PYC Therapeutics

Life-changing science

Q3 investor webinar

August 2025

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Q3 investor webinar agenda

- An introduction to PYC
- Near-term milestones
- Focus on Polycystic Kidney Disease and Phelan-McDermid Syndrome
  - Why is a disease-modifying approach so important in these two indications?
    - Potential for reversal compared to arrest of disease progression
    - How this translates to potential patient impact
    - Link to near-term milestones – what are we looking for?
- Q&A

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Introduction to PYC

An introduction to PYC Therapeutics

- PYC is a drug discovery and development company focused on creating life-changing new therapies for patients who have genetic diseases and no treatment options available today
- PYC's strategy is to use RNA therapeutics to increase gene expression in haploinsufficient diseases in tissues in which the delivery challenge has been overcome
- The Company has 3 clinical-stage assets that address the underlying cause of severe unmet medical needs
- The Company will present human safety and/or efficacy data across 4 indications over the coming 24 months[1]

1. Subject to the risks and uncertainties outlined in the Company's ASX filings of 17 February 2025

Highlights of PYC's pipeline – 3 clinical-stage assets

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1 **Disease-modifying drug candidates**

Each of PYC's pipeline programs address the root cause of the target disease

2 **In areas of major unmet need**

In a disease with no established standard of care and worth between $1 and $10 billion p.a.[1]

3 **With the highest probability of success**

5x

With a 5x higher probability of success than the industry average[2]

4 **Validated in patient-derived models**

A 'quantitative cure' for the single-gene disease targeted

5 **Generating human efficacy data in 2025**

Generating critical data this year - high-value human data readouts in major unmet patient needs[3]

1. Utilising the prevalence for each indication outlined and referenced on page 7 of this presentation and the median orphan drug price from Evaluate Pharma Orphan Drug Report 2019 ($150k p.a.)
2. King EA, Davis JW, Degner JF. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. PLoS Genet. 2019 Dec 12;15(12):e1008489. doi: 10.1371/journal.pgen.1008489. Pre-print version of article
3. Subject to the risks and uncertainties outlined in the Company's ASX disclosures of 17 February 2025

PYC has built a pipeline of drug candidates with the potential to become the standard of care in areas of major unmet need

1. Based on management's latest estimates accurate as at 1 August 2025 and subject to successful realisation of developmental milestones in each program as well as satisfaction of regulatory requirements and subject to all other risks customary to an early-clinical stage biotechnology company developing novel drug candidates
2. See references in Company presentation of 14 March 2024 for source material on prevalence by indication
3. PYC 97% ownership of VP-001 (3% ownership by Lions Eye Institute, Australia) and 100% ownership of all other pipeline programs

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Upcoming milestones

All 3 of PYC's clinical-stage programs will deliver human efficacy data over the coming 12 months[1]

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Program	2025 Q3	2025 Q4	2026 Q1	2026 Q2
Polycystic Kidney Disease	Phase 1a/1b study data to be presented at ANZSN conference[2]		Open-Label Multiple Ascending Dose data →	
Phelan-McDermid Syndrome	Pre-clinical data pack released[3]			
Retinitis Pigmentosa type 11		Updated Phase 1/2 study data and type D meeting with FDA		
Autosomal Dominant Optic Atrophy	SAD study data to be presented at NOSA and RANZCO conferences[4]			Open-Label Multiple Ascending Dose data →

1. Subject to the risks and uncertainties outlined in the Company's ASX disclosures of 17 February 2025
2. Australian and New Zealand Society of Nephrology 30 Aug – 3 Sep
3. Full pre-clinical data pack including Non-Human Primate data from Non-Good Laboratory Practice studies including benchmarking data to a clinically-validated reference molecule known as zorevunersen
4. Single Ascending Dose (SAD) study data to be presented at Neuro Ophthalmology Society of Australia conference 11-12 September and Royal Australian and New Zealand Society of Ophthalmology conference 14-17 November

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Polycystic Kidney Disease deep dive

Why is a disease-modifying approach in PKD so attractive?

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- The potential for substantial patient-impact driven by a combination of:
  - High prevalence;
  - High morbidity;
  - The absence of treatment options available for ~95% of patients[1]; and
  - Animal models of PKD suggesting that restoring the missing gene expression responsible for causing the disease can lead to regenerative changes in the kidney[2]

1. Otsuka's JYNARQUE® (tolvaptan) was approved in 2018 for the treatment of ADPKD with a black box warning – "for risk of serious liver injury". Approximately 95% of ADPKD patients cannot take or tolerate JYNARQUE® (tolvaptan) and hence have no treatment options available today. (See: Gansevoort RT, et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. Nephrology Dialysis Transplantation. 2016;31(3):337-48)
2. Dong, K., Zhang, C., Tian, X. et al. Renal plasticity revealed through reversal of polycystic kidney disease in mice. Nat Genet 53, 1649–1663 (2021). https://doi.org/10.1038/s41588-021-00946-4

The total addressable market for PKD exceeds US$15bn p.a.[1]

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- Tolvaptan is used by <7% of the addressable patient population[2]
  - Despite limited patient uptake, 2023 sales of Tolvaptan exceeded US$1.5bn[2]

Estimated number of patients with ADPKD due to *PKD1* mutation[3]

1. Market size is projected by multiplying patient prevalence (See: Willey C, et al. Analysis of Nationwide Data to Determine the Incidence and Diagnosed Prevalence of Autosomal Dominant Polycystic Kidney Disease in the USA: 2013-2015. Kidney Dis (Basel). 2019;5(2):107-17) in commercially accessible geographies by the median orphan drug pricing of $150k p.a. (Evaluate Pharma. Orphan Drug Report. 2019).
2. Otsuka Holdings Co., Ltd. Integrated Report 2024. Tokyo (Japan): Otsuka Holdings Co., Ltd.
3. Approximately 80-85% of ADPKD is associated with *PKD1* mutations (See: Cordido et al. The Genetic and Cellular Basis of Autosomal Dominant Polycystic Kidney Disease-A Primer for Clinicians. Front Pediatr. 2017;5:279.)

PYC-003 is the first drug candidate that directly targets the underlying cause of PKD to enter human trials

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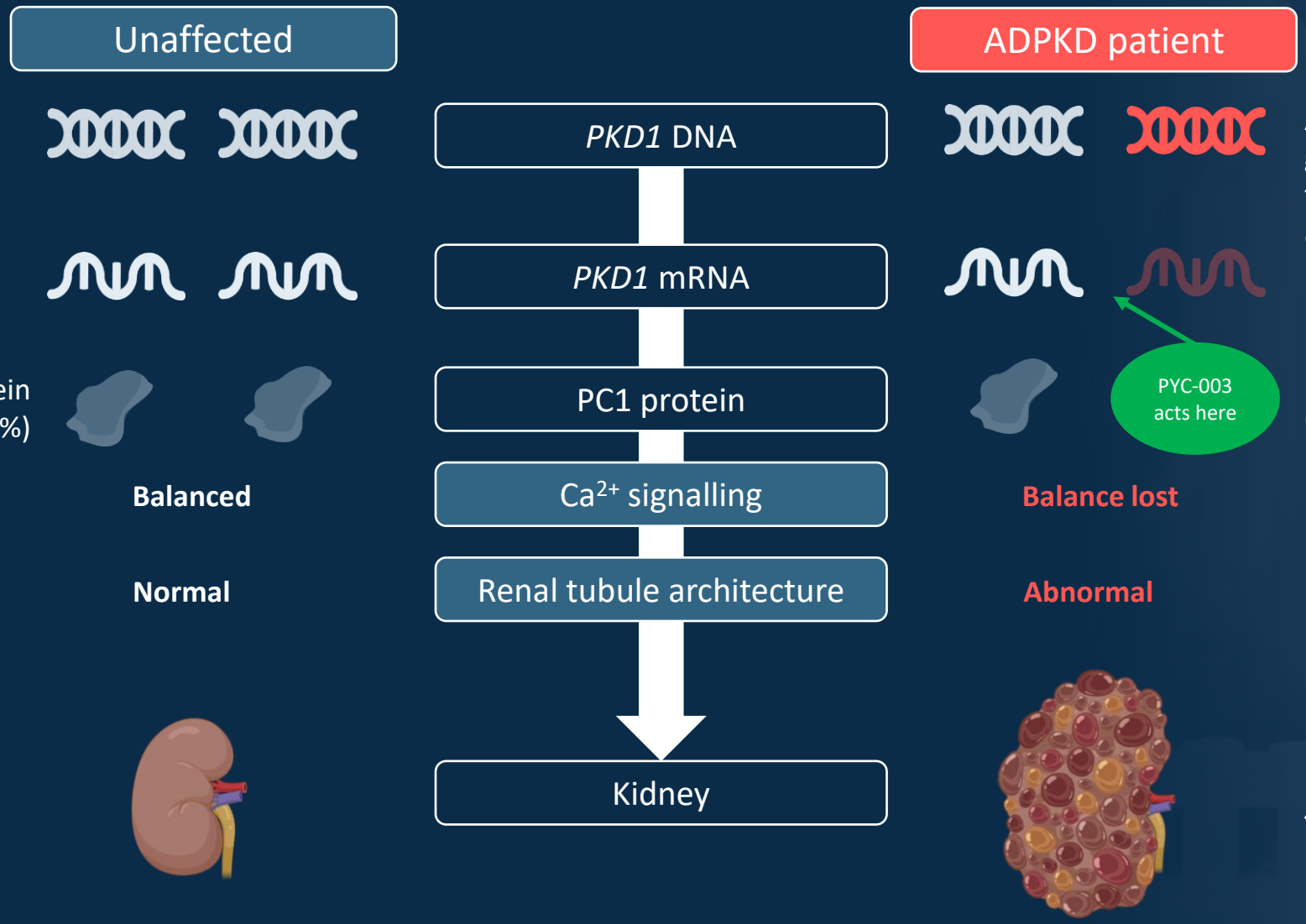


A mutation in one copy of the *PKD1* gene leads to limited or non-functional mRNA form the affected allele[1]

Haploinsufficient PC1 protein (~50% of wild-type levels)[2]

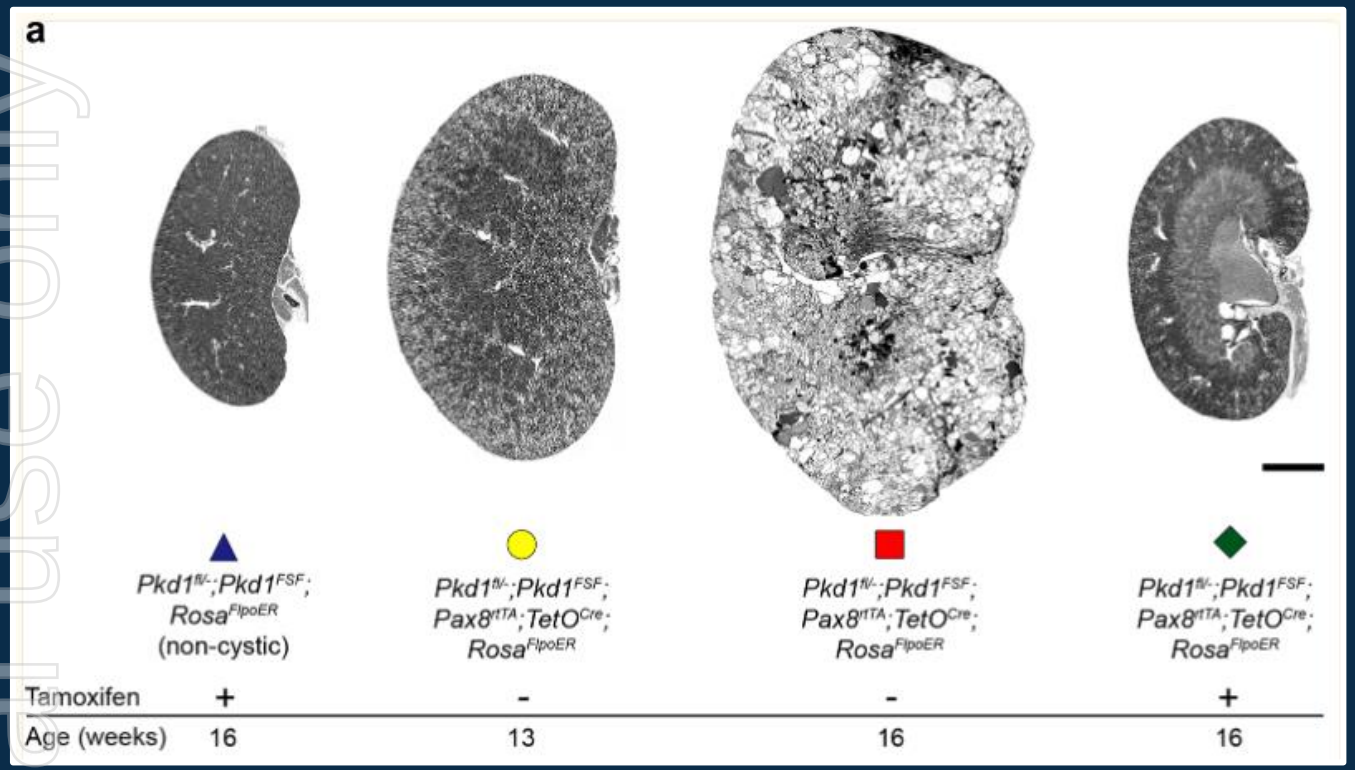
PC1 protein is the rate-limiting modulator of cystic disease[2]

It has a critical role regulating cystic proliferation and maintaining the normal structure of renal tubules[2]

PKD is characterized by cyst formation and enlargement in kidney due to deficient PC1 protein[2]

1. Cordido et al. The Genetic and Cellular Basis of Autosomal Dominant Polycystic Kidney Disease-A Primer for Clinicians. Front Pediatr. 2017;5:279.
2. Lee SH, Somlo S. Cyst growth, polycystins, and primary cilia in autosomal dominant polycystic kidney disease. Kidney Res Clin Pract. 2014;33(2):73-8.
Images created with BioRender

Re-expressing PC1 protein in animal models completely rescues the PKD phenotype[1]



Non-cystic reference → Baseline (time of treatment) → Untreated → PC1 re-expressed

"Even if one could have hypothesized that re-expressing PKD genes would slow disease progression, **the rapidity and completeness of the reversal are astonishing** and are likely indicative of a unique and previously **unappreciated regenerative potential of the kidney**"[2]

1. Dong, K., Zhang, C., Tian, X. et al. Renal plasticity revealed through reversal of polycystic kidney disease in mice. Nat Genet 53, 1649–1663 (2021). https://doi.org/10.1038/s41588-021-00946-4
2. Boletta, A. Reversing polycystic kidney disease. Nat Genet 53, 1623–1624 (2021). https://doi.org/10.1038/s41588-021-00963-3

"It remains possible that multiple pathways that are directly regulated by the polycystins concur in the prevention of cyst formation and may need to be concomitantly targeted. Thus, re-expressing the polycystins might ultimately remain the best — or possibly the only — way to revert the disorder"[1]

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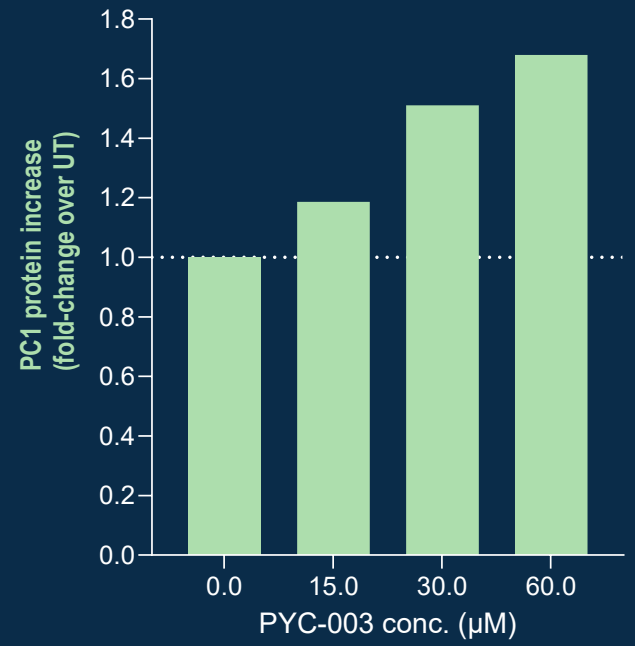
1. Boletta, A. Reversing polycystic kidney disease. Nat Genet 53, 1623–1624 (2021). https://doi.org/10.1038/s41588-021-00963-3

PYC-003 restores PC1 protein expression towards levels seen in unaffected individuals

PYC-003 increases PC1 expression back towards Wild-Type levels in patient-derived models

1.7-fold increase in PC1 protein in PKD patient-derived iPSCs[1]



1. Data collected from iPSC cells derived from the blood of an ADPKD patient and treated with increasing concentrations of PYC-003. Protein was extracted, and PC1 protein levels were measured by Western blot on Day 5 for ADPKD iPSC cells.

This control of target gene expression is complemented by a unique delivery profile *in vivo*

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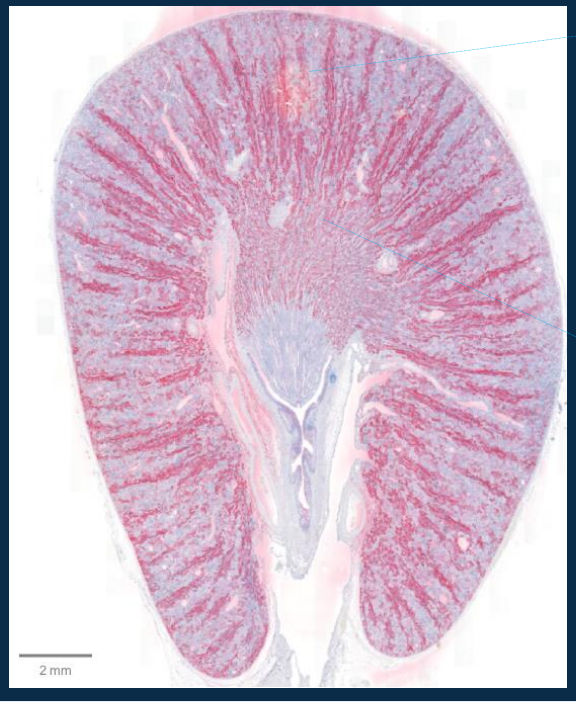
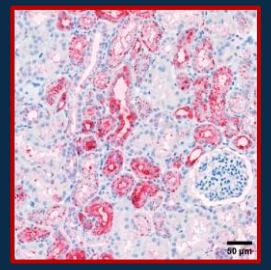
PYC-003 has a broad, even and deep distribution within the kidney at safe and well-tolerated doses in NHPs

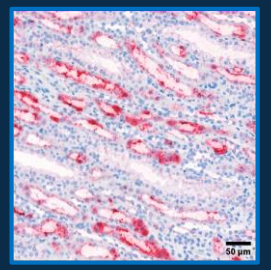
Distribution in NHP kidney[1]
PYC-003 treated



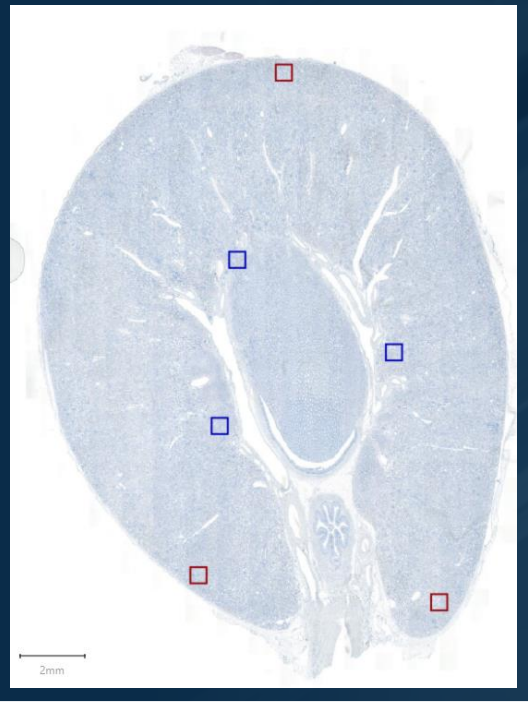
✓ **Cortex**



✓ **Medulla**



Distribution in NHP kidney
PBS Control



1. miRNAscope image of PYC-003 distribution to wild-type NHP kidney at a concentration of 59 µM – the peak tissue concentration following a single 3 mg/kg intravenous dose of the drug candidate

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Phelan-McDermid Syndrome (PMS) deep dive

PMS is caused by haploinsufficiency of the SHANK3 protein[1,2]

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Unaffected neurons

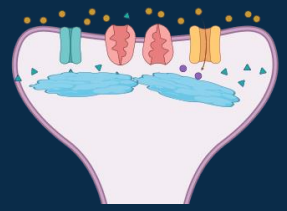
PMS neurons

Unaffected SHANK3 protein levels

SHANK3 protein

SHANK3 haploinsufficiency (50-65% of unaffected)

Proper synaptic protein interaction

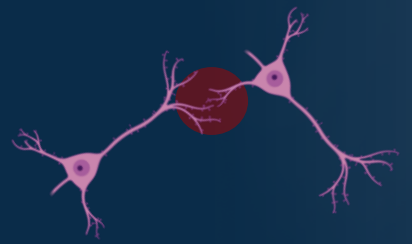


Synapse protein interactome

Impaired synaptic protein interaction

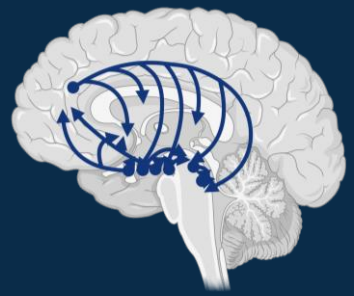
Correct synaptic function

Neuronal structure

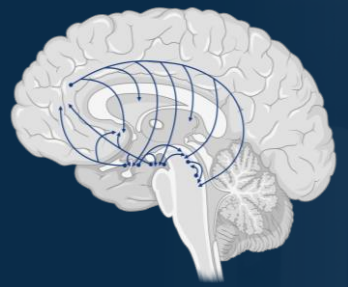


Abnormalities in synaptic structure and function

Functional neuronal communication, synaptic signalling, and plasticity



Synaptic activity



Impaired neuronal communication, synaptic signalling, and plasticity

Phelan-McDermid Syndrome

1. https://pmsf.org/about-pms/
2. Cochoy DM, 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

PMS also demonstrates potential reversibility in animal models

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"Genetic restoration of Shank3 in rodents has been shown to reverse core deficits even in adult animals"[1]

1. Delling, J.P., Boeckers, T.M. Comparison of SHANK3 deficiency in animal models: phenotypes, treatment strategies, and translational implications. J Neurodevelop Disord 13, 55 (2021). https://doi.org/10.1186/s11689-021-09397-8

Video interview – potential for reversibility in humans

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Clinical Trials in Phelan-McDermid syndrome - What we have learned https://www.youtube.com/watch?v=UdHmA-iqcXM&t=3480s

Video – patient journey and the phenomenon of regression

CureSHANK - Darus: A Regression Story (Phelan-McDermid syndrome) https://www.youtube.com/watch?v=Xdb11g2ZnG4

Video – neuronal communication (with and without PYC-002)

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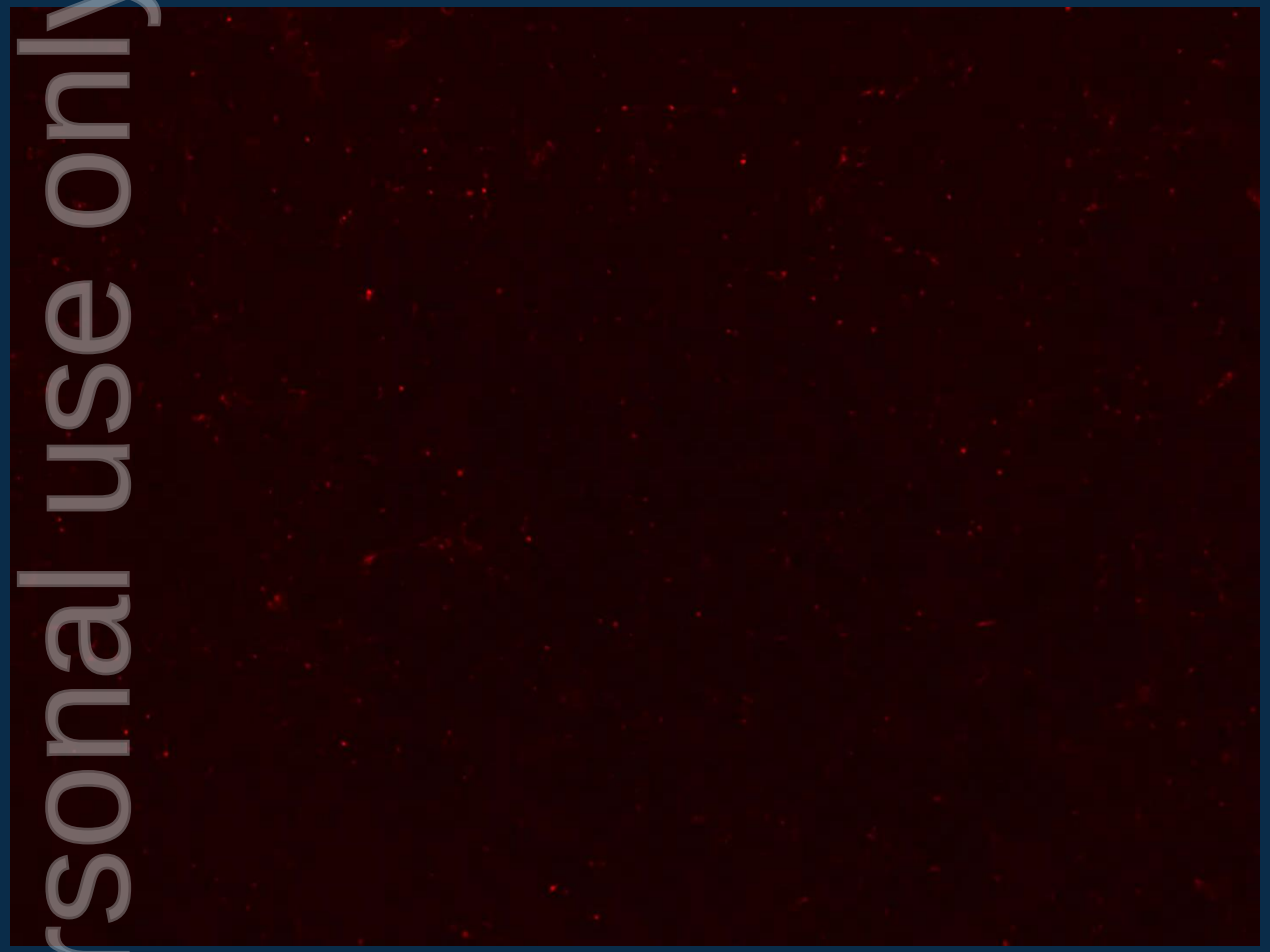
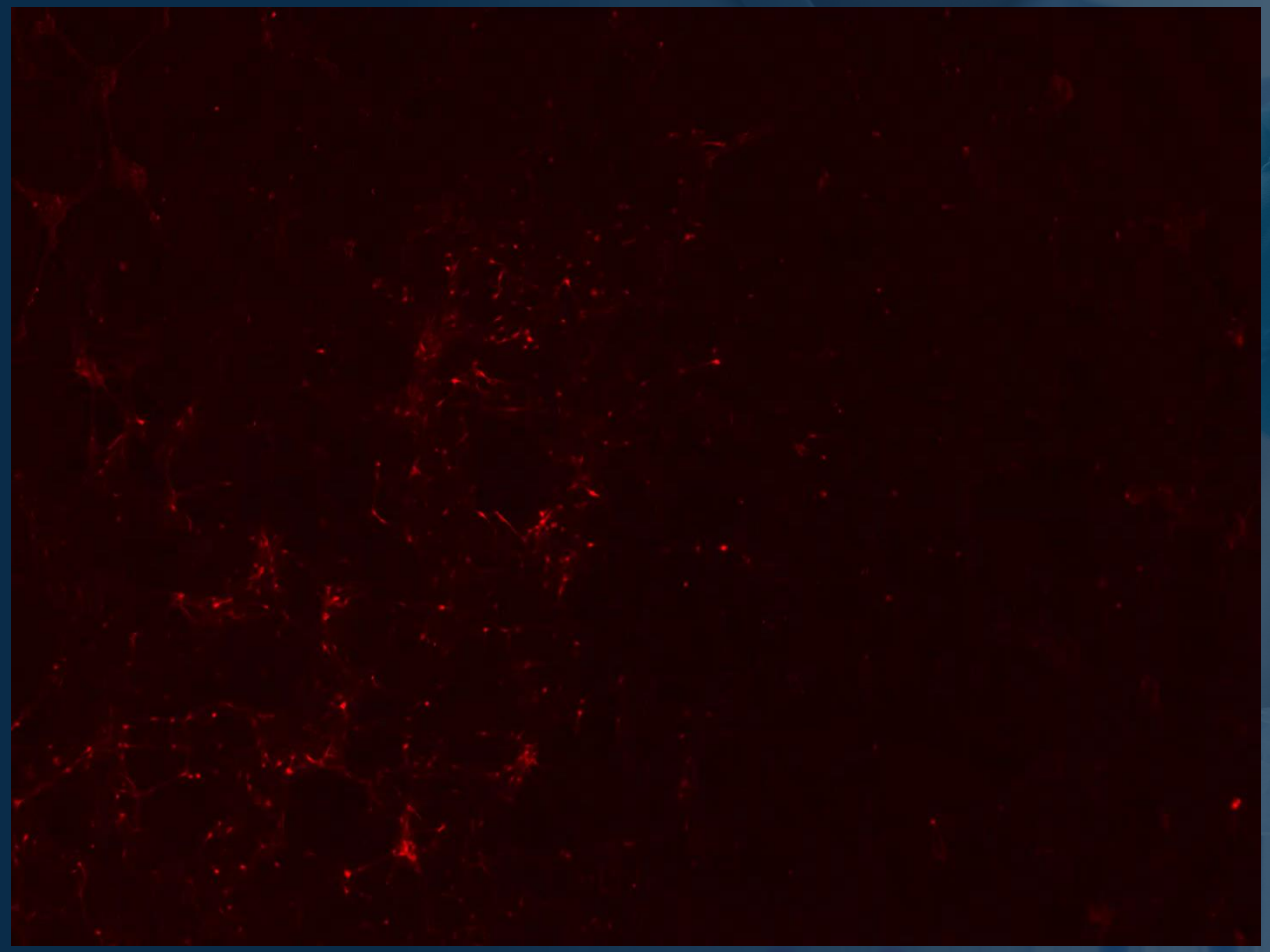
Untreated PMS-derived neurons



PYC-002 treated PMS-derived neurons (day 29)



Synthesis – 12-month forward view

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Q&A