A Nanocomplex Carrying siRNA Targeting TNFα with Potential to Blunt the Neuroinflammation that Underlies Opioid Tolerance

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Although opioids like morphine and fentanyl remain the most effective of pain medications, these drugs have serious side effects that include development of tolerance *i.e.*, the requirement for ever-increasing doses to maintain analgesia. Tolerance is a harbinger of drug addiction. According to the "proinflammatory hypothesis of drug abuse", opioids (and other addictive substances) trigger neuroinflammation *via* release of proinflammatory cytokines by microglia, the innate immune cells of the CNS. Tumor necrosis factor-alpha (TNFα) is a driver in a cytokine cascade that defines this neuroinflammation. We hypothesize that inhibiiton of TNFα expression may be useful in combatting opioid abuse by blunting the development of inflammation-related tolerance. There are currently no agents on the market that target the brain's innate immune system in ameliorating substance abuse. We are developing several novel therapeutic products based on a nanocomplex (termed scL) that binds to the transferrin receptor (TfR) on the endothelial cells that comprise the blood-brain barrier (BBB). These nanocomplexes are capable of actively ferrying diverse payloads across the BBB *via* TfR-mediated transcytosis and into individual neurons *via* TfR-mediated endocytosis. When mice were intravenously (i.v.) injected with scL nanocomplexes carrying fluorescent oligonucleotides or siRNA, these fluorescent payloads were carried into the deep brain. The siRNA delivered to the brain *via* scL nanocomplexes was seen primarily in neurons but to a lesser extent in astrocytes and microglia. To provide proof-of-concept for the therapeutic utility of the scL delivery system, we employed a nanocomplex carrying siRNA targeting the mRNA for TNFα. This scL-encapsulated siRNA was effective in suppression of TNFα expression in cultured cells and in the brains of mice to which this agent (termed scL-siTNF) was administered i.v. Moreover, scL-siTNF injected i.v. reduced neuronal apoptosis triggered by lipopolysaccharide, a prototypical activator of brain microglia, and rescued mice from otherwise lethal endotoxema.