PROMISE OF OCULAR GENE THERAPY

Principle of gene therapy is straightforward: therapeutic gene sequence is cloned to an expression system that is non-viral plasmid DNA or a viral vector. After it delivery to the target cells the expression system triggers the production of the protein that is encoded by the transgene. In principle, it is possible to express any protein by gene transfer into the target cells. In the post-genomic era more and more information is obtained about the role of different genes and the related proteins in the regulation of the functions of healthy and diseased cells. Such information provides the scientific community the genes for the gene therapy. Importantly, gene therapy is not limited to the treatment of hereditary diseases, and the point of gene therapy is not to correct gene defects in the genome. Instead, gene transfer guides the cells to produce the missing protein for the diseased tissue.

There are several modes of gene therapy. It can be divided based on the gene transfer method to viral vector mediated therapy and non-viral therapy by nanoparticulates. On the other hand, gene therapy can transduce the cells to produce the therapeutic protein for themselves or the cells can secrete the protein to the surrounding tissue and cells, like controlled release drug delivery device. The cells can be also transfected outside of the body and then transplanted to the eye for cell therapy or surgical transplantation.

The virus mediated gene delivery is the most commonly used mode of gene administration into the target cells. First generation of vectors was based on adenoviruses, but the safety was not adequate and currently other vectors are being investigated. Especially, the adeno-associated virus (AAV-2) based gene vectors have gained wide acceptance among the research community. The AAV delivers the gene efficiently to the retinal cells and the duration of effect after a single injection is even one year. Therefore, frequent administration is not needed. So far, the safety and gene transfer efficacy of the AAV-2 vectors seem to be good. Restoration of retinal function and even vision have been shown in animal studies and very recently also in human studies. A small group of retinal degeneration patients with impaired vision showed either improved vision or no change in two independent studies. This is the first report that shows clinical improvement of vision in retinal degeneration (1).

Nanoparticulates have also been used for ocular gene transfer. However, the gene transfer efficacy is low in vivo, even though some positive results have been obtained. It seems that retinal pigment epithelium (RPE) can be transfected more easily then the cells of the neural retina. The RPE transfection is limited by the barriers of the vitreous humor and neural retina, but if the differentiated RPE can be transfected, these cells will secrete the transgene product over prolonged period of two months (2,3). Interestingly, it seems that the activity of the transgene in the nucleus is the key factor, and not the extent of DNA delivery into the nucleus. RPE transfection is an interesting option, because this cell layer could secrete either neurotrophic factors to the neural retina or angiostatic factors to the chorioidea after transfection with appropriate genes.

Cell therapy is an exciting option for the ocular treatment. The cells can be stably transfected to secrete the protein permanently. RPE cell line, ARPE-19, seems to be suitable for long-term micro-capsulation. Presumably, these cells can maintain their viability over prolonged periods, because they do not need to proliferate (4). Adequate leakiness of the microcapsule wall is essential in avoiding the accumulation of secreted but yet unreleased protein accumulation in the microcapsules. Recently, cell encapsulation technology has been used in the eye to secrete ciliary neurotrophic factor

---

1 Centre for Drug Research. University of Helsinki. Finland. Arto.urtti@helsinki.fi
(CNTF) into the vitreous (5). The cylinder is placed surgically to the pars plana of the eye. The results in the clinical study have been promising. Improvement of vision was noticed in many patients with retinal degeneration.

The prospects of the ocular gene therapy are very promising. The first clinical positive results have been obtained and there are several new emerging technologies. These include for example siRNA and miRNA for gene silencing, antagonim molecules for the removal of silencing, induced pluripotent cells and their genetic modification, and the techniques for site-specific gene targeting in the genome. Interestingly, some siRNA gene silencing drugs (for the treatment of age related macular degeneration) are already in phase III clinical trials. It is evident that the development of novel gene therapies and gene based medicines for ocular treatment is progressing well.

REFERENCES