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NANOCARRIERS FOR NOSE-TO-BRAIN, NON-INVASIVE DELIVERY OF GENE THERAPY

Juan Sanchez-Ramos[1], Shijie Song[1], Xiaoyuan Kong[1], Gary Martinez[2], Shyam Mohapatra[3], Subra Mohapatra[4], Reka A Haraszti[5], Anastasia Khvorova[5], Neil Aronin[5], Vasyl Sava[1]

[1]University of South Florida, USA
[2]Moffitt Cancer Center and Research Institute, USA
[3]Nanomedicine Research Center, USA
[4]Department of Molecular Medicine, USA
[5]RNA Therapeutics Institute-UMASS, USA

The intranasal route of drug delivery has traditionally been used to administer small, lipophilic drugs that are rapidly absorbed into capillaries of the nasal epithelium, resulting in rapid onset of CNS actions. Many neuro-therapeutic agents, especially polynucleotides and proteins, do not readily cross the blood-brain barrier and cannot survive intact in the gut or blood. Hence, gene therapy for brain disorders has required direct neurosurgical microinjection or infusion into brain or cerebrospinal fluid. However, recent research has demonstrated direct nose-to-brain delivery of relatively large molecules, including neurotrophins (NGF and insulin-like growth factor [IGF]-1), neuropeptides, cytokines (interferon β-1b and erythropoietin as well as polynucleotides (DNA plasmids and genes). The present report describes development of a novel manganese-chelate nanocarrier system for direct nose-to-brain delivery of small interfering RNA (siRNA) or DNA. The manganese (Mn) chelate Mangafodopir served 2 functions: 1) as a marker of the NPs for intracerebral tracking with magnetic resonance imaging (MRI) and 2) as a cross-linker of the chitosan matrix in the nanocarrier structure. Using high field small animal MRI, the Mn-tagged NPs were visualized on T1-weighted images and were found to penetrate from nasal epitheliaum into olfactory bulb and across brain regions following intranasal instillation of the nanocarriers. In addition, Mn content of the nanocarrier did not impede the functional activity of siRNA directed against green fluorescent protein eGFP in transgenic green mice. Expression of eGFP mRNA in transgenic green mice was decreased by at least 50% in four brain regions. Those brain regions also exhibited significantly increased Mn signal in T1-weighted MR images. In separate experiments, we showed that mNPs loaded with dsDNA encoding the red fluorescent protein (RFP) was expressed in corpus striatum and other regions following intranasal administration. Hence, this novel nanocarrier system permitted *in vivo* tracking of the therapeutic agent and was effective in delivering nucleic acid payloads that exhibited the expected activity in brain tissue.

Biography

Juan Sanchez-Ramos received a PhD in Pharmacology and Physiology from the University of Chicago and a Medical Degree (MD) from the University of Illinois. He trained in Neurology at the University of Chicago and as a Fellow in Movement Disorders at the University of Miami. Currently, he is a Professor of Neurology at the University of South Florida in Tampa where he holds the Helen Ellis Endowed Chair for Parkinson's disease Research and is Director of the HDSA Center of Excellence for Huntington's disease. He is also Medical Director of the non-profit Parkinson Research Foundation based in Sarasota FL. In addition to teaching and attending to patients with Movement Disorders, he has directed basic research projects in neurodegeneration, neurotoxicology, adult stem cell biology and presently is focused on novel approaches for non-invasive delivery of gene therapy to brain.

jsramos@health.usf.edu