Seeing the Light with Retinal Gene Therapy: From Fantasy to Reality

Lancelot, 1st dog to benefit from retinal gene therapy

Sofia Sees Hope
LCA Meeting
Philadelphia, PA

Jean Bennett, M.D., PhD

Bennett & Maguire: Conflicts

Bennett, J, Jacobson, SG, Maguire, AM, Hauswirth, WW, Aguirre,GD, Acland, GD
"Method of treating or retarding the development of blindness,"
U.S. Patent 8,147,823 B2; April 3, 2012
2002: Bennett & Maguire waived any potential financial gain

Maguire

- PI of 2 CTA's from Spark for clinical trial efforts

Bennett:

- Scientific (non-equity-holding) founder of Spark Therapeutics
- SRAs from: Biogen, Limelight Bio, REGENX
- Founder of GenSight Biologics, Limelight Bio
- Intellectual property Licensing (UPenn)
- SABs: Akuous, Nightstar, ProQR, Roche, Odylia

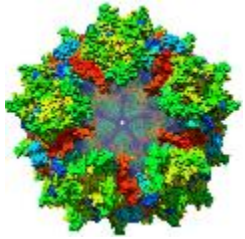
IRDs: Attempted Treatments

- Anticoagulants
- Cyclodialysis
- DMSO
- “Soviet Union” therapy: ENCAD (pigmentary retinal abiotrophy)
- Hormones
- Laser
- Ozone
- Mineral supplements
- Subcutaneous placental implantation
- IM injections cod liver oil
- Retrobulbar atropine
- Scleral trephination
- “Cuban” therapy (fatpad on sclera)
- Sympathectomy
- Atropine injections
- Saffron
- Gingko
- Electrical stimulation (galvanism)
- Vasodilation
- Zinc
- Bee stingvenom
- Diet
- Electricity
- Exercise
- Hyaluronidase
- Light deprivation
- Miotics
- Radiotherapy
- Tissue extracts
- Steroids
- Taurine
- Ultrasound
- α-omega
- Ocular muscle implantation
- Stem cell transplants
- Marijuana
- Bilberry

Modified from: G.A. Fishman, Survey of Ophthalmology 58:652-63 (2013)

Retinal Gene Therapy is Alive and Well!

- One approved retinal gene therapy: Luxterna (RPE65)
- Currently 707 people enrolled in trials
- 842 People are anticipated to enroll by end of 2018
- Subretinal & intravitreal delivery
- Majority of studies (640/707) use AAV (remainder lentivirus)
  - Mostly AAV2
  - Six trials use AAV8
  - Three use AAV5
  - One uses AAV4
  - Four use AAVtY2F
  - One plans AAV7m8
- >30 trial sites

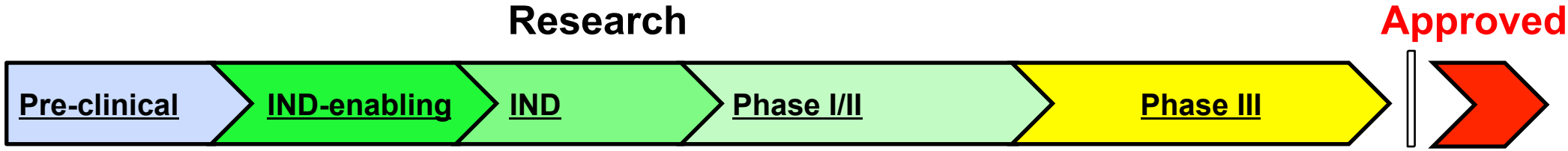


GENES and retinal disease

First Lab Studying
Human Retinal
Degenerations

https://sph.uth.edu/retnet

Genes and Gene Therapy Progress



ABCA4
AIPL1
BBS4
BEST1
PRPH2
PRPH8
PRPH31
RHO
RPGRIP1

CRB1
GUCY2D
LCA5
PDE6A
RdCVF
RDH12
RLBP1

ABCA4
CEP290
ChOps
CNGA3
CNGB3
Endostatin
GS030
MERTK
RGX-314
PDE6B
PEDF
RPE65
RPGR
RS1
S-FLT
MYO7A

CHM
ND4

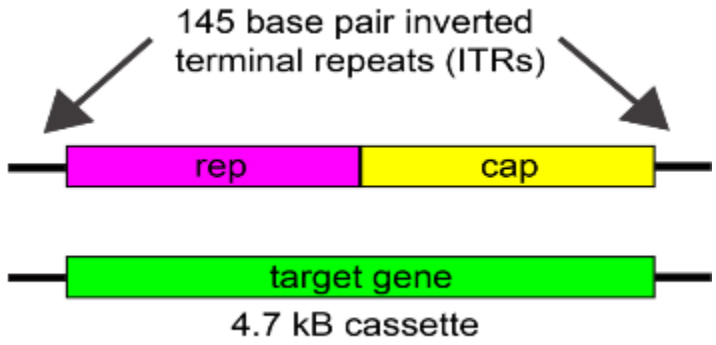
RPE65

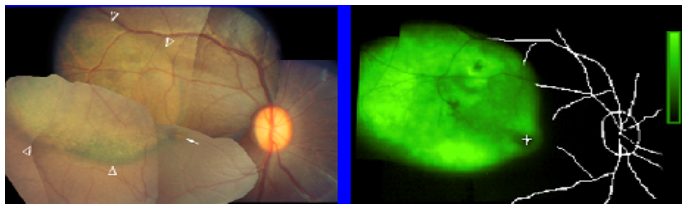
Center for Advanced Retinal & Ocular Therapeutics
PennCAROT

July 2019

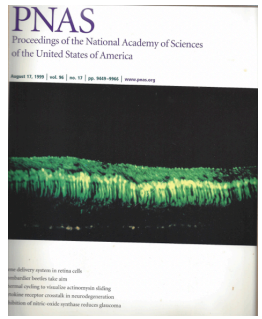
Adeno-associated virus (AAV)

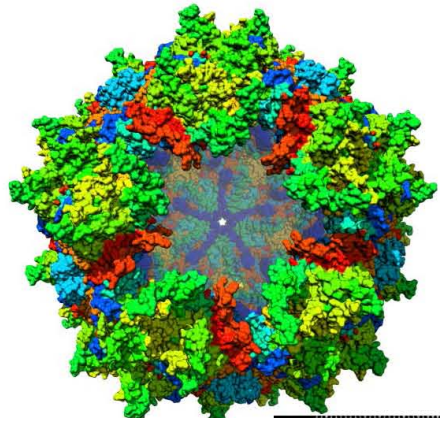
- **Non-pathogenic member of *Parvoviridae* family**
- **Non-enveloped single-stranded DNA**
- **Can infect post-mitotic cells**
- **Minimal DNA integration**
- **Stable in nucleus**
- **Capsid determines tropism**



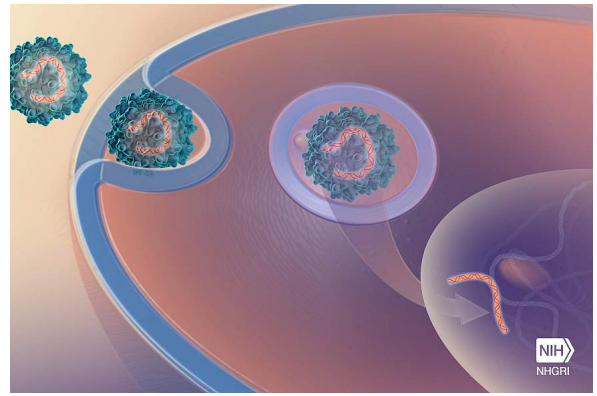


Bennett, Maguire, Cideciyan, Schnell, Glove,r, Anand, Aleman, Chirmule, Gupta, Huang, Gao, Nyberg, Tazelaar, Hughes, Wilson, Jacobson, PNAS 96:9929-5 (1999)



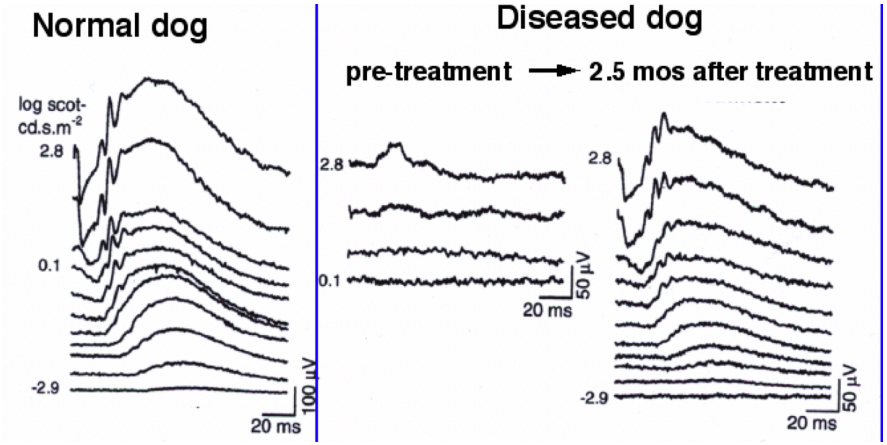


Model by Luk Vandenberghe



Preclinical Proof-of-Concept: Affected Briards

Pre Injection 3 Months Post Injection



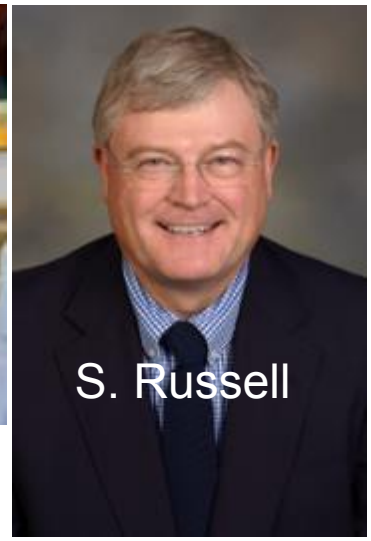
- Robust responses in dogs <2yo

Nat. Genet .Mutant of the Month

The Bennett Lab Shows Lancelot His Article

Acland et al, Nat Genet 28:92 (2001)
Bennicelli et al, Mol Ther 16:458 (2008)
Narfstrom & Rakoczy showed complementary results

Subretinal injection of AAV -LUXTURNA^{R} (voretigene neparvovec-rzyl)



Surgeon: J. Commander, MD, MEEI/Harvard
(after completing surgical training)

A.Maguire, MD (pioneer of technique) during injection of a clinical trial patient at CHOP

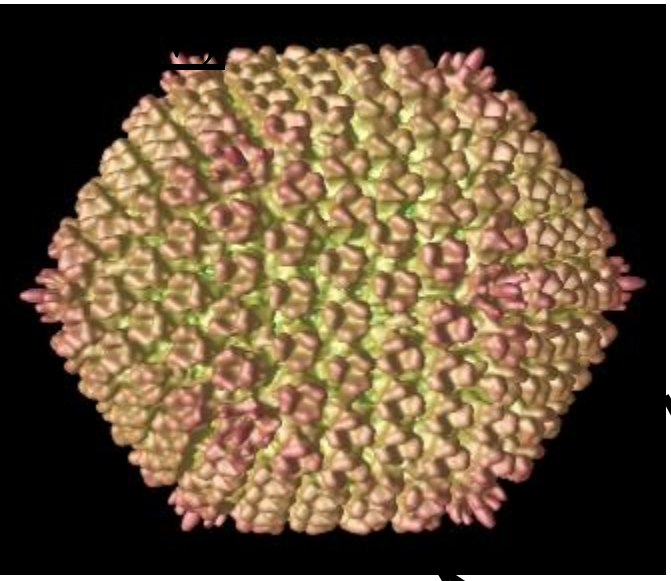
Additional surgeon in Phase 3: J. Haller

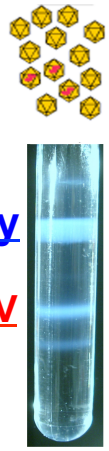
Assistants at CHOP:
E.Pierce
D. Gewaily,
J. Ruggiero

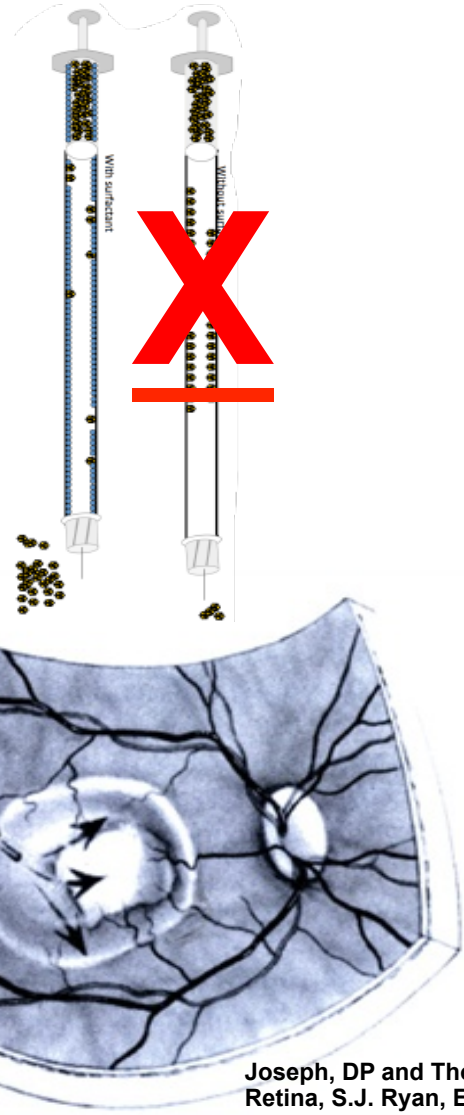
Accurate dosing assured by:

- Removal of “empty” capsids
- Surfactant to prevent loss of product to device

Viral vector (AAV2)

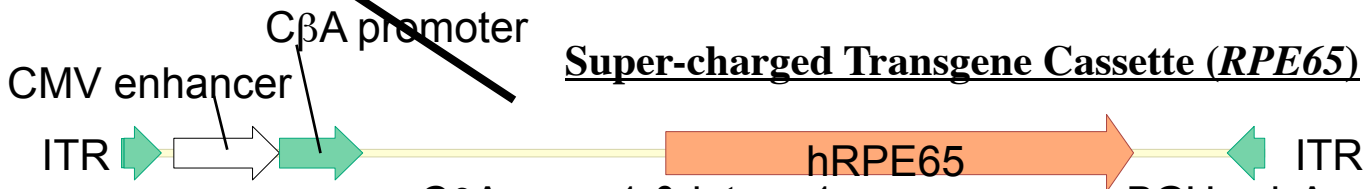






Joseph, DP and Thomas, MA, in Retina, S.J. Ryan, Editor-in-Chief, 3 Edition, Mosby, Inc., 2001, pg 2564

Super-charged Transgene Cassette (*RPE65*)



Bennicelli, Wright et al,
Mol Ther 16:458-65 (2008)

N. Dejneka
J. Bennicelli

Pediatric population essential to include in this progressively degenerative disease

- No path for pediatric drug development in ophthalmology
  - » We obtained approval and paved the way for all future pediatric gene therapy trials

Code of Federal Regulations
TITLE 45
DEPARTMENT OF HEALTH AND HUMAN SERVICESPART 46
PROTECTION OF HUMAN SUBJECTS
Subpart D: Protections for Children Involved as Subjects in Research

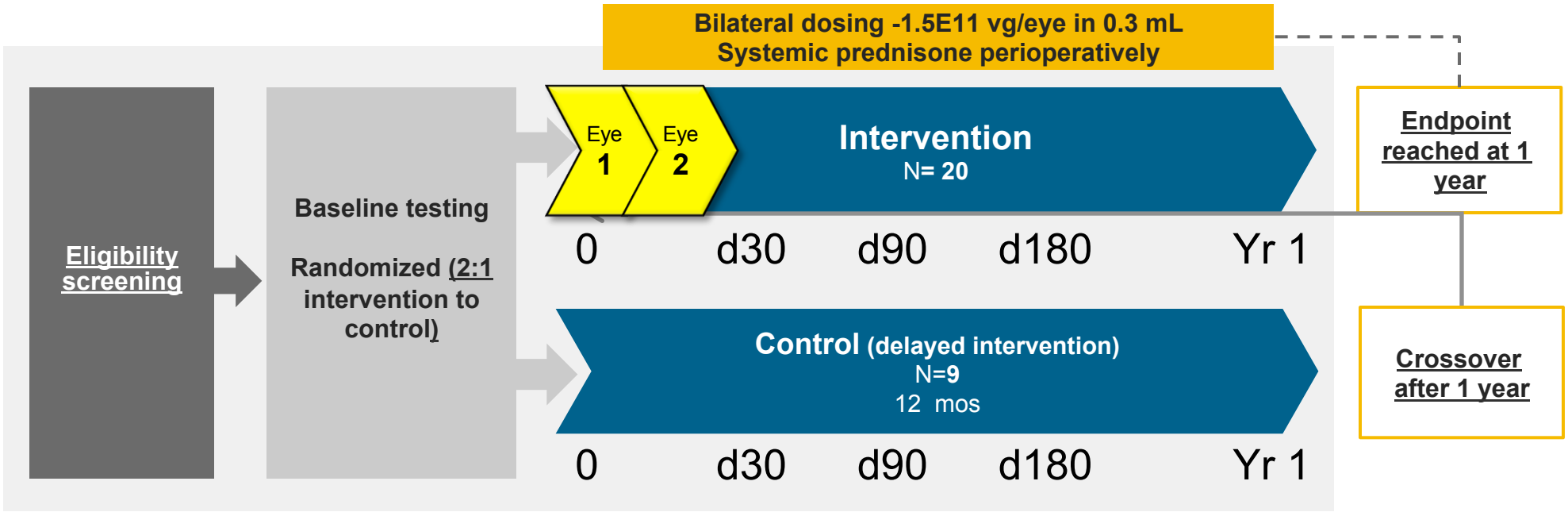
Document clinical meaningfulness

CHOP Phase 1: Exploratory Vision Test

David and Betsy Brint, parents of a child with LCA

Katherine High, Sponsor

Phase 3 Trial Design



Trial endpoints

Primary

- Mobility test (MT) change score at 1 year (binocular)

Secondary

- Full-field light threshold sensitivity testing (FST), averaged over both eyes
- MT change score, first injected eye
- Visual acuity (VA), averaged over both eyes

Russell S, et al. Lancet 2017; 390(10097):849-60.

Two sites (CHOP-Maguire & Ulowa-Russell)

Spark THERAPEUTICS

Post-launch…

- More patients treated with Luxturna post-approval than were treated in clinical trials
- Patients treated in >10 treatment centers in USA
- First patient treated in Paris, France January 2019

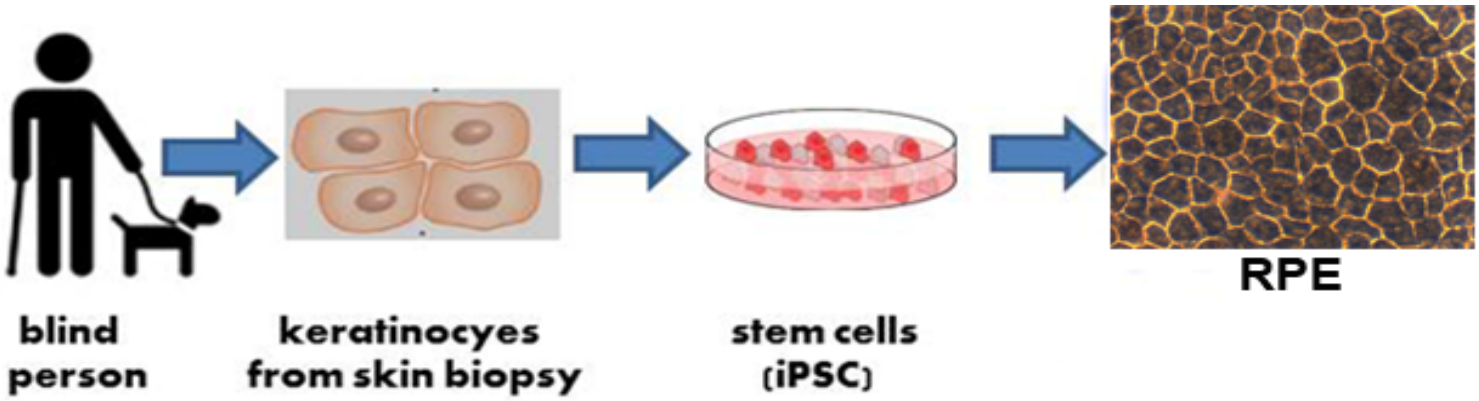
Monroe, 4yo
- Children's Hospital LA
- Able to see at night for the first time.

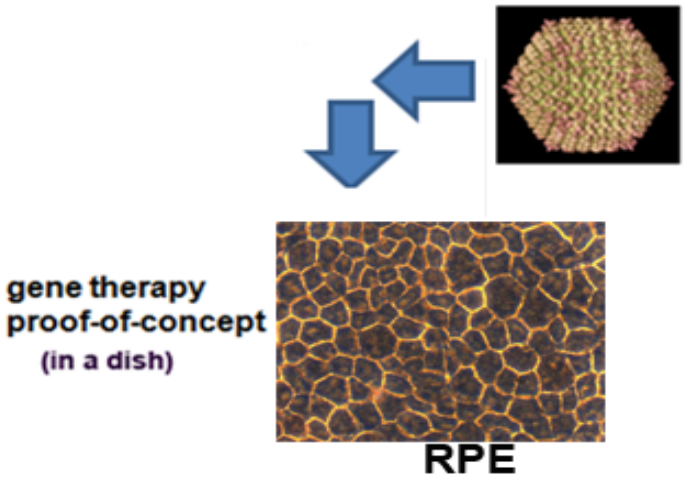
Creed, 9yo
- Bascom Palmer
- His dreams of throwing his blind cane into the lake fulfilled!

Jack, 13yo
- Treated at Harvard MEEI
- Reads books, sees white boards, rides his bike.

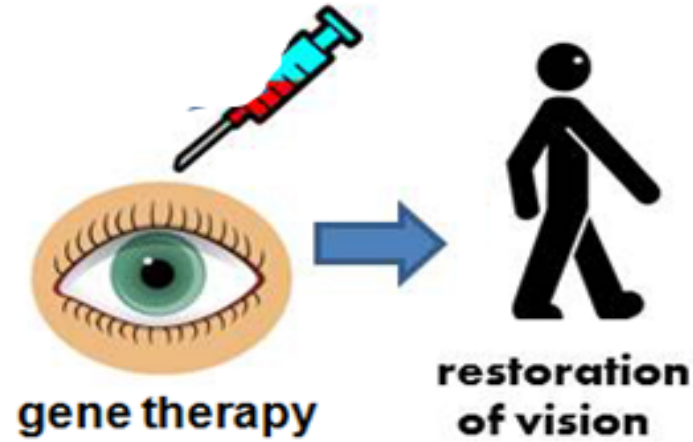
How can we accelerate progress?

In cases where animal models are unavailable or are irrelevant, it is now possible to obtain proof-of-concept data in a dish





Safety Studies In Wildtype Animals



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Bennicelli and Bennett, eLIFE, Aug 27;2:e01291. doi: 10.7554/eLife.01291 (2013).

Which LCA targets are the most challenging for gene therapy and why?

- Developmental conditions
- Large genes
- Slowly progressing diseases
- Don’t know enough about the natural history
- Assymetric disease
- Rapid degeneration

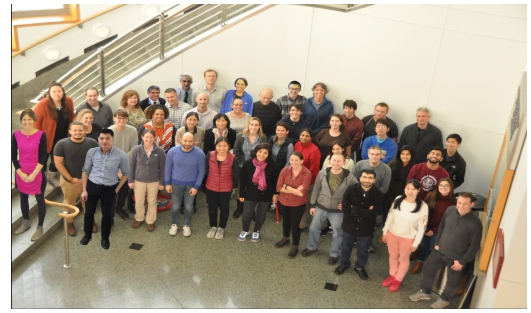
- Treat a fetus?
- Cargo capacity
- Takes too long to get results
- What outcome measures?
- How to interpret data?
- Need cells for gene therapy to be effective

Luxturna: Impact on Treatment for LCA

- 1st & only approved gene therapy for inherited disease in USA and Europe
- Unlocking the potential of the Human Genome Project
  - To provide therapeutic options for people who have had none
- Pioneering changes in medical practice
  - Motivating ophthalmologists and insurers to do genetic testing
  - Introducing handling and use of gene therapy vectors into pharmacies and operating rooms
- Created a path for genetic treatments to blindness

We are thankful to our clinical trial participants, team members, regulatory bodies and advisors ……..and the dogs who helped pave the way

We are grateful to:



- **Our Subjects & their Families**
- **DSMB**
- **IRB, RAC, FDA, EMA, FDA Advisory**
- **The Children's Hospital of Philadelphia**
- **Foundation Fighting Blindness**
- **Foundation for Retinal Research**
- **CAROT & F. M. Kirby Foundation**
- **Research to Prevent Blindness**
- **NEI/NIH**
- **Paul and Evanina Mackall Foundation Trust**
- **National Center for Research Resources**
- **Howard Hughes Medical Institute.**