

Conformational Control of Tubulin by Microtubule-Stabilising Agents: a Detailed Look into Epothilones

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In this project it is intended to investigate the basis of the conformational changes induced in tubulin by tubulin-binding agents. Changes in tubulin conformation interfere with the tubulin polymerization equilibrium, therefore with the cell cycle and ultimately with cell viability. Epothilones bind to tubulin in the taxane binding pocket, stabilize the microtubular form of the protein and possess strong cytotoxic activity. Despite the determination of two tubulin-bound conformations of epitholone A by NMR spectroscopy and electron crystallography and the synthesis of more than 500 epothilone derivatives, the structural aspects of the control that epothilones exert on the tubulin polymerization state remain obscure. It is planned to characterize the interplay between the epothilone binding mode and the conformation of tubulin in various polymerization states. This work will provide a framework for the understanding of the mechanisms of numerous other tubulin-binding agents (discodermolide, laulimalide, peloruside and others) and will open the door to the design of novel anti-cancer drugs with improved activity.

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