tumors experience coupled with changes in functional status as the disease progresses, integrated and timely rehabilitation consultation is feasible.

PEDIATRICS

PS1 – 158

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The Role of LIN28A in Neoplastic Transformation of Human Embryonic Stem Cells (hESCs)

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Human embryonic stem cells (hESCs) are known for their indefinite self-renewal ability and pluripotent nature. However, during long-term culture, normal hESCs can undergo neoplastic transformation and acquire enhanced self-renewal ability and aberrant differentiation potential. These transformed-hESCs (trans-hESCs) exhibit high expression of the pluripotent gene, LIN28A. LIN28A, an RNA binding protein, is known: for its role in self-renewal of hESCs, as a reprogramming factor for generating induced-pluripotent stem cells and as a potent oncogene in several poorly differentiated, highly malignant human cancers. Despite its multiple functions, how LIN28A contributes to neoplastic transformation of normal hESCs is poorly understood. Our preliminary data demonstrate that following LIN28A knockdown, trans-hESCs display normal hESCs morphology consisting of both pluripotent colony cells surrounded by more differentiated fibroblast-like cells. Neural precursors derived from LIN28A knockdown trans-hESCs also revert back to a state of normal cell morphology and growth. Further analyses revealed that the expression levels of stage-specific embryonic antigen (SSEA3), OCT3/4 and NANOG decreases and are comparable to that observed in normal hESCs following LIN28A downregulation. Expression of miRNA targets of LIN28A such as let7i and mir125b was increased to levels seen in normal hESCs. These preliminary results indicate that LIN28A is a major contributing factor to neoplastic transformation of hESCs and that this process can be reversed by cellular "reprogramming". This study will enhance our understanding of role of LIN28A in the transformation process in various human cancers thus, underscoring the value of hESCs and their neoplastic-derivatives as cellular and molecular model for studying tumor progression.

PS1 – 169

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Discovering the Treatment Refractory BTIC Population in Group 3 Medulloblastoma through Therapy Adapted Patient-Derived Human Mouse Xenograft (PDX) Model

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Medulloblastoma (MB), the most common malignant pediatric brain tumor, is categorized into four molecular subgroups. Given the high rate of metastatic dissemination at diagnosis and recurrence in Group 3 MBs, these patients have the worst clinical outcome with a 5-year survivorship of approximately 50%. By adapting the existing COG (Children's Oncology Group) Protocol for children with newly diagnosed high-risk MB, for treatment of immuno-deficient mice intracranially engrafted with human MB brain tumour initiating cells we aim to identify and characterize the treatment-refractory cell population in Group 3 MBs. Mice were sacrificed at multiple time points during the course of tumor development and therapy: (i) at engraftment; (ii) post-radiation; (iii) post-radiation and chemotherapy; and (iv) at MB recurrence. MB cell populations recovered separately from brains and spines were comprehensively profiled for gene expression analysis, stem cell and molecular features to generate a global, comparative profile of MB cells through therapy. We report a higher expression of CD133, Sox2 and Bmi1 in addition to increased self-renewal capacity following chemoradiotherapy treatment. The enrichment map constructed from global gene expression analysis showed an increase in pathways regulating self-renewal, DNA repair and chemoresistance post-therapy despite the apparent decrease in tumour size and vascularity. Additionally, from gene expression at MB recurrence, we identified a list of genes that negatively correlate with survival in patients diagnosed with Group 3 MB. A differential genomic profile of the "treatment-responsive" tumors against those that fail therapy may contribute to discovery of novel therapeutic approaches for the most aggressive subgroup of MB.

PS1 – 170

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Bmi1 is a Therapeutic Target in Recurrent Childhood Medulloblastoma

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Medulloblastoma (MB) is the most common malignant pediatric brain tumour, and is categorized into four molecular subgroups, with Group 3 MB having the worst prognosis due to the highest rate of metastatic dissemination and relapse. In this work, we describe the epigenetic regulator Bmi1 as a novel therapeutic target for treatment of recurrent Group 3 MB. Through comparative profiling of primary and recurrent MB, we show that Bmi1 defines a treatment-refractory cell population that is uniquely targetable by a novel class of small molecule inhibitors. We have optimized an in vivo mouse-adapted therapy model that has the advantage of generating recurrent, human, treatment-refractory MBs. Our preliminary studies showed that although chemoradiotherapy administered to mice engrafted with human MB showed reduction in tumour size, Bmi1 expression was enriched in the post-treatment residual tumour. Furthermore, we found that knockdown of Bmi1 in human recurrent MB cells decreases proliferation and self-renewing capacities of MB cells in vitro as well as both tumour size and extent of spinal leptomeningeal metastases in vivo. Oral administration of a potent Bmi1 inhibitor, PTC 028, resulted in a marked reduction in tumour burden and an increased survival in treatment cohort. Bmi1 inhibitors showed high specificity for MB cells and spared normal human neural stem cells, when treated with doses relevant for MB cells. As Group 3 medulloblastoma is often metastatic and uniformly fatal at recurrence, with no current or planned trials of targeted therapy, an efficacious agent such as Bmi1 inhibitor could be rapidly transitioned to clinical trials.