Steps Toward Gene Therapy for Angelman Syndrome
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SCIENTIFIC ABSTRACT
Gene therapy for central nervous system (CNS) disorders has seen a recent resurgence with the discovery of adeno-associated virus (AAV) vectors that are capable of crossing the blood-brain barrier (BBB), such as AAV9. The Gray lab has been focused on examining the translational potential of AAV9 to treat inherited CNS disorders. Initial studies demonstrated that AAV9 can achieve dose-dependent, widespread gene transfer to neurons and astrocytes in mice as well as in non-human primates, when injected intravenously or intrathecally. Using AAV9-mediated gene transfer as a platform approach to treat an inherited CNS disease, in 2015 Dr. Gray and colleagues at the NIH initiated a Phase I clinical to test intrathecal administration of scAAV9/JeT-GAN in patients with Giant Axonal Neuropathy. Using the same technology, clinical trials from Dr. Gray’s group are pending for Batten Disease, Aspartylglucosaminuria, Tay-Sachs disease, Krabbe disease, Charcot-Marie-Tooth disease type 4J, and Austin disease.

UBE3A gene transfer to treat Angelman syndrome (AS) has unique challenges that are likely to make gene therapy more complicated, but we undertook initial steps to assess the feasibility of UBE3A gene therapy. We designed an AAV vector carrying UBE3A, to mimic endogenous expression patterns as closely as possible. Preliminary data shows widespread UBE3A gene transfer in newborn AS mice that is well-tolerated, thus far. An update on the long-term safety and efficacy of these mice will be provided.