# Orthotopic intracranial tumour model in mice for investigating potential therapies for brain cancers

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Effective therapies that can induce durable responses against glioblastoma multiforme (GBM), the most common and most aggressive primary brain cancer in adults, are an unmet need. Overcoming the blood-brain barrier (BBB) remains a major challenge in the design and development of therapies that can specifically target cancers growing in the sanctuary of the brain. We have established an orthotopic, intracranial (ic) tumour model of GBM for the preclinical evaluation of investigational anti-cancer agents. GL261 murine glioma cells were engineered to constitutively express the luciferase gene, and GL261-luc cells were stereotaxically inoculated into C57Bl/6 wild-type or albino mice. Growth of ic tumours were monitored using IVIS optical imager. In this communication, we report the use of this orthotopic model to evaluate the potential of two investigational anti-cancer agents; DMXAA, a vascular disrupting agent developed at the ACSRC, and an analogue of omega-3 epoxy fatty acid, ethyl 16-{[(4-methylphenyl)carbamoyl]amino}hexadecanoate (CUT-EE) to cross the BBB and to inhibit growth of ic GL261-luc tumours. DMXAA was shown not to cause haemorrhagic necrosis, nor to provide a survival benefit against ic tumours using the same dosage that induced > 80% necrosis and a 50% cure rate against the same tumour implanted subcutaneously. Pharmacokinetic studies showed poor penetration of DMXAA into brain tissue. The area under the concentration curve ($AUC_{0-\infty}$) of DMXAA in brain was 80-fold lower than that determined in plasma, and provided a salient explanation for the poor antitumour activity against ic GL261 tumours. On the other hand, pharmacokinetic studies using a newly developed LC/MS/MS analytical assay for CUT-EE, showed that the agent accumulated in the brain over 72 h, whilst plasma levels decreased over the first 24 h. The $AUC_{0-\infty}$ of CUT-EE in brain tissue was > 100-fold higher than in plasma. CUT-EE inhibits proliferation of tumour cells in culture, including GL261, and the pharmacokinetic data indicate that CUT-EE has the ability to cross the BBB. The potential of CUT-EE to impede the growth of ic GL261 tumours is currently in progress. Future work in this project aims to identify the transporter proteins on the BBB that facilitate the transport of fatty acids such as CUT-EE into the brain.