MAPK-related signatures were downregulated upon MEKi treatment, while pathways related to upstream MAPK activators (including FGFR, NTRK and TGFB pathways) were upregulated, in both proliferating and senescent DKFZ-BT66. Genes regulated by the MAPK pathway and involved in OIS-SASP were identified by analyzing genes differentially regulated between proliferating and senescent DKFZ-BT66, and modulated upon MEKi treatment. Conclusion: This data suggests that MAPKi reverses OIS in senescent PA cells, while inducing the activation of MAPK upstream regulators in proliferating and senescent PA cells, identifying putative co-targets that could help prevent growth rebound upon MAPKi withdrawal. Furthermore, the identification of the MAPK-related OIS-SASP genes provide insight about the regulation of OIS-SASP by the MAPK pathway. Validation of this data with the ongoing phospho-proteomic analysis and in primary samples is needed.

LGG-05. GENERATION OF NOVEL MOUSE MODELS FOR BRAF V600E MUTANT GLIOMAGENESIS TO GAIN MECHANISTIC INSIGHTS INTO TUMOR FORMATION AND PROGRESSION

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Background: The BRAF V600E mutation occurs in ~ twenty percent of histologically diverse pediatric gliomas and is the second most common mutation in pediatric low-grade gliomas (LGG). BRAF V600E expression in LGG with balanced CDKN2A is associated with a higher rate for progression than for BRAF V600E wildtype tumors, and despite adjuvant therapy, consisting of resection, radiation and chemotherapy. Progression invariably occurs in BRAF V600E mutant CDKN2A deleted gliomas, marking a high-risk group. Here, we aim to overcome the lack BRAF V600E mutant glioma models that allow for studies of stem and progenitor cells and the immune system ability to understand progression. Methods: We develop novel immunocompetent, stem and progenitor cell-based mouse models for BRAF mutant gliomas, including genetically engineered mouse models (GEMMs), orthotopic glioma models derived from gliomas in GEMMs as well as in vitro models of those tumors. BRAF mutant mouse brains and cells were analyzed by immunofluorescence staining, flow cytometry, mass cytometry and RNA sequencing. Results: Ongoing model development studies indicate that BRAF V600E mutant gliomas in murine brain exhibit very similar neuroanatomical preferences to human gliomas. The BRAF V600E mutation exacerbates the heterogenous cell cycling pattern of normal neural stem and progenitors and expands a symmetrically dividing progenitor population. Cellular plasticity rather than cellular lineage hierarchy drives the generation of a therapy resistant stem cell pool. Transcriptomic analyses of neuroglial stem cells with induced BRAF V600E expression provide insights into mechanisms for neoplastic transformation and progression. Conclusion: Analyses of two independent BRAF V600E mutant mouse models provide novel insights into the role for tumor intrinsic factors, such as plasticity and stemness, and the tumor microenvironment in progression.

LGG-06. COMPREHENSIVE GENOMIC CHARACTERIZATION AND INTEGRATED CLINICAL ANALYSIS OF LOW-GRADE GLIOMAS IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1

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Background: Low-grade gliomas (LGGs) arising in children with neurofibromatosis type 1 (NF1) are usually not biopsied. To identify secondary genetic alterations or molecular features that may contribute to pathogenesis and correlate with clinical behavior, we initiated a comprehensive molecular and clinical analysis of pediatric NF1-LGGs. Methods: NF1-LGGs were analysed by whole-genome sequencing (31), targeted gene panel sequencing (9), RNAseq transcriptomal profiling (33) and genome-wide DNA methylation analysis (67). Clinical annotation was available for 48 subjects. Results: Most LGGs harbored bi-allelic *NF1* inactivation as the sole genetic abnormality, but 11% had additional alterations (*FGFR1* mutation, n=3; *PIK3CA* mutation, n=2; homozygous 9p21 deletion, n=2; *MYB:QKI* fusion, n=1; *SETD2* mutation, n=1; *EGFR* amplification, n=1). *FGFR1* mutation conferred additional growth advantage in multiple complementary murine *Nf1* models. 88% of NF1-LGGs resembled sporadic pilocytic astrocytoma (PA) by methylation, higher than that based on histology. Non-PA methylation patterns included low-grade glial/glioneuronal tumors, rosette-forming glioneuronal tumors, MYB/MYBL1-altered glioma, and high-grade astrocytoma with piloid features (2 tumors histologically diagnosed as LGG). In total, 18% of samples were classified as non-PA and/or harbored an additional non-*NF1* mutation. Non-PA methylation class tumors were more likely to harbor an additional non-*NF1* mutation (p=0.005). 7.7% of optic pathway hypothalamic gliomas (OPHGs) had other mutations or were not classified by methylation as PA, compared with 20.6% of NF1-LGGs arising elsewhere. There was no difference based on age for the presence of an additional non-*NF1* mutation or non-PA methylation class. Conclusions: Given the overall low occurrence of non-*NF1* mutations or non-PA methylation class tumors in this series, routine clinical biopsy of typically-appearing NF1-LGG may not be indicated, particularly for children with OPHG. Biopsy should be considered for non-OPHG tumors refractory to conventional treatment. As additional agents are developed and treatment strategies evolve, the rationale for biopsy of NF1-LGG may become stronger.

LGG-07. IS BRAF ALTERATION OR A HISTOLOGIC 'QUALIFIER' A PREDICTOR OF OUTCOME IN PEDIATRIC PILOCYTIC ASTROCYTOMA?

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Introduction: Pediatric pilocytic astrocytomas (PA) are the most common pediatric central nervous system tumor. Surgical resection is the primary treatment for PA with five-year survival rates up to 95%. Despite a favorable prognosis, our understanding about the prognostic value of histopathological findings, such as histopathologic qualifier* or *BRAF* alterations is evolving. Methods: Patients treated for a WHO grade 1 PA at Washington University in St. Louis/St. Louis Children's Hospital were analyzed for clinical details, including pathology diagnosis (*histopathologic qualifier refers to designations in the diagnosis such as "WHO Grade I pilocytic astrocytoma with increased proliferative index"). BRAF alterations include gene fusions and point mutations. Results: 224 patients were analyzed (51% female, mean age 9.6 years). Tumors were located in the cerebellum/fourth ventricle (50%), optic pathway/hypothalamus (15%), brainstem (12%), and cerebral cortex (11%). BRAF alterations were identified in 55/77 patients (71.4%) and additional histopathologic qualifiers were present in 27/220 patients (12.3%). 196 patients (87.5%) underwent surgical treatment and 22 (9.8%) had biopsy alone. 45 patients (22%) displayed tumor progression or recurrence after resection. The presence of a histopathologic 'qualifier' in the topline or *BRAF* alteration was not associated with tumor progression or recurrence (p=0.36, p=0.77). Ki-67 proliferative indices were not predictive of progression or recurrence (p=0.94), including when controlling for extent of resection and adjuvant therapy. *BRAF* alterations, specifically *KIAA1549* fusions, were associated with cerebellar/fourth ventricular tumor location (p<0.001) and younger patient age (p=0.03). Extent of resection was the only predictor of outcome identified in this study; patients with gross total resection had significantly lower rates of progression and recurrence (p<0.0001). Conclusion: *BRAF* alterations and histopathologic qualifiers were not associated with tumor progression or recurrence in pediatric PA, although *BRAF* fusions were more common in tumors located in the cerebellum/fourth ventricle and in younger patients.

LGG-08. TREATMENT OUTCOMES AND TOLERABILITY OF TRAMETINIB IN PROGRESSIVE CIRCUMSCRIBED LOW-GRADE GLIOMAS

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