gets. Of the 40 patients with results, 23 (58%) patients went on to receive genomics guided therapy. Limited availability of tissue has accounted for 6 (13%) patients' lack of results. Many guided therapy options are oral medications, which positively impact patient's quality of life. The learner will increase their knowledge of how molecular guided therapy is now innovatively being used to treat children with cancer, and the challenges involved.

TBIO-26. NON-CANONICAL OPEN READING FRAMES ENCODE FUNCTIONAL PROTEINS ESSENTIAL FOR CANCER CELL SURVIVAL

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The brain is the foremost non-gonadal tissue for expression of non-coding RNAs of unclear function. Yet, whether such transcripts are truly non-coding or rather the source of non-canonical protein translation is unknown. Here, we used functional genomic screens to establish the cellular bioactivity of non-canonical proteins located in putative non-coding RNAs or untranslated regions of protein-coding genes. We experimentally interrogated 553 open reading frames (ORFs) identified by ribosome profiling for three major phenotypes: 257 (46%) demonstrated protein translation when ectopically expressed in HEK293T cells, 401 (73%) induced gene expression changes following ectopic expression across 4 cancer cell types, and 57 (10%) induced a viability defect when the endogenous ORF was knocked out using CRISPR/Cas9 in 8 human cancer cell lines. CRISPR tiling and start codon mutagenesis indicated that the biological impact of these non-canonical ORFs required their translation as opposed to RNA-mediated effects. We functionally characterized one of these ORFs, *G029442*—renamed *GREP1* (Glycine-Rich Extracellular Protein-1)—as a cancer-implicated gene with high expression in multiple cancer types, such as gliomas. GREP1 knockout in >200 cancer cell lines reduced cell viability in multiple cancer types, including glioblastoma, in a cell-autonomous manner and produced cell cycle arrest via single-cell RNA sequencing. Analysis of the secretome of GREP1-expressing cells showed increased abundance of the oncogenic cytokine GDF15, and GDF15 supplementation mitigated the growth inhibitory effect of *GREP1* knock-out. Taken together, these experiments suggest that the non-canonical ORFeome is surprisingly rich in biologically active proteins and potential cancer therapeutic targets deserving of further study.

TBIO-27. RASOPATHIES AND BRAIN TUMOROGENESIS: ARE SOS1 MUTATIONS ARE CONCERNED?

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Germ line gain-of-function mutations in several members of the RAS/MAPK pathway, including PTPN11 are associated with signalopathies named Rasopathies and known as Noonan syndrome and closely related conditions. Patients harboring Rasopathies are at increased risk of myeloproliferative diseases and solid tumors, such as neuroblastoma. Mutations of SOS1, the gene encoding a guanine nucleotide exchange factor for Ras, represent the second most frequent genetic defect in Rasopathies. However, SOS1 mutations are rare in human malignancies and patients with germline SOS1 mutations may not be at increased risk of developing cancer. Here, we report a SOS1 variant found to segregate in a Tunisian pedigree with many members affected by brain tumors as well as epileptic disorder. During our genetic counselling for congenital heart diseases, a 9-year-old female born at Sfax from a consanguineous couple and having pulmonic valvular stenosis, has been investigated at the molecular level. Screening of mutations in the entire coding sequence of PTPN11, Braf and SOS1, was conducted using HRM analysis and bidirectional sequencing. Heterozygous single nucleotide substitution of SOS1 gene: c.1655 G>A was confirmed. This mutation affected the PH-REM linker domain with substitution of residue Arg552 to Lys: p.Arg552Lys. This mutation accounts for one-third of all mutations reported in SOS1 during Rasopathies. Although no other molecular exploration was done, family history revealed other affected children by neurodevelopmental and epileptic conditions as well as recurrent brain malignancies in the paternal family. Two aunts developed blindness and then died subsequently to tumor progression.

VIRAL/GENE THERAPY AND OTHER NOVEL THERAPIES

THER-01. AWAKING THE IMMUNE SYSTEM WITH AN IMMUNO-ONCOLYTIC VIRUS AS A THERAPEUTIC STRATEGY FOR DIPGS

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Diffuse intrinsic pontine glioma (DIPG) is an aggressive brain tumour, being the leading cause of paediatric death caused by cancer. Despite all the advances made regarding effective therapies, the survival is dismal. Our lab has engineered the oncolytic virus Delta-24-ACT armed with the costimulatory ligand 41BBL in order to increase the antitumoral effect of the adenovirus. 41BB is a costimulatory receptor which promotes the expansion of activated T cells and the generation and maintenance of CD8 T memory cells. Therefore, we propose the use of Delta-24-ACT as a therapeutic approach for DIPG tumours. We observed that Delta-24-ACT is able to infect and replicate in NP53 and PDGFB-driven, two DIPG murine cell lines. Furthermore, 41BBL is expressed in the membranes of the infected cells and results with immunogenic cell death as shown by the different DAMPs. Injection of Delta-24-ACT in DIPG model was safe, showed no sign of toxicity and led to a significantly increase in the median overall survival, generating anti-glioma memory in long-term survivors. Mechanistic experiments, showed an increase of T cell infiltration (mainly CD8), decrease of proliferating cells and a reduction of the number of vessels in FFPE brain samples in the treated mice. We are currently performing nanostring analyses to assess the changes in the transcriptional immune phenotype of treated versus control mice. In summary, our data suggest that Delta-24-ACT is safe and induces a potent antitumor immune response in DIPG models mainly based in the activation of CD8 lymphocytes recruited by the viral activity.

THER-02. EVALUATION OF THE ONCOLYTIC VIRUS DELTA24-RGD AS AN ANTI-TUMOR AGENT IN PRECLINICAL MODELS OF LOCALIZED AND DISSEMINATED AT/RT

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Current therapies for atypical teratoid/rhabdoid tumors (AT/RTs) are suboptimal, resulting in a 2-year OS below 20% and the development of severe side effects. Therefore, we need to explore alternative therapeutic approaches for this disease. Since the virus Delta24-RGD has already demonstrated its efficacy and safety as a therapeutic agent for brain tumors, including pediatric patients, here we propose to evaluate the anti-tumor effect of Delta24-RGD in AT/RT. In vitro, Delta24-RGD infects and replicates in AT/RT cultures followed by oncolysis, obtaining IC_{50} values below 1 PFU/cell. In vivo, a single local injection of Delta-24-RGD in three infratentorial AT/RT models (BT-12, CHLA-06 and CHLA-266) extended significantly the median OS (50 to 78 days BT-12; 21 to 31 days CHLA-06; 64 to 110 days CHLA-266). Delta-24-RGD also increased the survival of mice bearing supratentorial CHLA-266 tumors (from 93 to 132 days). Next, we evaluated the efficacy of Delta24-RGD in a model mimicking metastatic disease through intraventricular injection of BT-12-luciferase cells. Administration of Delta24-RGD inhibited tumor growth and development of metastases, leading to an increased OS and nearly 70% of long-term survivors. The interaction between Delta24-RGD and the immune system was evaluated in humanized mice models bearing CHLA-06. In this model, Delta24-RGD treatment extended OS (from 23 to 34 days) and we characterized the anti-tumor immune landscape in control and Delta24-RGD treated mice by transcriptional and functional analyses. These results underscore the potential of Delta24-RGD as a promising therapeutic choice for patients affected by AT/RT.

THER-03. IN VITRO EVALUATION OF THE EFFECT OF CANNABIDIOL ON PAEDIATRIC BRAIN TUMOUR CELL LINES USING A PULSED TREATMENT REGIME

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Paediatric brain tumours are the second most common cancer after haematological malignancies. Intermittent dosing regimens are typical for chemo-