GENE THERAPY
As early techniques move through clinical trials, new approaches emerge
by Howard Larkin in Chicago

Two decades on, retinal gene therapies targeting individual gene defects show real impact in clinical trials, making the eye one of the most successful target organs for gene therapy to date, presenters told the retina subspecialty day at the American Academy of Ophthalmology annual meeting.

At the same time, neuroprotective and anti-inflammatory gene therapies may slow progression of complex retinal diseases, and animal studies of optogenetic agents offer tantalising hints that one day vision may be restored even in patients without functioning photoreceptors.

However, many questions remain to be answered before any gene therapy enters the clinical realm, said James W Bainbridge MA, PhD, FRCophth, of Moorfields Eye Hospital and the UCL Institute of Ophthalmology, London, UK. Among other things, further clinical trials are needed to develop condition-specific optimal intervention windows that define when the benefits outweigh the risk, and when retinal degeneration has progressed too far for therapeutic benefit.

Therapy targets
The eye has many advantages over other organs for gene therapy, said Dr Bainbridge, whose pioneering work targeting Leber’s congenital amaurosis, established the short-term safety and efficacy of viral vectors delivered in the subretinal space. Because it is small and enclosed, stable results are possible with small amounts of vector, and its immune privilege reduces immune response. Function and structure changes are also easily observed.

Generally, photoreceptor and retinal pigment epithelium cells are targeted. Because direct injection of DNA is inefficient, vectors that insert genes into living cells are used, commonly adeno-associated viruses or lentiviruses. Subretinal injections are required to reach these cell layers.

The most developed gene therapy approach is treating loss-of-function conditions caused by a single known gene defect, Dr Bainbridge said. These conditions are generally recessive, and Leber’s is an example. “One can imagine that by simply replacing the defective gene and providing a normal copy one might expect improvement,” Dr Bainbridge said.


Dr Bainbridge is currently conducting an early phase II open-label study of larger doses of an AVV2 vector therapy targeting RPE65. So far the subretinal injections have generally been well-tolerated, immune responses infrequent and mild, with no signs of tumour formation to date.

He also reported, “Robust improvements in vision. That’s hugely exciting in a condition that before was considered untreatable.”

Another single-gene replacement therapy that has shown early success targets choroideraemia, said Ian MacDonald MD, of the University of Alberta, Canada. It also uses an AAV vector to target a CHM gene mutation that causes a deficiency of Rab escort protein-1, which is necessary for intracellular trafficking in the retina.

The vector is injected subretinally, ensuring delivery to photoreceptor and RPE cells. Despite the need to detach the macula using pre-injections of BSS prior to delivering the vector, the first six patients to undergo the treatment have tolerated it well and their retinas have reattached, demonstrating the short-term safety of the approach, Dr MacDonald said.

Since choroideraemia is progressive, typically resulting in a precipitous loss of central vision around age 50, slowing disease progress is an important endpoint. Technologies including microperimetry, OCT, electrophysiology and autofluorescence make it possible to monitor functional and structural changes in fellow treated and untreated eyes.

Other retinal gene therapy applications include suppressing toxic proteins created by single-gene mutations, which are often dominantly inherited, and treating diseases with a broader range of genetic origins by inserting genes that express anti-VEGF or neuroprotective factors, Dr Bainbridge said.

“At UCL, we have a pipeline of therapies that target not only RPE, but photoreceptors and complex diseases.”

These include clinical trials for photoreceptor degeneration including Stargardt disease and Usher syndrome, choroideraemia, and age-related macular degeneration.

Optogenetic approaches
Optogenetics is another approach that holds potential for treating a wide range of retinal disorders, said Luk H Vandenberghe PhD of the Massachusetts Eye and Ear Infirmary at Harvard Medical School, Boston, US. It does so by inserting genes expressing opsins that may re-activate damaged photoreceptor cells, or create light sensitivity in other retinal cells. When the correct opsin is deployed in the appropriate retinal neuron, this could restore light perception or vision in eyes with degraded retinas.

Three optogenetic molecular tools have drawn the most attention for this approach, Dr Vandenberghe said. They are channel rhodopsin, derived from algae, which depolarises cells in response to light; melanopsin, from retinal ganglion cells of vertebrates, where it is involved with regulating circadian rhythm and pupillary; and halorhodopsin, from archebacteria, which help single-cell organisms move toward light and can be used to hyperpolarise a neuron.

These sensor proteins can be placed in retinal ganglion cells, amacrine cells, bipolar cells to create photosensitivity, or into remnant cone cells to restore it, Dr Vandenberghe said.

“Each step we go deeper in the retina we capture more retinal processing, which may help restore a more natural form of vision.”

This may sound to some like science fiction, but we have proof of concept for three of these four strategies in animal models where fairly complex forms of light perception and vision can be restored.

However, many hurdles must be cleared before clinical applications are possible, Dr Vandenberghe noted. One is the difficulty of targeting genetic transfer to specific retinal cell targets. Another is that current photosensitive proteins require much light and have a dynamic range of one to two orders of magnitude, compared with seven or more for natural vision, and restored vision signals may not be tolerable, Dr Vandenberghe said.

These might be addressed with a head-mounted display with variable light sensitivity and signal modulation that might in turn be used to activate genetically treated cells in the retina. A successful optogenetic solution will likely require mutually supporting advances in basic optogenetics, gene therapy delivery, understanding of retinal circuitry and advanced optical-electrical engineering, he added.