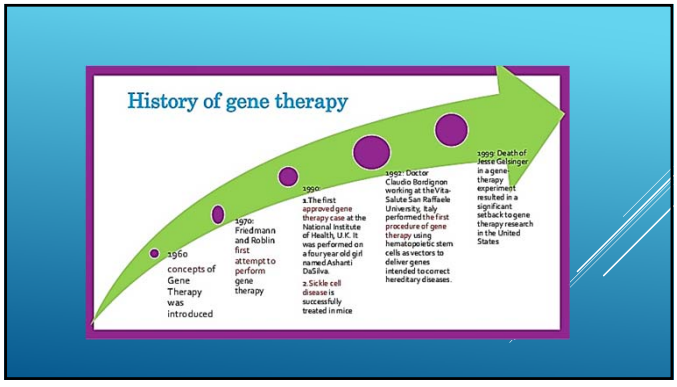
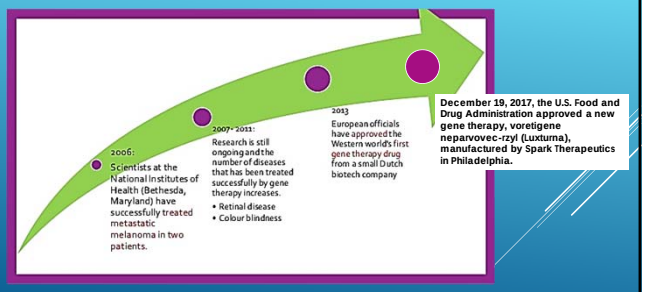
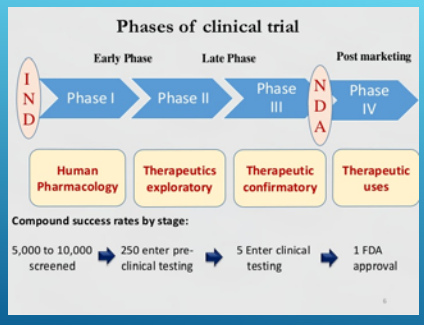
I have no conflict of interest to report



History of Gene Therapy



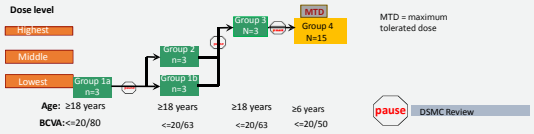
DRUG DEVELOPMENT PROCESS



Rare Disease

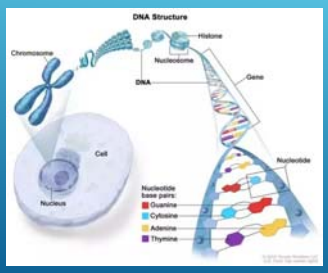
- Disease affecting <200,000 persons in US
- Optimal Pre-Clinical and early drug development
- Small trials <50 participants
- Trial flexibility
- Innovative endpoints
- Adaptive design
- Control can be concurrent or historical (fellow eye)

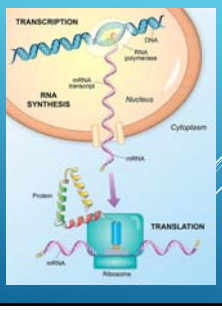
Example: Phase 1/2 – Study Design



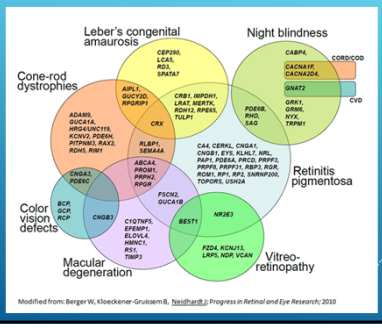
- Study Design
  - Dose escalation phase in adults
  - Early groups have worse visual acuity
  - Expansion group at maximum tolerated dose (MTD) in both children and adults
- Primary Endpoint is Safety

BACK TO THE BASICS



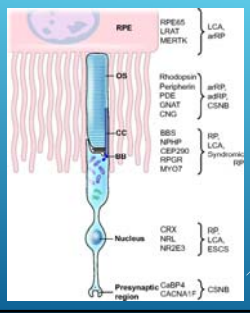


GENETIC EYE DISEASE



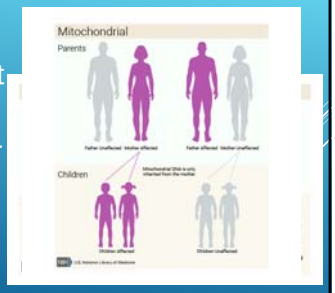
Modified from: Berger W, Kloeckener-Gruissem B, Neidhardt J: *Progress in Retinal and Eye Research*; 2010

LOCATION OF EXPRESSION OF RETINA-SPECIFIC GENES

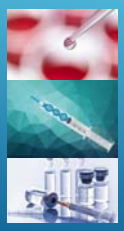


INHERITED EYE DISEASE

- Autosomal dominant
- Autosomal recessive
- X-linked (recessive or dominant)
- mitochondrial



CLINICAL TRIALS FOR GENETIC EYE DISEASE

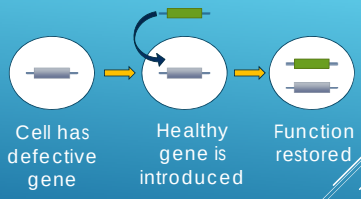


In the United States

- 75 Active clinical trials on clinicaltrials.gov under the search terms genetic and eye disease
- 32 involve treatment

WHY GENE THERAPY IN EYE DISEASE?

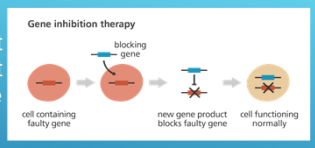
- Currently impossible to remove, treat, and re-graft neural tissue
- Accessibility
- Immune privilege

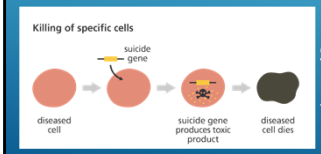


Giving patients a healthy version of a defective gene

TYPES OF GENE THERAPY

A new gene product can block the product of a faulty gene

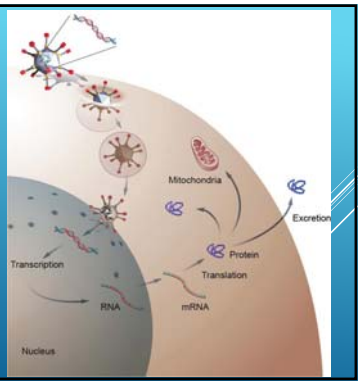




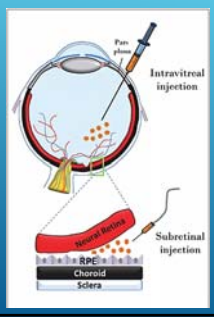
Suicide genes can be inserted to kill the target cell

HOW DOES IT WORK?

- A vector must be used to shuttle the DNA into the cell
- Viruses have special molecular mechanisms to efficiently deliver their genomes to a host cell
- The virus genome is removed and a new healthy gene is added to the vector



GENE THERAPY FOR EYE DISEASE



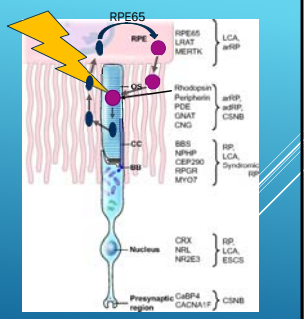
- In-vivo: Putting therapy into patient where the gene will enter the cells
- placed into the vitreous or directly under the light-sensing cells

LEBER CONGENITAL AMAUROSIS (LCA)

- Severe visual loss beginning in infancy
- Sensitivity to light
- Involuntary eye movements (nystagmus)
- Extreme farsightedness
- Pupils do not respond properly to light
- at least 14 genes known to be associated with LCA

RPE65 gene mutation

results in a loss of sensitivity to light and inability to generate functional visual pigment



PRECLINICAL STUDIES

Lancelot received gene therapy in 2001

Briard dogs with mutation in the *RPE65* gene are blind by 1 year

>50 Briard dogs have received gene therapy

Dogs treated early continue to have vision after 7 years

LANCELOT WAS SUCCESSFULLY TREATED WITH GENE THERAPY

LCA gene therapy trials

- safe
- Early visual improvements
- 2 of the 3 Phase I/II studies reported that the improvement in vision began to decrease after 1-3 years.
- Possibly due to differences in the vectors and delivery methods used

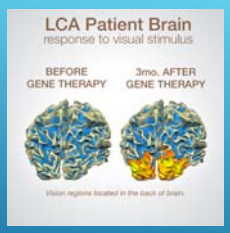
2015 Phase III for LCA treatment with gene therapy complete

- 27 out of 29 participants significantly improved their ability to navigate a mobility course in dim and bright settings
- These individuals were virtually blind before receiving the therapy

Spark Therapeutics received FDA approval

YANNICK WAS BLIND BEFORE THERAPY

Yannick Duwe received gene therapy in 2007. The treatment enabled him to use a computer instead of Braille, and work much easier and faster at school



CHOROIDEREMIA

- X-linked
- Night-blindness in teens
- Vision loss begins in the periphery, leading to tunnel vision and then blindness
- *CHM* gene makes a protein needed for nutrient transportation

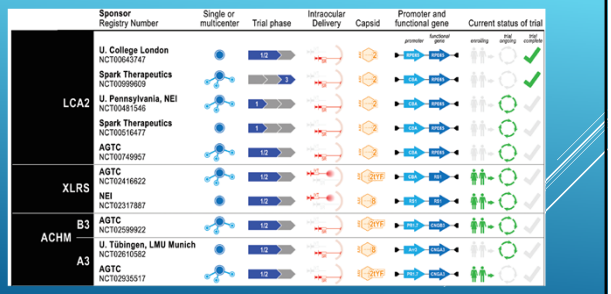
2012 Gene therapy trial in the UK
- 6 individuals were treated in 1 eye

4 years after treatment:
- 2 had significant vision improvement sustained while untreated eye declined
- 3 maintained vision in treated eye but not fellow eye
- 1 individual receiving low dose treatment had slow deterioration of vision in both eyes

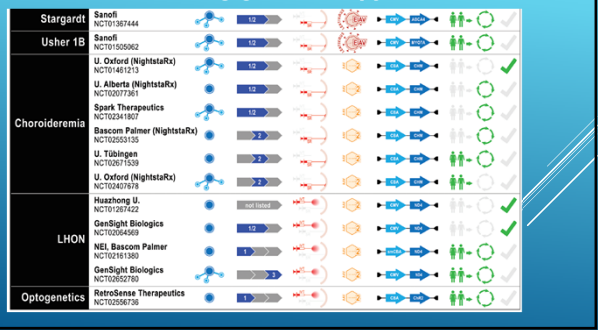
"And now to know that there is so much opportunity, there is so much that I can actually do and do the things that I have actually wanted to and continue to do the things I really enjoy."

JOE PEPPER WAS SLOWLY GOING BLIND UNTIL GENE THERAPY REVERSED HIS SIGHT LOSS

Current studies involving gene therapy



Current studies involving gene therapy



Thank you

Questions?