collected tumor tissue from pediatric ACP was cut into volumes of approximately 3 mm^3 and rested over a semi-permeable insert placed in the wells of a 6-well plate. Specimens were cultured in (1) Control media, media containing (2) Tocilizumab, (3) Trametinib, and (4) combination of Tocilizumab and Trametinib, for 24 and 96 hours. Specimens were harvested for paraffin embedding, protein and gene expression assays. Supernatants were collected to assay secreted components. Paraffin embedded specimens were sectioned and stained for H&E, Pan-CK, Beta-Catenin, cleaved Caspase-3, Ki-67, and Phospho-ERK. RESULTS: H&E staining revealed characteristic histologic features of ACP with epithelial cells with palisading nuclei, wet keratin and ghost cells. Tumor sections were markedly positive for epithelial cell markers, Pan-CK and Beta-Catenin. Ki-67 and cleaved Caspase-3 were restricted to a small fraction of cells, indicating low index of proliferation and apoptosis under the culture conditions. The response to drug treatments shall be determined using gene expression assays and evaluation of the secreted components. CONCLUSION: The organotypic chunk culture technique appears to maintain the viability and integrity of ACP tumors for several days and may serve as an appropriate model for pre-clinical studies to develop targeted therapeutics for pediatric ACP.

MODL-25. REPLICATION REPAIR DEFICIENT MOUSE MODELS PROVIDE INSIGHT ON HYPERMUTANT BRAIN TUMOURS, MECHANISMS OF IMMUNE EVASION, AND COMBINATORIAL IMMUNOTHERAPY

Melissa Galati[1], Li Li[1], Sumedha Sudhaman[1], Tatiana Lipman[1], Lucie Stengs[1], Dana Elshaer[1], Taylor Bridge[1], Dar'ya Semenova[1], Melissa Edwards[1], Karl Hodel[2], Victoria J. Forster[1], Nuno M. Nunes[1], Alberto Martin[3], Eric Bouffet[4], Zachary Pursell[2], Cynthia Hawkins[1], and Uri Tabori[1,4]; [1]The Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, ON, Canada, [2]Department of Biochemistry, Tulane University, New Orleans, LA, USA, [3]Department of Immunology, University of Toronto, Toronto, ON, Canada, [4]Division of Hematology and Oncology, The Hospital for Sick Children, Toronto, ON, Canada

Replication repair deficiency (RRD) is the leading cause of hypermutant brain tumours in children. RRD is caused by defects in one of four mismatch repair (MMR) genes and mutations in *POLE* or *POLD1*. Such tumours are resistant to common therapeutic agents and animal models are needed to study RRD in vivo and test novel therapies like immune checkpoint inhibitors (ICIs). To model RRD brain tumours specifically, we engineered a *Pole* mutant mouse model harbouring the S459F mutation (*PoleS459F*). We combined *PoleS459F* mice with conditional *Msh2* knockout (*Msh2LoxP*) and *Nestin-cre* mice. All *Nestin-cre+Msh2LoxP/LoxPPoleS459F/+* mice rapidly succumbed to posterior fossa brain tumours between 8.6 and 12.4 weeks. Importantly, tumours exhibited hallmark "ultrahypermutation" (~350 mutations/Mb) and the corresponding signatures characteristic of human combined MMR and *POLE*-proofreading glioblastoma. Interestingly, *Nestin-cre+Msh2LoxP/LoxPPoleS459F/S459F* mice failed to establish normal cerebella, suggesting such mutational loads may not support normal brain development. Furthermore, *OLIG2-cre+Msh2LoxP/LoxPPoleS459F/+* mice failed to develop tumors. Tumors transplanted into syngeneic vs immunocompromised animals egrafted well orthotopically in the mouse hindbrain but significantly less efficiently when engrafted subcutaneously. Furthermore, immunocompromised and subcutaneous tumors revealed striking differences in mutational burden and clonal architecture, suggestive of nonautonomous immunoediting. Finally, anti-PD1 was sufficient to treat subcutaneously engrafted tumors in immunocompetent animals. This first mouse model of immunocompetent, hypermutant brain tumors can be used to uncover unique characteristics of RRD tumour evolution and allow for immune based therapeutic preclinical testing. Experiments to assess combinational ICIs and other therapeutic interventions in orthotopically transplanted tumors will also be presented.

MODL-26. CHILDREN'S BRAIN TUMOR NETWORK: ACCELERATING RESEARCH THROUGH COLLABORATION AND OPEN-SCIENCE

Jena Lilly[1], Jennifer Mason[1], Elizabeth Appert[1], Allison Heath[1], Yuankun Zhu[1], Bo Zhang[1], Mateusz Koptyra[1], Mariarita Santi[1], Ian Pollack[2], Stewart Goldman[3], Sarah Leary[4], Anna Buccoliero[5], Mirko Scagnet[5], David Haussler[6], Derek Hanson[7], Jiangguo Zhang[8], Weiqing Wan[9], Chunde Li[9], Ron Firestein[10], Jason Cain[10], Joanna Phillips[11], Nalin Gupta[11], Sabine Mueller[11], Gerald Grant[12], Michelle Monje-Deisseroth[12], Sonia Partap[12], Jeffrey Greenfield[13], Brian Rood[14], Javad Nazarian[14], Eric Raabe[15], Eric Jackson[15], Stacie Stapleton[16], Robert Lober[17], David Kram[18], Phillip Storm[1], Rishi Lulla[19], Michael Prados[11], Adam Resnick[1], and Angela Waanders[3]; [1]Children's Hospital of Philadelphia, Philadelphia, PA, USA, [2]UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA, [3]Ann and Robert H Lurie Children's Hospital, Chicago, IL, USA, [4]Seattle Children's Hospital, Seattle, WA, USA, [5]Meyer Children's Hospital, Florence, Italy, [6]Genomic Institute, UCSC, Santa Cruz, CA, USA, [7]Joseph M, Sanzari Children's Hospital at Hackensack University Medical, Hackensack, NJ, USA, [8]Genebank, Beijing Genomics Institute, Shenzhen, China, [9]Beijing Tiantan Hospital Neurosurgery Center, Beijing, China, [10]Hudson Institute of Medical Research, Melbourne, Australia, [11]University of California San Francisco Benioff Children's Hospital, San Francisco, CA, USA, [12]Stanford University/Lucile Packard Children's Hospital, Palo Alto, CA, USA, [13]Pediatric Brain and Spine Center, Weill Cornell Medicine, New York, NY, USA, [14]Children's National Health System, Washington DC, USA, [15]Johns Hopkins, Baltimore, MD, USA, [16]Johns Hopkins All Children's Hospital, St Petersburg, FL, USA, [17]Dayton Children's Hospital, Dayton, OH, USA, [18]Wake Forest Baptist Health- Brenner Children's Hospital, Winston-Salem, NC, USA, [19]Hasbro Children's Hospital, Providence, RI, USA

The Children's Brain Tumor Network (formerly known as Children's Brain Tumor Consortium- CBTTC) is a global organization pioneering a model of open-science medical research to improve treatment and discover cures. Started in 2011, our objective was to utilize a regulatory, agreement, and governance architecture to remove existing research barriers that slowed down the pace of research and collaboration. Our network now includes 17 institutions working together to empower research. As of December 2019, over 3,600 subjects have been enrolled resulting in collection of over 45,000 specimens. Clinical data collection is longitudinal and includes medical history, diagnosis, treatment, pathology slides and reports, radiology imaging and reports, and outcome data. The tissue is collected flash-frozen, in freezing media, and fresh for the generation of pre-clinical models including cell lines. Blood is collected from the subject, with blood or saliva collected from the parents for germline comparison. Additionally, the Children's Brain Tumor Network- Pediatric Brain Tumor Atlas has generated 952 WGS and RNAseq, 221 proteomics, with annotated clinical data. All of this data, both generated raw and processed data, has been made available broadly to the scientific community via cloud-based platforms, including the Gabriella Miller Kids First Data Resource Portal, Cavatica, and PedCbioportal. As of January 2020, we have 45 approved biospecimen requests and 80 genomic/molecular data requests. In summary, the Children's Brain Tumor Network's goal is to accelerate the pace of discovery by providing resources and expanding the network of scientists working towards a cure.

MODL-27. MEK INHIBITION WITH TRAMETINIB SLOWS PROGRESSION OF MEDULLOBLASTOMA AND ATYPICAL TERATOID RHABDOID TUMOR IN ORTHOTOPIC XENOGRAFT MURINE MODEL

Sujata Mushrif[1], Long Hung[2], Sakunthala Muthugounder[2], and Shahab Asgharzadeh[2]; [1]SRCC Children's Hospital-Managed by Narayana Health, Mumbai, Maharashtra, India, [2]Children's Hospital of Los Angeles, Los Angeles, CA, USA

BACKGROUND: Combination of surgery, chemotherapy, autologous transplantation, irradiation constitutes treatment of CNS embryonal-cell tumors (Medulloblastoma-MBL, atypical teratoid rhabdoid tumor-AT/RT). Targeted agents to improve survival and decrease side effects are necessary. We hypothesize that inhibiting MAPK pathway in MBL and AT/RT may be beneficial. METHODS: IHC(pERK) was performed on clinical tumors. *Trametinib*(MEK inhibitor) was tested on MBL(UW228, D283, DAOY); AT/RT(CHLA06, BT12) cell-lines. Luminescent cell-viability assay was done(72 hrs) and with crystal violet assay(10 days). Orthotopic, xenografts of MBL and AT/RT were made in *NOD-Scid gamma* mice. Mice were given *Trametinib* daily by gavage for 6 weeks(0.6mg/kg b.w). Western blot was performed on protein from cell lines and tumor xenografts incubated with *Trametinib*. H&E staining was done on murine tumors. RESULTS: AT/RT(48%) and MBL(57%); Anaplastic(50%), Desmoplastic(40%), Classic(38%); Group 4(66%), Group 3(20%), SHH(55%), WNT(0%) showed presence of pERK(clinical samples). In-vitro, *Trametinib* completely abrogated the phosphorylation of ERK at 125nM in AT/RT and 50nM in MBL. The IC50 after 10 days exposure was 10nM for AT/RT and 35nM for MBL. *Trametinib* treated mice showed delay in tumor growth and significant survival advantage in both AT/RT (p=0.00336) and MBL (p=0.0069). Murine tumors showed decreased proliferation (H&E). CONCLUSION: *Trametinib* decreased cell proliferation, increased survival in our murine model in both MBL and AT/RT. Pre-clinical results indicate benefits in subgroups of AT/RT and MBL with active MAPK pathway.

MODL-28. IMMUNE PRIMING WITH INTERFERON-Γ COMBINED WITH EPIGENETIC MODULATION IN PEDIATRIC BRAIN TUMORS

Erin Crotty[1,2], Shelli Morris[2], Ken Brasel[2], Emily Girard[2], Alyssa Noll[2,3], Andrew Mhyre[2], and James Olson[1,2]; [1]Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Washington, Seattle