

### “Targeting Loop Dynamics in Beta/BetaIII Isotype Tubulin: The Application of In Silico Techniques in Combating Chemotherapy Drug Resistance”

**Ruoyi Jiang, Ward Melville High School, East Setauket, NY – 2009 National Individual Winner**

**Abstract:** Taxol, known by its generic chemotherapy drug name as Paclitaxel, is a flexible antimetabolic microtubule stabilizer that binds to the  $\beta$ -tubulin monomer of the tubulin heterodimer within microtubules and induces mitotic arrest followed by programmed cellular apoptosis. The taxane class of antimetabolic agents is used extensively in combination chemotherapy to treat a variety of malignant carcinomas including non-small cell lung cancer, ovarian cancer, AIDS-associated Kaposi's sarcoma and breast cancer. However, drug resistance in the form of isotype overexpression specific to carcinoma cells has been implicated as the most serious threat to the viability of chemotherapy agents. Here we present an extensive all-atom simulation study of the structure-based conformational changes associated with paclitaxel-tubulin drug interactions and the effect of isotype mutations on the character of lateral interactions between adjacent protofilaments and the luminal pharmacophore. An M-Loop hinge model for the mechanism of Taxol action was used to explain isotype overexpression and propose novel drugs that may overcome chemoresistance while justifying those that presently exist (IDN5390). This study used *in silico* techniques to improve novel drug compounds in a rational, structure-based manner, potentially increasing the effectiveness of chemotherapy drug targeting and the potency of combination chemotherapy treatments.

**Mentor:** Dr. Carlos Simmerling

### “Mathematical Modeling of a Eukaryotic Circadian Clock”

**Alexander Huang, Plano Senior High School, Plano, TX – 2007 National Individual Finalist**

**Abstract:** Circadian rhythms in biological organisms arise from cellular-level metabolic and genetic regulation. The regulation process in eukaryotes involves proteins and enzymes forming complex feedback processes to generate oscillations. Mathematical modeling of the regulation process allows a deeper understanding of the molecular mechanisms and functions of the rhythms. In this work, the circadian clock of fungus *Neurospora crassa* was studied in detail with a new mathematical model which provides a basis to understand the circadian mechanisms of other eukaryotes. The new model was established with activating-inhibiting feedback loops exerted on the expression of *frq* gene by proteins Frequency (FRQ) and White Collar Complex (WCC). The model has been successfully validated with various laboratory data and it entrains to a 24-hour period under circadian light-dark cycles. It demonstrated period sensitivity to the degradation of FRQ and provided molecular-level explanations for single-pulse suppression and cessation of clock activities under constant light. The model also predicts several new phenomena not yet seen in the laboratory and is thus ideal to serve as a tool to design future experiments. The work suggests similar genetic feedback models can be developed to study the circadian behaviors of higher eukaryotes.

**Mentor:** Professor Yi Liu