June 8, 2021

SECOND DRUG PROGRAM PROGRESSING TOWARDS HUMAN TRIALS

PYC's drug candidate for Autosomal Dominant Optic Atrophy (ADOA) has prevented the cell death that causes blindness in patients with this disease[1]

PYC will now accelerate this program towards clinical trials currently estimated to start in 1H 2023

This drug candidate has the potential to be the first disease-modifying therapy for patients with ADOA[2] *in an estimated US$2bn p.a. market*[3]

This program represents the second competitively differentiated drug candidate to combine PYC's dual precision drug design and delivery platforms to progress through non-clinical efficacy read-outs

This drug candidate has potential application in patient subgroups in other diseases with underlying mitochondrial dysfunction including glaucoma, Parkinson's Disease and Alzheimer's Disease[4]

PERTH, Australia and NEW YORK, New York – June 8, 2021 – PYC Therapeutics (ASX:PYC) is a biotechnology company combining two complementary platform technologies (selective drug delivery and precision drug design) to develop a new generation of RNA therapeutics to change the lives of patients with inherited diseases.

PYC today announced that studies in patient-derived cells show that its second drug candidate for Autosomal Dominant Optic Atrophy (ADOA) has rescued the critical functional deficit that causes blindness in patients with this disease[5] (see Figures 2 and 3 for the results and ASX announcements of 3 and 18 May for background information on ADOA and the functional deficits associated with this disease). The Company's Chief Scientific Officer, Professor Sue Fletcher, commented on the results: '*If the cell survival and functional benefits that we see in patient-derived models treated with this drug candidate are replicated in the clinic, this has the potential to change the lives of ADOA patients in a very meaningful way*'.

[1] In non-clinical cellular models derived from patients with ADOA

[2] Lenaers G, Hamel C, Delettre C, Amati-Bonneau P, Procaccio V, Bonneau D, Reynier P, Milea D. Dominant optic atrophy. Orphanet J Rare Dis. 2012 Jul 9;7:46. doi: 10.1186/1750-1172-7-46. PMID: 22776096; PMCID: PMC3526509.

[3] Based on a 2018 mean US orphan drug price of US$150,854 and an addressable patient population for this drug candidate of 9,000-16,000 patients

[4] See references 8 through 10 below

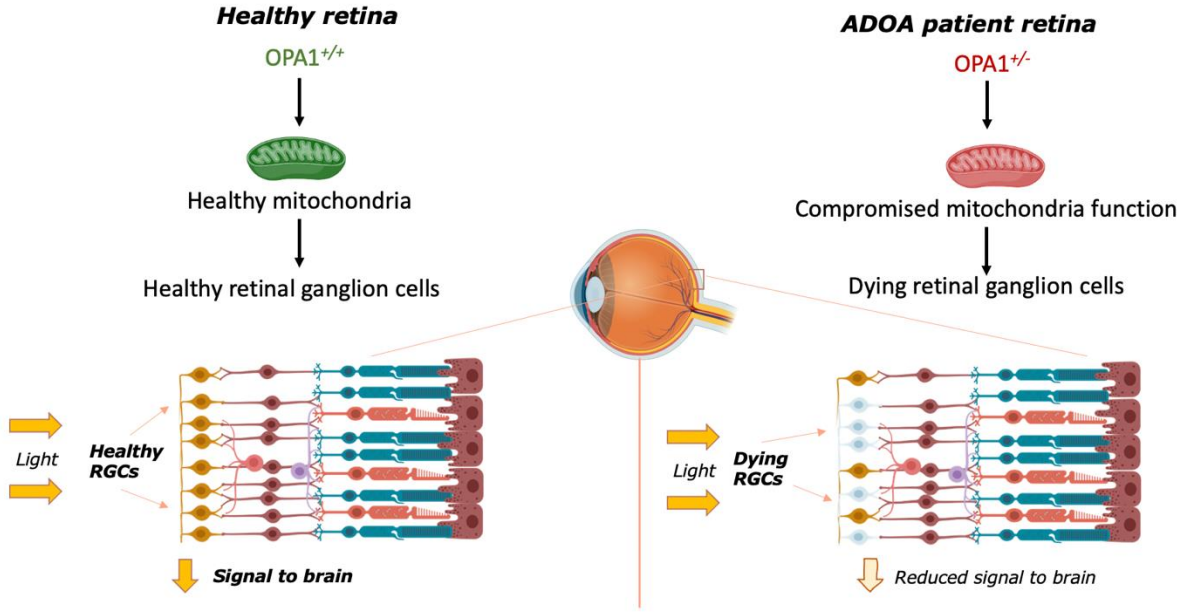
[5] This drug candidate is owned by PYC's 90% owned subsidiary, Vision Pharma Pty Ltd (Lions Eye Institute are the 10% minority shareholder in Vision Pharma Pty Ltd)

Background

ADOA is an orphan disease characterised by loss of vision in both eyes beginning in early childhood and often progressing to legal blindness in adulthood. The majority of ADOA cases are caused by mutations in a gene called *Optic Atrophy 1* (*OPA1*), leading to a deficit of OPA1 protein. The OPA1 protein is crucial for healthy functioning of the cell's powerhouses called mitochondria. The mitochondrial dysfunction in ADOA patients can cause death of the retinal cells that transmit visual signals to the brain. Mitochondrial dysfunction results in decreased levels of ATP, the principal molecule for storing and transferring energy within cells. The decreased ATP levels, in turn, result in greater vulnerability of the Retinal Ganglion Cells (RGCs) and it is RGC death in response to stressful stimuli that represents the underlying cause of blindness in ADOA (see Figure 1).

PYC's drug candidate works by increasing OPA1 protein levels in patient cells. The increase in OPA1 protein rescues mitochondrial function, increases ATP levels and enhances resistance to cell death. This drug candidate therefore has the potential to slow or even halt vision loss in ADOA patients.

Figure 1



Summary of today's results

PYC's ADOA drug candidate has now proven its ability to:

i) Increase levels of the OPA1 protein (see ASX announcement of 18 May 2021);
ii) Increase mitochondrial ATP production (see Figure 2); and
iii) Prevent apoptotic cell death (see Figure 3) in models derived from patients with ADOA, reducing apoptosis to levels close to those observed in healthy individuals.

PYC's ADOA drug candidate increases mitochondrial ATP levels in a mutation agnostic manner

Figure 2.

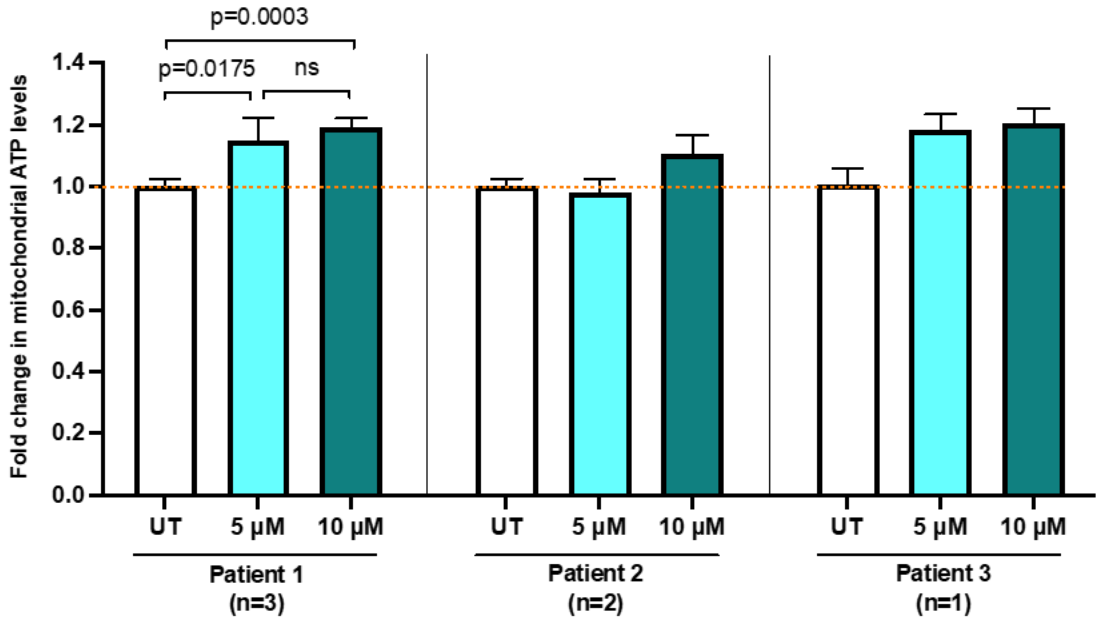


Figure 2[6]. Increasing levels of ATP in response to PYC's drug candidate in ADOA patient fibroblasts (Patients 1 and 3 harbour the c.2708_2711delTTAG deletion, Patient 2 harbours the c.985-1G>A mutation). The Untreated (UT) ADOA patient cells on the left have lower levels of ATP than the treated groups in the centre and on the right (for each patient assessed). ADOA is associated with reduced levels of mitochondrial ATP and consequently a vulnerability to apoptosis due to reduced stress tolerance. The response in patient cells with different mutations in *OPA1* illustrates the drug's mutation agnostic mechanism and expands the potential addressable patient population.

PYC's ADOA drug candidate prevents cell death in response to stress

The increase in mitochondrial ATP levels seen following treatment with PYC's ADOA drug candidate is associated with greater cell survival in the face of stressful stimuli (see Figure 3). Apoptosis in response to stress, resulting in the loss of RGCs, is the underlying cause of blindness in ADOA (see Figure 1). Rescue from apoptosis is the primary non-clinical predictor of efficacy of this drug candidate in clinical development.

[6] Patient fibroblasts were treated with PPMO at 5 and 10 µM for 7 days and were subsequently analysed for mitochondrial ATP. Bar graph represents fold change in mitochondrial ATP levels in patient fibroblasts treated with PPMO (mean+SEM). Untreated patient fibroblast was indexed to 1. Statistical differences were analysed using Student's t-test.

Figure 3

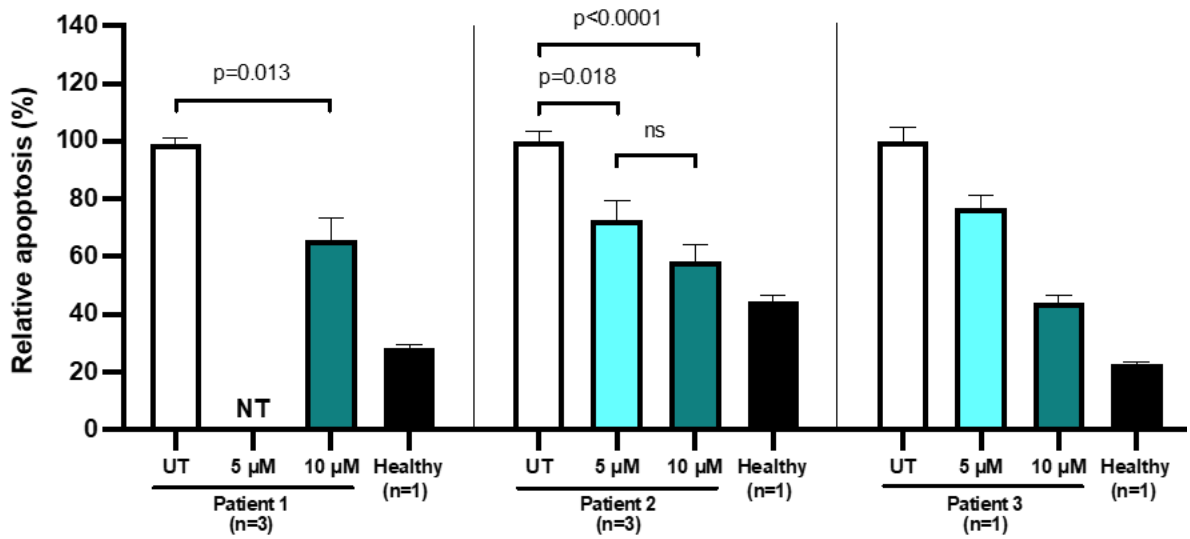


Figure 3[7]. A dose-dependent and mutation agnostic decrease in cells undergoing apoptosis (programmed cell death) following treatment with PYC's ADOA drug candidate in cells from three patients. The Untreated (UT) patient cells on the left of each graph have the highest rate of cell death following insult. Treatment with the drug reduces the number of cells dying. As the dose of PYC's drug is increased, the number of cells dying decreases towards levels observed in 'healthy' individuals (who do not have ADOA) on the right hand side.

Collaboration with global-leading expert to accelerate the drug candidate into clinical trials

PYC has appointed leading authority on ADOA, Dr. Patrick Yu Wai Man, to its scientific advisory board in support of the efficient translation of this drug candidate into clinical development. Dr. Yu Wai Man is a neuro-ophthalmologist with a major research interest in mitochondrial genetics and inherited eye diseases, including ADOA. Dr Yu Wai Man leads the Cambridge Clinical Vision Lab that was set up as a cross-cutting facility to support advanced therapeutics within the NIHR Cambridge Biomedical Research Centre. In parallel, he has established a strong collaborative link with the NIHR Moorfields Biomedical Research Centre to accelerate the development of effective therapies for inherited optic neuropathies. Speaking on PYC's OPA1 program, Dr. Yu Wai Man observed that "*Autosomal dominant optic atrophy caused by OPA1 mutations is an important cause of blindness in children and young adults. There is currently no treatment available to prevent progressive optic nerve degeneration and visual deterioration. The application of PMOs coupled with the use of an efficient delivery system in the form of cell-penetrating peptides (CPPs) is a promising strategy to safely upregulate OPA1 expression, with the aim of restoring mitochondrial function and promoting cell survival'.*

[7] Patient fibroblasts were pre-treated with PPMO at 5 and 10 µM for 7 days and were subsequently treated with apoptotic stimuli for 4 hr prior to analysis. Apoptotic cells were analysed using flow cytometry. Bar graph represents relative apoptosis in patient fibroblasts treated with PPMO@7-day post-treatment (mean+SEM). Patient fibroblast without PPMO treatment was indexed to 100% apoptosis. Statistical differences were analysed using Student's t-test. NT = not tested.

Applications of this drug candidate in other disease indications

The same mitochondrial dysfunction that underlies the cellular death and blindness seen in patients with ADOA is also implicated in a range of other diseases of both the eye and central nervous system. An increasing body of evidence supports the therapeutic potential of *OPA1* upregulation in glaucoma[8], Parkinson's Disease[9] and Alzheimer's Disease[10]. PYC's ADOA drug candidate therefore holds promise across a range of highly-prevalent disease indications with limited existing treatment options.

Next steps

PYC's ADOA program will now be accelerated towards clinical trials to improve the lives of patients with this progressive and blinding disease. The Investigational New Drug submission for this drug candidate is currently anticipated in 1H 2023. A comprehensive overview of the program and its competitive differentiation including the results from the critical non-clinical assays described above will be made available in the form of a technical presentation released to the Australian Securities Exchange in the near future. In parallel, PYC will evaluate the utility of this drug candidate in other diseases driven by mitochondrial dysfunction and in which this therapeutic approach holds significant promise.

About PYC Therapeutics

PYC Therapeutics (ASX: PYC) is a pre-clinical stage biotechnology company pioneering a new generation of RNA therapeutics that utilize PYC's proprietary library of naturally derived cell penetrating peptides to overcome the major challenges of current genetic medicines. PYC believes its PPMO (Peptide conjugated Phosphorodiamidate Morpholino Oligomer) technology enables a safer and more effective RNA therapeutic to address the underlying drivers of a range of genetic diseases for which no treatment solutions exist today. The Company is leveraging its leading-edge science to develop a pipeline of novel therapies including three preclinical stage programs focused on inherited eye diseases and a preclinical discovery program focused on neurodegenerative diseases. PYC's discovery and laboratory operations are located in Australia, and the Company recently launched an expansion into the U.S. for its preclinical, clinical, regulatory and business development operations. 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

[8] OPA1 increases the risk of normal but not high tension glaucoma. Yu-Wai Man et al. J Med Genet. 2010 February ; 47(2): 120–125; Down-regulation of OPA1 in patients with primary open angle glaucoma. Bosley et al. Molecular Vision 2011; 17:1074-1079; Overexpression of Optic Atrophy Type 1 Protects Retinal Ganglion Cells and Upregulates Parkin Expression in Experimental Glaucoma. Hu et al. Front. Mol. Neurosci., 28 September 2018

[9] Optic atrophy 1 mediates mitochondria remodeling and dopaminergic neurodegeneration linked to complex I deficiency. Ramonet et al. Cell Death and Differentiation (2013) 20, 77–85; Stem Cell Modeling of Mitochondrial Parkinsonism Reveals Key Functions of OPA1. Jonikas et al. ANN NEUROL 2018;83:915–925;

[10] Mitochondrial Bioenergetics Is Altered in Fibroblasts from Patients with Sporadic Alzheimer's Disease. Perez et al. Front. Neurosci., 06 October 2017; Impaired Balance of Mitochondrial Fission and Fusion in Alzheimer's Disease. Wang et al. The Journal of Neuroscience, July 15, 2009. 29(28):9090 –9103

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 Board of PYC Therapeutics Limited

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