

INTERVIEW

The Future of Gene Therapy for Rare Eye Diseases



PROFESSOR ANIZ GIRACH qualified as an Ophthalmologist (with a specialty in Retina) and worked in Cambridge (UK). After spending 11 years in the NHS, he joined the pharmaceutical industry with Eli Lilly, focusing on retinal diseases. He has in total 22 years of industry experience in roles with Merck (as their Global Head of Ophthalmology) and Alcon, where he was Vice President of Clinical Development, and ThromboGenics, where he was the Global Head of Ophthalmology/Chief Medical Officer overseeing the development and approval of Ocriplasmin (Jetrea) – a first in class biologic therapy for retinal disease. In addition to an Honorary Professorship at Wills Eye Hospital (Philadelphia, USA), he was recently the Chief Medical Officer at Nightstar Therapeutics, overseeing the development of gene therapies for inherited retinal diseases. He is a member of three Scientific Advisory Boards for international ophthalmic organizations currently, and reviewer for five peer-reviewed journals, including Eye and IOVS. He has edited four books and published over 60 abstracts/manuscripts in peer-reviewed journals in Ophthalmology, with numerous invited lectures at national/international ophthalmology meetings. His special interests are medical retina, vitreomacular interface abnormalities, inherited rare retinal diseases and gene therapy.

Q Rare eye diseases have traditionally been a field of considerable activity and success for the gene therapy community, and this position in the vanguard was recently cemented by the historic approval of Luxturna™, indicated for confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Where do you see the next successes happening?

AG: Over 10 years of hard work led to the long-awaited approval of Luxturna in late 2017, and we hope this will open the

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flood gates for further approvals of gene therapy for inherited retinal and other ocular diseases. There are a number of companies working in this space. Earlier this year, Nightstar Therapeutics started its global Phase 3 trial for choroideremia (NCT03496012), and they also have a Phase 1/2 trial ongoing in X-Linked Retinitis Pigmentosa (XLRP; NCT03116113),

which is a more devastating disease leading to blindness at an earlier age, typically patients are in their forties when they go totally blind. AGTC are also running a Phase 1/2 trial in XLRP (NCT03316560), with a codon-optimized AAV vector, just like Nightstar, and hope to have this completed later this year. AGTC also have a number of other early phase retinal programmes running, namely in achromatopsia CNGA3/CNGB3 (NCT02935517, NCT02599922) and X-linked retinoschisis (NCT02416622). MeiraGTX, which recently became public, also has a number of gene therapy programmes in its pipeline, most notable of which is the XLRP Phase 1/2 trial (NCT03252847), though the difference between this programme and the other two companies working in the same disease area is that MeiraGTX is utilizing a non-codon optimized vector. MeiraGTX is also working on achromatopsia (CNGB3), as well as Leber’s congenital amaurosis (*RPE65* mutation) and salivary gland dysfunction (NCT03001310, NCT02781480, NCT02446249). GenSight had a Phase 3 readout earlier this year from two studies in Leber’s hereditary optic neuropathy (NCT02652767, NCT02652780), and it is unclear whether they will pursue this indication further or not. Additionally, the company has an optogenetic trial looking at non-syndromic retinitis pigmentosa (NCT03326336). Although not gene therapy, another company that has stolen the limelight with impressive early data has been ProQR, based in the Netherlands. ProQR is showing much promise by addressing the problem of inherited retinal disorders through editing oligonucleotide technology, which addresses at the RNA level rather than DNA, to correct the defect. Impressive results published recently in the Leber’s congenital amaurosis 10, due to *CEP290* gene defect, Phase 1/2 trial (NCT03140969) bodes well for the future for RNA antisense oligonucleotide technology, and the impressive pipeline the company has to offer (NCT03605069, NCT02564354). Hopefully, the future will see one or more of these companies succeeding in bringing forward another approved therapy for these debilitating, and often blinding, conditions.

Q And where are the most significant remaining unmet needs against which gene therapy could have a positive impact?

AG: Currently, there are over 250 ocular gene therapy targets identified, most of these are for rare (orphan) diseases. Of course, the really common causes of blindness in the west are diseases such as diabetic retinopathy, which remains the most common cause of blindness in working-aged adults in the western hemisphere, and age-related macular degeneration (ARMD), particularly the 'dry' form of the disease, which is the most common cause of blindness in the elderly. Having a safe and efficacious treatment for these diseases would really be a significant breakthrough in ophthalmology.

Q As a certified ophthalmologist, do you have any lingering concerns about the commercial and practical feasibility of gene therapy in the rare eye disease arena?

AG: There are a number of issues worth considering here.

Most of the companies exploring gene therapies currently are targeting rare or orphan genetic diseases. These are often diseases that need a confirmatory molecular diagnosis. There is often a lack of genotyping being performed routinely in the real-world setting, mainly due to cost and inconvenience. Without a confirmed diagnosis, these patients may not be eligible for an approved (or experimental) gene therapy, and the challenge exists on how to make this testing more widespread and routinely performed.

Once a gene therapy treatment gets approved, the ideal (assuming the benefit:risk is positive) is to treat as early as possible, in order to prevent further worsening of the disease, however this could be challenging due

to label or reimbursement constrictions. Adequate data packages need to be developed to show the optimal timing of treatment, so that the clinician can better manage their patients.

Gene therapy treatments often attract premium pricing, and the exact cost burden to the healthcare systems needs to be sustainable, and

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more creative solutions to pricing/reimbursement need to be developed, such as the annuity model, that fully address the uncharted territory we are entering as a society.

The issue of second eye treatment is very important, not only from a regulatory/payor perspective but also from the patients' perspective. Adequate data packages need to be developed to fully satisfy the regulatory bodies that it is safe and efficacious to treat the second eye.

Although the biology of gene therapy indicates that one treatment should be life-long, there may be a future need to re-treat the same eye that has previously had gene therapy. Issues arise about the safety and efficacy of re-treatment that are worthy of note and consideration.

Surgical expertise is paramount, especially in those treatments that demand a high degree of skill in delivering the drug into the correct location, for example subretinal or supra-choroidal surgery. Questions arise on whether all retinal surgeons would be equally capable of safely delivering these therapies post approval, or whether a few 'specialized centers of excellence' may be a better model moving forward.

Q The long-standing challenge presented by pre-existing antibodies has come to the fore as gene therapy transitions from promising R&D area to commercial entity. Can you comment on this challenge – and on potential future solutions – for the rare eye disease field specifically? Is there any impact of the immunogenicity on second eye treatments?

AG: Historically, gene therapy applied systemically for non-ocular diseases has suffered from the issue of pre-existing antibodies, which can potentially affect both safety and efficacy outcomes for patients. Despite the fact that data in the literature sug-

gest that over 70% of the general population may have prior exposure, and therefore have pre-existing antibodies, to the adeno-associated virus (AAV), recent reports from subretinal AAV gene therapy trials suggests that pre-existing antibodies and neutralising antibodies does not have a significant impact on efficacy and safety outcomes. This may be in part be due to the small doses of gene therapy

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used in ocular diseases. Furthermore, most gene therapy trials have utilised oral steroid regimens both prior to and after gene therapy administration, in order dampen down any potential immune response.

With regards to the impact of immunogenicity issues on second eye treatment, this is a very interesting area of debate. Historically, gene therapy applications for the second time may excite more of an immune response. However, this is where applying gene therapy in eyes has a potentially unique advantage. The eye is a small partially enclosed organ and has a relative immune-privilege status, both of which would mean the doses of gene therapy needed to be safe and efficacious would be many-fold less compared to a similar systemically administered therapy. This small dose may be able to excite less of an immune response or be confined locally only, compared to larger doses, which may spill out into the systemic circulation causing a greater immunogenic response. This theory has been partially validated by the early reports coming out of the Luxturna and other subretinal administration trials, where even having pre-existing antibodies or neutralizing antibodies has not adversely affected a patient's safety or efficacy outcomes, albeit with peri-operative steroid cover. In cases of re-treatment of the same eye, there is inadequate data in the literature to know if the problem of immunogenicity still remains or not.

Q AAV is clearly coming of age as vector of choice for *in vivo* gene therapy, yet non-viral delivery technologies are also gaining considerable momentum currently across gene therapy – what's your view of their potential in relation to the retinal disease area?

AG: The last 10 years has seen substantial progress in the development and application of nonviral vectors in gene therapy. Nonviral vectors for gene delivery include naked DNA or DNA in combination with liposomes or with pegylated (polyethylene glycol-conjugated) nanoparticles with multiple components. These nonviral vectors are efficient at enhancing membrane penetration *in vitro*; however, their efficiency *in vivo* is significantly reduced. Furthermore, the duration of the gene expression is relatively short, and repeated administration may be needed. There are advantages to nonviral delivery systems: they are inexpensive and can carry large DNA molecules, and their structure can be modified to comply with specific needs, such as conjugation to short peptides for targeting. DNA delivery to some tissues such as skeletal muscle is reasonably efficient, though to date there is very little data available of their usage in the eye.

Q As with all rare disease indications, the importance of working effectively alongside patient advocacy groups is often crucial to the success of a clinical development programme – what are your tips for biotechs seeking to create and maintain successful partnership in this particular sphere?

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AG: Working alongside patient advocacy groups is critical in the rare disease space.

My tip would be to get to know them well and early on in your programme—they could be an invaluable asset, and may make the difference between success or failure. Ensure you have regular interactions with them, and keep them updated of your development programme progress—they may be able to help with enrolment in your trial programme often, such

is their ability to utilize social media to raise awareness on your behalf. They can also help with regulatory interactions and represent a ‘patient’ voice of reason with stubborn regulatory bodies.

Q You have been a strong advocate of the importance of natural history studies in rare diseases – can you summarise the value of this approach to clinical development for us?

AG: Natural history studies (NHS) have an immense value, especially when investigating rare or orphan diseases. Their advantages can be broadly summarized in the following ways:

Disease

NHS allows a better understanding of rare diseases, they allow a better opportunity to look for and find end points (including any surrogate markers). The time course of progression of a rare disease can be more accurately mapped out using an NHS, as can it potentially inform the duration of a subsequent interventional study. NHS can allow you to

study and identify the exact target population, and better understand fast as well as slow progressors in a disease.

Patients

NHS allows you to gauge how difficult it may be to recruit for a particular interventional trial, and indeed allow you to use an NHS as a 'pilot' study, where patients can roll over into an interventional trial having been in a NHS previously. NHS also provides an opportunity to engage with patient advocacy groups and engage with investigator sites prior to enrolling for an interventional trial.

AFFILIATION

Aniz Girach

Honorary/Visiting Professor of
Ophthalmology,
Wills Eye Institute, Philadelphia,
USA

