Can ‘Stealth’ Coatings For Therapeutic Nanoparticles Prevent Inflammatory Responses By The Brain’s Immune Cells?

Kyle Storey, Dr Andrew Morris, Dr Stuart Jenkins* Keele University, School of Medicine *s.i.Jenkins@keele.ac.uk

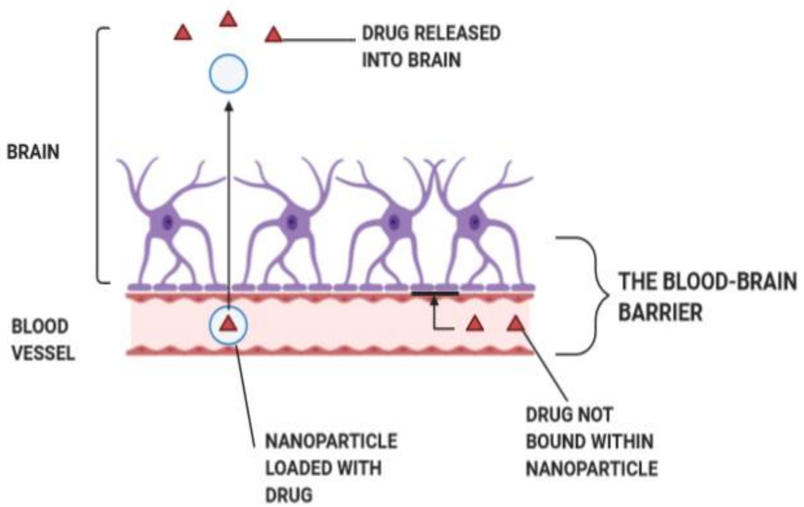
Neural Tissue Engineering Keele

Can we improve treatments for the brain?

- Neurological conditions such **as Alzheimer's disease**, or **Parkinson’s disease** are highly debilitating and lack effective treatments. These conditions can be partially treated with drugs, but many drugs **cannot** reach the brain.
- The brain is protected by the **blood-brain barrier**, a specialised separation of brain from blood, rejecting unwanted substances. Only extremely small molecules can get through… Such as **nanoparticles**!

Nanoparticles – a drug-delivery vehicle?

- Nanoparticles are versatile medical tools, used as drug delivery vehicles, with potential for treating conditions such as Alzheimer’s disease, stroke, or cancer
- Nanoparticles are small enough to get **inside** cells (like viruses do) enabling drug delivery
- But, the bodies immune cells have evolved to react to similarly-sized pathogens, ingesting and destroying them
- The blood-brain barrier and the body’s **immune cells**, are the main obstacles to overcome to enable nanoparticles to carry out their therapeutic benefit



Schematic demonstrating the blood-brain barrier, and nanoparticles loaded with drugs vs lone drugs crossing into the brain.

What happens if nanoparticles reach the brain?

- The **central nervous system** has specialised immune cells that help to protect the brain: **Microglia** and **astrocytes**,
- They dominate nanoparticle uptake inside the brain
- This **prevents** nanoparticles from releasing the drugs they carry at their desired targets, **preventing therapeutic benefit**
- If the brain’s immune cells do uptake the nanoparticles, what effect is this having on the **brain environment**?
- Is it causing **inflammation**? This can damage tissue
- **Dementia**-associated conditions and infections (such as meningitis) are **associated** with **inflammation**
- Could treatment with nanoparticles make things **worse**?

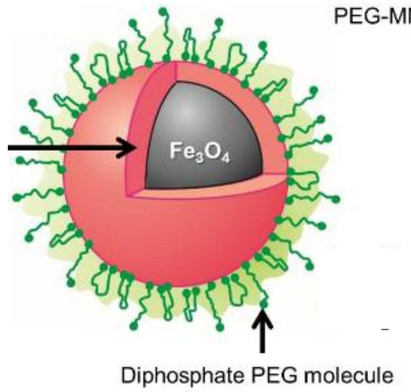
Brain immune cells dominate nanoparticle uptake: a problem?

Coloured microscopy images showing uptake for carboxymethyl dextran (CMX) coated nanoparticles (stained as red) for different types of cells in the brain. The brain’s immune cells (top two images) show the highest internalisation.
Jenkins *et al*., 2016, *J Controlled Release, Volume 224: Pages 136-145*

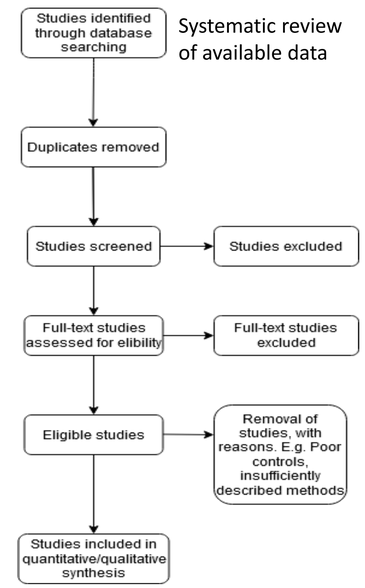
Can we prevent nanoparticle uptake by these immune cells and ensure they have their desired effect?

Could ‘STEALTH’ COATINGS limit immune clearance?

- Immune cells use proteins in the blood to recognise and attack things that are **non-self**
- Stealth coatings on the **outer surface** of nanoparticles prevent those proteins from binding and help **“hide”** the nanoparticle
- Stealth coatings have been shown to limit **peripheral** (not the brain) clearance, and **help cross the blood-brain barrier**
- We do not know how **microglia** and **astrocytes** react to stealth nanoparticle internalisation
- Do they become **inflammatory**? Potentially **causing damage**?



Stealth-coatings (e.g. polyethylene glycol, PEG) resist formation of a protein corona/shell, reducing immune uptake. But do they influence immune responses?
Jenkins, *et al*., 2016, *J Controlled Release, Volume 224: Pages 136-145*



Project: systematic review of literature, comparing neuro-immune responses to ‘stealth’ coated nanoparticles

- A literature search of published data will be carried out, identifying reports with **well characterised nanoparticles** and relevant **immuno-assays**, to identify potential properties associated with a **lack of toxicity** and i**nflammation**
- Once the data is assessed, **experimental** nanoparticles will designed **with** these features, and tested with neural cell cultures. This review and any data gathered could inform **future nanoparticle design for translating nanoparticle-mediated therapies to the clinic.**