PYC Therapeutics

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 pack[1] – 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

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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

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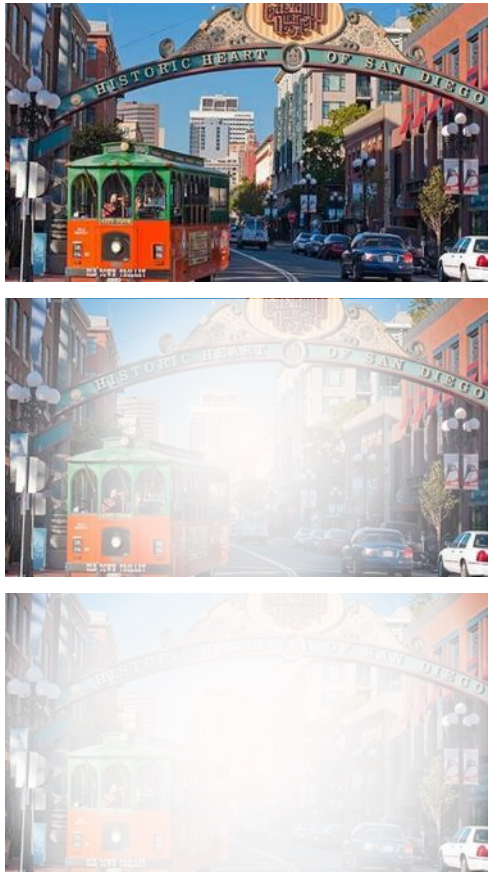
Autosomal Dominant Optic Atrophy (ADOA)

- 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 10[1]
- **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 studies[3]

Degenerative sight of an ADOA patient

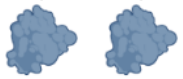


1. Yu-Wai-Man, P. et al. Ophthalmology. 2010;117(8):1538-46 doi: 10.1016/j.ophtha.2009.12.038
2. Amati-Bonneau, P. et al. OPA1-associated disorders: phenotypes and pathophysiology. The international journal of biochemistry & cell biology, 2009;41(10), 1855–1865. doi: 10.1016/j.biocel.2009.04.012
3. Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank. doi: https://doi.org/10.1101/2020.11.02.20222232
4. Althobaiti H, et al. Disentangling the Cost of Orphan Drugs Marketed in the United States. Healthcare (Basel). 2023;11(4).

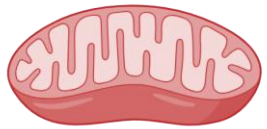
The deficiency of OPA1 protein in ADOA patients triggers a cascade of bioenergetic deficits that culminate in cell death and loss of vision

Unaffected bioenergetics

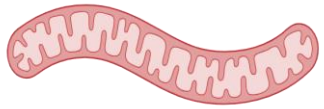
Wild type OPA1 protein expression (100%)



Slim and tight mitochondrial ultrastructure



Elongated mitochondria



Improved respiratory efficiency

More resistant to cell death

OPA1

Cristae ultrastructure

Morphology

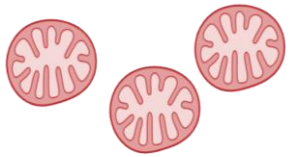
Bioenergetics

Cell-death

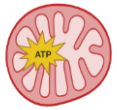
Bioenergetics in ADOA

Haploinsufficient ~50-70% expression

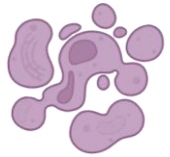
Disorganised mitochondria with wide cristae and cristae junctions



Fragmented mitochondria



Lower respiratory efficiency



Higher sensitivity to challenge

Loss of vision

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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

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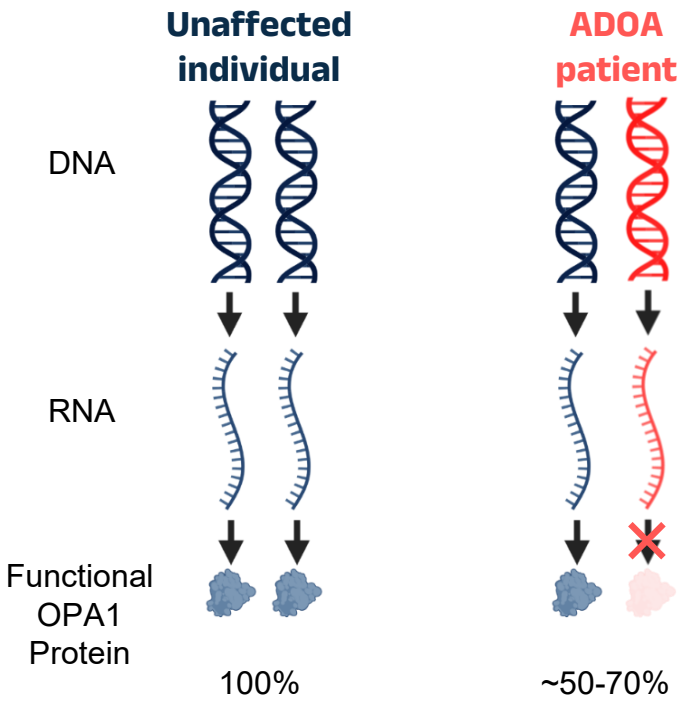
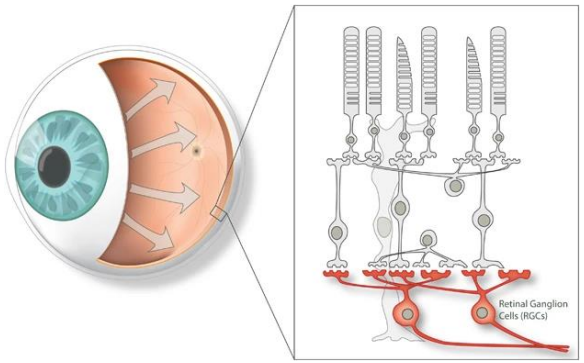
Mechanism of disease causation

ADOA patients have a mutation in one copy of the *OPA1* gene causing an **insufficient level of OPA1 protein in the RGCs**



In ADOA, the **retinal ganglion cells (RGCs),** that make up the optic nerve are affected

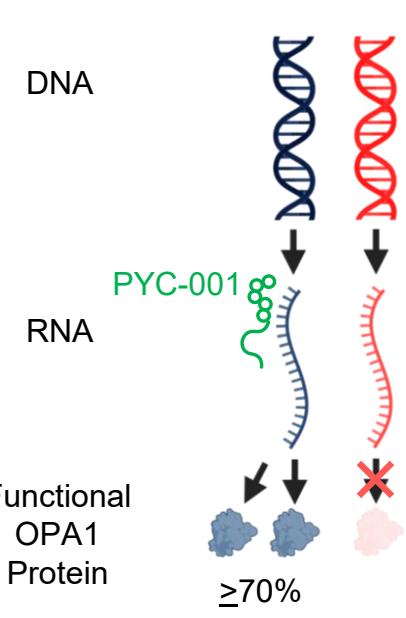


Decreased OPA1 protein leads to:

- Compromised mitochondrial function
- Reduced cellular bio-energetics
- Increased ROS and apoptosis
- RGC atrophy and vision decline

Treatment with PYC-001

PYC-001 treatment **increases functional OPA1 protein expression** in a **mutation agnostic manner** while maintaining **OPA1 isoform balance**



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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

Complexity of the actual human disease

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)

Link

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

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1. https://endpts.com/roche-launches-institute-of-human-biology-in-search-of-predictive-models/

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

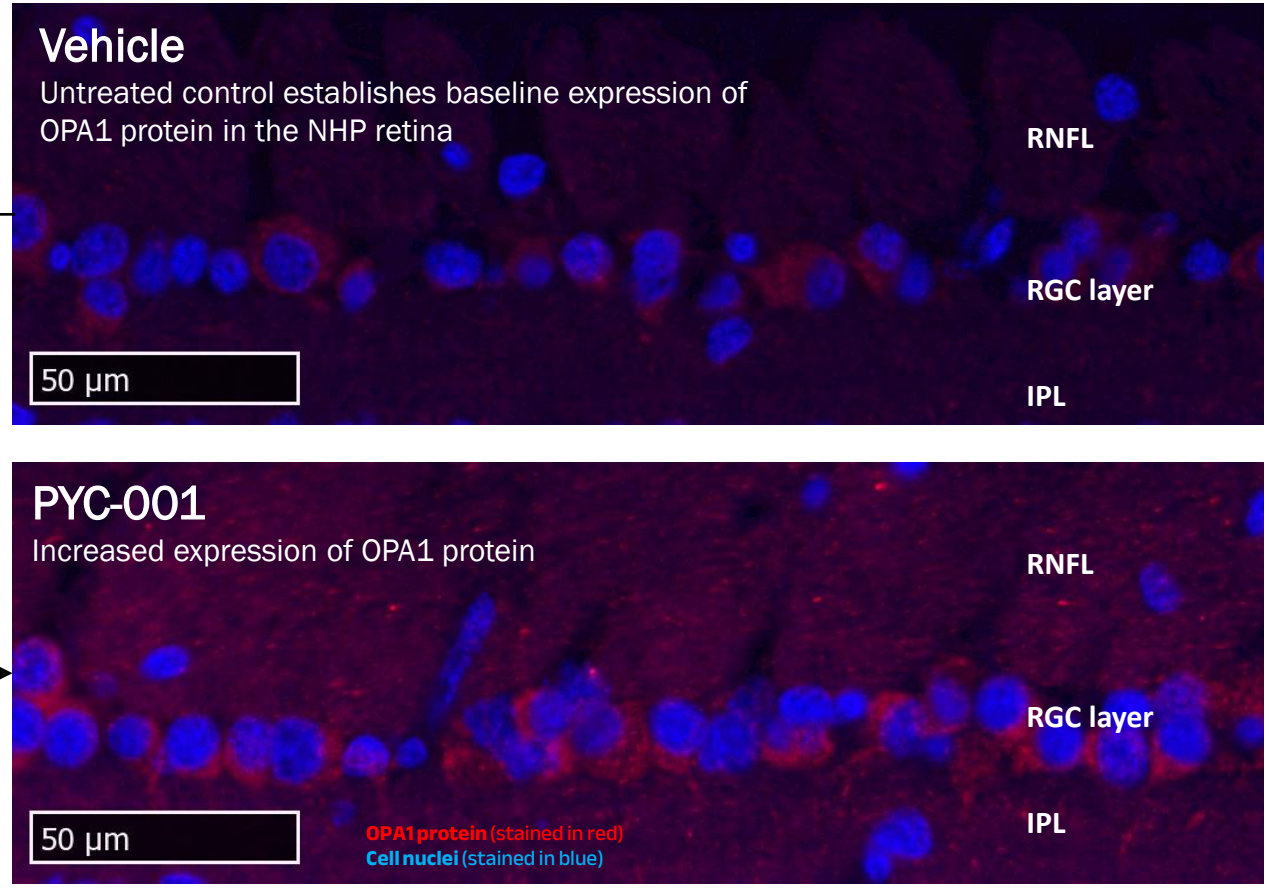
The limitations were really delivery"

George Yancopoulos, President and CSO, Regeneron

1. https://endpts.com/regeneron-brings-its-antibody-chops-to-gene-editings-biggest-problem/

PYC-001 increases OPA1 protein expression in the NHP retina

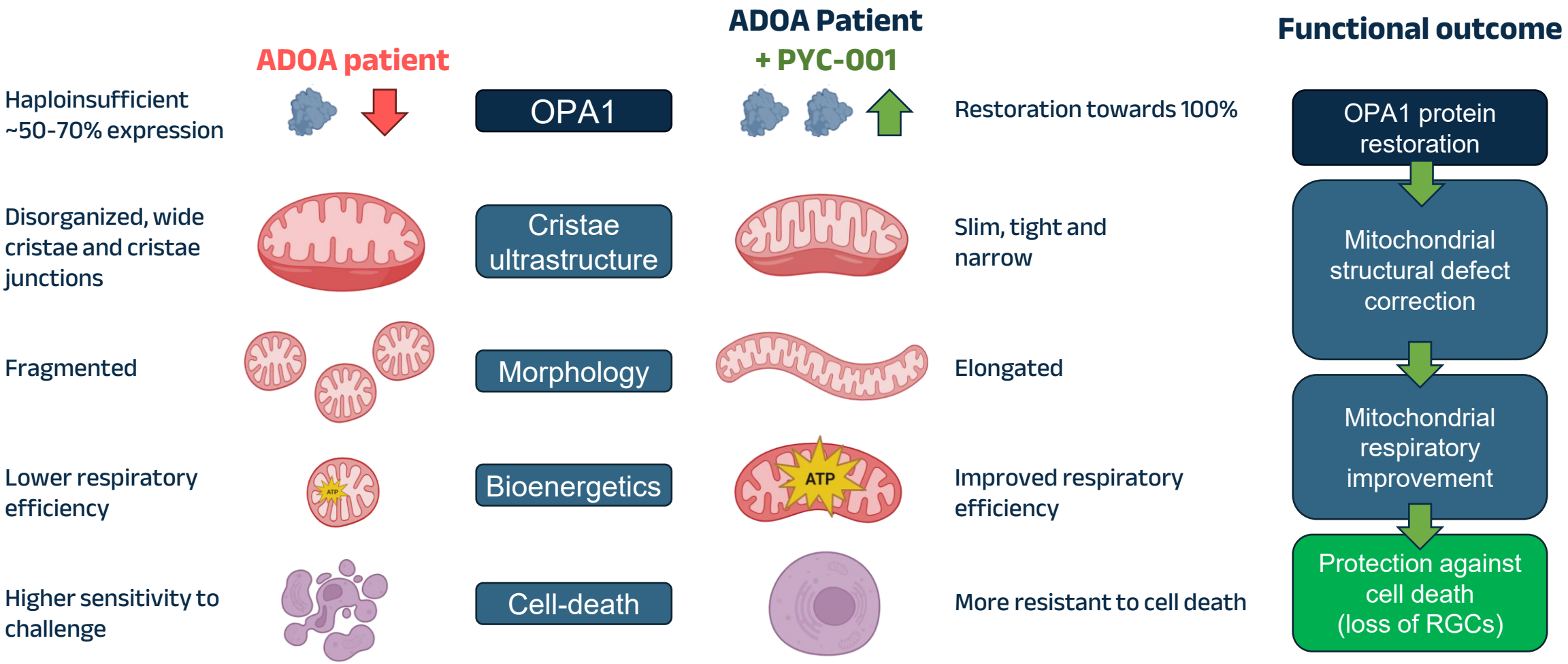
Single dose of PYC-001



- A single 15 µg dose of PYC-001 increases OPA1 protein expression in NHPs in the two cellular layers affected by ADOA[1]
- This result was achieved with a dose of PYC-001 that is safe & well tolerated in NHPs[1]
- The 1.6 fold increase in OPA1 protein expression seen *in vivo* in NHPs[1] is associated with rescue of the functional deficits seen in ADOA patient-derived models *in vitro*[2]

1. Refer ASX announcement 4 October 2023
2. Refer ASX announcement 3 April 2023

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



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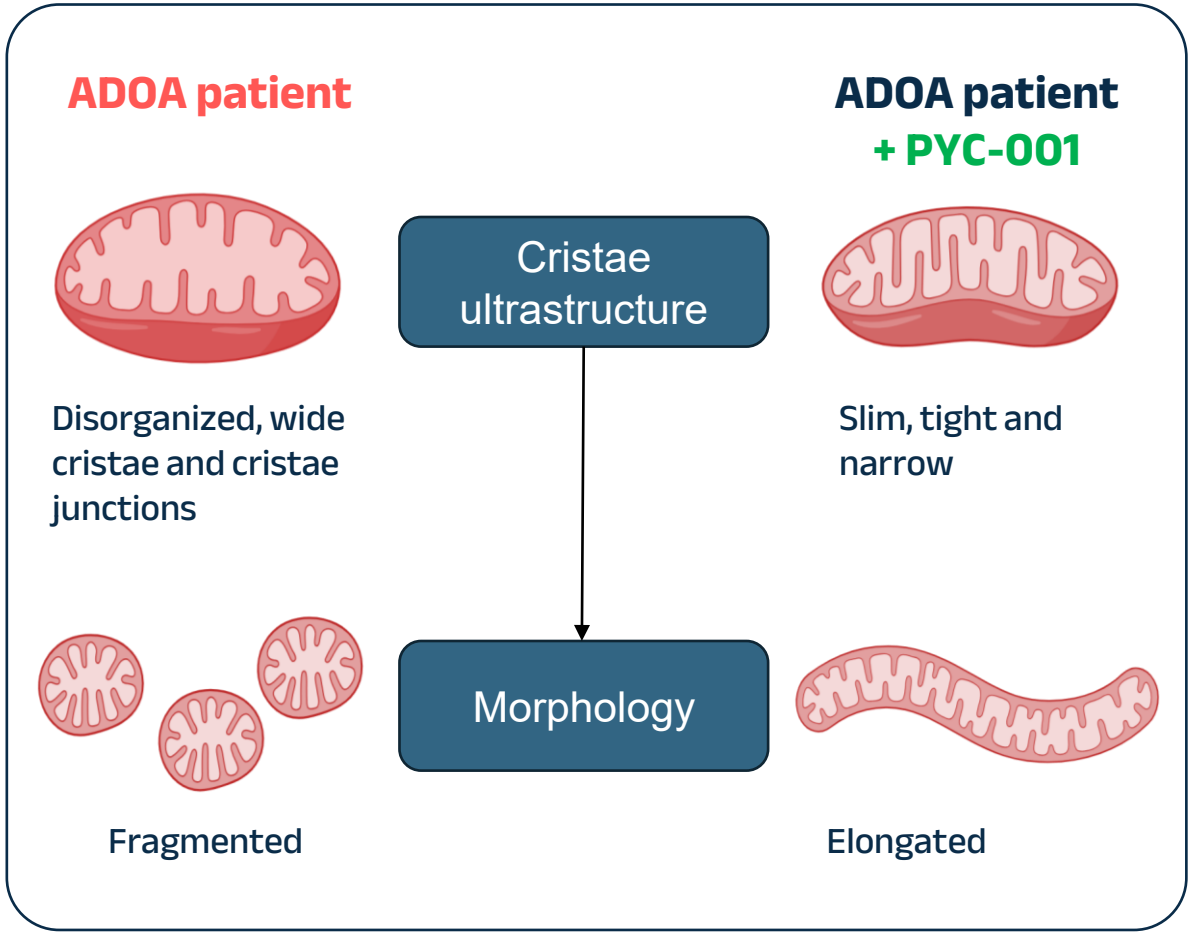
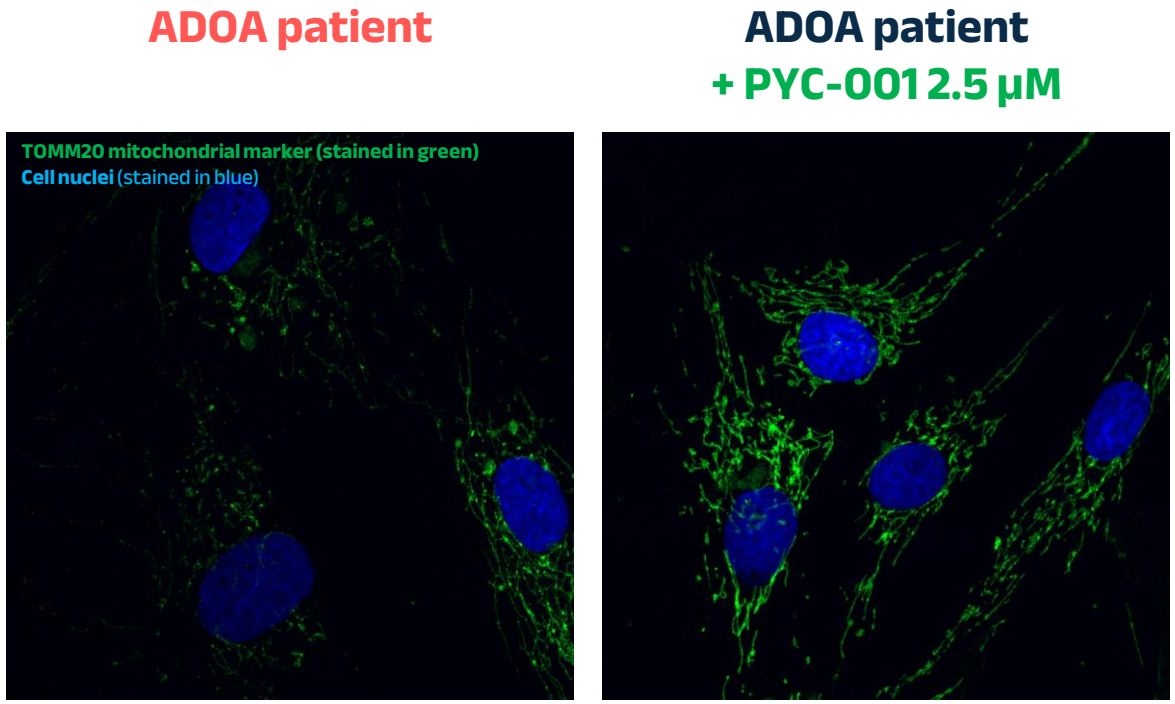
PYC-001 treatment restores mitochondrial structural defects in ADOA patient-derived models

Correction of mitochondrial structural defects in ADOA Patient Derived Models following treatment with PYC-001 [1]



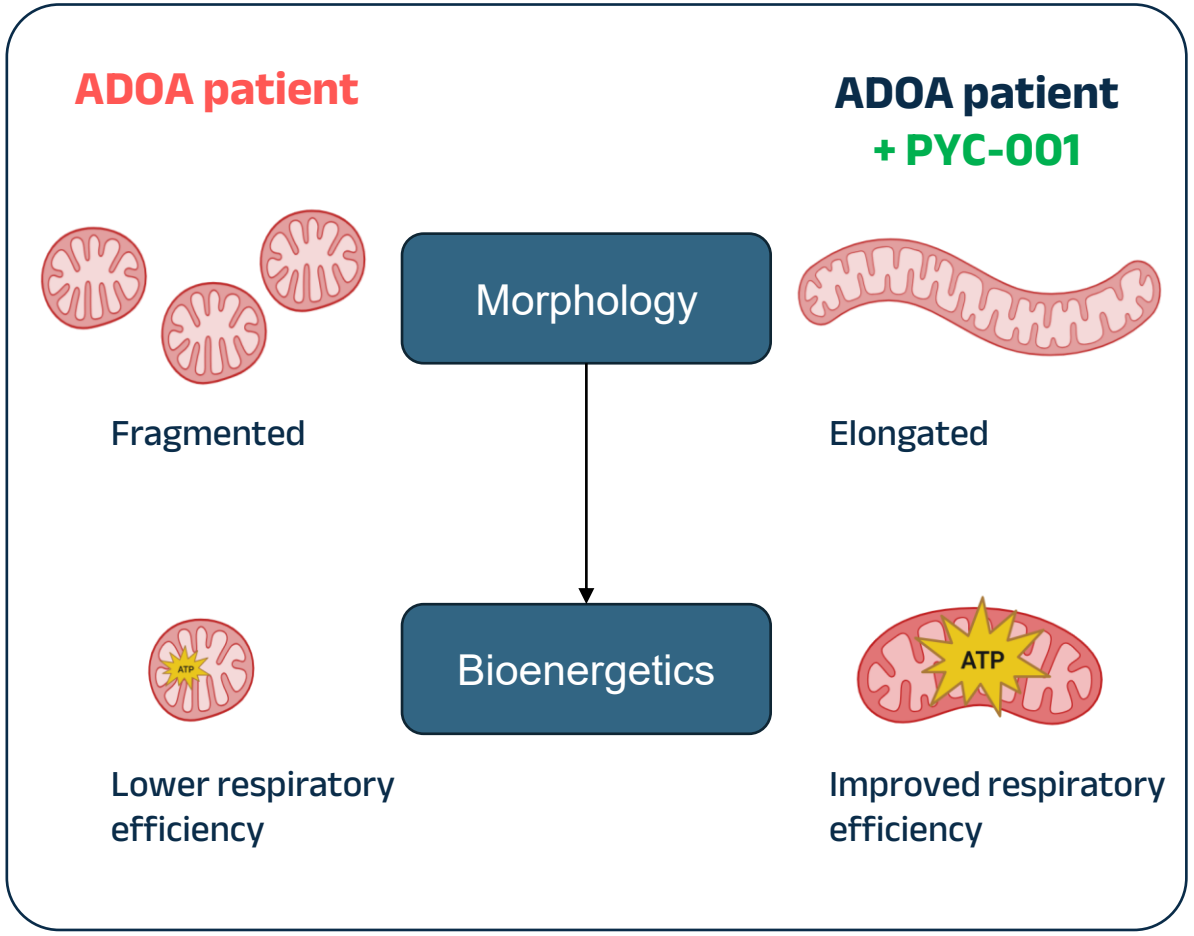


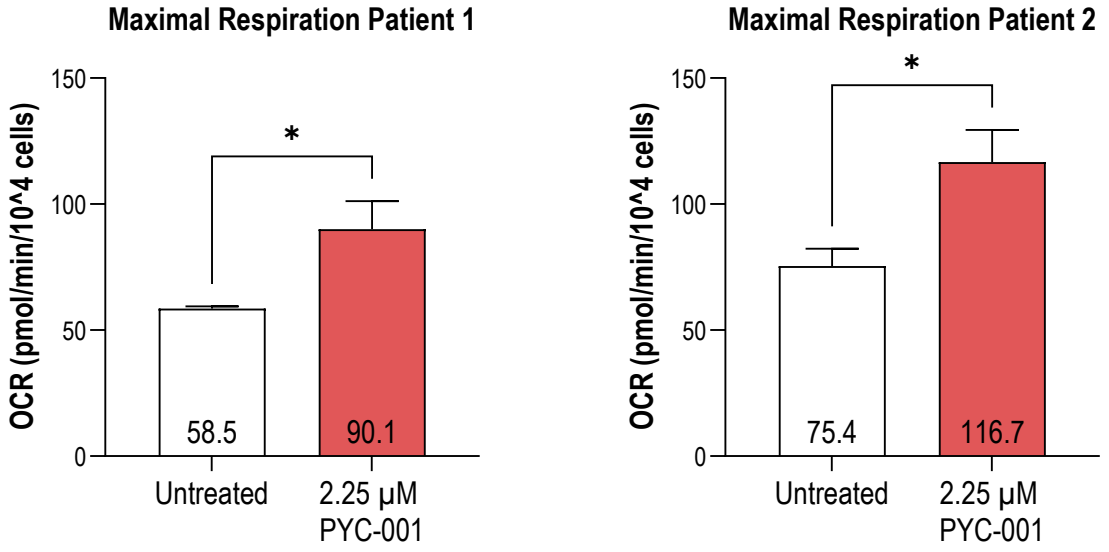
Treatment with PYC-001 restores cristae ultrastructure and morphology in ADOA patient cells

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-001[1]





✓ **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/10^4 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

Complexity of a living organism

Complexity of the actual human disease

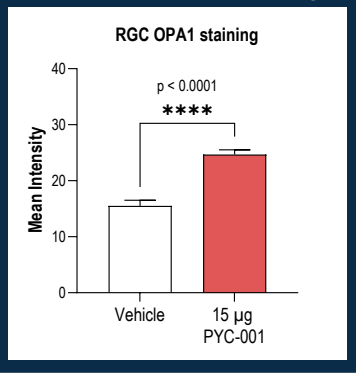
1. Is the drug safe and well tolerated in NHPs?

2. Does it reach the target cell in NHPs?

3. Does it correct the gene expression deficit?

4. Does it rescue the disease phenotype?

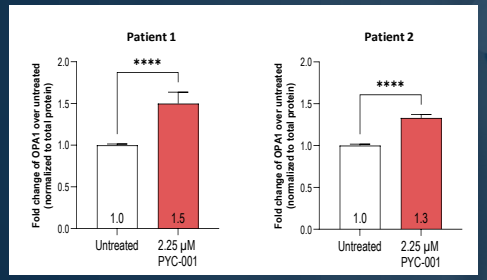
Non-Human Primates (NHPs)[1]



Link

~1.5-fold increase in OPA1 protein

Patient-derived 'retina-in-a-dish'[2]



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

1. This result was achieved at a dose that was safe and well-tolerated in NHPs illustrating that PYC-001 is pharmacologically active and capable of achieving the desired increase in OPA1 protein – the underlying cause of disease. Quantification of OPA1 protein by immunofluorescence in the Retinal Ganglion Cell (RGC) layer in NHPs with and without treatment with PYC-001. The results show a statistically significant ([p<0.0001] by unpaired t test) increase in intensity of OPA1 signal in the PYC-001 group following a single safe and well-tolerated dose of PYC-001. n = 4
2. Enriched iPSC-RGCs were treated with PYC-001 at indicated concentrations in triplicates and incubated for 5 days and cells were harvested for OPA1 protein assessment using a WB assay. Bar graph represents mean+S.D. n=1 biological replicate per patient line. Statistical difference was analyzed using Student's t-test. *p=0.05, **p=0.01, ***p=0.005, ****p<0.0001.

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

Managements best estimate 4 October 2023