S843

HEPCIDIN MIMETIC PTG-300 FOR TREATMENT OF INEFFECTIVE ERYTHROPOIESIS AND CHRONIC ANEMIA IN HEMOGLOBINOPATHY DISEASES

Greg Bourne[1], Li Zhao[2], Ashok Bhandari[2], Brian Frederick[2], Jaimee McMahon[1], Vinh Tran[2], Jenny Zhang[1], Adam Stephenson[1], Roopa Taranath[2], James Tovera[2], Thamil Annamalai[2], Larry Mattheakis[2], Dinesh Patel[2], Mark Smythe[1], David Liu[2]

[1]Protagonist Therapeutics Inc., Brisbane, QLD, Australia

[2]Protagonist Therapeutics Inc., Newark, CA, USA

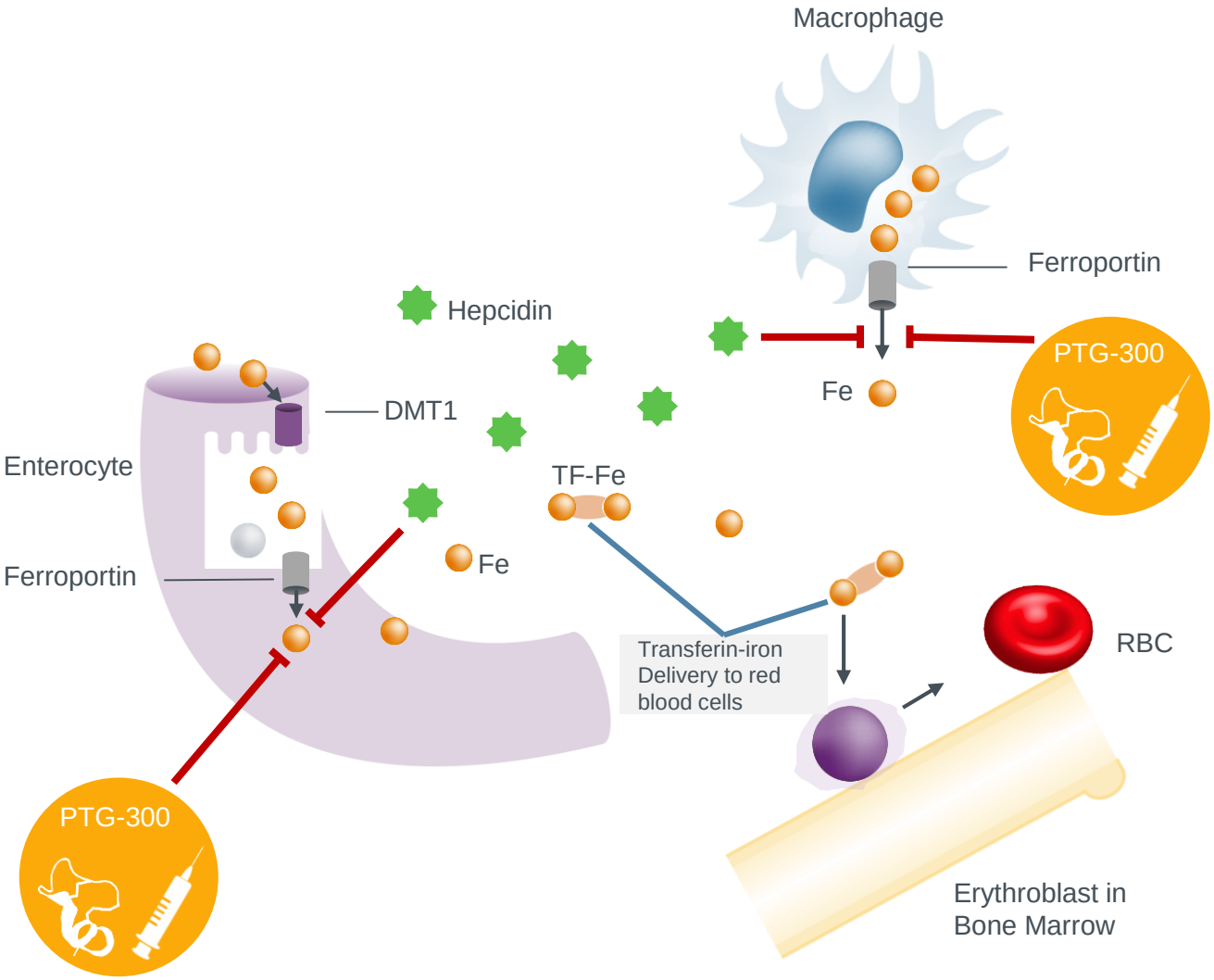
David Y. Liu, Ph.D.
Chief Scientific Officer, Head R&D
Protagonist Therapeutics, Inc.

Financial Disclosure

- Dr. Liu is an employee of Protagonist Therapeutics, who sponsored these studies

Hepcidin: Regulator of Iron Homeostasis

PTG-300: New Class of Agent – Hepcidin Mimetic

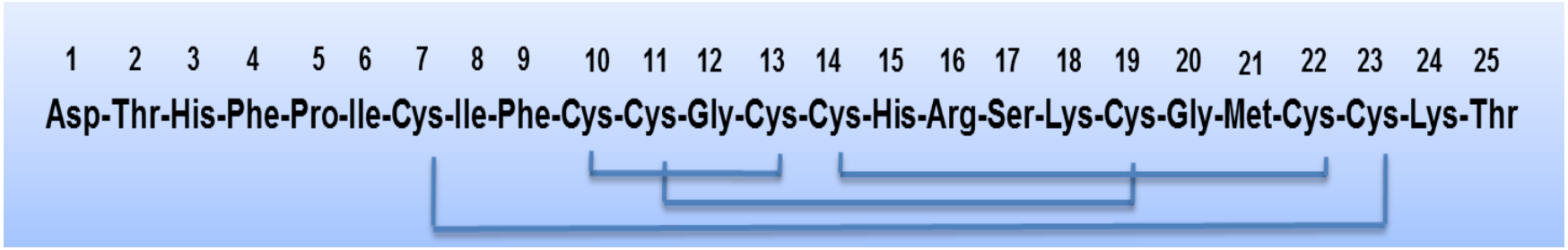


D'Angelo G. Role of hepcidin in the pathophysiology and diagnosis of anemia. *Blood Res*. 2013;48:10-15.

Treatment for Iron Loading Anemia

- Under conditions of ineffective erythropoiesis (IE), hepcidin levels are suppressed leading to increases in iron absorption from the GI tract and iron export from macrophages
  - Exacerbation of underlying IE through iron toxicity in developing erythrocytes in the bone marrow
- Agents with hepcidin activity may help correct iron distribution abnormalities with beneficial effects on erythropoiesis
- Treatment of anemia will relieve transfusion burden and secondary iron overload which otherwise requires palliative chelator therapy

Hepcidin – Complex Structure



25 amino acids in length with 4 disulfide bonds, resulting in the complex production of a correctly folded full-length hepcidin

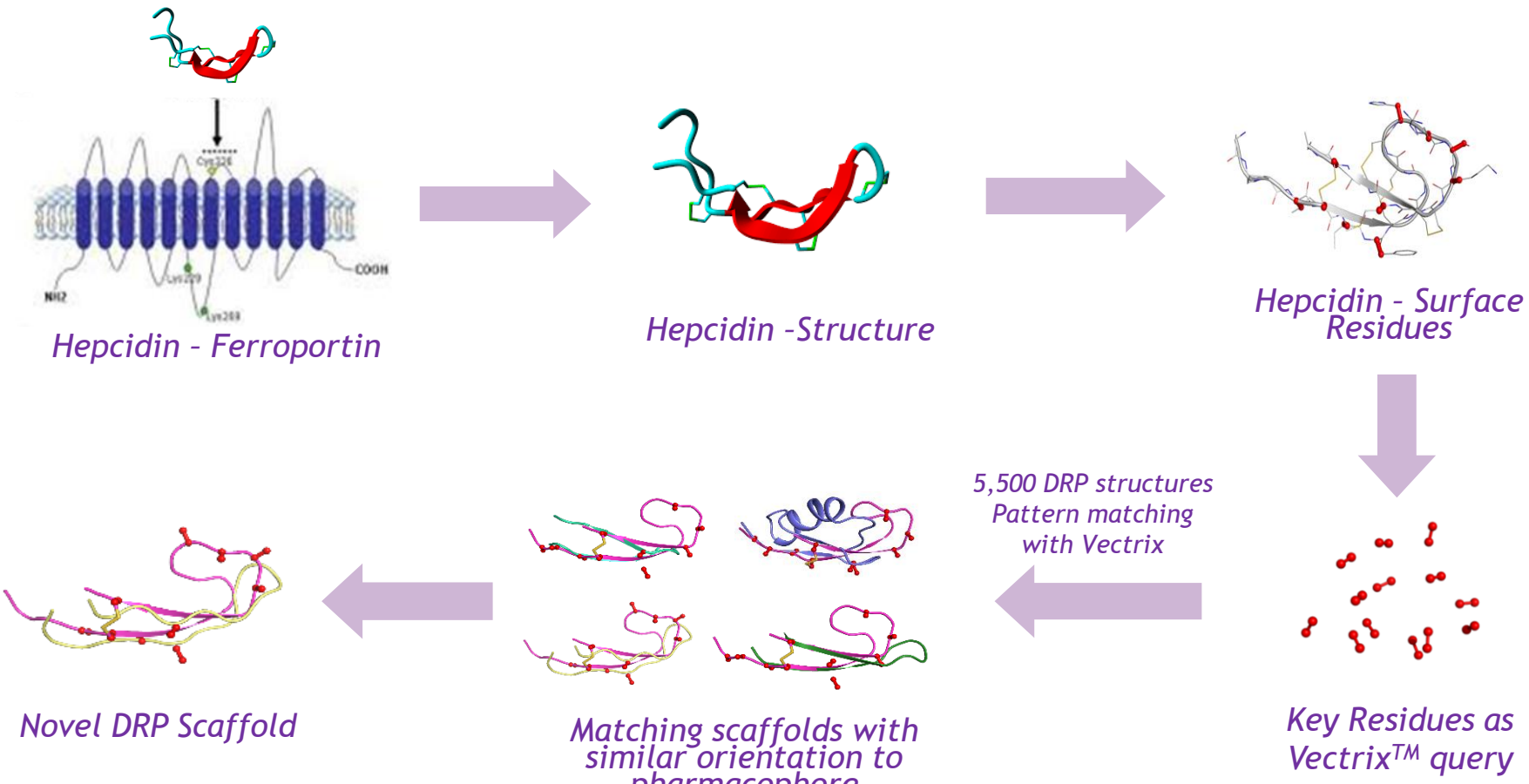
- 105 different folds of 4 disulfide bonds are possible
- Reported : 6-12% folding yield from linear
- Solubility, aggregation and stability issues

Ref: Zhang et al. Peptide Science 2010 94 257 – 264

PTG-300 Discovery of the Hepcidin Mimetic

An example of Vectrix™: Scaffold Hopping

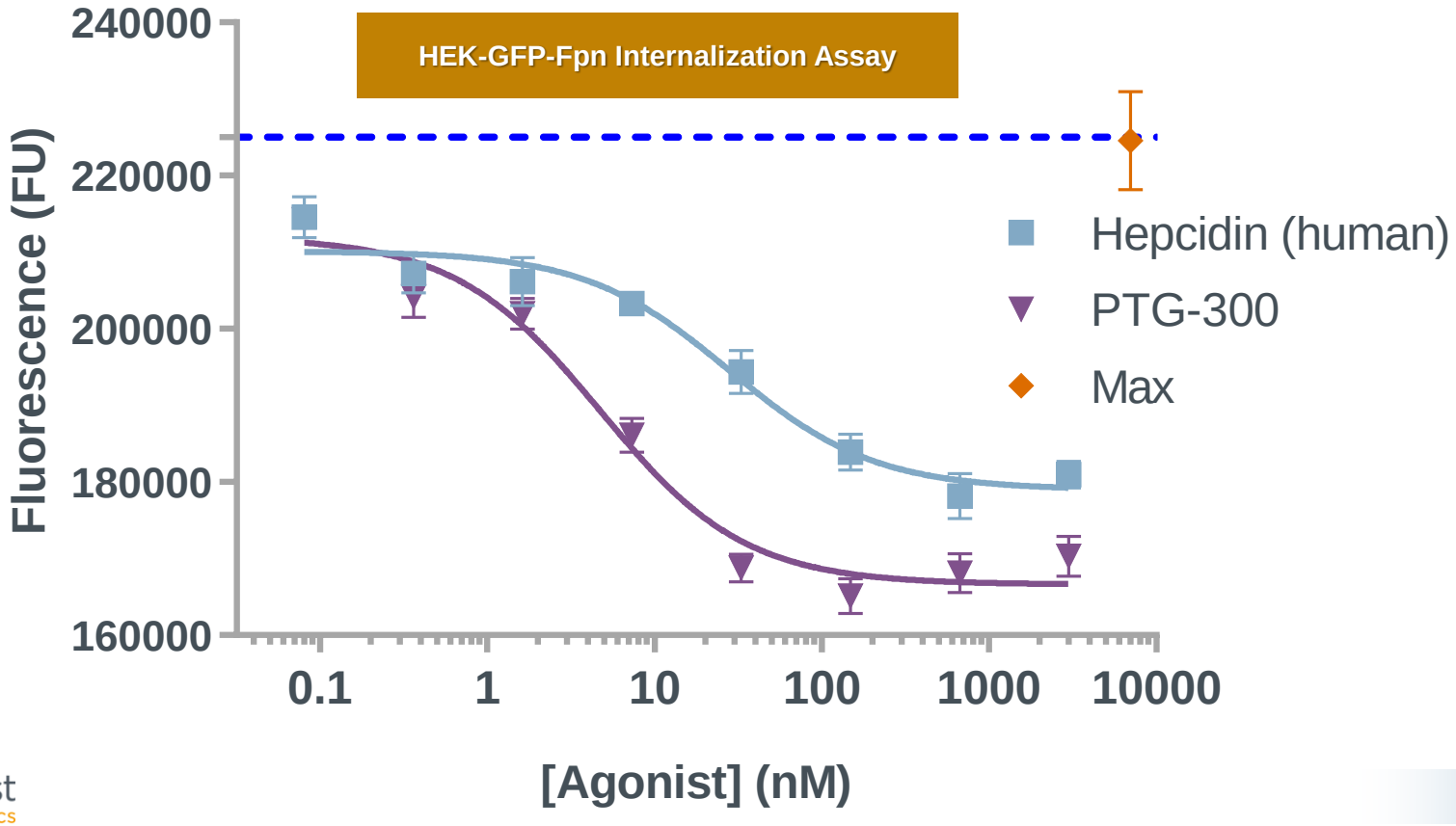
- Vectrix™ identifies a novel DSR peptide scaffold followed by phage display diversification and new chemistries for imparting drug-like properties



Discovery of PTG-300 Hepcidin Mimetic

Potential Treatment for Iron Loading Anemia in β-Thalassemia

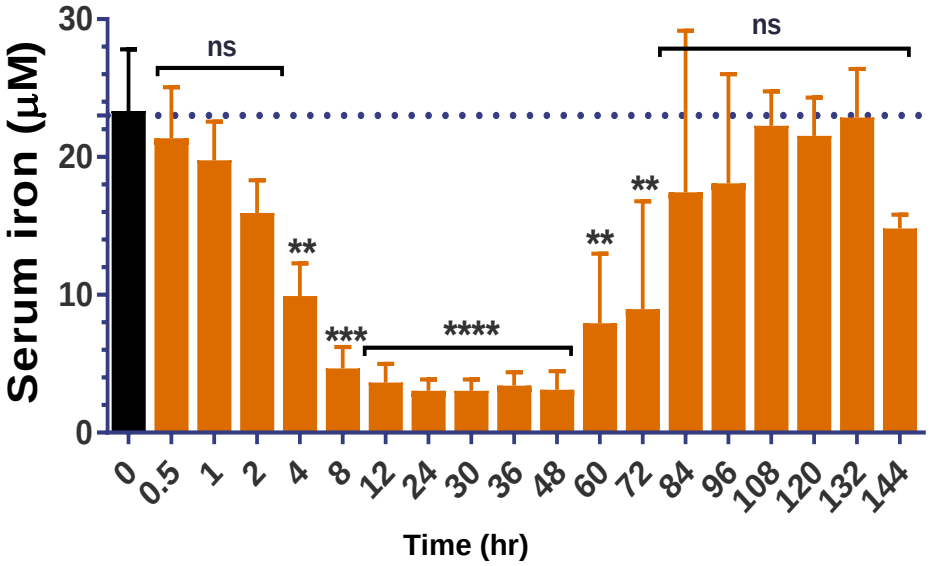
- Easier chemical synthesis, increased serum stability/aqueous solubility
- Increasing potency 6-fold compared to hepcidin
- 1 issued US patent and several pending applications



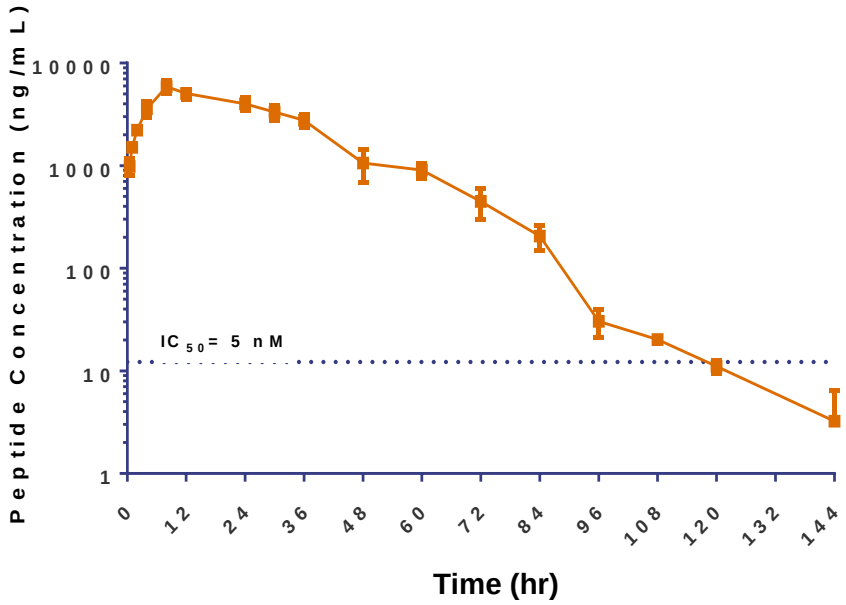
PTG-300 Reduces Serum Iron for >72 Hours

Serum PD Effect Consistent with PK in Cynomolgus Monkeys

PD – serum iron



PK – serum drug



Fsc% = 83% and $T_{1/2}$ 11.9 hours

ns p>0.05, * p≤ 0.05, ** p ≤0.01, ***p≤0.001, **** p≤0.0001

PTG-300 Reduces Serum Iron After an Oral Iron Challenge

Blockade of Enterocyte Ferroportin

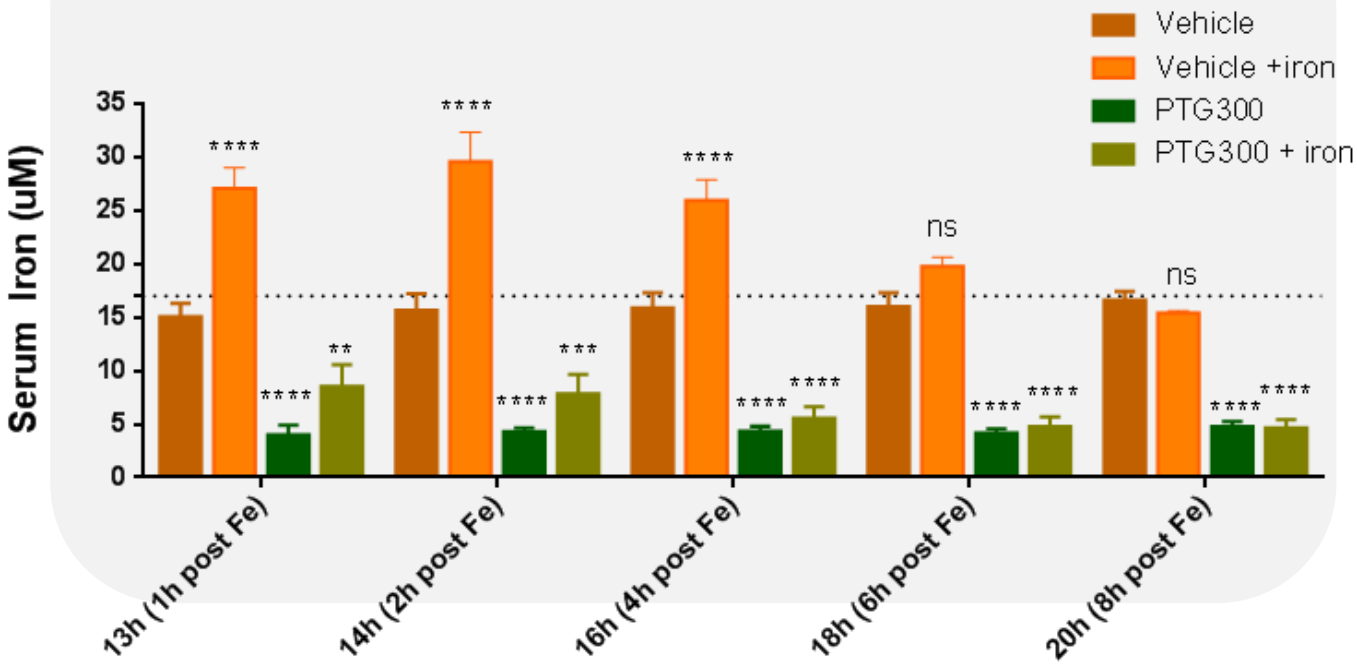
PTG-300
0.97 mg/kg s.c.

Wait 12 h

Oral Iron Gavage
2 mg/kg, iron

Measure "Serum Iron" after oral iron administration

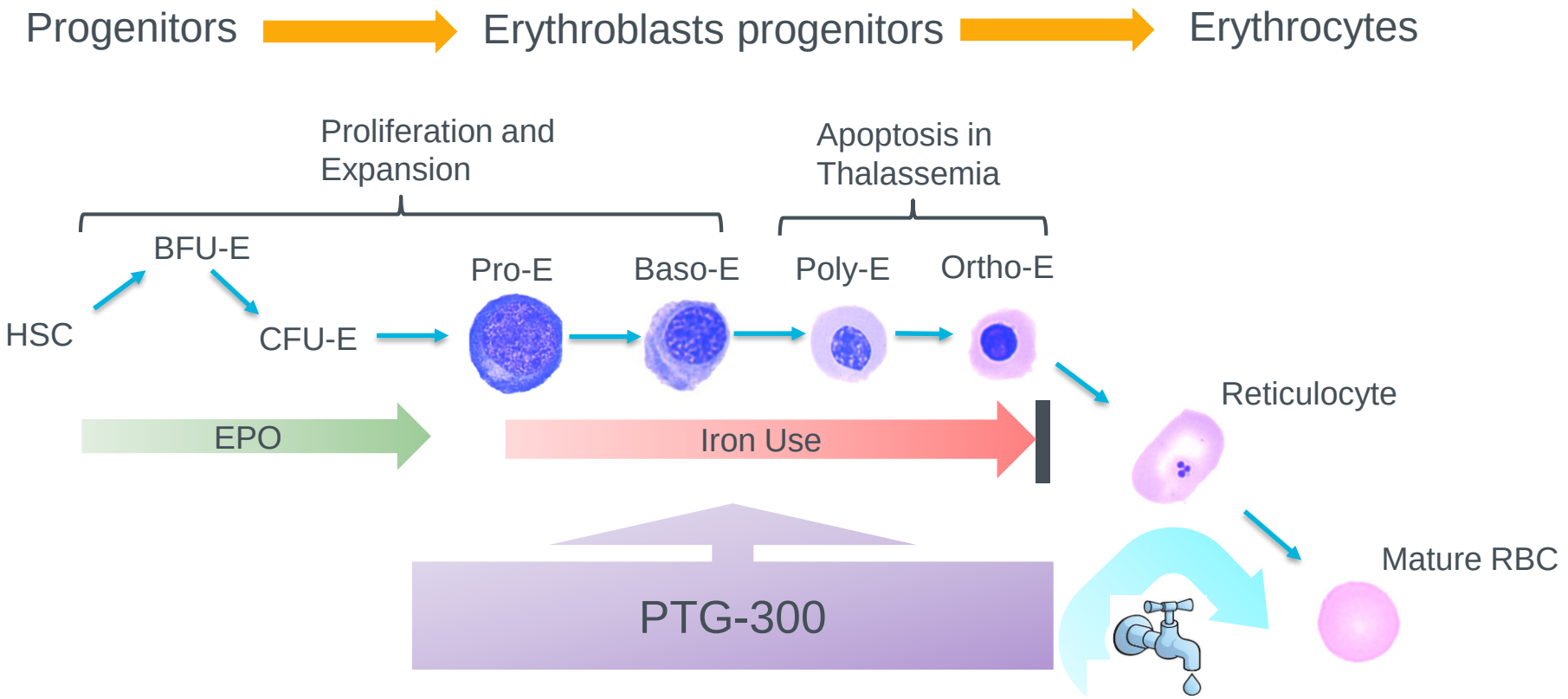
Serum Iron Levels Post Fe Challenge



ns p>0.05, * p≤ 0.05, ** p ≤0.01, ***p<0.001, **** p≤0.0001
Stats are compared to vehicle at time point

PTG-300: New Class of Erythropoietic Agent

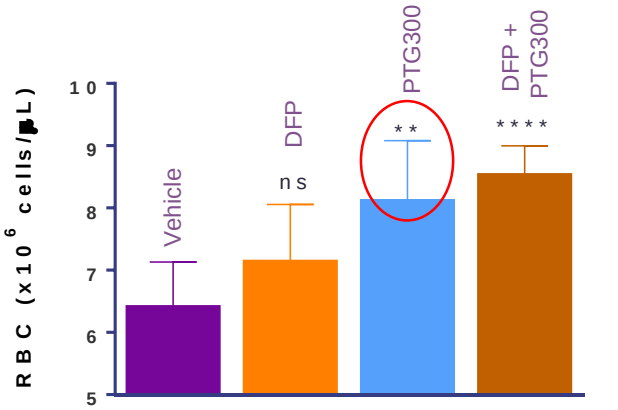
Treatment of Ineffective Erythropoiesis in Thalassemia/MDS/MF



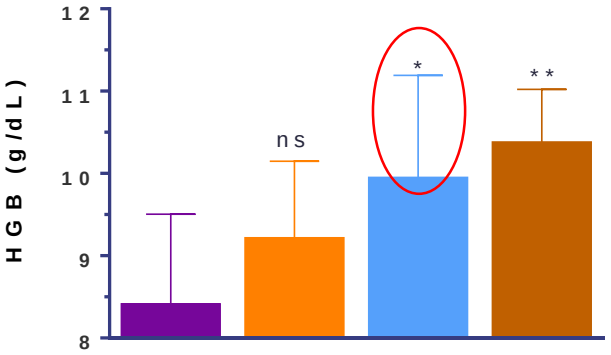
PTG-300: Efficacy based POC in β-Thalassemia Mouse Model

Improved Erythropoiesis

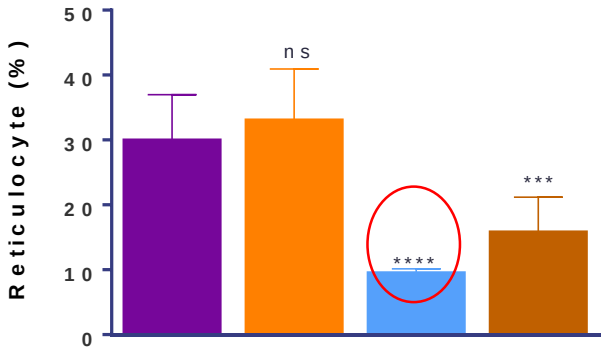
Red Blood Cells



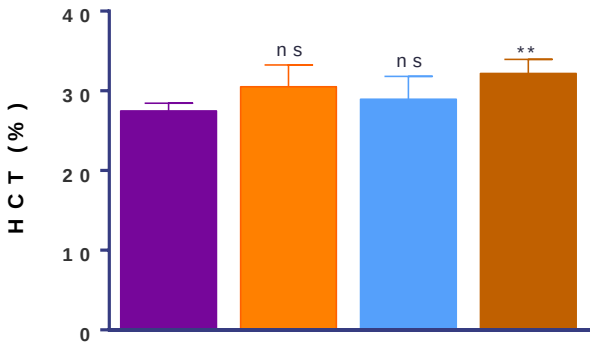
Hemoglobin



Reticulocyte (%)



Hematocrit



th3 + Vehicle | th3 + DFP | th3 + PTG300 | th3 + DFP + PTG300

- PTG-300 1 mg/kg dosed Q2D for 6 weeks ($Hbb^{th3/+}$ Mice)
- DFP (deferiprone, oral iron chelator) dosed at 1.25mg/mL
- *p≤0.05; **p≤0.01; ***p≤0.001; ****p≤0.0001; ns- not significant

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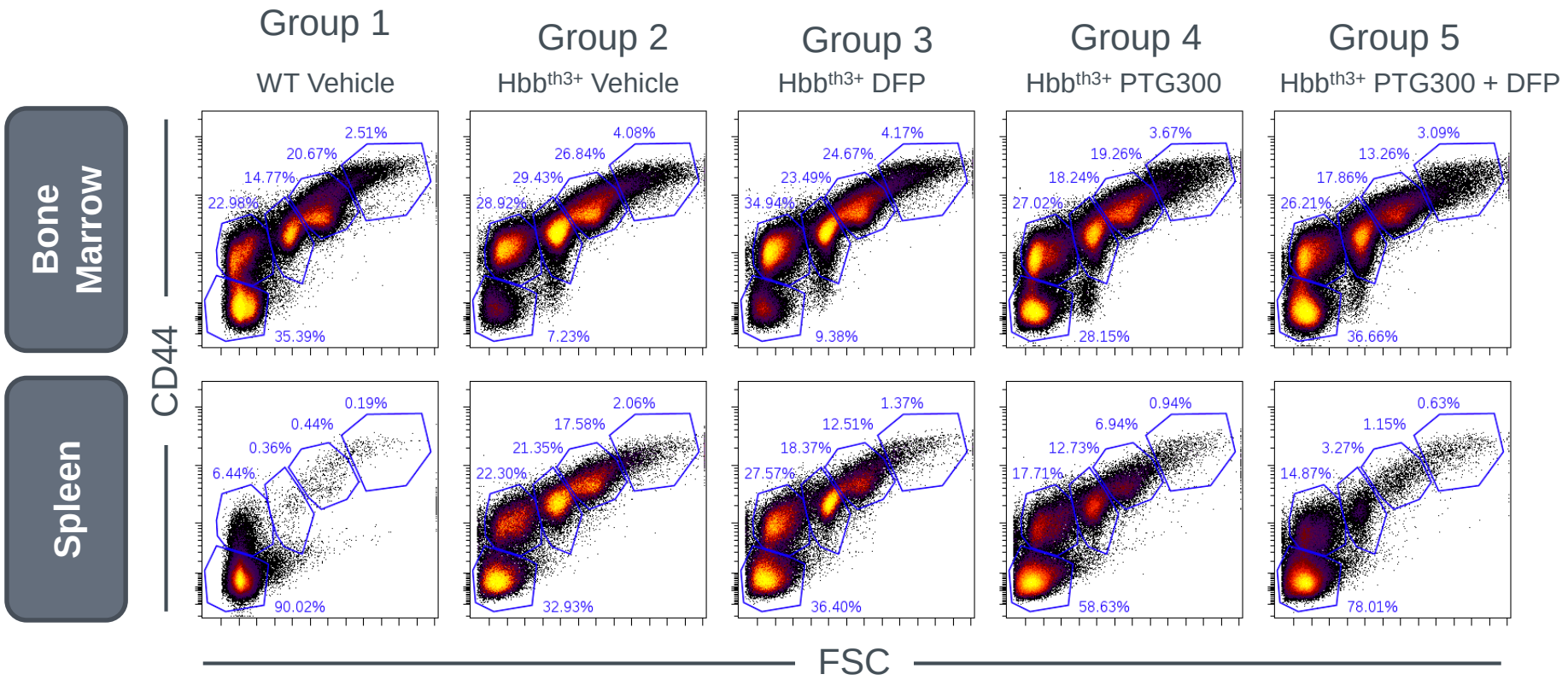
PTG-300 Improved RBC Maturation

Redistribution and Normalization of Erythroid Subsets



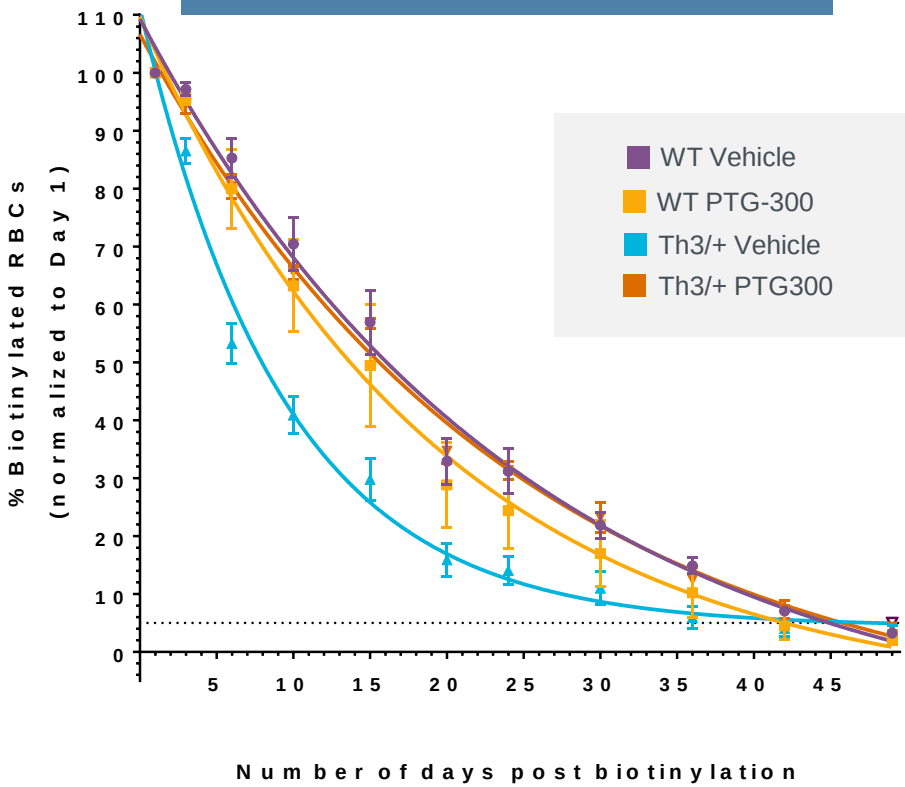
PTG-300 Improves RBC Survival in β-Thalassemia

Hbb$^{th3/+}$ Mouse Model

Dose PTG-300 (0.97 mg/kg, Q2D) → **4 weeks** → **Biotinylation NHS-PEG4-Biotin @ End of Week 4**

- Flow cytometry analysis over 7 weeks to measure RBC survival
- Continue dosing with PTG-300 for the entire duration

RBC survival in Male Hbb$^{th3/+}$ Mice



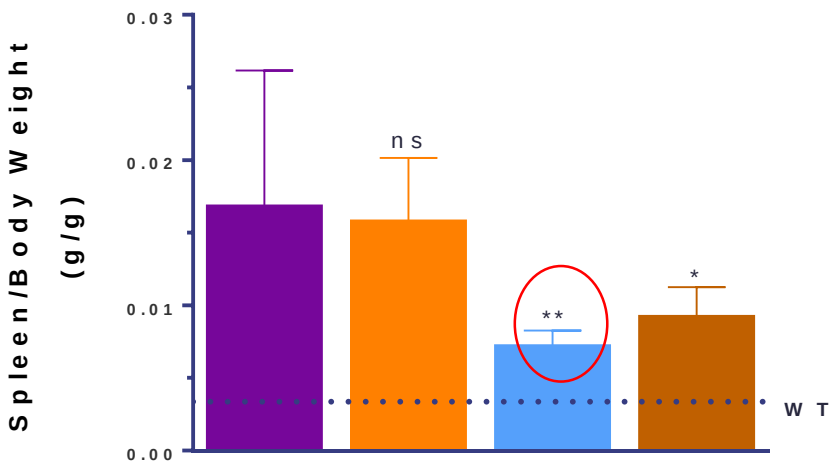
Half Life (Days)	
WT Vehicle	17.3 days
WT PTG-300	13.6 days
Hbb$^{th3/+}$ Vehicle	6.5 days
Hbb$^{th3/+}$ PTG-300	16.9 days

Protagonist Therapeutics

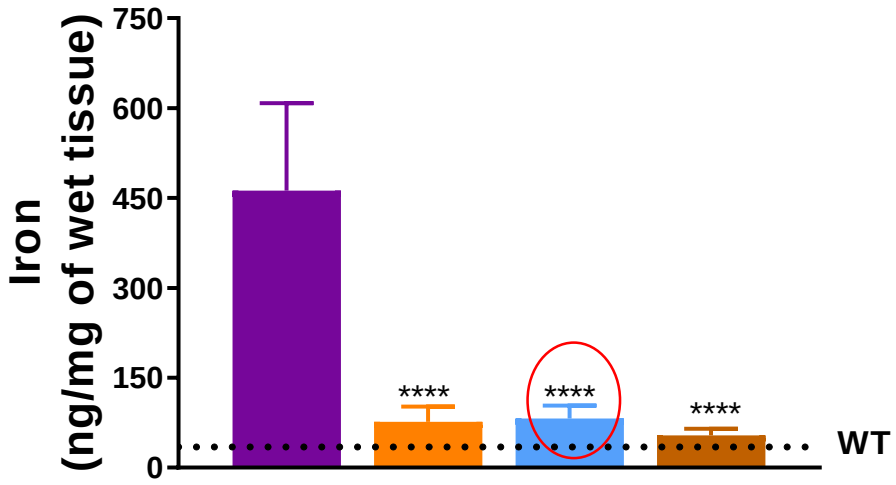
PTG-300: Efficacy based POC in β-Thalassemia Mouse Model

Decreased Splenomegaly and Liver Iron Overload

Spleen/Body Weight (g/g)



Non-heme Iron in Liver (ng/mg of wet tissue)



th3 + Vehicle | th3 + DFP | th3 + PTG300 | th3 + DFP + PTG300

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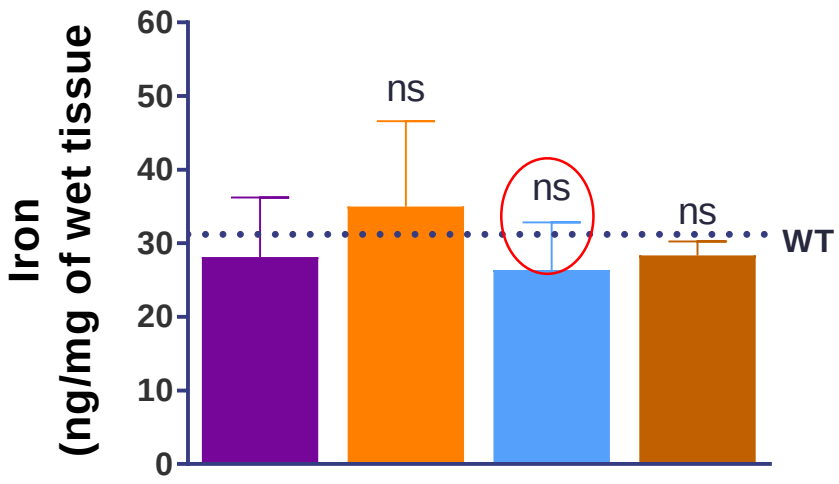
- *p≤0.05; **p≤0.01; ***p≤0.001; ****p≤0.0001; ns-not significant

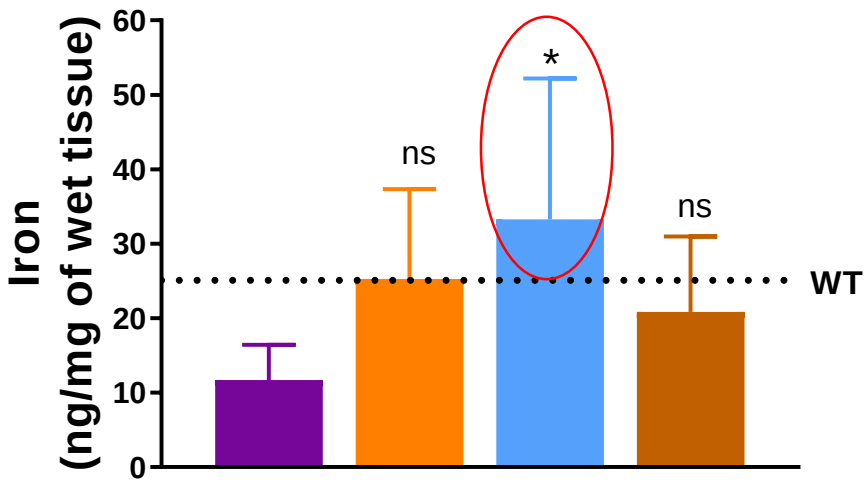
PTG-300: Efficacy based POC in β-Thalassemia Mouse Model

No Increase in Heart Iron and Some Iron Retention in Duodenum

Non-heme Iron in Heart



Non-heme Iron in Duodenum



th3 + Vehicle th3 + DFP th3 + PTG300 th3 + DFP + PTG300

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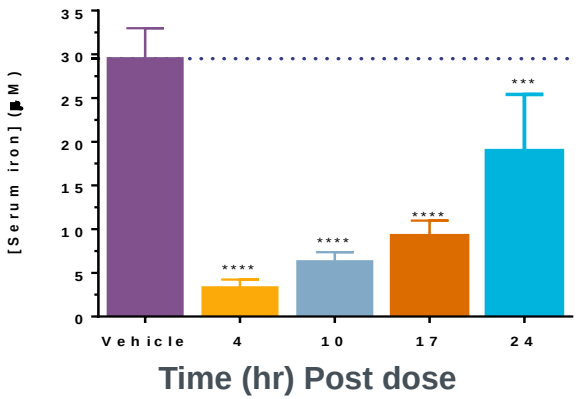
PTG-300 Efficacy with Potential for Weekly Dosing

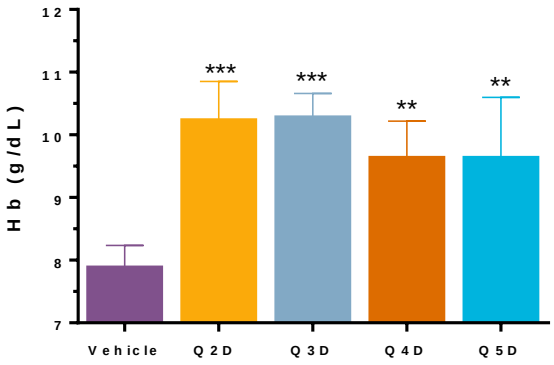
Transient Iron Restriction Improves Erythropoiesis in Hbb^{th3+} Mice

- PTG-300 decreases serum iron levels for 24h post dose
- Transient reduction in serum iron, during 24h post-dose, is sufficient to elicit efficacy with a Q4D or Q5D dosing regimen"

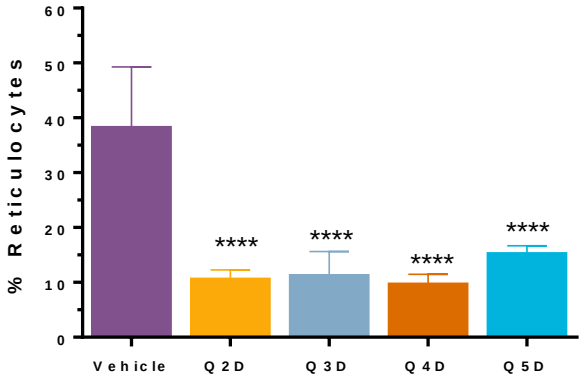
Serum Iron Levels



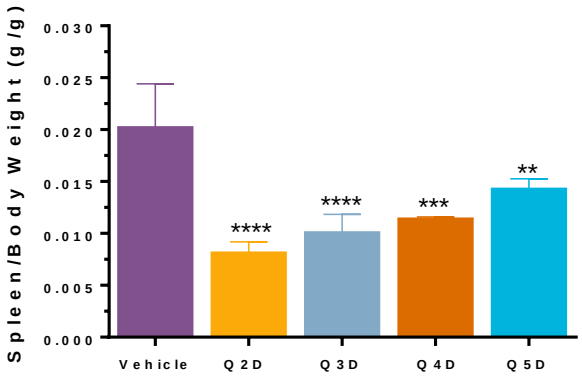
Chronic Hemoglobin



Chronic Study (Hbb^{th3+}) Mice: Reticulocyte Percentage



Chronic Study (Hbb^{th3+}) Mice: Spleen weight to Body Weight



ns p>0.05, * p≤ 0.05, ** p ≤0.01, ***p≤0.001, **** p≤0.0001

PTG-300: Summary of Efficacy in β-Thalassemia Mouse

- PTG-300, discovered through the optimization of a rationally designed scaffold, is a potent hepcidin mimetic with excellent drug-like characteristics
- Well-behaved pharmacodynamics and pharmacokinetic profile
  - Preclinical behavior translatable to humans?
  - Phase 1 in healthy subjects (Abstract S695, Saturday 5:00 pm in Room A13)
- Stimulation of effective erythropoiesis
  - Correction in precursor cell distribution
  - Increased RBC survival
  - Decreased splenomegaly and disease biomarkers
  - Relative ineffectiveness of oral iron chelator
- Reduction of liver iron overload through retention in enterocytes and potential redistribution to macrophages
- Transient iron reduction is sufficient for the correction of anmeia

PTG-300: Conclusions

- PTG-300 may potentially address pre-existing anemia *and* liver iron overload through iron restriction and redistribution to restore iron homeostasis

- Potential to address complications in β-thalassemia
  - Reduce primary iron overload
  - Reduce transfusions and subsequent secondary iron overload
  - Prevent splenomegaly and need for splenectomy with a reduction of thrombosis risk

- Potential to treat other diseases characterized by
  - Ineffective erythropoiesis, low hepcidin and iron overload, e.g. low risk MDS

PTG-300: Future

- Excellent non-clinical safety profile with exaggerated pharmacology
- Global Phase 2 trial in β-thalassemic patients to start in 2018 Q4
  - Received orphan status in the US
- Potential for broad spectrum of diseases for human trials
  - Ineffective erythropoiesis, low hepcidin and iron overload, e.g. low risk MDS
  - Primary iron overload, low hepcidin, e.g. hereditary hemochromatosis
  - Exaggerated erythropoiesis, e.g. polycythemia vera
  - Chronic liver fibrosis, e.g. NASH