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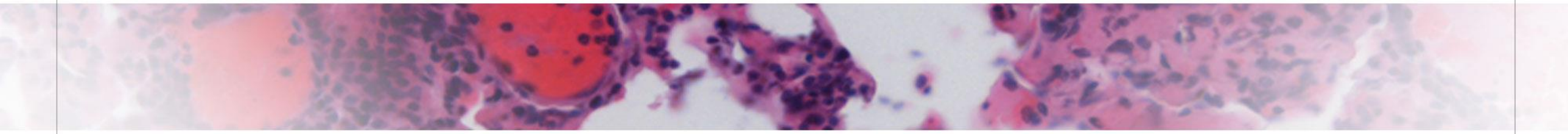

Abstract #139486

Selective Inhibition of ALK2 Signaling Suppresses Serum Hepcidin and Increases Serum Iron

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Keros Therapeutics, Lexington, MA

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American Society of Hematology Annual Meeting

Disclosure

All listed authors are employees of and shareholders in Keros Therapeutics, Inc.

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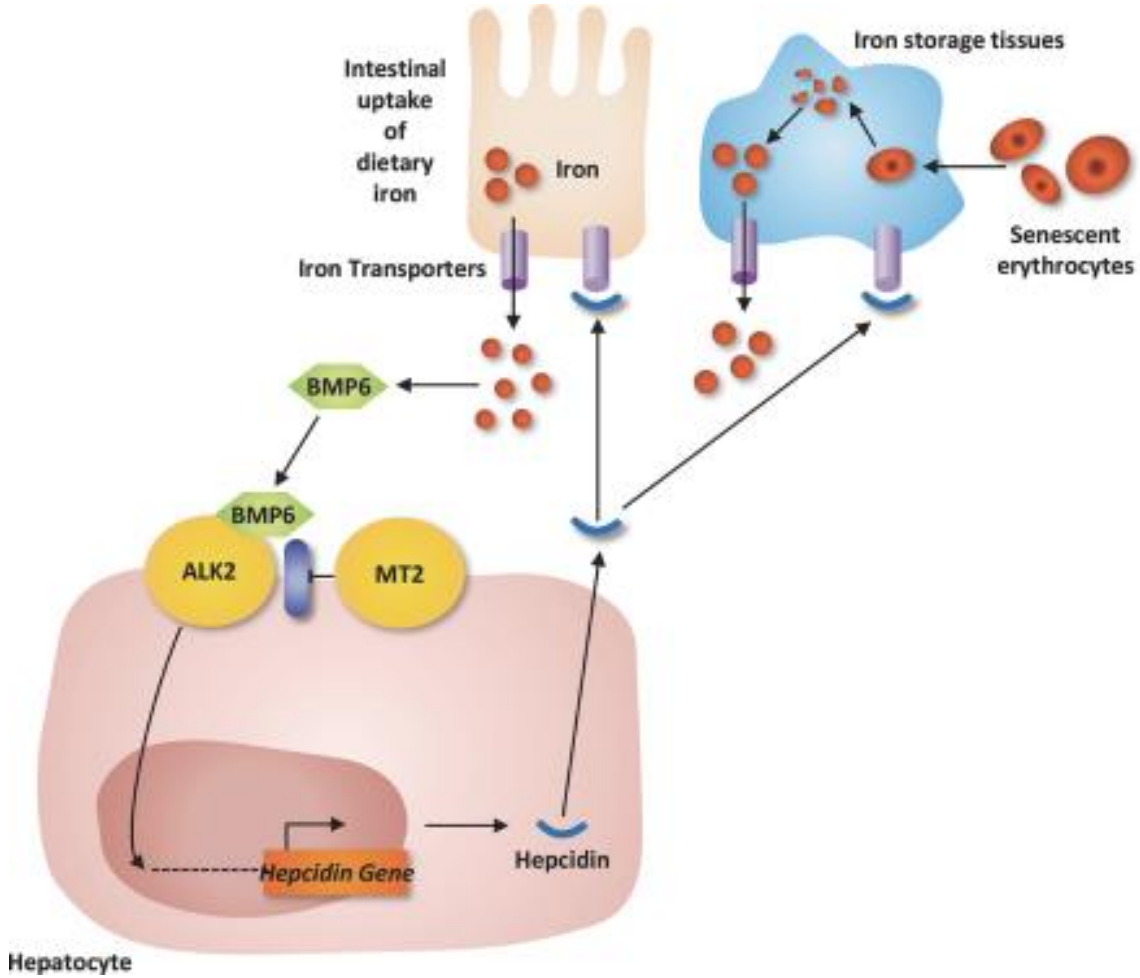
Introduction

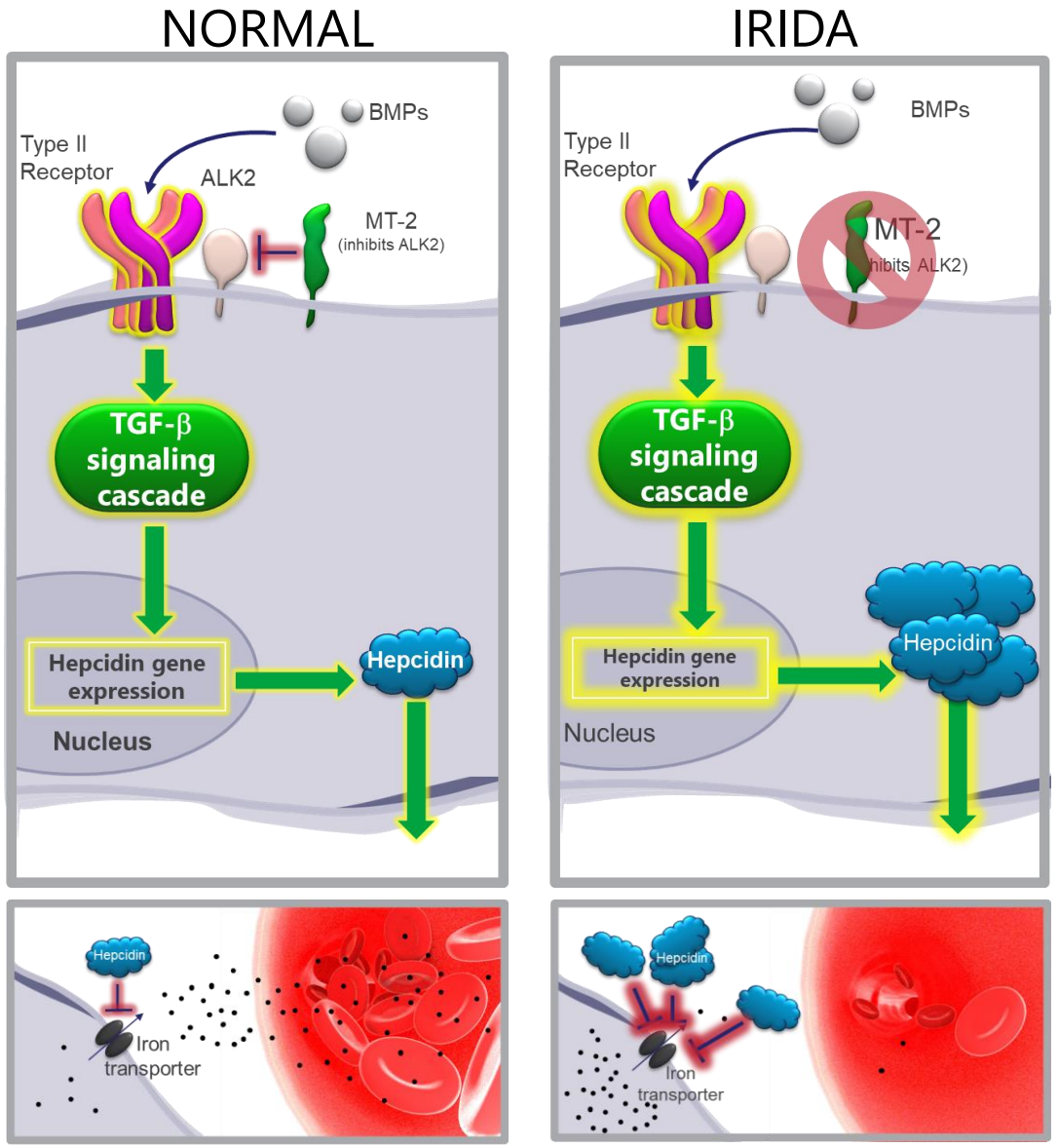
Hepcidin is a Key Regulator of Iron Metabolism

- Regulatory hormone that modulates iron distribution and bioavailability of iron by regulating ferroportin.

- Hepcidin is expressed, in part, in response to signaling through activin receptor-like kinase 2 (ALK2).



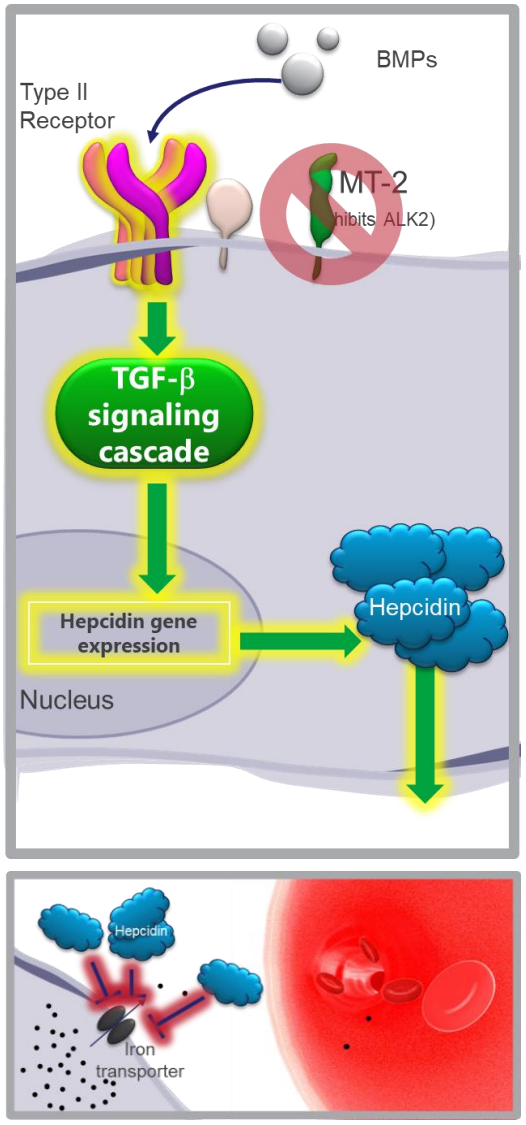
Loss of functional MT-2 Results in Iron Refractory Iron Deficiency Anemia



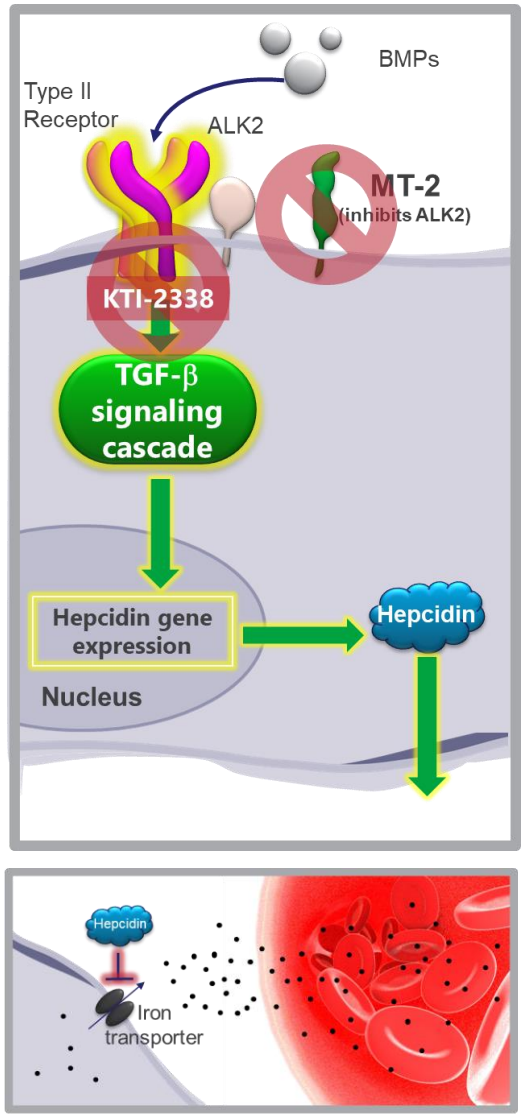
- ALK2 is activated through a signaling complex that forms between the ALK2 receptor complex (dimers of type 1 and type 2 receptors), the ligand BMP6, and co-receptor hemojuvelin (HJV).
- ALK2 signaling and subsequent hepcidin expression is downregulated by the transmembrane type II serine protease MT-2
- In IRIDA, lack of functional MT-2 results in continuous ALK2 activation, high hepcidin, low serum iron and anemia.
- Inhibition of ALK2 signaling and downstream SMAD phosphorylation may suppress hepcidin in IRIDA and potentially ameliorate anemia.

Loss of functional MT-2 Results in Iron Refractory Iron Deficiency Anemia

IRIDA



IRIDA + Treatment



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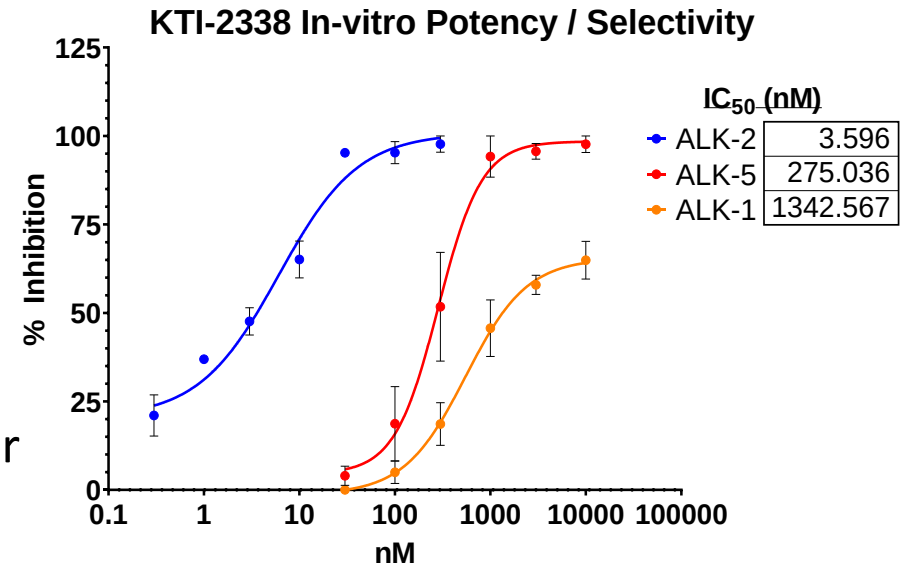
Characterization of KTI-2338 and KTI-A2.0MAb

Keros has multiple therapeutics designed to target ALK2 signaling:

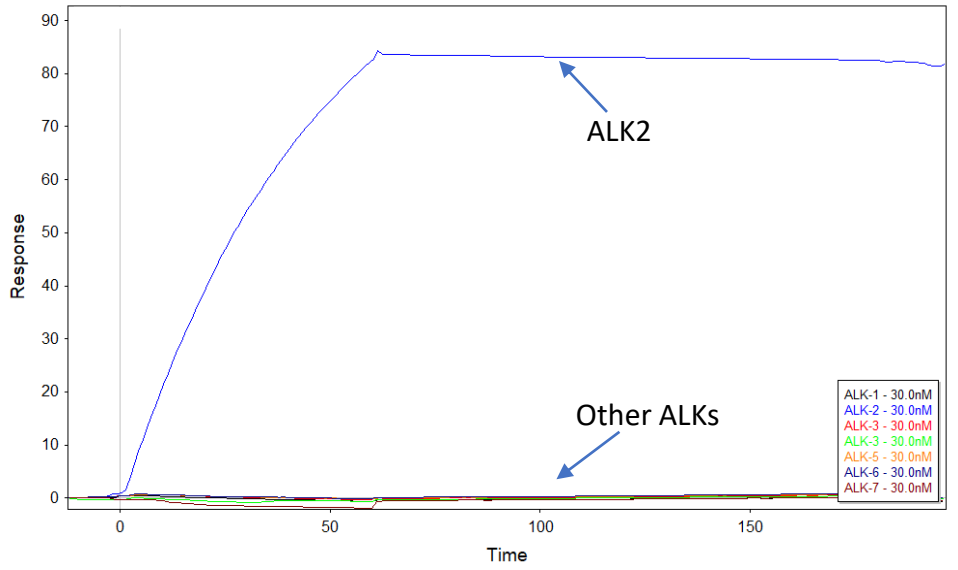
KTI-2338:

- A small molecule ALK2 kinase inhibitor
- Exhibited single-digit nanomolar potency against ALK2 in luciferase cell-based assays
- Observed to be highly selective for ALK2 compared to other structurally similar TGFβ type-1 receptors

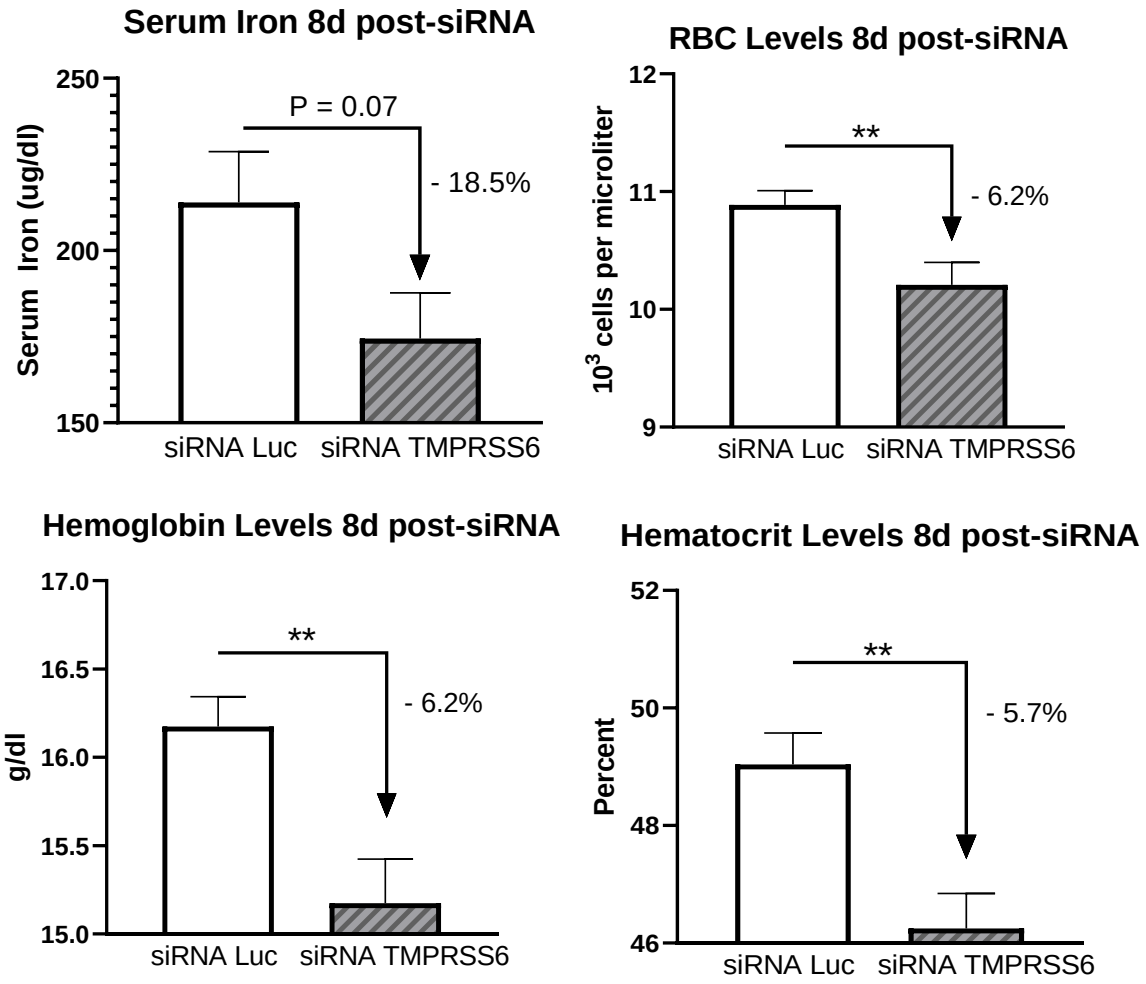


KTI-A2.0MAb:

- A novel, highly potent, neutralizing ALK2 antibody
- Exhibited picomolar potency in cell-based assays
- Demonstrated complete selectivity for ALK2 over other ALKs by Surface Plasmon Resonance (SPR)



Mice treated with TMPRSS6 siRNA phenocopy disease in IRIDA patients



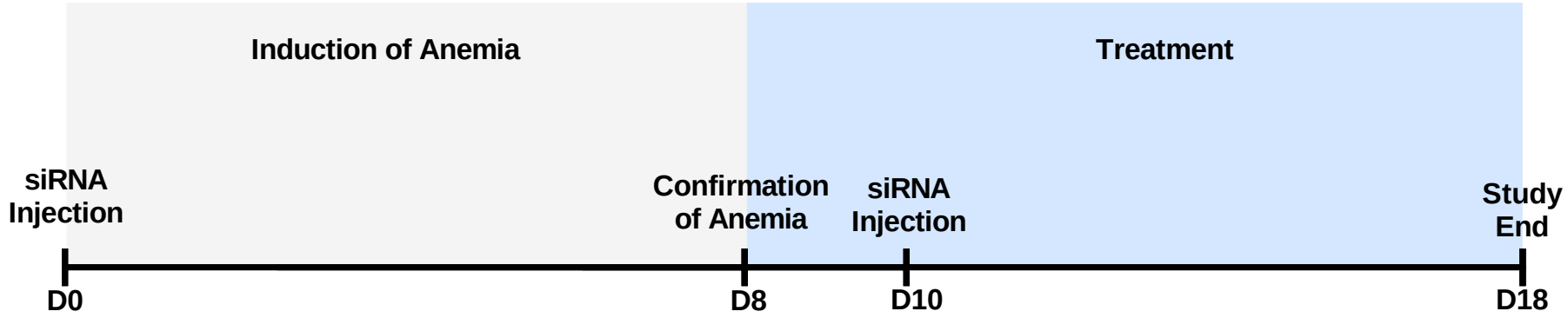
** P < 0.01 via unpaired two-tail t-test

- Eight-week-old, male, C57BL/6 mice were treated intravenously with lipid encapsulated siRNA targeted against either Luciferase (control) or TMPRSS6 (0.75 mg/kg).
- IV dosing of TMPRSS6-targeted siRNA decreases in serum iron and elicits anemia.

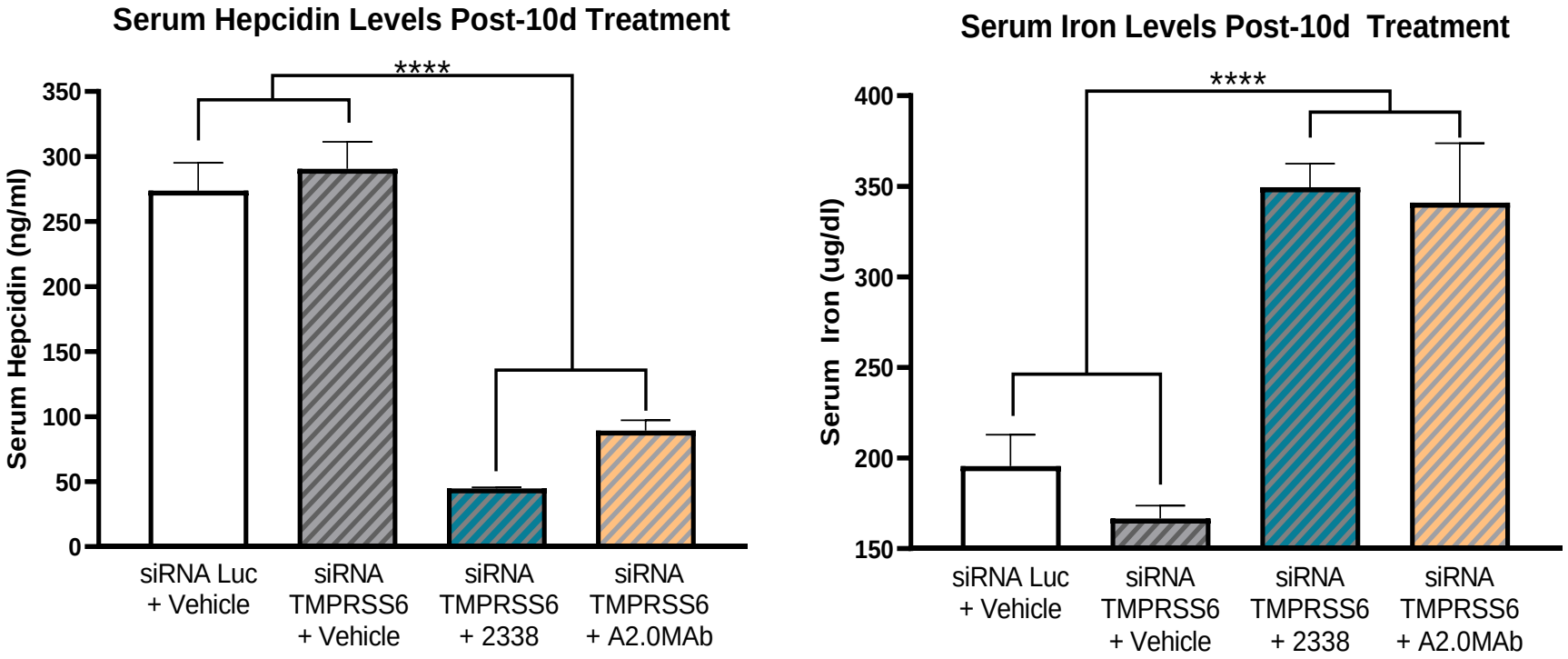
Therapeutic Intervention in IRIDA with KTI-2338 or KTI-A2.0MAb

- Following confirmation of disease at day 8 post initial siRNA administration, once-daily oral (KTI-2338 5 mg/kg) or twice-weekly intraperitoneal (KTI-A2.0MAb 5 mg/kg) treatment dosing commenced. A second siRNA administration was given on day 10.

- Studies were terminated 18d post initial siRNA administration. Hematological parameters, serum iron, and serum hepcidin were measured at the end of the study.



Therapeutic Dosing with KTI-2338 or KTI-A2.0MAb Resulted in Rescue of Disease Phenotype



* P < 0.05, ** P < 0.01, **** P < 0.0001 via two-way ANOVA

- Dosing with TMPRSS6 siRNA decreased serum iron in vehicle treated animals
- Treatment with either 2338 or A2.0MAb rescued the disease phenotype, decreasing serum hepcidin and increasing serum iron in animals treated with TMPRSS6 targeted siRNA

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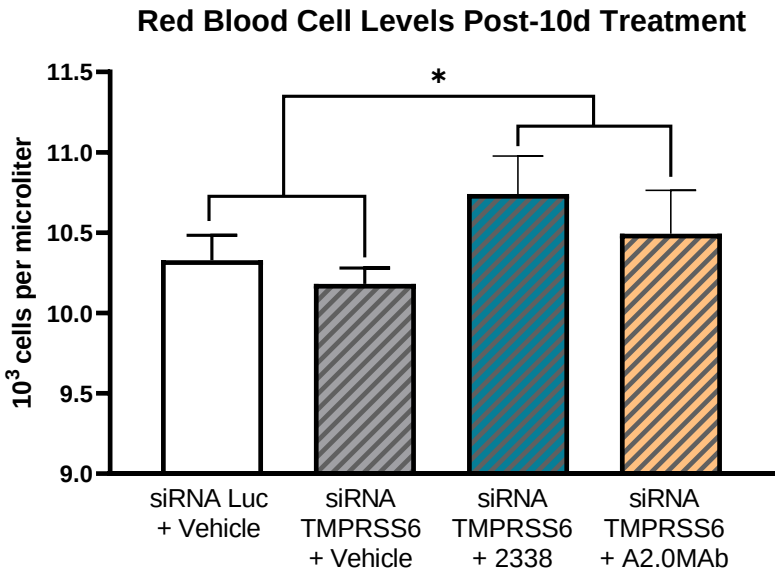

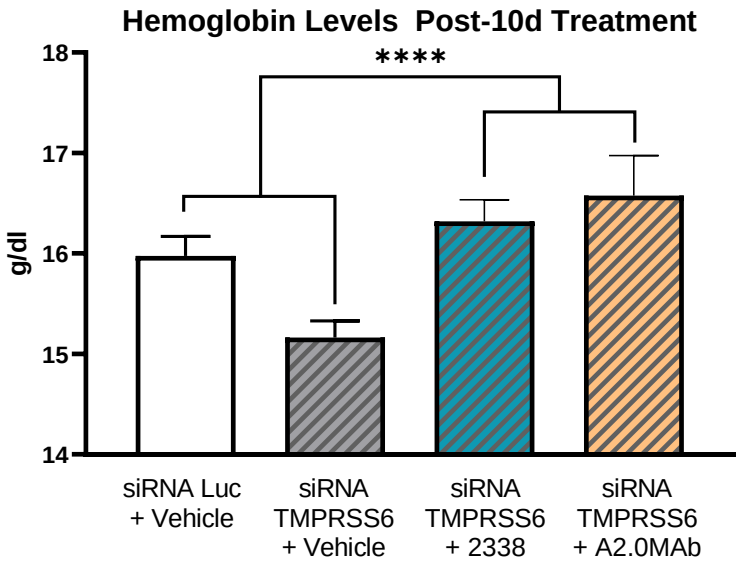

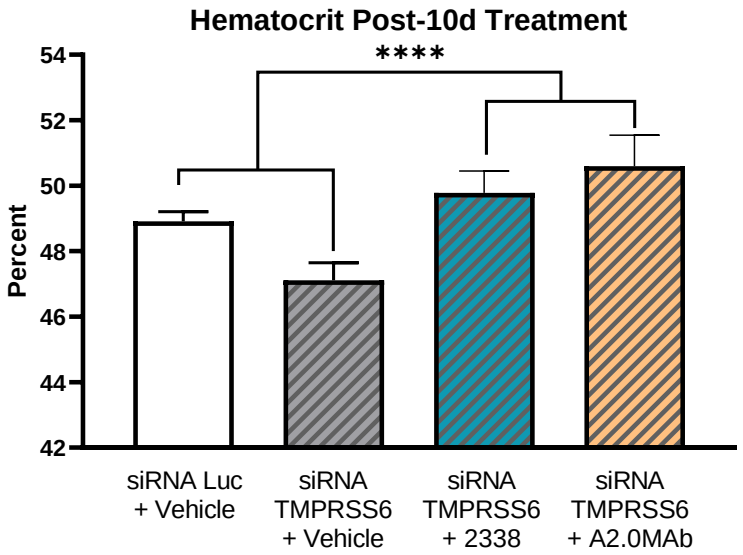

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- Dosing with TMPRSS6 siRNA decreased red blood cell levels, hemoglobin, and hematocrit in vehicle treated animals.
- Treatment with either 2338 or A2.0MAb rescued the disease phenotype, increasing red blood cell levels, hemoglobin, and hematocrit in animals treated with TMPRSS6 targeted siRNA.

Conclusions

- We evaluated multiple modalities of ALK2 inhibition, both a small-molecule ALK2 kinase inhibitor and a neutralizing ALK2 antibody, in a novel model of IRIDA.

- Inhibition of ALK2 signaling via either modality resulted in a decrease in serum hepcidin and increase in serum iron levels in a mouse model of IRIDA, confirming ALK2 as a key signaling element in the hepcidin-iron axis.

- These data support that ALK2 signaling is an integral part of hepcidin-mediated iron mobilization and illustrate the potential therapeutic benefit of ALK2 inhibition in anemia of high hepcidin.

- These data are consistent with observations in a Phase 1 clinical study in which KER-047, another small-molecule ALK2 kinase inhibitor currently in clinical development by Keros, was administered to healthy participants.

For more, see poster 769 Saturday Dec. 5, 2020.