CORPORATE PRESENTATION

SPARINGVISION

GENOMIC MEDICINES FOR OCULAR DISEASES

October 2024

OUR VISION

A FUTURE FREE FROM BLINDING RETINAL DISEASE

Pioneering genomics to save sight

6 products
Gene therapy, CRISPR

€135 million
Raised to date

Cash runway supporting development of 2 lead products through clinical readout

$2.7 billion
Peak sales estimated in 2035 with SPVN06 in retinitis pigmentosa (RP) alone

SPVN06: LEAD GENE THERAPY PROGRAM

- Clinical-stage product with the **potential to preserve vision at whatever time of intervention.**
- **Gene-agnostic AAV-based gene therapy approach**, with retinitis pigmentosa (RP) as first indication. Extension planned to dry AMD/ GA.
- PRODYGY **Phase I/II clinical trial ongoing in RP**. Positive initial safety data at 12 and 6 months presented at Retina Society and Euretina in Sep. 2024.

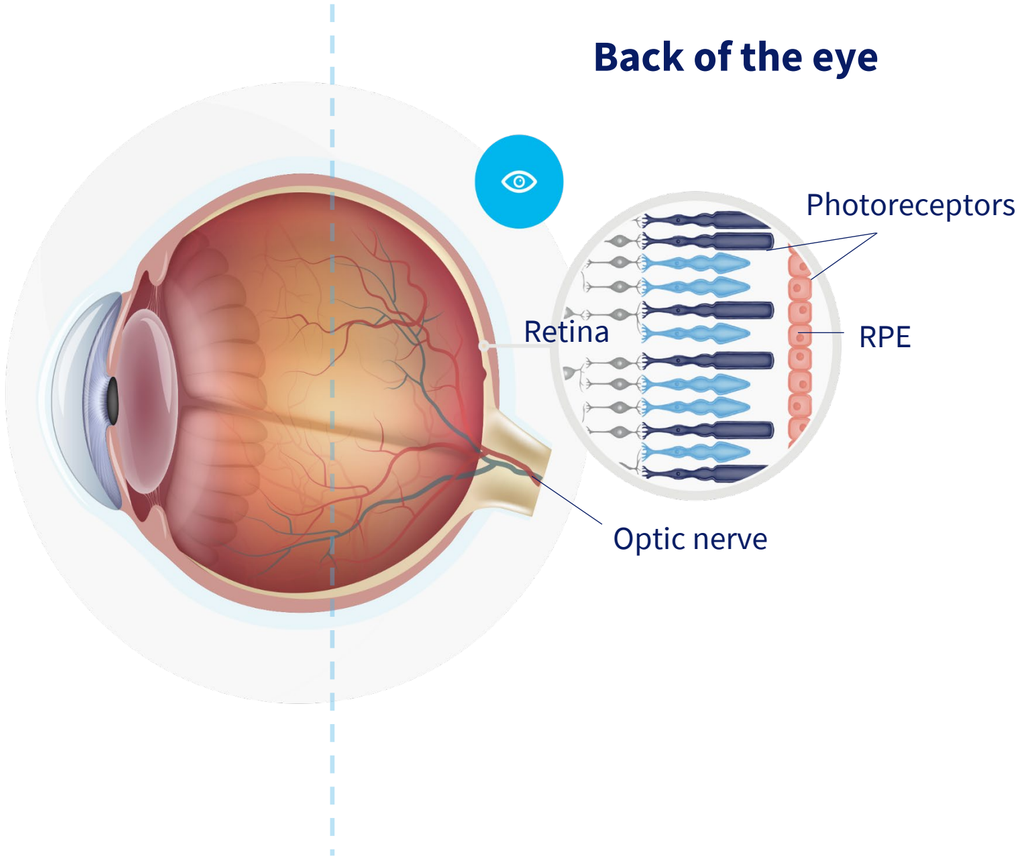
SPVN20: CO-LEAD GENE THERAPY PROGRAM

- Gene therapy product with the **potential to restore high acuity and color vision**
- **Gene-agnostic AAV-based gene therapy approach,** with late-stage RP as first indication
- CTA enabling studies ongoing; NYRVANA Phase I/II trial planned for 2025

4 OTHER GENOMIC PROGRAMS IN DEVELOPMENT

- **SPVN30**: Gene-agnostic AAV-based gene therapy approach. Research phase.
- **SPVN50/60/70**: CRISPR-based gene editing programs in ocular. Developed in partnership with Intellia THERAPEUTICS

A paradigm shift in genetic medicine: tackling prevalent diseases



Age related Macular Degeneration (AMD)	Dry AMD Geographic Atrophy Wet AMD	**~20MM AMD patients** (U.S.)[1] ~90% have dry AMD[1] **~1MM GA patients** (U.S.)[2]
Inherited Retinal Diseases (IRDs)	Retinitis Pigmentosa Choroideremia, Stargardt's, Usher, Rod-Cone Dystrophies	**~210,000 RP patients** (U.S./ EU)[3]
Glaucoma	Primary Open Angle Glaucoma Primary Angle Closure Glaucoma	**~4.3MM patients** (U.S.)[4]

Sources: 1. https://www.brightfocus.org/sites/default/files/Understanding-Macular-Degeneration-WCAG-2023.pdf ; 2. Cowen Ophthalmology Outlook 2022; 3. Cleveland Clinic/RP https://my.clevelandclinic.org/health/diseases/17429-retinitis-pigmentosa ; 4. Glaucoma: Facts & Figures | BrightFocus Foundation and Clearview Healthcare Partners 2024

Our pipeline

Matching the right technology to the right retinal disease

Product	Effect/MOA	Delivery	Transgenes	Lead indication	Preclinical			Phase I/II
					Discovery	Research	IND-enabling	
SPVN06	Vision preservation Gene Therapy	AAV	RdCVF/L	RP (stage 2 and 3)	✓	✓	✓	....
				Geographic Atrophy	✓	....		
SPVN20	Vision restoration Gene Therapy	AAV	GIRK	RP (stage 3 and 4)	✓	✓	....	
SPVN30	Vision restoration & preservation Gene Therapy	AAV	RdCVF + RdCVFL + GIRK	RP	✓	....		
SPVN50	Gene editing CRISPR	AAV or LNP	Target 1	Selected Undisclosed	✓	....		
SPVN60	Gene editing CRISPR	AAV or LNP	Target 2	Selected Undisclosed	✓			
SPVN70	Gene editing CRISPR	AAV or LNP	Target 3	To be selected				

A team of ocular genomics and industry experts

Stéphane Boissel
CEO

Daniel Chung
Chief Medical Officer

Mehdi Gasmi
Chief Scientific &Technology officer

Hélène Grimm
General Counsel

Florence Lorget,
Chief Development Sciences Officer

Anjeza Gjino
Chief Financial Officer
interim

Marie Uguen
Chief Regulatory and Quality Assurance Officer

- **Company creation:** 2016, spin-off from the Paris Vision Institute
- **Founders**: Profs. Thierry Léveillard and José-Alain Sahel; Dr. Deniz Dalkar, co-founder of Gamut Tx.
- **Headquarters**: Paris and Philadelphia, lab space with biolabs
- **Team:** 40c

Leading board of directors & investors

Joseph Papa (Chairman)
Frmr CEO, Bausch & Lomb

Laurent Arthaud
General Manager, BPI France

Stéphane Boissel
CEO, SparingVision

Jeanne Cunicelli
President, UPMC Enterprises

Sabine Dandiguian
Managing Partner, Jeito

Owen Smith
Partner, 4BIO Capital

Karen Wagner
Managing Partner, Ysios Capital

Russell Kelley, Ph.D.
Managing Director, RD Fund

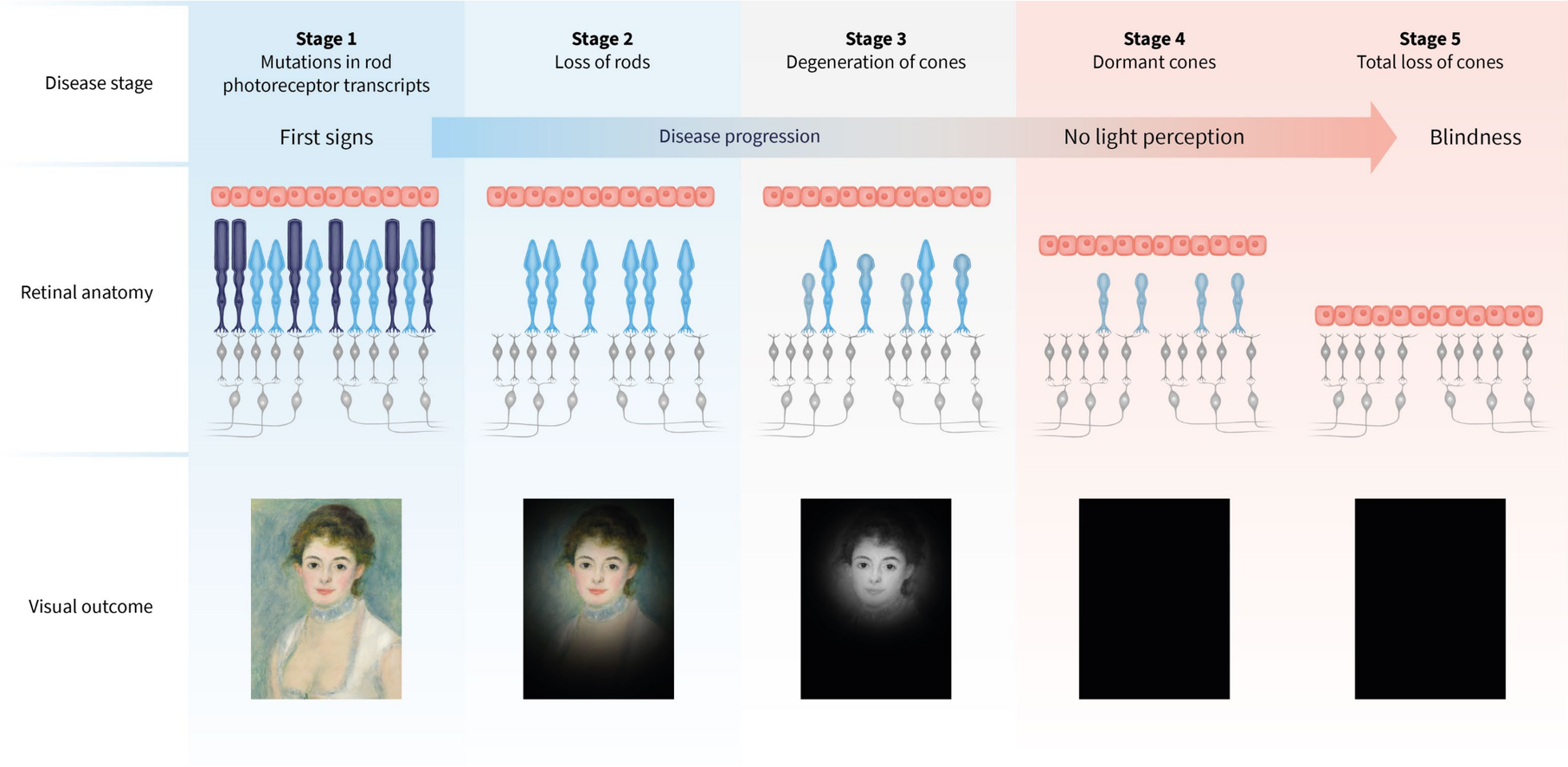
€135m

raised to date (Series A + Series B)

4BIO CAPITAL · AdBio partners · bpifrance · RD FUND RetinalDegenerationFund.org · FONDATION VOIR & ENTENDRE · Intellia THERAPEUTICS · Jeito · UPMC Enterprises · YSIOS CAPITAL

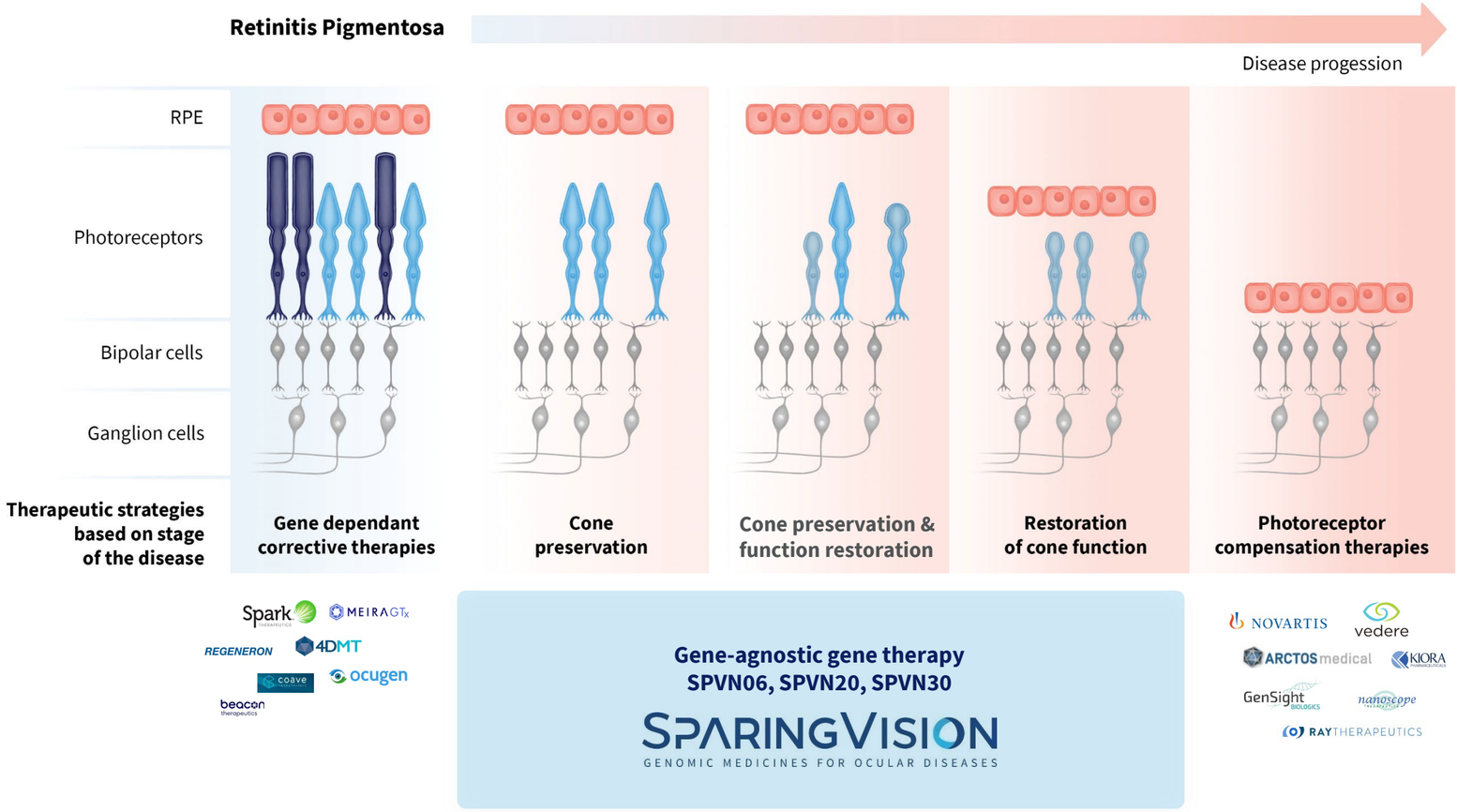
Evolution of Retinitis Pigmentosa

A slowly progressing disease, leading inevitably to blindness



Pioneering gene therapies for retinal diseases

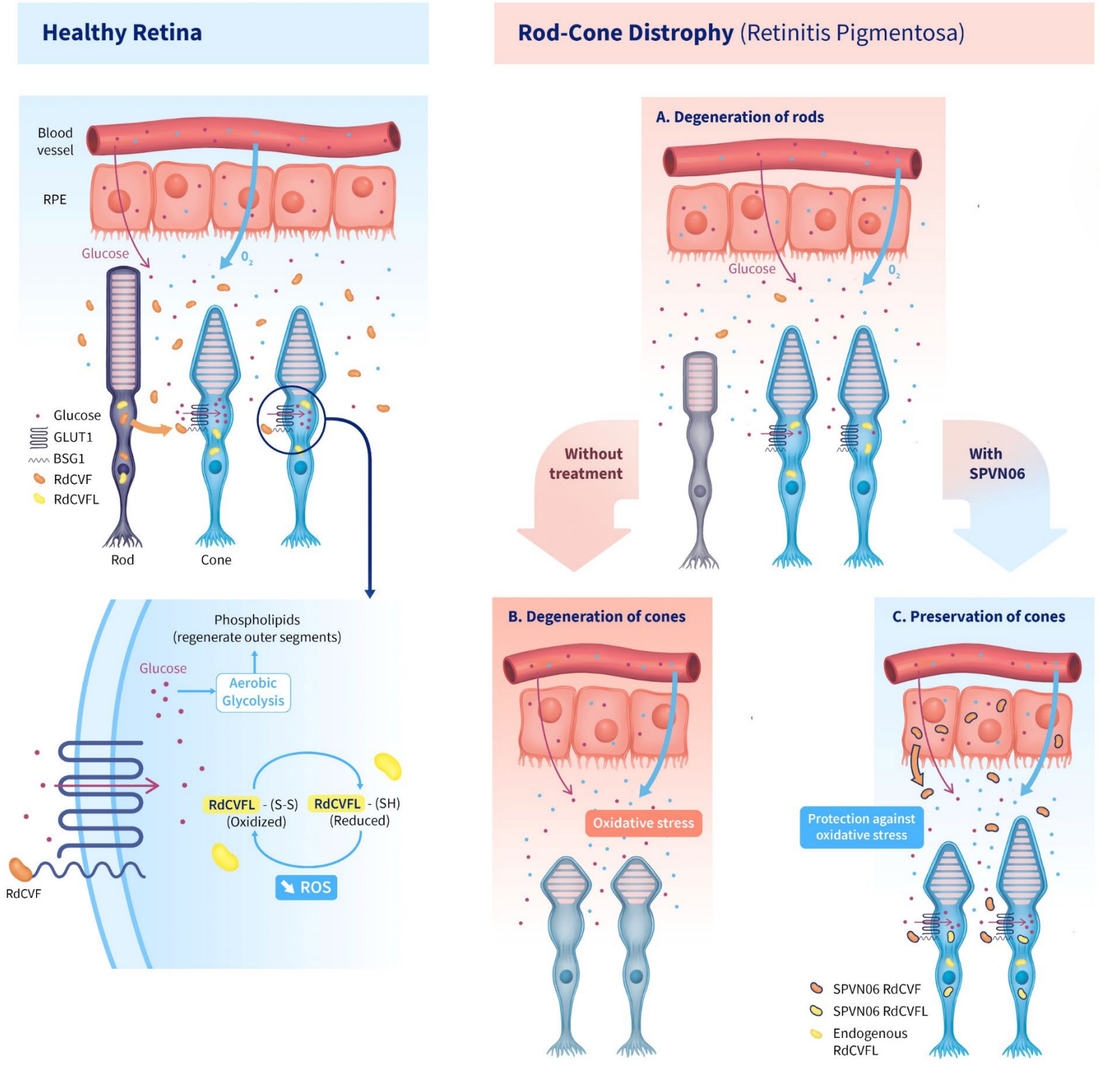
Large window of intervention, corresponding to the most common time of diagnosis



SPVN06: RdCVF/L synergize to protect photoreceptors

RdCVF stimulates glucose metabolism in cones, promoting renewal of their outer segments.

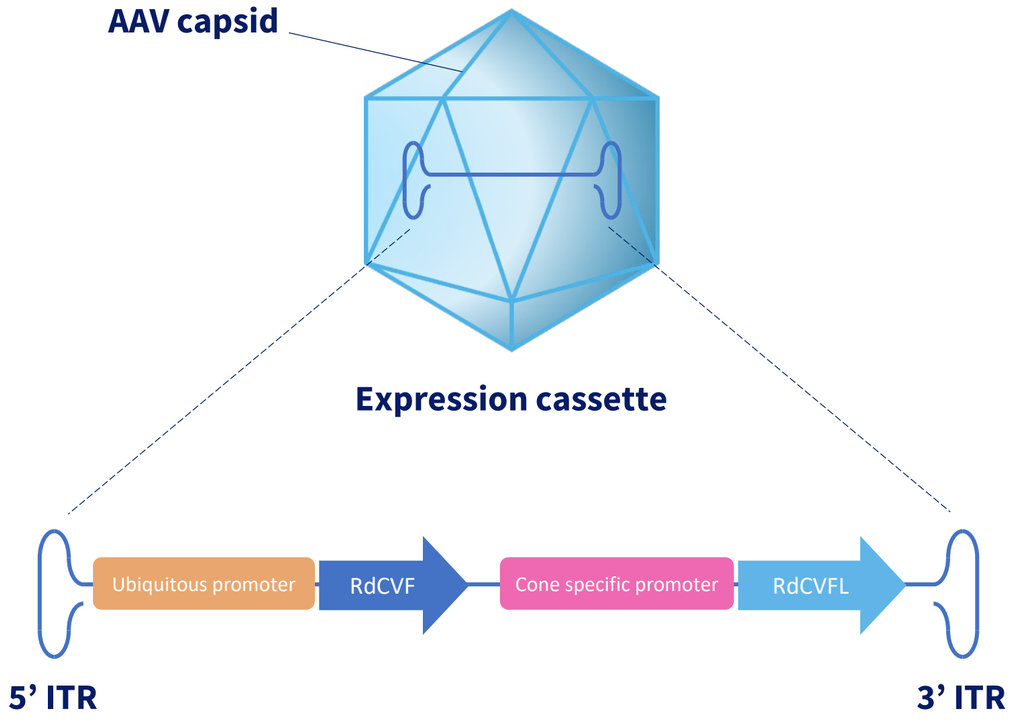
RdCVFL mitigates the effect of oxidative stress that increases in cones following rod death [1,2]



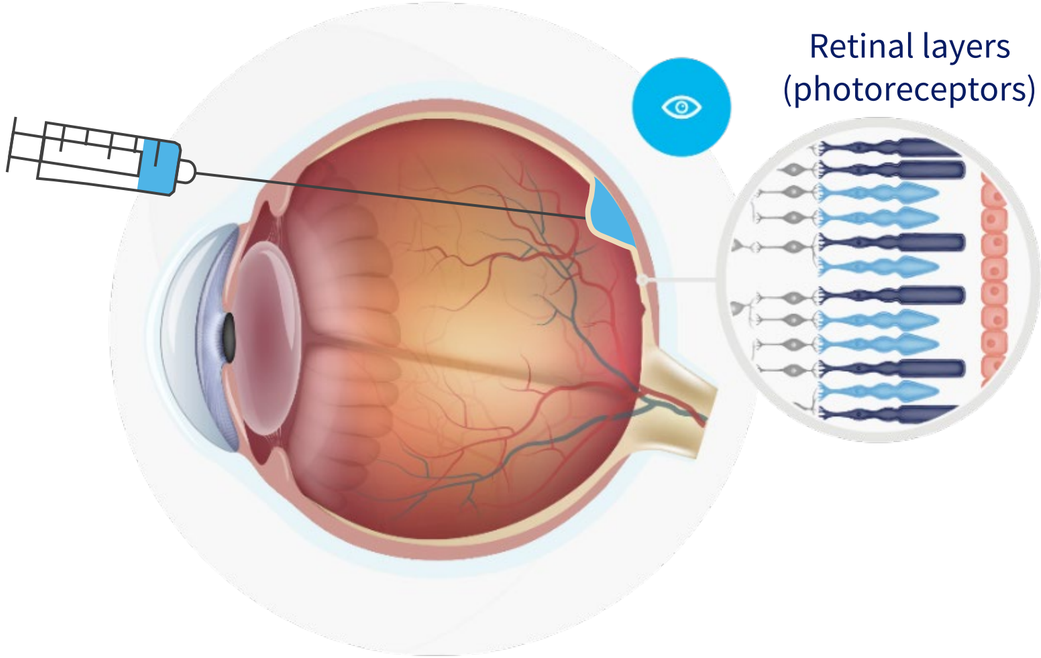
1. Byrne LC, et al. *J Clin Invest*. 2015;125(1):105-116
2. Mei et al. Redox Signal. 2016, 24, 909–923.

SPVN06 construct and route of administration

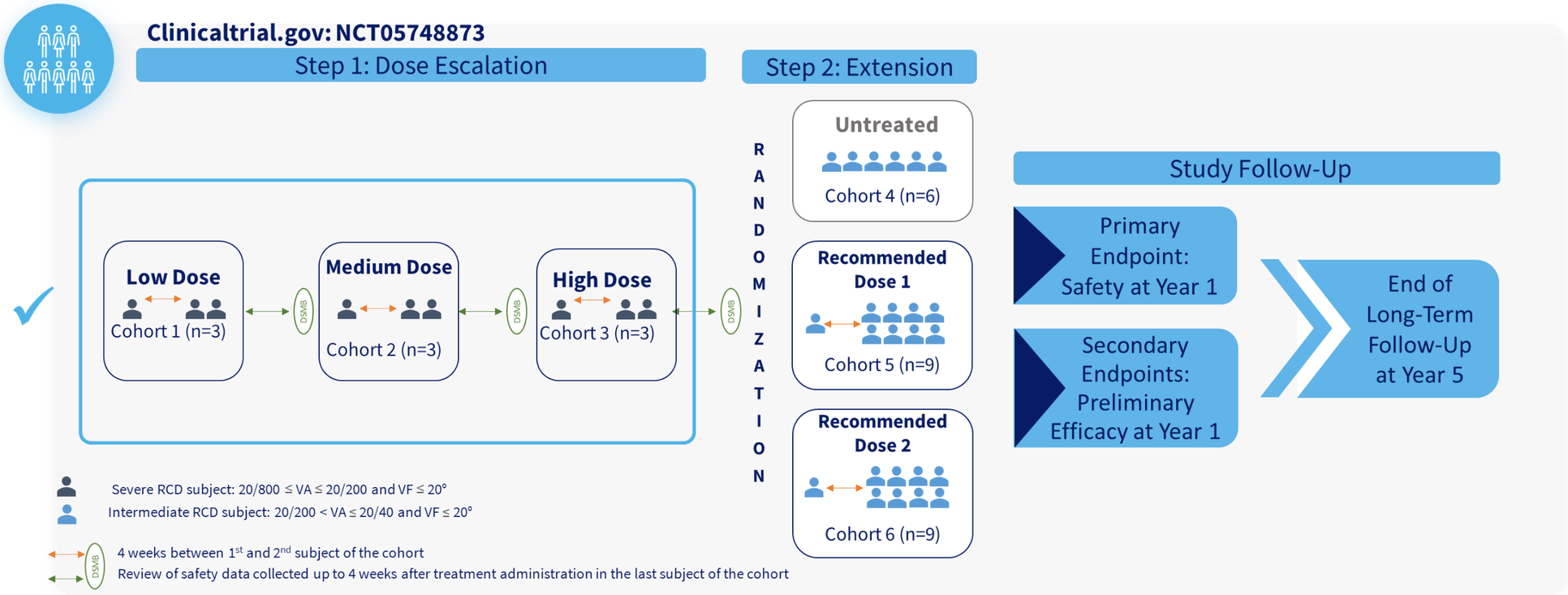
SPVN06 encodes the two synergistic isoforms of *NXNL1* (RdCVF and RdCVFL) into a single vector



One-time subretinal administration of SPVN06



PRODYGY phase I/II clinical trial: design

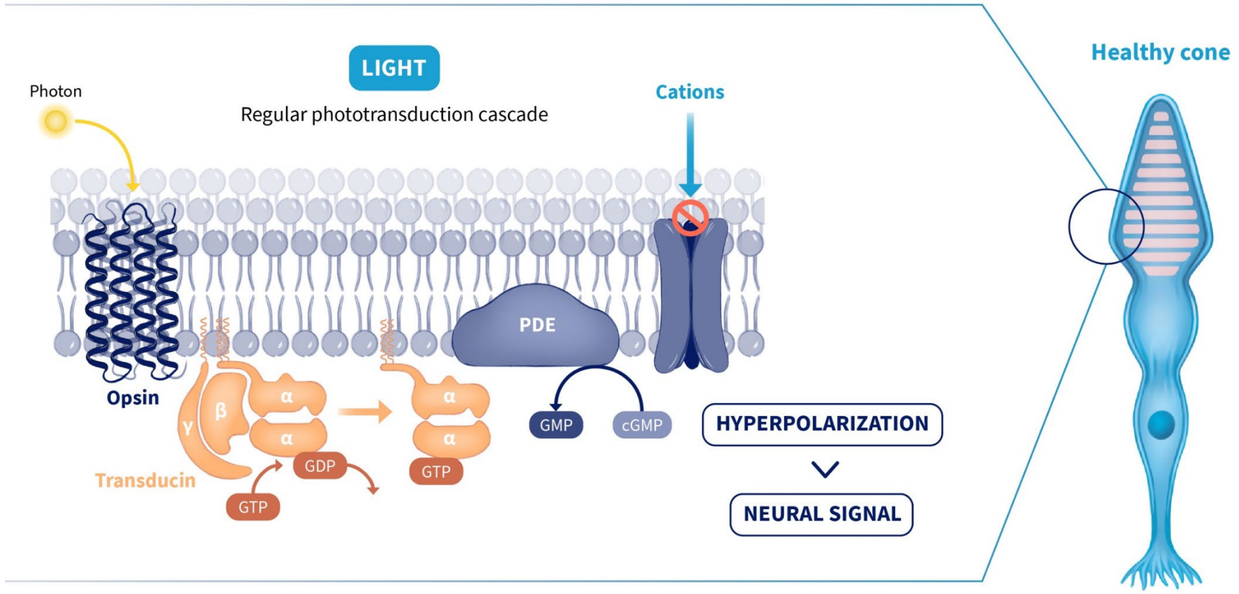


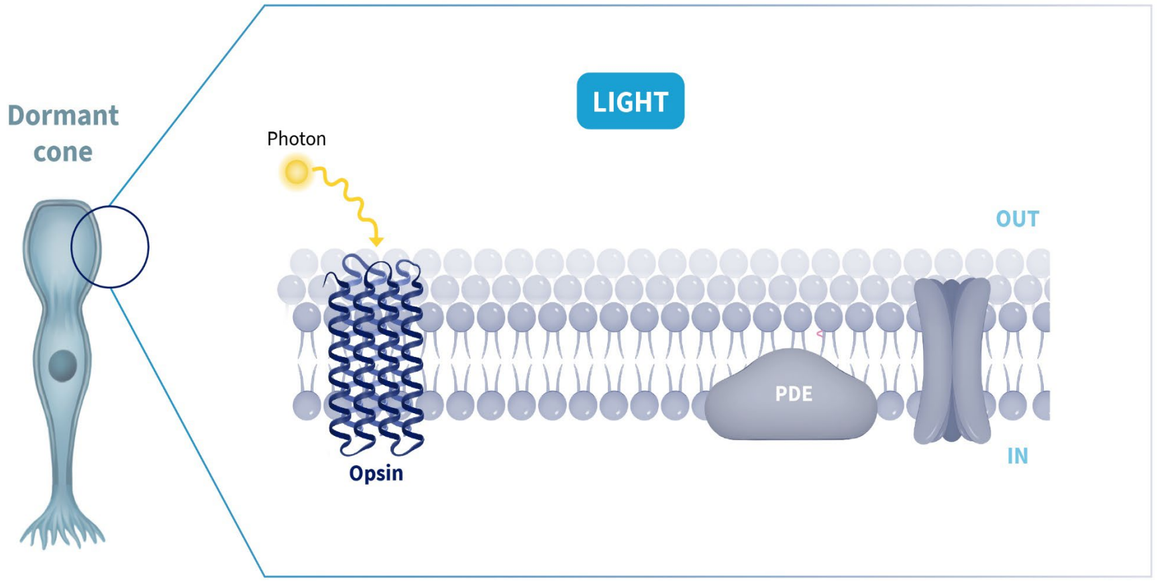
Next step: DSMB in Q4 2024 + enrollment of step 2 in Q1 / Q2 2025

Disclaimer: Dr. Jose-Alain Sahel and UPMC have financial interests in the study sponsor, SparingVision. These financial interests mean it is possible that the results of this research could lead to personal profit for Dr. Sahel and to institutional profit for UPMC. The conflicts of interest presented by these relationships are being managed by the University and UPMC.

Disruption of phototransduction cascade in RP

- Hallmark of cone degeneration is the atrophy of their outer segment → loss of phototransduction ability
- End stage of disease: cones become nonfunctional or **dormant**





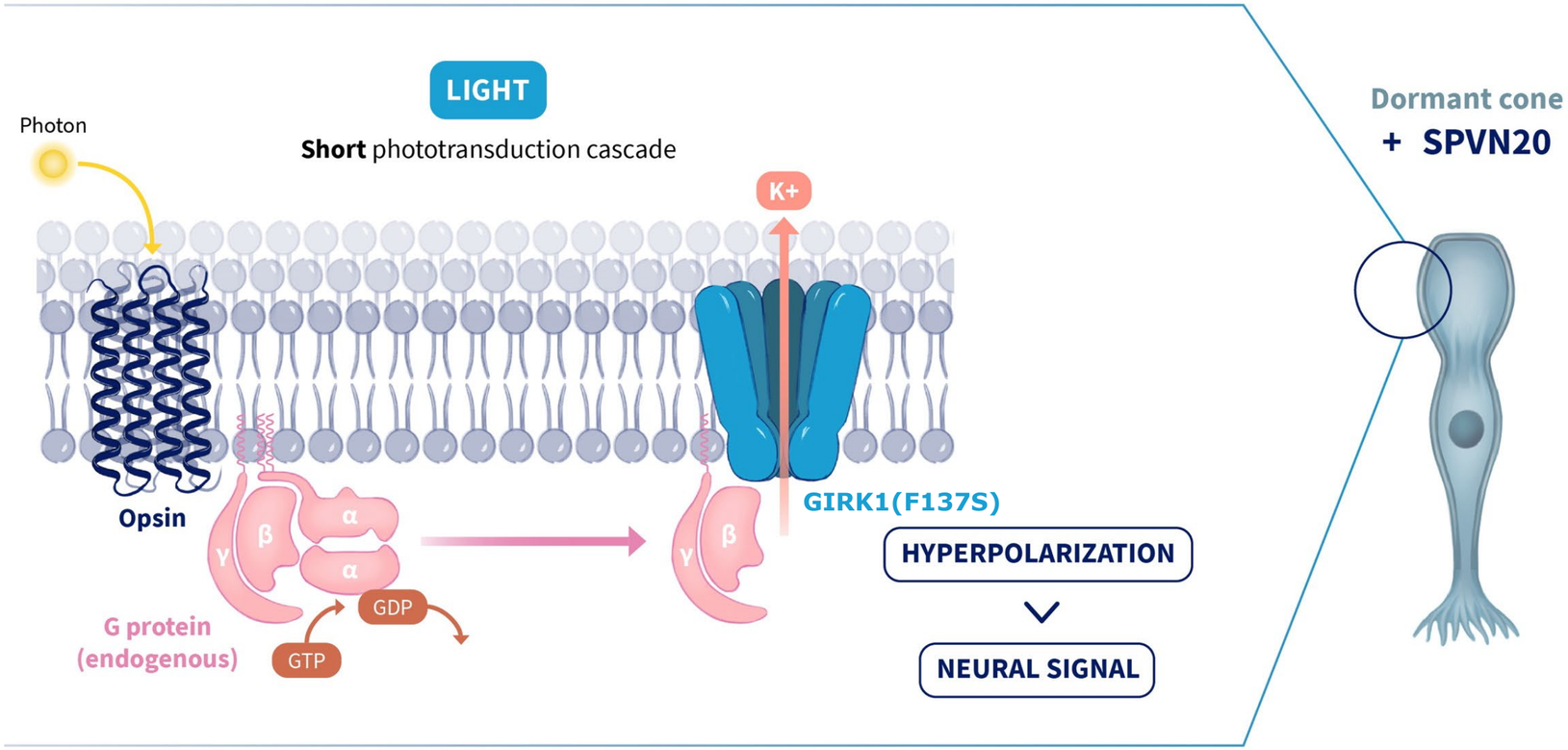
Healthy cone:

- Light stimulation leads to hyperpolarization of the photoreceptor, and transmission of neural signal

Dormant cone:

- Missing outer segment prevents phototransduction → no cone hyperpolarization, no signal transmission

SPVN20 provides an alternative phototransduction cascade

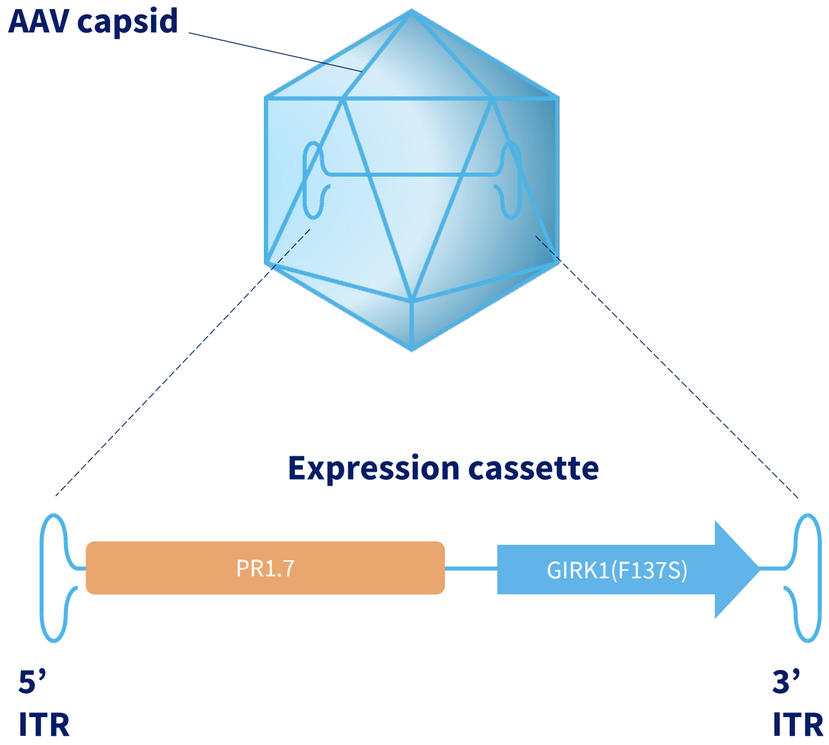


SPVN20

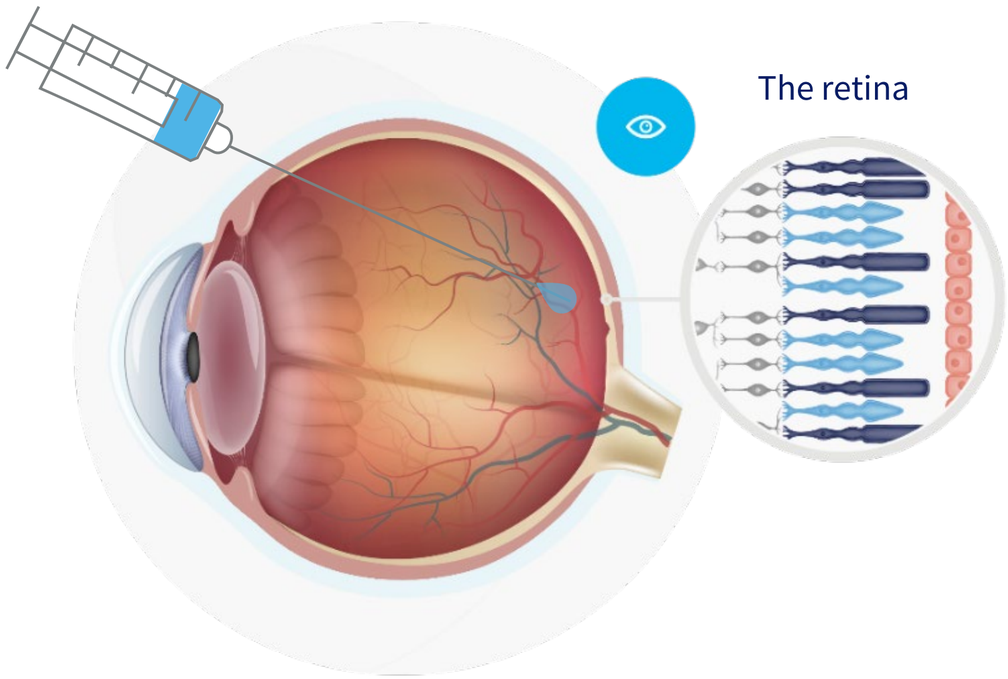
- GIRK1(F137S) expression on dormant cone membrane allows alternative phototransduction cascade
- Alternative phototransduction cascade relies on endogenous opsins and G proteins
- Expected restoration of neural signal

SPVN20 construct and route of administration

SPVN20 product construct using human GIRK potassium channel



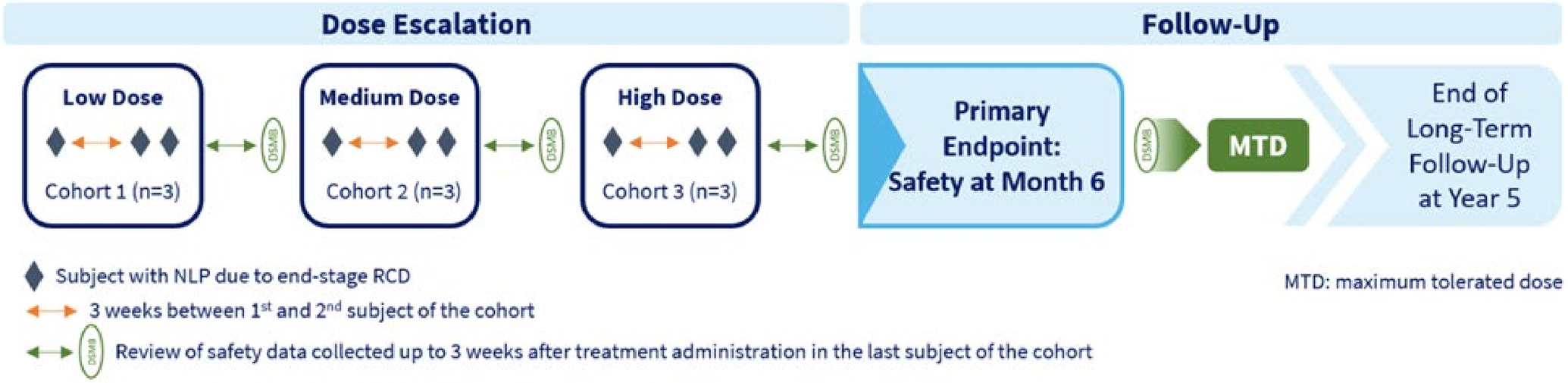
One-time intravitreal administration of SPVN20



SPVN20 proposed clinical study design

NYRVANA: FIH clinical trial with SPVN20

- Open-label, dose-escalation study, single intravitreal administration of SPVN20
- Endpoints: safety and tolerability, preliminary efficacy at 6 months + long-term follow-up
- 9 subjects with no light perception (NLP) due to end-stage rod-cone dystrophy (RCD), and who retain dormant cones



NLP: no light perception, RCD: rod-cone dystrophy

Strategic collaboration with Intellia: Deal highlights

- **Development of ocular CRISPR therapies directed to 3 targets:**
  - SparingVision to elect targets for drug development
- **Upfront paid in SparingVision shares, around $200M milestones/product and royalties:**
  - Intellia received 10% equity stake in SparingVision
- **Option right for Intellia on up to 2 of the 3 targets:**
  - Opt-in for commercialization rights in the US only
  - SparingVision eligible to receive option exercise fee, cost reimbursements (past) and royalties
  - Parties to share global development costs 50/50 from opt-in

SparingVision in brief

A technology-agnostic approach to treating blinding retinal diseases

- Applying the right technology to the right disease: this approach allowed us to expand our portfolio **from 1 to 6 programs in <3 years**,
- Gene-independent gene therapies + CRISPR developed in partnership with Intellia Therapeutics

Targeting diseases with high unmet patient need

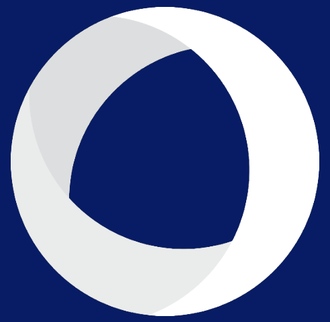
- Millions of patients suffering from blinding retinal diseases IRDs, Dry AMD – GA but no satisfactory treatment to date
- **Significant market opportunity** for the gene-independent GT approach : $2.7BN for SPVN06 in RP alone

Clinical-stage company with multiple near-term catalysts

- Lead program SPVN06 currently in phase I/II (PRODYGY); co-lead SPVN20 to enter the clinic in 2025
- 4 other programs in research phase

Led by a team of **ocular genomics experts**

- **A-team** with significant experience bringing products to market licensing and/or building companies
- Network of tier-1 KOLs and strong relations with patient community



SparingVision's 3-pillar strategy

Gene Therapy

SPVN06 in RP
SPVN06 in other Rod-Cone Dystrophies (RCDs) & Geographic Atrophy / dAMD

SPVN20 & 30 in Rod-Cone and Cone Dystrophies (RCDs / CDs)

CRISPR

Strategic alliance with exclusive rights to retinal targets for SparingVision

Intellia THERAPEUTICS

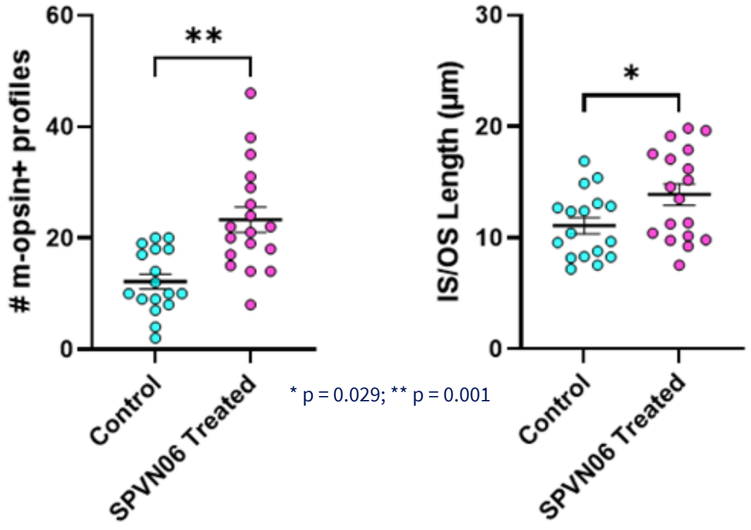
Horizon scanning

Identifying the future technologies to allow us to transform the treatment of retinal disease

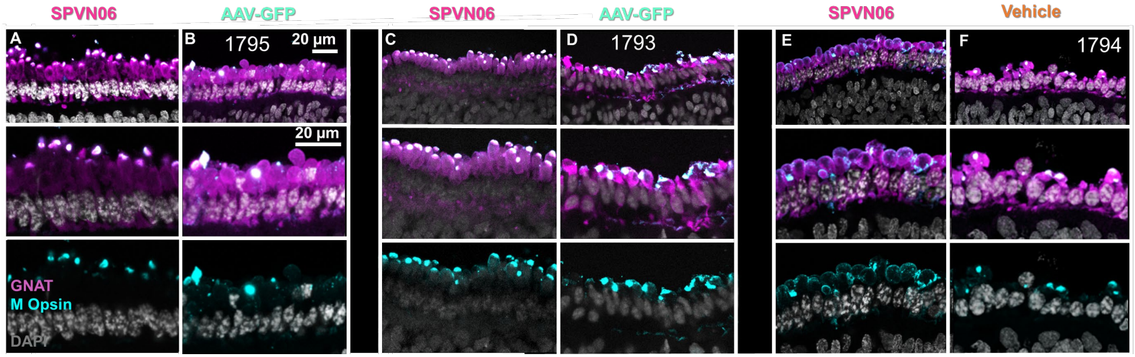
Applying a suite of technologies

Nonclinical pharmacology of SPVN06

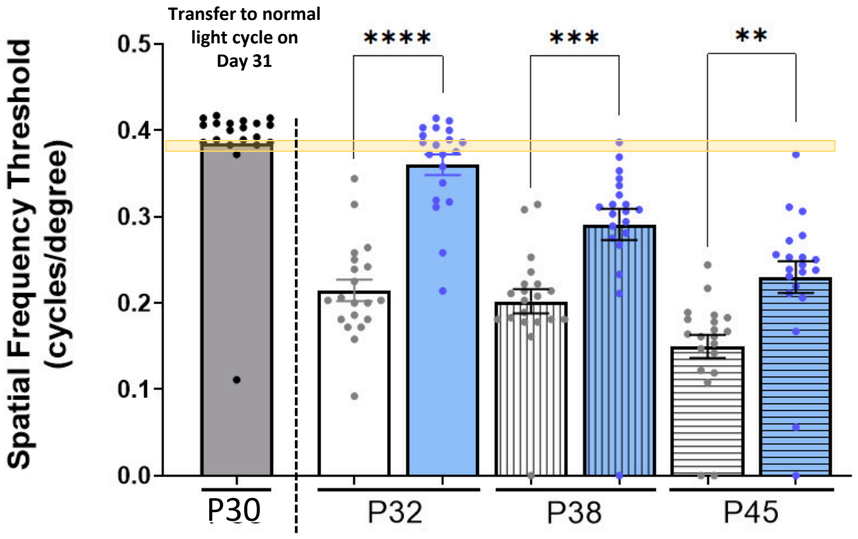
Structural protection of retinal degeneration in P23H pigs

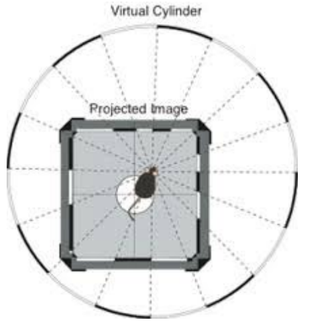


* p = 0.029; ** p = 0.001



Visual acuity measured by OKT in *rd10* mice





Vehicle
SPVN06 1E8 vg/eye
WT mice

Mean wildtype level

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

PHENOROD 2 natural history study

Analysis Population

- Adult subjects with RCD due to a variant in the gene *RHO*, *PDE6A*, or *PDE6B*
- BCVA ≥ 20/200 in at least one eye
- Horizontal diameter of binocular visual field ≥ 5° (III4e isopter)

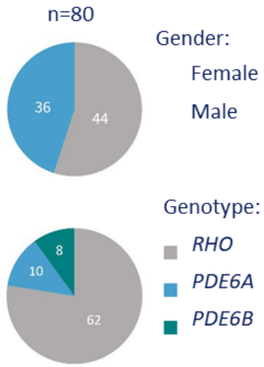
Primary endpoint: Proportion of patients whose disease progressed during the first year of follow-up.
- Disease progression defined as a loss greater than 110µm or 9% at Year 1,Fast progression defined as twice that threshold.

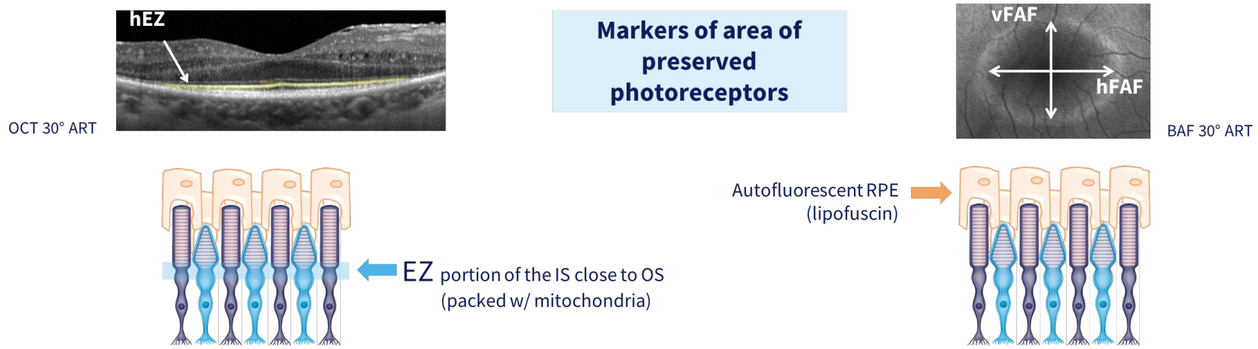
Structural parameters of retinal degeneration:

- horizontal width of the ellipsoid zone (hEZ) assessed by SD-OCT
- horizontal and vertical diameters of the inner ring of hyperautofluorescence (hFAF and vFAF) assessed by FAF
- All images were graded by an independent central reader, as a standardized procedure.

Patient Distribution:

At inclusion:	Age (years)	Disease Duration (years)	Monocular BCVA (LogMAR)	Hor. Diameter Binocular III4e (degrees)
n	*80*	*78*	*160*	*79*
Mean (SD)	47.5 (12.7)	34.9 (14.2)	0.28 (0.27)	54.8 (55.0)
Min ; Max	21 ; 68	5 ; 61	-0.14 ; 1.18	6 ; 178

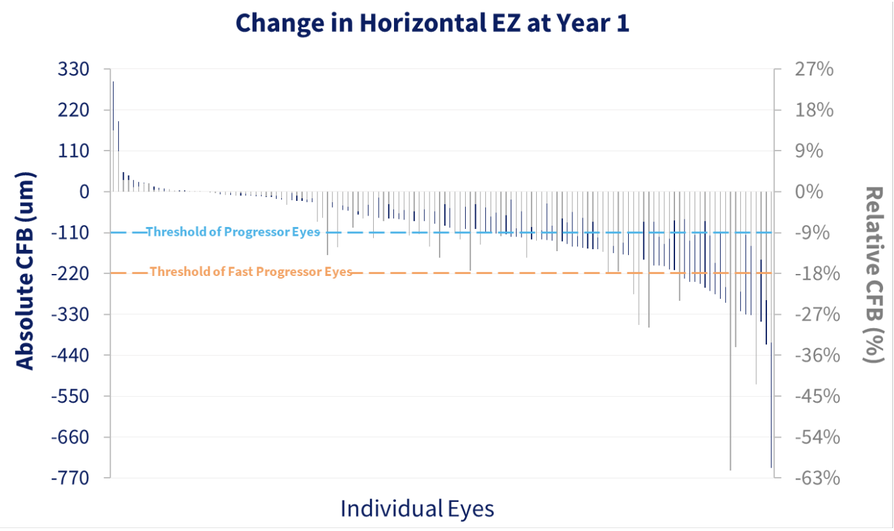




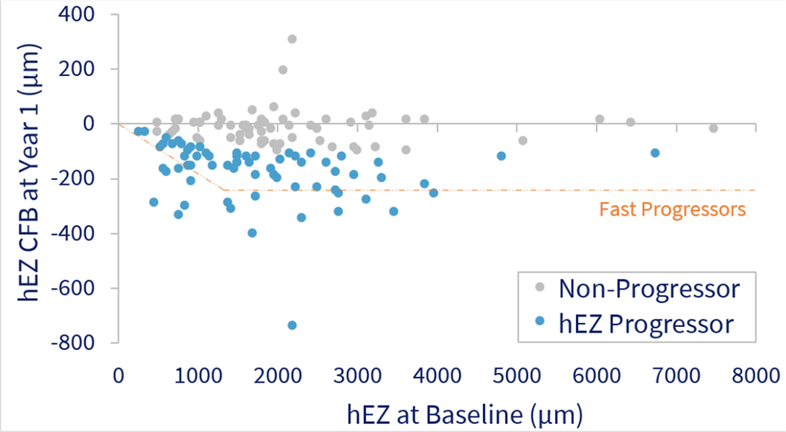
Strong interest for assessing the preliminary efficacy of SPVN06 at 12 months in PRODYGY trial

PHENOROD2 Individual hEZ Data

Disease progression was defined as a **loss greater than 110µm or 9% at Year 1,***
Fast progression was defined as twice that threshold.



CFB: change from baseline



Progressors :

- **51%** (66/130) eyes
- **74%** (52/70) patients (in at least one eye)

Fast Progressors :

- **18%** (23/130) eyes
- **30%** (21/70) patients (in at least one eye)

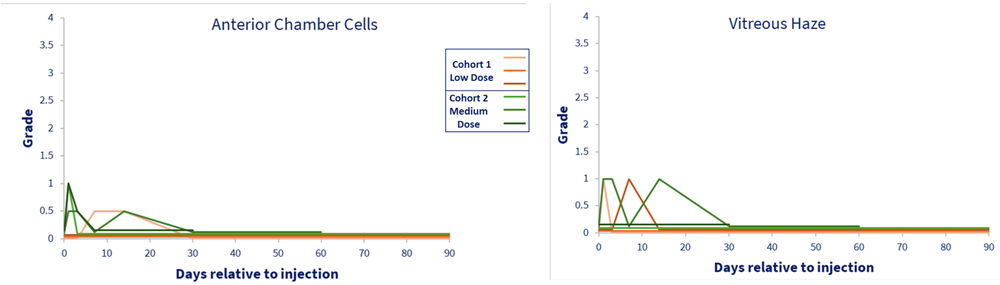
* Sujirakul T, Lin MK, Duong J, Wei Y, Lopez-Pintado S, Tsang SH. Multimodal Imaging of Central Retinal Disease Progression in a 2-Year Mean Follow-up of Retinitis Pigmentosa. *Am J Ophthalmol*. 2015 Oct;160(4):786-98.e4.
Internal source: 9% inter-reader variability reported for all 3 parameters by same Reading Center in a retrospective natural history study (PHENOROD1, NCT03975543).

PRODYGY - safety results

- **Continued favorable safety profile at 12 months for low dose and 6 months for medium dose:**
  - No serious adverse events
  - No discontinuation
  - No dose-limiting toxicity
- **DSMB #2 Review of safety data** at 6-months (low dose) and 1-month after injection in 3rd patient at medium dose :
  - 7 ocular AEs in treated eyes at low dose.
  - 15 ocular AEs in treated eyes at medium dose
    - Mild-to-moderate intensity, no sequelae.
    - Small macular hole in one patient during SRI procedure, spontaneous closure.

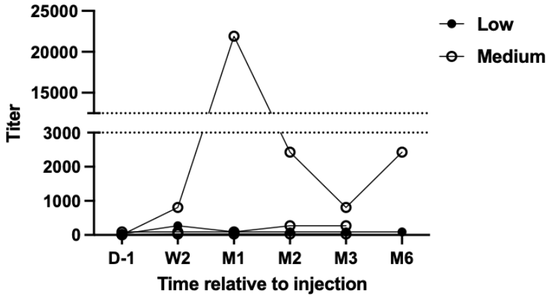
- Next DSMB: Q4 2024. Safety review of 3 doses in step 2 and recommendation of 2 doses for step 2 in less affected patients.

Intraocular inflammation in treated eyes



- **Transient low-grade intraocular inflammation**, resolved

Systemic immune response



- Levels of total antibodies (Tabs) against SPVN06 capsid in serum seem to increase with SPVN06 dose
- No T-cell response observed

Rationale for RdCVF/L in Geographic Atrophy

Dry Age-related Macular Degeneration (dAMD) is characterized by:

- Accumulation of lipid deposits (drusen) in the retina
- Lipofuscin accumulation in RPE cells
- Early cellular changes
- Inflammation & oxidative stress

Geographic Atrophy (GA) is a chronic and advanced form of dAMD characterized by:

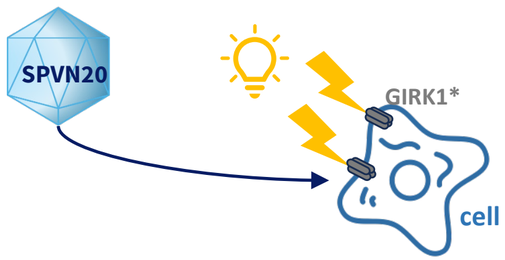
- Death of photoreceptors (PR) and RPE cells in the macula
- Significant & permanent central vision loss

Why use RdCVF/L in GA:

- AMD has a polygenic etiology, as well as contributing factors from the environment → perfectly suited for a gene-agnostic approach
- In early dAMD, parafoveal rods degenerate before cones, thus causing a deficit in RdCVF
- As for RP, there is a strong rationale to use the RdCVF/L neuroprotective effect to prevent cones death in GA
  - In both RP and GA, the photoreceptors are dying over time and could thus be identified as the target cells for SPVN06
  - RdCVF enhances cone survival by facilitating glucose uptake and metabolism
  - RdCVFL's antioxidant activity mitigates the accumulation of the reactive oxygen species (ROS)

Pharmacology of SPVN20 - *In vitro*

***In-vitro* patch-clamp recordings of GIRK1* currents support the mechanism of action of SPVN20**



light-induced currents

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cell size

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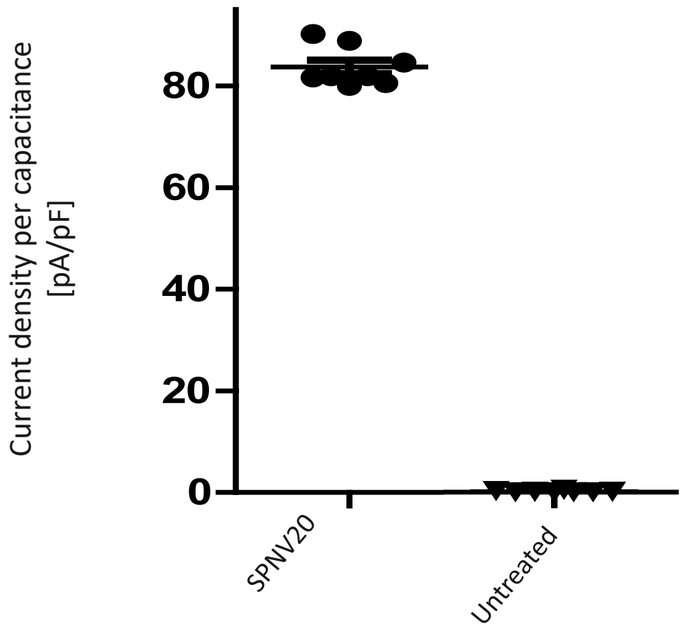


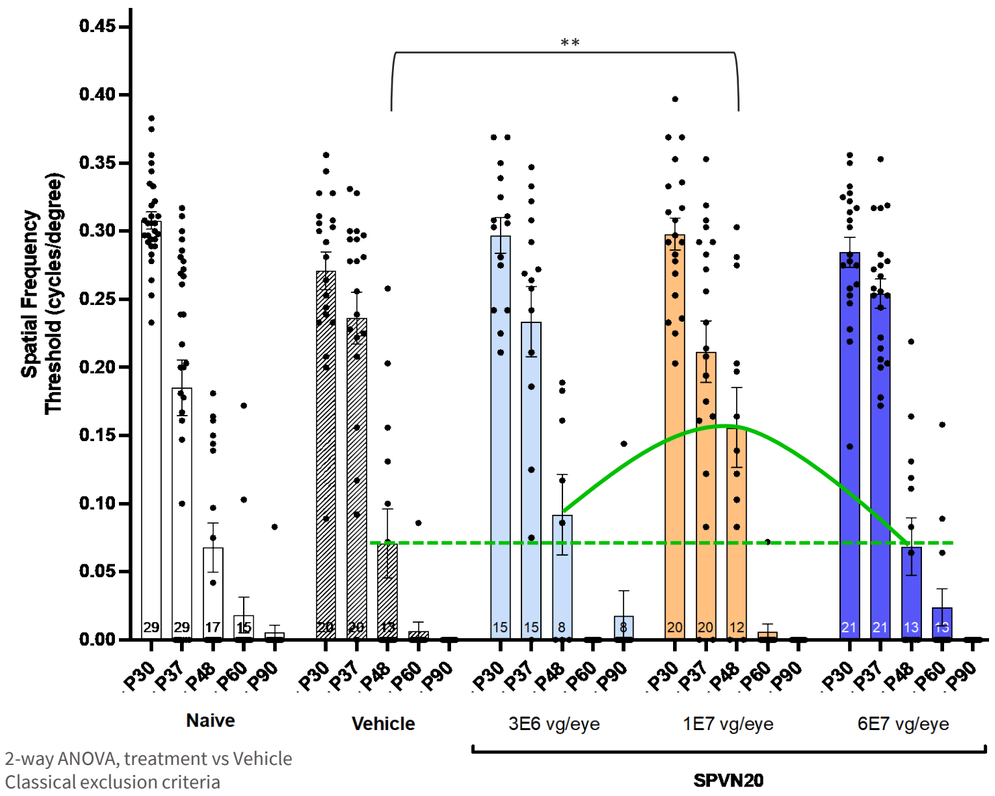
SPVN20 in vitro pharmacological responses

GIRK1*: GIRK1(F137S)

Pharmacology of SPVN20 – *rd10/rd10* mice

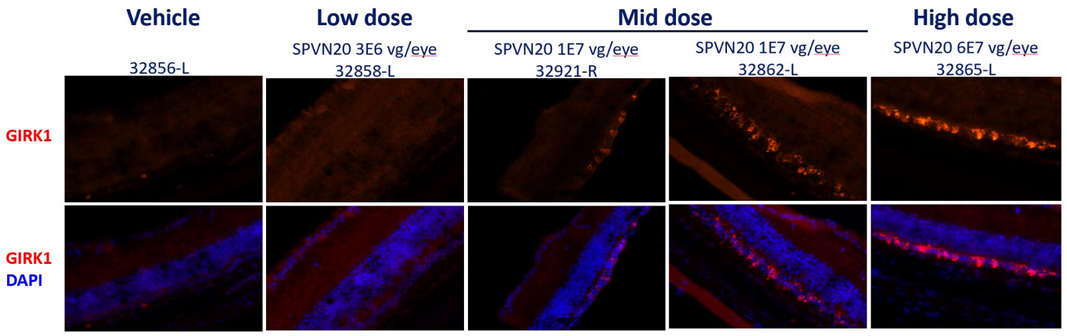
Pharmacology and safety established in a disease model harboring dormant cones, target cells for SPVN20

Significant response at P48 with apparent bell-shaped effect noted by OKT but not observed with ERG



2-way ANOVA, treatment vs Vehicle
Classical exclusion criteria

Dose response of GIRK1* retinal expression by immunofluorescence analyses



- SPVN20 subretinal administration was **well tolerated**, with no acceleration of the degenerative process
- **Pharmacology established** for the mid-dose group at P48 indicating with a bell-shape dose-response curve (consistent with GIRK biology)

Safety & Biodistribution of SPVN20 in NHPs

Safety and BD in healthy animals with clinically relevant ocular anatomy, including presence of a **fovea**, target tissue, and **healthy cones**

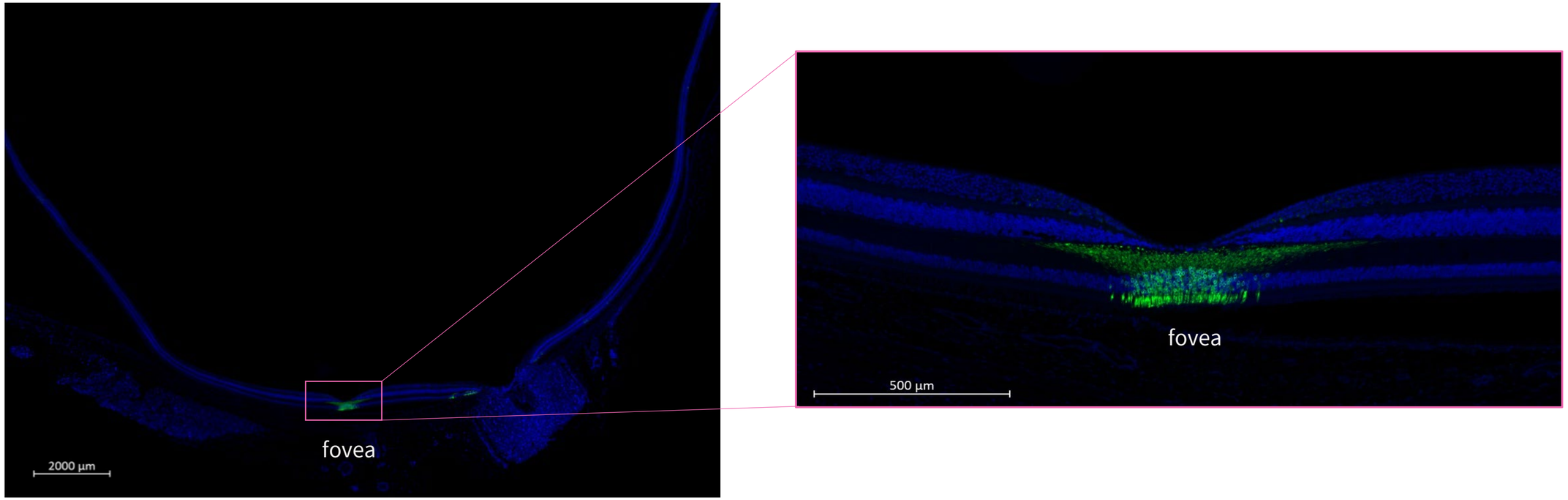
3-month pilot study and a 6-month GLP toxicology/BD study in African green monkeys

- Bilateral IVT administration up to 7E10 vg/eye was **well tolerated at both systemic and ocular levels**
- No SPVN-20 related adverse findings in overall gross health and safety pharmacology parameters (clinical observations, body weight, food consumption, and physical exams, clinical pathology, CV and CNS safety pharmacology)
- No drug-related effects on the ocular parameters (IOP, ffERG, mfERG, eye fundus imaging, slit lamp, cSLO/OCT, photophobia) except for a stippling of the EZ/IZ layer noted by OCT of unclear tox relevance (no functional or microscopic correlates). The eyes were generally quiet.
- GIRK1* protein expression in the fovea (cones) at both dose levels (7E9 and 7E10 vg/eye) at 3- and 6-month post SPVN20 dosing
- No drug-related microscopic findings in any tissues
- Distribution (vg) in systemic tissues was minimal. Shedding was transient

Biodistribution of SPVN20

SPVN20-mediated GIRK1* protein expression in the fovea of healthy NHPs

7E10vg/eye; 3 months post dosing



DAPI for nuclei
GIRK1