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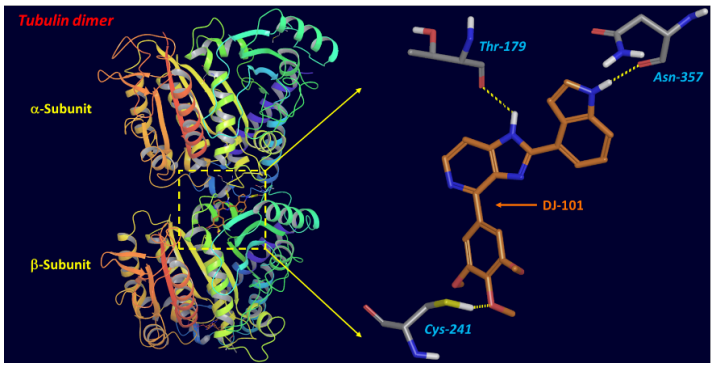
A NEW GENERATION OF ORALLY AVAILABLE TUBULIN INHIBITORS: THE DISCOVERY AND DEVELOPMENT

Wei Li
UTHSC, Tennessee

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 and immunotherapy, acquired drug resistance often develops quickly and the overall survival for malignant melanoma remains unsatisfactory. Chemotherapeutic drugs including tubulin inhibitors (e.g., paclitaxel) 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 that hinder the clinical efficacy with existing tubulin inhibitors; 3) are orally bioavailable and have excellent drug-like properties; and 4) are efficacious against both drug sensitive and drug resistant melanoma tumors in vivo. We have solved the X-ray crystal structures for many of these compounds to confirm their direct binding to tubulin (DJ-101 as an example shown in the figure). We have also developed nanoparticle formulations for these agents and showed that these targeted drug delivery approaches can improve the anticancer efficacy for these tubulin inhibitors.



Biography

Wei Li has been working at the College of Pharmacy, the University of Tennessee Health Science Center (UTCoP) since he obtained his PhD in chemistry from Columbia University in 1999. Currently, he is a Professor and the Director of the UTCoP Drug Discovery Center. His focus of research is Small Molecule Drug Discovery, and currently his research is mainly funded by NIH/NCI grants. He has published over 135 papers, 3 book chapters; five issued US patents, and additional patents from other countries. He is a frequent grant Reviewer for NIH study sections, and currently he is an Editorial Board Member for Current Medicinal *Chemistry, Molecules*, and Acta *Pharmaceutica Sinica B*.

wli@uthsc.edu