

5.) Summary written in Layman's terms.

Current therapies for medulloblastoma have increased five year survival rates as high as 80%. Although these results are excellent compared to other primary brain tumors, one in five children with medulloblastoma will die of their disease. Equally important, many survivors have long term disabilities secondary to both the disease and its treatment. As our patients are children, this represents a large burden of prolonged suffering, and missed life opportunities.

Significantly more effective and less toxic therapy is unlikely to come about through improvements in surgery or radiation. Rather, advances will occur by identifying genes or pathways that are altered in medulloblastoma, but not in normal tissues. The first two steps in this process are 1) the identification of appropriate targets, followed by 2) testing them in appropriate model systems.

Current model systems of medulloblastoma are lacking as they do not adequately mirror the human condition. Most medulloblastoma cell lines have extensive artifactual genetic changes secondary to their prolonged time in culture. Most mouse models of medulloblastoma are bred onto the *tp53* knockout background, while only a small percentage of human medulloblastomas have *TP53* mutations. We will create a novel mouse model of medulloblastoma that does not require *tp53* loss, which can also be used to define rational targets for future therapy. For a modest investment, we hope to both identify targets for medulloblastoma treatment, as well as provide a useful model for preclinical testing of medulloblastoma therapeutics.