

Novel anti-TMPRSS6 monoclonal antibody provides a potential therapeutic approach for the treatment of polycythemia vera

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Abstract

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) triggered by activating mutations in JAK2, an important kinase in the principal signaling pathway of the erythropoietin receptor. Most of the clinical manifestations of PV are caused by increased erythrocyte count, leading to increased risk of pulmonary hypertension and thrombosis. The mainstay of therapy for PV is therapeutic phlebotomy to reduce the hematocrit (HCT) level and minimize the risk of thrombosis, however, the effect of phlebotomy is transient until patients become iron deficient. Therefore, systemic iron restriction could be effective in treating PV patients.

Transmembrane serine protease 6 (TMPRSS6) is a negative regulator of hepcidin, the master regulator of iron homeostasis. Increasing genetic, preclinical and clinical evidence has demonstrated that inhibition of TMPRSS6 can potentially elevate hepcidin levels, thereby achieving systemic iron restriction.

Previously, we reported the generation of anti-TMPRSS6 antibody MWTx-003 and its efficacy in reducing iron overload and improving ineffective erythropoiesis in a mouse model of β -thalassemia. In this study, we explored therapeutic application of MWTx-003 in PV using a *Jak2^{V617F}* bone marrow transplantation mouse model. The mouse model exhibits typical PV phenotypes of erythrocytosis and elevated HCT levels. In the PV mice, treatment with MWTx-003 (2-10 mg/kg, i.p., every 4 days for 3 weeks) led to significantly reduced HCT levels, red blood cell (RBC) counts and hemoglobin (HGB) concentration that were comparable to that of wildtype control mice. These effects were evident in a dose-dependent manner and observed as early as two weeks into treatment. It is worth noting that in the 10 mg/kg dose group, increased spleen weight and expansion of early erythroid progenitors were observed after 3 weeks of treatment, consistent with the mechanism of action and of iron-restricted erythropoiesis in mice. Taken together, the anti-TMPRSS6 antibody offers a promising therapeutic approach in the management of PV, where erythrocytosis and high HCT levels are associated with poor outcomes. Phase I clinical trials with MWTx-003 in healthy volunteers have been initiated in China and the US.

Introduction

❖ Polycythemia vera (PV) is a rare blood disorder that causes bone marrow to produce too many red blood cells. It is known as Myeloproliferative neoplasm (MPN), and affects about 50 per 100,000 people in the U.S.

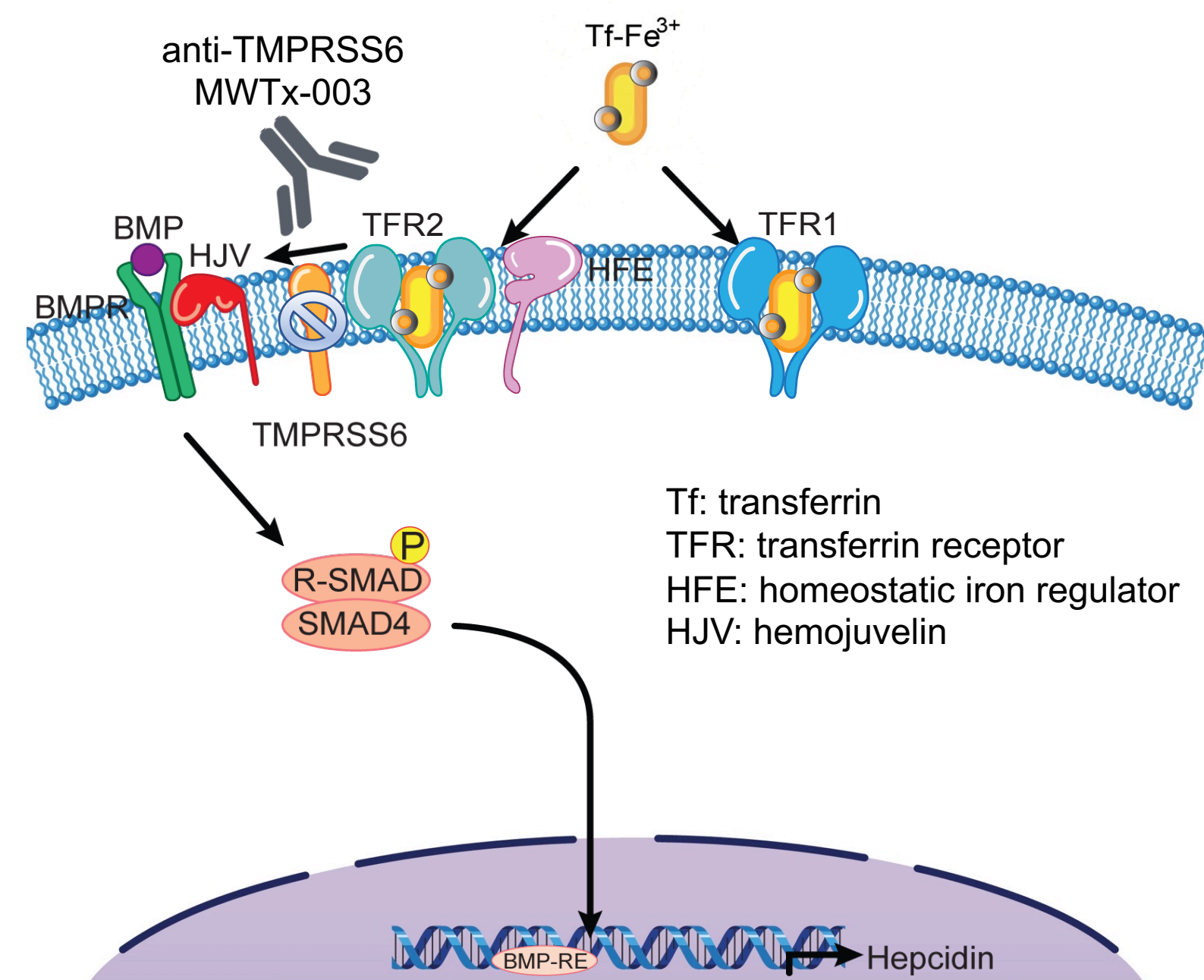
❖ PV is mostly triggered by activating mutations in JAK2 which is an important kinase in the principal signaling pathway of the erythropoietin (EPO) receptor. The V617F mutation is present in approximately 95% of patients with PV.

❖ Most of the clinical manifestations of PV are caused by an increased erythrocyte count, and thickening blood increases risk of pulmonary hypertension and thrombosis. There is no current cure for PV, and the most common treatment is phlebotomy to reduce the hematocrit (HCT) level to $\leq 45\%$, however, the effect of phlebotomy is transient, until patients become iron deficient. Therefore, systemic iron restriction is known to be beneficial for PV.

❖ TMPRSS6, a human type II transmembrane serine protease 6, is also called Matriptase-2. TMPRSS6 cleaves HJV and plays an important role in regulating hepcidin expression and iron metabolism.

❖ Previously, we reported identification and development of anti-TMPRSS6 monoclonal antibody MWTx-003, demonstrating potent induction of hepcidin and suppression of serum iron in preclinical models, including efficacy in reducing iron overload and improving inefficient erythropoiesis in a mouse model of β -thalassemia. In this study, we will explore the therapeutic benefit of treating PV with anti-TMPRSS6 MWTx-003.

❖ In January 2023, Disc Medicine in-licensed anti-TMPRSS6 MWTx-003 from Mabwell Therapeutics, and re-named it to DISC-3405. In October 2023, Disc Medicine announced the initiation of a Phase 1 study of DISC-3405 in healthy volunteers.



Workflow and Results

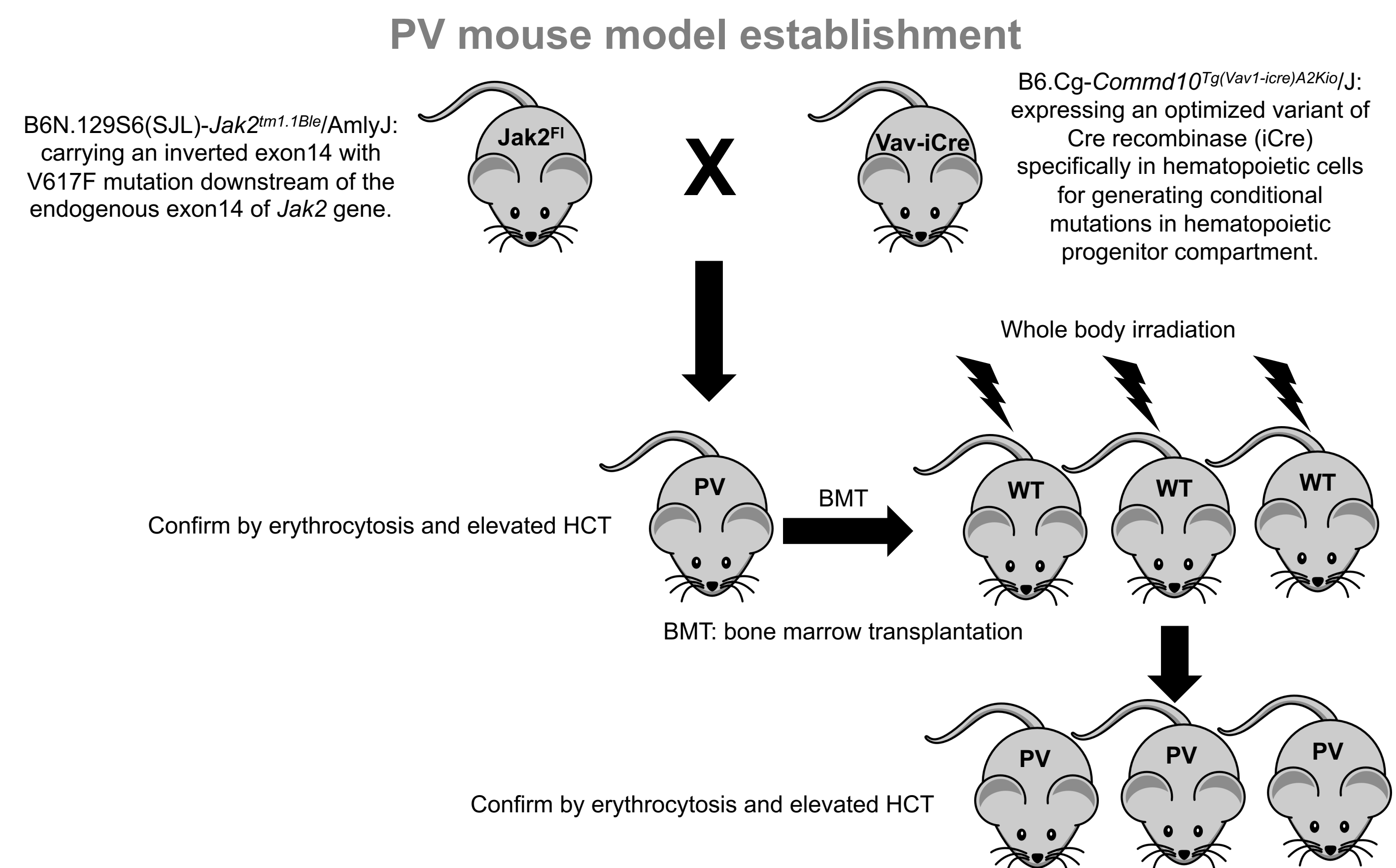


Table 1. Hematological parameters of WT and PV mice.

Mice	RBC ($10^{12}/L$)	HGB (g/dL)	HCT %	MCV (fL)	RDWc %
Wild-type C57BL/6J	10.57 $\pm$ 0.24	18.18 $\pm$ 0.60	44.43 $\pm$ 0.94	42.00 $\pm$ 0.00	19.55 $\pm$ 0.76
<i>Jak2^{V617F}</i> Vav-iCre	18.76 $\pm$ 2.35	27.91 $\pm$ 3.76	57.19 $\pm$ 1.58	29.33 $\pm$ 2.07	35.98 $\pm$ 0.63
3-week post BMT	13.51 $\pm$ 0.47	24.39 $\pm$ 1.45	61.57 $\pm$ 1.83	45.56 $\pm$ 1.29	27.68 $\pm$ 0.77
4-week post BMT	14.68 $\pm$ 1.62	24.41 $\pm$ 1.64	60.26 $\pm$ 2.45	41.13 $\pm$ 1.57	32.16 $\pm$ 2.79

RBC: red blood cell
HGB: hemoglobin
MCV: mean corpuscular volume
RDWc: red cell distribution width

anti-TMPRSS6 MWTx-003 treatment

Table 2. Experimental group assignment.

Group	Number of Animals	Whole Body Irradiation (Day -1)	Autologous Transplant (Day 0)	Test Article	Dosing Regimen
1	8	Whole body irradiation (1000 cGy)	5x10 ⁶ bone marrow cells, single dose IV	Mouse IgG2b (10 mg/kg)	IP, every 4 days for a total of 3 weeks, starting 4 weeks post BMT
2	8			Anti-TMPRSS6 MWTx-003 (10 mg/kg)	
3	8			Anti-TMPRSS6 MWTx-003 (5 mg/kg)	
4	8			Anti-TMPRSS6 MWTx-003 (2 mg/kg)	

❖ After 2 weeks' treatment with anti-TMPRSS6 antibody, a dose-dependent reduction in the HCT level, a RBC count, and HGB concentration was observed in mice receiving MWTx-003, compared with animals treated with isotype control antibody.

Table 3. Hematological parameters of PV mice after 2-week antibody treatment.

Mice	RBC ($10^{12}/L$)	HGB (g/dL)	HCT %	MCV (fL)	RDWc %
Wild-type C57BL/6J	10.62 $\pm$ 0.32	16.18 $\pm$ 0.54	44.67 $\pm$ 1.24	42.00 $\pm$ 0.00	19.73 $\pm$ 0.70
Prior to dosing (4-week post BMT)	14.68 $\pm$ 0.60	24.41 $\pm$ 1.64	60.26 $\pm$ 2.45	41.13 $\pm$ 1.57	32.16 $\pm$ 2.79
10 mg/kg mouse IgG2b	17.17 $\pm$ 0.60	28.50 $\pm$ 1.09	60.19 $\pm$ 2.53	35.00 $\pm$ 2.10	35.00 $\pm$ 2.27
2 mg/kg MWTx-003	16.94 $\pm$ 0.82	24.51 $\pm$ 2.46*	53.30 $\pm$ 5.07	31.57 $\pm$ 3.31	38.44 $\pm$ 3.38
5 mg/kg MWTx-003	15.65 $\pm$ 0.65	22.94 $\pm$ 2.11**	48.48 $\pm$ 4.55**	31.00 $\pm$ 3.21	38.26 $\pm$ 3.18
10 mg/kg MWTx-003	14.50 $\pm$ 3.22*	22.54 $\pm$ 3.48***	47.14 $\pm$ 7.94***	33.13 $\pm$ 4.67	34.38 $\pm$ 7.66

Results represents mean $\pm$ SD, *** P < 0.001, ** P < 0.01, * P < 0.05, compared to mlgG2b isotype control, using one-way ANOVA with Dunnett's multiple comparison adjustment. N=6 for mlgG2b group, N=8 for 10 mg/kg group, N=7 for both 5 mg/kg and 2 mg/kg groups.

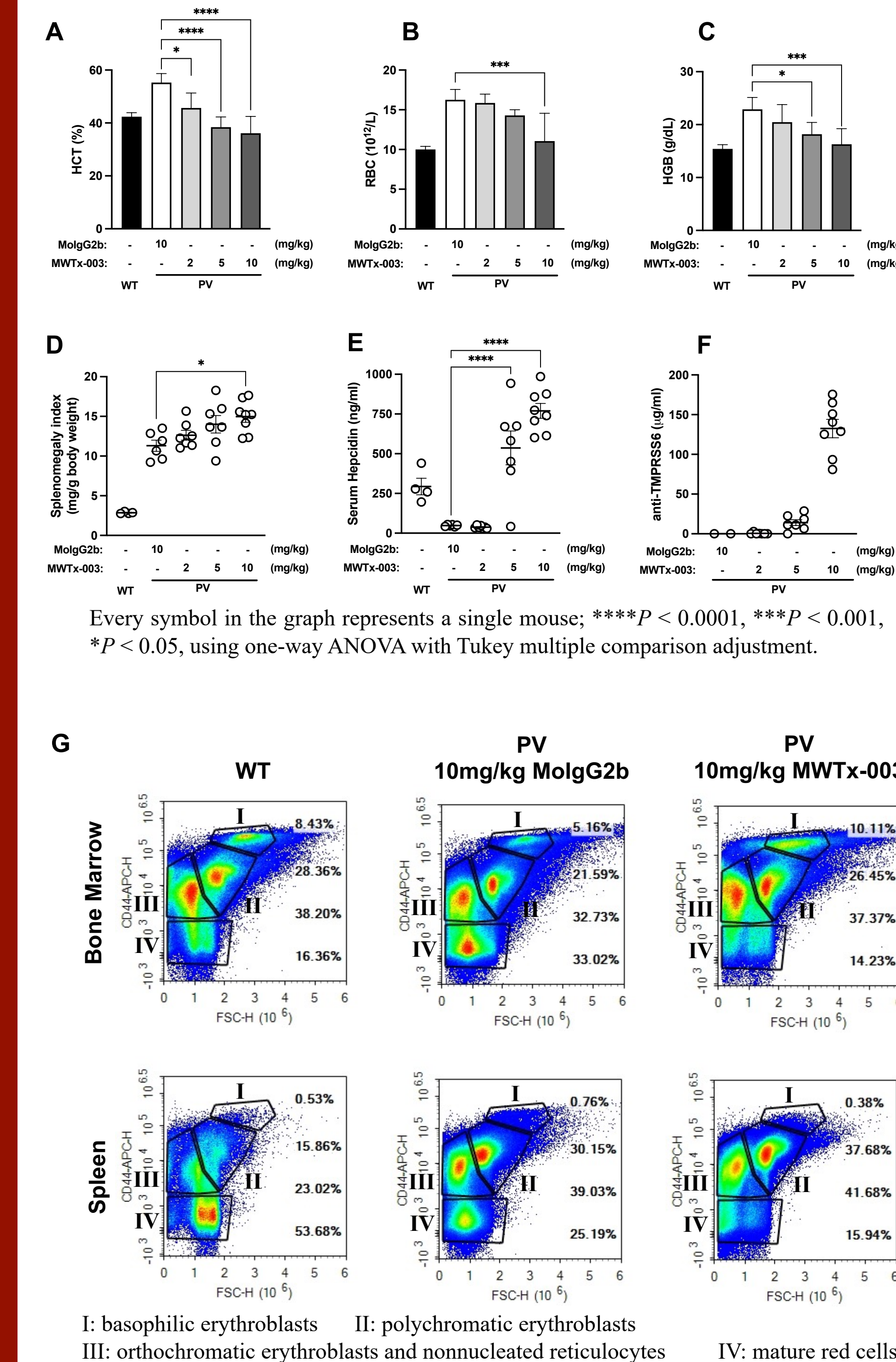


Figure A-H. Hematologic parameters and other findings after 3-weeks of MWTx-003 treatment.

❖ At the end of the 3-week treatment period, HCT levels in all MWTx-003 treated groups were further decreased in a dose-dependent manner to a similar or lower levels than seen in wild-type untreated animals (A). Circulating RBC numbers and HGB concentrations were also reduced, with some large reductions in erythrocytosis notable for 10 mg/kg dose group (B-C).

❖ Increased spleen weight and expansion of early erythroid progenitors were also observed in 10 mg/kg dose group, consistent with the mechanism of action and of iron-restricted erythropoiesis in mice. The sum percentage of cluster I and II erythroid progenitors in the MWTx-003 group is statistically different from that in the mlgG2b group (D&G).

❖ As expected, serum hepcidin was significantly elevated and sustained during the course of treatment (E).

❖ MWTx-003 treatment did not cause major changes in liver iron content, but a significant increase in iron deposits in splenic macrophages was observed in a dose-dependent manner, as evidenced by Perl's Prussian blue stained liver and spleen sections (H).

Conclusions and Discussion

❖ Anti-TMPRSS6 monoclonal antibody MWTx-003 offers a promising therapeutic approach in the management of PV, where erythrocytosis and high HCT levels associate with poor outcomes.

❖ Please contact Buxin Chen (bchen@mabwell-therapeutics.com) for any questions.