GenSight BIOLOGICS

GS010 Phase III data to-date

KOL breakfast and presentation

A LEADING GENE THERAPY BIOTECHNOLOGY COMPANY

GENSIGHT-BIOLOGICS.COM

Agenda

Topic	Timing	Speaker
Opening remarks	8:35 - 8:40	Bernard Gilly, CEO, GenSight
Introduction of speakers	8:40 - 8:45	Dr. Barrett Katz, CMO, GenSight
Disease overview	8:45 - 8:55	Dr. Sean Donahue
Natural history of LHON	8:55 - 9:10	Dr. Mark Moster
The patient experience	9:10 - 9:20	Andy Marks, patient advocate
Update on REVERSE results	9:20 - 9:40	Dr. Robert Sergott
Scientific rationale for the contralateral effect	9:40 - 9:55	Dr. David Calkins
Synthesis of discussion	9:55 - 10:05	Dr. José-Alain Sahel, co-founder
A patient case study	10:05 - 10:10	Dr. Sean Donahue
Closing remarks	10:10 - 10:15	Bernard Gilly, CEO, GenSight
Q & A	10:15 - 10:30	Participants

GenSight BIOLOGICS

KOL speakers

Dr. Sean Donahue	Coleman Professor of Ophthalmology, Neurology and Pediatrics Vice Chair of Clinical Affairs, Ophthalmology Vanderbilt University Medical Center *Nashville, TN*
Dr. Mark Moster	Neuro-Ophthalmology, Wills Eye Hospital, and Professor of Neurology and Ophthalmology at Thomas Jefferson University *Philadelphia, PA*
Dr. Robert Sergott	Director, Neuro-Ophthalmology, Willis Eye Hospital, and Director, William H. Annesley, Jr. EyeBrain Center, Thomas Jefferson University *Philadelphia, PA*
Dr. David Calkins	O'Day Professor, Vice Chair and Director for Research Vanderbilt Eye Institute, Vanderbilt University Medical Center *Nashville, TN*
Dr. José-Alain Sahel	Director, Institut de la Vision, Sorbonne-Université/Inserm/CNRS (*Paris*); Chairman, Department of Ophthalmology, Centre Hospitalier National de l'Ophthalmologie des XV-XX (*Paris*); Professor and Chairman, Department of Ophthalmology, University of Pittsburgh School of Medicine and UPMC

GenSight BIOLOGICS

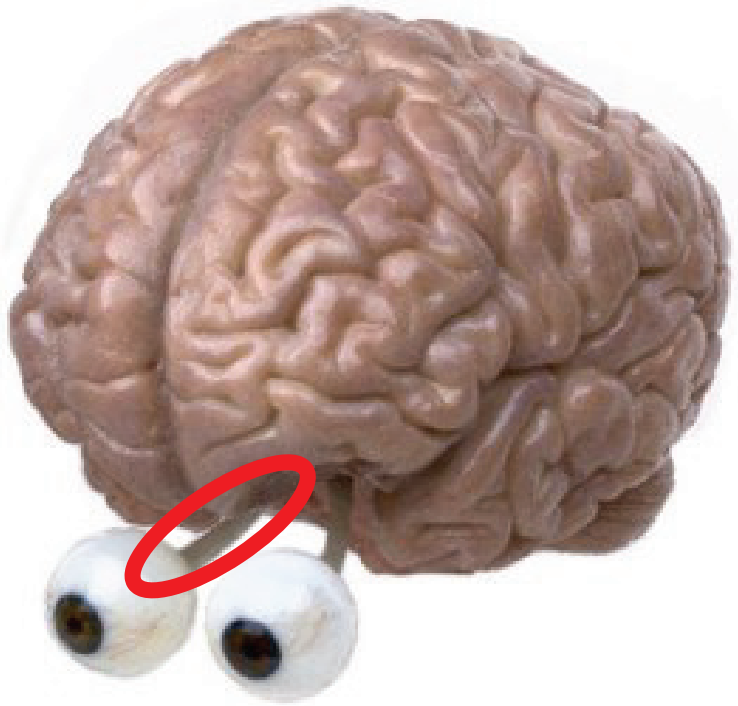
Disease Overview

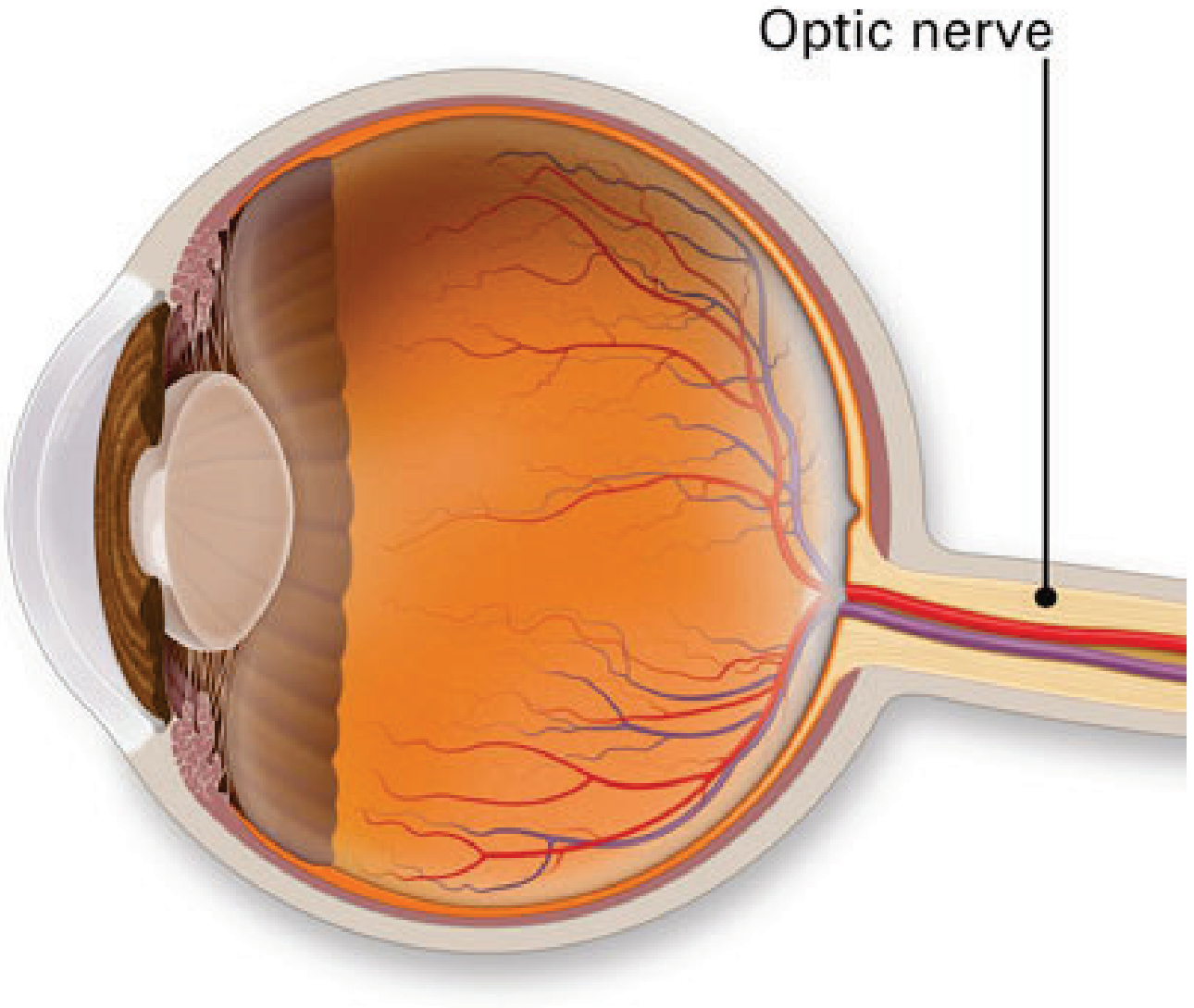
Dr. Sean Donahue

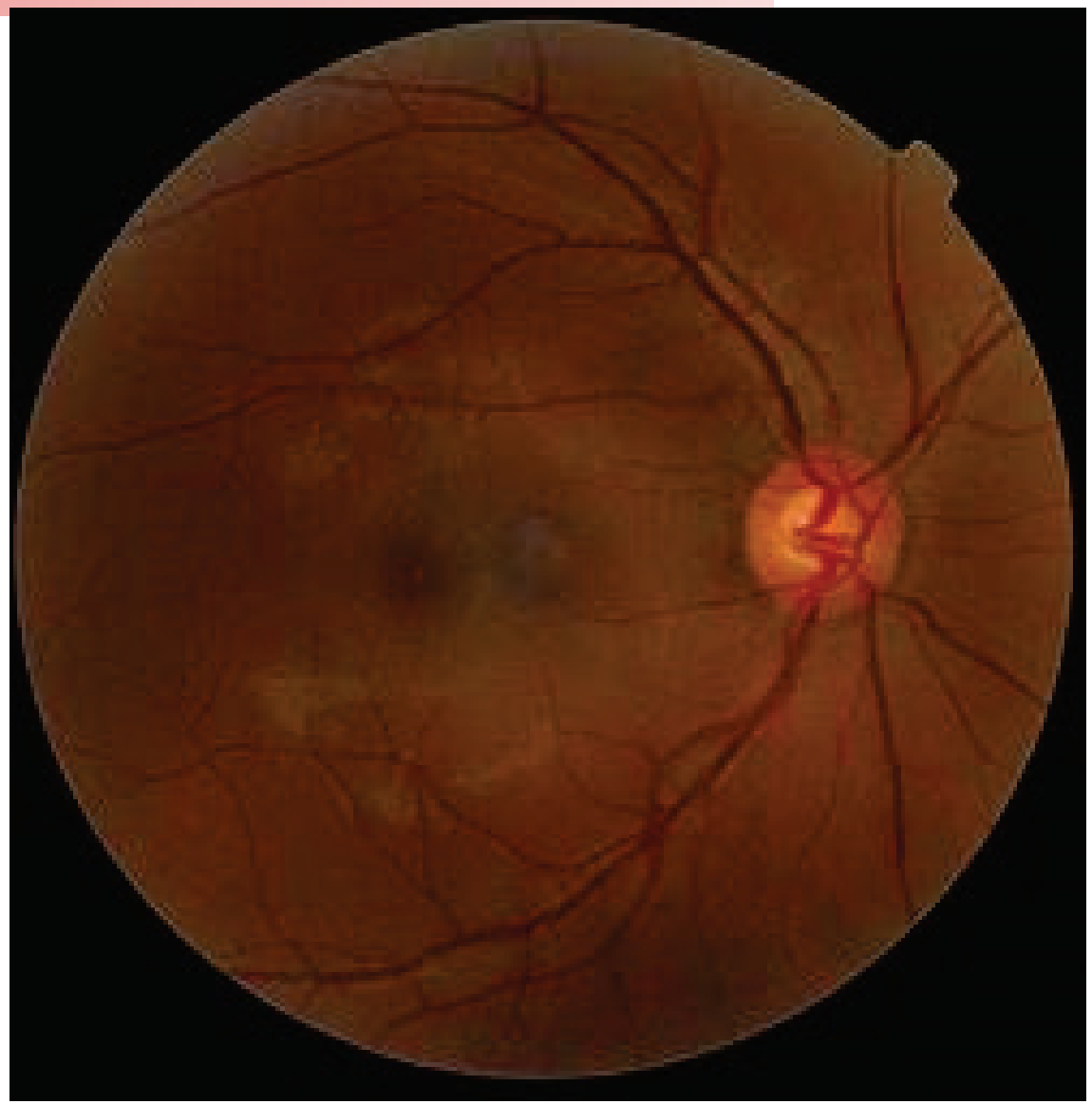
Leber Hereditary Optic Neuropathy

Sean P. Donahue, M.D., Ph.D.
Professor of Ophthalmology, Neurology,
& Pediatrics
Vanderbilt University Medical Center

Leber Hereditary Optic Neuropathy




Optic nerve



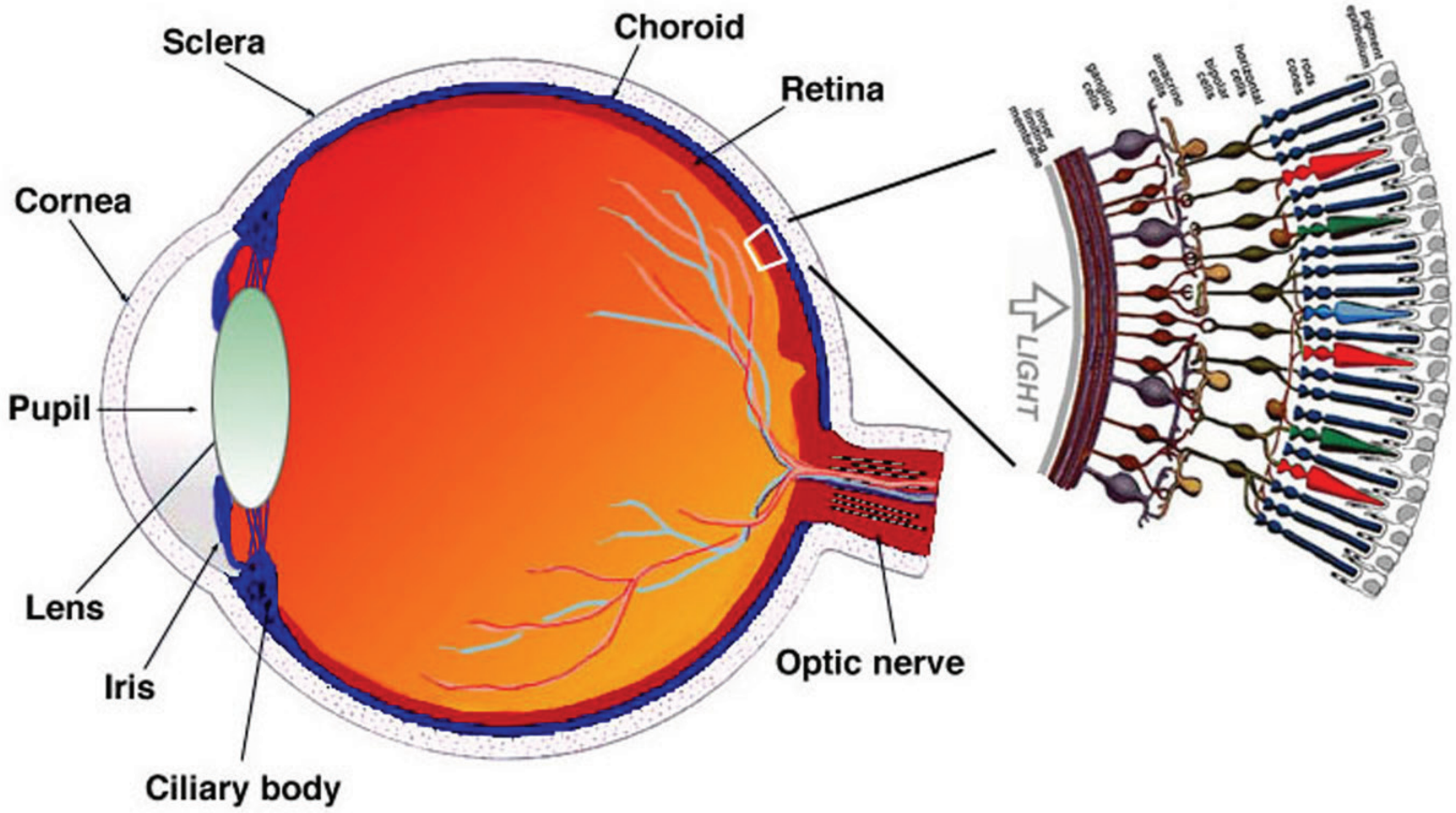
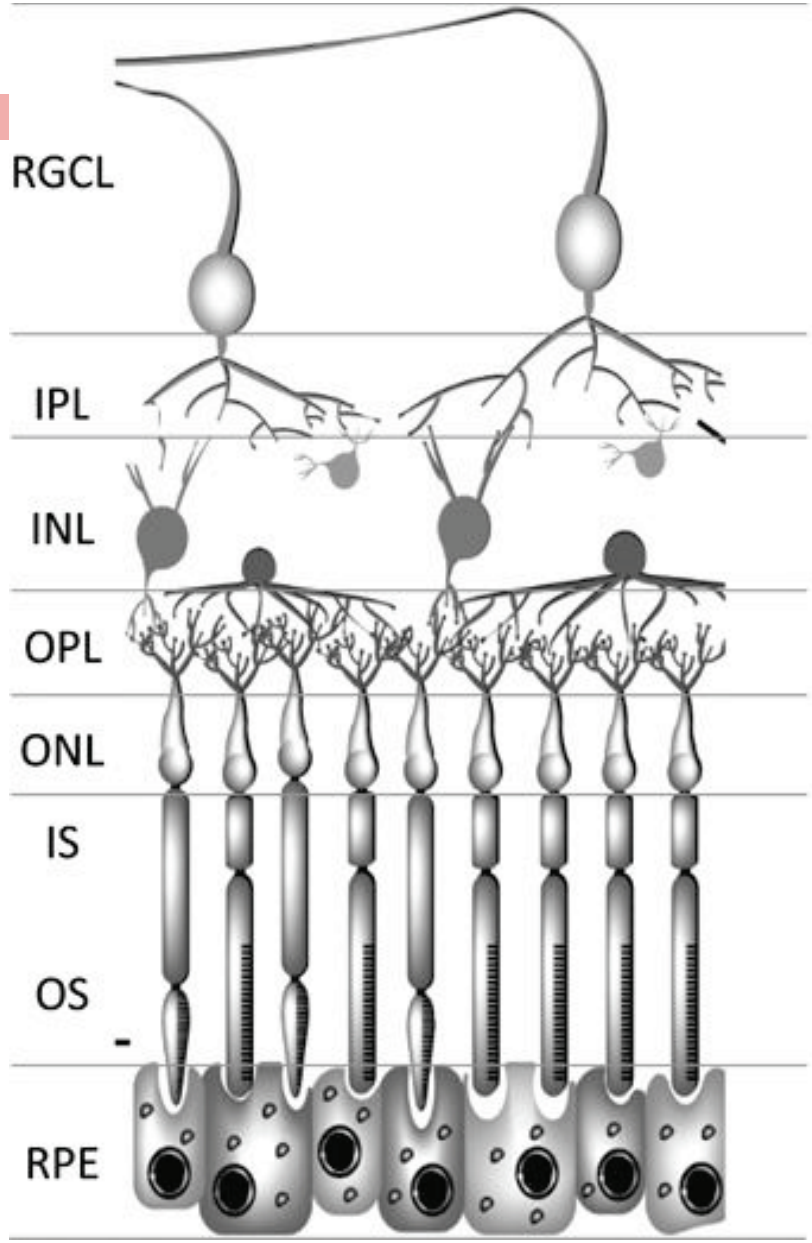


Fig. 1.1. A drawing of a section through the human eye with a schematic enlargement of the retina.



Retinal ganglion cells

Role of autophagy
Axonal protection
Reduce oxidative stress
Preserve mitochondrial function

Autophagy deficiency

Retinal ganglion cell death
Glaucoma
Axonal alterations

Evaluation of Vision Loss

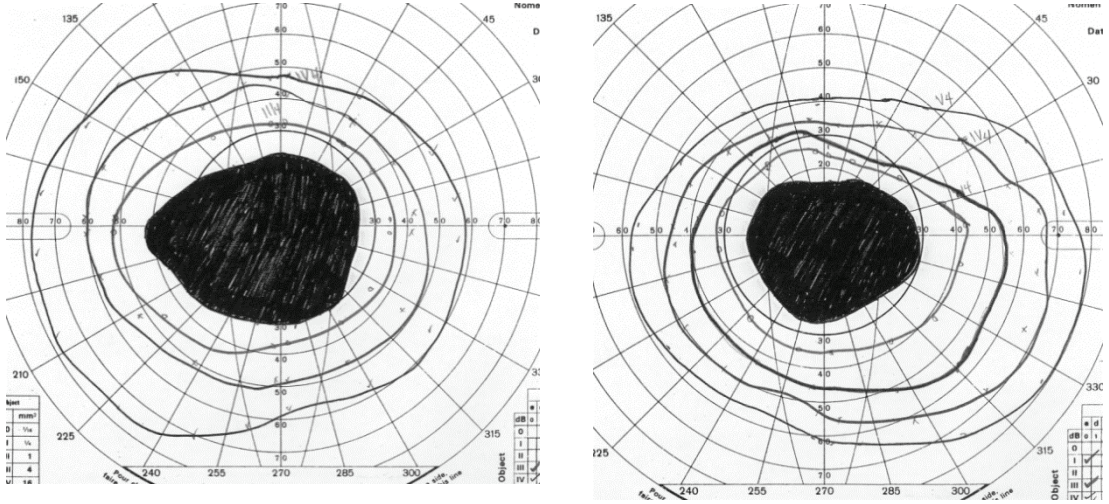
- Not caused by needing new glasses
- Can occur anywhere along visual pathways
- Test involves management of visual acuity, visual field (function)
- Evaluation of Optic Nerve (structure)
  - Appearance
  - Thickness
- Determination of cause of visual loss

Leber Hereditary Optic Neuropathy

- Very rare cause of vision loss
- Subacute sequential bilateral central visual loss
- Age of onset typically 18-30 (range 1-87)
- Male predominance (80-90%)
- Progression in each eye over weeks to months
- Recognized interval between eyes in 50% (days to months)
- > 97% bilateral within 1 year

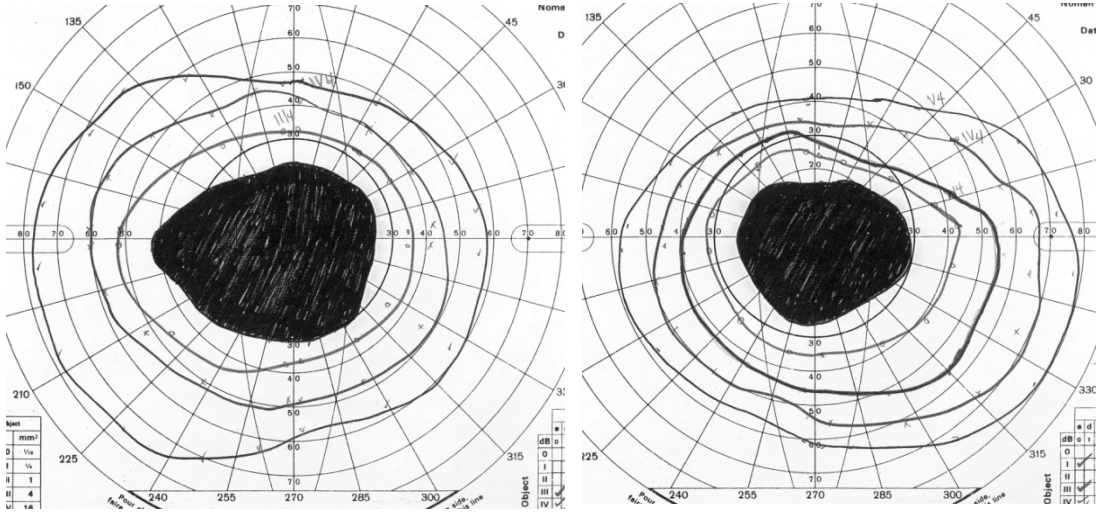
A 21 year old previously healthy man has painless loss of vision in both eyes progressive over one month

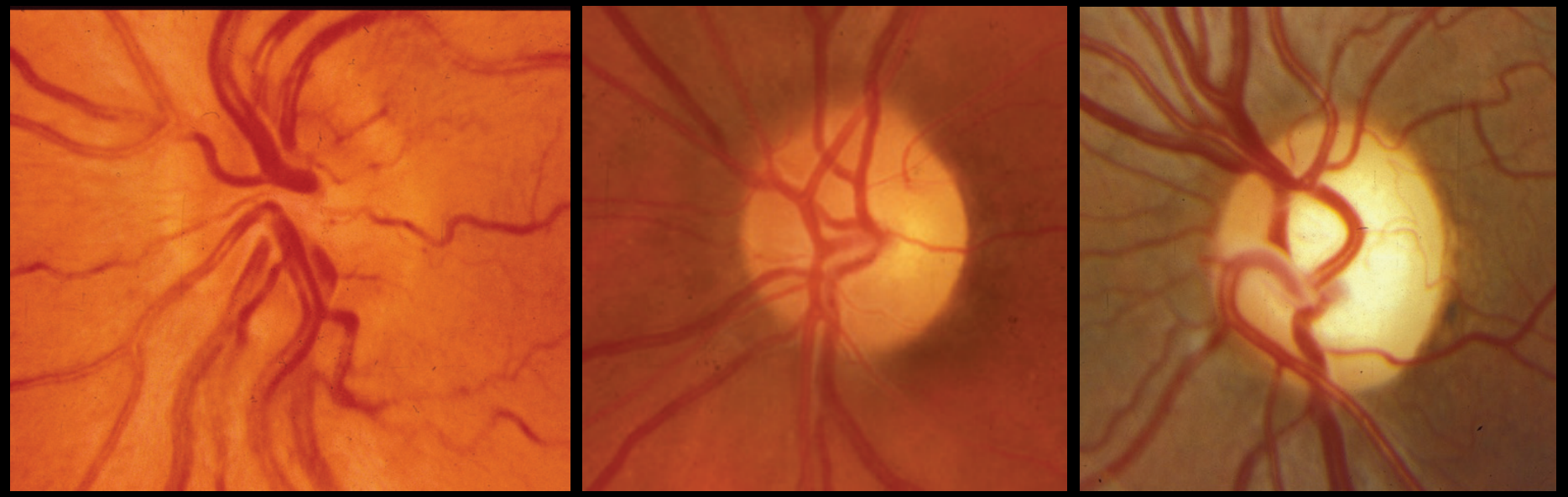
Vision is counting fingers in both eyes



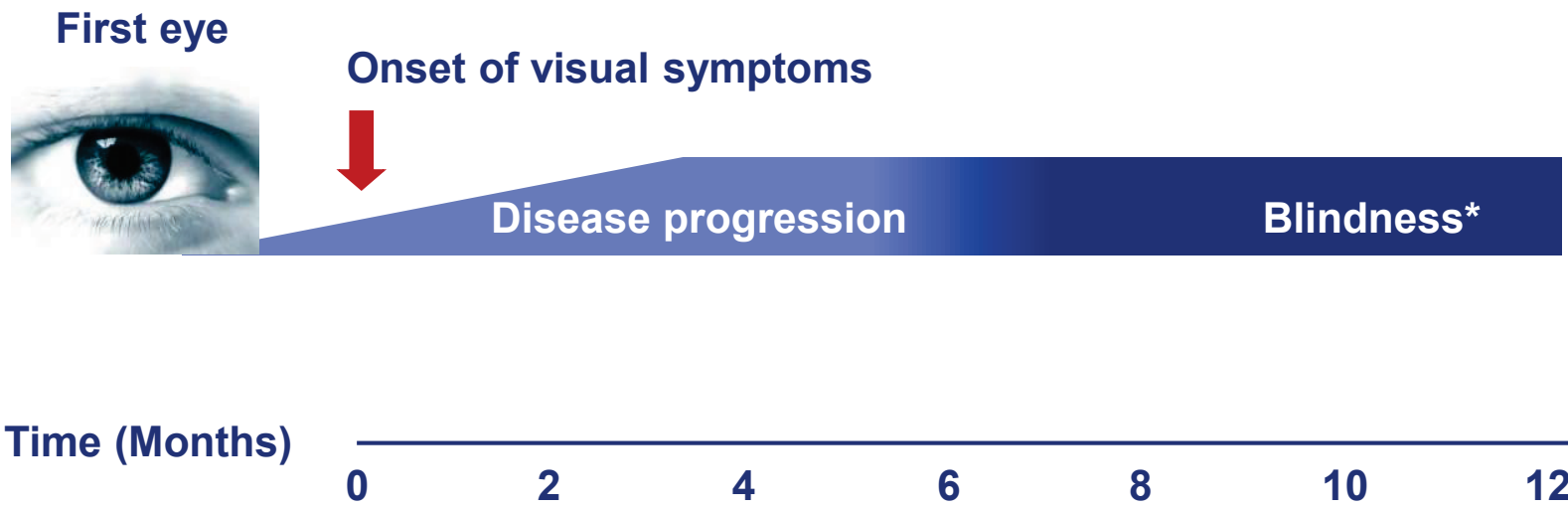
Leber Hereditary Optic Neuropathy

- **Acuity usually worse than 20/200**
- Color vision affected early
- Central defects





LHON – Typical Disease Course



- Painless central visual loss
- Severe reduction in visual acuity to ≤ 20/200
- Both eyes affected simultaneously ~ 25%

LHON – Typical Disease Course

First eye

Onset of visual symptoms

Disease progression

Blindness*

Time (Months)

0 2 4 6 8 10 12

Second eye

Disease progression

Blindness*

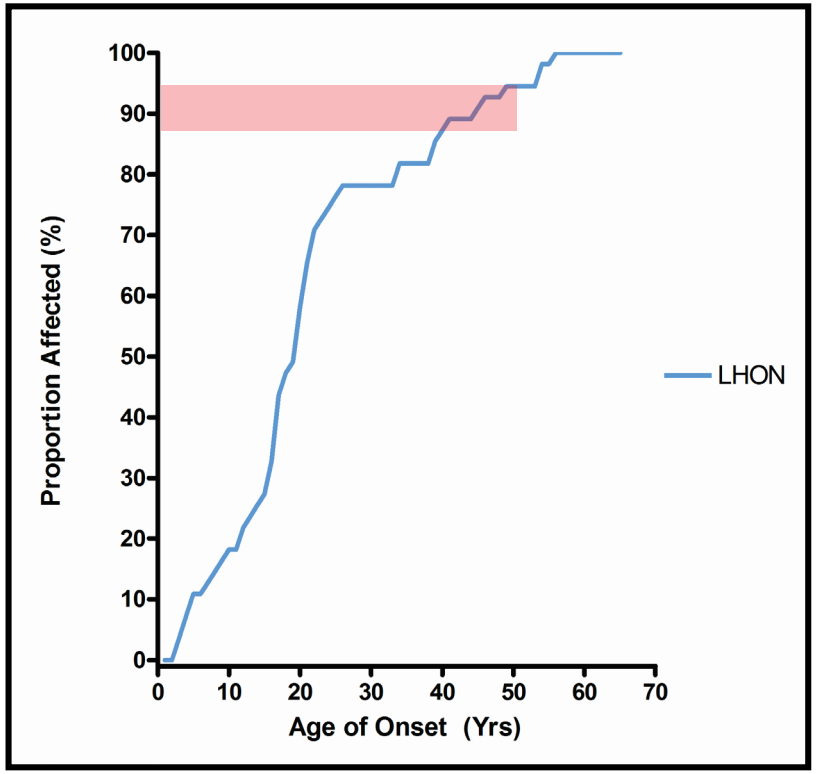
Onset of visual symptoms

* UK legal definition

Snellen < 3/60

LogMAR < 1.30

LHON – Typical Disease Course

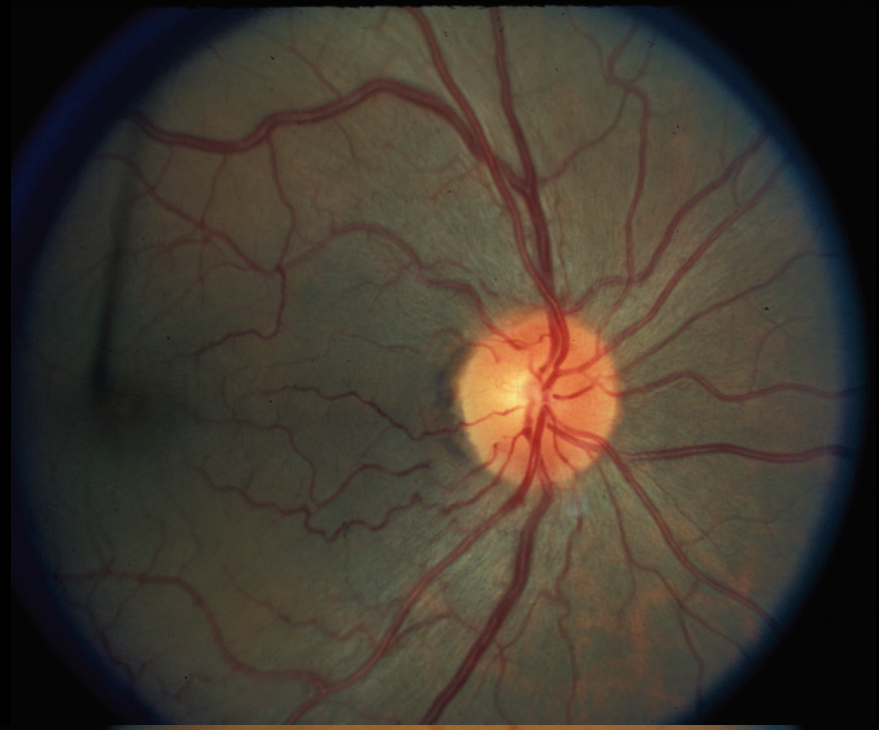
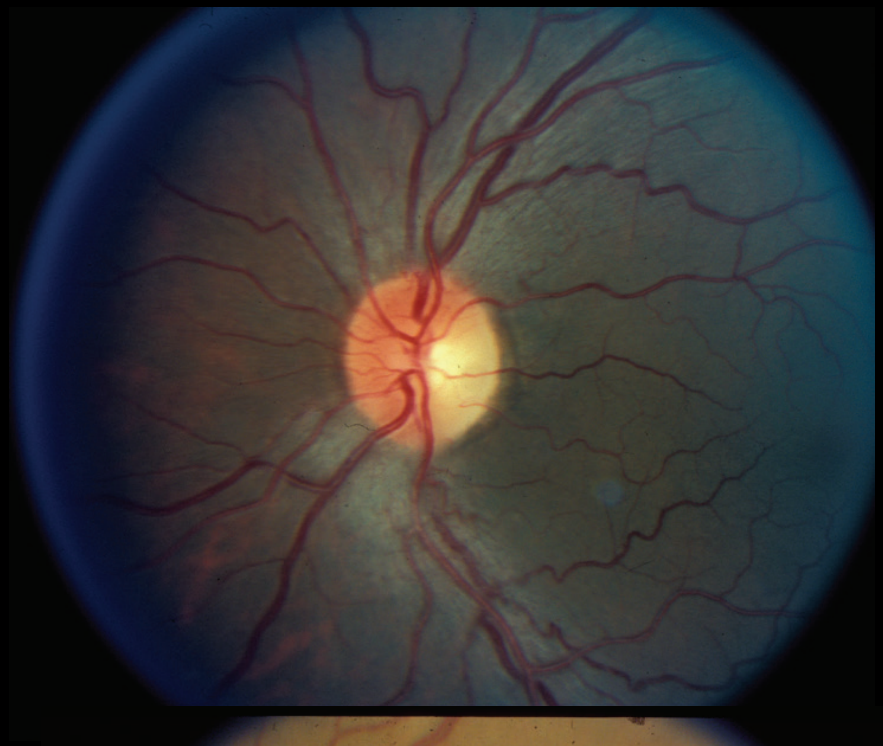
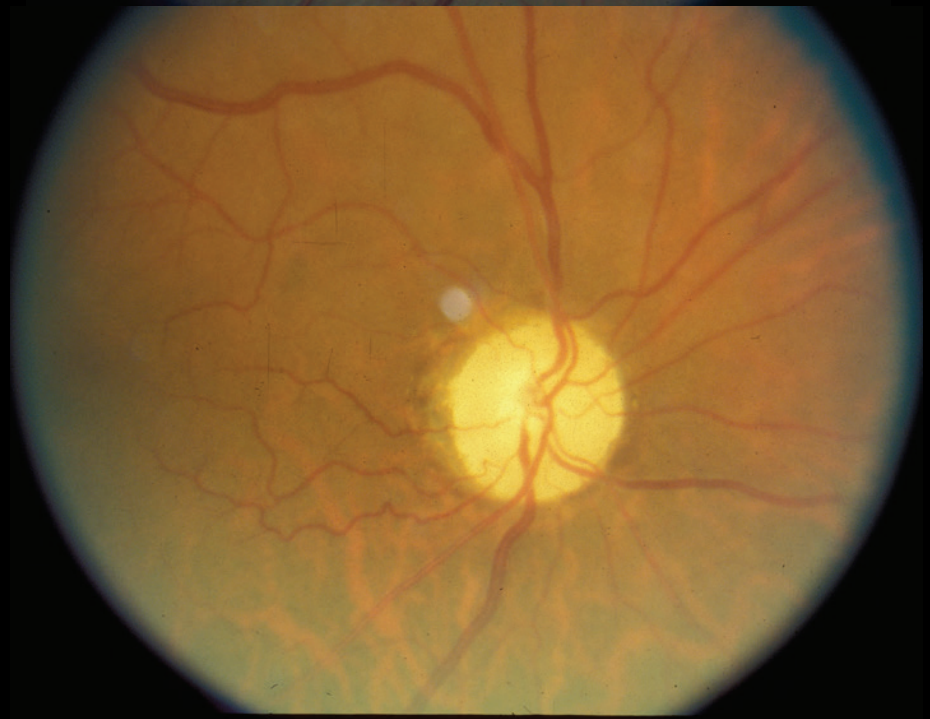
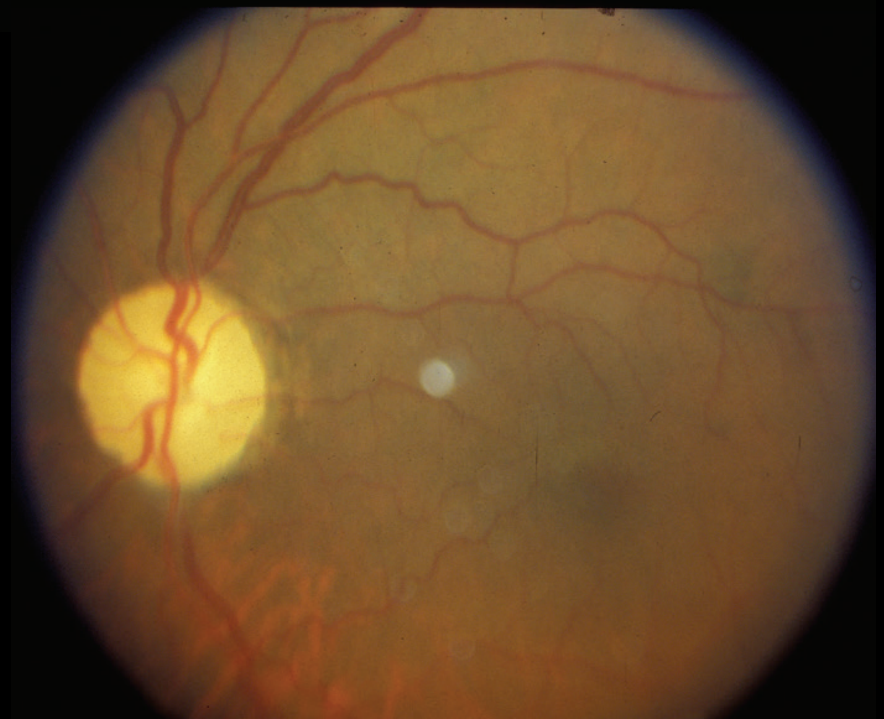


- Peak age of onset: 20-30
- Marked sex bias: 80% males

LHON – Burden of Disease

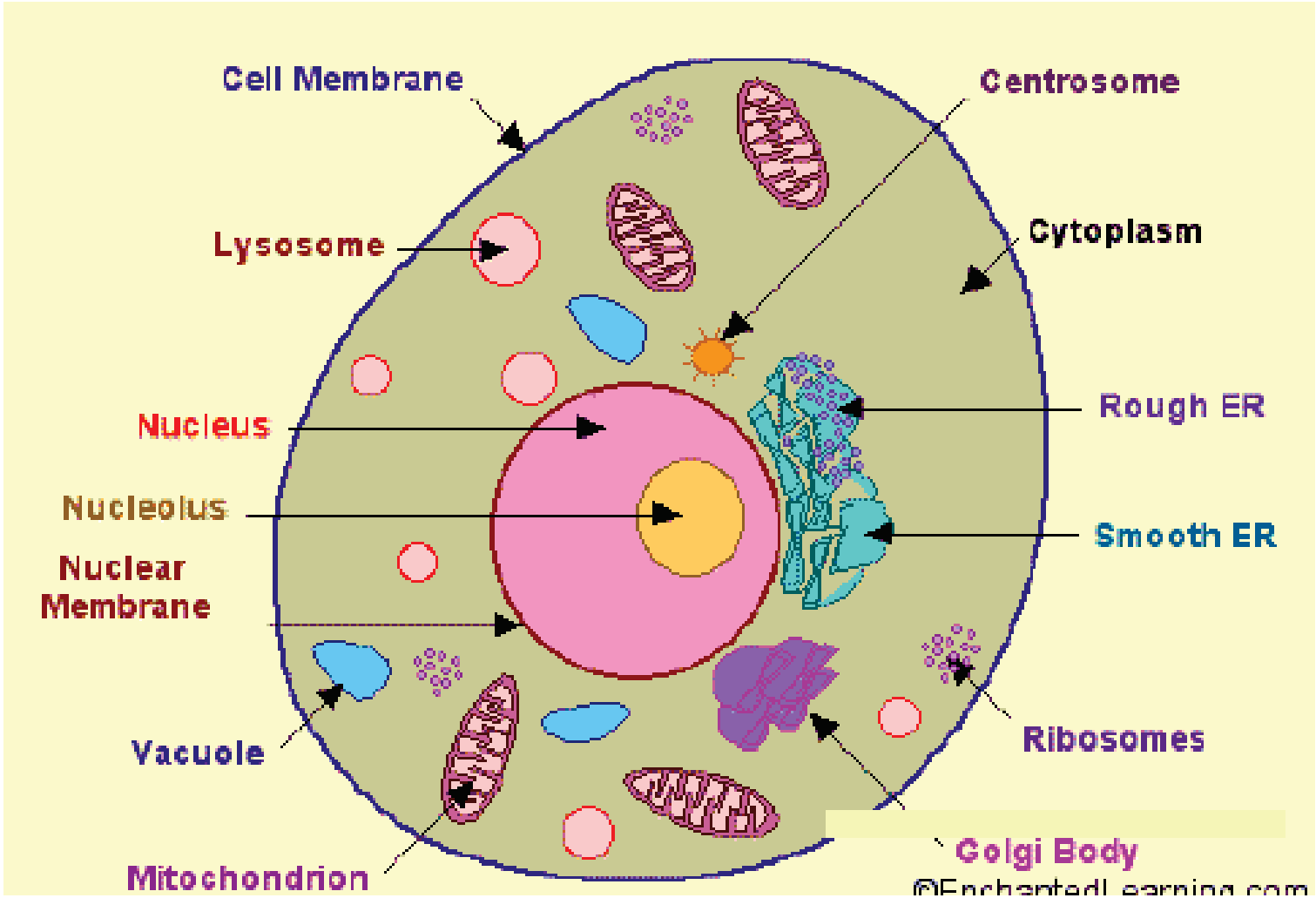
Quality of Life in Patients with Leber Hereditary Optic Neuropathy

Visual prognosis is poor with most patients remaining within the legal criteria for "blind registration"

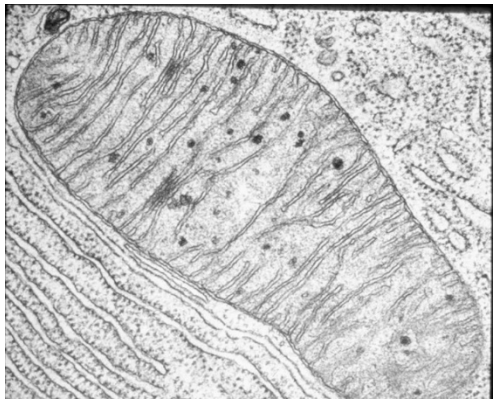





Why does this happen?

- Genetic Mutation
  in mitochondrial DNA
- All cells have DNA in the nucleus
- Mitochondria also have DNA
- This DNA is passed on by the mother
- Mutation in this DNA causes LHON

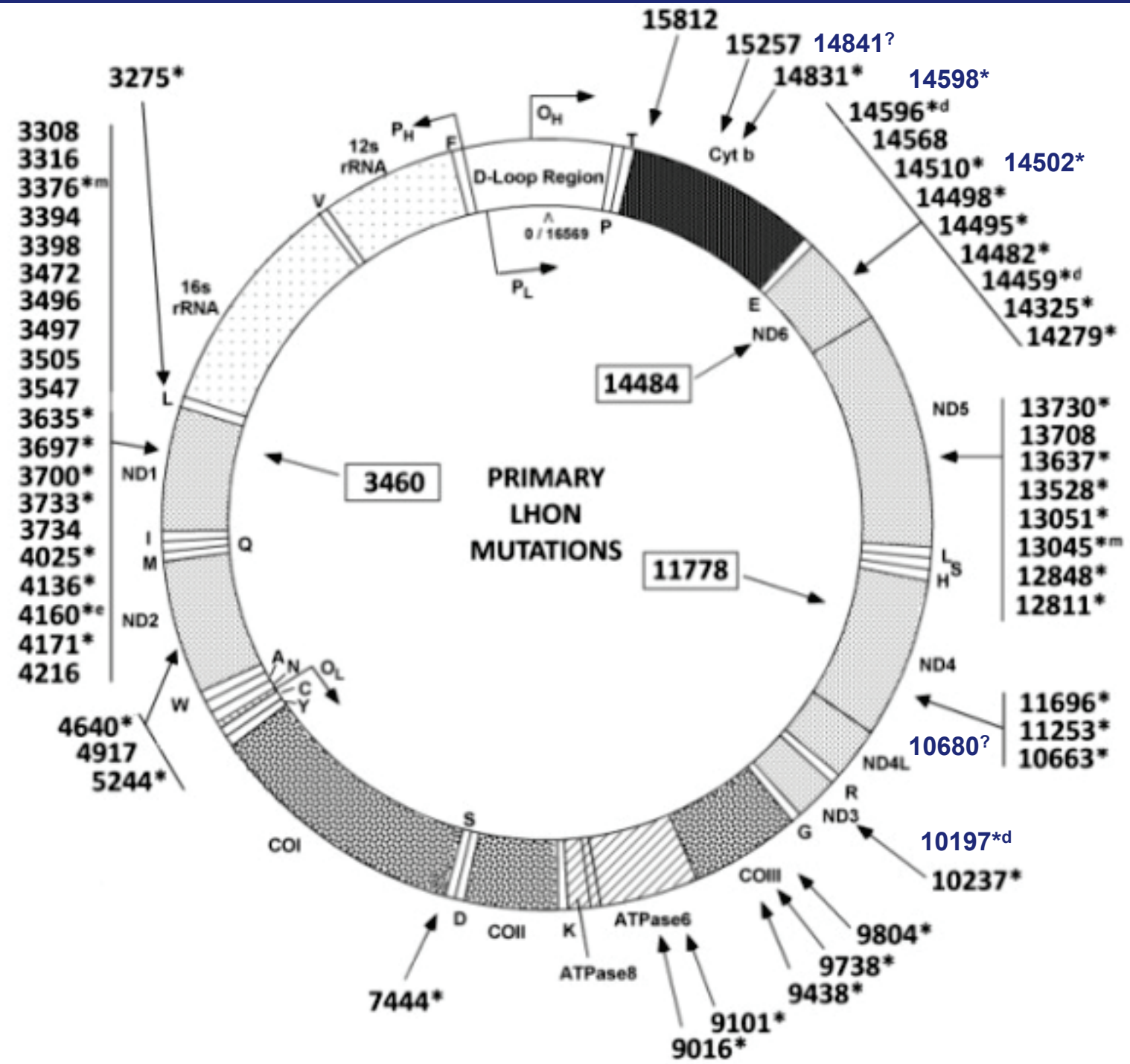

Cell Membrane
Centrosome
Lysosome
Cytoplasm
Nucleus
Rough ER
Nucleolus
Smooth ER
Nuclear Membrane
Vacuole
Ribosomes
Mitochondrion
Golgi Body

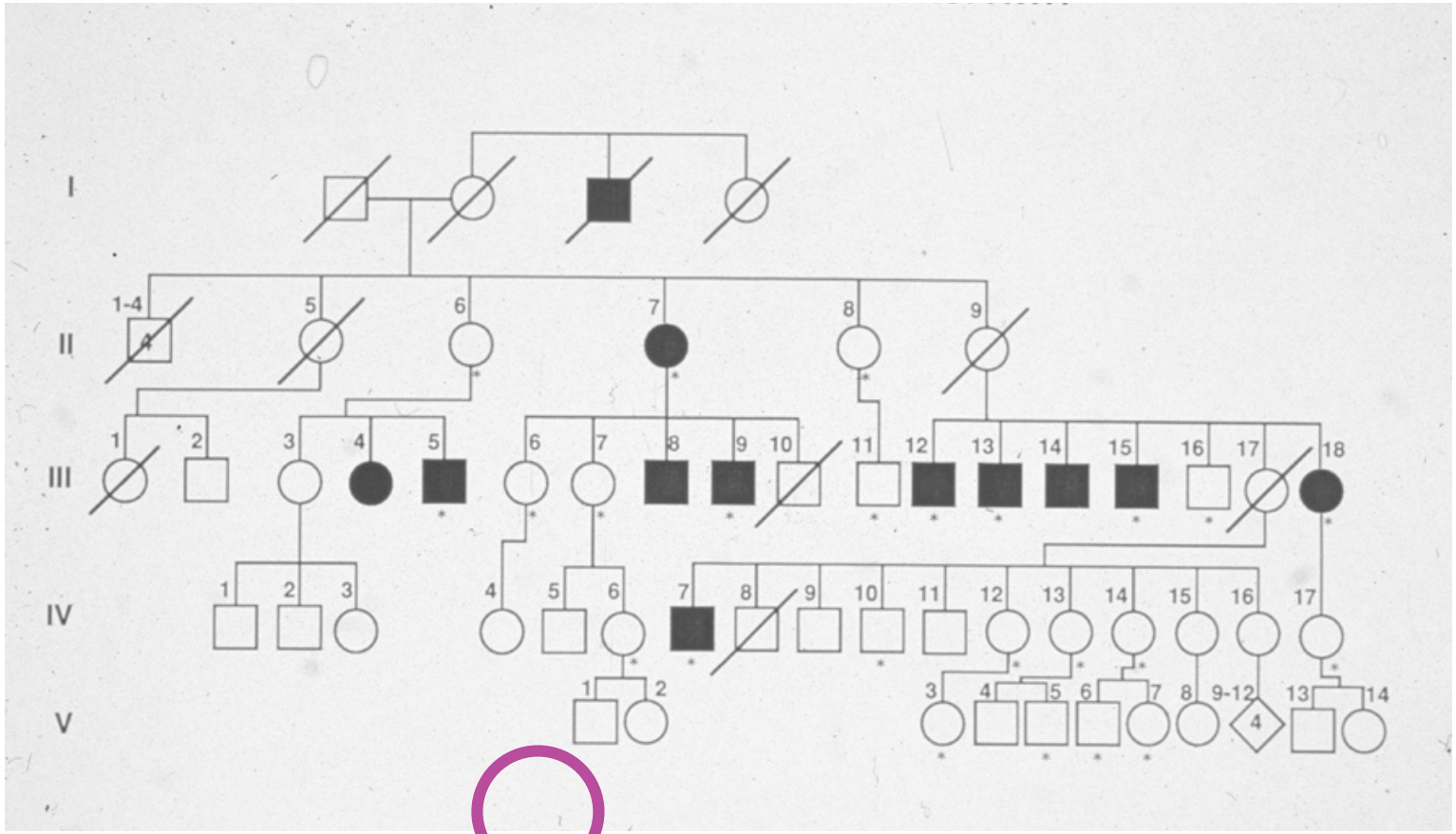
Mitochondrial Diseases



Mitochondria:

- Hundreds of mitochondria per cell
- Generate cellular energy (ATP)
- Some tissues most reliant on mitochondrial ATP
- Codes for 13 proteins envolved in energy production

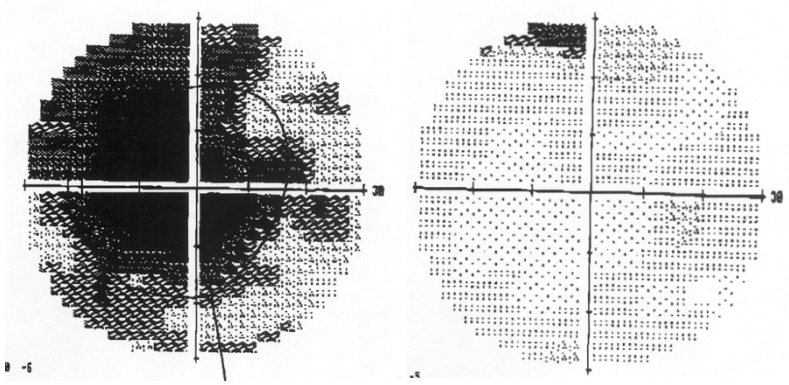

PRIMARY
LHON
MUTATIONS
15812
15257
14841?
14831*
14598*
14596*d
14568
14510*
14502*
14498*
14495*
14482*
14459*d
14325*
14279*
14484
ND6
E
ND5
13730*
13708
13637*
13528*
13051*
13045*m
12848*
12811*
11778
L
H
S
ND4
11696*
11253*
10663*
10680?
ND4L
R
ND3
10197*d
10237*
COIII
9804*
9738*
9438*
ATPase6
ATPase8
K
COII
D
9101*
9016*
7444*
S
COI
4640*
4917
5244*
W
A
N
C
Y
O_L
Q
I
M
ND2
3460
ND1
3308
3316
3376*m
3394
3398
3472
3496
3497
3505
3547
3635*
3697*
3700*
3733*
3734
4025*
4136*
4160*c
4171*
4216
3275*
L
16s
rRNA
V
12s
rRNA
F
P_H
O_H
T
Cyt b
D-Loop Region
0 / 16569
P
P_L


I
II
1-4
5
6
7
8
9
III
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
IV
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
V
1
2
3
4
5
6
7
8
9-12
4
13
14

Leber Hereditary Optic Neuropathy

Treatment

- Ideal “laboratory” for testing treatment efficacy
  - Sequential visual loss: therapeutic window
  - Accessibility via topical or intravitreal route
  - Implications for other optic neuropathies



Mitochondrial Diseases

Treatment

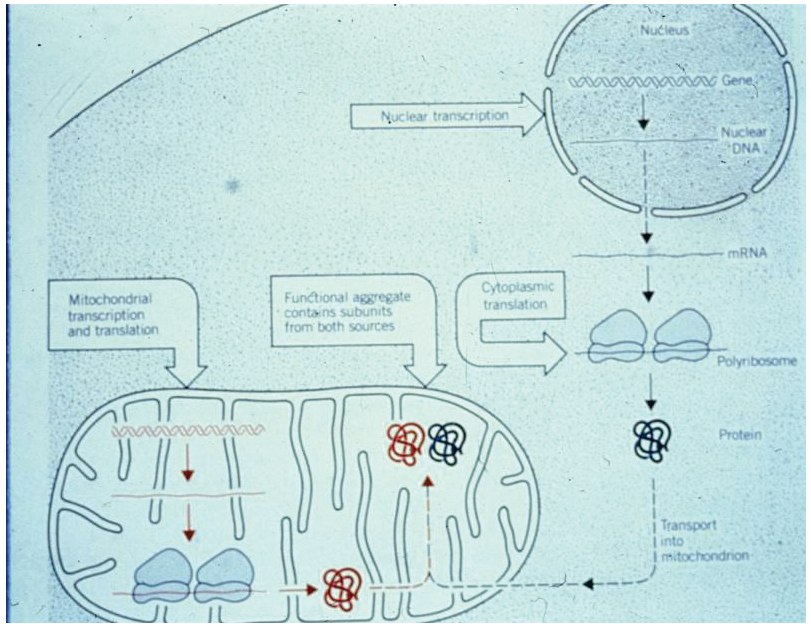
- Genetic counseling
- Symptomatic
- Disease-modifying
  - Mitochondrial diseases
  - Hereditary optic neuropathies

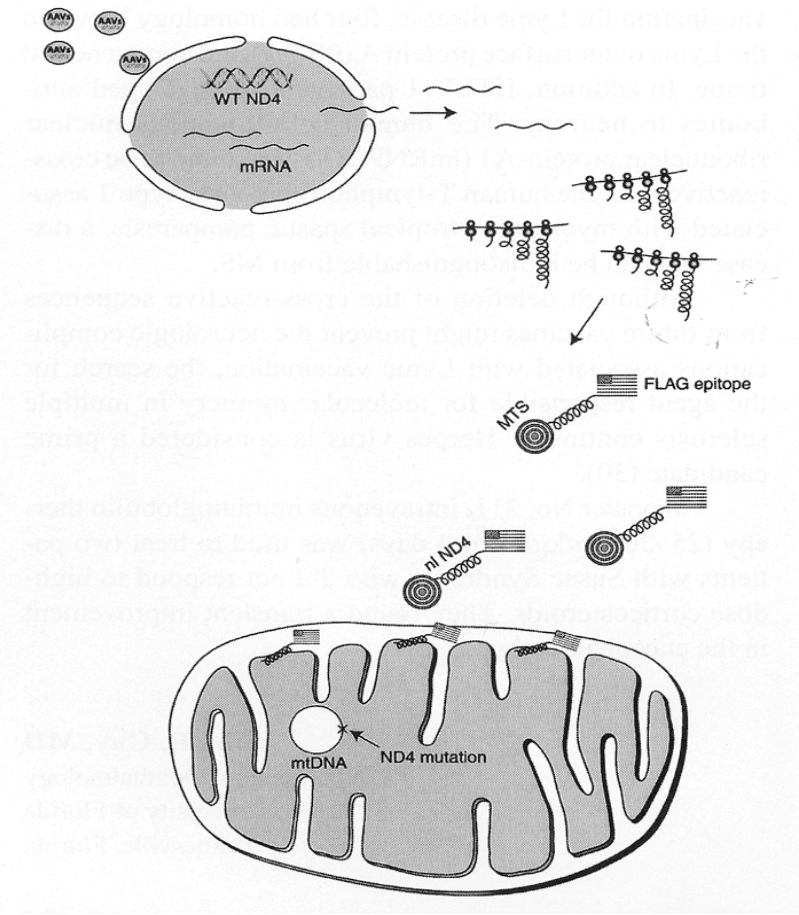
- Gene therapy

Leber Hereditary Optic Neuropathy

Treatment – Gene Therapy

- Allotopic Rescue





Expected course of vision and natural history of LHON

Dr. Mark Moster

EXPECTED COURSE OF VISION AND NATURAL HISTORY OF LHON

Dr. Mark Moster

Director, Neuro-Ophthalmology Fellowship

Wills Eye Hospital

Professor of Neurology and Ophthalmology

Sidney Kimmel Medical College of Thomas Jefferson University

Philadelphia, PA

LEBER HEREDITARY OPTIC NEUROPATHY

What happens to vision after initial visual loss?

Most commonly by far:

- Vision remains severely impaired in both eyes
- Approximately 75% worse than 20/200
- Legally blind
- Stable vision thereafter
- Vision does not slowly improve

RARELY, SPONTANEOUS IMPROVEMENT

- More common with the 14484 mutation
- Intermediately with 3460 mutation
- ***Least often with 11778 mutation***
  - ***Mostly in very young patients***

- But how common is this recovery with 11778?

LITERATURE REVIEW OF RECOVERY IN LHON : *3 ERAS*

1. Prior to availability of genotyping
2. Between genotyping and gene therapy
3. Era of gene therapy

ERA 1: *PRIOR TO GENOTYPING*

- Data not applicable
- We do not know whether patients really even had LHON
- We also do not know if they had the 11778 genetic mutation

ERA 2:
GENOTYPING AVAILABLE

- Numerous retrospective studies

NATURAL HISTORY – RETROSPECTIVE

- Newman 1991
  - 3/72 (4%)
  - One within first year
- Nikoskelainen 1996
  - 4/64 (6.25%)
  - No time Given

NATURAL HISTORY – RETROSPECTIVE

- Stone 1992
  - 5/136 patients (4%)
  - Mostly years later
- Riordan-Eva 1995
  - 1/83 patients (1%) (both eyes)
  - 11 and 4 mo[illegible]
- Mashima 2003
  - 1/20 patients (5%) (11 yo boy)
  - 24 months later
- Carelli 2011
  - [illegible]llen
  - [illegible] 28 months later

The m.11778A>G mtDNA mutation carries a poor visual prognosis

LITERATURE ON SPONTANEOUS RECOVERY RETROSPECTIVE STUDIES

Author, Year	Spontaneous Recovery	Total Patients
Newman, 1991	3	72
Stone, 1992	5	136
Riordan-Eva, 1995	1	83
Nikkoskaleinen, 1996	4	64
Mashima, 2003	1	20
Carelli , 2011	10	

Most often over 2 years after visual loss

ERA 3: GENE THERAPY

NATURAL HISTORY – PROSPECTIVE

Trial End Points and Natural History in Patients With G11778A Leber Hereditary Optic Neuropathy Preparation for Gene Therapy Clinical Trial

Byron L. Lam, MD; William J. Feuer, MS; Joyce C. Schiffman, MS; Vittorio Porciatti, PhD; Ruth Vandenbroucke, BA; Potyra R. Rosa, MD; Giovanni Gregori, PhD; John Guy, MD

JAMA Ophthalmol. 2014;132(4):428-436.

- **44 LHON patients carrying the m.11778G>A mtDNA mutation**
- **Patients were evaluated every 6 months over a period of 36 months**

NATURAL HISTORY – PROSPECTIVE

- Visual acuity improvement ≥ 15 ETDRS letters
- 13/88 eyes (15%) of 8/44 patients (18%) improved
- 7/88 eyes (8%) of 6/44 patients (14%) worsened
- 68/88 eyes (77%) of 38/44 patients (86%) were stable
- Average time to recovery = 27.5 months

FOR OVERALL POPULATION *NO IMPROVEMENT OVER TIME*

Table 1. Distribution of Clinical Factors Over Time

Characteristic	Mean (SD)[a]						
	Baseline	Month 12	*P* Value	Month 24	*P* Value	Month 36	*P* Value
Total No. of patients	44	40		31		18	
Visual acuity, ETDRS score	14.9 (18.3)	14.4 (19.3)	.65	14.1 (17.3)	.57	15.9 (19.6)	.20
Visual field, mean deviation	−24.4 (8.9)	−25.5 (6.6)	.33	−24.9 (7.1)	.82	−23.9 (7.0)	.23
RNFL thickness on OCT, µm	66.2 (23.9)	55.7 (5.9)	.006	55.3 (4.7)	.03	54.8 (4.3)	.23
PERG amplitude, % of normal	40.3 (18.3)	38.8 (19.2)	.99	42.2 (24.7)	.59	33.3 (13.5)	.13
PERG phase, % of normal	106.2 (7.2)	106.6 (8.0)	.64	107.2 (9.4)	.66	103.5 (9.1)	.07
No. of patients with onset ≤12 mo	13	12		9		4	
Visual acuity, ETDRS score	23.3 (21.4)	23.2 (28.3)	.78	18.6 (24.6)	.93	21.9 (28.4)	.41
Visual field, mean deviation	−20.6 (10.1)	−24.1 (7.9)	.33	−24.6 (6.0)	.79	−22.9 (5.1)	.26
RNFL thickness on OCT, µm	93.7 (24.2)	60.3 (4.6)	.001	57.9 (4.8)	.003	56.9 (3.9)	.06
PERG amplitude, % of normal	41.3 (17.0)	37.9 (16.6)	.98	37.8 (21.8)	.72	32.8 (18.3)	.79
PERG phase, % of normal	105.5 (5.4)	105.4 (5.2)	.67	106.2 (8.0)	.99	109.1 (7.5)	.32
No. of patients with onset >12 mo	31	28		22		14	
Visual acuity, ETDRS score	11.3 (15.9)	10.6 (12.7)	.35	12.2 (13.5)	.17	14.1 (17.4)	.18
Visual field, mean deviation	−26.0 (7.9)	−26.2 (6.0)	.83	−25 (7.6)	.99	−24.3 (7.6)	.62
RNFL thickness on OCT, µm	53.9 (8.8)	53.6 (5.3)	.52	54.1 (4.3)	.25	54.1 (4.4)	.07
PERG amplitude, % of normal	39.9 (19.1)	39.2 (20.5)	.99	43.8 (26.1)	.36	33.4 (12.7)	.11
PERG phase, % of normal	106.5 (7.9)	107.2 (9.1)	.84	107.6 (10.1)	.58	101.9 (9.1)	.02

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; PERG, pattern electroretinogram; RNFL, retinal nerve fiber layer.

[a] Data are based on the number of eyes evaluated. *P* values were determined for comparison of each follow-up visit with baseline by paired *t* test.

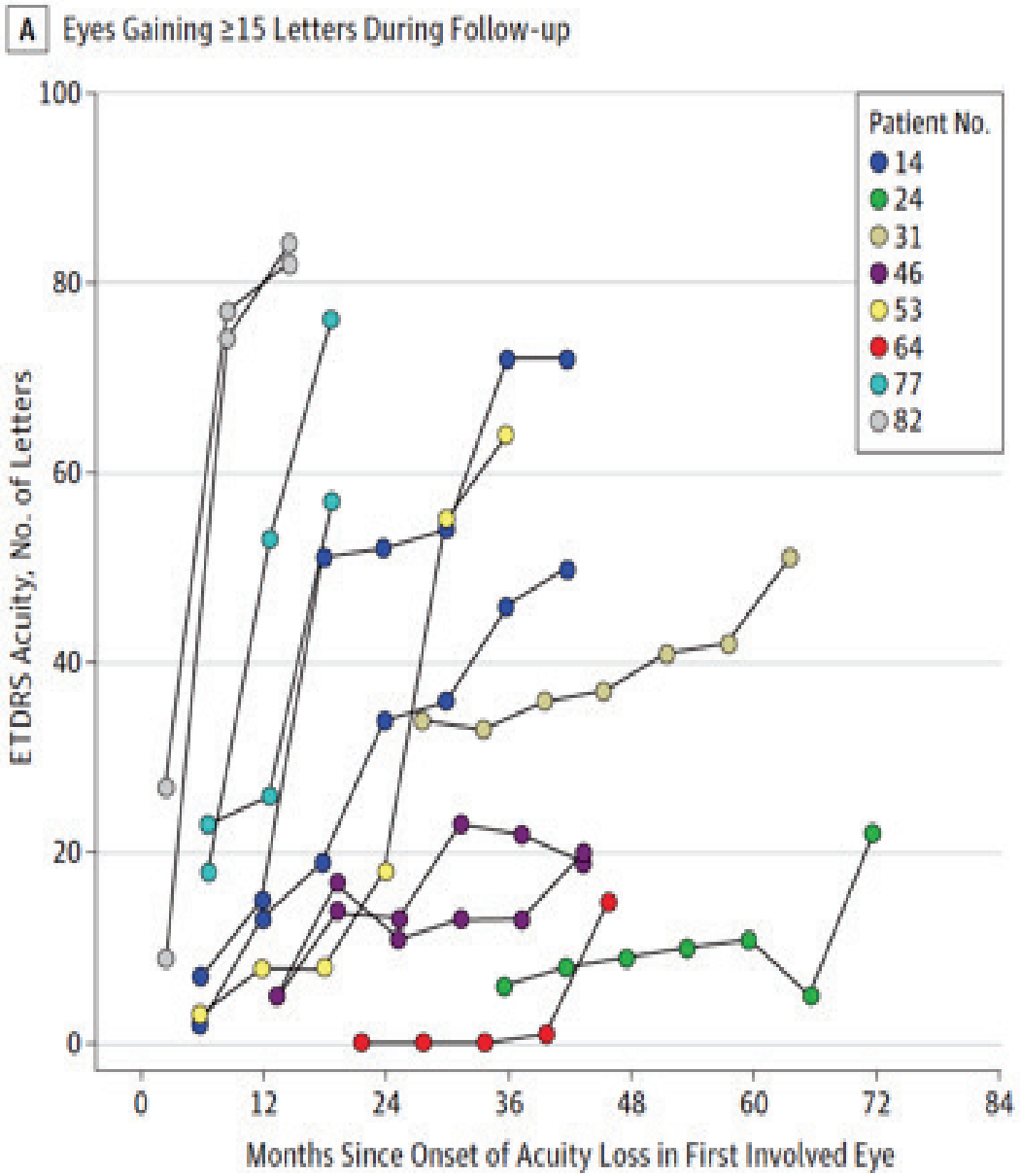
Lam BL et al. JAMA Ophthalmology. 132(4):428-36, 2014 Apr 01

Table 1. Distribution of Clinical Factors Over Time

Characteristic	Mean (SD)[a]						
	Baseline	Month 12	*P* Value	Month 24	*P* Value	Month 36	*P* Value
Total No. of patients	44	40		31		18	
Visual acuity, ETDRS score	14.9 (18.3)	14.4 (19.3)	.65	14.1 (17.3)	.57	15.9 (19.6)	.20
Visual field, mean deviation	−24.4 (8.9)	−25.5 (6.6)	.33	−24.9 (7.1)	.82	−23.9 (7.0)	.23
RNFL thickness on OCT, µm	66.2 (23.9)	55.7 (5.9)	.006	55.3 (4.7)	.03	54.8 (4.3)	.23
PERG amplitude, % of normal	40.3 (18.3)	38.8 (19.2)	.99	42.2 (24.7)	.59	33.3 (13.5)	.13
PERG phase, % of normal	106.2 (7.2)	106.6 (8.0)	.64	107.2 (9.4)	.66	103.5 (9.1)	.07
No. of patients with onset ≤12 mo	13	12		9		4	
Visual acuity, ETDRS score	23.3 (21.4)	23.2 (28.3)	.78	18.6 (24.6)	.93	21.9 (28.4)	.41
Visual field, mean deviation	−20.6 (10.1)	−24.1 (7.9)	.33	−24.6 (6.0)	.79	22.9 (5.1)	.26
RNFL thickness on OCT, µm	93.7 (24.2)	60.3 (4.6)	.001	57.9 (4.8)	.003	56.9 (3.9)	.06
PERG amplitude, % of normal	41.3 (17.0)	37.9 (16.6)	.98	37.8 (21.8)	.72	32.8 (18.3)	.79
PERG phase, % of normal	105.5 (5.4)	105.4 (5.2)	.67	106.2 (8.0)	.99	109.1 (7.5)	.32
No. of patients with onset >12 mo	31	28		22		14	
Visual acuity, ETDRS score	11.3 (15.9)	10.6 (12.7)	.35	12.2 (13.5)	.17	14.1 (17.4)	.18
Visual field, mean deviation	−26.0 (7.9)	−26.2 (6.0)	.83	−25 (7.6)	.99	−24.3 (7.6)	.62
RNFL thickness on OCT, µm	53.9 (8.8)	53.6 (5.3)	.52	54.1 (4.3)	.25	54.1 (4.4)	.07
PERG amplitude, % of normal	39.9 (19.1)	39.2 (20.5)	.99	43.8 (26.1)	.36	33.4 (12.7)	.11
PERG phase, % of normal	106.5 (7.9)	107.2 (9.1)	.84	107.6 (10.1)	.58	101.9 (9.1)	.02

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; PERG, pattern electroretinogram; RNFL, retinal nerve fiber layer.

[a] Data are based on the number of eyes evaluated. *P* values were determined for comparison of each follow-up visit with baseline by paired *t* test.


A
Eyes Gaining ≥15 Letters During Follow-up
ETDRS Acuity, No. of Letters
100
80
60
40
20
0
0
12
24
36
48
60
72
84
Months Since Onset of Acuity Loss in First Involved Eye
Patient No.
14
24
31
46
53
64
77
82

LAM ET AL 2014

- 12 “acute” patients with 12 month followup, only 3 patients (25%) had 15 ETDRS letter improvement at 12 months, representing 6/24 eyes (25%)
- Two of those 3 acute patients with improvement (#s 14 and 77) were younger than 18
- One was younger than 15
- One only had 1 follow up from baseline
- May have been on idebenone

LHON NATURAL HISTORY OF IMPROVEMENT: PROSPECTIVE STUDY

- 44 LHON patients (11778)
- Evaluated every 6 months for 36 months
- No visual improvement in overall population on any of monitored parameters
- Visual acuity "improvement" = ≥ 15 ETDRS letters
- ***13/88 eyes (15%) of 8/44 patients (18%) improved***
- 7/88 eyes (8%) [illegible]
- 68/88 eyes (77 [illegible] stable
- Average time to recovery = 27.5 months

Versus 14/37 (37.8%) GS010 eyes and 12/37 (32.4%) sham eyes

Lam BL et al. JAMA Ophthalmology. 132(4):428-36, 2014

ERA 3: GENE THERAPY OR IDEBENONE THERAPY

- Klopstock 2011
  - 0/28 (0 %)
  - Quoted in EPAR review
- Silva 2019
  - 9/61 (14.8%)
  - ***2 lines improvement***
- Lam 2014
  - 8/44 (18%)
  - ***27.5 months later***

Author, Year	Spontaneous Recovery	Total Patients
Klopstock, 2011	0	28
Lam, 2014	8	44
Silva, 2019 (2 lines)	9	61
	17 (12.8%)	133

Versus 14/37 (37.8%) GS010 eyes and 12/37 (32.4%) sham eyes

ERA 3

Author, Year	Spontaneous Recovery	Total Patients
Klopstock, 2011	0	28
Lam, 2014	8	44
Silva, 2019 (2 lines)	9	61
	17 (12.8%)	

Versus (65%) GS010 eyes and (46%) sham eyes for 0.2 logmar improvement

SUMMARY – NATURAL HISTORY

- Literature is sparse and anecdotal
- Vast majority remain stable with severe visual loss
- Spontaneous recovery may occur but in a small subgroup, and ***rarely, based on retrospective and prospective studies***
- Clinical experience – ***lack of improvement***
- Which subgroup?
    - *In subjects who present at younger age*
    - *Occurs suddenly,* ***years later***
    - ***Very rarely,*** *gradually, during 1st year*

LHON patient experience

Andy Marks, patient advocate

Update on REVERSE results

Dr. Robert Sergott

REVERSE readouts

Visual Function Perspective

The Retinal & Optic Nerve Structural Natural History Versus GS010 Data

Robert C. Sergott, MD
Director, Neuro-Ophthalmology, Wills Eye

Founding Director, William H. Annesley, Jr EyeBrain Center
Thomas Jefferson University

Initiating 2 Phase III trials at 9E10vg/eye

RESCUE

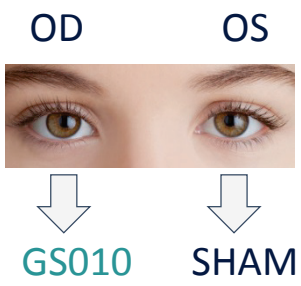
Onset of disease ≤ 180 days

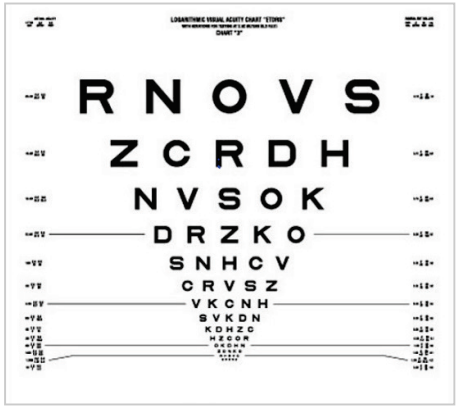
- Intravitreal administration
- Randomized, double-masked, sham-controlled, multi-center
- Expected number of patients = 36
- Primary endpoint: Change in visual acuity at week 48

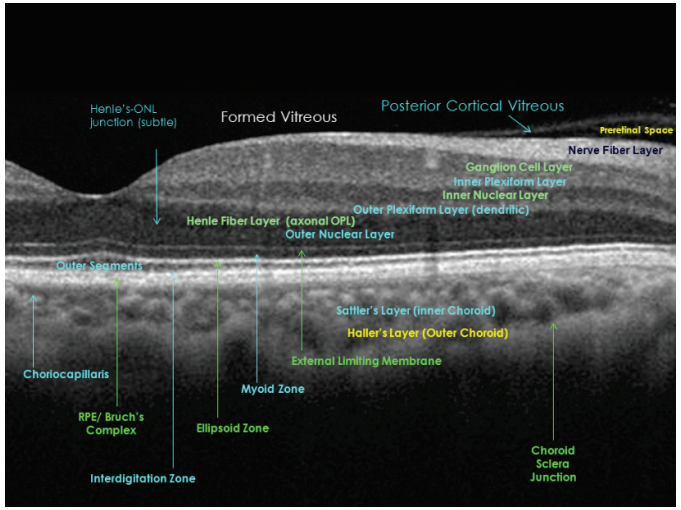
REVERSE

Onset of disease 181 to ≤ 365 days

- Intravitreal administration
- Randomized double-masked, sham-controlled, multi-center
- Expected number of patients = 36
- Primary endpoint: Change in visual acuity at week 48







Visual Acuity in REVERSE Subjects

“The data show that both the treated and the sham eye improved in both high and low contrast, defying the accepted natural history of this disease and improving upon it, based upon the clinical experiences of generations of neuro-ophthalmologists.

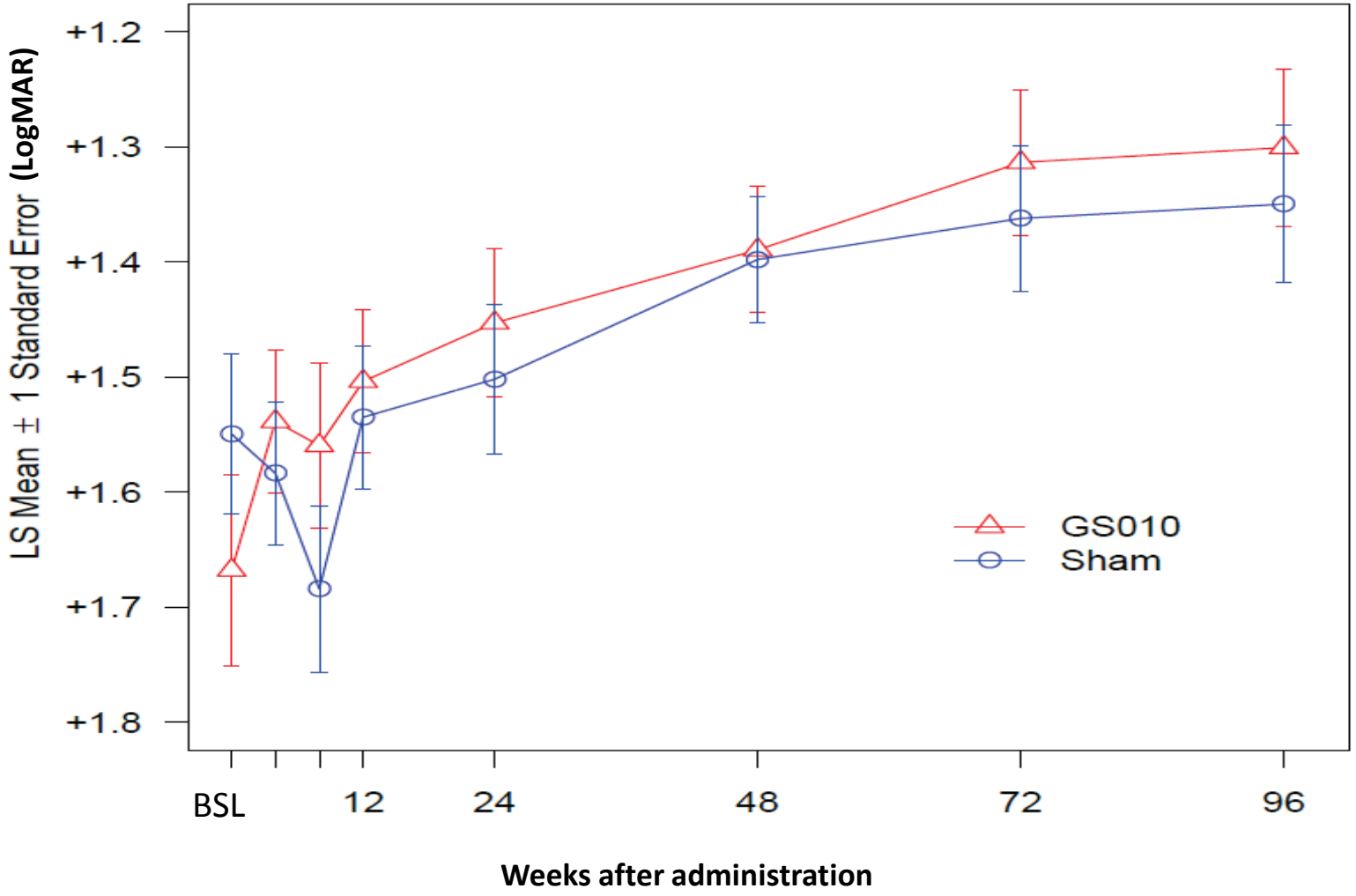
The behavior of the untreated eye must also make us re-examine what we thought we knew as possibly dogma and be open to the idea that gene therapy delivered into one eye may be able to access the contralateral eye.”

RC Sergott, Director, Neuro-Ophthalmology, Wills Eye
Director, William H. Annesley, Jr, EyeBrain Center,
Thomas Jefferson University, Philadelphia, PA

GenSight Press Release,
May 15, 2019

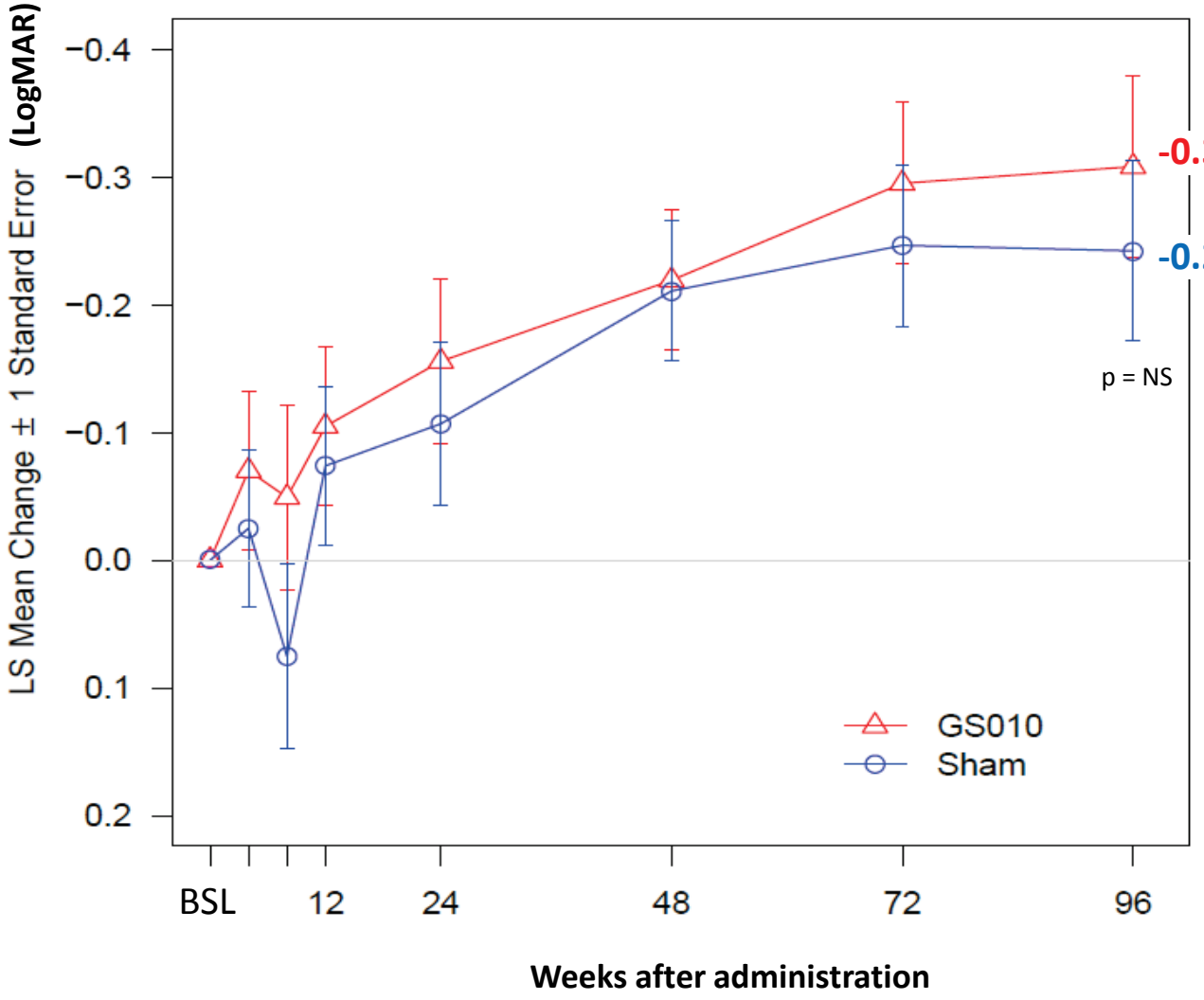
LogMAR Visual Acuity (actual values) up to Week 96

Bilateral improvement of visual acuity



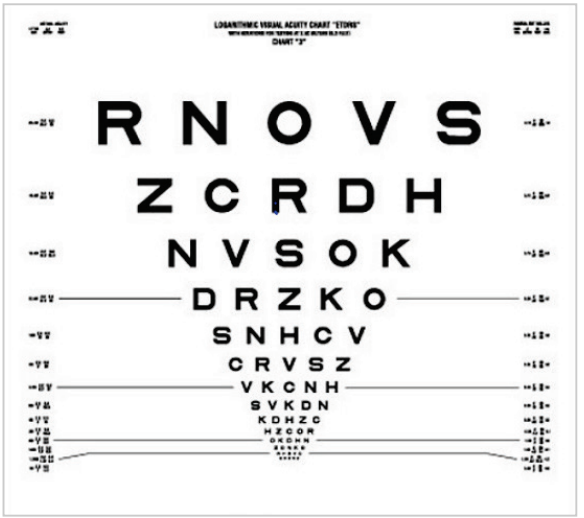
Change from Baseline in LogMAR Acuity to Week 96

Bilateral improvement of visual acuity



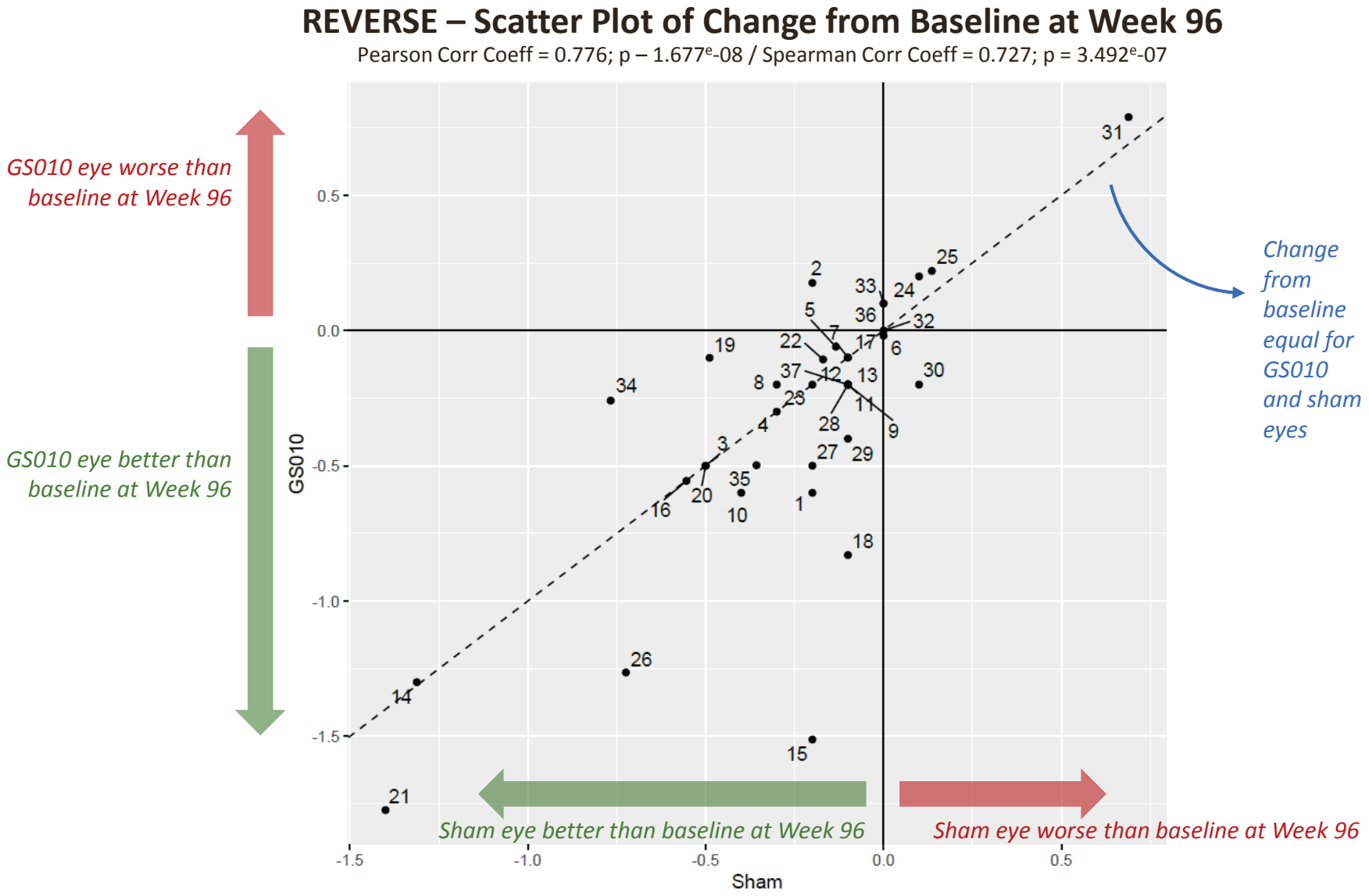
-0.308 LogMAR = +15.4 ETDRS LE

-0.259 LogMAR = +12.9 ETDRS LE



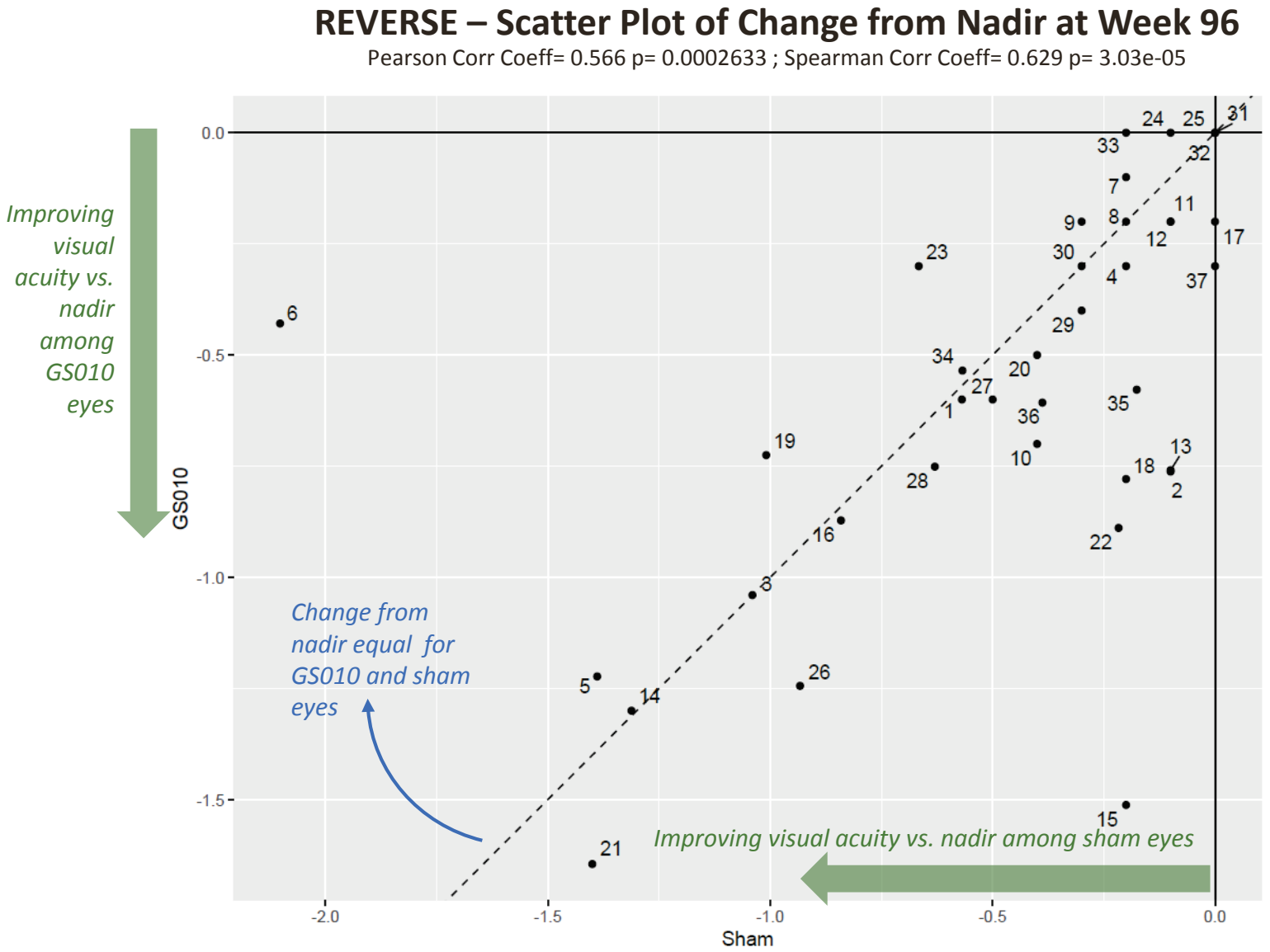
NS: not statistically significant

REVERSE: Visual Acuity Improvement in LogMAR, Change from **Baseline** at Week 96



- For most patients, eyes tracked tended to track together
- Most patients improved in both eyes relative to baseline
- Patients with large improvements from baseline tended to have GS010-treated eyes that outperformed their sham-treated eyes

REVERSE: Visual Acuity Improvement in LogMAR, Change from **Nadir** at Week 96



- For a greater number of patients, change from nadir is more pronounced in GS010-treated eyes
- Patients with large improvements from nadir tended to have GS010-treated eyes that outperformed their sham-treated eyes

Eye Responder Rate: (by SAP Definition)

Eyes with on-chart VA at Baseline and improvement of ≥ 15 ETRS letters at Week 96, or eyes **not** legally blind at Week 96

Significantly more GS010 eyes responded than Sham eyes

SAP Responder Definition 1: Change from Baseline of ETDRS score ≥ +15 letters, or BCVA > 20/200 at W96		
	GS010 Eyes	**Sham Eyes**
Responders	12 (32.4%)	6 (16.2%)
Non-Responders	25 (67.6%)	31 (83.8%)

p = 0.0578

Better Visual Acuity at Baseline = “Earlier” Treatment in the Course of the Disease

Eye Responder Rate: Santhera CRR Definition
(Recovery from Baseline)

Significantly more GS010 eyes responded according to Santhera CRR Definition than Sham eyes

Clinically Relevant Responder (CRR): Improvement from baseline of ETDRS score ≥ +10 letters, or from off-chart at baseline to at least 5 ETDRS letters at W96		
	GS010 Eyes	**Sham Eyes**
Responders	23 (62.2%)	16 (43.2%)
Non-Responders	14 (37.8%)	21 (56.8%)

p = 0.0348

Santhera reports:

- Natural History Study
  - **15%** of G11778A subjects show CRR from baseline in at least one eye.
    Median observation time was 14.9 months (ranged from 2.3 to 58.7 months).

Eye Responder Rate:
Change from Baseline in All Eyes ≤ -0.2 LogMAR

Significantly more GS010 eyes responded than Sham eyes

Responder Definition: Improvement from Baseline of at least 0.2 LogMAR		
	GS010 Eyes	**Sham Eyes**
Responders	24 (65%)	17 (46%)
Non-Responders	13 (35%)	20 (54%)

p = 0.0348

Eye Responder Rate: Change from Baseline in All Eyes ≤ -0.3 LogMAR

A third of eyes showed a clinically relevant improvement in BCVA at Week 96

Responder Definition: Improvement from Baseline of at least 0.3 LogMAR		
	GS010 Eyes	**Sham Eyes**
Responders	14 (37.8%)	12 (32.4%)
Non-Responders	23 (62.2%)	25 (67.6%)

p = 0.4795

Improvement of Visual Acuity Following Nadir

GS010 treated eyes gained more than 5 lines of acuity; a striking result given the known natural history of LHON

Change from NADIR* in LogMAR Visual Acuity		
		Week 96
	n	Mean (SD)
All-GS010 Eyes	37	-0.561 (0.439)
All-Sham Eyes	37	-0.463 (0.489)

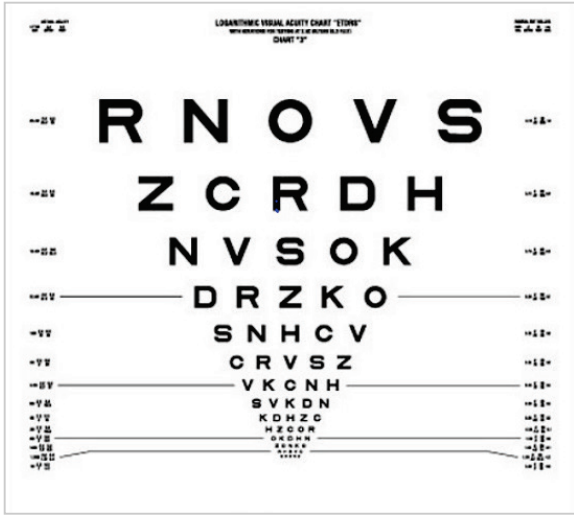
Mean change from post-treatment nadir was calculated using observed values (no data imputation)

* Nadir was defined as the **worst post-treatment LogMAR** value up to Week 96.

Improvement of Visual Acuity Following Nadir

GS010 treated eyes gained 28 ETDRS letters; a striking result given the known natural history of LHON

Change from NADIR* in ETDRS Letter Equivalents		
	Week 96	
	n	Mean (SD)
All-GS010 Eyes	37	+28.1 (22)
All-Sham Eyes	37	+23.2 (24)



Mean change from post-treatment nadir was calculated using observed values (no data imputation)

* Nadir was defined as the **worst post-treatment LogMAR** value up to Week 96.

Eye Responder Rate:
VA Improvement from NADIR of at Least -0.3 LogMAR

70% of GS010 eyes improved by at least 15 ETDRS letter equivalents compared to their nadir VA

Responders (Change from Nadir ≥-0.3 LogMAR)		
	GS010 Eyes	**Sham Eyes**
Responders	26 (70.3%)	19 (51.4%)
Non-Responders	11 (29.7%)	18 (48.6%)

p = 0.0196

* Nadir was defined as the **worst post-treatment LogMAR** value up to Week 96.

GEE model predicting BCVA > 20/200 with baseline as covariate

Based on generalized estimating equation (GEE) model to assess treatment effect:

GS010-treated eyes were significantly more likely to wind up with vision better than legal blindness (> 20/200) than sham-eyes (p=0.0032)

Odd ratio = 3.6

- ***Treatment with GS010 makes an eye > 3 times more likely to avoid legal blindness***

Contrast Sensitivity in REVERSE Subjects

Contrast Sensitivity (LogCS) at Week 96

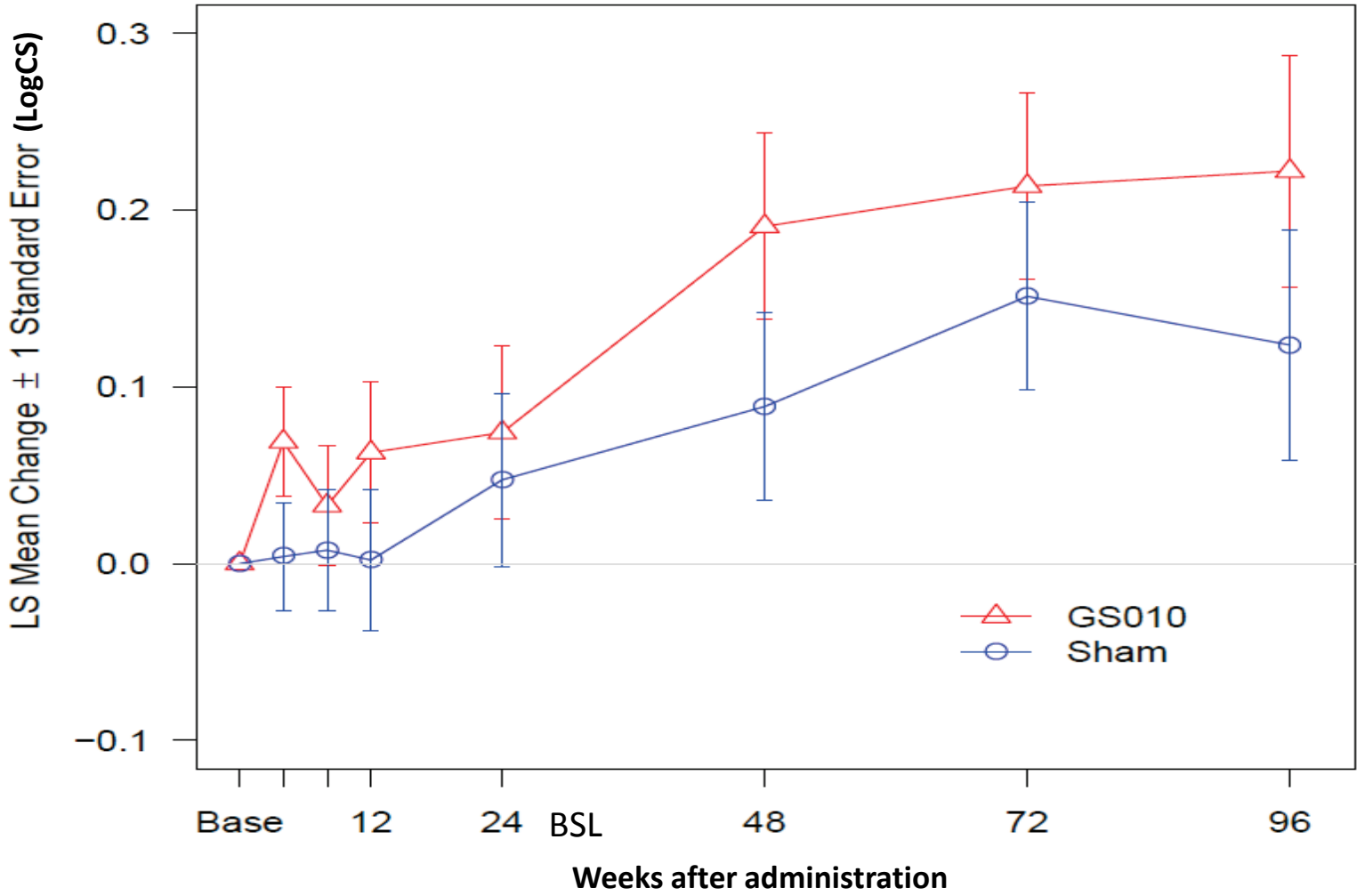
Change of Contrast Sensitivity (LogCS) from Baseline to Week 96				
	n	LS Mean (SE) [a]	95% CI [a]	P-value
All-GS010 Eyes	37	0.22 (0.06)	0.09, 0.34	
All-Sham Eyes	37	0.12 (0.06)	-0.01, 0.25	
Difference between GS010 and Sham Eyes (95% CI)	37	0.10	-0.02, 0.21	0.1036 [a]
Wilcoxon Signed-Rank Test				0.0326 [b]

[a] A mixed model of analysis of covariance (ANCOVA) was used with change from baseline as the response, and subject, eyes of the subject as random factor, treatment and the baseline value as covariates in the model.
P-value is used to assess the significance of the difference between All-GS010 and All-Sham with respect to change from baseline.
[b] P-value is used to assess the statistically significant difference between All-GS010 and All-Sham with respect to change from baseline by using Wilcoxon Signed-Rank Test.
Note: CI = Confidence Interval

LogCS data was imputed at Week 96 (a score of zero was assigned to missing values or when subject was unable to perform the test as their vision was too poor).

Change from Baseline in Contrast Sensitivity up to Week 96

Bilateral improvement of contrast sensitivity



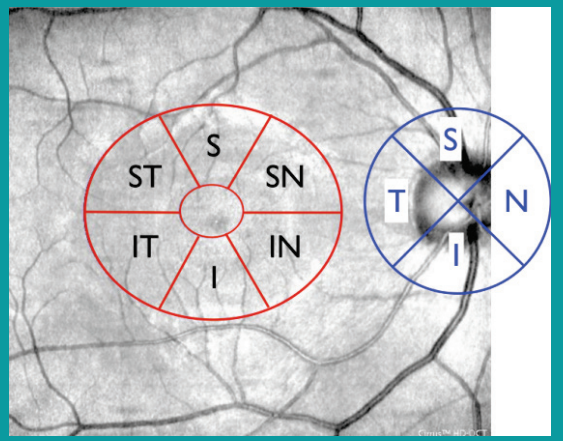
Eye Responder Rate: Improvement from Baseline ≥ 0.3 LogCS

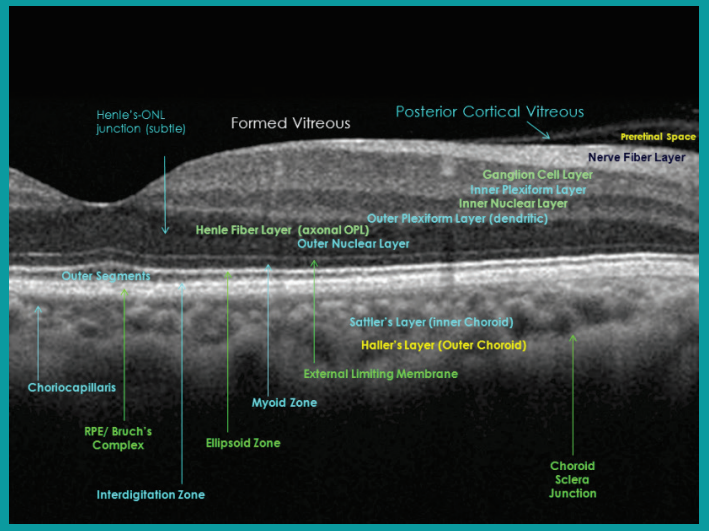
Clinically relevant gain of contrast sensitivity in 40% of GS010 eyes

Eye Responder: Change from Baseline ≥ 0.3 LogCS		
	GS010 Eyes	**Sham Eyes**
Responders	15 (40.5%)	11 (29.7%)
Non-Responders	22 (59.5%)	26 (70.3%)

p = 0.2059

Retina Anatomy in REVERSE Subjects vs Structural Natural History





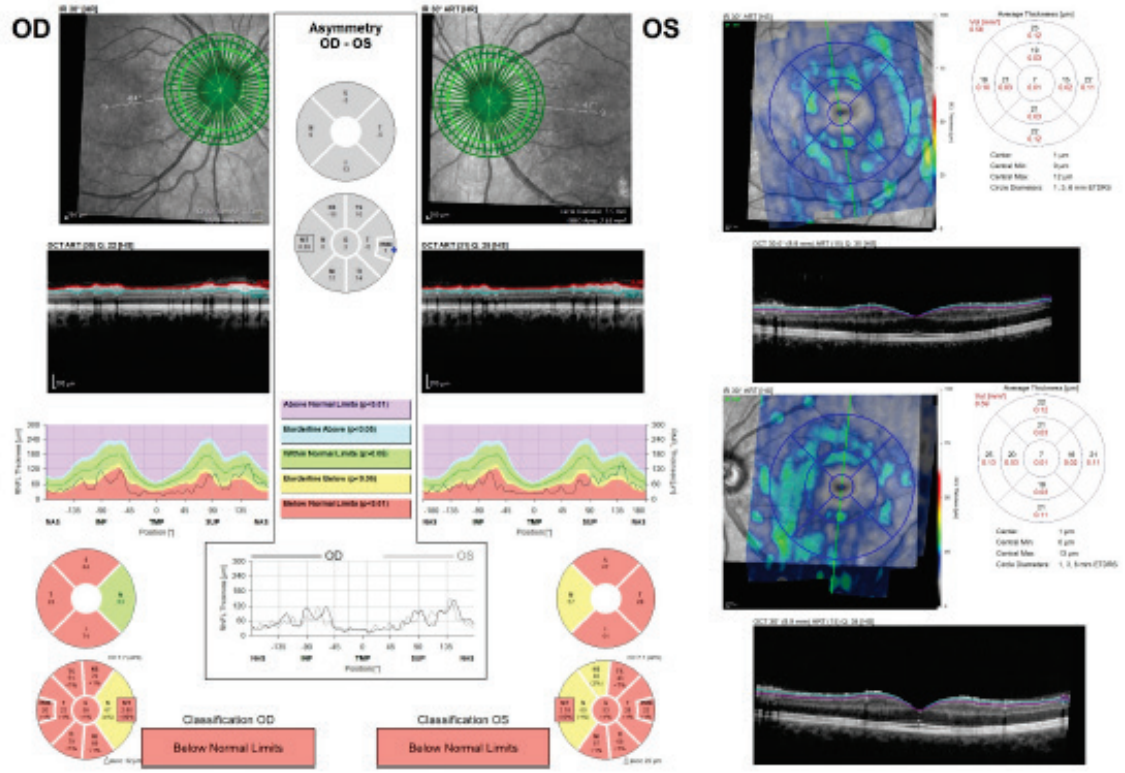
Secondary Efficacy Analyses - OCT

Change of GCL Macular Volume from Baseline to Week 96				
	n	LS Mean (SE) [a]	95% CI [a]	P-value
All-GS010 Eyes	36	-0.018 (0.012)	-0.041, 0.006	
All-Sham Eyes	36	-0.031 (0.012)	-0.054, -0.008	
Difference between GS010 and Sham Eyes (95% CI)	36	0.013	-0.016, 0.042	0.3528 [a]
Wilcoxon Signed-Rank Test				0.5413 [b]

[a] A mixed model of analysis of covariance (ANCOVA) was used with change from baseline as the response, and subject, eyes of the subject as random factor, treatment and the baseline value as covariates in the model.
P-value is used to assess the significance of the difference between All-GS010 and All-Sham with respect to change from baseline.
[b] P-value is used to assess the statistically significant difference between All-GS010 and All-Sham with respect to change from baseline by using Wilcoxon Signed-Rank Test.
Note: CI = Confidence Interval

Missing data were not imputed in this analysis.

REVERSE OCT HETEROGENEITY AT BASELINE



BUT DIFFERENCES WITH DURATION OF VISUAL LOSS & OCT CHANGES

➢ 75/76 eyes with thinning of PMB in all 4 quadrants and diffuse macular thinning

❖ Macular thinning showed ***absolute*** loss in 45 eyes and ***relative*** loss in 30 eyes compared to normative database

❖ All subjects had symmetric macula RNFL loss between the two eyes, except for 14 with relative loss.

In diabetic retinopathy, macular degeneration, multiple sclerosis, papilledema, and glaucoma:

Where a patient starts makes a difference in their prognosis

Quality of Life in REVERSE Subjects

Visual Functioning Questionnaire-25

	Composite Score [a]	Near Activities	Distance Activities	Dependency	Role Difficulties	General Vision	Mental Health
BASELINE Mean Score (SD)	44.81 (15.35)	23.7 (14.8)	35.5 (18.7)	31.8 (24.7)	34.5 (28.3)	30.8 (13.0)	32.1 (24.6)
Change from Baseline (Mean Score Increase and Mean Percent Increase [b])							
Week 48	+7.2 (+23.2%)	+10.4 (+65.1%)	+9.6 (+49.8%)	+12.4 (+100.6%)	+14.5 (+65.0%)	+10.3 (+50.9%)	+11.2 (+81.9%)
Week 72	+8.1 (+25.2%)	+9.5 (+58.1%)	+8.2 (+42.5%)	+18.9 (+130.2%)	+15.2 (+70.9%)	+11.9 (+54.1%)	+15.2 (+105.6%)
Week 96	**+9.5 (+28.8%)**	**+13.3 (+78.1%)**	**+10.7 (+47.4%)**	**+18.5 (+130.2%)**	**+15.9 (+78.9%)**	**+6.5 (+32.4%)**	**+16.1 (+108.2%)**
Clinically relevant score increase [c]	*+3.90 ; +4.34*	*+4.67 ; +6.06*	*+5.15 ; +5.38*	*+4.72 ; +4.98*	*+3.31 ; +4.70*	*+4.38 ; +4.82*	*+4.70 ; +4.88*

Composite score and subscales of interest showed continued improvement up to Week 96

a: The composite score is an average of the vision-targeted sub-scale scores, excluding the general health rating question.

b: Mean percent increase is the average of individual percent increases, not the percentage of mean score increase.

c: Range of clinically relevant score increase calculated in subjects with a clinically significant 15-letter BCVA improvement at 12 months. Suñer et al., *Invest Ophthalmol Vis Sci*. 2009;50(8):3629–35)

Maximum score per subscale and for composite score is 100.
Scores for the following subscales are not displayed: general health, ocular pain, social functioning, driving, and color vision.

Summary of Safety in REVERSE Subjects

Safety Follow-Up at Week 96

GS010 safety profile remains satisfactory

- GS010 was well tolerated 96 weeks after IVT injection
- No subject withdrawals
- No SAE in GS010 eyes
- 1 SAE (retinal tear) in SHAM eye of 1 subject
- Most common ocular AEs were considered related to injection procedure
- Intraocular inflammation and elevated intraocular pressure were considered likely related to GS010
  - Both responsive to treatment without sequelae

GS010 is a safe, sustained gene therapy with safe method of delivery

Re-Capitulation: Key Efficacy Results

Improvement in Visual Acuity from Baseline and Nadir

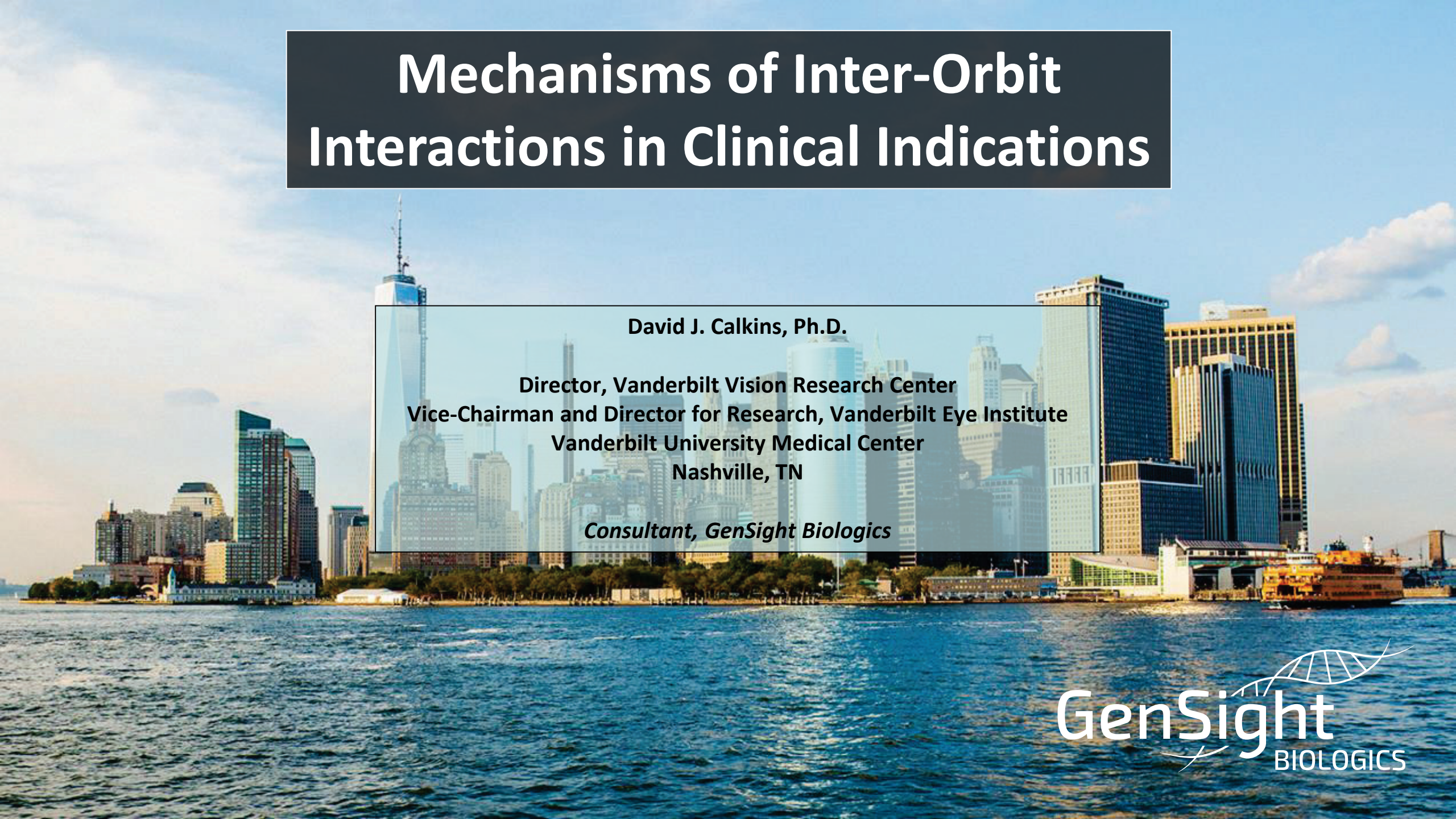
	Change from BASELINE					
	Week 72			Week 96		
LS Mean (SE) [a]	n	LogMAR	ETDRS Letter Equivalent	n	LogMAR	ETDRS Letter Equivalent
GS010 Eyes	37	-0.294 (0.063)	+15	37	-0.308 (0.068)	**+15**
Sham Eyes	37	-0.246 (0.063)	+12	37	-0.259 (0.068)	**+13**

	Change from NADIR [a]					
	Week 72			Week 96		
Mean (SD) [b]	n	LogMAR	ETDRS Letter Equivalent	n	LogMAR	ETDRS Letter Equivalent
GS010 Eyes	37	-0.548 (0.435)	+27	37	-0.561 (0.439)	**+28**
Sham Eyes	37	-0.451 (0.509)	+23	37	-0.463 (0.489)	**+23**

Scientific explanations behind a contralateral effect from unilateral injections

Dr. David Calkins

Mechanisms of Inter-Orbit Interactions in Clinical Indications



David J. Calkins, Ph.D.

Director, Vanderbilt Vision Research Center
Vice-Chairman and Director for Research, Vanderbilt Eye Institute
Vanderbilt University Medical Center
Nashville, TN

Consultant, GenSight Biologics

GenSight BIOLOGICS

My focus: why might the two eyes track in our LHON trial?

Gene Therapy for *ND4* LHON: Example of Response in Uninjected Eyes

- Gene therapy for *ND4* LHON, unilateral injection

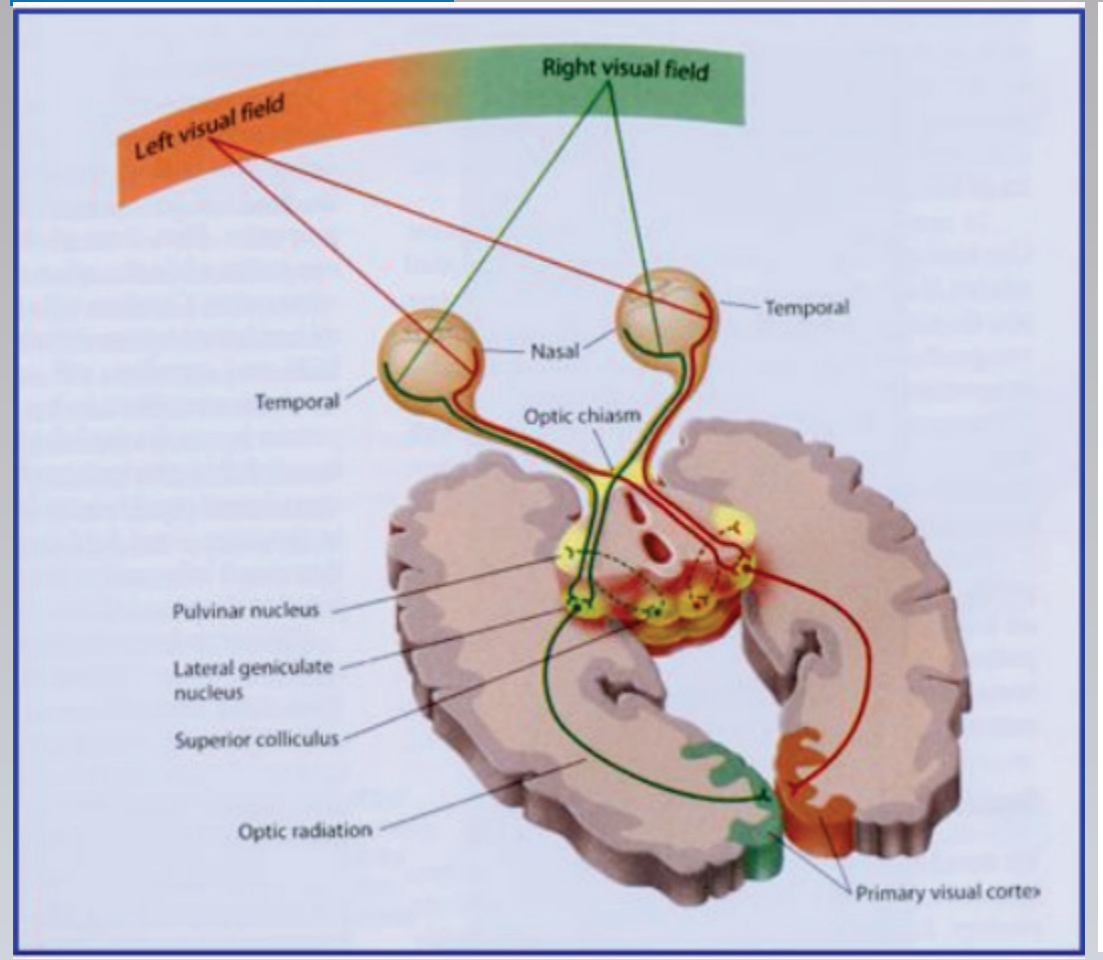
BCVA (LogMAR) Change from baseline to 36 months	Injected Eye Mean change	Uninjected Eye Mean change
Patients with ≤ 2 years duration (n=4)	- 0.30	-0.35

- 3 (75%) uninjected eyes in patients with ≤ 2 years of disease duration had improved by ≥ 0.3 LogMAR at 12 months. *Yang S et al., 2016*

A possible mechanism …

The Retinal Projection to the Brain

Some basic anatomy



Optic nerve joins the retina of the eye to the visual brain.

The two nerves cross at the **optic chiasm**, with 50% of each retina represented in the **lateral geniculate nucleus (LGN)**. Relay neurons in the LGN, however, are strictly **monocular**.

Each LGN projects to the **primary visual cortex (V1)**, with right V1 representing left visual field (and vice versa).

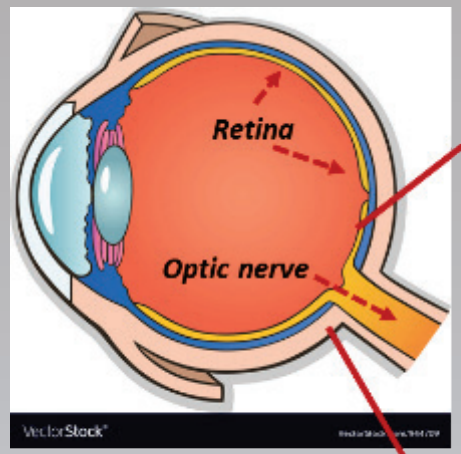
V1 is the first visual center where individual neurons can receive **binocular input**.

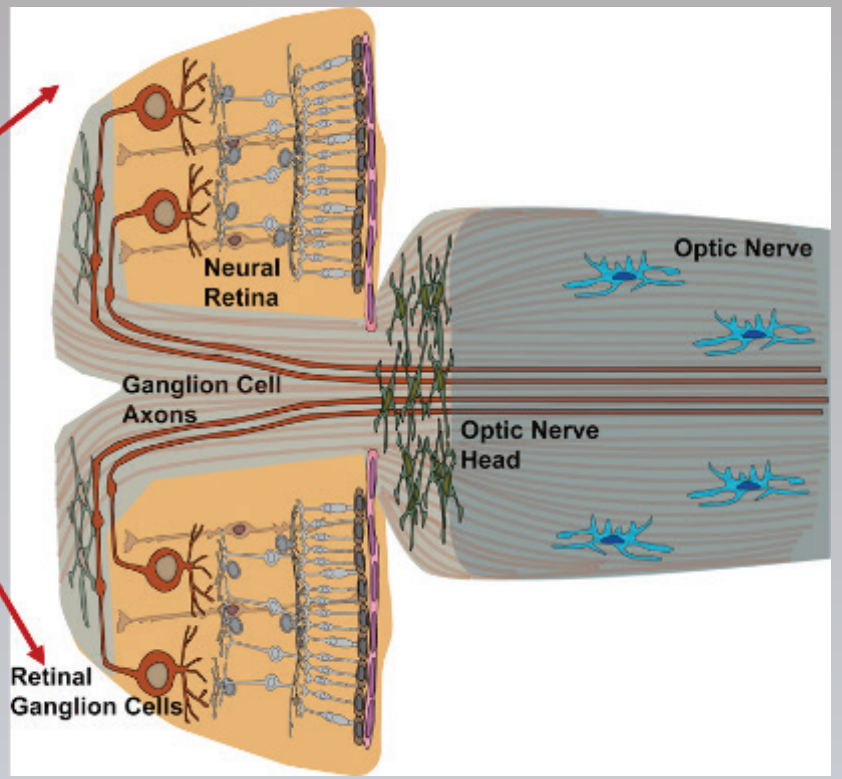
Trophic factors can reach the retinas of both eyes via upload from V1 neurons (Weber et al., 2010).

The veins of the orbit drain into either the **superior ophthalmic vein** or the **cavernous sinus** and then return to the heart. **They do not flow to the opposite eye directly.**

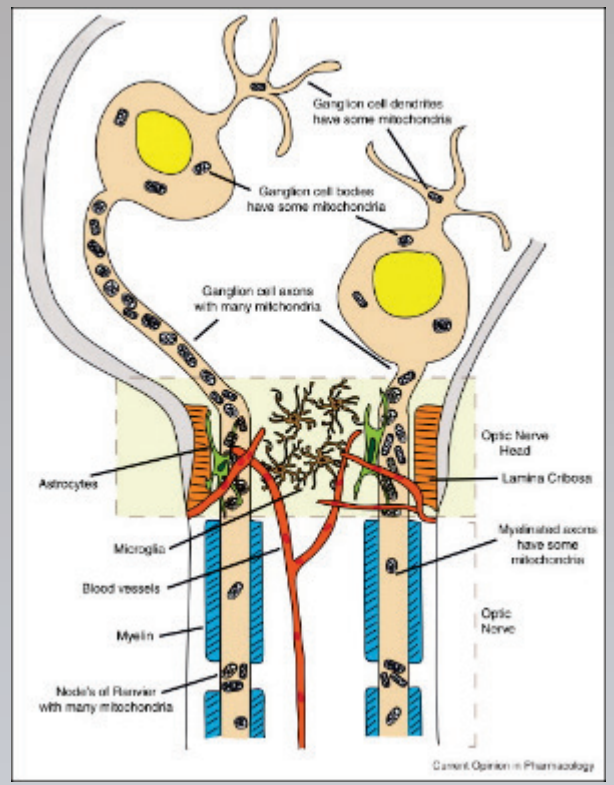
Closer look at optic nerve…

The Retinal Projection to the Brain





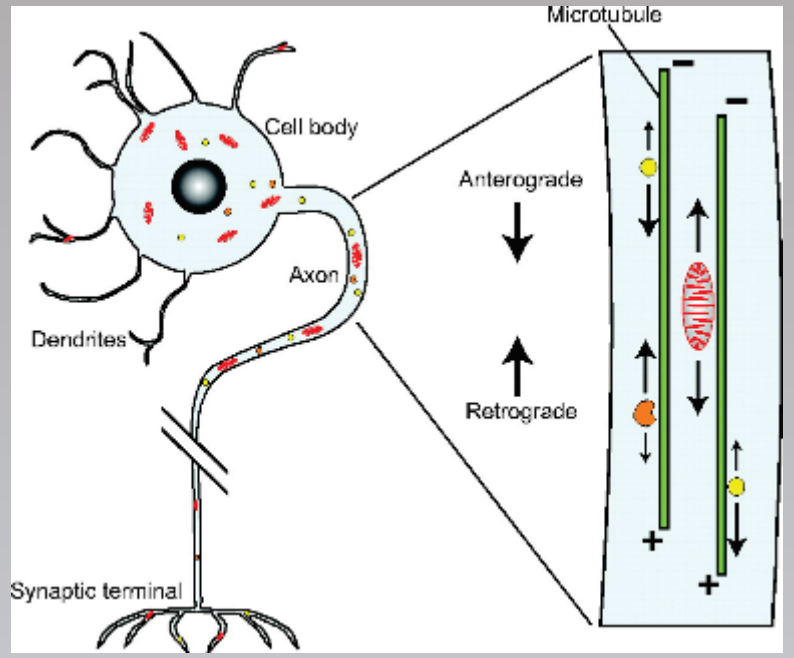
Osborne & del Olmo-Aguado, 2013



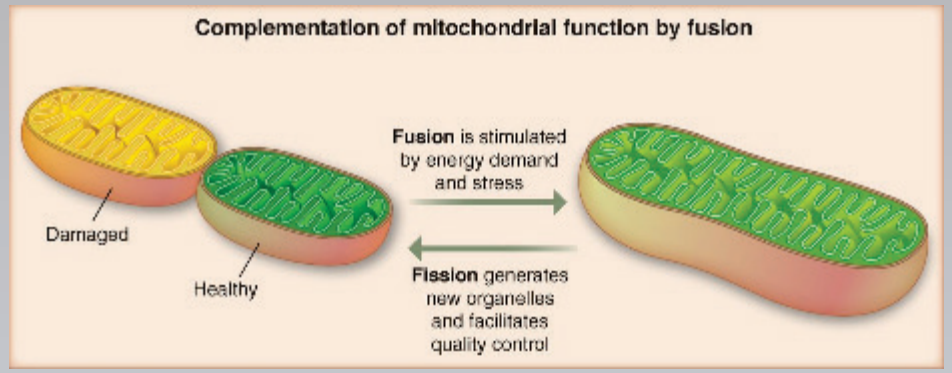
The retinal ganglion cell axon has a lengthy unmyelinated segment **full of mitochondria**, necessary to propagate visual signals from the retina to the brain. **Astrocyte glia** blanket the axon here, and at distinct nodes along the myelinated segment in the optic nerve.

Axons and mitochondria …

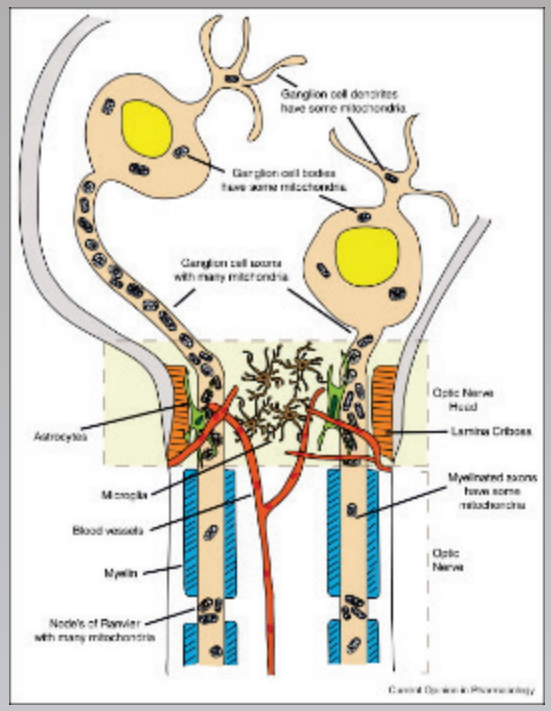
Mitochondria are in constant motion along axons, in both directions.



In retinal ganglion cells, like other neurons, mitochondria are in constant motion in both directions. As they move, mitochondria fuse as a form of **complementation to optimize function**. They **share proteins and miRNA**.



Osborne & del Olmo-Aguado, 2013

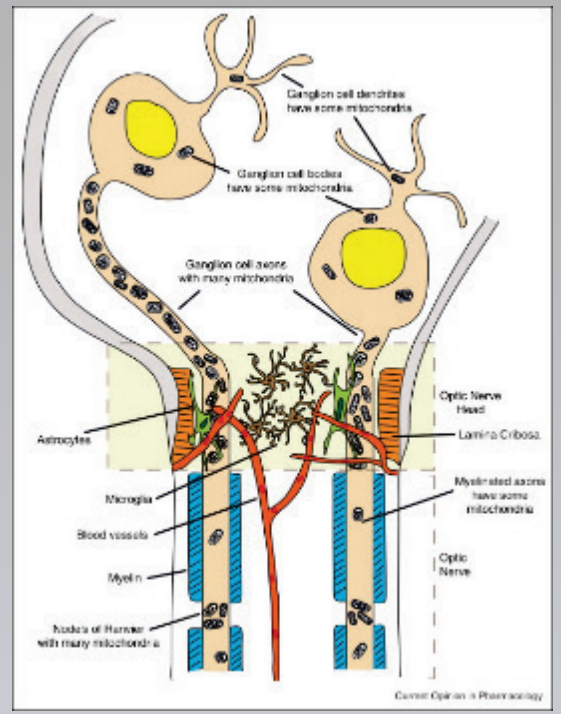


Vossel et al., 2010

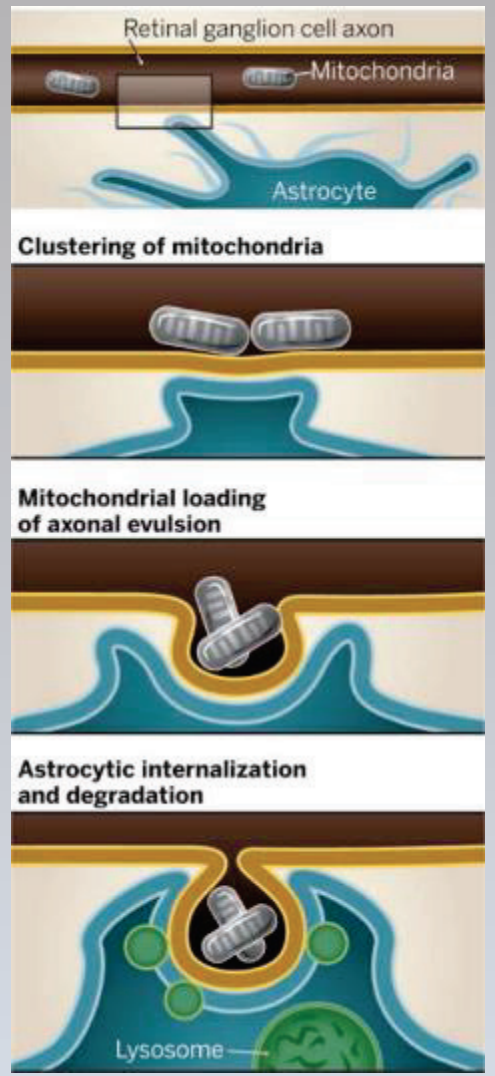
What is the role of astrocytes?

Astrocytes can both absorb and donate mitochondrial material to axons.

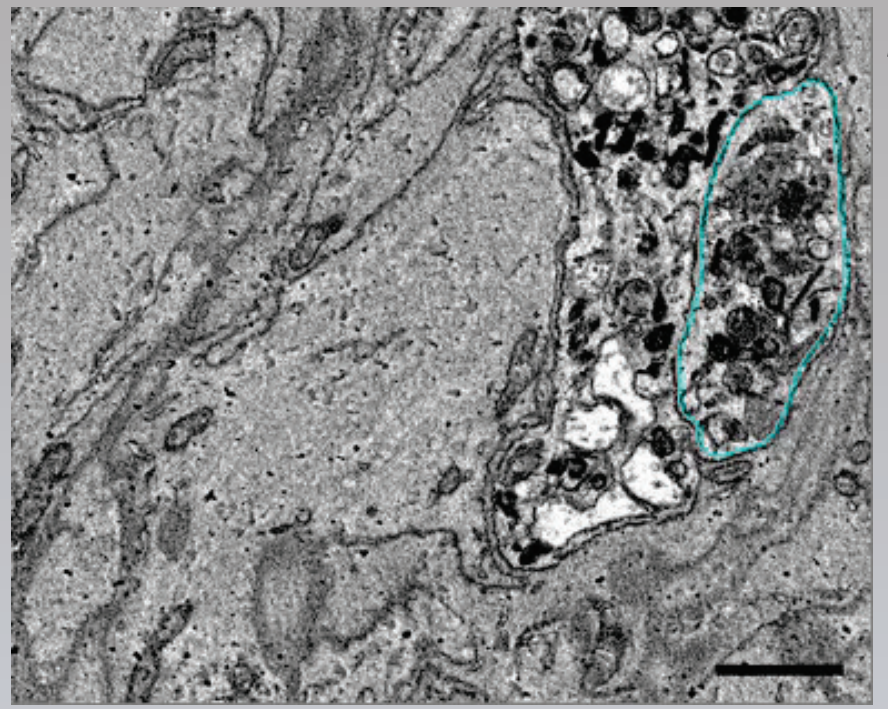
Astrocytes absorbing mitochondria from RGC axons



Osborne & del Olmo-Aguado, 2013



Burdett & Freeman, 2014

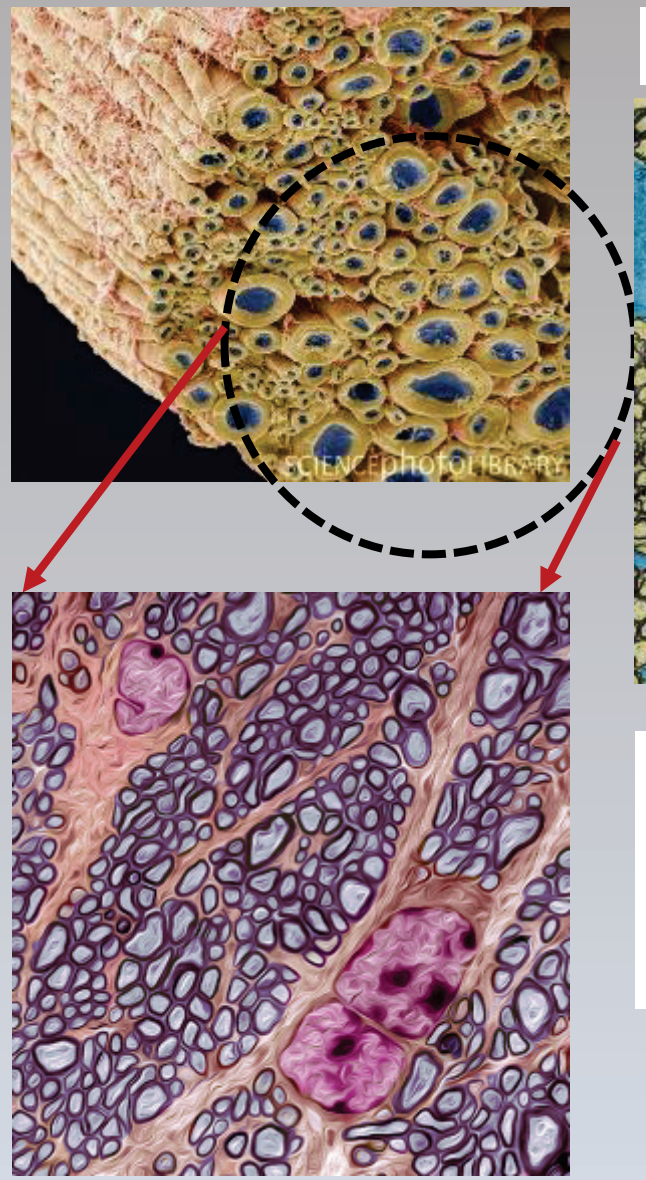


Davis et al., 2014

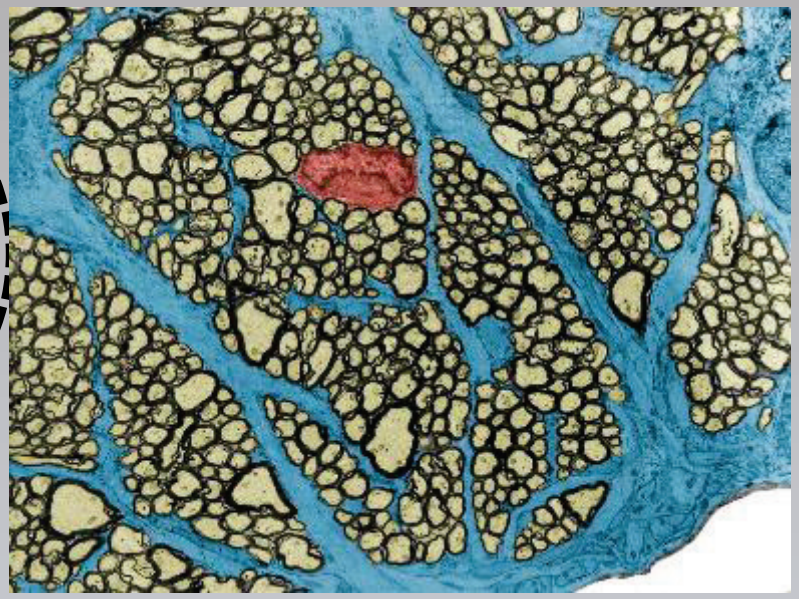
Astrocytes in the optic nerve engulfing an axonal evulsion with **mitochondria (red). Mitochondria undergo mitophagy in the astrocytes; miRNA and proteins in these mitochondria are packaged in endosomes.**

Astrocytes are not insulated …

Astrocytes in retina and optic nerve form an interconnected network



Astrocytes in optic nerve



Astrocytes in retina

Astrocytes in the optic nerve and in the retina form a dense network of interconnected processes. These connections are mediated by **gap junctions**, allowing astrocytes separated by great distances to communicate with one another.

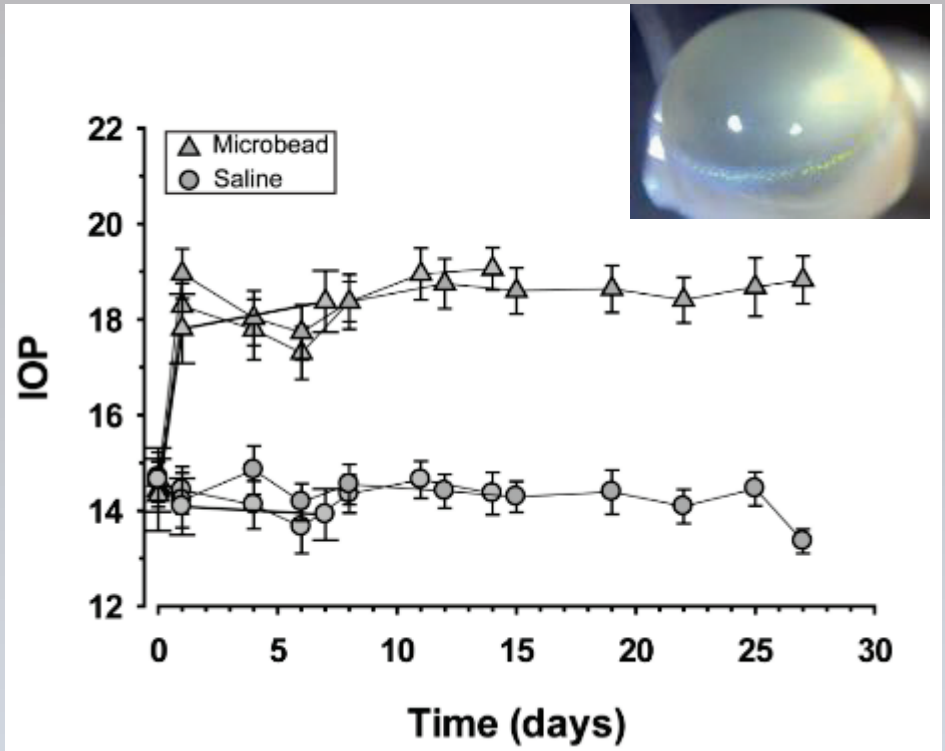
Could these networks cross between eyes?

Cooper et al., 2016

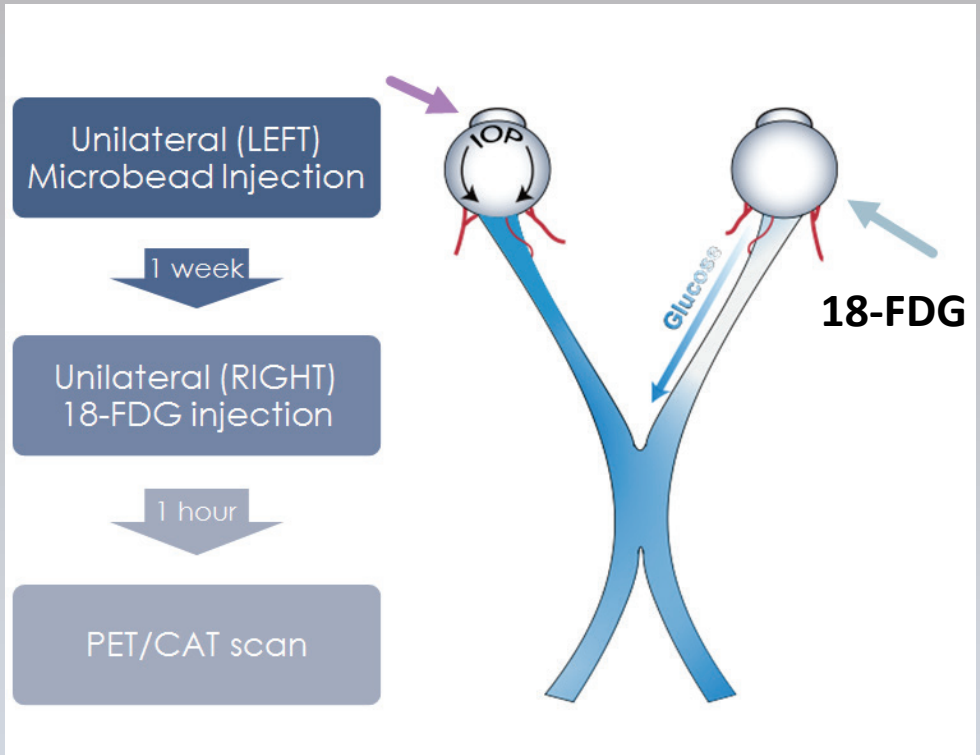
Maybe. Can the astrocyte network transfer glucose between the eyes in glaucoma?

The Experiment

Unilateral elevation of ocular pressure using microbead injection in mice



Naive eye receives injection of radiolabeled glucose (18-FDG).



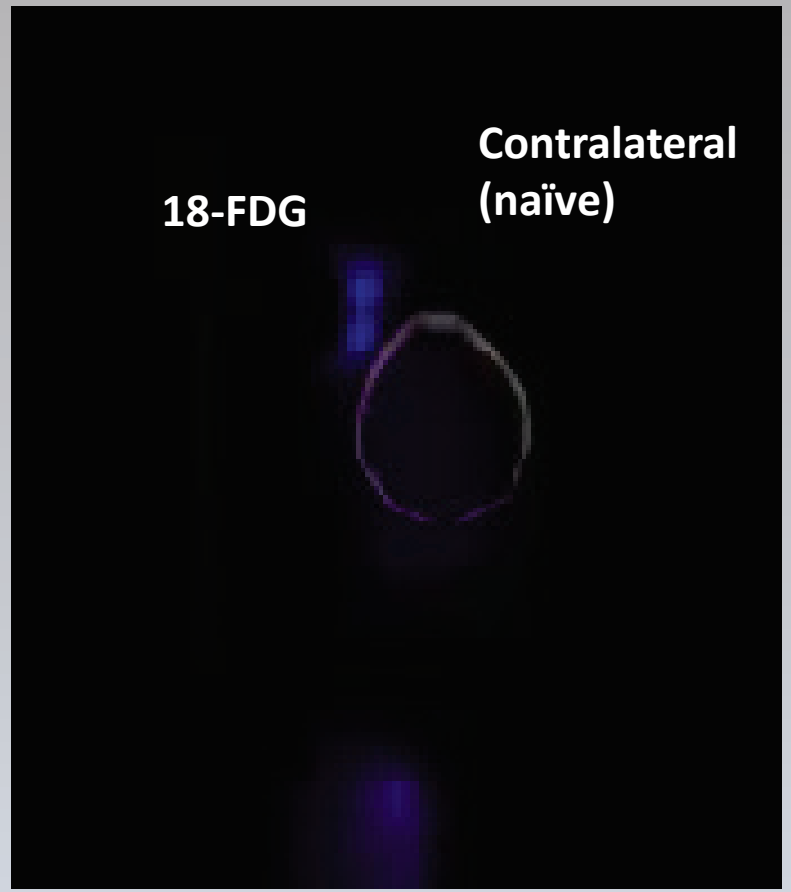
The result …

Naïve eye donates glucose to stressed eye.

Rostral

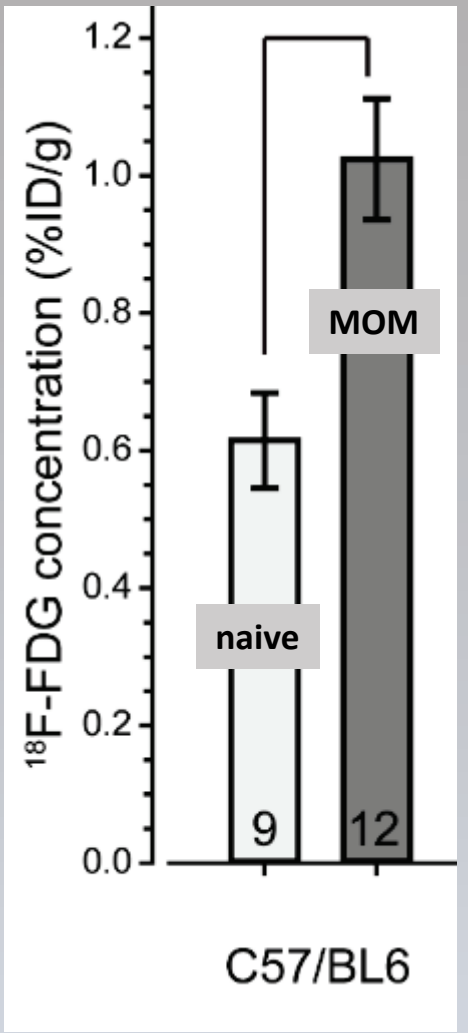
Caudal

Both eyes naive



Microbead Occlusion (MOM)

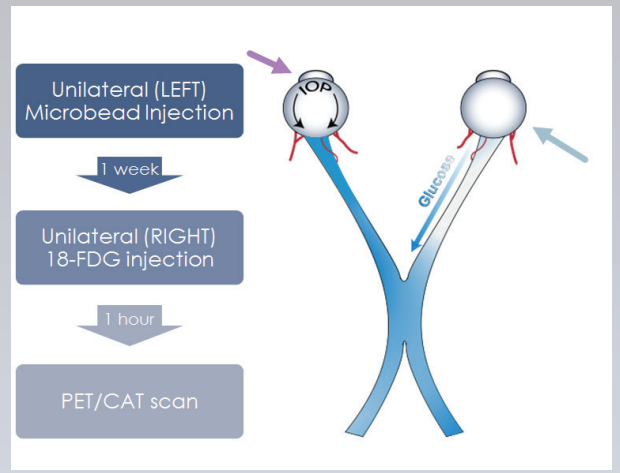
FDG in Contralateral Eye



Astrocytes?

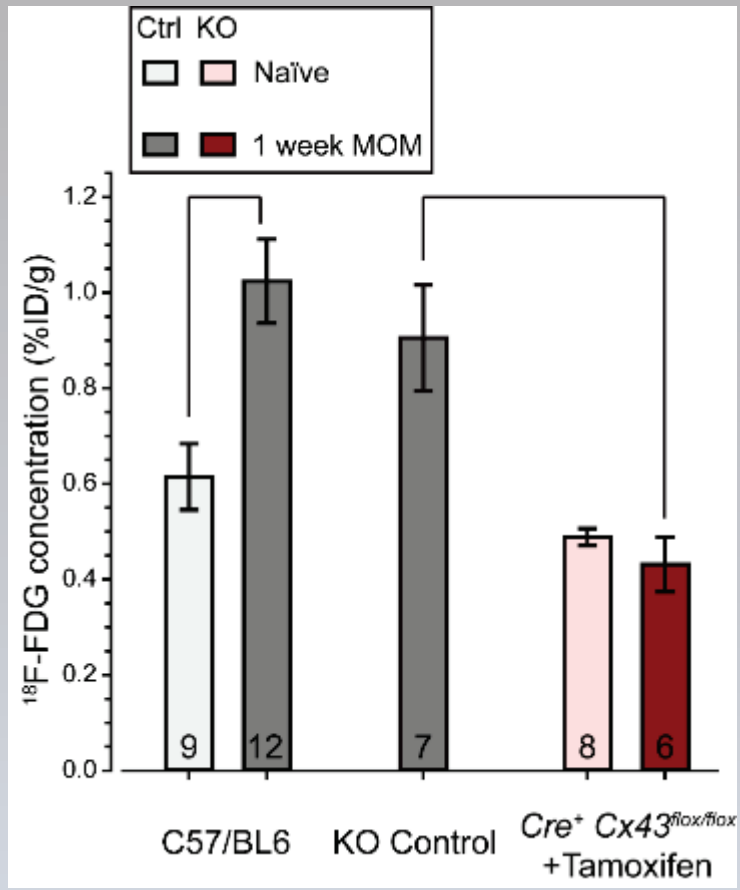
Knocking out functional gap junctions between astrocytes specifically (conditional knockout of Cx43) reduces glucose transfer between the eyes

Opposite eye receives injection of radiolabeled glucose (18-FDG).



Astrocyte Gap Junction Knock-out
1 week pressure elevation (MOM)

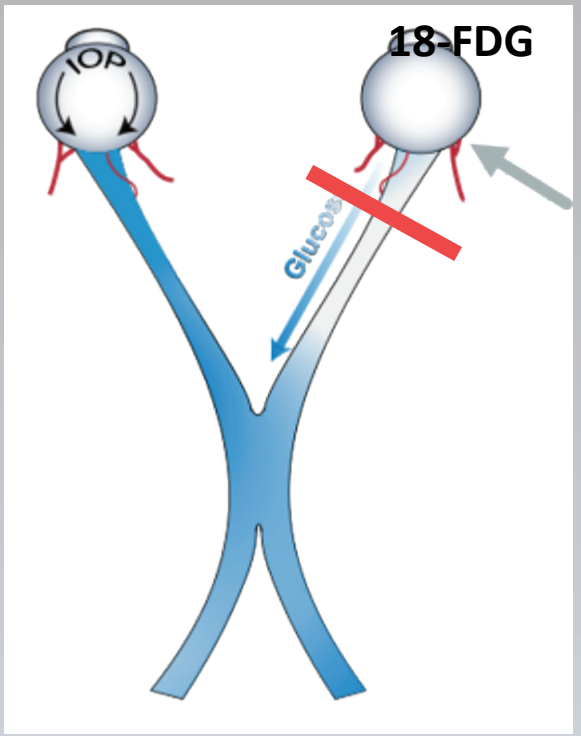
Knocking out gap junctions between astrocytes

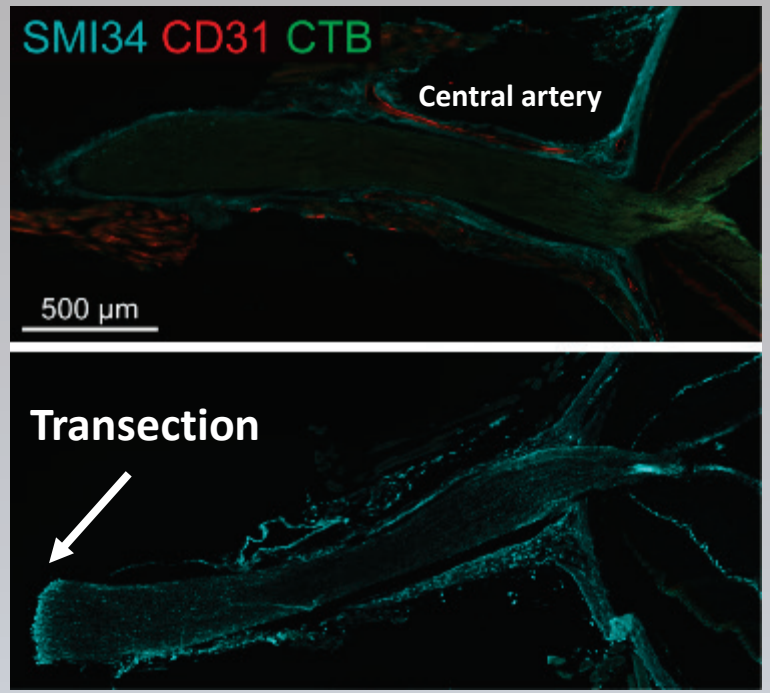


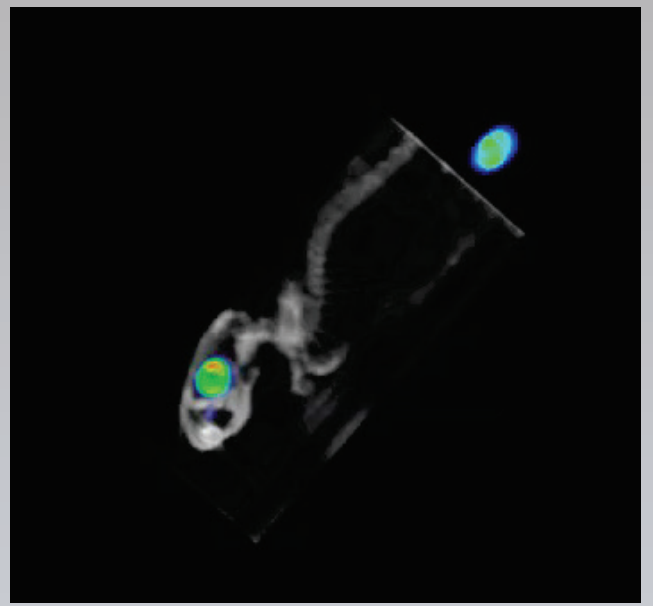
Does the transfer actually involve the optic nerves?

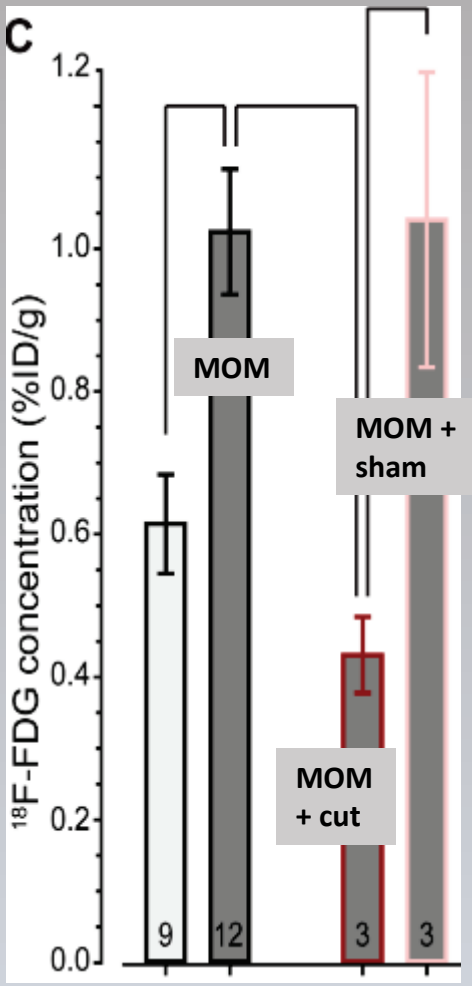
Yes. Cutting the contralateral projection prevents glucose transfer between the eyes.

MOM elevation + nerve transection, contralateral to FDG injection





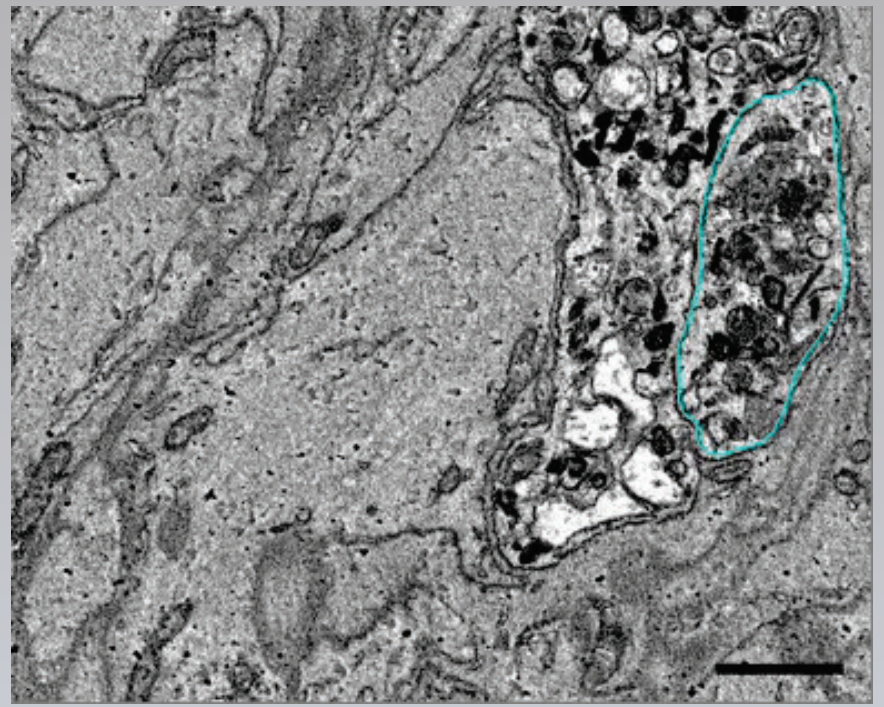




Bottom line …

Astrocyte networks can pass energy … what else?

Davis et al., 2014



Astrocytes in the optic nerve engulfing an axonal evulsion with **mitochondria (red). Mitochondria undergo mitophagy in the astrocytes; miRNA and proteins in these mitochondria are packaged in endosomes.**

Transfer of mitochondria from astrocytes to neurons after stroke.
Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, Ji X, Lo EH.
Nature. 2016 Jul 28;535(7613):551-5. doi: 10.1038/nature18928.

Glia-to-neuron transfer of miRNAs via extracellular vesicles: a new mechanism underlying inflammation-induced synaptic alterations.
Prada I, Gabrielli M, Turola E, Iorio A, D'Arrigo G, Parolisi R, De Luca M, Pacifici M, Bastoni M, Lombardi M, Legname G, Cojoc D, Buffo A, Furlan R, Peruzzi F, Verderio C. Acta Neuropathol. 2018 Apr;135(4):529-550.

Glia to axon RNA transfer.
Sotelo JR, Canclini L, Kun A, Sotelo-Silveira JR, Calliari A, Cal K, Bresque M, Dipaolo A, Farias J, Mercer JA.
Dev Neurobiol. 2014 Mar;74(3):292-30

Gap junctions mediate human immunodeficiency virus-bystander killing in astrocytes.
Eugenin EA, Berman JW.
J Neurosci. 2007 Nov 21;27(47):12844-50.

What it isn't …

Contralateral effect does not appear to be due to direct transfer of viral construct

We conducted a GLP single dose biodistribution study in tissues from male and female **Cynomolgus (macaque) monkeys** following intravitreal injection of GS010 at a low (4.3 x1010 vg/eye) or high (3 x1011 vg/eye) dose, where vg indicates “viral genome”.

In animals **receiving bilateral injections**, after 3 months:

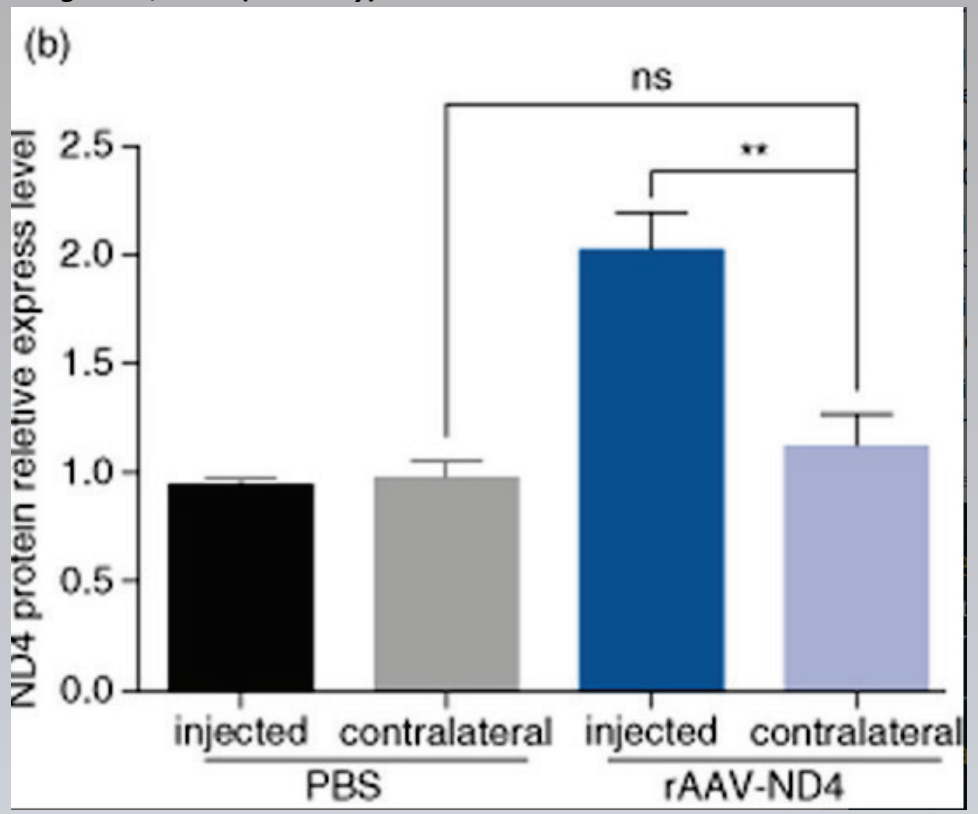
- **All retinas** (n=6 per dose) displayed high levels of GS010 vector DNA (from 6.1x104 to 2x106 transcripts/µg of DNA)

- Only two animals from the high-dose group showed quantifiable amounts of GS010 vector DNA **in the optic nerve** (only a few hundred transcripts/µg of DNA)

- Only one animal from the high-dose group showed quantifiable amounts of GS010 vector DNA **in the optic tract** (again, only a few hundred transcripts/µg of DNA)

- **All tissues harvested from optic chiasm, LGN, and V1 returned non-detectable or non-quantifiable levels of GS010 vector DNA**.

Yang et al., 2015 (rat study)



Most likely scenario…

Occam's Razor: Most parsimonious explanation

We conducted a GLP single dose biodistribution study in tissues from male and female Cynomolgus monkeys following intravitreal injection of GS010 at a low (4.3 x1010 vg/eye) or high (3 x1011 vg/eye) dose, where vg indicates “viral genome”.

In animals **receiving bilateral injections**, after 3 months:

- **All retinas** (n=6 per dose) displayed high levels of GS010 vector DNA (from 6.1x104 to 2x106 transcripts/µg of DNA)

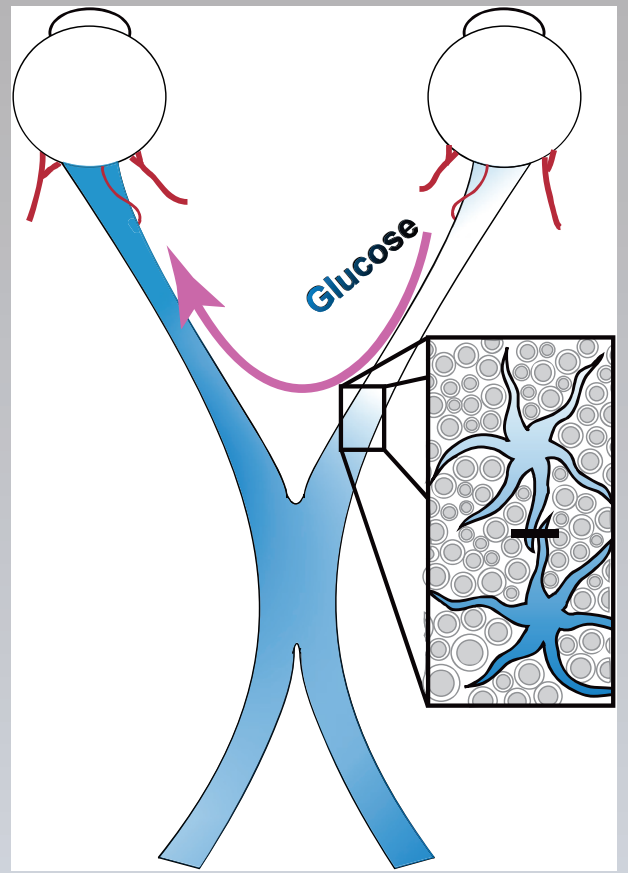
- Only two animals from the high-dose group showed quantifiable amounts of GS010 vector DNA **in the optic nerve** (only a few hundred transcripts/µg of DNA)

- Only one animal from the high-dose group showed quantifiable amounts of GS010 vector DNA **in the optic tract** (again, only a few hundred transcripts/µg of DNA)

- **All tissues harvested from optic chiasm, LGN, and V1 returned non-detectable or non-quantifiable levels of GS010 vector DNA**.

Contralateral

GS010 (rAAV2-ND4)



Neither rAAV2 or ND4 increases in tissue posterior to injection site.

In the metabolic scenario, the untreated contralateral eye remains “stressed” from LHON progression.

The treated eye begins to improve, thereby increasing metabolic resources available to its own optic projection and **for donation** to the fellow eye.

Over time, resources (glucose, ATP) travel via astrocyte networks from the treated eye to the untreated to improve overall performance.

Questions?

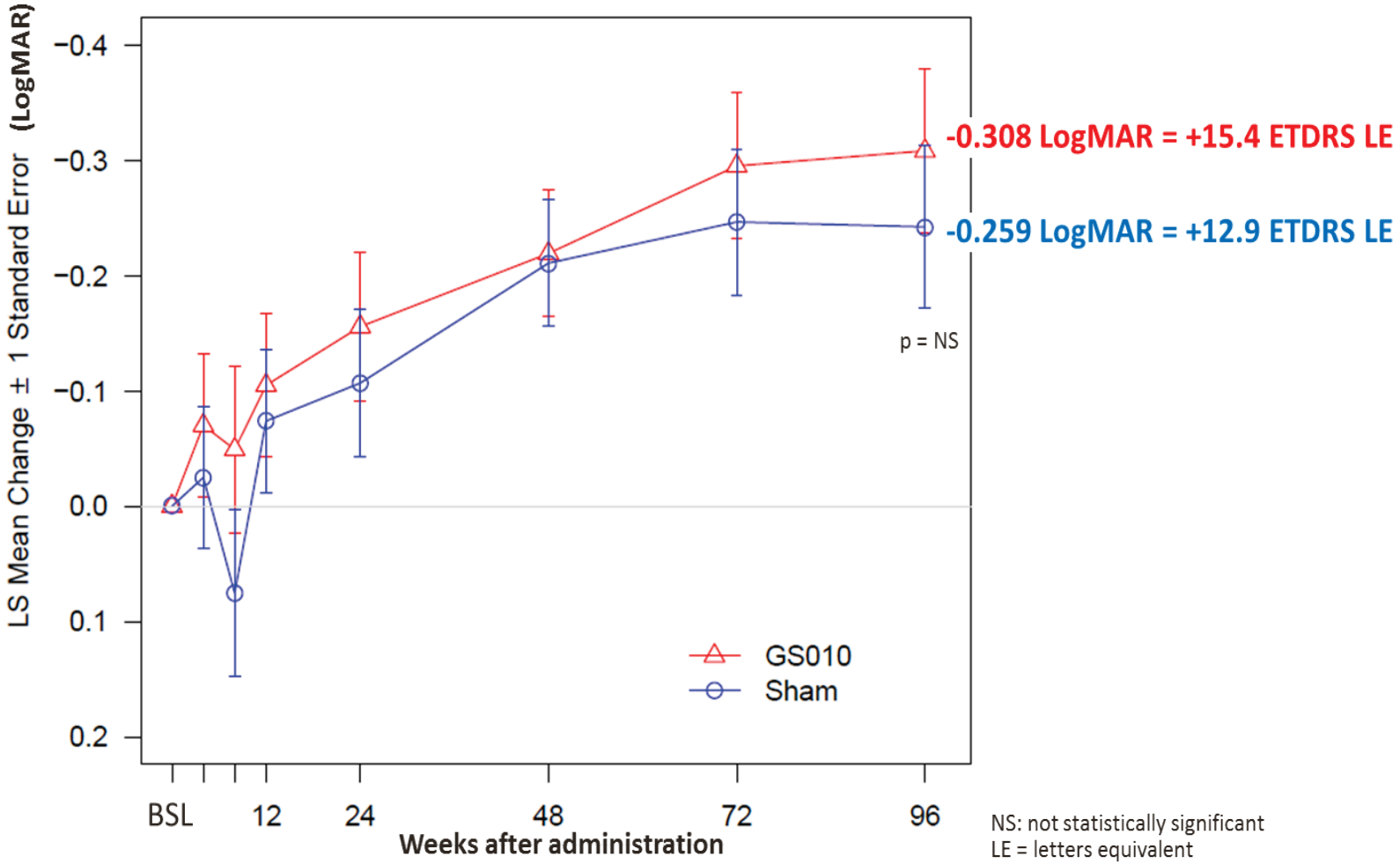
Synthesis of Discussion

Dr. José-Alain Sahel

Visual Acuity: REVERSE 96-week

Sustained bilateral improvement from baseline and nadir are statistically significant and clinically meaningful at Week 96

Mean visual acuity, difference from baseline, in LogMar



NS: not statistically significant
LE = letters equivalent

Mean visual acuity (BCVA) among GS010-treated eyes and sham-treated eyes evolved with similar trajectories, worsening to an initial low point, or nadir, before recovering at Week 96 by +28 and +23 ETDRS letters equivalent, respectively

GenSight BIOLOGICS

Natural History: REVERSE 96-week

REVERSE visual acuity improvements unlikely to stem from natural history

- In a **natural history study** conducted by Santhera[(1)], **15% of subjects** with the ND4 (*11778A*) mutation achieved the following definition of "clinically relevant recovery" (CRR) from baseline in at least one eye:
  - » Improved by at least 10 ETDRS letters from their on-chart visual acuity, or
  - » Improved from an off-chart level of visual acuity to being able to read at least 5 ETDRS letters (on-chart)

By comparison …

- **68% of REVERSE subjects** achieved this definition of CRR at Week 96, with GS010-treated eyes significantly more likely to achieve this than sham-treated eyes (62% vs. 43%, p = 0.0348, statistically significant difference).

"The data show that both the treated and the sham eye improved in both high and low contrast, defying the accepted natural history of this disease and improving upon it, based upon the clinical experiences of generations of neuro-ophthalmologists."

Dr. Robert C. Sergott

Director, Wills Eye Hospital, Neuro-Ophthalmology and Director, William H. Annesley, Jr, EyeBrain Center, Thomas Jefferson University, Philadelphia, PA

GenSight BIOLOGICS

Quality of Life: REVERSE 96-week

Improving quality of life scores provided by REVERSE patients reflect greater autonomy

- **Sustained improvements in** validated quality of life survey scores versus baseline at Week 48, Week 72 and Week 96
- Magnitudes of mean score improvement observed with GS010 **correlate with clinically meaningful improvements** in best-corrected visual acuity (BCVA)

NEI VFQ-25 Results from REVERSE

Mean change from baseline (absolute score and percent)

	Composite Score**	Near Activities	Distance Activities	Dependency	Role Difficulties	General Vision	Mental Health
Week 48	+7.2 *+23.2%*	+10.4 *+65.1%*	+9.6 *+49.8%*	+12.4 *+100.6%*	+14.5 *+65.0%*	+10.3 *+50.9%*	+11.2 *+81.9%*
Week 72	+8.1 *+25.2%*	+9.5 *+58.1%*	+8.2 *+42.5%*	+18.9 *+130.2%*	+15.2 *+70.9%*	+11.9 *+54.1%*	+15.2 *+105.6%*
Week 96	+9.5 *+28.8%*	+13.3 *+78.1%*	+10.7 *+47.4%*	+18.5 *130.2%*	+15.9 *+78.9%*	+6.5 *+32.4%*	+16.1 *+108.2%*
Clinically relevant difference*	+3.90 to +4.34	+4.67 to +6.06	+5.15 to +5.38	+4.72 to +4.98	+3.31 to +4.70	+4.38 to +4.82	+4.70 to +4.88

*Suñer *et al.* (2009): clinically relevant score differences based on a clinically significant 15-letter BCVA improvement at 12 months.
**The composite score is an average of the vision-targeted sub-scale scores, excluding the general health rating question.

GenSight BIOLOGICS

Patient Case Study

Dr. Sean Donahue

Patient case study (video)

Closing remarks

Bernard Gilly

Q & A

Moderated by Barrett Katz

Thank you

GenSight BIOLOGICS

APPENDIX

Bibliography – Contralateral Effect

Burdett TC, Freeman MR. Neuroscience. Astrocytes eyeball axonal mitochondria. Science. 2014 Jul 25;345(6195):385-6.

Davis CH, Kim KY, Bushong EA, Mills EA, Boassa D, Shih T, Kinebuchi M, Phan S, Zhou Y, Bihlmeyer NA, Nguyen JV, Jin Y, Ellisman MH, Marsh-Armstrong N. Transcellular degradation of axonal mitochondria. Proc Natl Acad Sci U S A. 2014 Jul 1;111(26):9633-8.

Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, Ji X, Lo EH. Transfer of mitochondria from astrocytes to neurons after stroke. Nature. 2016 Jul 28;535(7613):551-5.

Osborne NN, del Olmo-Aguado S. Maintenance of retinal ganglion cell mitochondrial functions as a neuroprotective strategy in glaucoma. Curr Opin Pharmacol. 2013 Feb;13(1):16-22.

Vossel KA, Zhang K, Brodbeck J, Daub AC, Sharma P, Finkbeiner S, Cui B, Mucke L. Tau reduction prevents Abeta-induced defects in axonal transport. Science. 2010 Oct 8;330(6001):198.

Weber AJ, Viswanáthan S, Ramanathan C, Harman CD. Combined application of BDNF to the eye and brain enhances ganglion cell survival and function in the cat after optic nerve injury. Invest Ophthalmol Vis Sci. 2010 Jan;51(1):327-34.

Yang S, He H, Zhu Y, Wan X, Zhou LF, Wang J, Wang WF, Liu L, Li B. Chemical and material communication between the optic nerves in rats. Clin Exp Ophthalmol. 2015 Nov;43(8):742-8.

Yang S, Ma SQ, Wan X, He H, Pei H, Zhao MJ, Chen C, Wang DW, Dong XY, Yuan JJ, Li B. Long-term outcomes of gene therapy for the treatment of Leber's hereditary optic neuropathy. EBioMedicine. 2016 Aug;10:258-68.