Identifying Novel Therapeutic Targets in Myeloproliferative Neoplasms

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Toward a Better Understanding of...

IDENTIFYING NOVEL THERAPEUTIC TARGETS IN MYELOPROLIFERATIVE NEOPLASMS

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A Myeloproliferative Neoplasm (MPN) is a clonal hematologic disorder in which red blood cells, platelets, or certain types of white blood cells are produced in excess by the bone marrow. Some MPNs can progress towards Acute Myeloid Leukemia (AML) in which the patient’s prognosis is extremely poor. Many MPNs have been linked with the presence of the JAK2V617F mutation or other lower frequency mutations in JAK2, CALR, and MPL which cause increased activity of JAK2, a non-receptor tyrosine kinase, leading to constitutive hyper-activation of the JAK-STAT signaling pathway. Recently, the emergence of JAK2 inhibitor therapy has benefited many patients with MPNs. However, not all of these patients respond to treatment with JAK2 inhibitors, indicating that other important signaling pathways may play a key role in the development of MPNs. In this ongoing study, Pevonedistat, a NEDD8-activating enzyme inhibitor is tested individually and in designed combinations with cytokines and other inhibitors to strategically target specific components of hyper-activated signal transduction pathways in order to promote apoptosis or suppress cellular proliferation. Cell viability assays are used to monitor the effects of Pevonedistat in cell lines that model growth and mutational characteristics of MPNs, such as Human Erythroleukemia (HEL) cells, a human mutant cell line of JAK2, and murine BaF3-MPL cells. Pevonedistat treatment of Myelofibrosis patient samples in colony forming unit (CFU) assays has shown promising results when compared to normal controls. Further testing will be performed on mice models with the ultimate goal of developing inhibitor therapies that may help to prevent the onset of AML and improve overall survival of patients.