Building a platform technology for targeted drug delivery to cancer metastases

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Prognosis for cancers of the brain, whether primary or metastasis, remains poor, even with advances in treatment for other cancers. This is due to the limited number of drugs that can cross the blood brain barrier (BBB). While methods of overcoming this barrier have been developed and employed with current treatment options, the majority are highly invasive and non-specific treatments, leading to severe neurotoxic side effects. A novel approach to address these issues is the development of therapeutics targeting receptor mediated transport mechanisms on the BBB endothelial cell membranes. We have developed aptamers as targeted delivery agents that can also cross the blood brain barrier. Aptamers are smaller than antibodies, and thus can more effectively deliver drugs into the tumour. Numerous studies have demonstrated that, despite theoretical implications of rapid renal clearance, nuclease degradation, and electrostatic repulsion, aptamers are effective agents for the delivery of cytotoxic agents. These agents can either be used as singular agents, or given their different mechanism of action and suggested lack of drug-drug interaction, alongside antibodies to have a greater efficacy against solid tumours. We have combined two aptamers for the targeted delivery of chemotherapeutics to brain metastases which can cross the blood brain barrier and also specifically target cancer cells. Using this approach, we intercalated doxorubicin into this bifunctional aptamer targeting the transferrin receptor on the blood brain barrier and epithelial cell adhesion molecule on the metastatic cells. The ability of the doxorubicin loaded aptamer to transcytose the blood brain barrier and selectively deliver the drug to epithelial cell adhesion molecule-positive tumours was evaluated in an in vitro model and confirmed for the first time in vivo. We show that co-localised aptamer and doxorubicin fluorescent signals are clearly detectable within the brain lesions 75 minutes post administration[1]. Following a short treatment schedule, brain metastases were shown to decrease following bifunctional-aptamer-doxorubicin treatment, as compared to control or free drug. As well, metastases decreased in bone and ovaries following treatment. Collectively, the results from this study demonstrate that through intercalation of a cytotoxic drug into the bifunctional aptamer, a therapeutic delivery vehicle can be developed for the specific targeting of epithelial cell adhesion molecule-positive brain and systemic metastases. We have now developed several aptamers to other promising cell surface receptors overexpressed on cancer cells and are building a platform to deliver drugs to a variety of other cancers that have metastasized, including ovarian, gastric, lung cancer and melanoma, as well as cancers developing in the brain, including glioblastoma and medulloblastoma.

References:

[1] Joanna Macdonald, Delphine Denoyer, Justin Henri, Adelaide Jamieson, Ingrid J.G. Burvenich, Normand Pouliot, and Sarah Shigdar. *Nucleic Acid Therapeutics*.2020.117-128.