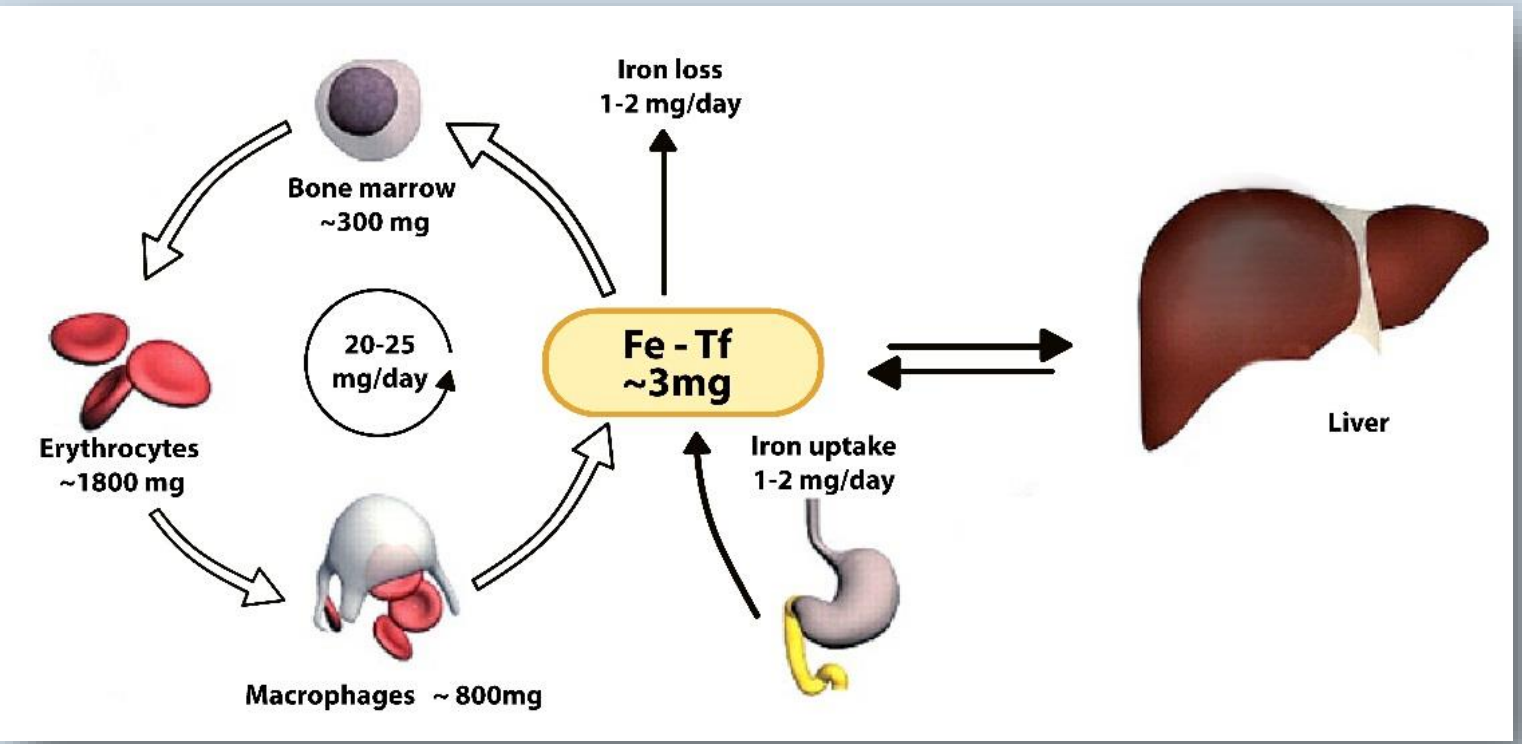
Physiology & Pathophysiology Of Iron Metabolism

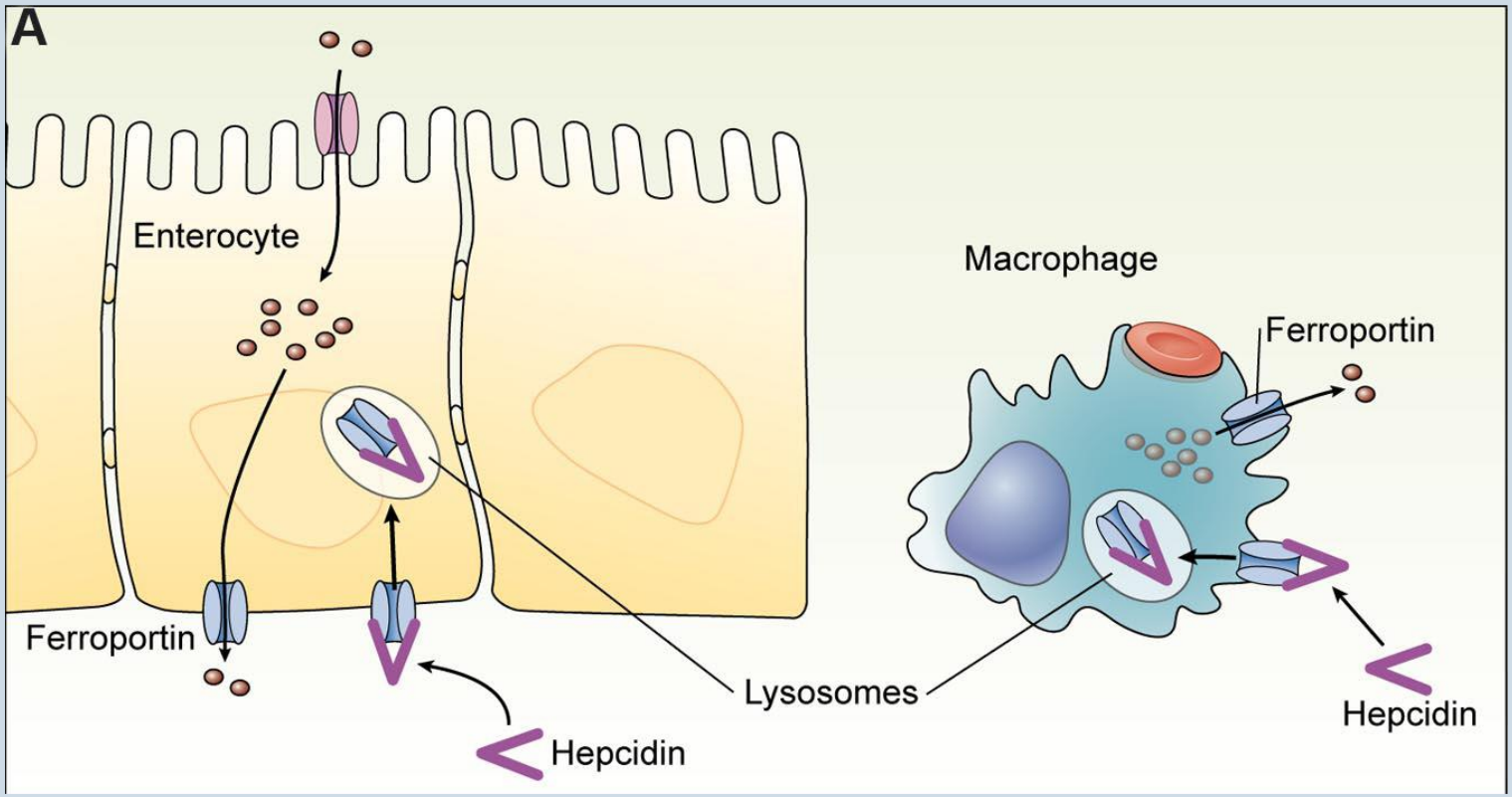
A Jaspers
CHU Liège

Iron metabolism



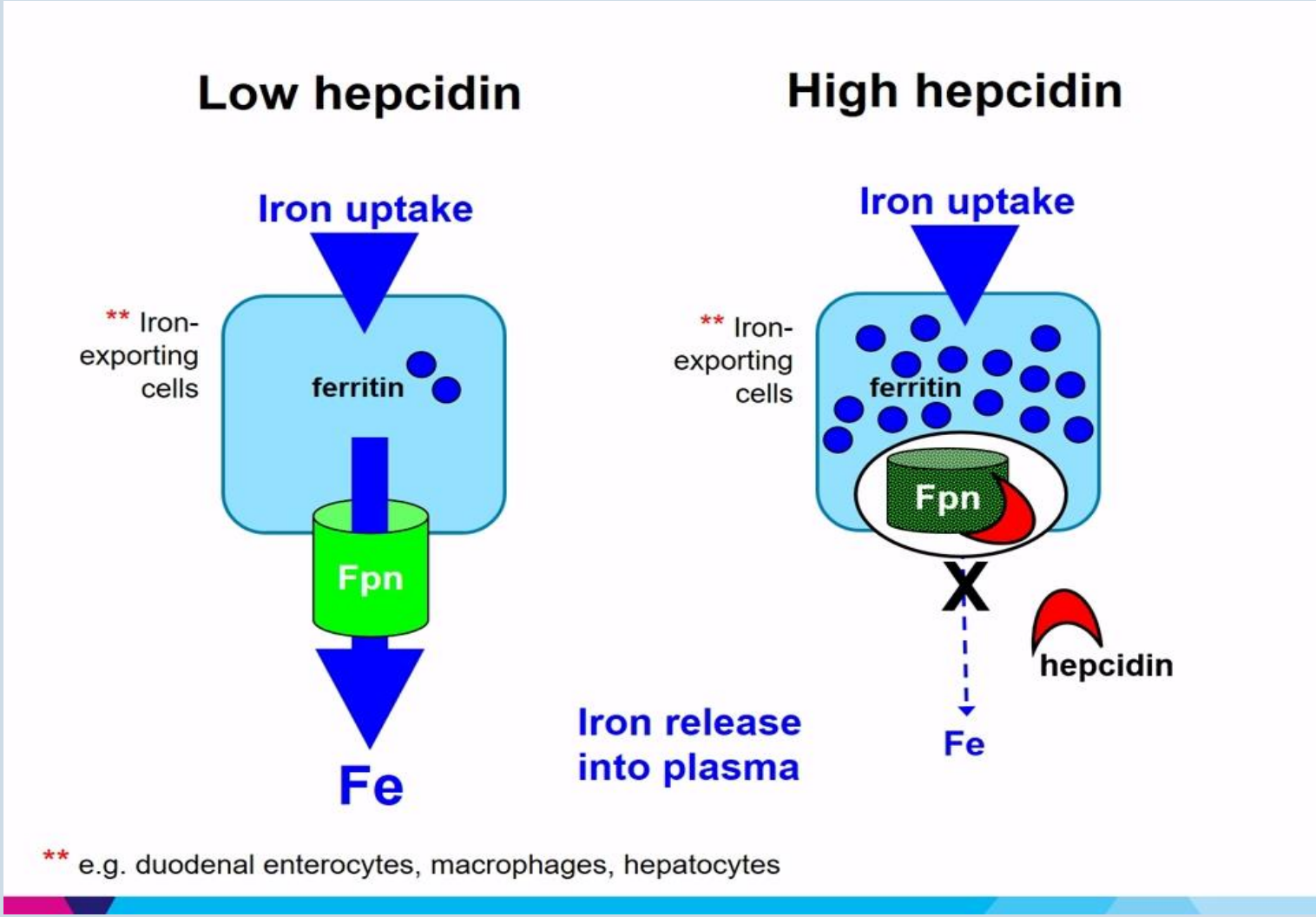
Swinkels, Clin Chem 2006

Hepcidin

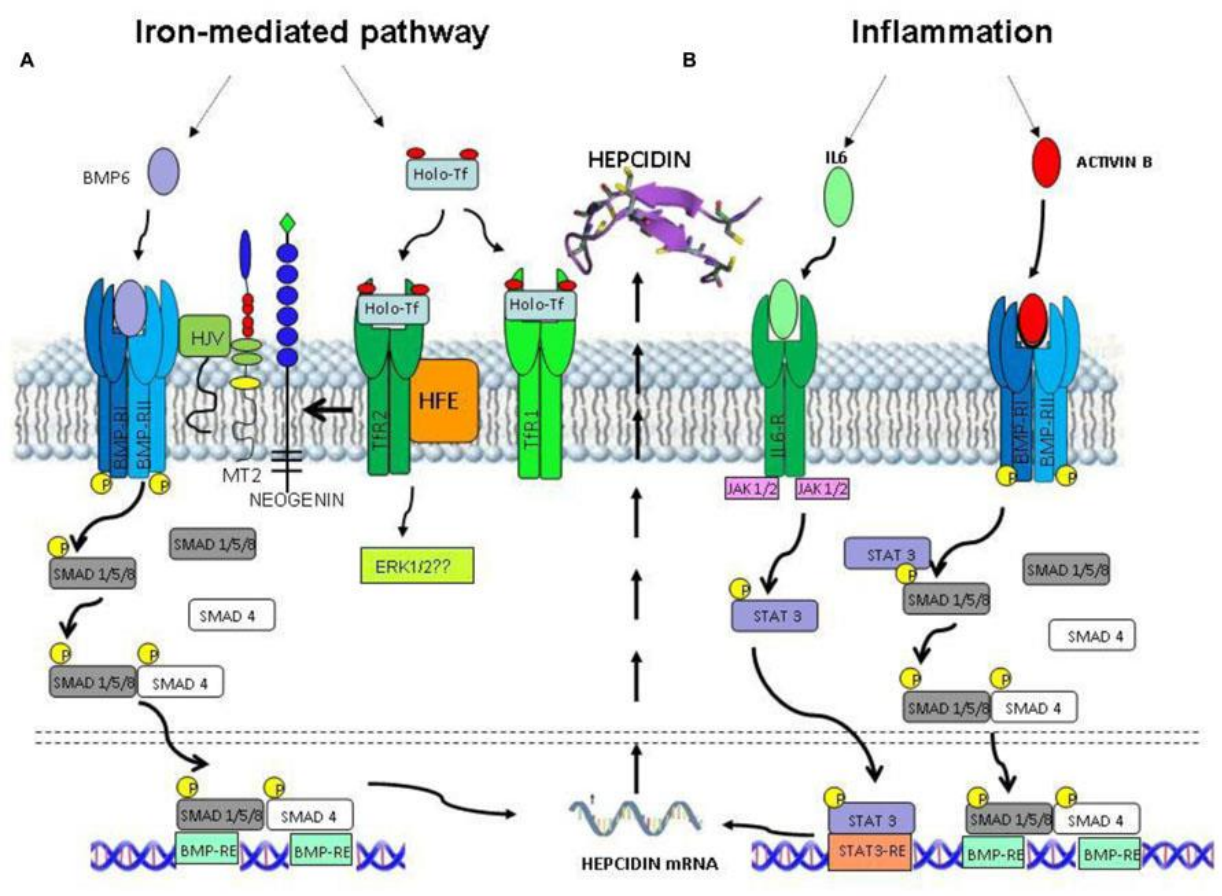


Andrews, Blood 2008

Hepcidin


Low hepcidin
Iron uptake
** Iron-exporting cells
ferritin
Fpn
Fe
High hepcidin
Iron uptake
** Iron-exporting cells
ferritin
Fpn
X
hepcidin
Iron release into plasma
Fe
** e.g. duodenal enterocytes, macrophages, hepatocytes

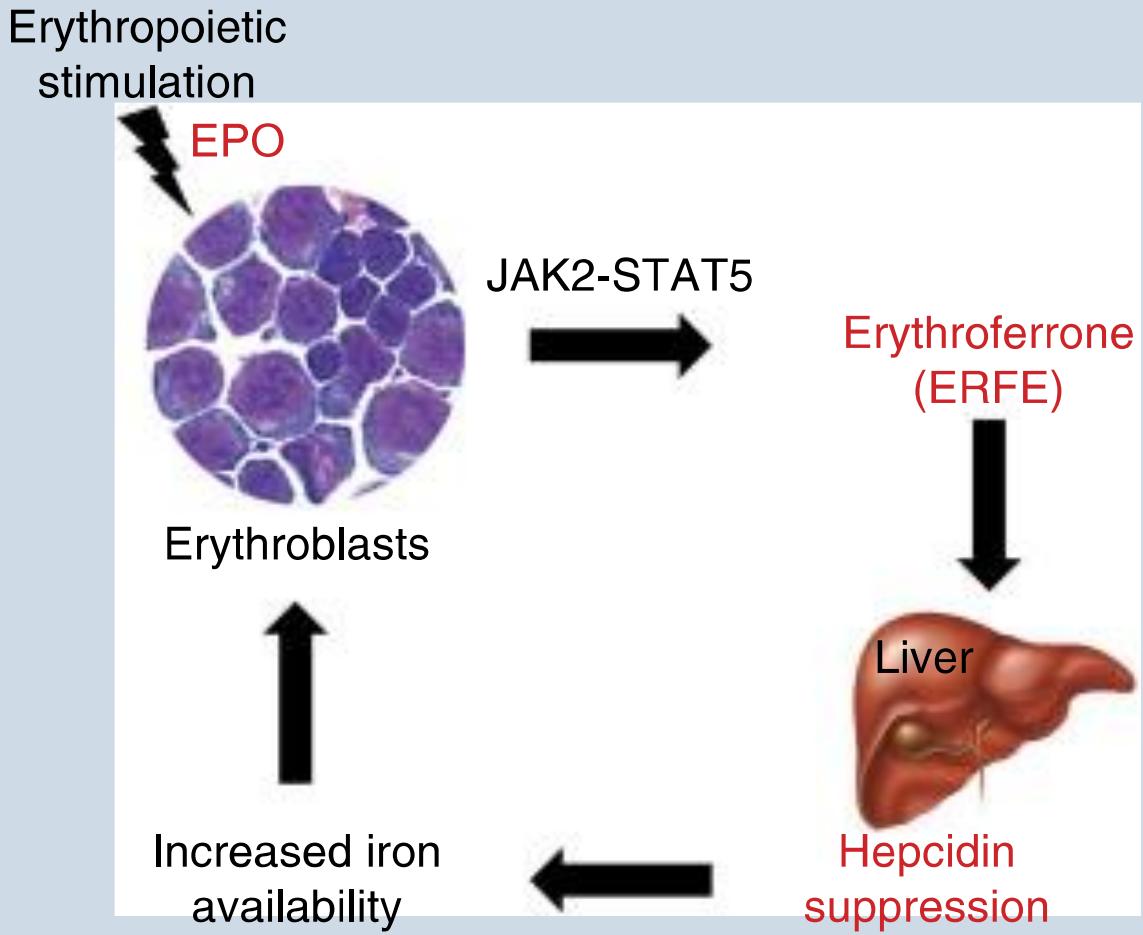
Regulation of hepcidin



↗ hepcidin if :
- Inflammation
- ↗ iron stores

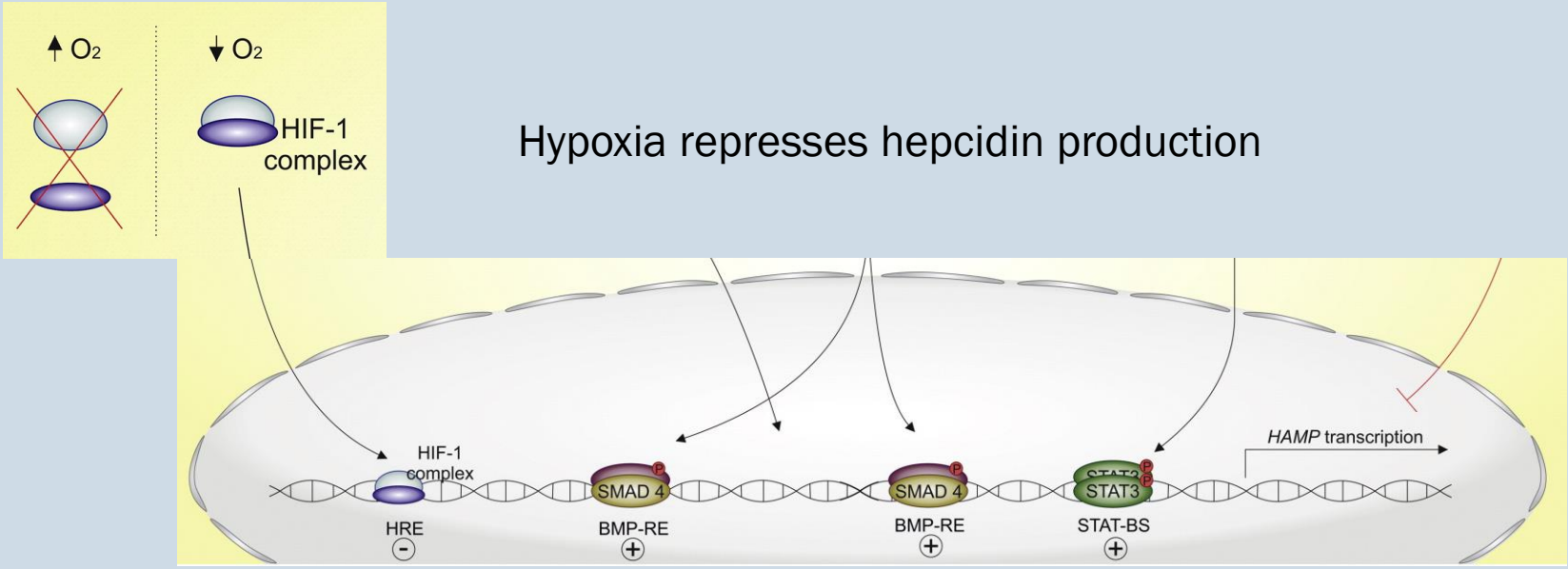
Poli, Front Pharmacol 2014

Regulation of hepcidin



Kautz, Nat Gen 2014

Regulation of hepcidin



Hypoxia represses hepcidin production

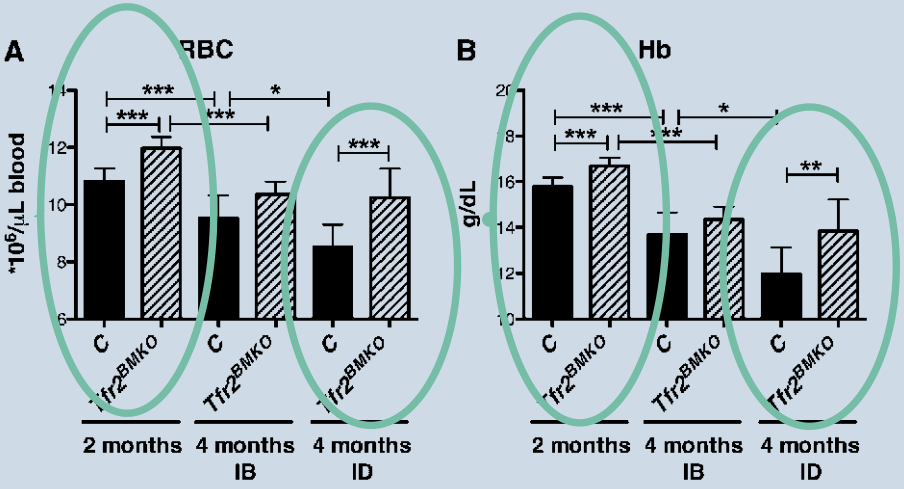
Silva, BBA 2015

TfR2

- Transmembrane protein homologous to TfR1 (erythroblast)
- Restricted to hepatocytes and erythroid cells
- In the liver
  - *Ability to bind iron-loaded Tf and function as a liver sensor of circulating iron excess -> hepcidin activator*
  - *>< TfR1 iron importer*
- Mutations in TfR2 (inactivation)
  - *Low hepcidin*
  - *=> iron overload (hemochromatosis type 3)*

TfR2

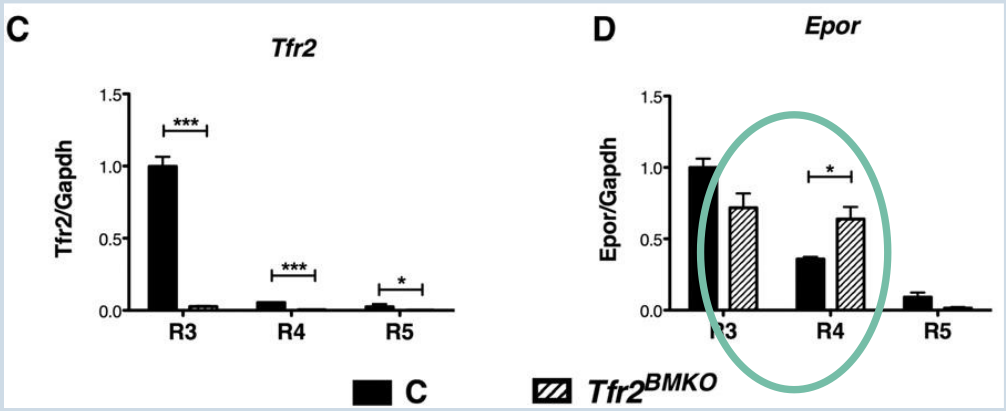
- In erythroid cells
  - *Partner of EpoR in immature erythroid cells*
  - *TfR2 limits erythroid expansion in mice*
- TfR2 deletion in BM
  - * ↗ RBC counts and Hb level
  - * Phenotype becomes more evident in iron deficiency



Nai, Blood 2015

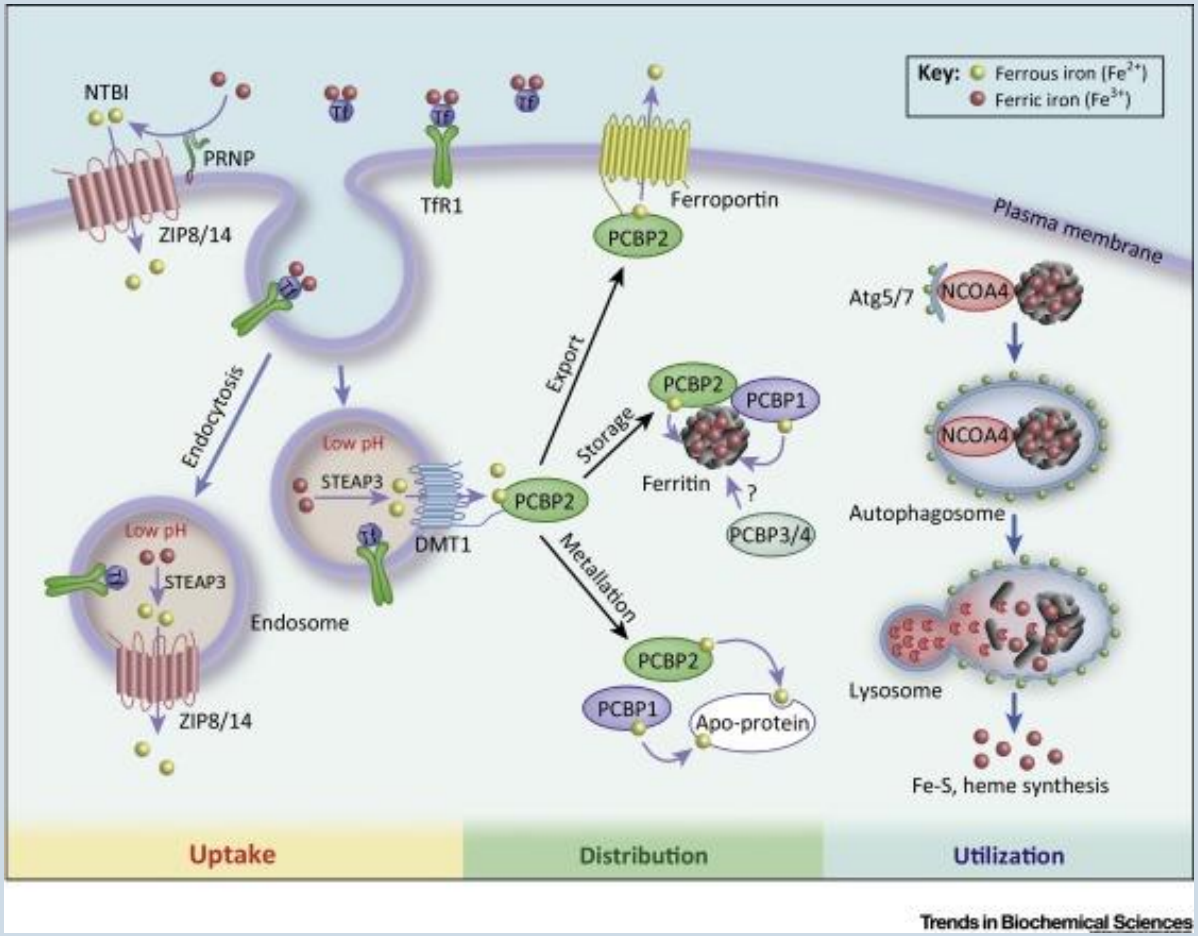
TfR2

- In erythroid cells
  - *Component of EpoR complex in immature erythroid cells*
  - *TfR2 limits erythroid expansion in mice*
- How ? TfR2 deletion in BM stabilizes EpoR on the erythroblast surface, thereby modulating erythroblast Epo sensitivity



Nai, Blood 2015

Pathways of intracellular iron uptake, distribution and utilization



Iron essential for Synthesis of :

- Iron-dependent enzymes
- Heme (cytochrome, myoglobin, hemoglobin)

Bogdan, Trends Biochem Sci. 2016

Ferritinophagy

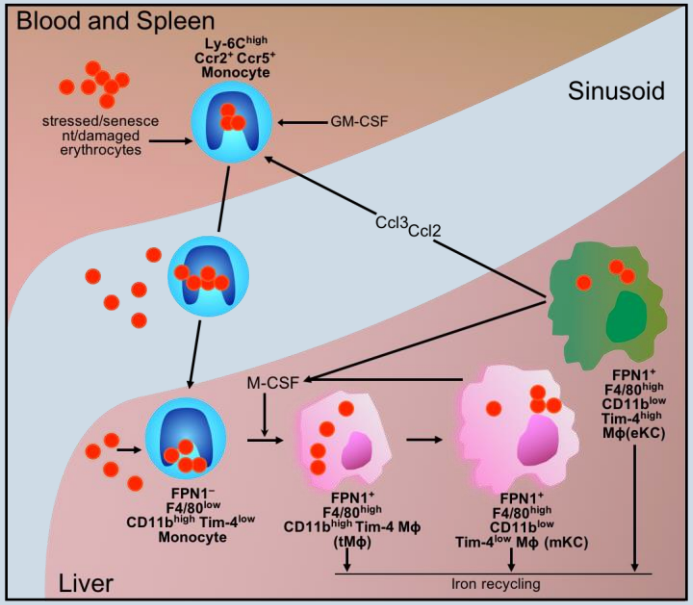
- Autophagic turnover of ferritin
- Process critical for regulation of intracellular iron bioavailability
- Nuclear receptor coactivator 4 (NCOA4) promotes ferritinophagy (Mancias 2014) through delivery of ferritin to the lysosome via autophagosomes
- Ferritinophagy is regulated by iron levels (Mancias 2015)

NCOA-4

- NCOA4 KO mice (Bellelli 2016)
  - *Accumulation of iron in liver & spleen, even if low iron diet*
  - *Mild microcytic anemia*
  - *If low iron diet : severe anemia as mice failed to release iron from ferritin storage*
  - *=>NCOA4 prevents iron accumulation and ensures efficient erythropoiesis, playing a central role in balancing iron levels in vivo*

Iron & macrophages

- Monocytes expressing high levels of lymphocyte Ag 6 complex, locus C1 (LY6C1 or Ly-6C)
  - *Ingest stressed and senescent erythrocytes*
  - *Do not differentiate into ferroportin-expressing iron-recycling macrophages, owing to the suppressive action of Csf2 expressed by senescent RBC in spleen*



Theurl, Nat Med 2016

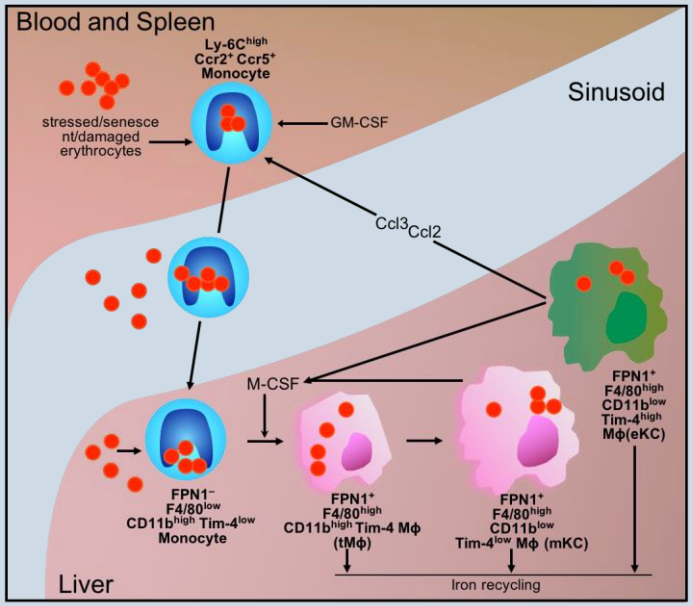
Iron & macrophages

- These monocytes
  - *Recruitment to the liver through macrophage (Kupffer cells)-derived chemotactic signals & GM-CSF*
  - *Differentiation into FPN1-expressing macrophages*
  - *Accumulation of a transient FPN1+Tim-4neg macrophage population*

    Alongside FPN1+Tim-4 high Kupffer cells
  - *Delivering iron to hepatocytes*

- Inhibition of monocyte recruitment to the liver during stressed erythrocyte delivery leads to kidney and liver damage

Tim-4 or Timd4 = embryonically derived T-cell Ig and mucin domain containing 4

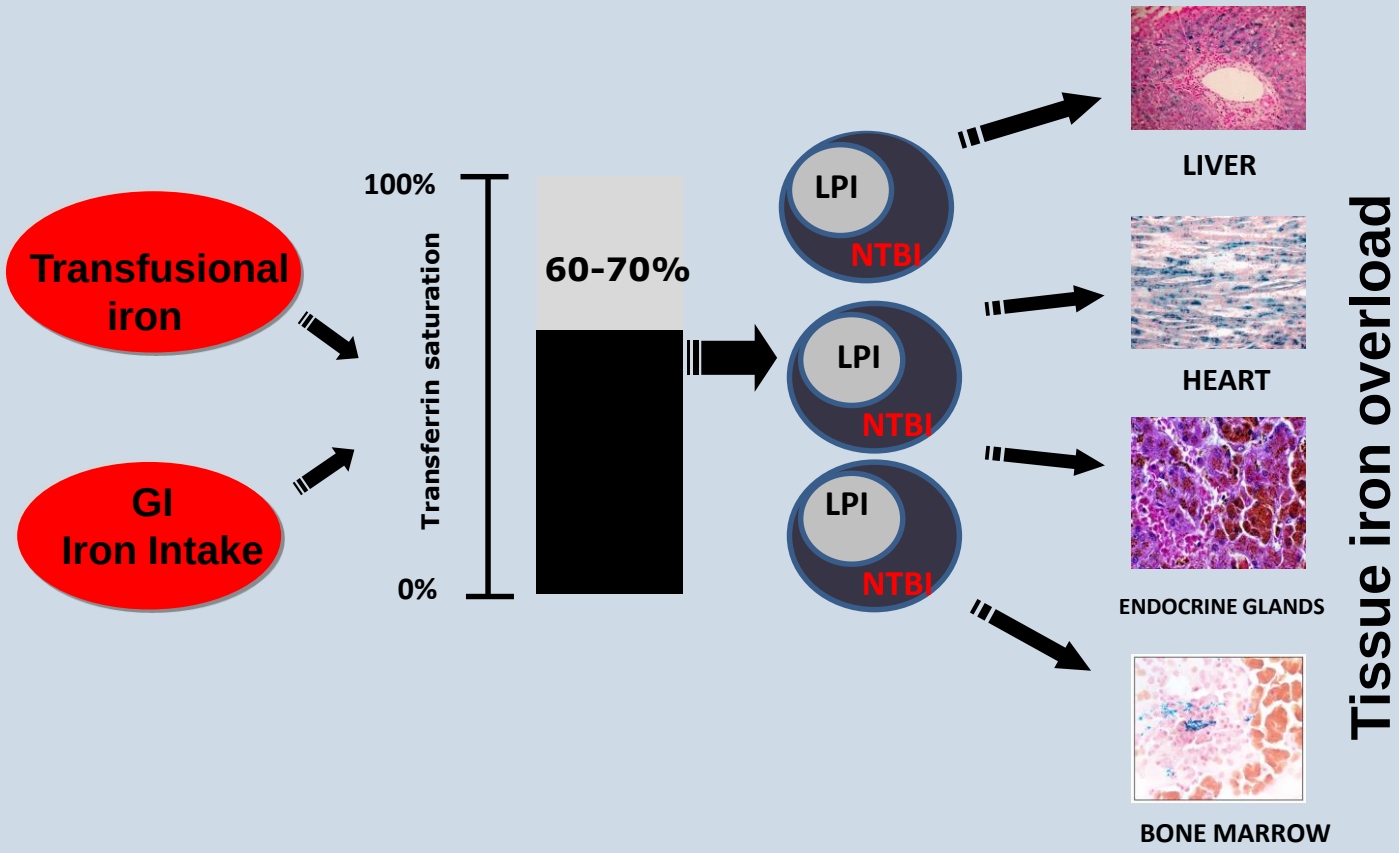


Theurl, Nat Med 2016

Iron & macrophages

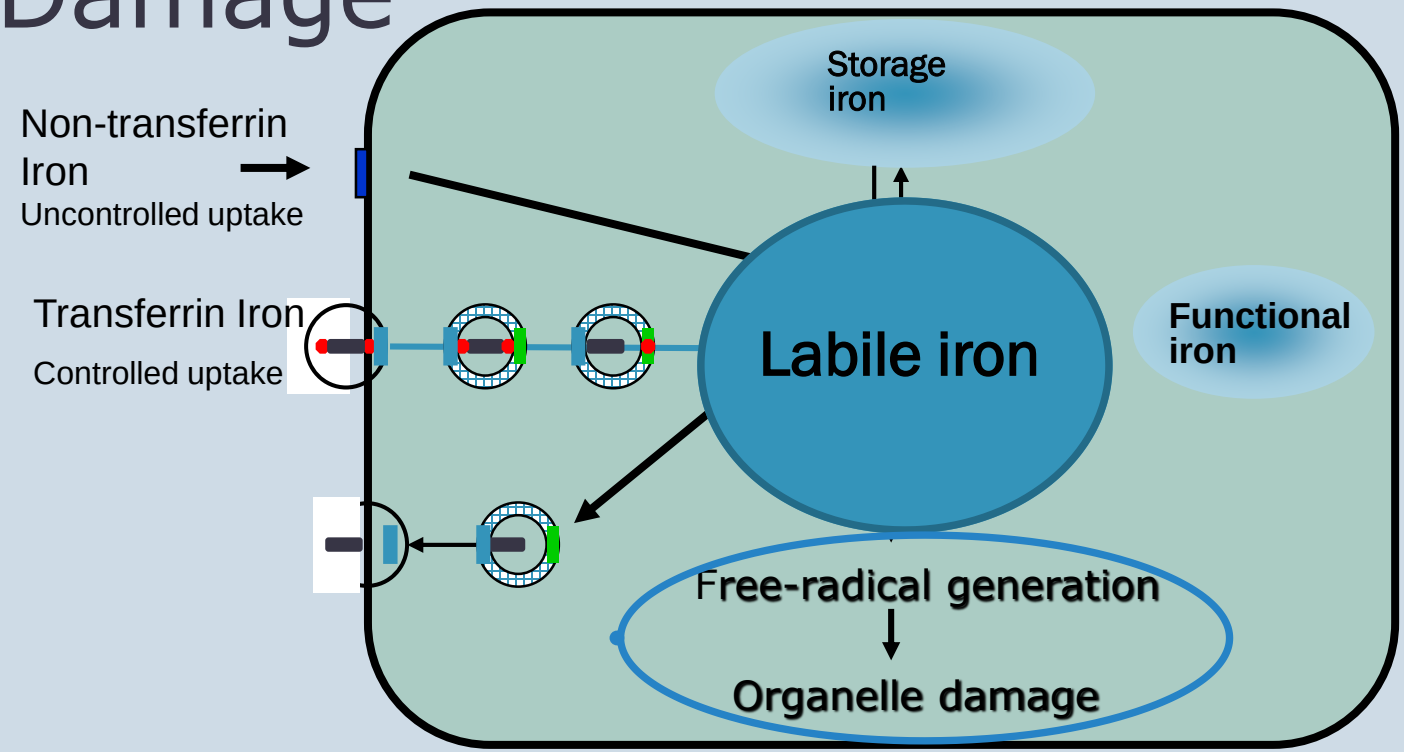
- Liver is primary organ supporting
  - *Rapid erythrocyte removal (together with spleen)*
  - *Iron recycling*
  - *Adaptation to body fluctuations in erythrocyte integrity*
- This liver-specific phenomenon is
  - *Transient*
  - *Dynamic*
  - *Controls iron homeostasis during erythrocyte damage*

Iron overload



Angelucci, Ann NY Acad Sci. 2016

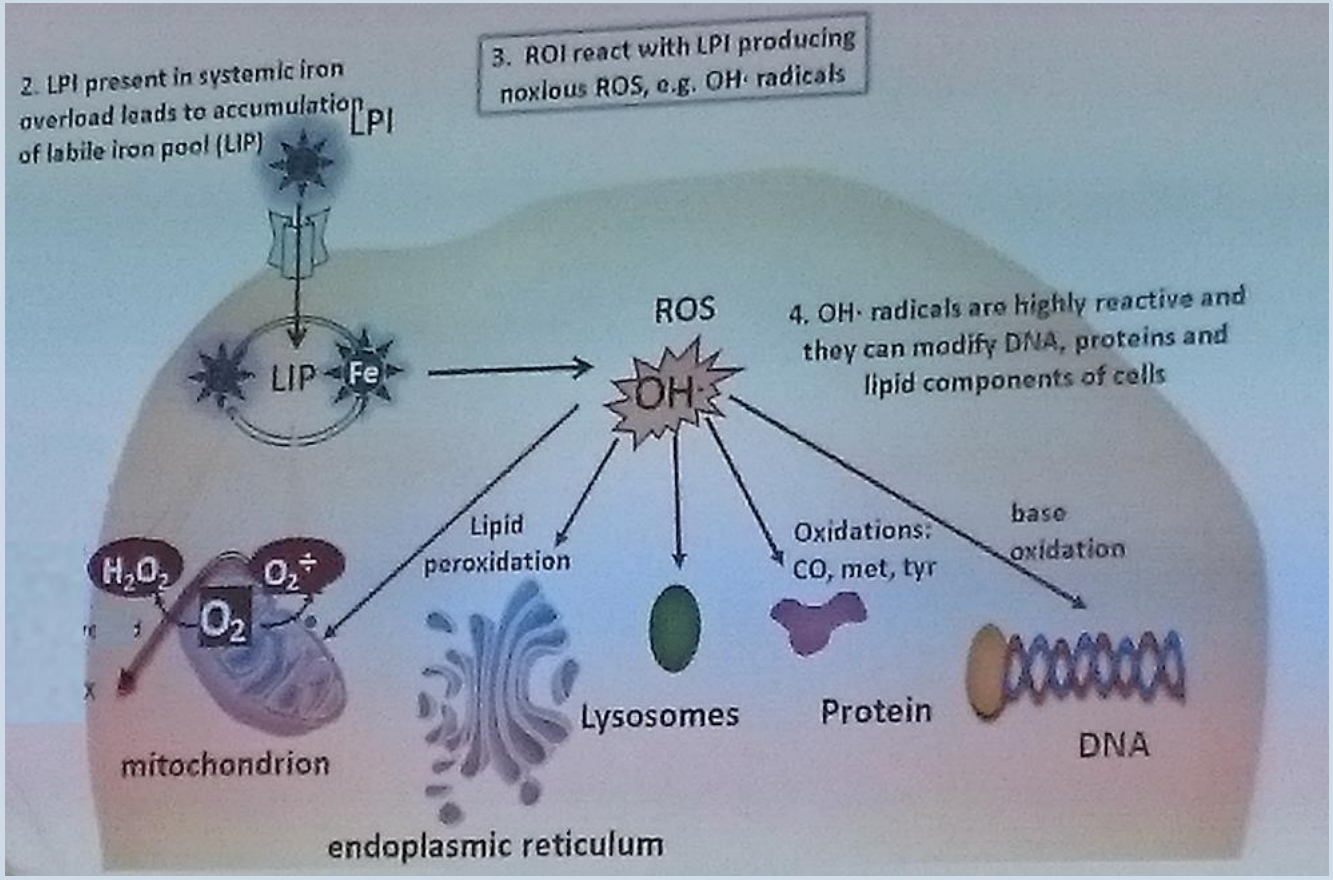
Uncontrolled Uptake of Labile Iron Leads to Cell and Organ Damage



An excessive rise in labile iron can promote the generation of reactive-O species (ROS) by reacting with respiratory O intermediates and thereby override the cellular antioxidant defences and chemically damage cell components and associated functions

Angelucci, Educational session, EHA 2017

How does labile iron cause cell damage ?



Iron overload & HCT

- Iron overload after HCT
  - *More infections*
  - *More VOD*
  - *More GvHD*
  - *More cell/tissue toxicity*
  - *Leukemic relapse ?*
- Goal after HCT
  - *Maintain labile iron and total body iron levels within a normal range*
  - *Minimize NTBI/LPI and ROS generation (reactive oxygen species)*
  - *Through normal transferrin saturation*

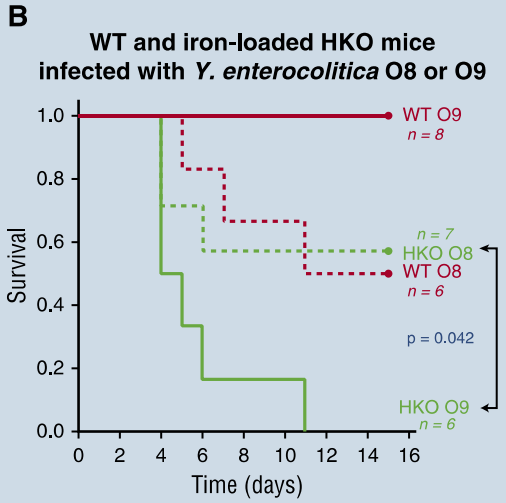
Management of iron overload after HCT

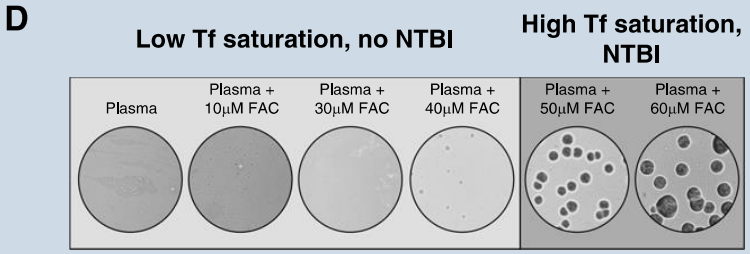
	Phlebotomy	Chelation
Pros	Efficient	Efficient
	Safe	Safe
	Inexpensive	Immediate effect on NTBI/LPI
	Permits complete iron removal	Hospital access not required
Cons	Requires sustained engraftment	Expensive
	Hospital access required	Warning on renal toxicity in case of cyclosporine concomitant use
	Immediate effect on NTBI/LPI to be verified	Possible increased toxicity in condition of low iron burden

Angelucci, Educational session, EHA 2017

Hepcidin & infections

- NTBI promoted the rapid growth of siderophilic but not nonsiderophilic bacteria in mice with either genetic or iatrogenic iron overload and in human plasma.
- Hepcidin was selectively protective against siderophilic extracellular pathogens (*Yersinia enterocolitica* O9) by controlling NTBI rather than iron-transferrin concentration.

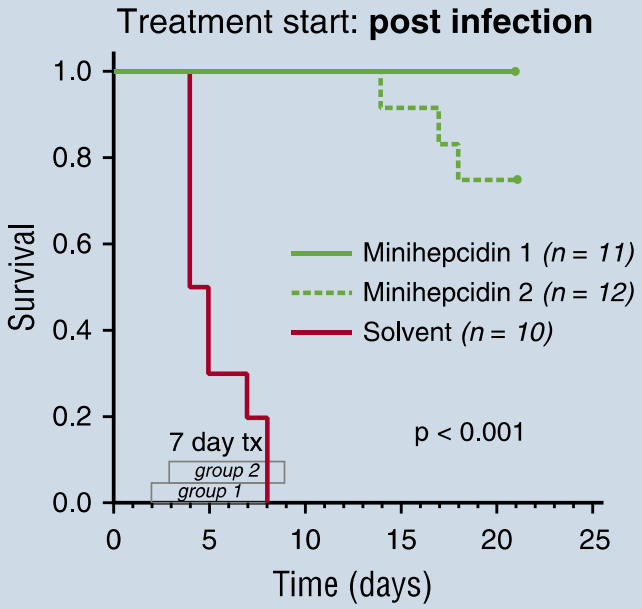




Stefanova, Blood 2017

Hepcidin & infections

- NTBI-dependent (particularly siderophilic) infections can be treated with hepcidin agonists in mouse models of hereditary hemochromatosis or parenteral iron overload.



Stefanova, Blood 2017

Iron chelation in Hemoglobinopathies

- Better monitoring ?
  - *Serum ferritin : different thresholds according to cardiac vs liver IO, major vs minor thalassemia, transfusion-dependent vs transfusion-independent*
  - *MRI :*
    - T2* iron concentration in Heart : threshold for IO : T2* < 20 msec
      Liver
    - R2 Ferriscan (spin density projection assisted R2 MRI)
      - *Review by a core laboratory*

Iron chelation in Hemoglobinopathies

- Dosing matters -> chelation adjustment
- Mode of administration
  - *Combination if rapid decrease is needed*
  - *Vitamin C may affect chelation*
- Dealing with compliance
  - *New deferasirox formulation : film-coated tablet*
    - More bioavailable : 14 mg DFX FCT = 20 mg DFX DT
    - Lower biovariability and limited food effect
    - No lactose in FCT : better GI tolerance ?
  - *New oral chelators in development (! Renal toxicity)*

Iron supplementation with ESA therapy

- Network meta-analysis on Erythropoiesis-stimulating agents (ESA) +/- IV or oral iron in anemic cancer patients (S812, oral session, Weigl)
  - *105 studies (24,867 patients), untreated or chemo or RTH*
  - *ESA use increases risk for thromboembolic events and mortality*
    - Iron supplementation does not significantly alter these findings
  - *ESA use increases hematological response*
    - Iron supplementation potentially advantageous (especially IV)
  - *ESA use decreases transfusion needs*
    - Iron supplementation further reduces transfusions

Thank you for attention

Hepcidin strategies

- Mini hepcidin (agonists)
- Inhibition of TMPRSS-6

Anti-hepcidin strategies

	Noxxon	Eli Lilly	Pieris	Ferrumax	Glycol-split heparins	Eli Lilly	Novartis	Abbvie
Drug	Lexaptepid-pegol NOX-94H	LY-2928057	PRS-080	FMX-8	RO-62 etc.	LY-3113593	CSJ137 (NOV958?)	h5F9-AM8
Target	**hepcidin**	**ferroportin**	**hepcidin**	**BMP6**	**BMP6**	**BMP6**	**BMP6**	**HJV (RGMc)**
Indications	MM, CKD, cancer	CKD	CKD	CKD	?	CKD receiving HD	HD patients on ESA with functional iron-deficiency	CKD likely
Phase	Phase II	Discontinued (PII)	Phase I	Discontinued (P0)	Discovery	Discontinued (PII)	Phase I/II	Phase I (?)
Modality	PEGylated Spiegelmer	IgG4	Anticalin scaffold	HJV-Fc fusion	Engineered heparins	IgG4	IgG1	unclear