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Studies of Ligand Binding to Tubulin by Electron Crystallography. K.H. Downing¹, H. Li², J.H. Nettles³, J.P. Snyder³, ¹Life Science Div, Lawrence Berkeley National Lab, Berkeley, CA 94720, ²Biology Dept, Brookhaven National Lab, Upton, NY 11973, ³Chemistry Dept, Emory Univ, Atlanta, GA 30322.

The electron crystallographic structure of tubulin bound to the anti-cancer drug Taxol (1,2) revealed the nature of the Taxol binding site. A number of other compounds with widely differing structures are now known that, like Taxol, stabilize microtubules. We are studying several of these, including epothilone, eleutherobin and discodermolide, and have collected 3-D electron diffraction data sets of each to around 2.8 Å. Difference maps show that they all bind in the same area as Taxol. However, the resolution of the tubulin-Taxol crystal structure, 3.5 Å, has required development of refinement and modeling procedures in order dock the drugs accurately enough to make chemical sense of the interactions. Many candidate ligand structures are tested for their fit to the experimental data by docking in orientations compatible with the density map, followed by structure refinement against the diffraction data. This approach converged to a stable solution for the epothilone-tubulin structure (3) that is consistent with a wealth of SAR data.

- (1) E. Nogales et al., Nature 391 199 (1998)
- (2) J. Löwe et al., J. Mol. Biol. 313 1045 (2001)
- (3) J.H. Nettles et al., Science 305 866 (2004)