Prospects for vision restoration in outer retinal degeneration

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Disclosures

• RVG is an unpaid consultant to Vedere, LLC and chairs its Clinical Scientific Advisory Board
• RVG is unpaid consultant to Bayon Pharmaceuticals which holds IP on some material in this talk
• RVG, TB, DB have provisional patent on some material discussed in this talk
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Charles Schepens, MD 1912-2006

- Founder of the Retina Society
- Pioneer in vitreoretinal surgery
- Launched first retina fellowship in US
- Invented the binocular indirect
The miracle of vision restoration

St. Mauro Abbott
Strategies for vision restoration

- Stem cell replacement
- Chip prosthetics
- Photoreceptive molecule gene therapy
Photovoltaic cells for vision restoration

Courtesy Daniel Palanker, PhD
Stem-cell Derived Retinal Cells Transplanted into the Retina of the Macaque

Chao JR et al., Transl Vis Sci Technol. 2017;6(3)
Chao JR et al., Transl Vis Sci Technol. 2017;6(3)
Gene therapy for vision restoration

https://www.today.com/health/dna-injection-slow-vision-loss-1B5977095
Channel opsins for vision restoration

Light-activated channels targeted to ON bipolar cells restore visual function in retinal degeneration

Pamela S Lagali¹,⁴, David Balya¹,⁴, Gautam B Awatramani¹,³,⁴, Thomas A Münch¹, Douglas S Kim², Volker Busskamp¹, Constance L Cepko² & Botond Roska¹
Restoration of high-sensitivity and adapting vision with a cone opsin

Michael H. Berry, Shakirah C. Unsworth, Quickilin Tan, Tamar Shemesh, Laura B. Smith, Alexander V. Shpaltsev, Michael A. Rovira, John G. Flannery, & Ehud Y. Isacoff

ARTICLE
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OPEN

Rhodopsin

50 pA
10 s

MWW-opsin

50 pA
10 s

Time (s)

5'  ITR  MWW  YFP  polyA  WPRE  ITR  3'

IRGC

MW-opsin

IRGC

rd1 uninjected retina

rd1 MWW-opsin injected retina

Light flash

1st 5th

1st 5th

Ctrl. rd1

MWW-Q.

MWW-Q.

Ctrl. rd1

(+)-9-cis

(-)-9-cis

(+)-9-cis

Ctrl. rd1

MWW-Q.

MWW-Q.

Ctrl. rd1

(+)-9-cis

(-)-9-cis

(+)-9-cis

Time (s)
Small molecule therapy for reversing blindness
Photoswitch compounds: chemical reanimation of the retina

Potassium channel
Multi-electrode arrays
Multielectrode array recording
Multi-electrode recording of blind mouse retina
5 minutes after administration of AAQ
Repetitive firing after AAQ
Restoration of the pupillary light response
Second generation photoswitches
(Lack of) Diffusion of xAQ following intravitreal injection in cadaver macaque eyes
Red-DAD: a 3rd Generation Photoswitch

Chemical Formula: C_{26}H_{35}N_{5}O
Molecular Weight: 444.60
Red-DAD HCl is highly soluble
DAD photosensitizes blind retina on multi-electrode array

Photoswitch Index $= \frac{\text{spiking frequency (light)} - \text{spiking frequency (dark)}}{\text{spiking frequency (light)} + \text{spiking frequency (dark)}}$
DAD specifically targets bipolar cells

with Mike Manookin
Current status

- Moving forward with BENAQ
- GMP-grade compound in cyclodextrin excipient
- Being tested in rd dogs by William Beltran
- Pursuing IND with Bayon Pharmaceuticals
What does the mouse see?
Retinotopic mapping of photoreceptors and ganglion cells differ.
Ganglion cell vision?
Synthetic vision drives overrides color opponency.
High density CMOS MEA

3D Brain/ALA Systems
4096 channel
Coverage of full retina on single array
Projector schematic
Stimulus: moving bar
Stimulus: Contrast grating
Machine learning of retinal output to projected images
Retinal acuity of wild-type and rd/rd mice

Wild-type

rd/rd

Wild-type

rd/rd
What information gives rise to acuity?
Stimulus: ETDRS Letters
Murine retinal acuity to ETDRS letters *in vitro*
Retinal acuity restored by BENAQ
Comparing two photoswitches

Wild type

\[ \text{DENAQ} \]

\[ \text{BENAQ} \]

\[ \text{rd/rd} \]
Real world application: facial reconstructions
Real world application: facial reconstructions
Real world application
Is this what the mouse sees?
Moving forward
Conclusions

- Multiple modalities (photovoltaic, stem cell, gene therapy, small molecule) hold the possibility of vision restoration in outer retinal degeneration.
- Small molecule azobenzene photoswitches chemically confer light sensitivity on blind retina.
- Successive generations of compounds have improved spectrum, kinetics, solubility, and cell-type specificity.
- BENAQ moving ahead to toxicology for human clinical trials.
- In vitro vision testing a powerful platform for decoding vision and comparing restoration techniques.
- In vitro vision may allow us insights into the visual code.
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