Gene Therapy in Retinal Diseases

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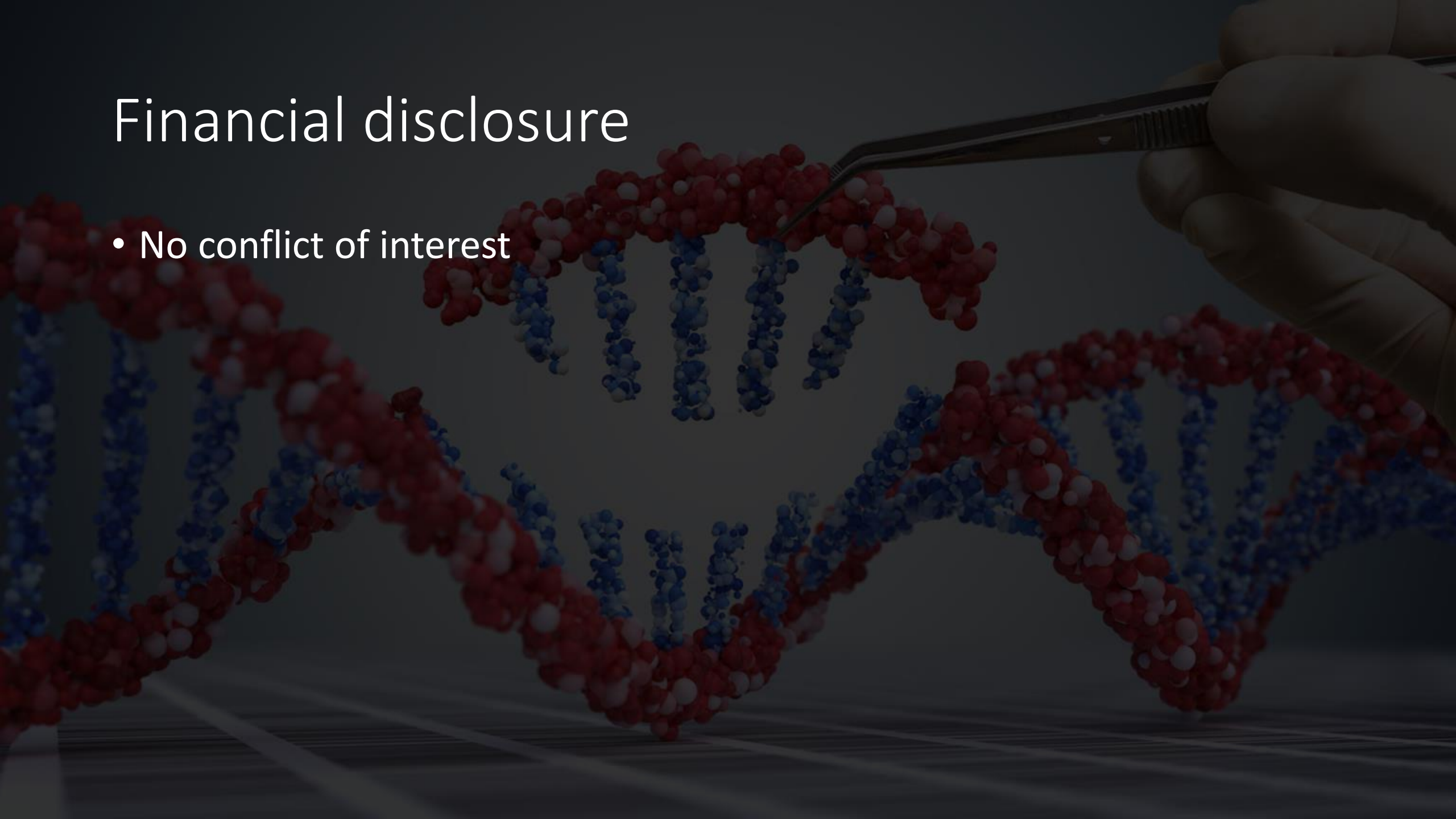
Financial disclosure

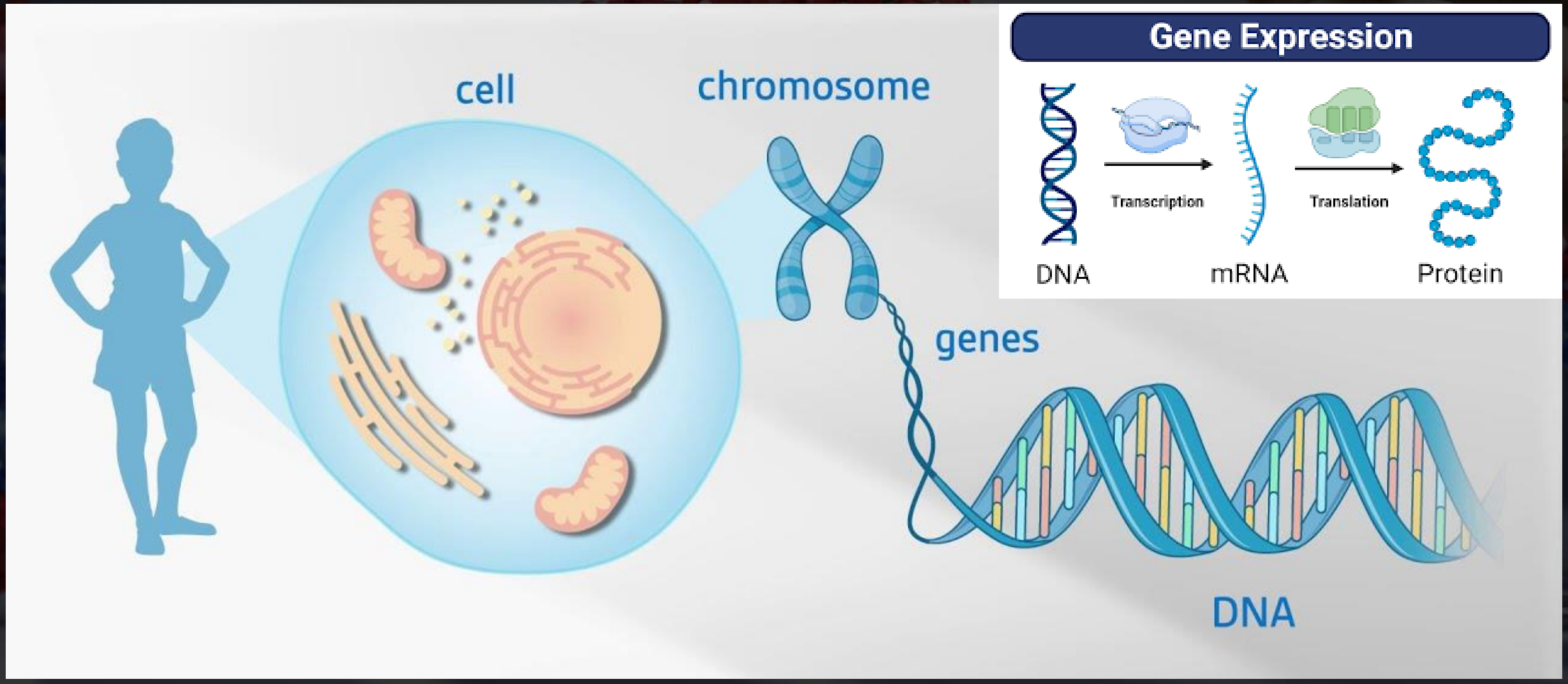
- No conflict of interest



Overview

- Genetic
- Gene therapy
- Different vectors
- Benefit of the eye
- Ongoing gene therapy trials in Ophthalmology
- Summary

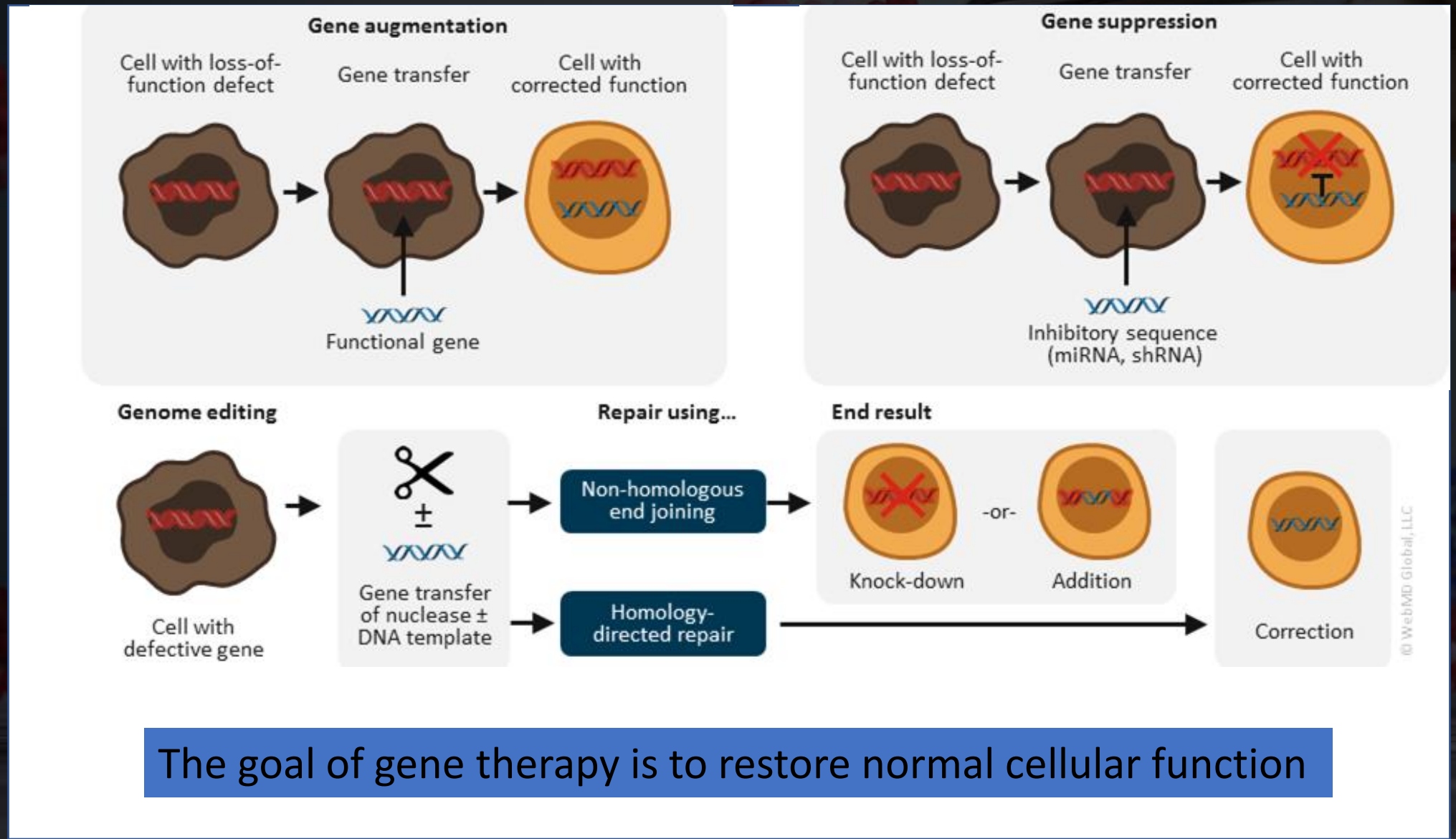
Genetic


cell
chromosome
genes
DNA
Gene Expression
Transcription
Translation
DNA
mRNA
Protein

Gene therapy

- Treatment with genetic material – DNA/RNA
- Mutaded/Non-functional gene -> functional gene
- Reduce the production of disease-causing protein
- Help cells produce proteins that help the immune system fight disease
- Possibility of curing chronic diseases
- Primarily focused on monogenetic diseases
- Development in the area is progressing rapidly

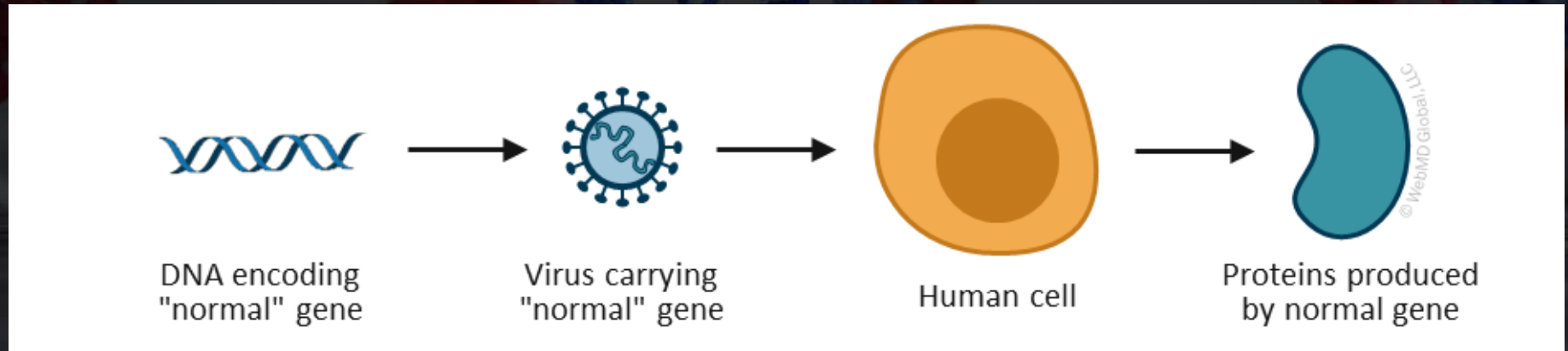
The evolving role of gene therapy



The goal of gene therapy is to restore normal cellular function

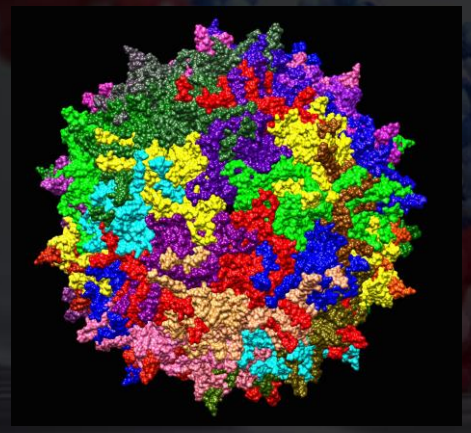
Vectors in gene therapy

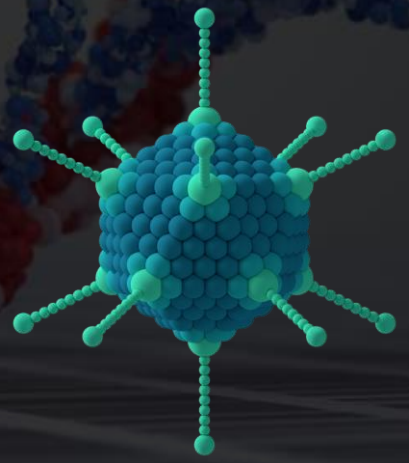
- Gene therapy involves use of a vector to carry the gene of interest into the host cell
- Vectors:
  - DNA
  - Nanoparticles
  - Virus
- Viruses are the most used in clinical gene therapy

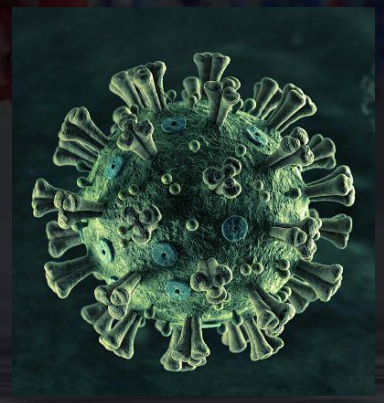


Virus vectors

Characteristic	AAV	Adenovirus	Lentivirus
Contagiousness	Low	Low	Low
Stability	Good	Good	Good
Packaging Capacity (kb)	5	36	8
Immunoreactivity	Low	High	Low
Episomal	Yes	Yes	No

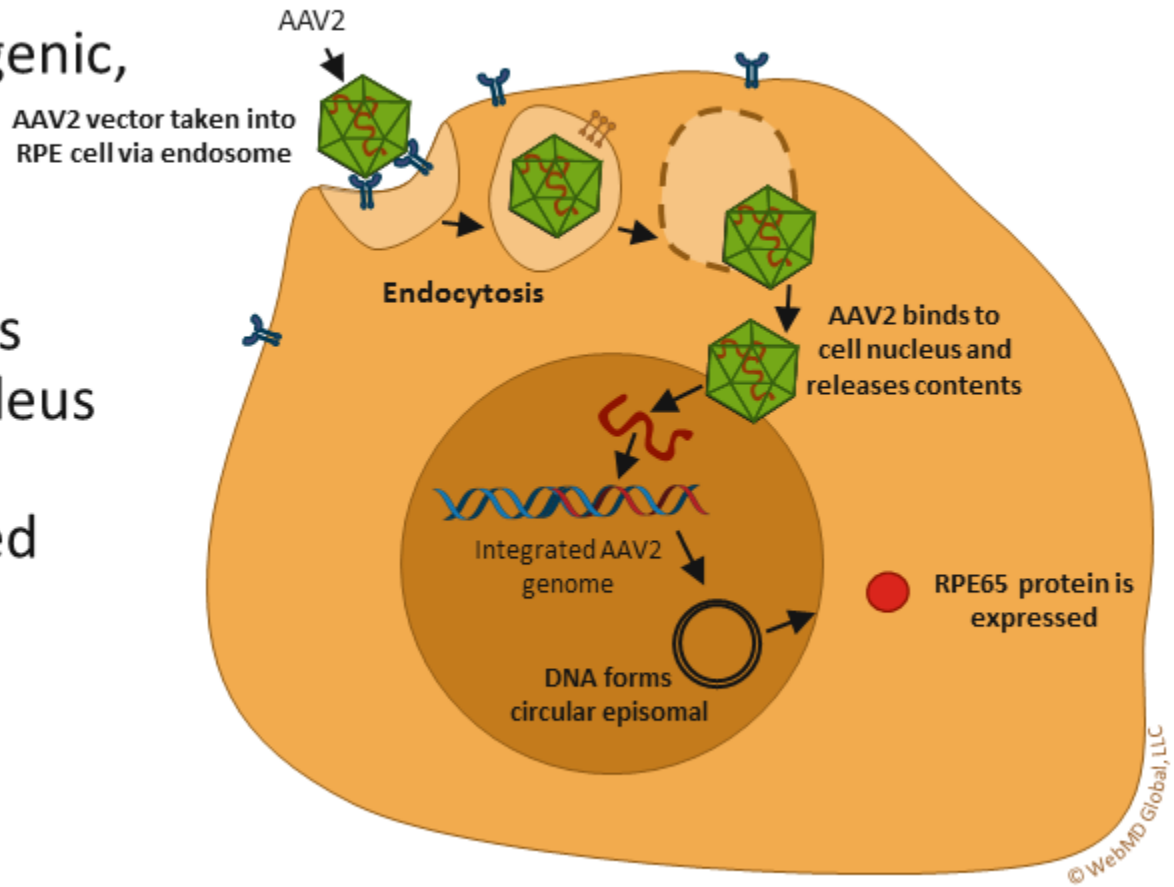






AAV – Adeno-Associated Virus

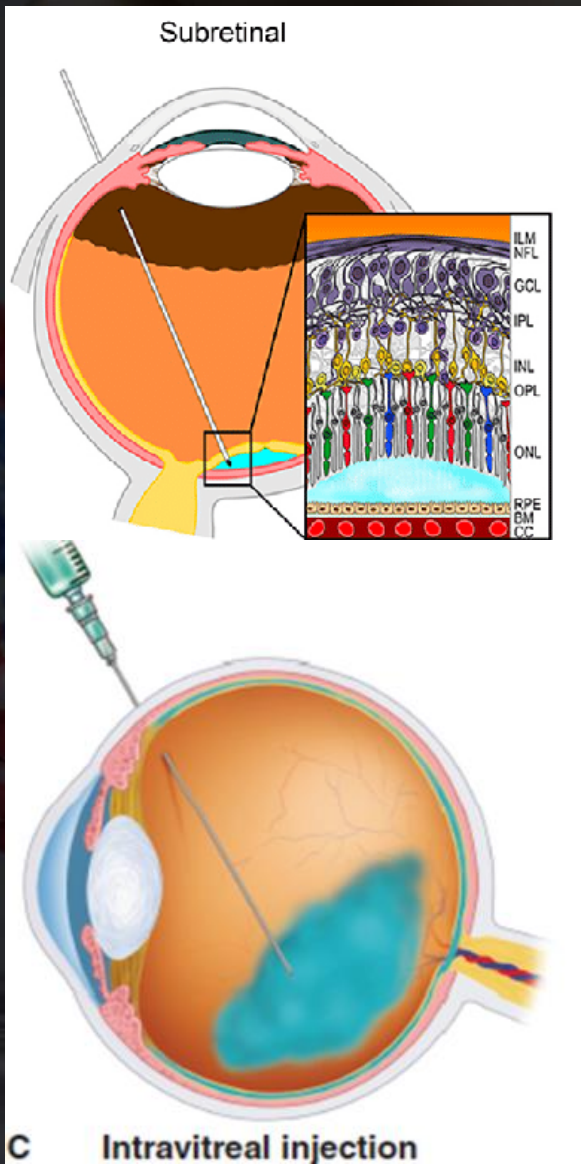
- AAV is particularly well-suited for gene therapy because it is nonpathogenic, nonimmunogenic and episomal. It does not integrate into the host DNA, but rather remains separate inside the nucleus where it is effectively expressed and translated into protein



Luxturna® FDA PI. 2017; Luxturna® EMA PI. 2018

Benefit of using the eye for gene therapy

- Easily accessible
  - Possibility to treat focally
  - Study the effect of the treatment
- Minimizes the systemic impact of the therapy
- Small organ
- Small volume of the substance is needed – reduces the challenge of producing the substance
- Immune privileged organ



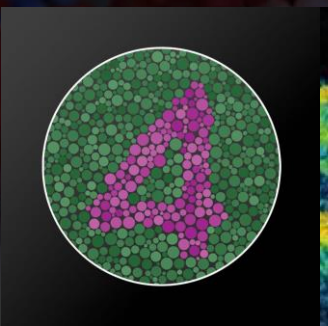
Who and how

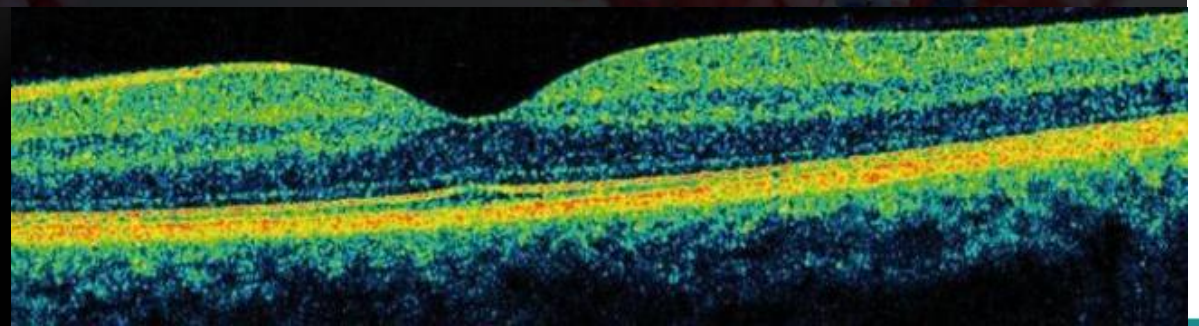
- Inheritable retinal degeneration
- Leber’s hereditary optic neuropathy
- Other monoclonal genetic defects

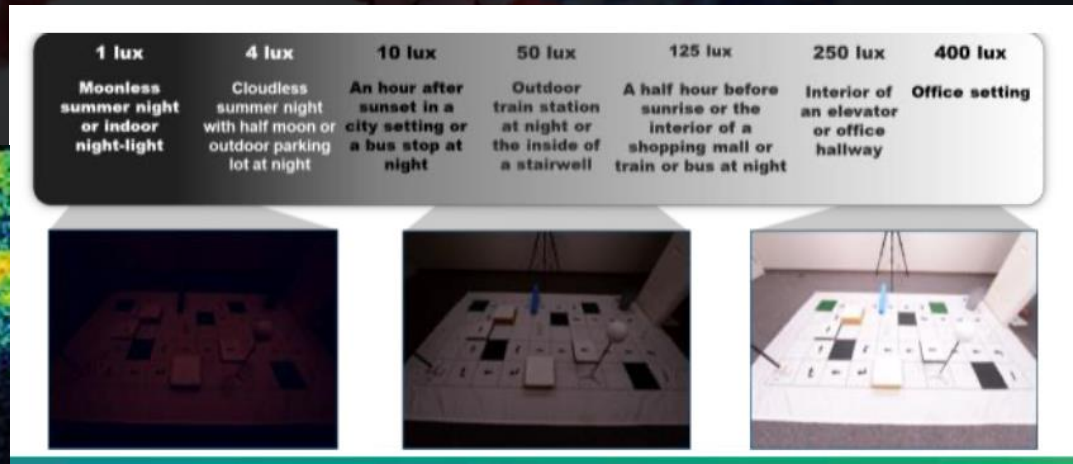
- Good collaboration with colleagues such as geneticists, paediatricians etc
- Referral to subspeciality (ERG)
  - Visual acuity, visual field, color vision, full-field ERG, multifocal mfVEP
  - Blood sampled for gene analysis – 322 genes

How to evaluate the effect of the treatment

- ETDRS
- OCT macula + angiography
- Color vision testing
- Visual field
- ERG
- Multi-Luminance Mobility Test - MLMT





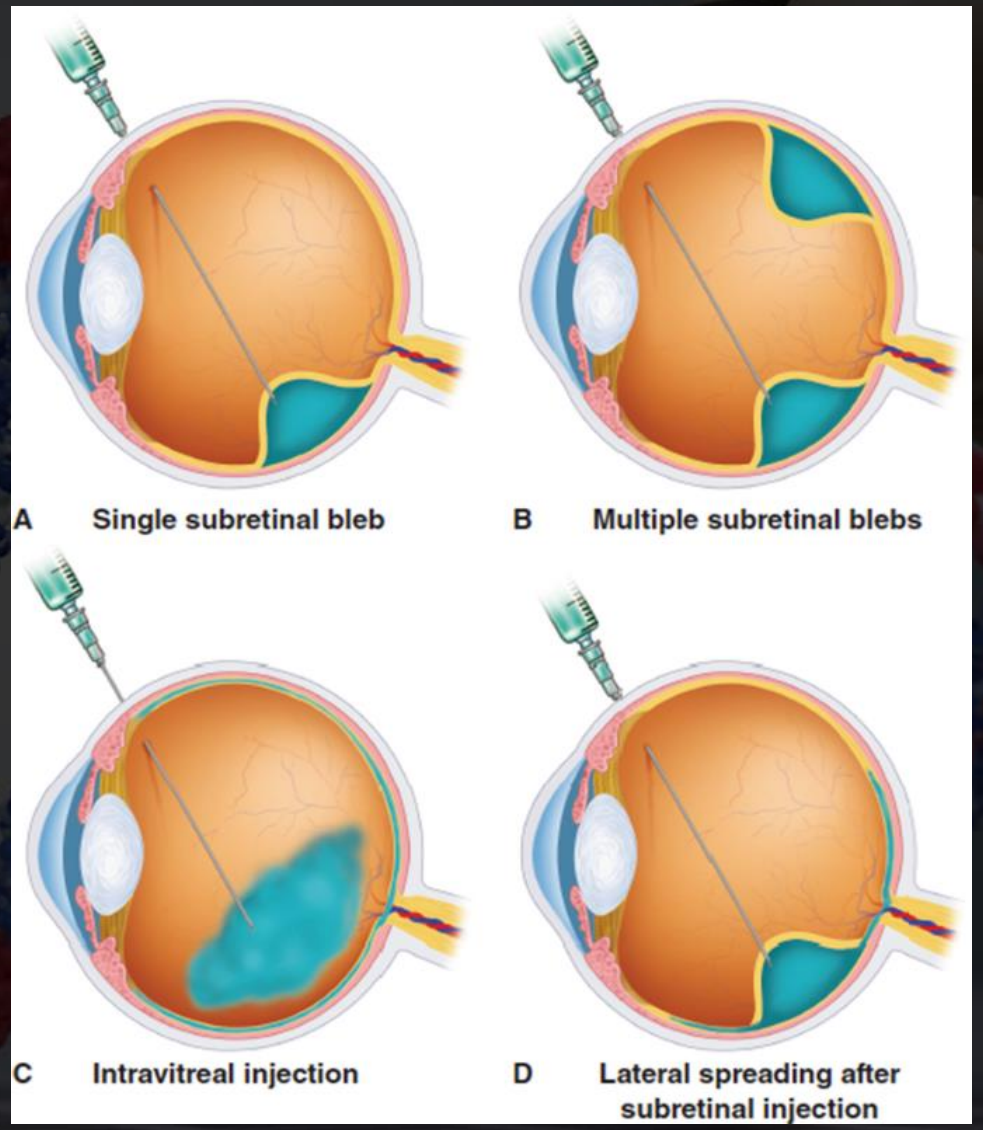


Age limitations?

- More important to find out if the cells have a potential for treatment than the patient's age
- OCT is the best way to find out if photoreceptors are present, indicating that RPE is treatable
- OCT should be combined with testing of the entire visual field to find out if a viable retina is present and if the patient will benefit from the treatment

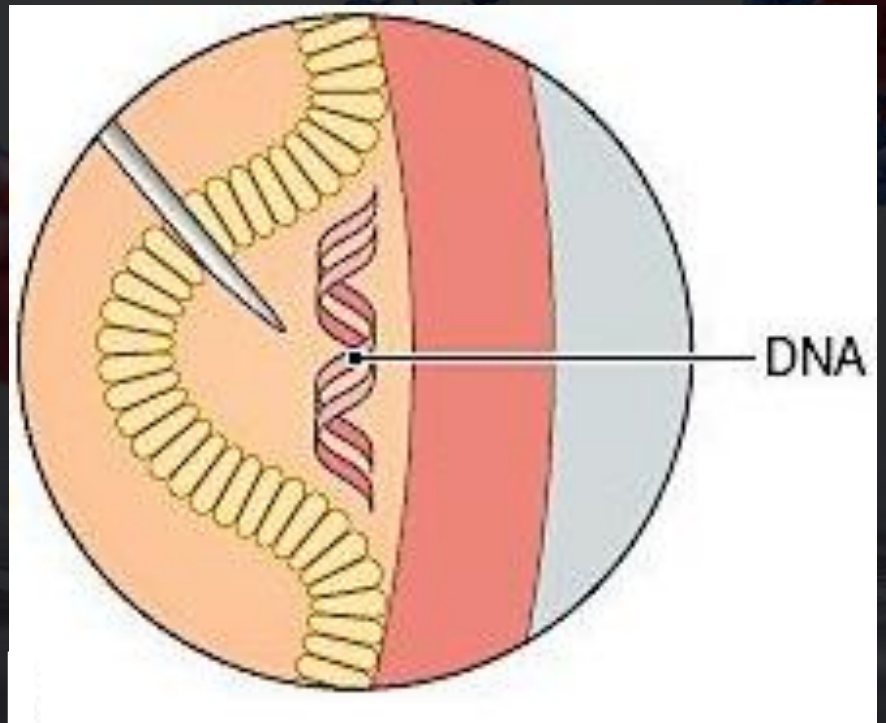
Does the degeneration continue after gene therapy?

- Subretinal injection with a bleb, limited area treated, degeneration continues outside the bleb
  - Several injections needed to treat the entire retina
- IVT treats the entire retina - theoretically the degeneration is inhibited – No evidence yet



How long will the treatment last?

- Possibly forever or as long as the cells in which the therapy works are viable



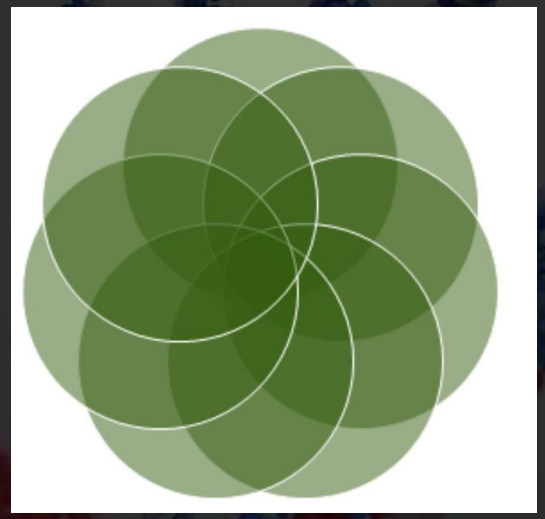
Almost 100 ongoing clincial trials – 12 eye diseases

Leber Congenital Amaurosi's (LCA)

Usher Syndrome

Leber Hereditary Optic Neuropathy (LHON)

Retinitis pigmentosa



X-linked Retinitis Pigmentosa

Choroideremia

Wet and Dry AMD

Achromatopsia

X-linked Retinoschisis

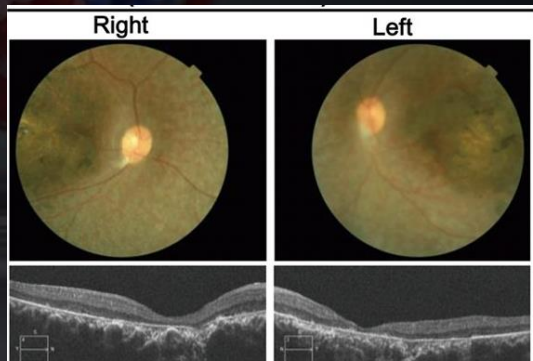
Bothnia Dystrophy

Gyrate Atrophy

Clinicaltrials.gov

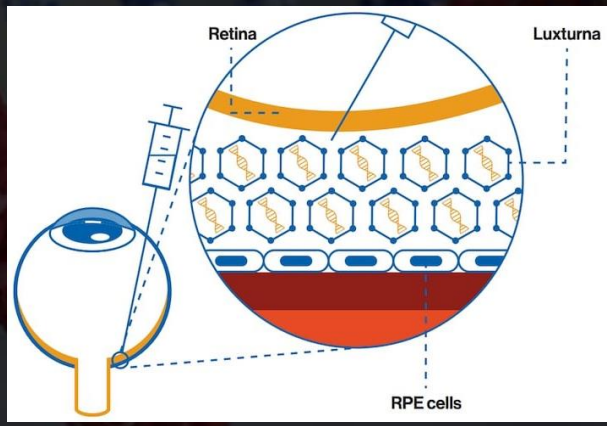
Leber Congenital Amaurosis (LCA)

- Autosomal recessiv
- 17 phenotypes involving several genes
  - RPE65, GUCY2D, SPATA7, CRX etc
- Important for the development of the retina
- Nystagmus, lagging or missing puppilary light-reflex, sevear visual defect, photophobia, high hyperopia, ocula-digital signs
- Retina: initially normal, later hyper pigmentation and atrophy
- Severe visual loss or blindness
- 10% of pediatric blindness

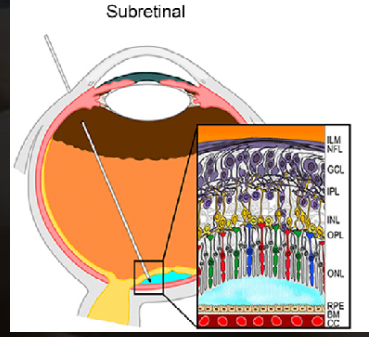


LCA- Gene Therapy

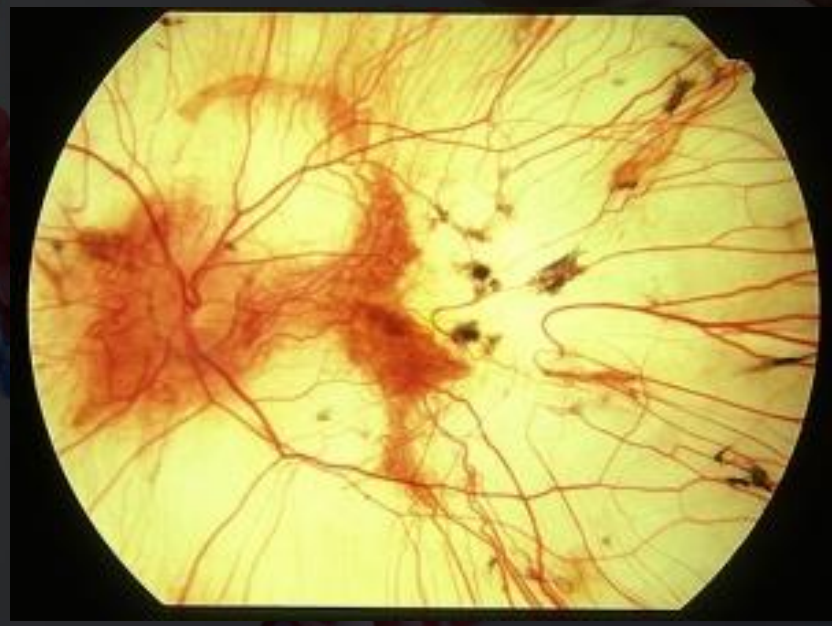
- Luxturna
- Approved in 2021
- Double mutation on *RPE65* gene
- Normal photoreceptors
- Gene therapy with a normal copy of *RPE65* gene
  - AAV2
  - Subretinal injection
- Showed significantly improved navigation
- Continued effect of treatment 3 years later



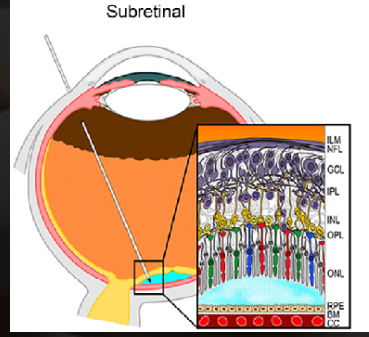
Choroideremia



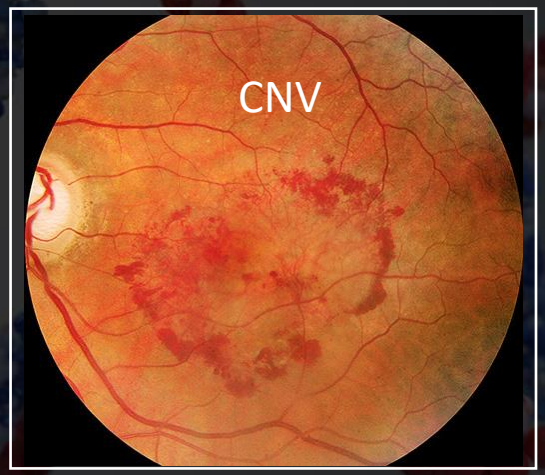
- Mutation in the *CHM* gene – codes for *RPE1* – intracellular transport
- Nyctalopia – tunnel vision – worse vision
- Progressive visual loss
- X-linked recessive
- Men
- 4% of all blindness
- Subretinal injection of AAV2-REP1
- Maintained and in some cases improved vision
- Long-term follow-up is required



Wet and Dry AMD

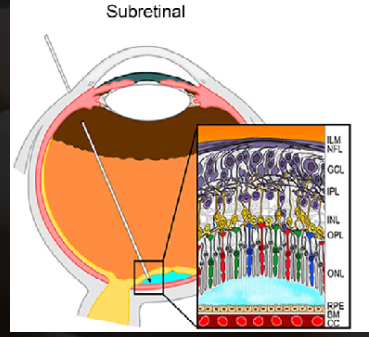


- Wet AMD with CNV
  - Subretinal injection with virus vector resulting in anti-VEGF production
    - ADVM-033 (AAV-Afibrecept)
      - Treatment is tolerable
      - 60% injection-free after 1 year
    - RGX-314 (AAV-monoclonal anti-VEGF antibody)
      - Treatment is tolerable
      - 80% reduction of anti-VEGF injection

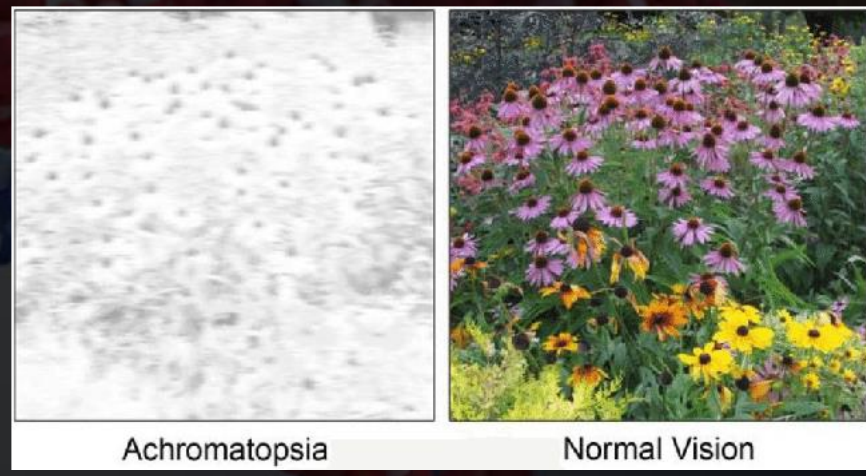


- Dry AMD with GA
  - AAV-CAGsCD5 – Block the formation of membrane attack complex, a part of complement system
  - S:t Eric Eye Hospital

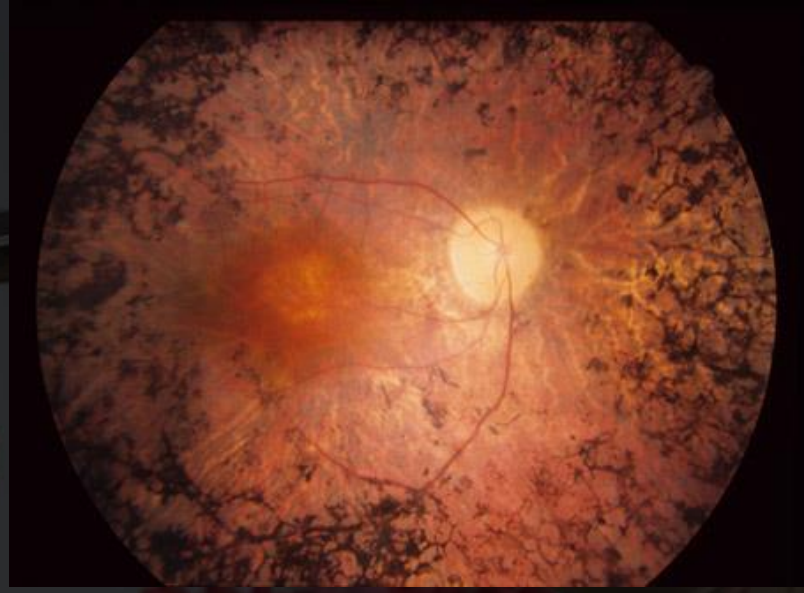
Achromatopsia



- Unusual bilateral autosomal recessive retinal diseases
- Mutation in one of six genes
  - *CNGA3 & CNGB3*
- Affects all three cones
- Poor central vision, photophobia, hemeralopia, severe loss of color vision
- Subretinal injection – AAV – *CNGA3/CNGB3*
- Secure and Tolerable
- Vision becomes better but is not maintained – recruit younger patients

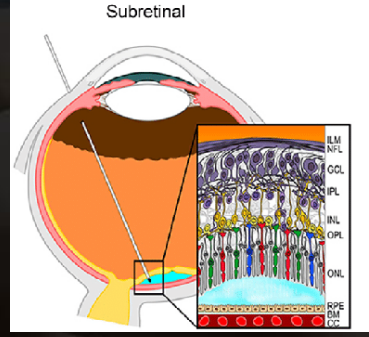


Retinitis pigmentosa

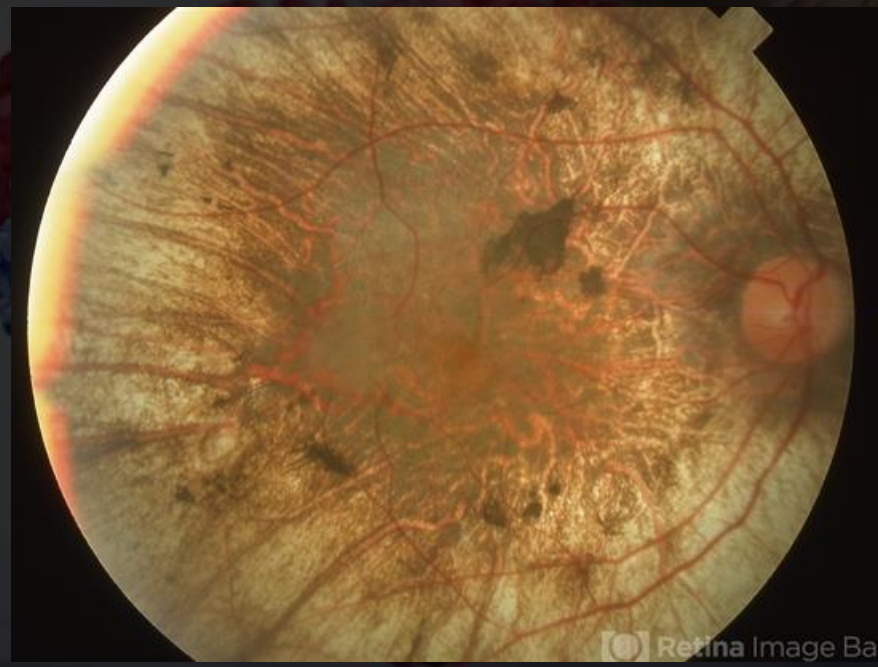


- Clinical and genetic heterogeneous disease
  - Only eye involvement or associated with a syndrome
- Inherited retinal disease
- Progressive dysfunction of rods, in the end degeneration of cones and RPE cells
- Nyctalopia and progressive visual field loss

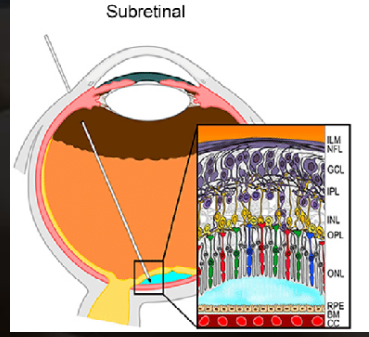
X-linked Retinitis Pigmentosa



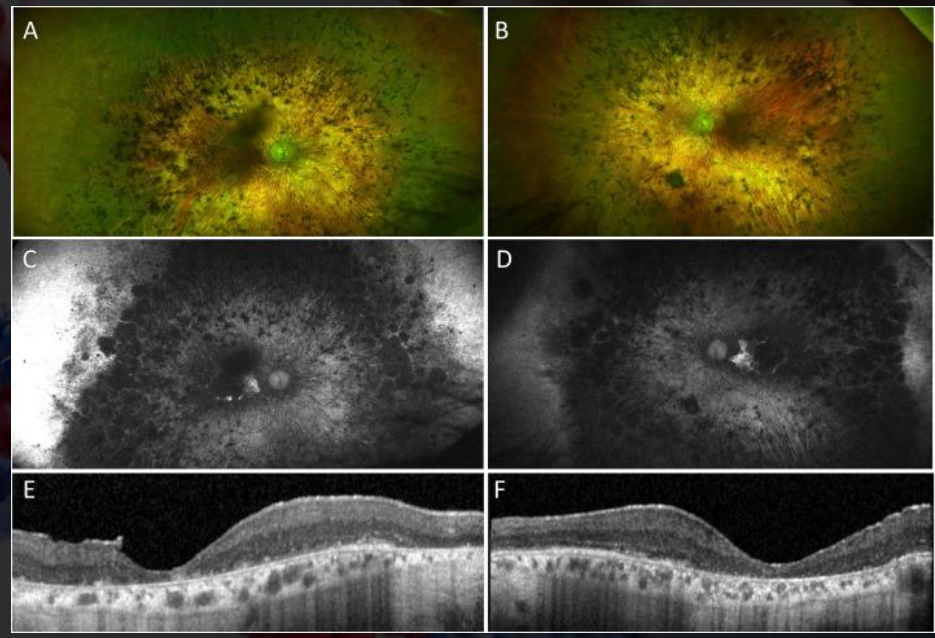
- Mutation in retinitis pigmentosa GTPase regulator (*RPGR*) gene
- Most common - 10-20% of all RP
- Most severe phenotype
- Early onset and fast progression to blindness
- No available treatment



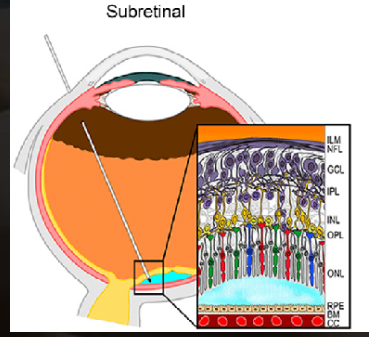
X-Linked Retinitis Pigmentosa



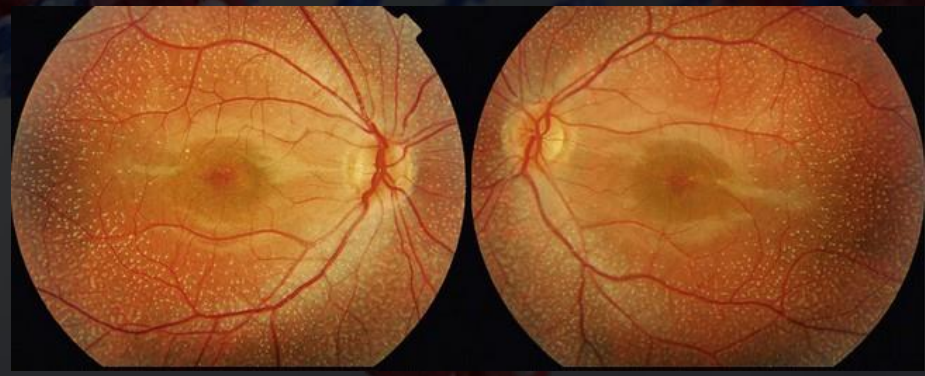
- Several clinical trials
- AAV8-RPGR
- Subretinal injection
- No significant difference
- Patient experiences subjective improvement
  - Better navigation
  - Manage better in dim-light
  - Feels better to be outside in the dark



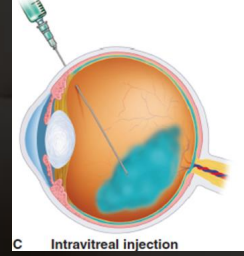
Bothnia Dystrophy



- Autosomal recessive
- High prevalence in north of Sweden
- Early onset of nyctalopia -> macular degeneration and loss of sight in adulthood
- Mutation of *RLBP1* gene
- A form of RP
- Gene therapy CPK850 – S:t Eric Eye Hospital
- Subretinal injection – 15 patients

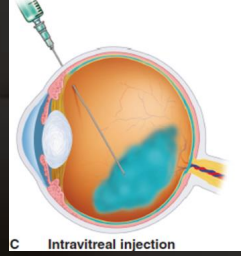


Usher Syndrome

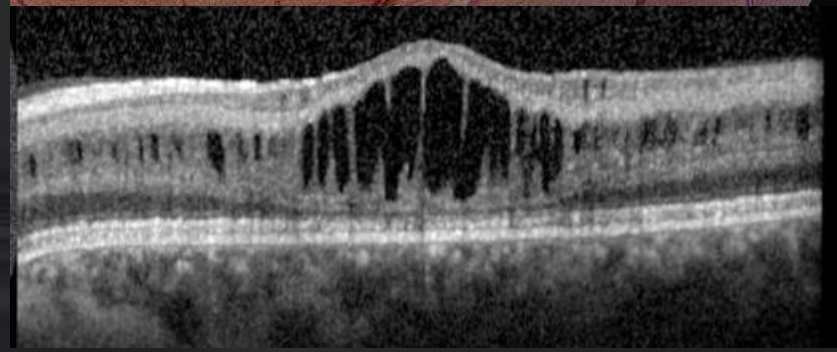


- Unusual autosomal recessive retinal disease - a form of RP
- Progressive visual- and hearing loss
- 3 subtypes
- Gene Therapy – Subtype 2 – mutation in exon 13 of *USH2A* gene
- Repated IVT every 6 months – RNA antisense oligonucleotide
- No results yet

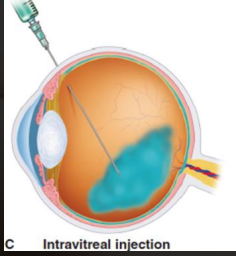
X-linked Retinoschisis



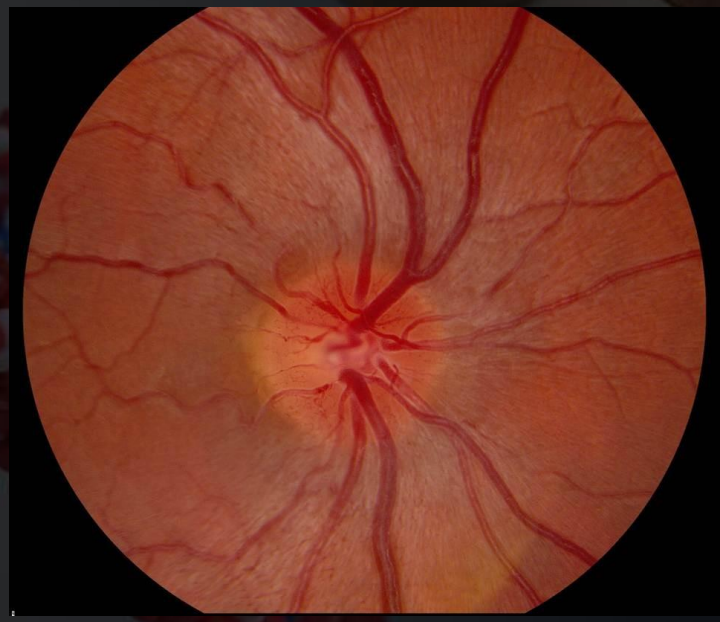
- Mutation of *RS1* gene -> abnormal function of retinoschisis protein -> separation of neuroretina, usually in the macula region -> vision decrease
- Young males
- Intravitreal injection - AAV-RS1
- Study test tolerability, dose, vision, OCT, ERG
  - Tolerable
  - One year data
  - No effect on vision, OCT or ERG



Leber Hereditary Optic Neuropathy (LHON)



- Rare, maternally inherited mitochondrial mutation
- Most common in young men
- Blindness initially in one eye, but shortly afterwards also in the other eye
- Optic nerve involvement - variable phenotype
- AAV-ND4 gene
- Intravitreal injection
- The virus vector -> retinal ganglion cell -> is transcribed -> transported to the mitochondrion

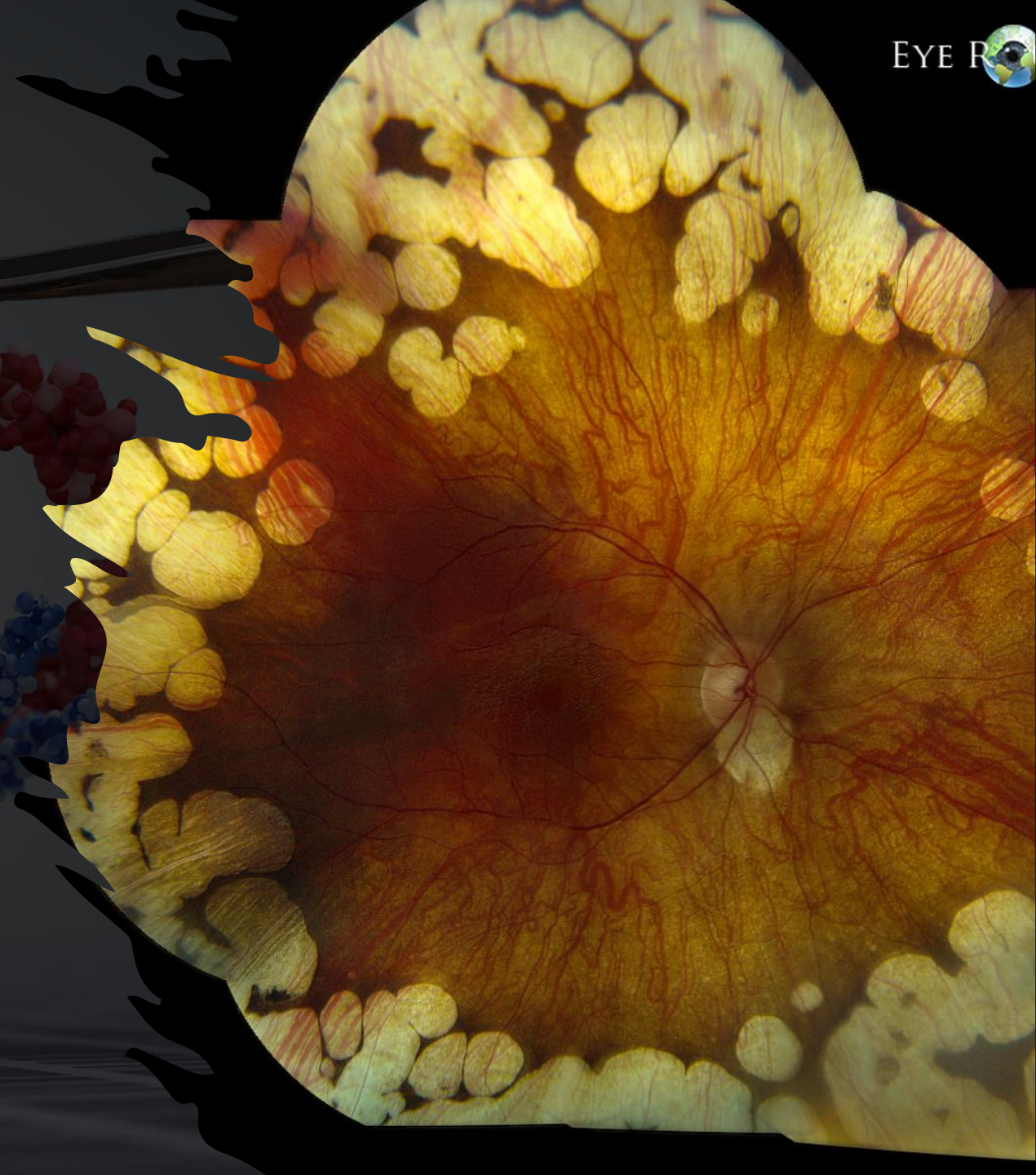


LHON

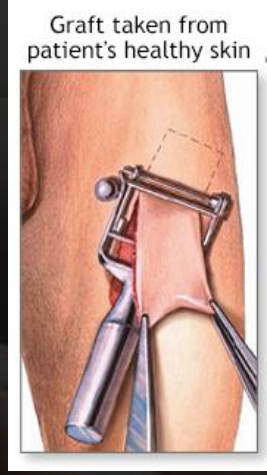
- 50 injections in one eye and placebo in the other
- 48 bilat injections
- Median duration of vision loss; 8 months
- Those who were injected in one eye also had an effect in the other eye -> difficult to interpret the results
- Improved vision by 3 lines
- Better results were hoped for
- Early treatment did not show better results

Gyrate Atrophy

- Unusual autosomal recessive retinal disease
- Progressive chorioretinal degeneration, early onset cataract and myopia
- Nyctalopia appears around 10 years of age
- Lack of OAT enzyme -> 20 fold increase of ornitin in plasma
- There is a treatment
  - Amino acide tablets
  - Diet low in protein, fruits and vegetables
  - No more then 200 calories/day from fat and carbohydrates



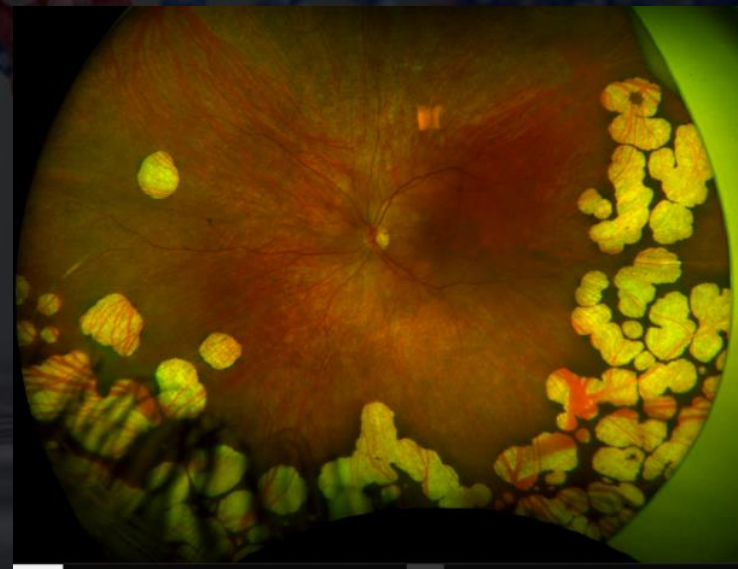
Gyrate Atrophy



- Skin biopsy from thigh 5x5 cm
- Keratinocytes are harvested, cultivated and normal OAT gene is implanted with retrovirus
- Keratinocytes with normal OAT gene are engraphted back to the thight

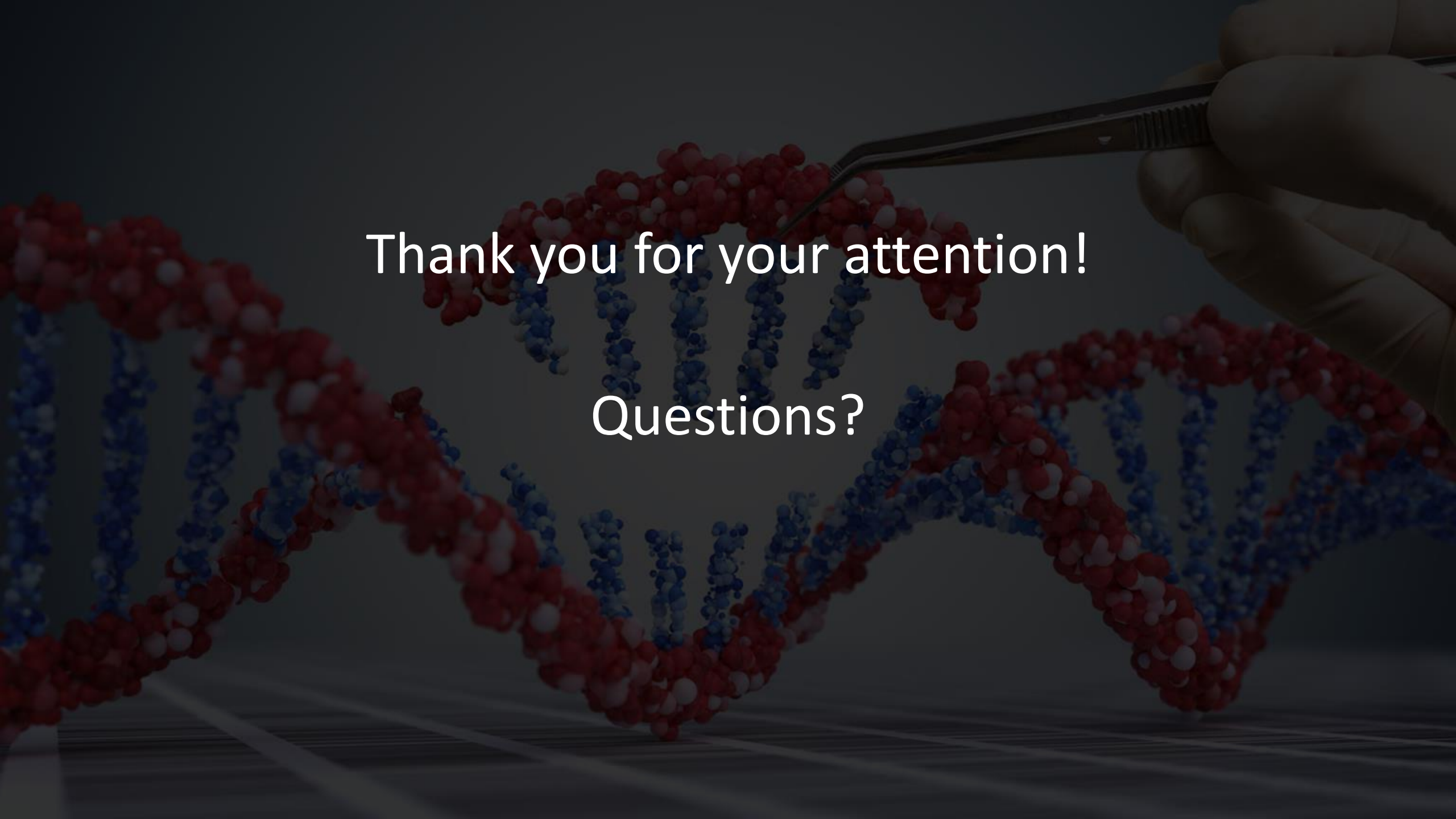
Study design

1. Can the cells express the gene
2. Amount and duration of expression
3. Are the levels enough to lower ornithin level in serum
4. Effect in the eye



In Summary

- We are entering a new era where patients with known genetic defects will be able to receive treatment in the future
- Luxturna – a milestone that shows that these treatments will be increasingly developed in the future
- Approved by both FDA and EMA
- 10 eye conditions are included in clinical studies with Gene Therapy
- It is important that these patients are cared for correctly


Thank you for your attention!
Questions?