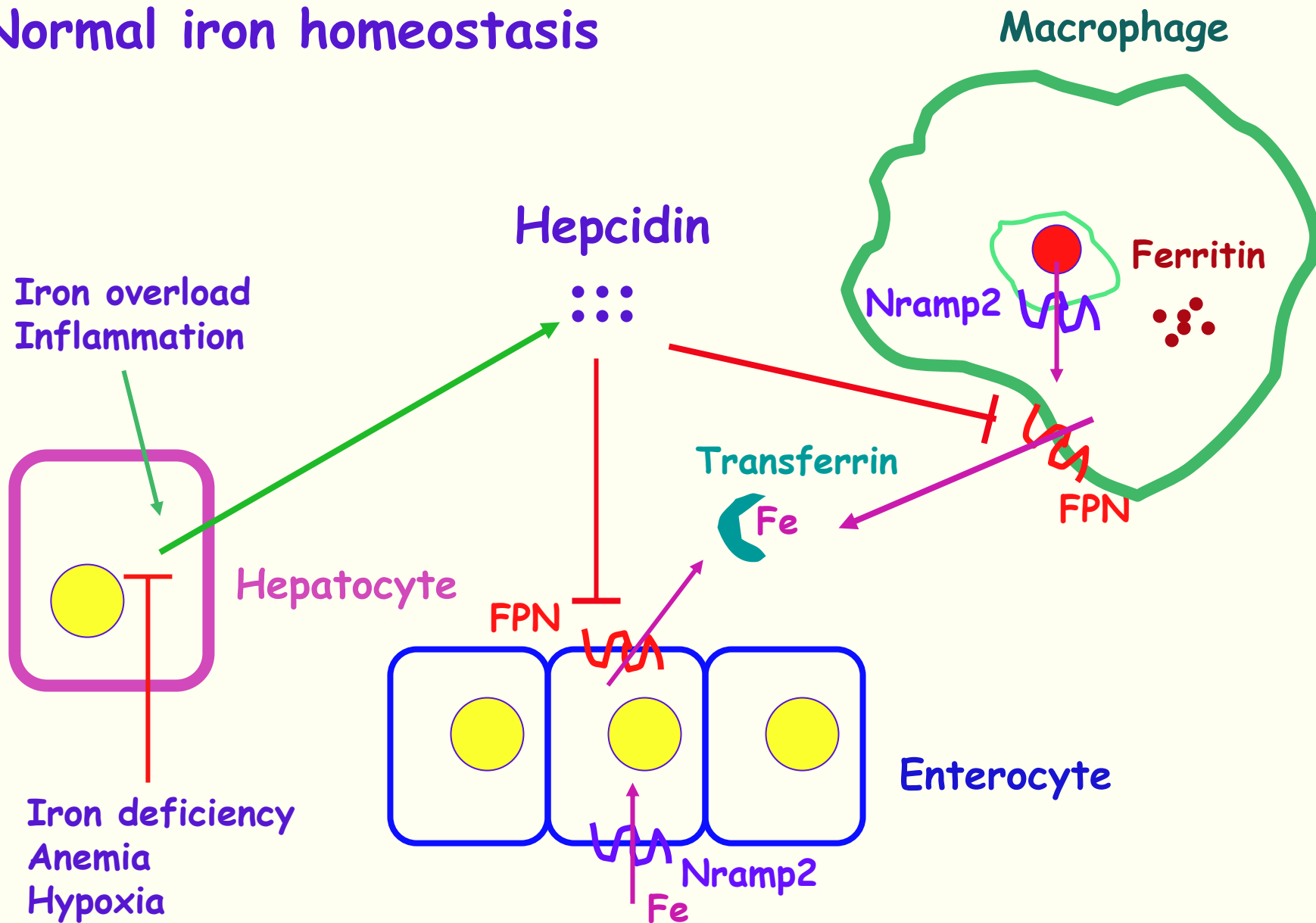


# Iron-based modulation of cytokine biosynthesis for treatment of intestinal inflammation

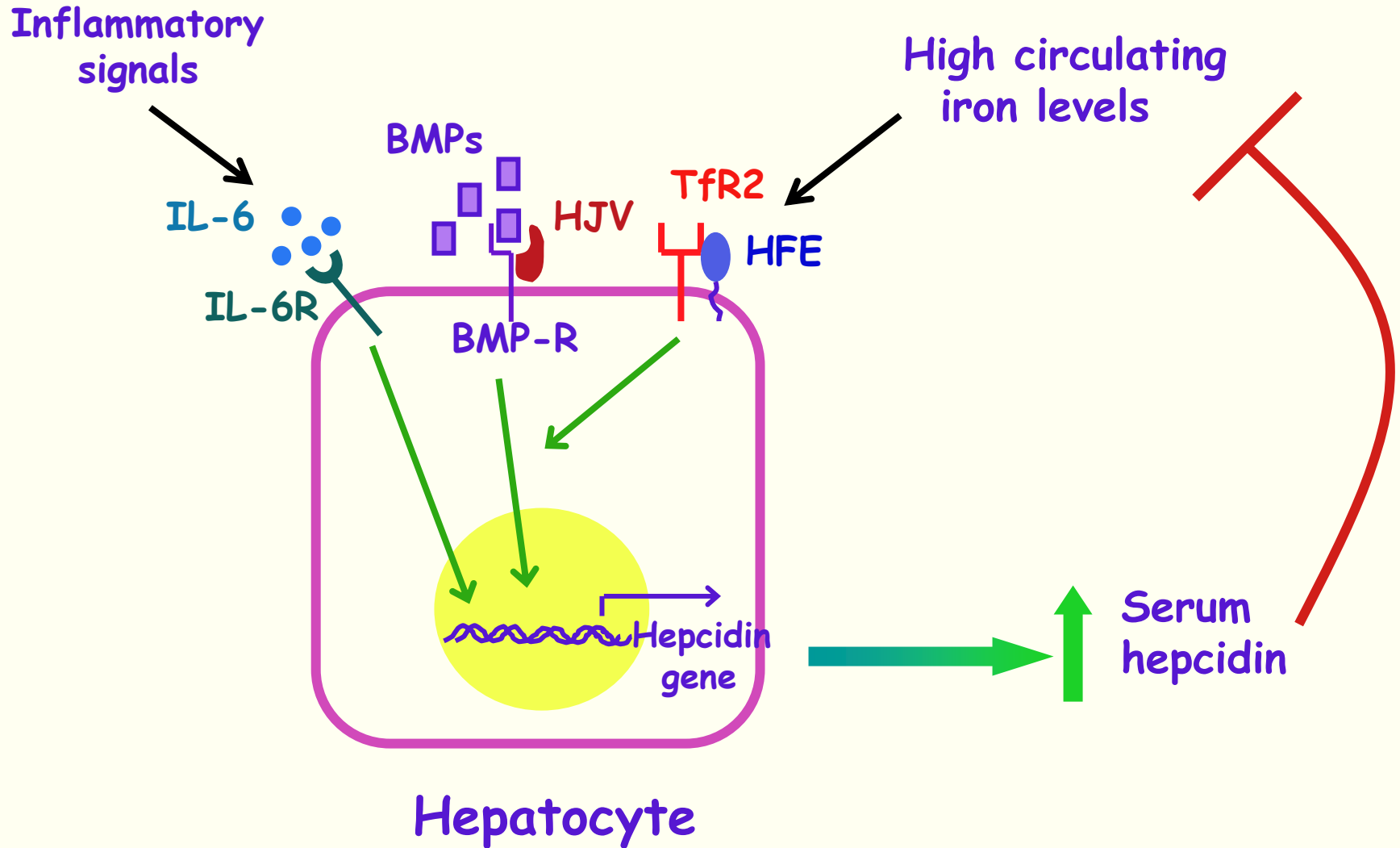
BMRP Proposal IBD-0253

Bobby J. Cherayil, MD  
Pediatric Gastroenterology Unit  
Massachusetts General Hospital

# Normal iron homeostasis



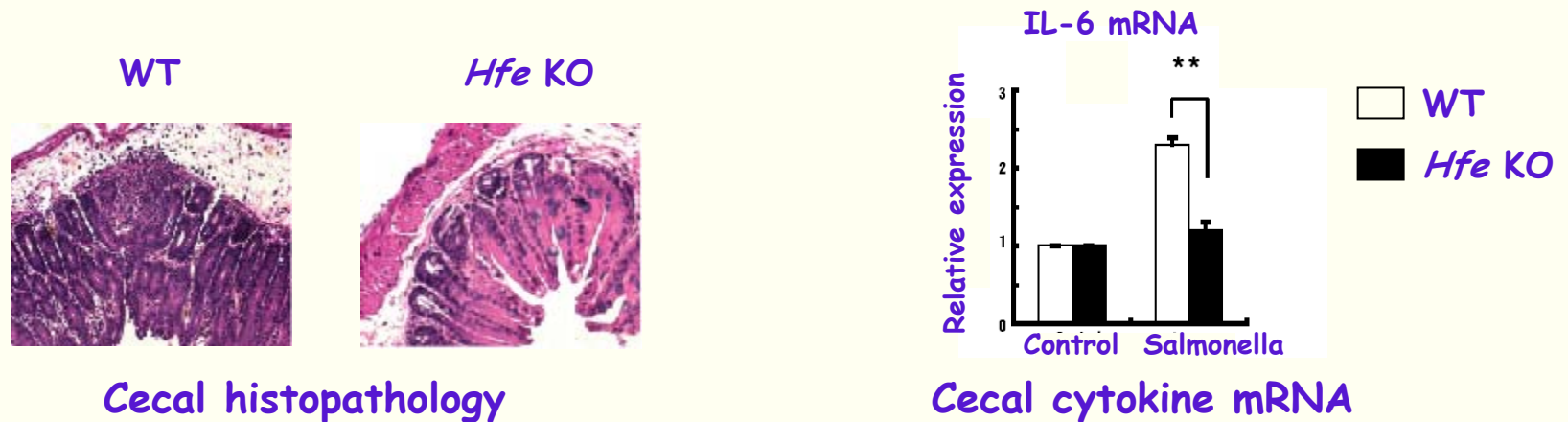
# Regulation of hepcidin expression



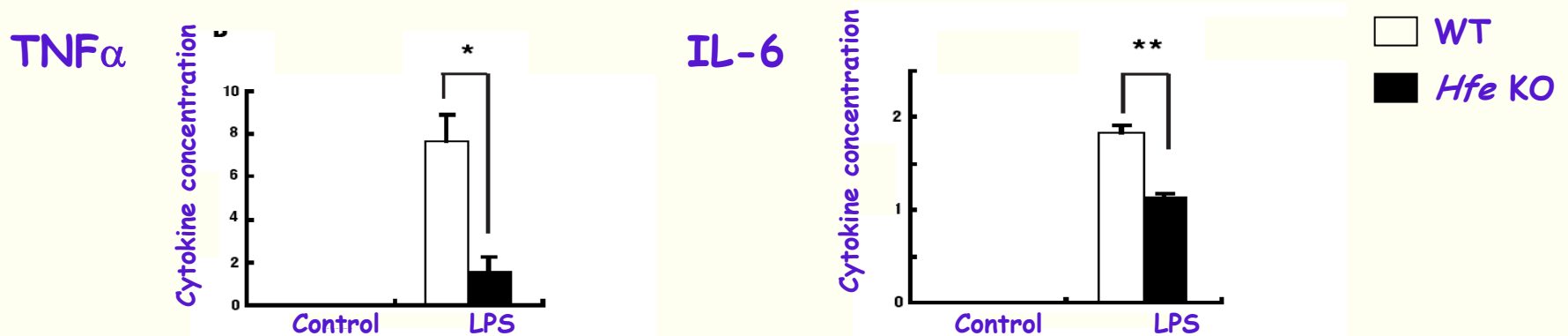
Low levels of hepcidin in *Hfe* KO mice are associated with attenuated inflammatory responses

J. Immunol. 2008; 181: 2723

*Hfe* KO mice have attenuated *Salmonella* enterocolitis

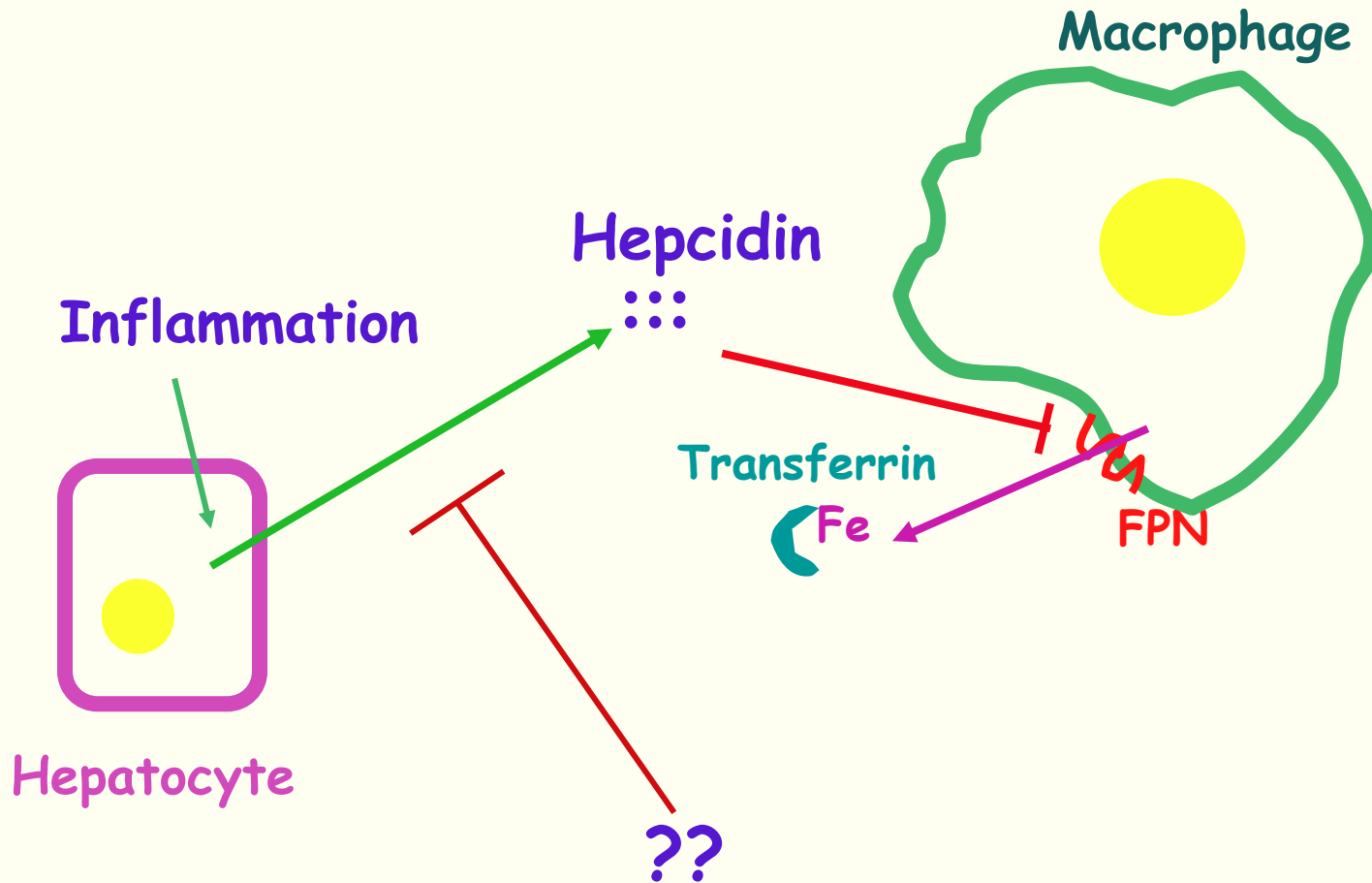


*Hfe* KO M $\phi$  have attenuated responses to LPS

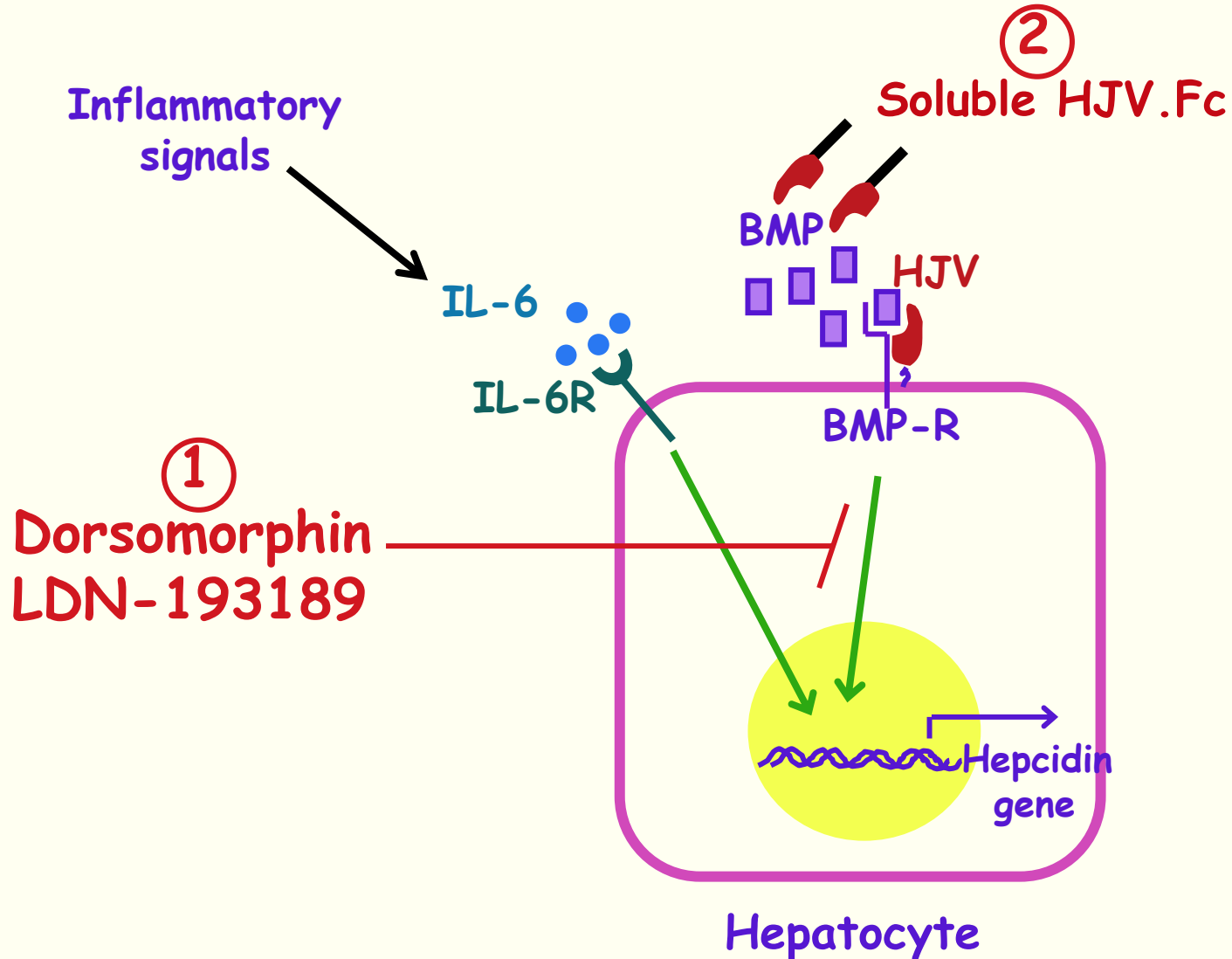


# Hypothesis

Inhibiting hepcidin expression in WT mice will reduce the severity of intestinal inflammation

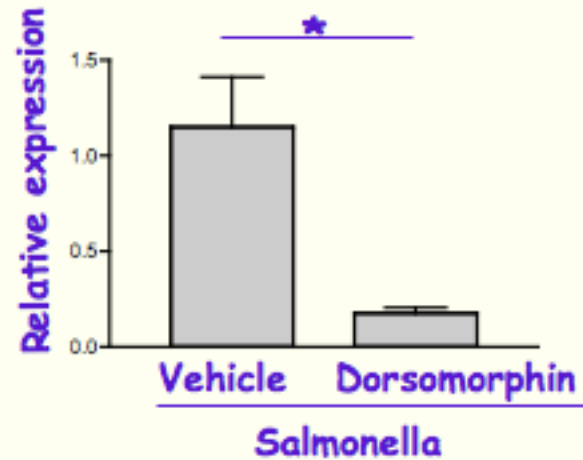
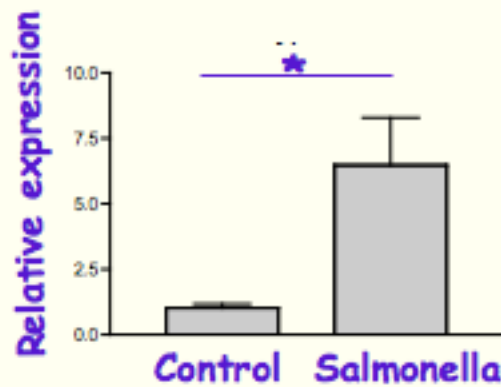


# Testing the hypothesis with 2 different inhibitors of hepcidin expression

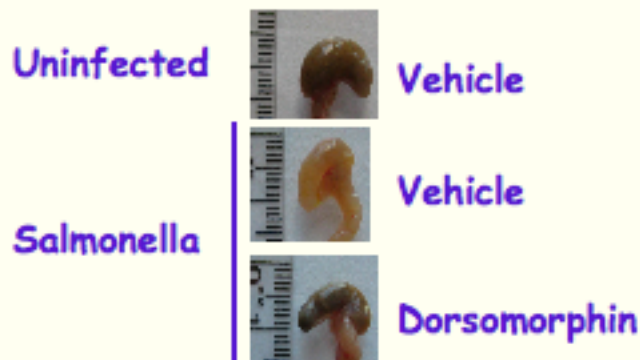


# Dorsomorphin treatment attenuates Salmonella enterocolitis in WT mice

Dorsomorphin inhibits hepcidin up-regulation during Salmonella infection



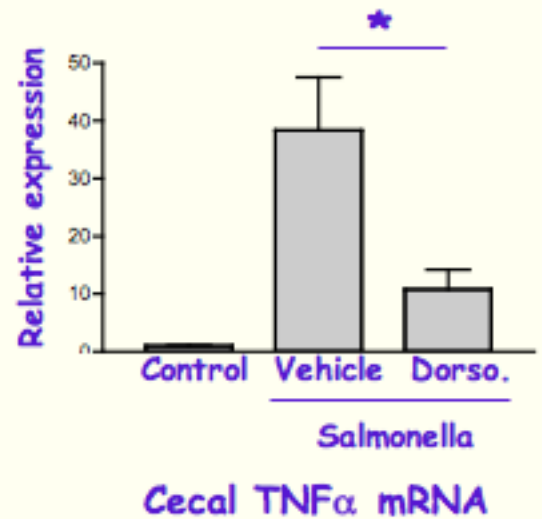
Dorsomorphin reduces severity of Salmonella enterocolitis



Gross view of cecum

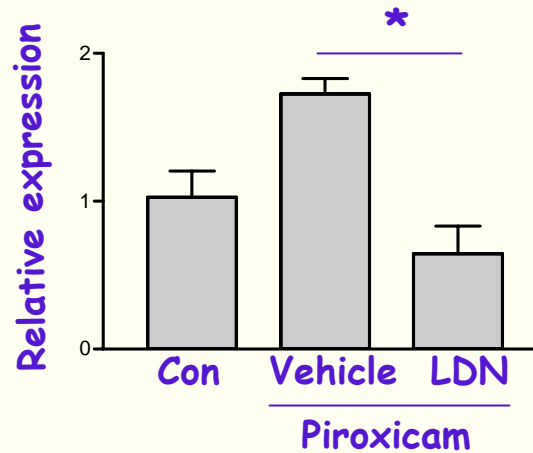


Histopath of Salmonella infected cecum

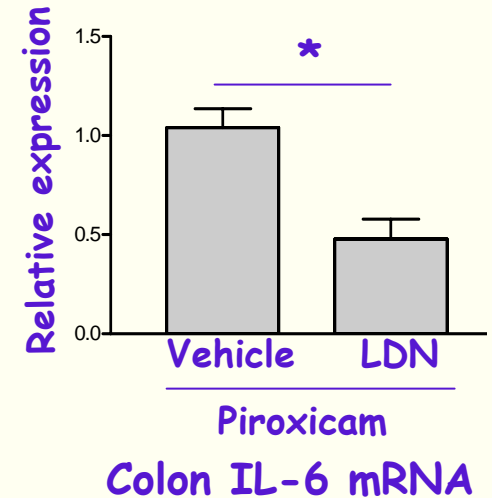
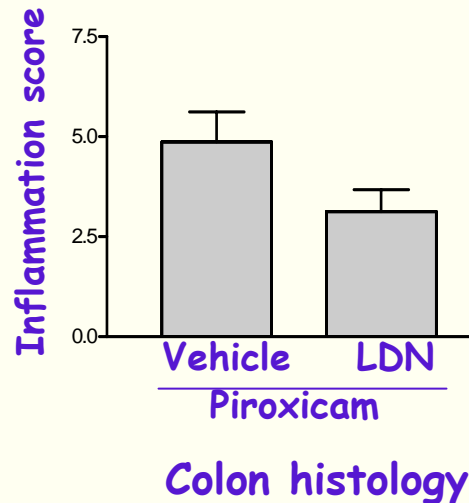
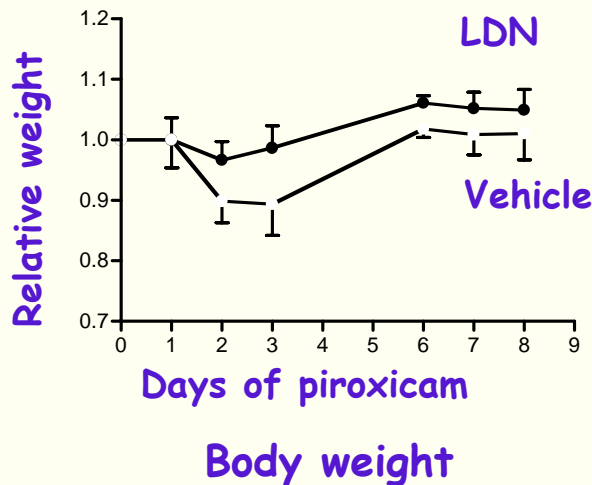


# LDN-193189 treatment attenuates colitis induced by piroxicam in IL-10 KO mice

LDN-193189 inhibits piroxicam-induced hepcidin up-regulation

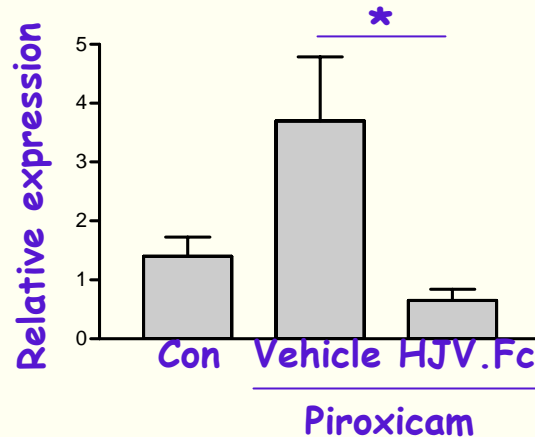


LDN-193189 reduces severity of piroxicam/IL-10 KO colitis

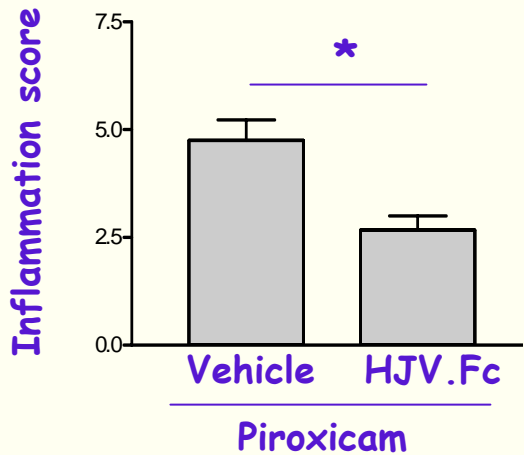


# HJV.Fc treatment attenuates colitis induced by piroxicam in IL-10 KO mice

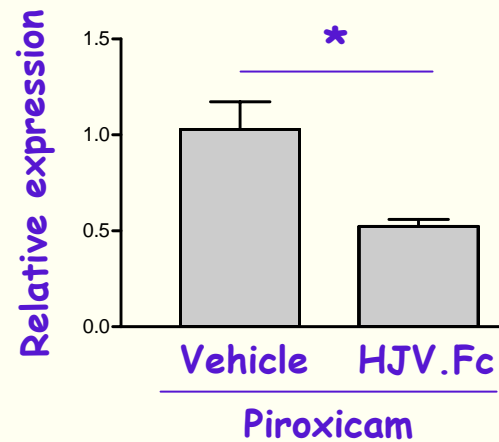
HJV.Fc inhibits piroxicam-induced hepcidin up-regulation



HJV.Fc reduces severity of piroxicam/IL-10 KO colitis

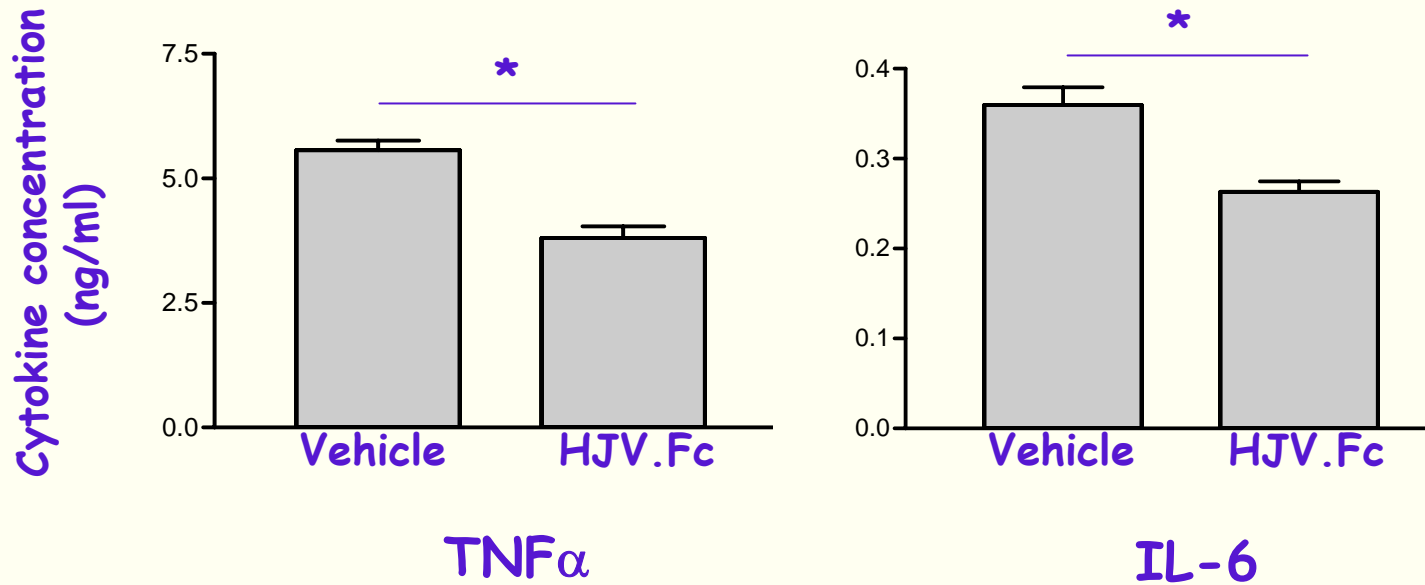


Colon histology



Colon IL-17 mRNA

# HJV.Fc treatment of WT mice reduces LPS-induced macrophage cytokine expression



# Conclusion

Inhibiting hepcidin expression and thereby lowering intra-macrophage iron levels may represent a viable strategy to treat inflammatory conditions such as IBD.

This approach could have the added advantage of increasing circulating iron levels and helping to correct the anemia that is often associated with chronic inflammation.

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