

## Scientific Abstract

Leber congenital amaurosis (LCA) is an incurable and untreatable group of early-onset molecularly heterogeneous retinal degenerative diseases that cause severe visual loss. One of the molecularly-defined LCA subtypes is caused by mutations in the RPE65 gene (chromosome 1p31). The *RPE65* gene encodes a 533-amino acid protein in RPE (retinal pigment epithelium) cells critical to the retinoid (vitamin A or visual) cycle: specifically RPE65 is necessary for 11-*cis* retinal to be synthesized and thus available to form the light-absorbing visual pigment in photoreceptors. Pre-clinical proof-of-concept studies in *RPE65* knockout mice and a naturally occurring dog with *RPE65* mutation have been performed to determine whether subretinal gene transfer can restore vision to these blind animals. In both mouse and dog models of *RPE65*-associated LCA, introduction of rAAV-*RPE65* by subretinal (but not intravitreal) injection has led to restoration of visual function; and, in the large animal model, the level of visual restoration has persisted unchanged for at least 3 years. The proposal is to translate these promising pre-clinical results to the clinic with the ultimate goal of helping those individuals with severe visual loss due to *RPE65* mutations. A Phase I open-label unioocular single-dose per patient dose-escalation trial using rAAV2-h*RPE65* is proposed. This should lead to a greater understanding of the safety and potential value of gene transfer in LCA associated with *RPE65* mutations and also will have implications for other forms of retinal degenerative disease amenable to this type of intervention.