Consideration on Usher Syndrome to prepare future therapies-retinal point of view

I Audo, S Mohand-Said, C Zeitz, C Bonnet, C Petit, JA Sahel

isabelle.audo@inserm.fr

www.institut-vision.org

RETINA FRANCE

FOUNDATION FIGHTING BLINDNESS

UPMC SORBONNE UNIVERSITÉS · Inserm · CNRS · QUINZE-VINGTS · Fondation Voir & Entendre · INSTITUT CARNOT Voir et Entendre

Current management…

- ✓ Sunlight protection (brown-orange filters)
- ✓ Avoid retinotoxic substances (tobacco, quinine derivatives…)
- ✓ Possibly vitamin A in absence of contraindication…
- ✓ Balanced diet with green vegetables and omega 3
- ✓ Hearing aids
- ✓ Low vision rehabilitation+++++
- ✓ Orientation and mobility training
- ✓ Educational program

=> Research challenges

- **✓ heterogeneous disorders**
- **✓ highly specialized network**

Therapeutic approaches

- ✓ Genetic targeted therapy
- ✓ Neuroprotection
- ➢ Artificial retinal implant
- ➢ Stem cell research
- ➢ optogenetics
- ➢ Sensory substitution
- ➢ …

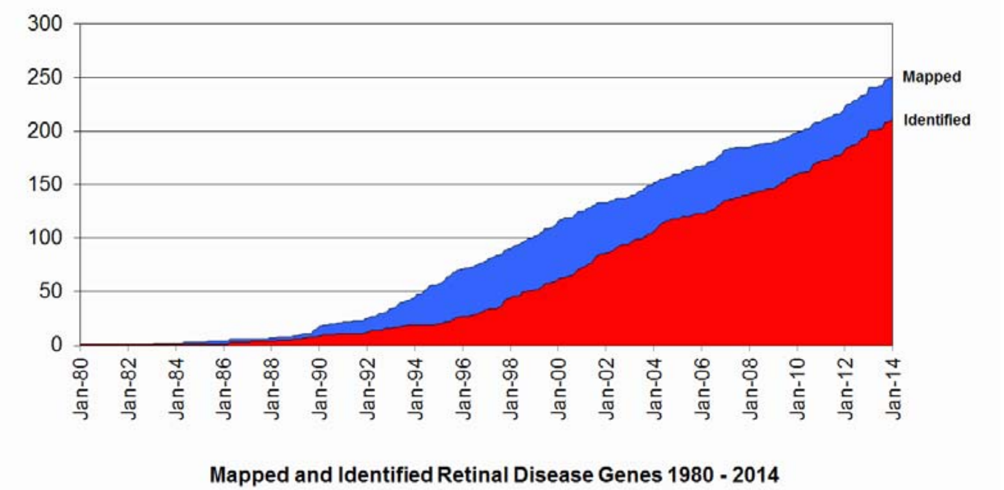
Therapeutic approaches

- Genetic targeted therapy
    - gene replacement
    - Antisense strategies
    - read-through…

(1) identification of the underlying gene defect

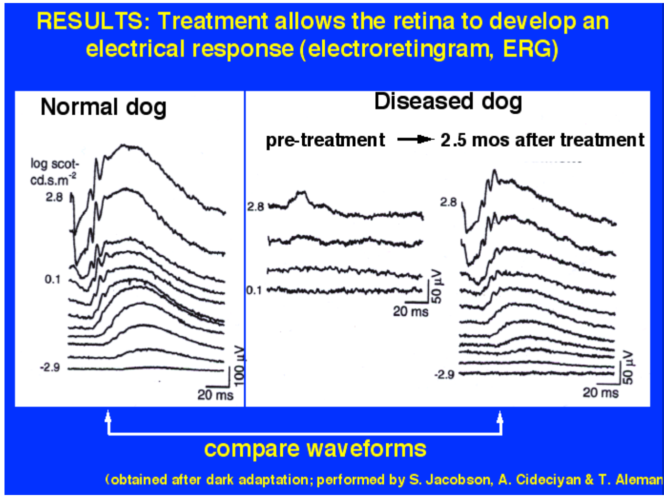
(2) genetic heterogeneity of the disease

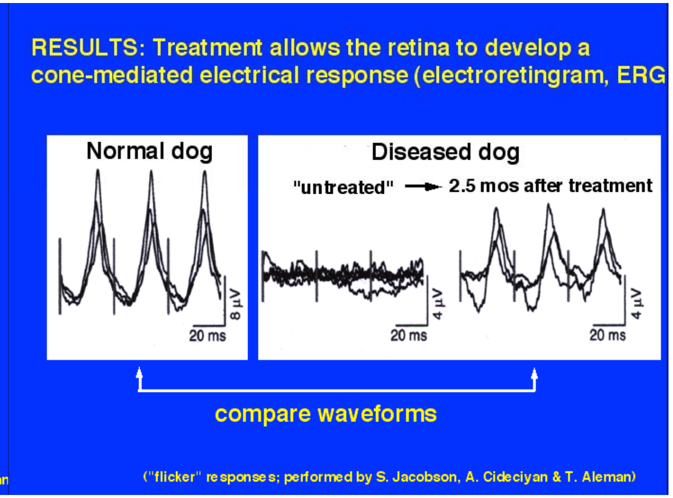
USHER type	GENES
USH1	***MYO7A*** (50% of USH1)
	USH1C
	CDH23
	PCDH15
	USH1G
	CIB2
USH2	***USH2A*** (80% of USH2)
	GPR98
	DFNB31
USH3	*CLRN1*



https://sph.uth.edu/Retnet/

AVV gene replacement therapy in Leber congenital amaurosis linked to *RPE65* mutations





Acland et al 2001

. Proof of concept on animal model

The NEW ENGLAND JOURNAL of MEDICINE

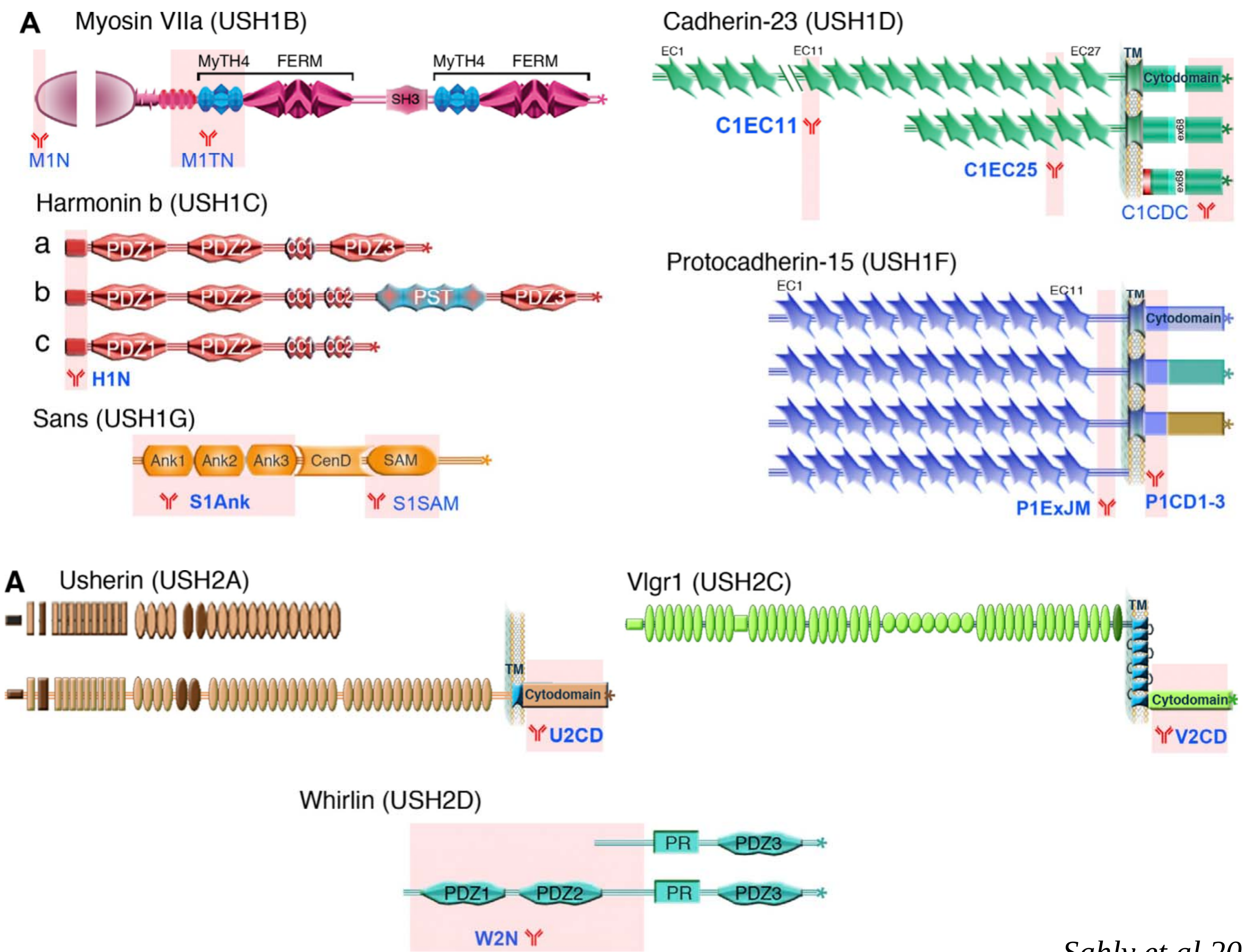
BRIEF REPORT

Safety and Efficacy of Gene Transfer for Leber's Congenital Amaurosis

Albert M. Maguire, M.D., Francesca Simonelli, M.D., Eric A. Pierce, M.D., Ph.D., Edward N. Pugh, Jr., Ph.D., Federico Mingozzi, Ph.D., Jeannette Bennicelli, Ph.D., Sandro Banfi, M.D., Kathleen A. Marshall, C.O.T., Francesco Testa, M.D., Enrico M. Surace, D.V.M., Settimio Rossi, M.D., Arkady Lyubarsky, Ph.D., Valder R. Arruda, M.D., Barbara Konkle, M.D., Edwin Stone, M.D., Ph.D., Junwei Sun, M.S., Jonathan Jacobs, Ph.D., Lou Dell'Osso, Ph.D., Richard Hertle, M.D., Jian-xing Ma, M.D., Ph.D., T. Michael Redmond, Ph.D., Xiaosong Zhu, M.D., Bernd Hauck, Ph.D., Olga Zelenaia, Ph.D., Kenneth S. Shindler, M.D., Ph.D., Maureen G. Maguire, Ph.D., J. Fraser Wright, Ph.D., Nicholas J. Volpe, M.D., Jennifer Wellman McDonnell, M.S., Alberto Auricchio, M.D., Katherine A. High, M.D., and Jean Bennett, M.D., Ph.D.

N. Engl. J. Med. 2008

(3) Size of USHER genes and multiple isoforms

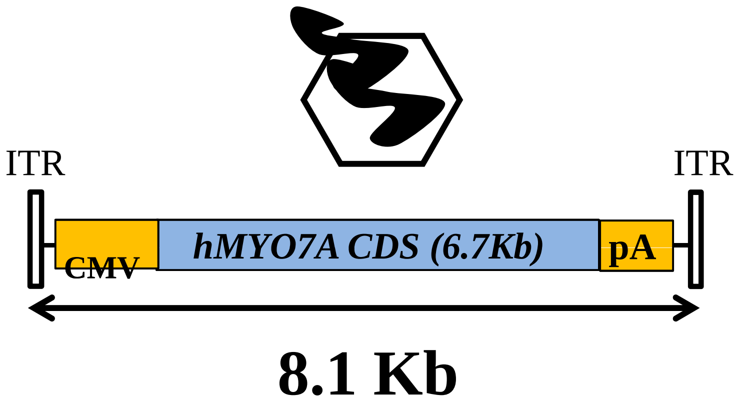


Sahly et al 2012

Strategies to increase AAV cargo capacity

1.Oversize AAVs:

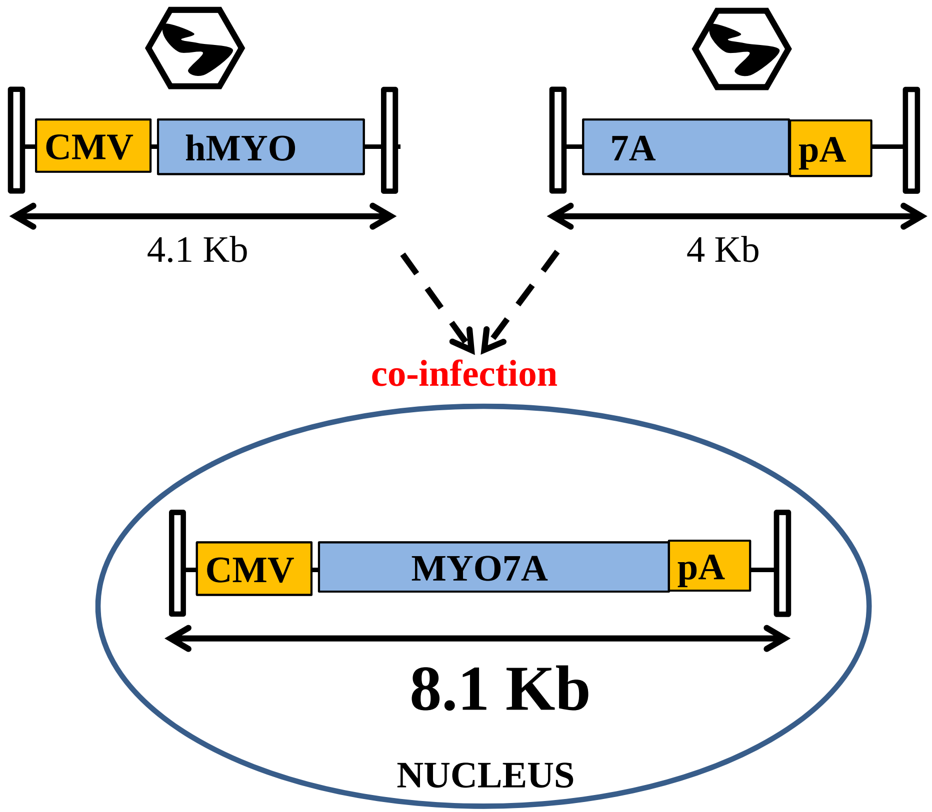
forcing a large gene into a **single** AAV



(Grieger et al. J. Virol. 2005; Wu et al. Hum. Gene Ther. 2007;Lu et al. Hum. Gene Ther. 2008; Allocca et al, JCI 2008; Monahan et al. Mol. Ther. 2010; Wu et al. Mol. Ther. 2010; Grose et al. Plos One 2012

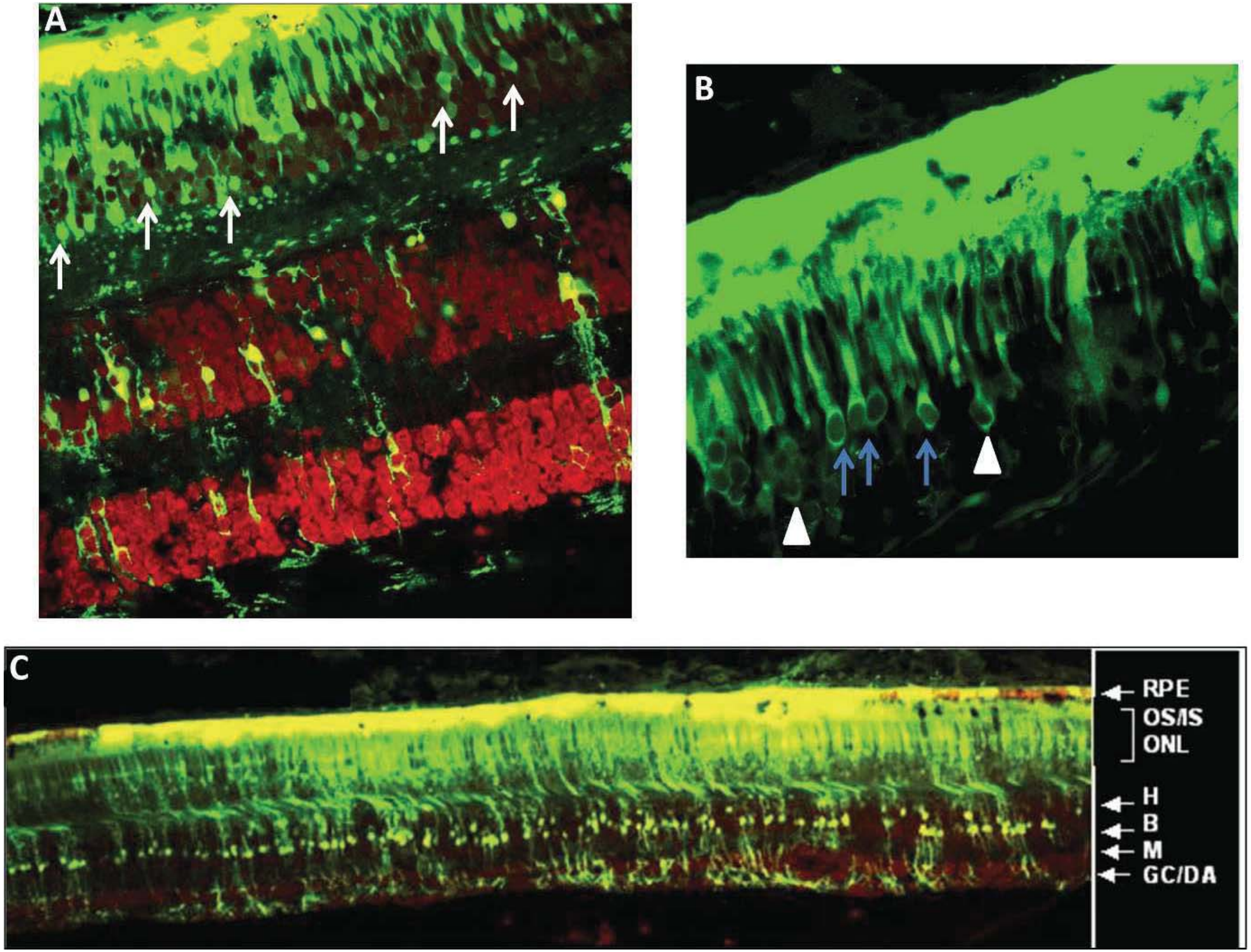
2. DUAL-AAVs:

based on the ability of **2 separate AAV genomes** to undergo intermolecular re-arrangements



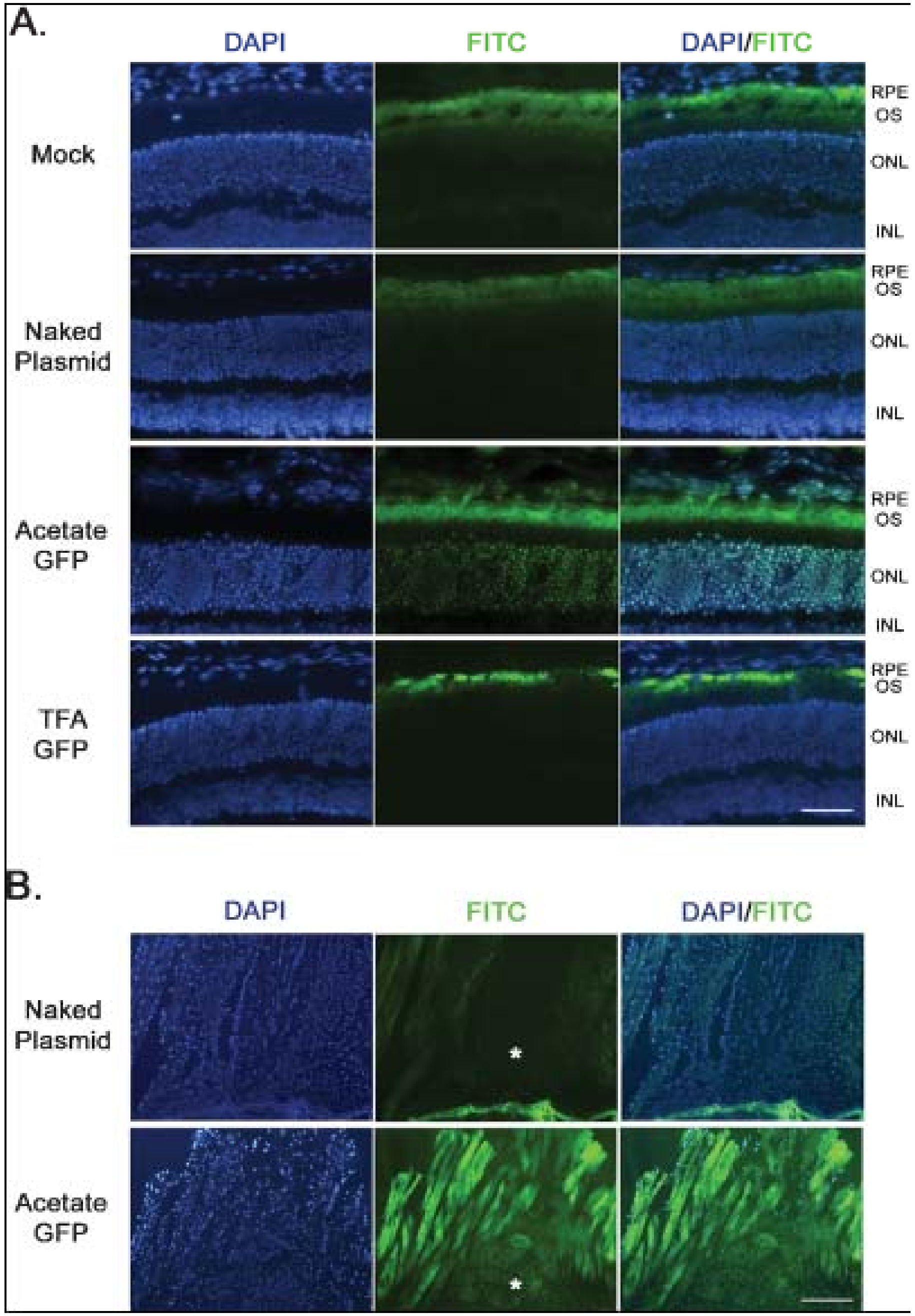
(Yan J. et al. J. Virol. 1999; Duan et al. Mol. Ther., 2001; Gosh et al. Mol. Ther. 2008)

Transduction of photoreceptors with Equine Infectious Anemia Virus (EIAV) lentiviral Vectors in NHP



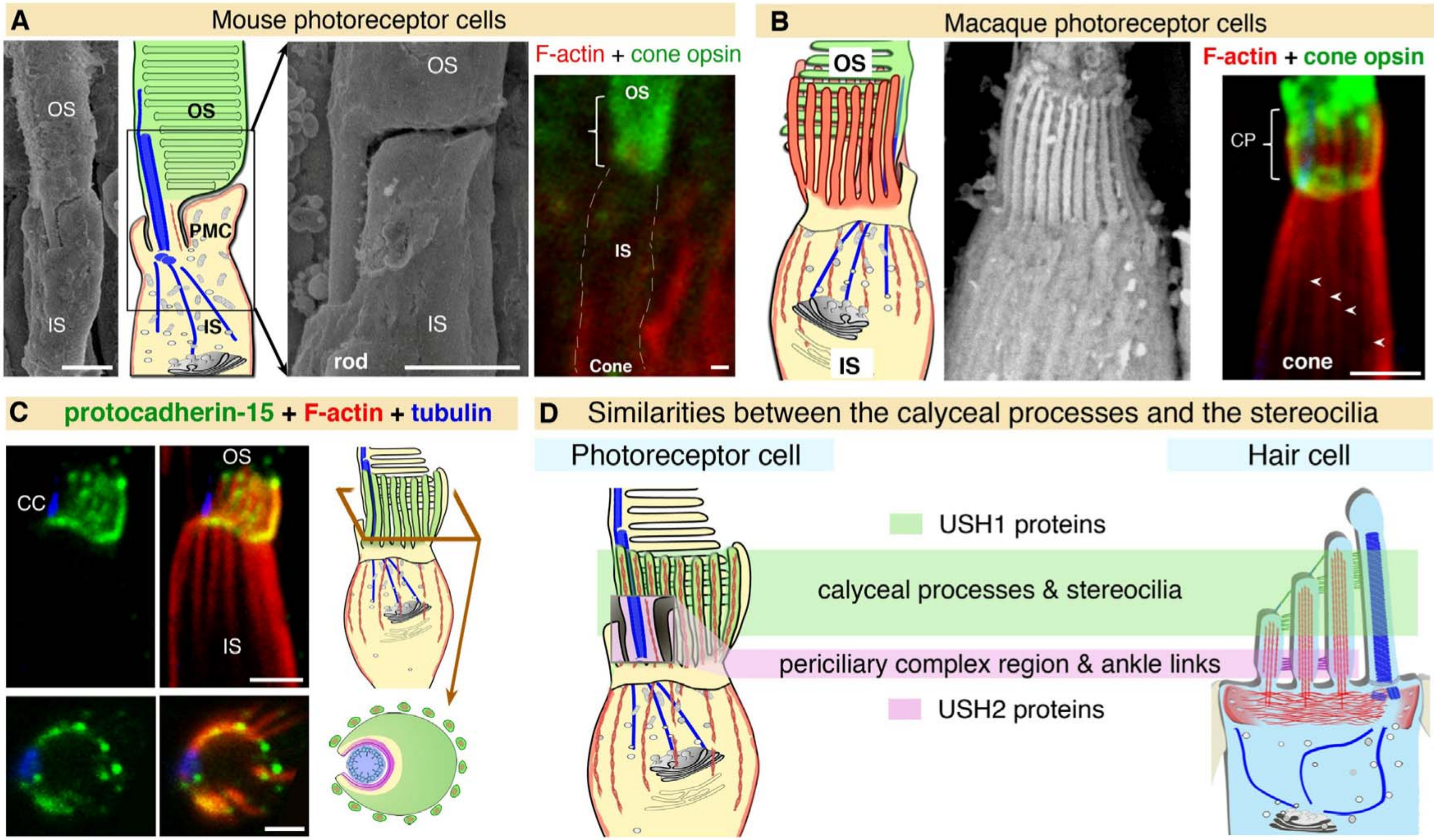
Binley et al IOVS 2013

Nanoparticle delivery



Farjo R et al 2006

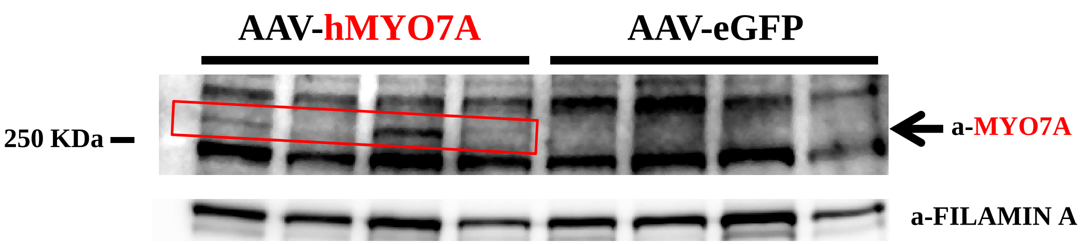
(4) Mice are not humans…



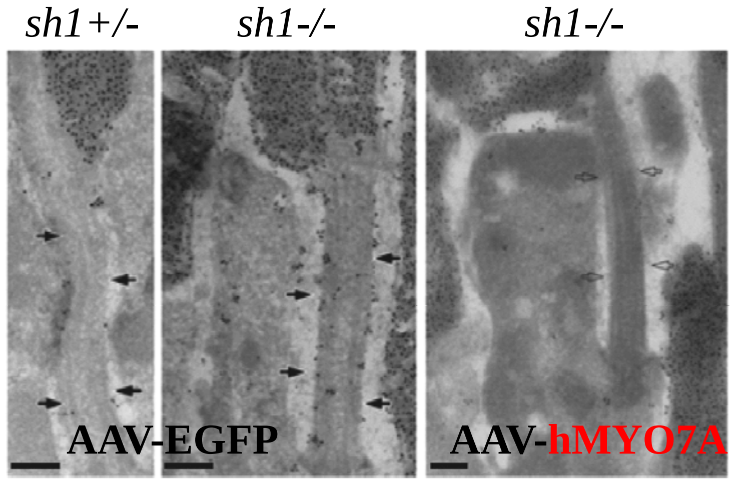
Sahly et al 2012

Oversize AAVs rescue with *hMYO7A* in the retina of *sh1-/-* mice

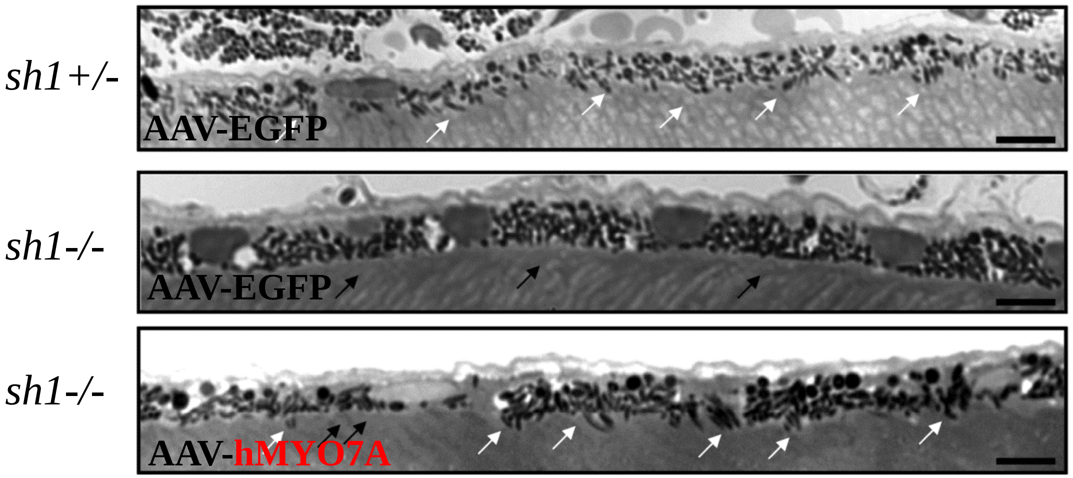
a. hMYO7A **expression in** ***sh1-/-*** **retina**



b. reduced *rho* accumulation at CC



c. re-localization of melanosomes in the RPE villi

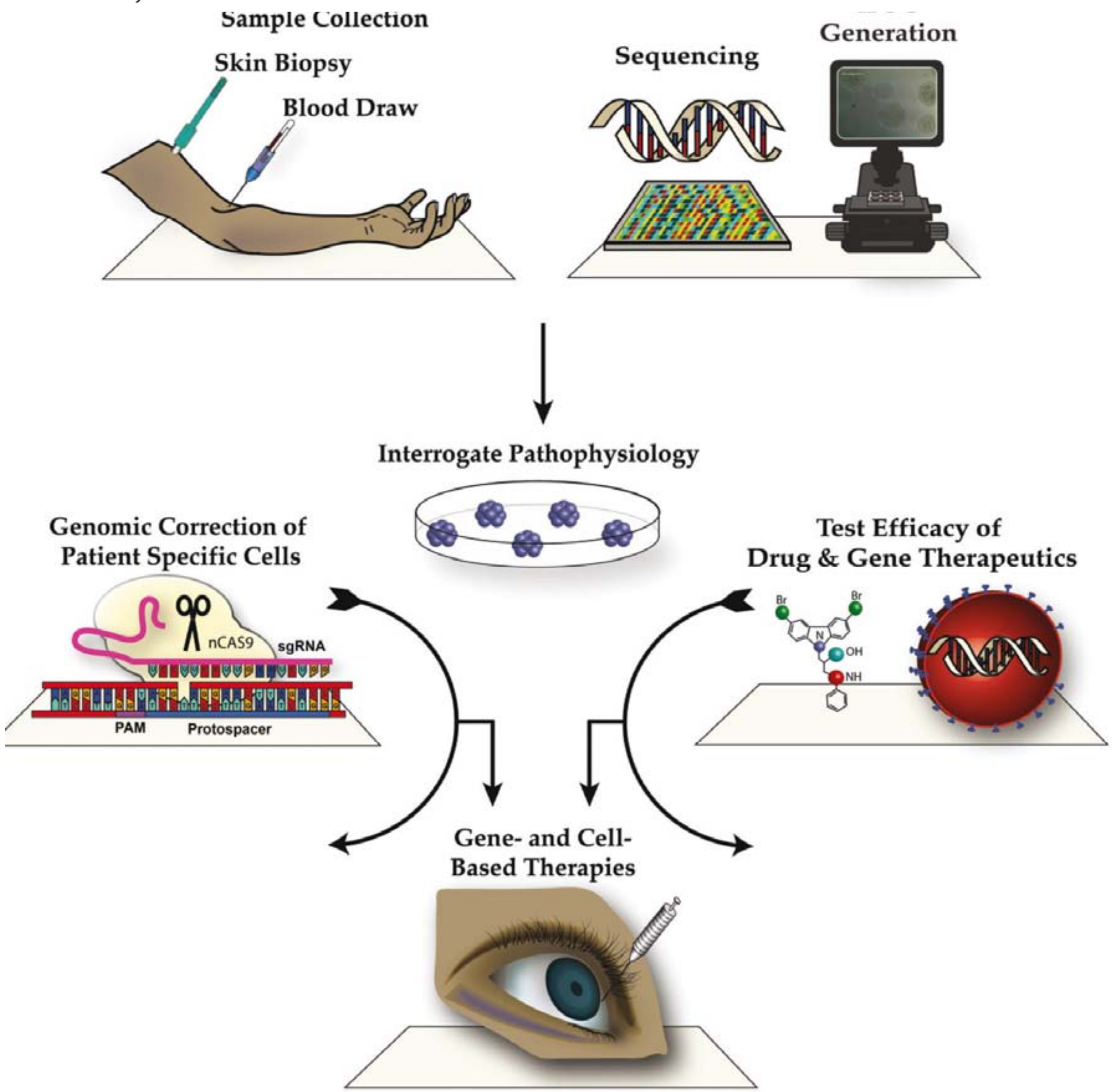


Colella et al., 2013

Human Molecular Genetics, 2014 **R1–R8**
doi:10.1093/hmg/ddu124

Stem cells for investigation and treatment of inherited retinal disease

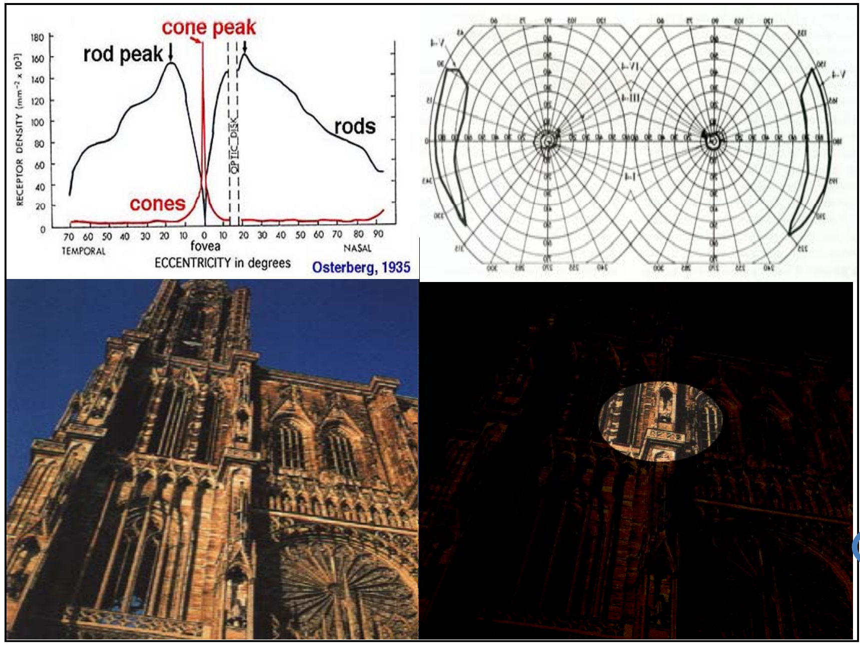
Budd A. Tucker[1], Robert F. Mullins[1] and Edwin M. Stone[1,2,*]



Therapeutic approaches

- ✓Genetic targeted therapy
- ✓ Neuroprotection
- ✓Artificial retinal implant
- ✓ Stem cell research
- ✓optogenetics
- ✓Sensory substitution
- ✓…

Gene-Independent approaches



Rod functional loss and apoptosis

Cone degeneration

BLINDNESS

Paul Sieving
"50% cone loss compatible with an acuity of 20/20"

- neuroprotection to prevent cone cell death (FGF, CNTF, GDNF, RdCVF, SOD/antioxydants)

Randomized Trial of Ciliary Neurotrophic Factor Delivered by Encapsulated Cell Intraocular Implants for Retinitis Pigmentosa

Am J Ophthalmol 2013

DAVID G. BIRCH, RICHARD G. WELEBER, JACQUE L. DUNCAN, GLENN J. JAFFE, AND WENG TAO, FOR THE CILIARY NEUROTROPHIC FACTOR RETINITIS PIGMENTOSA STUDY GROUPS

✓Increase in photoreceptor layer thickness

BUT

✓No effect on BCVA

✓Dose-dependant decrease in retinal sensitivity

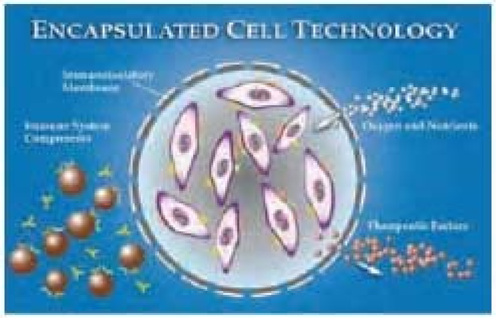


Figure 2. Encapsulated cell technology (ECT) shown to keep genetically modified RPE cells viable and producing CNTF for over 6 months.
COURTESY: NEUROTECH PHARMACEUTICALS

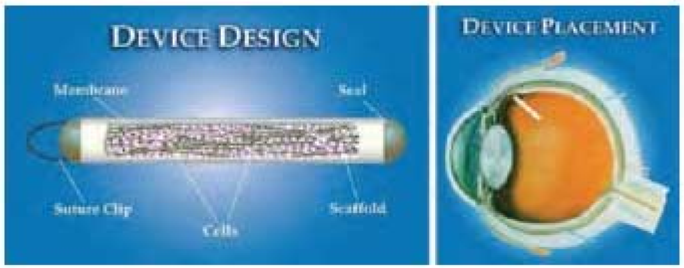
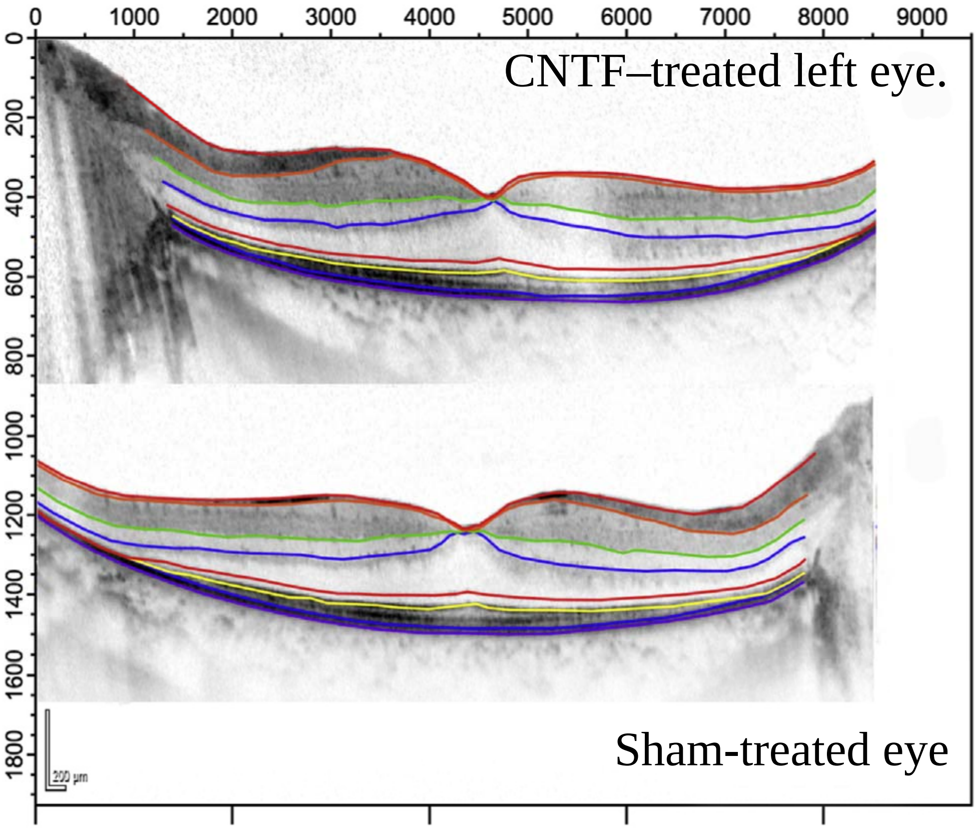
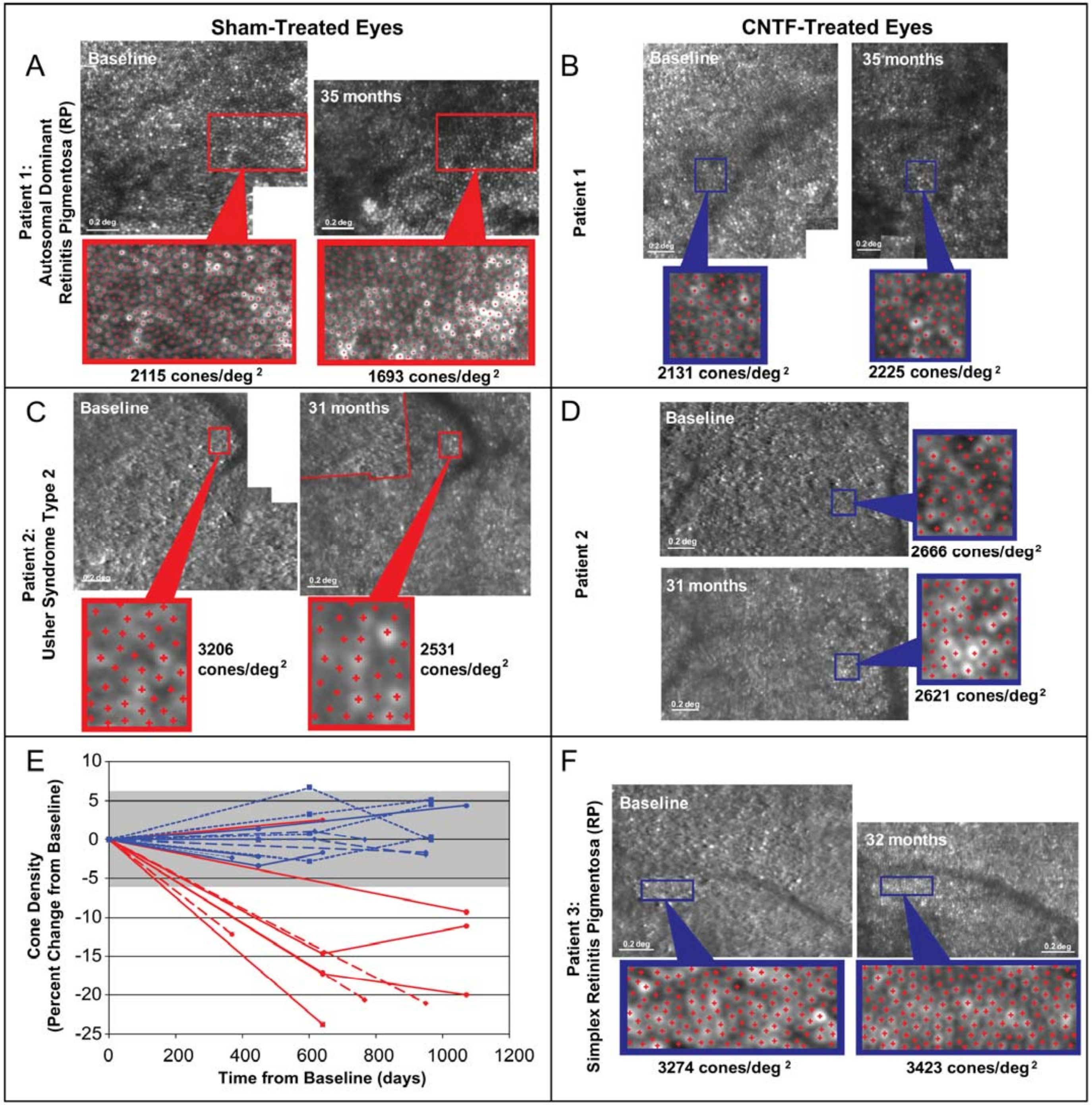


Figure 3. Neurotech Pharmaceuticals' NT-501 implant puts genetically engineered cells into an eye that produce ciliary neurotrophic factor (CNTF) for over 6 months.
COURTESY: NEUROTECH PHARMACEUTICALS

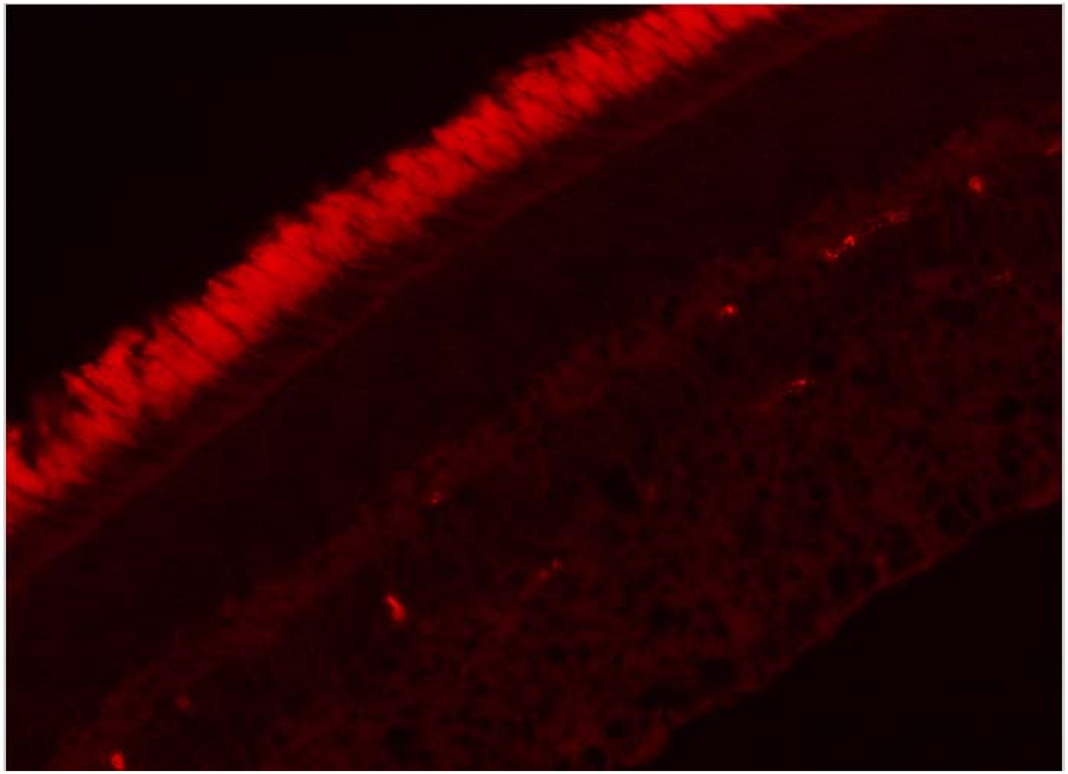




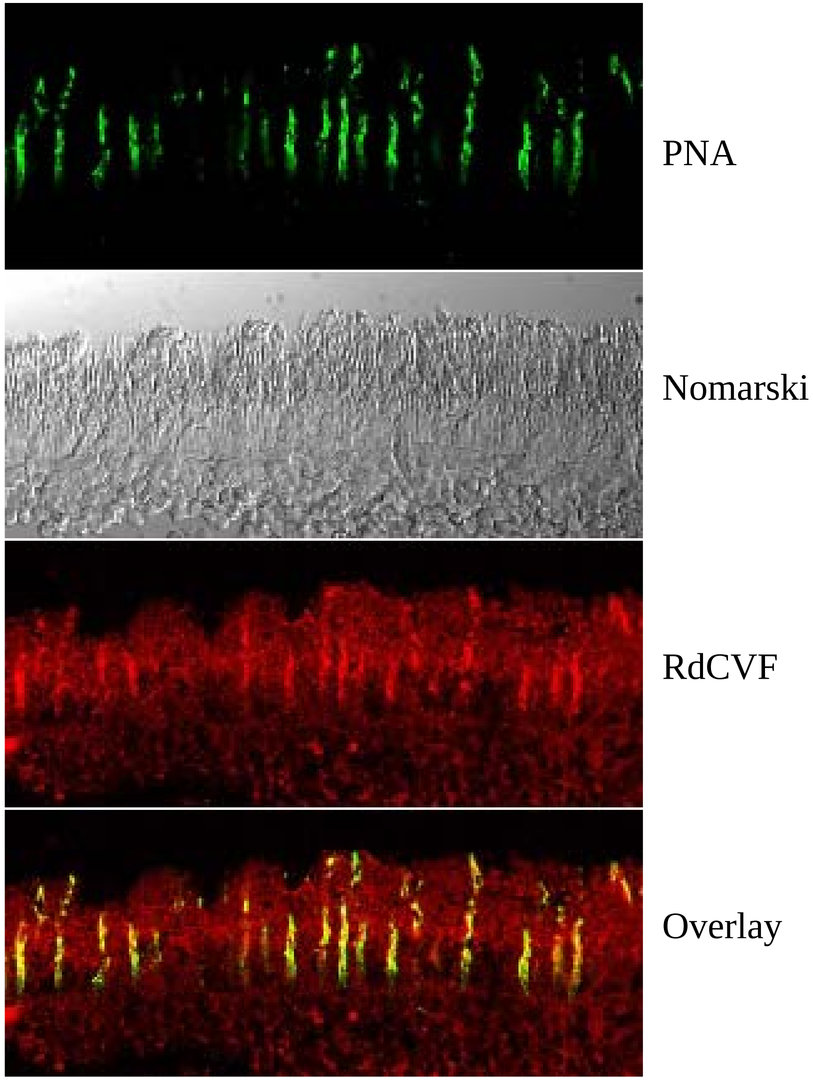
Talcott et al 2011

RdCVF polypeptide is present in the matrix surrounding cone photoreceptors

Leveillard et al, Nat. Gen., 2004

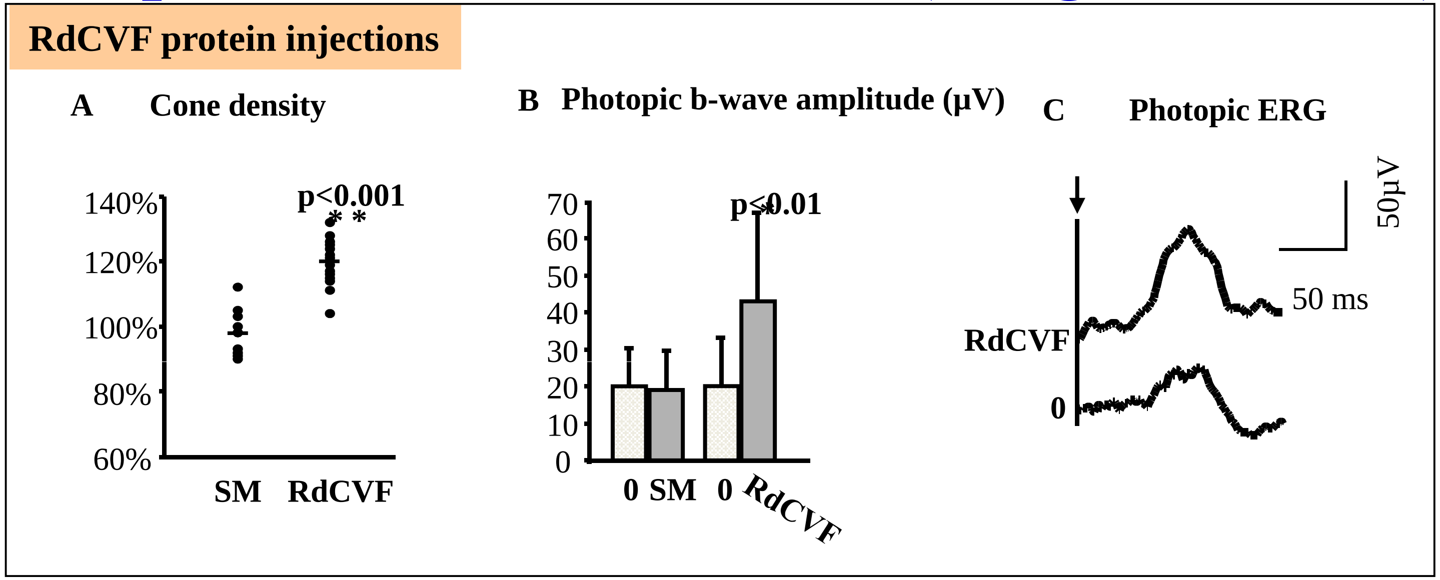


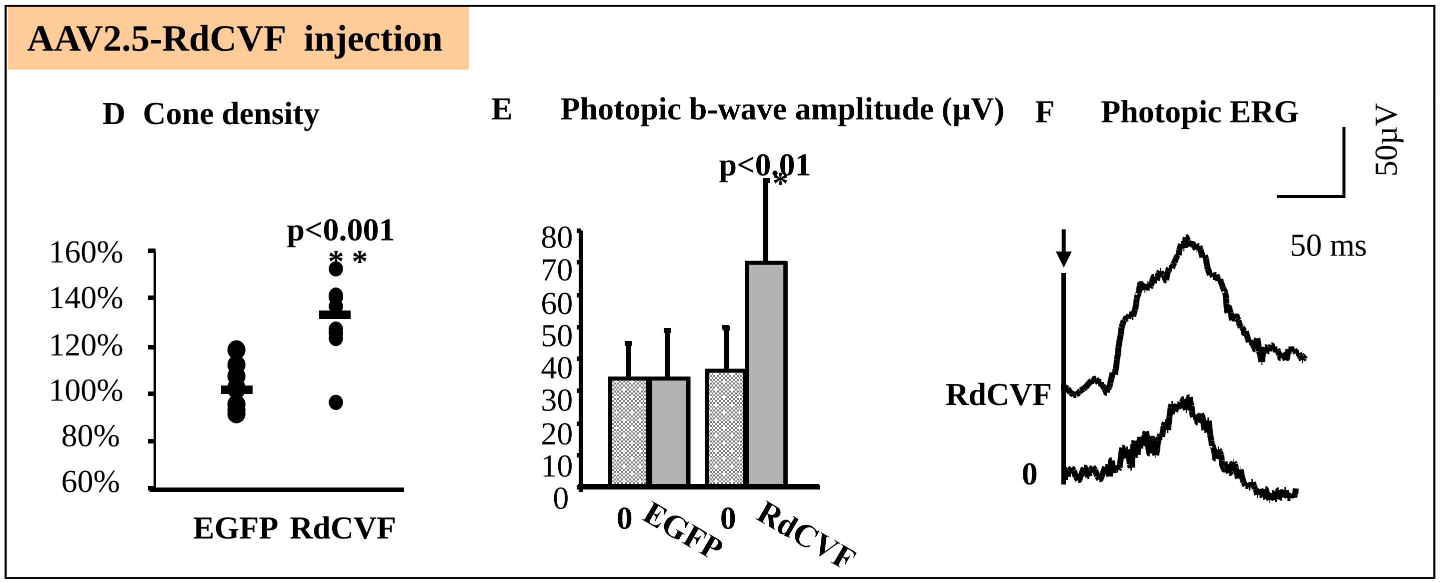
Anti-RdCVF (monoclonal)



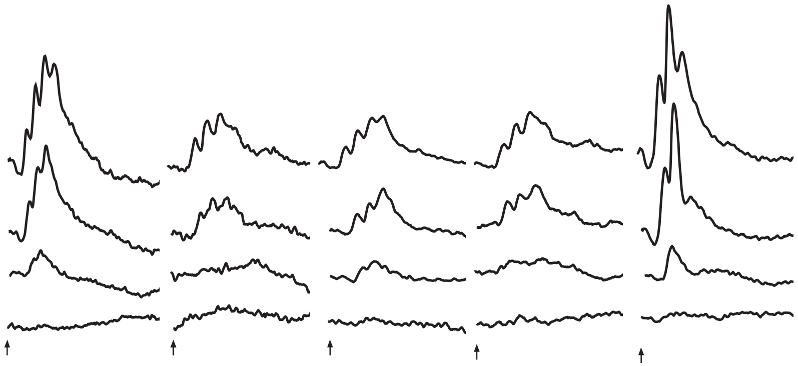
Anti-RdCVF (polyclonal)

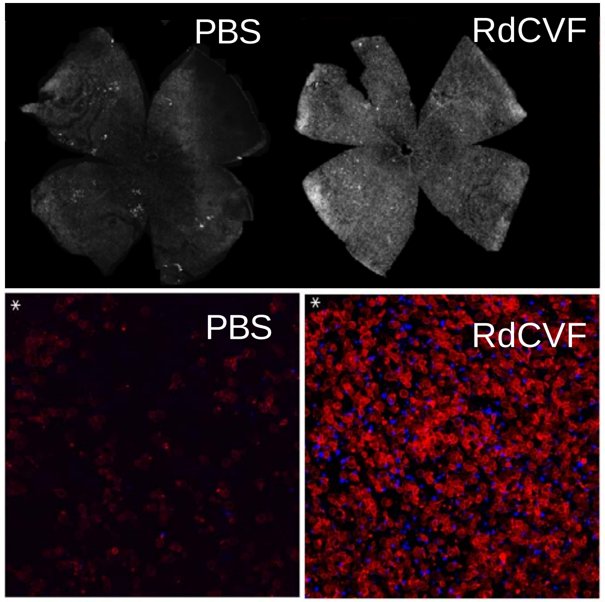
RdCVF protein increases cone survival and preserves cone function (Yang et al, 2009)

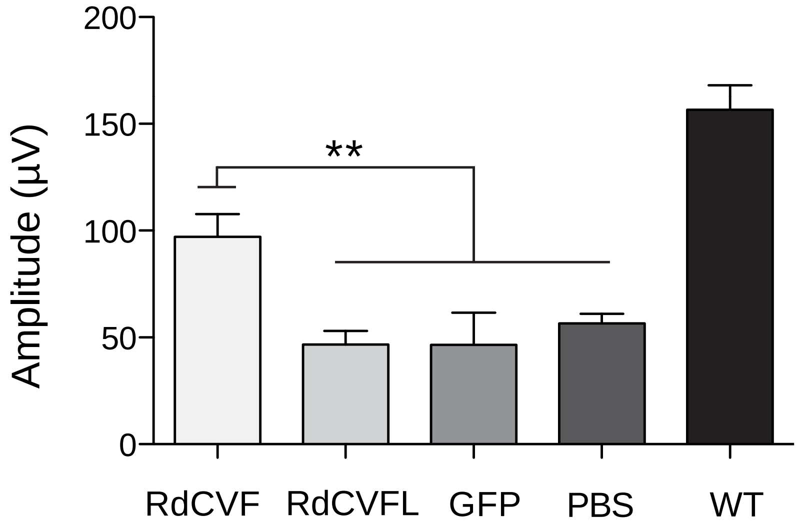


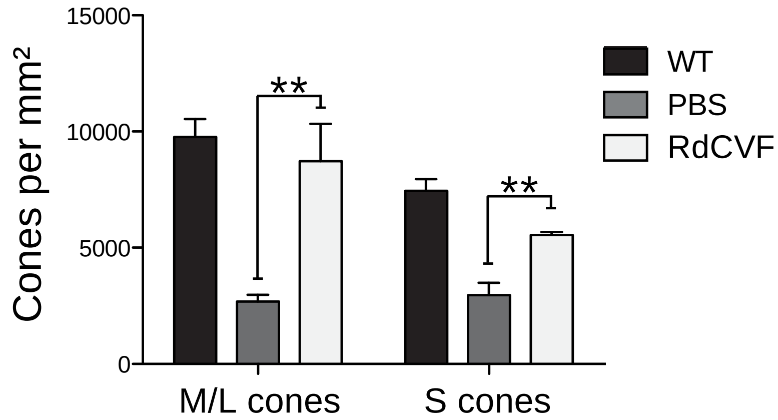


Systemic administration of AAV92YF-RdCVF rescues cones in the *rd10* mouse





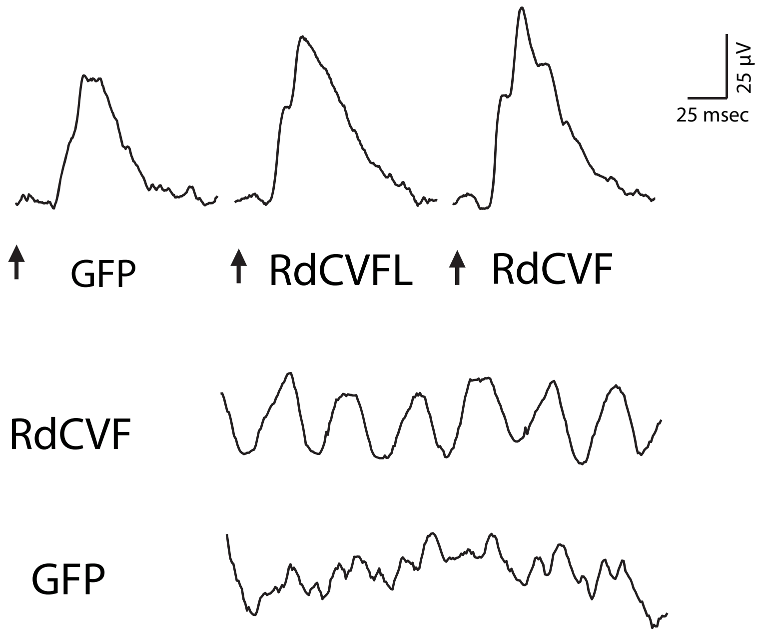


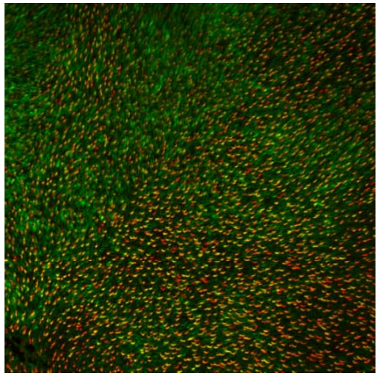


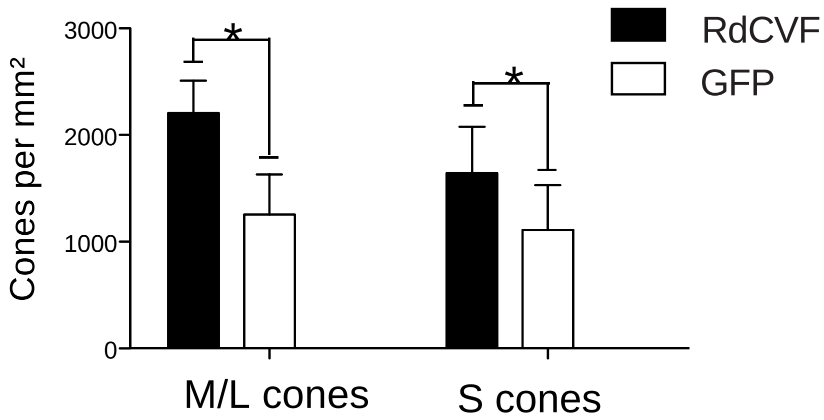
Leah Byrne, D. Dalkara, J. Flannery UC Berkeley

Intravitreal administration of 7m8-RdCVF rescues cones

7m8.GFP

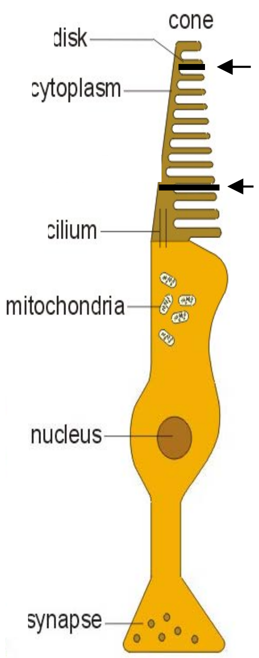


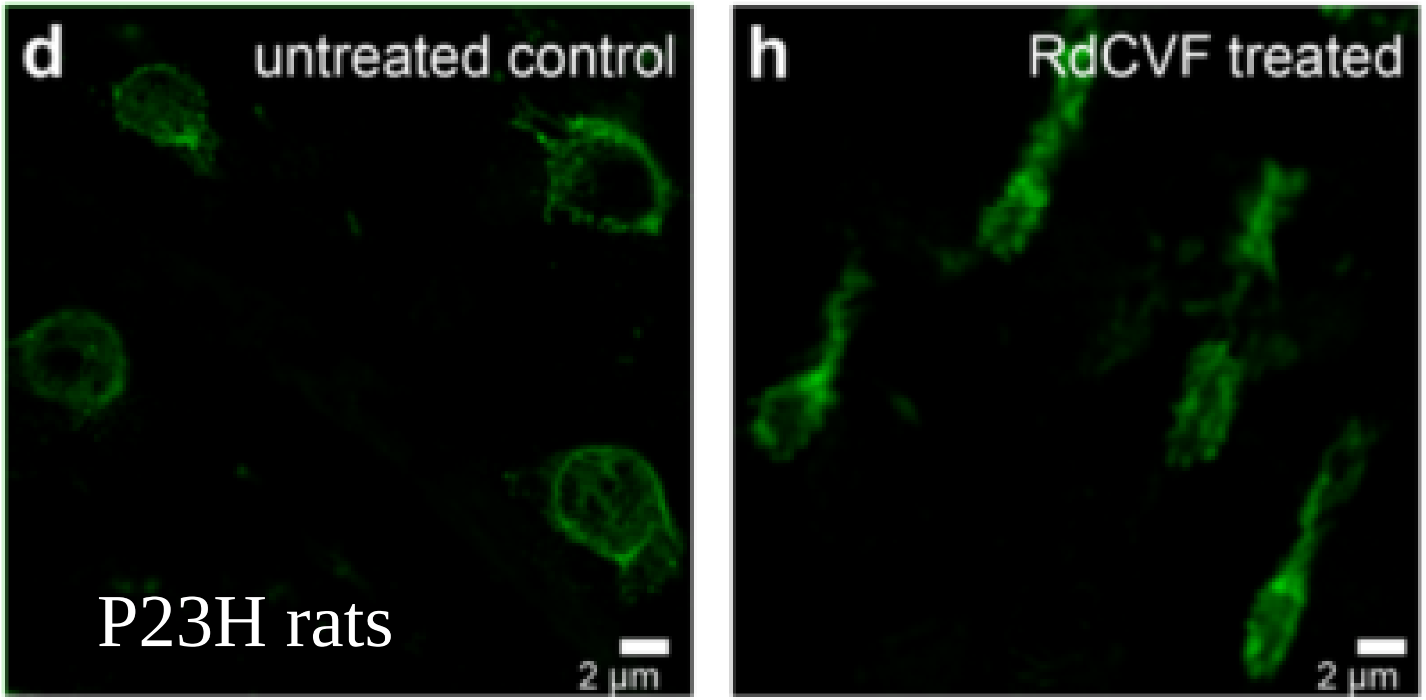




Leah Byrne, D. Dalkara, J. Flannery UC Berkeley

RdCVF preserves the morphology of the Cone outer segment

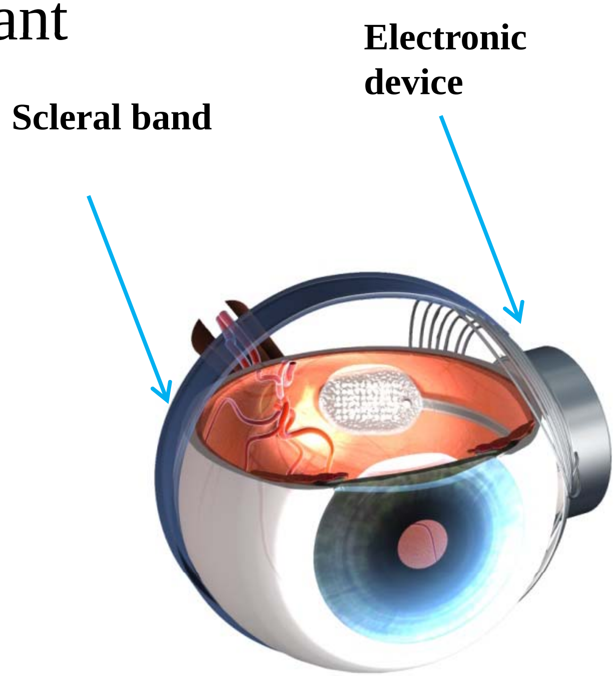


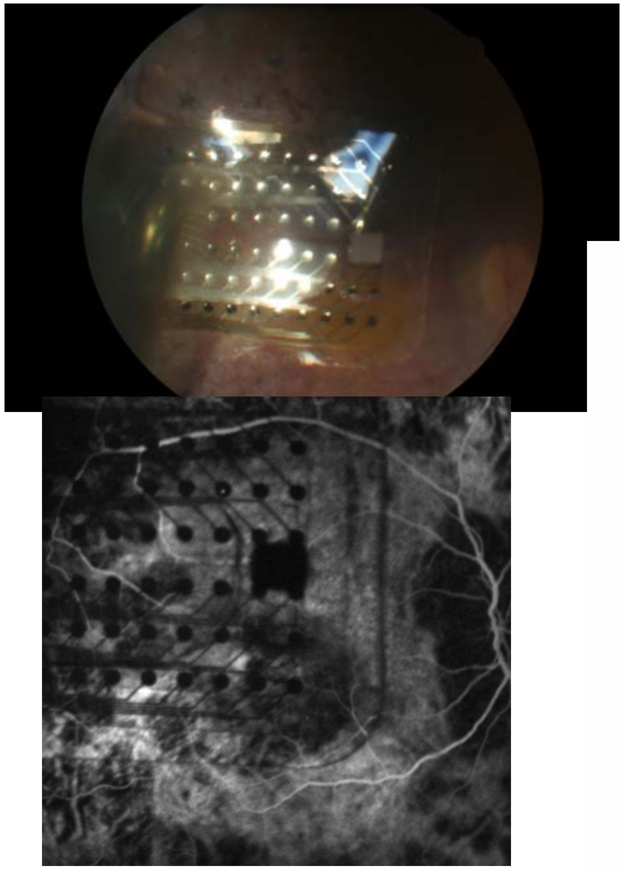


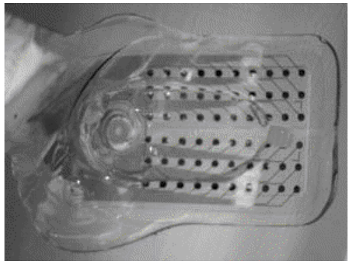
Ying Yang et al, Mol. Therapy, 2009

- to restore vision
    - artificial retinal implant

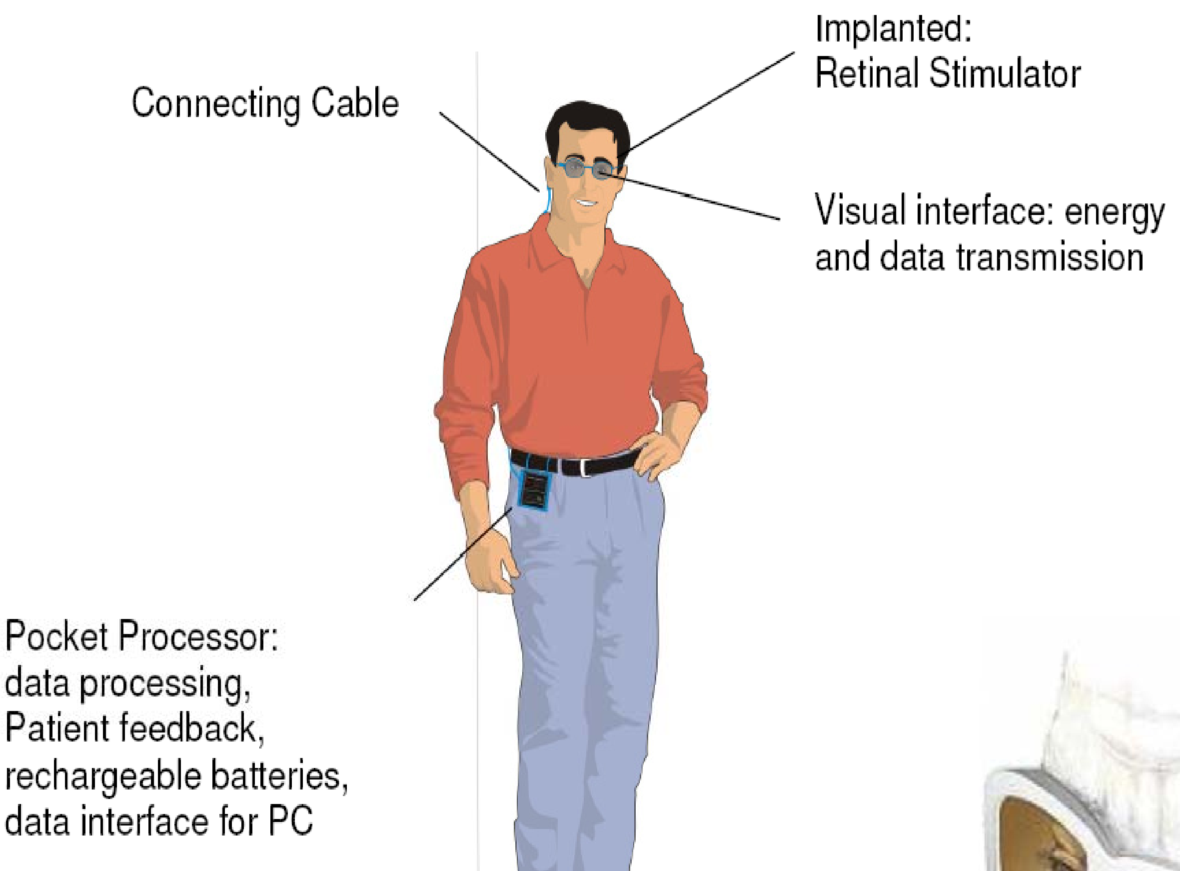
Second Sight Argus II Retinal Prosthesis Implan



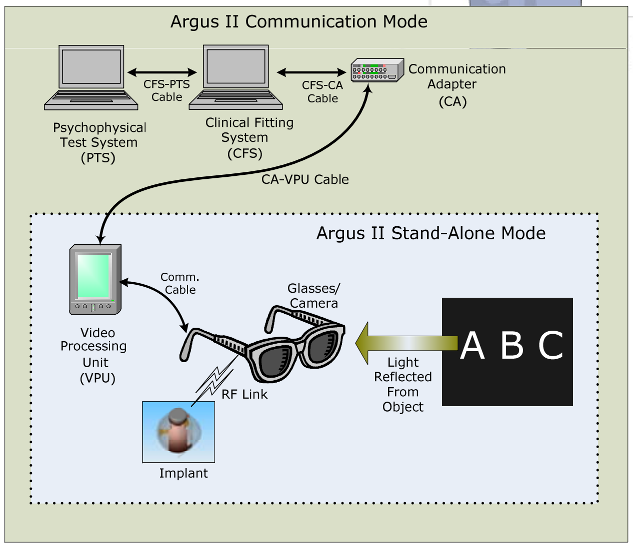




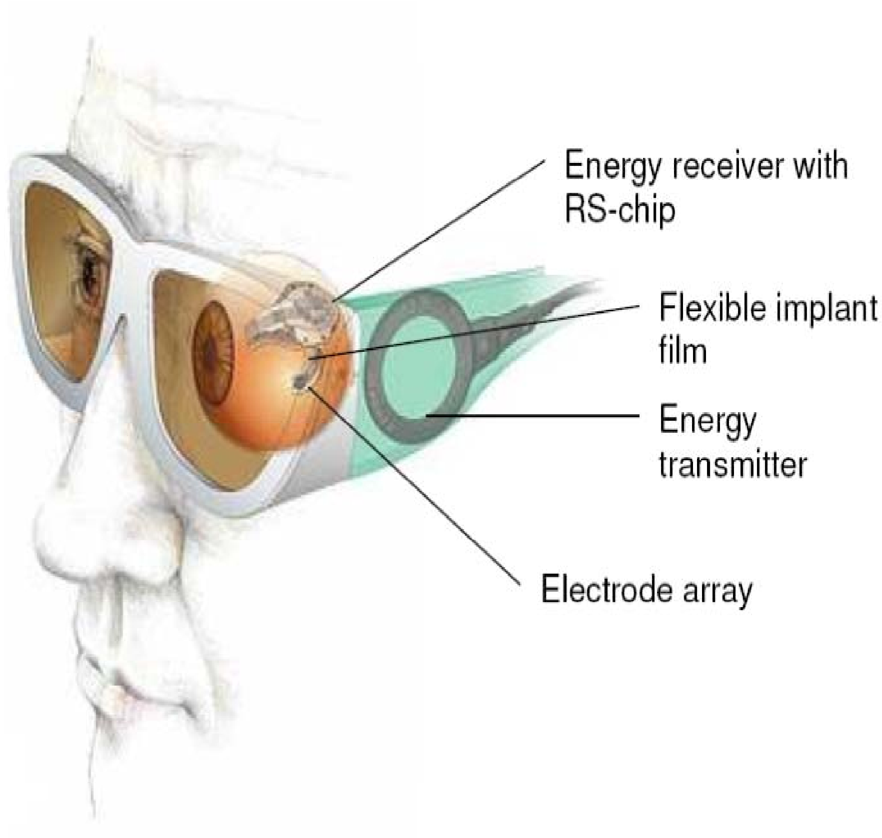
Argus II



Implanted:
Retinal Stimulator
Connecting Cable
Visual interface: energy
and data transmission
Pocket Processor:
data processing,
Patient feedback,
rechargeable batteries,
data interface for PC



Argus II Communication Mode
CFS-PTS Cable
CFS-CA Cable
Communication Adapter (CA)
Psychophysical Test System (PTS)
Clinical Fitting System (CFS)
CA-VPU Cable
Argus II Stand-Alone Mode
Comm. Cable
Glasses/ Camera
Video Processing Unit (VPU)
RF Link
Light Reflected From Object
A B C
Implant



Energy receiver with
RS-chip
Flexible implant
film
Energy
transmitter
Electrode array

Results
visual acuity test

96%

57%

23%

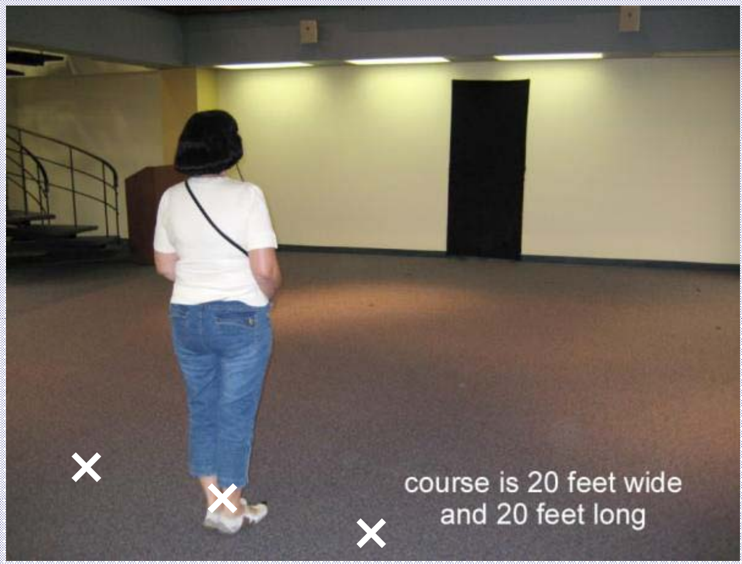
7 had 2.9 -1.6logMAR
best 1.8=20/1262

53-74%ON
vs.
10-16% OFF

All subjects had some visual benefit

Orientation et mobility

Test: find the door

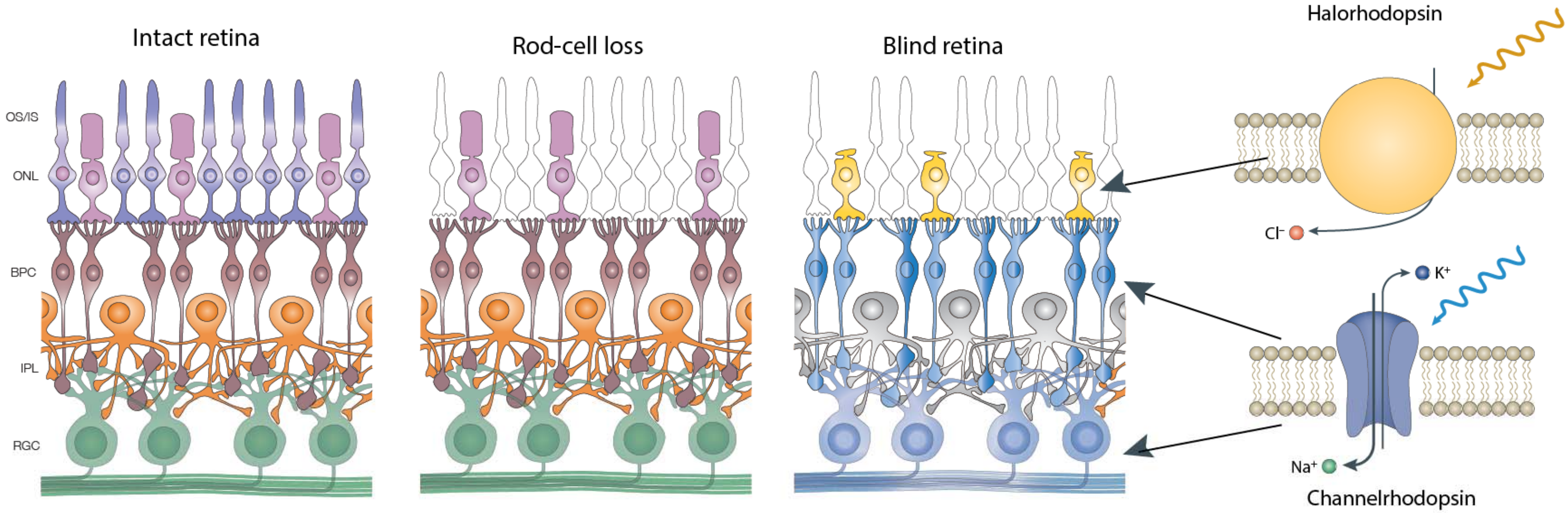


Test: follow the line

- **6 trials implant on / 6 trials implant off**
- **Test with both eyes**
- **Success = touch the door and follow the line**

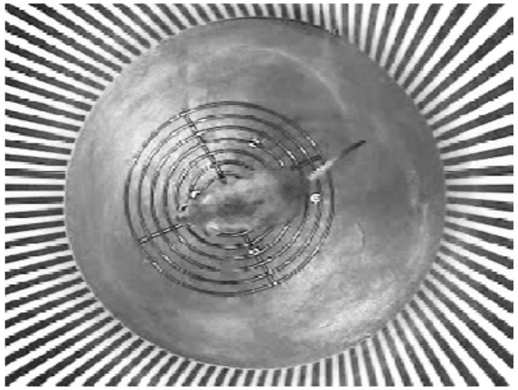
Optogenetics

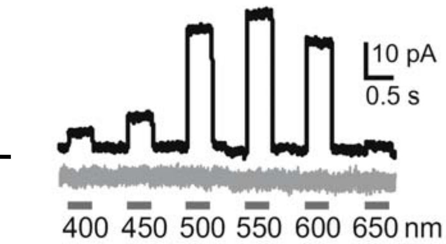
Goggles

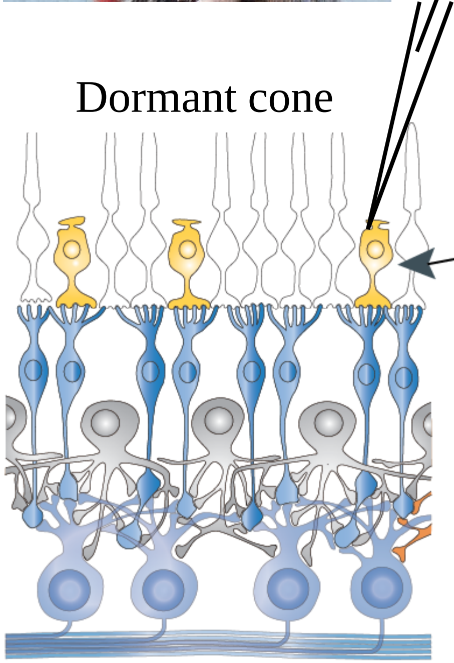


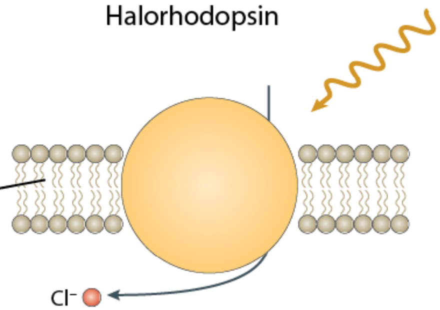
Zhuo Pan Ganglion cells, Botond Roska : Bipolar cells, Cone cells

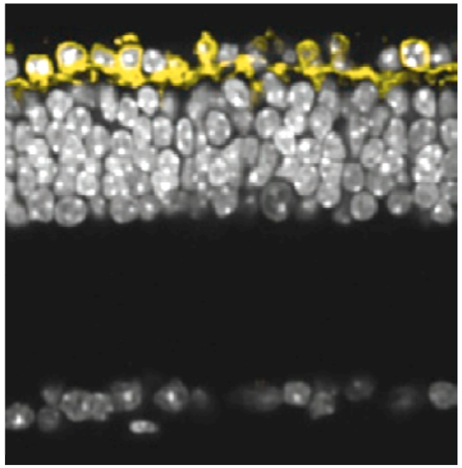
Vision restoration using optogenetics: re-activating dormant cones for optimal visual acuity







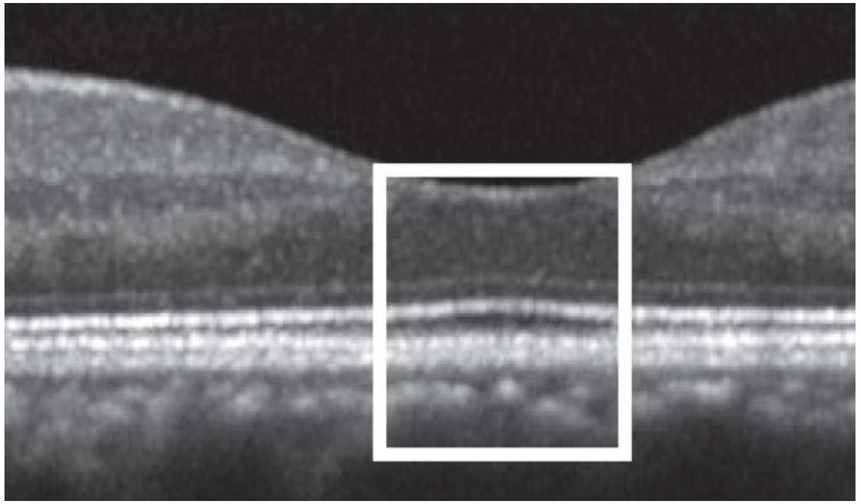


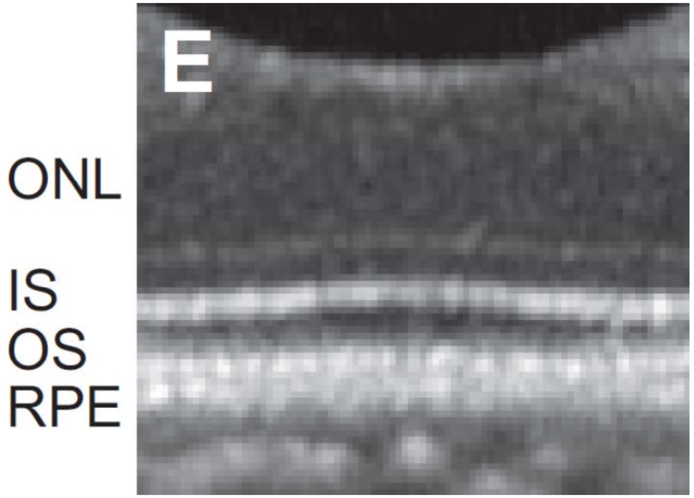


Busskamp et al., Science (2010)

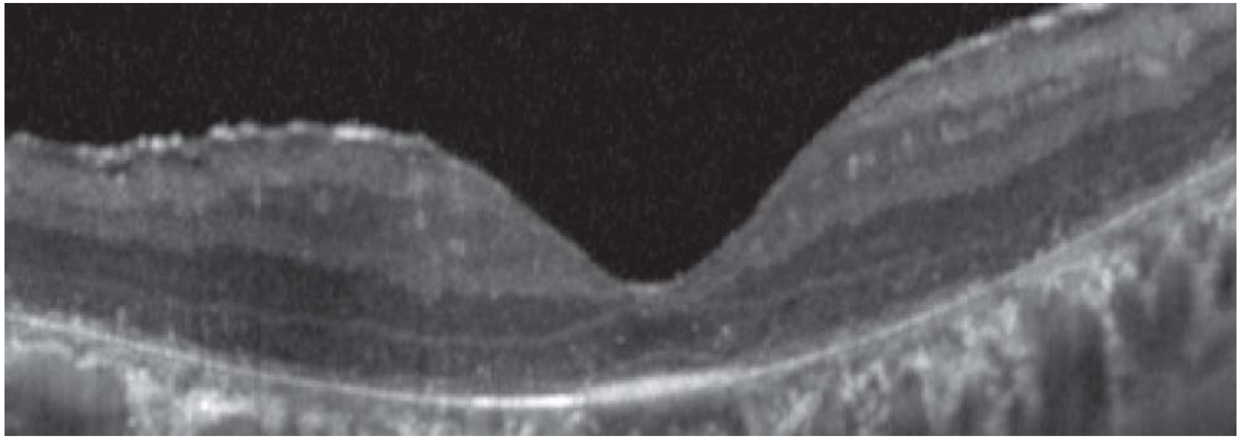
Patient suitable for cone reactivation

Normal person

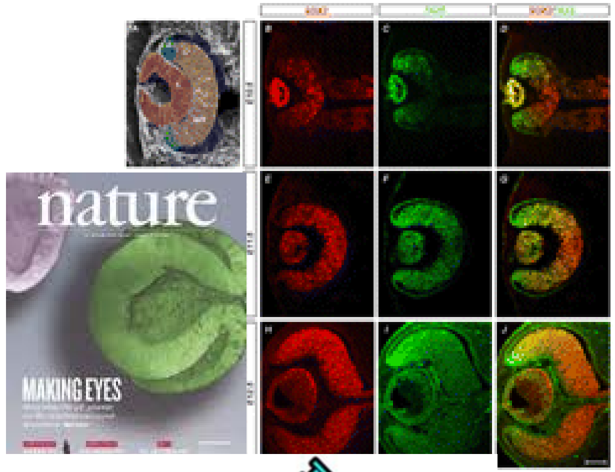


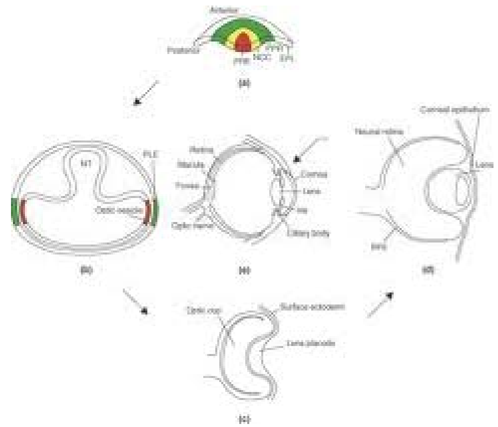


Retinitis pigmentosa patient with dormant cones

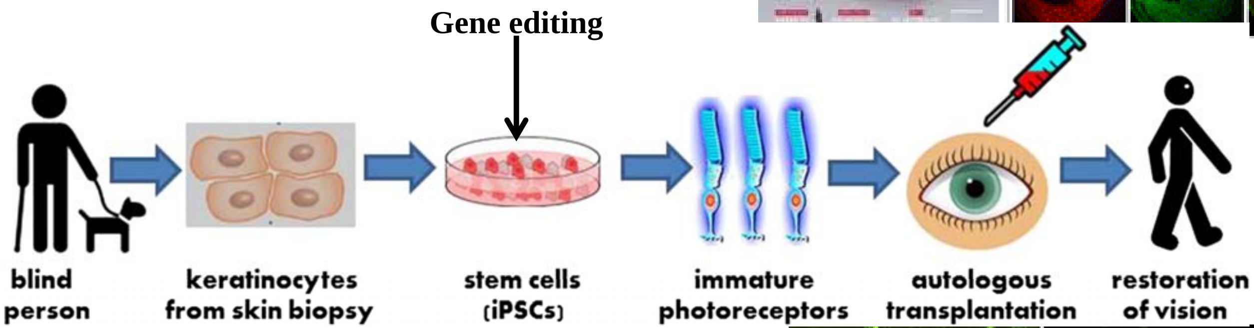


Stem cells

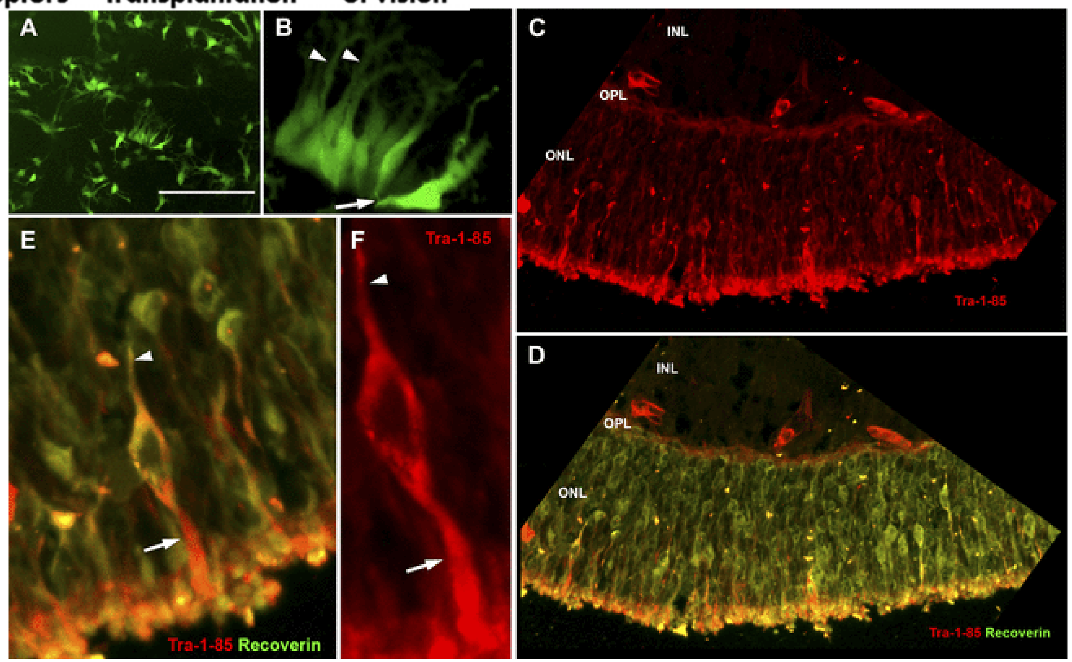




(Matsushima et al 2011)



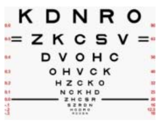
Adapted from Bennicelli et al 2013

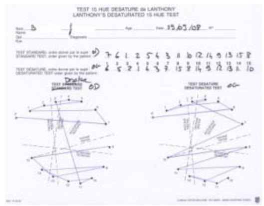


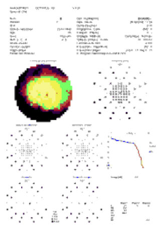
Tucker et al 2013

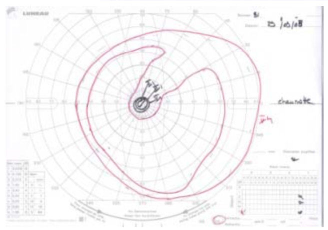
Need for precise phenotypic characterization, natural history studies an clinical endpoints

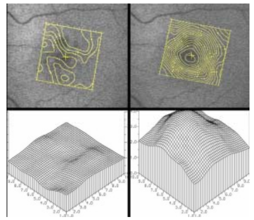
Psychophysics

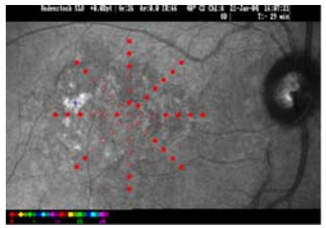


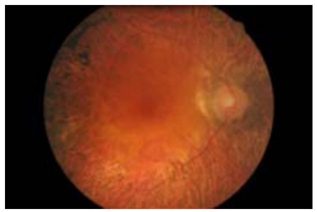


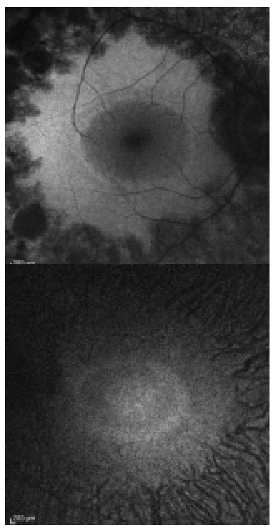


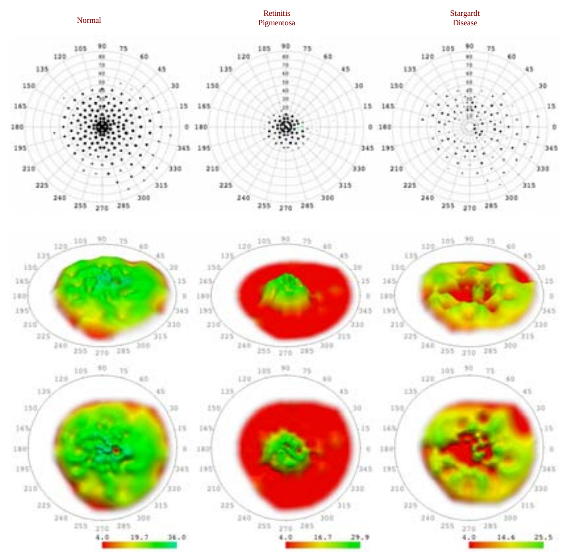








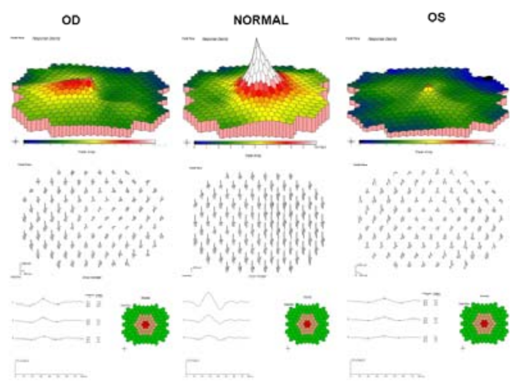


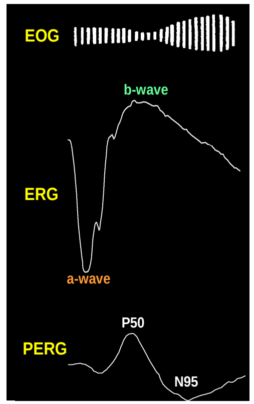


187point grid
GATE
algorithm

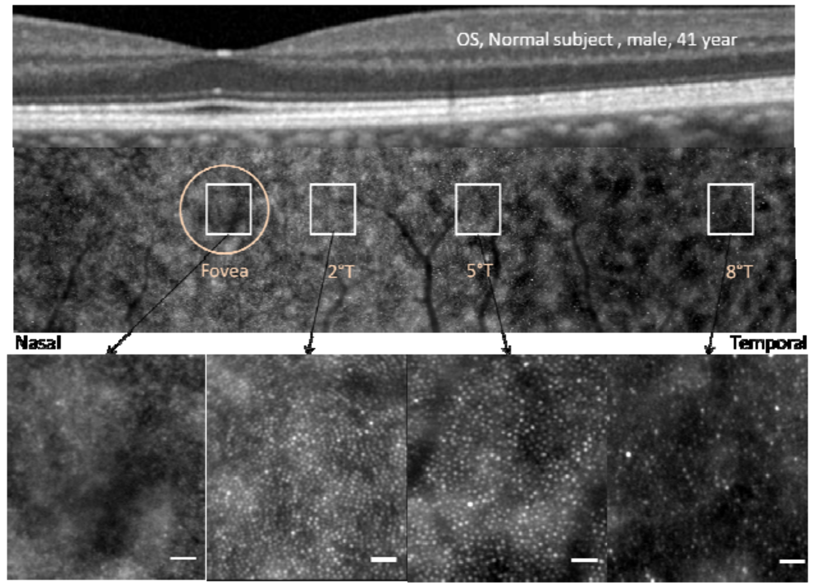
(R Welleber)

Electrophysiology





Retinal imaging



Clinical Investigation Center
Quinze-Vingts hospital

José-Alain Sahel
Saddek Mohand-Said
Isabelle Audo
Michel Paques
Caroline Laurent-Coriat,
Konstantinos Aliferis, Ieva Sliesoraityte
J. Haidar
C. Franchisseur
N. Vaissade, G. Henry
C. Chaumette, S. Sancho
A. Leseigneur, A. Girmens
L. Cousin, D. Santiard-Baron, etc

Equipe A-Z
Département de génétique
Institut de la Vision

Isabelle Audo
Shomi Bhattacharya
Kinga Bujakowska
Aline Antonio
Aurore Germain
Marie-Elise Lancelot
Elise Ohran
Christelle Michiels
Christina Zeitz

QUINZE-VINGTS
CENTRE HOSPITALIER NATIONAL D'OPHTALMOLOGIE
CENTRE D'INVESTIGATION CLINIQUE

CASEY EYE INSTITUTE

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To be continued…