Myeloproliferative neoplasms

Hyperactivation of the Janus kinase 2 (JAK2) signaling pathway leads to myeloproliferative neoplasms (MPNs) and targeting JAK2 can be used as an effective strategy for the treatment of MPNs. Here, our study indicated that WWQ-131 was a highly selective JAK2 inhibitor (IC50 =2.36 nM), with 182-fold and 171-fold more selective to JAK1 and JAK3, respectively. In JAK2V617F-dependent cell lines, WWQ-131 efficaciously inhibited cell proliferation, induced cell cycle arrest at the G2/M phase and apoptosis, and blocked the aberrant activation of JAK2 signaling pathway. In a mouse Ba/F3_JAK2V617F driven disease model, WWQ-131 effectively suppressed STAT5 phosphorylation in spleen and liver, and inhibited Ba/F3_JAK2V617F cells spreading and proliferation in vivo. In addition, WWQ-131 suppressed rhEPO-induced extramedullary erythropoiesis and polycythemia in mice, as well as hematocrits and spleen sizes, especially had no effect on white blood cell count. Furthermore, WWQ-131 (75 mg/kg) exhibited stronger therapeutic effects than fedratinib (120 mg/kg) in these two MPN models. Taken together, this study suggests that WWQ-131 will be a promising candidate for the treatment of MPNs [1)].

1)
Ge H, Wang C, Tian C, Diao Y, Wang W, Ma X, Zhang J, Li H, Zhao Z, Zhu L. Efficacy of WWQ-131, a highly selective JAK2 inhibitor, in mouse models of myeloproliferative neoplasms. Biomed Pharmacother. 2022 Oct 25;156:113884. doi: 10.1016/j.biopha.2022.113884. Epub ahead of print. PMID: 36306591.