

## THE POWER OF COLLABORATION: STUDIES OF TUBULIN-POLYMERIZATION PROMOTERS

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The plant natural product paclitaxel (Taxol™, **1**) and its semisynthetic analog docetaxel (**2**) are two of the most important anticancer agents developed over the last 30 years. They both act by binding to microtubules and stabilizing them to dissociation, thus disrupting the cell cycle. The epothilones, such as epothilone B (**3**) and the recently approved clinical agent ixabepilone (**4**), belong a new structural class of natural product anticancer agents, but act by the same mechanism as paclitaxel. The lecture will review our work on discovering the tubulin-binding conformation of paclitaxel by a combination of REDOR NMR and molecular modeling combined with the results of electron crystallographic studies. This work led to the design and synthesis of bridged paclitaxel analogs such as **5** that have tubulin-assembly and cytotoxic activities equal to or better than those of paclitaxel. Recent studies on the synthesis and tubulin-binding properties of bridged epothilones will also be discussed. This work would not have been possible without a highly collaborative approach involving scientists from four different universities, and the advantages of this type of collaboration will be discussed.

