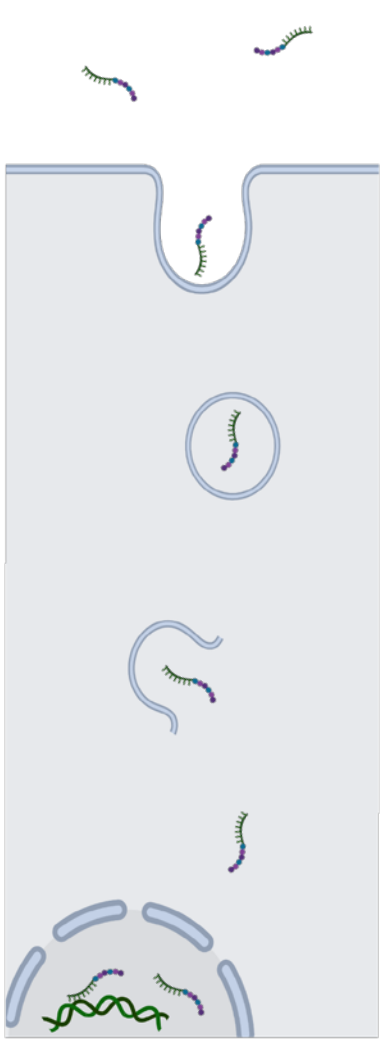
PYC THERAPEUTICS

Technical Presentation
October 2020

Key investment highlights



PYC is an RNA therapeutics company specialising in diseases of the eye

- **RNA therapeutics have come of age**
  But their ongoing success is impeded by inefficient or toxic delivery inside cells
- **PYC's cell-penetrating peptide (CPP) delivery platform solves this 'delivery' problem**
  PYC's competitive advantage is getting more drug safely into the target cell
- **PYC applies its advantages in precision drugs for eye disease: an area of unmet need**
  PYC's lead program is the first disease-modifying therapy for Retinitis Pigmentosa type 11 - a *USD1-2B p.a. target market*
- **PYC's technology scales rapidly in the eye: same delivery tech for other RNA cargoes**
  PYC has multiple drug programs, each progressing towards multi-billion dollar markets
- **Building on its success in the eye, PYC is expanding the application of its technology**
  The Company's initial focus outside the eye is on neurodegenerative diseases

Corporate overview

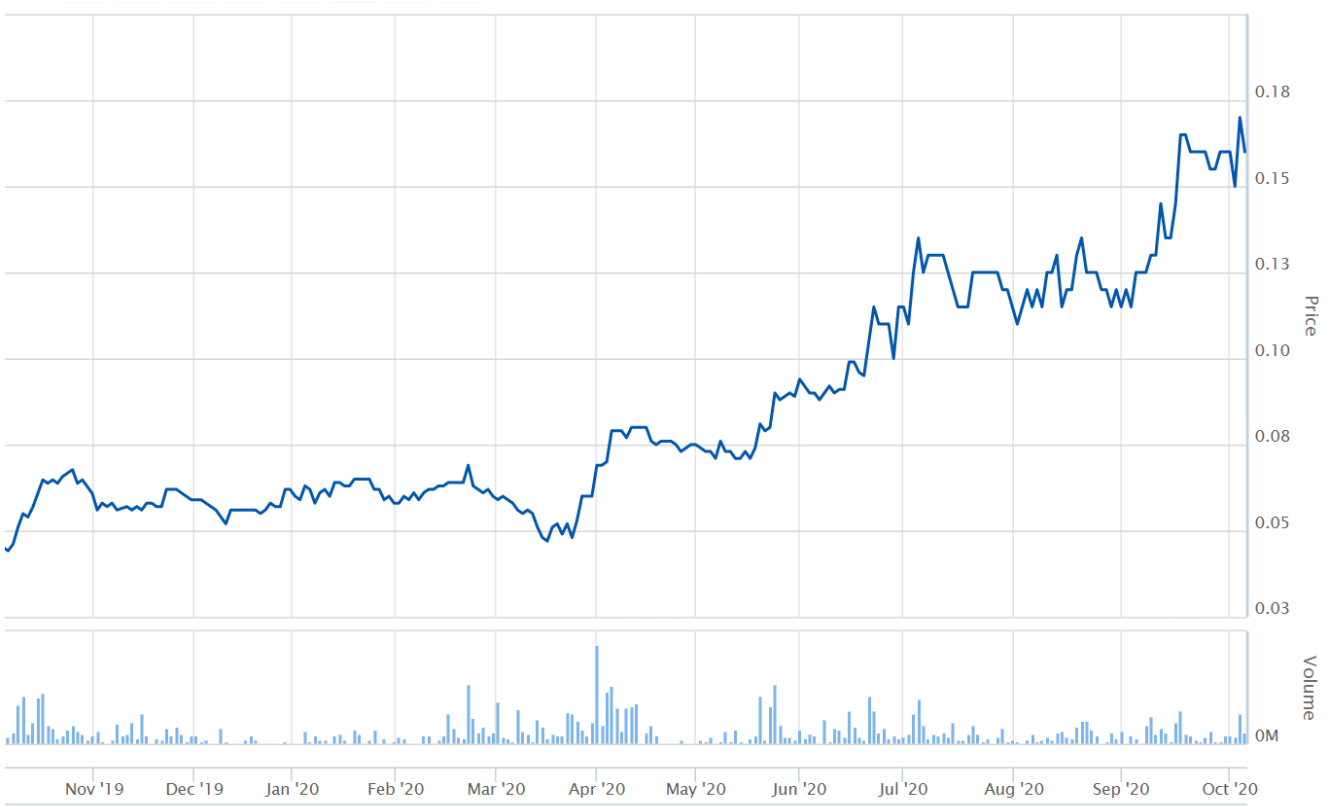
PYC Corporate Snapshot (ASX: PYC)

Financial Information (5 October 2020, AUD)	
Share price	**$0.17**
Number of shares	2,930M
Market Capitalisation	**$498M**
Cash (30-Jun-20)	$25M
Debt (30-Jun-20)	Nil
Enterprise Value	**$473M**

Board of Director
Alan Tribe – Chairman
Doug Huey – Executive Director
Dr Rohan Hockings – Executive Director
Dr Bernard Hockings – Non-Executive Director

Top Shareholders (5 October 2020)	%
Alan Tribe	30.1%
Sietsma Holdings	9.2%
Dr Bernard Hockings	9.0%
Anthony Barton	6.0%

Share Price Performance (12 months)



Leadership team

Executive management

Dr Rohan Hockings
MBBS (Hons), JD GDLP
Chief Executive Officer

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

Professor Sue Fletcher
PhD, BSc
Chief Scientific Officer

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

Kaggen Ausma
LLB, Becons (Hons)
Chief Business Officer

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

Advisory Board

Dr Fred Chen
MBBS (Hons), PhD, FRANZCO
Chair Ophthalmic Advisory Board

Retinal clinician, co-inventor of VP-001 and leader of Ocular Tissue Engineering Laboratory at Lions Eye Institute

Professor Judy Lieberman
MD, PhD
Scientific Advisory Board Member

Leader and pioneer in the field of siRNA, Chair in Cellular and Molecular Medicine at Boston Children's Hospital, Professor of Pediatrics at Harvard Medical School

Asc. Professor Rakesh N. Veedu
MSc, PhD, MRACI
Scientific Advisory Board Member

Extensive expertise in basic and translational research in the field of oligonucleotide therapeutic development

PYC trades at a substantial discount to its US peers

	Market Cap. USD M[1]	Cash, USD M[2]	Stage	IND date	Platform	Lead target
PYC THERAPEUTICS	330	18	Pre-clinical	1H 22	RNA delivery	Rare Ocular
AVIDITY BIOSCIENCES	1,250	345	Pre-clinical	2H 21	RNA delivery	Rare Muscle
Dyne THERAPEUTICS	1,040	375	Pre-clinical	1H 22	RNA delivery	Rare Muscle
STOKE THERAPEUTICS	1,160	215	IND	1H 20	RNA targets	Rare Neuro
PassageBio	750	380	IND	1H 20	DNA delivery	Rare Neuro
generation bio	1,390	340	Pre-clinical	2H 22	DNA delivery	Rare Liver

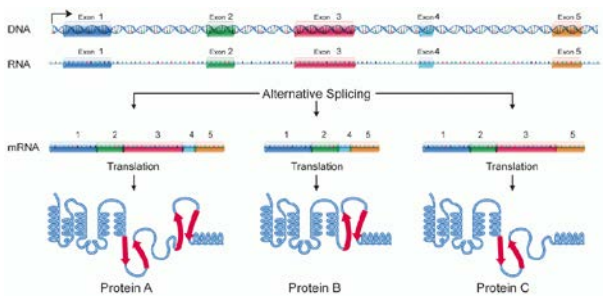
1 As at 18th September 2020, AUD:USD of 0.7
2 From SEC 10-Q and S-1 filings

PYC's Therapeutic Approach

PYC combines RNA drug design expertise with RNA drug delivery technology to create powerful precision therapies

World-class RNA drug design specialists

- Team led by Prof. Sue Fletcher – co-inventor of two FDA approved RNA therapeutics with others in late-stage clinical development
- RNA drugs are precision therapeutics that act on the inside of cells
- They occupy a unique position in the pharmaceutical landscape due to their balance of durability and titratability
- PYC has the capability to identify highly valuable targets and design tailored RNA intervention strategies to match



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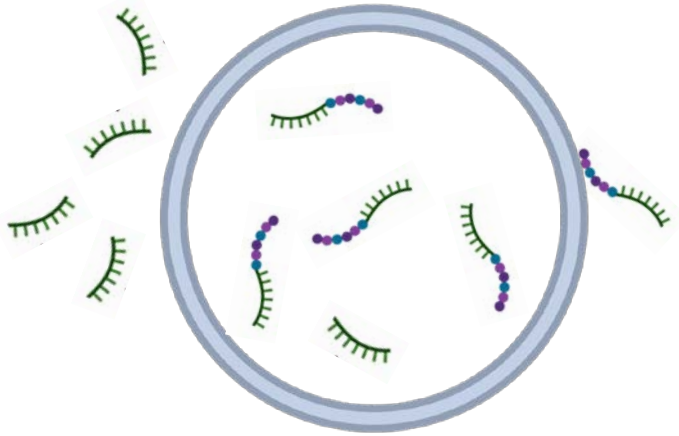
Delivery technology that enables RNA drugs to reach their target inside the cell

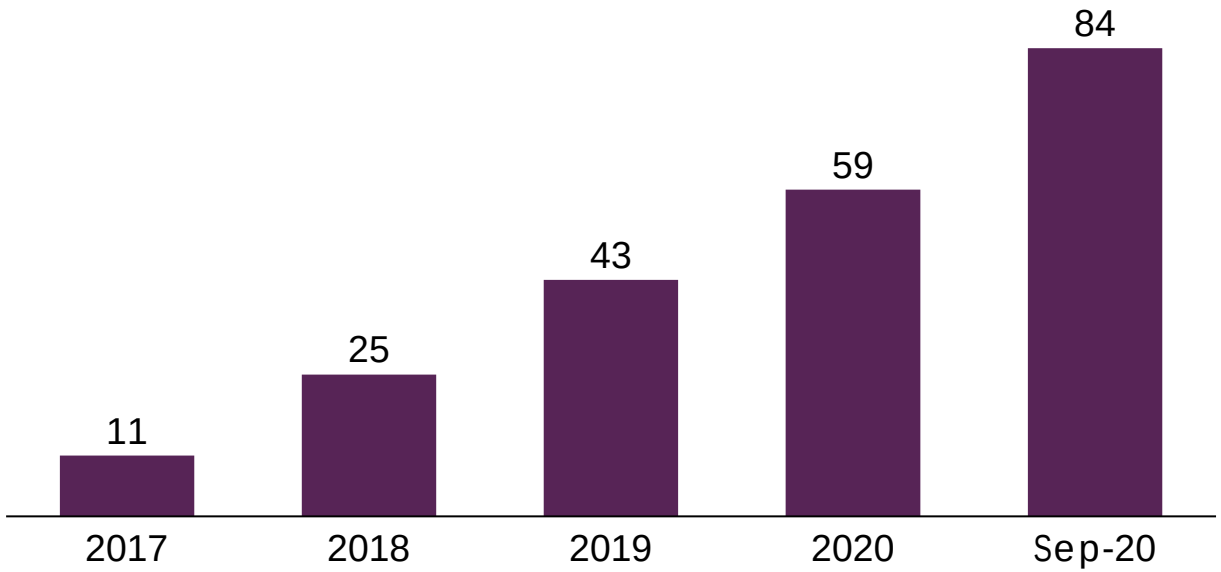
- The single greatest challenge for RNA drugs is the ability to cross the cell membrane to reach their target
- PYC's delivery technology safely delivers the RNA drug:
  - i) to the cell; and
  - ii) across the cell membrane where it can engage its intended target in the cell nucleus



PYC is in the right place at the right time – An RNA specialist in the era of precision medicine

"In the long run, oligonucleotides are likely to become a major class of therapeutics, on par with small molecules and biologics[1]"

Public RNA focused companies market capitalisation, USD B



	2017	2018	2019	2020	Sep-20
Companies, #	7	8	11	12	12
Ave. valuation, USD B	1.6	3.2	3.9	4.9	7.0

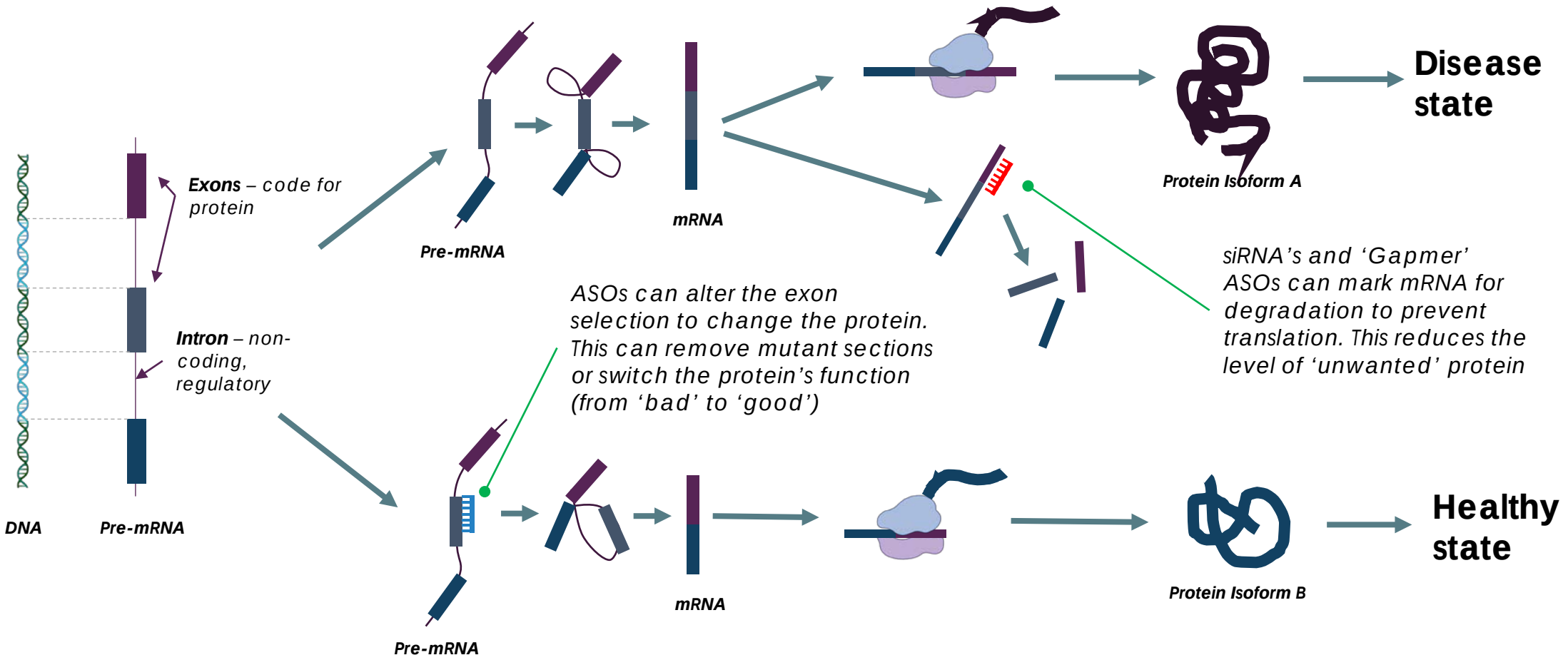
RNA therapy approvals

Drug	RNA drug	Approved
VITRAVENE 250 MG GANCICLOVIR SODIUM CAPSULES	ASO[2]	1998
KYNAMRO (mipomersen sodium) injection 200mg/ml	ASO	2013
EXONDYS 51 (eteplirsen) Injection	ASO (PMO[2])	2016
SPINRAZA (nusinersen)	ASO	2016
Tegsedi™ (inotersen)	ASO	2018
onpattro (patisiran) lipid complex injection	siRNA[2]	2018
VYONDYS 53 (golodirsen) Injection	ASO (PMO)	2019
GIVLAARI (givosiran)	siRNA	2019
Viltepso (viltolarsen) injection	ASO (PMO)	2020

1 Watts JK, Brown RH, Khvorova A. Nucleic Acid Therapeutics for Neurological Diseases. Neurotherapeutics. 2019;16(2):245-247
2 ASO: Antisense Oligonucleotide; PMO (phosphorodiamidate morpholino oligomer) are a chemical sub-class of antisense drugs; siRNA: small interfering RNA

Source: NASDAQ end of day quote 7 September 2020

PYC's drug design team know how to choose the right approach for the target indication



DNA —transcription→ ***pre-mRNA*** —splicing→ **mRNA** —translation→ **Protein** → **Function**

The cell transcribes the full gene – both protein coding and regulatory sequences

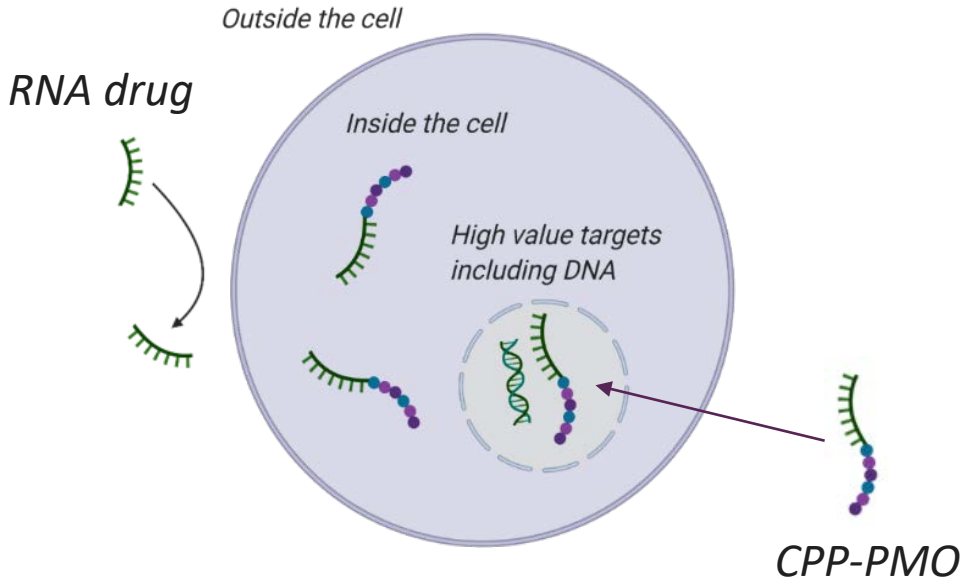
The cell then 'cuts' or splices the introns out to make mRNA

mRNA is then translated by the cell into protein

PYC's drugs can access cells (and diseases) beyond the reach of competitive RNA technologies

The challenge for most RNA drugs

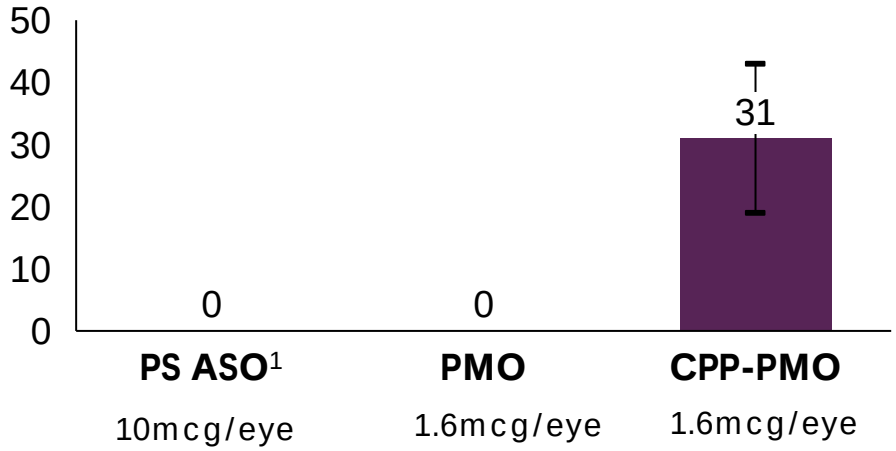
The cell membrane has evolved over hundreds of millions of years to keep foreign substances out



PYC's CPP-PMOs enable RNA therapeutics to target the previously unreachable

Exon skipping (%) in mouse Retinal Pigment Epithelium/ Choroid

Single IVT injection, day 5



PYC's Cell Penetrating Peptides

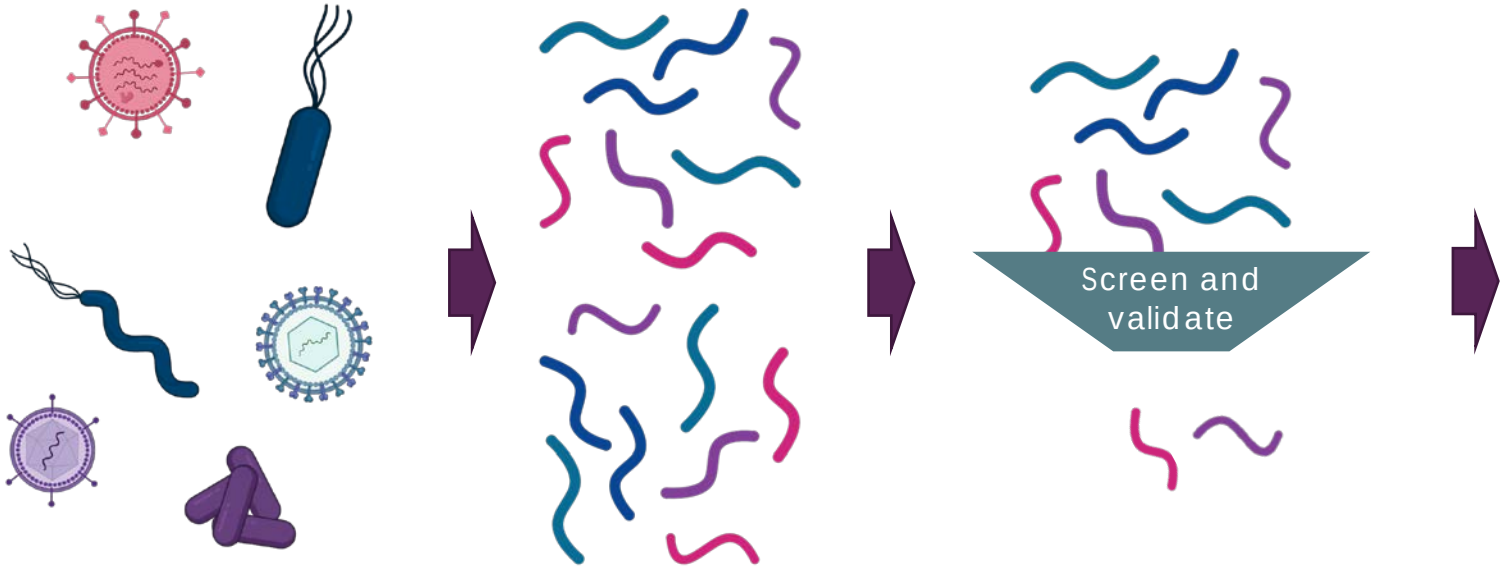
PYC's proprietary Cell Penetrating Peptides (CPPs) can deliver RNA drugs, like PMOs, inside cells that are beyond the reach of competitive technologies

1 PS: Phosphorothioate backbone antisense oligonucleotide;

PYC's proprietary delivery platform is unique - leveraging nature's solution to identify distinctive delivery vehicles

Microorganisms have evolved over millions of years to safely interact with the human body – PYC's libraries leverage this pressure to screen for safe, highly effective delivery peptides

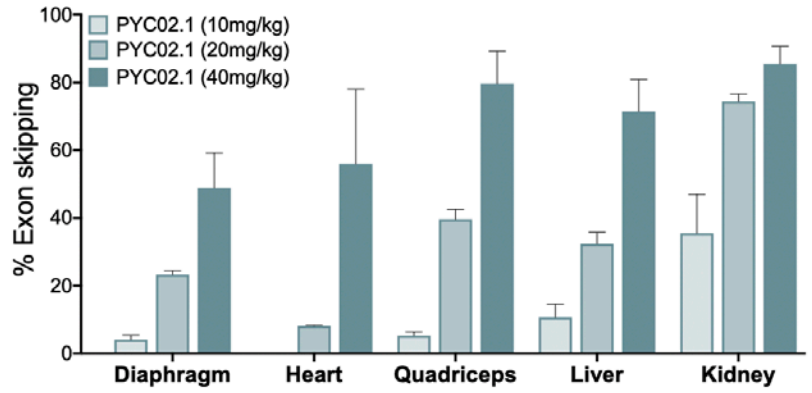
1 **Genomes of microorganisms broken down and expressed as short peptides**



2 **Peptides screened and validated for cell-penetration properties (effective delivery to the nucleus)**

3 **In vivo validation for each tissue and cargo type – with a focus on delivery of ASOs**

***Smn* exon skipping in mice,** IV injection day 2 n=2

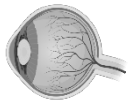
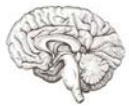


Created with BioRender.com

See ASX Announcement 14 October 2019

PYC's drug development pipeline

PYC is a multi-asset drug development company

Program overview			Indication and stage of development					Estimated market size
Organ	Program	Target	Discovery	Lead selection	IND-enabling	Clinical	Marketed	
Eye 	VP-001	PRPF31	Retinitis Pigmentosa Type 11					**US$1-2 billion p.a.**
	PYC-001	VEGF	Diabetic Retinopathy					**>US$5 billion p.a.**
	Multiple	Undisclosed	Discovery pipeline					**Multiples of programs**
CNS 	Multiple	Undisclosed	Discovery pipeline					**Multiples of programs**

Upcoming milestones

	2H20	1H21	2H21	1H22
VP-001 for RP11	▪ Orphan drug designation for VP-001 for RP11	▪ DRF studies in Rabbit and NHP ▪ Large animal PK data	▪ Large animal long term toxicity data	▪ Submission of IND and CTN
PYC-001 for DR		▪ Assessment of pro-survival effect of PYC-001 in patient derived models	▪ Assessment of anti-angiogenic effect of PYC-001 in a CNV model	
Pipeline	▪ Identify second ocular target	▪ Identify potential CNS delivery CPP and drug cargo in first indication		

PYC has deep (and evolving) IP protection supporting our platform from discovery through to drug

	Description	Status	Expiry
Libraries	2nd generation library construction and display	Granted	2027
Screening	Phenotypic screening of the peptide libraries	Granted	2025
CPPs	1st generation CPP	Granted	2037
	2nd generation CPP (Ocular leads)	Provisional	TBD
ASOs	RP11 program lead and associated molecules	PCT	TBD
	Program 2 & 3 ASOs	Provisional	TBD

Growing protection through IP coverage of the conjugate (CPP-ASO), new CPP's for new targets, and new ASOs for new indications

VP-001 for the treatment of RP11

PYC THERAPEUTICS

Executive Summary – VP-001 for Retinitis Pigmentosa type 11

1. Retinitis Pigmentosa type 11 (RP11) is a large target market with no disease-modifying therapies available for patients (nor in clinical development)

2. PYC's lead drug program (VP-001) holds the promise of rescuing progressive cell death and blindness in patients with RP11
   - PYC's delivery technology can reach the target cell following intravitreal injection - conferring a major competitive advantage over therapies requiring sub-retinal administration (*in vivo model*)
   - VP-001 engages its target and achieves the desired exon skipping effect (*patient derived model*)
   - VP-001 corrects the deficiency of the target protein once inside the cell (*patient derived model*)
   - The increase in the target protein rescues the downstream functional consequences of RP11 (*patient derived models*)

3. PYC's Cell Penetrating Peptide – Antisense Oligonucleotide conjugates show no evidence of toxicity in the retina (*animal models*)

4. VP-001 has an attractive path to market with small clinical trials and the potential for a single pivotal study

1. RP11 is a large target market with no disease-modifying therapies available for patients (nor in clinical development)

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There are a large number of patients with Retinitis Pigmentosa type 11 who have no available treatment options

Retinitis Pigmentosa is a genetic, blinding eye disease

- VP-001 will treat Retinitis Pigmentosa Type 11 (RP11)
  - **Severe, progressive blinding eye disease**
  - Onset between the ages of 10 and 20
  - Leads to blindness between 40-50 years of age
- There is **no treatment in market or in clinical development**

RP11 represents a 1-2B USD p.a. treatment market

- **4,000-8,000** patients in the western world
- **~250,000 USD p.a.** orphan drug pricing
- **1-2B USD p.a. market**
- Straightforward and low cost sales and distribution channel

VP-001 will serve a 1-2B USD p.a. market

Retinitis Pigmentosa (RP) prevalence proportion of people in the population with RP	1 in 2,500-4,000[1]
Proportion of RP that is autosomal dominant (adRP) Inherited in a dominant pattern	30-40%[1]
Proportion of adRP that is RP11 Patients is a disease causing mutation in PRPF31	8-10%[1]
Reimbursable RP11 patients Number of patients in the US, EU, and Japan	4,000-8,000 patients[1]
Median Rare Disease drug price Annual reimbursed cost for a rare disease drug	US$250,000 p.a.[2]
Total addressable market Margins assumed at 90% due to low COGs[3]	**US$1-2bn p.a.**

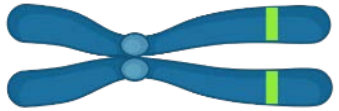
No competitors in market or in clinical development

1 Daiger et al. 'Genes and Mutations Causing Autosomal Dominant Retinitis Pigmentosa' Cold Spring Harb. Perspect. Med. 5 (2014); Ellingford et al. 'Molecular findings from 537 individuals with inherited retinal disease' J Med Genet 53, 761-776 (2016); Sullivan LS, Bowne SJ, Birch DG, et al. Prevalence of disease-causing mutations in families with autosomal dominant retinitis pigmentosa: a screen of known genes in 200 families. Invest Ophthalmol Vis Sci. 2006;47(7):3052-3064.
2 Based on Luxturna pricing over 4 years (450k USD per eye). Luxturna is a gene therapy for treatment of a rare inherited retinal disease, approved in 2017, marketed by Spark Therapeutics.
3 Sarepta Therapeutics' marketed Exondys 51 for a DMD subpopulation has margins which exceed 90% for a systemically delivered drug (much more product per dose)

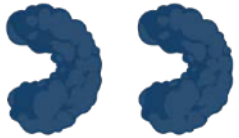
VP-001 targets a down-regulator of the gene underlying RP11

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

Eye with RP11

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

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

The lack of protein means the retinal cells in the eye don’t function correctly and start to die – causing blindness

PYC’s lead drug

Our drug knocks down a protein that down-regulates the RP11 target gene

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

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

DEEP-DIVE

Insufficient *PRPF31* protein drives RP11 and *CNOT3* expression controls *PRPF31* expression

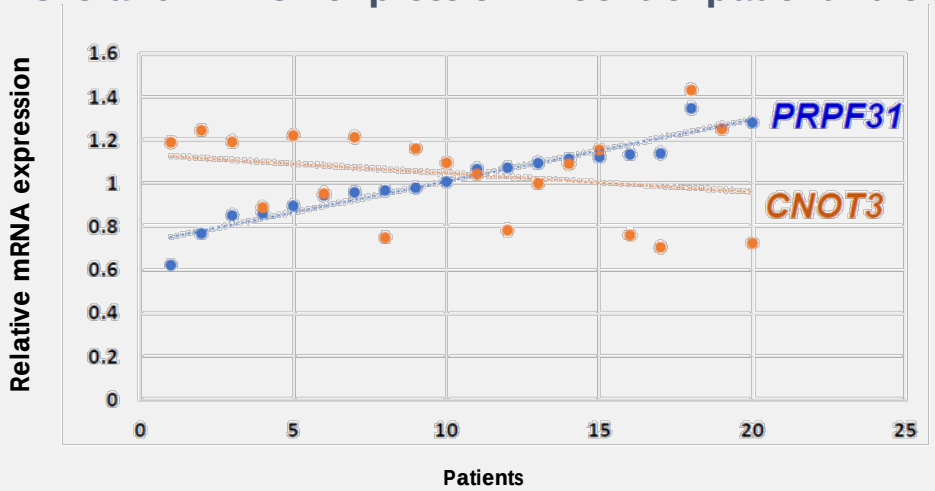
PRPF31 expression levels determine if a patient suffers vision loss

- RP11 patients have one healthy copy of *PRPF31* and one mutated, non-functional copy of *PRPF31*
- For most patients this leads to insufficient *PRPF31* protein for a healthy retina (~50% the PRPF31 protein of a healthy person)
- However, some patients have only one healthy copy of *PRPF31*, but late or no disease onset
- This is because their healthy gene produces ~1.2-1.4 fold more protein than other patients

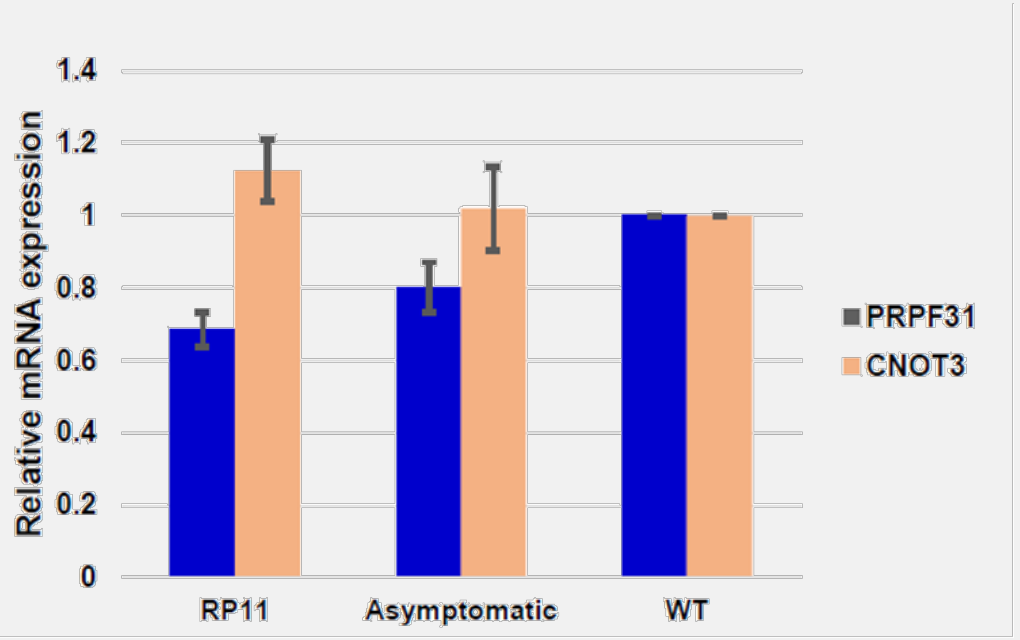
CNOT3 protein levels regulate *PRPF31* expression

- *CNOT3* is a negative regulator of *PRPF31*
- *CNOT3* expression is higher in RP11 patients compared to 'asymptomatic' family members with the same PRPF31 mutations

CNOT3 and *PRPF31* expression in control patient fibroblasts[1]



CNOT3 and *PRPF31* expression in iPSC-derived retinal pigment epithelium (RPE)[1]



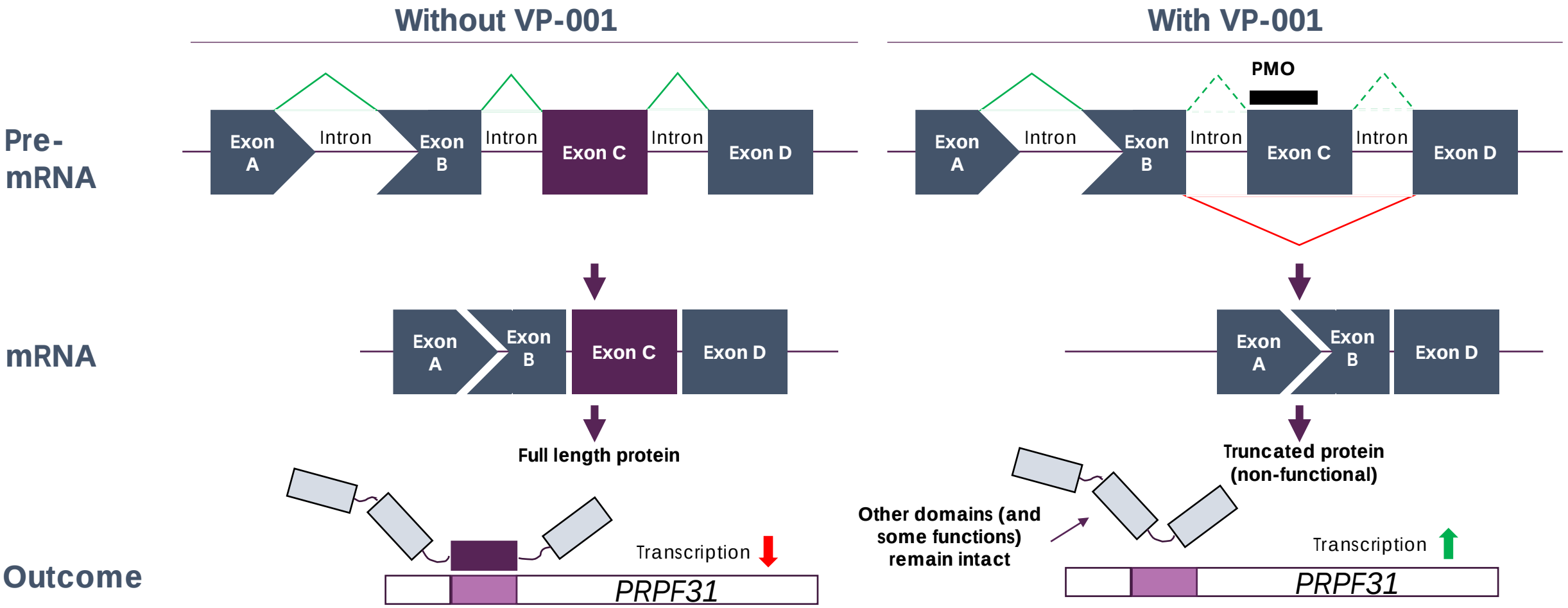
1 RT-qPCR analysis of PRPF31 and CNOT3 mRNA expression normalised with TATA-binding protein (TBP) expression in iPSCs-derived retinal pigment epithelium from RP11, asymptomatic and wild type (WT) individuals. Bar chart represent mean±standard error of the mean (SEM) from three independent RT-qPCR. Expression of CNOT3 and PRPF31 transcripts in wild type was set to 1. *p<0.05 compared with wildtype. #p<0.05 compared with asymptomatic subject

See ASX Announcement 14 October 2019

DEEP-DIVE

VP-001 uses an antisense oligo with a morpholino (PMO) backbone to reduce the functional effect of *CNOT3* on *PRPF31* expression

Schematic strategy of PMO-mediated *CNOT3* exon skipping



VP-001 uses a PMO to remove in-frame exons encoding functional domains downregulating *PRPF31* – the truncated CNOT3 isoform leads to an upregulation in *PRPF31* expression levels

2. VP-001 holds the promise of rescuing progressive cell death and blindness in patients with RP11

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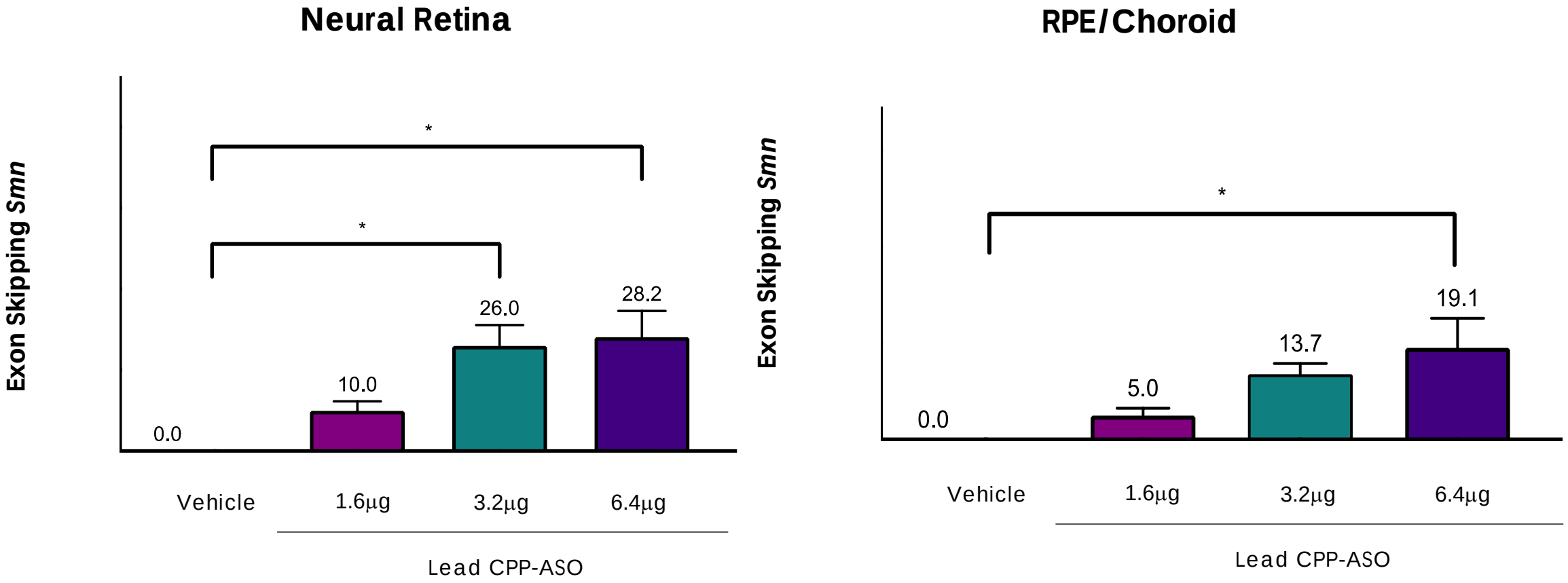
DEEP-DIVE

PYC's drug delivery technology can successfully deliver an RNA therapeutic into the nucleus of the target cell (the RPE) in mice

Delivery dose response (lead CPP with 'reporter ASO' targeting *Smn* gene after IVT administration)[1]

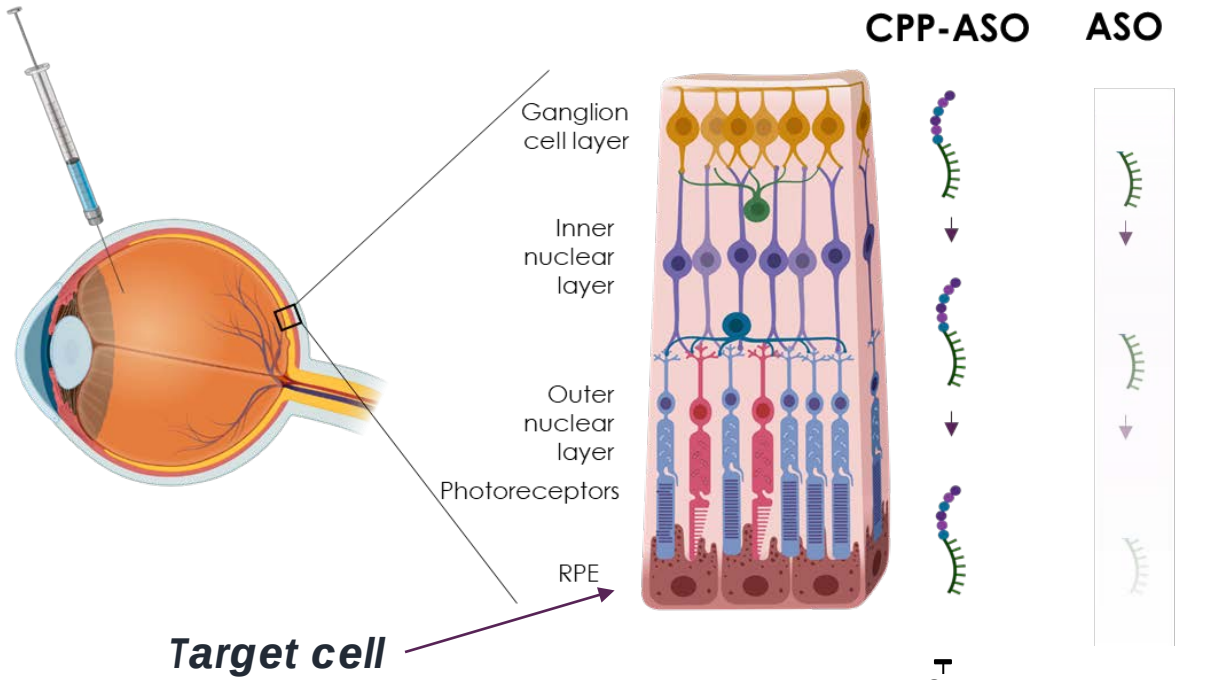


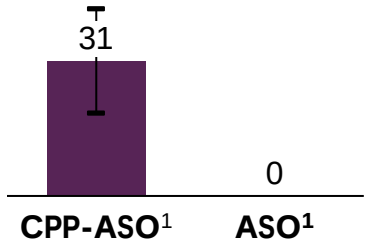
1 Day 28 post intravitreal injection in mice. A readout of drug delivery, Exon-skipping of Survival of Motor Neuron (Smn) in the mouse retina across 3 dose cohorts (n=12 for each dose cohort, n=4 for vehicle)

See ASX Announcement 22 July 2020

VP-001 is the only disease modifying therapy in development that treats the entire retina

Treating the disease requires a delivery technology to reach the deepest cells at the back of the eye

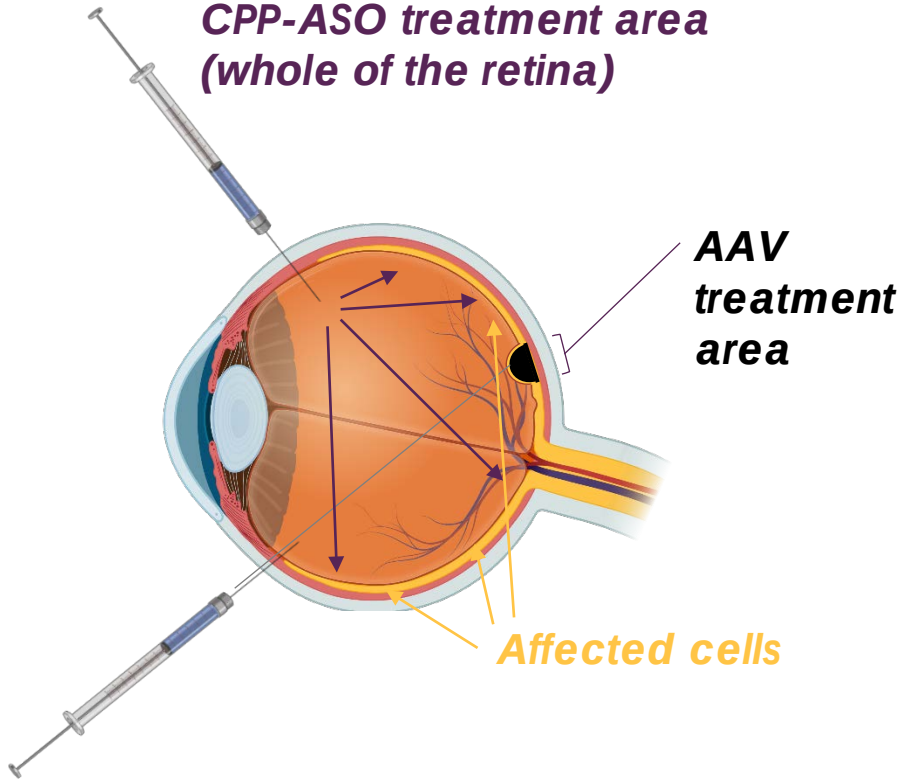




PYC's technology delivers the drug where others cannot – the cells where treatment is needed

Breadth of delivery is also required to treat the entire eye

- Cells degenerate across the entire retina causing it to 'leak' and the cells to die
- An effective treatment must treat a majority of the cells to prevent significant vision loss



1 Exon skipping at day 5 post 1.6μg Intravitreal administration in the mouse eye.

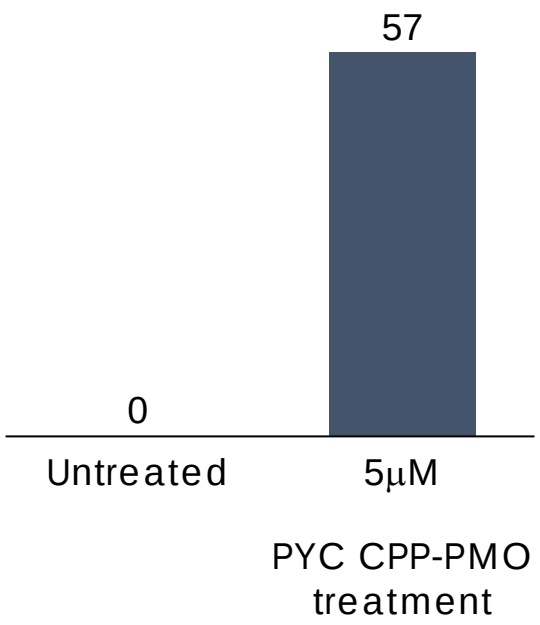
DEEP-DIVE

VP-001 achieves the desired exon skipping effect at the anticipated clinical concentration in patient derived models

We have proven that our drug modulates target gene expression in multiple patient derived models…

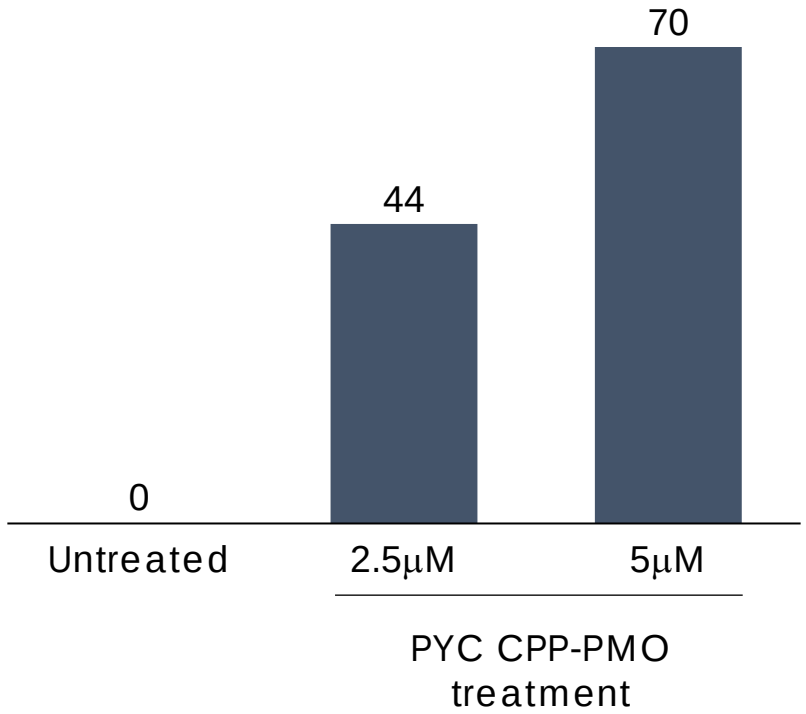
Exon skipping, retinal organoid

Day 14, 2 treatments (n=2)



Exon skipping, Retinal Pigment Epithelial

Day 5, single treatment

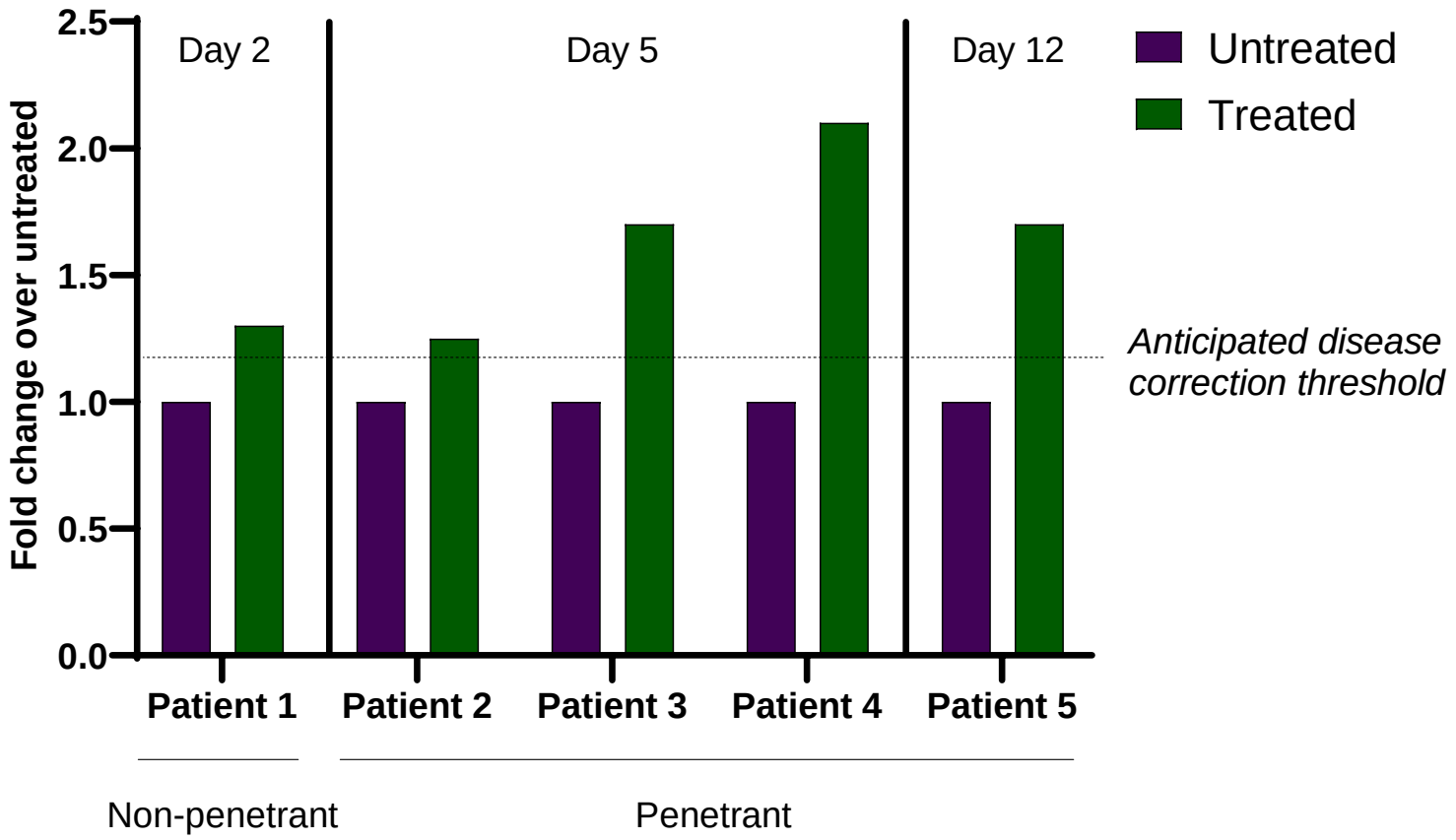


Exon skipping in patient retinal organoid models (n=2 patients with RP11), with and without PYC's drug treatment. Organoids (4-6 organoids combined) were treated with 5μM of drug administered twice over a 14 day time period. Due to the successful delivery up to 71% of RNA molecules have been altered (skipped) by the PMO (n=1 sample per treatment)
Exon skipping in patient derived RPE model (n=1), with and without PYC's drug treatment. (n=2 per treatment)
See ASX Announcement 1 April 2020

DEEP-DIVE

This exon skipping translates into an upregulation of the deficient protein at levels expected to rescue the disease

PRPF31 protein levels, RPE, 5μM treatment, (n=1 per patient)



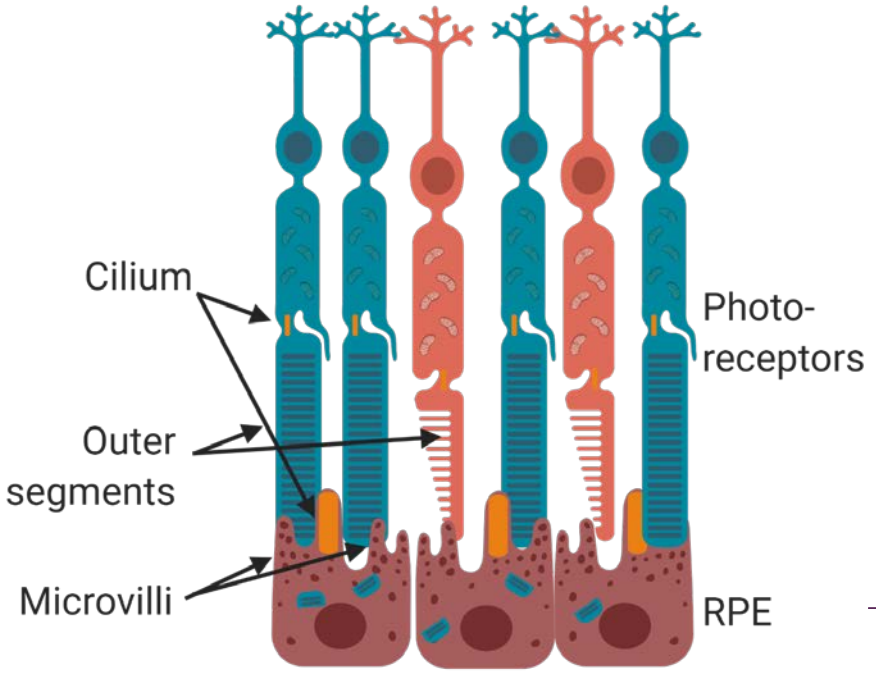
For anticipated disease correction threshold see 'Giulia Venturini, Anna M. Rose, Amna Z. Shah, Shomi S. Bhattacharya, Carlo Rivolta. CNOT3 Is a Modifier of PRPF31 Mutations in Retinitis Pigmentosa with Incomplete Penetrance. PLOS Genetics November 2012'

See ASX Announcement 7 October 2020

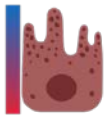
DEEP-DIVE

Upregulation of the target protein rescues the functional deficits associated with the disease

Structure of the Retina

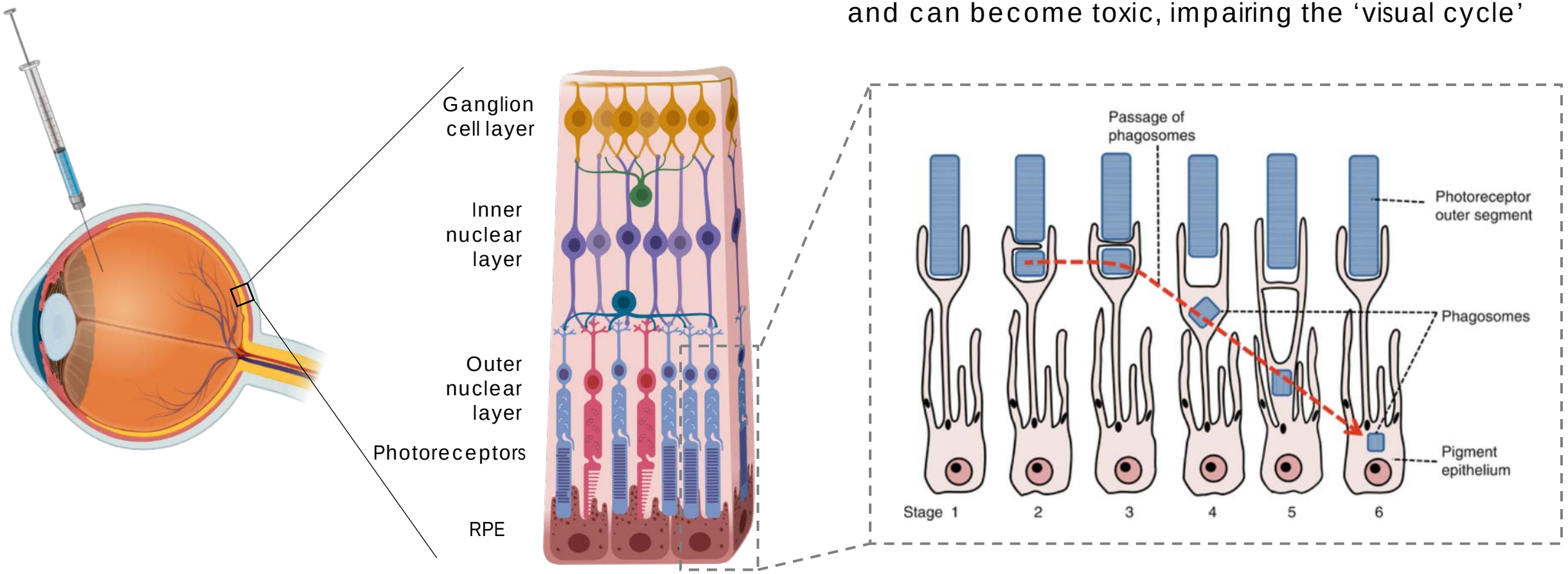


Impact of RP11

	Healthy	RP11	Impact of RP11	Restoration with VP-001
Cilia length			▪ Shorter ‘stunted’ connecting cilium in the photoreceptors	TBD
Phagocytosis			▪ Lower ‘phagocytosis’ of outer segments (lower ability of the RPE to dispose of the toxin)	✓
Cilia length			▪ Shorter and less frequent cilium on the RPE, showing poor RPE health	✓
Transepithelial resistance			▪ RPE cells are not tightly joined and become ‘leaky’, causing retinal degeneration	TBD
Microvilli health			▪ Short, less functional microvilli, which are the ‘arms’ that collect the outer segments during phagocytosis	TBD
Polarity			▪ RPE loses polarity – or simply the cell becomes ‘disordered’	TBD

RP11 patients experience lost functionality of Retinal Pigment Epithelial cells (RPE)

Structure of the Retina – target cells in the back of the eye (RPE)

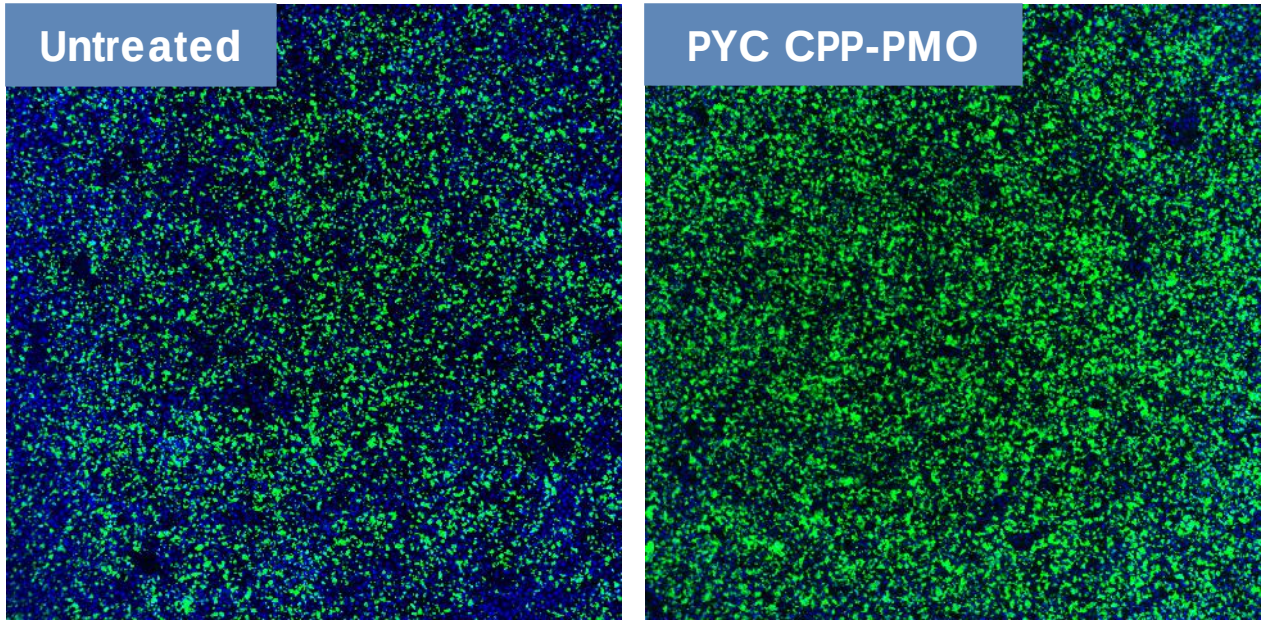


Phagocytosis – the 'self-repair' process where RPE cells 'clear away' debris from the photoreceptors. If outer segments are not phagocytosed, they build up and can become toxic, impairing the 'visual cycle'

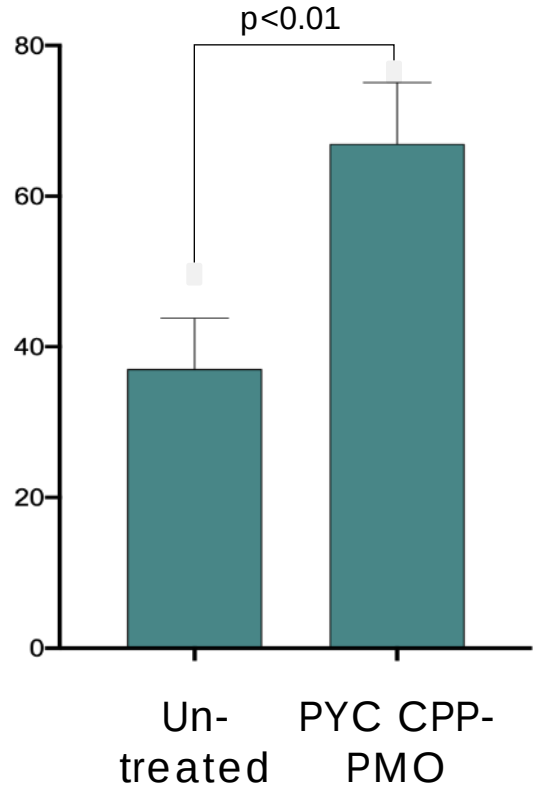
VP-001 restores RPE functionality in patient derived models

Phagocytosis assay, 5μM 6hr timepoint

A) Green 'specks' are Phagocytosed outer-segments (more green = improved functionality)



B) Intensity of phagocytosis per RPE cell



A) Phagocytosis in a patient with Retinitis Pigmentosa 11 with and without treatment with PYC's lead drug (more green = more phagocytosis). Photoreceptor outer segments have been labelled with a fluorescent green 'tag' and the ability of the RPE (nuclei stained in blue) to self- repair ('phagocytose') the green outer segments has been assessed. The cells treated with 5uM of PYC's drug demonstrate substantially greater ability to phagocytose the fluorescent green outer segments than the untreated cells. The Microscopic images taken 5 days post treatment at 10x magnification for both treated and untreated cells. These images are representative of a broader set of assays conducted across cells derived from multiple patients.
B) Comparison of the level of phagocytosis in RPE cells (signal intensity of green florescent 'tag' per cell actively phagocytosing) derived from a patient with RP11, with and without treatment with PYC's drug. Within 5 days, a single 5μM dose of drug (CPP-PMO, 2 samples) increased the phagocytosis ability of the diseased RPE cells by more than 1.5-fold (p=0.0083, two-tailed unpaired t-test) compared to untreated cells (4 samples).

See ASX Announcement 1 April 2020

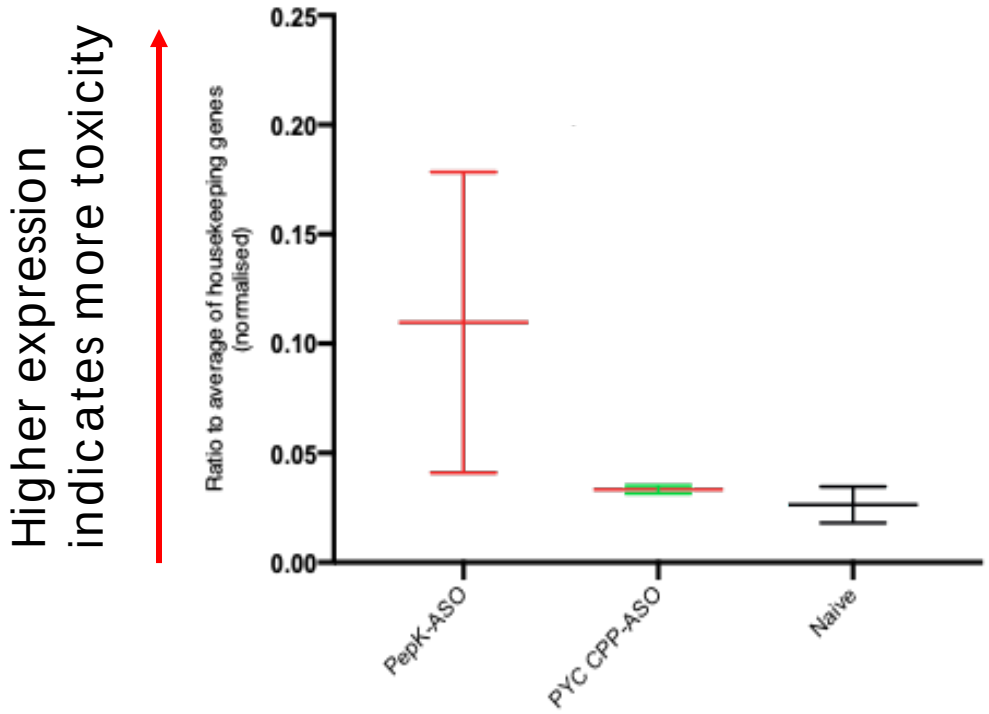
3. PYC's CPP delivery technology used in VP-001 is both safe and effective

DEEP-DIVE

PYC's lead drug is competitively differentiated in achieving this functional correction without causing toxicity in the retina

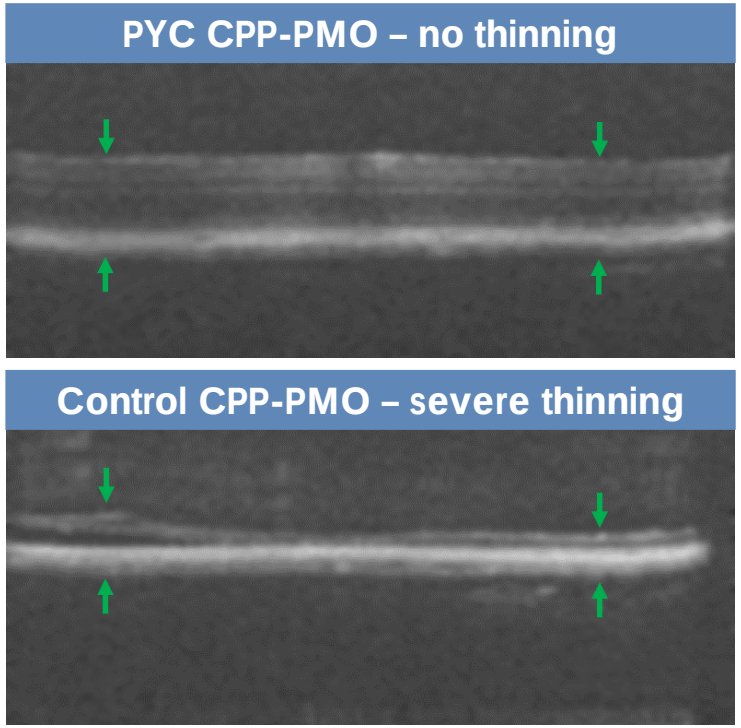
Retinal stress marker expression in mice

Day 5 post single 1.6µg IVT injection



Retinal thinning in mice

Day 21 post IVT injection OCT imaging



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 5 post intravitreal injection and normalised to a pool of 'house-keeping' genes. Notes i) PepK – a third-party delivery peptide that serves as the current benchmark for delivery peptides in clinical development (Red, n=6); ii) PYC's delivery peptide (Green, n=2); and iii) a control group which received no treatment (Black, n=3). One-way ANOVA p values – PepK:naïve 0.1379; PYC CPP:naïve 0.9892

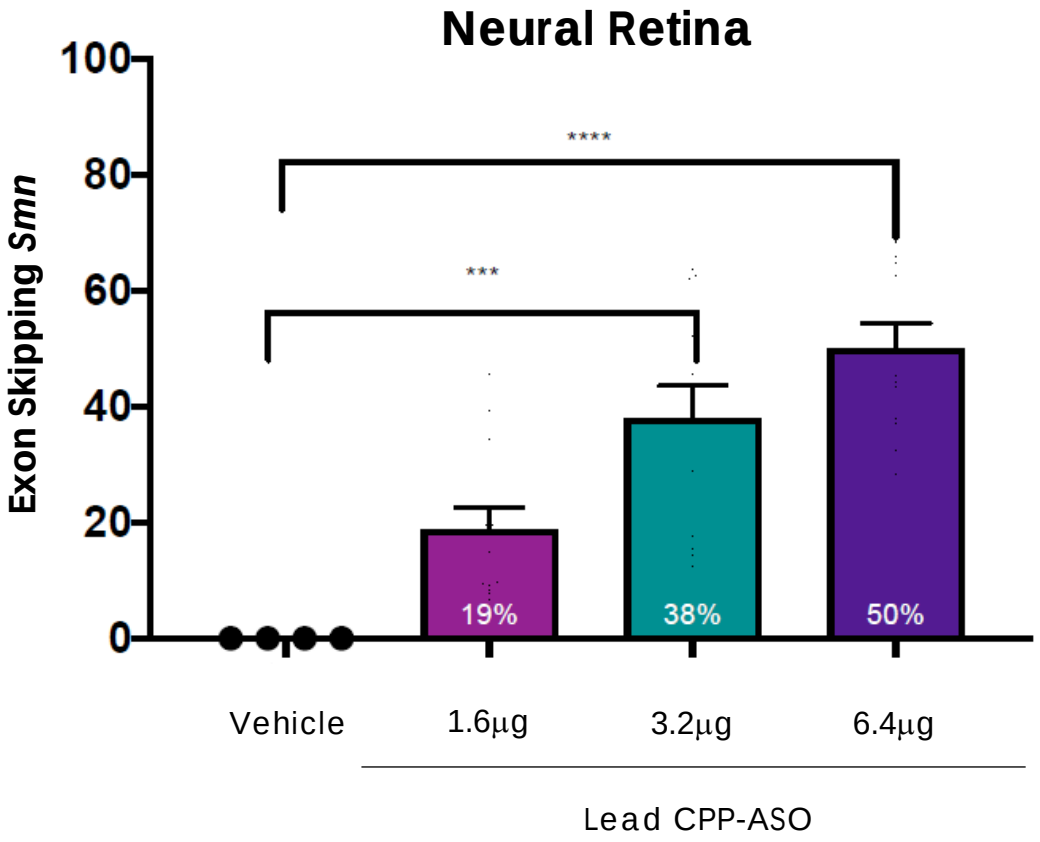
See ASX Announcement 8 April 2020

DEEP-DIVE

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

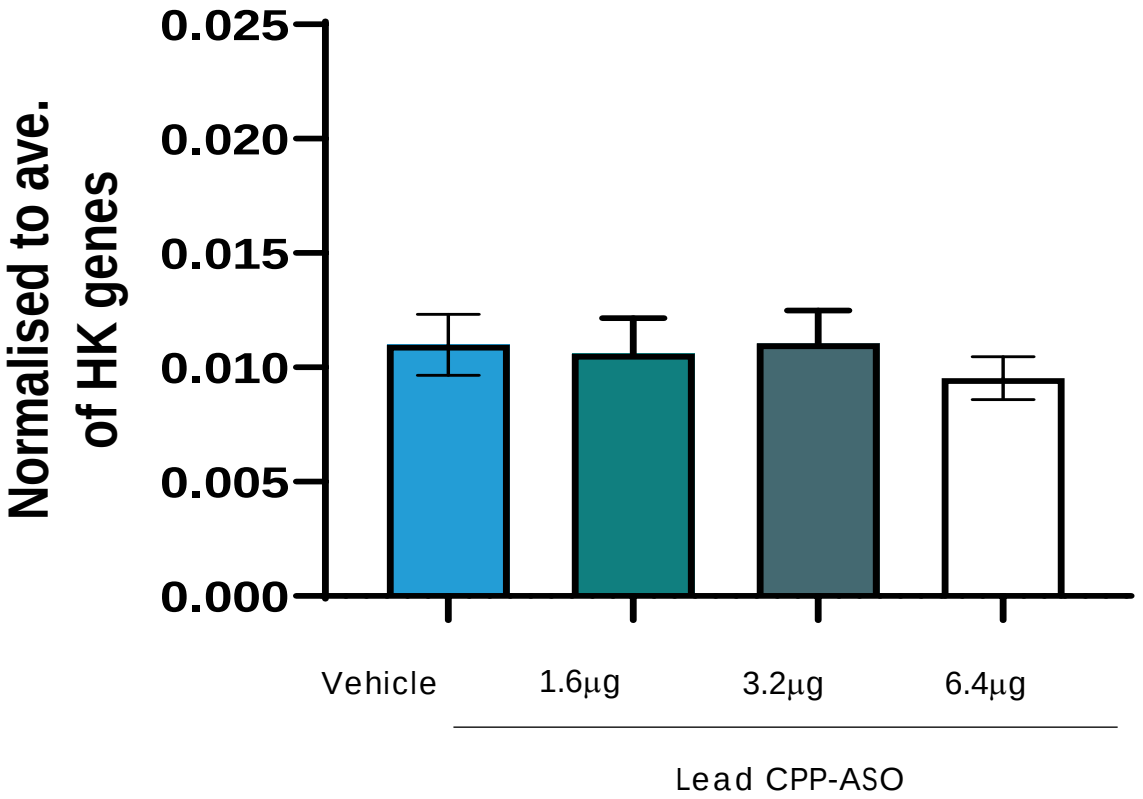
Dose dependant increase in effect …

Exon-skipping, Day 7 in the mouse eye



… and no increase in toxicity markers

Gfap expression, Day 7 in the mouse eye



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

4. VP-001 has an attractive path to market with small clinical trials and the potential for a single pivotal study

The path to market for VP-001 has several major advantages over conventional clinical development pathways

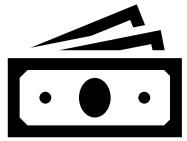
Stage	IND-enabling	Phase 1/2	Phase 2/3	Approval
Timeline	18 months	15 months	18 months	6 months

Higher probability of success

- Orphan genetic drugs have a ~45% chance of reaching market from Phase 1

Shorter time to market

- Combined clinical trials and single pivotal
- Favourable FDA pathways and Orphan status

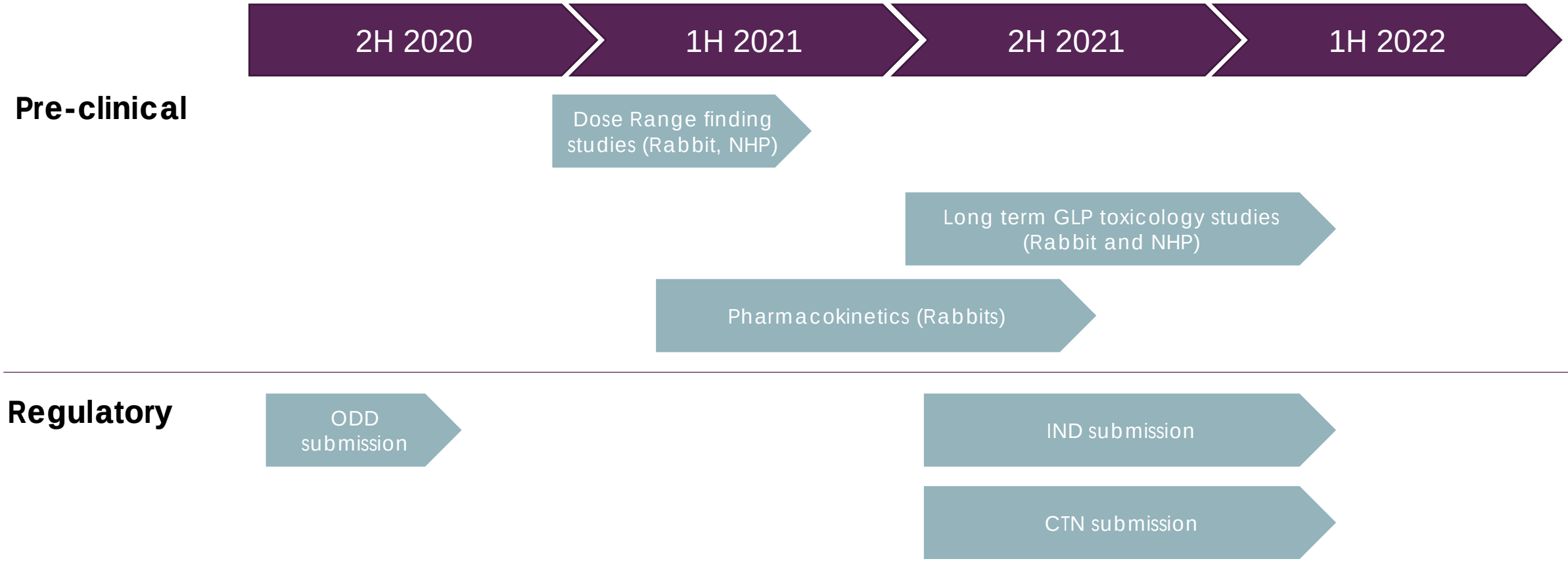


Lower cost

- Lower patient numbers
- 2 planned clinical trials
- Favourable FDA pathways

All numbers and timelines are estimates and are applicable to change and revision

VP-001 is on track for Clinical development starting in 2022



Ocular pipeline

PYC has the capability to rapidly scale its technology in the retina

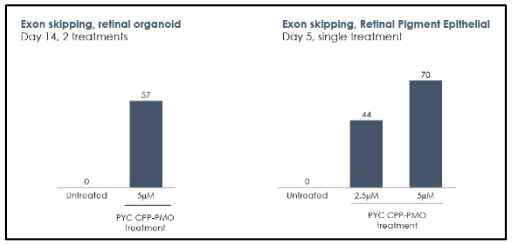
- ✓ Right Biology
- ✓ Right Indication
- ✓ Right Commercials

Does the drug engage the target safely?

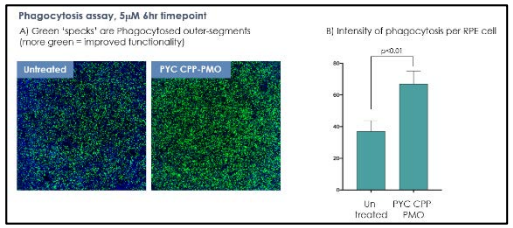
Does the drug alter the disease in a functional model?

Do we progress to IND-enabling studies?

PYC's 'RNA hub'



~3 months

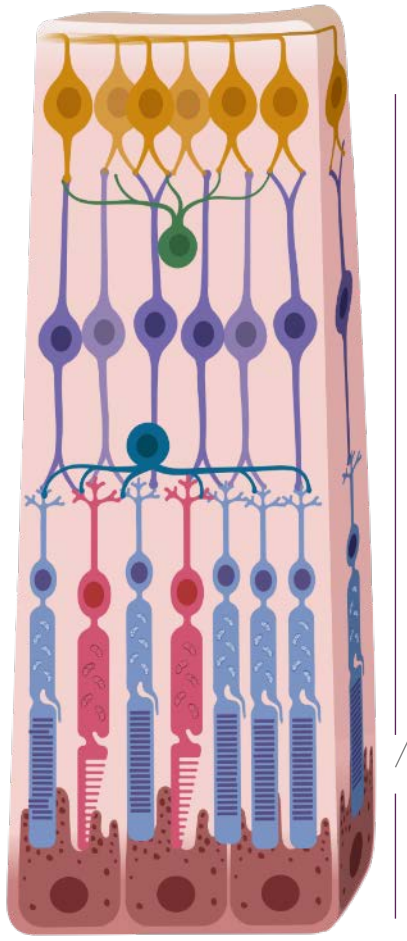


~6-12 months

3-6 months

Advancing our lead program into the clinic will validate our drug delivery platform for retinal disease

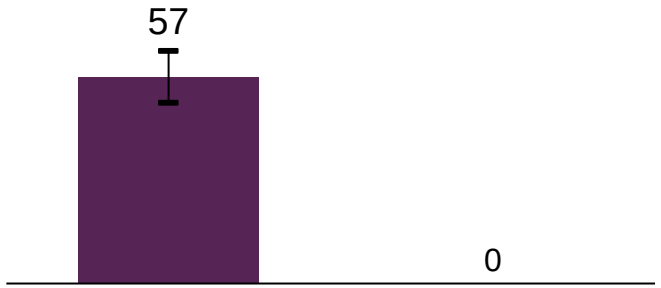
The Retina is a high value target

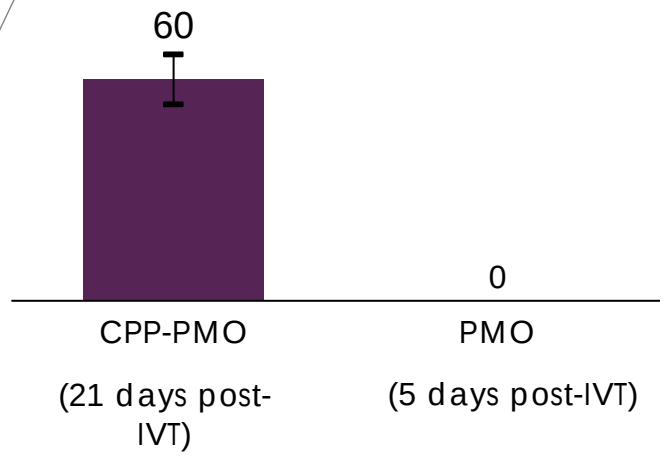


Proven Delivery in the Eye

1.6ug IVT injection in mice

% truncated SMN1 transcript





Develop Further Applications

Diseases primarily affecting the Photoreceptors

- Glaucoma
- Usher Syndrome
- Rhodopsin RP (most prevalent adRP in the US)
- >10 commercially viable Inherited Retinal Diseases

Diseases primarily affecting the RPE

- Diabetic retinopathy
- Wet age-related macular degeneration (wAMD)
- Dry age-related macular degeneration (dAMD)
- >5 commercial Inherited Retinal Diseases

PYC-001 – PYC's second drug development program

- Diabetic Retinopathy (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-Vascular Endothelial Growth Factor (VEGF) therapies and the need for longer acting drugs
- In addition, there is a growing body of evidence suggesting that prolonged VEGF inhibition is responsible for the death of sensitive nerve cells in the retina
- PYC has leveraged the unique advantages of its RNA therapeutics technology to create a modified VEGF therapy that addresses these shortcomings – 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 (a treatment for a blinding disease of childhood called Retinitis Pigmenotsa) and, as a result, is expected to have a rapid development pathway into the clinic

Common eye diseases are linked through dysfunction of blood vessels in the eye

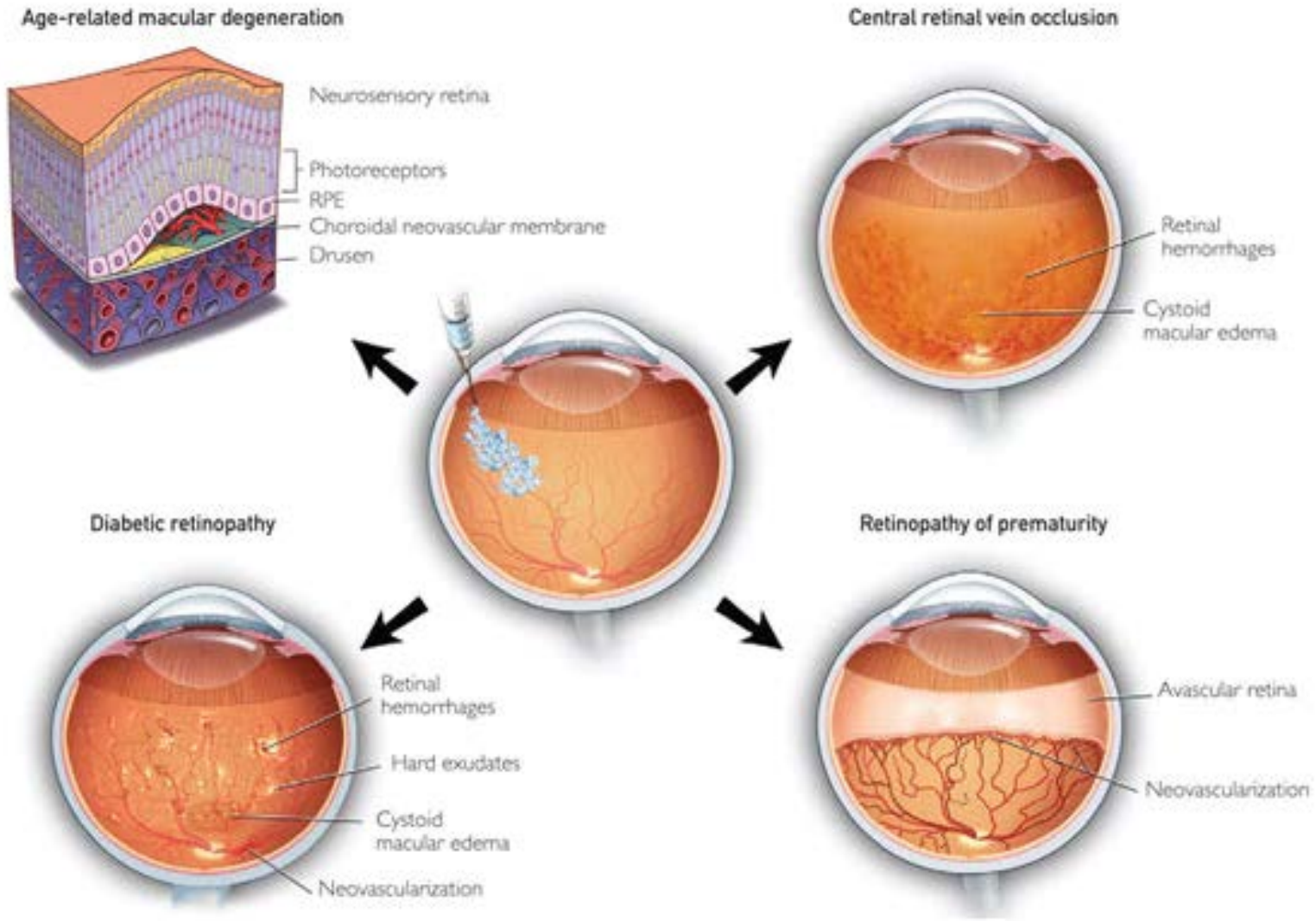
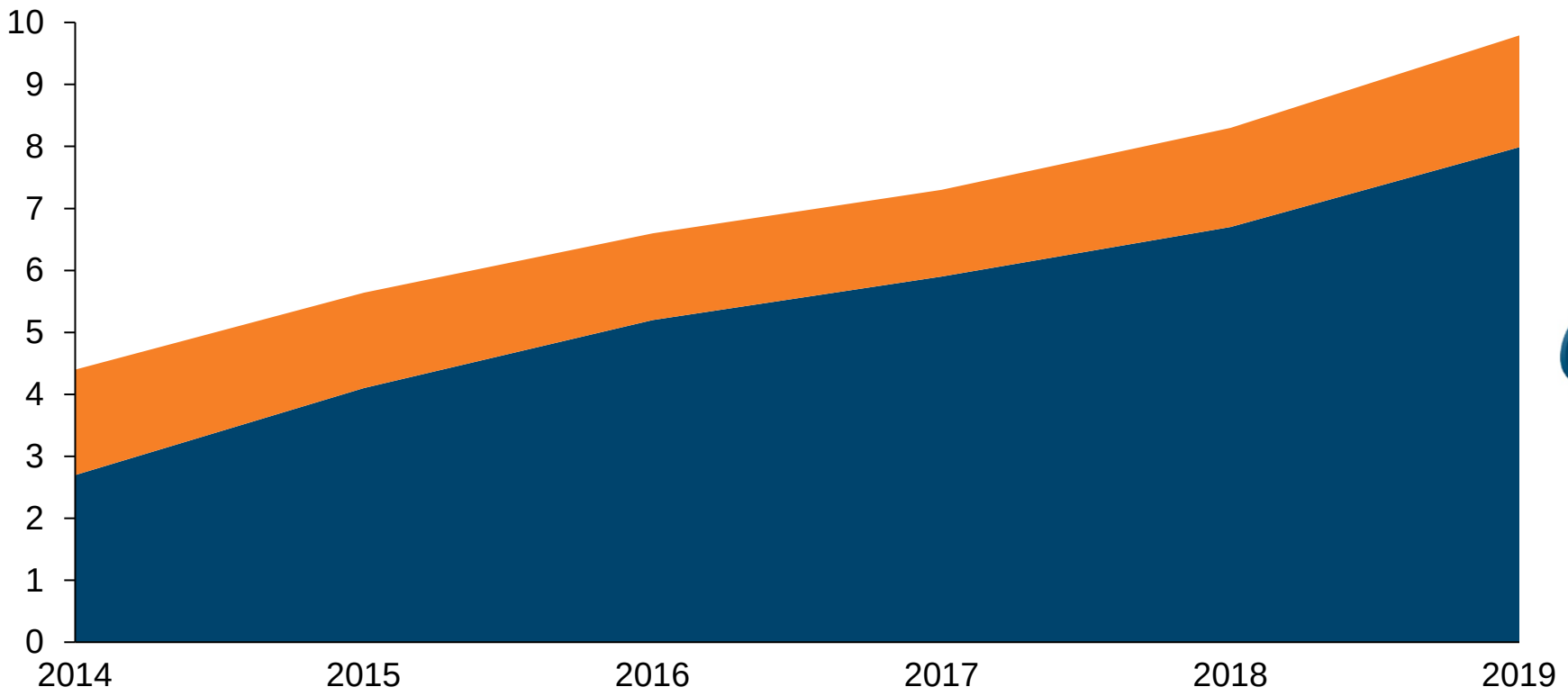


Image: Mayoclinic.com

Inhibiting new blood vessel growth (VEGF-inhibition) has been a major step forward in the management of these diseases

PYC THERAPEUTICS

Global ocular anti-VEGF sales, USD B



LUCENTIS®
RANIBIZUMAB INJECTION

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Source: Roche, Regeneron annual reports and financial statements

But… Inhibition of VEGF is known to cause retinal ganglion cells to die and is also suspected of being linked to macular atrophy

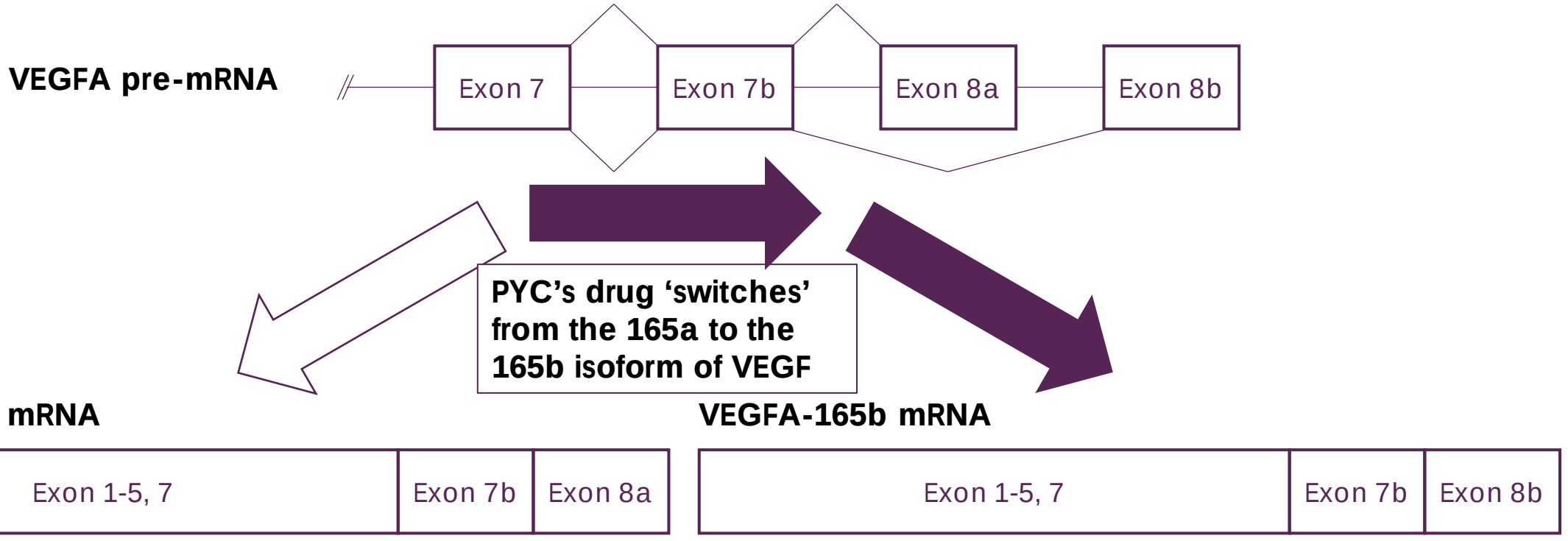
"***VEGF inhibition increased Retinal Ganglion Cells apoptosis and neuronal damage in diabetic retinopathy***" (1)

"***A majority of patients show Macular Atrophy after long-term anti-VEGF treatment***" (2)

"***An association between anti-VEGF treatment and atrophy development has been observed***" (3)

1 Mechanisms behind Retinal Ganglion Cell Loss in Diabetes and Therapeutic Approach. Int. J. Mol. Sci. 2020, 21, 2351; doi:10.3390/ijms21072351
2 Munk MR, Ceklic L, Ebneter A, Huf W, Wolf S, Zinkernagel MS. Macular atrophy in patients with long-term anti-VEGF treatment for neovascular age-related macular degeneration. Acta Ophthalmol. 2016 Dec;94(8):e757-e764. doi: 10.1111/aos.13157. Epub 2016 Jul 15. PMID: 27417506.
3 SriniVas R. Sadda,Robyn Guymer,Jordi M. Monés,Adnan Tufail,Glenn J. Jaffe. 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

There is an alternative method of inhibiting new blood vessel growth *without* the negative effects of VEGF inhibition



Increase leaky new blood vessel growth

Pro-survival

The current generation of VEGF inhibitors cause the loss of the 'pro-survival' signal that is likely the link between sustained exposure to these drugs and retinal cell death – PYC's drug overcomes this issue

Decrease leaky new blood vessel growth

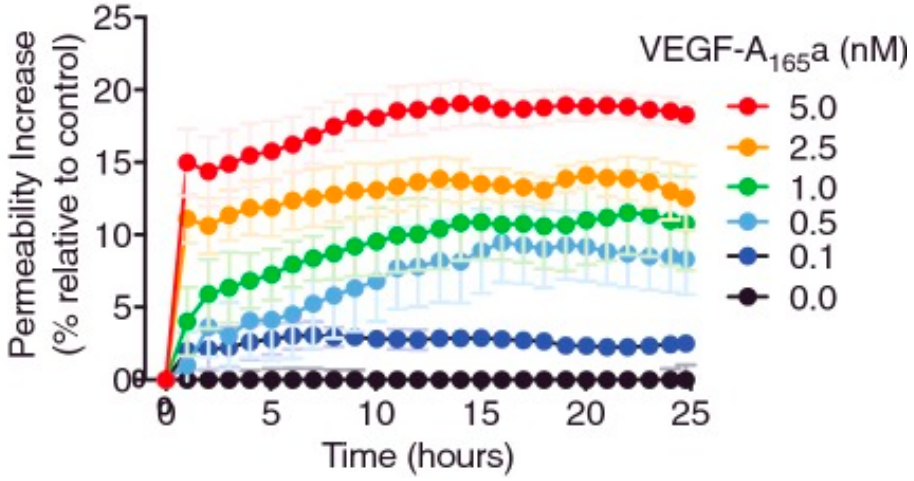
Pro-survival

A very subtle change in the ratio of protein regulated by this ‘switch’ is required to correct the disease process

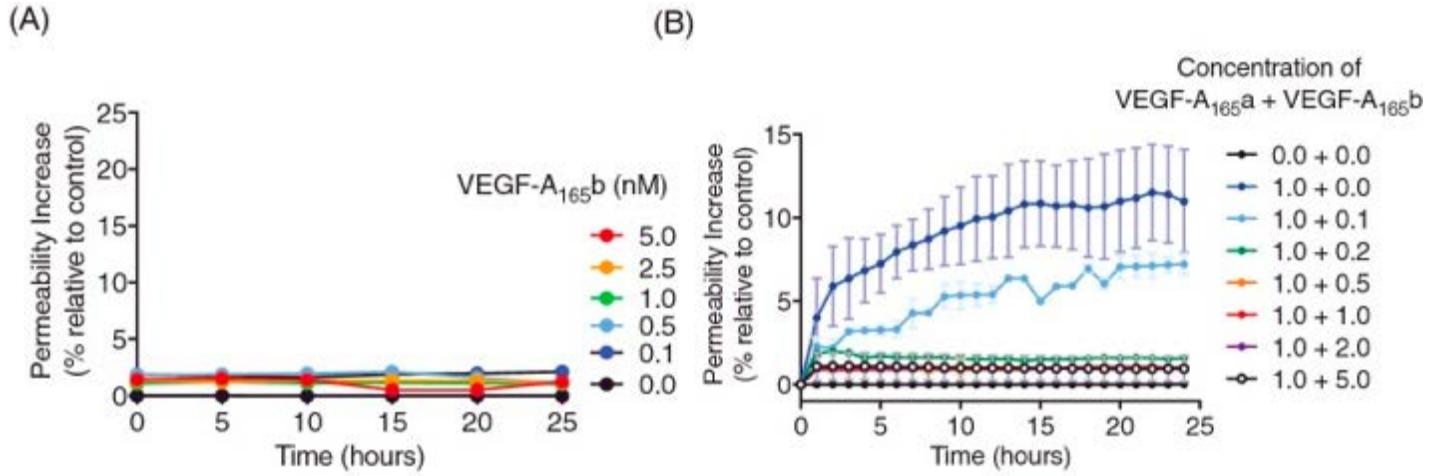
PYC THERAPEUTICS

VEGF-A_{165}a causes RPE tight junction breakdown

Worse outcome



VEGF-A_{165}b prevents VEGF-A_{165}a -induced changes in tight junctions



Ved N, Hulse RP, Bestall SM, Donaldson LF, Bainbridge JW, Bates DO. Vascular endothelial growth factor-A_{165}b ameliorates outer-retinal barrier and vascular dysfunction in the diabetic retina. Clin Sci (Lond). 2017 Jun 1;131(12):1225-1243

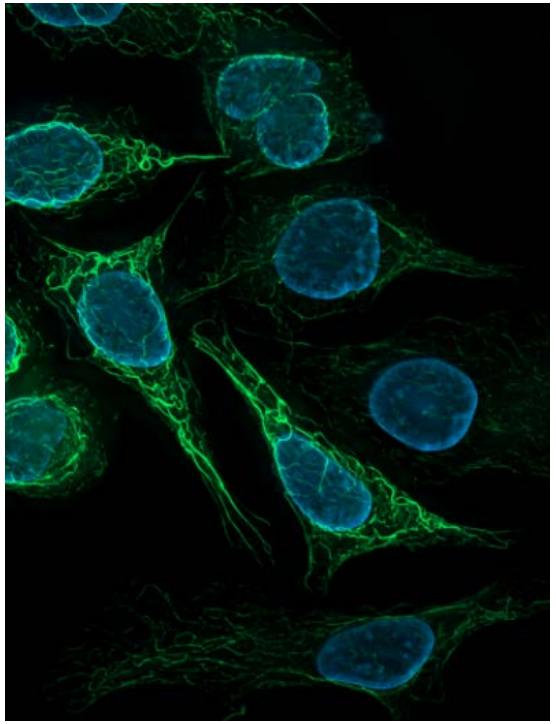
The therapeutic value of this approach has been recognised

"*This switch changes what would be otherwise mild effects from activation by VEGFA165b, to stronger activation of retinal endothelial cells. Isoform switching from VEGFA165a to VEGFA165b would be* ***an excellent target for therapeutic development***"

1 Kenneth P Mitton; Wendy A Dailey; Megan Moore; Alvaro E Guzman; Jennifer Felisky; Kaylee Moyer; Nahrain Putris; Peter Chen; Austen Knapp; Anju Thomas; Regan Miller; Brandon Metcalf. VEGFA Isoform Switching in Diabetic Retinopathy and ROP is a Significant Factor in the Activation of Human Retinal Endothelial Cells. Investigative Ophthalmology & Visual Science July 2019, Vol.60, 2669.

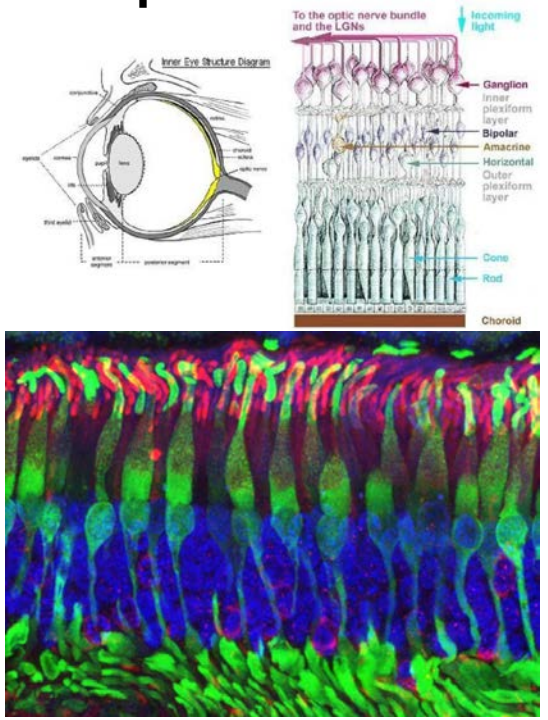
The program is expected to progress into Investigational New Drug enabling studies in 2021

Evaluation in patient cells



Expected 4Q 2020

Evaluation in animal models and/or patient derived models



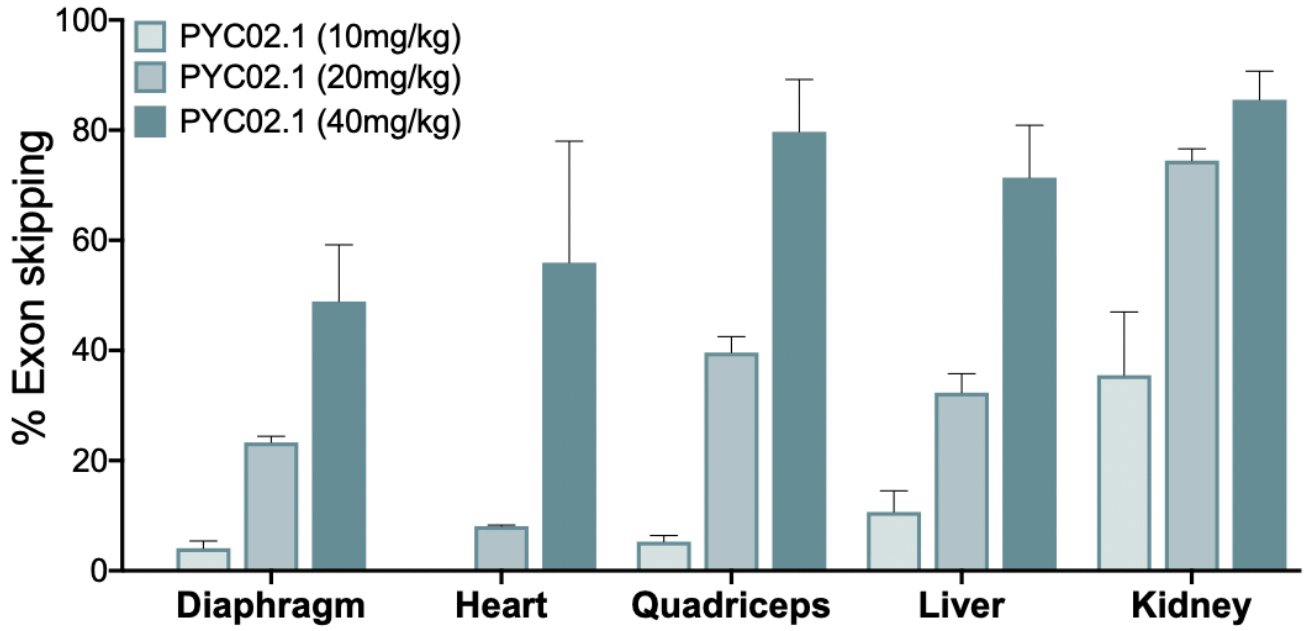
Expected 3Q 2021

IND-enabling decision in 2021

Leveraging the platform beyond the eye

PYC has multiple CPPs with demonstrated capability outside the eye

Intravenous administration of CPP-PMO(*Smn*) into mice n=2/dose



Systemic toxicity markers, 48hr post 32mg/kg injection in mice

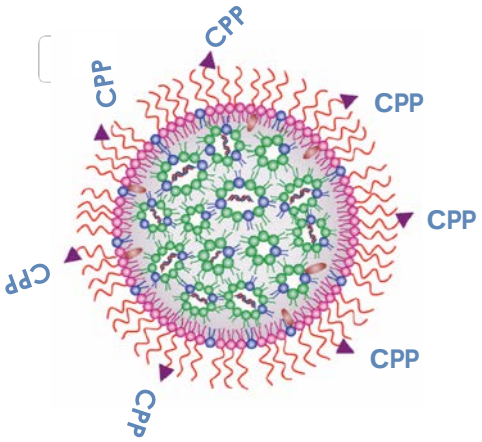
Lead CPP – PMO

		Linker 1	Linker 2
Liver	ALT	Normal	Normal
	AST	Normal	Normal
	Pathology	All score 0	All score 0
Kidney	Urea	Normal	Normal
	Creatine	Normal	Normal
	Pathology	All score 0	All score 0

See ASX Announcement 14 October 2019

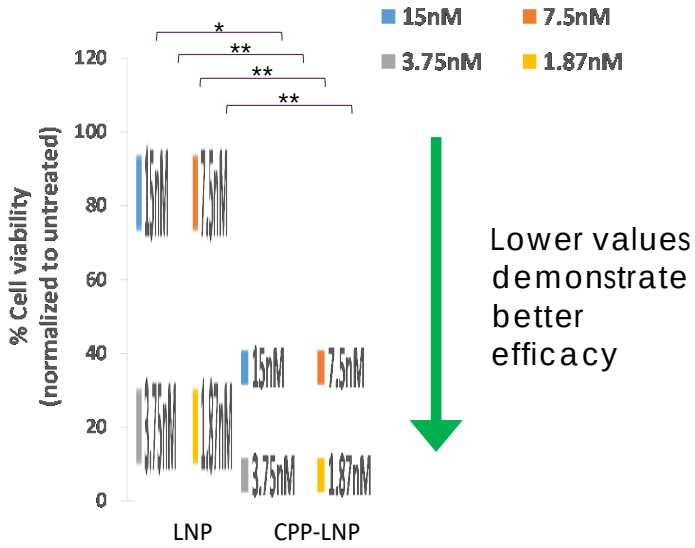
PYC is exploring CPP-LNP conjugates to deliver other high value cargoes to hard to reach tissues and cells

PYC is currently in 'proof of concept' studies for a CPP-LNP conjugate delivery system to enable the effective and safe delivery of negative charged molecules (siRNA, DNA plasmids, Cas9 and others

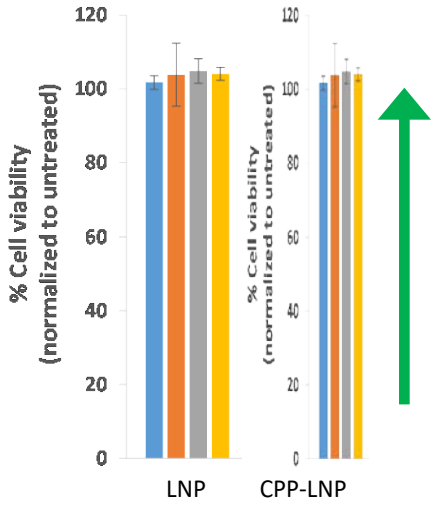


siRNA-induced cell death after treatment with LNP-CPP conjugates

PLK-1 siRNA



Control siRNA



OVACAR8 cells were treated for 72hrs with LNPs or CPP-LNPs at different PLK1-siRNA doses. Cell viat measured by XTT assay

See ASX Announcement 08 August 2020

Disclaimer

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