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Developing a novel drug delivery system utilising a spray device, pectin hydrogel and etoposide and olaparib-loaded nanoparticles for the local delivery to Glioblastoma Multiforme

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Glioblastoma multiforme (GBM) is a WHO grade 4 tumour carrying a dismal average survival time of 14 months from prognosis and a 16% 2-year survival rate. Current treatment consists of debulking surgery and oral temozolomide followed by concurrent chemoradiotherapy. Relapse from residual disease cells is inevitable, with 80% of tumours recurring within 2 cm of the primary tumour. This gives high precedence for a local drug delivery system (DDS) to target the local residual disease. A spray device and formulation (polymer-coated nanoparticles (PCNPs) and hydrogel) have been developed to achieve further penetration of drug into this 2 cm target area.

Pectin hydrogels have been repurposed for use within the brain parenchyma, having found to be non-toxic *in vitro* and *in vivo* at 200 µM for up to 2 weeks. Fluorescence from Cy5-pectin reduced to background levels after 2 weeks *in vivo*.

PCNPs were generated by creating etoposide and olaparib nanocrystals in aqueous medium before coating with a PEGylated lactide-based polymer. PCNPs were characterised using HPLC, DLS and TEM. PCNP stability was also evaluated after storage at 4 °C and at 37 °C in DMEM, PBS and artificial cerebrospinal fluid (aCSF) using DLS. The PCNPs were then sprayed from an Aptar Pharma device and characterised using TEM and DLS.

PCNP drug loadings of 44.0±0.2% and 25.5±0.8% (mean ± SD) for etoposide and olaparib, respectively, were achieved. Formulations were stable at 4 °C for up to 6 weeks and up to 48 hrs at 37 °C in DMEM, PBS and aCSF. Drug release was rapid, showing an initial burst of ~10% in 30 minutes, followed by ~85% at 24 hrs. The addition of hydroxypropyl-ß-cyclodextrin was required to ensure the stability of the PCNPs when sprayed from the device.

The hydrogel, PCNPs and a spray device have so far proven they are fit-for-purpose, warranting testing in pre-clinical brain tumour models. This DDS is currently being progressed to *in vivo* tolerability and efficacy studies, which are due to be completed soon.