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Dear Lauren's First and Goal Board of Directors:

We would like to update you on our progress since the last letter in December 2010. We have continued to build on our discovery that the tumor-promoting gene BRAF plays an important role in driving the growth of PA/PMA, and have also initiated several other avenues of research. Highlights over the last six months include opening of a clinical trial for pediatric low grade glioma patients, continued expansion of the Pilomyxoid Astrocytoma registry, our publication in *Clinical Cancer Research* describing how "oncogene-induced senescence" can affect growth of pilocytic and pilomyxoids tumors, completion of our initial survey correlating molecular alterations in pediatric low grade gliomas with clinical outcome, and the initiation of several new studies focused on PA/PMA in the optic nerve. Here is a brief summary of these exciting advances made possible by your generous donations:

1) A clinical trial using the BRAF inhibitor Sorafenib in children with low grade gliomas has begun to enroll patients. This trial grew directly out of work initially funded by your support. It is led by Dr. Matthias Karajannis at New York University, however Johns Hopkins will also enroll patients, and our laboratory will assist with pathology review and molecular correlations. It will take a number of years to enroll and follow patients. Hopefully this therapy will be able to slow the growth of aggressive PA/PMA and help children whose tumors cannot be surgically removed. Some of you may have seen recent news articles discussing the FDA approval of a new drug for treating melanoma. These melanoma drugs affect the same pathways which are activated in PA/PMA, and we anticipate that in addition to Sorafenib a number of agents targeting the BRAF pathway will ultimately be tested in children with low grade gliomas.

2) We have discovered a molecular mechanism which might explain why some pilocytic astrocytomas grow slowly, stop growing, or even shrink in the absence of treatment. This process is known as "oncogene induced senescence" and was originally described in skin moles. In the skin, it is known that an activated BRAF oncogene initially promotes growth in melanocytic cells that form moles, but eventually induces "senescence" which leads to growth arrest. Occasionally some cells in the mole can "escape" from senescence and progress to form a melanoma. We found that similar "oncogene-induced senescence" can occur in PA/PMA, and have identified some molecular changes that may allow the tumors to escape from this senescence and keep growing. Importantly, loss of one of these proteins, p16, may represent a new marker of tumors which will grow aggressively, and could potentially be used to more accurately direct therapy. Our paper describing this work was

recently published in a widely read journal (*Clinical Cancer Research* 2011 June, 17:3590-9). In the paper, we acknowledge the support or Lauren's First and Goal Foundation.

3) Our studies of Pilocytic astrocytomas and PMA in the optic nerve and hypothalamus are progressing quickly. These tumors represent an important but understudied subset of pediatric gliomas, in part because access to tissue from such cases can be difficult. In collaboration with researchers at the Armed Forces Institute of Pathology, we generated a "tissue microarray" containing 58 cases, and are using it to determine how similar PA/PMA at this site are to those in other locations in the brain. We have largely completed a wide range of molecular testing on these cases, including studies of chromosomal gains and losses, as well as expression of key proteins, and are beginning to correlate these findings with clinical features. Dr. Fausto Rodriguez, a new faculty member, and Dr. Charles Eberhart will present these initial findings at an ocular oncology meeting this fall.

4) We recently completed a molecular analysis of two types of BRAF genetic alteration in 106 low grade glioma patients. We found that changes activating BRAF were most common in tumors of the cerebellum and the optic pathways. This may help us to more accurately use Sorafenib and other new therapies. Dr. Rodriguez examined whether BRAF alterations were associated with clinical outcome, but did not find any significant association with progression free survival. Dr. Eberhart presented these and other findings from our group in a keynote talk at the 2011 Children's Tumor Foundation Annual Meeting. A paper describing the work was submitted earlier this month and is currently under review. It also acknowledges the support of Lauren's First and Goal Foundation.

5) In March 2011, Dr. Rodriguez published a paper in the journal Acta Neuropathologica describing how a molecular pathway known as PI3K/AKT is associated with aggressive biology in PA/PMA tumors. While these studies were performed before he came to Johns Hopkins, he is now performing additional research in this area as part of our team.

6) The Pilomyxoid Astrocytoma registry directed by Dr. Ken Cohen continues to grow. The registry was initiated with the goal of centralizing information on how these rare tumors behave in order to optimize therapies over time.

Funding Priorities

Your generous financial support has been instrumental in getting us to this point, and we hope you will continue to fund our work as we move forward translating the molecular discoveries we have made into new potential cures. As you have witnessed, the funds you have raised significantly help to advance our work and provide hope for PA/PMA children and their families.

Our main goals over the next two years include:

1) Continuing to develop pilocytic and pilomyxoid cell culture and xenograft models and test drugs such as Sorafenib.

2) Identifying new molecular markers of aggressive PA/PMA, including those associated with "oncogene induced senescence".
3) Continue examining the role of "senescence" in PA/PMA, and determining how to block tumor "escape" from this mechanism.
4) Examining molecular alterations in optic pathway PA/PMA.
5) Testing the role of mTOR/Akt signaling in PA/PMA.
6) Supporting the new Sorafenib clinical trial.
7) Developing new "transgenic" mouse models for pilocytic astrocytoma based on activation of BRAF in the brain. (This project would require at least $150,000 in funding).
8) Supporting Dr. Kenneth Cohen with the pilomyxoid registry.

Thank you once again for your investment and partnership! Your support has been instrumental in initiating a large number of meaningful projects. We are truly grateful.

Best Regards,

Charles Eberhart, M.D., Ph.D., Fausto Rodriguez, M.D. and Peter Burger, M.D.