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Development of microRNA encapsulated extracellular vesicles for *in vivo* treatment

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Abstract

Extracellular vesicles (EVs) transfer critical information for intercellular communication and function by releasing cargo microRNA (miRNA) into target acceptor cells. Upon vesicle fusion, miRNAs regulate gene function and translation and can influence complex genetic networks by inhibiting multiple messenger RNA (mRNA) transcripts. However, it is unknown how EVs transport miRNAs to alter synaptic function in the brain. The brain-enriched miRNA-137 (miR-137) is one of the strongest schizophrenia (SCZ)-associated genetic risk variants. Moreover, the gene targets of miR-137, including FMR1 and SYT1, are strong modulators of synaptic function. Therefore, effects of miRNA-137 treatment could suggest how synaptic function can be altered by specific EV cargo. Furthermore, lipid-based nanoparticles that are able to cross the blood brain barrier—such as EVs—may provide a useful therapeutic tool to target central nervous system disorders such as SCZ.

We have transfected a mouse neuroblastoma cell line (Neuro2A) with three different engineered plasmids causing over-expression miR-137, the antisense sequence designed to disinhibit target mRNA sequences, and a scramble miRNA control. We can reliably isolate EVs within the 50-200nm size range through size exclusion chromatography, quantify fluorescently labeled vesicles using nanoparticle tracking analysis, and characterize EVs with specific markers by western blot protein analysis. Future studies will include investigating the regulation of target gene and protein expression after miR-137 overexpression *in vivo*. Furthermore, we will begin intranasal treatment with EV miR-137 and explore its effects on synaptic function and behavior.