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# Synthetic nanocarriers for the delivery of polynucleotides to the eye

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ABSTRACT

This review is a comprehensive analysis of the progress made so far on the delivery of polynucleotide-based therapeutics to the eye, using synthetic nanocarriers. Attention has been addressed to the capacity of different nanocarriers for the specific delivery of polynucleotides to both, the anterior and posterior segments of the eye, with emphasis on their ability to (i) improve the transport of polynucleotides across the different eye barriers; (ii) promote their intracellular penetration into the target cells; (iii) protect them against degradation and, (iv) deliver them in a long-term fashion way. Overall, the conclusion is that despite the advantages that nanotechnology may offer to the area of ocular polynucleotide-based therapies (especially AS-ODN and siRNA delivery), the knowledge disclosed so far is still limited. This fact underlines the necessity of more fundamental and product-oriented research for making the way of the said nanotherapies towards clinical translation.

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## 1. Introduction

According to the World Health Organization (WHO), 285 million individuals (4.25% of the world's population) suffered from visual impairment in 2010, of which 246 million had low vision and 39 million were blind (Pascolini and Mariotti, 2011). Furthermore, it is predicted that by 2020, 76 million individuals will presumably suffer from blindness mainly due to cataract, glaucoma and age-related macular degeneration (AMD) (Pizzarello et al., 2004). This scenario underlines the necessity of more innovative and effective ocular therapy strategies. Nowadays approaches based on polynucleotide ocular delivery hold great promise since they may alter gene expression without affecting the structure and sequence of the gene.

The eye is an attractive organ for the development of polynucleotide-based therapies due to the fact that the target tissues are accessible without the need of systemic administration. However, apart from this, the eye is protected by extraordinary barriers, which are very difficult to circumvent, especially in the case of hydrophilic and high molecular weight molecules such as polynucleotides. These barriers are illustrated in Fig. 1, and are briefly described as follows.

In the anterior segment, the first barrier encountered by topically applied molecules is the tear film that is composed of three layers consisting of lipid, aqueous fluid and mucus layers. The presence of different enzymes and mucins in the tear film as well as its constant turnover protect the eye against external pathogens. This is followed by the glycocalyx which is formed by cell surface mucins and covers the surface of the corneal and conjunctival epithelia (Spurr-Michaud et al., 2007). The corneal barrier consists of a transparent and avascular multiple layer epithelium, a collagenous layer (stroma) and an internal endothelium. The corneal epithelium continues with the conjunctiva, a transparent and vascularized epithelial membrane that contains goblet cells which are responsible for the production of the mucin MUC5AC (Ruponen and Urtti, 2015). In addition, the presence of tight junctions in both tissues constitutes an obstacle for permeation of drugs, especially through the cornea (Yoshida et al., 2009). The aqueous humor is also part of the anterior segment and it is mostly composed of water and electrolytes, low molecular weight compounds and proteins (de Berardinis et al., 1965; Tripathi et al., 1989).

The posterior segment is protected by the sclera, which represents the continuation of the cornea, and it is formed by the vitreous humor, retina, choroid and optical nerve. The vitreous humor is a highly dense matrix mainly composed of collagen, hyaluronic acid (HA) and also proteoglycans that contain negatively charged glycosaminoglycans (GAGs), that can hinder the diffusion of drugs to the retina, even when they are directly injected into this compartment (Peeters et al., 2005). However, it can also serve as a reservoir for the sustained release of drugs (Bourges et al., 2003). The retina encompasses different cell layers consisting mainly of nerve cells (ganglion cell layer (GCL)), photoreceptors and retinal pigment epithelium (RPE).

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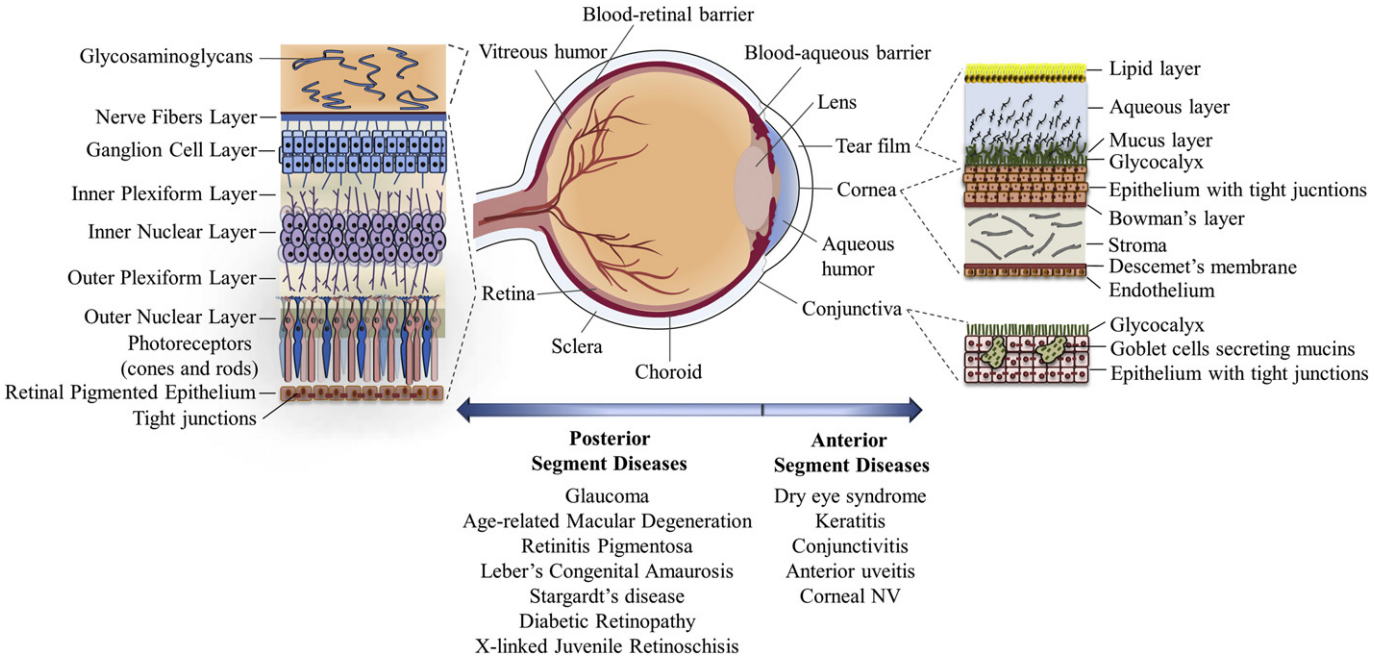


**Fig. 1.** Representation of the structure of human eye (in more detail the tear film, cornea, conjunctiva, vitreous humor and retina) and some examples of diseases affecting both anterior and posterior segments.

Both the anterior and posterior segments are also protected by blood-barriers, the blood-aqueous and the blood-retinal barriers, respectively. The blood-aqueous barrier contains the uveal endothelium and ciliary epithelium. This barrier restricts the access of compounds such as plasma albumin and hydrophilic drugs into the aqueous humor, but it is also responsible for the passage of nutrients essential for corneal function (del Amo and Urtti, 2008). The inner and outer blood-retinal barrier is formed by the retinal vessels' endothelial cells and the retinal pigment epithelium cells, respectively. In both parts of the blood-retinal barrier, the constituent cells are connected by tight junctions. This barrier plays a fundamental role in the regulation of nutrients flux and the restriction of drug diffusion into and out of the retina (Mannermaa et al., 2006).

There are several routes intended to reach either the anterior or posterior segments of the eye. Topical administration and subconjunctival injections are normally oriented towards treating the anterior segment whereas intravitreal (IVT) and subretinal injections are the most common methods used for the treatment of relevant diseases that affect the back of the eye.

In the next sections we will comparatively analyze the nanotechnology-based strategies that have been reported so far to deliver polynucleotides to both the anterior and posterior segments of the eye. We will highlight their potential for targeting specific tissues and thus, for the treatment of specific ocular diseases. We will conclude with a perspective of the challenges that need to be overcome for the clinical translation and industrial development of these nanomedicines.

## 2. Polynucleotides used for the treatment of ocular diseases

The polynucleotides that have been studied until now as potential treatments for ocular disorders are described below.

### *2.1. Plasmid DNA (pDNA)*

Plasmid DNA-therapeutics aims to express a specific therapeutic gene. Therefore, the plasmid needs to be internalized into the nucleus of the cell (which is still a challenge) where it will be transcripted into a messenger RNA (mRNA). Thereafter, the newly formed mRNA is transported into the cytoplasm where it is translated into the codified protein. The first nucleotide-based therapy reaching clinical trials was a pDNA construct proposed for the treatment of an immunodeficiency disease caused by an adenosine deaminase deficiency (Blaese et al., 1995). Since then, according to the clinical trials database (clinicaltrials.gov), several pDNA clinical trials have been conducted although only three of them have been oriented to the treatment of ocular diseases focusing on intraocular melanoma and allergic rhinoconjunctivitis.

### *2.2. Antisense oligonucleotides (AS-ODNs)*

AS-ODNs are synthetic single-stranded RNA fragments (13 to 25 nucleotides) firstly described in 1978 (Stephenson and Zamecnik, 1978), that bind to complementary intracellular mRNA strands by base pairing, forming a short double helix and ultimately blocking its transcription into the undesirable protein. AS-ODNs can also modulate gene expression by enzymatic degradation of targeted mRNA by ribonuclease H (Walder and Walder, 1988). The activity of AS-ODNs is highly limited due to their poor intracellular uptake and poor stability in biological fluids (Opalinska and Gewirtz, 2002).

The only AS-ODNs-based drug (without the association to any type of carrier) approved by the FDA for an ocular condition was registered in 1998. This nucleic-acid based drug, fomivirsen, was marketed as Vitravene® for the treatment of cytomegalovirus (CMV)-induced retinitis in immunocompromised patients (Crooke, 1998). However, in 2004 Novartis Ophthalmics discontinued the product due to the significant decrease of Vitravene® sales as a consequence of the low number of patients infected with CMV. Other AS-ODNs are currently under clinical trials for the treatment of different ocular diseases (see Table 1). For instance, aganirsen (GS-101) has completed a phase III clinical trial for the topical treatment of corneal neovascularization and it is currently in phase II for the treatment of AMD, neovascular glaucoma, retinopathy of prematurity and diabetic macular edema.

### *2.3. Small interfering RNA (siRNA)*

RNAi-based technology, namely siRNA is a promising alternative for treating eye diseases affecting both, the anterior and posterior segments of the eye. This is a double-stranded RNA (dsRNA) of 21–23 base pairs designed to specifically knockdown target genes (Elbashir et al.,

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