Prospects for vision restoration in outer retinal degeneration

2020 Schepens Lecture
Retina Society Meeting

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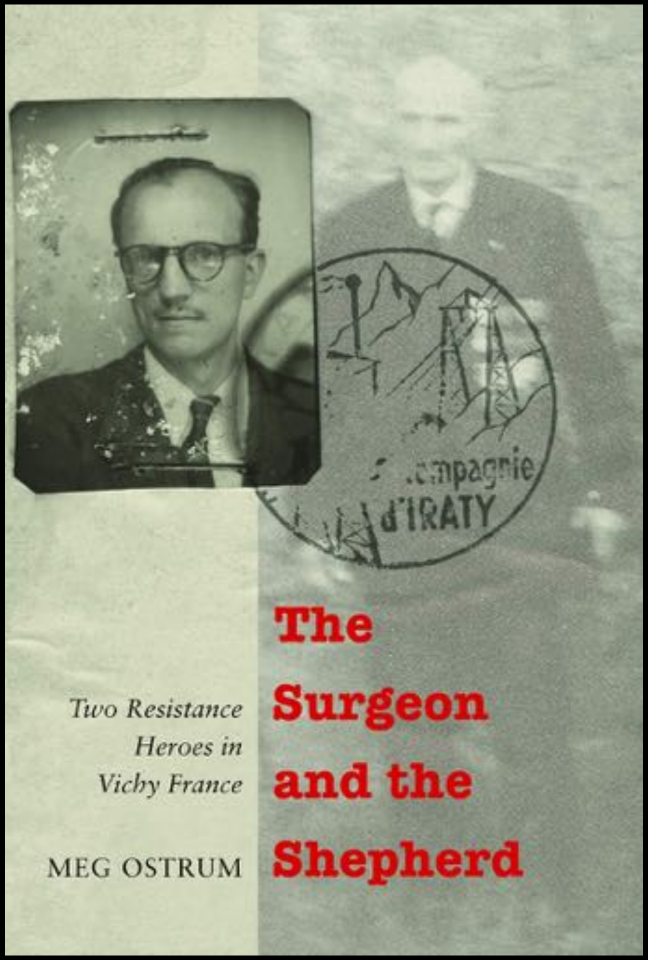
Department of Ophthalmology

University of Washington School of Medicine

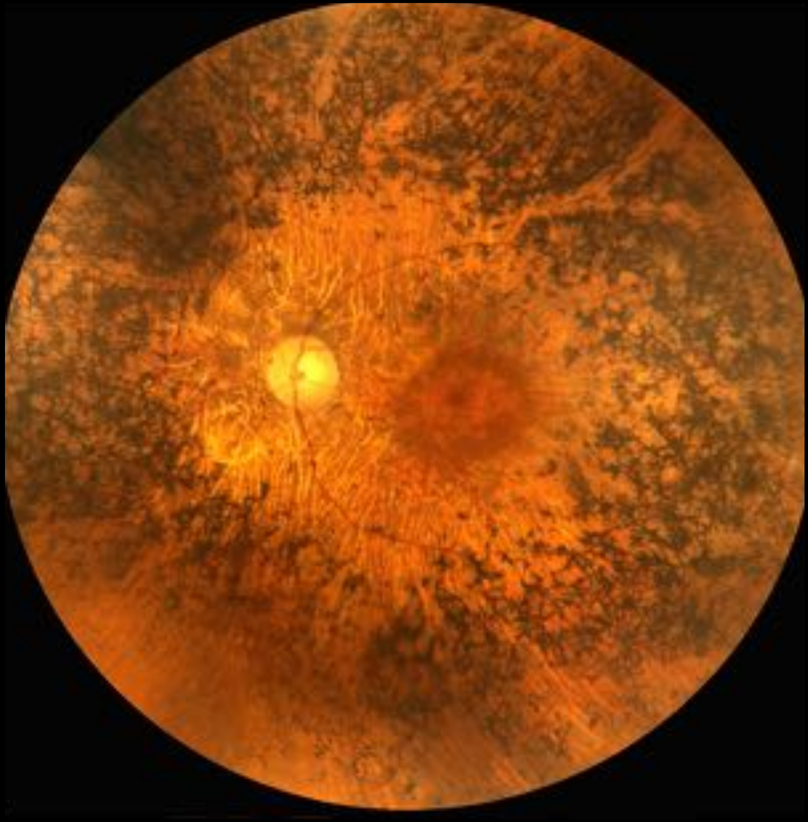
Disclosures

- 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

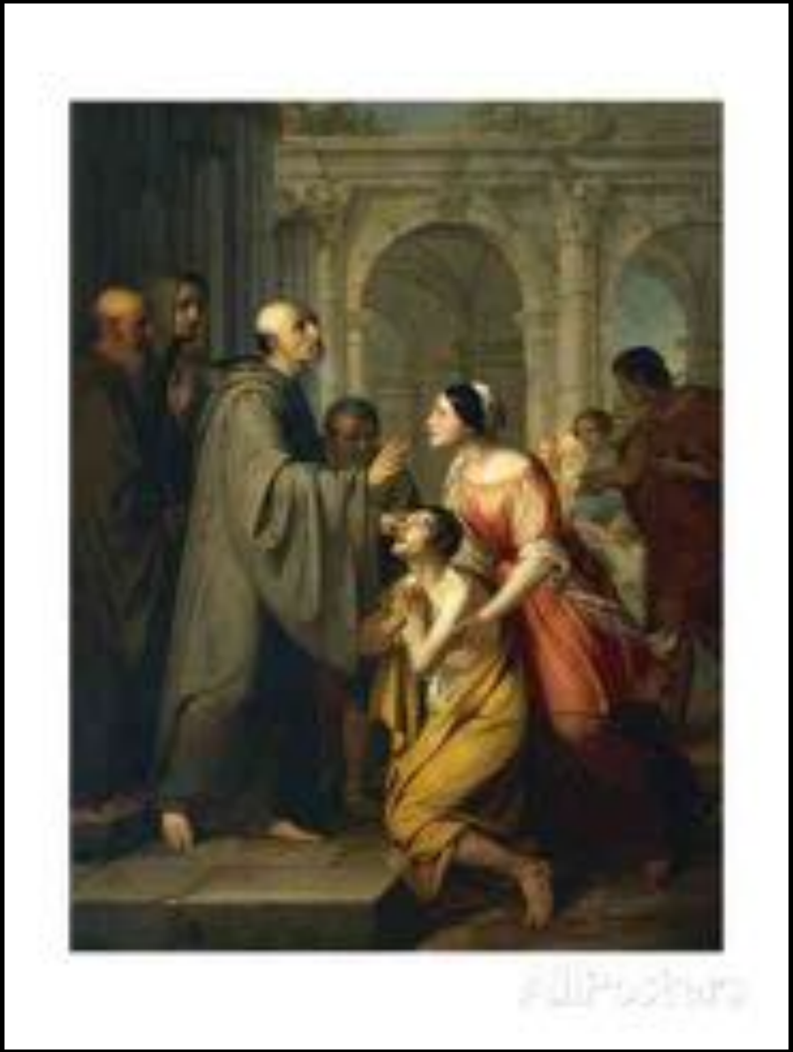
Charles Schepens, MD 1912-2006



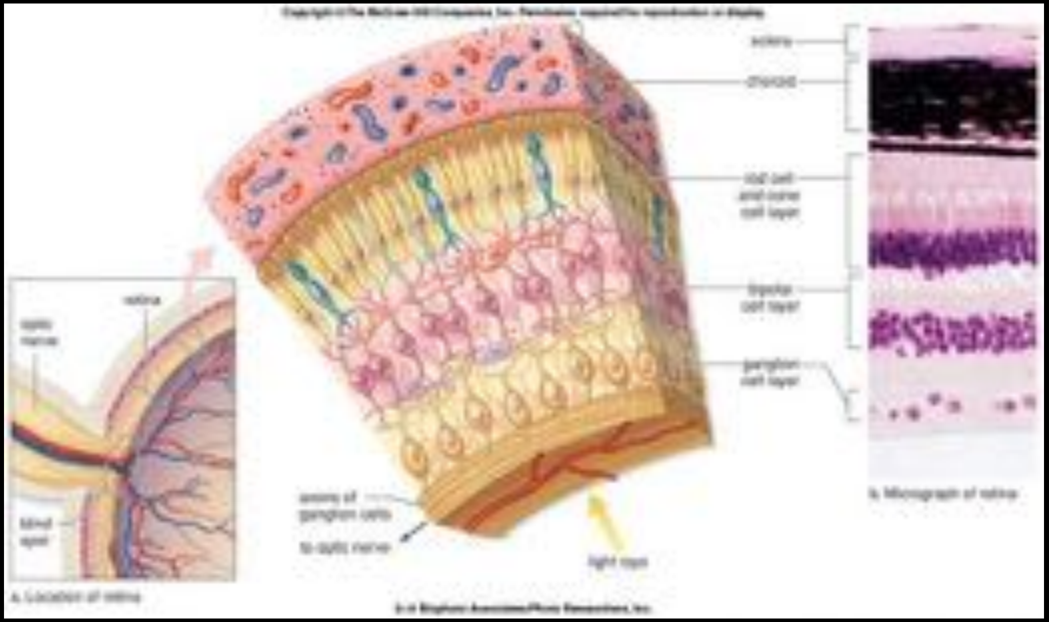
- Founder of the Retina Society
- Pioneer in vitreoretinal surgery
- Launched first retina fellowship in US
- Invented the binocular indirect

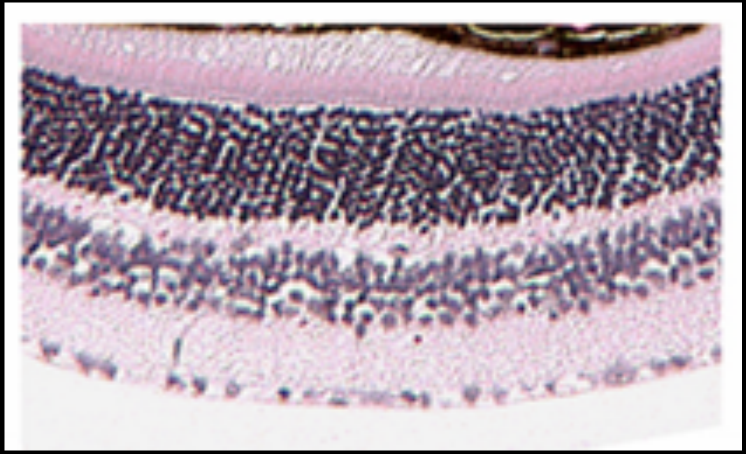



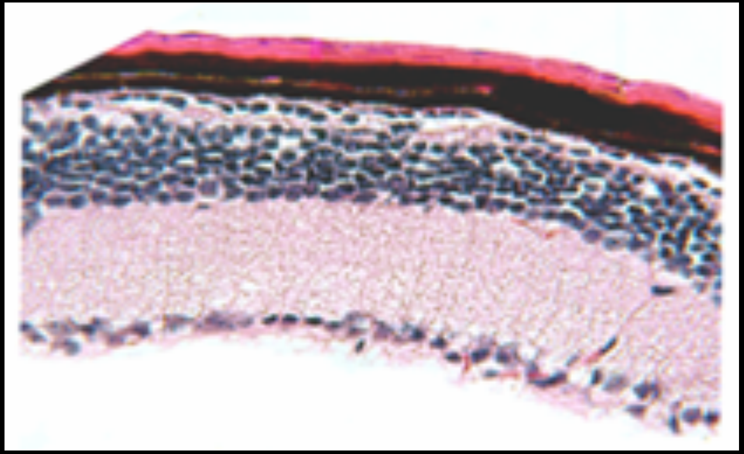
The miracle of vision restoration



St. Mauro Abbott



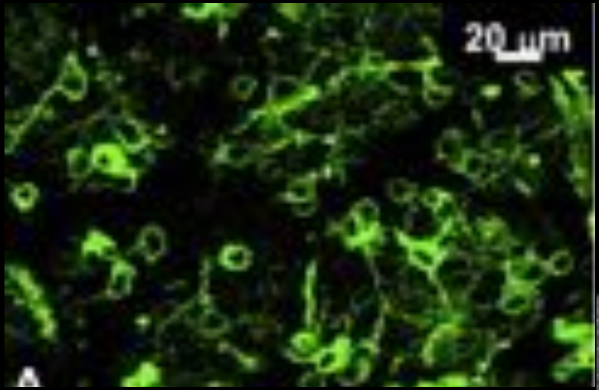




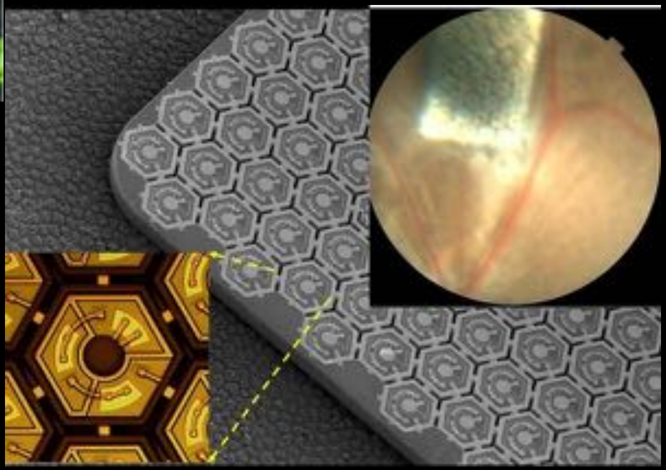
Strategies for vision restoration

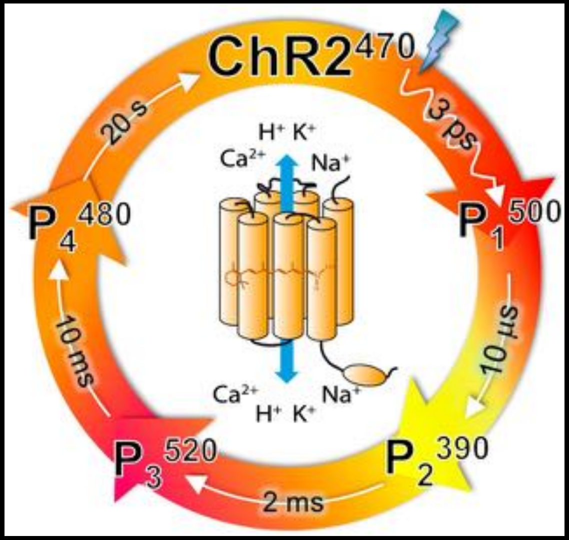
Stem cell replacement

Photoreceptive molecule gene therapy

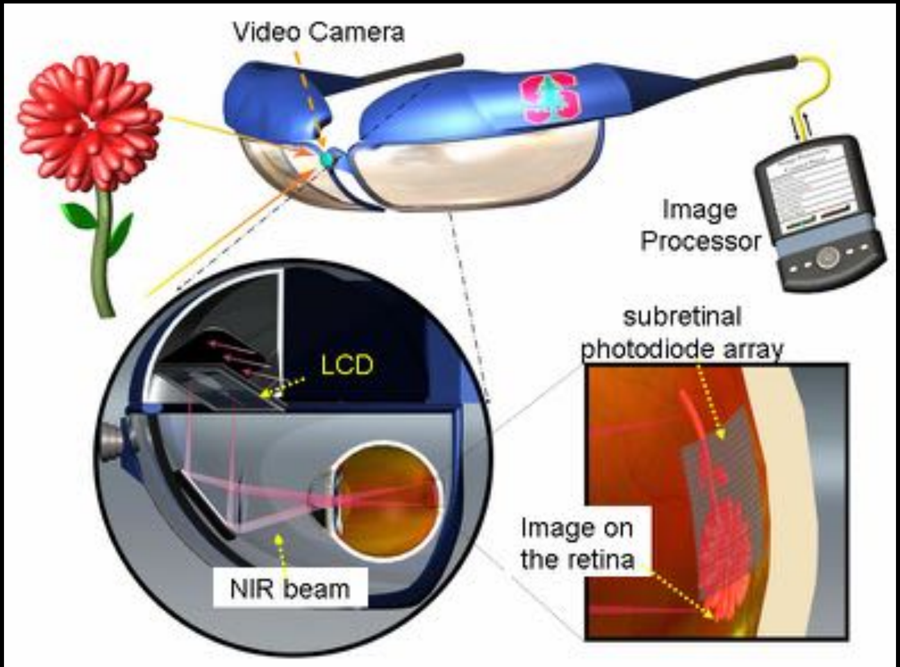


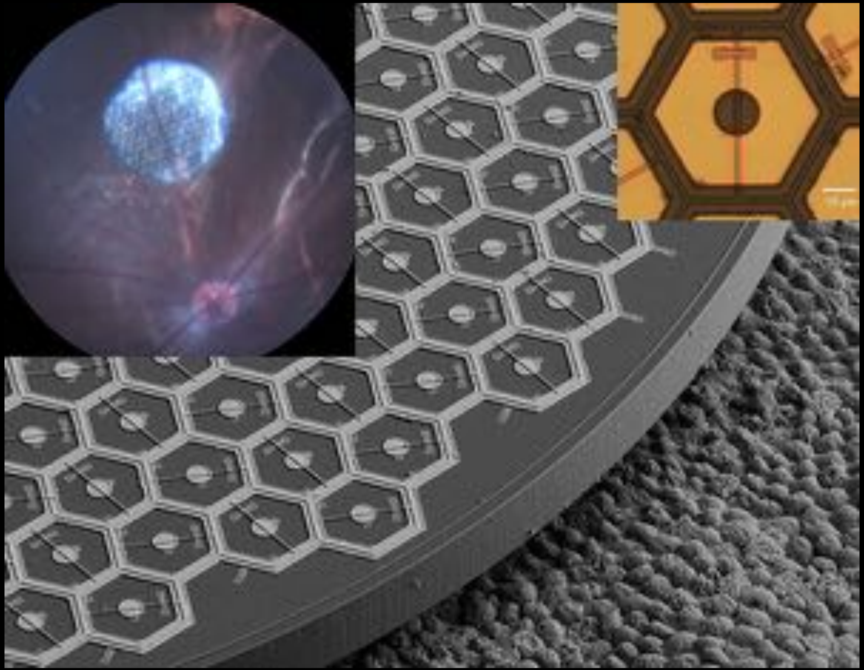
Chip prosthetics



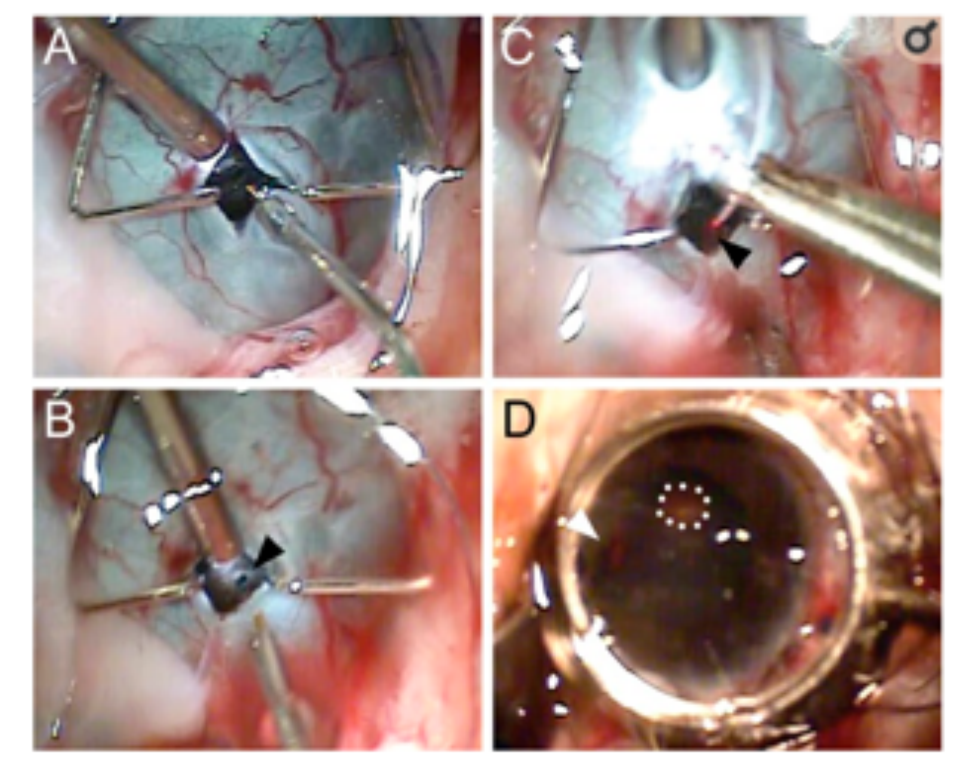


Photovoltaic cells for vision restoration

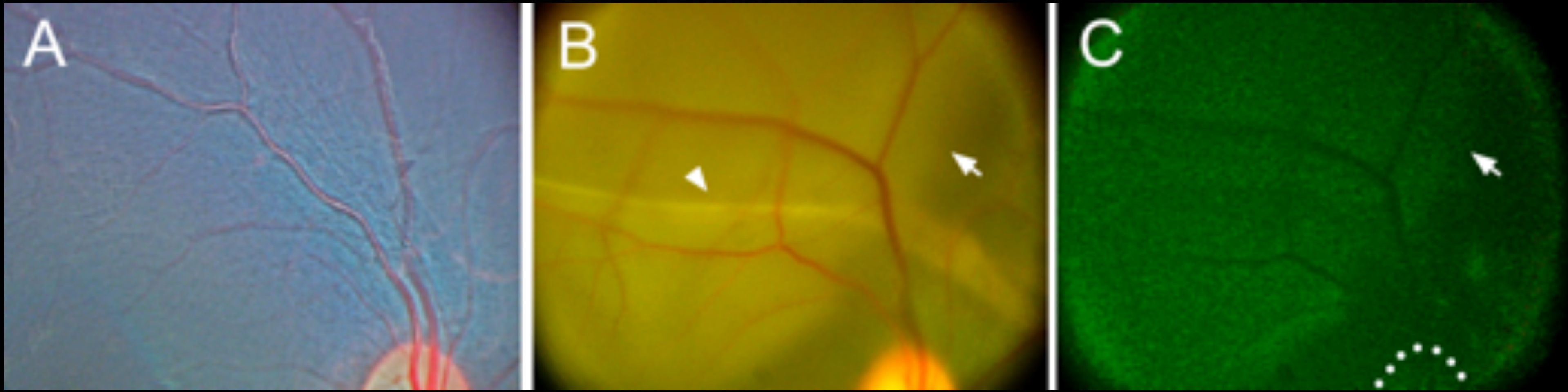




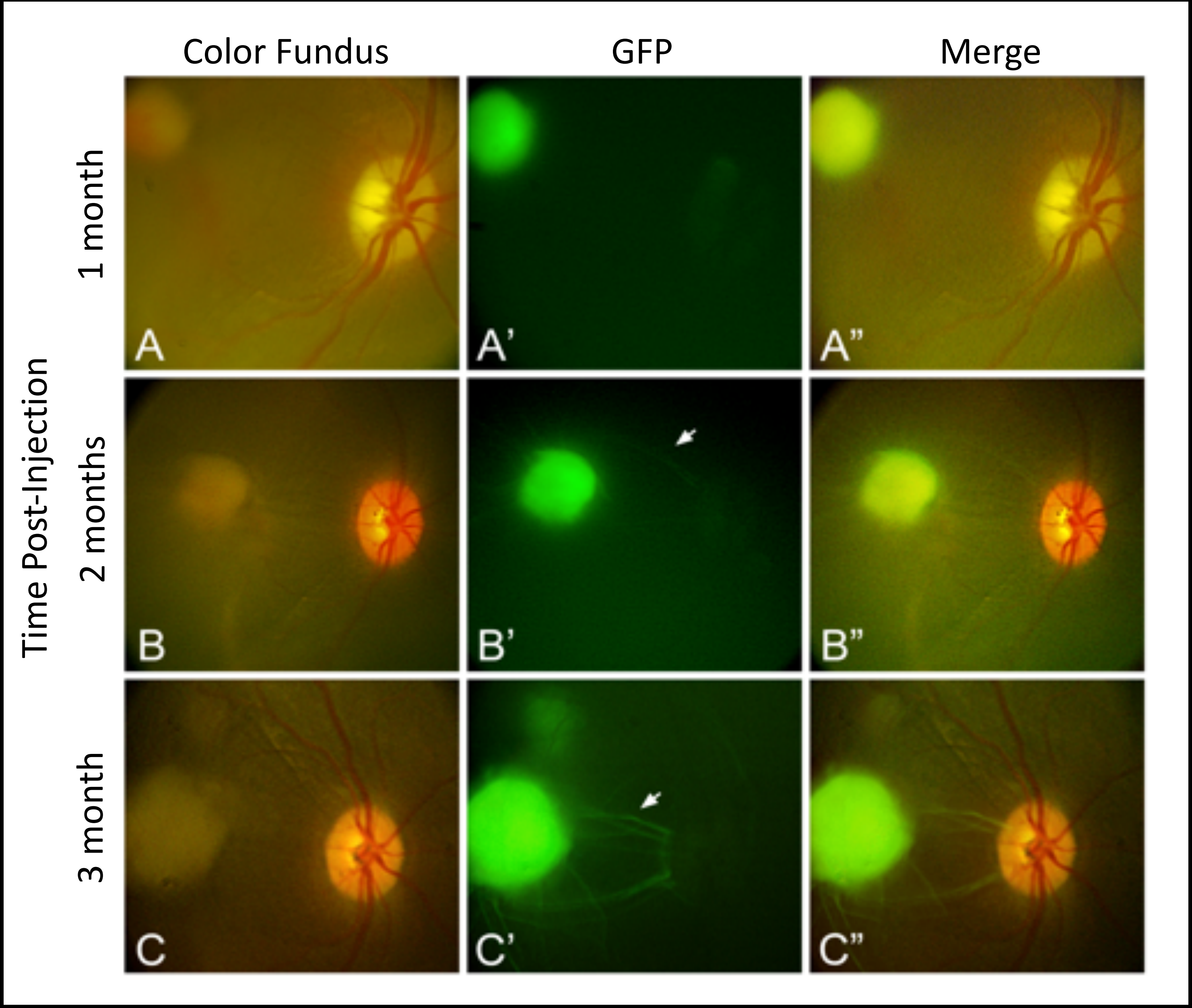
Courtesy Daniel Palanker, PhD



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

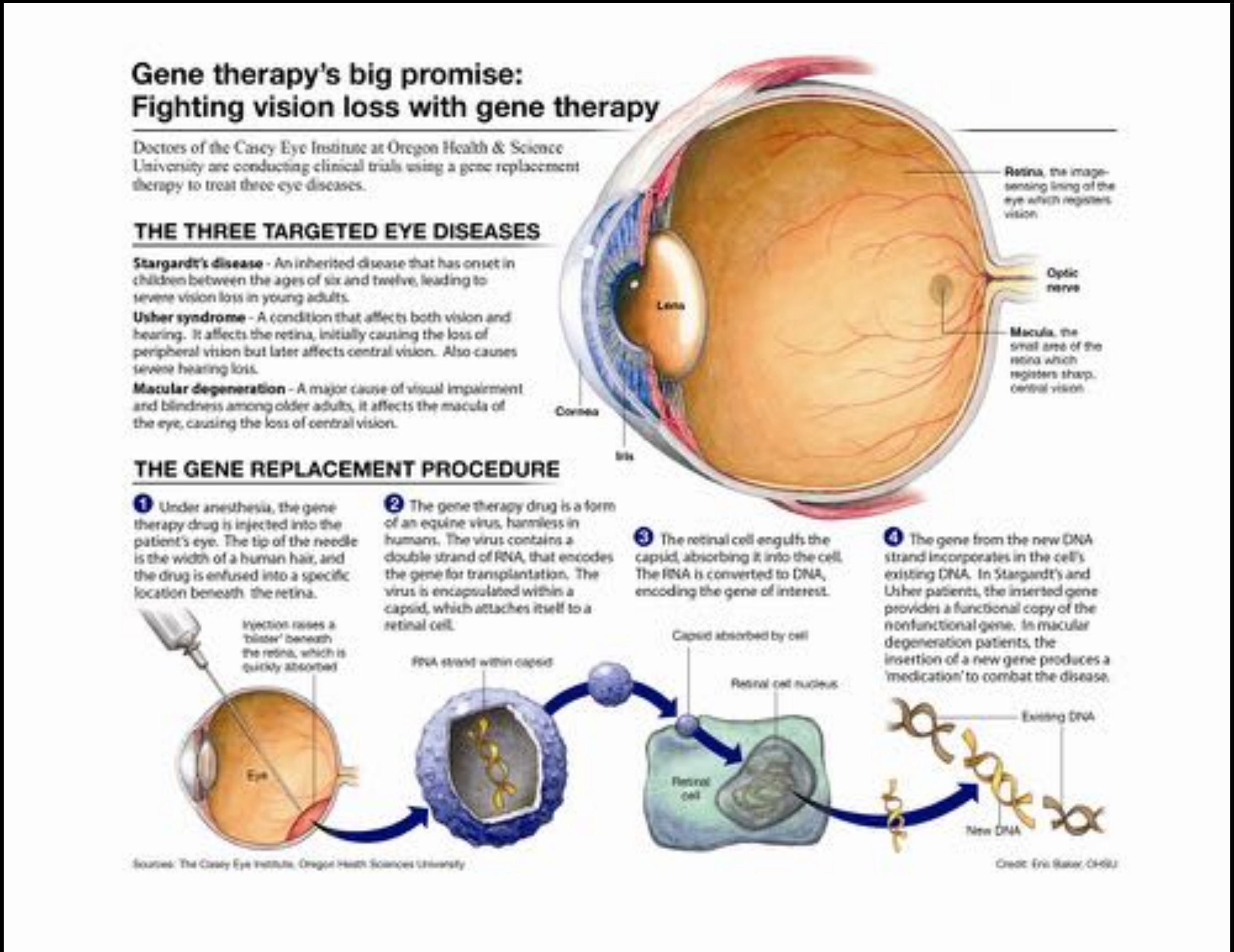


Chao JR et al., Transl Vis Sci Technol. 2017;6(3)



Chao JR et al., Transl Vis Sci Technol. 2017;6(3)

Gene therapy for vision restoration



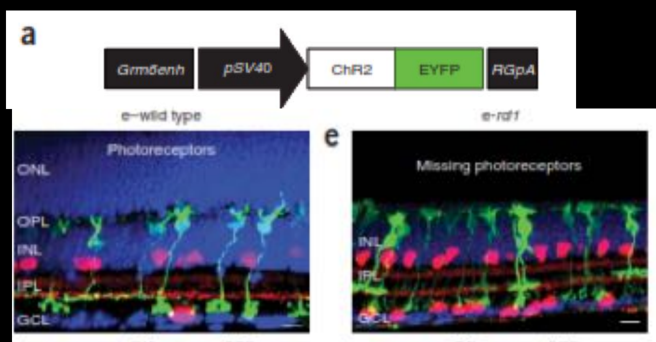
https://www.today.com/health/dna-injection-slow-vision-loss-1B5977095

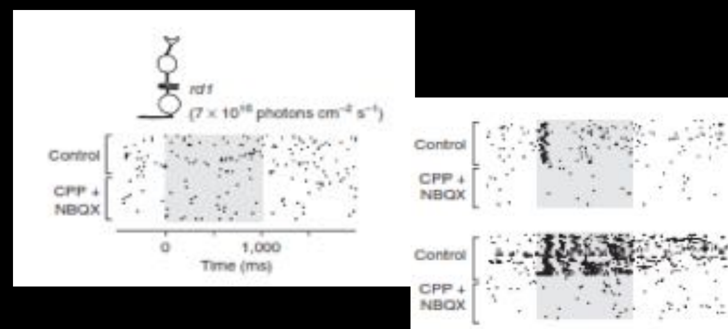
Channel opsins for vision restoration

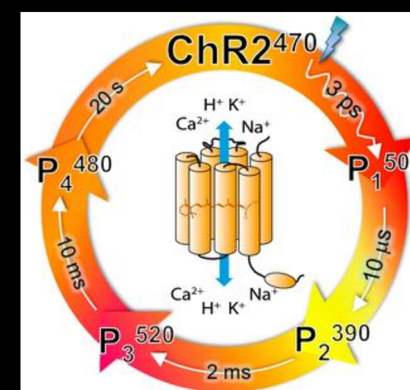
NATURE NEUROSCIENCE VOLUME 11 | NUMBER 6 | JUNE 2008

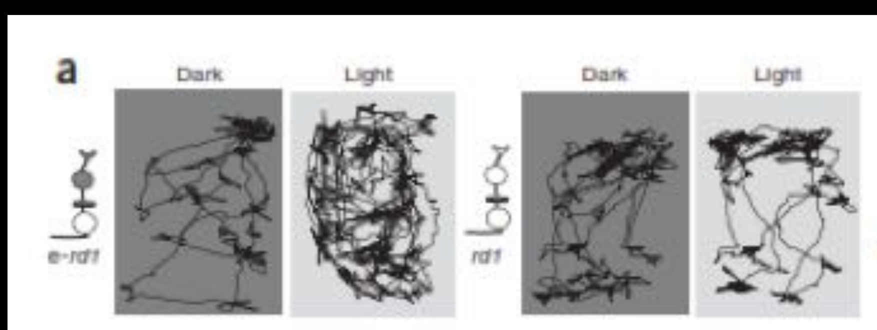
Light-activated channels targeted to ON bipolar cells restore visual function in retinal degeneration

Pamela S Lagali[1,4], David Balya[1,4], Gautam B Awatramani[1,3,4], Thomas A Münch[1], Douglas S Kim[2], Volker Busskamp[1], Constance L Cepko[2] & Botond Roska[1]









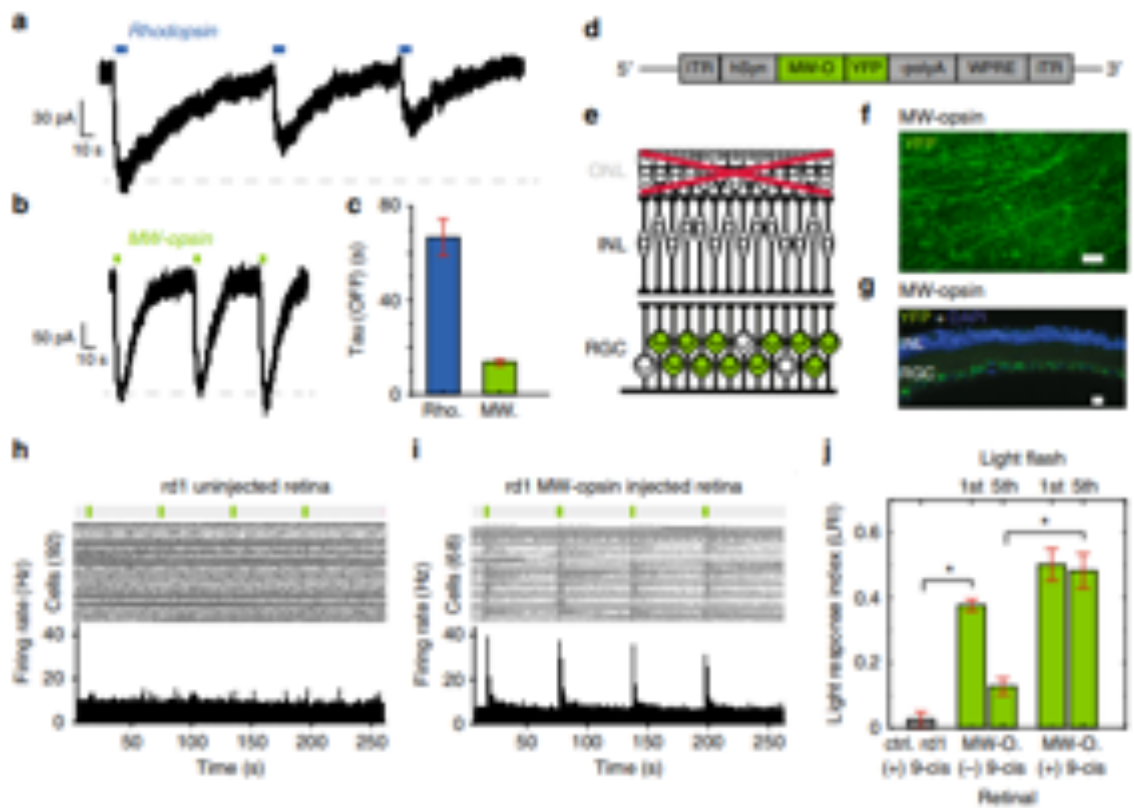
nature COMMUNICATIONS

ARTICLE

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

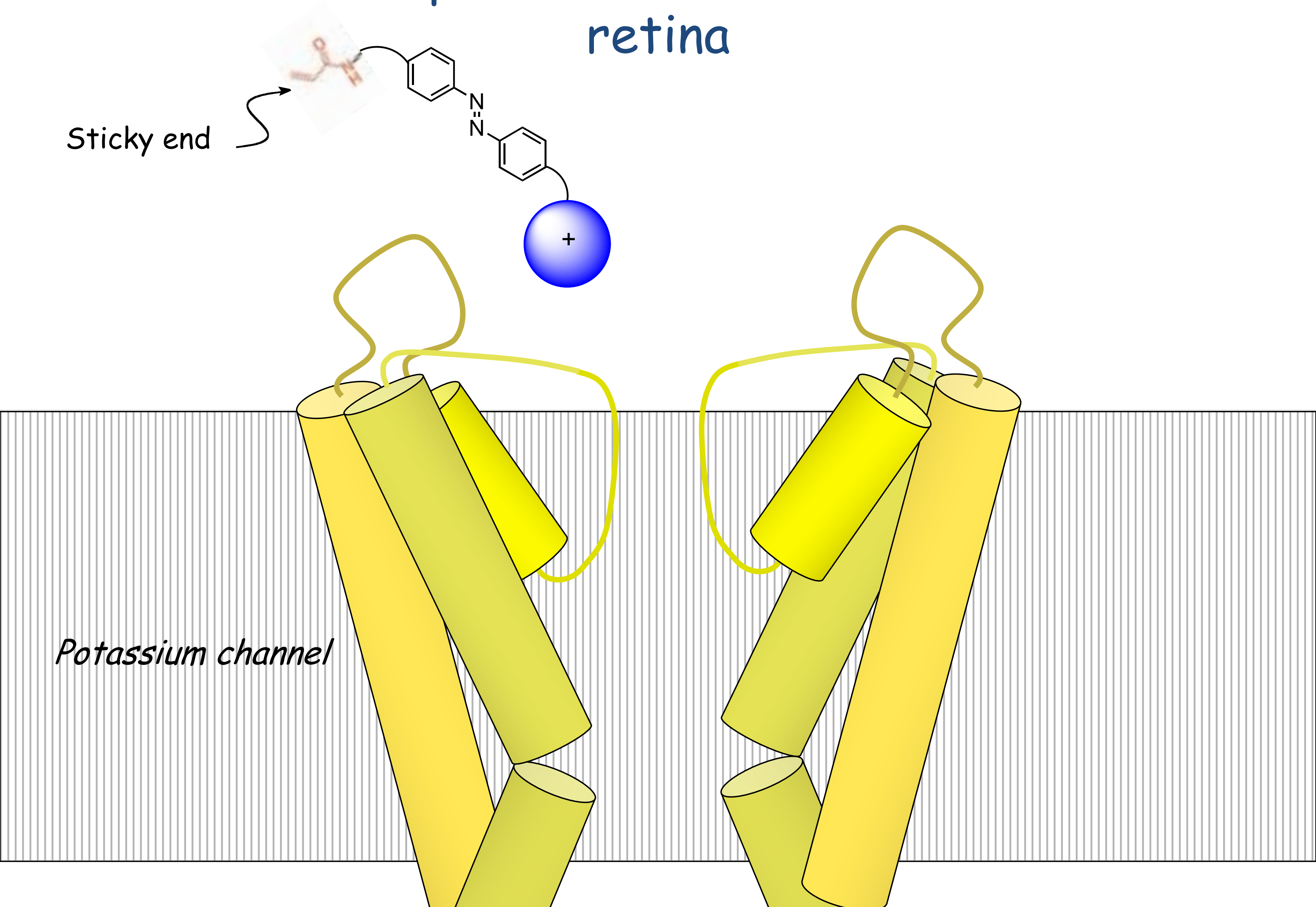
Restoration of high-sensitivity and adapting vision with a cone opsin

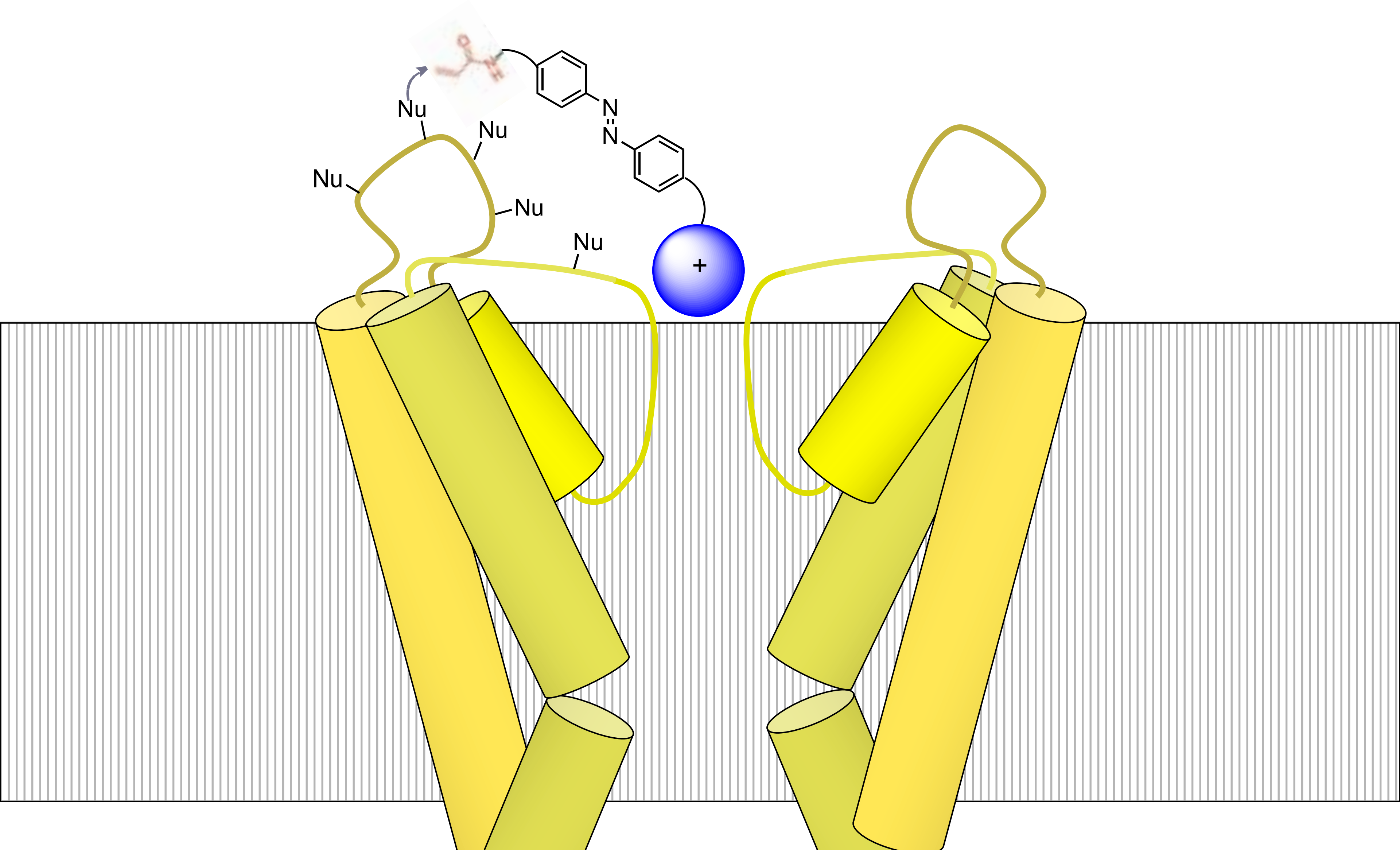
Michael H. Berry[1,2], Amy Holt[1], Autoosa Salari[1], Julia Veit[1,3], Meike Visel[1], Joshua Levitz[1,7], Krisha Aghi[3], Benjamin M. Gaub[3,8], Benjamin Sivyer[2,4], John G. Flannery[1,3,5] & Ehud Y. Isacoff[1,3,6]

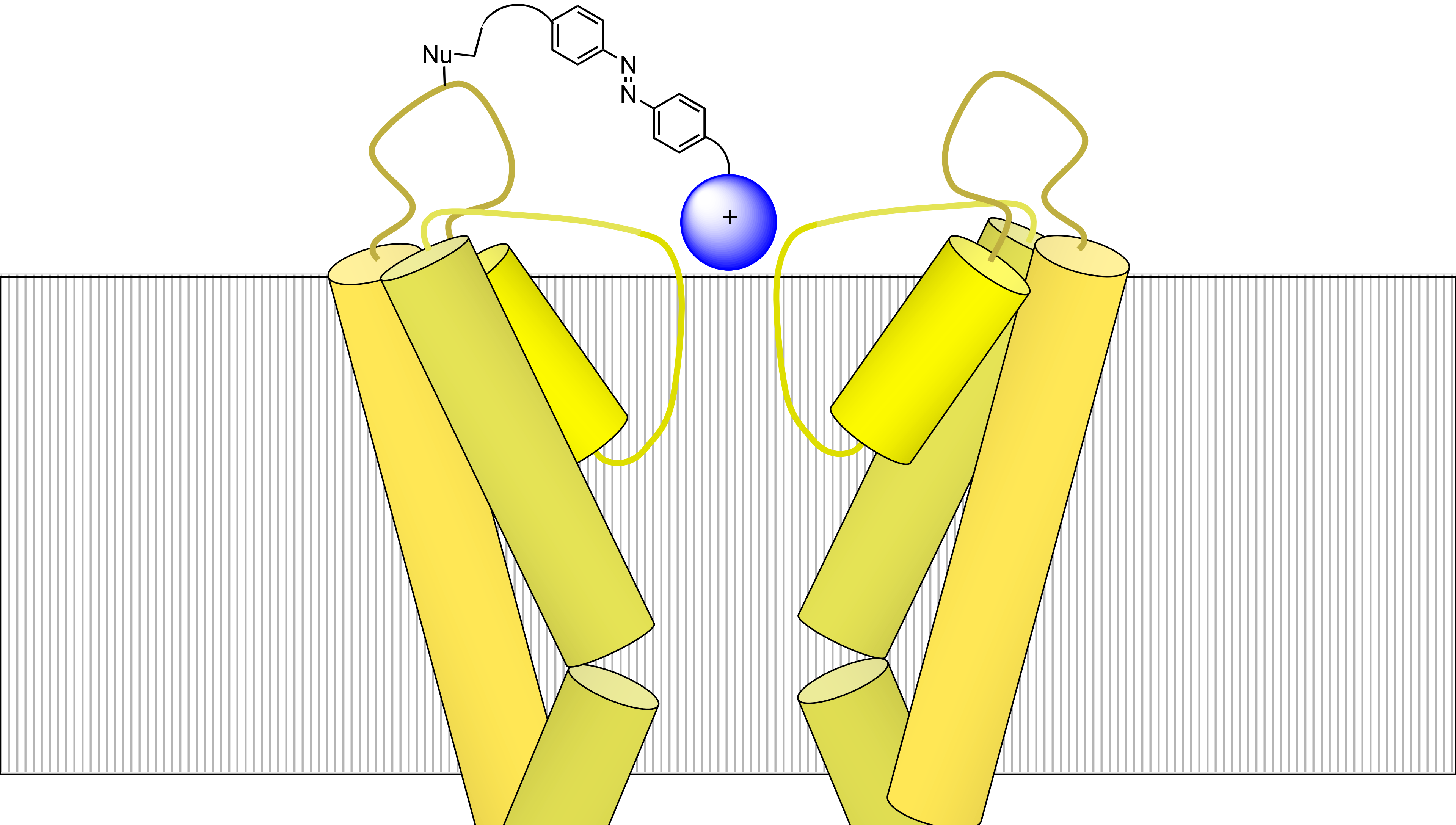


Small molecule therapy for reversing blindness

Photoswitch compounds: chemical reanimation of the retina




Nu
Nu
Nu
Nu
Nu
N
N
+



Nu
N
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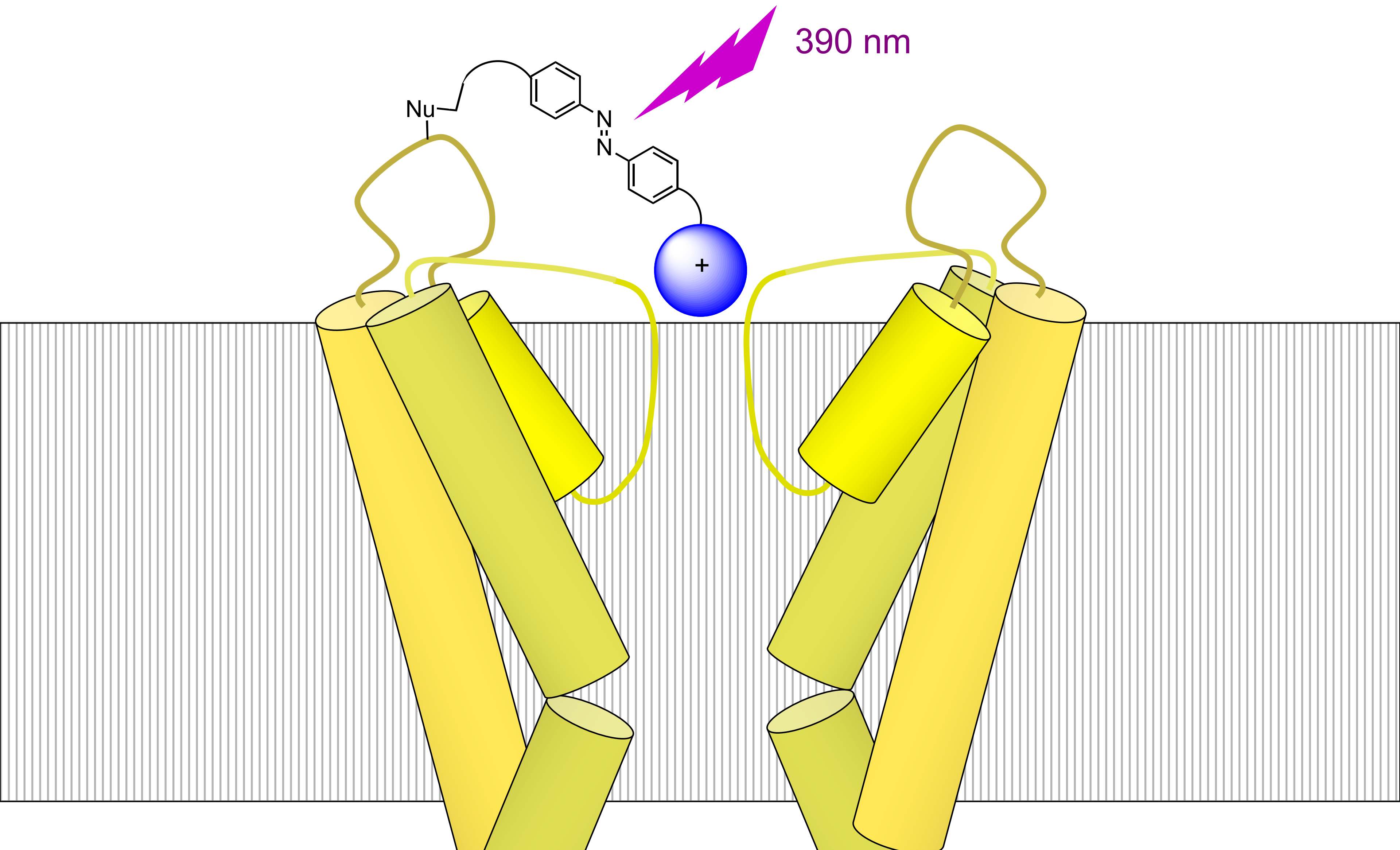
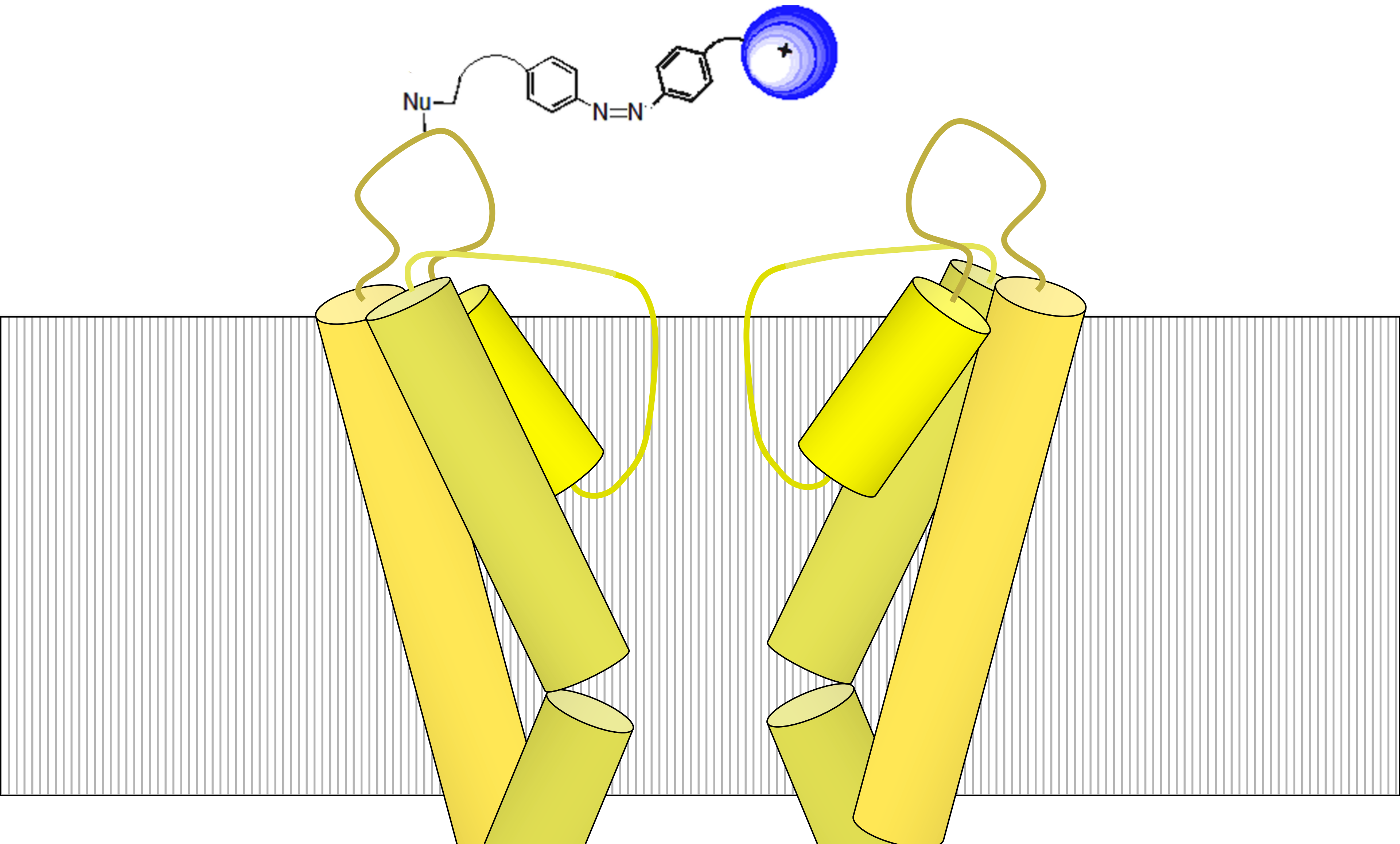
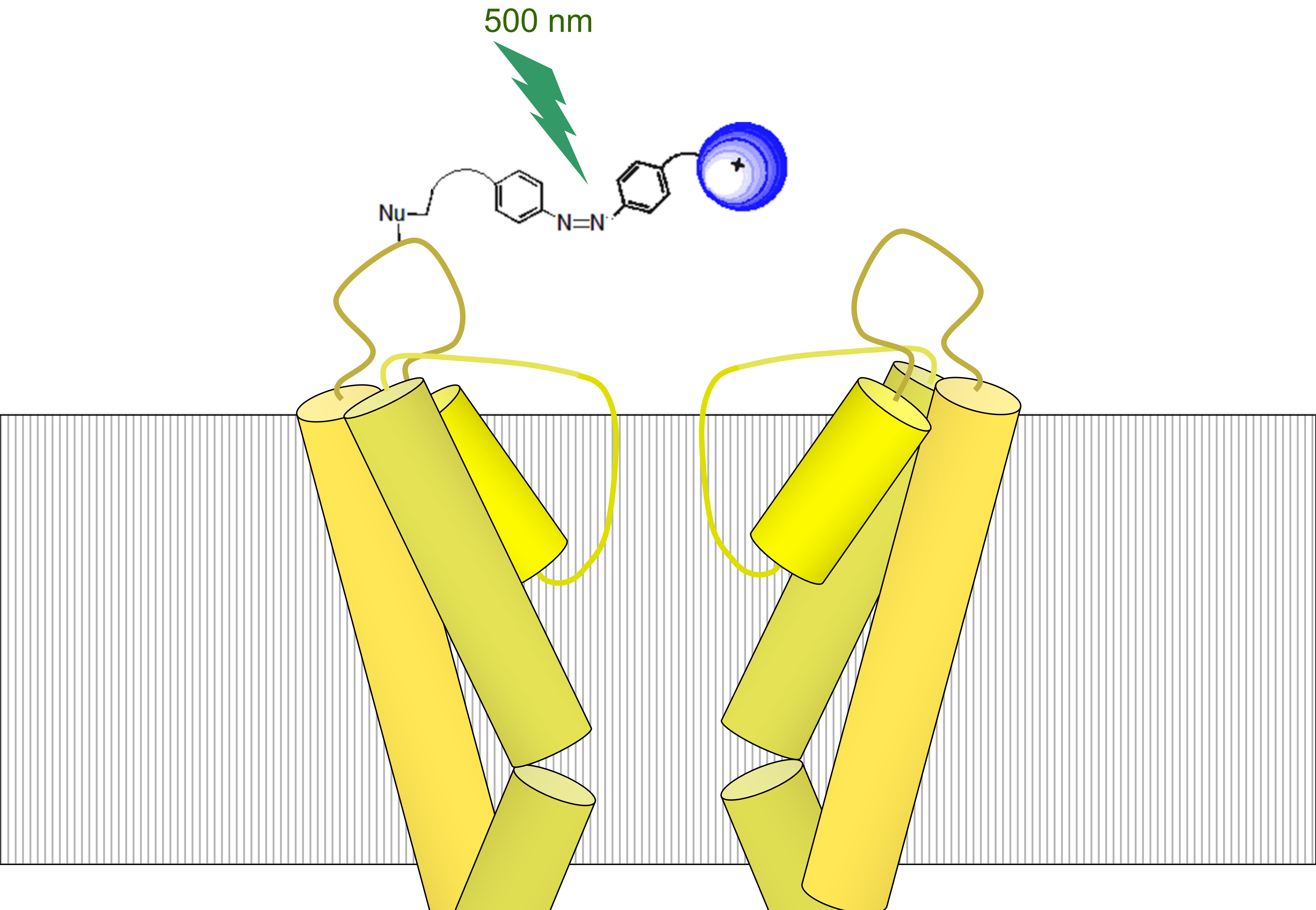
+

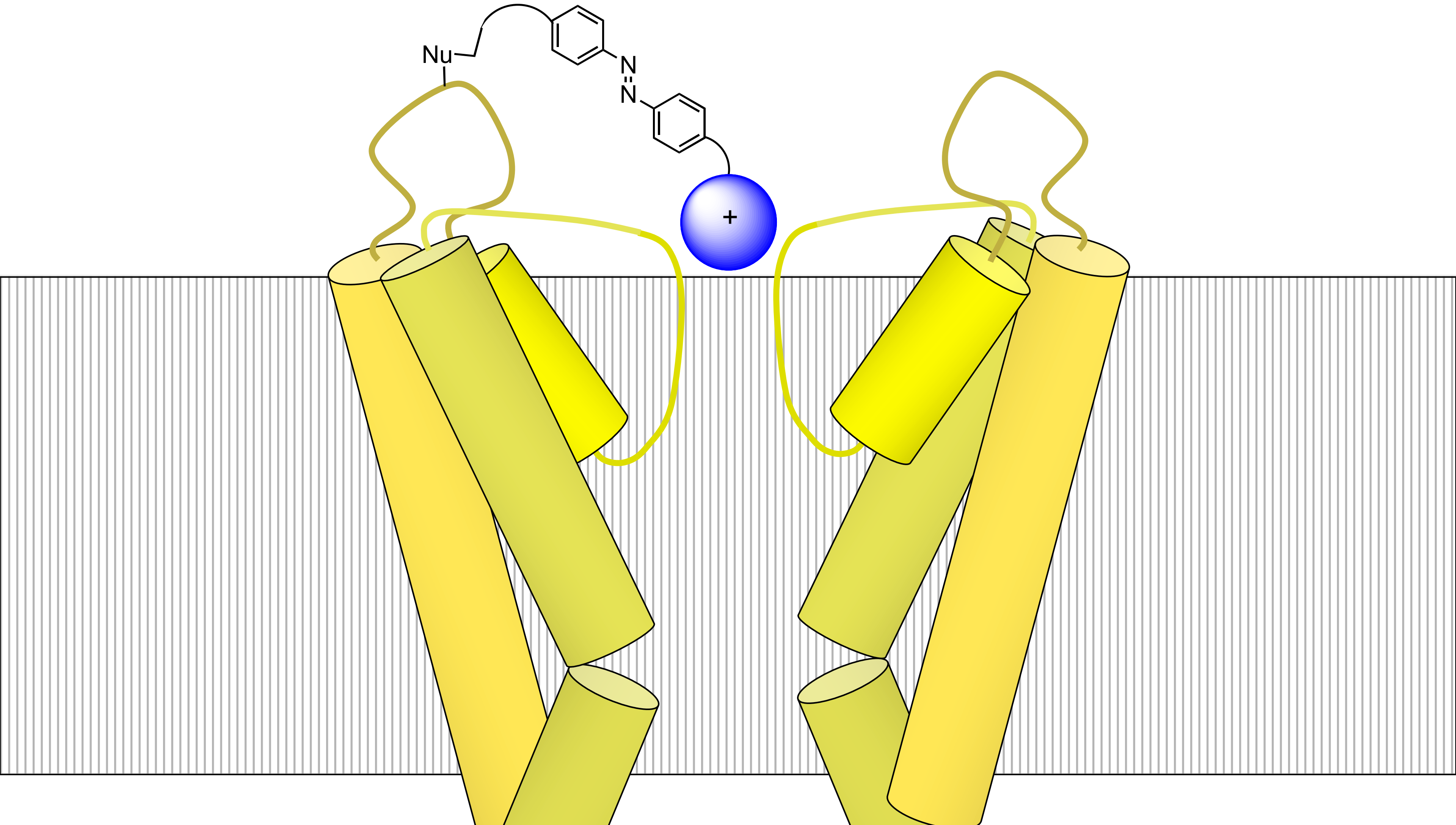


Nu
N
N
+
390 nm



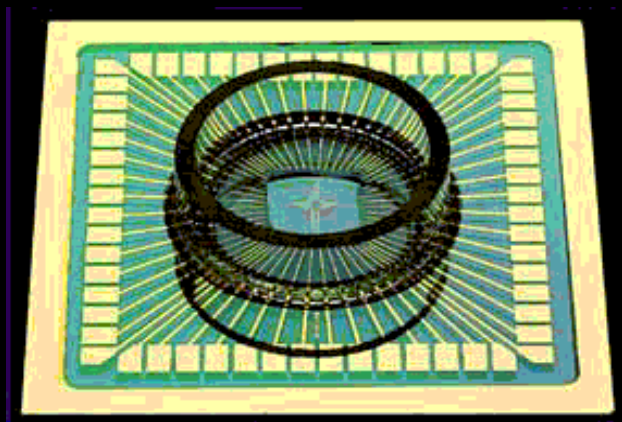
Nu
N=N

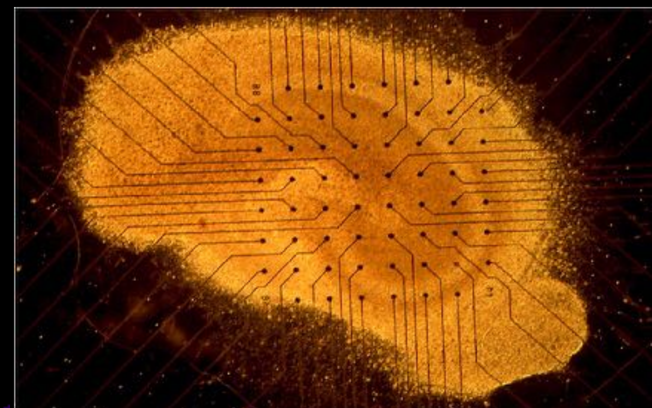

500 nm
Nu
N=N

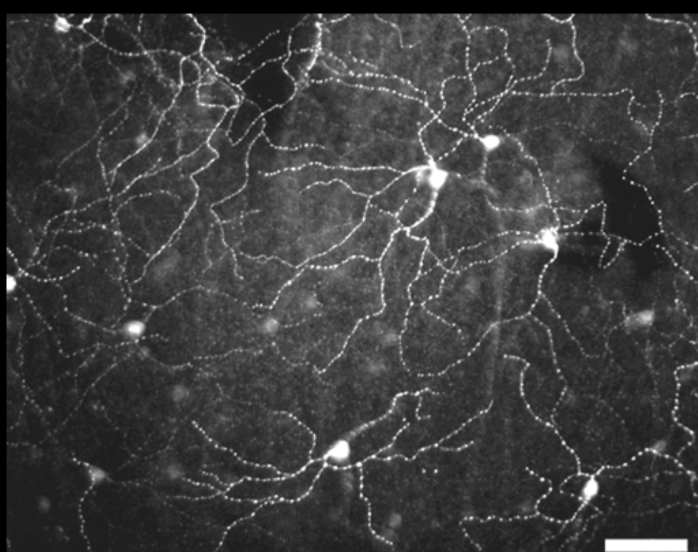


Nu
N
N
+

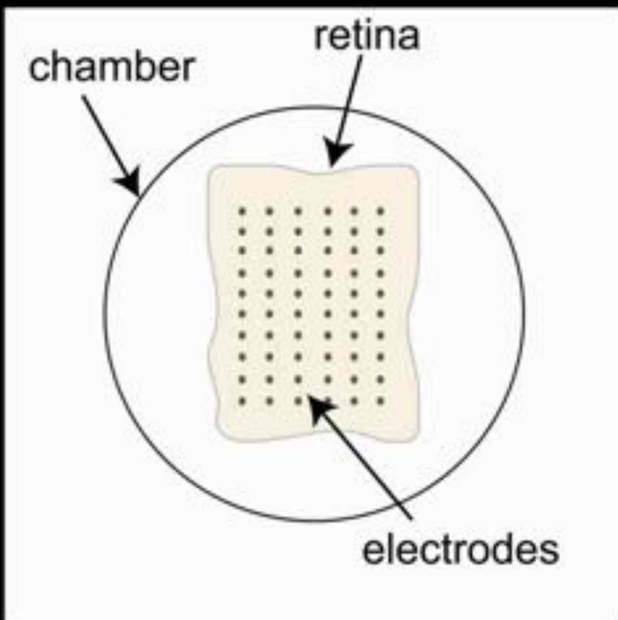
Multi-electrode arrays

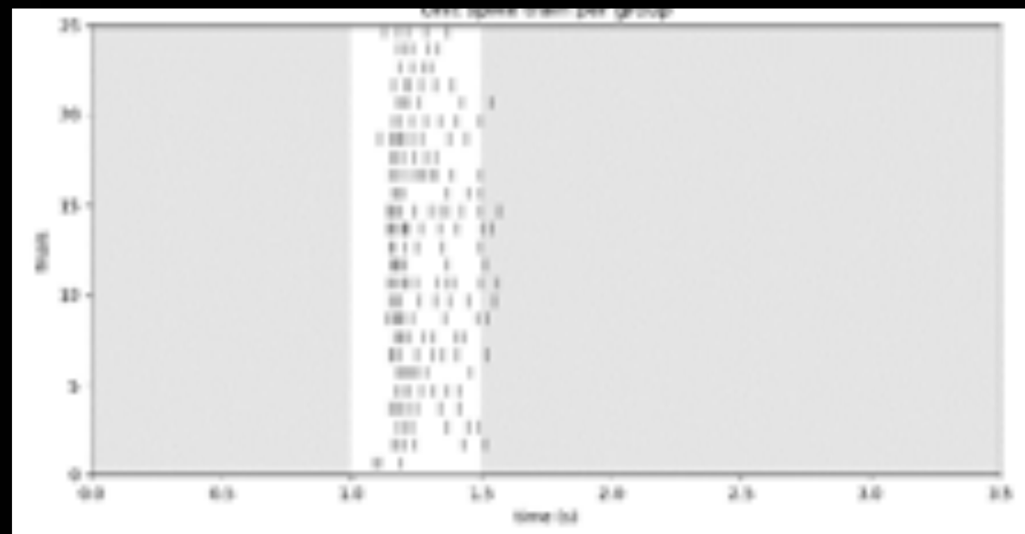




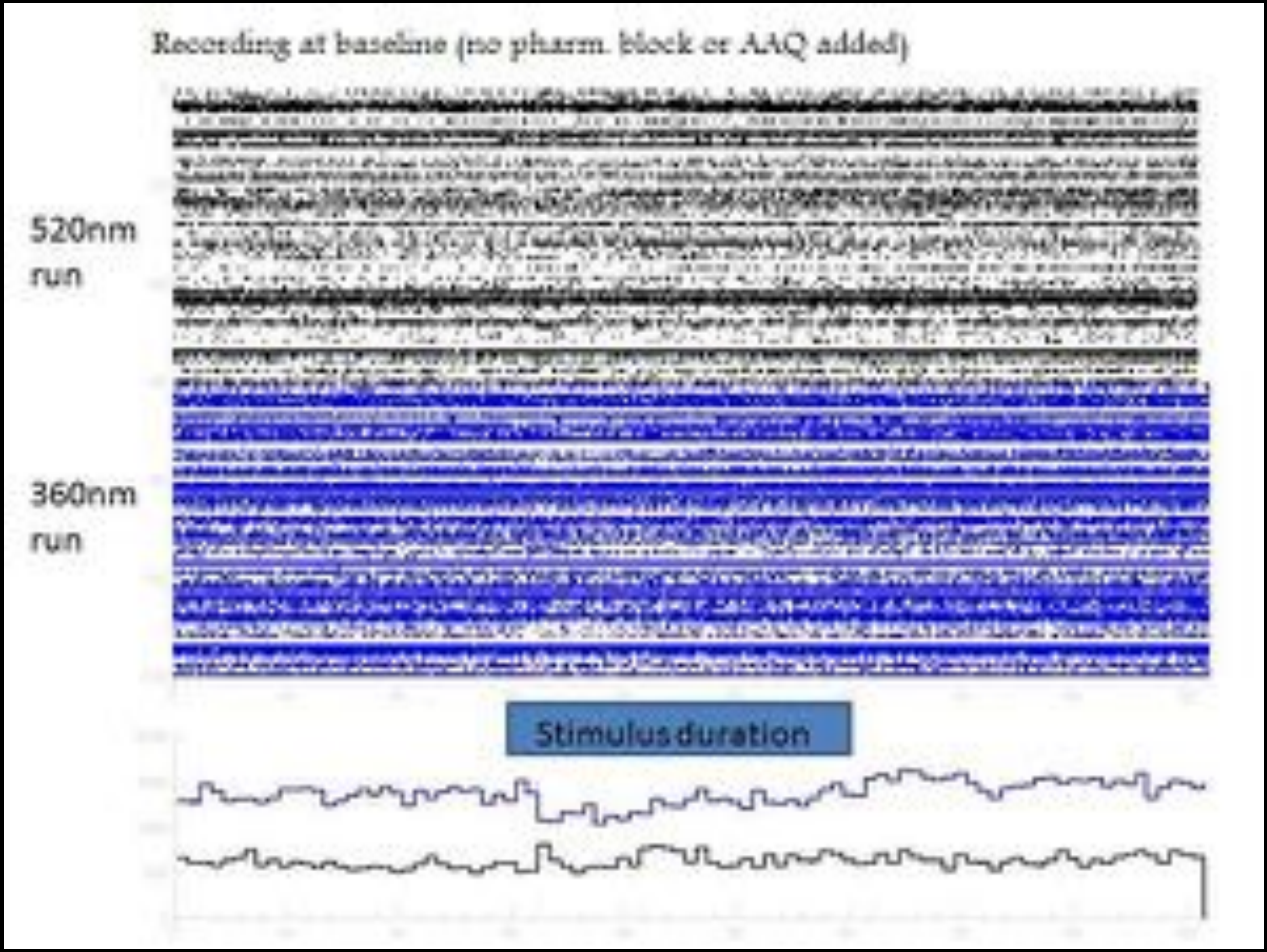


Multielectrode array recording

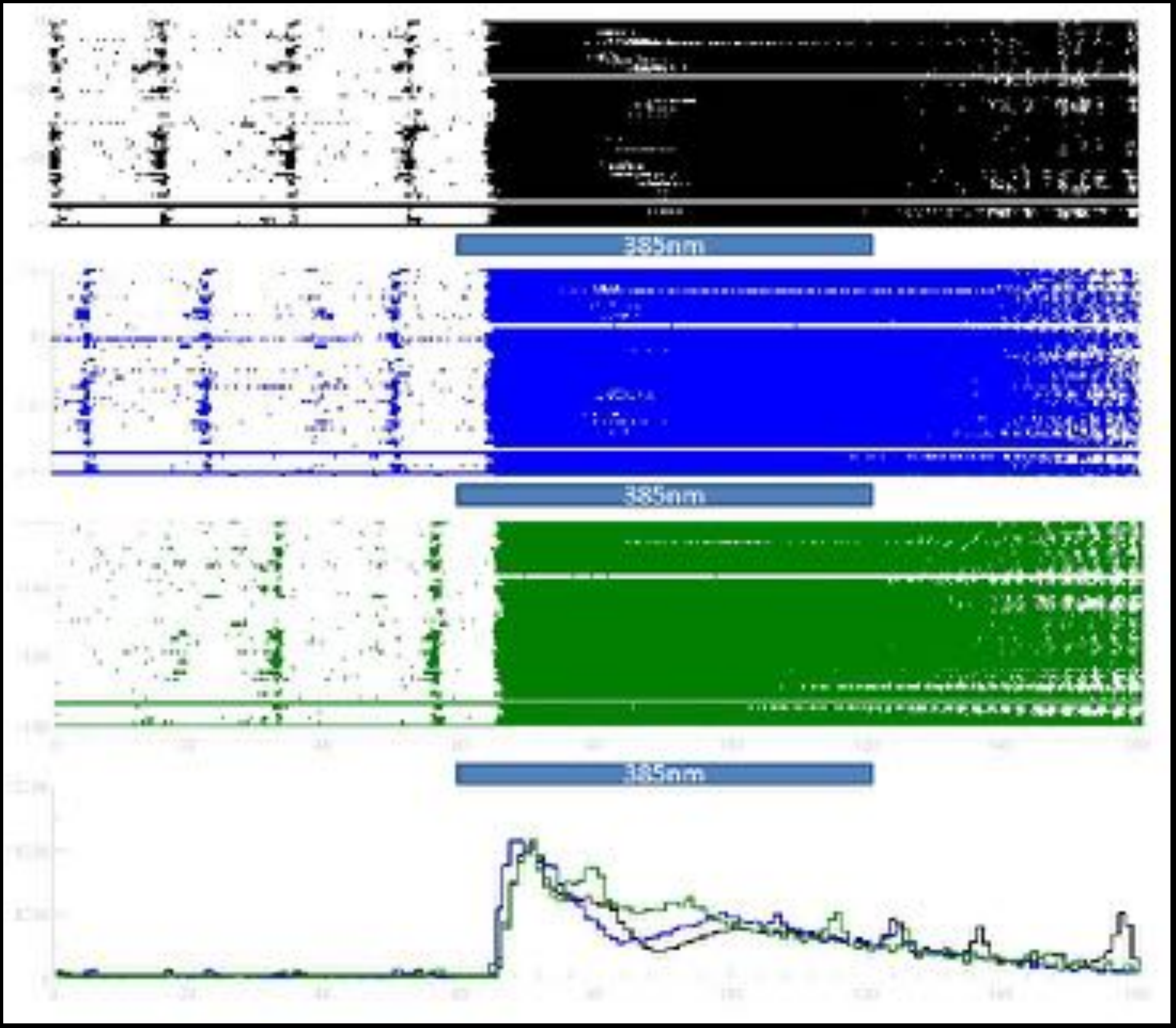




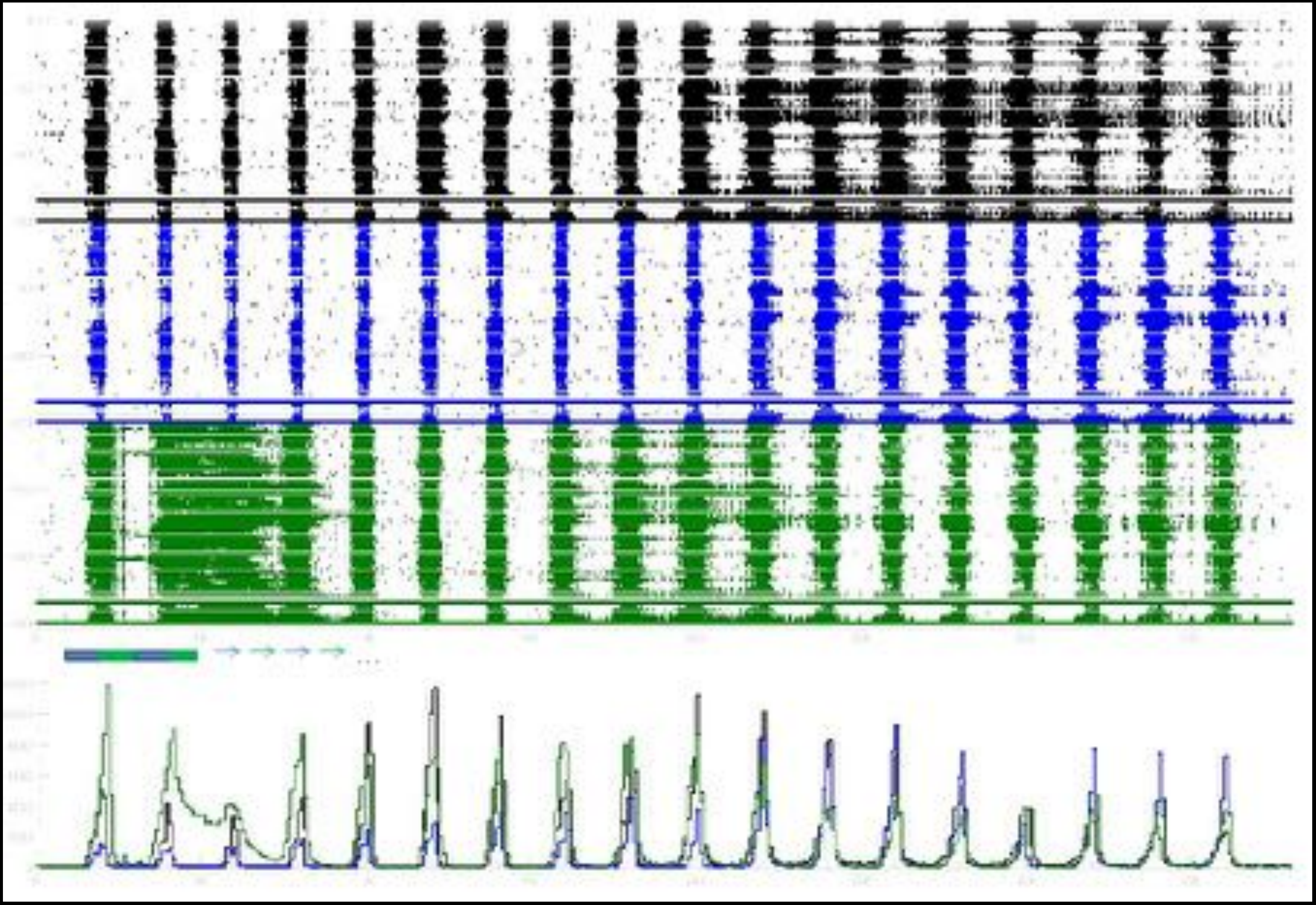
Multi-electrode recording of blind mouse retina



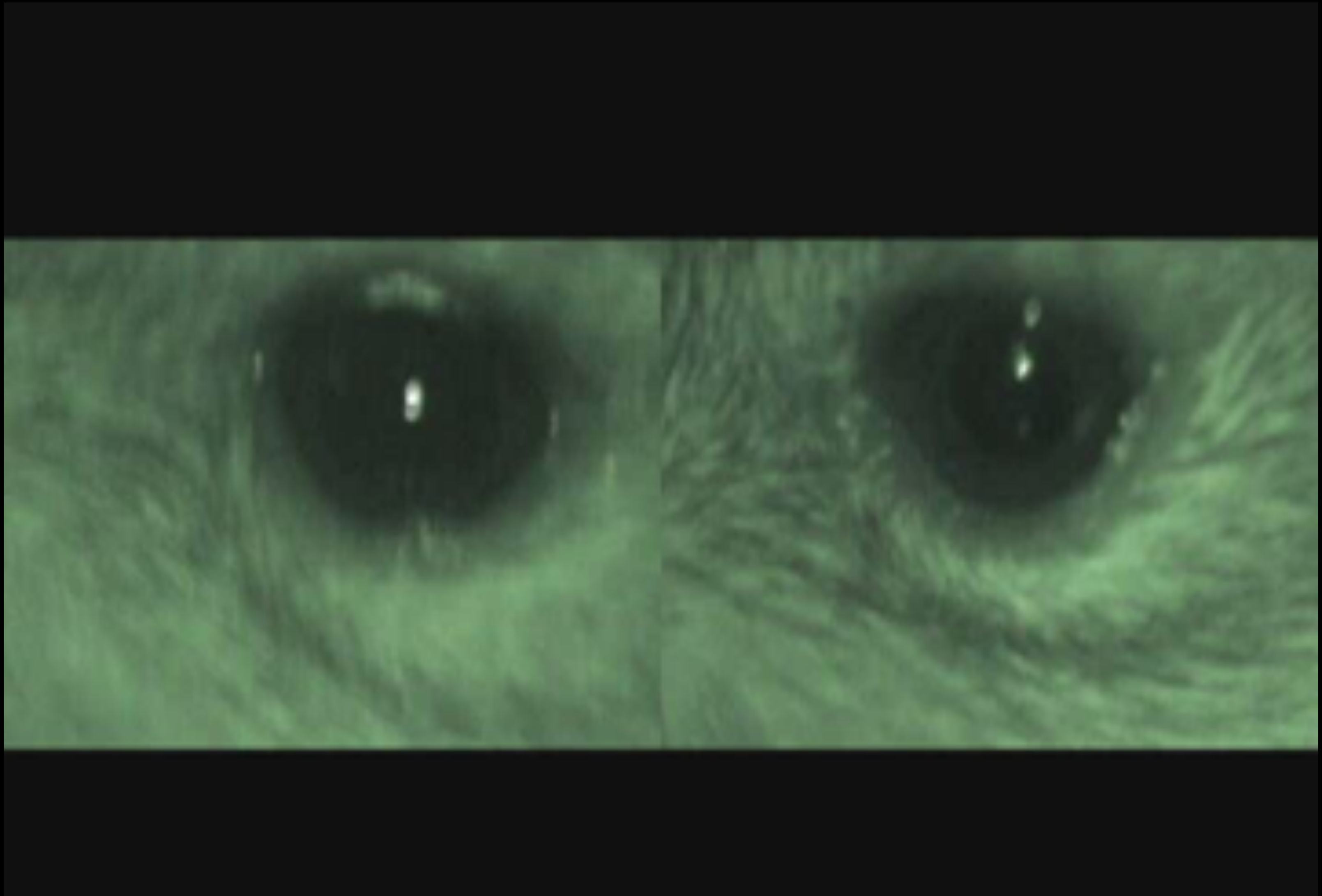
5 minutes after administration of AAQ



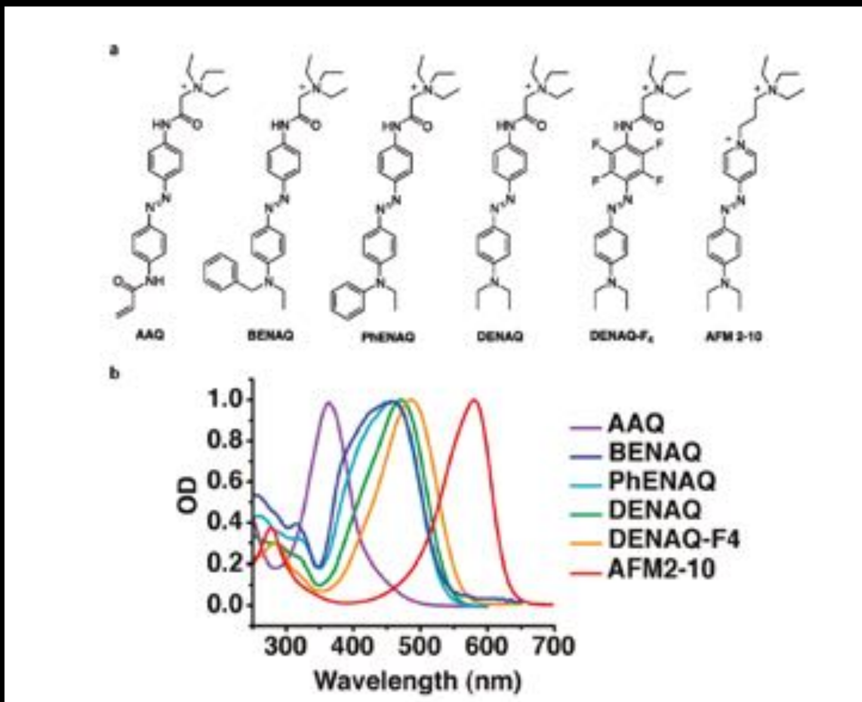
Repetitive firing after AAQ

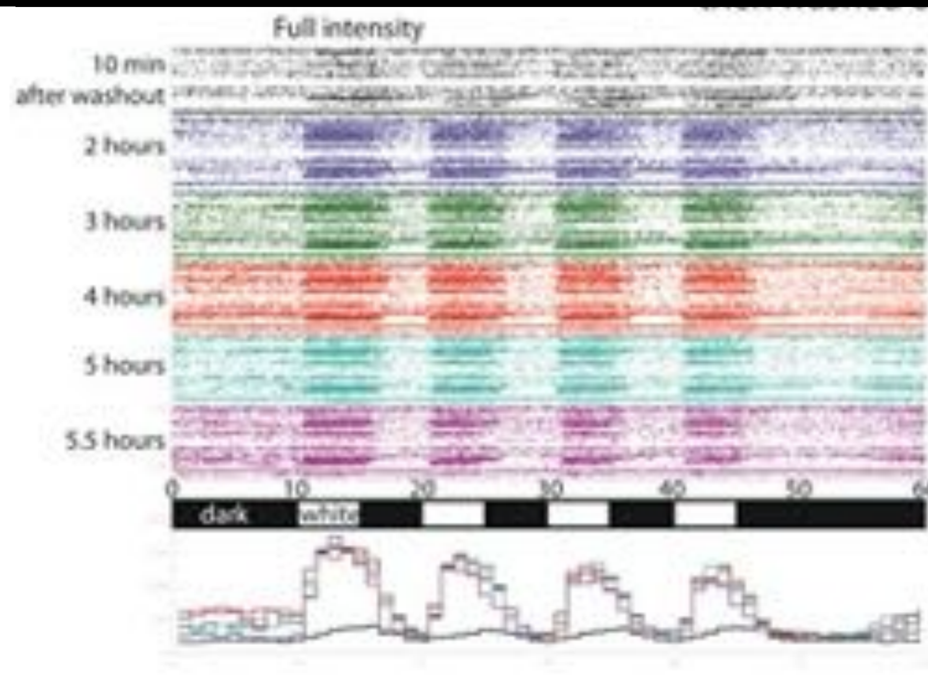


Restoration of the pupillary light response



Second generation photoswitches

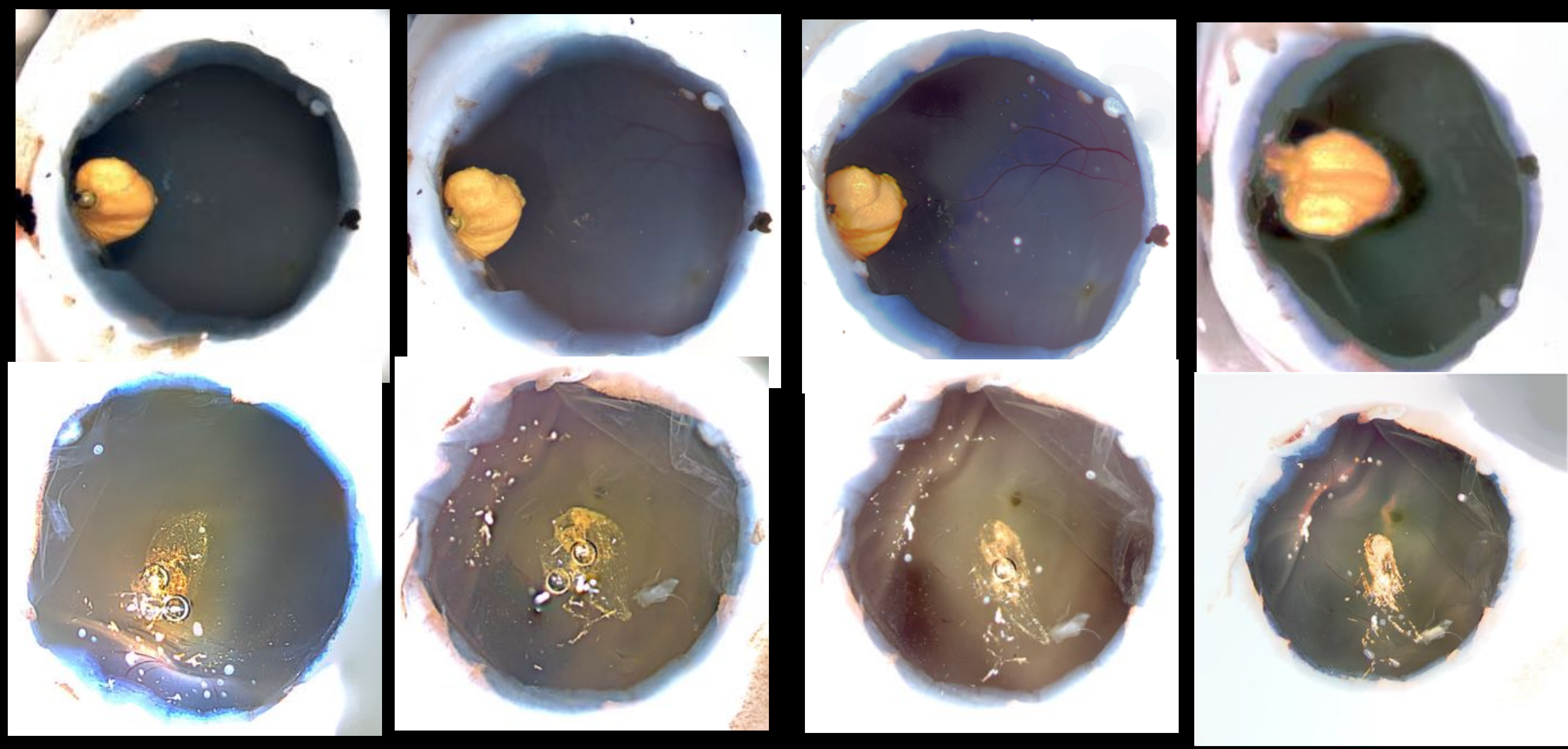




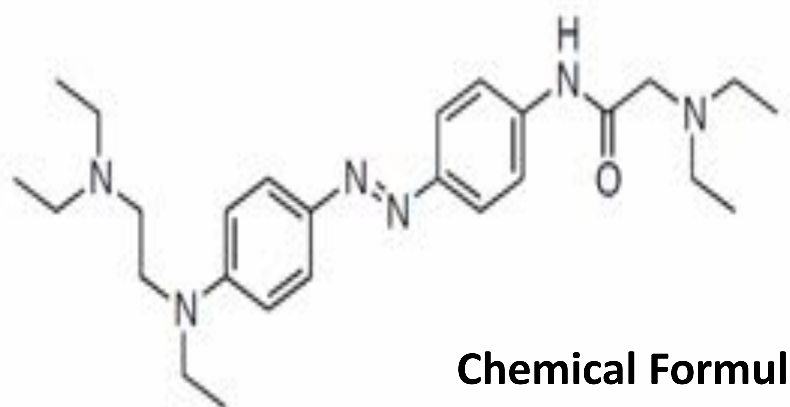
(Lack of) Diffusion of xAQ following intravitreal injection in cadaver macaque eyes

PhENAQ (5mM)

DENAQ (5mM)



Red-DAD: a 3rd Generation Photoswitch



Chemical Formula: $C_{26}H_{35}N_5O$
Molecular Weight: 444.60

Red-DAD HCl is highly soluble

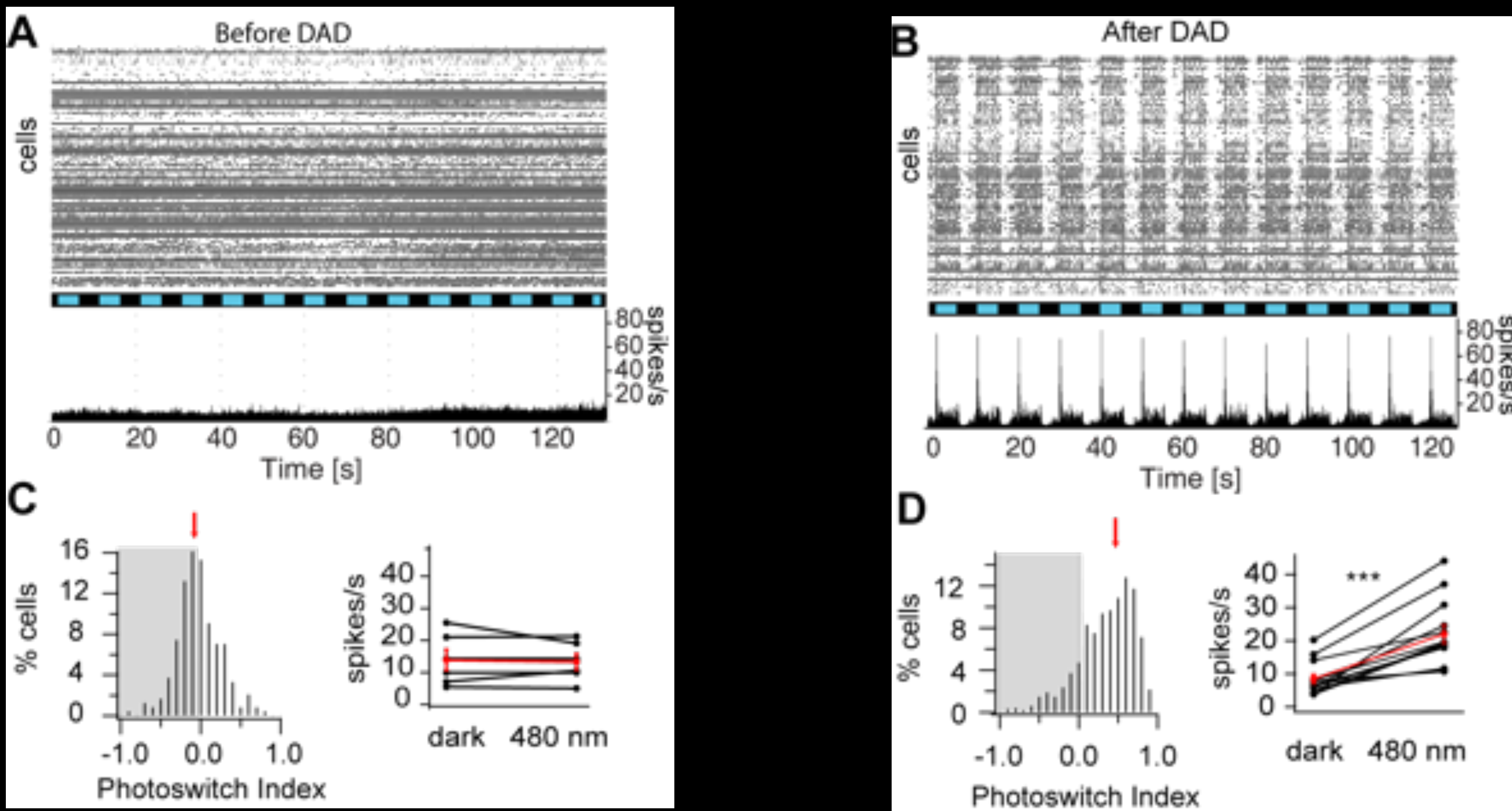
140325

Red-DAD (HCl) in Eylea

rD stock solution 100mM ddH2O

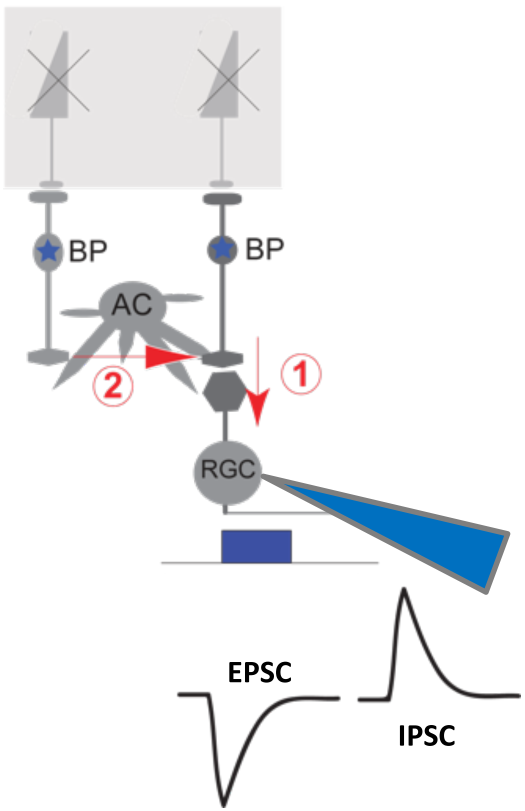
rD-HCl [mM]	0	0.25	1	5	25

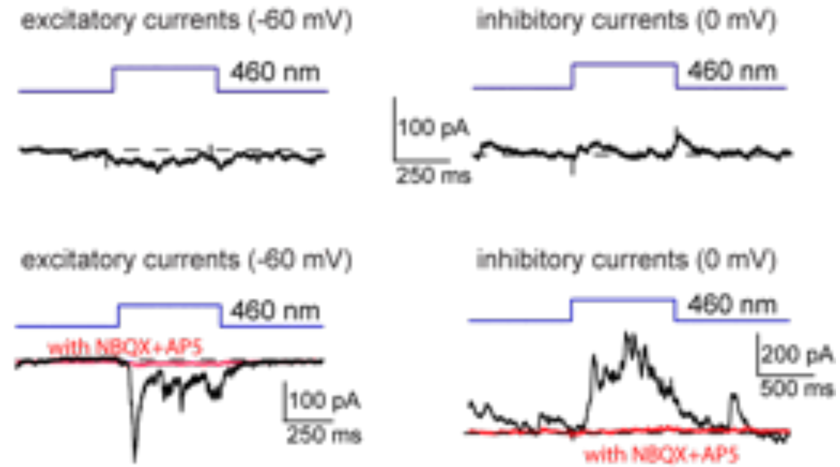
DAD photosensitizes blind retina on multi-electrode array

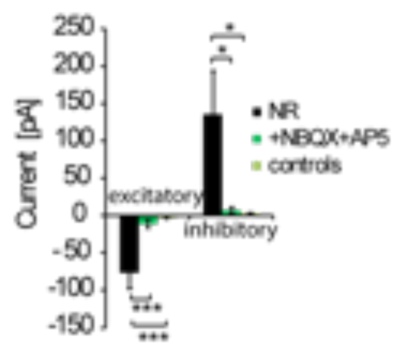


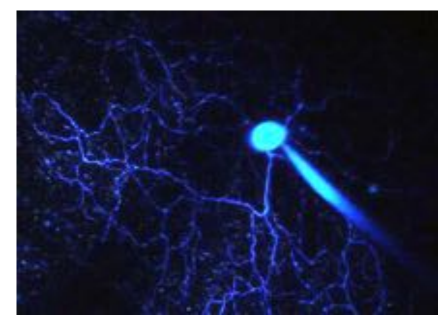
$$\text{Photoswitch Index} = \frac{\text{spiking frequency (light) - spiking frequency (dark)}}{\text{spiking frequency (light) + spiking frequency (dark)}}$$

DAD specifically targets bipolar cells



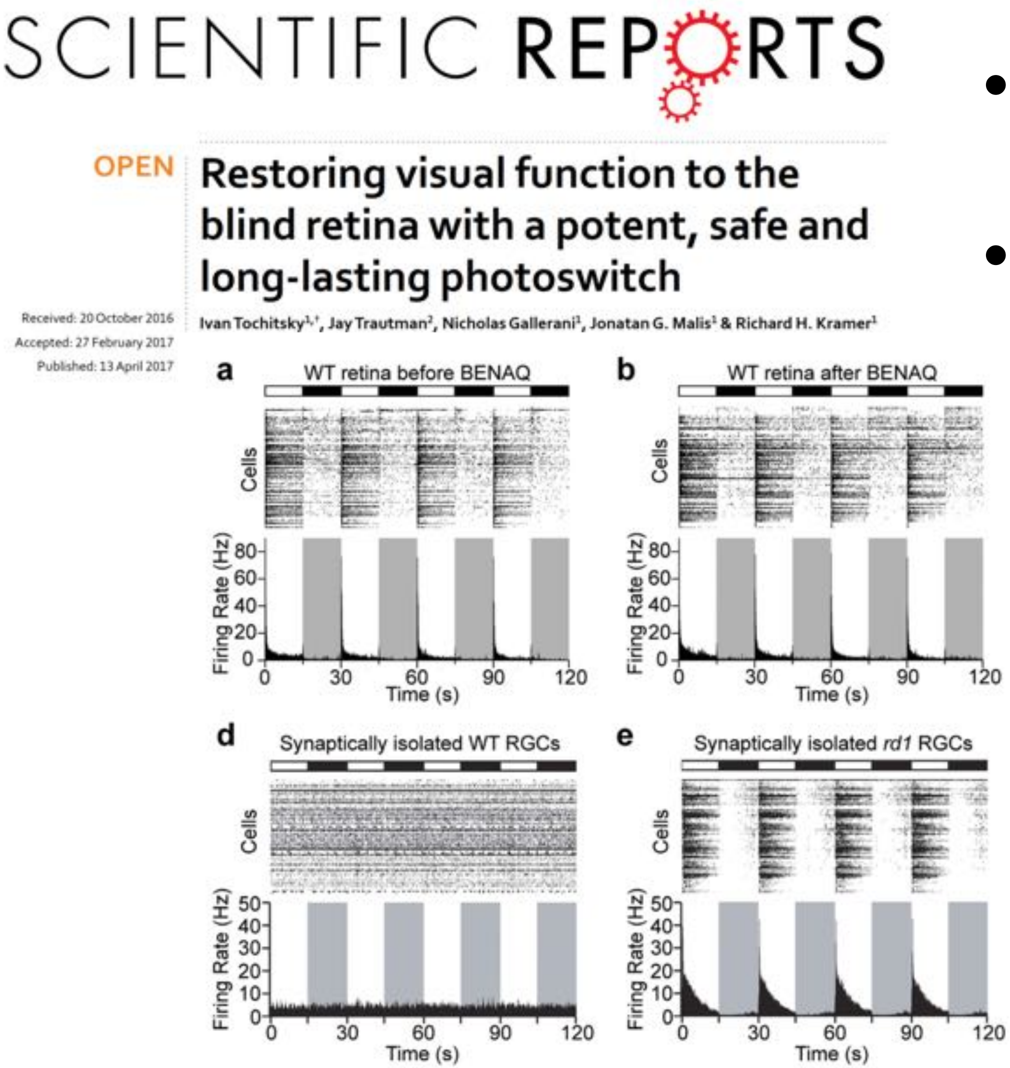






with Mike Manookin

Current status



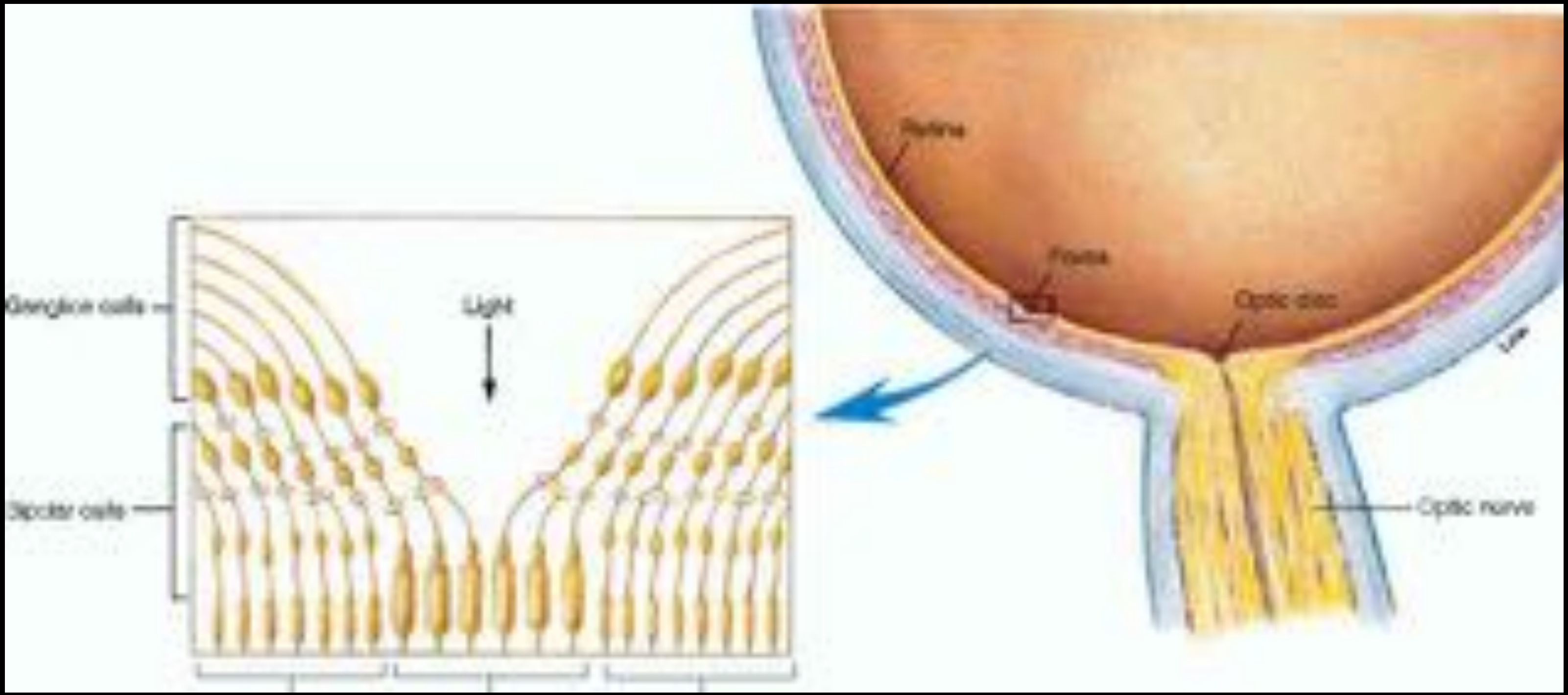
- Moving forward with BENAQ
- GMP-grade compound in cyclodextrin excipient

Being tested in *rd* dogs by William Beltran

Pursuing IND with Bayon Pharmaceuticals

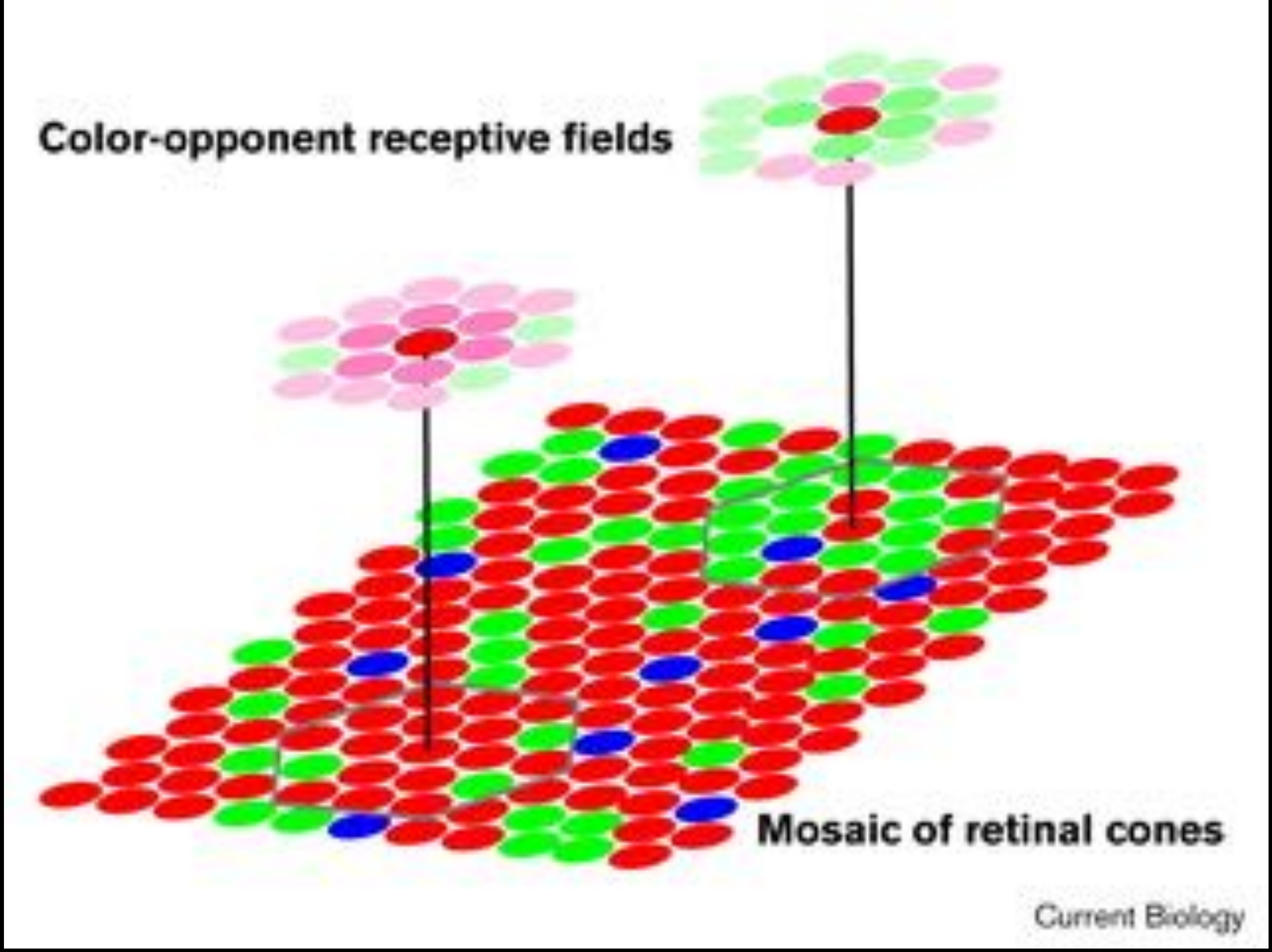
What does the mouse see?

Retinotopic mapping of photoreceptors and ganglion cells differ



Ganglion cell vision?

Synthetic vision drives overrides color opponency



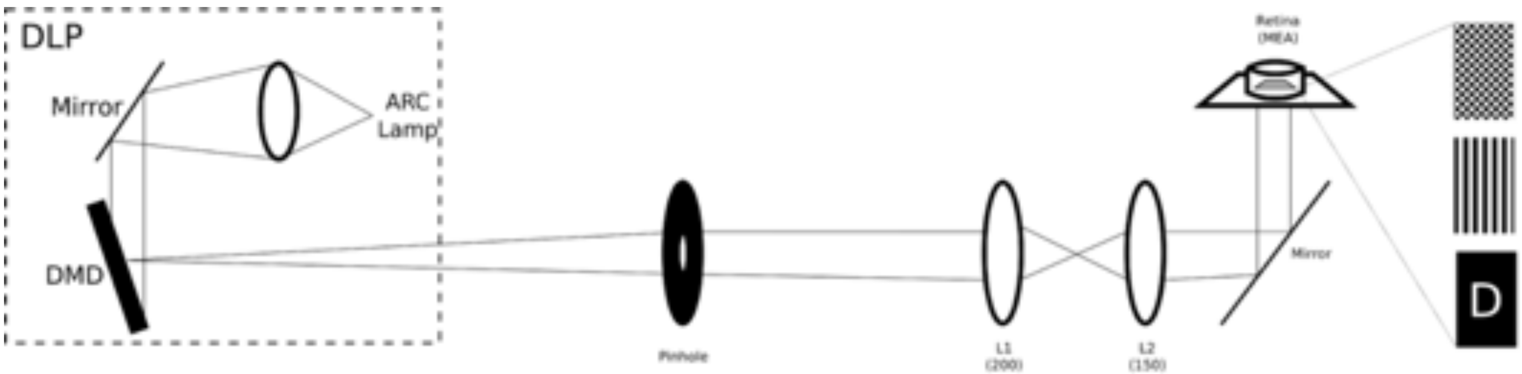
High density CMOS MEA

3D Brain/ALA Systems

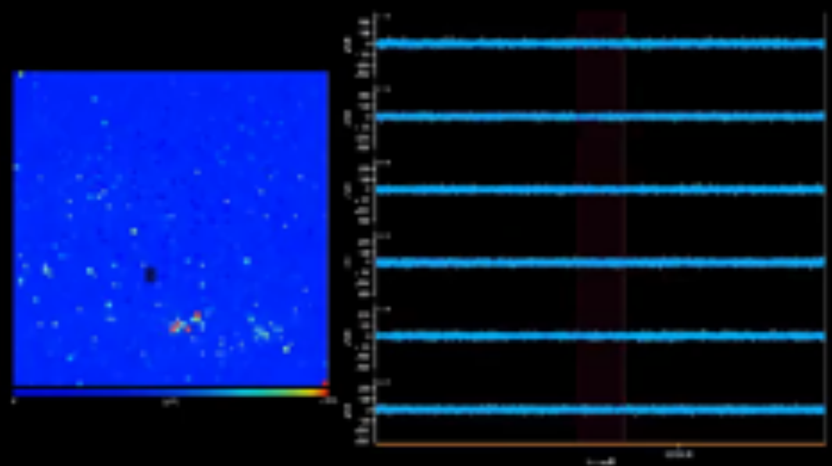
4096 channel

Coverage of full retina on single array

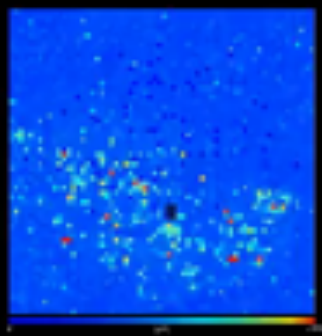
Projector schematic

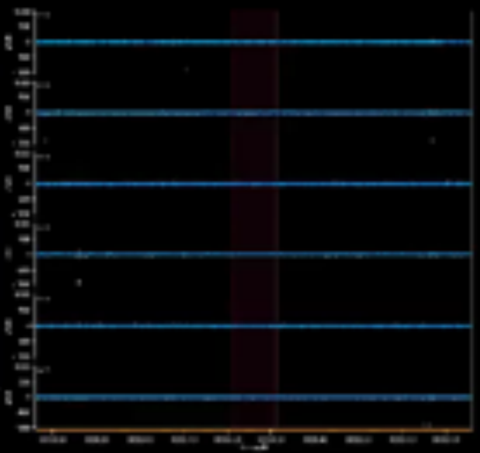


Stimulus: moving bar

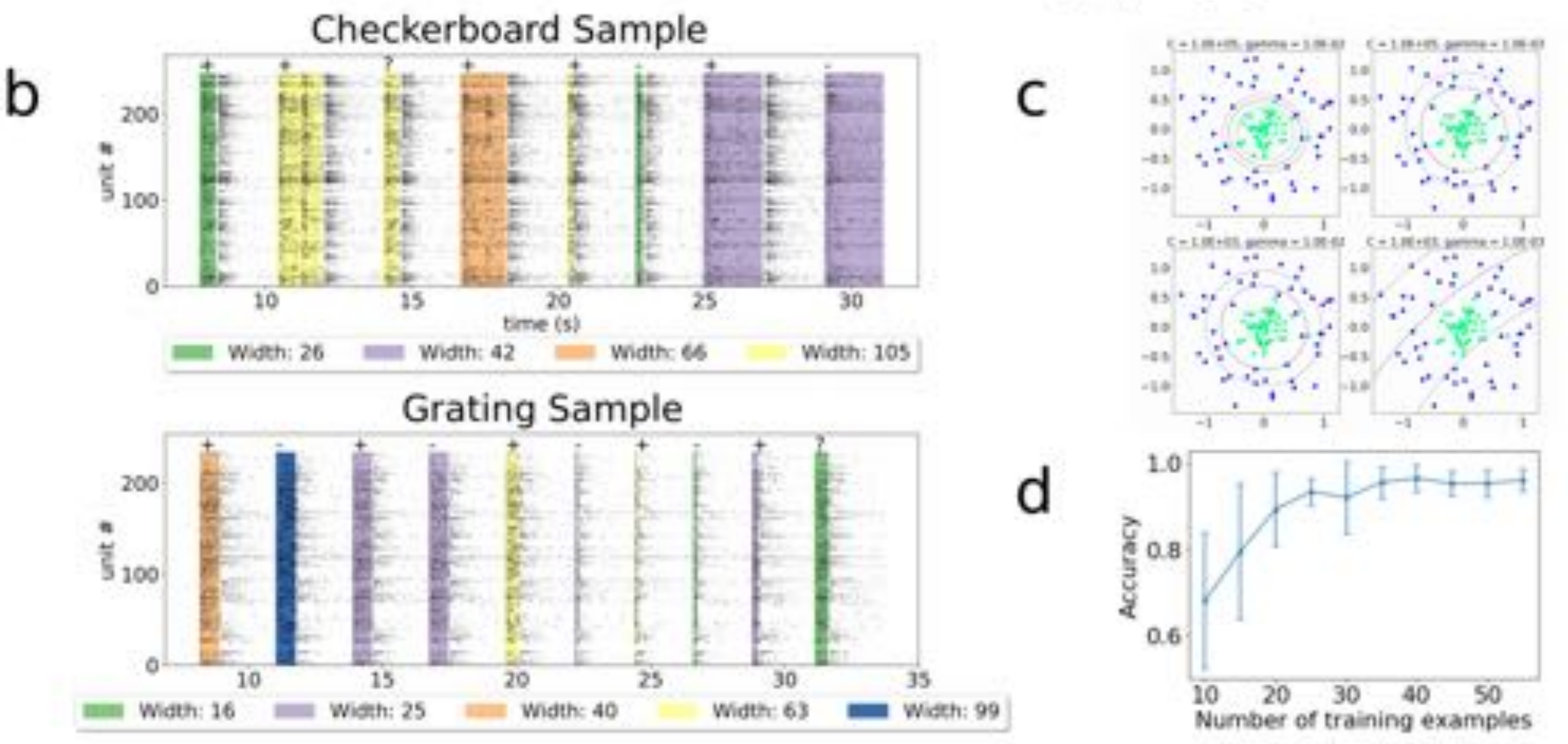


Stimulus: Contrast grating



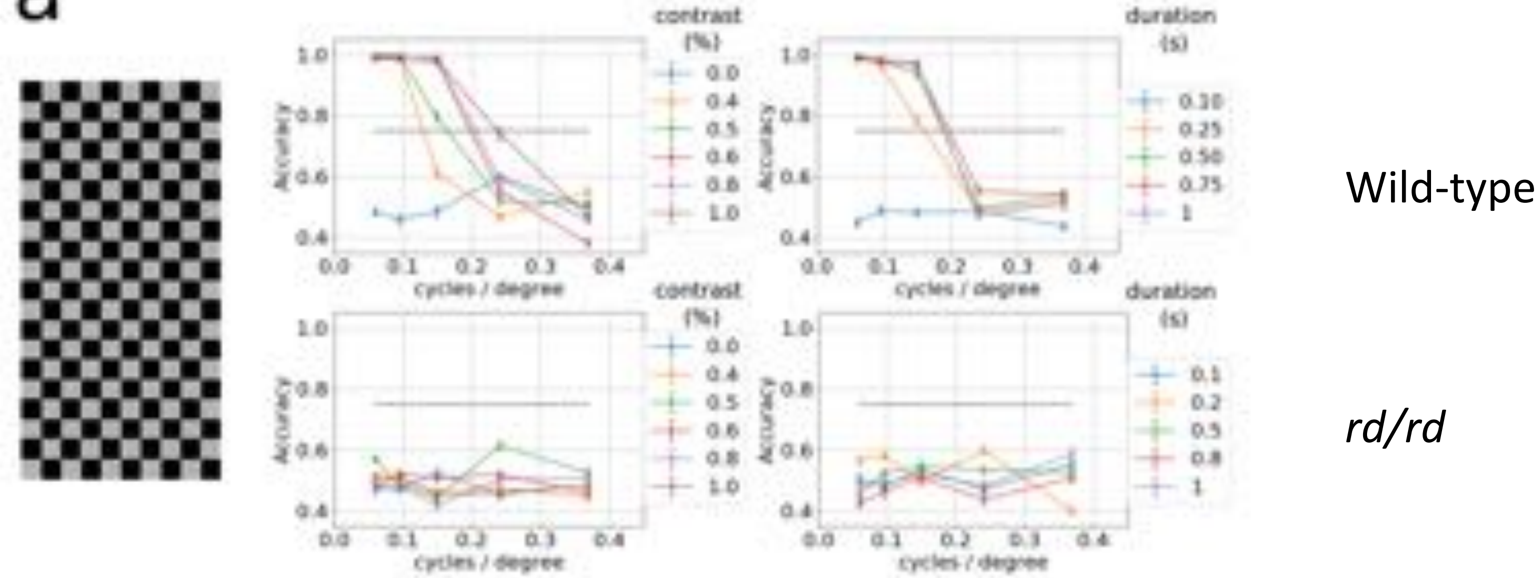


Machine learning of retinal output to projected images

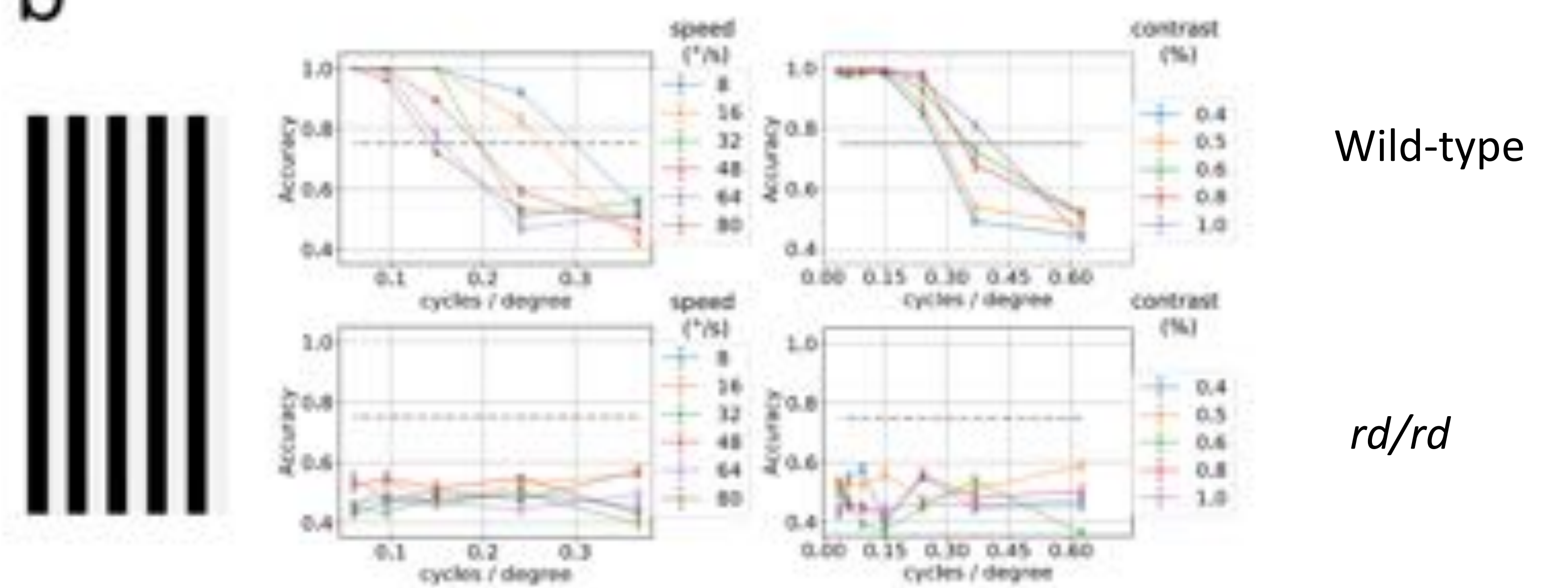


Retinal acuity of wild-type and *rd/rd* mice

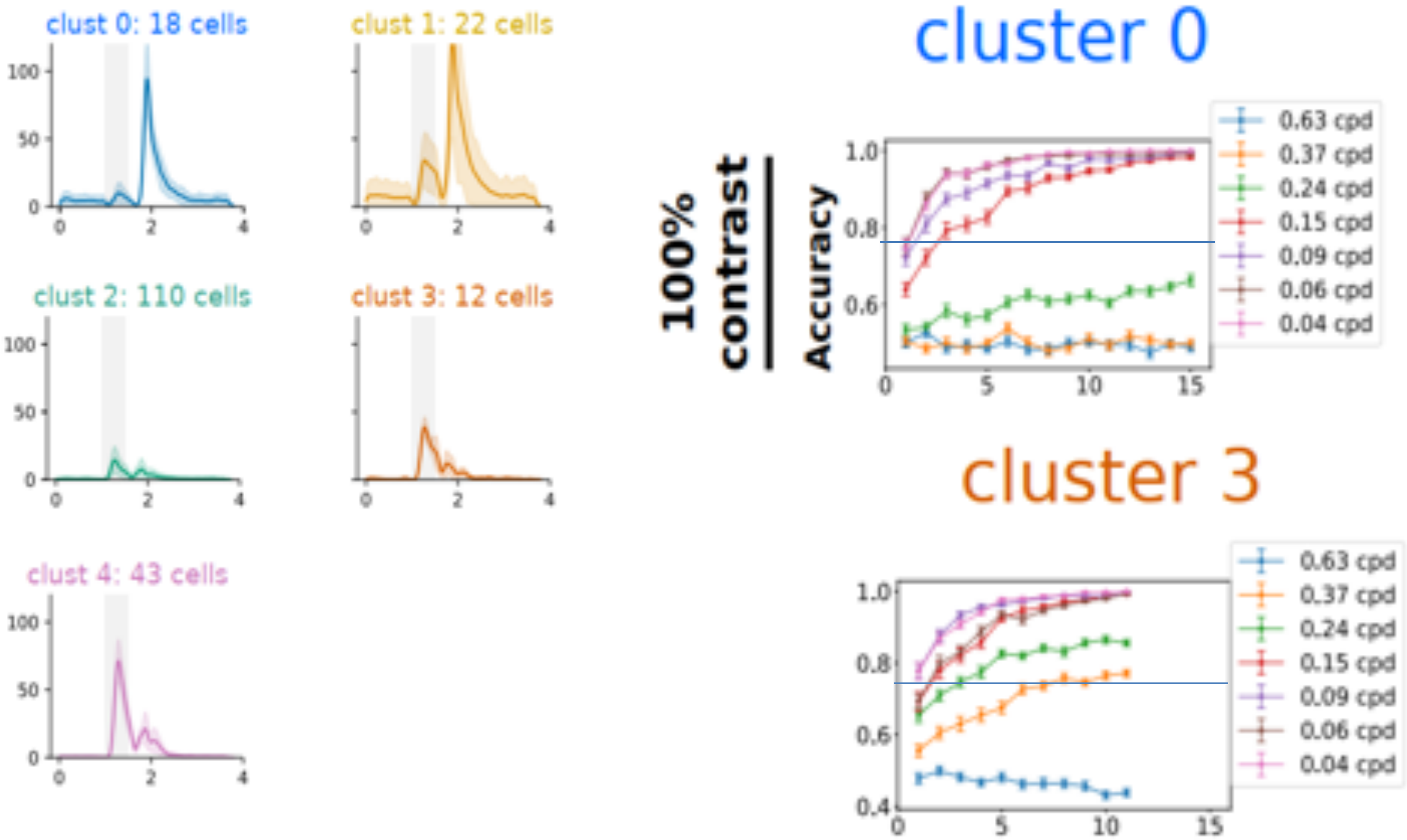
a



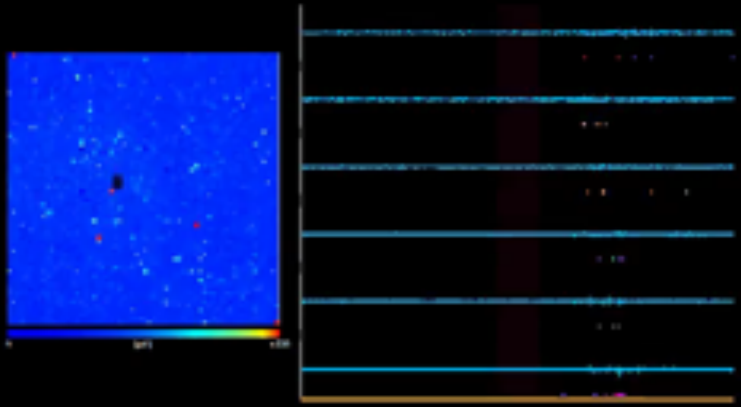
b



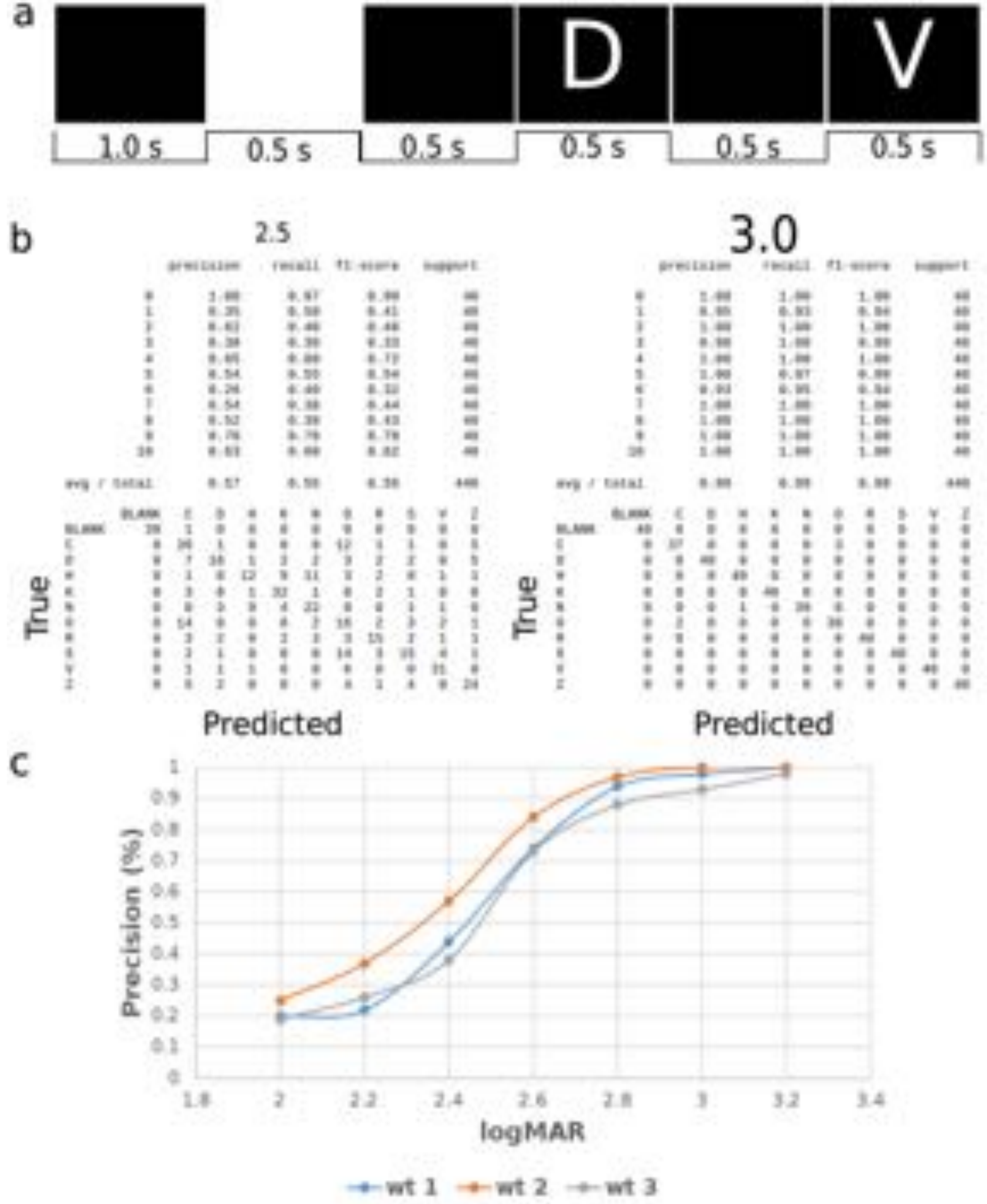
What information gives rise to acuity?



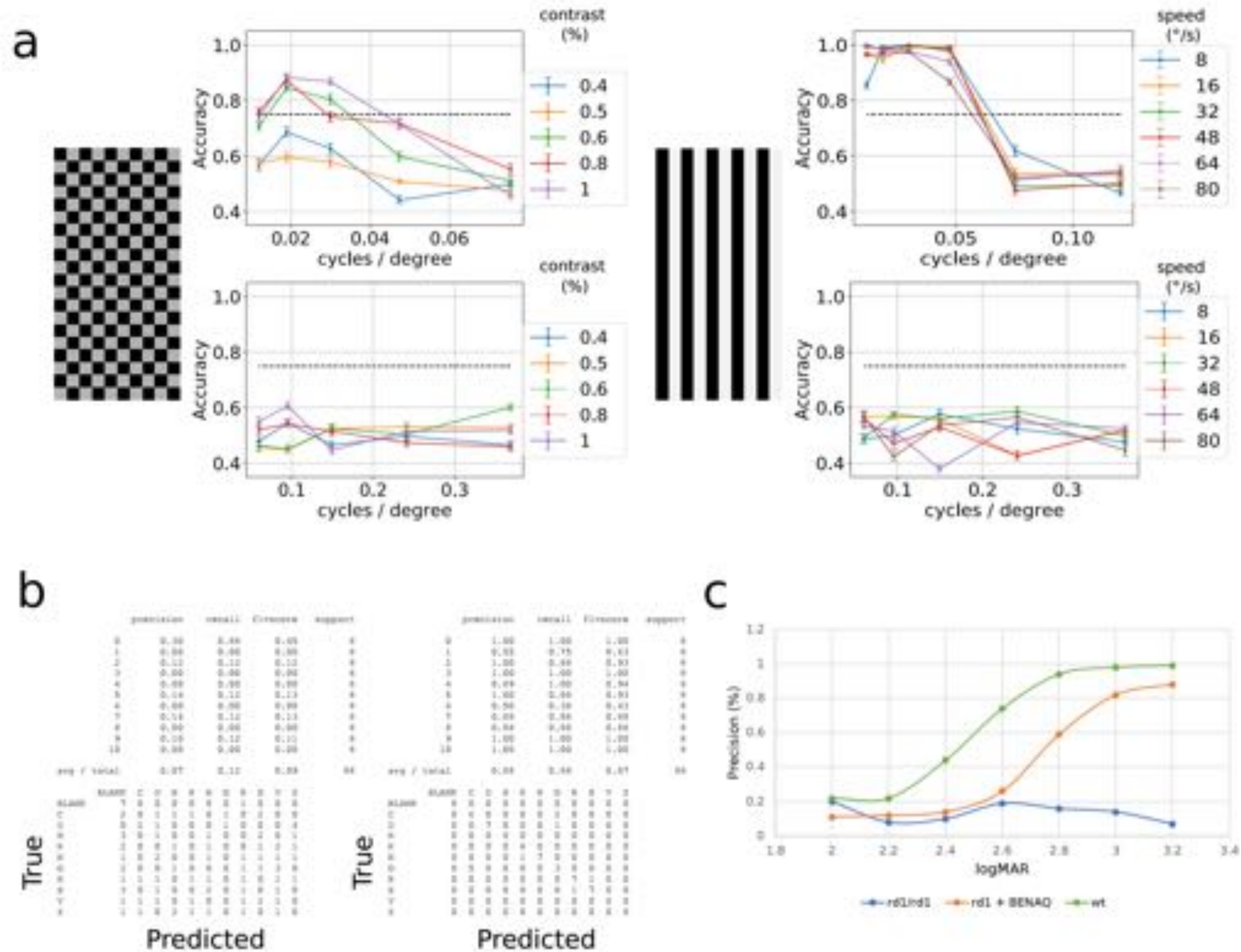
Stimulus: ETDRS Letters



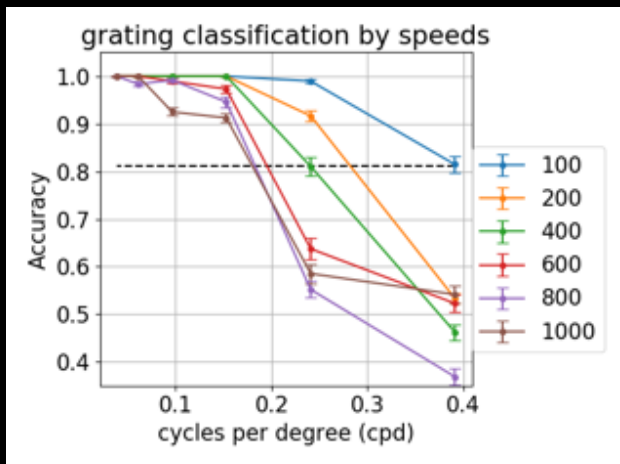
Murine retinal acuity to ETDRS letters *in vitro*



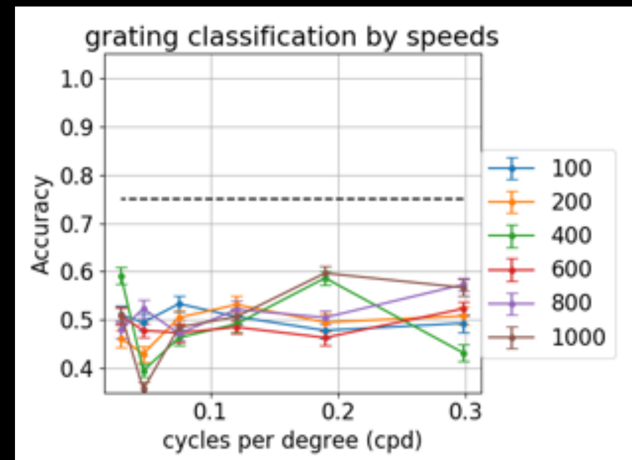
Retinal acuity restored by BENAQ



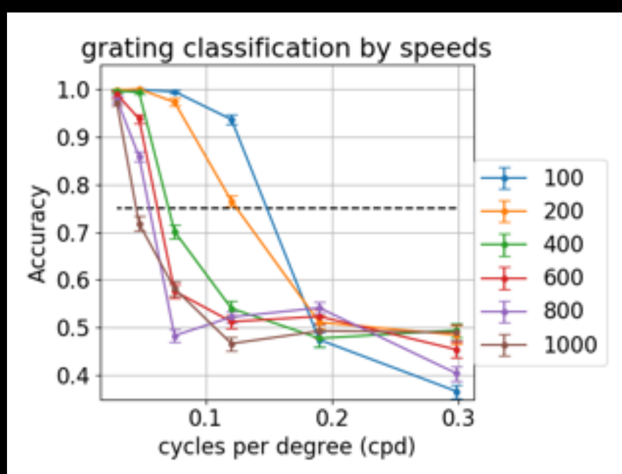
Comparing two photoswitches



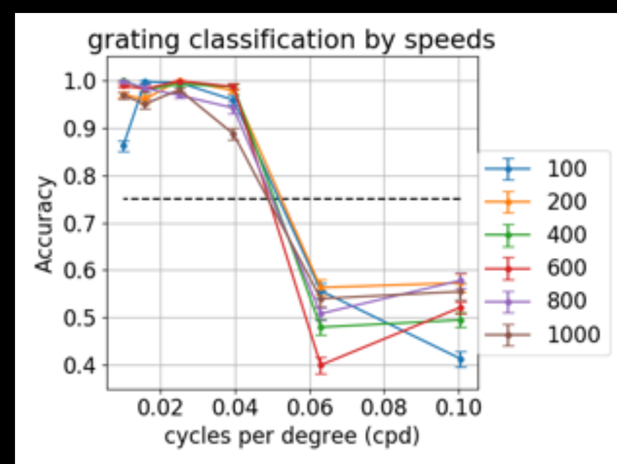
Wild type



rd/rd



DENAQ



BENAQ

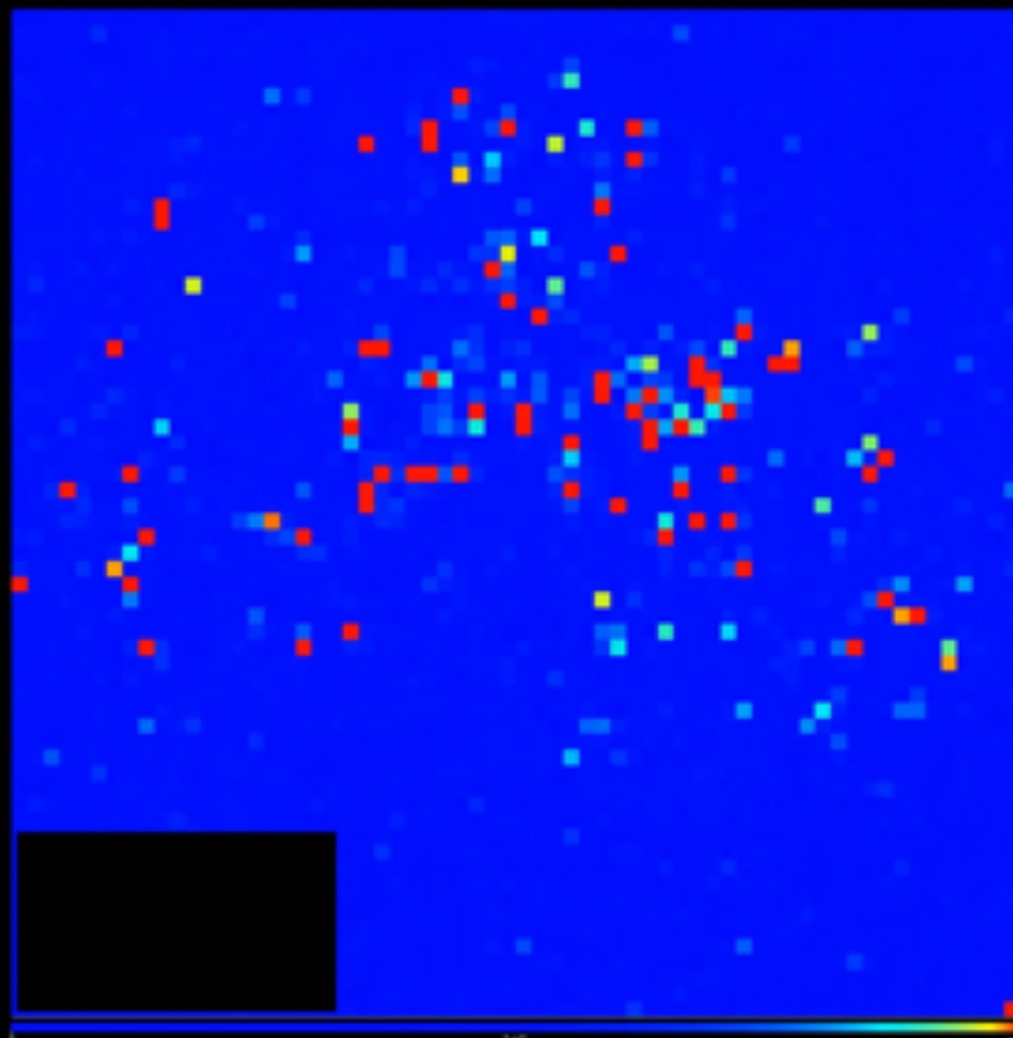
Real world application: facial reconstructions

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