RPE65 & Advances in Retinal Gene Therapy

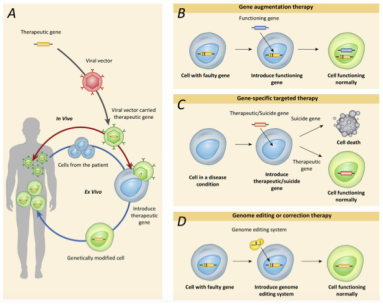
IAN DANFORD

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.

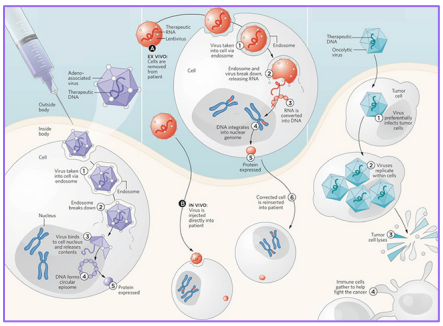
3 Basic Types of Gene Therapy

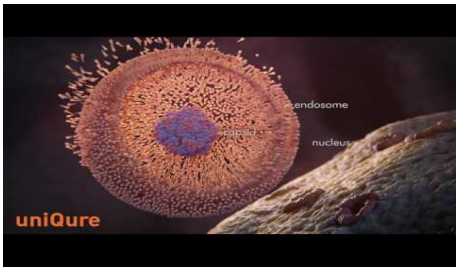
- "Gene Augmentation"
  - Introduce a normal, functioning gene to substitute for a non-functioning or under functioning gene
- "Gene-Specific Targeting Therapy"
  - Genetic material (DNA, RNA) introduced to indirectly alter inappropriate gene activity
- "Genome Editing"
  - Directly repair mutated genes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

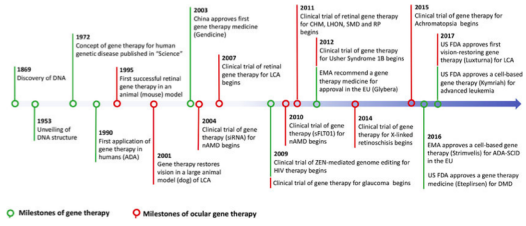




Eye and Gene Therapy

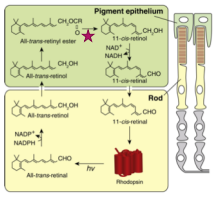
- Over half of clinical gene therapy trials target retinal diseases.
- The eye offers some advantages to for the development of successful gene therapies:
  - Relatively directly accessible for examination and follow-up (compared to assessing bone marrow, etc)—doesn't biopsy, blood draws, etc to assess 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

History and Timeline of Ocular Gene Therapy



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.



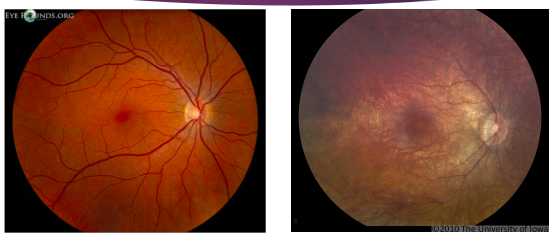
Leber's Congenital Amaurosis
Epidemiology

- 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

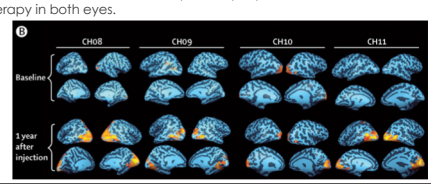
- In 2001 a preclinical study with the Briard dog model of LCA2 (predisposed to RPE65 -/- and consequent blindness) was performed
- Showed marked visual improvement using the AAV-mediated delivery of RPE65.
- This triggered the development of clinical trials in humans with LCA2.

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.

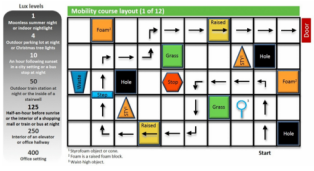
RPE65 Gene Therapy
Clinical Trials in Humans

- 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.



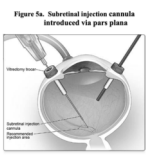
RPE65 Gene Therapy
Clinical Trials in Humans

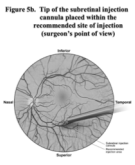
- Multi-luminance Mobility Test
  - Standardized obstacle course that study participants maneuvered through before and after treatment at various luminance levels.
  - Has served as an inclusion/exclusion criteria as well as a primary endpoint in RPE65 gene therapy studies.



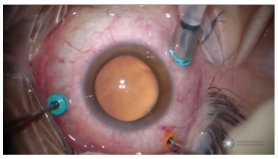
RPE65 Gene Therapy
The Surgery

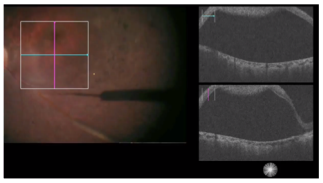
- Pars plana vitrectomy
- Use of a extremely small (41 gauge) needle to inject vector into subretinal space.
- Use of intraoperative OCT helps confirm injection site and avoid too much tension on macula.





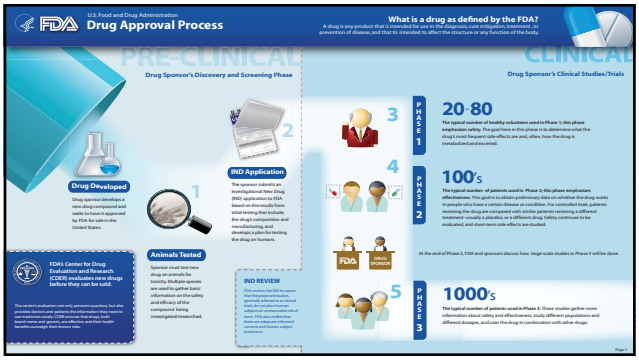
RPE65 Gene Therapy
The Surgery

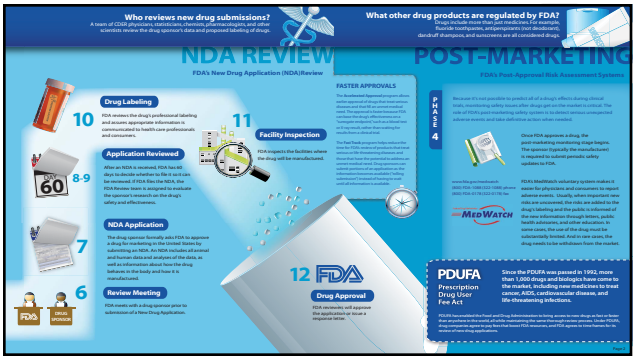




RPE 65 Gene Therapy
FDA Approval

- **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.





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.

Spark™ THERAPEUTICS

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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