

**PSEUDOLARIC ACID B, A NOVEL MICROTUBULE-  
DESTABILIZING AGENT THAT CIRCUMVENTS MULTI-DRUG  
RESISTANCE PHENOTYPE AND EXHIBITS ANTITUMOR  
ACTIVITY *IN VIVO*.**

Vincent K.W. Wong<sup>1,2</sup>, Pauline Chiu<sup>1,2</sup>, Stephen S.M. Chung<sup>3</sup>, Larry M.C. Chow<sup>4</sup>,  
Y.Z. Zhao<sup>4</sup>, Burton B. Yang<sup>5</sup>, Ben C.B. Ko<sup>1,2</sup>.

<sup>1</sup>Department of Chemistry

<sup>2</sup>Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug  
Discovery and Synthesis

<sup>3</sup>Institute of Molecular Biology, The University of Hong Kong, Pokfulam Road, Hong  
Kong Special Administrative Region, China

<sup>4</sup>Department of Applied Biology & Chemical Technology, Hong Kong Polytechnic  
University, Hong Kong Special Administrative Region, China

<sup>5</sup>Sunnybrook & Women's College Health Sciences Centre, and Department of Laboratory  
Medicine & Pathobiology, University of Toronto, Toronto, Canada

Pseudolaric acid B (PAB) is the major bioactive constituent in the root bark of *pseudolarix kaempferi* that has been used as an anti-fungal remedy in traditional Chinese medicine. We purified PAB to apparent homogeneity and showed that it exhibits potent growth inhibition towards a panel of cancer cell lines (average IC<sub>50</sub>=1 μM). We found that PAB induces cell cycle arrest at G<sub>2</sub>-M transition through the microtubules destabilization mechanism, leading to apoptosis. In addition, polymerization of purified bovine brain tubulin was dose-dependently inhibited by PAB, suggesting that tubulin is the direct target of PAB. However, PAB did not displace [<sup>3</sup>H] colchicine or [<sup>3</sup>H] vinblastine from tubulin binding in competition binding assays, suggesting that PAB interacts with tubulin through a novel binding site. Most importantly, PAB circumvents multi-drug resistant mechanism, displaying remarkable potency in P-glycoprotein overexpressing cells and we demonstrated that PAB inhibit tumor growth effectively *in vivo* using murine xenograft tumor model. Furthermore, we also found that the blood vessel density of the PAB-tumor was significantly reduced, suggesting that, similar to other microtubule-destabilizing compounds, PAB also exhibits anti-angiogenic activity *in vivo*.