Gene Therapy for the Rescue of Dysfunctional Retinal Pigment Epithelium

Category
Gene Therapy

Dbl3 AAV has been identified as a novel mutation-agnostic gene therapy to rescue defective RPE function

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Background

The retinal pigment epithelium (RPE) performs many critical functions that support photoreceptor health and integrity, including phagocytosis of outer segments, secretion of a variety of growth factors and transport of nutrients and metabolic end-products from the subretinal space to the blood.

Dysfunction and loss of RPE are major pathologies observed in various degenerative retinal diseases leading to blindness, including Stargardt disease, Best disease and subtypes of Retinitis Pigmentosa. Furthermore, the most common RPE disease is Age-related Macular Degeneration (AMD), in which the RPE ceases to function normally and phagocytose efficiently.

Traditional gene therapies currently being tested are limited to monogenic diseases (i.e. MerTK-associated retinitis pigmentosa) and are facing challenges to capture mutational variability across larger genes (i.e. ABCA4, the gene commonly mutated in Stargardt disease). On the other hand, AMD is not caused by a defect in a single gene, hence, simple gene therapy to replace a non-functional gene is not an option.

Tech Overview

UCL scientists have identified Dbl3 as a novel multifunctional molecular target promoting RPE fitness and function. Originally identified as a regulator of epithelial polarization and function(1), Dbl3 has been shown to control phagocytic internalization and clearance of Photoreceptor Outer Segment (POS) by the RPE(2), as well as expression of key genes involved in RPE functions. The group has established proof-of-concept that Dbl3 gene therapy improves retinal function in models of retinal degeneration and looking to further translate the technology into therapy potentially applicable to a range of ocular diseases.

Further Details:

1. Zihni et al., 2017

2. Zihni et al., 2021

Stage of Development

Proof of concept studies so far include:

- AAV generation and validation of optimal promoter and construct design
- In vitro/in vivo efficacy using functional and structural characterisation in:

  - MerTK-/- patient iPSC-derived RPE

  - RCS rats

  - Stargardt mouse model

- Toxicity tested in WT rats

See Figure 1.

IP Status

Patent application submitted

Patents

Patent application filed (PCT/GB2021/050402)

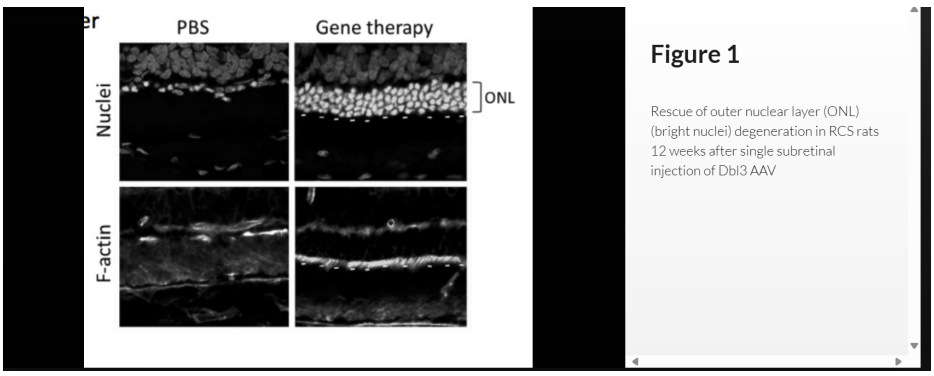

Figure 1

Rescue of outer nuclear layer (ONL) (bright nuclei) degeneration in RCS rats 12 weeks after single subretinal injection of Dbl3 AAV