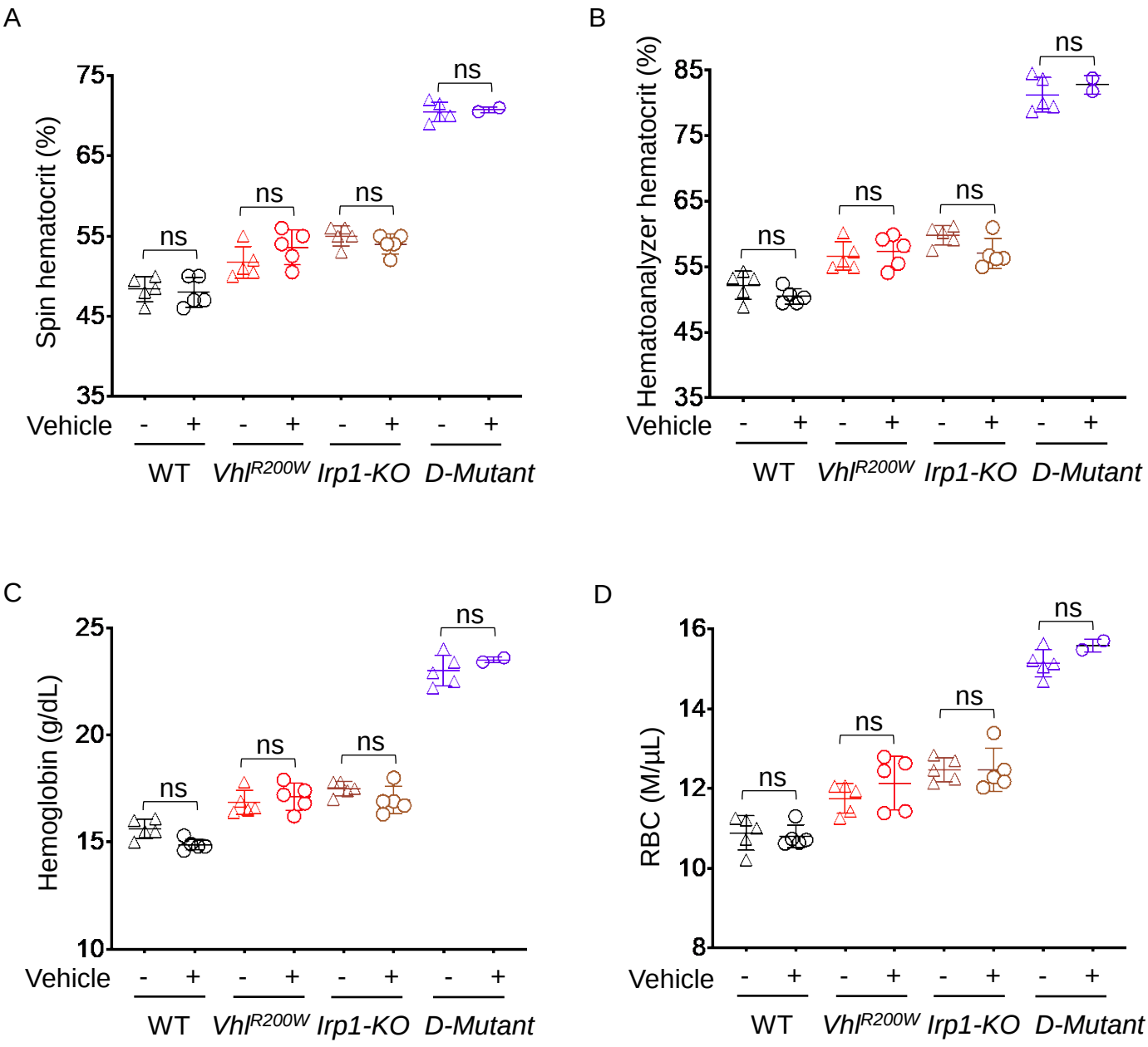
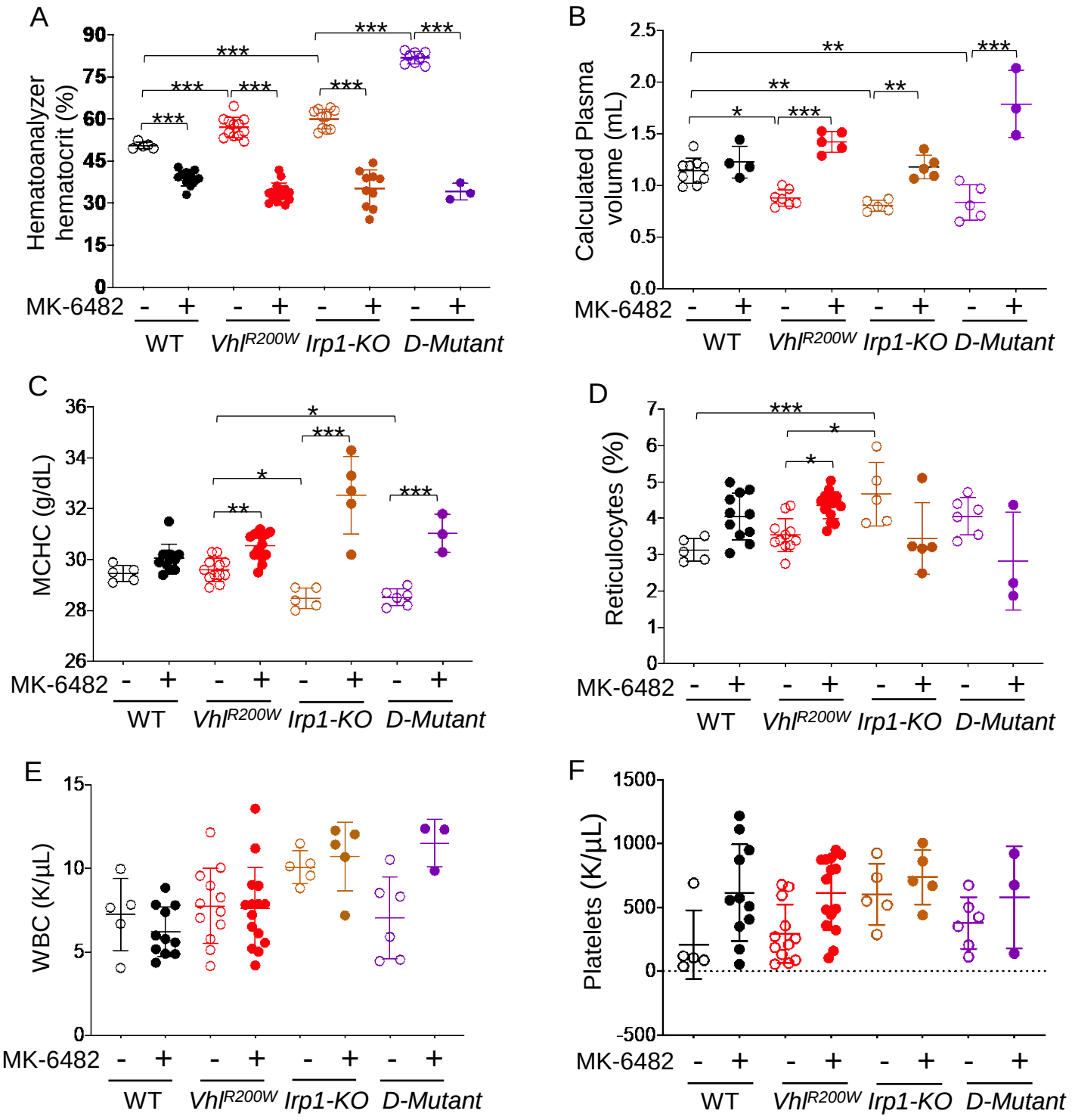
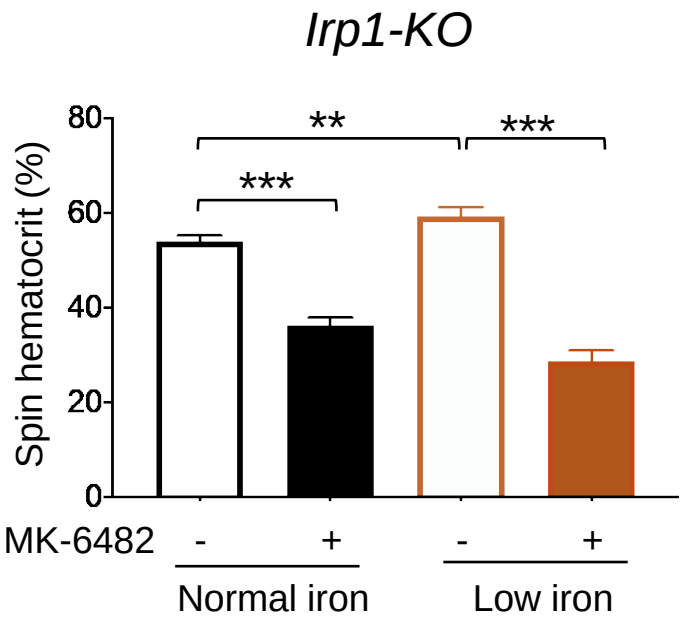


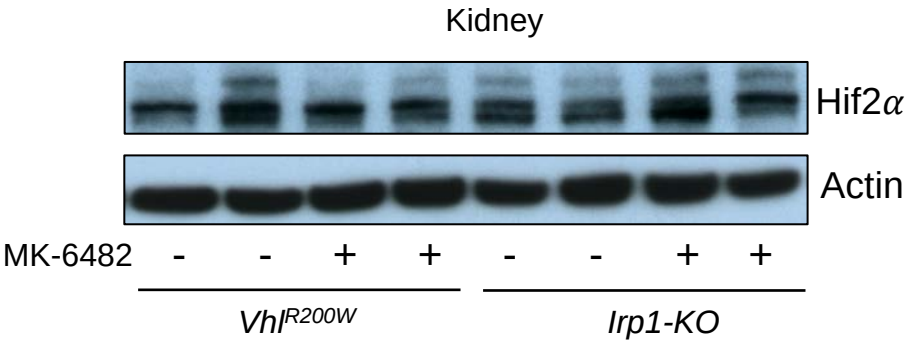
Supplementary Figure 1. Vehicle did not have any placebo effect on CBC parameters in WT, *Vhl*^{R200W}, *Irp1-KO* and the double mutant *Vhl*^{R200W};*Irp1-KO (D-Mutant)* mice. (A and B) Hematocrit levels obtained by centrifuging (spinning) the capillary with mouse blood and from blood analysis in IDEXX hematoanalyzer, (C) hemoglobin, and (D) RBC levels of 6-to 11-months-old WT, *Vhl*^{R200W}, *Irp1-KO* and double mutant *Vhl*^{R200W};*Irp1-KO* mice dosed by oral gavage with vehicle showed that the vehicle did not have any effect on the CBC parameters. ns = not significant. Double mutant *Vhl*^{R200W};*Irp1-KO* mouse is abbreviated as *D-mutant*.



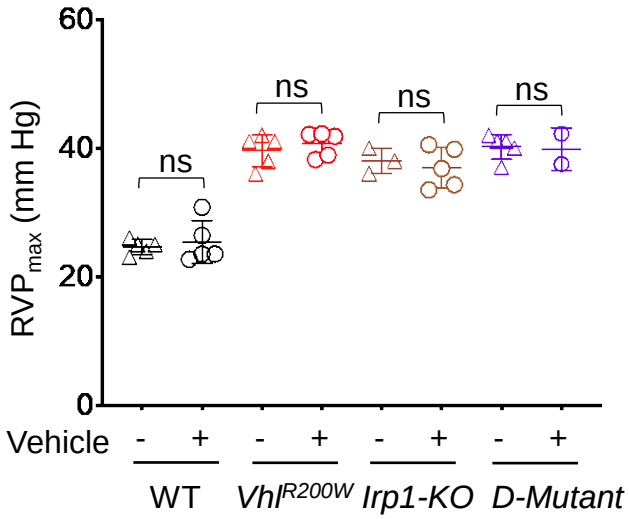
Supplementary Figure 2. MK-6482 reversed stress erythropoiesis in *Irp1-KO* mice. (A) Hematocrits obtained from blood analysis in IDEXX hematoanalyzer also showed that the drug MK-6482 reduced the elevated hematocrit levels in *Vhl*^{R200W}, *Irp1-KO* and *Vhl*^{R200W};*Irp1-KO (D-Mutant)* mice. (B) Plasma volumes, calculated from the weights of the mice and centrifuged hematocrit data, showed that the reduced plasma volumes in all mutant mice were increased on drug treatment. (C and D) MCHC and reticulocyte levels of untreated and drug treated *Vhl*^{R200W}, *Irp1-KO* and *Vhl*^{R200W};*Irp1-KO* mice showed that MCHC levels were decreased and reticulocytosis was increased in *Irp1-KO* mice, but these abnormalities in blood indices were reversed on drug treatment. (E and F) WBC and platelet levels of *Vhl*^{R200W}, *Irp1-KO* and *Vhl*^{R200W};*Irp1-KO* mice did not change significantly with mutation or drug treatment, although there were slight increases in platelet values in drug treated mice. ***$P < 0.001$, **$P < 0.01$, and *$P < 0.05$ by ordinary 1-way ANOVA (multiple comparisons). Double mutant *Vhl*^{R200W};*Irp1-KO* mouse is abbreviated as *D-mutant*.



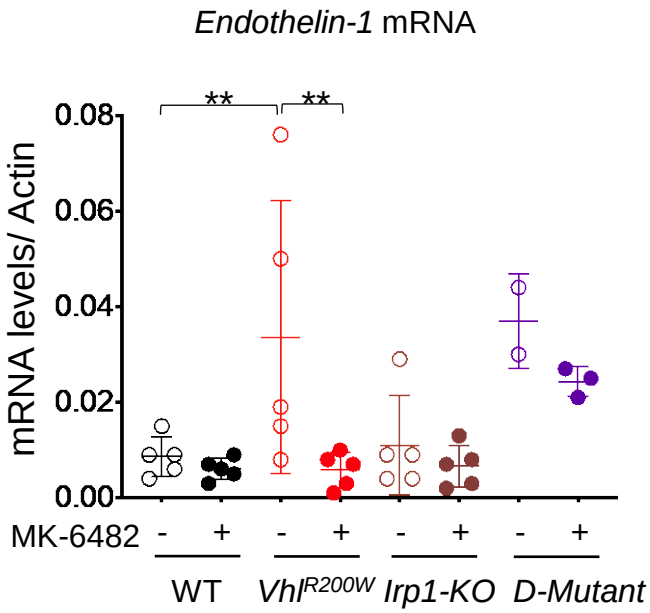
Supplementary Figure 3. MK-6482 reversed polycythemia also in normal iron diet *Irp1-KO* mice. Hematocrit levels, obtained by centrifuging (spinning) the capillary with blood from MK-6482 treated and untreated *Irp1-KO* mice on normal iron diet and low iron diet, showed similar therapeutic effect of the drug on the normal iron diet fed *Irp1-KO* mice and low iron diet fed *Irp1-KO* mice. ****P* < 0.001 and ***P* < 0.01, by ordinary 1-way ANOVA (multiple comparisons).



Supplementary Figure 4. MK-6482 did not have a significant effect on Hif2α level in *Vhl*^{R200W} mice and *Irp1-KO* mice. Immunoblot analyses of kidney lysates showed no significant changes in Hif2α protein levels on MK-6482 treatment in *Vhl*^{R200W} and *Irp1-KO* mice.



Supplementary Figure 5. Vehicle did not have any placebo effect on RVPs in WT, *Vhl*^{R200W}, *Irp1-KO* and the double mutant *Vhl*^{R200W};*Irp1-KO (D-Mutant)* mice. Right ventricular pressures measured by Millar cardiac catheterization method showed that the vehicle had no effect on the RVPs in WT, *Vhl*^{R200W}, *Irp1-KO* and *Vhl*^{R200W};*Irp1-KO* mice. ns = not significant. Double mutant *Vhl*^{R200W};*Irp1-KO* mouse is abbreviated as *D-mutant*.



Supplementary Figure 6. *Endothelin-1* mRNA levels decreased in *Vhl*^{R200W} mice upon treatment with MK-6482. *Endothelin-1* mRNA levels were elevated in the lungs of *Vhl*^{R200W} mice, but returned to normal levels upon drug treatment. ***P* < 0.01, by ordinary 1-way ANOVA (multiple comparisons). Double mutant *Vhl*^{R200W};*Irp1-KO* mouse is abbreviated as *D-mutant*.