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TGF-β1/Activin Receptor-Like Kinase inhibition restores marrow hematopoiesis in the Gata1low mouse model of myelofibrosis

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Megakaryocytes both from primary myelofibrosis patients (PMF) and the Gata1low mouse model express levels of TGF-β 3-4-fold ($p<0.001$) greater than normal, suggesting that increased release of TGF-β from these cells in the microenvironment may play an important role in disease progression. To test this hypothesis, 12 Gata1low mice were treated for 4 cycles with SB431542 ($C_{22}H_{16}N_4O_3$, MW=384.4), an inhibitor of TGF- β1/activin receptor-like kinases, for a total of 2 months. Mice were then sacrificed and analyzed for disease progression. In the blood, SB431542-treatment significantly increased platelet numbers (by 2-fold) and reduced white blood cell counts (20%) and poikilocyte frequencies (by 90%) without affecting hematocrit levels (which remained normal) or progenitor cell trafficking (which remained high). In the marrow, SB431542-treatment significantly increased total cell numbers [>2-fold] and frequency of progenitor cells (by 2-fold) and erythroid and megakaryocytic (by >50%) precursors while reducing fibrosis (>90%) and microvessel density (>90%). In addition, SB431542-treatment

reduced spleen weight by 50% and erythroblast and/or megakaryocyte frequencies in spleen and liver by 50%. Therefore, in the Gata1low mouse model inhibition of TGF-β1 efficiently reactivates hematopoiesis in marrow while reducing hematopoiesis in extramedullary sites suggesting a potential benefit for treatments targeting microenvironment abnormalities in PMF.

Keywords: Key words: Myelofibrosis, MegaKaryocytes, TGF beta1, Hematopoiesis

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