PhD proposal: LUE Interdisciplinaire

New Generation of Nanoliposome as Delivery System for Aging Brain Function (IMAGIN)

The impact of lifetime dietary habits and their role in physical, mental, and social well-being has been the focus of considerable research in recent years. Omega-3 (n-3) polyunsaturated fatty acids (PUFA) have been dietary components under the spotlight for decades. Indeed, as key regulating factors of neurotransmission, neurogenesis, and neuroinflammation, n-3 PUFA are fundamental in the development and function of the central nervous system (CNS) during aging. Of these n-3 PUFA, docosahexaenoic acid (DHA) (C22:6 n-3) is the most prevalent n-3 fatty acid in the brain tissue, and its deficiency has been linked to several neurocognitive disorders including anxiety-like behavior, major depressive disorder, schizophrenia with psychosis, impaired attention-span, and in particular, Alzheimer's disease (AD). Finding effective therapies for CNS disorders is one of the top priorities in Europe and worldwide. Moreover, the combinatorial effects of essential PUFAs on neuronal function are not yet clearly understood. We have developed natural lecithin rich in 15 different fatty acids (saturated, mono- and polyunsaturated) including DHA, eicosapentaenoic acid (EPA), linoleic, linolenic, and arachidonic acids, a composition that is very similar to that found in brain membrane phospholipids. Nanoliposomes derived from this natural lecithin, by virtue of their biomimetic composition similar to that of cell membranes, are biodegradable and biocompatible. They could thus demonstrate not only beneficial effects by themselves for the CNS, but could also potentially serve as drug carriers for targeted delivery through the blood brain barrier (BBB) to the CNS. We engineered nanoliposomes with controlled size from this natural product, herein called F22, which demonstrated positive effects in stimulating neurite outgrowth, network formation and activity in neuronal cultures (1). One of the aims of this project is to pursue these findings and test the potential neuroprotective effects of these biomimetic nanoliposomes in cell and animal models for AD. In order to achieve the overall objective of this multidisciplinary project, four laboratories will be associated. The objective of this project will be to study the efficiency and behavior as active drug delivery vectors of the targeted nanoliposome structures with controlled design and lipid composition, as well as the effects of these new potentially brain-active drugs on neuronal activity in cell and animal models. The results obtained will be used to engineer a biomimetic human-based model of the CNS that will provide the means for efficient and rapid pre-clinical testing of potential brain-targeted therapeutic compounds for AD.

1. Passei, E. et al. (2021). *International Journal of Molecular Sciences*, 22(21):11859.
2.Latifi, S. et al. (2016). Natural lecithin promotes neural network complexity and activity, Scientific Reports, 6, 25777.
3.Linder, M. et al. (2002). Enrichment of salmon oil with n-3 PUFA by lipolysis, filtration and enzymatic re-esterification. European Journal of Lipid Science and Technology 104, 455-462.
4. Colin, J. et al. (2017). Maintenance of membrane organization in the aging mouse brain as the determining factor for preventing receptor dysfunction and for improving response to anti-Alzheimer treatments. *Neurobiol Aging*, 54 :84-93.
5. Colin, J. et al., (2016). Improved neuroprotection provided by drug combination in neurons exposed to cell-derived soluble amyloid-β peptide. *J Alzheimers Dis.* 52:975-987.

This project is divided into several key steps:

1- Preparation of F22 (nanoliposomes from salmon lecithin), extracted from salmon heads through an enzymatic process.
2- Formulation of nanoliposomes as drug carrier by conjugation of selected peptides to the nanoliposome surface either before or after the nanoliposome preparation. PEGylated nanoliposomes will be functionalized with ligands including apolipoproteins to target receptors expressed on endothelial brain microvessels.
3- Encapsulation of curcumin in nanoliposomes. Curcumin is an active molecule with anti-inflammatory and antioxidant properties shown to provide beneficial effects to brain health, including reducing neurodegeneration in Alzheimer's disease. Characterization of curcumin-encapsulated nanoliposomes: various physico-chemical properties of active vectors will be determined (size, charge, morphology, etc).

4- Evaluation of neurotrophic and neurotoxic effects of the vectors with and without encapsulation in primary cultures of cortical neurons.
5- Studies of the different hybrid nanoliposome formulations and encapsulations as preventive or curative treatments against neurotoxicity, synaptotoxicity and apoptosis in *in cellulo* models and *in vivo* for Alzheimer's disease following induction of amyloid and/or oxidative stress in neurons.

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PROFILS: PHYSICO-CHEMISTRY, BIOLOGY