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The Brastianos laboratory studies genomic drivers of human brain tumors. A lack of understanding of the molecular drivers of many brain tumors has hampered the development of novel therapies for many brain cancers. Our overarching objective is to characterize molecular drivers of both progression in primary brain tumors and brain metastases, and accelerate the development of novel therapeutic approaches for these diseases. We recently discovered clinically significant genetic drivers in meningiomas, craniopharyngiomas, hemangioblastomas, glioneuronal tumors and brain metastases. We are currently investigating the role of these genomic drivers as potential therapeutic targets in several national NCI-sponsored multi-center clinical trials. Additionally, we are expanding our *in vitro* and *in vivo* investigations to further elucidate the molecular evolution of the metastatic process to the central nervous system.

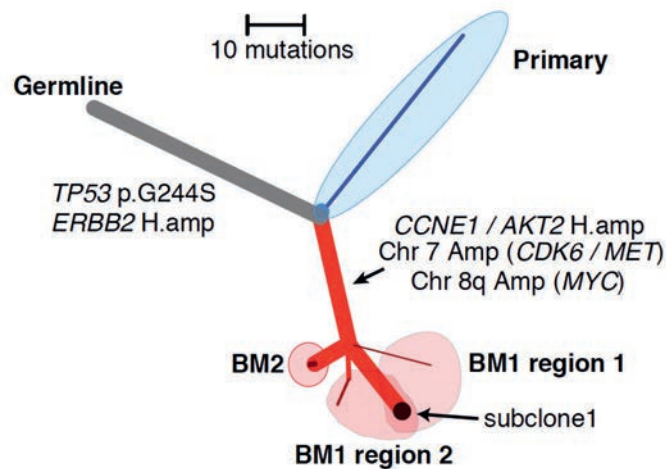
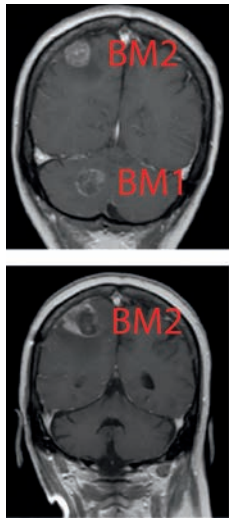
Characterizing Genomic Drivers of Craniopharyngiomas

Craniopharyngiomas are epithelial tumors that arise in the pituitary stalk along the path of the craniopharyngeal duct. There are two main subtypes of craniopharyngiomas, the adamantinomatous form that is more common in children, and the papillary form that predominantly occurs in adults. Craniopharyngiomas can cause profound clinical sequelae both through mass effect at presentation and through morbidity of treatment. No effective treatment besides surgery and radiation is known for craniopharyngiomas, and incomplete knowledge of the molecular mechanisms that drive craniopharyngiomas has limited the development of targeted therapies for this tumor. We recently comprehensively characterized the molecular drivers of craniopharyngiomas. We identified activating mutations in CTNNB1 in nearly all adamantinomatous craniopharyngiomas and recurrent mutations in BRAF (resulting in p.Val600Glu) in nearly all papillary craniopharyngiomas (Brastianos et al. *Nature Genetics* 2014). These findings have

important implications for the diagnosis and treatment of these neoplasms. We recently treated a patient with multiple recurrent papillary craniopharyngioma with a BRAF and MEK inhibitor and achieved an exceptional therapeutic response. We have initiated a national multicenter trial in craniopharyngiomas (Alliance A071601) to investigate the role of targeted therapies in these tumors. Circulating biomarkers and genomic analysis of craniopharyngiomas will be employed to investigate mechanisms of resistance.

Identifying Molecular Drivers of Meningiomas

Meningiomas are the most common primary nervous system tumor with no known effective systemic therapy. Recently, we comprehensively characterized meningiomas. Through whole-genome, whole-exome and targeted sequencing, we have demonstrated that meningiomas harbor recurrent oncogenic clinically actionable mutations in AKT1 (E17K) and SMO (W535L) (Brastianos et al. *Nature Genetics* 2013). Notably, these mutations were present



Representative phylogenetic tree of a primary tumor and 2 anatomically distinct brain metastases. Different regions of the brain metastases shared the same amplifications in *CCNE1*, *AKT2*, *CDK6*, *MET* and *MYC*, which were not present in the primary tumor biopsy.

in therapeutically challenging tumors of the skull base. We also recently identified potential genetics drivers of progression in meningiomas (*BAP1*, *TERT* promoter mutations, *DMD*). Because therapeutic targets for *SMO* and *AKT1* mutations are currently in clinical use in other cancers, we are now conducting a prospective national multicenter Phase 2 study (A071401) of targeted therapy in patients with recurrent or progressive meningiomas harboring clinically actionable mutations, respectively. The trial is activated at more than 400 sites throughout the US. We will be genomically characterizing prospectively collected samples to identify biomarkers of response and mechanisms of resistance.

Central Nervous System Metastasis Program

Brain metastases are a common complication of cancer, with a dismal prognosis. There is a limited understanding of the oncogenic alterations harbored by brain metastases and whether these are shared with their primary tumors or other metastatic sites. The objectives of the Central Nervous System Metastasis

Program are to (1) identify novel therapeutic targets through comprehensive genomic characterization, (2) functionally characterize candidate drivers through in vitro and in vivo models of metastasis, and (3) accelerate the application of our scientific findings to the clinical setting. In collaboration with many national and international institutions, currently we are comprehensively characterizing the genomics of brain metastases to understand the molecular pathways that drive these tumors. We have demonstrated that brain metastases harbor clinically actionable drivers not detected in the primary tumors. We are evaluating the roles of these genetic alterations using various assays of metastasis. Based on this work, we have now initiated a national genomically guided brain metastasis trial (A071701). Our hope is that the findings from our genomic and functional investigations will allow us to develop more rational therapeutic approaches for this disease.

Selected Publications:

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