CENTER FOR INTEGRATED PROTEIN SCIENCE MUNICH

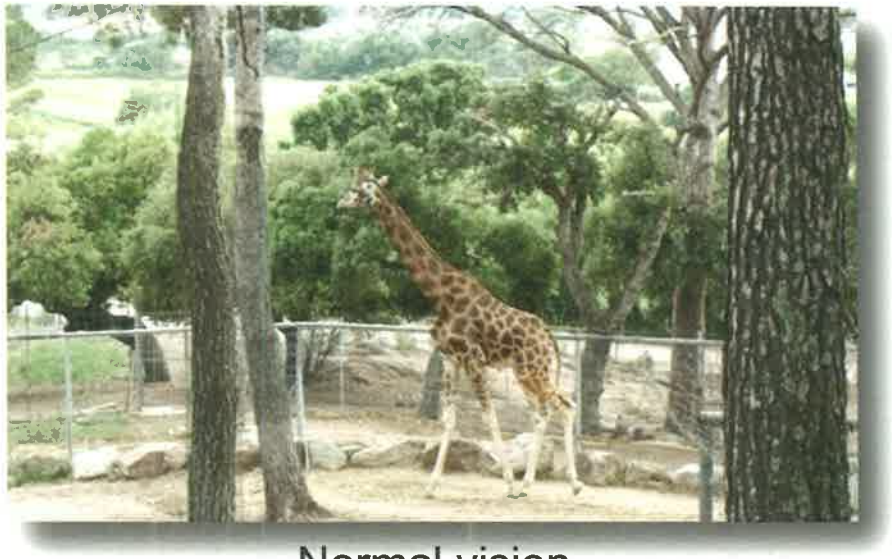
CIPSM

Center for Drug Research
Department of Pharmacy • Stylianos Michalakis

Development of Gene Therapies for Inherited Retinal Diseases

April 22 2017, Pharma 2030 Innsbruck

Inherited retinal diseases

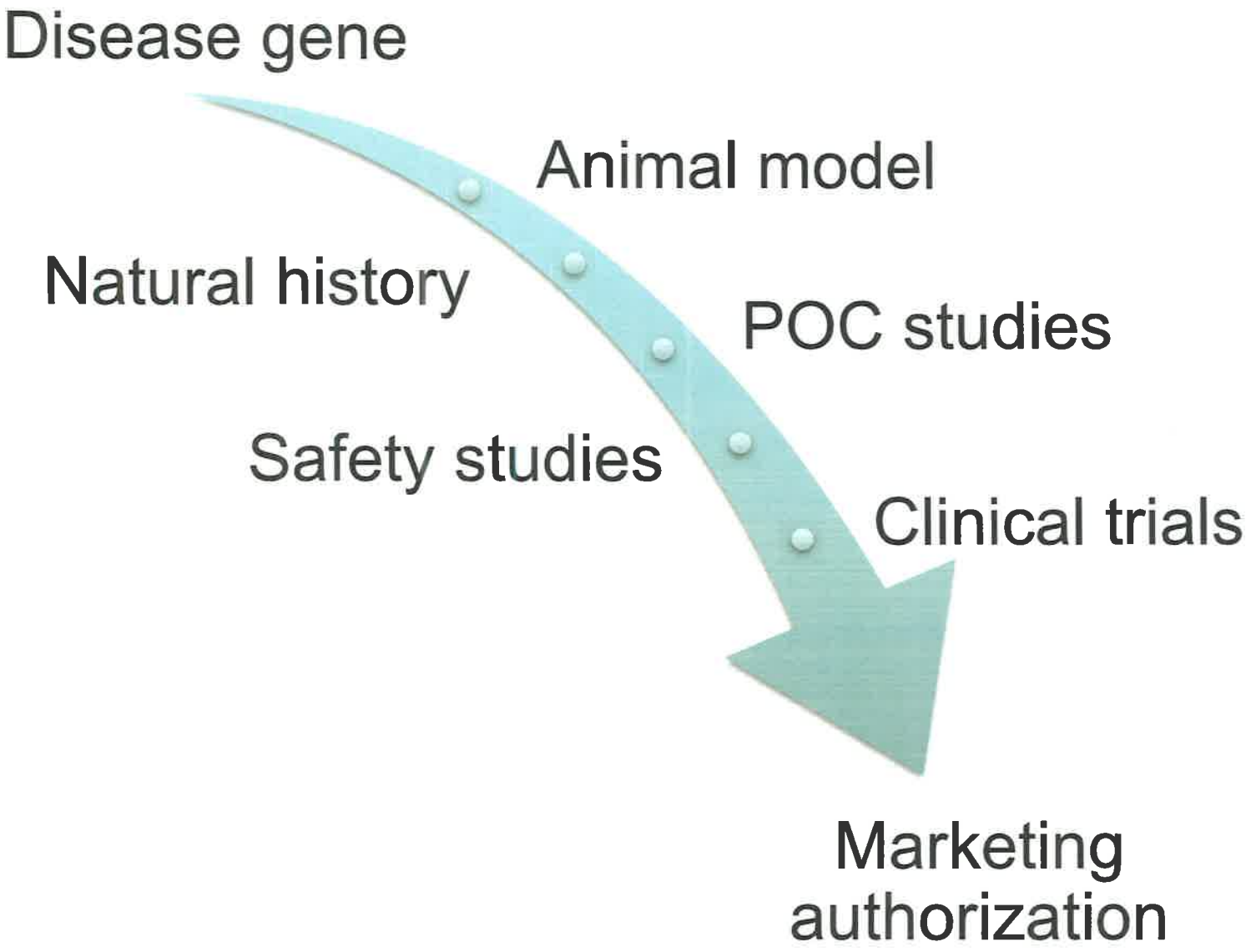


Normal vision

Achromatopsia

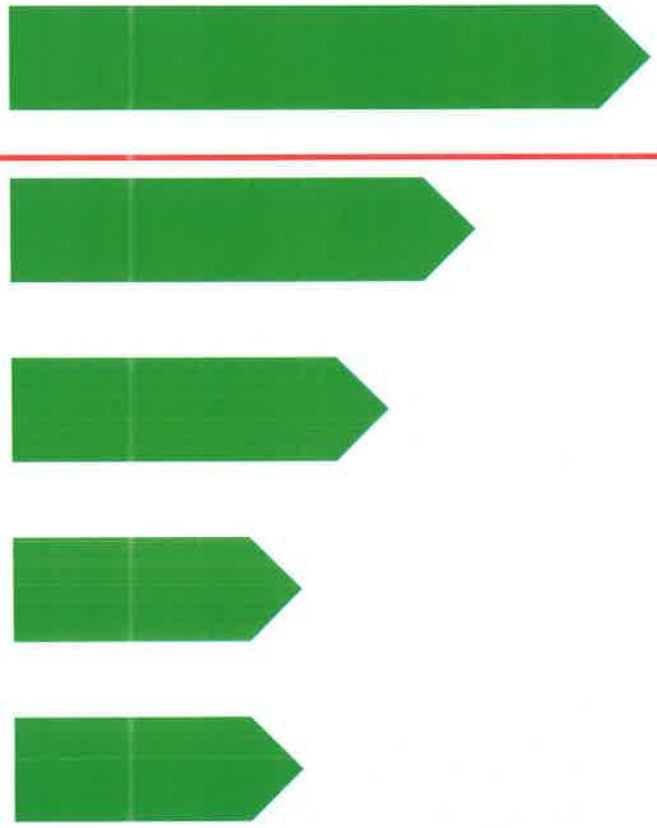
Retinitis pigmentosa

Development of gene therapies for retinal diseases



Gene therapy project pipeline

INDICATION	VECTOR TYPE	POC	PRECLINICAL	PH I/II	PH III	LAUNCH
Achromatopsia (*CNGA3*)	AAV					
arRP (*PDE6A*)	AAV					
arRP (*CNGB1*)	AAV					
arRP	AAV					
Wet AMD	AAV					



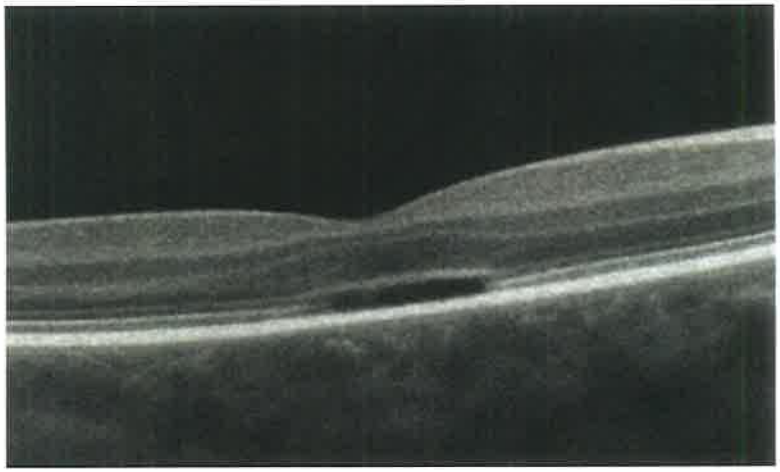
Clinical manifestation of achromatopsia

Congenital eye disease characterized by **loss** of cone function

achromatopsia

normal

- lack of color discrimination
- very poor visual acuity
- photophobia
- pendular nystagmus
- slow progressive foveomacular degeneration may occur

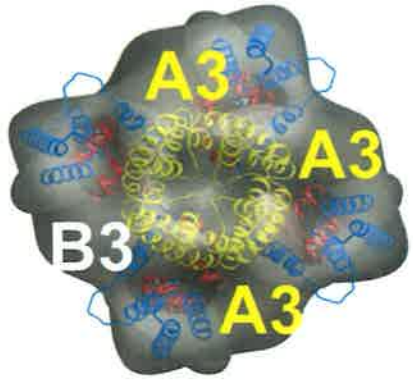


Genetic causes of achromatopsia

- Six known disease genes

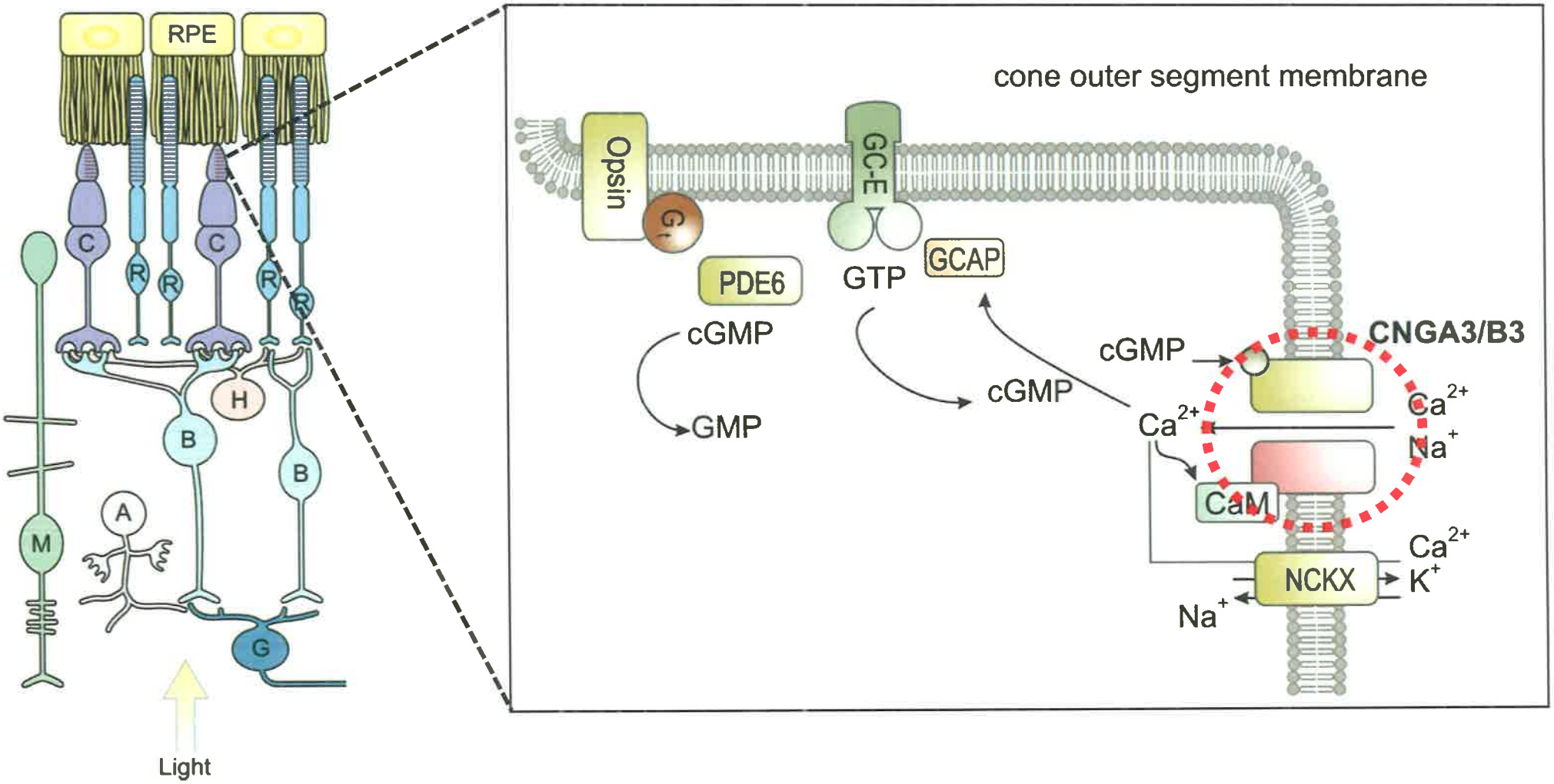
Disease gene	Frequency
CNGB3	61%
CNGA3	33%
GNAT2	1-2%
PDE6C	1-2%
ATF6	1%
PDE6H	0.5%

Cone cGMP-gated channel

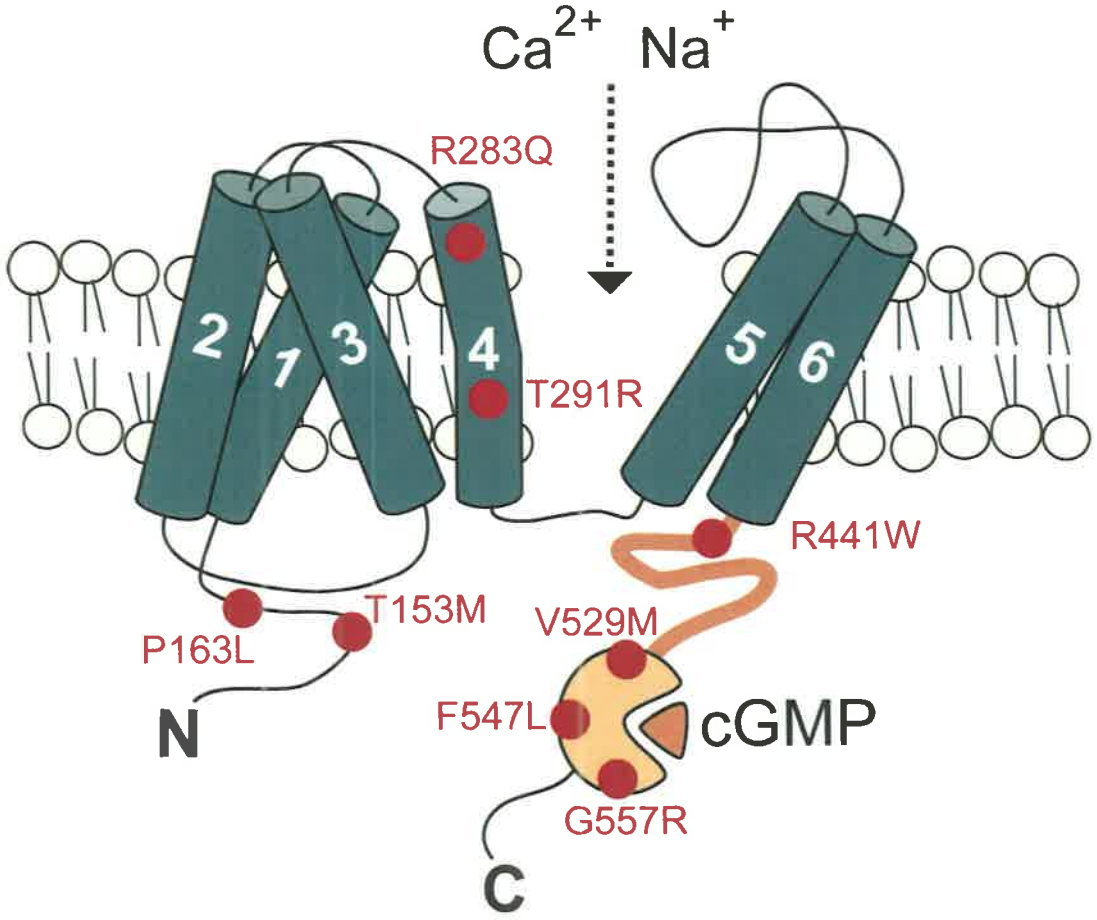


- Prevalence approx. 1:30,000

Visual transduction in cone photoreceptors



CNGA3 Achromatopsia Mutations

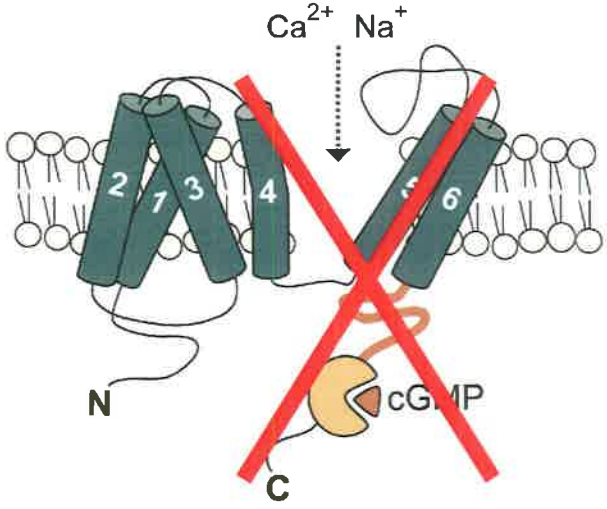


~ 750 patients in Germany

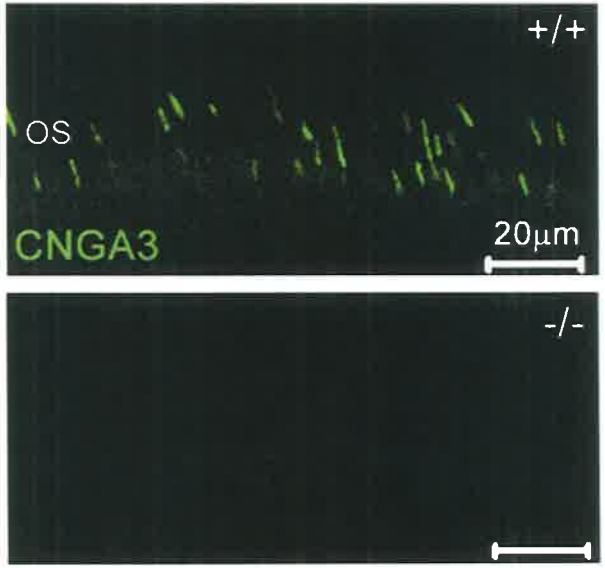
~ 4,000 patients in EU with CNGA3-linked achromatopsia

The *Cnga3* KO mouse model of achromatopsia

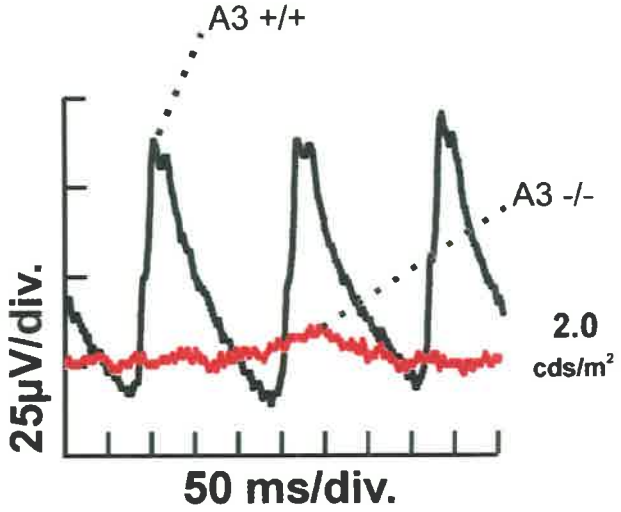
CNGA3



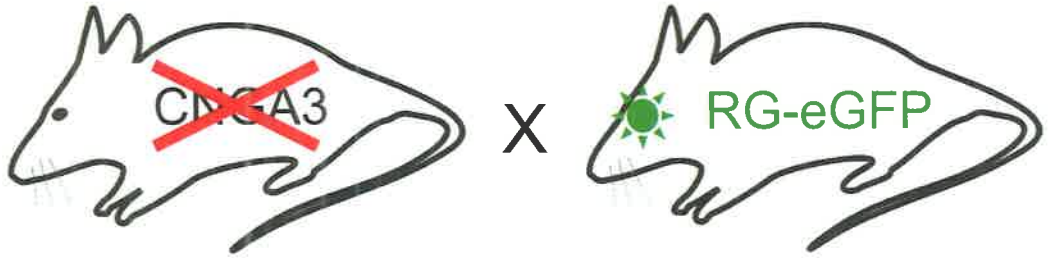
Biel et al. 1999, PNAS
Michalakis et al. 2005, IOVS



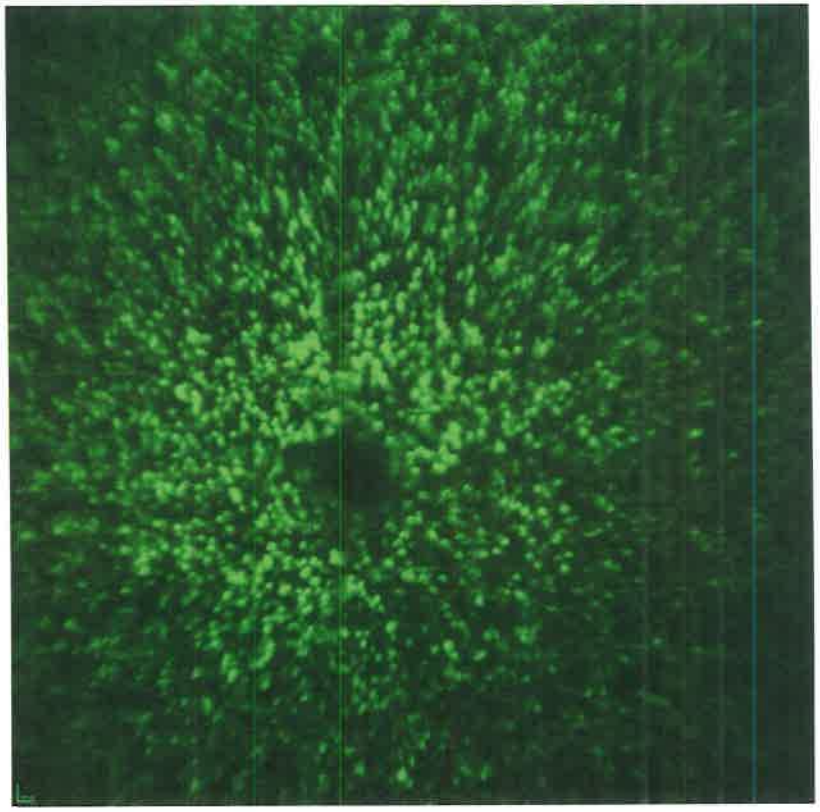
6 Hz flicker electroretinogram



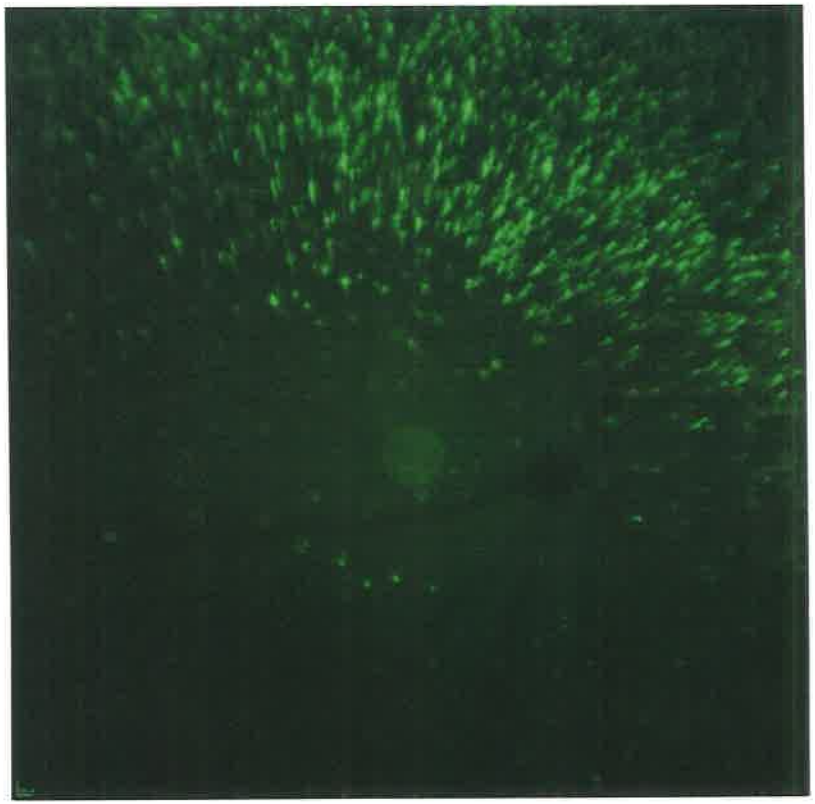
Progressive cone degeneration in *Cnga3* KO mice



RG-eGFP x CNGA3WT



RG-eGFP x CNGA3KO 5 months



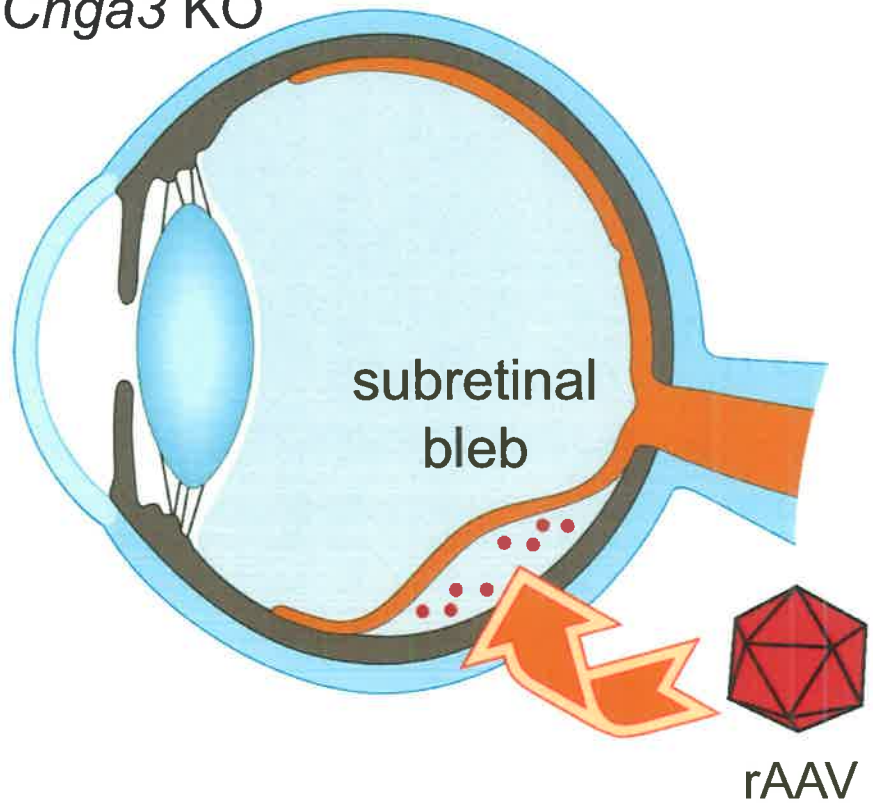
Considerations for the development of a treatment for CNGA3-linked achromatopsia

- genetically well defined
- autosomal recessive inheritance
- clinical signs are present at birth
- CNGA3 is exclusively expressed in cone photoreceptors
- cone degeneration shows slow progression

=> suitable for **gene supplementation** therapy

AAV-mediated gene supplementation therapy in *Cnga3* KO mice

Cnga3 KO



recombinant adeno-associated viral (rAAV) vector for cone-specific expression of CNGA3

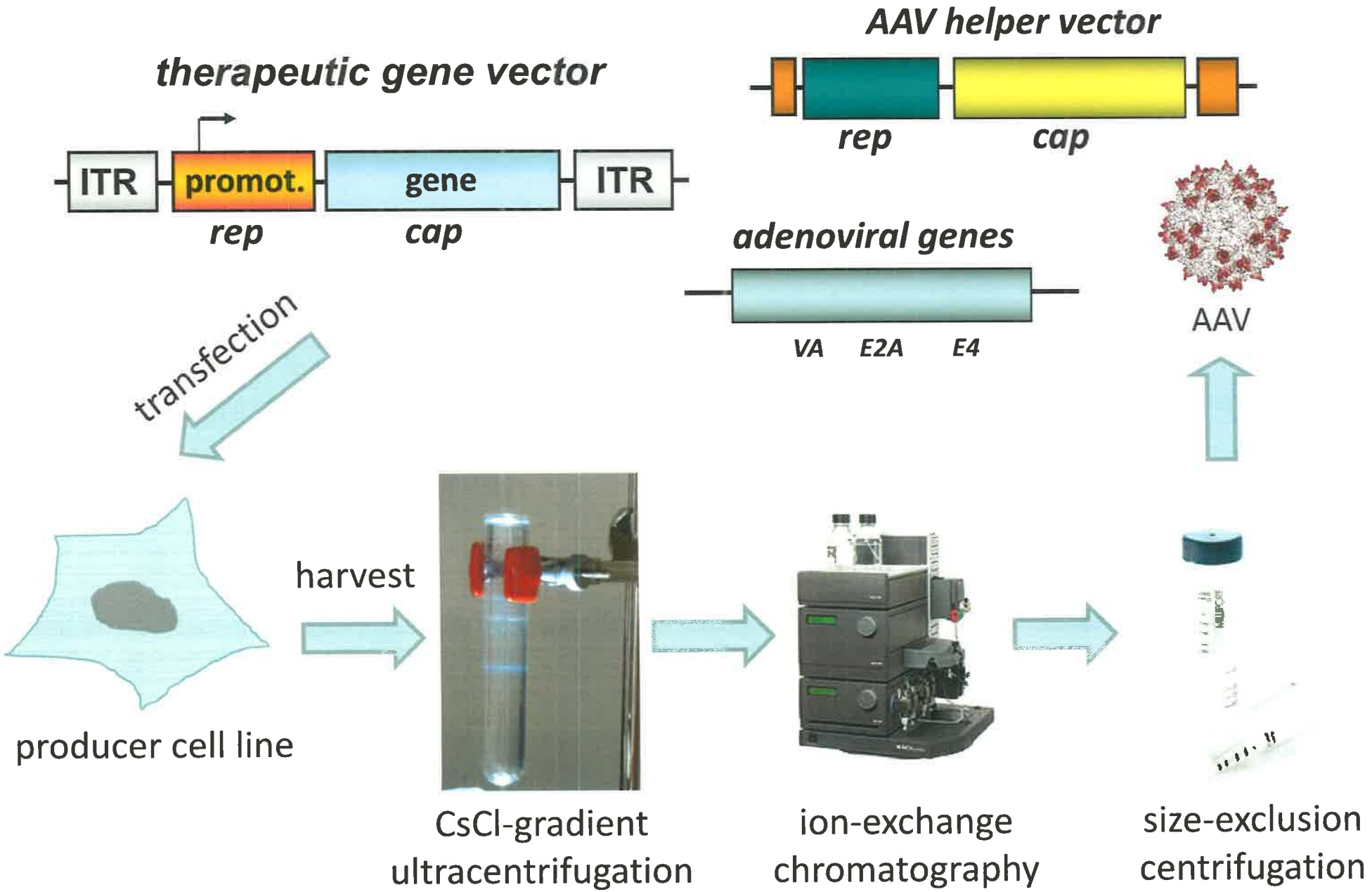
subretinal delivery of rAAV-CNGA3

Adeno-associated virus

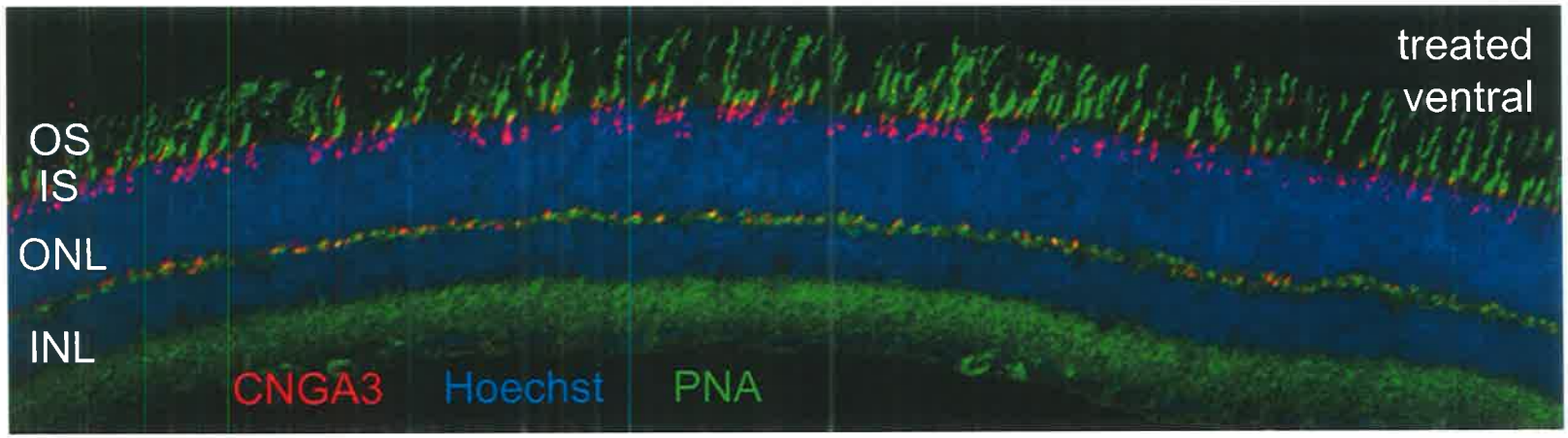
Genome: ssDNA, 4.7 kb
⦸: 25 nm

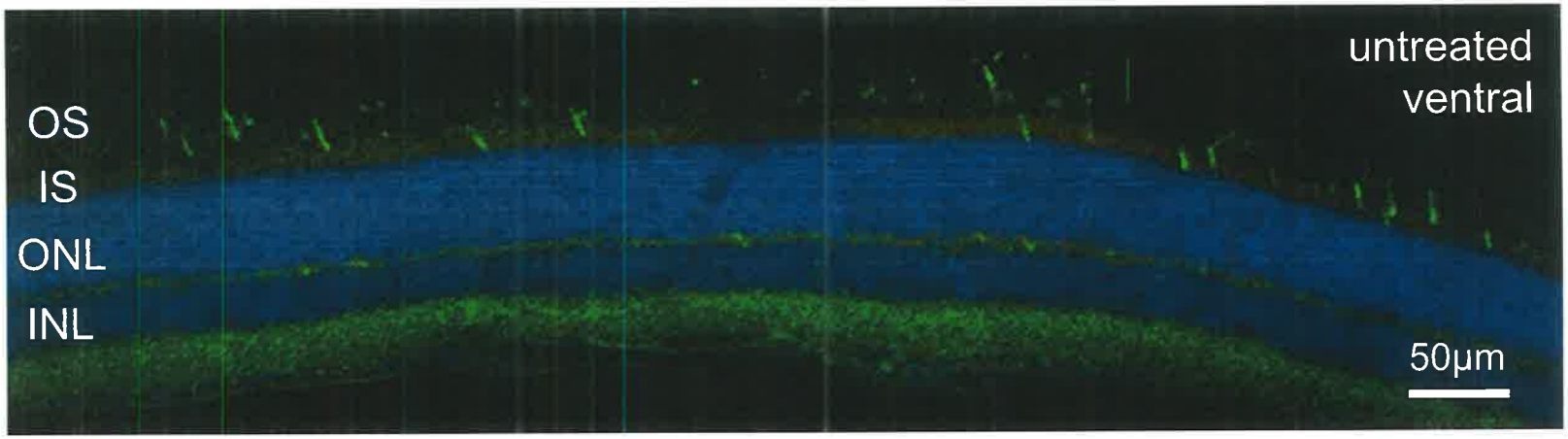
+ Low toxicity
+ Transduces many cell types (= broad tropism)
+ No genomic integration
+ Long-term expression
- Limited cloning capacity

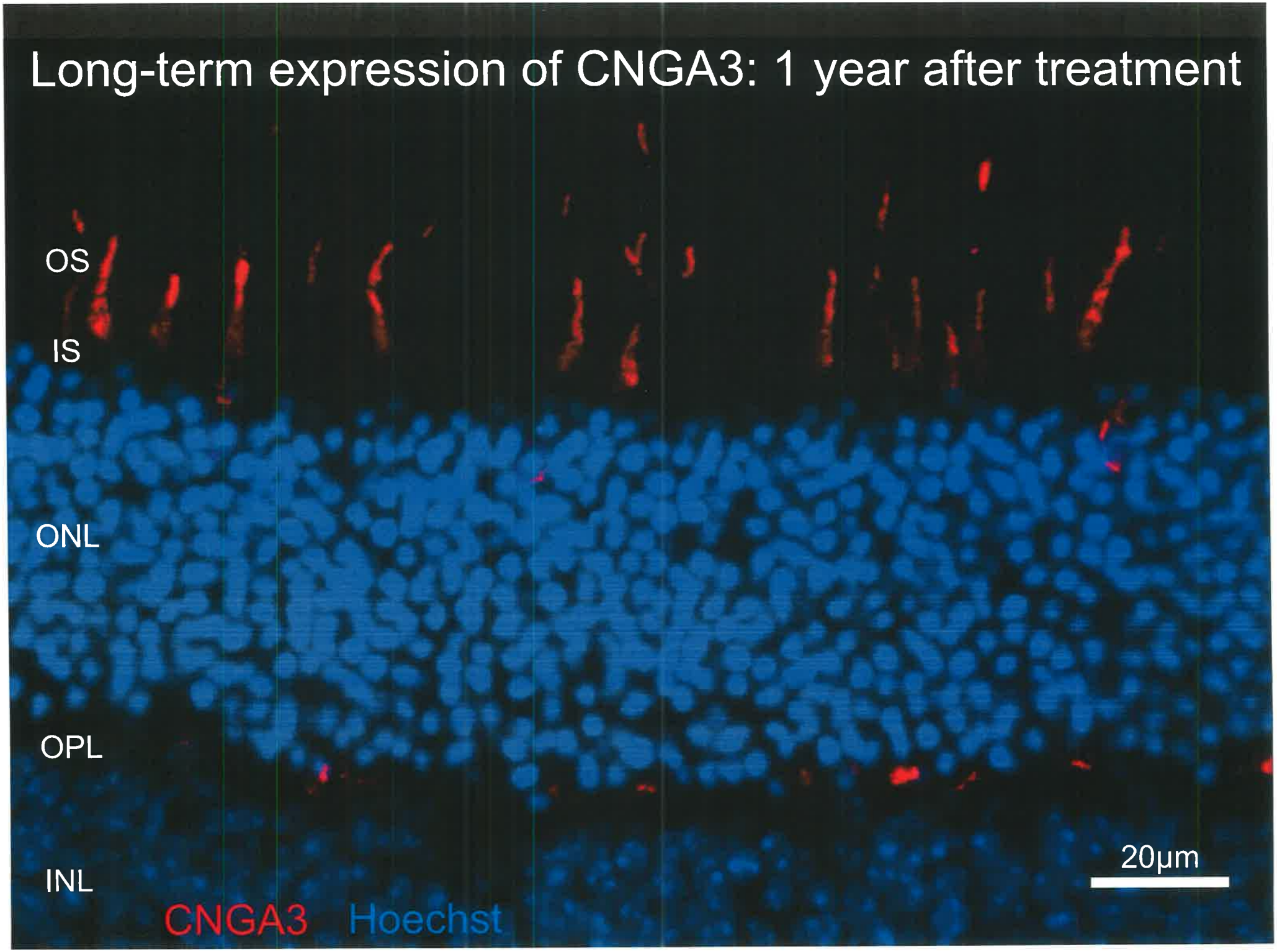
Recombinant adeno-associated virus (AAV) vectors



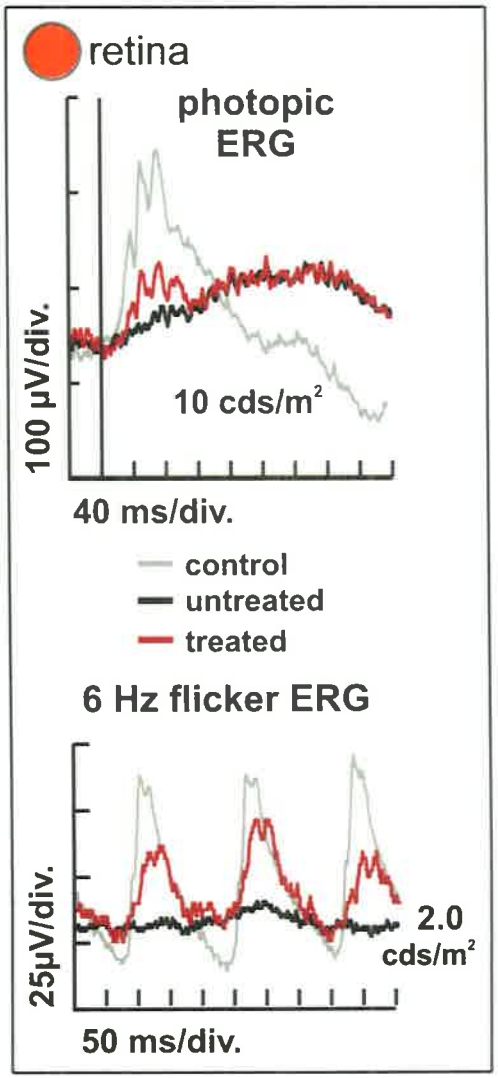
CNGA3 gene transfer rescues cone degeneration in CNGA3 KO mice

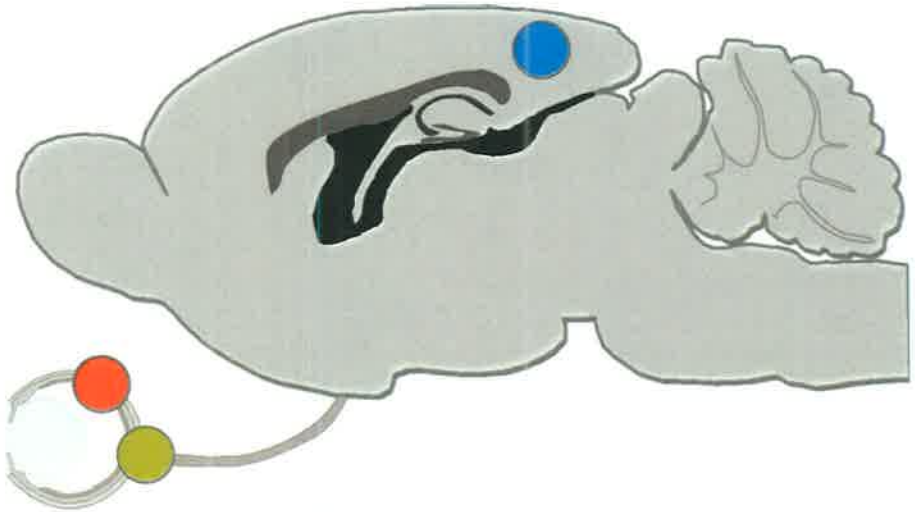


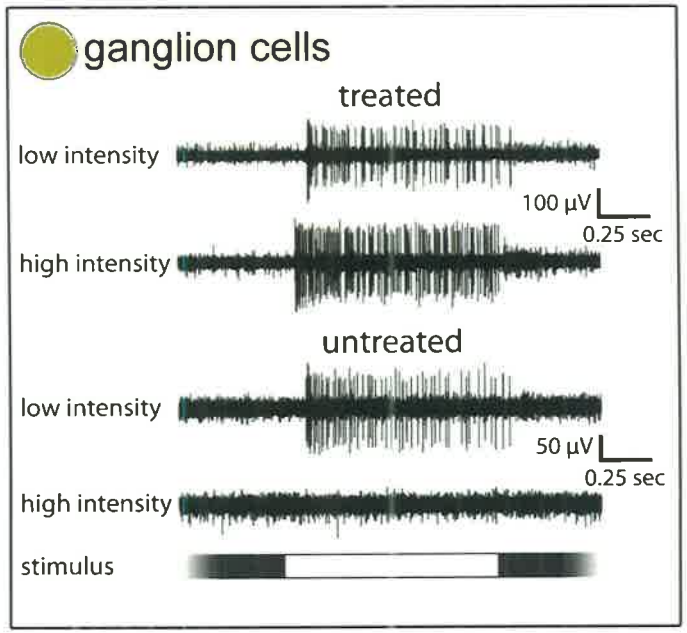


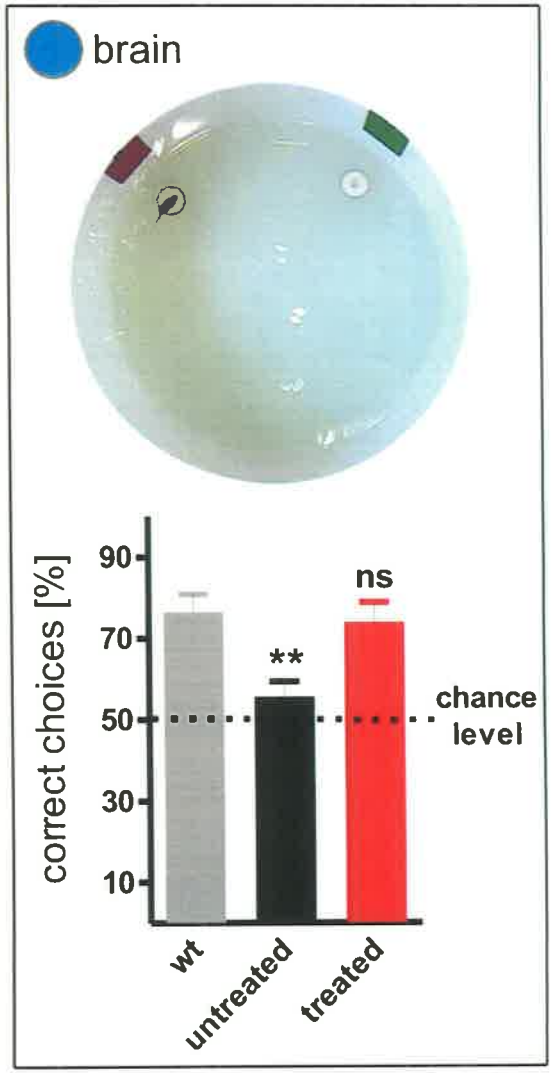

Long-term expression of CNGA3: 1 year after treatment
OS
IS
ONL
OPL
INL
20µm
CNGA3
Hoechst

Rescue of cone-mediated vision in CNGA3 KO mice





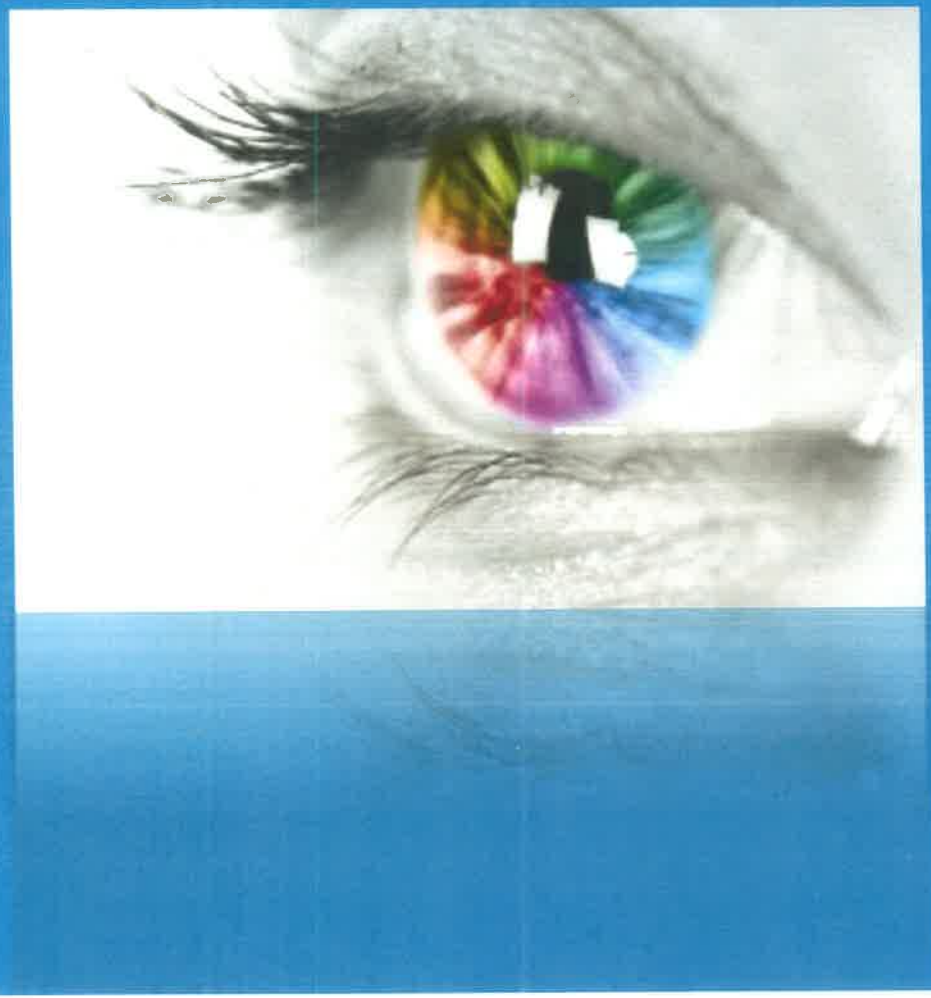




Summary of preclinical data for achromatopsia

- rAAV-mediated *CNGA3* supplementation treatment is efficient and robust
- The treatment was effective
  - ✓ with various AAV capsids (AAV5 and AAV8)
  - ✓ with various cone-specific promoters (S opsin, M/L opsin, cone arrestin)
  - ✓ at dosages ≥ 5 x 10E8 total vg
  - ✓ at early and mid-stages of the disease

Human gene therapy of *CNGA3*-linked achromatopsia



RD Cure: First German gene therapy trial on an inherited retinopathy - CNGA3-ACHM

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Martin Biel, München

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Dominik Fischer
Susanne Kohl
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Francois Paquet-Durand
Tobias Peters
Mathias Seeliger
Stephen Tsang
Marius Ueffing
Nicole Weisschuh
Barbara Wilhelm
Ditta Zobor
Eberhart Zrenner

aldevron

EFS | ATLANTIC BIO GMP

COVANCE

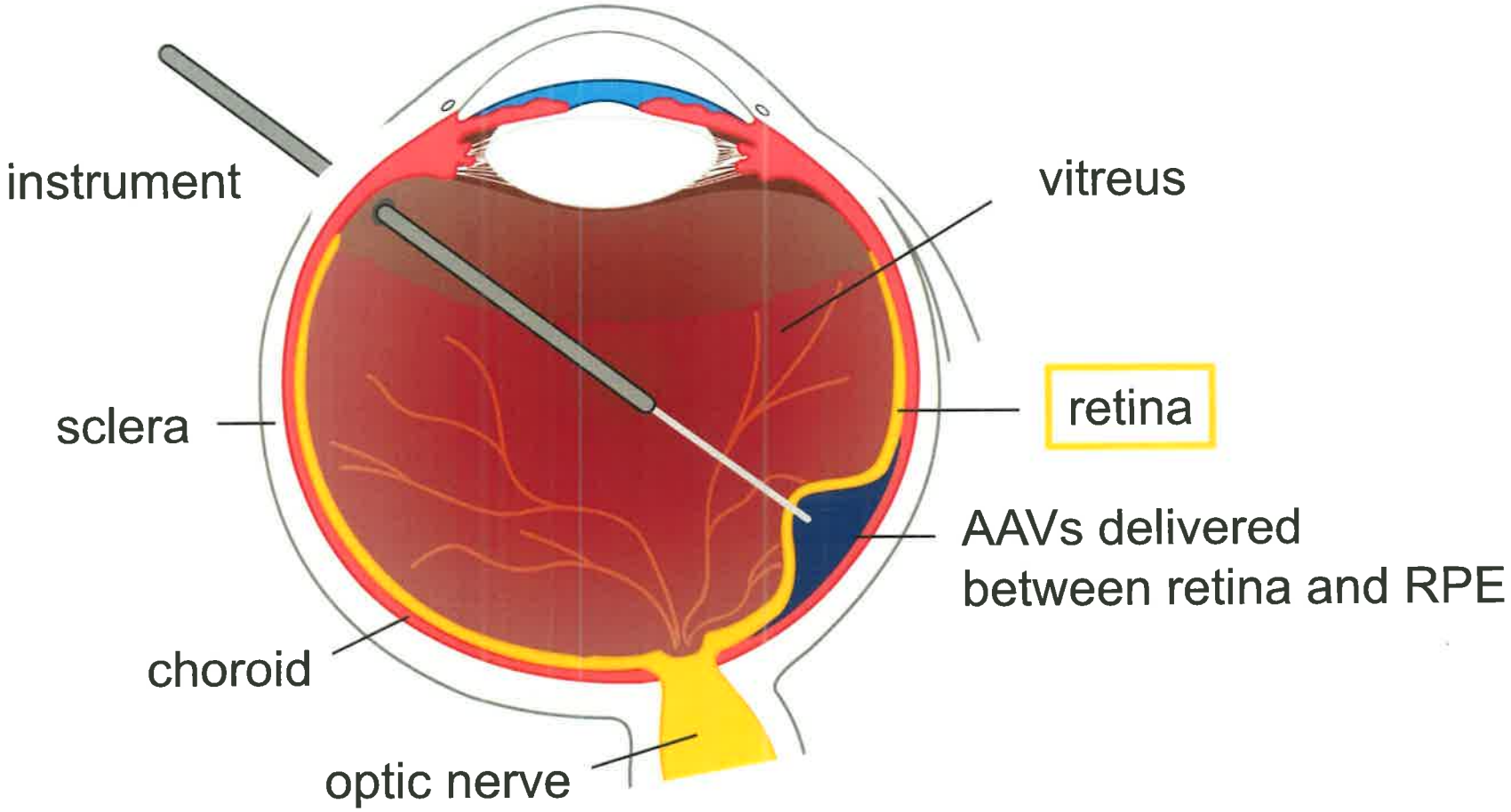
Phase I/II clinical trial: *CNGA3*-linked ACHM

„Safety and Efficacy of a Single Subretinal Injection of rAAV.hCNGA3 in Patients with CNGA3-linked Achromatopsia investigated in an exploratory, dose-escalation trial"

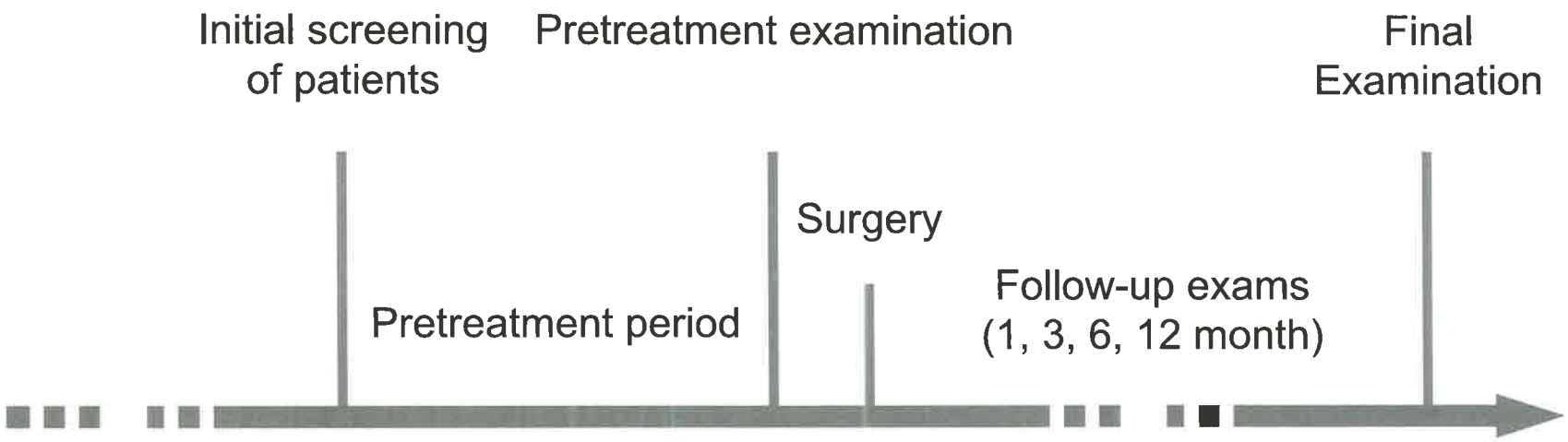
ClinicalTrials.gov Nr.: NCT02610582

CNGA3 gene therapy trial: vector delivery

Application of therapeutic AAVs via subretinal injection



CNGA3 gene therapy trial: study schedule



Low dose with 3 patients

☑ 4w ☑ 4w ☑

DMC

First patient 11/2015

Intermediate dose with 3 patients

☑ 4w ☑ 4w ☑

DMC

High dose with 3 Patients

☑ 4w ☑ 4w ☑

Last patient 11/2016

4w: four weeks (safety gap between individual patients)

DMC: Data Monitoring Committee (Independent external experts)

Gene therapy project pipeline

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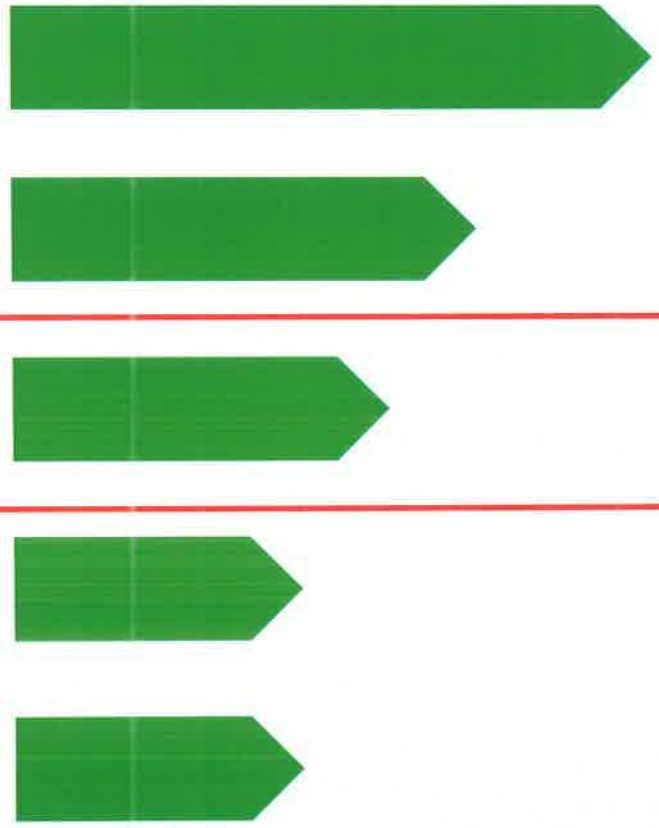
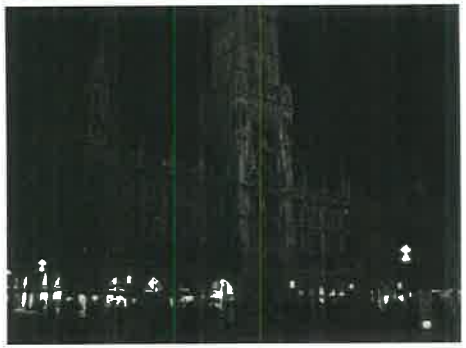


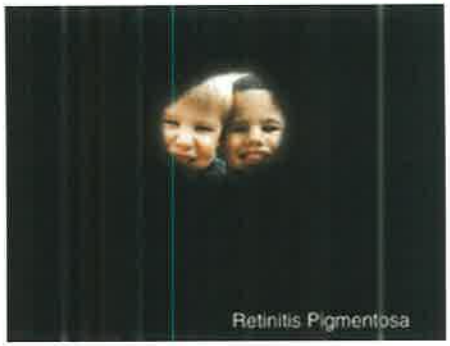
Clinical manifestation of retinitis pigmentosa (RP)

- Progressive retinal dystrophy
- Primary functional loss and degeneration of rods: night blindness
- Secondary loss of cones: visual field constriction, loss of central vision
- Approx. 30.000 patients in Germany
- About 60 disease genes known including ***CNGB1***

Night blindness

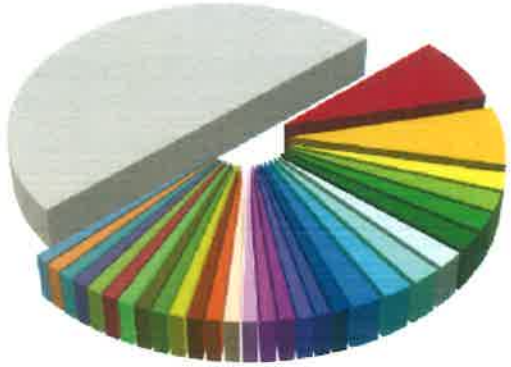


Tunnel vision



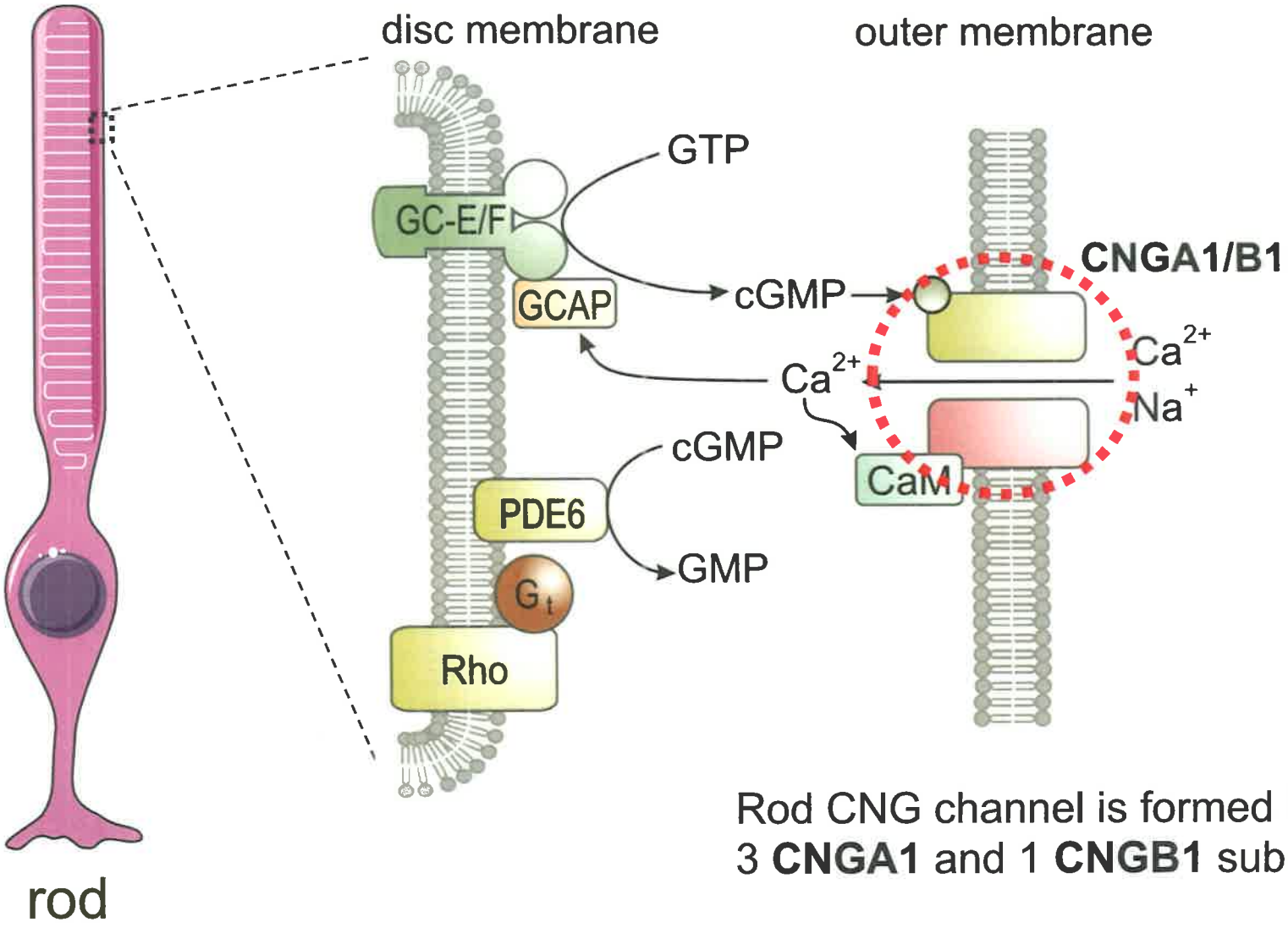
www.nei.nih.gov

Autosomal recessive RP (arRP) genes:



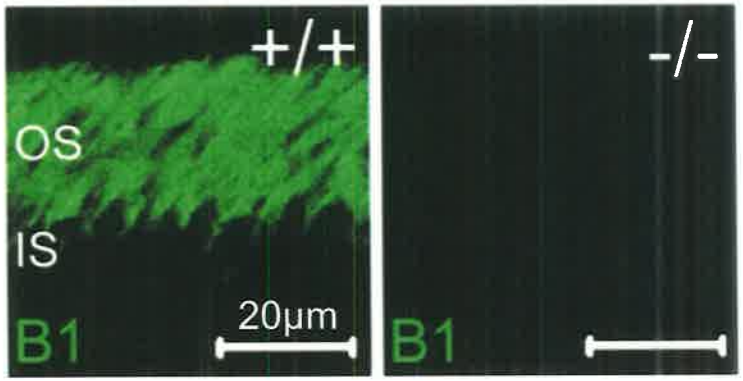
USH2A	8%
EYS	7%
CRB1	3%
PDE6A	2-4%
CNGB1	**2-4%**

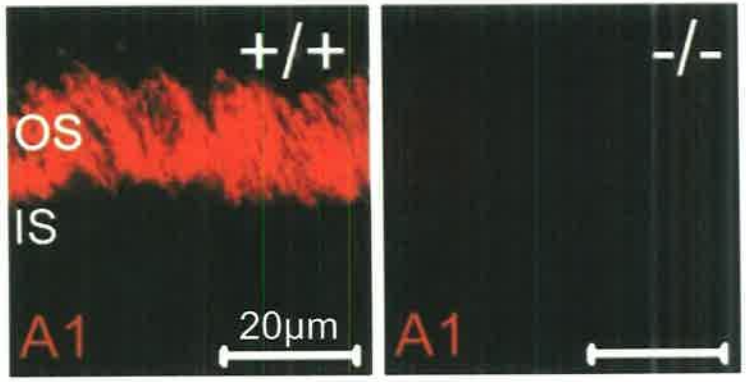
CNGB1 encodes the B subunit of the rod photoreceptor cyclic nucleotide-gated channel

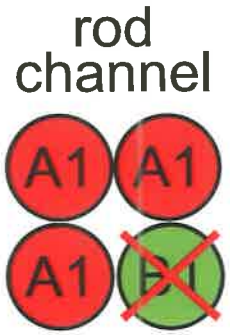


Rod CNG channel is formed by
3 **CNGA1** and 1 **CNGB1** subunits

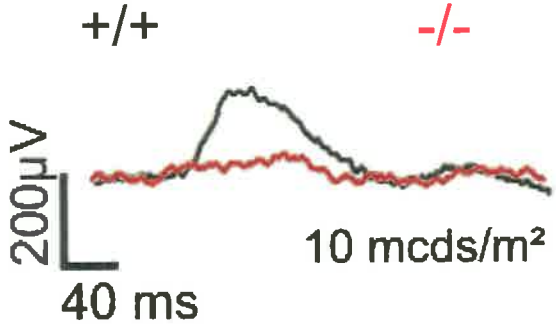
The *Cngb1* KO mouse model of RP







electroretinogram



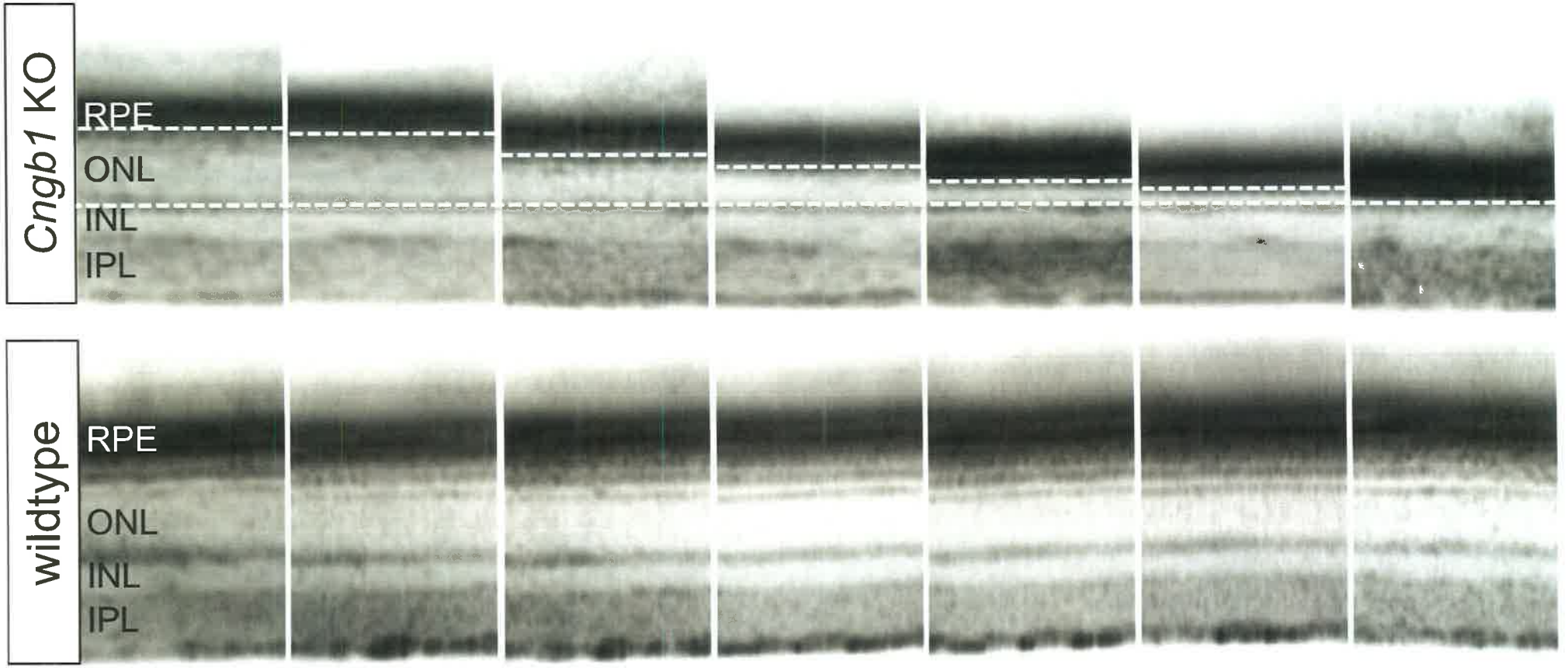
Hüttl et al. 2005, J Neursoci

Progressive degeneration of photoreceptors in *Cngb1* KO mice

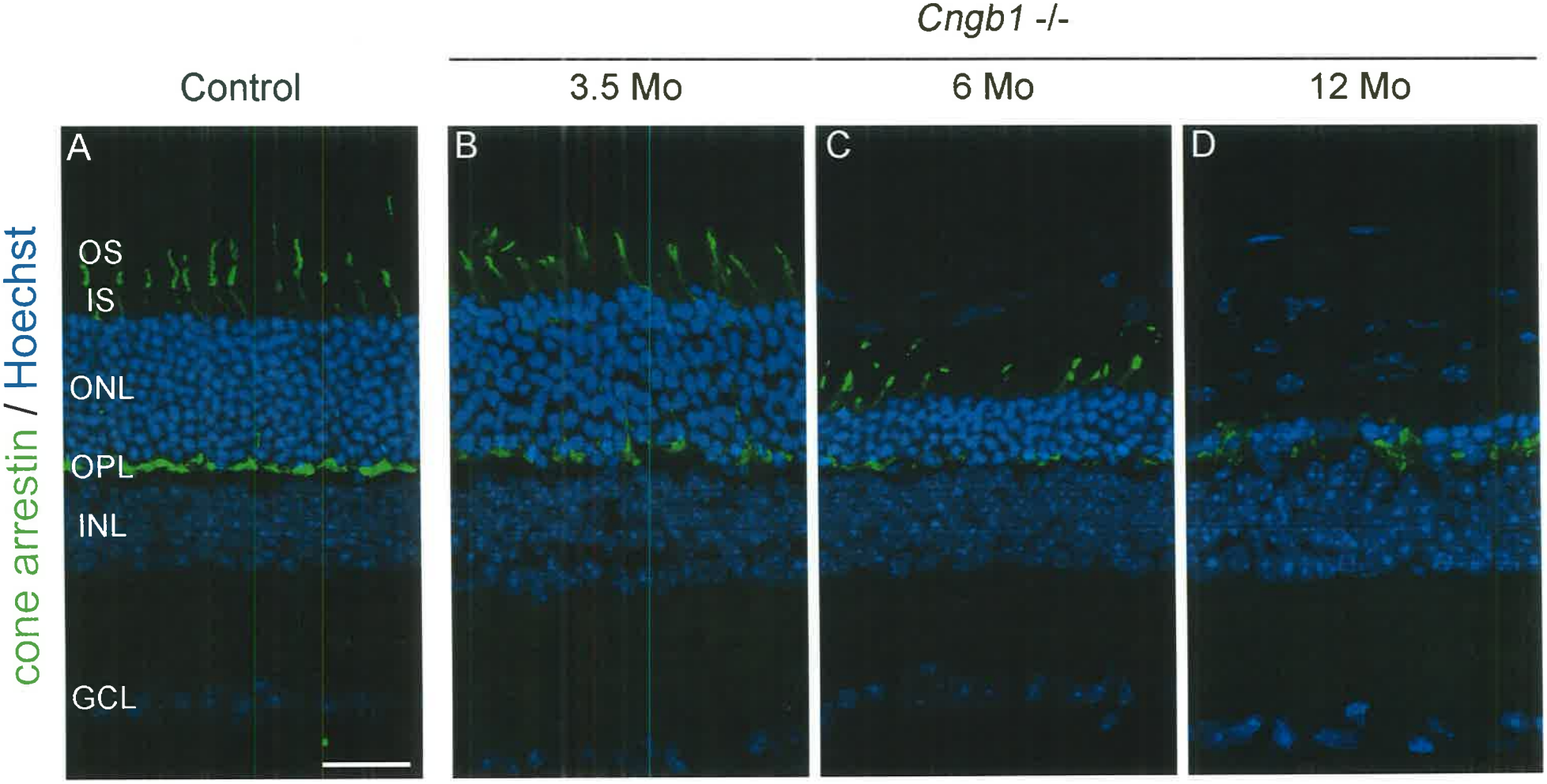
Night blindness

Complete blindness

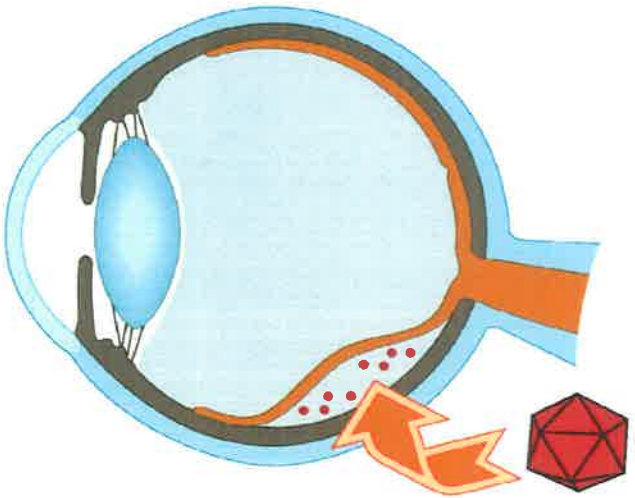
1 month | 2 months | 4 months | 6 months | 8 months | 10 months | 12 months



Secondary degeneration of cone photoreceptors in *Cngb1* KO mice



Development of a gene supplementation therapy for *CNGB1*-linked RP

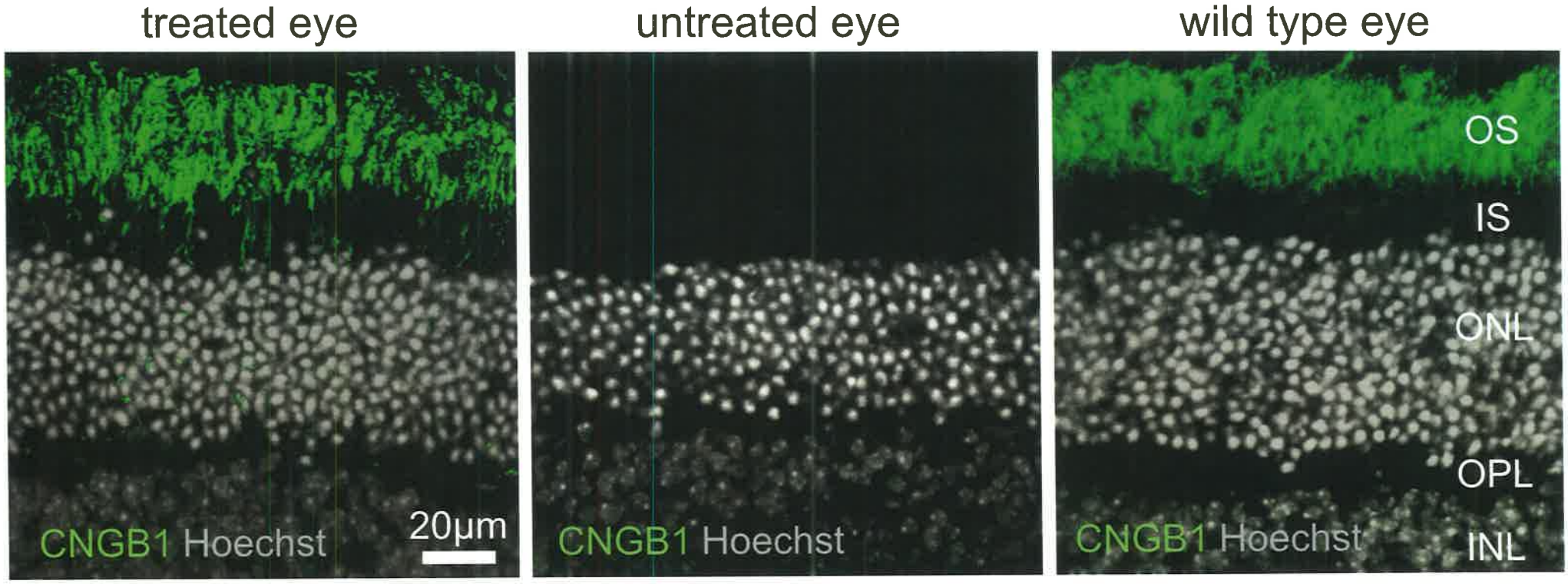


Cngb1 KO
mouse model of arRP

recombinant adeno-associated viral (rAAV) vector
for rod-specific expression of CNGB1

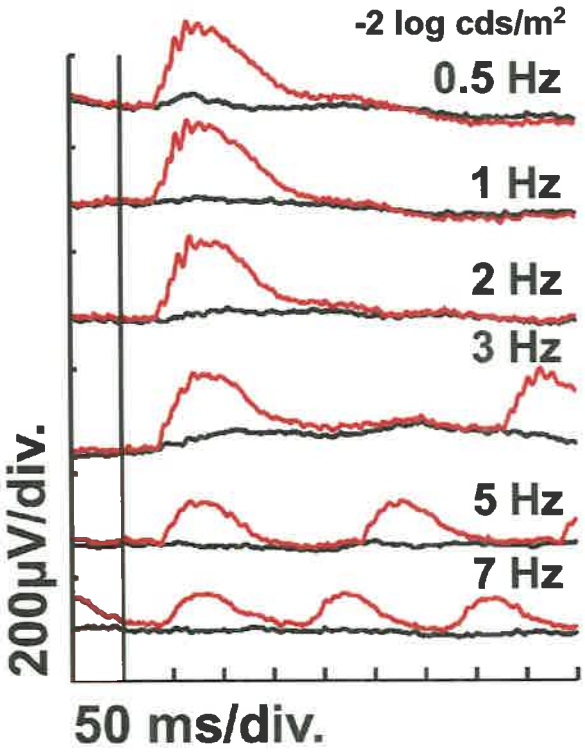
subretinal delivery of rAAV-CNGB1

rAAV-CNGB1 treatment leads to efficient and specific expression of CNGB1

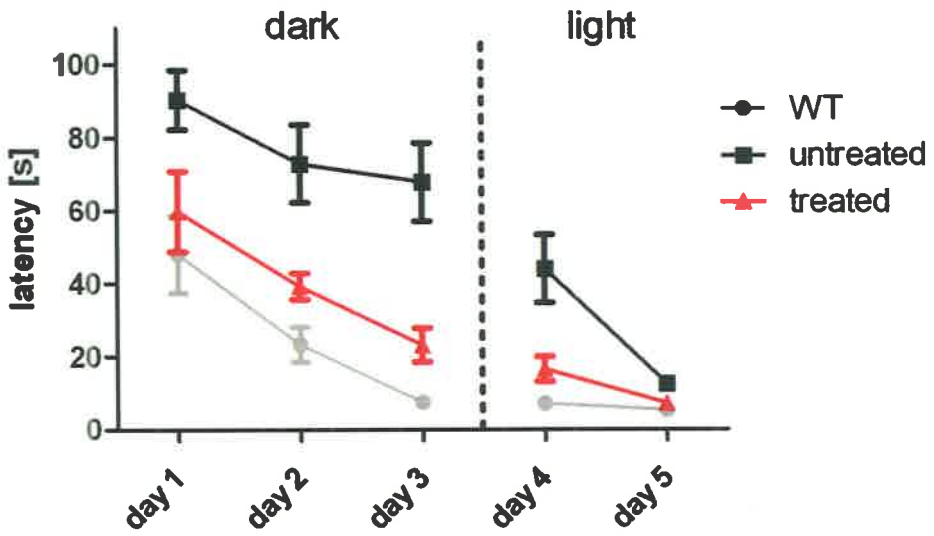


Rescue of rod-mediated light responses and vision

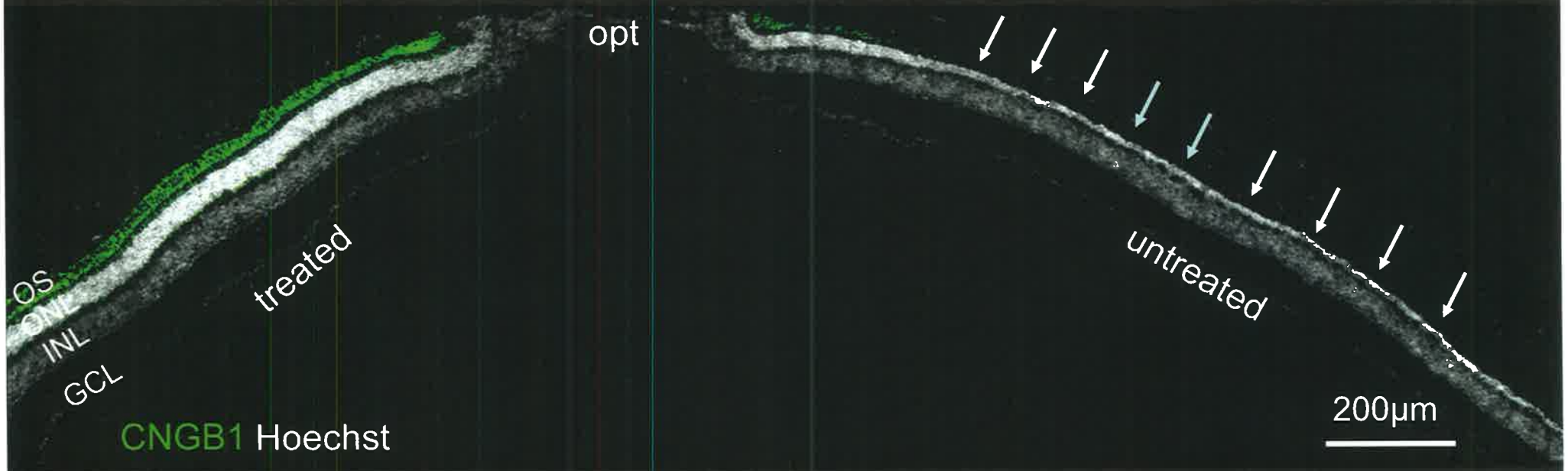
Scotopic flicker electroretinogram

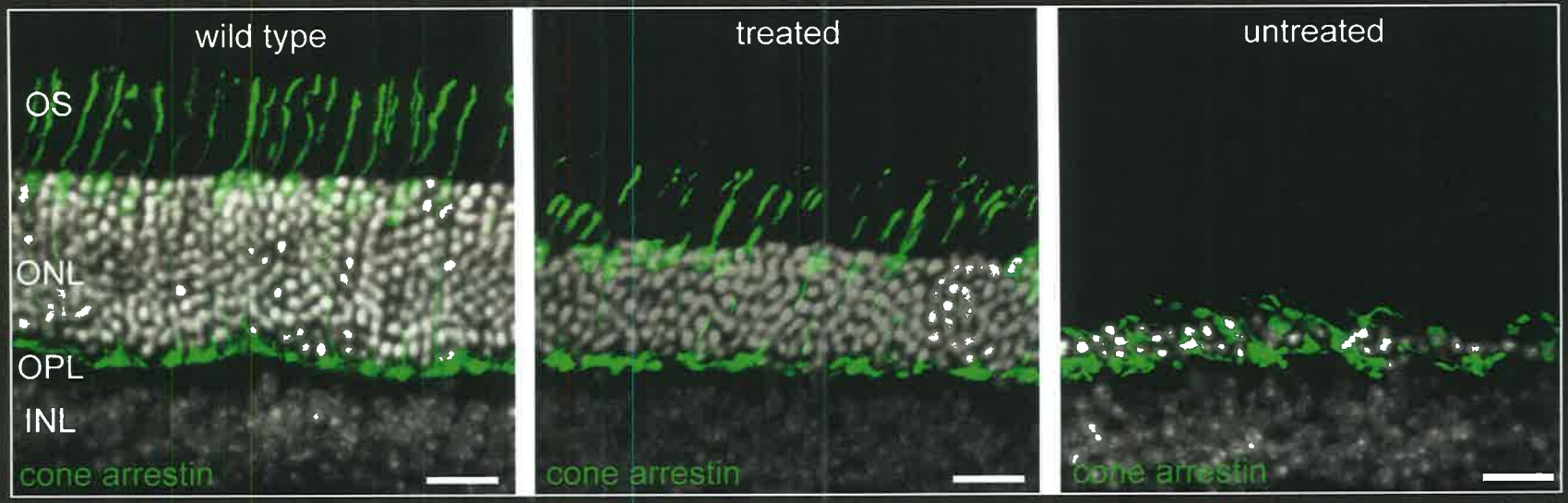


Rod vision dependent behavior



Long-term beneficial effect: 12 months after treatment





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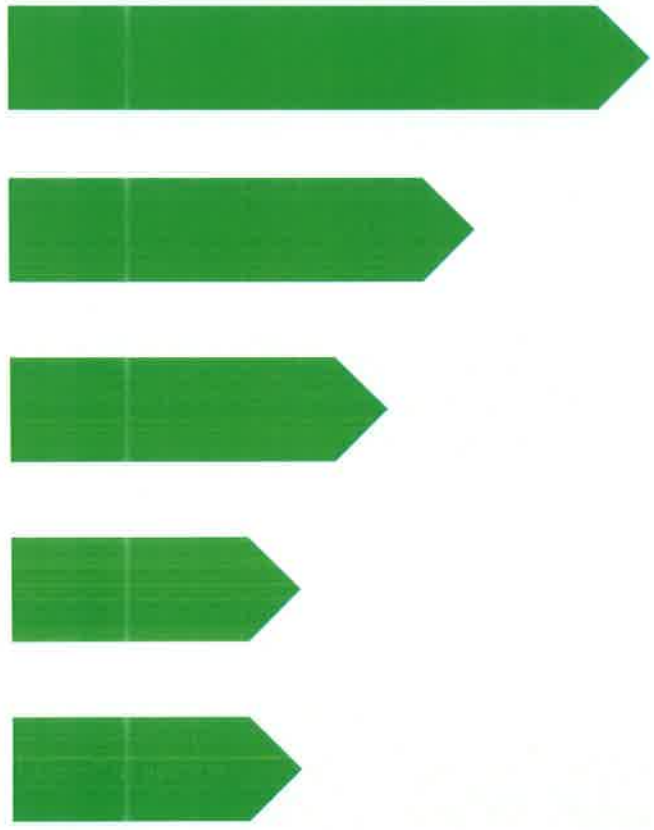

Graduate School of Systemic Neuroscience
LMU Munich

GRADUATE SCHOOL LIFE SCIENCE MUNICH

ViGeneron

TISTOU & CHARLOTTE KERSTAN STIFTUNG

CIPSM

Deutsche Forschungsgemeinschaft
DFG