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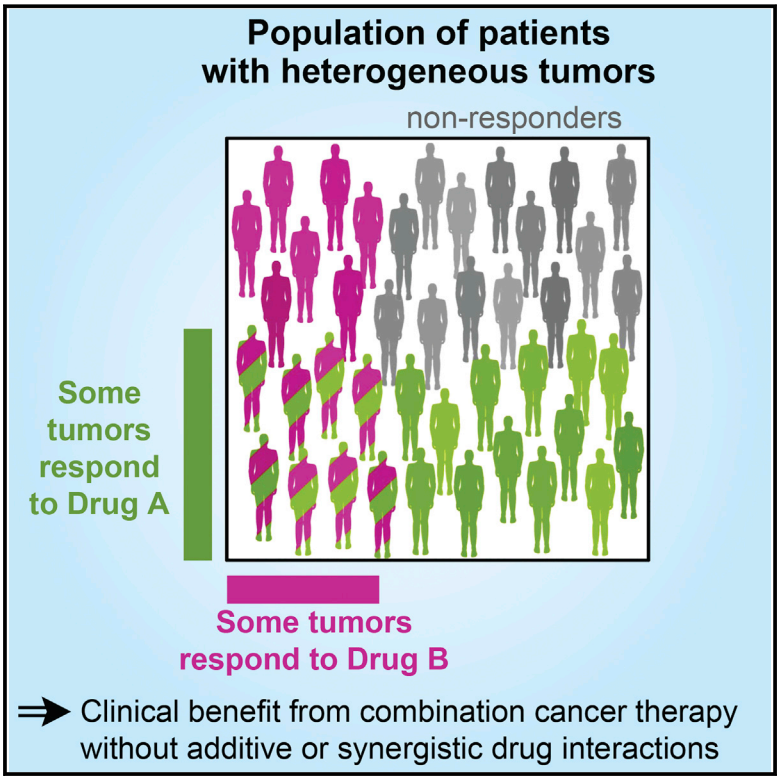
Combination Cancer Therapy Can Confer Benefit via Patient-to-Patient Variability without Drug Additivity or Synergy

Graphical Abstract



Highlights

- Anti-cancer drugs have variable efficacy within patient populations
- Drug combinations give each patient more chances that one drug could be effective
- Clinical efficacy of many combinations is accurately predicted without drug synergy
- Optimizing drug independence represents a new way to design cancer treatments

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In Brief

Patient-to-patient variability in response to single drugs is sufficient to explain the efficacy of a large number of combination cancer therapies without pharmacologically additive or synergistic effect in individual patients.

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SUMMARY

Combination cancer therapies aim to improve the probability and magnitude of therapeutic responses and reduce the likelihood of acquired resistance in an individual patient. However, drugs are tested in clinical trials on genetically diverse patient populations. We show here that patient-to-patient variability and independent drug action are sufficient to explain the superiority of many FDA-approved drug combinations in the absence of drug synergy or additivity. This is also true for combinations tested in patient-derived tumor xenografts. In a combination exhibiting independent drug action, each patient benefits solely from the drug to which his or her tumor is most sensitive, with no added benefit from other drugs. Even when drug combinations exhibit additivity or synergy in pre-clinical models, patient-to-patient variability and low cross-resistance make independent action the dominant mechanism in clinical populations. This insight represents a different way to interpret trial data and a different way to design combination therapies.

INTRODUCTION

The genetic and phenotypic heterogeneity of human cancers poses a substantial obstacle to effective therapy. Heterogeneity in drug response from one cell to the next within a single tumor (within-tumor heterogeneity) contributes to disease progression and drug resistance in each patient. Heterogeneity among patients (between-tumor heterogeneity) makes the effectiveness of therapy difficult to predict, even for patients whose tumors carry the best-available response biomarkers. Overcoming within-tumor heterogeneity was an early rationale for combination cancer therapy: Law (1952) and Frei et al. (1965) argued that cancer cells resistant to one drug might be killed by a second, different drug (and vice versa). Early clinical tests of sequential and combination regimens demonstrated that this logic was also applicable to between-tumor heterogeneity: patients whose cancers did not respond to one drug had a chance of responding to a second, different drug (Frei et al., 1961; Frei et al., 1965; Freireich et al., 1963).

In pharmacological terms, drugs in such a combination exhibit "independent action" whereby the response of an individual patient to two (or more) drugs equals the response to the more effective drug alone with no additional benefit from the less effective drug (with benefit measured by tumor shrinkage or duration of progression-free survival [PFS]). Independent drug action assumes no pharmacological interaction (neither additivity nor synergy) and is equivalent to Gaddum's 1940 definition of non-interaction (STAR Methods; Gaddum, 1940). Since then, clinical and pre-clinical studies have confirmed that any single drug may be active in a subset of tumors (Brugarolas et al., 2003; Pritchard et al., 2013), supporting the idea that individual tumors can be more sensitive to one drug in a combination than others (reflecting their sensitivity to the drugs given individually).

Many targeted therapies are currently combined based on molecular reasoning about the functions of targets (Kummar et al., 2010) or evidence of additive or synergistic effects in cell line and animal models. Clinical trials based on molecular reasoning have been successful: for example, co-inhibition of BRAF and MEK in the treatment of BRAF-mutant melanoma (Long et al., 2014). Unfortunately, the concept of drug independence and its distinction from additivity or synergy has been lost over time; a drug combination that is clinically superior (e.g., on a Kaplan-Meier plot) is generally called additive or synergistic even in the absence of a quantitative test of pharmacological interaction (such as Loewe Additivity or Bliss independence, which are applicable to cell culture experiments, but not clinical trials) (Eder et al., 2010). Distinguishing between drug interaction (additivity or synergy) and drug independence is important because the two are profoundly different at a mechanistic level; in the former case, benefit is conferred at the level of individual patients due to drug interaction within tumor cells, and in the latter case, benefit is conferred only at the level of patient populations due to variability in drug responses. The distinction influences the interpretation of clinical trial data, the choice between sequential and simultaneous treatment, and the design of new drug combinations.

In this paper, we attempt to distinguish between drug interaction and independence in three complementary ways: (1) by re-analyzing human clinical trial data in which single and combination therapies are compared, (2) by mining a database