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Inhibitors of histone deacetylase and MCL-1 synergistically reduce proliferation in malignant melanoma

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Melanoma is a skin cancer that arises in melanocytes; it is the fifth most common cancer in the United States with approximately 100,000 new cases per year. Current treatments for malignant melanoma are surgical excision, radiation therapy and systemic therapy; however, the five-year survival rate for patients with stage IV is 29.8%. There is an urgent unmet clinical need to investigate novel treatments for these patients. Panobinostat is an orally available histone deacetylase inhibitor used in several hematologic malignancies, but it was ineffective as a single agent against melanoma in Phase 1. To address the insufficiency of options for melanoma patients, we treated a panel of cultured melanoma cell lines with panobinostat and the novel preclinical MCL-1 inhibitor AZD5991. We hypothesized the addition of AZD5991 (currently in phase 3) would enhance the antiproliferative effect of panobinostat *in vitro*. MTT and ATP-based proliferation assays demonstrated a significant reduction in proliferation when treated with either panobinostat or AZD5991. Isobologram analysis revealed that much lower concentrations of each drug was required to increase caspase 3/7 activity, induce a panel of Growth and DNA Damage (GADD) gene transcripts, and reduce proliferation when the drugs were added in combination. These *in vitro* studies revealed that panobinostat and AZD5991 synergistically inhibit melanoma growth. Increased caspase activation and the accumulation of GADD transcripts suggests apoptosis is a key feature of the antiproliferative mechanism. Ongoing studies are focused to further characterize panobinostat/AZD5991- induced cell death and to validate our cell culture observations in patient-derived xenograft models.