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POSTER ABSTRACTS

102.IRON HOMEOSTASIS AND BIOLOGY

Novel Anti-TMPRSS6 Monoclonal Antibody Provides a Potential Therapeutic Approach for the Treatment of Polycythemia Vera

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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 hepcidin, the master regulator of iron homeostasis. Increasing genetic, preclinical and clinical evidence has demonstrated that inhibition of TMPRSS6 can potently elevated 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, a worsening splenomegaly and expansion of early erythroid progenitors were observed after 3 weeks of treatment, and these findings are typical 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. A Phase I clinical trial with MWTx-003 in healthy volunteers has been initiated in China.

Disclosures Chen: *Mabwell Therapeutics:* Current Employment. **Wang:** *Mabwell Therapeutics:* Current Employment. **Huang:** *Mabwell Therapeutics:* Current Employment. **Bujold:** *Mabwell Therapeutics:* Current Employment. **Du:** *Mabwell Therapeutics:* Current Employment.

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