

Computational Approaches to the Discovery of New Cancer Drugs

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Several proteins within the cell can exist as one of a number of distinct gene products, or isotypes. An example of one such protein is beta tubulin, which exists as at least eight distinct isotypes within the human genome. A number of chemotherapeutic drugs have already been discovered that bind to and affect tubulin dynamics, thereby halting chromosome segregation which results in cell death. To date, all drugs that target tubulin dynamics are relatively non-specific and result in the indiscriminant death of most dividing cells. Fortunately, the existence of several isoforms of beta tubulin provides us with the ability to design drugs that will differentiate between the tubulin isotypes expressed in different cells. Using data collected from molecular dynamics experiments of beta tubulin isotype models, we have examined the fundamental properties that distinguish each of these beta tubulin isotypes. Through our modeling effort, we have produced high-resolution models of pre-existing and potential drug binding sites within each of the tubulin isotype models. This has provided us with the molecular dimensions of each binding site, as well as the biochemical nature of the amino acids that constitute that site. Using these characteristics, we have designed several groups of novel drugs that possess better binding affinity for tubulin isoforms at these positions. The first family of novel drugs produced is based on colchicines as a scaffold for derivatization at three distinct carbon positions. We have performed in silico predictions of these drug molecules followed by chemical synthesis and testing in vitro on both cancerous and normal cell cultures. Our experimental results generally agree with the trends emerging from the computational predictions. The second group of drugs designed on the principles of higher specificity for selected targets are derivatives of taxol. They have now been synthesized and will soon be assessed for their cytotoxic effects. I will briefly mention several other projects underway in my group. The focus of these computational drug discovery efforts is a group of other key functional proteins and protein complexes, namely: ERCC1- XPA(F), p53-MDM2 and the hPNK pathway.

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