GenSight BIOLOGICS

KOL Breakfast

REVERSE Phase III Trial

June 12, 2018
New York City

www.gensight-biologics.com

Welcome

Thomas Gidoin
Chief Financial Officer

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Agenda

Time	Topics	Speaker
8.30	GenSight Biologics, Where We Stand	**Bernard Gilly** GenSight Biologics
8.40	LHON, an Overview	**Nancy J. Newman, MD** Emory University
8.50	Natural History of LHON	**Mark Moster, MD** Wills Eye & Jefferson Uni.
9.00	REVERSE Phase III Trial, Additional Data & *Post Hoc* Findings	**Robert C. Sergott, MD** Wills Eye & Jefferson Uni.
9.30	*REVERSE, an Unexpected Bilateral Effect of GS010*	**José-Alain Sahel, MD** Uni. of Pittsburgh & XV-XX
9.40	KOL Panel, How to Interprete REVERSE ?	**Barrett Katz, MD** GenSight Biologics
10.10	Patients Perspectives & Expectations	**Lissa Poincenot** LHON.org
10.20	Update on Regulatory Strategy for GS010	**Bernard Gilly** GenSight Biologics
10.30	Q&A Session	**Thomas Gidoin** GenSight Biologics
10.50	Closing Remarks	**Bernard Gilly** GenSight Biologics

GenSight Biologics, Where We Stand

Bernard Gilly
Co-founder & Chief Executive Officer

Corporate Overview

Clinical-stage gene therapy company

- Focused on severe retinal degenerative pathologies leading to blindness as well as CNS diseases
- Well positioned to advance disruptive gene therapy technologies in ophthalmology to commercialization

Two disruptive technology platforms

- Mitochondrial targeting sequence (MTS)
- Optogenetics

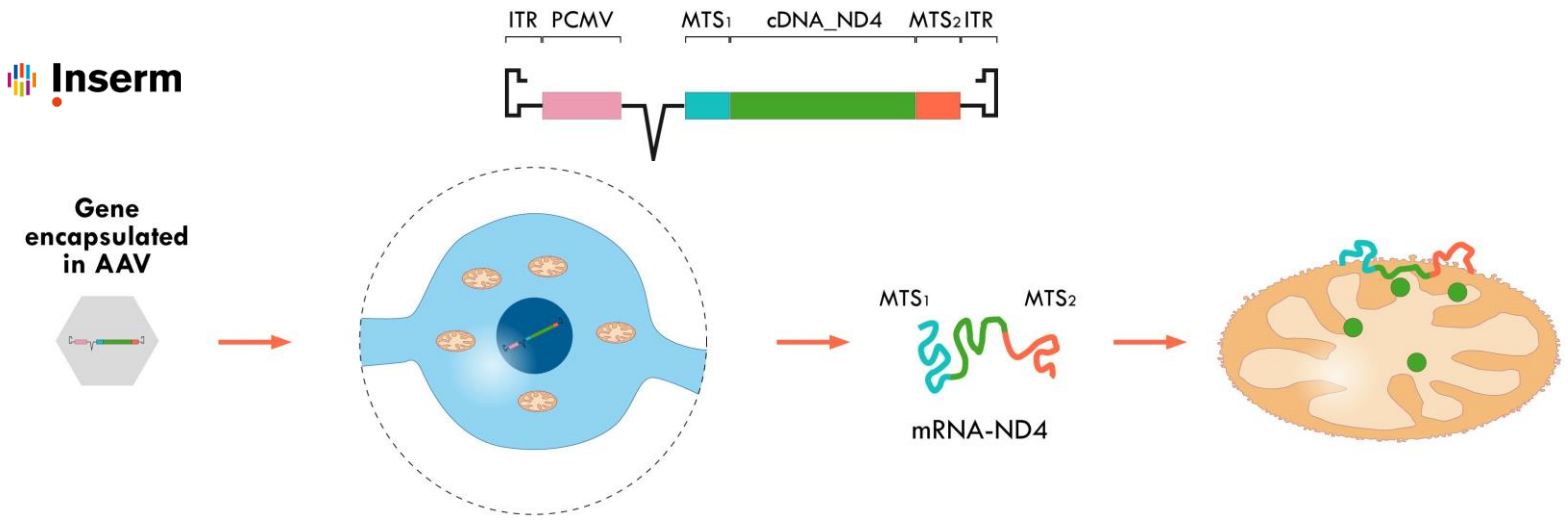
Lead projects target:

- GS010 - Leber Hereditary Optic Neuropathy (Phase III)
- GS030 - Retinitis pigmentosa and dry-AMD (First-in-Man in July 2018)

Listed on Euronext Paris (SIGHT)

- Established in 2012, IPO in July 2016 (€45m)
- GenSight Biologics Inc incorporated in the US in May 2017
- Cash position (end of March 2018): €49.2m

Mitochondrial Targeting Sequence (MTS) proprietary technology



1. Transduction of retinal cell with replacement mitochondrial gene
2. Transcription of replacement mitochondrial gene in the nucleus
3. Delivery of replacement gene mRNA to polysomes located at the mitochondrial surface
4. Synthesis, translocation and proper localization of replacement mitochondrial protein

The only technology that permits missing mitochondrial proteins to be ***actively*** shuttled into the mitochondrion to restore energy production

GS010: from bench to bedside

GS010 restores respiratory chain complex I in patients fibroblasts

C. Bonnet et al.
BBA
May 2008

GS010 prevents optic atrophy and visual loss in LHON rats

H. Cwerman-Thibault et al.
Molecular Therapy
Feb 2015

GS010 Phase I trial demonstrates safety and tolerability, as well as trends of efficacy

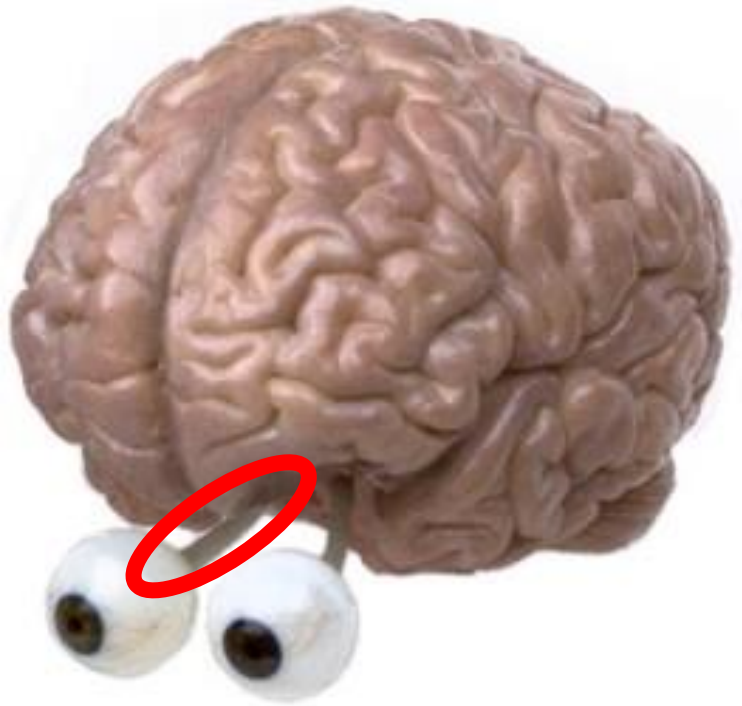
C. Vignal et al.
Ophthalmology
Feb 2018

Trial	Study Name	Recruitment	Data read out
CLIN01	-	Complete	2.5 years reported
CLIN03A	**RESCUE** 0-6 months	Complete	Topline expected October 18
CLIN03B	**REVERSE** 6-12 months	Complete	Topline reported in April 18
CLIN05	**REFLECT** Bilateral	Ongoing	Topline expected H1 20
CLIN06	**RESCUE-REVERSE Long-Term Follow Up**	Ongoing	Expected H2 2019
LHON REGISTRY	**REALITY**	Ongoing	Expected 2020

LHON,
An Overview

Nancy J. Newman, MD
Director, Neuro-Ophthalmology
LeoDelle Jolley Professor of Ophthalmology
Emory University School of Medicine, Atlanta, GA

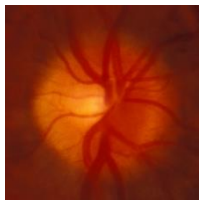
Leber Hereditary Optic Neuropathy

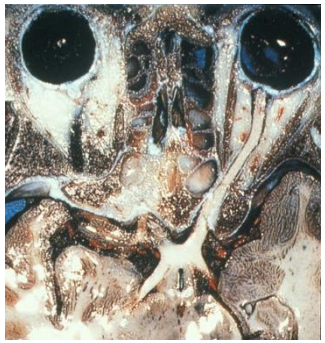


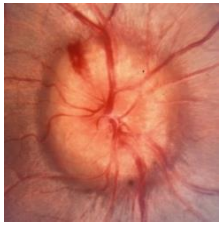
Optic Neuropathy

Causes

- Inflammatory
- Vascular
- Compressive/Infiltrative
- Toxic/Nutritional
- Hereditary
- Traumatic
- Elevated intracranial pressure
- Elevated intraocular pressure







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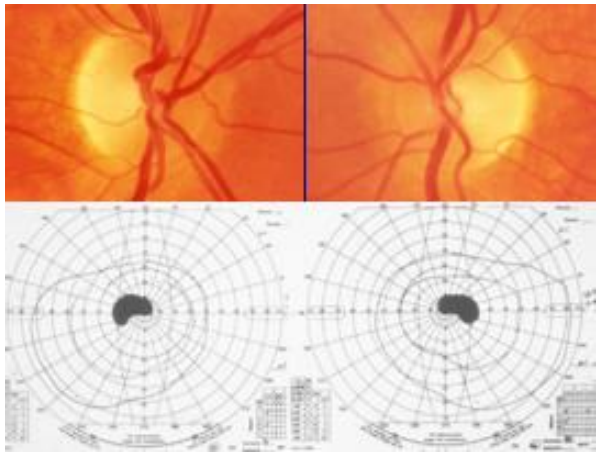
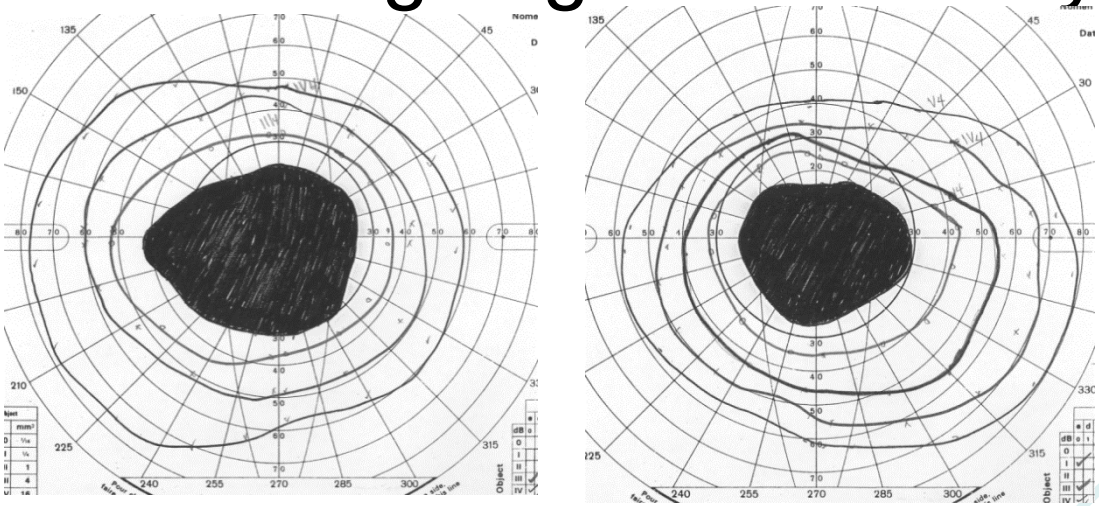
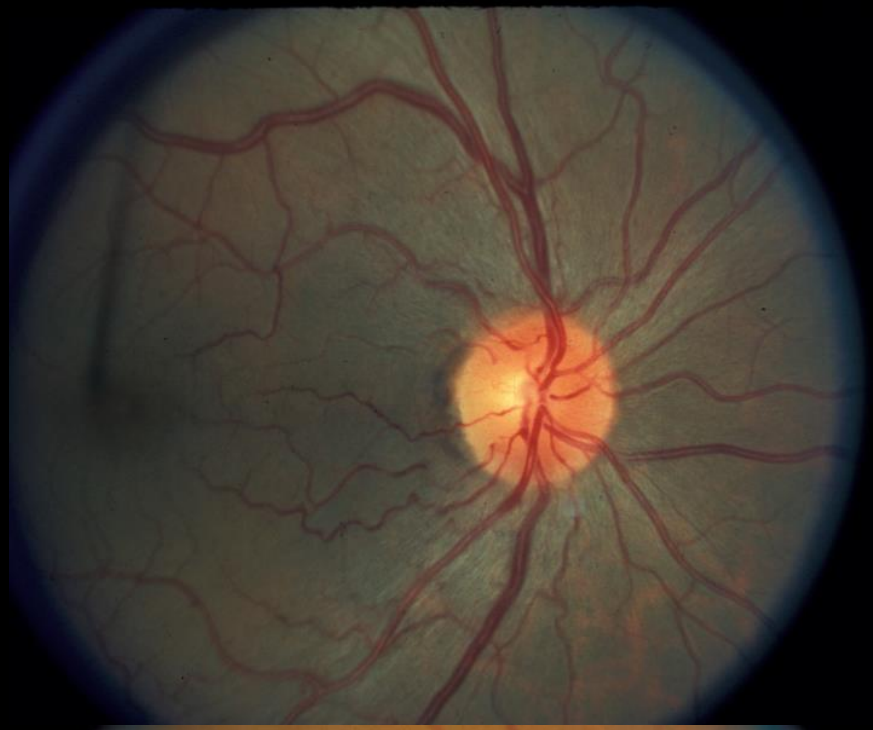
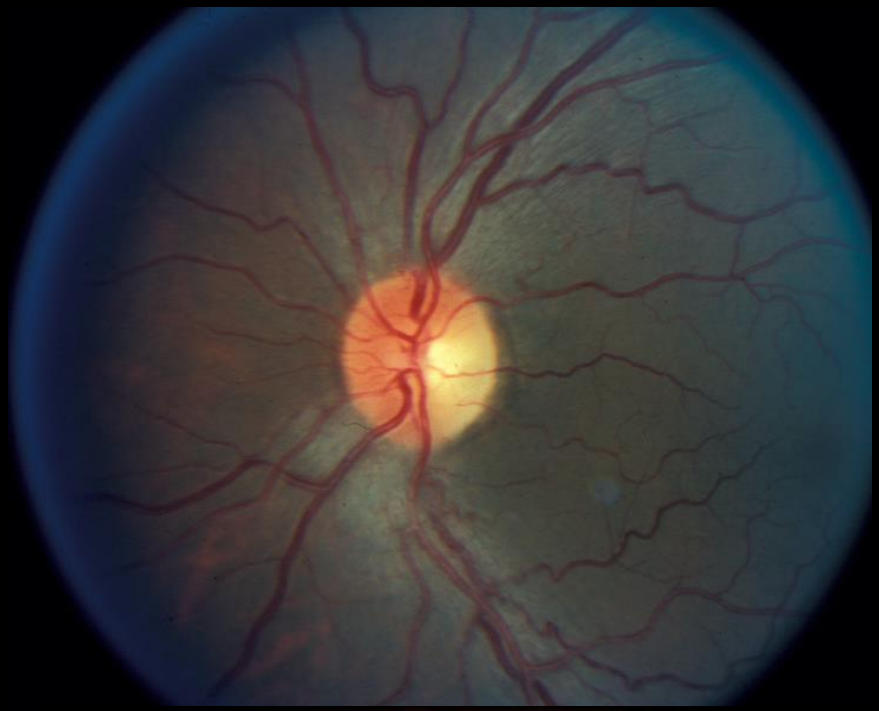
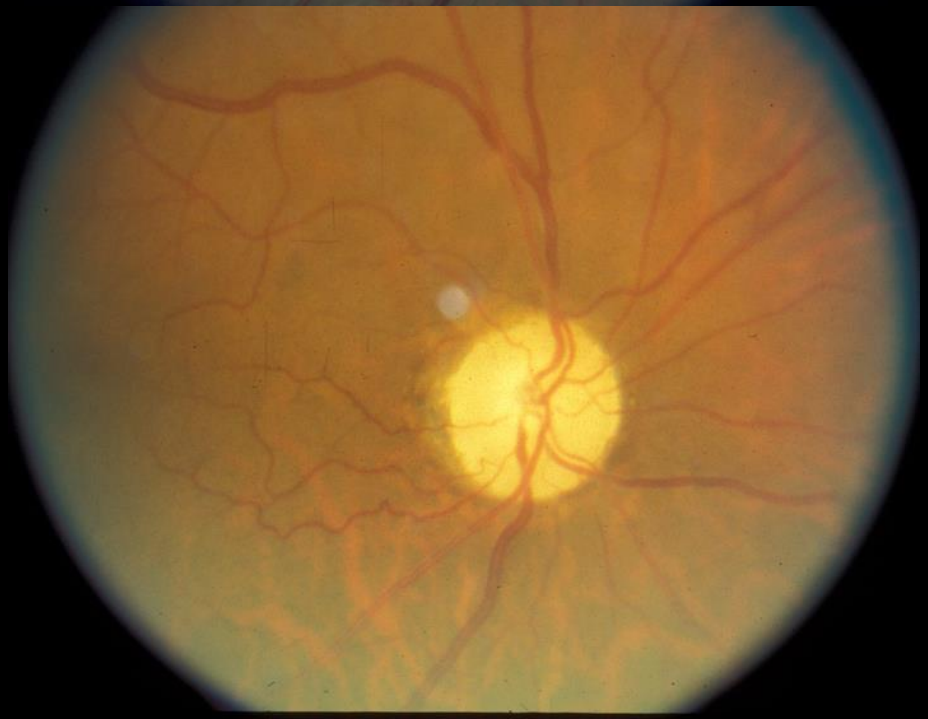
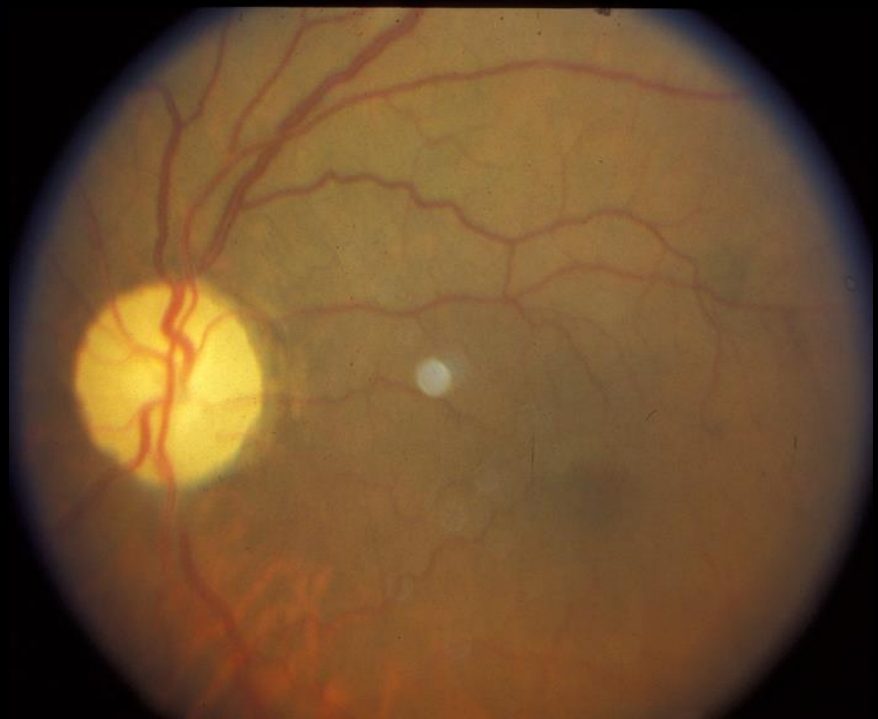
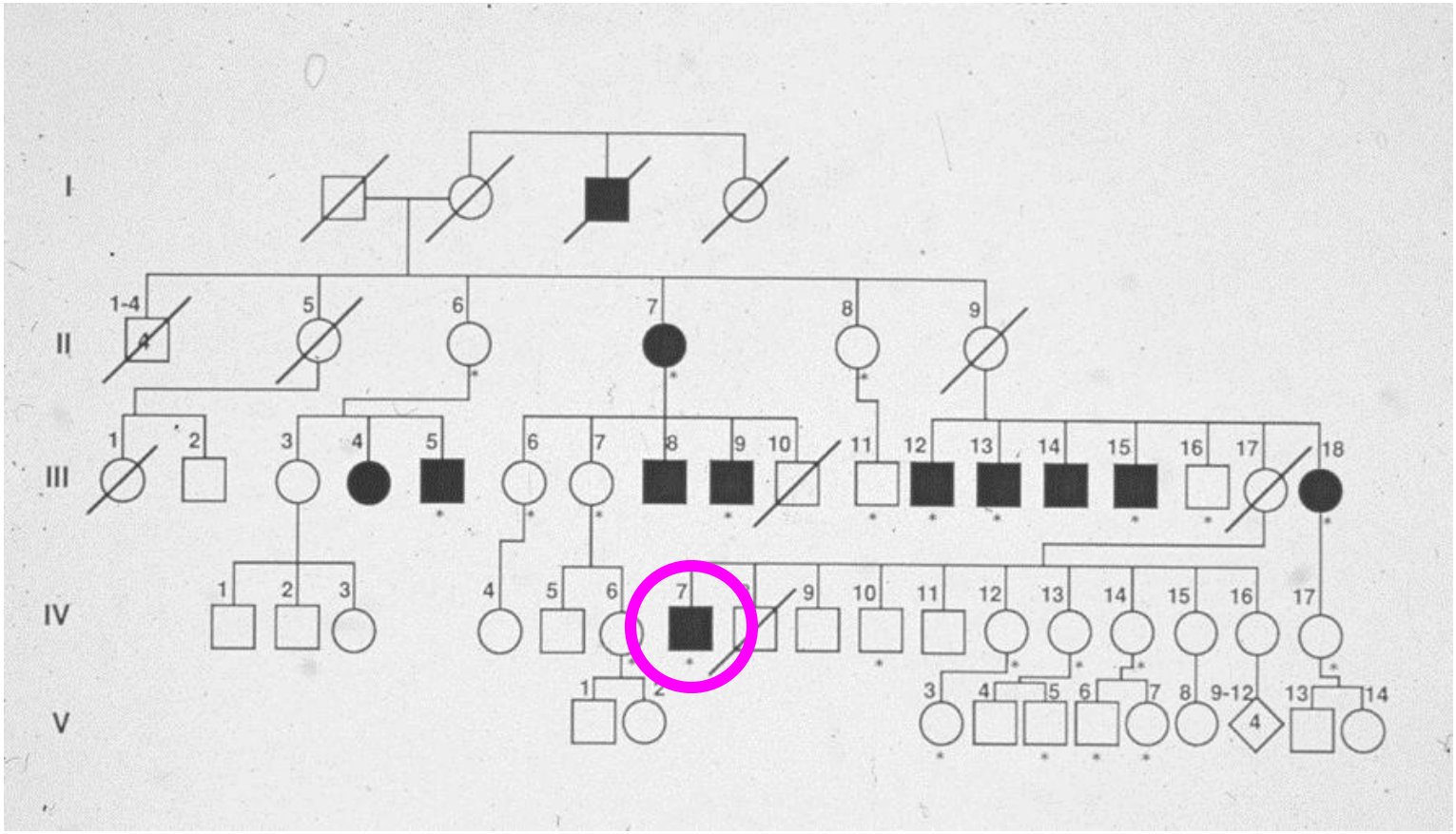


A 21 year old previously healthy man has painless loss of vision in both eyes progressive over one month

Vision is counting fingers in both eyes

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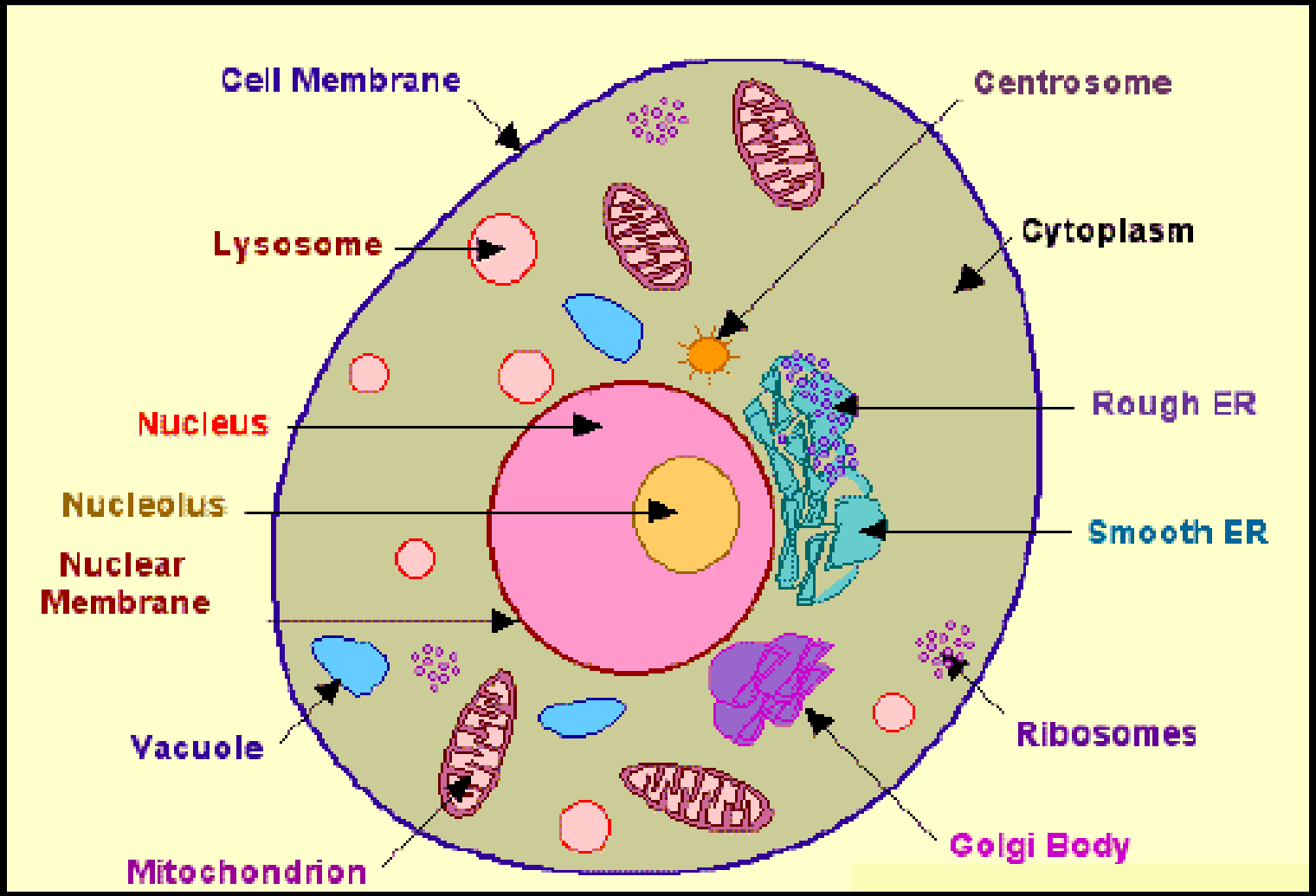
Cell Membrane
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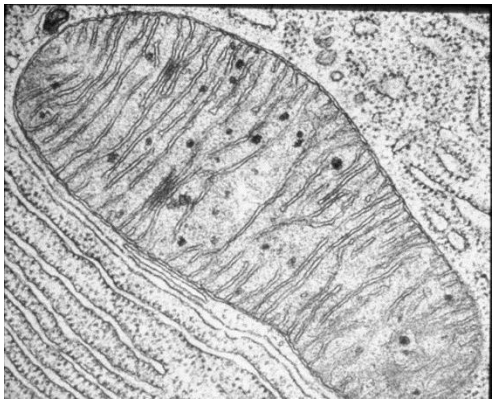
Nucleus
Rough ER
Nucleolus
Smooth ER
Nuclear Membrane
Vacuole
Ribosomes
Mitochondrion
Golgi Body

Mitochondrial Diseases

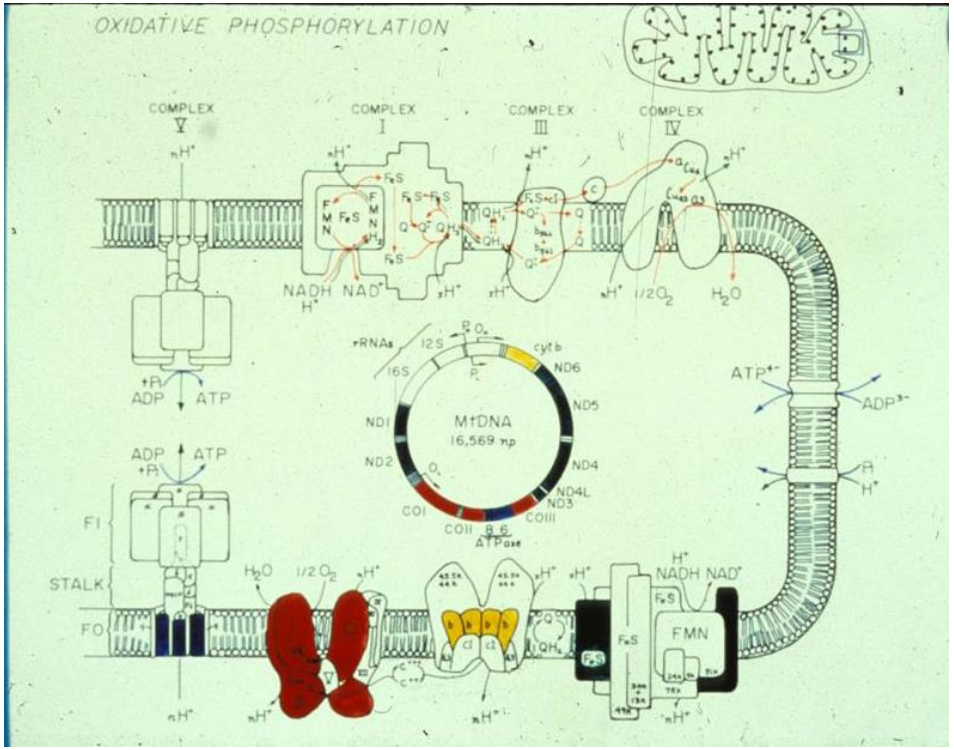


Mitochondria:

- Cytoplasmic organelles
- Hundreds of mitochondria per cell
- Generate cellular energy (ATP)
- Some tissues most reliant on mitochondrial ATP (CNS>Heart>Skeletal Muscle>Kidney>Liver)
- Each mitochondria contains 2-10 DNA molecules

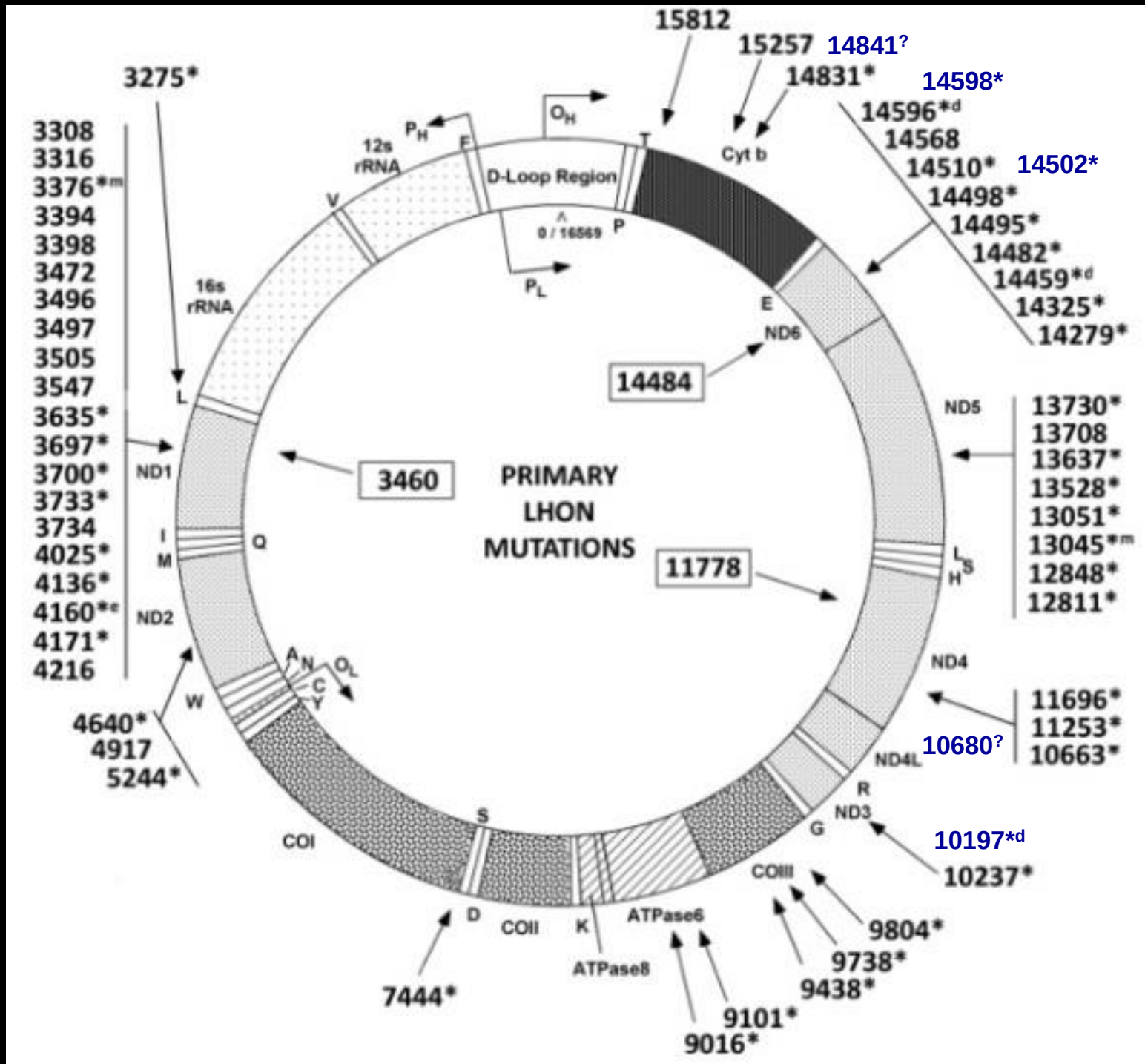
Mitochondrial Diseases

Mitochondrial DNA:



- Double-stranded rings

- Codes for
  - 13 proteins essential to oxidative-phosphorylation
  - All the components necessary to make these proteins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PRIMARY
LHON
MUTATIONS
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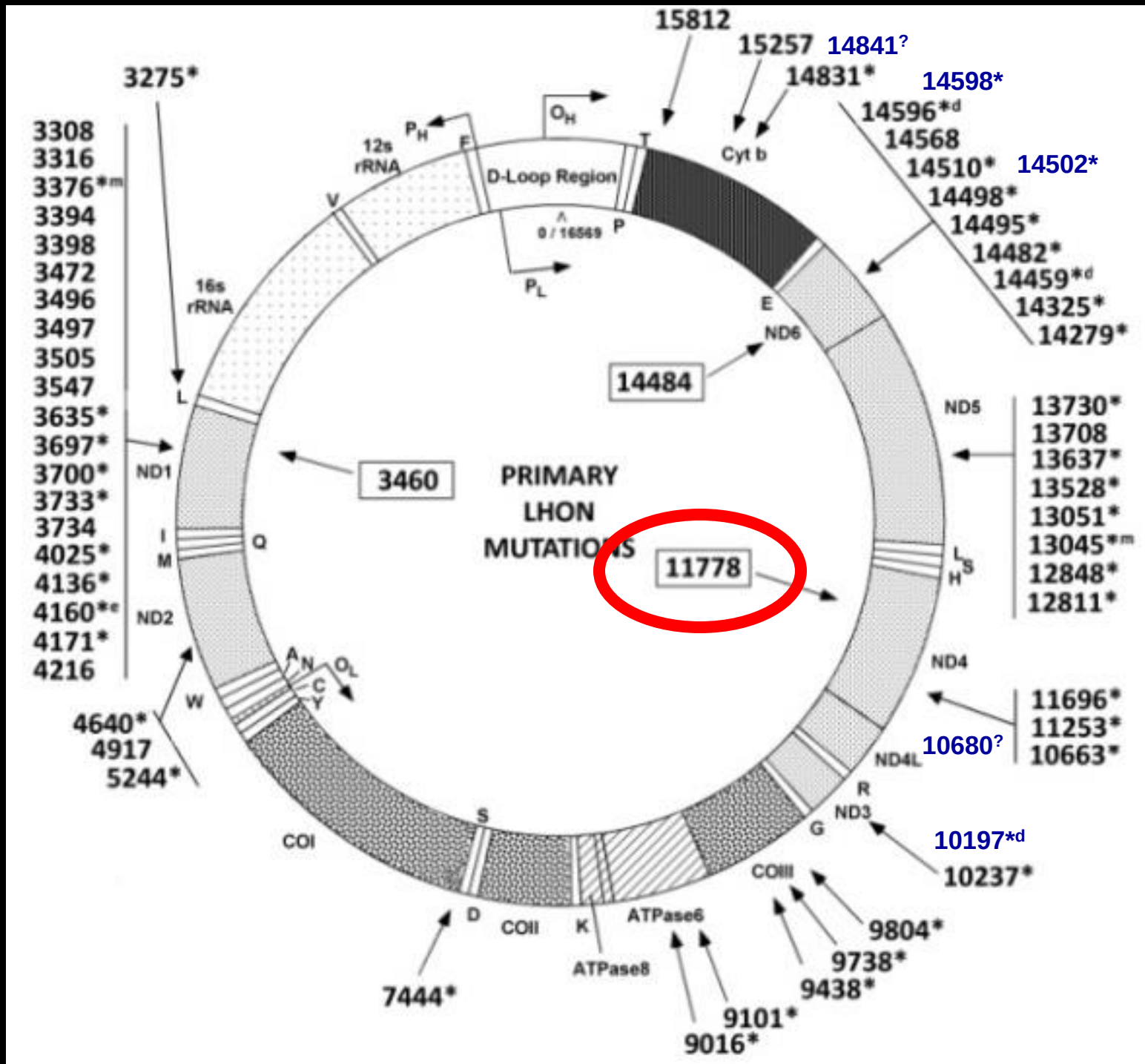
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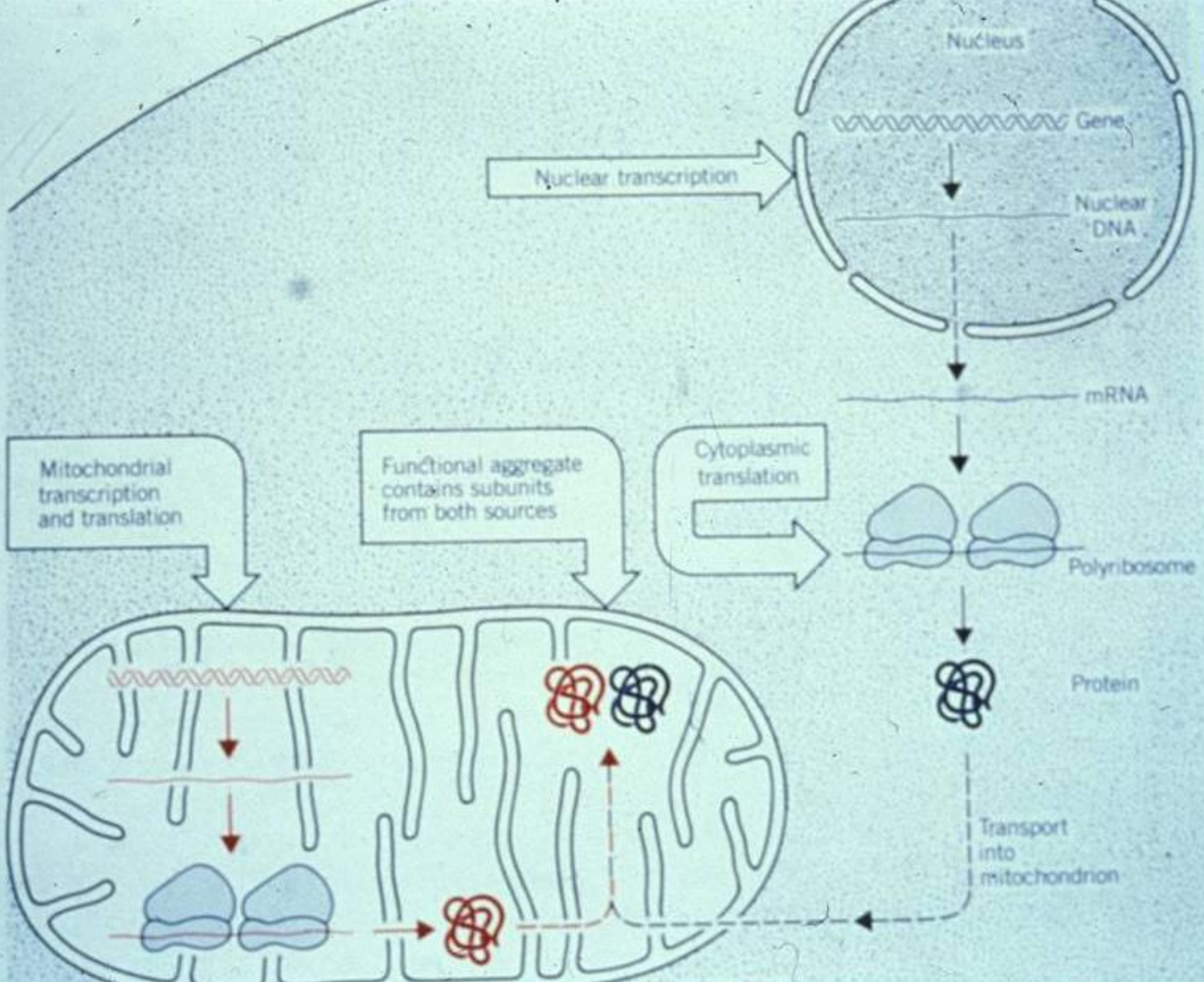
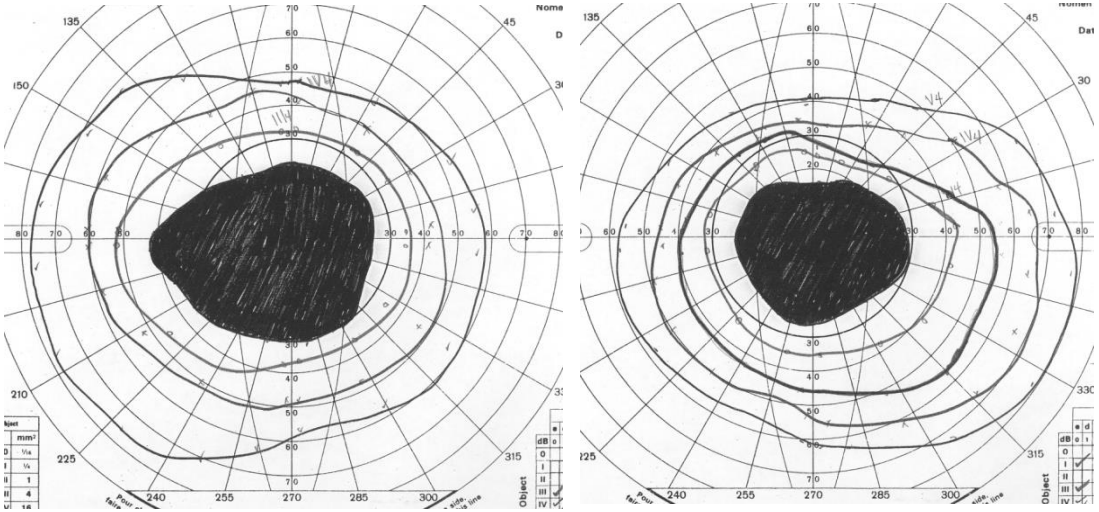

Nucleus
Gene
Nuclear transcription
Nuclear DNA
mRNA
Mitochondrial transcription and translation
Functional aggregate contains subunits from both sources
Cytoplasmic translation
Polyribosome
Protein
Transport into mitochondrion

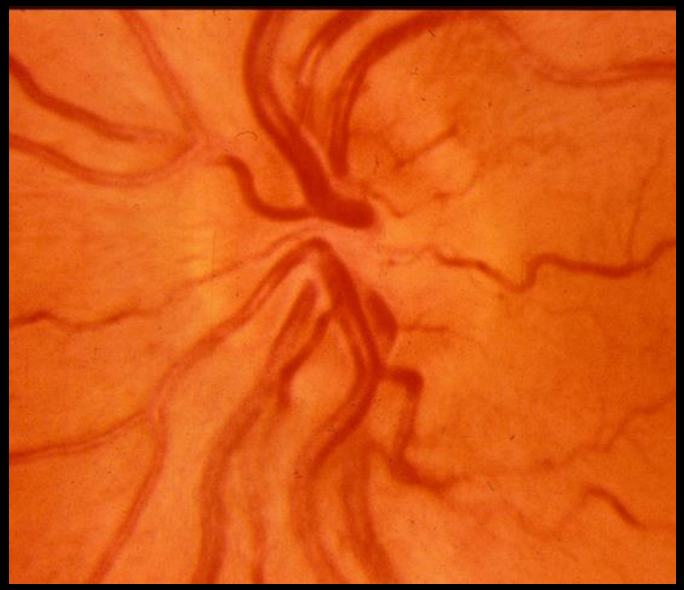
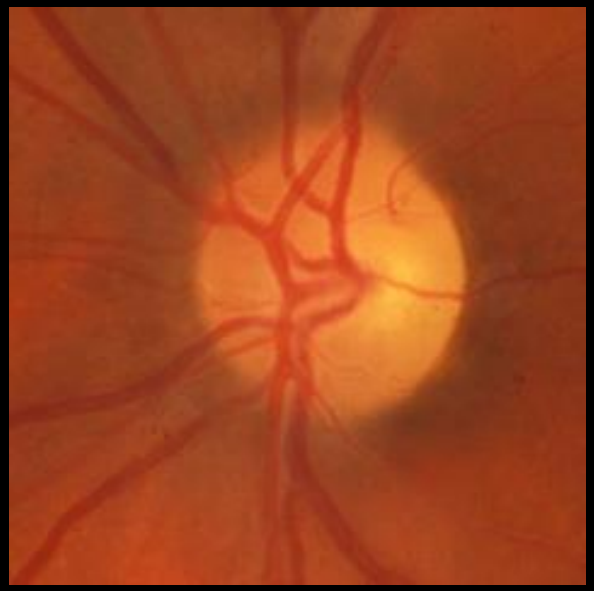
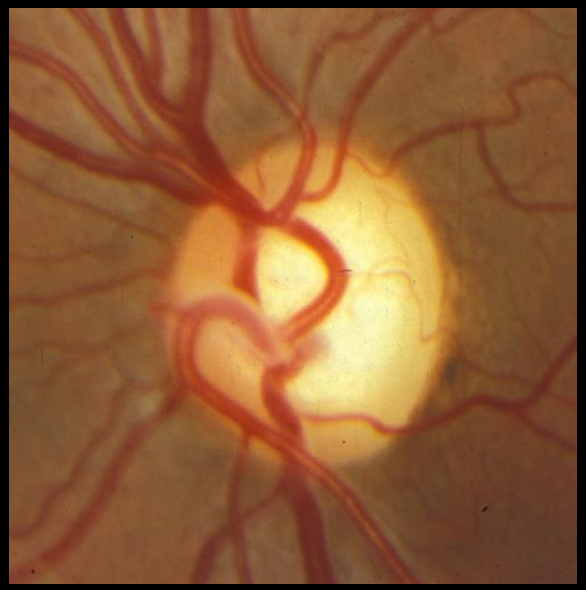
Leber Hereditary Optic Neuropathy

- 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

Leber Hereditary Optic Neuropathy

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



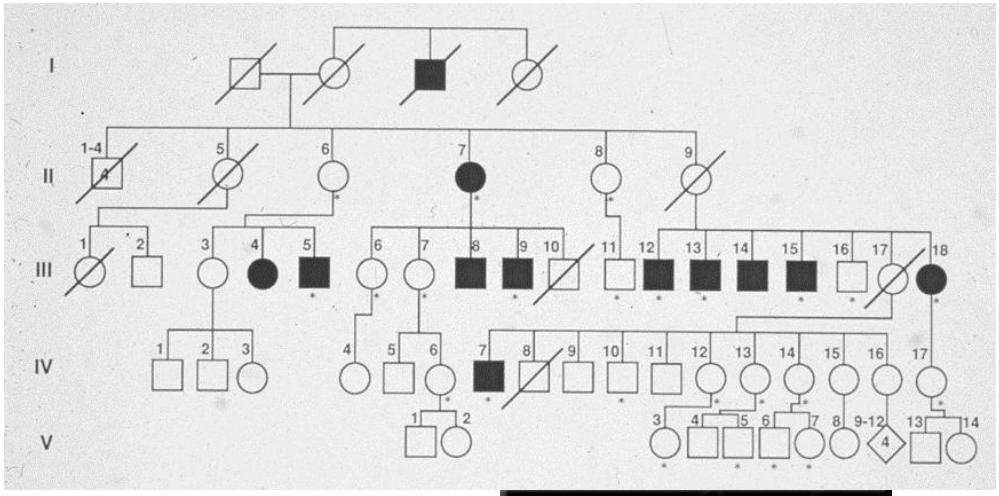




Leber Hereditary Optic Neuropathy

Determinants of Expression

- Vision loss in
  20-50% males
  4-32% females

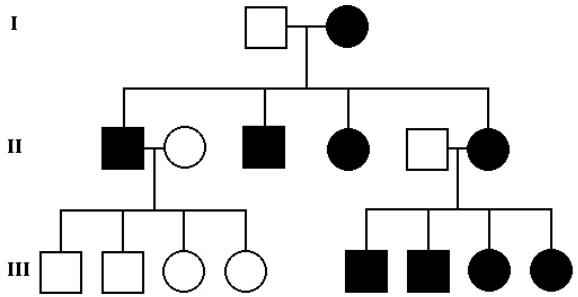
- mtDNA gene defect/heteroplasmy
- mtDNA haplotypes
- Nuclear DNA factors
- Environmental factors



Mitochondrial Diseases

Treatment

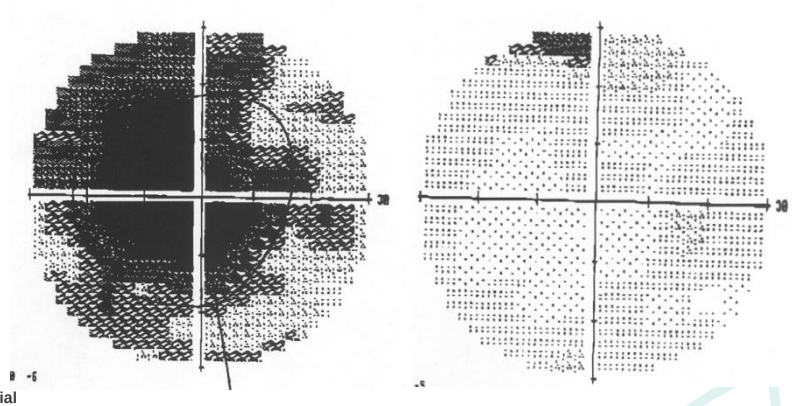
- Genetic counseling
- Symptomatic
- Disease-modifying
  - Mitochondrial diseases
  - Hereditary optic neuropathies
- Gene therapy



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



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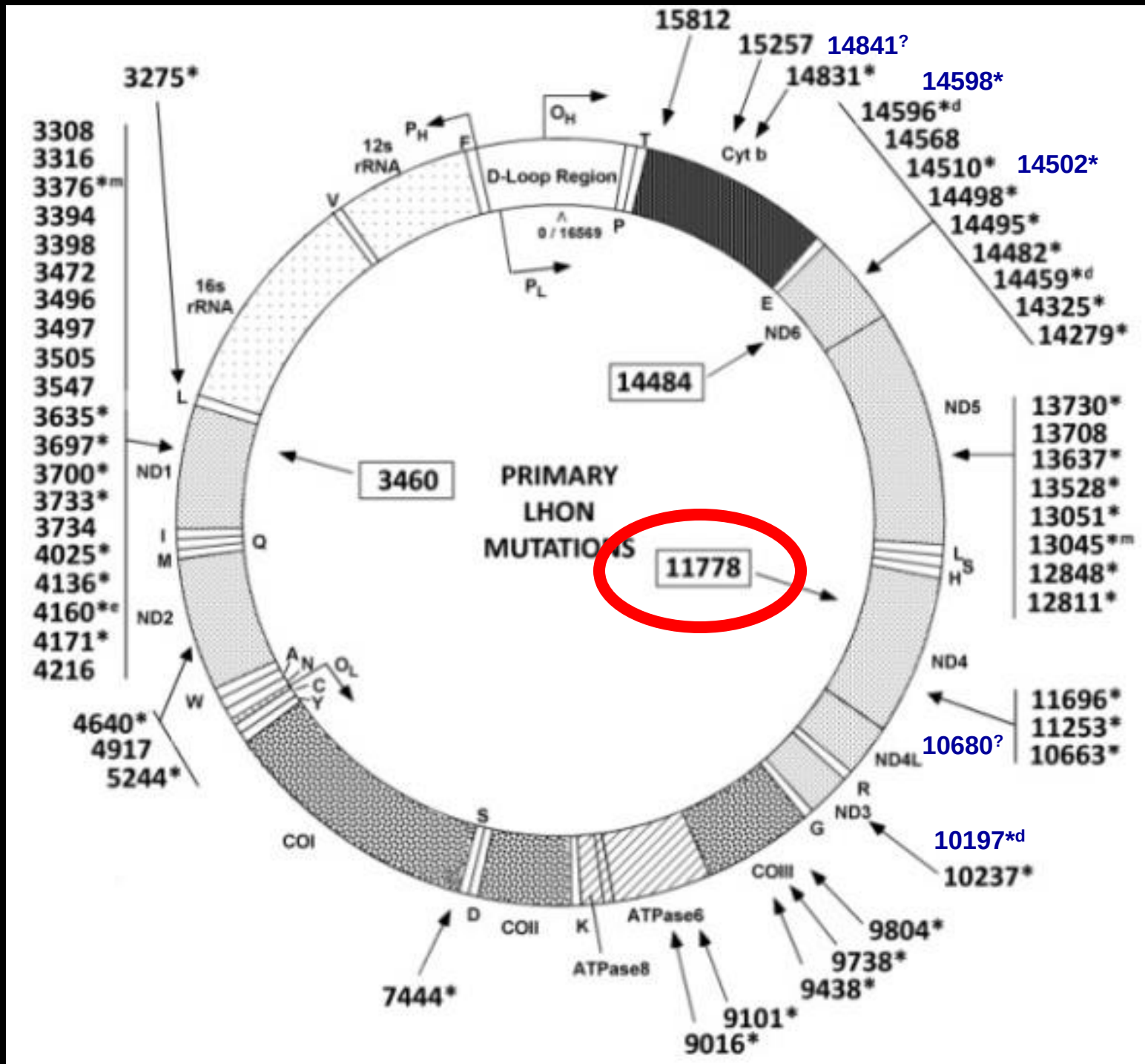
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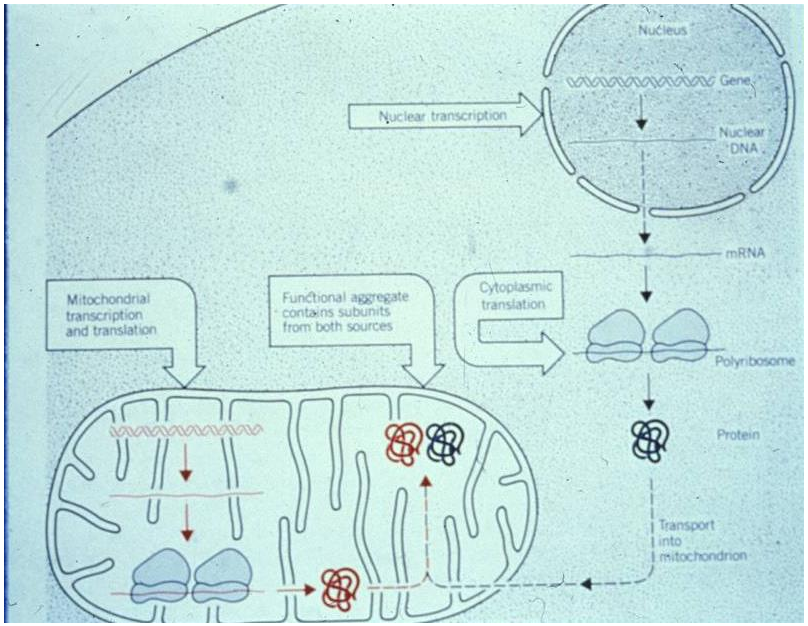
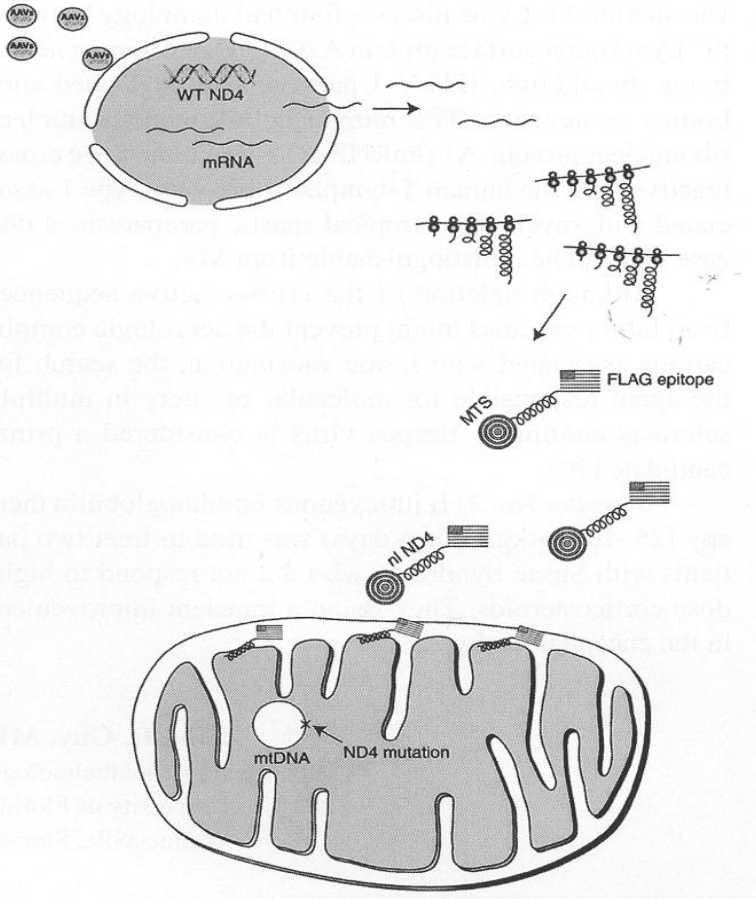
Leber Hereditary Optic Neuropathy

Treatment – Gene Therapy

- Allotopic Rescue





Natural History of LHON

Mark Moster, MD
Neuro-Ophthalmology, Wills Eye Hospital
Professor of Neurology and Ophthalmology,
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***

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: 11778 : *Prior to Gene Therapy* All *Retrospective*

- Stone 1992
  - 4% of 136 patients
  - ***Mostly years, one months***
- Riordan-Eva 1995
  - 1 of 83 (both eyes)
  - One at 11 and 4 months
- Mashima, 2000
  - 1 of 20 improved (11 year old boy)
  - ***Began at 24 months***
- Carelli 2011
  - 22% of 43 patients improved 2 lines
  - **average 27 months**

Era 3: *Gene Therapy*

Observational study 2008-2012

- 44 patients with 11778
- Evaluated every 6 months for 36 months
- No visual improvement in overall population on any of monitored parameters
- 13 eyes (8 patients) (18%) improved during follow-up
- 7 eyes (6 patients) (14%) worsened
- ***68 eyes of 38 patients (86%) were stable***
- Average time to recovery = 27.5 months

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

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

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***
- Clinical experience – ***lack of improvement***
- Which subgroup?

  In subjects who present at younger age

  Occurs suddenly, ***years later***

  Very rarely, *gradually, during 1st year*

Phase III REVERSE Results And Post-Hoc Analyses

Robert C. Sergott, MD
Director, Neuro-Ophthalmology, Wills Eye Hospital
Director, William H. Annesley, Jr, EyeBrain Center
Professor of Neurology and Ophthalmology,
Thomas Jefferson University, Philadelphia, PA

Phase III Clinical Trials RESCUE & REVERSE

➢ **Strategy of early treatment within the first year of onset of vision loss**

RESCUE

Vision loss duration of 6 months or less

NCT02652767

REVERSE

Vision loss duration of >6 months up to 1 year

NCT02652780

Week-48 results available

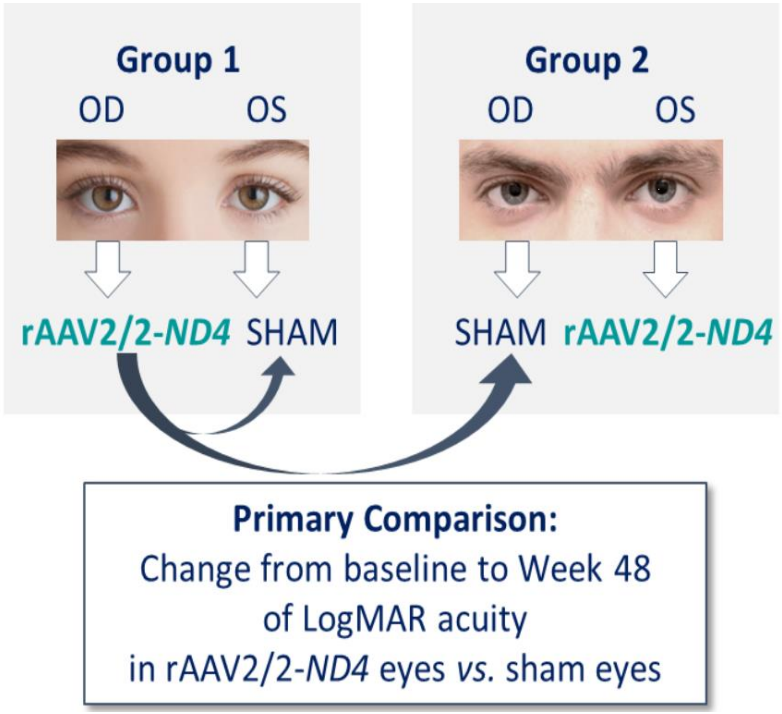
Is 6-12 months
really “early” for LHON?

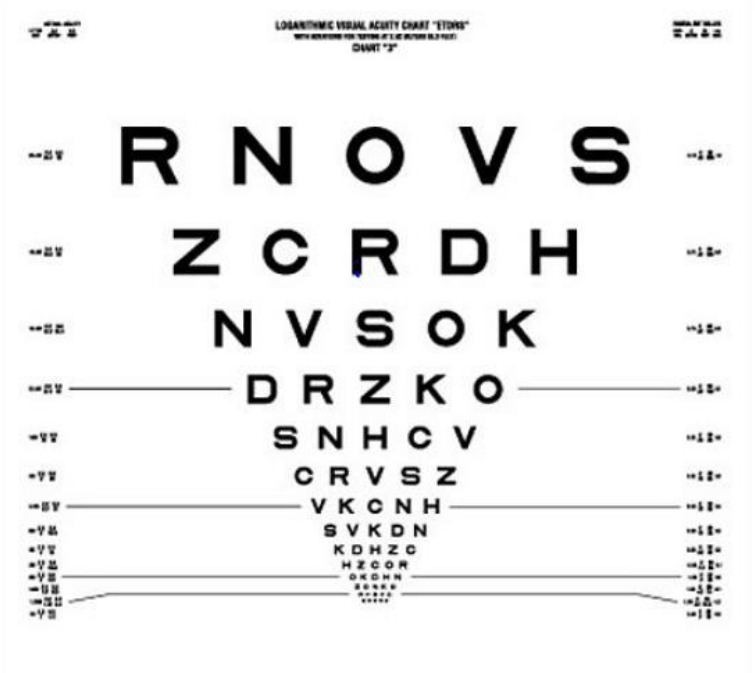
Phase III Clinical Trials RESCUE & REVERSE

LHON subjects enrolled :

- Confirmed G11778A mutation
- Baseline vision ≥ Count Fingers

Study Design





logMAR High Contrast

REVERSE: Demographics at baseline

Statistic	REVERSE
N subjects	37
Demographics	
N males (%)	29 (78.4)
Mean age - years (SD)	34.2 (15.2)
Median age - years (range)	30 (15,67)
Vision loss duration (VLD)	
Eyes with available data	74
Mean VLD - days (SD)	270.9 (59.4)
Median VLD - days (range)	262 (181,364)
Simultaneous bilateral onset	
N subjects (%)	7 (19%)

SD: standard deviation, VLD: vision loss duration
[a] comparison between RESCUE and REVERSE subjects, [b] p value from t-test, [c] p value from χ^2 test, [d] p values from paired t-tests

REVERSE: Visual acuity at baseline

Statistic	REVERSE	GS010 eyes	Sham eyes
N subjects	37		
N eyes with available data	74		
All eyes		Difference (NS)	
Mean LogMAR (SD)	1.6 (0.4)	1.66 (0.5)	1.55 (0.42)
Median LogMAR (range)	1.6 (0.7,3.2)	1.6 (0.8,3.17)	1.5 (0.7,2.81)
Best-seeing eyes			
Mean LogMAR (SD)	1.5 (0.4)	1.44 (0.33)	1.50 (0.38)
Median LogMAR (range)	1.5 (0.7,2.2)	1.45 (0.8, 2.09)	1.50 (0.7, 2.22)
Worst-seeing eyes			
Mean LogMAR (SD)	1.7 (0.5)	1.84 (0.55)	1.61 (0.48)
Median LogMAR (range)	1.6 (0.8,3.2)	1.6 (0.8, 3.17)	1.55 (0.9, 2.81)

[a] comparison between RESCUE and REVERSE subjects, [b] p-value for the difference in category distributions between RESCUE and REVERSE

logMAR: 0.0 = 20/20; 1.0 = 20/400

Even the best seeing eyes are legally blind

REVERSE: Top Line Results at Week 48 - SAFETY

Favorable safety profile of rAAV2/2-*ND4* (GS010) reported at 48 weeks**:**

- Most-common adverse events (AEs):
  - Ocular Inflammation: 33/37 GS010 eyes (3/37 SHAM eyes)
    - 8/37 GS010 eyes – Anterior uveitis only
    - 8/37 GS010 eyes – Intermediate uveitis only
    - 17/37 GS010 eyes – Anterior and intermediate uveitis
  - Punctate keratitis: 11/37 GS010 eyes (12/37 SHAM eyes)
  - IOP elevation: 10/37 GS010 eyes (1/37 SHAM eyes)

  ↳ Expected AEs, treatment responsive
- Only 1 Serious Adverse Event (systemic: myocardial infarction)
- No AEs led to discontinuation

REVERSE: Top Line Results at Week 48 - EFFICACY

- Clinically meaningful VA improvement in both eyes (-0.21 LogMAR on average)
- **No statistically significant difference** between treated and untreated eyes

Primary Efficacy Analysis

Change of LogMAR from Baseline to Week 48

Visual acuity (LogMAR)	n	LS Mean (SE) [a]	95% CI [a]	p-value
Change from Baseline to Week 48 **All-Treated Eyes**	37	**-0.218** (0.055)	-0.328, -0.108	
Change from Baseline to Week 48 **All-Sham Eyes**	37	**-0.211** (0.055)	-0.320, -0.101	
Difference between All-Treated Eyes and All-Sham Eyes Treatment Effect (95% CI)	37	-0.007 (-0.118, 0.103)		0.8942 [a]
Wilcoxon Signed-Rank Test				0.3875

[a] A mixed model of analysis of covariance (ANCOVA) was used with change from baseline at week 48 as the response, and subject, eyes of the subject as random factor, treatment and the baseline LogMAR value as covariates in the model.

Contradictory Data: Structure vs Function

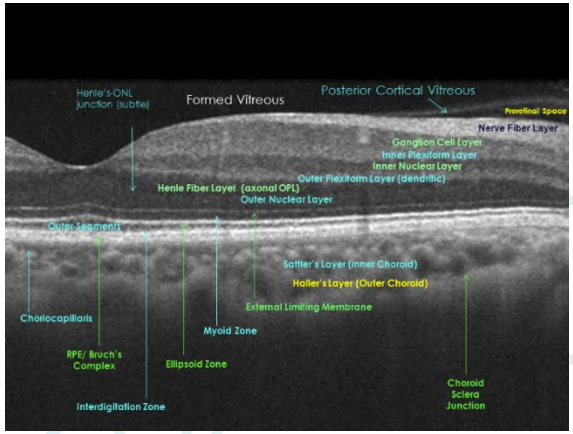
EFFICACY: tRNFL thickness significantly preserved in treated vs. untreated eyes

Secondary Efficacy Analysis
Change of RNFL Temporal Quadrant from Baseline to Week 48

RNFL Quadrant Temporal (µm)	n	LS Mean (SE) [a]	95% CI [a]	p-value
Change from Baseline to Week 48 **All-Treated Eyes**	37	**-0.6** (1.0)	-2.6, 1.4	
Change from Baseline to Week 48 **All-Sham Eyes**	35	**-3.4** (1.0)	-5.4, -1.3	
Difference between All-Treated Eyes and All-Sham Eyes Treatment Effect (95% CI)	35	**2.8 (0.2, 5.4)**		**0.0359** ANCOVA
Wilcoxon Signed-Rank Test				**0.0416**

[A mixed model of analysis of covariance (ANCOVA) was used with change from baseline at week 48 as the response, and subject, eyes of the subject as random factor, treatment and the baseline GCL Thickness/Volume value as covariates in the model.

First demonstration of neuro-protection of central nervous system AXONS in a human genetic disease



EFFICACY: GCL volume significantly preserved in treated vs. untreated eyes

➔ **Biological targets of rAAV2/2-*ND4* (GS010) were successfully engaged**

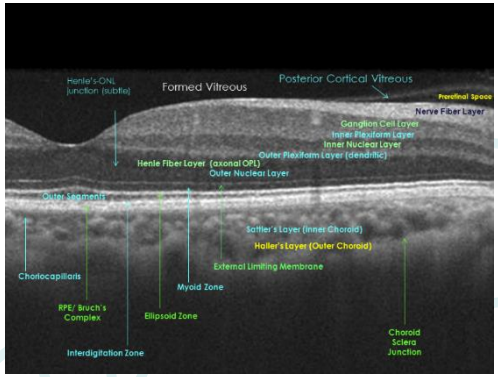
Secondary Efficacy Analysis

Change of GCL Volume from Baseline to Week 48

GCL Macular Volume (mm^3)	n	LS Mean (SE) [a]	95% CI [a]	p-value
Change from Baseline to Week 48 **All-Treated Eyes**	36	**-0.003** (0.012)	-0.028, 0.022	
Change from Baseline to Week 48 **All-Sham Eyes**	36	**-0.038** (0.012)	-0.062, -0.013	
Difference between All-Treated Eyes and All-Sham Eyes Treatment Effect (95% CI)	36	0.035 (0.006, 0.063)		**0.0189** ANCOVA
Wilcoxon Signed-Rank Test				**0.0448**

[a] A mixed model of analysis of covariance (ANCOVA) was used with change from baseline at week 48 as the response, and subject, eyes of the subject as random factor, treatment and the baseline GCL Thickness/Volume value as covariates in the model.

First demonstration of neuro-protection of NEURONS in a human genetic disease



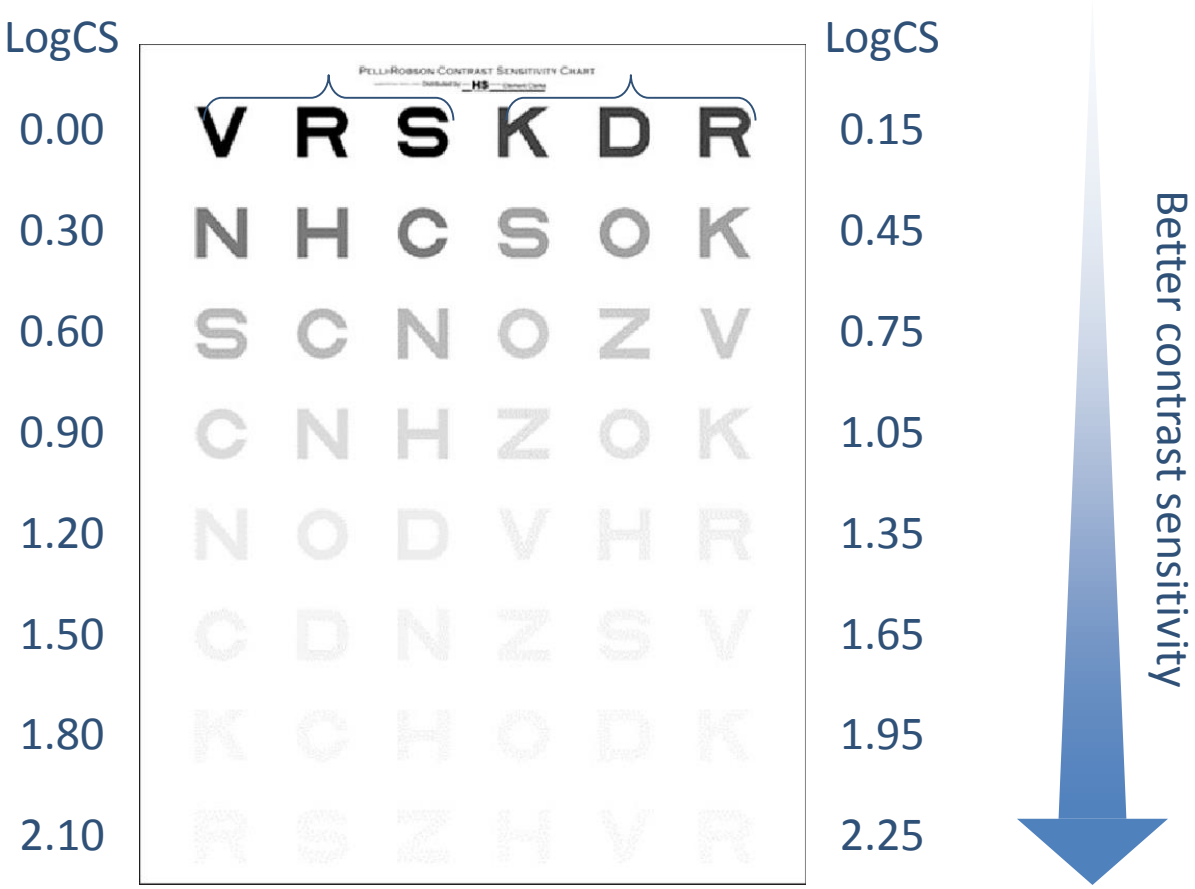
REVERSE: Results at Week 48 - Visual Field

- Humphrey® Visual Field (VF): mean deviation and foveal threshold
- **No difference** between treated and untreated eyes

VF Mean Deviation (dB)	Mean (SD)			
	n	GS010 eyes	n	Sham eyes
Baseline	37	-25.99 (8.37)	37	-24.94 (9.70)
Week 48	37	-22.83 (9.43)	37	-22.94 (9.80)
Change from baseline	37	3.15 (6.96)	37	2.00 (5.04)

REVERSE: Results at Week 48 - Contrast Sensitivity

Contrast sensitivity assessed using Pelli-Robson chart



Multiple sclerosis patients and controls have similar HCVA but MS patients have significantly lower LCVA

REVERSE: Results at Week 48 - Contrast Sensitivity

Contrast sensitivity assessed using Pelli-Robson chart

Log of Contrast Sensitivity (LogCS)	Mean (SD)			
	n	GS010 eyes	n	Sham eyes
Baseline	37	0.25 (0.40)	37	0.35 (0.46)
Week 48	37	0.45 (0.50)	37	0.43 (0.49)
Change from baseline	37	0.20 (0.36)	37	0.08 (0.28)

- At baseline: contrast sensitivity is worse in GS010 eyes (as seen with LogMAR visual acuity)
- **At Week 48:**
  - **In GS010-treated eyes, low contrast sensitivity: *almost doubled***
  - **In sham-treated eyes, low contrast sensitivity: *remained stable***
  - **Contrast sensitivity function anatomically located in the retinal ganglion cells**

P-value = 0.0220

REVERSE post-hoc analysis: visual acuity in on-chart best-seeing eyes

On-chart best-seeing eyes

Change from baseline in visual acuity (LogMAR)	n	Mean (SE)	95% Confidence Interval	ETDRS letters equivalent
Best-seeing GS010 eyes	12	-0.236 (0.082)	-0.405, -0.067	+12
Best-seeing Sham eyes	17	-0.075 (0.069)	-0.216, 0.067	+4
p-value [a]		*0.1466*		

[a] Significance of the difference between All-GS010 and All-Sham with respect to change of LogMAR from baseline

Source: PRA, *post-hoc* analysis

REVERSE post-hoc analysis: VA improvement, time from onset

On-chart eyes with VA improvement at Week 48

	Disease duration at baseline		
	6 to 9 months	9 to 12 months	Total
GS010 eyes	**12 (75%)**	4 (25%)	16
Sham eyes	8 (50%)	8 (50%)	16
Total	20	12	32

Source: PRA and internal *post-hoc* analysis

REVERSE post-hoc analysis: vision better than 20/200

- Based on generalized estimating equation (GEE) model to assess treatment effect, GS010-treated eyes were significantly more likely to be at or above the legal threshold for blindness (20/200) than sham-treated eyes (p=0.0005)

- Odds ratio = 18.45 (lower 95% boundary = 3.60) →

Treatment with GS010 makes an eye 18 times more likely to avoid vision worse than 20/200

Summary of Reverse Results : Visual Function

- **Primary efficacy endpoint of change of vision from baseline not achieved; both cohorts improved 0.2 logMAR from baseline**
- **GS010-treated eyes were significantly more likely to achieve 20/200 or better than sham eyes**
- **Contrast sensitivity showed almost doubling of CS in GS010 treated eyes compared to sham, a more sensitive test of visual function**
- **For subjects with better acuity at entry, (on chart, best eye) GS010-treated eyes improved by 0.236 logMAR compared to 0.075 for sham (delta of +8 ETDRS letters)**
- **Of eyes with vision loss 6-9 months, 75% showed improvement, compared to 25% for those with loss 9-12 months**
  - What was previously thought of as "early" is really "late"
- **When responder defined as improvement of 0.5 logMAR gain, 7 GS010 treated subjects were responders vs. but 1 for sham (p = 0.033)**

Summary of Reverse Results : Structure

- OCT data showed statistically significant protection of RGC layer from GS010 vs. sham (p=0.0189)
- OCT data showed statistically significant protection of tRNF from GS010 vs. sham (p=0.0359)

Possible Explanations

- **Default Fallacy: Because the results were unexpected placebo effect must be the cause**
  - Spontaneous improvement with 11778 LHON mutation exceedingly rare
- **High contrast visual acuity was the incorrect functional endpoint**
  - High contrast is an insensitive measure of visual function
  - Low contrast acuity much more sensitive and anatomically localizes to the retinal ganglion cells, the engaged biological target
- ***Hypothesis:* rAAV2/2-*ND4* (GS010) is systemically absorbed and smaller dose is delivered to the untreated eye**
  - Liver function tests may be transiently elevated in patients treated with rAAV2 vector
  - Neutralizing antibodies may form in patients [phase 1 results] and pre-clinical non-human primates
  - Retina & optic nerve are not immunologically compartmentalized protected zones

REVERSE topline results are only the start of the analysis

Remarkable structural success in eyes with very decreased vision and very severe baseline loss of RNFL and RGC

GenSight BIOLOGICS

REVERSE, an Unexpected Bilateral Effect of GS010

José-Alain Sahel, MD

Director, Institut de la Vision (Sorbonne-Universités/Inserm/CNRS), Paris
Chairman, Ophthalmology, Centre Hospitalier National d'Ophtalmologie des XV-XX, Paris
Professor and Chairman, Ophthalmology,
University of Pittsburgh School of Medicine and Medical Center

REVERSE results suggest a potential contralateral effect of GS010

GS010 mechanism of action:

- Allotopic expression of wild-type *ND4* gene can **rescue retinal ganglion cells (RGCs)** from LHON-induced apoptosis (Ellouze et al, AJHG, 2008)

Clinical observations 1 year after treatment with GS010:

- Improvement of visual acuity in both treated and untreated eyes **(in contrast to available natural history data)**
- Preservation of RNFL and GCL (retinal layers containing RGCs) in the treated eyes, and mild decrease in the untreated eyes
  - ➢ Biological targets of GS010 were engaged
- **Sustainability of effects** in both eyes for 1 year post-administration

These observations are unlikely to reflect a simple placebo effect in the untreated eye

Contralateral effects reported in the literature

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

- Other gene therapy for *ND4* LHON, unilateral IVT injection:

Visual acuity (LogMAR) Change from baseline to 36 months	**Injected Eye mean change**	**Uninjected Eye mean change**
Patients with ≤2 y duration (n= 4)	**–0.30**	**–0.35**

Negative change = visual acuity improvement

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

REFERENCE:
- Yang S, et al. Long-term outcomes of gene therapy for the treatment of Leber's hereditary optic neuropathy. EBioMedicine. 2016 Aug;10:258-68

Contralateral effect of anti-VEGF treatment

- Most common IVT drugs are anti-VEGF therapies (bevacizumab, ranibizumab)
  - Indication: vitreo-retinal disease producing macular edema secondary to increased vascular permeability

➢ Multiple clinical observations support the presence of **therapeutic effects on the untreated fellow eye** after an intravitreal injection in the contralateral eye

➢ Contralateral effect may be **facilitated by intraocular inflammation**

REFERENCES:

- Avery RL, et al. Intravitreal bevacizumab in the treatment of proliferative diabetic retinopathy. Ophthalmology 2006; 113(10): 1695, e1-15.
- Al-Dhibi H, Khan A. Bilateral response following unilateral intravitrealbevacizumab injection in a child with uveitic cystoid macular edema. J AAPOS 2009; 13: 400-402.
- Mintz-Hittner HA, Best LM. Antivascular endothelial growth factor for retinopathy of prematurity. Curr Opin Pediatr 2009;21:182-7.
- De Oliveira Maia Júnior O, et al. Bilateral choroidal neovascularization response to unilateral intravitreal Ranibizumab injection in a patient with angioid streaks. Rev Bras Oftalmol. 2013; 72 (4): 274-7
- Avery RL. Is a systemic effect of intravitreal anti-VEGF agents observable in the fellow eyes of patients treated for diabetic macular edema? Presentation at American Society of Retina Specialists, 2014.
- Avery RL, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. Br J Ophthalmol. 2014; 98 (2): 1636-1641.
- Hanhart J, et al. Fellow eye effect of unilateral intravitreal bevacizumab injection in eyes with diabetic macular edema. Eye 2014; 28: 646–653.
- Islidak H, et al. Therapeutic effect of anti-VEGF for age-related macular degeneration in the untreated fellow eye. Case Rep Ophthalmol Med 2018. Article ID 8561895

Contralateral axon regeneration follows unilateral stimulus

Unilateral eye injury in **animal models** triggers signals of axon regeneration:

- Response is also seen in **uninjured contralateral** retina/nerve
- Response in uninjured eye can sometimes be **delayed** by several weeks
- Response in uninjured eye is usually less important than in injured eye, but can sometimes be **not significantly different** from injured eye

➢ Caution is recommended when using contralateral retina/optic nerve as a control in study of degeneration

REFERENCES:

- Bodeutsch N, et al. Unilateral injury to the adult rat optic nerve causes multiple cellular responses in the contralateral site. J Neurobiol. 1999;30:116–128.
- Panagis L, et al. Unilateral optic nerve crush induces bilateral retinal glial cell proliferation. Eur J Neurosci. 2005 Apr;21(8):2305-9.
- Kanamori, et al. Long-term glial reactivity in rat retinas ipsilateral and contralateral to experimental glaucoma. Experimental Eye Research. Volume 81, Issue 1, July 2005, Pages 48-56.
- Gallego, et al. IOP induces upregulation of GFAP and MHC-II and microglia reactivity in mice retina contralateral to experimental glaucoma. Journal of Neuroinflammation 2012 9:92.
- Rojas, et al. Microglia in mouse retina contralateral to experimental glaucoma exhibit multiple signs of activation in all retinal layers. Journal of Neuroinflammation 2014 11:133.
- Cen, et al. Bilateral retinal microglial response to unilateral optic nerve transection in rats. Neuroscience. Volume 311, 17 December 2015, Pages 56-66.
- Sapienza *et al. Journal of Neuroinflammation* (2016) 13:44 DOI 10.1186/s12974-016-0509-7

Hypotheses to explain contralateral effect

Systemic effects of ocular gene therapy

- Small amounts of GS010 vector are detected in patients blood between 6h and 7 days after IVT injection
- IVT injection of AAV induces a systemic immune response (anti-AAV neutralizing antibodies)

  ➢ Is there another (non-systemic) route?

REFERENCES:

- Yamazaki M, et al. Neutralizing antibody titer against AAV post AAV-mediated intravitreal injection in cynomolgus monkey. ARVO Abstract 4548 - A0063. Honolulu, Hawaii, May 2018.
- Bouquet C, et al. Impact of sequential bilateral intravitreal injection of rAAV2/2-ND4 on ocular and systemic humoral immune status in non-human primates. ARVO Abstract 4537 - A0052. Honolulu, Hawaii, May 2018
- Katz B, et al. Intravitreal injection of rAAV2/2-ND4 in LHON: absence of correlation between ocular inflammation and humoral or cellular immune responses to AAV2. ARVO Abstract 4531 - A0046. Honolulu, Hawaii, May 2018.

Molecules can travel from one eye to the contralateral optic nerve

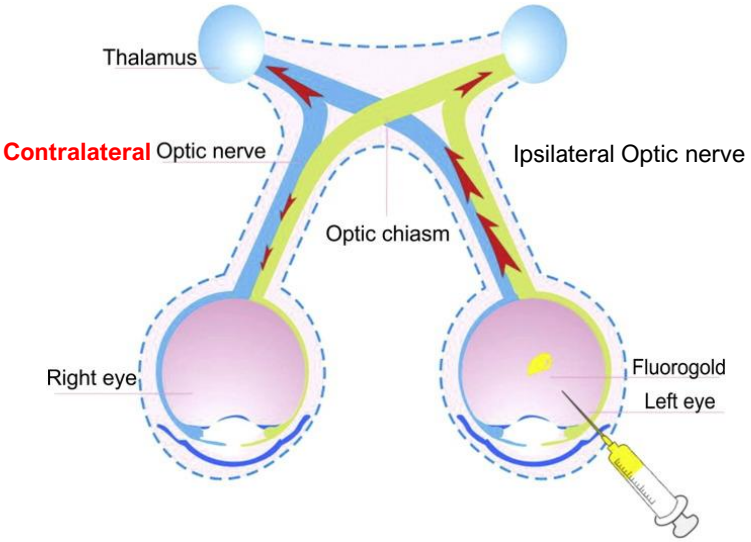
Fluorescent dye injected in **left eye** of rats:

- Most of the dye diffused to the **contralateral optic nerve**
- Only a small portion of the dye diffused to the posterior ipsilateral optic nerve

This phenomenon is also expected in humans:

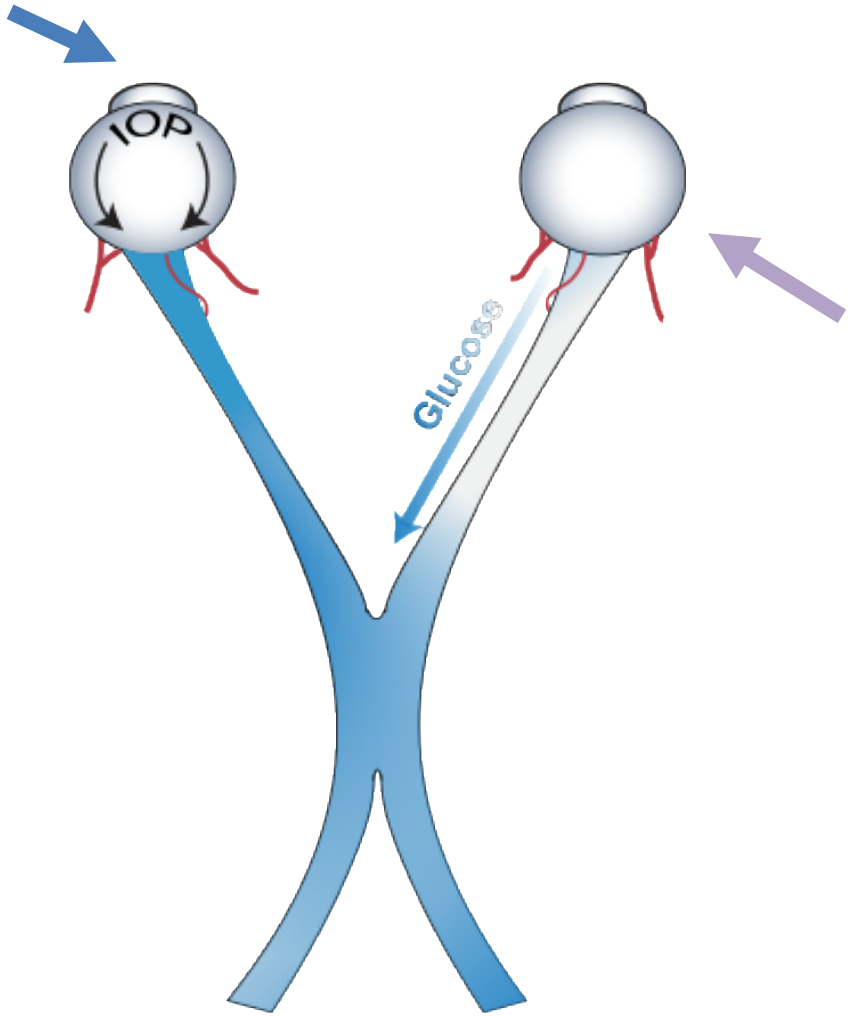
% RGCs that cross the optic chiasm	
Mice	95%
Primates	55%

Sprague-Dawley Rat



REFERENCE:
- Yang S, et al. Chemical and material communication between the optic nerves in rats. Clin Exp Ophthalmol. 2015 Nov;43(8):742-8

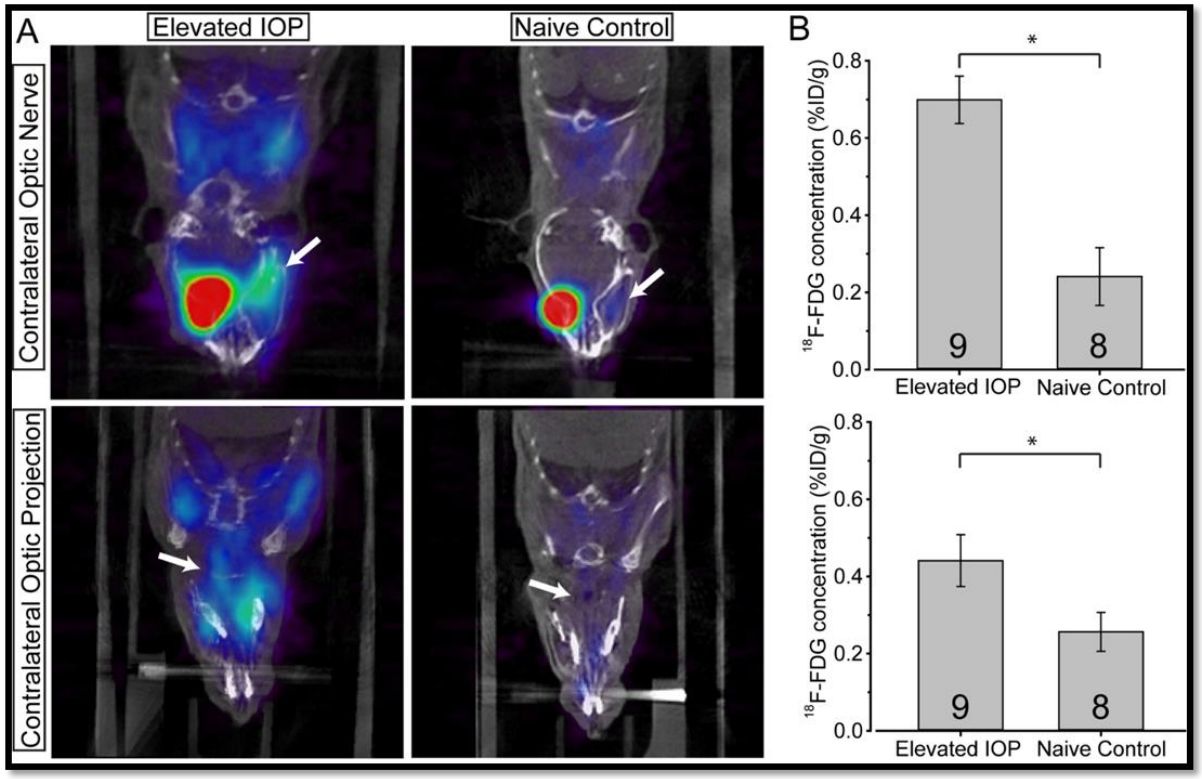
Experimental design: glucose transport measured via PET imaging

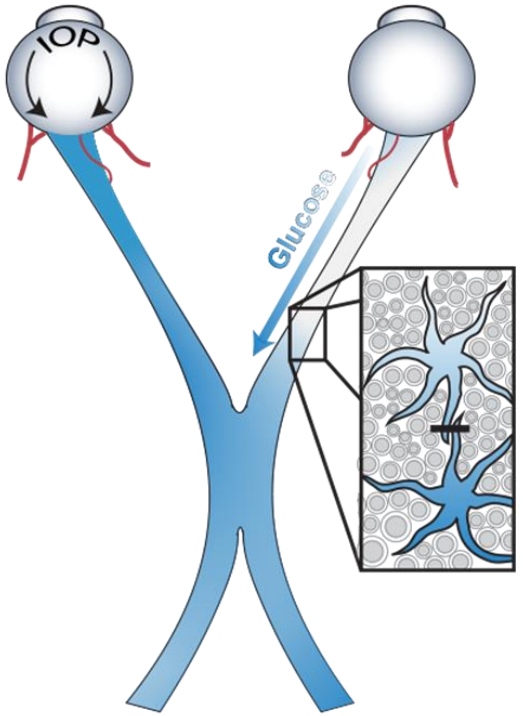


REFERENCE:

- Cooper et al. Abstract 2011 Energy Transfer Between Normal and Glaucomatous Optic Projections in Mice

Glaucomatous insult increases glucose mobility between optic projections, likely via astrocyte networks





REFERENCE:

- Cooper et al. Abstract 2011 Energy Transfer Between Normal and Glaucomatous Optic Projections in Mice

Regained vision in treated eye could induce reorganization of visual cortex

- **Experience modulates cortical circuits** through the concerted action of diverse cell types
  - Light stimulus induces specific changes in gene expression not only in neurons of the visual cortex, but also in non-neuronal cells responsible for neuronal connectivity, brain vasculature, and immunity

- We **hypothesize** that reactivation of the visual cortex following **treatment with GS010 in one eye** improved the functionality and maybe the connectivity of neurons connecting the macula of the **fellow eye**
  - In primates a significant number of optic fibers from the macula project on the ipsilateral cortex, with convergence of central fibers from both eyes (Parker A., 2007)

REFERENCE:

- Hrvatin S, at al. Single-cell analysis of experience-dependent transcriptomic states in the mouse visual cortex. *Nat Neurosci*. 2018 Jan;21(1):120-129
- Parker A. Binocular depth perception and the cerebral cortex, *Nat. Rev. Neurosci*. 2007, (8), 378-391.

KOL Panel, How to Interpret REVERSE?

Barrett Katz, MD
Chief Medical Officer

& Guest Speakers

Patients Perspectives & Expectations

Lissa Poincenot

LHON Advocate and Community Builder

Creator of LHON.org

Mother of an LHON Patient

Update on Regulatory Strategy for GS010

Bernard Gilly
Co-founder & Chief Executive Officer

Continuing engagement with EMA: Request post-REVERSE scientific advice

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Objectives

- Present and discuss statistically significant findings on structural anatomic endpoints – EMA aligned with FDA on the importance anatomic endpoints
- Present and discuss unexpected bilateral effect
- Highlight and discuss interesting trends from selected REVERSE post-hoc analyses
- Inform about refinement of REALITY study (Natural History) to include subjects treated with idebenone (Raxone) – indirect comparison to Raxone

Scientific Advice package to be sent on June 15 → advice expected Q3/Q4

Continuing engagement with the FDA: Request modification of SPA (REFLECT)

Objectives

- Present and discuss statistically significant findings on structural anatomic endpoints – EMA aligned with FDA on the importance anatomic endpoints
- Present and discuss unexpected bilateral effect
- Highlight and discuss interesting trends from selected REVERSE post-hoc analyses
- Discuss potential modifications (*under development*) to current SPA

MAA and BLA targeted for Q2 2019 as previously planned

Q&A Session

Thomas Gidoin
Chief Financial Officer

Closing Remarks

Bernard Gilly
Co-founder & Chief Executive Officer