



**A report on the Pediatric Low-Grade Astrocytoma Program  
Prepared for the Lauren's First and Goal Foundation  
September 29, 2010**

**Thank you**

---

The generous support of the Lauren's First and Goal Foundation continues to enable the PLGA Program to expand its efforts, all of which bring us closer to the singular goal of conquering pediatric low-grade astrocytomas. Over the past year, program leaders Drs. Charles Stiles and Mark Kieran, in collaboration with a global team of leading researchers and clinicians, have greatly advanced their work through conducting a clinical trial to test a potential new therapy, creating a PLGA-specific tissue bank, and identifying new drug-susceptible targets in LGA.

**Progress related to the RAD001 clinical trial**

---

RAD001 is a new oral mTOR inhibitor that has demonstrated excellent inhibition of this pathway at clinically achievable doses. The RAD001 clinical trial has been open for more than a year for children with low-grade gliomas. This drug targets mTOR, a central relay site within the cell that, when activated, results in increased proliferation, cell migration and angiogenesis. We are continuing to accrue patients to this trial to assess the response of children with low-grade gliomas to this drug. At present, eight patients have been recruited among participating medical centers, with three having been recruited at Dana-Farber.

**Progress related to the research objectives of the PLGA Program**

---

**Determining the genetic lesions of low-grade astrocytomas**

This year we published the initial results of OncoMap analysis of brain tumor specimens<sup>1</sup>. This paper is significant because it is the first application of paraffin-friendly assays to discover mutations in archived pediatric cancer specimens. The OncoMap detects one form of activated BRAF, the V600E mutation. We detected this mutation mainly in non-pilocytic astrocytomas. In particular, we found this mutation to be present in nearly 60% of the ganglioglioma subtype of LGA and in 20% of diffuse astrocytomas.

We have also continued to analyze archived glioma samples using the novel Fluorescence in situ Hybridization (FISH) assay we developed to detect a second important activating mutation in BRAF: a duplication in the BRAF gene. We detected BRAF duplication in all pilocytic astrocytomas analyzed, while duplication events were rarely detected in non-pilocytic gliomas. We are in the process of finalizing a publication reporting these results. Taken together, the OncoMap and FISH analyses support a new molecular stratification of pediatric low-grade gliomas based on BRAF mutations that may have immediate clinical impact.

---

<sup>1</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2774511/?tool=pubmed>

### **Personalized medicine for low-grade astrocytomas**

The ability to detect mutations in tumor tissue will allow doctors to use personalized medicine to match treatments targeted to specific mutations with specific patients most likely to benefit. However, mutation-detection assays must be validated and CLIA-certified before they can be used to inform clinical decisions for specific patients so that individual test results can be included as part of the patient's medical record. This year we have accomplished the rigorous validation necessary to earn CLIA-certification for two assays that detect the BRAF V600E and duplication mutations. These test results give neuropathologists new objective, diagnostic tools to distinguish classic pilocytic tumors from other non-pilocytic tumors. The tests also identify patients with the specific BRAF mutation who would likely benefit from drugs that are currently being developed to target activated BRAF.

We now provide the BRAF tests to all children treated at DFCI/CHB who are suffering from LGAs. We are also near completion of a protocol that will allow us to offer BRAF CLIA-certified tests to children who are not patients at DFCI/CHB. Generous support from private funders such as Lauren's First and Goal Foundation will allow us to offer this testing free of charge to patients. We believe that this patient registry will benefit all children who have LGAs because we will pre-identify a pool of patients eligible to participate in future BRAF inhibitor clinical trials. Patients who send tumor tissue for BRAF testing will also have the option of donating tissue remaining after the test for research to identify other, less common, genetic mutations that may cause this disease in tumors with normal BRAF.

### **International outreach for tissue banking**

We are fostering relationships with physicians in major population centers around the world to help us gather tissue samples for discovery of new genetic mutations driving pediatric brain tumors. We continue to receive a wide variety of samples from Cairo, Egypt and Istanbul, Turkey. We are also assembling a sample set enriched for archived tumors with rarer pathologies from domestic institutions, including Chicago's Children's Memorial Hospital, Children's National Medical Center, and Johns Hopkins University School of Medicine.

Dr. Yongji Tian finished his training this fall in the laboratory of PLGA Program neuropathologist Dr. Keith Ligon. Dr. Tian is a Chinese physician-scientist who spent a one-year fellowship developing a less-demanding, technically robust assay for BRAF mutations that is suited for use in emerging countries. He has submitted his results for publication and has returned to his position as a neurosurgeon at Beijing's Tian Tan Hospital armed with the molecular diagnostic tools needed to analyze tumor samples from his patients. We look forward to his continued collaboration with the PLGA Program.

### **Peer-reviewed funding**

We are cautiously optimistic that this year we have successfully parlayed our preliminary data funded through the generous donations of Lauren's First and Goal Foundation and others into a new program project grant from the National Cancer Institute. This \$10 million grant would fund PLGA program investigators in three projects and a tissue pathology core for the next five years. While we won't know for certain that this application will be funded until NCI's FY11 budget is finalized early next year, we are encouraged that our application earned a promising priority score from reviewers.

## **Future goals**

---

In addition to pursuing the BRAF-related and tissue-banking projects mentioned above, we continue to probe the feasibility of blocking Olig2 function in LGAs as a target of therapy. Olig2 is a transcription factor that is expressed in 100% of human astrocytomas irrespective of grade and is required for tumor formation in genetically-defined mouse models of astrocytoma. Targeting a transcription factor such as Olig2 remains a technical challenge, but we feel the potential payoff for patients is worth the effort. We have also begun supporting the work of a postdoctoral fellow training with Dr. Nathalie Agar who is considering the blood-brain barrier and developing ways to detect compounds directly in the brain using sophisticated imaging techniques. We anticipate that this will be an important tool in the preclinical evaluation of future therapies.

## **Conclusion**

---

The favorable reviews and priority score we received for our program project application was one of our proudest achievements of the past year. The preliminary data for the projects in that application simply would not have been possible without the funding provided by Lauren's First and Goal Foundation and other likeminded philanthropists. The successful funding of this NCI application will mark a maturation of our program and will provide a validation of the soundness of our approach. It will not, however, erase our need for your continued support. Your continued support is absolutely critical for us to incubate the next generation of projects designed to impact the treatment of children with LGAs. On behalf of the entire program, and especially the young patients and family members who will ultimately benefit from your investment, thank you so much for all that you do in the fight against PLGA.