**Functional Peptide-Based Nanomaterials for Delivery of microRNA to Medulloblastoma.**

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**Background:** Medulloblastoma (MB) is the most common malignant brain cancer in children, with 50 new diagnoses each year in the United Kingdom (UK). Treatments include chemotherapy, radiotherapy and surgery, but result in devasting side effects including later-in-life cancers, poor quality of life and neurological/mental health conditions. These side effects, as well as the development of chemoresistance in MB tumours, have resulted in the need for new therapeutics.

Specific microRNAs (miRNAs) containing a toxic 6-mer seed sequence exhibit tumour suppression properties on the RNA-induced silencing complex (RISC) protein, via death induced by survival gene elimination (DISE). However, the potential of DISE-dependent miRNA action in MB has not been established. Furthermore, several tumour suppressor miRNAs appear to be downregulated in MB, but mechanisms for miRNA-replacement therapy in MB have not been defined.

The development and progress of new MB therapeutics is hindered by blood brain barrier (BBB); a selective, semi-permeable membrane between the brain's interstitium and surrounding tight blood junctions, acting as an immune defence. Nonetheless, peptide and peptide-based nanoparticles have emerged as promising agents for small RNA delivery across the BBB.

We therefore hypothesised that peptide-based nanoparticles may be suitable vehicles for miRNA delivery into MB cells.

**Methods:** We analysed three DISE miRNAs (hybrid and wild-type) from the miR-34, miR-124 and miR-204 families for their effects on MB cell lines (DAOY and HD-MB03) through *in vitro* studies including cytotoxicity assays and eventually confocal microscopy. The self-assembling formation of complexes between the miRNA and the group's novel peptide (TY-28, with a sequence of GGGWGPIACDIFTNSRGKRA) was examined by agarose gel electrophoresis.

**Results:** Agarose gel electrophoresis indicated an optimum positive value (~25) for nitrogen/phosphorus ratio for each peptide/miRNA nanoparticle. This was further shown by dynamic light scattering. Cytotoxicity assays showed cell viability was significantly reduced when the chosen miRNAs were introduced into DAOY and HD-MB03 cell lines, respectively with up to 61 and 51% a reduction in cell viability.

**Conclusions:** The work conducted to date shows promise and contributes to addressing the gaps in MB management. Next steps will further characterise the physicochemical properties of the nanoparticles and demonstrate their ability to deliver miRNAs into MB cells in monolayer and 3D culture settings, in a functionally relevant manner.