

Not science fiction

Gene therapy for inherited eye diseases - The future is already here | Dr. Samer Khatib, Prof. Dror Sharon, Prof. Eyal Benin.

Degenerative retinal diseases are one of the main causes of blindness in the world. These diseases can be hereditary, purchased during life or multifactoriality (Caused by a combination of genetic and environmental factors), and in recent years this field is being transformed by the introduction of technologies innovative therapies including biological treatments, genetic, extracellular and even initial attempts at artificial vision.

In this brief review, we will focus on neurodegenerative genetic diseases and the development of gene therapy for them

The death of retinal cells, especially photoreceptors that are unable to divide and regenerate, is the main cause of vision loss in genetic diseases such as retinitis pigmentosa, Stargardt disease, Leber congenital amaurosis (LCA) and Best disease, when cellular death is caused by mutations (pathogenic changes) in different genes that are important for cell activity. Most of these diseases involve the retina and the eye only, but sometimes they may also be expressed as part of a multi-systemic syndrome with the involvement of additional tissues such as Usher syndrome in which the hearing system is also involved or Bardet Biedl syndrome (BBS) in which several additional systems are involved. To date, over 270 different genes which may cause hereditary retinal degeneration have been identified, indicating a great genetic variance, which is also

accompanied by variance in the clinical manifestations of the disease. In fact, this group of diseases is recognized as the most heterogeneous group of genetic diseases in humans. Trying to locate the gene causing the disease in patients and families with inherited retinal degeneration is now becoming the "standard of care" and an essential part for the diagnostic process, for two main reasons: One is the possibility of immediate implementation measures to prevent transmission of the disease to future generations in the family (Using prenatal diagnosis), and the second is the beginning of clinical application in the field of gene therapy aimed at overcoming the defect causing the disease. In fact, the eye and the retina are now the main organs in which this technology is applied because the eye is a small organ, surgically accessible, divided into anatomically defined sections and available for advanced methods of imaging and testing that enable low-risk treatment for systemic involvement and the possibility of examining treatment outcomes. **Gene therapy can be done in a number of ways**, when the most common is adding the gene (gene augmentation therapy) by injecting a viral carrier containing a normal copy of the gene that is defective in the patients. The virus, which in most clinical applications is a variant of AAV (Adeno-associated virus) which does not cause significant morbidity in humans, undergoes genetic modifications that prevent its ability to divide and insert a proper copy of the gene we want to "replace". The virus can be injected into the subretinal margin (in a short analysis) as has been done in most studies so far, or the vitreous cavity (in a therapeutic procedure). After the injection, the virus infects and penetrates the retinal cells, and the gene that it carries is released into the cell and

begins to manifest itself by creating the protein that was missing due to the genetic defect in the patient. The expression of the normal protein improves the cell code latch and prevents or slows the degenerative process. In addition, there are non-viral methods to deliver the healthy gene, such as the use of fatty carriers and micro-particle-based technology (nanoparticles).

Dog model

Recently, in December 2017, the American FDA agency approved the first gene therapy for degenerative retinal disease as a recognized and proven treatment in terms of safety and effectiveness, and that's for cases of congenital blindness (LCA) Caused by mutations in the RPE65 gene. This is a scientific and clinical journey which lasted about 17 years: In 2001, a group of researchers from Philadelphia, led by Professors Jacobson, Voswirth, and Bennett, reported that they had greatly improved the function of the retina in the model of a dog whose vision was impaired by the gene RPE65 Using an AAV viral carrier that carries the normal gene under the retina In 2008, the first 3 articles on treating patients with a defect in this gene were published, Total of 9 patients. In 2010, **three Israeli patients were treated in the same manner in the Department of Ophthalmology at Hadassah Medical Center, the fourth largest center in the world, with the help of a viral carrier of one of the American groups** .After another seven years of clinical trials in the second and third phases by Prof. Bennett's group, it was found that the treatment is safe and provides a certain improvement in vision functions, and as a result has been approved by the FDA. Since last December's approval, a number of

patients in the United States have been treated commercially, rather than experimentally. **This success and FDA approval are an important milestone, and are now a catalyst for the development of technology for the treatment of other genes that cause degenerative degenerative diseases. The hope is that now the route for approval and making the treatment available will be short and fast.**

Research and experimentation

Other diseases and genes that cause degeneration of the network are now in the process of developing and testing gene therapy. Model animals have been tested and are still being tested in many genes, and some have matured for clinical trials in patients, although not as approved treatments, but as part of their experience. One example is **Stargardt disease**, which causes inherited maculopathy (Damage to the center of vision in the macular retina) and is expressed in most cases in the teen years of life. About 95% of the cases are caused by a mutation in the ABCA4 gene, which in many populations (including Israel) is the leading gene in terms of its prevalence. Successful experiments in the animal model led to the development of gene therapy for a disease that was tested in two centers around the world, including Casey Eye Institute in Portland, USA and National Eye Hospital of Quinze-Vingts in France. To Note that to date the treatment has been considered safe in the context of treatment and administration, but no results have yet been published regarding its effectiveness. **Choroideremia** is another progressive degenerative disease that causes blindness and is now in the advanced stages of clinical trial in patients. This

disease is caused by mutations in the CHM gene that is expressed in the X chromosome and therefore is expressed mainly in the male. The first trial to test the safety of gene therapy was performed at Oxford University in England and later also in Philadelphia, and initial reports showed a good safety profile of the treatment with some improvement above baseline values in vision. In addition, clinical trials are being carried out in gene therapy of other retinal diseases such as XLRS (X-linked retinoschisis), which results in fragmentation in the neurosensory retinal layers and macular atrophy as well as retinal degeneration against the background of Usher syndrome caused by a mutation in the MYO7A gene. defect in the **In Hadassah Ein Kerem Hospital, after demonstrating efficacy in the Sheep model in collaboration with Prof. Ron Ofry of the Hebrew University and Prof. Elisha Gutwin of the Volcani Institute**

<https://www.youtube.com/watch?v=OaugUyMDkdk>

, A clinical trial is about to begin for gene therapy in patients with Achromatopsia which causes day blindness due to a CNGA3 gene. This is part of a multicenter global study, while studies are also being conducted to examine the efficacy of treatment of **Achromatopsia** in the context of CNGB3. Other clinical trials are being conducted to test Betis Imprint and efficiency of genetic treatments in diseases such as Neuropathy Optic Hereditary Leber (**LHON**) which is a mitochondrial disease that causes optic nerve degeneration, In addition to testing the efficacy of neuroproductive factors that may inhibit or halt the progression of retinal degeneration in genetic diseases in

clinical trials such as rod-derived cone capacity factor (**RdCVF**) by the group of **Prof. Jose Sahl of Paris**.

Stem cells

Parallel to the development of gene therapy, cellular curing technology is also developing in degenerative retinal diseases, based on the use of stem cells and master cells from various sources. This treatment may have an advantage over gene therapy in advanced cases in which most retinal cells have degenerated and there are no target cells to which the gene can be inserted.

There is no doubt that the path to finding a cure for all degenerative diseases of the retina is still long, including proof of the safety and efficacy of gene therapy in many genes, improving the ways of waiting, reducing possible toxicity of the treatment and developing complementary and alternative treatments such as intracellular therapies or in cases of highly advanced degeneration, **artificial vision systems**. It should also be emphasized that the course of approval of medical treatments has continued for years, due to the desire to carefully examine the safety and efficacy of the treatments without putting the patients at risk. **However, progress in recent years has been encouraging and there is hope that over the next 10-20 years a combination of different treatments will enable the maintenance of functional vision in a significant proportion of those with these diseases**