MODL-27. AN ORGANOTYPIC BRAIN SLICE CULTURE PLATFORM AS A NOVEL PRE-CLINICAL MODEL FOR DIFFUSE INTRINSIC PONTINE GLIOMA AND DIFFUSE MIDLINE GLIOMA

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High-grade pediatric brain tumors (PBTs) such as diffuse intrinsic pontine glioma (DIPG) and diffuse midline glioma (DMG) are devastating diseases with a median survival of just 11 months. Little progress has been made in identifying effective treatments due to the lack of effective pre-clinical models to accurately assess drug sensitivity. Historically, models of DIPG and DMG have been limited due to the low availability of surgical biopsies and small patient populations. Existing in vitro models are often unable to recapitulate growth and migration patterns seen in patients, while in vivo work is costly, time intensive, and many biopsies fail to establish in mice. We have developed an ex vivo organotypic brain slice culture (OBSC) platform to model DIPG and DMG. Through our partnership with the Ian's Friends Foundation and Children's Healthcare of Atlanta Biobank, we have seeded, grown, and treated several low-passage patient-derived PBT lines such as DIPG and DMG. Additionally, we can assess treatment response to a variety of agents used in clinical patient care. Viability assays revealed differences in the sensitivity of cell lines to individual agents, indicating that OBSCs have the potential to capture minute differences in efficacy between cell lines and drugs. When we assessed combination treatments, we found low doses of radiation with low doses of temozolomide were synergistic, but using higher doses of radiation was antagonistic, suggesting the OBSC platform has the potential to guide dosing strategies to maximize therapeutic synergy. Overall, these results suggest that OBSC PBT models have the potential to effectively model PBTs, including DIPG and DMG, to accelerate preclinical evaluation of therapeutics and guide drug development towards more effective treatment strategies.

MODL-28. PATIENT-DERIVED, THREE-DIMENSIONAL ORGANOID PLATFORM FOR PEDIATRIC BRAIN TUMOR MODELING

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Brain tumors have become the leading cause of cancer-related death in children. An important hurdle to scientific and clinical progress in the field has been the limited availability of preclinical tumor models. Historically, few pediatric brain tumor cell lines have been established and these often poorly recapitulate the phenotypes of the original tumors. In recent years, the Children's Brain Tumor Network (CBTN) has accelerated the development of patient-derived cell lines and xenografts, offering these resources to the community through open-source access. While these models are extremely valuable, their development process can be lengthy and result in clonally selected lines which presents a challenge for studying complex tumor biology. To address the need for three-dimensional tissue culture, our group in conjunction with CBTN, utilized organoid culture from fresh tissue specimens obtained directly from surgical resection of various pediatric brain tumor histologies. This resulted in the development and banking of over 30 organoid models, which included ependymoma, high-grade glioma, medulloblastoma, atypical teratoid-rhabdoid tumor, diffuse midline glioma, and low-grade glioma diagnoses. Tissue was processed within an hour post extraction and cultured with universal media composition for each diagnosis. Organoid growth was observed within 2-3 weeks of initiation and continued for up to three months before banking. Banked organoids established growth upon return to culture. Phenotypic analysis revealed organoid cell composition that represented clinical histology. Importantly, organoids returned to culture post-banking demonstrated similar cell composition to those in the original culture, indicating their utility for subsequent preclinical testing. Here we provide a simple and efficient workflow for the generation and characterization of three-dimensional tumor organoids generated from fresh surgical pediatric brain tumor tissue. The platform has the potential to accelerate investigations into tumor biology and empower a diverse array of translational studies for the pediatric brain tumor field.

MODL-29. MOLECULAR LANDSCAPE OF A COMPREHENSIVE PANEL OF PEDIATRIC BRAIN CANCER PATIENT-DERIVED ORTHOTOPIC XENOGRAFT (PDOX) MODELS INFORM UNIQUE TARGETS FOR DRUG RESPONSIVENESS

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Brain tumor is a leading cause of cancer related death in children. In addition to replicating histopathology, animal models faithfully replicating genetic/epigenetic abnormalities, molecular subtypes and broad inter-tumoral heterogeneities are needed. Through direct implantation of patient surgical or autopsied tumor tissues into matching locations in the brains of SCID mice, we developed a panel of 150 PDOX mouse models. Here, we report the analysis of 74 of the 150 PDOX models, 45 matching patient tissues and 60 non-tumorigenic samples to a well-annotated reference cohort of 2,801 methylation profiles of primary brain tumors. Our data showed that the lack of tumorigenicity was neither correlated with molecular subtypes nor predicted by low cell viabilities of the patient samples. Methylation profiling identified PDOX models representing nearly a full spectrum of molecular subtypes of pediatric brain tumors including GBM, medulloblastoma, ependymoma and ATRT. Direct comparison with the original patient tumors confirmed the replication of molecular subtypes. ONCOplot [FB1] analysis of PDOX models derived from matching pairs of primary and recurrent tumors (n=8) revealed close clustering with the patient tumors. Investigation of metastatic properties was performed in 13 MB models by harvesting and sub-transplanting matching PDOX primary tumors in the cerebella and metastatic tumors in the spinal cords. To confirm the potential and power of PDOX models in preclinical drug testing, we applied fractionated radiation (2 Gy/day x 5 days) and optimized multi-agent combinatory chemotherapies in MB models of the four major subgroups. High-throughput combination drug screening with ~ 8,000 drugs in PDOX-derived GBM cell lines and primary cultures of MB PDOX cells identified a library of ~ 3,500 drugs that were active in pediatric brain tumors. In summary, this study provides detailed information on molecular subclassification of a uniquely large cohort of PDOX models to serve as essential tools for brain tumor research.

MODL-30. CHILDREN'S BRAIN TUMOR NETWORK PRECLINICAL TUMOR MODELS DEVELOPMENT AND SHARING PLATFORM: COLLABORATIVE MODEL EMPOWERING PEDIATRIC BRAIN TUMOR DISCOVERY AND GLOBAL RESEARCH.

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Pediatric brain tumor preclinical field suffered for years from the lack of in vitro and in vivo models. With the explosion of novel therapy approaches for solid and brain tumors, including the immunotherapies it is essential to maximize the access to preclinical models for preclinical specificity, efficacy as well and safety. One of the many ways the Children's Brain Tumor Network (CBTN) accelerates the pediatric brain tumor research and discovery is through support of the tumor model development program. This program focuses on the generation, characterization, and distribution of diverse models to investigators worldwide provided free of charge. Here we present the resource platform with over 150 cell lines, organoids and patient derived xenografts (PDX) developed and/or propagated at D3b at CHOP on behalf of CBTN. This platform maximizes the tumor tissue use to generate a combination of cell line, organoids and/or xenograft models grown in animals. In recent years, consortium supported over 40 requests for cells lines used in basic biology and translational studies internationally. Current efforts focusing also on supporting large-scale data generation and testing through its collaborative model (Childhood Cancer Model Atlas, Procan, National Center for Advancing Translational Sciences) to maximize the molecular information available for each tumor model essential in preclinical screenings. The generated and returned to consortia data are bound with the deidentified patient clinical information and genomic data and freely available through Kid's First Data, Cavatica and PedcBio portals. These efforts have already attracted interest from pharma stakeholders previously not observed in pediatric brain environment. This open-source repository model is an example of a unique research partnership supported by patients and their families and built with one mission to bring fast change to kids suffering from brain tumors.