KER-050, AN INHIBITOR OF TGF-B SUPERFAMILY SIGNALING, PROMOTED THROMBOPOIESIS AND REVERSED IMMUNE THROMBOCYTOPENIA IN MOUSE MODEL OF DISEASE

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INTRODUCTION

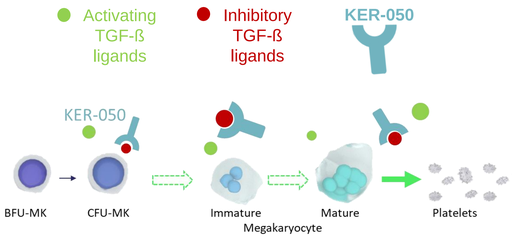
Thrombocytopenia can arise from multiple etiologies, such as myelodysplastic syndrome, primary myelofibrosis, and various autoimmune disorders.

The transforming growth factor-beta (TGF-β) superfamily has been described as a key regulator of hematopoiesis, including red blood cell and platelet production.

As a modified ActRIIa ligand trap, KER-050 is designed to inhibit a subset of TGF-β superfamily ligands, including activin A, activin B, GDF8, and GDF11. In a Phase 1 clinical study of healthy volunteers, KER-050 increased red blood cells and platelet levels.

Keros has previously demonstrated that KER-050 affects both early and late stages of erythropoiesis in preclinical studies.

The goal of these studies are to investigate the effect of KER-050 on the thrombopoiesis pathway.



METHODS

All studies used RKER-050, a research form of KER-050.

Fig 1. 11-week-old C57Bl/6 mice were given a single intraperitoneal (IP) dose of RKER-050 (10 mg/kg). Platelets and CD41+ cells were analyzed at multiple timepoints post dose. Ploidy levels were analyzed using a DNA stain. Platelets were analyzed using a Heska® HemaTrue (N=6/group).

Fig 2. 12-week-old C57Bl/6 mice were given anti-GPIbα antibody (0.08 mg/kg; SC) on Day 0, and then a single dose of RKER-050 (7.5 mg/kg; IP) on Day 4. Platelets were monitored throughout the study and CD41+ cells were analyzed on Day 10 (N=9/group).

Fig 3. 10-week-old C57Bl/6 mice were injected with a single dose of Anti-Activin A (5 mg/kg) or RKER-050 (10 mg/kg) then taken down 24 hours post dose. Platelets were recorded at takedown (N=9/group).

Fig 4. Bone marrow cells from 11-week-old C57Bl/6 mice were isolated and treated with Activin A (5 mg/kg), RKER-050 (10 mg/kg), or a combination of both for 6 days. Cells were harvested after 6 days and analyzed using flow cytometry (N=2).

Data were analyzed using Prism 9 (GraphPad Software, San Diego, CA, USA) using one-way ANOVA with Fisher's LSD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. Error bars = SEM.

RESULTS

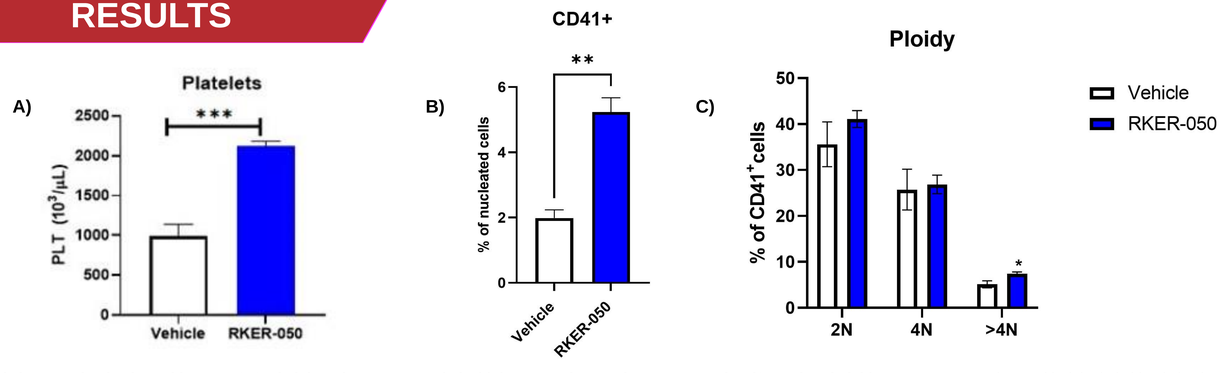


Figure 1: **Early increase in platelets with RKER-050 administration corresponded with increases in megakaryocyte number (CD41+) and ploidy. I**ncreases were observed in (A) whole blood platelet levels at 12 hours, and (B) CD41+ cells and (C) ploidy populations at 24 hours after treatment with RKER-050 indicating an early effect on progenitors of the thrombopoiesis pathway.

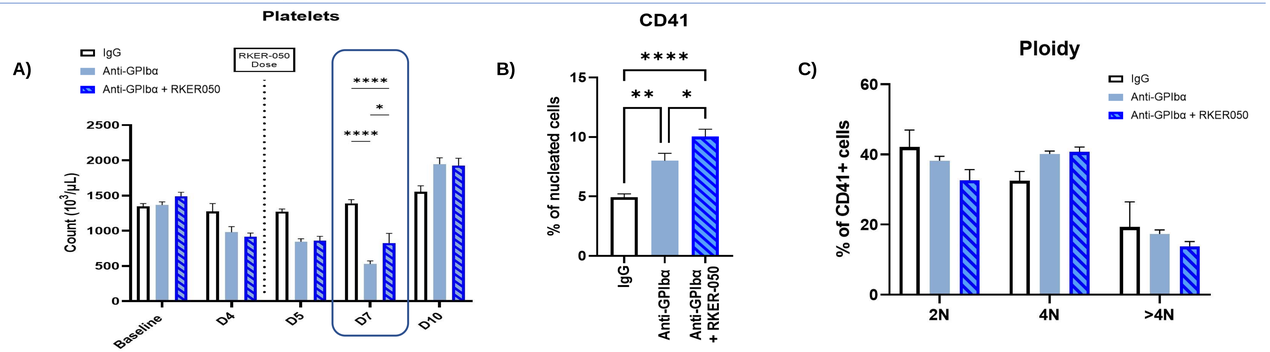


Figure 2: **RKER-050 administration led to faster recovery of platelet number, and increases in megakaryocyte number and ploidy, in a mouse model of immune thrombocytopenia (Morodomi et al).** (A) Murine platelet levels depleted with Anti-GPIbα recovered faster when treated with a single dose of RKER-050. Mice treated with RKER-050 showed (B) an increase in CD41+ cells and (C) higher 4N ploidy level at Day 10, similar to progenitor effects under homeostatic conditions. Future experiments will evaluate megakaryocyte changes at earlier timepoints.

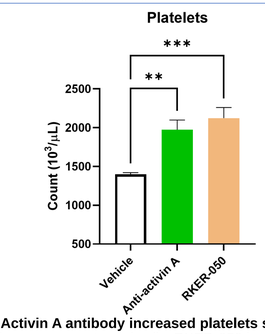


Figure 3: **Neutralizing Activin A antibody increased platelets similar to RKER-050 treatment.** Activin A is highly expressed by bone marrow stromal cells. RKER-050 is designed to bind activin A with high affinity and inhibit its signaling. Observed increases in platelets with the anti-activin A suggests that inhibition of activin A may be partly responsible for the increase in platelet levels observed with RKER-050.

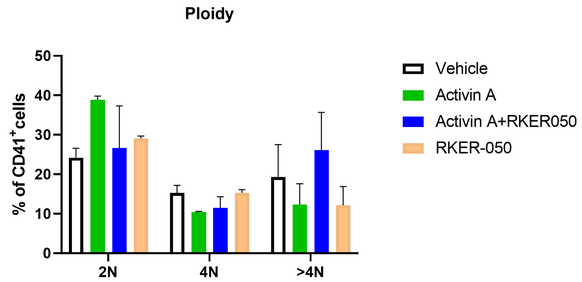
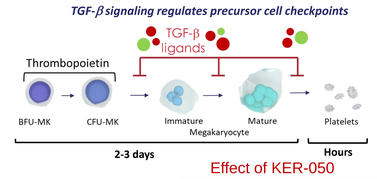


Figure 4: **Ex-vivo treatment with RKER-050 reversed activin-mediated changes in megakaryocyte precursors.** Higher polyploid levels appeared in Activin A+RKER-050 treated group compared to Activin A group, indicating that KER-050 inhibited the effects of Activin A on ploidy.

CONCLUSIONS

- Our data demonstrate a potentially novel effect of RKER-050 on thrombopoiesis. RKER-050 administration resulted in a rapid increase in platelets, consistent with an effect on terminal maturation.
- Treatment also increased the number of megakaryocyte progenitors and increased the number of polyploid megakaryocytes, demonstrating an effect on early stages of thrombopoiesis.



- Our results suggest that the effect of RKER-050 on megakaryocyte populations could be partially due to the inhibition of Activin A.
- Additionally, our data demonstrate that KER-050 has the potential to accelerate the rate of platelet recovery due to acute depletion and could represent a novel treatment for thrombocytopenia in patients with myelodysplastic syndrome (MDS), myelofibrosis and immune thrombocytopenia.
- POSTER #3675 presents data, including changes in platelets, from our ongoing Phase 2 clinical trial evaluating KER-050 in MDS patients.

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