EBERHARD KARLS UNIVERSITÄT TÜBINGEN

UKT

Centre for Ophthalmology

Visual Function Endpoints in Clinical Trials Clinical View

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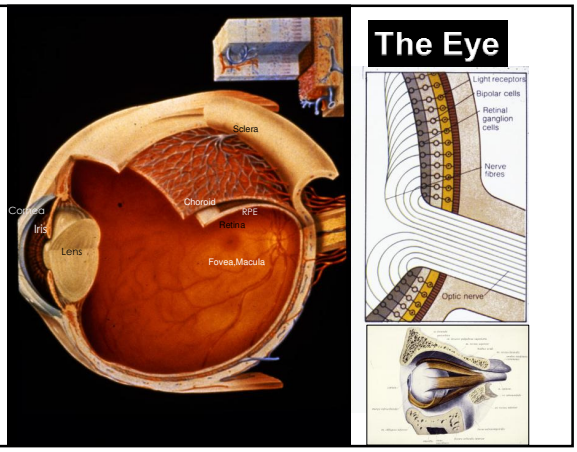
Content

Aim: Endpoints that assess Safety, Benefit, Reliability, and are feasible

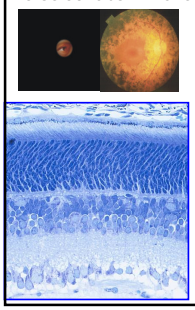
- Basics: Structure and Function
- Function Testing: Psychophysics in Ophthalmology
- Function Testing Electrophysiology in Ophthalmology
- Retinal Imaging
- Assessing Activities of Daily Living
- Patient Reported Outcomes (PRO) of Visual Function
- Examples from Ongoing Studies

- Financial Disclosure
- The author performs or performed advisory tasks during the 5 most recent years for Acucela, Allergan, Bayer, Boehringer Ingelheim, Merck, Neurotech, Pfizer, Retina Implant AG, Servier and QLT; he is shareholder of Retina Implant AG and inventor on patents concerning electronic subretinal implants.

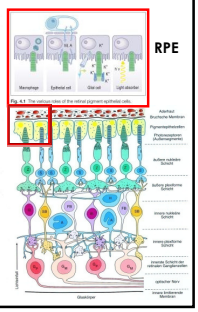


Retinal Structure and Function

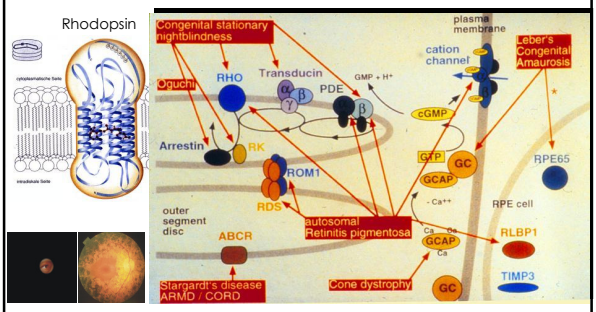
Rod Photoreceptors
High sensitivity
Low spatial resolution
No colour discrimination



Cone Photoreceptors
Low sensitivity
High spatial resolution
Colour discrimination

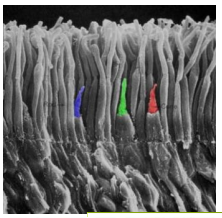


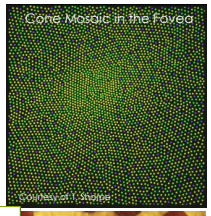
The Phototransduction process: many things can go wrong

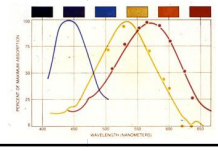


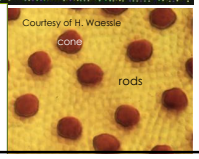
Courtesy of W. Baehr

The Short, Middle and Long Wavelengths Sensitive Cones









Information Processing in the Retina

~ 120 million photoreceptors

⇓

„The natural computer"

⇓

~ 1 million ganglion cell fibres sending pulses to the brain

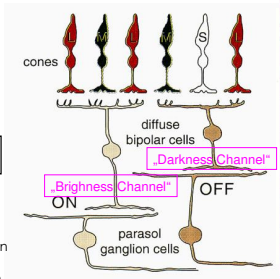
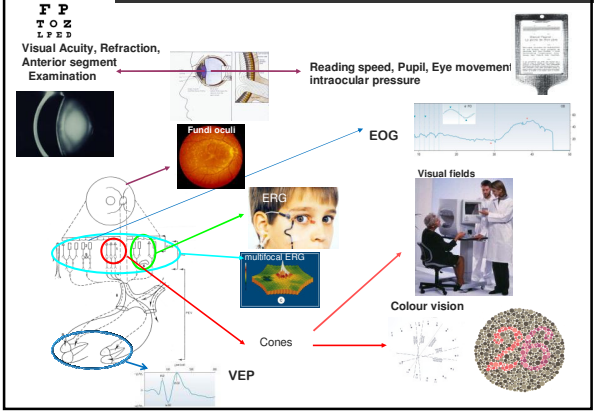


Table 4.1 – The various transmitters and modulators present in the retinal layers (modified from Vaney 1990 and Kolb et al 2001)

Neuroactive Substance	Cell Type
Glutamate	Photoreceptors (cones and rods), bipolar cells, ganglion cells
Gamma aminobutyric acid (GABA)	Horizontal cells, amacrine cells
Glycine	Amacrine cells, bipolar cells, ganglion cells
Taurine	Photoreceptors, amacrine cells, bipolar cells
Dopamine	Amacrine cells (including interplexiform cells)
Melatonin	Photoreceptors
Serotonin	Amacrine cells, bipolar cells (in non-mammalian vertebrates)
Acetylcholine	Amacrine cells (in the INL and displaced in the GCL)
Substance P	Amacrine cells, ganglion cells
Angiotensin II	Amacrine cells
Nitric oxide	Amacrine cells
Vasoactive intestinal polypeptide (VIP)	Amacrine cells
Somatostatin	Amacrine cells, ganglion cells
ATP	Amacrine cells, ganglion cells
Adenosine	Amacrine cells, ganglion cells
Brain-derived neurotrophic factor (BDNF)	Amacrine cells, ganglion cells
Kynurenic acid	Amacrine cells

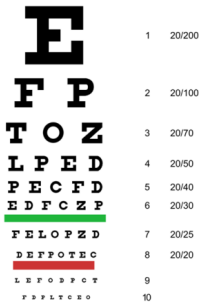
(courtesy of Paul R. Martin, 1998)

Retinal ophthalmic investigations Rationale



Functional Diagnostics
Best Corrected Visual Acuity (BCVA)

- Snellen chart

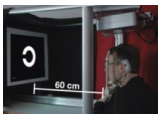


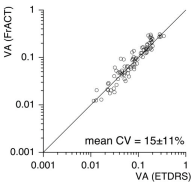
Functional Diagnostics
Best Corrected Visual Acuity (BCVA)

- Snellen chart
- ETDRS chart (Standard)

Functional Diagnostics
Best Corrected Visual Acuity (BCVA)

- Snellen chart
- ETDRS chart (Standard
- Freiburg Visual acuity Test (FRACT) with Landolt C-ring (Computer-Screen test)

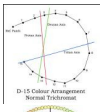


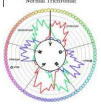


K. Schulze-Bonsel, et al., Visual Acuities "Hand Motion" and "Counting Fingers" Can Be Quantified with the Freiburg Visual Acuity Test. IOVS (2006) 47:1236-1240;

Functional diagnostics
Colour vision testing

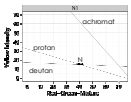
- **Colour vision: arrangement test**
  - Lanthony Panel D-15 Test
  - Roth 28-hue Test
  - Farnsworth-Munsell 28 or 100 Test





WEB based evaluation tool: http://www.torok.info/colorvision/dir_for_use.htm (Dr. Bela Török)

- **Anomaloscopy**

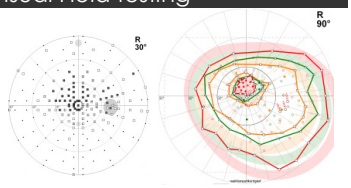


FunctionalDiagnostics
Contrast Vision

- Pelli-Robson Chart
- Mesoptometer
  - With and without glare
- Hamilton Veale Test

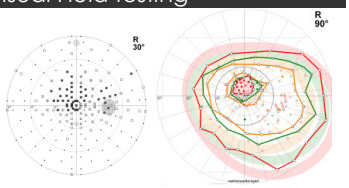
Functional diagnostics
Visual Field testing

- Visual field testing
  - Static perimetry 30°
  - Kinetic perimetry 90°



Functional diagnostics
Visual Field testing

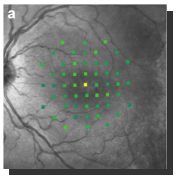
- Visual field testing
  - Static perimetry 30°
  - Kinetic perimetry 90°

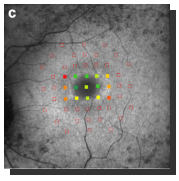


- Microperimetry

Central Vision

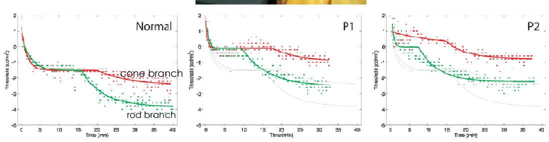
Eye Movement Compensated





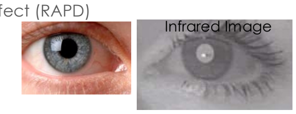
Functional diagnostics:
Dark Adaptation

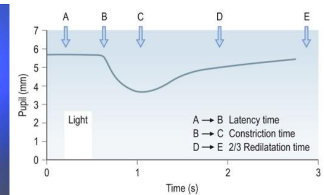
Adaptometer
(Roland Consult)



Functional Diagnostics
Pupillography

- Relative Afferent Pupillary Defect (RAPD)
- Pupillography





AMTECH Pupillograph

Summary 1 Psychophysics

Table 4.3b – Functional 'markers' of the various structures and cell populations of the visual system assessed by psychophysical tests, ordered according to peripheral retina (yellow), central retina (pink) and ascending visual pathways (final two rows).

Retinal Eccentricity	Structure of the Visual System	Psychophysics							Clinical Examination
		Visual Acuity	Colour Vision	Glare Sensitivity	Perimetry (visual fields)		Dark Adaptation	Pupillography	
		ETDRS Chart	D 15/28 Desaturated	Nyctometer Mesoptometer	Kinetic Cone System	Static Cone System	Cone and Rod System	Infrared Pupillometer	
Center and periphery	**Retinal pigment epithelium**						X	X	
>30° ecc. Peripheral retina: Rod dominated	**Outer** Photoreceptors; **Inner** Bipolar cells; Amacrine cells			Rod-cone interaction	Total area per isopter: III 4e and I 3e			X	Ophthalmoscopy Pigment changes Deposits Vessels etc.
<30° ecc. Central retina: Cone dominated	**Outer** Photoreceptors; Inner Bipolar cells; Amacrine cells	Foveola X	Foveola X	Cone-rod interaction		Threshold method	Threshold method	X	Ophthalmoscopy Fovea reflexes Autofluorescence Optic nerve head Pigment changes Deposits Vessels etc.
	Ganglion cells	X	X	X	X	X	X	X	OCT, NFL
Visual pathways	Afferent visual pathway	X	X	X	X	X	X	X	
	Efferent visual systems, including autonomous nerve system							X	Eye mobility, tests for diplopia, pupil investigation

OCT, optical coherence tomography; NFL, nerve fiber layer

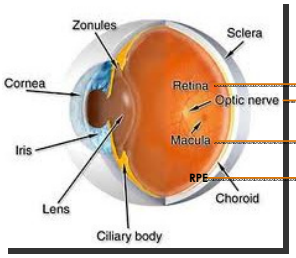
E. Zrenner, The role of electrophysiology and psychophysics in ocular toxicology. In: Clinical Ocular Toxicology (Edrs: FT Fraunfelder, WT Fraunfelder, W.Chambers), Chapter 4, pp.28-38, Saunders Elsevier, 2008

Surrogate Endpoints

- A ***surrogate endpoint***, according to the FDA is a biomarker that is "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict clinical benefit." The best surrogate endpoint is a biomarker that changes along with clinical endpoints.

Csaky et al. IOVS 2009

Clinical Electrophysiology of the Visual System



Electroretinogram (ERG)
Visually evoked potentials(VEP)
Multifocal ERG (mfERG)
Pattern ERG (PERG)
Electrooculogram (EOG)

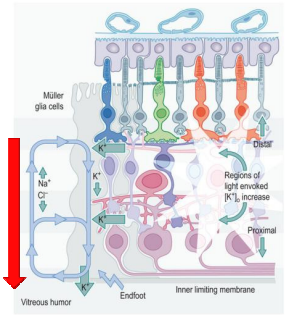
Categorization of function tests: Electroretinogram: sites of action

1) **RPE**

2) **Outer Retina**

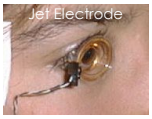
3) **Inner Retina**

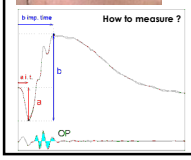
The Müller glia cell aligns the K^+ driven retinal currents perpendicularly, creating a vector directed towards the cornea

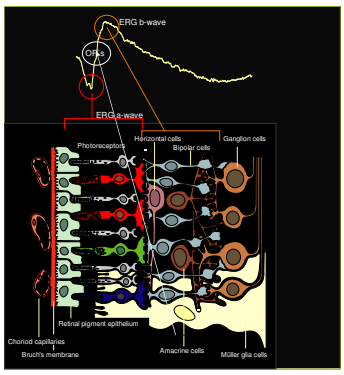


E. Zrenner, The role of electrophysiology and psychophysics in ocular toxicology. In: Clinical Ocular Toxicology (Eds: FT Fraunfelder, WT Fraunfelder, W.Chambers), Chapter 4, pp.28-38, Saunders Elsevier, 2008

Outer Retina: Origin of the ERG-responses

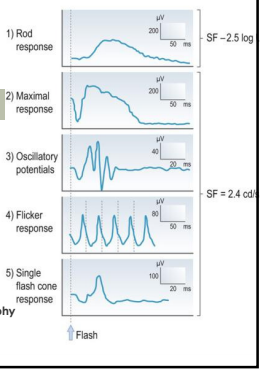






ISCEV Standard Ganzfeld ERG

1. Isolated rod responses
2. Rod and cone Max. Responses
3. Inner Retina OPs
4. Isolated Cone Responses
5. Cone flicker Responses

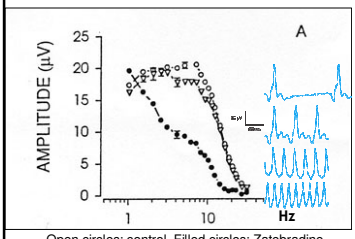


See: Marmor et al. Standard for clinical electroretinography (2008 update). Doc Ophthalmol 2009;118:69–77

For further Information see www.iscev.org

Investigating effects on temporal fidelity of retinal cells

Example: Effects of Zatebradine, an I_h channel blocker, 2.5 mg/kg, on flicker ERG



Open circles: control, Filled circles: Zatebradine, Triangles: 5 hrs after application

Gargini et al, Vision Research 39,1767-1774,1999

Doc Ophthalmol (2009) 118:69–77

Table 1 Examples of specialized types of ERG (not covered by this ISCEV standard)

Macular or focal ERG
Multifocal ERG (see published guidelines [4])
Pattern ERG (see published standard [5])
Early receptor potential (ERP)
Scotopic threshold response (STR)
Direct-current ERG
Long-duration light-adapted ERG (on-off responses)
Double-flash ERG
Chromatic stimulus ERG (including S-cone ERG)
Dark and light adaptation of the ERG
Dark-adapted and light-adapted luminance-response analyses
Saturated *a*-wave slope analysis
Specialized procedures for young and premature infants

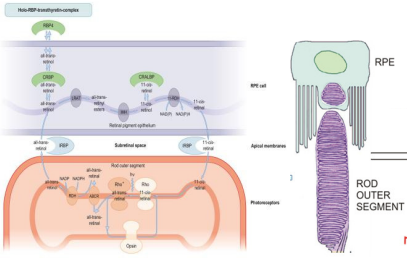
Assessing the RPE / Photoreceptor complex:

Retinoid visual cycle: 11-*cis*-retinal, is photoisomerized to all-*trans* retinal and reisomerized to 11-*cis*-retinal. **Formation of RPE Lipofuscin** is almost completely dependent on a normal visual cycle function.

Retinal Pigment Epithelial Cell (RPE)
(Storage, Isomerization,

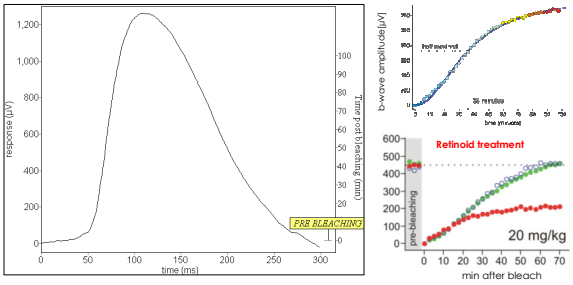
Inter-photoreceptor Matrix (IPM)
(Transport)

Photoreceptor Outer Segment (OS)
(Phototransduction)



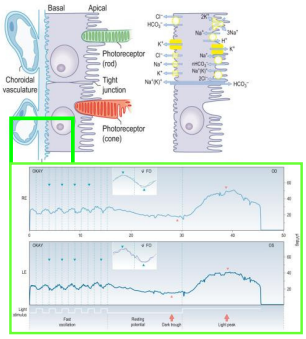
Assessing the RPE / Photoreceptor complex:
ERG amplitude recovery after bleaching

If retinoid cycle is affected, „time to reach threshold" during dark adaptation may be useful , after a bleach of 400 cd/m² (30 s)



Messias A, Zrenner E, Tzekov R, McGee D, Peters T, Wilhelm B, Baryluk A, Kubota R, Gekeler F.
Single doses of all-trans-N-retinylacetamide slow down the ERG amplitude recovery after bleaching..
Doc Ophthalmol. 120(2):165-74, 2010

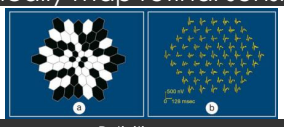
The Electro-oculogram:
assessing the integrity of the photoreceptor / RPE complex



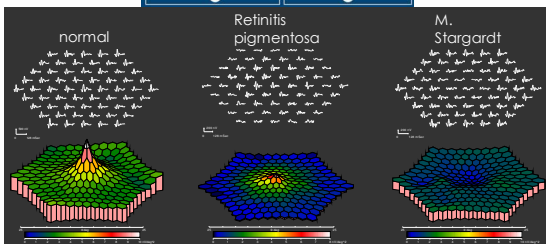
Marmor MF et al. ISCEV Standard for Clinical Electro-oculography. Doc Ophthalmol (2011) 122:1–7
see also www.iscev.org

Multifocal ERG (mfERG) allows to electrically map retinal sensitivity

Stimulus field
64 independently
Flickering Hexagons



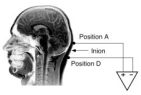
64 local ERGs

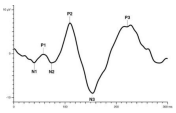


Hood DC et al., ISCEV Guidelines for clinical multifocal electroretinography (2007 edition)

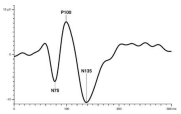
Visually evoked cortical Potentials (VEP)

- Visual pathway

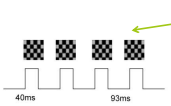




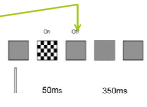
Flash-VEP



Pattern-VEP



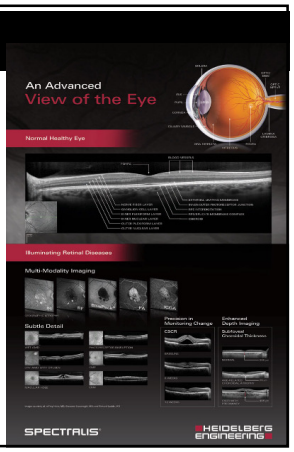
Pattern Reversal

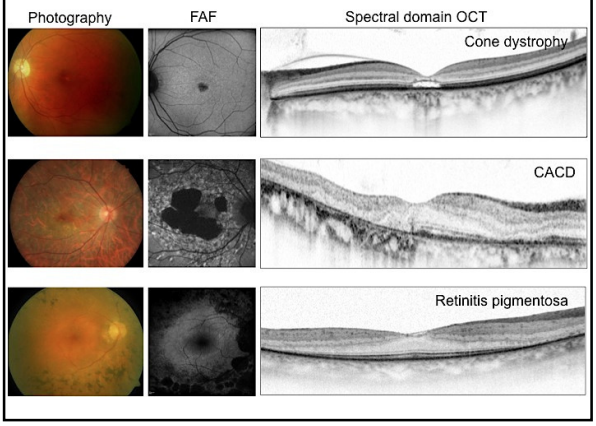


Transient

Retinal imaging

- Color photographs – posterior pole and periphery
- Fundus autofluorescence imaging (FAF)
- Fluorescence Angiography (FA)
- Optical coherence tomography (OCT)





Summary 2 Electrophysiology and Imaging

Table 4.3a – Functional 'marker' of the various structures and cell population of the visual system assessed by electro-physiological tests, ordered according to peripheral retina (yellow), central retina (pink) and ascending visual pathways (final two rows).

Retinal Eccentricity	Structures of the Visual System	Electrophysiology					Clinical Examination
		EOG	Ganzfeld ERG (ISCEV 2004) No Topographic Resolution		Mf ERG and PERG Topographical Map	VEP	
			Dark Adapted Rod ERG	Light Adapted Cone ERG	Light Adapted Cone ERG	Pattern or Flash	
Center and Periphery	**Retinal pigment epithelium**	X					
>30° ecc. Peripheral retina: Rod dominated	**Outer** Photoreceptors	X	**a-wave** Combined resp.				Ophthalmoscopy Pigment changes Deposits Vessels etc.
	Inner Bipolar cells		**b-wave** Rod resp.				
	Amacrine cells		Oscillatory potentials				
<30° ecc. Central retina: Cone dominated	**Outer** Photoreceptors	X		**a-wave** Single cone flash resp.	N1	X	Ophthalmoscopy Fovea reflexes Autofluorescence Optic nerve head Pigment changes Deposits Vessels etc.
	Inner Bipolar cells			**b-wave** Flicker resp. Single cone flash resp.	P1	X	
	Amacrine cells			Oscillatory potentials		X	
	Ganglion cells				N2	X	OCT:NFL
Visual pathways	Afferent visual pathway				Maculopapillar nerve fiber bundle	P100	Pupillary reflex
	Efferent visual systems, including autonomous nerve system						Eye mobility, tests for diplopia, pupil investigation

OCT:optical coherence tomography; NFL:nerve fiber layer

E. Zrenner, The role of electrophysiology and psychophysics in ocular toxicology. In: Clinical Ocular Toxicology (Edrs: FT Fraunfelder, WT Fraunfelder, W.Chambers). Chapter 4, pp.28-38, Saunders Elsevier, 2008

Patient Reported Outcomes (PRO)

- A PRO is a measurement of any aspect of a patient`s health status that is reported and or scored directly by the patient, free of interpretation by a physician, researcher or other person. It is an account of how the patient functions or feels relative to a health condition or therapy.
- Good measurements should have unidimensionality, hierarchical order, and equal interval spacing

Varma et al., IOVS 2010

Patient Reported Outcomes (PRO)

A PRO would measure any of the following:

- Symptoms
- Symptom impact and functioning
- Disability or handicap
- Adverse events
- Treatment tolerability
- Treatment satisfaction
- Health-related quality of life

Varma et al., IOVS 2010

PRO: Available instruments

- Activities of Daily Living Scale (ADVS)
  Reading, orientation/mobility, finding objects, social participation, financial handling…..
- Daily Living Tasks Dependent on Vision (DLTV)
- Impact of Vision Impairment (IVI)
- Macular Disease Quality of Life Questionnaire
- **NEI-VFQ 25** (most common, well-equipped)
- Visual Function Index (VF-14)
- Low-Luminance Questionnaire (LLQ)
- Miedziak's instrument
- Vision-specific sickness impact profile (SIPV)
- Turano's instrument
- Vision-Related Quality of Life Questionnaire
- Retinopathy-Dependent QOL

Varma et al., IOVS 2010

Ongoing Clinical trials in legally blind patients

Pathology	Gene	Phase	Sponsor	Vector	Dose	Route	Age	#	Start - end
Severe EORD	RPE65	I/II	U College, London	rAAV 2/2.hRPE65p.hRPE65	Up to $3.0X10^{12}$ vg	Subret	5 y - 30 y	12	01/2007 to 01/2013
LCA2	RPE65	I	Children hosp, Philadelphia	rAAV2-hRPE65v2	not given	Subret	8 y - older	12	09/2007 to 06/2009
LCA2	RPE66	I/II	Children hosp, Philadelphia	rAAV2-hRPE65v2	Up to $1.5X10^{11}$ vg	Subret	8 y - older	12	11/2010 to ...
LCA2	RPE65	III	Children hosp, Philadelphia	rAAV2-hRPE65v2	not given	Subret	3 y - older	12	09/2011 to 09/2017
LCA2	RPE65	I	U Pennsylvania	rAAV2-CB-hRPE65	not given	Subret	8 y - older	15	07/2007 to ...
LCA2	RPE65	I/II	Applied Genetic Technologies	rAAV2-CB-hRPE65	Up to $6.0X10^{11}$ vg	Subret	6 y - older	12	12/2008 to 12/2013
LCA2	RPE65	I	Hadassah-Hebrew U, Jerusalem	rAAV2-CB-hRPE65	$1.15X10^{11}$ vg	Subret		1	2010
LCA2	RPE65	I/II	University hospital, Nantes	rAAV 2/4.hRPE65p.hRPE65	Up to $4.8X10^{10}$ vg	Subret	6 y - older	9	10/2011 to 01/2013
Wet AMD	sVEGFR	I	Genzyme USA	AAV2-sFLT01	Up to $2.0X10^{10}$ vg	Intravit	Not given	34	12/2009 to 03/2013
Stargardt	ABCA4	I/II	Oxford Biomedica	eqLV-hABCA4	not given	Subret	18 y - older	28	06/2011 to 10/2013
Wet AMD	EA	I	Oxford Biomedica	eqLV-hEA	not given	Intravit	50 y - older	18	02/2011 to 06/2012
Wet AMD	PEDF	I	GenVec	AdGVPEDF.11D	not given	Intravit	50 -older		Closed

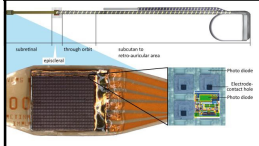
hEA : human endostatin-angiostatin fusion gene

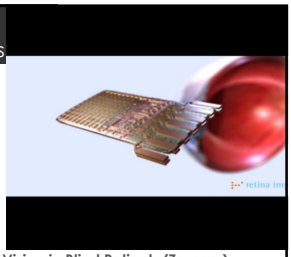
Upcoming Clinical trials in legally blind patients

Pathology	Gene	Phase	Sponsor	Vector
Usher 1	MYO7A	I	Oxford Biomedica	eqLV-hMYO7A
Choroideremia	CHM	I/II	University of Oxford	AAV-hCHM
ACHM	CNGB3			AAV-hCNGB3
arRP	MERTK			

Courtesy of Dr. Christian Hamel

Relevant studies
Subretinal electronic implants





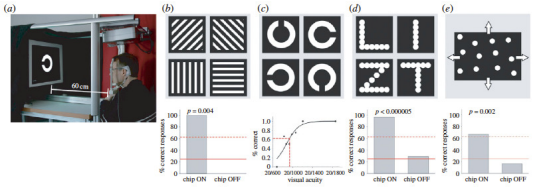
Safety and Efficacy of Subretinal Implants for Partial Restoration of Vision in Blind Patients (Zrenner)

- Primary Outcome Measures:
  - Activities of daily living and mobility significantly improve with implant-ON shown via activities of daily living tasks, recognition tasks, mobility, or a combination thereof
- Secondary Outcome Measures:
  - Visual acuity/light-perception and/or object-recognition measured with FrACT/BaLM/BaGA/VFQ-25
  - Patient long term safety and stability of implant function

Zrenner et al, Proc. R Soc. B 278: 1489ff, 2011

Functional diagnostics in subretinal electronic Implants

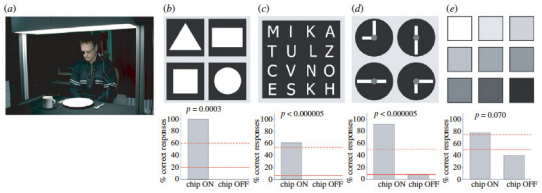
- BaLM (basic light and movement test)
- BaGA (recognition of stripe patterns)



Zrenner et al, Proc. R Soc. B 278: 1489-1497 (2011)

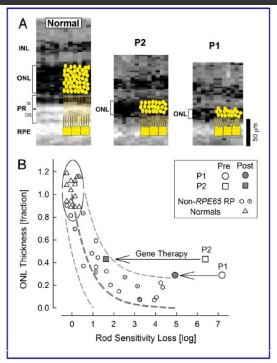
Functional diagnostics in subretinal electronic Implants

- Tasks of daily living (more naturalistic scenes)



Zrenner et al, Proc. R Soc. B 278: 1489-1497 (2011)

Gene therapy dramatically improves rod light sensitivity



U. Penn US study

Cideciyan et al., *PNAS*2008;105:15112

Summary

- Monitoring of visual function for safety and efficacy in very low and ultra-low vision patients is difficult
- The tools are there, but have to be selected depending on the cellular target structure
  - Psychophysics
  - Electrophysiology as surrogate marker
  - Retinal Imaging as surrogate marker
  - Assessment of Activities of Daily Living (ADL)
  - Patient Reported Outcomes (PRO) of visual function
- Some of the ongoing studies have developed novel tests in order to monitor ultra-low vision changes which, however , are not yet validated

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