European Journal of Pharmaceutics and Biopharmaceutics 95 (2015) 331–342

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review Article

Treatment of ocular disorders by gene therapy

M. Ángeles Solinís, Ana del Pozo-Rodríguez, Paola S. Apaolaza, Alicia Rodríguez-Gascón *

Pharmacokinetic, Nanotechnology and Gene Therapy Group (PharmaNanoGene), Faculty of Pharmacy, Centro de investigación Lascaray ikergunea, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain

ARTICLE INFO

Article history:
Received 19 September 2014
Accepted in revised form 15 December 2014
Available online 20 December 2014

Keywords:
Ocular disorder
Gene therapy
Viral vector
Non-viral vector
Clinical trial
Retina
Cornea

ABSTRACT

Gene therapy to treat ocular disorders is still starting, and current therapies are primarily experimental, with most human clinical trials still in research state, although beginning to show encouraging results. Currently 33 clinical trials have been approved, are in progress, or have been completed. The most promising results have been obtained in clinical trials of ocular gene therapy for Leber Congenital Amaurosis, which have prompted the study of several ocular diseases that are good candidates to be treated with gene therapy: glaucoma, age-related macular degeneration, retinitis pigmentosa, or choroideremia. The success of gene therapy relies on the efficient delivery of the genetic material to target cells, achieving optimum long-term gene expression. Although viral vectors have been widely used, their potential risk associated mainly with immunogenicity and mutagenesis has promoted the design of non-viral vectors. In this review, the main administration routes and the most studied delivery systems, viral and non-viral, for ocular gene therapy are presented. The primary ocular disease candidates to be treated with gene therapy have been also reviewed, including the genetic basis and the most relevant preclinical and clinical studies.

1. Introduction

Gene therapy, which involves intracellular delivery of genetic material either to block a dysfunctional gene or to deliver a gene as a therapeutic, has huge potential for treating diseases with a genetic component. In spite of the promising strategy that gene therapy supposes for several diseases, its potential risk still makes necessary studies to extend safeness and effectiveness concerns. Actually, clinical application of gene therapy is currently limited to serious diseases that have no cure. The eye possesses important advantages for gene therapy: a well-defined anatomy, it is relatively immune privileged, the accessibility, it is easily examined and, in the same subject one eye can be used as the experimental target and the other one as a control. The progresses in gene therapy hold considerable promise for the management of ophthalmic conditions, and ocular gene therapy has been extensively explored in recent years as a therapeutic avenue to target diseases of the cornea, retina and retinal pigment epithelium (RPE).

The success of gene therapy relies on the efficient delivery of the genetic material to target cells, achieving optimum long-term gene expression. In this review we focus on the main methods for gene delivery and on the application of gene therapy in ocular diseases.

2. Gene delivery to the eye: methods of administration

To treat ocular diseases with gene therapy three main parameters have to be perfectly selected: the administration route, the delivery system and, the use of specific promoter elements.

2.1. Ocular administration routes

Ocular gene delivery can be performed through different routes including topical instillation, periocular routes, intracameral injection, intravitreal injection, subretinal injection or suprachoroidal injection (Fig. 1). Each administration route shows advantages and disadvantages, and the selection should be based upon the targeted cells and the characteristics of the vector used [1,2].

2.1.1. Topical instillation

Topical administration is the easiest non-invasive method of drug delivery in the eye. However, ocular bioavailability of instilled molecules is very poor [3], especially in the case of large molecules such as nucleic acids. On the one hand, an important fraction of the low drug dose that can be administered topically is drained from

* Corresponding author. Pharmacy and Pharmaceutical Technology Laboratory, Pharmacy Faculty, University of the Basque Country UPV/EHU, Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain. Tel.: +34 945 01 30 94; fax: +34 945 01 30 40.

E-mail address: alicia.rodriguez@ehu.es (A. Rodríguez-Gascón).

http://dx.doi.org/10.1016/j.ejpb.2014.12.022
0939-6411/

the ocular surface [4] and, even absorbed into the systemic circulation through conjunctival and nasal vessels [5]. On the other hand, penetration of the cornea and conjunctival epithelia to reach the posterior chamber is limited by the size of nucleic acids [3]. Therefore, the topical route is usually limited to the treatment of diseases related to the anterior segment of the eye.

2.1.2. Periocular routes

The term periocular route includes the administration of drugs via peribulbar, retrobulbar, posterior juxtascleral, sub-tenon and subconjunctival injections [6], being this last one the most studied for delivery of nucleic acids.

Subconjunctival injection is a little invasive method that allows large administration volumes and can be repeated as necessary [3]. Through this route, drugs can penetrate to the anterior and posterior segments of the eye, but potential complications may appear due to systemic absorption [3]. Disposition of particles and molecules subconjunctivally injected depends on the particle size: larger particles (>200 nm) are retained for long time in the subconjunctival space and are more appropriate for sustained delivery to the anterior chamber [7]. Nucleic acids, due to their large molecular weight are also located in the injection site without major penetration into other ocular tissues or systemic circulation [8].

2.1.3. Intracameral injection

Delivery of nucleic acids into the anterior chamber induces transduction of anterior eye segment tissues, although the rapid turnover of aqueous humor and the short contact time with ocular tissues may result in low efficacy [3]. This kind of injection has produced stable protein expression in corneal endothelial cells and trabecular meshwork by using pseudotyped equine infectious anemia virus (EIAV) as vector [9]. Intracameral administration has been also used to control intraocular pressure (IOP) by gene therapy [10].

2.1.4. Intravitreal injection

Drug delivery by intravitreal injection has been extensively studied as a way to access to vitreous and retina structures. Administration into intravitreal humor is relatively easy and high doses are possible, although adverse events such as retinal detachment, endophthalmitis [11] and increase of IOP [12] may occur.

Several works about the distribution of nucleic acids after intravitreal injection have been carried out. Shen et al. [13] administered a short interfering RNA (siRNA) against vascular endothelial growth factor (VEGF) in mice. siRNA was detected in several ocular tissues, including ganglion cells and photoreceptors. In another study, the distribution of a siRNA against VEGF-A in rabbit eyes was similar [14].

2.1.5. Subretinal injection

Injection of the vectors into the subretinal space allows the contact of the nucleic acids with photoreceptors, outer retinal layers and RPE cells. Therefore, this route is useful for the treatment of retinal degenerations caused by gene mutations in photoreceptors or RPE. However, like intravitreal injection, subretinal administration is an invasive method and there is a risk of ocular damage, i.e. lesions in RPE, hemorrhages, retinal tears, sub- or pre-retinal fibrosis, and retinal detachment [3]. Subretinal administration has been used in clinical trials to treat Leber Congenital Amaurosis Type 2 (LCA2) with very promising results [15,16].

2.1.6. Suprachoroidal injection

Suprachoroidal administration, below the sclera and above choroid, has been also explored for drug delivery to the posterior segment of the eye [17]. This route of administration does not interfere with optical pathways and improves diffusional access to the choroid, but macromolecules are cleared rapidly and a sustained release formulation is necessary for longer duration [18]. Touchard et al. [19] have developed a transfection method called suprachoroidal electrotransfer, combining the administration of a non-viral plasmid DNA into the suprachoroidal space with the application of an electrical field. After administration in rat eyes, choroidal cells, RPE, and the outer segment of photoreceptors, were efficiently transduced for at least 1 month. In a previous work [20], the administration of a viral vector in the suprachoroidal space of rabbit eyes demonstrated robust transfection in all treated eyes at the level of the choroid, RPE, photoreceptors and, retinal ganglion cells 6 weeks after treatment.

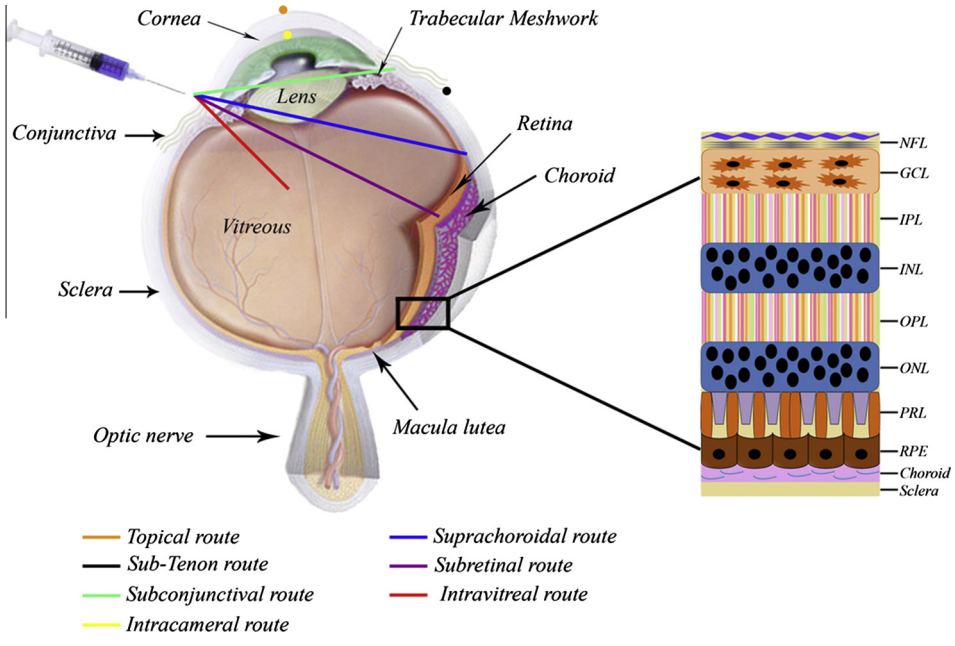

Fig. 1. Scheme of the different ocular administration routes. NFL: Nerve Fiber Layer, GCL: Ganglion Cells Layer, IPL: Inner Plexiform Layer, INL: Inner Nuclear Layer, OPL: Outer Plexiform Layer, ONL: Outer Nuclear Layer, PRL: Photoreceptor Layer, RPE: Retinal Pigment Epithelia. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)