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Myeloproliferative disorders

PRE-CLINICAL EFFICACY OF A NOVEL COMBINED PHARMACOLOGICAL APPROACH TARGETING JAK AND ERK IN A MYELOFIBROSIS MOUSE MODEL

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Introduction: Myelofibrosis (MF) is the most severe form of Philadelphia–negative myeloproliferative neoplasms (MPNs), characterized by high risk of leukemic transformation and reduced survival. Neoplastic transformation is linked to somatic mutations in JAK/STAT pathway arising in the hematopoietic stem cell compartment, while MF pathology is defined by clonal myeloproliferation, extramedullary hematopoiesis with splenomegaly, chronic inflammation and extensive bone marrow fibrosis.

Currently, the molecular basis of abnormal cytokine production and the altered interaction between malignant hematopoietic cells and the bone marrow microenvironment in MF pathogenesis remains unclear, and JAK1/2 inhibitors, while effective in reducing splenomegaly and inflammation-related symptoms, fail to address BM fibrosis and disease burden in most patients.

A key mediator in bone marrow fibrosis development is Osteopontin (OPN), a pro-fibrotic molecule induced by MAPK signalling and JAK/STAT pathway hyperactivation driving MF pathogenesis.

This study aimed at identifying a rapidly translatable and effective therapeutic strategy to counteract OPN production and provide a new potential druggable approach to restore bone marrow microenvironment in MF patients.

Methods: With the aim of defining a pharmacological strategy to restore bone marrow microenvironment in MF, we selected Cobimetinib - a MEK1 inhibitor of MAPK pathway already approved for clinical use - to test a combined treatment against OPN overproduction and JAK2 hyperactivation. Thrombopoietin receptor agonist-treated mice developing thrombocytosis, bone marrow fibrosis and splenomegaly were used to test a dual JAK/ERK inhibition strategy comprising Ruxolitinib and Cobimetinib, and its efficacy was evaluated in terms of symptoms improvement.

Results: The efficacy study in this murine model of myeloproliferation showed the ability of Cobimetinib monotherapy to reduce OPN plasma levels and to mitigate fibrosis to a greater extent than Ruxolitinib treatment alone. Strikingly, combined therapy Cobimetinib plus Ruxolitinib showed a synergistic effect in reducing MF-associated symptoms. Specifically, combined treatment has demonstrated greater efficacy in reducing spleen index if compared to Ruxolitinib treatment alone and in reducing bone marrow fibrosis when compared to Cobimetinib monotherapy.

Conclusions: These data demonstrate the translational relevance of the combined treatment of Cobimetinib and Ruxolitinib in counteracting MF hallmark of pathology in a preclinical model of myelofibrosis, defining a rationale for the development of novel combinatory therapy able to target both clonal myeloproliferation and fibrotic microenvironment in MF patients.