Dual inhibition of Jak2 and STAT5 enhances killing of myeloproliferative neoplasia cells

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Study Design
To investigate dual inhibition of the Jak-Stat pathway a model system, Ba/F3 cells reconstituted with erythropoietin receptor and the mutant form of Jak2 (BAFEJ), as well as the HEL and SET2 human leukemia cell lines that endogenously express Jak2 V617F were treated with pimozide, and Jak-inhibitor 1. Both led to a decrease in tyrosine phosphorylation of STAT5. The mechanism of action of pimozide was investigated with a) recombinant kinases b) the PTK (phosphotyrosine kinase) PamChip® – assay c) Western blot of the Jak downstream pathway MAP kinase d) measuring expression of STAT5 downstream target genes.

Key Findings
Pimozide is not a classical kinase inhibitor as a) it does not inhibit Jak family kinases, b) its pattern of inhibition of substrate phosphorylation catalyzed by extracts from Jak2 V617F-expressing cells using the PamChip® tyrosine kinase microarray system is clearly distinct from that mediated by a Jak inhibitor (including no inhibition of the phosphorylation of the Jak2 peptide by pimozide), c) other signaling pathways downstream of Jak2, such as the phosphorylation of extracellular signal-regulated kinase mitogen-activated protein kinases (MAPK) are not inhibited by pimozide (as they are with Jak inhibitor 1) in BAFEJ and HEL cells, d) inhibition of STAT5 phosphorylation by pimozide led to a decrease in expression of STAT5 target genes. Pimozide does lead to increased apoptosis.

“Author Quote”
“These data suggest that directly inhibiting STAT5, as well as simultaneously inhibiting both STAT5 and Jak2, may be effective strategies for the treatment of Myeloproliferative neoplasms”

Background
Myeloproliferative neoplasms (MPNs) are a group of clonal disorders that arise from the transformation of hematopoietic stem cells. There is currently no uniform treatment although a variety of kinases is implicated. The dual inhibition as proposed here is a good start for development of such a cure.

Conclusion
PamChip® microarrays played a role in the characterization of the mode of action of the cytotoxic agent pimozide as a potential inhibitor of Stat5.

Reference: