Selective targeting of Plaque Associated Microglia through systemic dendrimer administration in an Alzheimer's disease model

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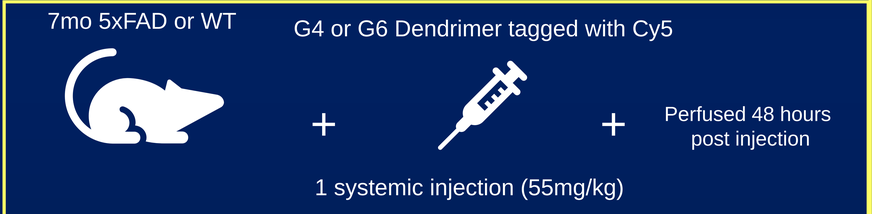
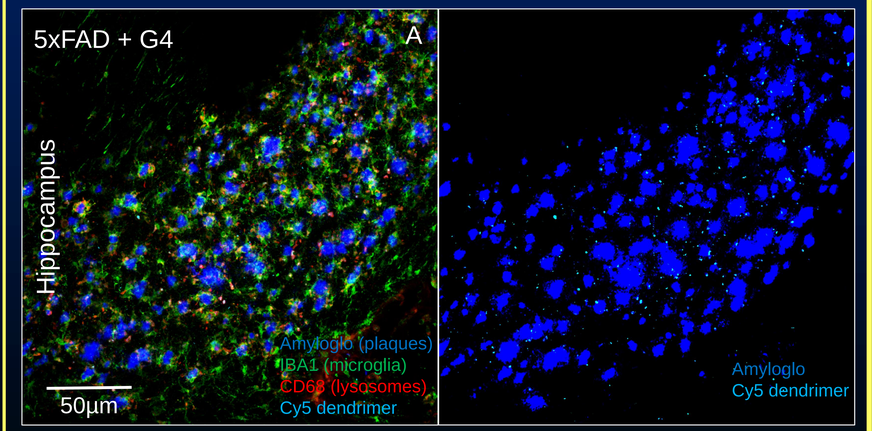
Introduction

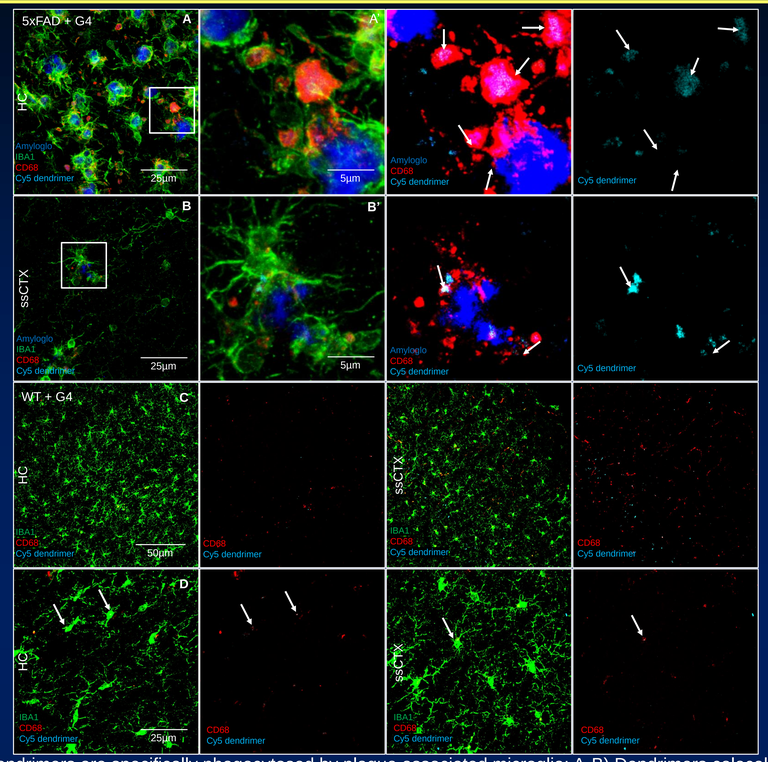
- Alzheimer's disease (AD) is a progressive, age-related neurodegenerative disorder that is triggered by the appearance and build-up of amyloid-β (Aβ) plaques in the cortex. Our lab and others have shown that microglia play an integral role in plaque formation and homeostasis.
- Currently, the role of plaque associated microglia in AD is unclear as brain wide microglial gene deletion and overexpression studies have shown contradicting results.
- Thus, there is a critical need to specifically target and modulate plaque-associated microglia over homeostatic microglia.
- Dendrimers are highly-branched, symmetric, and repetitive molecules which have been used clinically for nucleic acid and drug delivery in cancer.
- In the context of AD, however, dendrimers have not been well studied. Dendrimers have only been shown to cross the BBB during times when pathological insults such as stroke or traumatic brain injury compromise the BBB. In AD, traditional dendrimers do not bypass the BBB
- Recently, hydroxyl polyethylene glycol dendrimers have shown promise in bypassing the BBB and were shown to be taken up specifically by macrophages.
- In the AD brain, plaque associated microglia are the primary macrophages.
- Here, using generation 4 (G4) and generation 6 (G6) dendrimers, we sought to determine whether polyethylene glycol hydroxyl dendrimers can successfully bypass the BBB and be specifically taken up by microglia in the context of AD.
- Establishing the effectiveness of these dendrimers in targeting plaque associated microglia will allow us to tailor appropriate therapies towards this subset of microglia and develop therapeutic treatments with a greater precision.



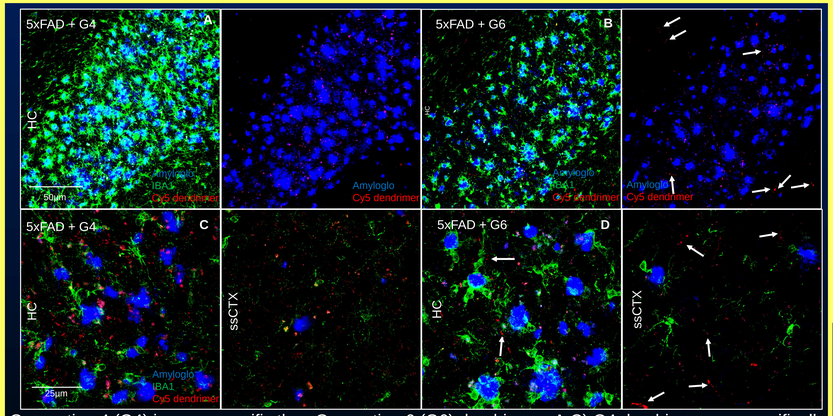
Experimental Design: 7mo 5xFAD mice were systemically injected with polyethylene glycol hydroxyl dendrimers conjugated to a Cy5 fluorophore. Mice were then perfused 48 hours and tissue was analyzed through immunohistochemistry. G4 dendrimers are smaller and less complex than G6 dendrimer



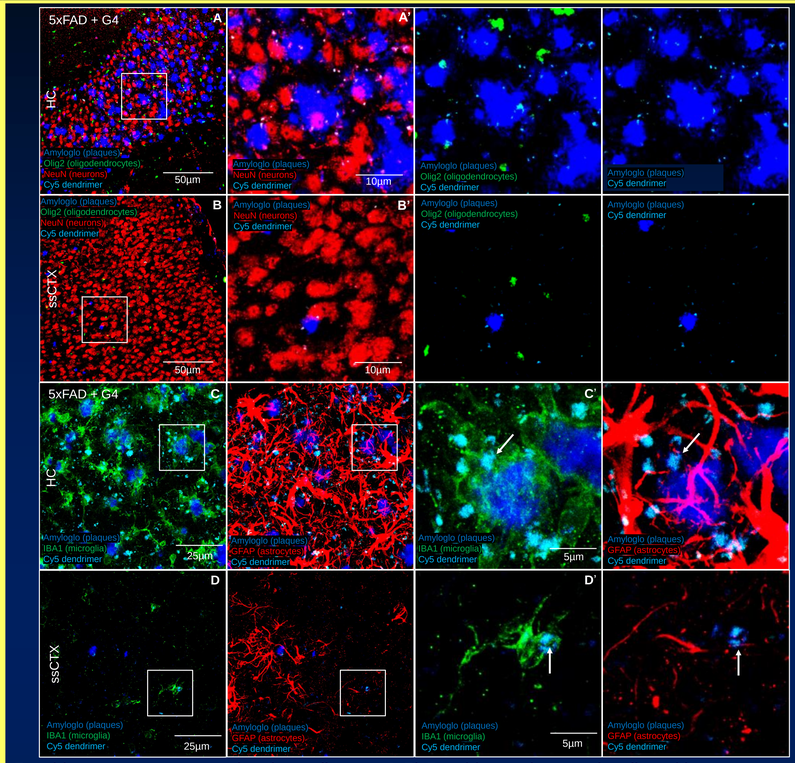
Systemically injected hydroxyl polyethylene hydroxyl dendrimers cross the blood-brain barrier and are plaque associated.



Dendrimers are specifically phagocytosed by plaque associated microglia: A-B) Dendrimers colocalize with microglial lysosomes in the hippocampus (A) and somatosensory cortex. C-D) In wild-type mice, trace amounts of dendrimers enter the brain, and are rarely taken up by microglia. Boxes represent area of interest magnified in A' and B', respectively. Arrows indicate areas where dendrimers colocalize with microglial lysosomes.



Generation 4 (G4) is more specific than Generation 6 (G6) dendrimers: A,C) G4 dendrimers are specifically taken up by plaque associated microglia as seen at 20x (A) and 63x (C) magnifications. B,D) G6 dendrimers are taken up by plaque associated microglia, but are also present in the blood vessels at 20x (B) and 63x (D) magnifications. Arrows indicate areas where dendrimers colocalize with blood vessels.



Dendrimers are not present in other cell types: A-B) Dendrimers do not colocalize with oligodendrocytes or neurons in the hippocampus (A) and somatosensory cortex (B). C-D) Dendrimers do not colocalize with GFAP labelled astrocytes in the hippocampus (C) and somatosensory cortex (D). Boxes represent area of interest magnified in A', B', C', and D', respectively. Arrows indicate instances where dendrimer colocalize with microglia and not astrocytes

Conclusions

- Systemically injected polyethylene glycol hydroxyl dendrimers cross the blood-brain barrier and primarily are plaque associated in a 5xFAD mouse model of AD.
- Plaque associated microglia phagocytose these dendrimers into their lysosomes.
- The dendrimers are not phagocytosed by homeostatic microglia and show little penetrance in the WT brain
- G4 dendrimers show greater promise in specifically targeting plaque associated microglia
- The dendrimers do not colocalize with GFAP astrocytes, oligodendrocytes, or neurons.
- Altogether, polyethylene glycol hydroxyl dendrimers demonstrate the potential to target and treat plaque associated microglia in AD.
- Future studies will look at the therapeutic value of these dendrimers in AD through dendrimer-drug conjugation.

Acknowledgements

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