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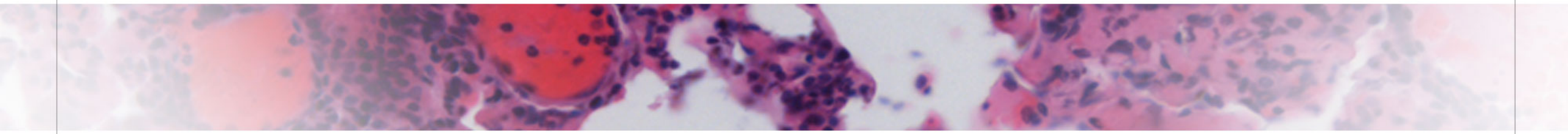

DISC-A, the First in a Novel Class of Potent and Selective Matriptase-2 Inhibitors for the Treatment of Hematologic Disorders Characterized By Low Hepcidin

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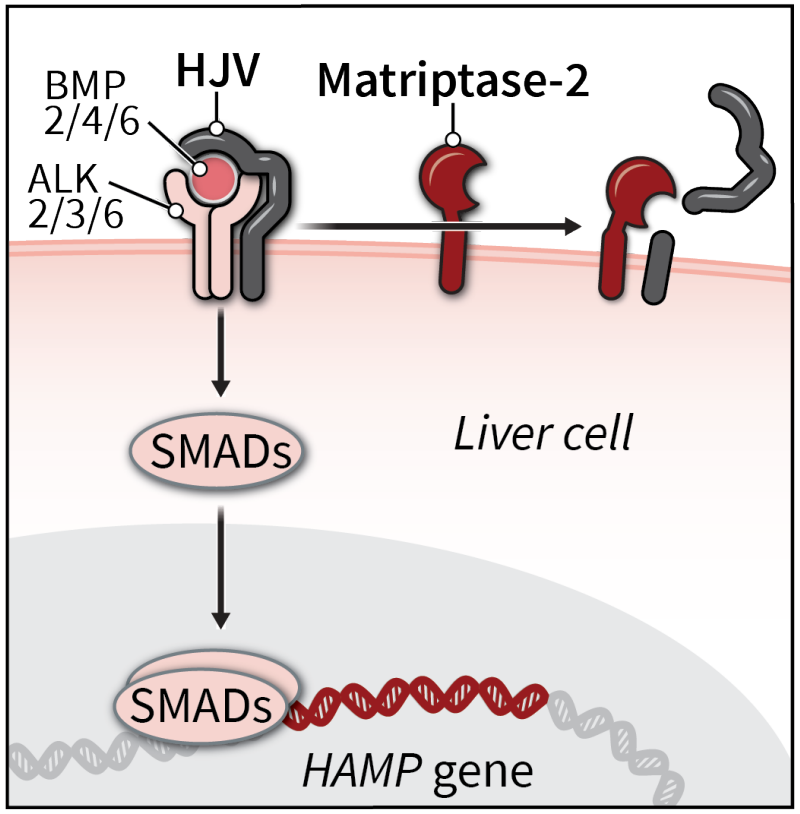
Disclosures

- Vu Hong, Cécile Blaustein, Sophia Nguyen, Will Savage, Maria Beconi and Srikanth Venkatraman: *Disc Medicine – employment and equity ownership*
- Brian MacDonald: *Disc Medicine - equity ownership and member of the Board of Directors*
- D Ravi Krishna Babu, Venkateshwar Rao*: Aurigene Discovery Technologies Limited - employment*

Mechanism of Action: Inhibiting Mat-2 to Increase Endogenous Hepcidin

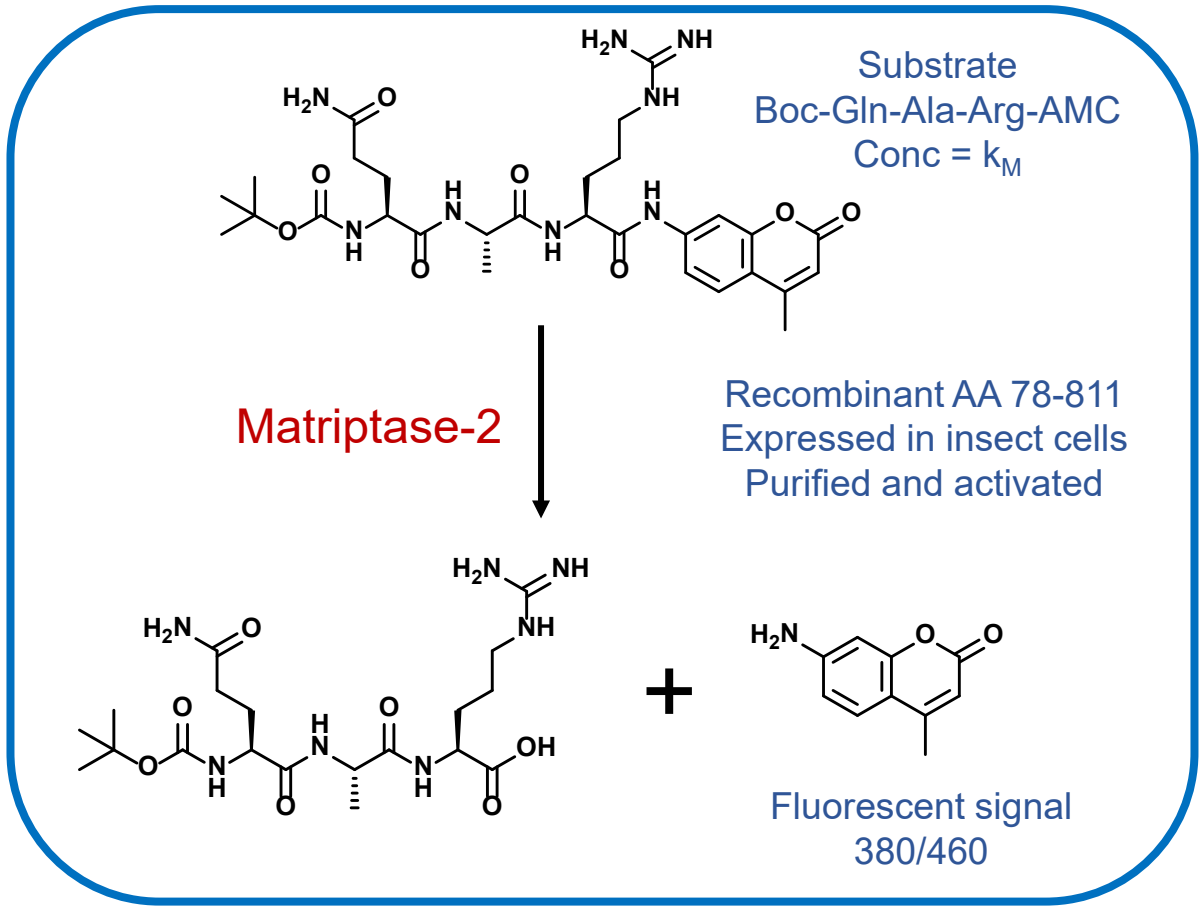


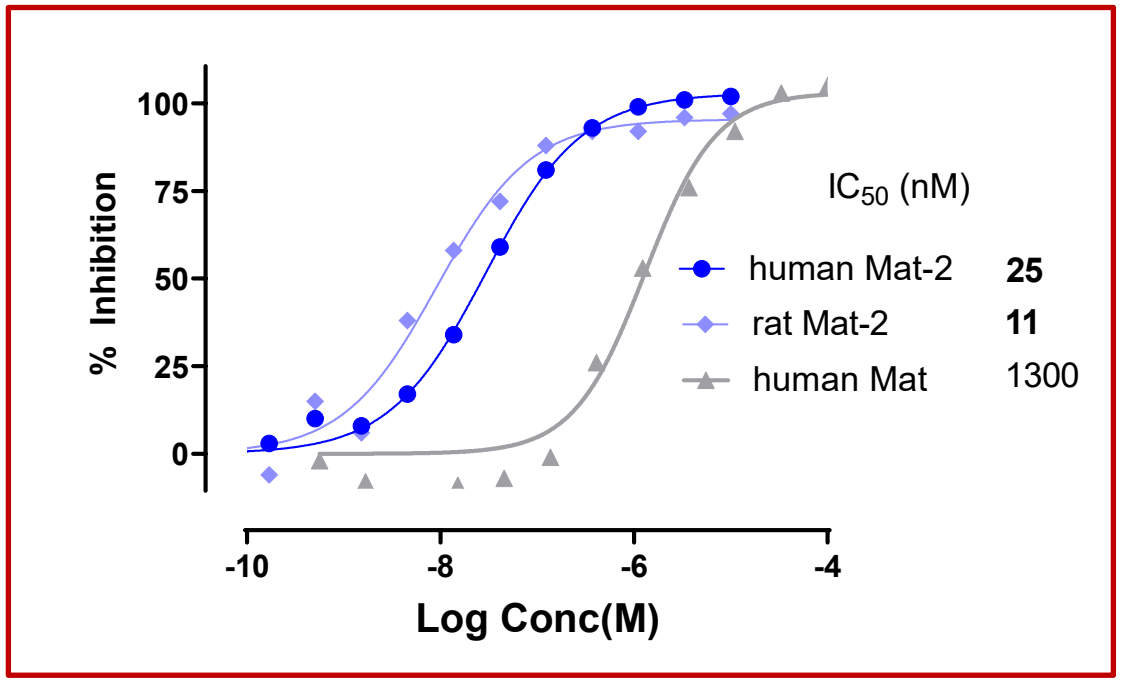
- Target and function is well-validated by human genetics
- Matriptase-2 (Mat-2) suppresses hepcidin levels by cleaving HJV and other components of the BMP signaling pathway
- Mat-2 inhibition restores signaling through HJV and increases hepcidin expression

- Our Mat-2 inhibitor program aims to develop a small molecule Mat-2 inhibitor as a potential treatment for rare hematologic disease caused by inappropriately low hepcidin
- DISC-A, an early lead potent Mat-2 inhibitor, has favorable pharmacokinetics and modulates hepcidin expression in vivo

Finberg et al, Blood 2010; Zhang et al, J Biol Chem 2010

DISC-A is a potent Mat-2 inhibitor and selective against Matriptase



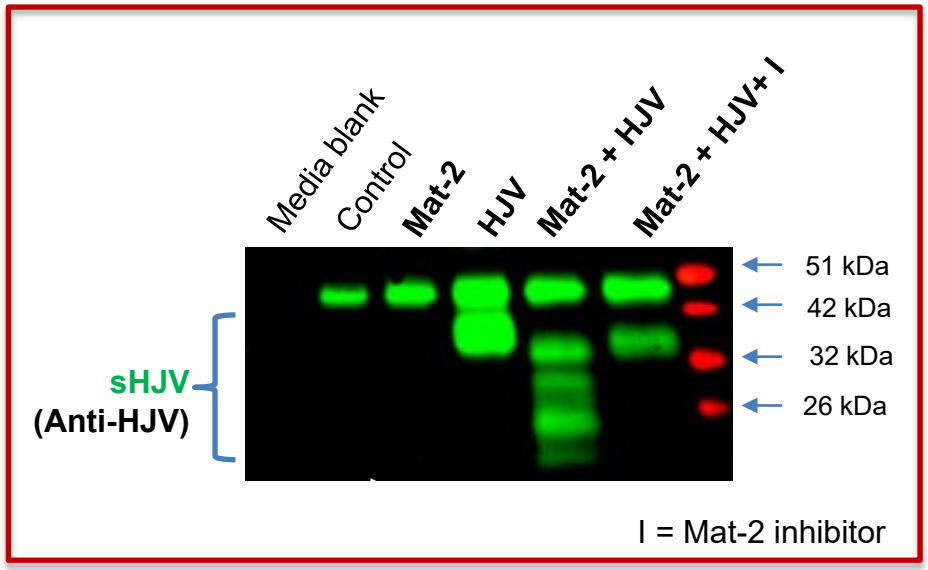


Decrease in fluorescence signal vs a non-inhibited control indicates inhibition of Mat-2 catalytic activity by compound of interest

DISC-A is a potent Mat-2 inhibitor (human and rat) and 50-fold selective against Matriptase

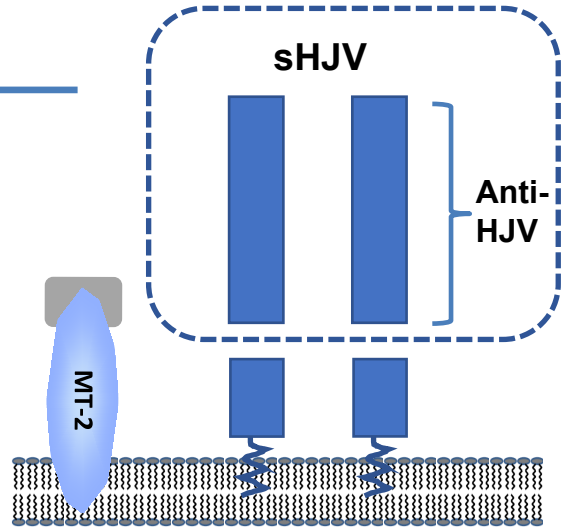
DISC-A shows a dose-dependent inhibition of HJV cleavage

Western Blot



DISC-A can inhibit HJV cleavage on cell surface and reduce formation of soluble HJV in cell culture

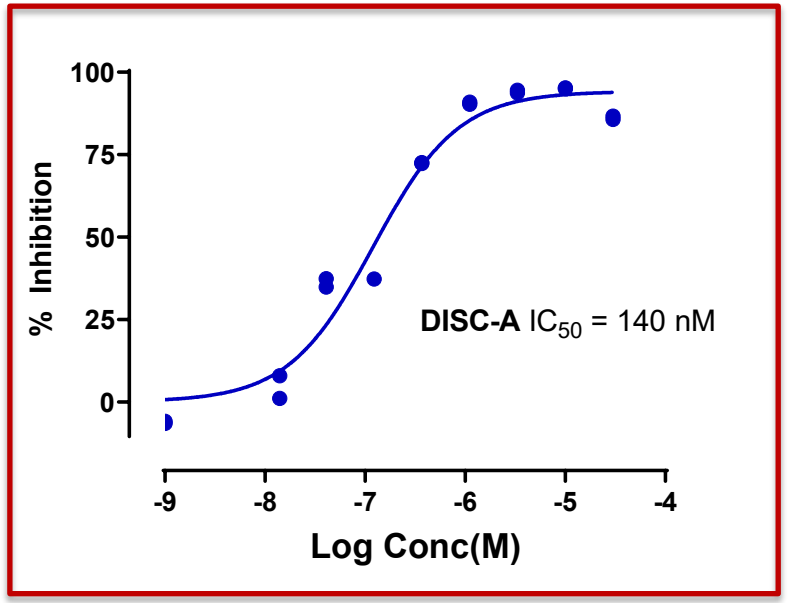
ELISA; WB
Mat-2 inhibitor decreases sHJV fragments



HEK293A cells

HEK293A cells are co-transfected with Mat-2 and HJV plasmids

ELISA



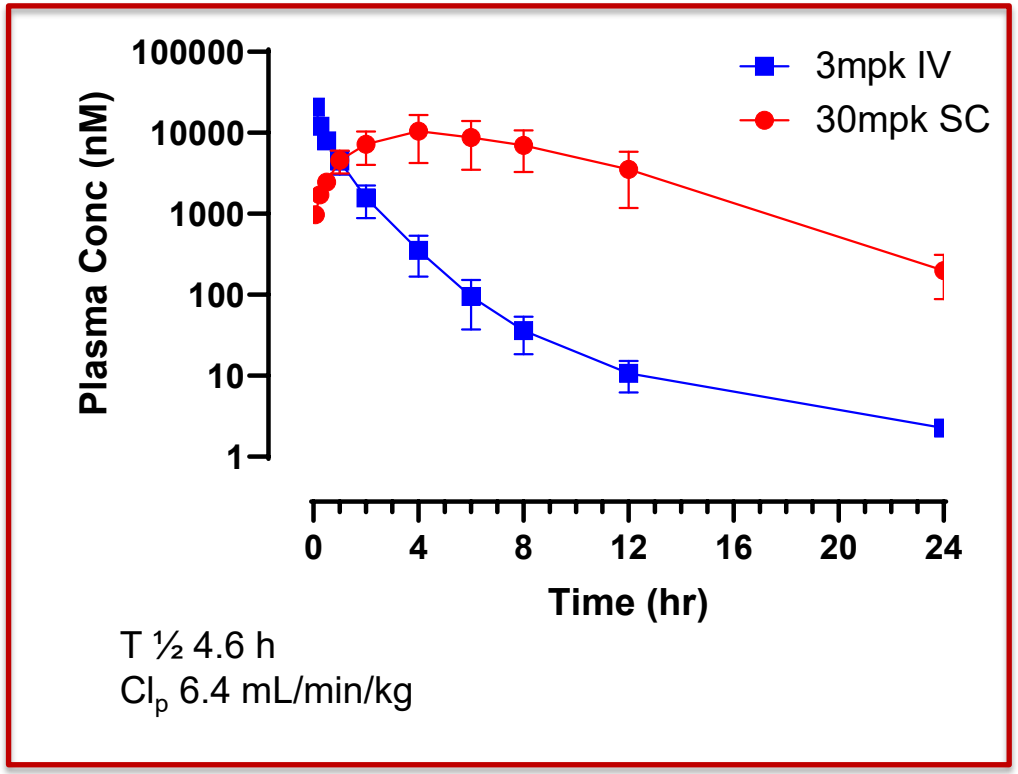
DISC-A shows a dose-dependent inhibition of HJV cleavage

DISC-A has favorable pharmacokinetics and safety profile

Low DDI potential and favorable safety profile	
CYP inh IC_{50}	>25 µM
CYP ind 3A4	No
r/h LM stab	Stable
hERG IC_{50}	>30 µM
Nav1.5 IC_{50}	>30 µM
Cav1.2 IC_{50}	>30 µM
Safety panel *	No hits

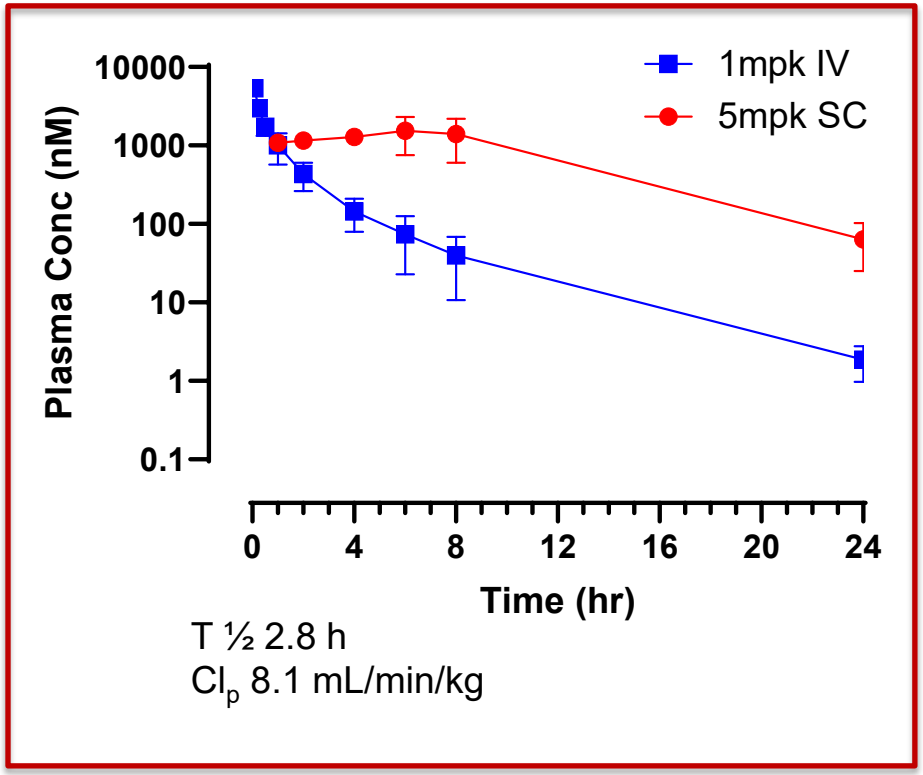
* 78 target panel

Rat PK



T ½ 4.6 h
Cl_p 6.4 mL/min/kg

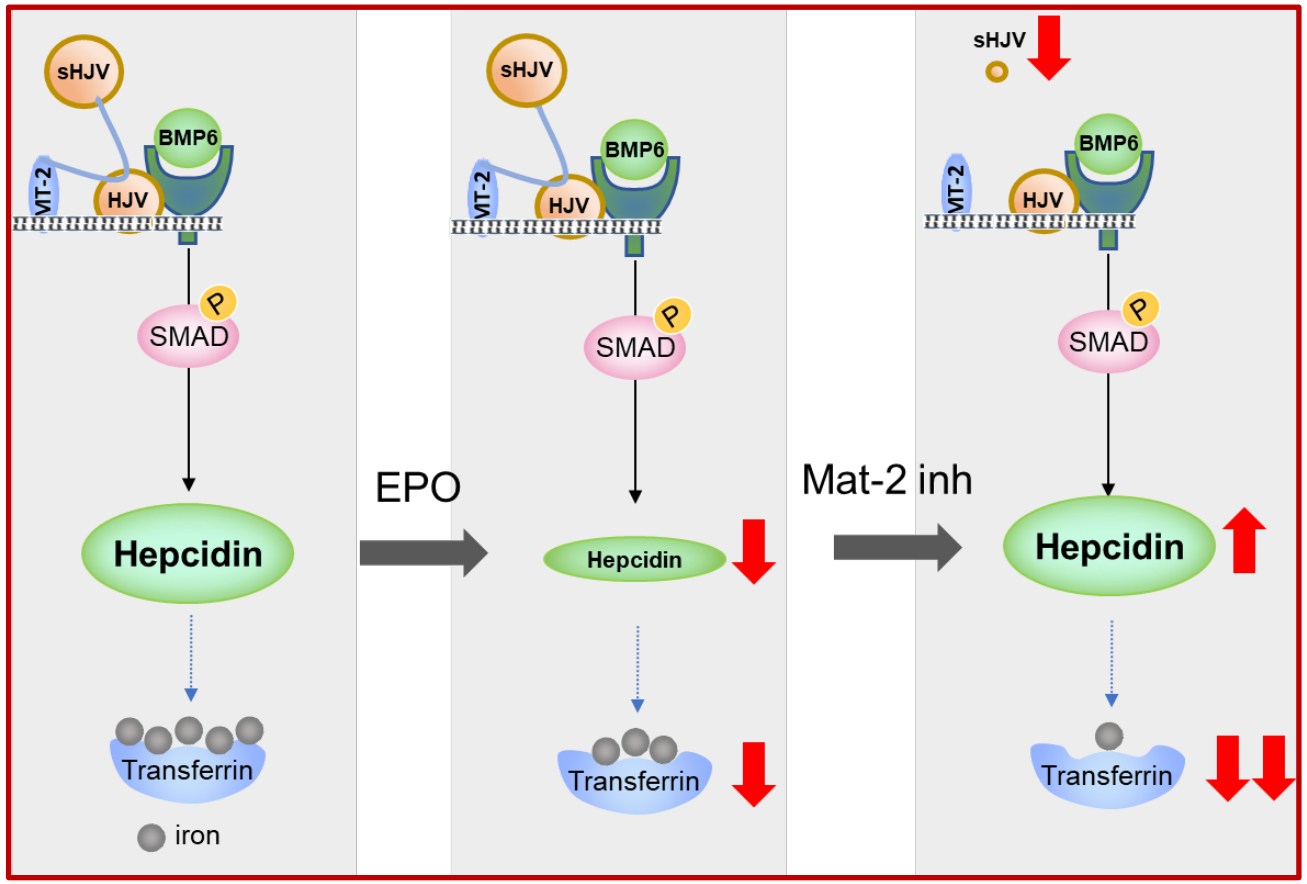
NHP PK



T ½ 2.8 h
Cl_p 8.1 mL/min/kg

- Favorable pharmacokinetics profile in rats and non-human primates (NHP)
- Low drug-drug interaction potential and favorable safety profile

Low hepcidin rat model induced by EPO and 45 ppm iron diet

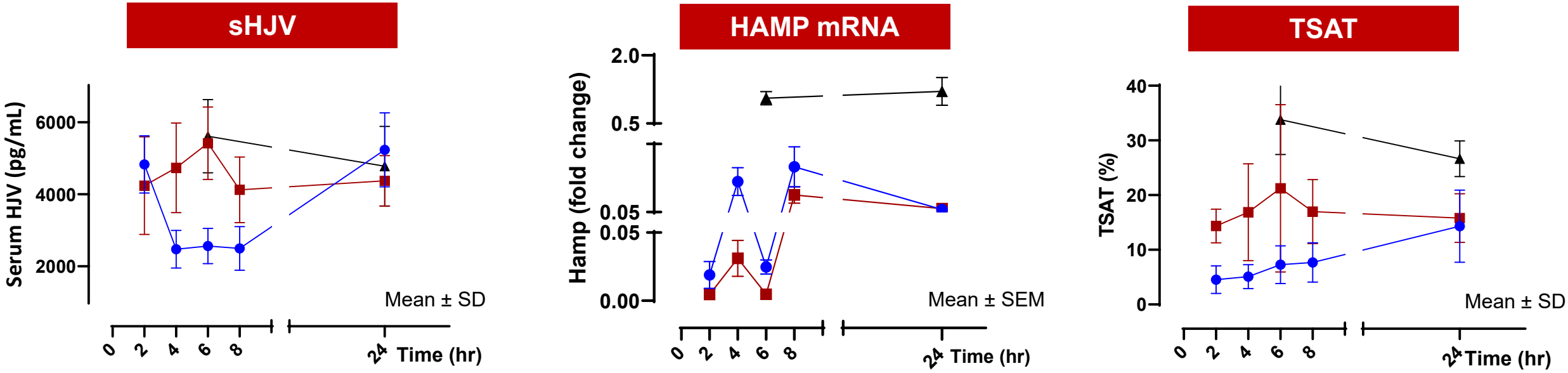


- Sprague-Dawley rats are placed on a standard iron diet (45 ppm) for 4 weeks, starting at 4 weeks of age
- Erythropoietin (EPO) is administered at 30 IU/animal/day for 4-consecutive days, before dosing with DISC-A
- The increased erythropoiesis leads to increased iron utilization and consequently suppressed hepcidin levels, measured by liver HAMP mRNA expression

DISC-A increases hepcidin and decreases sHJV and TSAT

in low hepcidin rat model

Rats, n= 9 per group, 45 ppm iron for 4 weeks, 30 IU/day EPO for 4 days, single dose SC DISC-A, 20mg/kg



EPO + DISC-A
EPO + Vehicle
Saline (No EPO)

- Reduction in sJHV, increase in HAMP liver expression and >50% decrease in TSAT up to 8 hr
- Robust pharmacokinetics/pharmacodynamics response (data not shown)

Conclusions

- DISC-A is a novel and potent inhibitor of Matriptase-2
- DISC-A inhibits Matriptase-2 proteolytic activity and prevents cleavage of HJV on cell surface
- A single subcutaneous administration of DISC-A at 20 mg/kg resulted in robust reduction in soluble HJV, >50% reduction in serum iron and increase in liver HAMP expression
- The favorable pharmacokinetics and drug-like properties suggest compounds from these chemical series have the potential for clinical therapeutic benefit.