**Lay Summary. October 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

Gene therapy based in viral vectors, particularly adeno-associated vectors (AAV), can reestablish the normal levels of non-functional proteins, like acid sphingomyelinase enzyme (ASM), by carrying a correct copy of the malfunctioning gene and inducing its expression in brain cells. Over the past several years, we discovered that injections of a particular type of AAV (AAV9) into cerebrospinal fluid (CSF) resulted in very robust gene expression levels.

Recently, we injected AAV9 carrying a correct copy of the ASM (AAV9-ASM) into the CSF and it resulted in a global brain expression of the new gene with no adverse effects, both in rodents and non-human primates. This result suggests the feasibility of this technique.

In addition, we found that high levels of ASM (over normal) cause elevated levels of another protein called CCL5. These results encourage us to use this protein as a marker of abnormally high levels of ASM. Hence, our next steps will be injecting different doses of AAV9-ASM into a NPDA mouse model to define an optimal dose of AAV9 vector to achieve normal levels of CCL5 and therapeutic levels of ASM in the brain.