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DEVELOPMENT OF PROHIBITIN LIGANDS TO TREAT CANCERS, CARDIAC AND IMMUNOLOGICAL DISORDERS

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Flavaglines are a family of anticancer natural products that relieve the resistance to cancer chemotherapies and display a strong cytotoxicity that is specific to cancer cells. We identified the first synthetic flavaglines that inhibit cell proliferation and viability (IC50≈1 nM) at lower doses than did the parent natural compounds. A ligand for affinity chromatography was synthesized based on our structure affinity relationship (SAR) information, and used for the identification of prohibitins-1 and -2 as the molecular targets. Prohibitin-1 (PHB1) and its homologue prohibitin-2 (PHB2) are pleiotropic proteins that act as a hub for many signalling pathways. We demonstrated that the binding of flavaglines to PHBs prevents the interaction between PHBs and C-RAF and, thereby, inhibits C-RAF activation and subsequently C-RAF-MEK-ERK signalling, which is critical to survival and proliferation of cancer cells. With our collaborators, we found that another PHB ligand, fluorizoline, also block C-RAF activation. Despite decades of research effort, clinically effective medicines targeting C-RAF and KRAS remain elusive. Our recent results open a novel avenue to inhibit both C-RAF and KRAS signalling with PHB ligands. We also demonstrated that these compounds protect the heart from the adverse effects of cancer chemotherapies involving anthracyclines. We showed that this cardioprotection is mediated by the activation of the mitochondrial PHB-STAT3 complex. In addition to these lines of research, we also developed new PHB ligands belonging to the class of triazines that modulate the biosynthesis of melanin in melanocytes and induce the death of cancer cells. The structure-activity relationships of these new drugs and their detailed mechanism of action will also be presented.

Biography

L Desaubry is a CNRS Research Director in the University of Strasbourg in France (website: http://desaubry.u-strasbg.fr/) and Adjunct Professor at Tianjin University of Science and Technology (TUST) in China. In 1992, he received a PhD degree in Medicinal Chemistry from Strasbourg University. Next, he worked as a Post-doctoral fellow at SUNY at Stony Brook, USA. He has completed Post-doctoral internship in Prof Pierre Chambon's laboratory previously to get a CNRS Research Senior Scientist at the University of Strasbourg-CNRS. He was promoted CNRS Research Director (corresponds to full professor) in 2014, and also became professor at TUST in 2015. He has published more than 70 publications and has been serving as an Editorial Board Member of *Frontiers in Chemistry, Medicinal Chemistry, Advances in Oncology Research and Treatments and The Open Medicinal Chemistry Journal*.

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

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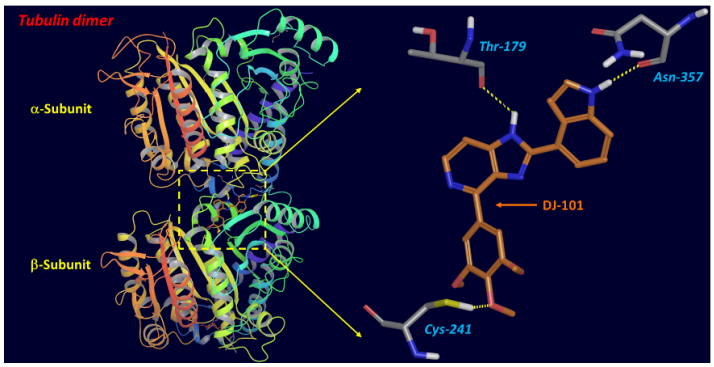
Malignant melanoma is the most aggressive form of skin cancer and it is highly resistant to most existing therapies. Despite recent advances in both targeted therapy and immunotherapy, acquired drug resistance often develops quickly and the overall survival for malignant melanoma remains unsatisfactory. 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*.

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