



Life-changing science

Investor update on ADOA drug program

5 October 2023



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Executive Summary

- An introduction to Autosomal Dominant Optic Atrophy (ADOA)
 - Patient journey
 - Underlying genetic cause of the disease
- An introduction to PYC-001 – a first-in-class investigational drug candidate for ADOA
 - PYC-001 addresses the root cause of ADOA
 - PYC-001 starts human trials ¹ with the highest probability of success in the clinic (monogenic disease)²
- Where does yesterday's NHP data fit into the picture?
 - Demonstrates that PYC-001 can overcome the biggest challenge for precision medicines – delivery to the target cell
 - Enables PYC to link the *in vivo* profile of the drug candidate to the results of the patient-derived models (that demonstrate functional rescue of the disease)
- The upshot is a drug candidate that is set to enter the clinic with a very strong non-clinical data pack¹ – good science with high potential impact for ADOA patients

1. Subject to regulatory approval

2. Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank. doi: <https://doi.org/10.1101/2020.11.02.20222232>



An introduction to Autosomal Dominant Optic Atrophy (ADOA)

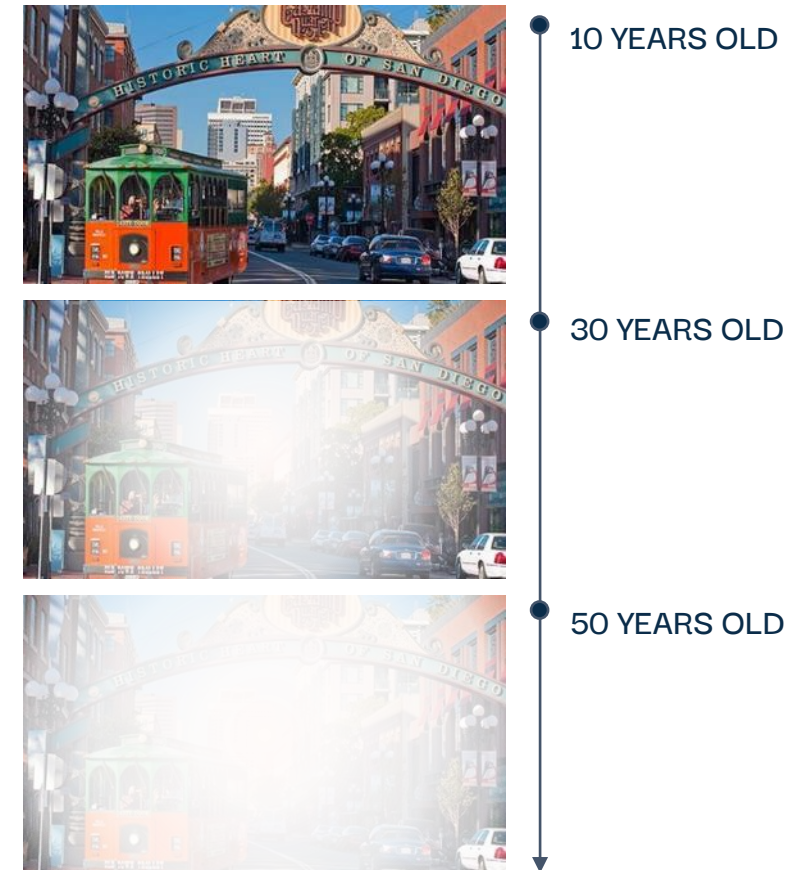


ADOA is a progressive and blinding eye disease of childhood for which there are no treatment options available

Autosomal Dominant Optic Atrophy (ADOA)

- An addressable market size of **~A\$2 billion** per annum^{1,2,4}
- **9,000 – 16,000** addressable patients in the western world^{1,2}
- Median age of onset at 7 years of age, with 80% of patients symptomatic before age 10¹
- **There are no treatments available** for patients with ADOA
- Caused by **haploinsufficiency of the *OPA1* gene** in Retinal Ganglion Cells that form the optic nerve of the eye
- ADOA is a monogenic disease: **2-5x higher likelihood of success** in human studies³

Degenerative sight of an ADOA patient



The deficiency of OPA1 protein in ADOA patients triggers a cascade of bioenergetic deficits that culminate in cell death and loss of vision

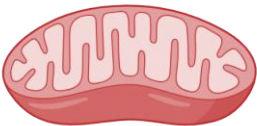
Unaffected bioenergetics

Wild type OPA1 protein expression (100%)



OPA1

Slim and tight mitochondrial ultrastructure



Cristae ultrastructure

Elongated mitochondria



Morphology

Improved respiratory efficiency



Bioenergetics

More resistant to cell death



Cell-death

Bioenergetics in ADOA



Haploinsufficient ~50-70% expression

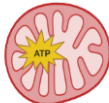
Disorganised mitochondria with wide cristae and cristae junctions



Fragmented mitochondria



Lower respiratory efficiency



Higher sensitivity to challenge



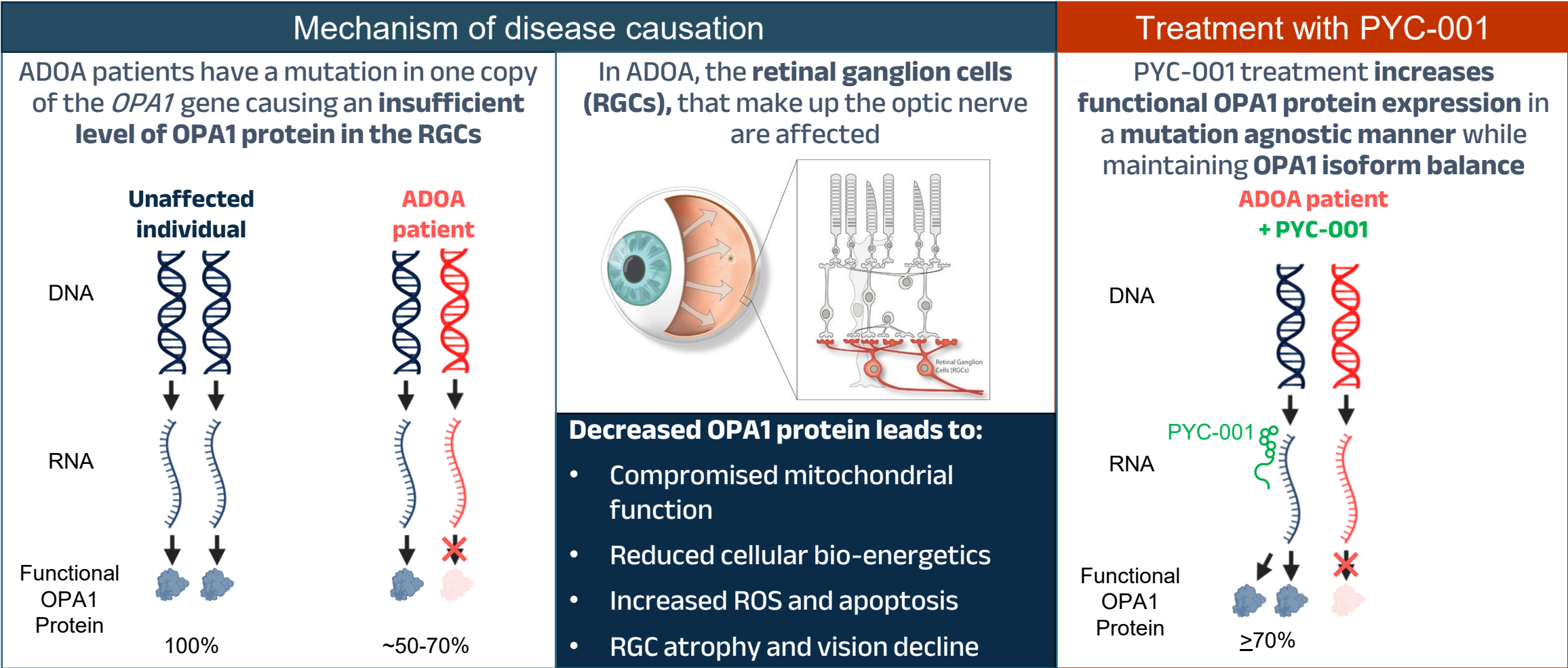
Loss of vision



An introduction to PYC-001 for ADOA



PYC-001 addresses the root cause of ADOA - insufficient expression of OPA1 protein in the cells that form the optic nerve





NHP results supporting clinical development of PYC-001



Non-clinical models provide early insight into clinical outcomes – particularly in monogenic diseases

“We need to understand as early as possible whether a drug candidate is safe and works in patients, not wait to find out in clinical trials which can be expensive and time-consuming”¹

Complexity of a living organism

1. Is the drug safe and well tolerated in NHPs?
2. Does it reach the target cell in NHPs?
3. Does it correct the gene expression deficit?
4. Does it rescue the disease phenotype?

Non-Human Primates (NHPs)



Complexity of the actual human disease

Patient-derived ‘retina-in-a-dish’



5. Is this drug safe and effective in humans?

The combination of these two models provides unique insight into the prospects of a successful path through the clinic

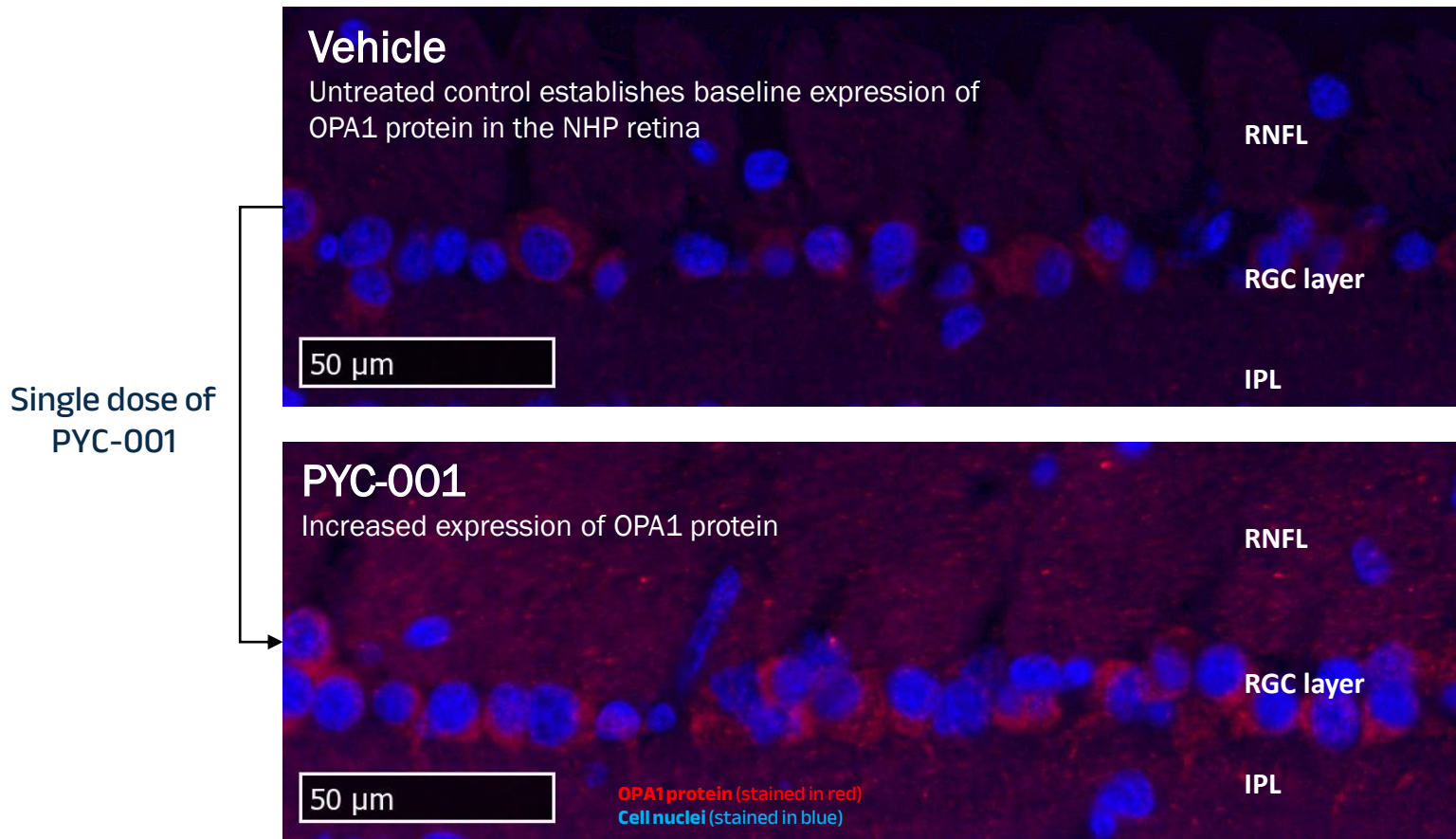
Drug delivery is critical to the success of RNA therapeutics in clinical development

“While everybody else was so hyped and giving Nobel Prizes for CRISPR and all that, we realized those weren’t really the limitations

The limitations were really delivery”

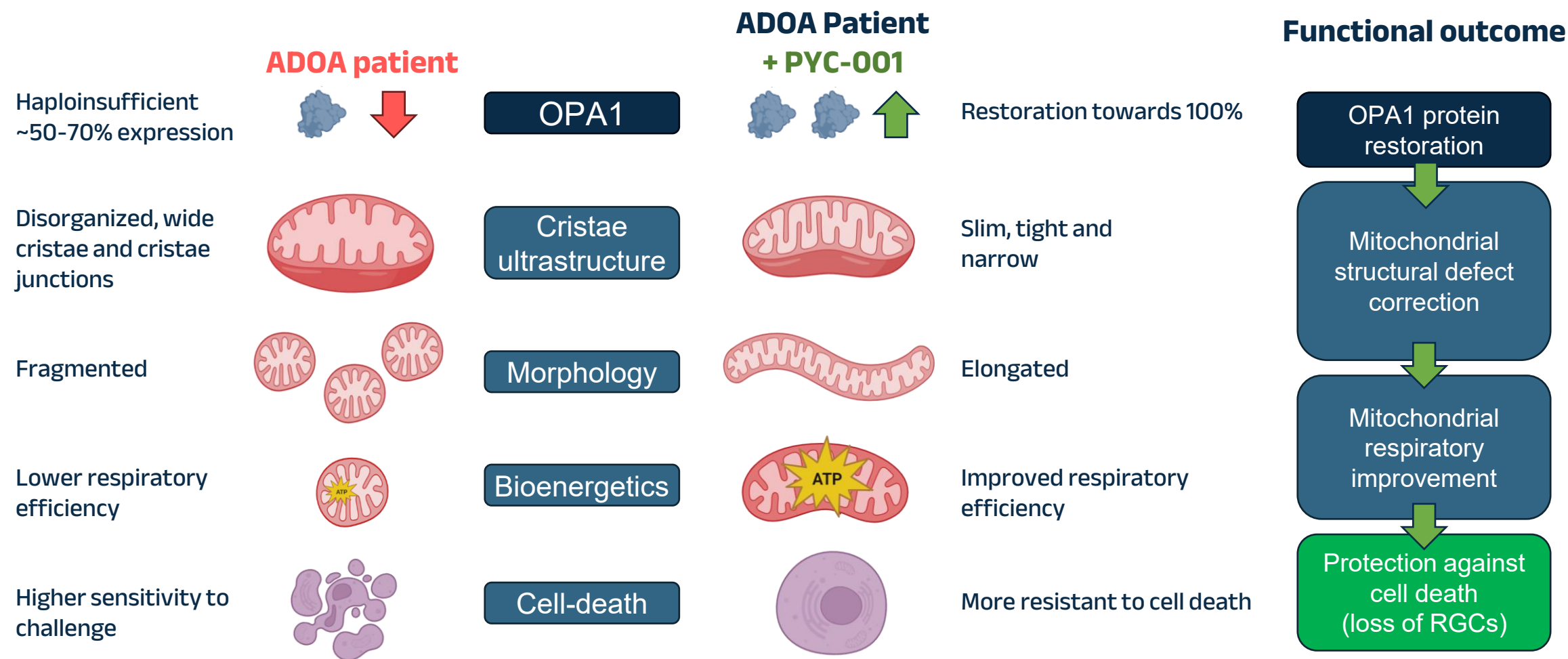
George Yancopoulos, President and CSO, Regeneron

PYC-001 increases OPA1 protein expression in the NHP retina



- A single 15 μ g dose of PYC-001 increases OPA1 protein expression in NHPs in the two cellular layers affected by ADOA¹
- This result was achieved with a dose of PYC-001 that is safe & well tolerated in NHPs¹
- The 1.6 fold increase in OPA1 protein expression seen *in vivo* in NHPs¹ is associated with rescue of the functional deficits seen in ADOA patient-derived models *in vitro*²

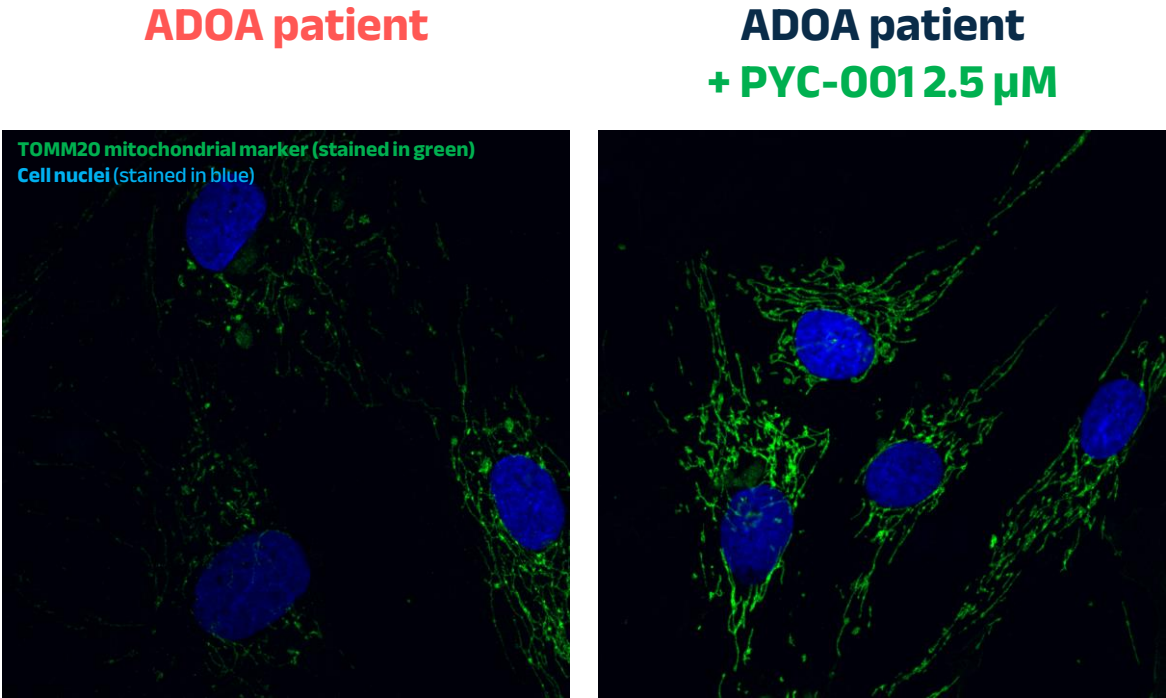
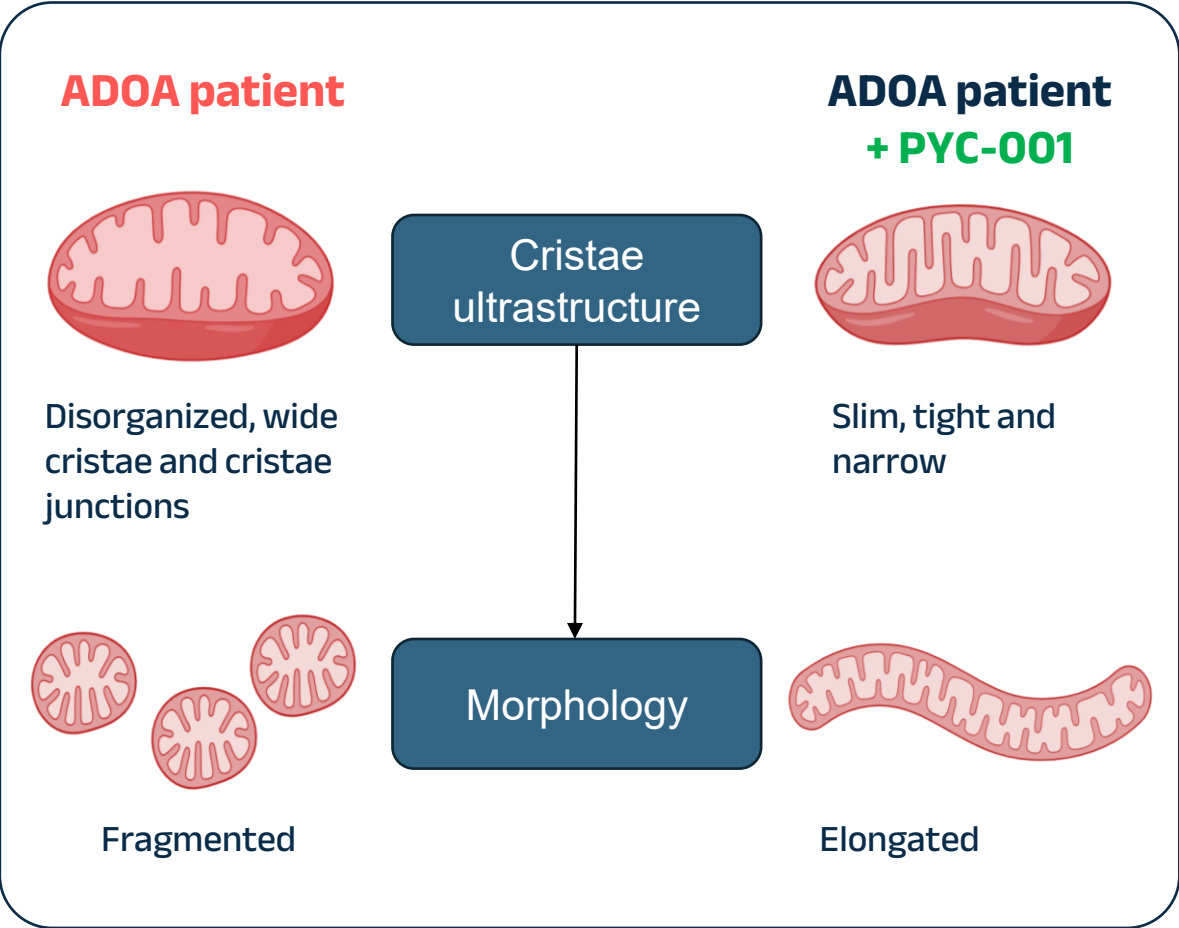
Patient-derived models enable PYC to evaluate the impact of PYC-001 on the disease-causing cascade that leads to blindness in ADOA



PYC-001 treatment restores mitochondrial structural defects in ADOA patient-derived models



Correction of mitochondrial structural defects in ADOA Patient Derived Models following treatment with PYC-001¹



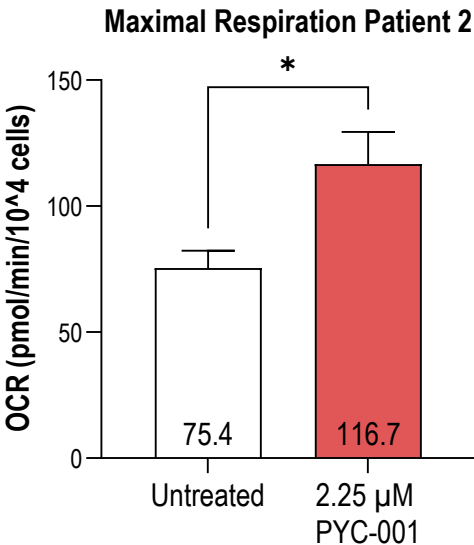
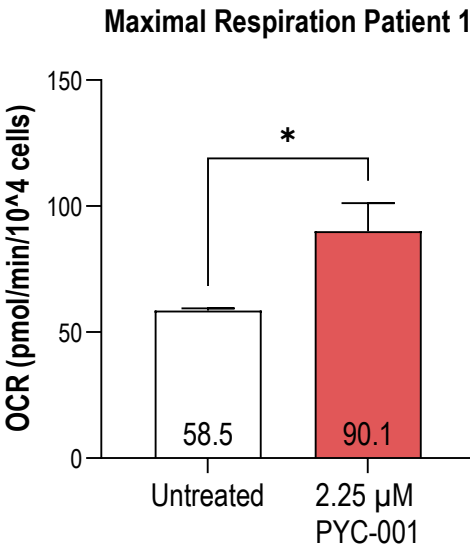
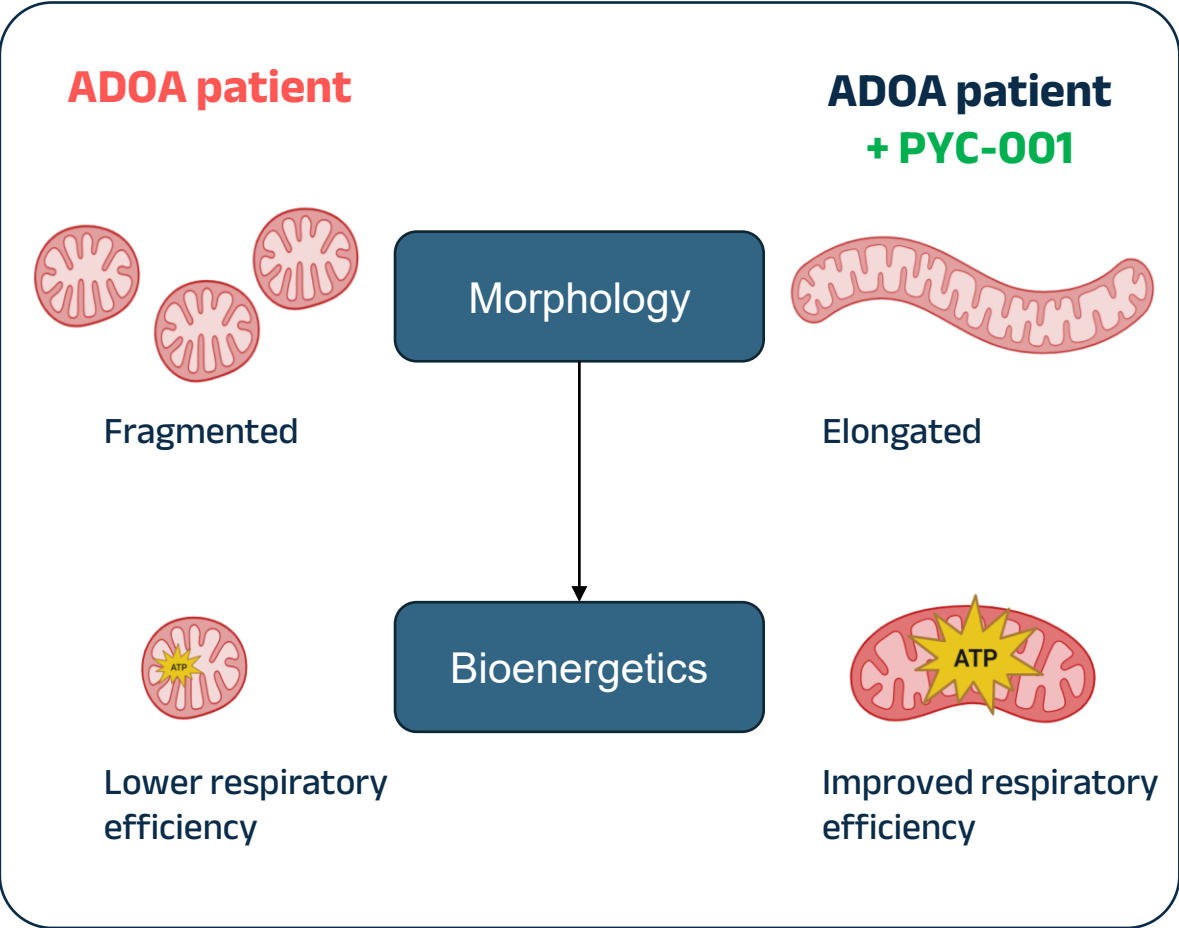
Treatment with PYC-001 restores cristae ultrastructure and morphology in ADOA patient cells

1. ADOA patient-derived fibroblast cells treated with vehicle control (galactose) compared to PYC-001 2.5 μM

PYC-001 treatment restores cellular bioenergetics in ADOA patient-derived models



~1.5-fold increase in cellular bioenergetics in ADOA Patient Derived Models following treatment with PYC-001¹



✓ **Restoration of RGC bioenergetics in a mutation agnostic manner**

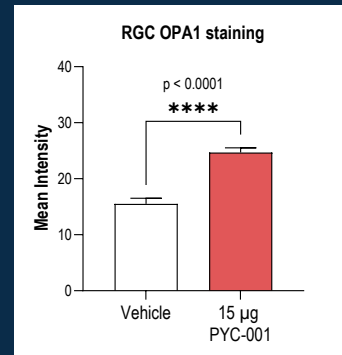
1. Enriched iPSC-RGCs were treated with PYC-001 at indicated concentration and incubated for 7 days and cells were measured for Oxygen Consumption Rate (OCR) using Seahorse Cell Mito Stress assay. Patient 1 and Patient 2 have different mutations in OPA1. Units are pmol/min/10⁴ cells. OCR normalized to total cell count and plotted against untreated control. Bar graph represents mean + SEM of >6 individual measurements. n=1 biological replicate. Statistical difference was analyzed using One-way analysis of variance (ANOVA). *p=0.05, **p=0.01, ***p=0.005, ****p=0.0001.

Both the NHP and patient-derived model data is linked by an increase in OPA1 protein expression of ~1.5-fold

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Complexity of a living organism

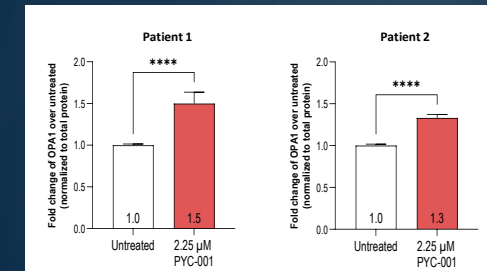
Non-Human Primates (NHPs)¹



Link
~1.5-fold
increase in
OPA1
protein

Complexity of the actual human disease

Patient-derived 'retina-in-a-dish'²



5. Is this drug safe and effective in humans?

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PYC is progressing PYC-001 into human trials next year

- FDA Pre-IND meeting late October 2023
- Natural History Study commencing 4Q23
- GLP animal studies commencing 4Q23 to support IND lodgement
- Anticipated IND lodgement Q2 2024