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TARGETS THE COLCHICINE BINDING SITE ON TUBULIN AND OVERCOMES TAXANE RESISTANCE

Kinsie E. Arnst[1], Yuxi Wang[2], Dong-Jin Hwang[1], Duane D. Miller*[1], and Wei Li*[1]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, the University of Tennessee Health Science Center, Memphis, TN. [2]State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China.

Antimitotics that target tubulin are among the most useful chemotherapeutic drugs, but their clinical activity is often limited by the development of multidrug resistance. We recently discovered the novel small molecule 2-(1H-indol-4-yl)-4-(3,4,5-trimethoxyphenyl)-1H-imidazo[4,5-c]pyridine (DJ101) as a potent and metabolically stable tubulin inhibitor that can circumvent the drug efflux pumps responsible for multidrug resistance of existing tubulin inhibitors. In this study, we further evaluated the mechanism of action of this drug. The basis for its activity was illuminated by solving the crystal structure of DJ101 in complex with tubulin at a resolution of 2.8Å (PDB 5H7O). Investigations of the potency of DJ101 in a panel of human metastatic melanoma cell lines harboring major clinically relevant mutations demonstrated IC_{50} values of 7-10 nM. Additional *in vitro* studies revealed DJ101 disrupted microtubule networks, suppressed anchorage-dependent melanoma colony formation and impaired cancer cell migration. Administration of DJ101 significantly inhibited A375 melanoma tumor growth and B16F10 melanoma metastasis in xenograft and lung metastasis models in mice. DJ101 also completely inhibited tumor growth in a paclitaxel-resistant xenograft mouse model of human prostate cancer (PC-3/TxR), where paclitaxel was minimally effective. Pharmacological screening data showed negligible interactions with physiologically important targets and observable toxicity was not apparent in animal studies, suggesting a good safety profile for DJ101. Our findings offer preclinical proof of concept for the continued development of DJ101 an improved generation of tubulin inhibitors for cancer therapy.