culture counting and ATPlite assays we found the WT+ and NP lines to have a significant ($P < 0.01$) decrease in growth compared to control and PP mutant. This was further supported by knockdown of MARCKS in a high expressing patient derived xenograft (PDX) line XD456 which resulted in increased neurosphere formation in a limiting dilution assay and increased cell growth by cell titer glow. We also found radiation sensitivity to enhance in the WT and NP expressing lines through a combination of clonogenic, comet and gamma-H2AX foci formation assays. Through orthotopic implantation of our MARCKS ED mutants into athymic nude mice, we saw a significant ($P < 0.05$) survival benefit and increased response to radiation in our WT+ line with 6 Gy total dose delivered (2 Gy, 3X in a week). Overall, MARCKS phosphorylation alters its tumor suppressive effects.

CSIG-11. ONCOSTREAMS: NOVEL STRUCTURES THAT SPECIFY GLIOMAS' SELF-ORGANIZATION, ARE ANATOMICALLY DISCRETE, FUNCTIONALLY UNIQUE, AND MOLECULARLY DISTINCT

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Whether tumors in general and gliomas in particular are self-organized has not been determined. Brain tumor self-organization would be revealed through individual recognizable structures. Here we demonstrate that brain tumors are indeed self-organized. Brain tumor self-organization is evidenced by the existence of oncostreams, multicellular structures composed of elongated glioma cells. Oncostream structure, function and molecular makeup was studied in several glioma models. In experimental mouse models, and in human GBM tumors, oncostreams were demarcated anatomically as multicellular arrangements of fusiform cells, 10–20 cells wide, of various lengths and distributed throughout the tumors. Using genetically engineered glioma models we found a negative correlation between oncostream density and survival, suggesting that oncostreams contribute to tumor aggressiveness. As oncostreams also reached tumor borders, it is likely that they participate in glioma invasion. Further, by placing slow moving glioma stem cells into oncostreams we detected that these function as streams that distribute glioma cells throughout the tumors. Importantly, we performed the molecular analysis of oncostreams using a Laser Microdissection Microscope to dissect oncostreams from surrounding tumor. The transcriptome landscape was analyzed by next generation sequencing using RNA-Seq and advanced bioinformatics algorithms. The molecular analysis showed that oncostreams are defined by a distinctive transcriptome landscape. We hereby show that oncostreams: (i) are anatomically discrete structures that reveal the existence of glioma self-organization, (ii) are functionally unique as they regulate glioma growth, invasion and spread, and (iii) molecularly distinct, their genetic landscape and associated gene networks differentiate oncostreams from surrounding glioma. Understanding glioma self-organization and its molecular basis will contribute to uncover novel targets for future translational development.

CSIG-12. EXPLORING THE FUNCTIONAL RELATIONSHIP BETWEEN CAPICUA (CIC) AND ATAXIN-1-LIKE (ATXN1L) IN GLIOMA

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BACKGROUND: Oligodendroglioma (ODG), a molecularly defined subtype of glioma, is a treatment responsive, slow growing tumour strongly associated with IDH mutation and 1p19q co-deletion. Mutations in *CIC*, located on chromosome 19q, have been found in up to 70% of IDH mutated, 1p19q co-deleted ODGs; suggesting that loss or altered function of *CIC* may be crucially associated with ODG's unique biology. *CIC* and *ATXN1L* have previously been implicated in neurodegeneration, however, this interaction has not been studied in cancer. **METHODS:** *CIC* and *ATXN1L* interaction was confirmed using immunoprecipitation and immunofluorescence in multiple cell lines. *CIC* and *ATXN1L* knockout (KO) cell lines were generated using CRISPR/Cas9 followed by gene expression profiling using Affymetrix microarray. Differential gene expression analysis was also performed on patient lower grade glioma (LGG) RNAseq data publicly available through TCGA. Functional biology experiments to further characterize *CIC*-*ATXN1L* interaction were also performed using KO cell systems. **RESULTS:** Immunoprecipita-

tion and immunofluorescence confirmed *CIC* and *ATXN1L* interaction within the cell nucleus of multiple cell lines. Differential expression (DE) analysis of *CIC* KO, *ATXN1L* KO and TCGA LGG cohort converged on activation of the MAPK pathway and dysregulation of central nervous system development; with significant overlap in differentially expressed genes ($n=110$). Furthermore, experiments using our KO cell systems suggest a functionally reciprocal relationship between *CIC* and *ATXN1L* and regulation of their respective pathways. **CONCLUSIONS:** *CIC* and *ATXN1L* form a functionally reciprocal relationship where loss of one partner leads to dysregulation of both partners. Although *CIC* mutations are predominant in ODGs, the *CIC*-*ATXN1L* axis may be exploited in other gliomas and cancers which rely on maintaining MAPK signaling such as EGFR amplified glioblastoma and may be a target for future prognostics and therapeutics.

CSIG-14. HEPARAN SULFATE MODULATES CELL SIGNALING BY RECEPTOR TYROSINE KINASES IN HUMAN AND MURINE GLIOBLASTOMA

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Heparan sulfate (HS) / Heparan sulfate proteoglycans (HSPGs) are implicated in tumor malignancy based on their ability to promote cell signaling and tumor invasion. The mechanisms by which they do this in an individual tumor type, however, are often poorly defined. Using both patient-derived glioblastoma (GBM) tumorsphere lines and a murine model for GBM, we investigate how cell surface HSPGs modulate cell signaling in infiltrating astrocytoma. In human tumorsphere lines, chemical ablation of cell surface HS reduced the phosphorylation of several receptor-tyrosine kinases (RTKs) including platelet-derived growth factor receptor α (PDGFR α). The reduction in PDGFR α activation was associated with decreased binding of tagged PDGF-BB ligand to the cell surface suggesting HS can promote ligand retention and activity at the cell surface. To ablate all HS production we established HS-deficient murine tumor-prone cells by knockout of *Ext1*, a glycosyltransferase required for HS chain elongation. HS-deficient cells had decreased growth in vitro, decreased invasion in a 3D spheroid invasion assays, and reduced activation of RTKs as detected by Western blotting compared to control cells. Preliminary in vivo experiments suggest HS-deficient cells also exhibit reduced growth in vivo and the structural role for HS in RTK signaling in glioma can now be addressed.

CSIG-15. PROTEOMIC AND PHOSPHOPROTEOMIC ANALYSIS OF HUMAN MEDULLOBLASTOMA REVEALS DISTINCT ACTIVATED PATHWAYS BETWEEN SUBGROUPS

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Deregulations in fundamental signaling pathways are key events in pathogenesis of cancer. One intriguing illustration that still holds blind spots is the pediatric brain tumor arising from the developing cerebellum: medulloblastoma (MB). Extensive high-throughput sequencing led to the characterization of four MB subgroups (WNT, SHH, Group 3 and Group 4) delineated with distinct molecular signatures and clinical outcomes. However, up-to-