Making strides in eyecare with modern gene therapy techniques

Several approaches are tackling defective genes in ocular pathogenic pathways

By Prof. Albert Augustin

According to the clinicaltrials.gov database, there are around 2,000 gene therapies currently under investigation worldwide in many areas of medicine. In recent decades, the discipline has rapidly evolved.

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Whilst the focus of most gene therapies has so far been on rare diseases, many additional drugs/products are currently being studied to treat disorders such as cancer as well as genetic and infectious diseases. And around 20 gene therapies are already available in the United States, having received Food and Drug Administration (FDA) approval.

The are several available approaches in gene therapy. We can replace a disease-causing gene with a healthy gene or deactivate a gene that is not functioning properly. In addition, a modified or completely new custom-designed gene can be introduced to treat a disease.

The basic principle is to target missing or faulty genes in monogenic diseases. Usually the "gene therapy drug" is given only once; it carries an instruction to change the sequence of one or more proteins. This change is necessary if those essential proteins are produced in a faulty manner: either they are not produced in sufficient quantities or the catalysis process controlled by the protein is not working correctly.

Major pathobiochemical or pathophysiological pathways have been investigated intensively. Gene therapy products include plasmid DNA and viral or bacterial vectors; in a subset of diseases, cells are extracted, genetically modified and then re-introduced into the body, however, more commonly a viral vector is used, which entails eliminating the virus gene and using its ability to penetrate the cell to safely deliver the new information.

From an immunological perspective, the eye is the ideal target for gene therapy, which thus makes it likely that, in the future, highly successful gene therapy approaches will lead to cures for certain diseases of the eye.

Retinal diseases

In 2017, voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) became the first FDA-approved ocular gene therapy. Also approved in Europe (since 2018), it is used to treat certain inherited retinal diseases such as RPE65-related Leber congenital amaurosis or retinitis pigmentosa.

As mentioned already, gene therapies focus on monogenetic diseases. The approach becomes much more complicated for diseases with many pathways involved, such as age-related macular degeneration (AMD). Hence, current methods focus on gene augmentation and/or suppression to enhance or reduce the production of a molecule that plays a crucial role in the pathogenesis of the disease.

In wet AMD, this is vascular endothelial growth factor (VEGF). Its

antibody (anti-VEGF) needs to be applied on a monthly basis, which may lead to both clinical and adherence problems. One way to overcome this is to employ a surgical intervention such as the implantation of a slow-release device. An alternative would be the augmentation of anti-VEGF production using a genetic approach.

One candidate that is currently being studied is RGX-314 (Regenxbio). This drug is delivered subretinally or suprachoroidally. It contains a novel adeno-associated viral vector (AAV8) and is currently in development for wet AMD, diabetic retinopathy and other retinal diseases.

As described above, the cells are transfected, which delivers the information to produce a protein. This protein is designed to neutralise VEGF and, by doing so, modify the pathway for the formation of new leaky blood vessels and retinal fluid accumulation.

Both approaches, subretinal and suprachoroidal, are surgically challenging. However, the suprachoroidal method, which our group used for the application of other drugs more than a decade ago, has been redesigned and appears to be a safe way to apply such a drug.

The positive interim results of two trials of RGX-314 (AAVIATE and ALTITUDE) using in-office suprachoroidal delivery were presented by Dr Robert L. Avery at the most recent meeting of the American Academy of Ophthalmology. The studies are including wet AMD and diabetic retinopathy patients without centre-involved diabetic macular oedema.

Another drug candidate in development is ADVM-022 (Adverum Biotechnologies), an adeno-associated virus vector encoding aflibercept. Results to date have shown that a single intravitreal administration of ADVM-022 is able to provide a safe and effective long-term treatment option for both wet AMD and diabetic macular oedema.

Looking at dry AMD, the approach is similar. Rather than focusing on genes that are responsible for the disease, we are trying to produce or antagonise factors that are part of the pathogenetic cascade. Inflammation has been shown to play a crucial role in the pathogenesis of dry AMD.

One way to tackle inflammation is by increasing the production of complement factor I (CFI), also known as C3b/C4b inactivator (a protein that regulates complement activation). Doing so has been shown to reduce complement activity and thereby inflammation.

About 3% of patients suffering from dry AMD have CFI mutations, with lower CFI levels giving a higher risk of dry AMD. GT005 (Gyroscope Therapeutics) is an AAV2 vector that delivers a plasmid construct expressing normal CFI; it is currently under investigation with promising results and no significant side effects so far, although the drug does need to be applied subretinally.

Proceeding with caution in a new era

As described, clinical studies of promising ocular gene therapies are underway. However, safety remains a concern in this area of therapeutic medicine, where retinal pigment epithelium (RPE) changes and inflammatory reactions can take place. Thankfully, there have been some reports that these potential side effects can be successfully controlled by topical steroids.

Until now, only patients who have been heavily pre-treated have been included in trials. As well as the need to conduct intensive safety assessments, before these new gene therapy approaches can be used on regular basis in real-world settings, Phase 3 trials need to be completed and surgical procedures taught.

And so, while we are entering a new era of drug therapy, with gene therapy having the potential to change the way many diseases are treated (which is good news for our patients), there is still much work ahead. Both drug safety and drug delivery issues present major challenges that need to be addressed.

One promising future approach lies in the CRISPR-Cas9 gene-editing tool, which has recently been introduced for the treatment of a hereditary human disease. It functions rather like a molecular scissor to snip parts of the DNA: in this way, we can insert, delete or modify genes.

After identifying the defective genes, this exciting technology will provide the next step in gene therapy. We are already underway and have identified the defective genes in other hereditary diseases. Thus, this new technology will first be used in diseases with a clearly defined genetic signature. ▮

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