

Prospects for vision restoration in outer retinal degeneration

2020 Schepens Lecture Retina Society Meeting

Russell N. Van Gelder, MD, PhD

Boyd K. Bucey Memorial Chair

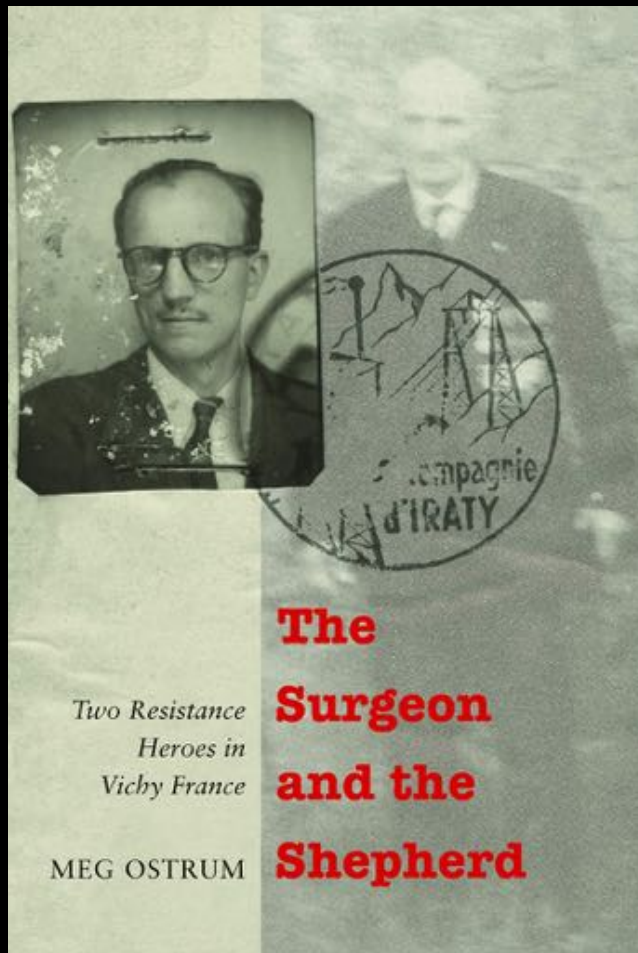
Department of Ophthalmology

University of Washington School of
Medicine

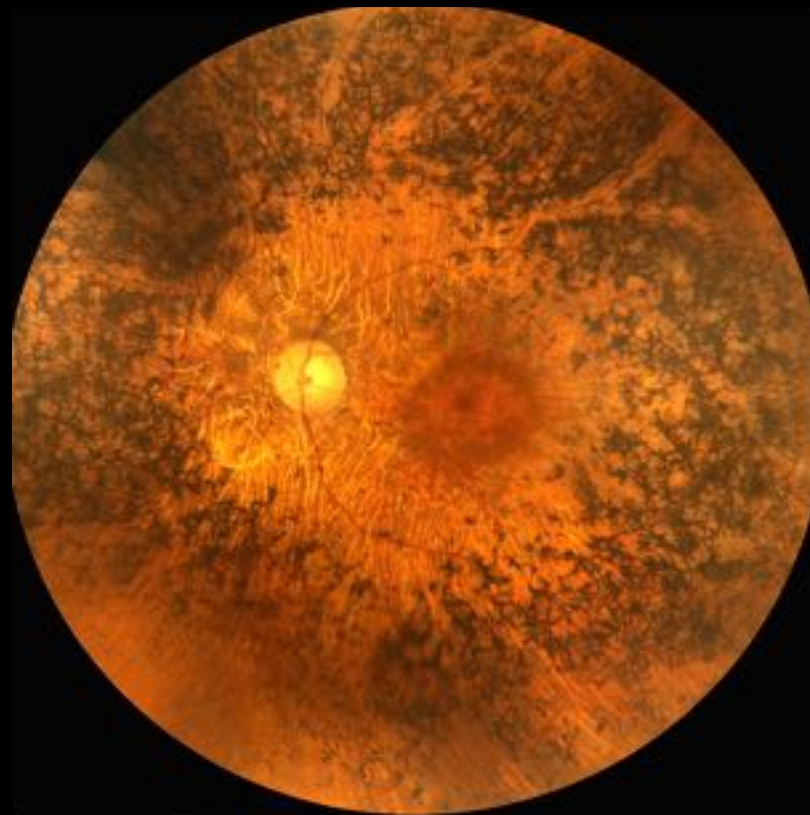
Disclosures

- 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
- RVG is funded by National Institutes of Health, Research to Prevent Blindness, and the Mark J. Daily, MD Research Fund

Charles Schepens, MD 1912-2006



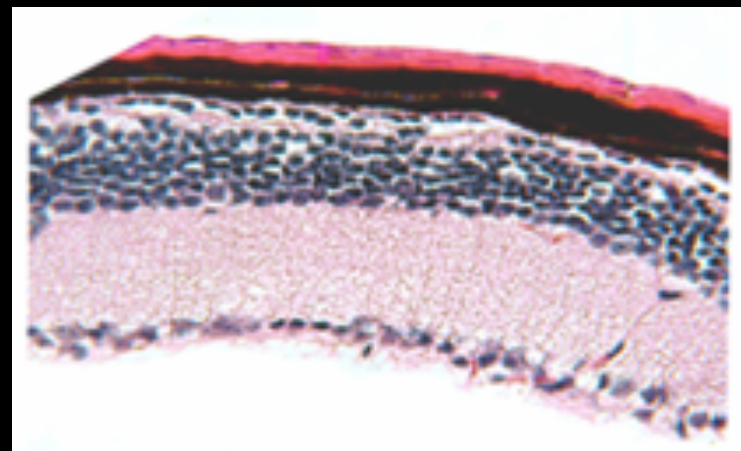
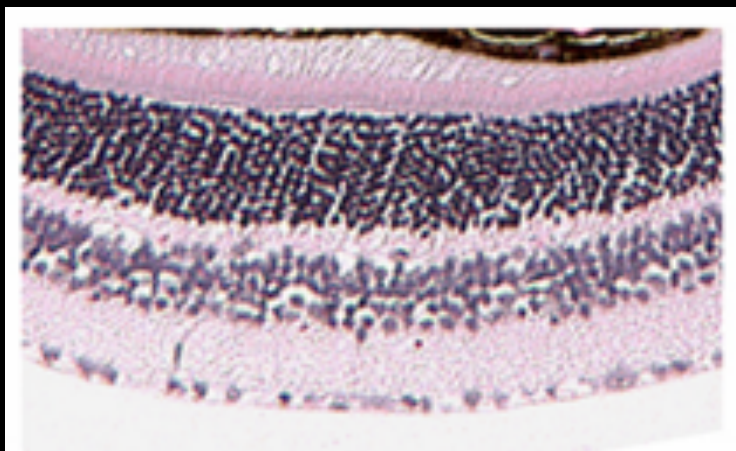
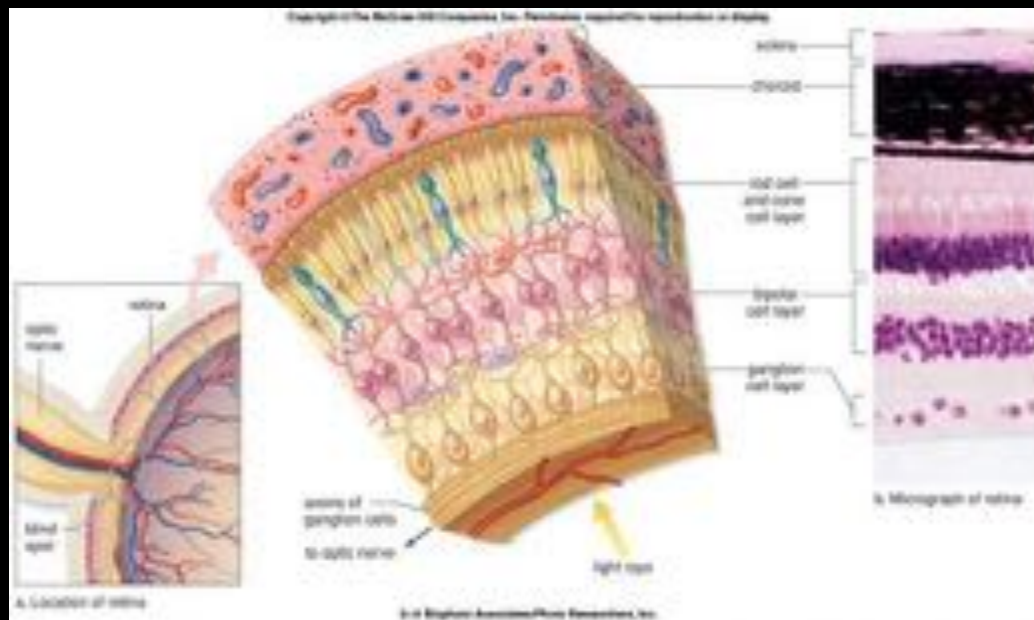
- Founder of the Retina Society
- Pioneer in vitreoretinal surgery
- Launched first retina fellowship in US
- Invented the binocular indirect



The miracle of vision restoration

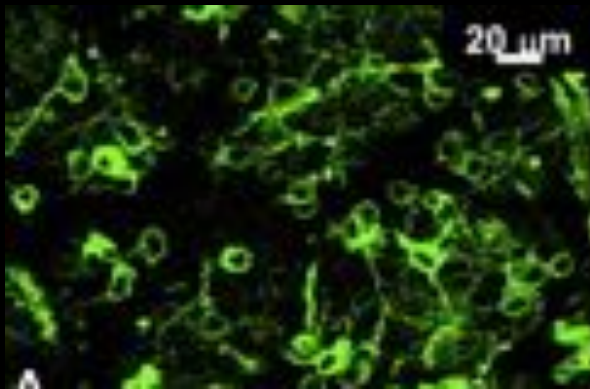


St. Mauro Abbott

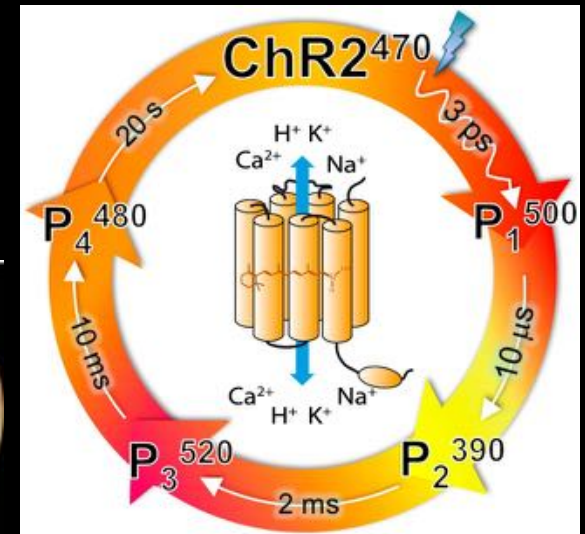


Strategies for vision restoration

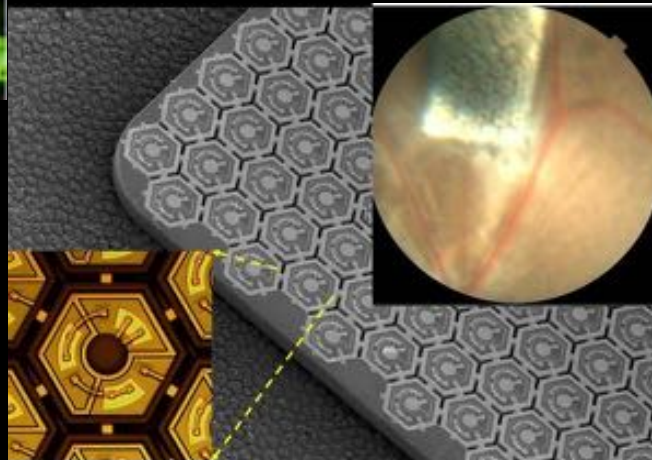
Stem cell
replacement



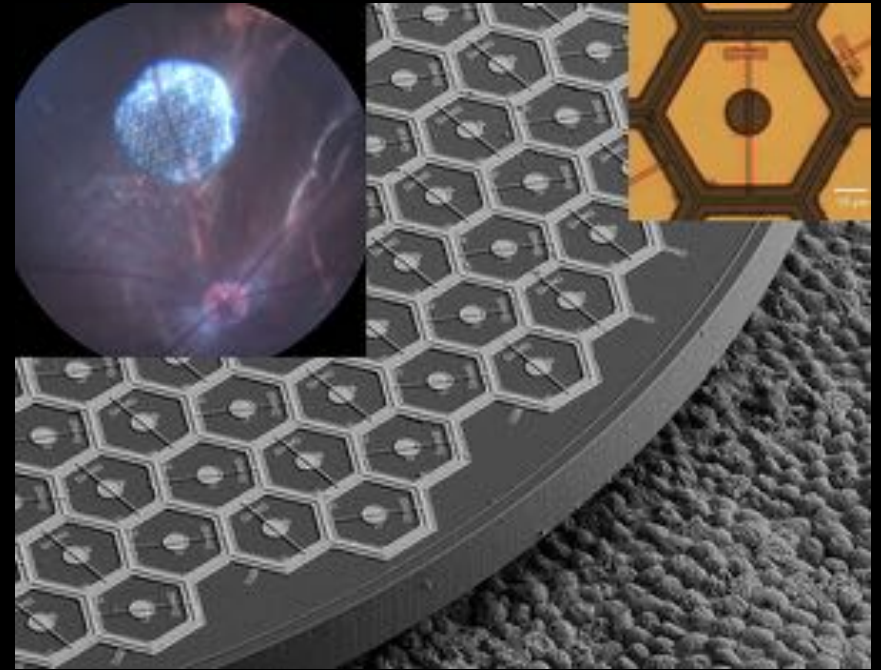
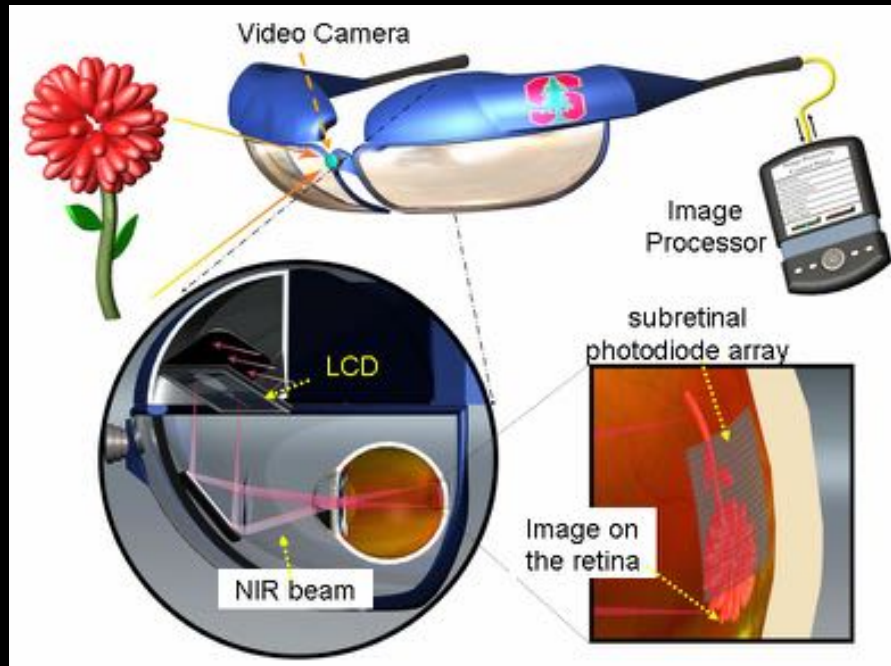
Photoreceptive
molecule gene
therapy



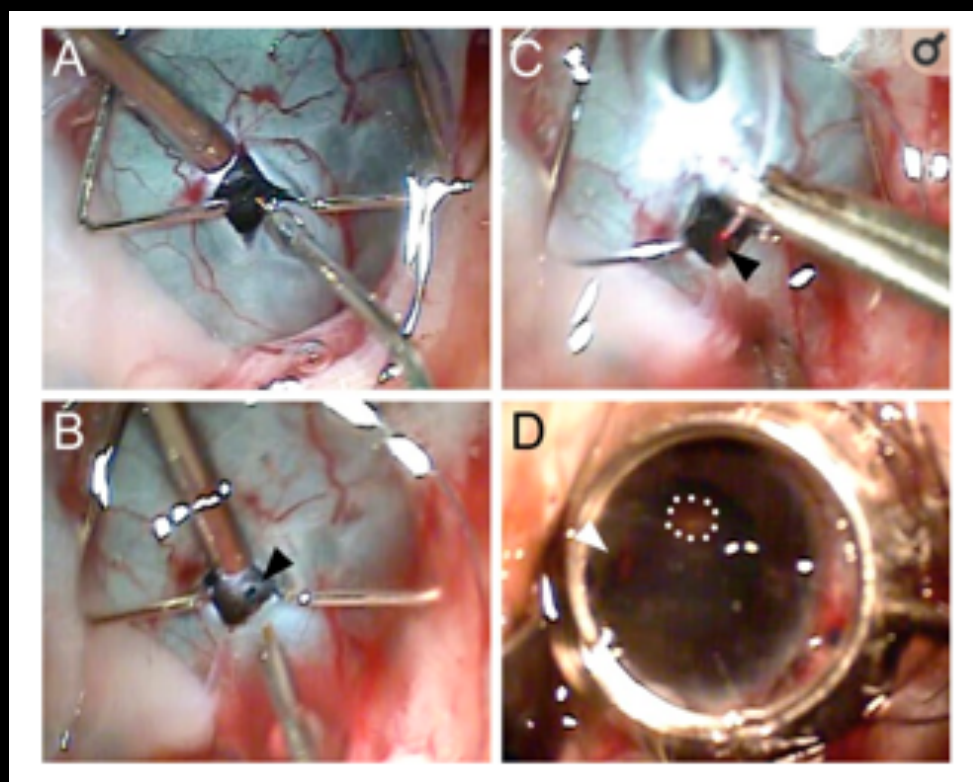
Chip prosthetics



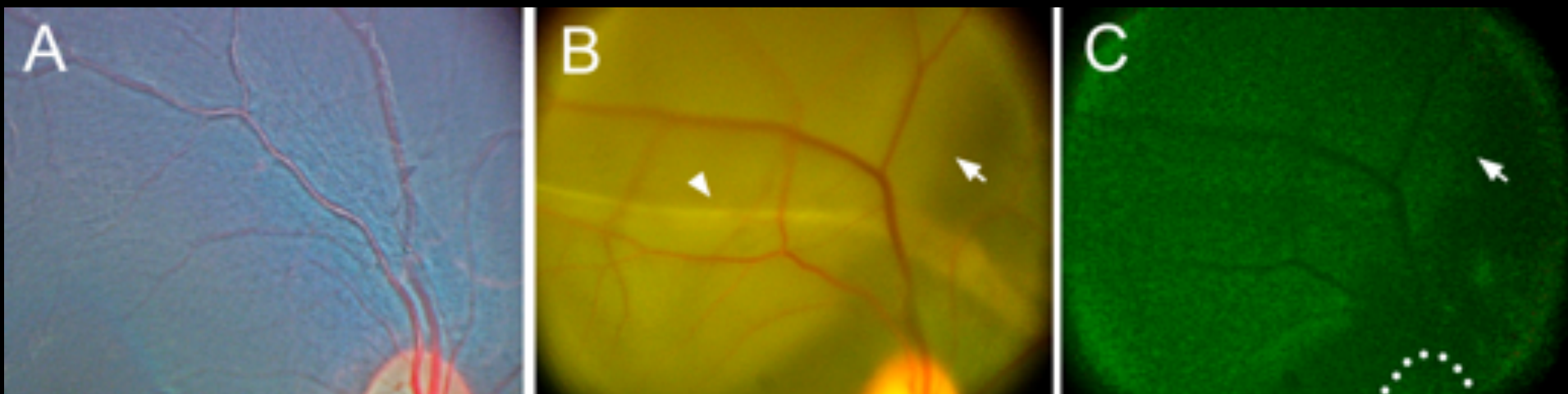
Photovoltaic cells for vision restoration

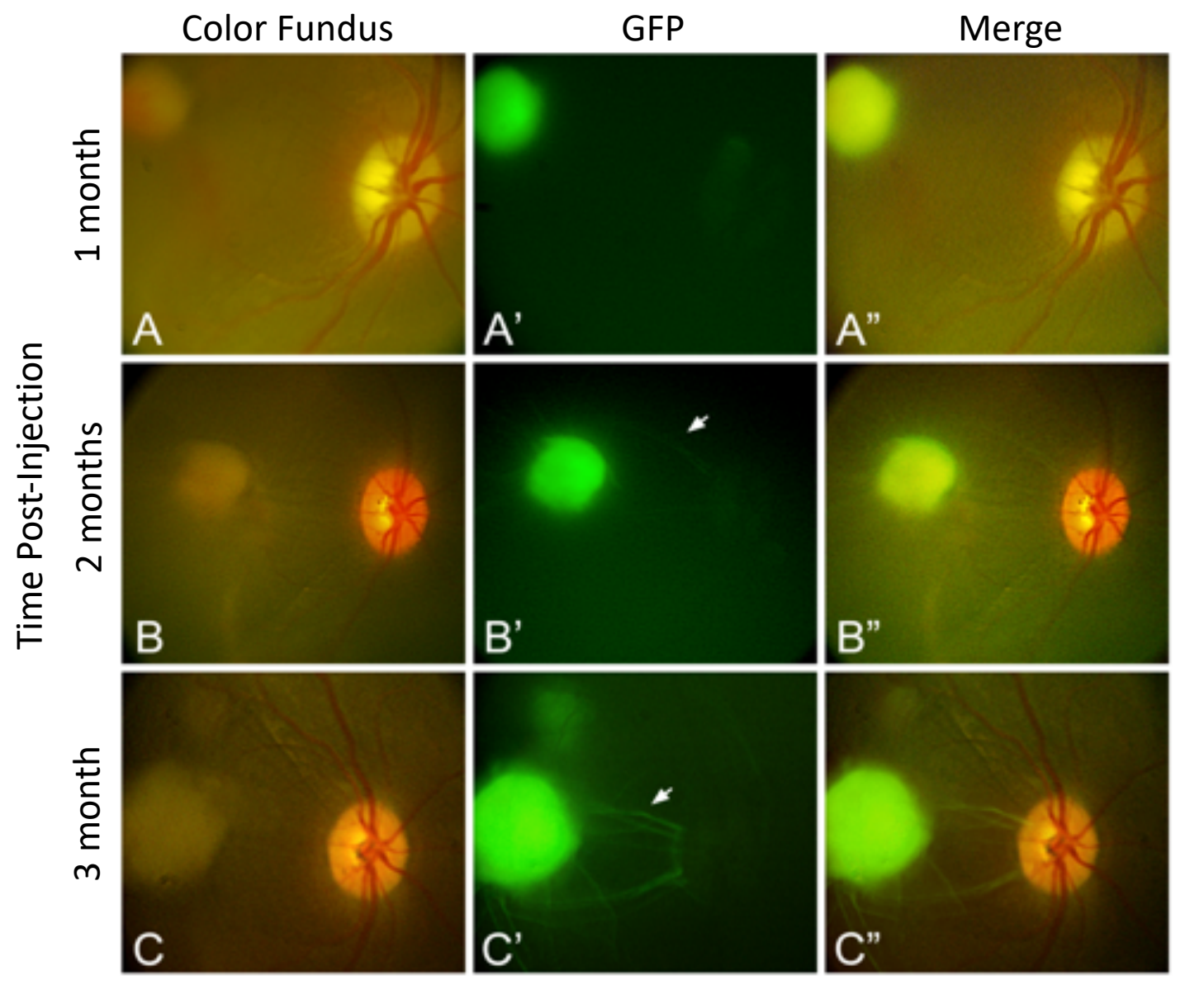


Courtesy Daniel Palanker, PhD



Stem-cell
Derived
Retinal Cells
Transplanted
into the
Retina of the
Macaque





Gene therapy for vision restoration

Gene therapy's big promise: Fighting vision loss with gene therapy

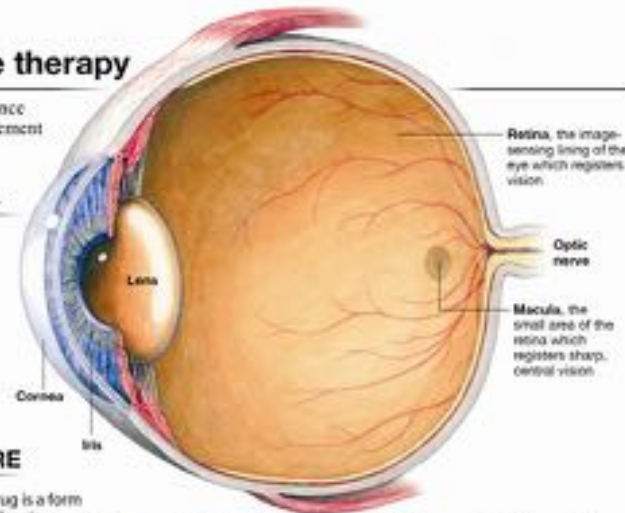
Doctors of the Casey Eye Institute at Oregon Health & Science University are conducting clinical trials using a gene replacement therapy to treat three eye diseases.

THE THREE TARGETED EYE DISEASES

Stargardt's disease - An inherited disease that has onset in children between the ages of six and twelve, leading to severe vision loss in young adults.

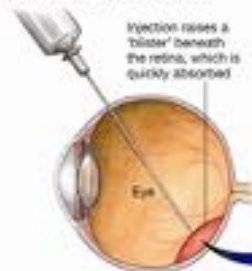
Usher syndrome - A condition that affects both vision and hearing. It affects the retina, initially causing the loss of peripheral vision but later affects central vision. Also causes severe hearing loss.

Macular degeneration - A major cause of visual impairment and blindness among older adults, it affects the macula of the eye, causing the loss of central vision.

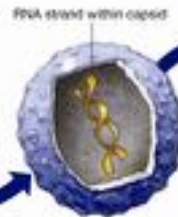


THE GENE REPLACEMENT PROCEDURE

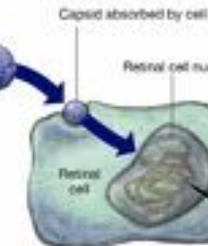
1 Under anesthesia, the gene therapy drug is injected into the patient's eye. The tip of the needle is the width of a human hair, and the drug is infused into a specific location beneath the retina.



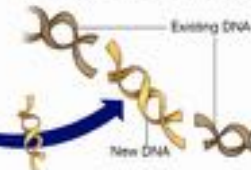
2 The gene therapy drug is a form of an equine virus, harmless in humans. The virus contains a double strand of RNA, that encodes the gene for transplantation. The virus is encapsulated within a capsid, which attaches itself to a retinal cell.



3 The retinal cell engulfs the capsid, absorbing it into the cell. The RNA is converted to DNA, encoding the gene of interest.



4 The gene from the new DNA strand incorporates in the cell's existing DNA. In Stargardt's and Usher patients, the inserted gene provides a functional copy of the nonfunctional gene. In macular degeneration patients, the insertion of a new gene produces a 'medication' to combat the disease.



Sources: The Casey Eye Institute, Oregon Health Sciences University

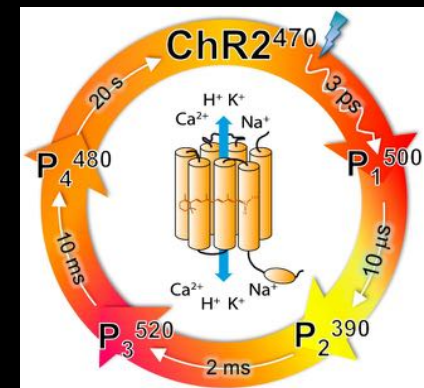
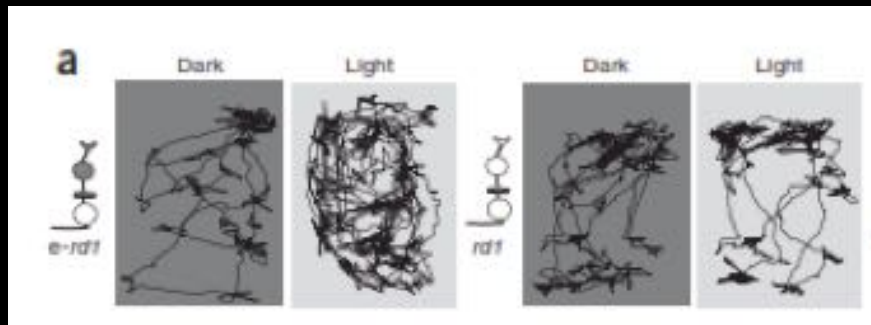
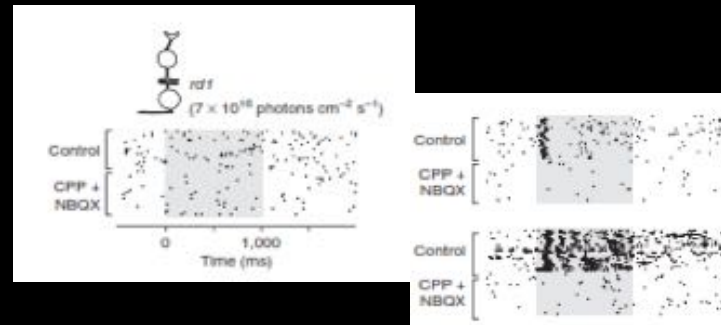
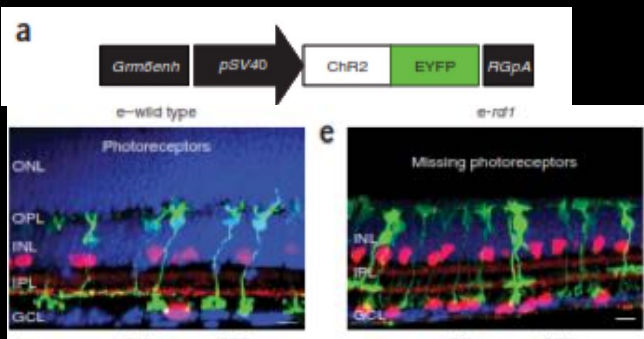
Credit: Eric Bakker, CHS92

Channel opsins for vision restoration

NATURE NEUROSCIENCE VOLUME 11 | NUMBER 6 | JUNE 2008

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

Pamela S Lagali^{1,4}, David Balya^{1,4}, Gautam B Awatramani^{1,3,4}, Thomas A Münch¹, Douglas S Kim², Volker Busskamp¹, Constance L Cepko² & Botond Roska¹



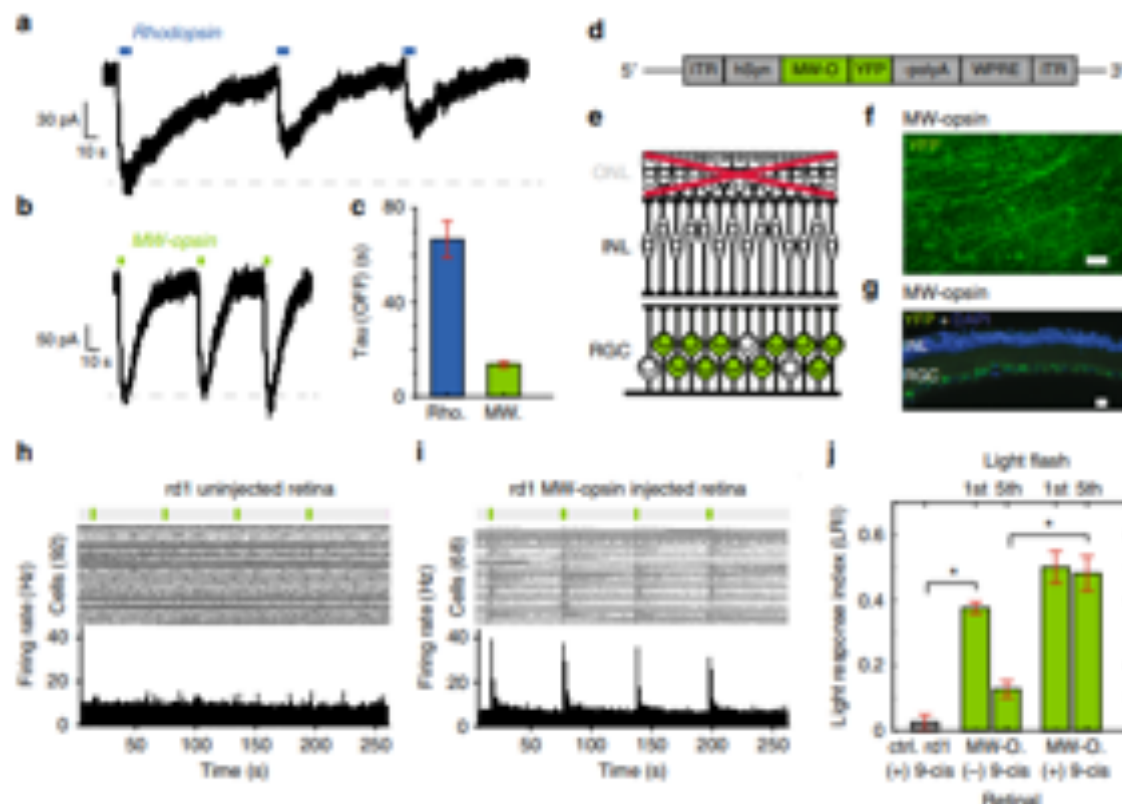
ARTICLE

<https://doi.org/10.1038/s41467-019-09124-x>

OPEN

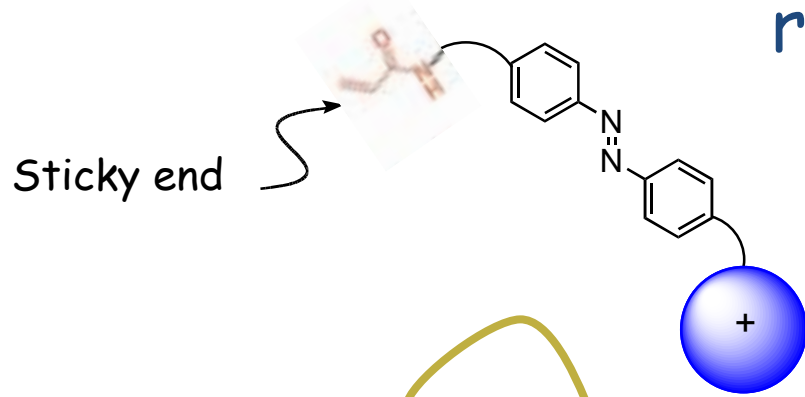
Restoration of high-sensitivity and adapting vision with a cone opsin

Michael H. Berry^{1,2}, Amy Holt¹, Autoosa Salari¹, Julia Veit^{1,3}, Meike Visel¹, Joshua Levitz^{1,7}, Krisha Aghi³, Benjamin M. Gaub^{3,8}, Benjamin Sivyer^{2,4}, John G. Flannery^{1,3,5} & Ehud Y. Isacoff^{1,3,6}

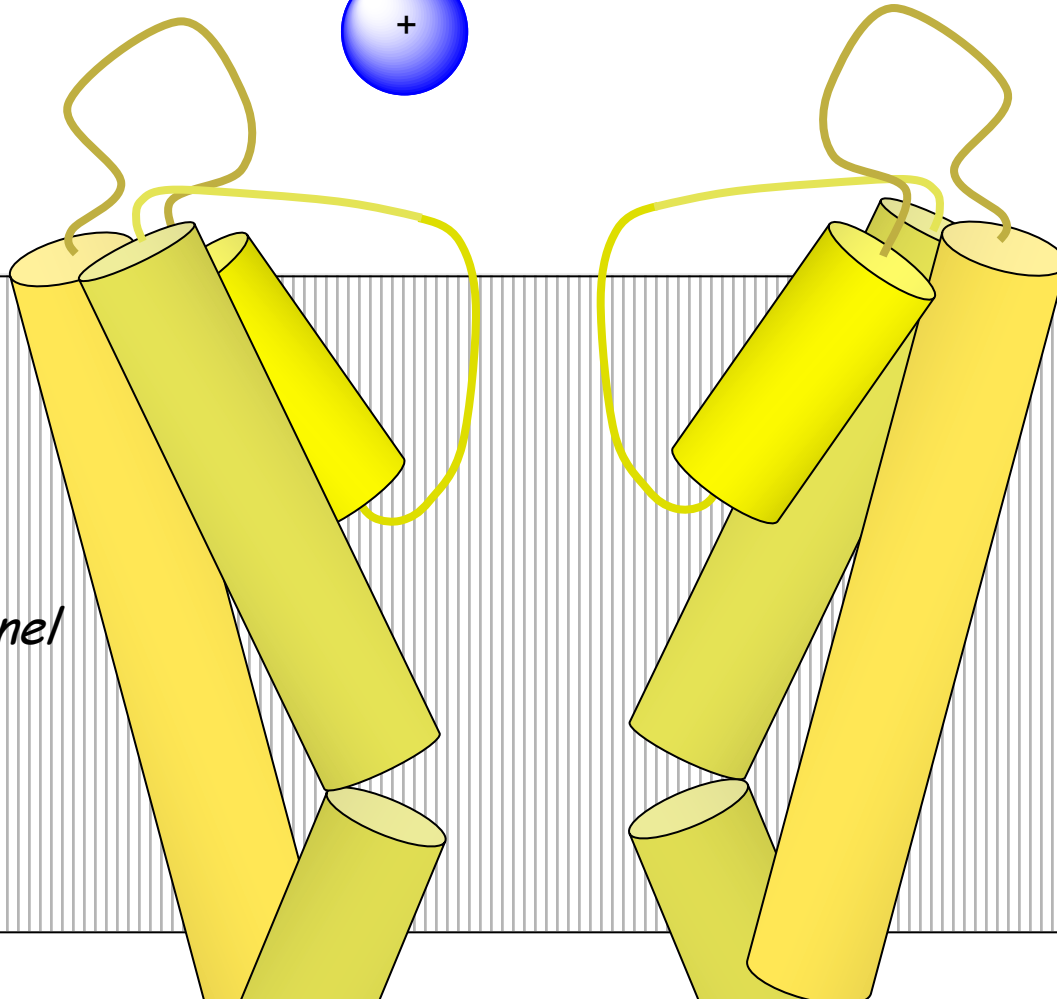


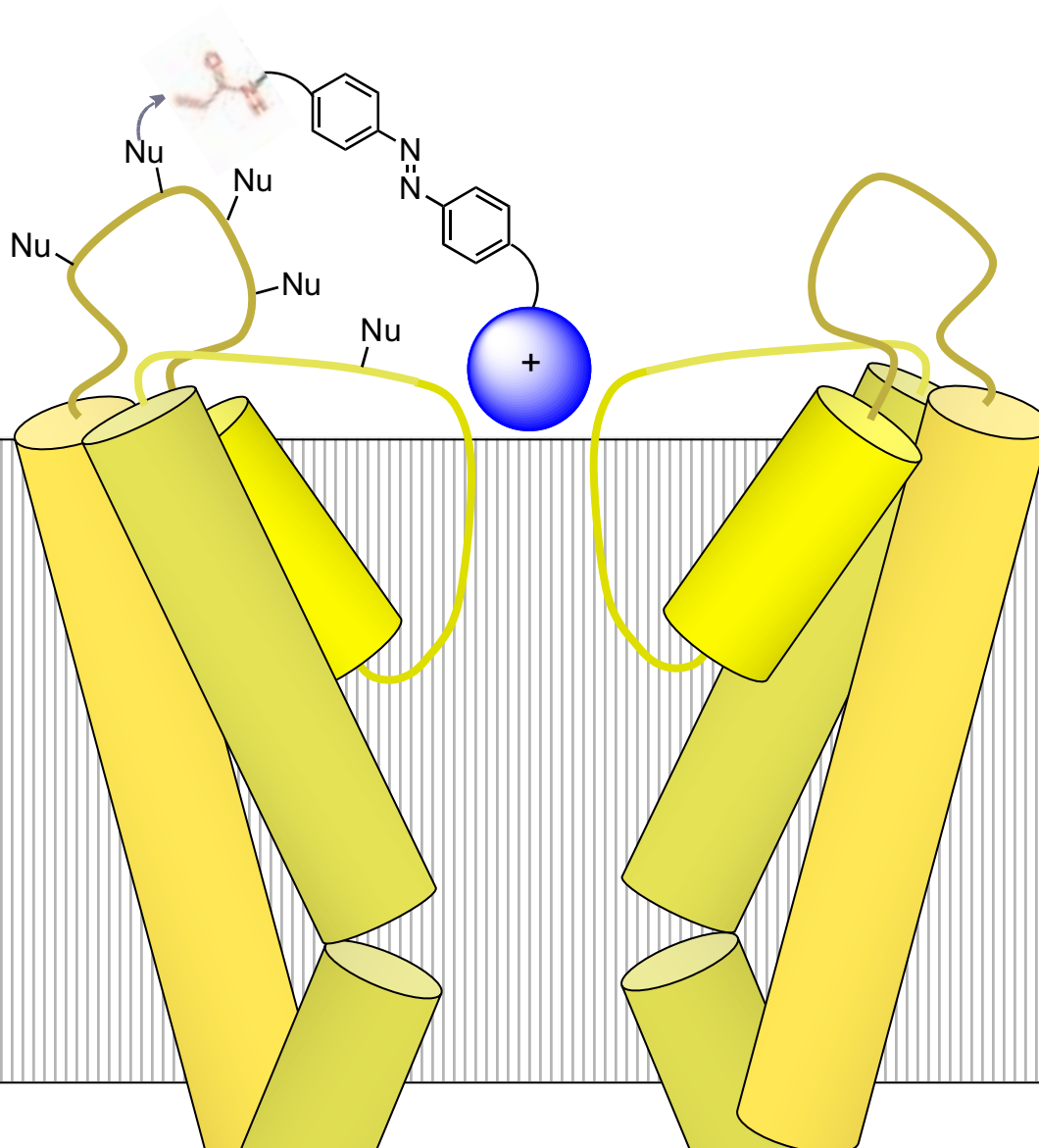
Small molecule therapy for reversing blindness

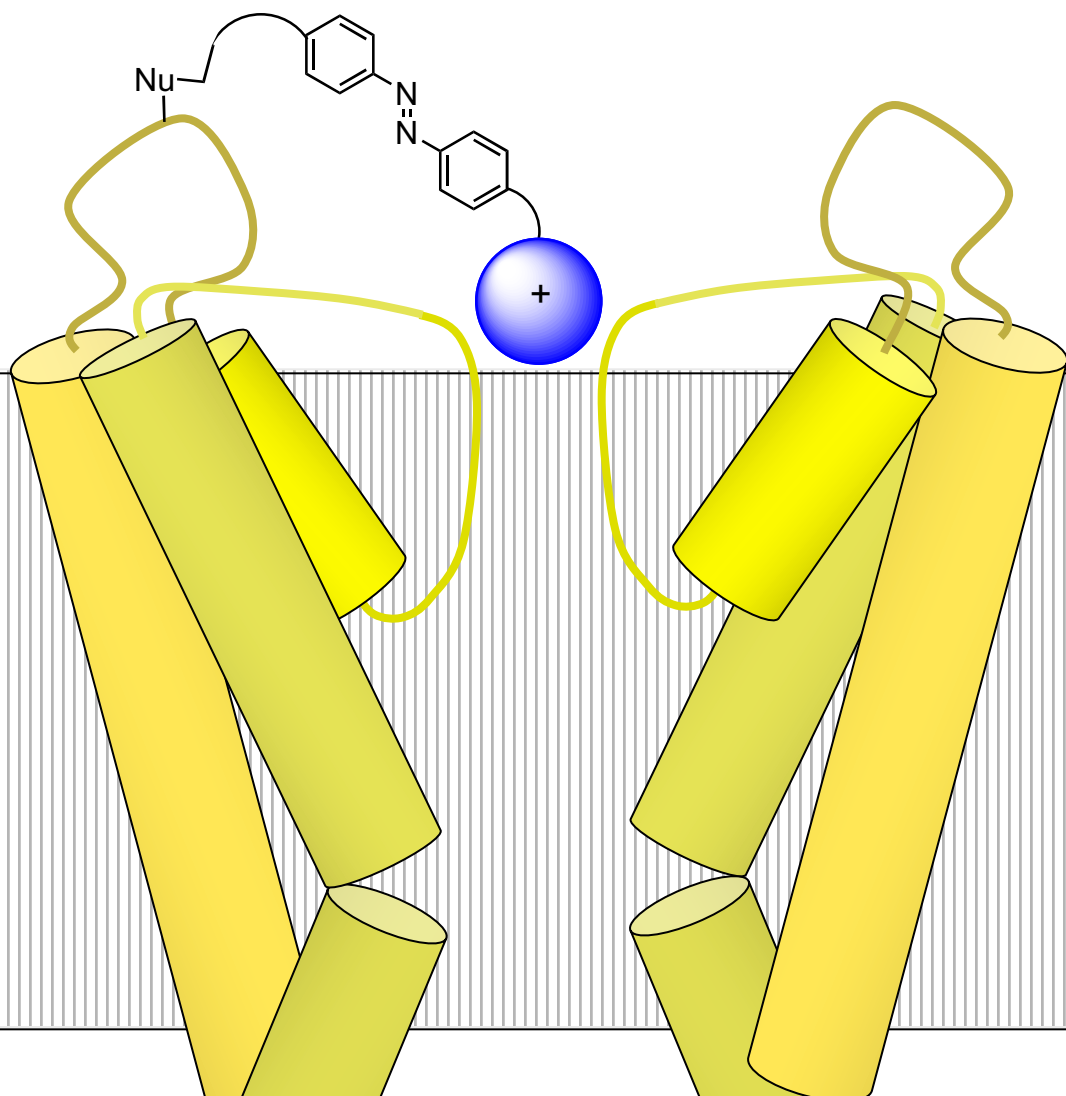
Photoswitch compounds: chemical reanimation of the retina

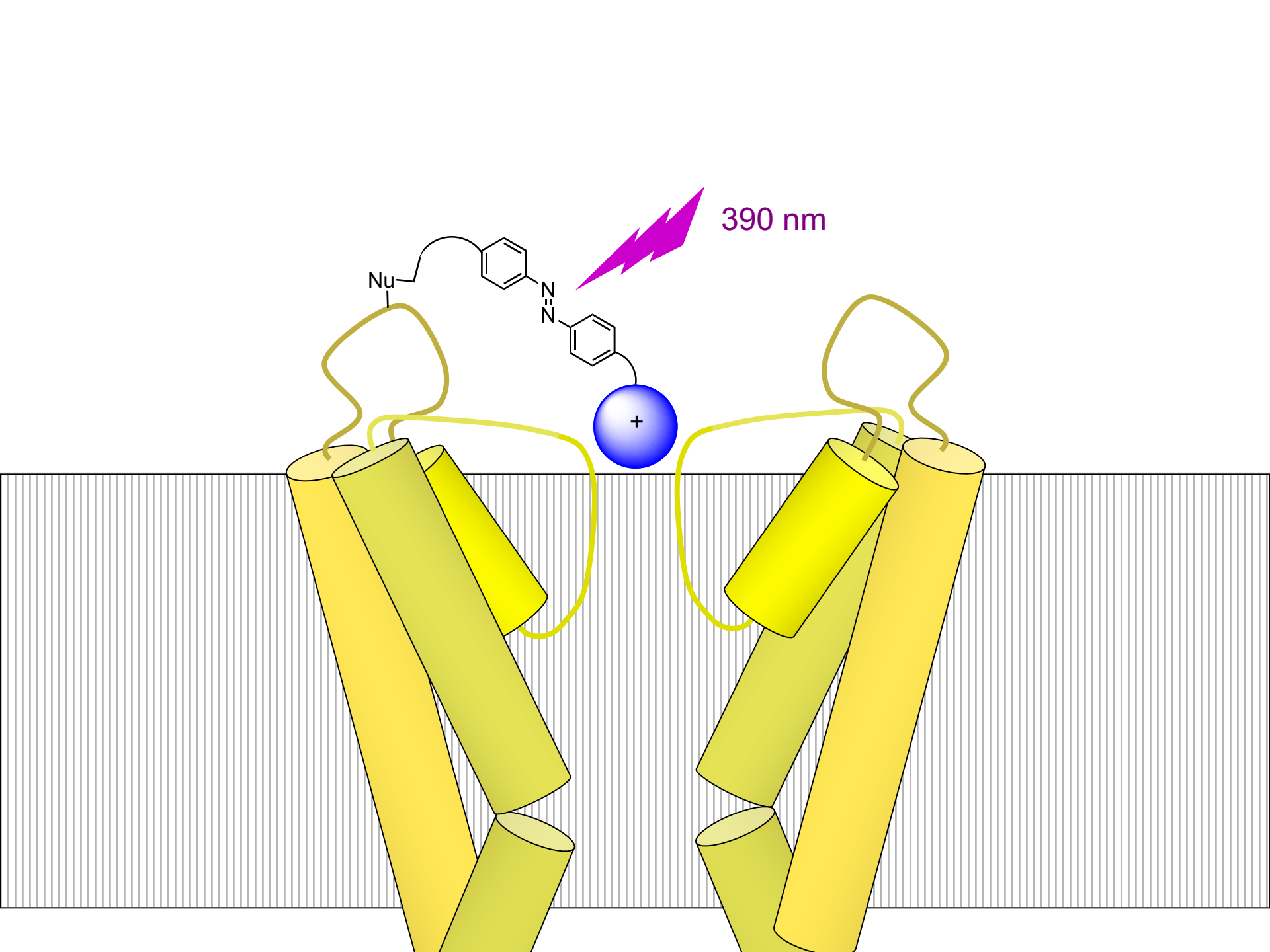


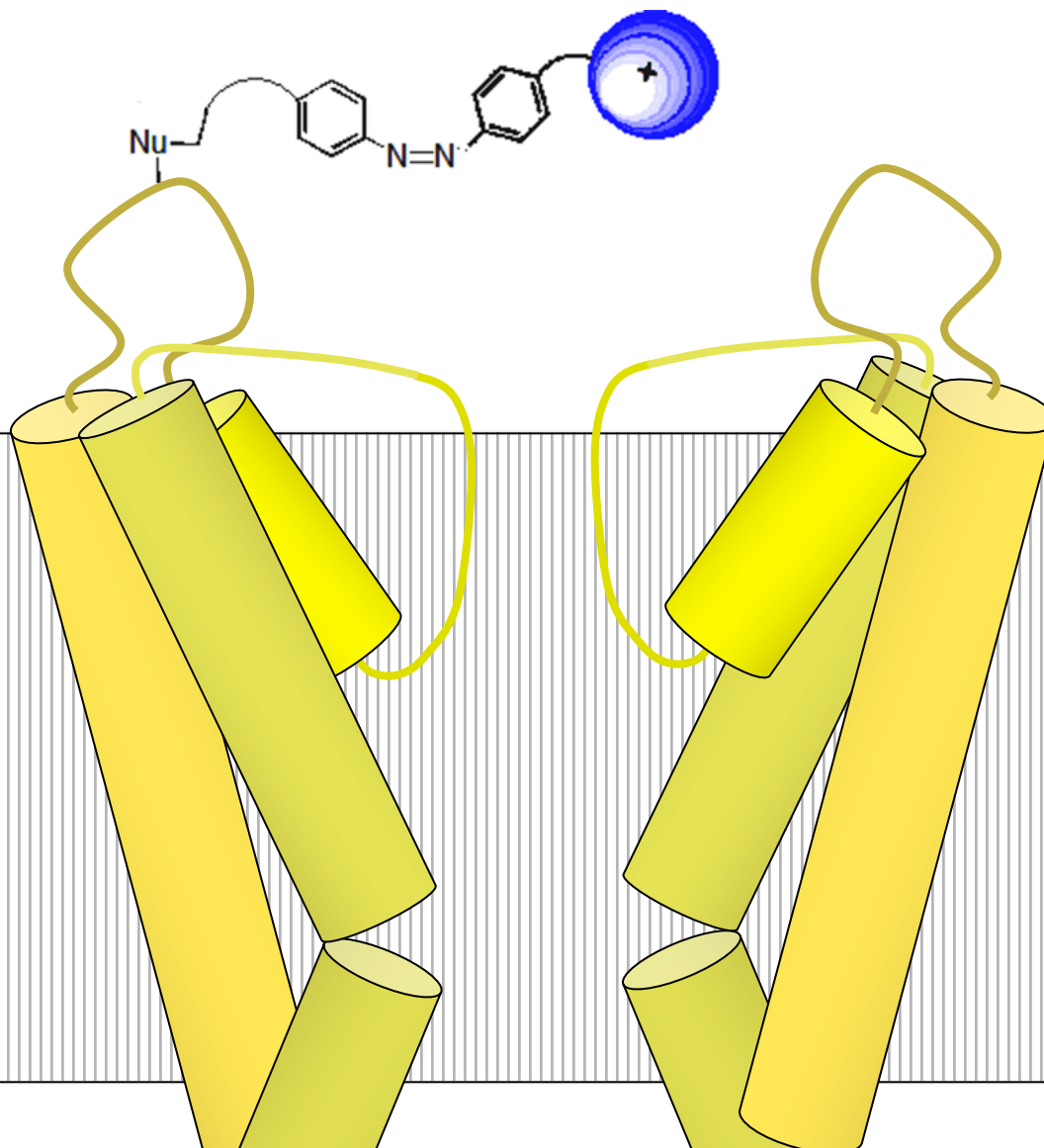
Potassium channel



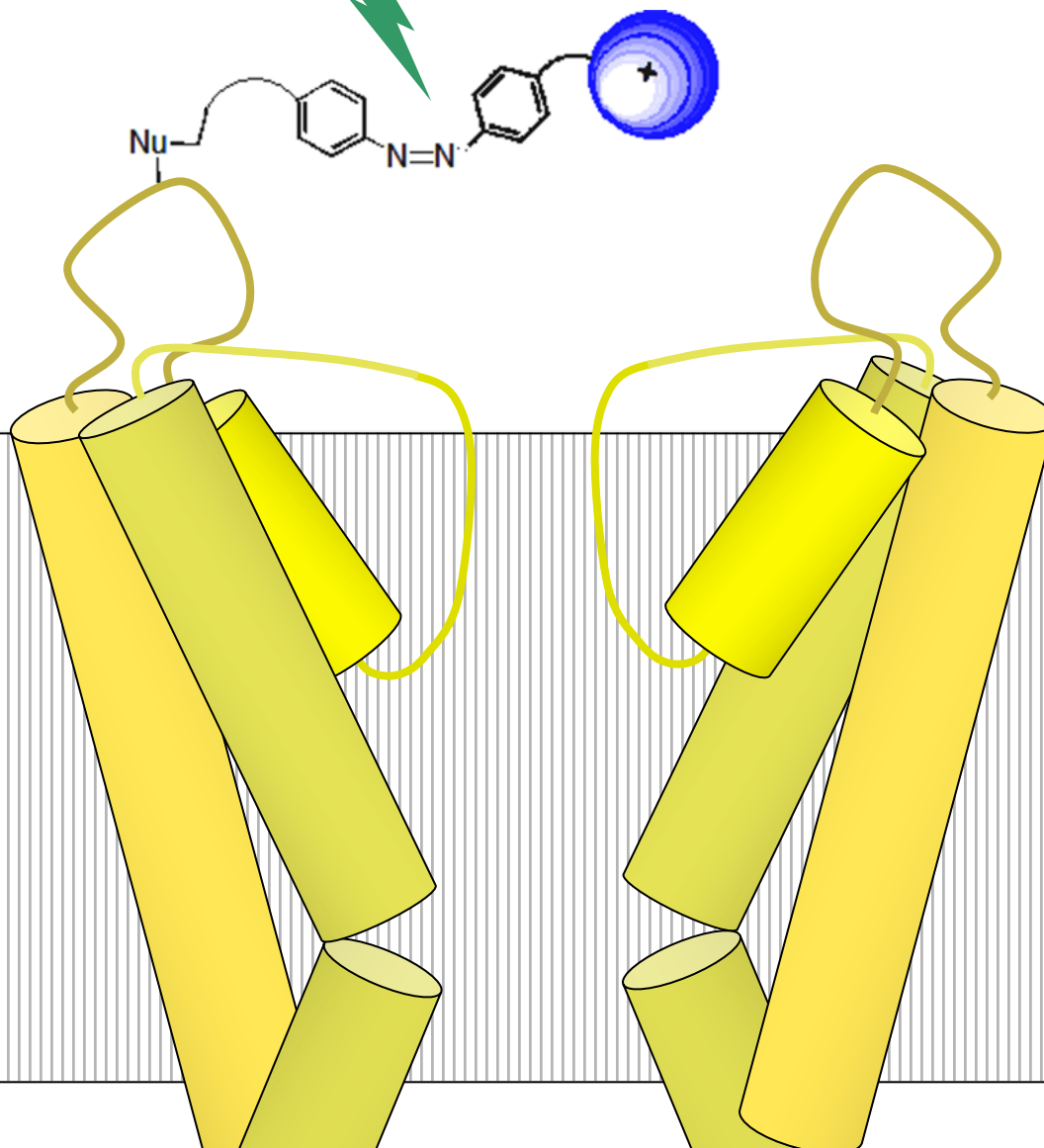


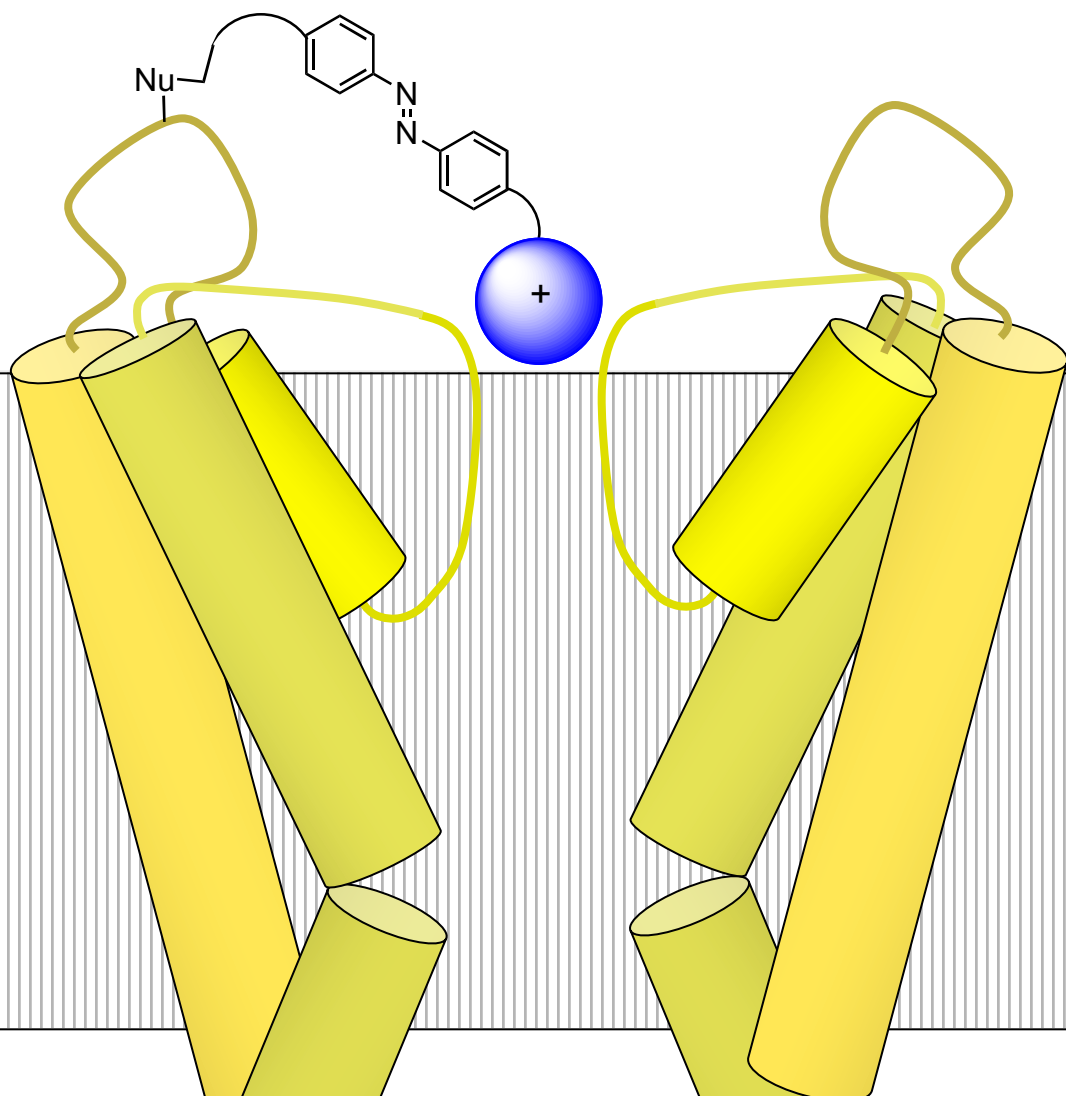




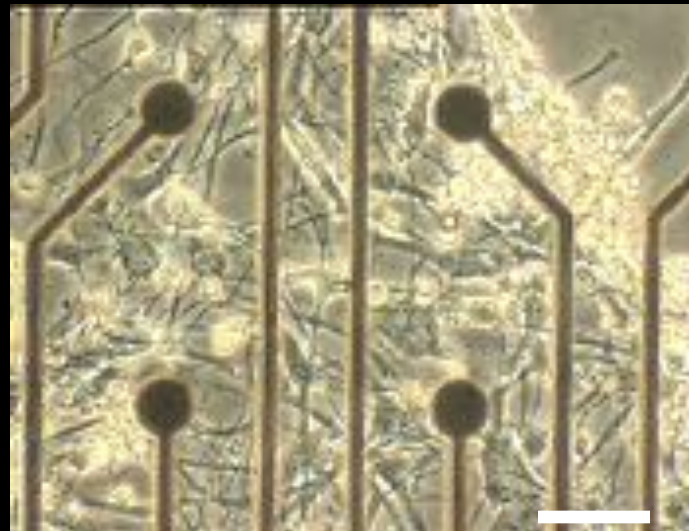
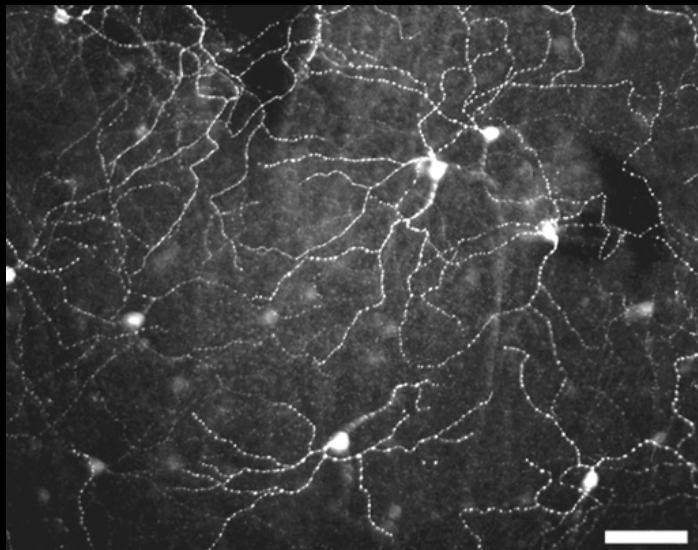
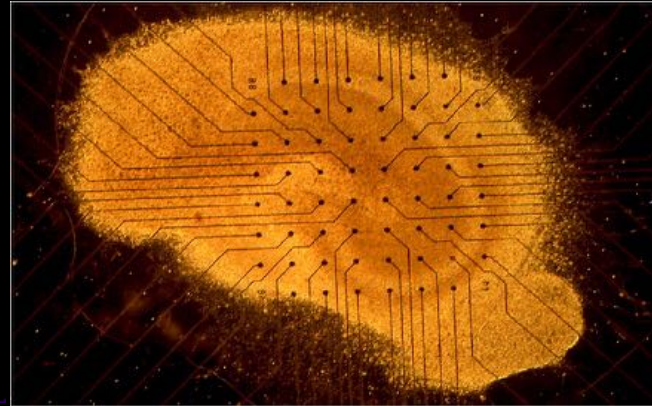
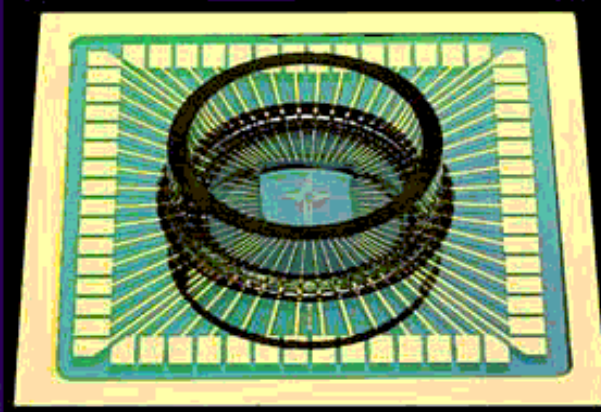


500 nm

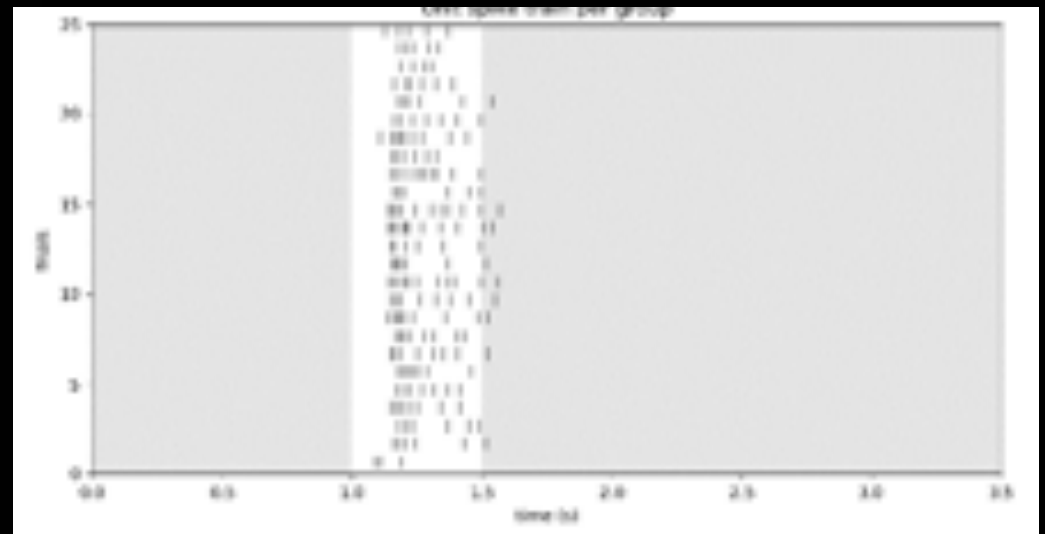
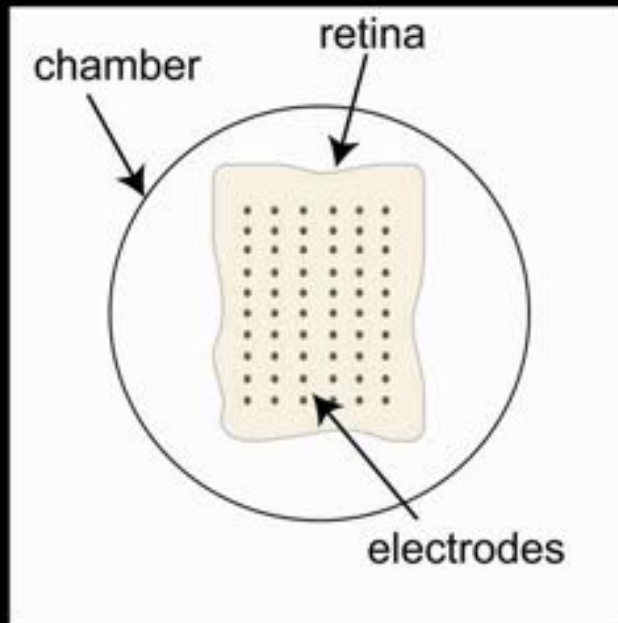




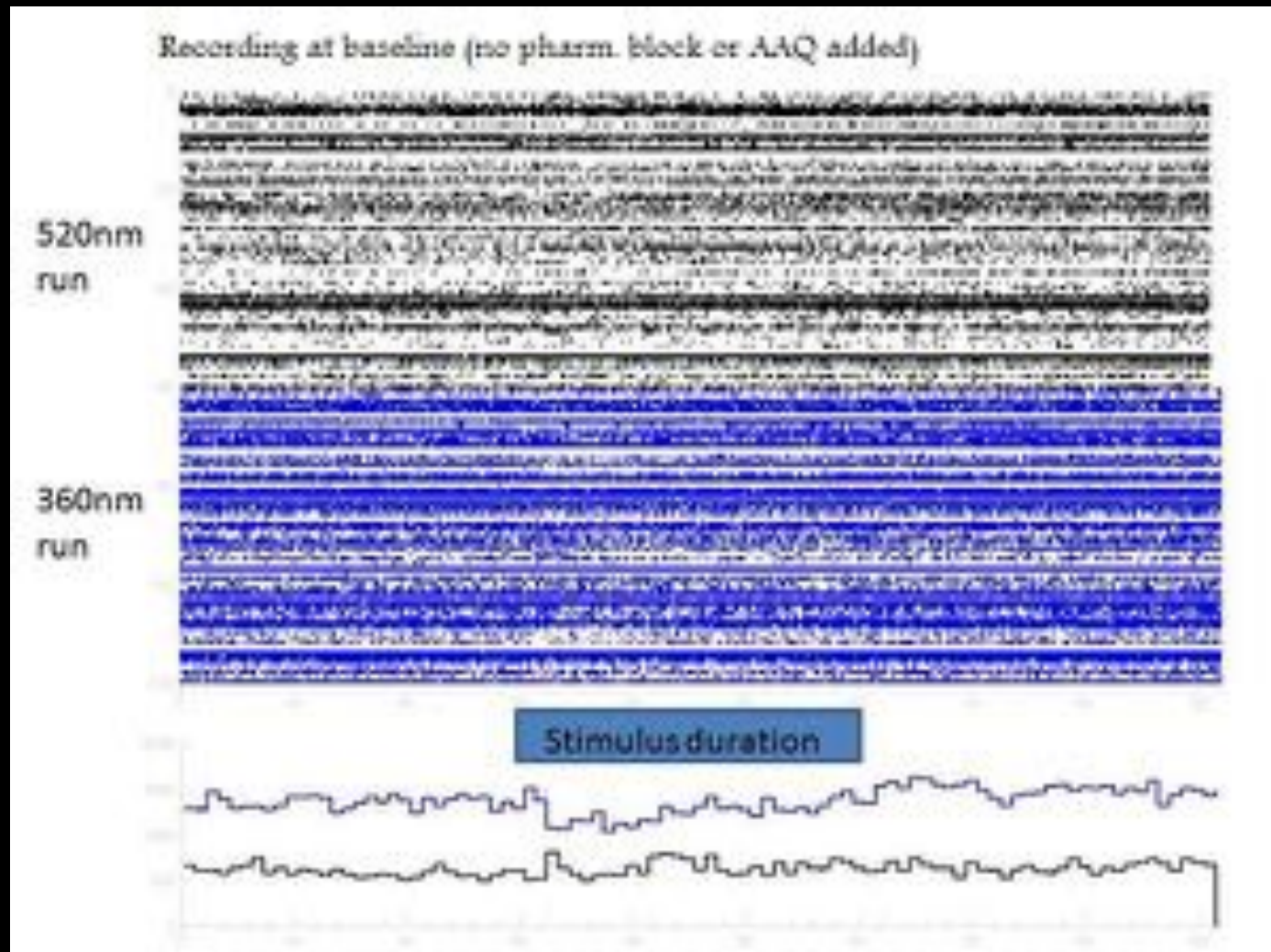
Multi-electrode arrays



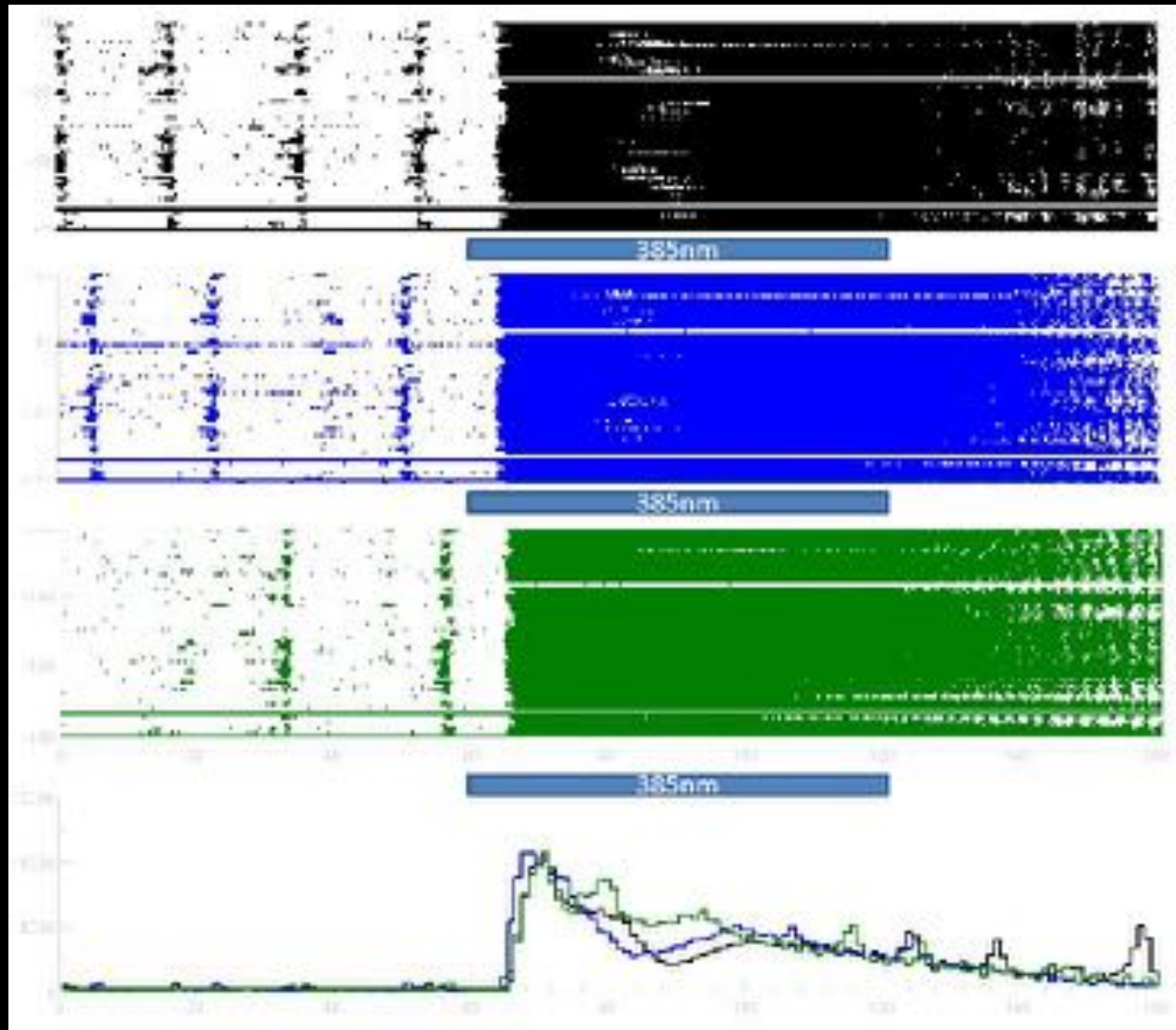
Multielectrode array recording



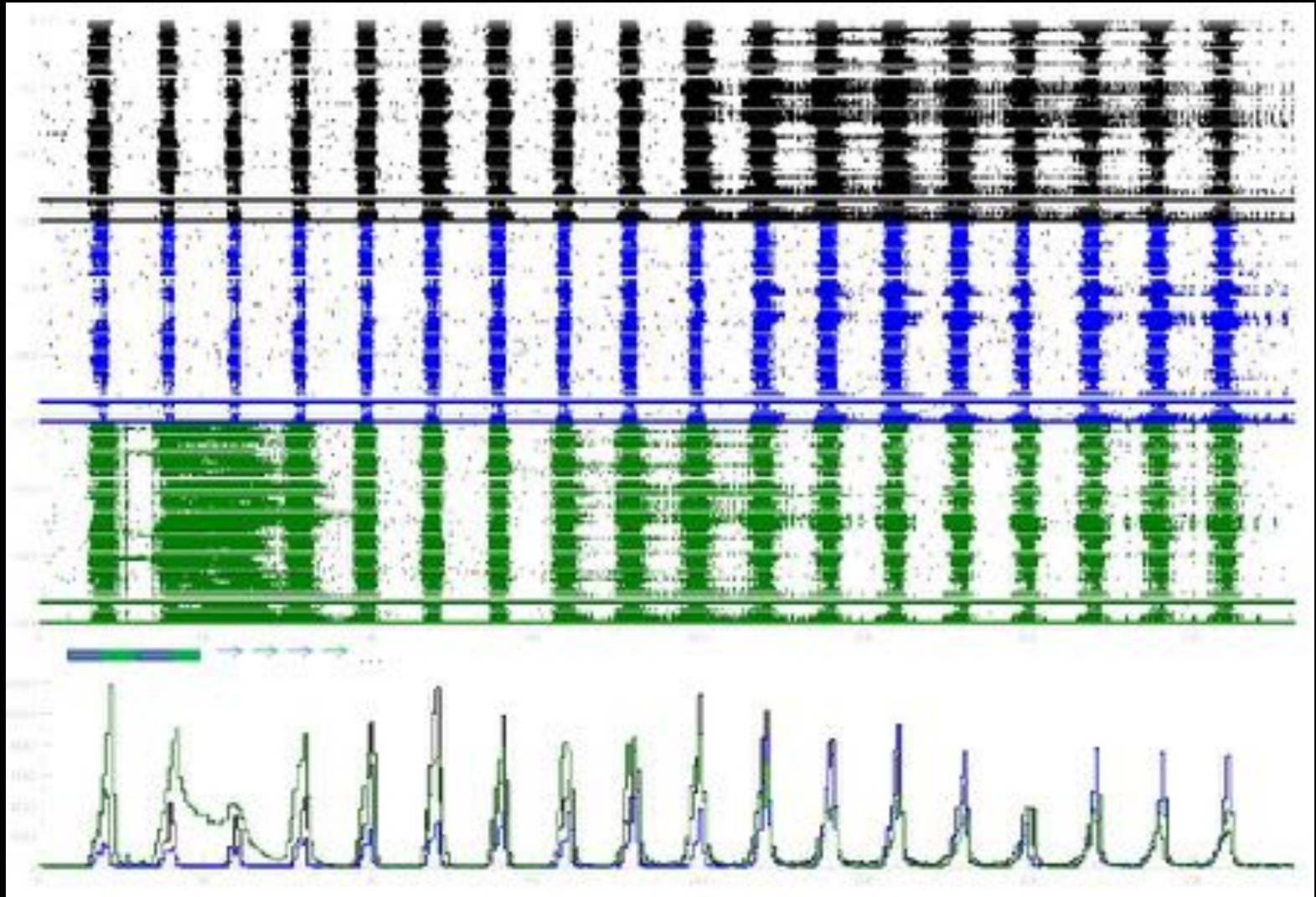
Multi-electrode recording of blind mouse retina



5 minutes after administration of AAQ



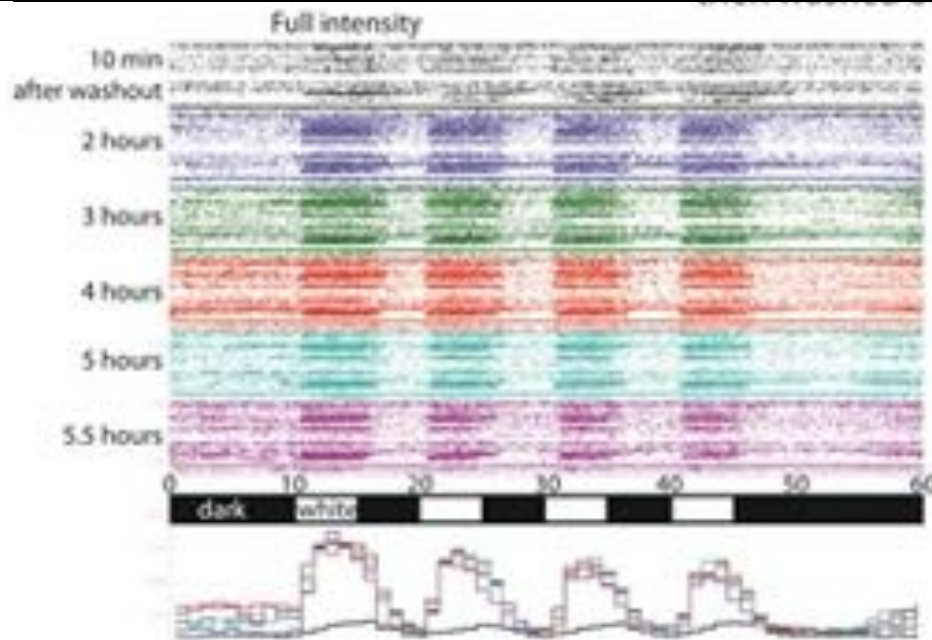
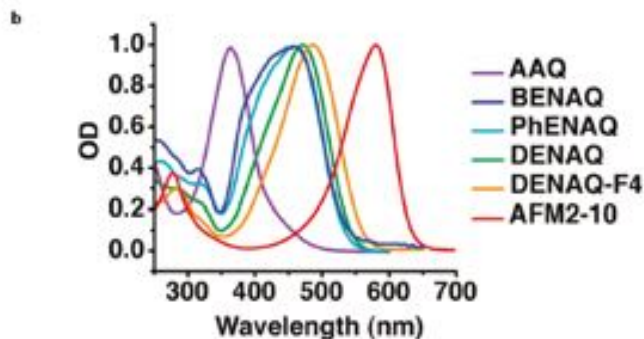
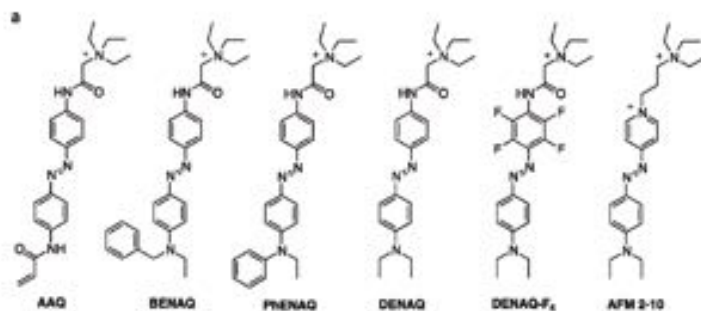
Repetitive firing after AAQ



Restoration of the pupillary light response

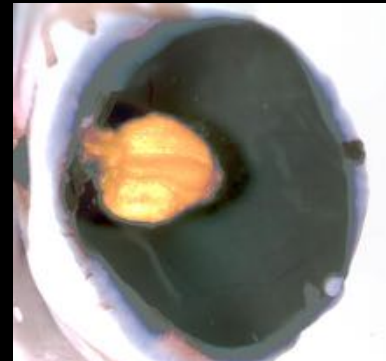
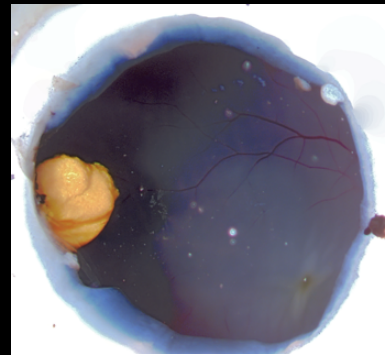


Second generation photoswitches

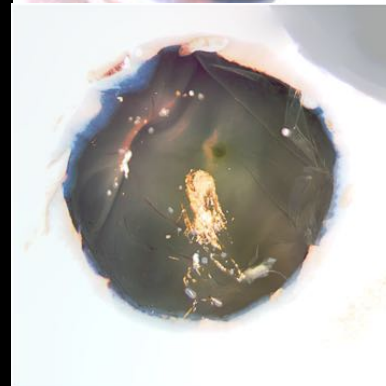
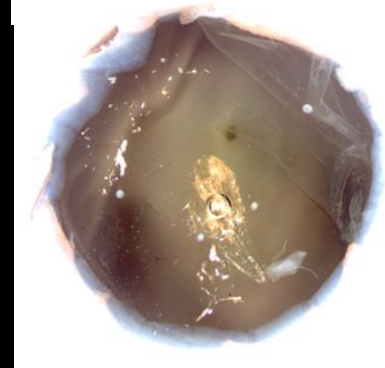
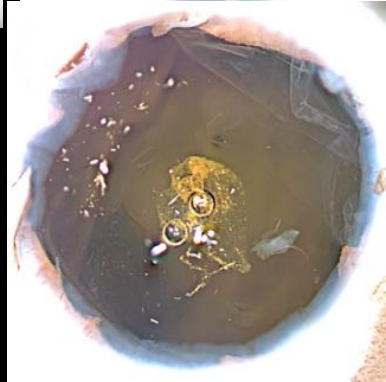
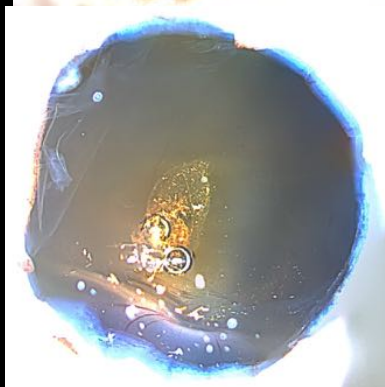


(Lack of) Diffusion of xAQ following intravitreal injection in cadaver macaque eyes

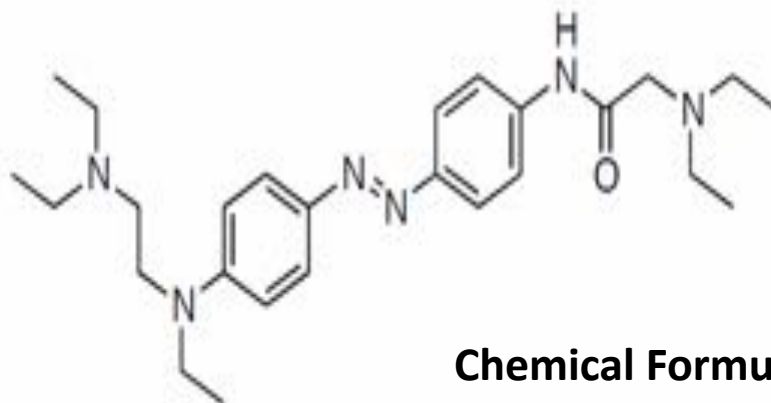
**PhENAQ
(5mM)**



**DENAQ
(5mM)**



Red-DAD: a 3rd Generation Photoswitch



Chemical Formula: C₂₆H₃₅N₅O
Molecular Weight: 444.60

Red-DAD HCl is highly soluble

140325

Red-DAD (HCl) in Eylea

rD stock solution 100mM ddH₂O



rD-HCl [mM]

0

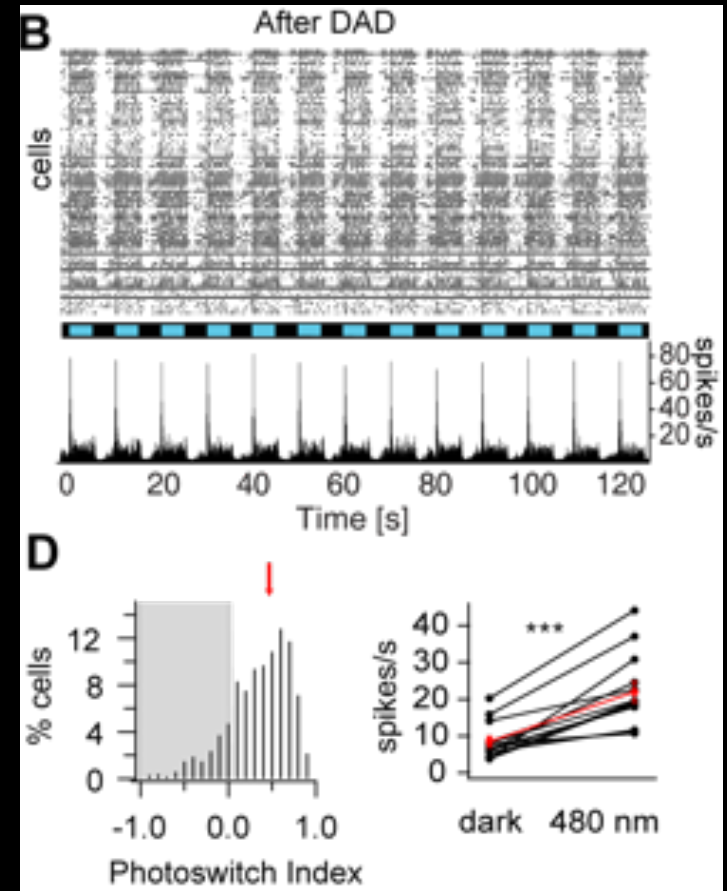
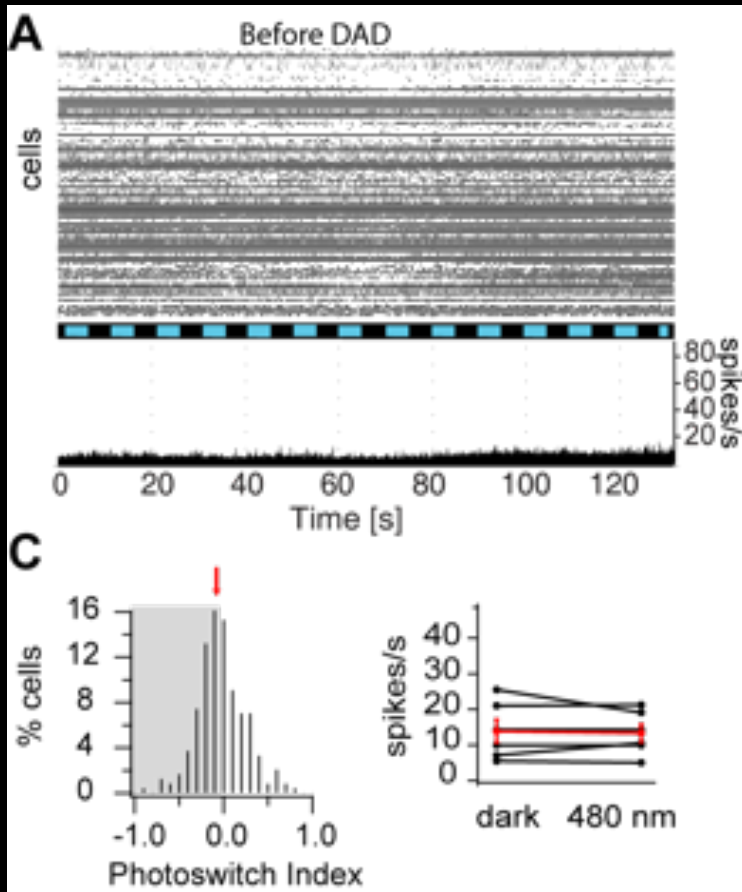
0.25

1

5

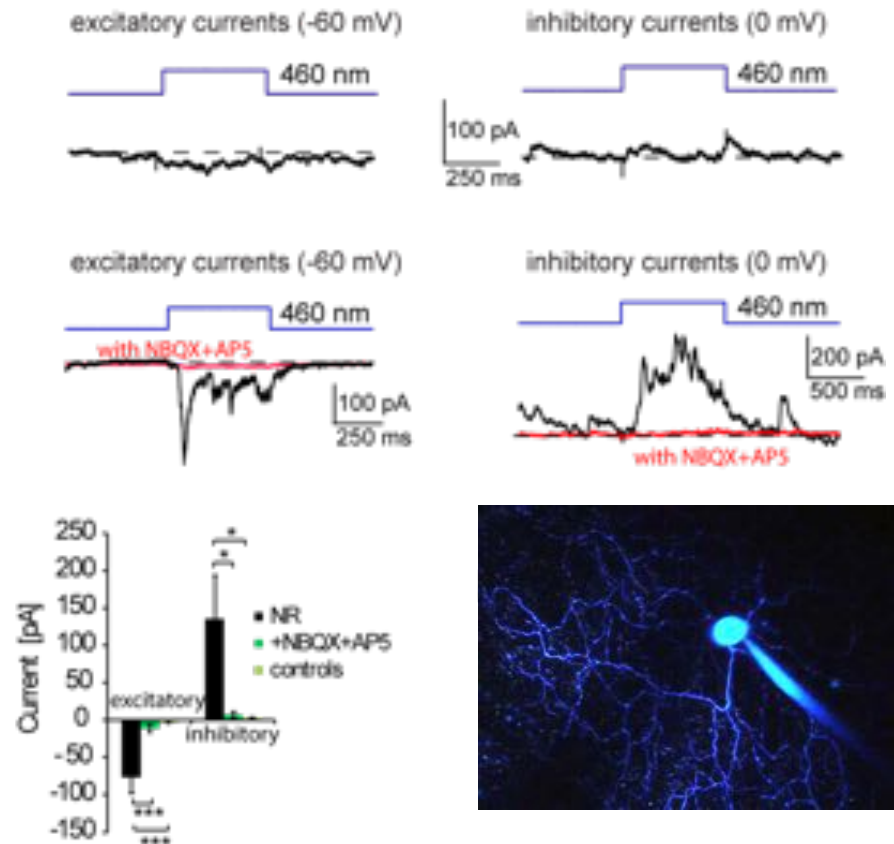
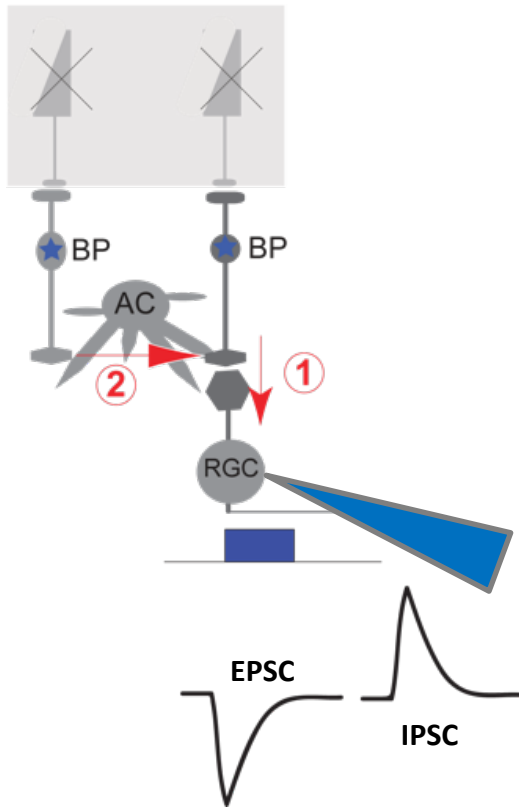
25

DAD photosensitizes blind retina on multi-electrode array



$$\text{Photoswitch Index} = \frac{\text{spiking frequency (light)} - \text{spiking frequency (dark)}}{\text{spiking frequency (light)} + \text{spiking frequency (dark)}}$$

DAD specifically targets bipolar cells



with Mike Manookin

Current status

SCIENTIFIC REPORTS

OPEN

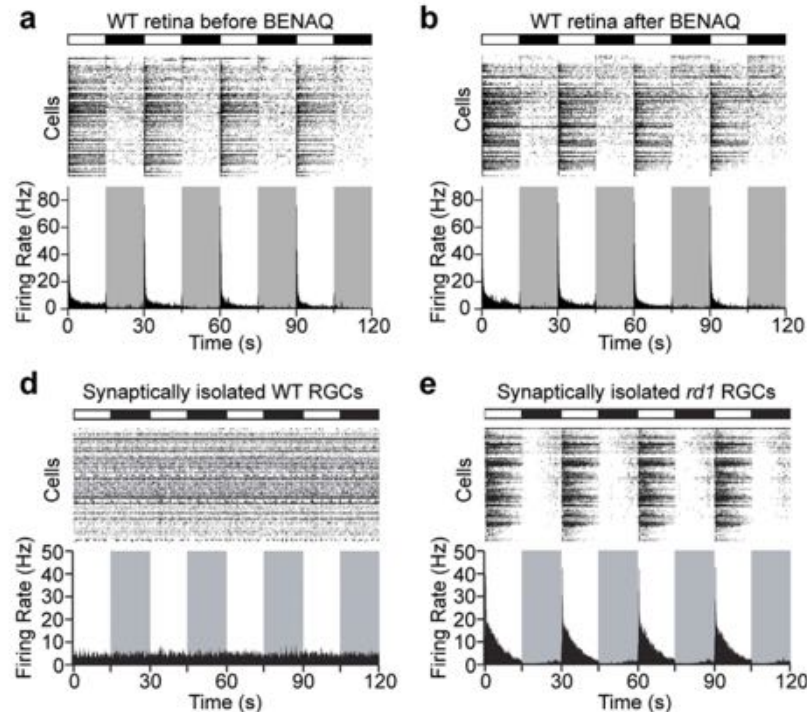
Restoring visual function to the blind retina with a potent, safe and long-lasting photoswitch

Ivan Tochitsky^{1,†}, Jay Trautman², Nicholas Gallerani¹, Jonatan G. Malis¹ & Richard H. Kramer¹

Received: 20 October 2016

Accepted: 27 February 2017

Published: 13 April 2017



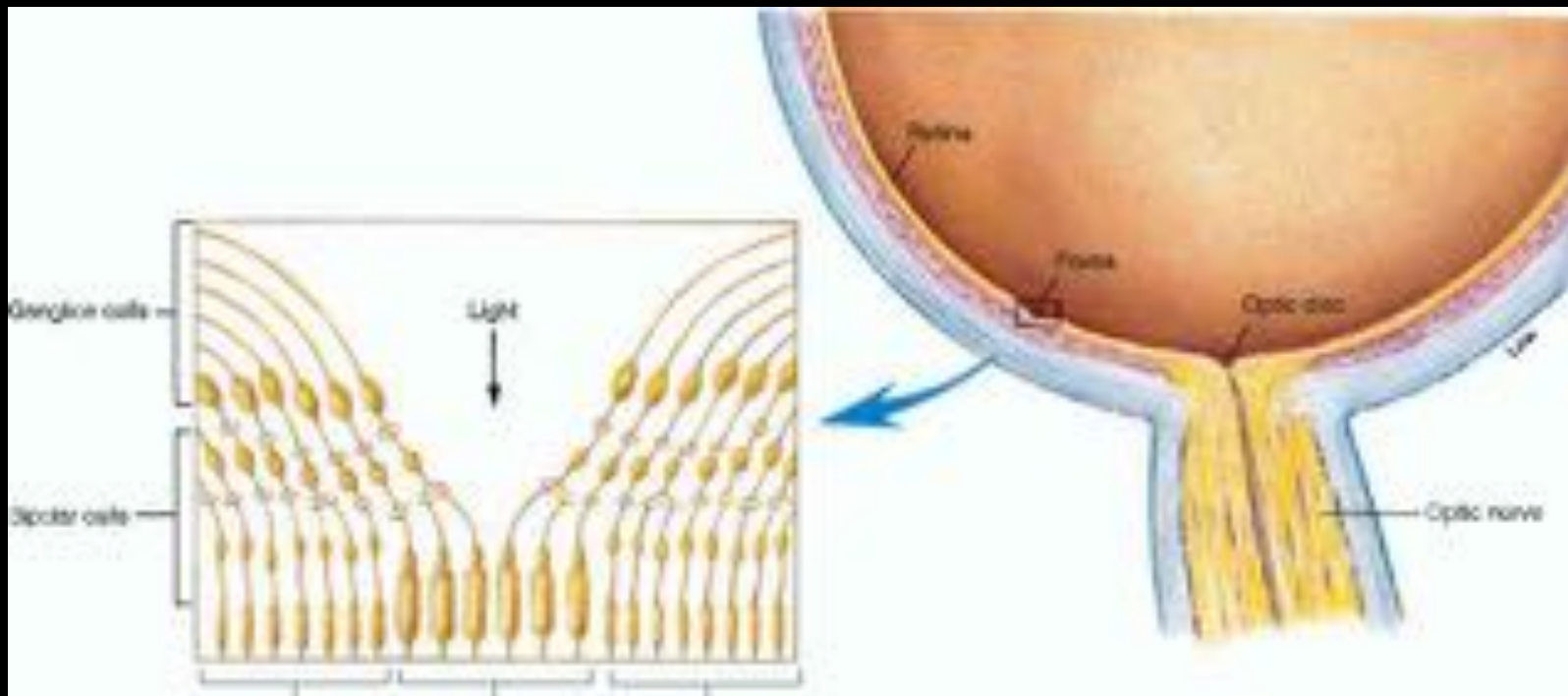
- Moving forward with BENAQ
- GMP-grade compound in cyclodextrin excipient
Being tested in *rd* dogs by William Beltran

Pursuing IND with Bayon Pharmaceuticals

What does the mouse see?



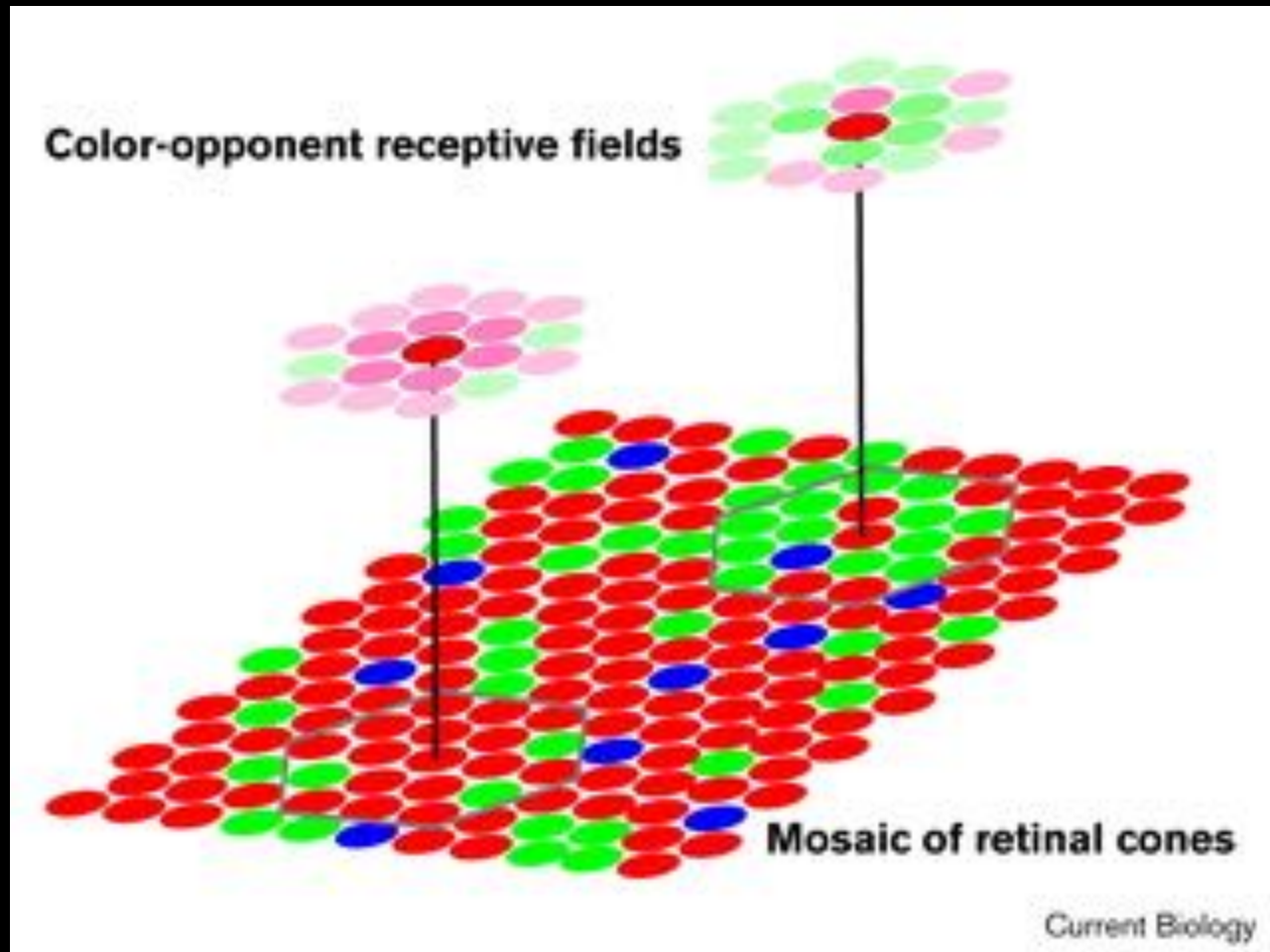
Retinotopic mapping of photoreceptors and ganglion cells differ





Ganglion cell
vision?

Synthetic vision drives overrides color opponency







High density CMOS MEA

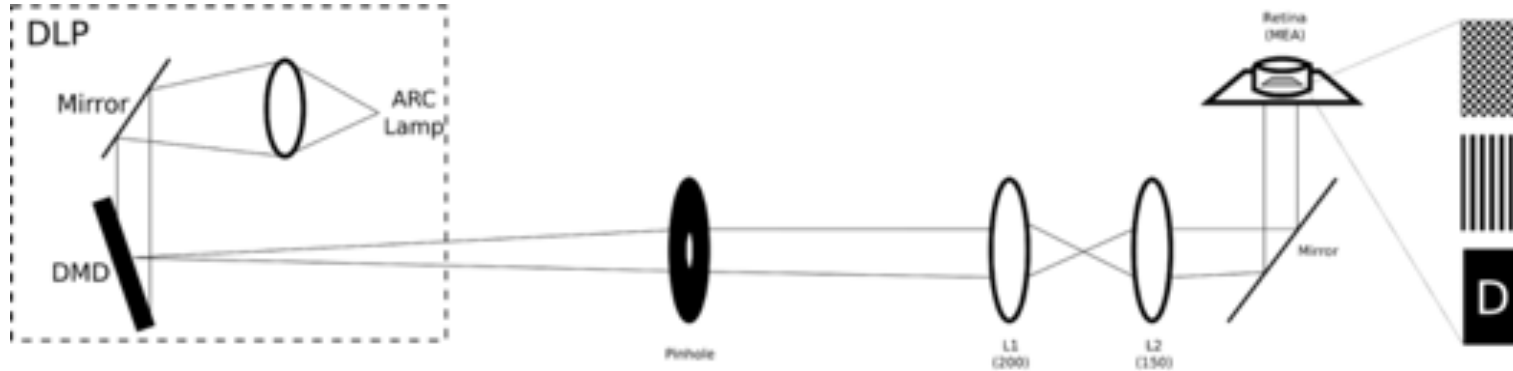
3D Brain/ALA Systems

4096 channel

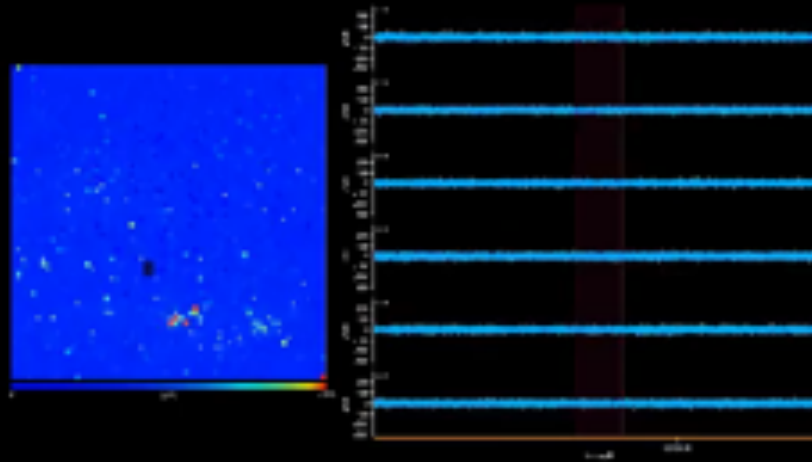
Coverage of full retina on
single array



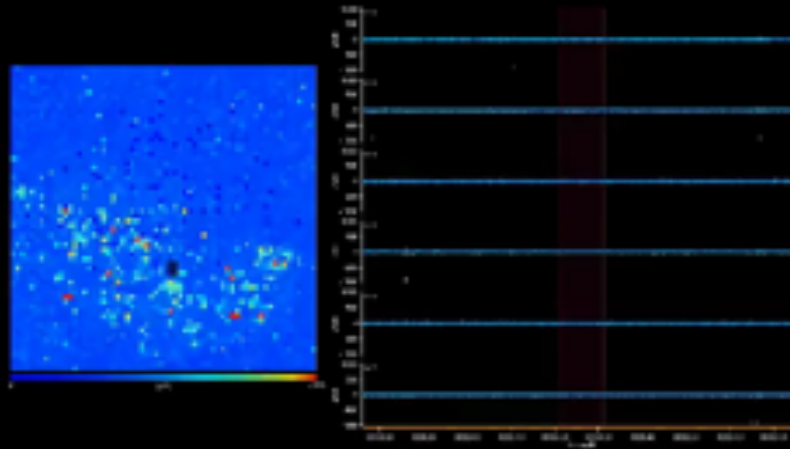
Projector schematic



Stimulus: moving bar

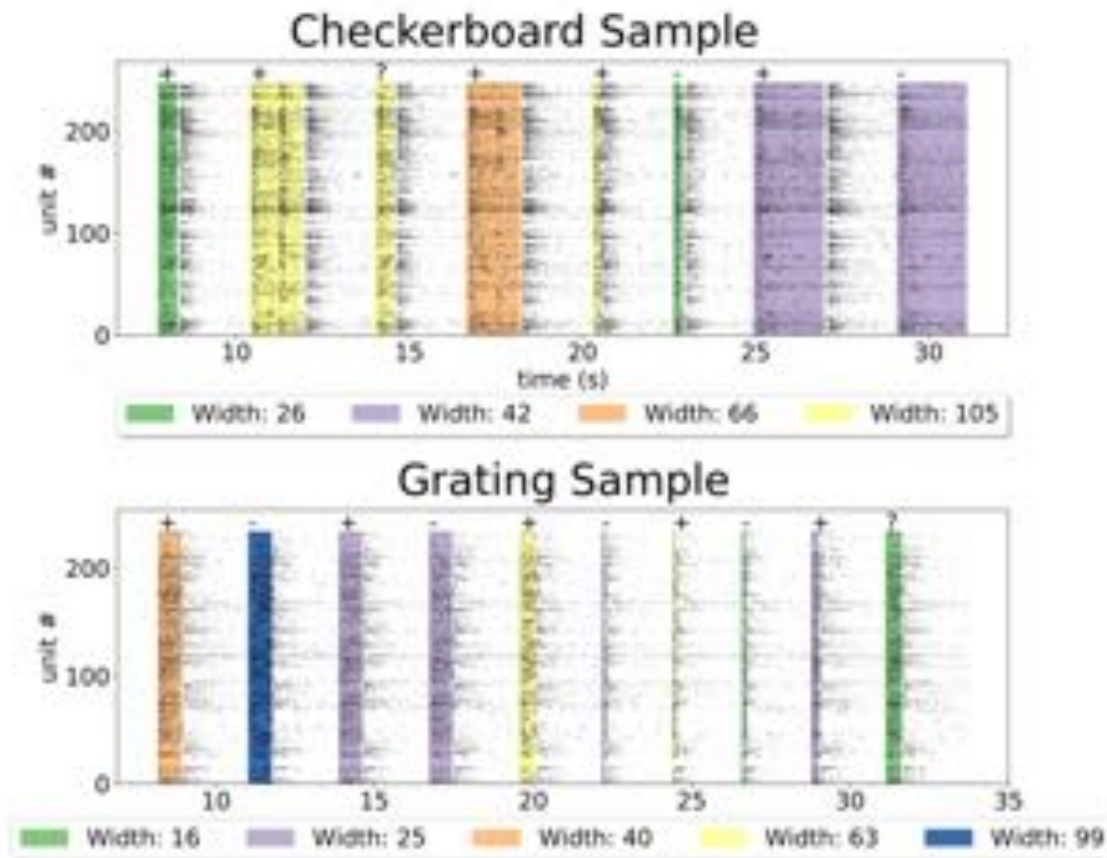


Stimulus: Contrast grating

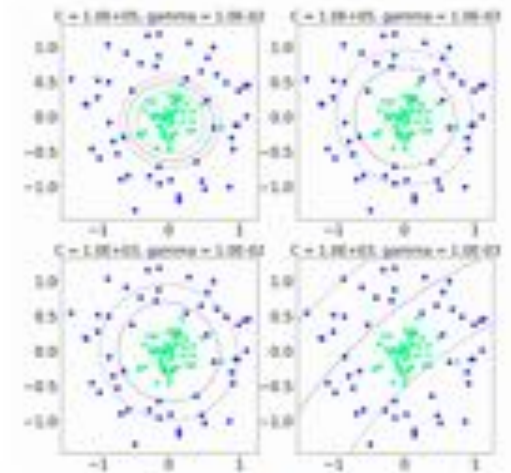


Machine learning of retinal output to projected images

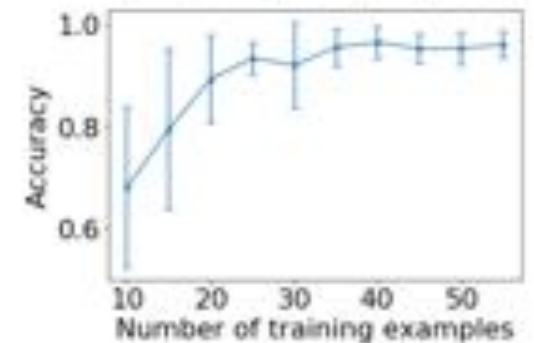
b



c

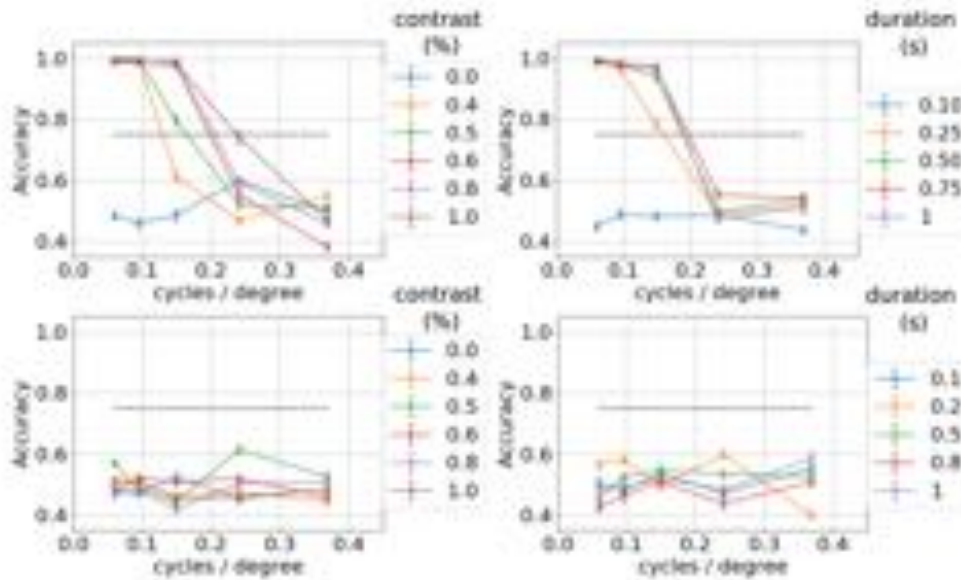
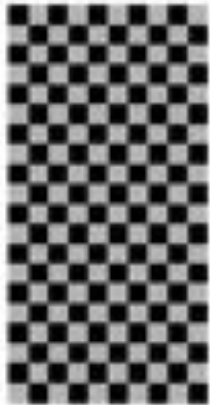


d



Retinal acuity of wild-type and *rd/rd* mice

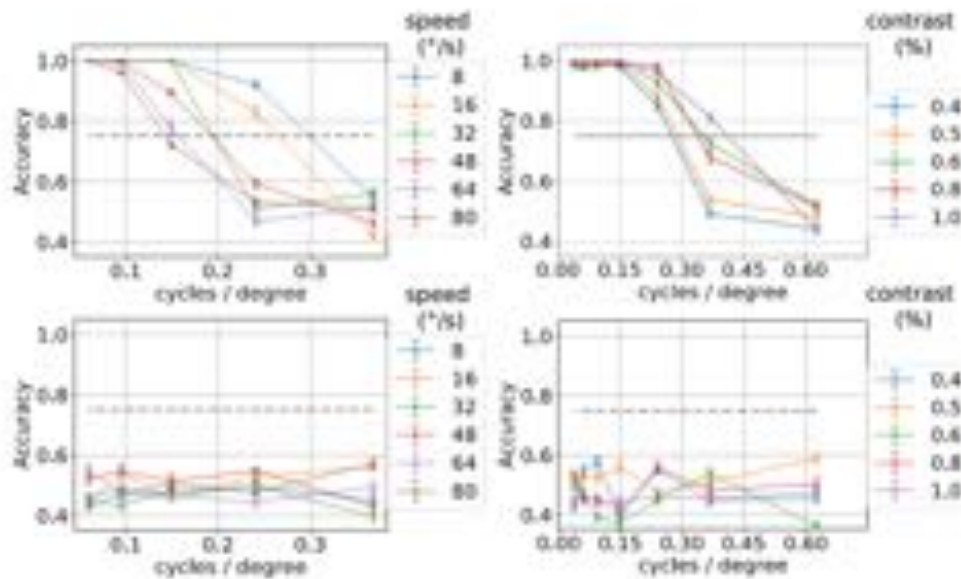
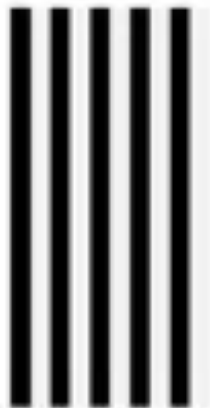
a



Wild-type

rd/rd

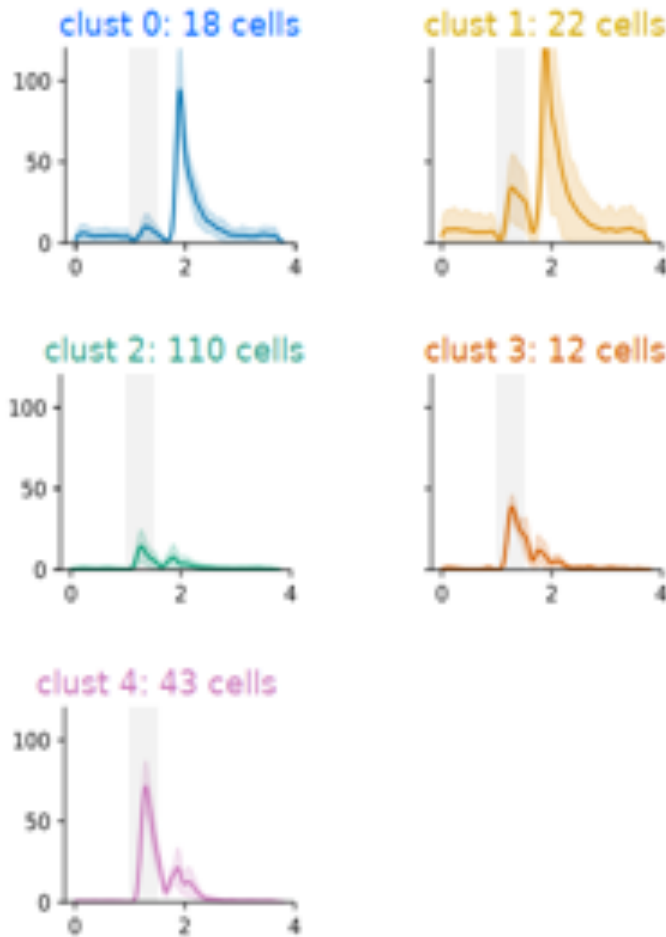
b



Wild-type

rd/rd

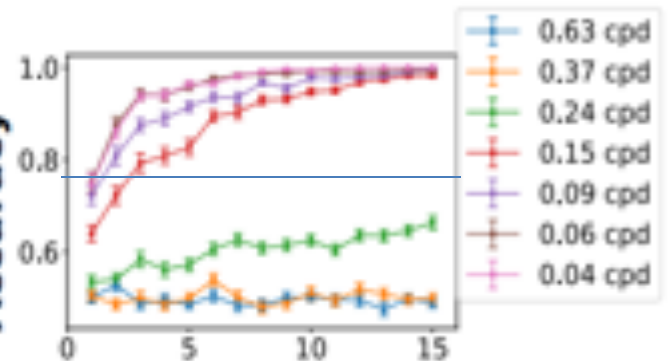
What information gives rise to acuity?



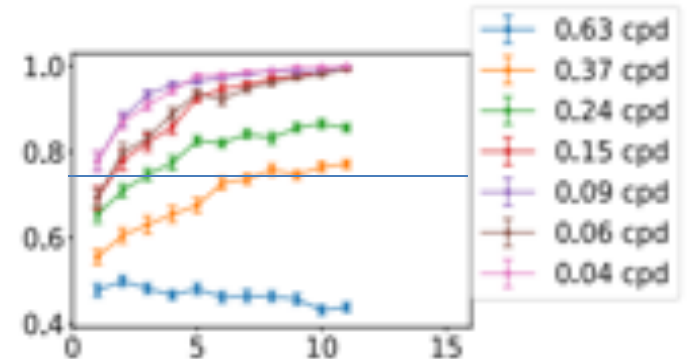
**100%
contrast**

Accuracy

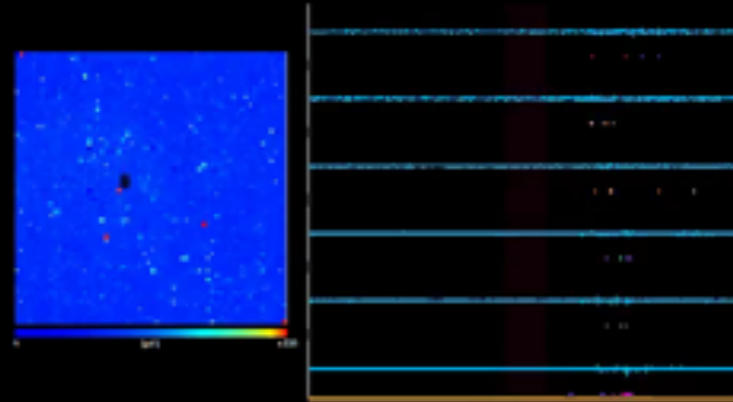
cluster 0



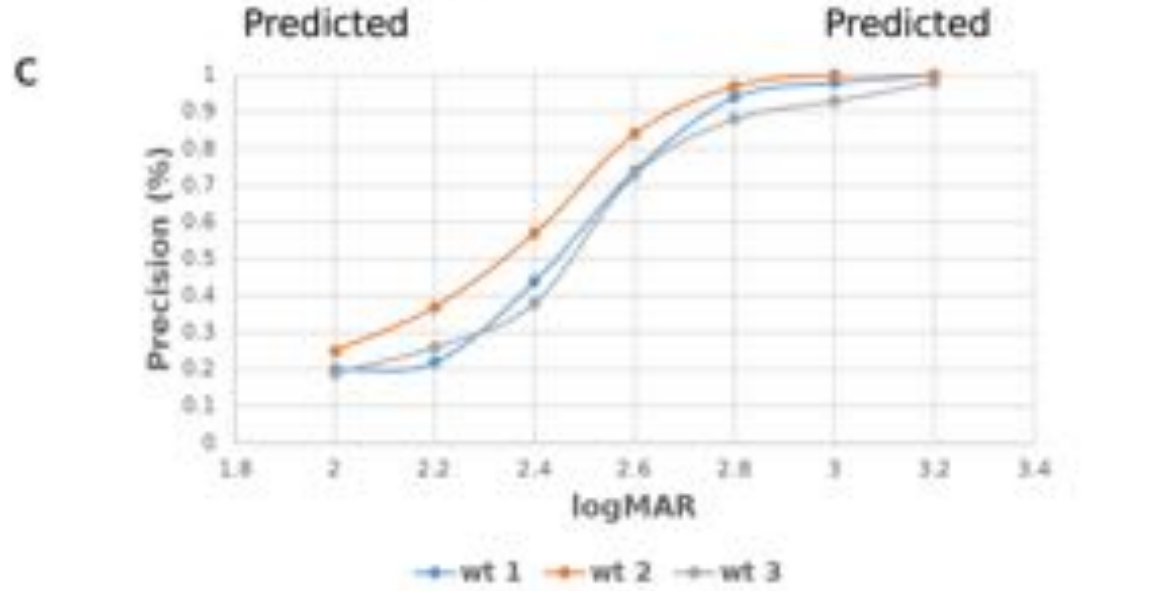
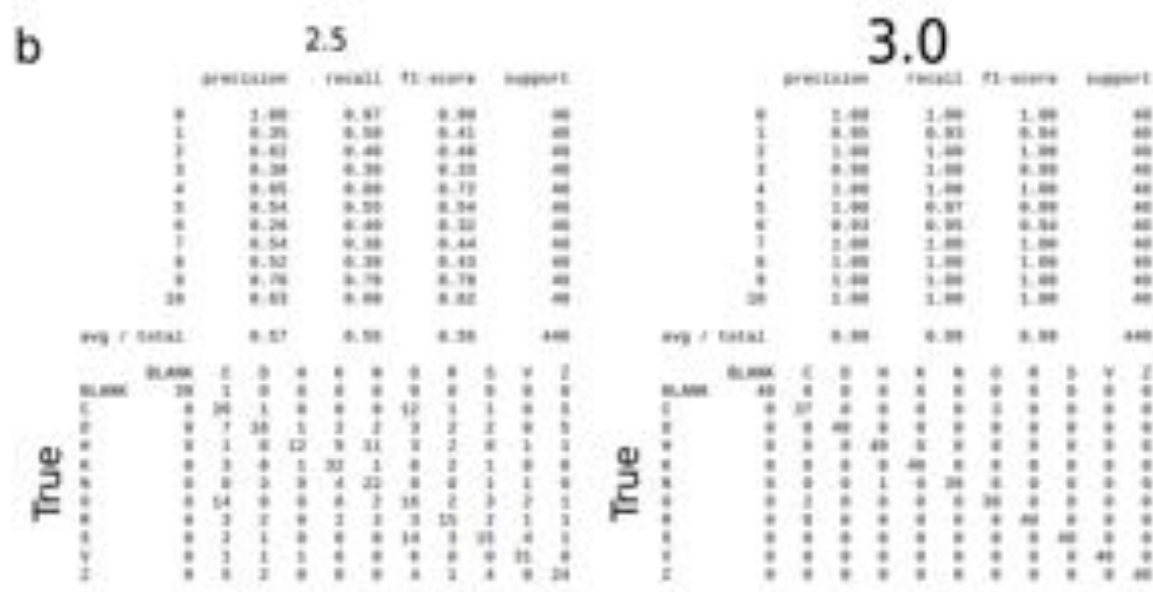
cluster 3



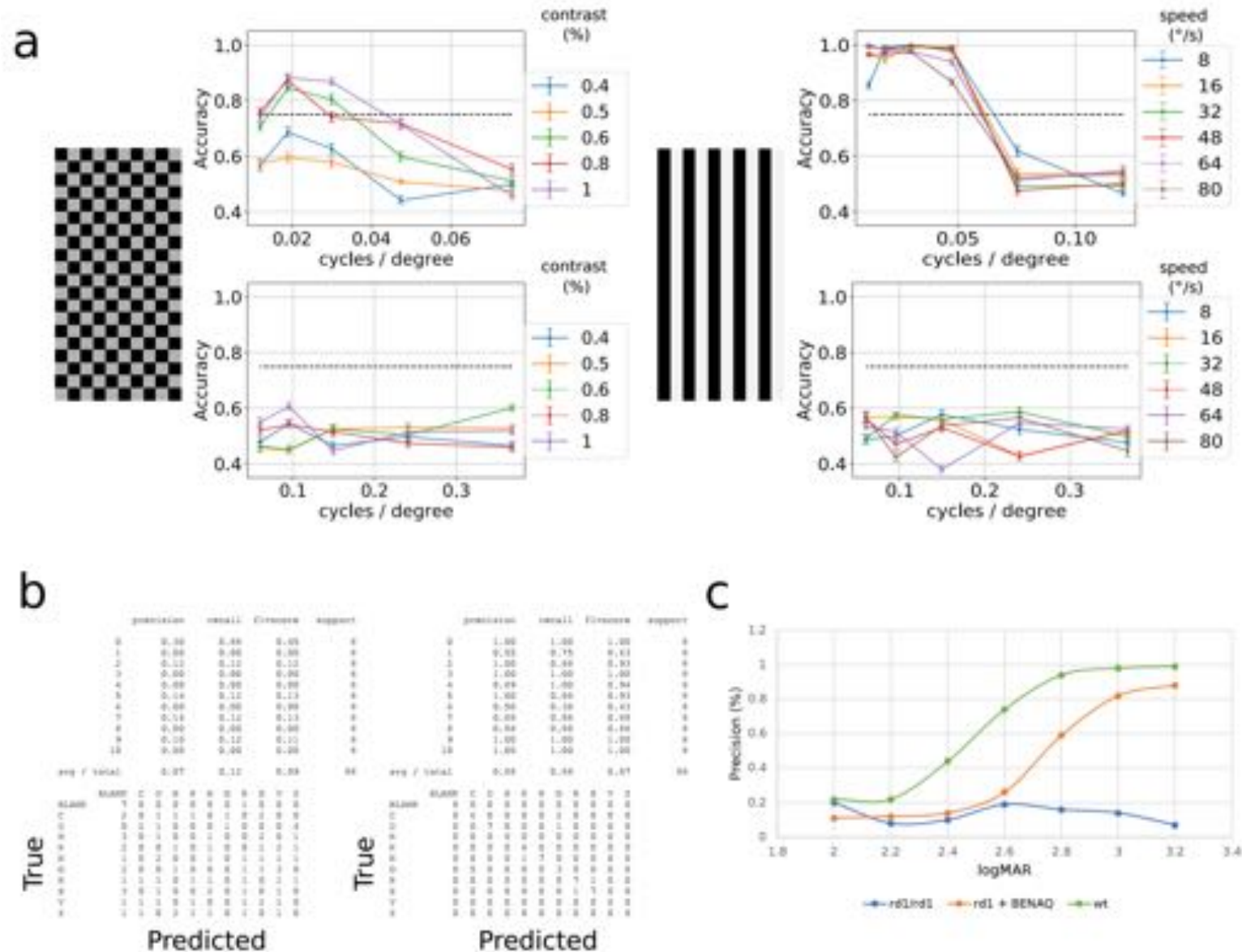
Stimulus: ETDORS Letters



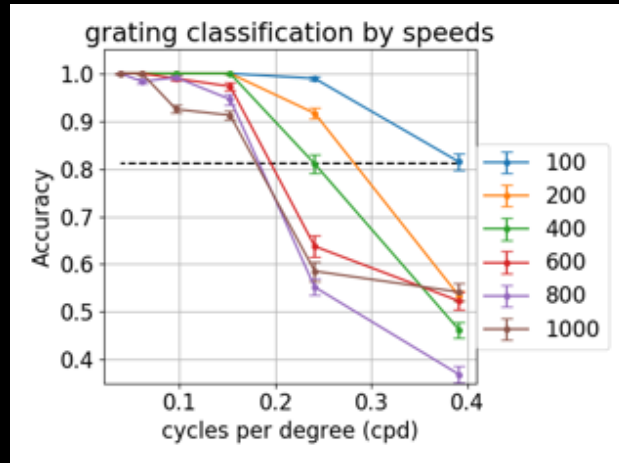
Murine retinal acuity to ETDRS letters *in vitro*



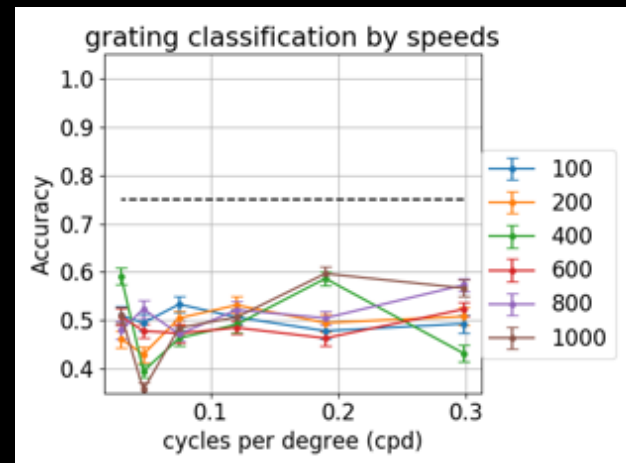
Retinal acuity restored by BENAQ



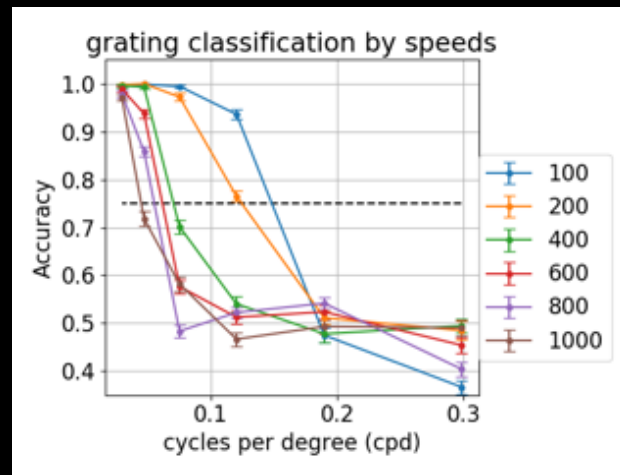
Comparing two photoswitches



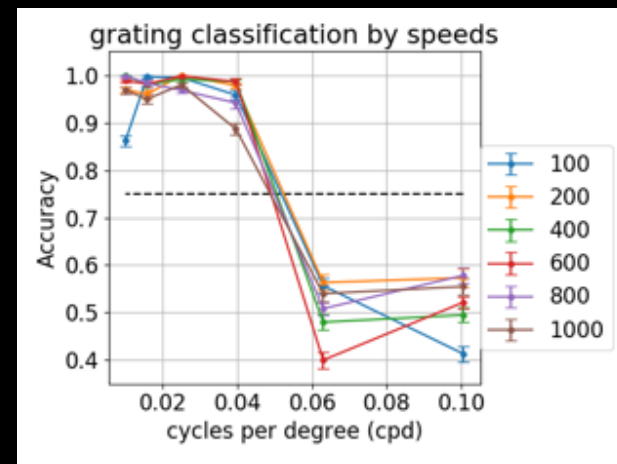
Wild type



rd/rd



DENAQ

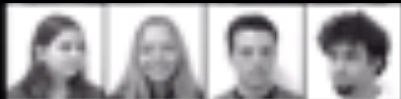
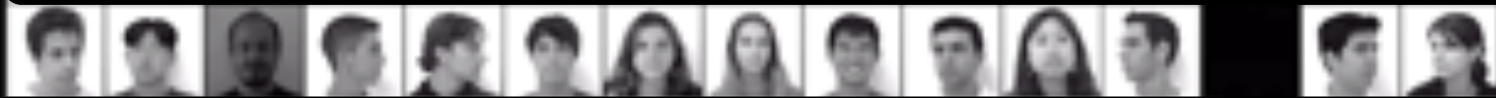
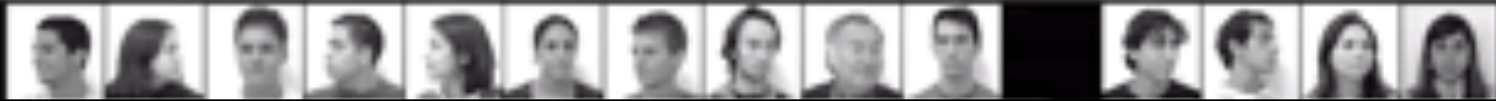


BENAQ

Real world application: facial reconstructions



Real world application: facial reconstructions



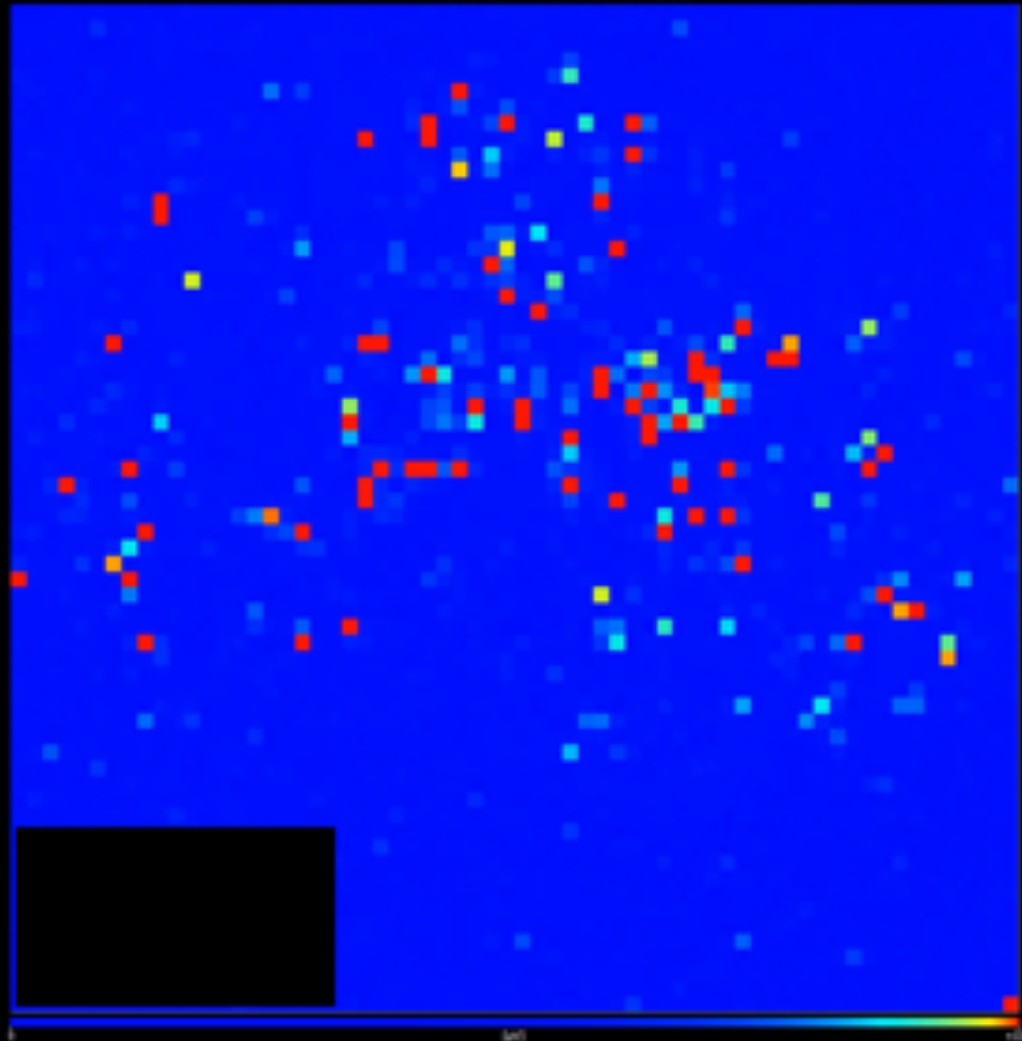
Real world application



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

Acknowledgments

Van Gelder Lab

- Darwin Babino, PhD
- Jack Sychev, MD
- Laura Laprell, PhD
- Kuldeep Kaur, PhD
- Joe Nemargut, PhD
- Tyler Benster
- Mike Manookin, PhD
- Angela Sandt

University of Washington

- Sewoong Oh, PhD
- Xiyang Liu

UC Berkeley

- Rich Kramer, PhD
- John Flannery, PhD

University of Pennsylvania

- William Beltran, DVM, PhD

NYU

- Dirk Trauner, PhD

Funding

NIH PN2 EY018241
NIH 1R24EY023937
Mark J Daly, MD Research Fund
Research to Prevent Blindness