PRE-REPORT

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Friedreich's Ataxia (also known as FA, FRDA) is a genetic, progressive, multi-systemic condition that is caused by the GAA trinucleotide repeat expansion in mitochondrial frataxin (FXN) gene. This project mainly focuses on reversing frataxin deficits in the central nervous system caused by the GAA trinucleotide expansion repeat in the mitochondrial FXN gene and to improve the symptoms of FA, such as, dysarthria (slow, slurred speech), progressive gait and limb ataxia, cardiomyopathy, diabetes, abnormal proprioception and vibratory sense, and loss of reflexes. For this goal, pAAV-CAG-GFP mammalian expression vector will be used with modified viral capsid, PHP.eB. Synthetically designed human FXN gene will be subcloned into the transfer vector and pAAV-CAG-GFP-hFXN human frataxin expressing vector will be produced in proper laboratory conditions. The expressing vector will be transfected into the conditional mouse model Fxn^{tm1Mkn}Tg(FXN)YG8Pook/2J with both FXN gene knocked out. The main reason why this particular mouse model was chosen is because, YG8sR model expresses a contracted human frataxin, leading to much greater FXN deficiency, which makes this model suitable for gene therapy studies in FA. Several tests and analysis will be performed on YG8Pook/2J, and on WT C57BL/6J mice before and after transfection such as, the wire-hanging test, notched bar test, the digit gait analysis, Western blot analysis, ELISA assay, electromyographic analysis, histological analysis, ultrastructural analysis, spectrophotometry, histoenzymatic staining, SDH staining, and Perl's enhanced iron staining. Results of the procedures in both mice models will be recorded, and at the end of these tests, an increase in frataxin levels in CNS, more specifically in proprioceptive and motor neurons in dorsal root ganglia, in cerebellum, and in striatum. In addition to this, for pre-symptomatic studies, FA symptoms should be prevented in accordance with the increased levels of frataxin. For post-symptomatic studies, we expect a rapid, and full recovery of the sensory neuropathy associated with frataxin deficiency.