

Progress Reported in Two Studies of Clinical Gene Transfer Into the Retina

Two new studies in the *New England Journal of Medicine* report improvements in the vision of patients with a genetic degenerative disease of vision subsequent to injection of adeno-associated virus (AAV) into the subretinal space.^{1,2} Both studies targeted Leber's congenital amaurosis, a group of inherited diseases causing reduced vision early in life and progressive blindness. The form of the disease treated in these studies is caused by mutation of the retinal pigment epithelium-specific 65-kDa protein gene (*RPE65*). Patients with mutations in this gene fail to convert all-*trans*-retinyl esters to 11-*cis*-retinal. In the absence of this ligand, the rod and cone photoreceptors cannot convert light to visual signals. As a single-gene defect, the disease was considered amenable to gene transfer, particularly because the death and degeneration of retinal cells are delayed for years after initial symptoms of blindness have become evident.

The vector used in both studies was an AAV vector expressing the *RPE65* complementary DNA. The study performed at the University of Pennsylvania used a vector produced at Children's Hospital of Philadelphia from which the transgene was expressed using the chicken β -actin promoter.² The study performed at the Institute of Ophthalmology, University College, London, used a vector produced by Targeted Genetics (Seattle, WA) from which the transgene was expressed using a 1,400-base pair fragment from the human *RPE65* promoter.¹ In both cases the virus was injected into the subretinal space and vision was tested over a number of subsequent months. The studies were based on pre-clinical efficacy and safety studies in a canine model. Interestingly, the London study involved pretreatment of patients with a 5-week course of immunosuppression. The volume of injected virus differed between the two studies, with up to 1 ml ($\sim 10^{11}$ particles) of virus injected in the London study and approximately one-tenth this volume ($\sim 10^9$ particles) injected in the Philadelphia study. Three patients were reported in each study.

The patients were monitored for immunologic responses, vector dissemination, and other adverse events. One patient in the Philadelphia study sustained an asymptomatic macular hole, apparently from the procedure. Neither significant inflammatory reactions nor vector spread were detected, although vector was detected in the tears of one study subject.

The results showed modest improvements in visual acuity and light sensitivity. All three patients in the Philadelphia study showed improvements in acuity and nystagmus (involuntary rapid and repetitive eye movements). In the London study there was no improvement in measured visual acuity or visual field in any of the patients, and the one patient with nystagmus did not improve. Patients in both groups showed improvement in the mobility testing. Because there was no measure of gene transfer efficiency or transgene expression, the relationship between these changes and the gene transfer is inferred, although the positive changes in all four patients occurred in the eye injected with AAV vector. However, one patient also exhibited improvement in the uninjected eye. Thus, overall, the data seem to indicate some efficacy. The reasons for the slight differences (if biologically relevant at all) in outcome between the two trials are also a matter of conjecture, and the ophthalmology testing procedures were not identical in the two studies.

Both reports present cautiously optimistic interpretation of the data and propose that the studies provide the basis for additional clinical studies in this and other retinal degenerative diseases. Indeed, the expectation is that younger patients, who may have a higher number of preserved retinal cells, may possess a greater chance for benefit from the procedure. Certainly longer follow-up data from these studies will be very helpful.

These studies highlight the continued and important diversification of gene transfer technology from the original focus on hematopoietic stem cells to other cell targets and pathologic conditions. Given the trial details noted above, the modest results, and the understandable lack of controls (e.g., placebo injections in the contralateral eye), a cautious outlook is warranted, but the trial clearly represents another step forward for the field.

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REFERENCES

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