Breaking Barriers in Brain's Health: Liposomes against Neurodegeneration

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Parkinson's disease (PD) is one of the most common neurodegenerative condition, with limited treatment options. The disease is characterized by the loss of dopaminergic neurons and abnormal accumulation and propagation of the neuronal protein alpha-synuclein (AS). An anti-AS antibody (SynO4) has previously shown a high affinity to AS aggregates,[1] suggesting that it can be used as a therapeutic agent to slow PD progression. However, SynO4's penetration into the brain, similarly to other antibodies, is very limited by the highly selective blood-brain barrier (BBB) (only around 0.01% of the injected dose penetrates the BBB), thereby curbing its therapeutic efficiency.[2] In addition, antibodies are limited with their ability to enter cell membranes and specifically neurons. This is a major obstacle for an effective reduction of intracellular AS aggregates and oligomers. During PD, the transferrin receptor is overexpressed on the BBB and in CNS neurons.[3] To overcome the brain-penetration challenge, we encapsulated the therapeutic Syn-O4 antibody within 100-nm lipid nanoparticles decorated with transferrin on their surface (Figure 1)[4]. Transferrin nanoparticles loaded with SynO4 demonstrated enhanced penetration across a supported BBB model and higher neuron cellular uptake and target engagement to intracellular neuronal alpha-synuclein aggregates compared to free SynO4. The efficacy of the TF-SynO4-lipo was tested in primary cortical neurons infected with a viral vector overexpressing A53T alpha-synuclein. The cells were treated overnight with either TF-SynO4-lipo or the free form of the mAb. TF-SynO4-lipo treatment reduced AS aggregation level significantly compared to PD-induced cells or free mAb treatment. Furthermore, *in vivo* studies show that systematic administration of transferrin-targeted liposomes efficiently crossed the BBB and were delivered to the neuronal cells in an AAV-based PD-like mouse model. The nanoparticles improved the therapeutic efficacy, including reducing AS aggregation and neuroinflammation. Taken together, the use of transferrin SynO4 liposomes and their ability to encapsulate therapeutic antibodies represents a promising therapeutic approach and a novel platform for effective drug delivery into the brain. Thereby, they can be considered an improvement of the treatment of PD and other neurodegenerative and CNS disorders[4].

References

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Figures

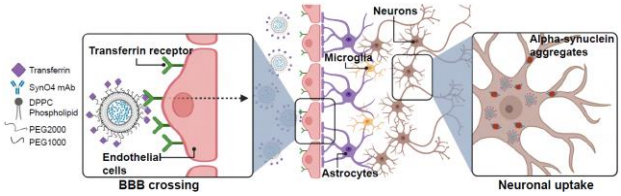

Figure 1. Brain targeted liposomes deliver anti-alpha-synuclein monoclonal antibody to reduce aggregation of alpha synuclein in early stage Parkinson disease mouse model. Through receptor-mediated transcytosis, the liposomes cross the BBB and are taken up by disease neuron cells; the antibody payload then targets the AS aggregation to inhibit neuron cell death.