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**ANR abstract/ BESHG abstract– max 300 words**

**Exploring the contribution of gene dosage effects of 17q gain on ESC and neuroblastoma proliferation**

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**Introduction:** Human embryonal stem cells (hESCs) share similarities to (embryonal) tumors, including a shortened G1/S-phase. Highly proliferative cells undergo replicative stress (RS) which can cause premature aging of ESCs and genomic instability and tumor initiation. MYC(N) overexpression also causes RS due to increased use of replication origins and nucleotide depletion. Neuroblastoma (NB), a MYCN-driven pediatric tumor arising from the sympatho-adrenergic progenitor (SAP) cells, typically presents with a low mutation burden but highly recurrent patterns of DNA copy number alterations including 1q and 17q gain. Chromosome 17q gains have also been reported to arise during *in vitro* culture in hESC lines, suggesting that dosage effects for 17q gain render proliferative advantages to both ESCs and NB cells through a common mechanism.

**Material and methods**: We analyzed DNA copy number effects in more than 300 NB transcriptomes and identified multiple dosage sensitive genes implicated in homologous repair and replication fork fidelity. SWGS was performed on hESC cells. RNA-sequencing was performed for differential gene expression analysis.

**Results:** We present our progress towards a novel ESC derived NB model approach to test our hypothesis for the role of dosage sensitive 17q-genes in ESCs and NB in acquiring a replicative stress resistor phenotype. We obtained a hESC cell line with partial 1q and 17q gain (ESC1q17q) as shown by SWGS. Transcriptome analysis confirmed 17q dosage effects in these cells. In addition, targeted exome sequencing for 300 cancer genes was done to exclude additional tumor driving events. Using the IncuCyte life imaging device, we determined growth characteristics of both the parental and ESC1q17q cells. To test the effects of 1q/17q gain on NB tumor formation, we first generated a protocol to differentiate hESC towards hSAP cells marked by expression of PHOX2B and MASH2. Future work includes transduction of inducible MYCN overexpression and compare the transcriptome of MYCN-ESC versus MYCN-ESC1q17q induced SAPs and perform further analysis of molecular effects of 1q/17q gain on their RS response.

**Conclusion:** We report on a novel hESC cell line with 1q/17q gain, explored differential gene expression and provide an update on a novel protocol for generating hESC derived NB tumors.