"Lirot", a Non-Profit Organization, is Promoting Basic and Applied Research for the Prevention of Blindness

"Lirot", a non-profit organization, was established in 2006 with the goal of preventing blindness. In order to fulfill our mission we support preventive ophthalmology, and increase research efforts in the field of ocular health. The research is intended to better understand the pathological processes that lead to the loss of vision in different diseases; an understanding which will enable future development of unique treatments for the prevention of the blinding processes, or at least slowing their rate of progression. Our goal is to enable patients to maintain normal vision for as long as possible.

The following review briefly summarizes few of the many research projects that were conducted thanks to funding in the total amount of more than 10 million NIS, through the efforts of "Lirot".

The projects may be summarized under three main categories:

<u>The genetics of hereditary diseases</u>

The majority of hereditary retinal diseases that cause significant loss of vision, including blindness, reflect gradual degeneration of the photoreceptors, and are grouped under the general name "retinitis pigmentosa". This group of diseases may be caused by a mutation in one of over 250 different genes coding for proteins that are involved in various cellular processes in the retina. Therefore, it is expected that the treatment of each patient's illness will be unique, dependent upon the gene involved The first pre-requisite for treatment is knowledge of the mutated gene that cause the retinal degenerative disease.

Several groups have focused on the study of the genetic mutations that cause degenerative retinal diseases and which are typical in the Israeli population. These groups are currently continuing their research within the framework of the Israeli Consortium for Inherited Retinal Dystrophy Diseases (see the article attached to this brochure). Studies within the consortium have led to the identification of new mutations in genes known to be responsible for the retinal dystrophy, and also discovered new genes, previously unknown that cause the development of Inherited Retinal Dystrophy.

A unique study revealed the importance of micro RNA molecules in the normal functioning of the pigment epithelial cells in the retina, which are associated with retinal photoreceptors and their proper functioning. Another research focused on the study of the normal development of the ganglion cells in the retina, which form the retinal nerve. Using an animal model, it was demonstrated that a gene coding for a protein that was known to be essential for the normal development of the brain, is also vital for the formation of a normal optic nerve, and may assist the development of future technologies for rehabilitation of damaged optic nerve and the treatment of glaucoma.

Pathological processes in hereditary eye diseases

Although degenerative retinal diseases may be caused by genetic mutations, they may also be caused by non-hereditary factors, such as age. These projects concentrated on studying the pathological mechanisms underlying cell degeneration in order to develop novel treatment approaches to stop the progression of the degeneration or at least slow it down.

Age-related macular degeneration (AMD) is the leading cause of blindness in people over the age of 60 in the developed world, including Israel. Today, there is no treatment for the dry form of AMD. A unique study examined the involvement of two types of white blood cells and their possible role as a new target for treatment was evaluated. It was found that in AMD patients there is activation of these cells in the blood, which enables their "recruitment" to the eye during illness. In addition, the activity of these cells was found to accelerate the development of the wet form of AMD. Preliminary findings in rodent models for AMD have indicated the possibility that inhibiting the activity of these cells may be used as an innovative treatment method for AMD.

Another study of the "aging processes" which occur in the retina examined the involvement of a unique protein known to be involved in age-dependent processes. Inhibiting the expression of this proteins in mice accelerated early degeneration of the retina. These, and other observations from the research group, suggest that developing drugs to augment the activity of this protein mught be a basis to prevent ocular aging and may prevent the development of AMD.

Treatments to prevent blindness or restore visual capabilities

One of the most fascinating studies focused on restoration of day vision in a sheep model which was identified by chance, as suffering from daytime blindness due to a mutation in a gene that code for protein essential for proper functioning of the photoreceptors responsible for daytime vision. Using molecular methods, the researchers were able to introduce a normal gene to the damaged photoreceptors, and restored the ability of the sheep to function in daylight conditions. Of course, the distance from here to human therapy is still large, but these results are proof of concept that such treatment is indeed possible.

Another fasicnating research direction is based on restoring vision through the use of stem cells as a source for retinal cells, to be used as replacements for degenerated or missing retinal cells. In the last decade, researchers in Israel have succeeded to specifically direct human embryonic stem cells to develop into retinal pigment epithelium (RPE) cells, which are the cells involved in the development of dry-type age-related macular degeneration, and are also involved in Best's hereditary macular dystrophy. The researchers demonstrated that implantation of the induced RPE cells in the eyes of rats that display retinal degeneration due to hereditary dysfunction of the

RPE, led to slowing of the degenerative process. These researchers have already started a preliminary clinical trial in Israel for treatment of patient with dry-AMD.

A slightly different approach to the use of stem cells is based on the assumption that adult bone marrow-derived stem cells are able to participate in the building of the retina in infants. Stem cells, isolated from human bone marrow, were injected to the eyes of 4-day old mice; at this age, the retina is not yet developed, and processes of maturation and differentiation to create the adult retina are still underway. It was found that the stem cells were integrated into the developing retina, and that most of them differentiated to form neural cells of the retina (ganglion cells). In a different study, an attempt was made to promote growth of damaged optic nerve fibers by grafting unique biological substances to the optic nerve. The results indicated partial growth of the damaged nerve, as demonstrated by a unique imaging method. In both cases, the results represent preliminary findings, which require additional research; nevertheless, they may indicate that the possibility of restoration of ganglion cells or nerve fibers in diseases such as glaucoma has been opened.

Several groups are involved in an alternative approach for restoring vision to the blind. One group develops a platform based on a range of innovative materials from the realm of nanomaterials that make it possible to build implants which accurately mimic the characteristics of the retina, and allow better correlation between the biological tissue of the eye and the implanted artificial system. Another group has developed a method to assess the efficacy of these treatments. The method is based on the projection of light patterns onto the eyes of laboratory rats using a small external projector attached to their heads. In parallel, the neural activity measured in their visual center, located in the cerebral cortex, is recorded. In the future, this method may aid the development of artificial retinal implants and their optimal adaptation to the visual system.

To summarize, "Lirot" association has acted and will continue to act to promote basic and applied research relevant to ophthalmological diseases, for the promotion of insights that will lead to the development of the means to prevent blindness and restore the sight of patients suffering from degenerative retinal diseases. Thanks to the activity of "Lirot" and with the increasing cooperation of the Chief Scientist of the Israeli Ministry of Health, the number of funded studies that focus on ocular health has risen many fold since "Lirot" was established 10 years ago.

The full article can be read on lirot's internet site.

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