

Non-technical abstract

Incurable blindness from infancy or early childhood profoundly disturbs the quality and direction of life for affected individuals and their families. The genetic forms of early blindness due to retinal degeneration are known as Leber congenital amaurosis (LCA). LCA remains without treatment but has recently benefited from increased understanding. The revolution in gene discovery over the past several years has now revealed that the group of clinical disorders known as LCA are a group of distinctly different molecular diseases with complex but comprehensible underlying biochemical pathways. One of the more common molecular forms of LCA is caused by mutations in *RPE65* (RPE stands for the retinal pigment epithelium cell in which the gene product is located and 65 refers to the weight of the protein). The product of this gene is part of the biochemical pathway in the RPE cell that recycles vitamin A to the light-sensing (photoreceptor) cells of the retina so that light can be absorbed and used for vision. When the gene is mutant, the pathway is essentially blocked and the cells are not able to process vitamin A normally. Small and large animal models of the *RPE65* form of LCA are available and in recent years, the concept of treating the blindness by replacing the defective gene has been tested. Both of these models of the human blindness have undergone surgical injection (between the light-sensing cells and the nearby RPE cells) of an inactive virus (specifically, adeno-associated virus) carrying a normal *RPE65* gene. Both sets of animals have shown major recovery of vision. The biochemical pathway has thus been restored and the cells are able to again process vitamin A. It is the purpose of this proposal to extend this work to people with blindness due to *RPE65* mutations. Patients with known *RPE65* mutations will be asked if they desire to participate in this trial of surgical injection in the retina (one eye only) of an extremely small amount of liquid containing the normal *RPE65* gene. The initial trial is one of safety and the patients will be monitored by clinical eye examinations for any side effects of a very low dose of virus-gene mixture.