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During formation of plexiform neurofibroma (PN), a complex tumor microenvironment (TME) develops, with recruitment of other cell types being critical for growth and progression. Approximately 10% of PN can undergo transformation into malignant peripheral nerve sheath tumors (MPNST) which is a substantial cause of mortality in older teenagers and young adults. We sought to apply single cell transcriptomic analysis to PN and MPNST to provide a clearer understanding of the complex TME and how this contributes to transformation and disease progression. Due to the cohesive cellularity of PN, single-cell RNA-sequencing is difficult and may result in a loss of detection of critical cellular subpopulations. Single-nuclei RNA-sequencing (snRNA-seq) is an alternative approach that can be applied to fibrous and bulk frozen tissues, such as NF1-associated PN. Our initial snRNA-seq analysis of PN indicates that PN have a TME comprised of a variety of cellular subpopulations, with the predominant fraction being fibroblast-like cells. snRNA-seq analysis of MPNST also shows high cellular heterogeneity, including distinct fibroblast-like subpopulations distinct from PN fibroblast clusters, increased proliferating populations and antigen presenting cells. MPNST cluster separately from PN, suggesting an evolutionary shift in tumor biology. We are currently validating our findings using Visium spatial transcriptomic profiling, allowing us to apply TME architectural context to the PN and MPNST subpopulations identified by snRNA-seq. These techniques provide a deeper understanding of the complex cellular heterogeneity of human PN and MPNST that has not previously been used to describe the TME of these tumors. The mechanisms of tumorigenesis and malignancy described can provide targets for novel therapies ultimately benefitting patients with these devastating tumors of childhood and early adulthood.

NFB-20. PRE-CLINICAL MODELS OF MISMATCH REPAIR DEFICIENT GLIOMAS

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INTRODUCTION: Lynch syndrome and Biallelic Mismatch Repair Deficiency (BMMRD) are hereditary tumor predisposition syndromes, resulting from one or two (respectively) germline alterations in DNA mis-match repair (MMR) genes. Currently, there are few treatments for mismatch repair deficient (MMRD) gliomas, in part due to a lack of suitable pre-clinical models for drug testing. The purpose of this study is to develop and characterize pre-clinical models of MMRD gliomas. METHODS: Primary cells were developed from patients diagnosed with MMRD gliomas and characterized through immunofluorescence staining (IF) for different cell type markers, western blot assays, and genome and transcriptome analysis. Murine models were generated through intracranial injection of mCherry-luciferase reporter expressing primary cells, and mice were monitored for evidence of engraftment and clinical symptoms. Drug screening on the cell lines was performed to identify potential therapeutic agents for in-vivo testing. RESULTS: The cell lines had similar characteristics as the primary glial tumors by IF staining and genome and transcriptome analysis. Adult NSG mice developed tumors around three weeks after intercranial transplantation of the tumor cells. These tumors closely resembled the primary patient tumors on histology. Preliminary drug testing on the cell lines showed efficacy of ONC201, ONC206, and RM006 against MMRD gliomas with IC50 concentrations of 1.77 µM, 185 nM, and 699 nM respectively. CONCLUSION: The generation of pre-clinical MMRD glioma models can lead to improved understanding of tumorigenesis, allowing for the identification of targetable molecules, and supporting novel treatment development.

NFB-21. NEUROFIBROMATOSIS TYPE I IN THE SETTING OF NEURO-ONCOLOGY

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Neurofibromatosis Type I (NF1) is an autosomal dominant genetic syndrome that is inherited or sporadic. Neuro-Oncology nurses are experienced in the multidisciplinary care of NF1 patients due to an increased incidence of brain tumors and the treatment of plexiform neurofibromas with Mek inhibitors. However, these children are also at higher risk of rare solid tumors, specifically malignant peripheral nerve sheath tumors (MPNST). Most brain tumors in NF1 have a good prognosis. Conversely, MPNST has an extremely poor prognosis. While patients with MPNST are often cared for by solid tumor care teams, the identification and diagnosis of the tumors occur under the care of the neuro-oncology care team. Complex care coordination for patients with NF1 and cancer is required. Specifically, patients with NF1 are more sensitive to chemotherapy, have a higher incidence of radiation-induced secondary tumors, and need monitoring for NF1 related health impacts. Nurses and nurse practitioners with expertise in neuro-oncology, NF1, and solid tumors must collaborate to provide comprehensive care. Teaching tools and clinical strategies have been developed to maintain patients' continuity with the primary oncology team while gaining the support of subspecialists. The genetic basis, inheritance pattern, and characteristics of Neurofibromatosis Type I will be discussed as well as rare oncologic diagnoses that are more prevalent in children/young adults with NF1. The multidisciplinary approach to the care of the patient with NF1 and a rare cancer diagnoses at a tertiary care center as well as the optimization of care of patients with NF1 and other underlying syndromes and rare cancers will be reviewed. Increased knowledge of NF1 and the associated health impacts and risk of cancers will improve the care of all patients with NF1.

NFB-22. NEUROFIBROMATOSIS THERAPEUTICS PROGRAM: DEVELOPMENT OF A PROGRAM

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Neurofibromatosis (NF) therapeutics is a vital field in the care of children with NF. Recent developments in the treatment of plexiform neurofibromas (PN) have increased the numbers of patients seen for therapy. The Neurofibromatosis Therapeutics Program (NTP) provides high quality care to patients receiving therapy for brain tumors and PNs, as well as tumors related to NF2. The program at Children's Hospital Colorado (CHCO) includes a physician, nurse practitioner, and nurse care coordinator. The team collaborates with other disciplines in the care of the NF patient with plexiform neurofibromas and/or CNS tumors. As the program grew, key players were identified in each subspecialty and educated about the NTP. We have ongoing regular communication with a large number of subspecialists regarding protocols, clinical care pathways, and mutual patients. In addition, an extensive tissue collection study of plexiform neurofibromas and brain tumors enhances NTPs devotion to both clinical and lab research. Weekly clinical care meetings ensure continuity in the care of the nearly 140 patients with NF1 and NF2 under our program. Monthly strategy and vision meetings focus on grant applications, education of primary care providers and subspecialists in our large catchment area, development of new clinical pathways, treatment roadmaps, and growth of our program. Over the last two years of being a formalized program, we have increased research on the epigenetics of plexiform neurofibromas, opened a Phase 2 clinical trial for a Mek inhibitor, and increased our patient volume. The Covid pandemic has increased our ability to manage treatment side effects virtually through telehealth and online patient portals. Future goals of the NTP include completion of a program website, quarterly patient and provider newsletters, educational offerings, collaboration with other centers on Mek inhibitor side effects, adolescent and young adult education on tumor risk, and transition to adult care.

NFB-23. EXTENT OF TUMOR BUT NOT LOCATION MAY BE PREDICTIVE OF LONGITUDINAL DISEASE SEVERITY IN CHILDREN WITH NF1-ASSOCIATED GLIOMAS REQUIRING TREATMENT

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BACKGROUND: Children with Neurofibromatosis Type 1 (NF1) are at risk for developing gliomas in multiple locations, particularly the optic pathway and brainstem. The goal of this study is to determine if glioma location in NF1 impacts tumor progression and accumulation of neurological deficits over time. METHODS: Retrospective chart review of 98 pediatric patients with NF1-associated gliomas between 1999-2021 at St. Louis Children's Hospital. Patients who had never received treatment were excluded from analysis. Each glioma was categorized into one of four locations: posterior fossa (PF, n=12, 21%), supratentorial midline (SM, n=33, 57%) supratentorial cortical (SC, n=4, 7%), brainstem (BS, n=9, 15%). Patients with gliomas in different locations had each tumor counted separately (58 total gliomas analyzed). RESULTS: No SC tumors progressed. Time to first progression was comparable across the other 3 locations, and there was no meaningful different in neurologic deficits over time by tumor location. The majority of patients who demonstrated three or more clinical or radiographic progressions had tumors in the SM region. Within the SM tumor group, each tumor was further characterized as a deep extensive glioma (DEG; 36%) or an optic pathway glioma without deep extension (nonDEG; 64%). DEG had a slightly higher number of neurological deficits at baseline (DEG 2.08, nonDEG 1.19), fewer patients with no neurologic deficits (8.3% DEG vs 28.6% nonDEG) and a higher proportion of patients with a first progression event (41% DEG vs 24% nonDEG). However, DEG and nonDEG had similar risk of subsequent progressions after the initial event. CONCLUSION: Among children with NF1 who required glioma treatment, location was not a significant predictor of multiple progression or neurologic morbidity over time. Within the SM location, DEGs represent a newly characterized group that exhibit potentially higher rates of progression and neurological deficits. Multi-institutional analysis is needed to confirm these findings.