PYC Therapeutics

Life-changing science

Corporate Presentation

3 February 2023

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Executive Summary

- **PYC is a drug developer:** PYC discovers and develops RNA therapies for patients with genetic diseases
- **Platform technology:** PYC's scalable drug delivery technology overcomes the major limitation on RNA therapies – reaching the target
- **Multi-asset pipeline:** PYC is developing multiple first-in-class drugs in commercially attractive markets (>A$1 billion p.a. each) for patients with no treatment options
- **Near-term catalysts:** human safety and efficacy read-outs are anticipated to begin this year

PYC Therapeutics

PYC discovers and develops RNA therapies to change the lives of patients with genetic diseases

PYC Therapeutics

There is an urgent need to create treatments for patients with rare genetic diseases

There are approximately 6,000 known rare diseases[1] affecting 400 million people worldwide

1 in every 2 patients diagnosed with a rare disease is a child

There are no treatment options available for ~95% of these diseases

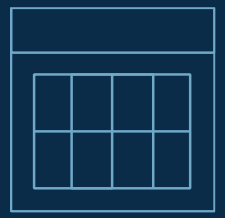
1. Haendel M, et al. How many rare diseases are there? Nat Rev Drug Discov. 2020;19(2):77-8.

PYC is creating therapies for these patients through a strategy anchored on four critical features

PYC Therapeutics

A HIGHER PROBABILITY OF SUCCESS

PYC focuses on monogenic indications. These have the highest likelihood of approval from the start of clinical trials to market of any indication*[1]



A FASTER PATH TO MARKET

The potential for approval following two clinical trials (not three) due to the absence of existing treatment options for patients with the targeted indications

LIKELY RAPID UPTAKE IN MARKET

First-in-class drugs in rare diseases achieve rapid market penetration with a very short lead time to peak sales

ORPHAN DRUG PRICING

Median list price of ~US$150,000[2] per patient per annum making for commercially attractive markets across the pipeline

*Monogenic indications compared to polygenic indications

1. Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank. doi: https://doi.org/10.1101/2020.11.02.20222232
2. EvaluatePharma. Orphan Drug Report. 2019.

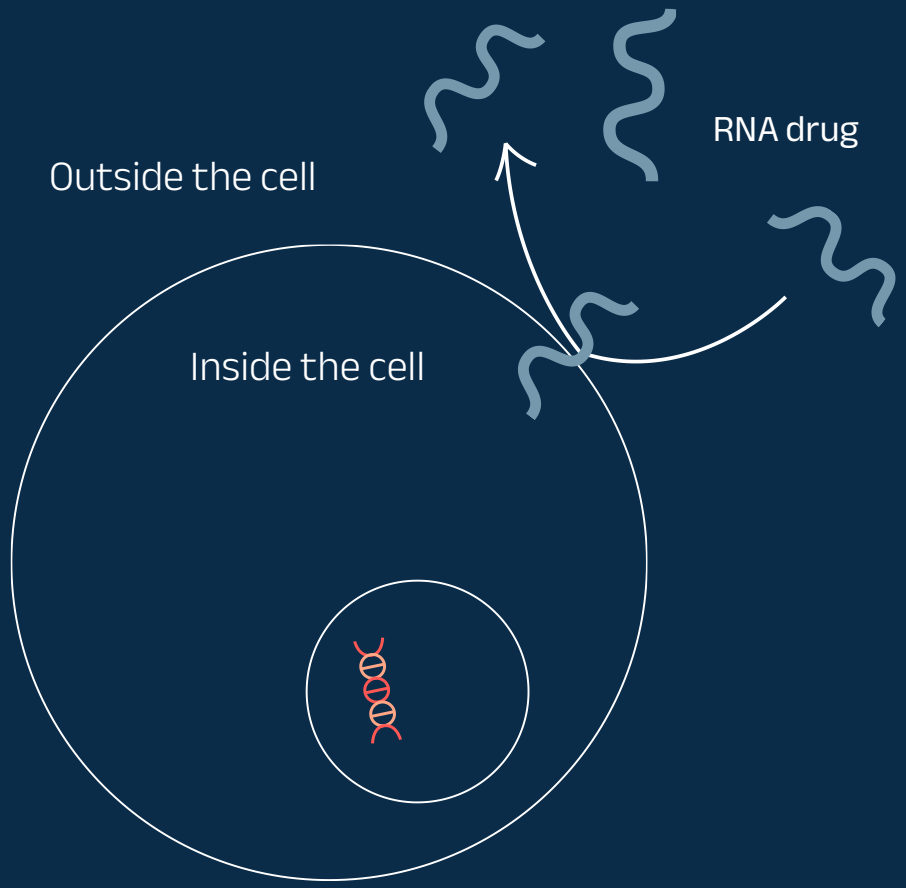
PYC's drug development efforts are supported by the dominant trend in the pharmaceutical industry today...

*"We are in the midst of a **therapeutic revolution**, the likes of which have not been seen..."*

*"RNA Therapeutics will **change the standard of care for many diseases**"*

1. Damase TR, et al. The Limitless Future of RNA Therapeutics. Front Bioeng Biotechnol. 2021;9:628137.

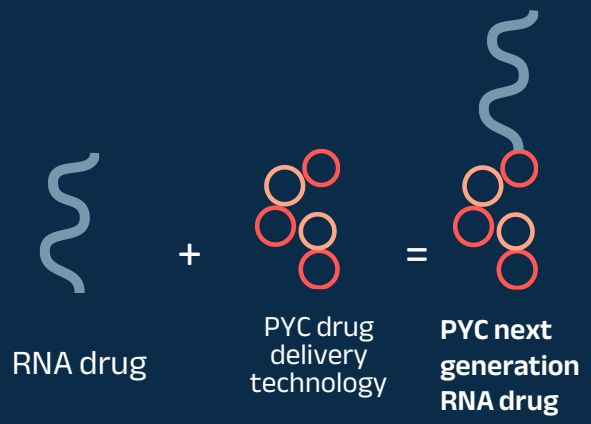
… However, RNA therapies have an ‘Achilles heel’ – they struggle to get inside the cells where their targets reside



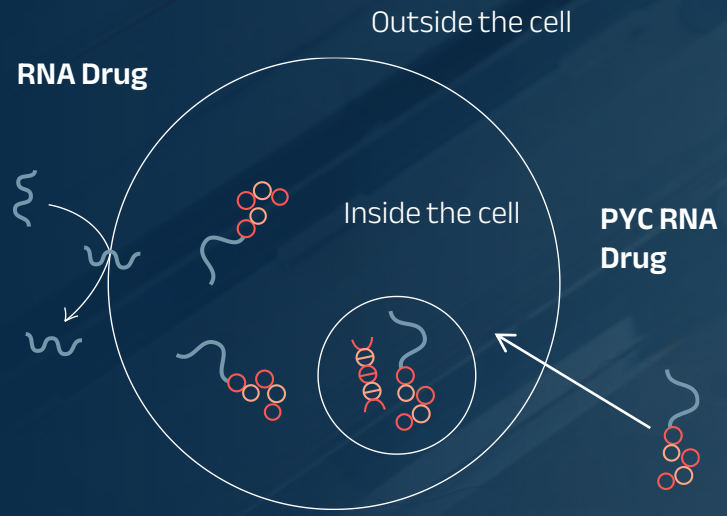
The ‘delivery challenge’ has limited the number of diseases for which RNA therapies have been successfully created

PYC's RNA delivery platform overcomes this primary challenge – ensuring enough drug reaches its target

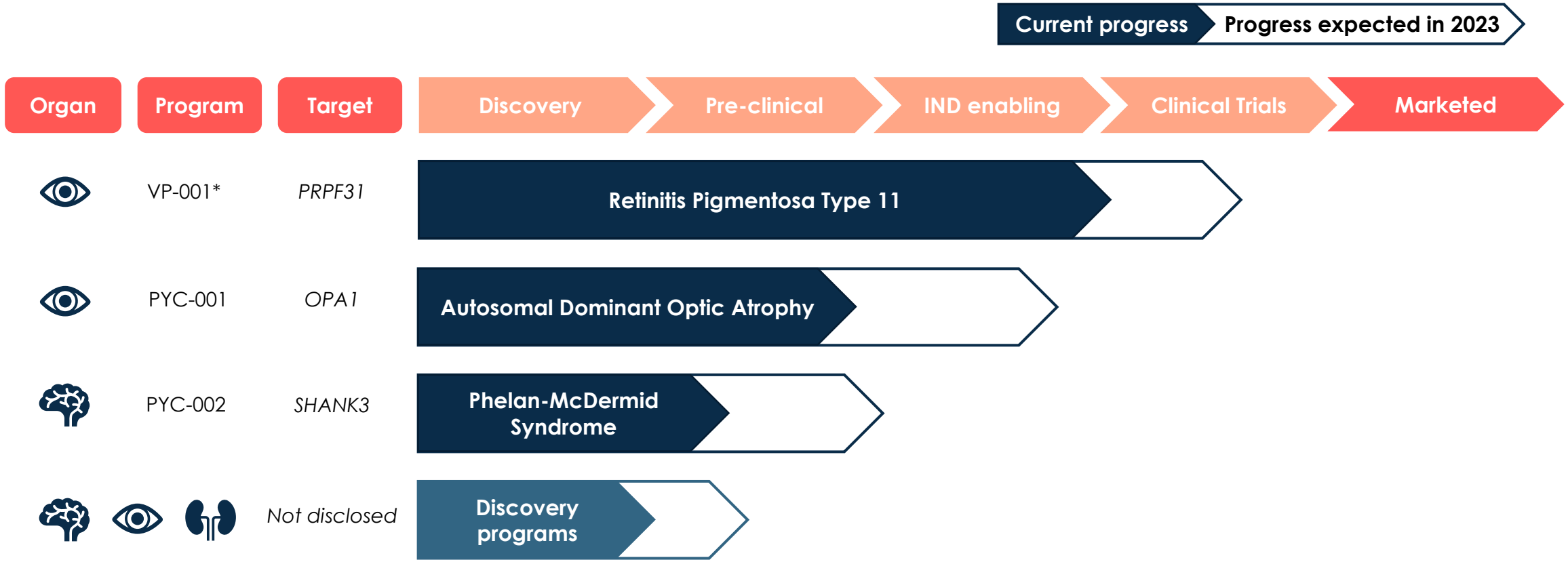
PYC combines existing RNA drug design technology with its proprietary drug delivery platform to create next generation RNA therapeutics



PYC's drug delivery platform is used to assist the RNA drug reach its target inside the cell



PYC has built a pipeline of RNA therapies on this platform technology



PYC's technology is a scalable platform with broad potential application across many different disease indications

PYC 95.2% ownership of VP-001 (4.8% ownership by Lions Eye Institute, Australia) and 100% ownership of all other pipeline programs

PYC is now focusing on scaling its platform into clinical read-outs across multiple indications

PYC Therapeutics

PYC IS HERE

1 From platform to program – making 'the drug'

2 Evolution to a clinical-stage multi-asset company

3 Scale into multiple clinical safety and efficacy read-outs

Objectives

- **Establish human safety** of PYC's platform technology
- **3+ first-in-class and potentially disease modifying drugs** into the clinic, **each with >$1bn p.a. markets**
- **Enter the transactional window** for genetic medicines (Phase 1/2)

2019 → 2020 2021 → 2022 2023 → 2024

PYC Therapeutics

Life-changing science

VP-001
Retinitis Pigmentosa Type 11 (RP11)

VP-001 for Retinitis Pigmentosa Type 11 (RP11)

1. RP11 is a progressive and **blinding eye disease**

2. There are **no treatments** available for patients with RP11

3. RP11 is caused by **insufficient expression of one gene** (*PRPF31*) in the retina

4. VP-001 restores PRPF31 expression back to levels seen in unaffected individuals in 'retina in a dish' models[1]

5. This increase in gene expression **visibly improves the appearance** of the cells affected in RP11 patient-derived models

6. Pre-clinical data support the potential of **VP-001 to drive disease modification in the clinic**

7. VP-001 is **expected to enter clinical studies** to evaluate its safety and efficacy in humans in 1H 2023[2]

8. Drugs targeting monogenic diseases are **2-5x more likely to succeed** in human studies[3]

PYC Therapeutics

1. Refer ASX announcement 7 October 2020
2. Subject to US FDA acceptance of PYC's planned IND in support of VP-001
3. Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank. doi: https://doi.org/10.1101/2020.11.02.20222232

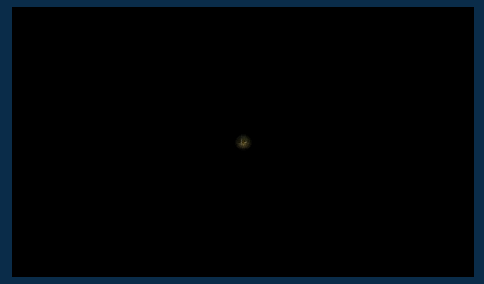
1. RP11 is a progressive and blinding eye disease

Degenerative sight of an RP11 patient

6 YEARS OLD

26 YEARS OLD

46 YEARS OLD



Retinitis Pigmentosa (RP)[1,2]

- A severe and progressive blinding eye disease that begins in childhood
- Affects 1 in every 3,500 people
- Patients experience night blindness followed by tunnel vision and ultimately loss of central vision and legal blindness
- There are no treatments available for patients with RP Type 11 nor are there any in clinical development

1. Daiger S et al. 'Genes and Mutations Causing Autosomal Dominant Retinitis Pigmentosa' Cold Spring Harb. Perspect. Med. 5 (2014)
2. Ellingford J et al. 'Molecular findings from 537 individuals with inherited retinal disease' J Med Genet 53, 761-776 (2016)

2. There are no treatments available for patients with RP11

PYC Therapeutics

5,000 – 10,000 patients

Estimated addressable RP11 patient population in the western world[1]

USD $150,000 p.a.

Median list price of orphan drugs (per patient[2])

Patients are waiting

RP11 patients on retinal disease registries are waiting for access to VP-001 – suggesting a rapid uptake in the event the drug is approved

FDA concessions

Potential to receive multiple FDA concessions:

- Orphan Drug Designation
- Rare Pediatric Disease Designation*
- Accelerated approval[3]

1. Sullivan, L et al. Genomic rearrangements of the PRPF31 gene account for 3% of autosomal dominant retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2006;47(10):4579-88
2. EvaluatePharma. Orphan Drug Report. 2019
3. FDA. Development and Approval Process | Drugs. 2022.

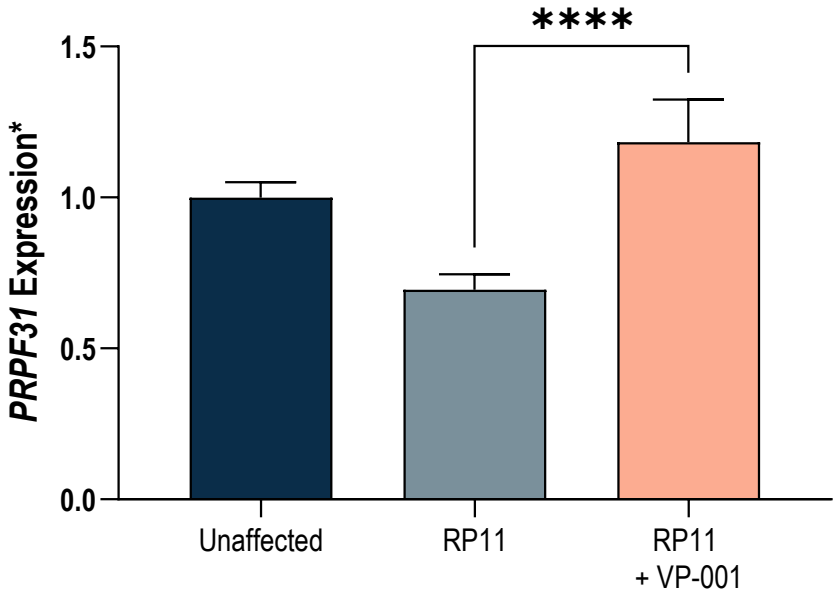
• Based on the median age of onset of RP11 of 17 years of age – see: Lisbjerg, K et al. Disease progression of retinitis pigmentosa caused by PRPF31 variants: A retrospective study with up to 36 years follow-up. Invest. Ophthalmol. Vis. Sci. 2022;63(7):4487 – F0274. Additional studies support the median age of onset in childhood.

3. RP11 is caused by insufficient expression of one gene (*PRPF31*) in the retina

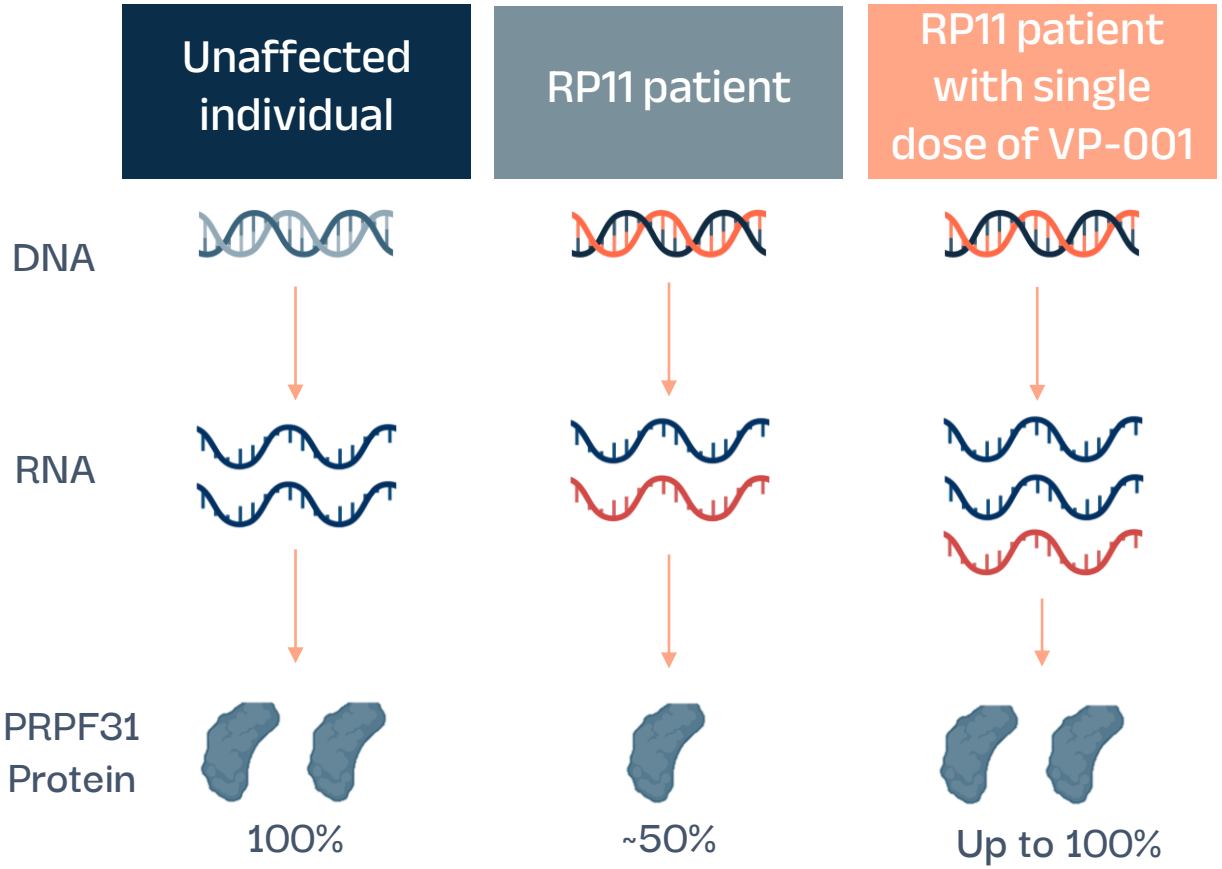
Unaffected individual	RP11 patient		
		**DNA**	RP11 patients have a **mutation in one copy** of the *PRPF31* gene
		**RNA**	The mutation leads to an **unstable RNA message** that is rapidly degraded
		**PRPF31 Protein**	This leads to cells in the retina having **half as much PRPF31 protein** as they require to function normally
100%	~50%		

4. VP-001 restores *PRPF31* expression back to levels seen in unaffected individuals in 'retina in a dish' models[1]

A single treatment of VP-001 restores *PRPF31* expression to wild-type levels in cellular models derived from patients with RP11



*PRPF31 mRNA expression in RP11 iPSC-RPE as measured by ddPCR (PRPF31_ex3-4 normalised to HPRT1 and SENP5). Student's t-test. **** = p<0.0001.*



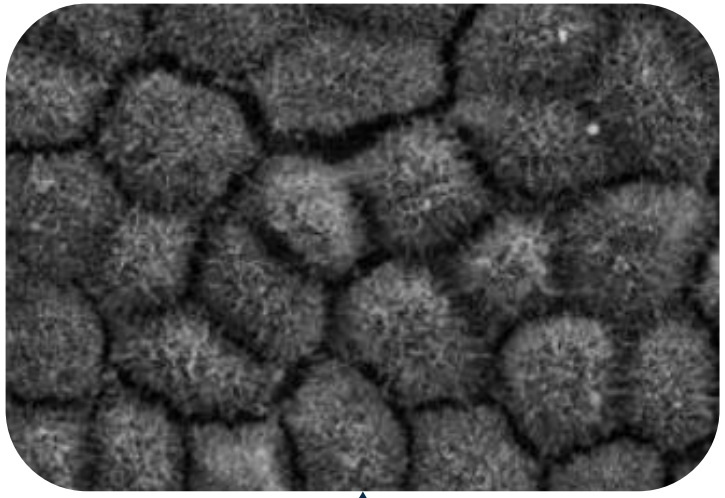
1. Refer ASX announcement 7 October 2020

5. This increase in gene expression visibly improves the appearance of the affected cells in RP11 'retina in a dish' models

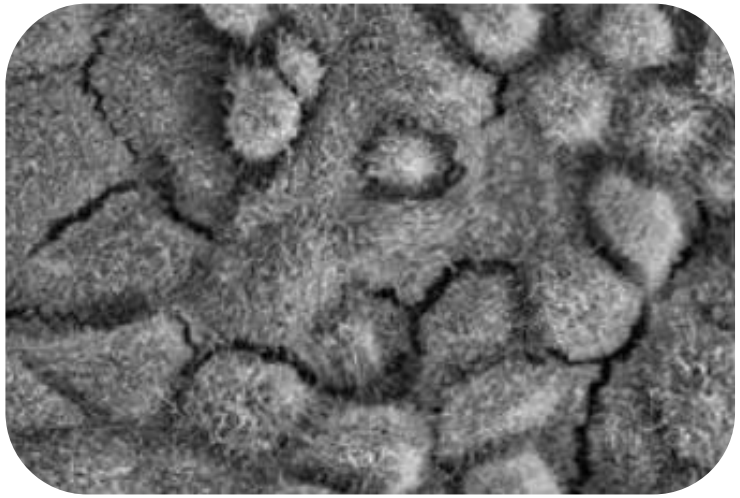
PYC Therapeutics

Retinal pigmented epithelium (RPE) cells derived from:

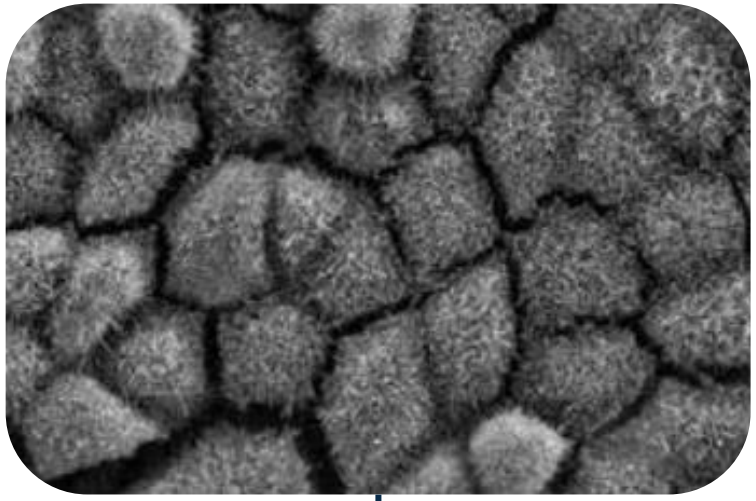
1. AN 'UNAFFECTED' INDIVIDUAL



2. A PATIENT WITH RP11



3. A PATIENT WITH RP11 AFTER A SINGLE DOSE OF VP-001



VP-001 restores RP11 patient-derived RPE cells back towards the appearance of cells from unaffected individuals[1]

1. Refer ASX announcement 16 December 2020

6. Pre-clinical data supports the potential of VP-001 to drive disease modification in the clinic

PYC Therapeutics

PK/Tox | **PD** | **Functional**

PK/Retinal Delivery → **Target engagement** → **Phenotypic rescue**

NHP
Durable drug presence in retina with NOAEL defined as highest dose assessed in GLP tox studies

Rabbit
Efficient distribution and delivery to target cell layer in retina with effective target engagement[1]

Mouse
Efficient distribution and delivery to target cell layer in retina with effective and durable target engagement[1]

RP11 Patient-Derived Cells
VP-001 demonstrates target engagement, ability to modulate *PRPF31* expression and morphological improvement in RP11 patient-derived models[2]

1. Target engagement in rabbit and mouse retina has been assessed with a reporter oligonucleotide that is effective in rabbits and mice respectively
2. See ASX announcements of 7 October, 16 December 2020

7. PYC is set to generate human safety and efficacy data for VP-001[1]

PYC Therapeutics

Phase 1/2 Human Trial → Pivotal Trial

Part 1

- Single Ascending Dose Study
- 3+3+3 dose escalation in RP11 patients
- Approx 1 year study

Outcome measures

- Safety and Tolerability

Part 2

- Multiple dose expansion study
- 3 groups of 10 patients each
- Two active groups plus control group
- Approx 2 year study

Outcome measures

- Safety and Tolerability
- Efficacy readout

Pivotal Trial

- Dependent on outcome of Phase 1/2 study

Natural History Study running concurrently

1. Pending confirmation of acceptance of PYC's Investigational New Drug application for VP-001 by the US Food and Drug Administration

8. Drugs targeting monogenic diseases are 2-5x more likely to succeed in human studies[1]

- RP11 has a single underlying genetic origin - it is **caused by mutations in the *PRPF31* gene**
- Disorders of this nature are known as 'monogenic' or 'Mendelian' disorders
- Drug targets associated with rare Mendelian disorders ***are at least five times as likely to be successful[1]*** when compared to the industry-wide benchmark

1. Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank. doi: https://doi.org/10.1101/2020.11.02.20222232

PYC Therapeutics

Life-changing science

PYC-001

Autosomal Dominant Optic Atrophy (ADOA)

PYC-001 for Autosomal Dominant Optic Atrophy (ADOA)

1. ADOA is a progressive and **blinding eye disease**

2. There are **no treatments** available for patients with ADOA

3. ADOA is caused by **insufficient expression of one gene** (*OPA1*) in the cells that form the optic nerve in the eye

4. PYC-001 increases *OPA1* expression in models derived from patients with ADOA[1]

5. PYC-001 is expected to **enter clinical trials next year** (2024)

PYC Therapeutics

1. Refer ASX Release 18 May 2021

1. ADOA is a progressive and blinding eye disease

ADOA patient sight deterioration

Autosomal Dominant Optic Atrophy (ADOA)

- A progressive and irreversible blinding eye disease
- 9,000 – 16,000 addressable patients in the western world[1,2]
- Median age of onset at 7 years of age, with 80% of patients symptomatic before age 10[1]
- There are no treatment options available for patients with ADOA

1.. Yu-Wai-Man, P. et al. Ophthalmology. 2010;117(8):1538-46 doi: 10.1016/j.ophtha.2009.12.038
2. Amati-Bonneau, P. et al. OPA1-associated disorders: phenotypes and pathophysiology. The international journal of biochemistry & cell biology, 2009;41(10), 1855–1865. doi: 10.1016/j.biocel.2009.04.012

2. There are no treatments available for patients with ADOA

PYC Therapeutics

9,000 – 16,000 patients

Estimated addressable ADOA patient population in the western world[1]

USD $150,000 p.a.

Median list price of orphan drugs (per patient[2])

Patients are waiting

ADOA patients on retinal disease registries are waiting for access to PYC-001 – suggesting a rapid uptake in the event the drug is approved

FDA concessions

Potential to receive multiple FDA concessions:

- Orphan Drug Designation
- Rare Pediatric Disease Designation*
- Accelerated approval[3]

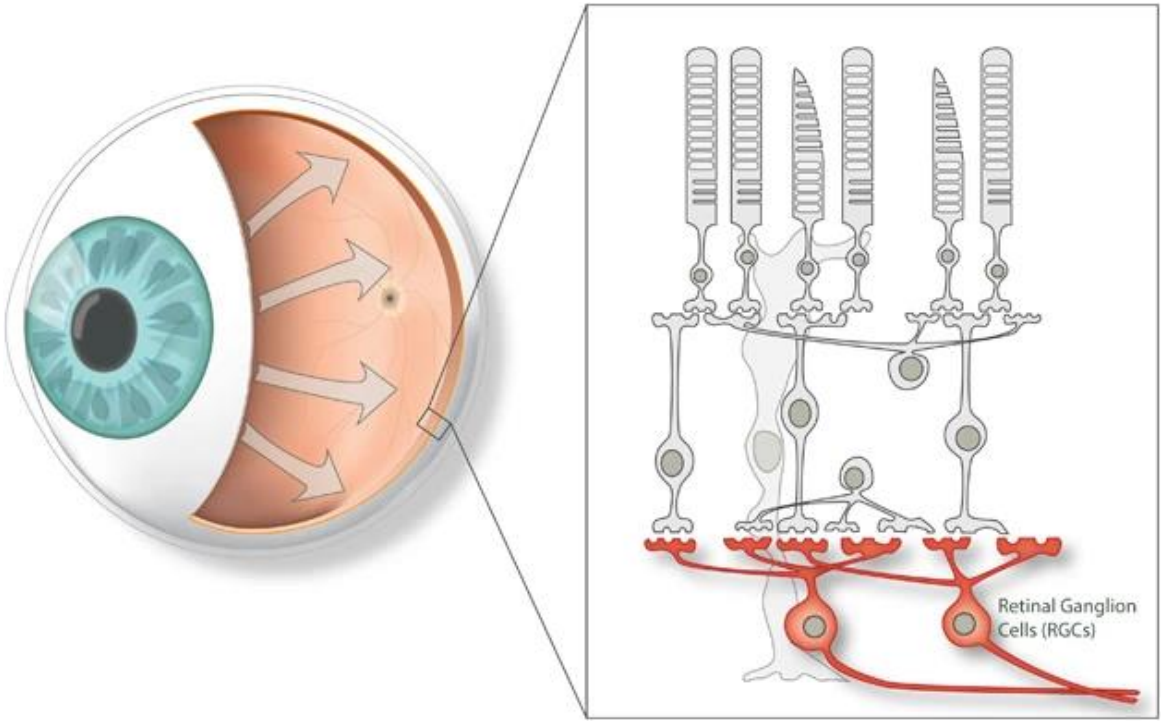
1.. Yu-Wai-Man, P. et al. Ophthalmology. 2010;117(8):1538-46 doi: 10.1016/j.ophtha.2009.12.038
2. EvaluatePharma. Orphan Drug Report. 2019.
3. FDA. Development and Approval Process | Drugs. 2022.
* Based on the median age of onset of RP11 of [x] years of age – see: [insert reference]

3. ADOA is caused by insufficient expression of one gene (*OPA1*) in the cells that form the optic nerve in the eye

PYC Therapeutics

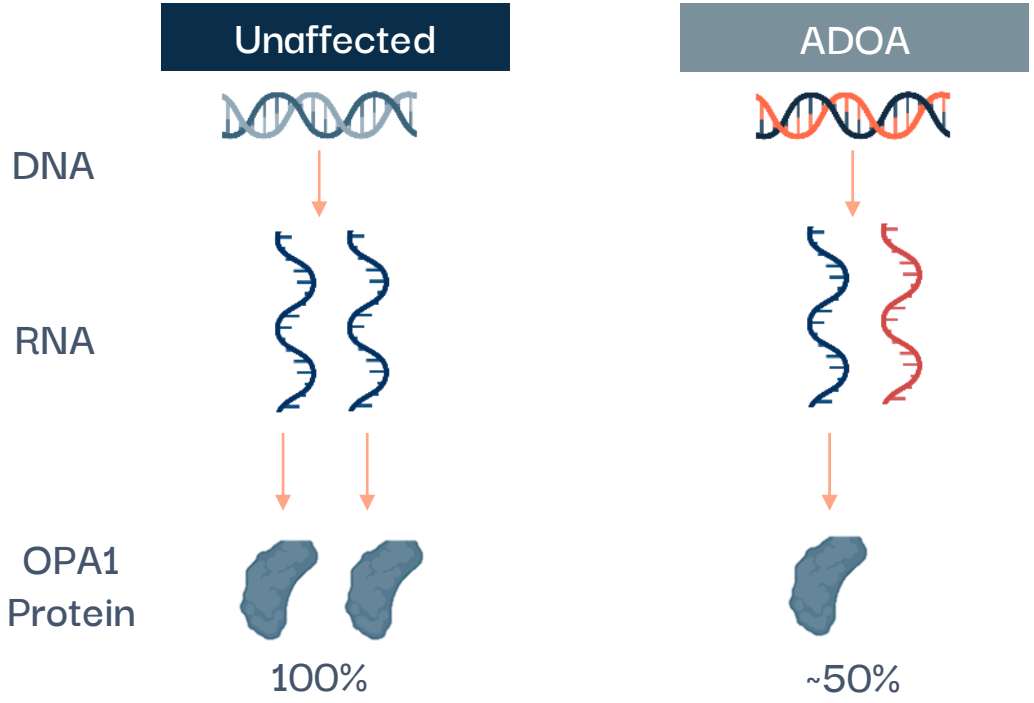
Affected cell type

In ADOA, these are the retinal ganglion cells (RGCs), that make up the optic nerve



Mechanism of disease causation

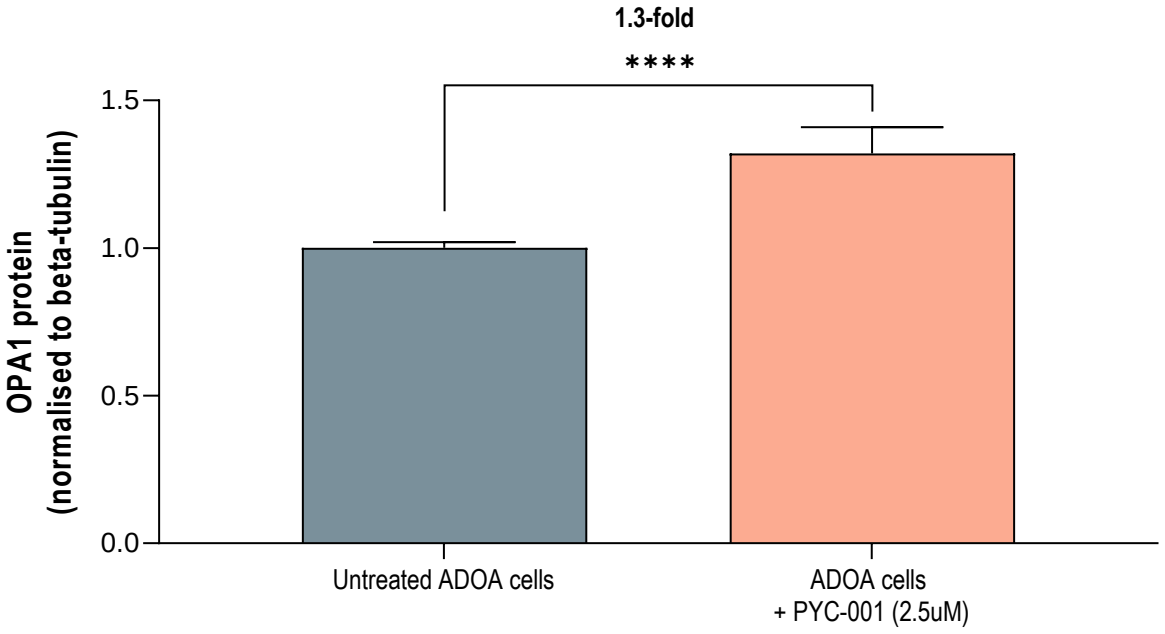
Patients with ADOA have a mutation in one copy of the *OPA1* gene causing an insufficient level of OPA1 protein in the RGCs



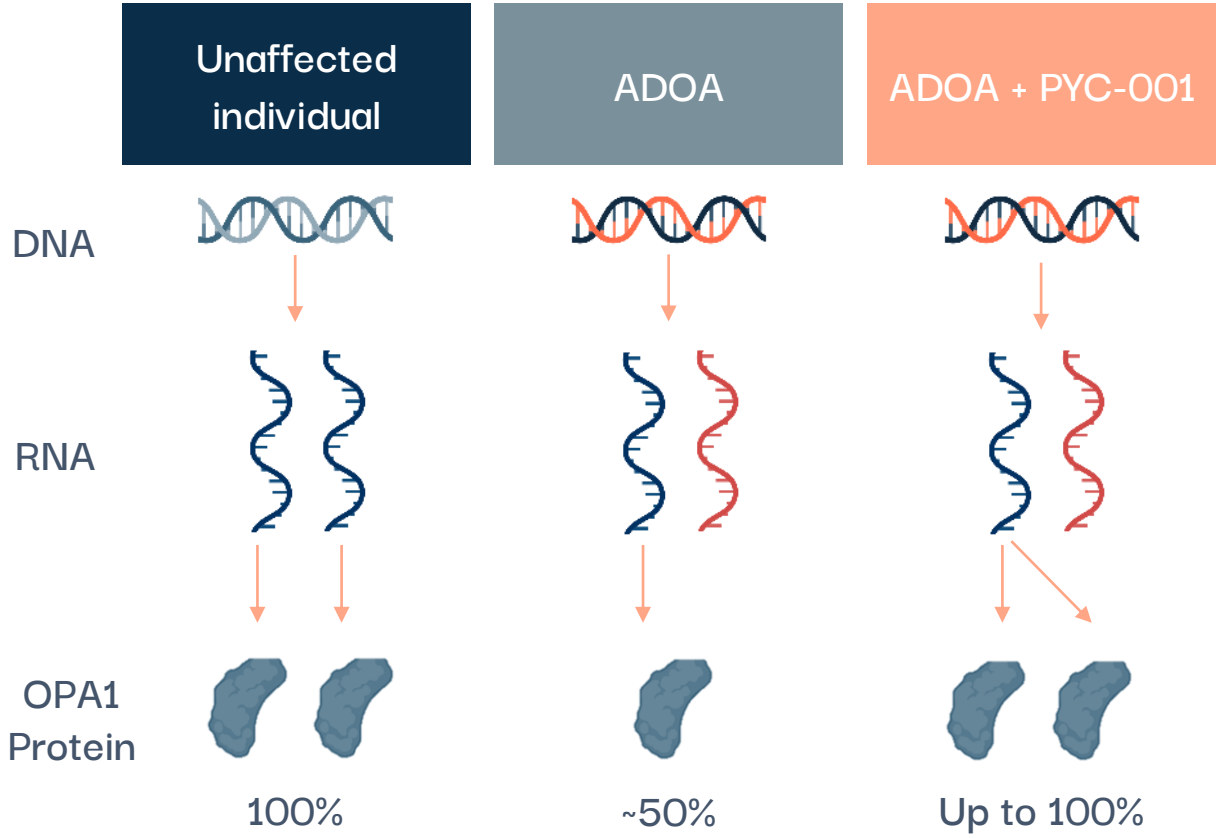
1. Wilson AM, Di Polo A. Gene therapy for retinal ganglion cell neuroprotection in glaucoma. Gene Ther. 2012;19(2):127-36.

4. PYC-001 increases *OPA1* expression in models derived from patients with ADOA[1]

Low dose PYC-001 treatment increases OPA1 protein expression in cells* derived from ADOA patients



*Normalised fold-change in expression of OPA1 protein assessed by western blotting. Bar graph represents mean ± SEM @ day 7 PPMO incubation, Patient; OPA1 c. 287delA n=3 biological replicate, 3 technical replicates. Student's t-test. **** = p<0.0001.*



*ADOA patient-derived fibroblasts used as tool cell line.
1. Refer ASX Release 18 May 2021

5. PYC-001 is expected to enter clinical trials next year^

	2023	2024
Anticipated development timeline and milestones	• Lead candidate selected • IND-enabling studies initiated • Initiation of natural history study in ADOA	• IND-enabling studies completed • IND submission • Initiation of a combined phase 1/2 clinical trial • First patient cohort dosed with PYC-001

^ Subject to successful completion of IND enabling studies and successful application with FDA

PYC Therapeutics

Life-changing science

PYC-002
Phelan-McDermid Syndrome

PYC-002 for Phelan-McDermid Syndrome (PMS)

1. Phelan-McDermid Syndrome (PMS) is a **severe neurodevelopmental disorder** caused by insufficient expression of the *SHANK3* gene in neurons in the brain

2. Patients with PMS have **no treatment options available** that address the underlying cause of the disorder

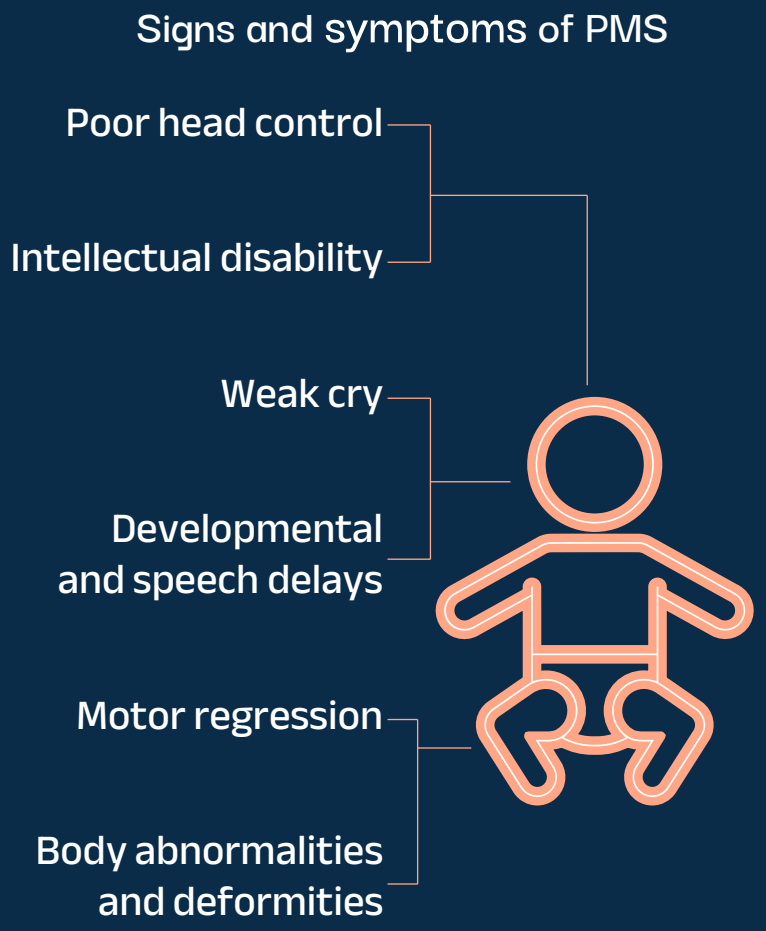
3. PYC has designed an **RNA therapy capable of restoring the *SHANK3* protein insufficiency** to wild type levels in cells

4. PYC's proprietary **drug delivery technology is capable of reaching the cells affected** in PMS (neurons) *in vivo* in animal models[1]

PYC Therapeutics

1. Refer ASX Release April 12, 2021

1. Phelan-McDermid Syndrome (PMS) is a severe neurodevelopmental disorder



Phelan-McDermid Syndrome (PMS)[1,2]

- Rare genetic neurodevelopmental disorder causing life-long disability
- ~28,000 addressable patients in the western world[1,2]
- Caused by a mutation in or loss of one copy of the *SHANK3* gene
- There are no therapies available that can increase the expression of *SHANK3* in the cell type affected in PMS (disease-modifying therapies).

1. Cochoy, D.M., Kolevzon, A., Kajiwara, Y. et al. Phenotypic and functional analysis of SHANK3 stop mutations identified in individuals with ASD and/or ID. Mol. Autism. 2015;6(23) doi: 10.1186/s13229-015-0020-5
2. Zeidan, J., Fombonne, E., Scorah, J., Ibrahim, A., Durkin, M. S., Saxena, S., Yusuf, A., Shih, A., & Elsabbagh, M. Global prevalence of autism: A systematic review update. Autism Research. 2022;1–13. doi: 10.1002/aur.2696

2. Patients with PMS have no treatment options available that address the underlying cause of the disorder

PYC Therapeutics

~28,000 patients

Estimated addressable PMS patient population in the western world[1,2]

USD $150,000 p.a.

Median list price of orphan drugs (per patient[3])

Disease-modifying potential

PYC's approach in PMS represents the first potentially disease-modifying treatment for patients with this disorder[4]

FDA concessions

Potential to receive multiple FDA concessions:

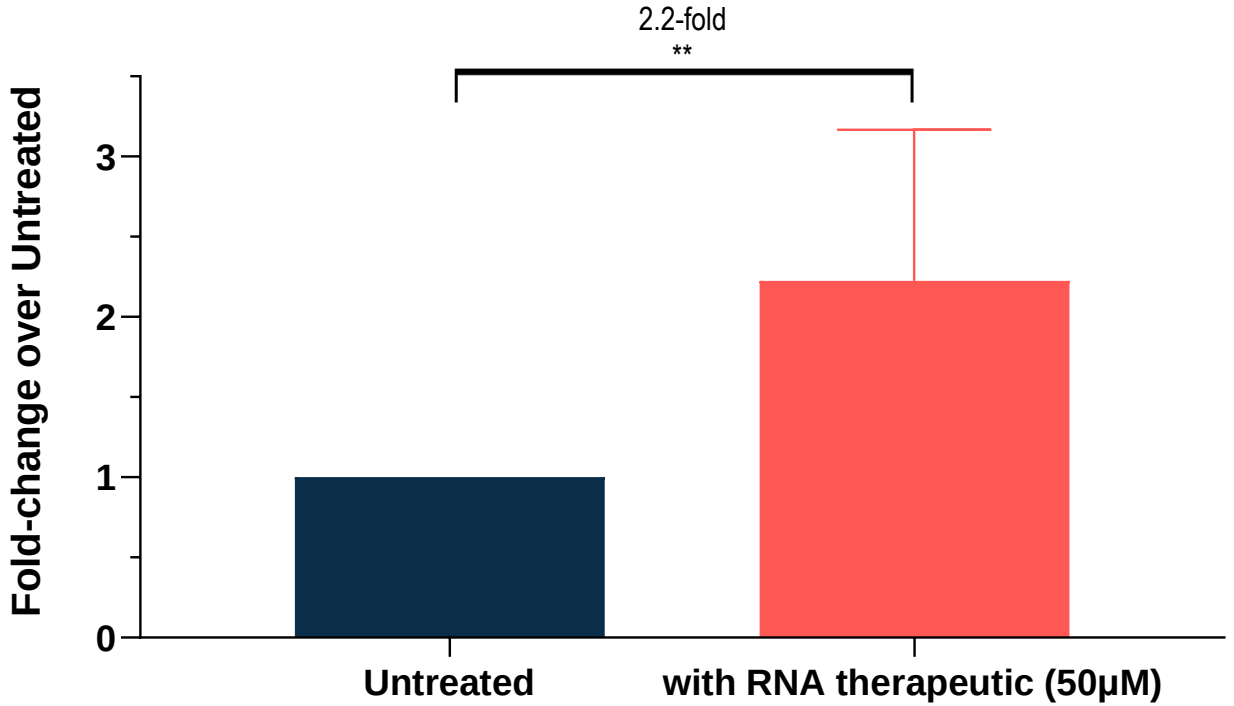
- Orphan Drug Designation
- Rare Pediatric Disease Designation
- Accelerated approval[5]

1. Cochoy, D.M., Kolevzon, A., Kajiwara, Y. et al. Phenotypic and functional analysis of SHANK3 stop mutations identified in individuals with ASD and/or ID. Mol. Autism. 2015;6(23) doi: 10.1186/s13229-015-0020-5
2. Zeidan, J., Fombonne, E., Scorah, J., Ibrahim, A., Durkin, M. S., Saxena, S., Yusuf, A., Shih, A., & Elsabbagh, M. Global prevalence of autism: A systematic review update. Autism Research. 2022;1–13. doi: 10.1002/aur.2696
3. EvaluatePharma. Orphan Drug Report. 2019.
4. Based on publicly available information
5. FDA. Development and Approval Process | Drugs. 2022.

3. PYC-002 addresses the root cause of PMS and has the potential to be a first-in-class disease-modifying therapy

PYC-002 hit sequences increase SHANK3 protein levels by **>2-fold** in a **neuronal cell line***[1]

Further studies are underway to confirm this effect in cellular models derived from patients with PMS as well as testing in animal models of the disease



*Normalised fold-change in expression of SHANK3 protein assessed by western blotting. SHANK3 protein expression is shown relative to the level in transfection control cells (a transfection control without an RNA therapeutic). Data are presented as mean +/- Standard Deviation (n = 3). ** = statistical significance of p≤0.01 calculated as two-way unpaired t-test between treatment and transfection control.*

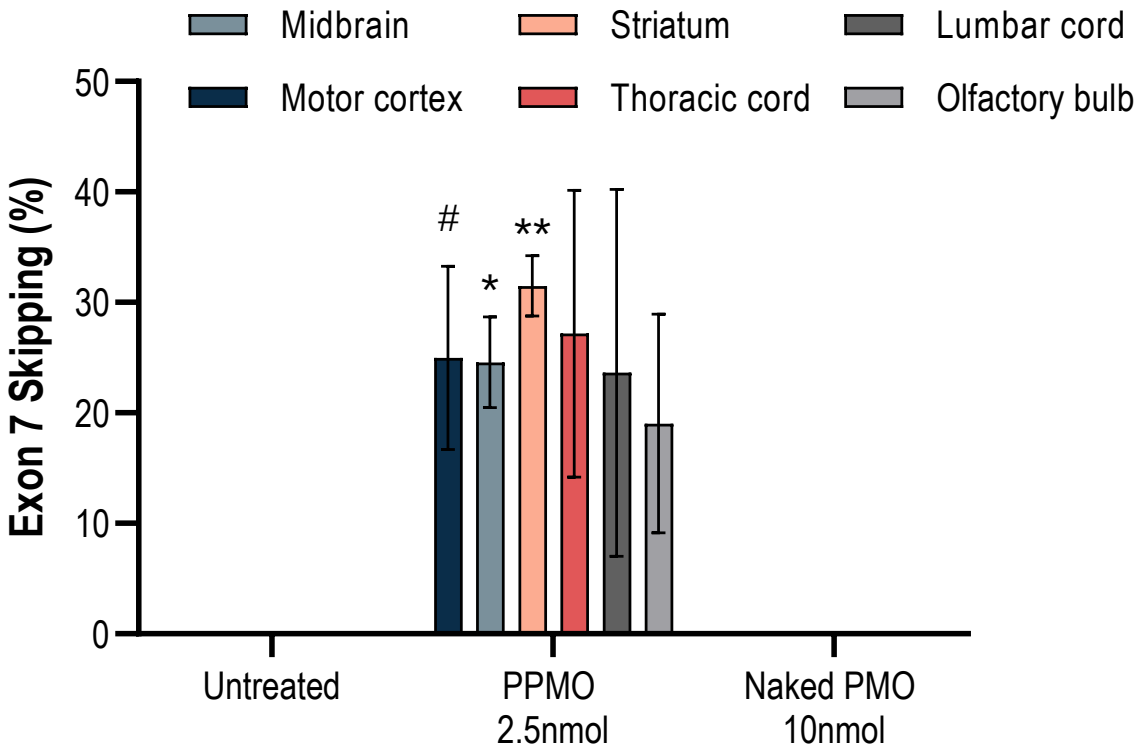
* SH-SY5Y cells used as a tool cell line
1. Refer ASX Release September 27, 2022

4. PYC's RNA drug modality effectively reaches the cells affected in PMS (neurons) *in vivo* (in animal models)

The advantages of PYC's next generation RNA drug ('PPMO') are clearly evident in animal models evaluating the ability of the RNA drug to engage its target in different regions of the brain relevant in PMS[1]

PPMO
- PYC's RNA modality
- Target engagement in all regions of the brain

'Naked' PMO
-Same RNA drug without PYC's delivery technology
- No target engagement observed in any brain region



*Smn exon-7 skipping in mouse brains 5 days post I.C.V. injection (a local injection into the right ventricle of mouse brain). N for each group: PPMO (2.5 nmol)=2; PMO=2. Statistical significance calculated as two-way unpaired ttest; #: p≤0.1, *: p≤0.05, **: p≤0.01*

1. Refer ASX Release April 12, 2021

PYC Therapeutics

Life-changing science

Corporate Overview

Executive & Board

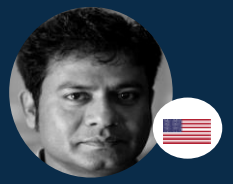
PYC's management has discovered and delivered drugs to market

Alan Tribe
Chairman

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

Dr Rohan Hockings
Chief Executive Officer

Dual-trained in medicine and law with experience across both disciplines in addition to roles in strategy consulting and private equity



Sri Mudumba
Chief Research Officer

Over 20 years of experience developing drug delivery products utilizing various therapeutic modalities and delivery vehicles from early research through to NDA

Andrew Taylor
Chief Financial Officer

Held senior finance positions in ASX listed organisations. Completed multiple equity raisings, debt refinances and M&A transactions.

Prof 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 and VP-001

Dr Michael Rosenblatt
Director

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

Jason Haddock
Director

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

Prof Ian Constable
Advisory board

Renowned Ophthalmologist for over 50 years. Founding Managing Director and now the Patron of the Lions Eye Institute Western Australia. Pioneered first in man gene therapy for macular degeneration

A/Prof Fred Chen
Advisory board

Ophthalmologist at Lions Eye Institute (LEI) , Royal Perth Hospital and Perth Children's Hospital Western Australia. Performed over 800 vitrectomy surgeries. Lead Research Scientist LEI's Ocular Tissue Engineering Laboratory

PYC Therapeutics

“ These [COVID] vaccines... are only the tip of the iceberg in the coming RNA medical technology revolution”[1]

Life-changing science

1 https://newsroom.unsw.edu.au/news/science-tech/rna-technologies-explained-long-and-short-it