A Novel miR-155 Therapy for the Treatment of Peripheral Neuropathy

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Peripheral neuropathy (PN) is defined as any defect or disorder of the nerve cells or nerve fiber structure that encompasses the peripheral nervous system due to disease or physical injury. The mechanisms by which PN can occur is extremely varied with etiologies including systemic illnesses (ex. diabetes), toxicity, hereditary, autoimmune, infection, and physical trauma. It is estimated that 2.4% of the world population suffers from PN. The quality of life of the patient is impaired particularly due to the chronic neuropathic pain associated with these neuropathies. This leads to excessive use of opioid-based pain medications and abuse. Therefore, there is an urgent need for development of novel therapeutics to treat the underlying cause of the nerve degeneration to alleviate and manage the neuropathic pain associated with it. Micro Ribonucleic acids (miRNAs) are small non-coding RNA molecules, expressed by eukaryotic cells, that regulate gene expression. MiRNAs regulate gene expression by binding to their target messenger RNAs (mRNAs) which may lead to repression, translation or degradation of the target mRNA. A single miRNA can bind to multiple mRNAs and can regulate protein expression of multiple genes, thereby regulating many cellular pathways together. MiR-155 is a highly conserved mammalian miRNA that is considered a master regulator of inflammation. MiR155 regulates the inflammatory cascades by regulating the expression of the suppressor of cytokine signaling 1 (SOCS1) gene. Therefore, higher levels of miR-155 will lead to more SOCS1 suppression and increased inflammation. SOCS1 has been shown to be downregulated in the spinal cord after an injury which was associated with increased neuropathic pain. Additionally, peripheral inflammation and neuropathic pain are also associated and higher inflammation which has been attributed to increased pain. Studies have shown that miR-155 based inhibition of SOCS1 can greatly enhance the expression of SOCS1 expression that results in significant reduction in pain. In addition of SOCS1, miR-155 is known to regulate several other genes that contribute towards inflammation such as Serum and glucocorticoid regulated protein kinase 3 (SGK3) and sirtuins 1. These molecules collectively control the inflammatory response in the peripheral system and inhibition of miR-155 has been attributed to increased expression of these genes and reduced inflammation. Hypothesis: We hypothesize that injury to peripheral nerves will cause inflammation due to reduced SOCS1 expression and targeting miR-155 will restore the SOCS1 which will reduce peripheral inflammation and neuropathic pain. The proposed study will test miR-155 inhibitors as a possible therapeutic strategy for treatment of neuropathic pain. To test our hypothesis, we propose the following aims. Aim 1: Evaluate the dose response of administering lipid nanoparticle encapsulated miR-155 inhibitors on expression of SOCS1 in control animals. Aim 2: Evaluate the effect of miR-155 inhibitors on reduction of pain in a rat model of spared nerve injury (SNI). Outcome: Completion of the proposed studies will provide a potential novel therapeutic approach to minimize the neurodegenerative morbidity and pain associated with peripheral nerve injury. The data generated from this study can be directly used for further detailed pre-clinical. Since, miR155

inhibitors have shown safe during phase1 trials for other indication suggesting that if the preclinical studies are successful then this can be taken for human trials rapidly. Further, these results can be applied to develop new therapies for other neurodegenerative disorders.