Synergy Screen of NIH Oncological Drug Set VII in Combination with Aurora Kinase B Inhibitor to Enhance Chemotherapeutic Sensitivity

Tandar, Clara (School: West High School)

Small-cell lung cancer (SCLC) is a highly aggressive form of lung cancer. Despite available chemotherapeutics, resistance develops rapidly, accounting for a 6%, 5-year survival rate. Strategies that involve inhibiting Aurora Kinase B (AURKB), a key enzyme in mitosis, have been shown to create vulnerability in SCLC mouse models. To explore the therapeutic potential of this vulnerability, the synergistic effects of Barasertib, an AURKB inhibitor, was tested in combination with 96 approved drugs from NIH Oncological Drug Set VII to elucidate drug combinations exhibiting synergistic cytotoxicity. The primary drug screen was conducted in vitro to determine the most effective combination of drugs using a CTG cell viability assay. From this, cell viability and a linear synergy score was used to select 12 drugs for further investigation in a secondary screen. The secondary screen data was analyzed using ZIP, Bliss, and HSA synergy models to identify the most promising synergistic drug pairs. Everolimus, temsirolimus, and AZD8055 in combination with Barasertib showed the greatest synergistic cytotoxicity among all SCLC cell lines. All three agents are inhibitors of mTOR, a key protein kinase that regulates cell growth, proliferation, and protein synthesis, suggesting a novel approach in SCLC drug therapy. This study is the first to suggest a synergistic effect between mTOR and AURKB inhibitors in increasing chemotherapeutic sensitivity in SCLC.

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