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Letter to the Editor

Cancer Research

Drug Combination Studies and Their Synergy Quantification Using the Chou–Talalay Method—Letter

John C. Ashton

Advances in the theory of combination therapy (1) and development of new targeted drugs are leading to a new emphasis on drug combination experiments. Many studies continue to use the median-effect method of Chou–Talalay (2). However, the median-effect method follows a similar logic to the defunct Scatchard analysis in pharmacology, which has been replaced by nonlinear modeling. Like Scatchard analysis, the median-effect method assumes idealized mass-action principles and relies on log-linearization. With widespread access to powerful desktop computers, nonlinear regression has replaced Scatchard analysis in pharmacology. This is because log-linearization skews the distribution of residuals in the experimental error and can lead to poor model fits compared with nonlinear regression. A similar problem occurs in median-effect analysis. Even more importantly, most response curves do not closely fit to idealized mass-action models. Poor model fits in drug combination analysis distort the estimates of the response to the individual drugs used in an experiment and, thus, distort the interpretation of drug combination. For instance, in our own work, we have found that complex changes in the slope of the response curve at moderately high concentrations of insulin-like growth factor 1 receptor inhibitors in combination experiments with crizotinib can reverse conclusions based on shorter dose ranges—such that a synergistic combination (3) erroneously appears to be inhibitory.

Both Scatchard and median-effect analysis date from a time before nonlinear regression was widely accessible. There is now no reason why the median-effect method should not go the same way as Scatchard analysis, and nonlinear regression be used to fit response models, rather than poorly fitting idealizations. The advantages of this approach are several: First, nonlinear regression allows greater flexibility in fitting more appropriate curves to data, which, second, yield more realistic response curves and, third, improved validity of conclusions. Finally, nonlinear regression can also solve an outstanding problem in median-effect analysis, the robust treatment of experimental error (4), a crucial element in any research project in this era of concern over the reproducibility of preclinical research (5).

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Department of Pharmacology and Toxicology, Otago School of Medical Sciences, University of Otago, Dunedin, New Zealand.

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Corresponding Author: John C. Ashton, University of Otago, Frederick Street, Dunedin 9016, New Zealand. Phone: 64-3-479-3040; Fax: 64-3-479-9140; Email: john.ashton@otago.ac.nz

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