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REVIEW PAPER

Frequently asked questions in drug combinations and the mass-action law-based answers

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Summary Drug combinations have been widely used in the treatment of the most dreadful diseases, such as cancer and AIDS. In the search for synergistic combinations for therapy, numerous articles have been published during the past century. However, the term "synergy" has at least 20 different definitions in literature but none supports others. The confusion on synergy claims has far reaching consequences in biomedical research, drug discovery and development, regulation, and medical care of patients. This article reviews the current status and enlists the frequently occurred pit-falls, misconceptions and common errors in drug combination studies. The questions and issues are contemplated to be answered and clarified with the physico-chemical algorithms of the mass-action law, specifically with the unified theory of the median-effect equation and its combination index theorem for drug combinations. The derived theory, algorithm and its computer simulation lead to a quantitative indexed bioinformatics, and econo-green bio-research using small number of data points.

Contents

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1. Introduction

Ever since the earliest days of recorded human history, drug combinations have been used in treating diseases and reducing suffering. The traditional Chinese medicine (TCM) is a typical example. Today, the combination approach is still the most widely used therapy in treating the most dreadful diseases such as cancer and AIDS. For over a century, medical scientists have been attempting to develop the way to assess quantitatively the maximum synergy in drug combination studies. However, this effort is marred by the long standing confusion and controversies in this field as manifested by over 20 definitions for synergy and differences in its determination. Some used the statistical approach; others used empirical or arbitrary modeling without scientific foundation or actually derived equations. This author has persistently used the algorithms derived from the mass-action law for a quantitative determination or simulation of synergism and antagonism.

A comprehensive article on the theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies based on the mass-action law has been published in Pharmacological Reviews [1]. In the same line of research, an article by Chou and Talalay [2] in 1984, introduced the concept of the combination index (CI) and the isobologram algorithm, as well as their software for computerized simulation. Both have received a tremendous response and the current application of this theory and method in broad biomedical disciplines is evident from the citation metrics (www.researcherid.com/rid/B-4111-2009). It is interesting to note that this article only received one citation, and five citations during the first two years, and it took over a quarter of a century to reach the current citation metrics and its broad applications.

The slow recognition and acceptance of this theory (and method) apparently have several reasons. Firstly, during the course of the century-old scholastic discussion of drug combinations, there are about 20 different definitions for synergy or synergism, but none supports the others [3]. The resulting detrimental effect to the biomedical endeavors by these confusions is enormous and the impact is immeasurable. For decades, the biomedical scientific communities as well as the governmental agencies, such as the FDA, United States Patent and Trademark Office (USPTO), as well as the NIH, the Environmental protection agency (EPA) or the DOA have no clear definition or consensus in dealing with "synergy claims" [4—8]. This is a serious matter since "synergy claims" have both academic and legal dimensions. Secondly, the drug combination theoretical studies have been dominated by statistical approaches which lack derivation of equations describing biological behavior [3,9—17]. As a consequence, there are algorithms or methods for drug combination analysis based on the statistical approach which lead to controversial results [4—6].

Thirdly, the development of the general theory of the median-effect equation by Chou [18] and its combination index theorem by Chou and Talalay [2,19] using the physicochemical principle have employed an unique approach. This approach using a system analysis that merges the mass-action law with mathematical induction and deduction [1,20,21] does not seem to have a precedence in biomedical sciences [22—29]. Thus, the resulting method for quantitative dose—effect analysis is, although at last, widely used by many biomedical researchers but many scientists still find the theory, especially the mathematical parts, not easy to understand. Therefore, the author finds that it is essential to have further explanation and clarifications.

The three and half decades of this author's theoretical work on the dose—effect principle of the mass-action law is summarized in Table 1, which is categorized into dose and effect; mass-action law plot and parameters, derived equations and algorithms, and indices and diagnostic plots. The abbreviations, definitions, and practical significance are also listed in Table 1.

The system analysis of biomedical systems with mathematical induction and deduction constitutes the main thrust in the present theoretical work. Its magnificent power can be illustrated by a simple example, *e.g.*, the right or wrong of