The Neuroscience Graduate Program

presents:

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IN A PHD THESIS DEFENSE

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Targeting a network of cancer control nodes through rescue of c-Cbl; A novel therapeutic approach for Glioblastoma multiforme

Glioblastoma multiforme is the most common primary brain tumor in adults, the most malignant of all intracranial tumors, and is associated with inevitable recurrence and 15 month mean survival despite multimodal therapy. The majority of GBM tumors maintain heterogeneous amplifications (many in the absence of genetic mutation) in receptor tyrosine kinases (RTKs), which are mediators of growth factor signaling. Our lab has discovered that control over RTK levels in normal CNS progenitors is maintained by the Redox/Fyn/c-Cbl (RFC) pathway whereby increased oxidative state results in activation of the E3 ubiquitin ligase c-Cbl and the subsequent internalization and degradation of target RTKs. RFC signaling is disrupted in GBM due to a physical sequestration of c-Cbl, preventing pro-oxidative chemotherapeutics from reducing pro-survival signaling through EGFR, PDGFRα, etc. Using a triangulating drug screen, we identified candidate c-Cbl restoring agents (CRAs) from a library of FDA-approved small molecules based on their ability to reduce signaling downstream of c-Cbl-targeted RTKs. Considering clinically relevant criteria, we focused our investigation on a generic, tetracyclic antidepressant. We discovered that this agent facilitated activation of RFC signaling and restored functional activity of c-Cbl. Rescue of c-Cbl resulted in distinct downstream effects of protein degradation and transcriptional modulation of a broad network of cancer control nodes. This translated into potent effects on GBM cell viability and tumor initiation potential. Ultimately, this approach was able to inhibit tumor progression and extend survival in an animal model of GBM, supporting its clinical utility. Our work supports the hypothesis that c-Cbl is a critical rheostat and higher level regulator in GBM that integrates multiple nodes of cancer control and that pharmacological rescue of c-Cbl represents a potentially powerful therapeutic approach for this disease.