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Novel small-molecule Stat5 Inhibitor for further optimization and clinical development for cancer therapy

Jak2-Stat5 signaling plays a significant role in promoting growth and progression of Bcr-Abl-driven hematological malignancies as well as prostate cancer. Bypassing tyrosine kinases compelled for Stat5a/b phosphorylation would be favourable for therapy development for Stat5a/b- controlled cancers. To identify small-molecule inhibitors of Stat5a/b for lead optimization and therapy development, *in silico* screening of chemical structure databases combined with medicinal chemistry was used for identification of a group of small-molecule forestalling to block SH2-domain-mediated docking of Stat5a/b to the receptor-kinase complex and subsequent phosphorylation and dimerization. The lead compound Inhibitor of Stat5, IST5-002, (IST5) binds directly to the SH2-domain of Stat5 in fluorescence polarization assays. We additionally tried the viability of the lead-compound IST5 in exploratory models and patient examples of two best-known Stat5a/b-driven tumors, prostate cancer (PC) and interminable myeloid leukemia (CML). IST5 forestalled both Jak2 and Bcr-Abl-interceded phosphorylation and dimerization of Stat5a/b, and specifically hindered the transcriptional action of Stat5a (IC_{50} 1.5μM) and Stat5b (IC_{50} 3.5μM). IST5 suppressed nuclear translocation of Stat5a/b, binding to DNA and Stat5a/b target gene expression. IST5 had no significant inhibitory activity on a panel of 52 kinases, including Jak2 and Abl. Importantly, no signs of toxicity were noted at the dose of 100 mg/kg in acute or chronic toxicity studies conducted in mice. IST5 incited broad apoptosis of PC cells, weakened development of PC xenograft tumors and prompted cell demise in quiet inferred PCs when tried *ex vivo* in explant organ societies. Critically, IST5 initiated hearty apoptotic passing of imatinib-delicate as well as imatinib-safe unending myeloid leukemia (CML) cell lines and essential CML cells from patients. IST5 gives a lead structure to advance synthetic alterations for clinical improvement for Stat5a/b-driven strong tumors and hematological malignancies.

Biography

Marja Nevalainen, MD, PhD is an internationally recognized leader in the field of cytokine and steroid hormone signaling in prostate cancer. Dr Nevalainen holds the title of Eminent Scholar at MCW. She is also Director of Prostate Cancer Center of Excellence at MCW Cancer Center, which is a multi-disciplinary hub for prostate cancer research with an international collaborative network. Dr Nevalainen serves as Assistant Dean for Research at MCW, and Associate Director of Education for the MCW Cancer Center. Her primary appointment is in the Department of Pathology, and a secondary appointment in the Department of Pharmacology and Toxicology.

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