198. Adeno-Associated Viral Gene Therapy To Treat Niemann-Pick Disease, Type C1

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Niemann-Pick disease, type C1 disease (NPC1) is a heritable lysosomal storage disease characterized by a progressive neurological degeneration that causes disability and premature death. NPC1 commonly manifests in childhood, and there are no approved treatments to delay, stop, or reverse the fatal neurodegeneration that is the hallmark of this disorder. New therapies for patients with NPC1 need to be developed. Defects in the *NPC1* gene are the cause of this disease. A murine model of NPC1, *Npc*^{nih} (also called BALB/(*cNctr-Npc1*^{m1N}/J), arising from a spontaneous frame-shift mutation in the *Npc1* gene has been described. *Npc*^{nih} homozygotes (*Npc1*$^{-/-}$) have an early, severe, and rapidly progressing disease, which is characterized by weight loss, ataxia, and lethality by 9 weeks of age. To test the potential efficacy of gene therapy with the goal of developing a new treatment for NPC patients, we constructed an adeno-associated virus (AAV) serotype 9 to deliver the human *NPC1* gene under the transcriptional control of the neuronal-specific promoter, mouse calcium/calmodulin-dependent protein kinase II (CaMKII). *Npc1*$^{-/-}$ mice received 1x10^{12} GC of AAV9-CaMKII-NPC1 or an equivalent reporter control, AAV9-CaMKII-GFP, between 20 and 25 days of life delivered by retro-orbital injection. To achieve neuronal transduction, we relied upon the well-established property of AAV9 vectors to cross the blood-brain barrier and transduce neurons after systemic delivery. Relative to the untreated or AAV-GFP treated *Npc1*$^{-/-}$ mice (n=15, mean survival 66 days, SD=0.89), the *Npc1*$^{-/-}$ mice that received AAV9-CaMKII-NPC1 exhibited an increased life span (n=9, mean survival 105 days, SD=30; P<0.02) Although the AAV9-CaMKII-NPC1 treated *Npc1*$^{-/-}$ mice did not achieve a normal life expectancy or the same weight of wild-type mice, our results demonstrate, for the first time, the potential efficacy of systemic AAV gene therapy as a therapeutic option in patients with NPC1.

199. Initial Safety Evaluation of rAAV-hCNGB3 Vectors in Nonhuman Primates

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Background: Studies in CNGB3-mutant dogs have shown that subretinal injection of AAV5-PR2.1-hCNGB3 can rescue the ACHM ERG phenotype (Komaromy, 2010). However, at high doses many of the animals developed chorioretinitis (Komaromy, unpublished data) and this toxicity is consistent with an immune response to a foreign protein (hCNGB3 has only 76% identity with canine CNGB3), but could also be a result of overexpression of hCNGB3. AGTC is developing a rAAV-hCNGB3 vector for treatment of humans with achromatopsia caused by CNGB3 mutations. Here we report an initial evaluation of the safety of rAAV-hCNGB3 vectors in nonhuman primates (macaque CNGB3 has 95% identity with hCNGB3), this study may contribute to our understanding of potential immune responses to the xenogeneic CNGB3 and help to guide the development of rAAV-CNGB3 gene therapy for human patients.

Methods: Eight cynomolgus macaques were assigned to four groups and received bilateral subretinal injections of AAV2tYF-hCNGB3, or AAV5-hCNGB3, as indicated in Table 1. Ophthalmic examinations, digital fundus photography, scotopic and photopic electroretinography (ERG) and visual evoked potentials (VEP), and histology were used to evaluate ocular tolerability of test article.

Table 1. NHP Study Design

Group	Test Article	No. of Animals	Dose Level (vg/eye)	Dose Concentration (vg/mL)
1 (Low)	rAAV5-PR2.1-hCNGB3	2	4.0E+10	2.88 E+11
2 (Low)	rAAV2tYF-PR2.1-hCNGB3	2	4.0E+10	2.88 E+11
3 (High)	rAAV5-PR2.1-hCNGB3	2	4.0E+11	2.88 E+12
4 (High)	rAAV2tYF-PR2.1-hCNGB3	2	4.0E+11	2.88 E+12

Results: Test article-related ophthalmic findings include mild (Trace to 1+) to moderate (2+) but occasionally moderately severe (3+) to severe (4+) anterior and posterior segment inflammatory response that resolved without sequelae. No test article-related ERG or cortical visual evoked potential (VEP) effects were observed. Microscopic findings associated with injection of the test articles included minimal retinal degeneration, hypertrophy of retinal pigment epithelium, and/or mononuclear cell infiltrates of the choroid and/or retina. Mononuclear cell infiltrates generally correlated with the subretinal foci noted ophthalmoscopically. The inflammatory response tended to be less in eyes given rAAV5-hCNGB3 versus rAAV2tYF-hCNGB3 and in eyes given 4 x 10^10 versus 4 x 10^11 vg/eye.

Conclusions: Both AAV2tYF-hCNGB3 and AAV5-hCNGB3 were well tolerated after subretinal injection in in NHPs at a dose level of 4 x 10^10 or 4 x 10^11 vg/eye. Test article related findings included dose-dependent ocular inflammation that resolved by Study Week 12. No test article-related ERG or cortical visual evoked potential (VEP) effects were observed. In contrast to the severe inflammation noted in dogs receiving high dose of AAV5-hCNGB3 that usually resulted in involuntary early termination of the animals, the milder test article-related findings in macaques receiving AAV-hCNGB3 vectors that expresses a highly homologous xenogeneic human protein is helpful for guiding future development of rAAV-CNGB3 gene therapy for human patients.

200. Advancing a State of the Art Gene Therapy for Parkinson's Disease

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The primary standard of care for Parkinson's disease (PD) is oral dopaminergic treatments and although these are initially highly efficacious, over time they lead to debilitating long term side effects that seriously impact on the quality of life and restrict the long-term effectiveness of such treatments.

OXB-102 is a lentiviral-based vector that delivers the genes encoding the three key enzymes in the dopamine (DA) biosynthetic pathway, tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC), and GTP-cyclohydrolase (CH1), to non-dopaminergic striatal neurons of the sensorimotor putamen, thus providing these cells with the ability to synthesise and release their own DA. The effectiveness of this strategy has already been demonstrated in rodents, non-human primates and Parkinson's (PD) patients (Palfi et. al, Lancet 2014) with a precursor gene therapy vector