Mouse model selection for pharmacological evaluation of AAV-based therapeutic agents for the treatment of Rod-Cone Dystrophies (RCD)

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Purpose

The selection of an appropriate pharmacology model is important for the successful development of any drug as it has the potential to provide functional POC and inform dose selection. This is paramount in the context of gene therapy where the clinical starting dose should provide meaningful benefits as patients cannot be redosed. To assess SPVN06 pharmacological activity, an AAV-based therapy that aims at slowing down cone degeneration, we evaluated 2 mouse models of rod-cone dystrophies (RCD) characterized by a loss of rods followed by a loss of cones eventually causing blindness. Functional and structural characterization of the retinal degeneration was performed in 2 mouse models of RCD: *rd10* (*Pde6b* recessive) and P23H/+ (Rho dominant mutation) mice.

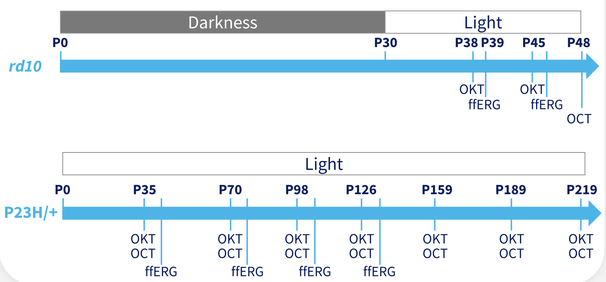
Materials & Methods

rd10 mice were housed either in normal light cycle (NLC) or in darkness (from birth to postnatal day (P) 30 before transfer to NLC on P31 to delay retinal degeneration). P23H/+ mice were housed in NLC. Animals were evaluated up to P48 (*rd10*) or P220 (P23H/+). Retinal histology, structure and function were evaluated by H&E and immunohistochemistry (IHC), optical coherence tomography (OCT), optokinetic (OKT) and full field retinography (ffERG).

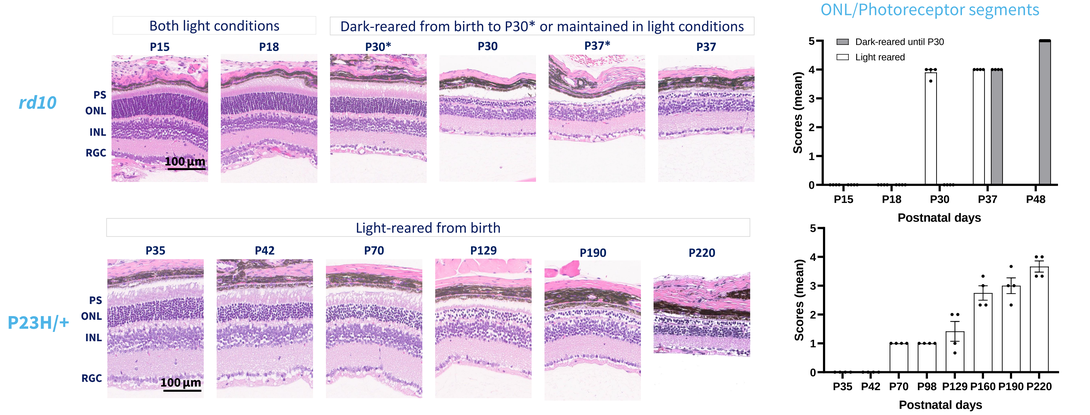
Results

In *rd10* mice, the outer nuclear layer (ONL) was significantly reduced in light-reared animals at P30 while it appeared intact in dark-reared mice. Once these dark-reared mice were transferred to NLC, there was a rapid degeneration with only 1 layer of nuclei remaining at P48. In the P23H/+ mice, ONL thickness decreased very slowly starting from P70 with only 1-3 nuclei layers at P220. In both models, cone and rod function (ffERG) were drastically reduced in comparison to WT mice as early as the first timepoint evaluated (P39 for the dark-reared *rd10* mice and P37 for P23H/+mice). Visual acuity (optokinetic tracking: OKT) in dark-reared *rd10* mice was reduced by 25% as early as P38 and ~50% at P45. On the contrary, P23H/+ visual acuity was generally comparable to WT levels until P220. Dark-reared *rd10* mice were eventually selected for the definitive pharmacological assessment. This housing condition allowed sufficient time for transgene expression following subretinal administration at P18 prior to rapid onset of the degeneration following light exposure, thus allowing the evaluation of a slow-down of retinal degeneration

Study design

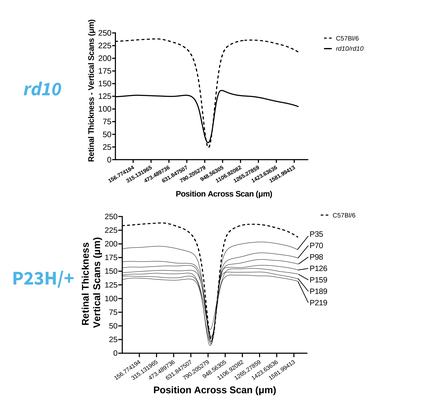


Histology



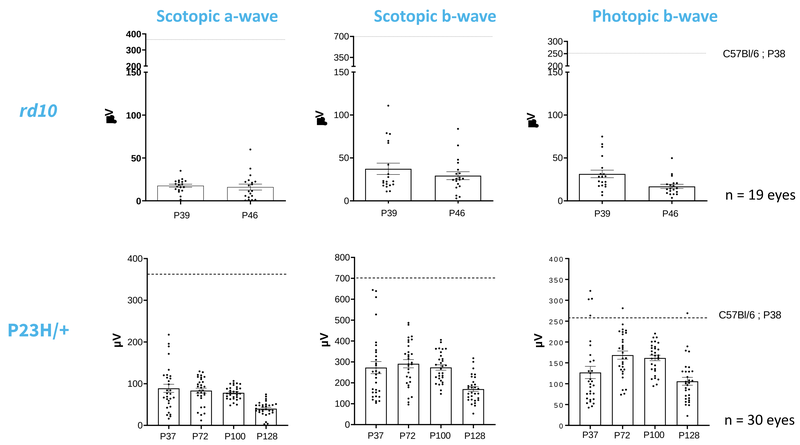
⇨The *rd10* mouse model is a fast-progressing model of RCD which undergoes rapid retinal degeneration upon exposure to light, with an almost complete loss of the photoreceptor segments (inner and outer segments) and the majority of the ONL by P30. In order to slow-down retinal degeneration, mice were dark-reared from birth to P30. In contrast, P23H/+ mouse model exhibits a slower retinal degeneration that spans over months when exposed to light conditions, (n ≥ 4 eyes)

Retinal thickness (OCT)



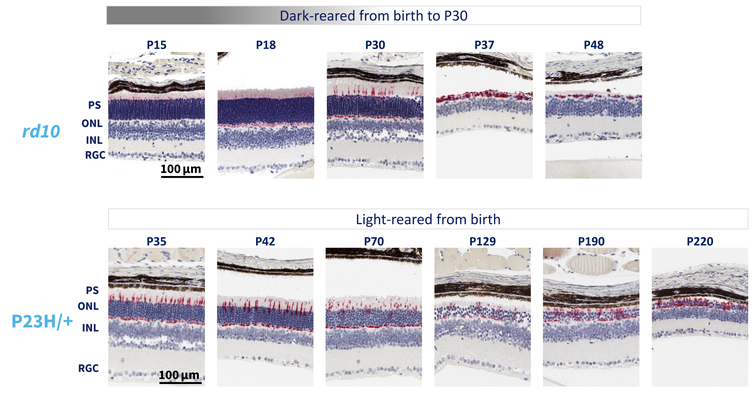
⇨Retinal thickness decreases more rapidly in *rd10* mice than in P23H/+ over time confirming *rd10* as a fast-progressing model of RDC

Retinal function (ffERG)



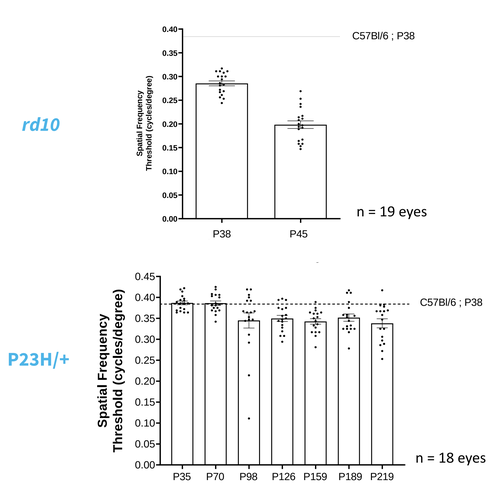
⇨In both models, photoreceptor function (ffERG) were drastically reduced in comparison to WT mice as early as the first timepoint evaluated.

Cone arrestin staining



⇨Cone arrestin staining confirms that the only row of nuclei that persists in the ONL at P48 in *rd10* retina is mainly composed by cone photoceptors. In the P23H/+ retina, most of the photoreceptors that persist at P220 are cone photoreceptors and their inner segments are still present.

Optokinetic tracking (OKT)



⇨Optokinetic tracking shows a decrease in *rd10* mice as early as P38 which continues at P45. On the contrary, it was almost maintained to WT levels until P220 in P23H/+ mice.

Conclusion

Our results highlight that the selection of the animal model, housing conditions and pharmacological assessments are critical and should be done in the context of the mechanism of action of the drug. Moreover, it is important that the model be characterized in the experimental conditions of the pharmacology study. The dark-reared *rd10* mouse model was eventually selected for the pharmacological assessment of SPVN06 using OKT as it provided the appropriate biological framework to evaluate a slow-down in visual acuity upon therapeutic intervention. The degeneration of the P23H model was too slow.

PS: photoreceptor inner and outer segments; ONL, outer nuclear layer; INL, inner nuclear layer; RGC, retinal ganglion cells

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