## Small-Molecule, Tubulin Binding, Vascular Disrupting Agents as Anti-Cancer Therapeutics

Kevin Pinney, Baylor University

Small-molecule, anti-cancer agents continue to show promise in numerous cancer treatment regimens, employed as single agents or more often in combination with other treatment modalities. A formidable challenge lies in the ability to selectively target appropriate therapeutic molecules towards cancer cells or crucial components of the tumor microenvironment. Progressive structure-activity relationship observations have guided a process of synthetic molecular evolution resulting in the discovery of a variety of highly potent inhibitors of tubulin assembly (polymerization). These compounds demonstrate dual-functionality in regard to biological activity, acting both as antiproliferative agents and as vascular disrupting agents (VDAs), which selectively disrupt blood flow to tumors. Interestingly, both of these mechanisms are based on the ability of these compounds to interact with the tubulin-microtubule protein system, and it is important to note that the VDA mechanism of action is distinct from that of angiogenesis inhibiting agents (AIAs) that have gained traction in the clinic. The discovery and development of dihydronaphthalene, benzosuberene, and indole-based anticancer agents will be presented along with a preliminary assessment of their ability to function both antiproliferatively and as VDAs. Certain of these anti-cancer agents demonstrate sub-nanomolar (to pico-molar) cytotoxicity (*in vitro*) against a variety of human cancer cell lines and are also exemplary in their ability to effect tumor vascular damage (*in vitro* and *in vivo* assessment). Strategies for the selective targeting of these agents as antibody-drug conjugates (ADCs) and separately towards tumor hypoxia will be described.