THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

JADITH ZIEGLER

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE

Department of Pathology

Wednesday, May 2, 2018 | 2:30 pm | Hensley Library, Biomedical Science Building Room 433

Novel Therapies Against Gliomas

COMMITTEE IN CHARGE: Chair: Rheal Towner, PhD, Courtney Griffin, PhD, Wei-Qun Ding, PhD, Priyabrata, Mukherjee, PhD, James Battiste, MD, PhD

ABSTRACT: Gliomas, specifically Glioblastomas, are deadly brain tumors that account for the majority of all CNS malignant tumors (47.1%). They have the highest number of all estimated new cases at a projected 29,320 in 2018, and there are currently no long-term treatments available for patients diagnosed with gliomas. Our goal is to find an efficient therapeutic drug that would help treat patients with GBM. We first tested the efficiency of AG488, a small molecule with anti-microtubule and tyrosine kinase (RTK) inhibiting qualities, in treating gliomas. We found that it significantly increased percent survival and decreased tumor volumes in a human G55 glioma xenograft model in nude mice. AG488 did not induce apoptosis in normal mouse brain tissue. Animal survival and tumor volume changes for AG488 were comparable to TMZ or anti-VEGF

therapies, however AG488 was found to be more effective in decreasing tumor-related vascularity (perfusion and MVD). We concluded that using agent AG488 in cell cultures and a mouse model is an effective therapy against high-grade gliomas.

We have also explored ELTD1, ([epidermal growth factor (EGF), latrophilin and seven trans-membrane domain-containing 1] on chromosome 1), as a therapeutic target using both a GL261 and G55 glioma mouse model, as it has been found to be a novel biomarker for high-grade gliomas and a novel regulator of angiogenesis, the formation of new blood vessels. The anti-angiogenic effect of ELTD1 antibody therapy was observed in MVD assessment, as well as from MR angiography and perfusion measurements, which indicated that anti-ELTD1 antibody therapy significantly decreased vascularization compared to untreated controls. Either as a single therapy or in conjunction with other therapeutic approaches, anti-ELTD1 antibody treatment could be a valuable new clinical anti-angiogenic therapeutic for high-grade gliomas as they target both glioma and endothelial cells.

Finally, we have characterized ELTD1 further in terms of its effect on glioma cells and its possible relationship with VEGFR2 (vascular endothelial growth factor receptor 2), a regulator of angiogenesis. Our results indicated that ELTD1 is a better therapeutic target than VEGFR2 as it effected glioma malignancy not only within *in vitro* but *in vivo* and in *ex vivo* studies. Additionally, we found through several experiments that there is a strong relationship between these two regulators. With the help of MRI, *in vitro* cell studies, *in vivo* mouse studies, *ex vivo* Immunohistochemistry, fluorescence microscopy, and other preclinical techniques, we are able to test potential therapies as well as develop a better understanding of gliomas and its malignancy.