Recovery of Cone-Mediated Vision in a Severe Ciliopathy after Gene Therapy: Use of Complementary Readouts in a Phase Ib/IIa Trial for *LCA5*-LCA

May 28, 2025

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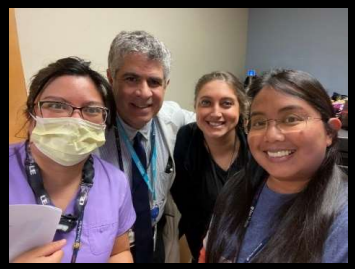
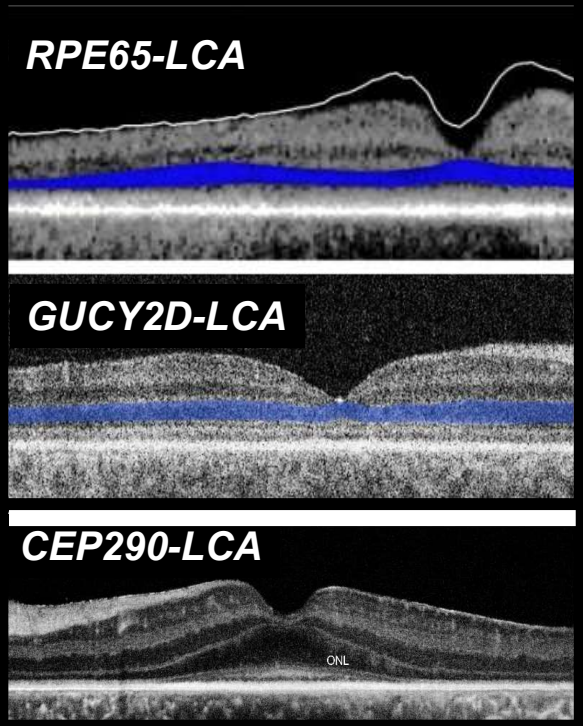


Outline

- Assessing safety + efficacy of gene-based Tx in a different scenario in LCA.
- Using mechanism-based complementary readouts.

LCA as Target for Gene Augmentation

Favored scenario: Structural-Functional Dissociation



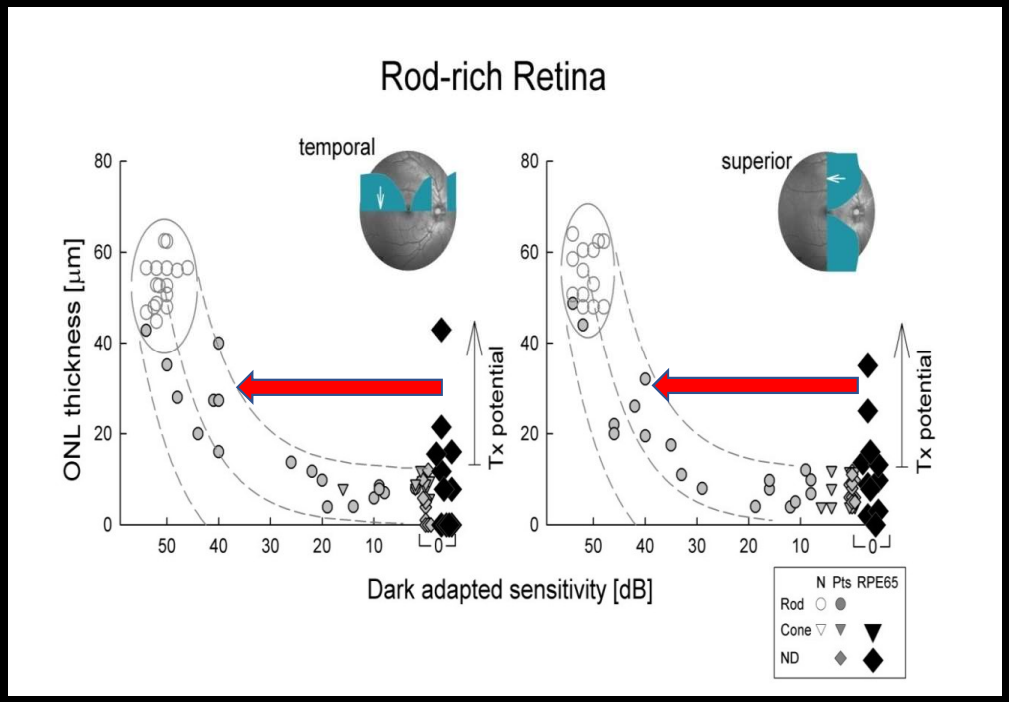
- Detectable photoreceptors in blind patients

Identifying photoreceptors in blind eyes caused by *RPE65* mutations: Prerequisite for human gene therapy success

Samuel G. Jacobson*†, Tomas S. Aleman*, Artur V. Cideciyan*, Alexander Sumaroka*, Sharon B. Schwartz*, Elizabeth A. M. Windsor*, Elias I. Traboulsi‡, Elise Heon§, Steven J. Pittler¶, Ann H. Milam*, Albert M. Maguire*, Krzysztof Palczewski‖, Edwin M. Stone**, and Jean Bennett*

PNAS | April 26, 2005 | vol. 102 | no. 17 | 6177–6182

A promising relationship between retinal structure and vision



Structural-Functional Dissociation:
Disproportionate loss of vision in spared photoreceptors

Identifying photoreceptors in blind eyes caused by *RPE65* mutations: Prerequisite for human gene therapy success

Samuel G. Jacobson*†, Tomas S. Aleman*, Artur V. Cideciyan*, Alexander Sumaroka*, Sharon B. Schwartz*, Elizabeth A. M. Windsor*, Elias I. Traboulsi‡, Elise Heon§, Steven J. Pittler¶, Ann H. Milam*, Albert M. Maguire*, Krzysztof Palczewski‖, Edwin M. Stone**, and Jean Bennett*

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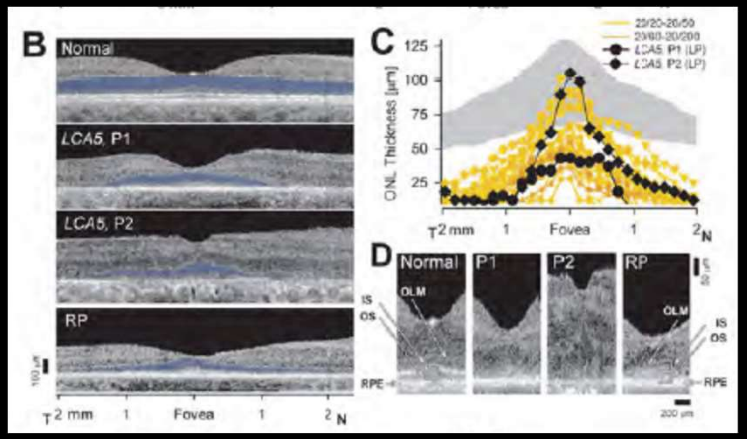
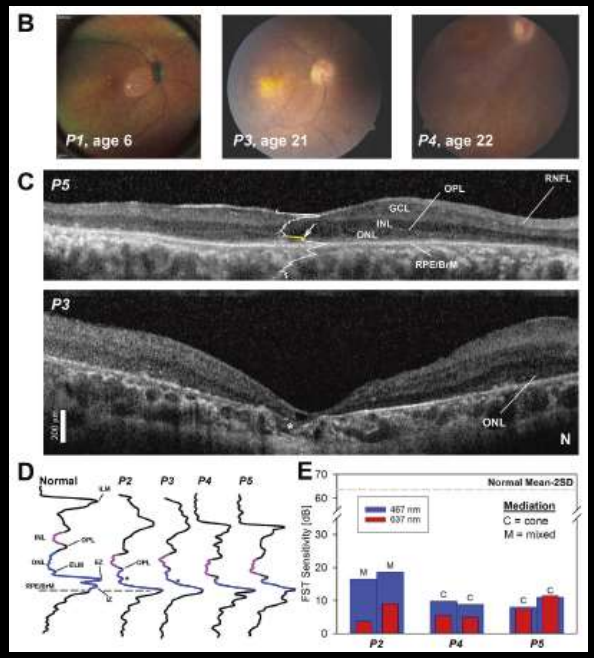
LCA5-LCA: A Severe IRD Model

Samuel G. Jacobson, MD, PhD





- ~2% of all LCA.
- Severe structural and functional phenotype.
- ONL and POS may be relatively spared.
- Detectable (mainly) cone function.

Leber congenital amaurosis caused by *Lebercilin* (*LCA5*) mutation: Retained photoreceptors adjacent to retinal disorganization

Samuel G. Jacobson,[1] Tomas S. Aleman,[1] Artur V. Cideciyan,[1] Alexander Sumaroka,[1] Sharon B. Schwartz,[1] Elizabeth A.M. Windsor,[1] Malgorzata Swider,[1] Waldo Herrera,[1] Edwin M. Stone[2]

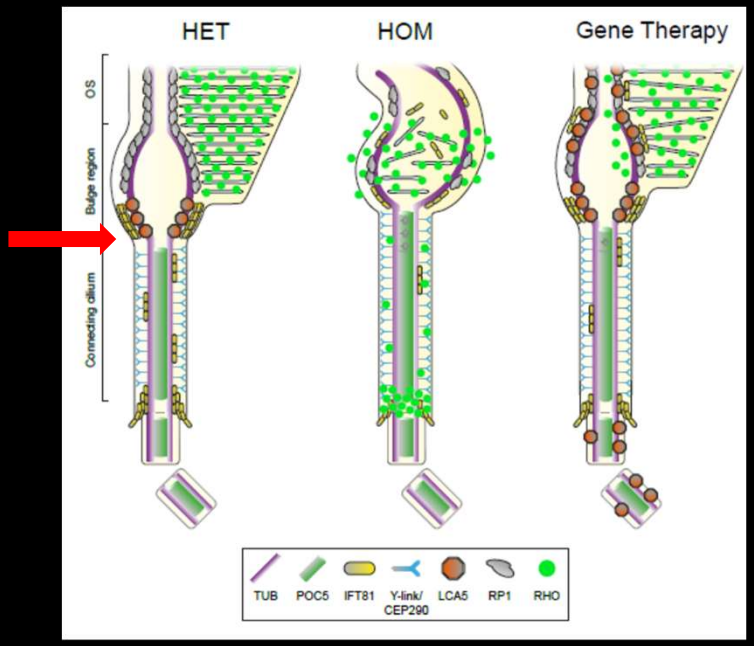
Molecular Vision 2009; 15:1098-1106

Treatment Potential for *LCA5*-Associated Leber Congenital Amaurosis

Katherine E. Uyhazi,[1,2] Puya Aravand,[1] Brent A. Bell,[1] Zhangyong Wei,[1] Lanfranco Leo,[1] Leona W. Serrano,[2] Denise J. Pearson,[1,2] Ivan Shpylchak,[1] Jennifer Pham,[1] Vidyullatha Vasireddy,[1] Jean Bennett,[1] and Tomas S. Aleman[1,2]

IOVS | May 2020 | Vol. 61 | No. 5 | Article 30

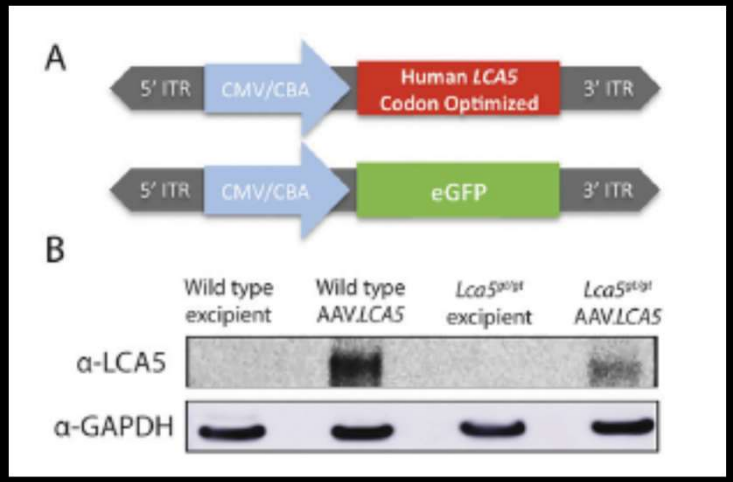
LCA5-LCA: a ciliopathy

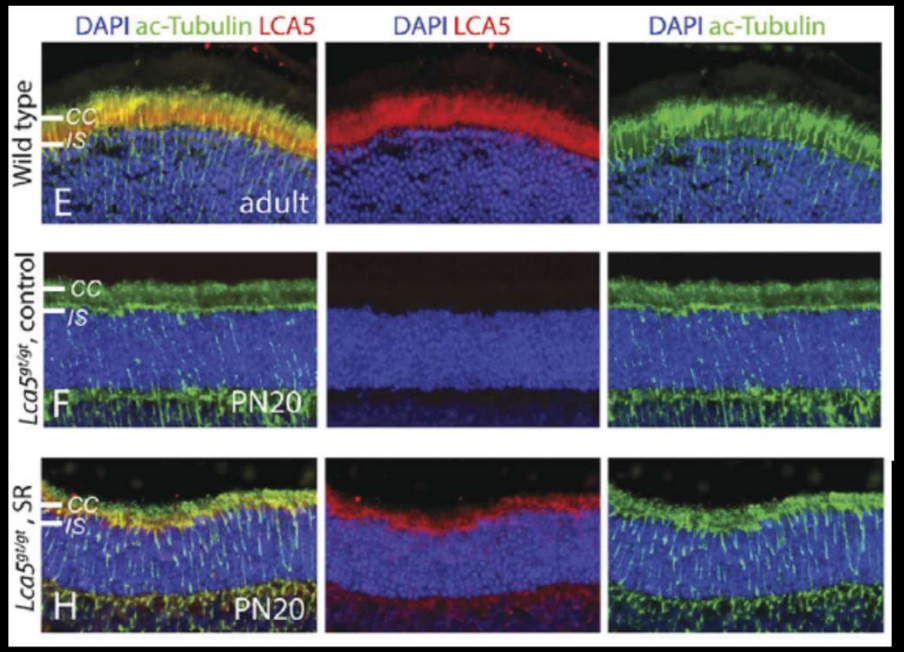


Faber et al. JCI Insight. 2023;8:e169162.

- *Lebercilin* localizes to the bulge region of the photoreceptor outer segment
- Involved in intraflagelar transport and outer segment morphogenesis.

Proof-of-Concept: Delivery of AAV8 human *LCA5*



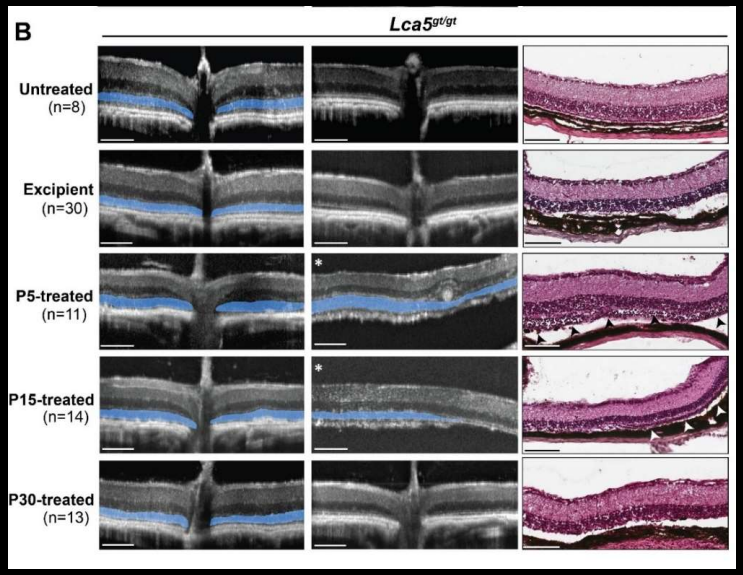


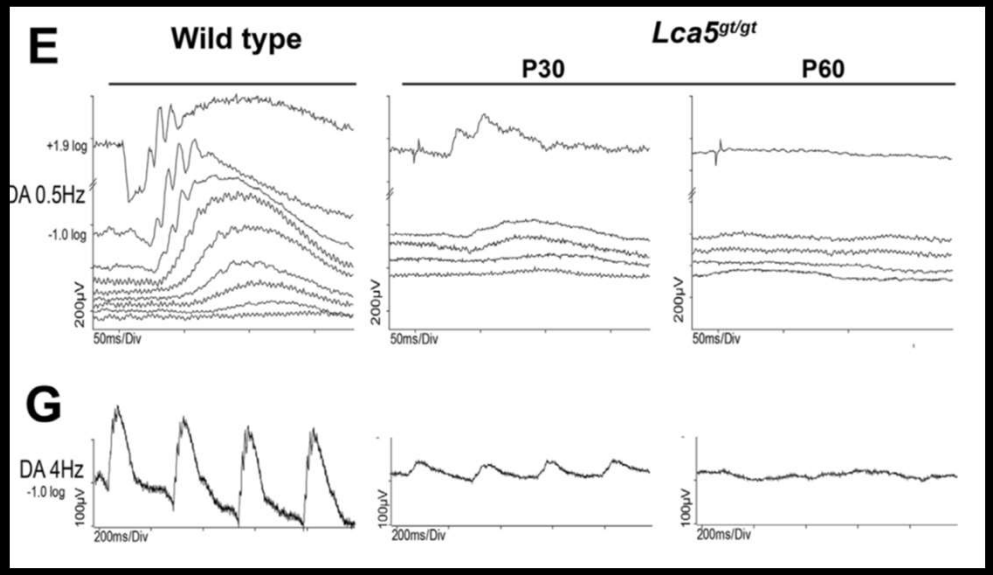
- AAV8.CMV/CBA.hLCA transgene causes strong lebercillin expression in photoreceptors.

Amelioration of Neurosensory Structure and Function in Animal and Cellular Models of a Congenital Blindness

Molecular Therapy Vol. 26 No 6 June 2018

Proof-of-concept: Treatment of a Severe IRD Model





- Documented rescue of structural and functional phenotype.
- Dependent on age at treatment.

Katerine Uyhazi, MD, PhD

Treatment Potential for *LCA5*-Associated Leber Congenital Amaurosis

Katherine E. Uyhazi,[1,2] Puya Aravand,[1] Brent A. Bell,[1] Zhangyong Wei,[1] Lanfranco Leo,[1] Leona W. Serrano,[2] Denise J. Pearson,[1,2] Ivan Shpylchak,[1] Jennifer Pham,[1] Vidyullatha Vasireddy,[1] Jean Bennett,[1] and Tomas S. Aleman[1,2]

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OPGx-LCA5-1001 Study to Treat a Severe Photoreceptor Disease

Protocol Design

- Phase 1b/2a, open-label of a uniocular subretinal injection of OPGx-LCA5.
- Nonrandomized, single ascending, dose escalation (**1E10 vg/eye**, 3E10 vg/eye, and 1E11 vg/eye) unilaterally injected.
- Minimum of 3 evaluable patients are treated at each dose level.
- Preliminary results to 1 year in three patients.

Protocol Design: OPGx-LCA5-1001 Study

Primary Objective	Primary Endpoints
Safety and tolerability	1. Number of dose limiting toxicity (DLT) events. 2. Number of procedure- or OPGx-hLCA5-related adverse events (AEs). 3. Change in vision and/orretinal structure.

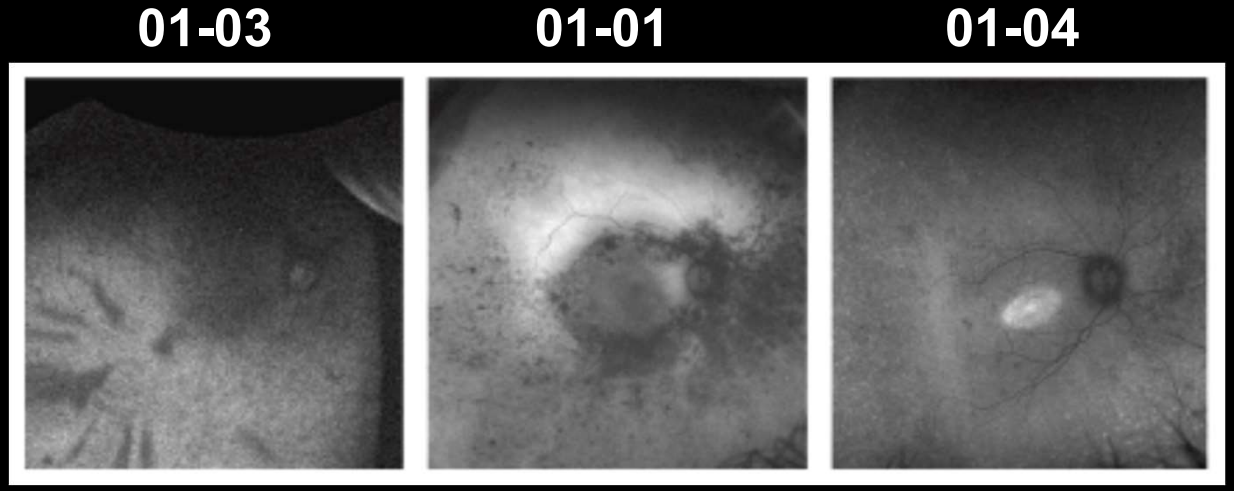
Secondary Objective	Secondary Endpoints (for presentation)
Assess the efficacy	1. Dark-adapted full-field sensitivity testing (FST). 2. Dark-adapted transient pupillary light reflexes (TPLR). 3. Best Corrected Visual Acuity. 4. Microperimetry 5. Orientation and Mobility.

Characteristics of Patients

Study ID	Age*/ Gender	Date IP Administration	Study Eye	LCA5 Variants† Allele 1/Allele 2	Visual Acuity‡		Refraction§		Foveal Thickness [µm]			
									BL		3MO	
					OD	OS	OD	OS	OD	OS	OD	OS
0103	26/M	07Aug2023	OS	Gln279*/Gln279*	HM	HM	+3.00	+3.00	121	NA	136	133.5
0101	34/F	11Sep2023	OS	Arg255Gln/del. Exon 1	20/300	20/400	-1.50	-2.50	123.5	127.1	127.1	119.3
0104	19/F	13Nov2023	OD	Arg255*/Arg255*	20/200	20/200	+2.25	+2.00	232.2	226.5	170.8	205.1

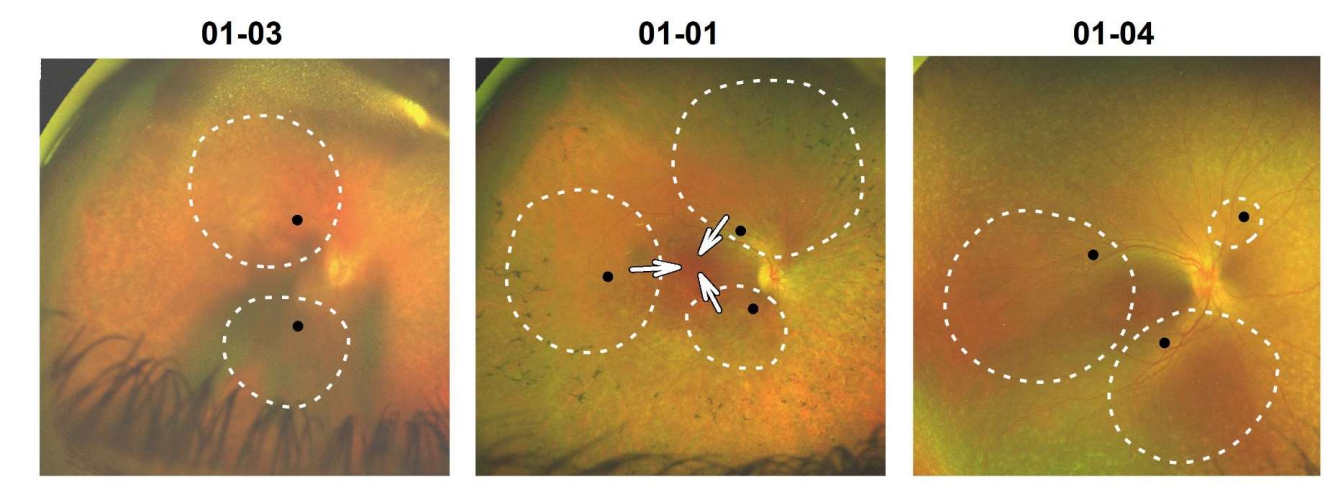
- Mutations led to non-functional proteins.
- Poor VA.

Same phenotype diverse severity



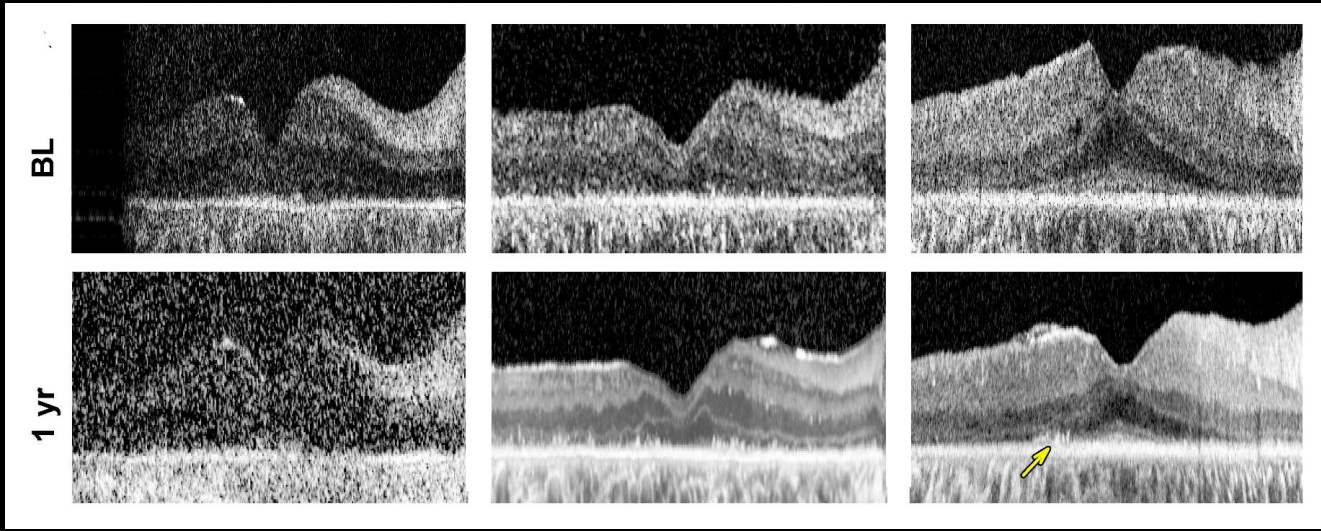
- Severe disease, ‘relative’ central to midperipheral sparing.

Uneventful Subretinal Injections



- 300 ml total volume.
- Multiple SR injections, shallow blebs that initially spare the fovea.
- Slow extension to the fovea during fluid air exchange.

Safety: Central Retinal Structure



- Retina reattached.
- No major changes post-TX.
- One patient showed hyperreflectivities above RPE; considered not inflammatory.

Safety and Tolerability

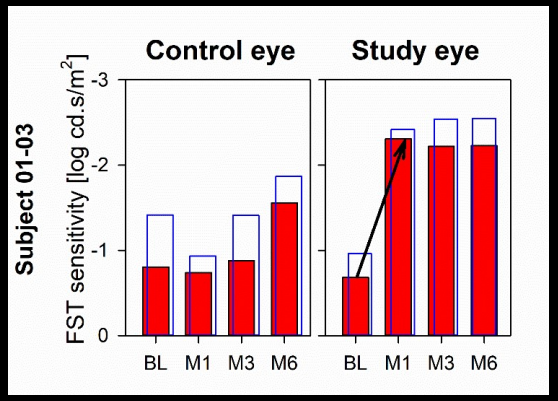
Subject	Date of onset	Date of Resolution	Diagnosis (if known) or Sign/ Symptoms (list one per AE)	Ocular AE?	Specify eye(s)	Severity	Unexpected	Serious	Frequency	Outcome	Relationship to Investigational Product	Action taken (Add all that apply):
0101	11-SEP-2023	12-SEP-2023	Eye Pain	Yes	Study	Grade 1 - Mild	No	No	Intermittent	Recovered/ Resolved	Unrelated	2 = Con Med (enter on Con Meds Page)
0101	18-SEP-2023	18-SEP-2023	Corneal Abrasion	Yes	Study	Grade 1 - Mild	No	No	Single Episode	Recovered/ Resolved	Unrelated	2 = Con Med (enter on Con Meds Page) 3 = Other
0103	07-AUG-2023	08-AUG-2023	Eye Pain	Yes	Study	Grade 1 - Mild	No	No	Intermittent	Recovered/ Resolved	Unrelated	2 = Con Med (enter on Con Meds Page)
0104	08-AUG-2023	14-NOV-2023	Eye Pain	Yes		Grade 1 - Mild	No	No	Continuous	Recovered/ Resolved	Unrelated	2 = Con Med (enter on Con Meds Page)

- No dose limiting toxicities.
- AE were anticipated, mild and not related to OPGx-LCA5.
- All resolved.

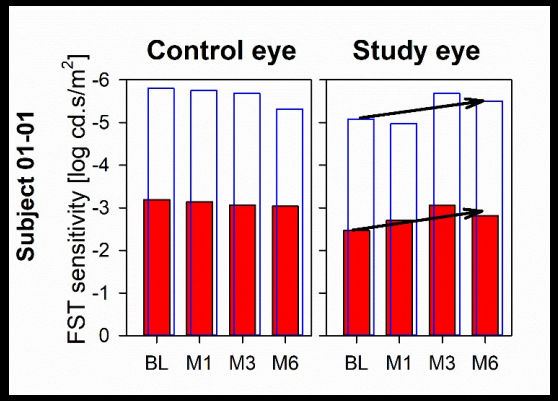
Full-fields Stimulus Testing

LARGE GAINS IN CONE-MEDIATED SENSITIVITIES

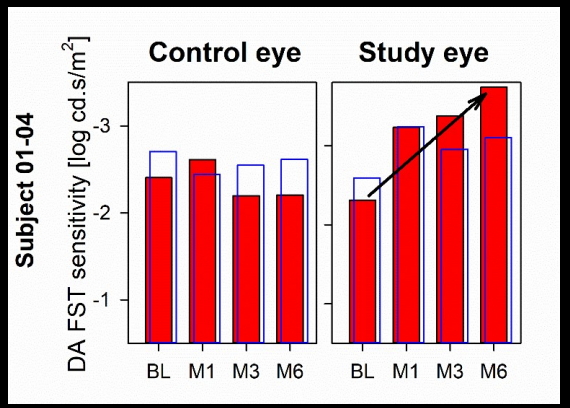
01-03



01-01



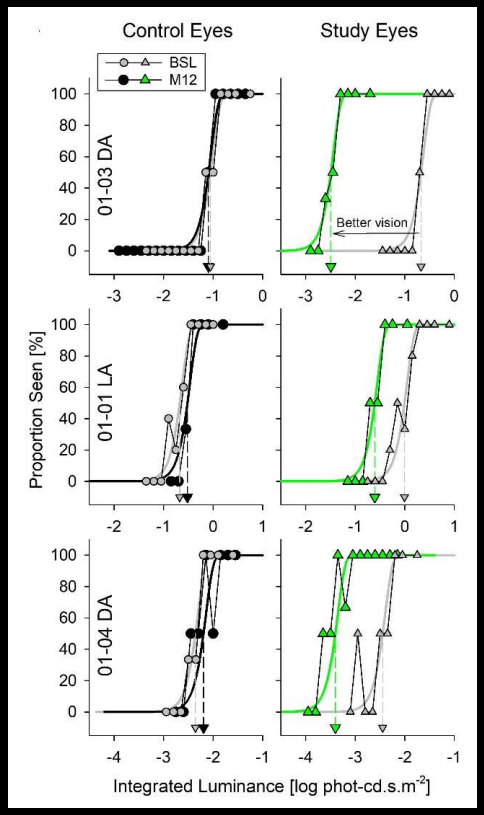
01-04

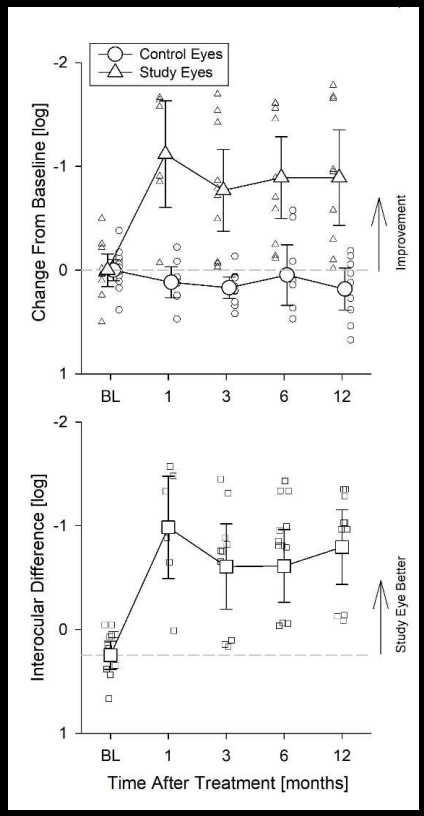


- ~1.5 log u. gain in cone-mediated sensitivity compared to control and to baseline (BL) in 01-03 and 01-04.
- Similar differences for red (red bars) and blue (blue outlined bars) stimuli = no change in photoreceptor mediation.
- Modest change in 01-01 – > rod mediated FST.

Gains in Cone Mediated Sensitivities

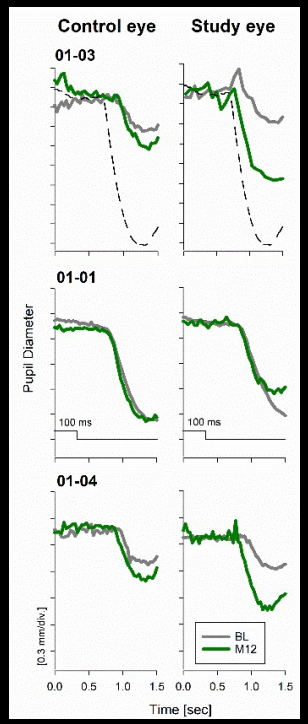
USE OF LIGHT-ADAPTED FSTs





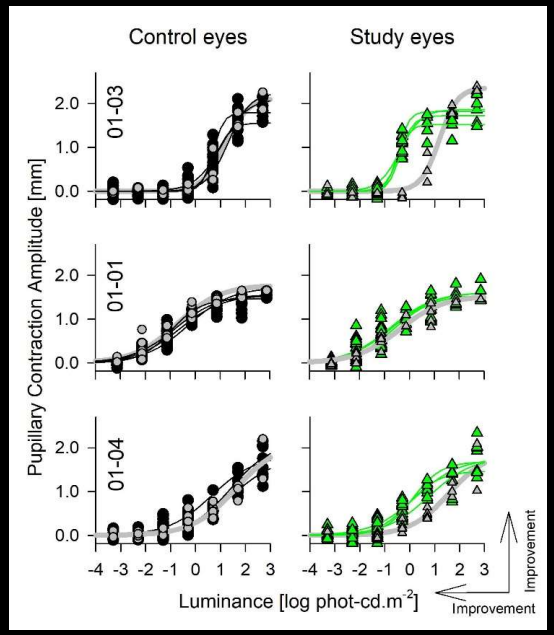
- Average 1 log unit gains in cone-mediated sensitivities (light adapted in 01-01)
- in all three patients compared to baseline (BL) and contralateral control eye

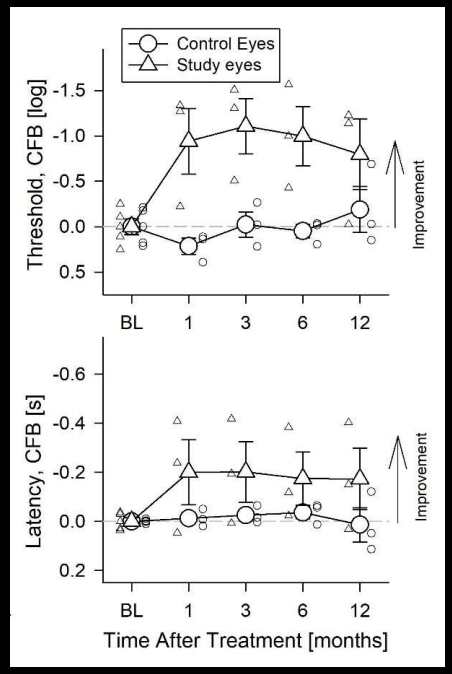
Pupillometry Objectively Confirms Efficacy



- Dark-adapted pupil responses are faster after treatment (*green traces*) compared to baseline (*gray traces*). Control eye is unchanged.

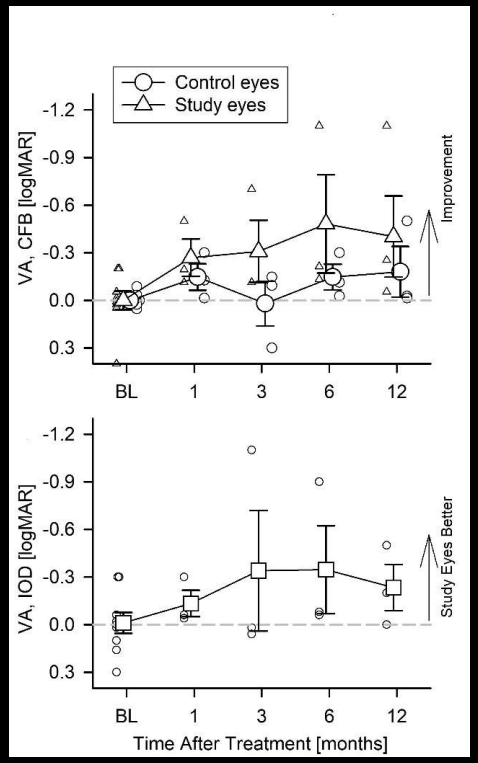
Pupillometry Objectively Confirms Efficacy





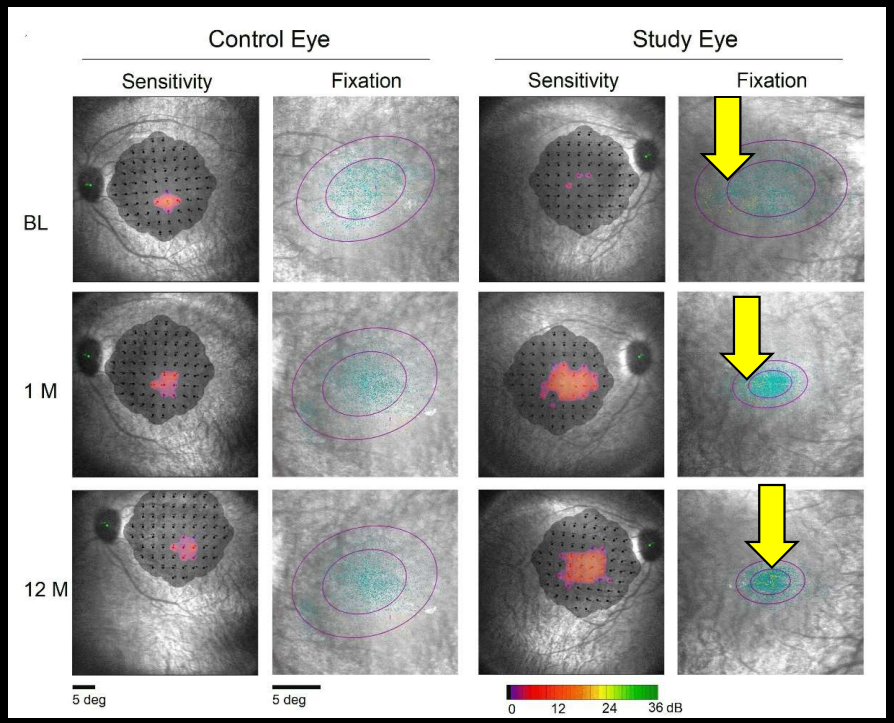
- Pupil responses are more sensitive (left shifted green symbols) compared to baseline (gray curves).
- Thresholds are improved by ~1 log u., faster TPLR is by ~0.2 seconds.
- Sensitivity gains objectively support FSTs gains.

Visual Acuity Gains



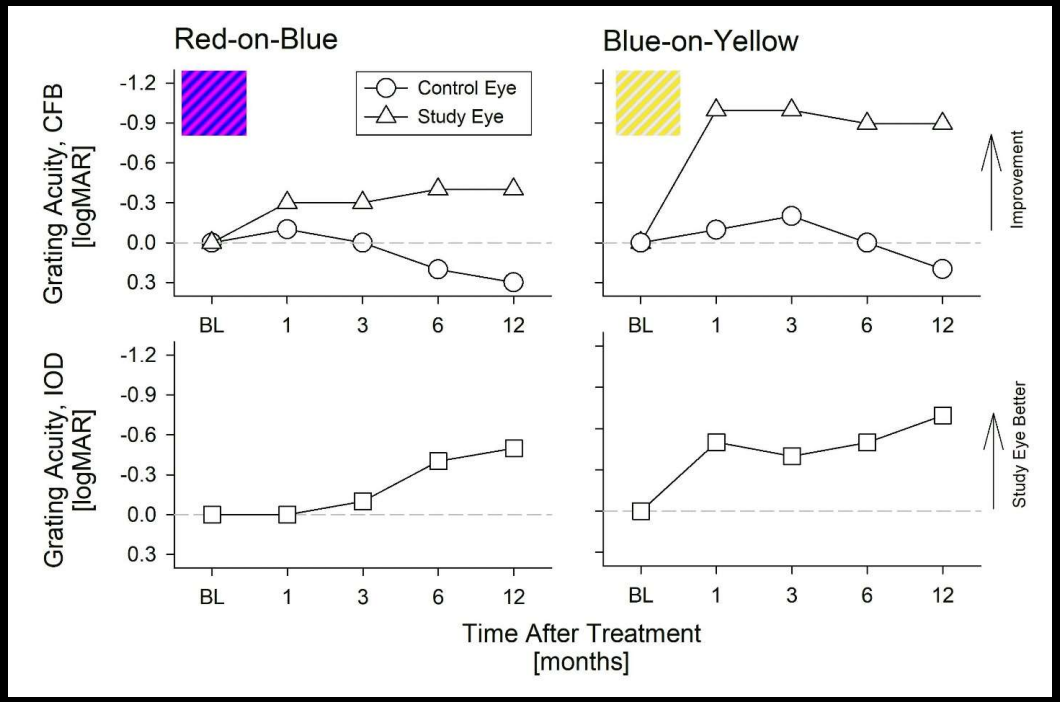
- Formed vision possible for the first time in most affected.
- On average better VAs in treated compared to baseline (BL) and untreated eye.

Restoration of the Fovea
Retina Tracking Perimetry [01-04]



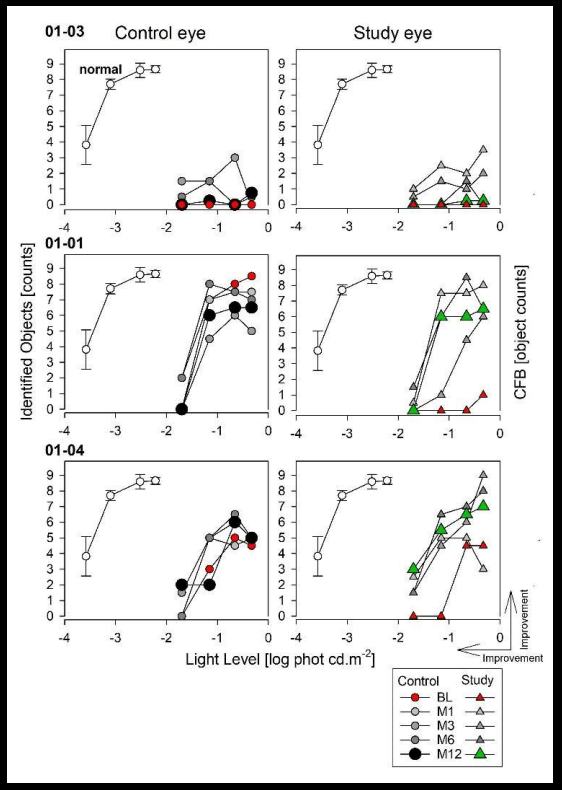
- Sensitivity gain post-treatment; no changes in control eye.
- Movement to a more stable fixation to the foveal center.

Chromatic Grating Acuity



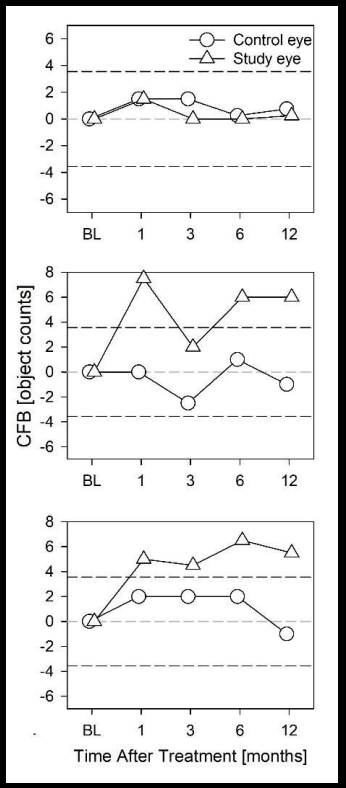
- Improvements in cone-specific resolution between 0.3 and 1 log MAR.

Functional Vision by D-MMLT



- Improved orientation and mobility (green up triangles) detected from earliest time point after treatment reproducible to 12 months post-treatment.

Functional Vision by D-MMLT



- Improvement in orientation and mobility (up triangles) in two patients exceeds variability of the test up to 12 months post-treatment.

Conclusions:

- Gene augmentation demonstrated robust biologic efficacy in LCA5.
- Efficacy corroborated through multiple mechanistically driven readouts.
- Treatment efficacy is possible in a severe neurodegeneration.
- Inclusion of earlier disease stages in clinical trials is needed.

Awarded FDA grant to continue trial.

Dosed 2 additional pediatric patients.