



Life-changing  
science

# PYC's VP-002 program for Autosomal dominant optic atrophy

**June 2021**

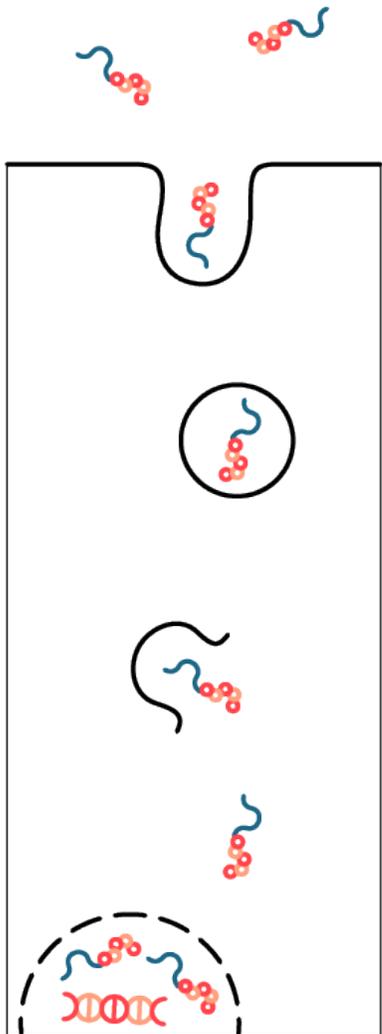
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## PYC is an RNA therapeutics company developing drugs for a range of genetic conditions



### Leading-edge RNA Therapeutics



Novel Technology Platform built on Cell Penetrating Peptide-PMO technology. PPMOs solve delivery challenge and get more drug safely into cells

### Programs in diseases of Eye and CNS



First focusing on three ocular diseases for clinical POC; Expanding discovery into high unmet need CNS conditions

### Attractive Commercial Opportunities



Dual lead programs are first disease modifying therapies for 2 important inherited retinal diseases (Retinitis Pigmentosa type 11 and Autosomal Dominant Optic Atrophy)

### Several Upcoming Catalysts Next 12-18 Months



Lead program VP-001 to enter clinic, multiple key preclinical data readouts, expand pipeline with 2-3 new development candidates

### Strong Corporate Profile and Leadership Team



Expanding core, U.S.-based leadership team and development functions; publicly-traded on ASX with multi-year cash runway

# PYC's core therapeutic technology brings together two distinctive components



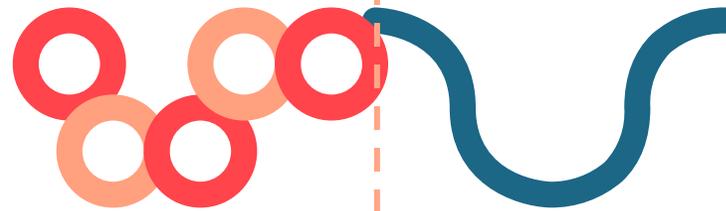
## PYC's library of Cell-penetrating peptides

Naturally-derived peptide library (500M sequences)

Sequence diversity—typically 20-30 amino acids long

Screened upfront (*in vitro* and *in vivo*) for efficacy and safety

Enable preferential delivery to target tissues and cells (and can be optimized for selectivity)



## PMO (Phosphorodiamidate Morpholino Oligomer)

Latest generation anti-sense oligonucleotide chemistry, neutral backbone

Precision and flexibility— up-regulate, down-regulate expression and isoform switch

Safer profile—avoids binding to splicing factors and other proteins inside cells

Durable profile—avoids intracellular degradation, allows for longer effect

Flexible and precise RNA therapeutic molecule with potential for broader therapeutic window, longer duration of effect and application to a range of tissue and cell types

# PYC is applying our technology to create life changing treatments, with an initial focus on diseases of the eye and CNS



## PYC is a multi-asset drug development company

Program overview			Indication and stage of development					Estimated addressable patients in Western World
Organ	Program	Target	Discovery	Lead selection	IND-enabling	Clinical	Marketed	
<b>Eye</b> 	VP-001	<i>PRPF31</i>	Retinitis pigmentosa type 11					
	VP-002	<i>OPA1</i>	Autosomal dominant optic atrophy					9,000 to 16,000
	PYC-001	<i>VEGF</i>	Diabetic retinopathy					
	Multiple	Undisclosed	Discovery pipeline					
<b>CNS</b> 	Multiple	Undisclosed	Discovery pipeline					

PYC has 100% ownership of PYC-001 and 90% ownership of VP-001 and VP-002 (10% ownership by Lions Eye Institute, Australia)

# PYC's VP-002 program for Autosomal Dominant Optic Atrophy



- **Treating an important unmet need:** PYC's VP-002 program is directed towards a rare inherited retinal disease called Autosomal Dominant Optic Atrophy (ADOA) that causes progressive blindness in patients. VP-002 addresses the most common cause of ADOA—a haploinsufficiency of the *OPA1* gene. There are currently no approved treatments, nor any in clinical development for this patient population.
- **Strong preclinical results:** Lead molecules have shown an ability to significantly increase the OPA1 protein by greater than 1.5 fold, as well as demonstrate correction of major functional deficits that drive the disease in patients—importantly including the protection of cells against apoptosis.
- **Competitively differentiated:** PYC's PPMO approach allows for a mutation agnostic therapy while retaining endogenous control over protein expression (avoiding overexpression of protein that can itself cause disease). PYC's approach also enables broader and more even distribution of drug across the retina, effective delivery into the target RGC cells, ability for broad OPA1 isoform upregulation and increased OPA1 protein upregulation resulting in improved effects on functional outcomes.
- **Path forward:** Lead PPMO molecule selection to be completed in early 2022 after *in vivo* evaluations of efficacy and biodistribution. IND-enabling studies scheduled through 2022 with Investigational New Drug filing anticipated in 1H 2023. The VP-002 program also has potential in indications outside of ADOA (both normal tension glaucoma and Parkinson's Disease) which will be further evaluated.

VP-002 program builds on PYC's ocular PPMO technology, and is expected to benefit from synergies with PYC's other lead program- VP-001 for Retinitis pigmentosa type 11

## Autosomal dominant optic atrophy (ADOA) is a genetic disease causing progressive blindness

- The majority of ADOA cases are caused by mutations in the *OPA1* gene leading to haploinsufficiency of the OPA1 protein<sup>1</sup>
- Characteristics of *OPA1* ADOA are:
  - **Severe, progressive blinding eye disease**
  - Onset between the ages of 5 and 20
  - Initially affecting central vision
  - Often progressing to blindness between 40-50 years of age

## VP-002 is a disease-modifying therapy addressing all patients with ADOA caused by haploinsufficiency of *OPA1*

- There are **no approved drugs (nor any in clinical development) for treatment of these patients**
- **9,000-16,000** estimated addressable patients in the western world<sup>1</sup>



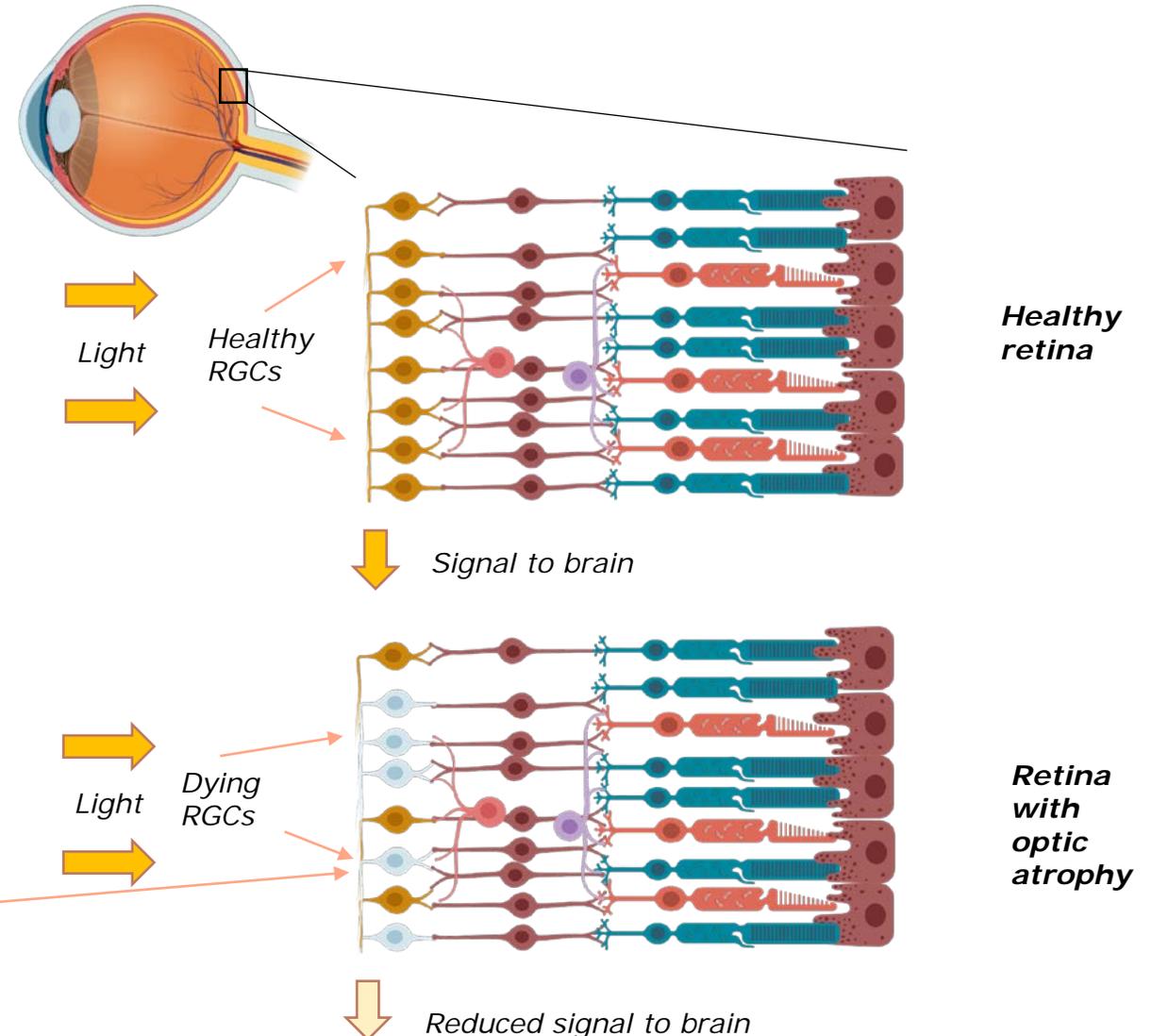
# ADOA is most frequently caused by mutations in the *OPA1* gene affecting the retinal ganglion cells

**ADOA is caused by the loss of the retinal ganglion cells (RGCs) that make up the optic nerve**

- This causes severe vision loss in the patient
- Vision loss often starts before the age of 10

**The cascade linking the *OPA1* protein insufficiency to the phenotype is well understood**

- **Decreased *OPA1* protein levels**  
↓
- Reduction in mitochondrial health (protein expression and mitochondrial fragmentation)  
↓
- **Reduced cellular bio-energetics** (ATP, membrane potential and oxygen consumption rate)  
↓
- Increase in reactive oxygen species and **apoptosis of retinal ganglion cells**  
↓
- Reduced vision

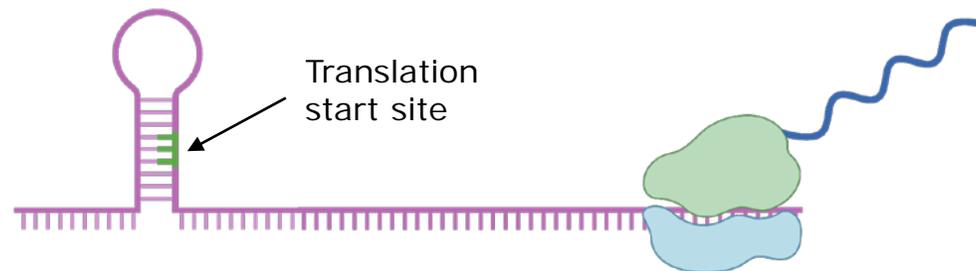


# PYC's PPMOs increase the translation rate of the healthy *OPA1* allele to increase *OPA1* protein levels

## Example of translations rate strategy

### Effect on mRNA

mRNA forms secondary structures due to Watson-Crick base pairing. This can inhibit the translation initiation machinery, reducing the translation rate of the mRNA



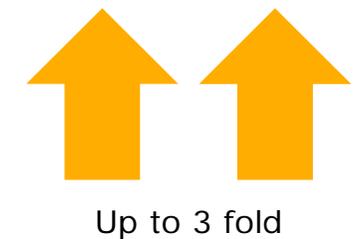
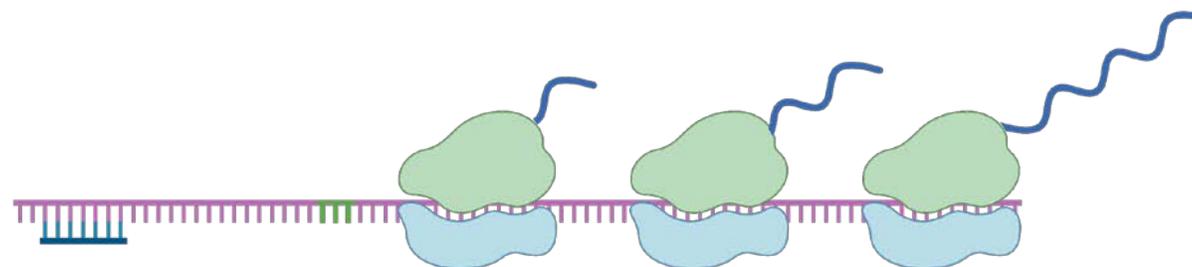
### Protein levels



PMOs can inhibit an mRNA's secondary structure by binding to the mRNA, 'opening' up the mRNA structure



This 'more open' mRNA structure enables the translation initiation machinery to engage the mRNA with more ease, increasing the translation rate of the mRNA



# Preclinical data support PYC's PPMOs as a differentiated disease-modifying approach to treat *OPA1* ADOA

## There is strong preclinical support for the VP-002 program (data broken out in subsequent slides)

-  Can **effectively reach the target neural retina cells *in vivo***, compared to alternative ASO approaches that show limited ability to reach these cells at much higher doses
-  Can **upregulate the target *OPA1* protein by > 1.5 fold** in a dose-dependent and mutation agnostic manner
-  Can **increase mitochondrial bioenergetics and ATP production** in a dose-dependent and mutation agnostic manner
-  Can protect cells from apoptosis in a mutation agnostic manner, **rescuing the critical functional deficit observed in ADOA patients** to near wild-type levels

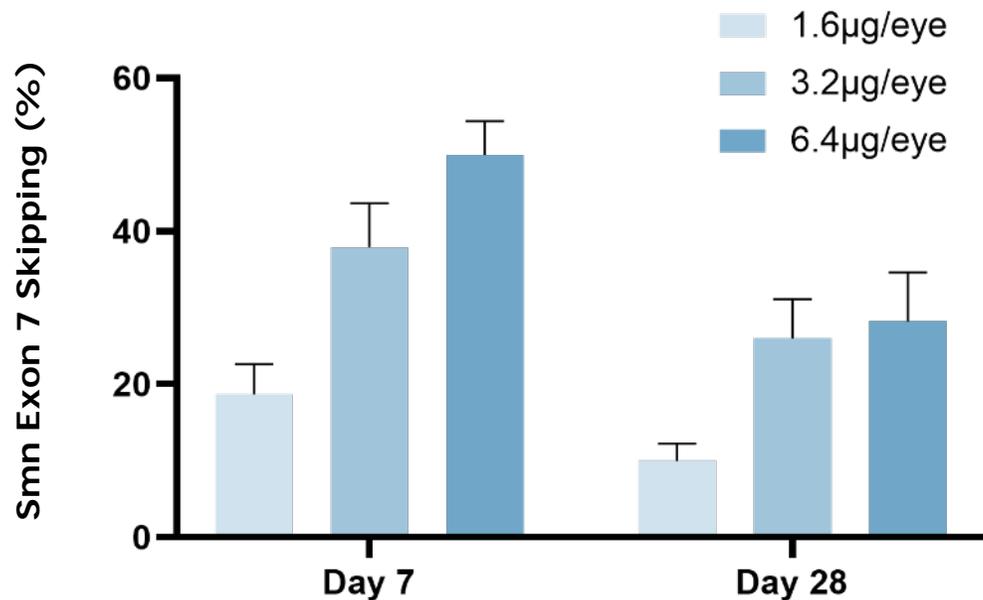
## VP-002 benefits from the inherent advantages of PYC's PPMO technology

-  **Precise therapeutic approach that avoids protein overexpression** (which itself can cause disease) and enables treatment for a broad cohort of patients
-  **Safety and durability profile of PYC's PPMO technology**, targeting 6-monthly intravitreal administration
-  Manufactured using **standard solid-phase chemistry resulting in favorable COGs** compared to gene-based or biologic approaches

# PYC's PPMOs can reach the target cell *in vivo*

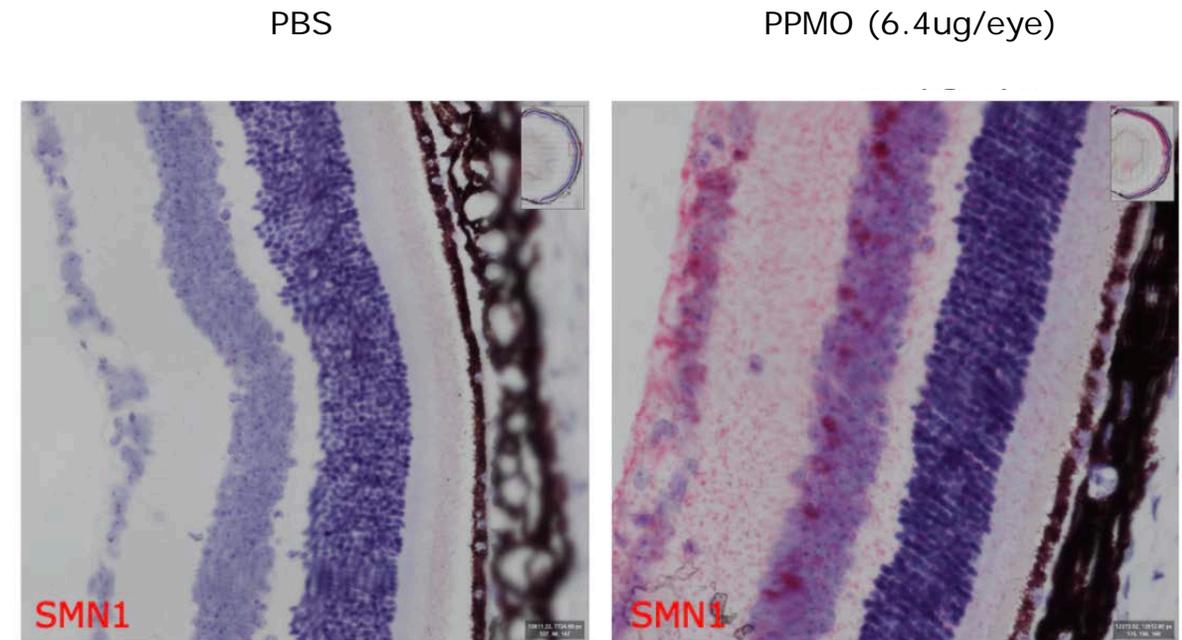
PYC's PPMOs demonstrate dose dependant uptake and long duration in the mouse neural retina

Exon-skipping in mouse neural retina, single IVT injection<sup>1</sup>



PYC's PPMOs demonstrate broad and deep distribution across the mouse retina

PPMO distribution in the mouse retina<sup>2</sup>, single 6.4µg<sup>1</sup> IVT injection

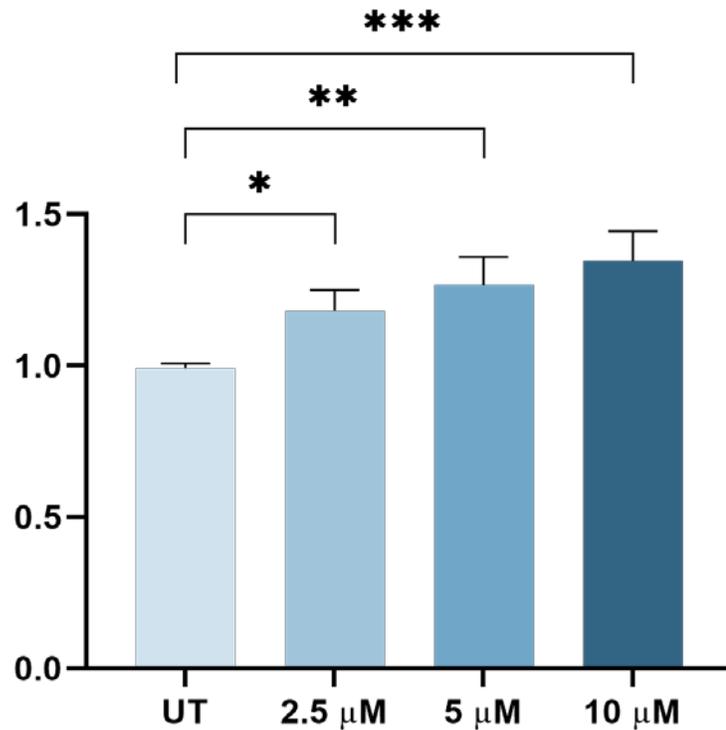


<sup>1</sup> 1.6µg is equivalent to 32.1µM concentration in the vitreous and 0.14nmols; 3.2µg is equivalent to 64.2µM concentration in the vitreous and 0.28nmols; 6.4µg is equivalent to 128.4µM concentration in the vitreous and 0.56nmols  
<sup>2</sup> PPMO localization us hybridization probes, using miRNAscope from ACDBio targeting SMN1 PPMO

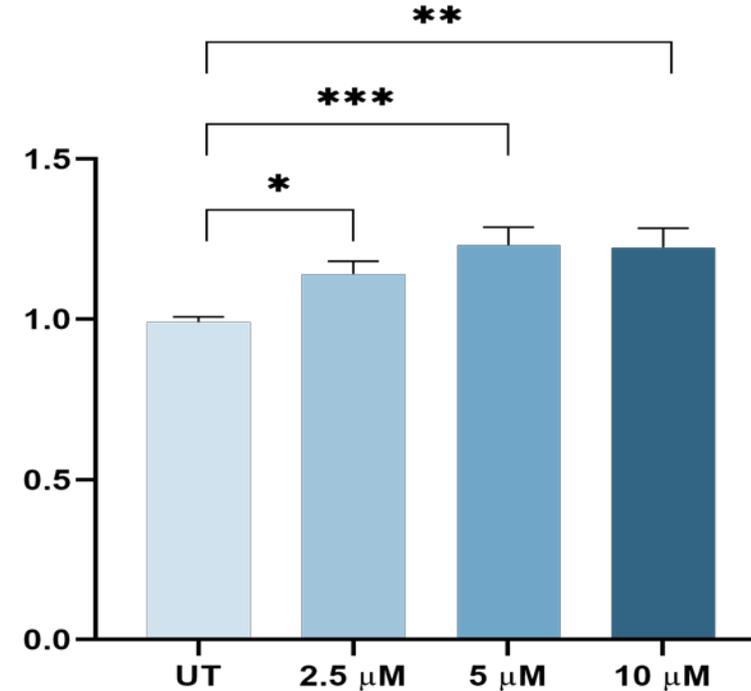
# PYC's PPMOs can increase the critical OPA1 protein in a dose-dependent and mutation agnostic manner

## Change in OPA1 protein levels, day 7 post PPMO treatment, patient fibroblasts

Patient 1, n=3



3 Patients (pooled), n=3 per patient



Statistical differences were analysed using one-way ANOVA; \* p < 0.05 \*\* p < 0.01 \*\*\* p < 0.001

Patient 1 & 3: c.2708\_2711 delTTAG

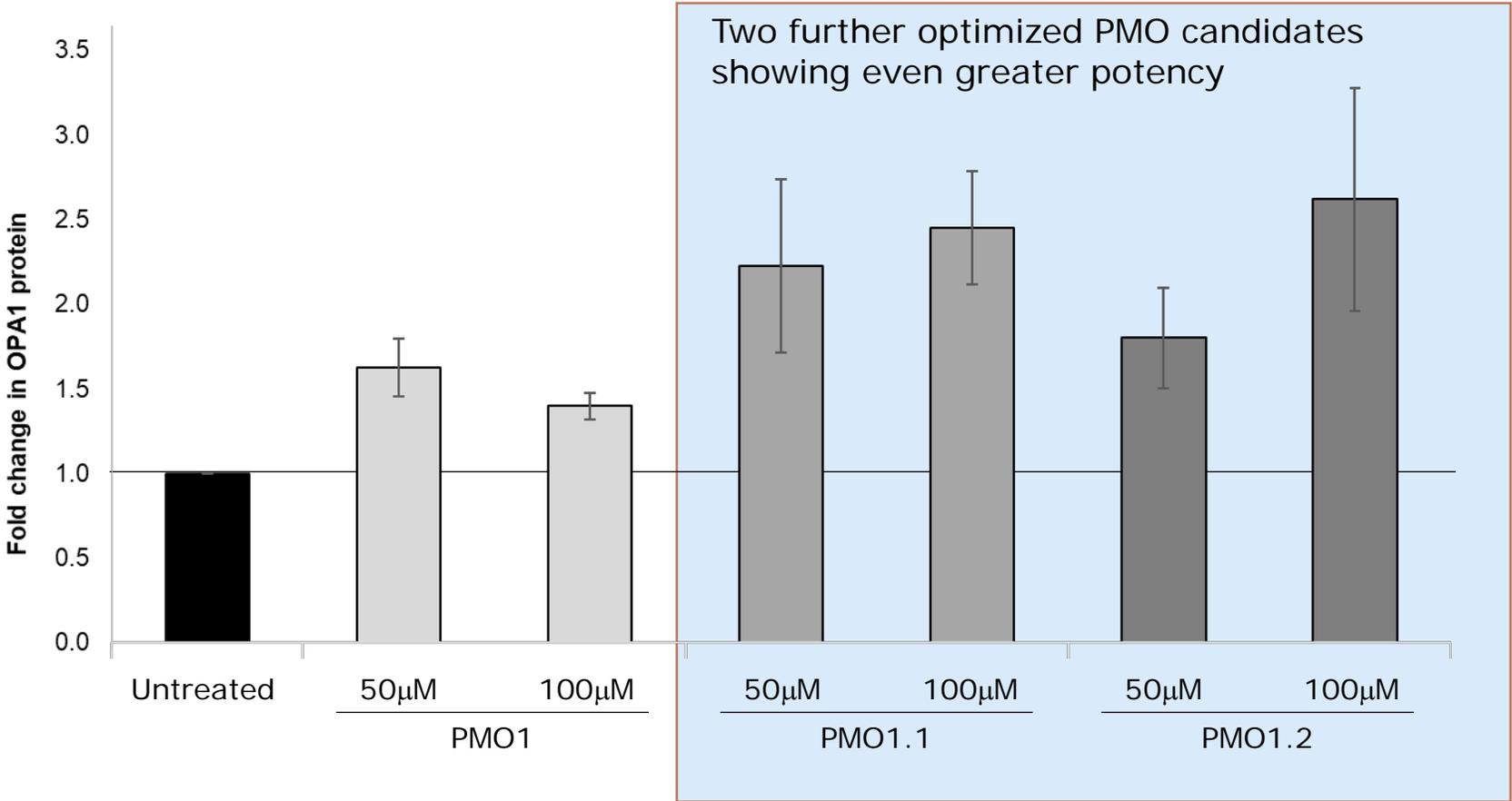
Patient 2: c.985-1G>A

See ASX Announcement 18 May 2021

# Further optimized PMO candidates have shown an ability to even further increase the OPA1 protein

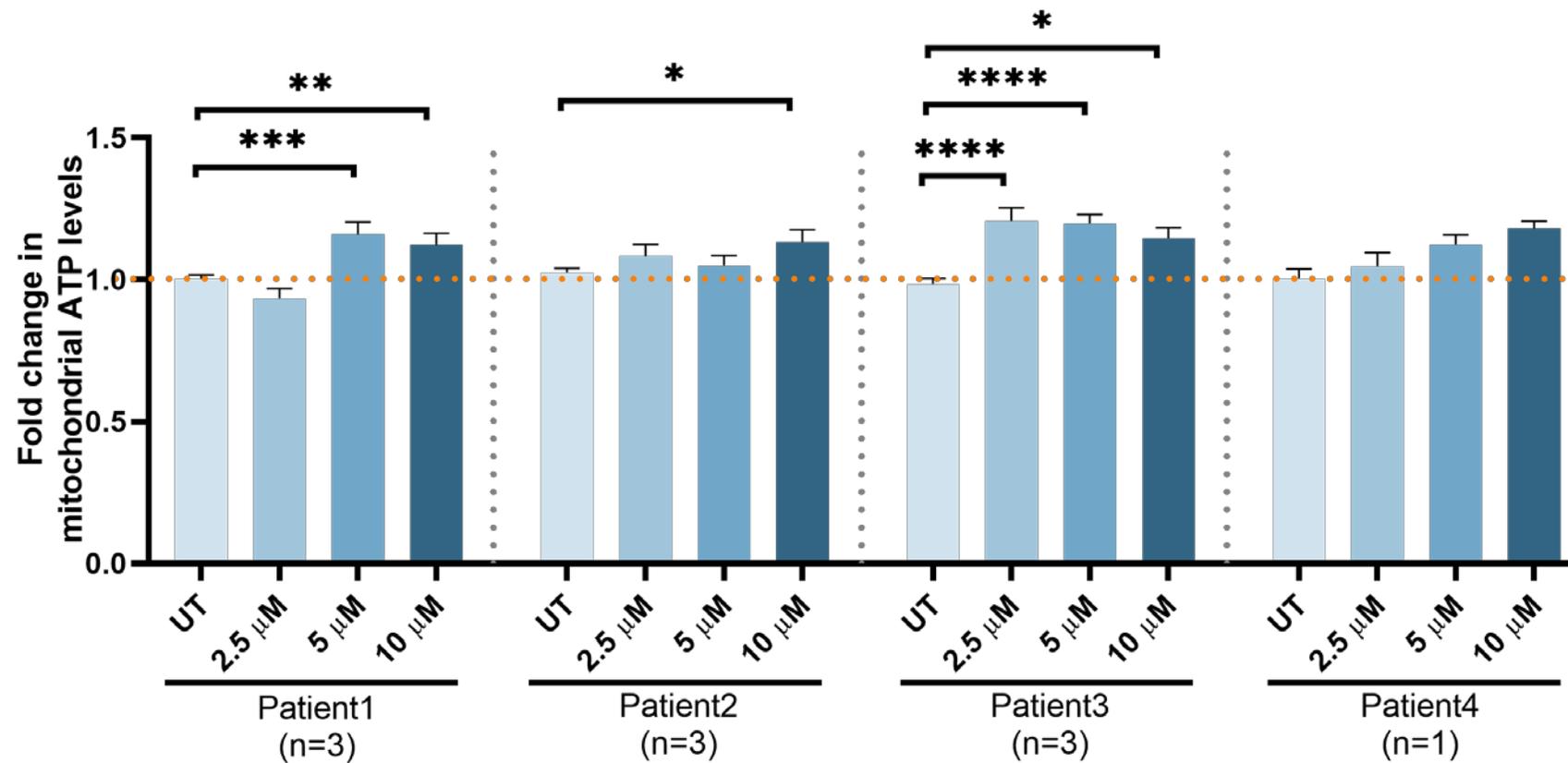


Change in OPA1 protein levels, day 2 post PMO transfection, patient fibroblasts (n=3)



# PYC's PPMOs can increase mitochondrial ATP production in a mutation agnostic manner

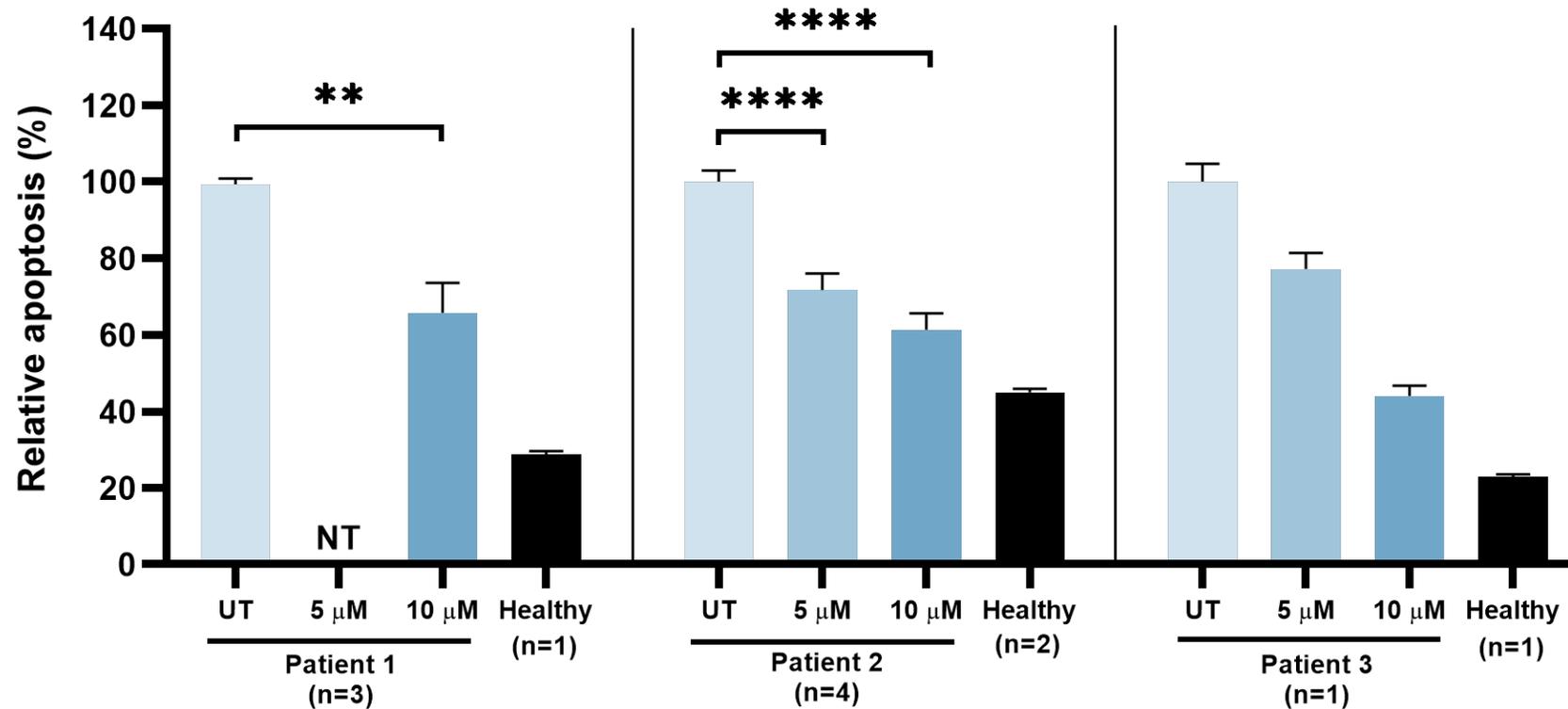
Change in mitochondrial ATP levels, day 7 post PPMO treatment, patient fibroblasts



Patient 1 and 3 harbour c.2708\_2711delTTAG deletion, Patient 2 harbours the c985-1G>A mutation. Patient fibroblasts were treated with PPMO at 5 and 10 µM, and 7 days subsequently were analysed for mitochondrial ATP. Bar graph represents fold change in mitochondrial ATP levels in patient fibroblasts treated with PPMO (mean+SEM). Untreated patient fibroblast was indexed to 1. Statistical differences one-way ANOVA; \* p<0.05 \*\* p<0.01 \*\*\* p<0.001 \*\*\*\* p<0.0001

# PYC's PPMOs can protect cells against Apoptosis in a mutation agnostic manner

## Apoptosis, relative to healthy cells day 7 post PPMO treatment, patient fibroblasts



Patient fibroblasts were pre-treated with PPMO at 5 and 10 μM for 7 days and were subsequently treated with apoptotic stimuli for 4 hr prior to analysis. Apoptotic cells were analysed using flow cytometry. Bar graph represents relative apoptosis in patient fibroblasts treated with PPMO 7 days post-treatment (mean+SEM). Patient fibroblast without PPMO treatment was indexed to 100% apoptosis. Statistical differences were analysed using one-way ANOVA; \* p≤0.05 \*\* p≤0.01 \*\*\* p≤0.001 \*\*\*\* p≤0.0001

# These demonstrated improvements in functional outcomes increase the chance of improving clinical symptoms in patients

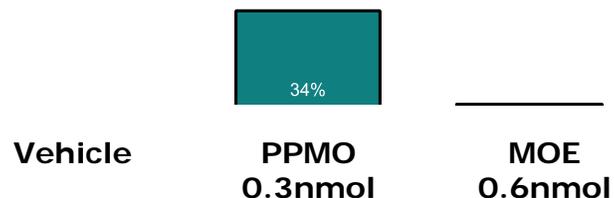


**Improvements in functional outcomes (increased bioenergetics and protection against apoptosis) have been linked to maintenance of visual acuity in *OPA1* mutation positive patients<sup>1</sup>**

PYC's PPMOs are being optimised to ensure optimal increases in OPA1 protein resulting in improved effects on functional outcomes, increasing the chance of seeing any potential improvement in clinical symptoms in ADOA patients. This is supported by two major advantages of PYC's PPMOs:

## High delivery efficacy

**Delivery efficacy in mouse neural retina, day 7 post single IVT injection**



## Optimal mechanisms of action

- PYC applied multiple upregulation strategies to identify the best engagement strategy to upregulate OPA1 protein levels
- This approach has identified strategies with the potential to upregulate OPA1 protein ~2 fold

# Preclinical data support PYC's PPMOs as a differentiated disease-modifying approach to treat *OPA1* ADOA



Can **effectively reach the target neural retina cells *in vivo***, compared to alternative ASO approaches that show limited ability to reach these cells at much higher doses



Can **upregulate the target *OPA1* protein by >1.5 fold** in a dose-dependent and mutation agnostic manner



Can **increase mitochondrial bioenergetics and ATP production** in a dose-dependent and mutation agnostic manner



Can protect cells from apoptosis in a mutation agnostic manner, **rescuing the critical functional deficit observed in ADOA patients** to near wild-type levels



Benefits from the **safety and durability profile of PYC's PPMO technology**

## Key Steps

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- Additional preclinical efficacy and safety assessments in patient-derived retinal models and animal models

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- Conclude lead selection and optimization of target PPMO molecule through multiple *in vitro* and *in vivo* assessments of safety, efficacy and biodistribution

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- IND-enabling studies (including dose-range finding toxicity followed by GLP toxicity) for lead PPMO molecule

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- Investigational New Drug filing with the FDA (clinical development anticipated to commence shortly thereafter)

## Target timing

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- Late 2021

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- Early 2022

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- Throughout 2022

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- 1H 2023