WP1130

WP1130 is a small molecule derived from a compound with Janus-activated kinase 2 (JAK2) kinase inhibitory activity. WP1130 induces rapid accumulation of polyubiquitinated (K48/K63-linked) proteins into juxtanuclear aggresomes, without affecting 20S proteasome activity. WP1130 acts as a partly selective DUB inhibitor, directly inhibiting DUB activity of USP9x, USP5, USP14, and UCH37, which are known to regulate survival protein stability and 26S proteasome function. WP1130-mediated inhibition of tumor-activated DUBs results in downregulation of antiapoptotic and upregulation of proapoptotic proteins, such as MCL-1 and p53. The results show that chemical modification of a previously described JAK2 inhibitor results in the unexpected discovery of a novel DUB inhibitor with a unique antitumor mechanism [1)].

WP1130 has been characterized as a deubiquitinase inhibitor that interferes with the function of Usp9X.

Increasing concentrations of WP1130 decrease the cellular viability of established, patient-derived xenograft (PDX) and stem cell-like glioblastoma cells.

Mechanistically, WP1130 elicits apoptosis and increases activation of caspases. Moreover, WP1130 and siRNAs targeting Usp9X reduce the expression of anti-apoptotic Bcl-2 family members and Inhibitor of Apoptosis Proteins, XIAP and Survivin. Pharmacological and genetic interference with Usp9X efficiently sensitized glioblastoma cells to intrinsic and extrinsic apoptotic stimuli. In addition, single treatment with WP1130 elicited anti-glioma activity in an orthotopic proneural murine model of glioblastoma. Finally, the combination treatment of WP1130 and ABT263 inhibited tumor growth more efficiently than each reagent by its own in vivo without detectable side effects or organ toxicity. Taken together, these results suggest that targeting deubiquitinases for glioma therapy is feasible and effective [2)].

1)
Kapuria V, Peterson LF, Fang D, Bornmann WG, Talpaz M, Donato NJ. Deubiquitinase inhibition by small-molecule WP1130 triggers aggresome formation and tumor cell apoptosis. Cancer Res. 2010 Nov 15;70(22):9265-76. doi: 10.1158/0008-5472.CAN-10-1530. Epub 2010 Nov 2. PubMed PMID: 21045142.

2)
Karpel-Massler G, Banu MA, Shu C, Halatsch ME, Westhoff MA, Bruce JN, Canoll P, Siegelin MD. Inhibition of deubiquitinases primes glioblastoma cells to apoptosis in vitro and in vivo. Oncotarget. 2016 Feb 10. doi: 10.18632/oncotarget.7302. [Epub ahead of print] PubMed PMID: 26872380.