

Scientific Abstract. Late infantile neuronal ceroid lipofuscinoses (LINCL) is a fatal childhood neurodegenerative lysosomal storage disease with no known therapy. There are estimated to be 200 to 300 children in the USA at any one time with the disease. LINCL is a genetic disease resulting from a deficiency of tripeptidyl peptidase (TPP-I), a proteolytic enzyme encoded by the CLN2, the gene that is mutated in individuals with LINCL. The subjects are chronically ill, with a progressive CNS disorder that invariably results in death, typically by age 8 to 12. This clinical study will evaluate the concept that persistent expression of the normal CLN2 cDNA in the CNS will result in the production of sufficient amounts of TPP-I to prevent further loss of neurons, and hence limit disease progression. To assess this concept, an adeno-associated virus vector (AAV2_{cu}hCLN2) will be used to transfer and express the human CLN2 cDNA in the brain of children with LINCL. The vector consists of the AAV2 capsid enclosing the 4278 bp single stranded genome consisting of the two inverted terminal repeats of AAV serotype 2 and an expression cassette composed of the human cytomegalovirus (CMV) enhancer; the chicken β -actin promoter / splice donor and 5' end of the intron; the 3' end of the rabbit β -globin intron and splice acceptor; the human cDNA for CLN2 with an optimized Kozak translation initiation signal; and the polyadenylation / transcription stop from rabbit β -globin. The proposed study will include 10 individuals and will be divided into two parts. Group A, to be studied first, will include 4 individuals with the severe form of the disease. Group B of the trial will include 6 individuals with a moderate form of the disease. Following direct intracranial administration of the vector, there will be neurological assessment using the LINCL clinical rating scale and magnetic resonance imaging/magnetic resonance spectroscopy assessment of the CNS in regions of vector administration. The data generated will help evaluate two hypotheses: (1) that it is safe to carry out direct intracranial administration of the AAV2_{cu}hCLN2 vector to the CNS of individuals with LINCL; and (2) that administration of the AAV2_{cu}hCLN2 vector will slow down or halt the progression of the disease in the central nervous system.