CALIFORNIA STATE SCIENCE FAIR
2014 PROJECT SUMMARY

Name(s)

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Project Number

S1709

Project Title

Development of a Novel Computer-Aided Framework for the Discovery of Synergistic Chemotherapy Combinations

Abstract

Objectives/Goals

Drug discovery requires approximately 13 years of research and $1 billion to introduce a new treatment for patients. Combination therapy is promising, but current trial-and-error drug screening methods are expensive, time consuming, and often identify combinations too toxic for clinical use. Therefore, our goal was to create a novel interdisciplinary approach that rationally guides and accelerates the discovery of safe, synergistic drug pairs.

Methods/Materials

We analyzed 1.6 billion gene expression values from the Cancer Genome Project to construct molecular signatures predictive of resistance and sensitivity to eight common chemotherapy agents. We then computationally screened the Connectivity Map dataset (7,000 genomic profiles) to discover secondary drugs that synergize by knocking down resistance genes and increasing expression of sensitivity genes. In parallel, we used gene set enrichment analysis (GSEA) to elucidate synergy mechanisms. We also devised an innovative machine learning methodology, training neural networks to predict synergy through assessment of a drug combination's molecular and chemical properties. Finally, predictions were validated with LDH cell viability assays conducted on MCF-7 human and 4T1.2 mouse breast cancer cells.

Results

After computationally screening 10,563 potential anti-cancer drug combinations, we identified 40 as synergistic. Rigorous in vitro validation confirmed our top five predictions. Although individual administration of doxorubicin (10 uM) and adiphenine (120 uM) killed only 40% and 5% of cancer cells respectively, simultaneous dual therapy yielded 79% inhibition. Moreover, prior exposure to NS-398 nearly doubled the inhibition level of mitomycin C from 36% to 67%. Additionally, GSEA and pathway analysis revealed highly enriched gene sets that explain possible synergy mechanisms.

Conclusions/Discussion

Through integration of biological experimentation with bioinformatics, statistical, and machine learning analyses, we discovered five synergistic drug pairs, three of which are novel. Additionally, our neural network predicted synergy with an accuracy rate of 87%, offering an 18% to 27% improvement over existing prediction models. On average, our discovered dual therapies are also two to four times more synergistic than current combinations researched, allowing for enhanced efficacy, prevention of drug resistance, and significant toxicity reductions.

Summary Statement

We developed a novel computational framework with rigorous in vitro validation to accelerate the drug discovery process of synergistic chemotherapy combinations that enhance efficacy, prevent drug resistance, and reduce toxicity.

Help Received

Used lab equipment at City of Hope under the supervision of Dr. Draganov and Dr. Lee; received mentoring from Dr. Beck (Harvard Medical School); Mr. Spenner provided feedback and sponsored our project.