# CALIFORNIA STATE SCIENCE FAIR
# 2013 PROJECT SUMMARY

**Name(s)**

**Prem M. Talwai**

**Project Number**

**S1425**

**Project Title**

## A Novel Mathematical Model of Targeted Cancer Therapy along p53 Proteasomal Degradation Pathways

**Abstract**

**Objectives/Goals**

The objective of this project is to derive a mathematical model for describing multi-substrate enzyme kinetics, particularly focusing on the harmful degradation of the tumor suppressor protein p53, which is mediated by the oncogene MDM2. The mathematical model will then be used to determine whether the ubiquitin ligase MDM2 or the ubiquitin-conjugating enzyme E2D3 plays a larger role in the degradation process. This discovery will help identify new potential targets for cancer therapy.

**Methods/Materials**

A novel system of nonlinear partial differential equations incorporating initial concentration variables was derived in order model the enzyme mechanism. The nonlinear system was subsequently linearized using perturbation methods and solved using conventional linear algebraic techniques. The resulting solution to the model was validated against experimental results from gel-electrophoresis experiments conducted by Lai et al. Four dynamic modules were then constructed using the Mathematica program to capture the influence of initial concentration variables on the role played by E2D3 and MDM2 in the degradation process. The model was simulated for various values of the rate constants in order to confirm the observed patterns.

**Results**

Through growth rate analysis, it was concluded that although MDM2 and E2D3 initially compete for influence in the degradation process, MDM2 plays the larger role. Therefore the derived mathematical model demonstrates that targeting MDM2 with drugs such as Gleevec and Nutlin-3 will reduce unregulated p53 degradation and consequently redeem the integrity of the genome.

**Conclusions/Discussion**

My mathematical enzyme kinetic model allowed for the identification of MDM2 as a new potential target for cancer therapy. Furthermore, many of the relationships between enzymes, substrates, and products identified during the course of this project can be extrapolated to any biological process governed by a compulsory-order multi-substrate enzyme mechanism. The extension of the results obtained in this project may therefore lead to similar discoveries of key biomolecules driving various other vital biological processes. In future study, the computational results obtained in this project may be further verified by in vitro experimentation. In addition, a stochastic kinetics formalism may be adopted on the same problem in order to characterize random molecular motion and probabilistic enzyme binding.

**Summary Statement**

I developed a novel mathematical enzyme kinetic model of MDM2-mediated degradation of p53 which enabled me to identify MDM2 as a new potential target for cancer therapy.

**Help Received**