SPARINGVISION

GENOMIC MEDICINES FOR OCULAR DISEASES

Development of a Mutation-Independent Gene Therapy for Cone Reactivation in the Treatment of Retinitis Pigmentosa

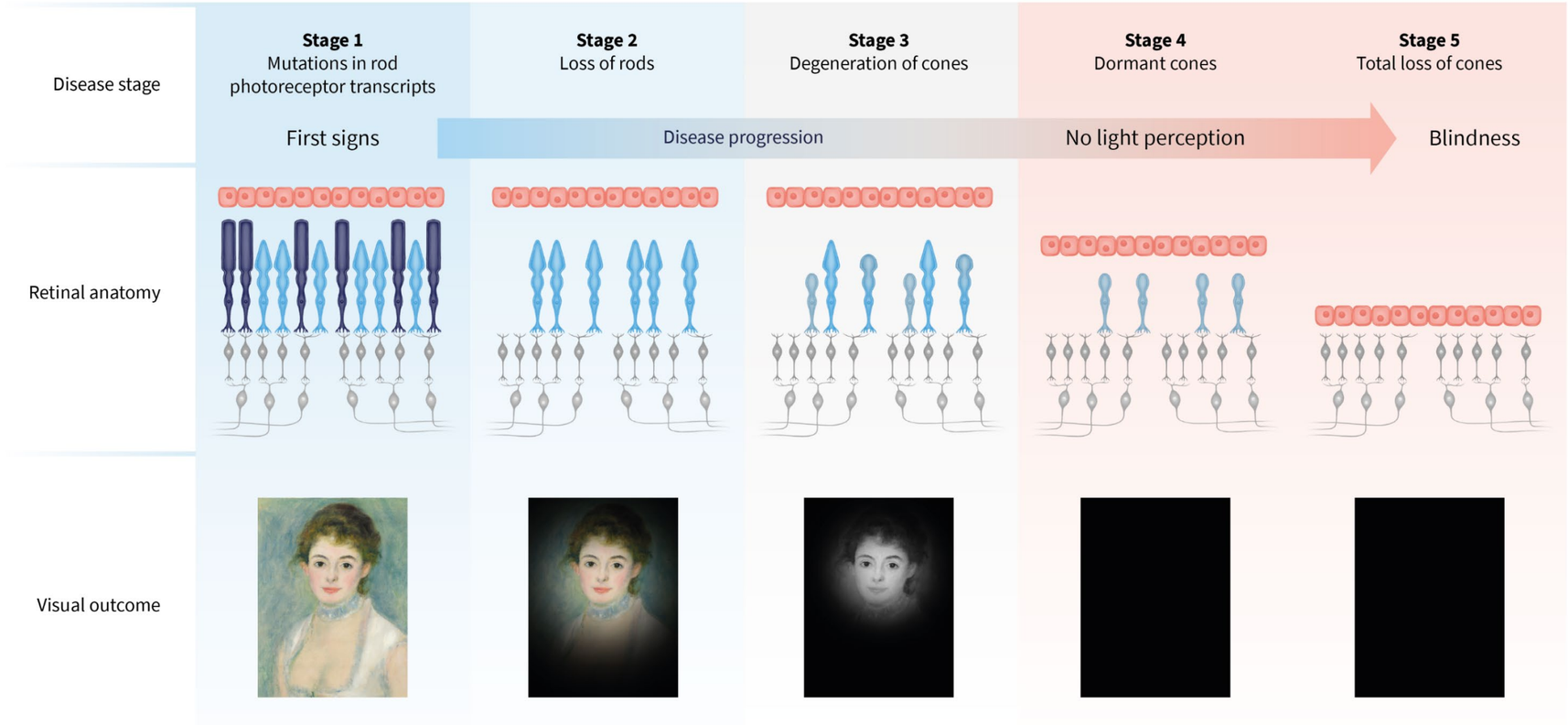
HANEN KHABOU, PH.D.

ASGCT ANNUAL MEETING, LOS ANGELES - MAY 20TH, 2023

Disclosure

I am an employee of SparingVision and hold shares in the company.

Retinitis Pigmentosa: progressive vision loss



- Most frequent inherited blindness, affecting 1.5 million people worldwide
- Rare: prevalence is 1/4000
- Progressive rod loss, followed by cone loss
- Eventually can lead to blindness

Mutation-independent gene therapy for RP treatment

High genetic heterogeneity

- Gene addition therapy for each gene not possible
- Only for recessive forms
- Unknown mutation → gene addition not possible

→ **Necessity to develop mutation-independent gene therapies**

1) Prevention of cone degeneration with Rod-derived Cone Viability Factor, RdCVF/RdCVFL

→ e.g. SPVN06, approved for clinical testing in patients

2) Restoration of cone activity

→ Development of SPVN20: Restoration of a short phototransduction cascade

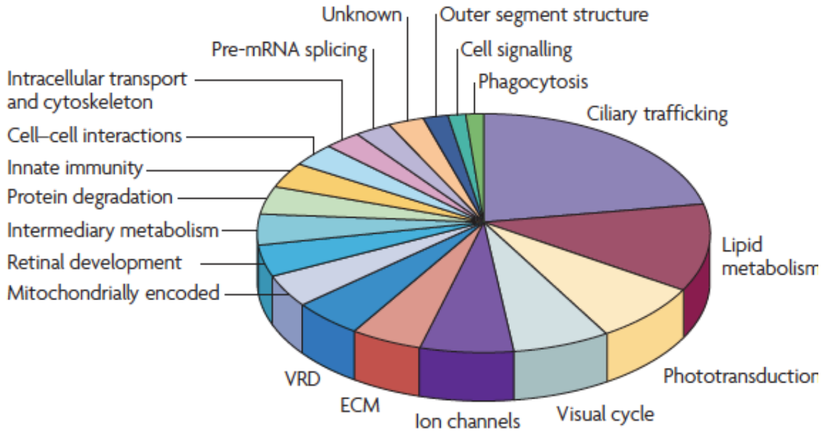
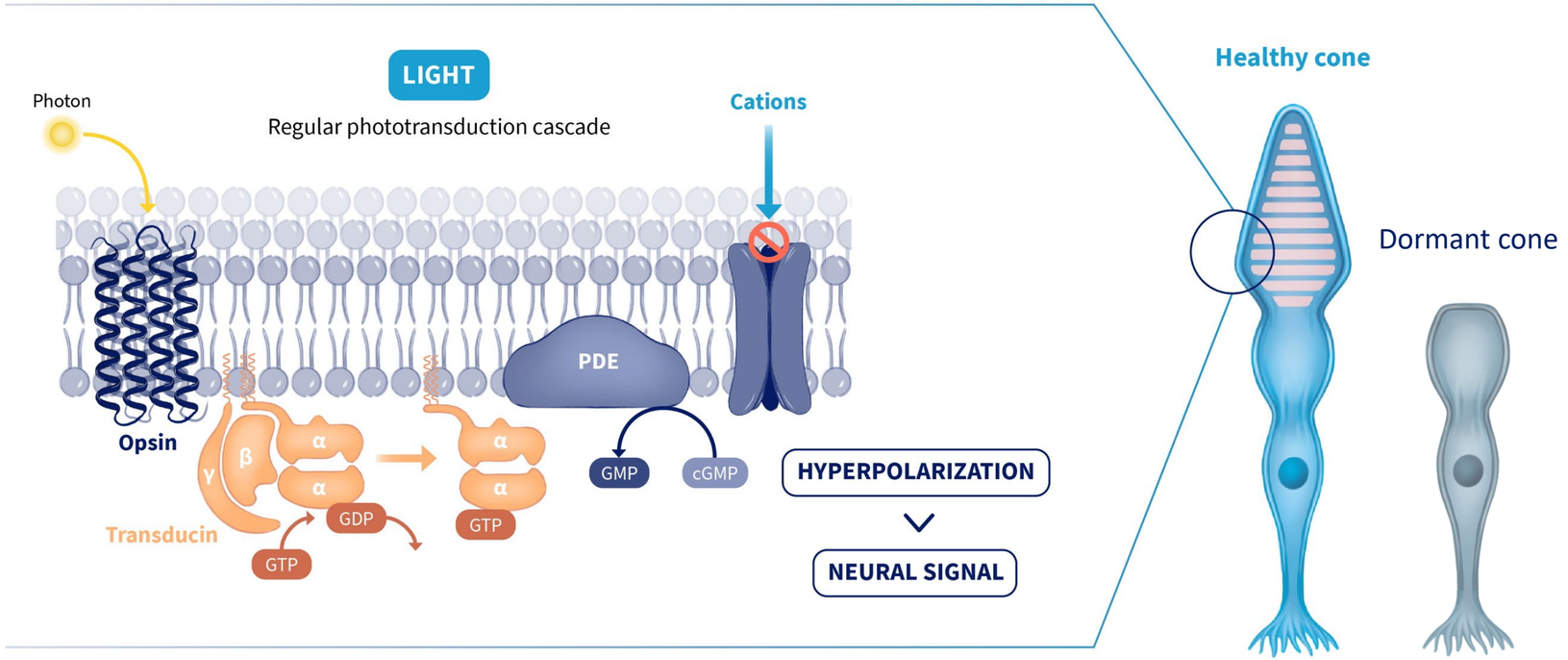


Figure 2 | **Functional categorization of genes that influence photoreceptor degeneration.** Pie chart showing the functional categorization of 146 genes implicated in PR degeneration. The data are from the Retinal Information Network

Wright et al., Nat Review Genetics, 2010

Phototransduction cascade in cone photoreceptors



- Phototransduction cascade: process with series of proteins involved in conversion of light to hyperpolarization of the photoreceptor

- In RP, proteins of the phototransduction cascade in cones are abnormal, e.g.
  - Phosphodiesterase (PDE)
  - Transducin (GNAT2)

Simon et al. (preprint), Hassal et al., 2020

→ **Dysfunctional cone**

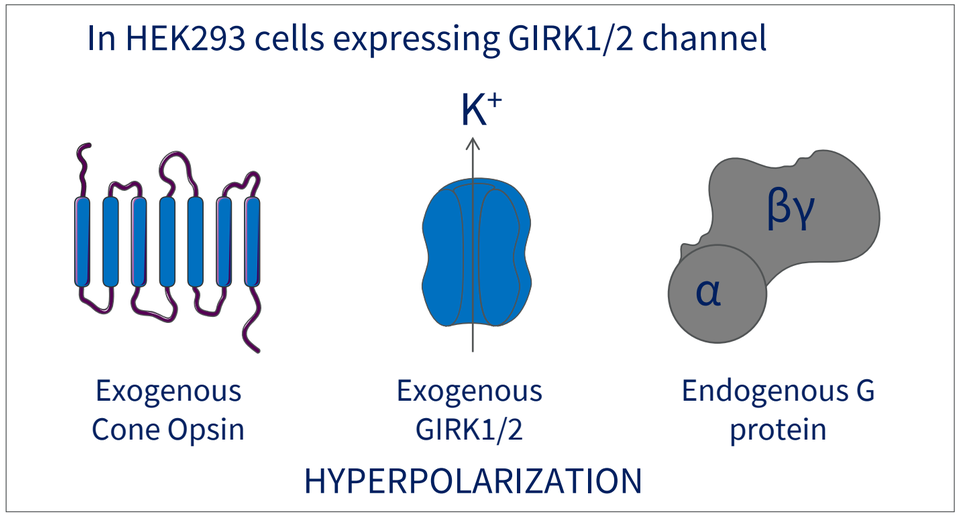
Can we provide an alternative phototransduction cascade?

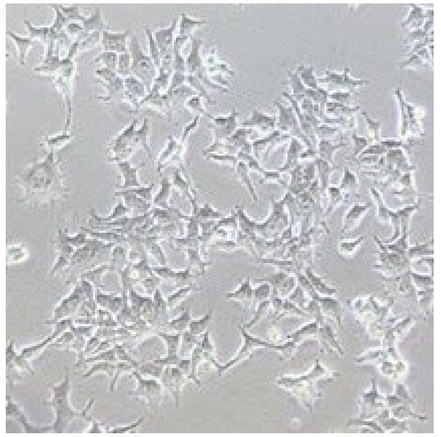
GIRK links GPCR activity to hyperpolarization

- **G-protein coupled inward rectifying K+ channel (GIRK)**
  1. Activation of a **G-protein coupled receptor (GPCR)**
  2. Recruitment of a G protein
  3. Activation of GIRK
  4. GIRK hyperpolarizes neurons

- Four distinct mammalian genes (GIRK1-4)
  - GIRK1-3 broadly expressed in the CNS
  - GIRK4 expressed mainly in the heart

Cone Opsin + GIRK1/2 *in vitro*





The cone opsin activates the GIRK channel via an endogenous G protein

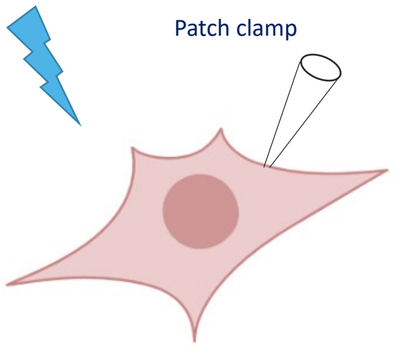
↓

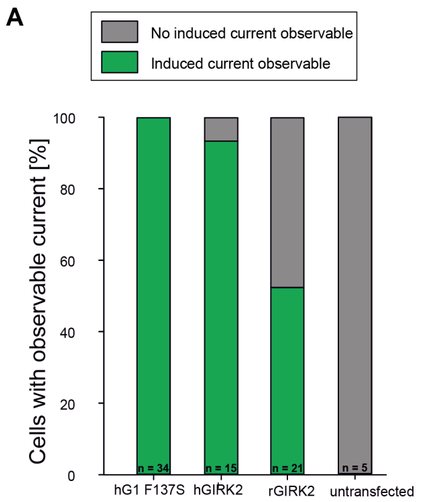
Light modulation

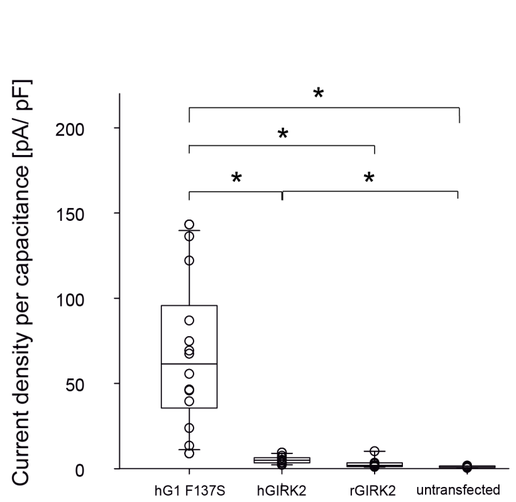
Masseck *et al.*, Neuron 2014

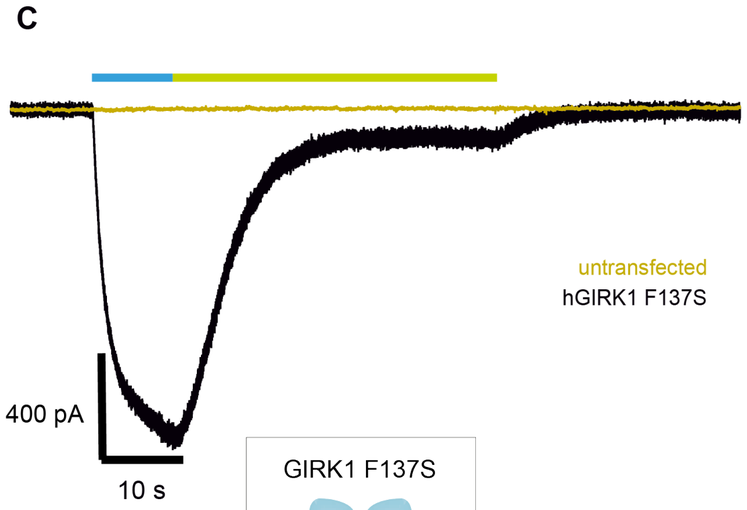
Light-responses recorded in vitro in cells co-expressing opsin and GIRK channels

Evaluation of GIRK effect in HEK cells stably expressing melanopsin using single cell patch clamp recordings









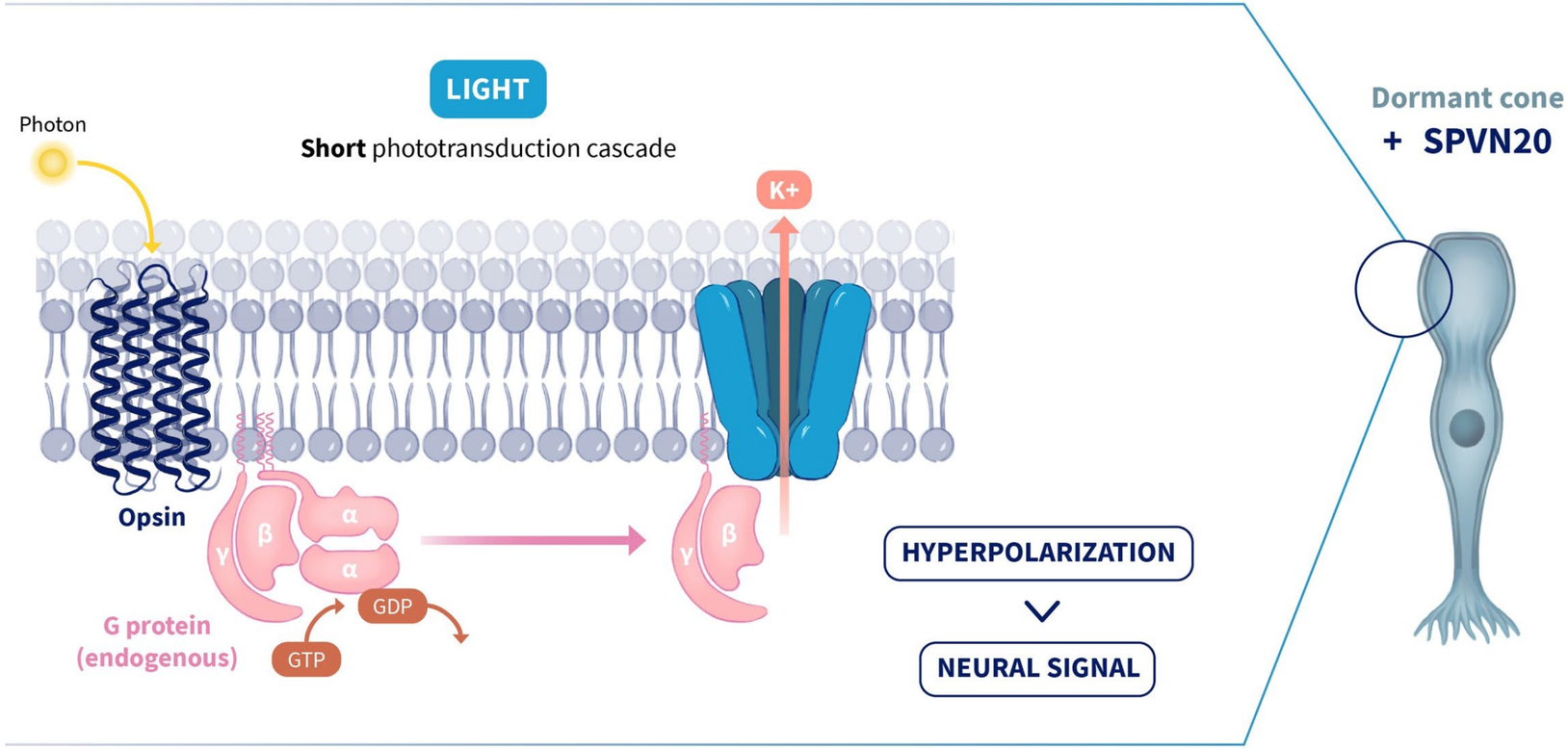
Mutated GIRK1 forms functional homomers

GIRK currents recorded upon light stimuli

→ **HEK cells become light – sensitive and –responsive**

→ **hGIRK1(F137S) is the most efficient variant: selection for development**

SPVN20: Restoration of cone activity using a ‘short’ phototranduction cascade?



- Activated opsin recruits an endogenous G-protein
- GIRK activated by the G-protein

→ Short phototransduction cascade relying on endogenous opsins: color vision expected to be restored

In vivo proof-of-concept in rd10 mice: vision restoration with GIRK1(F137S)

Objective: evaluation of GIRK effect on visual improvement

rd10/rd10 mice, single bilateral subretinal AAV8 administration

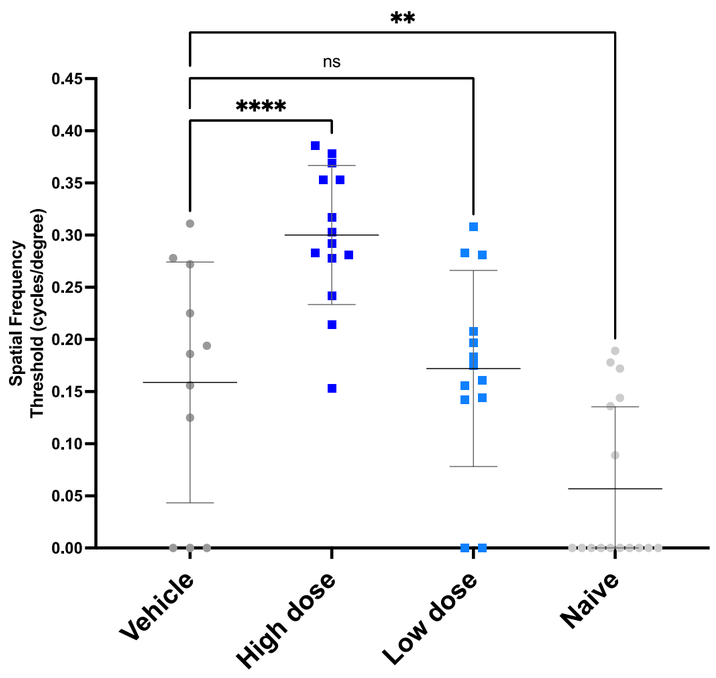
Arm	Treatment	Dose (vg/eye)	Number of animals (n=47)
1	Vehicle	-	8
4	AAV8-PR1.7-hGIRK1(F137S)	Higher dose	8
5		Lower dose	8
6	Uninjected	-	7

Optokinetic Reflex

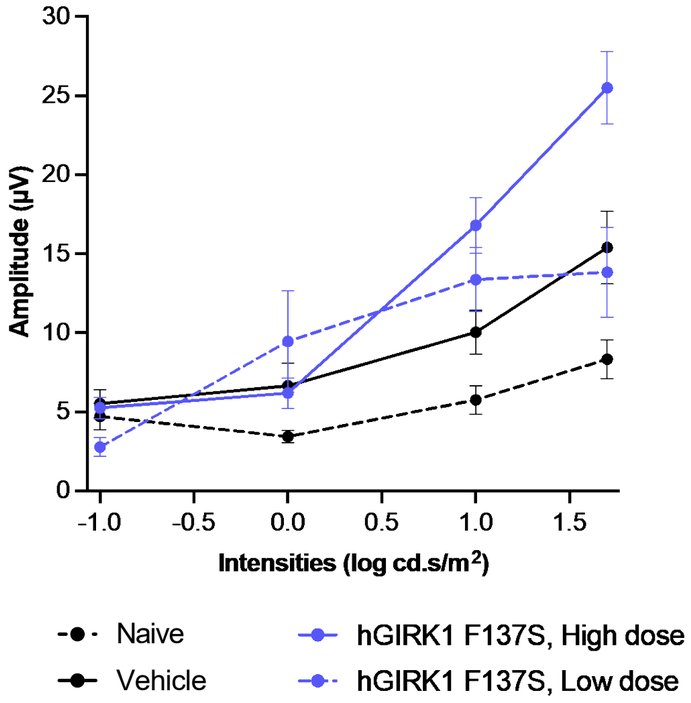
Electroretinogram schematic

In vivo proof-of-concept in rd10 mice: vision improvements, AAV8-GIRK subretinal delivery

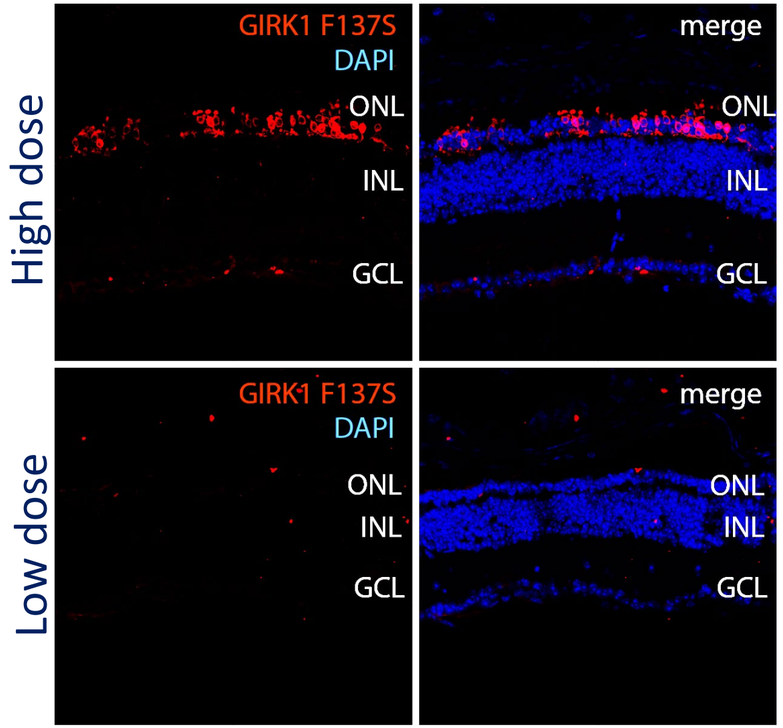
OKT at P37



ERG at P37



Histology at P60



→ Significant visual improvements 3 weeks after delivery

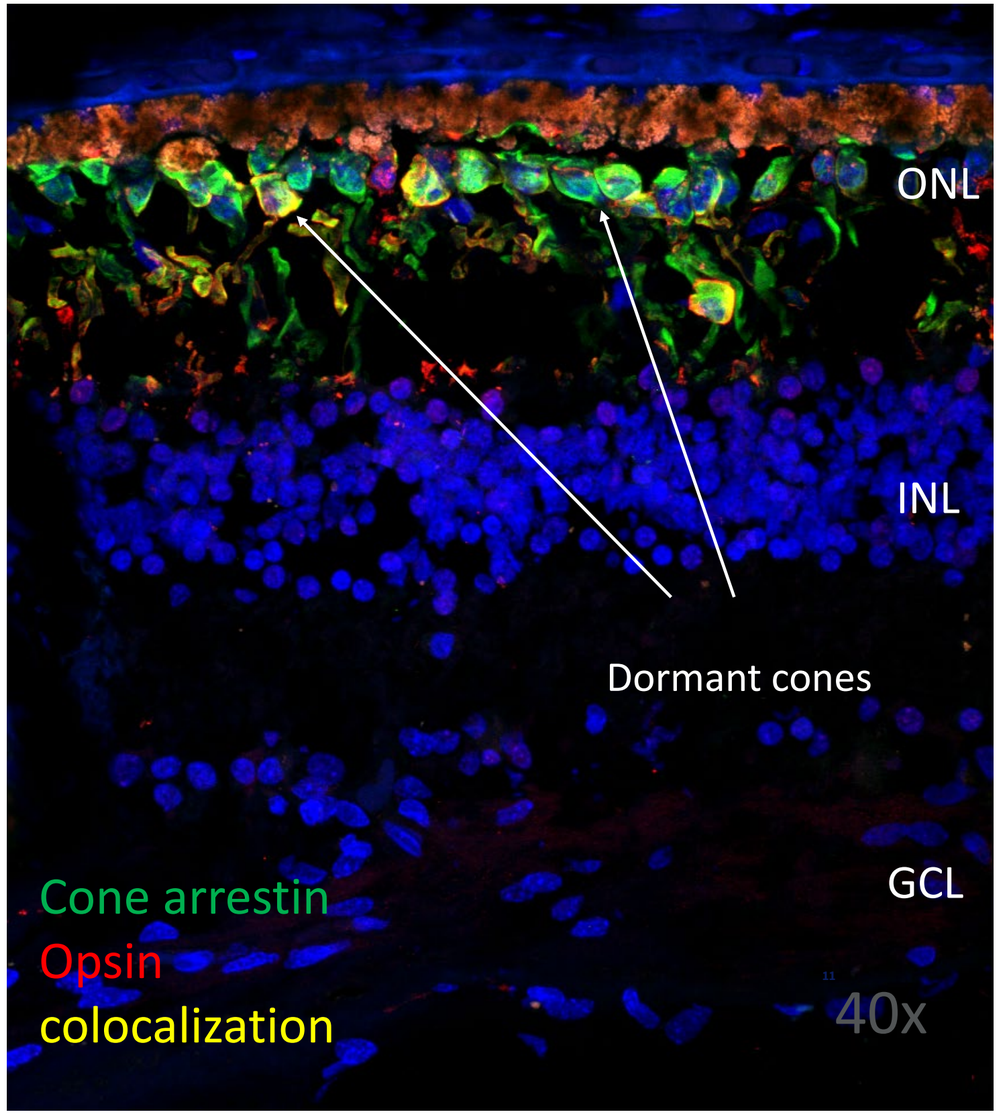
Statistical test: 1-Way ANOVA. Comparison with vehicle group*, p>0.05; **, p<0.01; ***, p>0.001

→ Higher dose at P37: significant vision improvements, consistent with GIRK expression

→ Effect no longer recorded at P48 or P60

→ Promising results in an extremely fast RP model

RP patients in late stage maintain cone opsin and arrestin



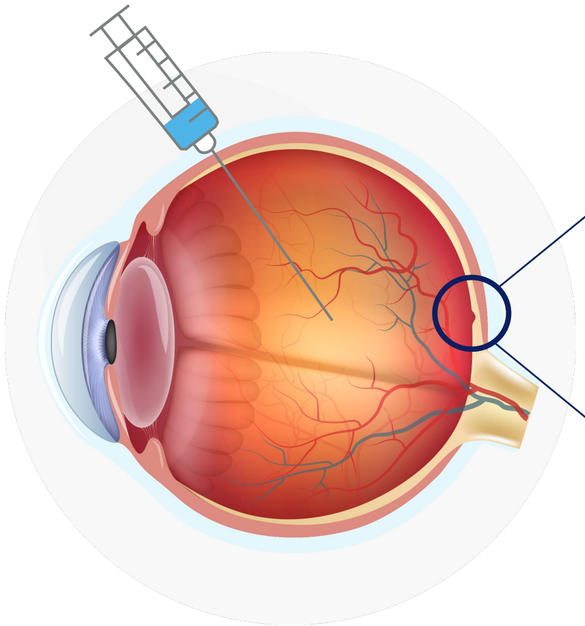
Simon et al., under revision

- 5 RP patients (FFB/Cleveland Clinic collection)
- Age: 63-92 years old
- Dormant cones were found in 4/5 RP patients

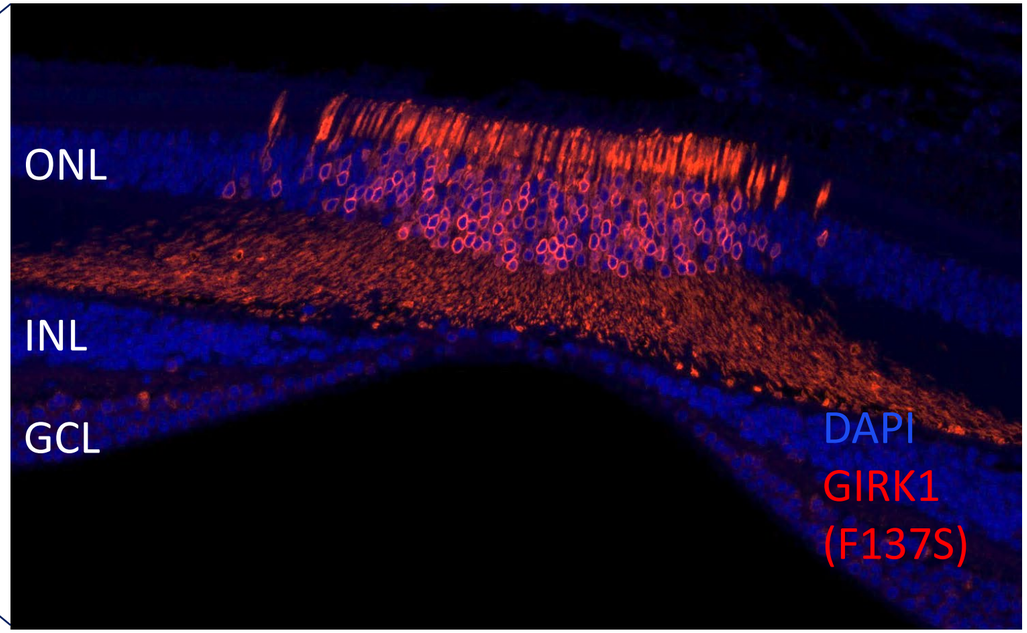
➢ **Strategy can be applied to human patients**

In vivo intravitreal delivery of SPVN20 in healthy NHPs results in strong GIRK expression in foveal cones

Intravitreal injection of SPVN20, $7^{e}10$ vg/eye
Necropsy at D84 and anti GIRK immunohistochemistry



Fovea



High number of foveal cones express GIRK1(F137S), at the cone membrane

Conclusions

AAV-GIRK gene therapy proof-of-concept

- GIRK provides restoration of a short phototransduction cascade
- GIRK restores cone function and improves vision in mouse models of RP

SPVN20 development

- CTA enabling studies underway, CTA planned for 2024
- Focus on IVT delivery, that is noninvasive to the retina, especially in fragile RP retinas
- Histology from RP patients' retinas support AAV-GIRK gene therapy rationale

→ Therefore, strong rationale to develop a gene therapy to deliver GIRK to late-stage RP patients with the aim of restoring vision

Acknowledgments

Institut de la Vision

Deniz Dalkara
Mélissa Desrosiers
Guillaume Labernede
Camille Robert

Ruhr University

Brix Mücher
Stefan Herlitze

SparingVision

Mehdi Gasmi
Florence Lorget
Cardillia-Joe Simon
Brynne Freshour
Lucie Churet
Mélanie Marie
Anne-Sophie Gautron

Cleveland Clinic/FFB

Vera Bonilha
Bela Anand-Apte

EyeCRO

Rafal Farjo
Alain Quimbao
Phillip Vanlandingham
Erin Livingston

Virscio

Quincy Edwards
Matthew Lawrence

StageBio

Dane Brady
Craig Zook