

# Meghan Logun

Mentor: Lohitash Karumbaiah

Oral Presentation

Class of 2020, Graduate

## Small Molecule GAG-Antagonist Surfen Decreases Glioma Cell Infiltration *In Vitro* and Attenuates Tumor Growth in Rat Model of Glioma

Authors: Meghan Logun, Akshaya Narayanan, Wujun Zhao, Leidong Mao, Lohitash Karumbaiah

Glioblastoma multiforme (GBM) is a stage four astrocytoma comprising the majority of primary malignant brain tumor diagnoses in the United States. Conventional therapies are ineffective, leading to patient death within 15 months of diagnosis. Chondroitin sulfate proteoglycans (CSPGs) and their glycosaminoglycan (GAG) side chains are key components of brain extracellular matrix (ECM) implicated in promoting tumor invasion and spread. We hypothesize that glioma cell invasion is triggered by selective expression of oversulfated CS-GAGs in the tumor microenvironment and that preventing tumor cell interactions with CS-GAGs will dampen glioma invasion and spread.

Microfluidics devices with mono- and oversulfated CS-GAG matrices were used to evaluate F98 rat glioblastoma cell infiltration *in vitro*. Cell infiltration was compared across unsulfated hyaluronic acid (HA) and 4,6-sulfated CS-GAG (CS-E) matrices, and media only controls. The small molecule GAG-antagonist (surfen) was introduced to inhibit cell interaction with sulfated GAGs and evaluate if inhibition subsequently halted cell infiltration within hydrogel matrices. Focal adhesion protein colocalization was quantified within antagonist-containing and control hydrogels to determine influence of CS-GAGs on migratory cell phenotype. *In vivo* tumor inductions in Sprague Dawley rats were performed stereotactically to induce frontal lobe tumors accurately mimicking human GBM. F98 cells either in media only or media containing surfen were inoculated at a depth of ~3 mm to evaluate effects of surfen on glioma formation and invasion over 21 days *in vivo*. MR imaging was used to track progress and quantify tumor volume and angiogenesis.

Our results demonstrated enhanced preferential cell migration into hydrogel matrices containing disulfated CS-E compared to unsulfated hydrogels ( $p < 0.05$ ). F98 cells invading into CS-E hydrogels displayed enhanced colocalization ( $p < 0.05$ ) of focal adhesion proteins compared to cells within unsulfated hydrogels. This effect was significantly reduced in cells within CS-E hydrogels containing surfen ( $p < 0.05$ ). F98 cells inoculated within rats developed into diffusely invasive tumors after 14 days, but when inoculated in media containing surfen tumors were contained to more defined margins and smaller gross size after 7 days ( $p < 0.05$ ). These results suggest that sulfated CS-GAGs may directly induce tumor invasion, and this signaling mechanism can be disrupted by surfen to restrict invasion.

Our results suggest that heightened presence of extracellular CS-E induces enhanced cellular migration in a GAG sulfation-dependent manner, and perturbing cellular interactions with CS-E has consequences for gross tumor formation and invasion. Identification of the role of CS-GAGs in glioma behavior would advance our understanding of glioma invasion, and contribute to design of novel therapeutic interventions.