Implantable Peptide-Hydrogel Drug Delivery System for Treating Glioblastoma Multiforme

*Gregory, A.J.[1], Miller, E.M.[1], and Alexander-Bryant, A.A[2].

[1]Graduate Research Assistant, Bioengineering Department, [2]Professor, Bioengineering Department, Clemson University

aricag@g.clemson.edu

Keywords: Peptide, Drug Delivery, Glioblastoma Multiforme, Brain

Abstract: Gliomas represent approximately 80% of all malignant brain tumors, and glioblastoma multiforme (GBM) accounts for nearly half of gliomas [1]. GBM is the most common and aggressive primary brain tumor. Therefore, new therapeutic strategies are needed to improve the survival rate of those affected. Chemotherapy with Temozolomide (TMZ) is commonly used in treatment. TMZ is an orally delivered drug that is stable in an acidic pH environment like the stomach, and begins to convert to its active form at a neutral pH in the bloodstream. However, studies show that full conversion of TMZ to its active form occurs at a more basic pH [2]. Further, after TMZ is converted to its active form, it is unable to cross the blood brain barrier, thereby lowering its effectiveness [2]. Therefore, we propose an innovative local delivery strategy using hydrophilic and alternating hydrophobic amino acids to form a hydrogel that will encapsulate TMZ and convert the drug to its active form.

Peptide Sequences were designed, synthesized, and formed into hydrogels for the delivery of temozolomide. Preliminary studies were conducted to validate the effectiveness of TMZ in a high pH environment. TMZ was dissolved in water at pH 2.5, 7.5, and 12 and incubated with LN-18 human glioblastoma cells at a final concentration of 200uM. Cytotoxicity of TMZ was determined by MTT assay after 72-hours. For drug loading, 0.03mg of TMZ was combined with 1mg/mL, 0.5mg/mL, 0.1mg/mL, 0.05mg/mL, 0.01mg/mL of peptide, and allowed to shake for 24 hours. The amount of TMZ loaded was determined by HPLC.

Our results demonstrated that TMZ at higher pH resulted in increased cytotoxicity in LN-18 cells. We also demonstrated that the proposed peptide-hydrogel efficiently loads TMZ. In conclusion, Temozolomide is more effective in a higher pH environment likely due to increased conversion of the drug to its active form. Future studies will determine the cell viability of LN-18 cells treated with the TMZ-loaded peptide-hydrogel compared to TMZ delivered alone.

[1] Siegel, R.L. *et al*. (2015) *CA Cancer J Clin* 65(1):5-29. [2] Andrasa, Melinda, et al (2010) *Journal of Chromatography B* 878(21):1802-1808.