



June 18, 2010

Dear Supporters of Pilocytic and Pilomyxoid Astrocytoma Research,

We would like to update all of you on our progress since our last letter. We are excited to inform you that the research you supported has helped to form the basis for a clinical trial targeting the molecular alterations present in pilocytic astrocytoma! As described below, we are moving forward with these studies, as well as other areas we hope will lead to more effective, less toxic therapies for PA/PMA and other pediatric low grade gliomas.

- 1) We have continued our collaboration with a team of researchers at New York University (NYU), Drs. Matthias Karajannis, Jeff Allen and David Zagzag, in order to expand the number of piloid tumors with frozen material available for molecular analysis. To date, we have performed BRAF analysis on approximately 130 pediatric low grade tumors, and we hope to publish this work soon.
- 2) Because it is now clear that activation of the BRAF gene plays a key role in most pilocytic astrocytoma, we are increasingly focused on testing Sorafenib and other drugs that inhibit these pathways in order to prepare for trials in children. As we mentioned before, we generated a number of primary pilocytic astrocytoma cultures, and have begun to test the ability of several drugs that inhibit BRAF to slow their growth.
- 3) A clinical trial using the BRAF inhibitor Sorafenib in children with low grade gliomas will open soon. Dr. Karajannis at NYU is organizing the trial, however Johns Hopkins will also enroll patients. The molecular tests you helped to develop through your generous support will play a key role in helping us to structure and interpret the results from this clinical trial.
- 4) Dr. Peter Burger's paper on the pathological features of an expanded series of PMA cases acquired in collaboration with Washington University in St. Louis, Memorial-Sloan Kettering Cancer Center in New York, and the University of California in San Francisco has been favorably reviewed and is under revision.
- 5) We have been examining an exciting genetic mechanism which might explain why some, but not all, pilocytic astrocytoma grow slowly or stop growing. Some even seem to shrink in the absence of treatment. In the skin, it is known that an activated BRAF oncogene initially promotes growth in cells, but eventually induces "senescence" which leads to growth arrest. A number of experiments we have performed over the last year suggest that similar "oncogene-induced senescence" may be occurring in PA/PMA. If we can better understand how this functions, we may be able to force more tumors to stop growing.



Funding Priorities

Your generous financial support has been instrumental in getting us to this point, and we hope you will continue to help 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 have truly helped 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 models and test drugs such as Sorafenib.
- 2) Supporting the new clinical trial.
- 3) Developing new “transgenic” mouse models for pilocytic astrocytoma based on activation of BRAF in the brain. Please be aware that this project would require at least \$150,000 in funding.
- 4) Examining the role of “senescence” in PA/PMA.
- 5) Supporting Dr. Kenneth Cohen with the pilomyxoid registry.

Thank you once again for your investment and partnership! You have truly been instrumental in initiating a large number of meaningful projects.

Best Regards,

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