Poster ID
P225

Gene-Independent Strategies for Cone Preservation in Inherited Rod-Cone Dystrophies

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Disease Background

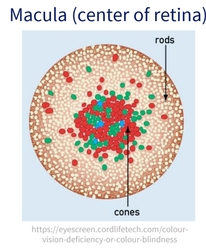
- Rod-cone dystrophies (RCD) are a heterogenous group of rare inherited retinal disorders sequentially affecting rod and cone photoreceptor cells on the retina:
  1. **Rods** degenerate due to a pathogenic gene variant
     - First symptom is typically night blindness
  2. **Cones** degenerate subsequently, due to loss of trophic support from rods
     - Progressive loss of color vision and visual field constriction leading to "tunnel" vision
     - In advanced stage, loss of visual acuity
- To date, RCD have been associated with variants in more than **300 genes**. Modes of inheritance can be dominant, recessive, or X-linked.
  - Clinical development of genotype-dependent therapies will not be possible for all pathogenic gene variants
- Currently, only one treatment is approved to treat a specific form of RCD caused by variants in the *RPE65* gene (Luxturna®, Novartis) → 1-3% of the RCD population
  - Unmet medical need remains high for RCD patients
- Gene-independent therapies could represent a broader treatment option for RCD patients

SPVN06: *RdCVF/RdCVFL*

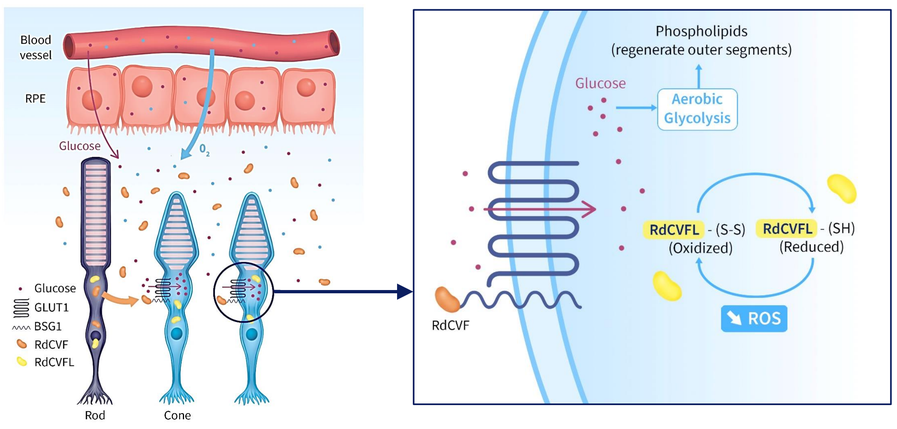
I. Healthy Retina

Rods :
- Low thresholds of light sensitivity and saturation → vision in dim-light conditions

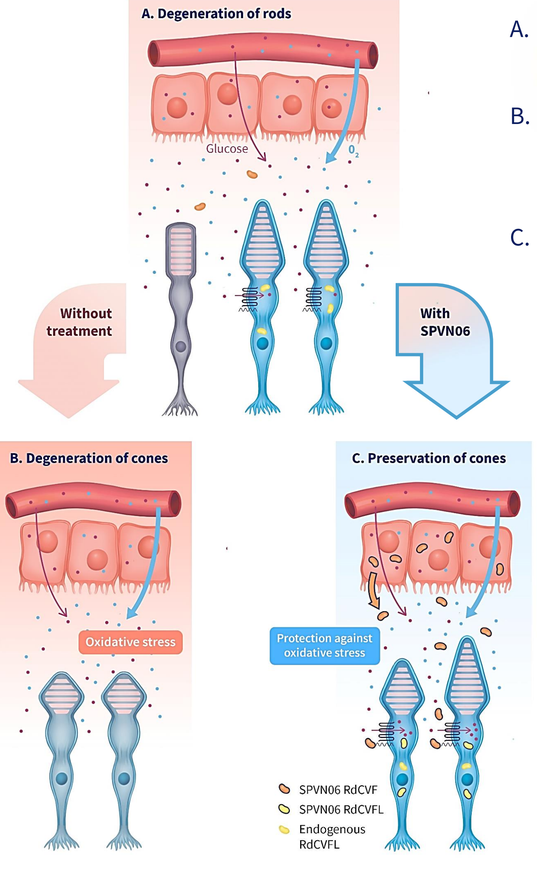
Cones :
- Activated at higher light intensities → vision in daylight conditions
- Higher density in center of macula (fovea) → visual acuity
- 3 types (red, green, or blue)→ color vision



- **RdCVF** (rod-derived cone viability factor) = **trophic factor** secreted by rods to **promote cone metabolism** by stimulating aerobic glycolysis [1]
- **RdCVFL** (long isoform of RdCVF) = **thioredoxin** that helps **mitigate oxidative stress** in rods and cones [2]
  - RdCVF/L are two isoforms of *NXNL1* gene acting synergistically to promote cone function



II. Mechanism of Action of SPVN06 in Rod-Cone Dystrophy



A. Rods degenerate due to a pathogenic gene variant → they stop secreting RdCVF to support cone metabolism

B. Cones degenerate due to lack of RdCVF, but also to increased oxidative stress (as rods no longer consume the large quantities of oxygen present in the retina)

C. The **dual mechanism of action** of SPVN06 gene-independent therapy includes:

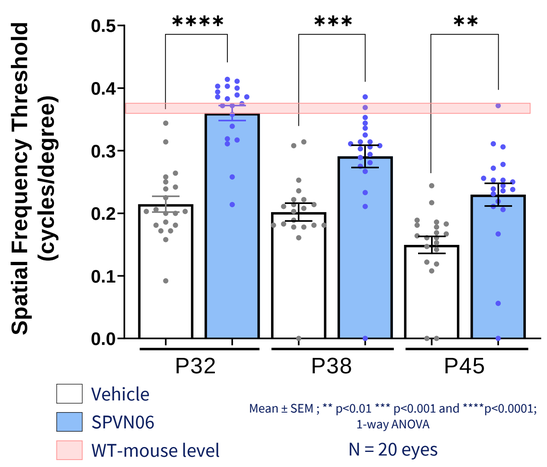
- ❖ Expression of RdCVF in cells surrounding photoreceptors (e.g., RPE) to provide trophic support to cones
- ❖ Overexpression of RdCVFL in cones to boost their natural defense mechanism against oxidative stress

➢ SPVN06 aims to **slow down cone degeneration** and **prolong useful central daylight vision**, <u>regardless of the pathogenic gene variant</u>

III. Proof of Concept of SPVN06

Highly significant protection of the visual function

- *rd10* mouse model of RP: recessive biallelic mutations in *PDE6b* gene
- Animals reared in darkness until P31
- Bilateral subretinal injections at P18, with SPVN06 at 1E8vg/eye or vehicle
- Optokinetic tracking (OKT) at Day 14 (P32), Day 20 (P38), and Day 27 (P45) → equivalent to visual acuity testing



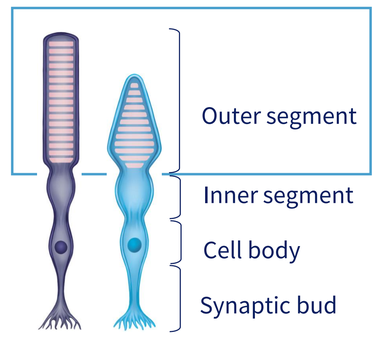
See also ESGCT 2022 **poster #P228** by Gautron *et al.*
Nonclinical safety and pharmacokinetic assessment of SPVN06, an AAV-based gene therapy for the treatment of rod-cone dystrophies

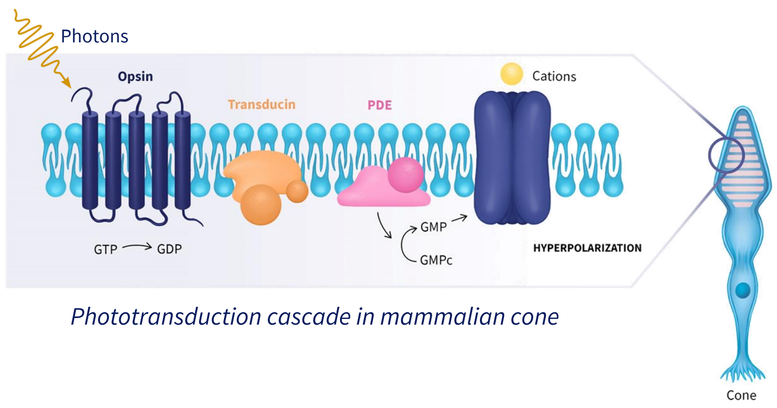
SPVN20: *GIRK*

I. Healthy Retina

- Cone and rod photoreceptors are retinal cells capable of **phototransduction**, *i.e.*, transformation of light energy into electrical signal → transmitted to brain to process visual scene
- Phototransduction cascade involves opsins expressed on the membrane of the photoreceptor **outer segments**

Phototransduction occurs in outer segments

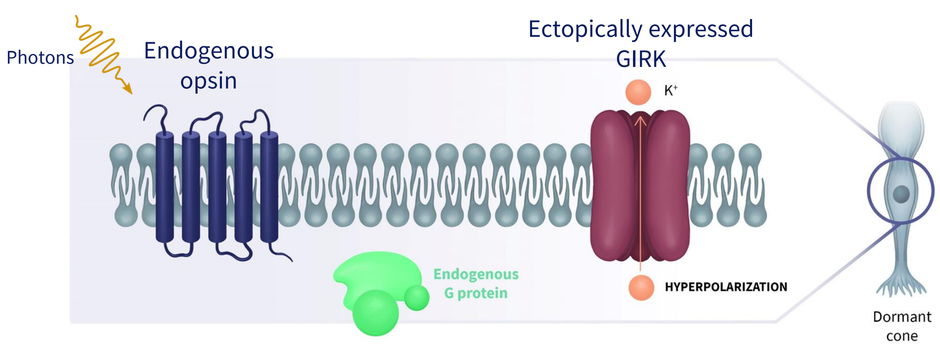




Phototransduction cascade in mammalian cone

II. Mechanism of Action of SPVN20 in Rod-Cone Dystrophy

- In RCD, outer segments degenerate = ↘ phototransduction activity
- GIRK is a G-coupled gated inward rectifying potassium channel mostly expressed in neurons of the brain, that can hyperpolarize excitable cells
  - When ectopically expressed in dormant cones, GIRK is able to restore a **short phototransduction cascade** using endogenous opsins present on the membrane of the **cell body**



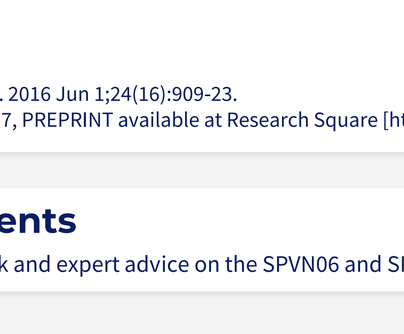
➢ SPVN20 aims to **restore photosensitivity** in dormant cones, therefore **improving visual acuity and color vision** in patients with RCD, <u>regardless of the pathogenic gene variant</u>

III. Proof of Concept of SPVN20

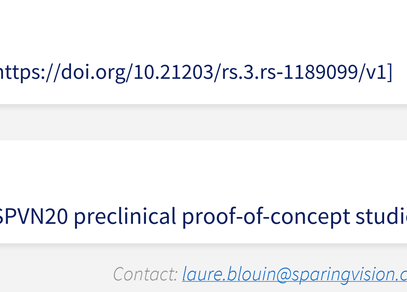
Remaining cone opsins are still functional and able to induce a light response in RP mice [3]

- huP347S$^{+/-}$ mouse model of RP: mutation in monoallelic knocked-in human *RHO* gene
- At P15, unilateral subretinal injection with of AAV-GIRK (and PBS-pluronic 0.001% in contralateral eye)
- At Day 45 (P60), optokinetic tracking → equivalent to visual acuity testing, and electroretinogram (ERG) → measures the electrical response of the retina to a light stimulus

<u>Photopic response (ERG)</u>



<u>Visual acuity (OKT)</u>



PBS (control)
GIRK
WT-mouse level

Mean ± SEM ; ** p<0.01;
Unpaired two-tailed non-parametric Mann-Witney's test
N = 6 eyes

See also ESGCT 2022 **poster #P219** by Kabou *et al.*
AAV delivery of G-protein gated K+ channel increases cone-mediated vision in the rd10 mouse model of Retinitis Pigmentosa

Conclusions

RdCVF/RdCVFL and *GIRK* gene therapies have respectively demonstrated preliminary efficacy in slowing down cone degeneration or restoring their function in animal models of RCD. As these approaches are independent from the underlying genotype, they have the potential to treat a wide range of rod-cone dystrophies, thereby addressing the high unmet need.

References

1. Aït-Ali N, Fridlich R, Millet-Puel G, *et al*. Rod-derived cone viability factor promotes cone survival by stimulating aerobic glycolysis. *Cell*. 2015 May 7;161(4):817-32.
2. Mei X, Chaffiol A, Kole C, *et al*. The Thioredoxin Encoded by the Rod-Derived Cone Viability Factor Gene Protects Cone Photoreceptors Against Oxidative Stress. *Antioxid Redox Signal*. 2016 Jun 1;24(16):909-23.
3. Simon CJ, Khabou H, Finzi M, *et al*. Reactivating the phototransduction cascade by universally applicable gene therapy preserves retinal function in Rod-Cone dystrophy. 2022 Jan 17, PREPRINT available at Research Square [https://doi.org/10.21203/rs.3.rs-1189099/v1]

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