Life-changing science

PYC Therapeutics

Corporate Presentation

April 2021

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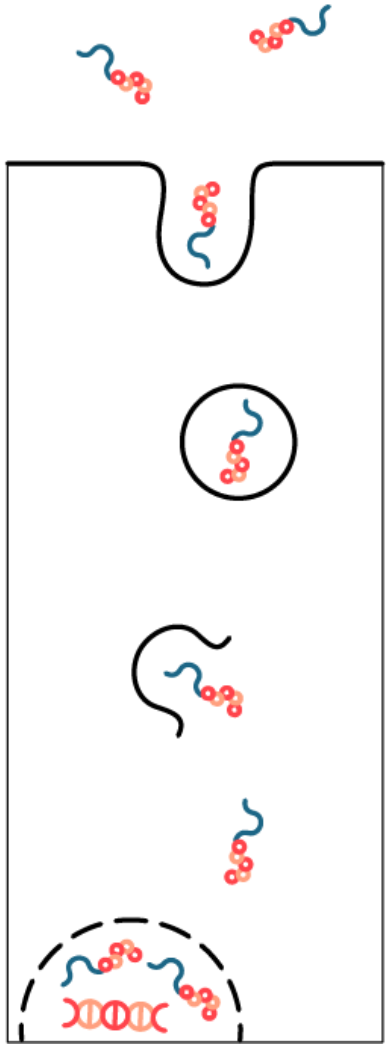
Highlights

PYC is an RNA therapeutics company focused on applying distinctive P-PMO technology



Leading-edge RNA Therapeutics

Novel Technology Platform: Cell Penetrating Peptide-PMOs solve delivery challenge and get more drug safely into cells

Development 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

Lead and second program are first disease modifying therapies for 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 growing Executive Leadership team built across the US and Australia

Leadership team

Sahm Nasseri
Chief Executive Officer US, Exec. Director

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

Dr Sue Fletcher
Chief Scientific Officer

Leading global expert and pioneer in RNA therapeutics with over 30 years experience developing RNA drugs. 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 Glenn Noronha
Chief Development Officer

Over 20 years experience leading drug development programs, including 6 ocular programs from discovery to clinical development and approval. Previous C-suite and leadership roles at Clearside, Foresight, BridgeBio, and Alcon

Dr Rohan Hockings
MD Australia, Exec. Director

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

Kaggen Ausma
Chief Business Officer

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

Board

Alan Tribe
Chairman

Experience commercialising Australian technology in US markets, and managing and leading growth companies across technology, resources and retail

Dr Michael Rosenblatt
Director

Senior Partner with Flagship Pioneering, previously EVP and Chief Medical Officer Merck. Deep experience in leading numerous drug development programs, and guiding strategies at biopharma and academic institutions

Jason Haddock
Director

Over 20 year experience in finance, operations, and commercialisation of biotechnology companies including at Array BioPharma and Bristol Myers Squibb

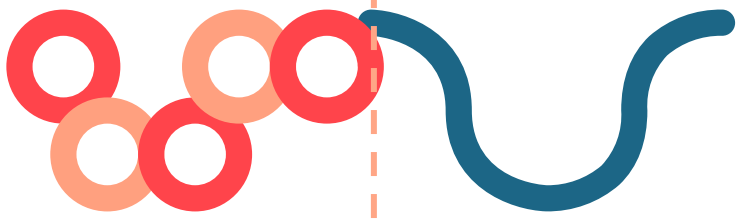
PYC Therapeutics

Platform Technology: Proprietary P-PMOs

PYC's core therapeutic technology brings together two distinctive components

Cell-penetrating peptide

- 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 generate anti-sense oligonucleotide chemistry, neutral charge
- Precision and flexibility— up-regulate, down-regulate and isoform switch
- Safer profile—avoid binding with charged splicing factors inside cells
- Durable profile—avoid intracellular degradation, allows for longer effect

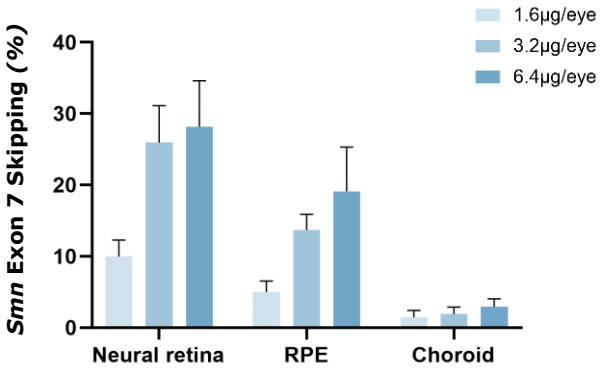
Flexible and precise RNA therapeutic molecule with potential for broader therapeutic window, longer duration of effect and application to a range of tissue and cell types

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

PYC Therapeutics

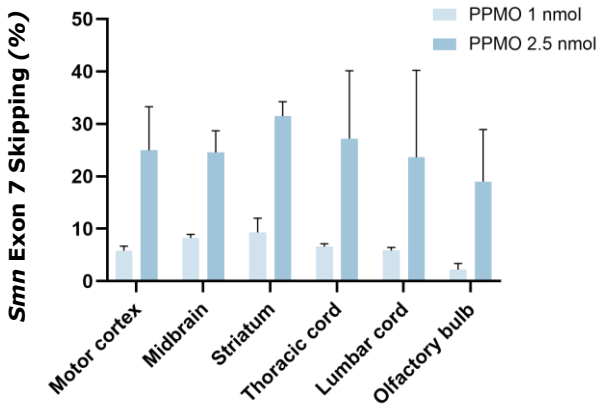
Retinal delivery

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



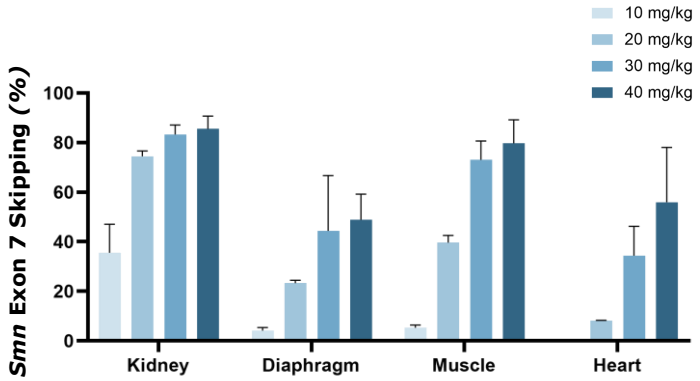
Brain delivery

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



Systemic delivery

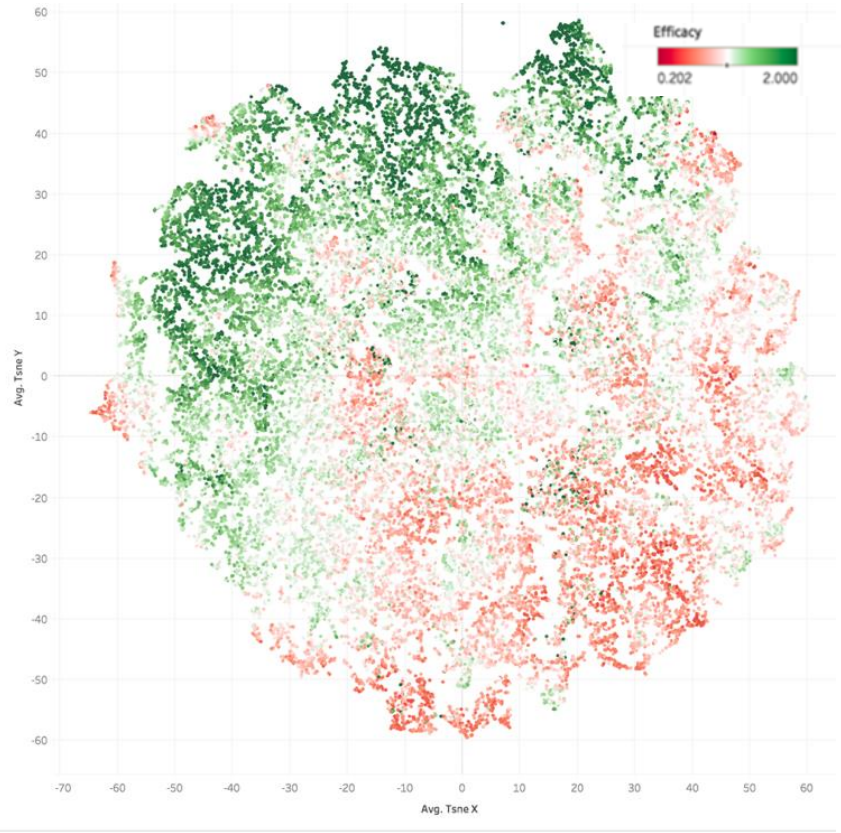
PMO delivery systemically, *Day 2 in the mouse post single IV injection*



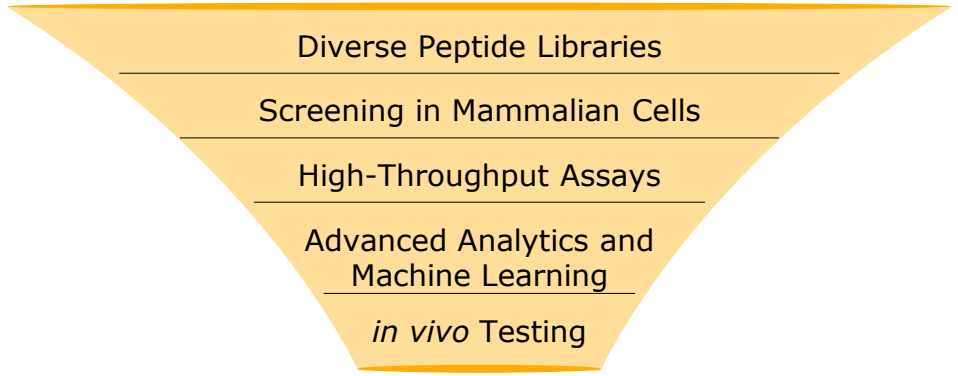
See ASX Announcement 22 July 2020; 12 April 2021; 14 October 2019

Choosing the right peptide for the right application (cell, tissue, indication) is a key development step

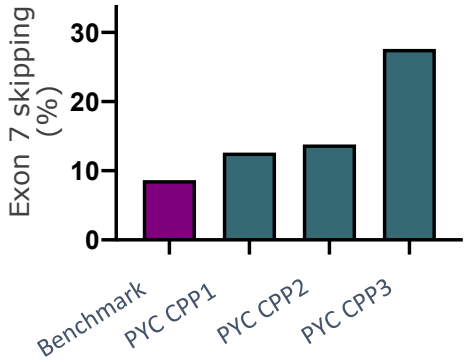
PYC's library leverages millions of years of evolution by micro-organisms to create a structurally diverse set of potential CPPs



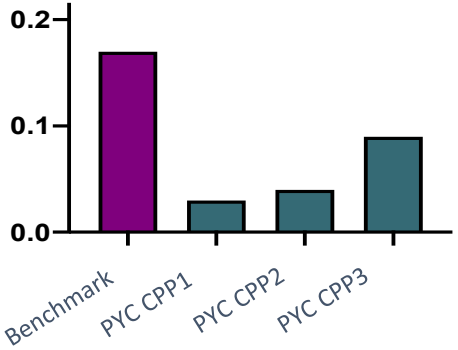
This is combined with an efficient screening and validation pipeline



Smn exon 7 skipping in mice
RPE/Choroid (5 days)



Retinal toxicity in mice
Gfap score[1] (5 days)

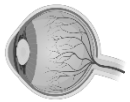
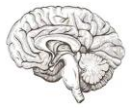


1 Glial fibrillary acidic protein (GFAP) is a protein biomarker for glial activation in response to retinal pathologies
Jünemann AG, Rejdak R, Huchzermeyer C, et al. Elevated vitreous body glial fibrillary acidic protein in retinal diseases. Graefes Arch Clin Exp Ophthalmol. 2015;253(12):2181-2186. doi:10.1007/s00417-015-3127-7

See ASX Announcement 14 October 2019

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

Program overview			Indication and stage of development	Estimated patients in western world
Organ	**Program**	**Target**	**Discovery → Lead selection → IND-enabling → Clinical → Marketed**	
Eye 	VP-001	*PRPF31*	Retinitis pigmentosa type 11	**4,000 to 8,000**
	VP-002	*OPA1*	Autosomal dominant optic atrophy	**9,000 to 16,000**
	PYC-001	*VEGF*	Diabetic retinopathy	**>5 million**
	Multiple	Undisclosed	Discovery pipeline	**Multiples of programs**
CNS 	Multiple	Undisclosed	Discovery pipeline	**Multiples of programs**

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

1 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 Therapeutics

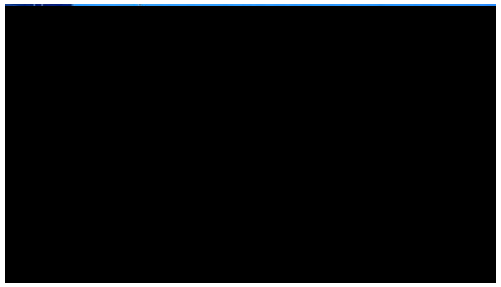
VP-001 for the treatment of Retinitis pigmentosa type 11

Matthew, living with RP11

VP-001 for Retinitis pigmentosa type 11

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

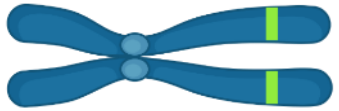
- There is **no treatment for patients with RP11**
- **4,000-8,000** patients in the western world
- Unmet need with no other drugs in clinical development

See ASX announcement 'Technical Presentation - October 2020' dated 9 October 2020;

VP-001 targets a negative regulator of the gene underlying RP11

Healthy eye

We all have two copies of each gene in our chromosomes

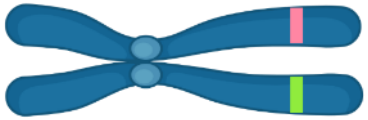


Our body uses these genes to 'code' proteins in our cells

These proteins help our bodies function, including helping us to see

Patients with RP11

Patients with RP11 have only one healthy gene (and one mutated gene)



This leads to insufficient healthy protein (PRPF31) being made by the cell (*haploinsufficiency*)

Insufficient PRPF31 means the retinal cells in the eye don't function correctly and start to die – causing blindness

VP-001

VP-001 skips an exon in a gene (*CNOT3*) that acts as a negative regulator of *PRPF31*

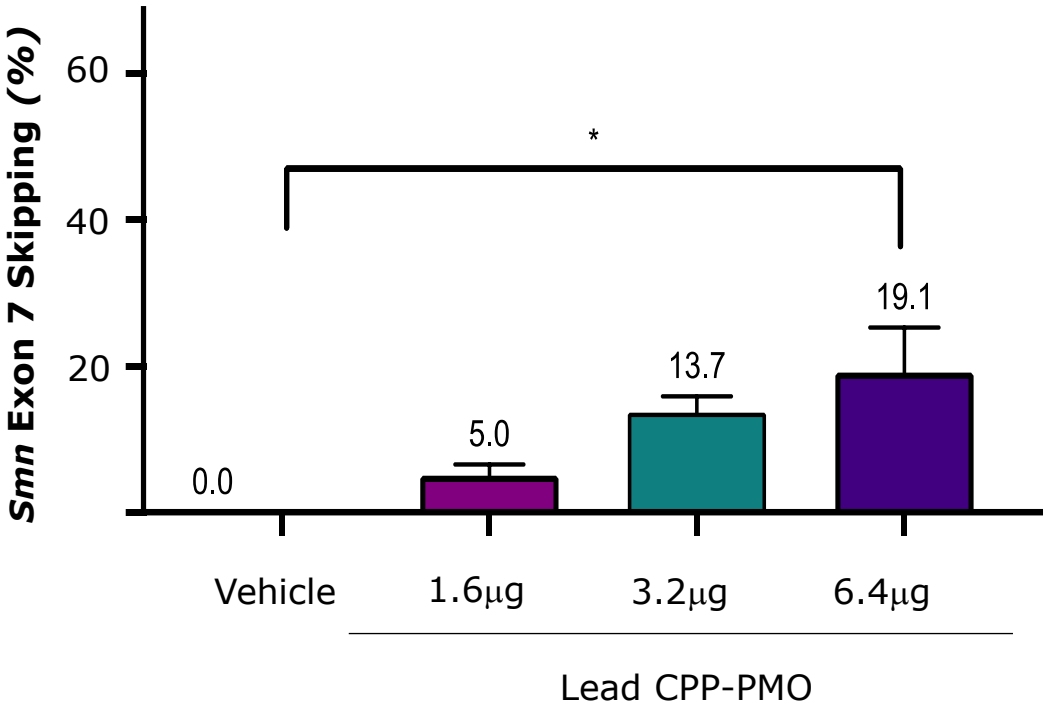
This increases the amount of PRPF31 protein from the healthy copy of the gene

The additional healthy protein restores the eye's ability to function properly and prevents further degeneration

VP-001 has already demonstrated a strong preclinical efficacy signal *in vivo* and in patient derived models

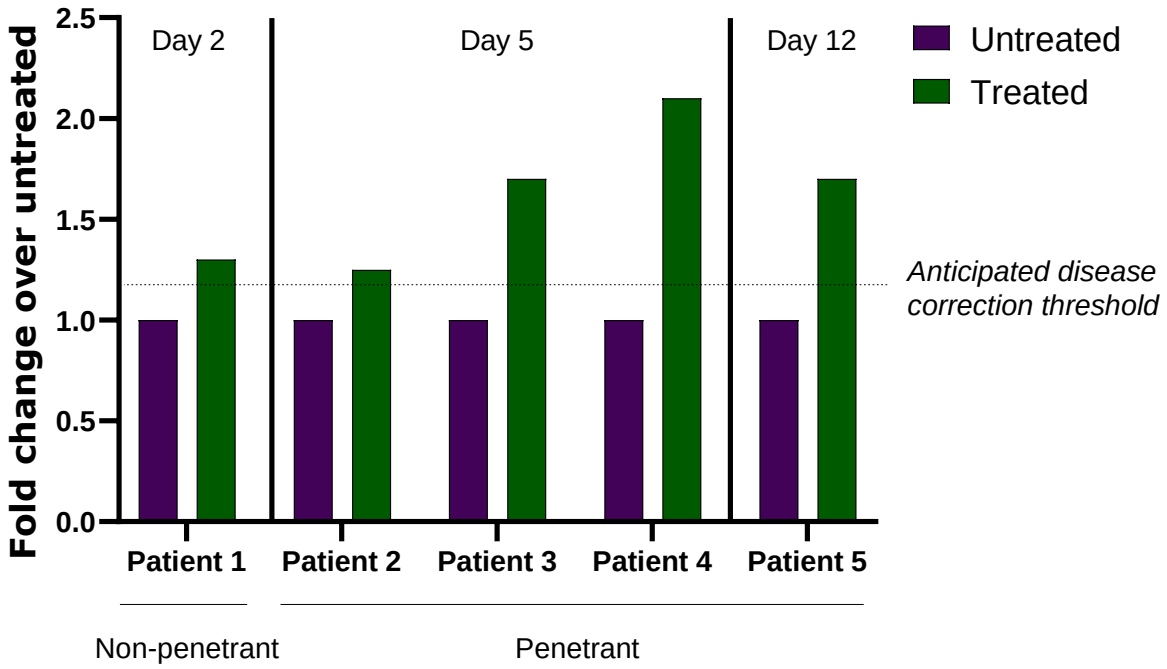
PYC has demonstrated delivery to the target cells, Retinal Pigment Epithelium (RPE), for 28 days in the mouse

Exon 7 skipping in RPE[1], *Day 28 in the mouse eye post IVT*



And shown upregulation of the target protein, PRPF31, in patient iPSC derived RPE pathogenic mutations in *PRPF31* (each patients with a different mutation)

PRPF31 protein levels[2], *RPE, 5µM treatment, (n=1 per patient)*



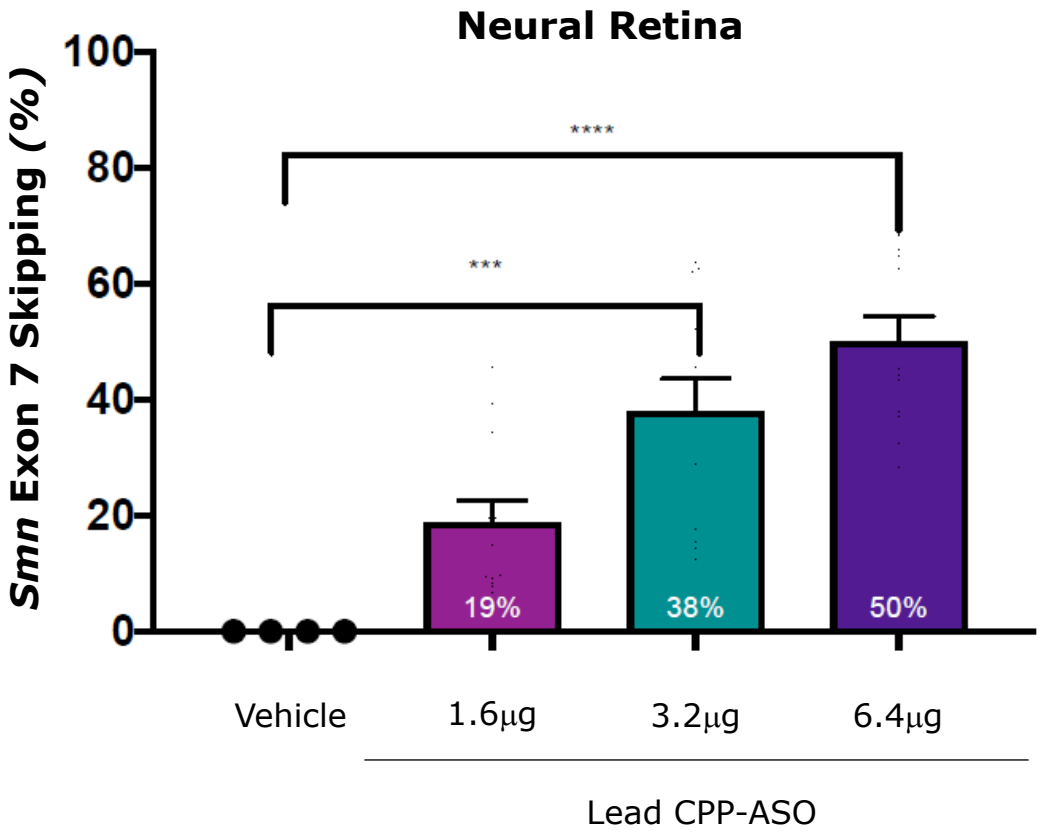
1 Day 28 post intravitreal injection in mice. A readout of drug delivery, Exon-skipping of Survival of Motor Neuron (*Smn*) in the mouse retina across 3 dose cohorts (n=12 for each dose cohort, n=4 for vehicle)
2 For anticipated disease correction threshold see 'Venturini, G. CNOT3 Is a Modifier of PRPF31 Mutations in Retinitis Pigmentosa with Incomplete Penetrance. PLOS Genetics November 2012'

See ASX Announcement 22 July 2020; 7 October 2020

The dose dependant response shows no increasing acute toxicity in the mouse

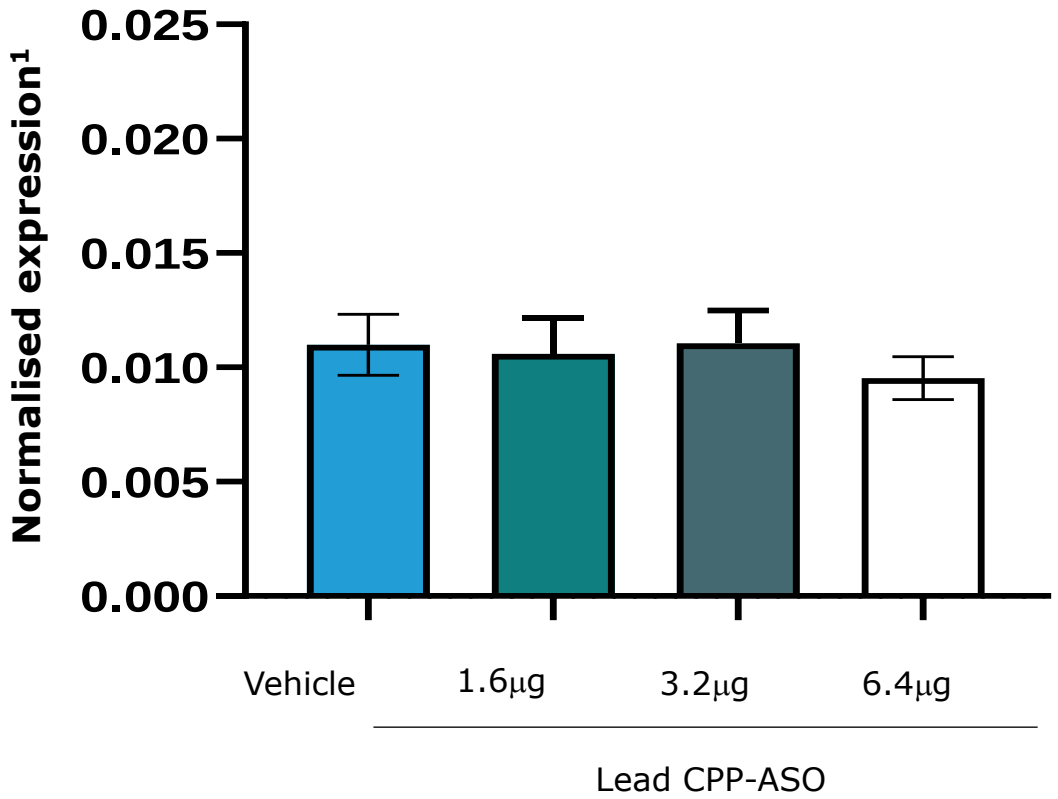
Dose dependant increase in effect …

Exon 7 skipping, Day 7 in the mouse eye



… and no increase in toxicity markers

Gfap expression, Day 7 in the mouse eye

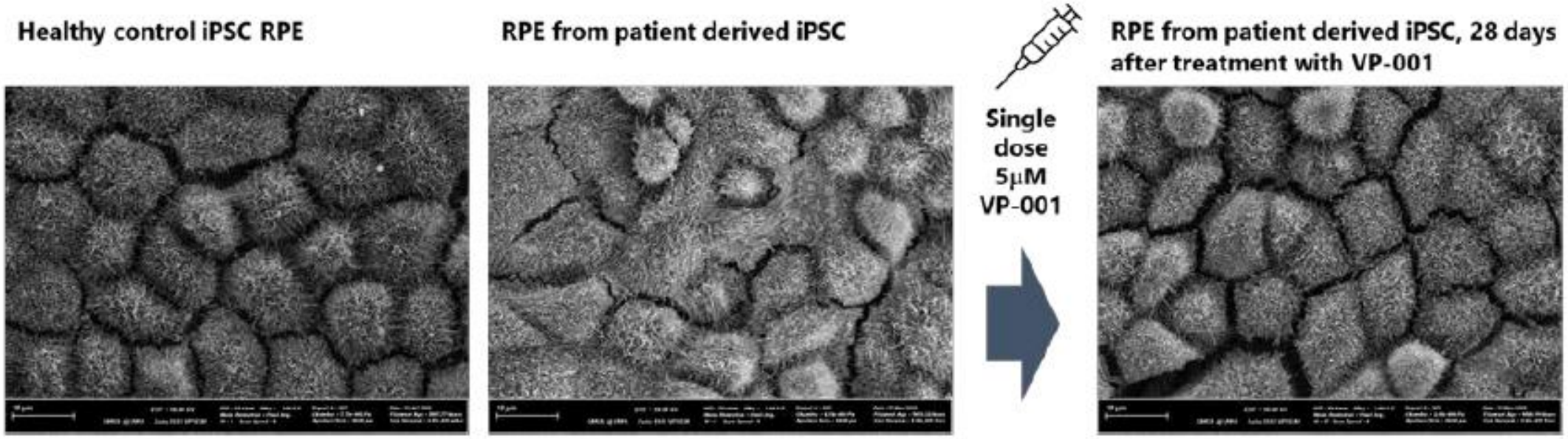


1 Toxicity determined by treating mouse retinas with 1.6 micrograms of an Antisense Oligonucleotide (ASO) delivered by each peptide and then measuring retinal stress based on levels of Glial Fibrillary Acidic Protein (GFAP). GFAP levels have been measured after retinal harvesting from mice at day 7 post intravitreal injection and normalised to a pool of 'house-keeping' genes.

See ASX Announcement 22 July 2020

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[1]

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

See ASX Announcement 16 December 2020

VP-001 Key Takeaways and Next Steps

1. RP11 represents a large, underserved market with no disease-modifying therapies available nor in clinical development
2. To date, VP-001 has been shown to:
   - Reach the target cell following intravitreal injection - conferring a major competitive advantage over therapies requiring sub-retinal administration[1]
   - Engage its target and achieve the desired exon skipping effect[2]
   - Correct the deficiency of the target protein once inside the cell[2]
   - Increase the rescue of downstream functional consequences of RP11[2]
3. VP-001 has shown no evidence of toxicity in the retina[3]

Next Steps:

- Larger animal (rabbit and NHP) PK, Ocular distribution and Dose-range finding studies in 1H21, data reported in 3Q21
- Submit IND to U.S. FDA during the first half of 2022

1 In in vivo model
2 In patient-derived model
3 In animal model

PYC Therapeutics

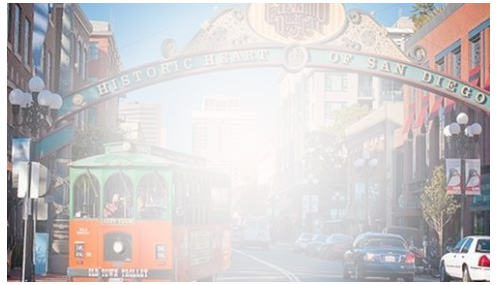
VP-002 for the treatment of Autosomal dominant optic atrophy

Elina, living with ADOA

VP-002 for Autosomal dominant optic atrophy

Autosomal dominant optic atrophy (ADOA) is a genetic, blinding eye disease

- ADOA-*OPA1* is a form of RP caused by mutation in the *OPA1* gene[1]
  - **Severe, progressive blinding eye disease**
  - Onset between the ages of 5 and 20
  - Primarily affects central vision
  - Leads to blindness between 40-50 years of age



VP-002 has the potential to be transformational to patients

- There is **no treatment for patients with ADOA**, nor in clinical development
- **9,000-16,000** patients in the western world[1]

1 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

ADOA is largely caused by mutations in the OPA1 gene affecting the retinal ganglion cells

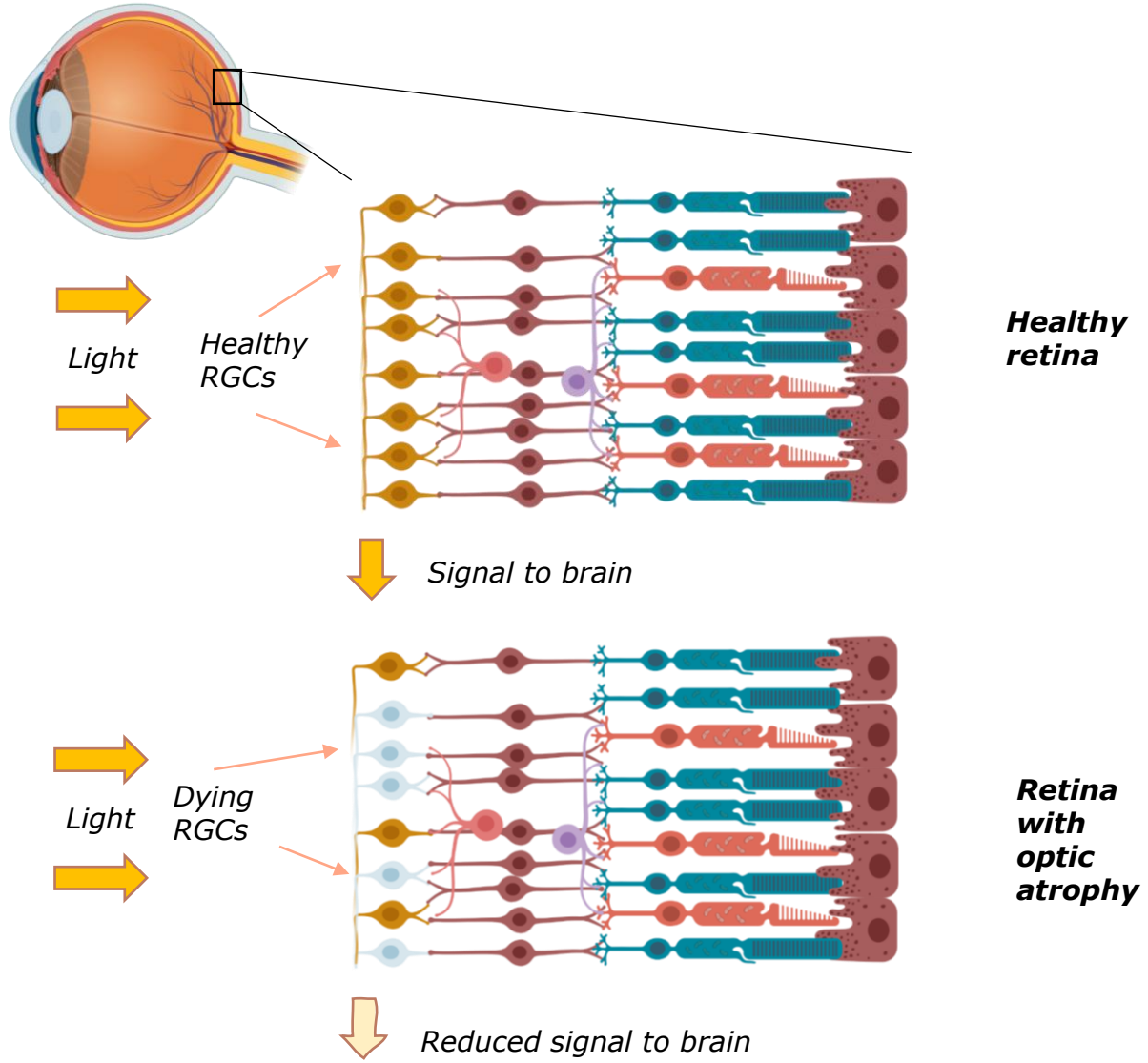
PYC Therapeutics

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

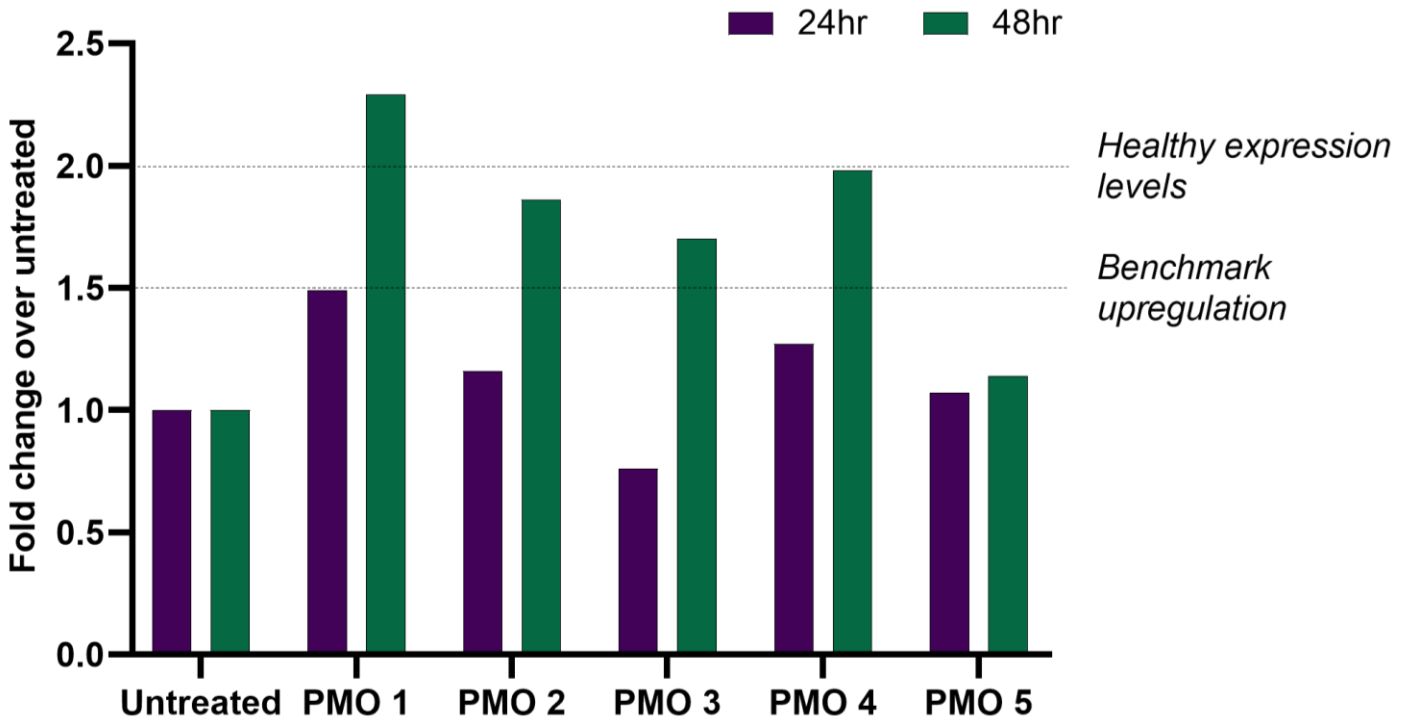
- ~70% of all ADOA is caused by mutations in mutation in one gene, *OPA1*
- ~75% of cases caused by *OPA1* mutations are due to low levels of the OPA1 protein



Created with BioRender.com

We have shown an ability to increase the critical OPA1 protein levels across a range of potential PMO candidates

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

See ASX Announcement 12 October 2020

VP-002 Key Takeaways and Next Steps

- PYC has designed multiple PMOs capable of correcting the OPA1 protein haploinsufficiency in cells derived from ADOA patients
  - Achieved >100% protein upregulation in patient fibroblasts
- PYC has filed for intellectual property protection for this drug program
- Currently conducting lead selection work

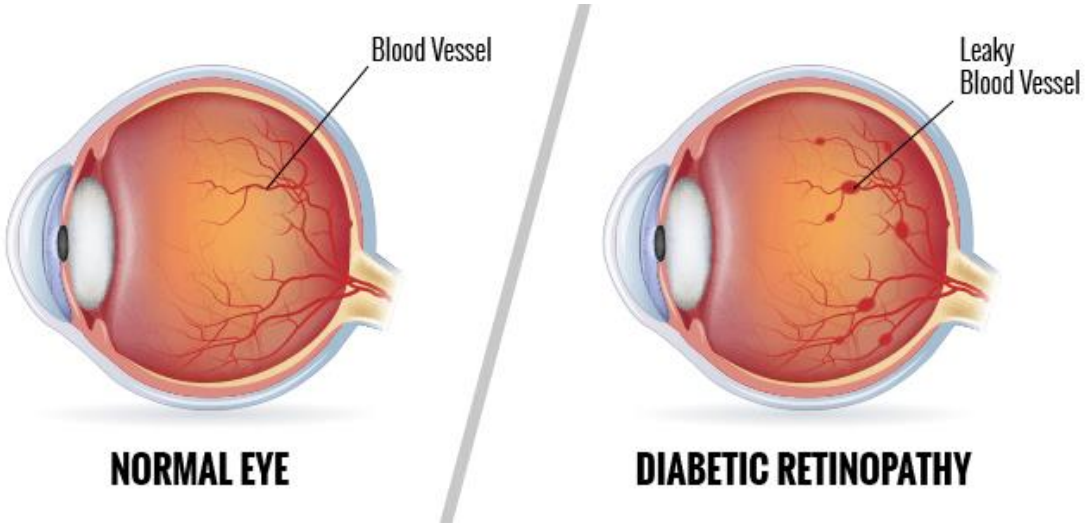
Next Steps:

- Report results from patient-derived preclinical models in the first half of 2021, leading to lead selection and optimization
- Report additional preclinical efficacy and safety data from patient -derived retinal models and animal models by year end 2021

PYC Therapeutics

Beyond Rare Ocular Disease: PYC-001 for Diabetic Retinopathy

Diabetic Retinopathy



- Diabetic retinopathy (DR) is caused by changes in the blood vessels of the retina. In some cases, blood vessels may swell and leak fluid, or grow on the surface of the retina, resulting in loss of vision.
- The incidence of DR is expected to grow from ~8 million Americans in 2010, to ~11 million in 2030, and over 14 million by 2050.[1]
- DR is the leading cause of vision loss in adults aged 20–74 years.
- Current treatment options for DR are limited due to a lack of response to first line anti-VEGF (vascular endothelial growth factor) therapies and the need for longer acting drugs.
- ***However,*** there is a growing body of evidence suggesting that prolonged VEGF inhibition is responsible for the death of sensitive nerve cells in the retina.[2,3,4]

[1] National Institutes of Health Diabetic Retinopathy Data and Statistics
[2] Potilinski, et al. "Mechanisms behind Retinal Ganglion Cell Loss in Diabetes and Therapeutic Approach." Int. J. Mol. Sci. 2020, 21, 2351
[3] Munk, et al. "Macular atrophy in patients with long-term anti-VEGF treatment for neovascular age-related macular degeneration." Acta Ophthalmol. 2016 Dec;94(8):e757-e764.
[4] SriniVas et al. "Anti–Vascular Endothelial Growth Factor Use and Atrophy in Neovascular Age-Related Macular Degeneration Systematic Literature Review and Expert Opinion." Ophthalmology: Journal of the American Academy of Ophthalmology

PYC-001 Key Takeaways and Next Steps

- PYC has leveraged the unique advantages of its RNA therapeutics technology to create a modified VEGF therapy that addresses these shortcomings.

- PYC's approach alters the type of VEGFA produced by cells in the eye to a type not expressed highly in the disease (isoform switching) This drug promises to:
  - Retain the ability of the current generation of drugs to stop blood vessels destroying the retina;
  - Add a 'pro-survival' effect to help protect sensitive neurons from dying; and
  - Significantly extend the dosing interval between treatments for patients

- The drug leverages all of the intracellular delivery work undertaken for PYC's lead program, VP-001, and, as a result, is expected to have a rapid development pathway into the clinic

Next Steps:

- Report results from patient-derived preclinical models in the first half of 2021

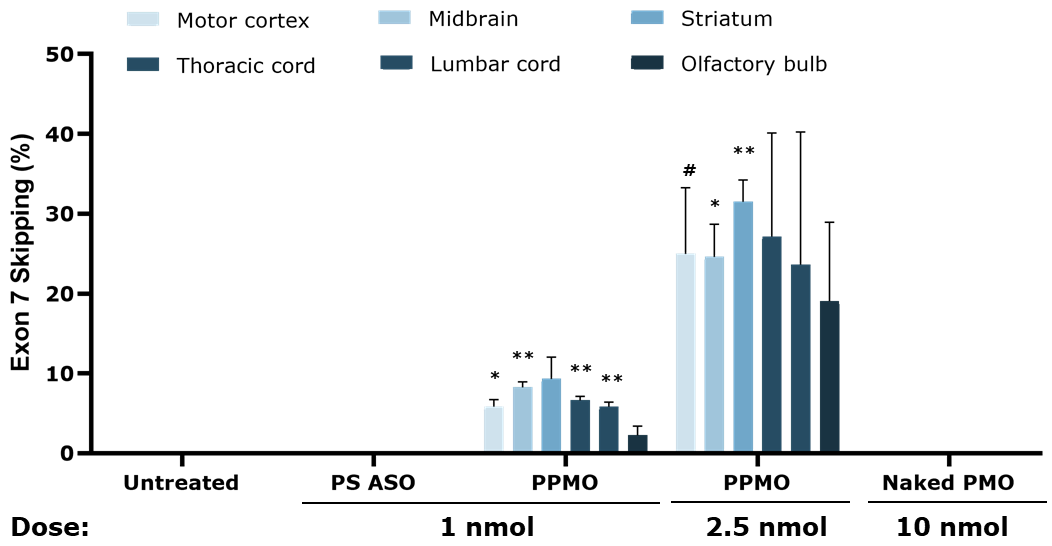
- Report additional preclinical efficacy and safety data by year end 2021

PYC Therapeutics

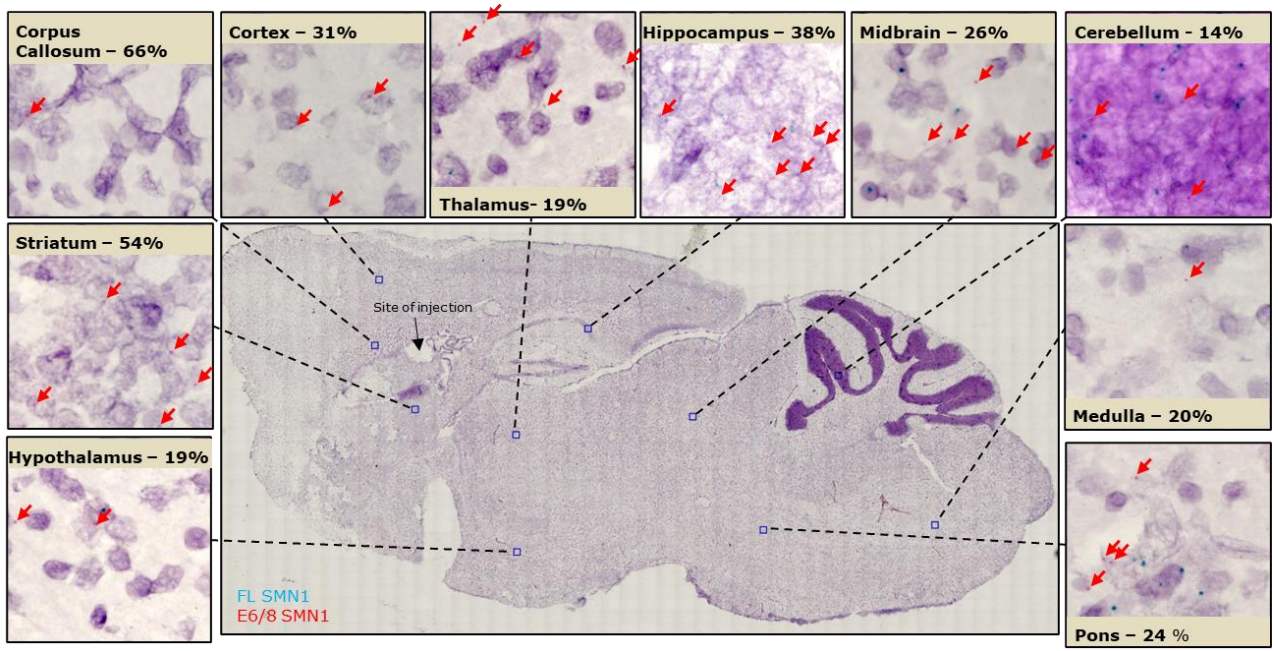
P-PMOs in the Central Nervous System and Other High Unmet Need Conditions

Initial results show great promise for PYC's P-PMOs in the CNS

PMO delivery to the brain, *Smn exon 7 skipping, Day 5 post single I.C.V. injection in mice*[1]



PMO distribution in the brain, *Smn exon 7 skipping, Day 5 post single I.C.V. injection in mice*[2]



1 n=2 for all groups expect PYC PPMO 1nmol group where n=3. Statistical significant calculated compared to control as unpaired two-way t-test, #: p≤0.1 *: p ≤ 0.05; **: p ≤ 0.01

2 RNA in situ hybridization (ISH:Basescope) signals detected using full length Smn (blue dots) and E6/8 Smn (red dots)-specific probes in PYC CPP-PMO (SMN1) treated mouse brain section. All sections were counterstained with hematoxylin. Brain regions were identified, magnified and the exon 7 skipped (E6/8) transcripts were shown as red punctate dots indicated by red arrows. The percentage of Smn transcripts that were exon 7 skipped, E6/8 was determined by random sampling and the averages were indicated next to the brain region.

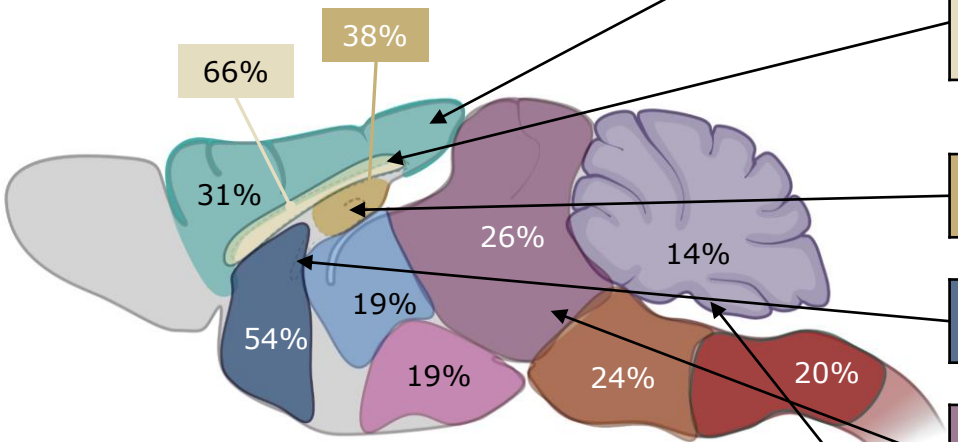
See ASX announcement 12 April 2021

… and this indicates we can access regions of the brain that matter in neurodegenerative diseases

PYC Therapeutics

MOUSE

% denotes *Smn* exon 7 skipping, Day 5 post single I.C.V. injection in mice



Cortex
Alzheimer's disease
Amyotrophic Lateral Sclerosis
Frontotemporal dementia

Corpus Callosum
Neurometabolic disease
Acquired demyelinating disease

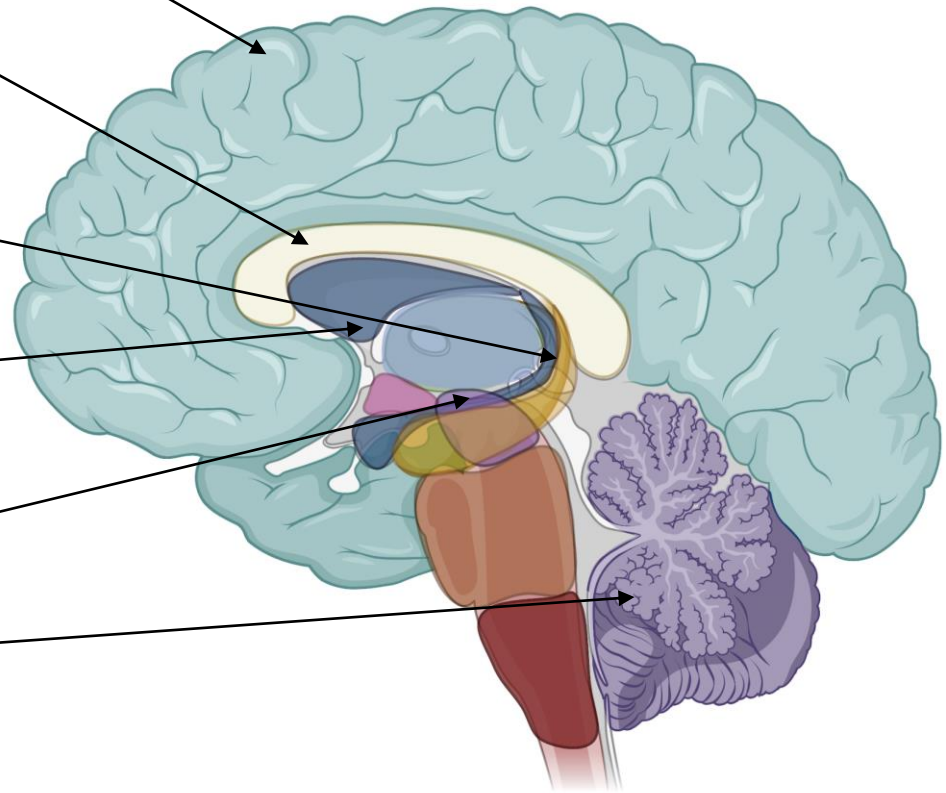
Hippocampus
Alzheimer's disease

Striatum
Huntington's disease

Midbrain
Parkinson's disease (Substantia nigra)

Cerebellum
Spinocerebellar ataxia

HUMAN

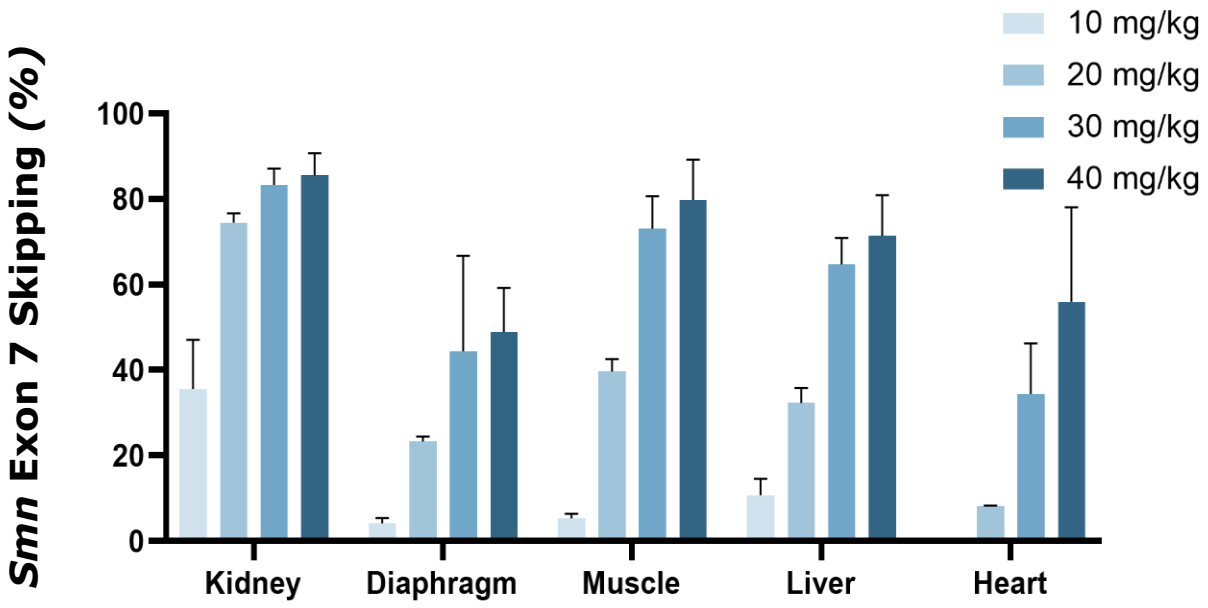


Created with BioRender.com

PYC's P-PMO technology has demonstrated broad potential including preferential delivery to high value organs

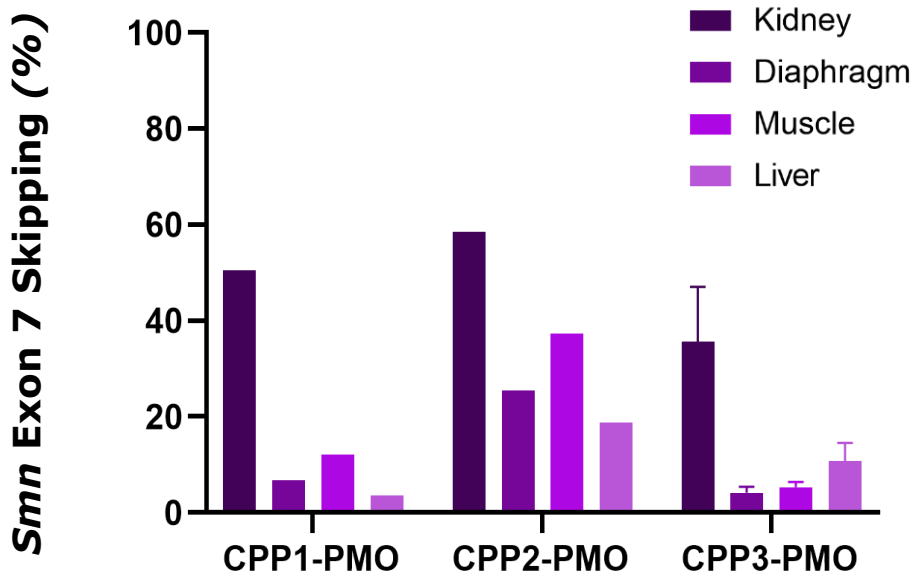
CPP-PMOs demonstrate strong uptake across high value tissues include heart and diaphragm …

Exon 7 skipping (%) in tissue [1], *Single I.V. injection in mice, day 2*



… and preferential delivery to certain organs such as the Kidney

Exon 7 skipping (%) in tissue [1], *Single I.V. injection in mice, day 2*

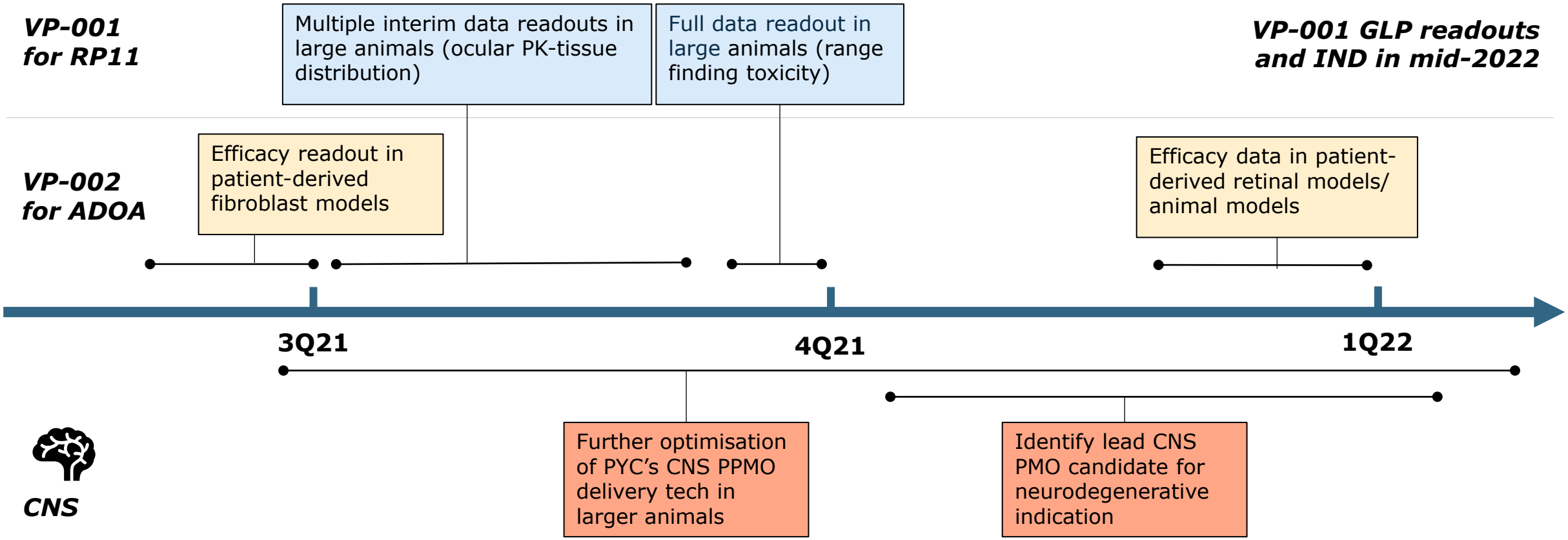


1 Day 2 post intravenous injection in mice. A readout of drug delivery, Exon-skipping of Survival of Motor Neuron (Smn) in the mouse tissue across 3 dose cohorts (n=2 for each dose cohort)
2 PS: Phosphorothioate backbone antisense oligonucleotide;

See ASX Announcement 14 October 2019

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



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