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Brastianos Laboratory

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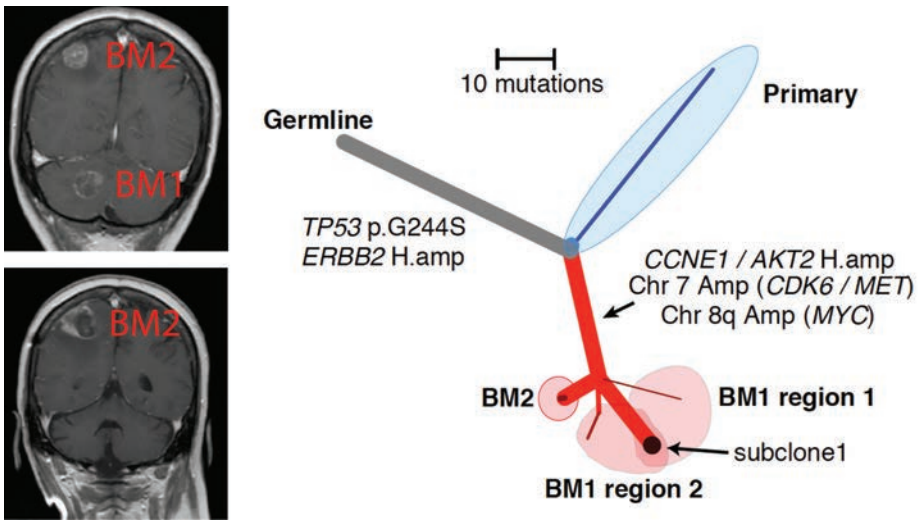
The Brastianos laboratory studies molecular drivers of human brain tumors. A lack of understanding of the molecular drivers of many brain tumors has hampered the development of novel therapies for many brain cancers. Our overarching objective is to characterize the tumor and immune microenvironment in 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 a rare brain tumor that can cause profound clinical sequelae both through mass effect at presentation and through morbidity of treatment. Historically, 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 initiated a national multicenter trial in craniopharyngiomas (Alliance A071601) to investigate the role of targeted therapies in these tumors. In patients with newly diagnosed papillary craniopharyngioma, we showed that all patients who received one or more cycles of vemurafenib/cobimetinib had dramatic responses to therapy (Brastianos et al. *NEJM* 2023)

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 and 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 in therapeutically challenging tumors of the skull base. We also recently identified potential genetics drivers of progression in meningiomas (BAP1, TERT promoter mutations, DMD). Our lab is working on developing better preclinical models of meningioma with the goal of testing new therapeutic targets in this disease. 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 (Brastianos et al. *JCO* 2023).



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.

Central nervous system metastasis center

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 Center are to (1) identify novel therapeutic targets through comprehensive molecular 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. We are comprehensively characterizing the tumor and immune microenvironment of brain metastases to understand how they evolve in the CNS. We have demonstrated that brain metastases harbor clinically actionable drivers not detected in the primary tumors (Brastianos, Carter et al. *Cancer Discovery* 2015). We are evaluating the roles of these genetic alterations using various assays of metastasis (Shih, Nayyar et al. *Nature Genetics* 2020) and inhibiting pathways commonly altered in brain metastases with novel therapies. In addition, using single-cell RNA sequencing, we are characterizing the dynamic changes in immune microenvironment during treatment (Prakadan et al. *Nature Communications* 2021). Based on the work in the lab, 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:

Brastianos PK et al. BRAF-MEK Inhibition in Newly Diagnosed Papillary Craniopharyngiomas. *N Engl J Med*. 2023 Jul 13;389(2):118-126.

Alvarez-Breckenridge C, .. **Brastianos PK****, Carter SL.** Microenvironmental landscape of human melanoma brain metastases in response to immune checkpoint inhibition. *Cancer Immunol Res*. 2022 Jun 15:canimm.CIR-21-0870-E.2021.

Prakadan SM, Alvarez-Breckenridge C.A., Markson SC, … Carter SL**, **Brastianos PK****, Shalek AK**. Genomic and transcriptomic correlates of immunotherapy response within the tumor microenvironment of leptomeningeal metastases. *Nat Commun*. 2021 Oct 12;12(1):5955

Brastianos PK*, Kim AE*, et al. Palbociclib demonstrates intracranial activity in progressive brain metastases harboring cyclin-dependent kinase pathway alterations. *Nature Cancer*. 2021; May;2 (5):498-502.

Shih DJH, Nayyar N,…Carter SL*, **Brastianos PK***. Genomic characterization of human brain metastases identifies drivers of metastatic lung adenocarcinoma. *Nat Genet*. 2020; Apr;52(4):371-377.

Brastianos PK, et al. Single-arm, open-label phase 2 trial of pembrolizumab in patients with leptomeningeal carcinomatosis. *Nat Med*. 2020; Aug;26(8):1280-1284.

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