

Evaluating the Role of the Epo Axis in a Murine Model of Jak2V617F Mediated MPN



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Erythropoietin in JAK2V617F MPN

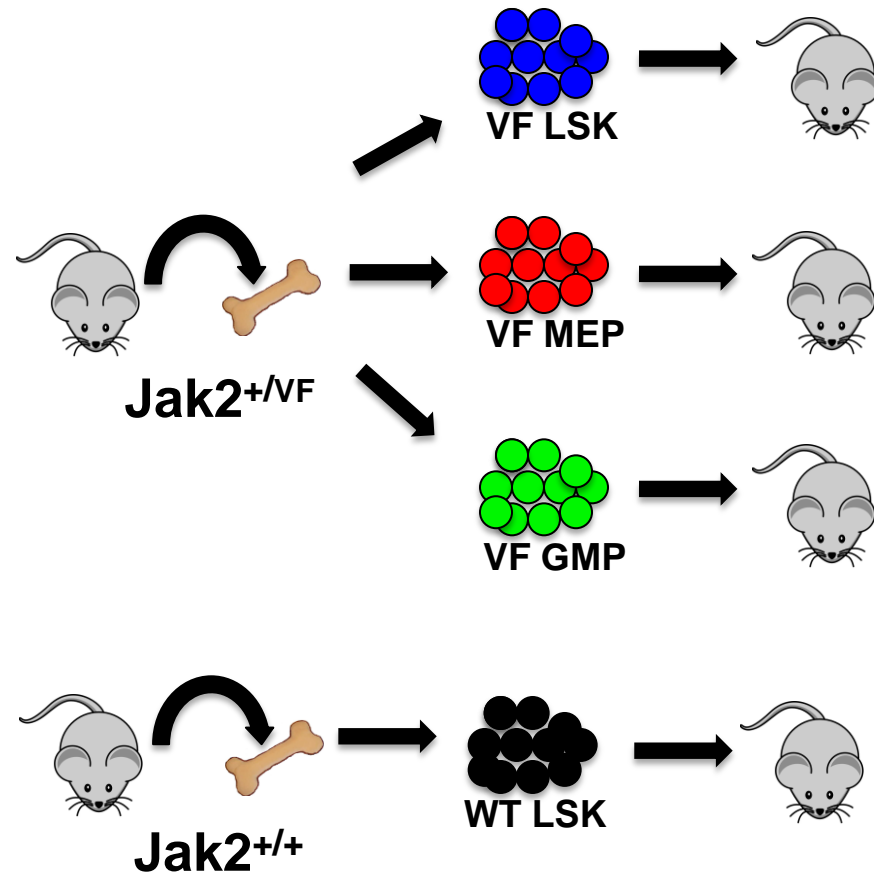
- EPO signaling reported to be the fundamental defect in PV (Prchal, NEJM 1974; Vainchenker, Nature 2005)
- Epo^{-/-} and EpoR^{-/-} mice develop BFU-E and CFU-E progenitors. EpoR^{+/-} mice no phenotype (Lodish, Cell 1995)
- JAK2V617F mutant CD34⁺CD38⁻CD90⁺Lin⁻ cells demonstrate enhanced erythroid colony formation in methylcellulose culture (Jamieson, PNAS 2006)
- JAK2V617F mutant CD34⁺CD38⁺ cells demonstrate enhanced erythroid colony formation in methylcellulose containing SCF, IL3 and EPO at concs < 0.5 U/mL (Delhommeau, Blood 2007)

The MPN-initiating cell population is contained within the HSC compartment

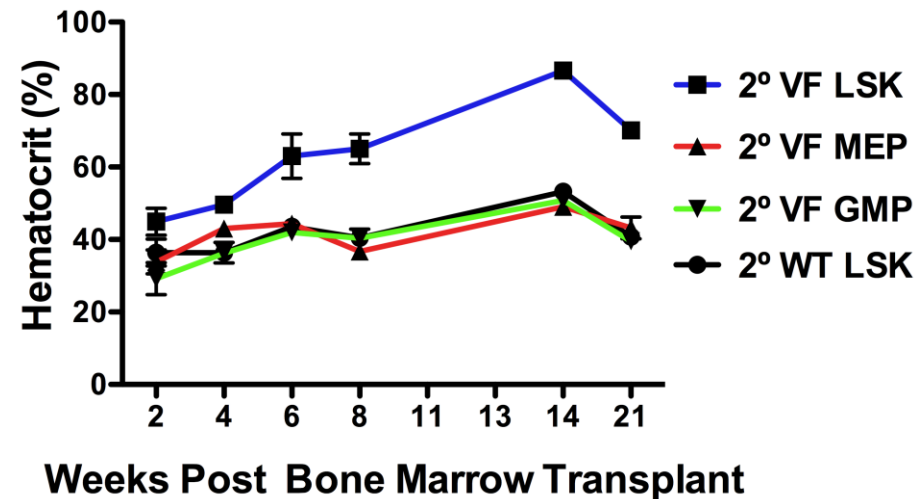
45.2 DONOR

45.1 RECIP

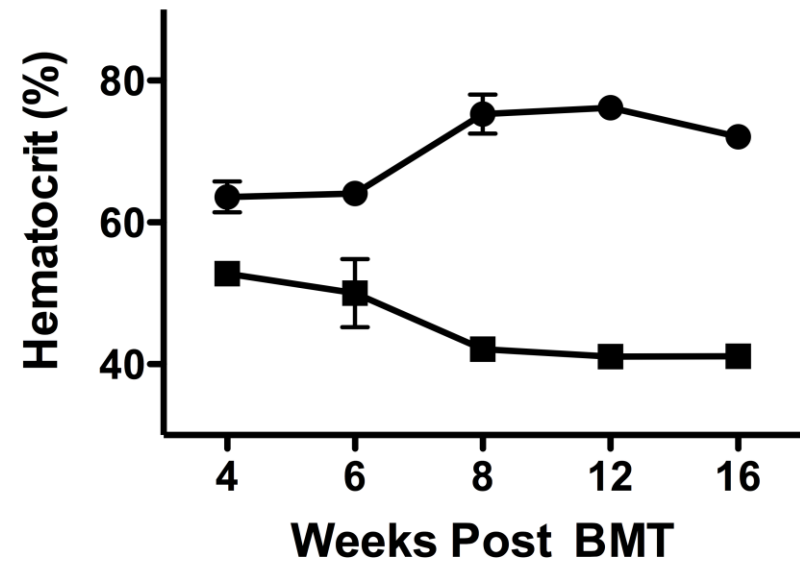
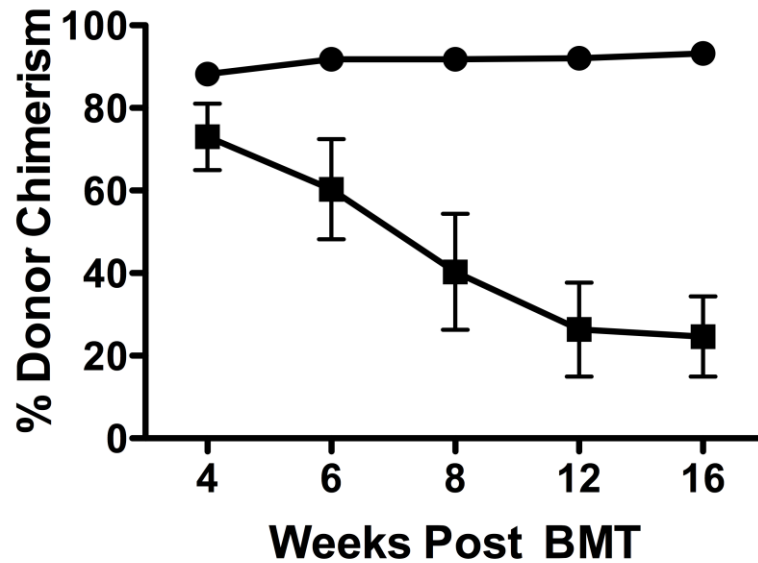
11 Gy



2° bone marrow recipients

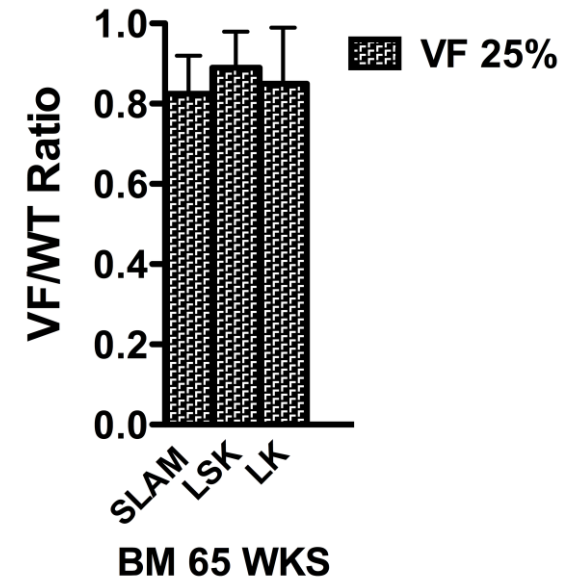
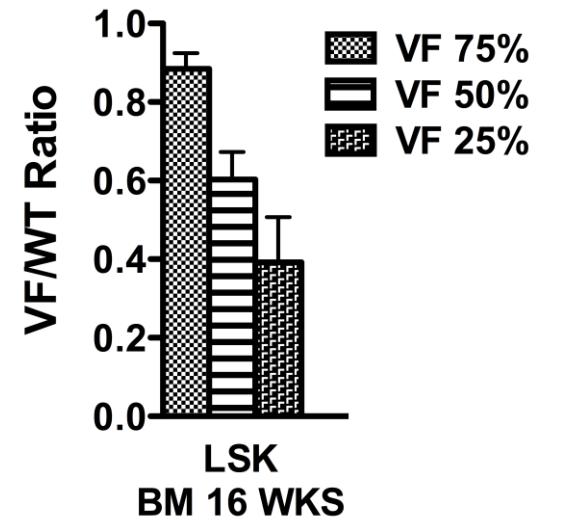
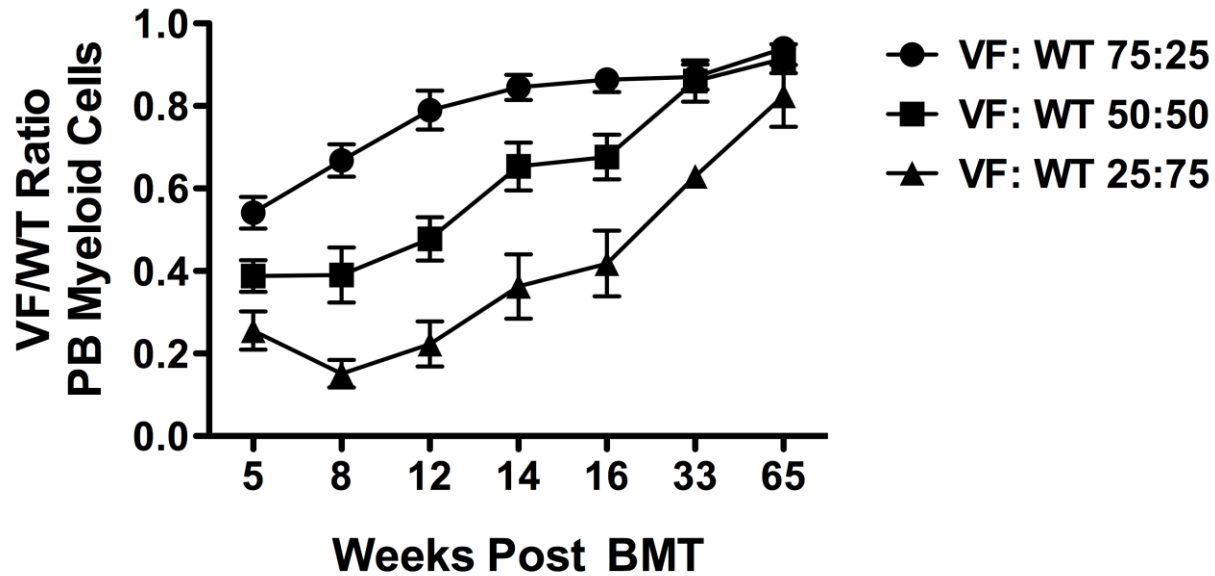


MPN-initiating cells are contained within the long-term HSC compartment (CD150+CD48-LSK)



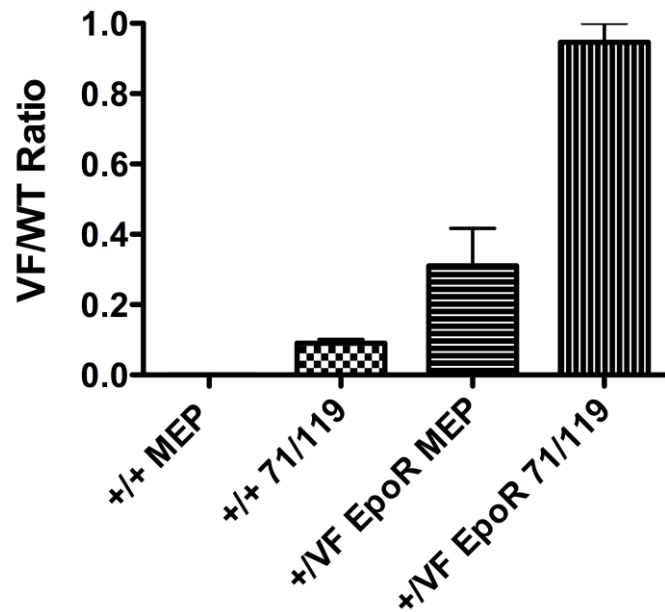
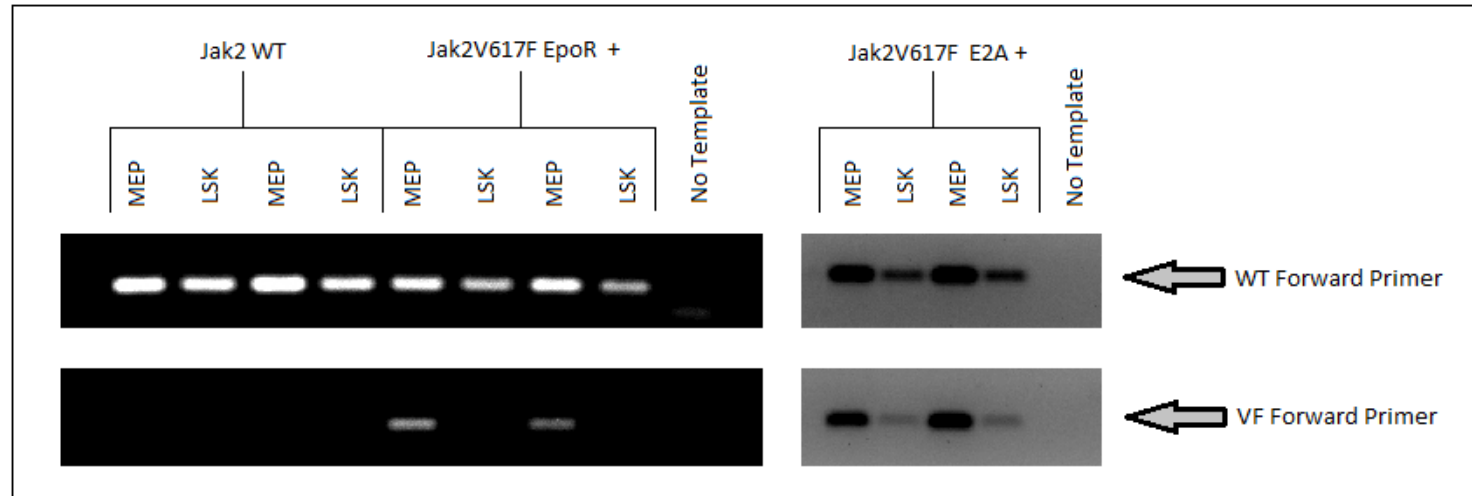
● VF LT-HSC
■ VF ST-HSC + MPP

Jak2V617F HSCs achieve clonal dominance over time

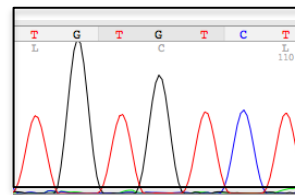


What role (if any) does erythropoietin play in the initiation and maintenance of Jak2V617F mediated MPN?

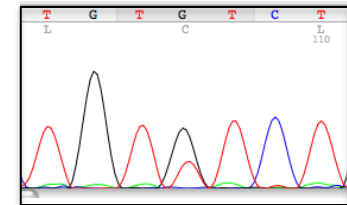
Expressing Jak2V617F in erythroid lineage only



+/+ CD71+Ter119+

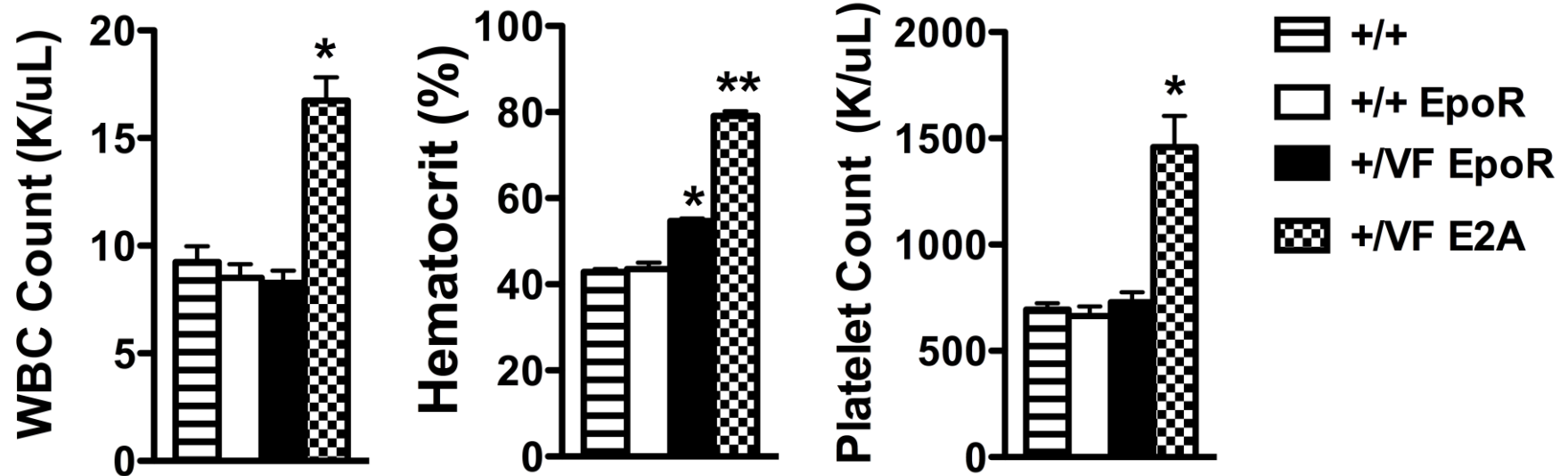


+/VF EpoR CD71+Ter119+



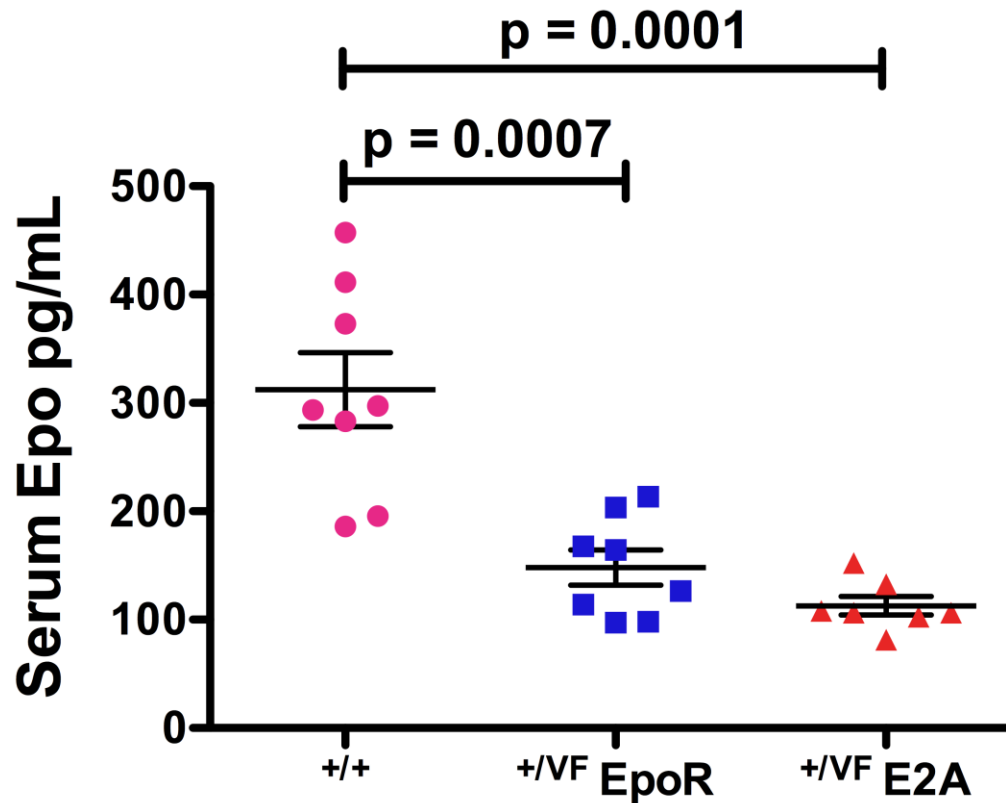
Jak2 G1849T

Erythroid-lineage restricted Jak2V617F expression results in elevated hematocrit

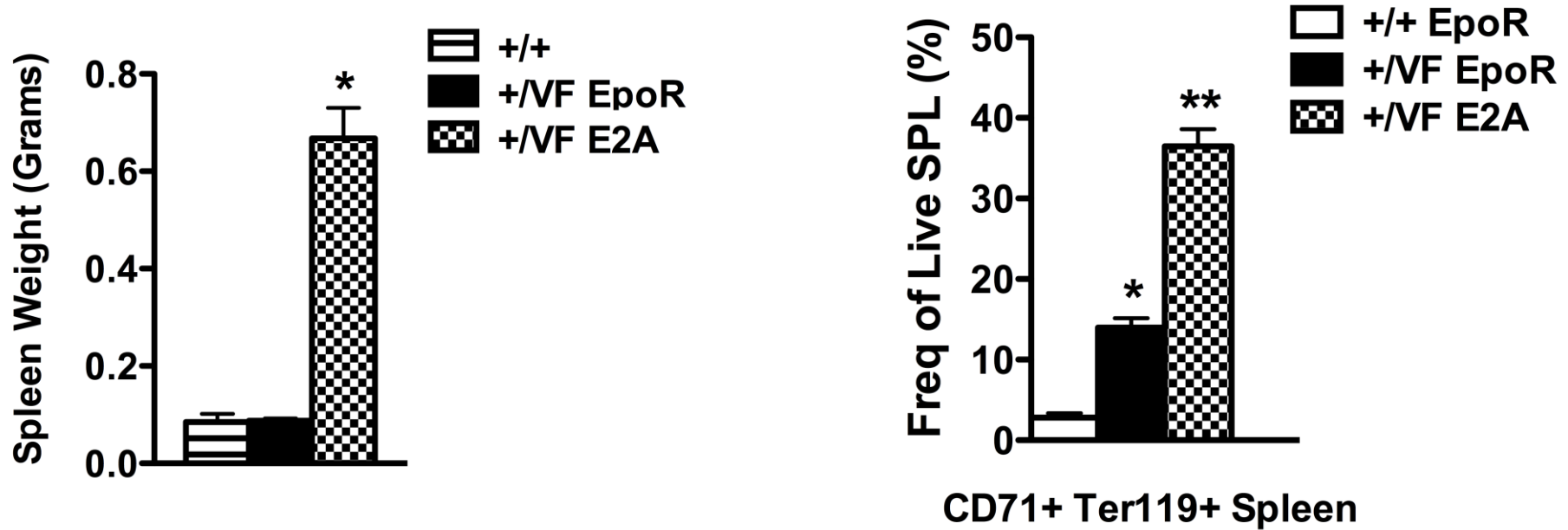


All mice aged 8-12 weeks

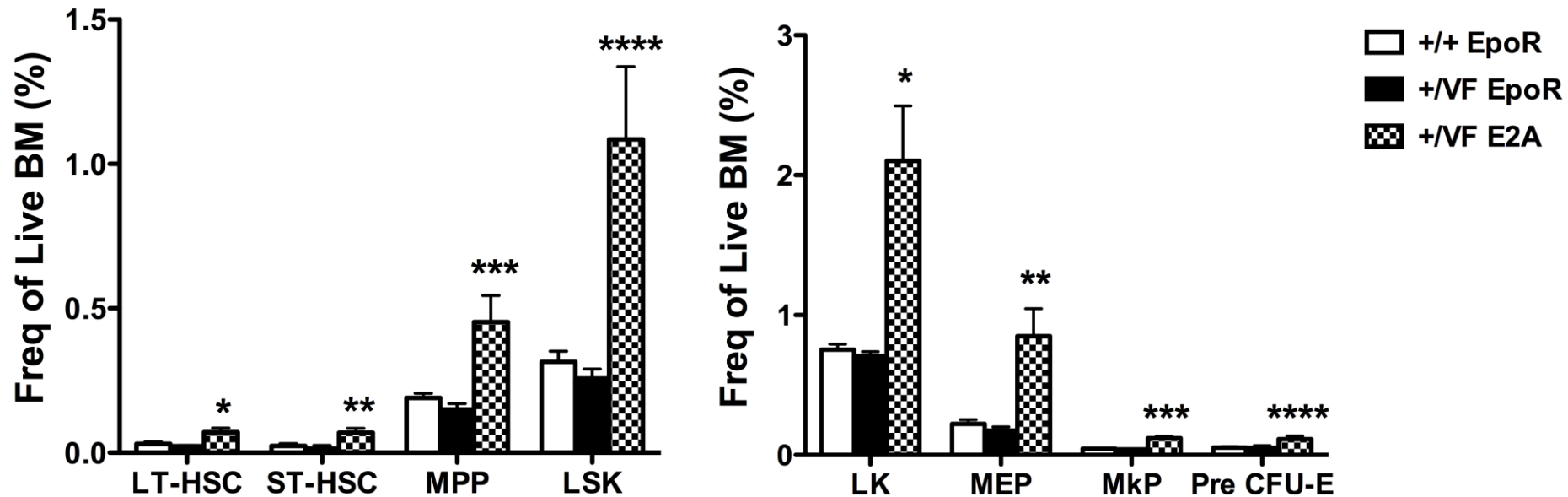
Erythroid-lineage restricted Jak2V617F expression results in suppressed serum Epo levels



Erythroid-lineage restricted Jak2V617F expression results in an attenuated MPN phenotype



Jak2V617F EpoRCre mice do not have expanded HSCs or myeloid progenitors



Conclusions

- The LT-HSC population maintains Jak2V617F MPN in vivo
- Erythroid lineage restricted Jak2V617F expression results in a markedly attenuated MPN phenotype
- Cytokine receptors that employ Jak2 signaling and are expressed in HSCs (e.g. TpoR) may mediate clonal dominance and could represent therapeutic targets in JAK2V617F MPN

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Children's Hospital Boston

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- Ursula Klingmuller



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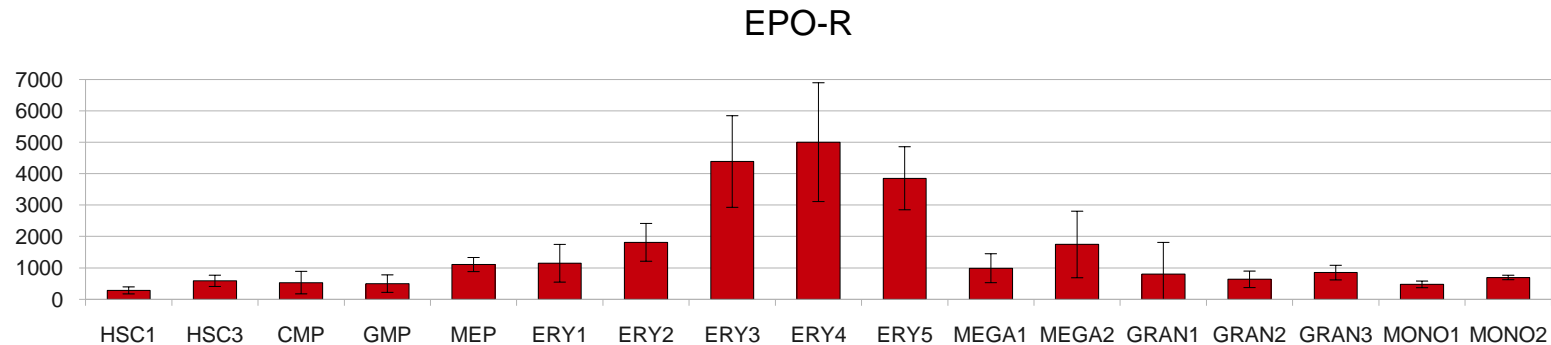


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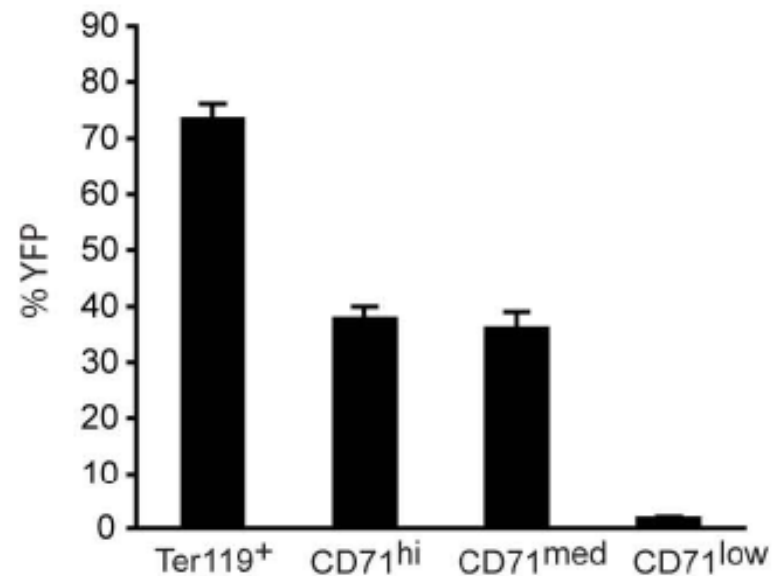
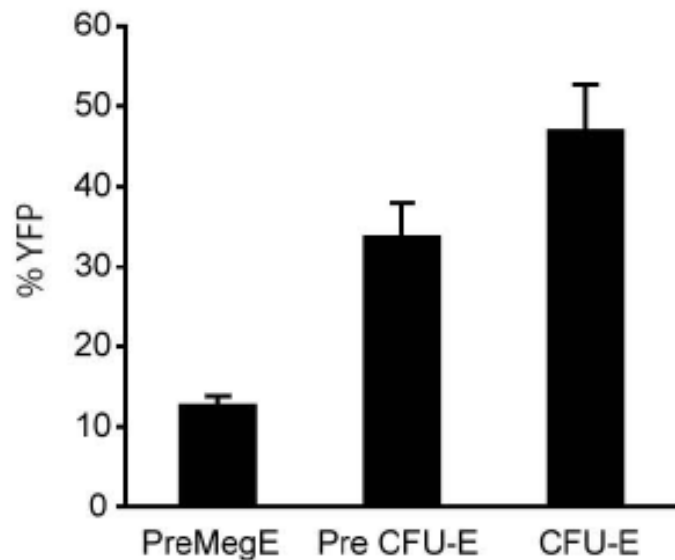


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EpoR maximally expressed on committed erythroid progenitors



www.broadinstitute.org/dmap



Walkley, Blood 2001