clinical response of ALK positive neuroblastoma patients to the first generation ALK inhibitor has been rather disappointing.

Here we report the appearance of a novel ALK mutation in neuroblastoma together with other chromosomal aberrations that mediate neuroblastoma initiation and progression.

Material and methods Genomic tumour DNA from biopsy samples were extracted and exome sequencing was performed through paired-end sequencing on Illumina plateforms.

The novel *ALK-I1171T* mutant was biochemically analysed by western blot and neurite-outgrowth assay in PC12 cells, and foci formation assay in NIH3T3 cells.

Results and discussions Analyses of genomic tumour DNA from biopsy samples initially showed an 11q deletion, 17q gain with a mutation of the ALK gene at protein position 1171, which mediate an amino acid change from isoleucine to threonine. We show that mutation of I1171 to threonine generates a potent gain-of-function mutant, as observed in two independent systems. Firstly, in PC12 cell lines expressing ALK-I1171T display ligand independent activation of ALK, neurite outgrowth and further downstream signalling activation. Secondly, ALK-I1171T meditate foci formation in a NIH3T3 transformation analysis. Finally, pharmacological inhibition of ALK-I1171T employing ceritinib, an FDA approved ALK inhibitor show 14-fold better ability to abrogate ALK-I1171T compared with crizotinib.

Conclusion This study suggests that ceritinib presents a viable therapeutic option for ALK-positive neuroblastoma.

PO-315 THE MUTATIONAL AND TRANSCRIPTOME LANDSCAPE OF INFANT B-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA: THE INTERFANT TREATMENT PROTOCOL EXPERIENCE

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Introduction Infant B-cell precursor acute lymphoblastic leukaemia (iBCP-ALL) has dismal prognosis, especially with *MLL*-gene rearrangements (*MLL*r) which are hallmark clonal leukemogenic drivers. Molecular pathogenesis of *MLL*r-iBCP-ALL remain somehow enigmatic and *in vivo* recreation of *MLL*r-iBCP-ALL is challenging.

Material and methods We performed whole-genome, exome, targetted and RNA-sequencing on an Interfant study discovery cohort of 50 iBCP-ALLs (27MLL-AF4+, including relapses, 5MLL-AF9+and 10non-MLL). An independent validation cohort of 82iBCP-ALLs (43MLL-AF4+, 11MLL-AF9+, and 28non-MLL) was used for targeted DNA-sequencing/qRT-PCR.

Results and discussions iBCP-ALL shows an extremely low frequency of somatic mutations, irrespective of the presence/subtype of MLLr, with the predominant leukemic clone carrying a mean of 2.5 non-silent mutations. Recurrent mutations were exclusively found in *KRAS* and *NRAS*, which were more frequent in the MLL-AF4+than in MLL-AF9+/non-MLL iBCP-ALL due to common *NRAS* mutations found in MLL-AF4 +infants (32% vs 6%; $p<0.01$). These mutations were subclonal and frequently lost at relapse, despite a larger number of non-silent but non-recurrent mutations (19.5 mutations/patient). RNA-seq/qRT-PCR validation revealed that there are deregulated protein coding genes related to three importants pathways such as cell cycle regulation, DNA integrity check point and DSB DNA repair. Also, deregulated LncRNAs werefound that could provide further mechanisms of tumorigenesis. Furthermore, different isoforms of the reciprocal fusion *AF4-MLL* were expressed only in 55% of the t(4;11)+patients, and HOXA cluster genes are uniquely expressed in *AF4-MLL*-expressing t(4;11)+patients. AF4-MLL/HOXA-expressing patients displayed higher 2 year event-free survival than patients lacking AF4-MLL expression (65% vs 34%, $p=0.15$). Opposite to paediatric/adult BCP-ALLs, BCR repertoire analysis revealed only minor, non-expanded B-cell clones in t(4;11) +iBCP ALL.

Conclusion iBCP-ALL shows a silent mutational landscape regardless the *MLL* status. The expression of *AF4-MLL* associates to a better prognosis and specific upregulation of HOXA cluster genes. A pre-BCR early progenitor/stem cell may represent the cell-of-origin for both the t(4;11) and RAS mutations.

PO-316 GENOME-WIDE GENE EXPRESSION ANALYSIS OF A MURINE MODEL OF PROSTATE CANCER CELL PROGRESSION: TOWARDS IDENTIFICATION OF HIGH-POTENTIAL THERAPEUTIC TARGETS

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Introduction Prostate cancer (PC) is the most frequently diagnosed cancer among men and the second leading cause of male cancer-related deaths worldwide. The poor prognosis of PC is largely due to late diagnosis of the disease when it has progressed to advanced stages marked by androgen-independence. We construe that these direly needed advances are limited by our poor understanding of early events in the progression of PC and that would thus represent ideal targets for early intervention. To begin to fill this void, we interrogated molecular 'oncophenotypes' that embody the transition of PC from an androgen-dependent (AD) to –independent (AI) state.

Material and methods We have previously established AD and AI murine PC cell lines, PLum-AD and PLum-AI, respectively, which recapitulate primary and progressive PC morphologically and genetically. We statistically surveyed global gene expression in these cell lines by microarray analysis. Differential profiles were functionally interrogated by pathways, gene set enrichment and topological gene-gene network analyses – features built in the commercially available software Ingenuity Pathways Analysis.

Results and discussions Gene expression analysis of PLum-AD and PLum-AI transcriptomes (n=3 each), revealed 723 differentially expressed genes (392 upregulated and 331 downregulated) in PLum-AI compared with PLum-AD cells. Gene set analysis demonstrated enrichment of biological functions and pathways in PLum-AI cells that are central to tumour aggressiveness including epithelial-to-mesenchymal transition (EMT), cell migration, and cell invasion. Further analysis demonstrated that the p38 mitogen activated protein kinase (MAPK) was predicted to be significantly activated in the PLum-AI cells.