Applications of Gene Therapy in Retinal Disorders

An essay
Submitted for partial fulfillment
Of master degree in ophthalmology

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Cairo - 2014

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ACKNOWLEDGEMENT

Praise to Allah, who gave me everything, keep me guided and who allowed this work to be done.

It's indeed an honor for me to be supervised by Prof. Hassan Ezzaldin Alsamaa professor of ophthalmology in faculty of medicine, Ain Shams University, who gave me encouragement, guidance and support from the initial to the final level enabled me to develop an understanding of the subject. He helped me in doing a lot of research and I came to know about so many new things.

I am also heartily thankful to my supervisor, Dr. Tamer Fahmy Eliwa lecturer of ophthalmology in faculty of medicine, Ain Shams University. He gave me moral support and guided me in different matters regarding the topic. He had been very kind and patient while suggesting me the outlines of this work and correcting my doubts.

I thank them for their overall supports and without them this work could not have come to reality.

Lastly, I offer my regards and blessings to all of those who supported me in any respect during the completion of the project.

Rabab Alaraby Ali

AIM OF THE WORK

To review current literature and research in the field of gene therapy in treating acquired and inherited retinal disorders and its future prospects and applications.

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Abb.	Full term
AAV	Adeno-associated viral vector
AAV2-hRPE 65 V2	Adeno-associated viral vector of human Retinal pigment epithelium specific 65-KD protein
AAV2-sFLT01	Adeno-associated viral vector of protein VEGF/PlGF (placental growth factor) binding domain of human VEGFR1/Flt-1 (hVEGFR1) fused to the Fc portion of human IgG(1)
AAV vector-PEDF	Adeno-associated viral vector of human pigment epithelium derived factor
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4 gene.
Ad	Adenovirus
ADA	Adenosine deaminase deficiency
Ad PEDF.	Adenovirus vector for pigment epithelium drived factor
AdV-TK	Adenoviral mediated delivery of herpes simplex thymidine kinase
AIPL1 gene	Aryl hydrocarbon receptor interacting protein-like 1 gene.
AMD	Age related macular degeneration
AREDS	Age-Related Eye Disease Study
ARMS2 gene	Age-related maculopathy susceptibility protein 2 encoding gene.
bHLH	Basic helix-loop domain
CEP290gene	Centrosomal protein 290kDa encoding gene
CFB gene	Complement factor B gene
CFH gene	Complement factor H gene
CFI gene	Complement factor I gene
CNGB3 gene	Cyclic nucleotide gated channel beta 3 gene
CR Ad	Conditionally replicating adenovirus
CRB1 gene	Crumbs homolog 1 encoding gene
CRX gene	Cone-rod homeobox encoding gene
DNA	Deoxyribonucleic acid
EIAV	Equine infectious anemia virus
ELOVL4	Elongation of very long chain fatty acids protein 4

Abb.	Full term
FAF	Fundus autofluorescence
GUCY2D	Guanylate cyclase 2D, membrane retinal enzyme gene
GPR98	G protein-coupled receptor 98 protein gene
HIV 1	Human immunodeficiency virus type 1
HDL	High density lipoprotien
HPV	Human papilloma virus
h TERT	Human telomerase reverse transcriptase
I-CreI gene	Clamydomonas reinhardtii homing endonucleases gene
IQCB1	IQ calmodulin-binding motif-containing protein 1
ITR	Inversed terminal repeat
LCA	Leber congenital amaurosis
LRAT	Lecithin retinol acyltransferase enzyme
MRI	Magnetic resonance imaging
MERTK	Proto-oncogene tyrosine-protein kinase MER enzyme encoding gene
MYo7A	Myosin VIIA protein encoding gene
MYCN	N-myc proto-oncogene protein encoding gene
NMNAT1	Nicotinamide mononucleotide adenylyltransferase 1 enzyme encoding gene
PEDF	Pigment epithelium drived factor
PPRPE	Preserved para arteriolar retinal pigment epthelium
PR	Phoptoreceptors
PROM1	Prominin 1 glycoprotein encoding gene
RDS	
RSC	Royal college of surgeons rats
rAAV	Recombinant adeno-associated virus
RB1	Retinoblastoma protein tumor suppressor
RDH12	Retinol dehydrogenase 12 enzyme gene
ROP	Retinopathy of prematurity
RPE	Retinal pigment epithelium
SPATA7	Spermatogenesis-associated protein 7

Abb.	Full term
STGD	Stargrdt's disease
SPATA7	Spermatogenesis-associated protein 7
STGD	Stargrdt’s disease
TAL	(transcription activator-like) effectors
TULP1	Tubby-related protein 1 encoding gene
TK	Tumor killer
USH2A	Usher syndrome 2A protein encoding gene
VEGF	Vascular endothelial growth factor
VSV-G	Glycoprotein of vesicular stomatitis virus.

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Introduction.

INTRODUCTION.

As gene therapy begins to produce its first clinical successes, interest in ocular gene transfer has grown owing to the favorable safety and efficacy characteristics of the eye as a target organ for drug delivery. Important advances also include the availability of viral and non-viral vectors that are able to efficiently transduce various ocular cell types, the use of intraocular delivery routes and the development of transcriptional regulatory elements that allow sustained levels of gene transfer in small and large animal models after a single administration. The design of improved viral vectors and therapeutic gene expression cassettes has enabled long-lasting therapeutic efficacy tailored to the appropriate disease and cellular target. **(*Colella et al.,2009;Liu et al., 2011).***

The first experiments in humans with severe inherited forms of blindness seem to confirm the good safety and efficacy profiles observed in animal models and suggest that gene transfer has the potential to become a valuable therapeutic strategy for otherwise untreatable blinding diseases. ***(Colella et al.,2009).***

The preliminary positive results obtained in the recent clinical trials for Leber's congenital amaurosis show the potential of gene transfer for the treatment of ocular diseases. Higher doses of vector, younger treatment ages and appropriate clinical read-outs will be instrumental in defining the therapeutic potential of this approach for LCA caused by RPE65 mutations. trials ***(Bainbridge et al., 2008; Hauswirth et al.,2008; Maguire et al., 2008).***

More importantly, the promising safety and efficacy results observed in these first attempts in humans encourage the application of a similar strategy to other blinding diseases. The possibility of packaging the large ABCA4 gene in an adeno-associated viral (AAV) vector ***(Allocca, M. et al. 2008)*** or an lentivirus (LV) and the efficacy observed after their delivery in animal models ***(Kong et al. 2008)*** are important steps towards developing human clinical trials for the common Stargrdt disease or for the other retinal degenerations associated with ABCA4 mutations ***(Molday,.2007).***

Regarding wet type of age-related macular degeneration, which is a leading cause of blindness amongst the elderly, clinical trials of gene therapy showed a decrease in the size and prominence of CNV lesions in the high-dose treatment group. Such treatments are promising because the genes delivered could provide protection in the long-term without the need for repeated injections **(*Campochiaro et al 2006)***.

Retinoblastoma, which is the most common primary retinal malignancy in childhood, has many treatment modalities available, but finding a safer and more efficient one remains a major challenge . In clinical trials of gene therapy, Tumor regression was observed at higher doses of treatment, though all ultimately required enucleation, indicating that suicide gene therapy should not be used alone but might be considered as an adjuvant to standard therapies. ***(Chévez-Barrios et al, 2005).***

Although there is currently no cure for retinitis pigmentosa (RP), well-characterised animal models and a developed understanding of the genetic basis of the disease allow gene therapy to be a potentially viable therapeutic strategy for severe retinitis pigmentosa (i.e. receptor tyrosine

kinase Mertk deficiency) ***(Smith, A.J. et al. 2003 ;Tschernutter,et al. 2005)***.

For several of these diseases, gene transfer of neurotrophic molecules can be considered a strategy to slow or halt the progression of degeneration of photoreceptors ***(Buch, et al. 2006]*** or retinal ganglion cells alone or in combination with gene-replacement or gene-silencing approaches **(*Liu et al., 2011).***