Lay Summary. April 1st, 2013

TITLE: AAV9-mediated human acid sphingomyelinase expression in nonhuman primate brain: Preclinical development of gene therapy for Niemann-Pick disease type A.

Dr. Lluis Samaranch; Sponsor: Dr. Krystof Bankiewicz

Niemann-pick disease type A (NPDA) is a disorder characterized by a mutation in *SMPD1* gene that causes an insufficient activity or deficiency of the acid sphingomyelinase enzyme. This results in the toxic accumulation of shpingomyelin in the cells. Gene therapy based in viral vectors, particularly adeno-associated vectors (AAV), can direct long-term expression levels of defective proteins, like acid sphingomyelinase enzyme, by carrying a correct copy of the defective gene and inducing its expression in brain cells. AAV efficacy and safety has been amply demonstrated in the brain and some AAV-based gene therapies have progressed to Phase I/II clinical trials.

Recently we described that direct injection of an engineered, non-pathogenic virus (adeno-associated virus serotype 9 or AAV9) into the cerebrospinal fluid (CSF), which bathes the brain, results in a global expression of the transgene carried by the AAV, both in rodents and non-human primates. The delivery into the CSF, throughout intrathecal or cisterna magna, is a relatively simple procedure achievable in neonates and offers the possibility of significant therapeutic efficacy in NPDA. When we tested this system in an animal model with an AAV9 that carried a foreign reporter gene, we found that the long-term expression of that foreign protein in the brain activated an unwanted immune response. Before proceeding with our study for NPDA, we tested the delivery of this AAV9 vector but carrying a self-recognized protein. The expression of the self-protein in the brain was safe and there was no immune response. This preliminary data support the feasibility and safety of delivering AAV9 encoding human acid sphingomyelinase globally into the brain by injection of the vector into the cisterna magna with no immune response.

Our next steps will be delivering AAV9 vector carrying a correct copy of hASM, which is defective in NPDA patients, into the CSF of non-human primates.