PYC Therapeutics

27 September 2022

NEW CENTRAL NERVOUS SYSTEM (CNS) DRUG PROGRAM ADDED TO PYC'S PIPELINE

Highlights

PYC has added a third drug program in a new target tissue to its pipeline

The progress follows *in vitro* results demonstrating an ability to **correct the faulty gene expression** responsible for causing Phelan-McDermid Syndrome

Phelan McDermid Syndrome (PMS) is one of the **most common monogenic forms** of severe neurodevelopmental disorder characterised by autism spectrum disorder, speech and developmental delays and epilepsy

PYC is now working with the Phelan McDermid Syndrome Foundation, clinicians and researchers to advance the **first disease-modifying approach** for the treatment of PMS into clinical development

The new program in the CNS demonstrates the **scalability of PYC's platform** technology across multiple target tissues

Technical Highlights

- Phelan McDermid Syndrome (PMS) affects ~1 in every 8,000 to 15,000 children[1] and the underlying cause of PMS is insufficient expression of the *SHANK3* gene affecting neurons in the brain
- PYC has developed a precision RNA therapeutic that is designed to address the underlying cause of PMS (by increasing *SHANK3* expression) *in vitro* in a manner that is consistent with disease correction
- PYC has previously demonstrated the ability of its proprietary drug delivery technology to effectively reach neurons in the brain *in vivo* (see ASX announcement of 12 April 2021)
- The next phases of the research program will be to combine the two elements of PYC's technology (drug delivery and RNA therapeutic) into a single molecule and assess these 'conjugates' in both patient-derived and animal models before progressing to clinical studies

[1] Phelan McDermid Syndrome Foundation

PERTH, Australia and California, USA – 27 September 2022 – PYC Therapeutics (ASX:PYC) is a biotechnology company combining two complementary platform technologies:

- RNA drug design capabilities; and
- a proprietary drug delivery technology.

Together they are being developed to create a new generation of RNA therapeutics to change the lives of patients with genetic diseases.

PYC is adding a third investigational drug program for the treatment of Phelan McDermid Syndrome (PMS) to its pipeline. PMS is a neurodevelopmental disorder characterised by developmental and speech delays, behavioural problems and compromised ability to perceive pain and regulate body temperature.

The creation of a disease-modifying therapy for patients with PMS represents an area of major unmet patient need. Effective treatment of the underlying cause of this disorder would represent a life-changing paradigm for PMS patients and their families.

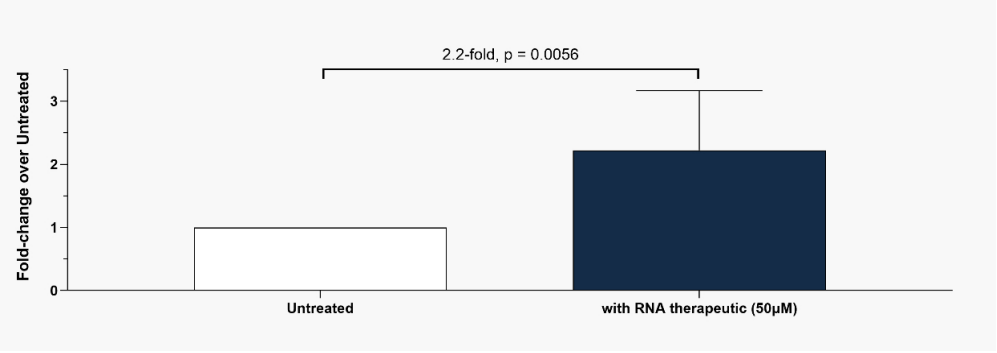
Consistent with PYC's strategy, PMS is a monogenic disease in which the underlying cause is insufficient expression of the *SHANK3* gene in the target cell (neurons) in the brain. The new pipeline addition represents PYC's first program in the Central Nervous System (CNS) - demonstrating the scalability of the Company's platform technology into target tissues beyond the eye.

PYC has designed an RNA therapy to address the underlying cause of PMS

The underlying cause of PMS in the majority of patients is a deletion or mutation affecting one copy of the *SHANK3* gene, causing a ~50% decrease in expression of the SHANK3 protein. It is this deficiency of *SHANK3* expression in neuronal cells in the brain that causes PMS.

PYC has designed and validated an RNA therapeutic capable of increasing *SHANK3* expression in cells by ~2-3 fold. The extent of protein upregulation observed in these *in vitro* studies is sufficient to correct the underlying SHANK3 protein deficiency that causes PMS.

Figure 1. 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). SH-SY5Y cells transfected with an RNA therapeutic (antisense oligonucleotide) at 50μM concentration demonstrate ≥ 2-fold upregulation of SHANK3 protein relative to SH-SY5Y cells treated with a transfection control (without the 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.



PYC is now working to reproduce these results in human primary cells derived from patients with PMS (patient-derived models).

RNA therapies have an established development path in the treatment of CNS diseases

The results described in Figure 1 have been achieved with a 'naked' RNA therapeutic (an RNA therapeutic that does not make use of a drug targeting or delivery technology). There is an established development pathway for the use of 'naked' RNA therapies in the treatment of Central Nervous System disorders that benefits the PYC *SHANK3* program.

In addition to this established pathway, PYC has an opportunity to utilise its proprietary drug delivery technology to further improve the properties of the candidate that it will select for clinical development in PMS. PYC has previously described the improved profile of drug delivery within the brain associated with the use of its platform technology. PYC's proprietary platform technology is a world-leading drug delivery technology that exploits small protein fragments (peptides) derived from nature to carry drug molecules safely into cells, including to the neurons affected in PMS *in vivo* (See ASX announcement of 12 April 2021).

PYC is working with the PMS Foundation and research clinicians to advance the program to the clinic

The scientific mission of the Phelan McDermid Syndrome Foundation (PMSF) is to improve the quality of life of those affected by Phelan-McDermid Syndrome worldwide, and to build a future free of Phelan-McDermid syndrome by investing in and advancing drug development.

PMSF is the leading source worldwide for information about this rare genetic condition; working closely with researchers, pharmacological companies, biotechnology, academic institutions, and other external scientists with the ultimate goal of finding effective treatments for Phelan-McDermid Syndrome (PMS).

PYC recognises the value of the patient experience and voice, and greatly appreciates the critical information provided by PMSF that can guide and support research.

Dr Kate Still, Scientific Director of the Phelan-McDermid Syndrome Foundation, commented "Our families face complex challenges every day, but they are resilient and interested in clinical research. They are looking for transparency from drug developers, for their voices to be heard, and for meaningful assessment of symptoms which most strongly impact quality of life".

PYC will advance this work as it becomes a clinical-stage company in ophthalmology

Today's announcement expands the number of programs in PYC's pipeline progressing towards testing in humans to three:

- the Company's lead Retinitis Pigmentosa type 11 program is anticipated to enter a combined phase 1/2 clinical trial in the first quarter of next year;
- PYC's second ophthalmology program, an investigational drug known as PYC-001 for the treatment of Autosomal Dominant Optic Atrophy, is anticipated to progress into clinical trials in 2024; and
- the new program in the CNS for the treatment of Phelan-McDermid Syndrome that will now progress into testing in patient-derived and animal models.

About PYC Therapeutics

PYC Therapeutics (ASX: PYC) is a biotechnology company creating a new generation of RNA therapies by combining its drug design capabilities with a proprietary drug delivery platform.

The Company is leveraging its leading-edge science to develop a pipeline of novel therapies including two programs focused on inherited eye diseases and pre-clinical discovery programs focused on neurodevelopmental and kidney diseases. PYC's discovery, pre-clinical and laboratory operations are located in Australia and its translational, clinical and regulatory operations are located in the United States. For more information, visit pyctx.com, or follow us on LinkedIn and Twitter.

Forward looking statements

Any forward-looking statements in this ASX announcement have been prepared on the basis of a number of assumptions which may prove incorrect and the current intentions, plans, expectations and beliefs about future events are subject to risks, uncertainties and other factors, many of which are outside the Company's control. Important factors that could cause actual results to differ materially from assumptions or expectations expressed or implied in this ASX announcement include known and unknown risks. Because actual results could differ materially to assumptions made and the Company's current intentions, plans, expectations and beliefs about the future, you are urged to view all forward-looking statements contained in this ASX announcement with caution. The Company undertakes no obligation to publicly update any forward-looking statement whether as a result of new information, future events or otherwise.

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

This ASX announcement was approved and authorized for release by the CEO of PYC Therapeutics Limited

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