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Characterizing Effects of Pevonedistat in Myeloproliferative Neoplasms

Abigail J. Wong

Mentor: Stephen Oh

Myeloproliferative neoplasms (MPNs) are hematologic malignancies that cause uncontrolled blood cell growth and can progress to secondary acute myeloid leukemia (sAML). While there are therapies for AML and MPN patients, only a fraction of them are suitable to the individual, and the progress of standard chemotherapy has remained largely stagnant over the past few decades. Therefore, the investigation of MPN drug candidates such as pevonedistat is imperative. Pevonedistat is a NEDD8 activating enzyme inhibitor currently in clinical trials for AML. The inhibitor is known to impede NF-kB signaling as well as other signaling pathways associated with MPN pathogenesis; therefore, it is crucial to characterize the effects of pevonedistat on a variety of pathways. While the JAK-STAT pathway is primarily associated with AML and myelofibrosis, inhibition of JAK2 does not completely diminish MPN pathogenesis. Therefore, it is likely that activation of other signaling processes drive cell proliferation in addition to JAKSTAT. Previous studies in the Oh Lab have shown that the NF-kB pathway is hyperactivated in sAML and MF hematopoietic stem and progenitor cells (HSPC), identifying the NF-kB pathway as a potential target of pevonedistat. We have found that pevonedistat lowers cell viability in human erythroleukemia (HEL) cell line in a dose-dependent manner. Furthermore, pevonedistat in combination with JNK-IN-8, an inhibitor of the JNK-AP1 pathway, lowers cell viability in an additive fashion. The combination of pevonedistat and JNK-IN-8 may be superior to pevonedistat alone, and thus we are currently exploring this possibility.