Iron Overload

Dick Wells

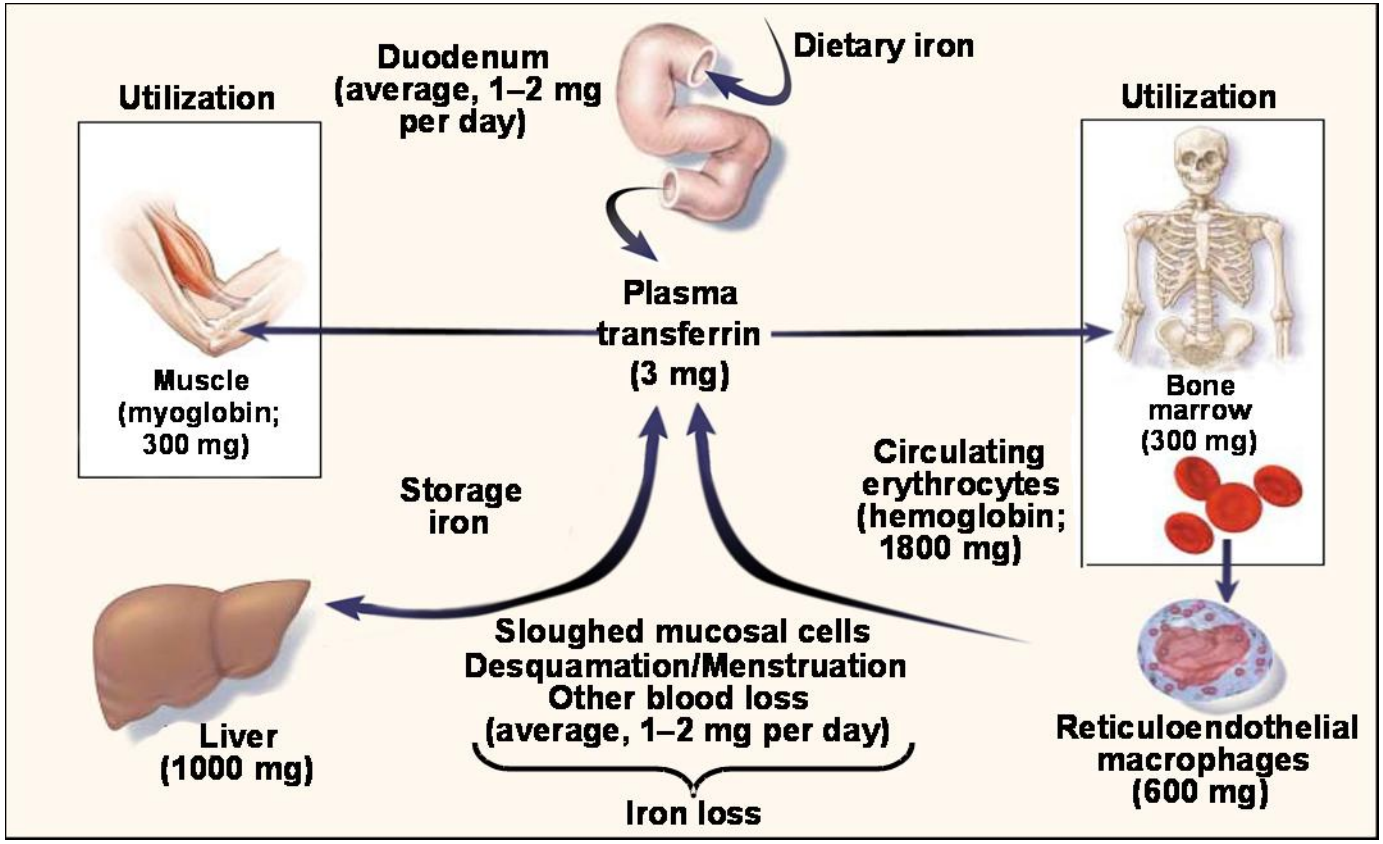
Outline

- A functional definition of iron overload
- Iron toxicity – from atoms to organs
- Treatment of iron overload

Am I overloaded yet?

A functional definition of iron overload

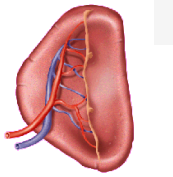
Body Iron Distribution



There is no physiologic mechanism to remove excess iron

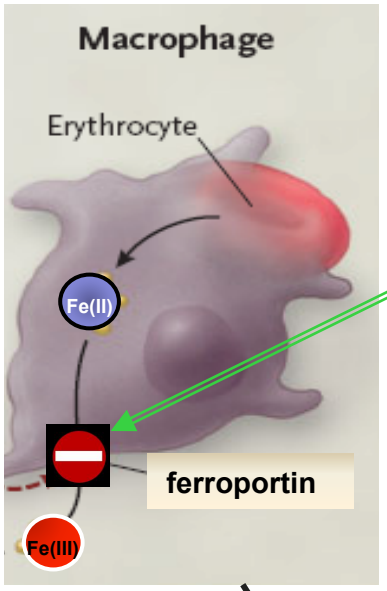
Andrews NC. *N Engl J Med*. 1999;341:1986–1995

The Iron Balance

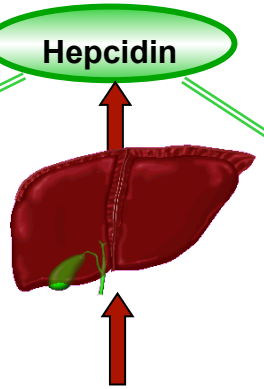


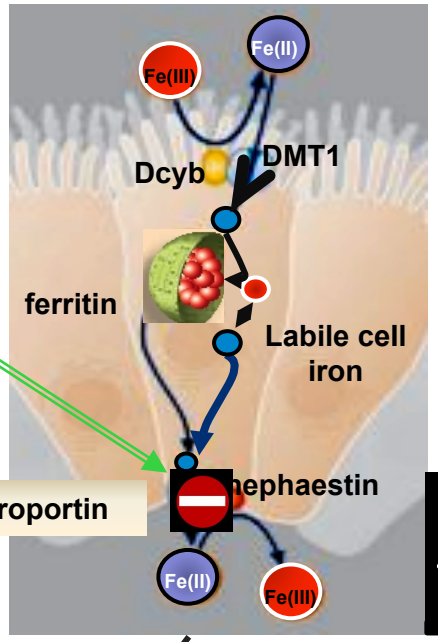
spleen

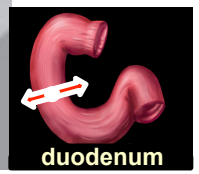
1 % blood cells digested/d
25 mg iron released

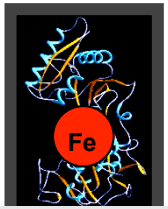


Hepcidin blocks ferroportin, preventing iron export into plasma





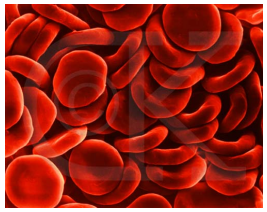




Absorption of iron balances daily loss

Iron released into plasma is incorporated into transferrin

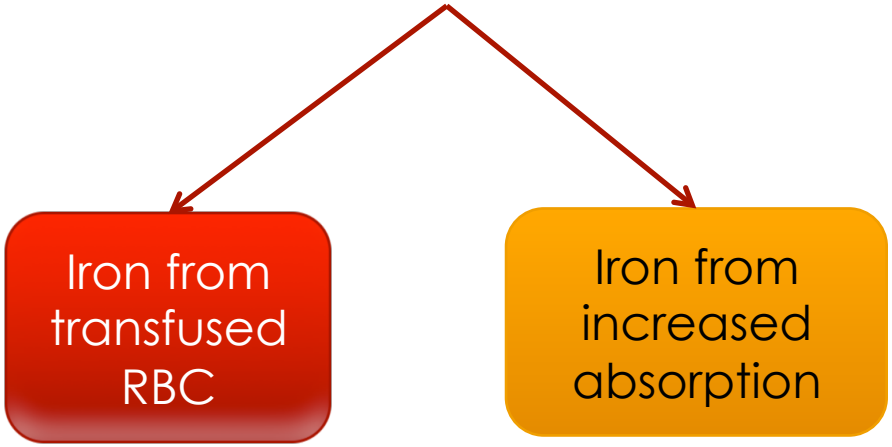
TfSat normally 0.2-0.55
(No non-Tf-bound iron)



Transferrin iron is used for production of new blood cells

Transfusion therapy results in iron overload

- Normal iron influx through gut is 1–2 mg/day
- 1 blood unit contains 200-250 mg iron
- **Iron overload can occur after 10–20 transfusions**

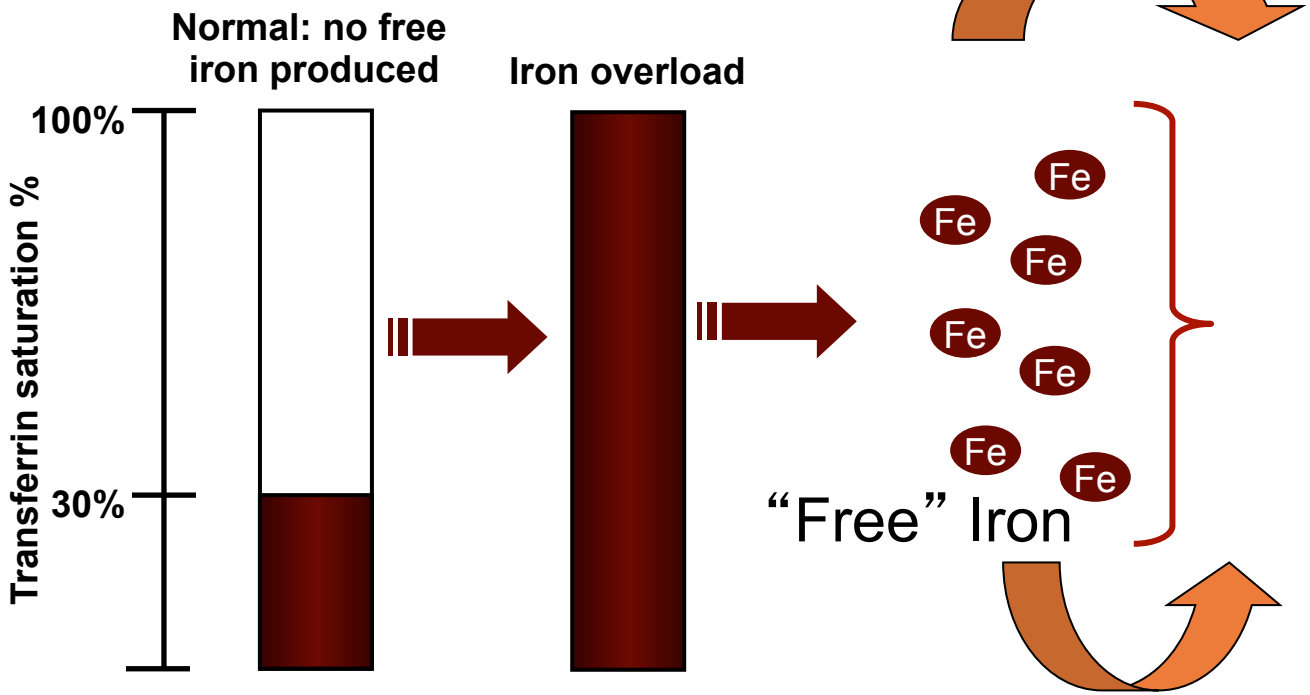


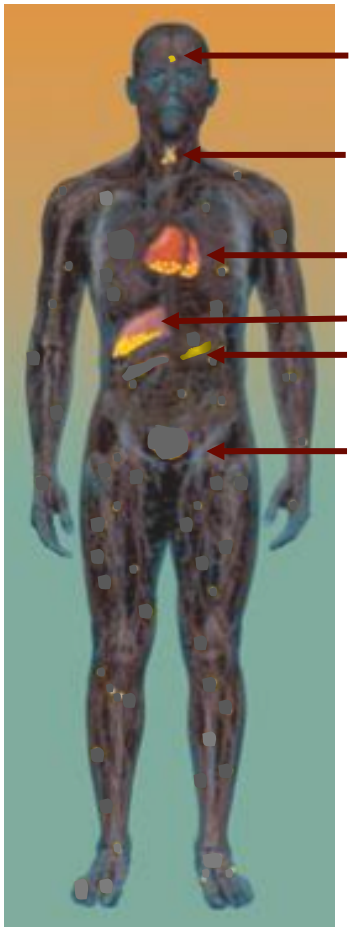
Free Iron:
The Essence of Iron Overload

Saturation of transferrin due to
- **Frequent blood transfusions, and**
- **Ineffective erythropoiesis leading to increased iron absorption**

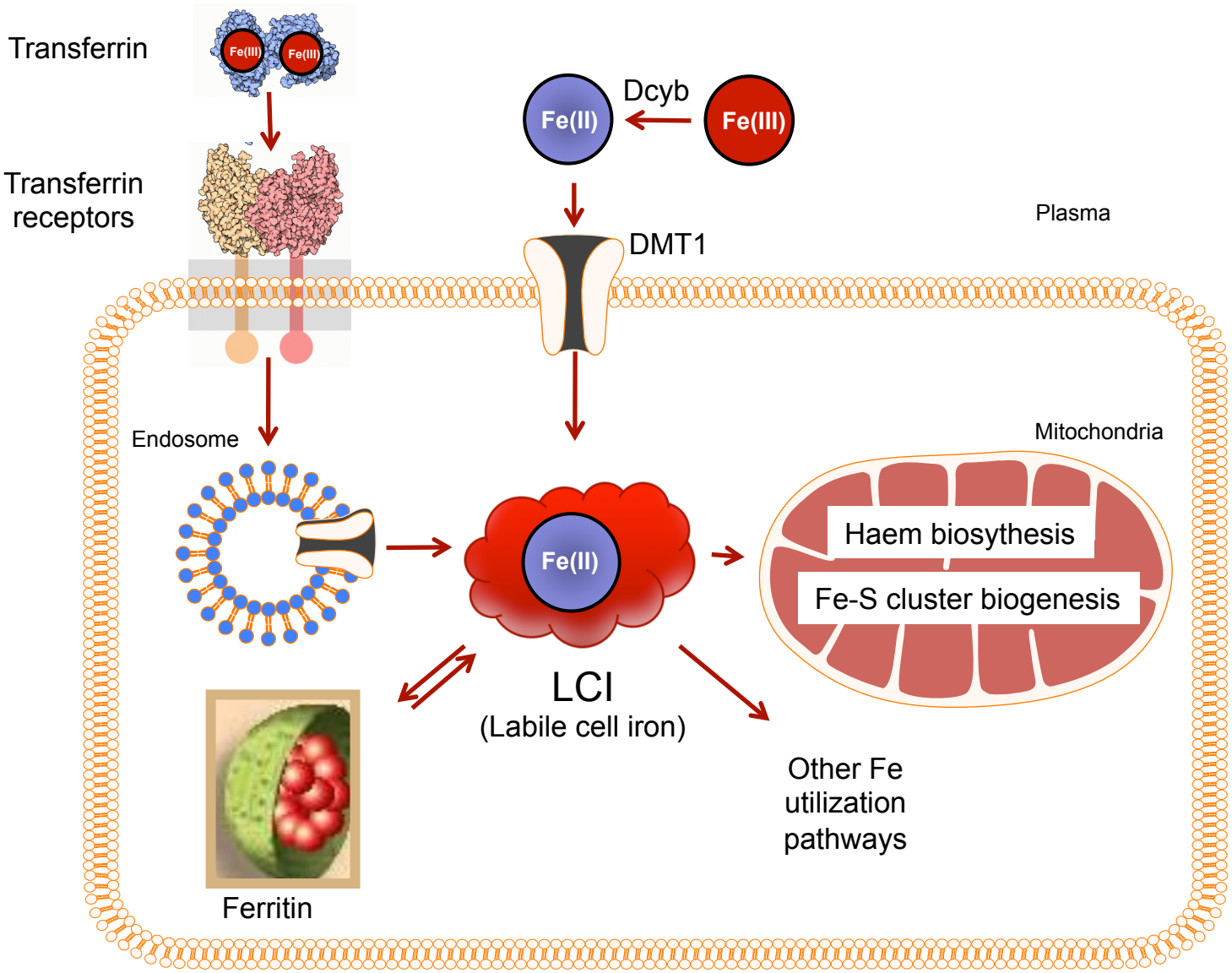
Subsequent formation of free iron in plasma

Uncontrolled iron loading of organs





Free iron in our cells



Summary
Iron Balance

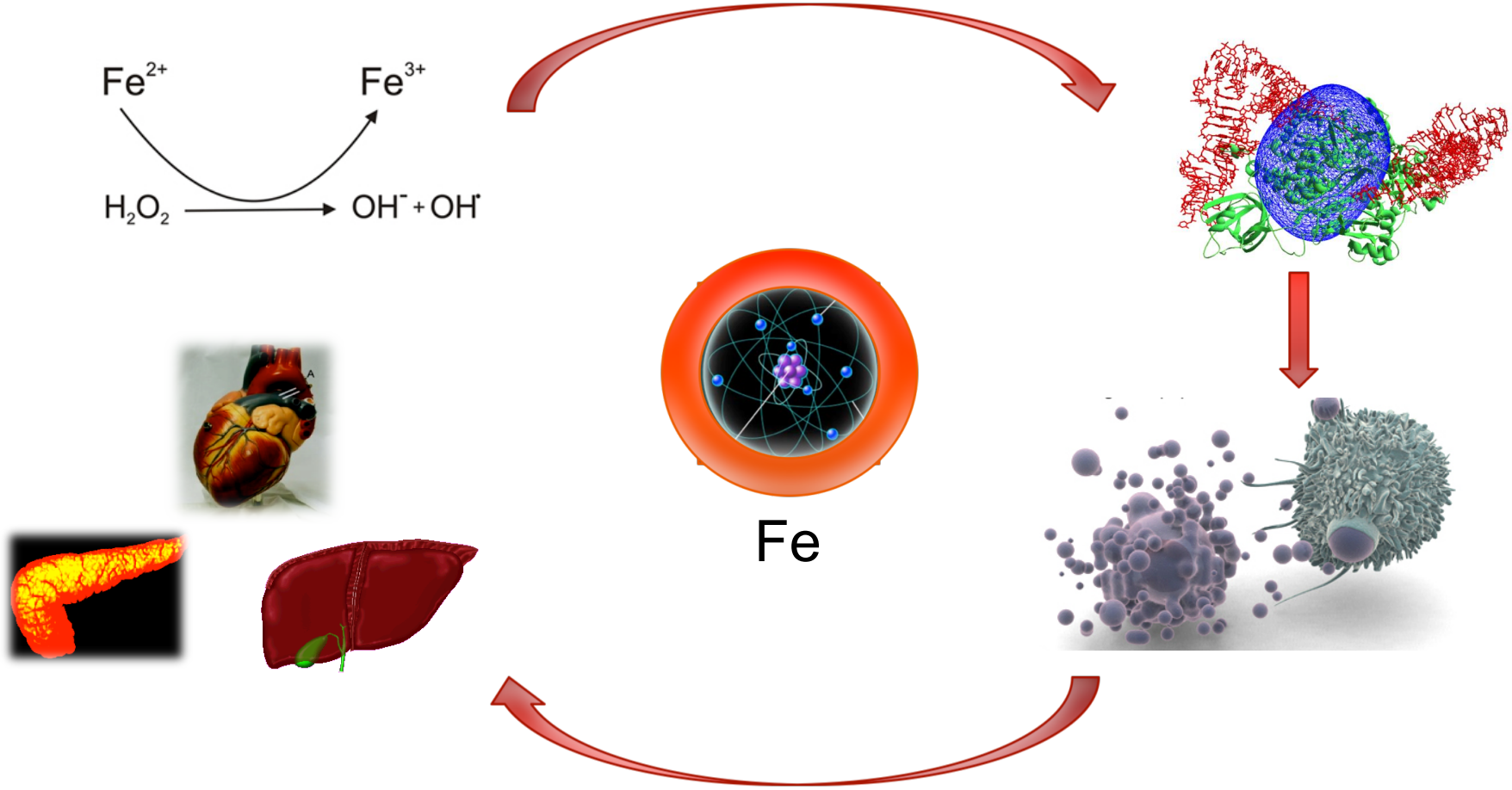
- There is no mechanism for excreting excess iron
- Iron normally is as
  - Haemoglobin an
  - Transferrin (plasm
  - Ferritin (intracellu

What problems are caused by free iron?

- "Free" iron is rare
- When iron stores are high, free iron appears in the plasma and can get into cells

Iron supports dangerous radicals

Iron Toxicity:
From Atoms to Organs



Iron and Free Radicals

- Cell metabolism produces **hydrogen peroxide** (H_2O_2) as a biproduct

- H_2O_2 is not itself very toxic
  - Reactive oxygen intermediate (ROI)

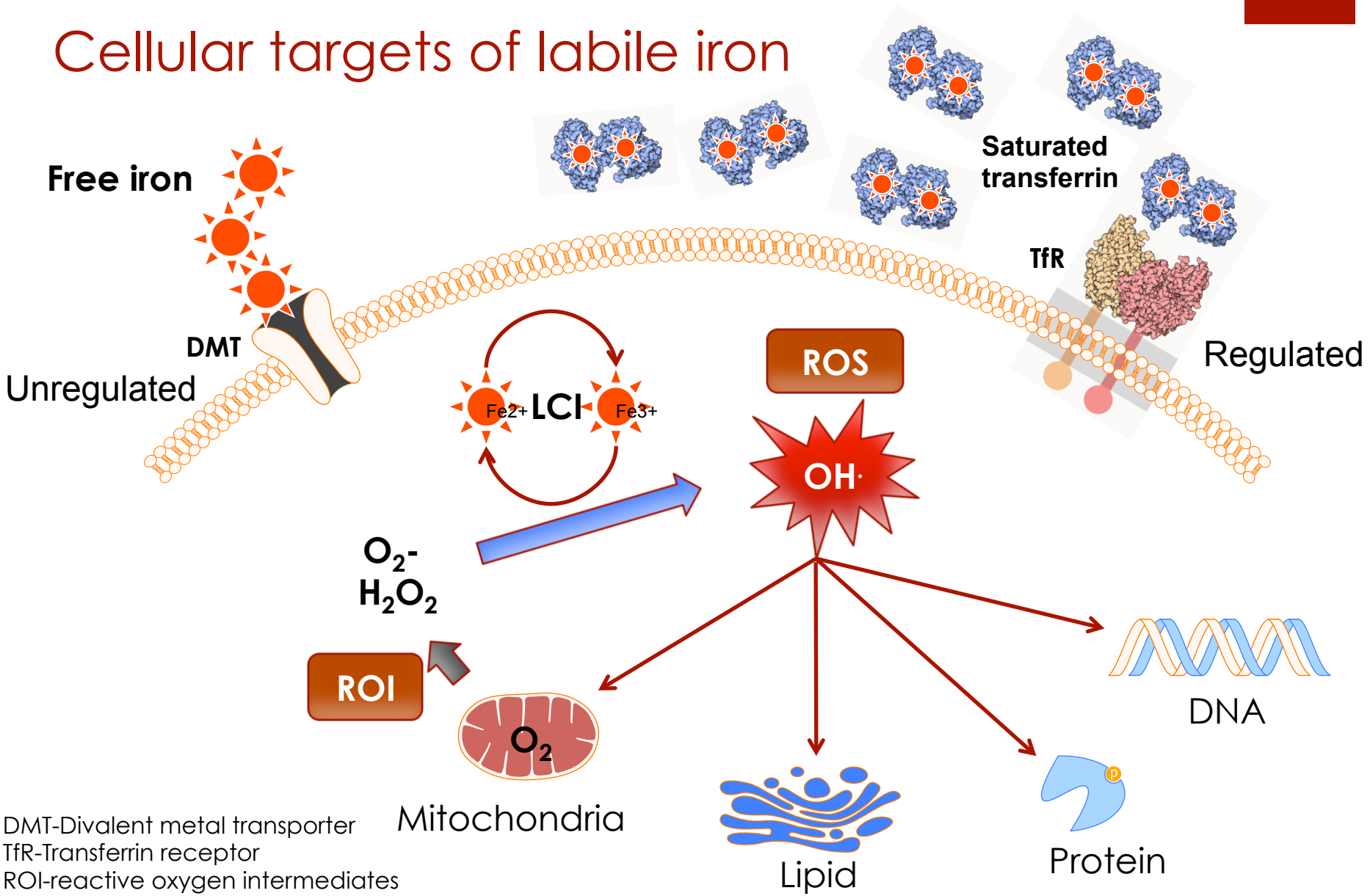
- **Free iron** reacts with H_2O_2 to form highly toxic free radicals
  - Reactive oxygen species (ROS)

H_2O_2 Reactions

Fenton Reaction

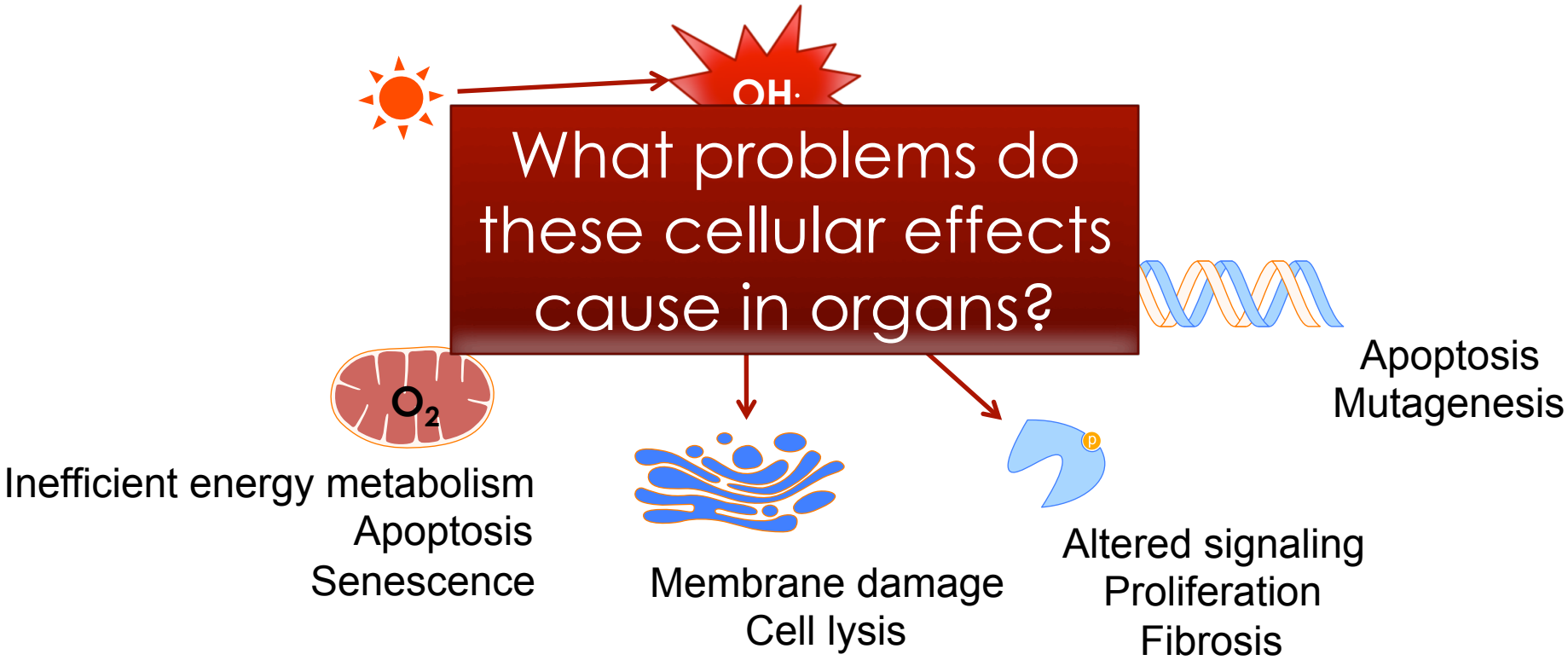
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\bullet + OH^-$$
$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OOH\bullet + H^+$$

Cellular targets of labile iron

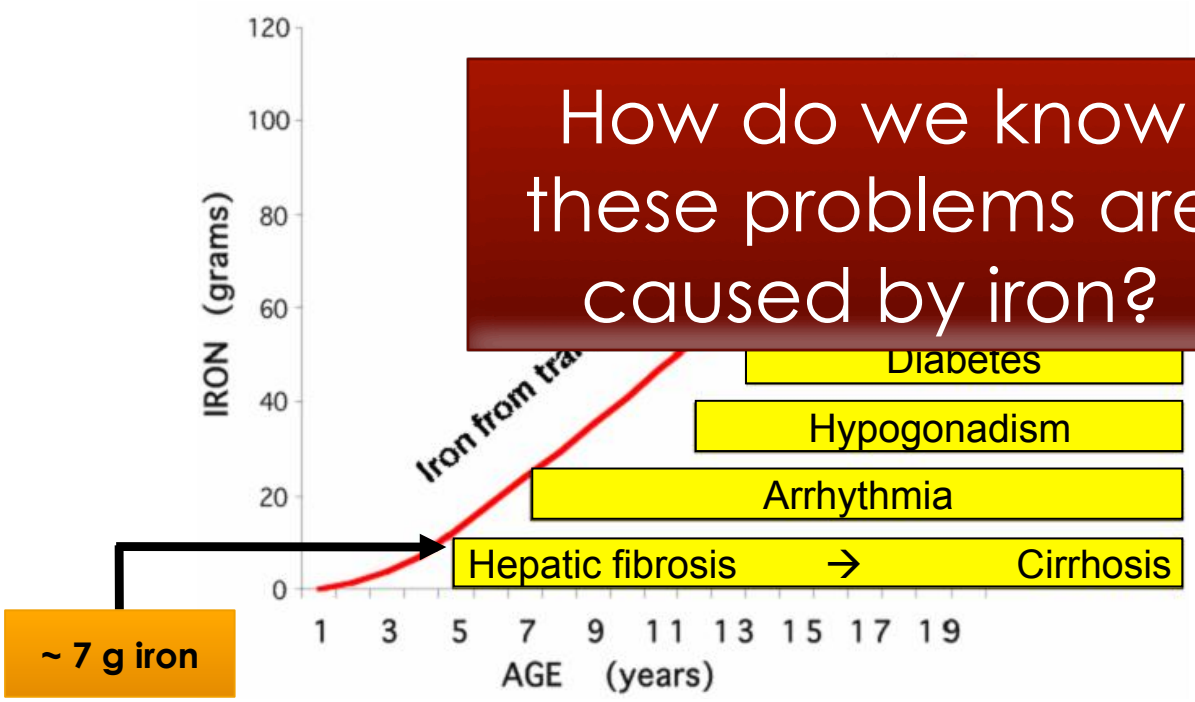


DMT-Divalent metal transporter
TfR-Transferrin receptor
ROI-reactive oxygen intermediates
ROS-reactive oxygen species

Cellular Effects of Free Iron

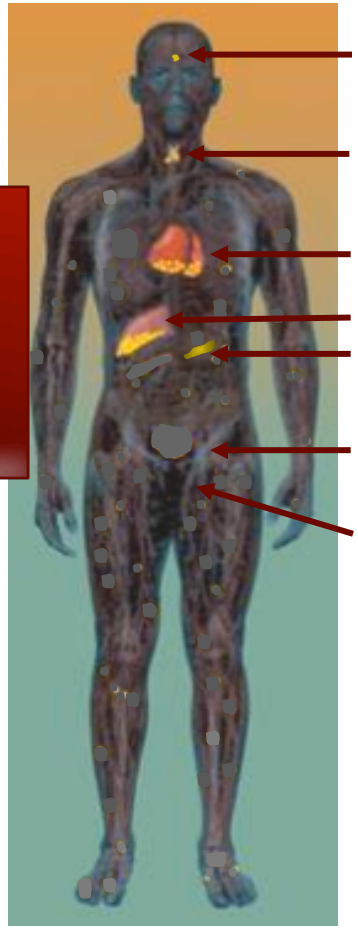


Iron Overload
Morbidity and Mortality

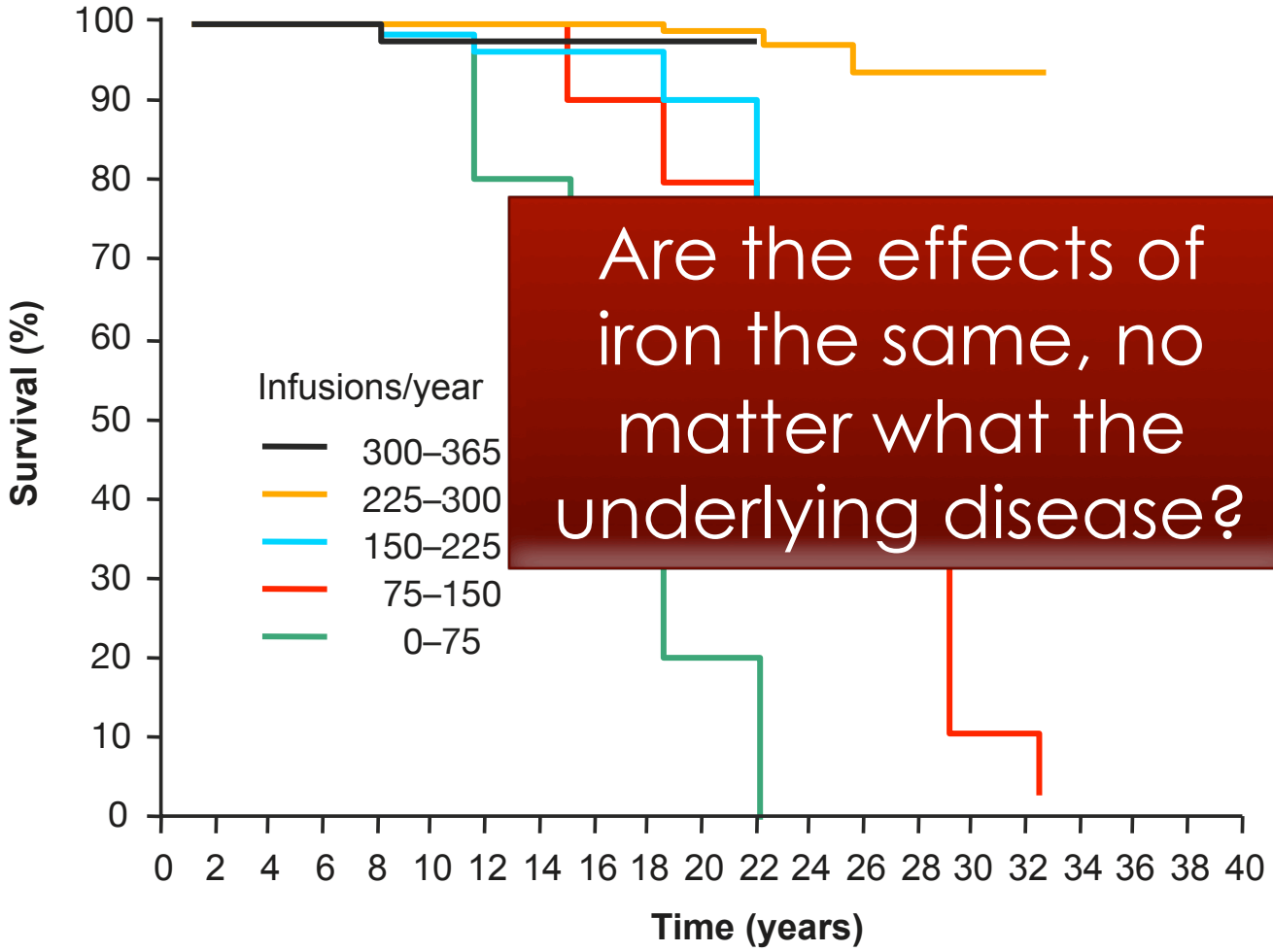


How do we know these problems are caused by iron?

Uncontrolled iron loading of organs



Iron Overload
Effect of iron chelation



Are the effects of iron the same, no matter what the underlying disease?

ıtion = survival

Comparison of organ dysfunction in thalassaemia major and sickle cell disease

Characteristic	Thalassaemia major	Sickle cell disease	p value
Age	18.4 ± 2.1	14.8 ± 1.0	NS
Duration of transfusion	12 years	6 years	
Serum ferritin (µg/L)	2,122 ± 289	2,916 ± 233	0.04
Liver iron (mg Fe/g dry wt)	14.8 ± 2.2	14.3 ± 1.4	NS
Transfusions (n/year)	12.2 ± 1.8	6.0 ± 0.6	0.002
Cardiac disease	20%	0%	0.002
Gonadal failure	33%	0%	< 0.001
Growth delay	27%	9%	NS
Hypothyroidism	7%	0%	NS
Viral hepatitis	33%	2%	< 0.001
Fibrosis	81%	29%	0.02

Despite similar Fe measures, SCD patients have fewer end-organ complications

Factors

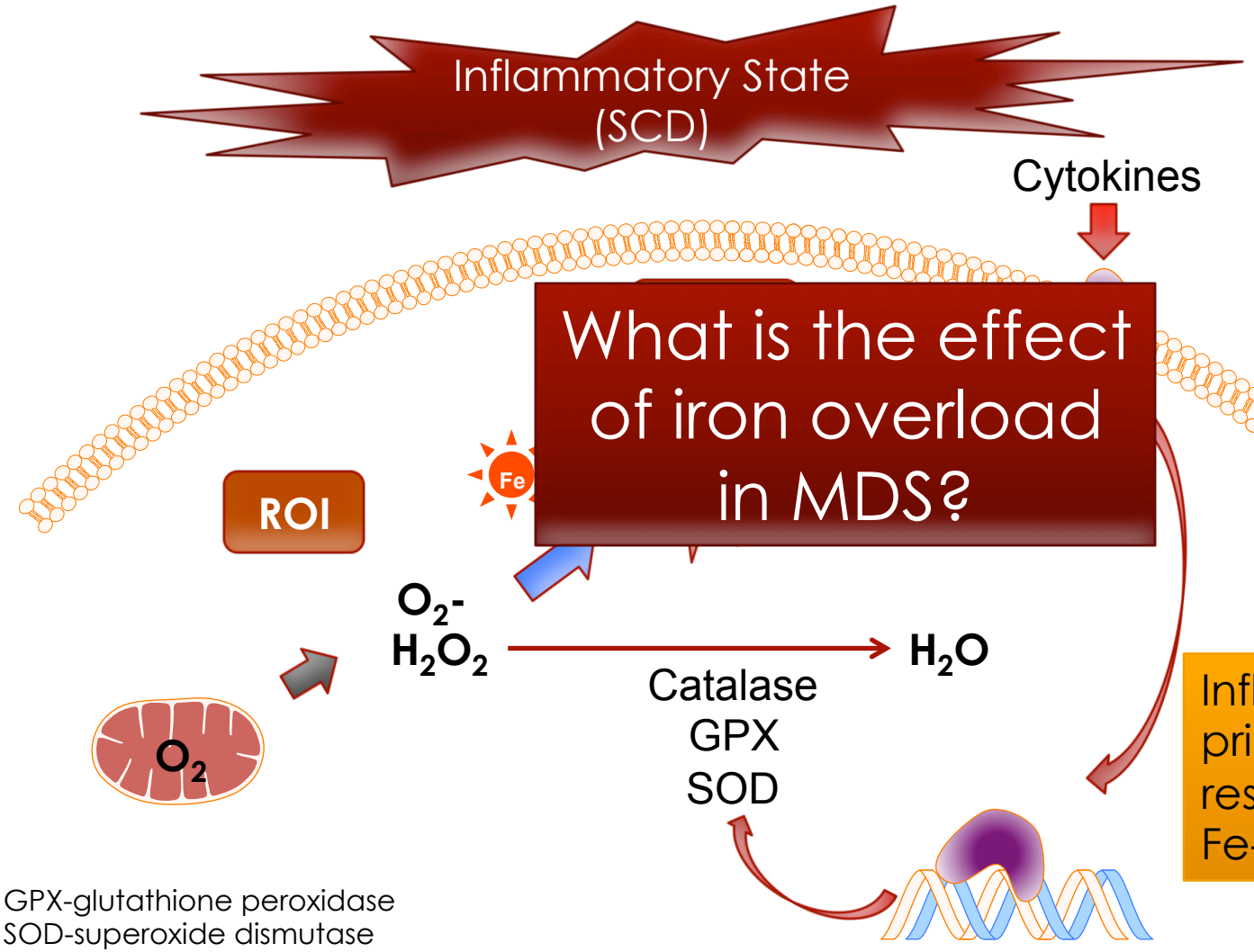
1. Duration of transfusion
2. TM vs. SCD

Why should this be?

NS = not significant.

Vichinsky E. Am J Hematol. 2005;80:70-4.

Inflammation Primes the Antioxidant Response

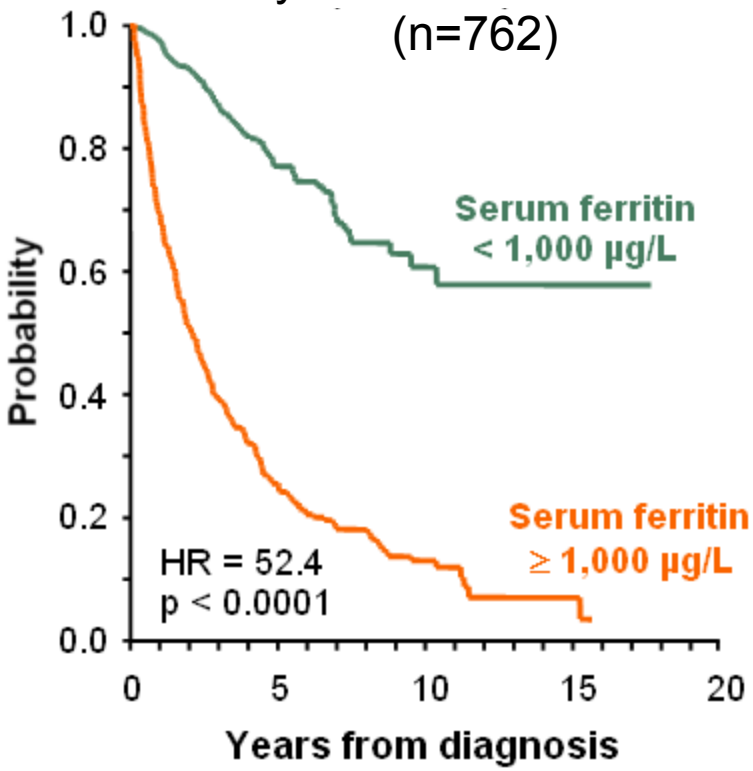


Inflammation in SCD primes the antioxidant response and reduces Fe-catalyzed ROS

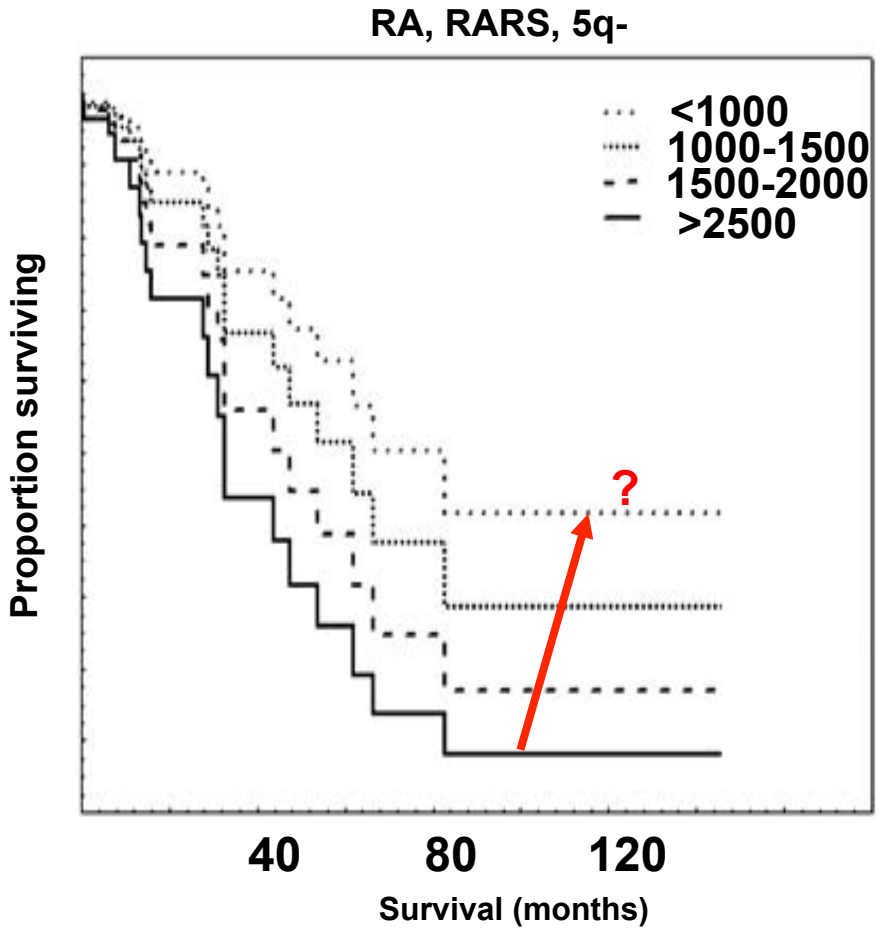
GPX-glutathione peroxidase
SOD-superoxide dismutase
ROI-reactive oxygen intermediates
ROS-reactive oxygen species

Does iron overload contribute to mortality in MDS?

Registry data
Overall survival
by serum ferritin level
(n=762)

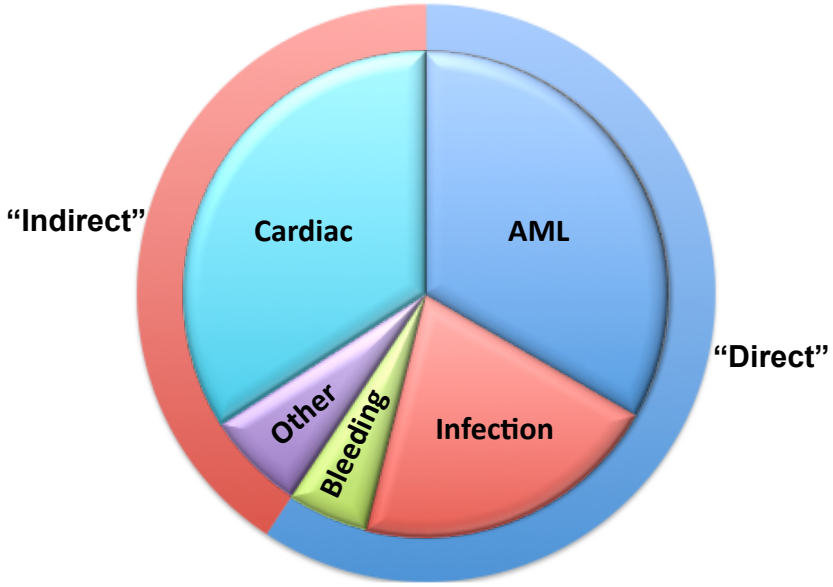


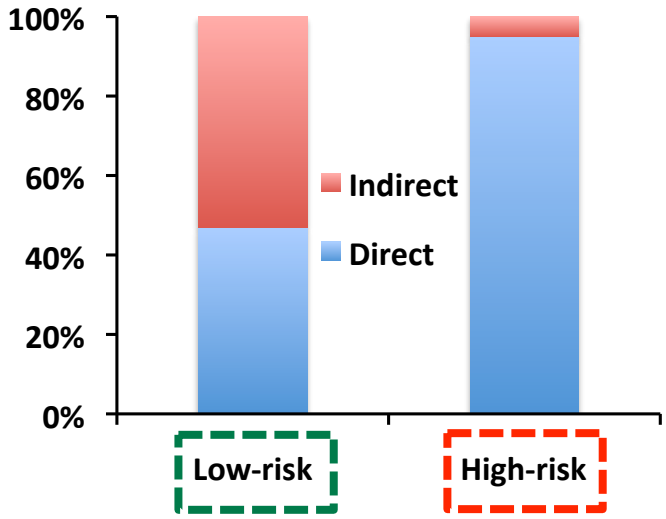
Sanz et al., Blood 2008 112 (abstract 640)



Malcovati et al., Haematologica, 2007

MDS Classification: Causes of death in MDS



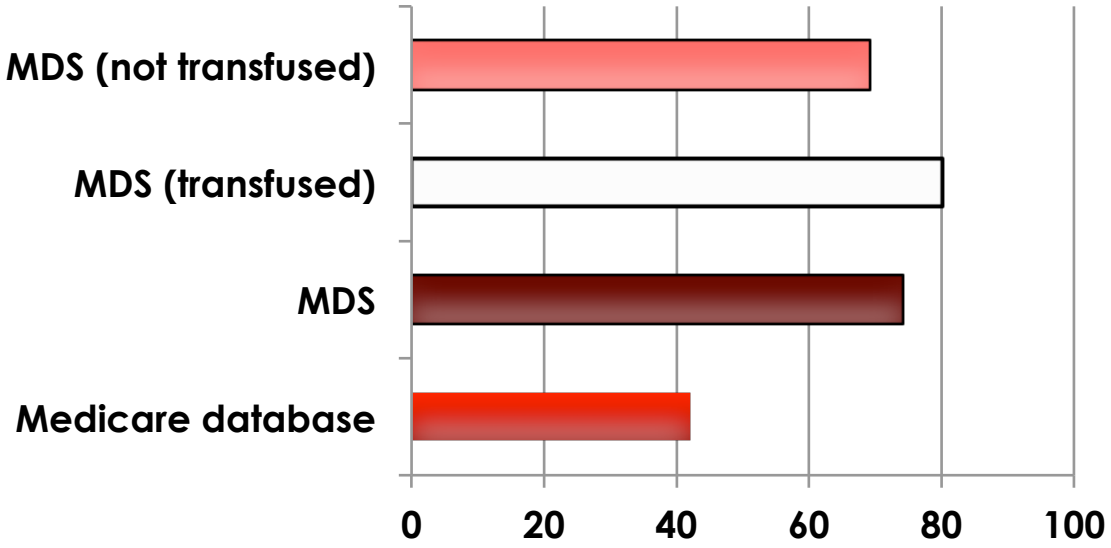


The goals of therapy are different in low-risk and high risk MDS

Malcovati et al., J. Clin. Oncol. 2005

Balduini et al., Hematologica 1999

The heart in MDS



Rates of heart disease in US medicare patients

"MDS cardiomyopathy": chronic anaemia + iron overload + the aged myocardium

Goldberg et al., ASH 2008

Cardiac iron in patients with MDS

	N	Cardiac iron	Units transfused	Serum ferritin (µg/L)	Chelated
Jensen et al. 2003	12	9	44–254	1,740–8,715	0
Chacko et al.					6
Konen et al.					7
Di Tucci et al					2
Pascal et al.					54

HOWEVER: There is **no obvious relationship** between cardiac iron and heart problems in MDS

Pascal et al., ASH 2010, Abstract 2906

Di Tucci AA, et al. Haematologica. 2008;93:1385-8.
Chacko J, et al. Br J Haematol. 2007;138:587-93.
Jensen PD, et al. Blood. 2003;101:4632-9.
Konen E, et al. Am J Hematol. 2007;82:1013-6.

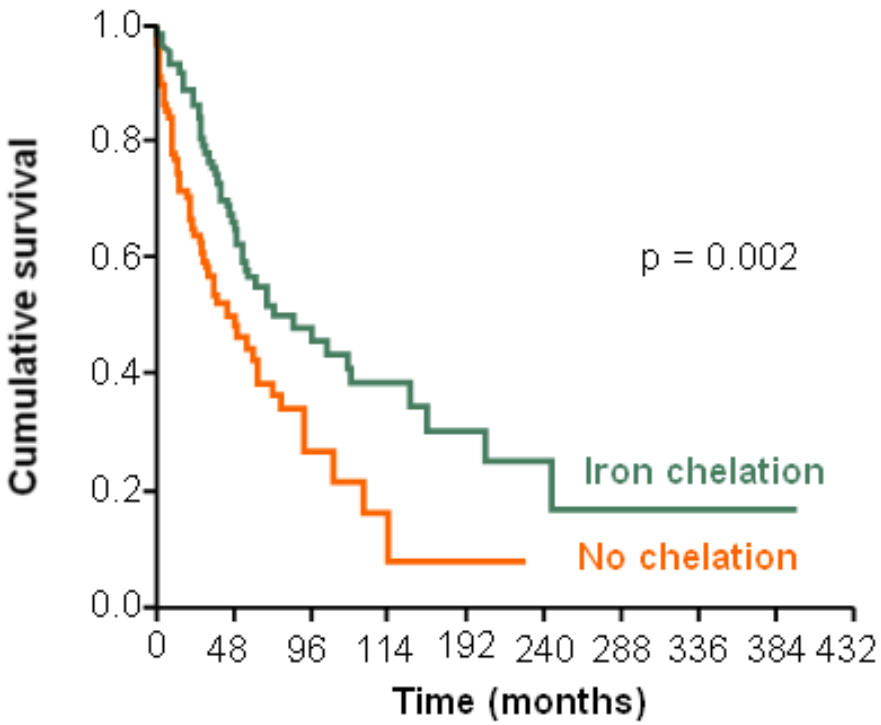
Should iron chelation be given in MDS?

Ferroscepticism

TELESTO

- DeLoughery TG. Iron: The fifth horseman of the apocalypse? Am J Hematol. 2009
- Myelodysplasia paranoia: iron as the new radon. Leuk Res. 2009
- Tefferi A, Stone RM. Iron chelation therapy in myelodysplastic syndrome—Cui bono? Leukemia. 2009

Iron chelation and survival in MDS



Fox Blood 2009; 114 (abstract 1747)

Leitch (Clin Leuk Res 2008)

- **178 pt**
- **OS in ICT >160 mo**
- **OS in non-ICT = 40 mo**
- **p<0.03**

- **Rose** (ASH 2007)
  - **170 pt**
  - **OS 115 vs. 51 mo**
  - **p< 0.0001**

- **Fox** (ASH 2009)
  - **186 pt (matched pairs)**
  - **OS in ICT = 75 mo**
  - **OS in non-ICT = 49 mo**
  - **P=0.002**

Available online at www.sciencedirect.com
ScienceDirect
Leukemia Research 32 (2008) 1338–1353
Leukemia Research
www.elsevier.com/locate/leukres

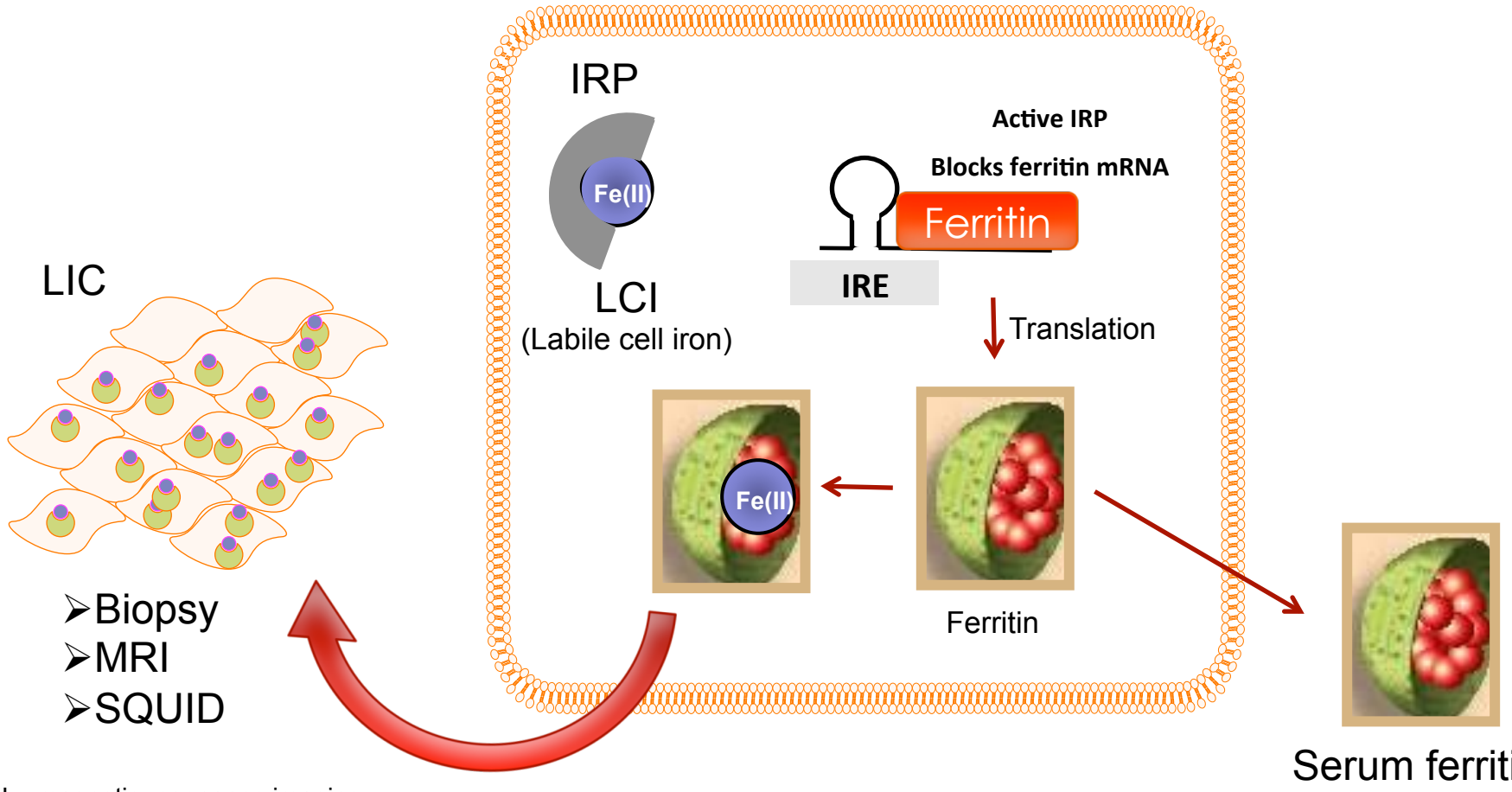
Invited editorial

Iron overload in myelodysplastic syndromes: A Canadian consensus guideline

Richard A. Wells[a,*], Brian Leber[b], Rena Buckstein[a], Jeffrey H. Lipton[c], Wanda Hasegawa[d], Kuljit Grewal[e], Karen Yee[c], Harold J. Olney[f], Loree Larratt[g], Linda Vickars[h], Alan Tinmouth[i]

- Lower-risk MDS if life exp > 1y
- Higher-risk MDS if BMT candidate
- Either desferal or exjade as first line
- Target ferritin < 1000 ng/mL

Direct and Indirect Measurement of Iron



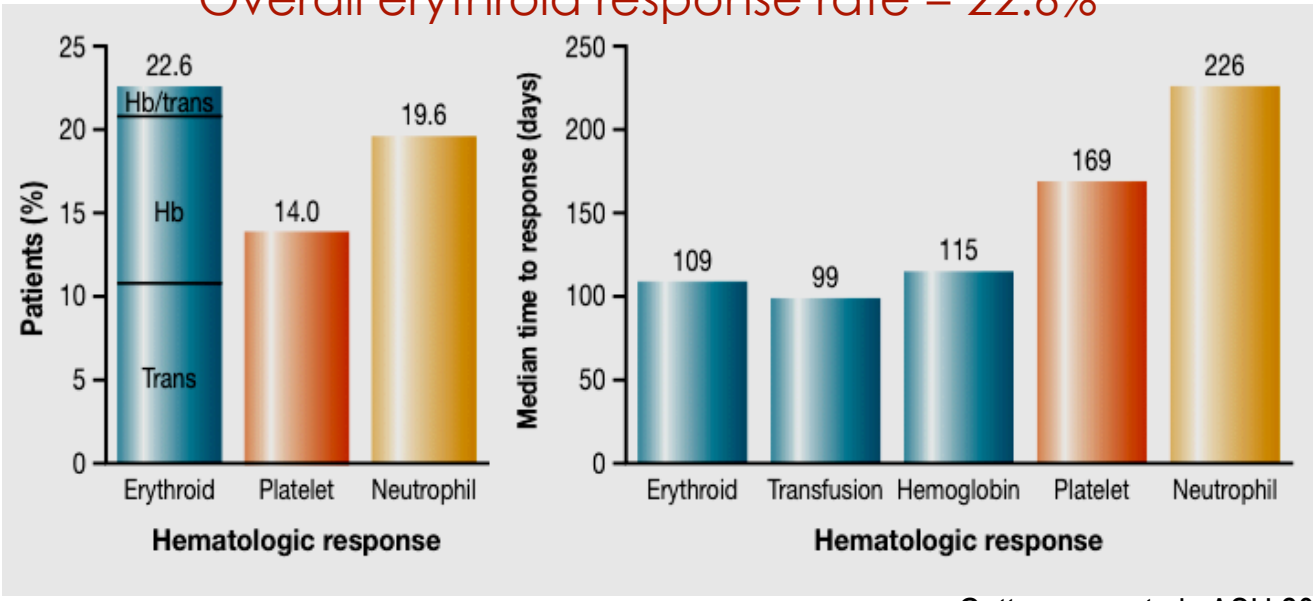
MRI = magnetic resonance imaging;
SQUID = superconducting quantum interference device.

Unexpected effects of iron in MDS

Iron and Haematopoiesis in MDS

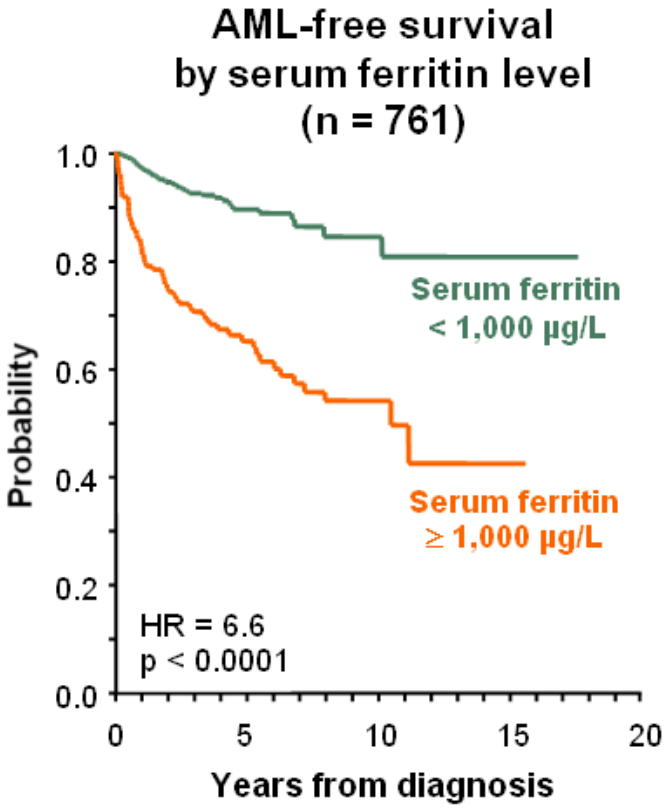
Analysis of trial data to study haematological responses in the MDS patients in EPIC (N=341)

Overall erythroid response rate = 22.6%



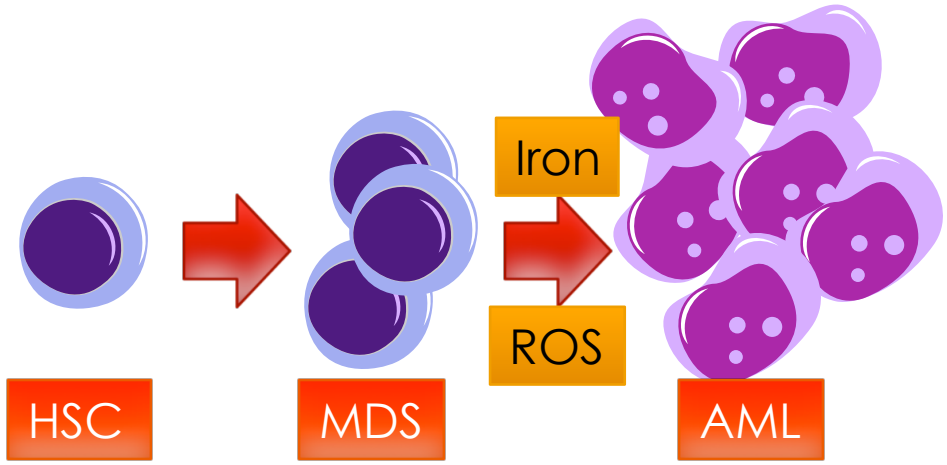
Gattermann et al., ASH 2010, Abstract 2912

Iron and AML in MDS



Sanz G, et al. Blood. 2008;112:[abstract 640].

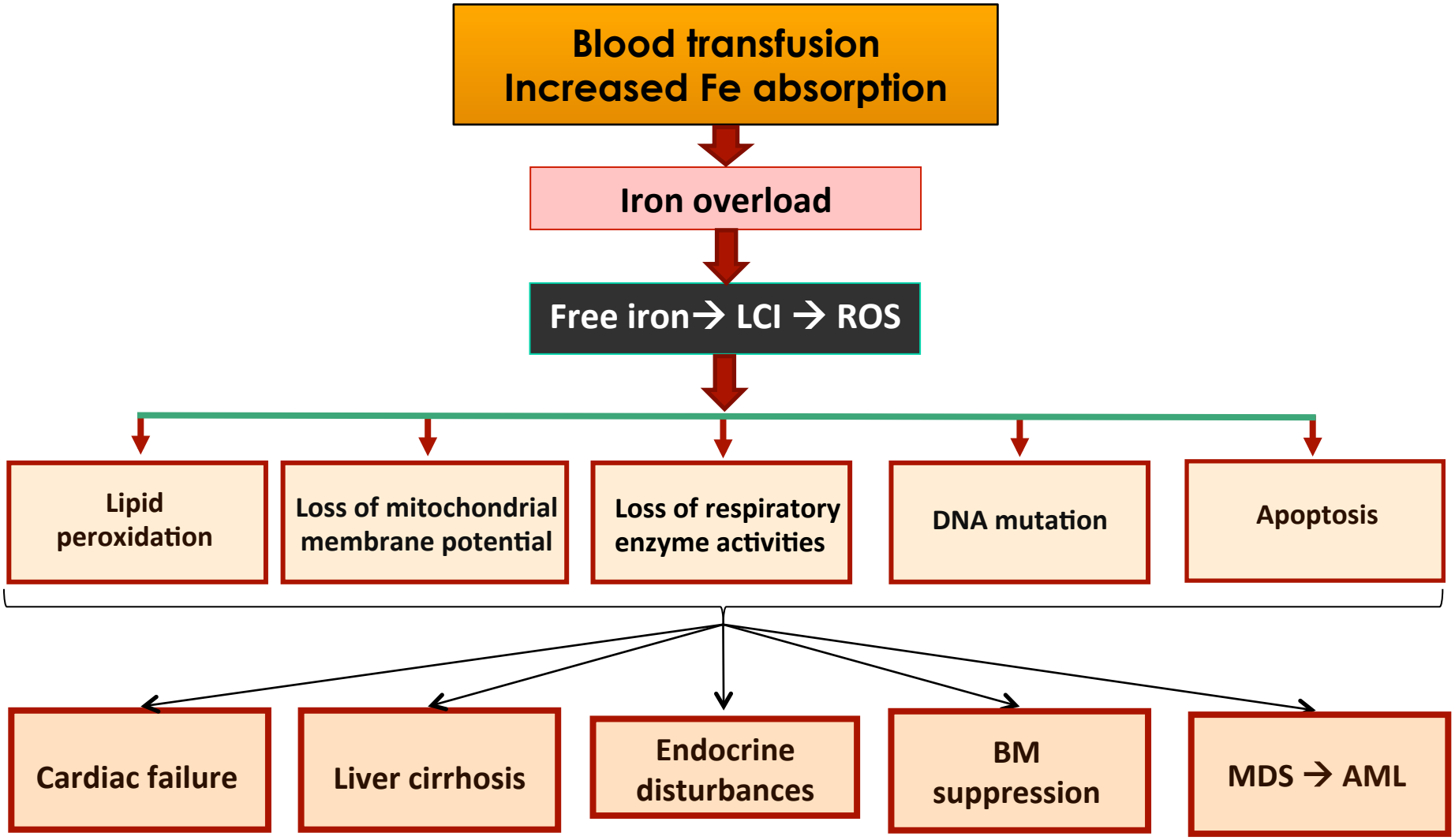
How could IOL promote development of AML?



- Fe causes DNA damage in vitro
- Fe accelerates development of AML in mouse model

Chan et al., ASH 2010, Abstract 122

Summary
Iron Toxicity



Conclusions

- Iron is both essential and toxic -- balance is maintained by an intricate network of proteins
- Chronic RBC transfusion overwhelms this network, resulting in the presence of “free iron”, which causes cell and organ damage via generation of free radicals
- Fe toxicity leaves different footprints in TM, SCD, and MDS
- Chelation therapy can prevent chronic Fe toxicity but must be monitored by indirect (ferritin) or direct (LIC) means

Any questions?