PROGRESS AND PITFALLS IN THE MODELING AND SIMULATION OF TUBULIN-DRUG INTERACTIONS

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The first reliable three-dimensional model of tubulin in atomic detail was reported in 1998 [1]. This long sought-after structure, deposited in the Protein Data Bank (PDB) as entry 1TUB, was solved by electron crystallography of Zn^{2+}–stabilized sheets of bovine tubulin bound to paclitaxel (*Taxol*®), the protoypical microtubule-stabilizing agent (MSA). Subsequent refinement of this antiparallel association of tubulin protofilaments improved the resolution to 3.5 Å (PDB entry 1JFF) [2].

The complex formed between two α,β-tubulin heterodimers and the stathmin-like domain of the RB3 protein (T_2R) resembles a short protofilament, does not assemble further and can be crystallized. Despite the moderate diffracting power of these crystals, X-ray crystallography and soaking experiments were used to unravel the binding mode of vinblastine (*a.k.a.* vincaleucoblastine) at 4.2 Å resolution [3] thirty years after this plant alkaloid was shown to induce the formation of highly birefringent crystals of microtubular protein [4].

More recently, additional co-crystallization of T_2R with tubulin tyrosine ligase (TTL) in the presence of epothilone A (EpoA) made possible the determination of a T_2R-TTL-EpoA assembly at 2.3 Å resolution [5]. This complex provided a structural explanation to the ability of MSAs to promote microtubule assembly and stability.

These and other examples highlight the notable progress in our understanding of the affinity determinants for a large number of tubulin-binding drugs which has been further extended by the discovery of novel binding sites and pharmacophoric features [6]. This knowledge can now be advantageously and judiciously used to rationalize numerous structure-activity relationships and to attempt structure-based ligand optimization and/or virtual screening.

References

1. Nogales, E. et al. *Nature* (1998) 391, 199–203.
2. Löwe, J. et al. *J. Mol. Biol*. (2001) 313, 1045–1057.
3. Gigant, B. et al. *Nature* (2005) 435, 519–522.
4. Strahs, K.R.; Sato, H. *Exp. Cell Res*. (1973) 80, 10–14.
5. Prota, A.E. et al. *Science* (2013) 339, 587–590.
6. Prota, A.E. et al. *Proc Natl Acad Sci U S A*. (2014) 111, 13817–13821.