Targeted Brain Delivery of Nrf-2 Gene and ?-Synuclein Binding Peptide using Functionalised Gold Nanoparticles for Disease-modifying Therapy of Parkinson’s Disease

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Institution
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Parkinson's disease & PD-related disorders

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Research Abstract
Parkinson’s disease (PD) is a chronic and debilitating neurodegenerative movement disorder that is set to rise in incidence with a rapidly ageing global population. As current clinical treatments offer only symptomatic control with no curative options, there is an urgent need for novel therapeutic approaches that can delay further neurodegeneration and enhance the overall quality of life in PD patients. Recent emerging evidence on the prion-like spreading neuronal accumulation of misfolded ?-synuclein proteins as well as the oxidative stress induced demise of dopaminergic neurons have revealed promising molecular targets for potential disease modifying therapies. Capitalising on the facile synthesis, low cytotoxicities and unique optical properties of gold nanoparticles (AuNPs), we propose the development of two types of novel AuNPs bearing leptin-receptor targeting peptides, namely (a) leptin-poly(ethylene glycol)(PEG)-poly(ethyleneimine)(PEI)-AuNP and (b) ?-synuclein inhibitor-/leptin-PEG-AuNP for the respective delivery of the Nrf-2 antioxidant gene (pNrf-2) and ?-synuclein peptide inhibitor across the blood brain barrier (BBB). In this study, detailed physicochemical characterisation as well as the evaluation of the cytotoxic and inflammatory properties of the functionalised AuNPs will be studied in a panel of brain-relevant cell types. The BBB permeability of the functionalised AuNPs and pNrf-2 complexes will be evaluated in a well-characterised in vitro transwell co-culture model; with cellular localisation examined using advanced microscopic techniques. The neuroprotective effects of inhibiting ?-synuclein aggregation and upregulation of Nrf-2 antioxidant proteins using the functionalised AuNPs will be examined in a dopaminergic cell line. It is envisioned that upon the successful establishment of their respective neuroprotective effects, both types of functionalised AuNPs could be simultaneously administered for maximal clinical benefits.

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