SPVN06, a novel mutation-independent AAV-based gene therapy, dramatically reduces vision loss in the *rd10* mouse model of rod-cone dystrophy

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Purpose

Rod-Cone dystrophies (RCD) are inherited neurodegenerative diseases characterized by photoreceptor degeneration, eventually causing blindness. In all RCD, degeneration is first observed in rods, and subsequently in cones, in large part due to a lack of trophic support. Greater than 1.5 million individuals worldwide are affected by RCD with numerous genes identified. **The intended biological effect of SPVN06 is the slow-down of cone cell degeneration, mediated by RdCVF and RdCVFL transgene expression in retinal cells, regardless of the causative mutation.** SPVN06 early nonclinical development included several pharmacology studies in *rd10* mice, a fast-progressing model of RCD.

SPVN06

SPVN06 is a novel AAV-based drug candidate encoding within the same vector the human cDNAs for trophic factor Rod-derived Cone Viability Factor (RdCVF) and thioredoxin enzyme RdCVF-Long (RdCVFL), both isoforms of the *NXNL1* gene. RdCVF and RdCVFL expressions have been shown to synergistically prevent loss of cone function through a dual mechanism of action:

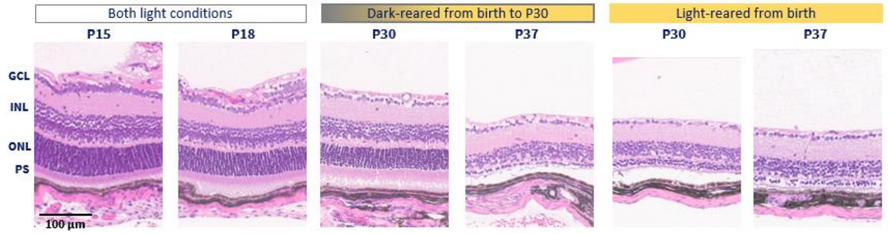
- stimulation of aerobic glucose metabolism by RdCVF secreted by rods,
- prevention of oxidative damage by RdCVFL (intracellular).

Methods

20 *rd10* mice were born and raised in darkness until transferred to regular cyclic light (~40 lux within cages) on postnatal day P31 up to study termination at P48. The studies were conducted at EyeCRO. At P15 or P18, the animals received a bilateral subretinal administration of 1 µL of vehicle or SVPN06 at 1E8 vg/eye. SPVN06 effect on retinal function and structure was evaluated by full-field electroretinography (ffERG), optokinetic (OKT), optical coherence tomography (OCT) and histology. Retinal biodistribution of SPVN06 DNA and transgene RdCVF/L mRNA was quantified 1-month after injection by qPCR and RTqPCR.

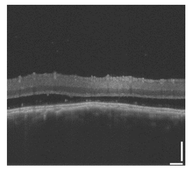
rd10 mouse model: a fast-progressing model of RCD

Histological evaluation of the retina of dark-reared and light-reared naïve *rd10* mice



GCL: ganglion cell layer; INL: Inner nuclear layer; ONL: outer nuclear layer; PS: photoreceptor segments

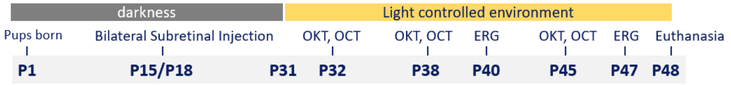
Spontaneous transient retinal detachment



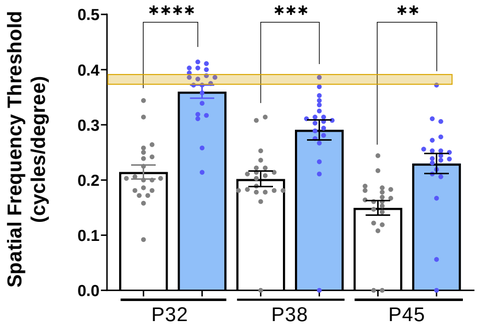
rd10 naïve retina at P48, Fundus Circle OCT

The *rd10* mouse model is an **aggressive 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.

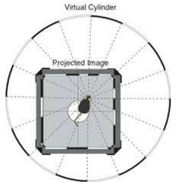
Significant improvement of visual function by OKT



Visual acuity measured by OKT



Mean ± SEM ; ** p<0.01 *** p<0.001 and ****p<0.0001; 1-way ANOVA; n=20 eyes

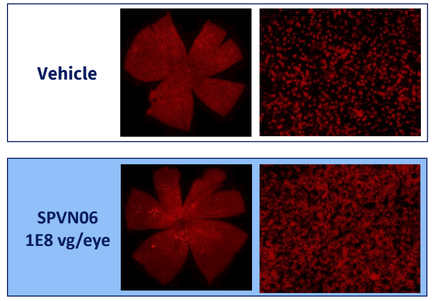


Vehicle

SPVN06 1E8 vg/eye

WT mouse level

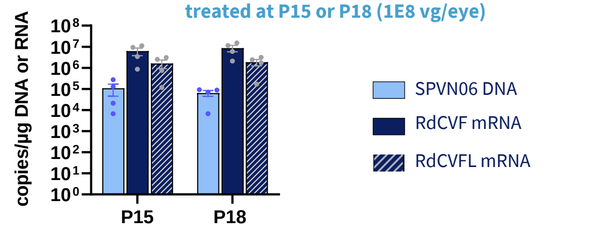
Cone density assessment



Retinal flat mounts, PNA staining x40, Optic Nerve Area

Biodistribution

SPVN06 and transgene quantification in *rd10* mouse retina treated at P15 or P18 (1E8 vg/eye)



Results and Discussion

A **highly significant protection of the visual function (OKT)** was noted at P32 ($p<0.0001$) when the animals received SPVN06 1E8 vg/eye at P18. The level of visual function in SPVN06-treated eyes was similar to wild-type (WT) levels in a majority of the eyes at P32. Only ~50% of the visual function remained in vehicle-treated animals. At the later timepoints (P38 and P45), the difference between the 2 groups remained significant, although visual loss continued in both vehicle and SPVN06-treated eyes due to the progressive nature of the disease that involves other physiopathology mechanisms.

There were no significant SPVN06-related changes in OKT when injection was conducted at P15, suggesting that the stage of the retina maturation is important for this product. The retina is fully mature at P21.

There was no SPVN06-related effect on the ffERG or on the retina morphology (measure of the photoreceptor outer nuclear layer by OCT) detected - data not presented.

Analysis of PNA staining on flat mount retinas showed a **greater cone density in SPVN06 treated-eyes at P48**. Histology evaluation (H&E staining) at the same timepoint showed that **treatment was well tolerated** but didn't reveal an obvious protection of the outer nuclear layer and/or photoreceptor inner/outer segments.

Conclusion

SPVN06 subretinal administration at 1E8 vg/eye dramatically protects retinal degeneration in *rd10* mice, a fast-progressing model of RCD, supporting clinical development (abstracts #3709194 & #3713301).

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