Isn't It Ironic: BMPs and the Relationship Between Iron and Bone

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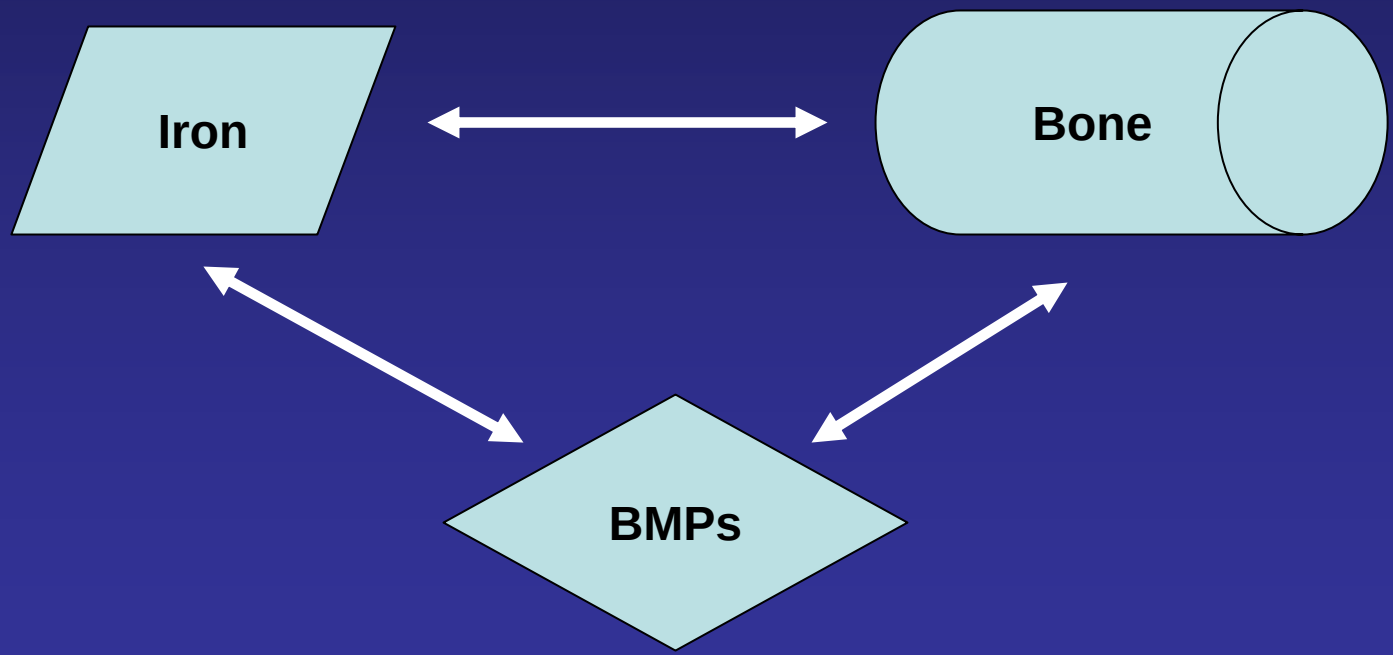
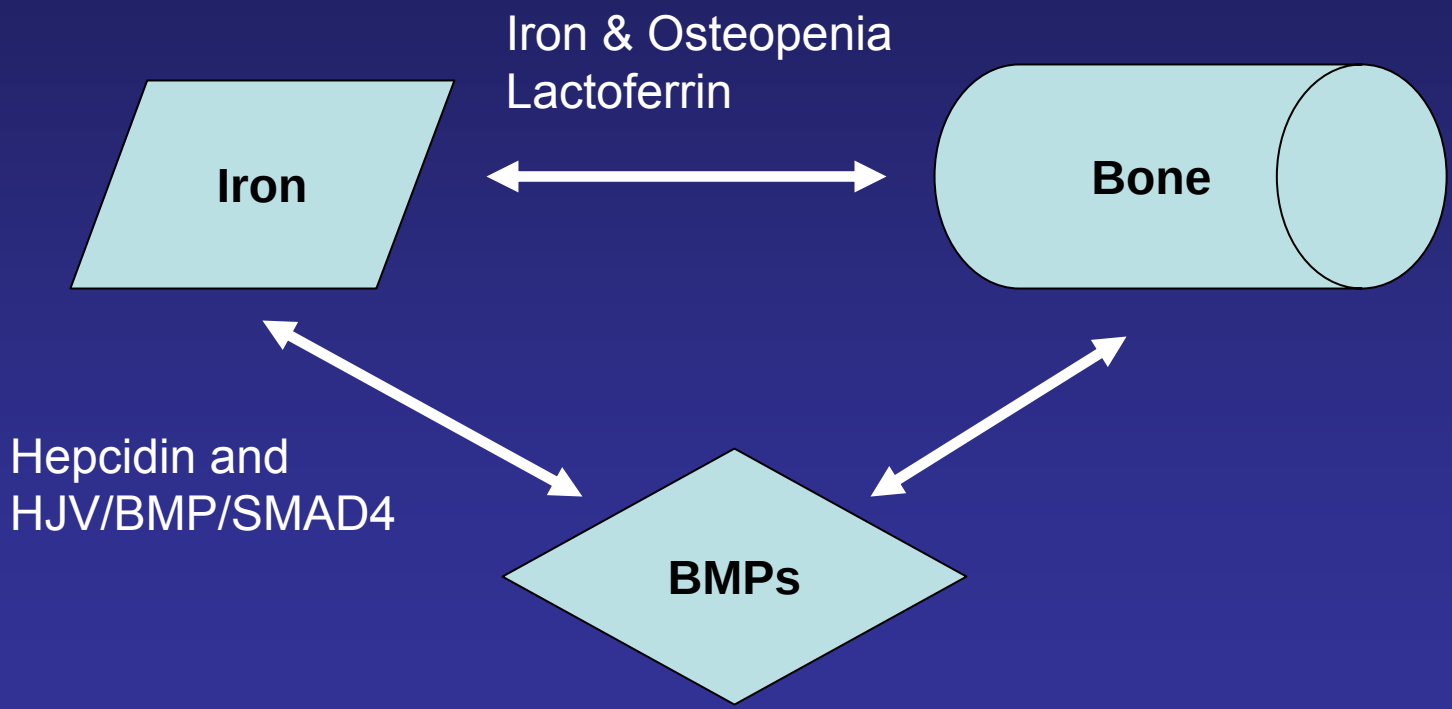
Associate Professor of Pediatrics,
Biochemistry & Molecular Biology
Saint Louis University School of Medicine

General Outline



General Outline



Iron & Bone: Hereditary Hemochromatosis

- Autosomal recessive disorder
- Due to common mutation in HFE gene
- Low clinical penetrance
- Hepatic iron overload
- Low hepcidin levels

Iron and Osteopenia

- Sickle Cell Disease
- Thallesemia
- HH
- Transfusion iron overload
- Post-menopause

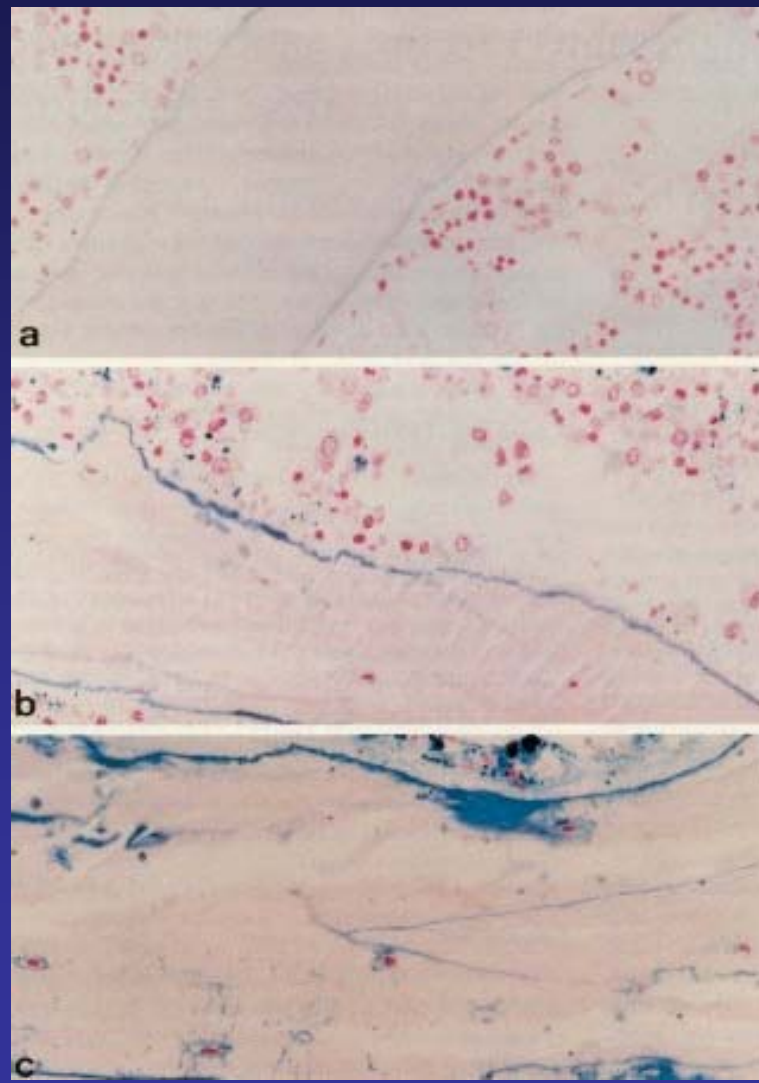
Bone Disease in Hemochromatosis

- Fractures
  - case reports
- Osteoporosis
  - 29-34%
- Osteopenia
  - 71-79%

Stainable bone iron in undecalcified, plastic-embedded sections. Occurrence in man related to the presence of "free" iron

H Laeng, T Egger, C Roethlisberger and H Cottier

- 2.3% of 1536 iliac crest biopsies in patients without HH
- 4/4 with HH
- 11/15 vertebral bone fragments with HH
- Correlates with presence of NTBI
- Found at “osteoid seam”

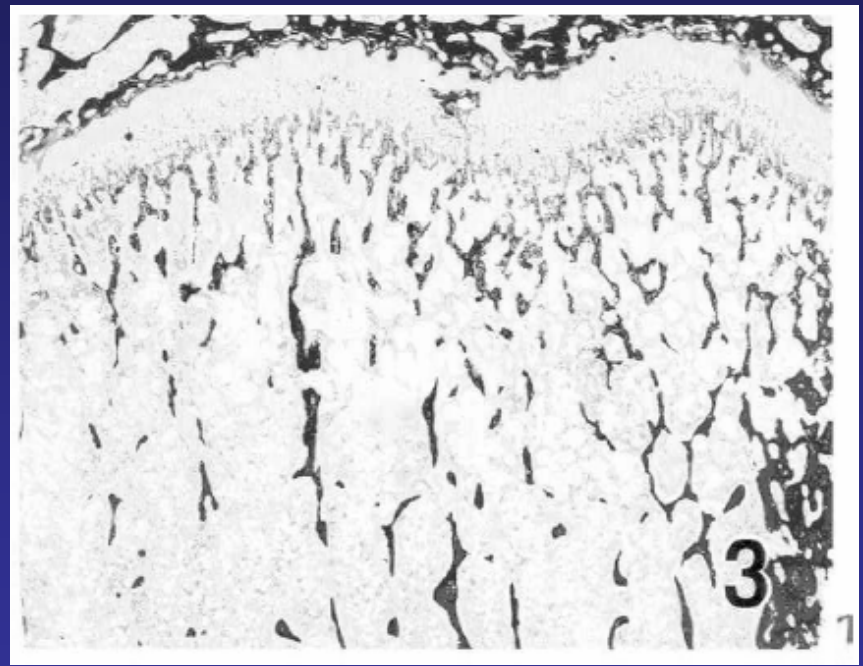


American Journal of Pathology, Vol 131: 344-350, 1988

Iron Lactate-Induced Osteopenia in Male Sprague-Dawley Rats

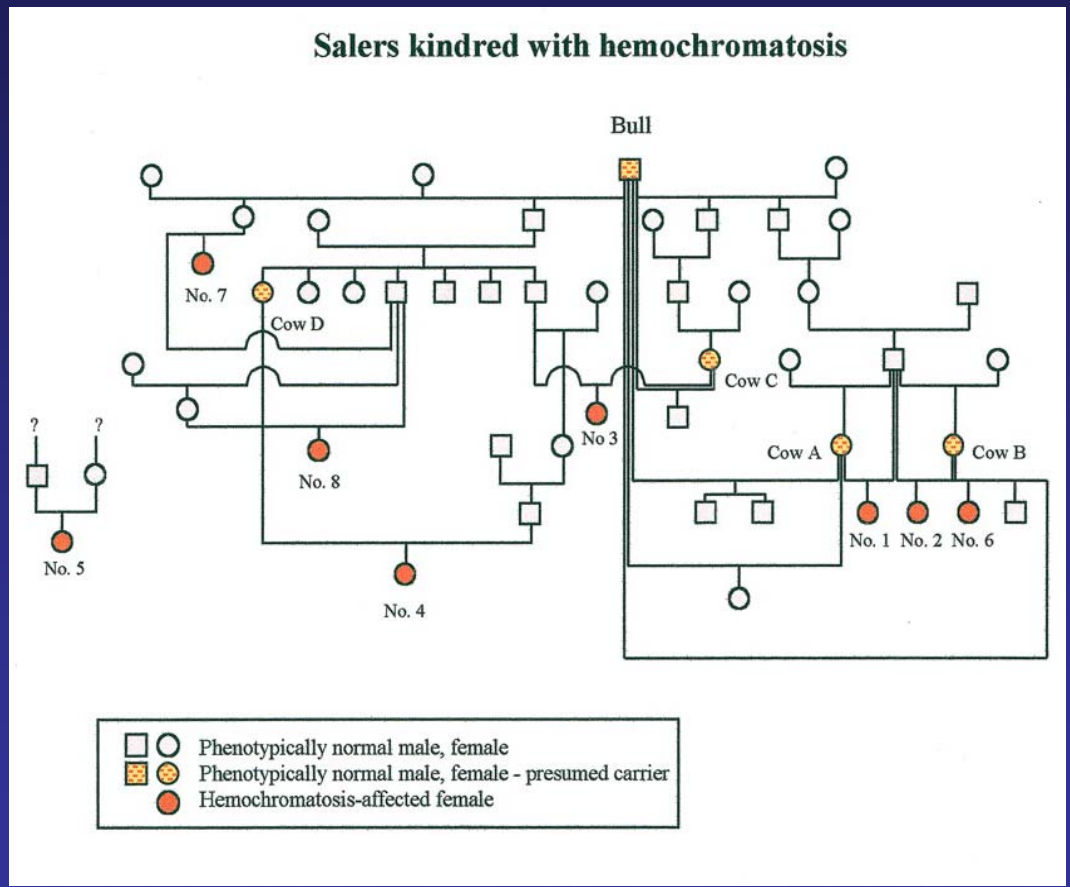
SHUUICHI MATSUSHIMA,[1,2] MARIKO HOSHIMOTO,[1] MIKINORI TORII,[1] KIYOKAZU OZAKI,[2] AND ISAO NARAMA[2]

[1]*Pathology Section, Drug Safety Evaluation, Developmental Research Laboratories, Shionogi & Co, Ltd, Toyonaka, Osaka, Japan*
[2]*Research Institute of Drug Safety, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka, 573-0101, Japan*

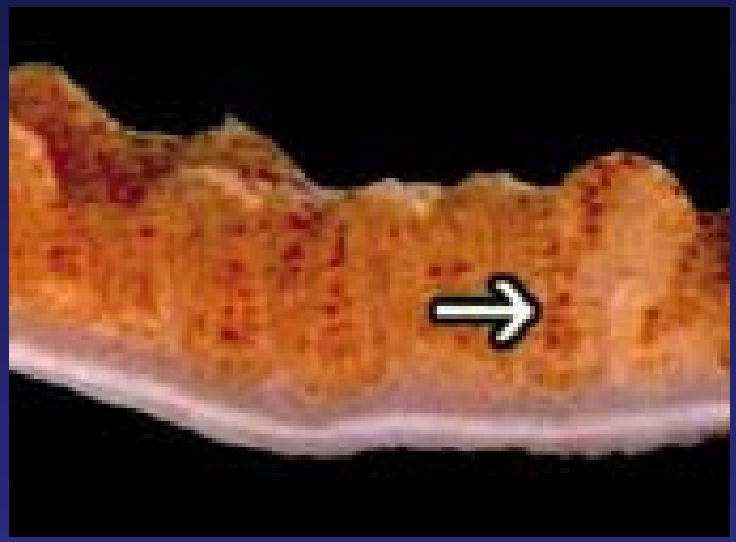


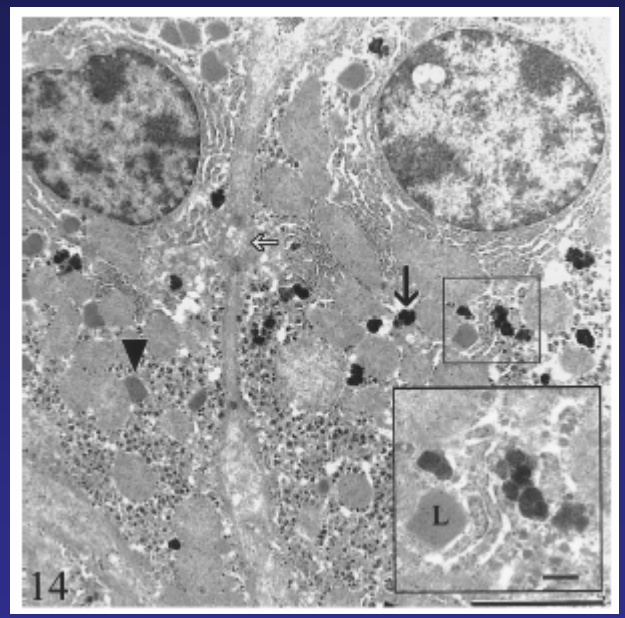
TOXICOLOGIC PATHOLOGY, vol 29, no 6, pp 623–629, 2001

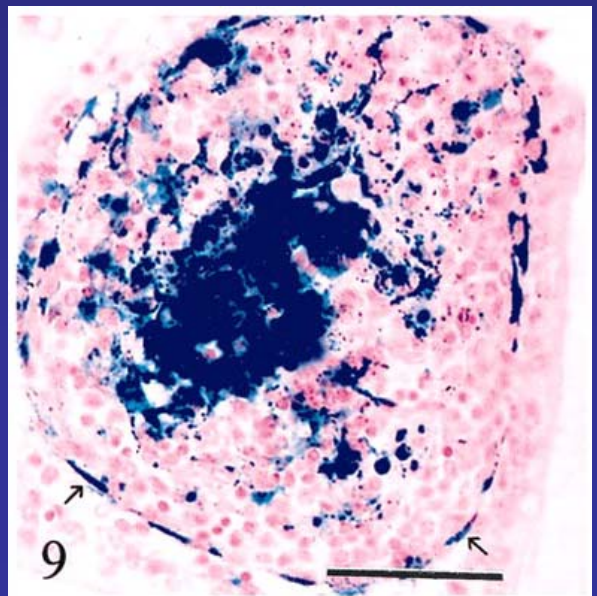
Hemochromatotic Salers Cattle



Hemochromatotic Salers Cattle

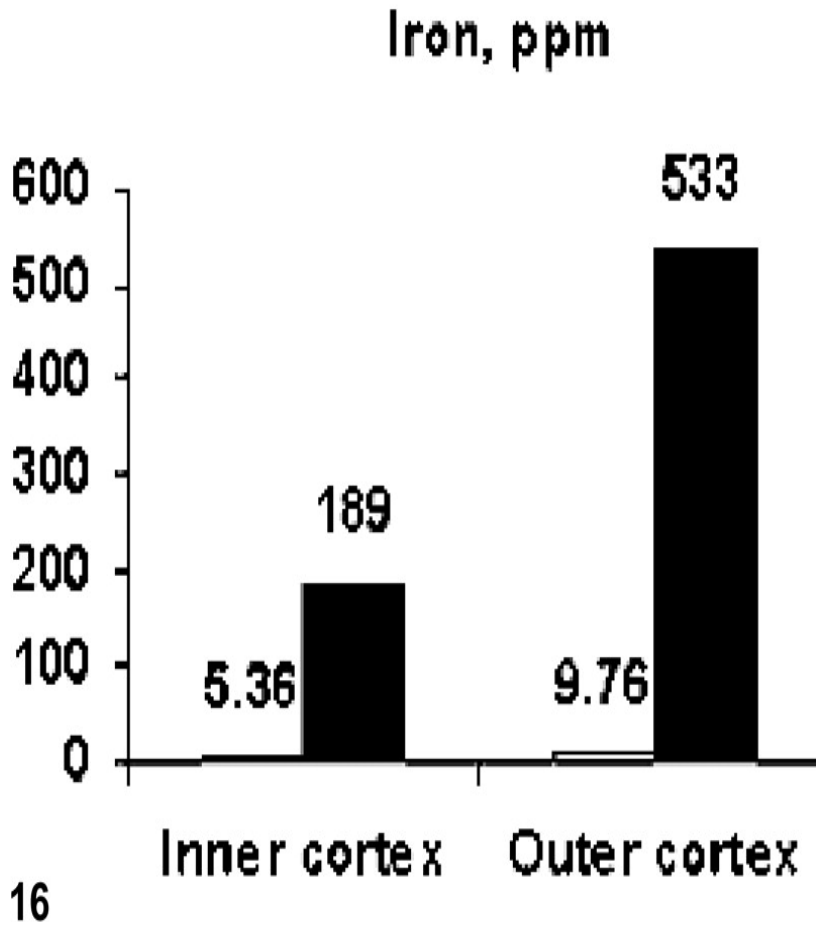




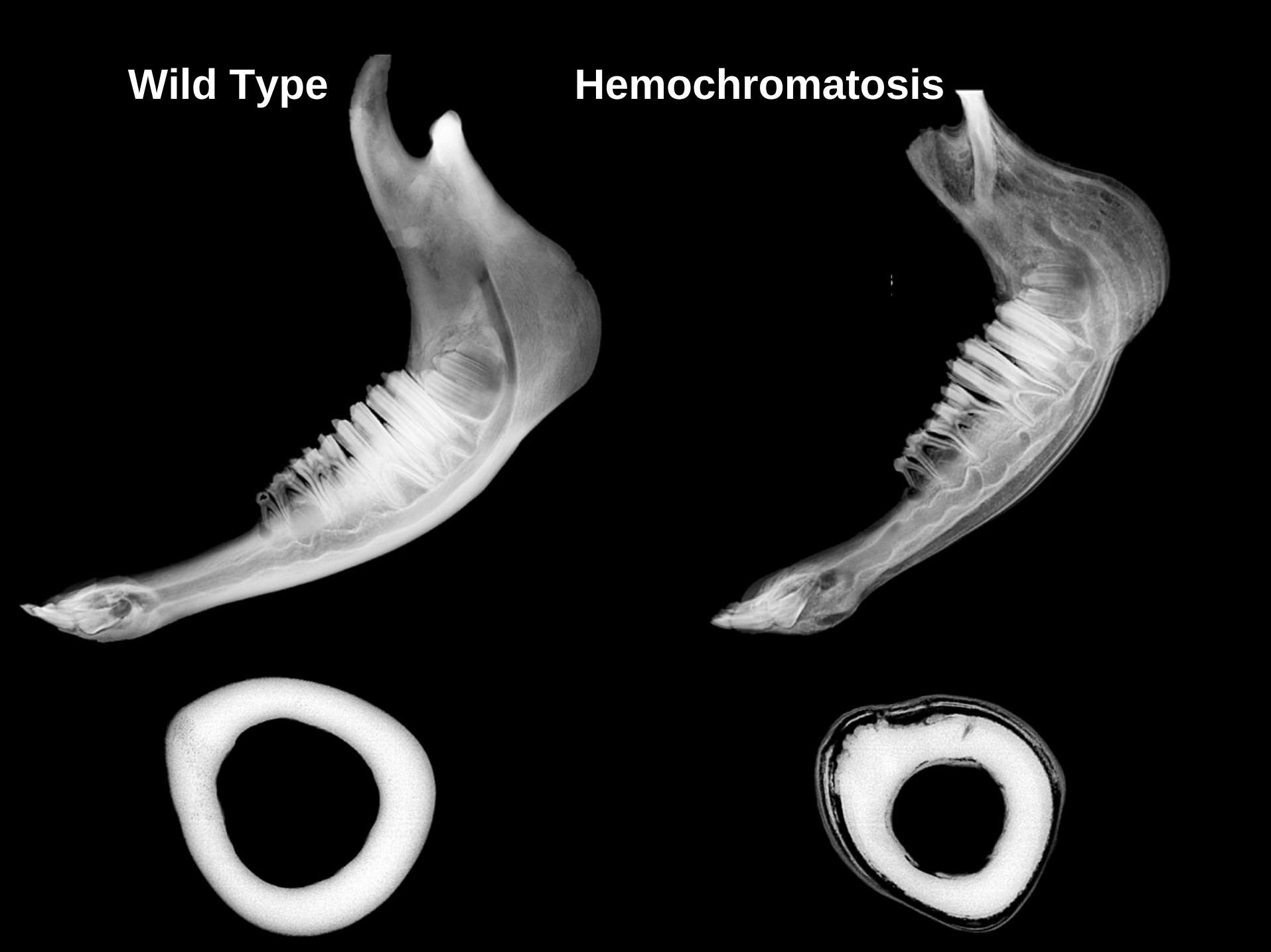


Skeletal Changes in Hemochromatosis of Salers Cattle

R. W. NORRDIN, K. J. HOOPES, AND D. O'TOOLE



Vet Pathol **41**:612–623 (2004)


Wild Type
Hemochromatosis

Age-associated Iron Accumulation in Bone: Implications for Postmenopausal Osteoporosis and a New Target for Prevention and Treatment by Chelation

Liu G, Men P, Kenner GH, Miller SC

- Ovarectomized rat model of postmenopausal osteoporosis
- Severity of osteoporosis associated with iron accumulation in bone
- Mitigated by bone-targeted chelator

Biometals. 2006 May 11

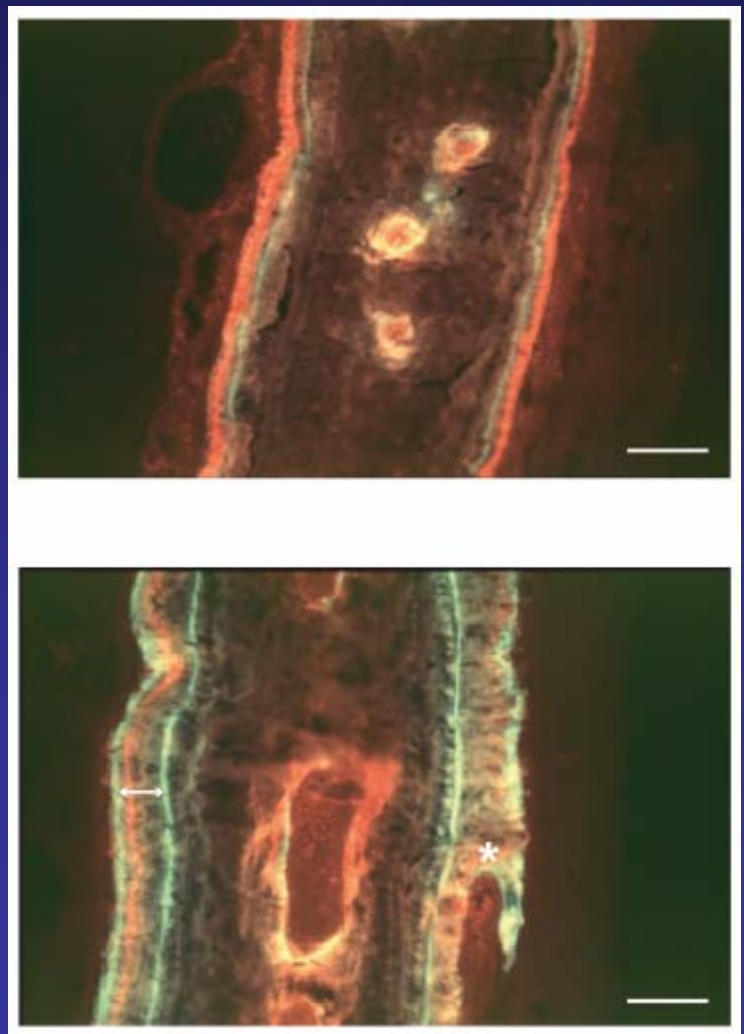
Potential Mechanisms for Iron-Related Osteopenia

- Hypogonadism
- Hyperparathyroidism
- Iron toxicity
- “Unknown factor”

Lactoferrin Is a Potent Regulator of Bone Cell Activity and Increases Bone Formation *in Vivo*

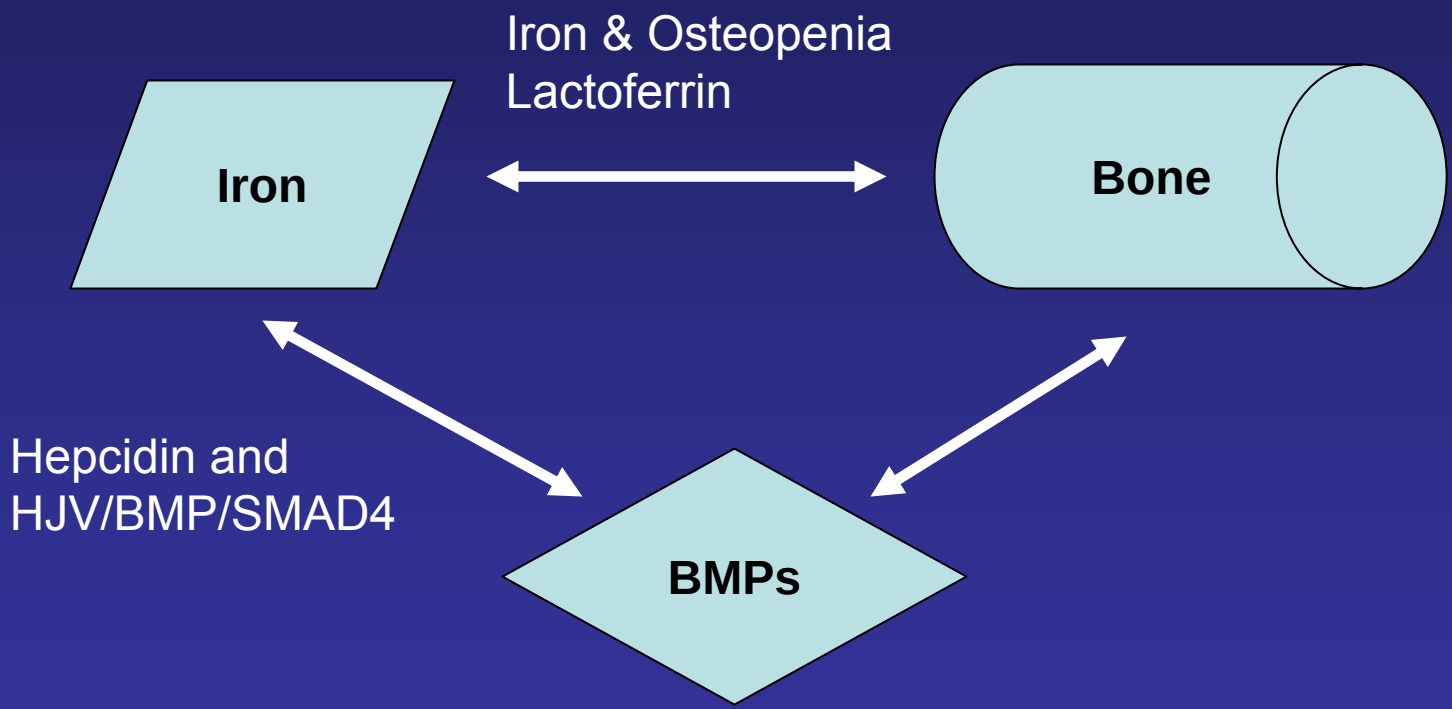
JILLIAN CORNISH, KAREN E. CALLON, DORIT NAOT, KATE P. PALMANO, TATJANA BANOVIC, USHA BAVA, MAUREEN WATSON, JIAN-MING LIN, P. C. TONG, QI CHEN, VINCENT A. CHAN, HELEN E. REID, NICK FAZZALARI, HEATHER M. BAKER, EDWARD N. BAKER, NEILL W. HAGGARTY, ANDREW B. GREY, AND IAN R. REID

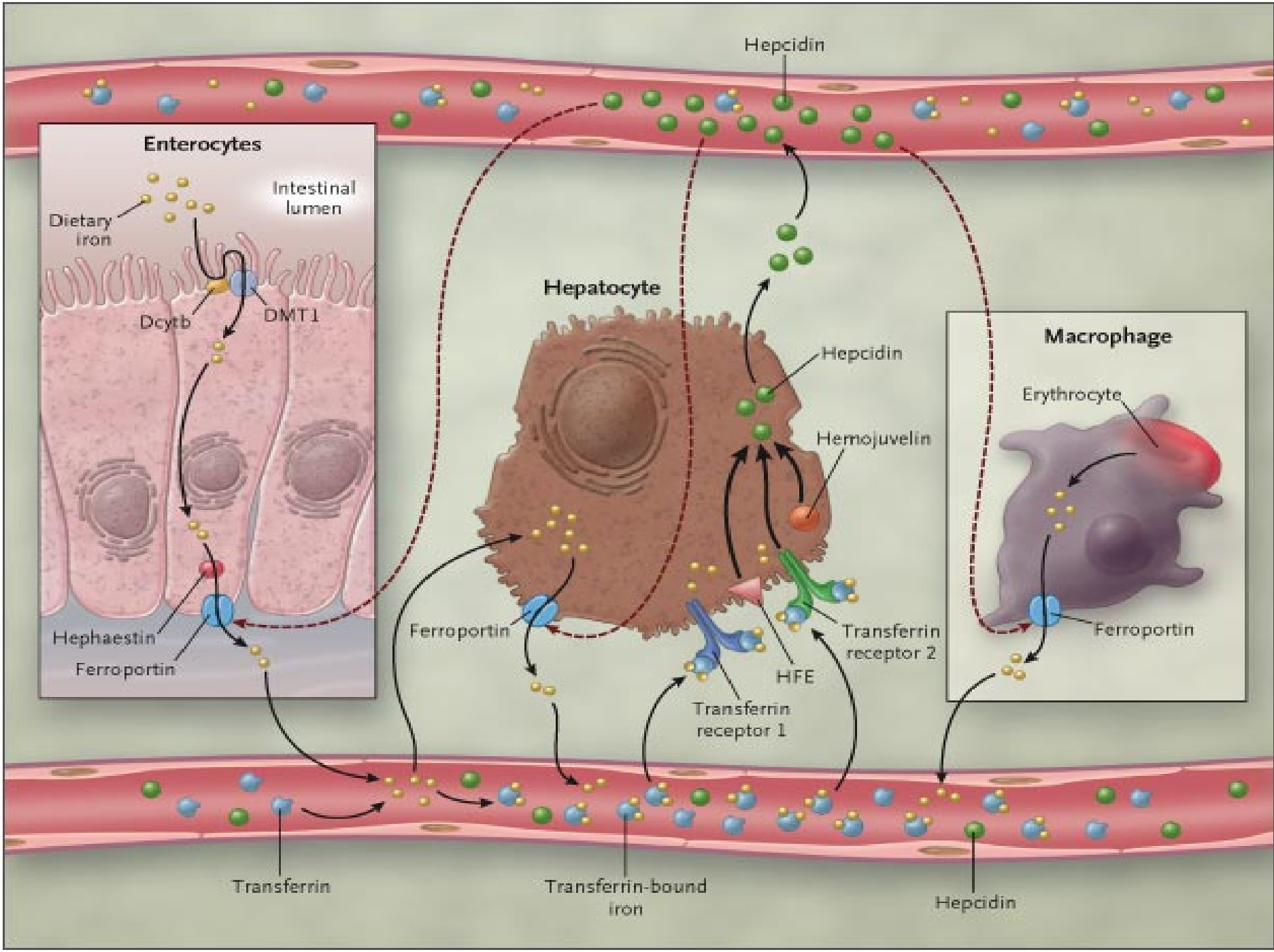
- Lactoferrin
  - Member of transferrin family
  - Iron binding protein
  - Produced by exocrine glands, neutrophils
- Anabolic to bone
  - Stumulator of osteoblast proliferation, differentiation
  - Inhibitor of osteoclastogenesis



Endocrinology 145(9):4366–4374, 2004

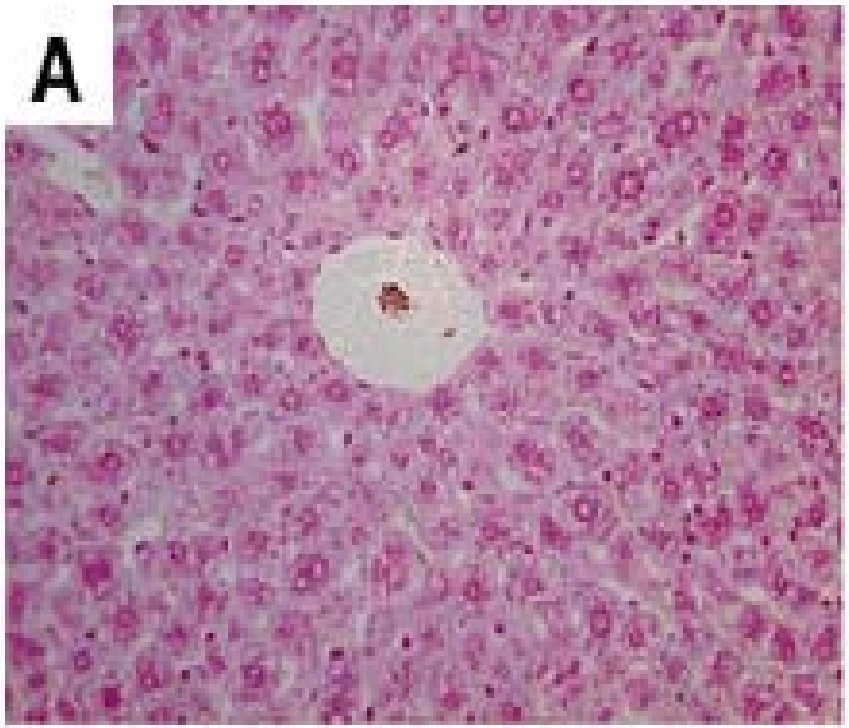
General Outline

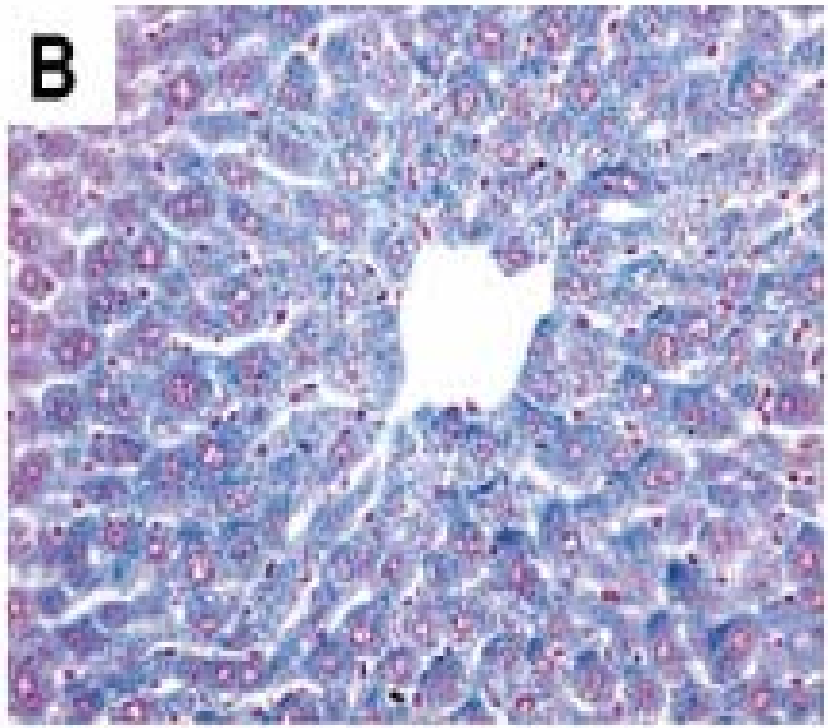



Hepcidin
Enterocytes
Intestinal lumen
Dietary iron
Dcytb
DMT1
Hephaestin
Ferroportin
Hepatocyte
Hepcidin
Hemojuvelin
Ferroportin
Transferrin receptor 2
HFE
Transferrin receptor 1
Macrophage
Erythrocyte
Ferroportin
Transferrin
Transferrin-bound iron
Hepcidin

A role of SMAD4 in iron metabolism through the positive regulation of hepcidin expression

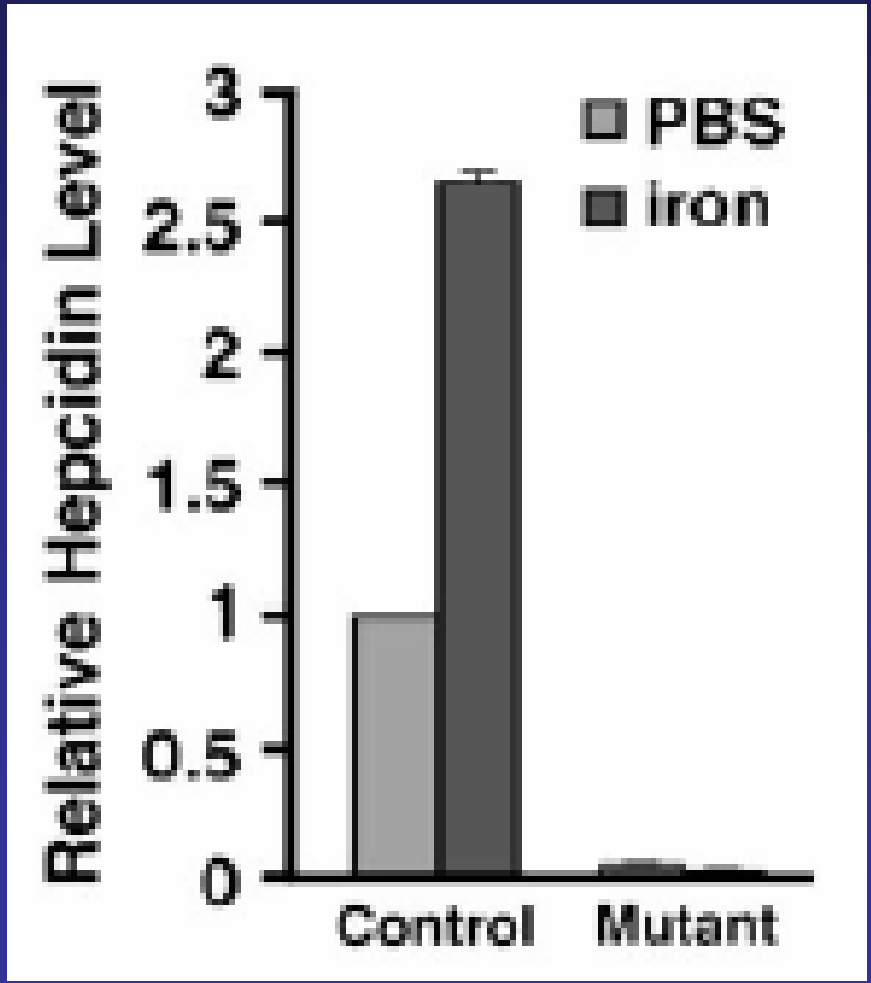
Rui-Hong Wang,[1,5] Cuiling Li,[1,5] Xiaoling Xu,[1] Yin Zheng,[1] Cuiying Xiao,[1] Patricia Zerfas,[2] Sharon Cooperman,[3] Michael Eckhaus,[2] Tracey Rouault,[3] Lopa Mishra,[4] and Chu-Xia Deng[1,*]



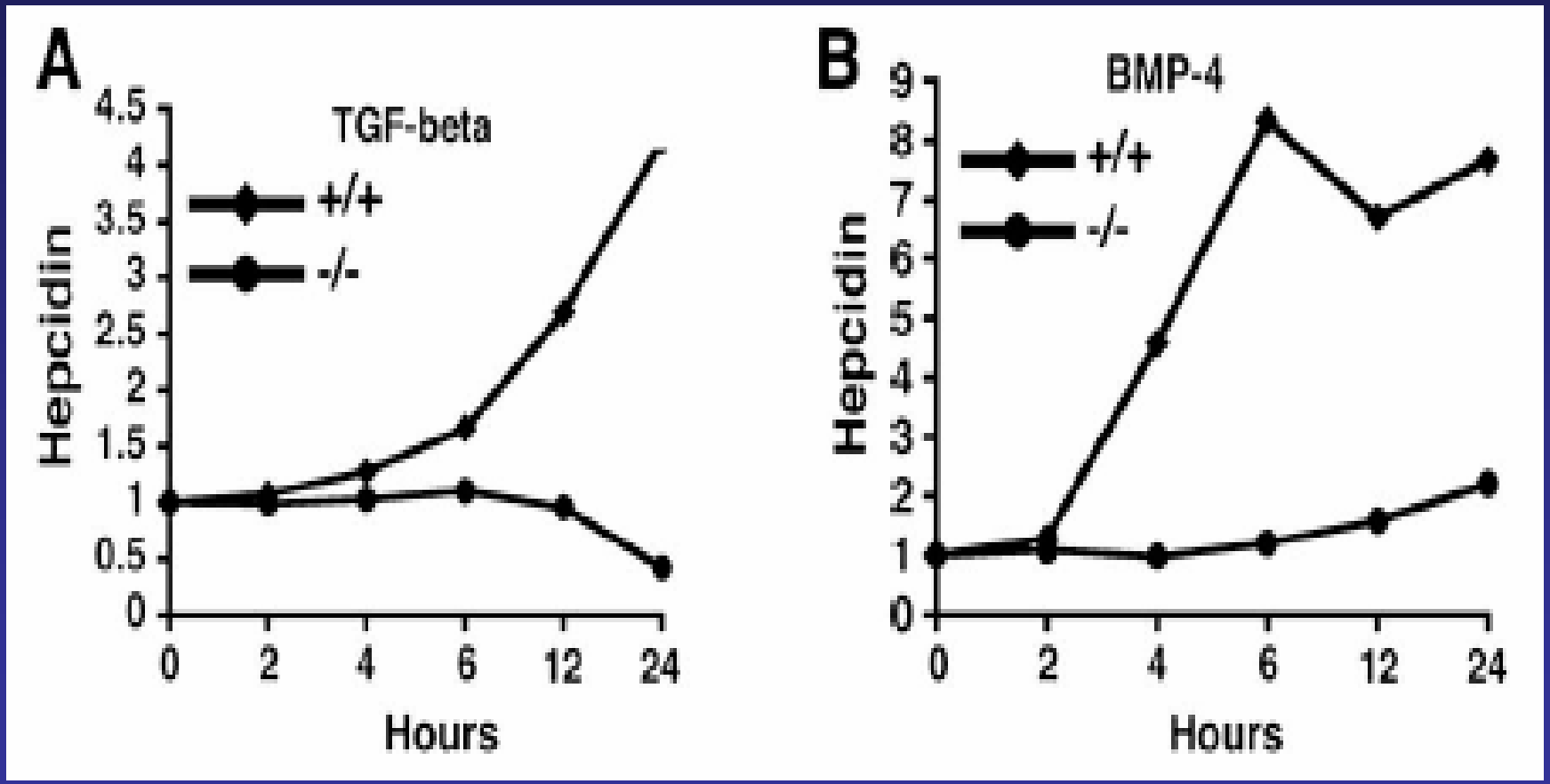


CELL METABOLISM : DECEMBER 2005 VOL. 2, P. 399-409

Loss of Hepcidin Regulation in Haptocellular SMAD4 KO Mice

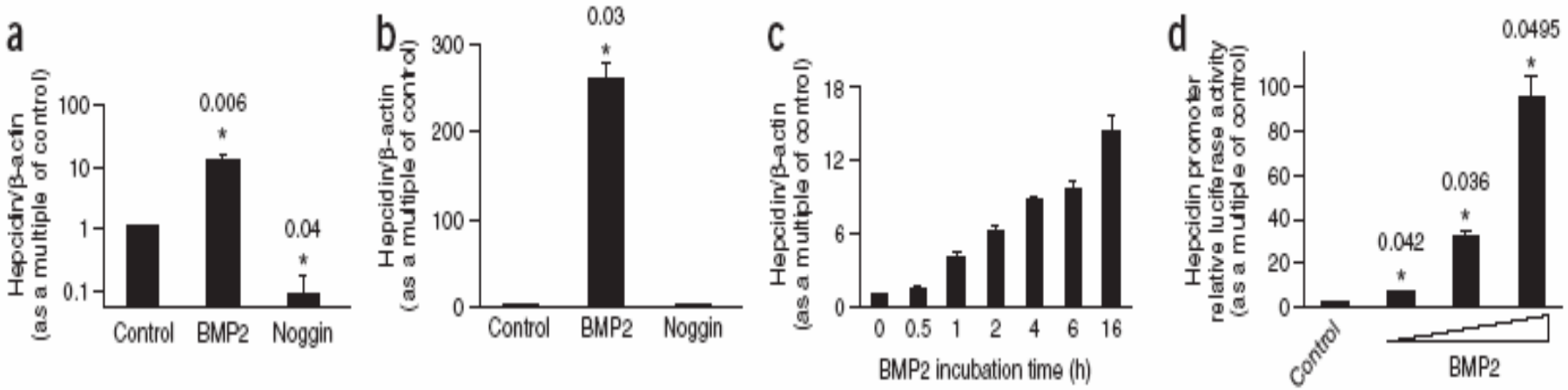


BMPs Regulate Hepatocellular Hepcidin Expression

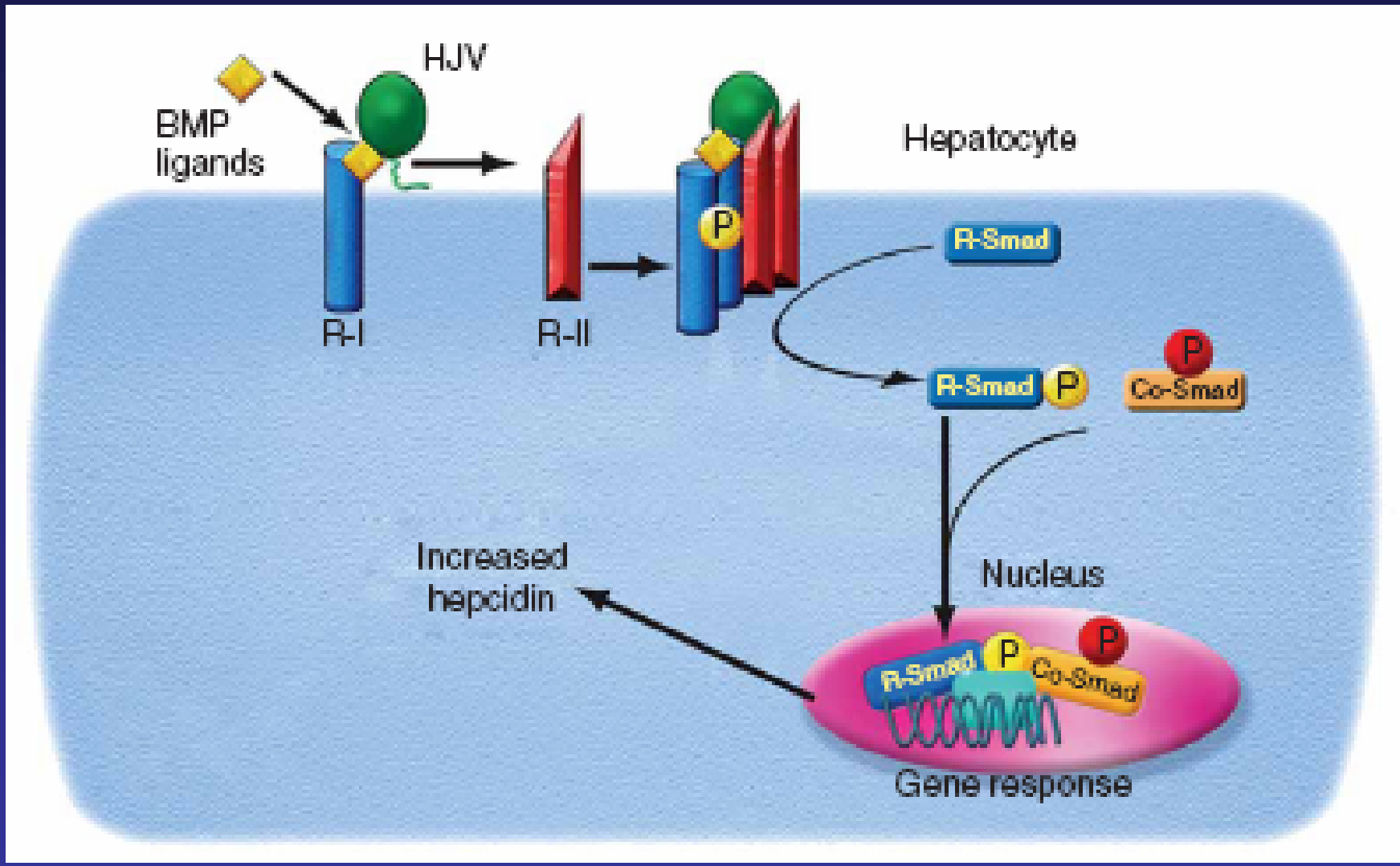


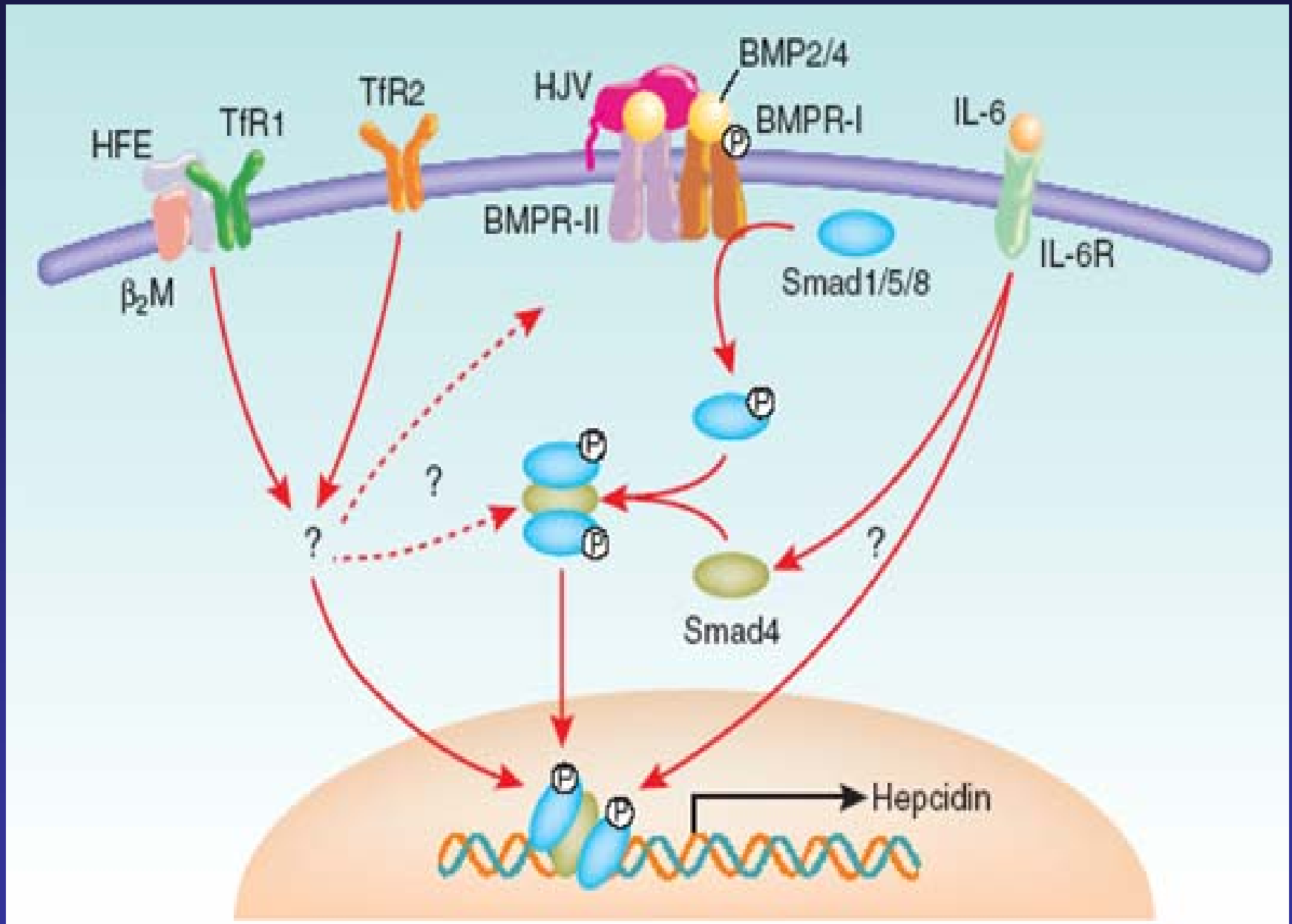
Bone morphogenetic protein signaling by hemojuvelin regulates hepcidin expression

Jodie L Babitt[1], Franklin W Huang[2,7], Diedra M Wrighting[2,7], Yin Xia[1,7], Yisrael Sidis[3,7], Tarek A Samad[4], Jason A Campagna[4], Raymond T Chung[5], Alan L Schneyer[3], Clifford J Woolf[4], Nancy C Andrews[2,6] & Herbert Y Lin[1]



NATURE GENETICS VOLUME 38 NUMBER 5 MAY 2006

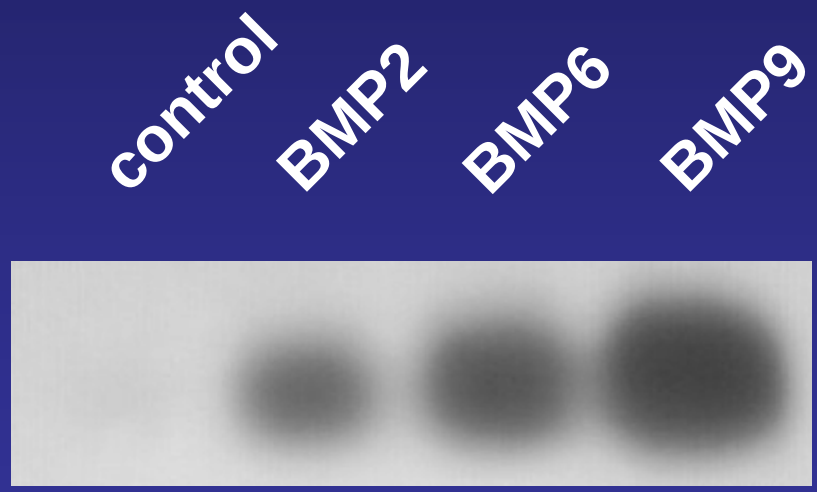

HJV
BMP
ligands
Hepatocyte
R-I
R-II
P
R-Smad
R-Smad
P
P
Co-Smad
Increased
hepcidin
Nucleus
R-Smad
P
P
Co-Smad
Gene response


BMP2/4
HJV
TfR2
TfR1
HFE
BMPR-I
IL-6
BMPR-II
Smad1/5/8
IL-6R
β_2M
?
?
?
Smad4
Hepcidin

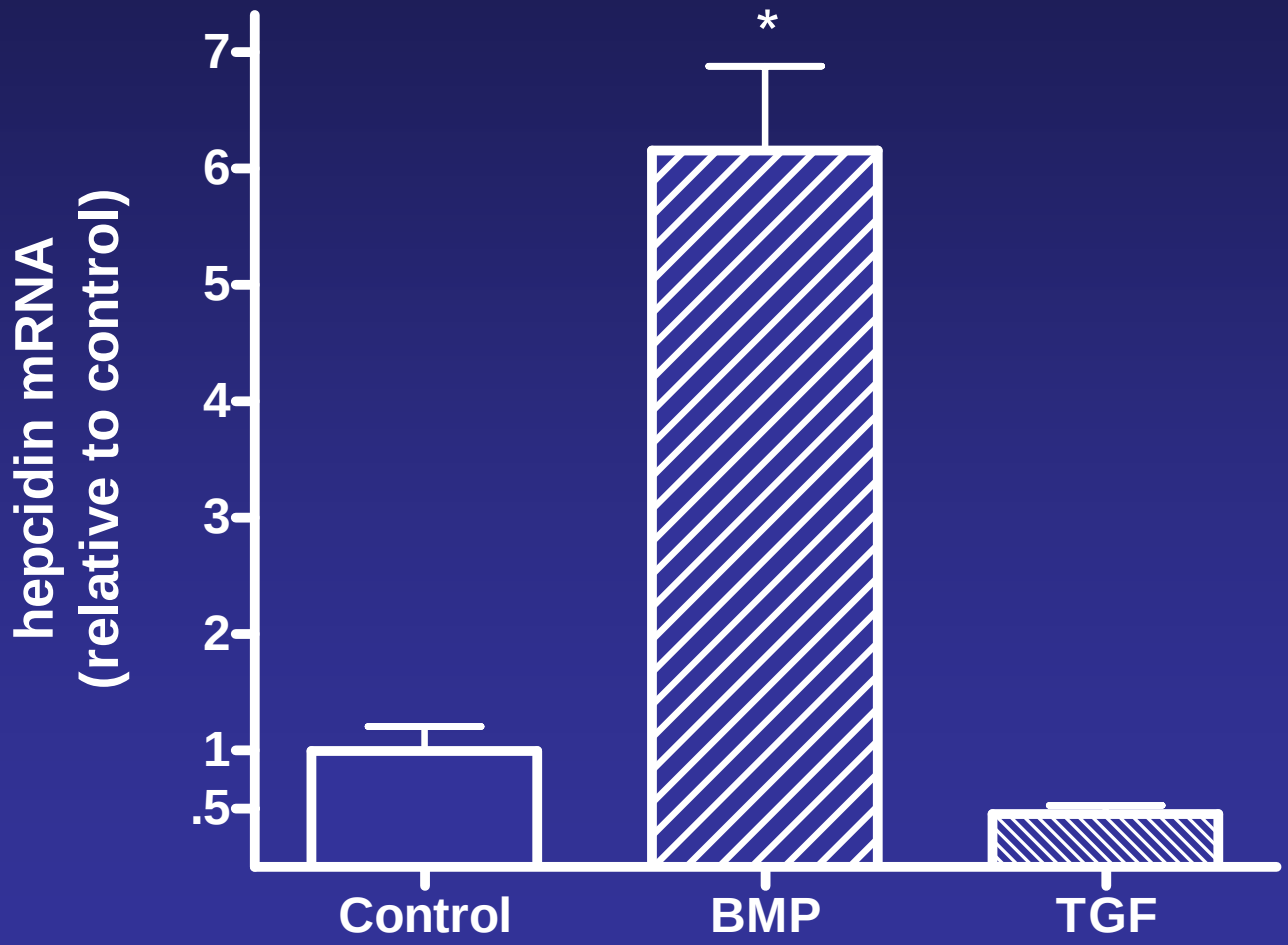
Name[a]	Alternative name	Potential functions	Bone induction model studied
BMP-2	BMP-2A	Cartilage and bone morphogenesis	Rodent, subcutaneous
BMP-3	Osteogenin	Bone formation	Rodent, subcutaneous
BMP-3B	GDF-10	Bone formation	NS
BMP-4	BMP-2B	Cartilage and bone morphogenesis	Rodent, subcutaneous
BMP-5	–	Bone morphogenesis	NS
BMP-6	Vgr-1	Cartilage hypertrophy	Rodent, subcutaneous
BMP-7	OP-1	Bone differentiation	Rodent, subcutaneous
BMP-8	OP-2	Bone formation	NS
BMP-8B	OP-3	NS	NS
BMP-9	GDF-2	NS	NS
BMP-10	–	NS	NS
BMP-11	GDF-11	NS	NS
BMP-12	GDF-7, CDMP-3	Ligament and tendon development	NS
BMP-13	GDF-6, CDMP-2	Cartilage development and hypertrophy	NS
BMP-14	GDF-5, CDMP-1, CDMP-2	Mesenchymal condensation and chondrogenesis	Rodent, subcutaneous, intramuscular
BMP-15	CDMP-1	NS	Rodent, subcutaneous
BMP-16	–	NS	NS
TGF-β1	–	NS	Primate, intramuscular
TGF-β2	–	NS	Primate, intramuscular

From Ramoshebi LN *et al*: Exp Rev Molec Med, 2002

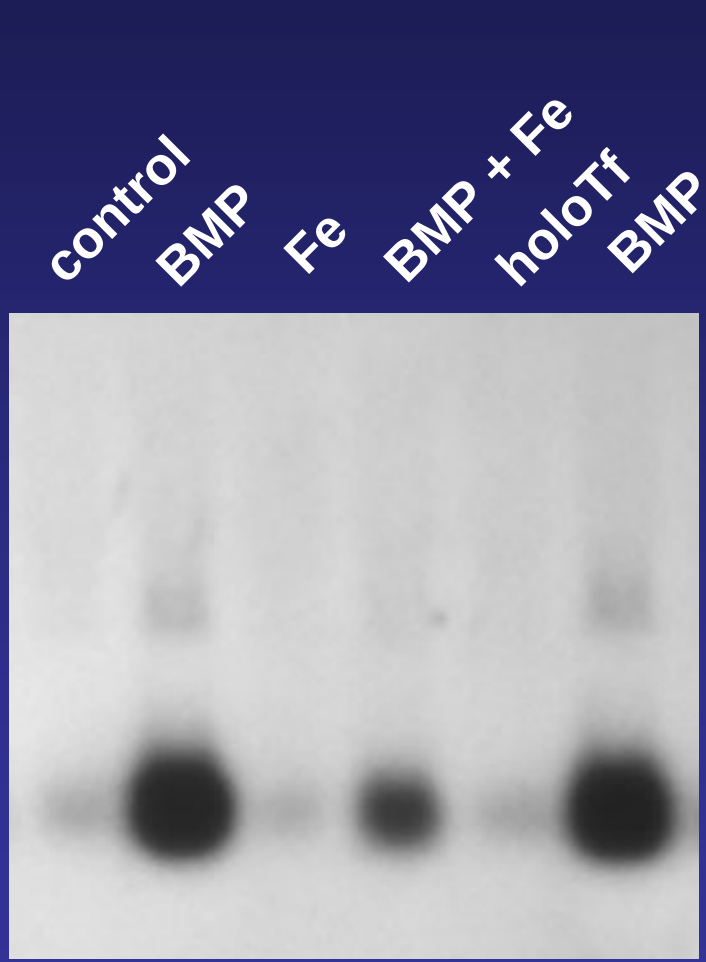
Effect of BMPs on Hepcidin mRNA in HuH7 Cells

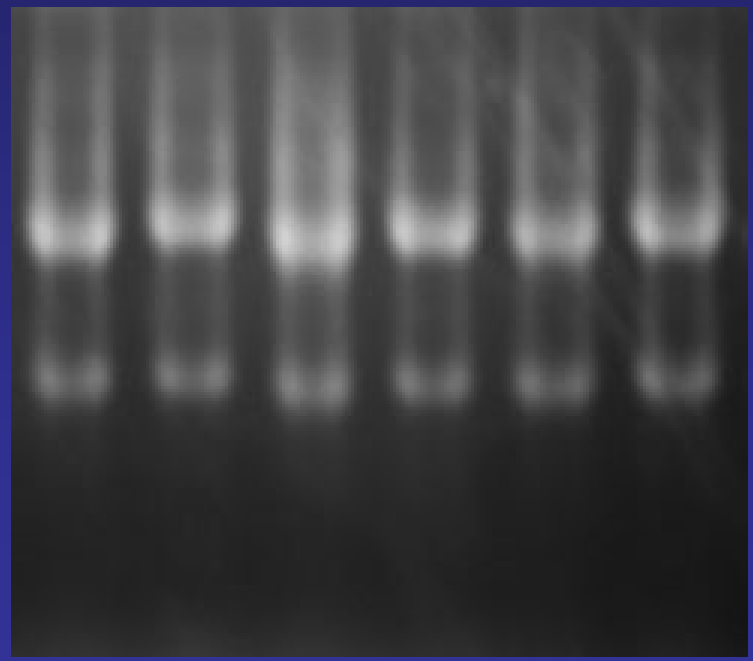


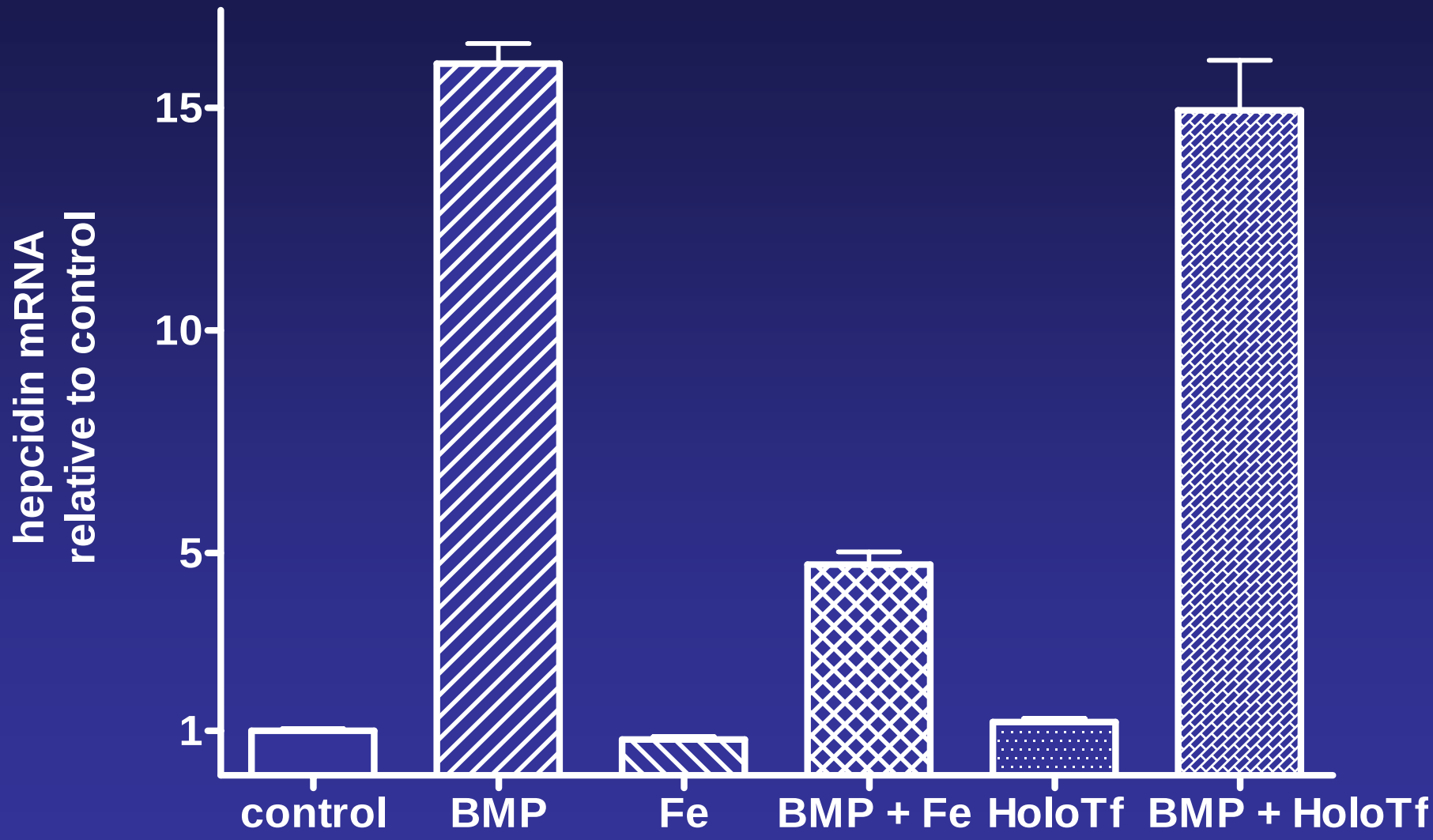
TGFβ and BMP Regulation of Hepcidin in Human Hepatoma (HuH7) Cells



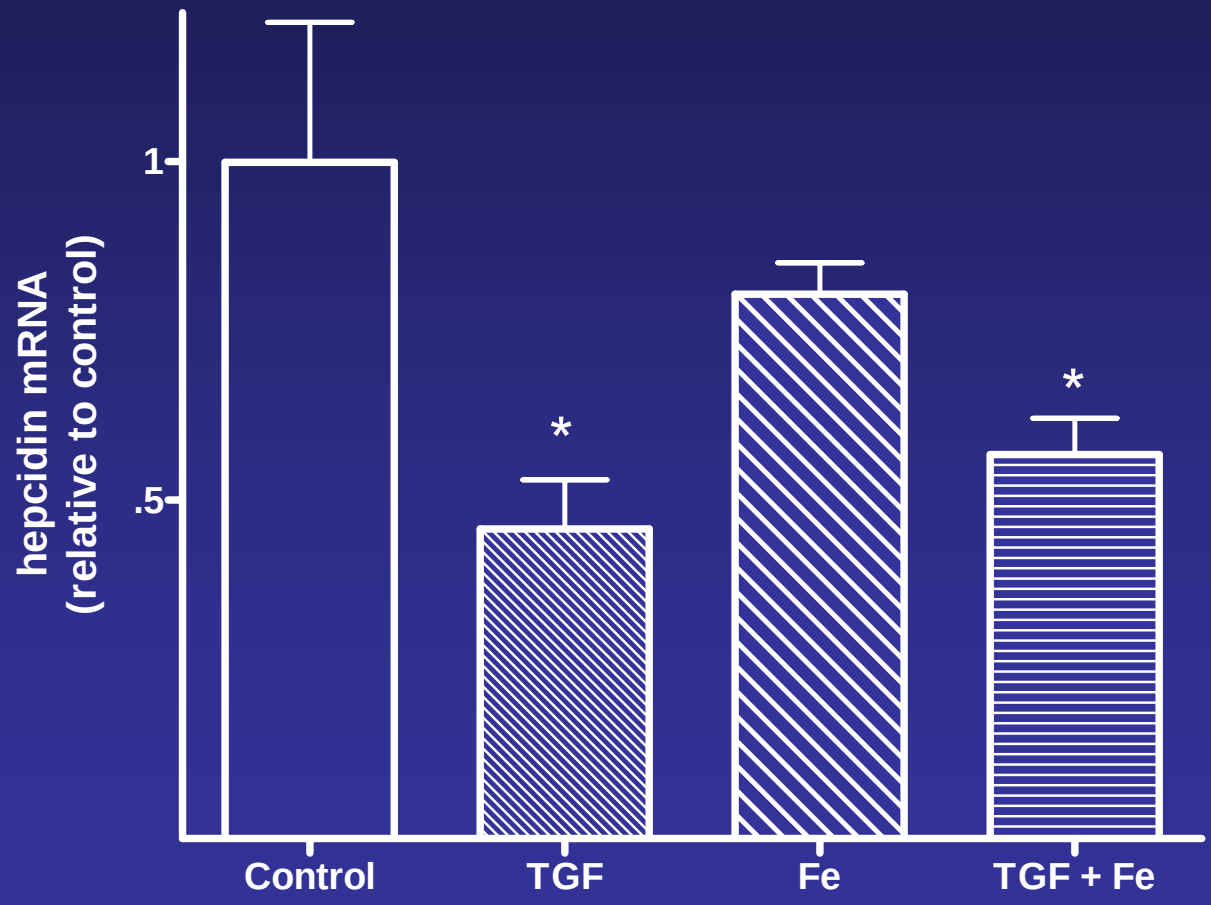
Effect of Iron on BMP-Induction of Hepcidin Expression



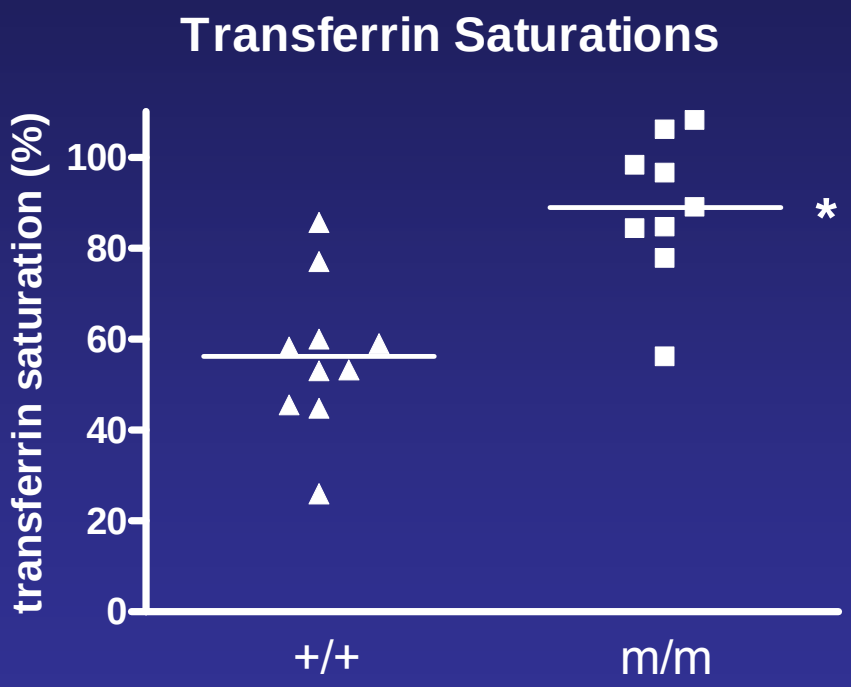


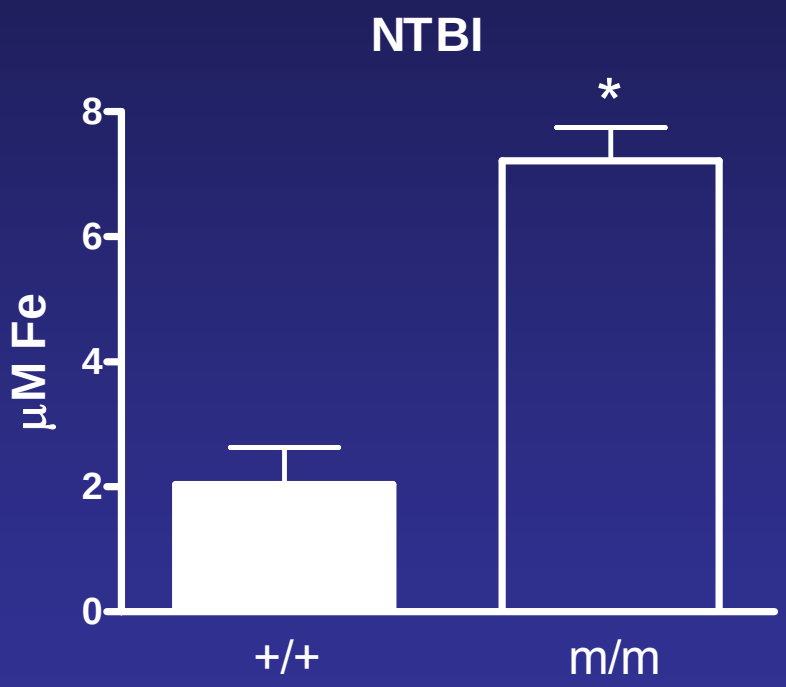

hepcidin mRNA
relative to control
15
10
5
1
control
BMP
Fe
BMP + Fe
HoloTf
BMP + HoloTf

Effect of Iron on TGFb Signaling in HuH7 Cells



NTBI in Hemochromatosis





Increased NTBI and Decreased Hepcidin

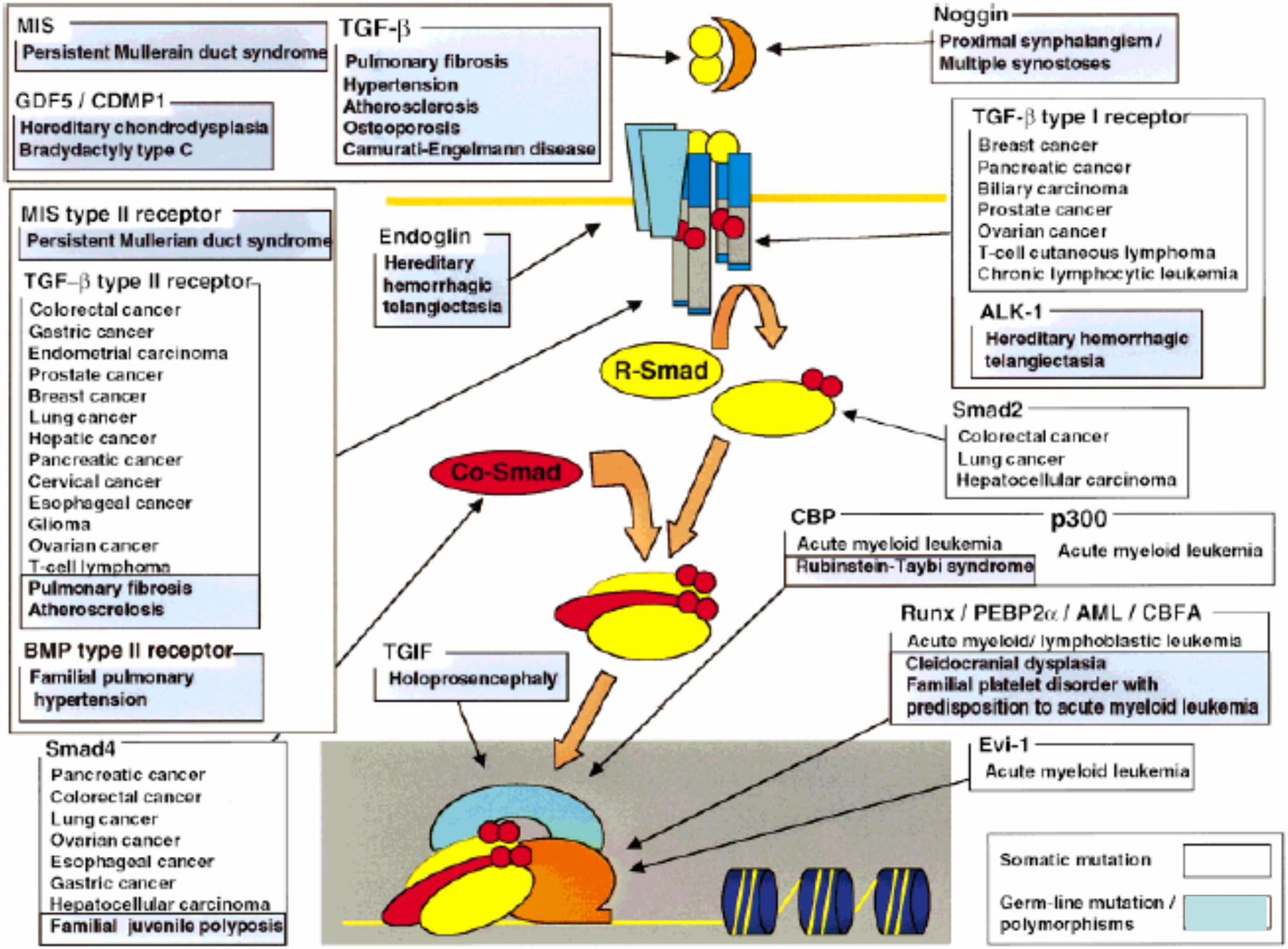
- HFE, TfR2, HJV associated HH
- Atransferrinemia
- Acute hemolysis

Increased NTBI, Decreased Hepcidin, Osteopenia

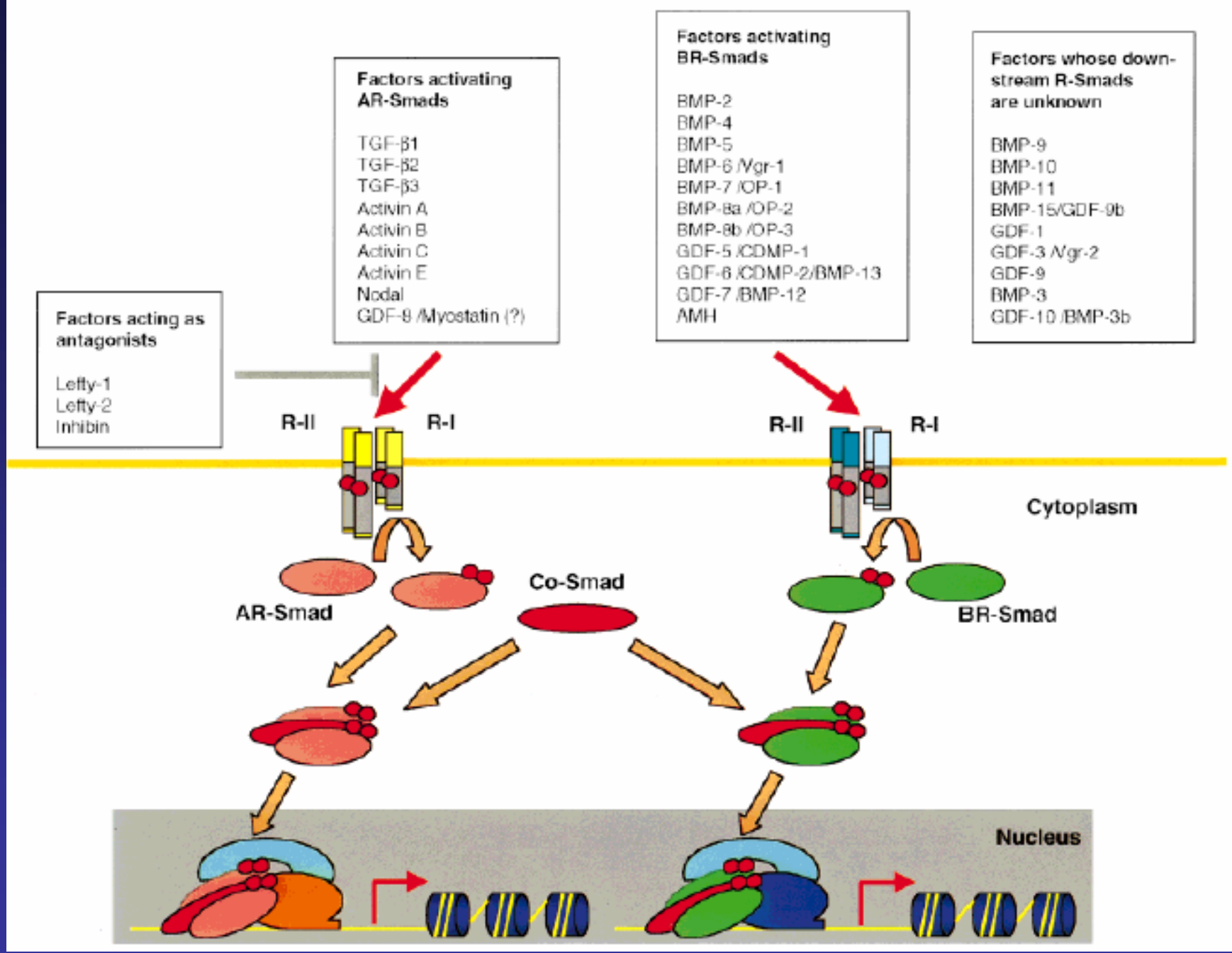
- HH
- Sickle cell
- Beta thalassemia

Speculative Model

- Holotransferrin increases hepcidin
- Elemental iron decreases BMP signaling
- In iron overload, increased elemental iron attenuates BMP signaling
- Decreased BMP signaling leads to
  - Decreased hepcidin
  - Osteopenia



JOURNAL OF CELLULAR PHYSIOLOGY 187:265±276 (2001)



JOURNAL OF CELLULAR PHYSIOLOGY 187:265±276 (2001)