Getting the brain to take its medicine – using a double targeting modality for more effective delivery

Joanna Macdonald, Justin Henri, Sarah Shigdar*

School of Medicine
Deakin University
Geelong, Victoria, Australia
Sarah.Shigdar@deakin.edu.au

A quarter of all cancer patients will be diagnosed with metastatic brain cancer following primary malignancy treatment, and the prognosis for these patients is very poor. The treatment of these metastatic tumours is greatly hindered by the presence of the blood brain barrier which restricts the overwhelming majority of small molecules from entering the brain. A novel approach to overcome this barrier is to target receptor mediated transport mechanisms present on the endothelial cell membranes, in particular the transferrin receptor. Given their specificity, safety profile and stability, nucleic acid based therapeutics are ideal for this purpose. Therefore, in this study an aptamer targeting the transferrin receptor was fused with an aptamer that binds to a cell surface marker on breast cancer cells, the epithelial cell adhesion molecule (EpCAM). The initial fusion of the two sequences enhanced the binding affinity of both aptamers while maintaining specificity, which was confirmed through flow cytometry and confocal microscopy. Using an in vitro blood brain barrier model, the aptamers ability to transcytose the barrier and target a specific population of cells was confirmed through the implementation of a co-culture of EpCAM positive and negative cells. Additionally, we confirmed the aptamers ability to transcytose the blood brain barrier in a healthy mouse model as well as a xenograft model of triple negative breast cancer (MDA-MB-231-BR) following a single i.v. injection (40 nmol/kg)1. Further, we confirmed this bifunctional aptamer was able to specifically enter the brain in an animal of breast cancer brain metastases. These promising results demonstrate that through the fusion of two aptamer sequences, a bi-functional aptamer can be generated which has the potential to be developed for the specific treatment of EpCAM positive brain metastases.

References