Recent advances in understanding molecular mechanisms of iron homeostasis: lessons for optimizing iron availability in chronic kidney disease

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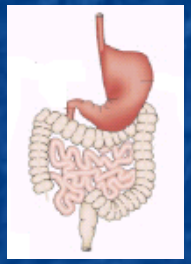
Iron distribution in humans

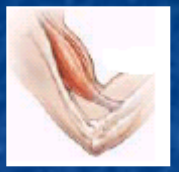
Daily absorption 1-2 mg



1-2 mg

Other tissues

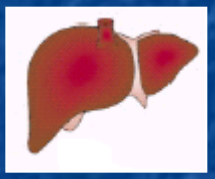
Muscles



300 mg

Storage

Liver



1000 mg

Plasma
Tf-Fe
3mg

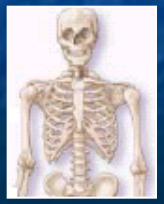
30mg

30mg

Recycling

Red blood cells

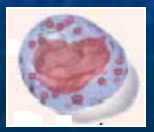
Marrow



300 mg

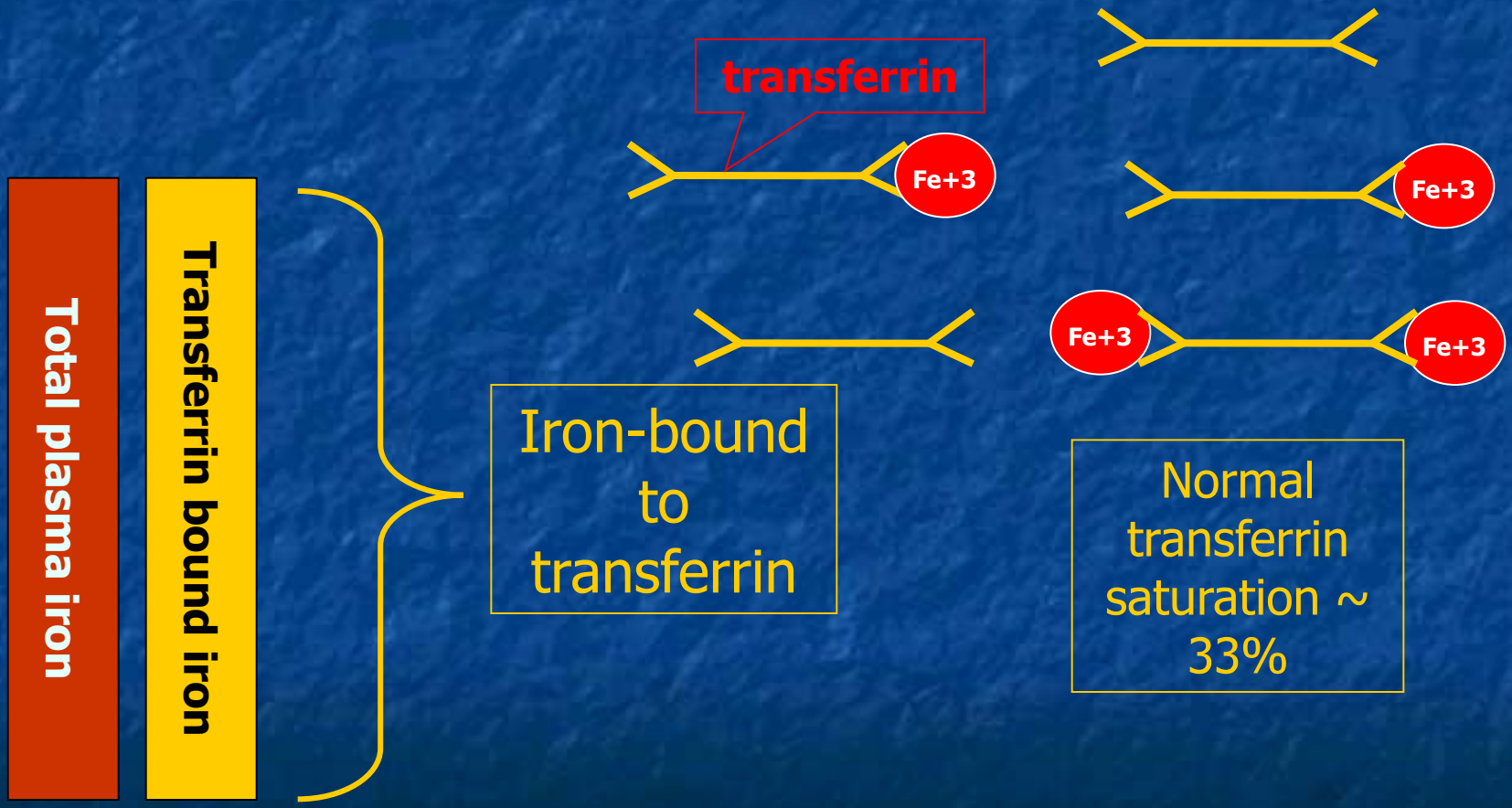
1800 mg

Macrophages
RES

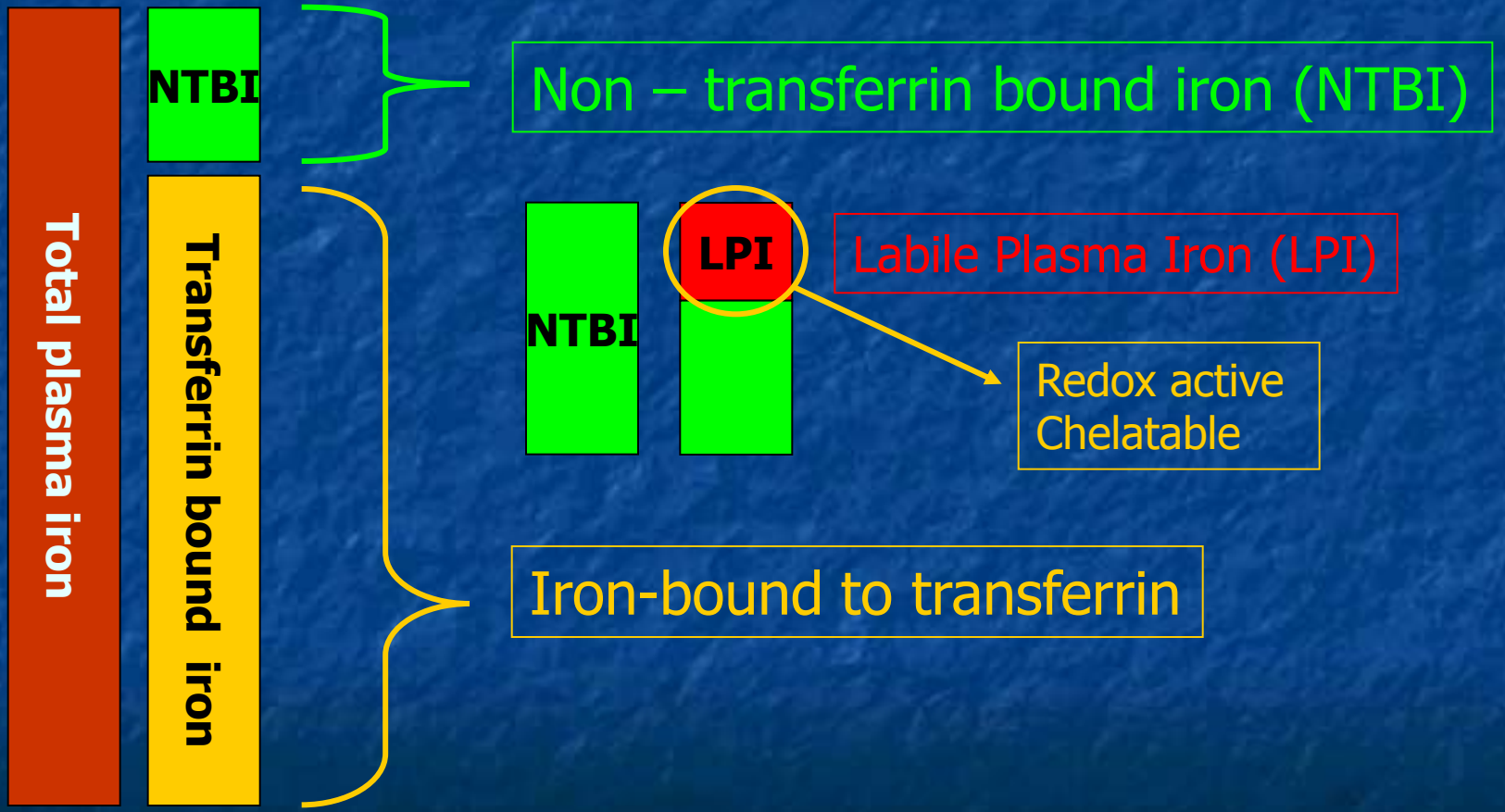


600 mg

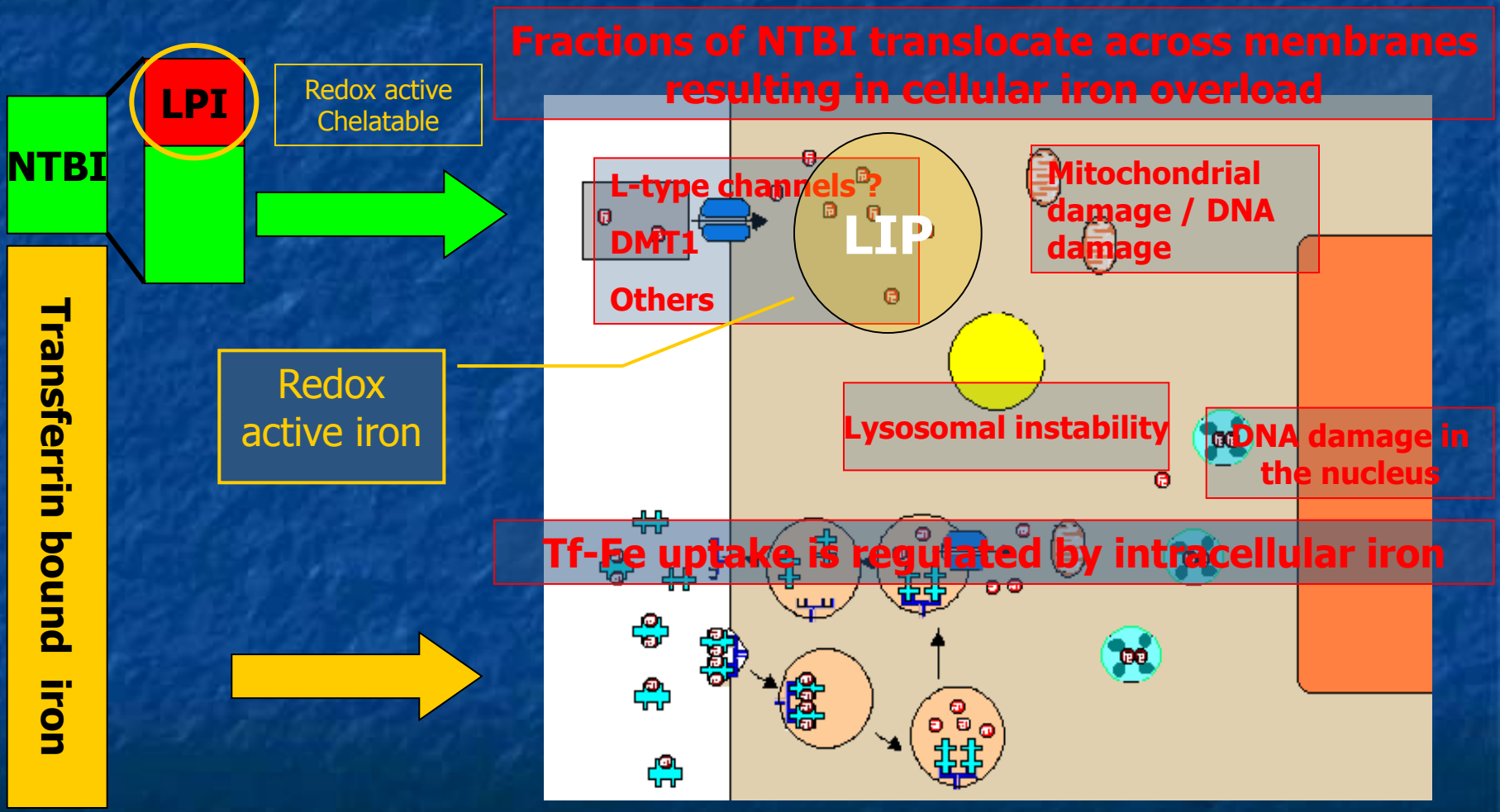
Plasma iron in health



Plasma iron in iron overload



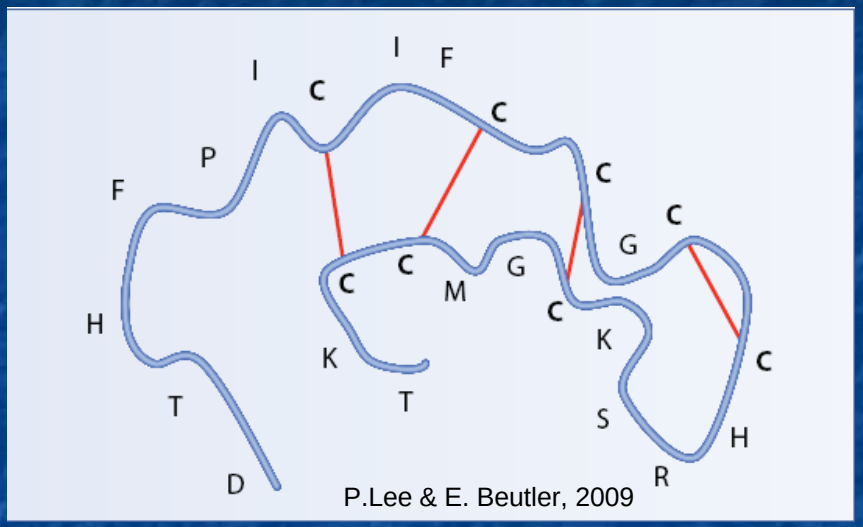
NTBI toxicity



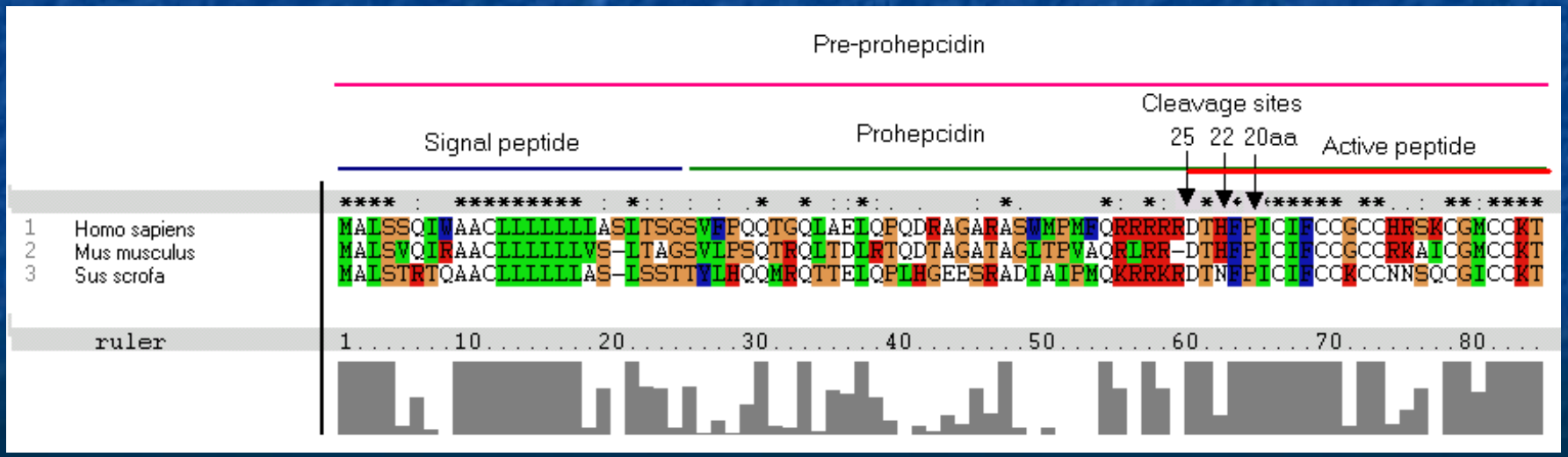
Hepcidin

Biologicaly active hepcidin (25aa)

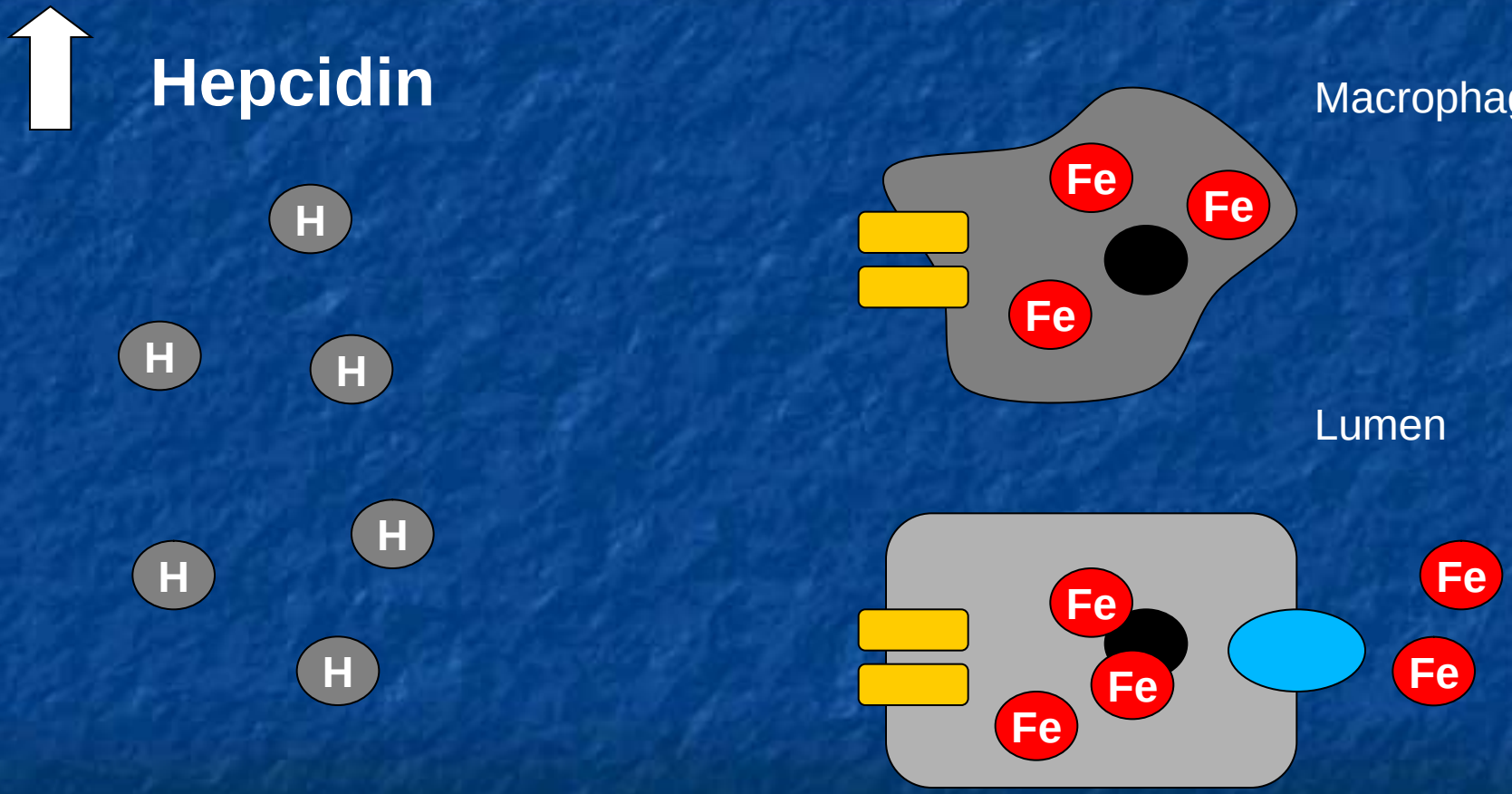
Renal elimination



P.Lee & E. Beutler, 2009

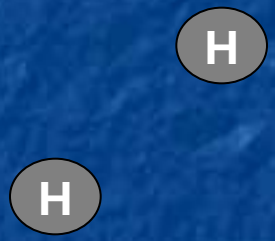


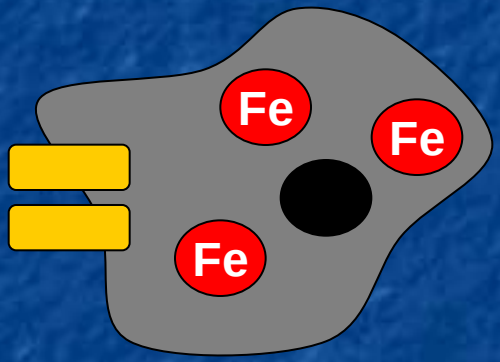
Hepcidin: negative regulator of iron absorption and RE release



Hepcidin and iron overload

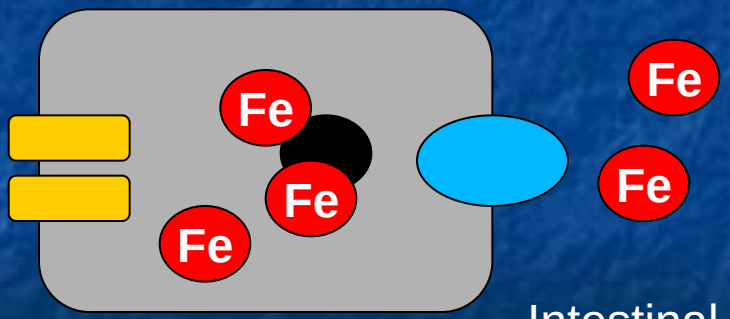
Hepcidin





Macrophages

Enterocytes

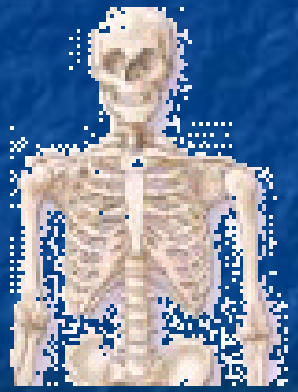


Intestinal lumen

Regulation of hepcidin production

Anemia / hypoxia

Increased erythropoietic demand for iron

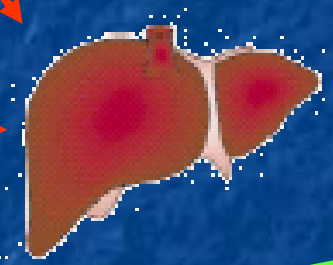


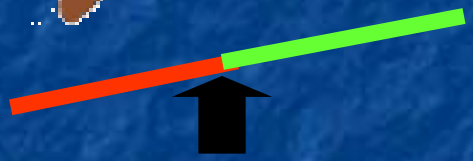
Bone marrow

Inflammation

IL-6

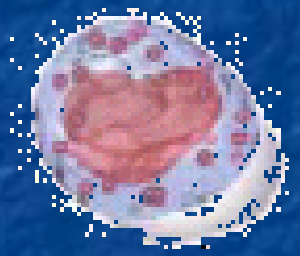
IL-1



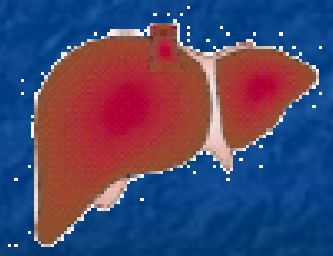


Final hepcidin production

Increased iron stores

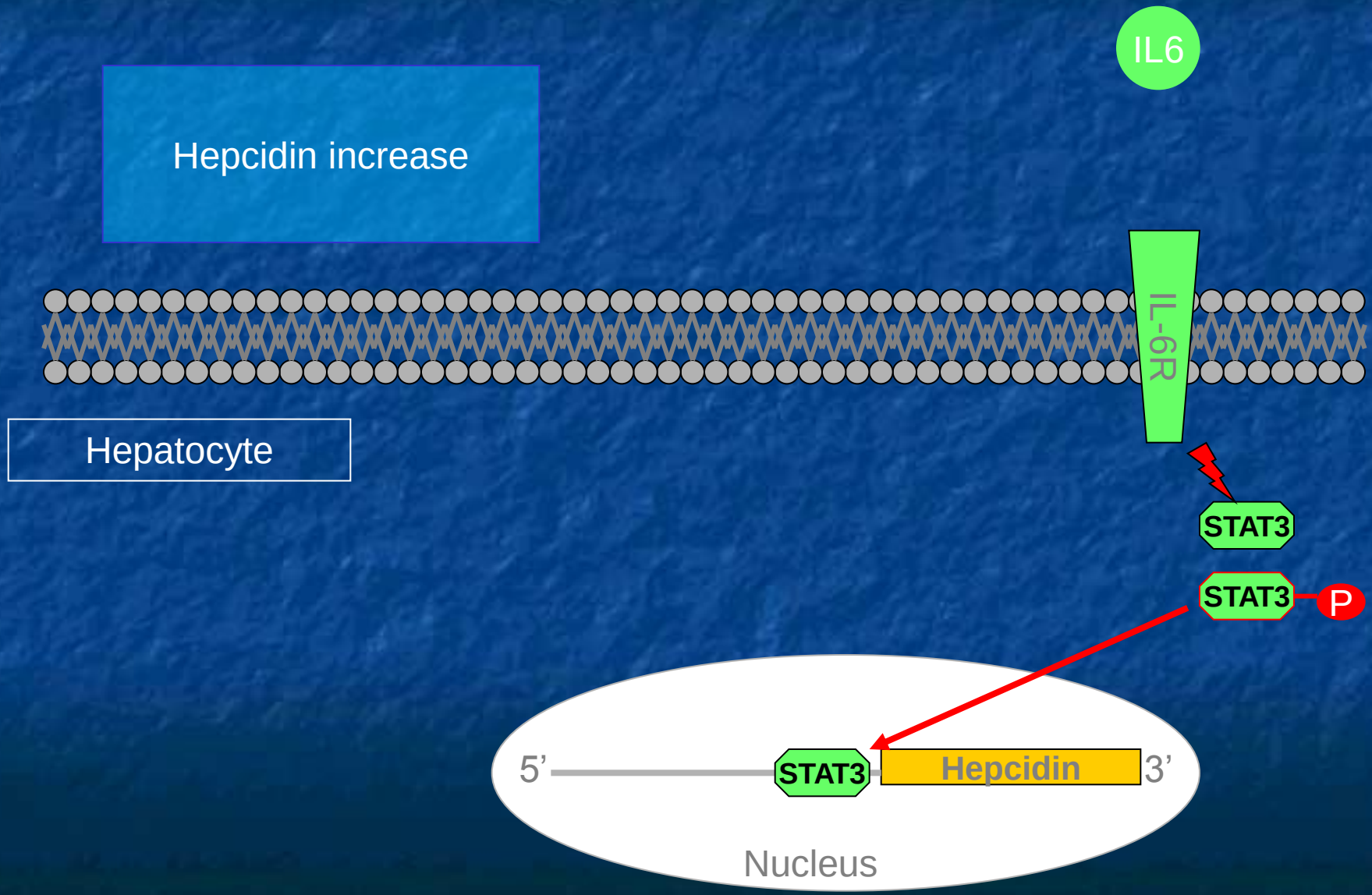


Macrophages

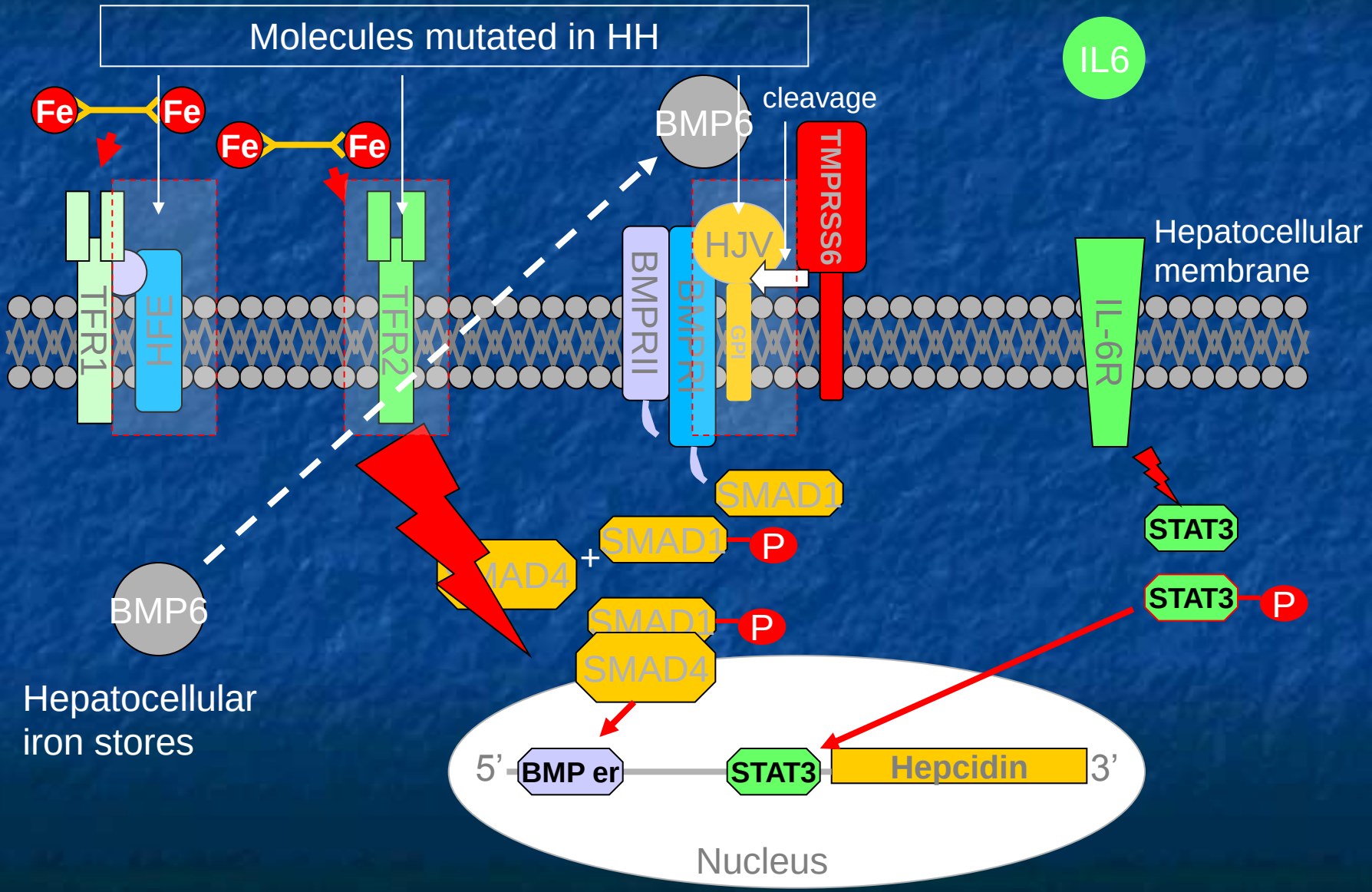


Liver

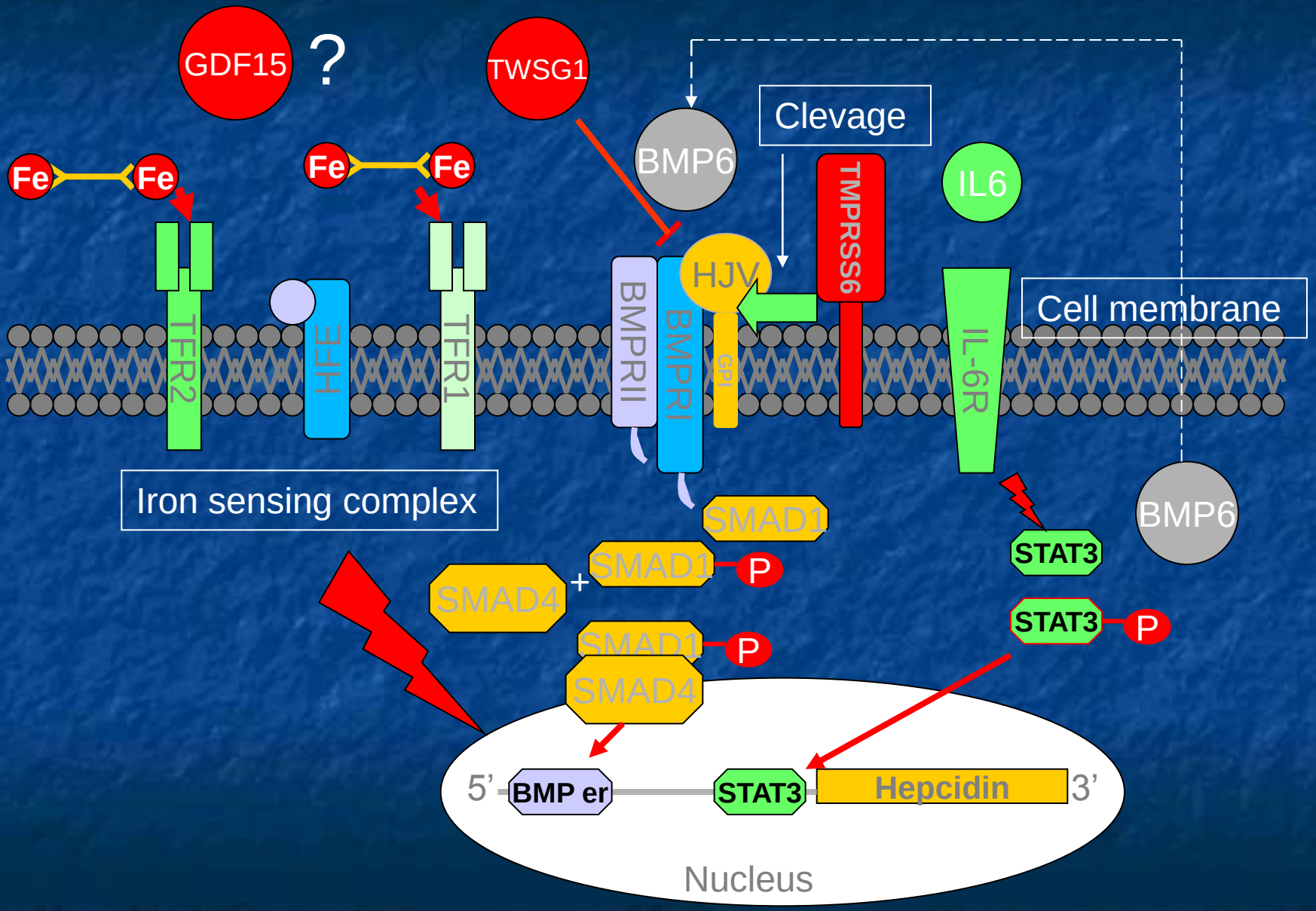
Hepcidin upregulation by IL-6



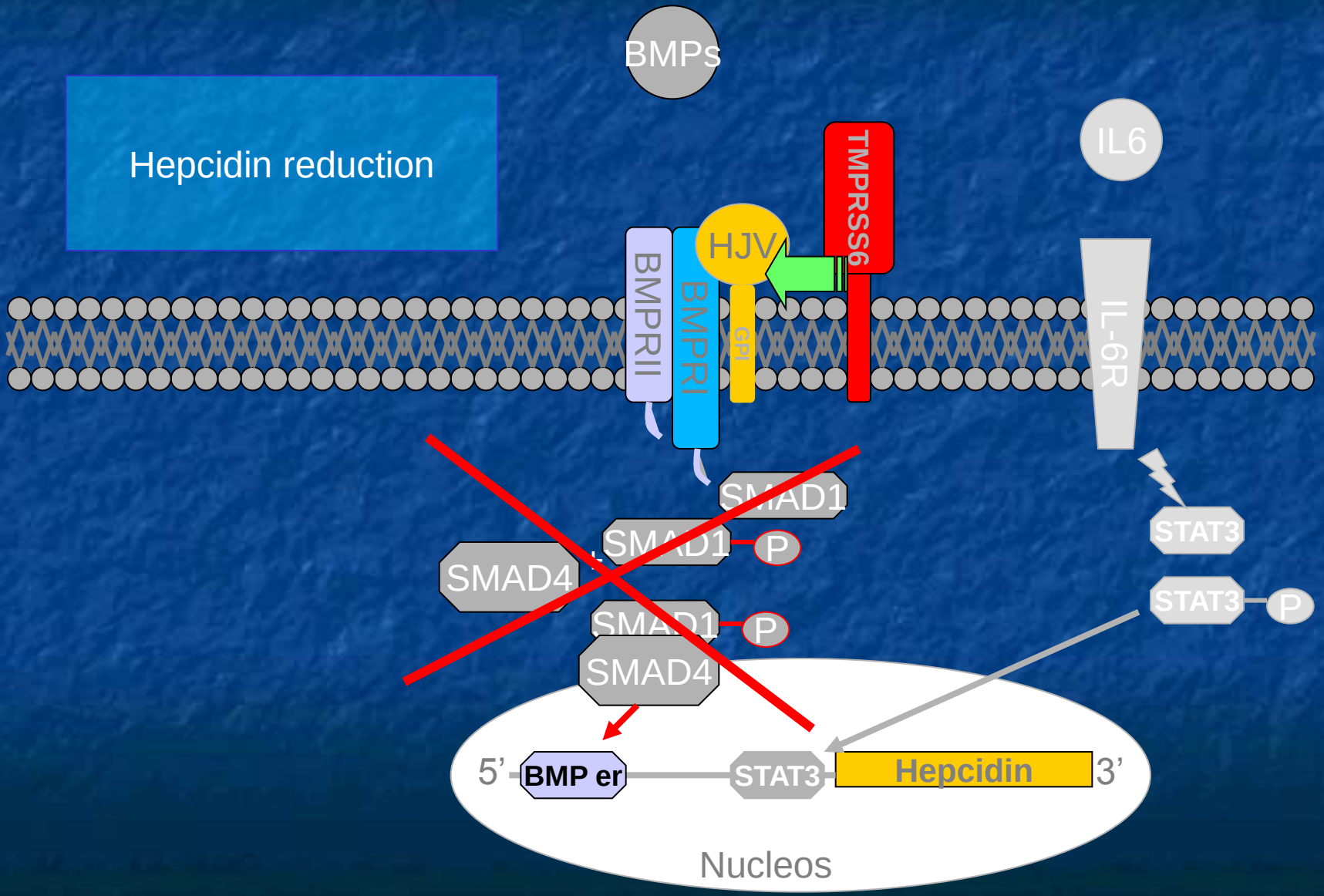
Regulation of hepcidin production – iron stores and transferrin saturation (hepatic cell)



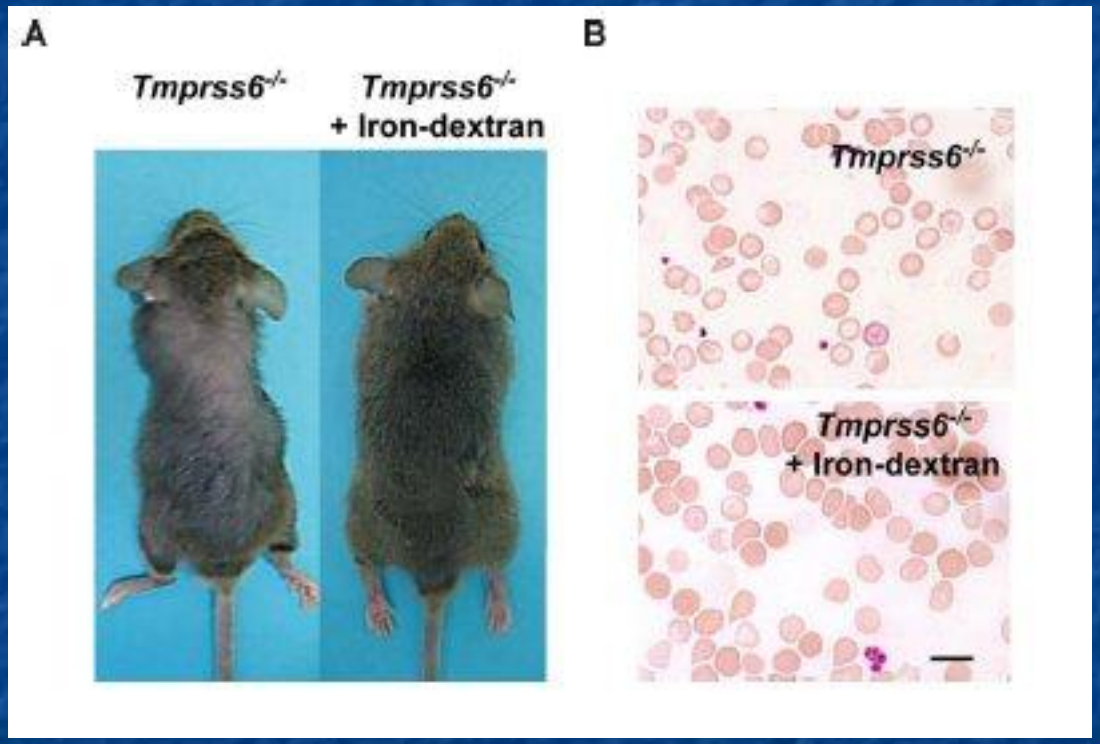
Hepcidin downregulation by erythroid marrow



Hepcidin regulation and Matriptase-2



Tmprss6 $^{-/-}$ mice and IRIDA (Iron Refractory Iron Deficiency Anemia)



IRIDA

Hypochromic, microcytic anemia

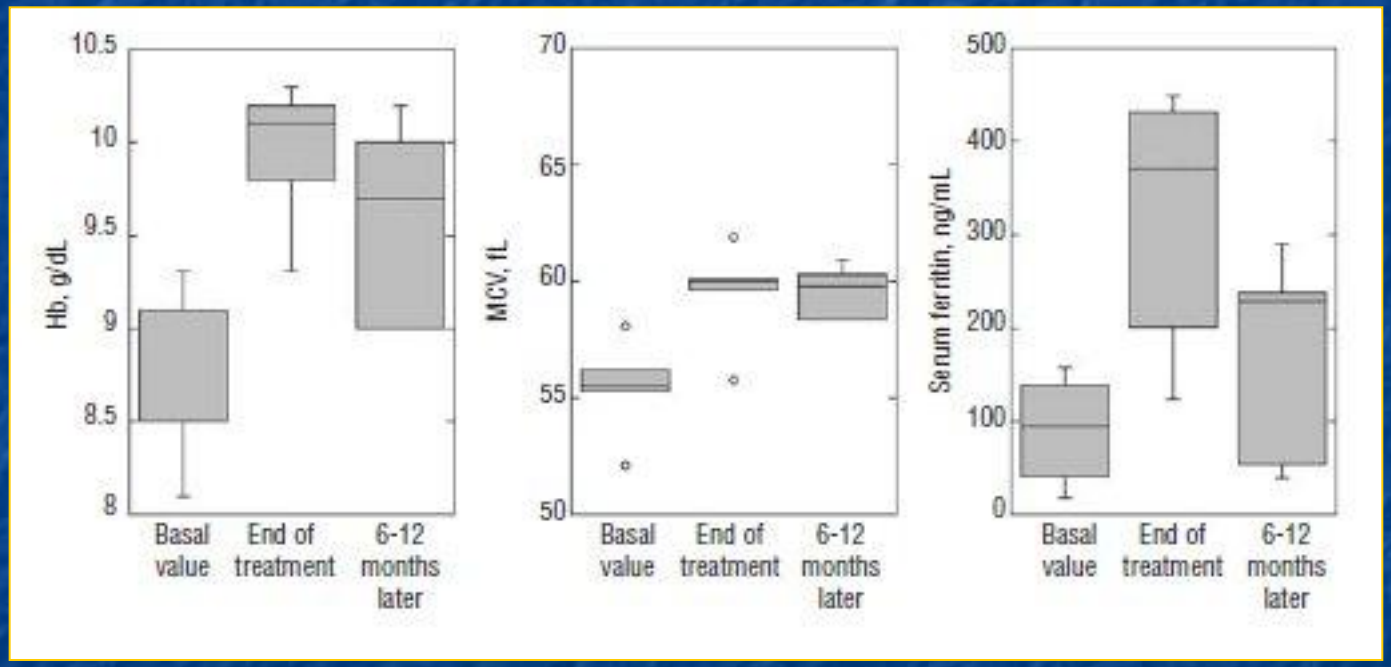
Low TS, Ferritin

Inappropriately high hepcidin

Refractory to oral iron administration

Folgueras et al. Blood 2009

IRIDA: partial restoration of anemia after iv iron administration



Melis et al. Hematologica 2008

Hepcidin in human disease

Normal

HFE Hemochromatosis

TFR2 Hemochromatosis

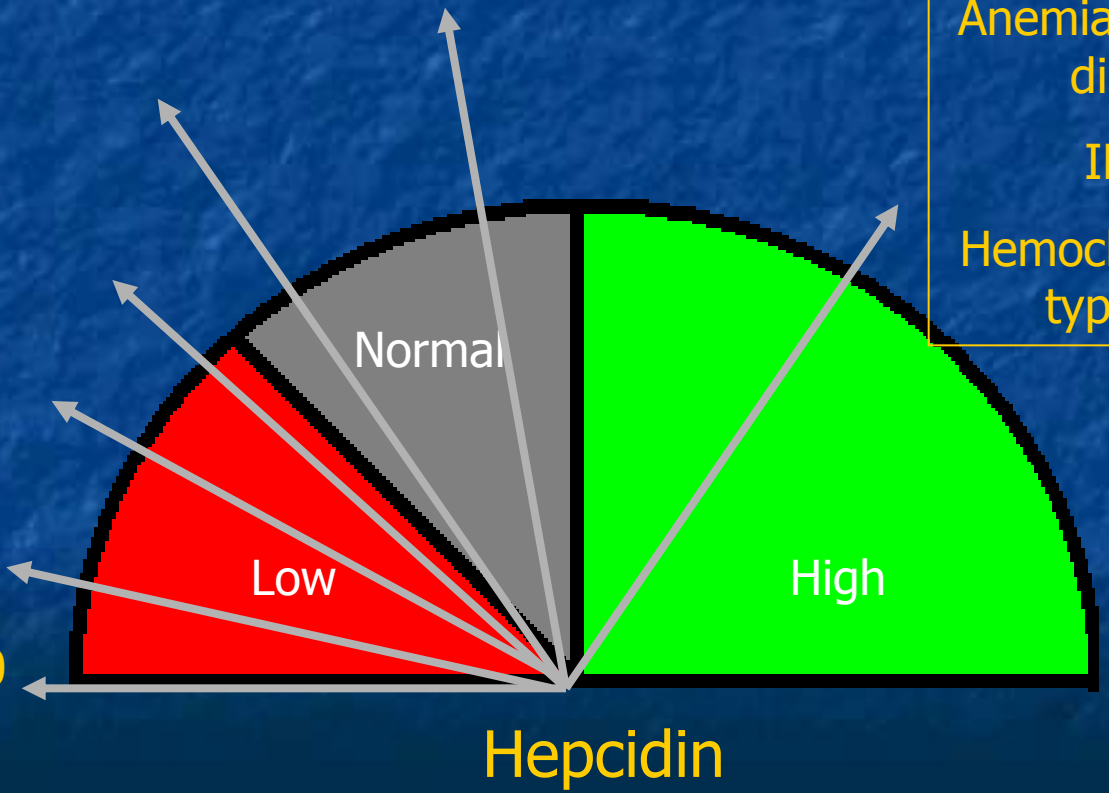
HJV (HEMOJUVELIN)

HAMP (HEPCIDIN)

Anemia of chronic disease

IRIDA

Hemochromatosis type 4(M)



"...Anemia, ESA resistance, hypoferremia, and high serum ferritin is not uncommon in the CKD/ESRD population..."

- "...A 55 year-old woman with hemodialysis-dependent end-stage renal disease (ESRD) secondary to diabetic nephropathy had persistent anemia despite escalating erythropoiesis-stimulating agent (ESA) dosing. Serum hemoglobin level was 7.5 g/dl (reference range, 12-16 g/dL), and hematocrit was 23.4 % (reference range, 36-46 %). Serum iron was 22 µg/dL (reference range, 30-160 µg/dL), total iron binding capacity was 188 µg/dL (reference range, 230-404 µg/dL), and serum transferrin saturation was 11.7%, consistent with low circulating levels of iron. However, the serum ferritin was elevated at 1315 ng/mL (reference range, 10-200 ng/mL)..."

Babitt et al. Am J Kidney Dis. 2011

Hepcidin in HD-CKD

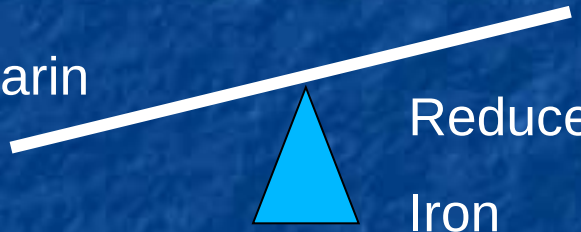
Anemia

ESAs

Dialysis clearence

Hypoxia

Heparin



Reduced GFR

Iron

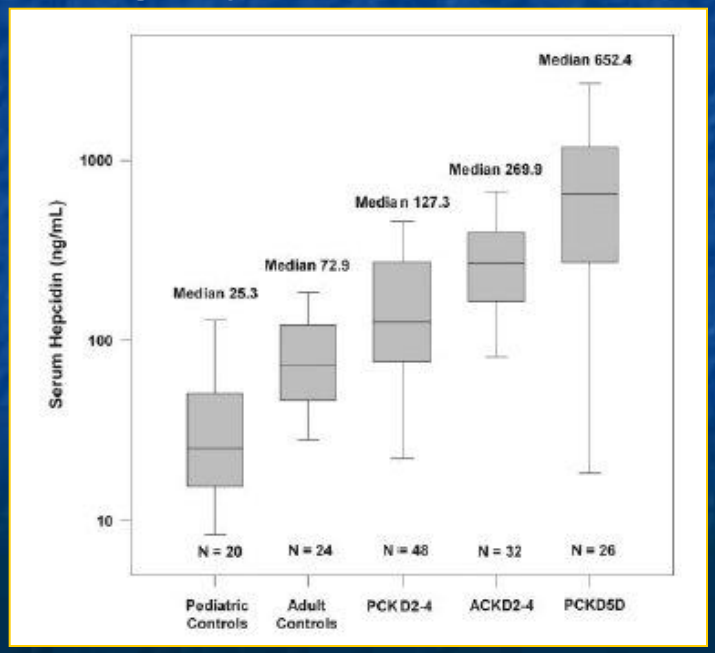
Inflammation

- Hepcidin as a biomarker
  - Prediction of ESA response?
  - Prediction of response to iv iron?
- Hepcidin lowering agents
  - Treatment of functional iron defficiency?

Babitt et al. Am J Kidney Dis. 2011

Is Hepcidin corelated with eGFR?

- Competitive ELISA
- Negative correlation with eGFR
- Corellation with serum ferritin

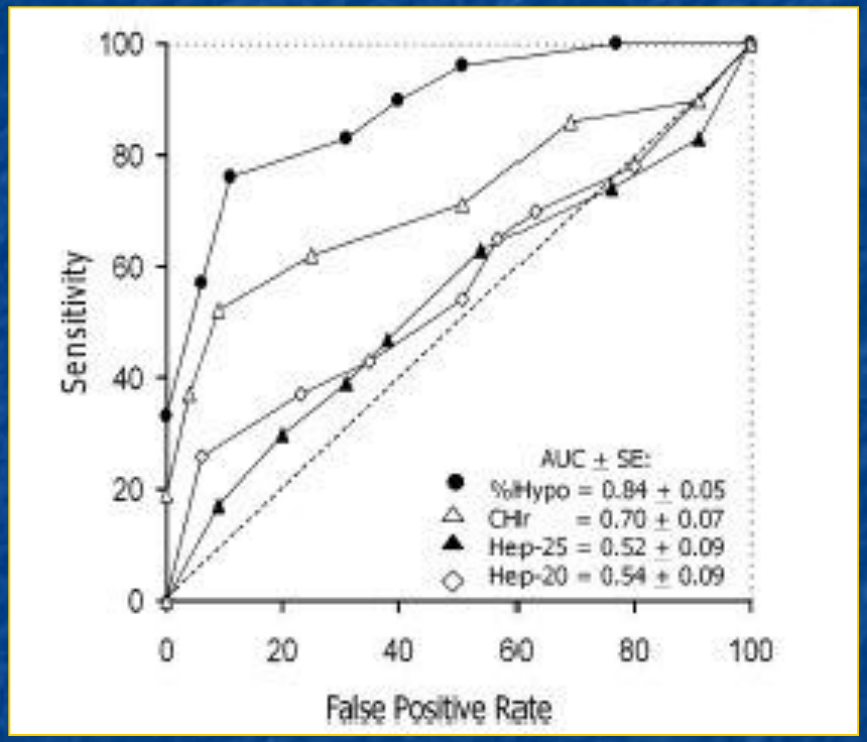


Zaritsky et al. Clin J Am Soc Nephrol, 2009

- Mass spectometry
- Bioactive hepcidin 25 increased only in HD-CKD patients
- Negative corellation with eGFR for total hepcidin (20,22,25) but not hepcidin-25
- Correlation with serum ferritin

Peters et al. Nephrol Dial Transplant , 2010

Hepcidin and prediction to iv iron response



Study underpowered

- 56 chronic HD pts
- slow bolus injection at the end of 16 consecutive dialysis sessions
- Responders Increase in Hb >1 g/dL above the baseline
- Hep-25 may be a useful biomarker for iron stores and bone marrow iron availability
- %Hypo , CHr, TSAT and ferritin

Tessitore et al. Nephrol Dial Transplant, 2010

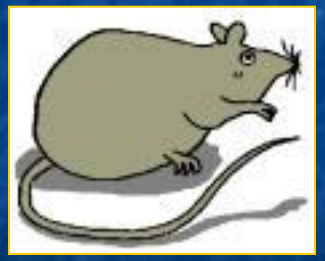
Hepcidin lowering agents

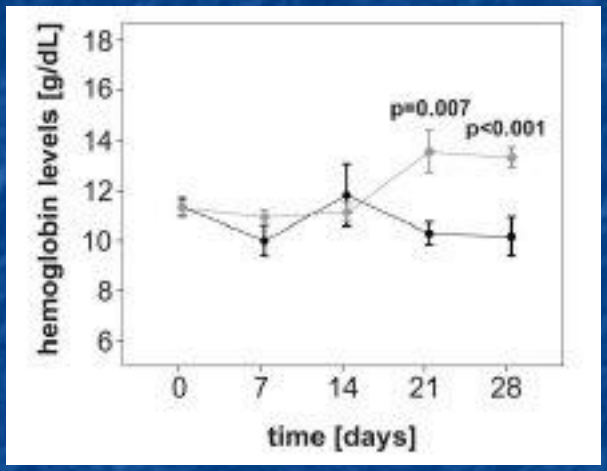
PG-APS

Group A Streptococcal Peptidoglycan Polysaccharide

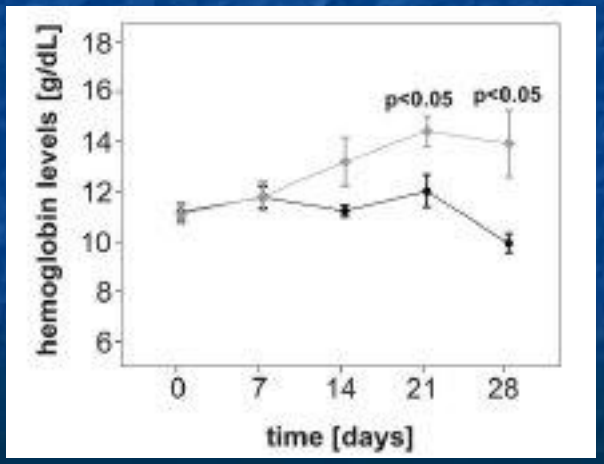
Hb: 2g/dL drop from baseline

Treatment with LDN-193189 or HJV.Fc protein





Treatment with LDN-193189



Treatment with HJV.FC protein

Theurl et al. Blood , 2011

Iron deficiency and functional iron deficiency

- Absolute iron deficiency – minimal or no iron stores (typically TS<20% and Ferritin <200ng/dl)
- Functional iron deficiency – inadequate release of iron to support the needs of erythropoiesis despite the presence of adequate iron stores
  - ESA treatment
  - Inflammation
  - ~30% of patients will respond to iv iron

Besarab Nat. Rew. Nephrol, 2010

Causes of ID in ESRD

- Reduced dietary intake
- Impaired absorption
- Blood losses (including GI)
- Increased requirements of ESA treatment
- Blood drawing
- Dialysis blood losses (4.5-6mg/day)

Iron balance in HD-CKD

A HD-CKD patient has a net loss of iron estimated to

1.5-3 gr / year!

Most commonly used iv iron preparations

Generic name	Packing
Ferric gluconate	62,5 mg/5/ml
Iron sucrose	100 mg/5ml
Iron dextran (HMW-LMW)	100 mg/2ml

Therapy of absolute iron deficiency

- Calculation of iron needs
  - Total iron deficit [mg] = body weight [kg] x (target Hb – actual Hb) [g/l] x 0.24 + depot iron [mg]
  - estimated ongoing blood losses during the period of correction (eg. ~600-700mg for 3 months)
- When >1gr, administration of 100mg three times a week
  - Eg. Bolus 100mg in 5 minutes, 100mg in 100ml 0.9% NaCl over 30min, etc.
- PD-CKD patients
  - Eg. 200mg diluted in 400-500ml 0.9% NaCl over 2 hours
  - SmPC iron sucrose maximum dose : 500mg in 500ml 0.9%NaCl over not less than 3 ½ hours

NKF Guidelines

- The preferred route of administration is IV in patients with HD-CKD. (STRONG RECOMMENDATION)
- The route of iron administration can be either IV or oral in patients with ND-CKD or PD-CKD
- HD-CKD:
  - Serum ferritin >200 ng/mL
  - AND TSAT >20%, or CHr >29 pg/cell
- ND-CKD and PD-CKD:
  - Serum ferritin >100 ng/mL
  - AND TSAT >20%.

Is there an upper limit for ferritin?

- NKF Guidelines "...there is insufficient evidence to recommend routine administration of IV iron if serum ferritin level is greater than 500 ng/mL. When ferritin level is greater than 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb and TSAT level, and the patient's clinical status..."
- RES capacity ~ 5gr of iron
- If ferritin >500 ng/ml iron deficiency is unlikely
- Secondary hemochromatosis - Persistent increase TS>50% , typically ferritins exceeding 4.000ng/ml (pre ESA era)

Periodic vs regular low-dose iron administration

- Periodic repletion dosing (Course of iv doses eg. 100mg in 10 sessions – up to 1000mg)
- Regular low-dose administration (eg. 22-65 mg/week)
- Potential benefits of regular low-dose IV iron therapy
  - Longer term stabilization of Hb levels / less Hb variability
  - Reduced fluctuations in iron stores
  - More efficient erythropoiesis / reduced ESA resistance
  - Reduction in need for (and any adverse effects of) higher ESA doses

Benefits of iron administration

- CVD risk
  - Reduced ESA dosage
  - Reduction in platelet count
- Overall morbidity and mortality
  - Low serum indices associate with high mortality and hospitalization in HD-CKD pts
  - Iron sufficiency favorably affects long term survival

Savings for the budget of your dialysis unit!

Benefits of iron administration

- Non hematological benefits
  - Improved physical performance - favorable adaptation to aerobic exercise.
  - Thermoregulation impaired ability to maintain core body temperature in response to cold-stress.
  - Improved cognitive function
  - Restless leg syndrome: RCT showed that addition of iron in hemodialysis patients with restless leg syndrome results in improvement.
  - Improved Immune function
  - Aluminum absorption (iron depletion increases absorption)

Safety concerns

- Acute adverse events after iv administration - Allergy or toxic reactions
- Risk of infection (in vitro studies show suppression of phagocytosis by iron, human data directly linking intravenous iron to exacerbation of existing infection or infection-related mortality are lacking)
- Risk of increased cardiovascular morbidity and mortality
- Nephrotoxicity (induction of tubular and endothelial cell death, transient proteinuria and tubular damage - greater with iron sucrose or iron gluconate compared to iron dextran)

Allergy and toxic reactions

- Mechanism
  - Immune mechanisms (including mast cell–mediated processes leading to a clinical syndrome resembling anaphylaxis)

    More common with iron dextran

  - Release of bioactive, partially unbound iron into the circulation, resulting in oxidative stress and hypotension (labile or free iron reactions)

    More common with iron sucrose and iron gluconate

Are life threatening adverse events common?

US FDA data 2001-2003

Rate per million	Iron formulation
0.6	Iron sucrose
0.9	Sodium Ferric gluconate
3.3	Low molecular weight dextran
11.3	High molecular weight dextran

Chertow et al Nephrol Dial Transplant 2004

- Iron sucrose, gluconate and LMW dextran are safe with incidence of SAEs <1 in 200.000
- Other studies find no difference betwwen iron sucrose, gluconate and LMW dextran

Iron sucrose in patients intolerent to other forms of iron

- 130 pts intolerent to iron dextran or sodium ferric gluconate
- Administration of iron sucrose
- 14 non serious AEs in 8 patients (diarrhea, nausea, moderate hypotension, taste disturbancies, vomiting, skin irritation
- Safe alternative for pts intolerent to other forms

Table 1. The most common manifestations of a history of parenteral iron intolerance

Symptom	Patients	%
Skin irritation	42	32.3
Allergic dermatitis	20	15.4
Dyspnea, isolated	18	13.8
Hypotension, decreased blood pressure	18	13.8
Urticaria, isolated	15	11.5
Back pain	14	10.8
Hypersensitivity	8	6.2
Dyspepsia	7	5.4

Charytan et al. Nephron Clin Pract, 2004

Undesirable effects (iron sucrose)

Frequency	Undesirable effects
Common (>1/100 to <1/10)	transient taste perversions (in particular metallic taste)
Uncommon (≥1/1,000 to <1/100)	hypotension and collapse; tachycardia and palpitations headache dizziness bronchospasm, dyspnoea, chest pain and tightness nausea, vomiting, abdominal pain, diarrhoea pruritus, urticaria, rash, exanthema; erythema.muscle cramps, myalgia fever, shivering, hot flushes, injection site irritations such as superficial phlebitis, burning, swelling.
Rare (≥1/10,000 to <1/1,000)	anaphylactoid reactions (rarely involving arthralgia); peripheral oedema; fatigue, asthenia; malaise.paraesthesia
Isolated cases	reduced level of consciousness, light-headedness, confusion; angio-oedema and swelling of joints

SmPC Ferrovin 100 mg/5 ml

Conclusions

- Iron deficiency is prevalent in CKD and should be trated
- Inconsistent and anadequate absorption of iron in CKD often leads to administration of iv iron
- Hemodialysis patients have an ongoing and substantial need for iron
- Oral iron is ineffective in achieving the iron parameters sought in dialysis patients
- IV iron improves the response to ESA therapy
- Hepcidin impairs iron absorption and recycling through the RES – potential for developing new agents for the treatment of anemia of chronic disease