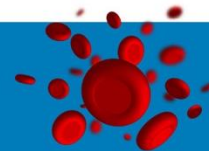
Tools

- ✓ HRG1 antagonists



Conclusions

- ✓ Erythropoiesis and iron homeostasis exert a reciprocal control
- ✓ Iron is essential for erythropoiesis, but when in excess worsens ineffective erythropoiesis
- ✓ Deregulation of iron homeostasis in ineffective erythropoiesis is mainly mediated by the erythroid regulators ERFE and FGL1
- ✓ Disease-specific drivers of systemic iron dysregulation exist
- ✓ Targeting iron homeostasis is a powerful therapeutic approach for ineffective erythropoiesis



Acknowledgements

Antonella Nai Laura Silvestri Alessia Pagani

Simona Di Modica



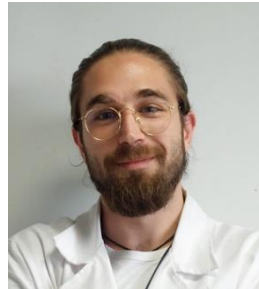
Mariateresa Pettinato



Regulation of Iron Metabolism Unit



Valeria Furiosi



Emanuele Tanzi



Anxhela Dano



Rossana Carleo



Assunta Cancellara



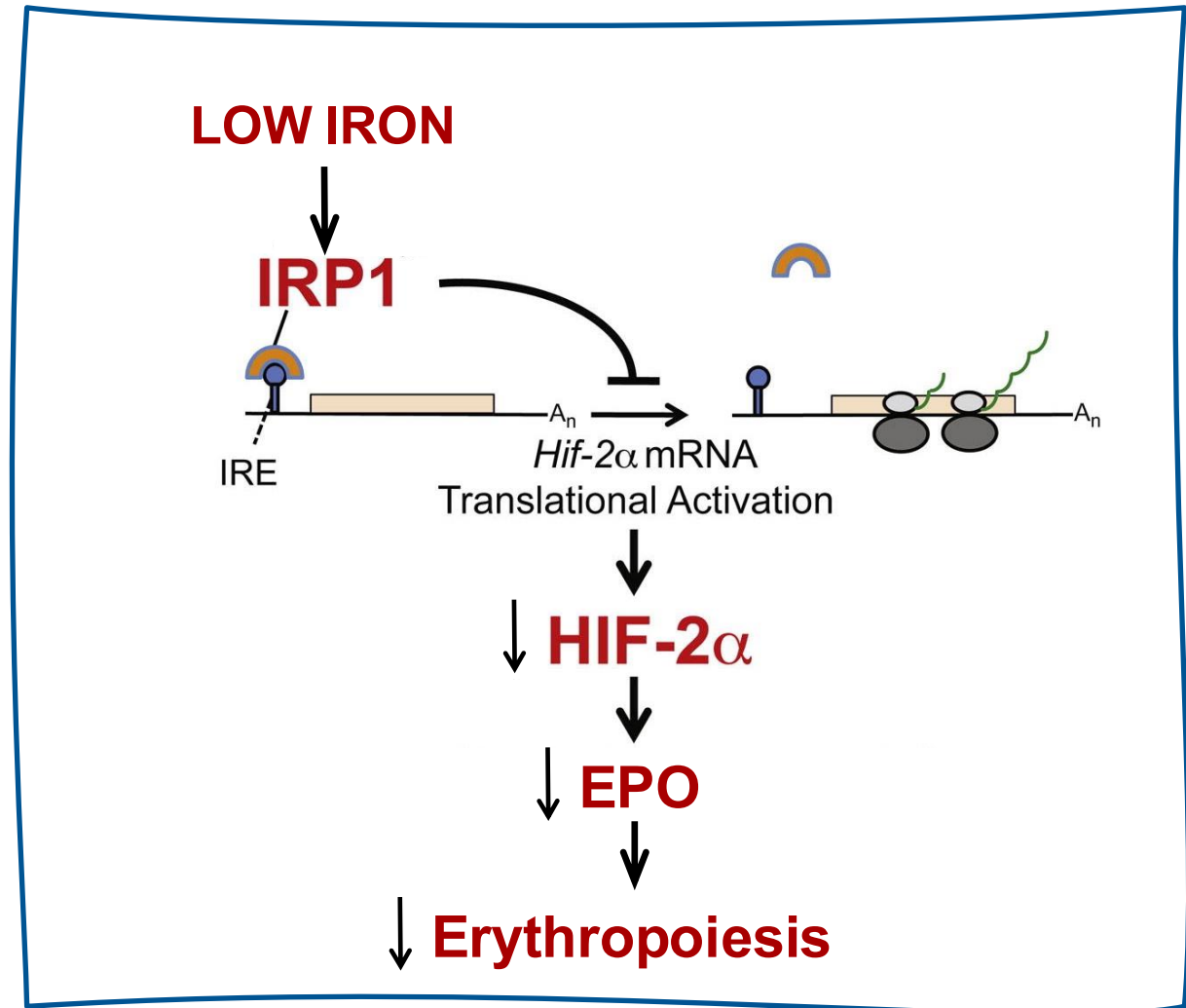
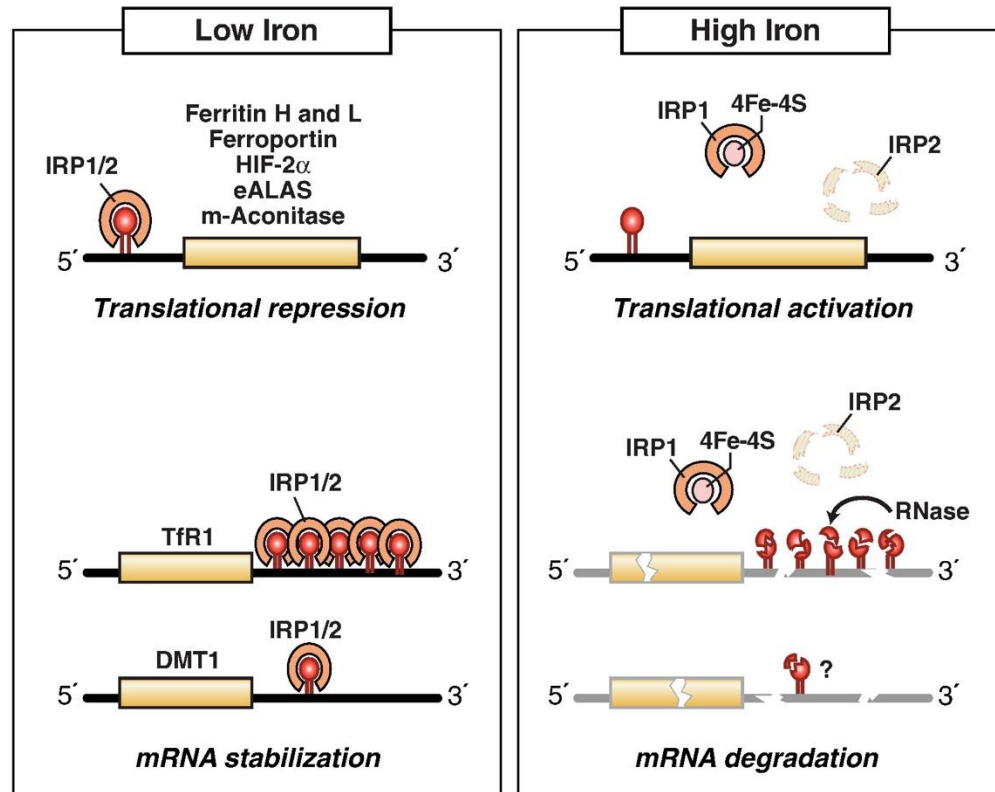
Ministero della Salute



MEETING DEL CLUB DEL GLOBULO ROSSO 2026

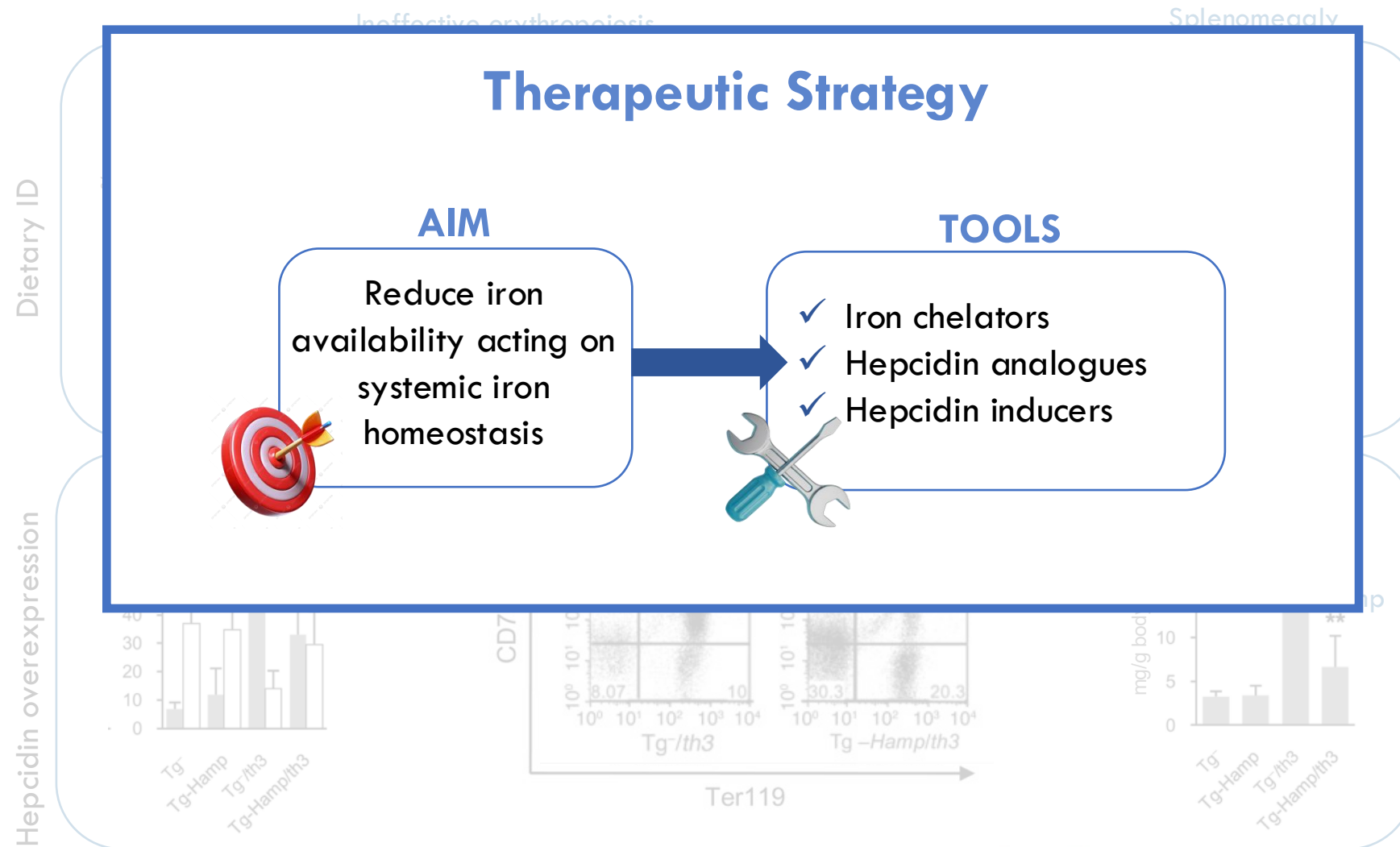
NAPOLI, 28-29 SETTEMBRE 2026

IRE-IRP system



Modulating iron homeostasis to ameliorate IE

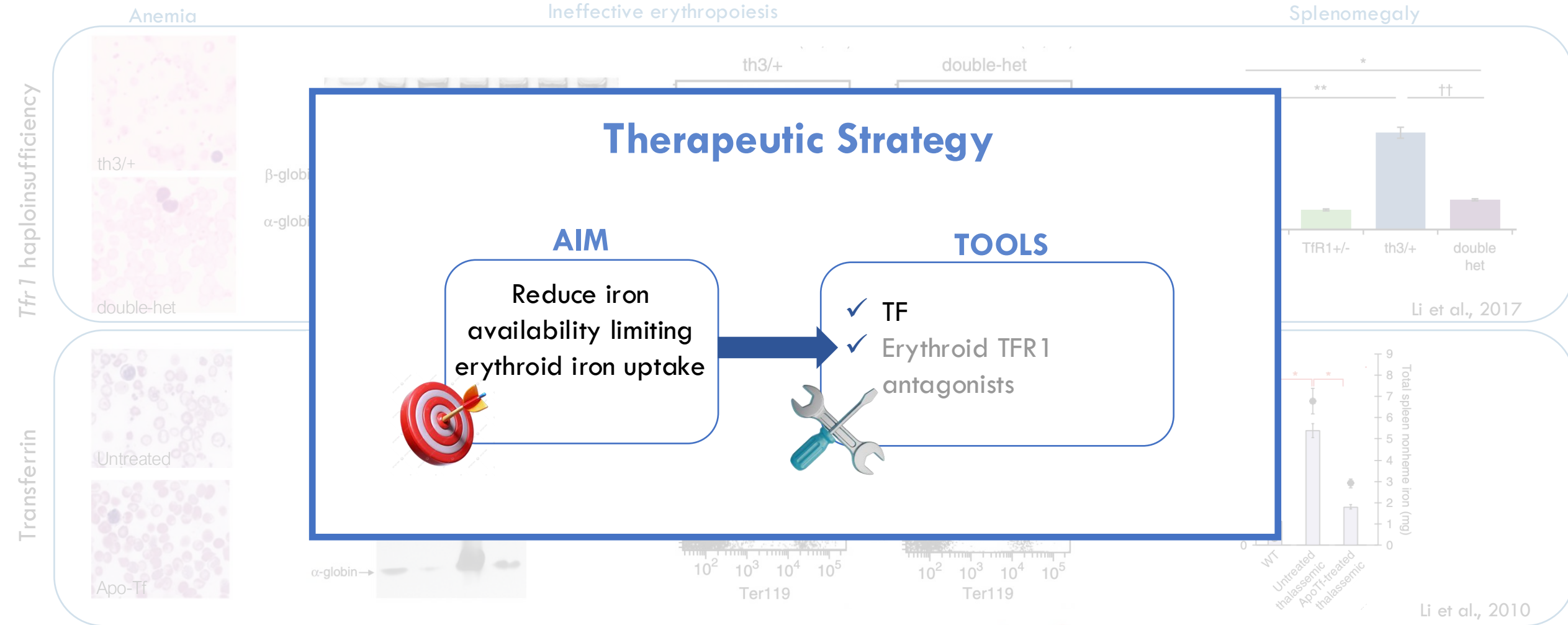
1. Iron deficiency/restriction



Gardenghi et al., 2010

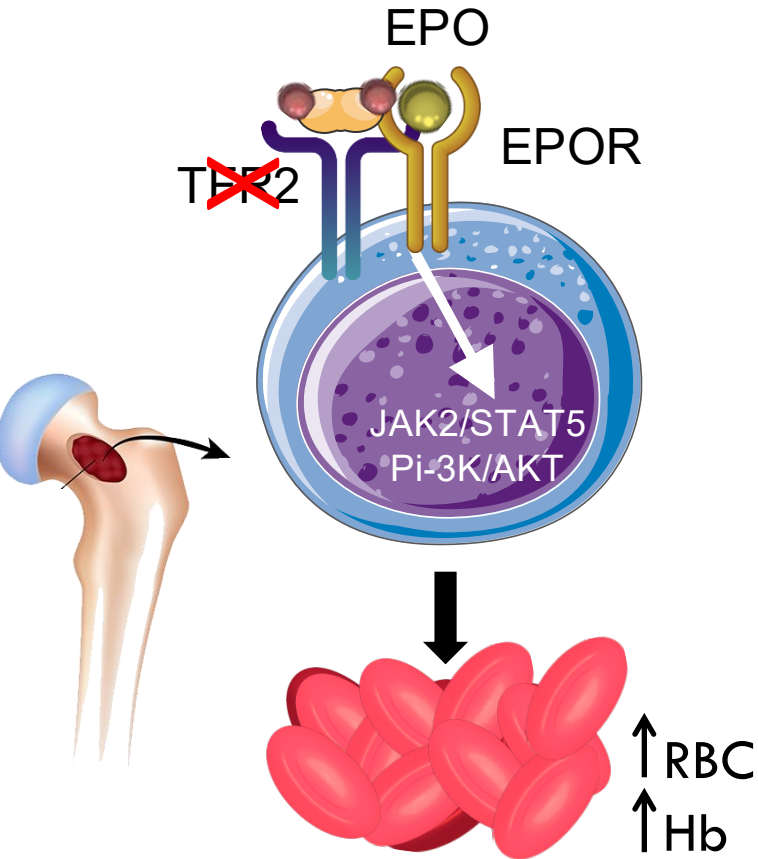
Modulating iron homeostasis to ameliorate IE

1. Iron deficiency/restriction
2. Reduce erythroid iron-uptake



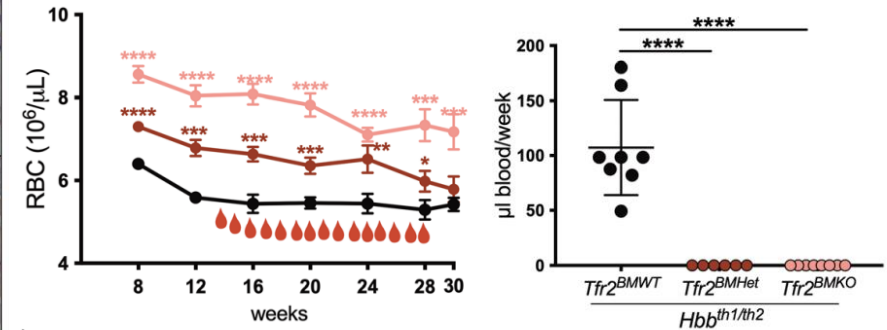
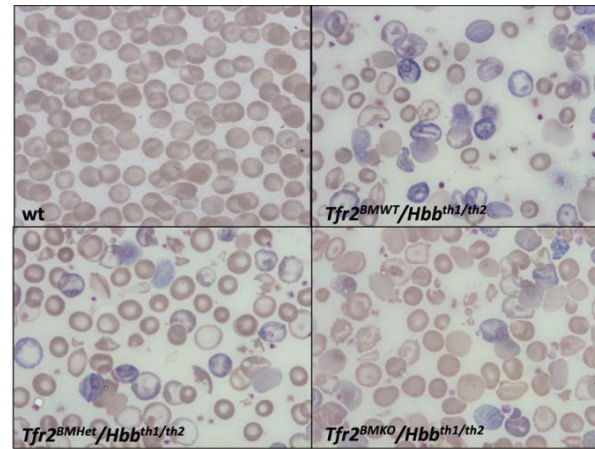
Modulating iron homeostasis to ameliorate IE

1. Iron deficiency/restriction
2. Reduce erythroid iron-uptake
3. Decrease erythroid iron-sensing

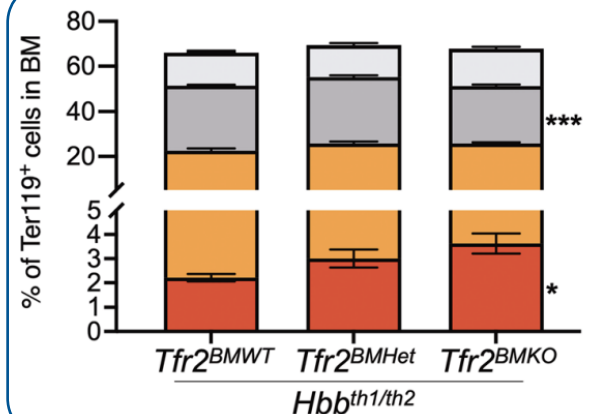


Nai et al., 2015

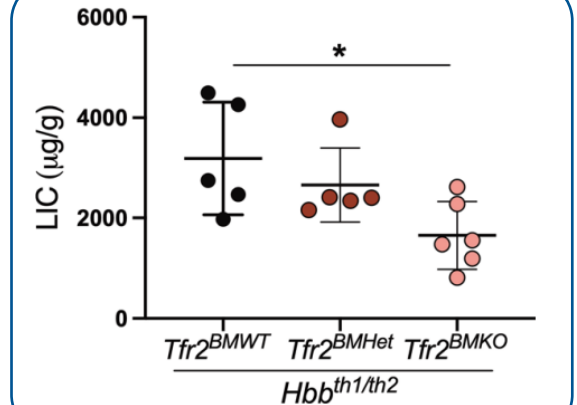
Anemia



Ineffective erythropoiesis



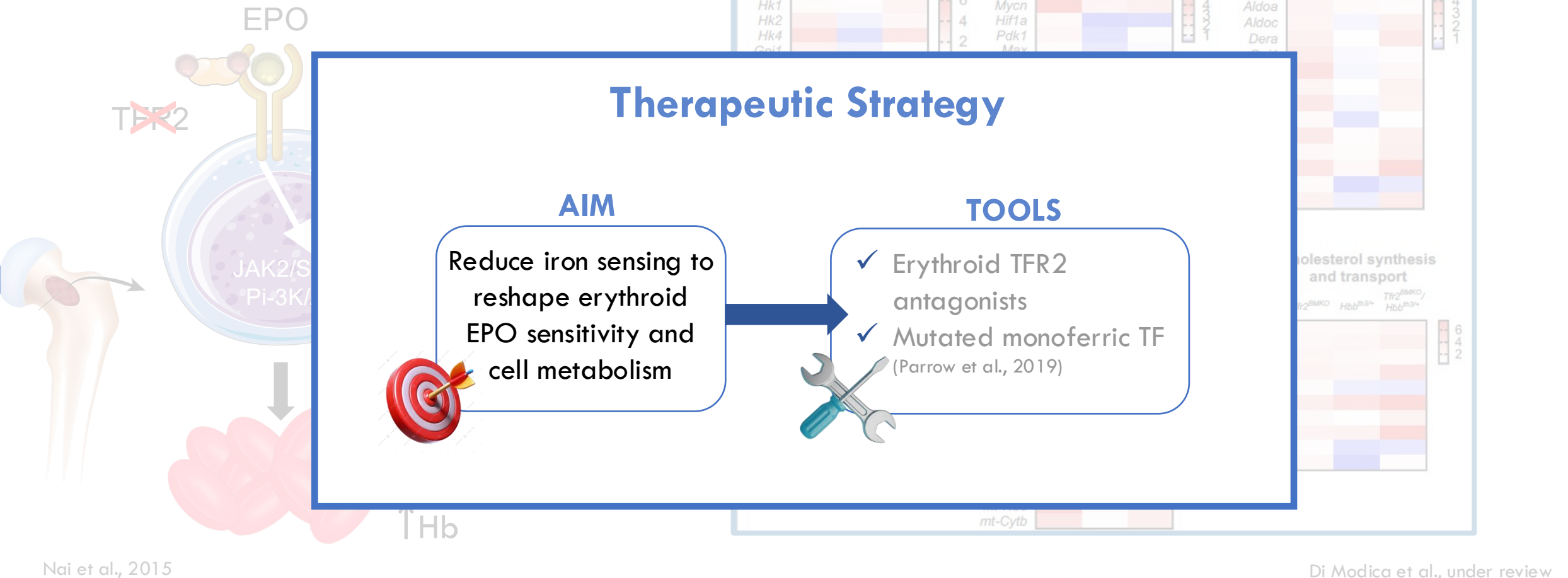
Iron-overload



Artuso et al., 2018; Di Modica et al., 2022; Tanzi et al., 2024

Modulating iron homeostasis to ameliorate IE

1. Iron deficiency/restriction
2. Reduce erythroid iron-uptake
3. Decrease erythroid iron-sensing



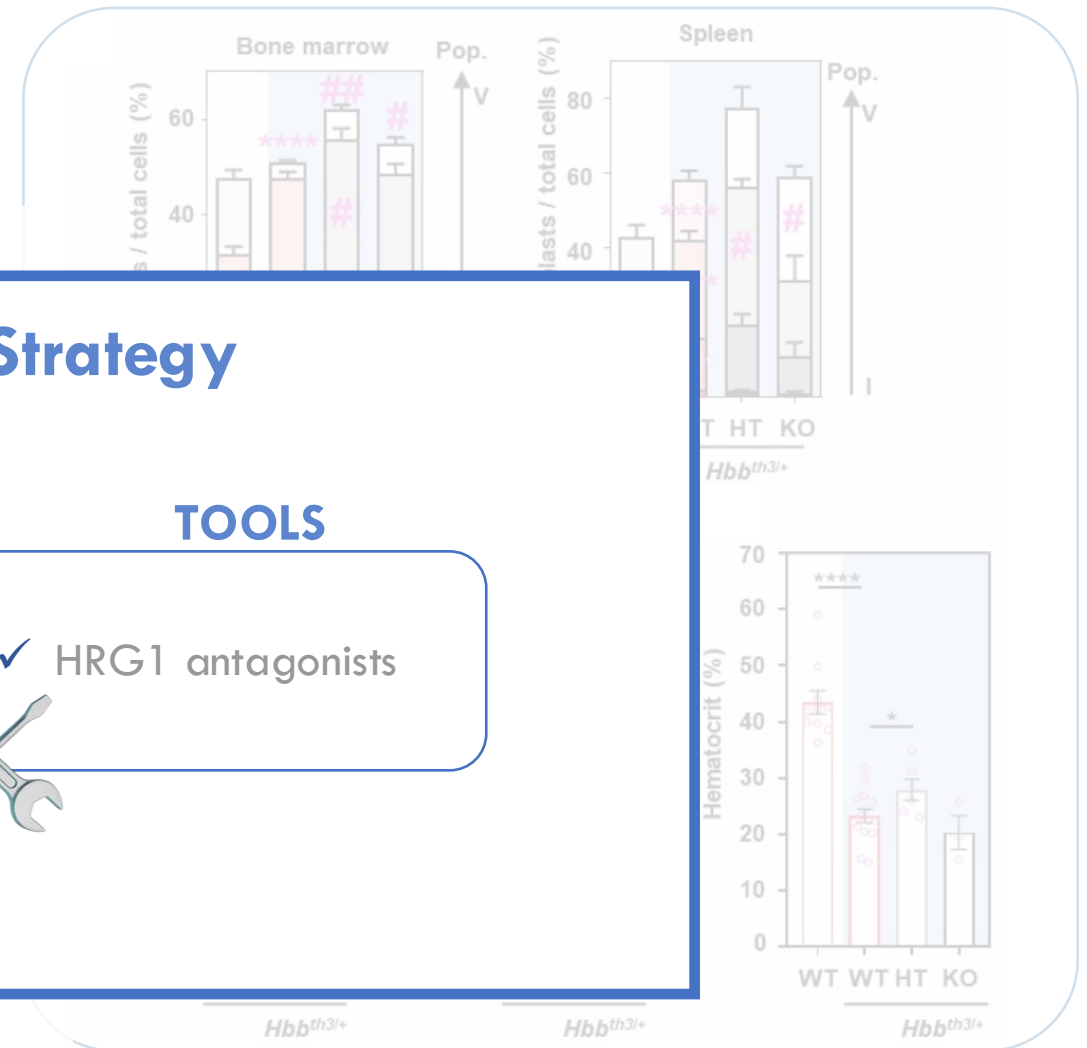
Nai et al., 2015

Di Modica et al., under review

Modulating iron homeostasis to ameliorate IE

1. Iron deficiency/restriction
2. Reduce erythroid iron uptake
3. Decrease erythroid iron sensing
4. Limit erythroid heme uptake

Hrg1 haploinsufficiency improves anemia and IE



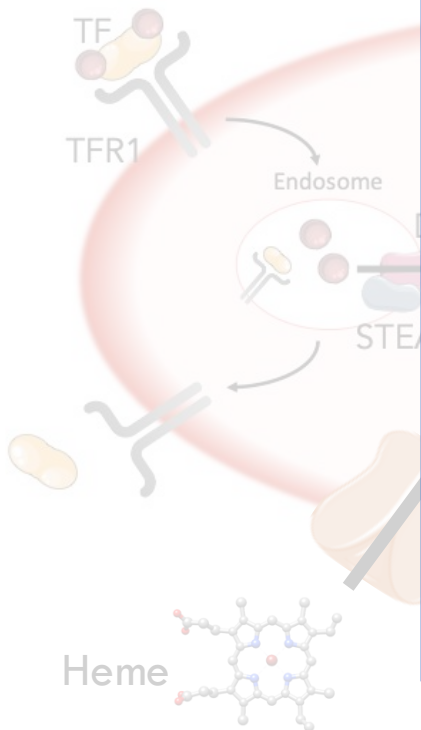
Therapeutic Strategy

AIM

Reduce heme uptake
to limit toxicity

TOOLS

✓ HRG1 antagonists



Belot et al., 2026