Combinatorial Drug Screening Identifies Ewing Sarcoma-specific Sensitivities

Improvements in survival for Ewing sarcoma pediatric and adolescent patients have been modest over the past 20 years. Combinations of anticancer agents endure as an option to overcome resistance to single treatments caused by compensatory pathways. Moreover, combinations are thought to lessen any associated adverse side effects through reduced dosing, which is particularly important in childhood tumors. Using a parallel phenotypic combinatorial screening approach of cells derived from three pediatric tumor types, we identified Ewing sarcoma-specific interactions of a diverse set of targeted agents including approved drugs. We were able to retrieve highly synergistic drug combinations specific for Ewing sarcoma and identified signaling processes important for Ewing sarcoma cell proliferation determined by EWS-FLI1. We generated a molecular target profile of PKC412, a multikinase inhibitor with strong synergistic propensity in Ewing sarcoma, revealing its targets in critical Ewing sarcoma signaling routes. Using a multilevel experimental approach including quantitative phosphoproteomics, we analyzed the molecular rationale behind the disease-specific synergistic effect of simultaneous application of PKC412 and IGF1R inhibitors. The mechanism of the drug synergy between these inhibitors is different from the sum of the mechanisms of the single agents. The combination effectively inhibited pathway crosstalk and averted feedback loop repression, in EWS-FLI1-dependent manner. Mol Cancer Ther; 16(1); 88-101. ©2016 AACR.