Hybrid Nanomedicines for the Central Nervous System: Optimization, Targeting, and Scale-up

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Nanomedicines (NMeds) are one of the most versatile and investigated tools to ameliorate the therapeutic approach for difficult-to-treat pathologies, such as neurodegenerative diseases, thanks to high drug loading, protection of the cargo, and specific targeting. The retina is a difficult-to-reach tissue that is part of the Central Nervous System (CNS) and it is protected by several barriers. To deliver a neuroprotective peptide to the retina, hybrid NMeds composed of poly(lactic-co-glycolide) (PLGA) and lipids were optimized and coated with Hyaluronic Acid (HA) to improve biocompatibility upon intravitreal injection. The optimized NMeds were then embedded in a thermosensitive hydrogel that solidifies *in vivo* after administration, to obtain a depot system that can delay the mobility of NMeds for up to 36h.

For CNS delivery, hybrid NMeds were optimized using PLGA and Cholesterol, and decorated on the surface with the BBB-targeting peptide g7. These NMeds demonstrated high efficacy in delivering Cholesterol to the brain of Huntington's disease mice models, rescuing both the motor and cognitive impairment in symptomatic and pre-symptomatic animals. These NMeds require to be scalable before preclinical studies. Formulation of those NMeds was investigated with a microfluidic device that would improve scalability. Unfortunately, our results demonstrated that the translatability of a benchtop protocol to a microfluidic device is not linear and requires a huge work to obtain the same characteristics of the already optimized NMeds.

Altogether, these results confirm that hybrid NMeds are promising tools for innovative treatments, but the scalability via microfluidic technology must be adequately and individually investigated.