

A large, stylized letter 'P' graphic composed of two concentric, thick, curved segments. The outer segment is a light orange color, and the inner segment is a darker red color. It is positioned on the left side of the slide, partially overlapping the dark blue background.

Life-changing  
science

# August Investor Update

**August 2021**

The purpose of this presentation is to provide an update of the business of PYC Therapeutics Limited (ASX:PYC) ['PYC']. These slides have been prepared as a presentation aid only and the information they contain may require further explanation and/or clarification. Accordingly, these slides and the information they contain should be read in conjunction with past and future announcements made by Phylogica and should not be relied upon as an independent source of information. Please contact PYC and/or refer to the Company's website for further information.

The views expressed in this presentation contain information derived from publicly available sources that have not been independently verified. No representation or warranty is made as to the accuracy, completeness or reliability of the information.

Any forward looking statements in this presentation have been prepared on the basis of a number of assumptions which may prove incorrect and the current intentions, plans, expectations and beliefs about future events are subject to risks, uncertainties and other factors, many of which are outside PYC's control. Important factors that could cause actual results to differ materially from assumptions or expectations expressed or implied in this presentation include known and unknown risks. Because actual results could differ materially to assumptions made and PYC's current intentions, plans, expectations and beliefs about the future, you are urged to view all forward looking statements contained in this presentation with caution.

This presentation should not be relied on as a recommendation or forecast by PYC. Nothing in this presentation should be construed as either an offer to sell or a solicitation of an offer to buy or sell shares in any jurisdiction.

# Who's on today's call

## PYC US Development and Corporate Hub

**Sahm Nasser**, Chief Executive Officer US 



Extensive experience in commercial drug development with Merck, incl. product leadership, investor relations and business development. Consultant with McKinsey & Co prior to Merck.

**Dr Glenn Noronha**, Chief Development Officer 



Over 20 years leading drug development programs in ophthalmology, oncology, CNS and GI; multiple retina programs spanning candidate nomination through clinical development and approval. Previous C-suite & leadership roles at BridgeBio, Clearside and Alcon

**Kaggen Ausma**, Chief Business Officer 



Previous roles in McKinsey & Co across Strategy, Commercial, VC and PE, and public market finance with CLSA Asia-Pacific

## PYC Australia Discovery Hub

**Professor Sue Fletcher**, Chief Scientific Officer 



Leading global expert and pioneer in RNA therapeutics. Co-inventor of Exondys-51, Vyondys-53, and Amondys-45, commercialised by Sarepta. Prof. Fletcher leads PYC's discovery team and is the co-inventor of VP-001

**Dr Rohan Hockings**, Chief Executive Officer Australia 



Experience across both clinical and commercial roles including Private Equity, Commercial Law, and Strategy, prior to joining PYC

# PYC's distinctive PPMO technology offers key advantages

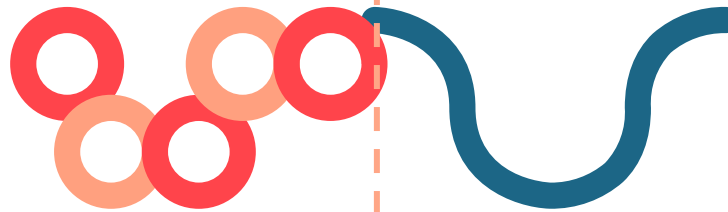
## Cell Penetrating Peptide

Naturally-derived

Sequence diversity

Screened upfront for efficacy and safety

Enable preferential delivery to target tissues and cells



## PMO (Phosphorodiamidate Morpholino Oligomer)

Latest generation ASO, neutral (uncharged)

Precision and flexibility

Safer profile

Durable profile

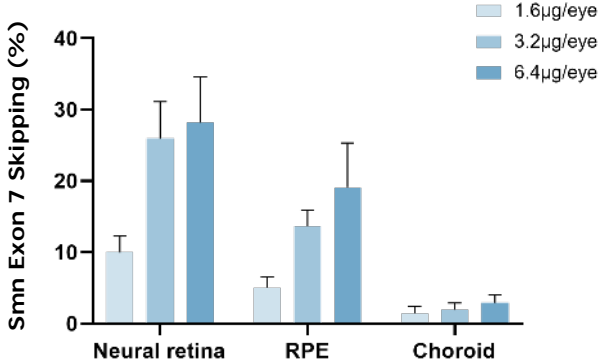
Flexible and precise RNA therapeutic molecule with potential for broader therapeutic window, longer duration of effect and application to a range of tissue and cell types

# PYC's platform has been preclinically validated across a range of applications - ocular, CNS and systemic



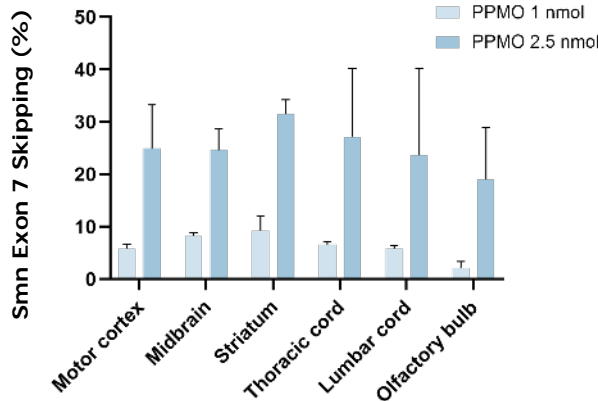
## Retinal delivery

**PMO delivery in the retina**, Day 28 in the mouse eye post single IVT injection



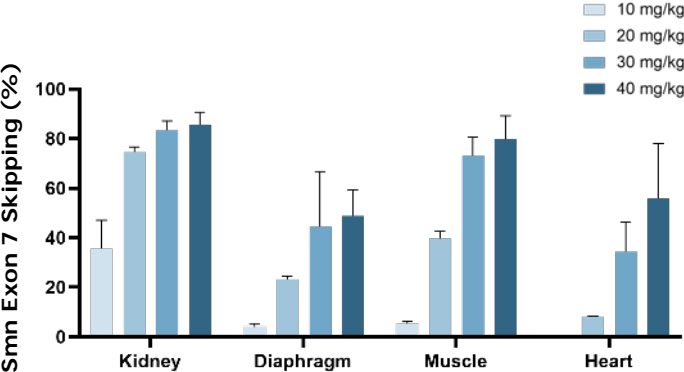
## Brain delivery

**PMO delivery in the brain**, Day 5 in the mouse brain post single ICV injection



## Systemic delivery

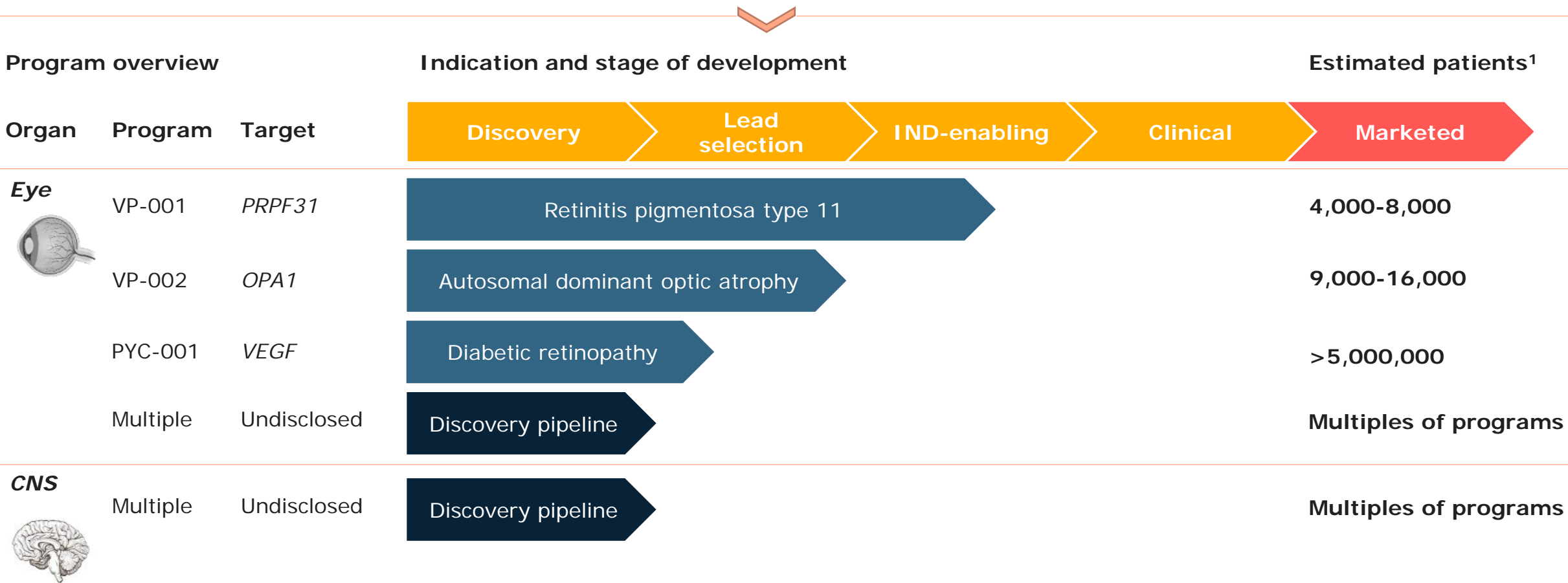
**PMO delivery systemically**, Day 2 in the mouse post single IV injection



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



## PYC is a multi-asset drug development company



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

<sup>1</sup> See ASX announcement 'Technical Presentation - October 2020' dated 9 October 2020; National Eye Institute (US) prevalence estimates for Diabetic Retinopathy ; see Nasca A, et al. 'Not only dominant, not only optic atrophy: expanding the clinical spectrum associated with OPA1 mutations.' *Orphanet J Rare Dis.* 2017 May 12;12(1):89

# PYC has made important progress in the second quarter



Commenced larger animal preclinical studies for VP-001 program for Retinitis Pigmentosa type 11, with readouts in 2 species expected in early 4Q. IND filing on-track for mid-2022



Released critical *in vivo* and *in vitro* data for PYC's second program targeting OPA1 for the treatment of Autosomal Dominant Optic Atrophy, enabling progression to lead selection and preclinical development. IND filing targeted 1H2023



Successfully delivered high levels of PYC's PPMO to the mouse brain in first proof-of-concept data in Central Nervous System (CNS) discovery efforts, potentially overcoming a major barrier to other CNS targeted drugs



Continued to build PYC's presence in the U.S. including HQ in San Diego, build out of drug development team and broad engagement with US investor and BD community

# PYC is making good progress towards our critical 2021 deliverables shared at the beginning of this year

## Execute



- ☒ VP-001 through large animal studies in mid-2021 paving the way for IND submission in mid-2022
- ☒ VP-002 for ADOA proof-of-concept and preclinical efficacy readout
- ☐ PYC-001 for DR to proof-of-concept readouts

## Establish



- ☒ Establish US management team
- ☒ Build US preclinical and clinical development capabilities
- ☒ Appoint US based and industry experienced Board Directors
- ☒ Engage with US capital markets and drive business and corporate development

## Expand



- ☐ Expand Ocular pipeline towards additional development programs
- ☒ Showcase distinctive delivery of PPMO into the Central Nervous System (CNS)
- ☐ Identify first CNS development program for important neurodegenerative disease



# We are looking forward to numerous critical value inflection points throughout 2021

**VP-001** for Retinitis pigmentosa type 11

**VP-002** for Autosomal Dominant Optic Atrophy

**VP-001**  
*for RP11*

Multiple interim data readouts in large animals (ocular PK-tissue distribution)

Full data readout in large animals (range finding toxicity)

**VP-001 GLP readouts and IND in mid-2022**

**VP-002**  
*for ADOA*

Efficacy readout in patient-derived fibroblast models

Efficacy data in patient-derived retinal models/animal models

3Q21

4Q21

1Q22



**CNS**

Further optimisation of PYC's CNS PPMO delivery tech in larger animals

Identify lead CNS program for neurodegenerative indication



**Ocular**

- **Proof of concept data for PYC-001** for Diabetic Retinopathy in 2021
- Anticipate **development of further ocular drug candidates** leveraging the de-risked ocular PPMO platform



**Autosomal dominant optic atrophy  
(ADOA) program targeting  
mutations in the *OPA1* gene**

***Elina, living with ADOA***

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

- Characteristics of *OPA1* ADOA are:
  - **Severe, progressive blindness**
  - Caused by mutations in the *OPA1* gene leading to haploinsufficiency of the *OPA1* protein<sup>1</sup>
  - Onset between the ages of 5 and 20
  - Primarily affects central vision
  - Leads to blindness between 40-50 years of age

## 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>



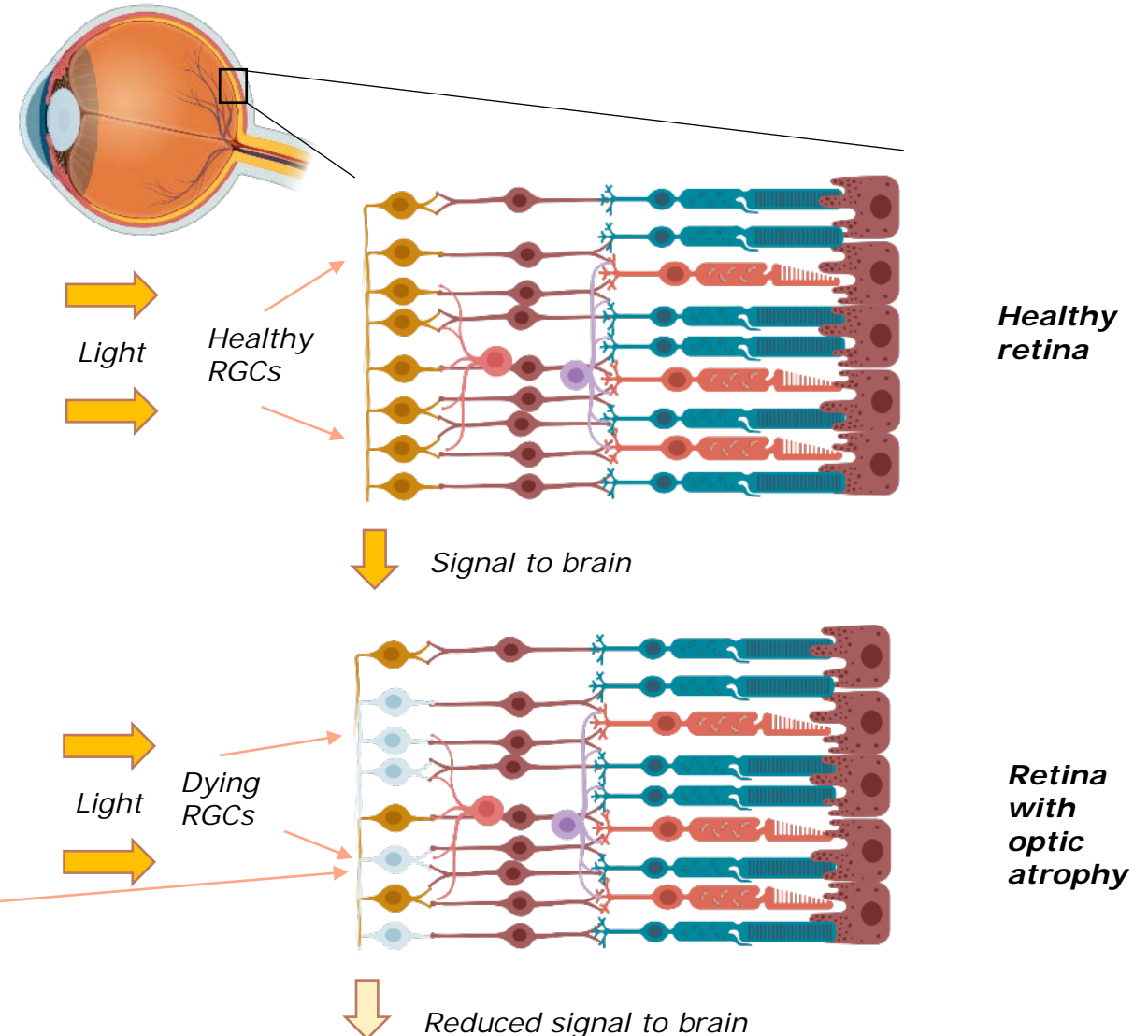
# ADOA is most frequently caused by mutations in the *OPA1* gene, affecting the retinal ganglion cells

ADOA is caused by mutations in the *OPA1* gene that result in the loss of retinal ganglion cells (RGCs), which make up the optic nerve

- This causes severe vision loss, often beginning before the age of 10

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

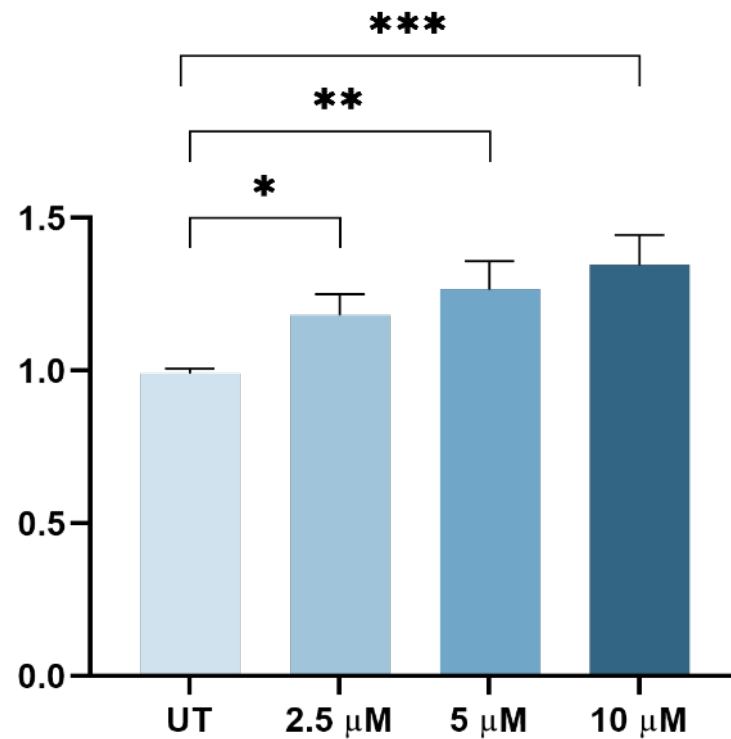
- Decreased *OPA1* protein levels
- Reduction in mitochondrial health (protein expression and mitochondrial fragmentation)
- Reduced cellular bio-energetics (ATP, membrane potential and oxygen consumption rate)
- Increase in reactive oxygen species and **apoptosis**
- Atrophy of retinal ganglion cells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



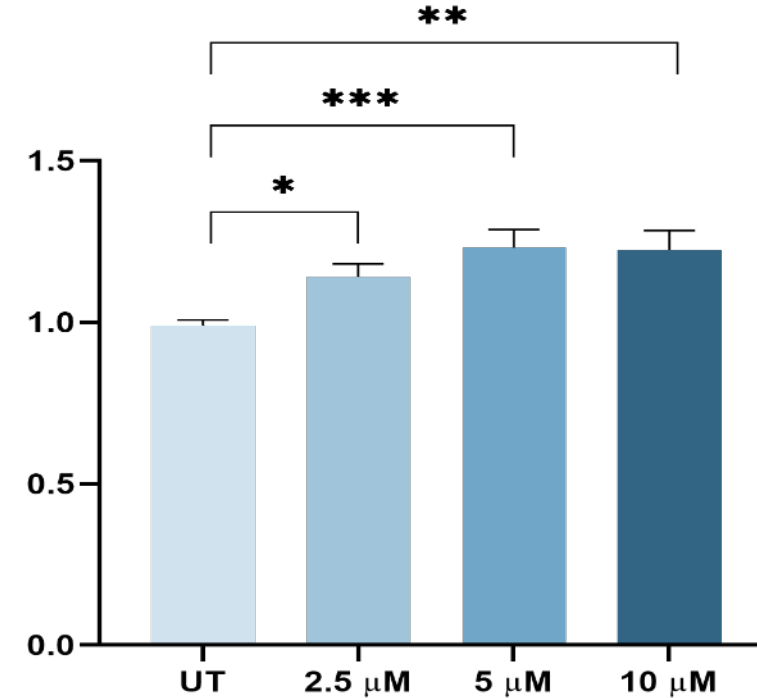
# PYC's PPMOs have shown an ability to increase the critical OPA1 protein in a dose-dependent and mutation agnostic manner

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

Patient 1, n=3



3 Patients (pooled), n=3 per patient

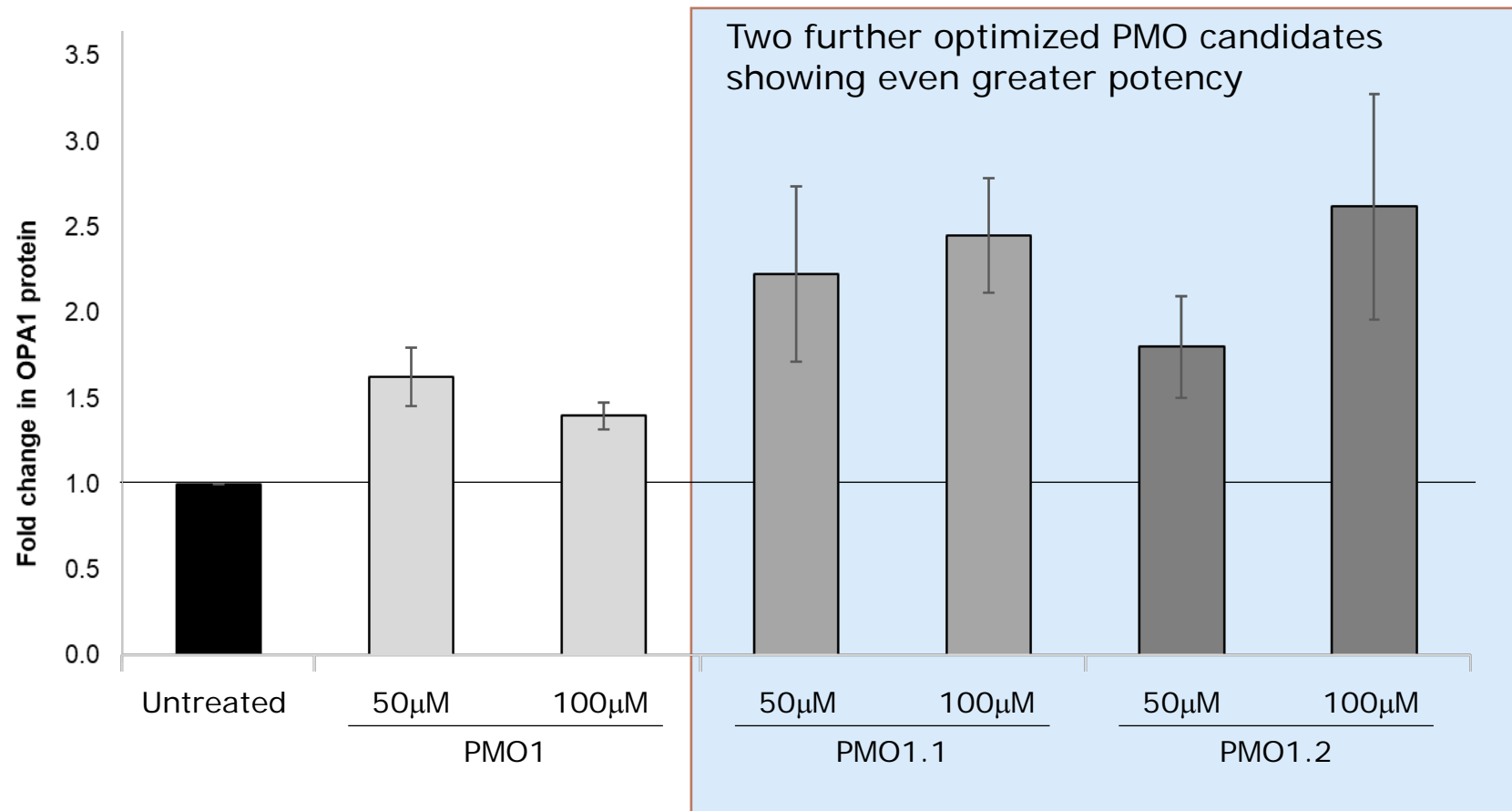


Statistical differences were analysed using one-way ANOVA; \* p<0.05 \*\* p<0.01 \*\*\* p<0.001  
Patient 1 & 3: c.2708\_2711 delTTAG  
Patient 2: c.985-1G>A

See ASX Announcement 17 May 2021

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

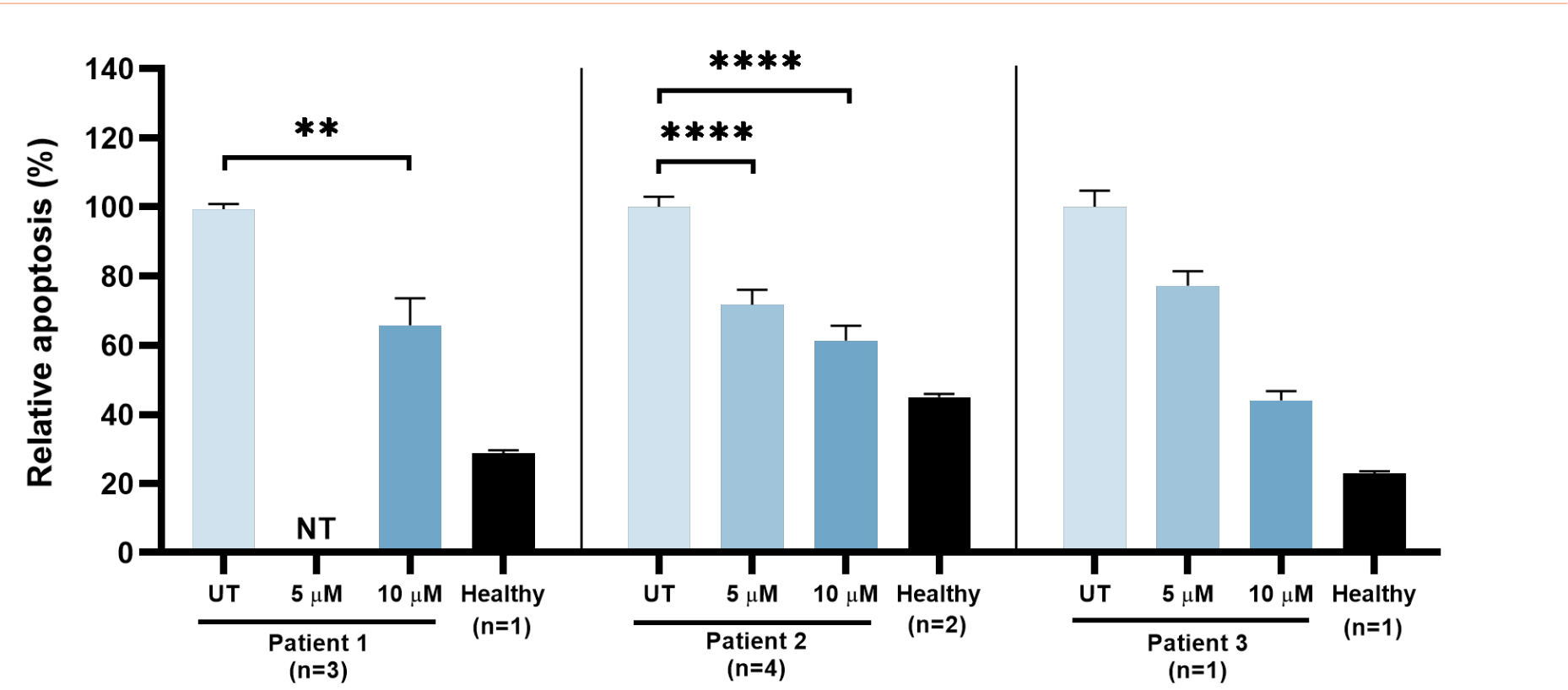
**Change in OPA1 protein levels, day 2 post PMO transfection, patient fibroblasts (n=3)**



# PYC's PPMOs have shown an ability protect cells against Apoptosis in patient derived models in a mutation agnostic manner



Relative apoptosis, day 7 post PPMO treatment, patient fibroblasts



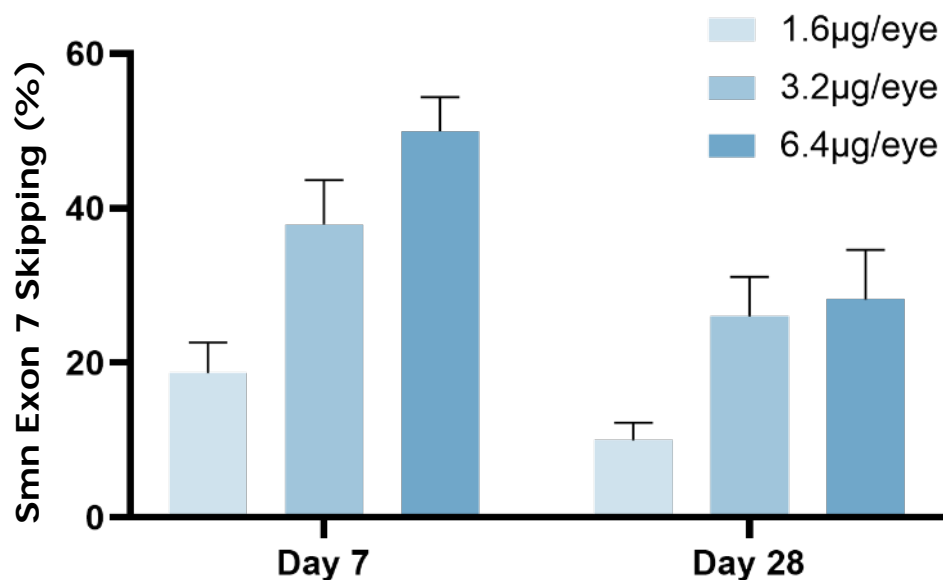
Patient fibroblasts were pre-treated with PPMO at 5 and 10 μM for 7 days and were subsequently treated with apoptotic stimuli for 4 hr prior to analysis. Apoptotic cells were analysed using flow cytometry. Bar graph represents relative apoptosis in patient fibroblasts treated with PPMO 7 days post-treatment (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



# PYC's PPMOs can reach the target cell *in vivo* and show functional delivery to mouse retinal ganglion cells

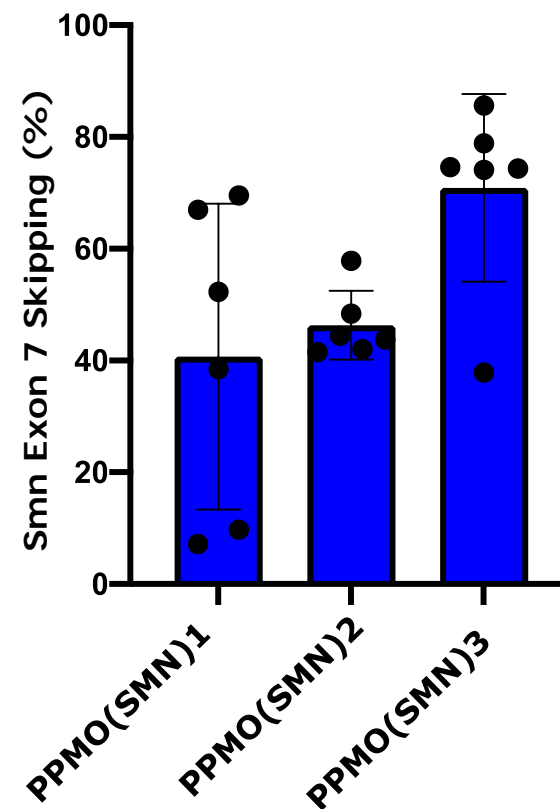
PYC's PPMOs demonstrate dose dependant uptake and long duration in the mouse neural retina

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

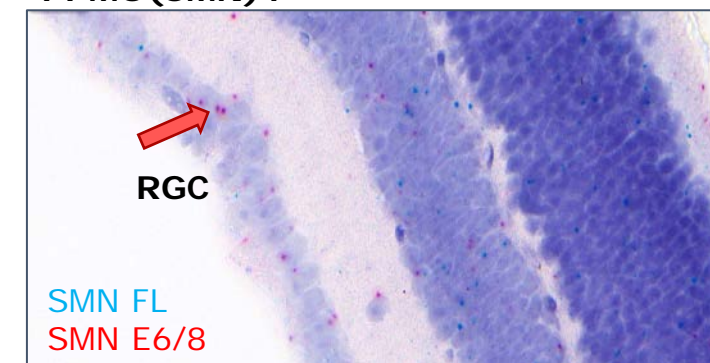


PYC's PPMOs demonstrate uptake in the Retinal Ganglion Cells in a mouse model

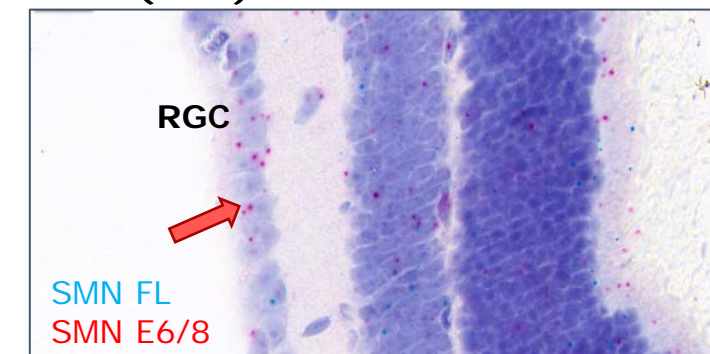
PPMO uptake in the mouse retina<sup>2</sup>, Day 7 single 1.6 µg<sup>1</sup> IVT injection



PPMO(SMN)1







PPMO(SMN)3



<sup>1</sup> 1.6 µg is equivalent to 32.1 µM concentration in the vitreous and 0.14 nmols; 3.2 µg is equivalent to 64.2 µM concentration in the vitreous and 0.28 nmols; 6.4 µg is equivalent to 128.4 µM concentration in the vitreous and 0.56 nmols  
<sup>2</sup> PPMO localization us hybridization probes, using Basescope from ACDBio targeting SMN1 PPMO. Red dots are exon skipped mRNA, blue is full length mRNA



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

-  Can **upregulate the target OPA1 protein by >1.5 fold and increase mitochondrial bioenergetics and ATP production** in a dose-dependent and mutation agnostic manner
-  Can protect cells from ADOA patients from apoptosis in a mutation agnostic manner, **rescuing the critical functional deficit observed in ADOA patients** to near functional levels observed in healthy cells with no mutations present
-  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
-  Benefits from the **positive attributes observed in the profile of PYC's PPMO technology**

# Path forward for the VP-002 program

## Key Steps

- Additional preclinical efficacy and safety assessments in patient-derived retinal models and animal models
- Conclude lead selection and optimization of target PPMO molecule through multiple *in vitro* and *in vivo* assessments of tolerability, efficacy, and biodistribution
- IND-enabling studies (including dose-range finding tolerability followed by GLP toxicity) for lead PPMO molecule
- Investigational New Drug filing with the FDA (clinical development anticipated to commence shortly thereafter)

## Target timing

- Late 2021
- Early 2022
- Throughout 2022
- 1H 2023



## **VP-001 for the treatment of Retinitis pigmentosa type 11**

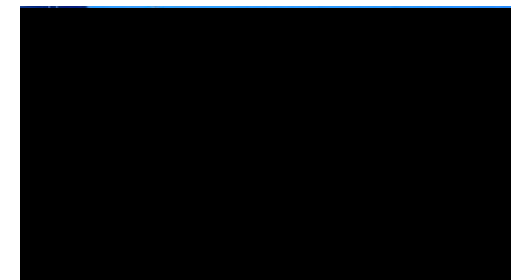
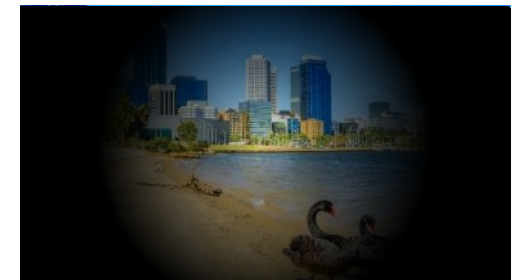
***Matthew, living with RP11***

## Retinitis pigmentosa (RP) is a genetic, blinding eye disease

- Retinitis pigmentosa type 11 (RP11) is a form of RP caused by mutation in the *PRPF31* gene
  - **Severe, progressive blinding eye disease**
  - Onset between the ages of 10 and 20
  - Leads to blindness between 40-50 years of age

## VP-001 has the potential to be transformational to patients

- There is **no treatment for patients with RP11**
- **4,000-8,000** patients in the western world
- Unmet need with no other drugs in clinical development



# VP-001 has demonstrated the ability to correct important functional deficits associated with RP11

**Scanning electron microscopy of retinal pigmented epithelium (RPE) derived from control and patient iPSC.** Images selected as representative of full data set.



**These results demonstrate VP-001's ability to correct the structural deficiency in patient derived retinal cells that is one of the key causes of vision loss in RP11 patients<sup>1</sup>**

<sup>1</sup> Buskin A. Disrupted alternative splicing for genes implicated in splicing and ciliogenesis causes PRPF31 retinitis pigmentosa. Nat Commun. 2018 Oct 12;9(1):4234.



# PYC has assembled a world class clinical advisory board of leaders in the Retinitis Pigmentosa field



## PYC's Clinical Advisory Board for the development of VP-001

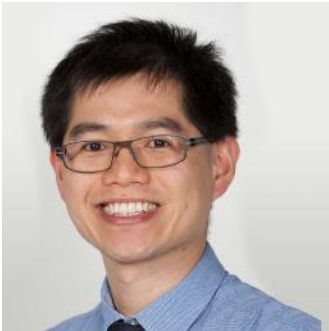
---



**Mark Pennesi, M.D., Ph.D.**  
Professor of Ophthalmology and Chief  
of the Ophthalmic Genetics Division,  
Casey Eye Institute at Oregon Health  
and Science University



**Jacque L. Duncan, M.D.**  
Professor of Clinical Ophthalmology,  
University of California San Francisco



**Fred K Chen, M.D., Ph.D.**  
Ophthalmologist, Head of the Ocular  
Tissue Engineering Lab, Lions Eye at  
Lions Eye Institute in Western  
Australia



**David Birch, Ph.D.**  
Scientific Director, Retina Foundation  
of the Southwest, Rose-Silverthorne  
Retinal Degenerations Laboratory

# 2021's key milestones for VP-001 centre on large animal studies

## Commenced

### Rabbit pharmacokinetics [PK] and tissue distribution

### Rabbit Dose-range finding [DRF] toxicity study

### Non-human primates [NHPs] DRF toxicity study

### GLP animal toxicity studies

### Formal regulatory (FDA) engagement

#### Timeline

3Q21

3Q21

Late 3Q21

Initiate in late 2021

Late 2021

#### Impact of the milestone

Following an intravitreal injection of VP-001:

- Understand ocular tolerability in a large eye
- Confirm low to no systemic levels,
- Obtain an initial understanding of the ocular biodistribution in a larger animal eye, and
- In part, inform a dosing paradigm

In a dose descending tox evaluation obtain data to:

- Understand at what dose toxicity may be observed, and
- Inform through these early data what doses may be selected for further tolerability evaluations including for the GLP study in rabbits

In a dose descending tox evaluation obtain data to:

- Understand at what dose toxicity may be observed, and
- Inform through these early data what doses may be selected for further tolerability evaluations including for the GLP study in NHPs

Under GLP conditions:

- Evaluate toxicity data at more than one dose to support the FIH clinical study planned for 2H22
- Obtain acute and Chronic tox information, and
- Inform doses for the FIH clinical trial

Informs our development planning including the:

- Early regulatory strategy, and confirms path for
- GLP tox studies,
- FIH clinical trials, and
- CMC efforts to support clinical studies

#### VP-001 Probability of success

***Increasing probability of approval for VP-001***

# What we are looking for from larger animal studies

## Targeted outcomes from upcoming VP-001 larger animal studies:



VP-001 achieves appropriate distribution in a larger animal retina, reaching relevant cell layers



VP-001 dosing in a larger animal eye provides information to inform dosing for GLP toxicity studies, thereby providing guidance for dosing in a first-in-human clinical trial



VP-001 has duration of effect supporting a 2-4 times a year or less frequent intravitreal dosing regimen



VP-001 demonstrates target engagement in a larger animal eye following intravitreal dosing



# 2021 is a transformative year for PYC Therapeutics



- Furthest a PYC Therapeutic has ever advanced in preclinical development—testing VP-001 in larger animals ahead of IND submission
- Multiple ocular assets running in parallel with key catalysts throughout 2021
- Expansion into the CNS, a highly attractive new therapeutic area with significant unmet patient needs
- Execution of a new operating model across Australia and the US to ensure access to critical expertise and partners to unlock the full potential of PYC's science

