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POSTER ABSTRACTS

102.IRON HOMEOSTASIS AND BIOLOGY

Selective Inhibition of Repulsive Guidance Molecule C/Hemojuvelin (RGMc/HJV) with SRK-256 to Mobilize Iron in Functional Iron Deficiency

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Functional iron deficiency is a serious condition marked by serum iron restriction in the presence of adequate iron stores that can lead to anemia, worsening quality of life, and leading to poor patient outcomes. Functional iron deficiency is characterized by abnormally high levels of hepcidin given serum iron status; it is frequently observed in diseases with chronic inflammation, such as anemia of chronic disease, chronic kidney disease, and myelofibrosis. Current treatments to address this patient population involve non-specifically targeting hepcidin and come with risks of off-target side effects.

The secretion of hepcidin from the liver hepatocytes is linked to circulating serum iron levels and is controlled by the Bone Morphogenic Protein (BMP) 2/6 signaling pathway. Repulsive Guidance Molecule C or Hemojuvelin (RGMc/HJV) is a BMP 2/6 co-receptor in liver hepatocytes. Human genetic mutations in this gene result in juvenile hemochromatosis and genetic mouse studies have demonstrated that RGMc/HJV has a specific role in maintaining systemic iron homeostasis through modulation of hepcidin expression.

We have generated a highly selective, fully human antibody (SRK-256) against RGMc/HJV which binds to the target with 39 pM affinity. SRK-256 has no detectable binding to RGMa or RGMb, thus avoiding potential side effects of targeting these gene family members with key physiological roles outside of iron metabolism. A high-resolution crystal structure (2.2 Å) elucidates not only the mechanism of action of SRK-256 directly competing for BMP binding to RGMc via contacts within the BMP binding domain, but also identifies binding to regions within this domain highly unique to RGMc over RGMa and RGMb, thus supporting the selectivity of the molecule. This mechanism of action is corroborated by *in vitro* assay data demonstrating that SRK-256 blocks signaling by BMP 2, 4, and 6. Pharmacodynamic and pharmacokinetic data supportive of a monthly subcutaneous dosing regimen in human patients has been generated in cynomolgus macaques, where SRK-256 demonstrates a dose-proportional duration of effect on suppression of hepcidin expression and elevation of transferrin saturation and achieves ~95% bioavailability via subcutaneous dosing. Furthermore, in the rat peptidoglycan-polysaccharide (PGPS) model of anemia of chronic disease, we have shown that in contrast to treatment with erythropoiesis stimulating agent alone (EPO, serum iron 47.7 ± 9.8 μg/dL), SRK-256 can restore serum iron to normal levels (Healthy control, serum iron 231.9 ± 12.0 μg/dL; SRK-256, serum iron 248.7 ± 60.9 μg/dL; and SRK-256+EPO, serum iron 277.6 ± 92.9 μg/dL) in the context of inflammation-driven, iron-restricted anemia (Figure 1). SRK-256 represents a potent and selective potential therapy for the treatment of patients with iron-restricted anemias across diseases of chronic inflammation.

Disclosures Cortes: *Scholar Rock:* Current Employment, Current equity holder in publicly-traded company. **Nicholls:** *Scholar Rock:* Current Employment, Current equity holder in publicly-traded company. **Streich:** *Scholar Rock:* Current Employment, Current equity holder in publicly-traded company. **Boston:** *Scholar Rock:* Current Employment, Current equity holder in publicly-traded company. **Pal:** *Scholar Rock:* Current Employment, Current equity holder in publicly-traded company. **Regmi:** *Scholar Rock:* Current Employment, Current equity holder in publicly-traded company. **Cote:** *Scholar Rock:* Current Employment, Current equity holder in publicly-traded company. **Canonico:** *Scholar Rock:* Current Employment, Current equity holder in publicly-traded company. **Qatanani:** *Scholar Rock:* Current Employment, Current equity holder in publicly-traded company.

SRK-256 Increases Serum Iron in the PGPS Rat Model of Anemia of Chronic Disease

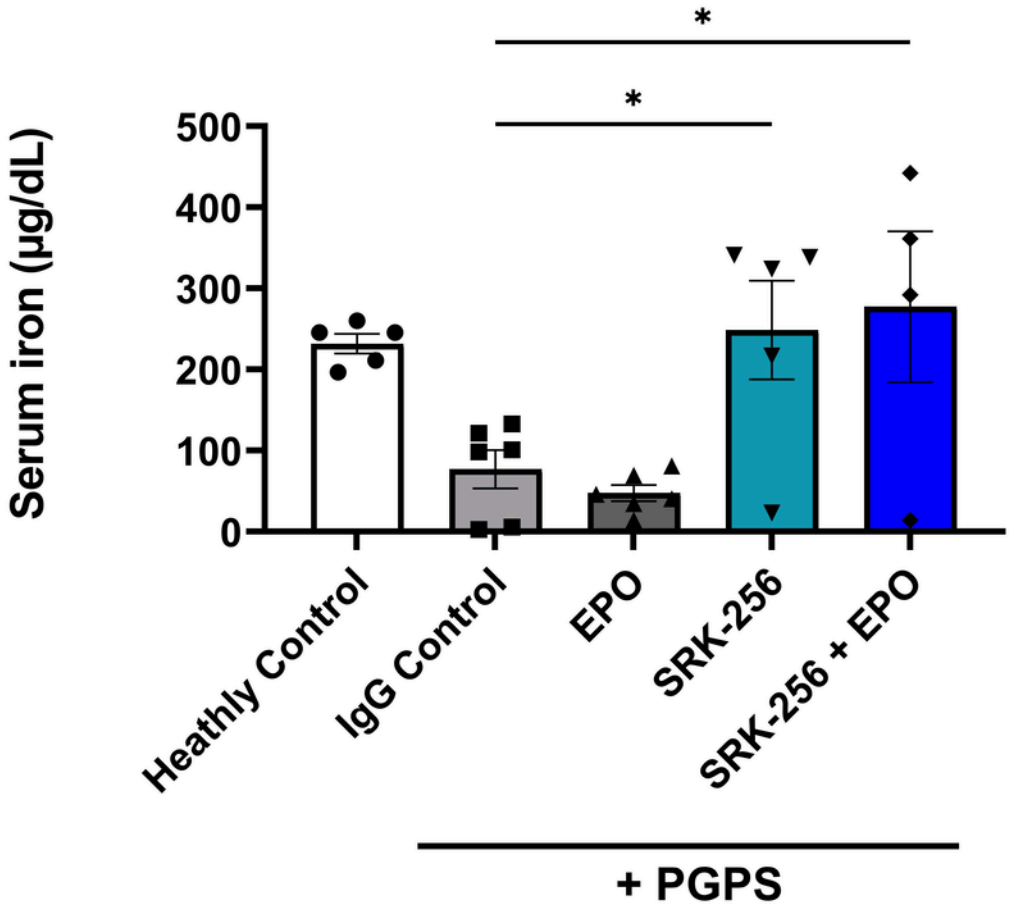

Figure 1: Serum iron 48 hours following treatment with EPO (darbepoetin alpha (10ug/kg)) and/or SRK-256 (20mg/kg) in PGPS-treated rats. Data is mean ± SEM. Ordinary one-way ANOVA to IgG control group was applied. *p<0.05.

Figure 1

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