



# Recovery of Cone-Mediated Vision in a Severe Ciliopathy after Gene Augmentation: One Year Results of a Phase Ib/IIa Trial for *LCA5-LCA*

May 4, 2025

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## Disclosures

VR Intellectual property licensing through the Univ. of Pennsylvania

### Clinical trial support

Opus Genetics

Atsena Therapeutics

Editas Medicine

Spark Therapeutics

Beacon

### Additional Support

Research to Prevent Blindness

Mackall Trust Fund

F.M. Kirby Foundation

Pennsylvania Lions Sight Conservation & Eye Research Foundation



# Thanks to my closest collaborators!



## Clinical Team

- Elena Aleman
- Jean Bennett
- Emma Bedoukian
- Artur Cideciyan
- Alexandra Garafalo
- Katherine Maguire
- Albert Maguire
- Erin O'Neil
- Kelsey Parchinski
- Alejandro Roman
- Arlene Santos
- Drew Scoles
- Alexander Sumaroka
- Malgorzata Swider
- Katherine Uyhazi
- Mariejel Weber

## CAROT

- Junwei Sun
- William Chung
- Shangzhen Zhou
- Tiffany Kincaid
- Jieyan Pan

## FFB:

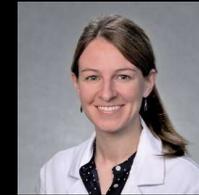
- David Brint
- Rusty Kelley
- Peter Ginsberg
- Jason Menzo

## Opus:

- Ash Jayagopal
- Sarah Tuller
- Ben Yerxa



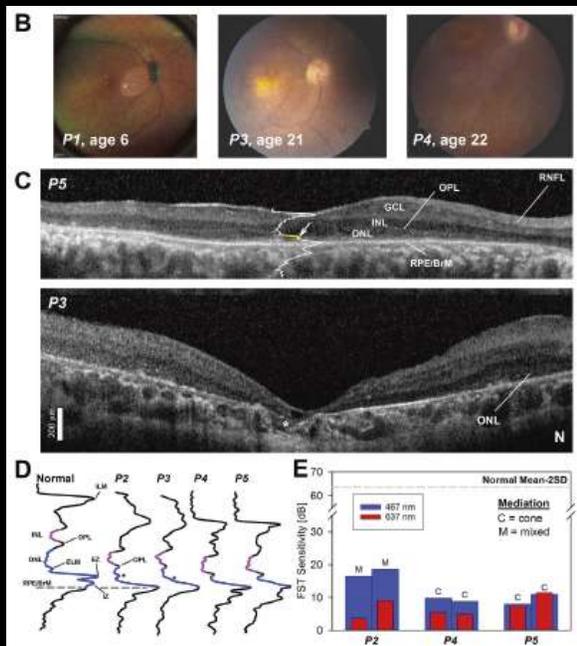
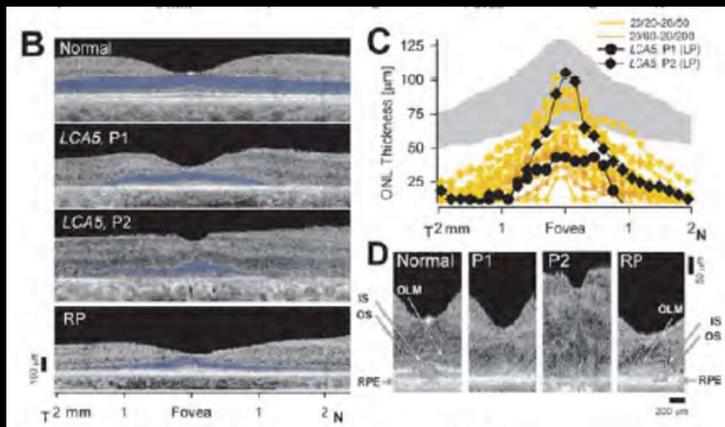
Jean Bennett & Albert M. Maguire



Artur V. Cideciyan



# 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,<sup>1</sup> Tomas S. Aleman,<sup>1</sup> Artur V. Cideciyan,<sup>1</sup> Alexander Sumaroka,<sup>1</sup> Sharon B. Schwartz,<sup>1</sup> Elizabeth A.M. Windsor,<sup>1</sup> Malgorzata Swider,<sup>1</sup> Waldo Herrera,<sup>1</sup> Edwin M. Stone<sup>2</sup>

*Molecular Vision* 2009; 15:1098-1106

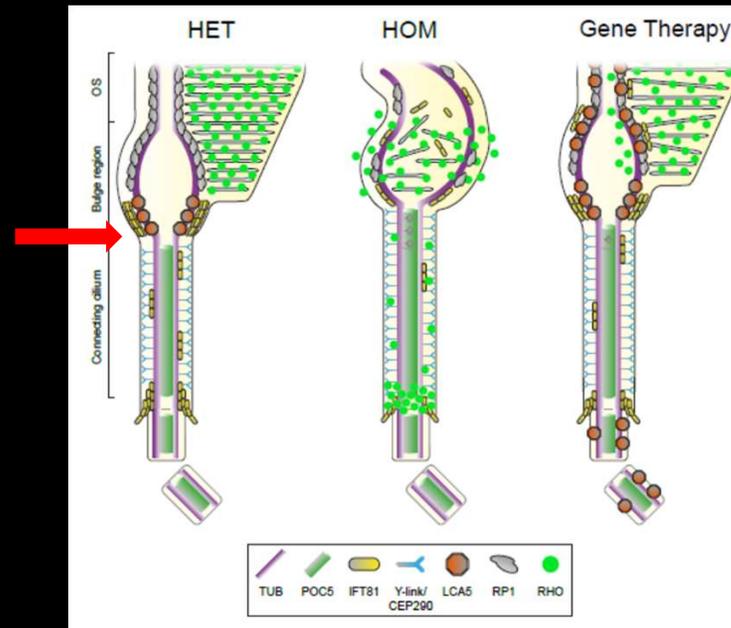
**Treatment Potential for *LCA5*-Associated Leber Congenital Amaurosis**

Katherine E. Uyhazi,<sup>1,2</sup> Puya Aravand,<sup>1</sup> Brent A. Bell,<sup>1</sup> Zhangyong Wei,<sup>1</sup> Lanfranco Leo,<sup>1</sup> Leona W. Serrano,<sup>2</sup> Denise J. Pearson,<sup>1,2</sup> Ivan Shpylychak,<sup>1</sup> Jennifer Pham,<sup>1</sup> Vidyulatha Vasireddy,<sup>1</sup> Jean Bennett,<sup>1</sup> and Tomas S. Aleman<sup>1,2</sup>

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



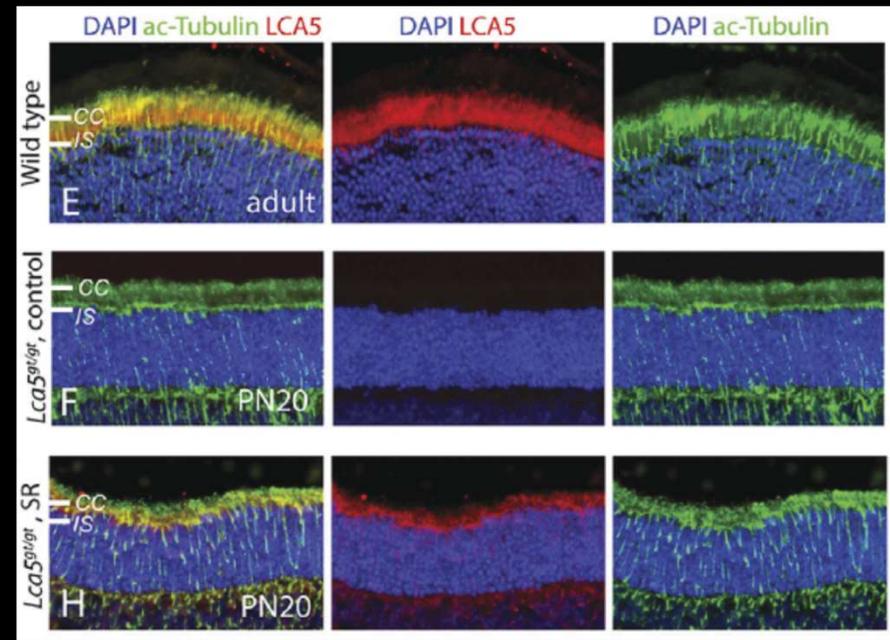
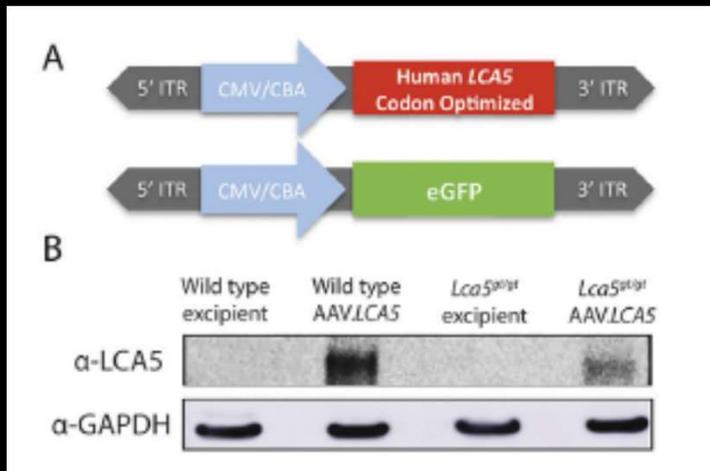
## LCA5-LCA: a ciliopathy



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

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

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



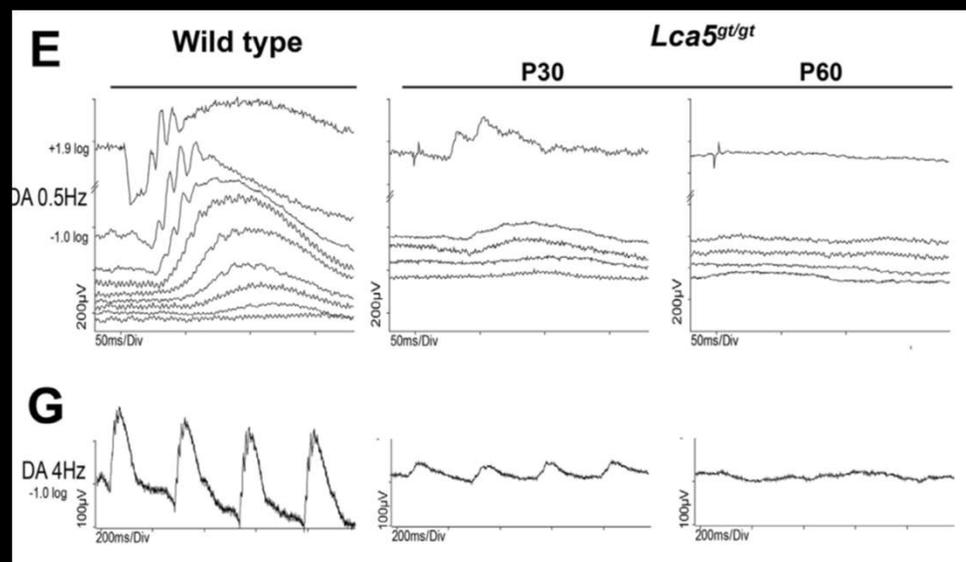
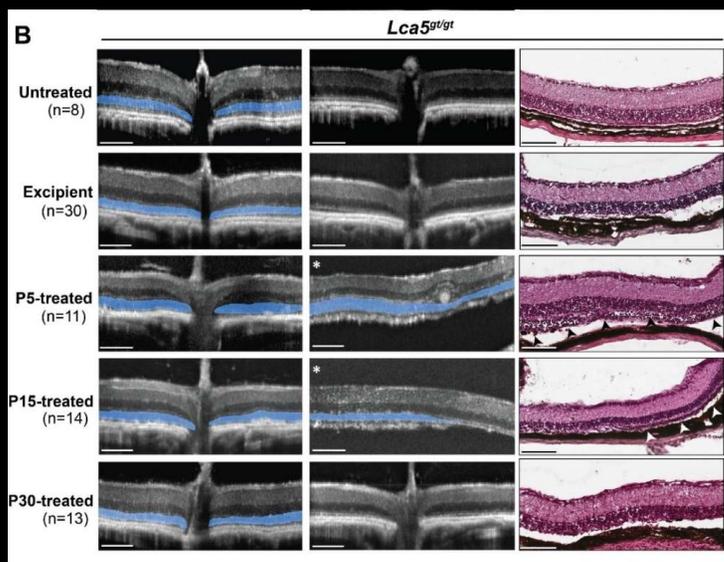
- AAV8.CMV/CBA.hLCA transgene causes strong lebercillin expression in photoreceptors.

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

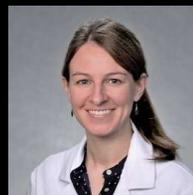
Yan Song,<sup>1</sup> Para Aravand,<sup>1,2</sup> Sergei Nikonorov,<sup>1,2,3</sup> Larissa Luo,<sup>1,2</sup> Arkady Lyubskiy,<sup>1,2</sup> Jenette L. Benavides,<sup>1</sup> Jeyan Pan,<sup>1</sup> Zhongyong Wei,<sup>1</sup> Yan Shykhahk,<sup>1</sup> Prasad Harima,<sup>1</sup> David J. Benetti,<sup>1</sup> Nikolaos Constantinos,<sup>1</sup> Albert M. Maguire,<sup>1</sup> Jennifer Pham,<sup>1</sup> Anwar I. den Hollander,<sup>1,2</sup> Frans P.M. Cremers,<sup>1,2</sup> Robert K. Koehnke,<sup>1</sup> Ronald Roepman,<sup>1</sup> Fany Nishina,<sup>1</sup> Shaoguo Zhou,<sup>1</sup> Wei Pan,<sup>1</sup> Gui-shuang Yang,<sup>1</sup> Tomas S. Aleman,<sup>1</sup> Henry de Abajo,<sup>1</sup> Han McKinnon,<sup>1</sup> James Sun,<sup>1</sup> Isaac Mills,<sup>1</sup> and Ivan Mody,<sup>1</sup>

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,<sup>1,2</sup> Puya Aravand,<sup>1</sup> Brent A. Bell,<sup>1</sup> Zhangyong Wei,<sup>1</sup> Lanfranco Leo,<sup>1</sup> Leona W. Serrano,<sup>2</sup> Denise J. Pearson,<sup>1,2</sup> Ivan Shpylychak,<sup>1</sup> Jennifer Pham,<sup>1</sup> Vidyullatha Vasireddy,<sup>1</sup> Jean Bennett,<sup>1</sup> and Tomas S. Aleman<sup>1,2</sup>



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



## Protocol Design

- Phase 1b/2a, open-label of a unocular 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
<b>Safety and tolerability</b>	<ol style="list-style-type: none"><li>1. Number of dose limiting toxicity (DLT) events.</li><li>2. Number of procedure- or OPGx-hLCA5-related adverse events (AEs).</li><li>3. Change in vision and/orretinal structure.</li></ol>
Secondary Objective	Secondary Endpoints (for presentation)
<b>Assess the efficacy</b>	<ol style="list-style-type: none"><li>1. Dark-adapted full-field sensitivity testing (FST).</li><li>2. Dark-adapted transient pupillary light reflexes (TPLR).</li><li>3. Best Corrected <b>Visual Acuity</b>.</li><li>4. Microperimetry</li><li>5. Orientation and Mobility.</li></ol>



# Characteristics of Patients

Study ID	Age <sup>†</sup> / Gender	Date IP Administration	Study Eye	LCA5 Variants <sup>†</sup> Allele 1/Allele 2	Visual Acuity <sup>‡</sup>		Refraction <sup>§</sup>		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

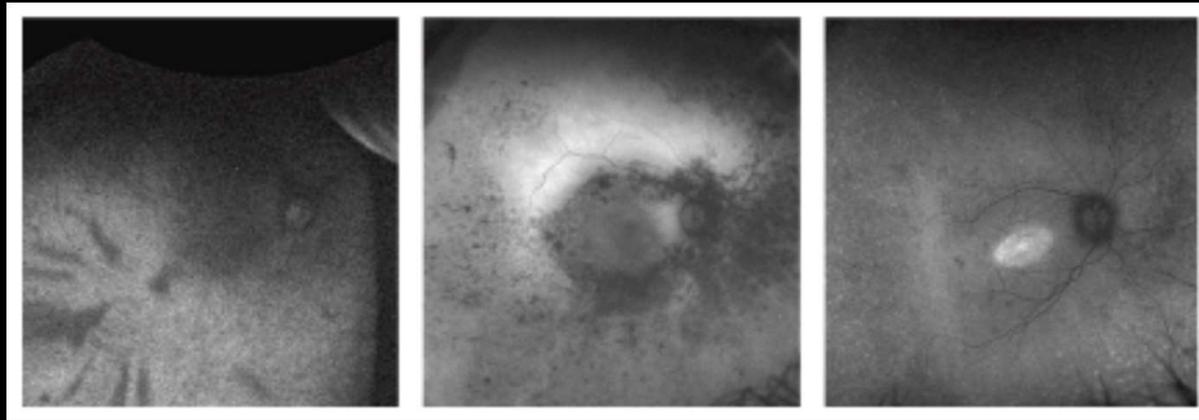
- Mutations led to non-functional proteins.
- Poor VA.

## Same phenotype diverse severity

01-03

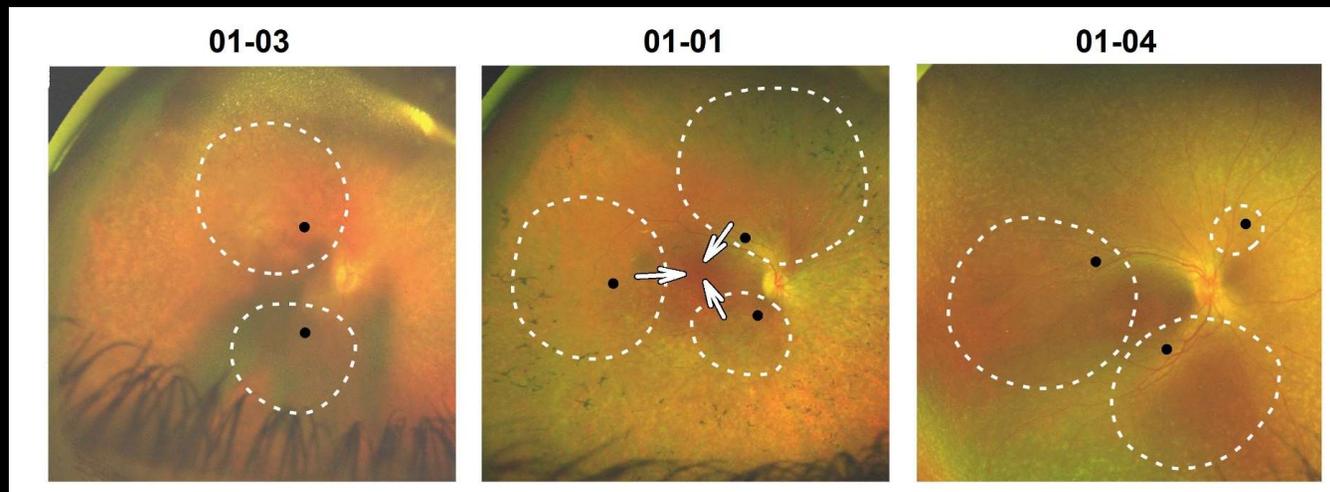
01-01

01-04



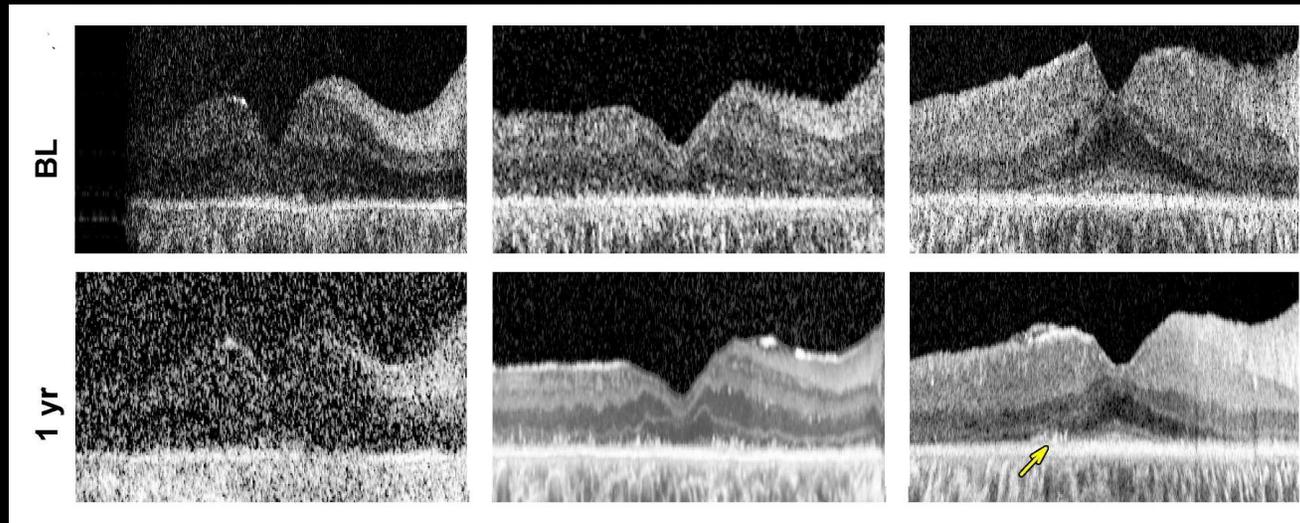
- Severe disease, 'relative' central to midperipheral sparing.

# 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

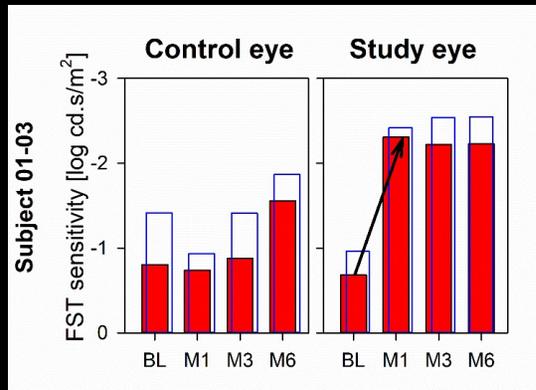
Subject	Date of onset	Date of Resolution	Diagnosis (if known) or Sign/Symptoms (list one per AE)	Ocular AE?	Specify eye(s)	Severity	Unexpected	Serious	Frequency	Outcome	Relationship to Investigational Product	Action taken (Add all that apply):
0101	11-SEP-2023	12-SEP-2023	Eye Pain	Yes	Study	Grade 1 - 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.

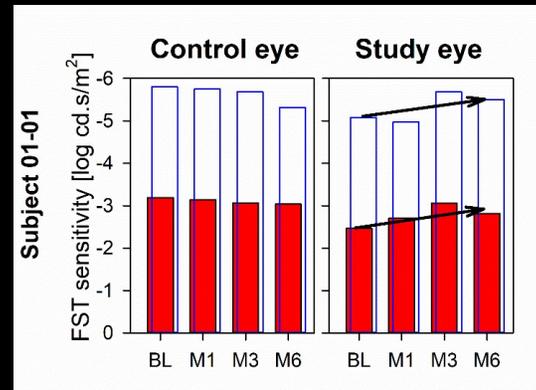
# Full-fields Stimulus Testing

## LARGE GAINS IN CONE-MEDIATED SENSITIVITIES

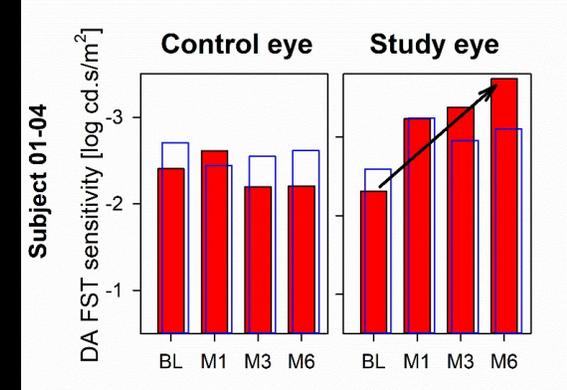
01-03



01-01

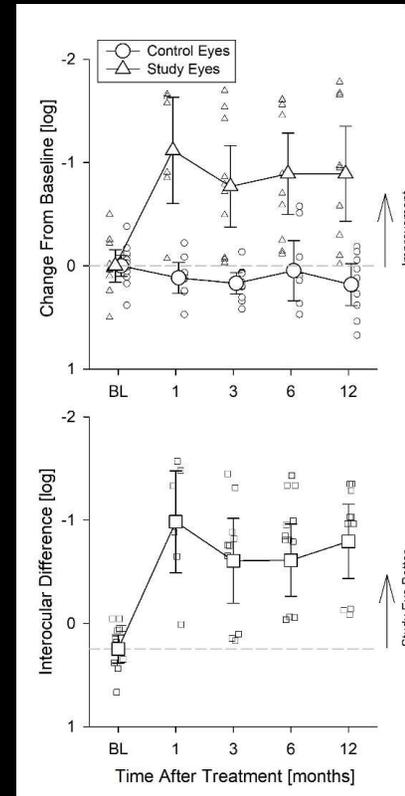
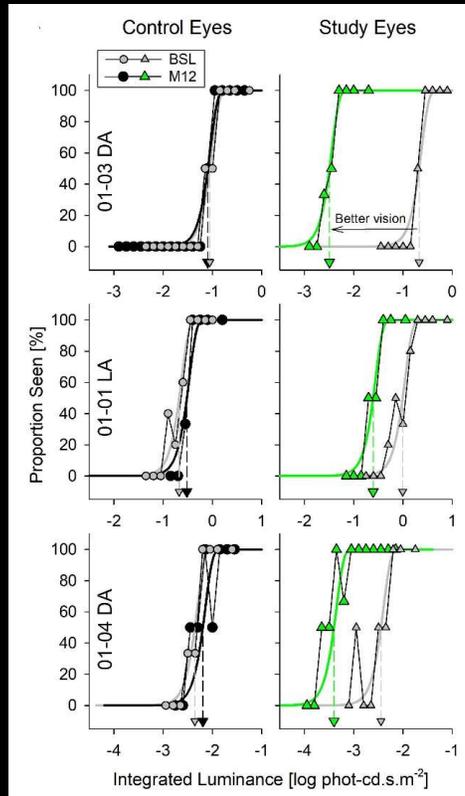


01-04



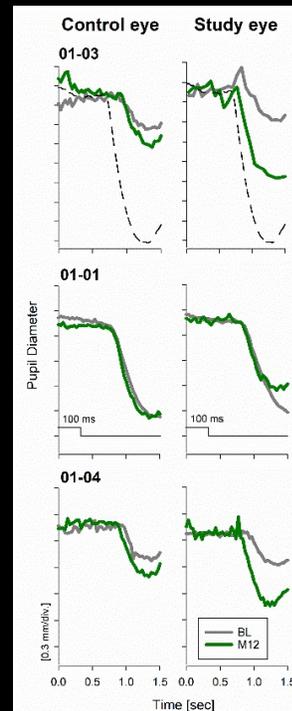
- Up to 1.5 log u. gain in cone-mediated sensitivity compared to control and to baseline (BL).
- Similar differences for red (red bars) and blue (blue outlined bars) stimuli = no change in photoreceptor mediation.

# Gains in Cone Mediated Sensitivities



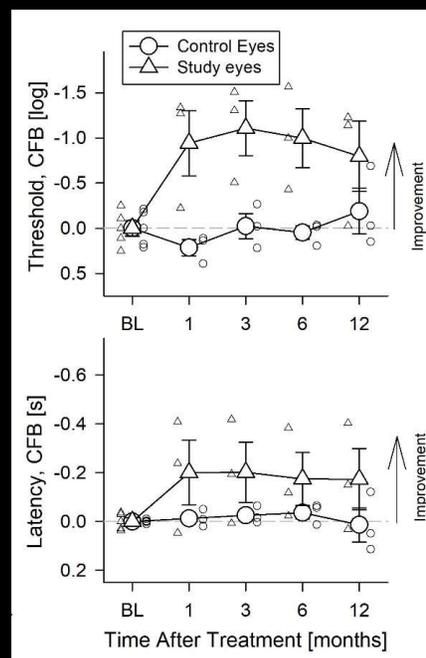
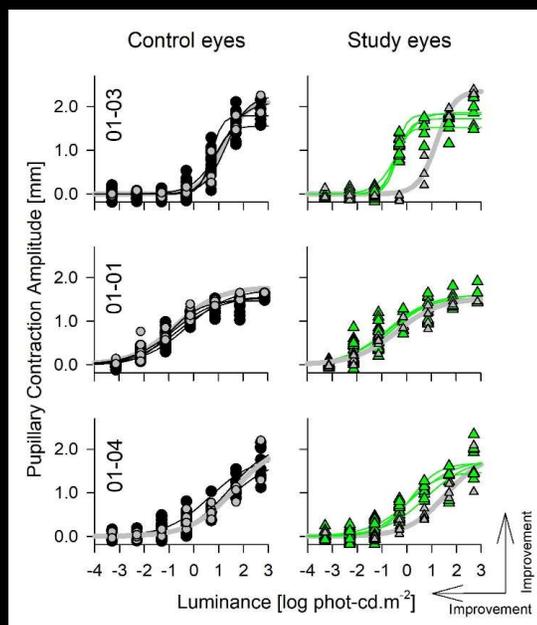
- Average 1 log unit gains in cone-mediated sensitivities (light adapted in 01-01)
- in all three patients compared to baseline (BL) and contralateral control eye

# Pupillometry Objectively Confirms Efficacy



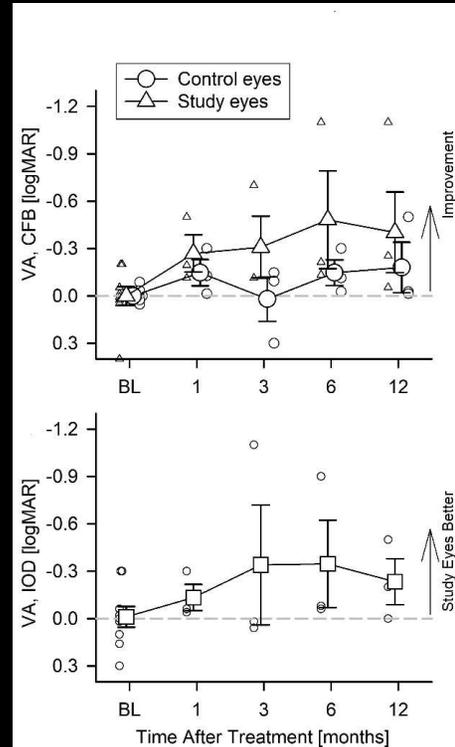
- Dark-adapted pupil responses are faster after treatment (*green traces*) compared to baseline (*gray traces*). Control eye is unchanged.

# Pupillometry Objectively Confirms Efficacy



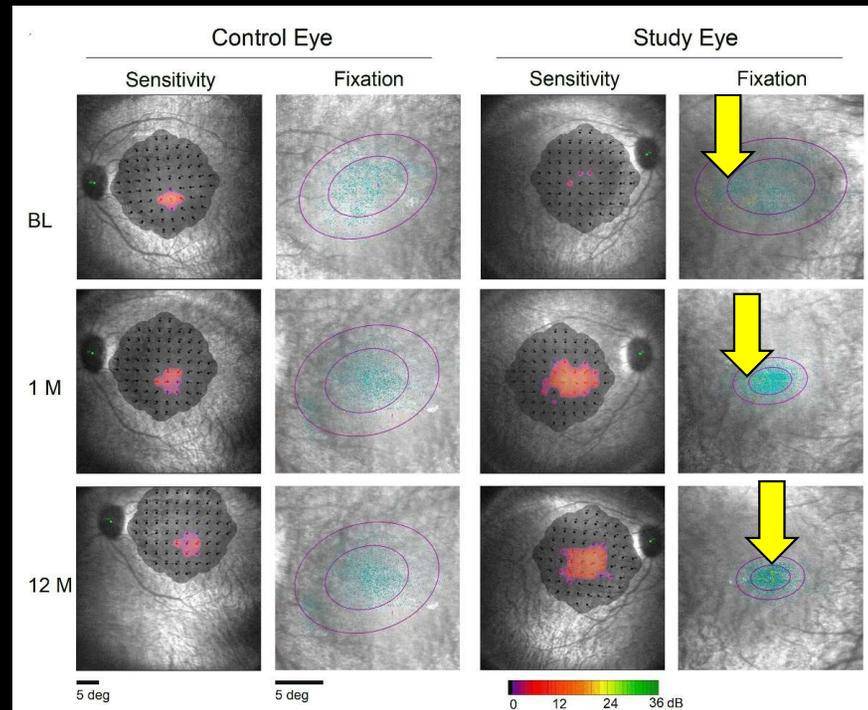
- Pupil responses are more sensitive (left shifted green symbols) compared to baseline (gray curves).
- Thresholds are improved by ~1 log u., faster TPLR is by ~0.2 seconds.
- Sensitivity gains objectively support FSTs gains.

# Visual Acuity Gains



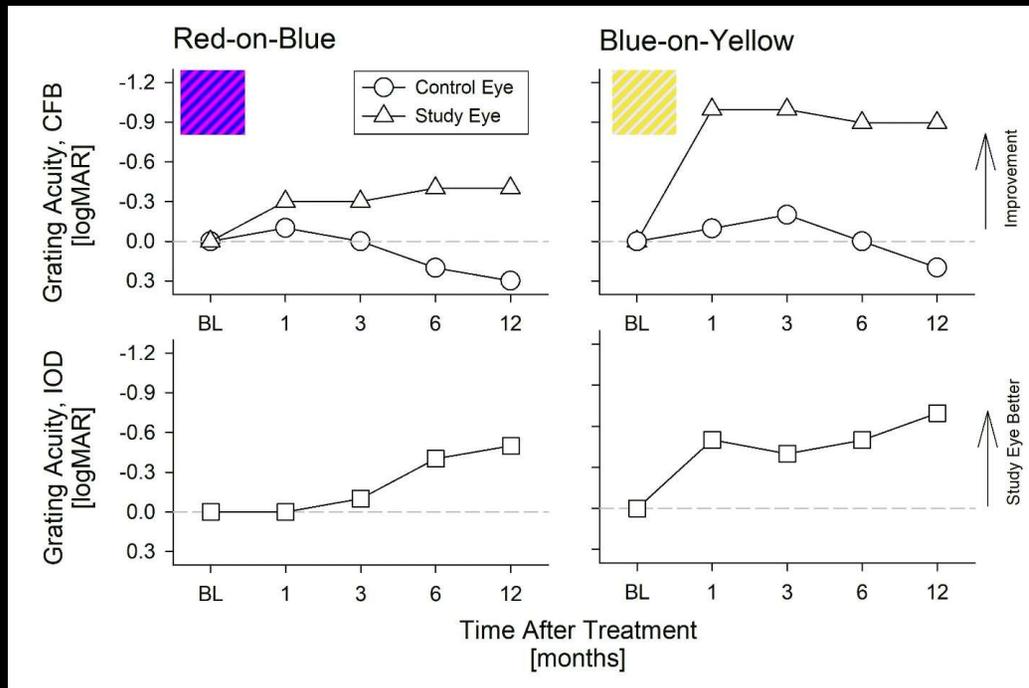
- Formed vision possible for the first time in most affected.
- On average better VAs in treated compared to baseline (BL) and untreated eye.

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



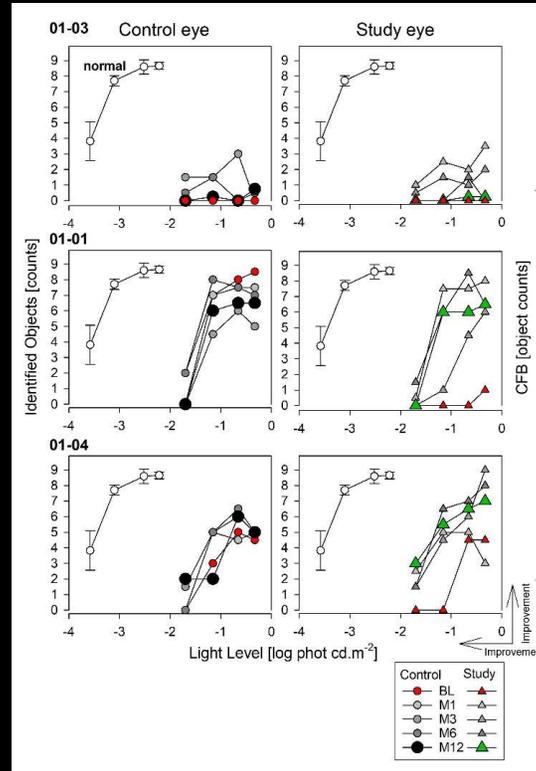
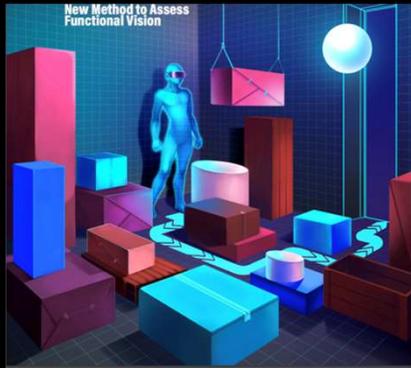
- Sensitivity gain post-treatment; no changes in control eye.
- Movement to a more stable fixation to the foveal center.

# Chromatic Grating Acuity



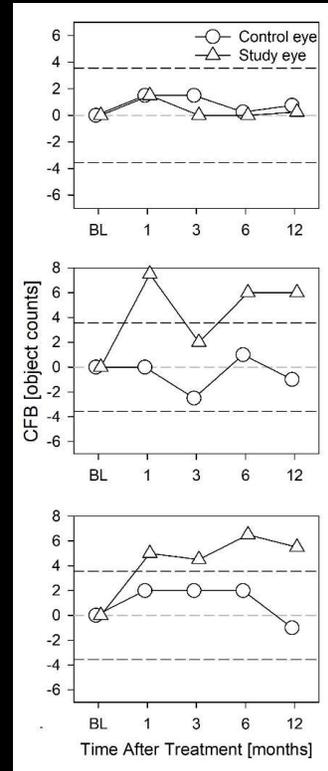
- Improvements in cone-specific resolution between 0.3 and 1 log MAR.

# 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.**