Executive summary – PYC's third drug development program

- Autosomal Dominant Optic Atrophy (ADOA) caused by mutations in the *Optic Atrophy 1* (*OPA1*) gene affects >8,000 patients in the Western World
- ADOA is a 'monogenic' disease (a disease caused by a mutation in a single gene) where the mechanism of disease is caused by haploinsufficiency (insufficient protein levels caused by a loss of function mutation in one of the two copies of the *OPA1* gene)
- PYC has designed an oligonucleotide capable of correcting the OPA1 protein haploinsufficiency in cells derived from ADOA patients (>100% protein upregulation in patient fibroblasts)
- PYC has filed for intellectual property protection over this drug program
- The Company will now create a drug through conjugation (joining) of this oligonucleotide to one of PYC's proprietary Cell Penetrating Peptides (CPP) and validate this drug in more sophisticated ADOA patient disease models before deciding whether to progress the candidate into clinical development
- This drug development program will benefit from a number of synergies with PYC's lead drug program and is expected to have a rapid development pathway

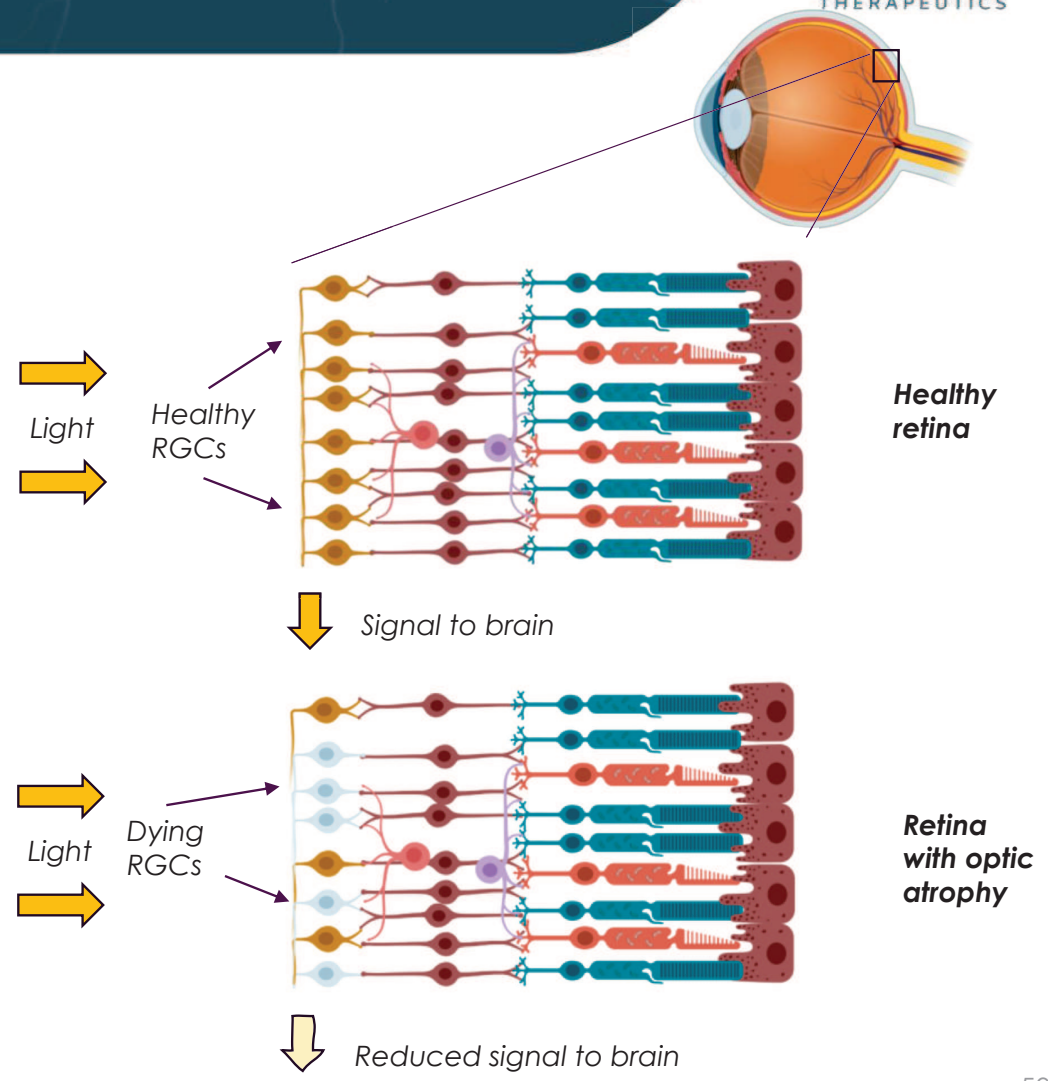
Autosomal Dominant Optic Atrophy

ADOA is caused by the optic nerve cells (retinal ganglion cells, RGCs) losing their ability to transmit visual signals to the brain

- **This can cause severe vision loss in the patient**
- **Vision loss often starts before the age of 10**

Affects approximately 1 in 30,000 people

- **~70% of all ADOA is caused by mutations in mutation in one gene, *OPA1***
- **~75% of cases caused by *OPA1* mutations are due to low levels of the OPA1 protein**



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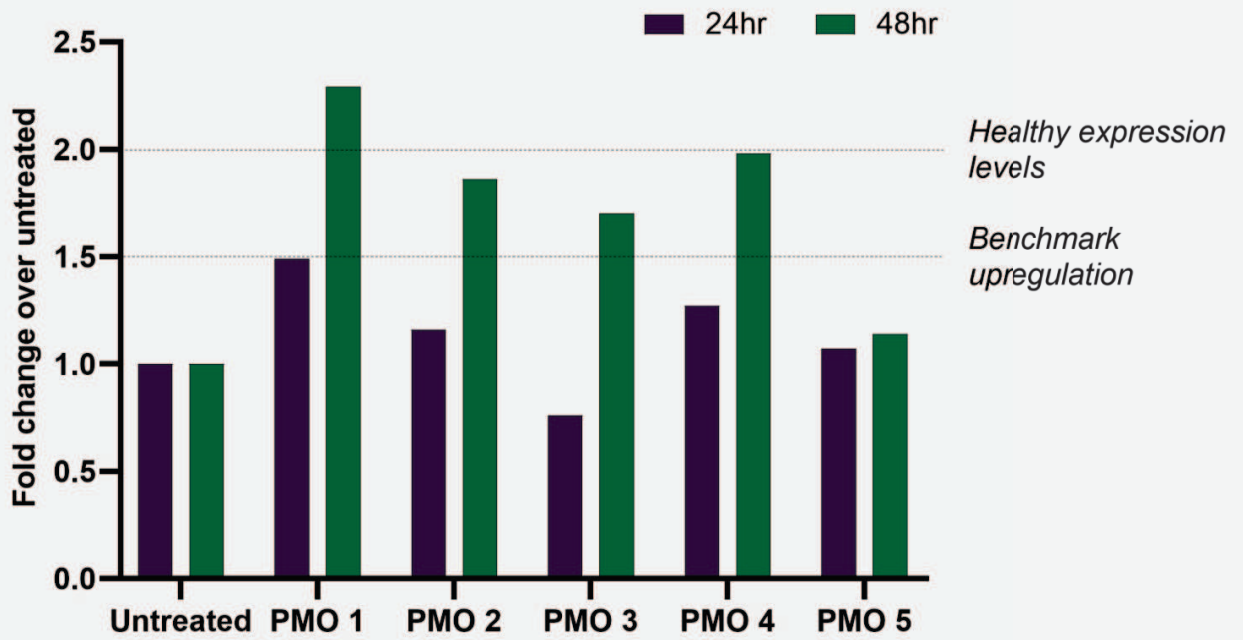
This increase has been replicated in ADOA patient fibroblasts

Change in OPA1 protein levels, 50μM PMO treatment, patient fibroblasts



For upregulation benchmark see poster 'Antisense oligonucleotide mediated increase of OPA1 expression using TANGO technology for treatment of autosomal dominant optic atrophy' Fig.6 at *https://www.stoketherapeutics.com/wp-content/uploads/ASGCT2020_final.pdf*

PYC's path to validating a therapeutic for ADOA

- ☐ Validate CPP-PMO conjugate in multiple human cell models
- ☐ Validate leads in ADOA patient-derived target cell models for target engagement
- ☐ Validate leads in ADOA patient-derived target cell models for functional readouts
- ☐ Complete preliminary toxicology and QC studies
- ☐ Determine if there is an appropriate in vivo efficacy model