Nanoparticles crossing the blood-brain barrier for cholesterol delivery to Huntington's disease brain

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Huntington disease (HD) is a rare, inherited adult-onset disease caused by an expansion of CAG repeats in the huntingtin gene. HD is characterized by cognitive, motor and psychiatric symptoms. At the cellular level, mutant huntingtin results in neuronal dysfunction and death mainly of striatal neurons and cortical neurons projecting to the striatum.

HD is associated with reduced cholesterol synthesis in the brain, especially in the striatum (Shankaran, 2017). The enhancement of endogenous cholesterol biosynthesis in the striatum through a gene therapy approach restores synaptic transmission, reduces mutant huntingtin aggregates and attenuates behavioural deficits in a transgenic HD mouse model (Birolini, 2021).

To counteract the negative consequences of reduced cholesterol synthesis, strategies aimed at supplementing exogenous cholesterol to the HD brain have been investigated (Valenza, 2015; Birolini, 2020). However, delivering cholesterol to the brain is challenging due to the blood-brain barrier, which prevents it from reaching the brain. Here we describe a new generation of brain permeable nanoparticles optimized to deliver a therapeutic dose of cholesterol to the brain of HD mouse models. These NPs rapidly reach the brain and target neurons and glial cells. Moreover, cholesterol is released in a controlled manner within the brain and accumulates over time, while being rapidly removed from peripheral tissues and plasma. The systemic and repeated injections of these NPs prevent cognitive decline, and ameliorated motor defects in HD animals, without any inflammatory reaction. In summary, these findings highlight the potential benefit and safety of cholesterol delivery through advanced brain-permeable nanoparticles for HD treatment.

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