

# RPE65 & Advances in Retinal Gene Therapy

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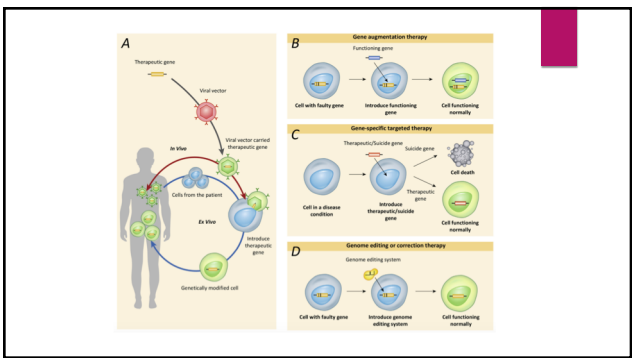
## Gene Therapy

- In broad strokes:
  - Introduction of functioning genes into cells and tissues hampered by a mutated, defective gene.
- Diseases being treated with gene therapy currently tend to be defined by cells either not expressing an important gene (actually absent) or producing a dysfunctional copy of a gene (functionally absent).
- More difficult to "fix" a disease caused by a gene that is only partially effective or too effective.



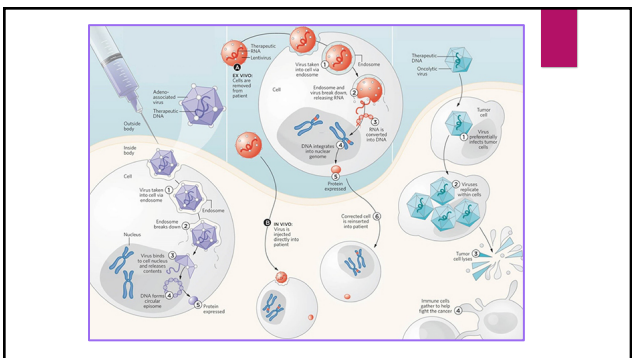
## 3 Basic Types of Gene Therapy

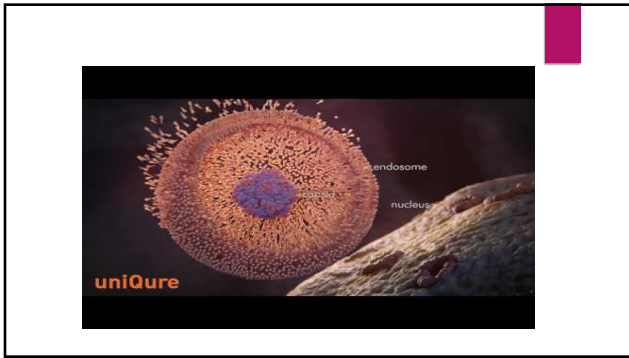
- "Gene Augmentation"
  - Introduce a normal, functioning gene to substitute for a non-functioning or under-functioning gene
- "Gene-Specific Targeting Therapy"
  - Genetic material (DNA, RNA) introduced to indirectly alter inappropriate gene activity
- "Genome Editing"
  - Directly repair mutated genes to become normal functioning genes (CRISPR)



## Inserting Genes

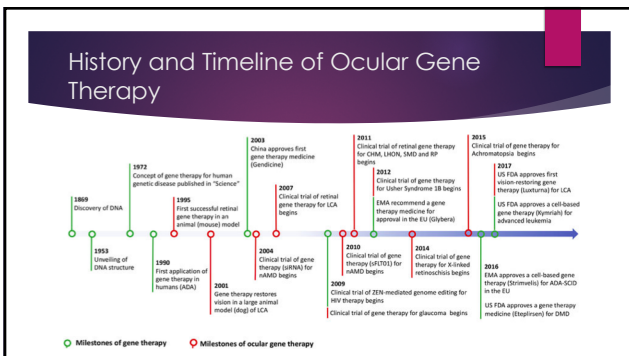
- Gene therapy uses "vectors" to package and deliver functional DNA into cells without the functional gene.
- Researchers are discovering many different kinds of vectors, but viruses have been the most effective—particularly the Adeno-associated viruses (AAV).
- AAV works well for gene therapy because:
  - It does not cause disease
  - The immune system tends to not react to it strongly
  - It does not insert the gene into the patient's DNA (next slide)





## Eye and Gene Therapy

- ▶ Over half of clinical gene therapy trials target retinal diseases.
- ▶ The eye offers some advantages to for the development of successful gene therapies:
  - ▶ Relatively directly accessible for examination and follow-up (compared to assessing bone marrow, etc)—doesn't biopsy, blood draws, etc to assess retinal health.
  - ▶ Enclosed structure and small—compared bone marrow, etc
  - ▶ Blood-retinal barrier prevents transmission of gene therapy products to the rest of the body



## RPE65 Gene

- ▶ The best known and most successful example of retinal gene therapy is treatment of **Leber's Congenital Amaurosis Type 2 (LCA2)** by replacing mutant **RPE65** with a normal copy of the gene.
- ▶ RPE65 gene encodes for the enzyme all-trans retinyl ester isomerase.
- ▶ Without this enzyme there is accumulation of All-trans-retinyl ester which leads to rapid visual decline and can over time lead to cell death of the photoreceptors and RPE cells.

## Leber's Congenital Amaurosis

### Epidemiology

- ▶ Birth prevalence of LCA is **2-3 per 100,000 births**.
- ▶ Onset of severe vision loss at **birth or within first year of life (in most cases)**.
- ▶ **Most common cause of inherited blindness in childhood**.
- ▶ Is the cause of blindness in more than **20%** of children attending schools for the blind.
- ▶ **RPE65** mutations account for **3-16%** of LCA cases.

## Leber's Congenital Amaurosis

### Clinical Findings

- ▶ Visual acuity usually around 20/200 to count fingers.
- ▶ Sluggish pupils
- ▶ Nystagmus
- ▶ Night blindness
- ▶ Light sensitivity
- ▶ Oculodigital sign\*
- ▶ Early on fundus exam usually appears normal...

## Leber's Congenital Amaurosis Type 2

Fundus Findings

## RPE65 Gene Therapy

Proof of Principle in Animal Model

- In 2001 a preclinical study with the Briard dog model of LCA2 (predisposed to RPE65 -/- and consequent blindness) was performed
- Showed marked visual improvement using the AAV-mediated delivery of RPE65.
- This triggered the development of clinical trials in humans with LCA2.

## RPE65 Gene Therapy

Clinical Trials in Humans

- In 2008 several clinical trials (phase I) found visual improvement after gene therapy with RPE65.
- In one of the seminal studies, all 12 subjects safely had stable improvement in vision and retinal function
- These 12 patients had received subretinal injections of AAV2-hRPE65v2 in their worse seeing eye.
- Visual improvement was durable for at least 3 years—observation still ongoing.

## RPE65 Gene Therapy

Clinical Trials in Humans

- Functional MRI studies revealed increased visual cortex activation and improved function and structure of visual pathway in patients who had received gene therapy in both eyes.

## RPE65 Gene Therapy

Clinical Trials in Humans

- Multi-luminance Mobility Test
  - Standardized obstacle course that study participants maneuvered through before and after treatment at various luminance levels.
  - Has served as an inclusion/exclusion criteria as well as a primary endpoint in RPE65 gene therapy studies.

## RPE65 Gene Therapy

The Surgery

- Pars plana vitrectomy
- Use of an extremely small (41 gauge) needle to inject vector into subretinal space.
- Use of intraoperative OCT helps confirm injection site and avoid too much tension on macula.

# RPE65 Gene Therapy

## The Surgery

# RPE 65 Gene Therapy

## FDA Approval

- General FDA approval process:**
  - Once enough preclinical research and clinical trials have been completed to confirm a therapy's safety profile and efficacy an application can be sent to the FDA.
  - FDA approval allows the company with the therapy to **begin marketing** their treatment.
- Applications will have their clinical results, safety information, labeling information, suggested patient population, and directions for application of the treatment.

**PRE-CLINICAL**  
Drug Sponsor's Discovery and Screening Phase

- 1** **Drug Development**  
Drug sponsor develops a drug to be tested and sent to the FDA for safety clinical trials.
- 2** **IND Application**  
The sponsor submits an Investigational New Drug (IND) application to FDA. Once approved, the sponsor may begin clinical testing. The drug sponsor may conduct early testing and manufacturing and manufacturing later for testing the drug on humans.
- 3** **Phase 1**  
The typical number of healthy volunteers used in Phase 1 trials phase experiments varies. The purpose is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized in humans.
- 4** **Phase 2**  
**100's**  
The typical number of patients used in Phase 2 drug phase evaluation experiments. The goal is to learn preliminary data on whether drug may improve the target condition or condition. For controlled trials, patients receiving the drug are compared with a control patient receiving either a placebo or a different drug. Safety concerns for patients and adverse side effects are monitored.
- 5** **Phase 3**  
**1000's**  
The final number of patients used in Phase 3. Phase studies get a more information about safety and effectiveness, study whether population and different drugs, and how the drug is metabolized with other drugs.

**CLINICAL**  
Drug Sponsor's Clinical Studies/Trials

**FDA Center for Drug Evaluation and Research (CDER)** evaluates drug applications you can file

**Animals Tested**  
Sponsor must test new drugs on animals for safety. Multiple species are tested against basic information on the safety and efficacy of the drug.

**IND REVIEW**  
Sponsor submits an Investigational New Drug (IND) application to FDA. Once approved, the sponsor may begin clinical testing. The drug sponsor may conduct early testing and manufacturing and manufacturing later for testing the drug on humans.

**What is a drug as defined by the FDA?**  
A drug is any product that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.

**NDA REVIEW**  
FDA's New Drug Application (NDA) Review

**Who reviews new drug submissions?**  
A team of CDER physicians, scientists, chemists, pharmacologists, and other scientists review the drug sponsor's data and proposed labeling of drug.

**What other drug products are regulated by FDA?**  
Most drug products are approved through the New Drug Application (NDA) process. However, some drug products, such as biologics, are approved through a different process, the Biologics License Application (BLA). The FDA also regulates off-label use of drugs, which is the use of a drug in a way that is not approved by the FDA.

- 10** **Drug Labeling**  
The drug sponsor provides labeling and other appropriate information to support the safety, efficacy, and quality of the drug.
- 8-9** **Application Reviewed**  
After an NDA is received, CDER has 60 days to decide whether to refer it to an advisory committee. The FDA Review Team is assigned to evaluate the sponsor's data and drug safety and effectiveness.
- 7** **NDA Application**  
The drug sponsor formally asks FDA to approve a new drug by submitting an NDA. An NDA includes all relevant information and data on the drug, as well as information about how the drug will be manufactured.
- 6** **Review Meeting**  
CDER sponsors a review panel to submission of a New Drug Application.
- 11** **Facility Inspection**  
CDER inspects the facilities where the drug will be manufactured.
- 12** **FDA Drug Approval**  
FDA issues an approval to the application or issues a complete response.

**FASTER APPROVALS**  
The FDA has several programs that allow for faster review and approval of certain drugs. These include Priority Review, Breakthrough Therapy, and Accelerated Approval. The FDA also has several programs that allow for faster review and approval of certain biologics, including Priority Review, Breakthrough Therapy, and Accelerated Approval.

**Med Watch**  
FDA's MedWatch system is a national safety surveillance system that allows for the timely identification, assessment, and communication of drug-related safety concerns. MedWatch is a national system for reporting and responding to adverse events and other drug-related safety concerns.

**PDUFA Prescription Drug User Fee Act**  
Since the PDUFA was passed in 1992, more than 1,000 drugs and biologics have come to the market. In 2012, drug review periods for final action, FDA, cardiovascular disease and life-threatening conditions.

# RPE 65 Gene Therapy

## FDA Approval

- Luxterna**
  - Approved December 2017
  - First directly administered gene therapy approved by FDA which targets a specific genetic defect.
  - Came after Phase III clinical trial in 31 patients.

# RPE 65 Gene Therapy

## Benefits & Risks

- Pros**
  - Sustained increased visual acuity
  - Sustained increased practical vision (i.e. ability to navigate environment)
  - Quality of life
- Cons**
  - Risk of macular hole (typically not clinically significant)
  - While vision can be restored, retinal degeneration may not be halted—still need longer term data
  - Other less significant issues: cataract formation, mild uveitis, eye itchiness...



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