Fluorinated Polymer-Iron Oxide Probes - Uniting siRNA therapeutics to Treat and MRI to Measure Response in Medulloblastoma

Helen Forgham, Jiayuan Zhu, Xumin Huang, Ruirui Qiao, and Thomas P. Davis*

The University of Queensland
Australian Institute of Bioengineering & Nanotechnology
Brisbane, QLD, Australia
H.Forgham@uq.edu.au
R.Qiao@uq.edu.au

Malignant brain cancer Medulloblastoma accounts for 20% of all paediatric brain cancers [1]. Current treatments are ineffective long-term for approximately one third of patients [1]. Additionally, survivors of medulloblastoma are routinely left with devastating side effects stemming from the therapeutic attempts made to eradicate tumours [2]. siRNA therapeutics have the potential to target oncogenic drivers through destroying mRNA encoding the corrupted protein. However, designing siRNA therapeutics for medulloblastoma is challenging. To facilitate passage across the physiological barriers that prevent access to the brain and into cancer cells a biologically tuned delivery vector must be used. Hybrid polymer-iron oxide nanoparticles (HPIO-Nps) possess notable characteristics that warrant their investigation to address these challenges. Additionally, the innate superparamagnetic property of iron oxide provides contrast for magnetic resonance imaging (MRI) and by doing so, offers the potential to track delivery efficiency at the tumour site, as well as investigation of siRNA therapeutic response over time.

In this study we have used a combination of thermo-decomposition to produce iron oxide nanoparticles (3nm) and RAFT polymerisation to produce fluorinated polymers. The final fluorinated hybrid nanoparticles (fHPIO-Nps) were formed through ligand exchange chemistry. The size and charge of fHPIO-Nps measured using dynamic light scattering was 22 nm and 24 mV, respectively. fHPIO-Nps demonstrate good colloidal stability over time (24 h) and siRNA binding efficiency and serum stability - Gel shift assay binding of 25 nM siRNA demonstrate at 10 µg iron oxide. Serum stability was observed for over 5 hours. siRNA uptake and gene silencing measured in D425 medulloblastoma cells and non-cancerous HCM3 and hMECd3 cells showed that fHPIO-Nps were able to deliver siRNA at pH 7.4, but only effective at releasing siRNA at pH 5.6 (100% gene silencing efficiency). In *in vivo* studies, where intranasal delivery was applied, fHPIO-Nps successfully delivered over 3-days an escalating quantity of Cy 5.5 labelled siRNA to the brain – first visible at 2 h; and additionally, reduced luciferase protein expression following a 3-day gene silencing programme (2.5mg/Kg, 1.5 mg/Kg, respectively). Importantly, no acute toxicity was observed throughout the treatment period, including redness, discomfort, or damage to the nasal passage. Here we present our latest exciting research findings that support ongoing work into intranasal delivery of fHPIO-Np-siRNA for medulloblastoma. Our impending studies aim to demonstrate the potential of fHPIO-Nps to deliver therapeutically active siRNA and monitor affect using MRI *in vivo*.

References:

[1] Rossi, A.; et al. *Clin Cancer Res* **2008**, *14*, 971-976
[2] Frič, R., et al. *Scientific Reports* **2020**, *10,* 9371