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Discovery of novel tubulin inhibitors and their synergy with BRAF inhibitors for malignant melanoma

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Malignant melanoma is the most aggressive form of skin cancer and it is highly resistant to most existing therapies. Despite recent advances in both targeted therapy (e.g. BRAF inhibitors vemurafenib and dabrafenib; MEK inhibitor trametinib) and immunotherapy (ipilimumab; pembrolizumab), acquired drug resistance often develops quickly and the overall survival for malignant melanoma remains unsatisfactory. Chemotherapeutic drugs including tubulin inhibitors (e.g., paclitaxel or vinblastine) are used in treating malignant melanoma clinically, but their efficacy is often limited by the ABC-transporter mediated drug efflux and non-specific tissue distribution, leading to dose limiting toxicity. We have discovered several sets of novel tubulin inhibitors that: 1) target the colchicine binding site in tubulin and have broad spectrum of potent anticancer activity; 2) effectively circumvent major drug resistance mechanisms (P-gp, BCRP, and MRPs) that hinder the clinical efficacy with existing tubulin inhibitors; 3) are orally bioavailable and have excellent drug-like properties; 4) are efficacious against both drug sensitive and drug resistant melanoma tumors *in vivo*; and 5) have strong synergy with approved BRAF inhibitors for BRAF-resistant melanoma tumors. We have also developed nanoparticle formulations for these agents and showed that these targeted drug delivery approaches can significantly improve the anticancer efficacy for these tubulin inhibitors.

Biography

Wei Li has been on faculty at University of Tennessee Health Science Center, USA after obtaining his PhD in Chemistry from Columbia University in the City of New York in 1999. He is currently a Professor and the Faculty Director of Shared Analytical Instrument in the university. He has publised over 114 peer-reviewed papers and three book chapters, is an inventor of a number of issued patents, and serves as the Editor of the Anticancer Section of Current Medicinal Chemistry. He is a frequent grant reviewer for NIH and other funding agencies, and his current research is supported by multiple NIH grants.

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