STATE-OF-THE-ART OF GENE THERAPY FOR INHERITED RETINAL DYSTROPHIES

Mireia Coll Tané

Biomedical Science Degree 2012/2013

Universitat Autònoma de Barcelona

cbateg Center of animal biotechnology and gene therapy

INTRODUCTION

Inherited retinal dystrophies (IRDs) constitute a large group of genetically and phenotypically heterogeneous diseases that are characterized by progressive loss of photoreceptor cells leading loss of vision. Many of the genes causing IRDs have now been identified, and could ultimately be amenable to treatment by gene-replacement therapies. There is also a robust proof of concept for gene transfer in animal models of retinal dystrophy. Furthermore, three independent clinical trials have shown the vision improvement in patients with an early-onset autosomal recessive retinal dystrophy. In addition, substantial progress has also been made in the development of treatment strategies for autosomal dominant diseases: a promising approach is the gene silencing using RNA-interference (RNAi).

OBJECTIVES

Review the recent progress in retinal gene therapy for IRDs:

- Candidate genes
- Preclinical studies
- Current clinical trials

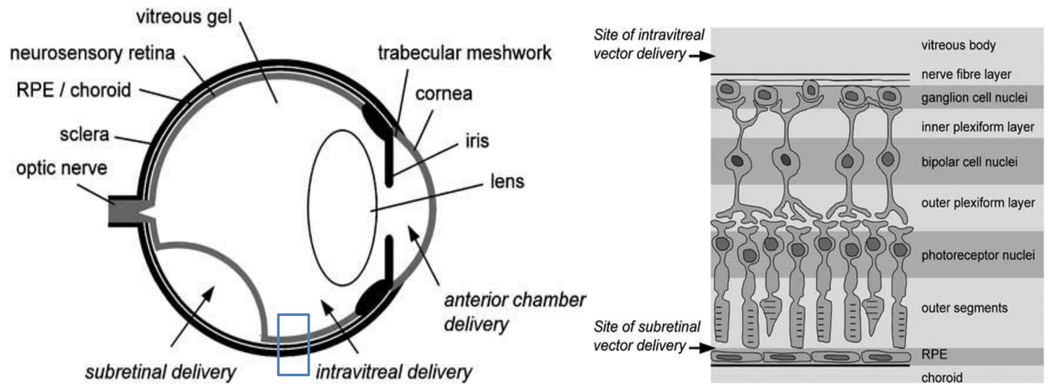
METHODOLOGY

I have performed an exhaustive search and a posterior selection of the latest original articles and reviews in the field.

GENE THERAPY FOR INHERITED RETINAL DYSTROPHIES

Gene-based therapy is defined as the introduction, using a vector, of nucleic acids into cells with the intention of altering gene expression to prevent, cease or reverse a pathological process.

In the following figure show the location of proteins whose genes are candidates for gene-based therapy. Most of the candidate genes have protein products that are located in the outer segments (OS) of the photoreceptor cells or in the retinal pigment epithelium (RPE). Five of these genes are examined in deeper detail. Abbreviations: ONL, outer nuclear layer; AR, autosomal recessive; AD, autosomal dominant; EIAV, Equine Infectious Anemia Virus.



Schematics diagrams of the eye and the retina layers, and the sites of vector delivery. From *Bainbridge JWB, Tan MH, Ali RR. Gene therapy progress and prospects : the eye. Gene Therapy. 2006;:1191–7.*

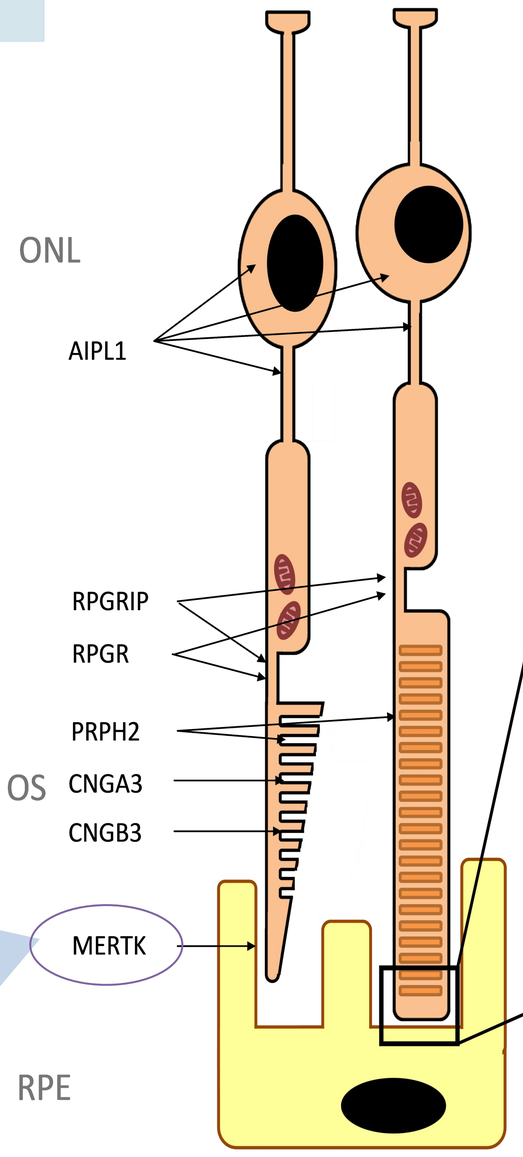
VECTORS

Adeno-associated virus (AAV)	Lentivirus
• Transduce photorreceptors and RPE • Low immunogenicity • Non pathogenic	• Transduce RPE • Non immunogenic

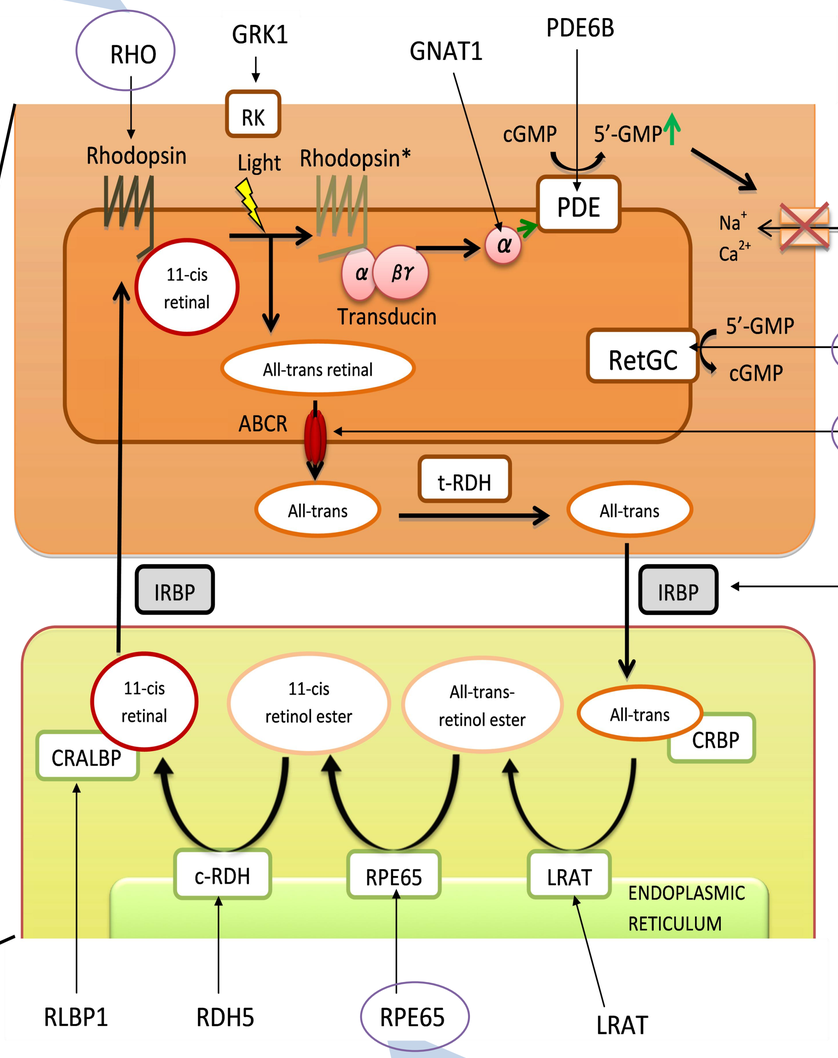
COLOR CODE

1. Disease (heritance)
2. Target
3. therapeutic approach
4. Preclinical studies
   - Vector
   -Animal model
5. Clinical trial
   - Vector
   - Phase: clinicaltrials.gov identifiers
   - Preliminary data

1. RHO-linked retinitis pigmentosa (AD)
2. Photoreceptors
3. The approach involves the use of two components: one that suppress both mutant and wild-type RHO alleles and another that provide a RHO gene replacement
4. Preclinical studies
   - AAV2/5
   - P347S mice



1. MERTK-associated retinitis pigmentosa (AR)
2. RPE
3. Gene addition
4. Preclinical studies
   - Lentivirus and AAV8
   - Royal College of Surgeons rat
5. Clinical trial
   - Lentivirus
   - Phase I/II: NCT01482195
   - Three patients have been treated showing no adverse effects



1. Leber Congenital Amaurosis 1 (AR)
2. Photoreceptors
3. Gene addition
4. Preclinical studies
   - AAV2/8 and AAV5
   - *Gucy2e-/-* mice and GC1/GC2 double knock-out (GCdko) mice

1. Stargardt disease (AR)
2. Photoreceptors
3. Gene addition
4. Preclinical studies
   - EIAV lentivirus and "heterogeneous" AAV
   - *abca4-/-* mice
5. Clinical trial
   - EIAV lentivirus
   - Phase I/II: NCT01367444
   - No preliminary data available

1. Leber Congenital Amaurosis 2 (AR)
2. RPE
3. Gene addition
4. Preclinical studies
   - AAV8
   - Briard dogs and *Rpe65−/−* mice
5. Clinical trial
   - AAV2
   - Phase I/II : NCT00481546, NCT00516477, NCT00643747
   - Phase III: NCT00999609
   - Long-term vision improvement. Re-administration of the vector in the contralateral eye is safe and efficacious.

CONCLUSIONS

The retina is one of the most promising target tissues for gene therapy.

Gene therapy will soon become a realistic treatment choice for many more retinal dystrophies.

The main challenge over the next years is to rescue the vision of more IRDs mouse models, to translate more of the bench findings into clinical studies for more IRDs and to optimize treatments in patients already available.