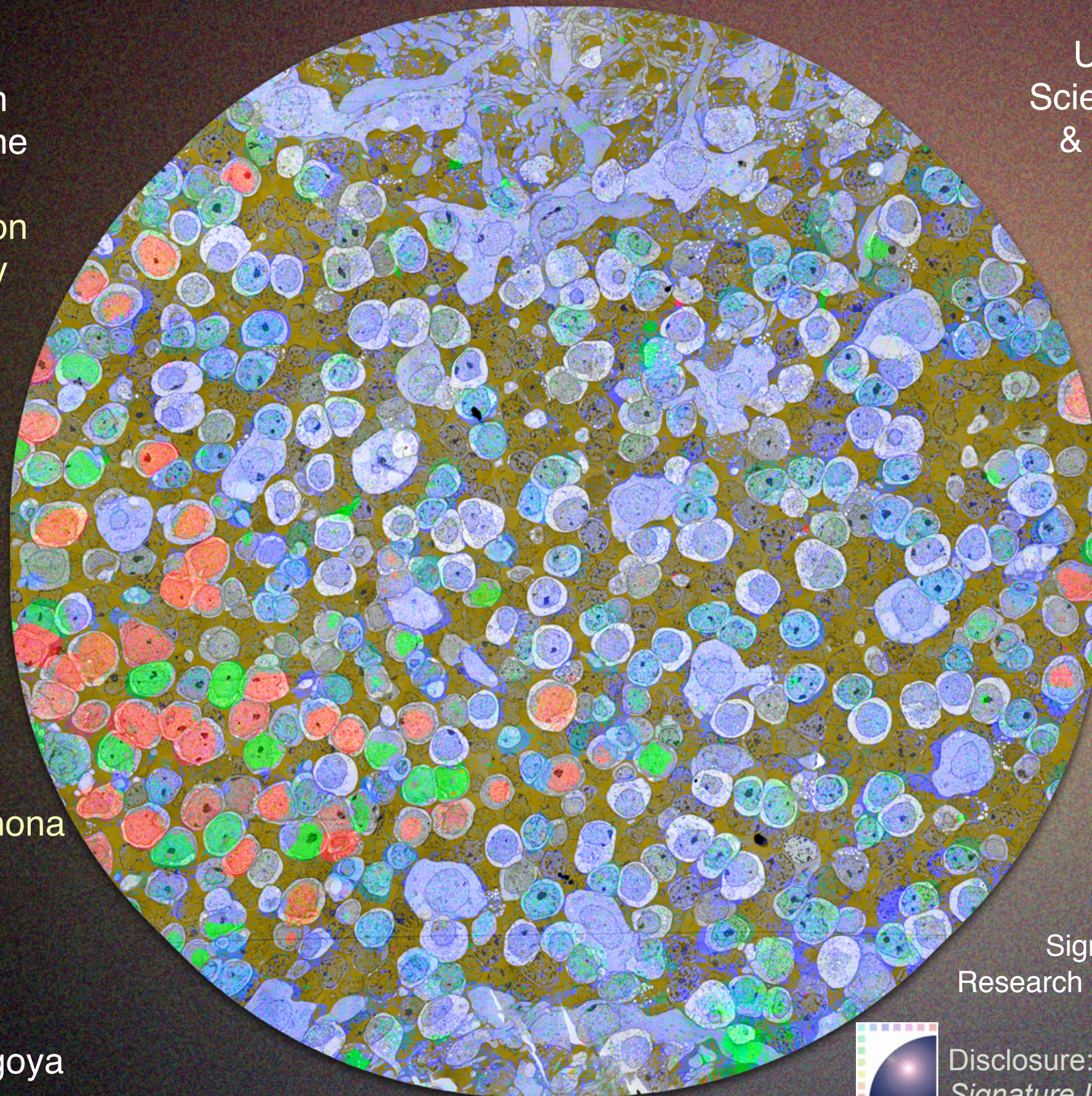


RETINAL REMODELING & NEURODEGENERATION



University of Utah
School of Medicine
MarcLab
James R Anderson
Crystal Sigulinsky
J Scott Lauritzen
Rebecca Pfeiffer
Jefferson Brown
Danny Emrech
Jia-Hui Yang
Bryan W Jones
Carl B Watt
Maggie Shaw
Kevin D Rapp
Hope Morrison
Noah T. Nelson
Nathaniel Nelson
Felix Vazquez-Chona

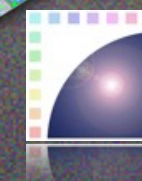
Mei University
Mineo Kondo

University of Nagoya
Hiroko Terasaki

University of Utah
Scientific Computing
& Imaging Institute
Pavel Koshevoy
Elizabeth Jurrus
Tolga Tasdizen
Ross Whitaker
Ethan Kerzner
Mariah Meyer
Alan Morris

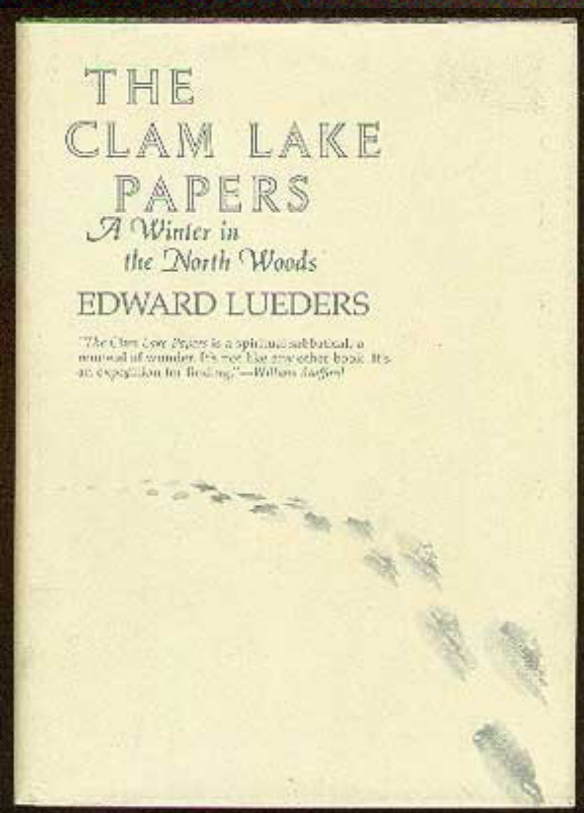
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NIH R01 EY015128
NIH P30 EY014800
NIH T32 EY024234
NIH R01 EB005832
NSF 0941717

Signature Immunologics
Research to Prevent Blindness



Disclosure: REM is a principal of
Signature Immunologics, Inc.

Edward Lueders
b 14 February 1923



Ed Lueders at 90
Jazz Piano



Guy Tal Photography



P.O. Box 750397
Torrey, UT 84775
USA

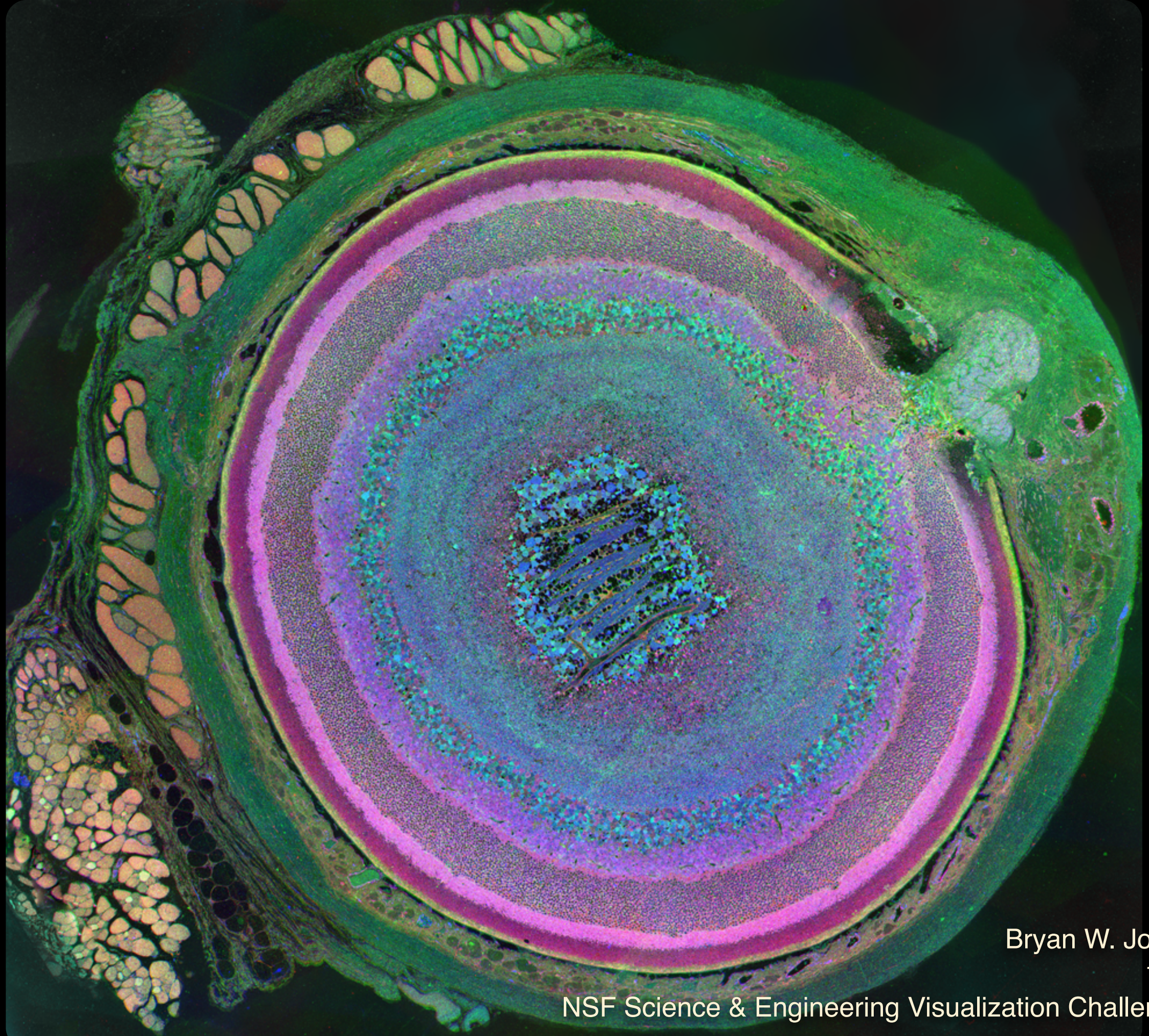
Email: info@guytal.com

guytal.com

Late Autumn on the Plateau
© Guy Tal 2015



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WWW.GUYTAL.COM



Bryan W. Jones PhD
1st Place

NSF Science & Engineering Visualization Challenge 2011

Connectomics and retinal complexity

Degeneration kinetics

Remodeling

Neurodegeneration

Connectomics and retinal complexity

Connectomics and retinal complexity

A connectome is the complete graph (the adjacency matrix) of a neural volume that describes all partners and non-partners.

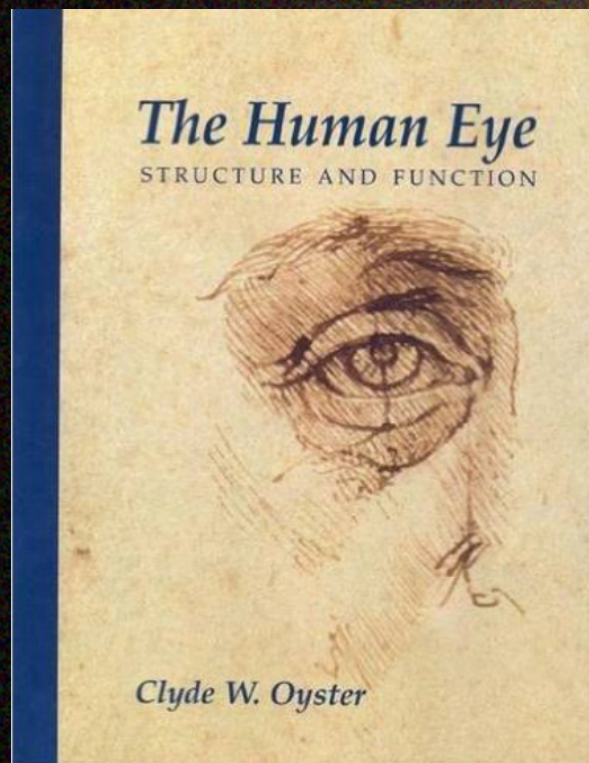
Building retinal connectomes

Robert E Marc, Bryan W Jones, J Scott Lauritzen, Carl B Watt & James R Anderson

Current Opinion in Neurobiology 2012, 22:568–574

THE SEEDS OF CONNECTOMICS

CLYDE W. OYSTER
1940-2016



1978
A plan for a complete
retinal network map





Jia-Hui Yang MS
Ultramicrotomy



James Anderson PhD
Sr Software Dev



J Scott Lauritzen PhD
Janelia Farm

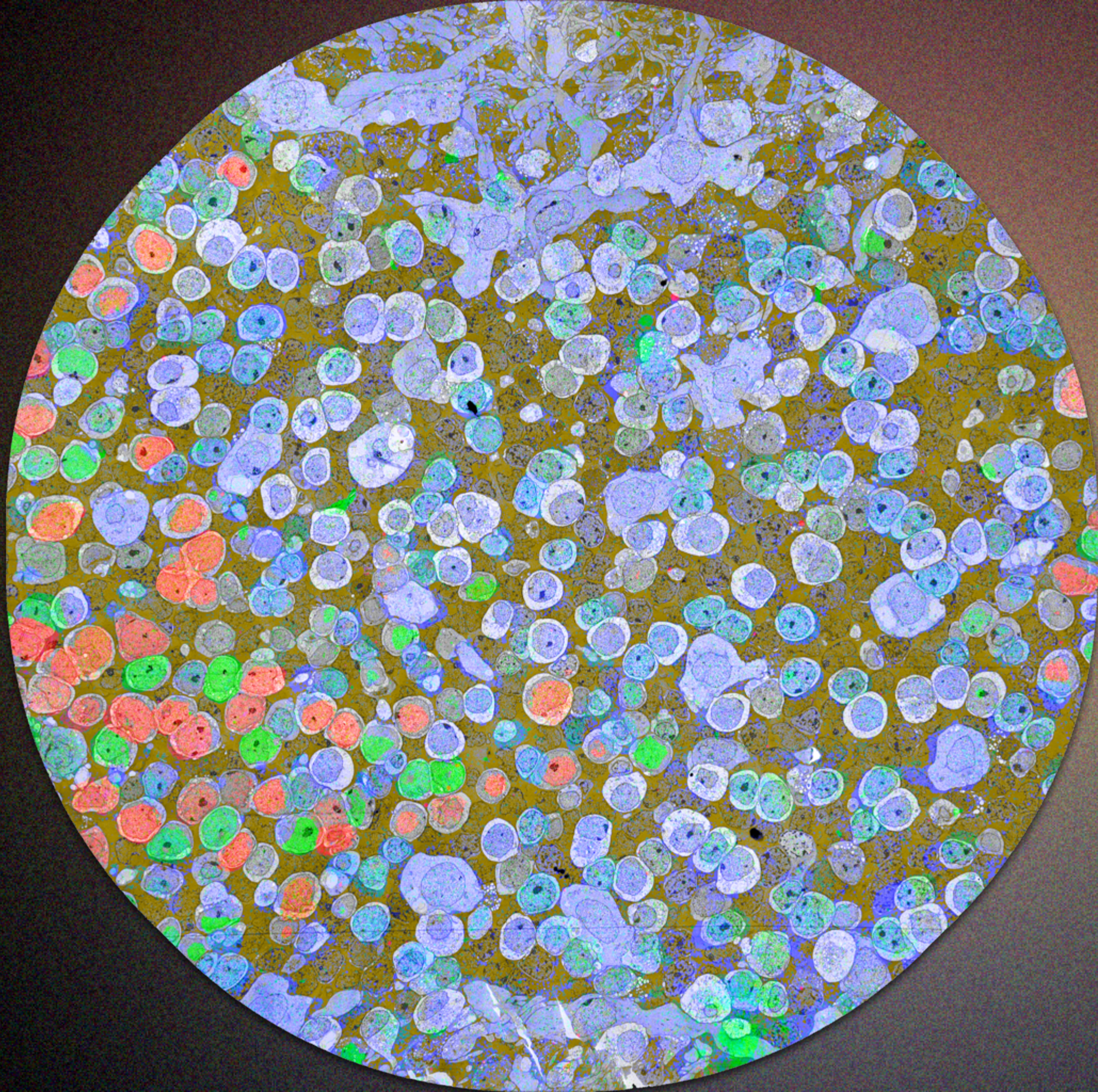


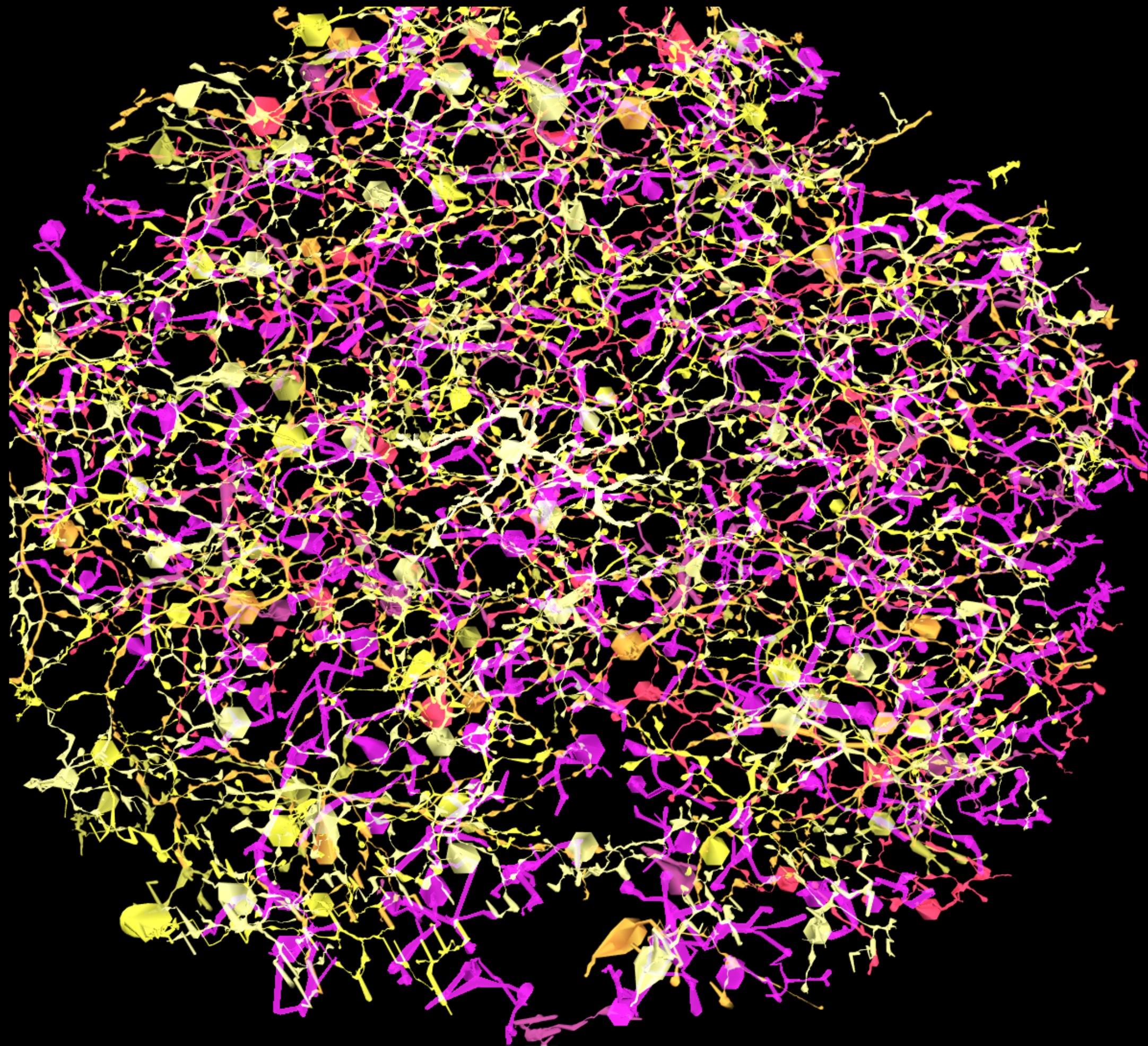
Noah Nelson
Cal Tech

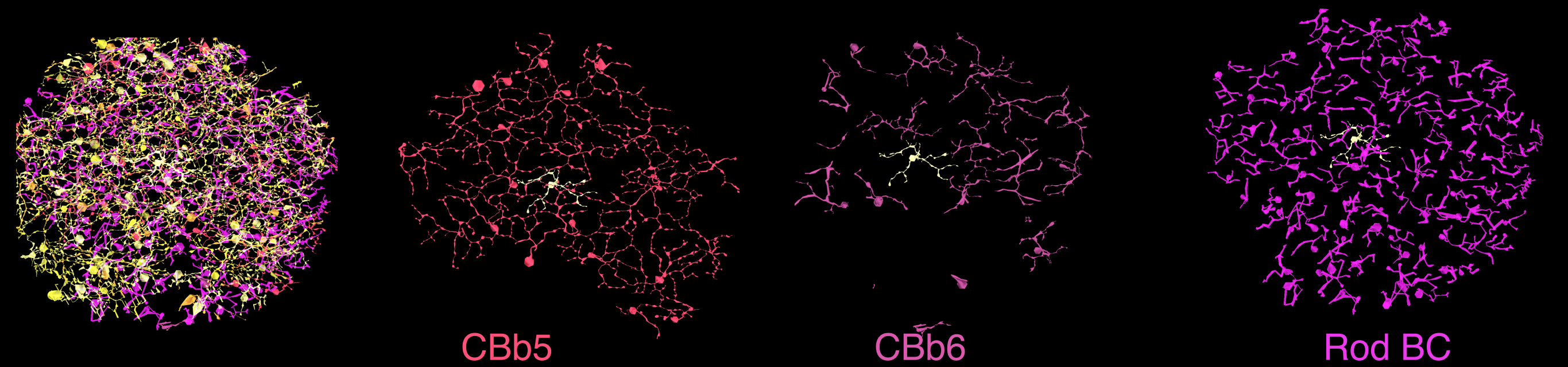
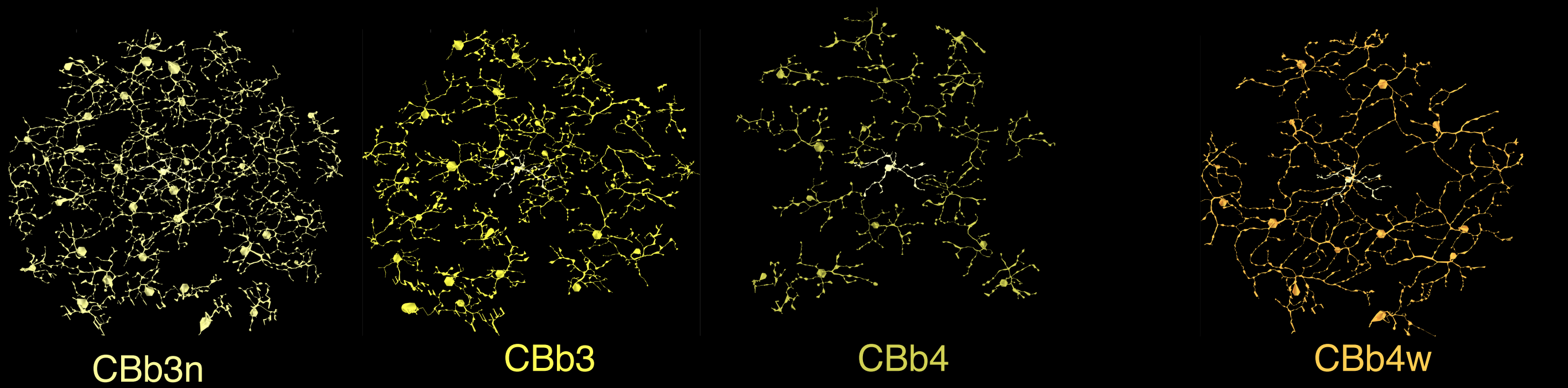
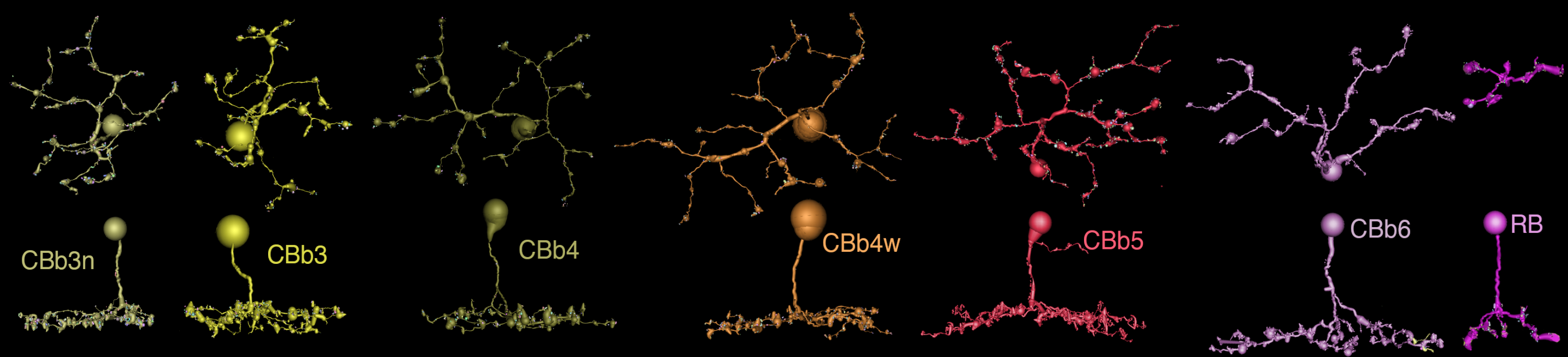
Crystal Sigulinsky PhD
Connectomics
Annotation
Retinal Networks



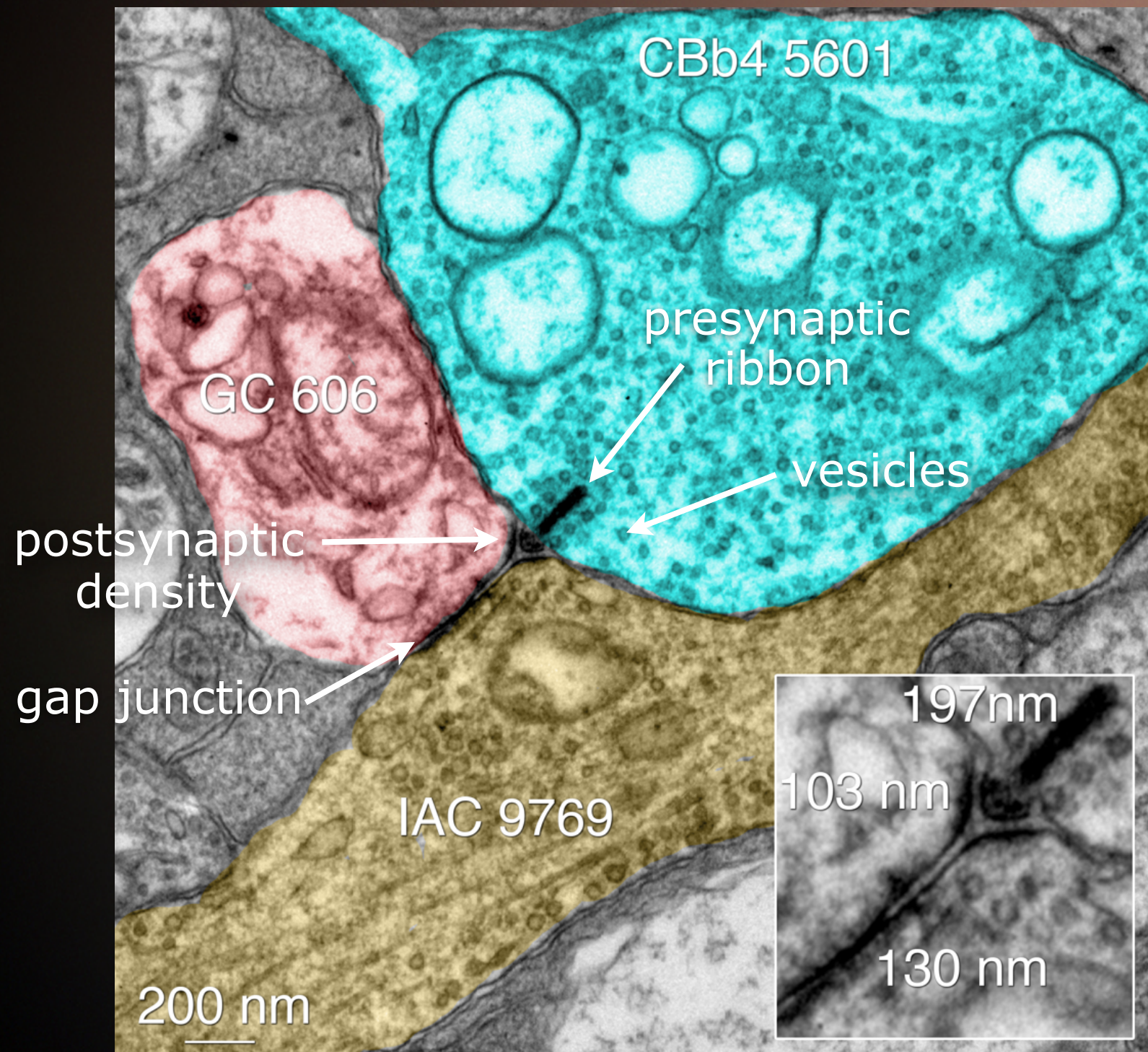
Danny Emrich
Annotation
Rock Star







Marc RE et al 2013 Retinal Connectomics: Towards Complete, Accurate Networks. *Prog Ret Eye Res*. Marc RE et al 2014 High-Resolution Synaptic Connectomics in *New Techniques in Neuroscience*. Springer.



G gap junction



A adherens junction



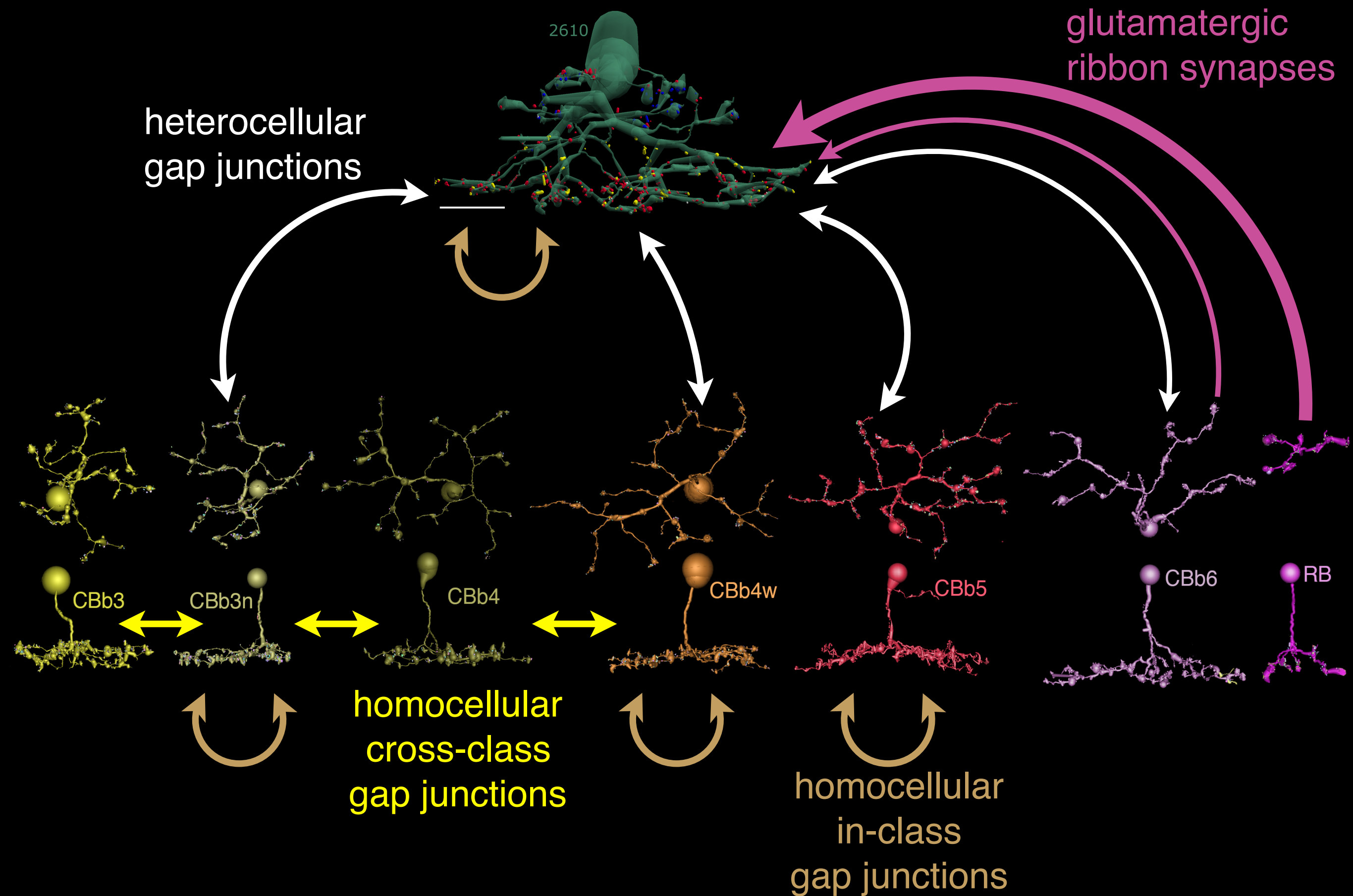
S synapse

..... presynaptic
..... postsynaptic

T Touch
no specialization

Five types of cell
adjacency
T, A, SA, GA, SGA

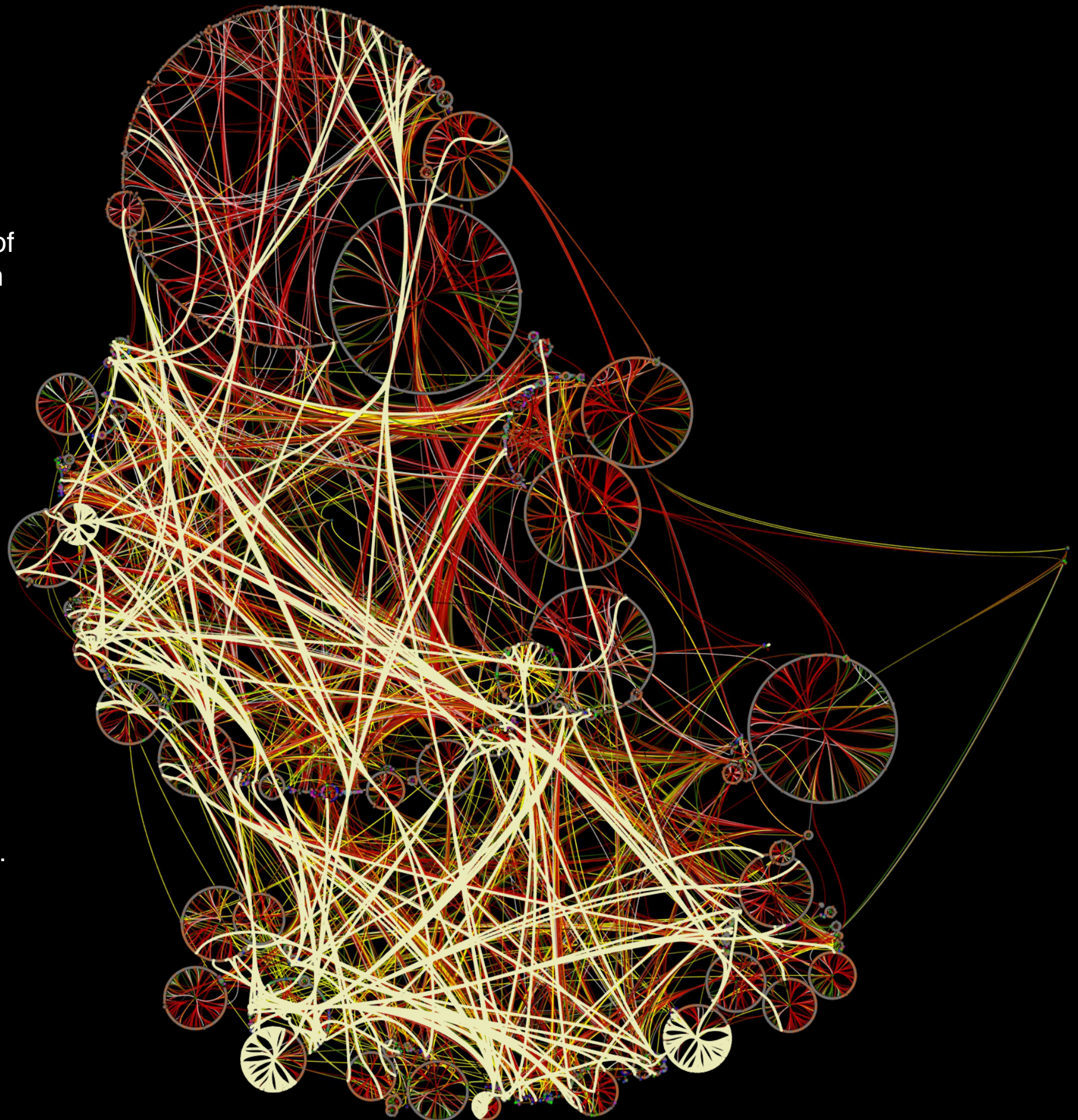
Glycinergic AII amacrine cell

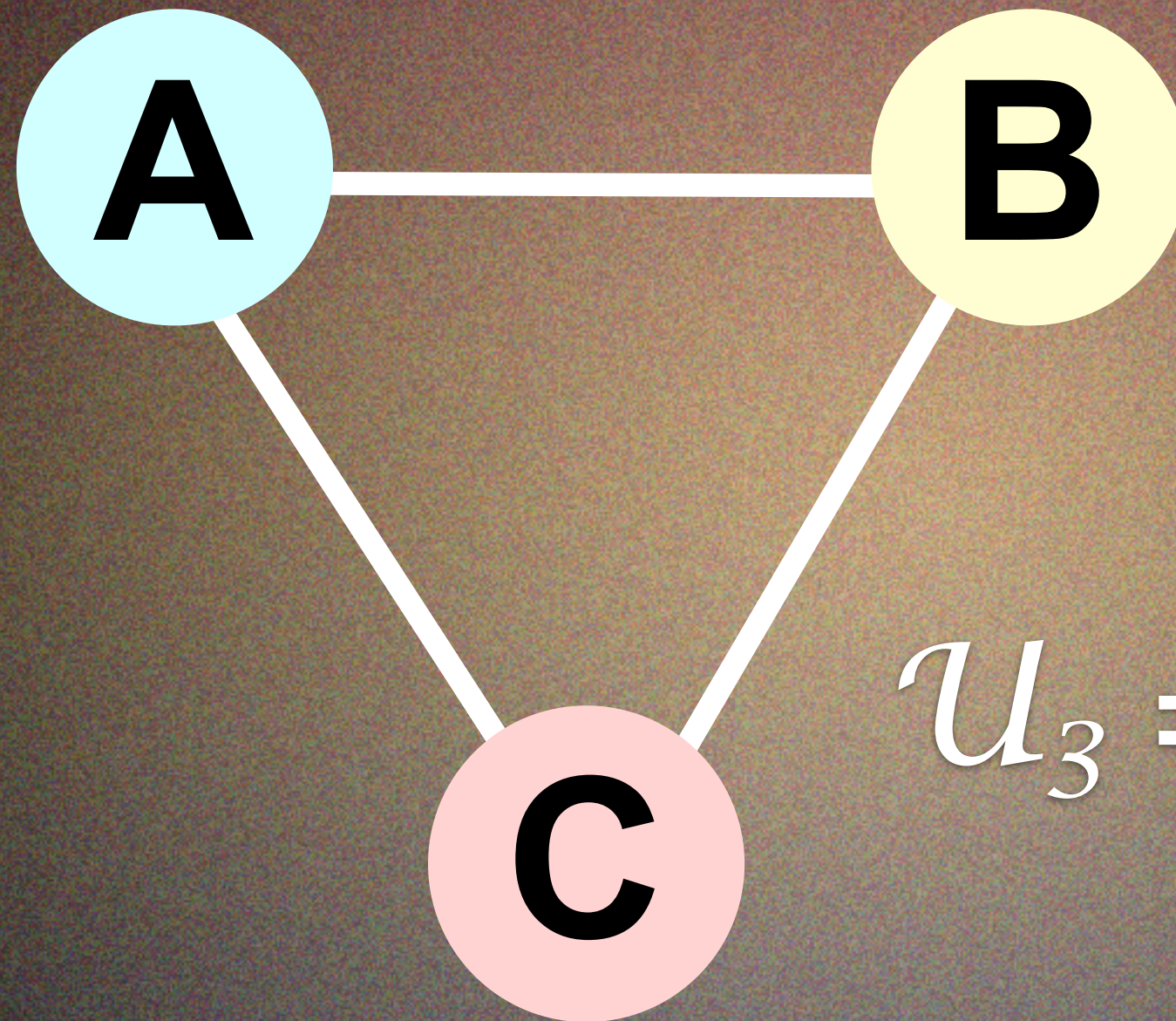


CBb3n

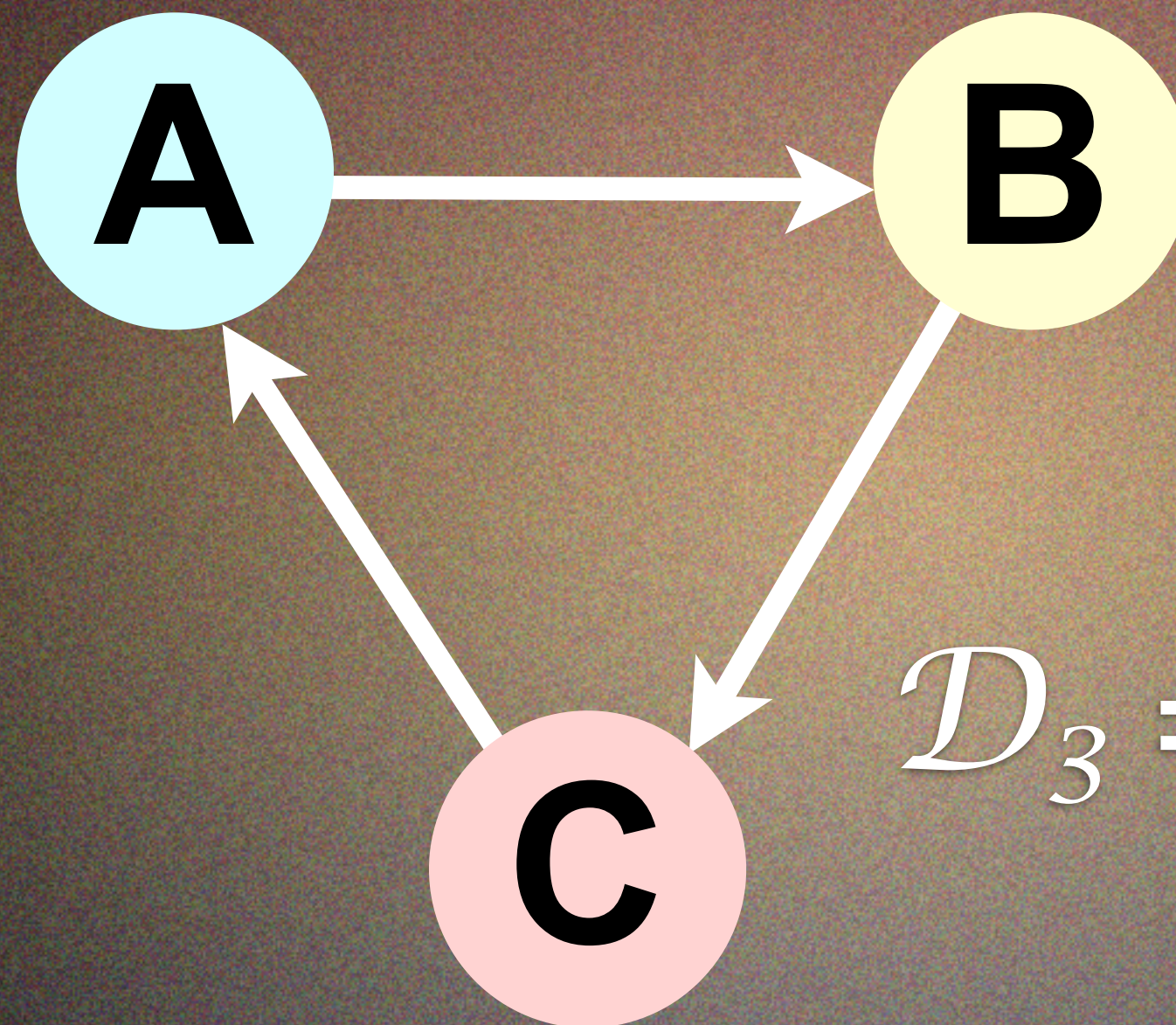
Rod-cone crossover connectome of mammalian bipolar cells. Lauritzen JS, Sigulinsky CL, Anderson JR, Kalloniatis M, Nelson NT, Emrich DP, Rapp C, McCarthy N, Kerzner E, Meyer M, Jones BW, Marc RE. J Comp Neurol. 2016 Jul 22. doi: 10.1002/cne.24084. PMID: 27447117

A multi-scale computational model for the study of retinal prosthetic stimulation. Loizos K, Lazzi G, Lauritzen JS, Anderson J, Jones BW, Marc R. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:6100-3. doi: 10.1109/EMBC.2014.6945021. PMID: 25571389

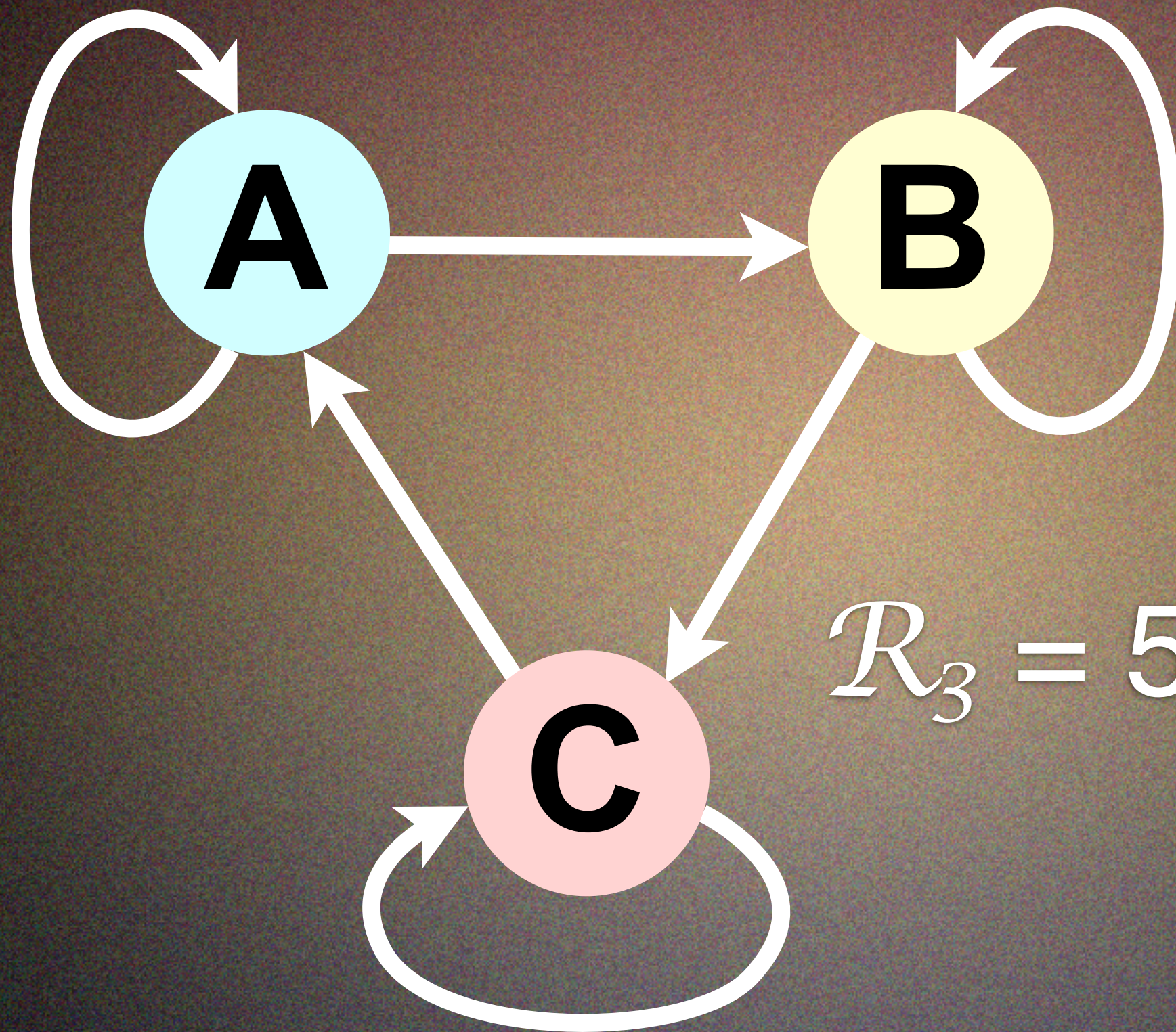




$$\mathcal{U}_3 = 8$$



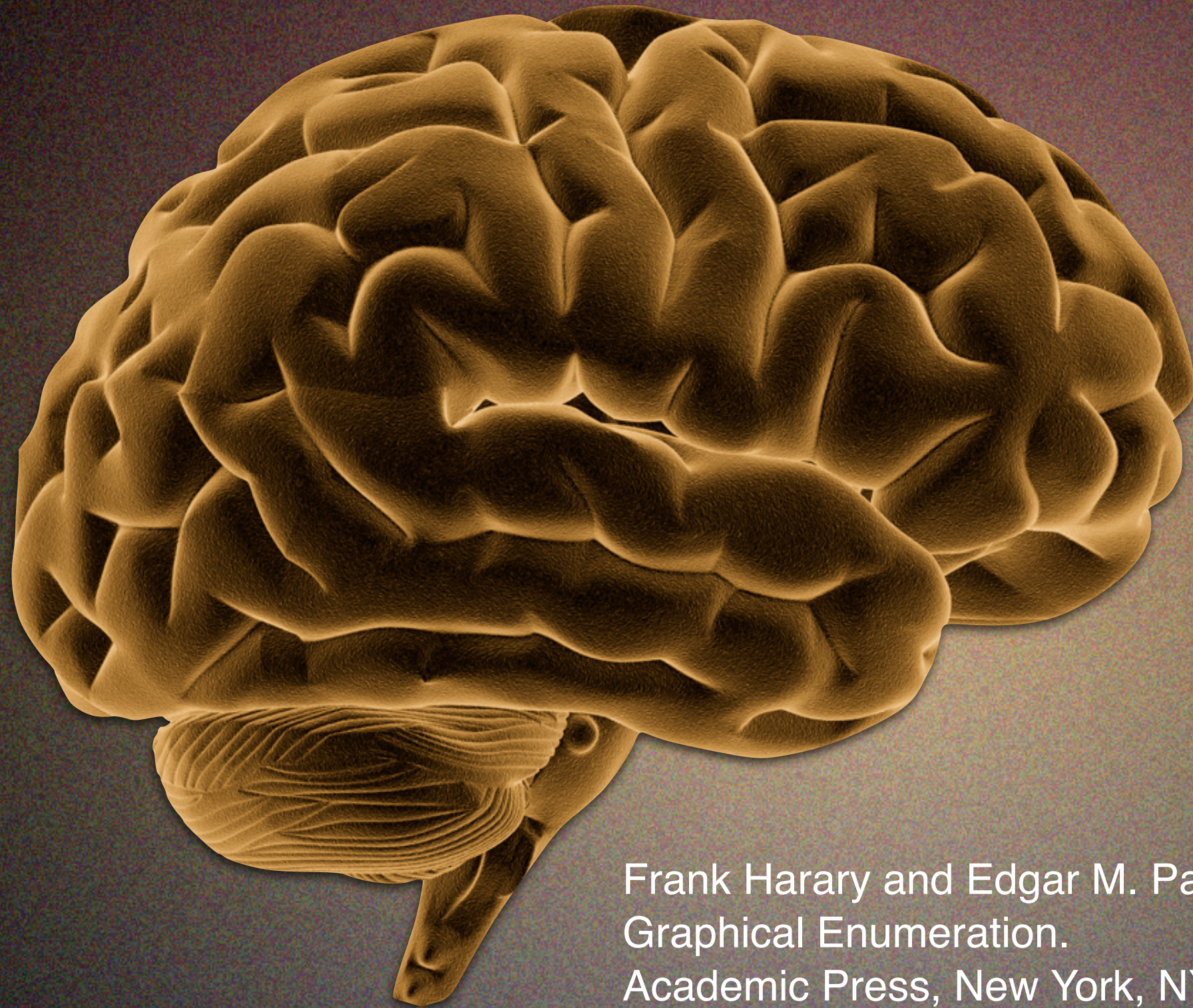
$$\mathcal{D}_3 = 64$$



$$\mathcal{R}_3 = 512$$



Frank Harary PhD
1921-2005
University of Michigan
New Mexico State Univ

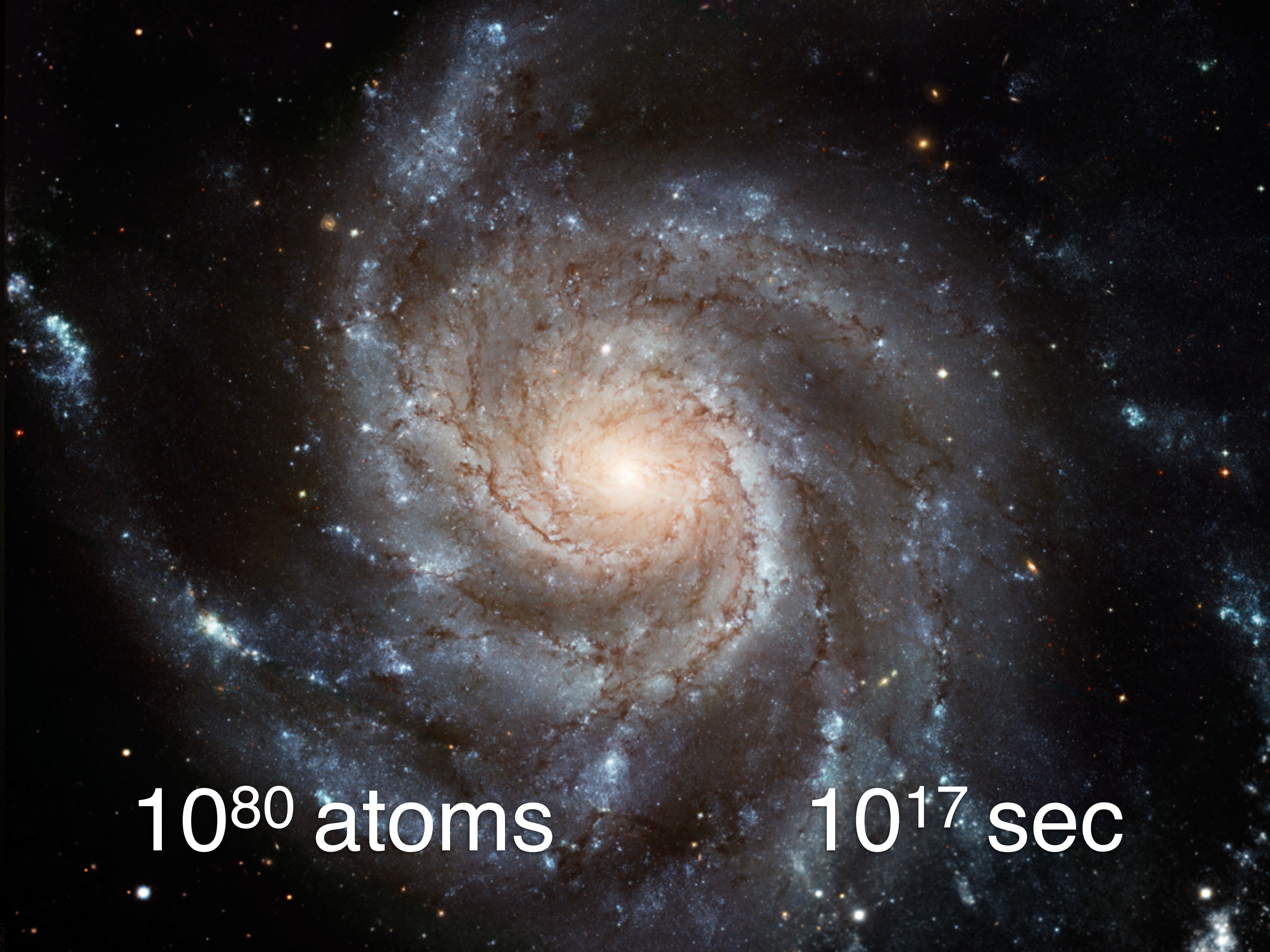


Frank Harary and Edgar M. Palmer (1973)
Graphical Enumeration.
Academic Press, New York, NY

$$\mathcal{D}_{1000} = 9 \times 10^{300728}$$



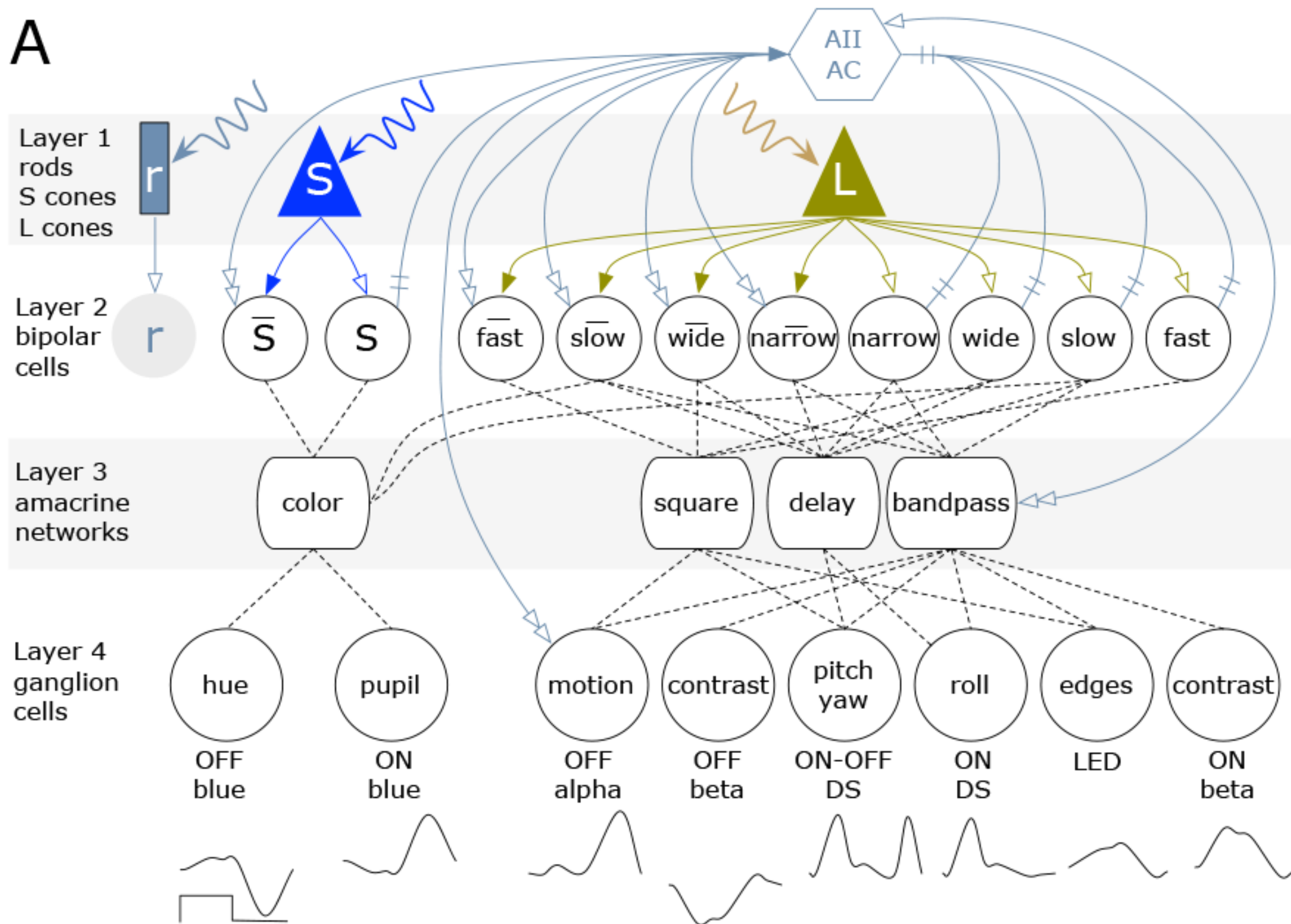
$$D_{70} = 9 \times 10^{1473}$$



10^{80} atoms

10^{17} sec

A



Marc R1, Pfeiffer R, Jones B. 2014 Retinal prosthetics, optogenetics, and chemical photoswitches. ACS Chem Neurosci. 2014 5:895-901.

Connectomics and retinal complexity

Degeneration kinetics

Remodeling

Neurodegeneration

Degeneration kinetics

Retinal degenerations in the mammalian retina progress through three phases.

Phase 1: the expression of a primary insult leading to photoreceptor stress.

Phase 2: the period of photoreceptor death.

Phase 3: Global remodeling of the remnant neural retina, resembling CNS responses to deafferentation or trauma.

Marc RE, BW Jones, CB Watt and E Strettoi 2003 Neural Remodeling in Retinal Degeneration. Progress in Retinal and Eye Research 22: 607-655.

Degeneration kinetics

Retinal degenerations in the mammalian retina progress through ~~three~~ four phases.

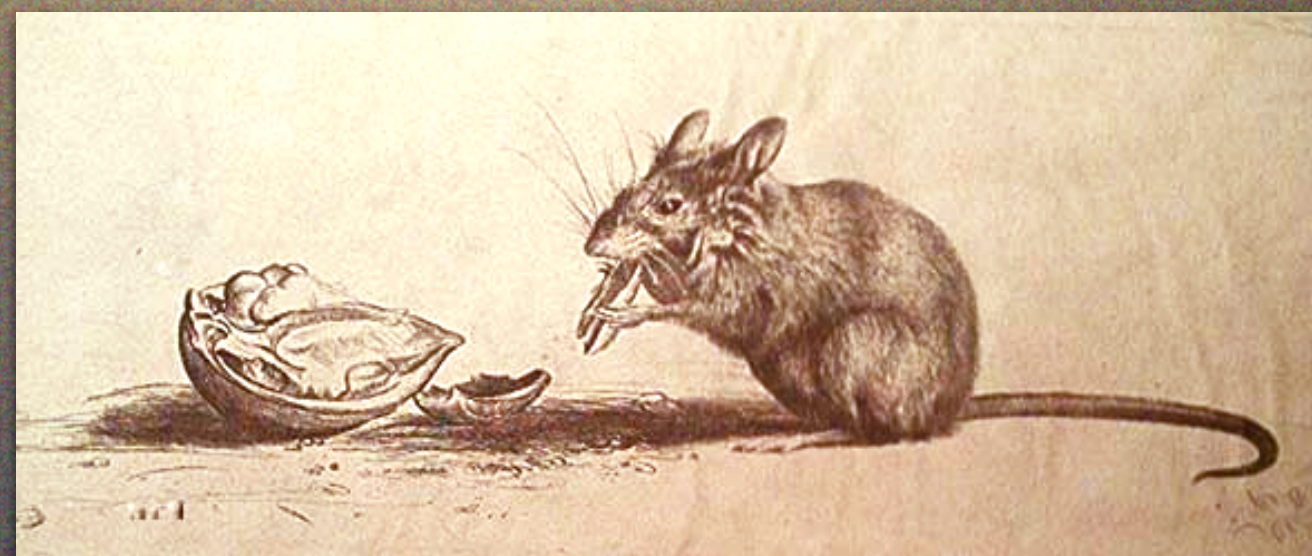
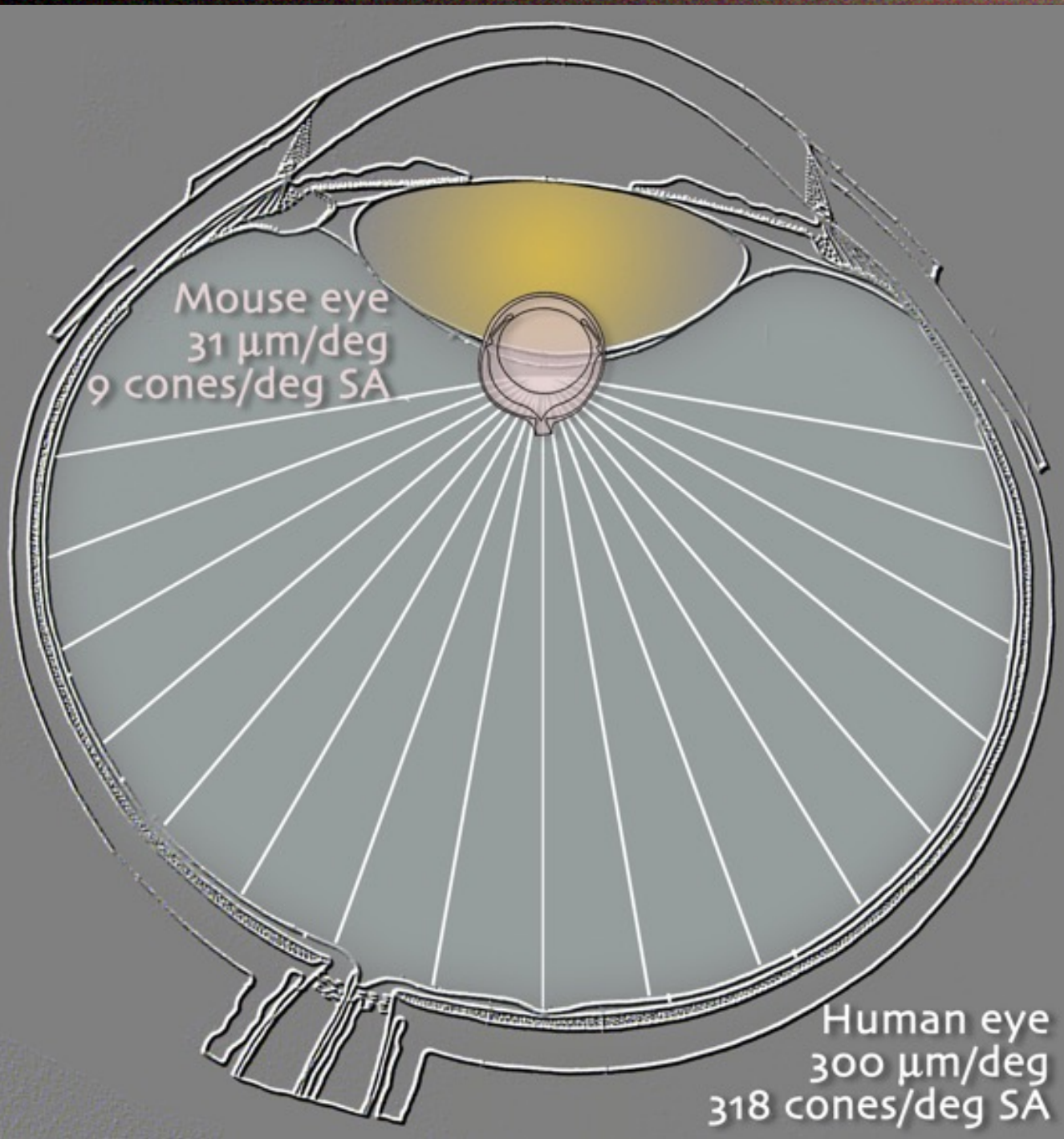
Phase 1: the expression of a primary insult leading to photoreceptor stress.

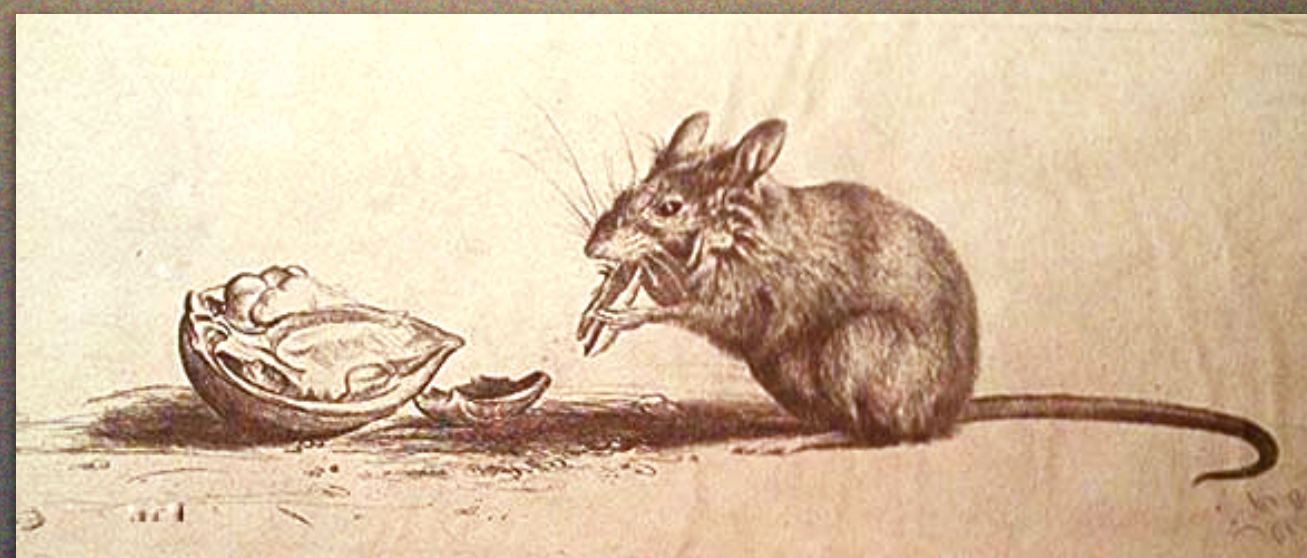
Phase 2: the period photoreceptor death.

Phase 3: Global remodeling of the remnant neural retina, resembling CNS responses to deafferentation or trauma.

Phase 4: Global neurodegeneration.

Size, not speed





RETINAL REMODELING & NEURODEGENERATION KINETICS

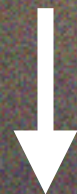
$\phi 1$ PR Stress



$\phi 2$ PR Death

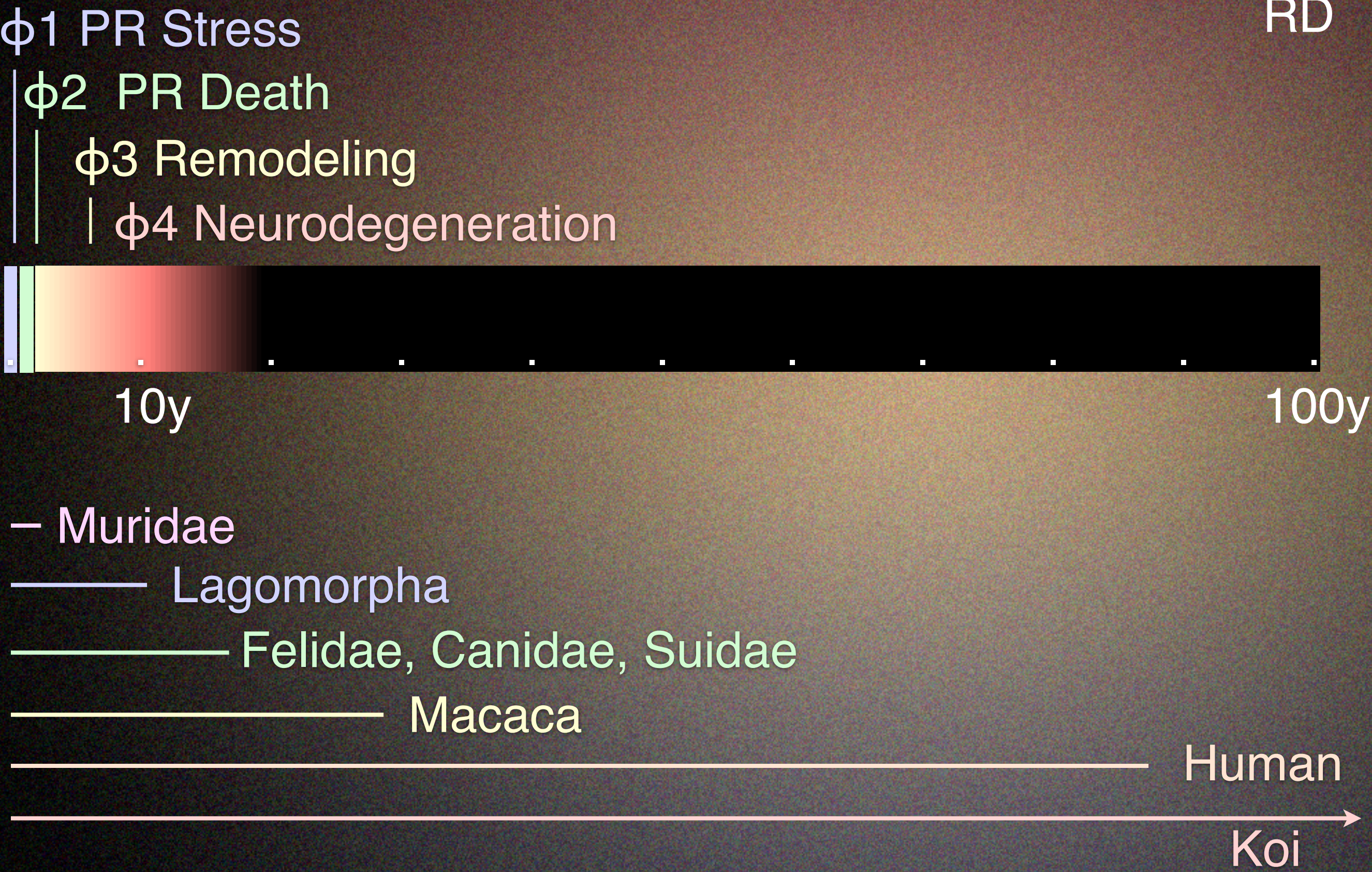


$\phi 3$ Remodeling

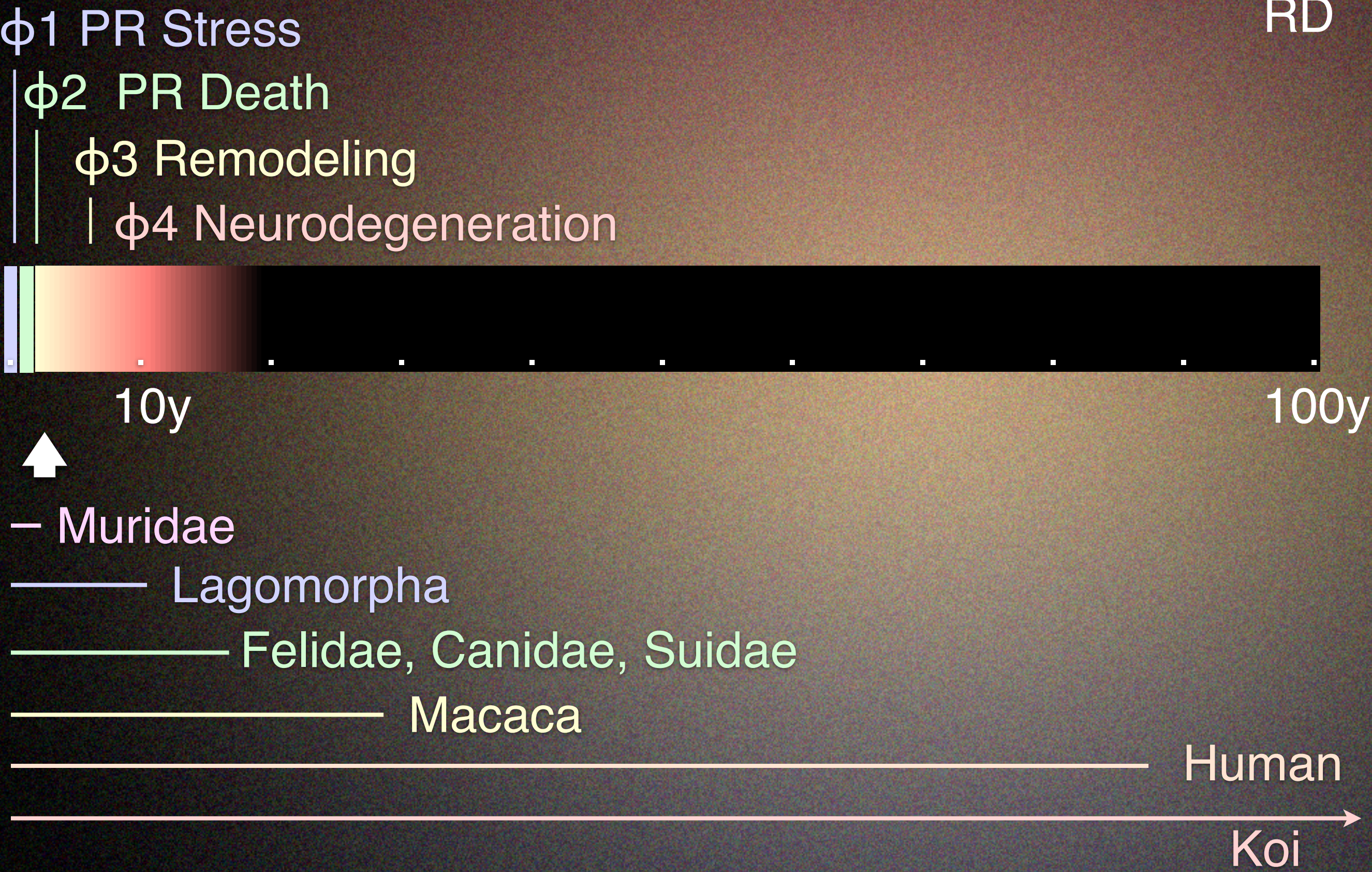


$\phi 4$ Neurodegeneration

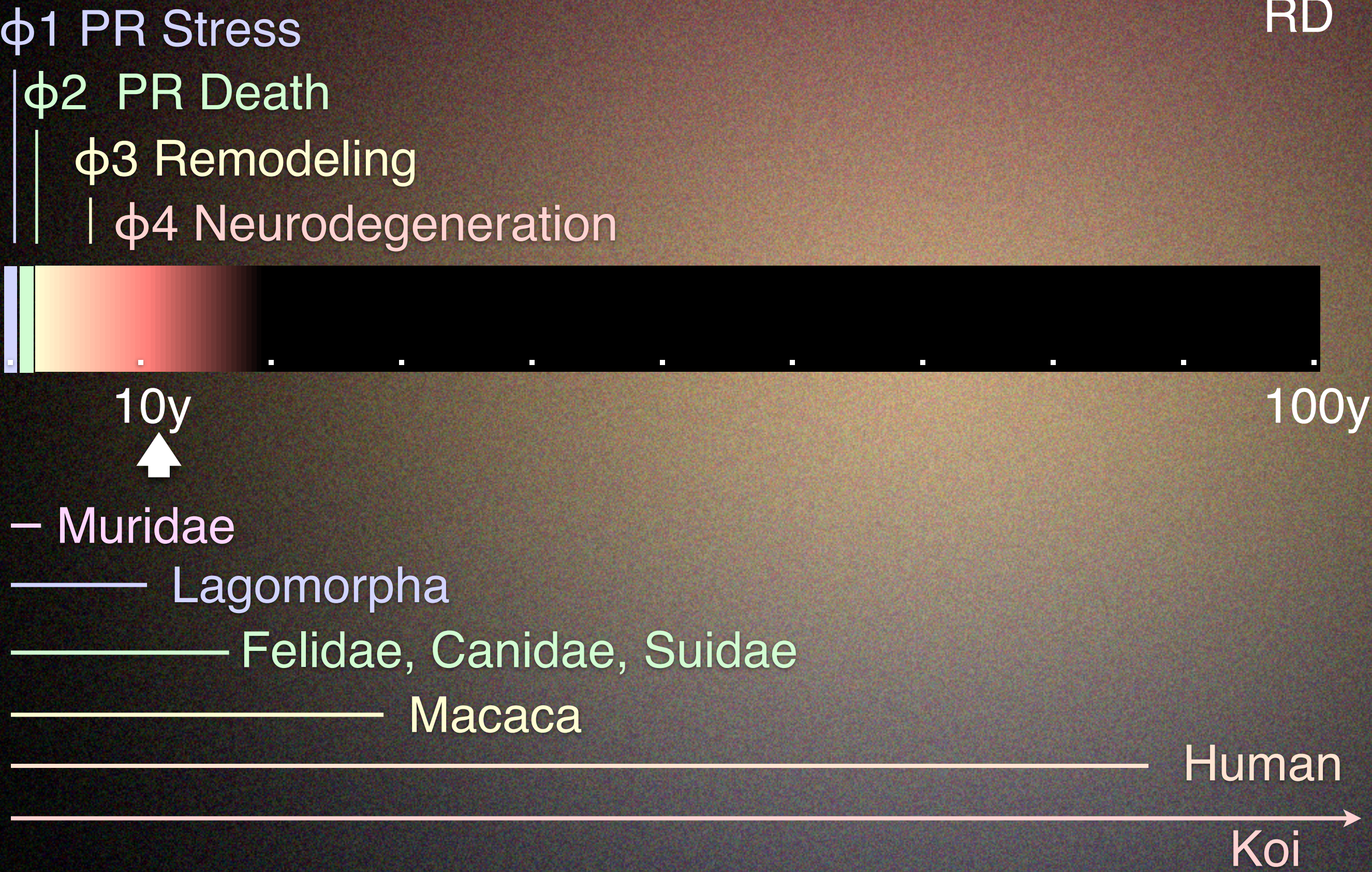
RETINAL REMODELING & NEURODEGENERATION KINETICS



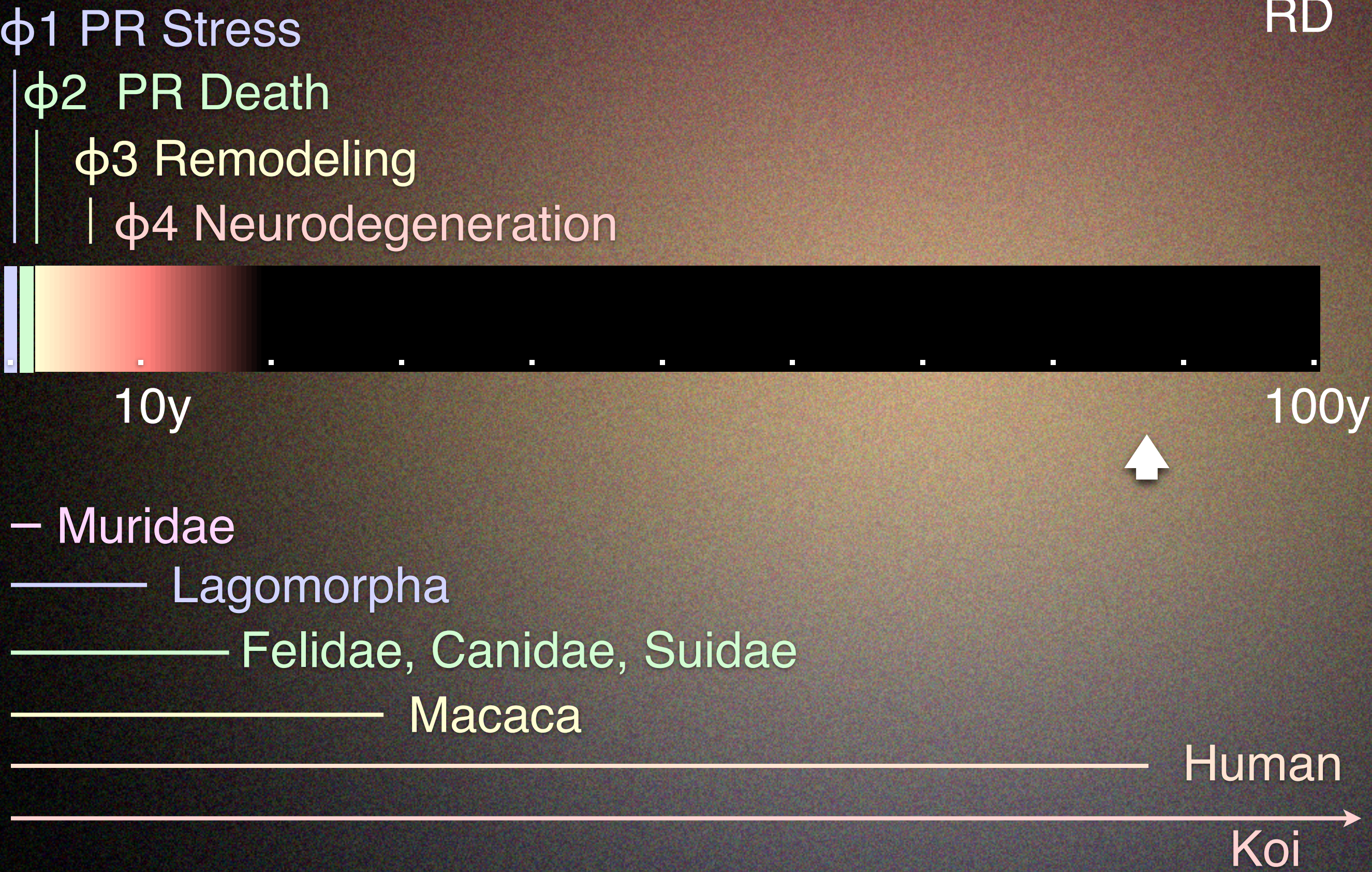
RETINAL REMODELING & NEURODEGENERATION KINETICS



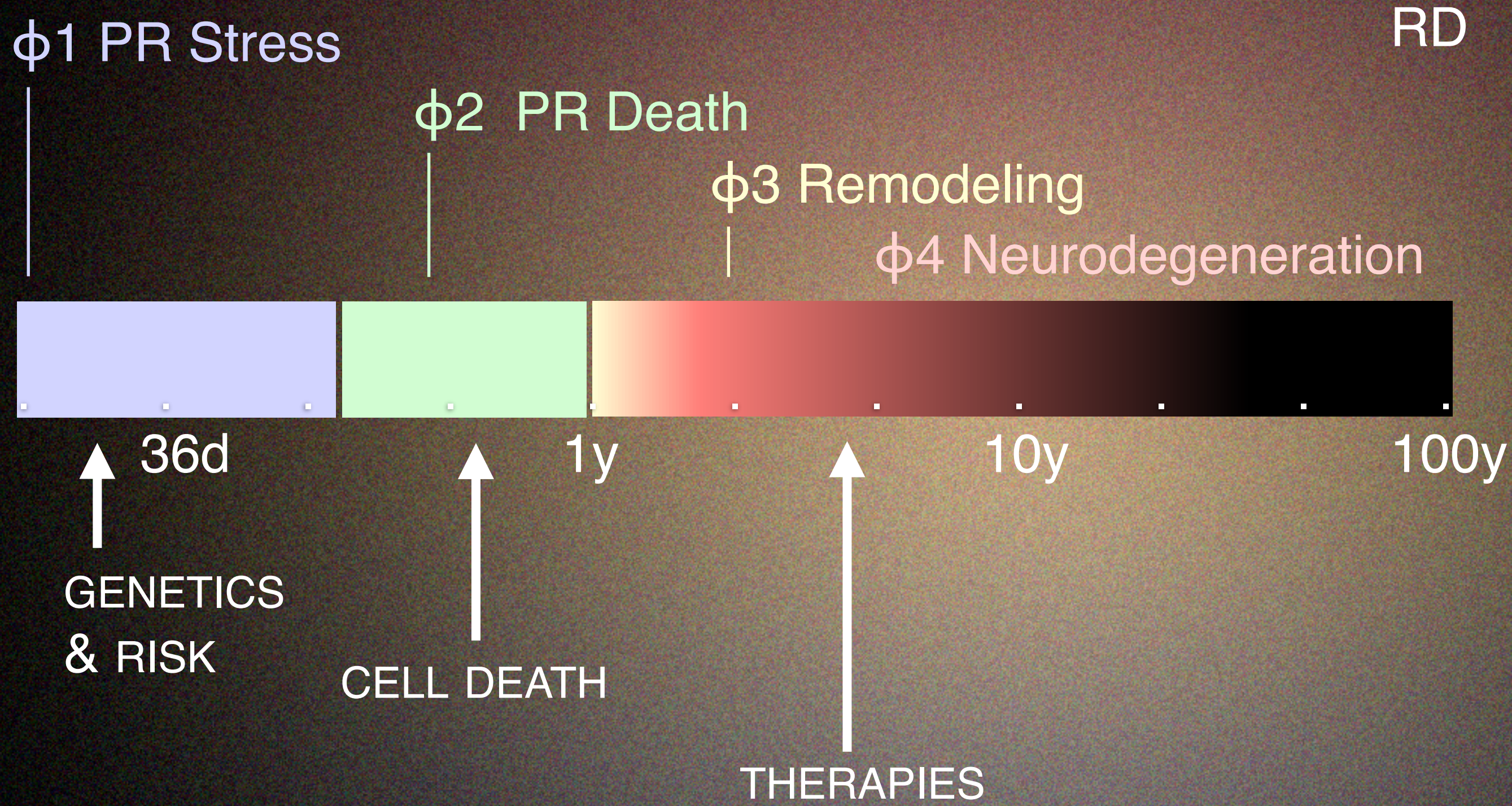
RETINAL REMODELING & NEURODEGENERATION KINETICS



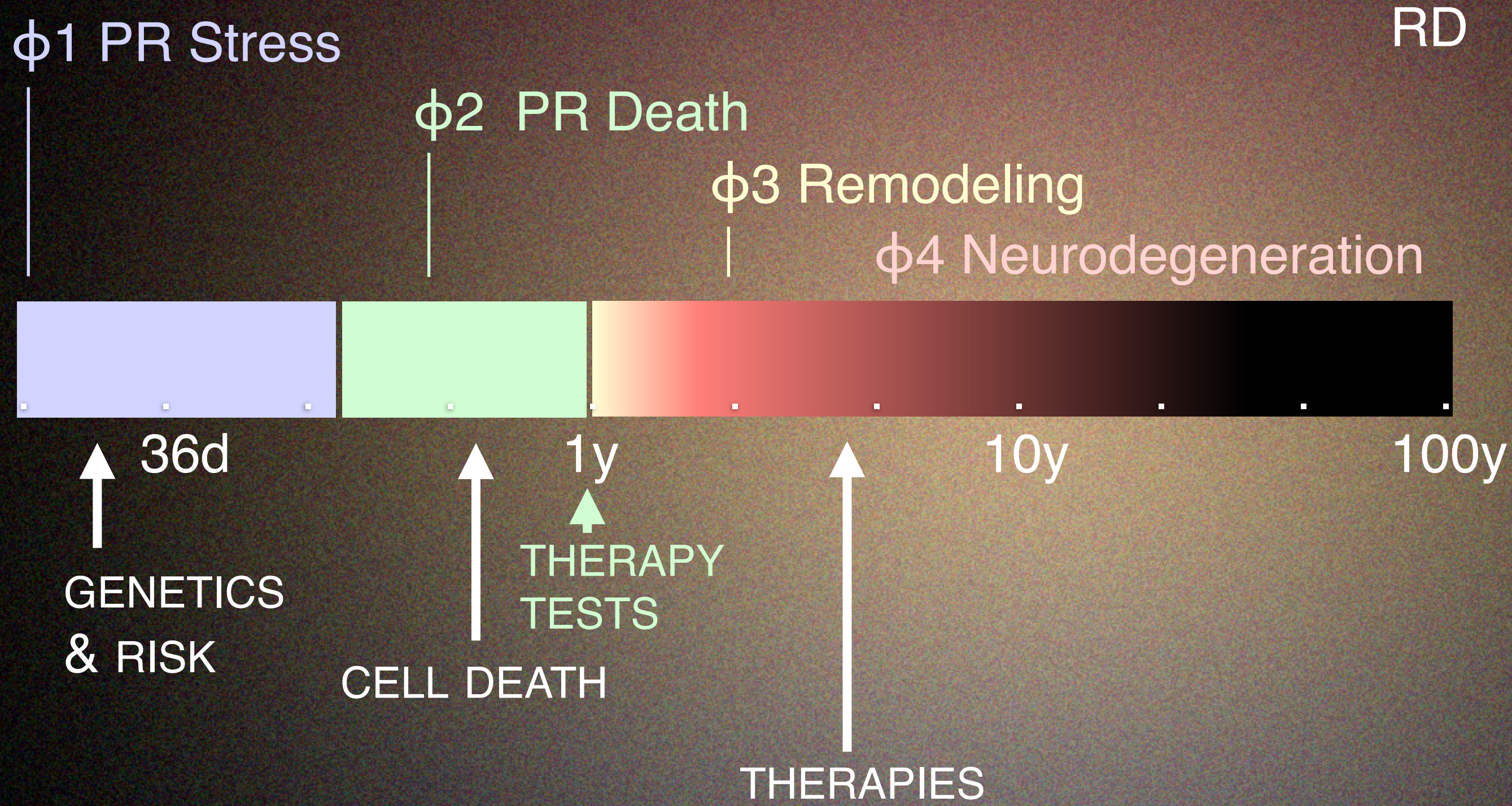
RETINAL REMODELING & NEURODEGENERATION KINETICS



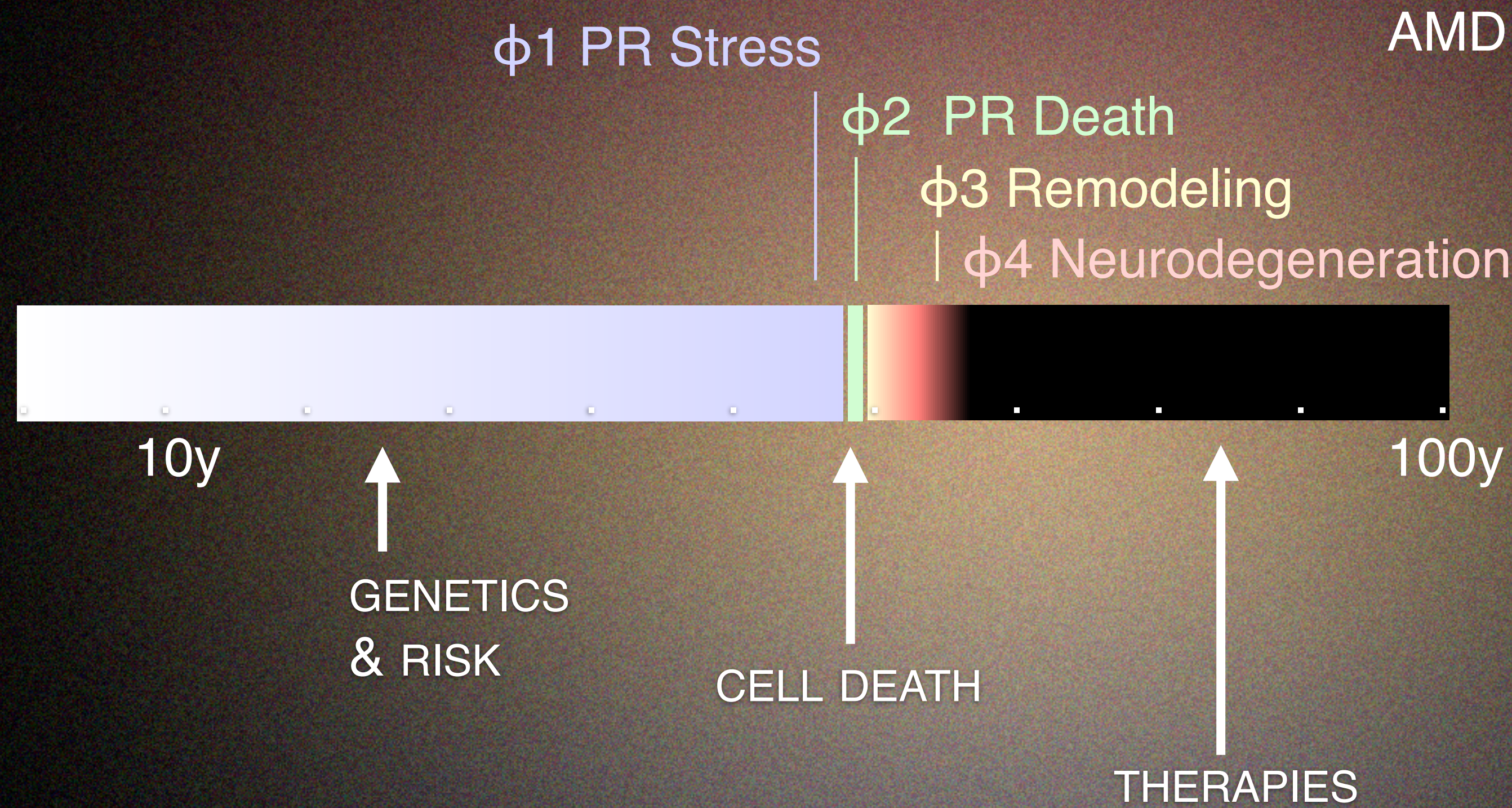
RETINAL REMODELING & NEURODEGENERATION KINETICS



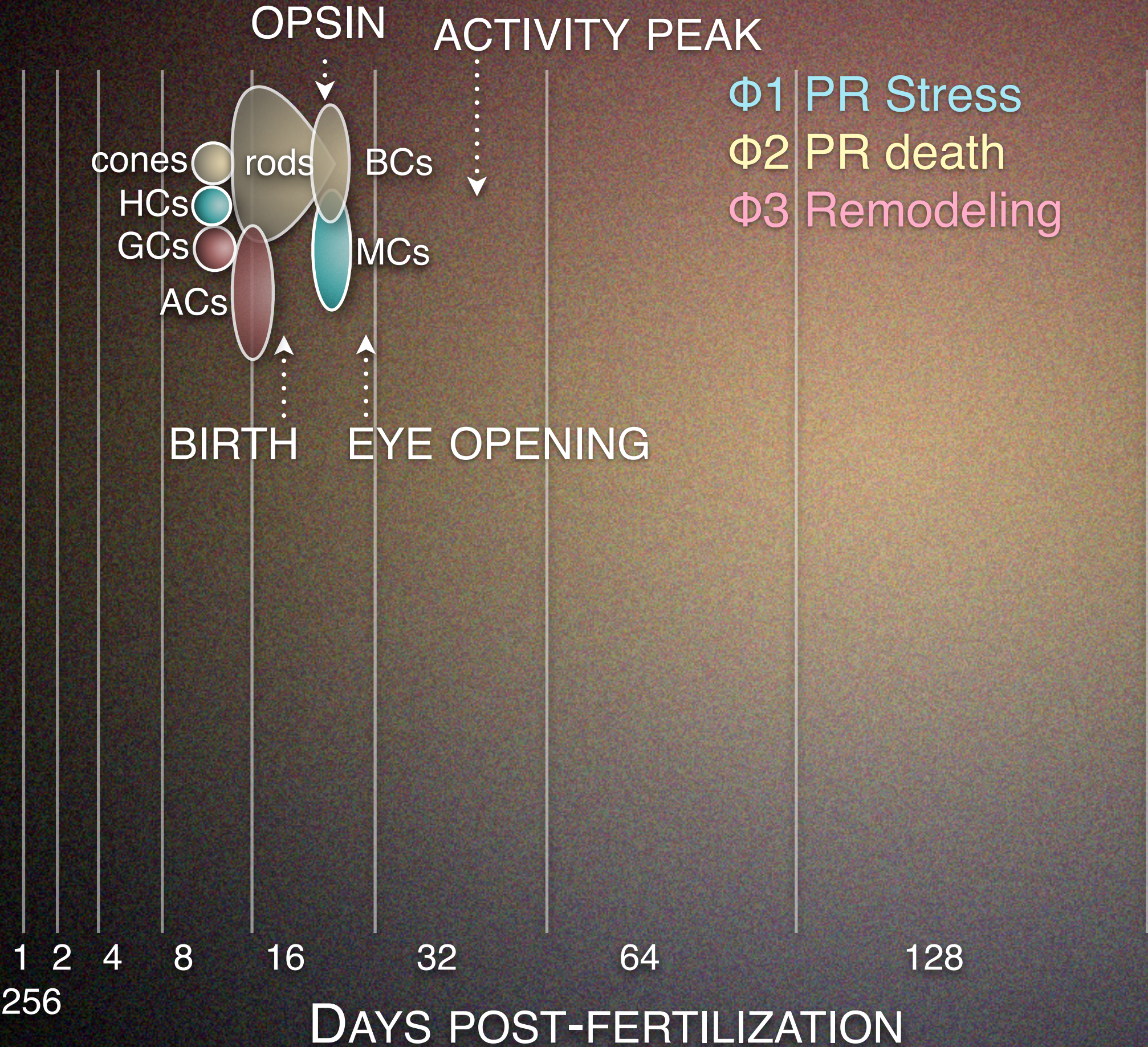
RETINAL REMODELING & NEURODEGENERATION KINETICS



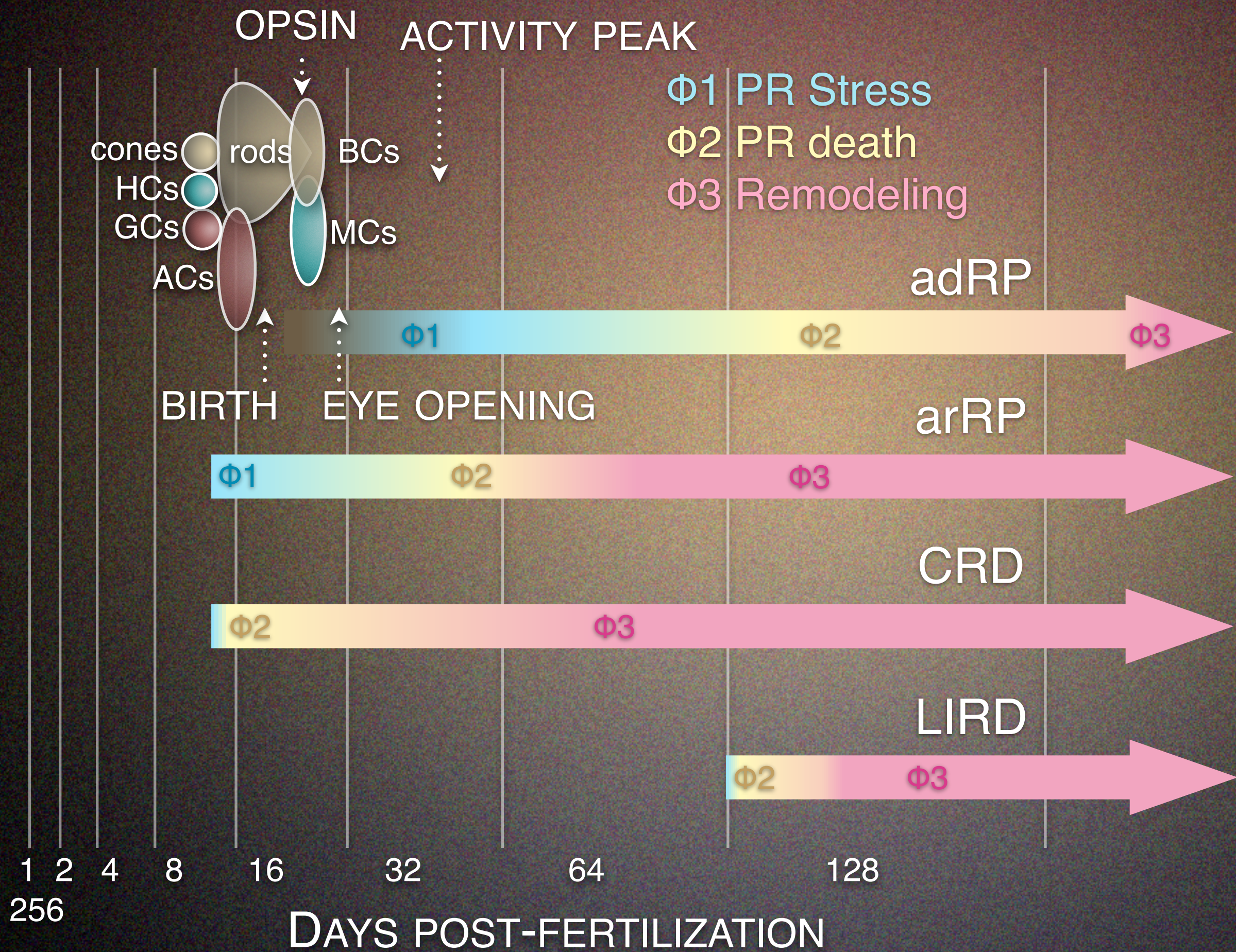
RETINAL REMODELING & NEURODEGENERATION KINETICS



RETINAL REMODELING KINETICS IN MOUSE MODELS



RETINAL REMODELING KINETICS IN MOUSE MODELS



Connectomics and retinal complexity

Degeneration kinetics

Remodeling

Neurodegeneration

Remodeling

Retinal remodeling is a collection of molecular / cellular revisions triggered by RP, other retinal degenerations and AMD

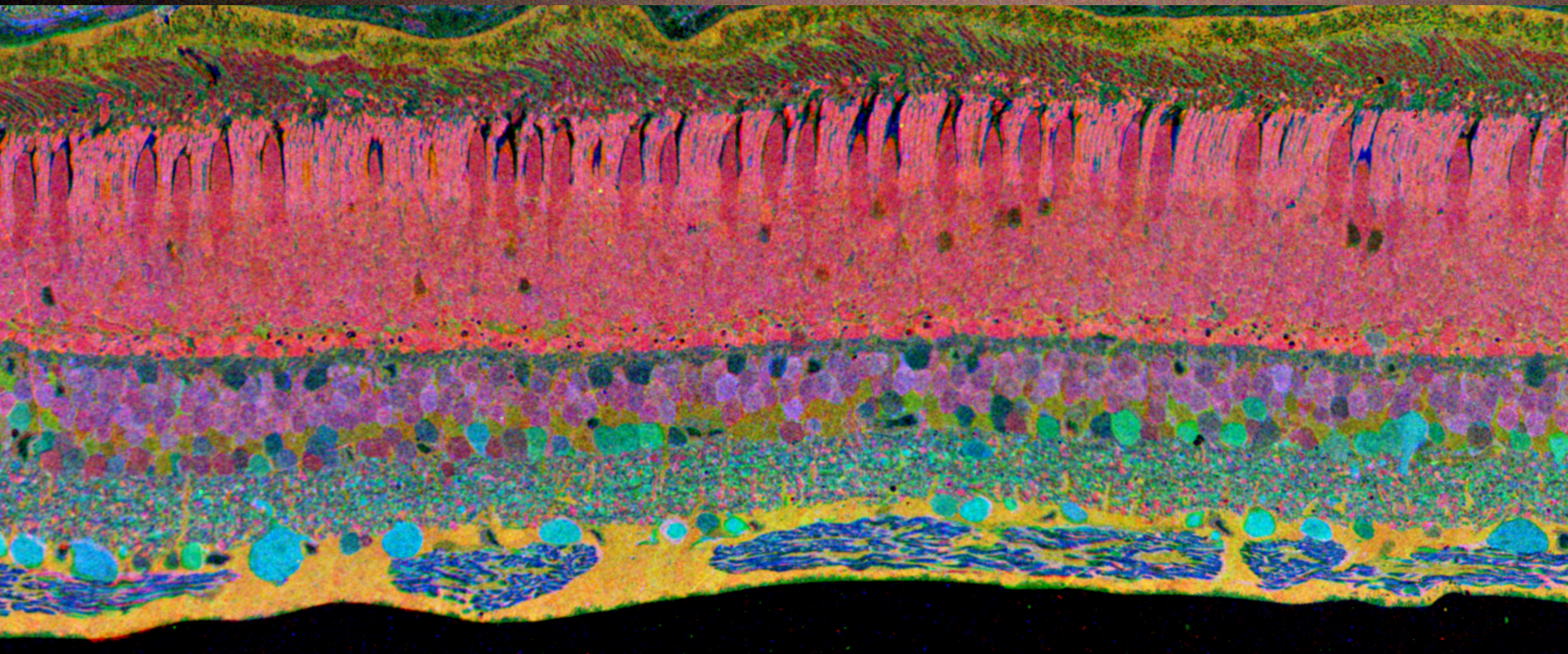
These revisions include neuronal rewiring and reprogramming; neuritogenesis and synaptogenesis; self-signaling; neuronal migration; neuronal death; glial hypertrophy; altered glial gene expression; vascular remodeling; retinal pigmented epithelium (RPE) invasion and hyperpigmentation. Some revisions begin as soon as photoreceptor stress is initiated, while others are manifest only upon complete local photoreceptor loss.

Remodeling impacts the timing and potential outcomes of gene therapy, survival factor treatments, stem or progenitor cell implantation, retinal transplantation, and bionic implants.

Marc RE 2010 Injury and Repair: Retinal Remodeling. Encyclopedia of the Eye (Elsevier) Vol 2, pp: 414-420.

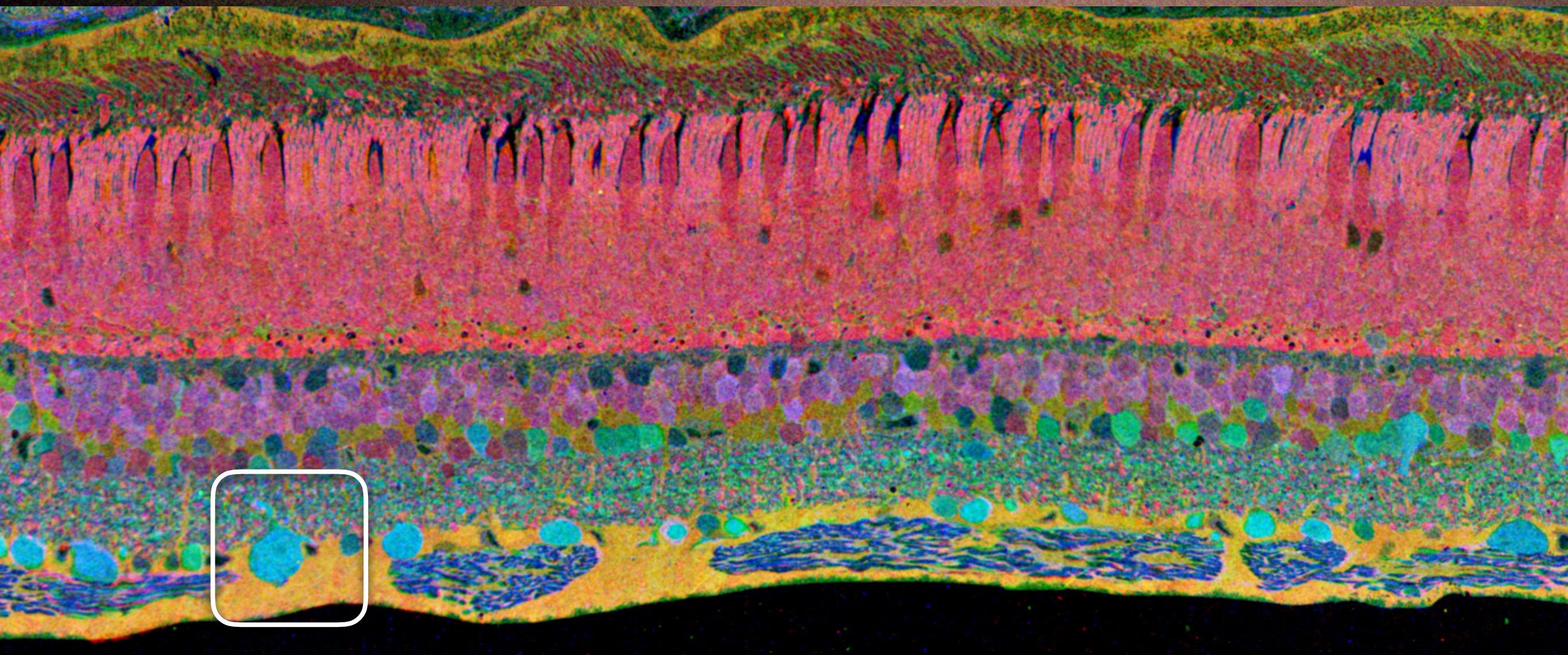


Ann Milam



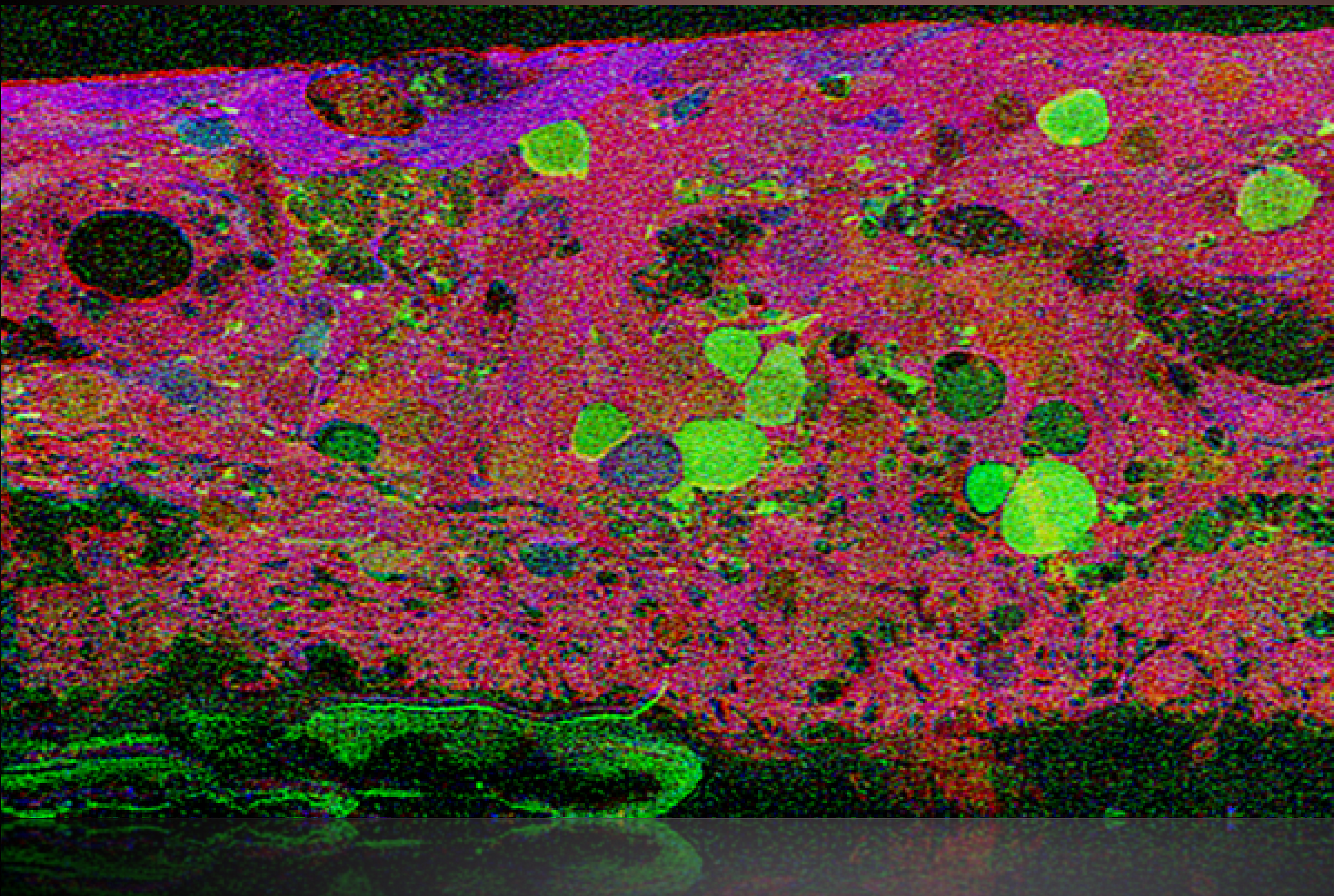
taurine glutamine glutamate

Macaque τ QE



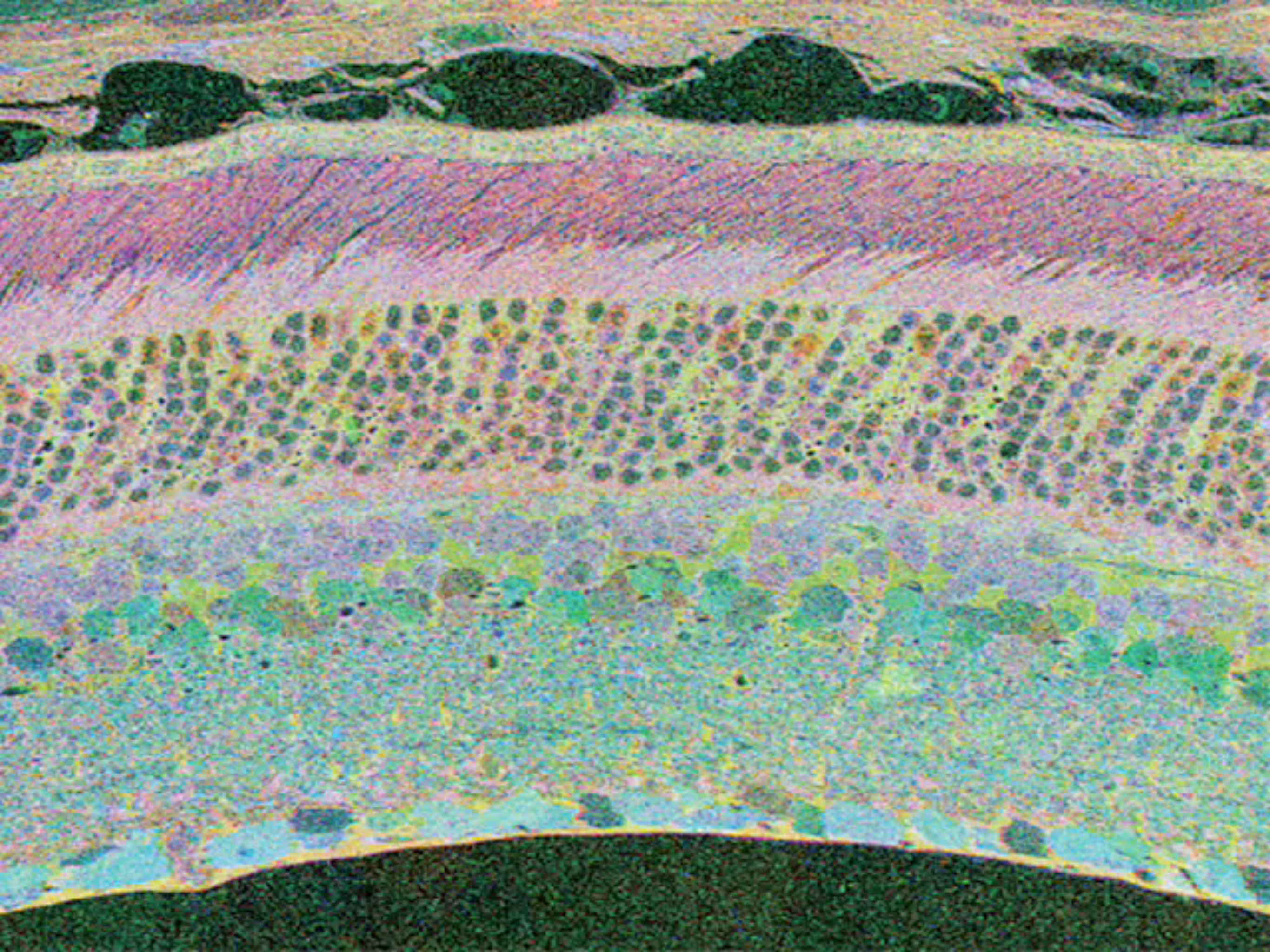
taurine glutamine glutamate

Macaque τ QE





Bryan W. Jones PhD
Assoc Professor
Moran Eye Center



$\phi 1$ $\phi 2$ $\phi 3$ $\phi 4$
 PR Stress PR Death Remodeling Neurodegeneration



Photoreceptor axon growth
& retraction

Bipolar cell dendrite truncation

Glial seal formation

Glial hypertrophy (proliferation)

Vascular invasion (CNV & GC arcade)

RPE invasion

Neuritogenesis (axonogenesis)

Microneuroma evolution

A_{II} AC lobule truncation

Ectopic Synaptogenesis

Migration & Emigration

Cell death

$\phi 1$
PR Stress

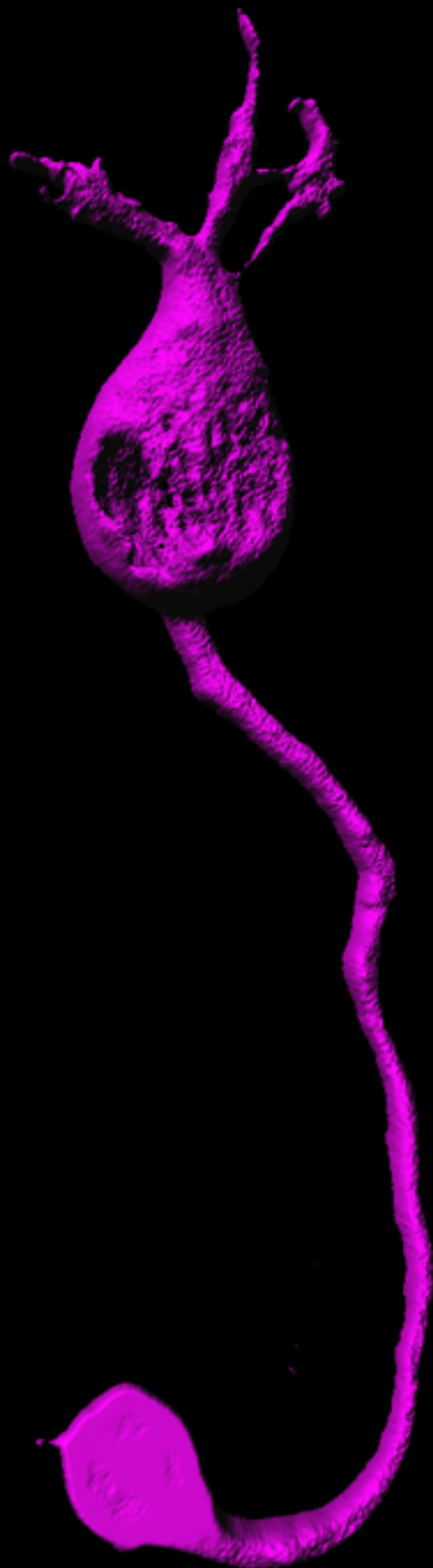
$\phi 2$
PR Death

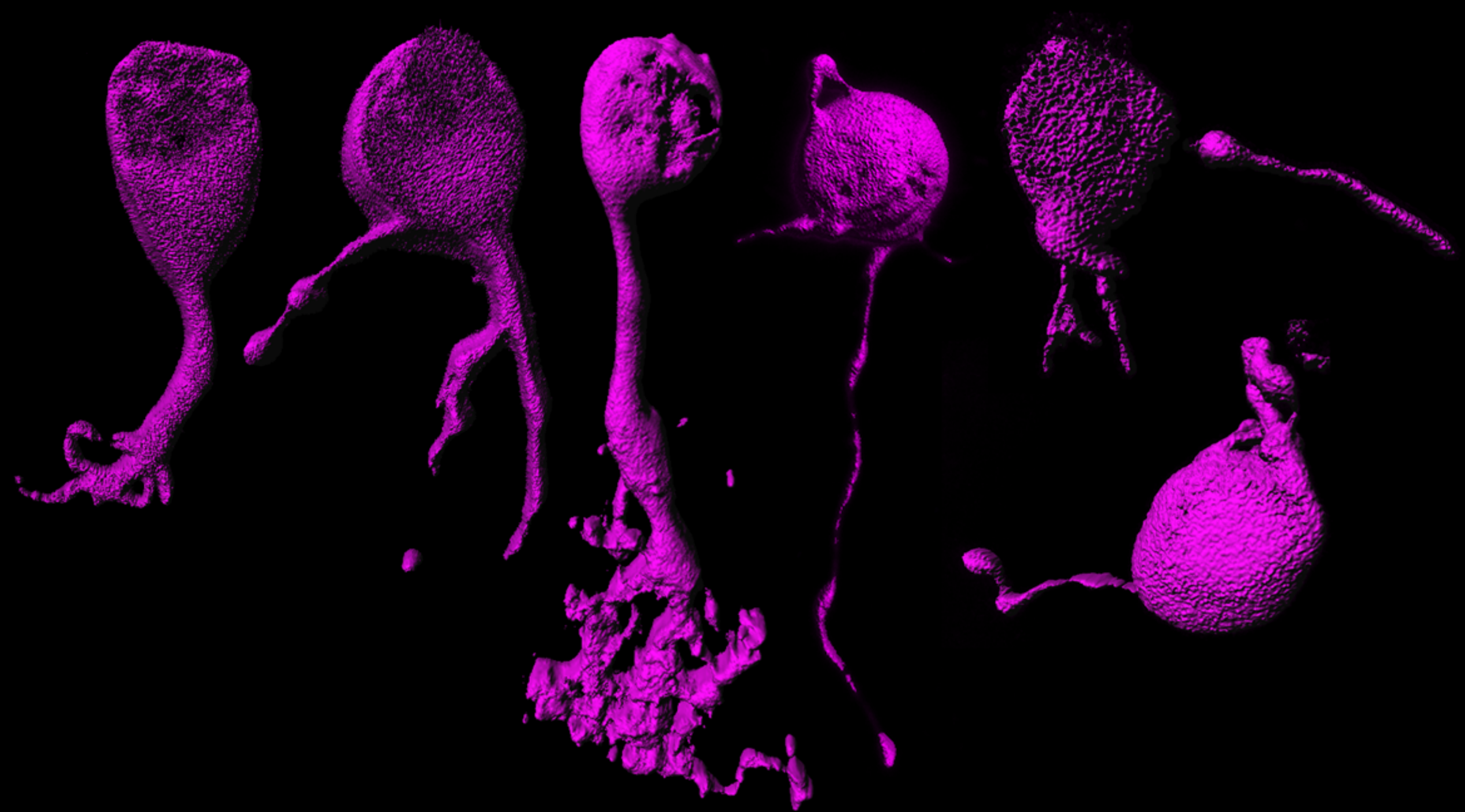
$\phi 3$
Remodeling

$\phi 4$
Neurodegeneration

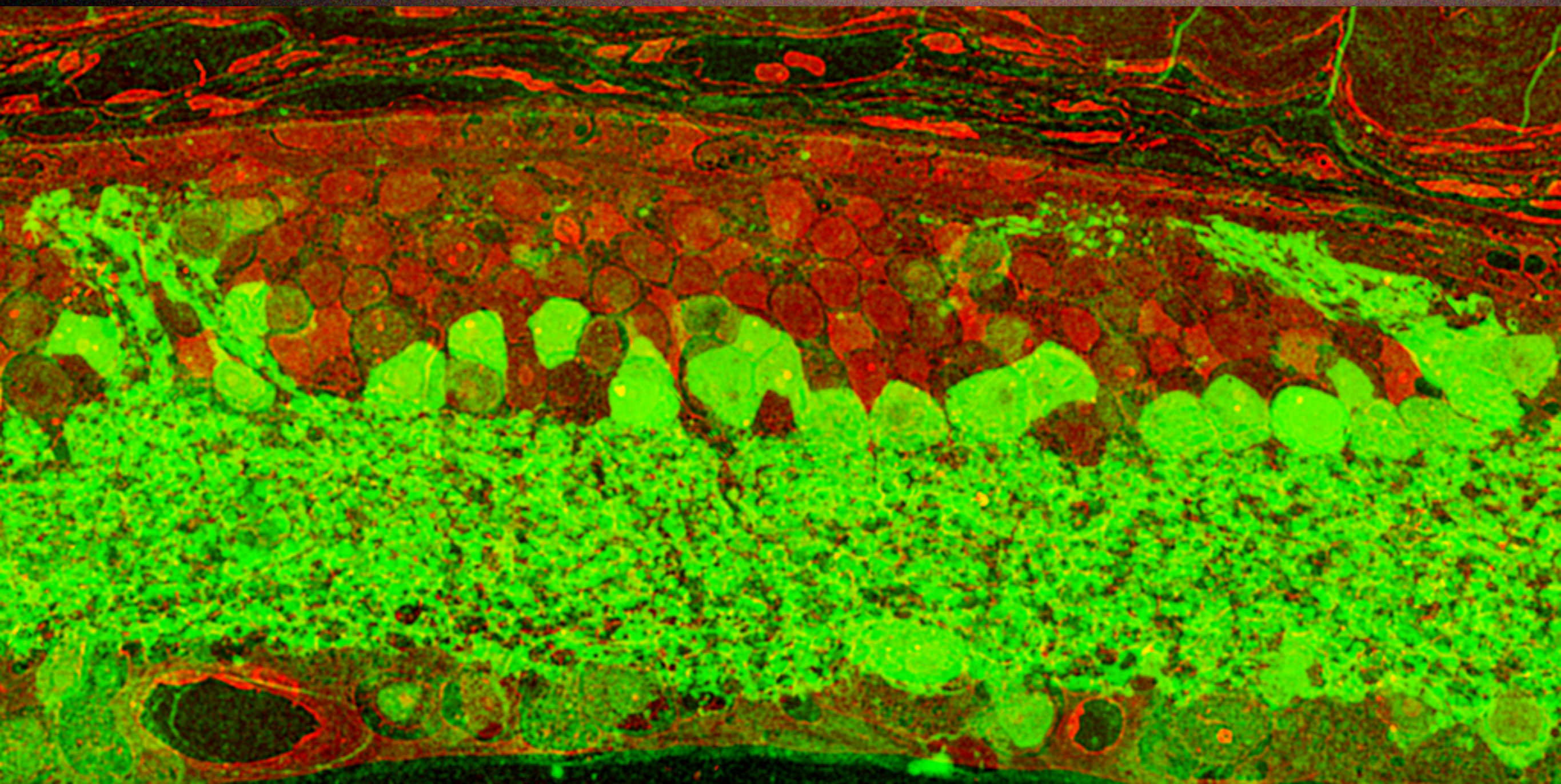


Altered networks
Self-signaling



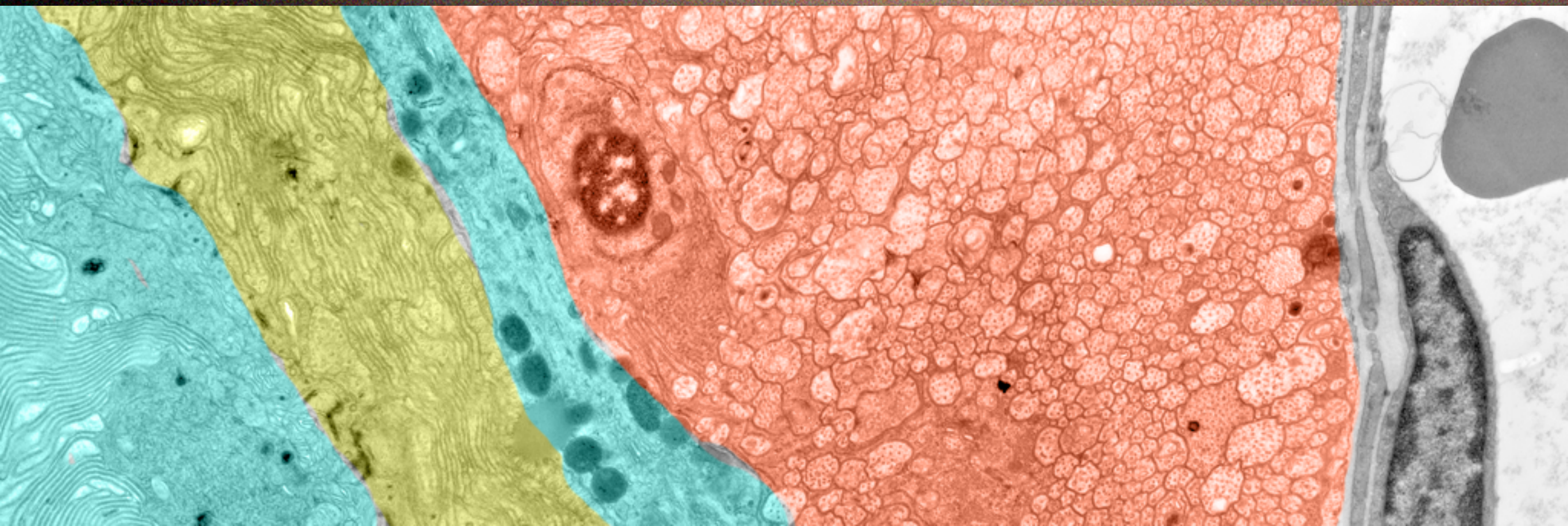


RETINAL REMODELING :: MICRONEUROMAS



Jones BW, et al 2003 Retinal remodeling triggered by photoreceptor degenerations. J Comp Neurol 464: 1-16.

RETINAL REMODELING :: GLIAL SEAL ... NOT A SCAR



RPE

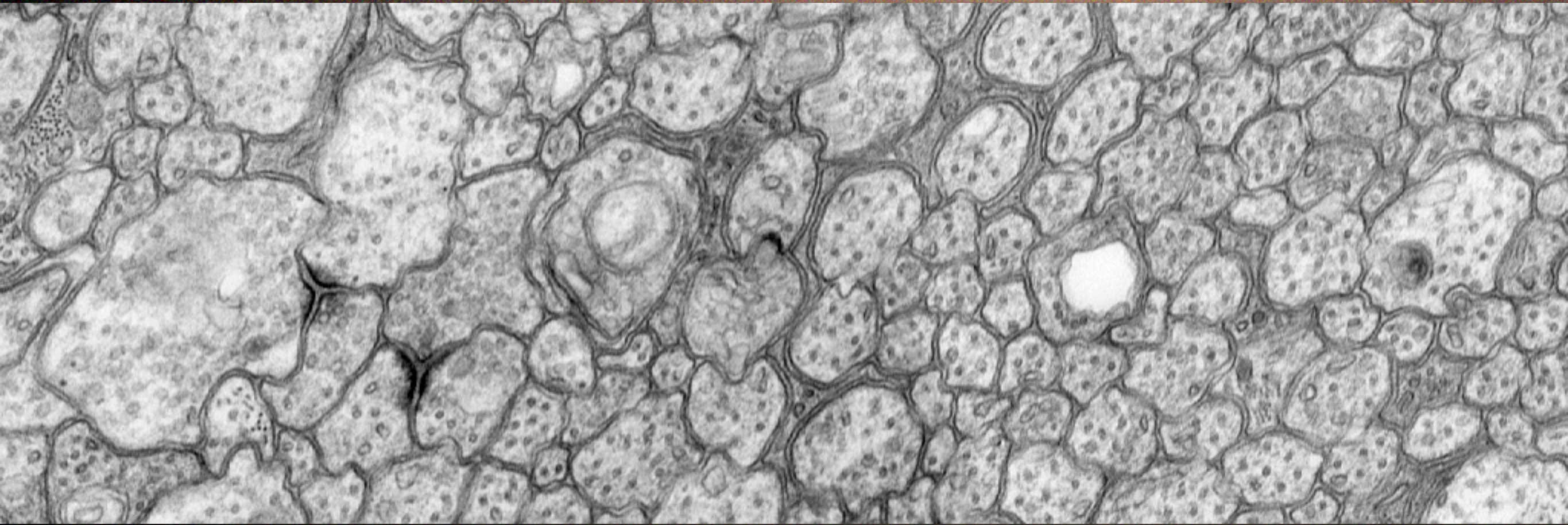
MC SEAL

RPE

MICRONEUROMA

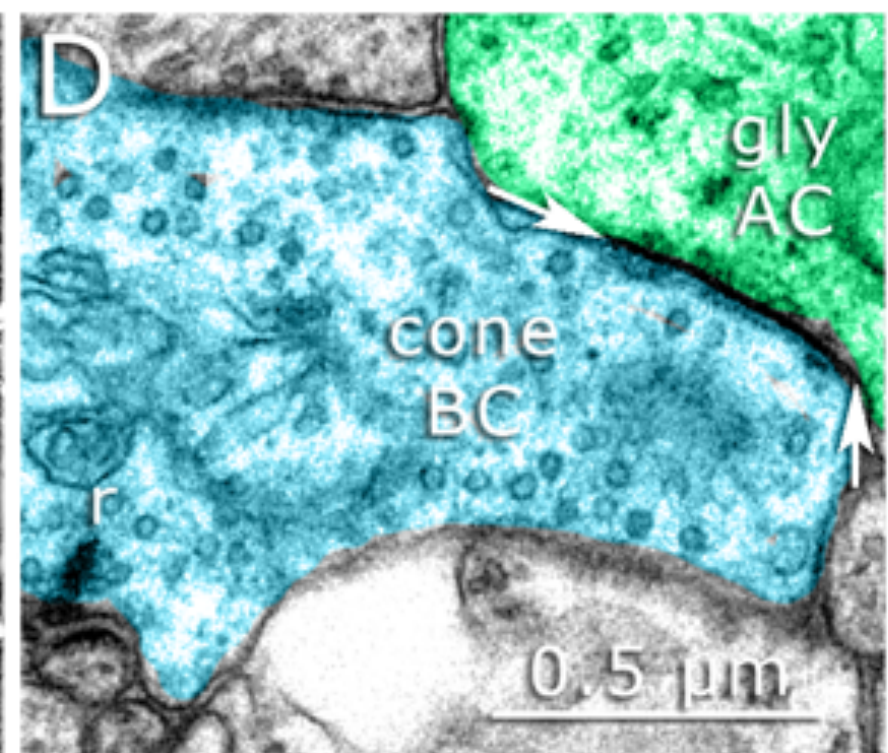
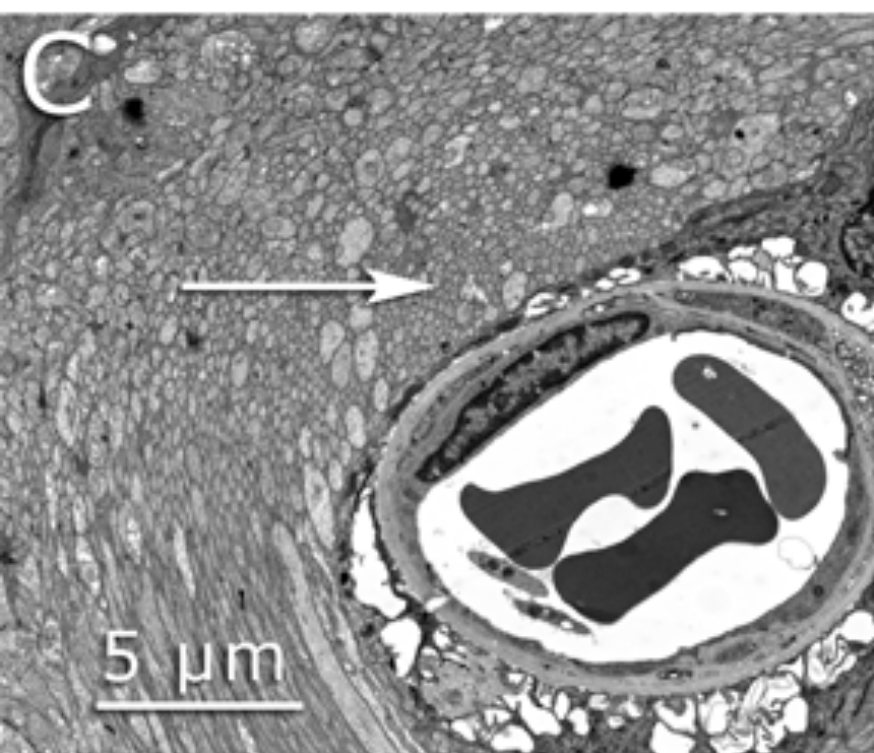
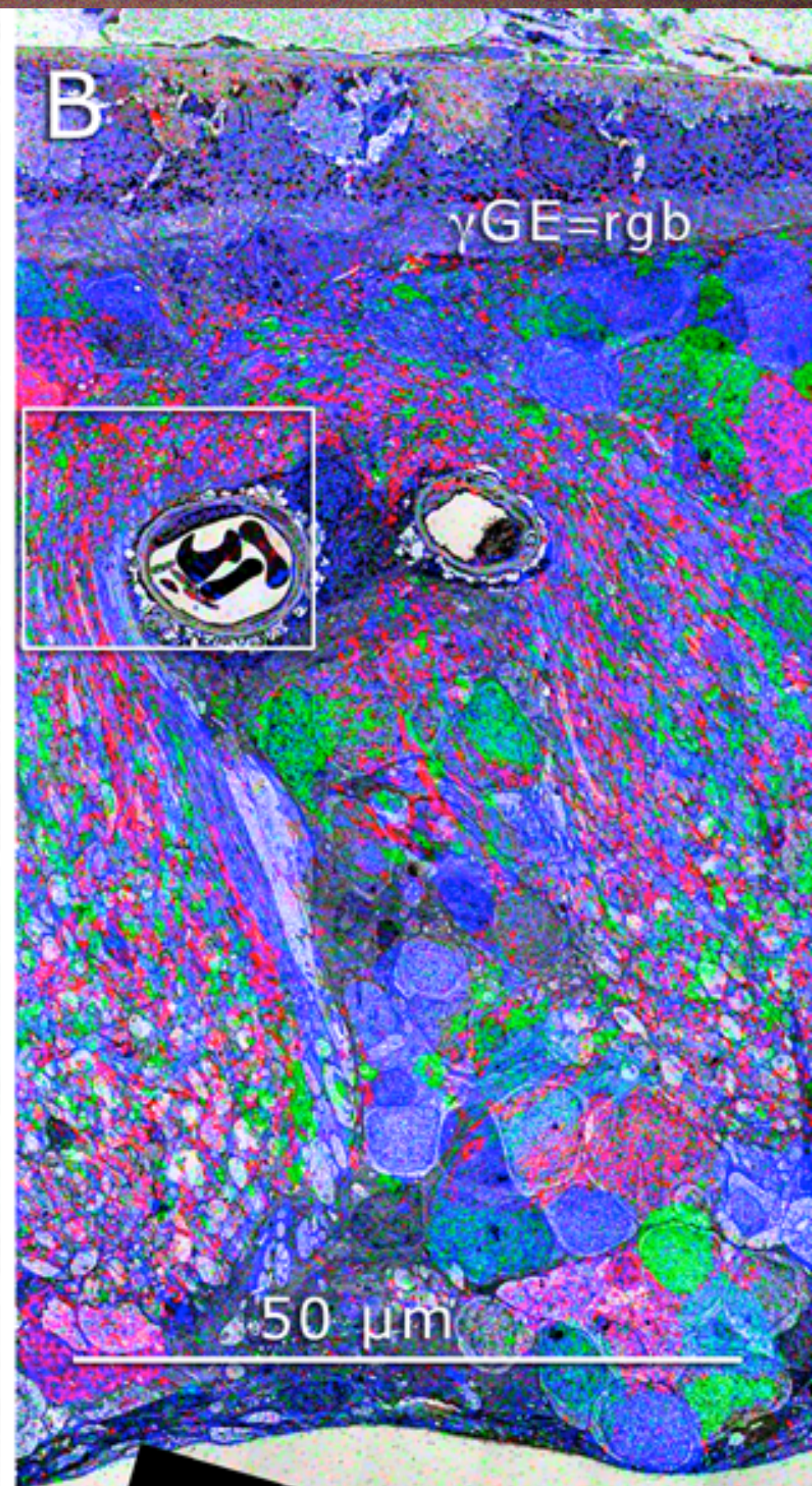
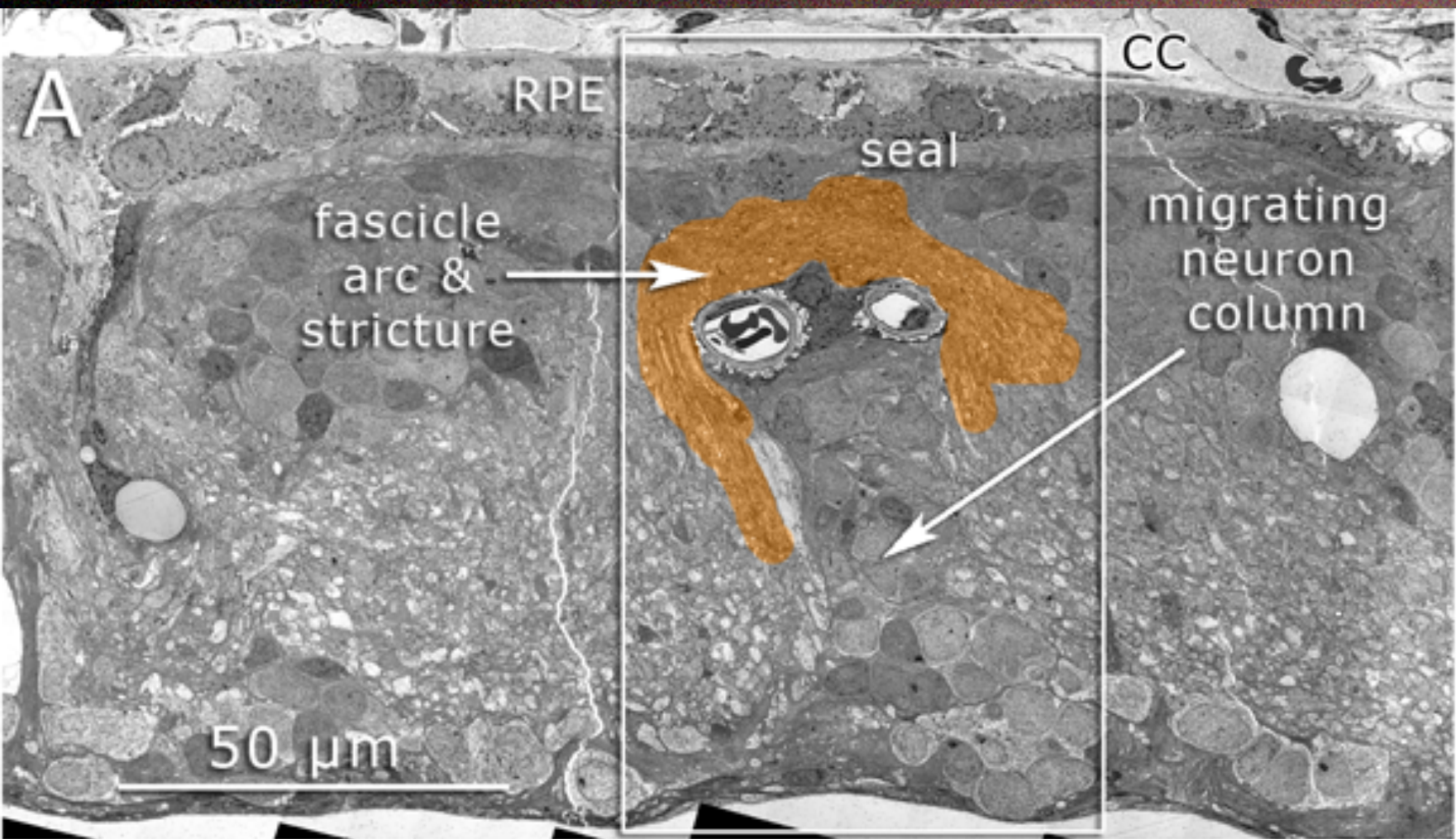
CAPILLARY

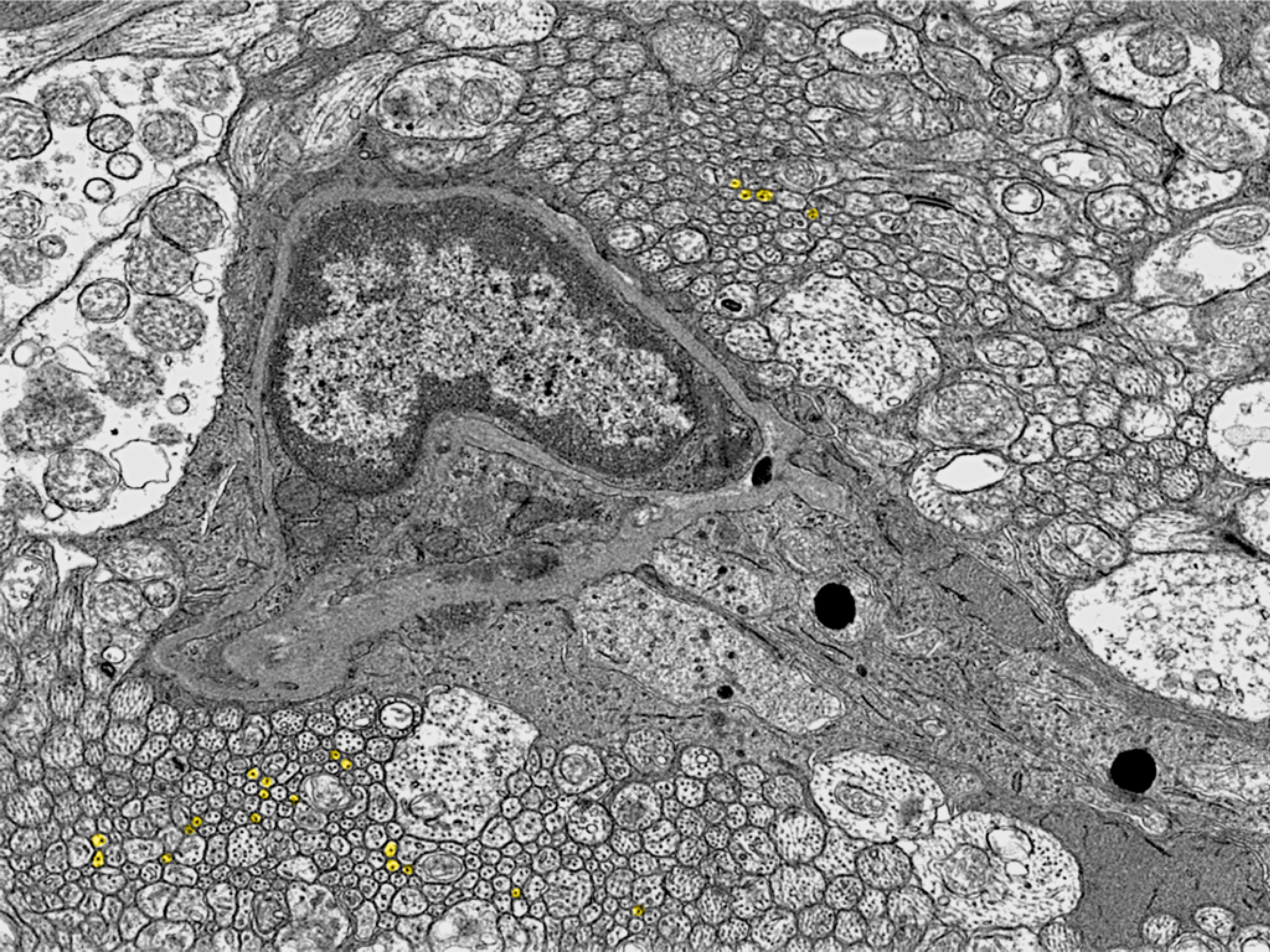
RETINAL REMODELING :: MICRONEUROMAS & NEURITOGENESIS

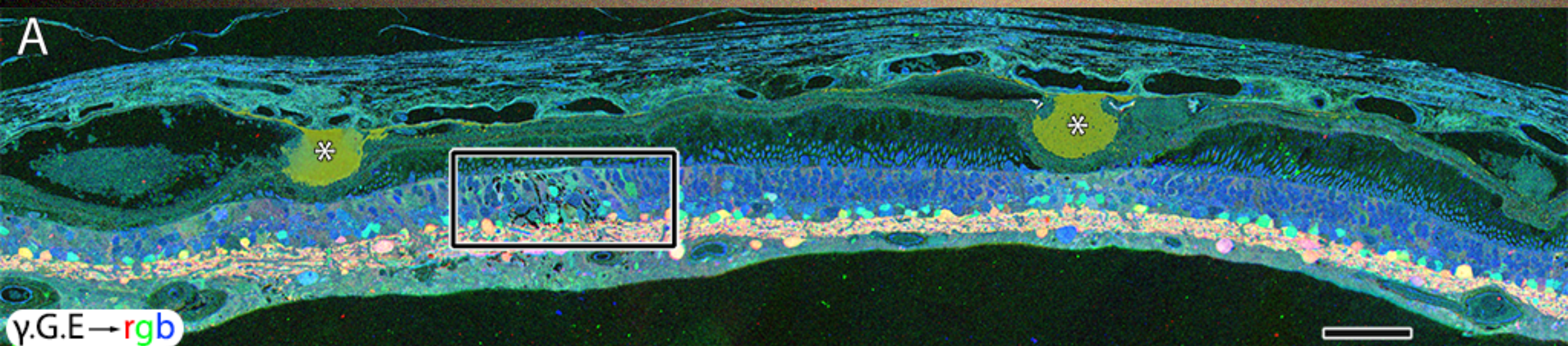
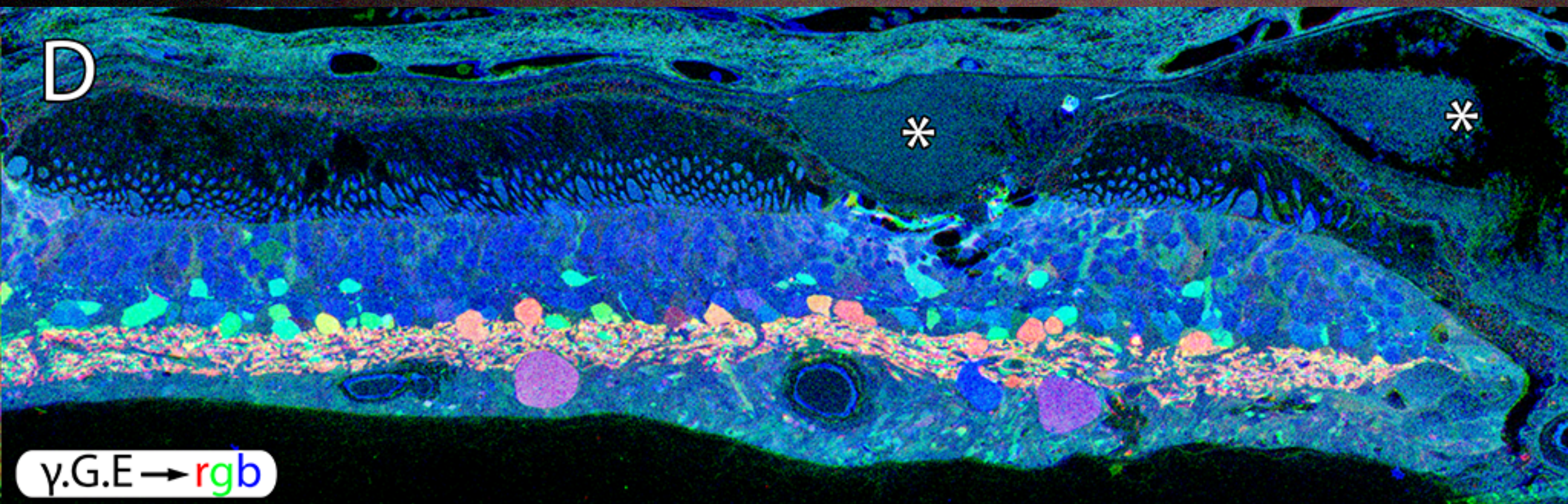


Jones BW, et al 2003 Retinal remodeling triggered by photoreceptor degenerations. J Comp Neurol 464: 1-16.
Marc RE, BW Jones and CB Watt 2005 Retinal remodeling: Circuitry revisions triggered by photoreceptor degeneration. In Plasticity in the Visual system: from Genes to Circuits. Eds, Pinaud et al., Springer, pp. 33-54.

RETINAL REMODELING :: MICRONEUROMAS & NEURITOGENESIS





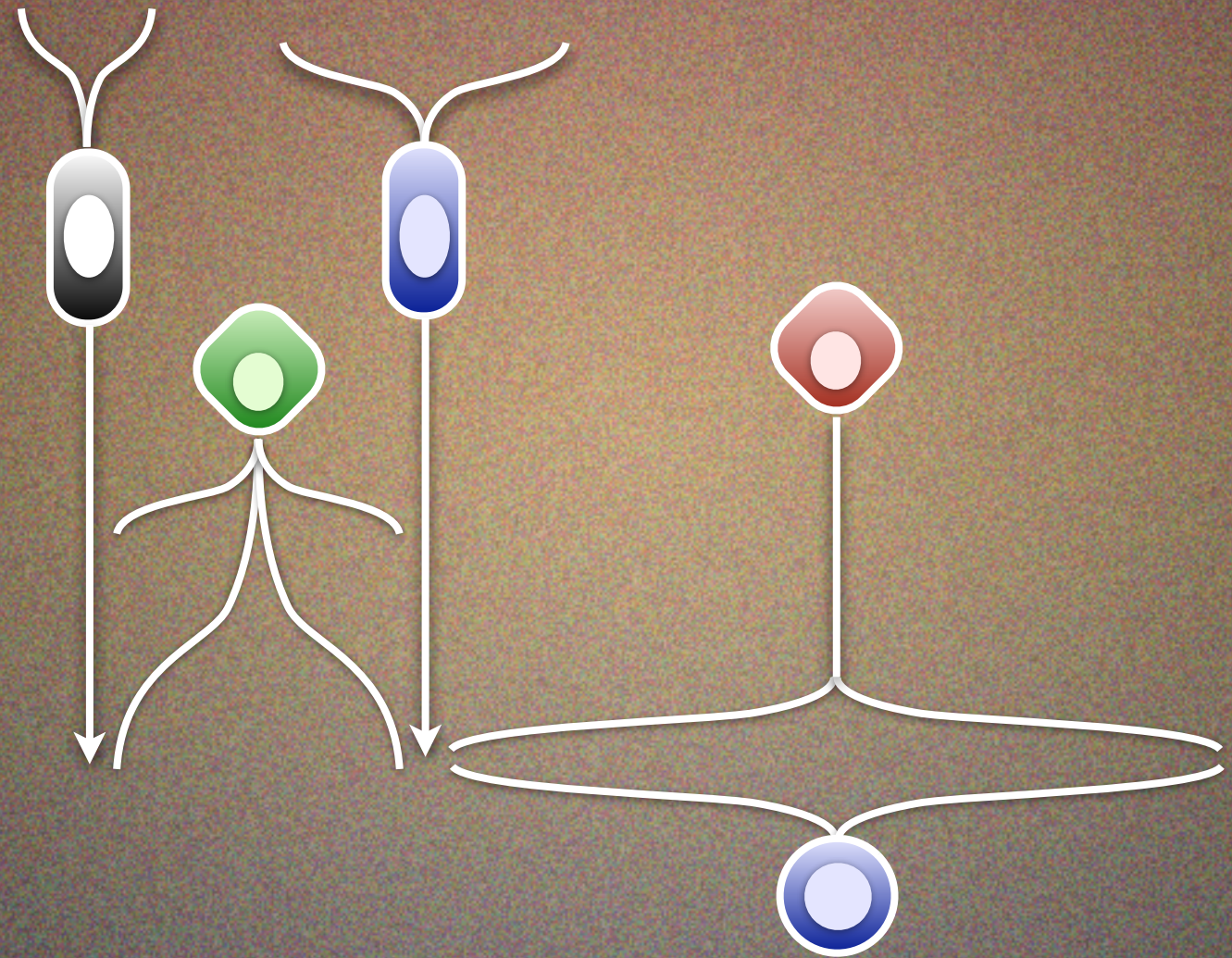


Frontiers in Cellular Neuroscience 2016 Apr 28;10:103. doi: 10.3389/fncel.2016.00103. eCollection 2016.
 Retinal Remodeling and Metabolic Alterations in Human AMD.
 Jones BW, Pfeiffer RL, Ferrell WD, Watt CB, Tucker J, Marc RE.

RETINAL REMODELING :: MICRONEUROMAS & NEURITOGENESIS

All classes of neurons
show new neurite
growth in phase 3
restructuring

This leads to the
formation of retinal
microneuromas ...
new circuitry

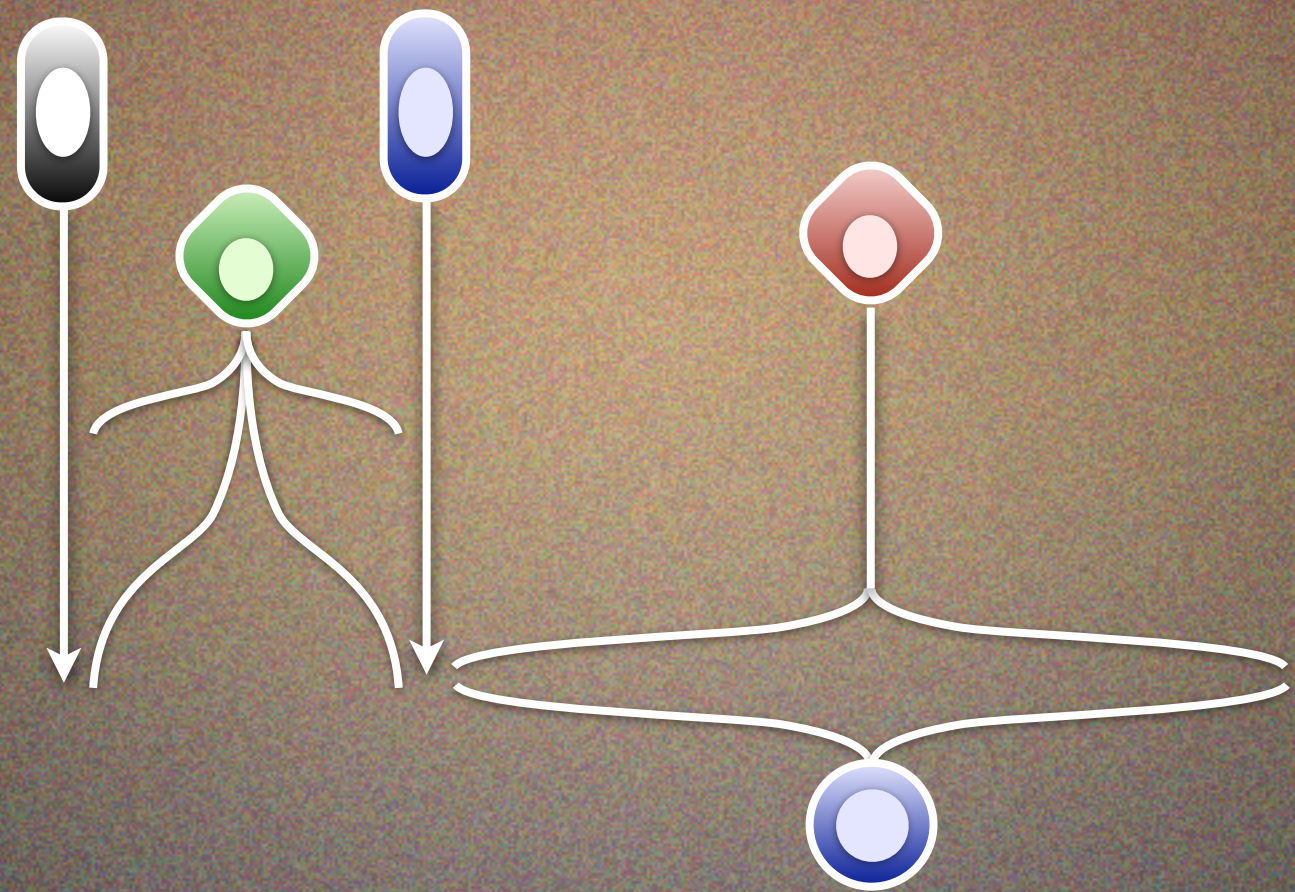


Jones BW, et al 2003 Retinal remodeling
triggered by photoreceptor degenerations. J
Comp Neurol 464: 1-16.

RETINAL REMODELING :: MICRONEUROMAS & NEURITOGENESIS

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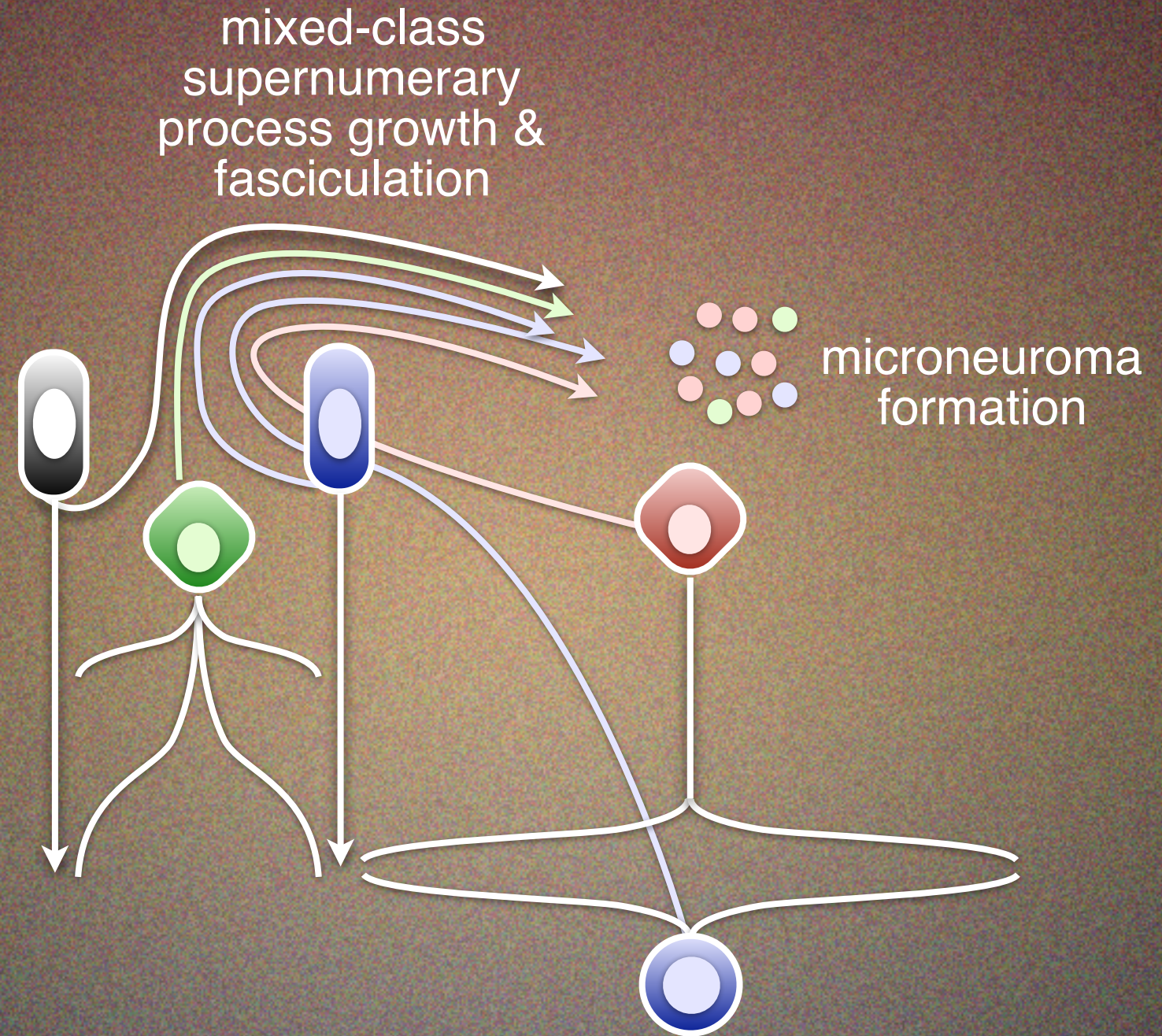


Jones BW, et al 2003 Retinal remodeling
triggered by photoreceptor degenerations. J
Comp Neurol 464: 1-16.

RETINAL REMODELING :: MICRONEUROMAS & NEURITOGENESIS

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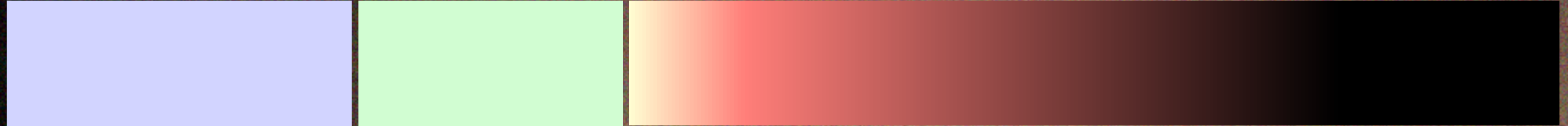
This leads to the
formation of retinal
microneuromas ...
new circuitry



Jones BW, et al 2003 Retinal remodeling
triggered by photoreceptor degenerations. J
Comp Neurol 464: 1-16.

RETINAL REMODELING :: REPROGRAMMING

$\phi 1$	$\phi 2$	$\phi 3$	$\phi 4$
PR Stress	PR Death	Remodeling	Neurodegeneration



Rod BC polarity switch
ON mGluR6 $\rightarrow$ OFF KA/AMPA

GluR2R elevation / GluR5 suppression
Retinoic Acid Receptor (RAR/RXR) pathway signaling
Retinoid sensing (CRABP II)
CaMK II $\alpha \rightarrow \beta$ switch

Glial metabolomic plasticity

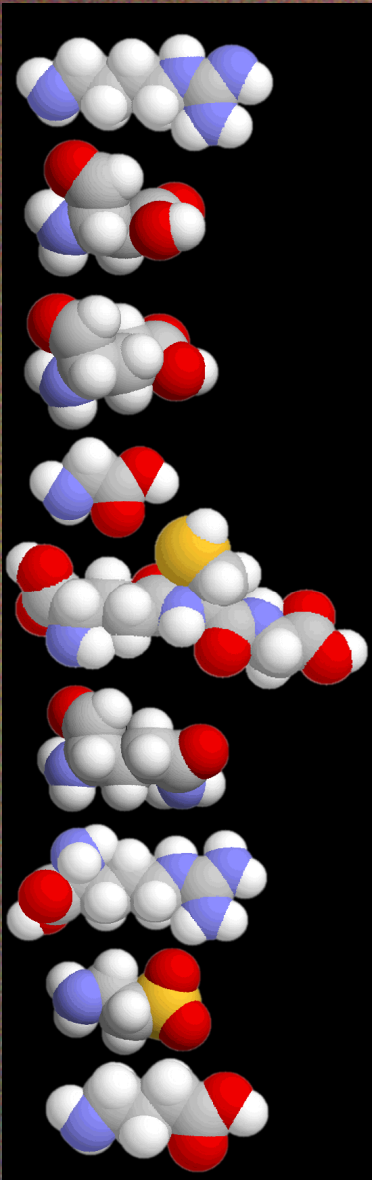
GC channel switching (HCN)

RETINAL REMODELING ::

REPROGRAMMING :: SELF-SIGNALING

Computational
Molecular Phenotyping

Excitation Mapping



AGB
asp
glu
gly
GTH
gln
arg
tau
GABA

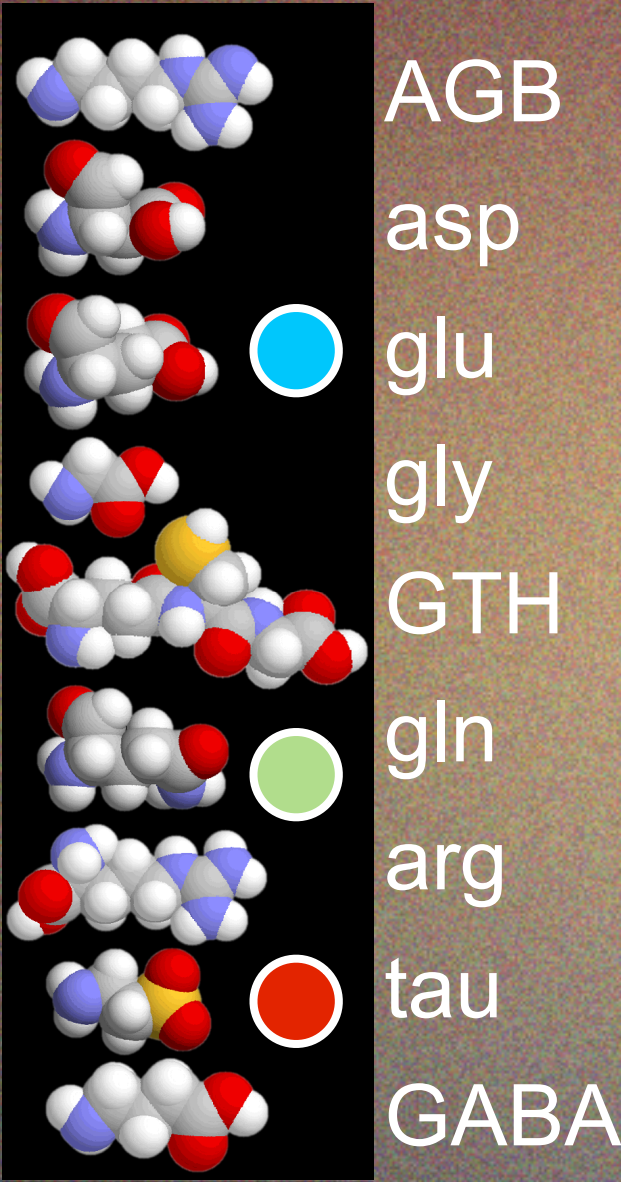


RETINAL REMODELING ::

REPROGRAMMING :: SELF-SIGNALING

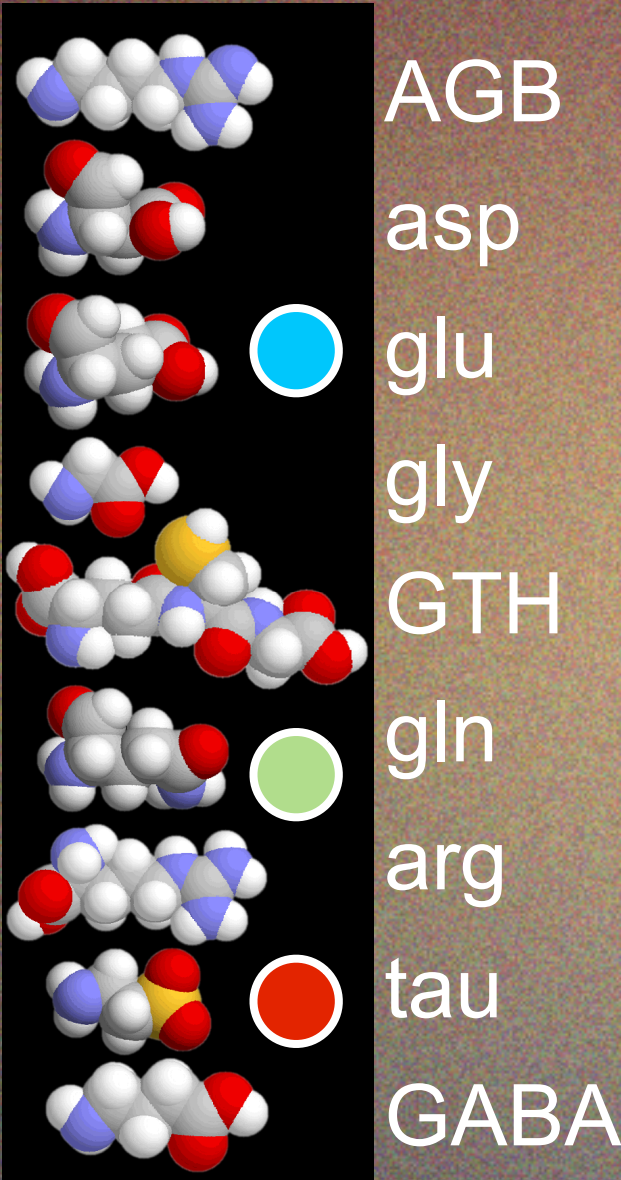
Computational
Molecular Phenotyping

Excitation Mapping



Computational
Molecular Phenotyping

Excitation Mapping

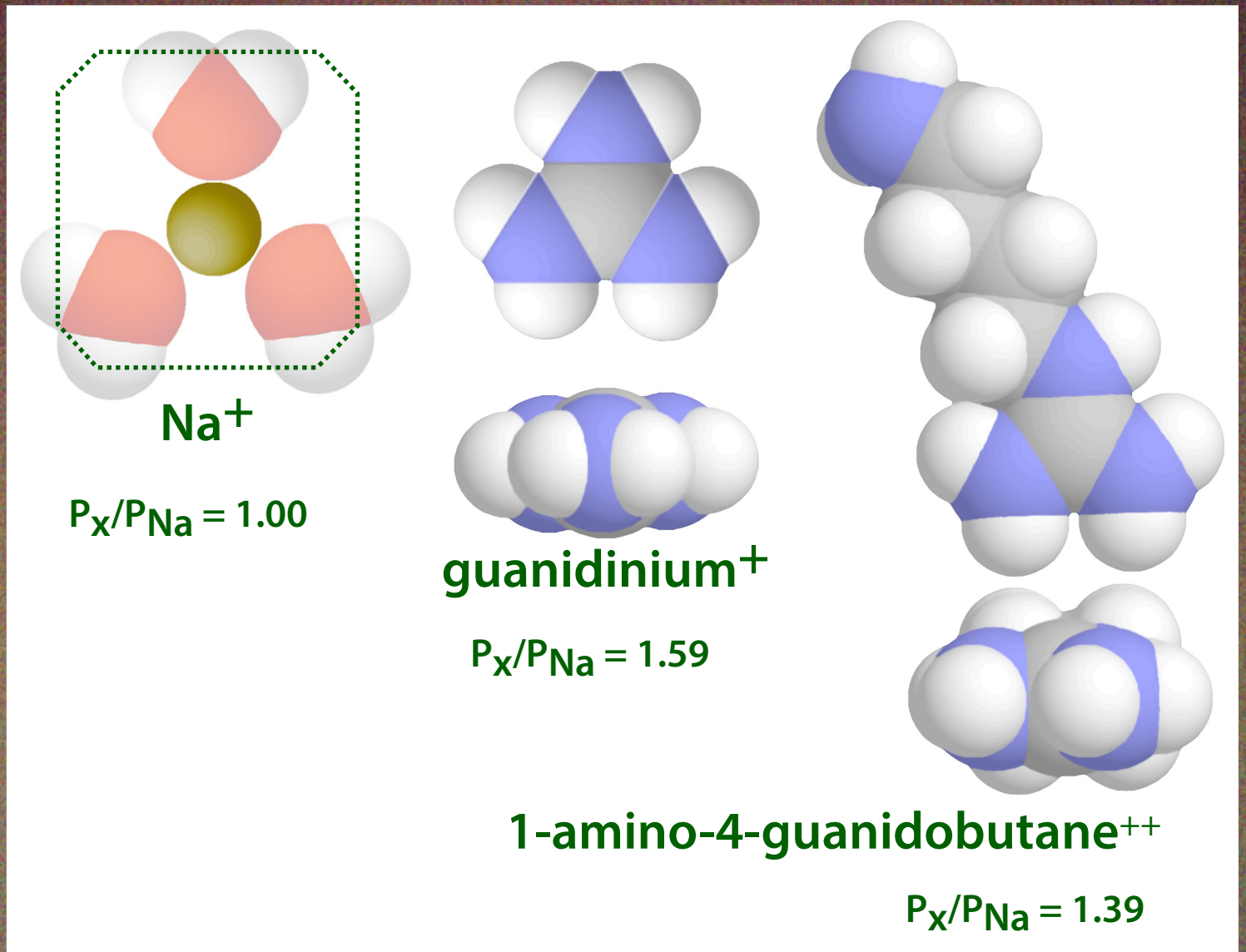


RETINAL REMODELING ::

REPROGRAMMING :: SELF-SIGNALING

Computational
Molecular Phenotyping

Excitation Mapping

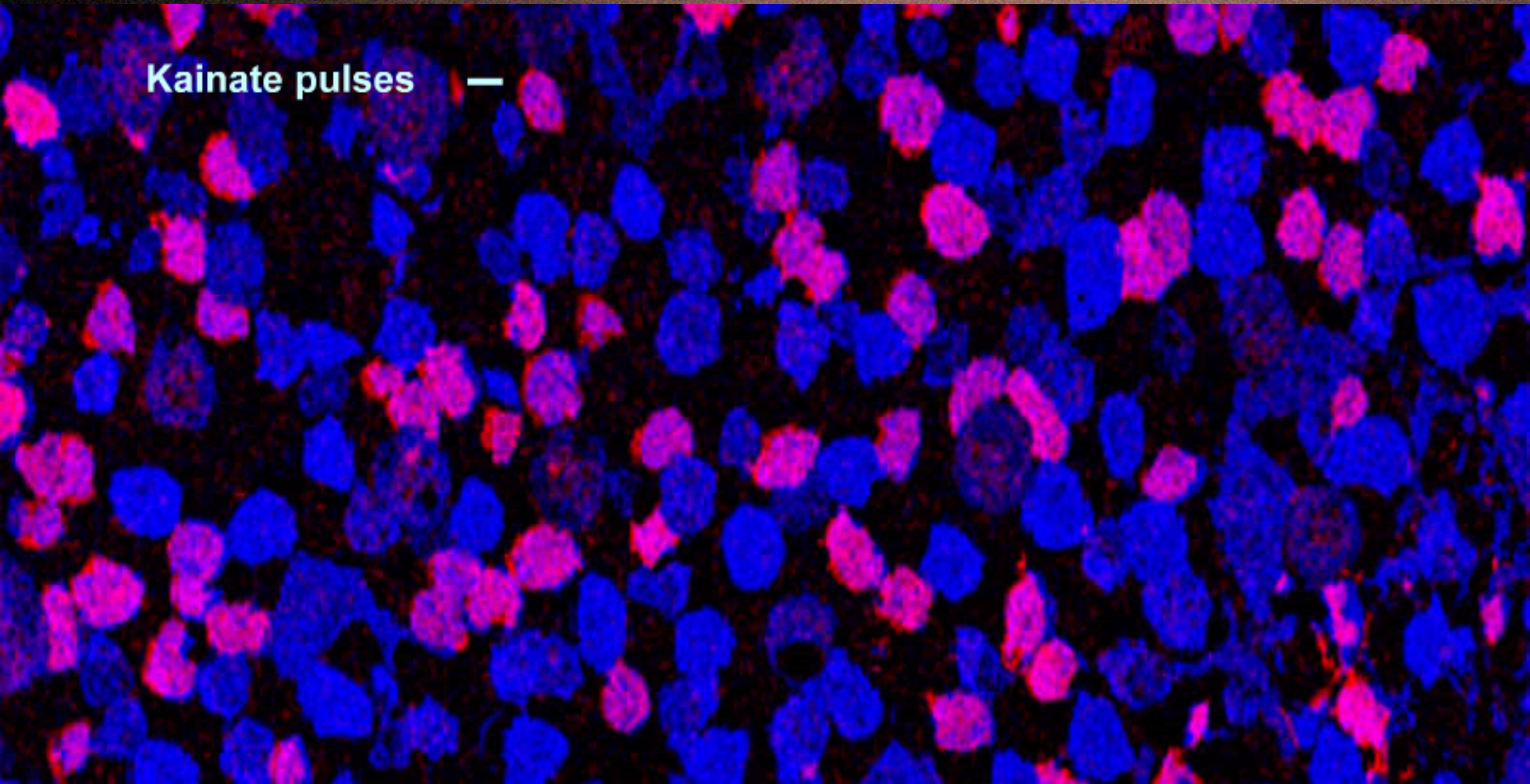


Excitation mapping using
Channel-Permeant Organic Cations

1999 Marc RE. Mapping glutamatergic drive in the vertebrate retina with a channel permeant organic cation. J Comp Neurol

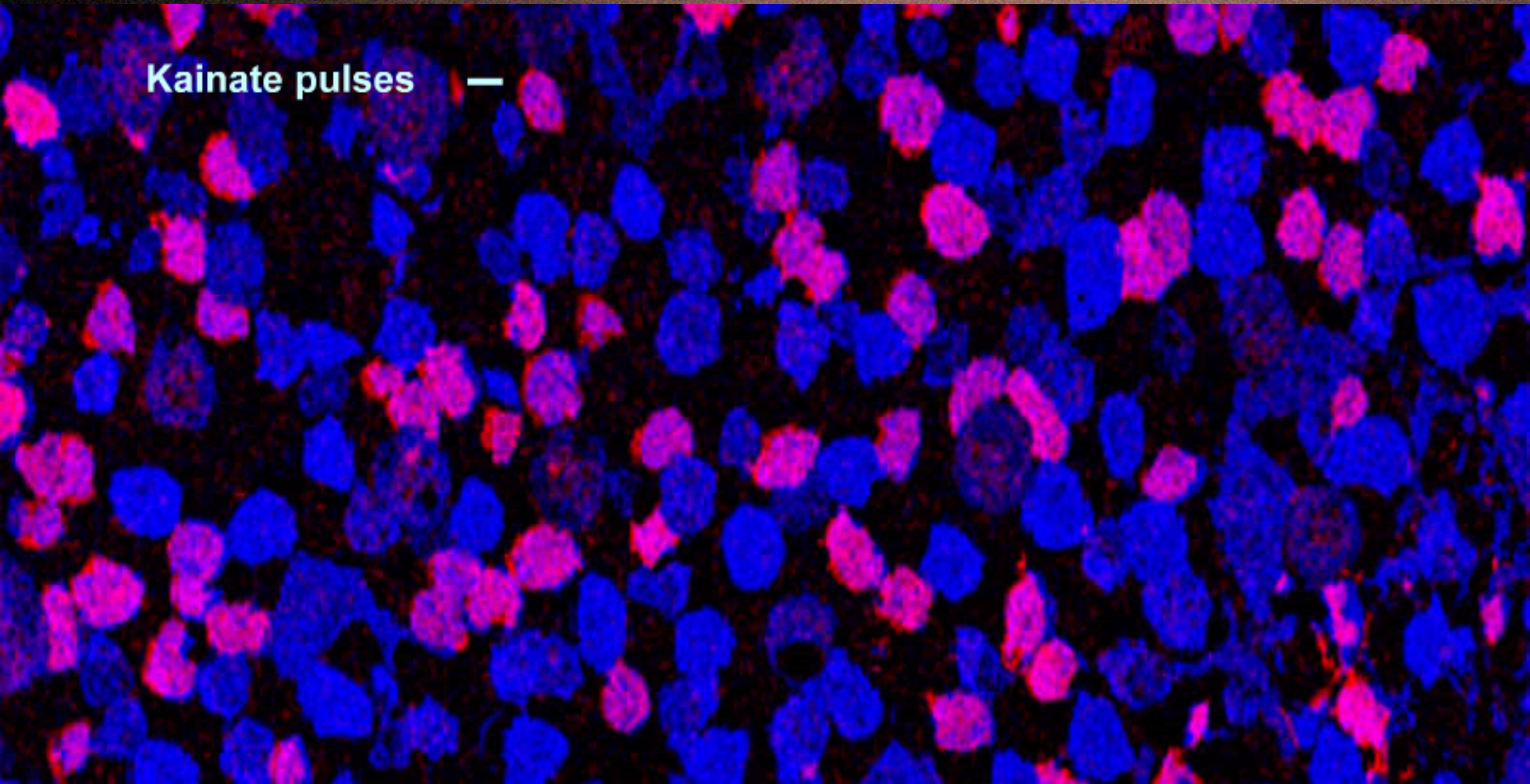
RETINAL REMODELING :: REPROGRAMMING :: SELF-SIGNALING
KA activation in rabbit retina

Gly.AGB.Glu :: rgb



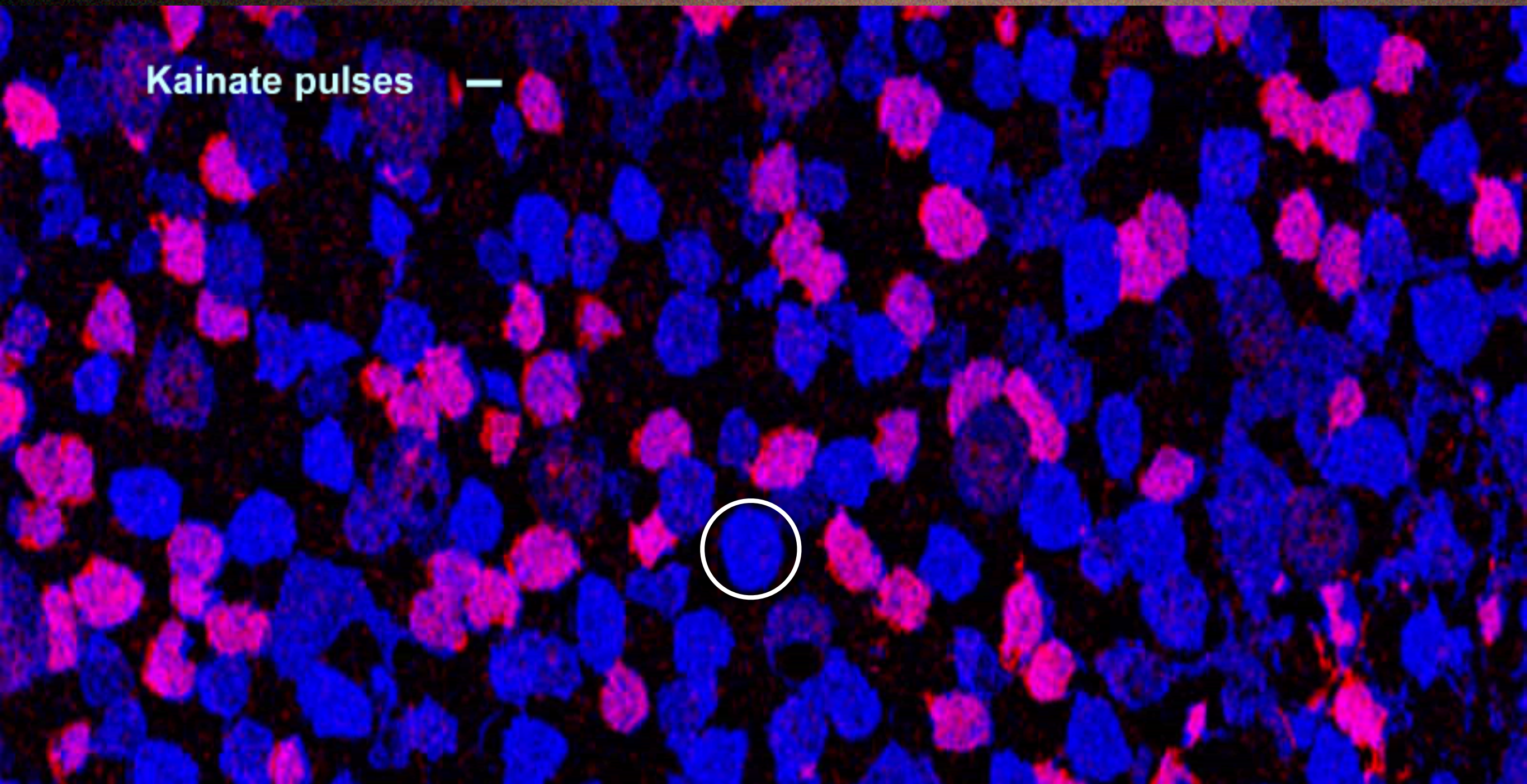
RETINAL REMODELING :: REPROGRAMMING :: SELF-SIGNALING
KA activation in rabbit retina

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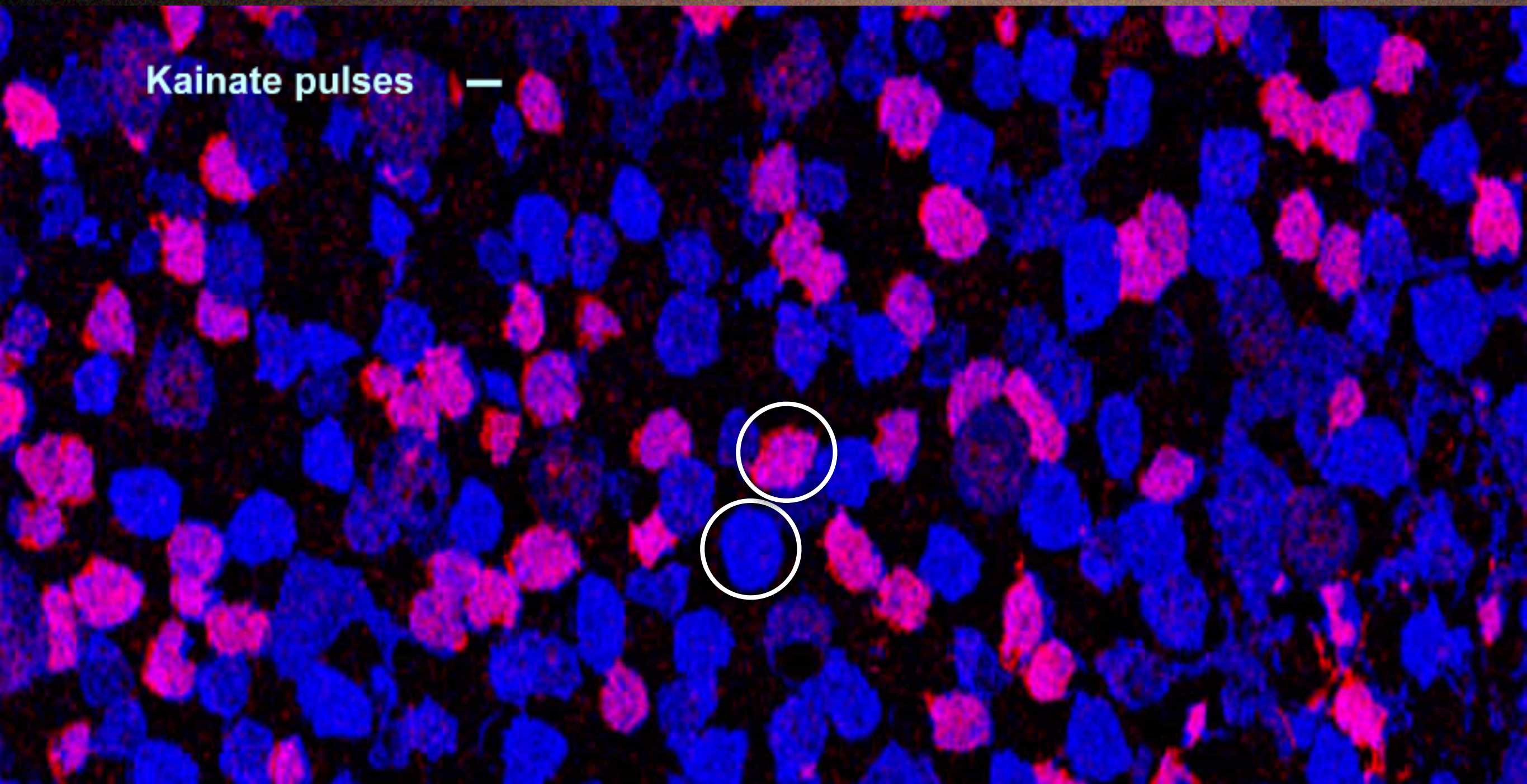
RETINAL REMODELING :: REPROGRAMMING :: SELF-SIGNALING
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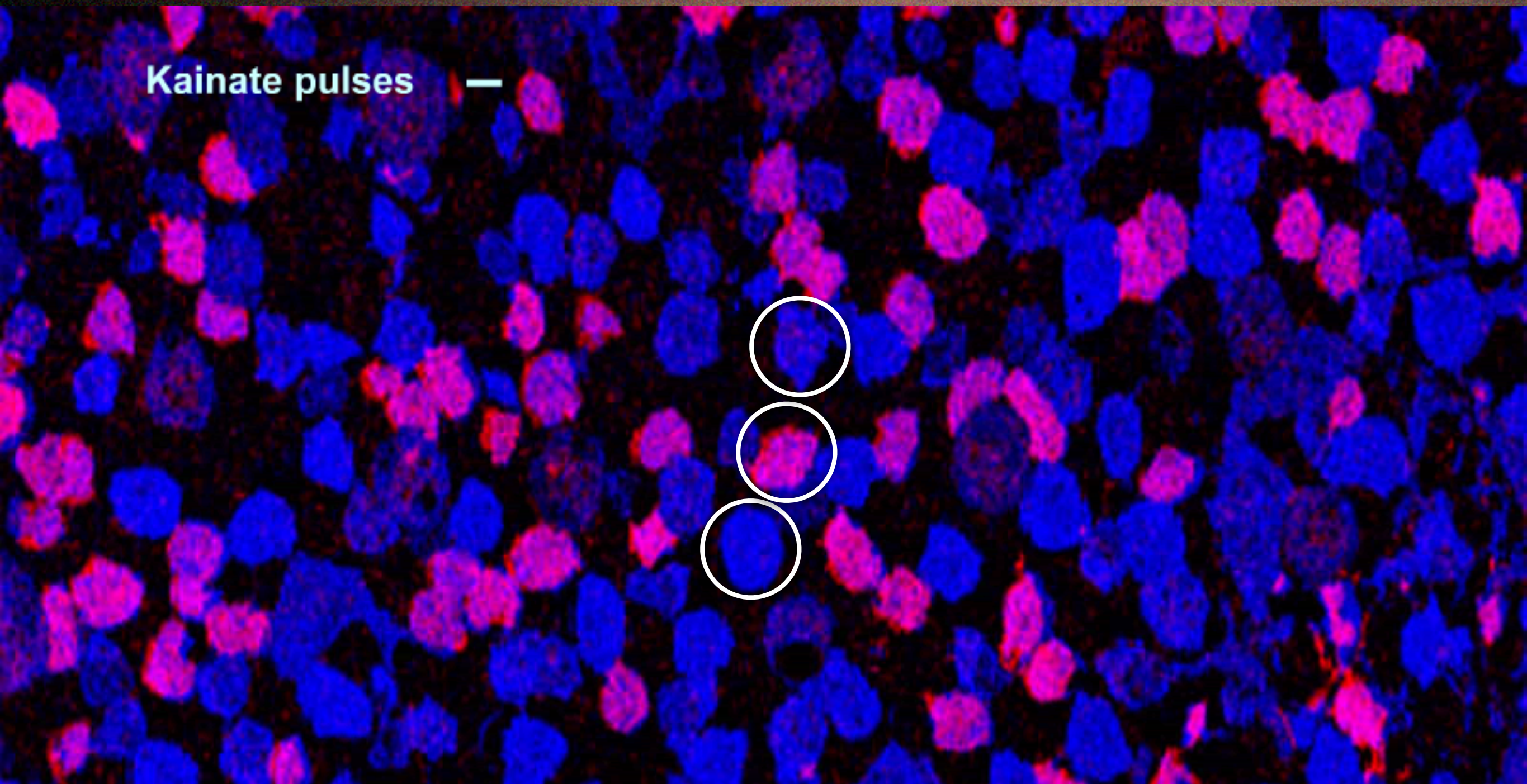
RETINAL REMODELING :: REPROGRAMMING :: SELF-SIGNALING
KA activation in rabbit retina

Gly.AGB.Glu :: rgb



RETINAL REMODELING :: REPROGRAMMING :: SELF-SIGNALING
KA activation in rabbit retina

Gly.AGB.Glu :: rgb





Rob Lucas PhD
University of Manchester

In vivo excitation mapping in wt mouse

C3H mouse

Intravitreal AGB 45'

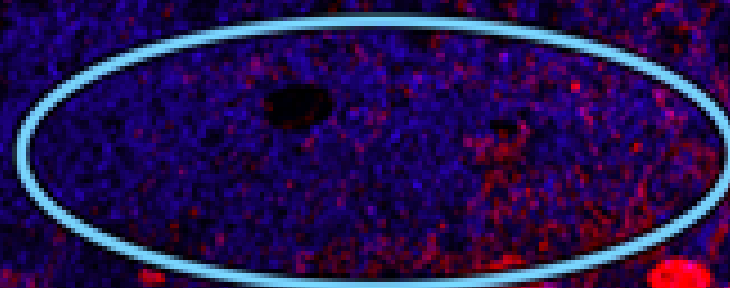
Light stimulated

GABA.glu :: rb

HCS



all BCs

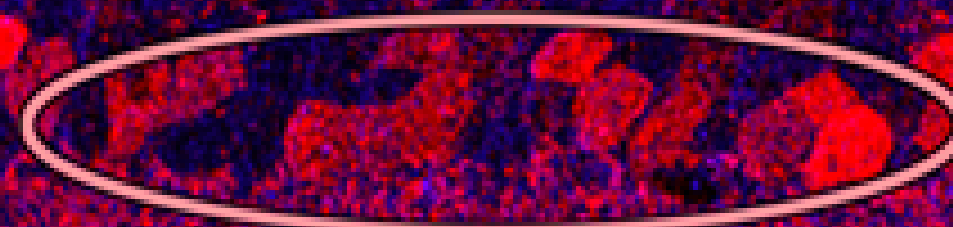


MCs →

HCS

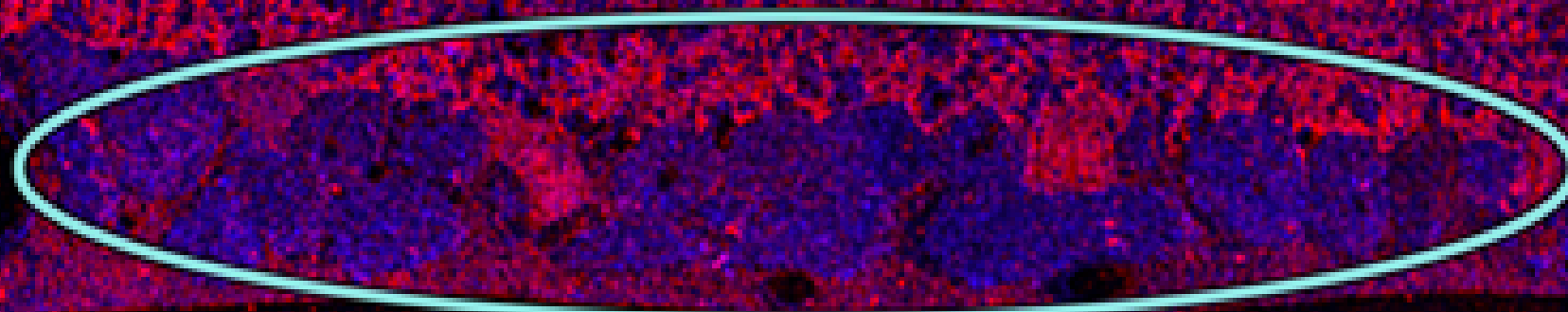


HCS



ACs

GCs



In vivo excitation mapping in wt mouse

C3H mouse

Intravitreal AGB 45'

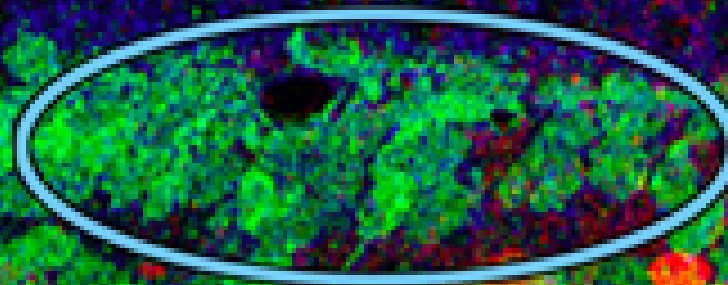
Light stimulated

GABA.AGB.glu :: rgb

HCS



all BCs



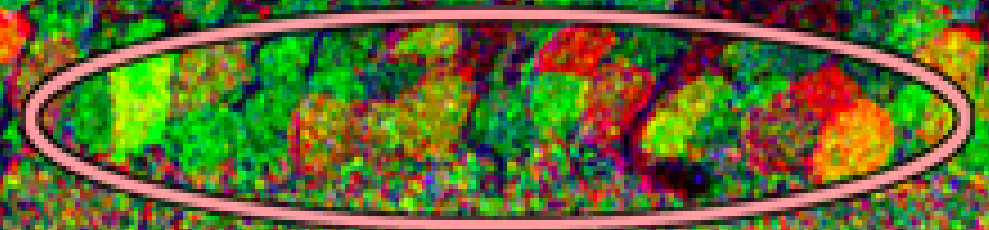
HCS



HCS

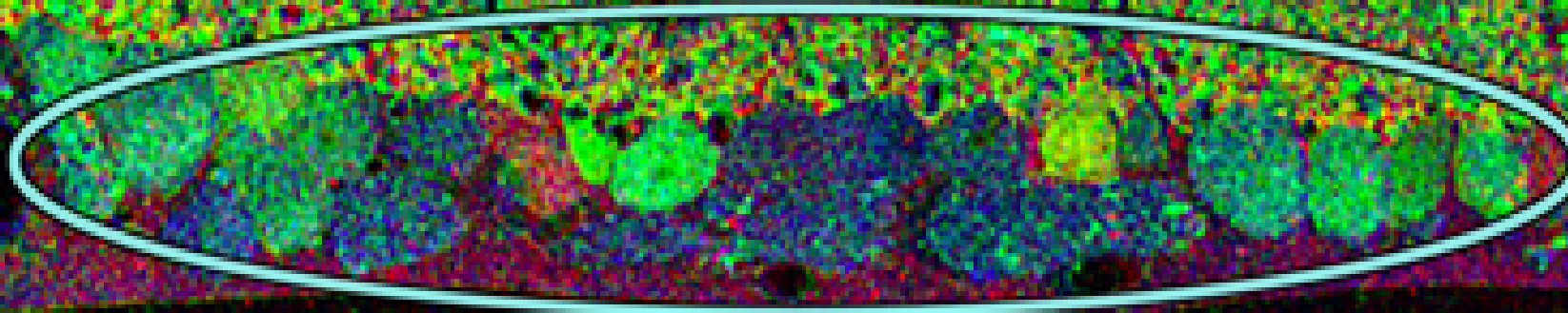


MCs →



ACs

GCs



All BCs are activated

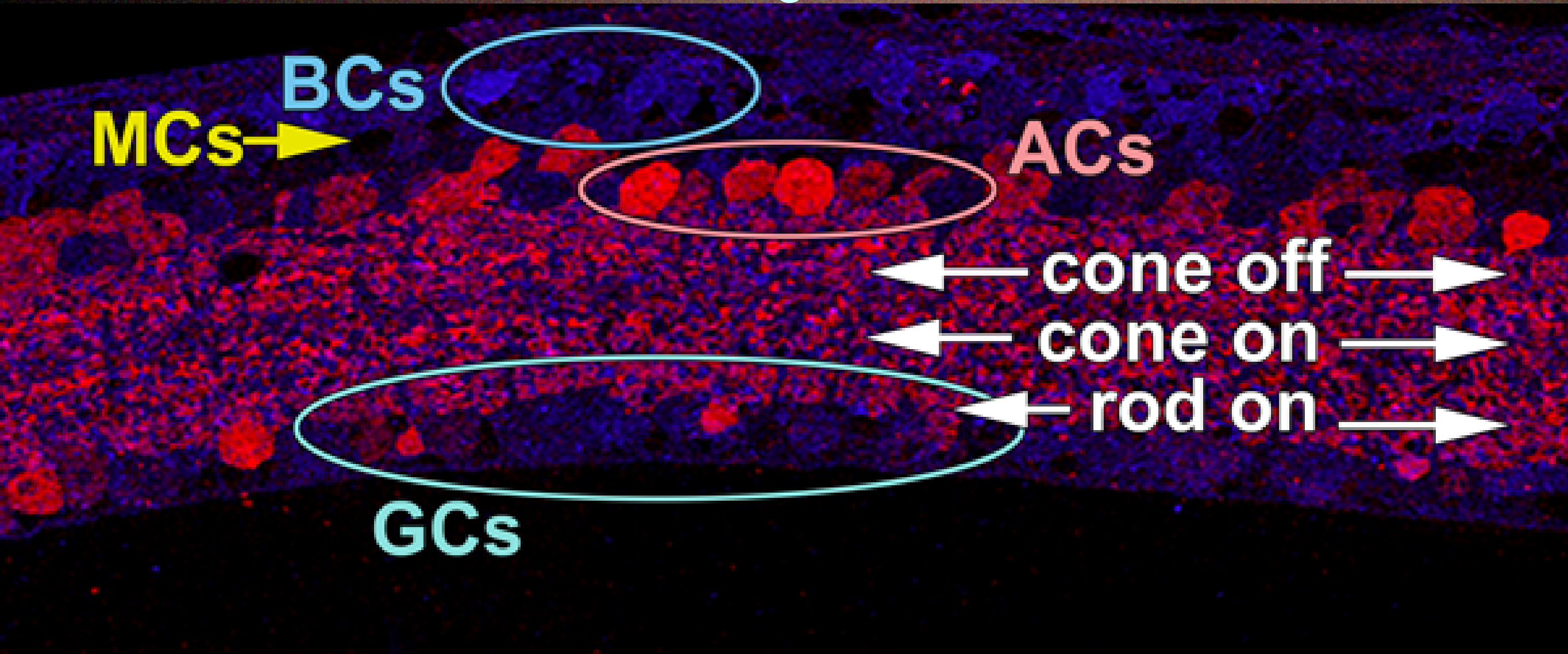
In vivo excitation mapping in rdcl mouse

rdcl mouse

Intravitreal AGB 45'

Light stimulated

GABA.glu :: rb



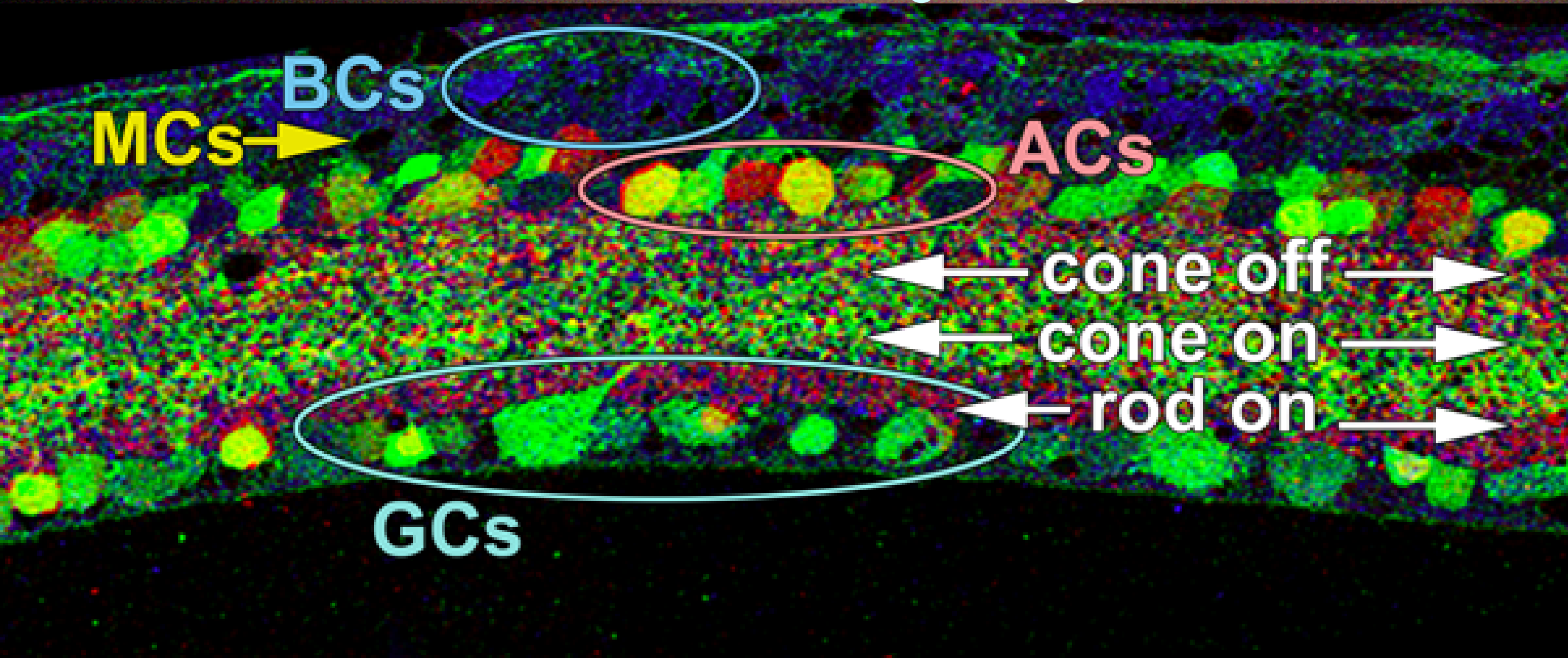
In vivo excitation mapping in rdcl mouse

rdcl mouse

Intravitreal AGB 45'

GABA.AGB.glu :: rgb

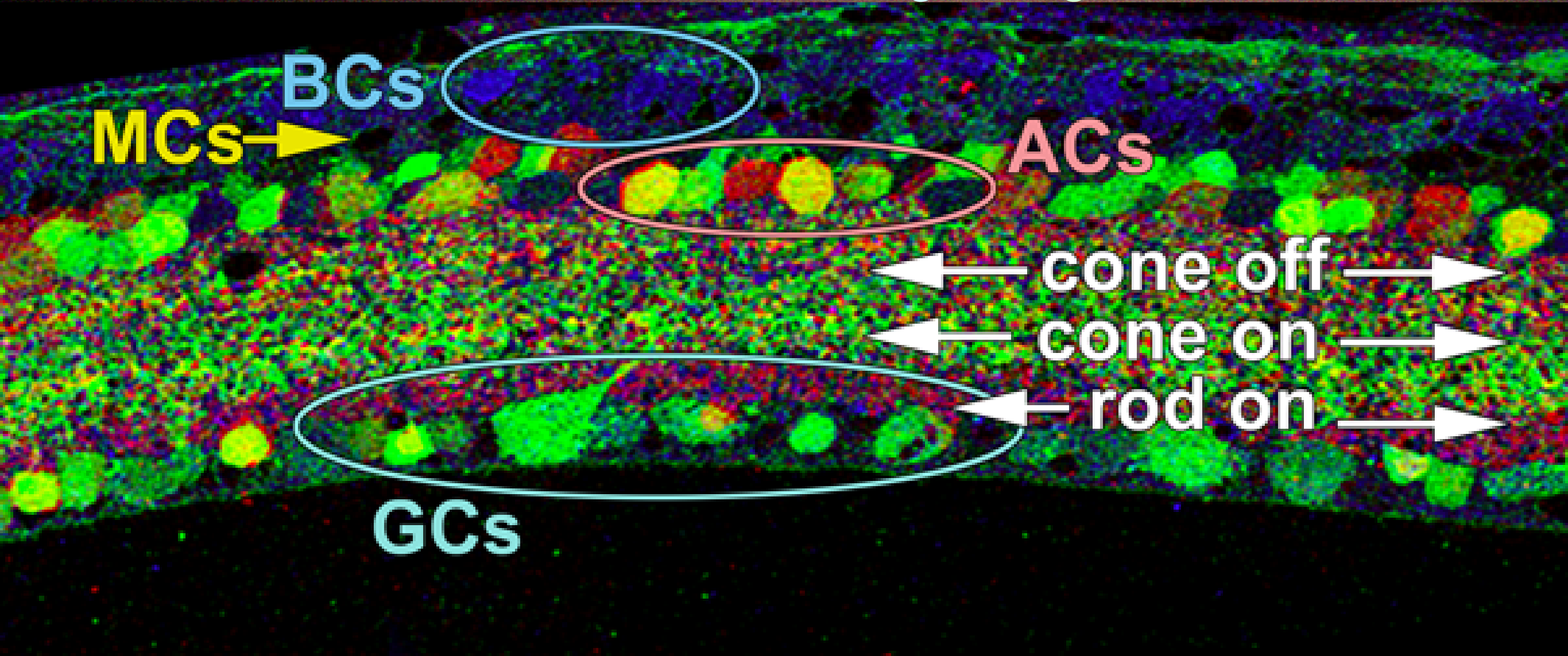
Light stimulated



All BCs are inactivated

In vivo excitation mapping in rdcl mouse

GABA.AGB.glu :: rgb



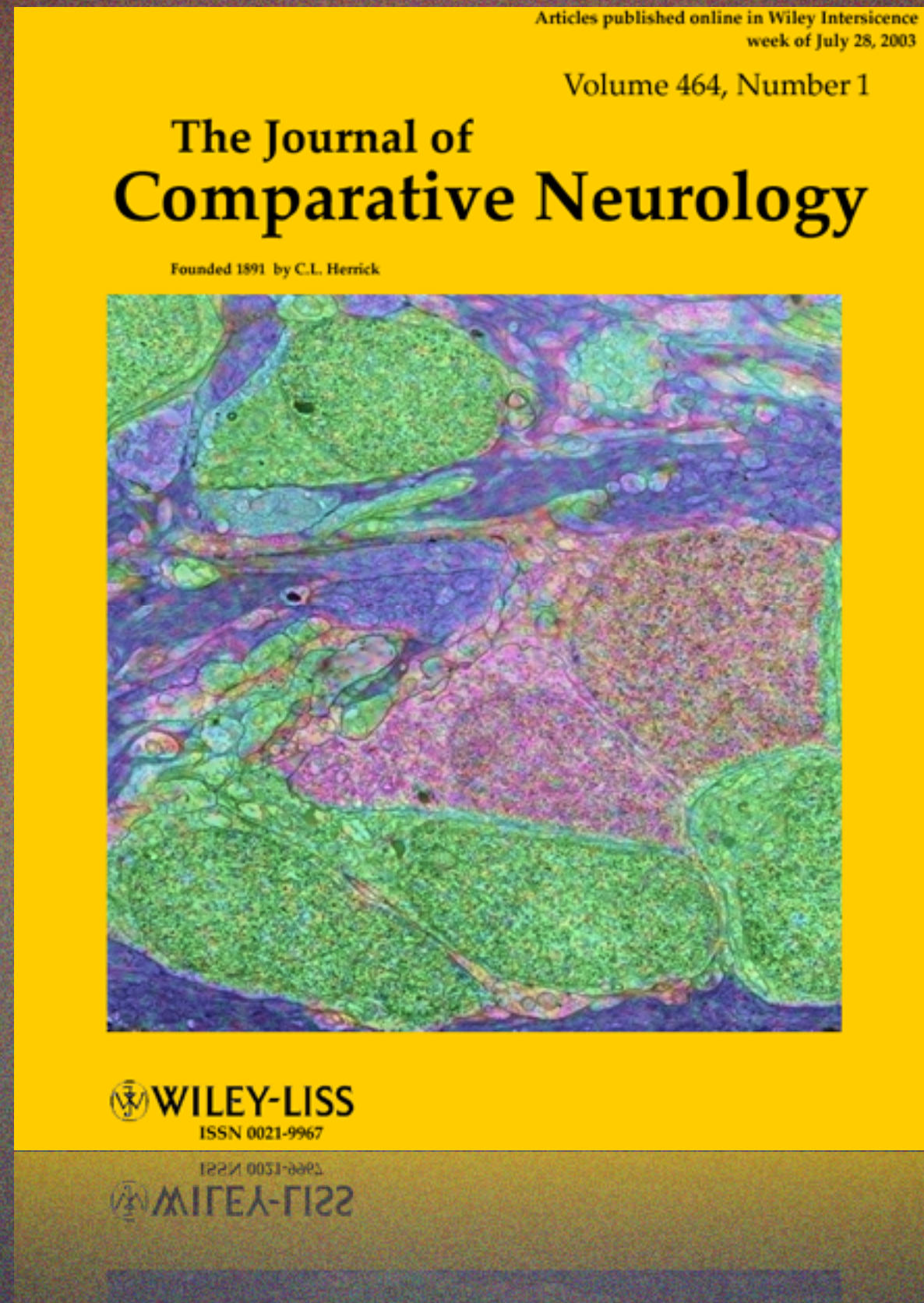
A paradox:

In remodeling, ACs & GCs continue to encode signals via iGluRs.
Conversely, BCs possess no *in vivo* iGluR- or mGluR6-transduced currents.
Spontaneous self-signaling drives oscillatory networks

Connectomics and modeling suggest that microneuromas contain resonant networks

Jones BW, et al 2003 Retinal remodeling triggered by photoreceptor degenerations. J Comp Neurol 464: 1-16.

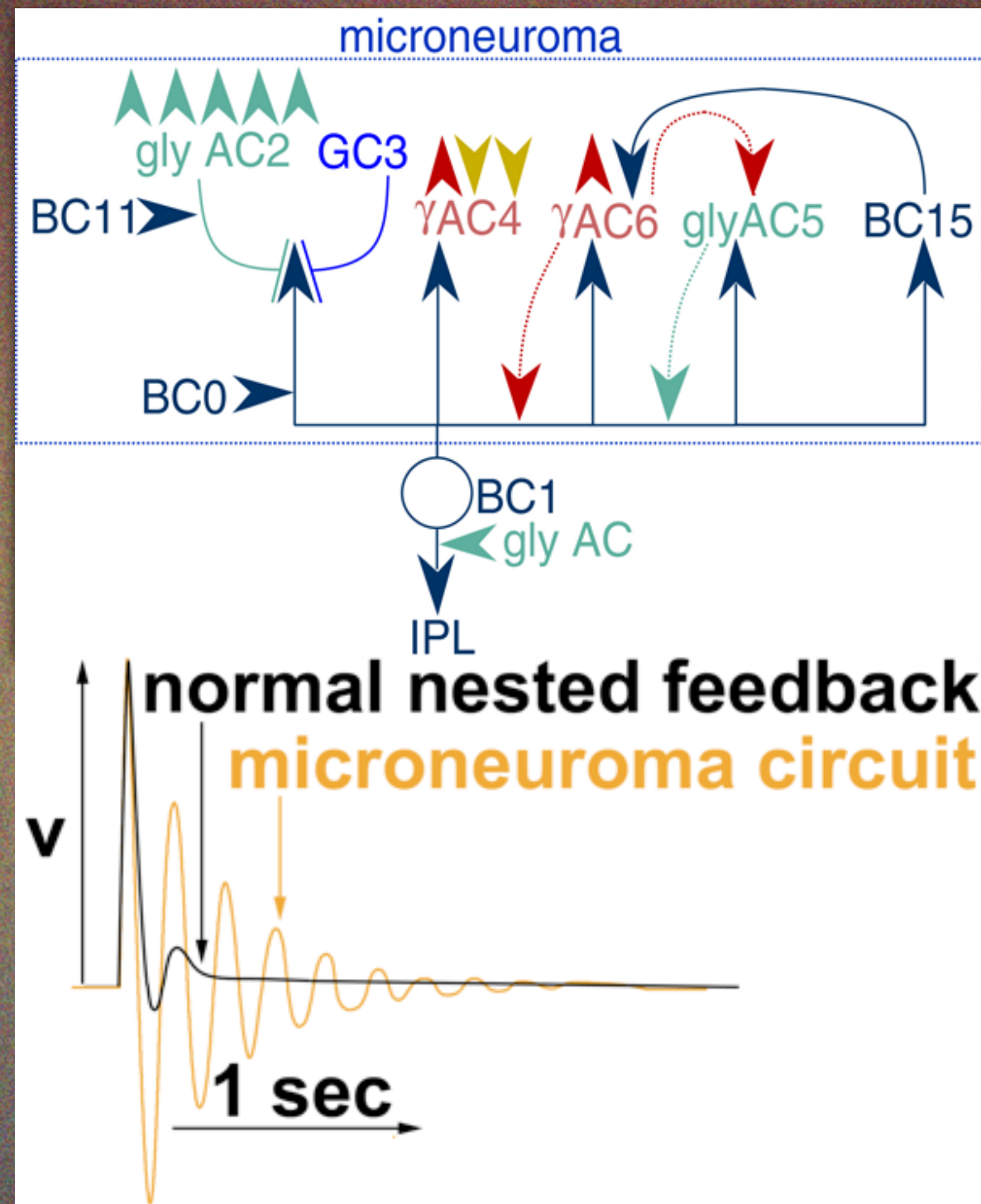
Marc RE, et al. 2005 Retinal remodeling: Circuitry revisions triggered by photoreceptor degeneration. In Plasticity in the Visual system: from Genes to Circuits. Eds, Pinaud et al., Springer, pp. 33-54.



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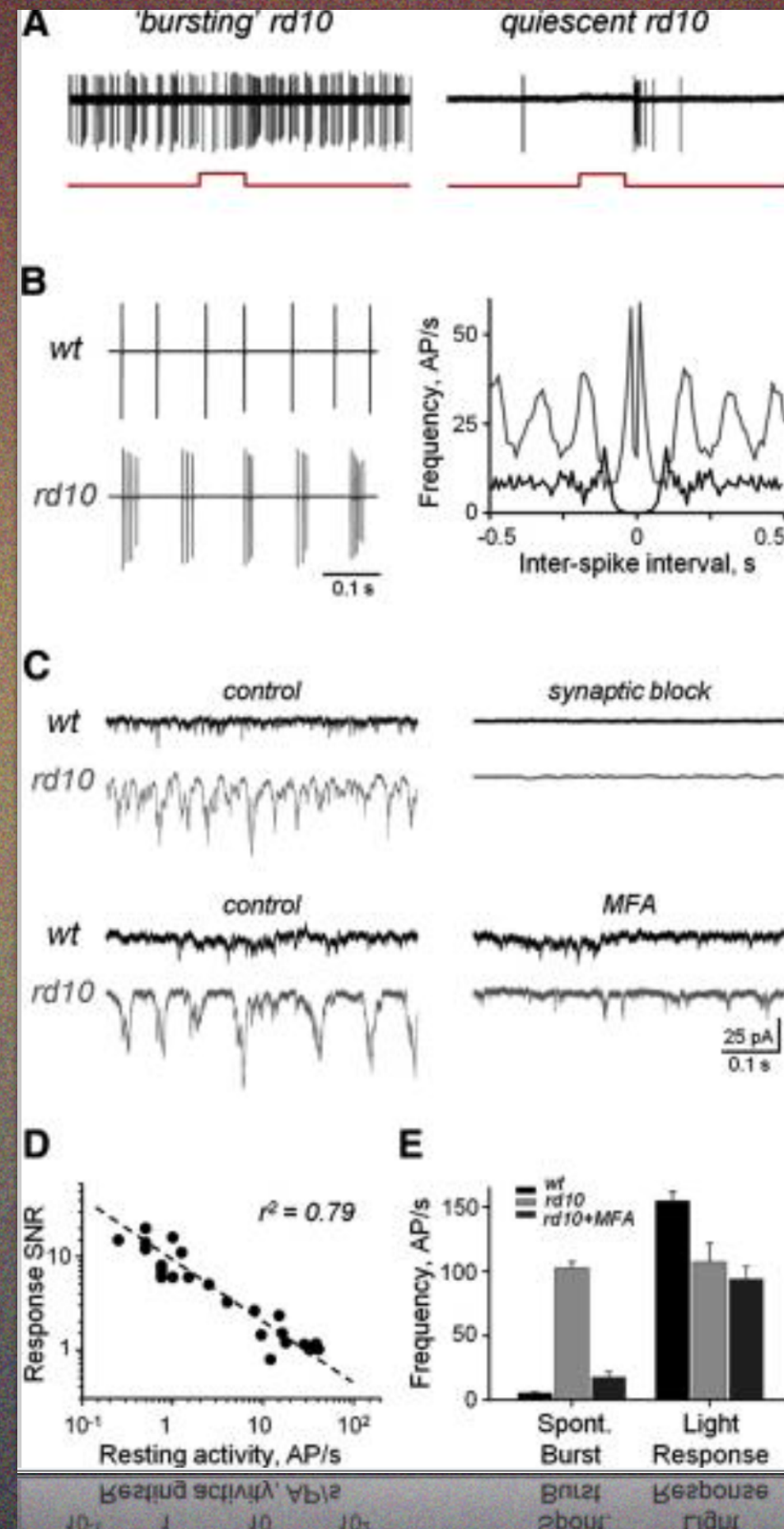
Marc RE, et al. 2005 Retinal remodeling: Circuitry revisions triggered by photoreceptor degeneration. In Plasticity in the Visual system: from Genes to Circuits. Eds, Pinaud et al., Springer, pp. 33-54.



Indeed retinal degenerations exhibit resonant networks

Toychiev et al., 2013, Block of gap junctions eliminates aberrant activity and restores light responses during retinal degeneration. J Neurosci. 33:13972-7.

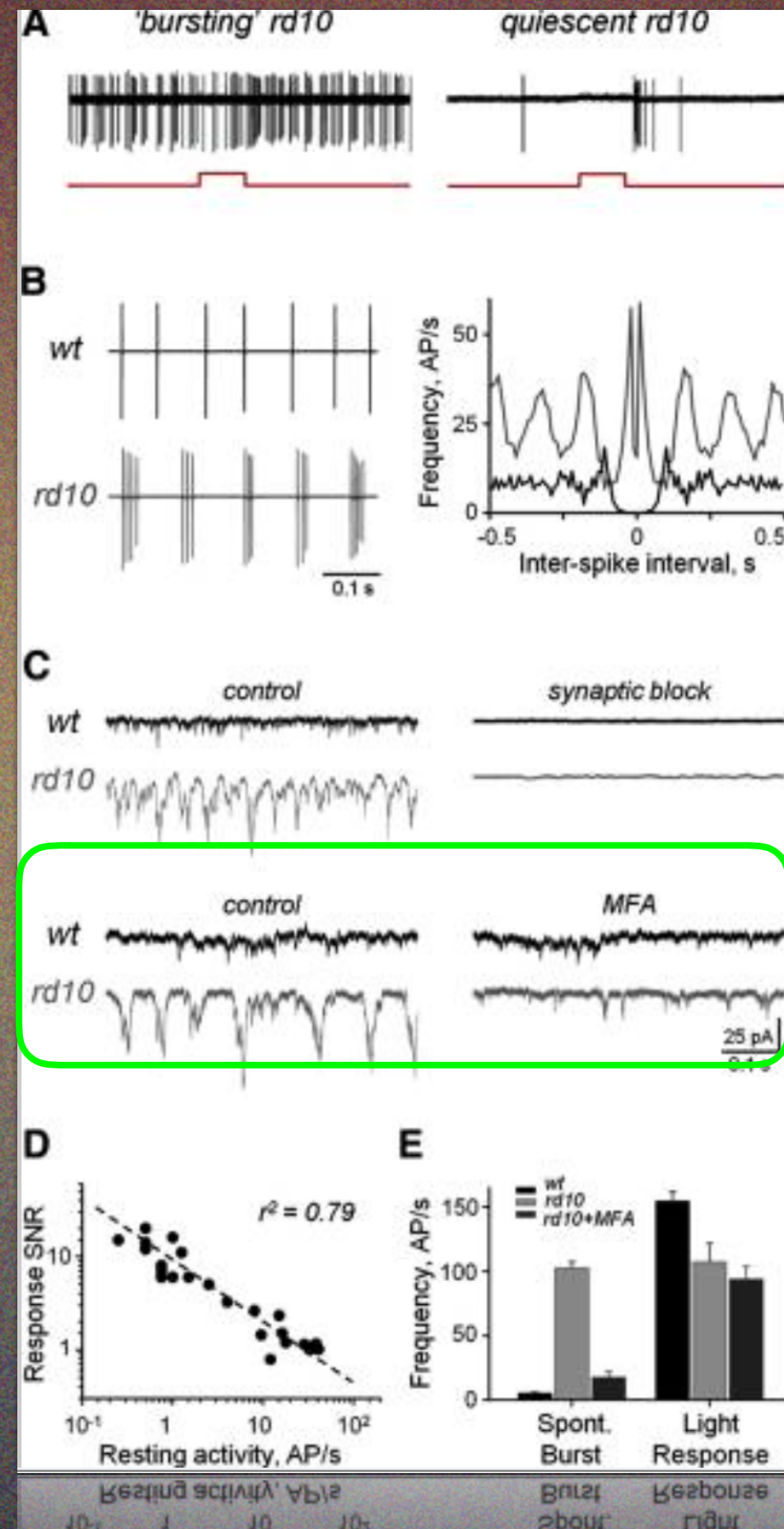
Meclofenamic acid



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Meclofenamic acid

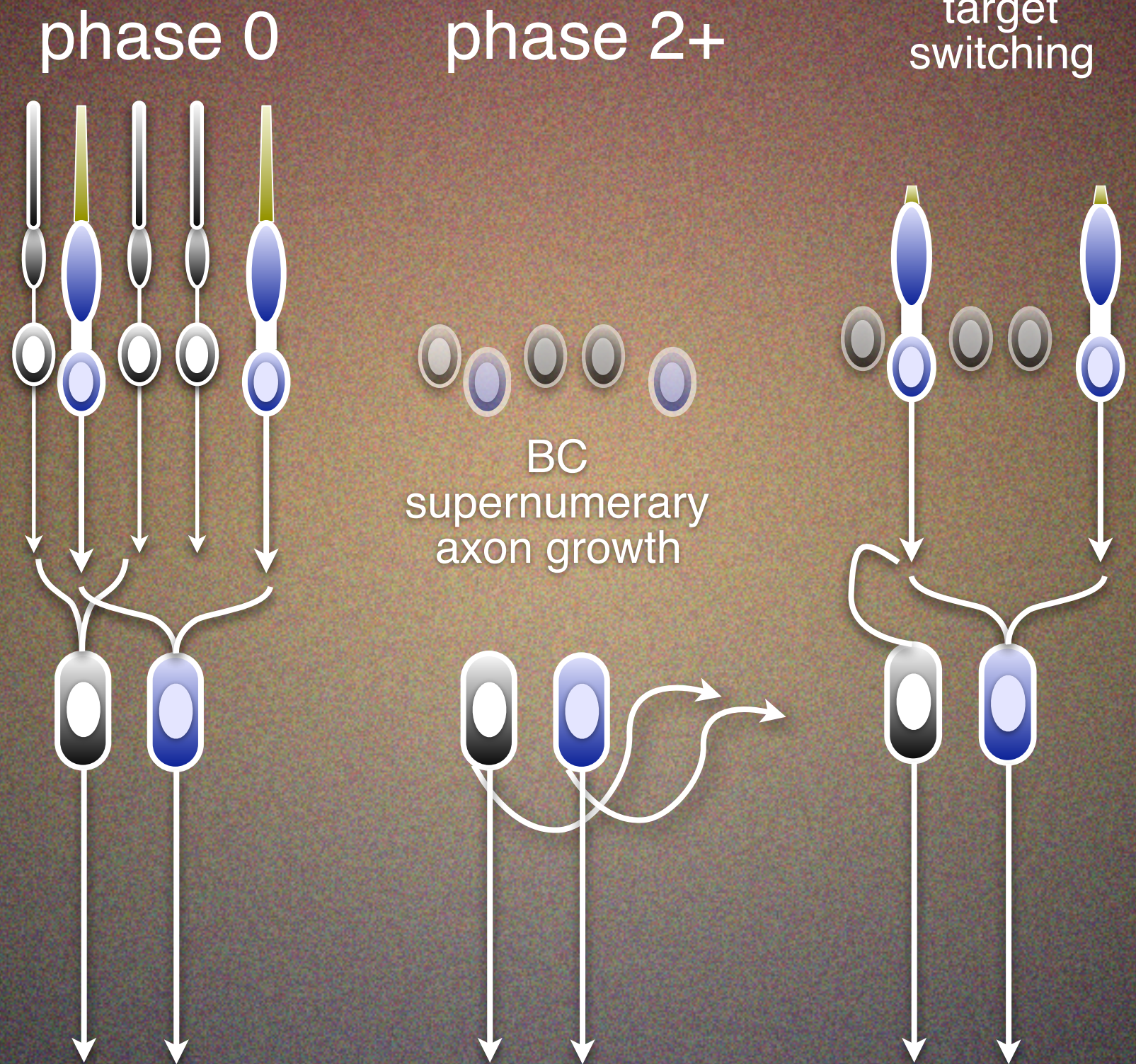


Reprogramming mGluR → iGluR switch

In cone-decimating RP,
survivor BCs form new
axons &
microneuromas

In cone-sparing RP,
circuitry remains
nominally stable,
though rod BCs show
target switching

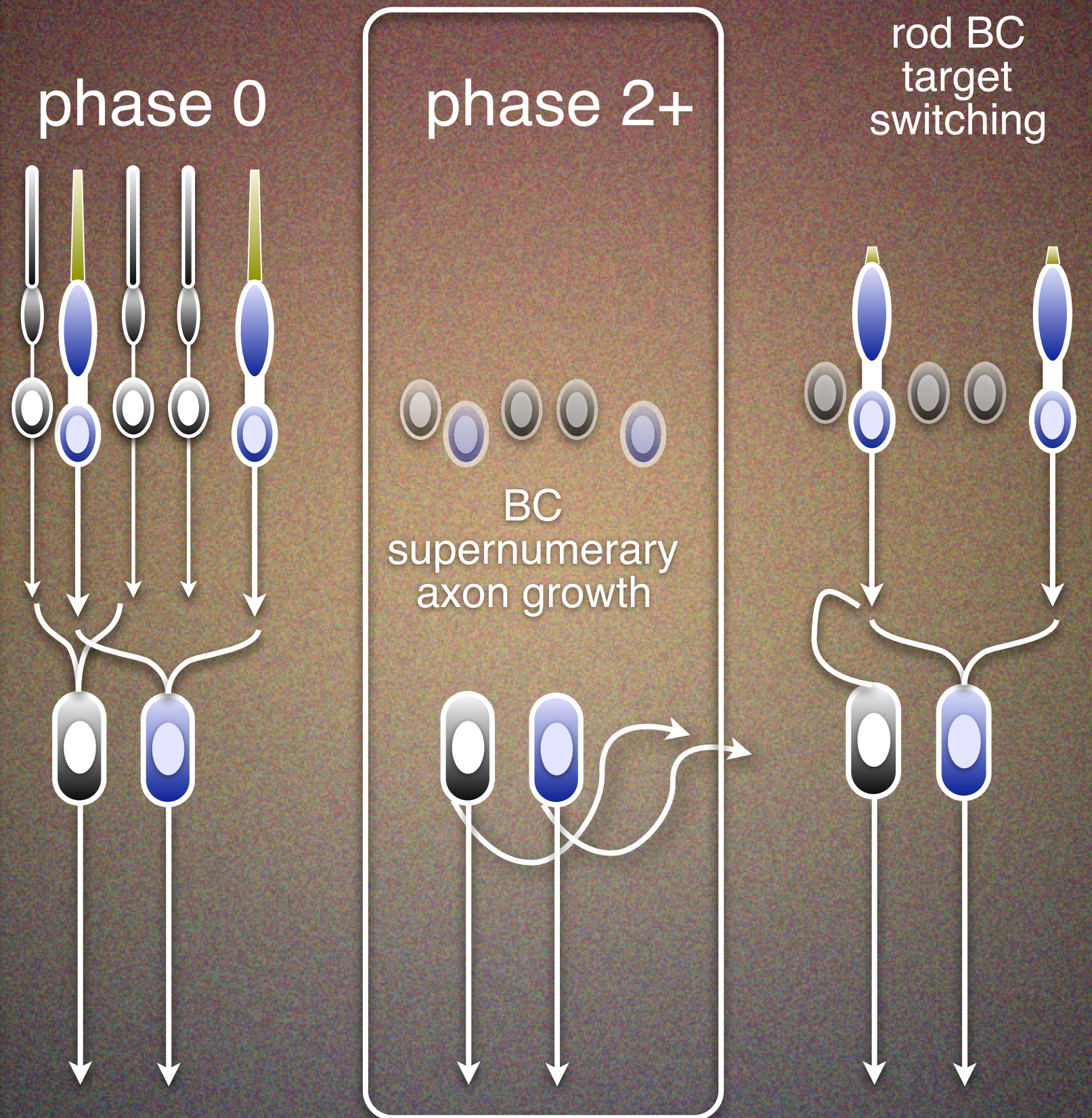
Marc et al. 2007 Neural repro-
gramming in retinal degenerations.
Invest Ophthalmol Vis Sci 48:
3364-3371..



In cone-deciminating RP, survivor BCs form new axons & microneuromas

In cone-sparing RP, circuitry remains nominally stable, though rod BCs show target switching

Marc et al. 2007 Neural reprogramming in retinal degenerations. Invest Ophthalmol Vis Sci 48: 3364-3371..

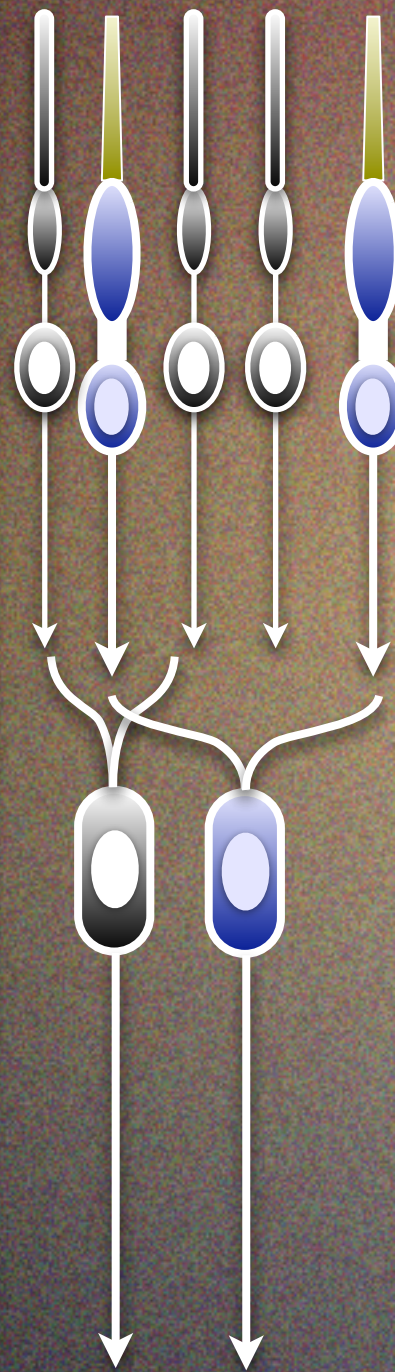


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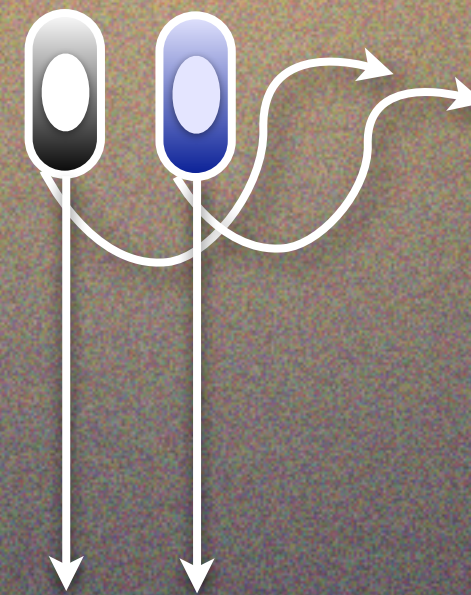
Marc et al. 2007 Neural repro-
gramming in retinal degenerations.
Invest Ophthalmol Vis Sci 48:
3364-3371..

phase 0

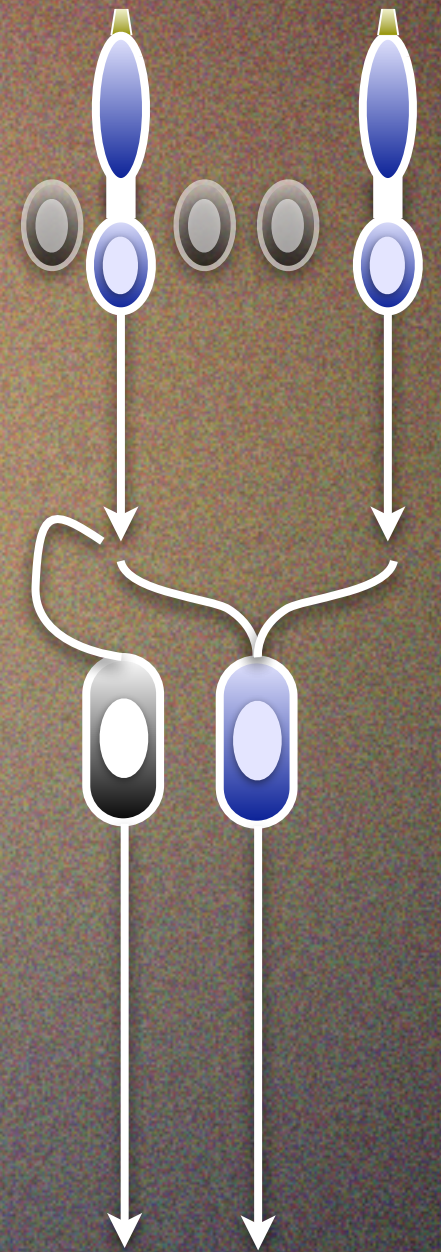


phase 2+

BC
supernumerary
axon growth



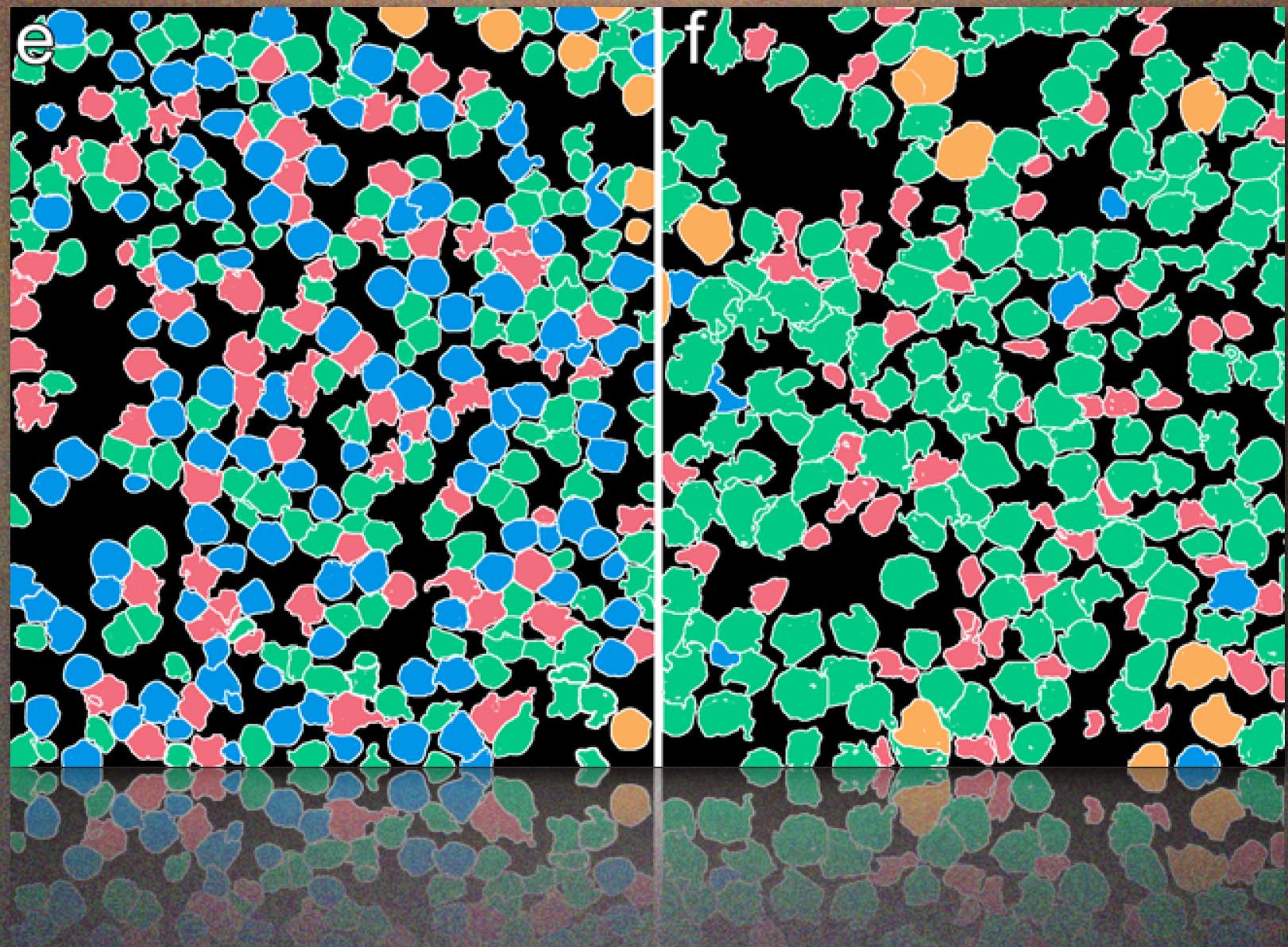
rod BC
target
switching

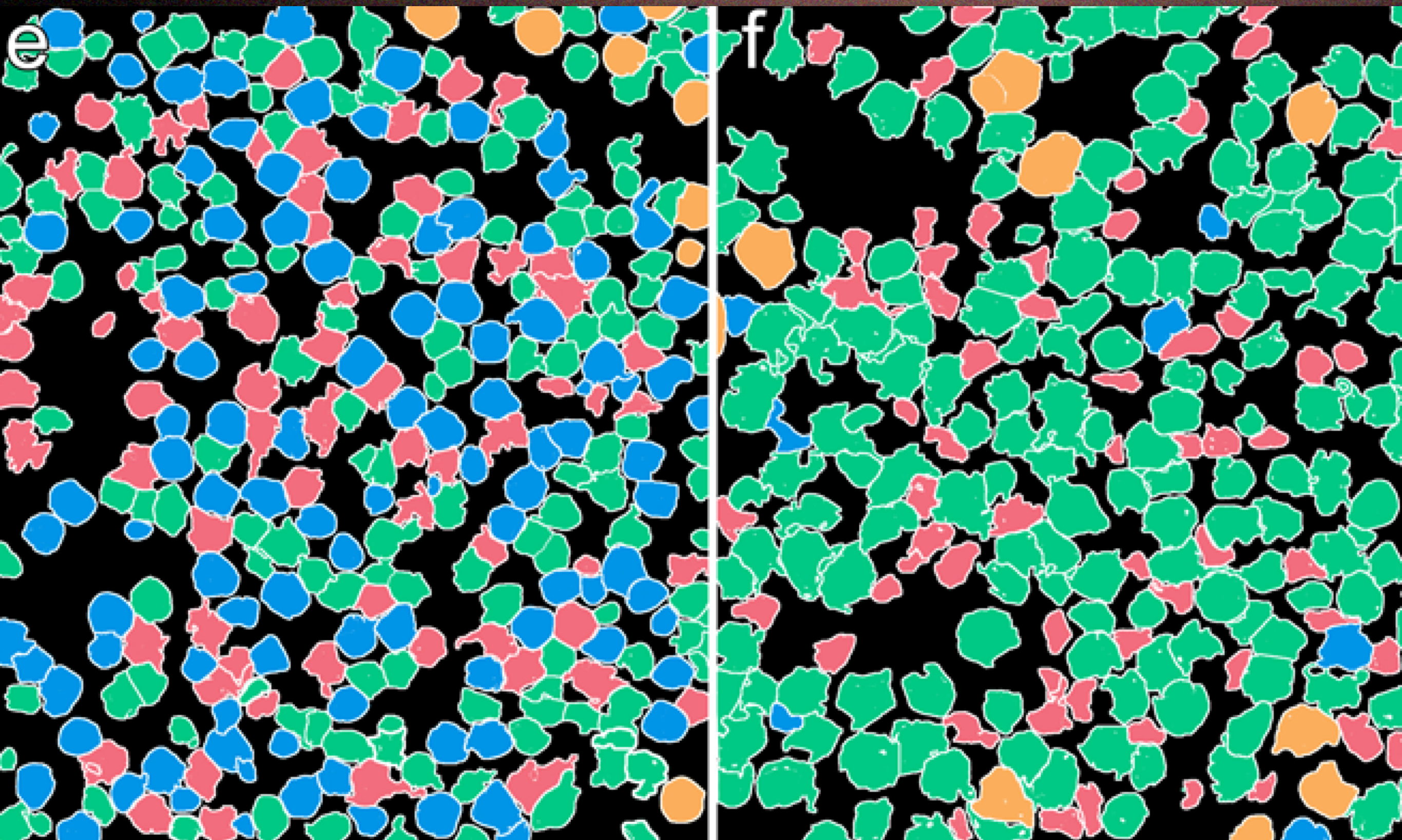


Human Cone Sparing RP

Despite morphological
deconstruction of cones,
they rescue BC
responses ...
but there are too many
OFF-like BCs

Marc et al. 2007 Neural repro-
gramming in retinal degenerations.
Invest Ophthalmol Vis Sci 48:
3364-3371. PMC2408857.





40% OFF, 30% ON, 30% rod

80% OFF, 17% ON, 3% rod



Mineo Kondo
Chair of Ophthalmology
Mei University



Hiroko Terasaki
Chair of Ophthalmology
Nagoya University

兔

Jones BW, Kondo M,
Terasaki H, Watt CB,
Rapp K, Anderson J, Lin
Y, Shaw MV, Yang J-H,
Marc R 2011

Retinal Remodeling in
the Tg P347L Rabbit, a
Large-Eye Model of
Retinal Degeneration.
J Comp Neurol 519(14):
2713-2733

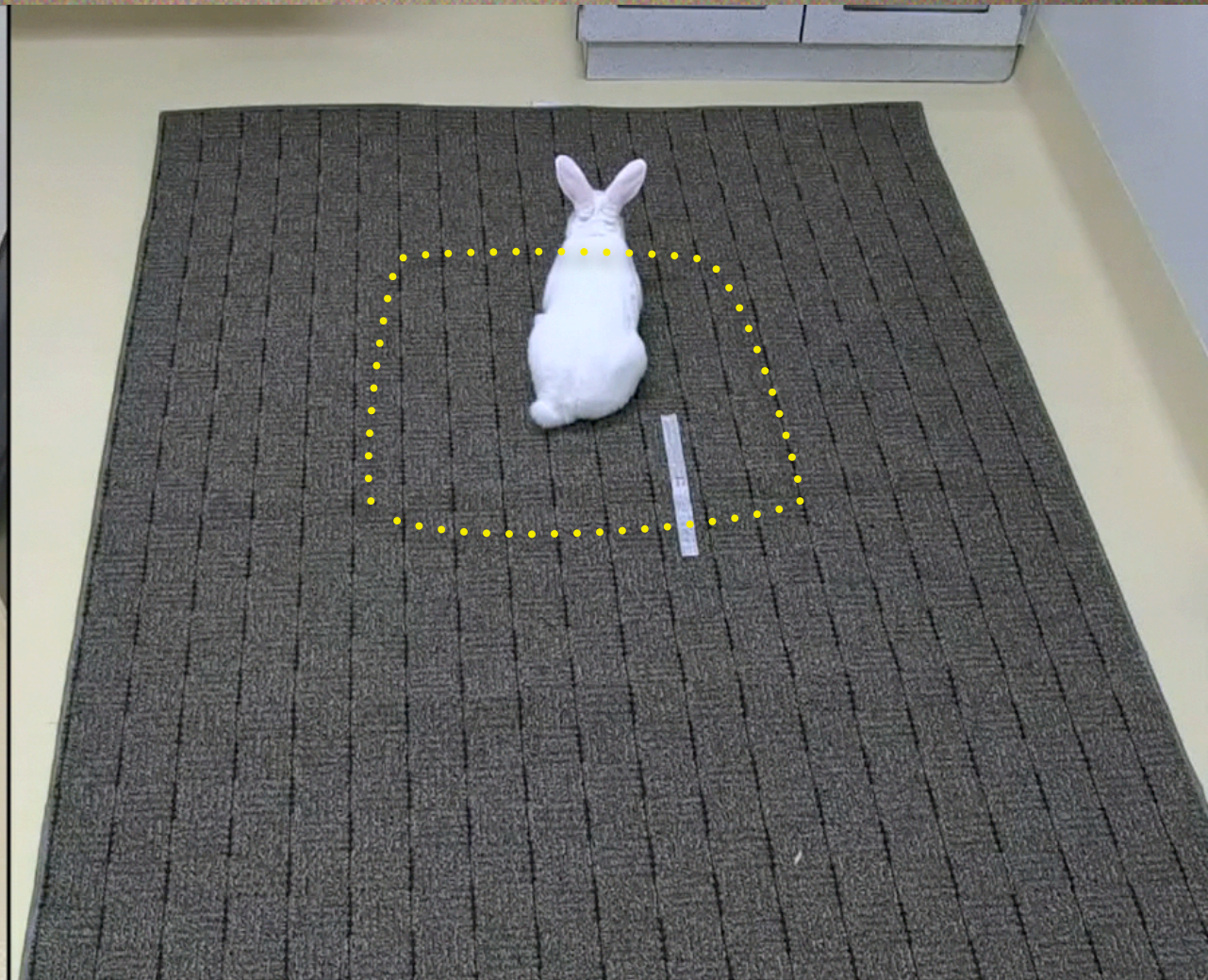
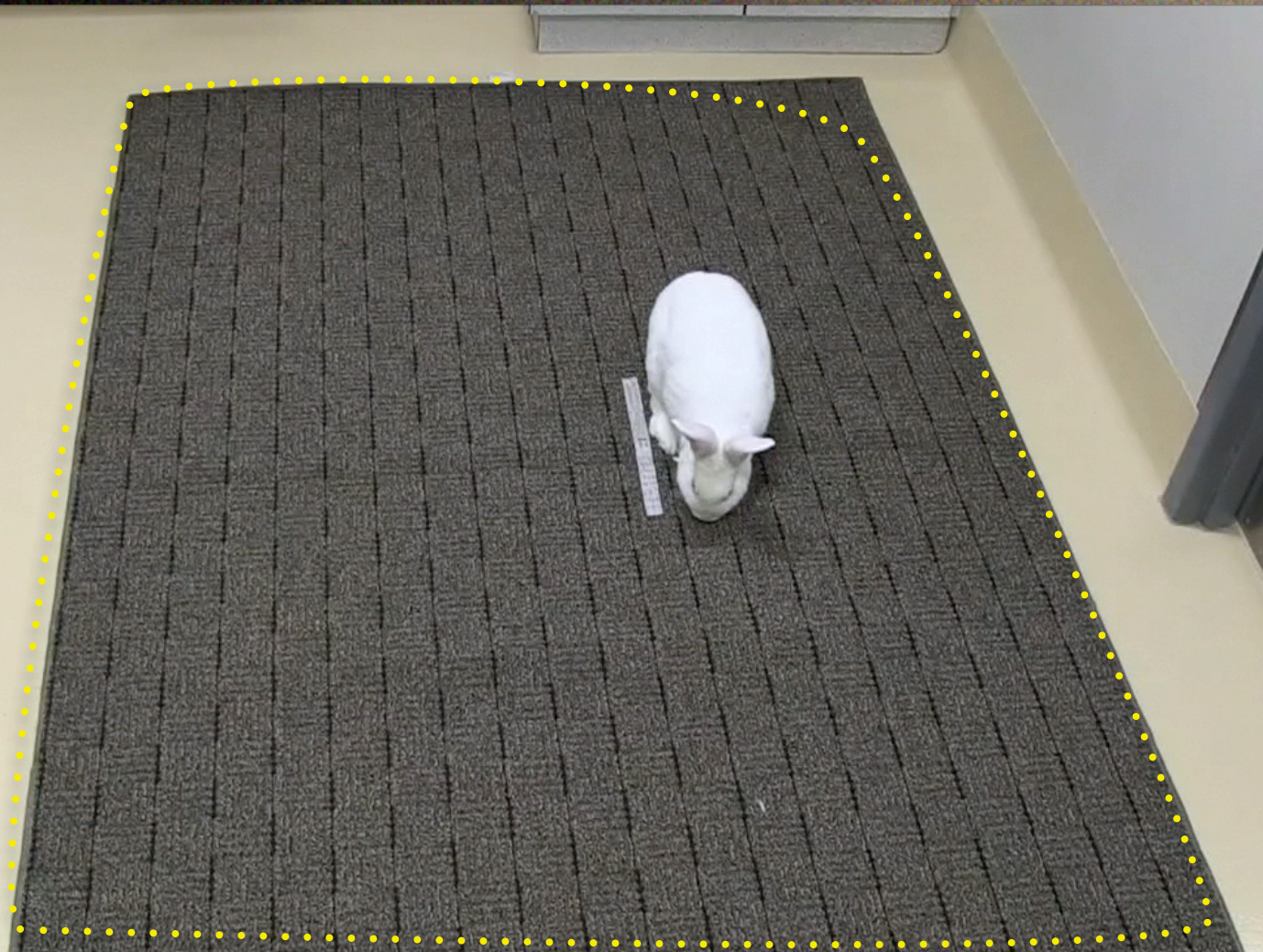


兔

Tg P347L Rhodopsin Rabbit

WT Littermate

Tg



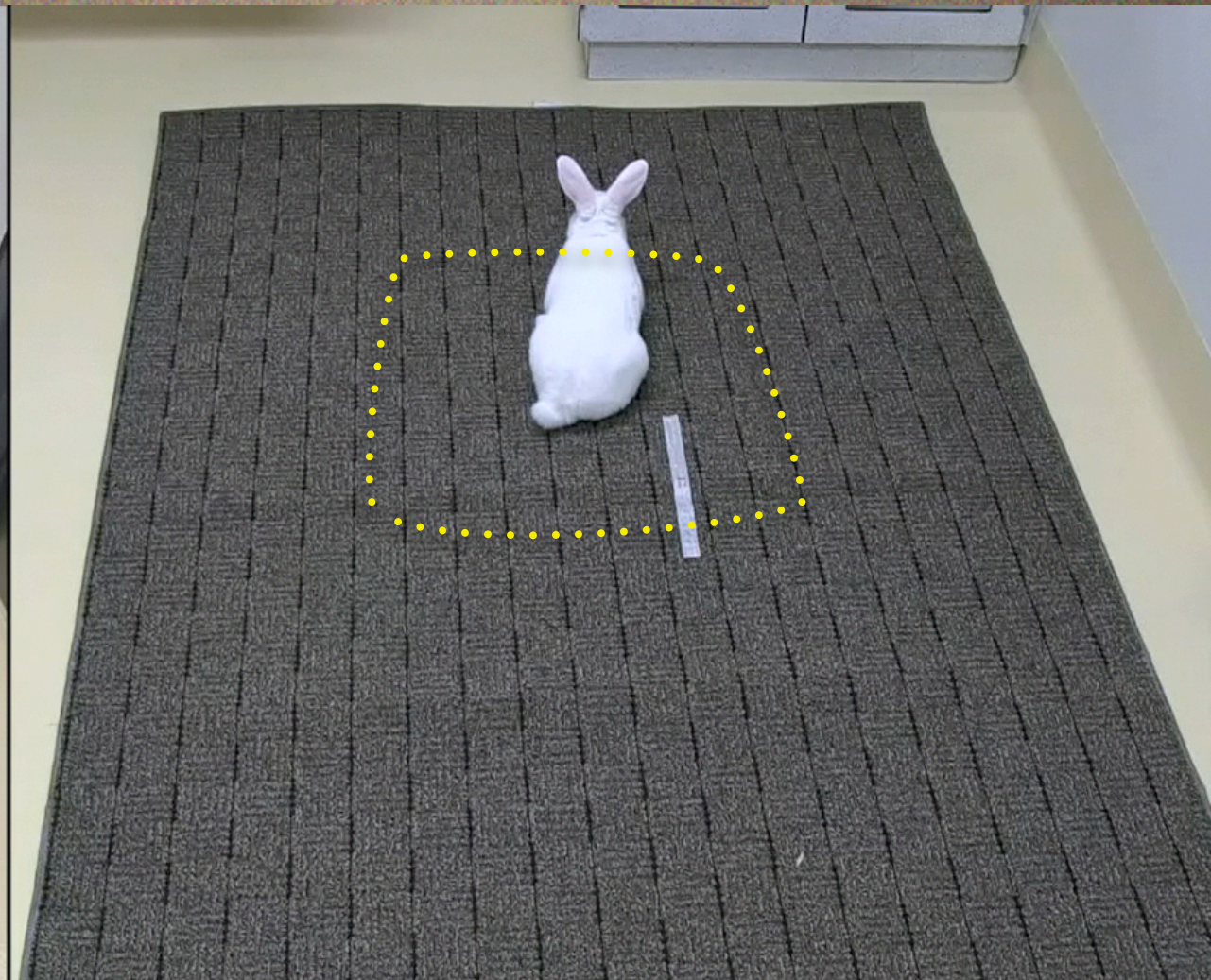
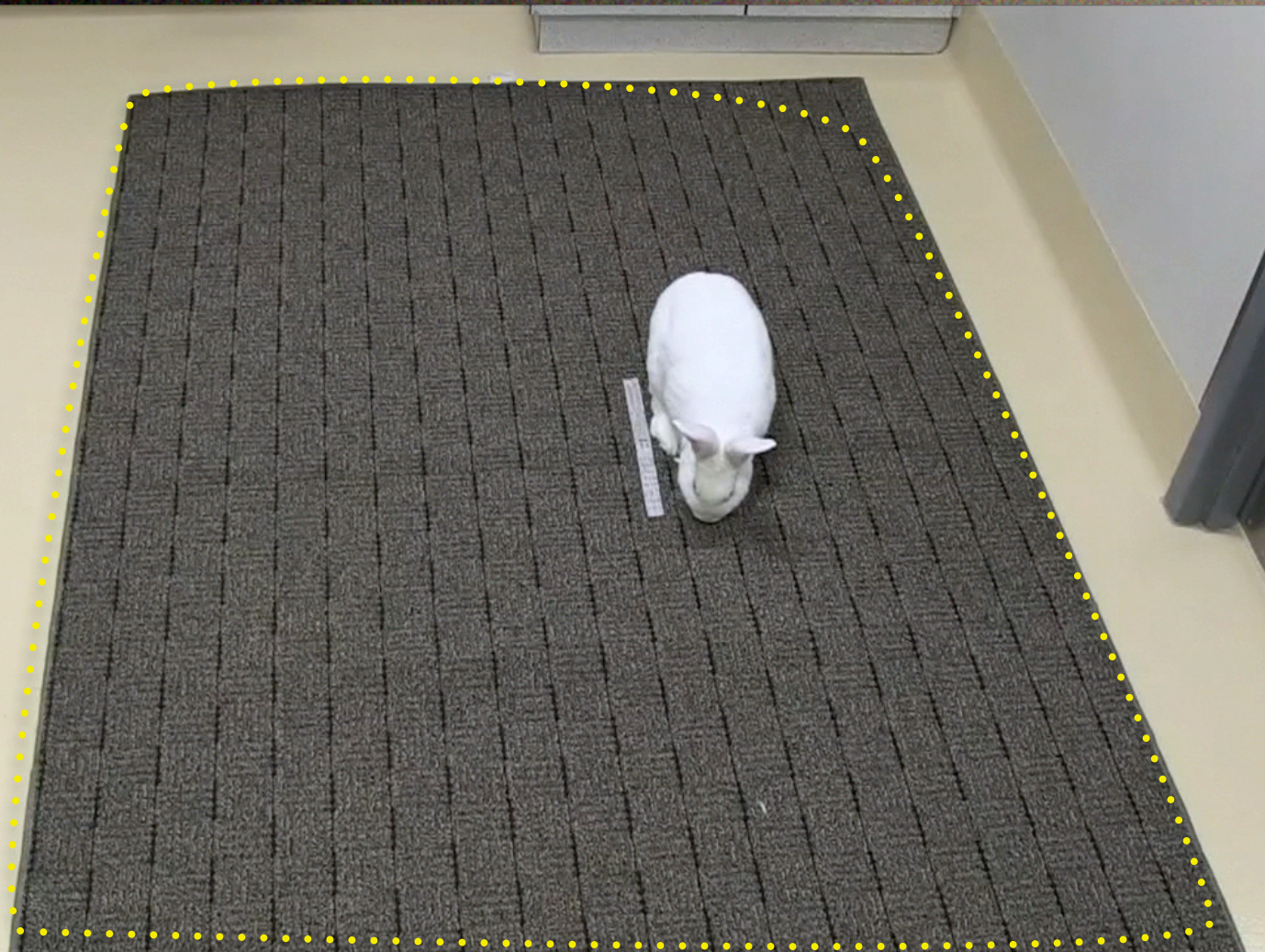
5.7 min navigation session 8x speed

兔

Tg P347L Rhodopsin Rabbit

WT Littermate

Tg

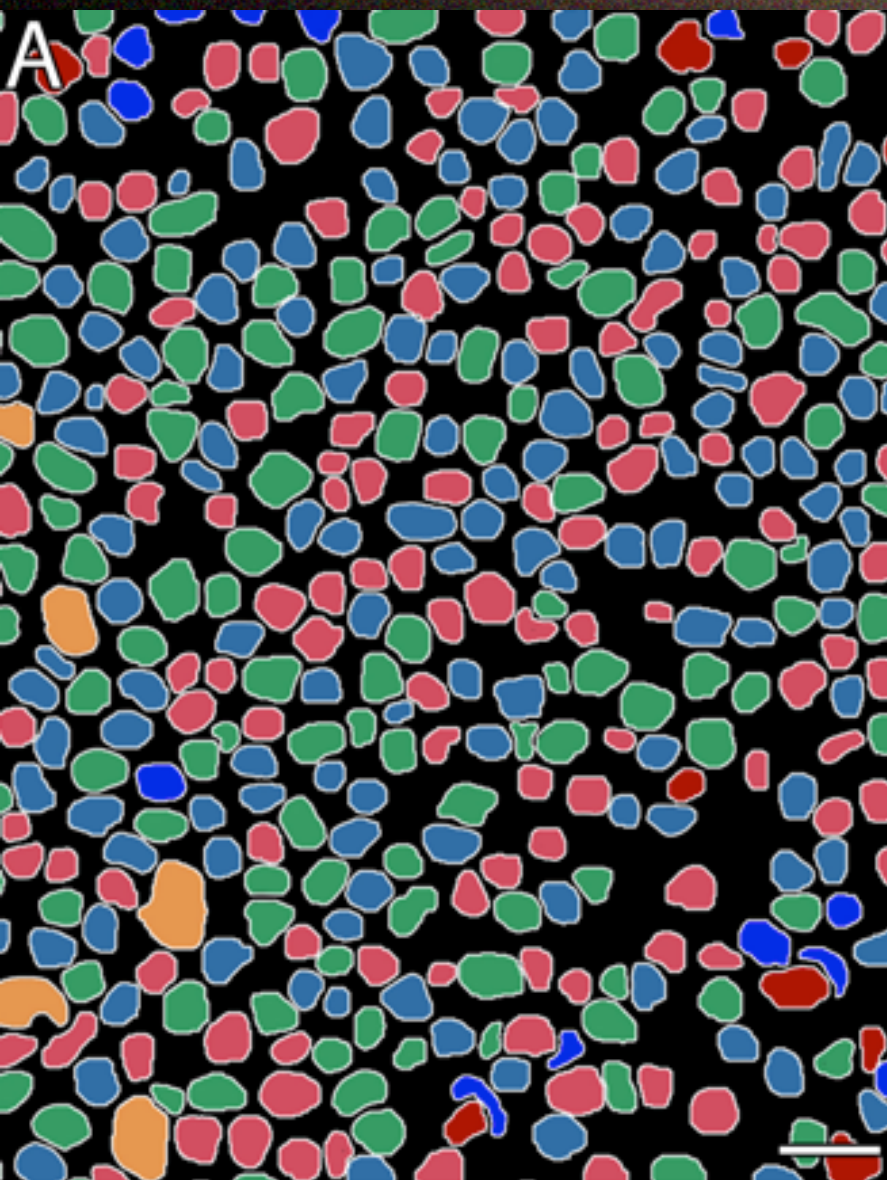


5.7 min navigation session 8x speed

兔

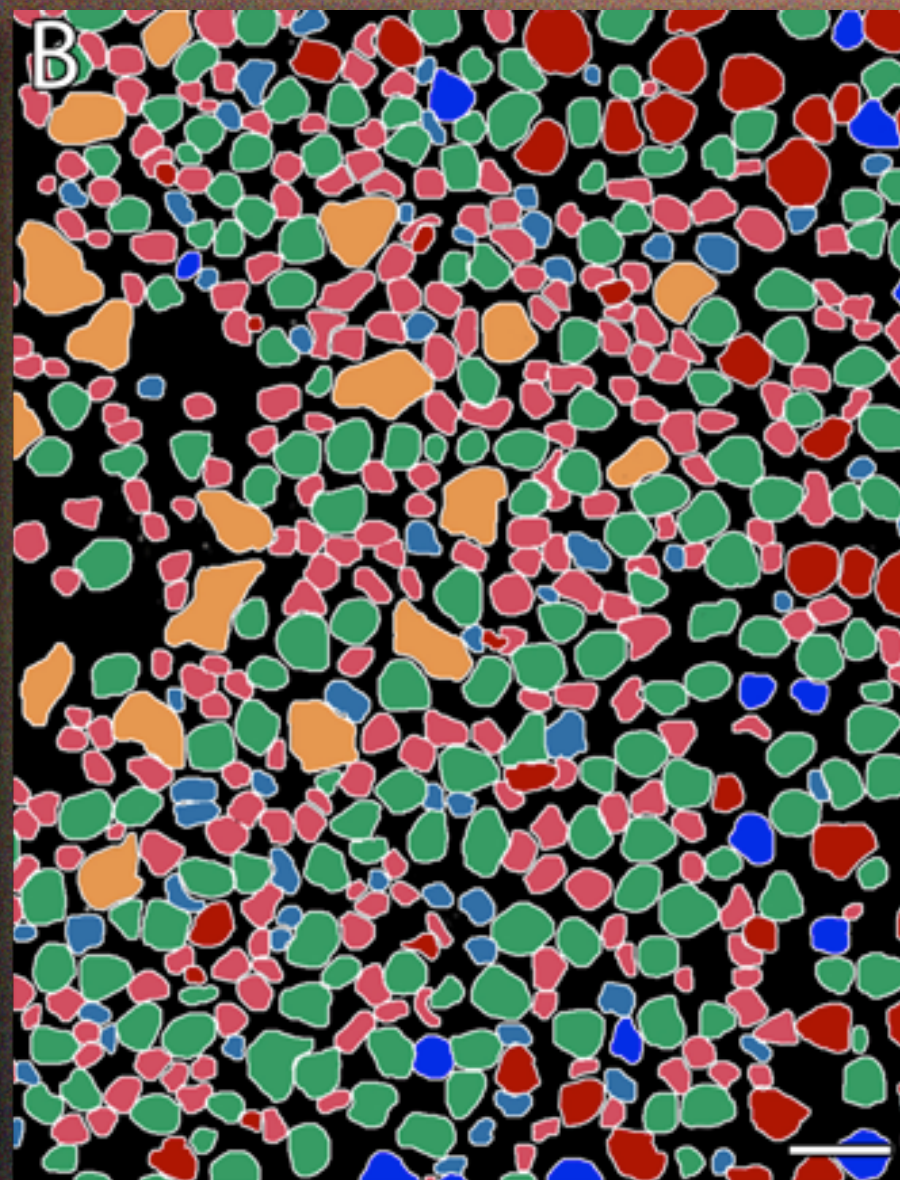


REPROGRAMMING IN RABBIT RP



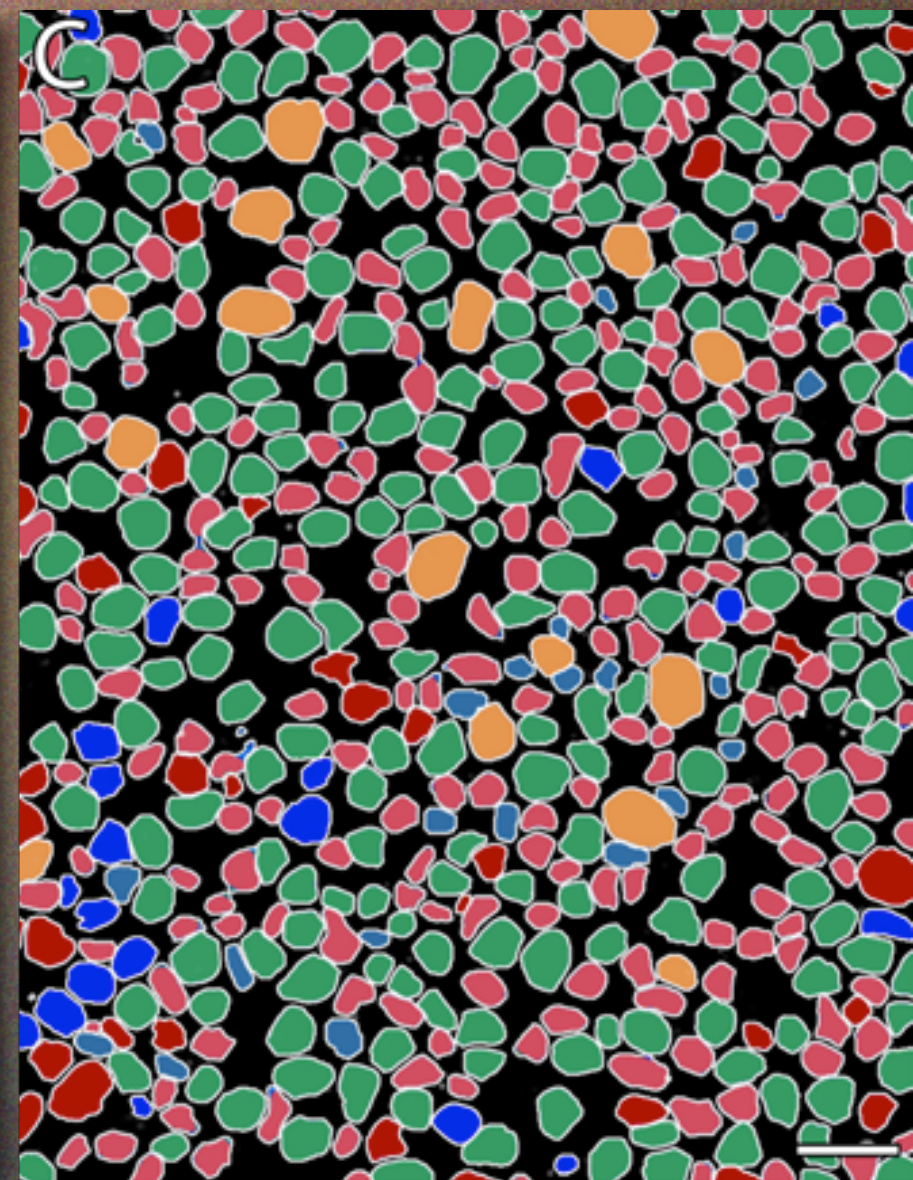
wt

OFF 37% ON 30% rod 33%



4 mo Tg P347L

OFF 39% ON 41% rod 20%

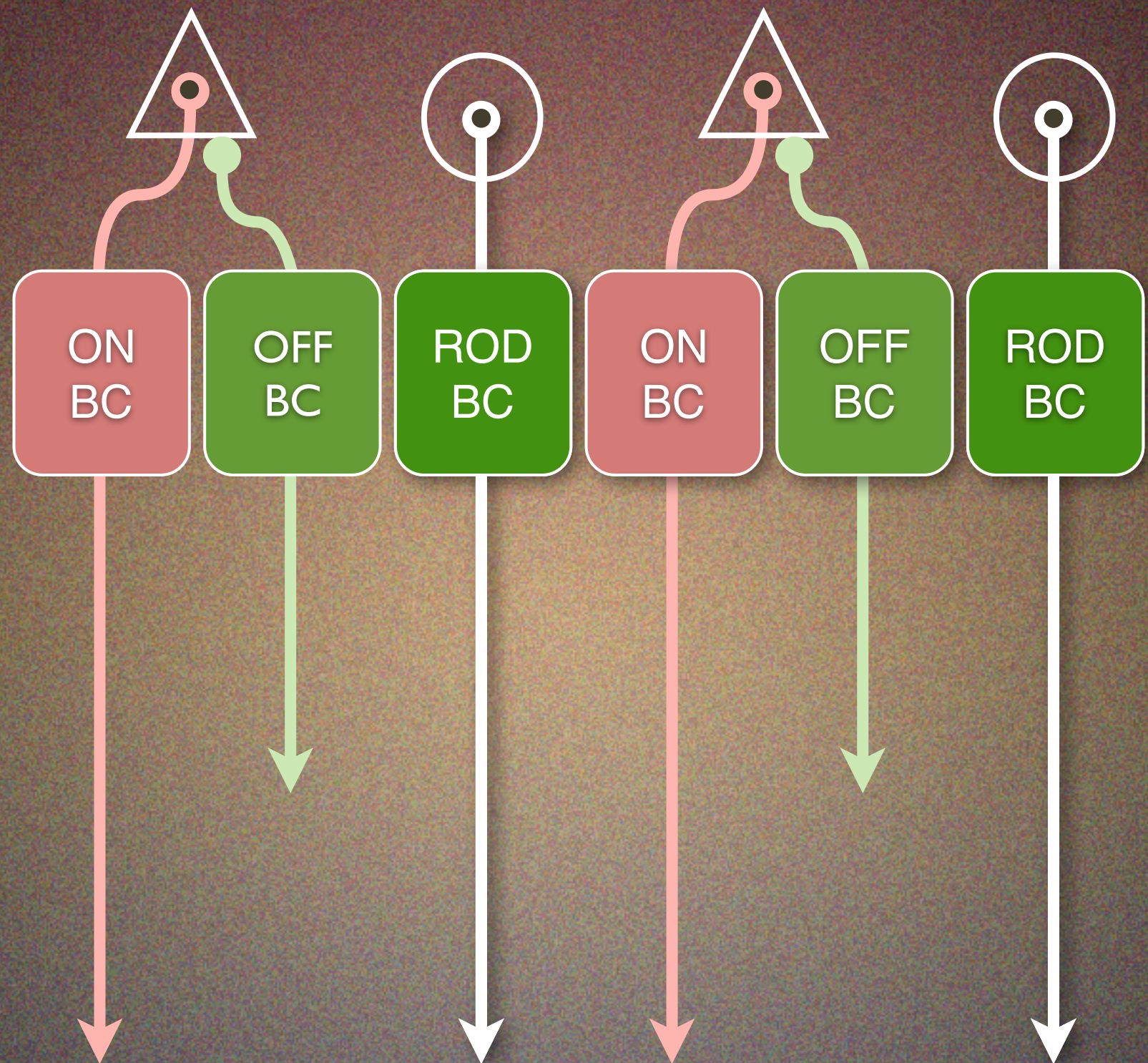


10 mo Tg P347L

OFF 56% ON 40% rod 4%

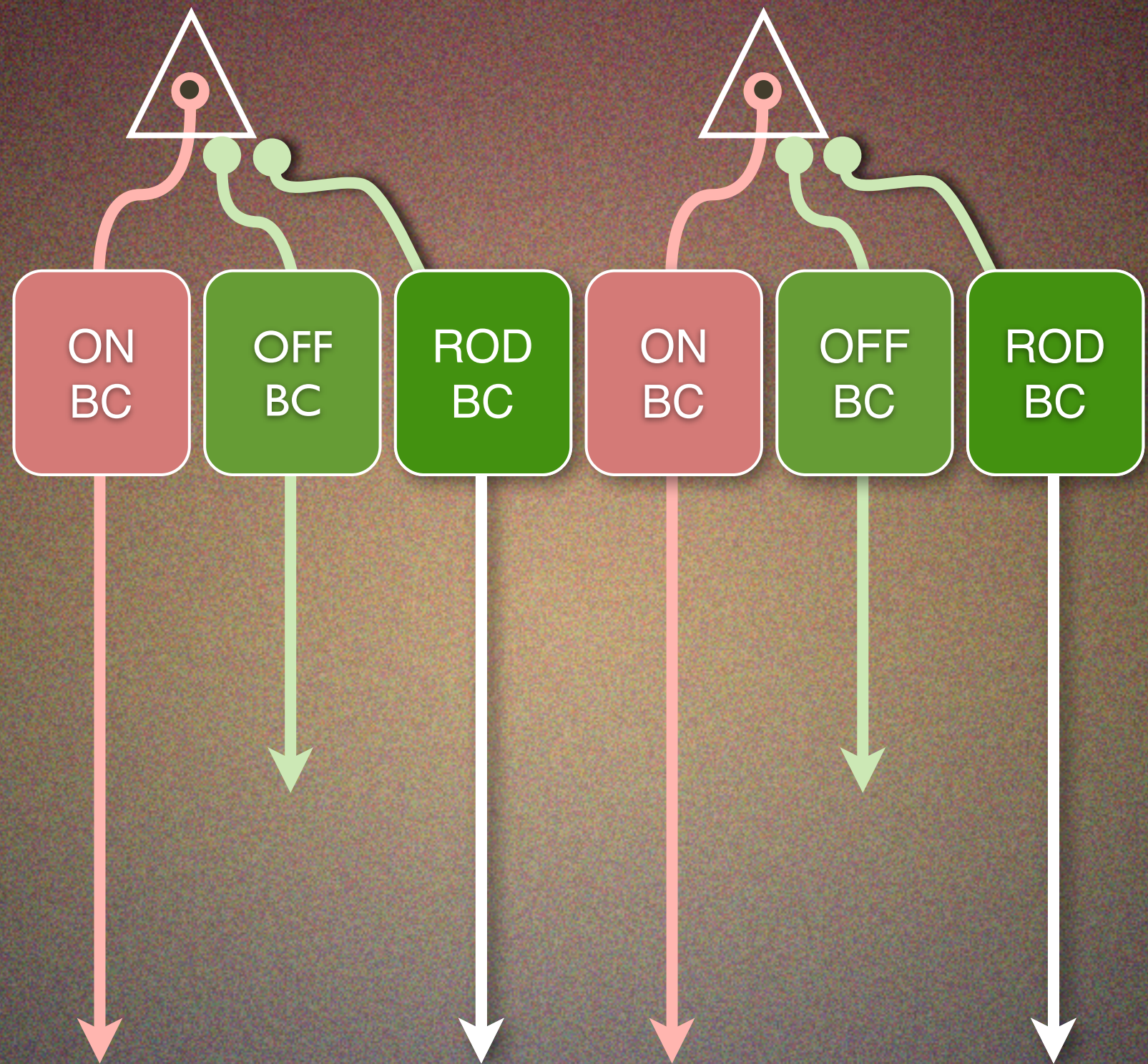
Cone Sparing RP

Rod BCs lose rod contacts, make ectopic cone contacts, express iGluRs, doubling the OFF BC cohort and corrupting cone pathways



Cone Sparing RP

Rod BCs lose rod contacts, make ectopic cone contacts, express iGluRs, doubling the OFF BC cohort and corrupting cone pathways



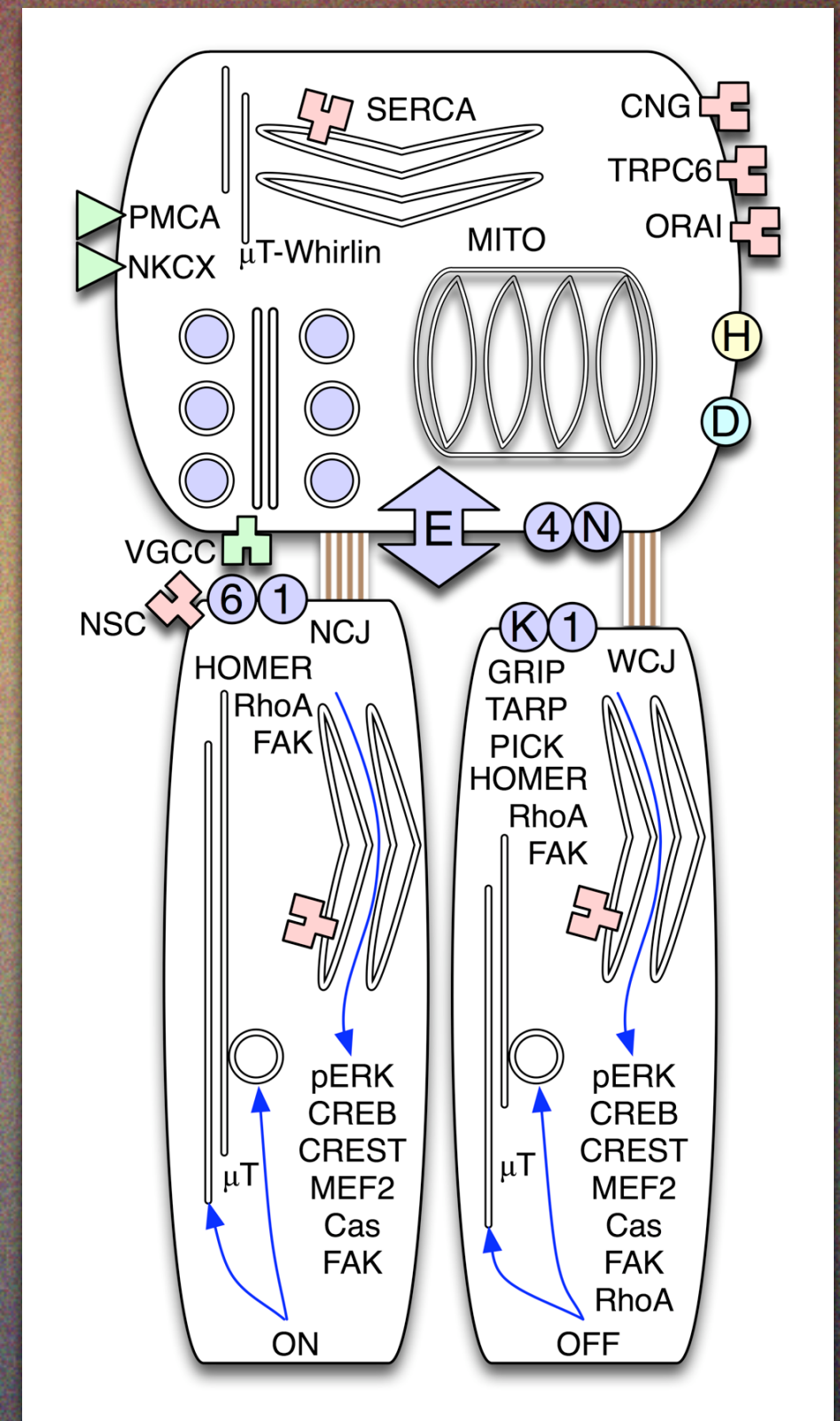
RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID

RAPID GLUTAMATE RECEPTOR 2 TRAFFICKING DURING RETINAL DEGENERATION

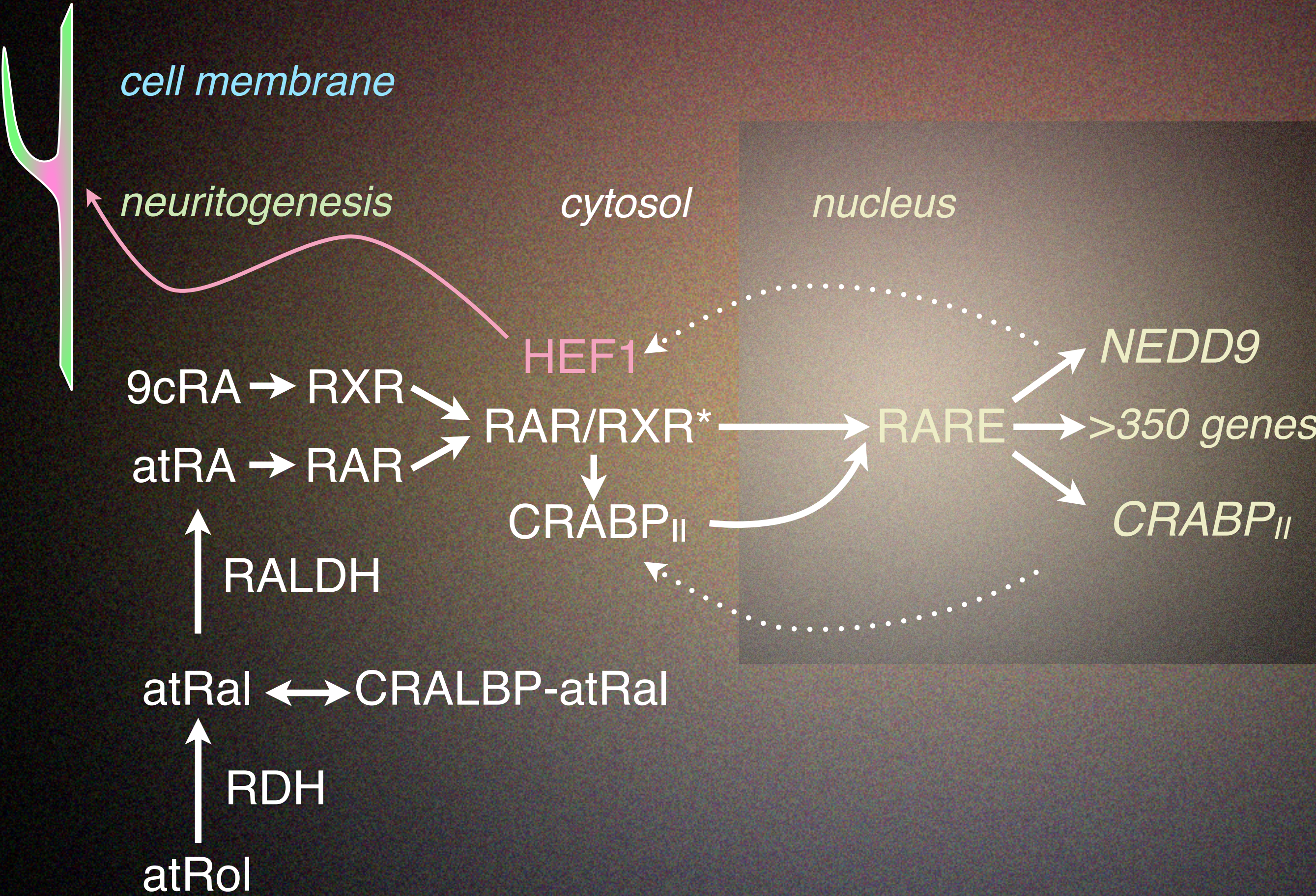
Lin, Jones, Liu, Vazqu  z-Chona, Lauritzen, Ferrell, & Marc;
Mol Neurodegener 2012

RETINOID RECEPTORS TRIGGER NEURITOGENESIS IN RETINAL DEGENERATIONS

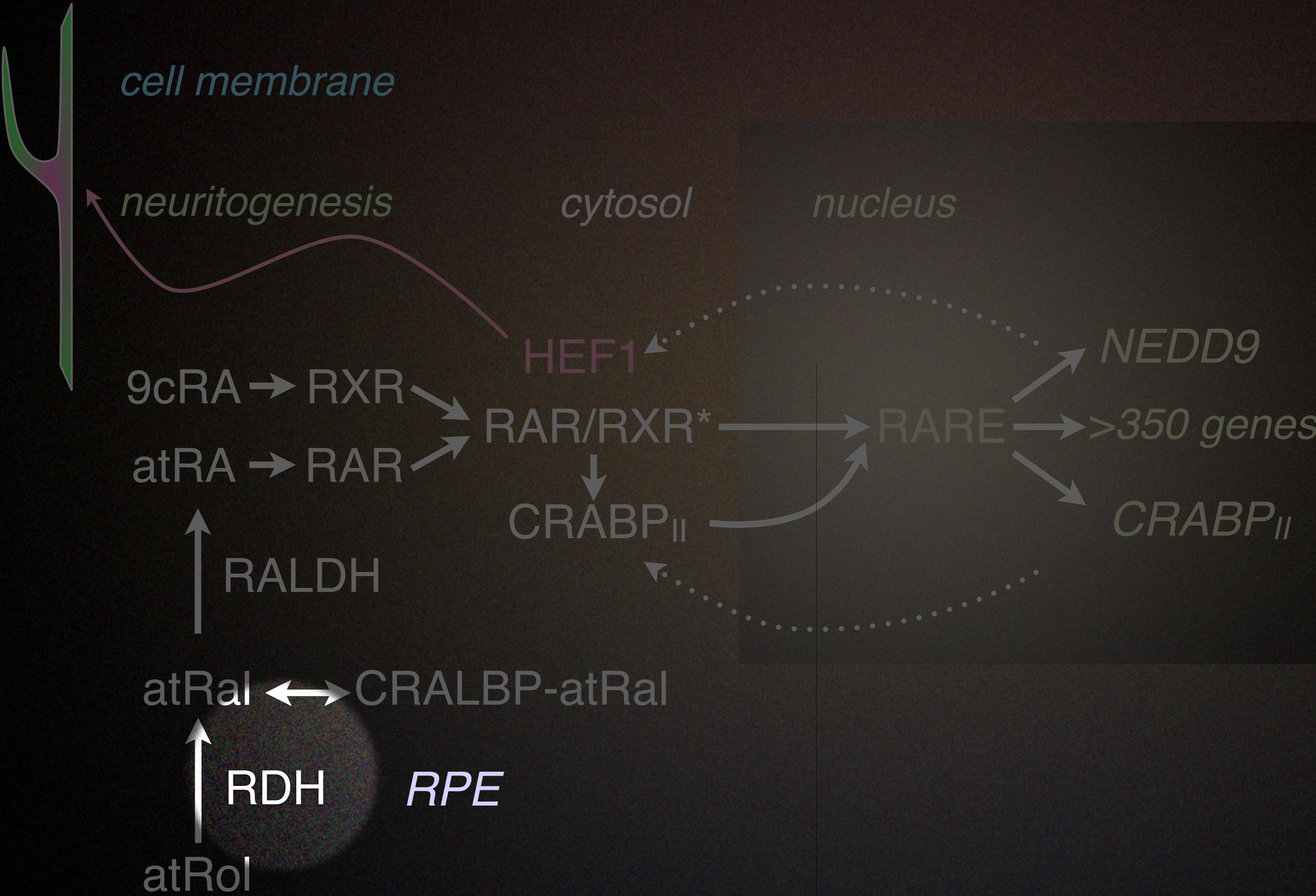
Lin , Jones, Liu , Tucker, Rapp, Luo, Baehr, Bernstein, Watt,
Yan, Shaw, Marc; FASEB J 2012



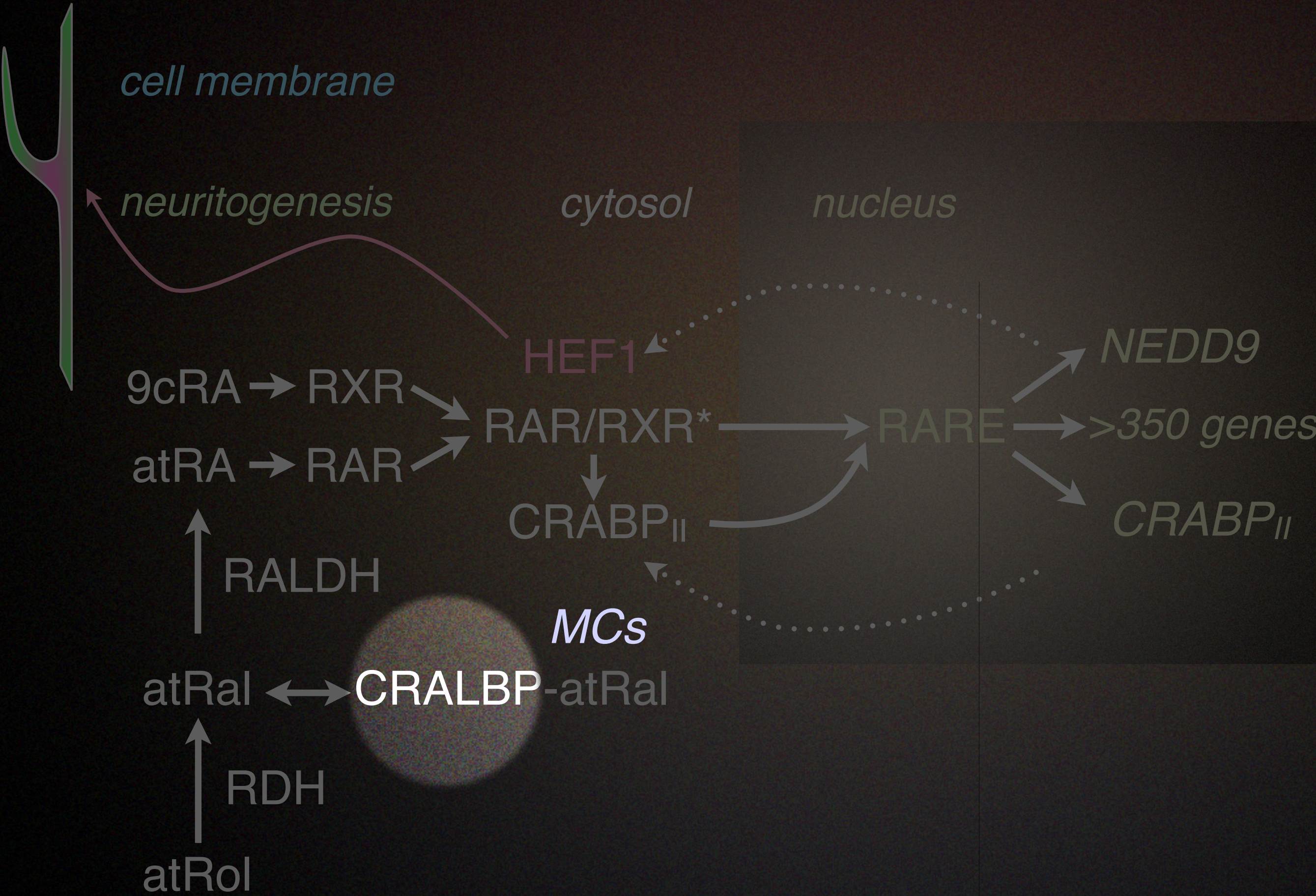
RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID



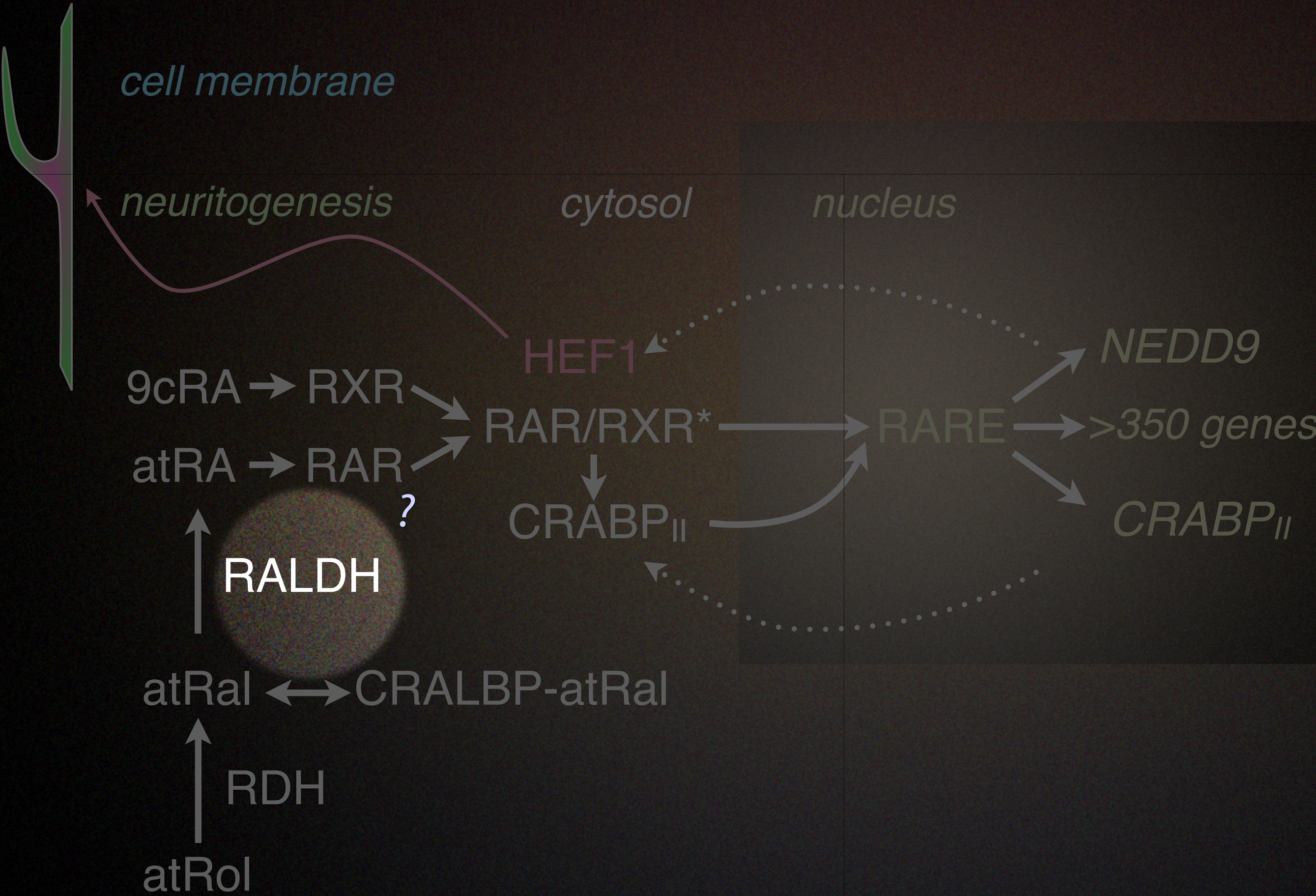
RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID



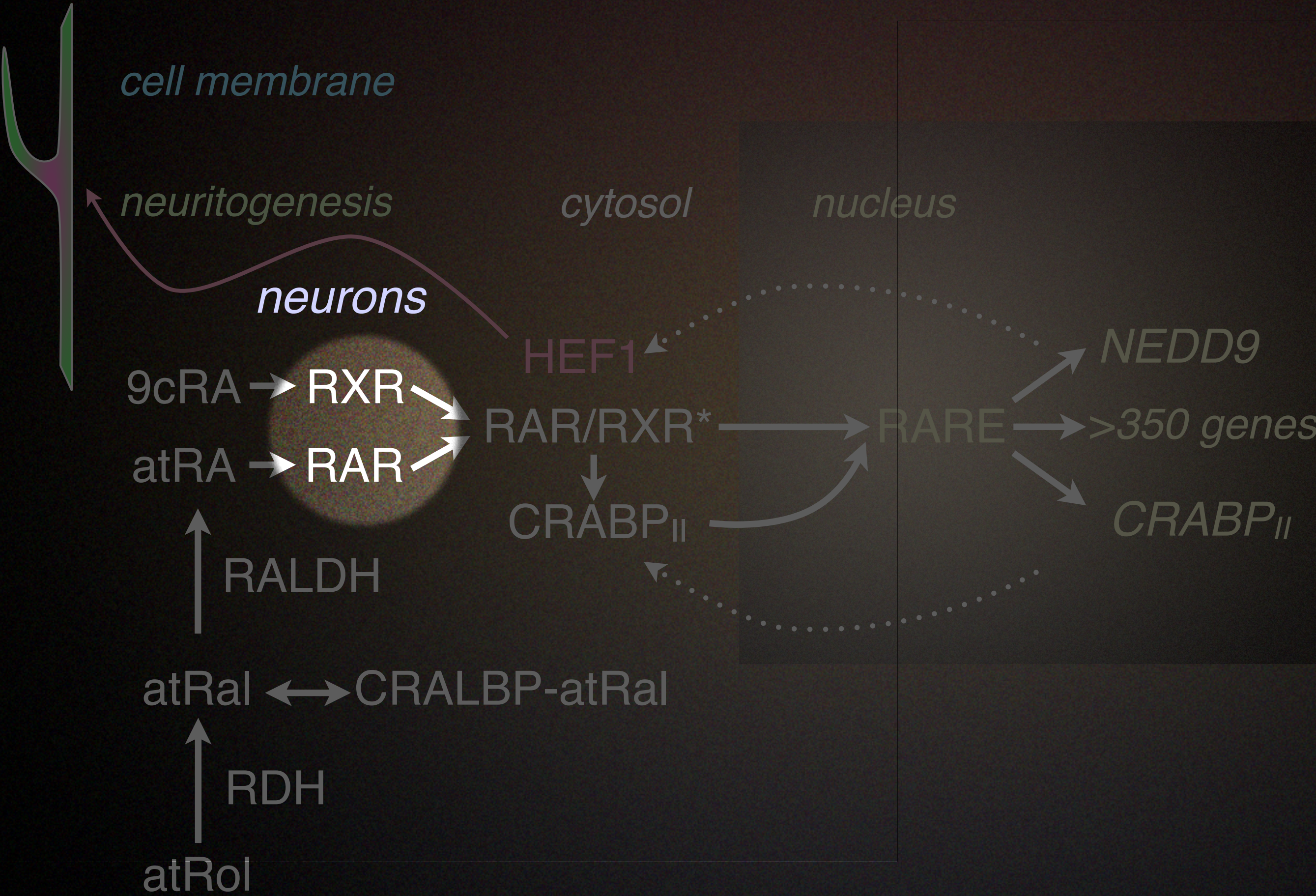
RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID



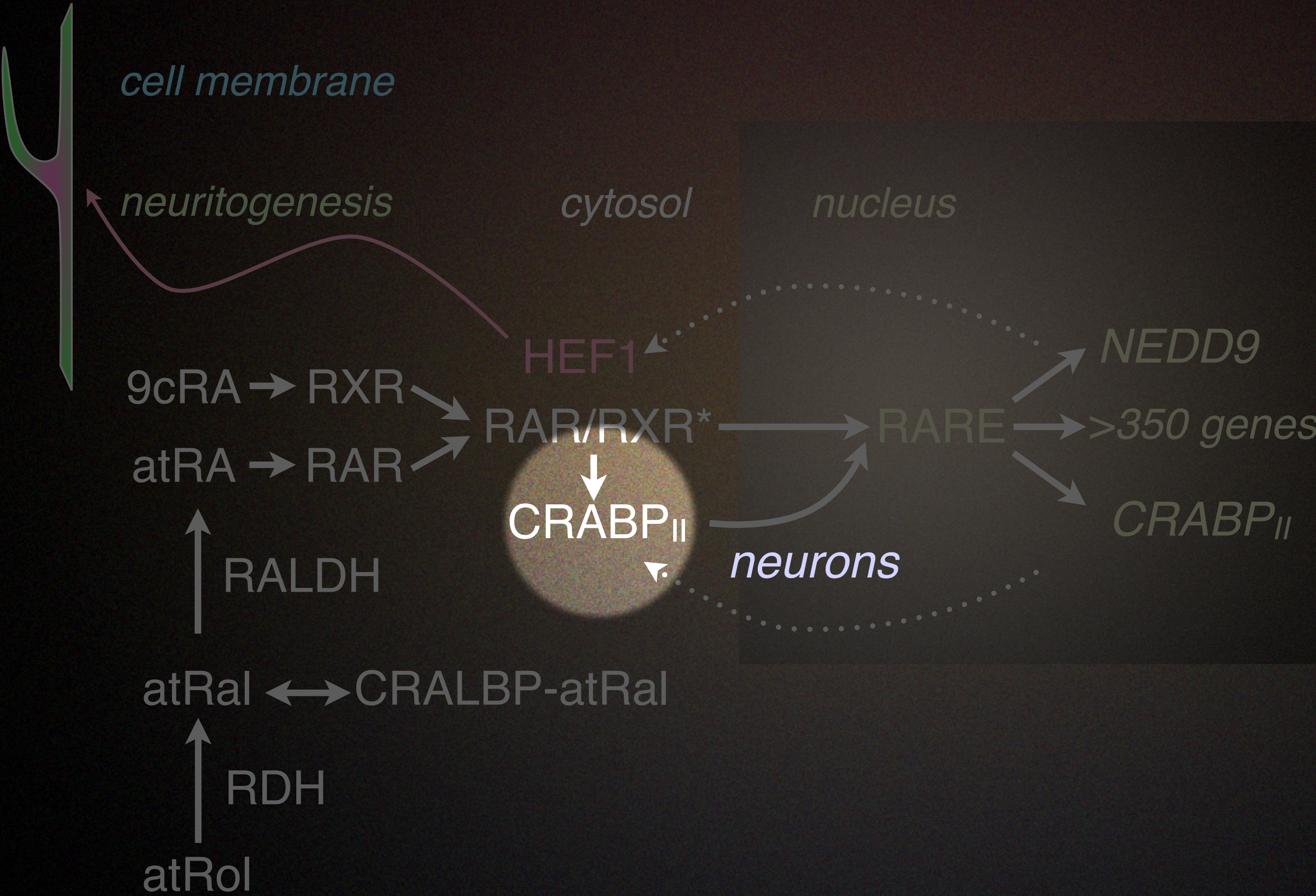
RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID



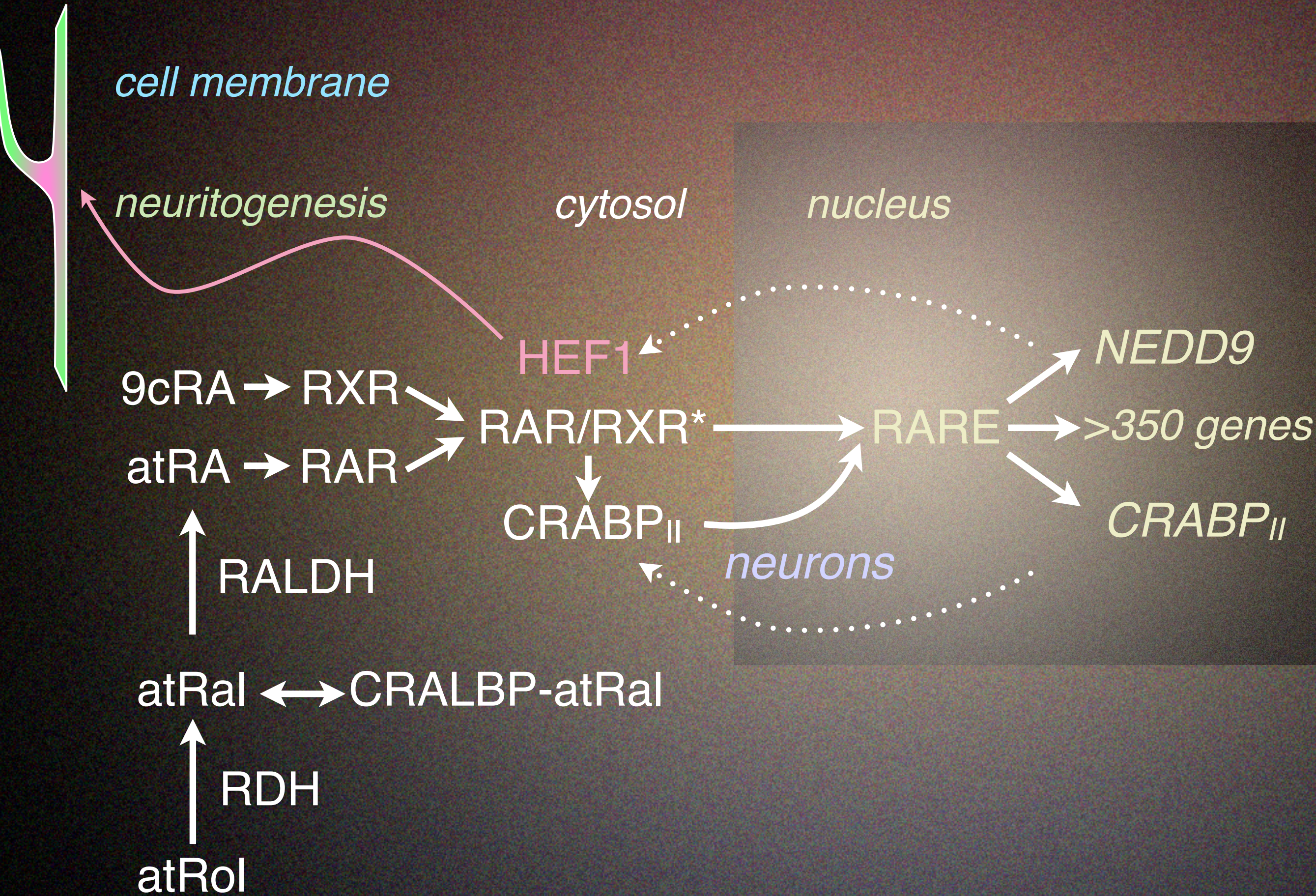
RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID



RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID

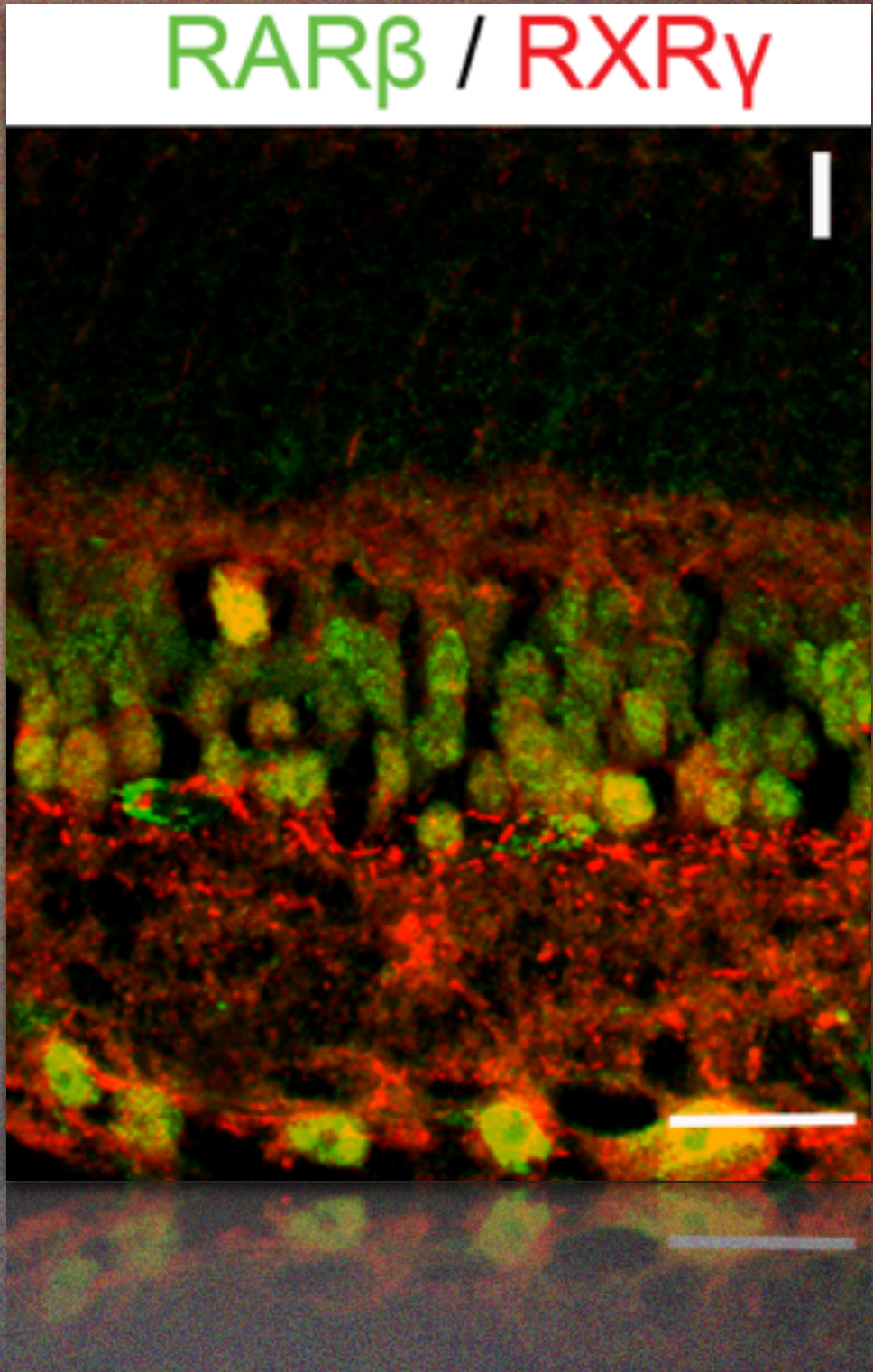
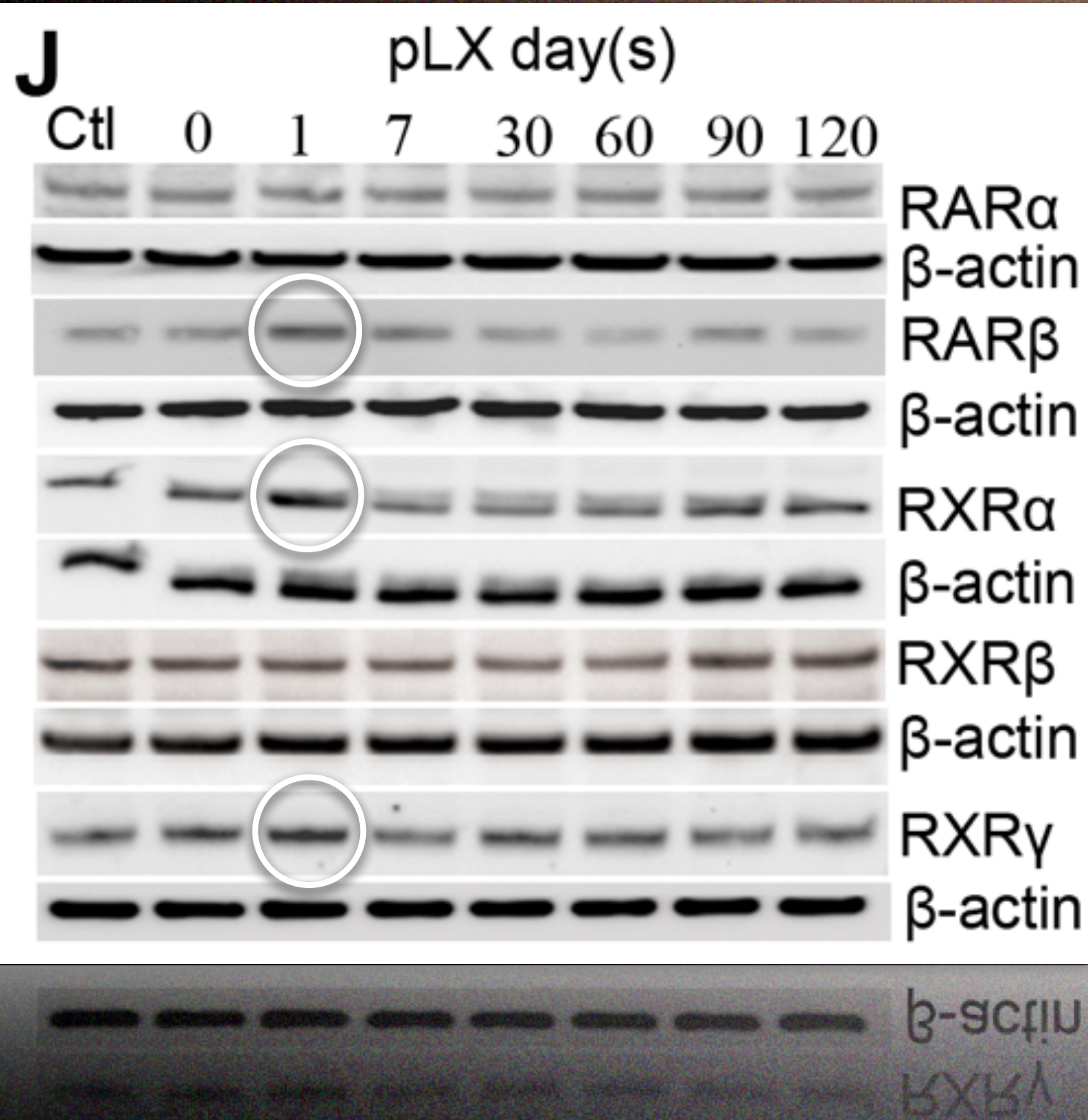


RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID



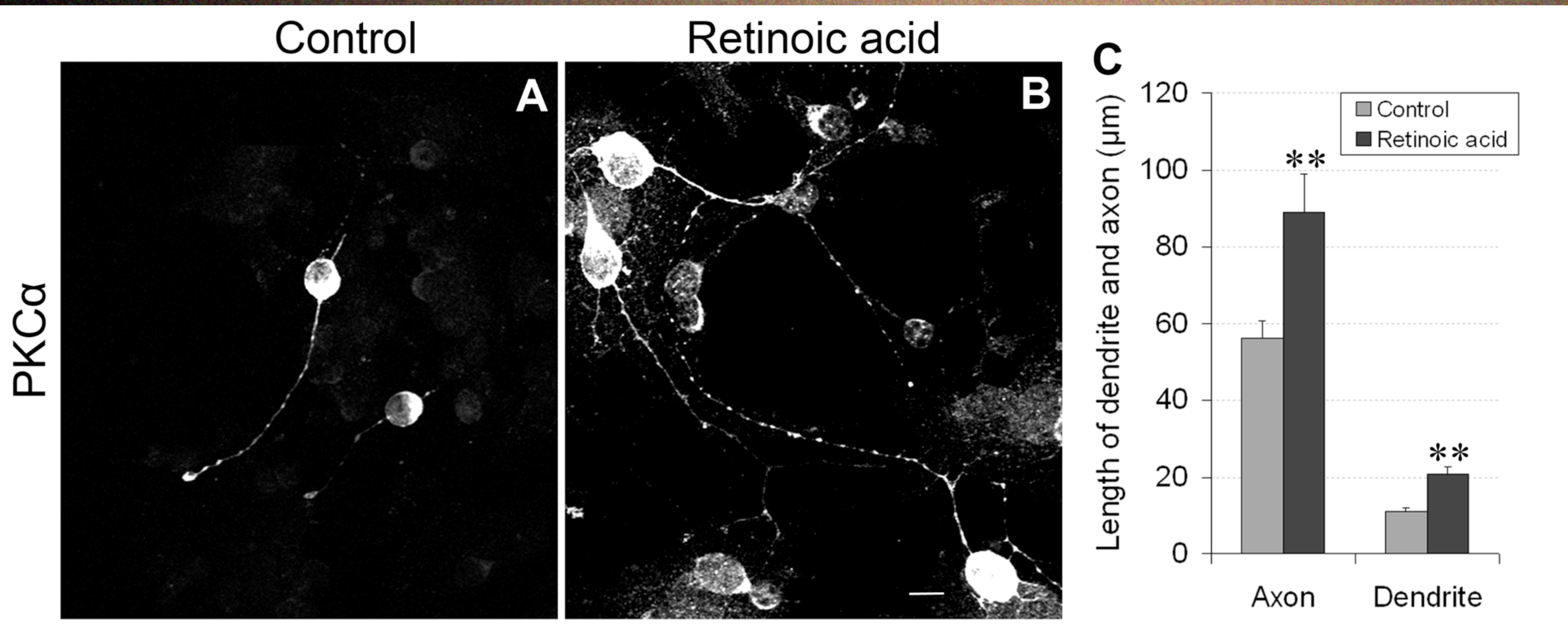
RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID

RAR/RXR = EXPRESSED BY NEURONS



RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID

RA induces neuritogenesis *in vivo* & *in vitro*
Citral blocks neuritogenesis

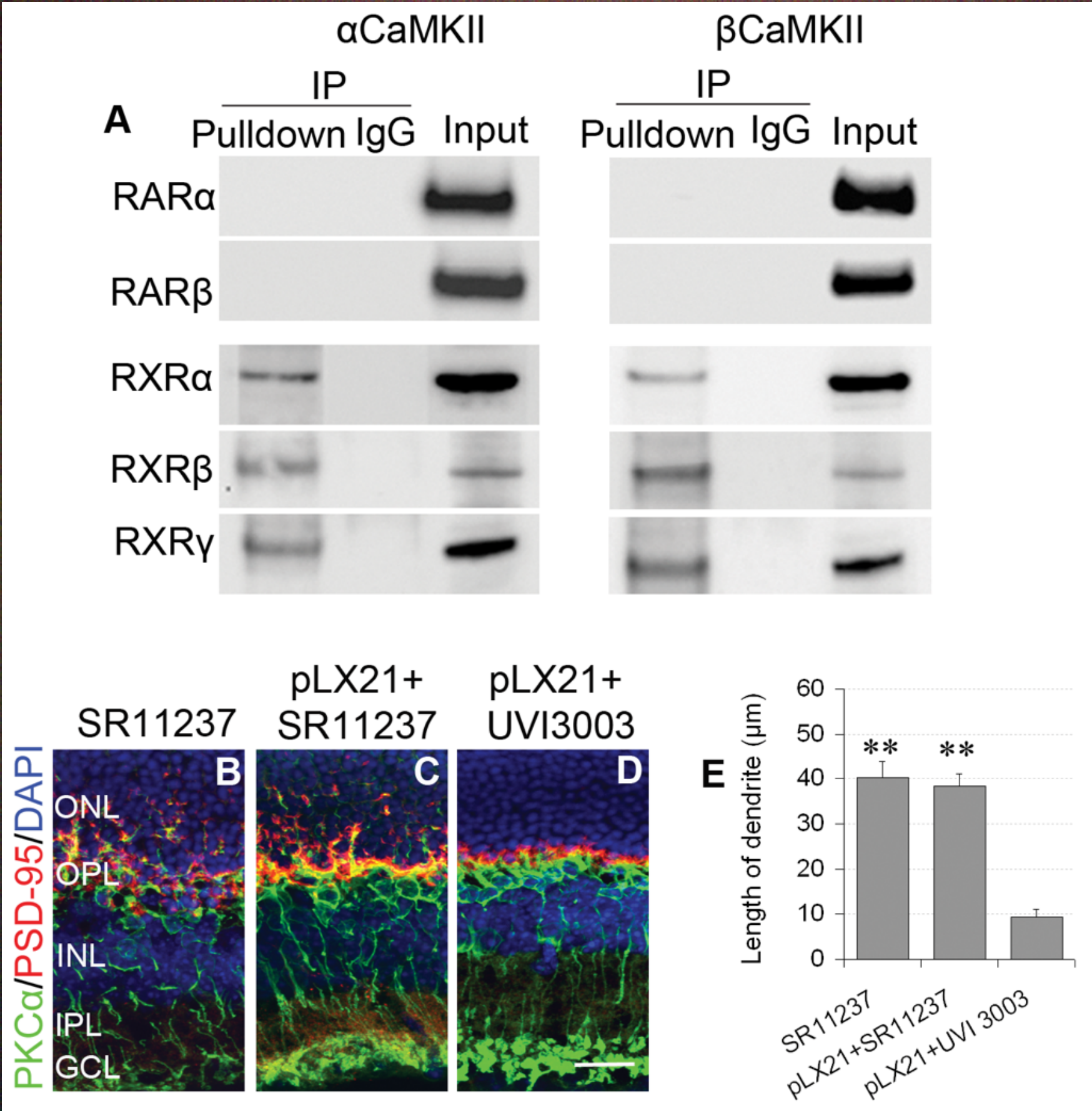


RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID

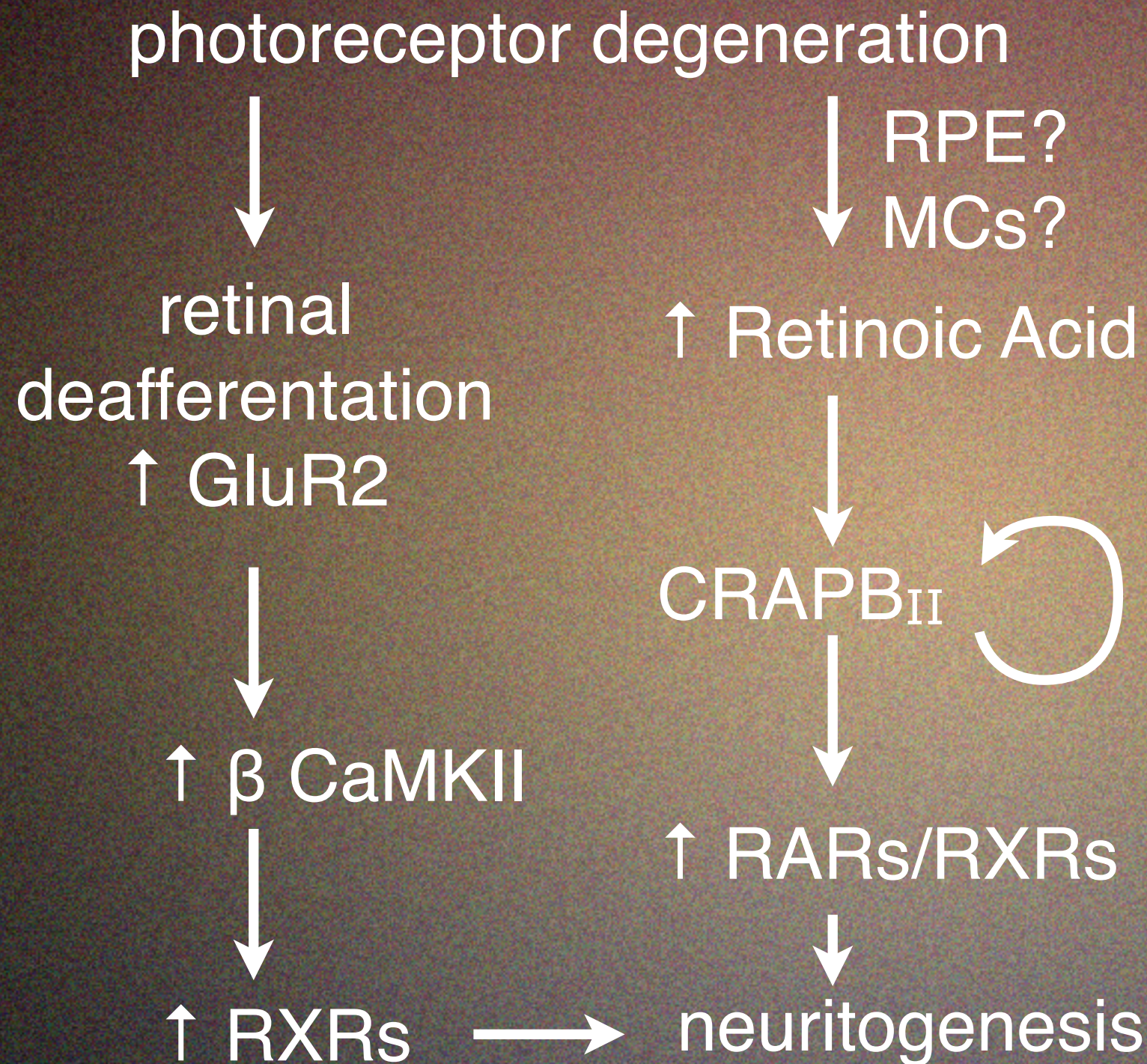
CaMKII
pulls down
RXRs

RXR Ag SR11237
drives
neuritogenesis

RXR Xg UVI3003
blocks
neuritogenesis



RETINAL REMODELING :: REPROGRAMMING & RETINOIC ACID



Lin et al. 2012 FASEB J. 26:81-92.

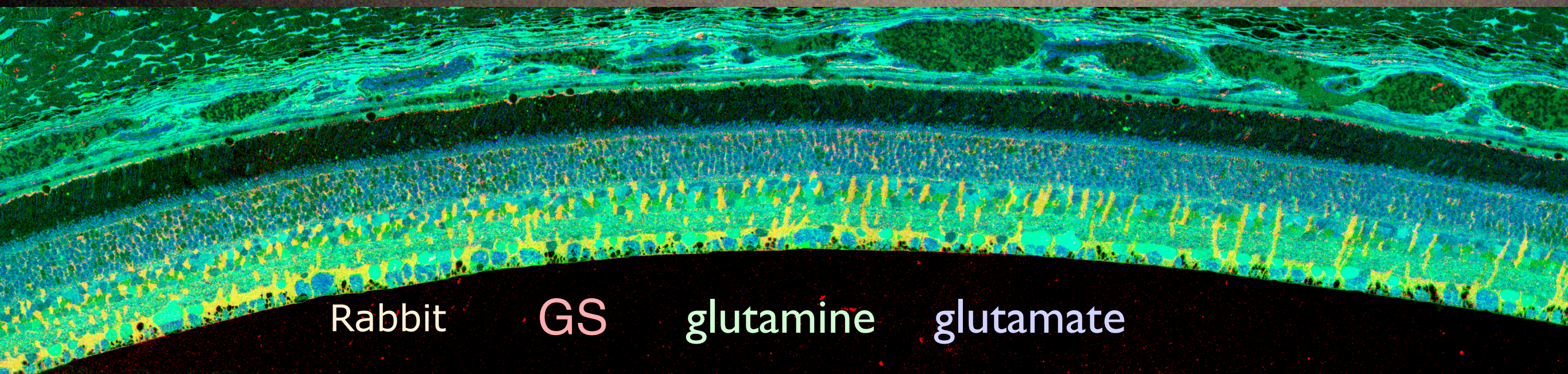
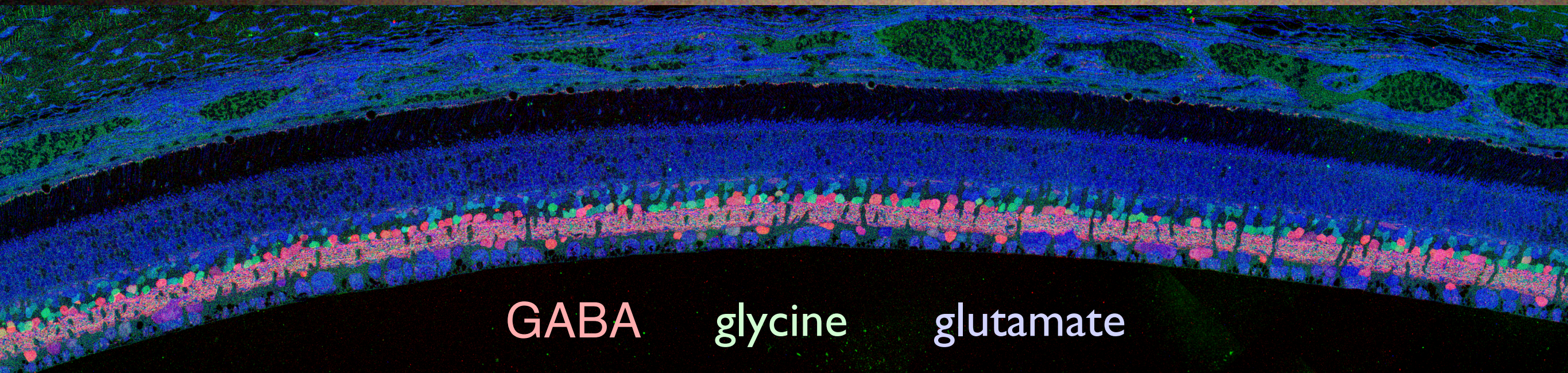
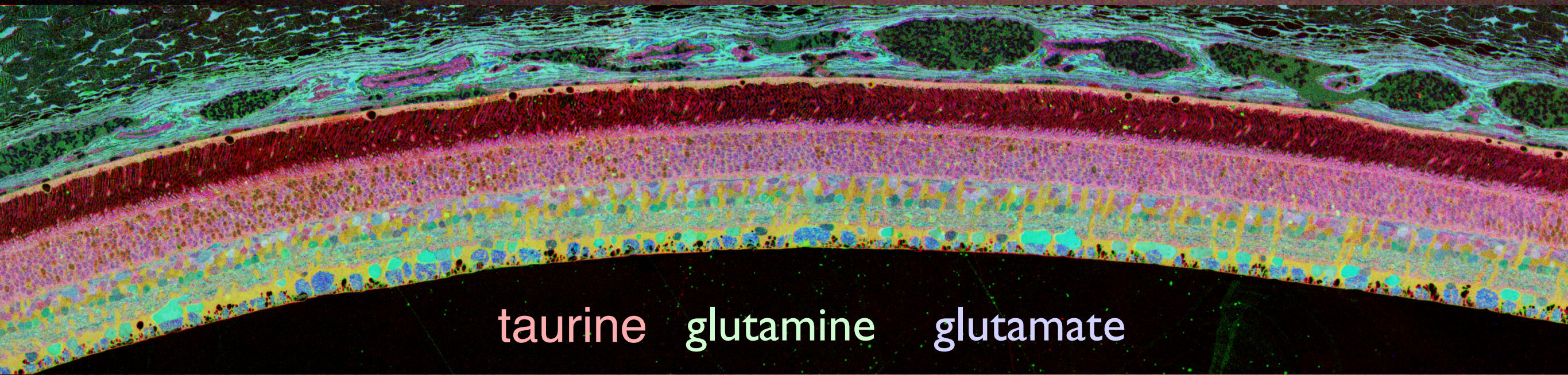
Retinoid receptors trigger neuriteogenesis in retinal degenerations.

Reprogramming

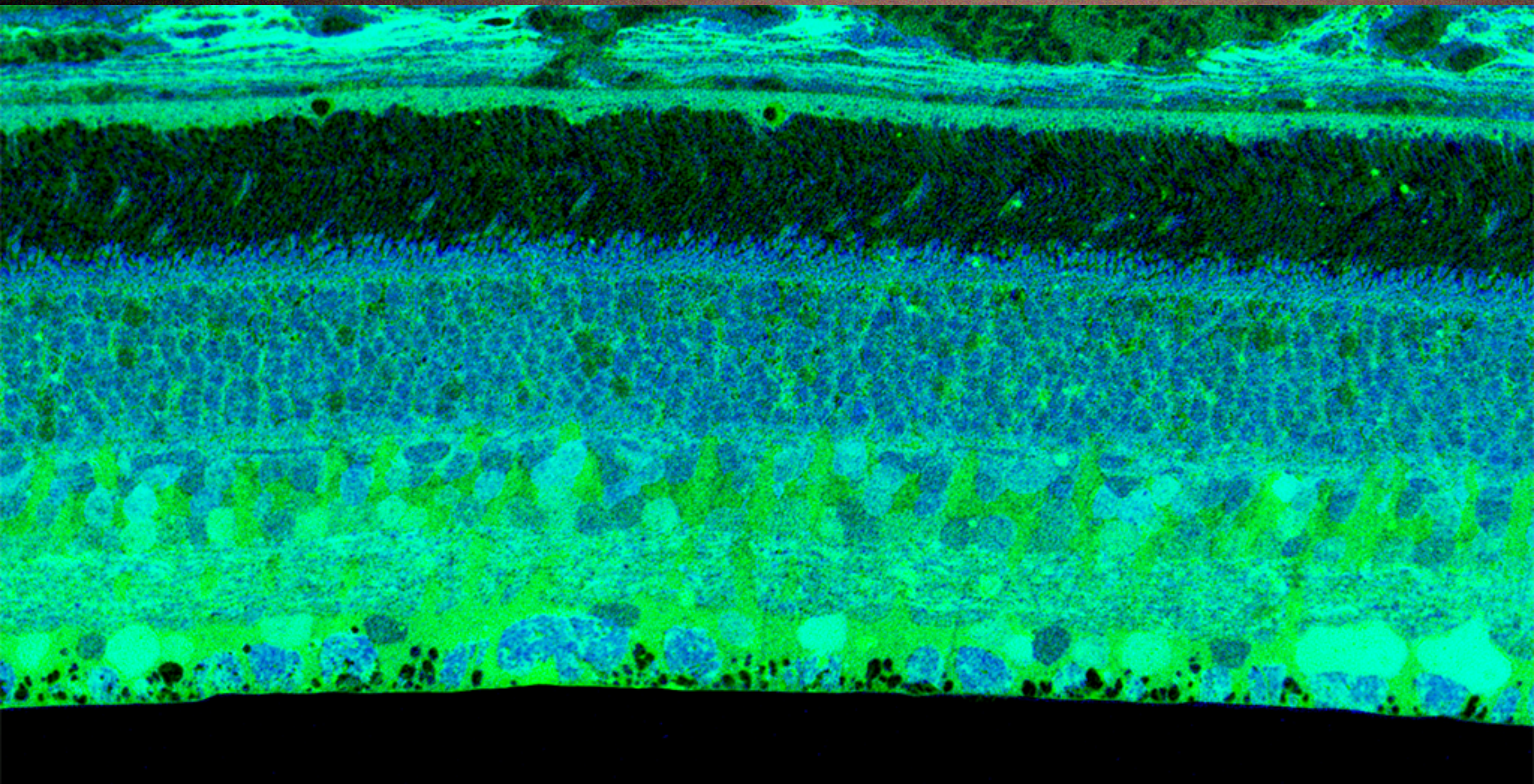
Müller cell metabolic chaos

Rebecca Pfeiffer
Graduate Student
Neuroscience

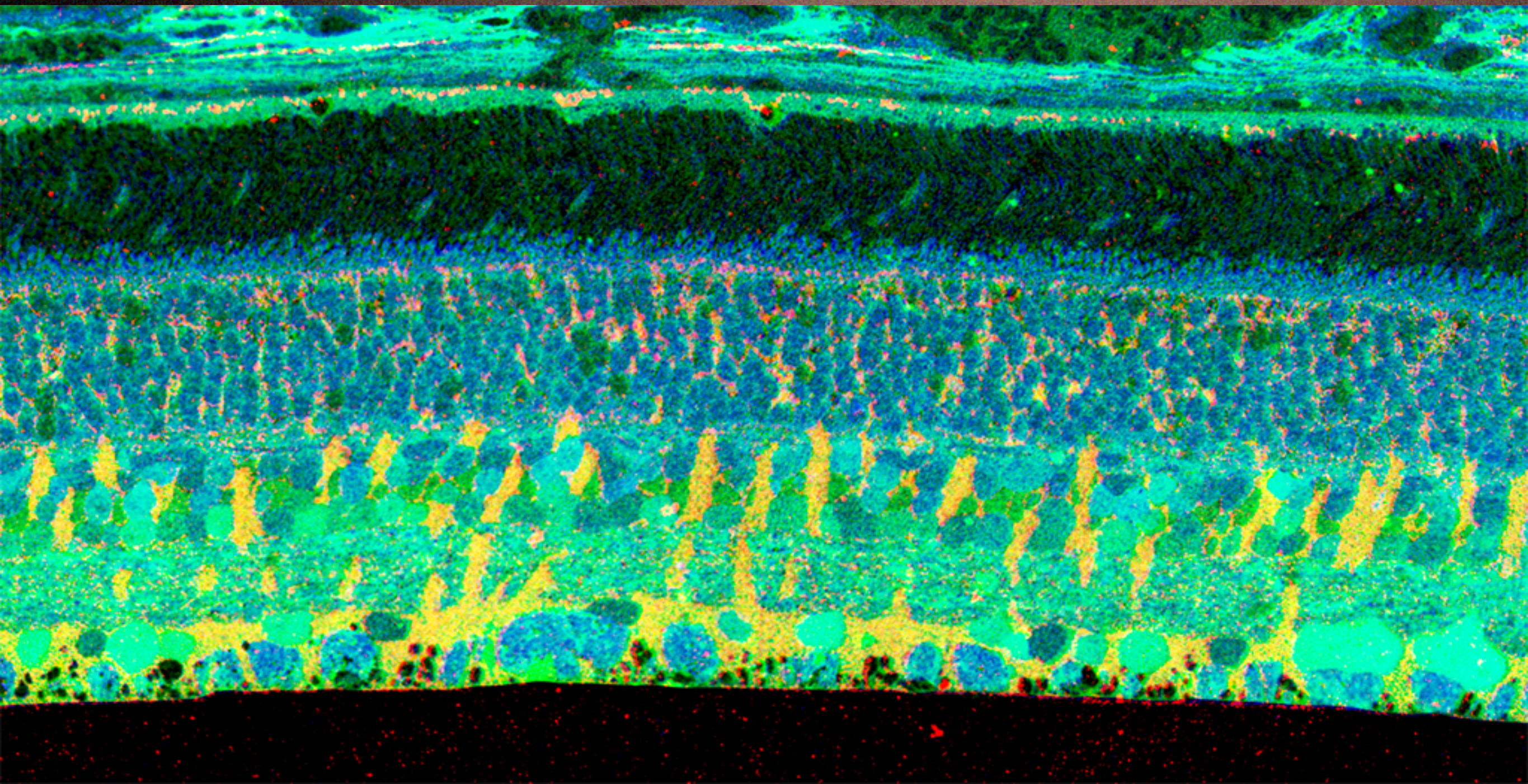




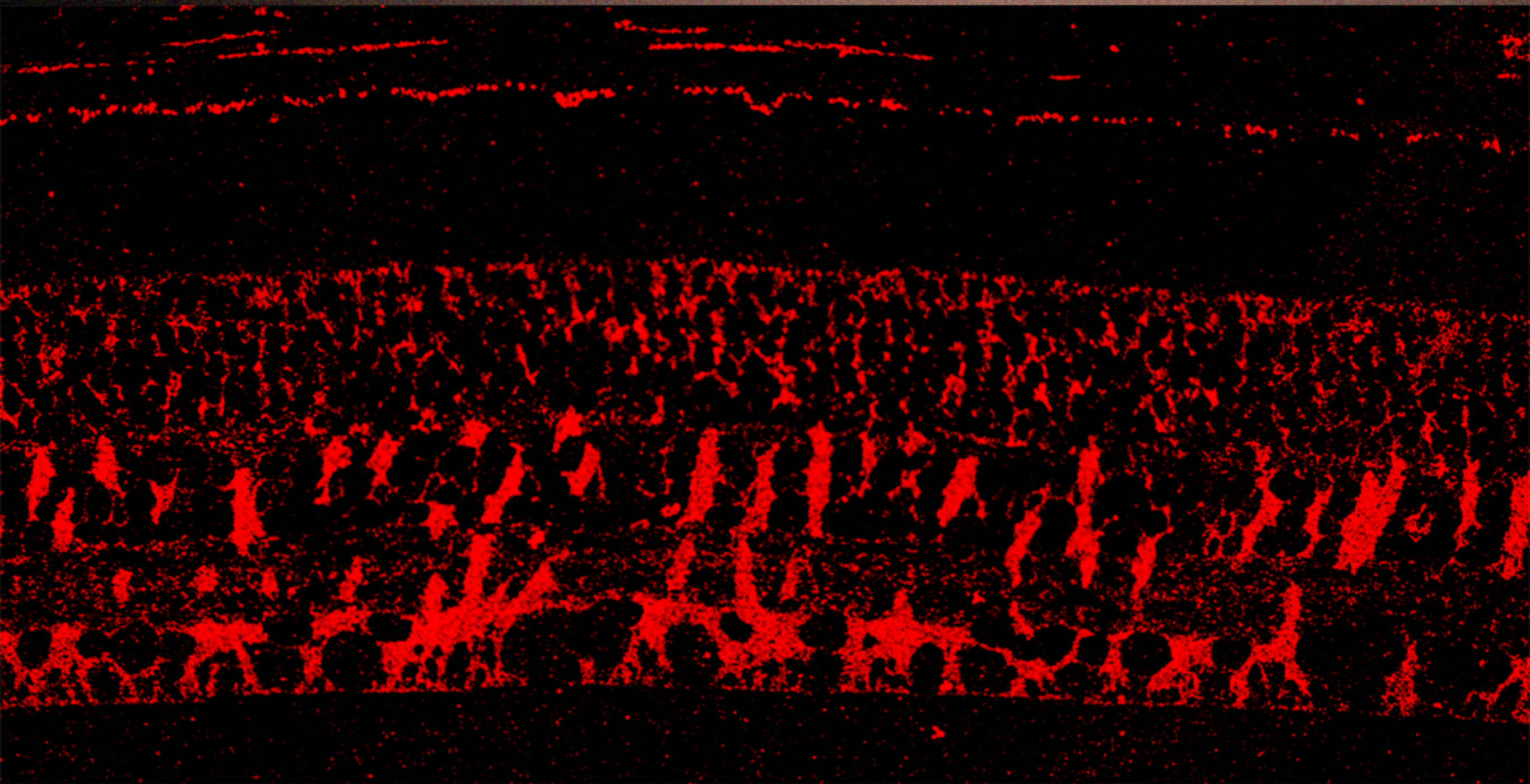
glutamine glutamate



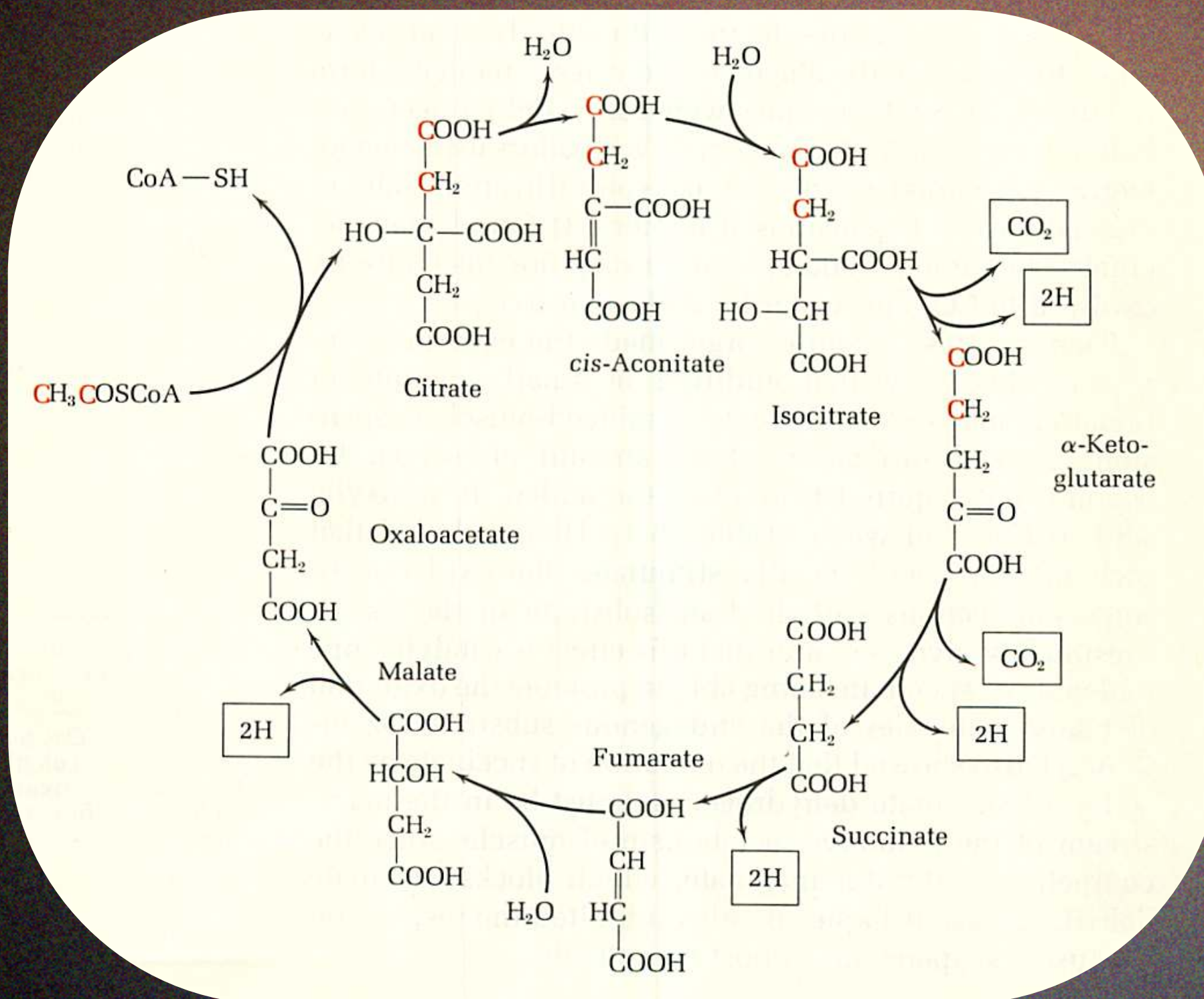
GS glutamine glutamate

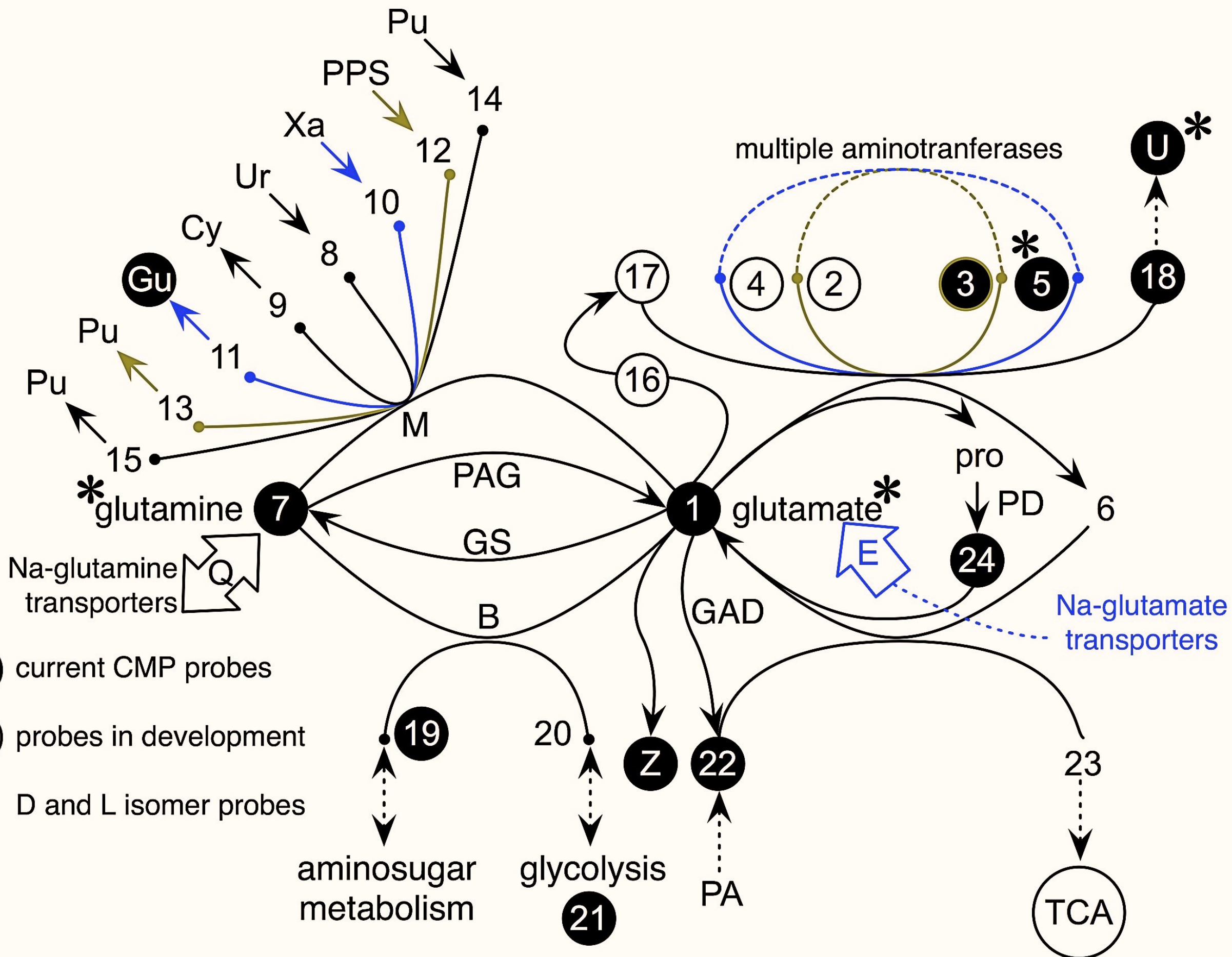


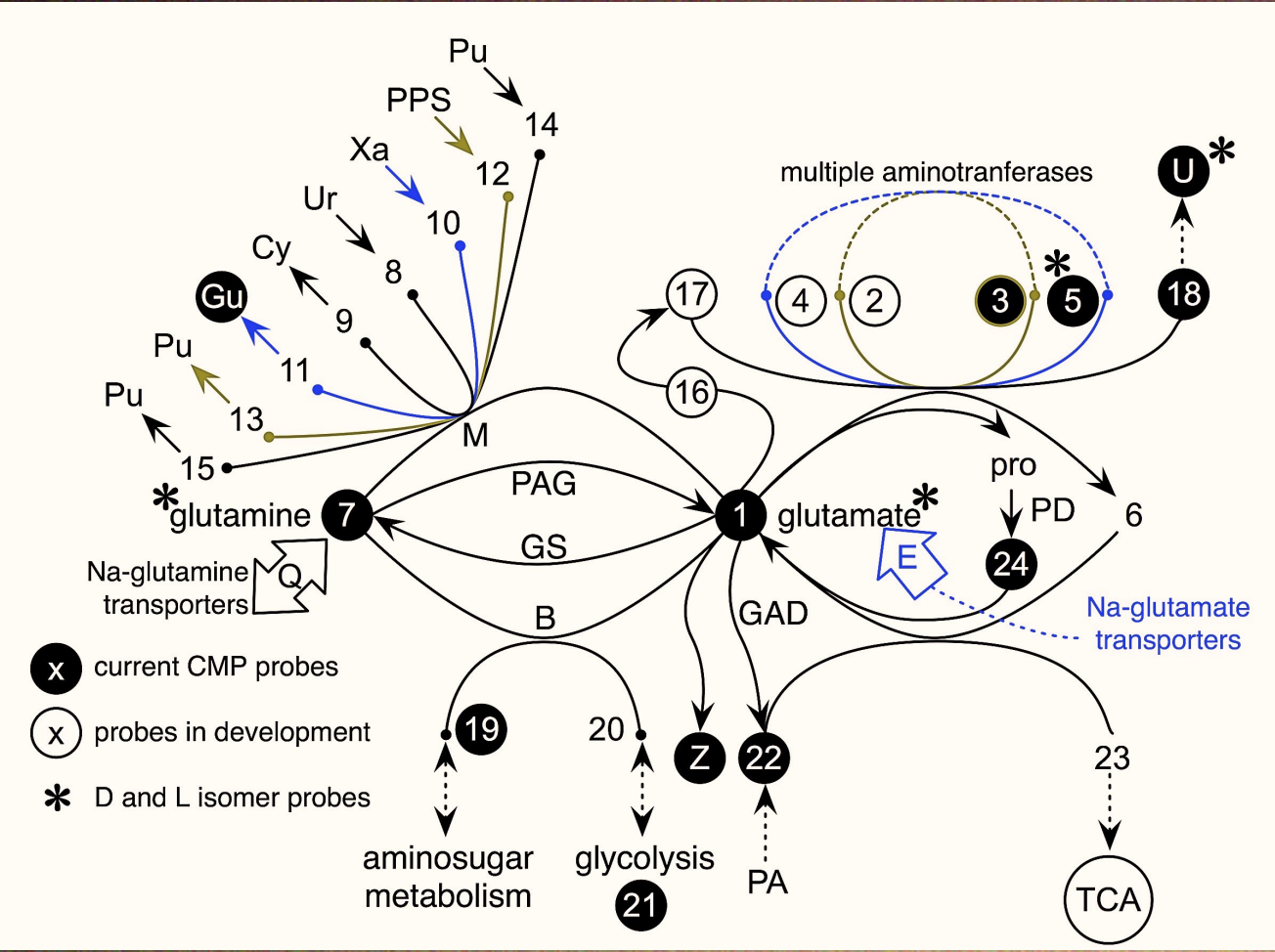
GS



Biochemistry, 1970, 1st edition, Albert Lehninger

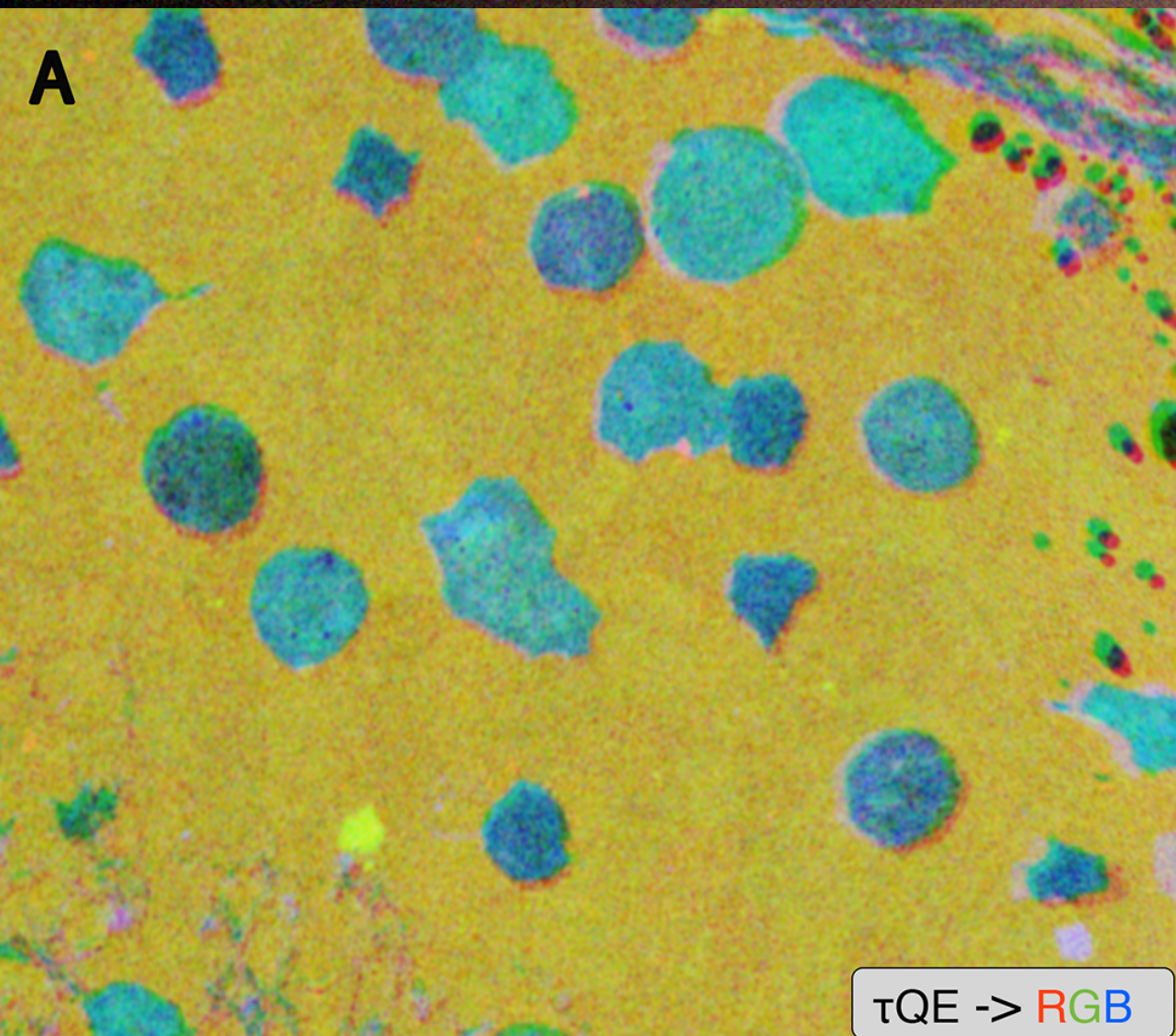




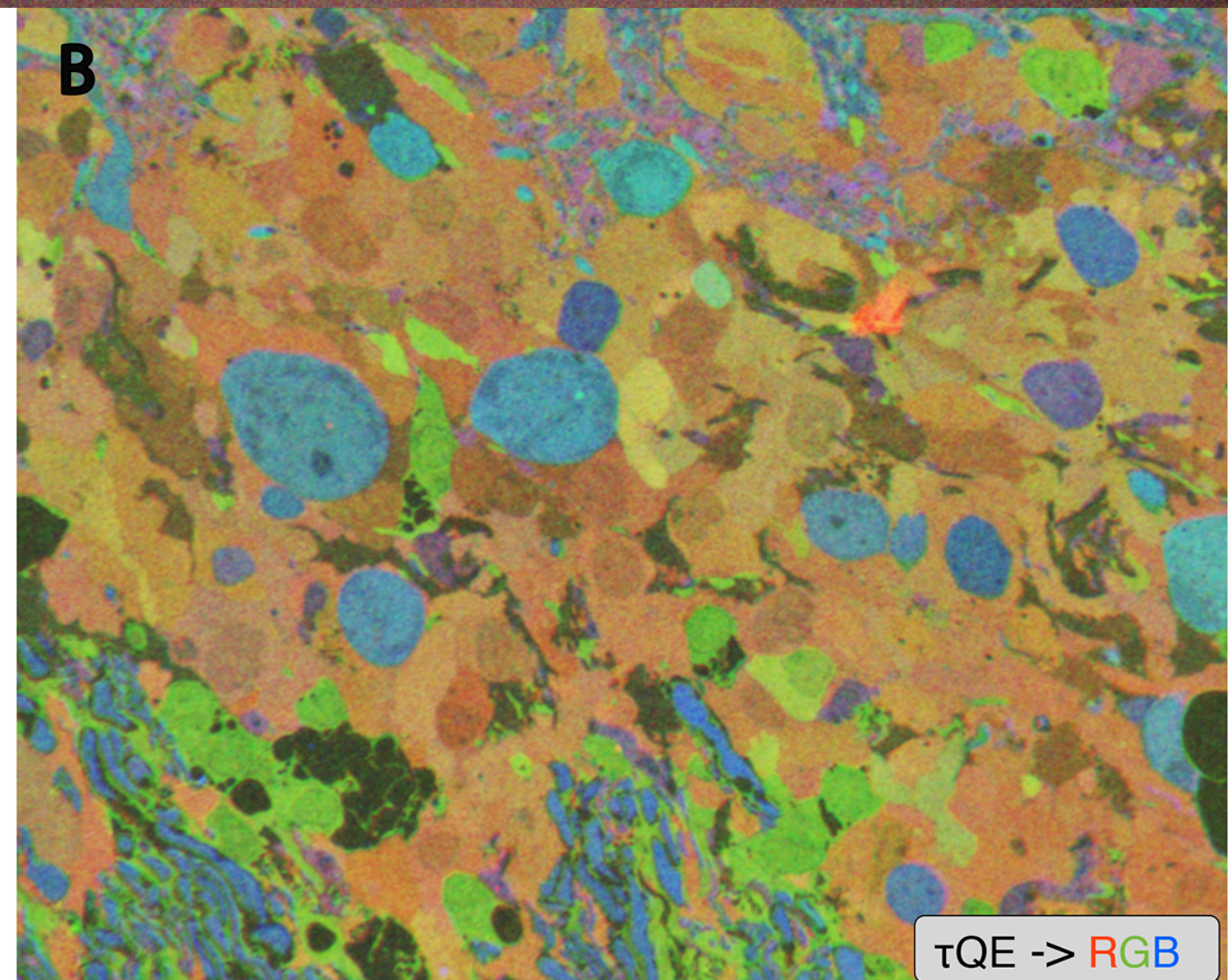


- GAD glutamate decarboxylase
U arginine synthesis
Z glutathione synthesis
M multiple transaminases

RETINAL REMODELING :: MÜLLER CELL METABOLIC CHAOS



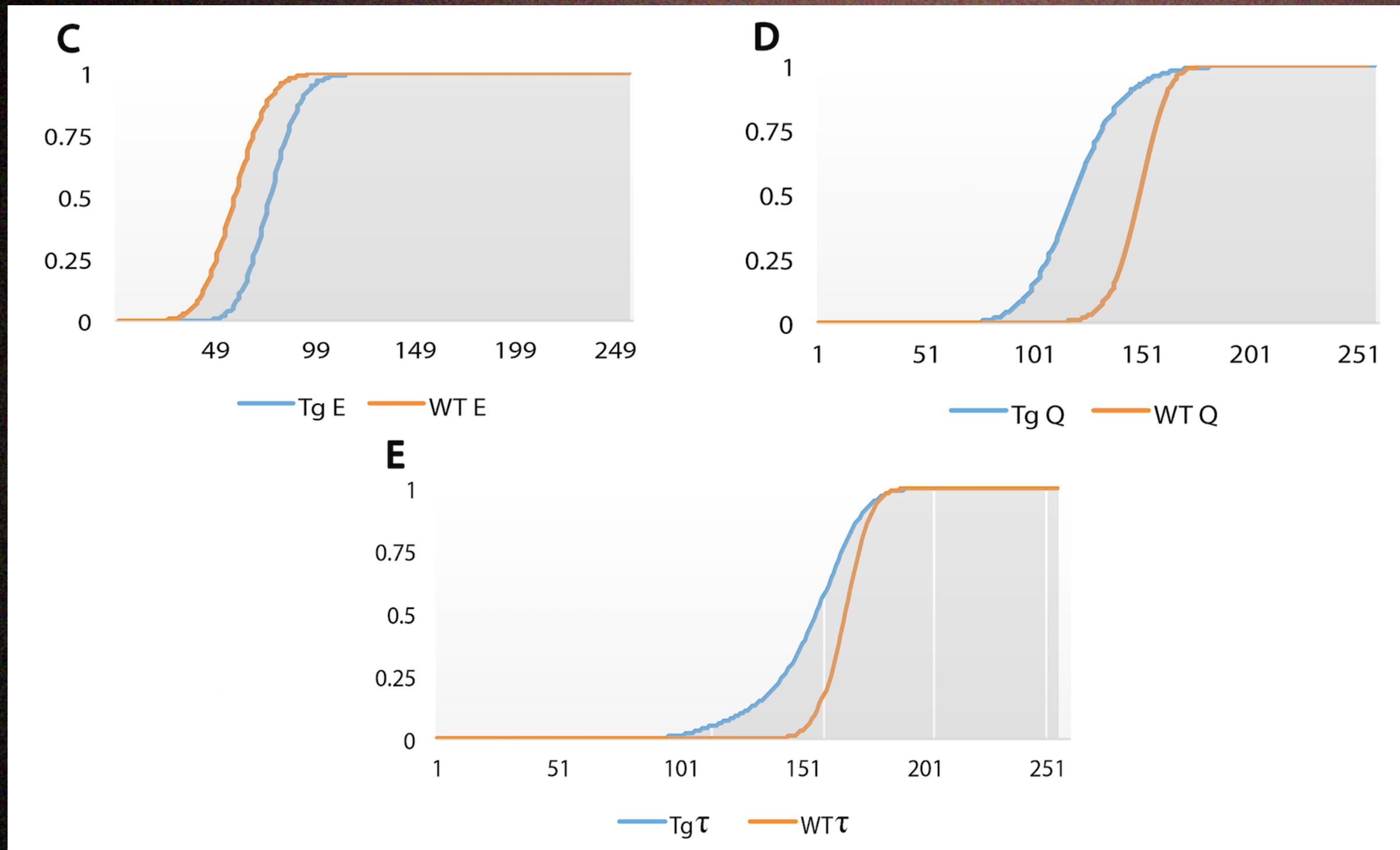
wt



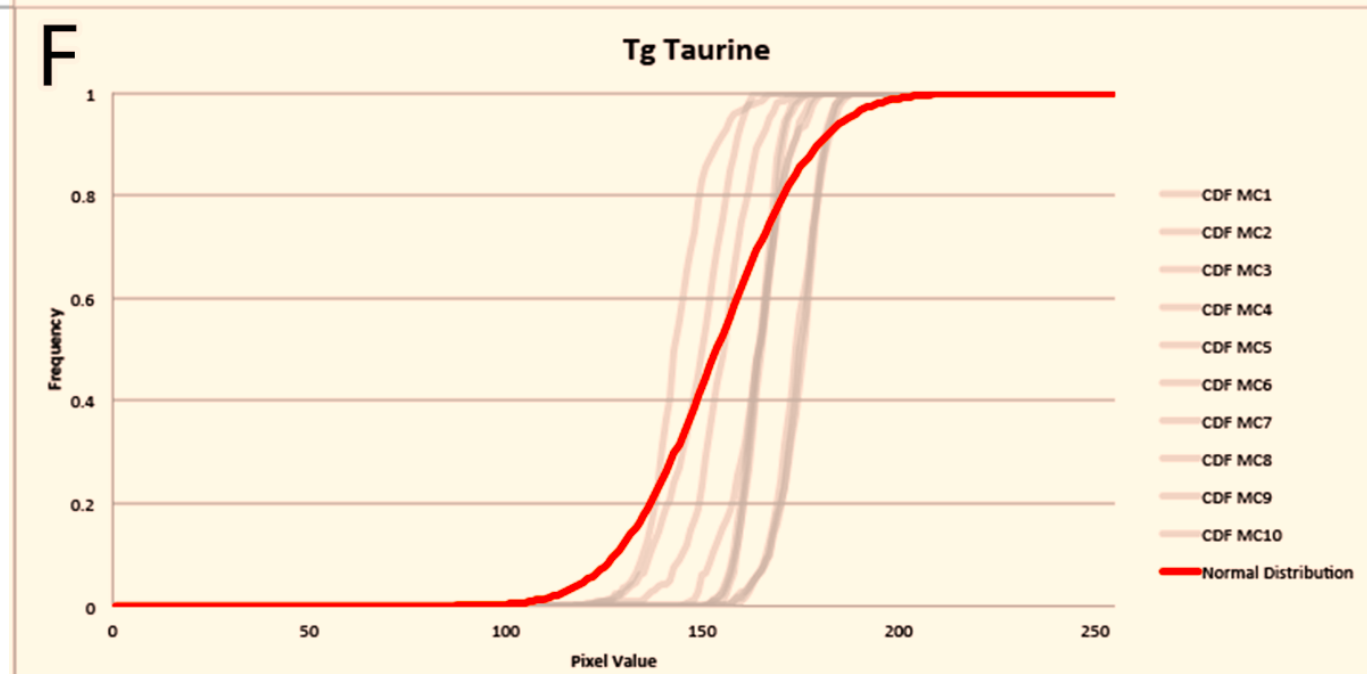
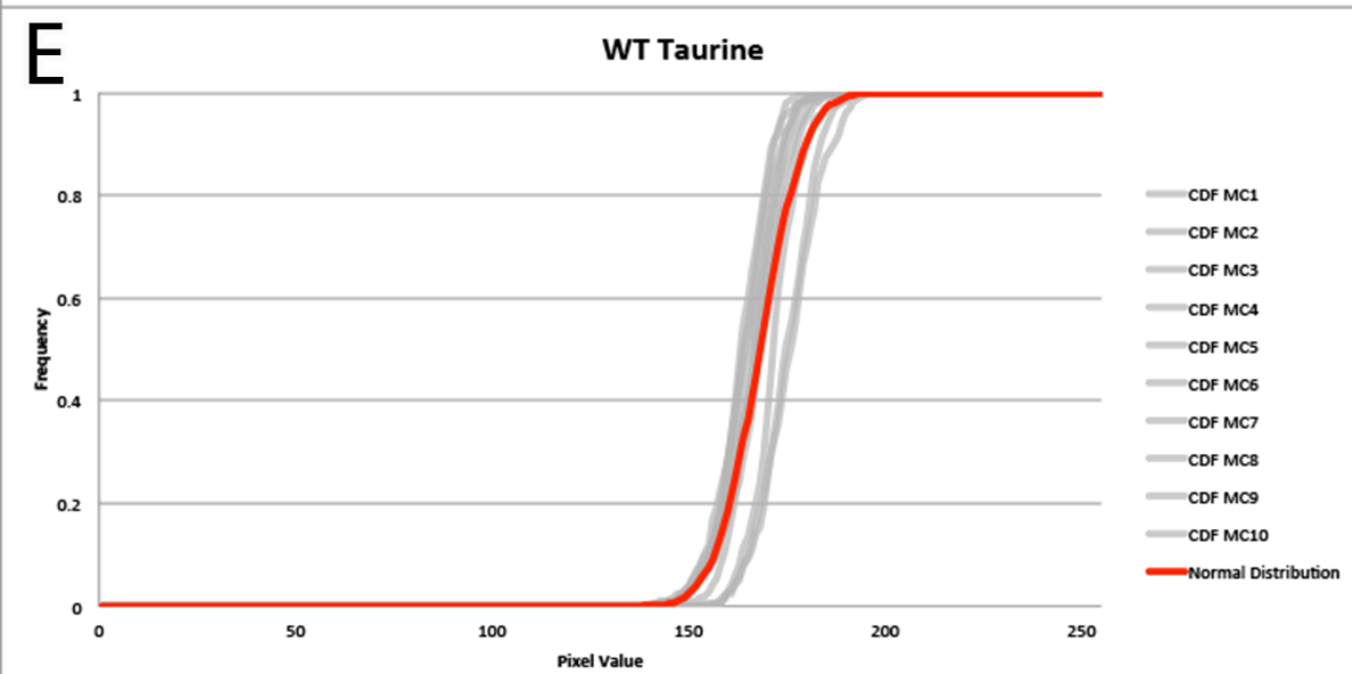
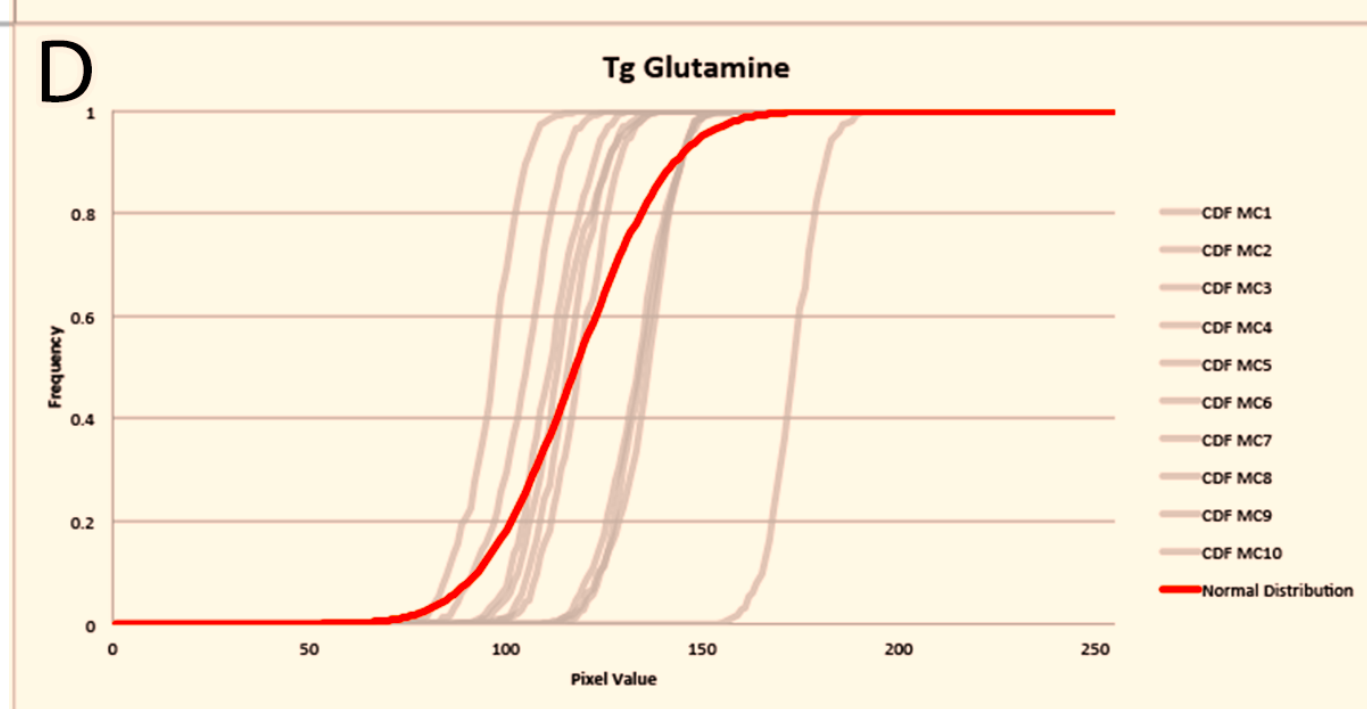
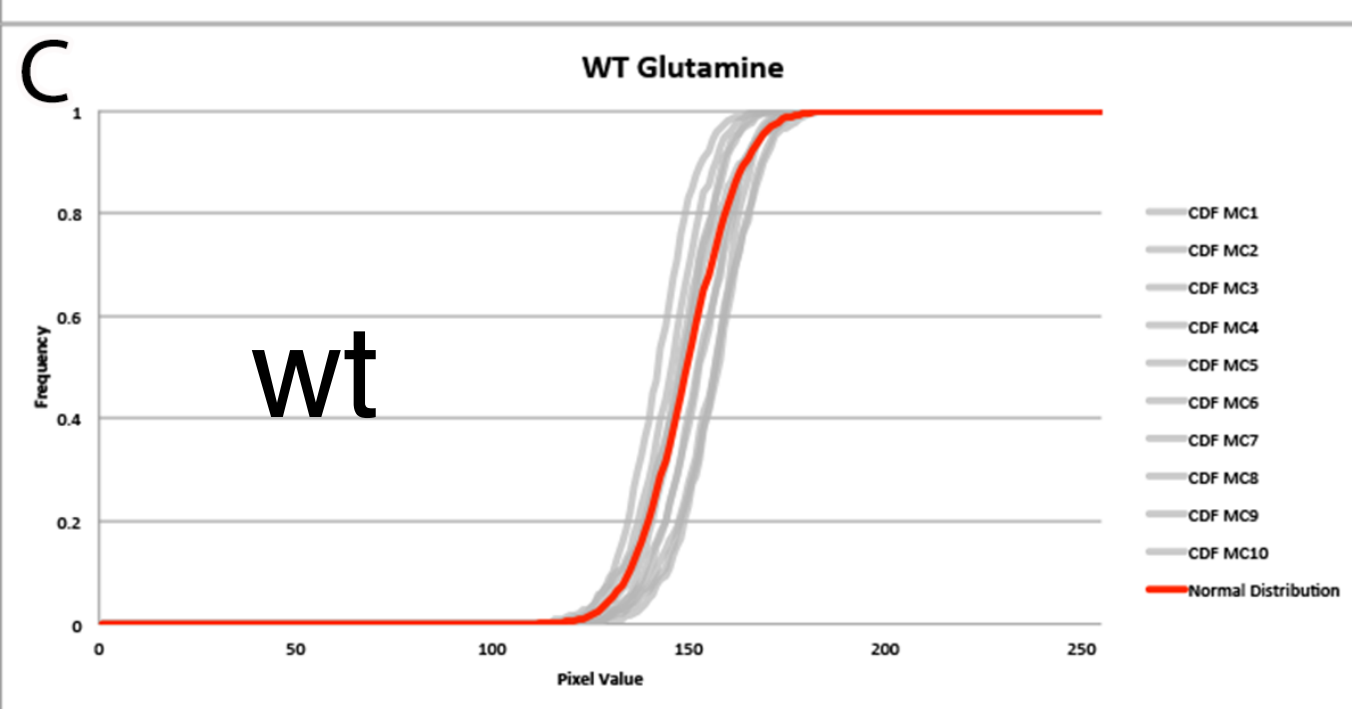
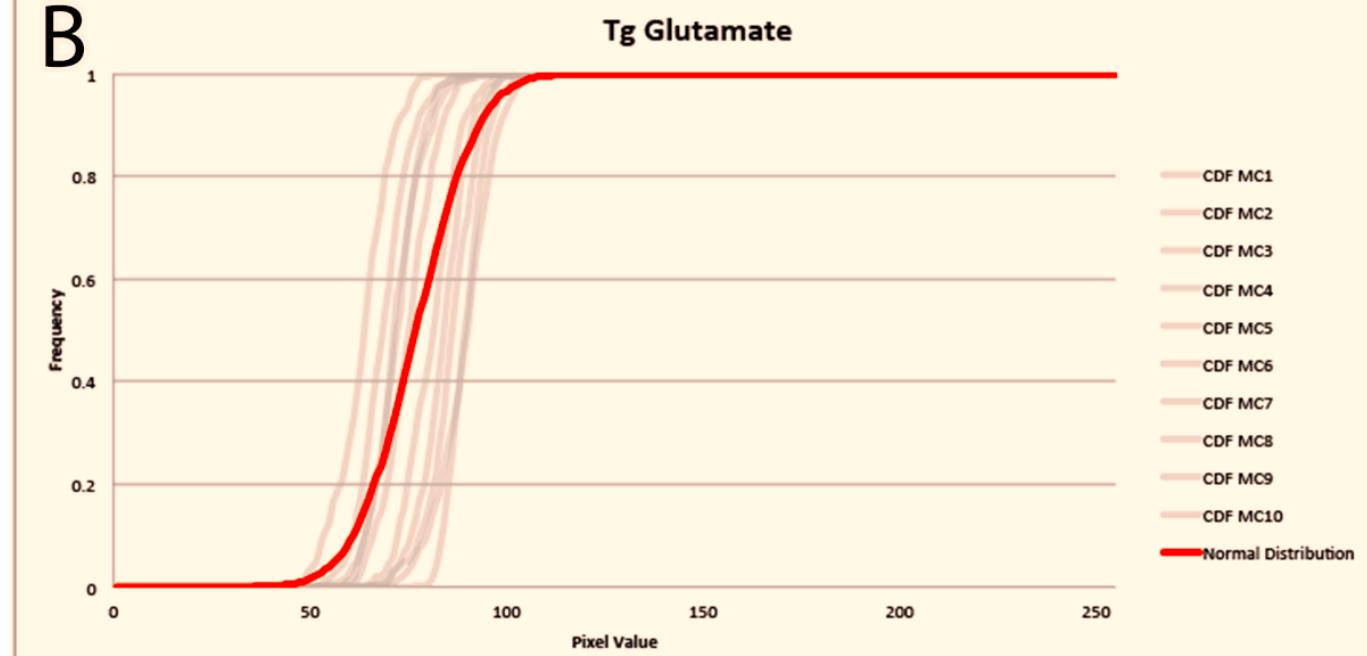
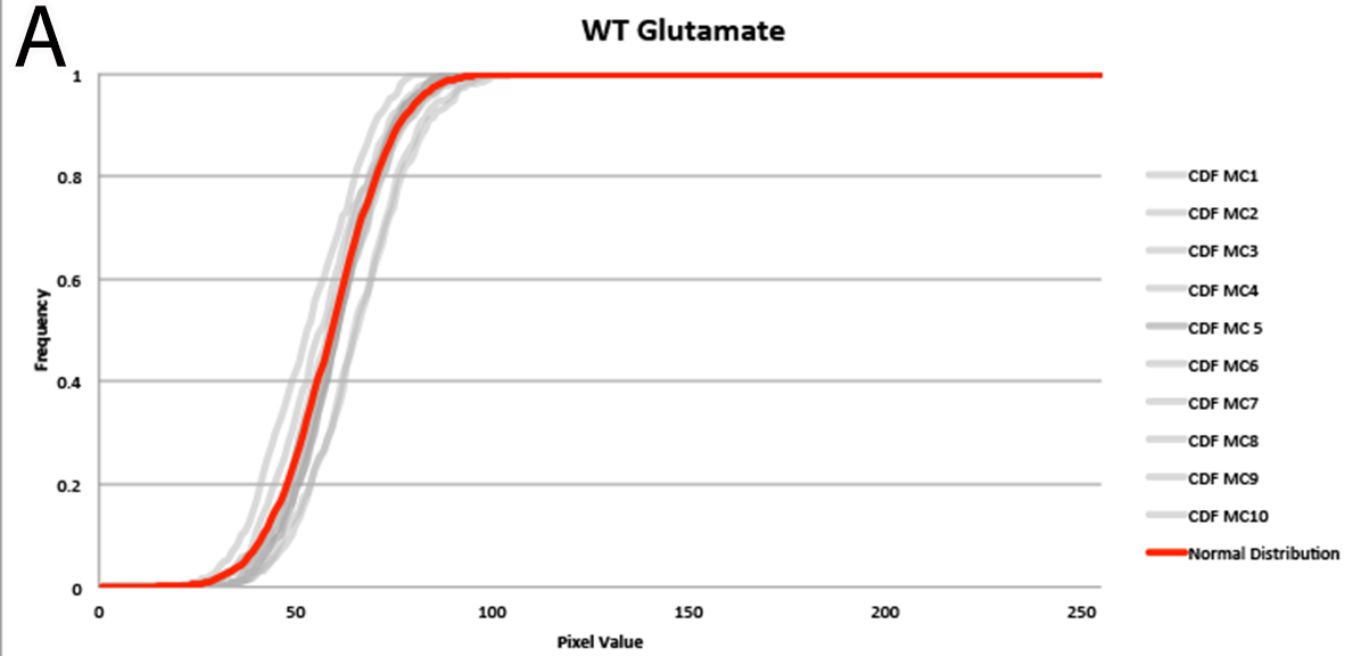
2y Tg P347L

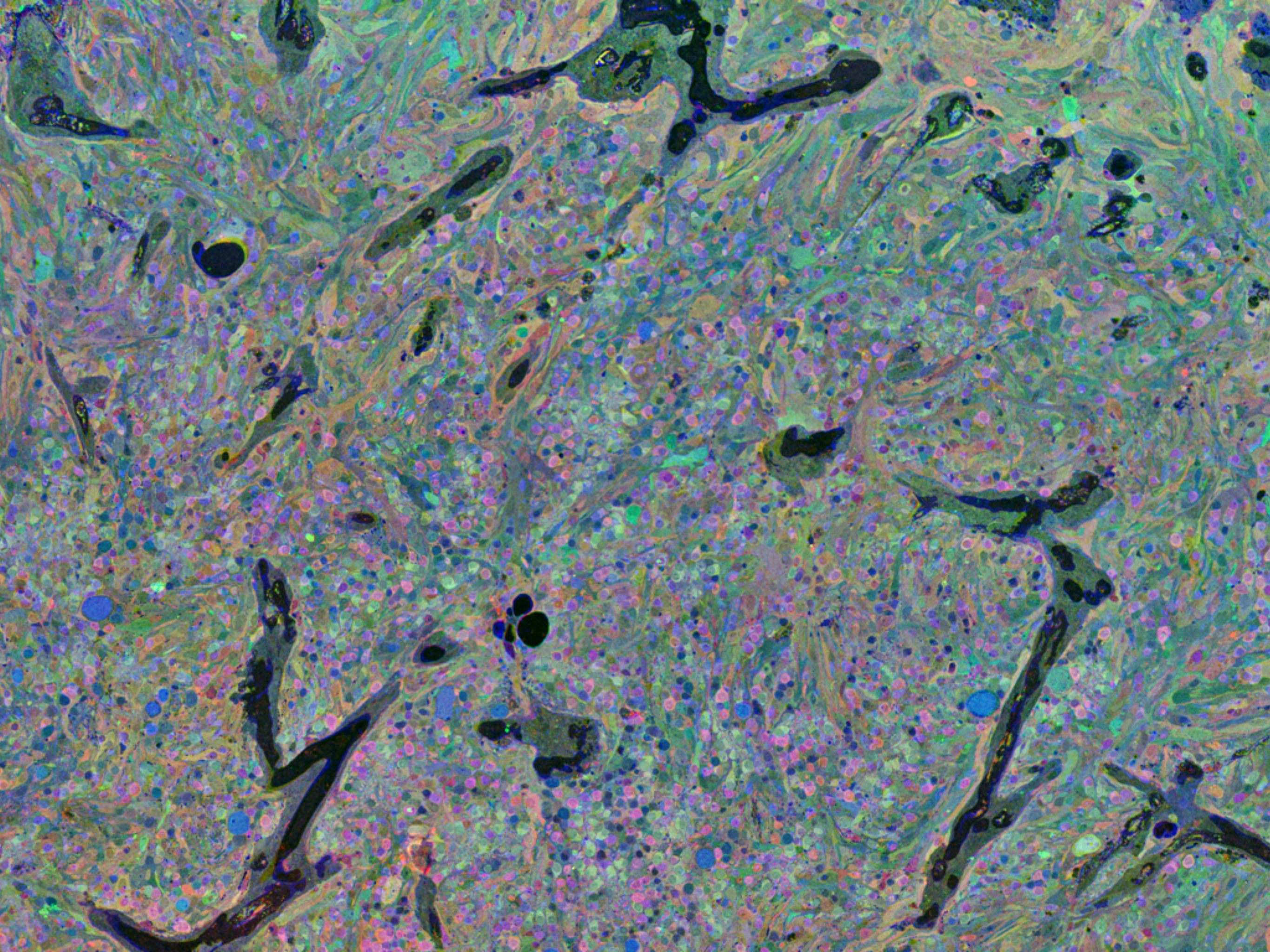
Pfeiffer RL, Marc RE, Kondo M, Terasaki H, Jones BW. 2016 Müller cell metabolic chaos during retinal degeneration. *Exp Eye Res.* 2016 pii: S0014-4835(16)30095-1. doi: 10.1016/j.exer.2016.04.022. PMID: 27142256. PMCID : PMC5031519.

RETINAL REMODELING :: MÜLLER CELL METABOLIC CHAOS

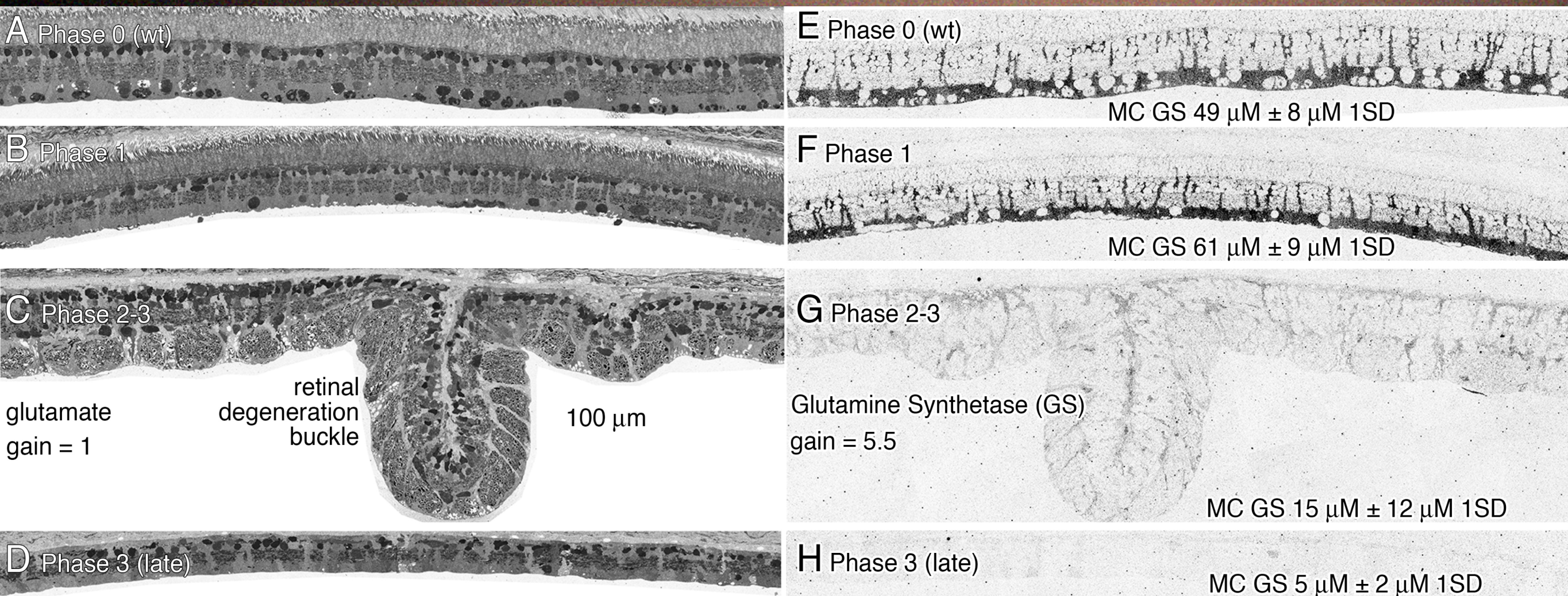


Pfeiffer RL, Marc RE, Kondo M, Terasaki H, Jones BW. 2016 Müller cell metabolic chaos during retinal degeneration. *Exp Eye Res.* 2016 pii: S0014-4835(16)30095-1. doi: 10.1016/j.exer.2016.04.022. [Epub ahead of print]. PMID: 27142256. PMCID : PMC5031519.



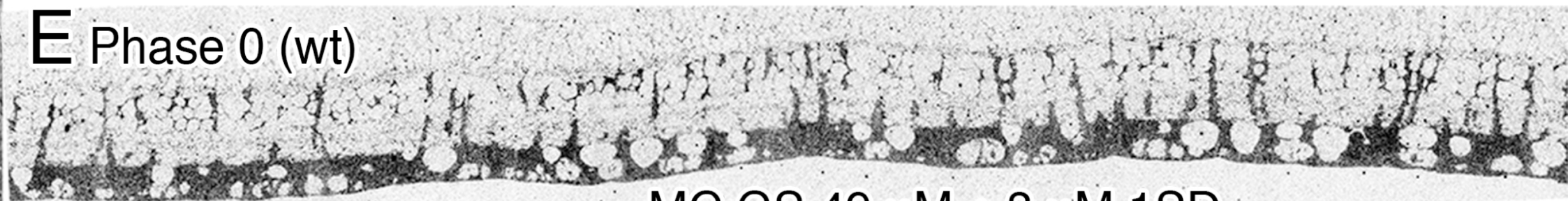


RETINAL REMODELING :: MÜLLER CELL METABOLIC CHAOS



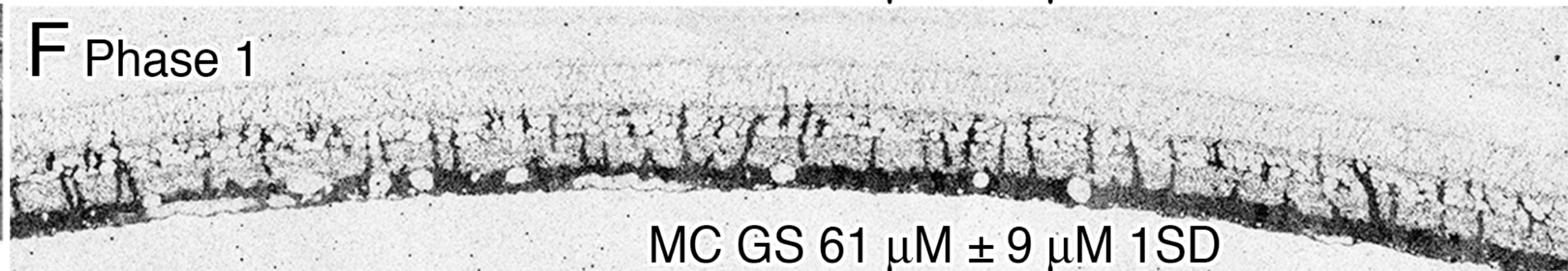
NEARLY COMPLETE LOSS OF GLUTAMINE SYNTHETASE

E Phase 0 (wt)



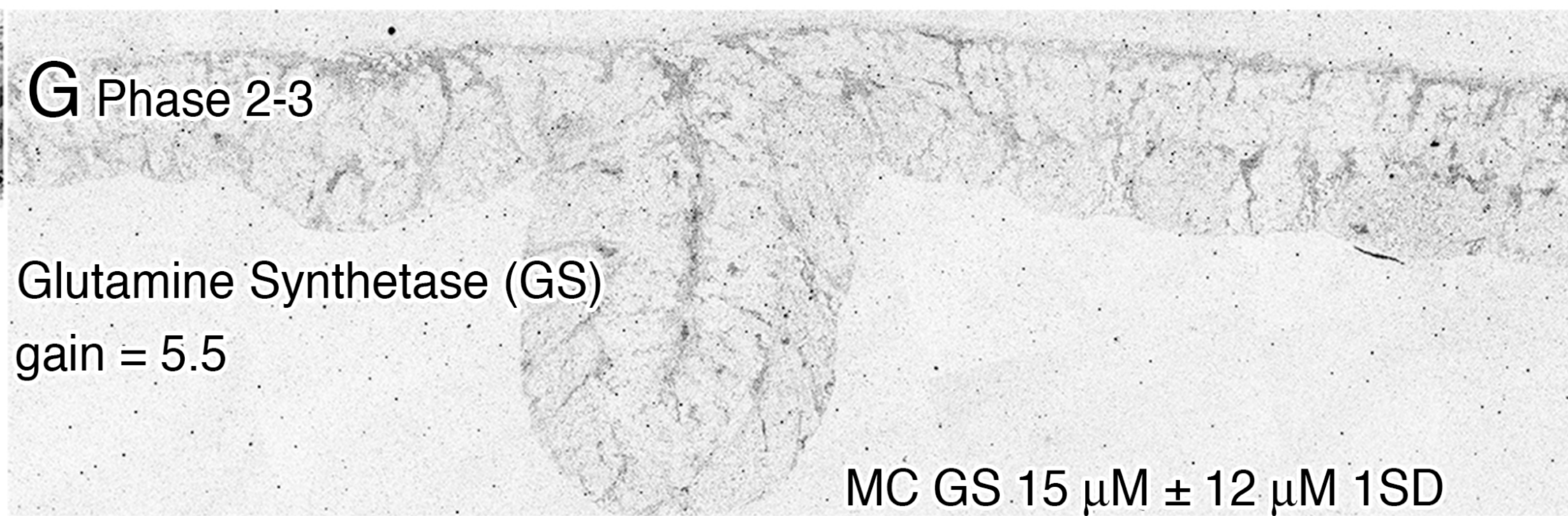
MC GS $49 \mu\text{M} \pm 8 \mu\text{M}$ 1SD

F Phase 1



MC GS $61 \mu\text{M} \pm 9 \mu\text{M}$ 1SD

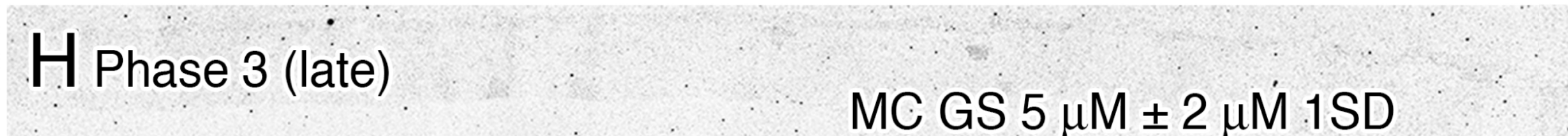
G Phase 2-3



Glutamine Synthetase (GS)
gain = 5.5

MC GS $15 \mu\text{M} \pm 12 \mu\text{M}$ 1SD

H Phase 3 (late)



MC GS $5 \mu\text{M} \pm 2 \mu\text{M}$ 1SD

Connectomics and retinal complexity

Degeneration kinetics

Remodeling

Neurodegeneration

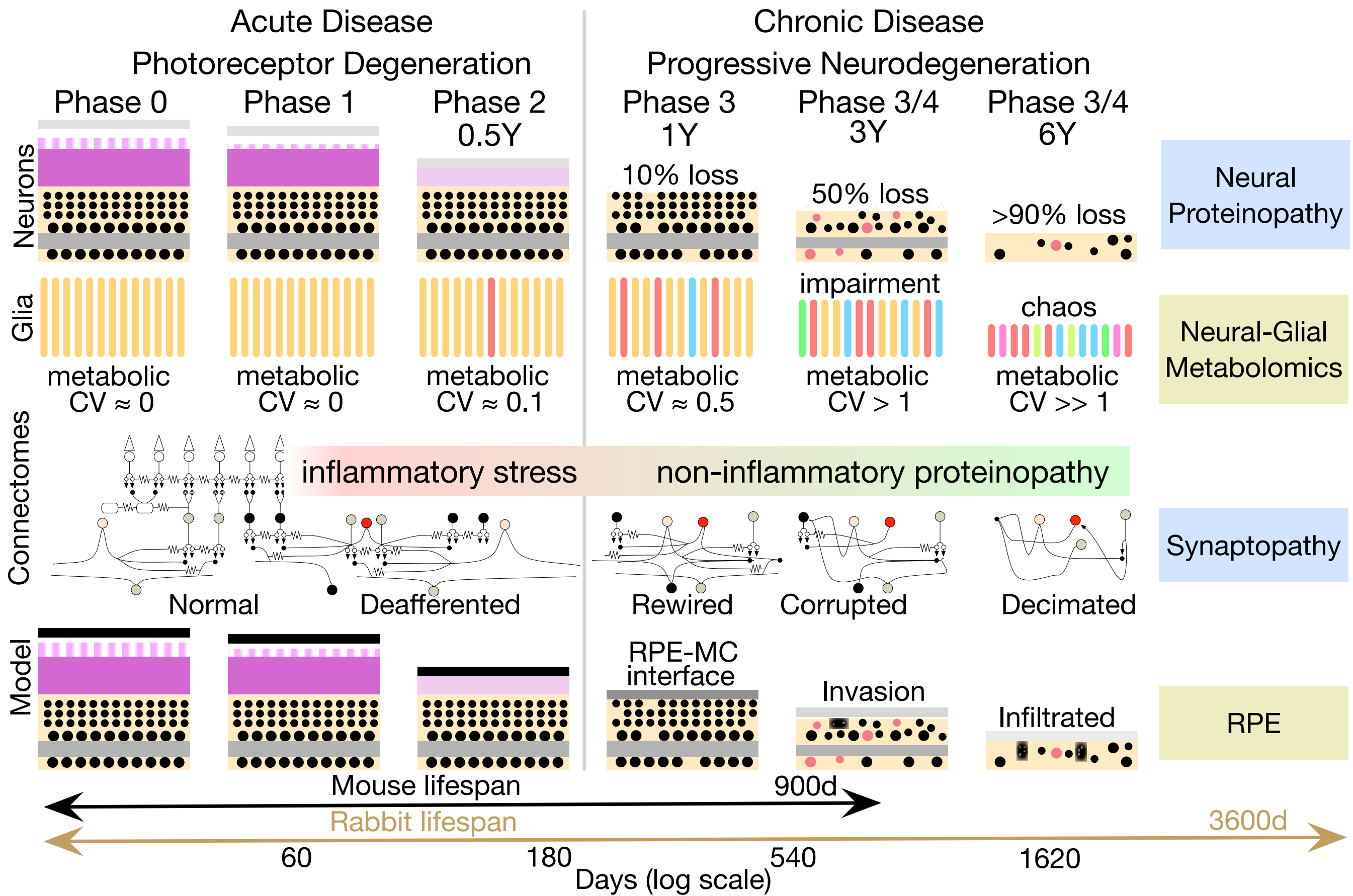
Neurodegeneration

Based on analyses of mouse, rat, and short term 2y Tg P347L rabbit and Tg P23H pig models, we concluded that remodeling reached stasis: that retinas were aggressively remodeled but stable. That conclusion is wrong.

Longitudinal analyses of the Tg P347L rabbit, a model with a lifespan 4x that of a mouse, shows that remodeling is relentlessly progressive, with continuing neuronal death until > 90% of neurons are gone.

Phase 4 neurodegeneration never stops.

RETINAL NEURODEGENERATION



RETINAL NEURODEGENERATION

CNS neurodegenerations are proteinopathies

Alzheimer's Dementia (AD): β -amyloid, α -synuclein, tau

NFT Senile Dementias (SD): tau

Dementia with Lewy Bodies Disease (DLB): α -synuclein

Multiple system atrophy (MSA): α -synuclein

Huntington's Disease: huntington, mHTT

Parkinson's Disease: α -synuclein

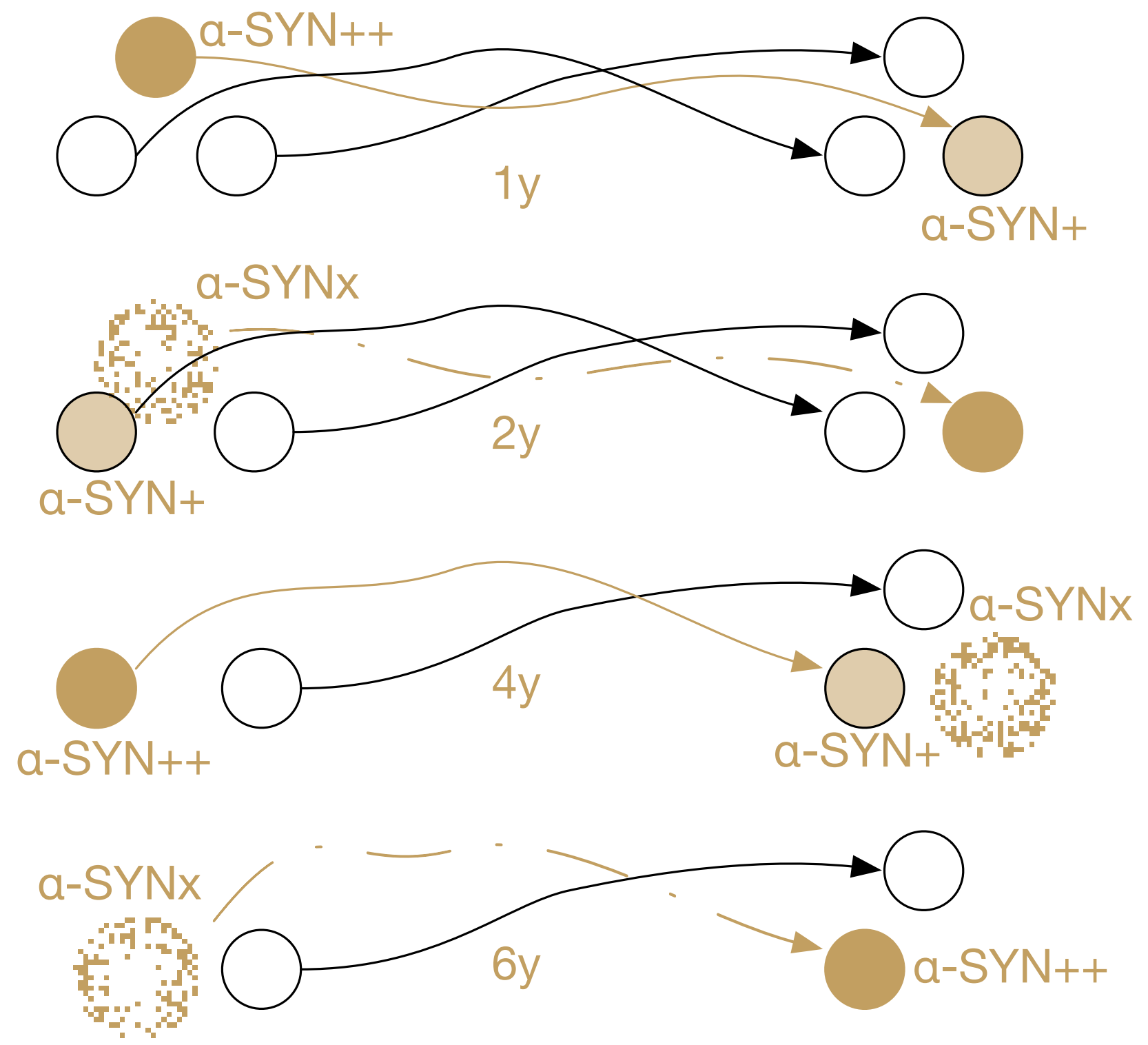
Traumatic Brain Injury: α -synuclein, tau

Creutzfeld Jakob Disease: prion protein

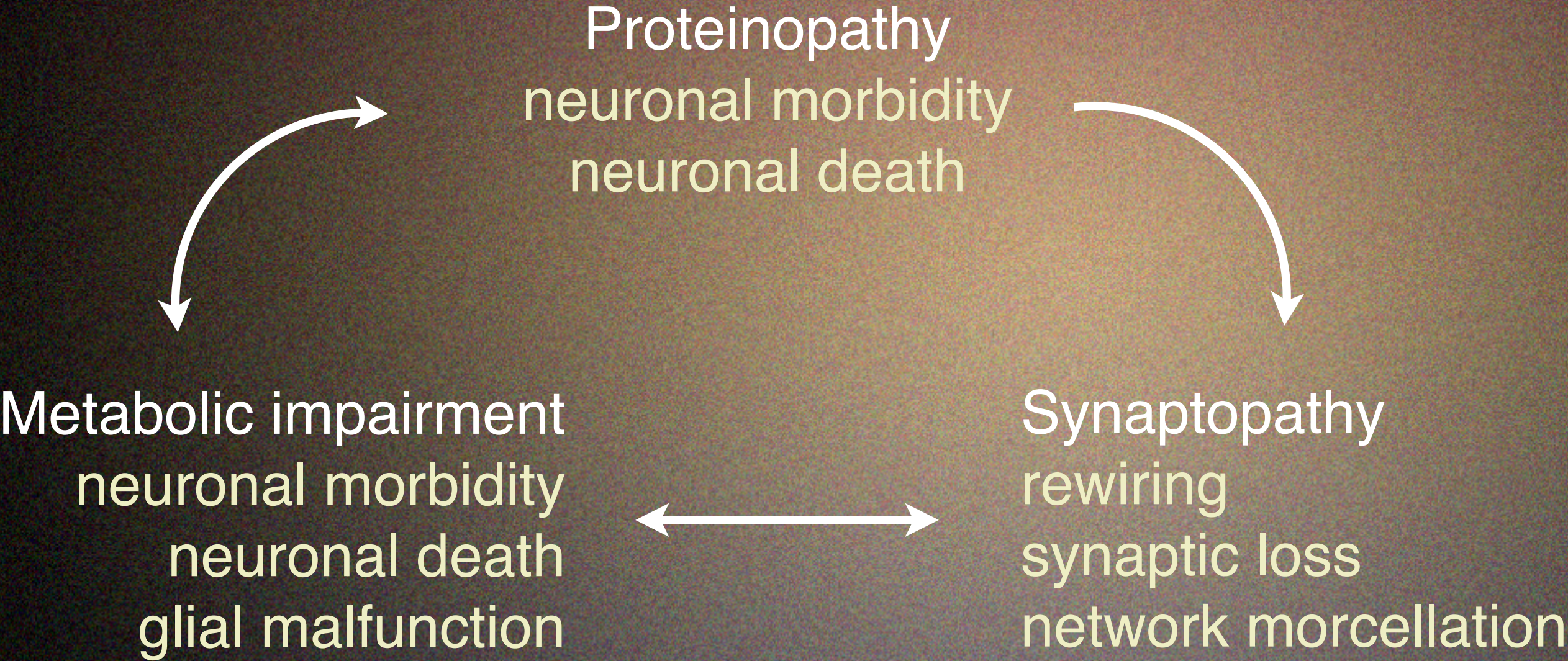
Amyotrophic Lateral Sclerosis & FTLD: TDB-43

Protein oligomers, aggregates or tangles cause ER stress
and slow neuronal death

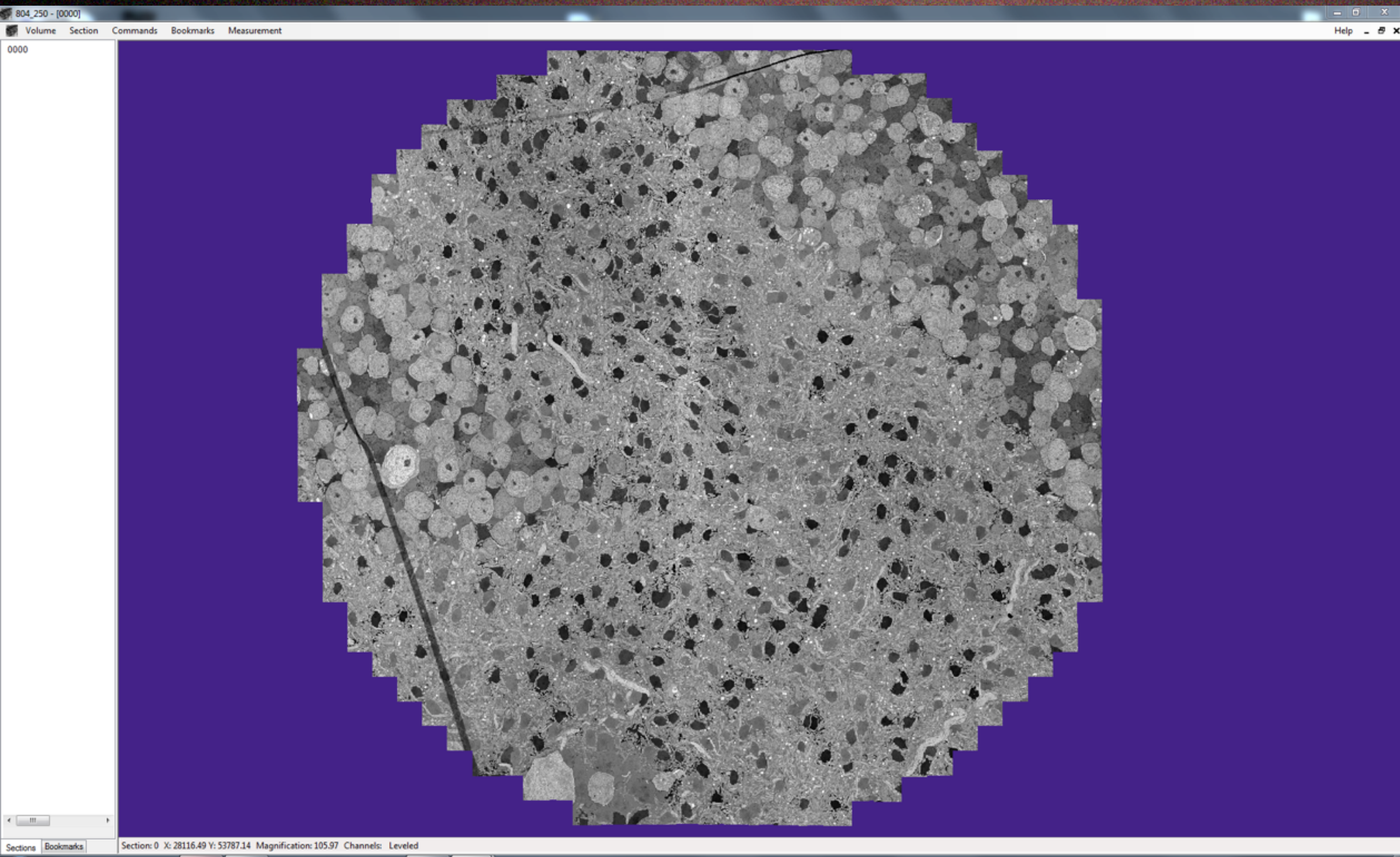
RETINAL NEURODEGENERATION

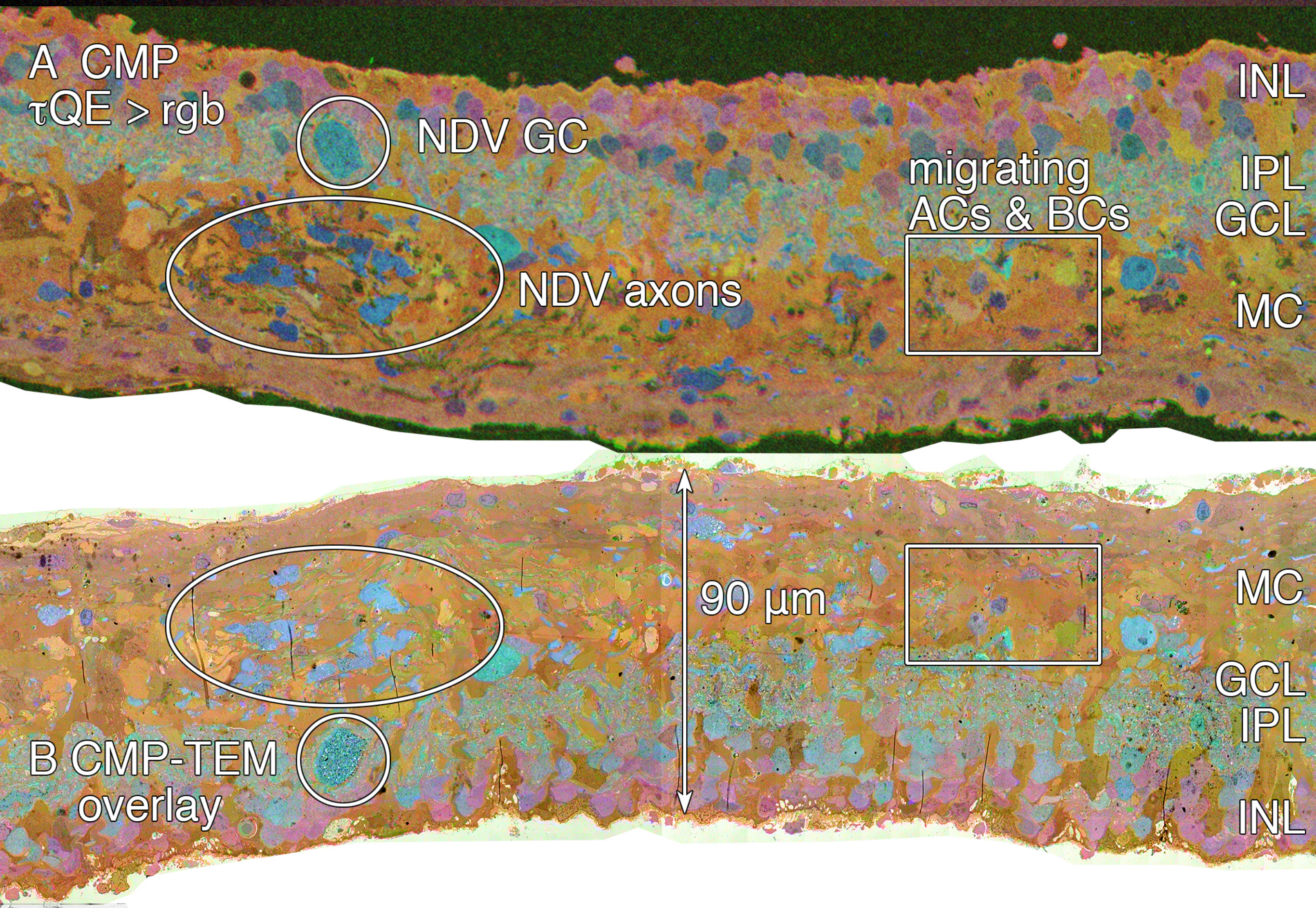


RETINAL NEURODEGENERATION



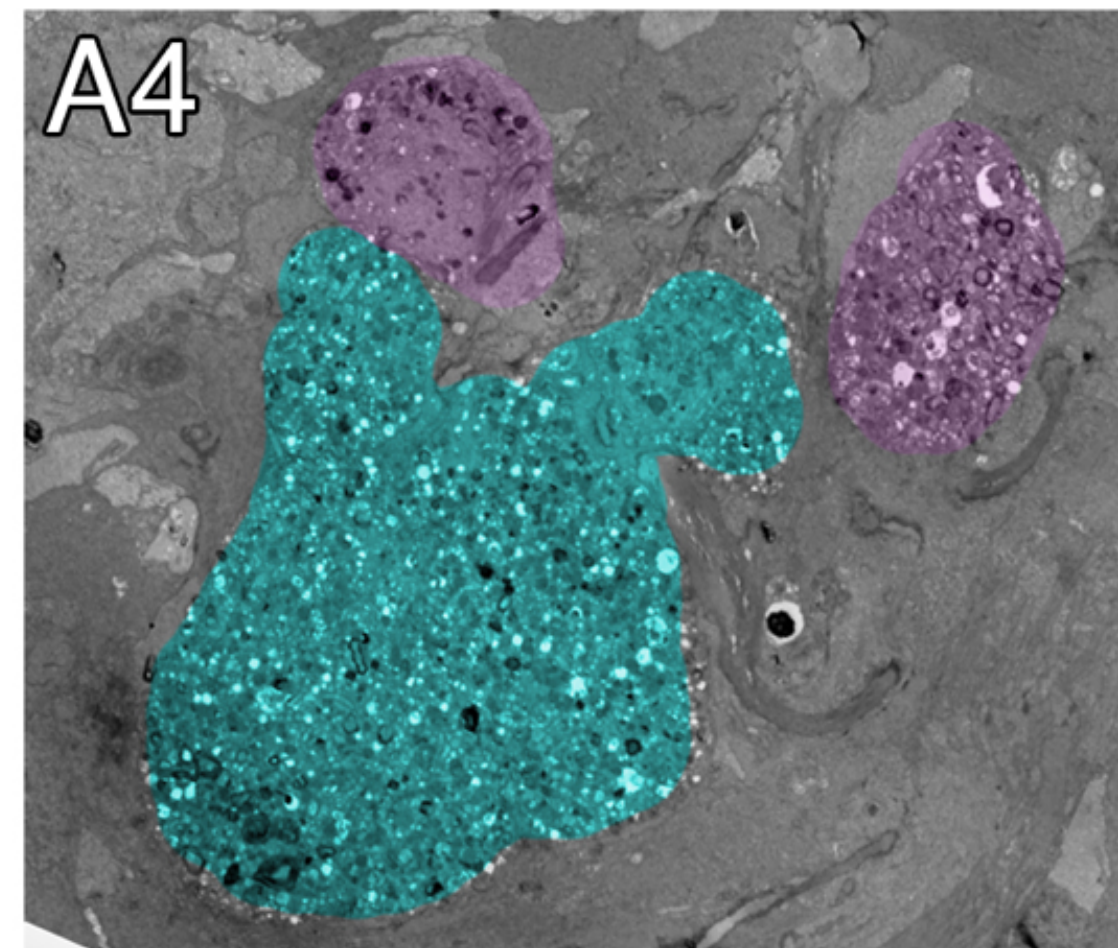
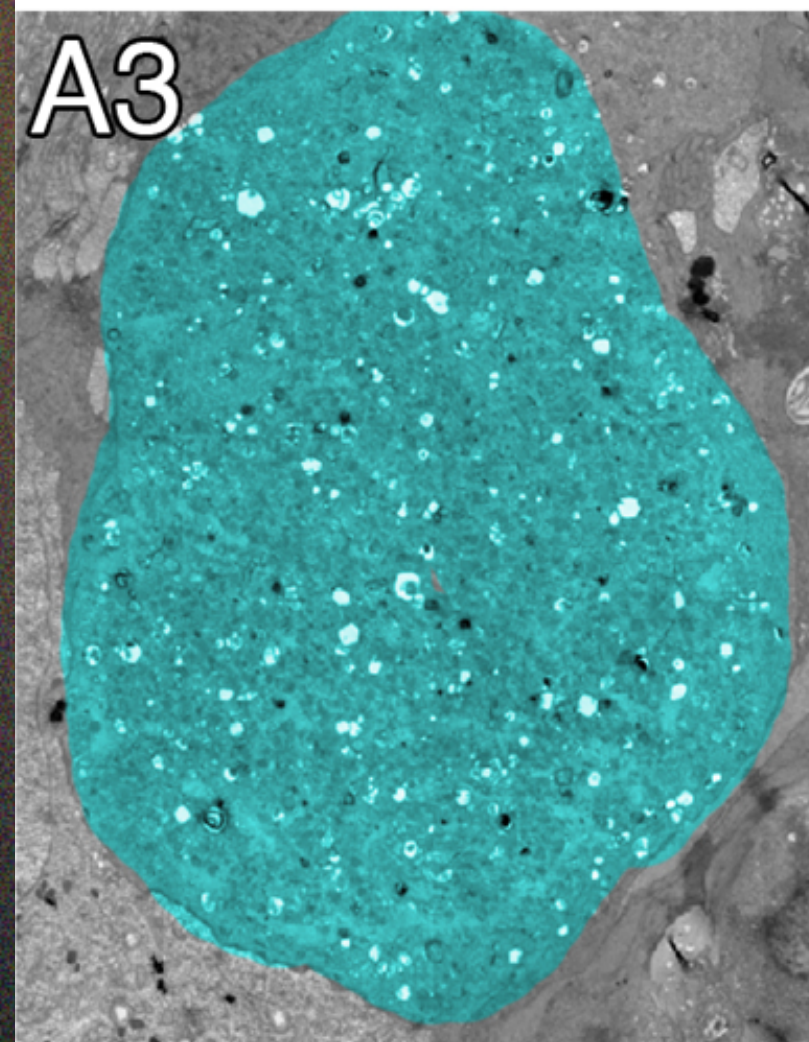
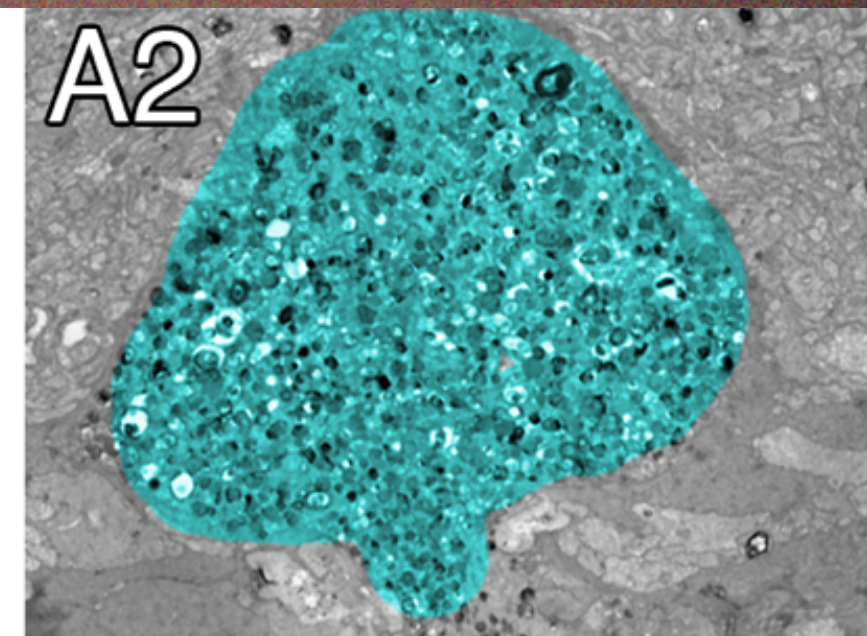
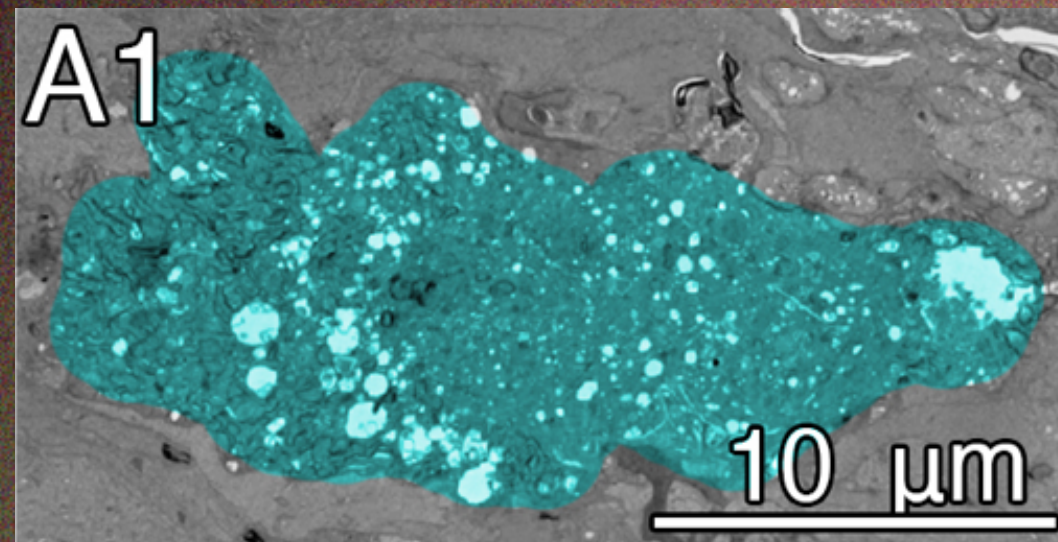
TgP347L PC1-z800-m106 Retinal Pathoconnectomics





RETINAL NEURODEGENERATION

Most neurons and
all τ QE ganglion
cells show
neurodegeneration



RETINAL NEURODEGENERATION

α -Synuclein & α -Synucleinopathies

Alzheimer's Dementia (AD)

Dementia with Lewy Bodies (DLB)

Multiple system atrophy (MSA)

Parkinson's Disease (PD)

Traumatic Brain Injury (TBI)

RETINAL NEURODEGENERATION

α -Synuclein & α -Synucleinopathies

Alzheimer's Dementia (AD)

Dementia with Lewy Bodies (DLB)

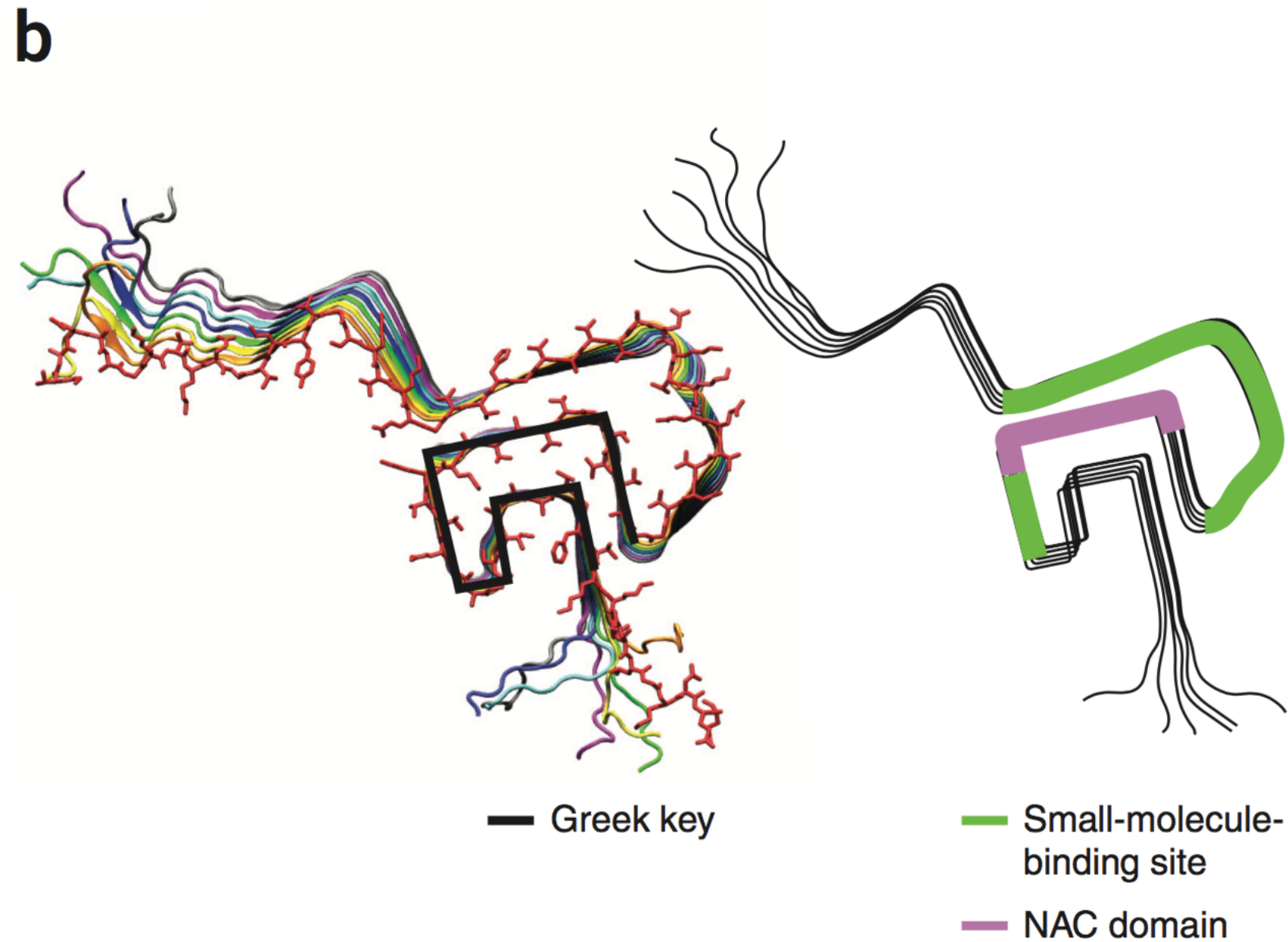
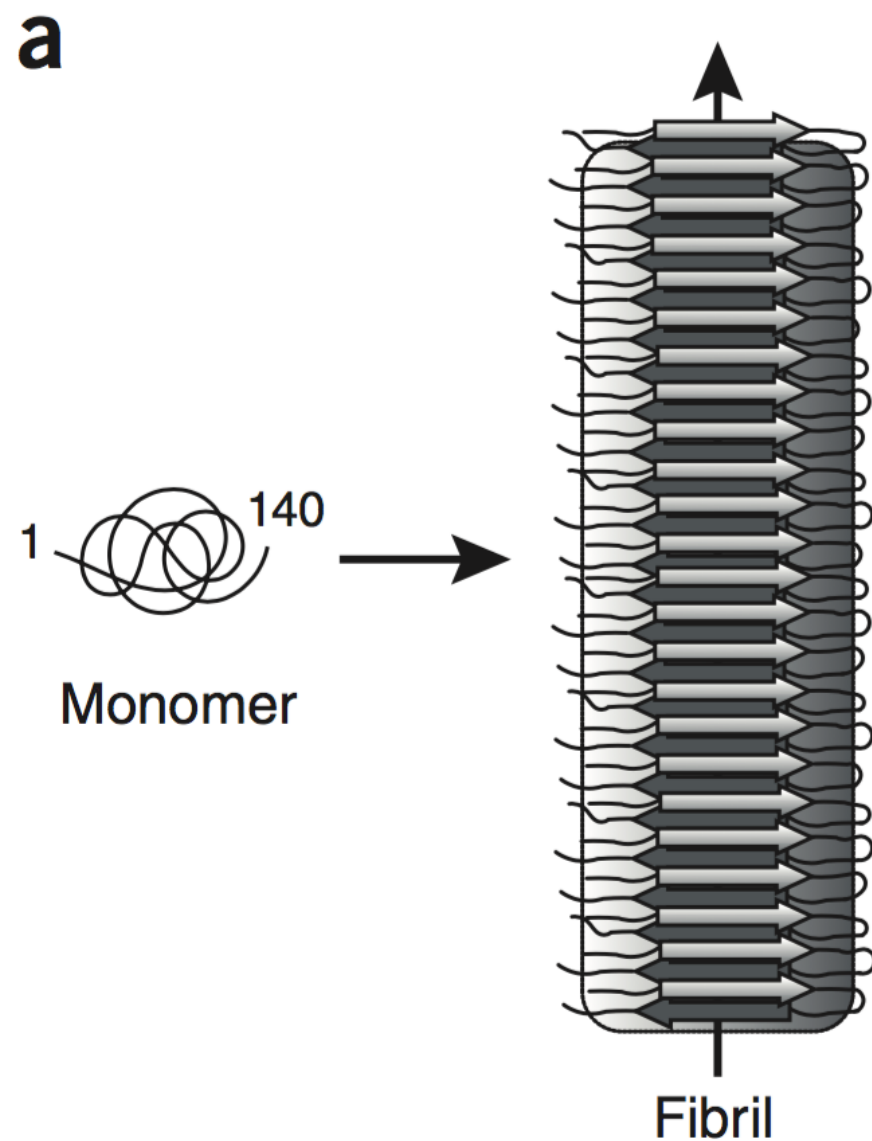
Multiple system atrophy (MSA)

Parkinson's Disease (PD)

Traumatic Brain Injury (TBI)

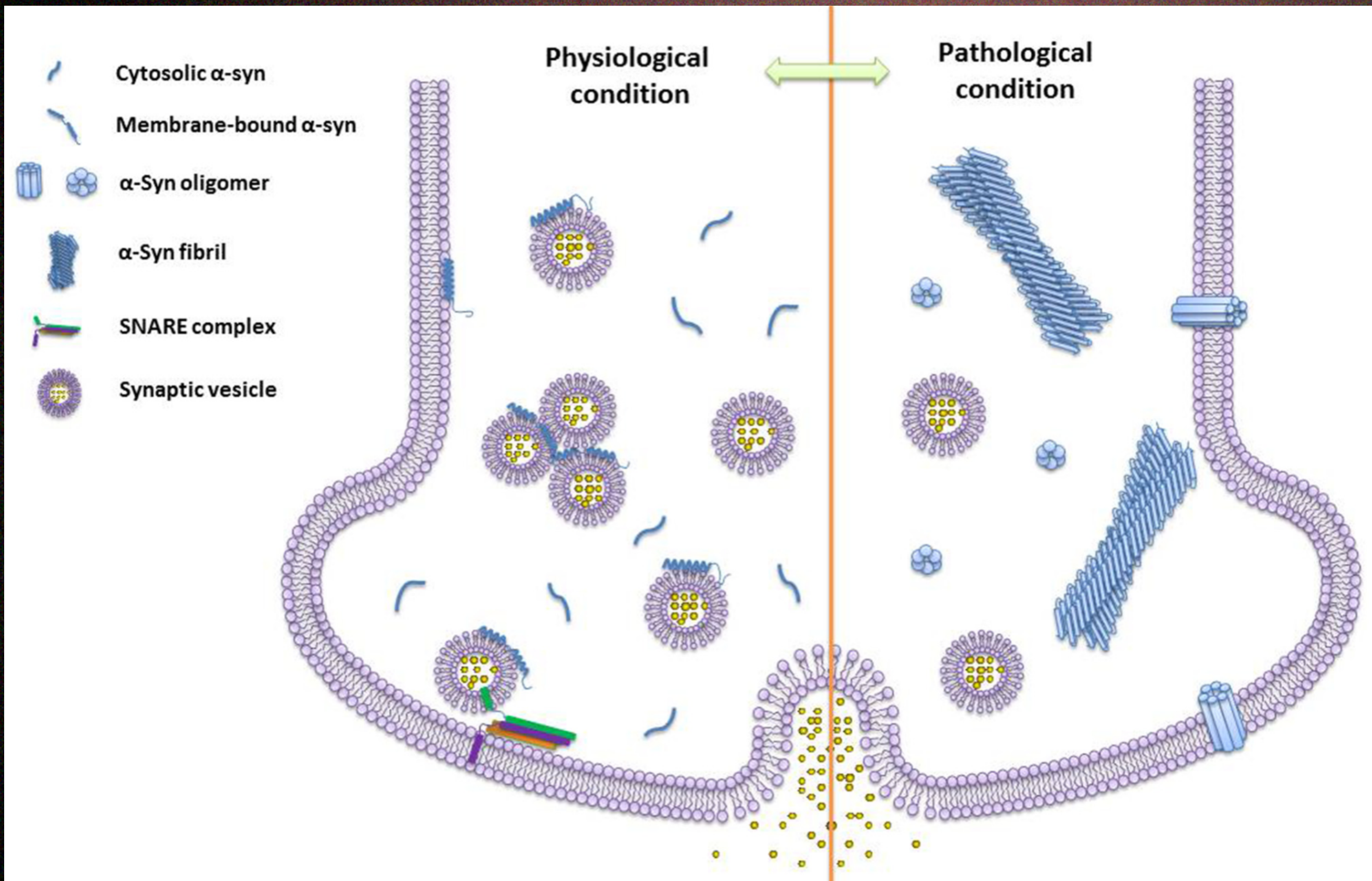
Retinal Degenerations (RD)

RETINAL NEURODEGENERATION



Wouter Peelaerts & Veerle Baekelandt 2016 -synuclein folds: the cards are on the table.
NATURE STRUCTURAL & MOLECULAR BIOLOGY VOLUME 23

RETINAL NEURODEGENERATION :: α -SYNUCLEIN



Frontiers in Molecular Neuroscience 20 June 2016 | <http://dx.doi.org/10.3389/fnmol.2016.00048>. Versatile Structures of α -Synuclein. Chuchu Wang, Chunyu Zhao, Dan Li, Zhiqi Tian, Ying Lai, Jiajie Diao and Cong Liu.

RETINAL NEURODEGENERATION :: α -SYNUCLEIN



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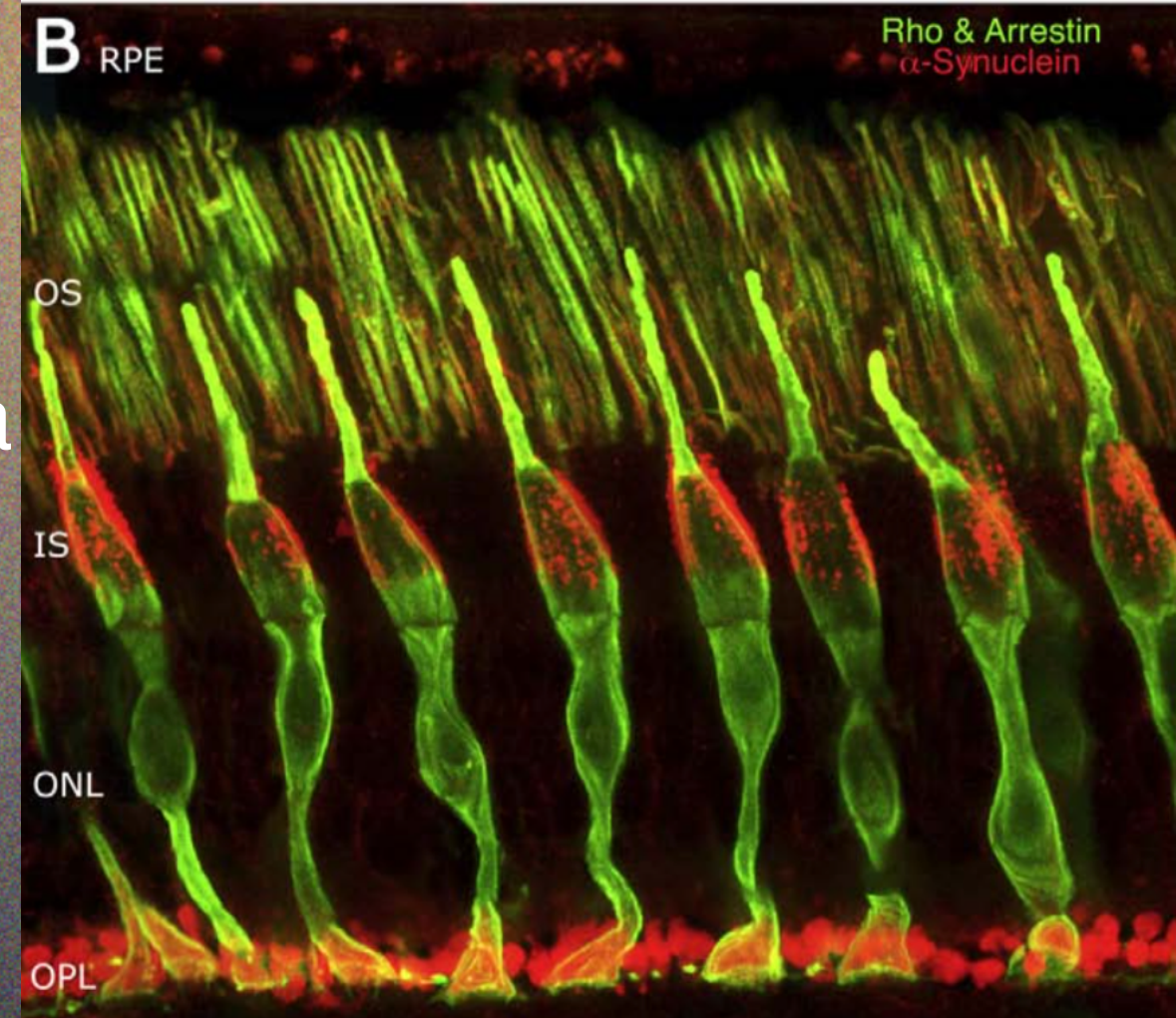
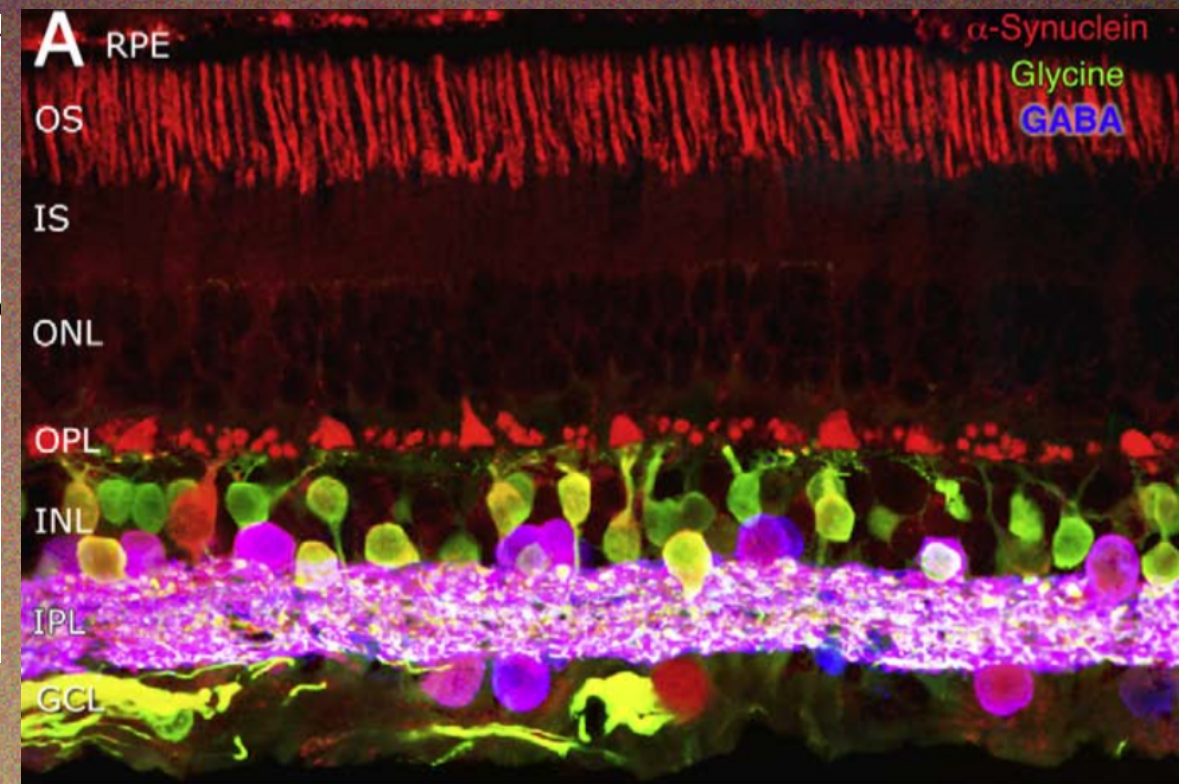
Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Cellular responses following retinal injuries and therapeutic approaches for neurodegenerative diseases

Nicolás Cuenca ^{a, b, *, 2}, Laura Fernández-Sánchez ^{a, 1, 2}, Laura Campello ^{a, 1, 2},
Victoria Maneu ^{c, 2}, Pedro De la Villa ^{d, 2}, Pedro Lax ^{a, 2}, Isabel Pinilla ^{e, 2}

α -synuclein is abundant in the retina



Neurodegeneration

A wt P- α -SYN α -SYN UBQ

osl

ONL

INL

IPL ONL P- α -SYN = 37 μ M

GCL INL P- α -SYN = 5 μ M

B Tg P- α -SYN α -SYN UBQ

INL

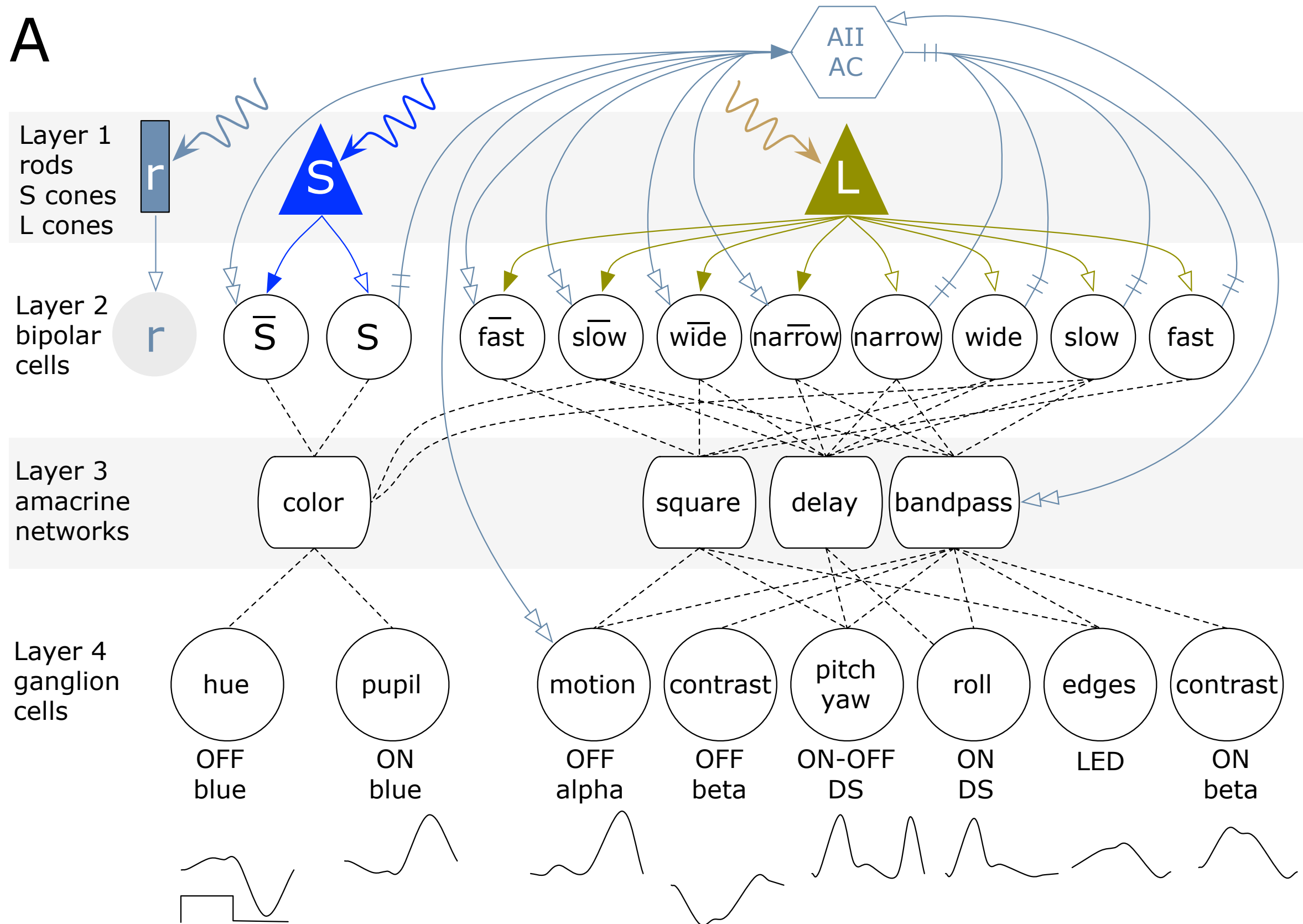
IPL

GCL

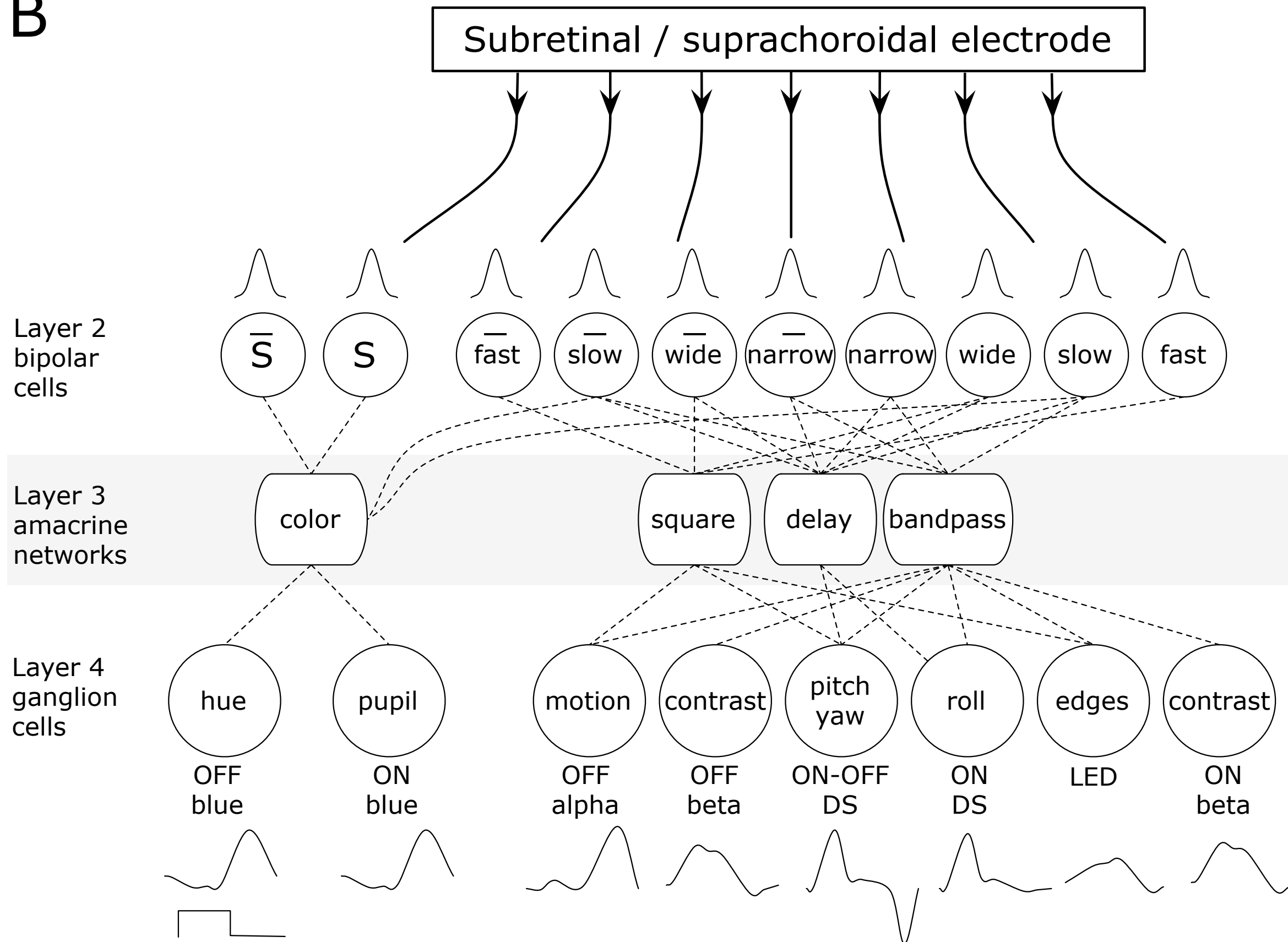
INL P- α -SYN = 83 μ M

100 μ m

A



B

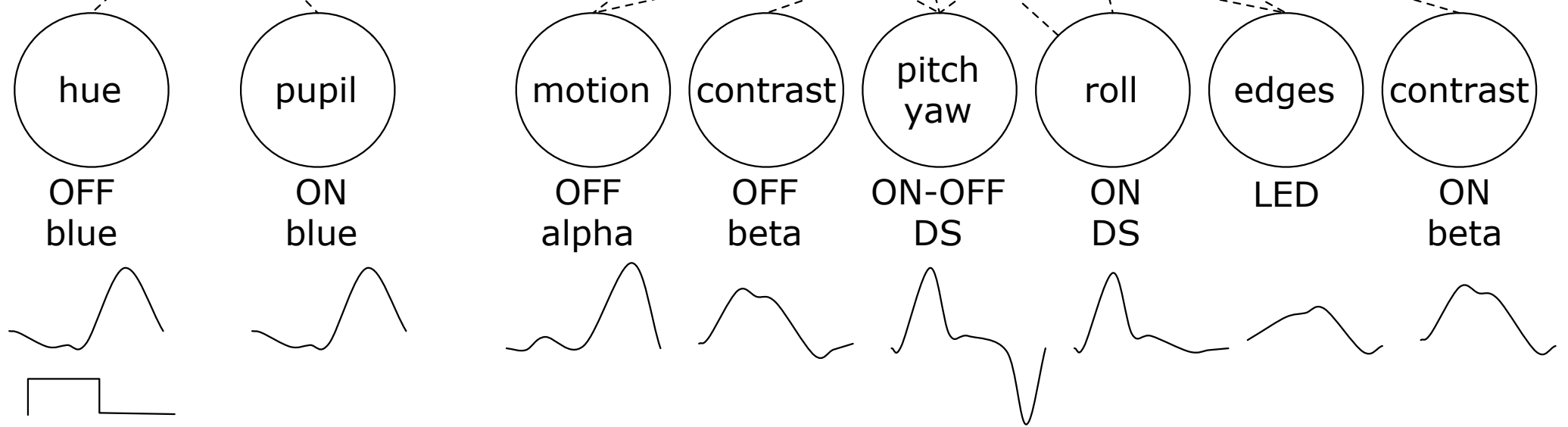


C

Layer 4

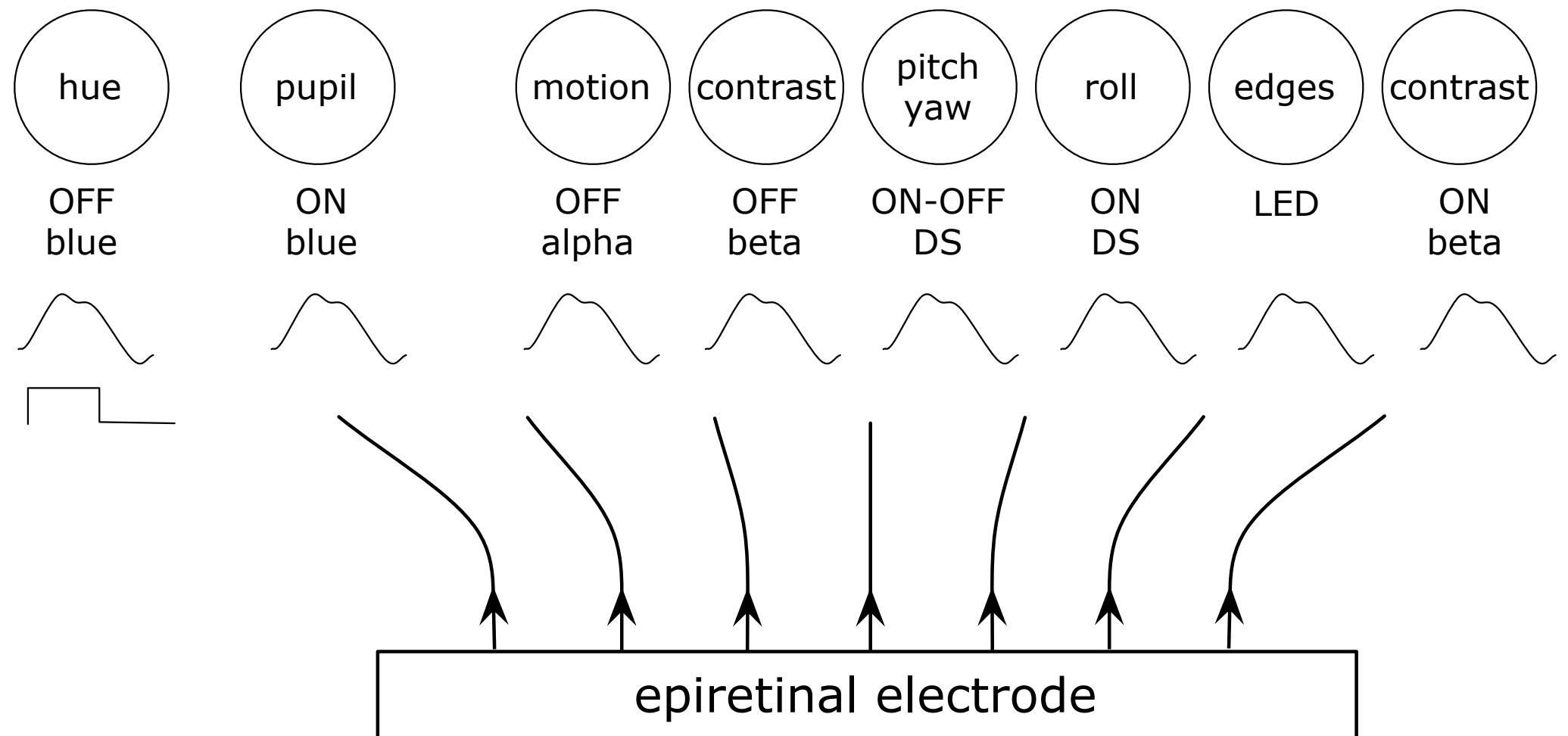


Layer 4
ganglion
cells



C

Layer 4
ganglion
cells



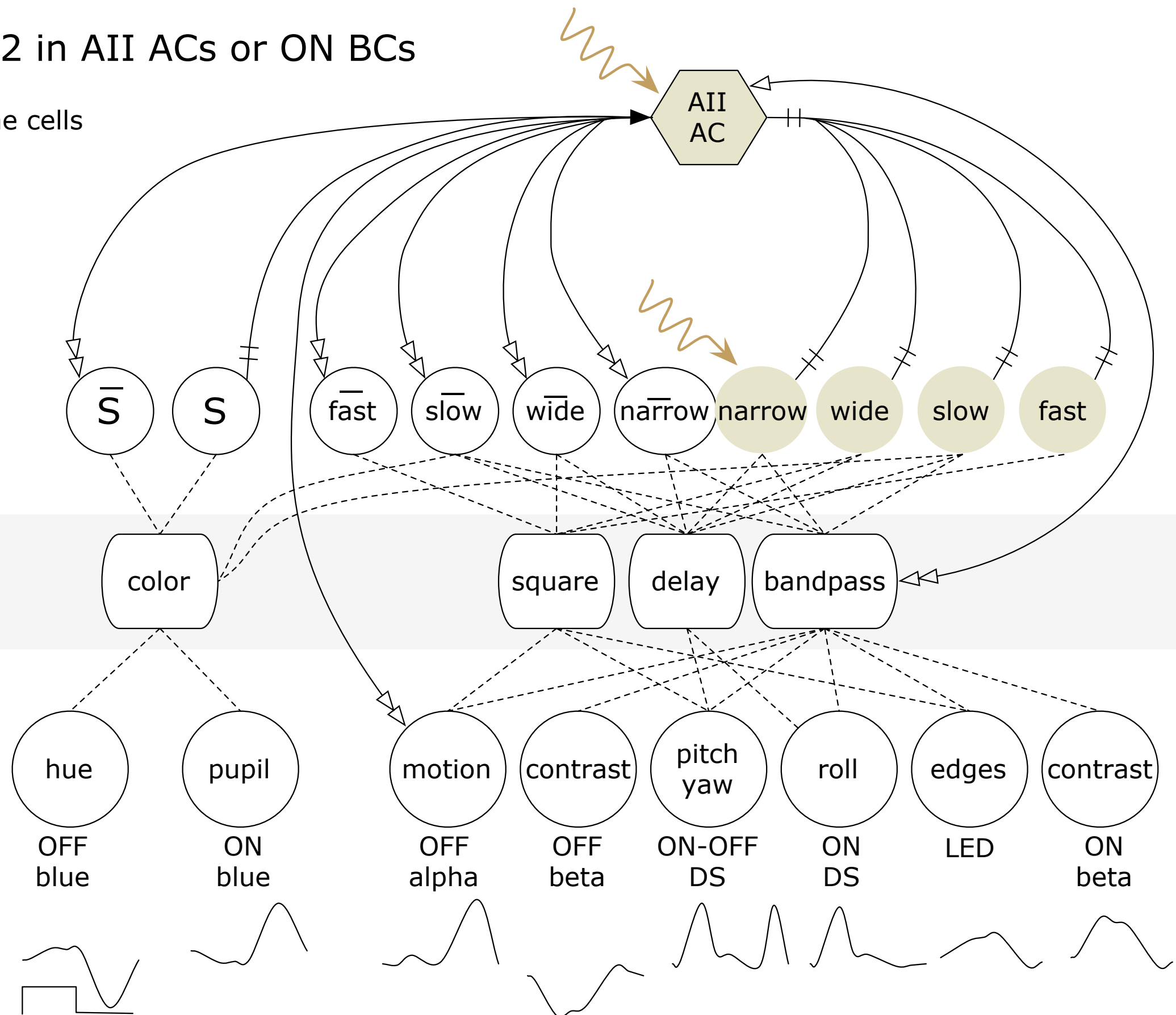
A ChR2 in AII ACs or ON BCs

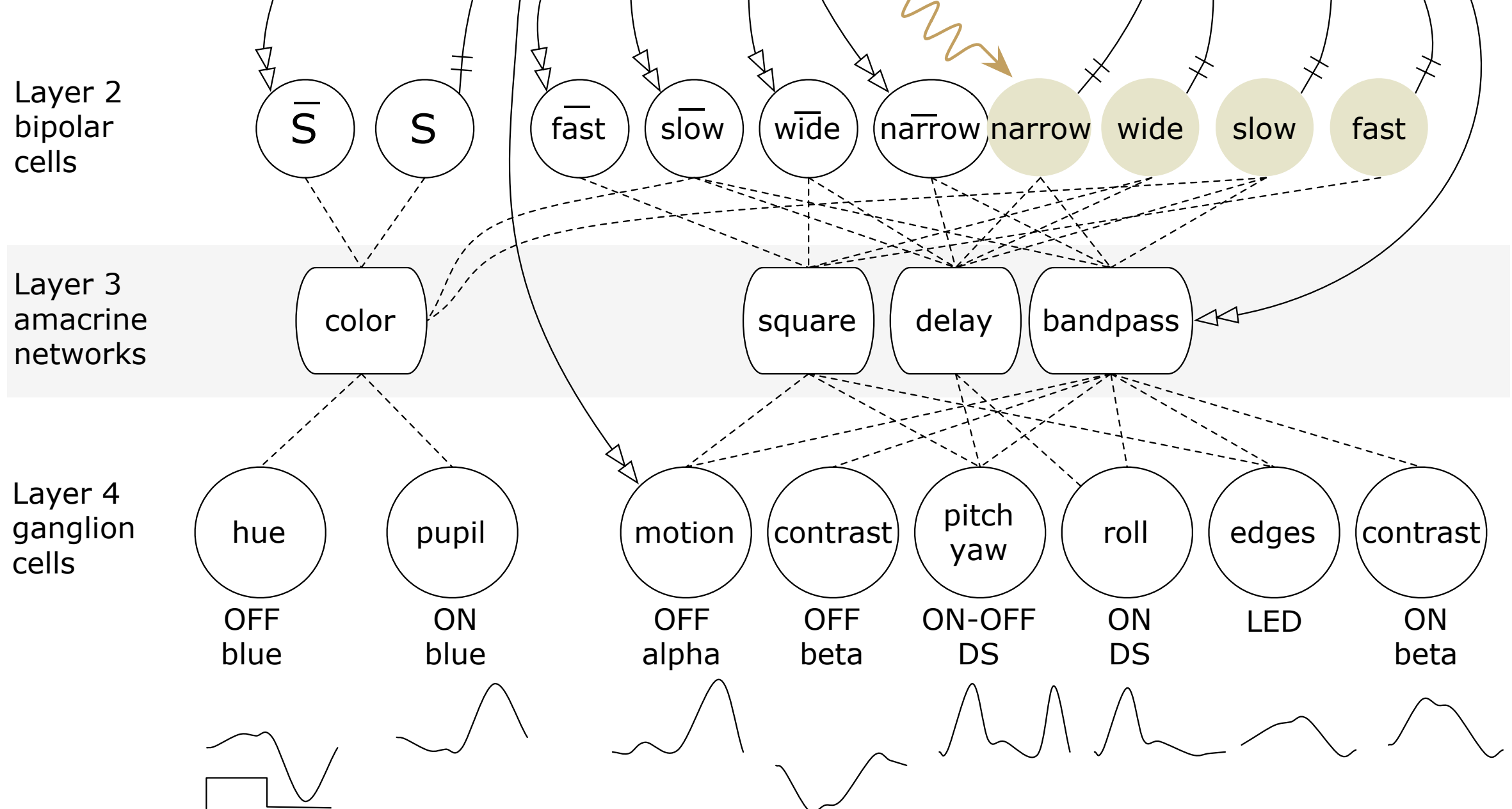
Layer 2.5
AII amacrine cells

Layer 2
bipolar cells

Layer 3
amacrine networks

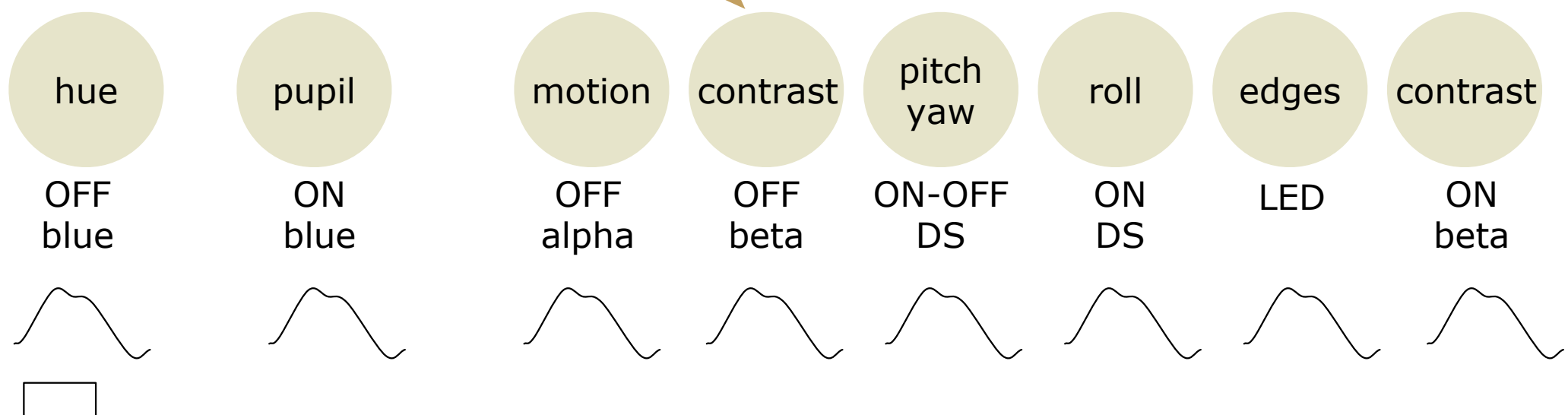
Layer 4
ganglion cells



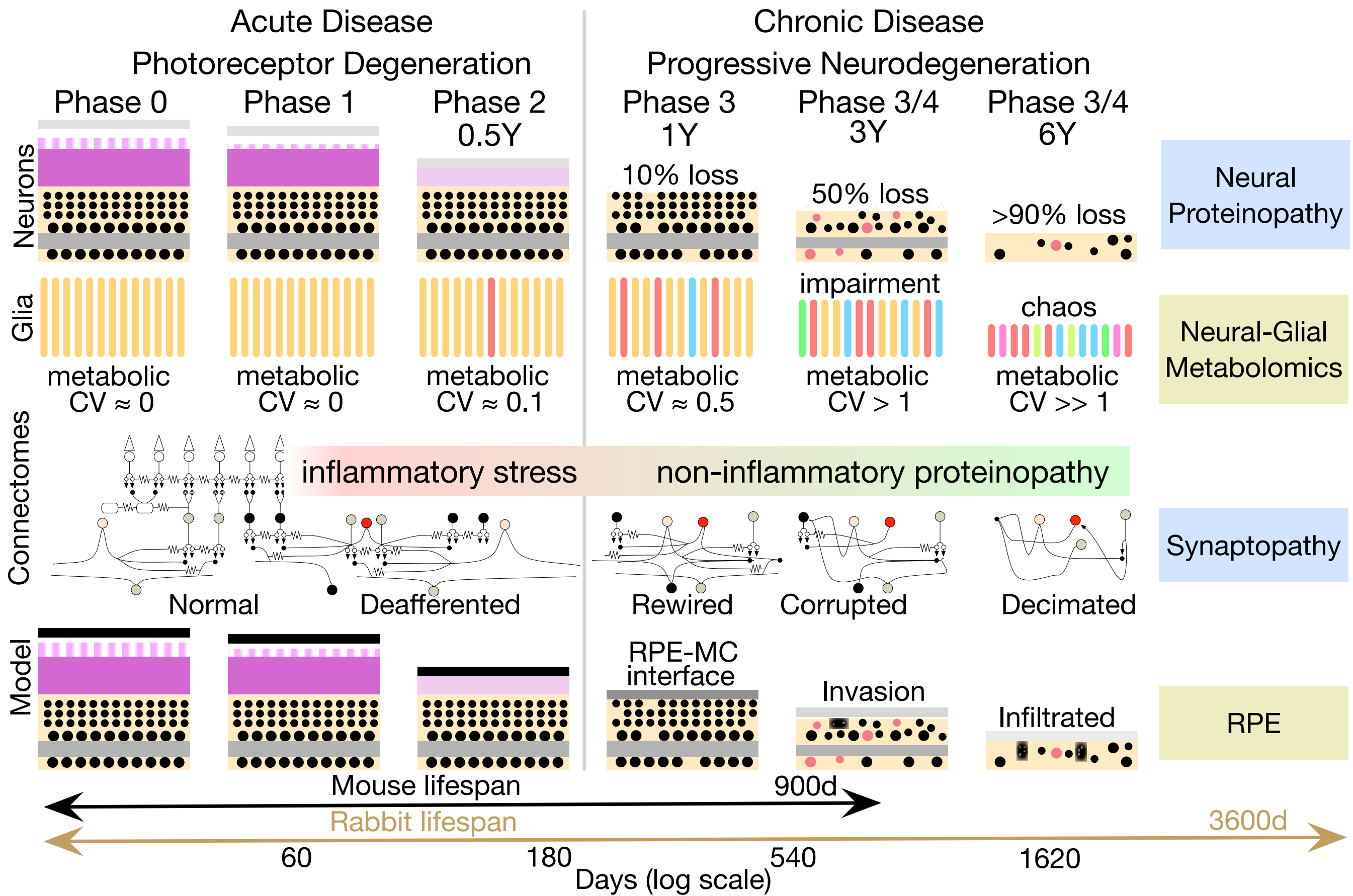


B ChR2 or DENAQ in GCs

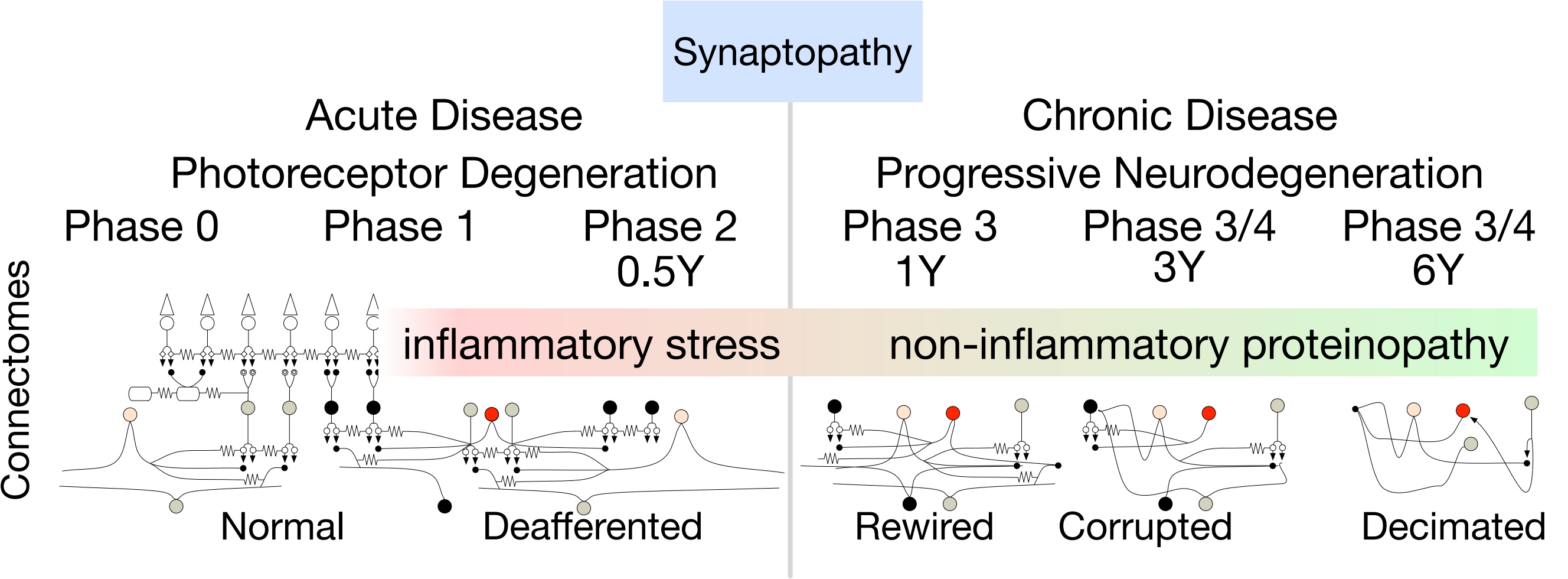
Layer 4 ganglion cells



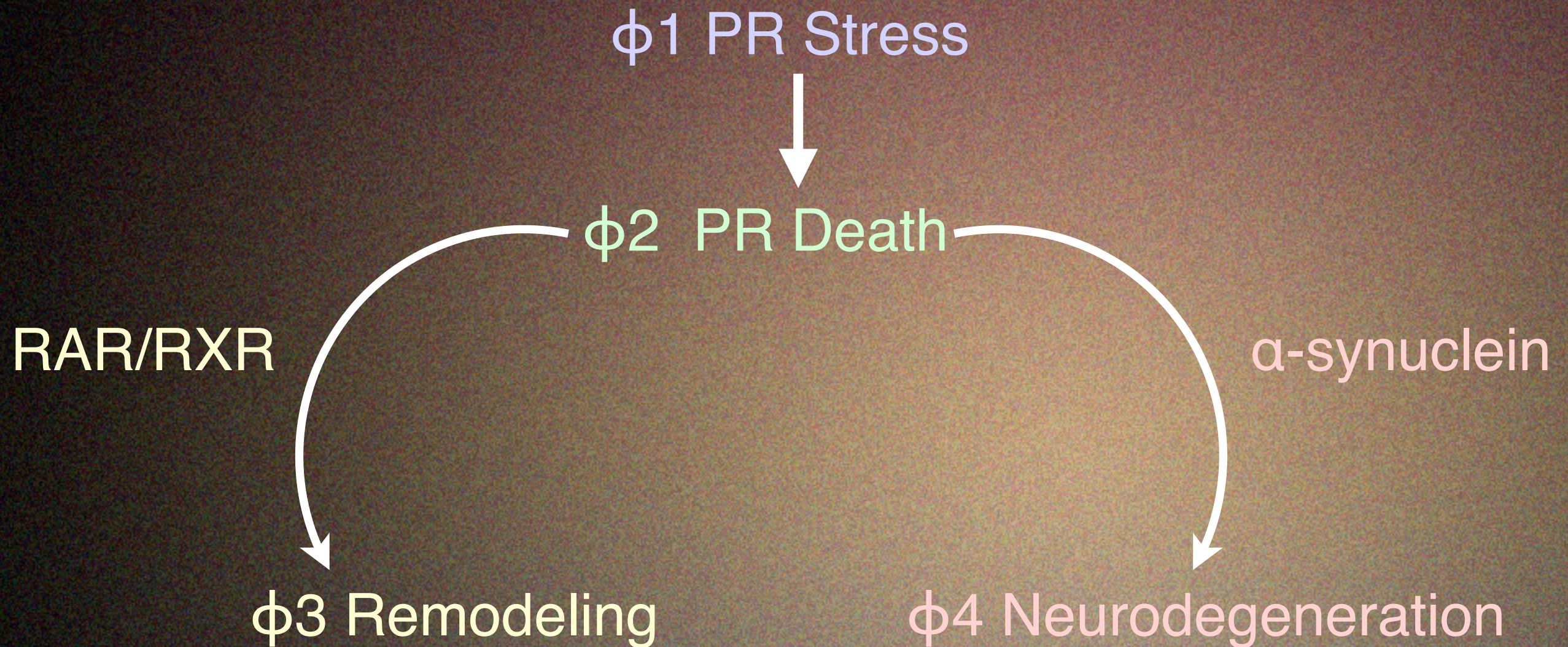
RETINAL NEURODEGENERATION



RETINAL NEURODEGENERATION



RETINAL REMODELING & NEURODEGENERATION



Retinal degenerations are really three diseases.

(1) The initial disease that causes photoreceptor death

(2) Retinal Remodeling $\equiv$ CNS Epilepsy

(3) Retinal Neurodegeneration $\equiv$ CNS Proteinopathies



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