**Developing theranostic porous silicon nanoparticles for brain cancer treatment**

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Brain cancers are deadly. The most common aggressive form of such; glioblastoma multiforme (GBM), has a five-year survival rate of only 5 *per cent*. The mortality rate has remained the same for decades, and the bottlenecks are three-fold. Firstly, the selective permeability of the blood–brain barrier (BBB), and the inherent drug efflux mechanisms, result in poor chemotherapy effectiveness. Secondly, the aggressiveness of brain cancer leads to a diffuse tumour-tissue boundary, rendering complete surgical removal difficult. Thirdly, challenges arise from the conventional MRI of the tumour progression, owing to the non-specificity of contrast agents to brain tumour progression after medical treatment.

Harnessing the advantages of nanomedicine, this project has led to novel developments and discoveries that directly address those bottlenecks. We derived a transferrin-functionalised porous silicon nanoparticle (pSiNP) and demonstrated its capability to transverse the BBB via receptor-mediated pathways, and target-release chemotherapeutics and siRNA within GBM cells to further enhance specific killing and drug-resistance gene-downregulation in GBM cells. At the same time, contrast agent-modified pSiNP can provide better MRI contrast comparing to conventional Gadovist, highlighting that pSiNP is a valuable toolbox to improve the standard of care of brain cancer.

The migration ability of GBM cells internalised bare pSiNP were also shown to be hampered, indicating the potential of pSiNP treatment in suppressing brain cancer invasion. Importantly, pSiNP is highly tolerable and non-toxic, which foreseeably will enable more flexible treatment regiments.

In addition, this project incubated the development of a BBB organoid-on-chip platform to accurately and robustly predict and model pSiNP penetration across the BBB. This platform can potentially fast track the screening of most central nervous system therapeutics, which would otherwise be evaluated in animal models.

These developments have resulted in eight publications in high impact international journals, and attracted more than $830K of external funding from Foundation of Children and CSIRO Probing Biosystems Future Science Platforms, benefiting the development of better CNS cancers for many years to come.