Update on potential therapies for inherited retinal dystrophies

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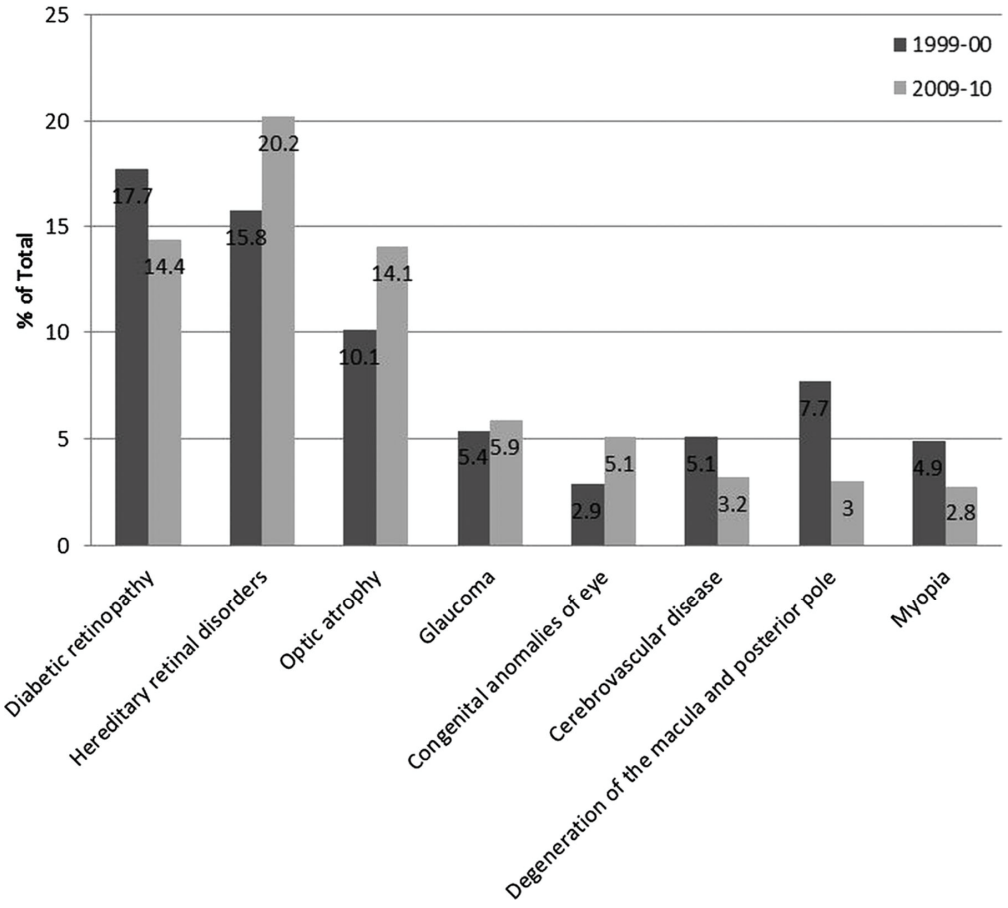
Clinical research associate, Nuffield laboratory of Ophthalmology, Oxford

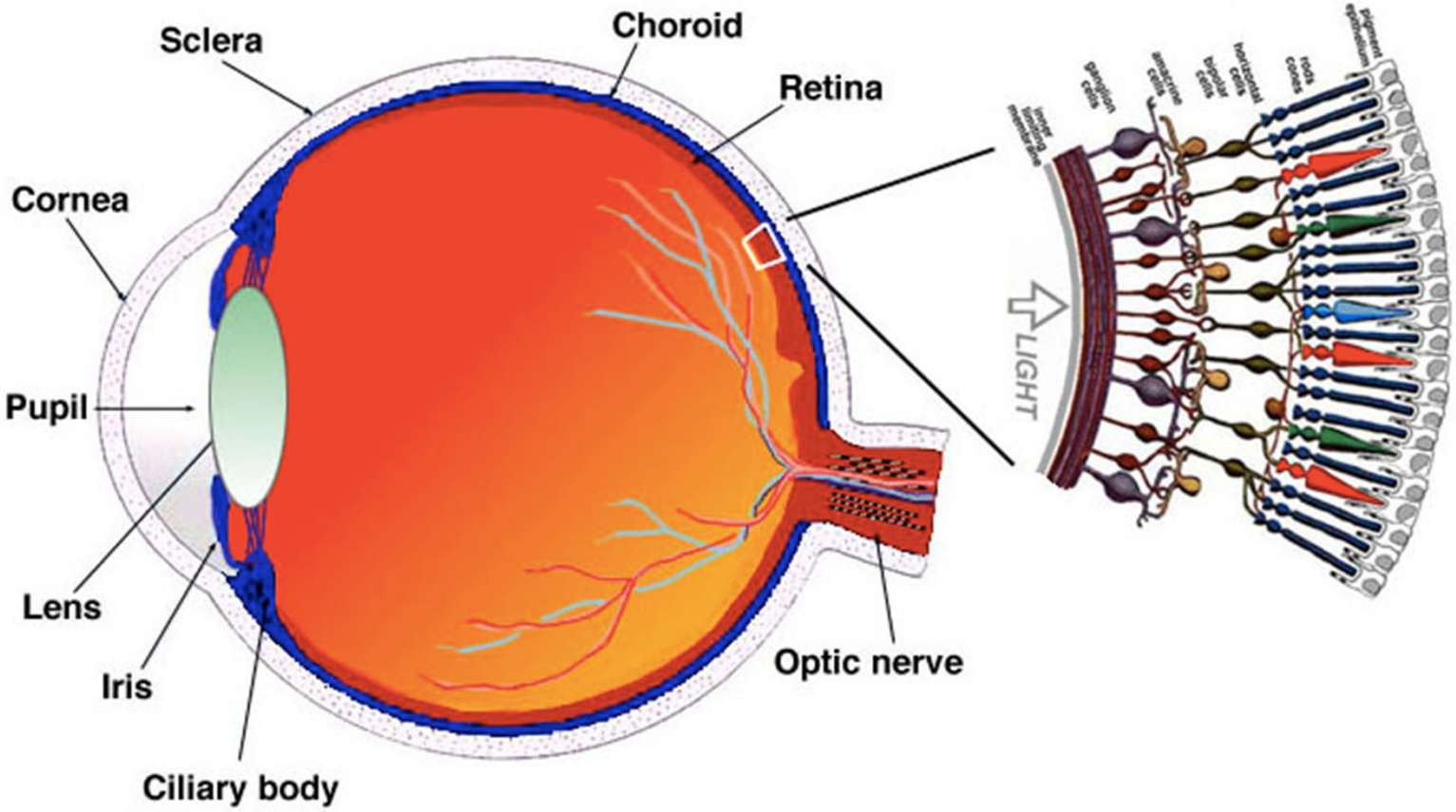
RETINA UK

Inherited retinal degenerations

- Affect 1/3000 people
- Commonest cause of blindness in working age population (age 16-64)

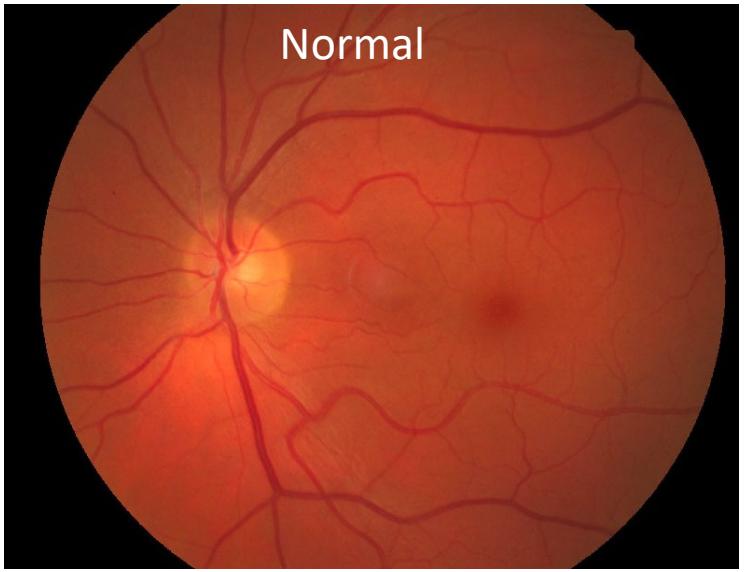


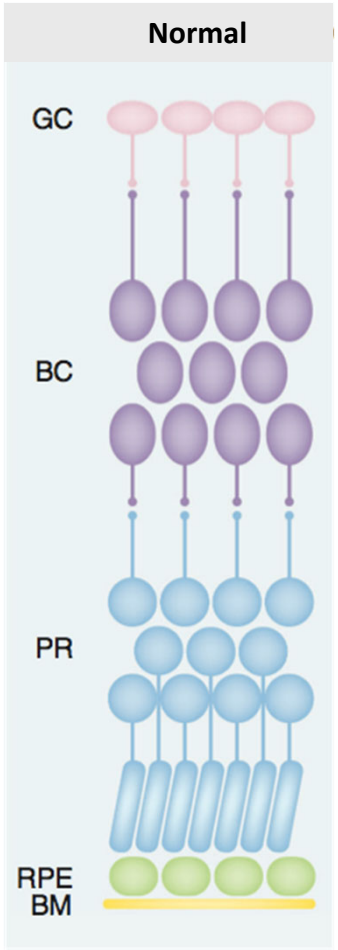
Liew, Michaelides & Bunce, 2014

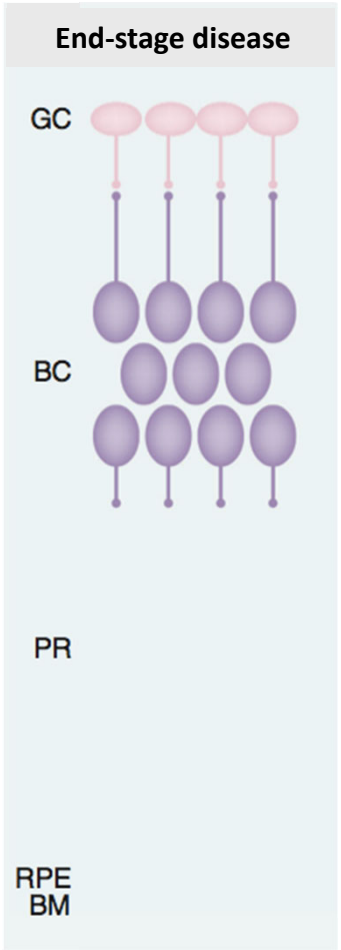


http://webvision.med.utah.edu

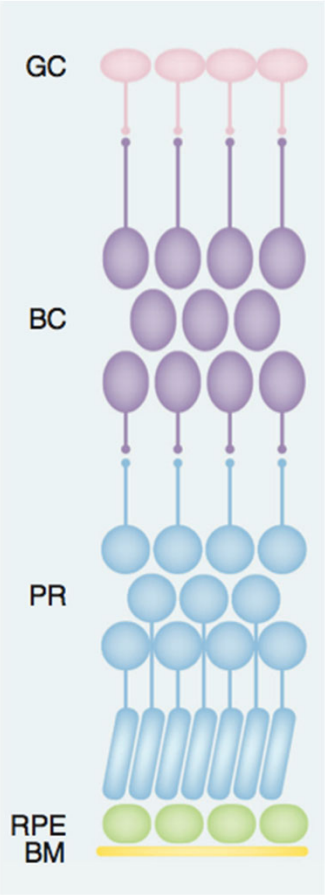
Retinal degenerations

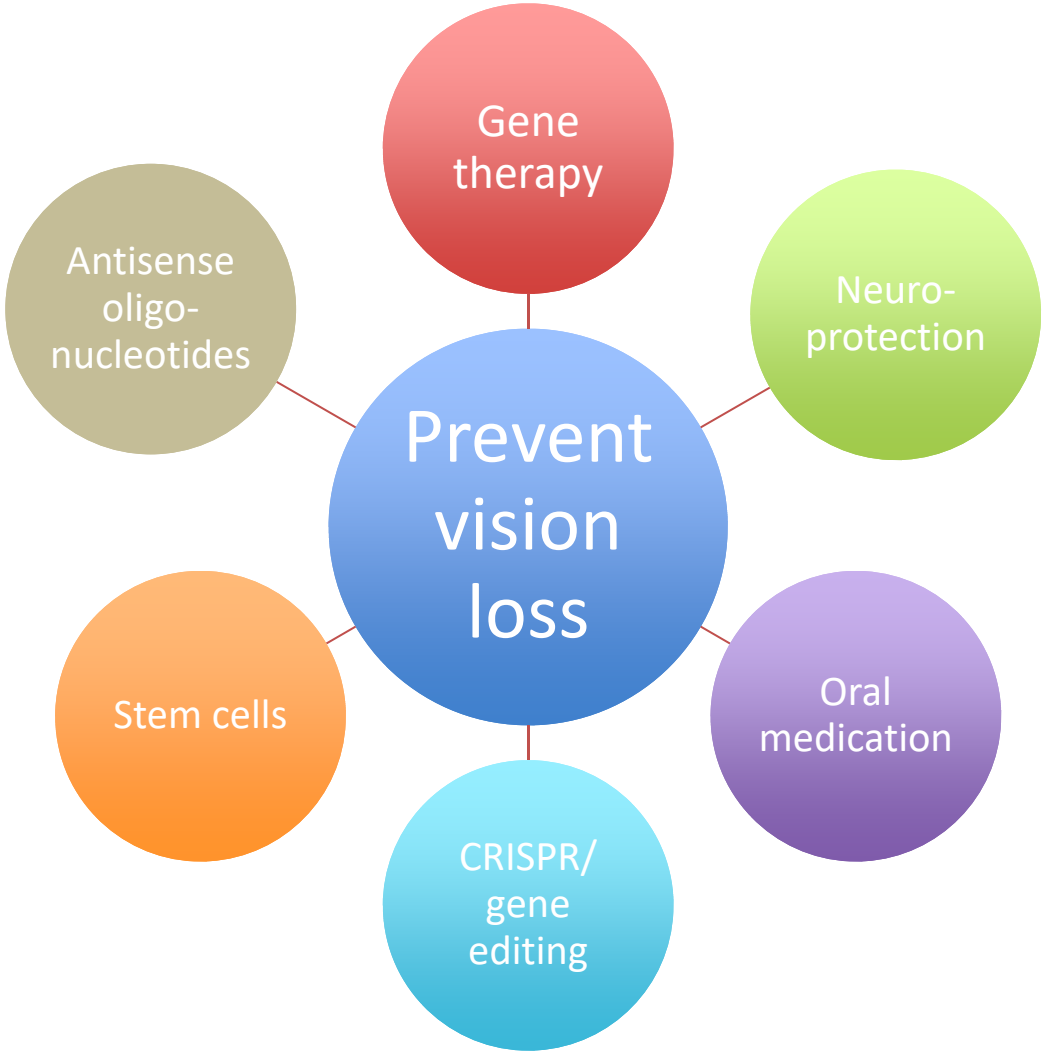




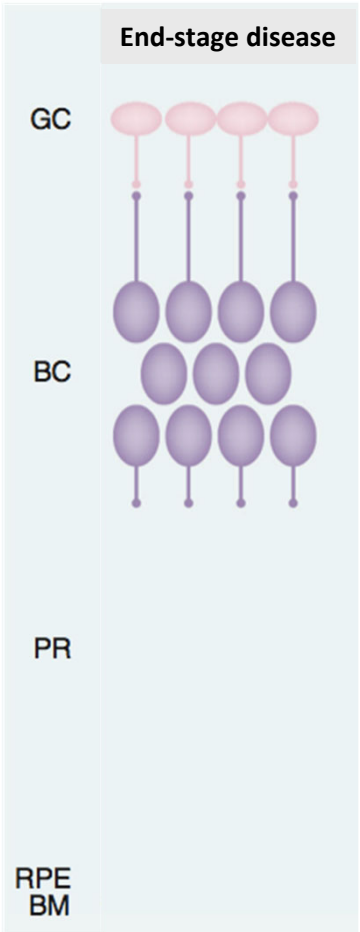


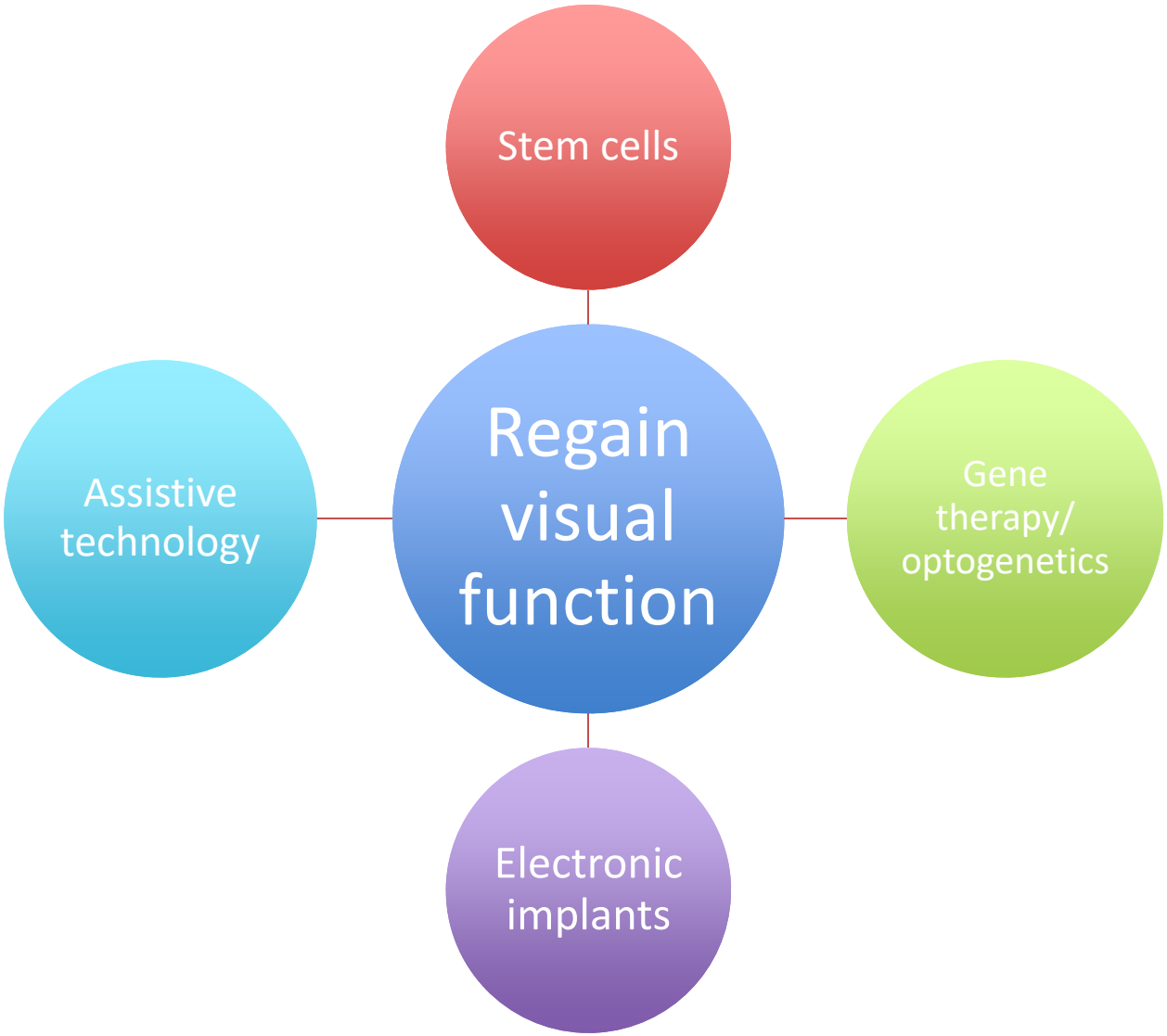
Early disease



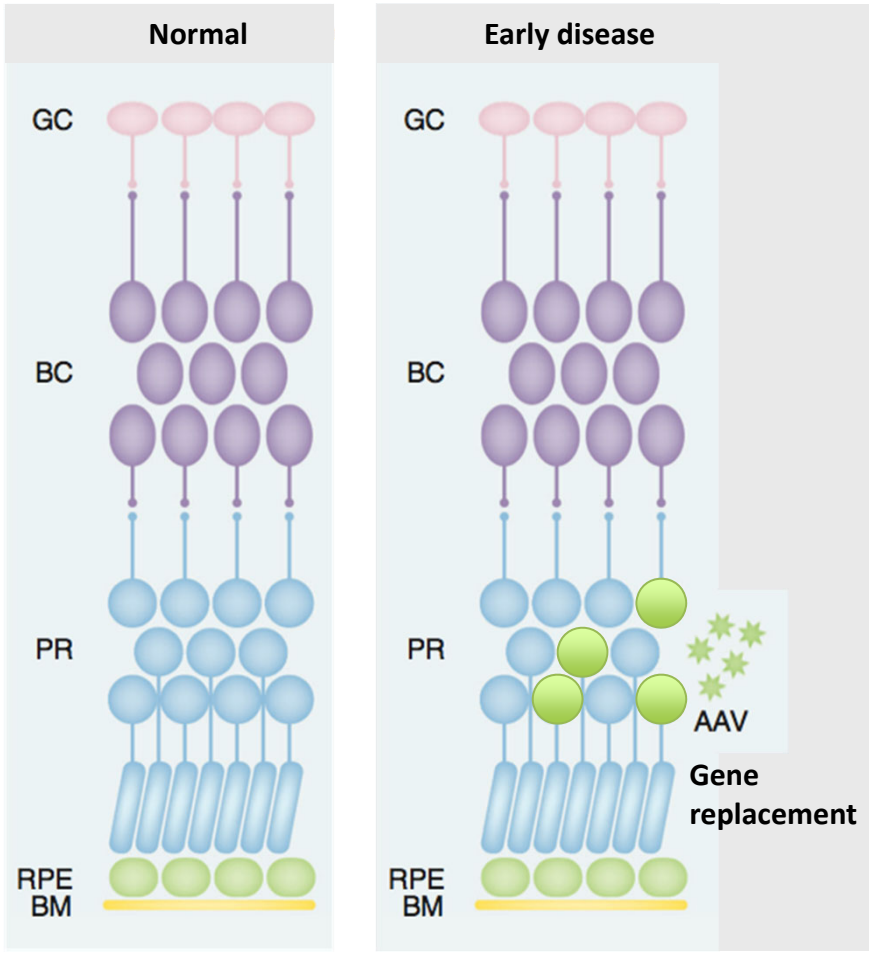


Advanced/ end-stage disease



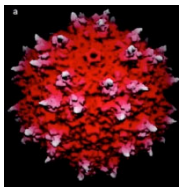


1. Gene therapy



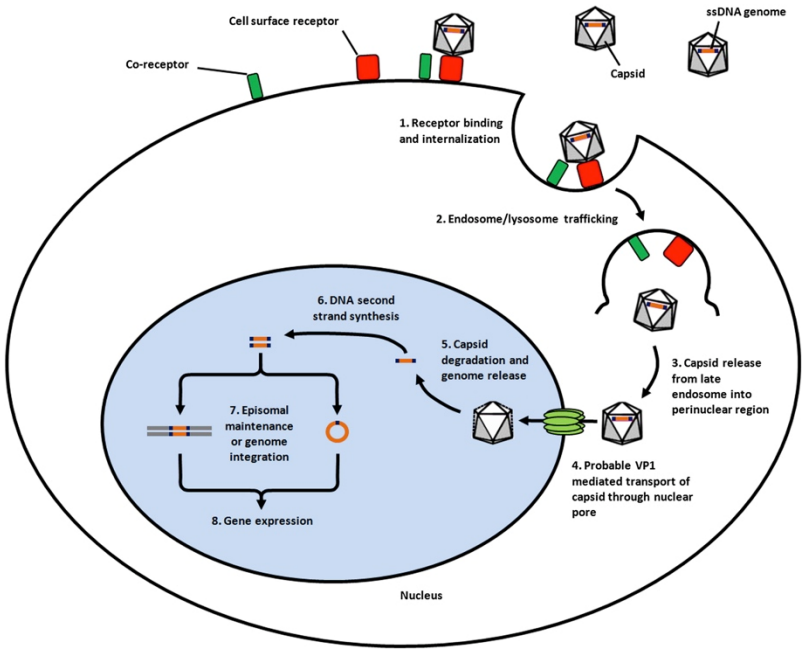
Express melanopsin

Adeno-associated viral vectors



Wild type AAV

Gene therapy AAV

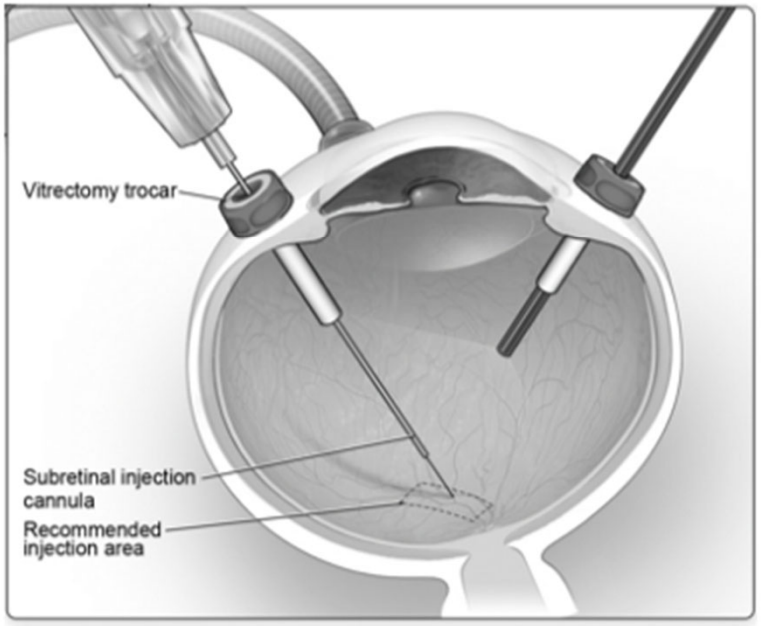


Viral DNA remains in cell for its lifetime➔one-off treatment

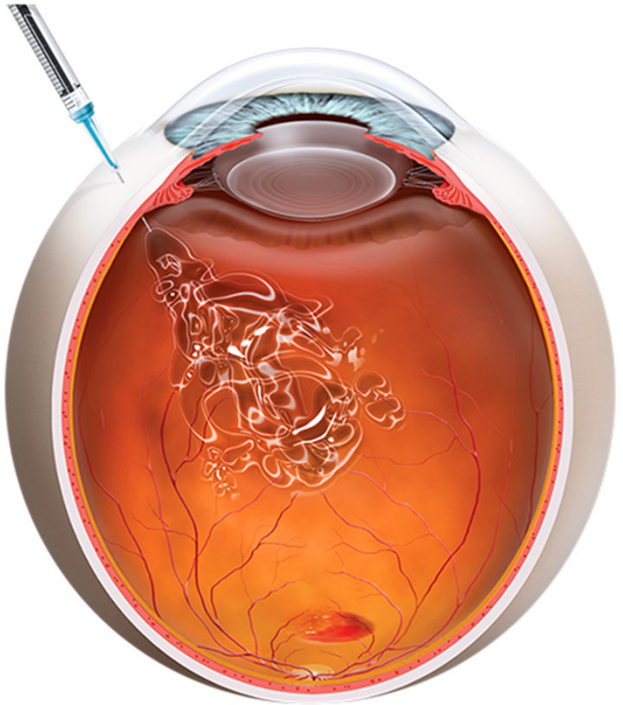
Lipinski et al, 2013

Subretinal injection

Figure 5a. Subretinal injection cannula introduced via pars plana

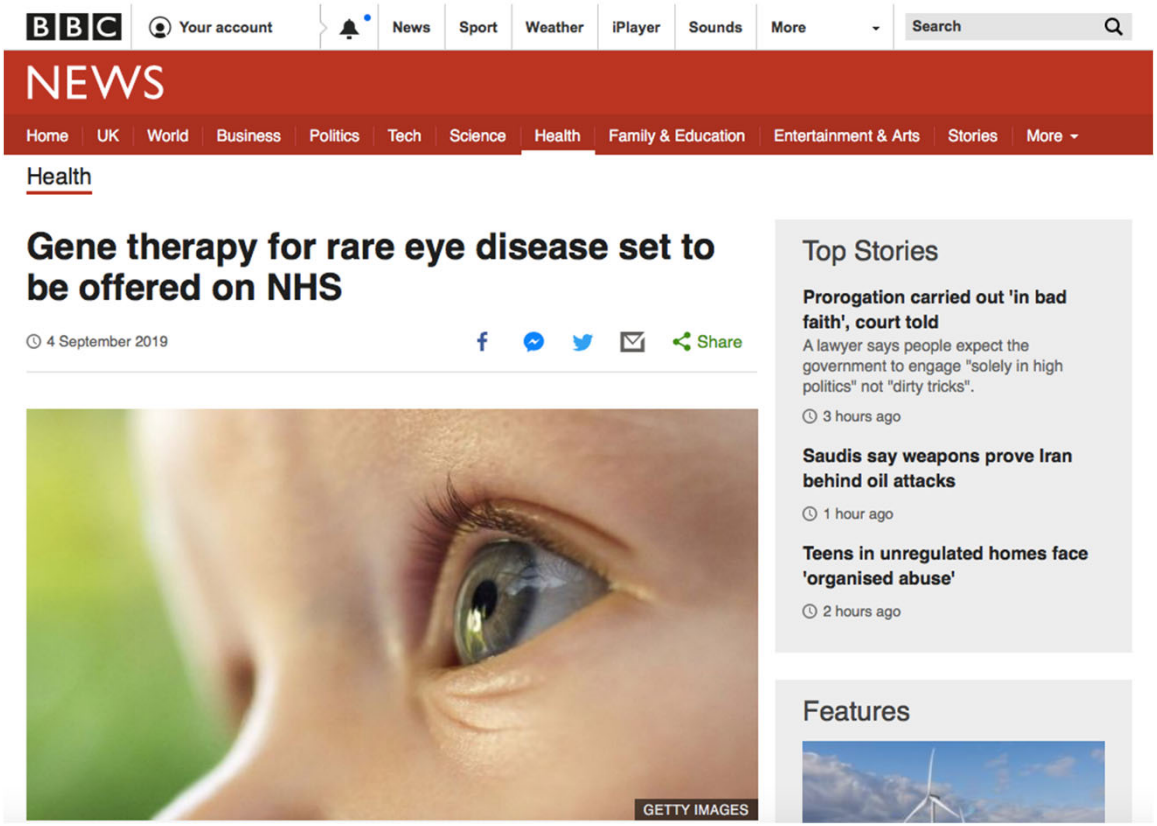


Intravitreal injection



from Spark Therapeutics

FDA approval Dec 2017
EMA approval Nov 2018
Cost $425,000 per eye



Disease	Gene	Vector	Delivery	Sponsor
LCA/RP	**RPE65**	**AAV**	**Subretinal**	**Spark therapeutics**
Achromatopsia	CNGA3	AAV	Subretinal	AGTC, Tubingen Hospital
Achromatopsia	CNGB3	AAV	Subretinal	AGTC, MeiraGTx*
Choroideremia	CHM	AAV	Subretinal	Spark therapeutics, Tubingen, Nightstarx*
LCA/RP	RPE65	AAV	Subretinal	MeiraGTx*
X-linked RP	RPGR	AAV	Subretinal	AGTC, MeiraGTx*, NightstaRx*
RP	MERTK	AAV	Subretinal	King Khaled Eye Hospital
RP	PDE6B	AAV	Subretinal	Horana
X-linked retinoschisis	RS1	AAV	Intravitreal	AGTC, NEI
Stargardt	ABCA4	EIAV	Subretinal	Sanofi
Usher type 1	MYO7A	EIAV	Subretinal	Sanofi

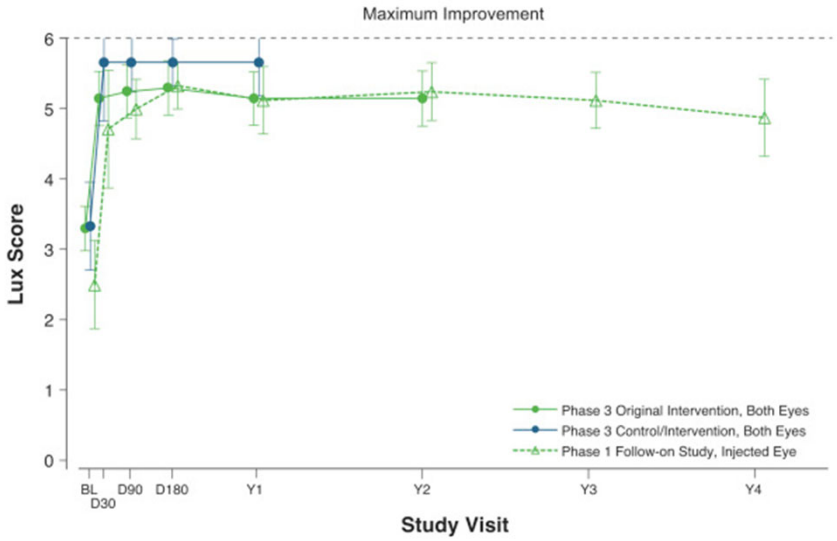
* recruiting in the UK

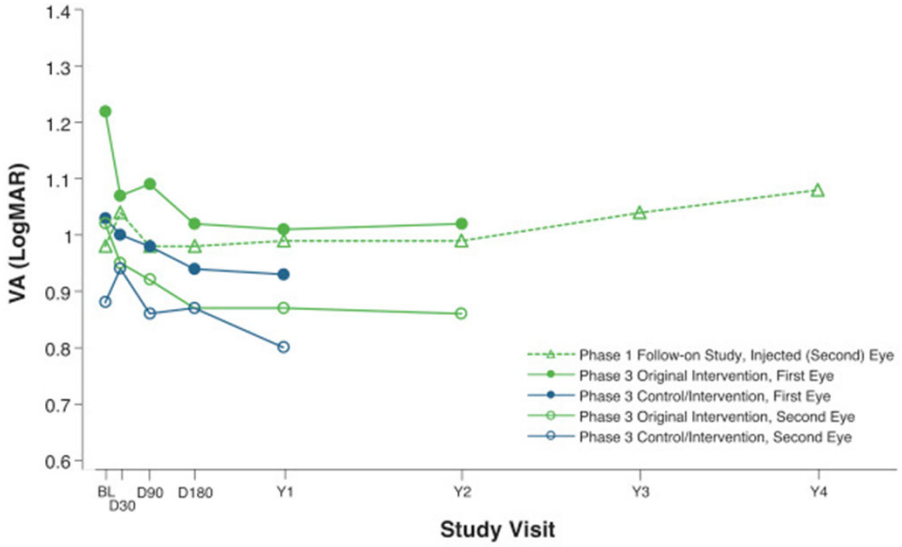
Ophthalmology
Volume 126, Issue 9, September 2019, Pages 1273-1285

Original Article

Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in *RPE65* Mutation–Associated Inherited Retinal Dystrophy: Results of Phase 1 and 3 Trials

Albert M. Maguire MD [1, 2], Stephen Russell MD [3], Jennifer A. Wellman MS [2, 4], Daniel C. Chung DO, MA [2, 4], Zi-Fan Yu ScD [5], Amy Tillman MS [5], Janet Wittes PhD [5], Julie Pappas BA [6], Okan Elci PhD [6], Kathleen A. Marshall COT [2], Sarah McCague MS [2], Hannah Reichert BS [7], Maria Davis BA [7], Francesca Simonelli MD [8], Bart P. Leroy MD, PhD [9, 10], J. Fraser Wright PhD [2, 4], Katherine A. High MD [2, 4], Jean Bennett MD, PhD [1, 2]

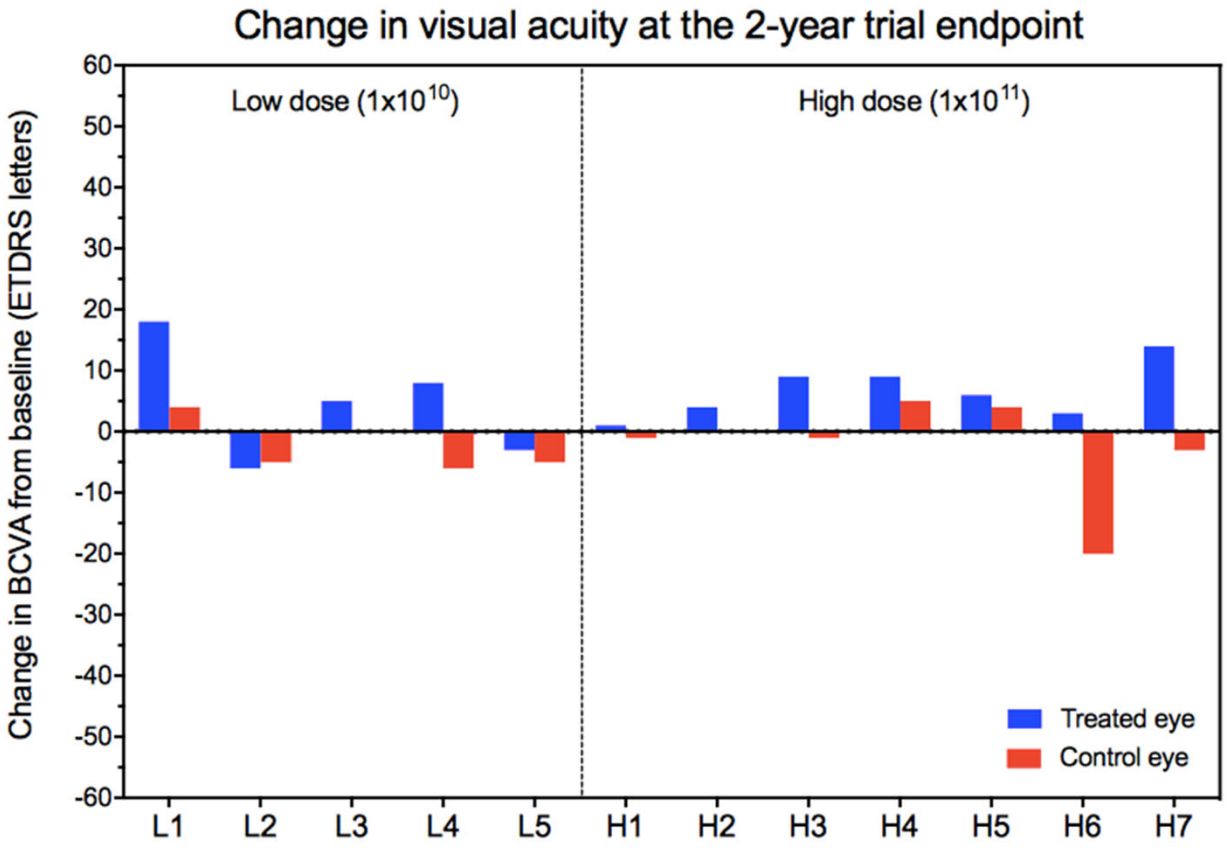




Beneficial effects on vision in patients undergoing retinal gene therapy for choroideremia

Kanmin Xue, Jasleen K Jolly, Alun R. Barnard, Anna Rudenko, Anna P. Salvetti, Maria I. Patrício, Thomas L. Edwards, Markus Groppe, Harry O. Orlans, Tanya Tolmachova, Graeme C. Black, Andrew R. Webster, Andrew J. Lotery, Graham E. Holder, Susan M. Downes, Miguel C. Seabra & Robert E. MacLaren

Nature Medicine **24**, 1507–1512 (2018) | Download Citation



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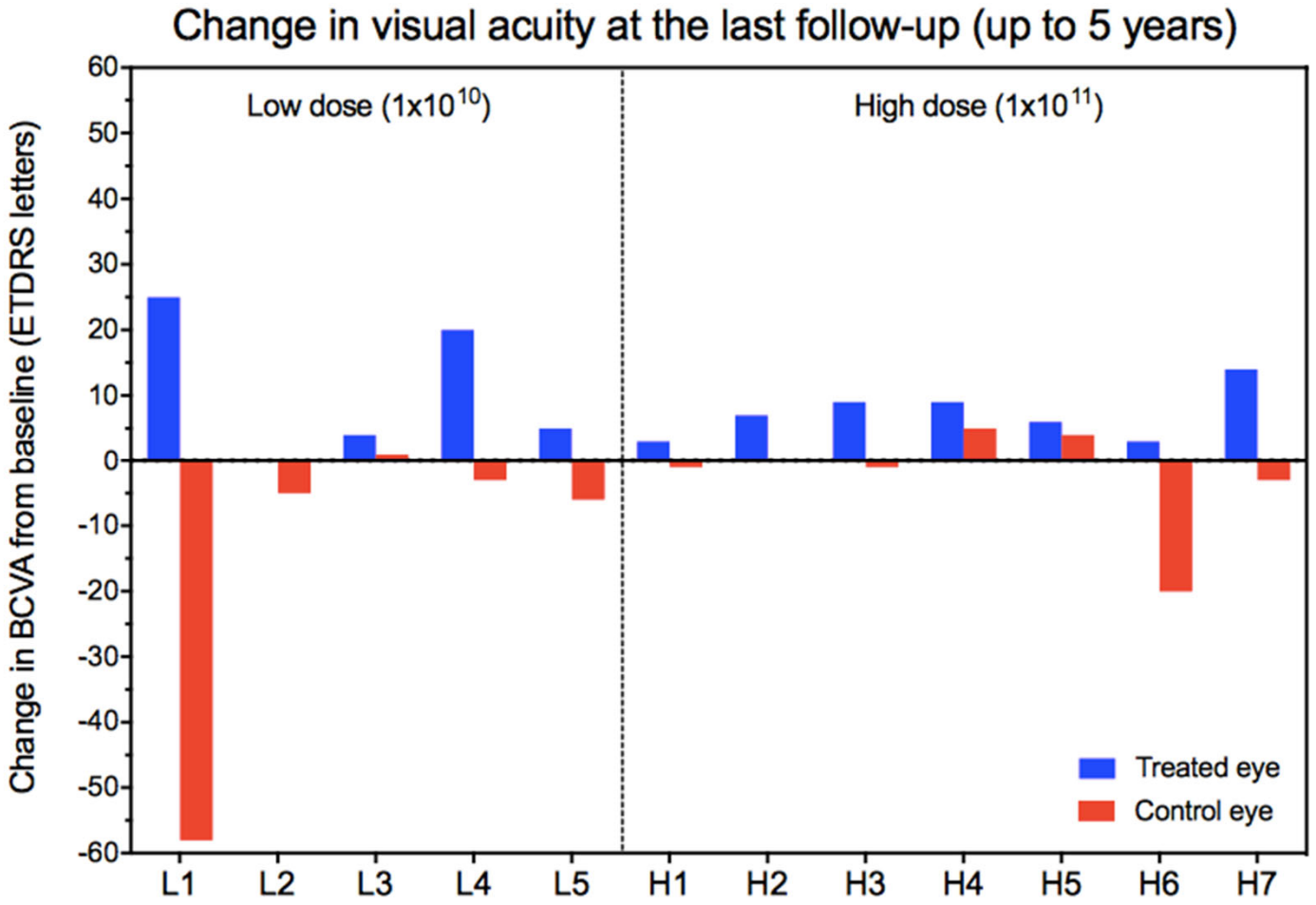


2. Antisense oligonucleotides

2. Antisense oligonucleotides

DNA

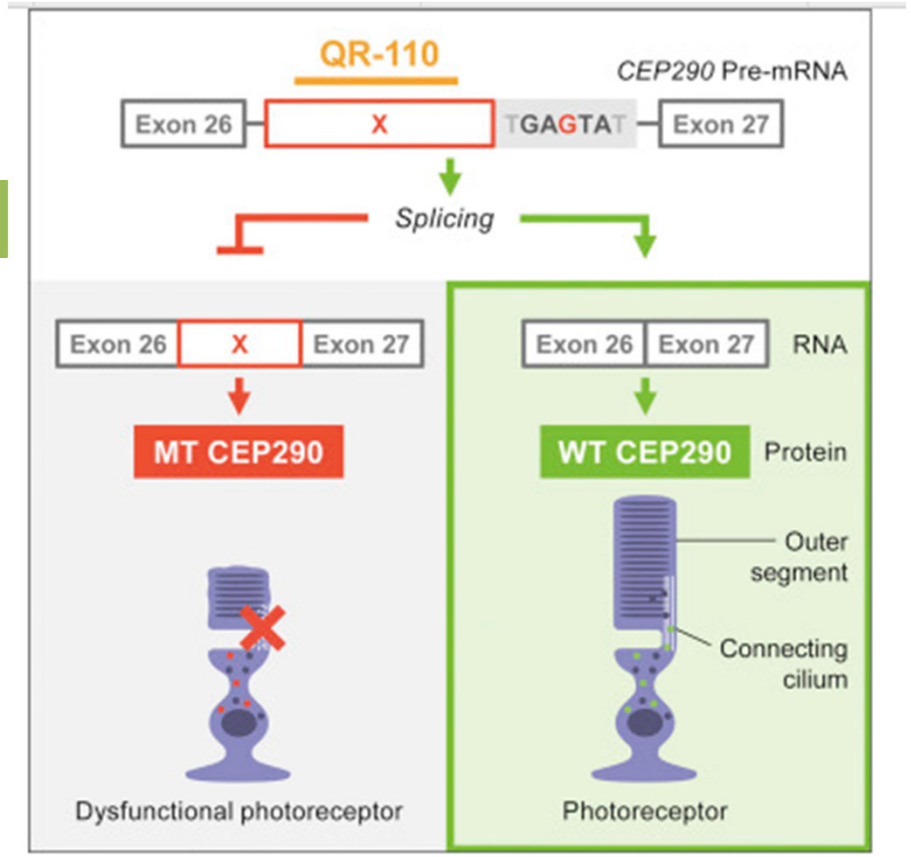
↓

RNA

↓

Protein

Exon



Dulla et al 2018

nature medicine

SUPPLEMENTARY INFORMATION

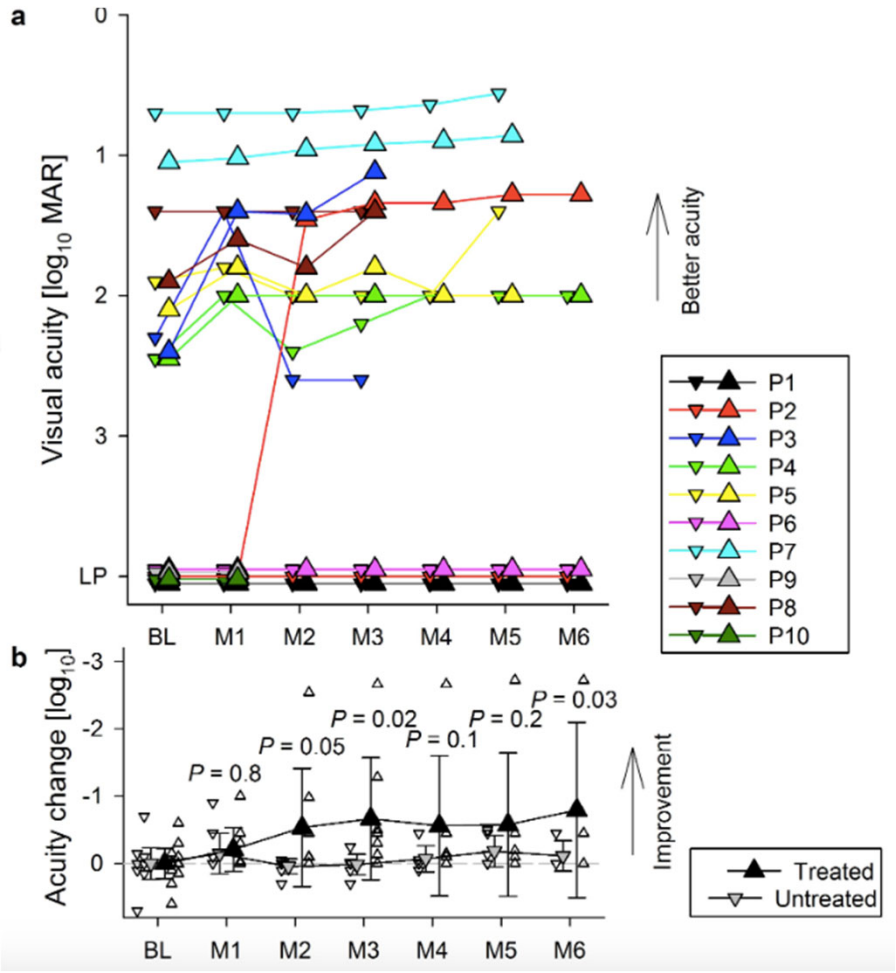
https://doi.org/10.1038/s41591-018-0295-0

In the format provided by the authors and unedited.

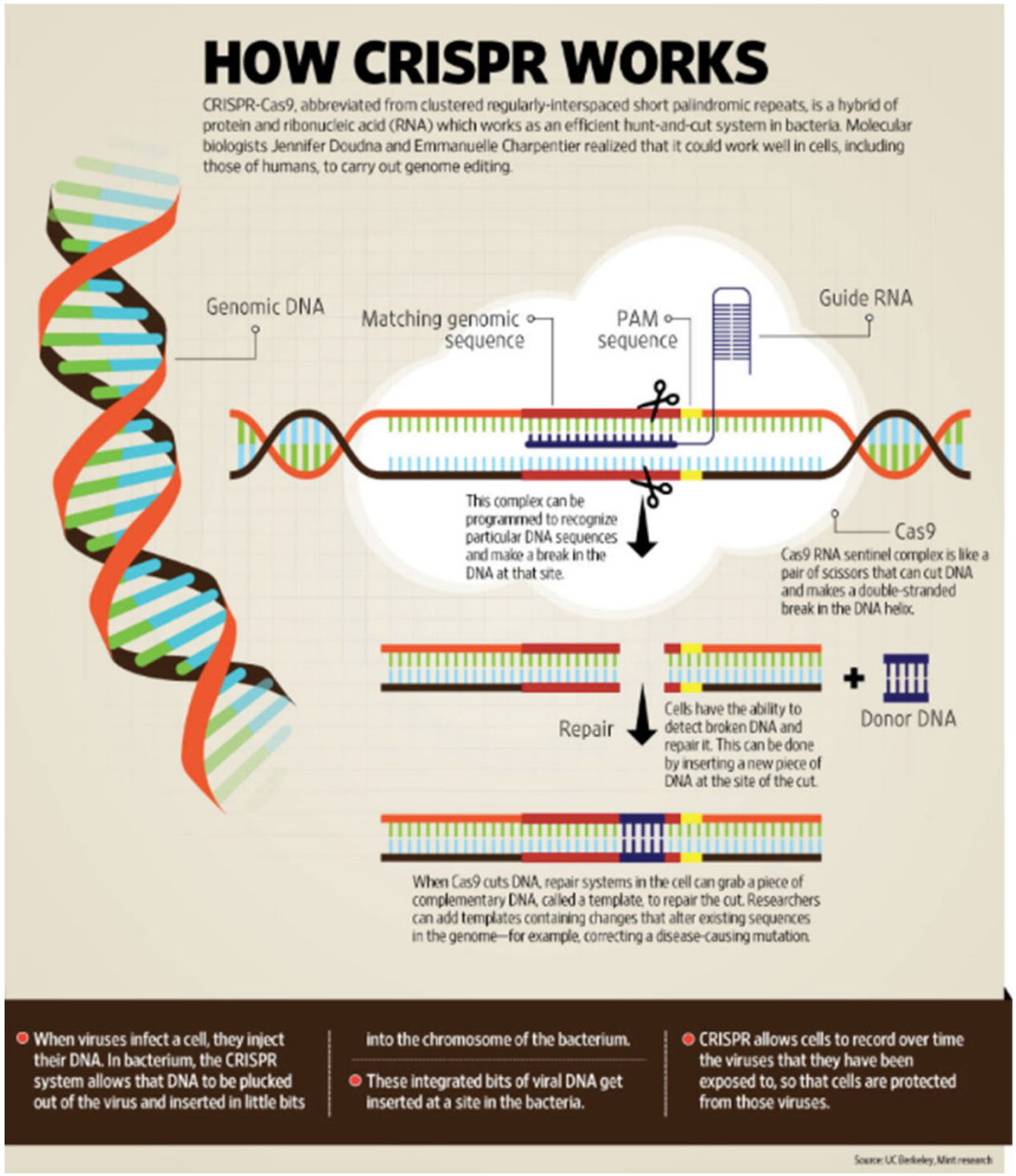
Effect of an intravitreal antisense oligonucleotide on vision in Leber congenital amaurosis due to a photoreceptor cilium defect

Artur V. Cideciyan[1*], Samuel G. Jacobson[1*], Arlene V. Drack[2], Allen C. Ho[3], Jason Charng[1], Alexandra V. Garafalo[1], Alejandro J. Roman[1], Alexander Sumaroka[1], Ian C. Han[2], Maria D. Hochstedler[2], Wanda L. Pfeifer[2], Elliott H. Sohn[2], Magali Taiel[4], Michael R. Schwartz[4], Patricia Biasutto[4], Wilma de Wit[4], Michael E. Cheetham[5], Peter Adamson[4,5], David M. Rodman[4], Gerard Platenburg[4], Maria D. Tome[4], Irina Balikova[6], Fanny Nerinckx[6], Julie De Zaeytijd[6], Caroline Van Cauwenbergh[6], Bart P. Leroy[6] and Stephen R. Russell[2]

- All patients had same splice site mutation on one allele c.2991+1655A>G/p.(Cys998*)
- Intravitreal injection every 3 months
- Gain in vision at 3 months in some patients



3. CRISPR



UC Berkeley, www. futurism.com

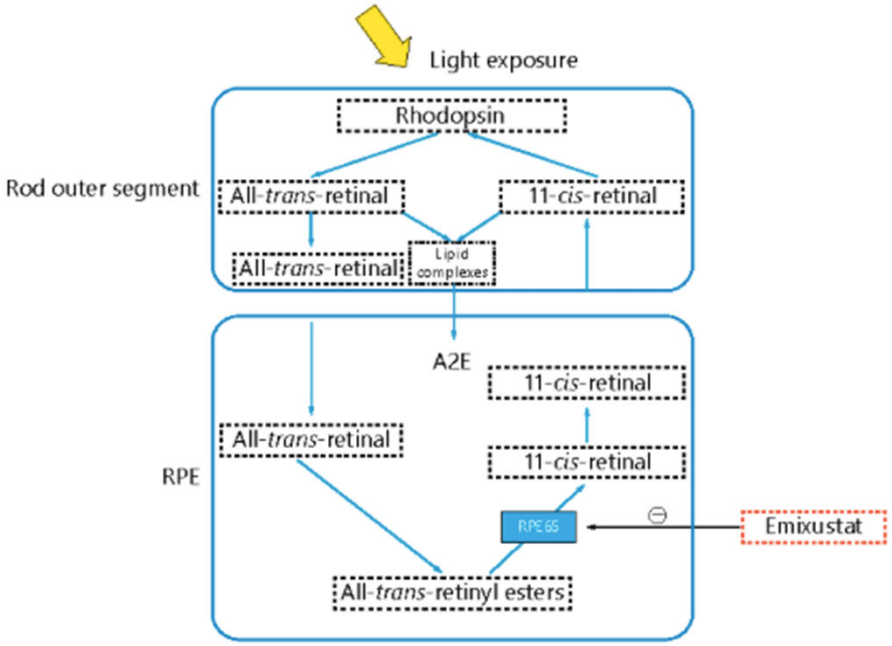
Allergan and EDITAS are now recruiting patients with CEP290 mutations
Clinical trials.gov:
To recruit up to 18 patients (children and adults)

- Drug: AGN-151587

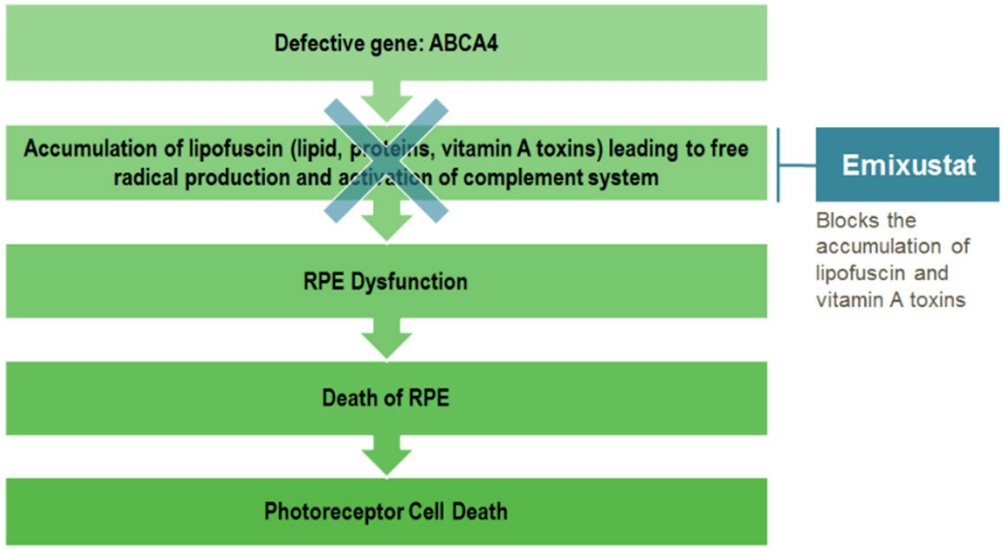
- Bascom Palmer Eye Institute
  Miami, Florida, United States
- Massachusetts Eye and Ear Infirmary
  Boston, Massachusetts, United States
- W.K. Kellogg Eye Center - University of Michigan
  Ann Arbor, Michigan, United States
- Casey Eye Institute - OSHU
  Portland, Oregon, United States

4. Oral medications for Stargardt disease: (i) Emixustat

http://webvision.med.utah.edu



Jack et al, Developments in Ophthalmology 2016



www.acucela.com

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	162 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	This is a multicenter, randomized, double-masked, placebo-controlled study to evaluate the efficacy and safety of emixustat compared to placebo in subjects who have Macular Atrophy secondary to Stargardt disease.
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	Double-Masked
Primary Purpose:	Treatment
Official Title:	A Phase 3 Multicenter, Randomized, Double-Masked Study Comparing the Efficacy and Safety of Emixustat Hydrochloride With Placebo for the Treatment of Macular Atrophy Secondary to Stargardt Disease
Actual Study Start Date :	November 7, 2018
Estimated Primary Completion Date :	February 2022
Estimated Study Completion Date :	April 2022

Oral medications for Stargardt disease:

http://webvision.med.utah.edu

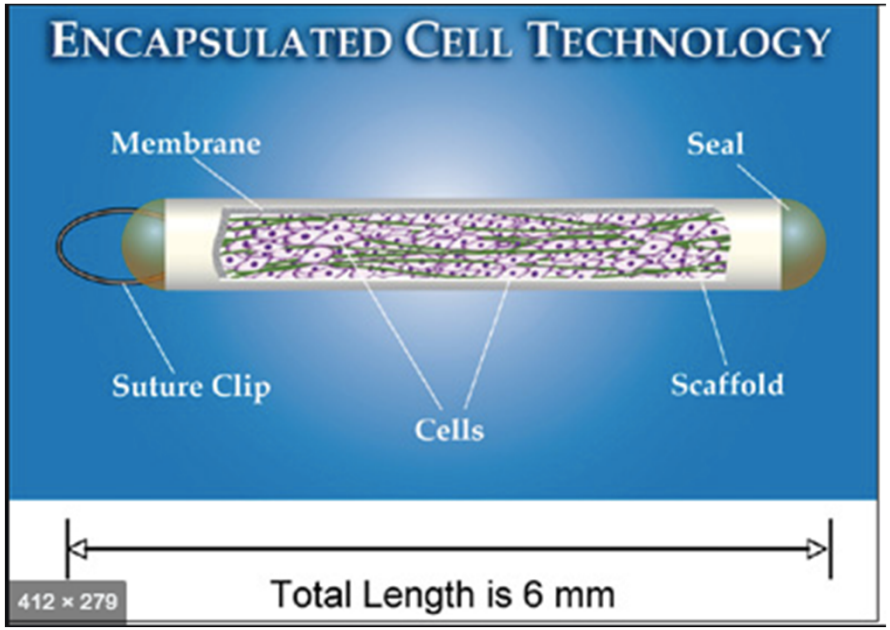
(ii) Remofuscin

- Recruiting Southampton, UK

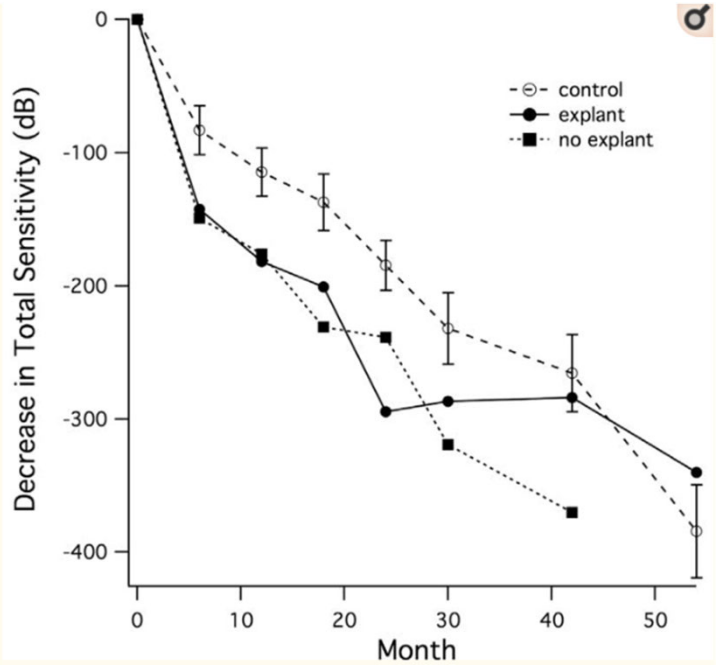
(iii) ALK001

- Inhibit formation of vitamin A dimers/ toxic waste products
- Recruiting USA

5. Neuroprotection
eg. ciliary neurotrophic factor



Neurotech USA



Birch et al, 2013

Current limitations of therapies to prevent visual loss

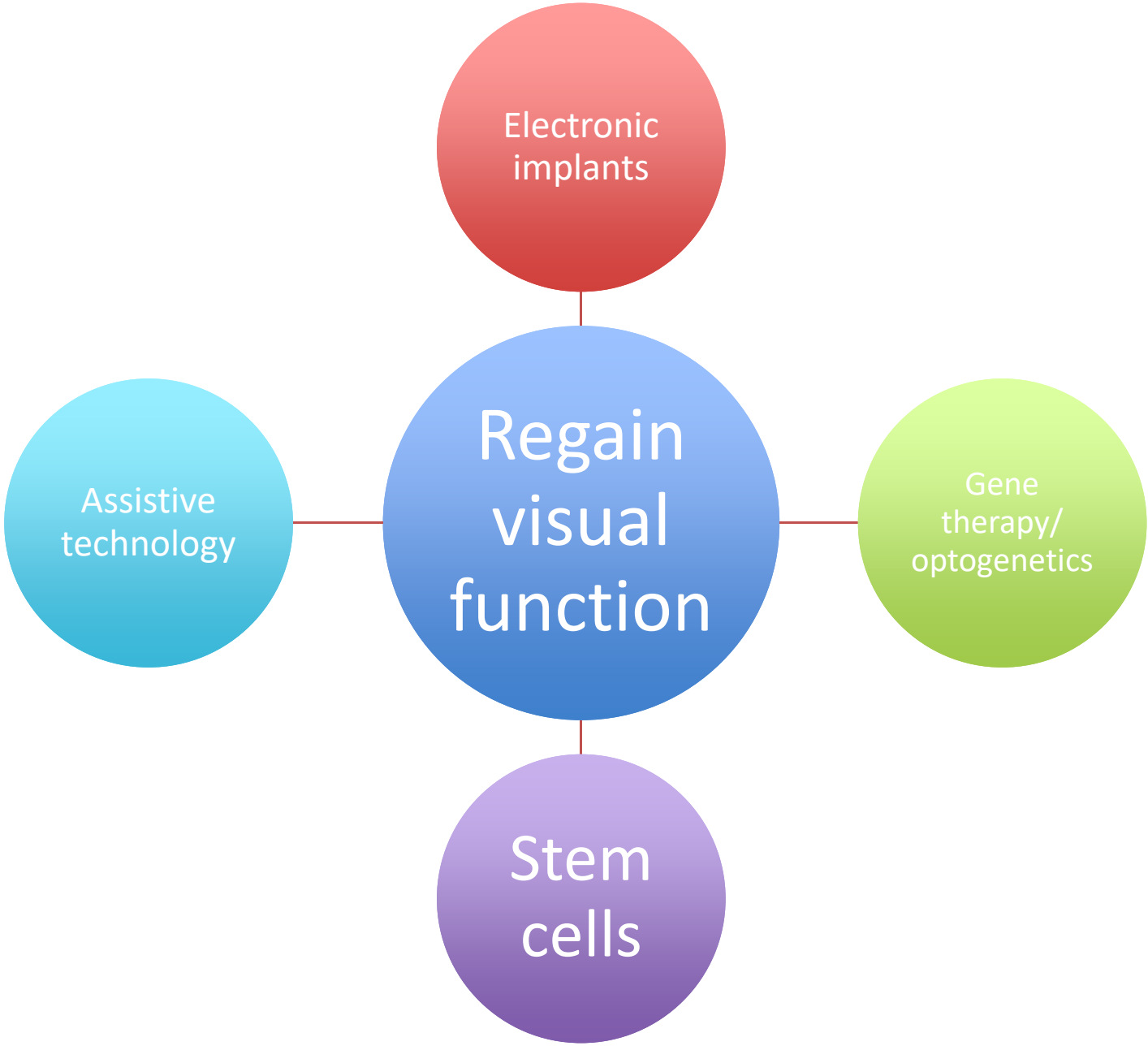
1. Genetic mutation not always known:

   -molecular diagnosis can be made in approx 2/3 adults and 85% children (Duncan et al, 2018; Birtel et al 2019)

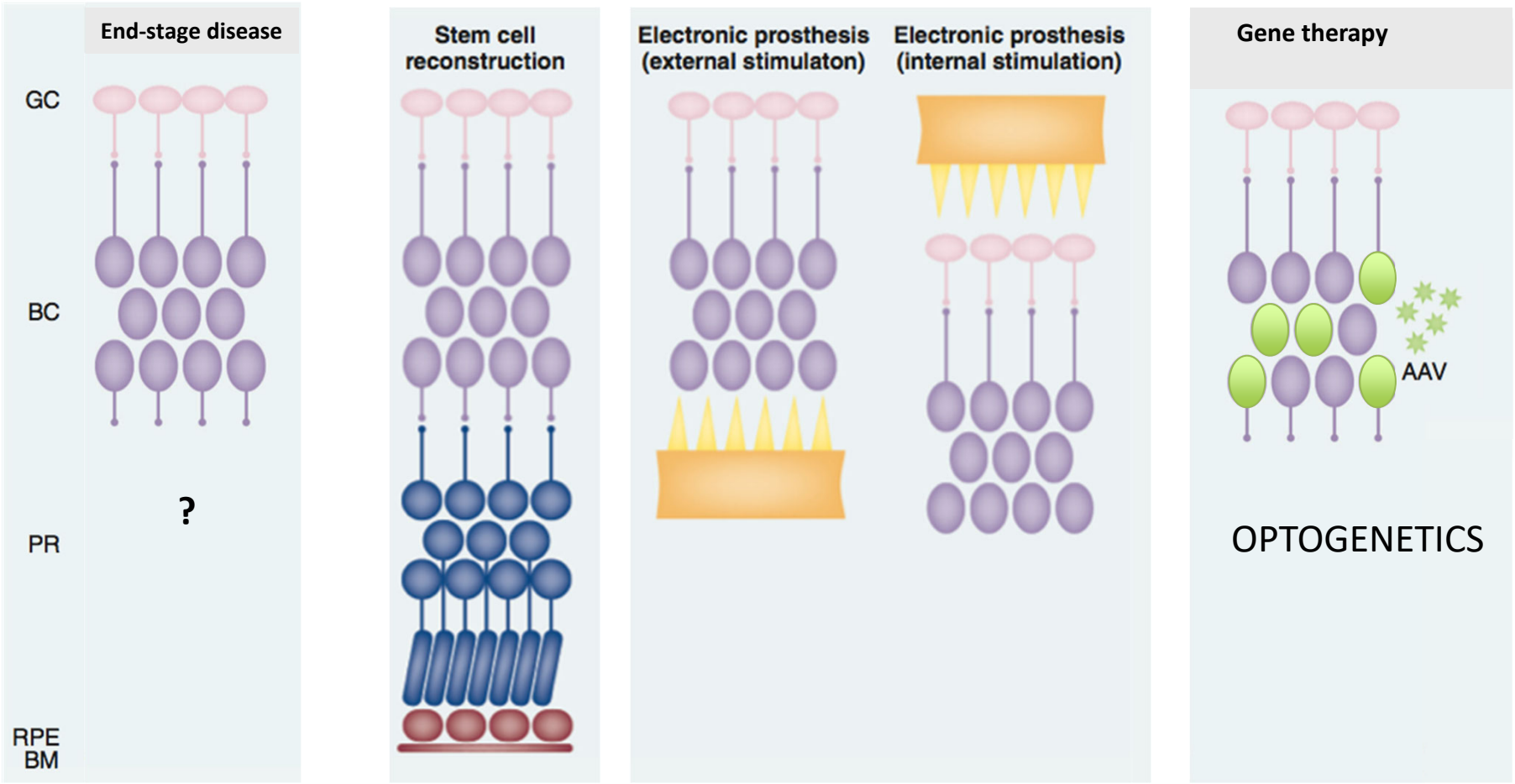
2. Large number of causative genes identified to date

3. Gene may not be amenable to current strategies e.g. autosomal dominant disease, large gene size

4. Patients present after photoreceptors degenerated

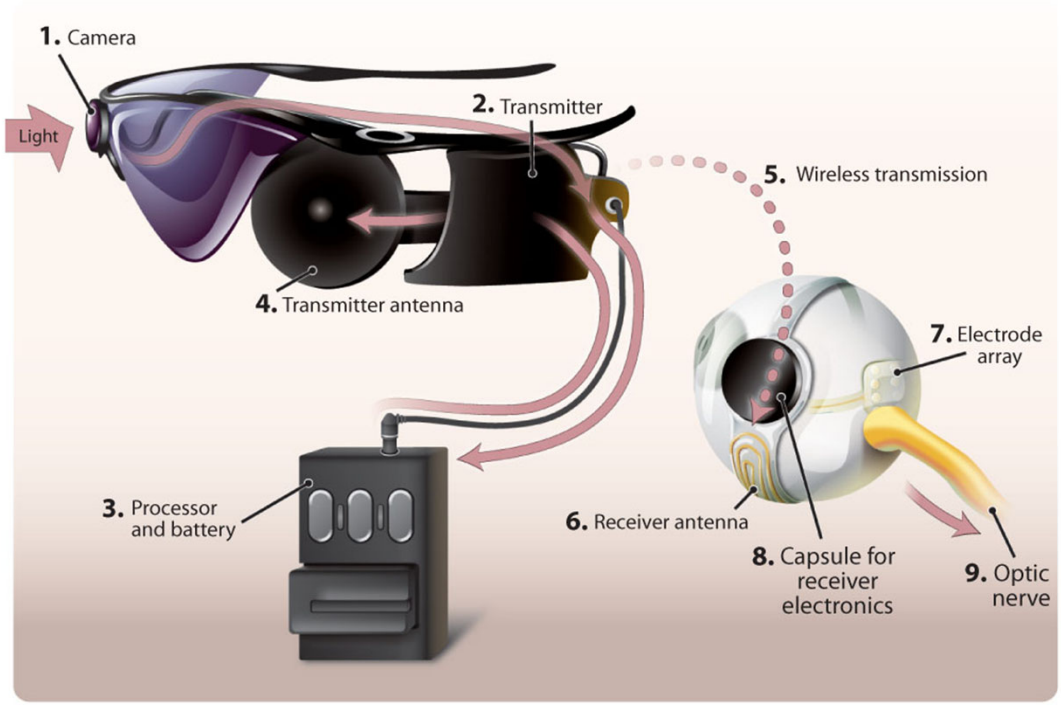

Electronic implants
Assistive technology
Regain visual function
Gene therapy/ optogenetics
Stem cells

Treatment options for end stage degeneration

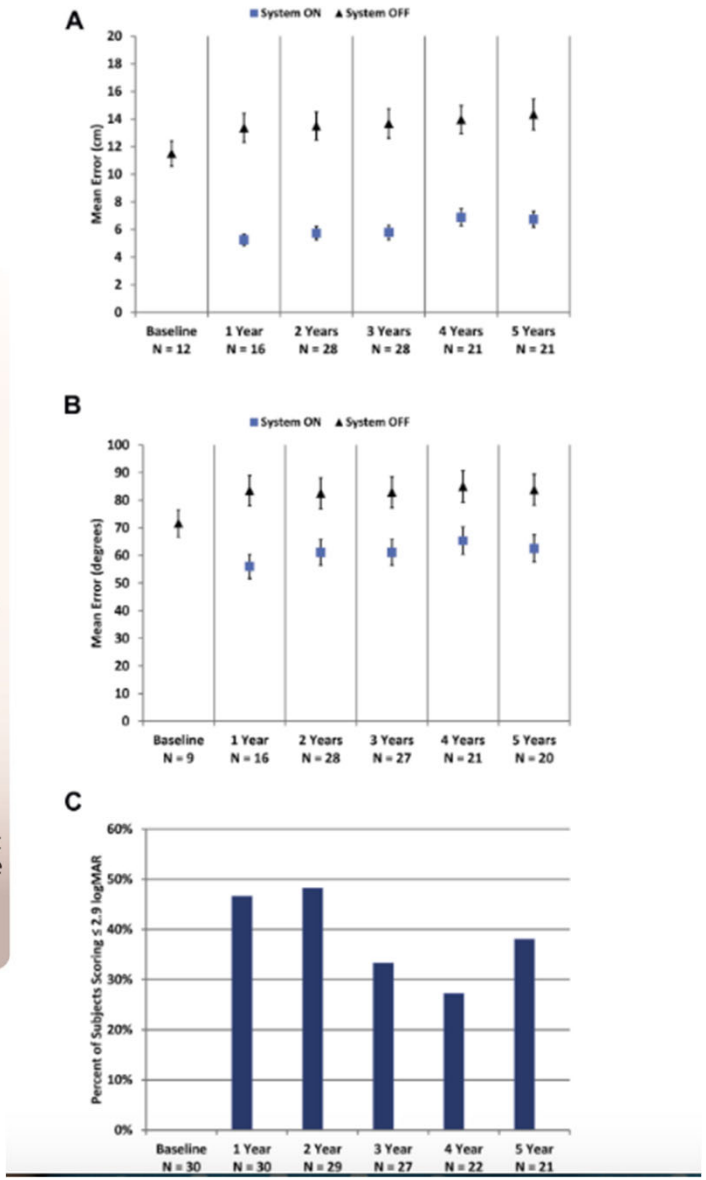


1. Retinal Implants

(i) Argus II implant (epiretinal)

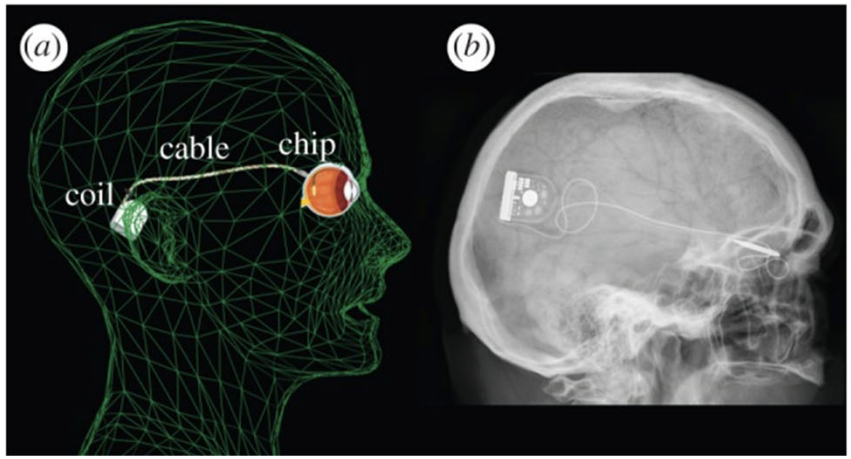


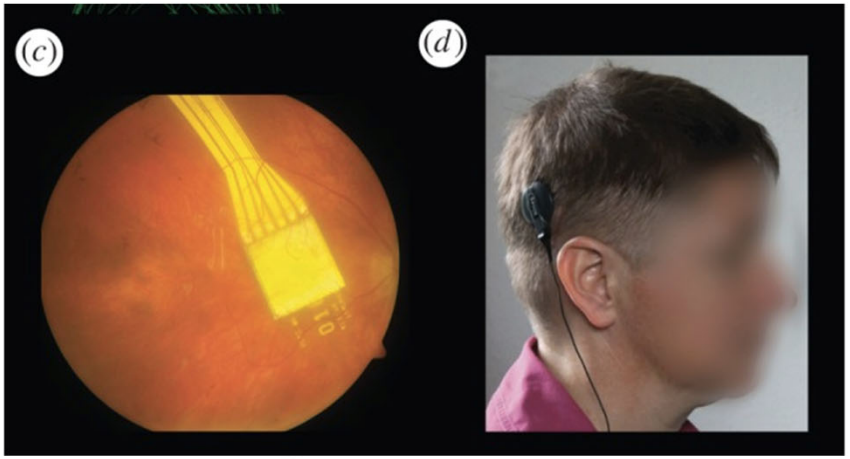
Zrenner E, Sci Trans med, 2013

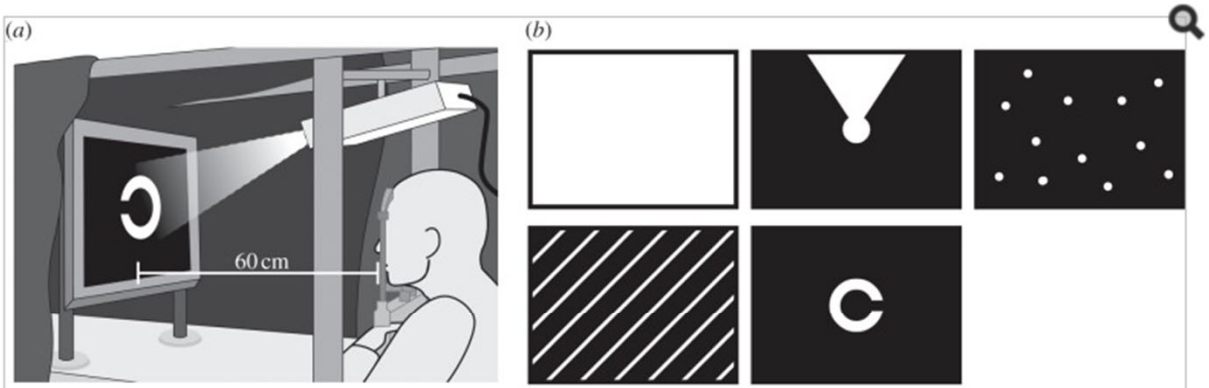


da Cruz et al, Ophthalmology, 2016

(ii) Alpha IMS/AMS (subretinal implant)







(c)

	S2	S3	S4	S5	S6	S7	S8	S9
light	yes	yes	yes	yes	yes	yes	yes	yes
location	yes	no	yes	yes	yes	yes	yes	yes
motion	no	no	3° per sec	no	7° per sec	5° per sec	35° per sec	5° per sec
grating acuity	no	no	0.33 cpd	0.1 cpd	0.3 cpd	0.5 cpd	3.3 cpd	1.0 cpd
Landolt C	no	no	no	0.01	no	no	0.04	no

Proc Biol Sci. Apr 22, 2013; 280(1757): 20130077. PMCID: PMC3619489
doi: 10.1098/rspb.2013.0077

Artificial vision with wirelessly powered subretinal electronic implant alpha-IMS

Katarina Stingl,[1] Karl Ulrich Bartz-Schmidt,[1] Dorothea Besch,[1] Angelika Braun,[7] Anna Bruckmann,[1] Florian Gekeler,[1] Udo Greppmaier,[7] Stephanie Hipp,[1] Gernot Hörtdörfer,[3] Christoph Kernstock,[1] Assen Koitschev,[8] Akos Kusnyerik,[1,4] Helmut Sachs,[5] Andreas Schatz,[1] Krunoslav T. Stingl,[6] Tobias Peters,[2] Barbara Wilhelm,[2] and Eberhart Zrenner[1]

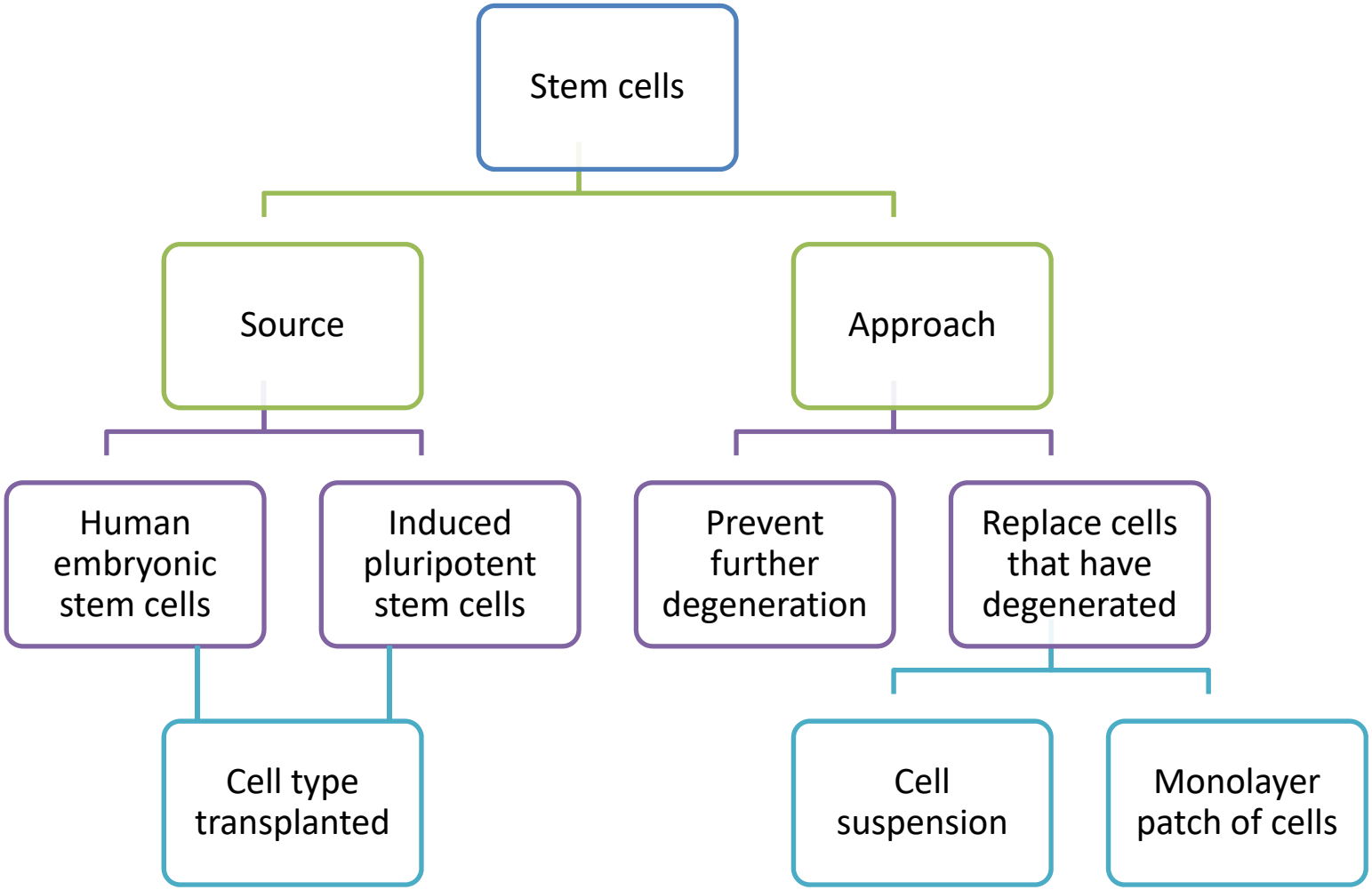
(iii) Cortical implant

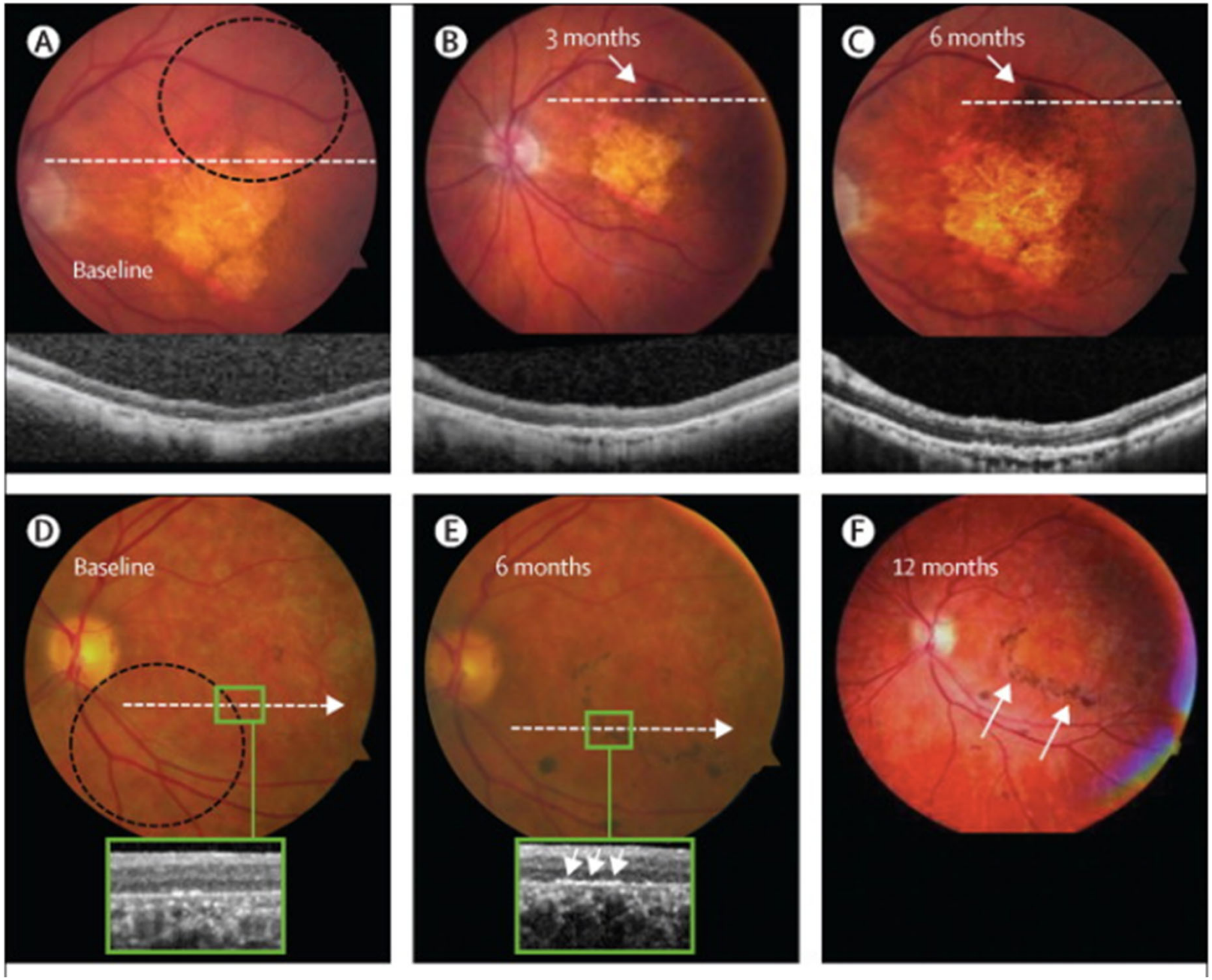
www.prostheticbody.com

Limitations of retinal implants

- Complex surgery
- Limited visual field
- Quality of vision limited by number of pixels
- Interface problems between implant and retina
- Cost

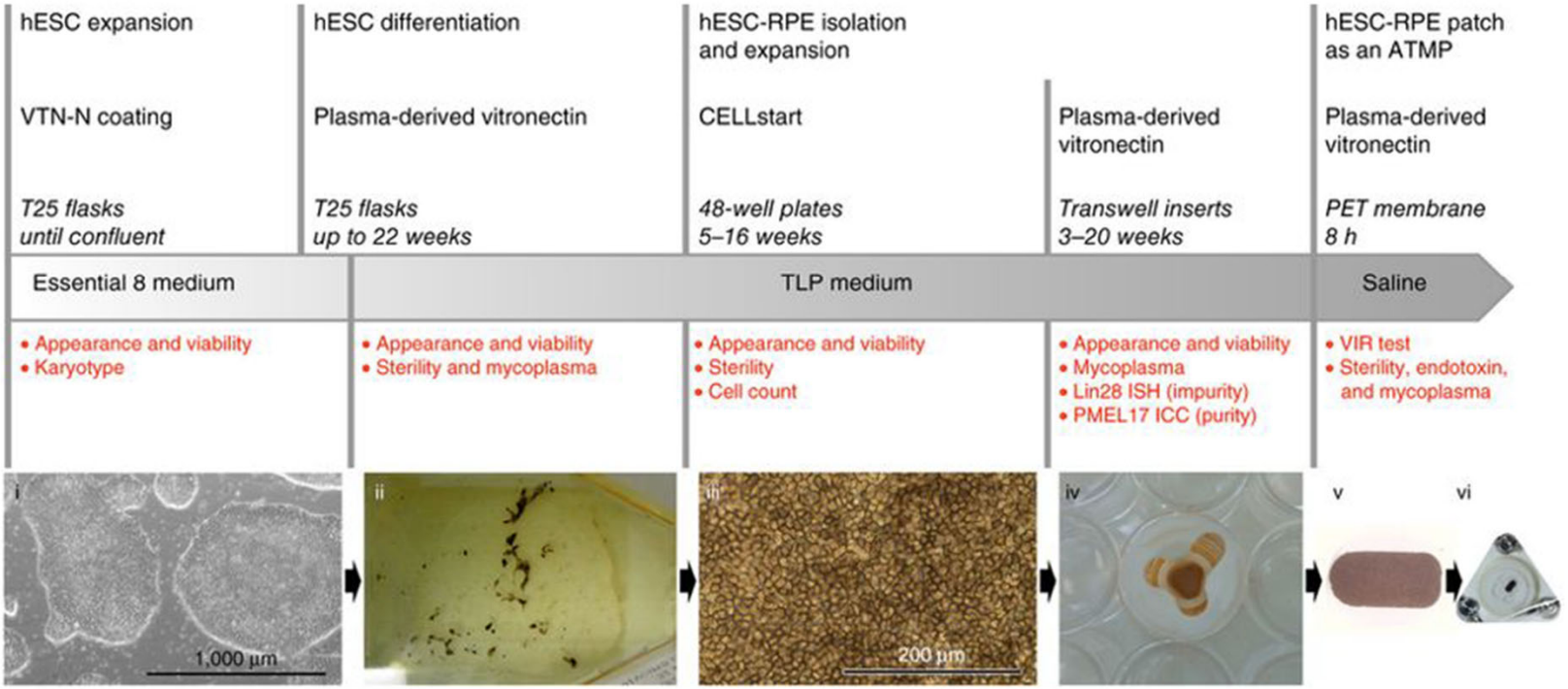
2. Stem cells


Stem cells
Source
Approach
Human embryonic stem cells
Induced pluripotent stem cells
Prevent further degeneration
Replace cells that have degenerated
Cell type transplanted
Cell suspension
Monolayer patch of cells

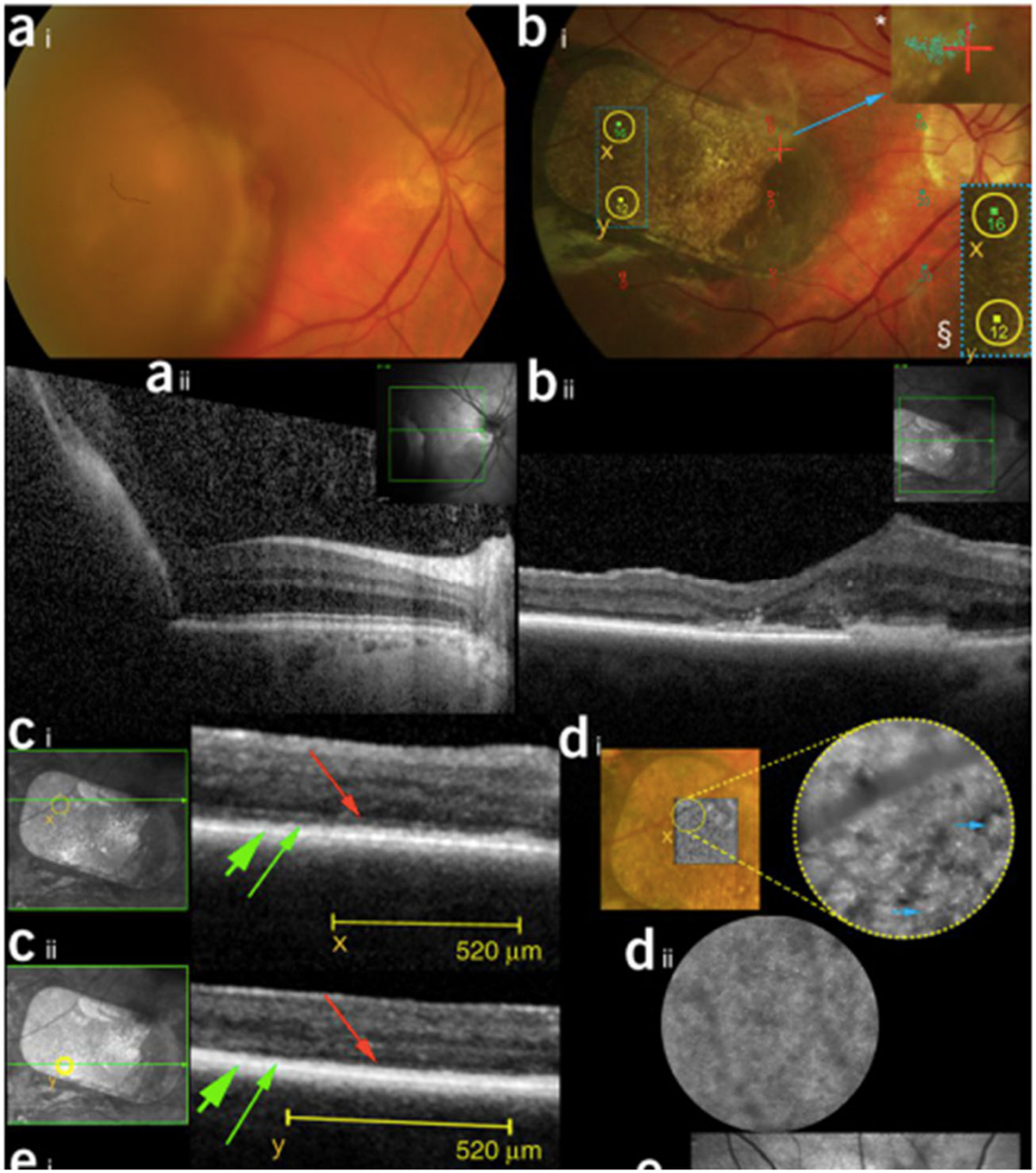


Schwartz et al, Lancet 2015

From: Phase 1 clinical study of an embryonic stem cell–derived retinal pigment epithelium patch in age-related macular degeneration



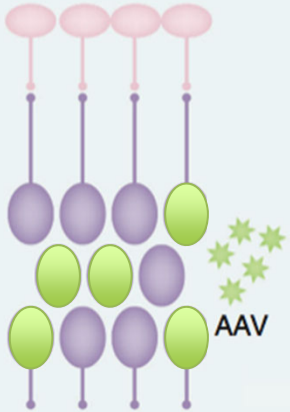
da Cruz et al, Nature Biotechnology, 2018



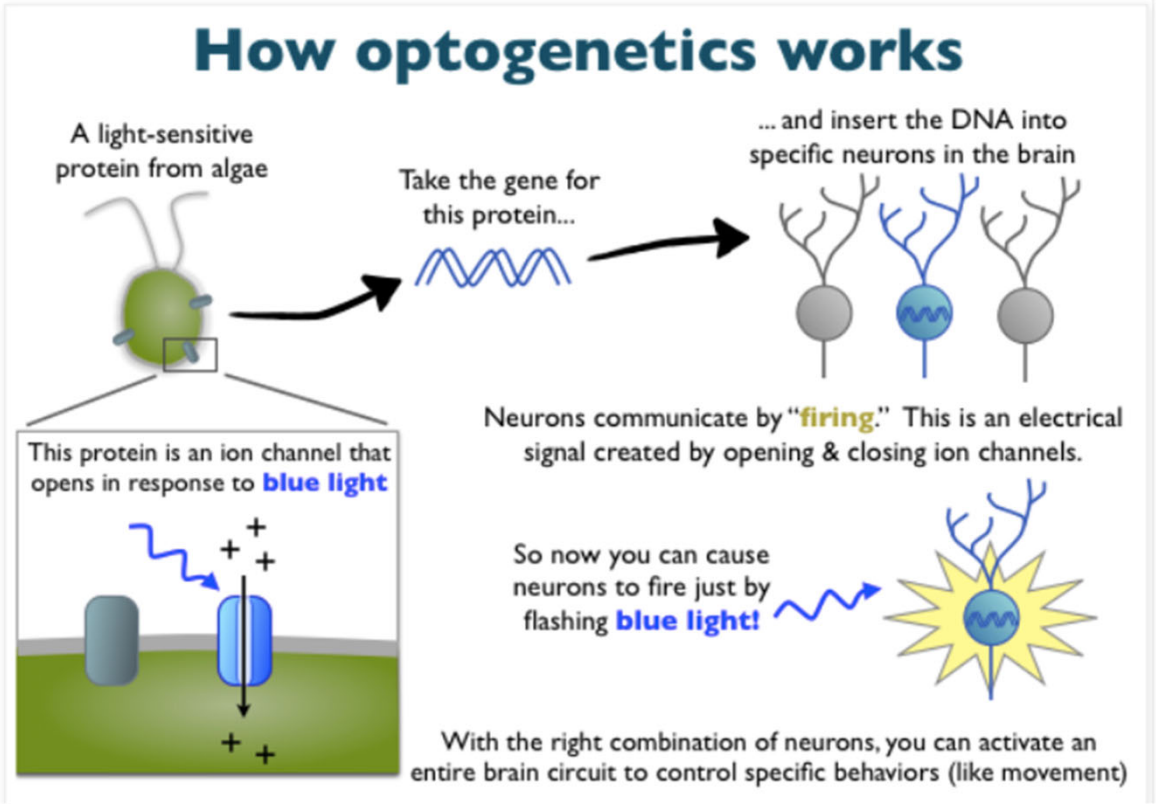
da Cruz et al, Nature Biotechnology, 2018

3. Optogenetics - making cells light sensitive by genetic modification

Gene therapy

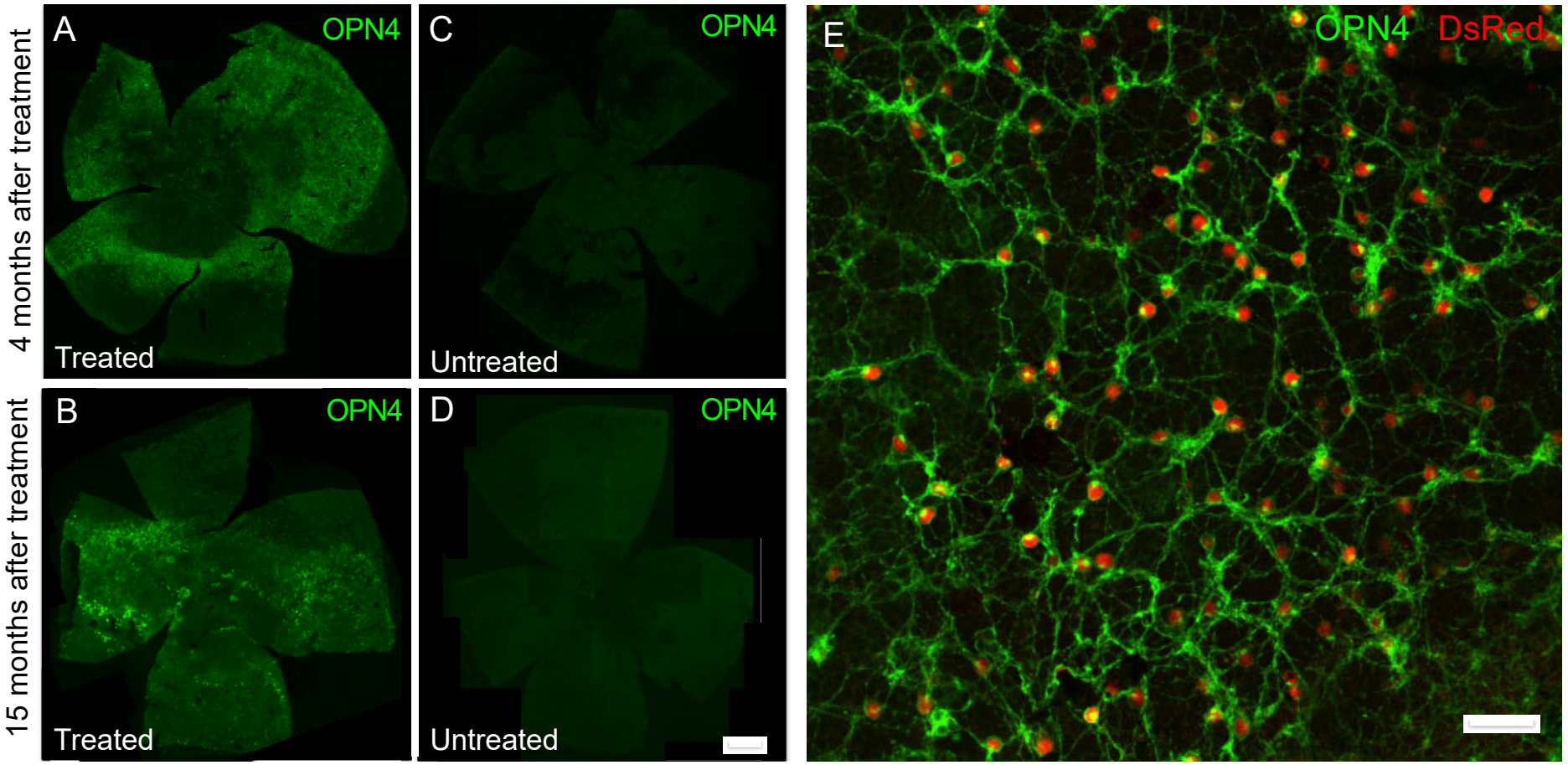


OPTOGENETICS



http://www.wiringthebrain.com/2013/09/why-optogenetics-deserves-hype.html

Human melanopsin expression is sustained in the degenerate *rd1* retina at 15 months

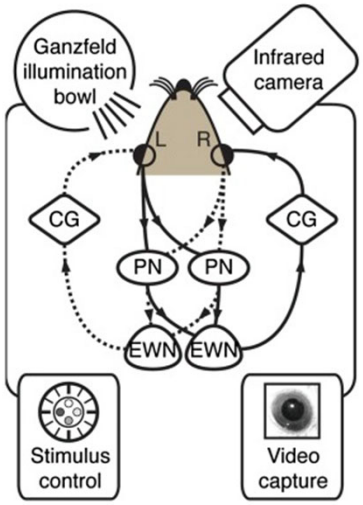


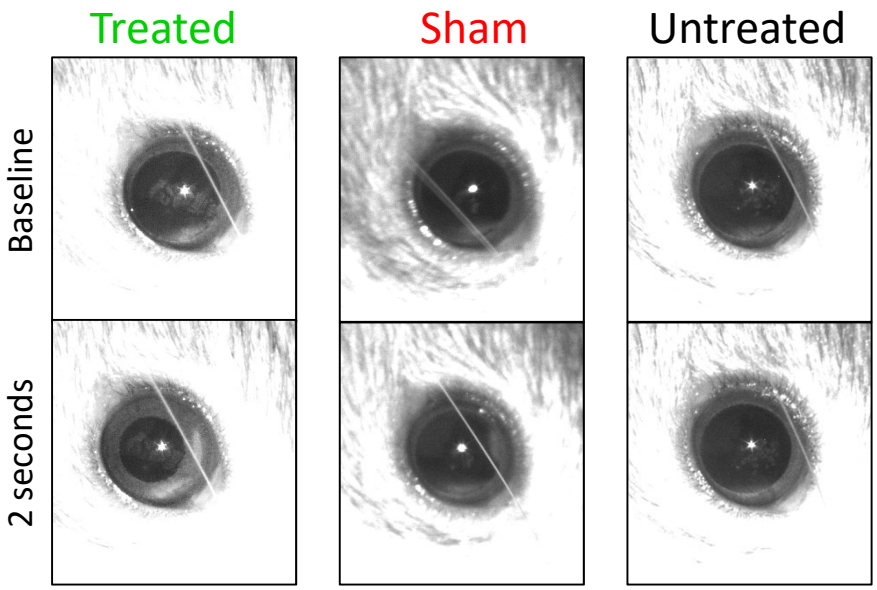
de Silva et al, PNAS 2017

Function

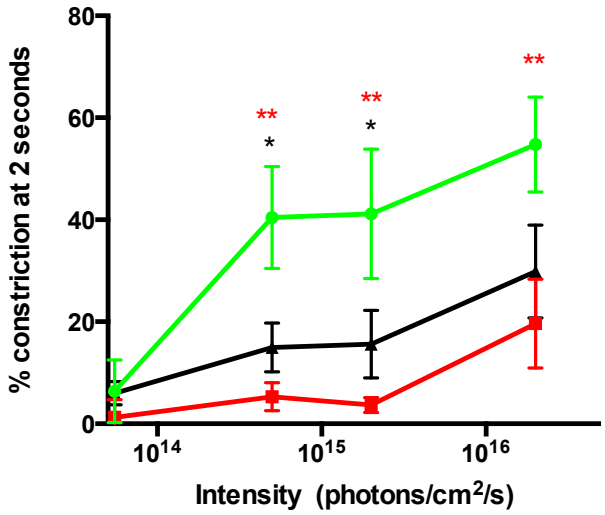
Melanopsin treated eyes show increased pupil constriction to light

2 second white light stimulus

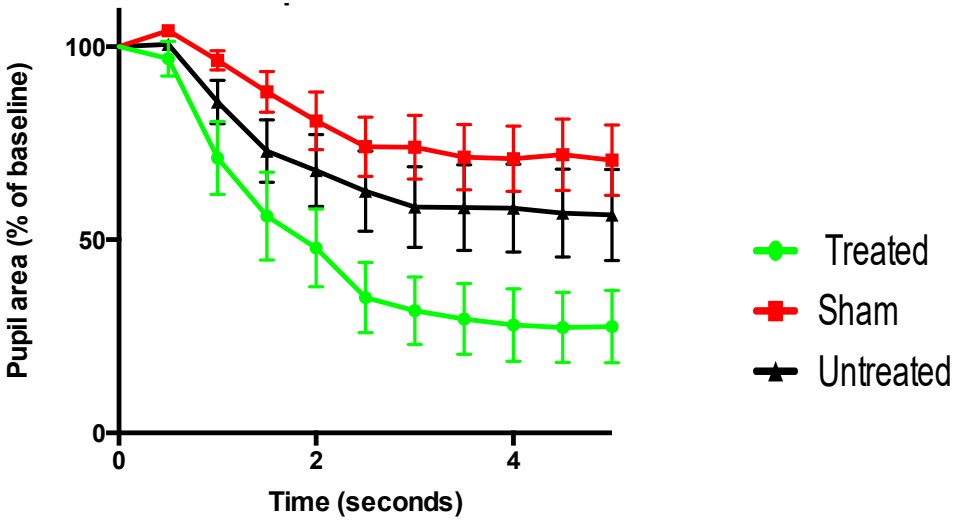




Irradiance-response curve



Time course of constriction at $2x10^{16}$ photons/cm^2/s

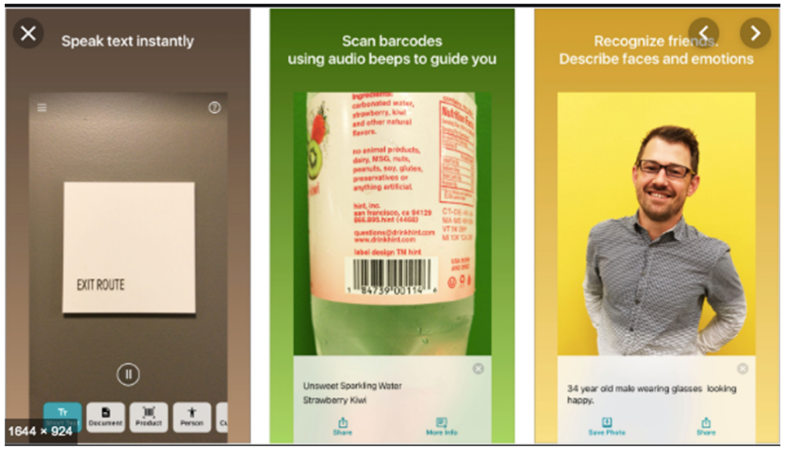


Clinical trials

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Dose-escalation Study to Evaluate the Safety and Tolerability of GS030 in Subjects With Retinitis Pigmentosa	• Non-syndromic Retinitis Pigmentosa	• Combination Product: Gene therapy: GS030-DP AND Medical device: GS030-MD AAV2 7m8, Chrimson, Intravitreal	• UPMC Eye Center Pittsburgh, Pennsylvania, United States • Centre Hospitalier National d'Ophtalmologie (CHNP) des Quinze-Vingts Paris, France • Moorfields Eye Hospital NHS Foundation Trust, 162 City Road London, United Kingdom
2	☐	Recruiting	RST-001 Phase I/II Trial for Advanced Retinitis Pigmentosa	• Advanced Retinitis Pigmentosa	• Drug: RST-001 AAV2, Channelrhodopsin, intravitreal	• Univeristy of California, San Francisco- Dept. of Ophthalmology San Francisco, California, United States • Duke Eye Center Durham, North Carolina, United States • Cincinnati Eye Institute Cincinnati, Ohio, United States • Retina Foundation of the Southwest Dallas, Texas, United States

4. Assistive technology

Seeing AI



Be My Eyes