OXFORD UNIVERSITY INNOVATION

Adjunct treatment for gene therapy

OUI Project 14650

Summary

- Adjunct therapy for GT
- Inventor was affiliated to the MacLaren Laboratory; now an independent PI
- Potentially broadly applicable to improve safety and efficacy of potential new GTs
- May make viable developmental GT products that would otherwise not work clinically
- Preliminary *in vivo* efficacy data
- Further research ongoing
- Available for partnering now

Optimising GT safety and efficacy

Improving the viability of potential new GT products

- GT products have reached the market, e.g. Luxturna® (RPE65) and Zolgensma® (SMA)
- Further potential GTs are in advanced development (including two from Oxford)
- Many more are in early trials: the US FDA has received more than 900 INDs (FDA)
  - Encompass a wide range of diseases and the technical challenges involved will vary
- Common challenge: obtaining efficacy whilst maintaining safety
- The level of transduction contributes to efficacy and may (indirectly) affect toxicity
  - If transduction is inherently poor, higher doses (10^n viral particles) will be needed
  - However, higher doses may not be possible due to dose-dependent toxicity
  - Some otherwise promising GTs may thus be rendered clinically unviable
- Achieving adequate transduction may be a particular problem for dual-vector AAV GTs
- **A simple method for increasing transduction could be of broad utility**

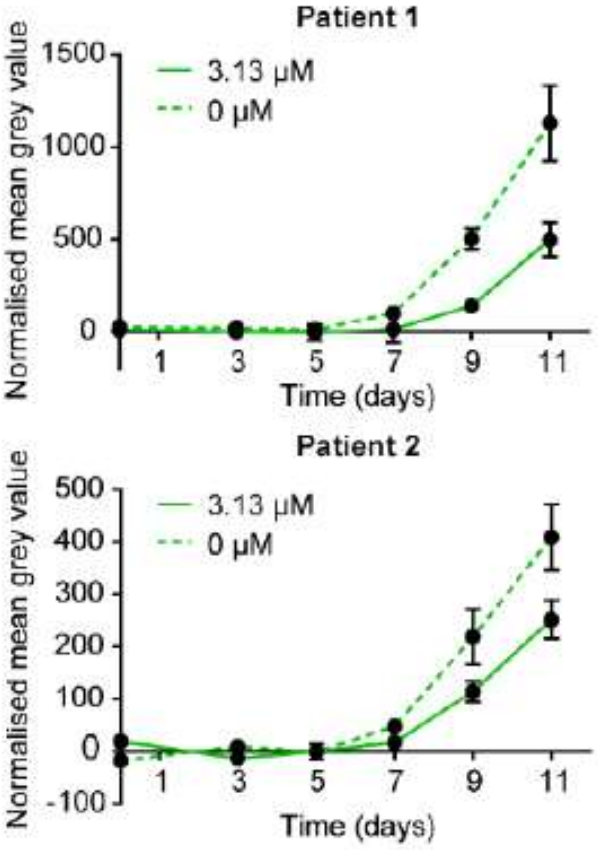
Oxford's adjunct treatment for GT

Increased transduction through the co-administration of HCQ

- Adjunct treatment comprising co-administration of hydroxychloroquine ("HCQ")
  - Long-established, well understood and inexpensive anti-malarial drug
- HCQ is mixed with the GT at the time of administration
- Exact MOA of HCQ in this application remains unclear
- (Near-)optimal HCQ dose for retinal applications has been established experimentally
  - Retinal diseases have been the focus of research to date; however, potentially applicable elsewhere
- Increases the level of transduction **by around three-fold**
  - Potentially significant increase: if the 20% transduction obtained using a *non-toxic* GT dose provided only a marginal (or insufficient) clinical effect, 60% transduction could make it very viable clinically
  - Circumvents dose limitations imposed by dose-dependent toxicity
  - Potentially of particular benefit for dual-vector GT products (where "double-transduction" is needed)
- **May make unviable GTs viable, and viable GTs better**
  - Improve the competitive position of a given GT against those of alternative GT products

Selected data (i)

Increased transgene expression in human retina *ex vivo*

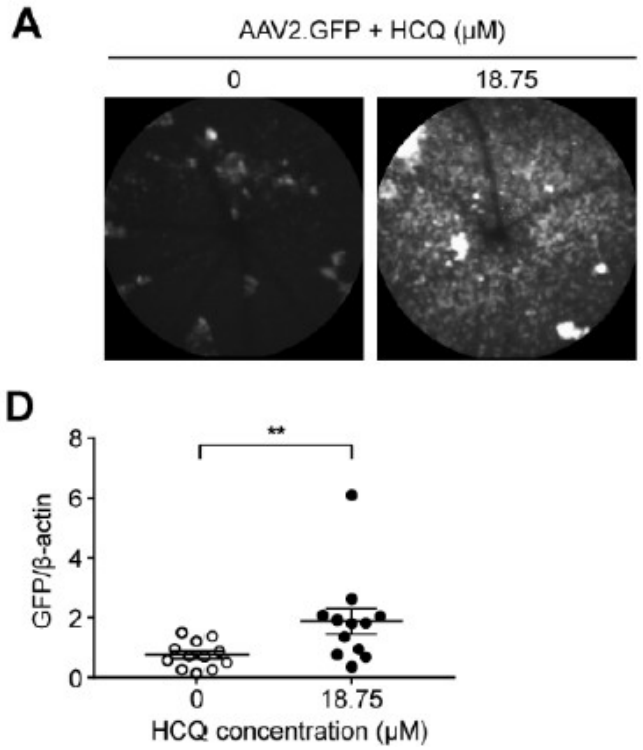


- Retinal explants from two patients were treated with AAV2.GFP combined with either 0µM or 3.13µM HCQ
- GFP fluorescence was quantified using mean grey values of the explants imaged under standardised conditions
- Both patients showed consistently increased fluorescence from day 7 onwards
- At day 11, there was a mean two-fold increase in mean grey value
- Note: the 3.13µM HCQ used was non-optimal

Data from Chandler *et al.* (2019) https://doi.org/10.1016/j.omtm.2019.05.012

Selected data (ii)

Co-administration of HCQ increases transduction by 4.6-fold *in vivo*



- Mice were injected sub-retinally in one eye with AAV2.GFP and either 3.13μM or 18.75μM HCQ, and with AAV vector only in the fellow eye
- A: Increased retinal fluorescence in eyes receiving AAV2.GFP plus 18.75μM HCQ compared with those receiving AAV vector alone
- D: Eyes that received AAV2.GFP with 18.75μM HCQ showed a mean 4.6-fold increase in GFP protein level compared with paired eyes that received AAV vector alone
- No detectable change in lamellar retinal architecture relating to the administration of HCQ (data not shown)

Data from Chandler *et al.* (2019) https://doi.org/10.1016/j.omtm.2019.05.012

Intellectual property

- PCT application published as WO 2019/155016
- Claim 1

  A method of improving the efficiency of transduction of viral vectors into cells, wherein the method comprises administering to a cell an antimalarial agent and a viral vector.

- Some objections raised in ISR & WO but commercially useful claims likely to be secured
- Due to enter regional/national phase in Q3 2020

- Fully owned by, and all rights assigned to, OUI

Further development and partnering

- Further *in vivo* studies ongoing
  - Examination of increased transduction in a dual-vector system
    - Therapeutically-useful levels of transduction may otherwise be difficult to achieve

- Available for commercial partnering, e.g. via:
  - Option or licence (probably on a product-by-product basis, potentially to multiple licensees)
  - Translational collaboration
  - Spin-out formation

Any questions?

OUI Project 14650

Adjunct treatment for gene therapy

OUI contact: bob.fishleigh@innovation.ox.ac.uk

www.innovation.ox.ac.uk

linkedin.com/company/oxford-university-innovation

twitter.com/OxUInnovation