Introduction

In many cancer settings, it is evident that combination drug therapies show increased efficacy compared to monotherapies. However, it is infeasible to experimentally evaluate the vast number of possible drug combinations when designing new therapies. To overcome this problem, many computational methods have been developed to estimate combination drug efficacy prior to experimental testing using existing pre-clinical datasets. These methods have focused on identifying optimized drug therapies and scaffolds, but they have very limited potential to be translated to independent pre-clinical or to clinical drug discovery.

Recent evidence has suggested that independent drug action, where the effect of a drug combination is equal to the sum of the single doses of each drug in the combination, with no synergy or additivity, may explain the effectiveness of many clinical drug combinations.2 In light of these findings, we developed IDACombo, a method which estimates drug combination efficacy based on independent drug action using the GSDC and CTRPv2 monotherapy cancer cell line screen datasets.

Using resources from the Minnesota Supercomputing Institute (MSI), we have validated our method against measured drug combination efficacies from cancer cell line screens and against published clinical trial results for cancer drug combinations. We have also generated prospective predictions of efficacy for thousands of drug combinations to aid researchers in identifying new candidates for clinical development.

Purpose of this work

Our work seeks to address two challenges in the field of cancer drug combination development:

**Challenge 1:** It is infeasible to experimentally test all possible drug combinations.

*Example: Pre-clinical testing with 100 drugs in 1000 cell lines*

- Monotherapy: 100 drugs × 1000 cell lines = 100,000 experiments
- 2 Drug Combos: 100 drugs × 1000 cell lines = 4,950,000 experiments
- 3 Drug Combos: 100 drugs × 1000 cell lines = 167,000,000 experiments

**Challenge 2:** Even with pre-clinical testing, most oncology clinical trials do not currently lead to FDA approval

- 15% success rate
- 10% overall approval

**Hypothesis**

We hypothesized that it is possible to create a computational method capable of using monotherapy cancer cell line screens to predict the clinical efficacy of unlabeled drug combinations.

How the IDACombo algorithm works

We designed IDACombo to work on the principle of independent drug action (IDA), predicting that the efficacy of a drug combination in a given cell line or patient will be equal to the effect of the single best drug in that combination. Importantly, IDACombo predictions are concentration-dependent, which allows us to predict combination efficacy specifically when each drug is used at its clinically relevant concentration. Furthermore, predictions represent an average response across populations of cells/tissues/patients, which mirrors the way treatment efficacies are measured in clinical trials.

**In vitro validation of IDACombo**

We utilized three high-throughput cancer cell line drug combination screens to validate whether or not IDACombo’s predicted drug combination efficacies match measured drug combination efficacies. For each screen, IDACombo was used to predict drug combination efficacies using the monotherapy data from the screen, and then measured drug combination efficacies were compared to predicted drug combination efficacies also available in each screen (Figure 2).

**Clinical validation of IDACombo**

IDACombo was used to predict drug combination efficacies for thousands of 2-drug combinations consisting of pairs of clinically advanced drugs for which monotherapy data with high confidence was available. These predictions are plotted in a heatmap in Figure 6. The clear clustering in this heatmap indicates the same mechanism of action is not predicted to combine well together via IDA.

**Prospective analyses with IDACombo**

We utilized CTRPv2, ALMANAC, and GDSC datasets to validate whether IDACombo’s predicted drug combination efficacies match clinical trial outcomes. We computed predicted drug combination efficacies on the basis of monotherapy drug response curves to ~800,000 combinations.

**Results**

- Predicted drug combination efficacies were generally below 10% viability between predicted and observed values.
- Notably, these predictions show clear clustering at least in part due to drug mechanism of action. Note: Only drugs with at least one comboscore squares represent missing values. Notably, these predictions show clear clustering at least in part due to drug mechanism of action.

**Conclusions**

These results demonstrate that IDACombo can be used with monotherapy cell line screening data to accurately predict drug combination efficacy both in vitro and in previously untreated patients. This provides a framework for translating monotherapy cell line data into clinically meaningful predictions of drug combination efficacy. Critically, while it is currently infeasible to experimentally test the vast number of possible cancer drug combinations, the algorithmic simulations can be used to computationally predict the efficacies of hundreds of millions of drug combinations in a matter of weeks. This enables driven drug combination selection and could significantly speed up the rate of novel cancer drug combination discovery.

**Acknowledgements**

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*References*

1. C. H. Wong, A Landscape of Pharmacogenomic Interactions in Cancer. Density or in EGFR WT lung cancer. A)

2. S. O’Neil et al., 2016


5. N. H. et al., 2016

6. C. H. et al. Clinical trial outcomes for cancer drug combinations can be predicted using cancer cell line monotherapy screening experiments (Figure 3A). In part due to drug mechanism of action. Note: Only drugs with at least one comboscore squares represent missing values. Notably, these predictions show clear clustering at least in part due to drug mechanism of action. Note: Only drugs with at least one comboscore squares represent missing values. Notably, these predictions show clear clustering at least in part due to drug mechanism of action.