Peculiarities of the eye as a target for gene therapy

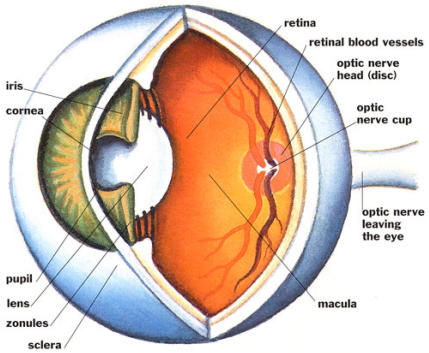
The eye is a site of immune-priviledge

Most cells in the post-natal eye are terminally differentiated and prone to degenerative processes

Its compartmentalized anatomy (blood-retina barrier) enables local vector delivery in small volume with low likelihood of systemic dissemination

The eye is readily accessible for *in vivo* assessment by optical imaging and electrophysiological techniques

Many animal models available

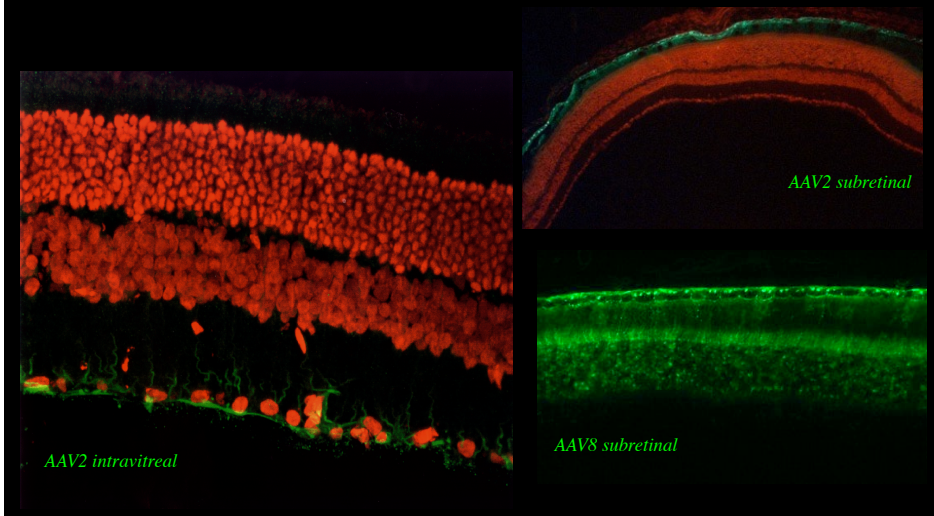


Out of 20 gene therapy clinical trials for eye diseases, 18 are directed toward retinal disorders, 1 for glaucoma, and 1 for the cornea.

Top 10 recent eye-research advances toward the market

1. Blindness (RetroSense Therapeutics)
2. Leber congenital amaurosis (Spark Therapeutics)
3. Usher syndrome (ReNeuron)
4. Retinitis pigmentosa (jCyte)
5. Retinoschisis (Applied Genetic Technologies Corporation)
6. Choroideremia (Spark Therapeutics)
7. Age-related macular degeneration (StemCells Inc)
8. Stargardt disease (VM200, Vision Medicines)
9. Wet AMD (Retinostat, Oxford BioMedica)
10. X-linked Retinitis Pigmentosa (Applied Genetic Technologies Corporation)

AAV efficiently transduces both RPE and photoreceptors



LCA is a form of Retinitis Pigmentosa

- RP affects 50,000–100,000 people in the United States and about 1.5 million people worldwide
- Impaired adaptation, night blindness, and loss of mid-peripheral visual field in adolescence. Progressive loss of far-peripheral visual field and eventually central vision. The majority of patients are legally blind by age 60.
- Inherited by an autosomal dominant, autosomal recessive, X-linked, or digenic mode.
- Genetic heterogeneity
- Mutations identified in 120+ genes.

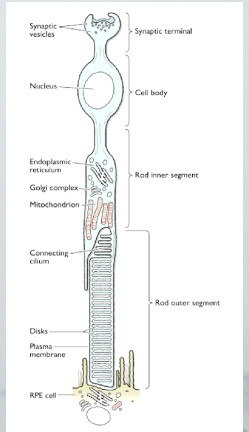


Figure 1. Rod photoreceptor cell with associated RPE cell. Schematic diagram of rod photoreceptor cell and RPE cell. The different portions of the rod cell are labeled. The rod outer segment is composed of approximately 1000 stacked membrane discs enclosed within the plasma membrane. The interaction between the outer segment and adjacent RPE cell is shown.

Disease Category	Mapped Genes (not Cloned)	Mapped and Cloned Genes
Retinitis pigmentosa, autosomal dominant	RP9, RP17	CRX, FSCN2, HPRP3, IMPDH1, NRL, RP1
Retinitis pigmentosa, autosomal recessive	RP22, RP25, RP26, RP28, RP29	ABCA4, CNGA1, CNGB1, CRB1, LRAT, RGR, RHO, RLBP1, RPE65, SAG,
Retinitis pigmentosa, X-linked	RP6, RP23, RP24	RP2, RPGR

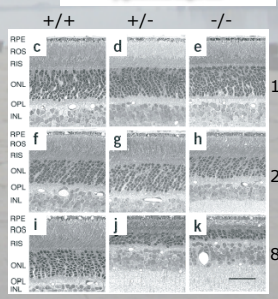
Pathophysiology of Retinitis Pigmentosa

RP is a rod-cone dystrophy in which the genetic defects cause cell death (apoptosis), predominantly in the rod photoreceptors; less commonly, the genetic defects affect the RPE and cone photoreceptors.

RP has significant phenotypic variation, as there are many different genes that lead to a diagnosis of RP, and patients with the same genetic mutation can present with very different retinal findings.

The outer segments progressively shorten, followed by loss of the rod photoreceptors that leads to vision loss. As rods are most densely found in the midperipheral retina, cell loss in this area tends to lead to peripheral vision loss and night vision loss.

Cone photoreceptor death occurs in a similar manner to rod apoptosis with shortening of the outer segments followed by cell loss. This can occur early or late in the various forms of RP.

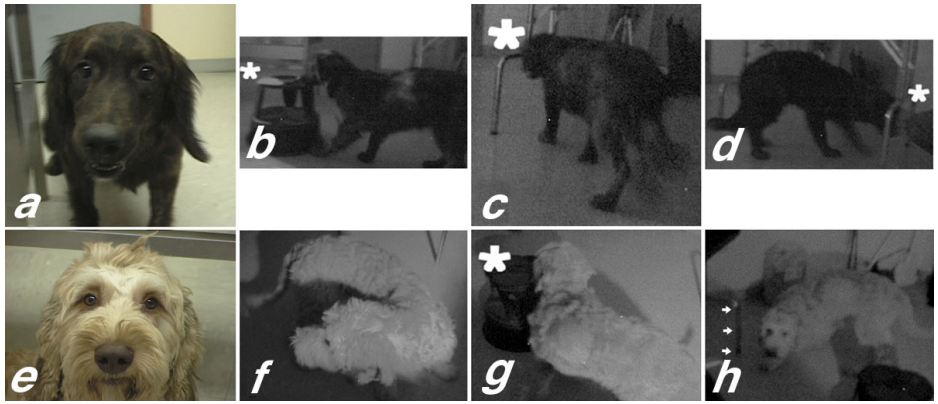


letter

Gene therapy restores vision in a canine model of childhood blindness

Gregory M. Acland[1], Gustavo D. Aguirre[1], Jharna Ray[1], Qi Zhang[1], Tomas S. Aleman[2], Artur V. Cideciyan[2], Susan E. Pearce-Kelling[1], Vibha Anand[2], Yong Zeng[2], Albert M. Maguire[2], Samuel G. Jacobson[2], William W. Hauswirth[3] & Jean Bennett[2]

Ambulatory Vision in Dim Light in RPE65-/- Dogs Without (a-d) or After (e-h) Treatment with AAV-RPE65. Dog BR46 (panels a-d) is untreated and has a "staring look" in bright light (a). When this dog attempts to navigate an obstacle course in dim red light, it bumps into obstacles in its path (b), to the left (c) and to the right (d). Dog BR33 (panels e-h), treated with AAV-RPE65 in its right eye, searches in dim red light for objects on the right side (f), not the left . This animal bumps into obstacles on the left (untreated) side (g) but not on the right (h). *, collisions with obstacles; arrows in (h) delineate an obstacle that was avoided.



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The relationship between the neurosensory photoreceptors and the adjacent retinal pigment epithelium (RPE) controls not only normal retinal function, but also the pathogenesis of hereditary retinal degenerations. The molecular bases for both primary photoreceptor[1] and RPE diseases[2–4] that cause blindness have been identified. Gene therapy has been used successfully to slow degeneration in rodent models of primary photoreceptor diseases[5,6], but efficacy of gene therapy directed at photoreceptors and RPE in a large-animal model of human disease has not been reported. Here we study one of the most clinically severe retinal degenerations, Leber congenital amaurosis (LCA). LCA causes near total blindness in infancy and can result from mutations in *RPE65* (LCA, type II; MIM 180069 and 204100). A naturally occurring animal model, the *RPE65*$^{-/-}$ dog, suffers from early and severe visual impairment similar to that seen in human LCA. We used a recombinant adeno-associated virus (AAV) carrying wild-type *RPE65* (AAV-*RPE65*) to test the efficacy of gene therapy in this model. Our results indicate that visual function was restored in this large animal model of childhood blindness.

- RPE65 is an evolutionary conserved 65 kDa membrane-associated protein involved in retinoid metabolism
- Rpe65 deficiency in mice results in accumulation of all-trans retinyl esters, loss of rhodopsin, and slow retinal degeneration
- RPE65-/- dogs bear a homozygous 4-bp deletion resulting in a frameshit and a premature stop codon

HUMAN GENE THERAPY 17:845–858 (August 2006)

Safety in Nonhuman Primates of Ocular AAV2-*RPE65*, a Candidate Treatment for Blindness in Leber Congenital Amaurosis

SAMUEL G. JACOBSON,[1] SANFORD L. BOYE,[2] TOMAS S. ALEMAN,[1] THOMAS J. CONLON,[3] CAROLINE J. ZEISS,[4] ALEJANDRO J. ROMAN,[1] ARTUR V. CIDECIYAN,[1] SHARON B. SCHWARTZ,[1] ANDRAS M. KOMAROMY,[5] MICHELLE DOOBRAJH,[1] ANDY Y. CHEUNG,[1] ALEXANDER SUMAROKA,[1] SUSAN E. PEARCE-KELLING,[6] GUSTAVO D. AGUIRRE,[5] SHALESH KAUSHAL,[2] ALBERT M. MAGUIRE,[1] TERENCE R. FLOTTE,[3] and WILLIAM W. HAUSWIRTH[2,3]

- No systemic toxicity, only modest local inflammation
- No photoreceptor abnormalities after AAV delivery

BRIEF REPORT

Safety and Efficacy of Gene Transfer for Leber's Congenital Amaurosis

Albert M. Maguire, M.D., Francesca Simonelli, M.D., Eric A. Pierce, M.D., Ph.D., Edward N. Pugh, Jr., Ph.D., Federico Mingozzi, Ph.D., Jeannette Bennicelli, Ph.D., Sandro Banfi, M.D., Kathleen A. Marshall, C.O.T., Francesco Testa, M.D., Enrico M. Surace, D.V.M., Settimio Rossi, M.D., Arkady Lyubarsky, Ph.D., Valder R. Arruda, M.D., Barbara Konkle, M.D., Edwin Stone, M.D., Ph.D., Junwei Sun, M.S., Jonathan Jacobs, Ph.D., Lou Dell'Osso, Ph.D., Richard Hertle, M.D., Jian-xing Ma, M.D., Ph.D., T. Michael Redmond, Ph.D., Xiaosong Zhu, M.D., Bernd Hauck, Ph.D., Olga Zelenaia, Ph.D., Kenneth S. Shindler, M.D., Ph.D., Maureen G. Maguire, Ph.D., J. Fraser Wright, Ph.D., Nicholas J. Volpe, M.D., Jennifer Wellman McDonnell, M.S., Alberto Auricchio, M.D., Katherine A. High, M.D., and Jean Bennett, M.D., Ph.D.

BRIEF REPORT

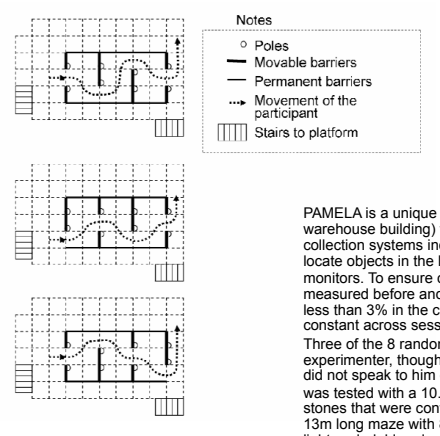
Effect of Gene Therapy on Visual Function in Leber's Congenital Amaurosis

James W.B. Bainbridge, Ph.D., F.R.C.Ophth., Alexander J. Smith, Ph.D., Susie S. Barker, Ph.D., Scott Robbie, M.R.C.Ophth., Robert Henderson, M.R.C.Ophth., Kamaljit Balaggan, M.R.C.Ophth., Ananth Viswanathan, M.D., F.R.C.Ophth., Graham E. Holder, Ph.D., Andrew Stockman, Ph.D., Nick Tyler, Ph.D., Simon Petersen-Jones, Ph.D., Shomi S. Bhattacharya, Ph.D., Adrian J. Thrasher, Ph.D., M.R.C.P., F.R.C.P., Fred W. Fitzke, Ph.D., Barrie J. Carter, Ph.D., Gary S. Rubin, Ph.D., Anthony T. Moore, F.R.C.Ophth., and Robin R. Ali, Ph.D.

- 3 patients in each study
- The procedure appear safe and might be beneficial - longer follow-up needed

The NEW ENGLAND JOURNAL of MEDICINE MAY 22, 2008

Schematic of maze used for assessment of visual mobility



see Movie

PAMELA is a unique mobility research facility (in a specially designed, converted warehouse building) that incorporates a sophisticated set of monitoring and data collection systems including starlight video cameras, Laser scanners which can locate objects in the laboratory within 1-2cm, eye tracking systems and heart rate monitors. To ensure consistent light levels the illumination of the platform was measured before and after testing, and found to vary by less than 5% overall and less than 3% in the critical area of the mobility maze. Dark adaptation time was held constant across sessions and the maze was randomly configured for each test.

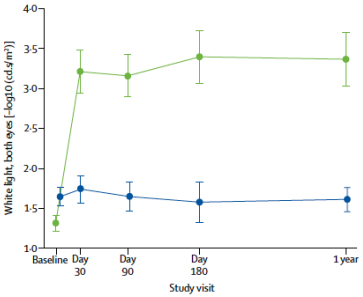
Three of the 8 random configurations are illustrated in **Supplementary Figure 1**. The experimenter, though not masked to the treatment eye, stood behind the subject and did not speak to him except to read instruction from a printed script. Visual mobility was tested with a 10.8m x 7.2m raised platform with concrete paving assessed stones that were configured to simulate an outdoor pavement. Subjects negotiated a 13m long maze with 8 moveable barriers (1.8m x 1.2m) painted in colours matching light or dark blue denim, and the entire platform area was illuminated from overhead to calibrated light levels ranging from 240 lux (moderate office lighting) to 4 lux (UK night time pedestrian lighting standard). The subject was positioned at one end of the maze and instructed to walk through at a normal comfortable pace without touching the barriers. The experimenter followed along just behind to ensure the subject's safety. Total travel was recorded with a stopwatch along with mobility errors (touching a barrier, loss of orientation). The barriers were randomly re-positioned before each run and the subject was given 15 minutes to adapt to changes in illumination levels.

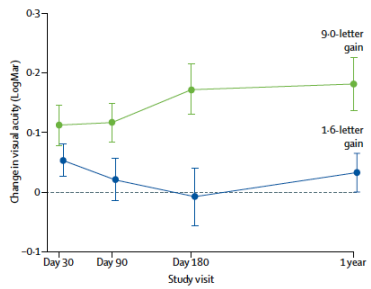
Vitrectomia e iniezione sotto-retinica di AAV-Rpe65

Vitrectomy and Subretinal Injection of Recombinant Adeno-Associated Virus Vector in Three Patients

Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with *RPE65*-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial

Stephen Russell, Jean Bennett, Jennifer A Wellman, Daniel C Chung, Zi-Fan Yu, Amy Tillman, Janet Wittes, Julie Pappas, Okan Elci, Sarah McCague, Dominique Cross, Kathleen A Marshall, Jean Walshire, Taylor L Kehoe, Hannah Reichert, Maria Davis, Leslie Raffini, Lindsey A George, F Parker Hudson, Laura Dingfield, Xiaosong Zhu, Julia A Haller, Elliott H Sohn, Vinit B Mahajan, Wanda Pfeifer, Michelle Weckmann, Chris Johnson, Dina Gewaily, Arlene Drack, Edwin Stone, Katie Wachtel, Francesca Simonelli, Bart P Leroy, J Fraser Wright, Katherine A High, Albert M Maguire





Lancet 2017; 390: 849–60

Experimental gene therapy for blindness considered by FDA

CNN Health + International Edition +

Christian Guardino is one patient who benefited from an experimental gene therapy treatment to improve vision loss. Earlier this year he auditioned for the show "America's Got Talent."

Vision quest: gene therapy for inherited vision loss

Biomedical research and clinical trials are fundamentally high-stakes endeavours, the results of which are often portrayed in hyperbolic categories. Failed phase 3 trials are called epic disappointments, while successful treatments become game changers or magic bullets. Better still, they receive US Food and Drug Administration (FDA) approval.

Nevertheless, there are few clinical success stories that follow such an impressive narrative arc as Luxturna (voretigene neparvovec-rzyl), which, on Dec 21, 2017, became the first directly administered gene therapy approved by FDA to treat children and adults with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Mutations in the *RPE65* gene can impair the production of an enzyme critical to the retinoid cycle and contribute to progressive vision loss, resulting in complete blindness by childhood or adolescence, once considered untreatable. A follow-on phase 1 trial published by Jean Bennett and colleagues in *The Lancet* in 2016 showed that subretinal injection of a normal copy of the *RPE65* gene via an adeno-associated virus vector contralateral to a previously treated eye was safe and yielded durable mobility and light sensitivity responses. Importantly, this phase 1 trial also paved the way for a successful phase 3 trial of voretigene neparvovec reported by Stephen Russell and co-authors in *The Lancet* in 2017, by prompting development, with FDA input, of a standardised and clinically meaningful multiluminance mobility test as a primary endpoint.

The story of voretigene neparvovec is an illustration of the value of the iterative clinical trials process—each phase providing value in determining the safety, efficacy, and effectiveness of a treatment—but it is also symbolic of a new era in gene therapy. Where previous explorations had been limited to oncology, the application to inherited vision loss is hope-inspiring and will spur novel interventions for some of the most clinically challenging conditions. It is worth acknowledging these triumphs of ingenuity and perseverance not simply as failures or successes but as validation of the biomedical research enterprise itself. ■ *The Lancet*

See Articles *Lancet* 2016; **388**: 661-72
See Articles *Lancet* 2017; **390**: 849-60

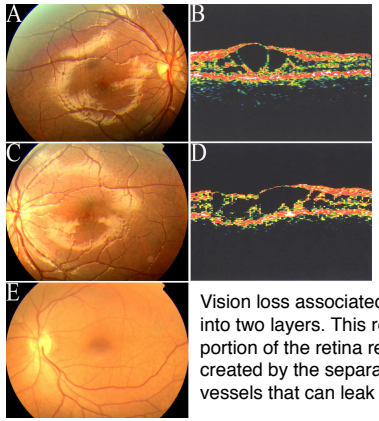
Spark Therapeutics announced that Luxturna will be available in the first quarter of 2018 from retinal surgeons trained by the company. Spark Therapeutics said it will announce pricing in early January. Industry estimates of the price range from $500,000 to $1.5 million.

Trade Name (Proper Name)	Cost	Indication and type of therapy	Manufacturer	Patient Population
Kymriah (tisagenlecleucel)	$475,000	CAR-T cell therapy for treatment of patients up to 25 years old with B-cell acute lymphoblastic lymphoma	Novartis	1.6 per 100,000 (6500 new cases per year in the US)
Yescarta (axicabtagene ciloleucel)	$373,000	CART-T cell therapy for treatment of adult patients with non-Hodgkin's lymphoma	Kite Pharma (bought by Gilead)	3.8 per 100,000 (7500 new cases per year in the US)
Luxturna (voretigene neparvovec-rzyl)	$850,000 ($425,000 per eye)	AAV therapy for patients with biallelic RPE65 mutation-associated retinal dystrophy	Spark Therapeutics, Inc	1 in 50,000 worldwide
Strimvelis (GSK2696273)	$648,000 (594,000 Euros)	CAR-T cell therapy for patients with severe combined immunodeficiency (ADA-SCID)	Glaxosmithkline	Between 1 in 200,000 to 1 in 1 million per year
Glybera (alipogene tiparvovec)	$1.2 million (1 million Euros) Withdrawn	AAV therapy for Lipoprotein lipase deficiency	uniQure	1 in 1 million in the US per year

Top 10 recent eye-research advances toward the market

1. Blindness (RetroSense Therapeutics)
2. Leber congenital amaurosis (Spark Therapeutics)
3. Usher syndrome (ReNeuron)
4. Retinitis pigmentosa (jCyte)
5. Retinoschisis (Applied Genetic Technologies Corporation)
6. Choroideremia (Spark Therapeutics)
7. Age-related macular degeneration (StemCells Inc)
8. Stargardt disease (VM200, Vision Medicines)
9. Wet AMD (Retinostat, Oxford BioMedica)
10. X-linked Retinitis Pigmentosa (Applied Genetic Technologies Corporation)

Juvenile Retinoschisis

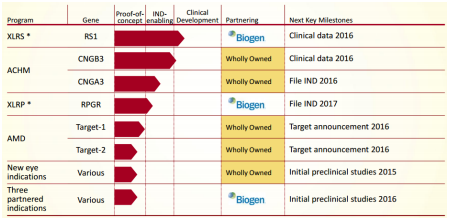


Juvenile retinoschisis, also known as X-linked retinoschisis, occurs almost exclusively in males. Although the condition begins at birth, symptoms do not typically become apparent until after the age of 10. About half of all patients diagnosed with juvenile retinoschisis first notice a decline in vision. Other early symptoms of the disease include an inability of both eyes to focus on an object (strabismus) and roving, involuntary eye movements (nystagmus).

Vision loss associated with juvenile retinoschisis is caused by the splitting of the retina into two layers. This retinal splitting most notably affects the macula, the central portion of the retina responsible for fine visual detail and color perception. The spaces created by the separated layers are often filled with blisters and ruptured blood vessels that can leak blood into the vitreous body.

agtc

- 27 participants, phase I/II study
- AAV2-hRS1 intravitreal injection



Program	Gene	Proof-of-concept	IND-enabling	Clinical Development	Partnering	Next Key Milestones
XLRS *	RS1				Biogen	Clinical data 2016
ACHM	CNGB3				Wholly Owned	Clinical data 2016
	CNGA3				Wholly Owned	File IND 2016
XLRP *	RPGR				Biogen	File IND 2017
AMD	Target-1				Wholly Owned	Target announcement 2016
	Target-2				Wholly Owned	Target announcement 2016
New eye indications	Various				Wholly Owned	Initial preclinical studies 2015
Three partnered indications	Various				Biogen	Initial preclinical studies 2016

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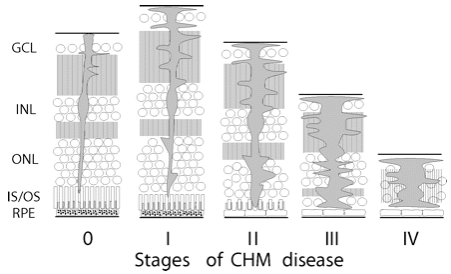
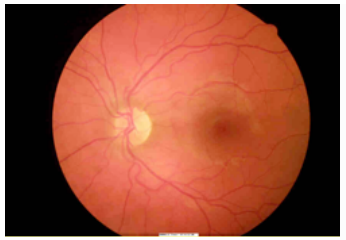
Gene therapy arrives at the macula

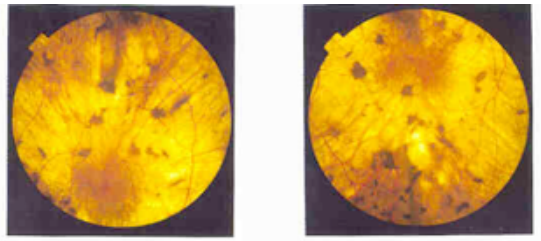
Choroideremia

Choroideremia is a rare inherited cause of blindness that affects around 1 in 50,000 people, which is caused by a lack of RAB Escort Protein-1 (**REP-1**) There is currently no cure. It is caused by defects in the CHM gene on the X chromosome. Without the protein produced by the CHM gene, pigment cells in the retina of the eye slowly stop working, then die off. As the disease progresses, the surviving retina gradually shrinks in size, reducing vision.





healthy retina



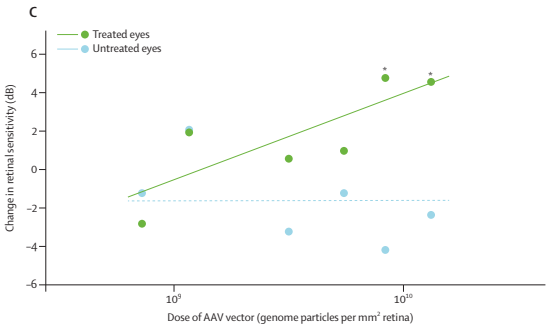
retina damaged by Choroideremia

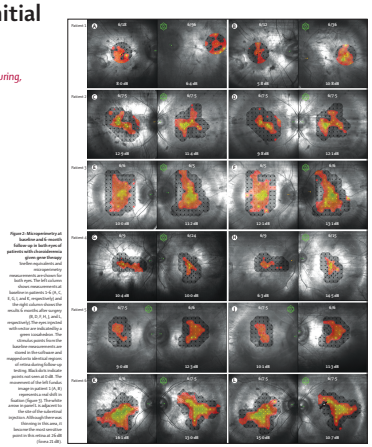
Gene therapy arrives at the macula

Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial

Robert E MacLaren, Markus Groppe, Alun R Barnard, Charles L Cottriall, Tanya Tolmachova, Len Seymour, K Reed Clark, Matthew J During, Frans P M Cremers, Graeme C M Black, Andrew J Lotery, Susan M Downes, Andrew R Webster, Miguel C Seabra

www.thelancet.com **Published online January 16, 2014 http://dx.doi.org/10.1016/S0140-6736(13)62117-0**





The objective of the Phase I/II trial is to assess safety and efficacy with two different doses of AAV2-REP1 in 12 patients. Results published in The Lancet in January 2014 reported that six months after treatment with this therapy, the first six patients showed improvement in their vision in dim light and the two patients who had impaired visual acuity at the start of the trial were able to read more lines on the eye chart.
The study is on-going and the next 6 patients are receiving a higher-dose. The Company will shortly announce its plans for Phase III studies.

Spark THERAPEUTICS

NightstaRx

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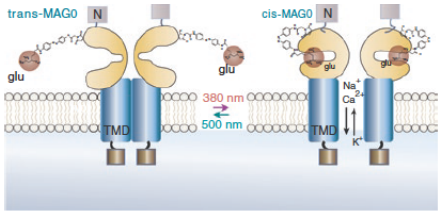
Optogenetic gene therapy

RetroSense THERAPEUTICS

LiGluR Restores Visual Responses in Rodent Models of Inherited Blindness

Natalia Caporale[1], Kathleen D Kolstad[1], Trevor Lee[1], Ivan Tochitsky[2], Deniz Dalkara[1], Dirk Trauner[3], Richard Kramer[1,2,4], Yang Dan[1,2,5], Ehud Y Isacoff[1,2,4] and John G Flannery[1,2,6]

www.moleculartherapy.org vol. 19 no. 7, 1212–1219 july 2011



The light-gated ionotropic glutamate receptor (LiGluR) is modified with a cysteine in position 439 (L439C) for the covalent attachment of a photoisomerable molecule ("photoswitch") that reversibly activates the receptor. At one wavelength, the glutamate fits into the binding pocket, opening the ion channel and at a second wavelength, it withdraws it to close the channel, thus enabling the channel to be turned on and off with light.

The intravitreal delivery of AAV2-LiGluR restored light responsiveness to the RGCs of adult rd1 mice, which had lost all photoreceptors

A Phase I/II trial is starting with 15 severely affected patients, who are expected to benefit most from the treatment

Vision is restored by bestowing light sensitivity to retinal ganglion cells, which normally don't process light (they perform image-processing functions downstream) but survive after photoreceptors are lost.

Unlike gene replacement, however, the optogenetic approach has the potential to work independent of the patient's disease-causing gene

Published online: September 27, 2016

Research Article

TRANSPARENT PROCESS OPEN ACCESS

EMBO Molecular Medicine

Red-shifted channelrhodopsin stimulation restores light responses in blind mice, macaque retina, and human retina

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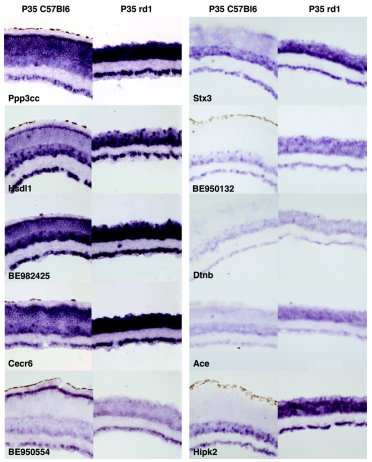
Optogenetics is a biological technique which involves the use of light to control cells in living tissue, typically neurons, that have been genetically modified to express light-sensitive ion channels.

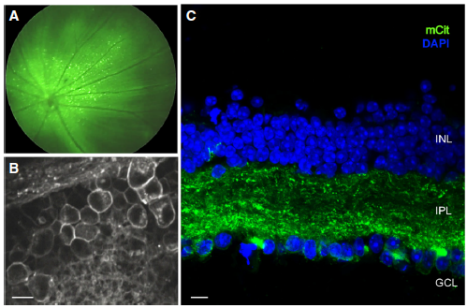
The key reagents used in optogenetics are light-sensitive proteins. Neuronal control is achieved using **optogenetic actuators** like channelrhodopsin (ChR2, ChR1, VChR1, and SFOs), halorhodopsin, and archaerhodopsin.

RETINAL DEGENERATION 1 PDE6BRD1

Retinal degeneration (Pde6brd1)

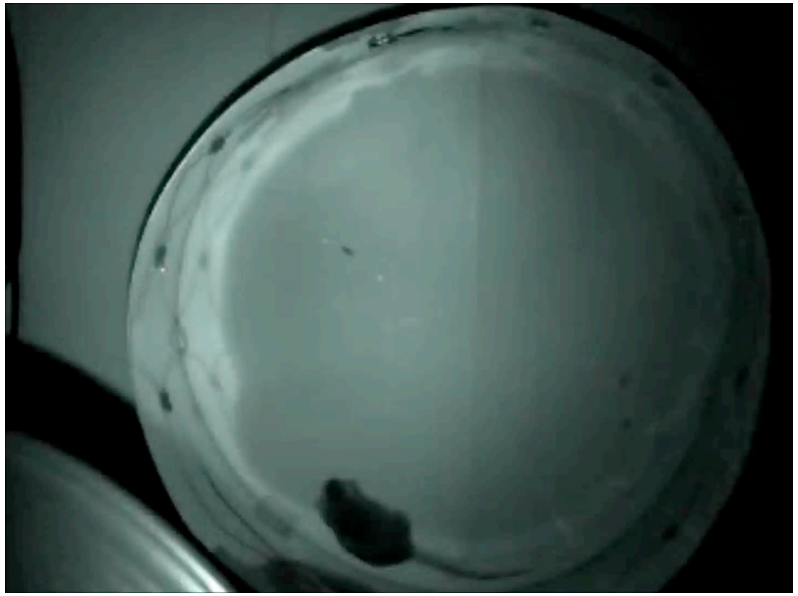


Intravitreal injection of an AAV2 encoding ReaChR-mCitrine under a pan-neuronal hSyn promoter to target retinal ganglion cells (RGCs) in blind rd1 mice (4–5 weeks old).



rd1 mouse explores the circular open-field in the darkness. Upon sudden illumination of the chamber with orange light (590 nm, ~1015 photons cm-2 s-1) the mouse remains unaffected.

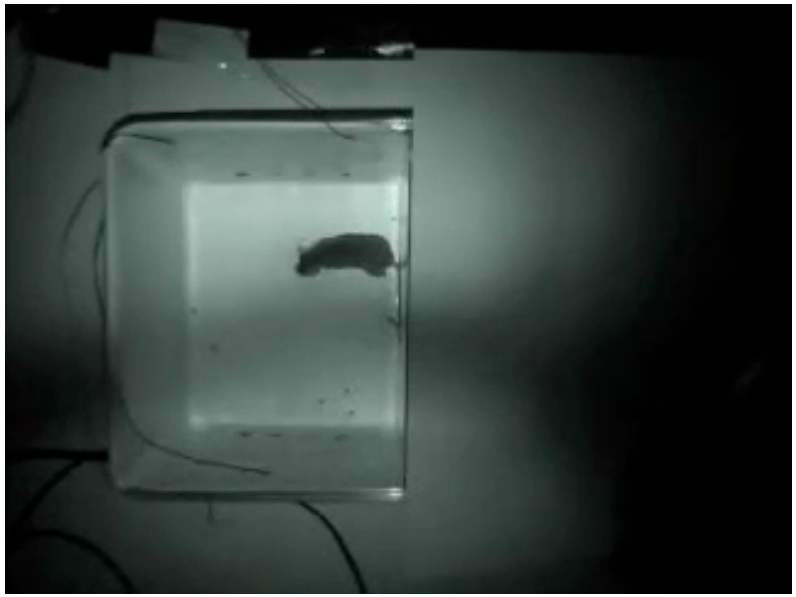
ReaChR-treated rd1 mouse explores the circular open field in darkness similar to the untreated rd1 mouse. Upon sudden illumination of the chamber with orange light (590 nm, ~1015 photons cm-2 s-1) the ReaChR-treated rd1 mouse is immediately immobilized. The ReaChR-treated rd1 mouse recovers and begins to move after about 1 minute following light onset.



Top 10 recent eye-research advances toward the market

1. Blindness (RetroSense Therapeutics)
2. Leber congenital amaurosis (Spark Therapeutics)
3. Usher syndrome (ReNeuron)
4. Retinitis pigmentosa (jCyte)
5. Retinoschisis (Applied Genetic Technologies Corporation)
6. Choroideremia (Spark Therapeutics)
7. Age-related macular degeneration (StemCells Inc)
8. Stargardt disease (VM200, Vision Medicines)
9. Wet AMD (Retinostat, Oxford BioMedica)
10. X-linked Retinitis Pigmentosa (Applied Genetic Technologies Corporation)

ReaChR-treated mouse exhibits robust light aversion in a light/dark box chamber. When the light side was illuminated by orange light (590 nm, ~1015 photons cm-2 s-1) the mouse spent most of the time during a 5 minute trial on the dark side. At the end of the video the mouse could be seen resuming its exploration of the dark chamber when the orange light was switched off.



Usher syndrome

The major symptoms of Usher syndrome are hearing loss and retinitis pigmentosa.

	Type 1	Type 2	Type 3
Hearing	Profound deafness in both ears from birth	Moderate to severe hearing loss from birth	Normal at birth; progressive loss in childhood or early teens
Vision	Decreased night vision before age 10	Decreased night vision begins in late childhood or teens	Varies in severity; night vision problems often begin in teens
Vestibular function (balance)	Balance problems from birth	Normal	Normal to near-normal, chance of later problems

11 genetic loci have been found to cause Usher syndrome:

- Type 1 Usher syndrome: *MY07A*, *USH1C*, *CDH23*, *PCDH15*, *SANS*
- Type 2 Usher syndrome: *USH2A*, *VLGR1*, *WHRN*
- Type 3 Usher syndrome: *USH3A*

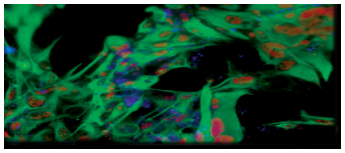
Phase I/II approved in 2015

ReNeuron

The treatment involves the injection of human retinal progenitor cells (hRPCs), which are more mature than embryonic stem cells, but haven't completely developed into photoreceptors.

Human retinal progenitor cells (hRPCs)
hRPCs are cells that differentiate into components of the retina. These cells are used allogeneically and are grown using a patented low-oxygen cell expansion technology licensed from the Schepens Eye Research Institute at Harvard Medical School.

jCyte™



Both jCyte and ReNeuron use hRPCs. However, there are two key differences between the two therapies.

1) jCyte's hRPCs are used to release neuroprotective proteins to preserve cones, the retinal cells that enable to read, perceive colors and see in lighted conditions. While the ReNeuron hRPCs are also designed to preserve cones, they may also develop into new photoreceptors and integrate into the patient's retina to restore vision.
2) jCyte's hRPCs will be injected into the patient's vitreous, the gel-like substance that fills the middle of the eye. The ReNeuron therapy will be injected underneath the retina, a delicate procedure that carries more risk for damage or complications.

"jCyte's hRPCs don't have to integrate into the host tissue to be effective, they are floating in the clear vitreous gel and their status could be visualised using a standard slit lamp or indirect ophthalmoscope"

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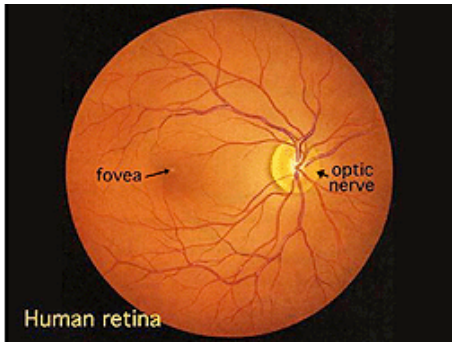
The human retina



In the center of the retina is the **optic nerve**, a circular to oval white area measuring about 2 x 1.5 mm across.

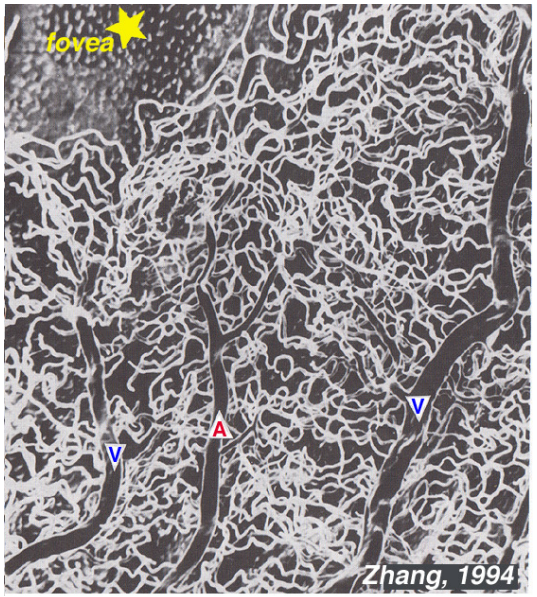
From the center of the optic nerve radiate the major blood vessels of the retina.

Approximately 5 mm to the left of the disc, can be seen the slightly oval-shaped, blood vessel-free reddish spot, the fovea, which is at the center of the area known as the macula

A circular field of approximately 6 mm around the fovea is considered the **central retina** while beyond this is peripheral retina stretching to the ora serrata, 21 mm from the center of the optic disc. The total retina is a circular disc of approximately 42 mm diameter.

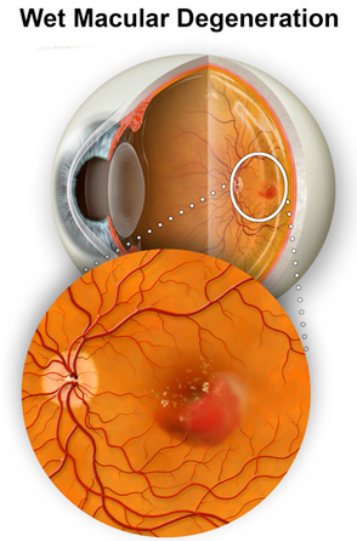
Macular vessels

There as a ring of blood vessels in the macular area around a blood vessel- and capillary-free zone 450-600 micron in diameter, denoting the fovea. The macular vessels arise from branches of the superior temporal and inferotemporal arteries.



Age-related macular degeneration (AMD)

AMD is a chronic condition that causes central vision loss and it is a leading cause of blindness in people aged 60 and older. There are 2 forms of AMD—wet and dry. Dry AMD is more common (8/10) but wet AMD is responsible of most cases of blindness



Wet AMD occurs when abnormal blood vessel grow in the back of the eye. As the blood vessels grow, they can leak blood and fluid, which damage the macula—the part of the retina that lets you see the color and fine detail, causing central vision loss

Normal vision

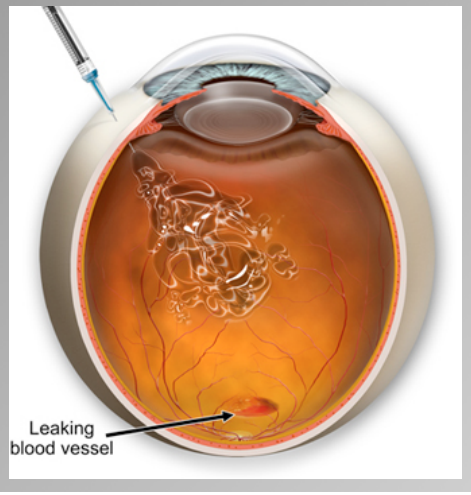
The same scene as viewed by a person with age-related macular degeneration

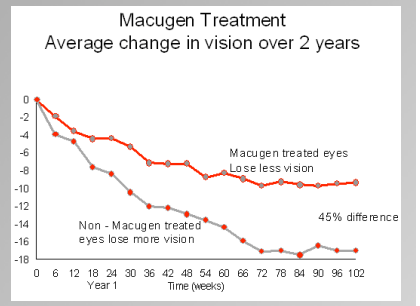
Anti-VEGF for wet AMD

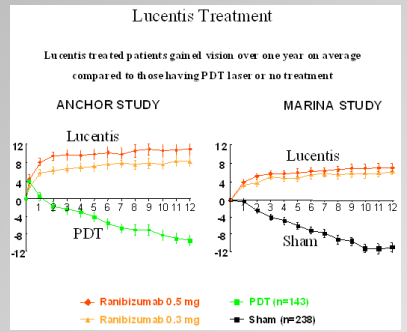
Macugen (Pegaptanib sodium - pegylated aptamer that binds VEGF165)

Lucentis (ranibizumab) - recombinant humanized Fab that binds all VEGF isoforms

Intravitreal injection into the back of the eye

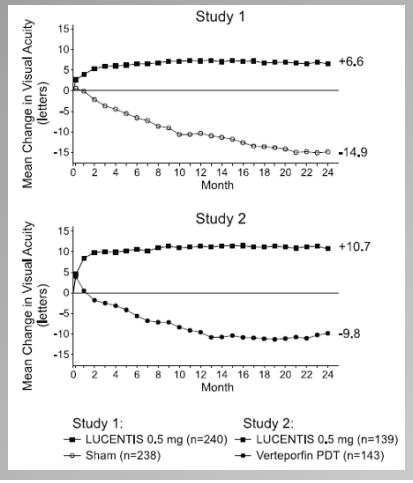


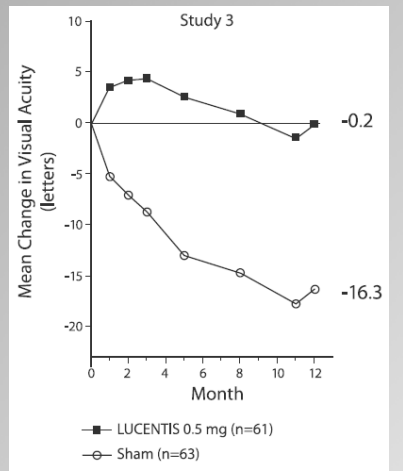




LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be treated regularly.





Comparison of AMD Treatments Trials (CATT): Lucentis - Avastin Trial

A multicenter clinical trial to compare the relative safety and effectiveness of two drugs currently used to treat advanced age-related macular degeneration (AMD).

NEI Press Release - 2008

Lucentis was approved by the U.S. Food and Drug Administration (FDA) in June of 2006 for the treatment of advanced, or wet, AMD. The approval was based on evidence from clinical trials showing that Lucentis slows the rate of progression of vision loss from wet AMD. In addition to a low rate of developing vision loss, approximately one-third of patients treated in these trials had some improvement in vision, as measured on an eye chart, at 12 months.

Avastin is a drug closely related to Lucentis. It was approved by the FDA in 2004 as an intravenous treatment for patients with advanced colorectal cancer and therefore has been available for what is called off-label use for other health conditions. It has been widely used off-label to treat wet AMD. Avastin is thought to remain in the eye longer than Lucentis and therefore possibly allow for less frequent injections.

The additional 5% risk of serious adverse events has to be weighed against the cost benefits. A dose of Ranibizumab costs 40 times as much as a dose of Bevacizumab: this difference has important economic implications when extrapolated to the more than 250,000 patients who are treated for wet AMD annually in the US. For those who are uninsured or unable to afford Lucentis, receiving Avastin may be an informed decision worth taking.

ORIGINAL ARTICLE

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration

The CATT Research Group

N Engl J Med 2011; 364:1897-1908 | May 19, 2011

BACKGROUND

Clinical trials have established the efficacy of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). In addition, bevacizumab is used off-label to treat AMD, despite the absence of similar supporting data.

METHODS

In a multicenter, single-blind, noninferiority trial, we randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart.

RESULTS

Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, P=0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P>0.20). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

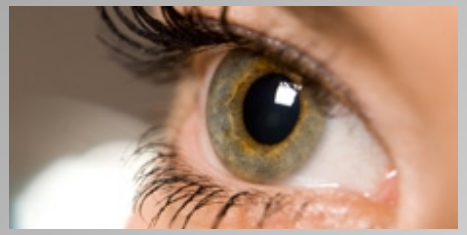
CONCLUSIONS

At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study. (Funded by the National Eye Institute; ClinicalTrials.gov number, NCT00593450.)

NEWS

Caso Avastin: respinti i ricorsi di Novartis e Roche. Confermata multa da 180 milioni

2 dicembre 2014



Il Tar conferma la sanzione da 180 milioni di euro respingendo i ricorsi di Roche e Novartis. Le due multinazionali del farmaco dovranno quindi pagare la salata multa inflitta dall'Antitrust perché ritenute colpevoli di aver fatto "cartello" per favorire il farmaco più caro (Lucentis) per la cura della maculopatia senile. Un accordo che è costato al Servizio sanitario nazionale 1,2 miliardi di euro.

Safety and Tolerability of Sub-retinal Transplantation of hESC Derived RPE (MA09-hRPE) Cells in Patients With Advanced Dry Age Related Macular Degeneration (Dry AMD)

ClinicalTrials.gov Identifier: NCT01344993

Embryonic stem cell trials for macular degeneration: a preliminary report

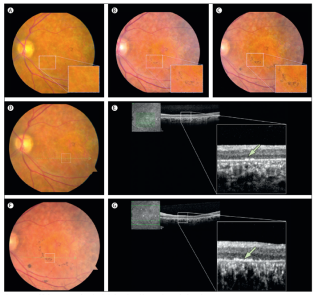
Steven D Schwartz, Jean-Pierre Hubschman, Gad Heilwell, Valentina Franco-Cardenas, Carolyn K Pan, Rosaleen M Ostrick, Edmund Mickunas, Roger Gay, Irina Klimanskaya, Robert Lanza

Summary

Background It has been 13 years since the discovery of human embryonic stem cells (hESCs). Our report provides the first description of hESC-derived cells transplanted into human patients.

Methods We started two prospective clinical studies to establish the safety and tolerability of subretinal transplantation of hESC-derived retinal pigment epithelium (RPE) in patients with Stargardt's macular dystrophy and dry age-related macular degeneration—the leading cause of blindness in the developed world. Preoperative and postoperative ophthalmic examinations included visual acuity, fluorescein angiography, optical coherence tomography, and visual field testing. These studies are registered with ClinicalTrials.gov, numbers NCT01345006 and NCT01344993.

Findings Controlled hESC differentiation resulted in greater than 99% pure RPE. The cells displayed typical RPE behaviour and integrated into the host RPE layer forming mature quiescent monolayers after transplantation in animals. The stage of differentiation substantially affected attachment and survival of the cells in vitro after clinical formulation. Lightly pigmented cells attached and spread in a substantially greater proportion (>90%) than more darkly pigmented cells after culture. After surgery, structural evidence confirmed cells had attached and continued to persist during our study. We did not identify signs of hyperproliferation, abnormal growth, or immune mediated transplant rejection in either patient during the first 4 months. Although there is little agreement between investigators on visual endpoints in patients with low vision, it is encouraging that during the observation period neither patient lost vision. Best corrected visual acuity improved from hand motions to 20/800 (and improved from 0 to 5 letters on the Early Treatment Diabetic Retinopathy Study [ETDRS] visual acuity chart) in the study eye of the patient with Stargardt's macular dystrophy, and vision also seemed to improve in the patient with dry age-related macular degeneration (from 21 ETDRS letters to 28).



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