

Identifying Novel MPNST Therapies using a DUSP Inhibitor in a New Patient Derived Xenograft Mouse Model

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INTRODUCTION: Neurofibromatosis Type 1 (NF1) affects 1:3500 people and is characterized by multiple benign tumors within peripheral nerves. NF1 occurs because of mutation or loss of the NF1 tumor-suppressor gene through either inheritance or sporadic mutation, resulting in constitutively active RAS-GTP and over activation of the MAP-Kinase pathway. While most neurofibromas remain benign, approximately 10% of NF1 patients develop malignant peripheral nerve sheath tumors (MPNSTs), often within a neurofibroma. MPNST are highly aggressive soft tissue sarcomas with a 20% five-year survival rate.

HYPOTHESIS: After ERK is phosphorylated by MEK, levels of dual specificity phosphatases (DUSP) increase, and act as negative regulators to dephosphorylate pERK. DUSPs may help cells with high levels of RAS-GTP signaling, including MPNST, to adapt to high levels of growth signals that would normally be toxic. We hypothesized that inhibiting DUSPs would be selectively toxic to cells from NF1-driven tumors.

METHODS: We tested the DUSP inhibitor BCI, alone or in combination with small molecule compounds targeting survival pathways such as BCL-XL, ROS generation or epigenetic modulation. Drugs were tested on WT, *NF1*^{-/-} Schwann cells and MPNST cell lines, and assessed for cell survival after 3 days of treatment using the MTS assay. Combination testing was performed both concurrently and sequentially with BCI. We also tested BCI in a patient derived xenograft (PDX). PDX MPNST tumors were transplanted subcutaneously in mice and measured every 3-4 days. Mice were administered 10 or 25 mg/kg BCI or vehicle for 21 days by IP injections 5X/wk, or until tumors reached 10% body weight.

RESULTS: BCI diminished survival of NF1-deleted cells and MPNST cell lines. Bivalent bromodomain inhibitors had additive effects in MPNST cell lines. Treatment of PDX MPNST tumor-bearing mice with the DUSP inhibitor BCI resulted in acute hyperactive MAPK activation and reduced tumor volume.

CONCLUSIONS: BCI effectively inhibits MPNST cell growth, in vitro and in a PDX model. Cell culture data support potential utility of drug combinations with BCI. The data support further investigation of DUSP inhibition in MPNST.

ACKNOWLEDGEMENTS: AM was supported by NIH grant T35DK060444. This study was supported by a Synodos Grant from the Children's Tumor Foundation to DL and NR, and a grant from CancerFree Kids to AR.