Gene therapy 'cure' for blindness wanes

Two independent academic groups at the University of Pennsylvania (UPenn) in Philadelphia and University College London's (UCL) Institute of Ophthalmology reported long-term results for a gene therapy of Leber's congenital amaurosis (LCA), a rare form of inherited childhood blindness. Both trials, testing a single eye in each patient, found that efficacy diminished after three or more years, sounding a cautious note amid the technology's rapturous renaissance (*N. Engl. J. Med.* **372**, 1887–1897, 2015; *N. Engl. J. Med.* **372**, 1920–1926, 2015).

The trials consisted of early dose-escalation studies delivering the *RPE65* gene within a recombinant adeno-associated virus 2 (rAAV2) vector by injection into the eye. The US group used a high expression promoter and, by contrast, the UK group used the native one, which some critics say may not be potent enough for clinical benefit. Three patients in the US study—of the 15 enrolled—showed an improvement measured as visual function and electroretinography for up to three years after which the benefit diminished. Of the 12 patients tracked in the UK study who received different doses of vector, 6 showed some improved retinal sensitivity for up to three years before decline set in. But comparison is difficult, even within the same trial, as patients had different levels of blindness and were treated with different doses, scientists caution.

With retinal gene therapy's longevity now under scrutiny, doubts spilled over to the most advanced LCA treatment, developed by Spark Therapeutics. The Philadelphia-based biotech is running a phase 3 trial of SPK-RPE65, a similar AAV2-based vector and the same promoter as that in the UPenn study. Spark's stock fell 6% in trading the day the data were released. Spark's treatment for LCA—which appears at birth and causes severe vision loss at an early age—is the farthest along among the three groups. This news and the recent negative phase 2b results from San Diego-based Celladon's heart failure gene therapy have restrained newly found enthusiasm for gene therapies (*Nat. Biotechnol.* **33**, 5, 2015).

Many moving parts—including promoter, dosage and antigenicity—still need to be worked out, but experts remain optimistic about gene therapy. These studies are important milestones, demonstrating safe administration and stable expression over several years, says Lyndon Da Cruz, retinal specialist at the Moorfields Eye Hospital in London, who was not involved in the trial. One reason for the waning benefit is that although the therapy can improve how viable photoreceptor cells function, the current vectors likely cannot rescue already damaged photoreceptor cells. "We think the improvements diminished because the loss of photoreceptor cells continued. There was no evidence that degeneration was prevented," says Robin Ali of the UCL Institute of Ophthalmology who led the UK study.

The UPenn study tested patients ages 16 or older who had had more than a decade of disease progression. "We still don't know if treating children earlier will provide a longer run for the therapy," says Da Cruz. According to Ali, earlier intervention with a more efficient vector to restore *RPE65* levels is more likely to achieve a sustained benefit.

The question of age will be addressed by Spark's trial, which is targeting patients as young as age four. There may be an age at which adding back RPE65 (retinal pigment epithelium (RPE)–specific protein), an enzyme necessary to regenerate visual pigment, will not be effective, says Alan Wright of the University of Edinburgh in Scotland. But, the UK study did include two six year olds, with one showing improvement, and neither study discerned a correlation between age and benefit, says Ali.

One reason for optimism, says Jean Bennett, professor of ophthalmology at UPenn and scientific director of Spark's trial, who was not involved in the recently published studies, is that three or more years out, the three UPenn-treated patients still had improved retinal sensitivity.

Jeffrey Marrazzo, Spark's CEO, maintains that their product formulation can maximize the amount of product delivered to tissue, and the manufacturing process they employ to remove empty viral capsids will make a difference in their trial.

Amsterdam-based uniQure's gene therapy is the only one approved so far and costs $1 million (*Nat. Biotechnol.* **33**, 217–218, 2015). But this high price is not likely to sit well with payers if *RPE65* efficacy is short-lived. Marrazzo says Spark is beginning to conceptualize the therapy's value but data from the ongoing trial are crucial for the discussion with payers. Allan Marchington, of Apposite Capital, a London-based investment firm, says there is value in improving a child's sight for even three years but more data are needed before the health economics of this gene therapy will crystallize. According to Da Cruz, targeting rare diseases is only the beginning—lower prices will be feasible when a single gene therapy can be shown to modify diseases affecting larger populations, such as macular degeneration, even if the treatment does not result in a cure.

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Gene therapy's therapeutic payload may need topping up.

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