Development of a multifunctional peptide hydrogel for codelivery of chemotherapy and siRNA therapy for glioblastoma treatment.

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Traditional treatment methods for glioblastoma multiforme (GBM) are largely unsuccessful, with a 5-year survival rate of 5.6%.[1] Only one chemotherapy is FDA-approved for systemic GBM treatment: temozolomide (TMZ) is a hydrophobic prodrug that is stable in an acidic pH and begins converting to its active form at a physiological pH of 7.4.[2] However, complete conversion of TMZ is observed only at a higher pH, and only about 30% of administered TMZ reaches the central nervous system.[2–4] Therefore, there is a need for new treatment methods which maximize TMZ efficacy at the tumor site. The **goal** of this project is to develop a self-assembling peptide hydrogel which will both act as a codelivery vehicle and induce TMZ conversion upon delivery via hydrogel degradation products.

The primary **objective** of the project is to develop a novel drug delivery system which significantly improves GBM treatment and prognosis. Drug-loaded biodegradable hydrogels provide sustained drug release over extended periods of time, protect the loaded cargo from degradation, and deliver multiple therapies concurrently.[5–7] Peptides can self-assemble into several different supramolecular structures, including nanospheres, nanofibers, nanoribbons, and hydrogels. These structures can be used to deliver a wide variety of cargo such as drugs, contrast agents, and genetic molecules like siRNA.[8] Because they are naturally biocompatible, peptide-based self-assembling materials are especially promising for clinical applications where biocompatible and biodegradable materials are necessary.[9] The ability of self-assembling nano- and micro-sized peptide networks to enable controlled drug release makes them ideal for use in drug delivery applications.[9] Peptide hydrogels can also deliver nano-sized drug delivery systems (DDSs) (e.g. liposomes), which allows for extended treatment while retaining the therapeutic efficacy provided by the DDS, such as cell internalization or endosomal escape.[5] For this application, the DDS will be a peptide complexed with siRNA (siRNA-NP) to silence an oncogene associated with TMZ resistance.

This project represents a **significant** expansion of the drug delivery field, because using hydrogel degradation products to convert a prodrug is a novel concept. Additionally, the locally injectable hydrogel can be used to treat both resected and inoperable GBM tumors and the synergistic effect of siRNA and TMZ therapies will increase anti-cancer efficacy. Together, these features could improve GBM treatment for the first time in over 20 years. We **hypothesize** that a co-loaded peptide hydrogel will effectively deliver bioactive siRNA-NP complexes and convert TMZ to its active form upon release, resulting in improved treatment of both inoperable and resected GBM tumors. The hypothesis will be tested using three specific aims:

Aim 1. Synthesize and characterize a multifunctional peptide hydrogel capable of TMZ and siRNA-NP codelivery. Based on our preliminary data, we hypothesize that a short peptide sequence consisting of alternating amino acids will assemble into an injectable, viscous hydrogel capable of co-loading TMZ and siRNA-NP.
Aim 2. Assess TMZ and siRNA-NP loading/release and TMZ conversion as the hydrogel degrades. Charged regions are hypothesized to allow loading of TMZ, while siRNA-NP loading will rely on physical entrapment in the gel.
Aim 3. Determine the overall anticancer efficacy of loaded peptide hydrogels in GBM cells in vitro and in vivo. In vitro assays will be conducted on U87MG and LN18 human GBM cell cultures to determine overall anticancer efficacy of the hydrogel delivery system on tumorigenic and drug resistant cells. The project will culminate in an orthotopic murine model study to confirm translatability of results.

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