

A novel, potent and selective dual inhibitor of JAK1 and JAK2 for treatment of myeloproliferative neoplasms

C. J. Burns

Cytopia Research Pty Ltd, Melbourne, VIC, Australia

Activating mutations of the tyrosine kinase JAK2 are associated clinically with myeloproliferative neoplasms (MPNs), most notably Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis. Inhibitors targeting this signalling pathway may therefore prove useful treatments of these diseases. CYT387 is a novel and potent inhibitor of JAK2 and JAK1, with excellent selectivity against a panel of over 150 kinases. CYT387 is an orally bioavailable small molecule that binds competitively to the ATP binding site, confirmed by the X-ray crystal structure of the JAK2 kinase domain in complex with CYT387. The compound blocks JAK2-driven cellular proliferation of both cell lines and primary cells from MPN patients, as well as inhibiting downstream signalling events including phosphorylation of STAT3, STAT5 and, in a pathway dependent manner, ERK1/2. CYT387 is efficacious in vivo in a number of JAK2 driven processes, including a mouse model of MPNs. Together the data indicate that CYT387 is an appropriate candidate for clinical evaluation as a treatment of MPNs, and a Phase I/II trial has been initiated.