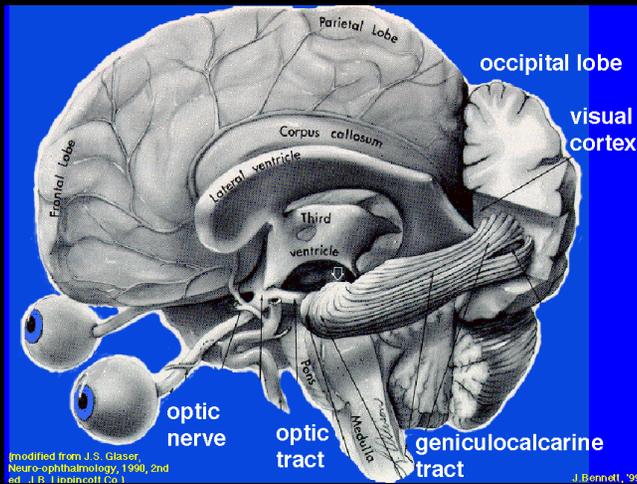


The Importance of Primates (and Other Animals) in Translational Research for Inherited Blindness



Lancelot, 1st dog to benefit from retinal gene therapy

Neuroscience Forum

NAM

October 4, 2018

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,”

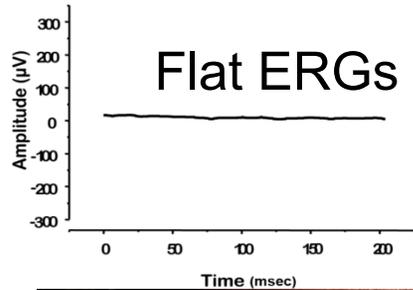
U.S. Patent 8,147,823 B2; April 3, 2012

2002: Bennett & Maguire waived any potential financial gain

-
- Academic initiated study which led to spin-out of a CHOP company (Spark, of which Bennett is a non equity-holding founder) to fund Phase 3
 - Maguire is PI of 2 CTA's from Spark for clinical trial efforts
 - Bennett has SRAs from Biogen and Limelight Bio and through J. Wilson/UPenn from REGENX

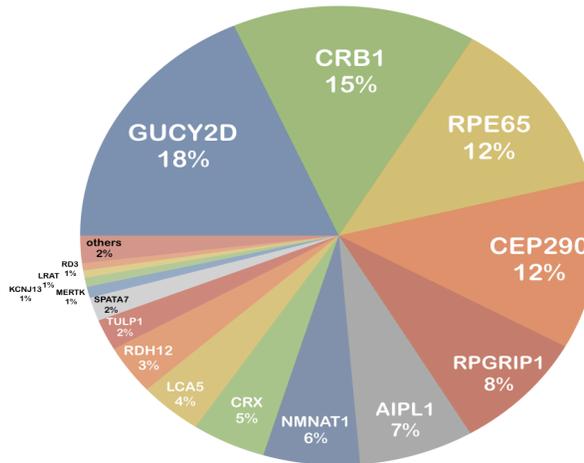
Other: Bennett: Founder of GenSight Biologics, Limelight Bio;
Intellectual property Licensing (UPenn)

Retinal Pigmented Epithelium 65 kDa Protein (RPE65)-Mediated Disease



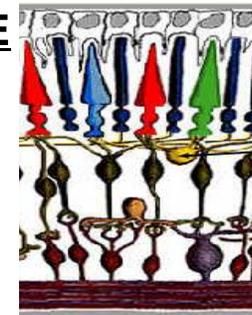
- LCA, Early Onset RP
- Progressive degeneration
 - ~3,000 cases in USA
 - Severely abnormal vision

~550 RPE65



U. Zurich

RPE

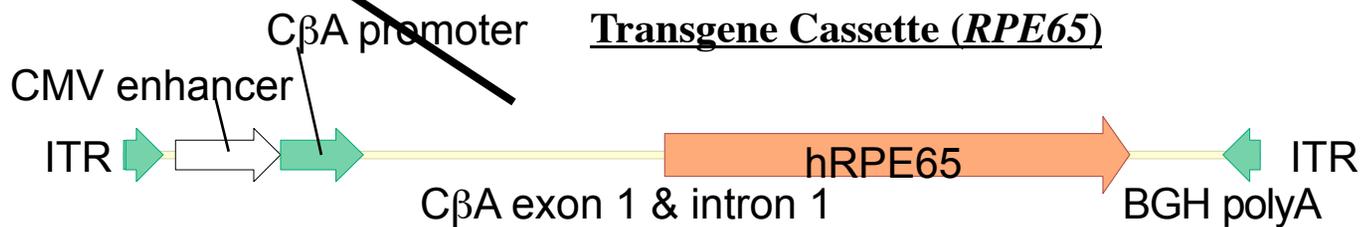
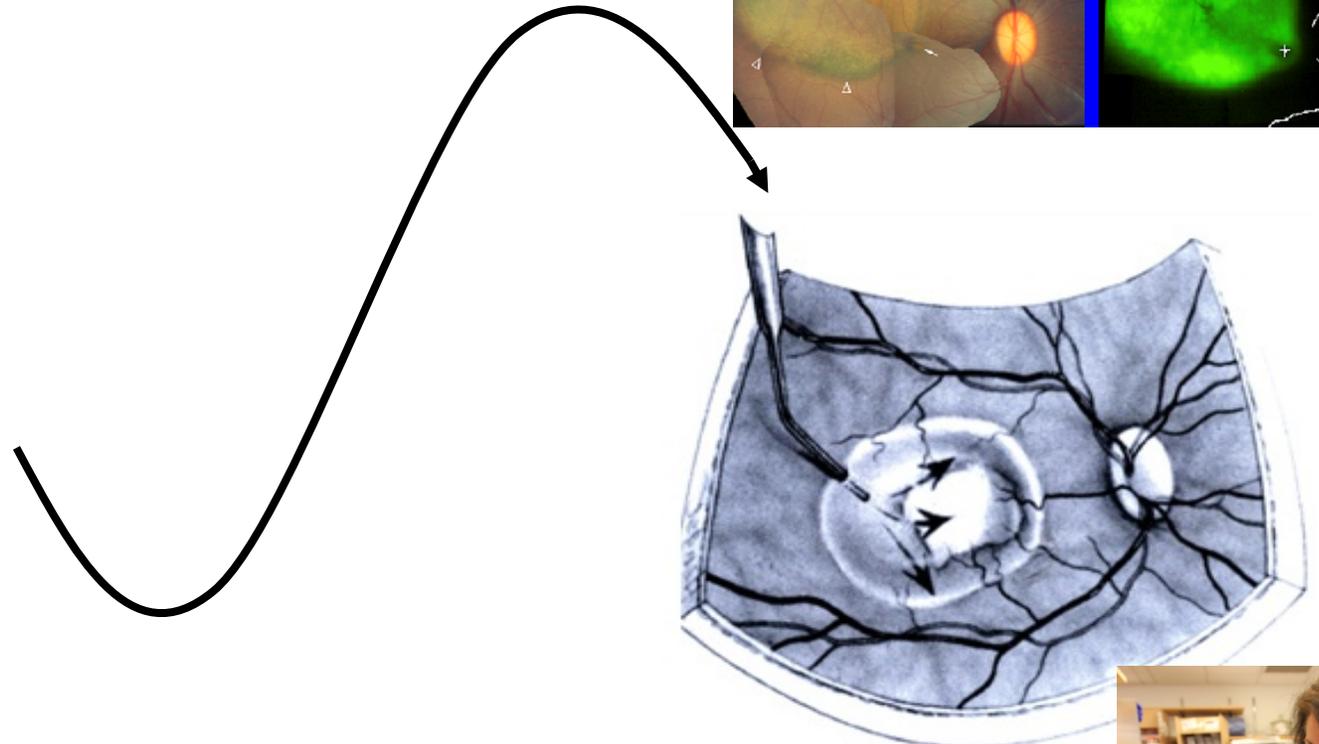
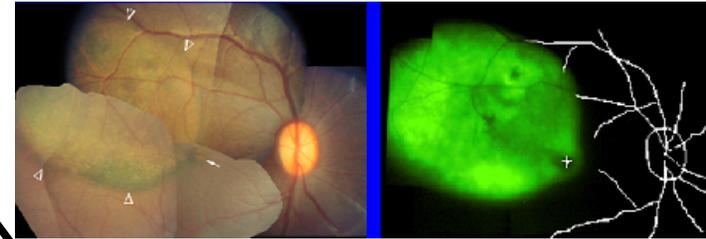
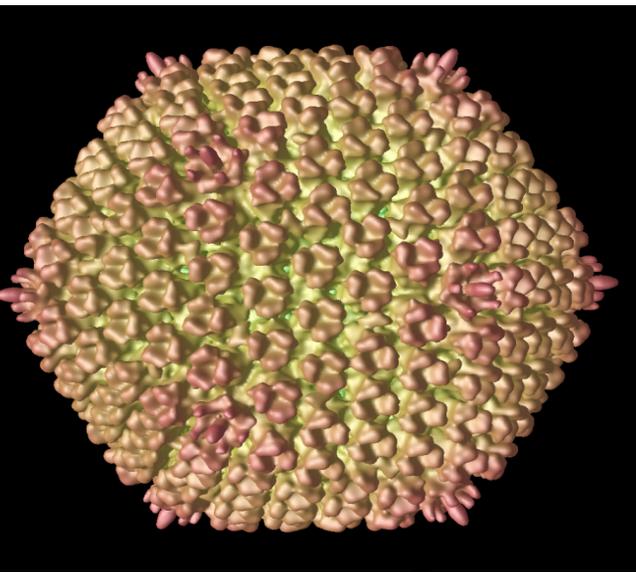


11-
cis

Treatment strategy for LCA-RPE65

(delivers the RPE65 isomerohydrolase to RPE cells thereby restoring the visual cycle)

Viral vector (engineered AAV)



Jeannette Bennicelli

Affected Briards: Mobility

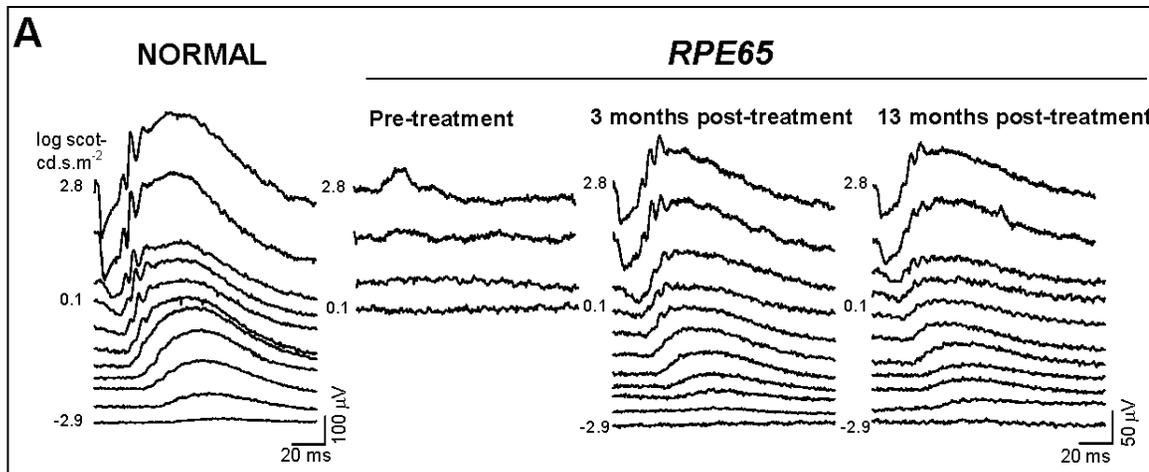
Pre Injection



3 Months Post Injection



ERGs



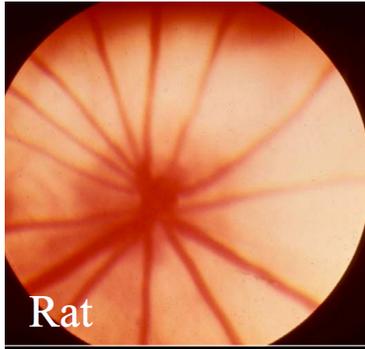
Gene therapy restores vision in a canine model of childhood blindness

Gregory M. Acland¹, Gustavo D. Aguirre¹, Jharna Ray¹, Qi Zhang¹, Tomas S. Aleman², Artur V. Cideciyan², Susan E. Pearce-Kelling¹, Vibha Anand², Yong Zeng², Albert M. Maguire², Samuel G. Jacobson², William W. Hauswirth³ & Jean Bennett²

To gain assurance that the dose/procedure/reagent would be safe in children, we tested it first in non-human primates.

WHY?

Note: All of our NHPs are “recycled”



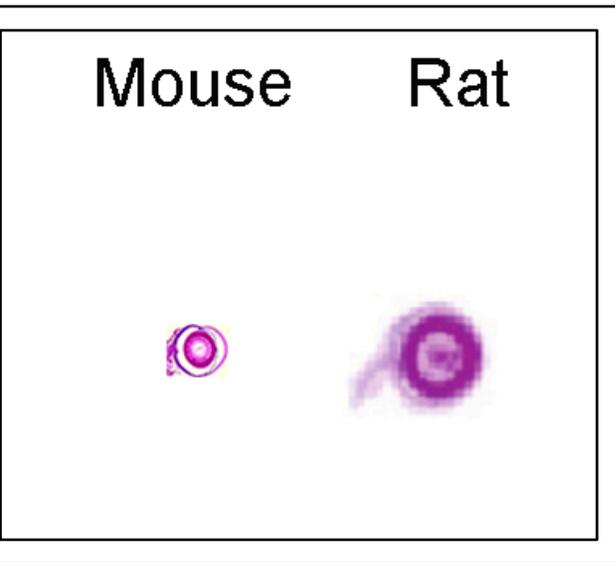
Rat

Rodents



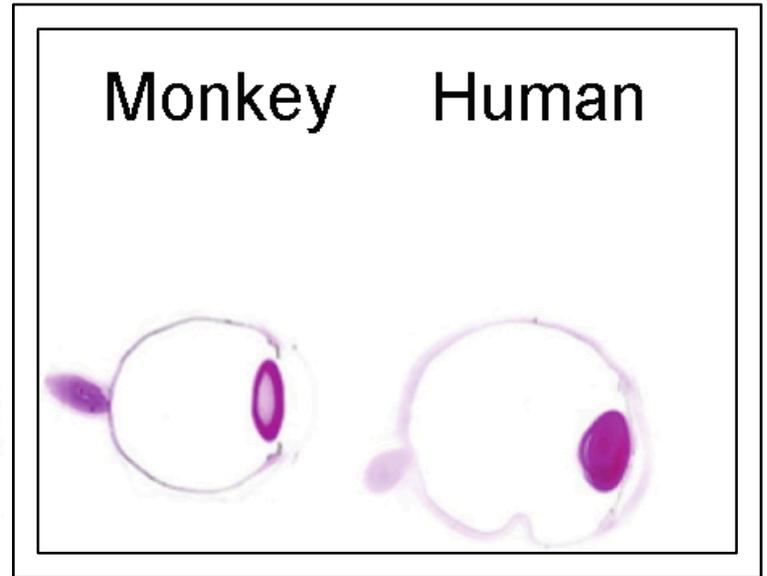
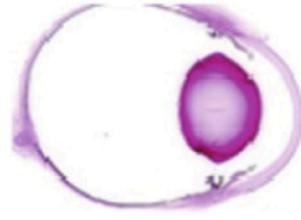
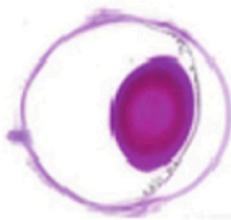
Primate

Primates



Rabbit

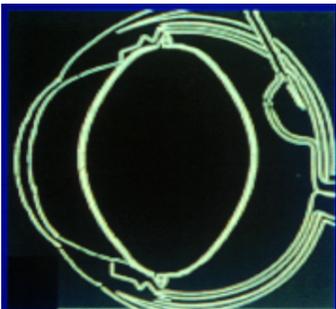
Dog



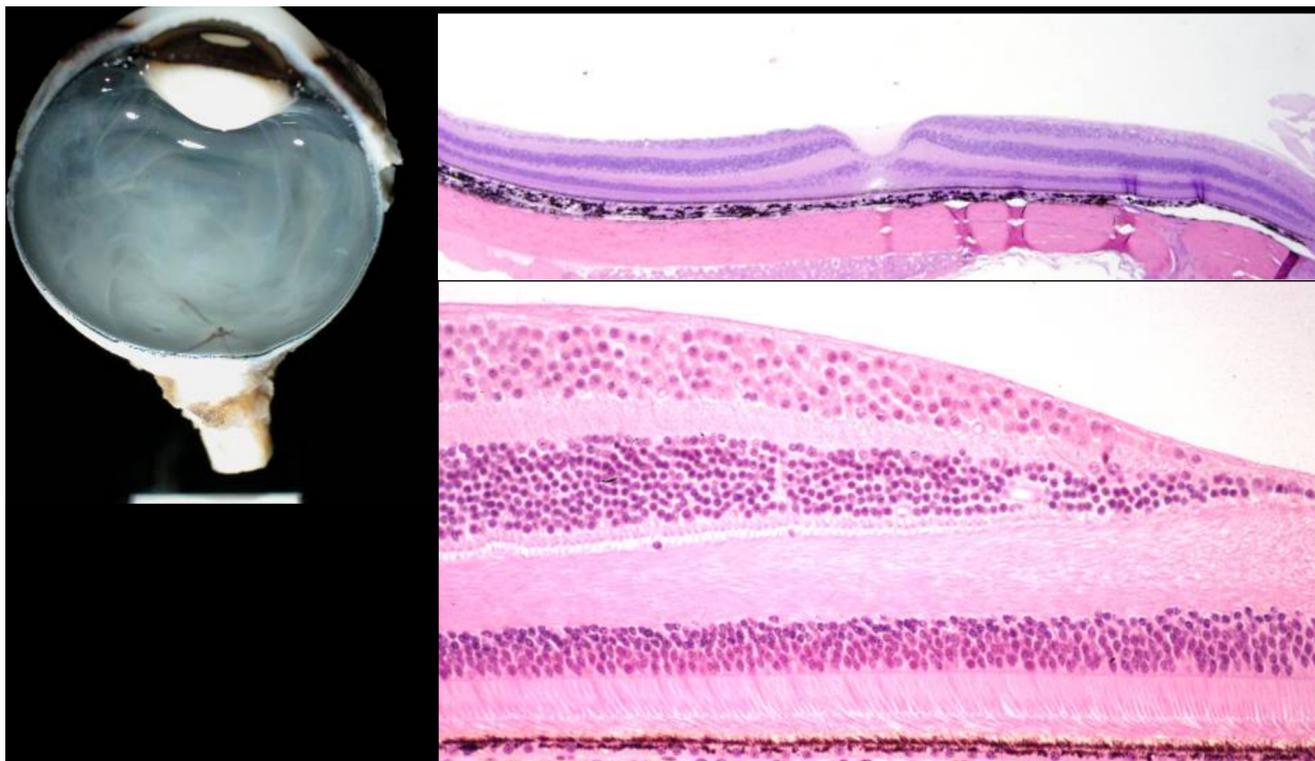
Monkey

Human

Modified from A.S. Faqui, A comprehensive guide to toxicology in drug development. Academic



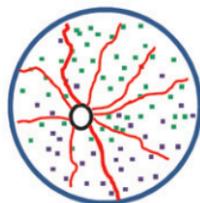
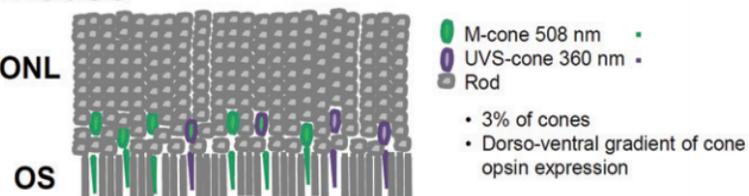
Only Primates have a Macula



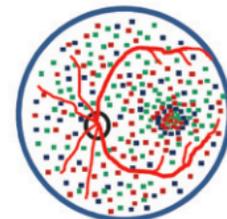
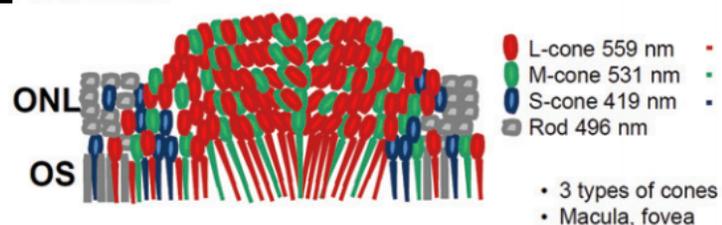
- Visual acuity
- Color vision

Dick Dubielzig, U Wisconsin-Madison

Mouse



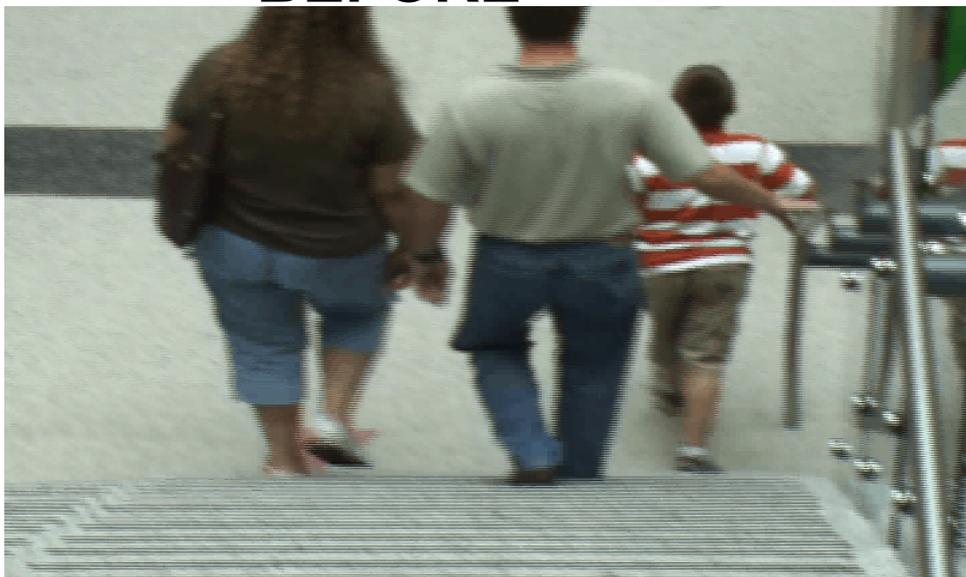
Human



Kostic & Arsenijevic, J Path238:300 (2016)

Thanks to NHPs, Children born blind due to RPE65 deficiency safely underwent gene therapy and now have improved vision

BEFORE



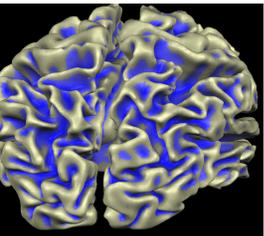
AFTER



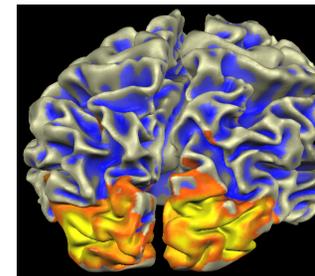
Modified from Whitecoat Productions (BIO)

First child in USA to enroll in gene therapy trial for non-lethal disease

-



What the subjects said....



- I can see my child's face
- I can find my plate and fork in a restaurant
- I can read books
- I can meet my friends downtown
- I can see fireflies
- I can see patterns
- I can see stars! They are not star-shaped!
- When can I have my second eye injected?



Readministration of AAV

- Is it possible to improve visual function further by treating contralateral eyes?
- Chief concern: Immune responses to initial AAV2 exposure would limit benefit or result in harm
- Efficacy after readministration of AAV in human has only been described in one other clinical trial where AAV was used to vaccinate against HIV

The Plan: Re-Administration Studies in 2 models:

- Affected dogs, in which efficacy could be evaluated
- Unaffected non-human primates (NHPs) immunized with AAV2

Evaluate:

- Visual function, Transgene expression, Stability, Histopathology, Immune response

Contralateral Eye Readministration of AAV

Readministration in large animal models results in benefit and is safe



Results similar to STM 3, 88ra54 (2011)

- Proceed with studies in humans!
- The humoral data allowed us to drop our exclusion of subjects with high anti-AAV2 titers

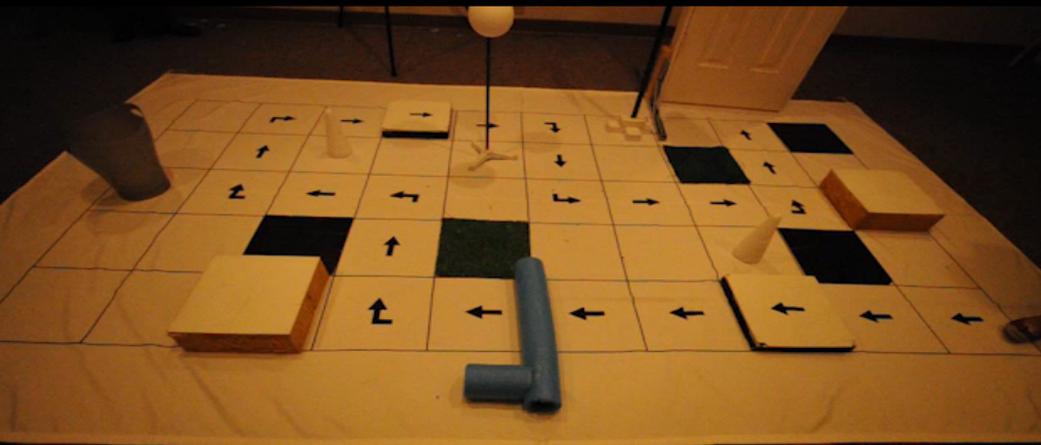


Center for Retinal and Ocular Therapy
PennCAROT

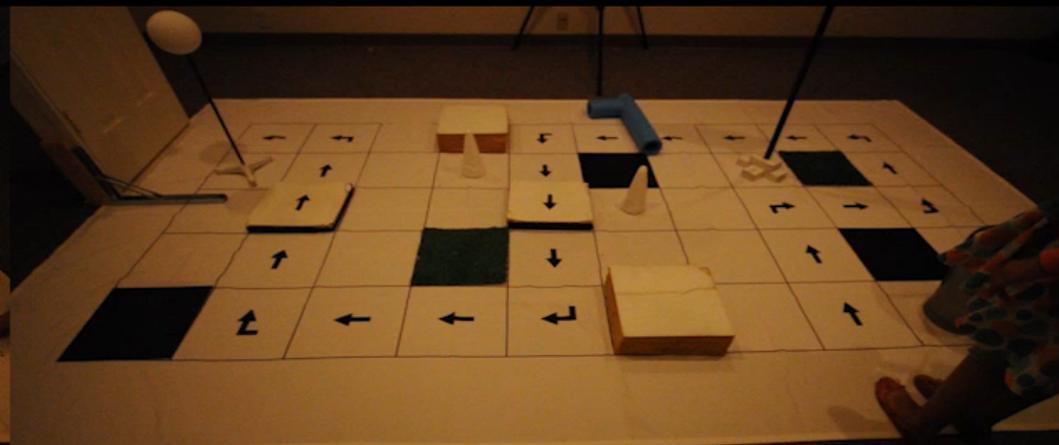
Amado et al STM 2 (2010)

Phase 3 Trial Results: Excellent Safety Profile Mobility Test (Primary Outcome Measure)

Baseline Visit
4 Lux
Result: Fail

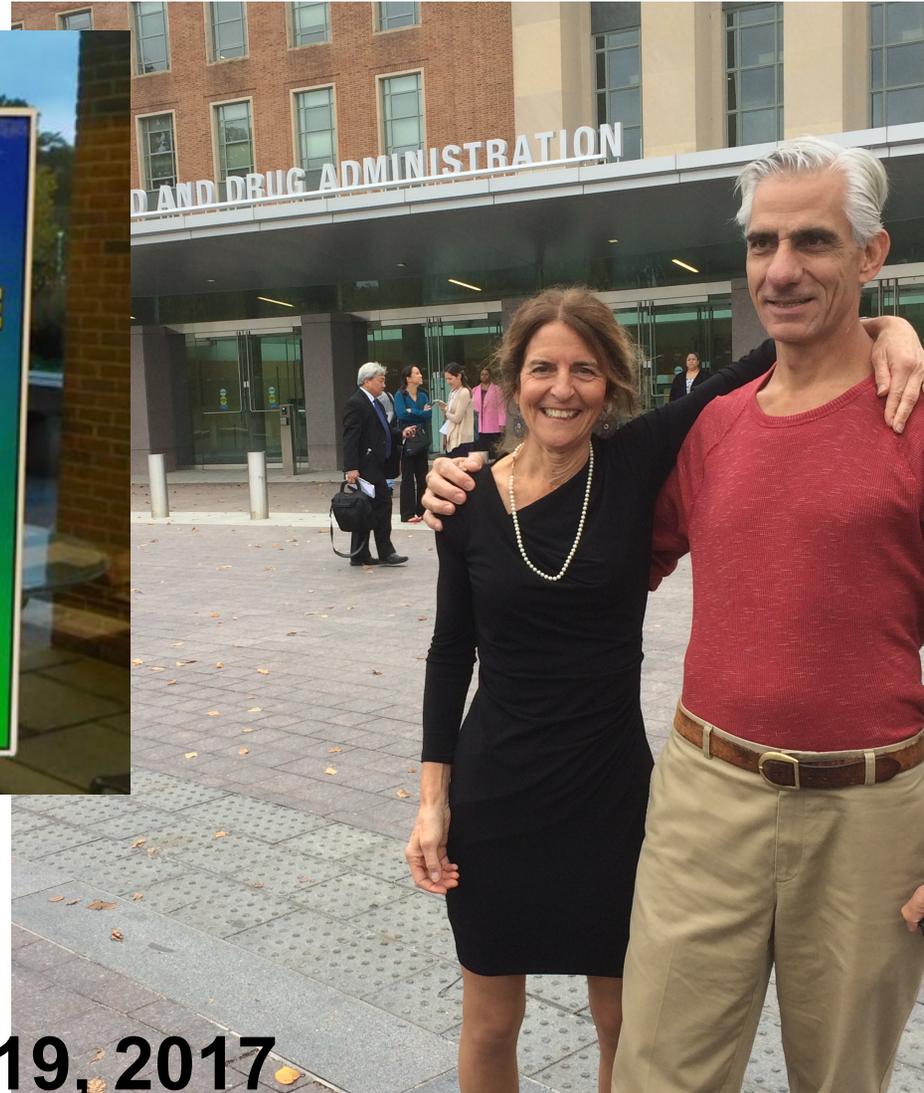
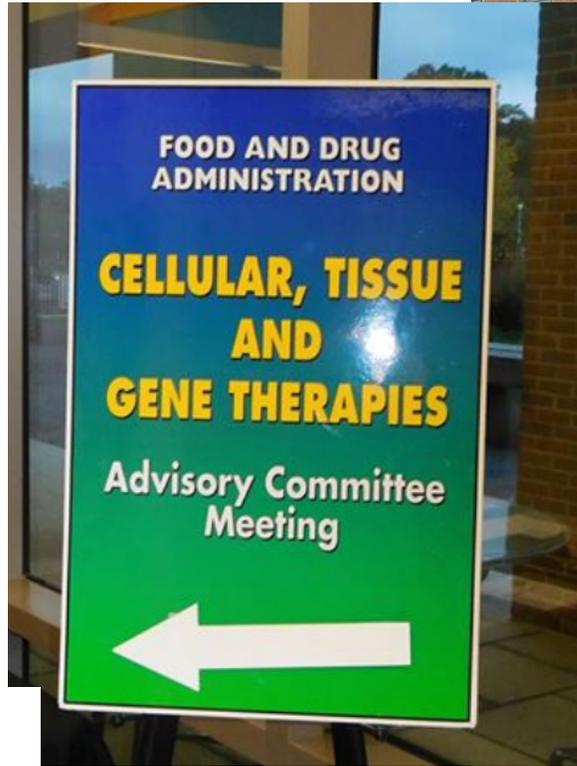


1-Year Visit After
SPK-RPE65 Administration, 4 lux
Result: Pass



10 Years Later.....

**FDA Advisory Meeting
October 12, 2017**



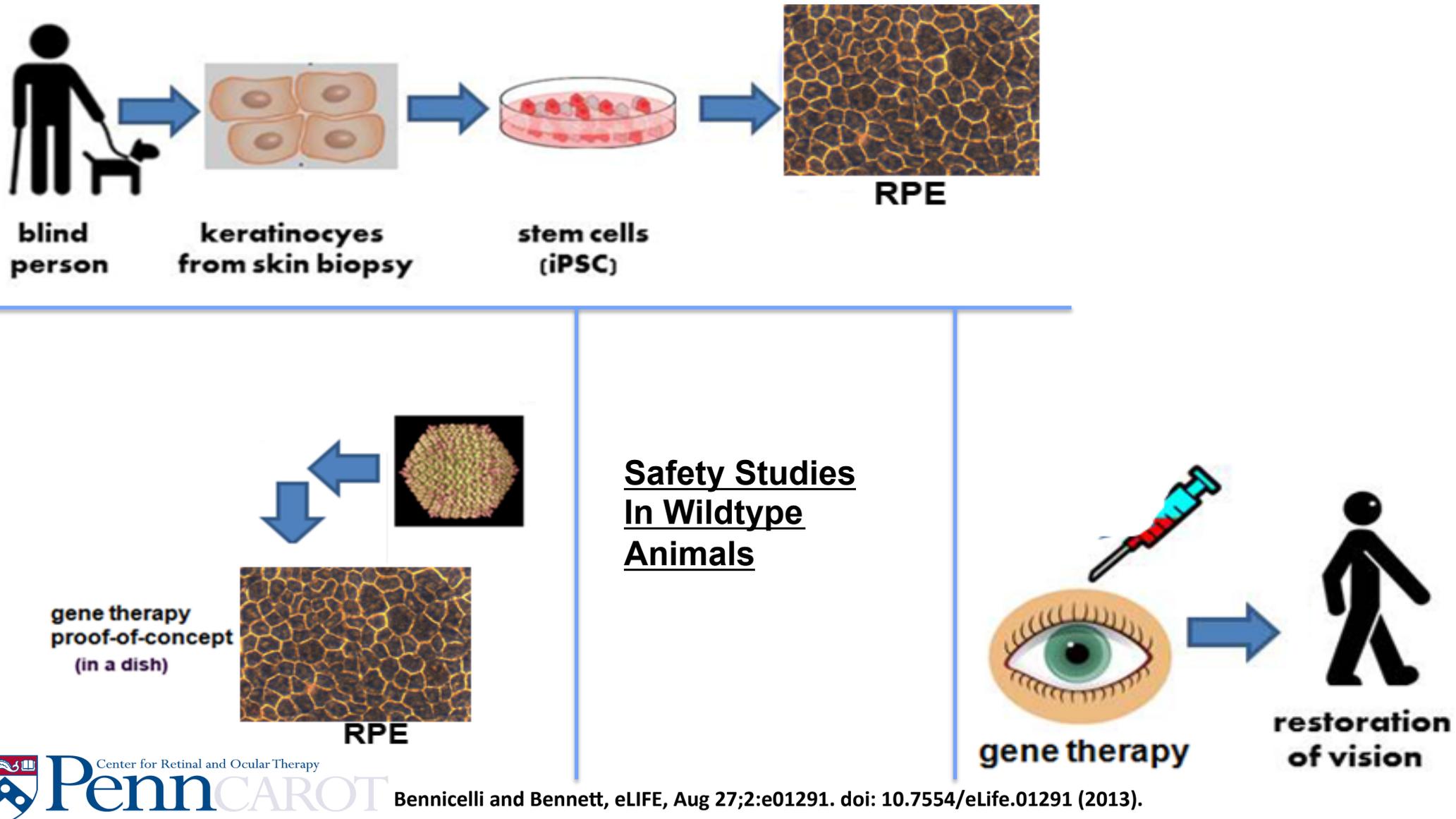
Our STN: BL 125610/0

**December 19, 2017
BLA APPROVAL**

Spark Therapeutics, Inc.
Attention: Jim Wang, MBA, PhD
3737 Market Street, Suite 1300
Philadelphia, PA 19104

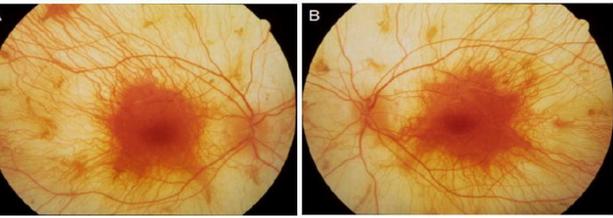
- **FDA approved voretigene Dec. 19, 2017**
 - The 1st gene therapy recombinant virus in the USA delivered directly to a person
 - The 1st gene therapy worldwide for retinal disease
- **EMA recommended approval of voretigene on Sept 20, 2018**

Induced Pluripotent Stem Cells (iPSCs) from CHM patients were used to make retinas in a dish and develop CHM gene therapy

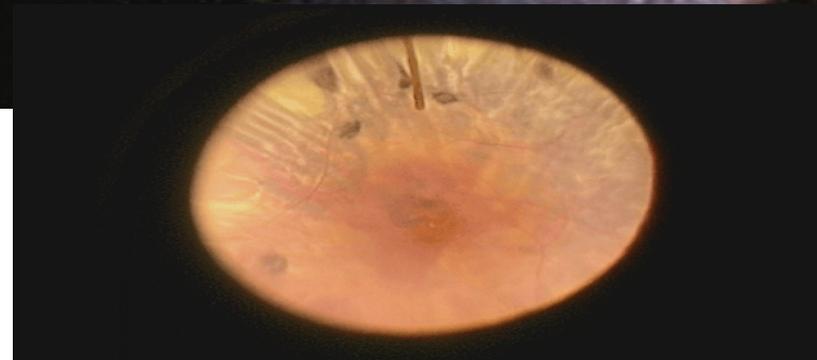
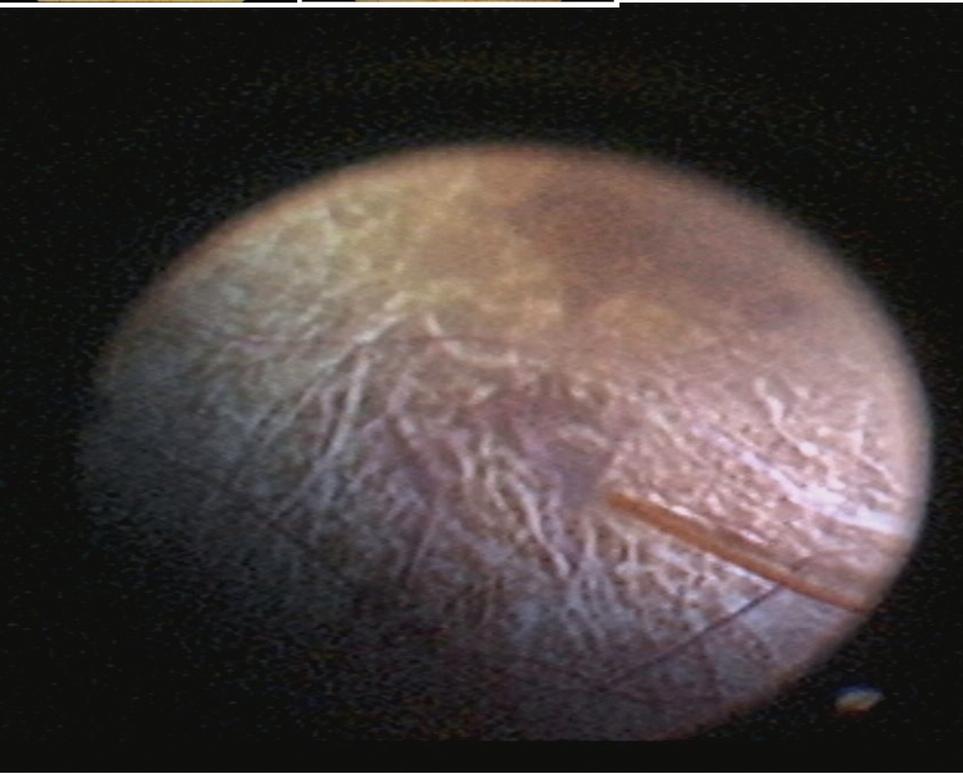


Choroideremia Sub-Foveal Gene Therapy Injection

Safety Studies in NHPs have led to this trial as well as ~30 Additional Trials



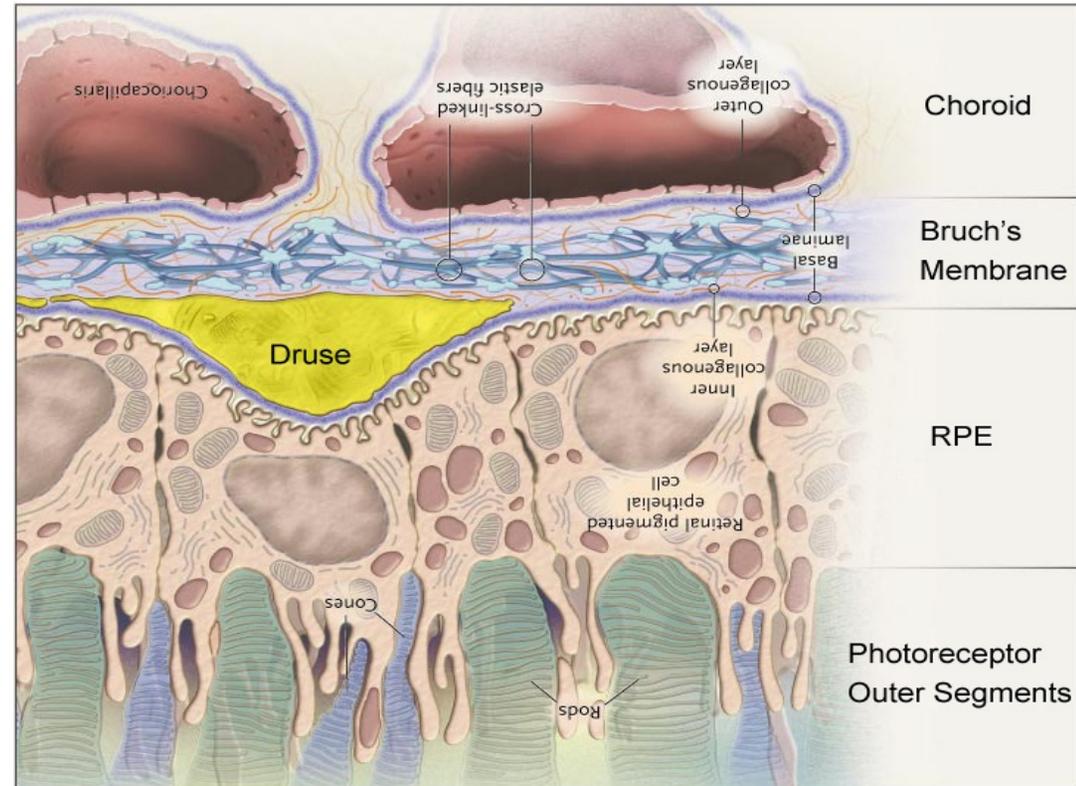
CAROT: Intra-operative video
(A. Maguire, surgeon)



Procedure is safe

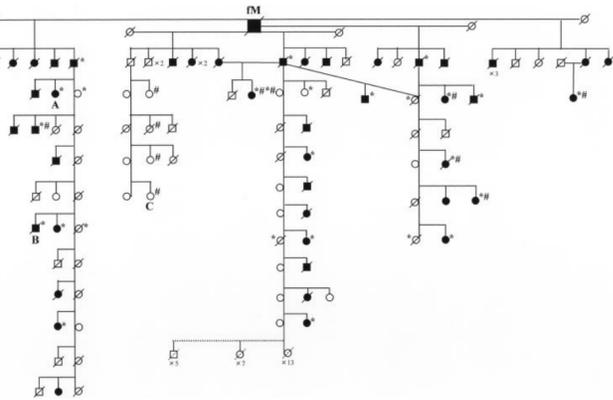
A Great Target for Gene Therapy: Macular Degeneration

- Age-related
 - Most common cause of irreversible vision loss developed world
 - Drusen are common feature



(From Johnson & Anderson NEJM 2004)

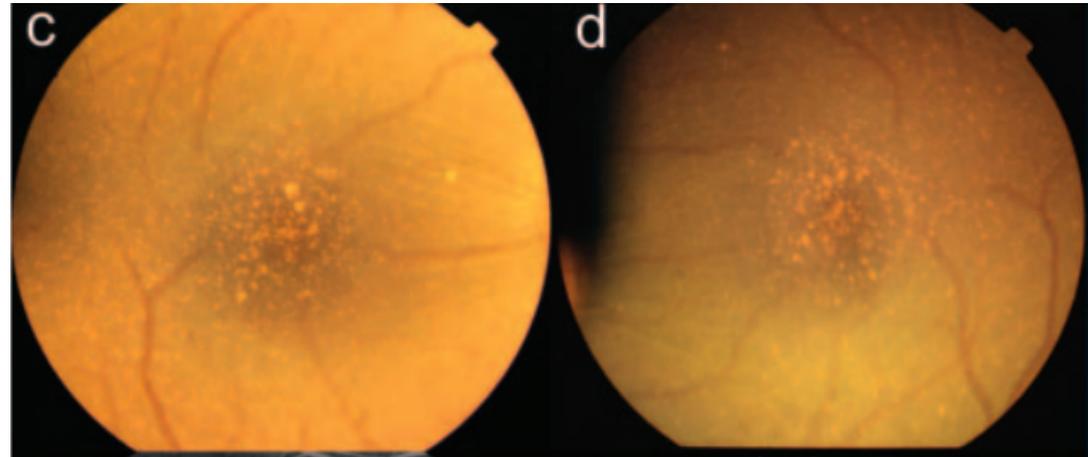
Inherited Drusen in Cynomolgus Monkeys



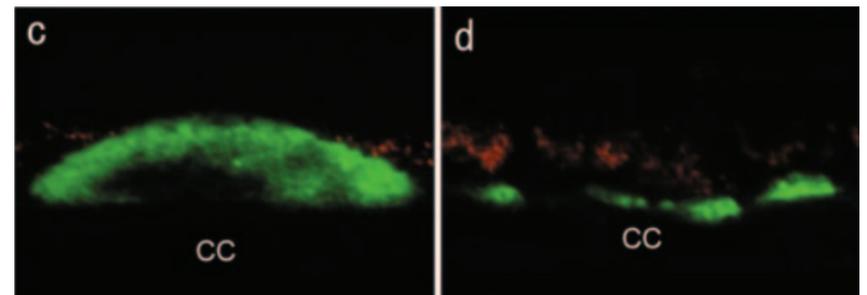
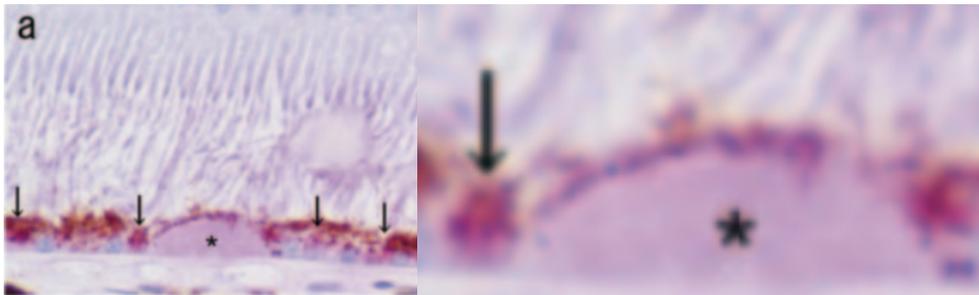
Early-Onset Macular Degeneration with Drusen in a Cynomolgus Monkey (*Macaca fascicularis*) Pedigree: Exclusion of 13 Candidate Genes and Loci

Umeda et al, IOVS 46:683 (2005)

- Excluded genes associated with AD, AR and XL retinal and macular degeneration
- Immunohistochemistry reveals drusen contain activated complement factors
- Onset: ~2 yrs of age



14yo female, Tsukuba Primate Center



All male squirrel monkeys (Saimiri) are color blind

L opsin missing



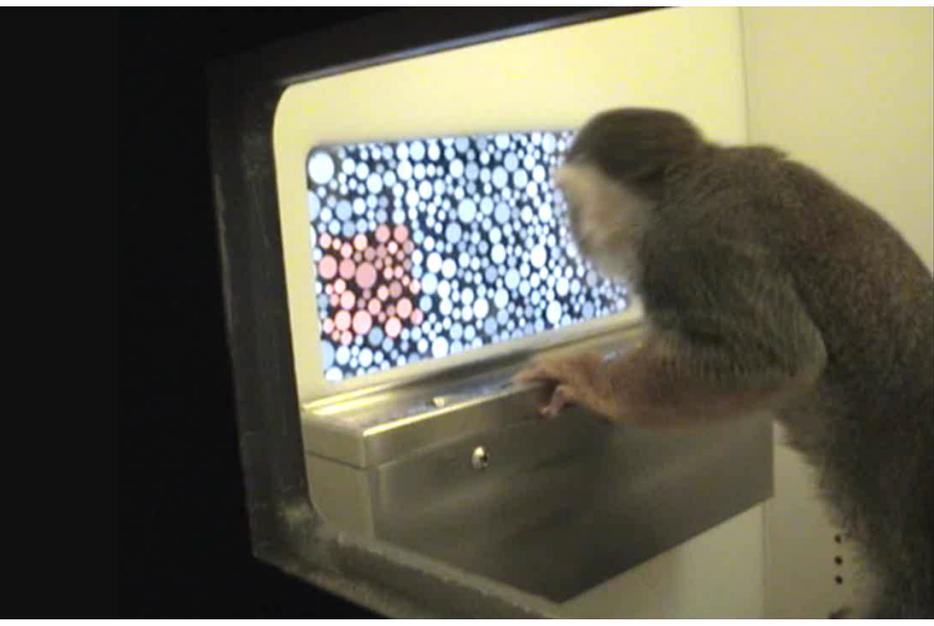
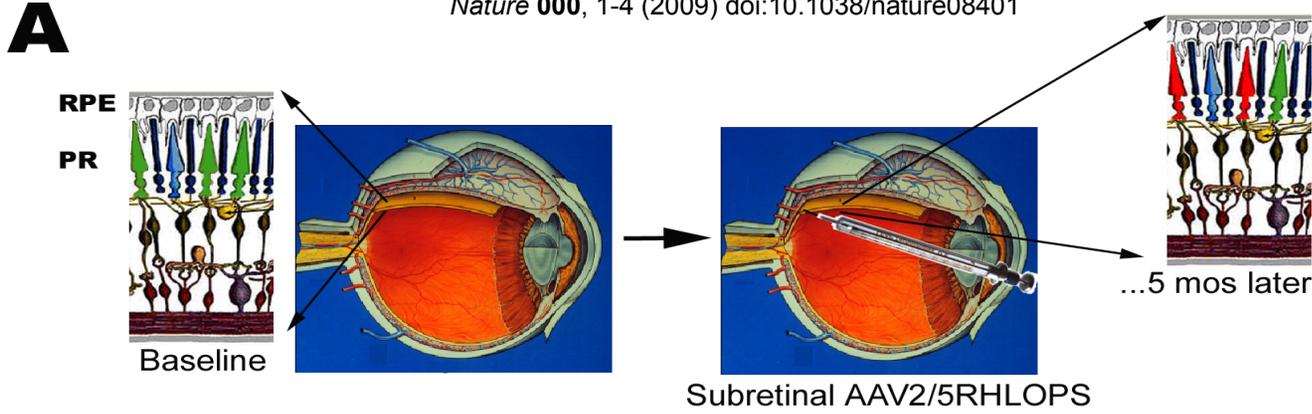
L opsin present



Gene therapy for red-green colour blindness in adult primates

Katherine Mancuso¹, William W. Hauswirth², Qihong Li², Thomas B. Connor³, James A. Kuchenbecker¹, Matthew C. Mauck³, Jay Neitz¹ & Maureen Neitz¹

Nature 000, 1-4 (2009) doi:10.1038/nature08401



BEFORE

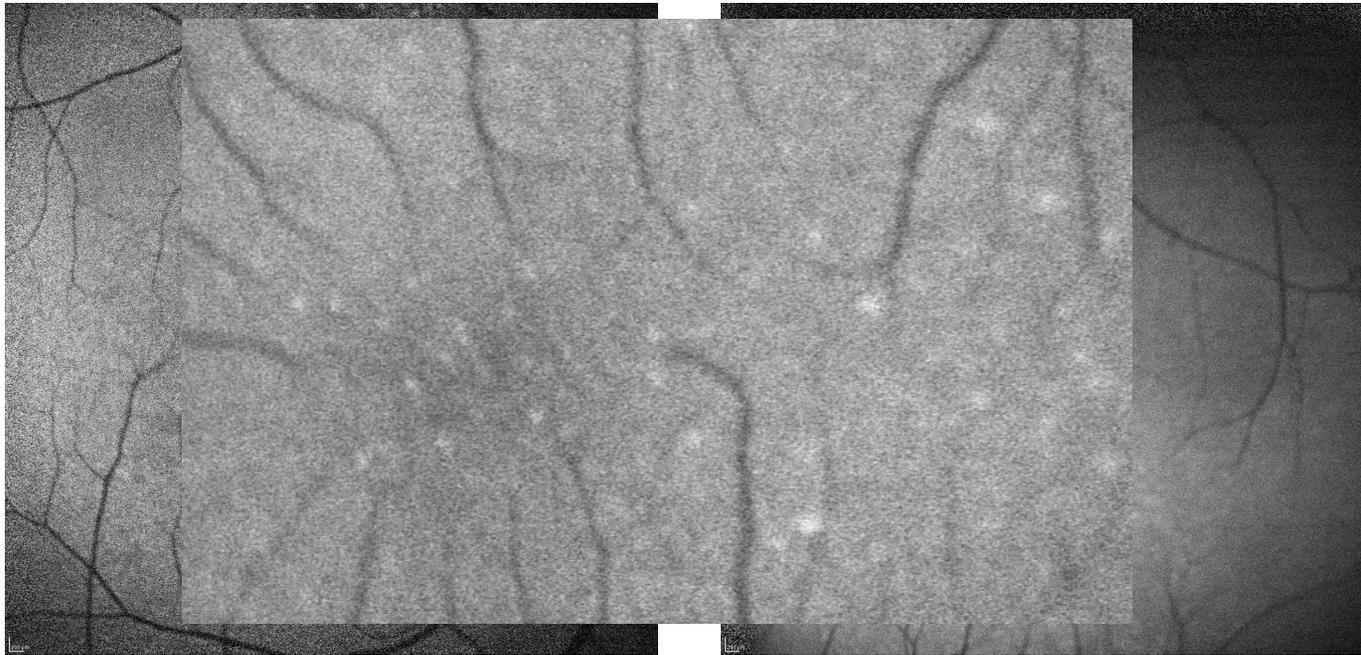


AFTER

Movies generously provided by Dr. Jay Neitz

How can we make the most of animals with a unique phenotype?

- One of ~1,000 NHPs I evaluated had “retinal spots” suggesting macular degeneration
- Genetic analysis showed variants in the Stargardt-disease gene
- Attempts were made to arrange for breeding of this animal, but these failed
- We need to establish/advertise programs where such unique animals can be studied



Right

Left

Conclusions (1): Use of NHP Models for Retina Translational Studies

Benefits

- Anatomic/Immunologic/ Physiologic similarities to humans
- Similar delivery methodology
- Most informative for safety in humans
- Most informative for studies of higher systems
- Possible to share/recycle animals

Challenges

- Small “n”
- Only 1 genetically characterized model
- Generally, minimal pedigree information available
- Minimal experience in development of outcome measures
- Long gestation
- Years to reach maturity
- Few sites for breeding in captivity
- Biohazard concerns

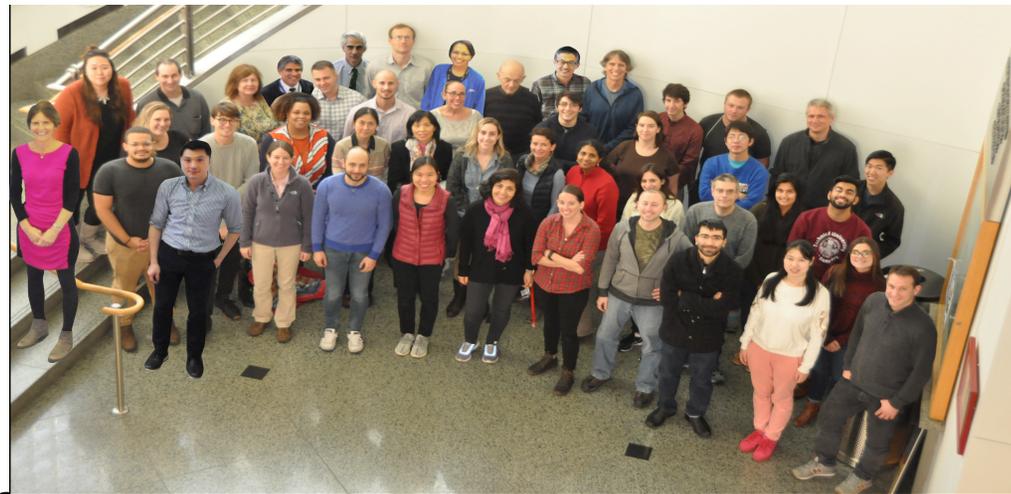
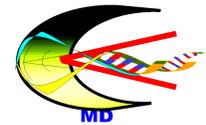
Conclusions (2): Use of NHP Models for Retina Translational Studies

Recommendations

- Focus on the three “R’s”
- Phenotypically normal animals
 - Invaluable for safety studies prior to “first in human”
 - Share data/resources
- Spontaneous mutants:
 - Observe/share phenotype info
 - Maintain breeding records
 - Support of longterm maintenance/studies
- Engineered animals
 - Target diseases unique to primates
 - Plan longterm care
 - Plan breeding & appropriate experiments
- Centralized supply of unique models



The Children's Hospital
of Philadelphia®



Center for Advanced Retinal Ocular Therapeutics



We are grateful to:

• Our Subjects and their Families

- DSMB
- IRB, RAC, FDA, FDA Advisory
- The Children's Hospital of Philadelphia
- Foundation Fighting Blindness
- Foundation for Retinal Research
- F. M. Kirby Foundation
- Research to Prevent Blindness
- Paul and Evanina Mackall Foundation Trust
- National Center for Research Resources
- Howard Hughes Medical Institute.



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Research Resources



PENN
Medicine

Research to Prevent Blindness