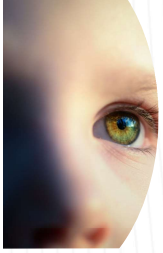

VP-001 as an interventional therapy for patients with PRPF31 mutation-associated retinal dystrophy

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RP11 is a progressive, blinding eye disease of childhood for which there are no treatments available

Retinitis Pigmentosa type 11 (RP11) & VP-001

- Dominantly inherited, severe and progressive **blinding eye disease** that begins in childhood
- **5,000 – 10,000** addressable patients in the western world[1-3]
- There are no treatments currently available nor are there any in clinical development
- **RP11 is a monogenic disease**: 2-5x higher likelihood of therapeutic success in human studies[4]
- Caused by **haploinsufficiency of *PRPF31*** expression in retinal pigment epithelium and photoreceptors
- **VP-001 restores *PRPF31* expression** towards levels seen in unaffected individuals
- This increase in gene expression **improves the structure** of cells in RP11 patient-derived models

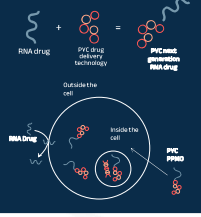
RP11 patient vision deterioration

The Delivery Challenge of Antisense Therapies

PYC's technology overcomes the primary challenge for genetic medicines – delivering enough drug to the target

RNA therapies are an approved class of drug but their efficacy is limited by an inability to reach their target inside the cell

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

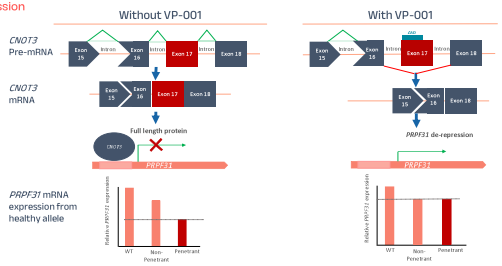


Antisense Therapies for Retinal Disease

- Antisense oligomers (ASO) are synthetic nucleic acid analogues that can be designed to modify pre-mRNA splicing or protein expression for treatment of diseases
- Suboptimal ASO delivery presents an ongoing challenge and limits the realisation of potential therapeutics[6]
- Antisense therapies for retinal disease are particularly limited in their ability to achieve adequate cellular uptake in the retina[7]
- PYC's cell-penetrating peptide (CPP) platform facilitates phosphorodiamidate morpholino oligomer (PMO) delivery to the cell layer in the eye affected by RP11

VP-001 is designed to skip exon 17 in *CNOT3* gene message in order to achieve upregulation in retinal *PRPF31* expression

CNOT3 is a negative regulator of *PRPF31*[5]; modulation of *CNOT3* function by ASO-mediated exon skipping enhances *PRPF31* expression



Methods

- **Patient-derived retinal pigment epithelium (iPSC-RPE) and retinal organoids (RO):** Dermal fibroblasts were collected from RP11 patients and family members by the Australian Inherited Retinal Disease Registry, with informed consent (Perth, Western Australia). Fibroblasts were reprogrammed to iPSCs, and gene-corrected isogenic control iPSC lines generated. RP11 and control iPSCs were differentiated into enriched monolayers of iPSC-RPE or 3D retinal organoids.
- **In vitro studies:** iPSC-RPE were treated with VP-001, followed by half media changes every 2-3 days to mimic vitreal clearance. *CNOT3* exon 17 skipping was quantified by RT-PCR analysis of total RNA. PRPF31 transcript was quantified utilizing specific droplet-digital PCR (ddPCR) assays. Cell morphology and surface topography was captured by scanning electron microscopy of iPSC-RPE monolayers.
- In vitro studies were performed on 45-day old ROs after a single treatment of VP-001, followed by half media changes every 2-3 days for 28 days. PRPF31 protein was quantified utilizing QuPath on CRX-immunopositive photoreceptors, from >500 photoreceptors/treatment group.
- **Ocular PK** study in NHP: Cynomolgus monkeys were dosed bilaterally with VP-001 by IVT injections of 30 µg/eye . Ocular tissues were dissected from the eyes of two animals after euthanasia at 1, 7, 28, 56, 84 and 112 days post injection. VP-001 was quantitated by hybridization ELISA.

In vitro evaluation of VP-001 demonstrates restoration of healthy *PRPF31* expression and increased PRPF31 protein in patient-derived models

VP-001 rescues the haploinsufficient gene expression (*PRPF31*) that causes RP11 in patient-derived iPSC-RPE and demonstrates a prolonged duration of effect

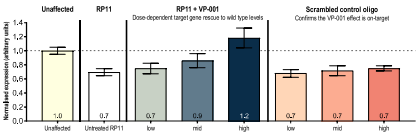


Figure 1. *CNOT3* exon 17 skipping in RP11 patient iPSC-RPE increases *PRPF31* mRNA to levels seen in unaffected control iPSC-RPE

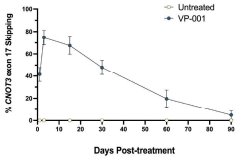


Figure 2. Target engagement persists up to 90-days after a single treatment of VP-001 in unaffected control iPSC-RPE

VP-001 treatment increases PRPF31 protein expression in RP11 patient-derived retinal organoid photoreceptors

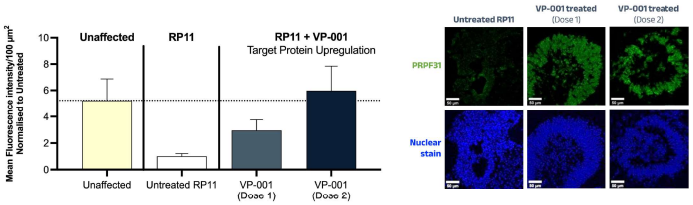


Figure 3. Preliminary data; *CNOT3* exon 17 skipping in RP11 patient ROs increases PRPF31 protein 28-days post treatment; after a single treatment with VP-001

Correcting the *PRPF31* gene insufficiency rescues the morphological appearance of affected cells in RP11

Figure 4. VP-001 improves the morphology of RP11 patient-derived iPSC-RPE following a single dose 28-days post treatment

VP-001 has PK and safety profiles favorable to an ocular therapeutic

The VP-001 half-life profile in NHPs supports an extended dosing interval in RP11 patients

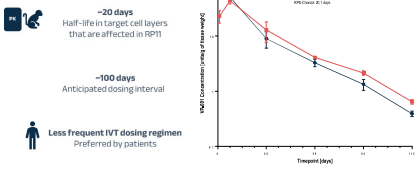


Figure 5. VP-001 has a half-life of 19 and 20-days in the retina and RPE-choroid, respectively in non-human primates (NHP) after a single treatment, thus supporting a ~3-4 monthly dosing regimen in RP11 patients

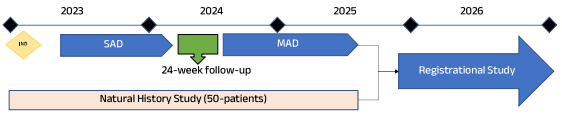
GLP toxicology studies in NHPs demonstrate the safety and tolerability of VP-001 at clinically translatable doses

Dose of VP-001	µg/eye	# of eyes dosed	# of eyes with no adverse findings at 12-weeks
Control	0	12	12
Low	5	12	12
Medium	15	12	12
High	50	12	12

Table 1. All doses tested in the GLP toxicology study in NHP were well-tolerated and safe throughout the 12-week study period

Clinical Path: PYC anticipates dosing of first patient in May 2023

The Phase I study, named Platypus, will be conducted in the USA at 6 sites and is a single ascending dose (SAD) study conducted to evaluate the safety and tolerability of a single dose of intravitreally administered VP-001



Conclusion

Preclinical findings to support clinical development of VP-001

- Restoration of gene expression and cellular morphology in patient-derived RPE
- Ability to increase PRPF31 protein levels above disease correction threshold in patient-derived organoids
- Ability to reach the target cells in the deepest layer of the retina and showed sustained tissue concentration over a 12-week period; supporting a 3-monthly dosing regimen
- Well tolerated as shown in single and multiple dose NHP toxicology studies
- Patient preferred dosing interval of 3-4x p.a. informed by drug candidate half-life administered via outpatient injection
- An IND for VP-001 has been cleared. VP-001 is expected to progress to a primary efficacy signal in a registrational study within 48 months

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