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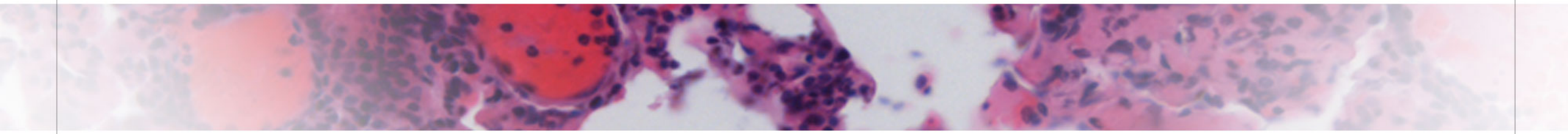
#2599



DISC-0974, a novel, first-in-class, anti-hemojuvelin monoclonal antibody decreases hepcidin and increases transferrin saturation in a non-human primate model of cytokine (IL-6) induced hypoferremia

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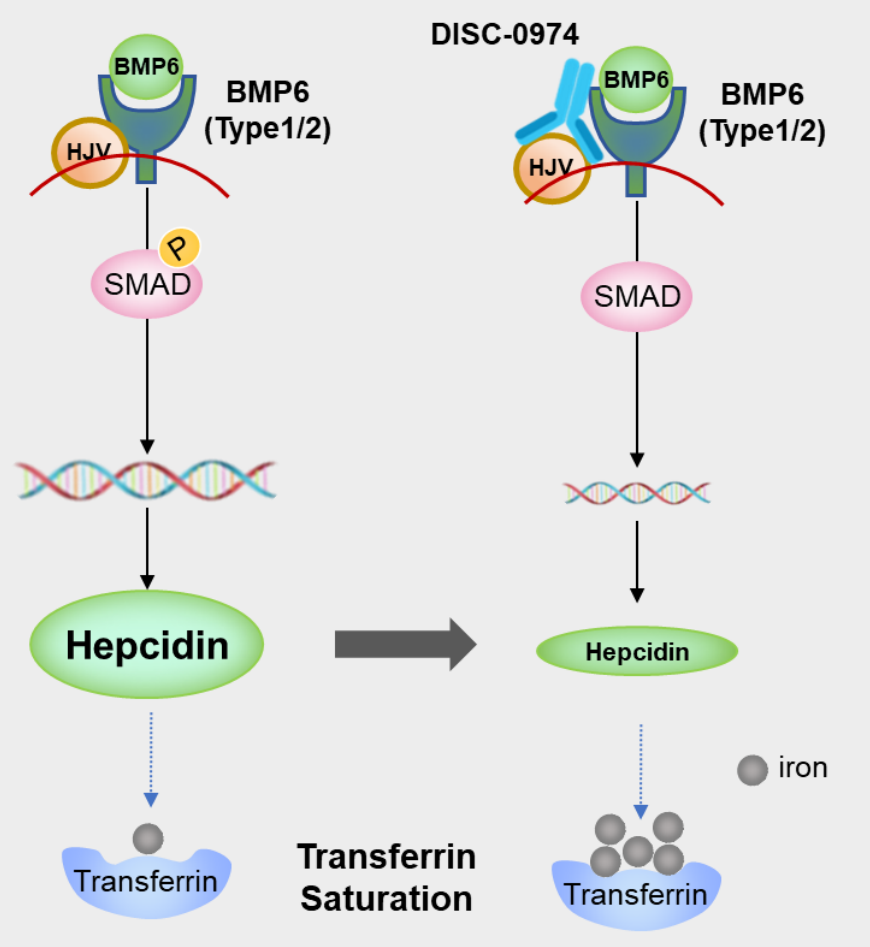
Disclosures

- Cécile Blaustein, Sophia Nguyen, Christopher King, Vu Hong, Will Savage, Srikanth Venkatraman, Maria G. Beconi: *Disc Medicine – employment and equity ownership*

- Brian MacDonald: *Disc Medicine - equity ownership and member of the Board of Directors*

DISC-0974 is a potent regulator of hepcidin expression



- Humanized anti-hemojuvelin (HJV) mAb antibody
- Inhibits the interaction between HJV and BMPs, decreasing SMAD-P and reducing hepcidin expression
- Pathway and biology validated by human genetics

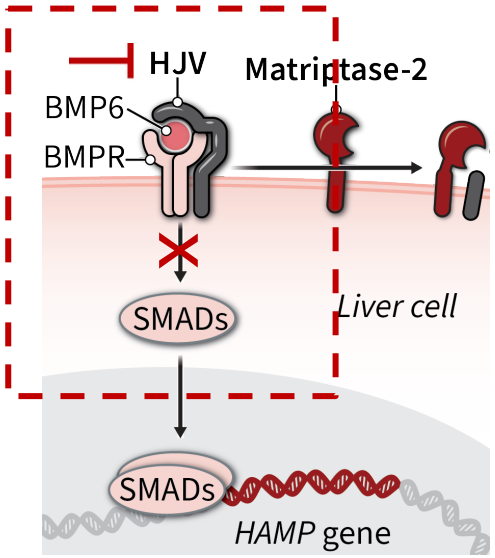
  HJV loss of function variants cause juvenile hemochromatosis, disorder characterized by low serum hepcidin and high serum iron that leads to progressive tissue iron overload [Roetto 2003, Papanikolaou 2004]
- High affinity for human, rat and cynomolgus monkey HJV (100, 240 and 110 pM Kd, respectively) [Kovac 2016]

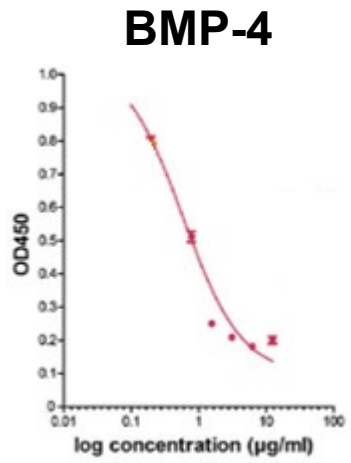
DISC-0974 inhibits interaction between HJV and BMP ligands and receptors

DISC-0974 MoA

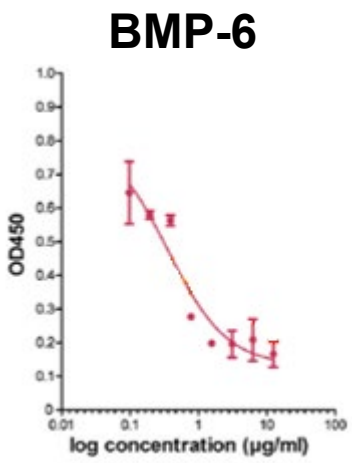
Ligand-Binding Assays
Inhibits Binding of HJV to BMPs and Neogenin

Gene-Reporter Assay
Prevents BMP Signaling

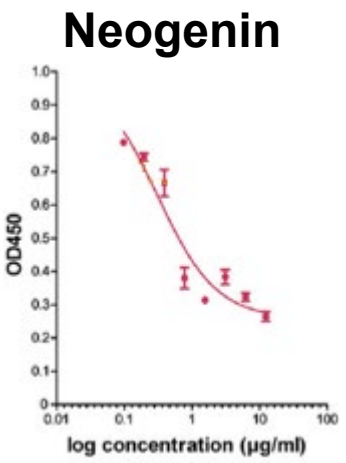




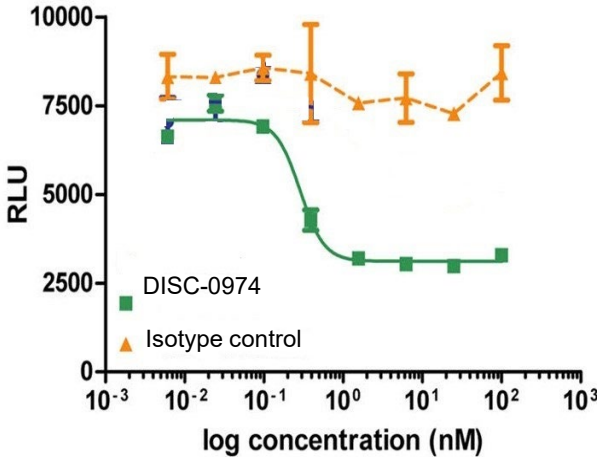
IC_{50}
4.04 nM



IC_{50}
2.43 nM



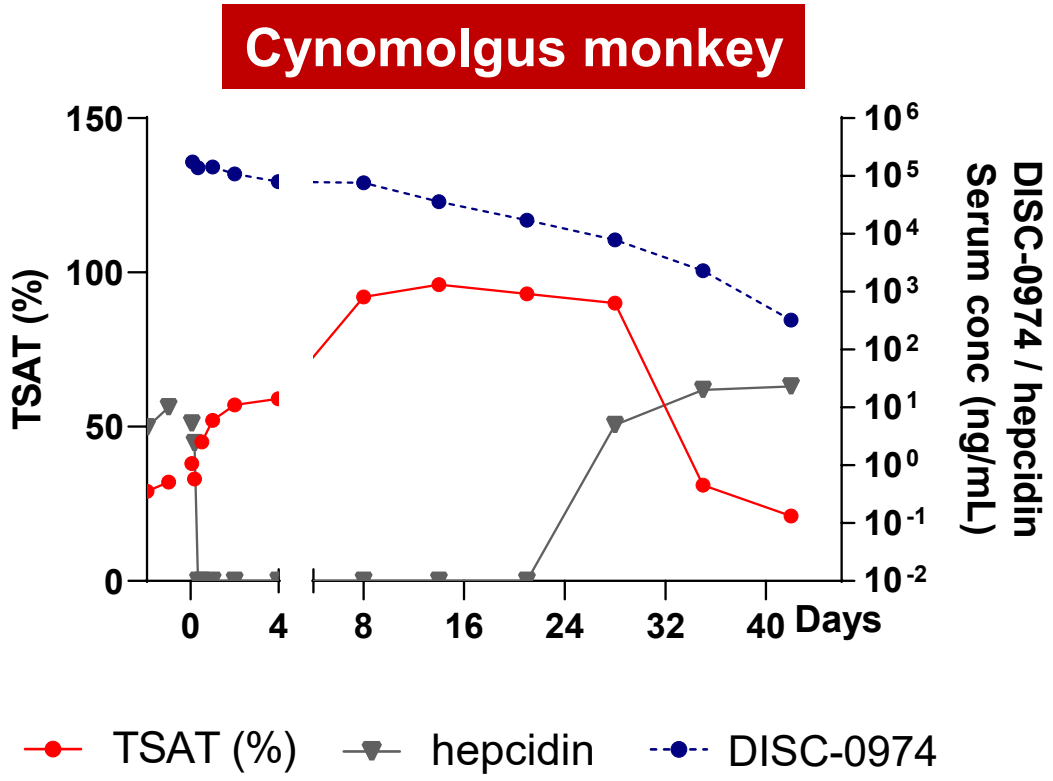
IC_{50}
2.12 nM



IC_{50}
0.37 nM

Modified from Kovac et al. (2016) *Haematologica*

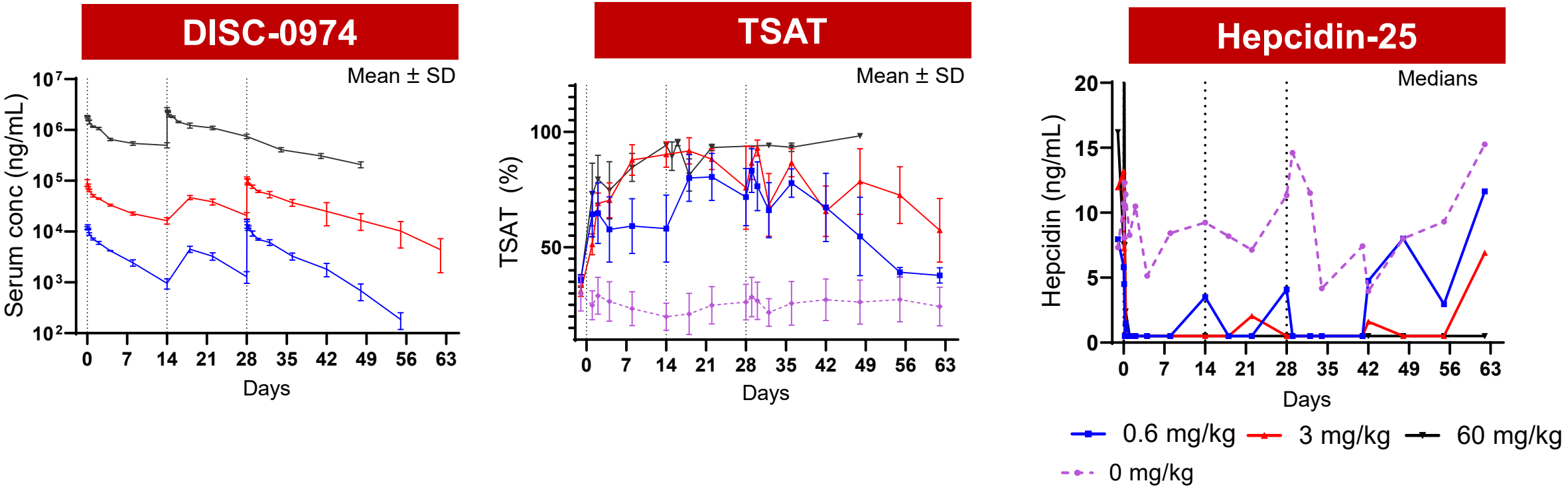
DISC-0974 has strong PK-PD (TSAT and hepcidin) correlation



- Single 5 mg/kg IV dose selected to saturate PD response
- Maximum PD effect (TSAT saturation, hepcidin-25 decrease) within the first week post-dose
- Return of hepcidin and TSAT to baseline consistent with the decrease in ‘0974 concentrations

PD modulation by DISC-0974 is robust, durable and dose-dependent

Dose-range finding studies in cynomolgus monkeys



0.6 mg/kg: TSAT not saturated, hepcidin returns to baseline after each dose

3 and 60 mg/kg: TSAT saturated, hepcidin suppressed through last dose (3 mpk) and end of study (60 mpk)

Hepcidin expression is upregulated in response to inflammatory factors

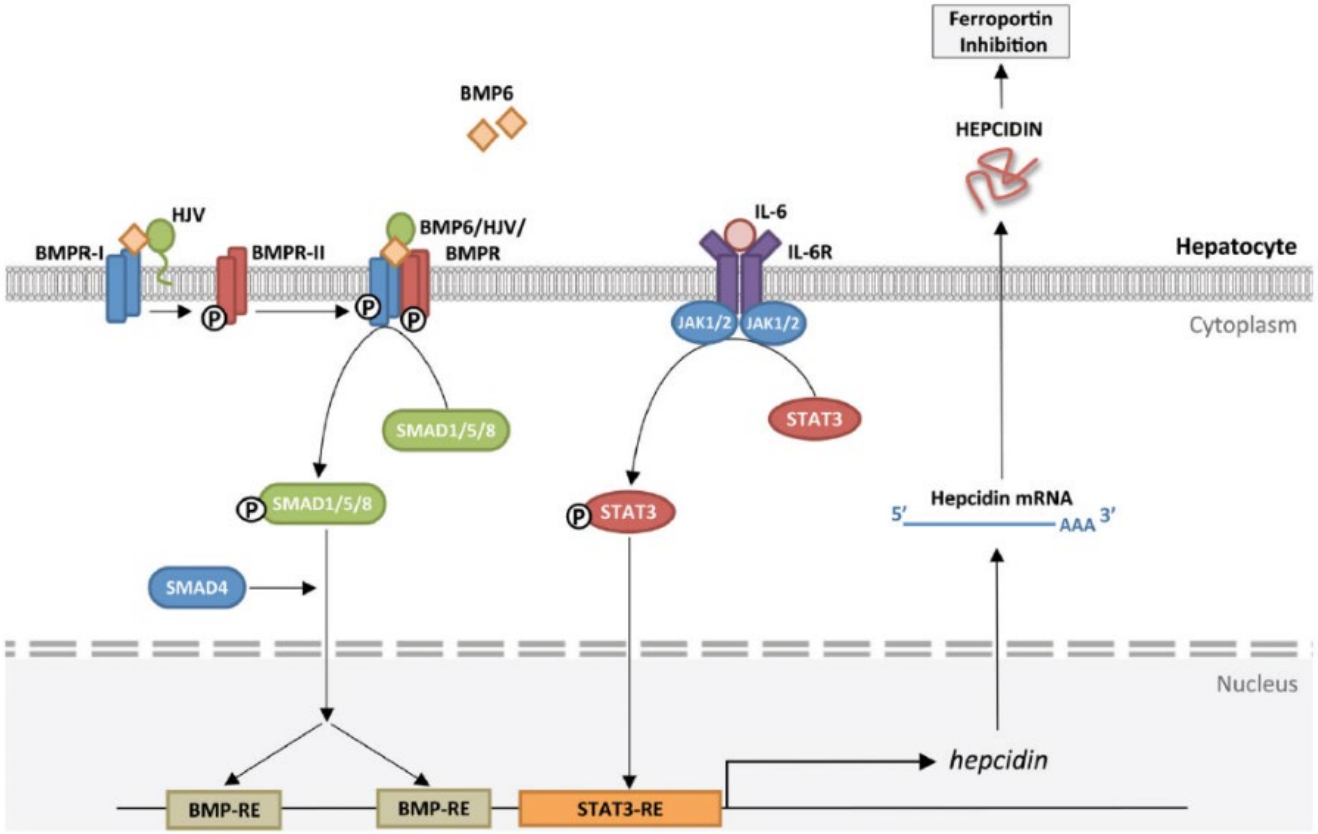


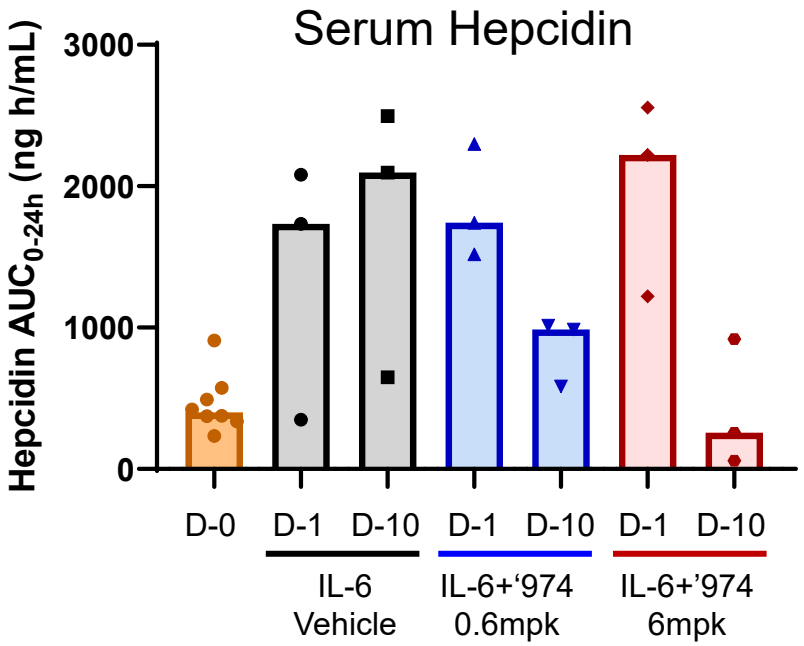
Figure source Babitt 2006

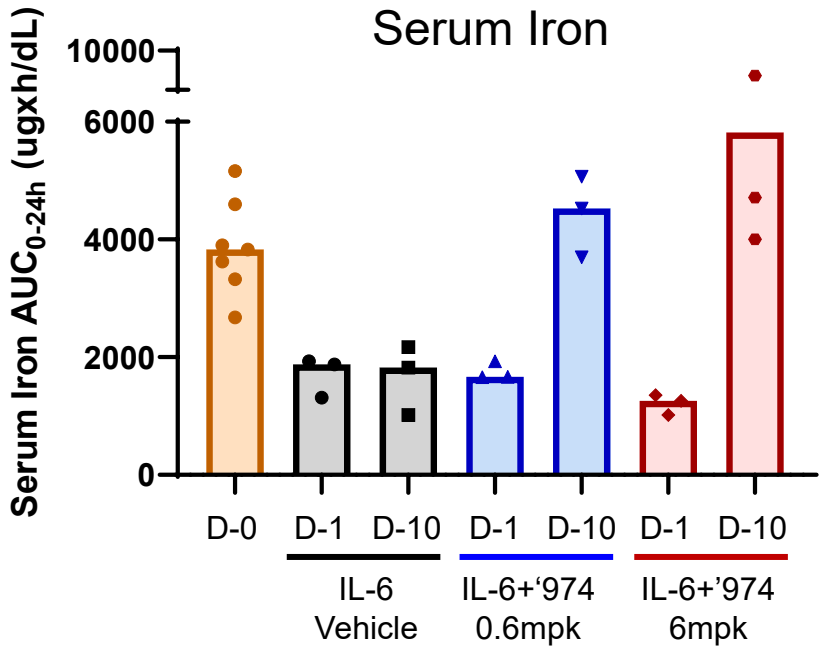
- Hepcidin expression is upregulated in response to inflammatory factors such as IL-6 and Oncostatin M
- The hepcidin response to inflammation is greatly diminished in the absence of active signaling through the BMP6-HJV pathway
  - In BMP6$^{-/-}$ mice or HJV$^{-/-}$ mice, HAMP expression in response to inflammatory stimuli does not reach the level seen in unchallenged WT mice [Besson-Fournier 2017, Fillebeen 2018]

DISC-0974 reduced hepcidin in a model of cytokine-induced hypoferremia

NHP: Inflammation (cytokine IL-6)-induced hepcidin

	Day-1	Day-4	Day-10
Gr1	IL-6	vehicle	IL-6
Gr2	IL-6	0.6 mpk '0974	IL-6
Gr3	IL-6	6 mpk '0974	IL-6

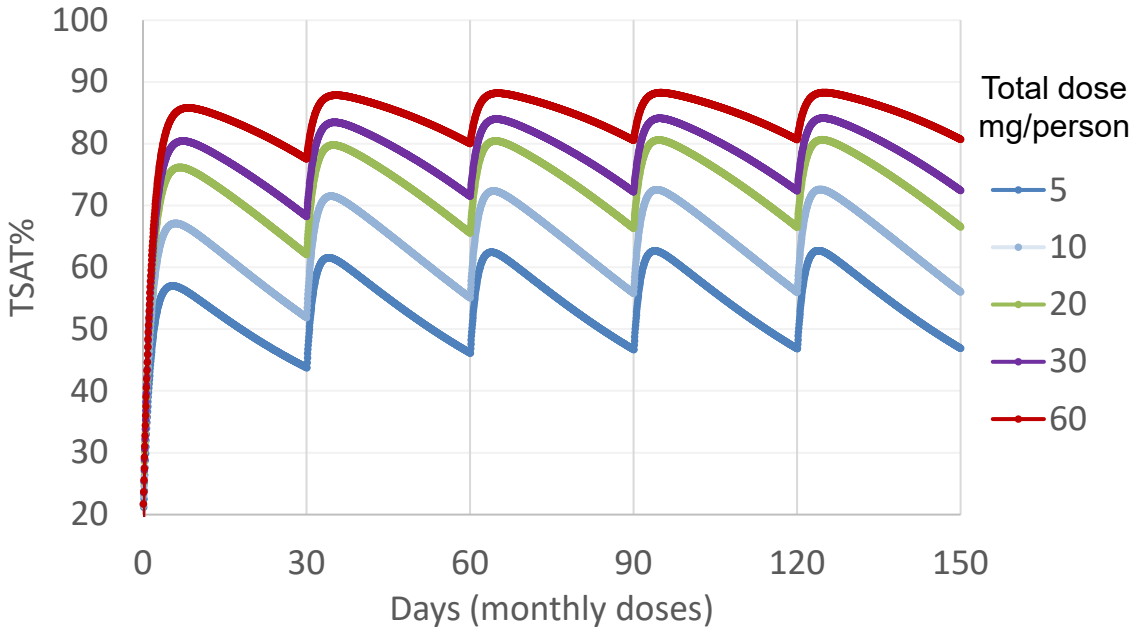




TSAT % median 24 hr post IL-6	
Baseline	39.0
IL-6 control	18 – 22
0.6 mpk '0974	34.9
6.0 mpk '0974	43.2

- Dose-dependent prevention of serum hepcidin increase and serum iron decrease

Potential for very low dose in human, controlled TSAT range



Initial estimates suggests low dose (~5 – 20 mg per person) will be efficacious

- PK/PD model constructed from NHP data to predict the human response
- TSAT response is described by a delayed-response
- Supports once a month dosing in human
- TSAT and iron response predicts efficacy at low doses in clinical studies

Conclusions

- DISC-0974 a humanized mAb blocks HJV binding to BMPs to decrease hepcidin
- Decreased hepcidin and increased TSAT in healthy rats (not shown) and NHPs, in a dose-dependent manner consistent with the mechanism of action
- Effectively modulated hepcidin and TSAT in inflammation models
  - Specifically, prevented serum hepcidin-25 increases and hypoferremia after IL-6 administration to NHPs
- Given the similarity in the hepcidin regulation pathways between humans and NHPs, DISC-0974 is anticipated to be effective in the treatment of anemia of inflammation in humans by lowering cytokine-induced increases in hepcidin and improving iron availability for erythropoiesis
  - Pharmacokinetic projections support once a month doses in human
  - PK/PD modeling predicts DISC-0974 will be efficacious at low doses in patients with anemia secondary to elevated hepcidin