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Brief Overview of Tobey MacDonald's Laboratory Research project for Swim Across America:

Cancer is the leading cause of death due to disease in children and brain tumors are the leading cause of death due to cancer in children. My laboratory studies the most common malignant brain tumor of childhood, known as *medulloblastoma*. We are specifically interested in preventing the spread or metastasis of this tumor since that is how this tumor kills patients. The very high risk for metastasis is also the reason why children with this disease, even the very young, will receive radiation to their entire brain as prophylactic treatment against further tumor spread. For survivors of this disease, this treatment causes severe and long lasting problems with learning, memory and brain development.

With support from **Swim Across America** (**SAA**), we set out to determine the exact genetic cause(s) that promotes medulloblastoma metastasis so that we could then design new therapies to specifically target the specific genetic change within the tumor to prevent its spread without hurting the normal brain. To accomplish this goal, we first amassed a collection of primary medulloblastoma tumors and their matching metastatic tumors from pediatric patients so that we could interrogate the genetics of each tumor to see exactly how similar or different these tumors really are from one another. Previously, scientists just assumed that a tumor arising in one part of the brain was genetically identical to the tumor found to have spread to other parts of the brain. In other words, "the same tumor is simply moving from point A to point B". From the 1st year of our studies supported by **SAA**, we have discovered that the primary and metastatic tumors within the same individual are indeed genetically different. This in itself is a brand new discovery that has far reaching implications clinically, not only for medulloblastoma, but for all metastatic human cancers. By comparing these differences across a series of patients, we have been able to hone in on 3 distinct genetic changes that we believe are the critical elements allowing for medulloblastoma tumor spread and subsequent growth at a distant site. We have now chosen to focus on our top candidate molecule based on its potential important role in other human cancers such as leukemia, breast, colon, and lung cancer.

We have now begun testing the inhibition of this molecule in our genetically engineered mouse model that spontaneously develops medulloblastoma in a fashion that is identical to that seen in humans. In our pilot study, we treated 10 mice with a drug inhibitor of this molecule 3 times a week for only 2 weeks. To our amazement, 50% of the treated mice appear to be surviving long-term without any evidence of tumor or other noticeable problem or toxicity, while 100% of the untreated mice given a placebo have all died of their disease within 17 weeks of life. We are **very excited** by these results and in our 2nd year of SAA support, we plan to further test the inhibition of this molecule in our model using a drug that is actually currently in human clinical trials. We will investigate varying doses and duration of this drug treatment to see if we can further improve survival without causing toxicity. Finally, to confirm that the specific genetic change is indeed the "master switch" controlling tumor development and spread, we will cross our mouse that develops medulloblastoma with a mouse that is lacking the single candidate molecule to see whether medulloblastomas can no longer develop and/or spread under this condition. If we can confirm our preliminary findings with each of these proposed investigations, then we strongly believe that we have discovered a novel treatment for this disease.