SELECTIVE TARGETING OF CTNBB1-, KRAS- OR MYC-DRIVEN CELL GROWTH BY COMBINATIONS OF EXISTING DRUGS

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The aim of combination drug treatment in cancer therapy is to improve response rate and to decrease the probability of the development of drug resistance. Preferably, drug combinations are synergistic rather than additive, and, ideally, drug combinations work synergistically only in cancer cells and not in non-malignant cells. We have developed a workflow to identify such targeted synergies, and applied this approach to selectively inhibit the proliferation of cell lines with mutations in genes that are difficult to modulate with small molecules. The approach is based on curve shift analysis, which we demonstrate is a more robust method of determining synergy than combination matrix screening with Bliss-scoring. We show that the MEK inhibitor trametinib is more synergistic in combination with the BRAF inhibitor dabrafenib than with vemurafenib, another BRAF inhibitor. In addition, we show that the combination of MEK and BRAF inhibitors is synergistic in BRAF-mutant melanoma cells, and additive or antagonistic in, respectively, BRAF-wild type melanoma cells and non-malignant fibroblasts. This combination exemplifies that synergistic action of drugs can depend on cancer genotype.

Next, we used curve shift analysis to identify new drug combinations that specifically inhibit cancer cell proliferation driven by difficult-to-drug cancer genes. Combination studies were performed with compounds that as single agents showed preference for inhibition of cancer cells with mutations in either the CTNBB1 gene (coding for β-catenin), KRAS, or cancer cells expressing increased copy numbers of MYC. We demonstrate that the Wnt-pathway inhibitor ICG-001 and trametinib acted synergistically in CTNBB1-mutant cell lines. The ERBB2 inhibitor TAK-165 was synergistic with trametinib in KRAS-mutant cell lines. The EGFR/ERBB2 inhibitor neratinib acted synergistically with the spindle poison docetaxel and with the Aurora kinase inhibitor GSK-1070916 in cell lines with MYC amplification.

Our approach can therefore efficiently discover novel drug combinations that selectively target cancer genes.

Reference
1. Uitdehaag et al. (2014) PLOS ONE 9(3) e92146