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Biomaterial-based local drug delivery to brain tumors

“As we progress towards an era of individualized medicine, equipped to target specific molecules and pathways in glioblastoma and other brain tumors, we need to continue to develop local drug-delivery systems as a crucial corollary.”

Keywords: biomaterial • glioblastoma • interstitial drug delivery • mass spectrometry imaging • microparticles • PLGA/PEG • polymer

“I don't expect to get yesterday's medicine. If I can help it, I'd like to get tomorrow's medicine.”

– Elizabeth Edwards

Glioblastoma (GBM) is the most prevalent and aggressive malignant brain tumor with a median survival from diagnosis of 12–15 months. Standard-of-care treatment consists of radical surgery followed by radiotherapy with concomitant systemic temozolomide. Nevertheless, due to the infiltrative nature of GBM, this treatment strategy almost universally fails to eradicate minimal volume residual disease, which typically recurs within 2 cm from the original lesion [1]. A homogeneous treatment regime and regrowth of the tumor locally present a firm clinical and scientific rationale in which to develop innovative therapies delivered interstitially. There is a critical need to develop more effective and targeted chemotherapy regimes that can eradicate residual GBM cells following neurosurgical resection, thereby improving local control within the brain parenchyma beyond the surgical cavity wall and reducing the risk of tumor recurrence [2]. The opportunity to deliver therapeutic cancer drug concentrations locally creates the possibility of improving both the safety (low toxic dose systemically) and efficacy (high effective dose locally) of cancer chemotherapy, thereby enhancing the benefit of surgery, as well as continuing antineoplastic treatment during the interval between surgery and commencement of systemic adjuvant therapy.

Although a myriad of drug-polymer devices have been developed to date, the Food and

Drug Administration and National Institute for Health and Clinical Excellence has solely approved the use of chemotherapy impregnated polymeric wafers (Gliadel®) for local chemotherapy delivered via a biomaterial, for the treatment of primary and recurrent malignant glioma. These wafers which are neurosurgically implanted at the time of tumor resection, gradually release the chemotherapeutic agent carmustine, which then diffuses into the surrounding brain and targets the residual cancer cells that have infiltrated the brain tissue. These studies and trials offer hope to this mode of intracavity drug delivery, with results showing a moderate but significant survival benefit of 2.3 months and 1.8 months median survival for newly diagnosed and recurrent high-grade gliomas, respectively [3,4]. The treatment has nevertheless shown limited efficacy mainly due to: (i) poor drug diffusion, restricted to 2–3-mm bordering the implant; (ii) implants not maintaining close contact with the resection cavity rim and falling to the bottom of the cavity; (iii) only one drug being delivered [5]. OncoGel™, a controlled-release formulation of paclitaxel in ReGel™, comprising a thermosensitive triblock copolymer (PLGA-PEG-PLGA), has shown much preclinical promise. This system is water soluble at 2–15°C and turns into a viscous gel at body temperature [6]. Preclinical and early clinical investigations demonstrated OncoGel™'s ability to physically target paclitaxel to brain tumor tissue via intralesional injection into the tumor cavity following resection, with an acceptable safety profile and moderate increase in survival in a rat gliosarcoma model [7].



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Our partners at the School of Pharmacy, University of Nottingham, have developed a novel formulation of PLGA/PEG copolymer microparticles which creates a moldable paste when mixed with liquid. At body temperature only, the paste hardens into a solid matrix, potentially releasing multiple drugs simultaneously over several weeks. We have previously described this PLGA/PEG formulation as the only drug-delivery formulation to our knowledge that can be pasted onto the tumor resection cavity wall, thereby potentially offering closer proximity of drug depot to residual tumor cells than existing methods. The material has clear clinical utility as we have demonstrated the relative ease of application *ex vivo*, distinguished the biomaterial on MRI/CT clinical scans and shown that the material can withstand a 6-week clinically relevant radiotherapy dosing schedule [8].

The rationale of these polymer-based approaches is to improve upon drug efficacy, increase exposure time of tumor cells to drug, protect drugs from degradation and clearance by the immune system until its release from the polymer and reduce the debilitating sequels of current systemic chemotherapeutics, allowing oncological treatment to be maintained in the interval between surgery and radiotherapy.

“...the only drug-delivery formulation to our knowledge that can be pasted onto the tumor resection cavity wall...”

However, it is not clear whether the failure of chemotherapy drugs to achieve durable responses in GBM is due to the intrinsic resistance of residual disease or the lack of drug penetration at therapeutic doses. The former can realistically only be overcome using next-generation molecularly targeted chemotherapeutics, whereas the latter is a considerable obstacle for more efficacious drug delivery in the future. However, given the difficulty associated with measuring chemotherapeutic drug distribution in the central nervous system, tissue-based pharmacokinetic measurements are typically not achievable in human clinical settings. Therefore, drug distribution has been measured in the brains of rodents and nonhuman primates as surrogate models to advance drug selection for the treatment of brain tumors. Such approaches rely on high numbers of animals and cannot address how nonlabeled native drugs released from a local delivery system behave when diffusing throughout brain tissues. Technologies that utilize mass spectrometry (MS) as a detector for diverse analytes could potentially overcome some of these limitations, by directly measuring individual molecular species in complex samples. One

such method is liquid extraction surface analysis MS (LESA-MS), a novel ambient surface profiling technique that combines liquid extraction of analytes from a solid surface (e.g., organ-specific tissue) with nano-electrospray MS [9,10]. The distribution of drugs could thus be characterized rapidly by analyzing anatomical contexts *ex vivo*, such as brain-slice cultures, where the delivery system can be incorporated. LESA-MS presents added benefits including the ability to discriminate multiple drugs simultaneously, lower costs, little-to-no sample preparation, rapid analysis and analysis in an ambient environment – features important for effective spatially-resolved drug localization.

“...we anticipate loading drug amounts in our polymer system based on drug release data from *in vitro* and *in vivo* studies, ensuring that the early burst release is less than the maximum tolerated doses.”

Drug delivery using a single local administration requires careful consideration of potential damage to healthy neural cells. Understanding drug distribution from the polymer is crucial to predict the effect on tumor cells and normal brain. One difficulty is that therapeutic doses and maximum tolerated doses typically relate to systemic delivery. To overcome this we anticipate loading drug amounts in our polymer system based on drug release data from *in vitro* and *in vivo* studies, ensuring that the early burst release is less than the maximum tolerated doses. Selection of locally delivered chemotherapeutic agents that display widespread brain tissue distribution will benefit brain tumor patients by potentially offering more efficacious treatment directly at the site of the tumor.

As we progress towards an era of individualized medicine, equipped to target specific molecules and pathways in GBM and other brain tumors, we need to continue to develop local drug-delivery systems as a crucial corollary. Drug-delivery innovations will enable us to expand the selection of chemotherapeutics that will become amenable for use in the clinic, ultimately to the benefit of the patients and their families.

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