AAV-mediated gene therapy attenuates loss of vision in a mouse model of Bardet-Biedl-Syndrome 10

Izabela P. Klaska[1], Monika Pianka[1], Jasmin Patel[1], Toyin Adefila-Ideozu[1], Edward Fletcher[1], Tijmen Vermeule[1], Gemma Estrada Girona[1], Yanai Duran[1], Sophia Kleine Holthaus[1], Arlene V. Drack[2], Anastasios Georgiadis[1]

1. MeiraGTx UK, 34-38 Provost Street, London N1 7NG

2. Department of Ophthalmology and Visual Sciences, University of Iowa

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Introduction

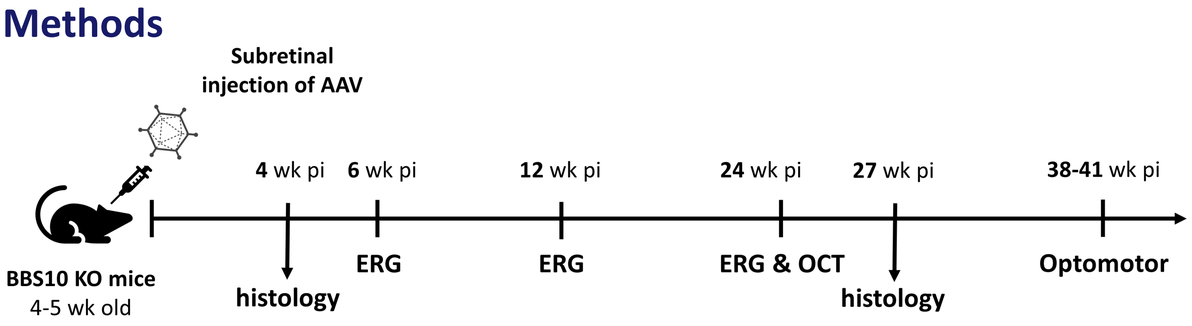
Bardet-Biedl syndrome (BBS) is a group of inherited, autosomal recessive ciliopathies characterised by disturbances of cilia function in multiple cell types, leading to obesity, renal failure, and blindness.

More than 20 causative genes are known with many mutations disabling the function of the BBSome, a protein complex regulating the movement of cargo proteins in and out of cilia. Mutations in the *BBS10* gene are the second most common cause of BBS and account for more than 20% of all cases.

Recently, a proof-of-concept study by Hsu et al. 2023, demonstrated the potential of subretinally delivered AAV gene therapy using mouse *Bbs10* in a *Bbs10*-deficient mouse model.

In this study, we set out to optimise and identify an AAV8 vector carrying the human *BBS10* gene providing sustained efficacy and a good safety profile for clinical translation.

Methods

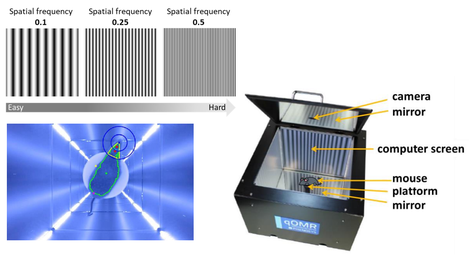


Two different promoters carrying the human *BBS10* transgene were tested. The RK promoter drives expression specifically in photoreceptors, whilst the constitutive CAG promoter drives expression in all transduced cells.

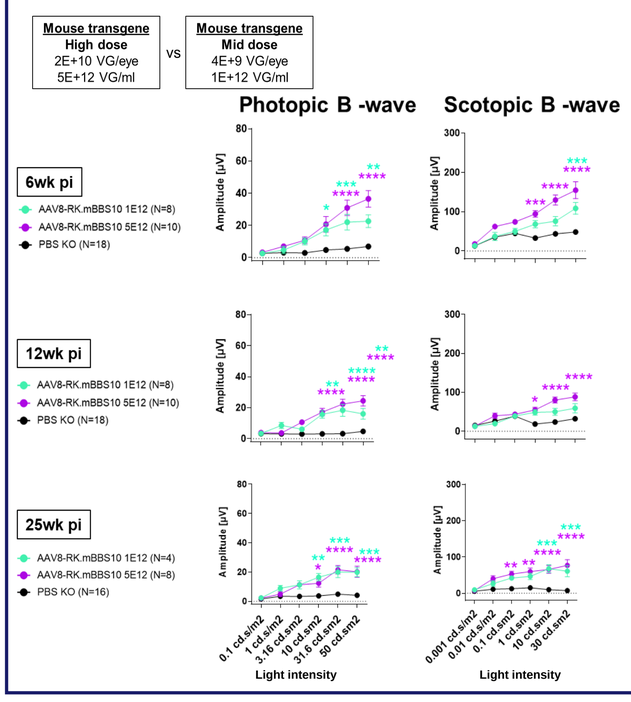
Electroretinography (ERG) measures the electrical activity of the retina in response to a light stimulus under dark- (scotopic) or light-adapted (photopic) conditions allowing assessment of retinal function. The a-wave (negative potential) and b-wave (positive potential) are the primary ERG components used for quantification of responses.

Optical coherence tomography (OCT) is a noninvasive retinal imaging technique which allows assessment of retinal thickness.

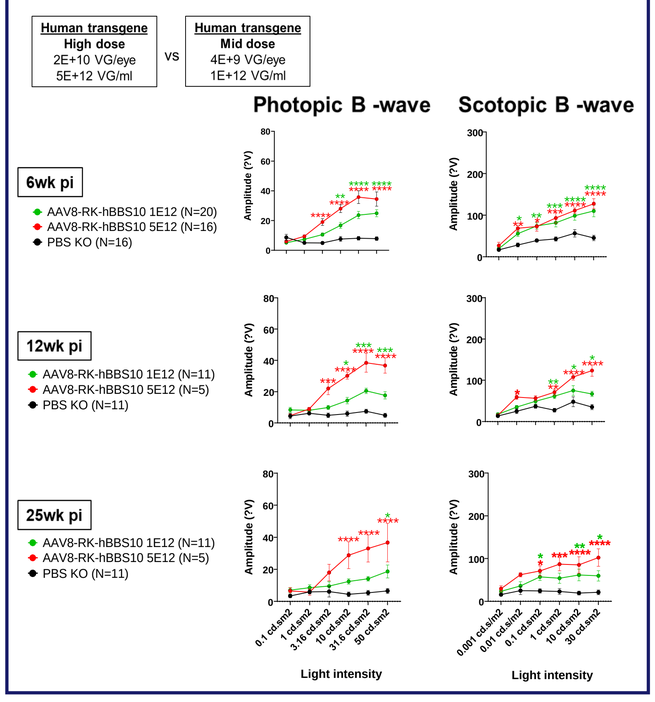
Optomotor response (OMR) is a reflex behaviour used to assess visual function. To evoke OMR, a mouse watches a defined pattern rotating within a cylinder. Stimulus-correlated head movements are then quantified.



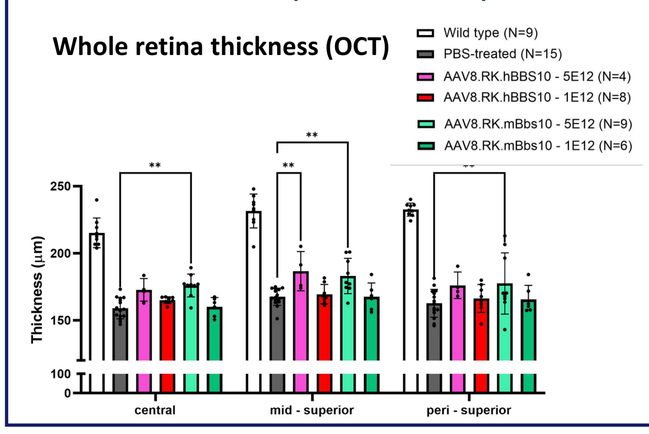
Both mid- (mint) and high (purple) doses of AAV8-RK-mBBS10 rescue ERG responses up to 25 weeks post injection



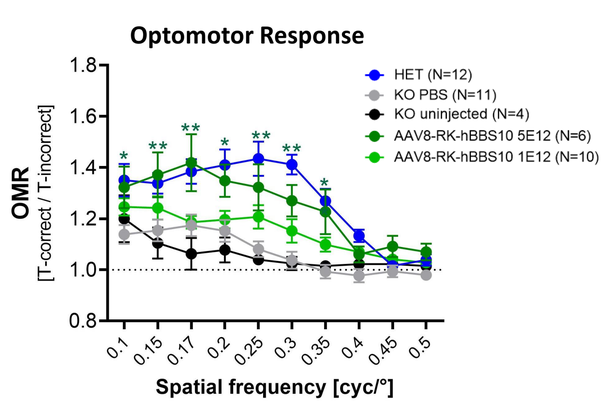
Process optimised AAV8-RK-hBBS10 promotes sustained ERG rescue using both mid- (green) and high- (red) dose



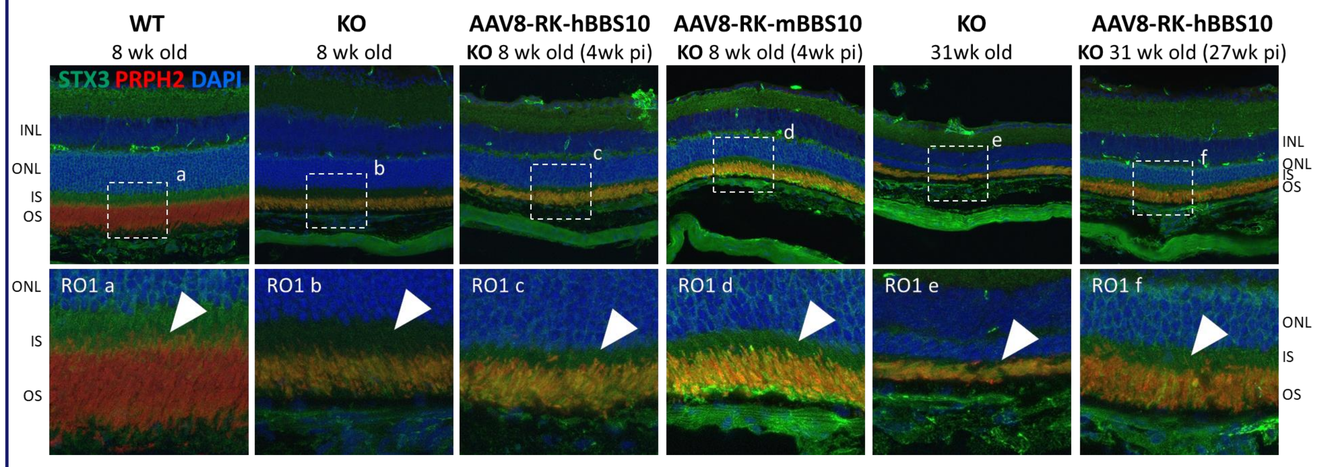
AAV8-RK-hBBS10 and AAV8-RK-mBBS10 preserve structure of the retina 25 weeks post delivery



Process optimised AAV8-RK-hBBS10 preserves functional vision until 38-41 weeks post delivery

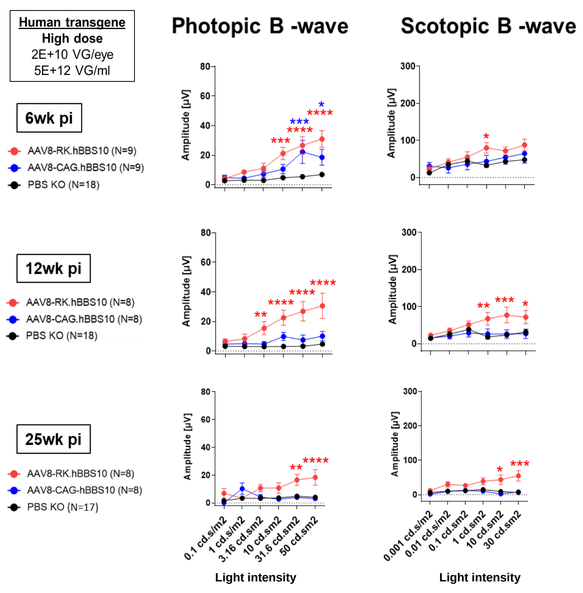


AAV8-RK-hBBS10 treatment partly corrects STX3 mis-localization

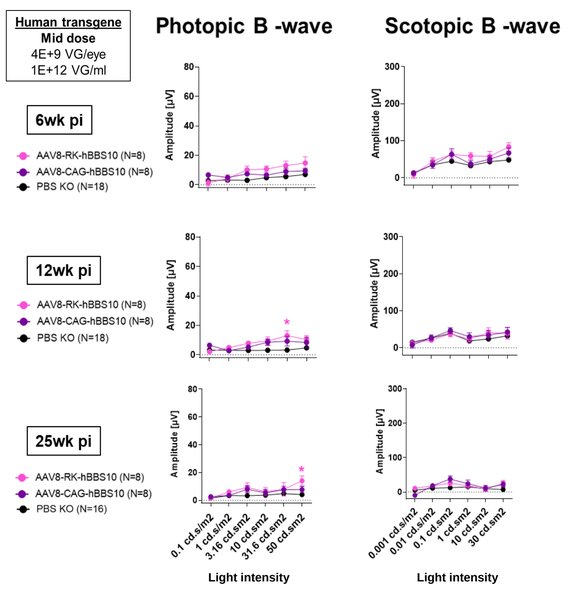


In WT mice, syntaxin 3 (STX3) is expressed in the inner photoreceptor segments (IS). In Bbs10 KO mice, STX3 mis-localizes into the outer photoreceptor segments (OS) where it overlays with peripherin 2 (PRPH2). Following treatment, STX3 mis-localization is partly corrected (retention of some STX3 in IS). Arrowheads point to the IS retina layer where STX3 should normally be expressed.

High dose of AAV8-RK-hBBS10 (red) shows superior efficacy compared to AAV8-CAG-hBBS10 (blue)

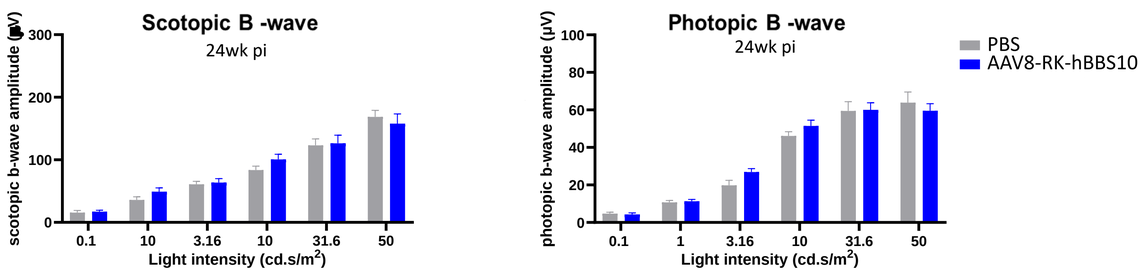


Mid doses of AAV8-RK-hBBS10 and AAV8-CAG-hBBS10 have minimal impact on ERG responses

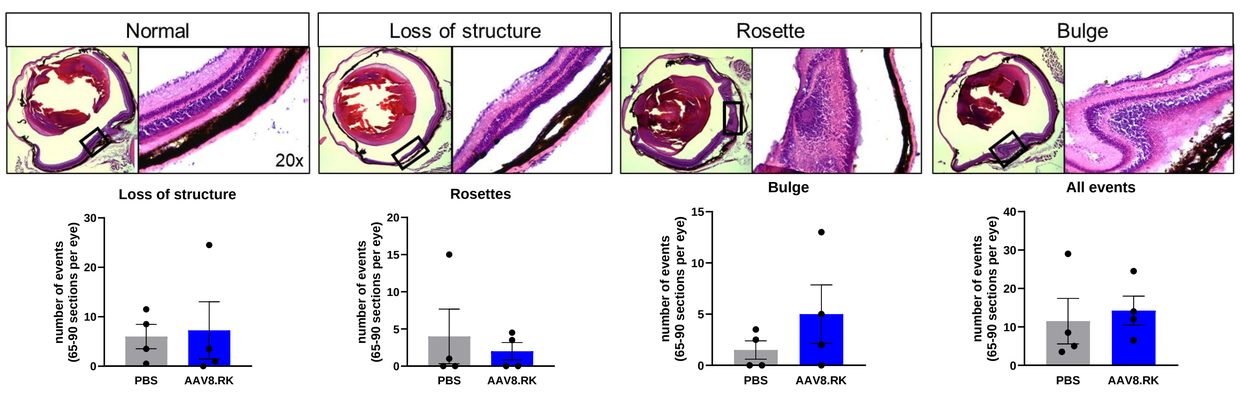


Treatment of WTs with mid-dose of AAV8-RK-hBBS10 is safe

Injections of wild type mice with AAV8-RK-hBBS10 did not lead to any significant reduction in retinal function (ERG, top panel) or retinal thickness (histology, bottom panel) at two consecutive timepoints.



Histological assessment confirms good safety profile



Conclusions

- Subretinal administration of AAV8-RK-hBBS10 results in significantly increased retinal function and thickness in Bbs10 KO mice up to 6 months pi.
- AAV8-RK-mBbs10 construct shows more pronounced therapeutic effects than AAV8-RK-hBbs10 indicating that the therapeutic effect of the AAV8-RK-hBbs10 is underestimated in Bbs10-deficient mice due to species differences between the human and mouse gene sequence.
- AAV8-RK-hBbs10 made using “process optimised” vector production protocol leads to significantly more prominent rescue of retinal function.
- Process optimised AAV8-RK-hBbs10 preserves functional vision in Bbs10 KO.
- AAV8-RK-hBbs10 has a good safety profile for clinical translation.

References

Hsu Y, Bhattarai S, Thompson JM, Mahoney A, Thomas J, Mayer SK, Datta P, Garrison J, Searby CC, Vandenberghe LH, Seo S, Sheffield VC, Drack AV, 2022. Subretinal gene therapy delays vision loss in a Bardet-Biedl Syndrome type 10 mouse model. Molecular Therapy-Nucleic Acids, 31, pp.164-181.