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Opinion Article

Exosome-Mimetic Nanovesicles for RNA Delivery across the Blood-Brain Barrier: Implications for Neurodegenerative Disease Treatment

Thierry Philip*

Department of Chemical Engineering and Biotechnology, University of Oxford, Oxford, United Kingdom

DESCRIPTION

The Blood Brain Barrier (BBB) remains a formidable obstacle in the development of effective therapeutics for neurodegenerative disorders. While various nanoparticle formulations have demonstrated some success in BBB penetration, efficiency and specificity remain significant challenges. Our research presents a novel approach utilizing Exosome Mimetic Nanovesicles (EMNVs) engineered to closely resemble naturally occurring exosomes while incorporating specific targeting capabilities for enhanced BBB penetration and neuronal delivery of therapeutic RNA cargoes. These synthetic vesicles, approximately 80nm-120nm in diameter, were fabricated through sequential extrusion of neuroblastoma cells pretreated with neurotropic factors to enrich for specific membrane proteins known to facilitate BBB transcytosis.

Comprehensive proteomic characterization of our EMNVs confirmed enrichment of key BBB-penetrating proteins, including transferrin receptor, low-density Lipoprotein Receptor-Related Protein 1 (LRP1), and Glucose Transporter 1 (GLUT1). Additionally, we observed high expression of neuronal targeting proteins such as Neural Cell Adhesion Molecule (NCAM) and Rabies Virus Glycoprotein (RVG) like peptides. Small RNA sequencing revealed negligible endogenous microRNA content following RNase treatment and ultracentrifugation, creating an ideal blank slate for therapeutic RNA loading. Using an optimized electroporation protocol, we achieved approximately 78% encapsulation efficiency for siRNA targeting mutant Huntingtin (mHTT), a key pathogenic protein in Huntington's disease, without significant alterations to vesicle integrity or surface protein functionality.

In vitro BBB models utilizing human brain microvascular endothelial cells demonstrated superior transcytosis capabilities of our EMNVs compared to conventional liposomal formulations and unmodified exosomes isolated from various cell sources. Transwell experiments showed approximately 27% penetration of fluorescently labeled EMNVs across the endothelial barrier within 6 hours, compared to only 8% for standard liposomes. Subsequent co-culture experiments with primary cortical neurons confirmed both effective uptake of transcytosed vesicles and functional delivery of siRNA cargo, resulting in approximately 62% knockdown of target mRNA expression. Importantly, these EMNVs demonstrated minimal inflammatory activation of microglia and astrocytes, suggesting excellent biocompatibility within the Central Nervous System (CNS) microenvironment.

Biodistribution studies in wild-type mice revealed substantial brain accumulation following intravenous administration, with approximately 4.3% of the injected dose detected in brain tissue at 24 hours post-injection, a significant improvement over conventional delivery systems typically achieving less than 1% brain delivery. Confocal microscopy of brain sections confirmed widespread distribution throughout the cortex and striatum, with particular enrichment in neurons rather than glial cells. In the R6/2 transgenic mouse model of Huntington's disease, biweekly administration of mHTT-siRNA-loaded EMNVs resulted in approximately 68% reduction in mutant huntingtin protein expression throughout the striatum, accompanied by significant improvements in motor function and survival compared to control groups.

CONCLUSION

Safety evaluations revealed no significant alterations in blood chemistry, complete blood counts, or histopathological findings across major organs following repeated administration. Additionally, multiplex cytokine analysis demonstrated minimal inflammatory activation compared to lipid nanoparticle formulations currently in clinical development. The scalability of this platform was confirmed through successful production using a GMP-compatible methodology yielding consistent vesicles with batch-to-batch variation below 10% for all essential quality attributes. These exosome-mimetic nanovesicles represent a promising approach for RNA-based therapeutics across the BBB, potentially addressing a critical unmet need in the treatment of various neurodegenerative disorders where altered protein expression contributes to pathogenesis.

Correspondence to: Thierry Philip, Department of Chemical Engineering and Biotechnology, University of Oxford, Oxford, United Kingdom, E-mail: thierryphilip08@gmail.com

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