RNA-Based *OPA1* Upregulation in ADOA: First-in-Human STK-002 Study in Mitochondrial Optic Neuropathy

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Jeff Hoger	Employee of Stoke Therapeutics
Alice Wyse Jackson	Employee of Stoke Therapeutics
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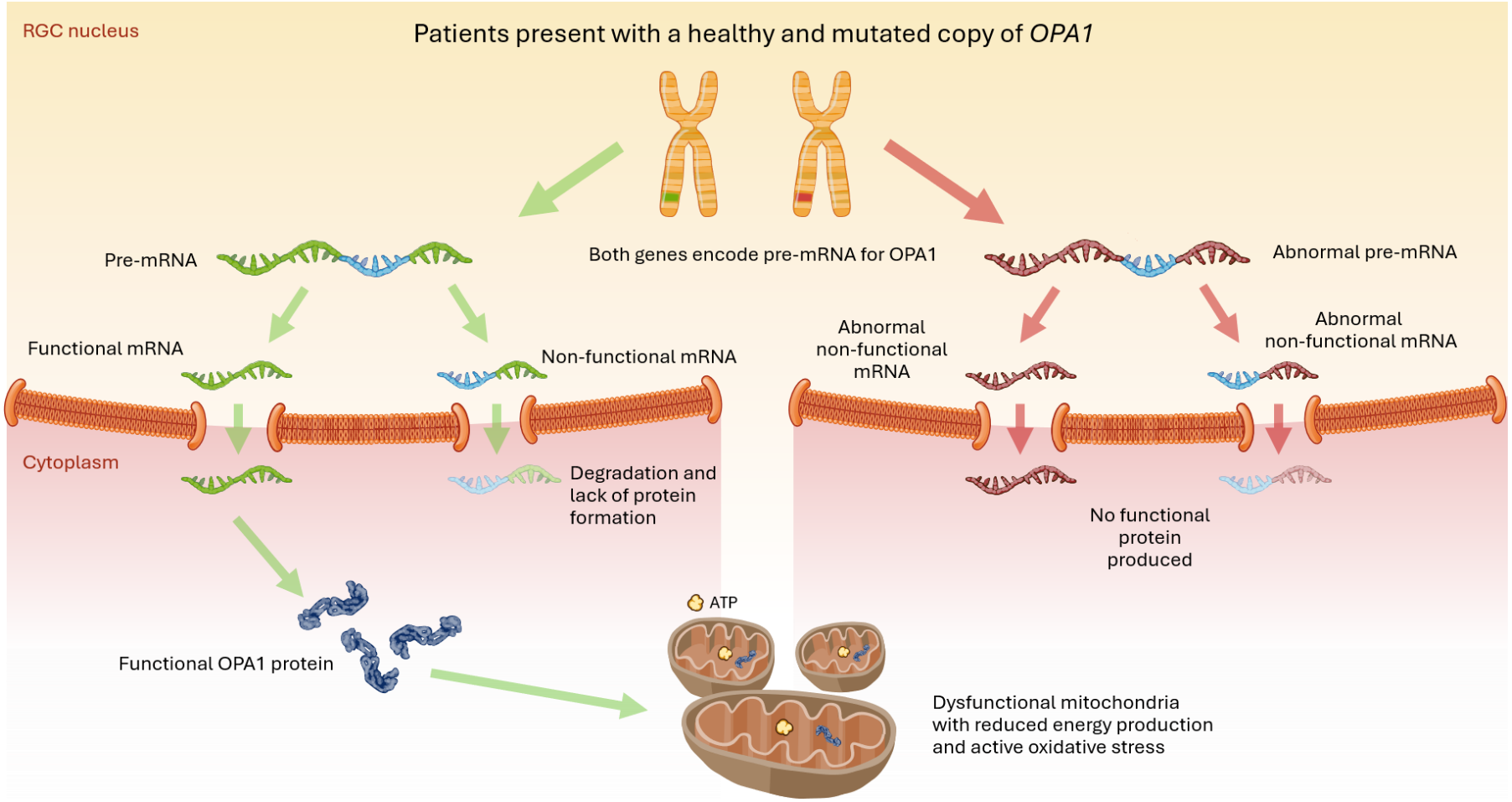
Barry Ticho	Employee of Stoke Therapeutics
Steven Gross	Employee of Stoke Therapeutics
Patrick Yu-Wai-Man	Consulting services for Stoke Therapeutics

ADOA is a hereditary optic neuropathy primarily caused by *OPA1* gene variants that lead to reduced functional OPA1 protein expression[1–4]



ADOA, autosomal dominant optic atrophy; mRNA, messenger ribonucleic acid; OPA1, OPA1 mitochondrial dynamin like GTPase; RGC, retinal ganglion cell.

1. Almind GJ *et al. BMC Med Genet* 2012; 13: 65. 2. Cohn AC *et al. Am J Ophthalmol* 2007; 143 (4): 656–662. 3. Chun BY *et al. Curr Opin Ophthalmol* 2016; 27: 1855–1865. 4. Lim KH *et al. Nat Commun* 2020; 11 (1): 3501.

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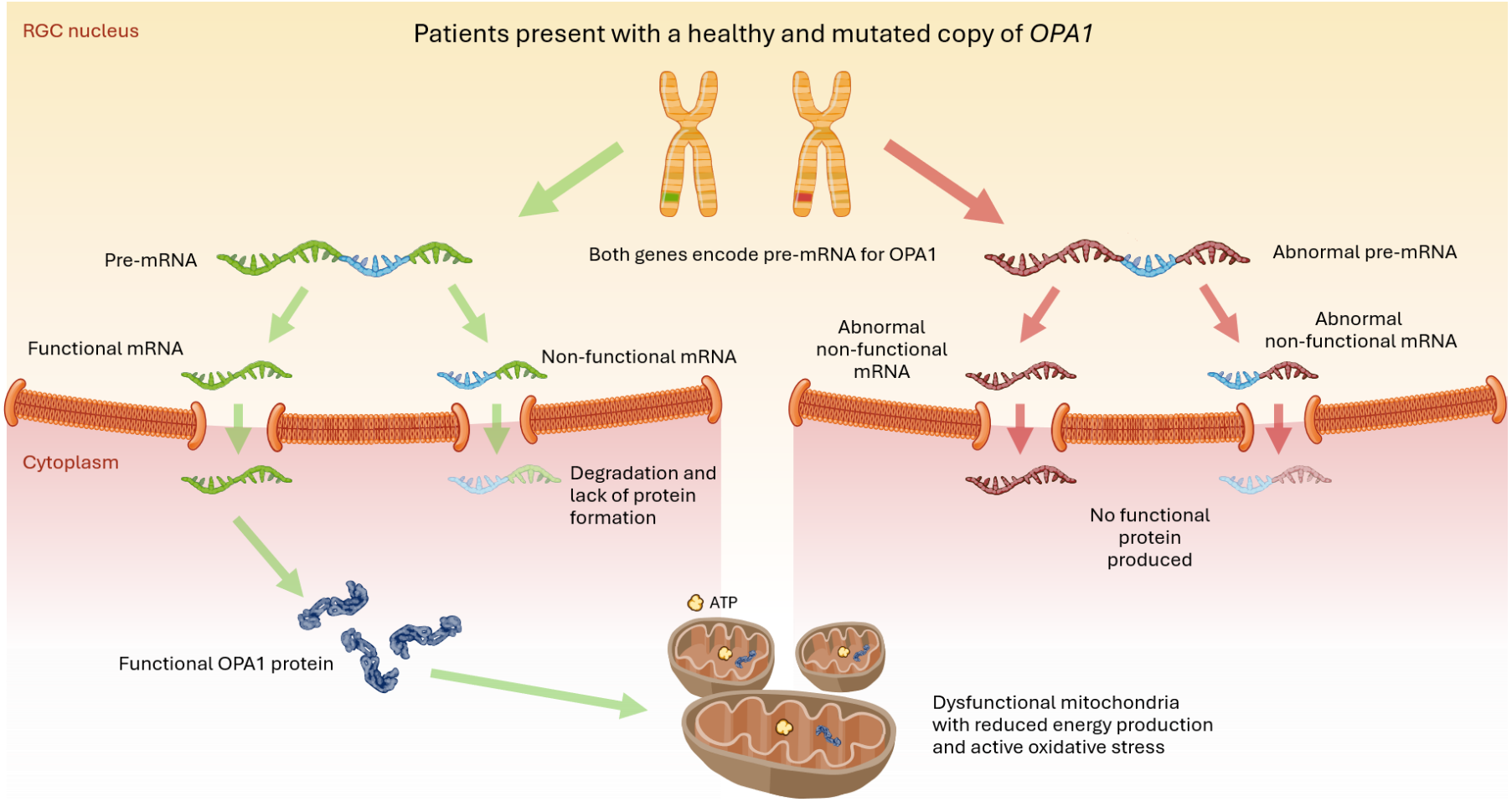
OPA1 deficiency leads to mitochondrial dysfunction, impaired energy production, RGC vulnerability, and vision loss[1]



ATP, adenosine triphosphate; mRNA, messenger ribonucleic acid; OPA1, OPA1 mitochondrial dynamin like GTPase; RGC, retinal ganglion cell.

1. Chun BY *et al*. *Curr Opin Ophthalmol* 2016; 27: 1855–1865.

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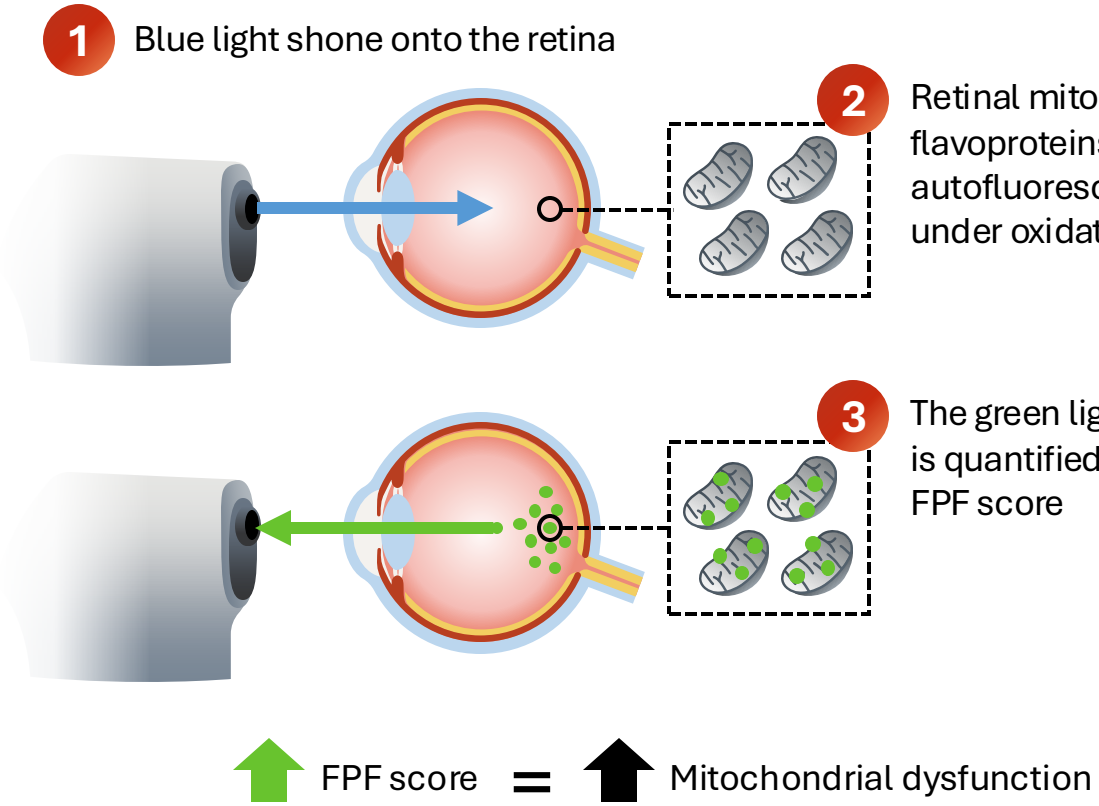
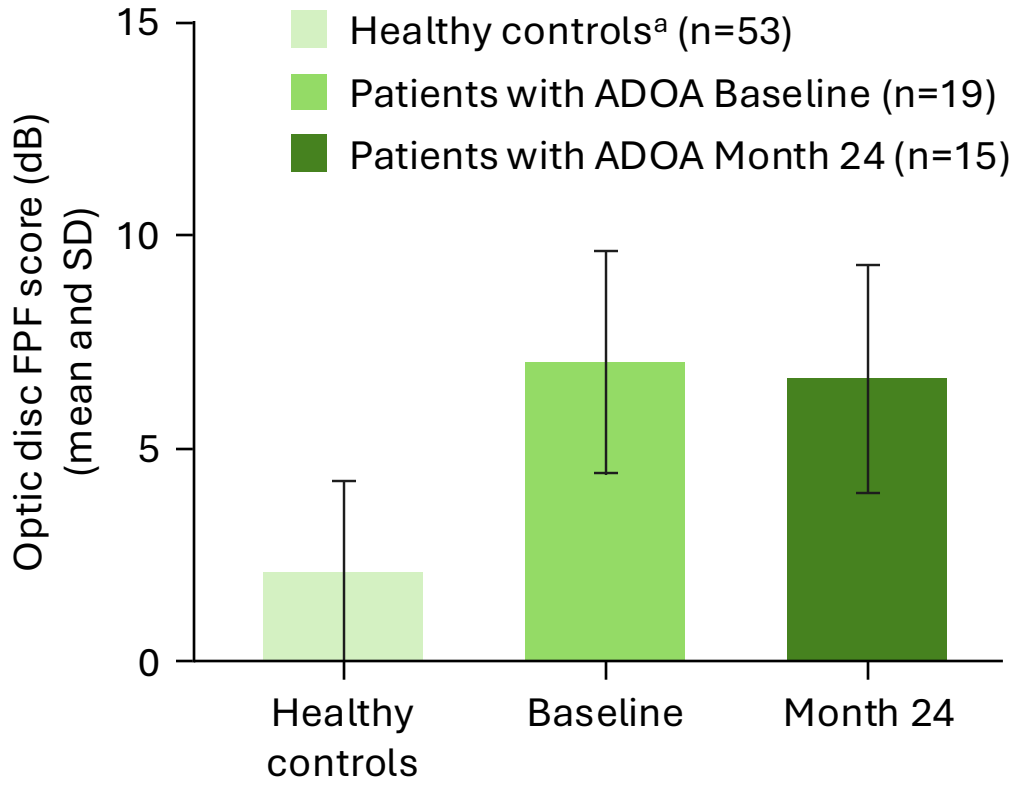
Mitochondrial dysfunction is increased in patients with ADOA compared with healthy controls

OcuMet Beacon™ imaging



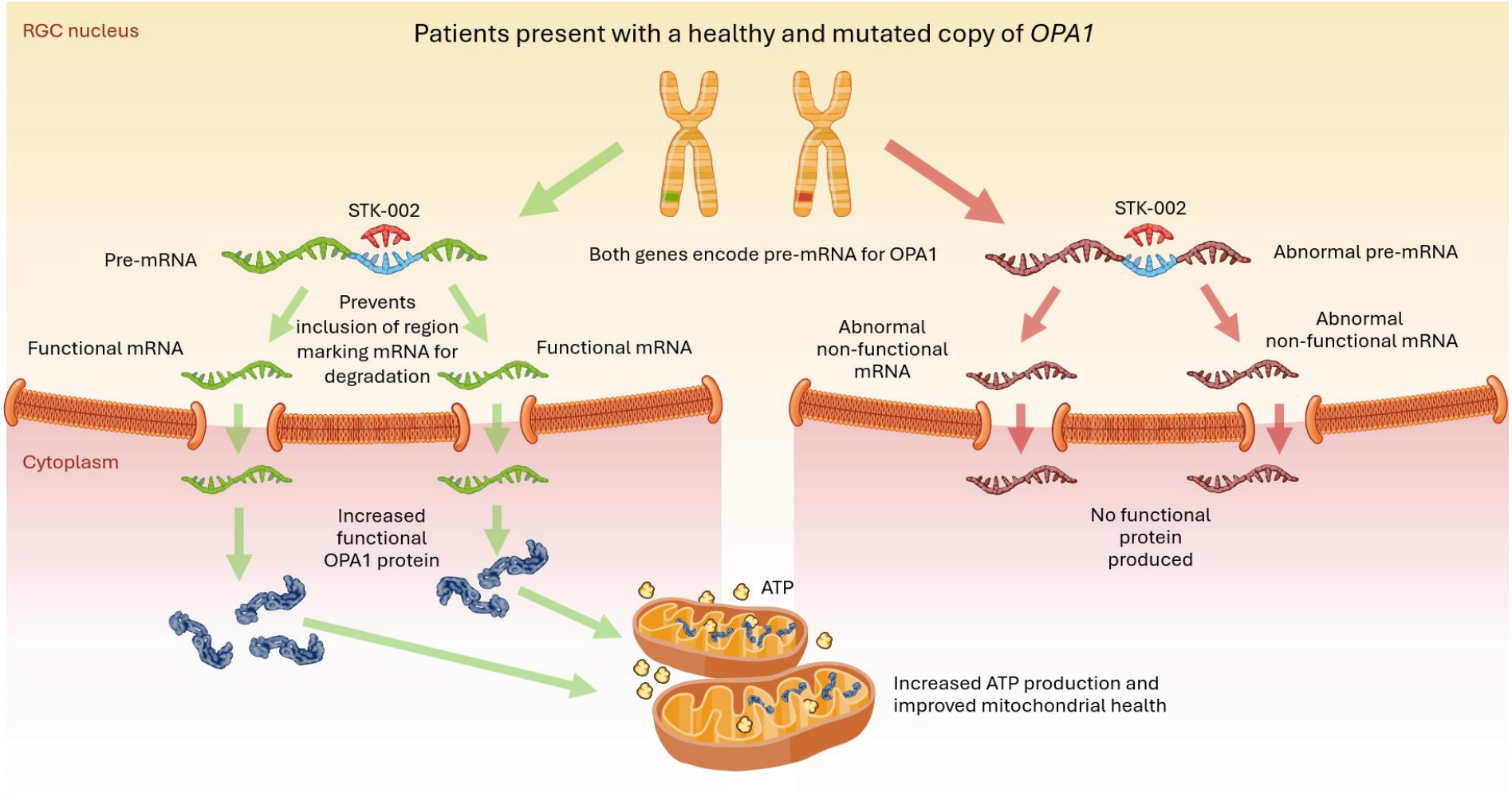
FALCON natural history study



Month 24 data cut: July 11, 2025.
[a]Healthy control data from patients aged 30–60 years supplied by OcuSciences Inc.
ADOA, autosomal dominant optic atrophy; FPF, flavoprotein fluorescence; SD, standard deviation.
1. Liao YJ *et al*. ARVO 2026, May 3–7, 2026, Denver, CO, USA. Poster 3230.

STK-002 is designed to increase OPA1 protein expression in ADOA by enabling the healthy copy of the *OPA1* gene to produce more functional mRNA

STK-002 is an RNA-based investigational antisense oligonucleotide



ADOA, autosomal dominant optic atrophy; ASO, antisense oligonucleotide; ATP, adenosine triphosphate; mRNA, messenger ribonucleic acid; OPA1, OPA1 mitochondrial dynamin like GTPase; RGC, retinal ganglion cell; RNA, ribonucleic acid.

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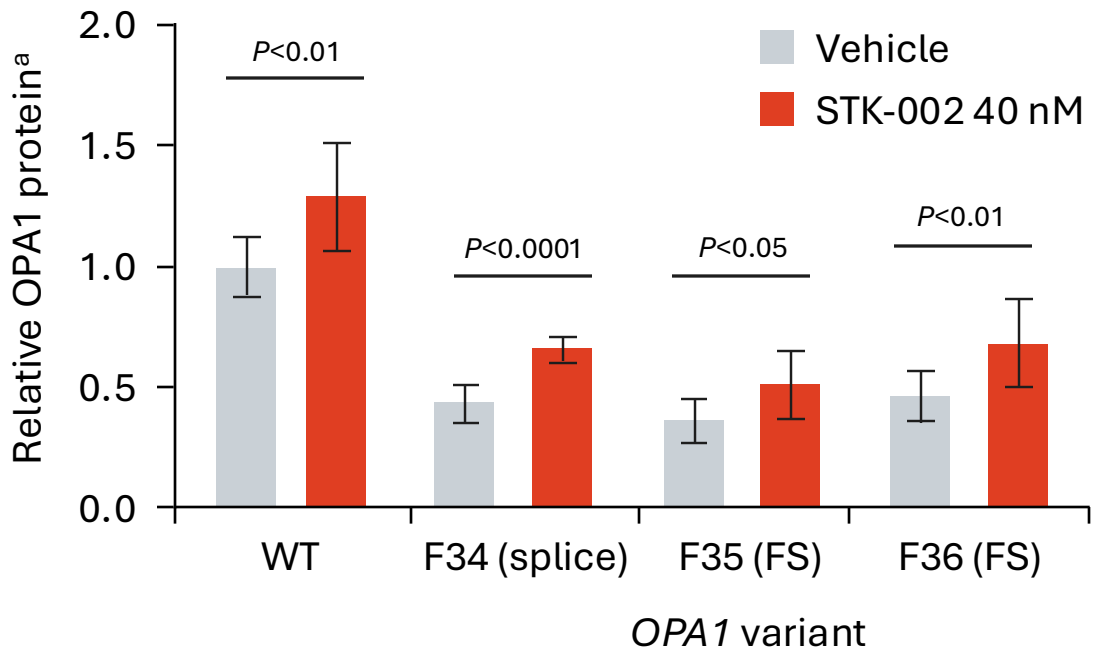
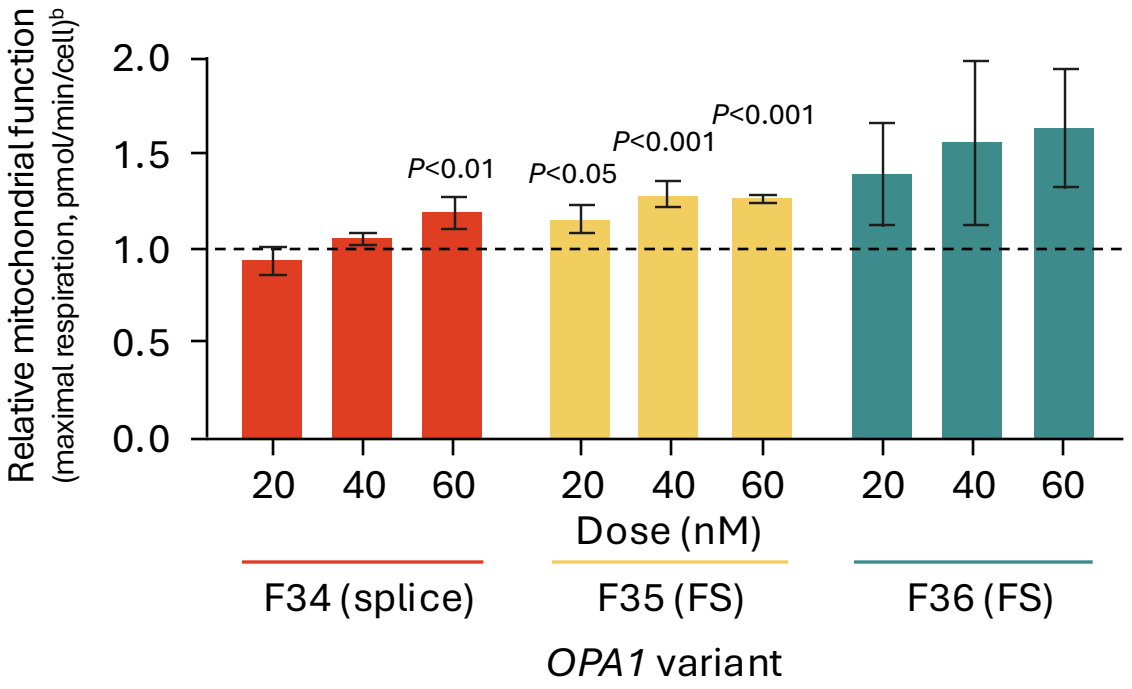
STK-002 has been shown to statistically significantly increase OPA1 protein and improve mitochondrial function in ADOA patient-derived cells

Increased OPA1 protein expression



Improved mitochondrial function

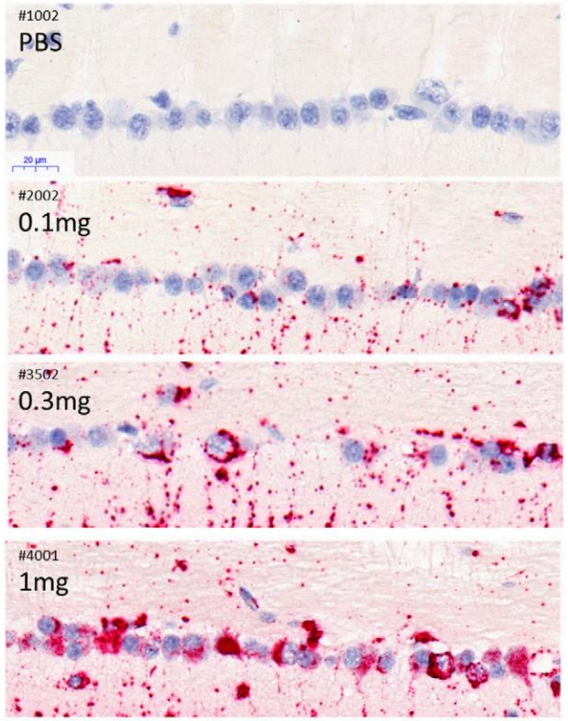


STK-002 demonstrated activity across cells carrying different *OPA1* variants

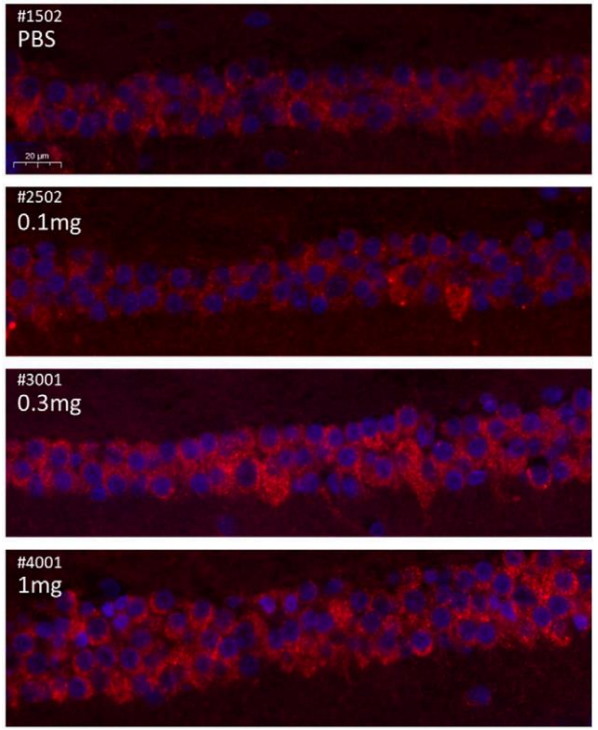
[a]Mean (SD) OPA1 protein levels (n=9) plotted relative to WT Vehicle group. Statistical analysis by unpaired t-tests. [b]Mean (SD) maximal respiration determined by OCR (pmol/min/cell) under basal and stress conditions, normalized to cell count (n=3) plotted relative to Vehicle (1.0) for each cell type. Statistical analysis by ordinary one-way ANOVA and Dunnett's multiple comparison test.
ADOA, autosomal dominant optic atrophy; FS, frameshift; mRNA, messenger ribonucleic acid; OCR, oxygen consumption rate; OPA1, OPA1 mitochondrial dynamin like GTPase; SD, standard deviation; WT, wild-type.
Figures adapted from Venkatesh A *et al. Nucleic Acid Ther* 2024; 34(5): 221–236. Licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/

A single intravitreal dose of STK-002 increased retinal OPA1 protein by 47% at 4 weeks in wild-type non-human primates versus control

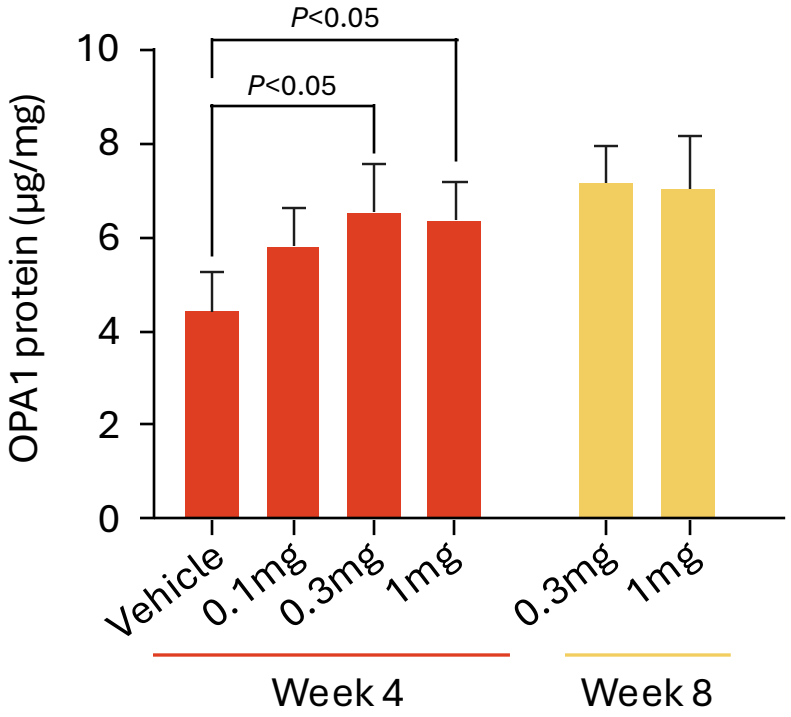
STK-002 detected in RGC layer



OPA1 protein in RGC layer



OPA1 protein in retinal lysates



The preclinical data support the clinical evaluation of STK-002

Retinas were collected at 4 or 8 weeks after intravitreal dosing.
OPA1, OPA1 mitochondrial dynamin like GTPase; PBS, phosphate-buffered saline; RGC, retinal ganglion cell.
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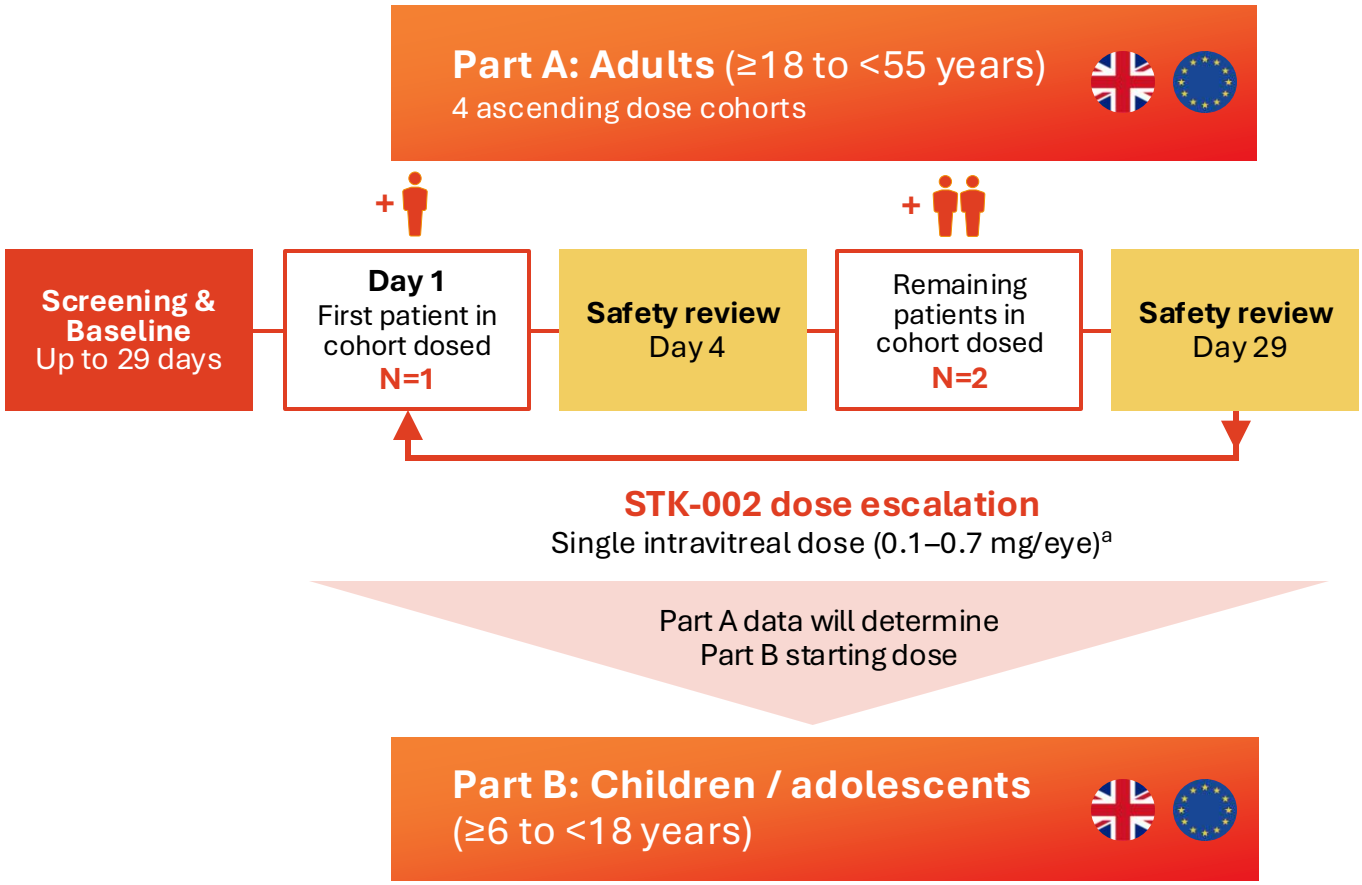
OSPREY is a Phase 1 first-in-human study of STK-002

Evaluating the safety and tolerability of a single intravitreal injection of STK-002 in patients with *OPA1*-associated ADOA



Principal focus

- Safety and tolerability

Other measures

- Visual function – LCVA
- Ocular structure – OCT
- Mitochondrial stress – OcuMet Beacon™ imaging

Recruitment ongoing[1]

Eight clinical trial sites are active in the UK, Germany, Denmark, Italy, and Austria.

[a]Patients will receive a single intravitreal injection of STK-002 to the most affected or, if both eyes are of equal severity, the non-dominant eye.

ADOA, autosomal dominant optic atrophy; LCVA, low contrast visual acuity; OCT, optical coherence tomography; OPA1, OPA1 mitochondrial dynamin like GTPase.

1. ISRCTN.com. ISRCTN41725621. Available at: https://www.isrctn.com/ISRCTN41725621. Accessed July 2026.

Conclusions

- The FALCON natural history study showed that retinal mitochondrial stress is elevated in ADOA versus healthy controls[1]
- STK-002 is designed to increase OPA1 protein expression by leveraging the healthy copy of the *OPA1* gene[2,3]
- Following a single intravitreal dose, STK-002 reached the RGCs and increased retinal OPA1 protein by up to 47% after 4 weeks in non-human primates[3]
- These findings support the advancement of STK-002 into OSPREY, a first-in-human Phase 1 study in people with ADOA[4]

STK-002 is one of the first RNA-based therapeutics to enter clinical development in ophthalmology, and has the potential to be the first disease-modifying therapy for ADOA

ADOA, autosomal dominant optic atrophy; OPA1, OPA1 mitochondrial dynamin like GTPase; RGC, retinal ganglion cell; RNA, ribonucleic acid.

1. Liao YJ *et al*. ARVO 2026, May 3–7, 2026, Denver, CO, USA. Poster 3230; 2. Lim KH *et al*. *Nat Commun* 2020; 11(1): 3501; 3. Venkatesh A *et al*. *Nucleic Acid Ther* 2024; 34(5): 221–236; ISRCTN.com. ISRCTN41725621. Available at: https://www.isrctn.com/ISRCTN41725621. Accessed July 2026.

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Thank you

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