Rational Discovery and Optimization of Synergistic Chemotherapy Combinations: A Novel Framework Integrating Gene Perturbation Analysis and Machine Learning Algorithms

Wang, Steven (School: Clongowes Wood College SJ)
Jin, Andrew (School: Clongowes Wood College SJ)

Although the failure of single-targeted chemotherapy agents is inevitable, recent studies demonstrate that combinatorial dual therapy can effectively treat most cancers. However, two major obstacles hinder current multi-component drug design efforts: trial-and-error screening methods are too expensive and time-consuming to be practical, and the majority of identified combinations are too toxic for clinical application. In this study, we created a novel interdisciplinary approach integrating gene expression perturbation models, artificial neural networks (ANN), and in vitro experimentation to rationally guide and accelerate the discovery of synergistic drug pairs. After analyzing more than 1.6 billion gene expression values, evaluating 7,000 drug-associated perturbation profiles, and computationally screening 10,563 potential combinations, we discovered and experimentally validated four dual therapies (three of which are novel) that synergize by knocking down resistance-associated genes and activating sensitivity-associated genes. The doxorubicin-adiphenine combination exhibited especially potent synergy, almost doubling the effect of doxorubicin while keeping toxicity constant. Furthermore, we created an ANN (86.7 percent classification accuracy, 100 percent sensitivity, and 85.2 percent specificity), utilizing molecular and chemical characteristics to accurately predict a second type of drug combinations that synergizes through complementary pathway mechanisms. Since synergistic dual therapies offer increased anti-proliferative effects, reduced toxicity, and prevention of drug resistance, our interdisciplinary framework is a valuable tool for future combinatorial treatment design efforts.

Awards Won:

Third Award of $1,000