Speaker: Mark D. Pegram, MD
Associate Director for Clinical Research, SCI
Susy Yuan-Huey Hung Professor

Title: *Clinical Challenges in Dose Selection for Combination Therapy*

Abstract:

A theoretical model for describing drug interactions was first proposed in 1872 by Fraser in reporting data describing the pharmacological antagonism between atropine and physostigmine [Prichard & Shipman, 1990]. The experiments involved 3 variables, the respective drug concentrations and the biological effect, therefore the data were plotted in 3 dimensions, allowing antagonism to be visualized by inspecting the shape of the 3-D surface. This presentation will examine the inherent difficulties in analyzing combined drug effects and evaluate modern methods of describing these interactions. Researchers have traditionally used two-dimensional (2-D) methods to approximate the actual three-dimensional (3-D) nature of drug interactions. Chou and Talalay approached the problem from the perspective of classical enzyme kinetics. A very general equation, which they called the 'median effect equation', was used for linearizing the sigmoid shaped dose-response curves. This information identified the appropriate equation of additivity which was subsequently used to calculate the combination index (CI). These equations yield solutions of unity when additive interactions are present, and <1 or >1 when synergy or antagonism is present, respectively [Chou & Talalay, 1984]. However, 2-D methods are often inadequate when used to analyze synergistic and antagonistic drug interactions for anticancer therapies. Consequently, 3-D response surface approaches were developed to directly elucidate the shape of the dose-response surface, identifying regions of statistically significant synergy and antagonism, and quantitates these effects. This method facilitates the rigorous analysis of drug-drug interactions and offers investigators a powerful tool to analyze combinations of anticancer drugs. Finally, assessing the efficacy of a combination of antitumor agents by analyzing *in vivo* human tumor xenograft growth is an increasingly popular experimental design. But unfortunately, applying *in vitro* analytical methods outlined above is severely challenged by feasibility issues due to very large numbers of animal subjects required to generate *in vivo* tumor growth trajectory data for different drug doses and schedules. Consequently, we previously proposed a model-based approach that accounts for differences in timing and order of drug administration, both when individual mice are fit and when expected trajectories are predicted for a group. The advantages offered by our method for comparing entire individual growth curves using the group statistic and individual Ds statistics include: (i) increased power over methods that use only univariate summaries of data, (ii) avoiding problems associated with naïve pooling of data across mice, (iii) providing a means for recognizing heterogeneity of responses, and (iv) permitting the use of mice with missing data points. The use of a combined growth and drug effect model provides a formal means for defining additivity of response to drug combinations, relative to which synergism and antagonism can be interpreted [Lopez, *et al*., 1999].

References:

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