**Neuronal Membrane-Coated Mesoporous Ceria Nanoparticles for Blood−Brain Barrier Crossing and Mitigation of Neurodegeneration**

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**Background and aims.** The clinical translation of neurodegenerative therapeutics has been hindered by the restrictive blood-brain barrier (BBB), limiting the free access of antigens and therapeutics to the brain parenchyma, thereby limiting their therapeutic efficacy. Addressing this challenge, we have developed a biologically inspired nanoformulation using a neural cell membrane and mesoporous ceria nanoparticles (NM@MCN-MM) for enhanced antioxidant activity and neuroprotection.

**Methods.** NM@MCN-MM was synthesized by fabricating mesoporous ceria nanoparticles using a soft template method, followed by encapsulation within Neuro-2a (N2a) cell membranes. The formulation was characterized for morphology, size, entrapment efficiency, *in vitro* release behaviour and stability. Intracellular uptake was assessed through flow cytometry and confocal microscopy. The BBB permeability was determined *in vitro* using a static transwell model. Neuroprotective efficacy was evaluated by assessing mitochondrial dysfunction, oxidative stress, and calcium imbalance, common hallmarks of neurodegenerative diseases. The brain targeting properties were assessed through LC-MS/MS and optical live imaging using indocyanine green as a fluorescent probe.

**Results.** NM@MCN-MM exhibited preserved biomimetic activity, potent antioxidative properties, and the ability to mitigate key pathological features of neurodegeneration. The cell membrane coating enhanced systemic circulation, reduced immunogenicity, and improved BBB permeation and brain homing. These findings suggest the formulation’s potential to address the multifactorial challenges in neurodegenerative diseases. The *in vitro* BBB permeability, determined through a static model of cultured astrocytes and brain endothelial cells, provided compelling evidence of the formulation’s potential to pervade the BBB *in vivo*. The pharmacokinetics and brain distribution study performed on C57BL/6 mice following intravenous administration emphasize the system’s attributes, such as high bioavailability, low clearance, and high brain uptake compared to the free drug.

**Conclusion/Discussion.**The NM@MCN-MM nanoformulation demonstrates significant promise as a brain-targeted antioxidant and neuroprotective strategy for neurodegenerative disorders, with the potential for broader therapeutic applications in neurodegeneration.