
Erasmus MC

Universitair Medisch Centrum Rotterdam



Achromatopsie dag

12 maart 2016

Dr. Alberta Thiadens, oogarts

Prof. Caroline Klaver, oogarts & epidemioloog

Erasmus MC Rotterdam

UMC St Radboud Nijmegen

Kegels

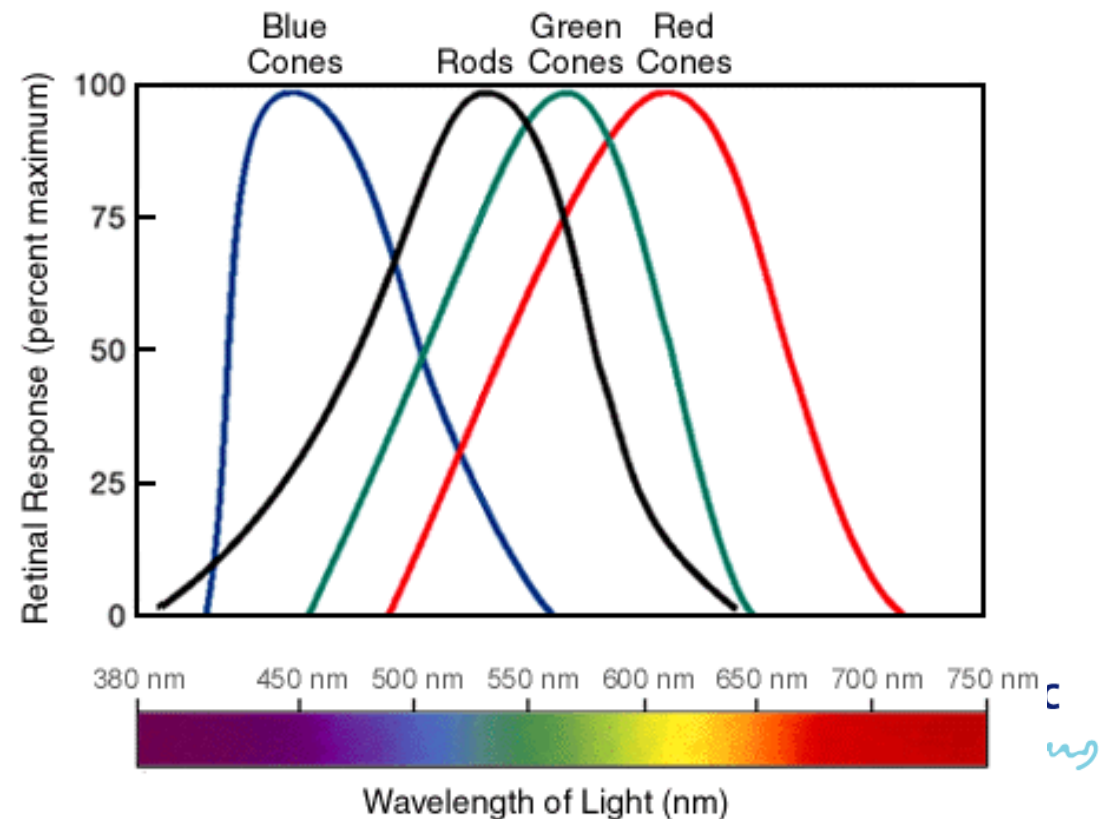
- 10% kegels (3-6 miljoen)
- Blauwe kegel: chrom. 7, afwezig in de fovea
- Rode/groene kegel: Xq28 in head-to-tail tandem array

Verdeling

Rood (P): 60%

Groen (D): 30%

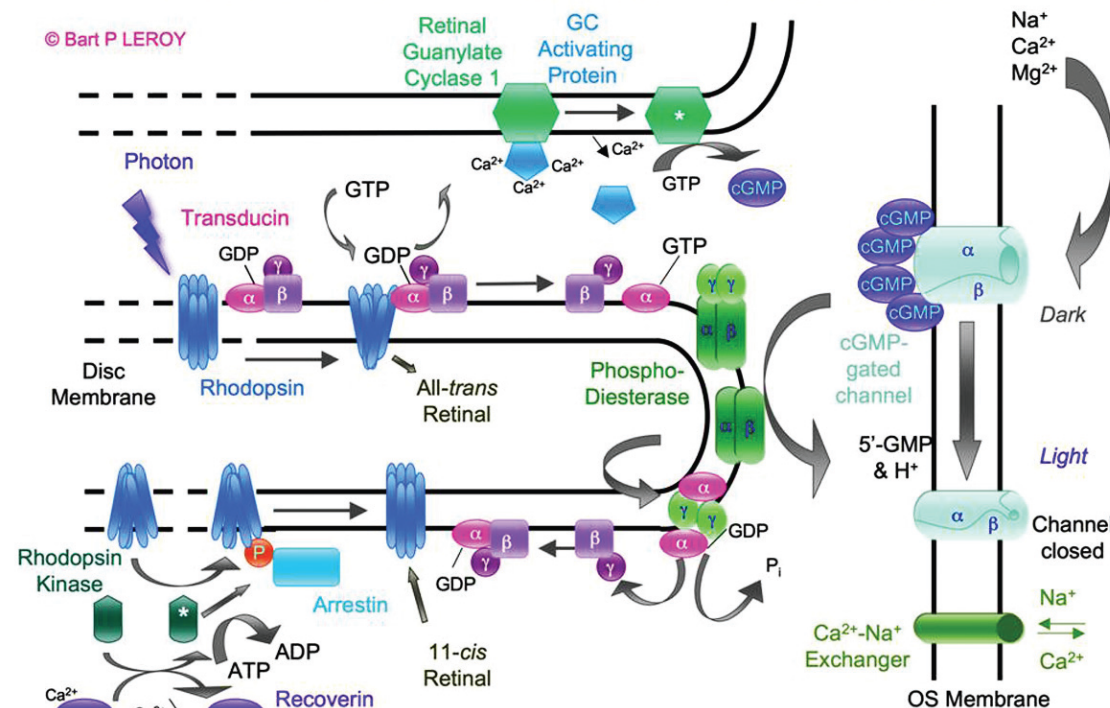
Blauw (T): 5%



Opsine

- Opsine membraaneiwit gelegen in buitensegment kegel
- Foton \sim chromofoor 11-*cis*-retinal \rightarrow all-*trans* retinal
- Hierdoor kan opsine binden aan transducine:
- Start fototransductie cascade

The Phototransduction Cascade

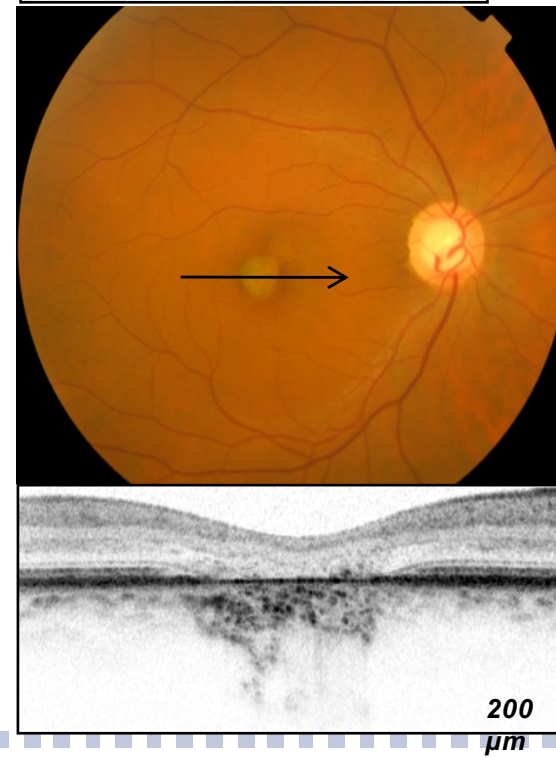
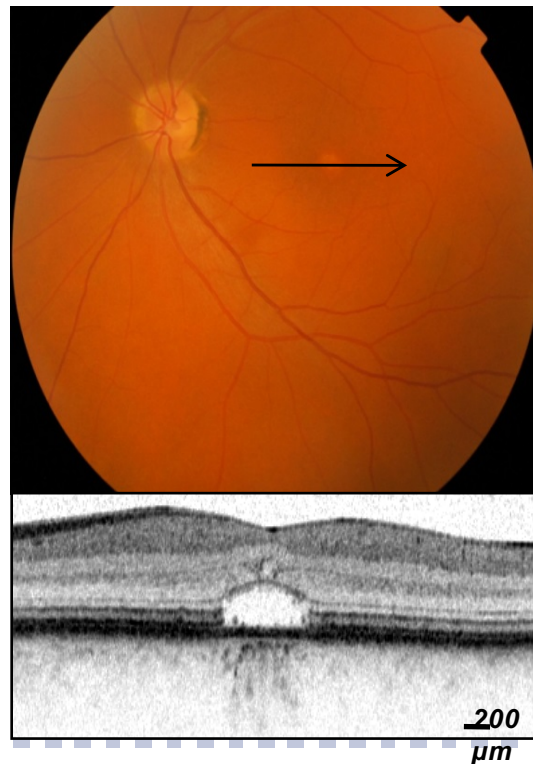
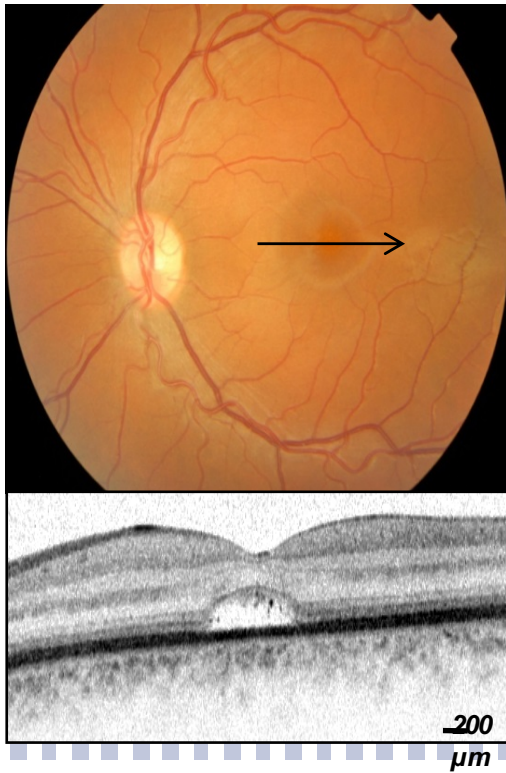
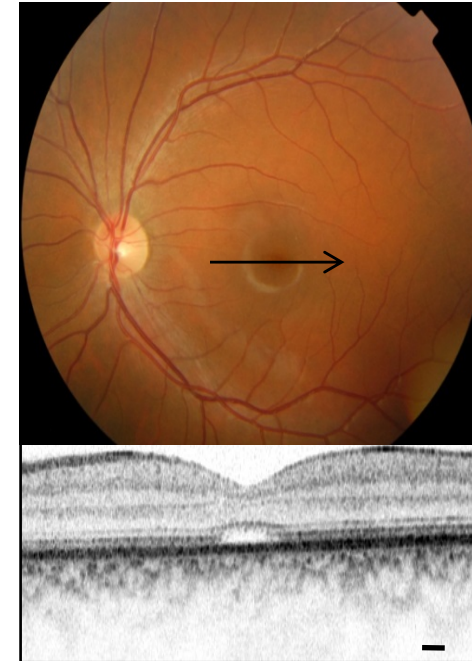
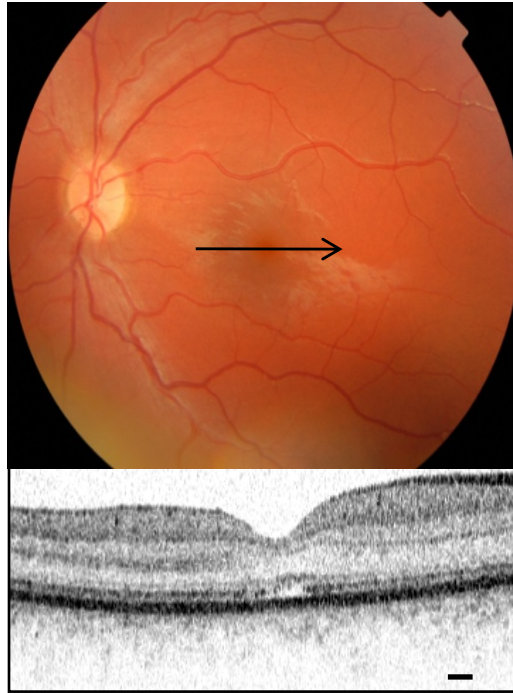


Achromatopsie

- Fotofobie
- Visus ~0.1
- Nystagmus
- Refractie afwijking
- Kleurenzien in alle assen gestoord
- ERG



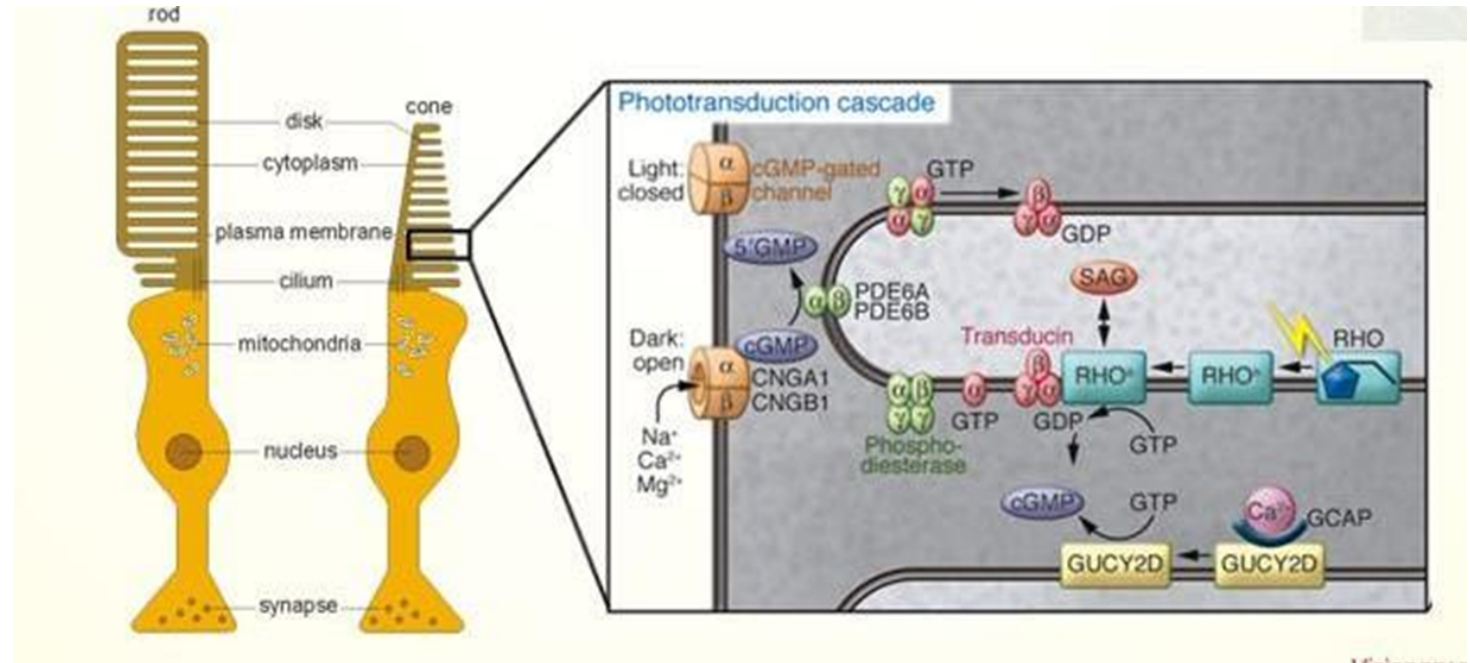
IOVS, Thiadens/Klaver



musMC
zapung

Genetische oorzaak

- CNGB3
 - CNGA3
 - GNAT2
 - PDE6C
 - PDE6H
- (1 case, Kohl)
- ATF6



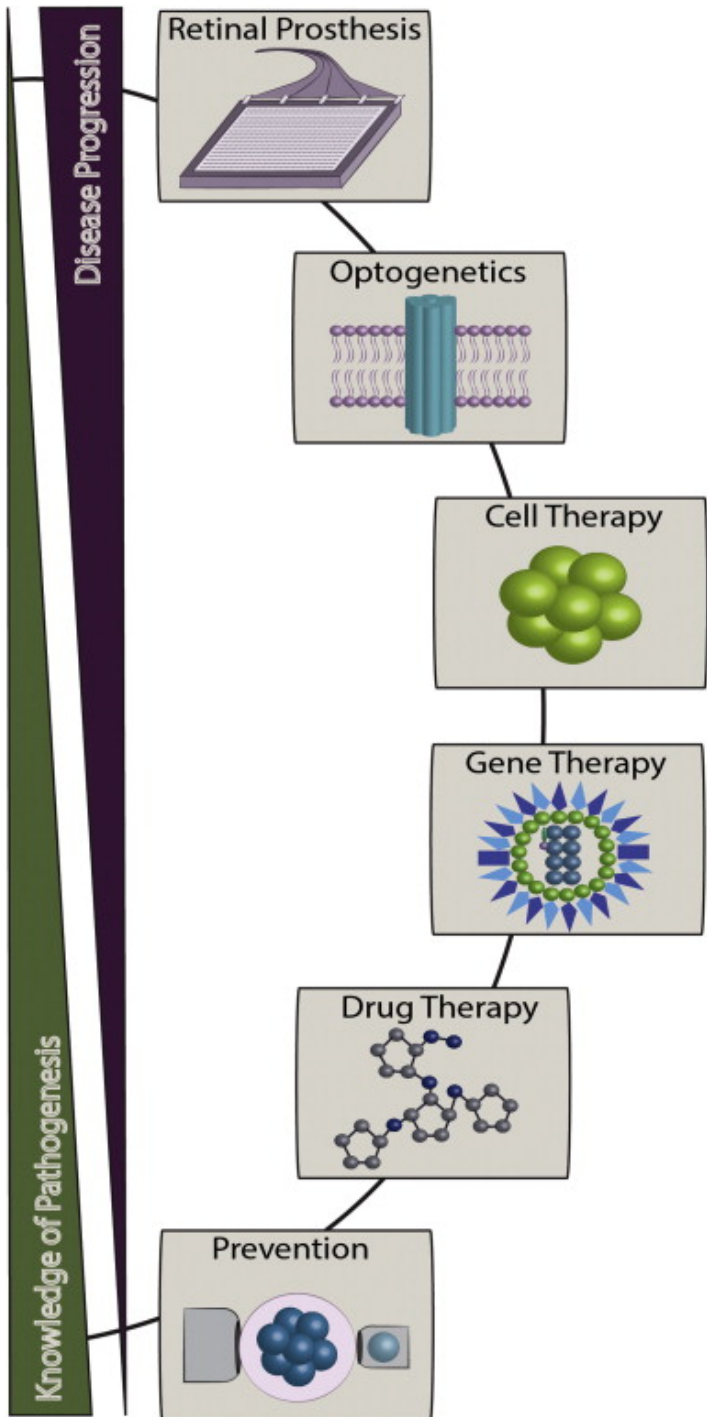
>90% in NL verklaard door CNGB3

De stand van zaken

Achromatopsia: On the Doorstep of a Possible Therapy

Ditta Zobor^a Gergely Zobor^a Susanne Kohl^b

^aInstitute for Ophthalmic Research, and ^bMolecular Genetics Laboratory, Institute for Ophthalmic Research, University of Tübingen, Tübingen, Germany



Retinal prosthesis: retina chip (Stingl Tubingen)

Optogenetics: neuronen moduleren tot lichtgevoelige cellen

Cell therapy: IPSc mutatie onafhankelijk (CHM MacLaren 2014, CEP290 Ali 2012): omdat ze te groot zijn om in AAV te verpakken of IPSc en CRISPR/CAS

-CNTF: CNGB3 (Komaromy/ Sieving)

Gene therapy: AAV gene specific augmentation therapy
CNGB3: Tubingen (Zrenner) / London (Michaelides) /USA (NEI)

CNGA3 : Tubingen (Zrenner/Kohl)

Drug therapy: QLT (9-*cis*-retinal) bij RPE65 en LRAT (Scholl & Zrenner)

Prevention: vitamine A beperkt dieet ABCA4

Lopende trials

CNGA3: Phase 1-2 efficacy&safety trial

- Inclusie okt 2012: 30 achromatopsie patiënten uit Italië en Duitsland
- Hiervan: 9 patiënten geselecteerd voor injecties: 1^e in nov. 2015 en 2^e in feb.
- Injecties subretinaal AAV-vector
- Tussen elke patiënt 4 weken pauze: dus in de herfst alle patiënten 1^e keer behandeld
- Nu geen verder inclusie: maar afhankelijk van 1e resultaten en funding gaat de studie verder voor alle CNGA3 patiënten in Europa

CNGB3: Phase 1-2 efficacy&safety trial

- Eind 2016 zal een nieuwe trial starten in London Moorefields ziekenhuis
- Feb 2016 is gestart in National Eye Institute (NEI), USA
- Nu nog geen werving

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5 studies found for: Achromatopsia
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Rank	Status	Study
1	Active, not recruiting Has Results	<u>CNTF Implants for CNGB3 Achromatopsia</u> Conditions: Eye Disease; Achromatopsia Intervention: Biological: NT-501 CNTF-releasing implant
2	Recruiting	<u>Clinical and Genetic Characterization of Individuals With Achromatopsia</u> Condition: Achromatopsia Intervention:
3	Recruiting	<u>Safety and Efficacy of a Single Subretinal Injection of rAAV.hCNGA3 in Patients With CNGA3-linked Achromatopsia</u> Condition: Achromatopsia Intervention: Drug: rAAV.hCNGA3
4	Not yet recruiting	<u>Safety and Efficacy Trial of AAV Gene Therapy in Patients With CNGB3 Achromatopsia</u> Condition: Achromatopsia Intervention: Biological: rAAV2tYF-PR1.7-hCNGB3
5	Recruiting	<u>Inherited Retinal Degenerative Disease Registry</u> Conditions: Eye Diseases Hereditary; Retinal Disease; Achromatopsia; Bardet-Biedl Syndrome; Bassen-Kornzweig Syndrome; Batten Disease; Best Disease; Choroidal Dystrophy; Choroideremia; Cone Dystrophy; Cone-Rod Dystrophy; Congenital Stationary Night Blindness; Enhanced S-Cone Syndrome; Fundus Albipunctatus; Goldmann-Favre Syndrome; Gyrate Atrophy; Juvenile Macular Degeneration; Kearns-Sayre Syndrome; Leber Congenital Amaurosis; Refsum Syndrome; Retinitis Pigmentosa; Retinitis Punctata Albescens; Retinoschisis; Rod-Cone Dystrophy; Rod Dystrophy; Rod Monochromacy; Stargardt Disease; Usher Syndrome Intervention:

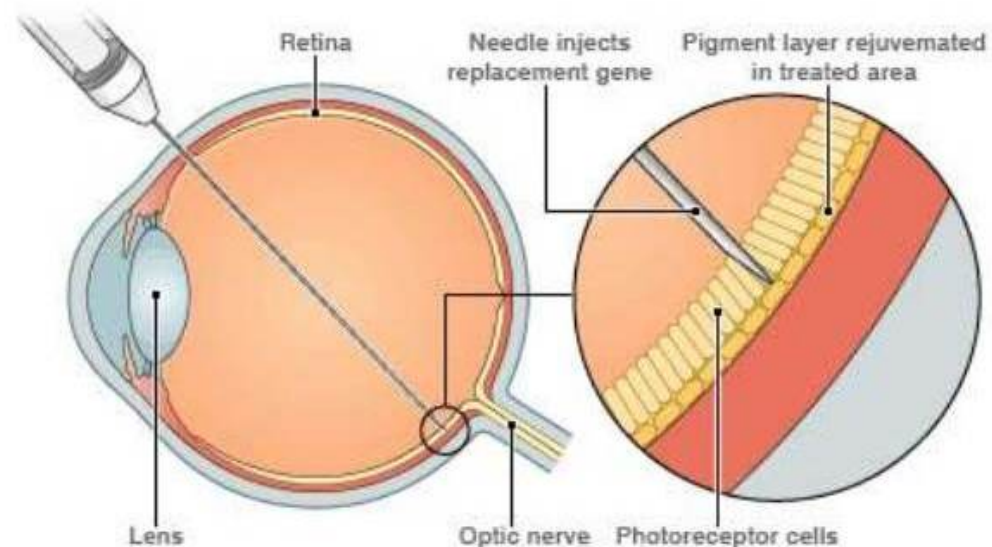
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† Indicates status has not been verified in more than two years

Clinical trials

AAV gene replacement therapy

- Honden (Komaromy 2010)/muizen (Michalakis 2012 en Pang 2012)/ schapen (Banin 2014) : *CNGB3*, *CNGA3*, *GNAT2* subretinaal injectie
- Conclusie: dat kegels die niet hebben gefunctioneerd sinds geboorte toch geactiveerd kunnen worden, effect hield aan tenminste 8 mnd na injectie



CNGB3 muizen: Ali et al. 2011

Long-term and age-dependent restoration of visual function in a mouse model of CNGB3-associated achromatopsia following gene therapy

Livia S. Carvalho¹, Jianhua Xu², Rachael A. Pearson¹, Alexander J. Smith¹,
James W. Bainbridge¹, Lysie M. Morris², Steven J. Fliesler^{3,4,5,6}, Xi-Qin Ding^{2,*}
and Robin R. Ali^{1,*} *Human Mol Gen*

- Subretinale injectie vector AAV in CNGB3 -/- muizen
- CNGB3 eiwit gevonden en ook toename levels CNGA3
- Zowel toename buitensegmenten als kegel dichtheid
- Kegels ERG amplitudes tot 90% vergeleken met WT
- Significante verbetering visus
- 6 maanden oude muizen, maar beter resultaat visus in 2-4 weken oude muizen

CNGA3 muizen: Hauswirth & Pang et al. 2015

ORIGINAL ARTICLE *Human Mol Gen*

Vitreale delivery of AAV vectored Cnga3 restores cone function in $CNGA3^{-/-}/Nrl^{-/-}$ mice, an all-cone model of CNGA3 achromatopsia[†]

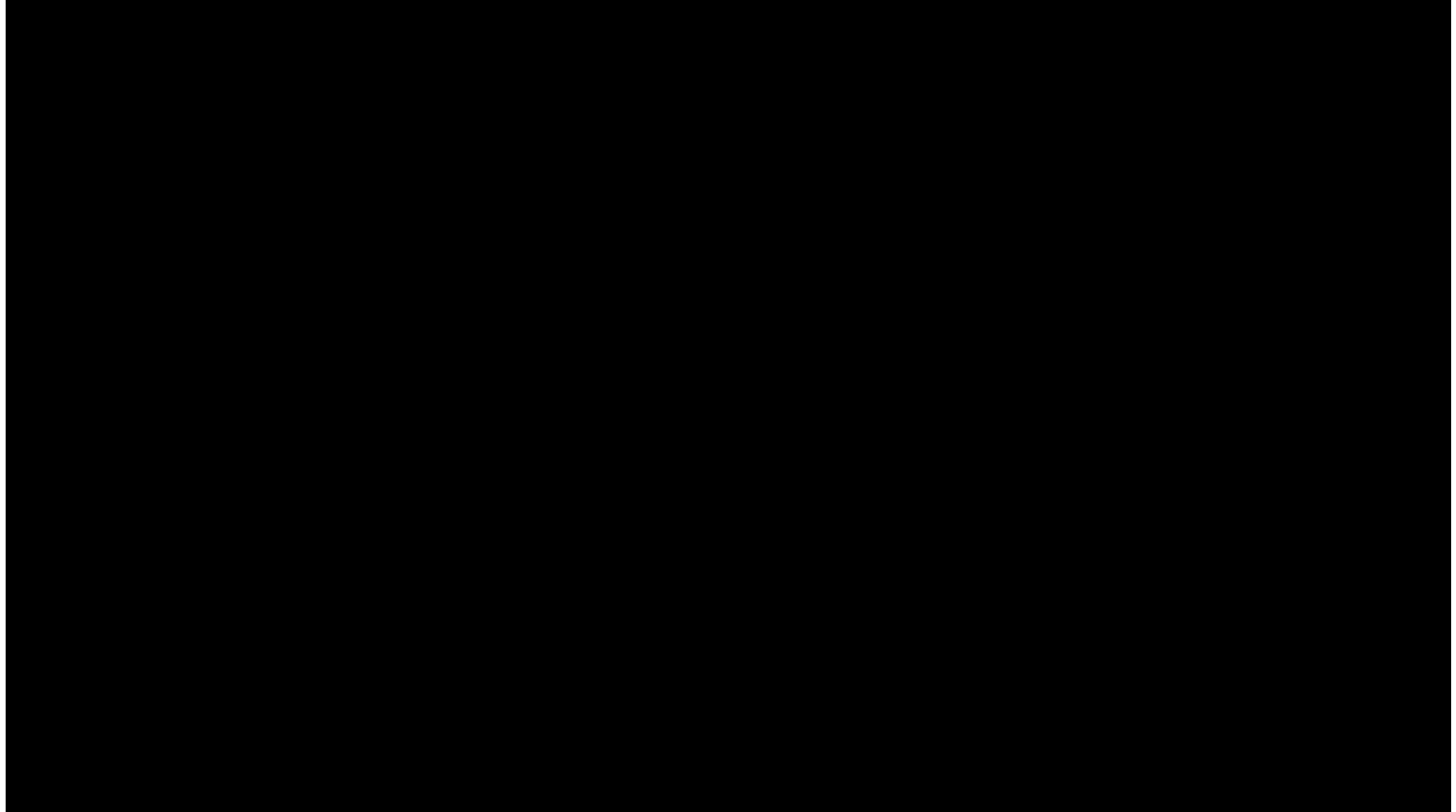
Wei Du¹, Ye Tao¹, Wen-Tao Deng¹, Ping Zhu¹, Jie Li¹, Xufeng Dai^{1,2}, Yuxin Zhang^{1,3}, Wei Shi¹, Xuan Liu¹, Vince A. Chiodo¹, Xi-Qin Ding⁴, Chen Zhao³, Stylianos Michalakis⁵, Martin Biel⁵, Zuoming Zhang^{6,*}, Jia Qu^{2,*}, William W. Hauswirth^{1,*} and Ji-jing Pang^{1,2,3,*}

- Intravitreale injectie AAV-CNGA3 vector
- Toename kegelfunctie: ERG
- Verbetering kegel structuur zichtbaar

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CNGB3 AAV-gene replacement therapy



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Ciliary Neurotrophic Factor (CNTF) implant

CNTF promoot overleving en functie van zenuwcellen in het netvlies
Tijdelijk effect: OS korter -> regrowing cone OS en regeneratie

Transient Photoreceptor Deconstruction by CNTF Enhances rAAV-Mediated Cone Functional Rescue in Late Stage *CNGB3*-Achromatopsia

András M Komáromy^{1,2}, Jessica S Rowlan¹, Amanda T Parton Corr¹, Shelby L Reinstein¹, Sanford L Boye³, Ann E Cooper¹, Amaliris Gonzalez⁴, Britt Levy¹, Rong Wen⁵, William W Hauswirth^{3,6}, William A Beltran¹ and Gustavo D Aquirre¹

Na 1 jaar geen effect meer gemeten bij N=5 *CNGB3*-patiënten:

Retina

***CNGB3*-Achromatopsia Clinical Trial With CNTF: Diminished Rod Pathway Responses With No Evidence of Improvement in Cone Function**

Wadih M. Zein,¹ Brett G. Jeffrey,¹ Henry E. Wiley,¹ Amy E. Turriff,¹ Santa J. Tumminia,¹ Weng Tao,² Ronald A. Bush,³ Dario Marangoni,^{3,4} Rong Wen,⁵ Lisa L. Wei,¹ and Paul A. Sieving^{1,3}



Conclusie

- Gen therapie nog in kinderschoenen
- Op dieren niveau wel veelbelovende resultaten
- Mogelijkheden meedoen aan trial:
<https://clinicaltrials.gov/>

Dank u voor uw aandacht

Vragen?

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Oogartsen
Alberta Thiadens en Caroline Klaver

