OXFORD UNIVERSITY
INNOVATION

Gene therapy for retinitis pigmentosa

OUI Projects 15619 & 15879

Summary

- Gene therapy for retinitis pigmentosa (“RP”)
- From the MacLaren Laboratory
  - Six developmental GT products already out-licensed by OUI
  - Two in advanced clinical development
- AAV-based rhodopsin block-and-replace GT
- Employs a mirtron to block expression of the endogenous defective rhodopsin
- Further pre-clinical and clinical development planned
- Available for partnering now

Retinitis pigmentosa

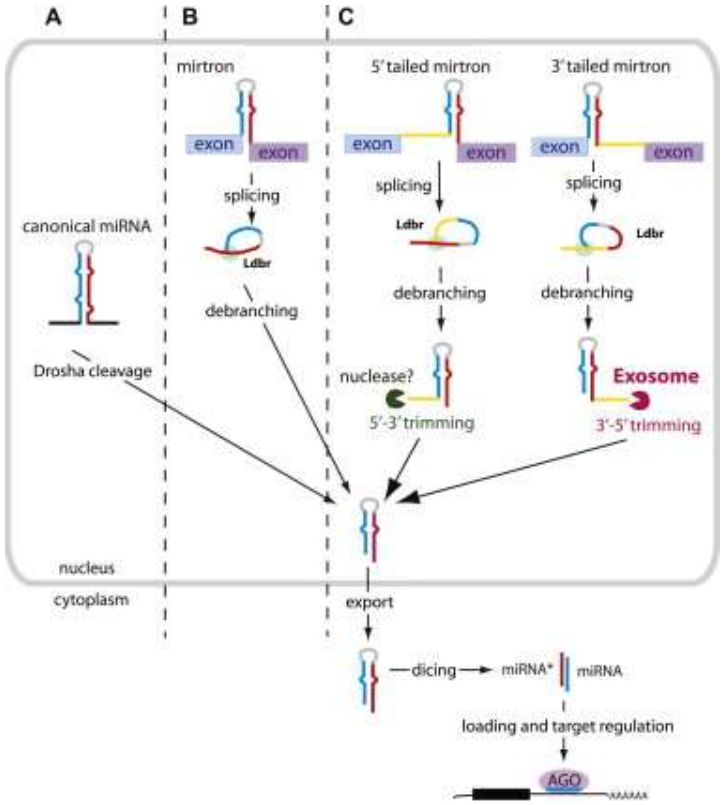
The most common form of retinal degeneration

- Prevalence: ~1/3,500
- Heterogeneous both clinically and genetically
- 15-35% are of autosomal dominant RP
- ≤50% of these are caused by rhodopsin gene mutations
- Target patient population:
  - ≤50% of 15-35% (say, 25%) of ~1/3,500
  - Therefore approximate as 1/3,500 ÷ 2 ÷ 4 = 1/28,000
  - Therefore 27,900 current patients in MM8 (population ~780m)
- Theoretical current market @US$425/eye = 28,500 x 2 x US$425K = **~US$24bn**

Oxford's developmental GT for RP

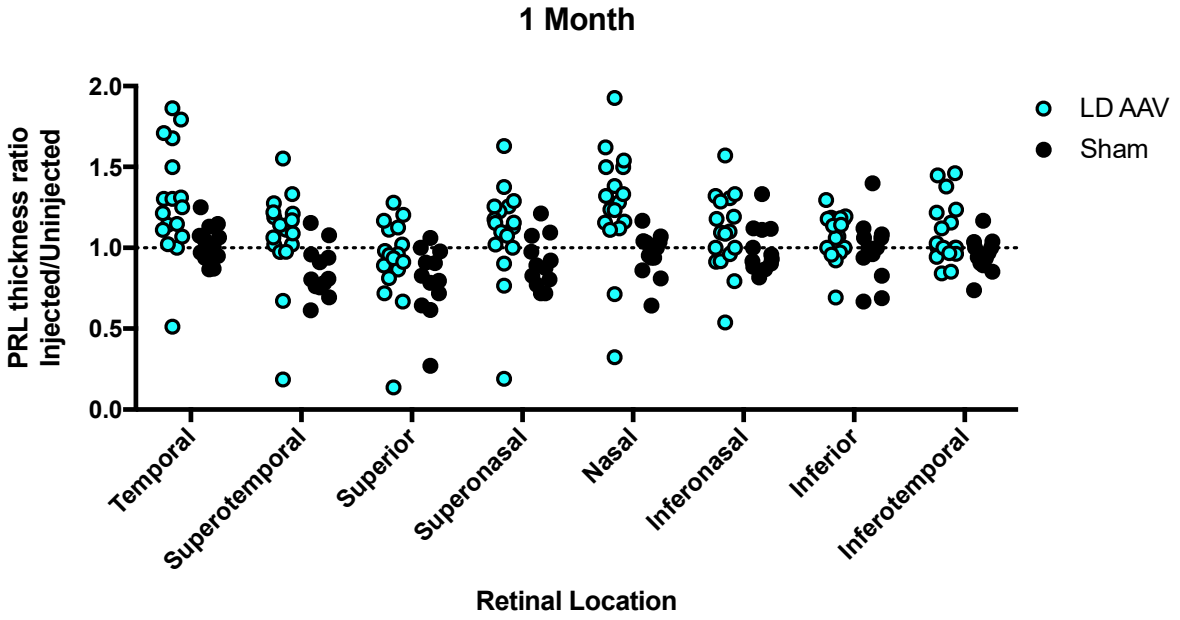
Supported by a broader GT technology platform

- AAV-based rhodopsin block-and-replace GT
- Construct delivers replacement rhodopsin gene
- Uses a **mirtron** to block expression of the endogenous defective rhodopsin
  - Type of microRNA located in the introns of mRNA
  - Created through the splicing-out of introns
  - Modulate gene expression through mRNA destabilisation, inhibition of translation or target mRNA cleavage
  - First identified in *D. melanogaster* and *C. elegans* but also found in mammals and plants
- Mirtron located in 5'-UTR of the transgene



Selected data (i)

Preservation of the photoreceptor layer *in vivo*



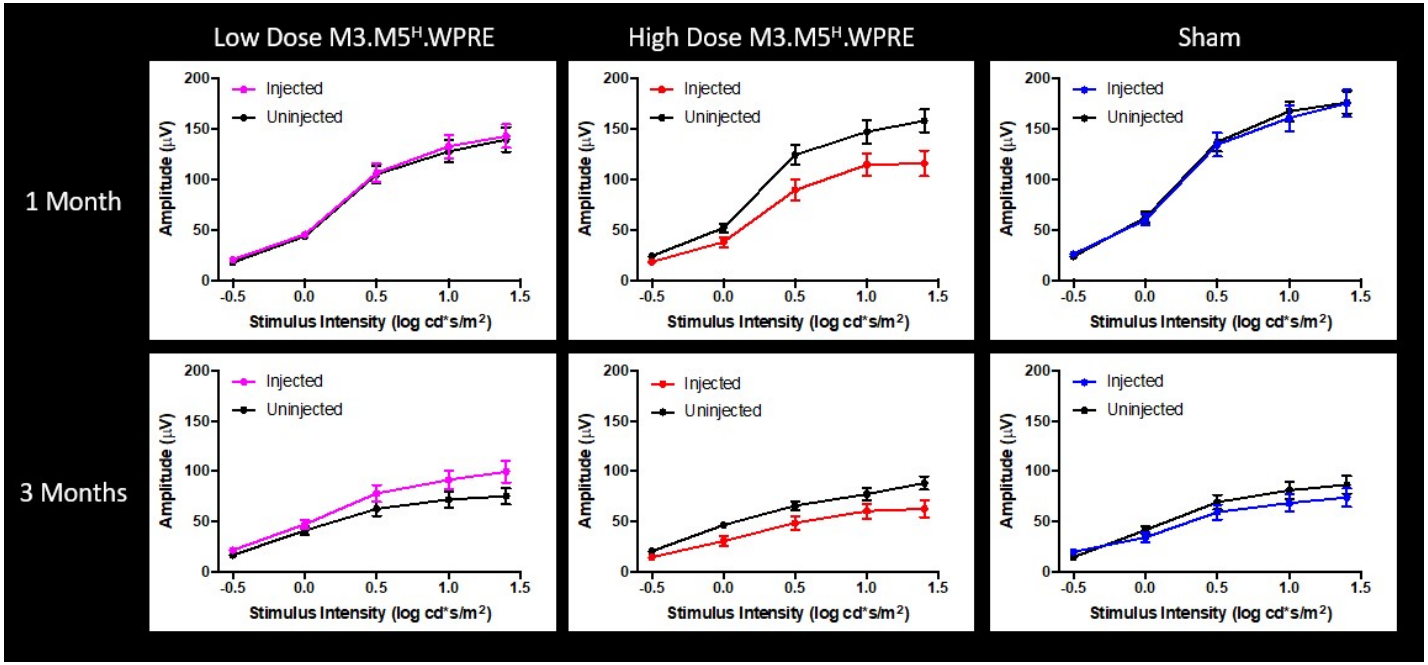
Source: PCT patent appln. published as WO 2020/084318

Early evidence that subretinal delivery of low dose (LD: 2x10^{8}gc) AAV-M3/5.RHO leads to relative preservation of the photoreceptor layer (PRL) as measured in *vivo* by SD-OCT.

The ratio of PRL thickness in injected versus uninjected eyes is shown as a function of retinal location for LD and sham-injected groups one month post-injection. Note increased retinal thickness (ratio>1) in LD but not in sham-injected eyes along the horizontal meridian (nasal and temporal retina).

Selected data (ii)

Functional benefit *in vivo*



Evidence of light-adapted electroretinography analysis.

Represents signal from cone photoreceptors. Small benefit seen at low dose, whilst high dose and sham seem to have deleterious effects, more so in high dose group.

Source: PCT patent appln. published as WO 2020/084318

Intellectual property

- PCT application published as WO 2020/084318
- Claim 1

  A method of treating a retinal disease in a subject in need thereof, the method comprising administering to the subject a vector that comprises a mirtron for knocking down expression of a target gene expressed in the retina.

- Some objections raised in ISR & WO but commercially useful claims likely to be secured
- Due to enter regional/national phase in Q2 2021

- An additional patent application (OUI Project 15879), also at the PCT stage, protects the mirtron-related technology more generally

- Both applications fully owned by, and all rights assigned to, OUI

Further development and partnering

- Based on the MacLaren Laboratory's experience in GTs for retinal diseases, the data obtained to date for the developmental RP GT are considered very promising
- Further development planned, potentially through to Phase I/II clinical trials
  - Application for additional public research funding pending

- Available for commercial partnering, e.g. via:
  - Option or licence
  - Translational collaboration
  - Spin-out formation
- Tentative pharma/biotech licensing interest has already been expressed

Any questions?

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