May 18, 2021

PYC ANNOUNCES SECOND DRUG PROGRAM WITH EFFICACY DATA IN PATIENT CELL MODELS

PYC is developing a disease-modifying precision therapy for patients with a blinding eye disease called Autosomal Dominant Optic Atrophy (ADOA) caused by mutations in the OPA1 gene

The mutation in the OPA1 gene leads to an insufficient level of OPA1 protein, which is the underlying cause of ADOA in these patients

PYC's investigational drug has successfully restored levels of the OPA1 protein towards normal in cells from all 4 patients with ADOA assessed

This investigational therapeutic has the potential to be the first disease-modifying therapy for patients with ADOA[1] in an estimated US$2bn p.a. market[2]

PERTH, Australia and NEW YORK, New York – May 18, 2021 – PYC Therapeutics (ASX: PYC) is a biotechnology company combining two complementary platform technologies (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 its second investigational drug candidate restores the levels of the target protein (OPA1) towards normal in models derived from patients with the indicated disease – Autosomal Dominant Optic Atrophy (ADOA)[3]. ADOA is an orphan indication with no preventative or curative therapies currently available to patients[4].

This investigational drug will now be assessed in functional models to determine whether the increase in OPA1 protein successfully rescues the behavioural deficits seen in cells from ADOA patients that lead to loss of vision. These results are expected over coming weeks. Positive outcomes in these models will see the program accelerated towards first in human studies to improve the lives of patients with this progressive and blinding disease.

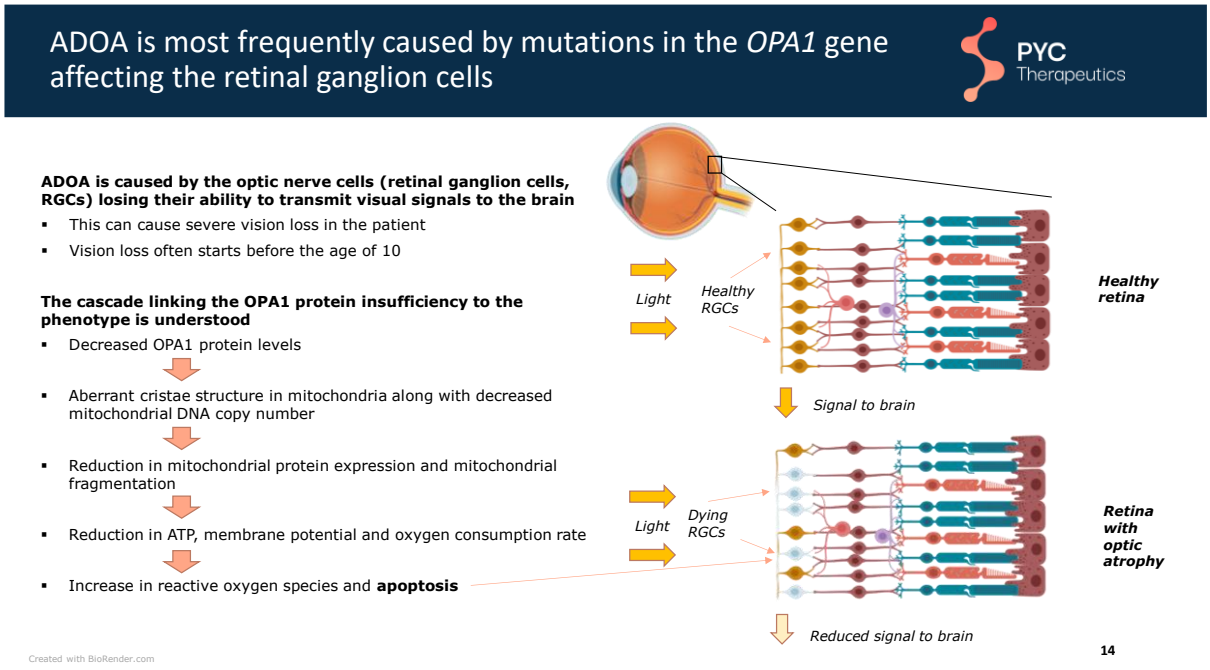
How vision is compromised in Autosomal Dominant Optic Atrophy (ADOA)

The target cells for PYC's *OPA1* (ADOA) program are the Retinal Ganglion Cells (RGCs) within the retina. The RGCs make up the optic nerve that enables the transmission of visual signals from the retina to the brain. The majority of cases of ADOA are caused by

[1] 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.
[2] Based on a 2018 mean US orphan drug price of US$150,854 and an addressable patient population for this investigational drug of 9,000-16,000 patients
[3] This investigational therapeutic 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)
[4] 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.

insufficient levels of OPA1 protein in the RGCs. The decreased levels of OPA1 protein cause the RGC's energy production system (the mitochondria) to function at lower levels. The consequence of this inadequate performance by the mitochondria is insufficient production of a molecule called ATP – the principal molecule for storing and transferring energy within cells. The decreased levels of ATP within the RGCs leaves them vulnerable to cell death under stress. The death of the RGCs ultimately results in the progressive loss of vision seen in patients with ADOA due to the interruption of the communication between the retina and brain. An attractive disease-modifying strategy to treat ADOA is therefore to increase the levels of the OPA1 protein to prevent the process that leads to cell death.

Figure 1. An overview of ADOA: cause and consequences



PYC's investigational drug is effective at increasing OPA1 protein levels in all patient samples tested

The efficacy of this investigational therapeutic (a cell penetrating Peptide-PMO conjugate also known as a PPMO) was assessed in cells derived from 4 different patients, each of whom has ADOA due to a mutation in the *OPA1* gene. The results show that the PPMO corrected OPA1 protein levels in the patient-derived cells towards the level of this protein that is observed in individuals not affected by this disease (see Figure 2).

Figure 2

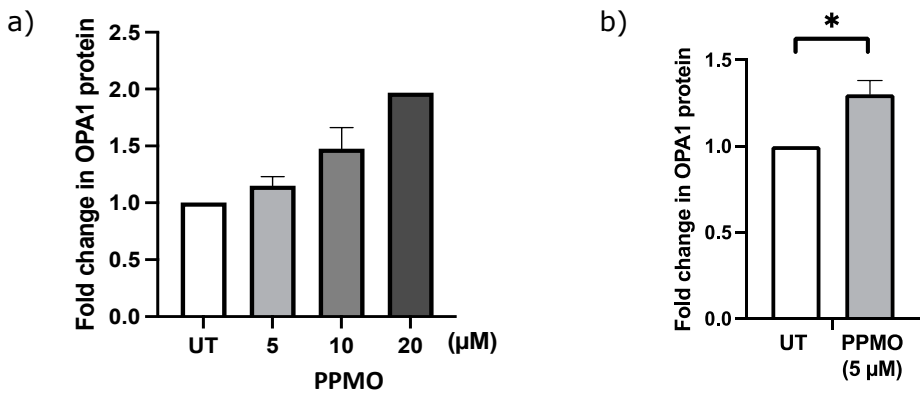


Figure 2a) demonstrates a dose-response to PYC's investigational OPA1 drug in an ADOA patient fibroblast assay[5]. The objective for the investigational therapy is to elevate the deficient OPA1 protein levels in the ADOA patient cells back towards levels seen in people without ADOA (unaffected individuals have approximately 2-fold higher OPA1 protein levels than ADOA patients). Figure 2b) is an assessment of PYC's investigational OPA1 drug's ability to increase expression of the OPA1 protein across four different patient tissue samples at the anticipated approximate human therapeutic dose of 5 μM[6] (the result is statistically significant with p<0.05 on student's t-test).*

Next steps

This investigational therapy will now be assessed for the ability to rescue the functional deficits observed in cells from ADOA patients. These assays focus on the ability of the cells to:

i) produce increased levels of ATP in response to treatment with the drug (ATP production is decreased in ADOA); and
ii) resist programmed cell death (apoptosis) under stress (sensitivity to apoptosis is increased in ADOA) (see Figure 1).

In addition to assessing the ability of the current lead PPMO sequence to address the functional deficits observed in ADOA patients, PYC has further optimised the sequence of the oligonucleotide (or PMO) that forms part of this investigational therapy, leading to a 2-3 fold improvement in OPA1 protein upregulation when compared to the results presented above. These 'second generation' sequences will now be assessed in conjunction with PYC's proprietary delivery technology and are expected to form part of the final optimised *OPA1* therapeutic.

Successful functional studies over coming weeks will see this program accelerate towards first in human testing. This therapy is expected to benefit from a rapid Investigational New Drug (IND)-enabling pathway due to the synergies between this program and PYC's lead drug program – the world's first disease-modifying therapy for patients with Retinitis Pigmentosa type 11.

About PYC Therapeutics

PYC Therapeutics (ASX: PYC) is a development-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.

[5] n of 3, 2 and 1 samples respectively for the 5, 10 and 20μM doses
[6] These results were obtained with a research-grade CPP-PMO so further efficacy improvements are expected when the higher purity material used in IND-enabling studies is available

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 Board of PYC Therapeutics Limited

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