



# Intracranial MEMS based temozolomide delivery in a 9L rat gliosarcoma model

Byron C. Masi<sup>a,b</sup>, Betty M. Tyler<sup>c</sup>, Hansen Bow<sup>c</sup>, Robert T. Wicks<sup>c</sup>, Yuan Xue<sup>b</sup>, Henry Brem<sup>c,d,e</sup>, Robert Langer<sup>a,b</sup>, Michael J. Cima<sup>b,f,\*</sup>

<sup>a</sup> Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

<sup>b</sup> The David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

<sup>c</sup> Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA

<sup>d</sup> Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA

<sup>e</sup> Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA

<sup>f</sup> Department of Materials Science & Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

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## ABSTRACT

Primary malignant brain tumors (BT) are the most common and aggressive malignant brain tumor. Treatment of BTs is a daunting task with median survival just at 21 months. Methods of localized delivery have achieved success in treating BT by circumventing the blood brain barrier and achieving high concentrations of therapeutic within the tumor. The capabilities of localized delivery can be enhanced by utilizing micro-electro-mechanical systems (MEMS) technology to deliver drugs with precise temporal control over release kinetics. An intracranial MEMS based device was developed to deliver the clinically utilized chemotherapeutic temozolomide (TMZ) in a rodent glioma model. The device is a liquid crystalline polymer reservoir, capped by a MEMS microchip. The microchip contains three nitride membranes that can be independently ruptured at any point during or after implantation. The kinetics of TMZ release were validated and quantified *in vitro*. The safety of implanting the device intracranially was confirmed with preliminary *in vivo* studies. The impact of TMZ release kinetics was investigated by conducting *in vivo* studies that compared the effects of drug release rates and timing on animal survival. TMZ delivered from the device was effective at prolonging animal survival in a 9L rodent glioma model. Immunohistological analysis confirmed that TMZ was released in a viable, cytotoxic form. The results from the *in vivo* efficacy studies indicate that early, rapid delivery of TMZ from the device results in the most prolonged animal survival. The ability to actively control the rate and timing of drug(s) release holds tremendous potential for the treatment of BTs and related diseases.

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## 1. Introduction

Brain cancer only accounts for 1.4% of all cancer diagnoses and 2.3% of all cancer deaths (American Cancer Society, Cancer Facts, 2011), yet it remains one of the most intimidating and challenging cancers to treat. The most common and aggressive form of adult malignant brain tumor is glioblastoma multiforme (GBM) [1], and despite the best treatment, the median survival of people diagnosed with this disease is just 21 months [2].

Treatment generally involves a combination of surgical resection, radiotherapy, and chemotherapy [3]. Chemotherapy is conventionally administered systemically via intravenous injection or oral formulations. Current BT therapy is largely based around the Stupp protocol, a combination of radiotherapy with oral

administration of the alkylating agent temozolomide (TMZ). This combination has been shown to increase median survival from 12 months with radiotherapy alone to approximately 15 months with combined radiotherapy and oral TMZ [4]. One of the major limitations to the development of more effective brain tumor therapies is the presence of the blood–brain barrier, which prohibits the transfer of molecules that are larger than 500 Da or are non lipid-soluble [5]. Unfortunately, most chemotherapeutics do not fit these criteria; systemic toxicity is often reached before obtaining a therapeutically effective concentration in the brain when the delivery method is either intravenous or oral.

Various localized delivery methods, such as convection enhanced delivery or locally implanted drug depots, have therefore been studied as an alternative mechanism of drug delivery to the brain [6–15]. One successful method has been the implantation of a biodegradable, drug-eluting polymer wafer during surgical resection of the tumor. The drug delivery system, Gliadel<sup>®</sup>, is based on this technology and provides for the controlled release of the

\* Corresponding author. The David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139, USA  
E-mail addresses: [mjcima@mit.edu](mailto:mjcima@mit.edu), [M.J.Cima@mjcima@mit.edu](mailto:M.J.Cima@mjcima@mit.edu) (M.J. Cima).