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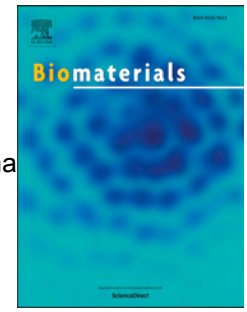

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An adherent tissue-inspired hydrogel delivery vehicle utilised in primary human glioma models

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Abstract

A physical hydrogel cross-linked *via* the host-guest interactions of cucurbit[8]uril and utilised as an implantable drug-delivery vehicle for the brain is described herein. Constructed from hyaluronic acid, this hydrogel is biocompatible and has a high water content of 98%. The mechanical properties have been characterised by rheology and compared with the modulus of human brain tissue demonstrating the production of a soft material that can be moulded into the cavity it is implanted into following surgical resection. Furthermore, effective delivery of therapeutic compounds and antibodies to primary human glioblastoma cell lines is showcased by a variety of *in vitro* and *ex vivo* viability and immunocytochemistry based assays.

Keywords: glioma, hydrogel, blood-brain barrier, cucurbit[8]uril, drug-delivery, hyaluronic acid

1. Introduction

Glioblastoma (GB) is the most common primary malignant brain cancer in adults and one of the most aggressive cancers. The median survival in the general patient population is just 4.6 months.[1] Even in optimally treated patients the median survival is 14 months with a 26% two year survival rate.[2, 3, 4, 5] GB infiltrates the brain tissue diffusely making complete surgical excision impossible.[6] The majority of patients (90%) will suffer recurrence within 2 cm of the resection cavity due to the presence of residual disease.[7]

Current standard of care involves surgical resection of the tumour, concomitant radiotherapy and alkylating chemotherapy (CRT), followed by adjuvant chemotherapy.[2] TMZ is the major chemotherapeutic agent used to treat GB as it is one of the few molecules that readily cross the blood-brain barrier (BBB).[8] Following uptake into the brain, TMZ is hydrolyzed into its active form MTIC enabling methylation of the O-6 position on guanine residues, resulting in cytotoxic DNA damage.[9] However, TMZ also degrades to MTIC in the blood stream which does not cross the BBB and can cause systemic toxicity, including bone marrow suppression.[10] Such toxicity sometimes requires dose reduction or termination of concomitant or adjuvant chemotherapy. Therefore, despite the use of TMZ, surgical resection and radiotherapy as standard of care, patient survival rates remain poor.

At the end of surgery, a localised and sustained delivery of patient-tailored chemotherapy to the resection cavity walls could significantly enhance patient survival opportunities by circumventing the BBB to eradicate the local, residual disease. A recent clinical trial (NCT01310868) evaluated the use of local DNA cross-linking chemotherapy (carmustine) in patients undergoing advanced surgical resection.[11] The trial delineates the benefit of anti-neoplastic effects from the increasingly aggressive neuro-oncological care patients receive, determining that the carmustine wafer added no additional patient benefit following fluorescence-guided surgery.[12] The carmustine implant takes the form of drug-loaded wafers produced from 1,3-bis-(*p*-carboxyphenoxy)propane (CPP) and sebacic acid (SA) monomers (20:80 molar ratio) connected with anhydride bonds. The rigid wafers (Gliadel®) are administered at the end of surgery to the tumour bed.[13, 14] Such implants have the potential to cause a mechanical mismatch between the implant and surrounding tissue that could result in encapsulation of implants by fibrous tissue and a foreign body reaction. [15, 16] Once in contact with physiological fluid, carmustine is released through erosive dissolution of the matrix in a 2–3 week period.[17, 18, 19, 20] The permanent shape and stiffness of the implant (14 mm diameter, 1 mm depth) compromise tissue–wafer contact, which limits tumour penetration by the carmustine.[3, 21, 22, 19] Due to the strong lipophilicity of carmustine, facile

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