

Present-day cancer researchers are seeking more precise therapy options for cancer patients which can deliver the most potent effect to tumors, while protecting the surrounding healthy tissues. Our lab studied how tumors respond to combinations of chemotherapy drugs (specifically, histone deacetylase inhibitors or HDACi's) and protons, a type of charged particle ionizing radiation used in radiotherapy. HDACi's prevent histone deacetylase enzymes from compacting nuclear DNA, thus maintaining DNA in a more "open" configuration. We were interested in whether the HDACi 4-(dimethylamino)-*N*-[7-(hydroxyamino)-7-oxoheptyl] benzamide (M344) would increase the radiosensitivity of irradiated cells, making them more susceptible to DNA damage through the induction of lethal DNA double strand breaks (DSBs). We used neonatal human fibroblasts (NFF28) as our cell model. Cells were pre-treated with the HDACi SAHA/Vorinostat - a current FDA-approved chemotherapeutic drug and established radiosensitizer - or the experimental HDACi M344. This treatment was followed by irradiation with 200 MeV protons at the NASA Space Radiation Laboratory with doses between 0–400 cGy. The vehicle control (DMSO-treated) and HDACi-treated cells showed a biphasic dose response with a higher slope at low doses (0–50 cGy), indicating low dose hypersensitivity, followed by a reduced slope at higher doses (100–400cGy). Cells treated with SAHA showed significantly increased levels of DNA DSBs and radiosensitization, however, M344 dose responses were similar to our vehicle control cells with almost no radiosensitizing effect on normal cells, regardless of dosage. These results demonstrated that M344 may be an attractive chemotherapeutic adjuvant for proton radiotherapy by sparing normal tissues.