Intranasal lipid nanoparticles for targeted mRNA delivery to the brain in neurodegenerative diseases

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The complexity of the brain, together with its blood–brain barrier (BBB), poses a major challenge for the biodistribution of therapeutic molecules. In recent years, gene therapy, particularly mRNA-based technologies highlighted during the COVID-19 pandemic, has emerged as a powerful platform for the development of novel treatments. In this context, lipid nanoparticles (LNPs) have gained significant attention as promising drug delivery systems for neurodegenerative diseases (NDs) [1].

The intranasal route represents a promising alternative for direct brain delivery, as it bypasses the BBB. This non-invasive and patient-friendly approach enables repeated or self-administered dosing, improving therapeutic adherence. Additionally, by avoiding first-pass metabolism, it enhances bioavailability and reduces systemic side effects, making it suitable for mRNA-based treatments.

The development of effective intranasal LNP formulations for NDs requires optimization of particle size, surface charge, and lipophilicity, as well as ensuring stability in the nasal environment. Furthermore, the selection of appropriate delivery devices and consideration of disease-specific factors are essential. Standardized protocols and rigorous biosafety evaluations are also critical to facilitate clinical application [2].

The aim of this work is to develop and optimize a LNP formulation capable of achieving efficient gene delivery to the brain while maintaining stability, biocompatibility, and suitability for non-invasive administration. Initially, three LNP formulations with distinct lipid compositions were evaluated for cellular uptake and transfection efficiency in BV2 cells. The most promising candidate was selected for *in vivo* studies to assess the biodistribution of the LNPs across different brain regions.

The physicochemical properties of the LNP formulations were consistent. However, the formulation showing the highest cellular uptake and transfection efficiency (F2) demonstrated consistently higher transfection efficiency under all tested conditions in the BV2 cell line. *In vivo* studies showed that the intraparenchymal administration in the striatum and the *SNpc* enable effective transfection of viable cells. Notably, intranasal administration of the F2 LNPs resulted in transfection of brain regions relevant to Alzheimer's disease and Parkinson's disease.

These results demonstrate that intranasal administration of optimized F2 LNPs enable targeted gene delivery to key CNS areas. This approach provides a strong foundation for the development of novel therapeutic strategies for major neurological disorders, leveraging the advantages of minimally invasive and region-specific delivery.

Literature:

[1] Shukla AK, Nilgirwar PS, Bali SD. Chapter 5 - Current pharmacological treatments for neurodegenerative diseases. In: Koduru TS, Osmani RAM, Singh E, et al., editors. The neurodegeneration revolution. Cambridge: Academic Press, Elsevier; 2025. p. 117–126. doi: 10.1016/B978-0-443-28822-7.00005-2.

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Short CV:

Francesc Xavier Mulet i Piera holds a Bachelor's degree in Biochemistry and Biomedical Sciences from the University of Valencia, and a Master's Degree in Research, Development and Innovation of Drugs from the University of Navarra. He is currently pursuing his PhD at the Department of Pharmaceutical Sciences at the University of Navarra, where his research focuses on the development and characterization of RNA-loaded lipid nanoparticles (RNA-LNPs) for intranasal brain delivery. His work aims to evaluate their therapeutic potential in Parkinson's disease. In parallel, he is developing a novel neuromelanin-based mouse model of Parkinson's disease that closely reproduces key histological features observed in human patients. By combining innovative drug delivery approaches with more physiologically relevant disease models, his research aims to bring experimental therapies closer to clinical application.