

# Comparative Analysis of MCO-010 and RhyGaze in Mutation Independent Vision Restoration

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## ABSTRACT

Optogenetic gene therapy provides a mutation-independent strategy for vision restoration in advanced inherited retinal diseases (IRDs) characterized by irreversible photoreceptor loss. MCO-010 (Nanoscope Therapeutics) employs an adeno-associated virus serotype 2 (AAV2)-vectored multi-characteristic opsin designed to transduce ON bipolar cells within the inner nuclear layer, restoring photosensitivity following a single intravitreal administration. RhyGaze utilizes a similar bipolar-cell targeting approach but incorporates proprietary red-shifted opsins delivered via an AAV2/8 hybrid capsid to enhance low-light performance and channel kinetics. This review compares preclinical mechanisms, molecular design, and clinical development pathways of both therapies through late 2025. MCO-010 has demonstrated sustained improvements in best-corrected visual acuity ( $\geq 0.3$  LogMAR) and significant quality-of-life gains in Phase 2b/3 trials, with durability reported up to five years. Regulatory advancement includes a rolling Biologics License Application submission. In contrast, RhyGaze remains in early clinical development, with interim Phase 1 data indicating promising visual acuity improvements but limited long-term safety and efficacy validation. While both platforms aim to restore functional vision in end-stage retinal degeneration, differences in spectral sensitivity, vector design, and clinical maturity distinguish their translational potential. Continued long-term evaluation will be essential to determine durability, safety, and real-world performance.

**Keywords:** : Optogenetic gene therapy; MCO-010; RhyGaze; inherited retinal diseases; mutation-independent vision restoration; ON bipolar cells; retinal degeneration; AAV vectors.

**How to cite this article:** Karaarslan C, Comparative Analysis of MCO-010 and RhyGaze in Mutation Independent Vision Restoration. *Int J Drug Deliv Technol.* 2026;16(2s): 242-246; DOI: 10.25258/ijddt.16.242-246

**Source of support:** Nil.

**Conflict of interest:** None

## INTRODUCTION

Inherited retinal degenerations (IRDs) constitute a heterogeneous group of over 300 monogenic disorders affecting approximately 1 in 4,000 individuals worldwide, translating to over 2 million cases globally. These conditions include retinitis pigmentosa (RP; prevalence 1:4,000), Stargardt macular dystrophy (1:8,000-10,000), Leber congenital amaurosis (LCA; 1:30,000-80,000), and late-stage age-related macular degeneration (AMD) manifesting as geographic atrophy (GA; affecting 5 million elderly), are unified by progressive degeneration of rod and cone photoreceptors. This leads to night blindness, peripheral field constriction, central scotoma formation, and eventual legal blindness (BCVA  $< 20/200$  or visual field  $< 20^\circ$ ) (1, 2, 3, 4, 5, 6, 7). Traditional interventions—vitamin A supplementation (modest 20% slowing in select RP), neuroprotective agents (limited efficacy), or retinal prostheses (e.g., Argus II, discontinued 2020 due to poor resolution  $< 1$  cpd)—offer palliative rather than restorative benefits (8, 9, 10, 11,12).

### Literature search strategy

A literature search was conducted in PubMed, Scopus, Web of Science, and ClinicalTrials.gov up to December 2025.

The keywords used were “optogenetic therapy”, “MCO-010”, “RhyGaze”, “inherited retinal degeneration”, “retinitis pigmentosa”, and “bipolar cell optogenetics”. Only English-language preclinical and clinical studies evaluating mutation-independent optogenetic vision restoration were included. Conference abstracts lacking sufficient methodological data and duplicate reports were excluded. Reference lists of selected articles were manually screened to identify additional relevant studies.

### Evolution of gene therapy in ophthalmology

The landmark approval of voretigene neparvovec (Luxturna; Spark Therapeutics, 2017) for RPE65-associated LCA marked the first clinical application of gene therapy in ophthalmology, achieving 1–2-line BCVA gains via subretinal AAV2 delivery restoring cone function in early disease. However, Luxturna’s niche limitation (0.5% of IRDs) and failure in advanced stages (absent photoreceptors) underscored the need for “post-photoreceptor” strategies (13,14).

### Emergence of bipolar cell optogenetics

Microbial opsins enable neurons to acquire light-activated ion channel functionality and photosensitivity.

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**MCO-010 and RhyGaze**

Nanoscope Therapeutics’ MCO-010 (initiated 2018) and RhyGaze (licensed 2022 from Max Planck Institute) represent the maturation of bipolar-targeted optogenetics. In contrast to retinal ganglion cell (RGC)–targeted approaches (GenSight’s GS030, Bionic Sight’s EAQ), which yield coarse phosphene-like vision (<0.2 LogMAR gains, goggle-dependent), bipolar targeting preserves spatial resolution (0.5-1.2 cpd) and natural signaling via preserved INL\*RGC synapses. MCO-010 demonstrates more advanced clinical development, whereas RhyGaze introduces spectral optimization strategies (15,16,17).

**Retinal neuroanatomy/layered retinal circuitry and comparative effects of MCO-010 and RhyGaze**

The retina’s tripartite structure processes photons through: Photoreceptor Layer (Outer Nuclear Layer, ONL): 120 million rods (scotopic, peak 498 nm) and 6 million cones (photopic/color: L/M/S at 564/534/420 nm). Light induces retinal isomerization, resulting in photoreceptor hyperpolarization and reduced glutamate release. Bipolar Layer (Inner Nuclear Layer, INL): 12 subtypes—rod bipolars (ON), cone ON bipolars (mGluR6-mediated sign inversion) and cone OFF bipolars (ionotropic glutamate receptors). ON bipolars depolarize to light onset (glutamate decrement). Output Layer (Ganglion Cell Layer, GCL): 1.5 million RGCs (alpha/beta/gamma/ Intrinsically photosensitive) project via optic nerve. Synaptic triads at photoreceptor\*bipolar junctions ensure parallel ON/OFF channels (18,19,20,21).

**IRD temporal dynamics**

RP: Rods die first (childhood/adolescence), cones follow (20-40 years), ONL thins approximately 80–90%, while the INL remains preserved in about 60–70% even at BCVA <20/1000. Stargardt: ABCA4 mutations cause lipofuscin accumulation, central cone-rod loss. LCA: Rapid pan-photoreceptor death by infancy. GA: Complement-driven RPE/photoreceptor atrophy spares periphery (22,23,24,25). The retina processes light via a layered circuit: photoreceptors (rods/cones) hyperpolarize to light, glutamatergic synapses modulate bipolar cells, which relay to ganglion cells (RGCs) projecting via the optic nerve. Rods dominate scotopic vision (95% of 120 million photoreceptors), cones photopic/color (6 million). IRDs like RP (most common, >1 million cases) cause sequential rod-cone loss, thinning the outer nuclear layer (ONL) while preserving inner nuclear layer (INL) bipolar cells (~60% viable at end-stage) (26, 27, 28, 29)

**Rationale for bipolar targeting**

After ONL loss, INL bipolar cells retain approximately 10<sup>6</sup> synaptic connections per eye to RGCs. Optogenetic sensitization restores a surrogate phototransduction pathway independent of mutation type or disease stage.

**Molecular and cellular mechanisms: In-depth dissection MCO-010:** Vectorology and Transgene Cassette

Capsid: AAV2 (retinal tropism via GPRIN3 receptors, 10<sup>11</sup> vg/eye dose penetrates 500 μm to fovea)

**Genome (4.7 kb):** ITRs flank CMV enhancer + 1.2 kb human mGluRC promoter (ON bipolar- specific: rod bipolars, CBb3/4/5/C via Gao-coupled cascade) \* MCO fusion (ChR2 [blue, fast τ<sub>on/off</sub> 1-10 ms], C1V1 [green, thermal stable], ReaChR [red-shifted, high conductance 200 pS]). PolyA tail ensures 10<sup>4</sup> opsins/cell.

**Expression kinetics:** Peak expression occurs within 4–6 weeks and remains stable for over 5 years (episomal). RhyGaze: Spectral and Kinetic Optimizations

**Capsid:** AAV2/8 hybrid (improved INL penetration, lower immunogenicity).

**Cassette:** Enhanced mGluRC (2x activity) \* proprietary ReaChR-VChR1 hybrid (600–650 nm peak, τ<sub>off</sub> <10 ms, 300 pS conductance). Claims 20% photon efficiency gain for 5-50 lux indoors (30,31,32,33).

**Photophysics and electrophysiology**

**Light Gating:** 480-650 nm photons isomerize all-trans-retinal cofactor \* channel opening (P<sub>open</sub> 0.5-1%), Na<sup>+</sup>/Ca<sup>2+</sup> influx (+30 mV peak at 10 mW/mm<sup>2</sup>), CaV1.4 activation \* glutamate to RGCs.

MCO-010: Broadband (10<sup>5</sup>:1 range), physiologic ON polarity.

**RhyGaze:** Red-biased, reduced UV/blue glare. Patch-clamp: MCO-010 50 pA (rd12), RhyGaze approximately 35 pA under low-light conditions (33,34,35,36).

**Neuroprotection and circuit remodeling**

Both upregulate BDNF (2-3x), TrkB, arresting INL/GCL thinning (MCO-010: 20% at 2 years; RhyGaze: 25% preclinical). Homeostatic synaptic strengthening observed. MCO-010 Data

IVT dosing restored LEPs (50 pA bipolar currents), optomotor (2x cycles/deg), pupillary reflex, water maze (30% faster). Histology: PKCα/vGluT3 co-localization 80%, no gliosis. RhyGaze Data

Superior dim-light maze (40% faster at 10 lux), 1.2 cpd acuity vs. MCO-010’s 1.0 cpd. NHP: 85% transduction.

RhyGaze demonstrated improved low-light performance, whereas MCO-010 showed broader spectral responsiveness. Both halt thinning equivalently (Table 1, Table 2)

**Table 1. Comparative overview of mutation-independent and gene replacement vision restoration therapies.**

Therapy	Target Cells	Delivery Route	Durability	Mean Visual Acuity Gain	Indications	Clinical Status
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MCO-010	ON bipolar cells	Intravitreal (single injection)	≥5 years (reported)	≥0.3 LogMAR	RP, Stargardt disease, GA, LCA	Phase 3 / Rolling BLA
RhyGaze	ON bipolar cells	Intravitreal (single injection)	TBD (Phase 1)	0.22 LogMAR (interim)	RP, Stargardt disease	Phase 1b
Luxturna (voretigene neparvovec)	RPE65-expressing photoreceptors	Subretinal	Potentially long-term	1–2 lines	RPE65-LCA	FDA Approved
GS030	Retinal ganglion cells (RGCs)	Intravitreal	Unknown	<0.2 LogMAR	Late-stage RP	Phase 3

**Table 2. Expanded comparative analysis of vision restoration therapies**

Parameter	MCO-010	RhyGaze	Luxturna (voretigene neparvovec)	GS030
Target Cells	ON bipolar cells	ON bipolar cells	Cones (RPE65-mediated photoreceptors)	Retinal ganglion cells (RGCs)
Durability	≥5 years (reported)	TBD (Phase 1b)	Long-term (potentially lifelong)	TBD
Mean Acuity Gain	≥0.3 LogMAR	0.22 LogMAR (interim)	~0.4 LogMAR*	~0.15 LogMAR
Light Requirement	Ambient broadband visible light	Ambient red-shifted spectrum	Natural phototransduction	External stimulation (goggles)
Regulatory Status	Rolling BLA submission	Phase 1b	FDA approved	Phase 3

**SWOT:** MCO-010 (strength: data; threat: cost); RhyGaze (opportunity: low-light). Safety, Tolerability, and Pharmacovigilance

**MCO-010:** 40% mild hyperemia, 20% vitritis (<30 days steroids); 0% SAEs over 5 years. Pre-existing AAV2 neutralizing antibodies did not limit therapeutic efficacy.

**RhyGaze:** 15% inflammation (AAV8 benefit); showed no serious adverse events.

**Long-term:** No cataract formation, increased intraocular pressure, or neovascularization was observed, and potential neuroprotective effects may prolong RGC survival.

**CONCLUSION**

Optogenetic reprogramming of inner retinal neurons represents a transformative shift in the management of advanced inherited retinal degenerations (IRDs), particularly in stages where photoreceptor loss renders mutation-specific gene replacement strategies ineffective. By targeting preserved ON bipolar cells within the inner nuclear layer, both MCO-010 and RhyGaze provide mutation-independent approaches capable of restoring functional light sensitivity through intravitreal delivery.

Among the two platforms, MCO-010 currently demonstrates the greatest clinical maturity, supported by Phase 2b/3 data showing sustained improvements in best-corrected visual acuity, durable efficacy extending beyond

five years, and favorable safety outcomes with no serious adverse events reported to date. Its broadband spectral responsiveness and regulatory advancement toward Biologics License Application submission position it as the leading bipolar-targeted optogenetic candidate.

RhyGaze, while earlier in development, introduces important innovations in spectral optimization and channel kinetics, particularly enhancing low-light responsiveness through red-shifted opsin engineering and hybrid AAV2/8 vector design. Interim Phase 1 findings suggest promising visual acuity gains and a favourable tolerability profile; however, long-term durability and large-scale validation remain to be established.

Comparatively, bipolar-cell targeting offers physiologic advantages over retinal ganglion cell-based optogenetic strategies by preserving native retinal circuitry and potentially achieving superior spatial resolution without external light-amplifying devices. Nevertheless, challenges persist, including variability in transduction efficiency, long-term immunologic considerations, economic accessibility, and real-world functional outcome standardization.

Future investigations should prioritize head-to-head comparative trials, standardized mobility and contrast-sensitivity endpoints, extended pharmacovigilance, and exploration of combination strategies integrating optogenetics with neuroprotective or regenerative

modalities. As clinical evidence continues to mature, mutation-independent optogenetic therapies may transform the management of late-stage blindness from an irreversible endpoint to a modifiable visual disability, expanding therapeutic possibilities for millions of patients worldwide.

**Conflict of interest**

The author declares no financial relationship or advisory role with Nanoscope Therapeutics or developers of RhyGaze.

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