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Selective Inhibition of ALK-2 Signaling Ameliorates Disease in a Novel Model of Iron Refractory Iron Deficiency Anemia (IRIDA)

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June 2020
Iron in Focus

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Disclosure

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

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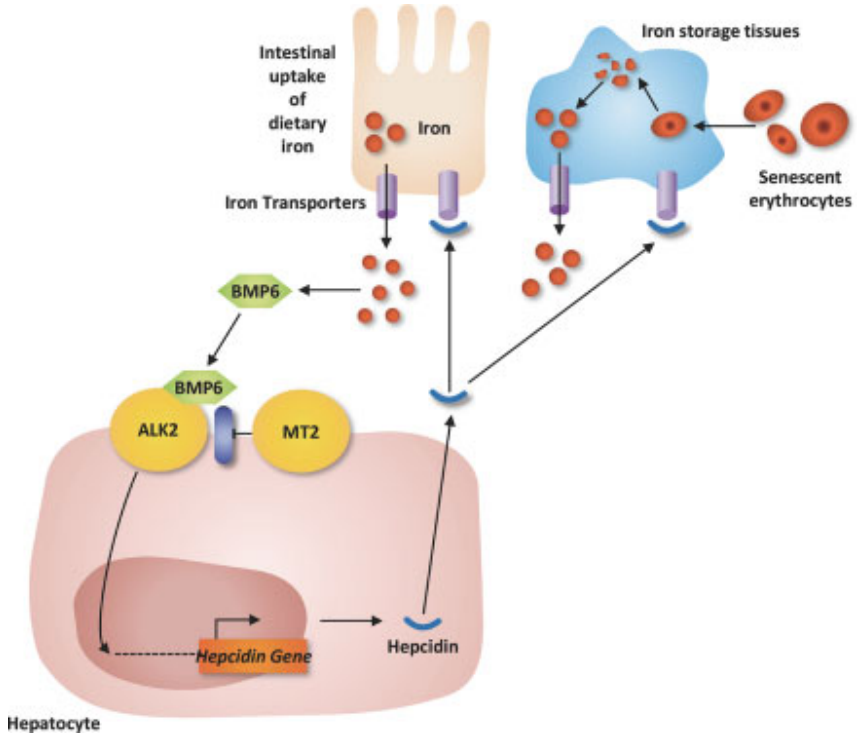
Hepcidin is a Key Regulator of Iron Metabolism

- Encoded by the HAMP gene
- Hepcidin acts to regulate serum iron by sequestering iron in storage tissues and preventing uptake of dietary iron
- Expressed, in part, in response to signaling through activin receptor-like kinase 2 (ALK2)
- 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)



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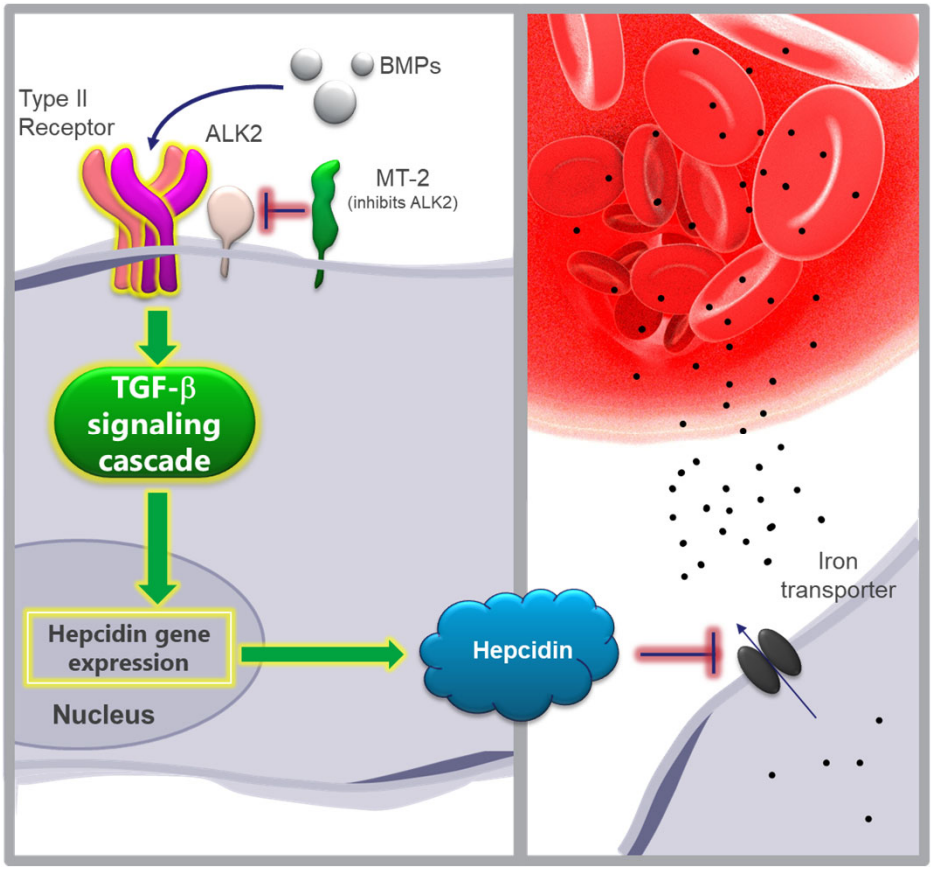
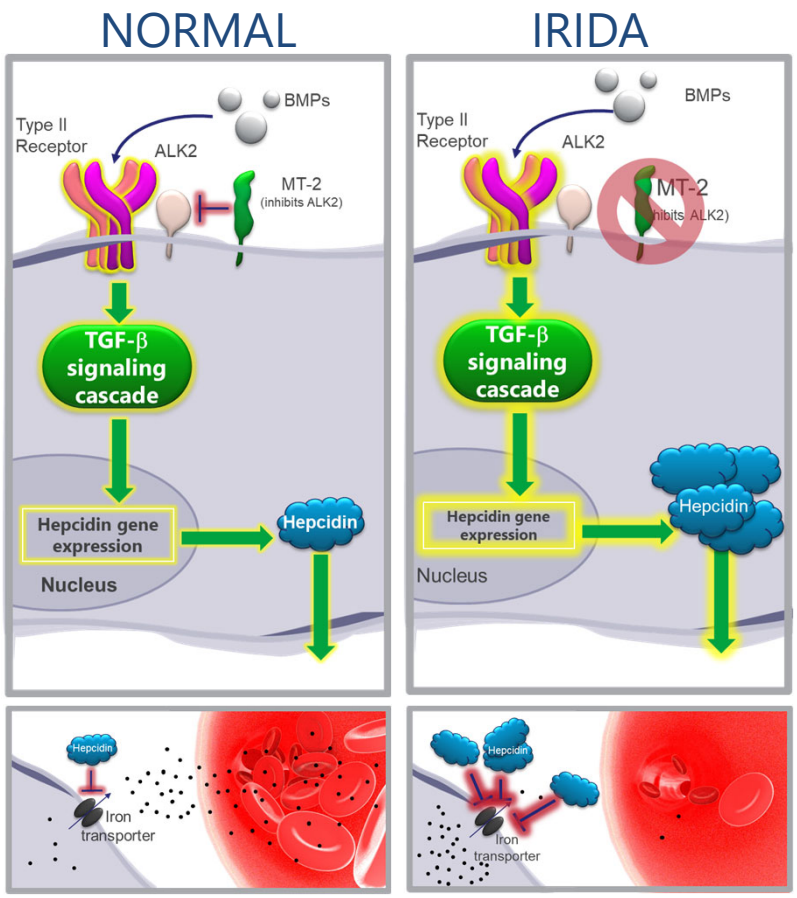
MT-2 Regulates ALK2 Signaling and Downstream Hepcidin Levels

- ALK2 signaling and subsequent hepcidin expression is downregulated by the transmembrane type II serine protease MT-2
- MT-2 acts by cleaving HJV from the cell surface, preventing ALK2 signaling
- MT-2 is encoded by the gene TMPRSS6
- ALK2: Positive Regulator
  MT-2: Negative Regulator



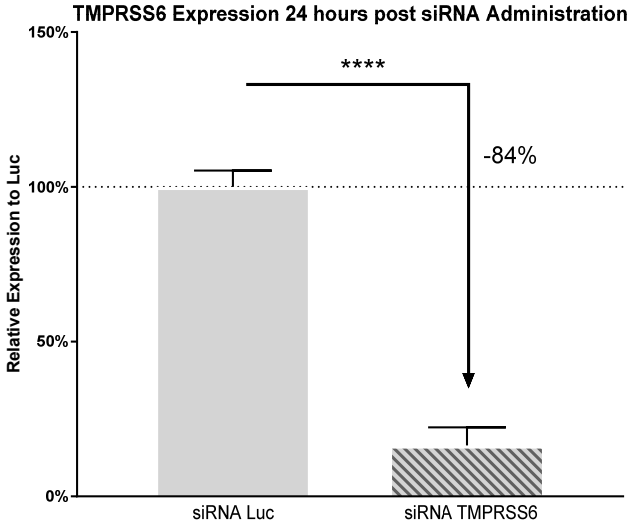
Loss of functional MT-2 Results in Iron Refractory Iron Deficiency Anemia (IRIDA)

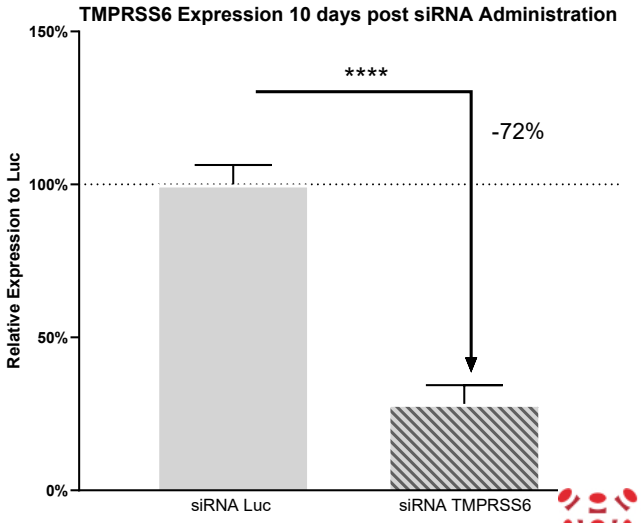
- Lack of functional MT-2 results in continuous ALK2 activation, high hepcidin, low serum iron and anemia.
- Inhibition of BMP signaling and downstream SMAD phosphorylation may suppress hepcidin in IRIDA, ameliorating disease
- Patients with IRIDA present with microcytic anemia that is symptomatic and poorly responsive to oral iron



IRIDA Can Be Modeled in Mice by Knocking Down TMPRSS6

- siRNA was utilized to knock down TMPRSS6 expression in WT mice
- TMPRSS6 expression was reduced by > 80% within 24 hours of administration
- Knockdown was confirmed to persist through 10 days following injection





**** P < 0.0001 via unpaired two-tail t-test

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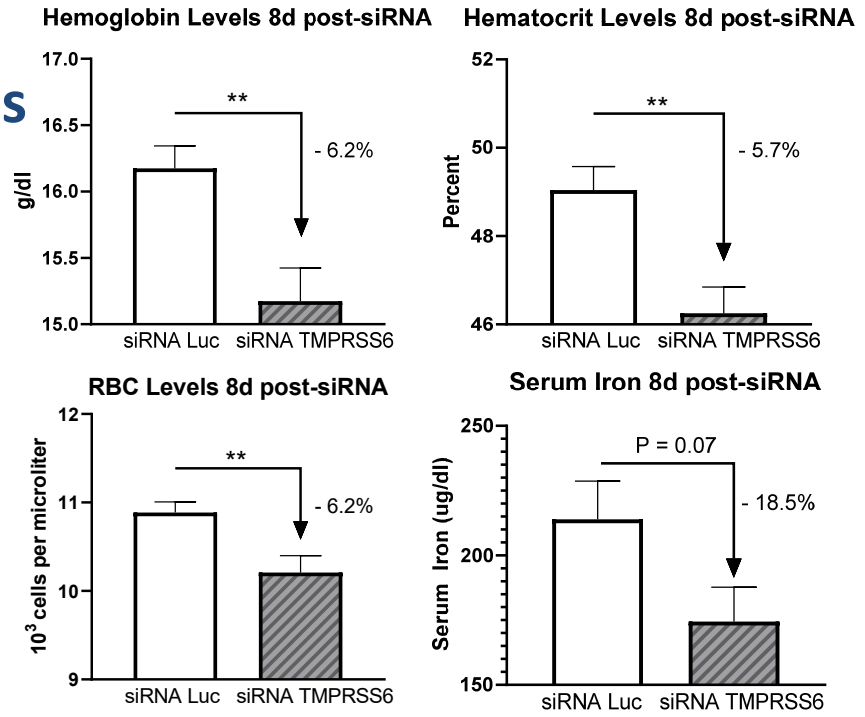
Changes in mice treated with TMPRSS6 siRNA phenocopy changes observed in patients with IRIDA

- 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 demonstrates anemia and decreases in serum iron.



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

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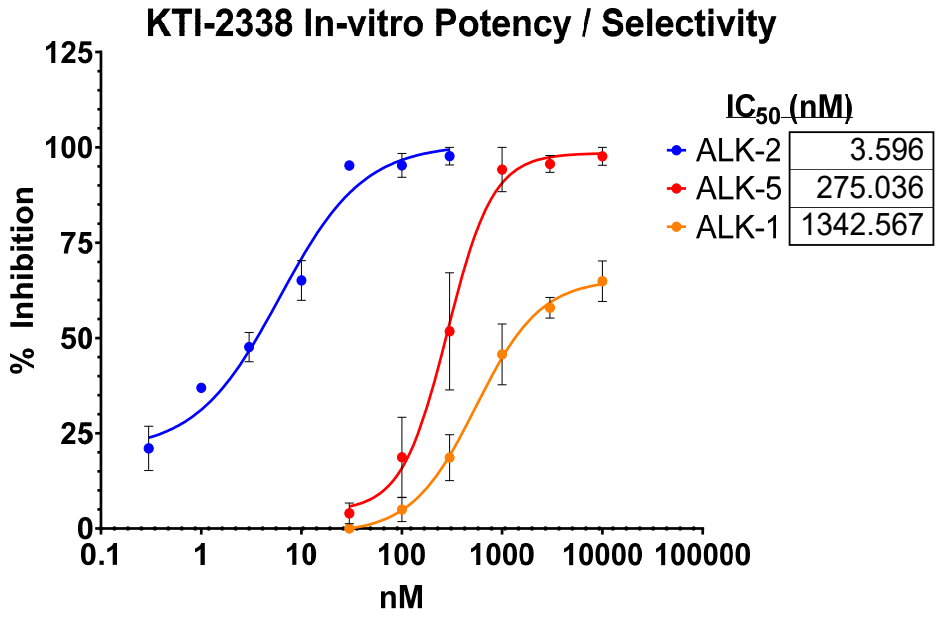
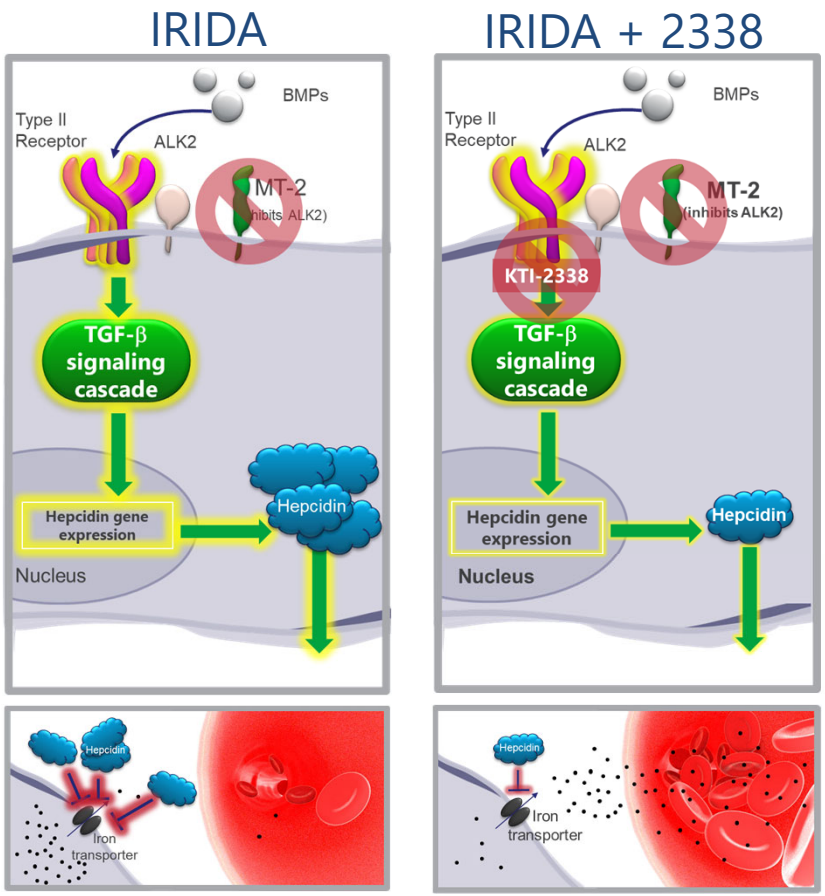
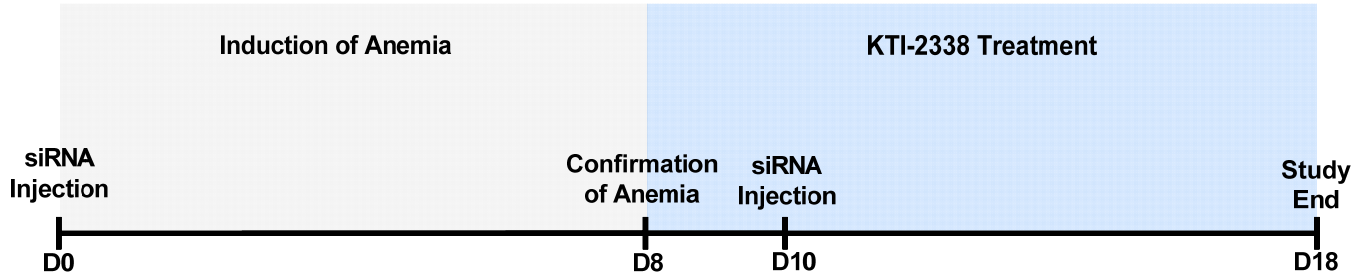
KTI-2338 is a selective small molecule ALK2 inhibitor





Therapeutic intervention in the siRNA model of IRIDA with the ALK2 inhibitor KTI-2338

- Following confirmation of disease, once-daily treatment dosing commenced at day 8 post initial siRNA administration with a second siRNA administration on day 10.
- Studies were terminated 18d post initial siRNA administration. Following takedown, hematological parameters, serum iron, and serum hepcidin were measured.



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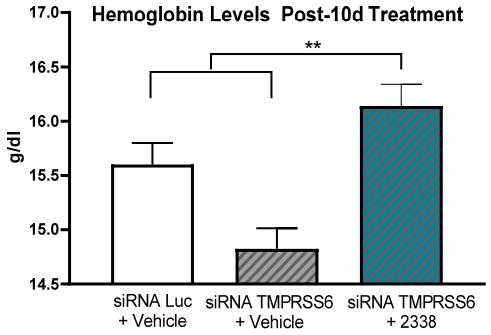
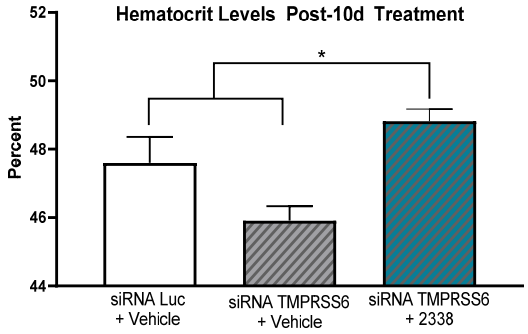
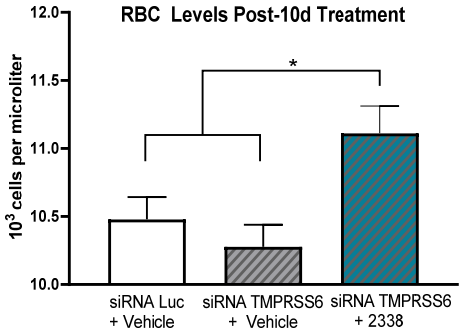
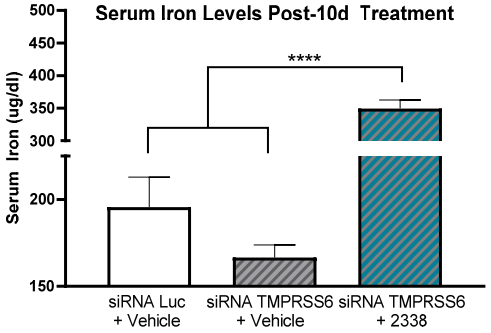
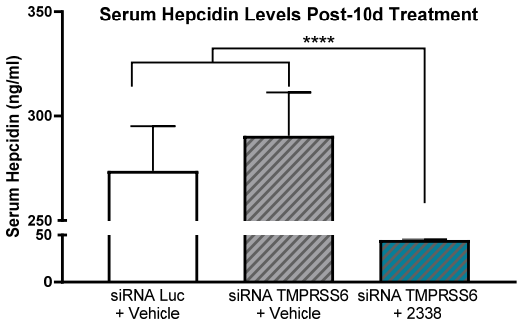
Therapeutic Dosing with KTI-2338 Resulted in Improvement of Hematologic Parameters, Serum Iron, and Serum Hepcidin











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

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Summary/Discussion

- A novel siRNA-based murine model of IRIDA recapitulates the biology observed in patients with IRIDA
- The kinase inhibitor, KTI-2338, potently and selectively targeted the ALK2 receptor in preclinical studies
- Selective ALK2 inhibition with KTI-2338 resulted in improvement of hematologic parameters, serum iron, and serum hepcidin in a murine model of IRIDA
- ALK2 inhibition has potential to improve iron levels and anemia in patients with IRIDA
- ALK2 modulation of hepcidin potentially represents a promising therapeutic for anemia due to elevated hepcidin such as anemia of inflammation

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Poster Presentations by Keros Research Colleagues:

ADMINISTRATION OF KER-050, A NOVEL ACTRIIA LIGAND TRAP, TO HEALTHY PARTICIPANTS ELICITED ROBUST AND SUSTAINED...
Ordonez C. Jun 12, 2020; 294723; EP806

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KER-050, A NOVEL INHIBITOR OF TGFB SUPERFAMILY SIGNALING, INDUCES RED BLOOD CELL PRODUCTION AND IS A POTENTIAL...
Feigenson M. Jun 12, 2020; 294703; EP786

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KER-050, A NOVEL MODIFIED ACTRIIA LIGAND TRAP, INCREASES RED BLOOD CELL PRODUCTION IN CYNOMOLGUS MONKEYS
Babbs K. Jun 12, 2020; 294699; EP782

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Acknowledgements

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