

Lay Summary

Oligodendroglial tumors are the third most common form of brain tumor and are considered, as a group, relatively treatment responsive. BNIP3 is a pro-cell death gene increased in hypoxic (low oxygen) regions of solid tumors. Unfortunately, this increased BNIP3 expression fails to induce cell death within tumors. We have recently discovered that BNIP3 is mutated in glioblastoma multiforme (GBM, WHO grade IV) tumors, the most common primary brain tumor in adults. These mutations block BNIP3's killing activity, thereby promoting tumor cell survival. In this proposal, we are investigating the expression of BNIP3 in hypoxic regions of oligodendrogliomas and determining the presence of BNIP3 mutations in these tumors. Results will be correlated with 1p/19q deletions, overall survival and time-to progression in oligodendroglioma patients. This research may lead to improved understanding of resistance to therapy and towards the development of targeted therapies.

Progress: Co-expression of BNIP3 with markers of low oxygen supports our hypothesis that BNIP3 is expressed in hypoxic regions of oligodendrogliomas. In approximately half of samples examined so far, we have an unexpected finding of BNIP3 expression in the nucleus rather than in the cytoplasm. In our preliminary analysis, almost all of the tumors with nuclear BNIP3 expression do not have BNIP3 mutations. We have performed sequencing of the BNIP3 gene for 45 oligodendroglioma tumors. To date, 5/21 oligodendroglioma and 5/24 anaplastic oligodendroglioma (AO) harbor a BNIP3 mutation. The frequency of BNIP3 mutations in oligodendrogliomas as a group (22%) is similar to that found for PEST mutations in GBM (~17%, Zhang S et al, submitted). In collaboration with Dr. Arie Perry (Washington University, St. Louis MO), we have also completed analysis for chromosome 1p/19q deletions in 49 oligodendroglioma patients. We have also obtained clinical outcomes for these patients, for which follow-up data is available for 48 (98% of cohort).

Future directions: We will complete co-expression studies of BNIP3 with markers of hypoxia in the remaining oligodendroglioma tumor sections along other samples to be obtained (see below). We are generating Kaplan-Meier curves for time-to-progression (TTP) and overall survival (OS) for our oligodendroglioma patient cohort based on the following: (i) W.H.O. grade II or III; (ii) 1p/19q deletion status; (iii) BNIP3 mutation; and (iv) primary expression of BNIP3 in nucleus. Preliminary analysis suggests that we may require an additional 25 to 50 samples to obtain statistical significance. Alternatively, obtaining more long-term follow-up data may obviate the necessity for other samples.

Overall, we have met the major goals of our oligodendroglioma research project during the year of funding from the NBTF.