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Abstract

Approximately 12,000 new spinal cord injuries (SCI) occur in the United States each year, in addition to an existing patient population of approximately 243,000. The majority of those sustaining a SCI are young and healthy with life expectancies and lifetime medical costs ranging from approximately 20-40 additional years and $800,000 to $2,400,000, respectively. Spinal cord injury (SCI) leads to permanent motor and sensory deficits resulting from the regenerative failure of damaged axons. Strategies for improving axonal regeneration include antagonism of growth- inhibitory molecules and their receptors; delivery of growth-promoting stimuli through cell transplantation and neurotrophic factor delivery; and manipulation of cyclic nucleotide levels. While all these approaches have achieved varying degrees of improvement in plasticity, regeneration, and function; it is clear that no single therapeutic will achieve adequate functional recovery. Recently, combinatorial strategies incorporating two or more of the above therapeutic modalities have achieved synergistic increases in axonal regeneration and functional recovery. In order to realize the full potential of combinatorial therapy, there is a need for the development of platform technologies capable of simultaneously delivering multiple bioactive molecules targeting different barriers to axonal regeneration. The objective of this proposal is to develop novel neuron-specific nanotherapeutics for combinatorial therapy of drug and small interfering RNA (siRNA) targeting both extrinsic and intrinsic barriers to promote axonal regeneration. The approach is based upon 1) anti-NgR1 antibody (Ab) conjugated to the nanoparticle surface that will specifically deliver the nanotherapeutics to neurons and interfere with the function of existing NgR1 receptors by antagonizing the binding of myelin-associated inhibitors, 2) RhoA siRNA to block the common intracellular signal transduction pathways responsible for both myelin- and CSPG-mediated growth inhibition, and 3) rolipram (Rm), a phosphodiesterase 4 (PDE4) inhibitor to increase intrinsic neuronal growth capacity by preventing injury-induced reductions in cAMP levels. The central hypothesis is that these neuron-specific nanotherapeutics will improve axonal regeneration and functional recovery following SCI. We formulated this hypothesis, in part, based upon our strong preliminary data, which show that poly (lactide-co-glycolide)-graft- polyethylenimine (PgP) and IgG-conjugated PgP (PgP-Ab) are efficient carriers for both plasmid DNA and siRNA capable of transfecting neural cell lines and primary neurons *in vitro*, as well as endogenous spinal cord cells *in vivo*.