Neural stem cells & Retinal regeneration

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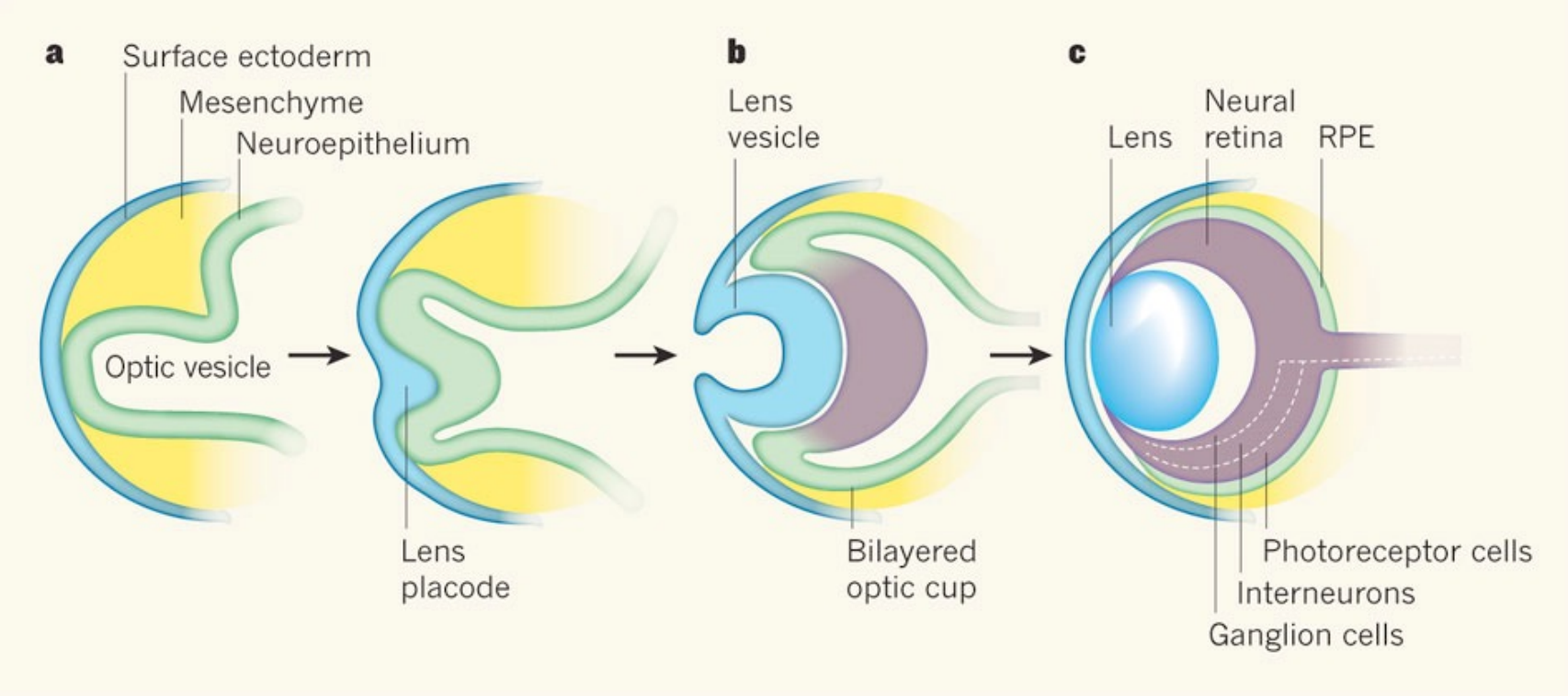
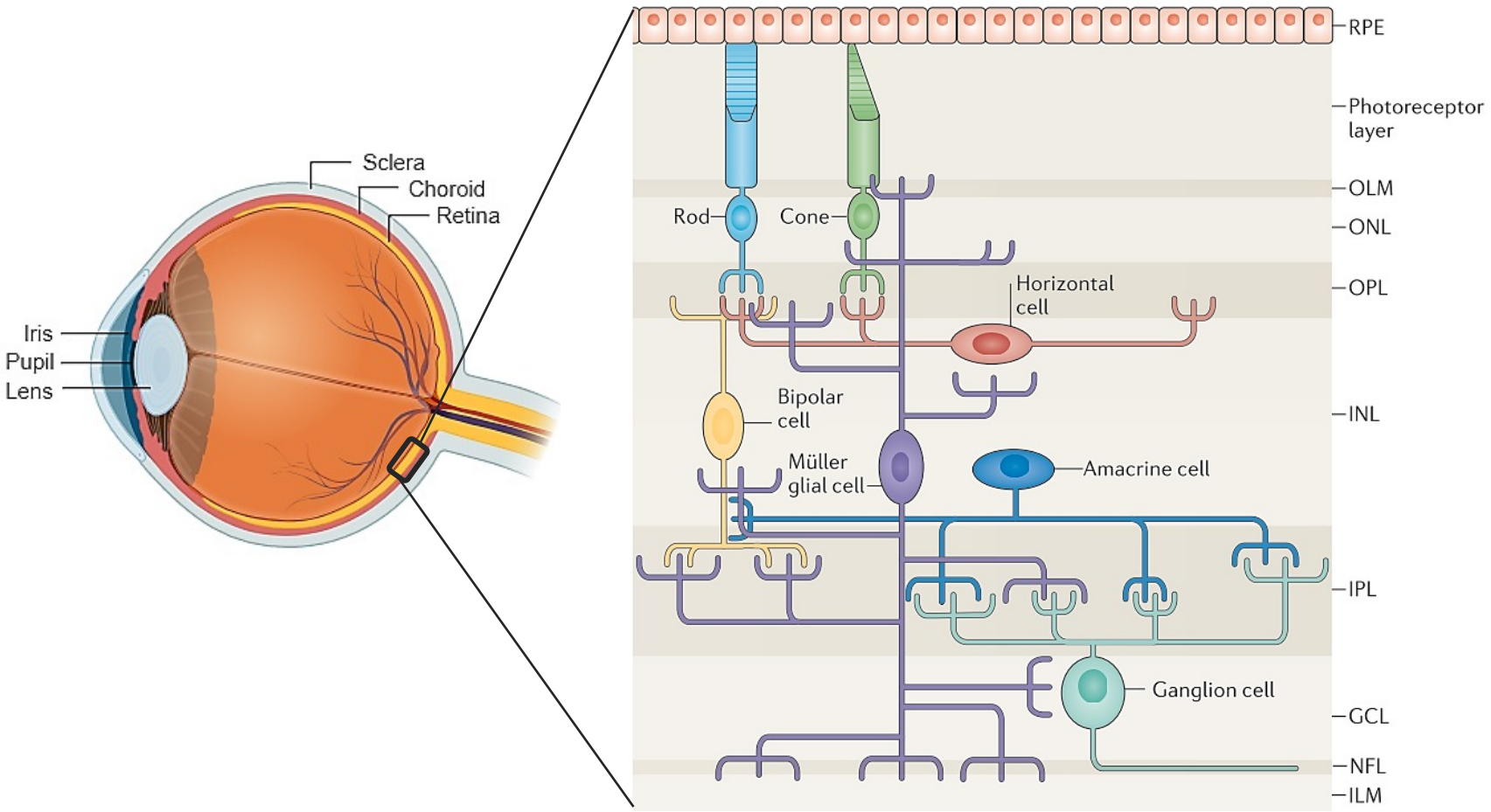
Retinal development in vertebrates



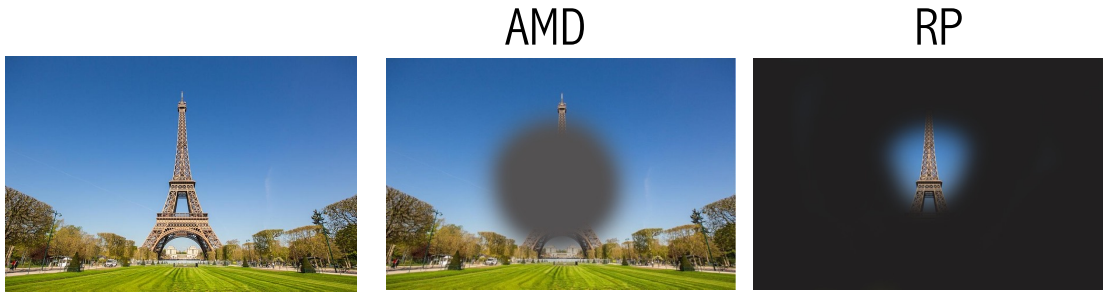
Ali & Sowden, Nature 2011

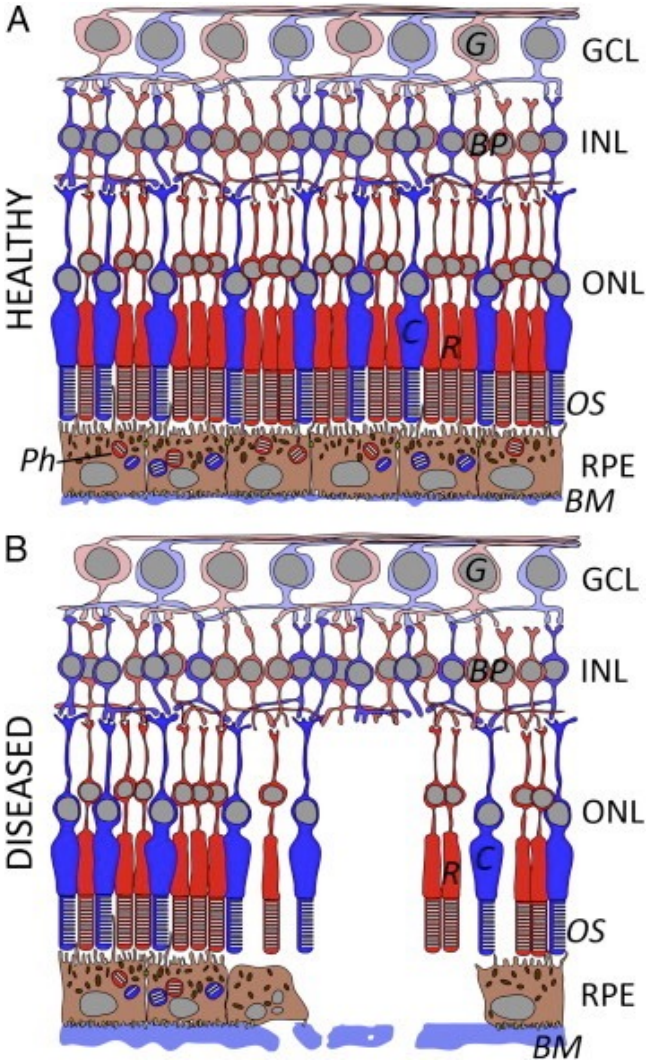


Goldman & al., 2014

Patients with retinal degenerative diseases in Europe

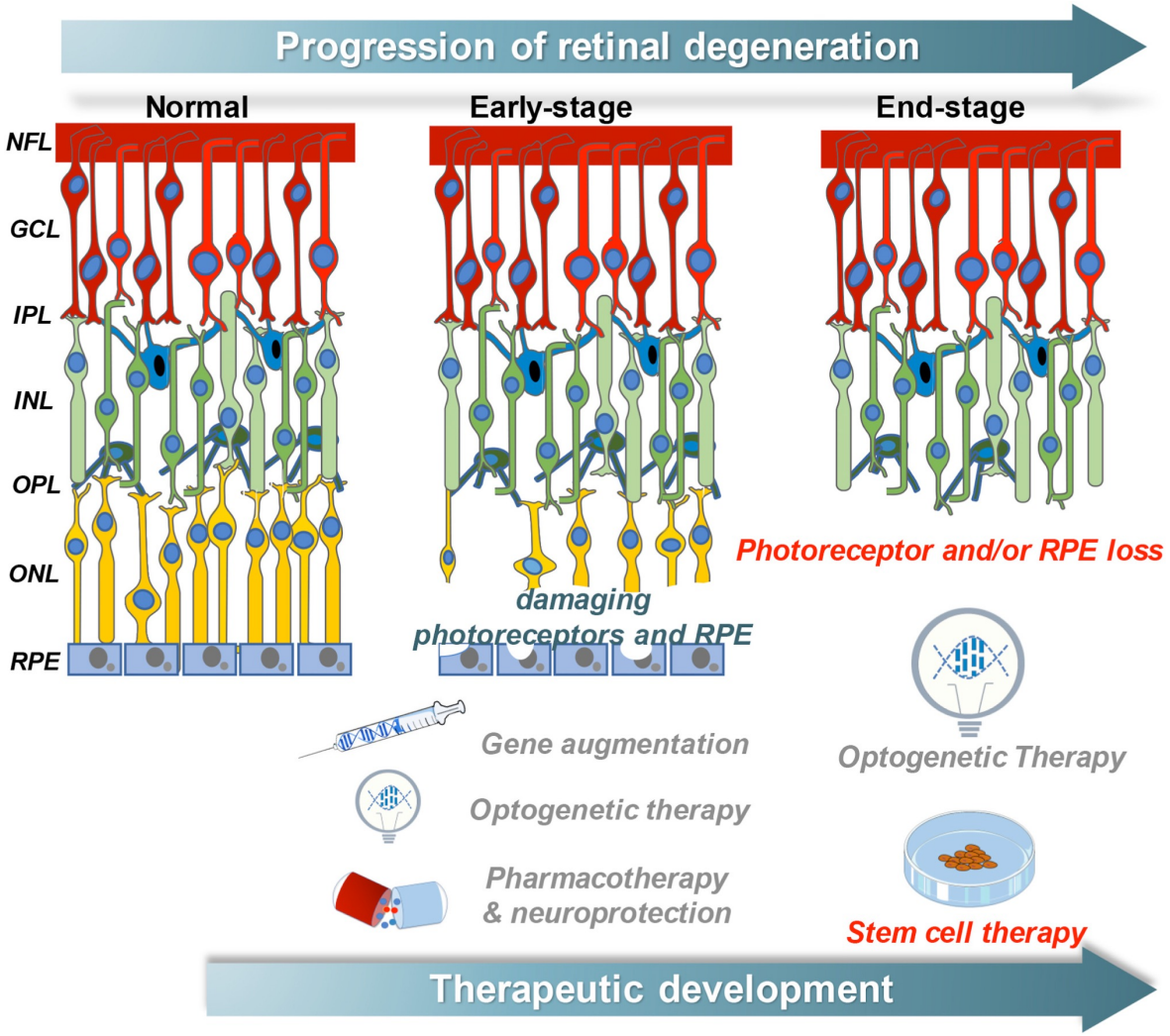
- AMD: > 10 millions (25% at 75 years-old; 60% at 90 years-old)
- Retinitis pigmentosa: 400 000
- Glaucoma: > 9 millions





Yvon et al., 2015

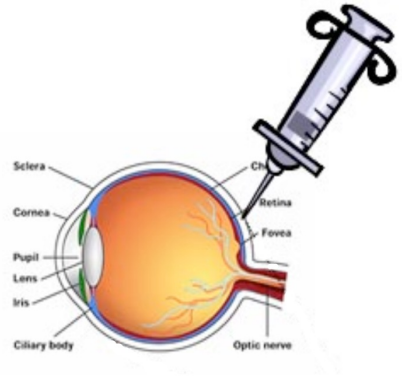
THERAPIES



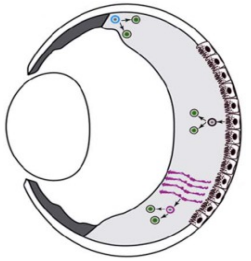
Zhang et al., Experimental Eye Research 2020

CELL THERAPIES

- Transplantation from stem cell-derived retinal cells

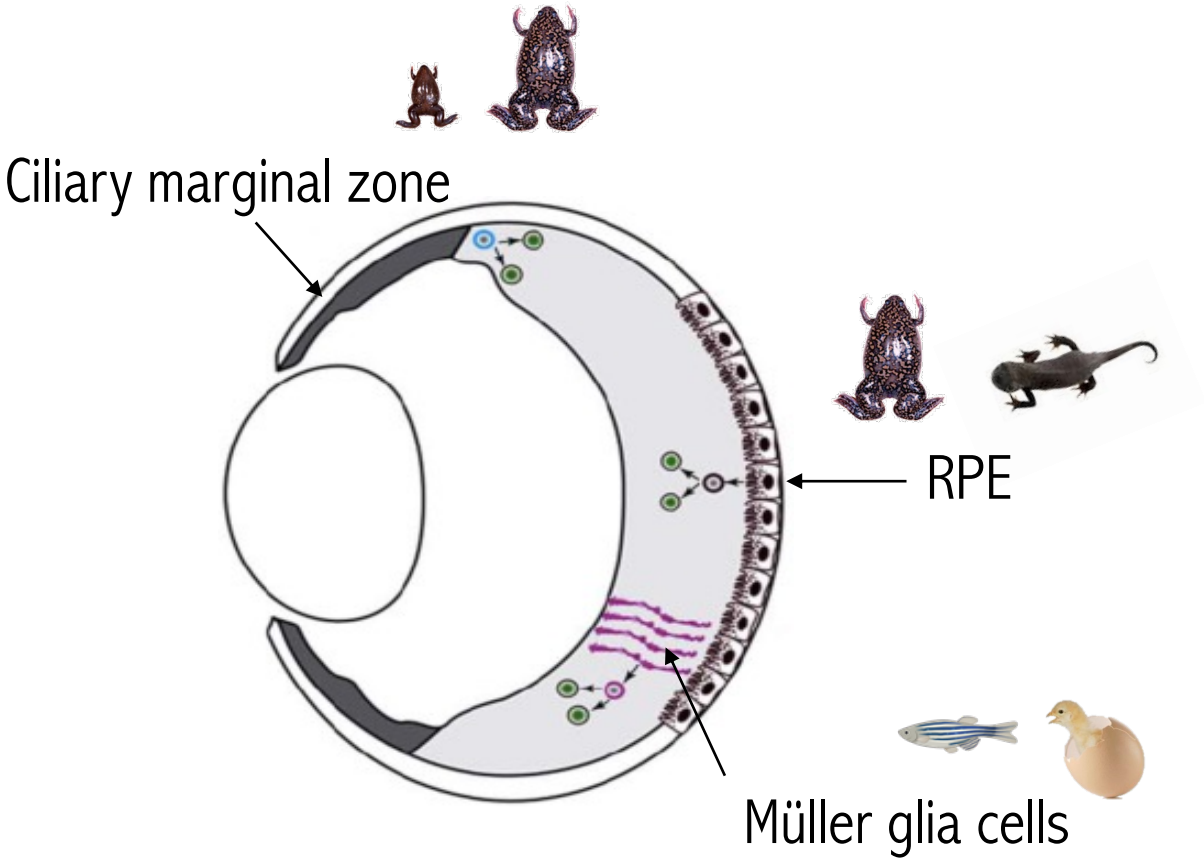


- Regeneration from endogenous stem cells



Cellular sources for retina regeneration

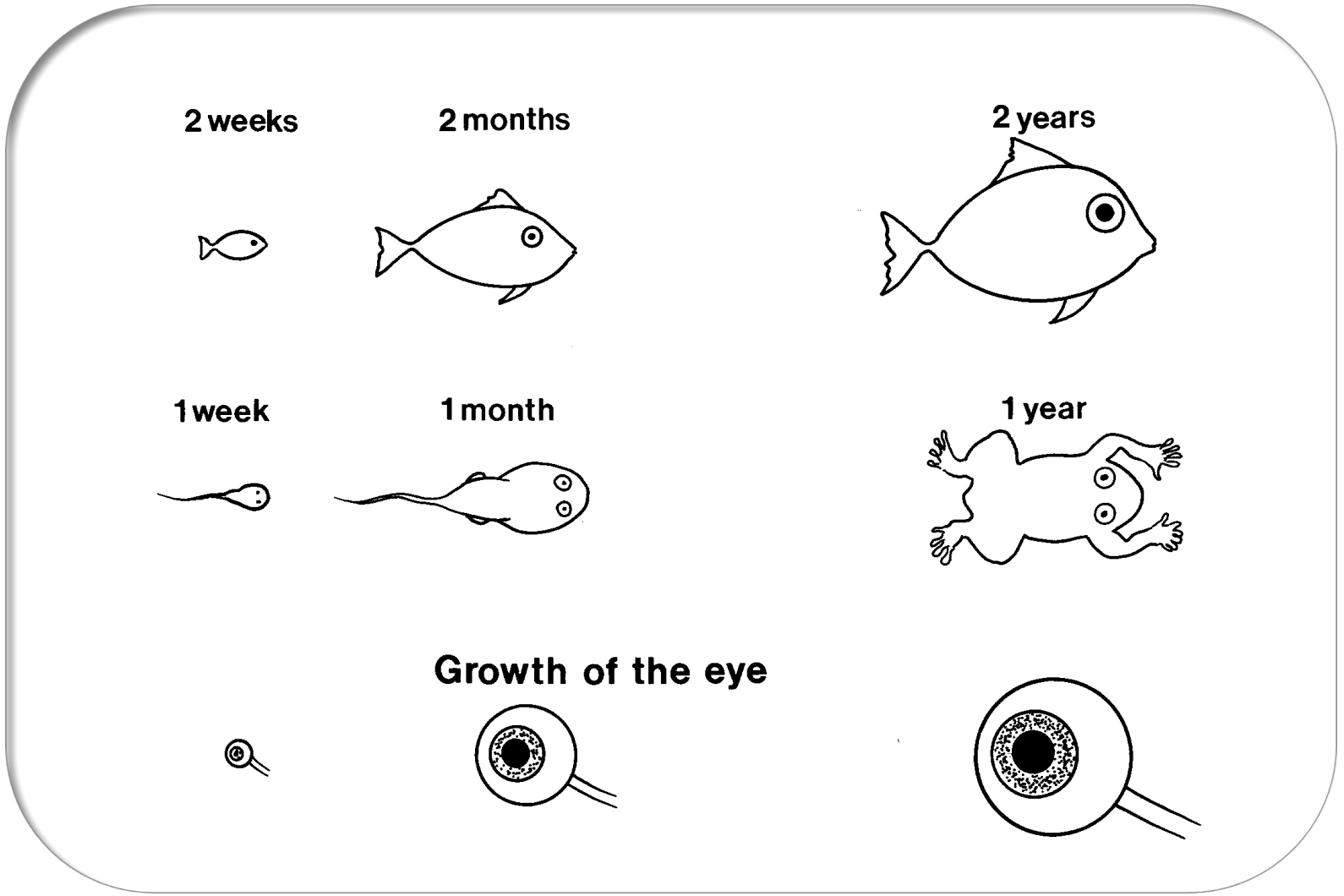
No regeneration



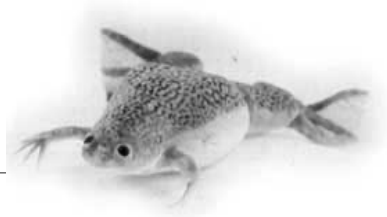
Adapted from Karl & Reh 2010

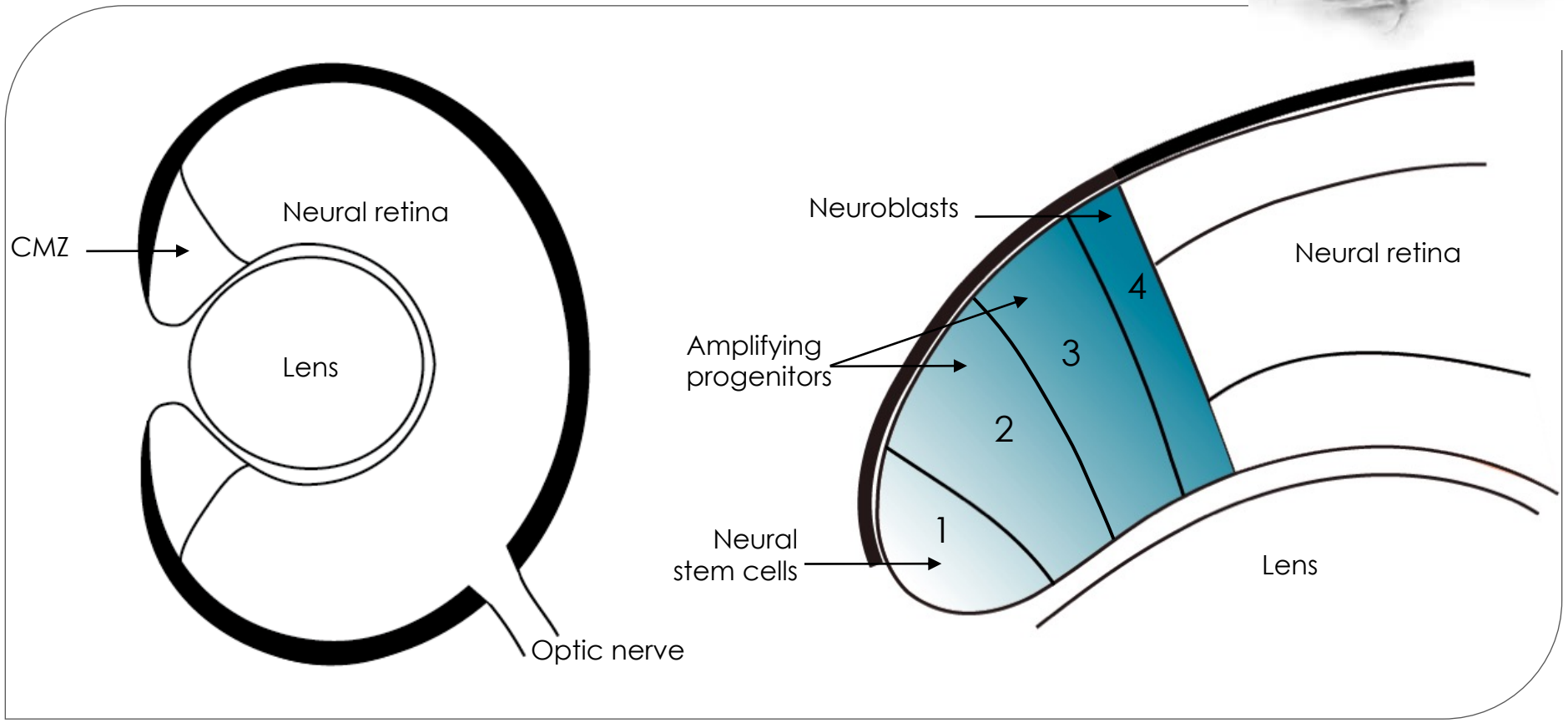
Ciliary marginal zone stem cells

Continuous growth in fish and amphibians



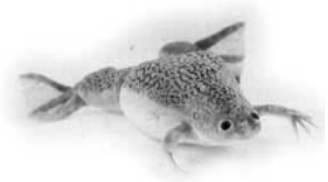
Retinal stem cells in the ciliary marginal zone



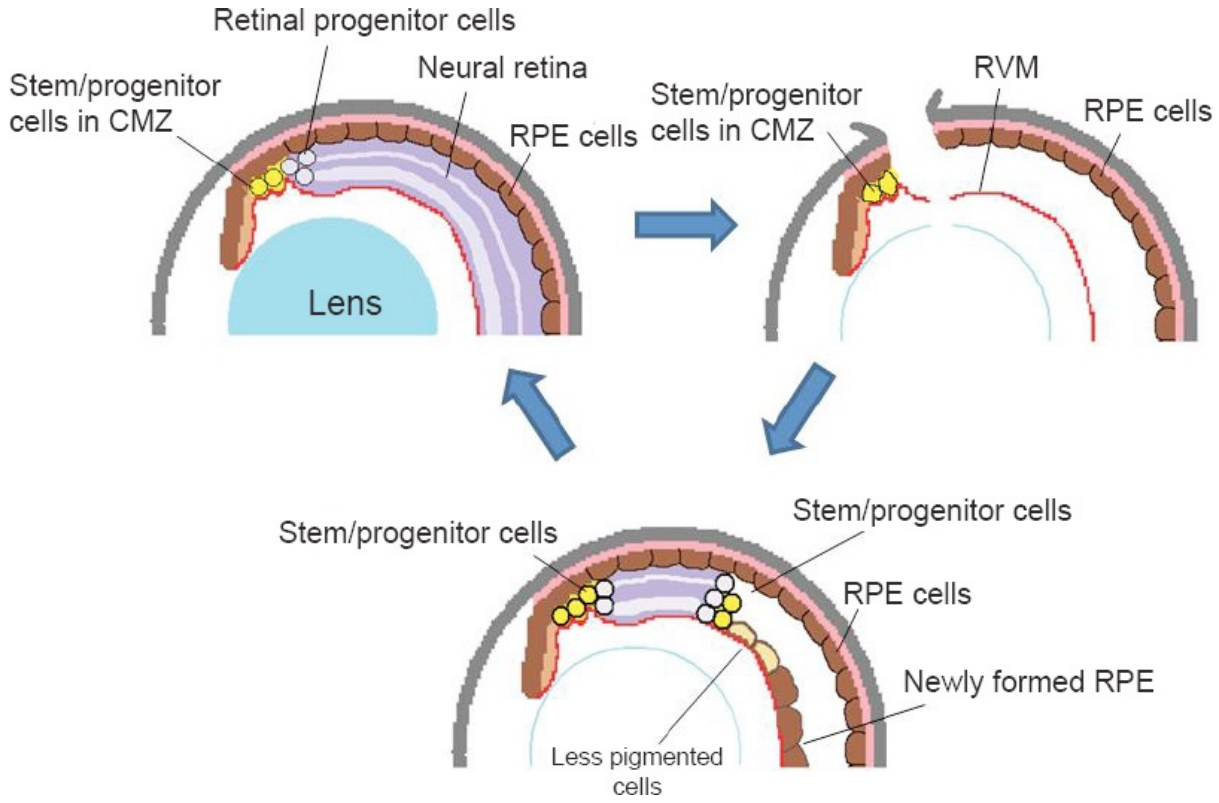


Perron et al., 1998

Regeneration in *Xenopus tropicalis*



Xenopus tropicalis



Araki et al., 2014

Cell Identification of a Proliferating Marginal Zone of Retinal Progenitors in Postnatal Chickens

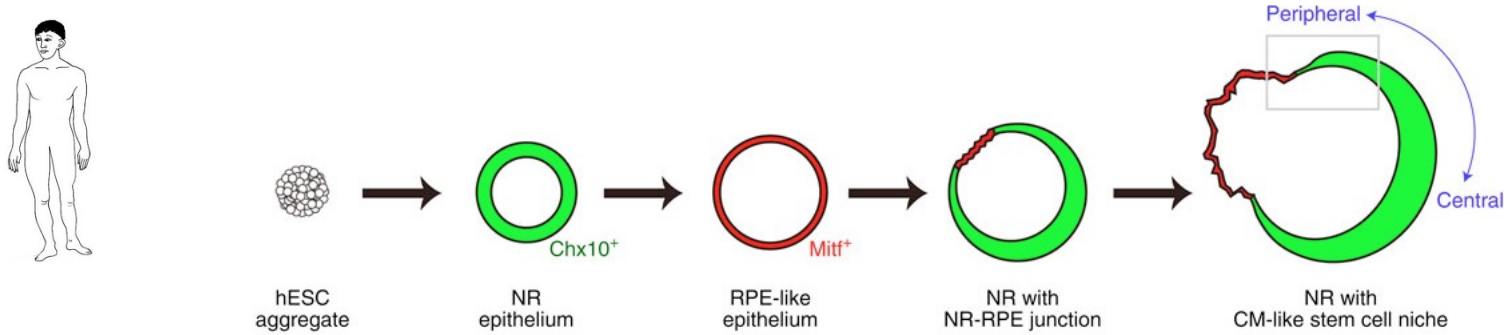
Developmental Biology **220,** 197–210 (2000)
doi:10.1006/dbio.2000.9640, available online at http://www.idealibrary.com on IDEAL®

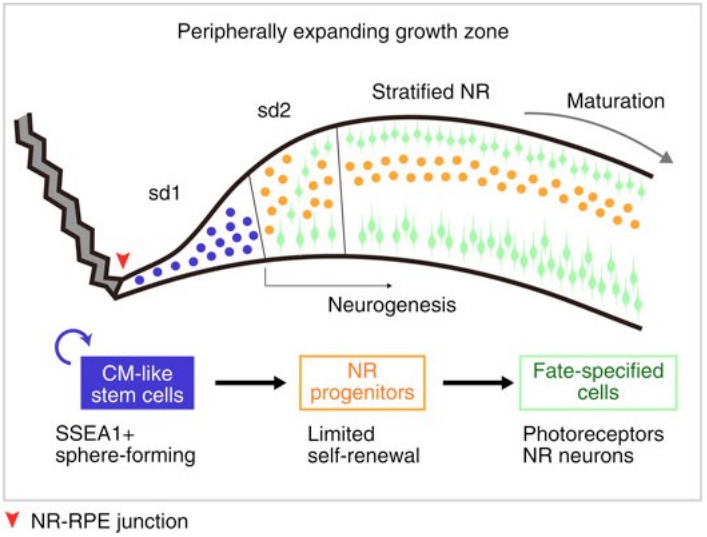
Identification of a Proliferating Marginal Zone of Retinal Progenitors in Postnatal Chickens

Andy J. Fischer and Thomas A. Reh[1]
Department of Biological Structure, University of Washington, Seattle, Washington 98195

Only amacrine and bipolar cells are produced by progenitors at the retinal margin of postnatal chicks

Generation of a ciliary margin-like stem cell niche from self-organizing human retinal tissue





Kuwahara et al., 2015 Nature Com


nature communications
https://doi.org/10.1038/s41467-024-47933-x
Article
Single-cell analyses reveal transient retinal progenitor cells in the ciliary margin of developing human retina
Birthe Dorgau[1,5], Joseph Collin[1,5], Agata Rozanska[1], Darin Zerti[1,2], Adrienne Unsworth, Tamil Dhanaseelan[1], Rachel Queen[1] &
Received: 11 July 2023
Accepted: 12 April 2024
Published online: 26 April 2024
Science Translational Medicine
HOME › SCIENCE TRANSLATIONAL MEDICINE › VOL. 17, NO. 791 › IDENTIFICATION AND CHARACTERIZATION OF HUMAN RETINAL STEM CELLS CAPABLE OF RETINAL...
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RESEARCH ARTICLE
RETINAL DISEASE
Identification and characterization of human retinal stem cells capable of retinal regeneration
HUI LIU, YUNLONG MA, NA GAO, YIJUN ZHOU [...] AND
SCIENCE TRANSLATIONAL MEDICINE • 26 Mar 2025 •
+14 authors
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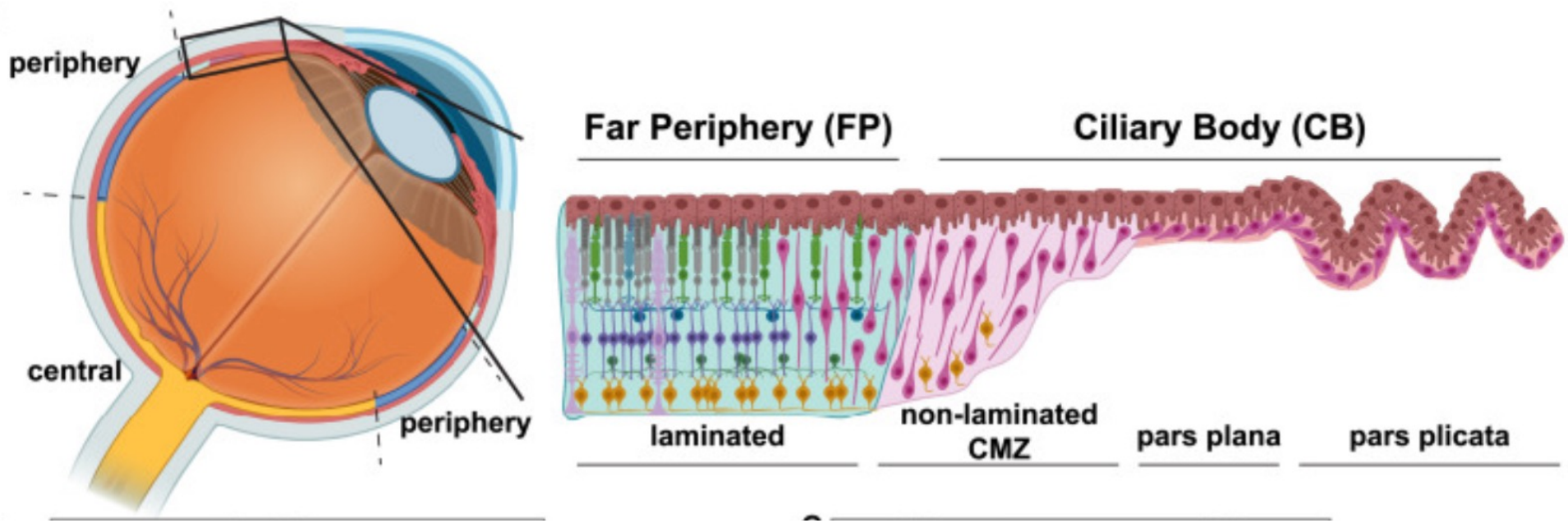
ranslmed.adp6864
Cell Reports
CellPress
Volume 44, Issue 4, 22 April 2025, 115460
Article
Ciliary marginal zone of the developing human retina maintains retinal progenitor cells until late gestational stages
Kiara C. Eldred [1], Sierra J. Edgerton [1], Isabel Ortuño-Lizarán [1 2], Juliette Wohlschlegel [1], Stephanie M. Sherman [1], Sidnee Petter [1], Gracious Wyatt-Draher [1], Dawn Hoffer [1], Ian Glass [3 4], Anna La Torre [5], Thomas A. Reh [1 6]

Developing human retina maintains a zone of proliferating cells at the ciliary margin

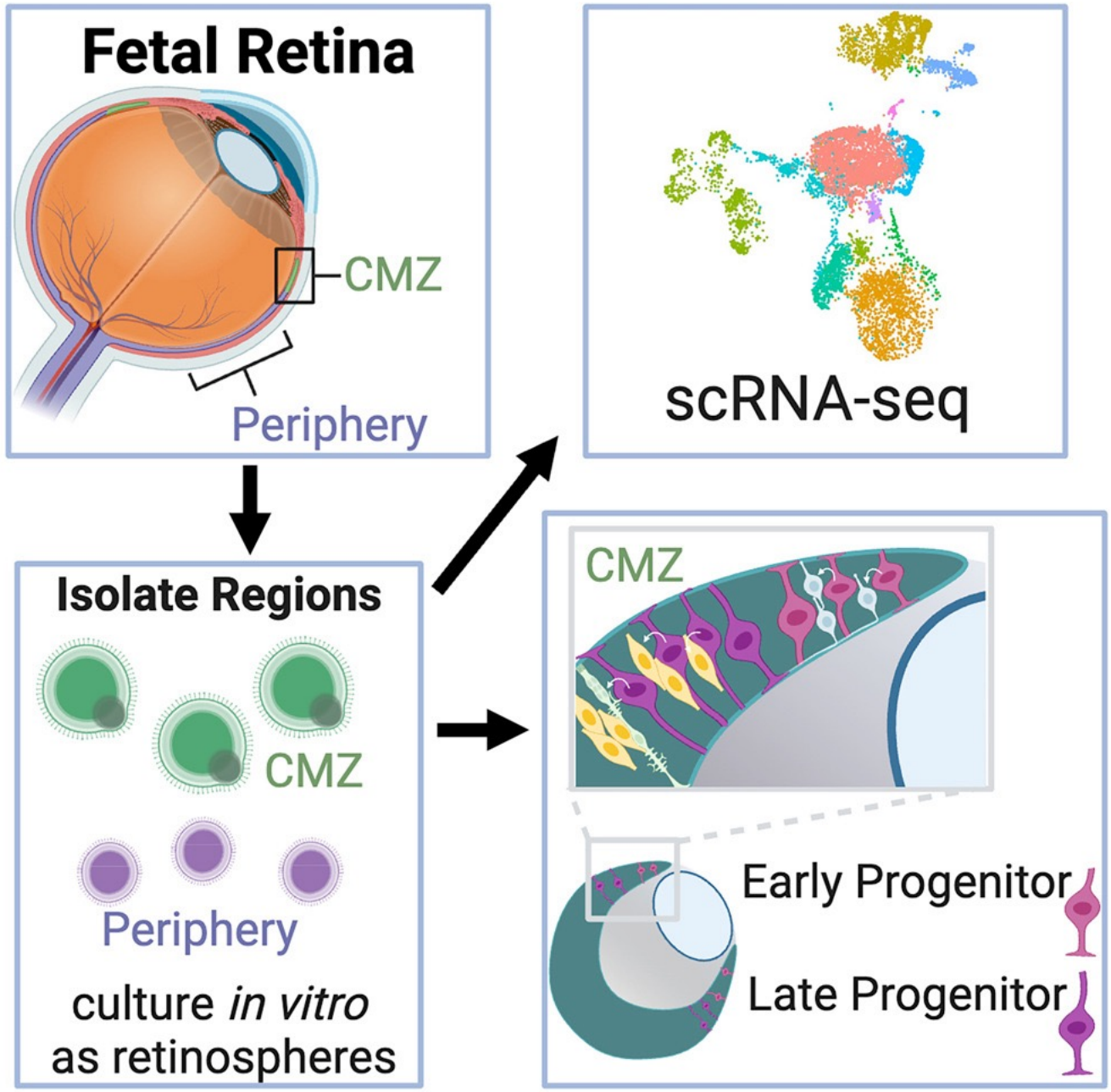


Cells in the CMZ remain mitotically active after the rest of the retina is no longer proliferating

Eldred et al., Cell Reports 2025

Early progenitors, located at the tip of the CMZ, give rise to early-born cell types such as ganglion cells.

Late progenitors, located further out in the far periphery of the retinosphere, give rise to late-born cell types such as rods.



Eldred et al., Cell Reports 2025

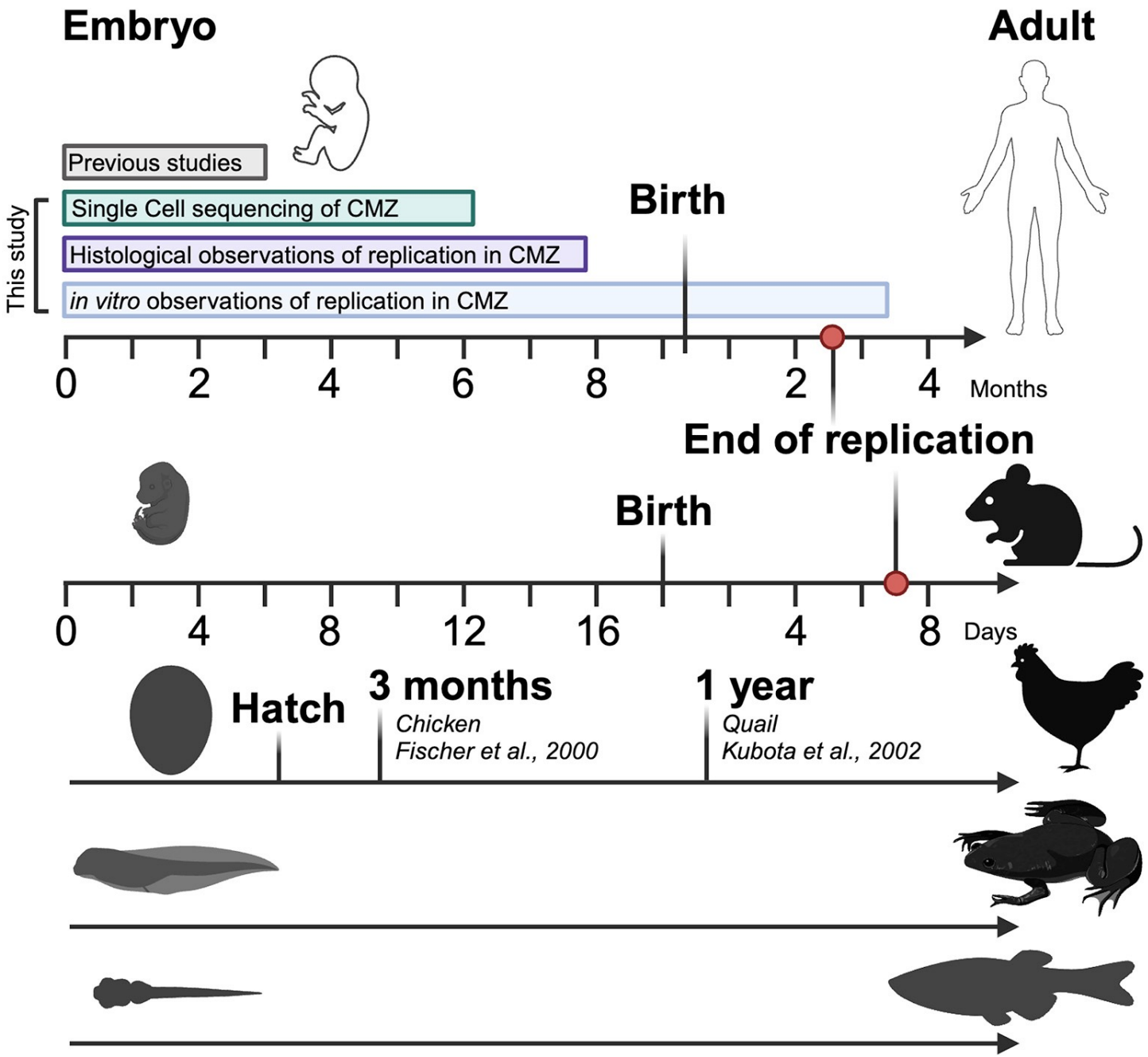
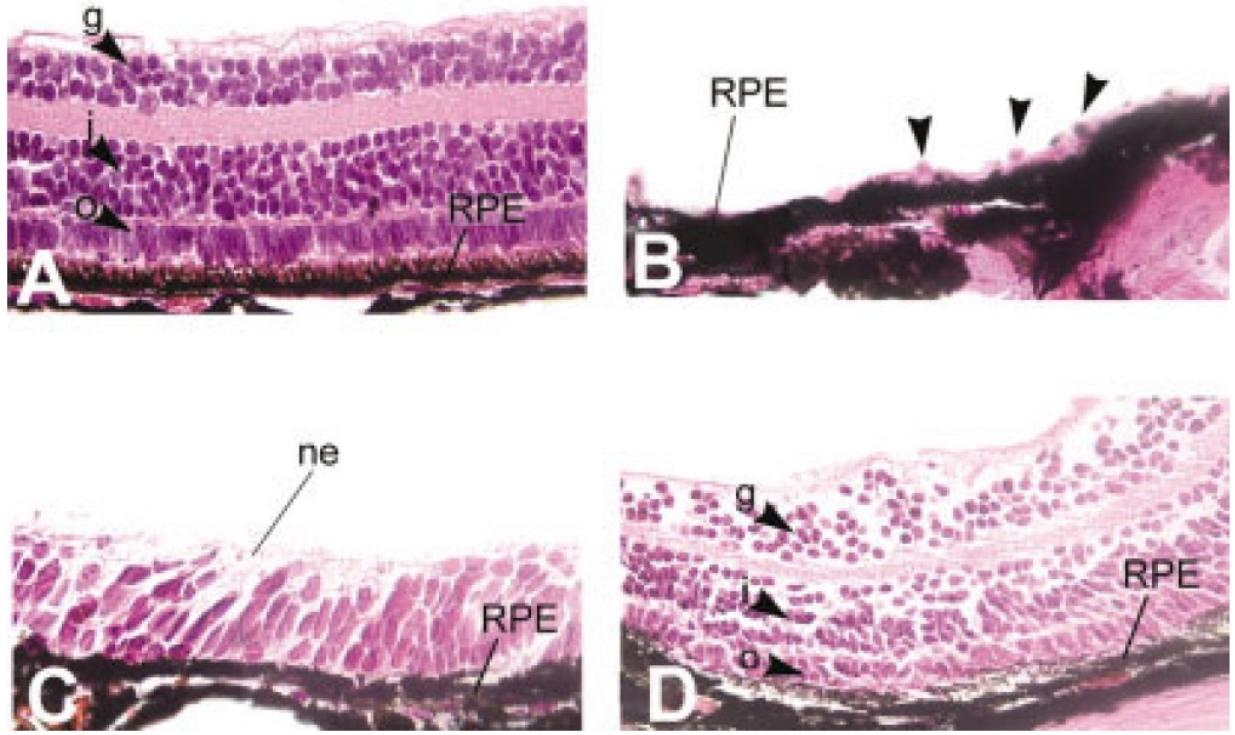


Diagram of timing of CMZ development across organisms

Eldred et al., Cell Reports 2025

Retinal Pigment Epithelium

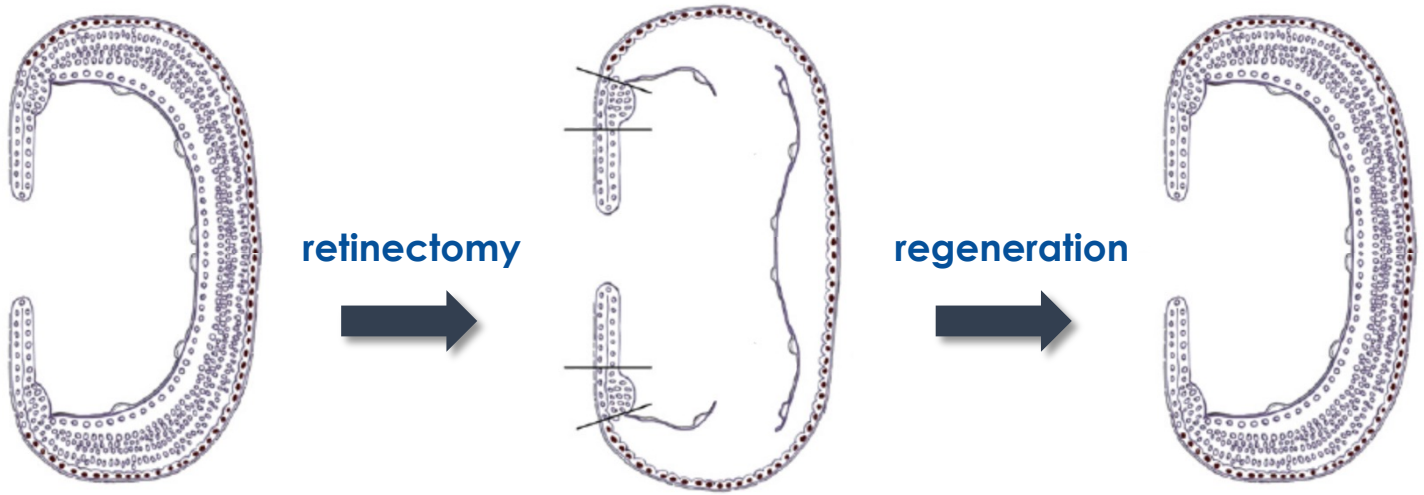
Regeneration in the Newt from the RPE



Del Rio-Tsonis and Tsonis, 2003

Regeneration in post-metamorphic *Xenopus*

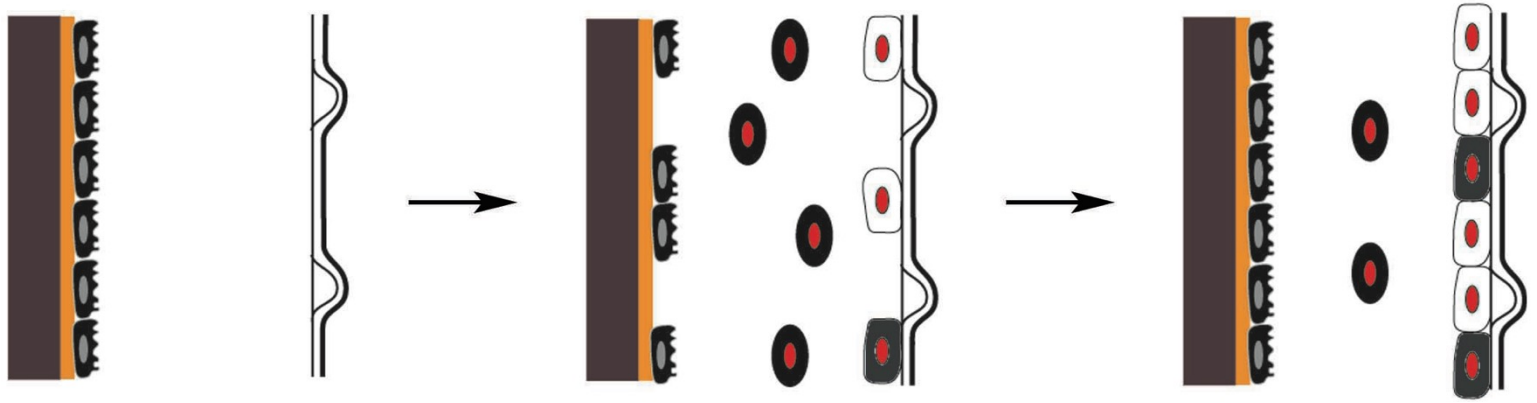
Xenopus laevis



Yoshii et al., 2007

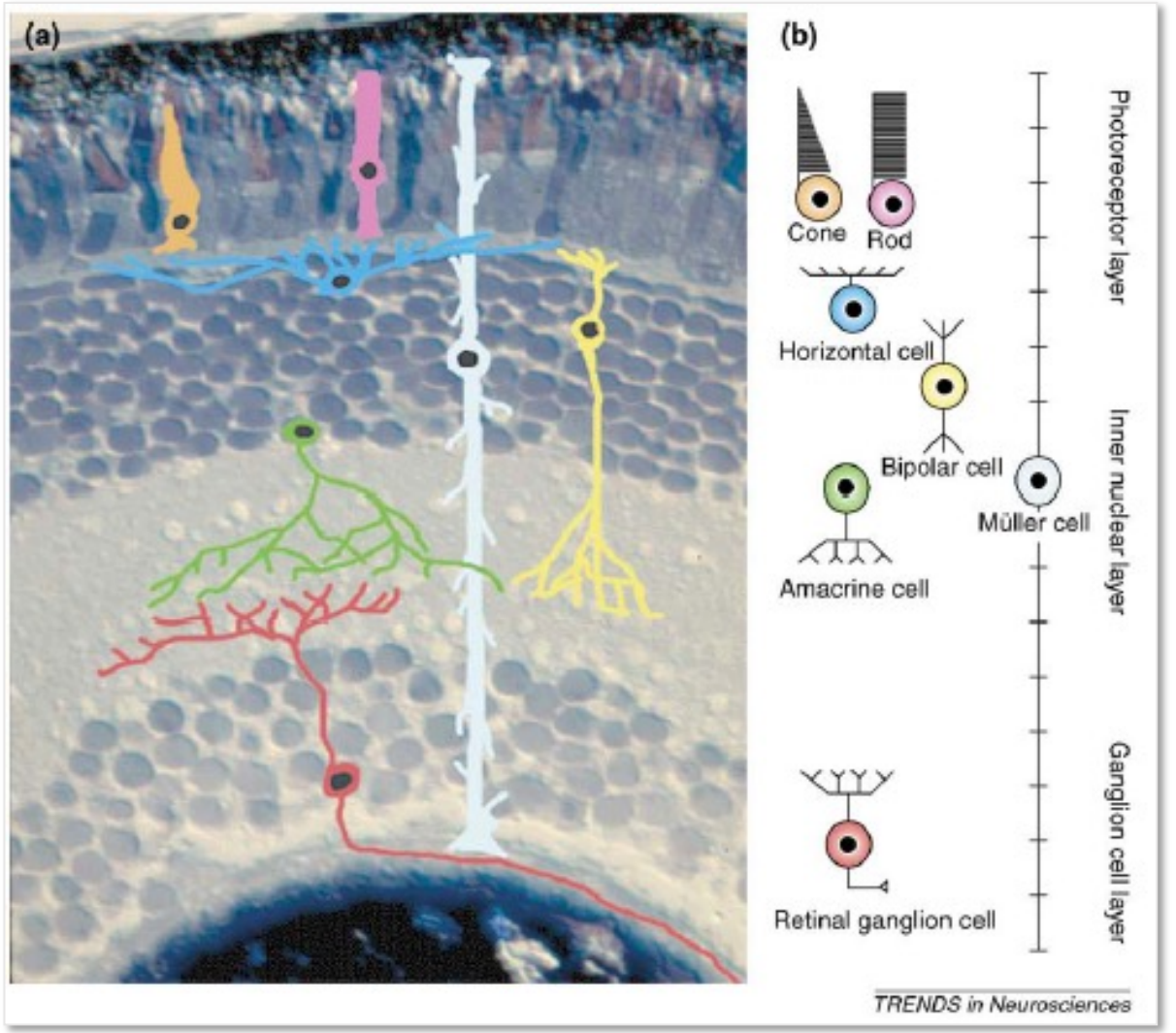
Regeneration in post-metamorphic *Xenopus*

Xenopus laevis

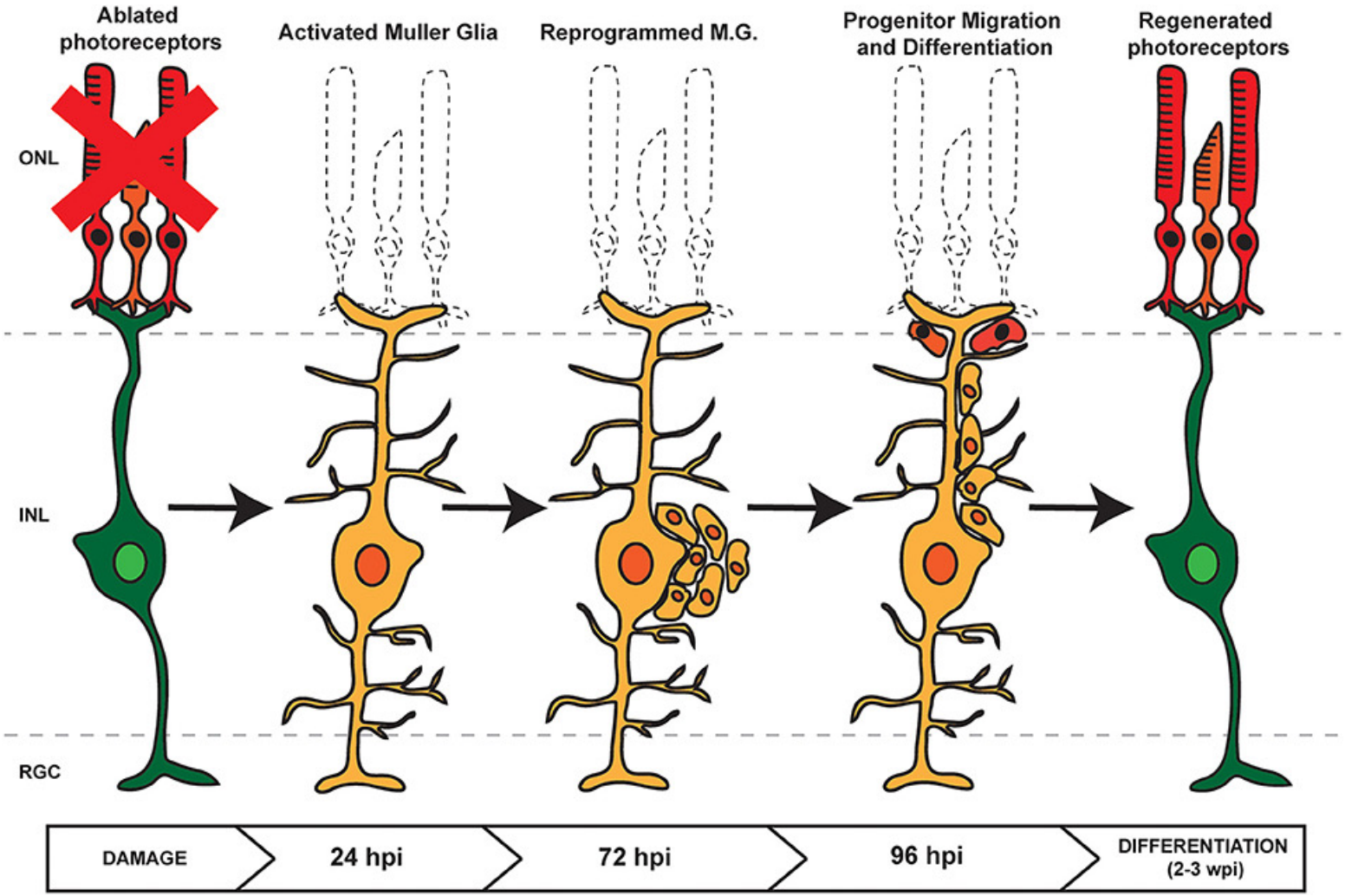


Hidalgo et al., 2014

Müller cells


(a)
(b)
Cone
Rod
Horizontal cell
Bipolar cell
Müller cell
Amacrine cell
Retinal ganglion cell
Photoreceptor layer
Inner nuclear layer
Ganglion cell layer
TRENDS in Neurosciences

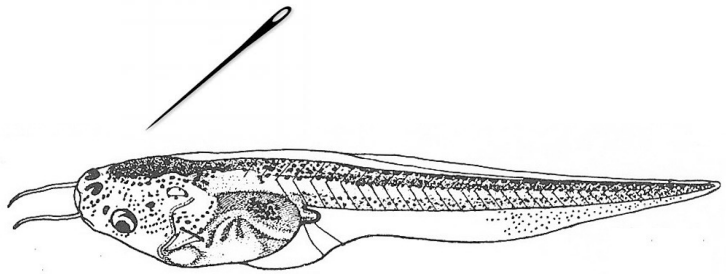
Müller glia regenerative potential in the fish retina

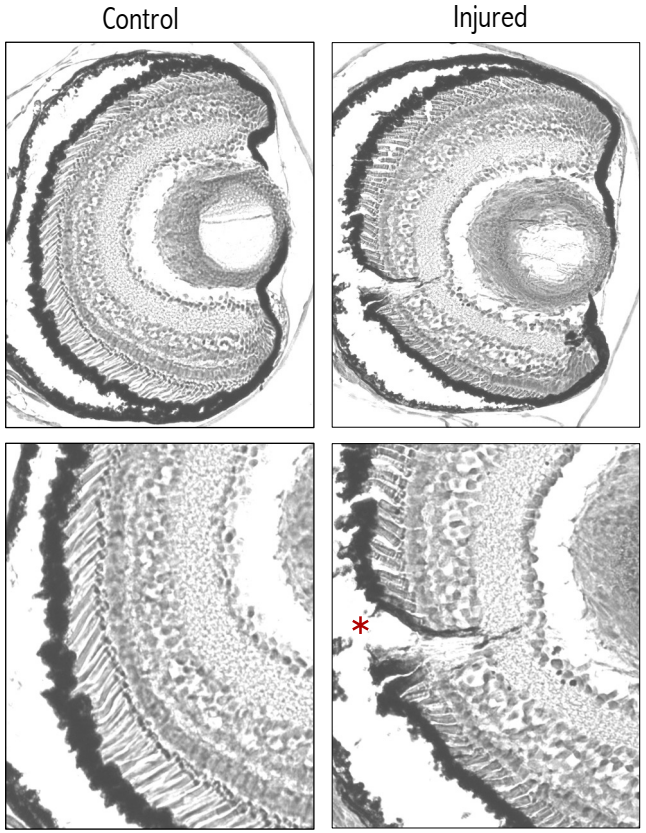


- Can amphibian also recruit their Müller cells in case of injury?
- What are the mechanisms that sustain or constrain Müller cell response to injury?
- Are intrinsic and/or extrinsic factors key regulators of regeneration?
- Can we awake mammalian dormant Müller cells for therapeutic purposes?

New models of retinal injury/degeneration in *Xenopus*

Mechanical injury

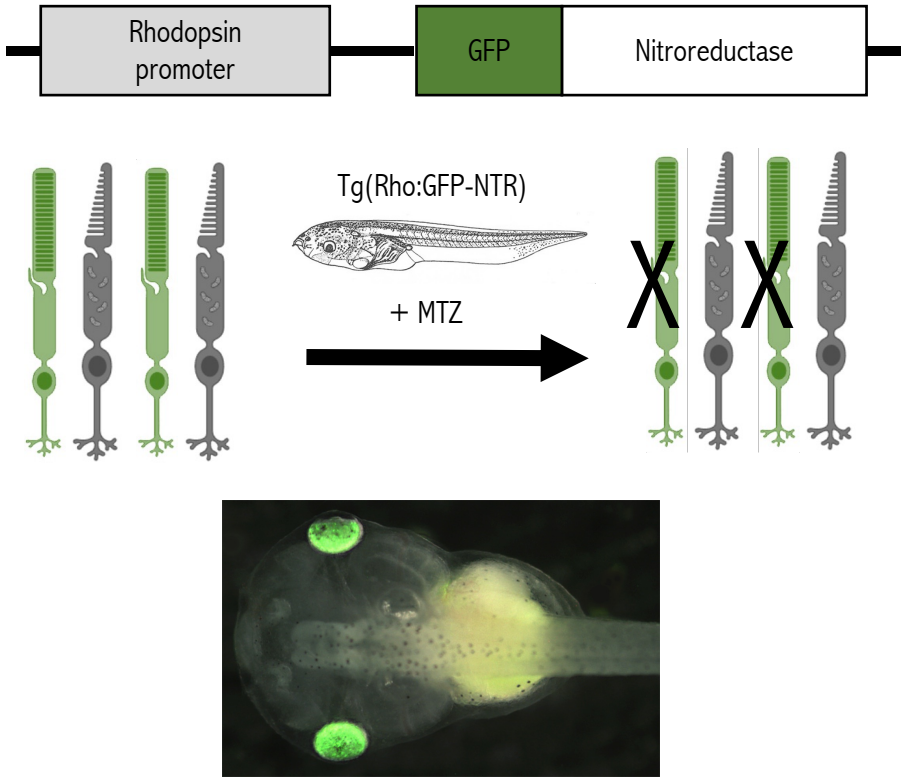


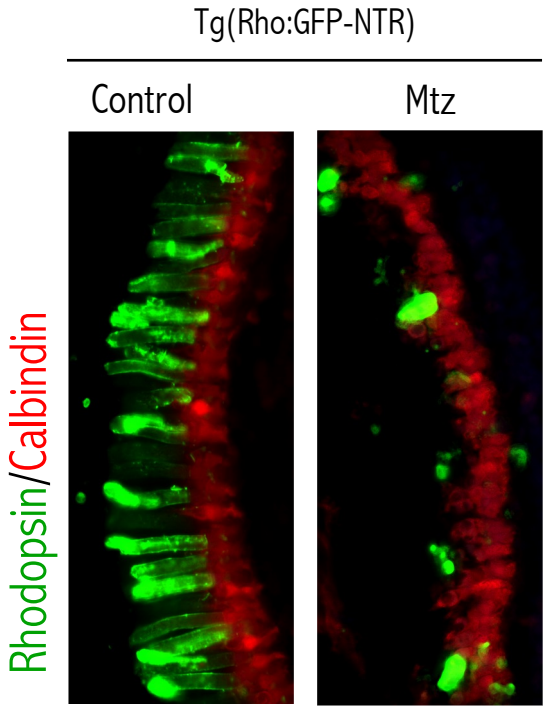


Langhe et al., Glia 2017

New models of retinal injury/degeneration in *Xenopus*

NTR-MTZ Conditional photoreceptor ablation

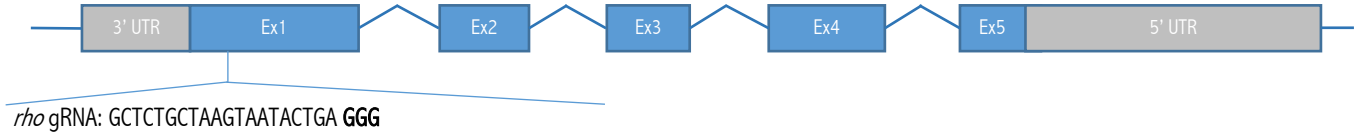




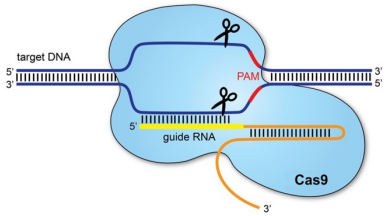
Langhe et al., Glia 2017

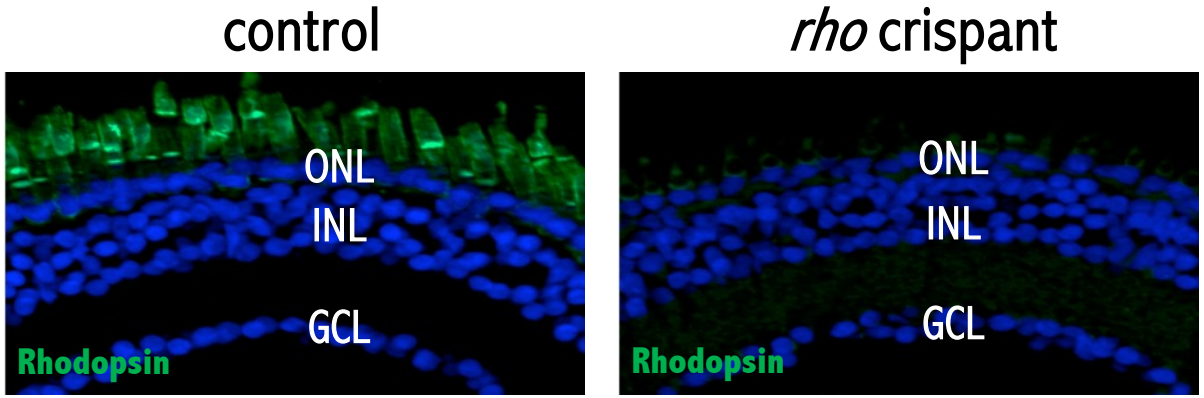
New models of retinal injury/degeneration in *Xenopus*

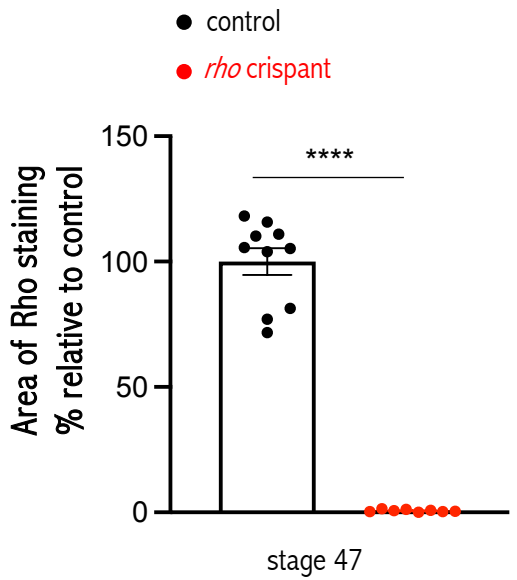
CRISPR-dependent photoreceptor degeneration as a model of retinitis pigmentosa



rhodopsin gene

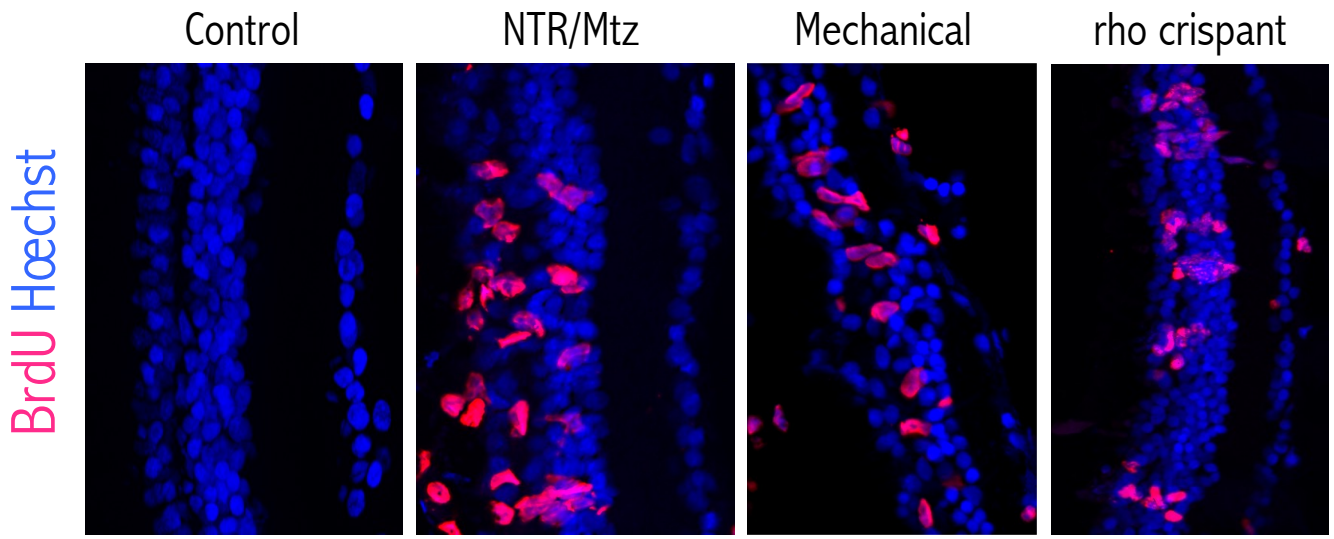


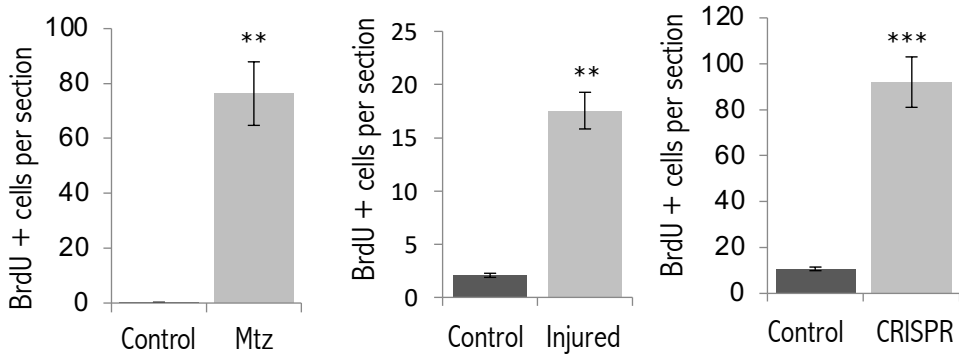




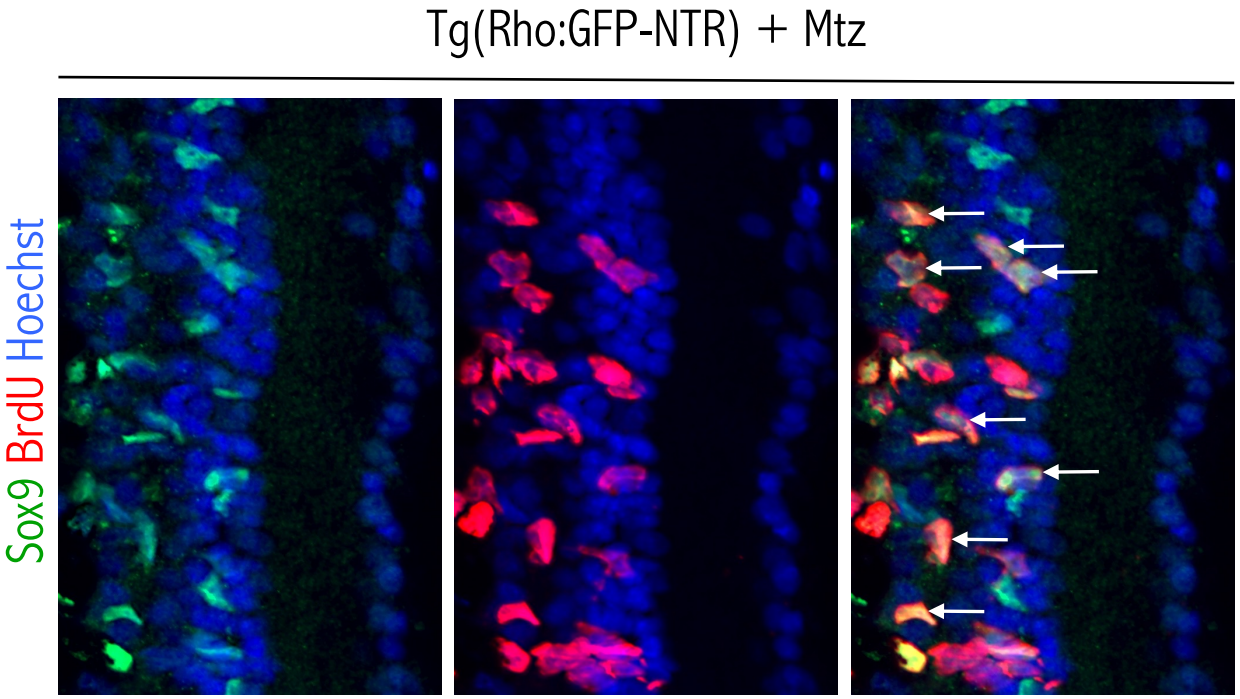
unpublished

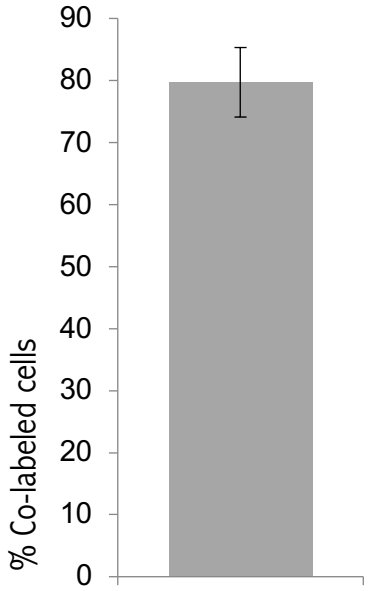
Proliferative response after retinal injury



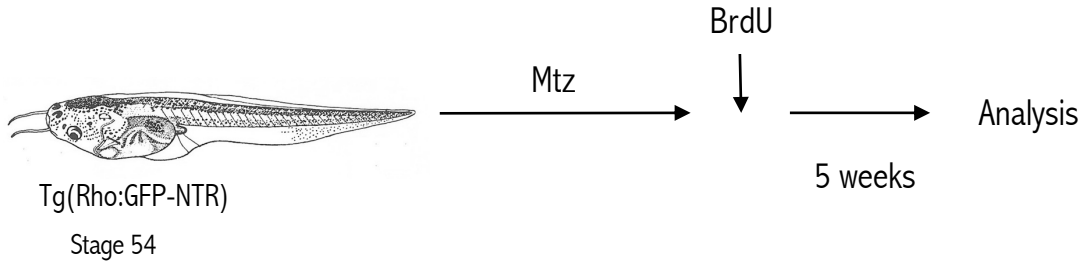


Müller cells proliferate following retinal injury

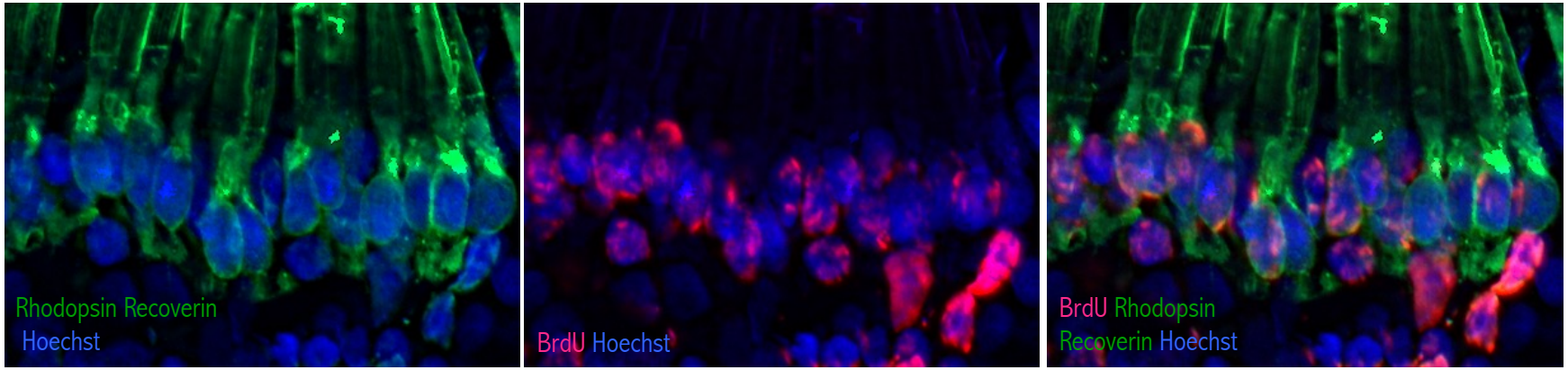




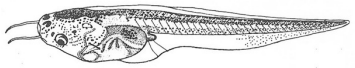
Müller cell-dependent photoreceptor regeneration

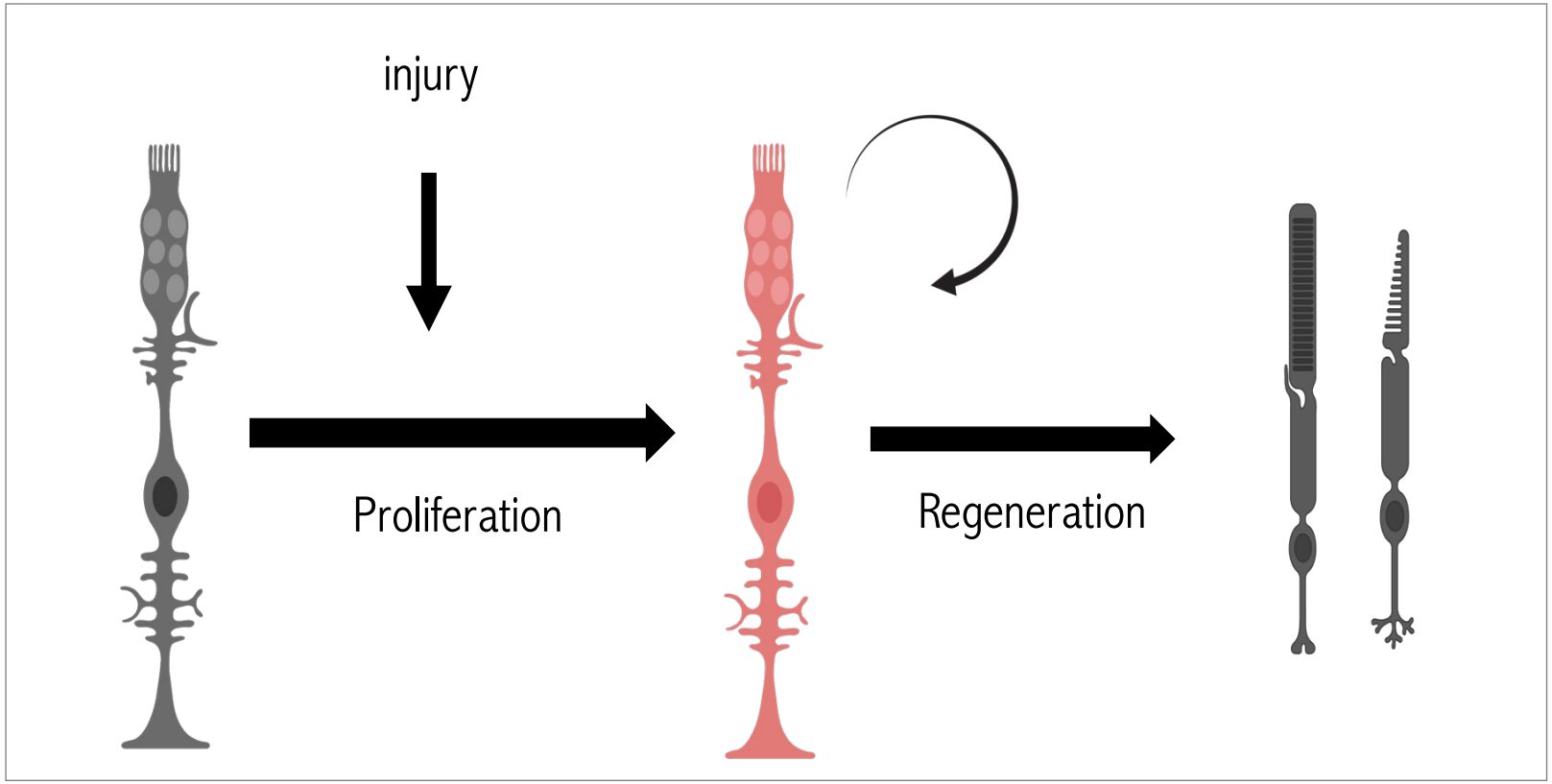


Tg(Rho:GFP-NTR) + Mtz



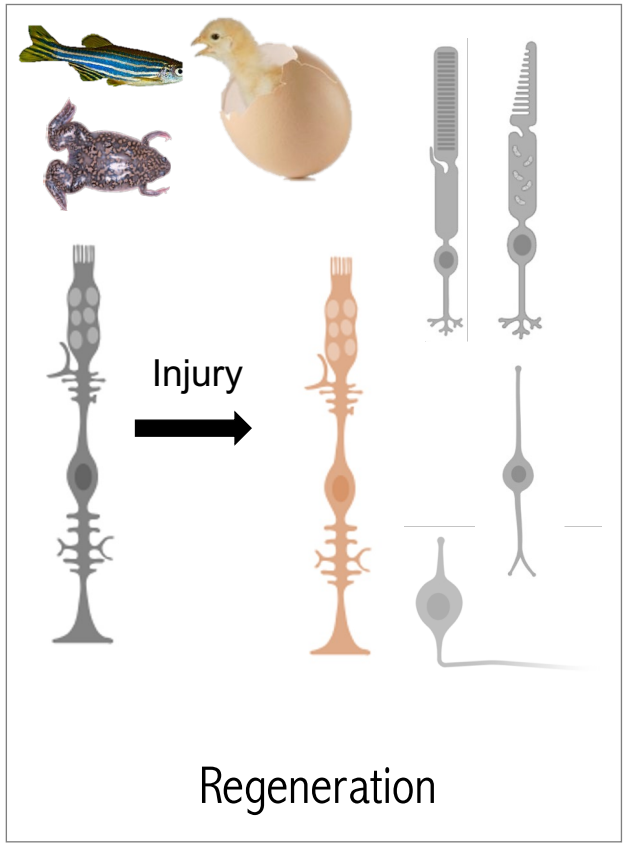
Müller glial cell potential for retinal tissue repair in *Xenopus*

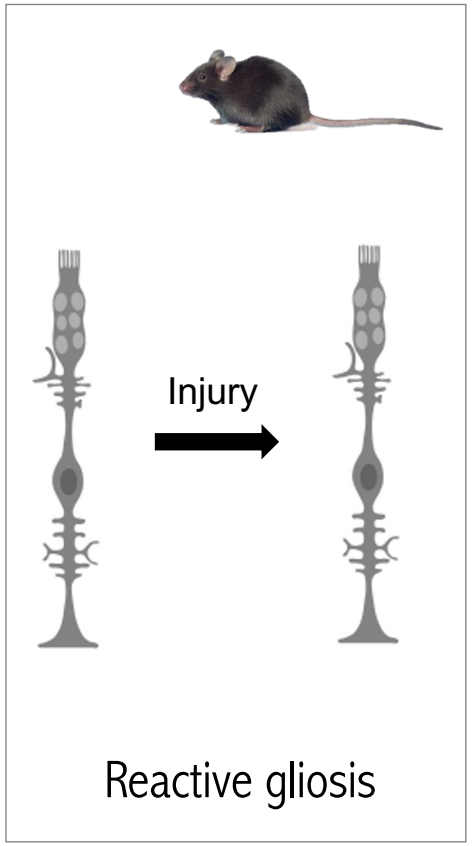




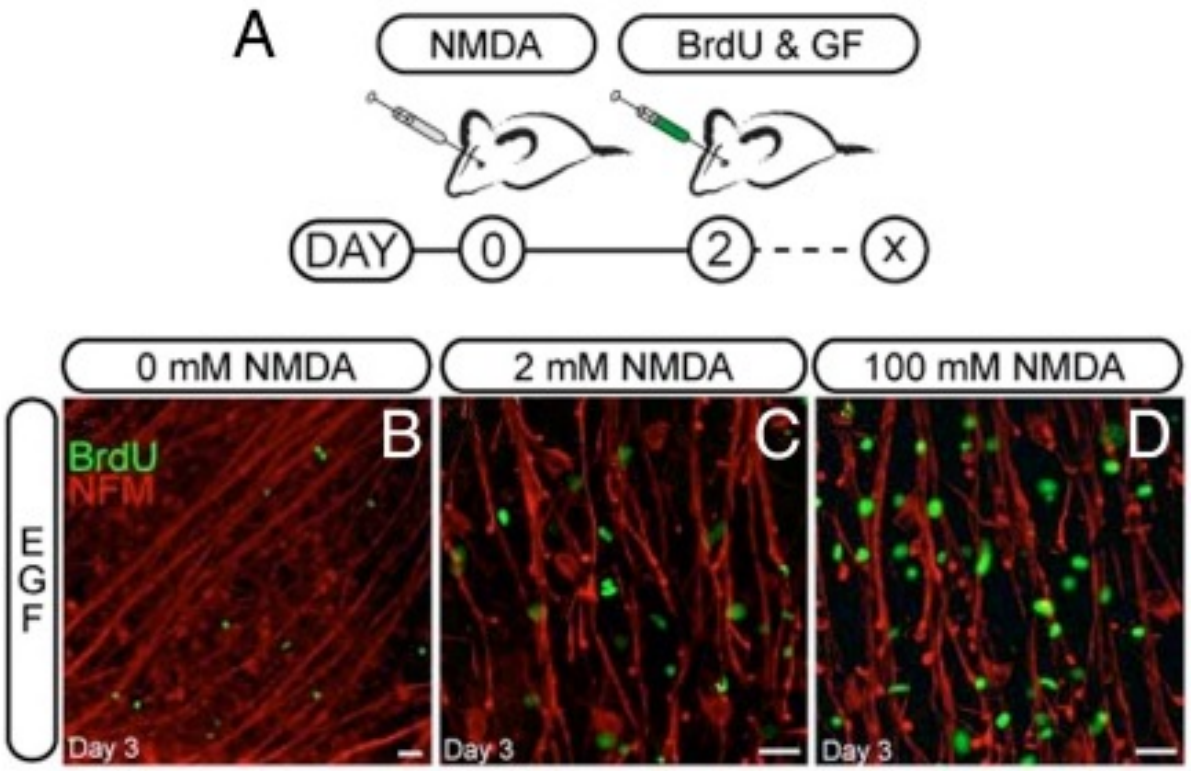
Langhe et al., Glia 2017
Parain et al., Cells 2022

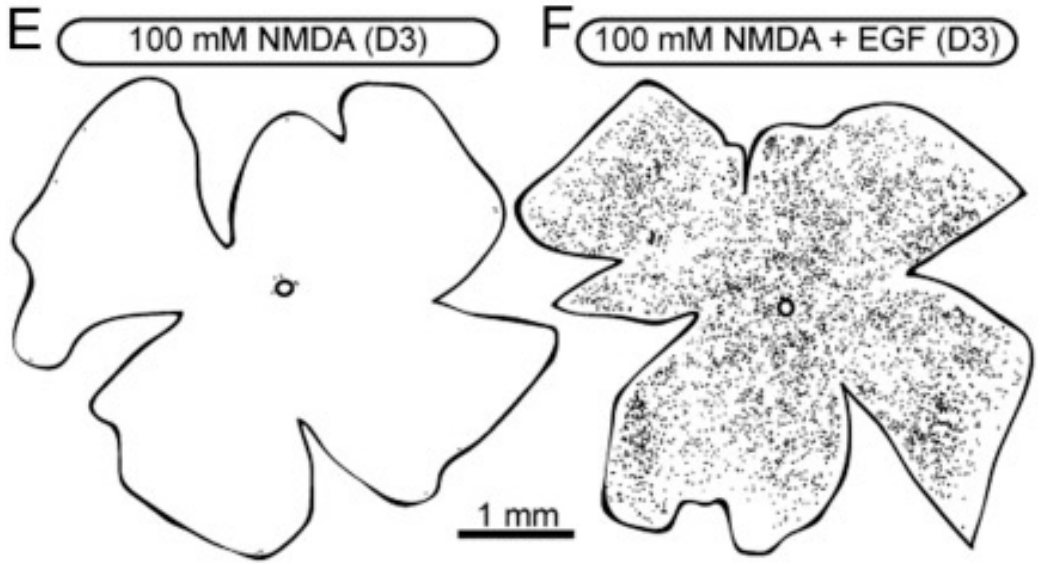
Müller glial cell potential for retinal tissue repair





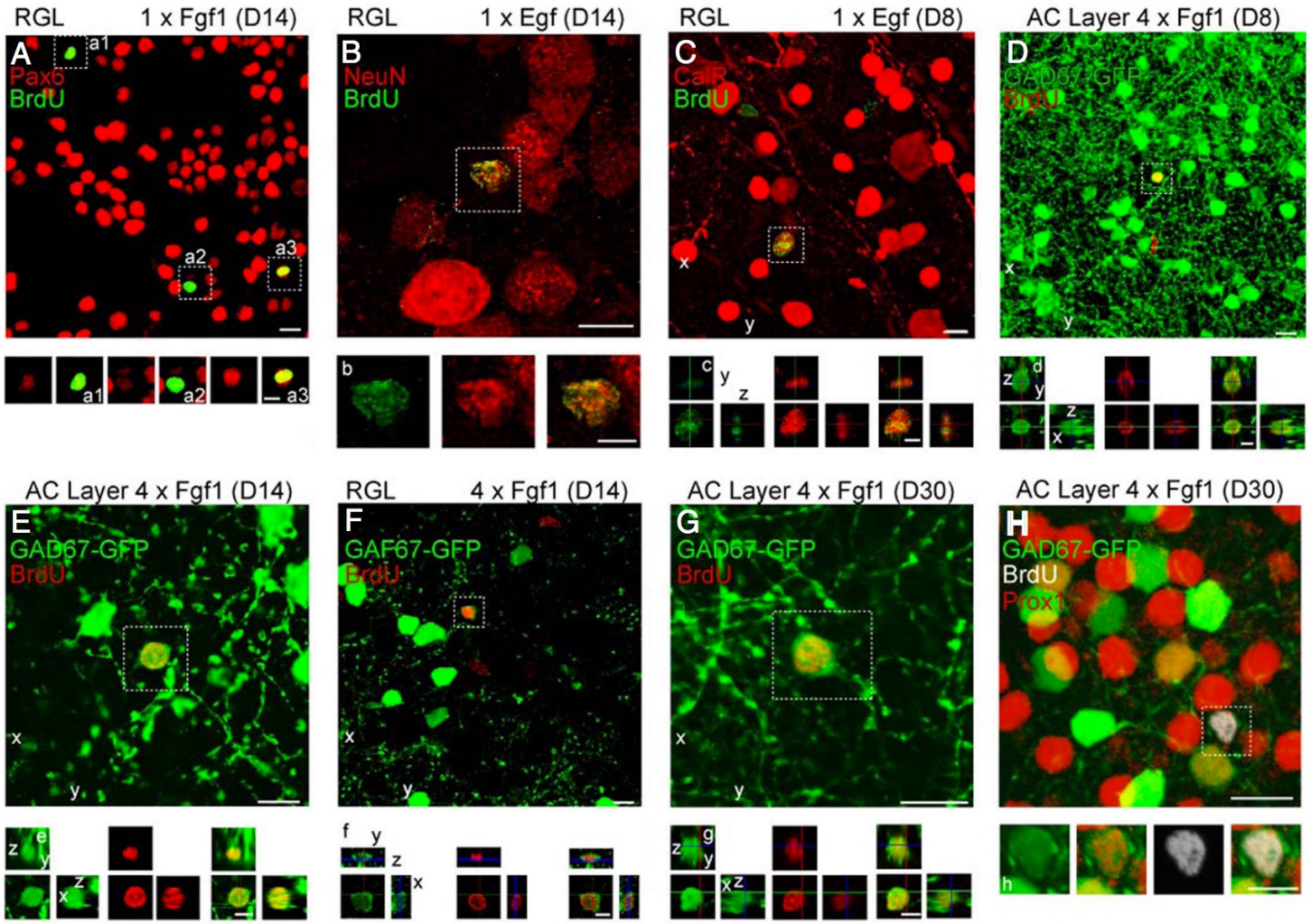
EGF triggers Müller glia proliferation in adult mouse retina following NMDA damage





Karl et al., PNAS 2008

Some of these BrdU+ cells developed characteristics of retinal neurons

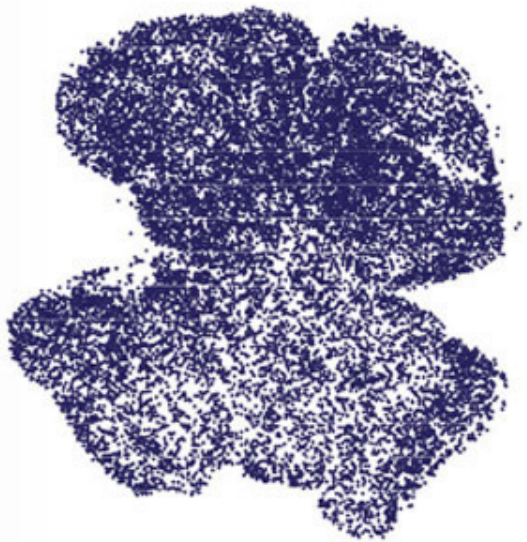


Karl et al., PNAS 2008

MÜLLER GLIA PROLIFERATIVE RESPONSE

JUVENILE

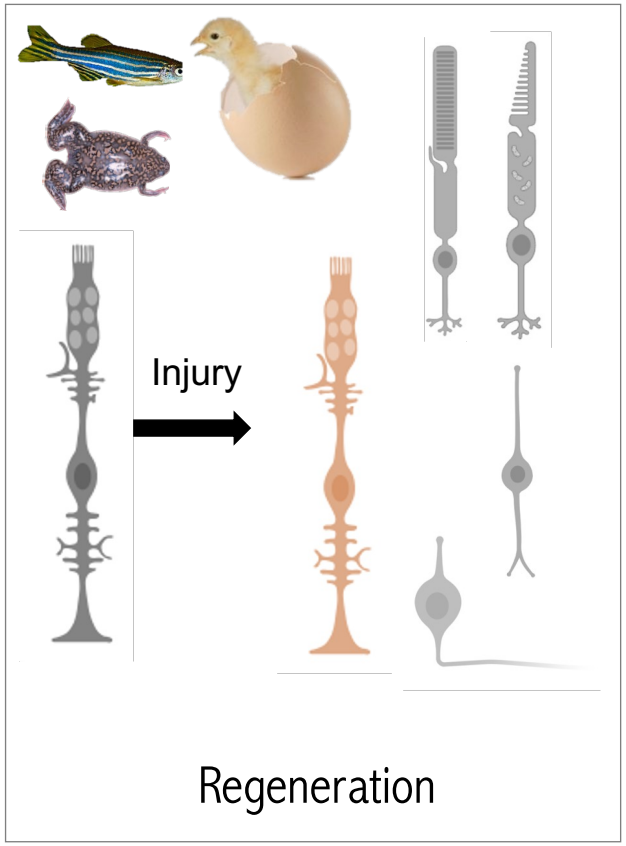
ADULT

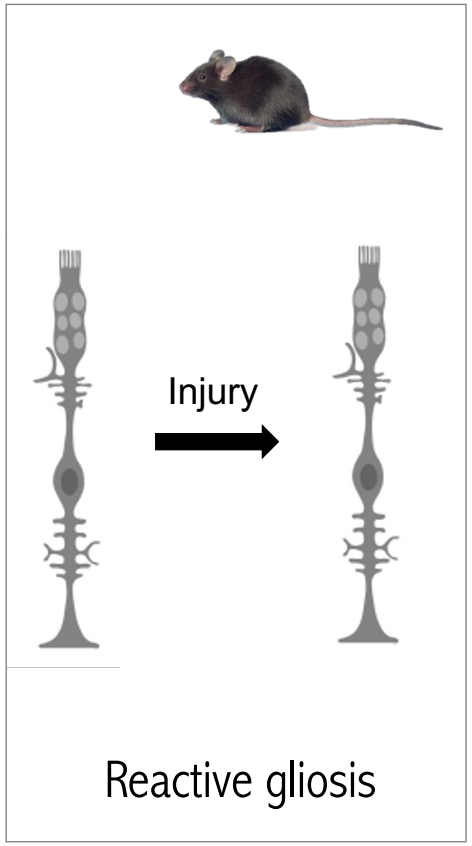


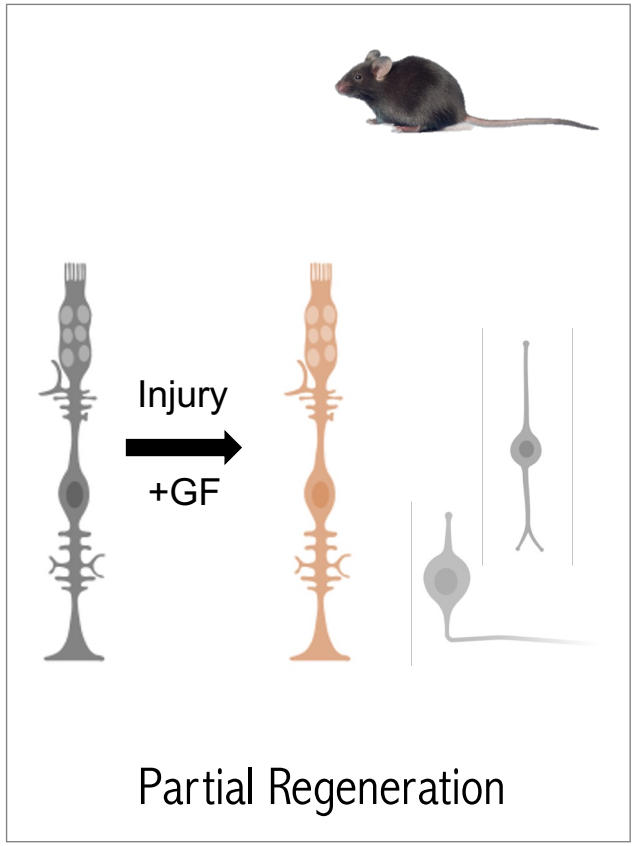
REGENERATIVE COMPETENCE

Mike O. Karl

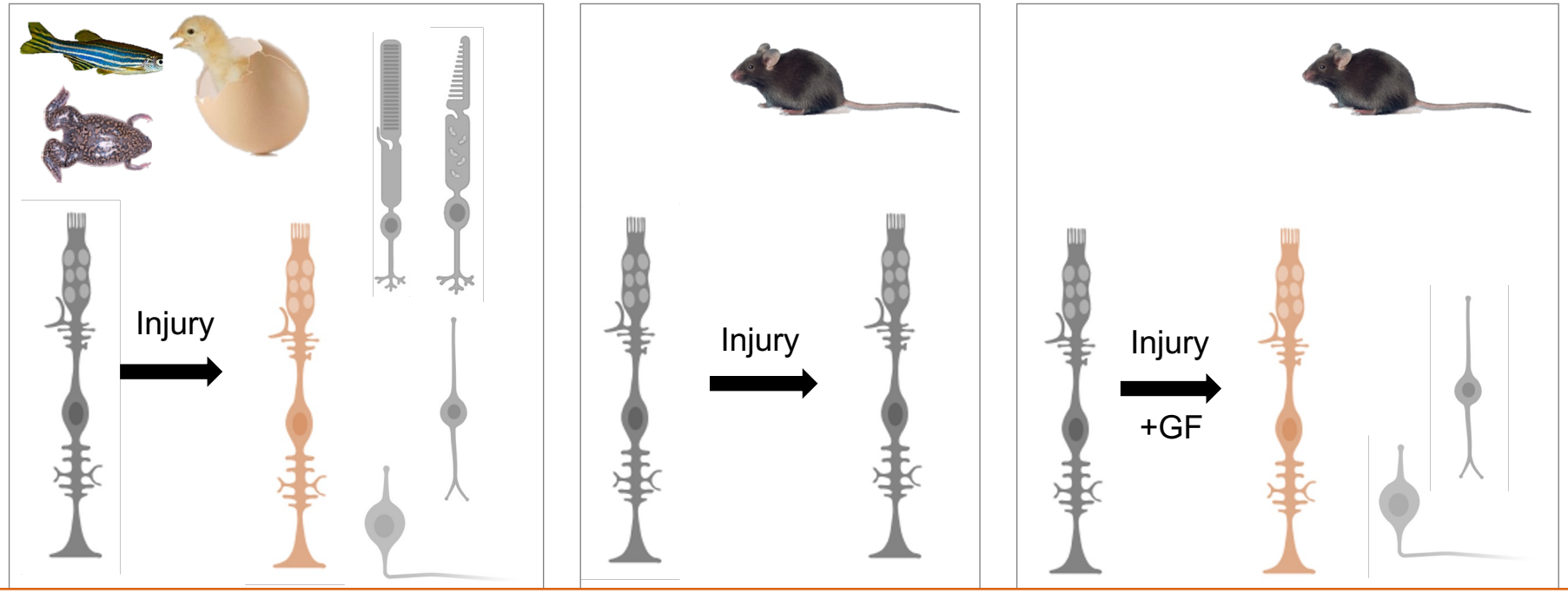
Müller glial cell potential for retinal tissue repair



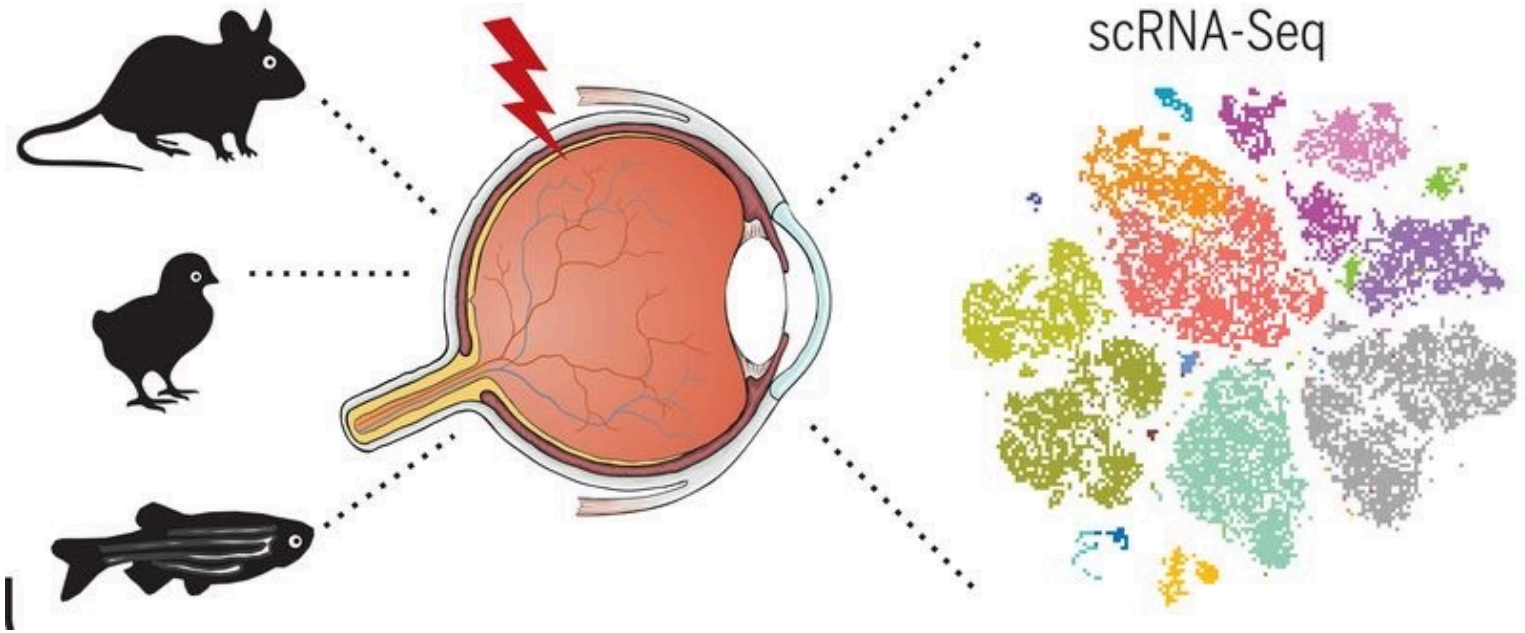




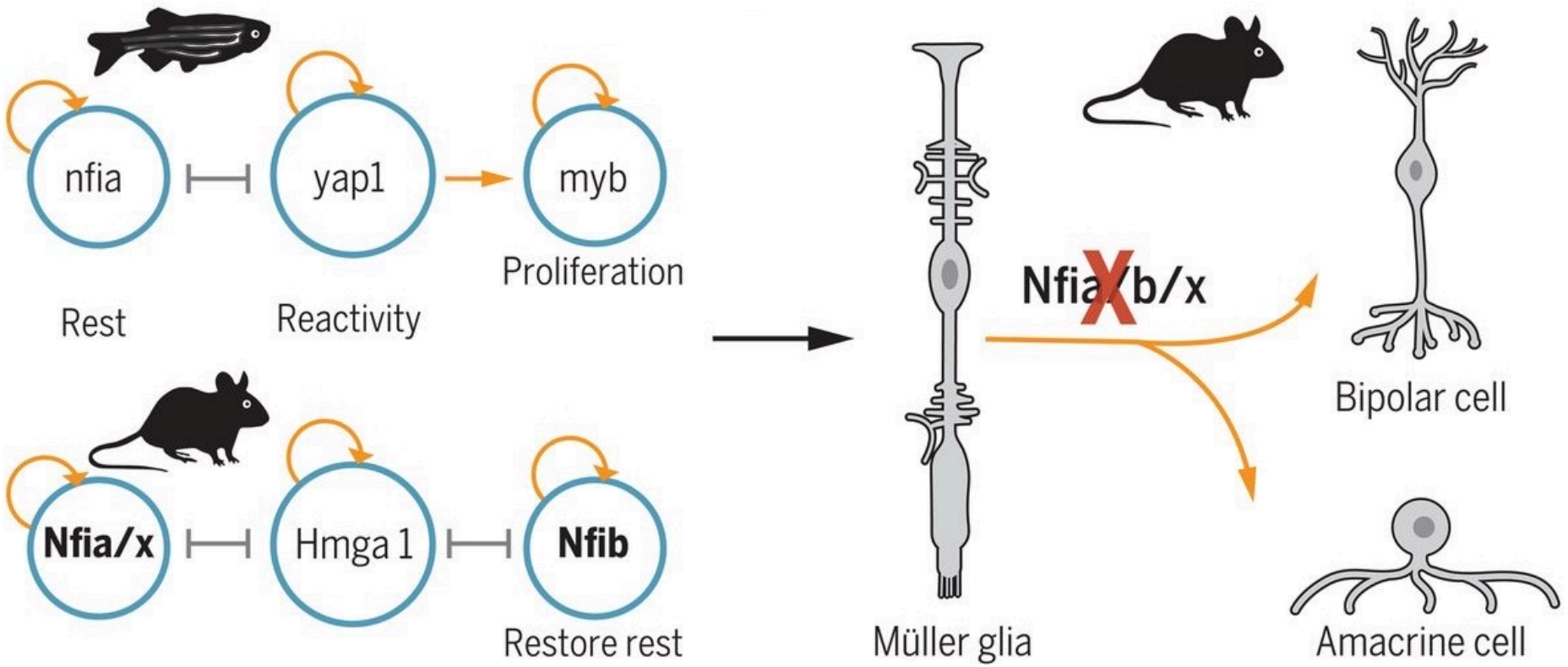
Müller glial cell potential for retinal tissue repair



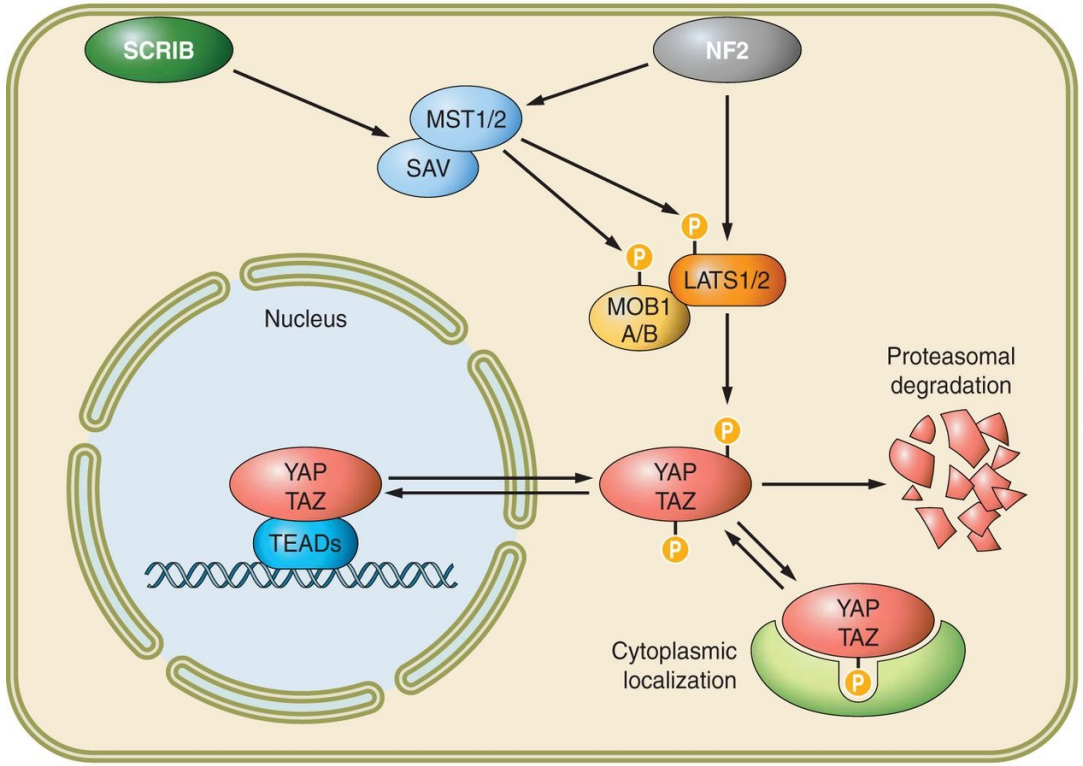
What are the mechanisms that sustain or constrain Müller cell proliferation upon injury?



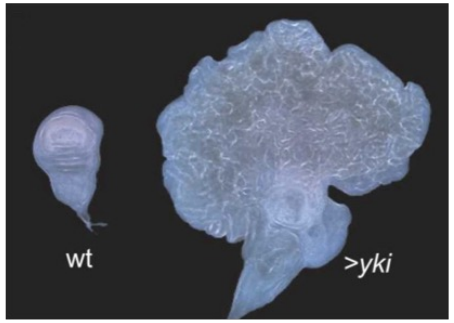
Hoang Science 2020


nfia
yap1
myb
Proliferation
Rest
Reactivity
Nfia/x
Hmga 1
Nfib
Restore rest
Müller glia
Nfia/b/x
Bipolar cell
Amacrine cell

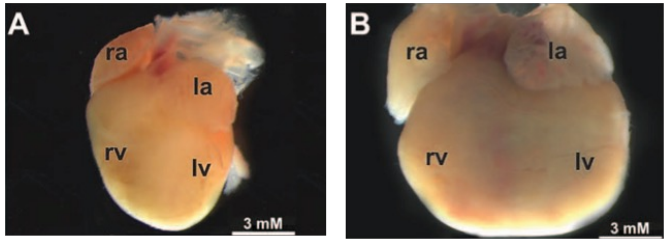
The Hippo pathway



From Piccolo et al., 2014



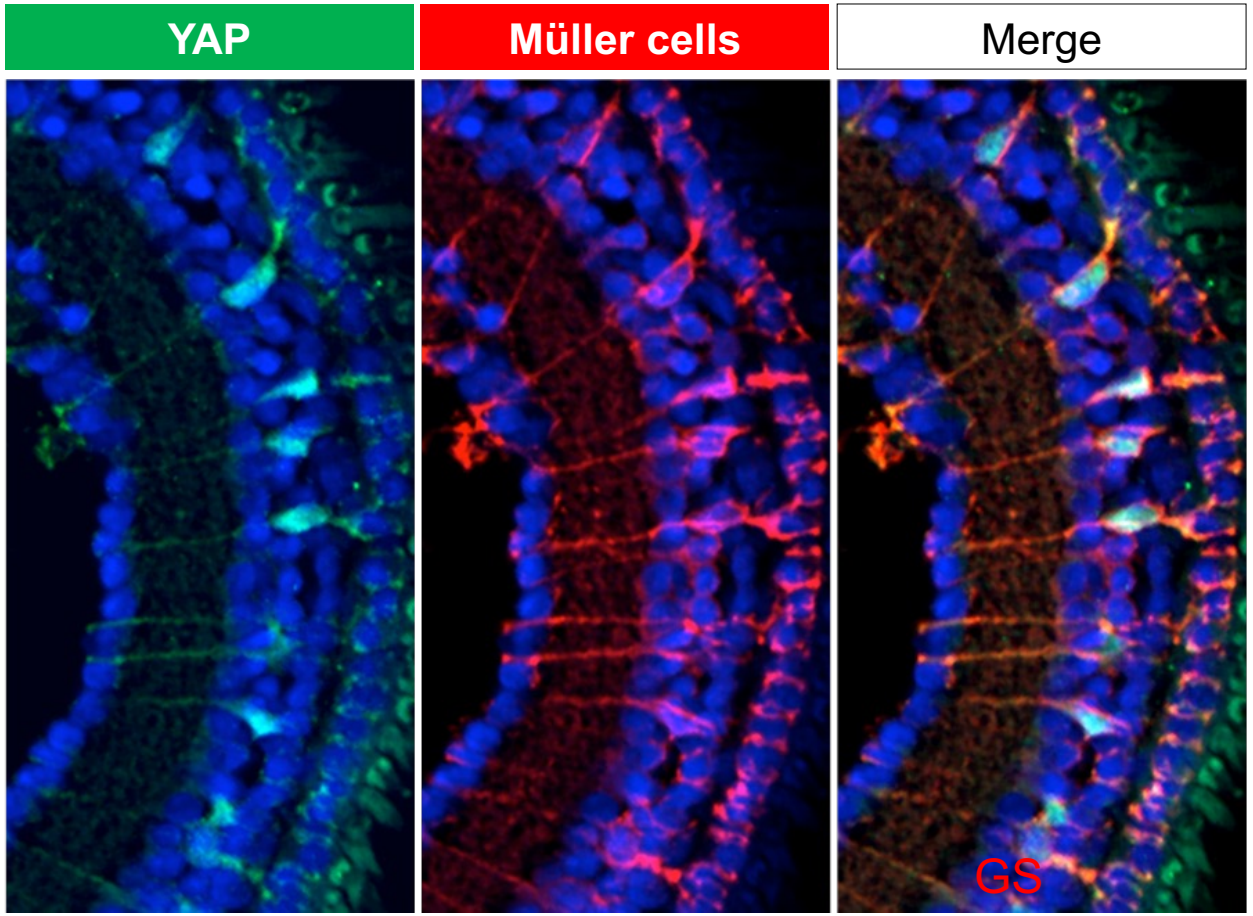
Todd Heallenet al. 2011



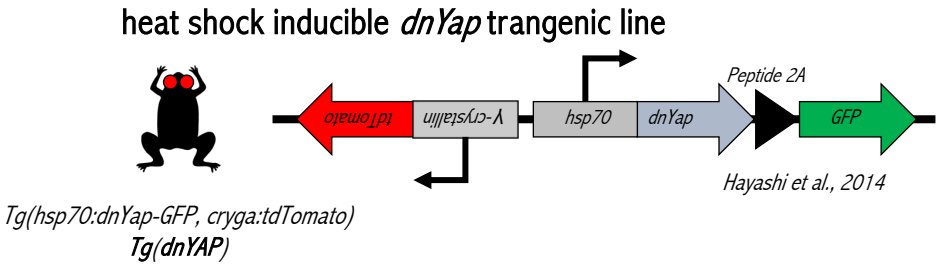
Pan et al. 2007

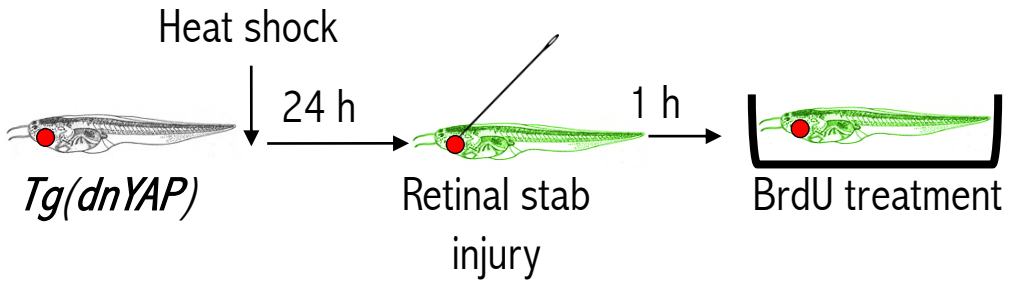
Pan et al. 2007

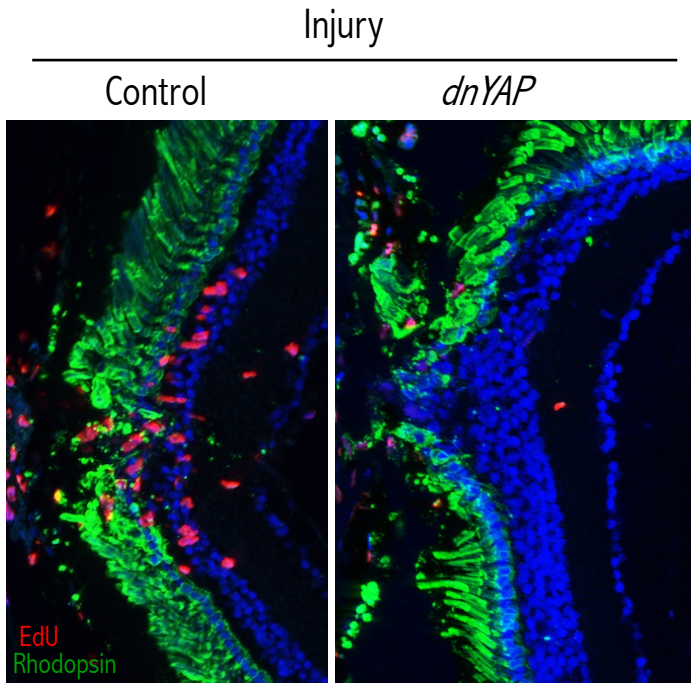
YAP is expressed in *Xenopus* Müller cells



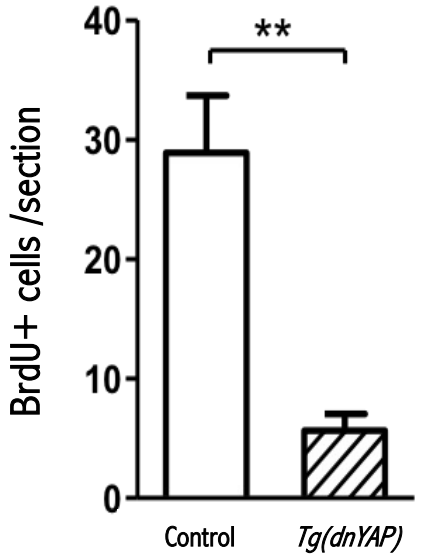
Inhibition of YAP prevents Müller glia proliferation upon acute retinal damage



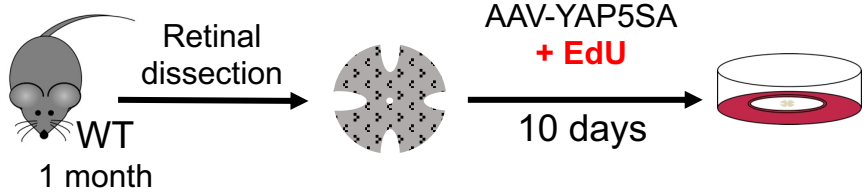




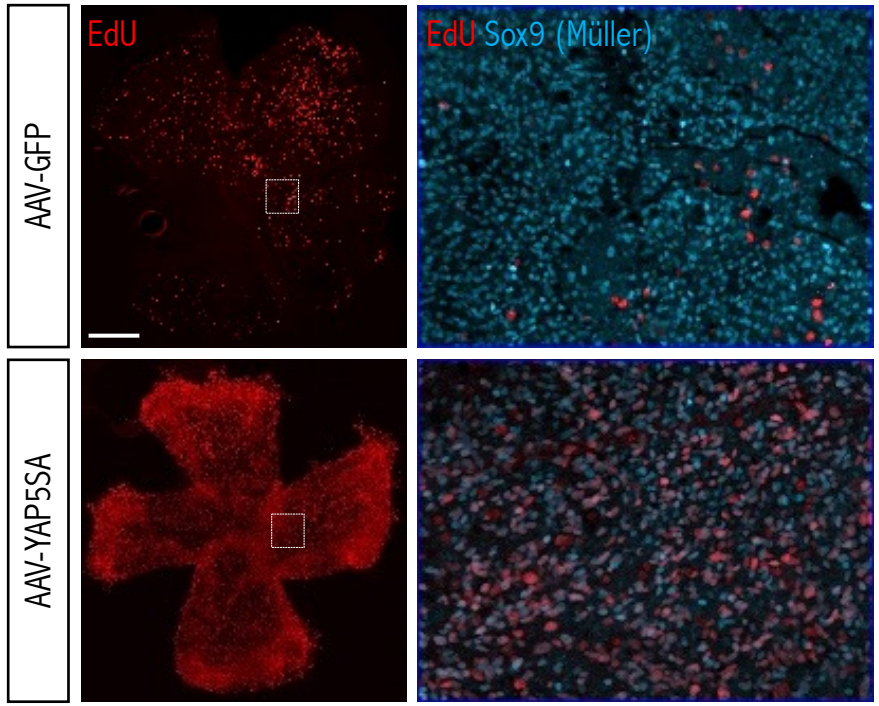
Photoreceptors Proliferation Nuclei

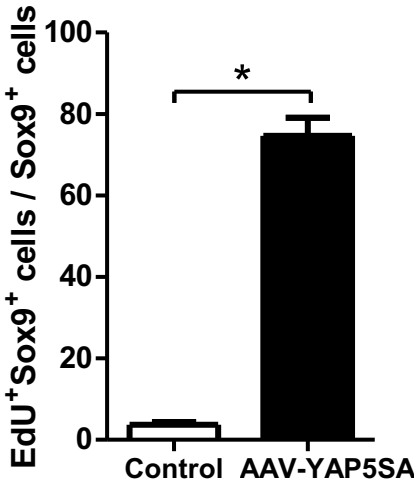


Forced YAP expression in mouse Müller glia cells stimulates their proliferation

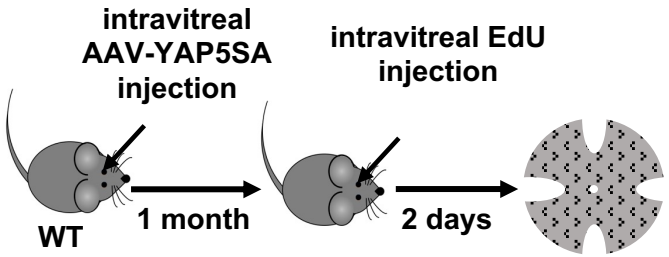


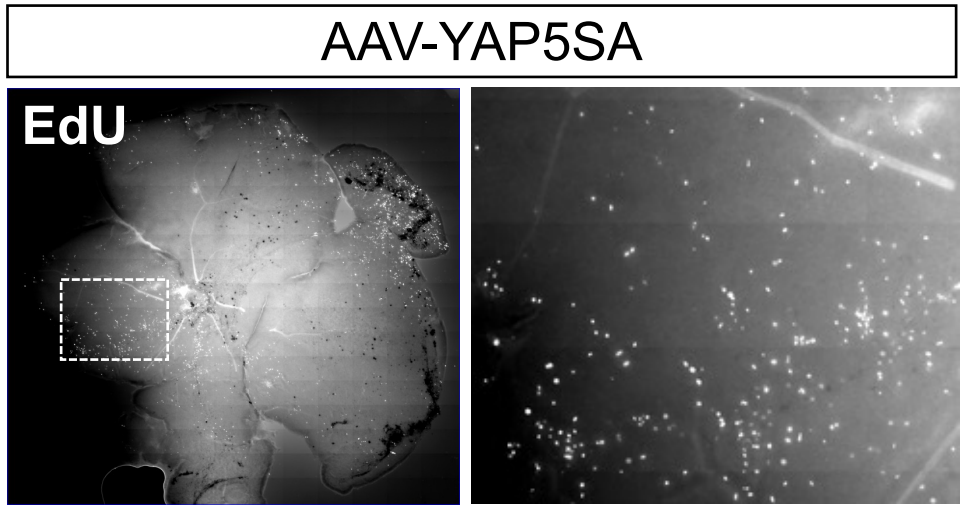
Klimczak et al., 2009

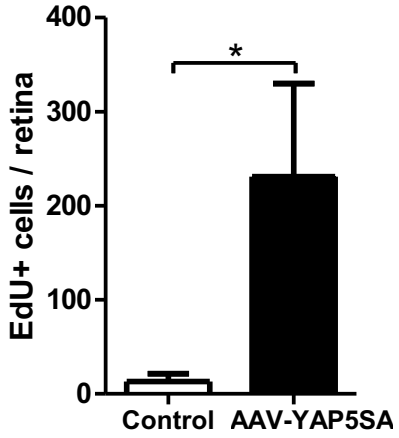


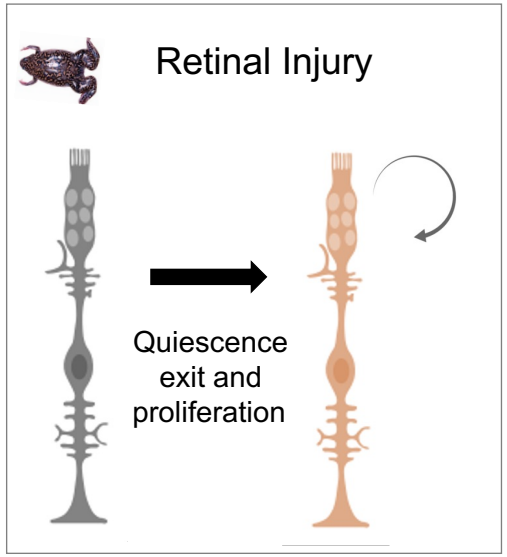


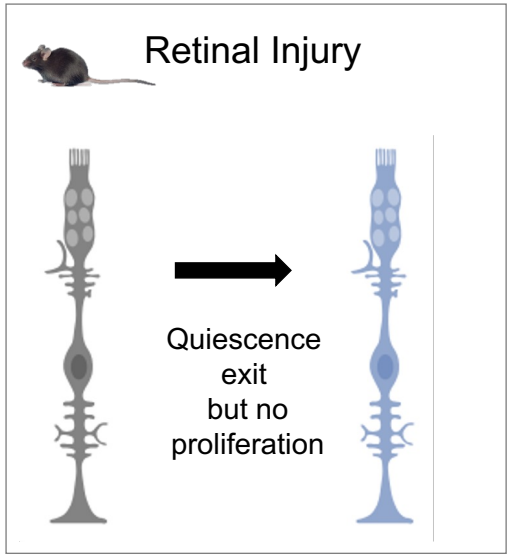
Forced YAP expression in mouse Müller glia cells stimulates their proliferation *in vivo*

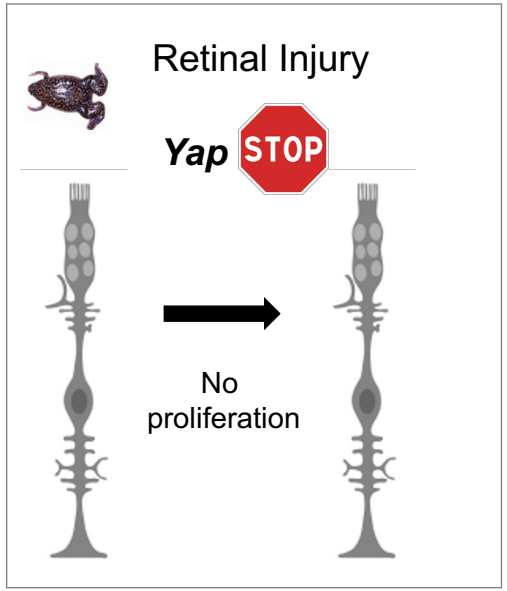


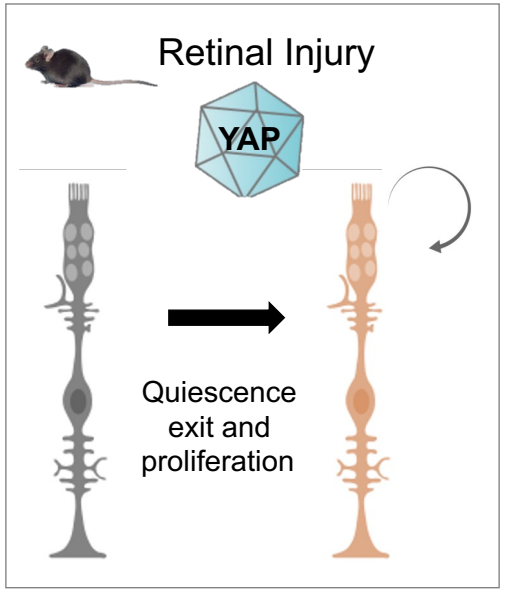












Hamon *et al. Cell Reports* 2019

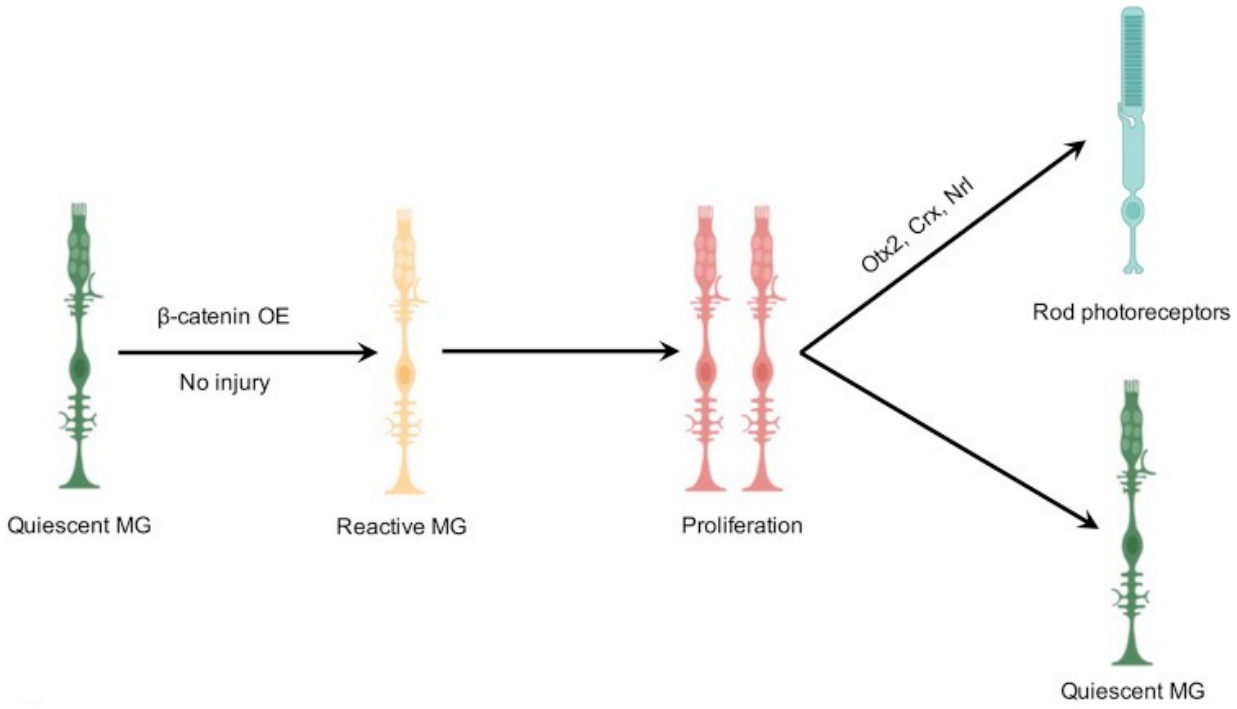
- What about neuron regeneration?

LETTER

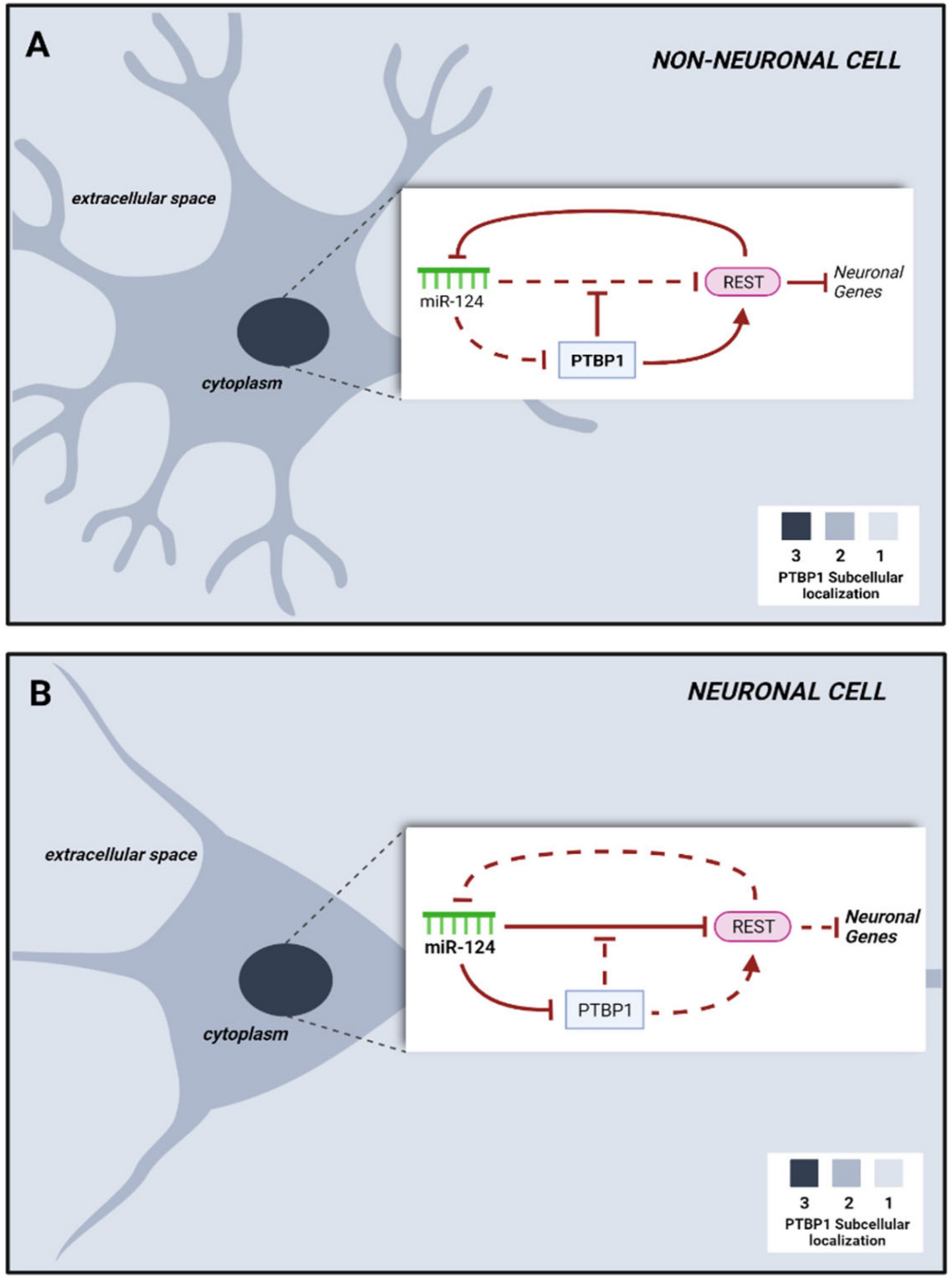
https://doi.org/10.1038/s41586-018-0425-3

Restoration of vision after de novo genesis of rod photoreceptors in mammalian retinas

Kai Yao[1], Suo Qiu[1,2], Yanbin V. Wang[3,4], Silvia J. H. Park[3], Ethan J. Mohns[5], Bhupesh Mehta[4,6], Xinran Liu[7], Bo Chang[8], David Zenisek[3,4], Michael C. Crair[3,5], Jonathan B. Demb[3,4] & Bo Chen[1,9,10]*



ShH10-GFAP-mediated gene transfer of Otx2, Crx, and Nrl



Contardo et al. *Biomedicines* 2022

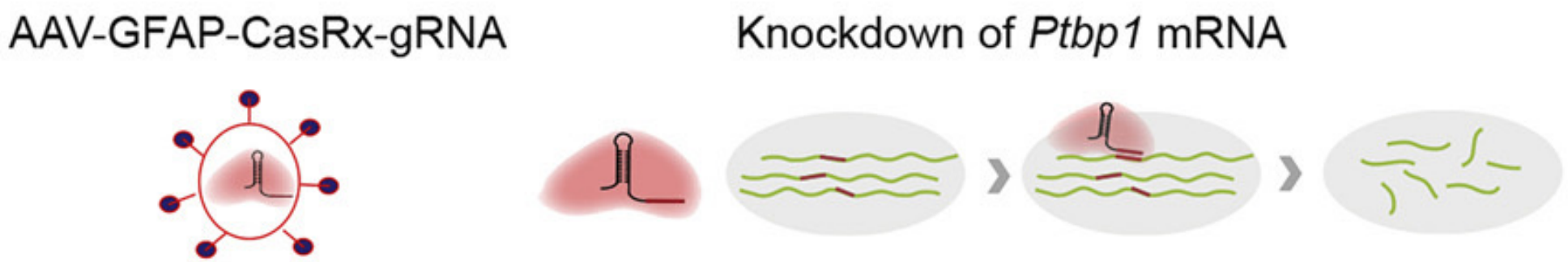
Cell

Article

Glia-to-Neuron Conversion by CRISPR-CasRx Alleviates Symptoms of Neurological Disease in Mice

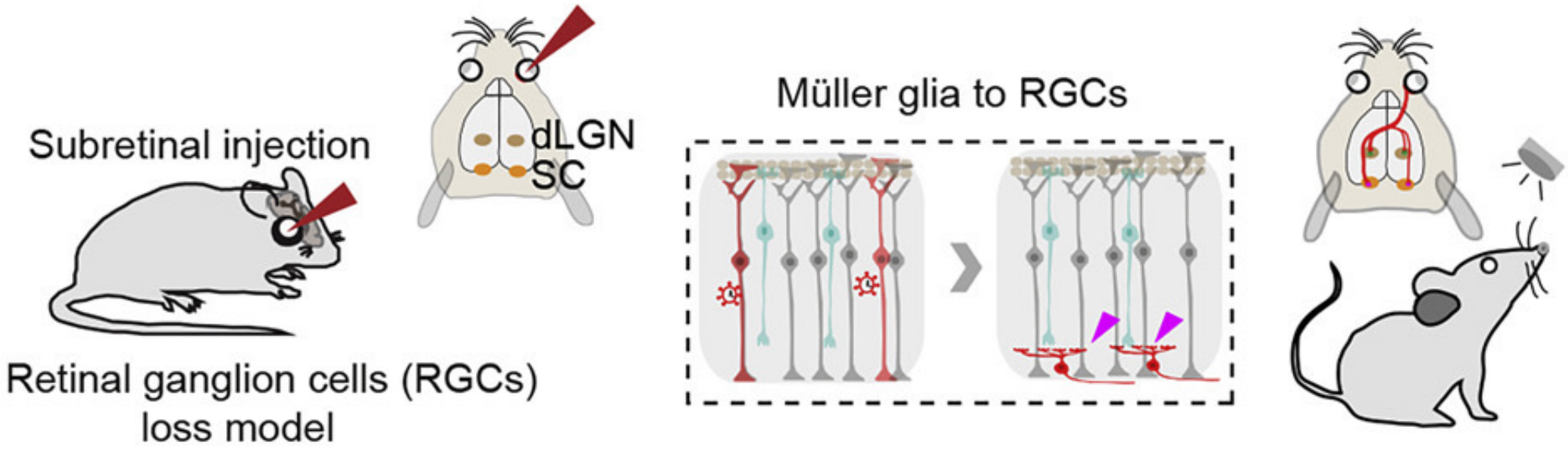
Authors

Haibo Zhou, Jinlin Su, Xinde Hu, ..., Haishan Yao, Linyu Shi, Hui Yang

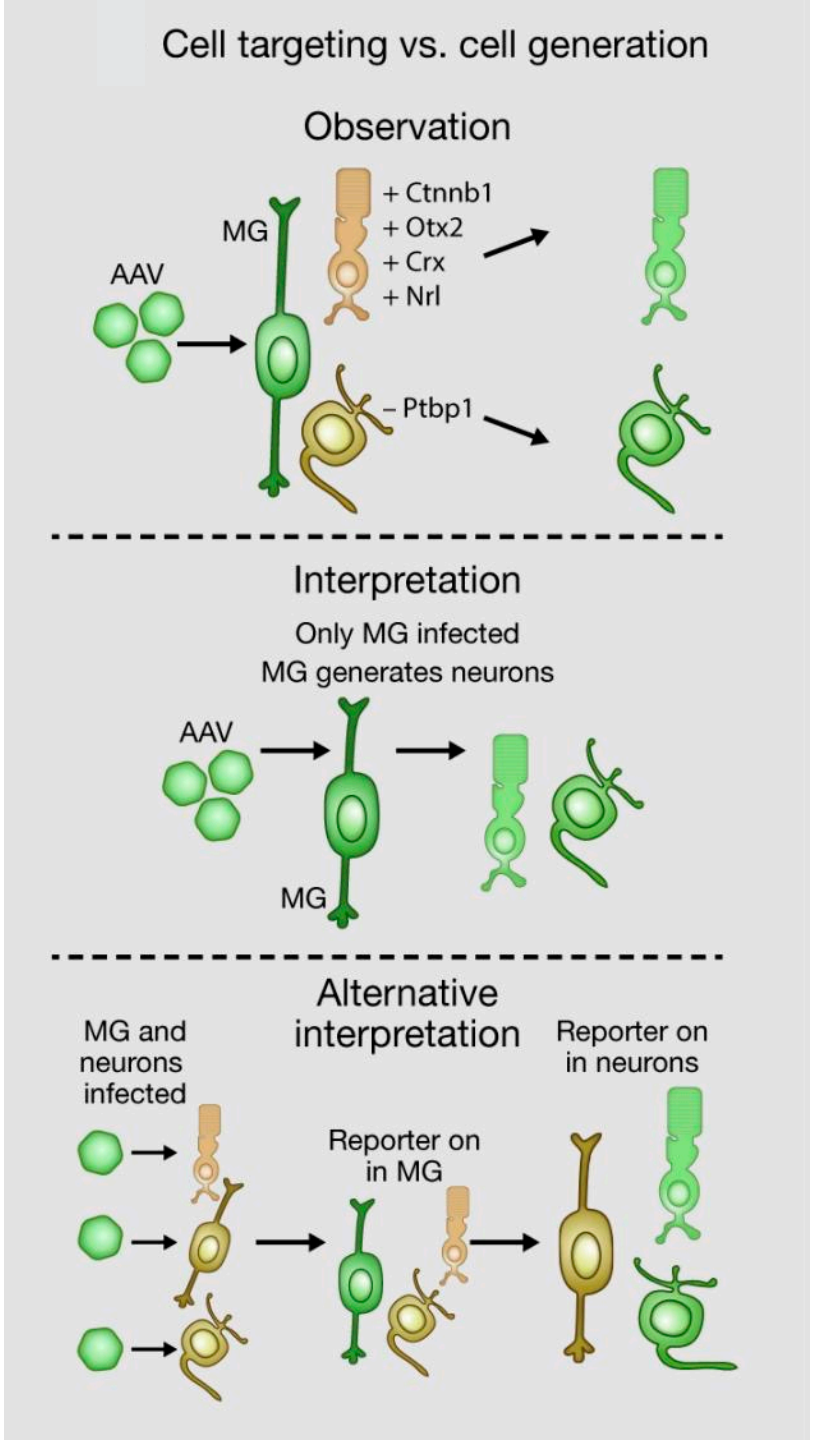


Cell 2020 181590-603.e16DOI: (10.1016/j.cell.2020.03.024)

Ptbp1 downregulation converts MG into RGCs by direct transdifferentiation



Cell 2020 181590-603.e16DOI: (10.1016/j.cell.2020.03.024)



Blackshaw & Sanes, JCI 2021

Cell Reports

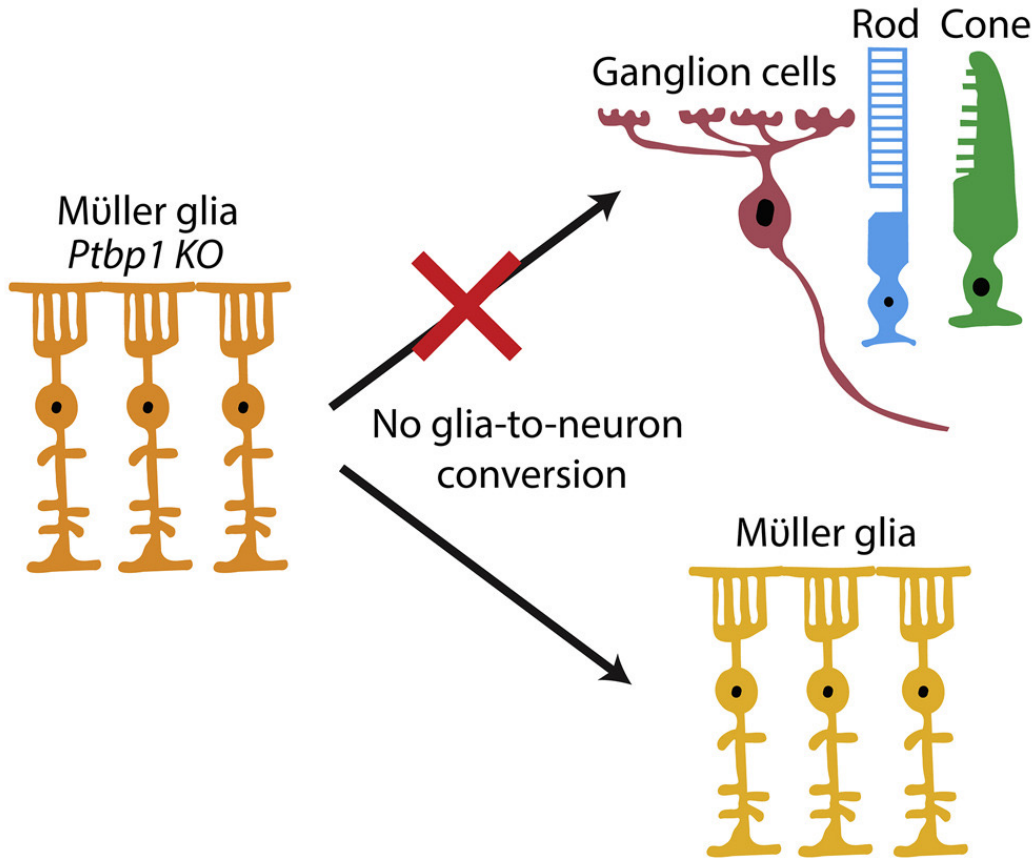
Report

Genetic loss of function of *Ptbp1* does not induce glia-to-neuron conversion in retina

Authors

Thanh Hoang, Dong Won Kim, Haley Appel, ..., Minzhong Yu, Neal S. Peachey, Seth Blackshaw

- *Ptbp1* is genetically disrupted selectively in adult mouse Müller glia
- The fate of cells lacking *Ptbp1* is analyzed with lineage tracing and molecular markers
- *Ptbp1* deletion does not lead to glia-to-neuron conversion in retina
- scRNA-seq shows that glial identity is maintained after *Ptbp1* deletion



Cell Reports 2022 39DOI: (10.1016/j.celrep.2022.110849)

Report

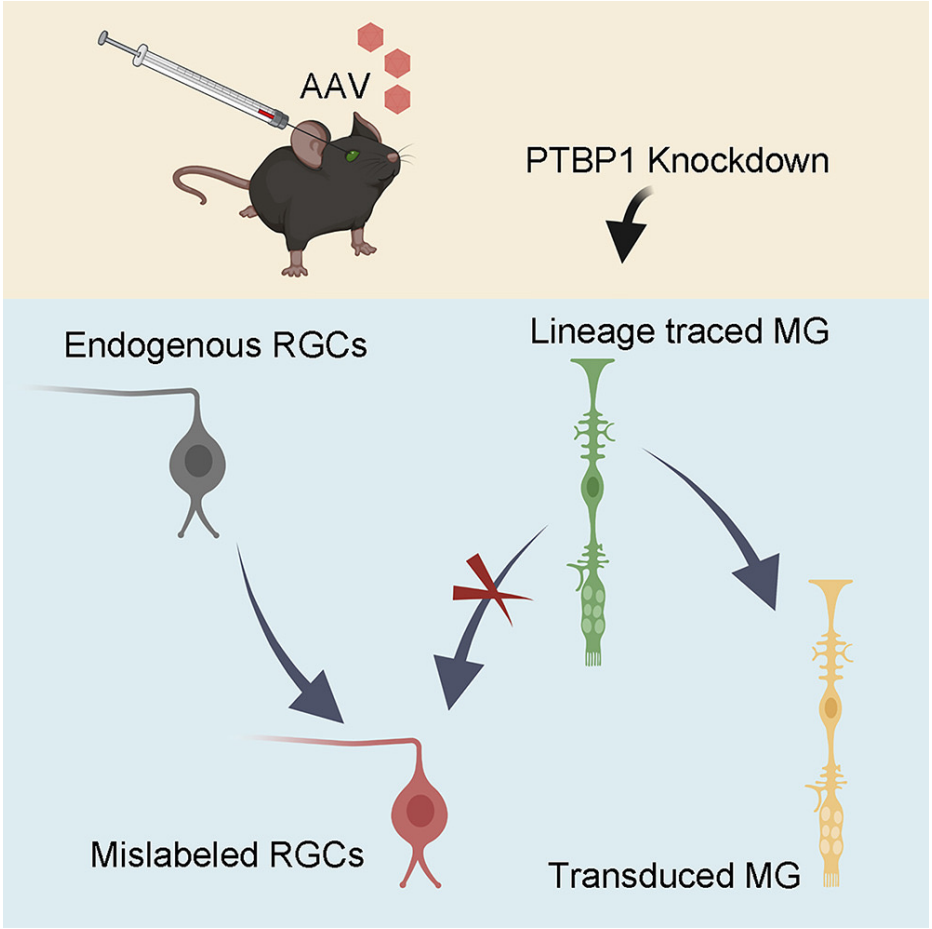
Cell Reports

Critical examination of Ptbp1-mediated glia-to-neuron conversion in the mouse retina

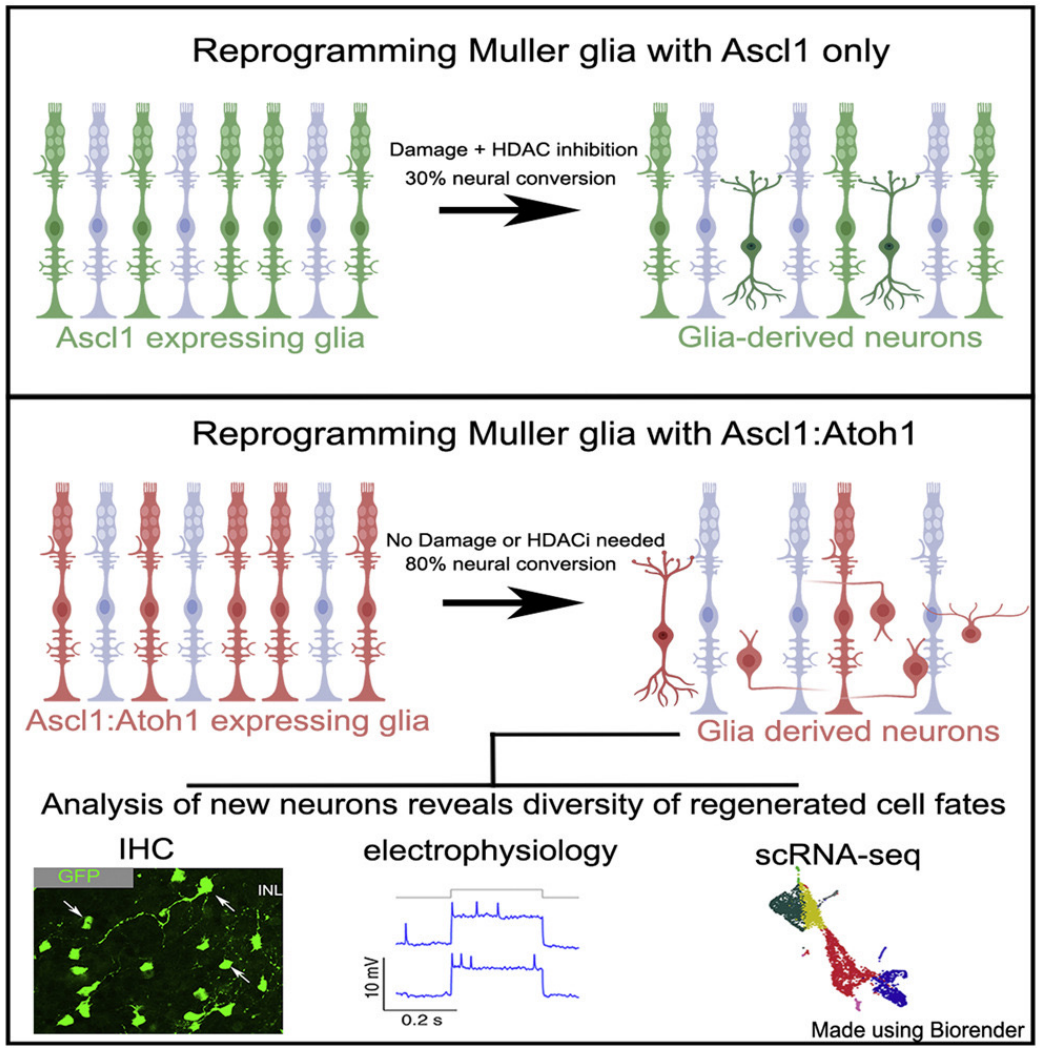
Authors

Ye Xie, Jing Zhou, Bo Chen

- AAV-based Cre recombination is unsuitable for examining MG-to-RGC conversion
- Lineage-traced MG are not converted into RGCs after *Ptbp1* downregulation
- NMDA-induced injury does not facilitate MG-to-RGC conversion after *Ptbp1* downregulation
- Stringent fate mapping is required for critical examination of glia-to-neuron conversion



Cell Reports 2022 39DOI: (10.1016/j.celrep.2022.110960)



Cell Reports 2021 37DOI: (10.1016/j.celrep.2021.109857)

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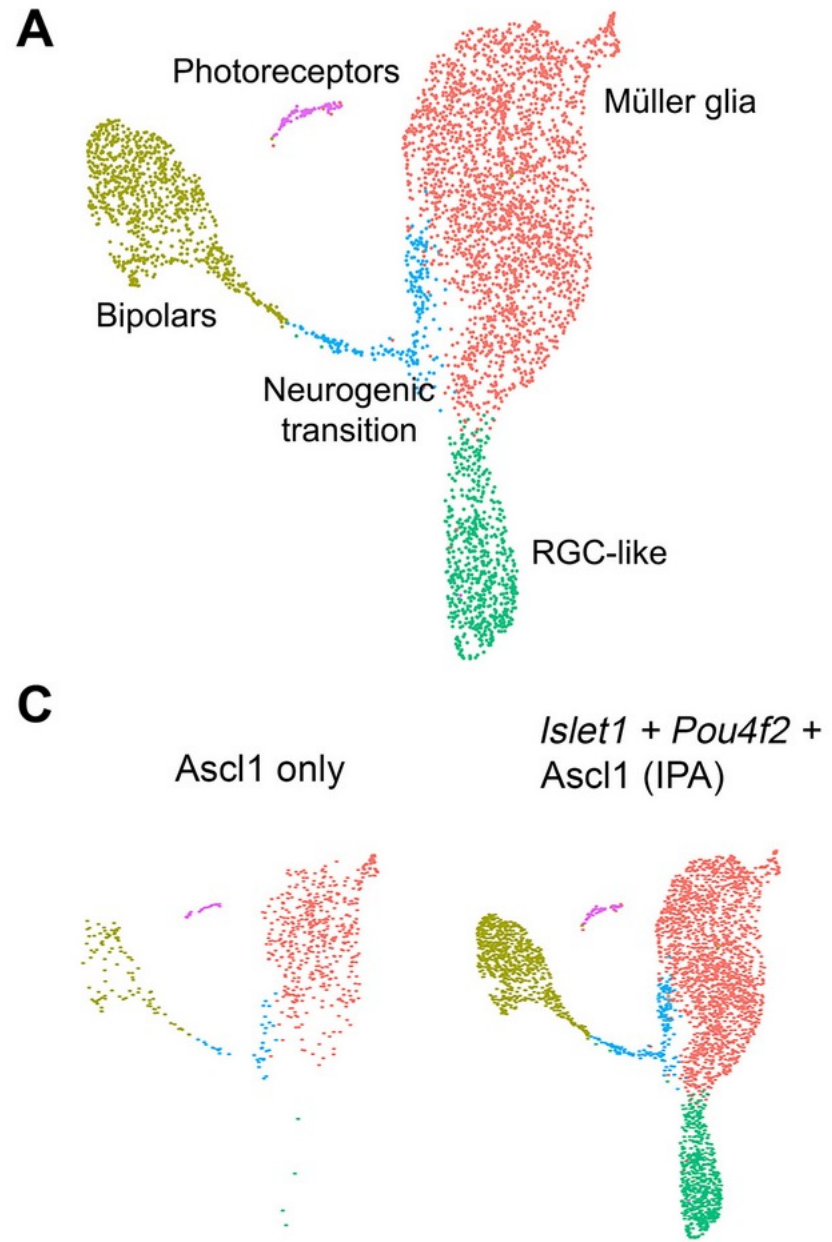
HOME > SCIENCE ADVANCES > VOL. 8, NO. 47 > REPROGRAMMING MÜLLER GLIA TO REGENERATE GANGLION-LIKE CELLS IN ADULT MOUSE RETINA WITH DE-...

RESEARCH ARTICLE | DEVELOPMENTAL BIOLOGY

Reprogramming Müller glia to regenerate ganglion-like cells in adult mouse retina with developmental transcription factors

LEVI TODD, WESLEY JENKINS, CONNOR FINKBEINER, MARCUS J. HOOPER, PHOEBE C. DONALDSON, MARINA PAVLOU, JULIETTE WOHLSCHLEGEL, NORIANNE INGRAM, FRED RIEKE, AND THOMAS A. REH Authors Info & Affiliations

SCIENCE ADVANCES • 23 Nov 2022 • Vol 8, Issue 47 • DOI: 10.1126/sciadv.abq7219



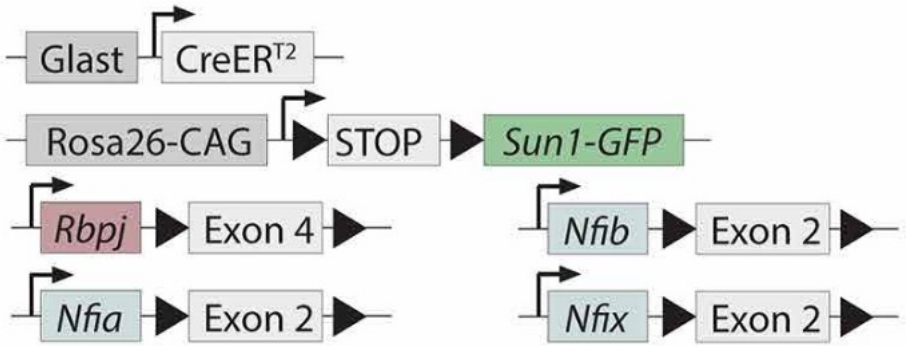
SCIENCE ADVANCES | RESEARCH ARTICLE

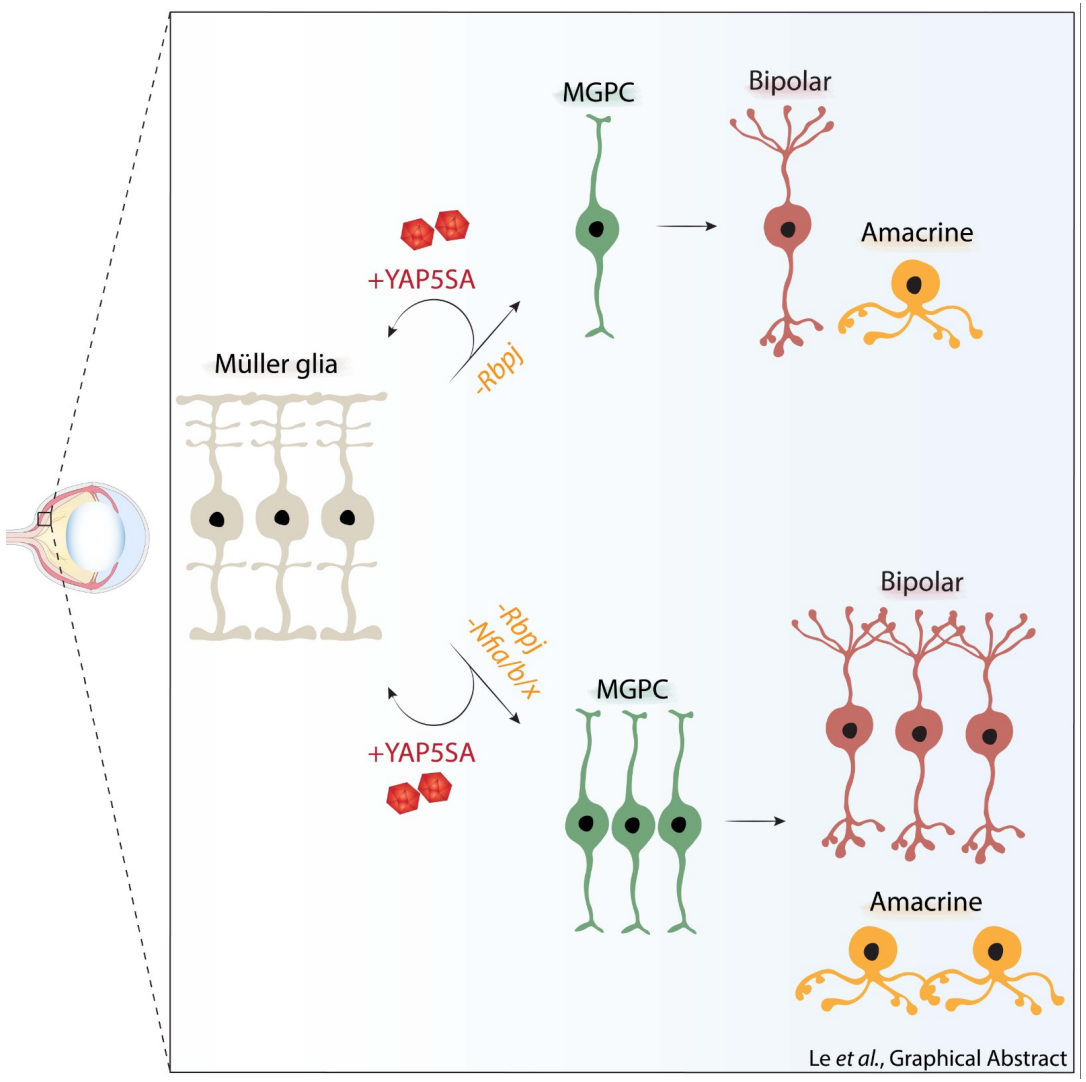
REGENERATION

Robust reprogramming of glia into neurons by inhibition of Notch signaling and nuclear factor I (NFI) factors in adult mammalian retina

Nguyet Le[1], Trieu-Duc Vu[2,3], Isabella Palazzo[1], Ritvik Pulya[1], Yehna Kim[1], Seth Blackshaw[1,4,5,6,7]*, Thanh Hoang[2,3,8]*

July 2024





AAV-mediated expression of proneural factors stimulates neurogenesis from adult Müller glia *in vivo*

Marina Pavlou, Marlene Probst, Elizaveta Filippova, Lew Kaplan, Aric R. Prieve, Fred Rieke, Thomas A. Reh

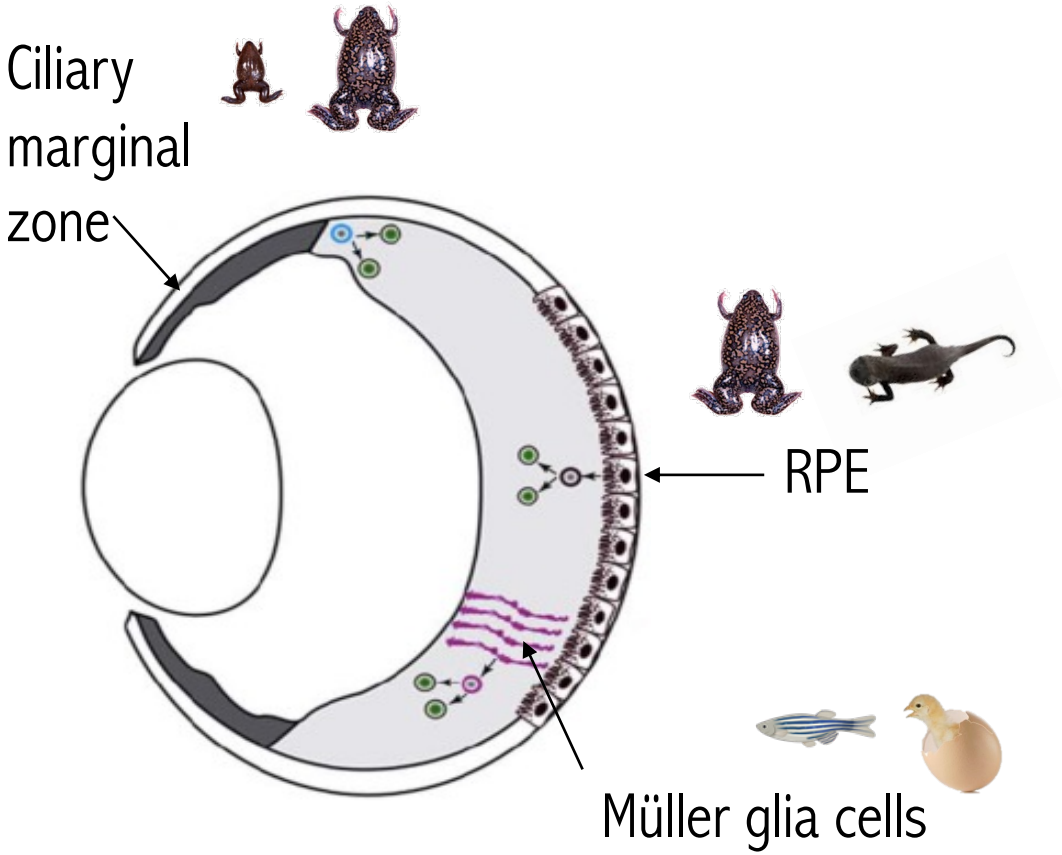
bioRxiv
THE PREPRINT SERVER FOR BIOLOGY
Posted September 15, 2024

Viral-mediated Oct4 overexpression and inhibition of Notch signaling synergistically induce neurogenic competence in mammalian Muller glia.

Nguyet Le, Sherine Awad, Isabella Palazzo, Thanh Hoang, Seth Blackshaw

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY
Posted September 19, 2024

key step forward in developing a cellular reprogramming approach to regenerative medicine

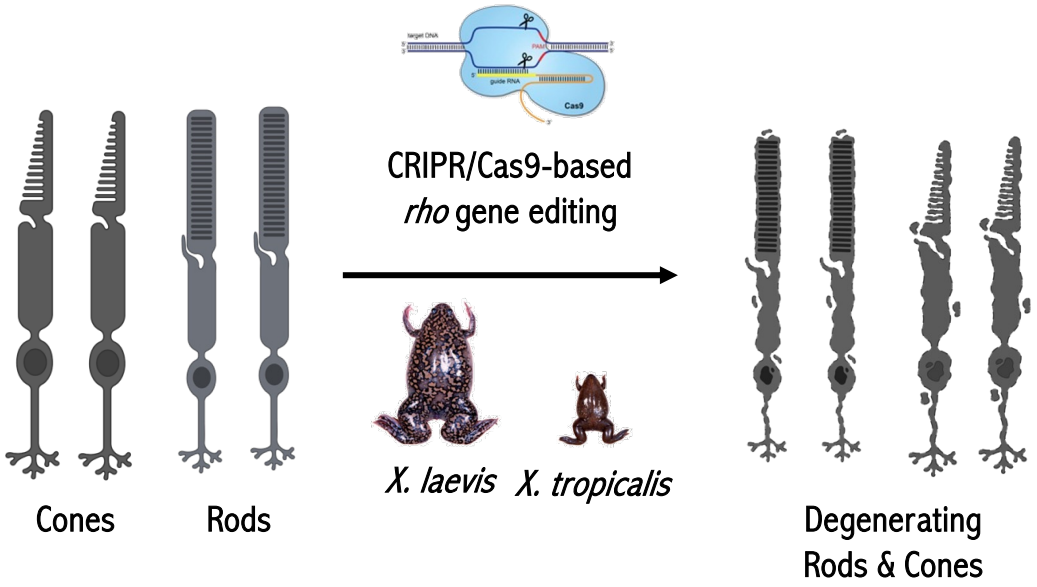


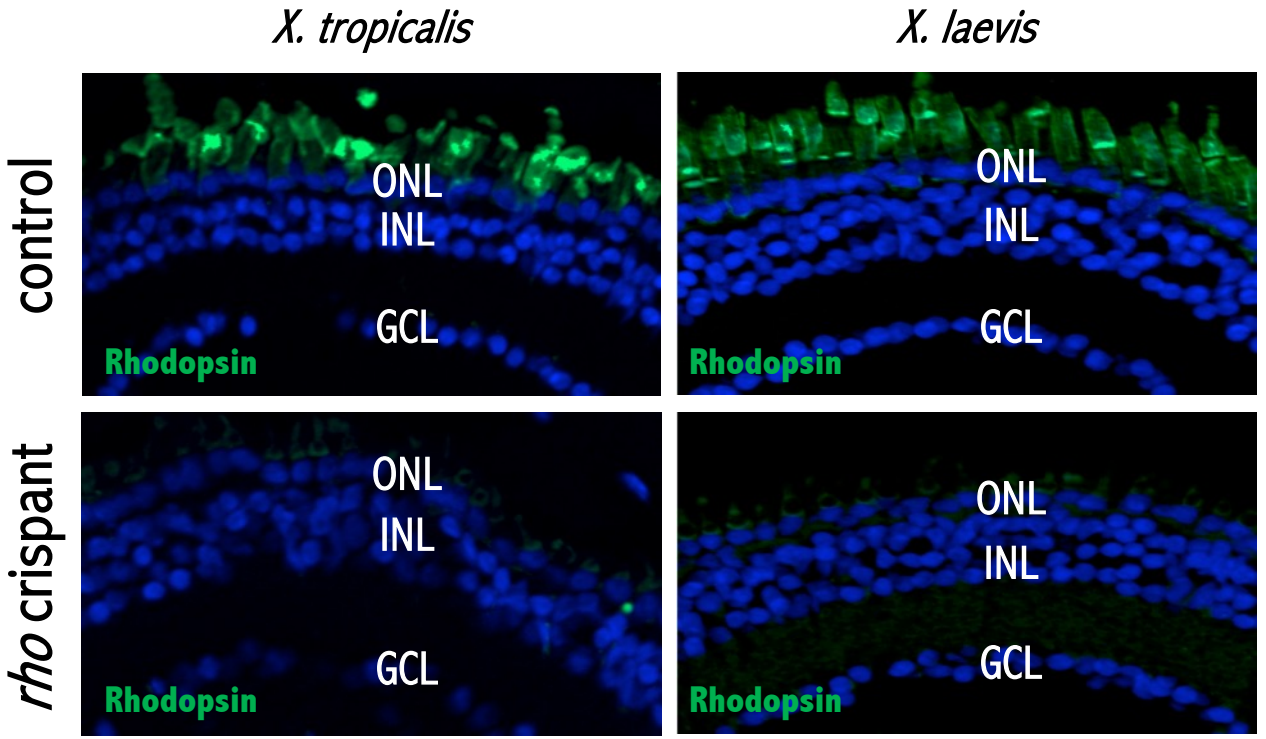
Retinectomy
- *X. laevis* → RPE + CMZ
- *X. tropicalis* → CMZ

Do Müller cells from *X. laevis* and *X. tropicalis* respond similarly to retinal injury?

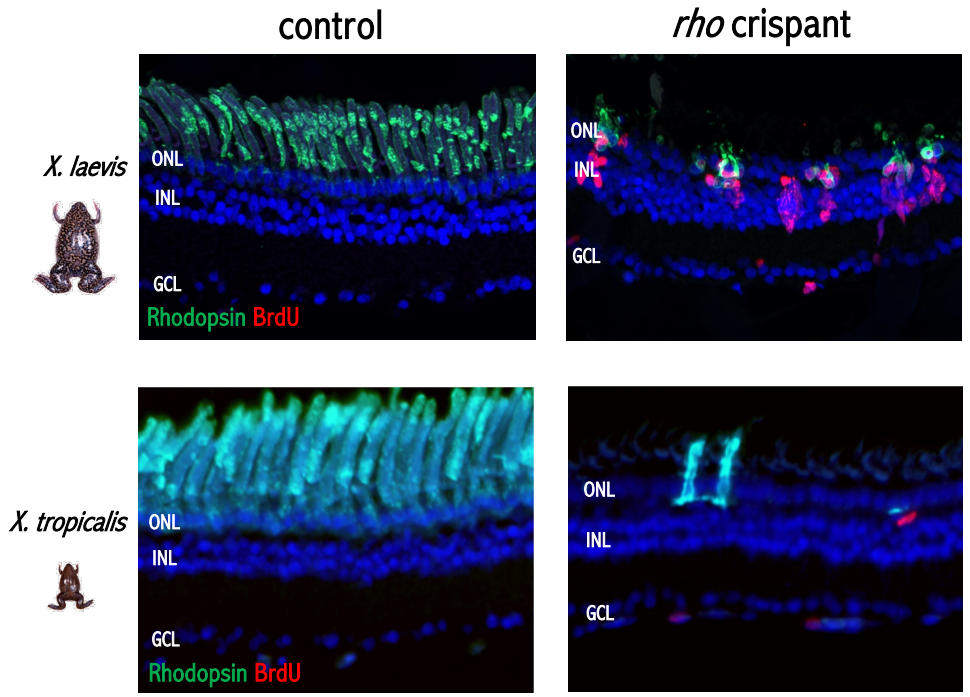
Adapted from Karl & Reh 2010

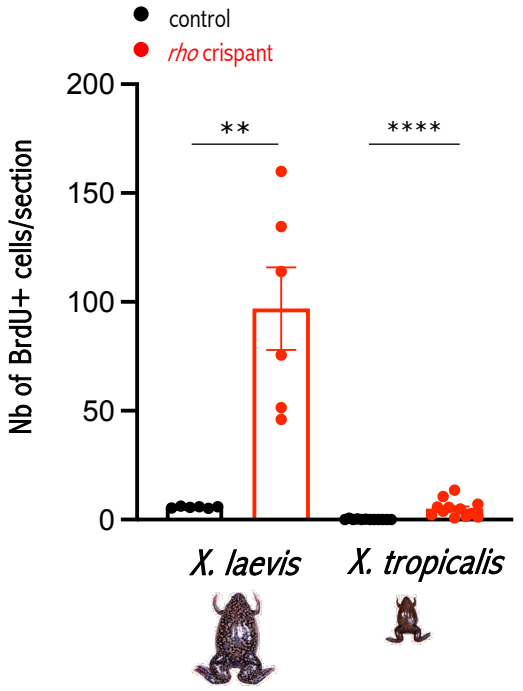
CRISPR-dependent photoreceptor degeneration as a model of retinitis pigmentosa

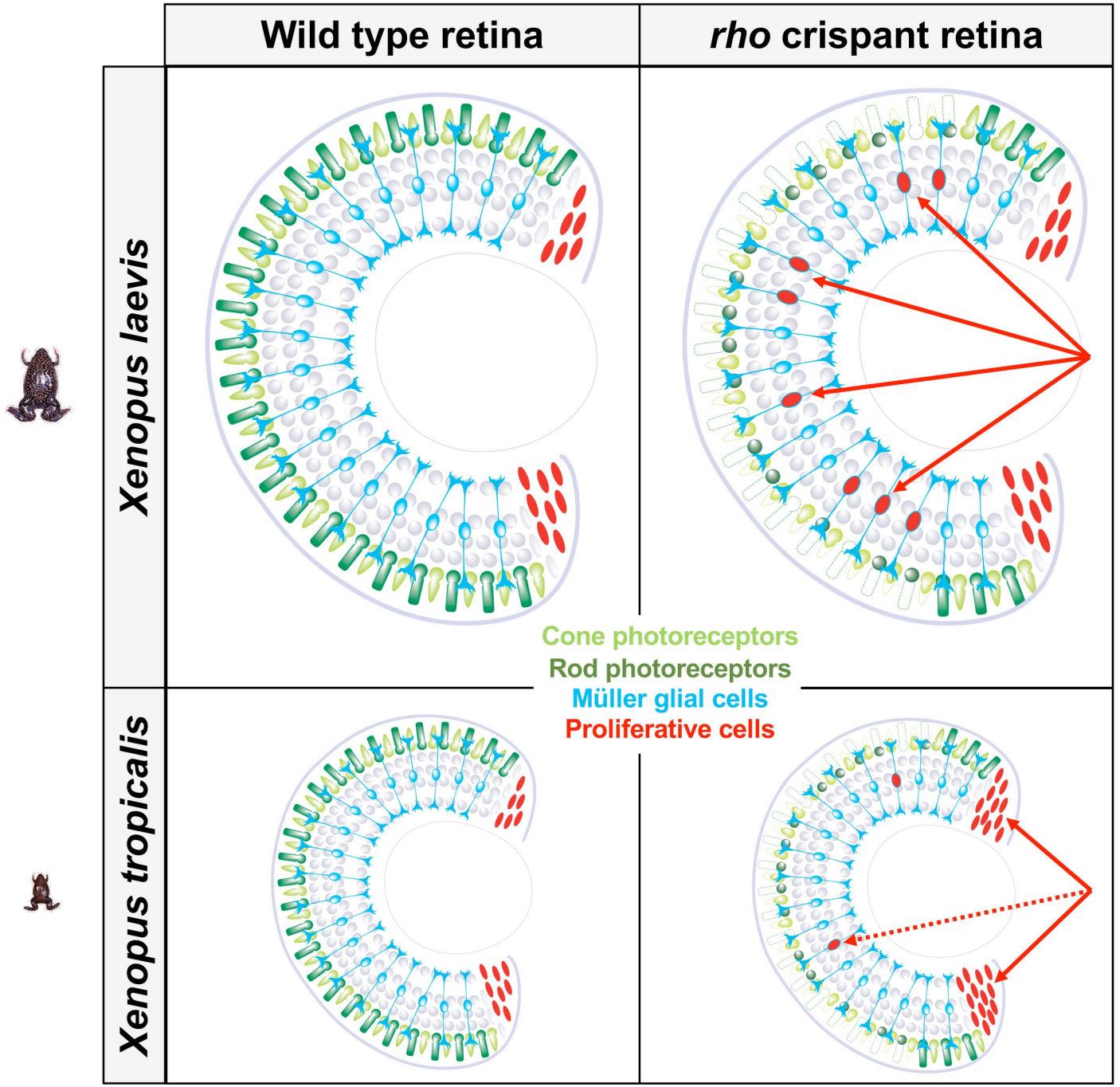




Müller cell response to photoreceptor degeneration in *X. laevis* and *X. tropicalis*



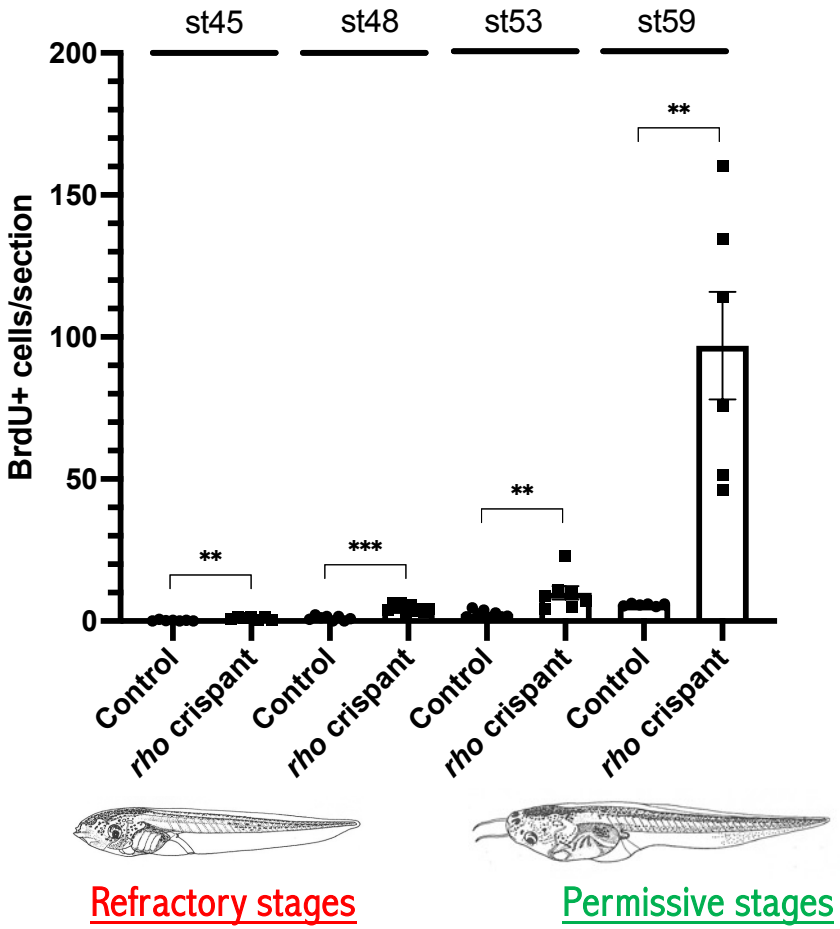




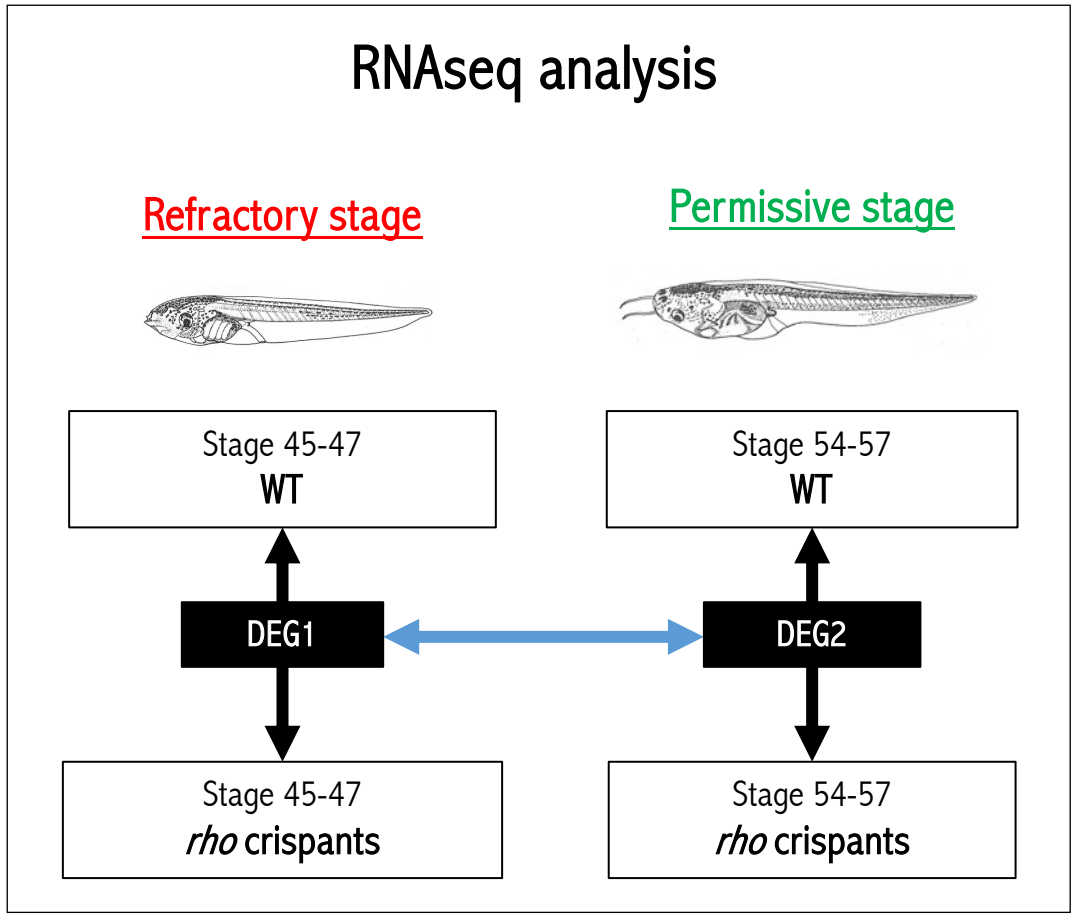
Parain et al. Cells 2022

Müller cell response also differs at different stages in *X. laevis*

X. laevis



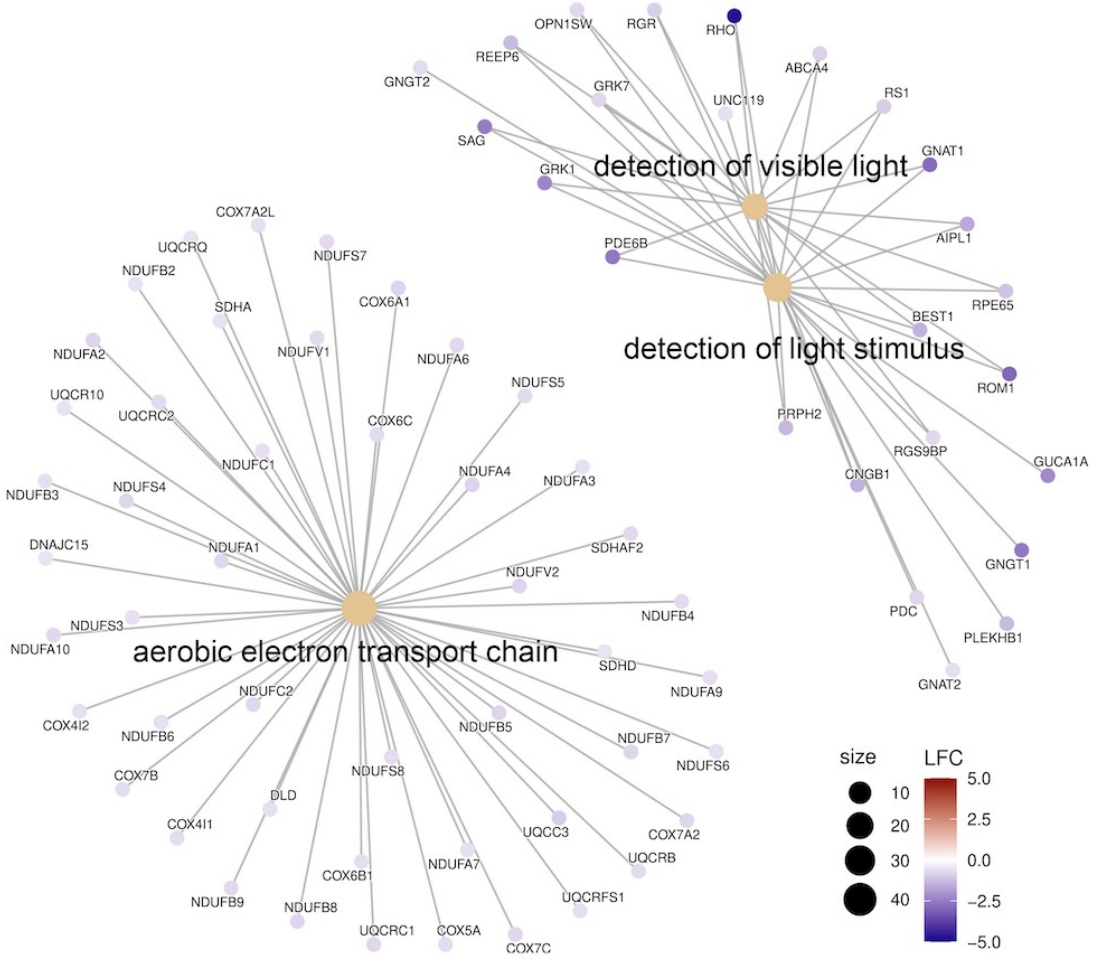
Comparing the transcriptome following injury at refractory and permissive stages

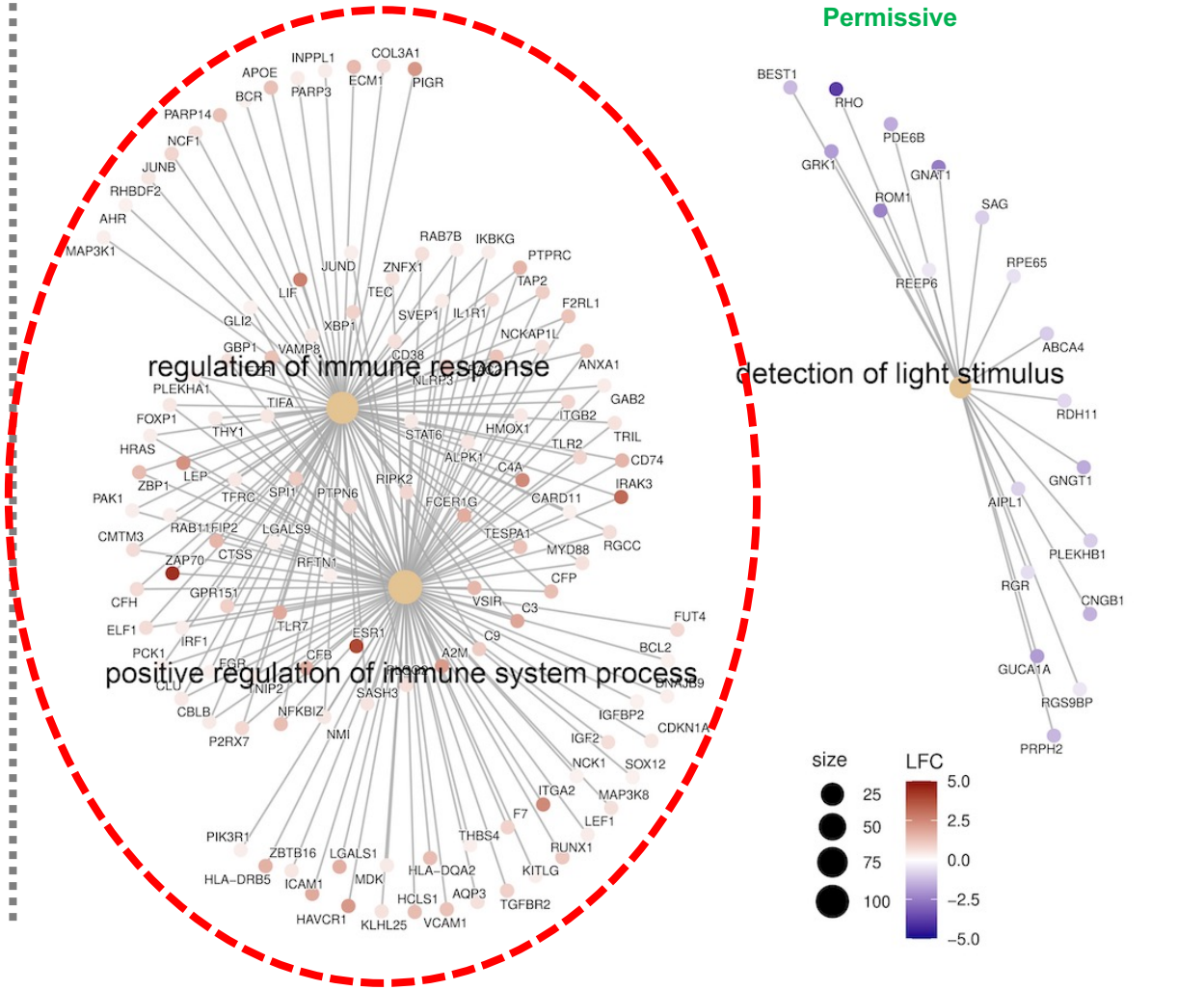


Immune response is upregulated only at permissive stages following injury

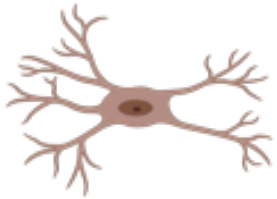
Refractory

Permissive

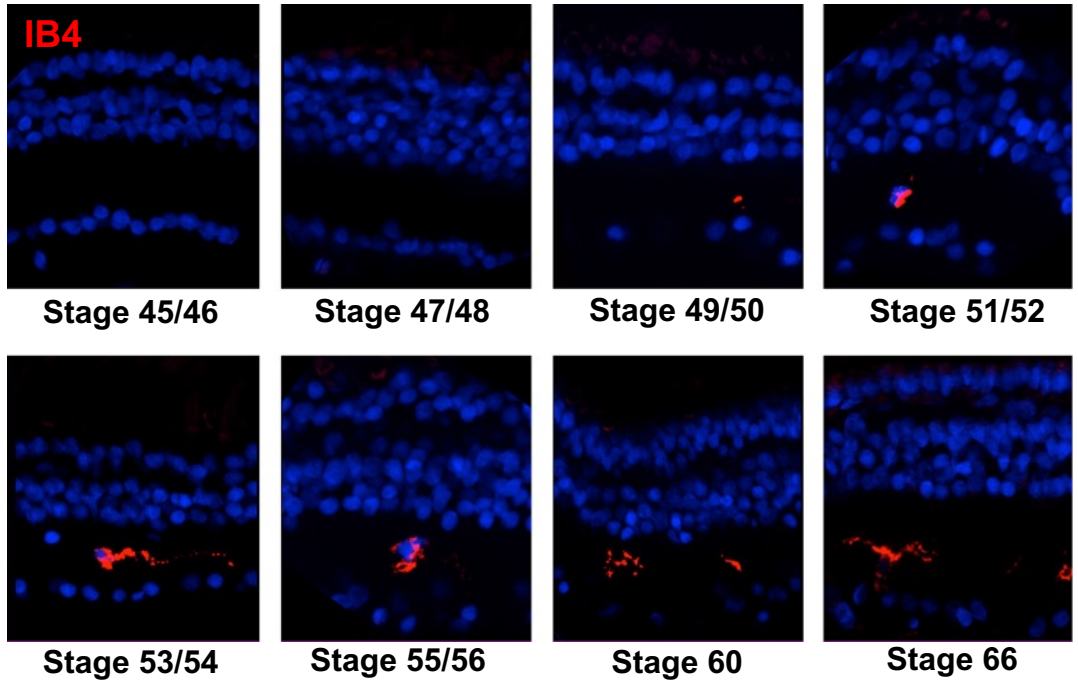




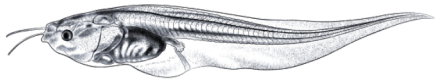
Evolution of microglia at different stages in physiological conditions



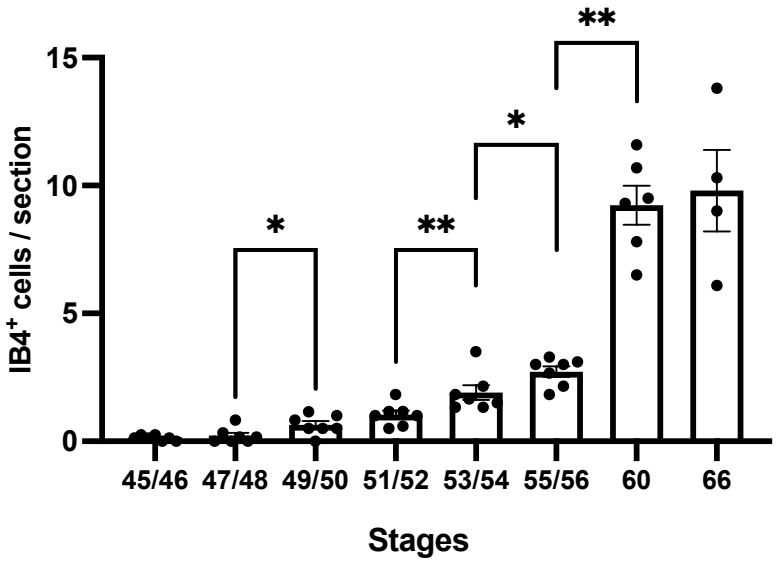
Microglia



Refractory stages



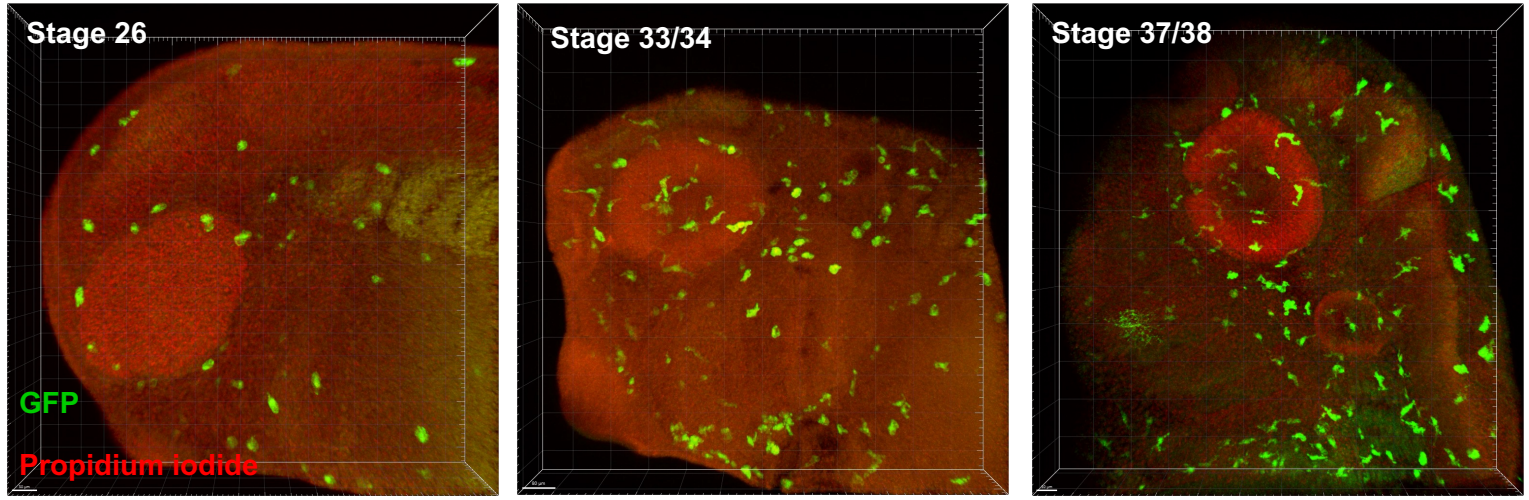
Permissive stages

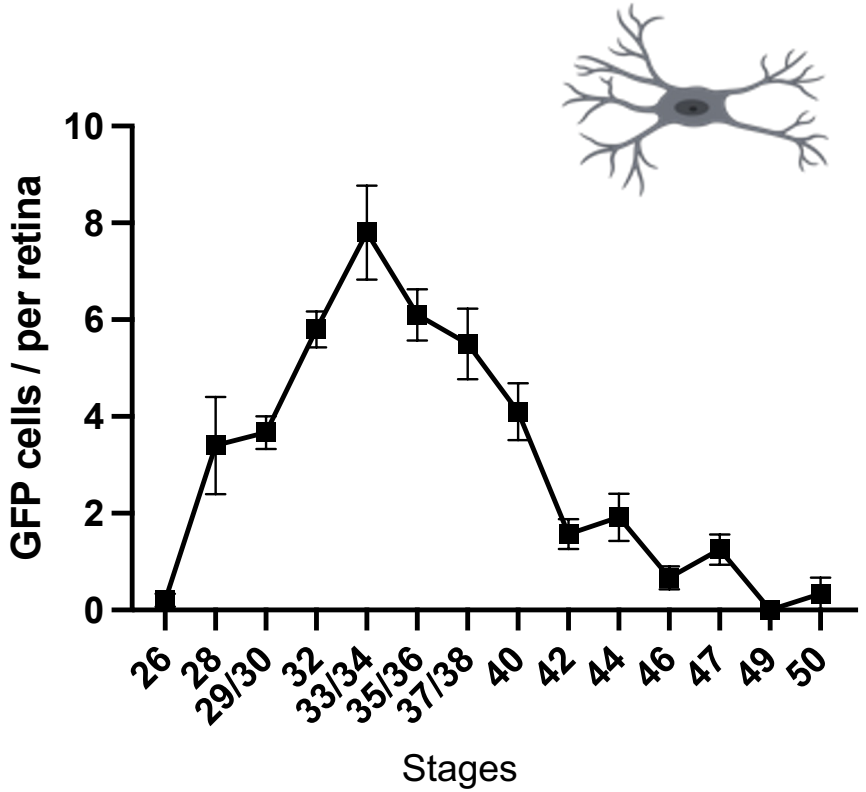


Retinal infiltration with microglia coincides with a shift in the proliferative capacity of Müller cells

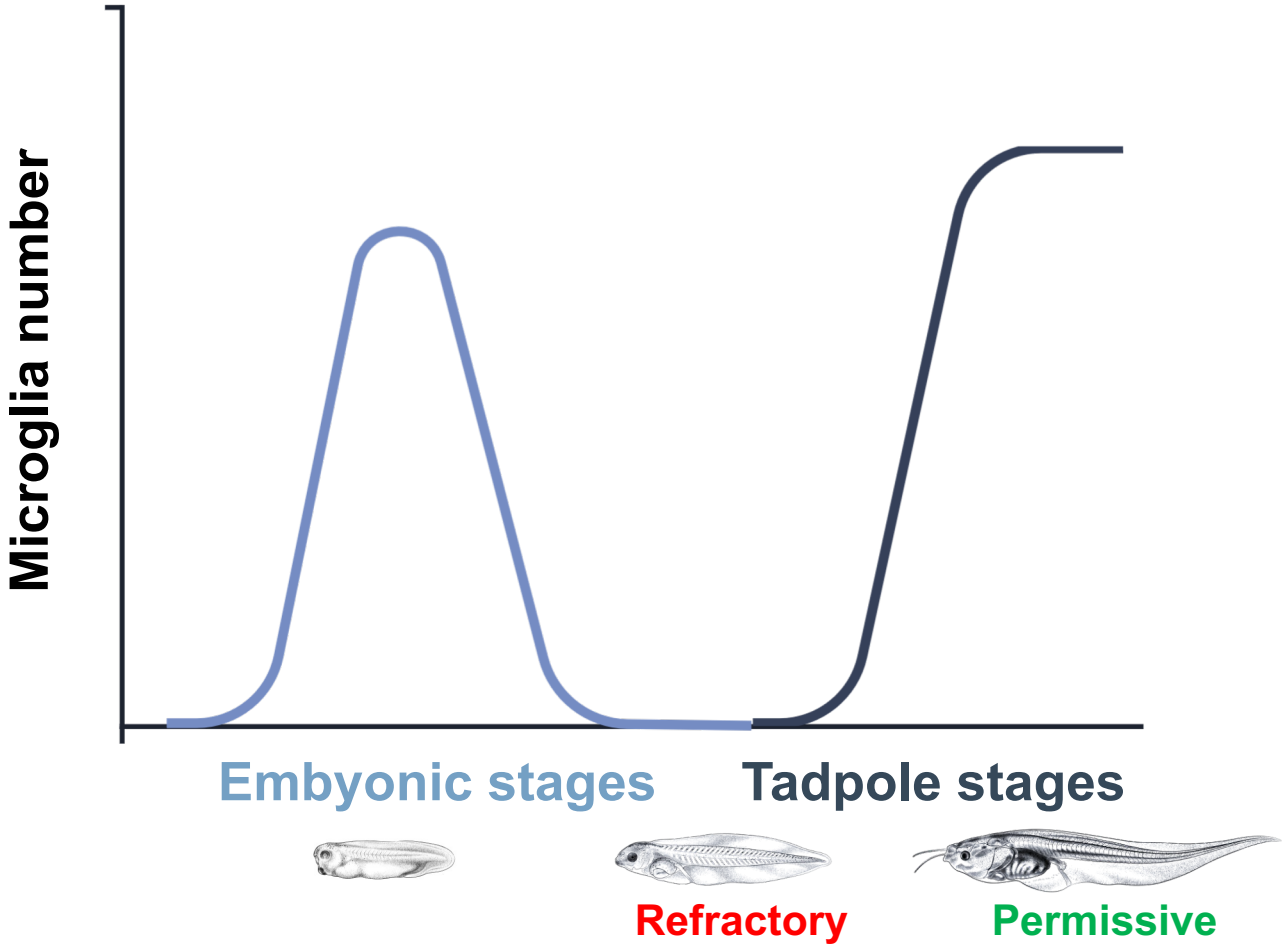
Dynamic retinal colonization of microglia during development

lurp1:GFP (from Jacques Robert, University of Rochester)





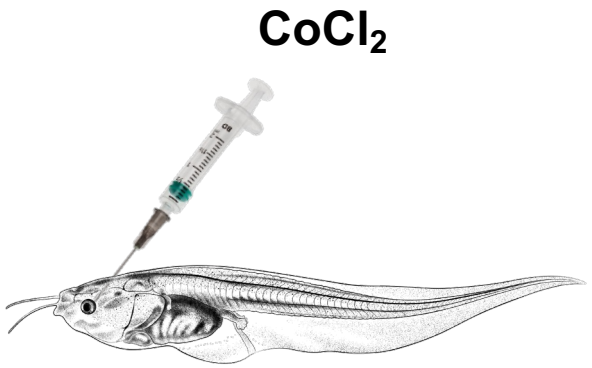
Two waves of microglia colonization in the *Xenopus* retina

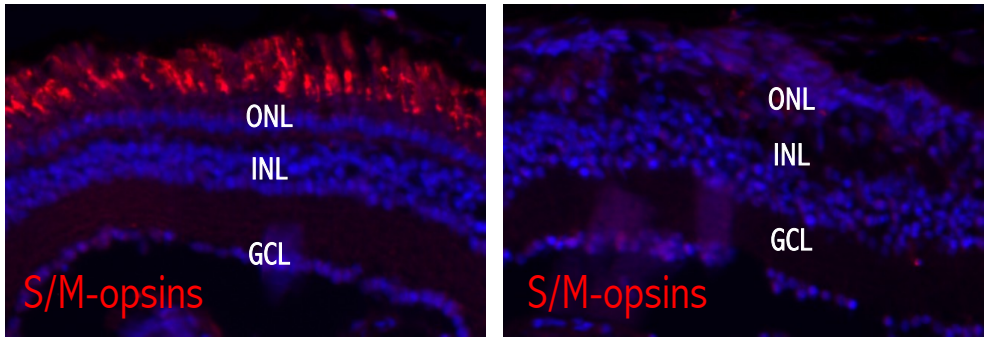


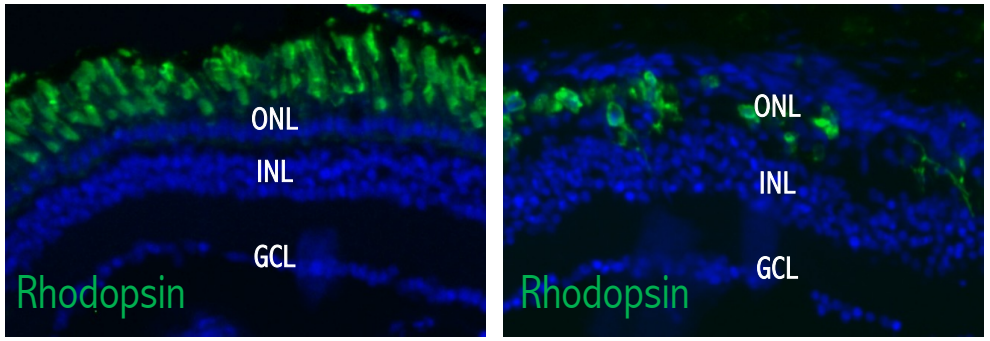
Are Müller cells refractory because of a limited inflammatory microenvironment?

Can we trigger Müller cell proliferative response at the refractory stage by generating neuroinflammation?

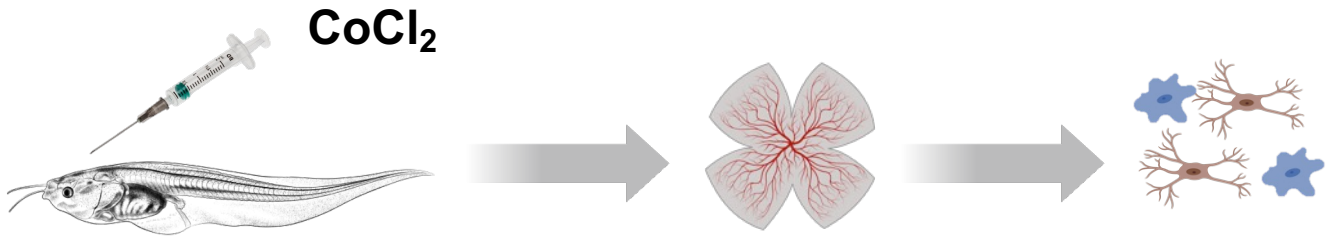
$CoCl_2$: a novel model to induce retinal degeneration in *Xenopus*



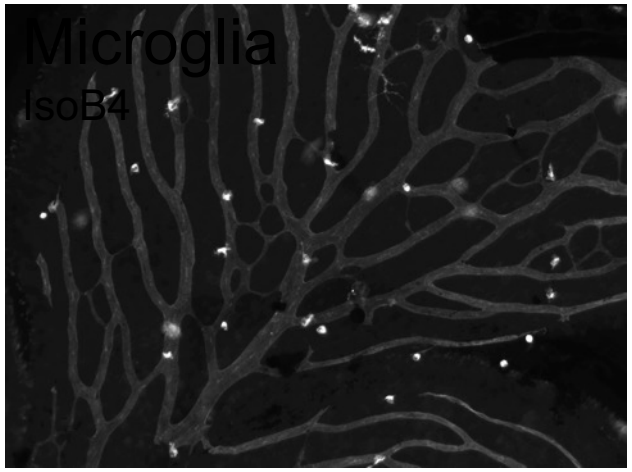




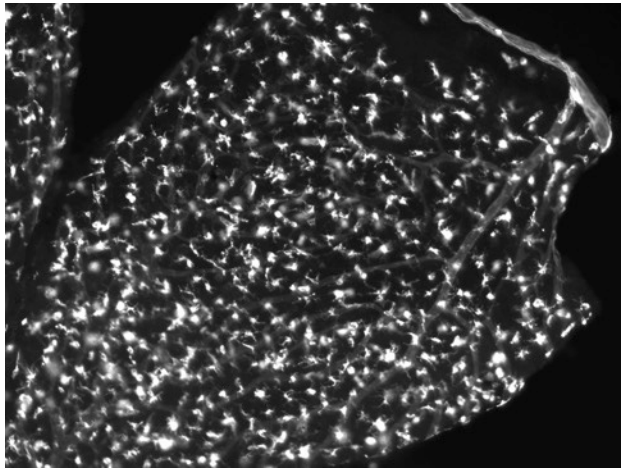
$CoCl_2$ intraocular injections leads to a severe inflammatory response

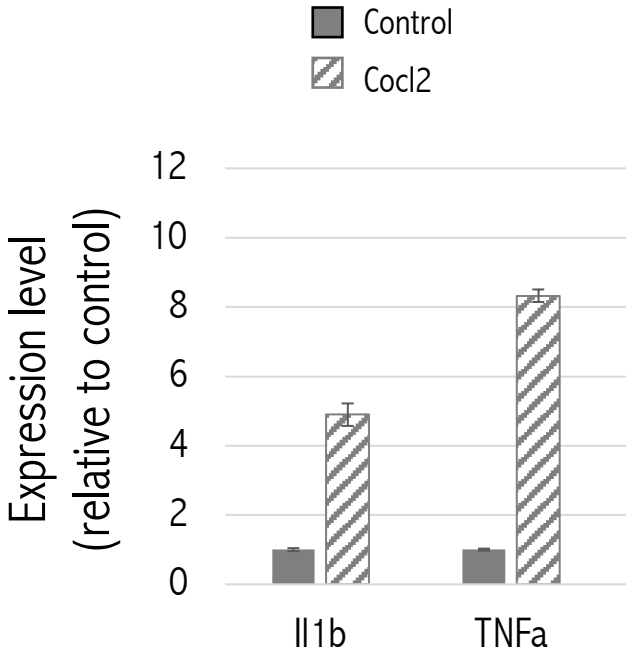


Control

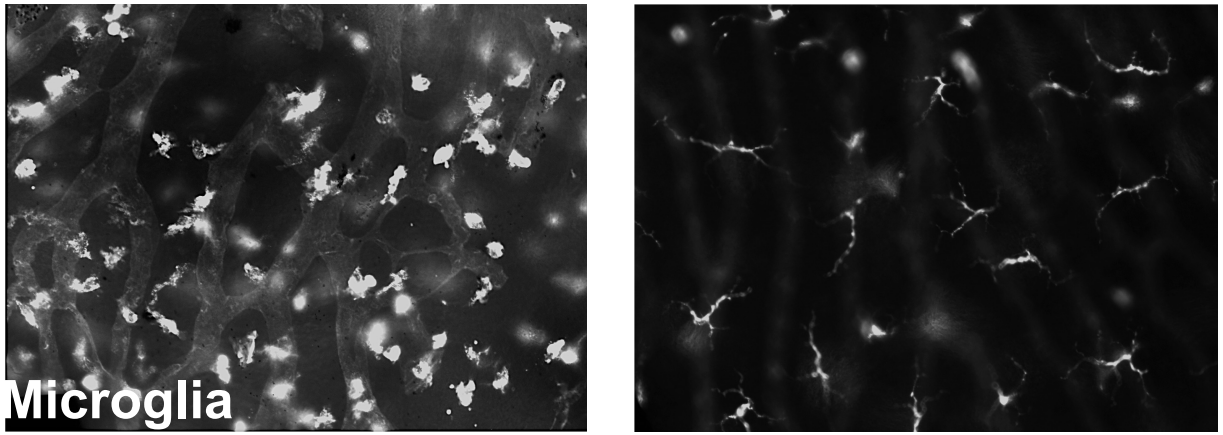


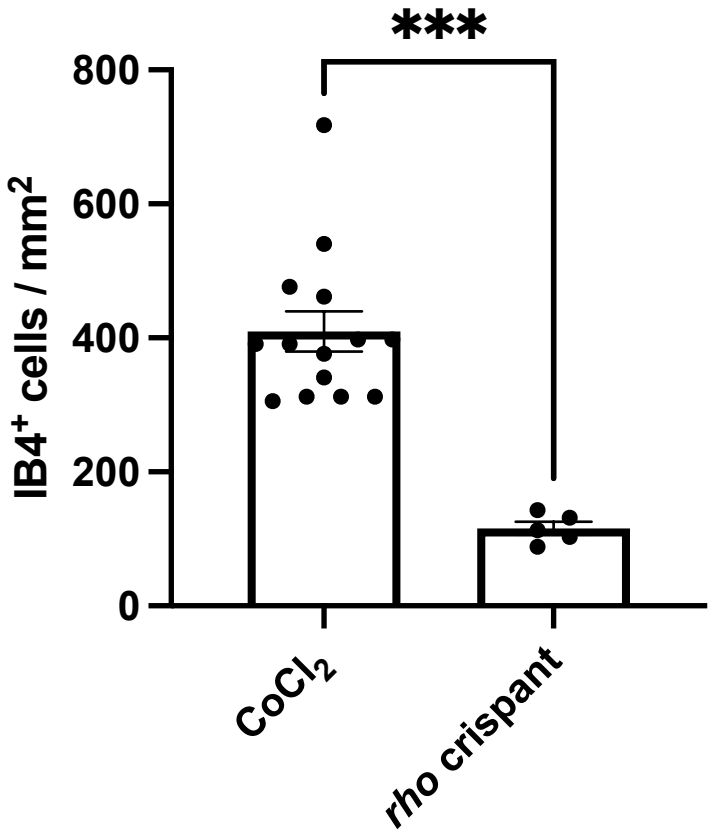
$CoCl_2$





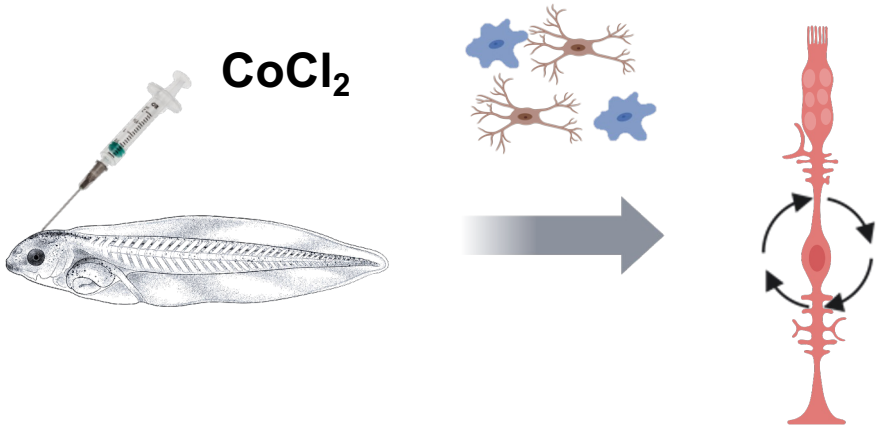
The increase in microglia is higher in $CoCl_2$ tadpoles than in *rho* crispant

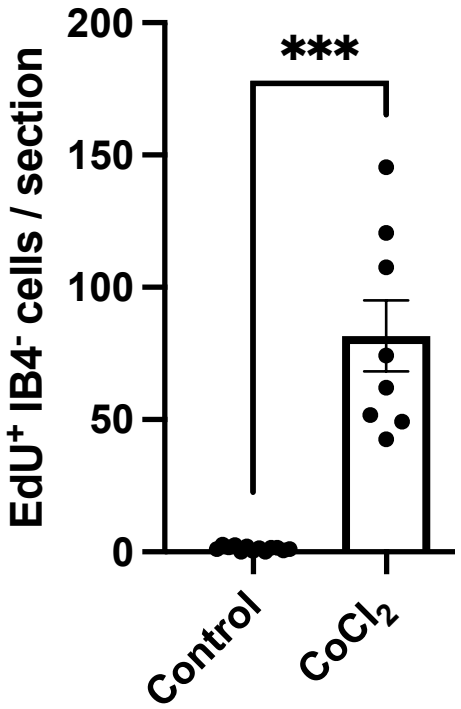




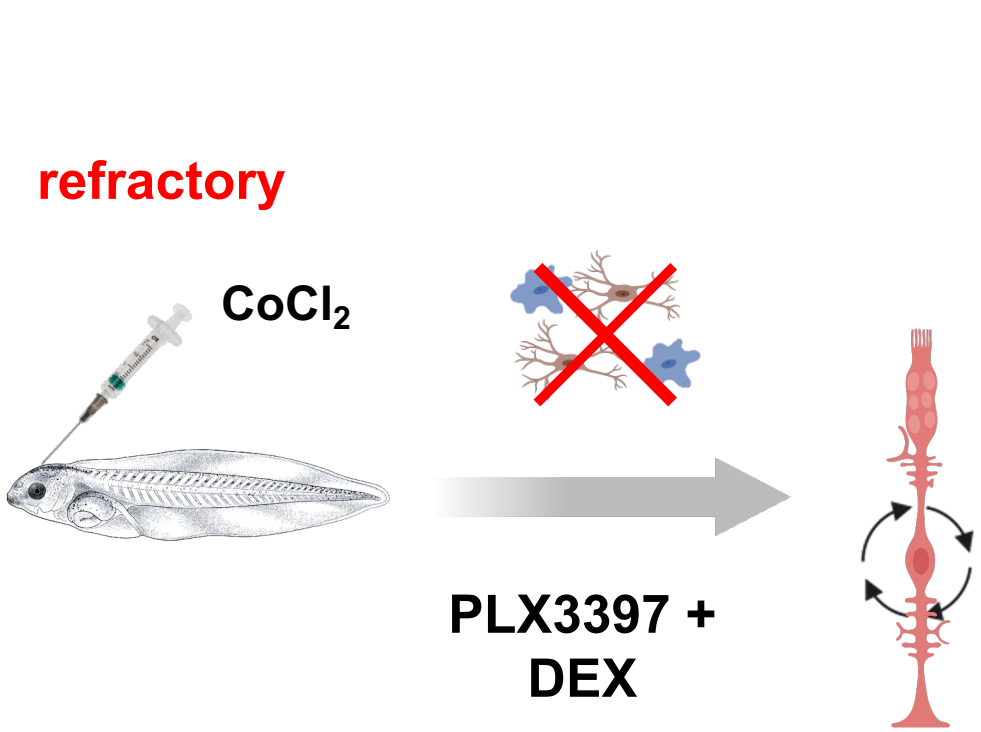
Microglia activation triggers a proliferation response of refractory Müller cells

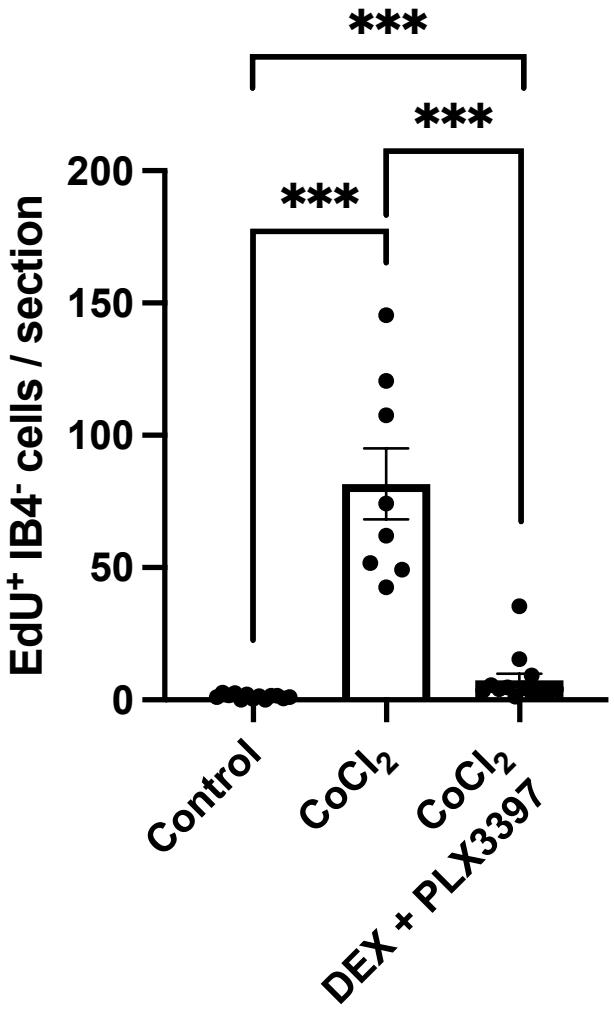
refractory

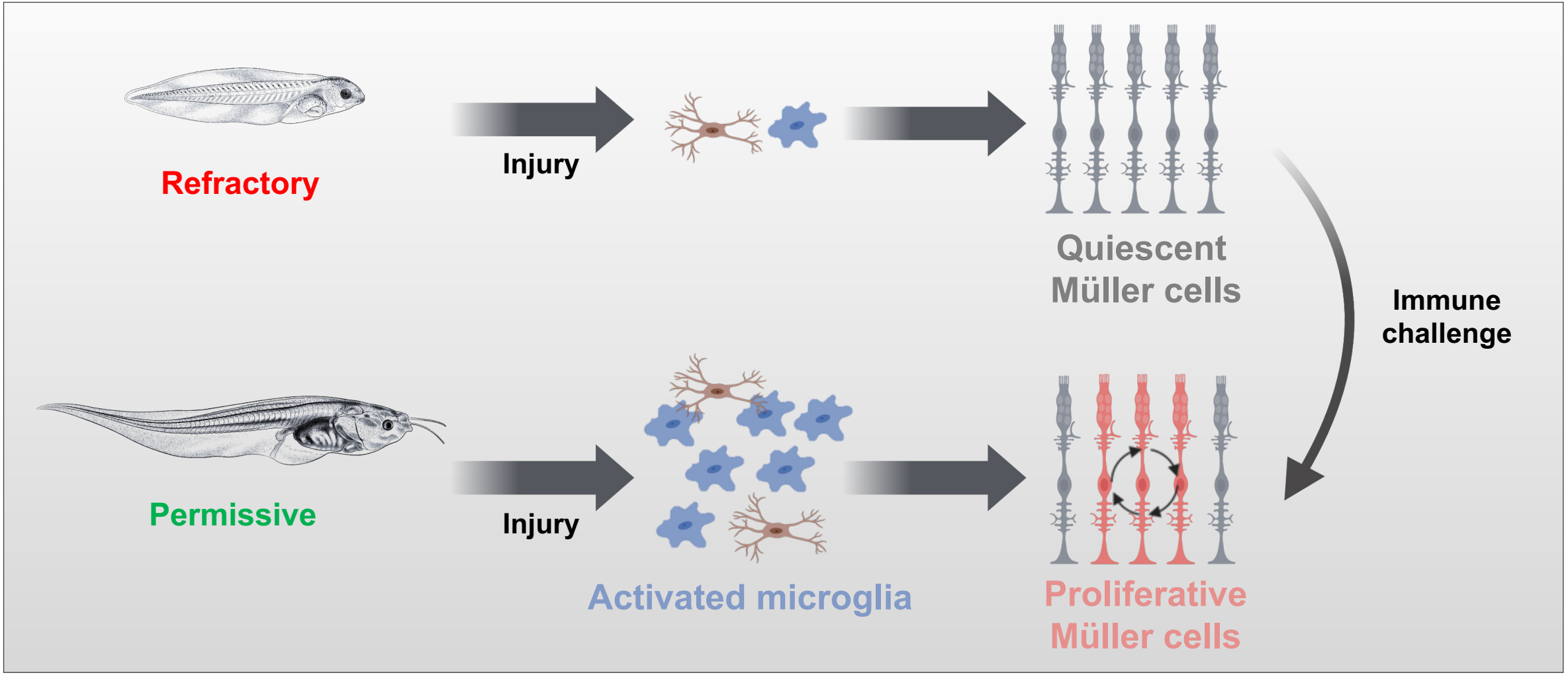




Microglia activation mediates $CoCl_2$ dependent proliferative response of refractory Müller cells







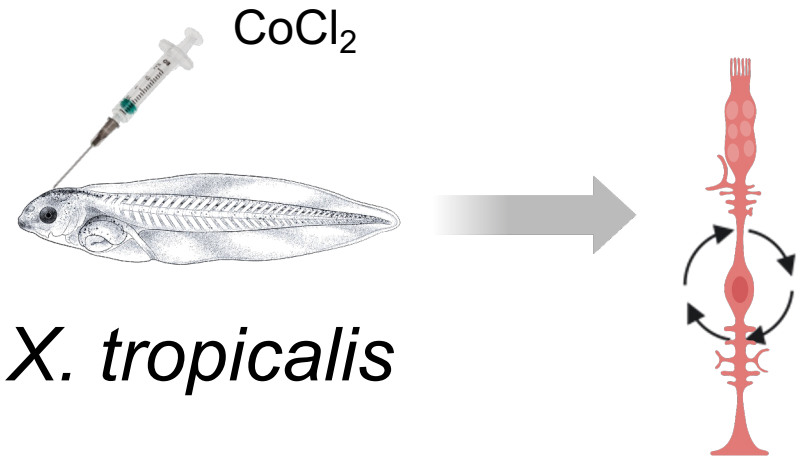
Unpublished

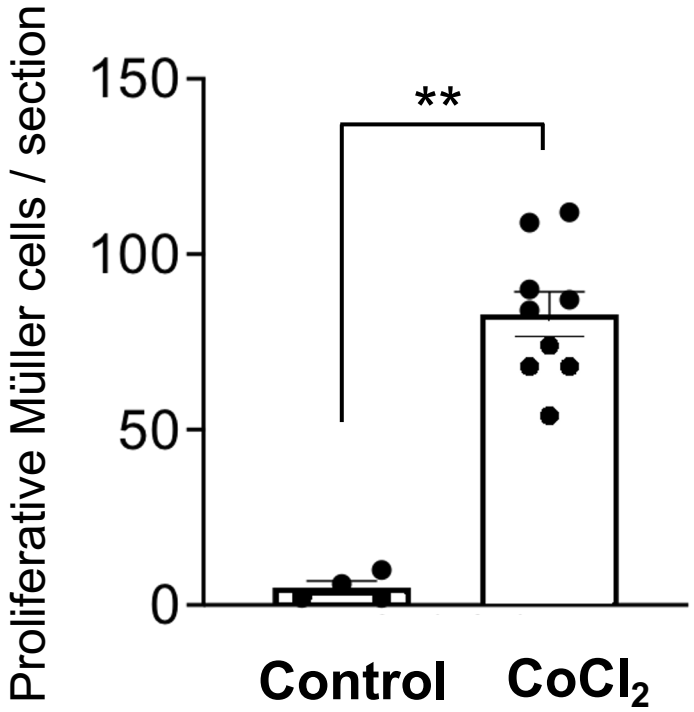
Can an immune challenge awake refractory Müller cells in other species?

X. tropicalis

Mouse

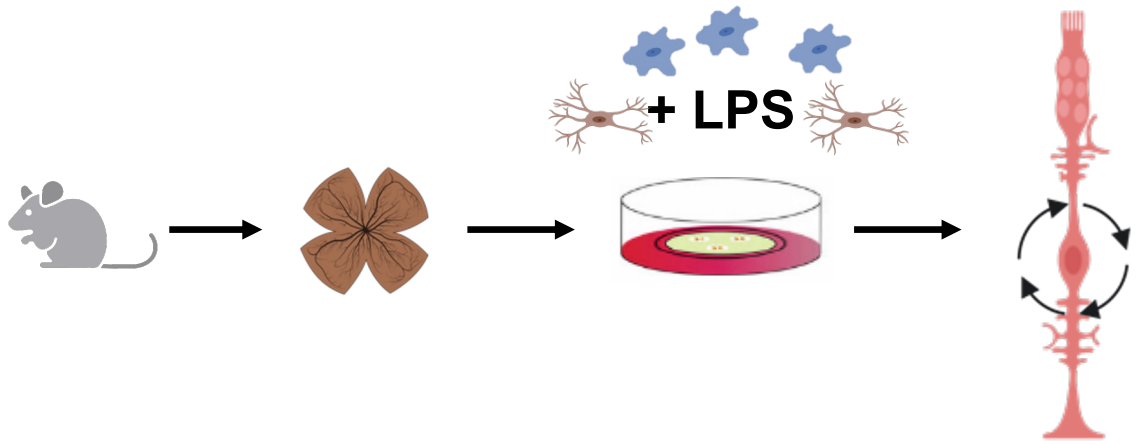
$CoCl_2$ triggers a proliferation response of *X. tropicalis* Müller cells

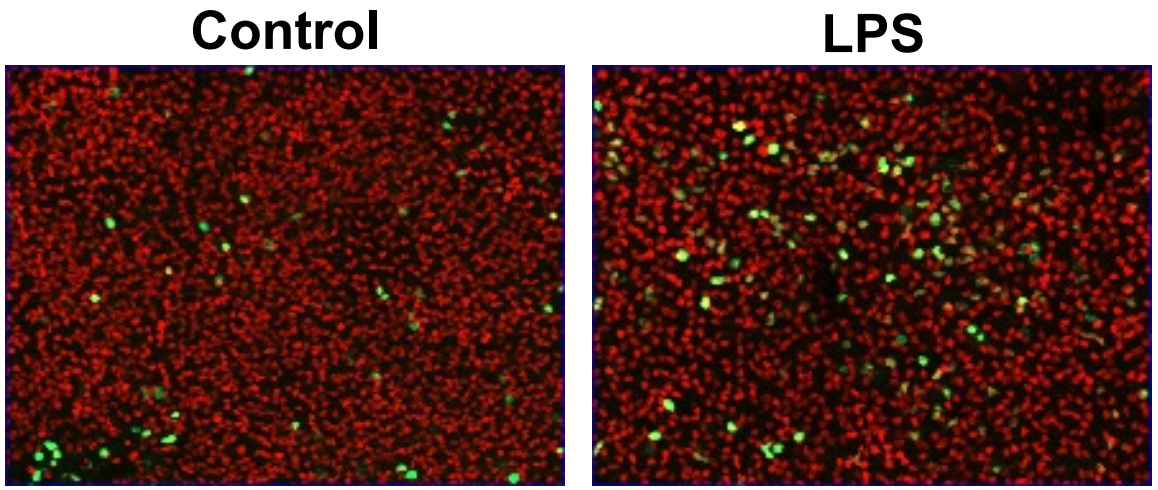


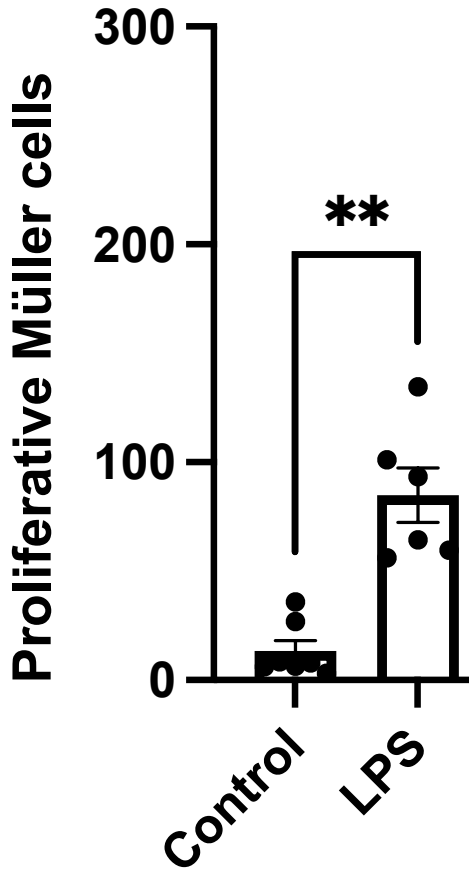


Parain et al., Glia 2024

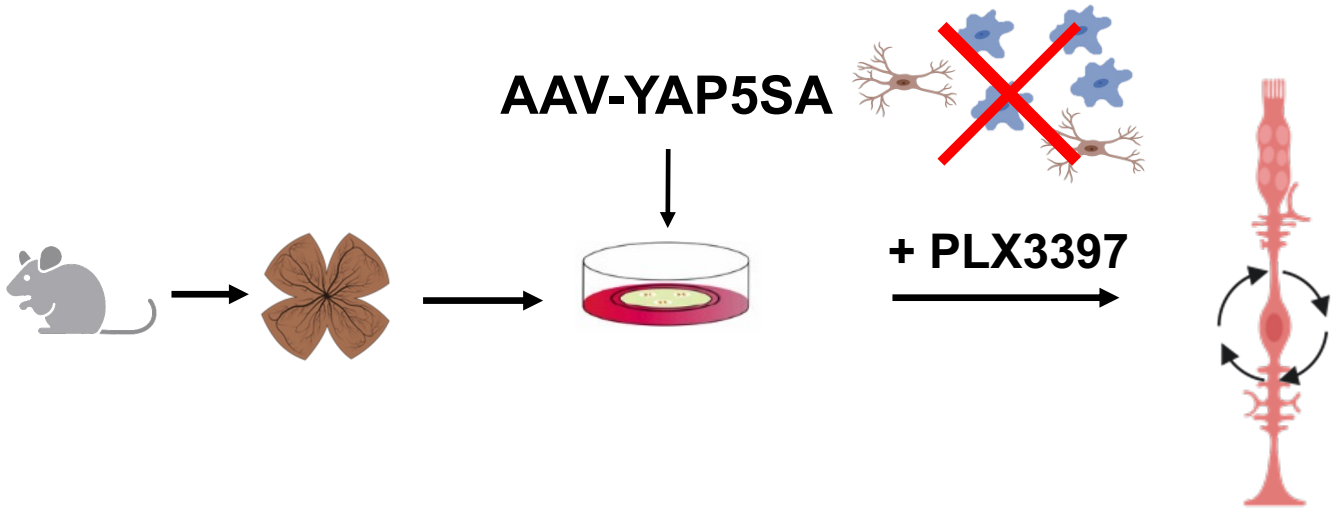
An immune challenge promotes mouse Müller cell proliferation

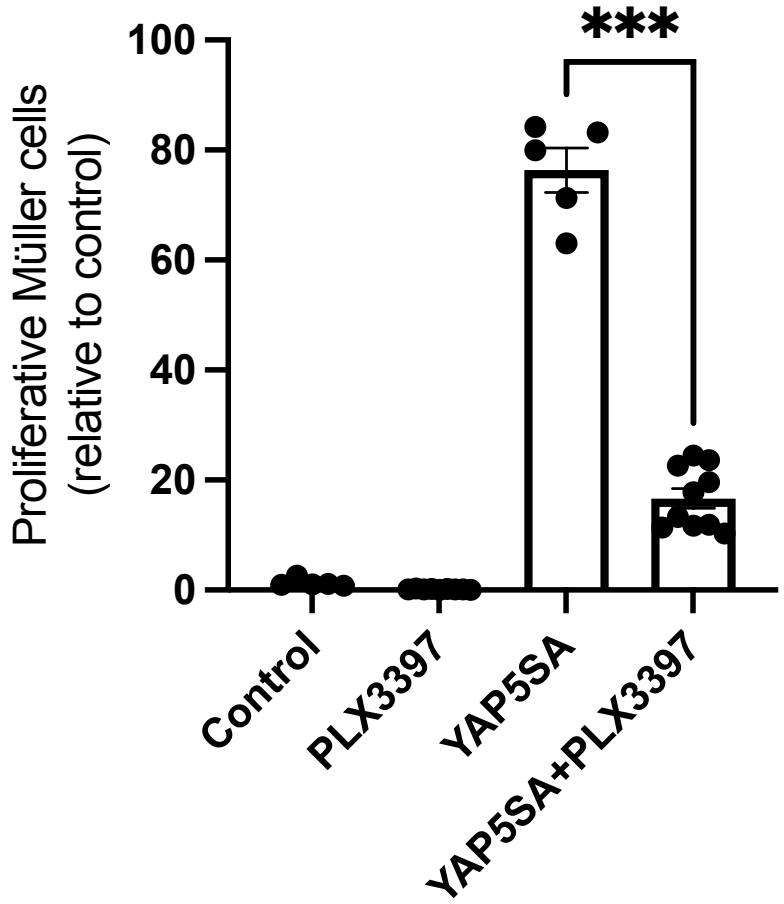






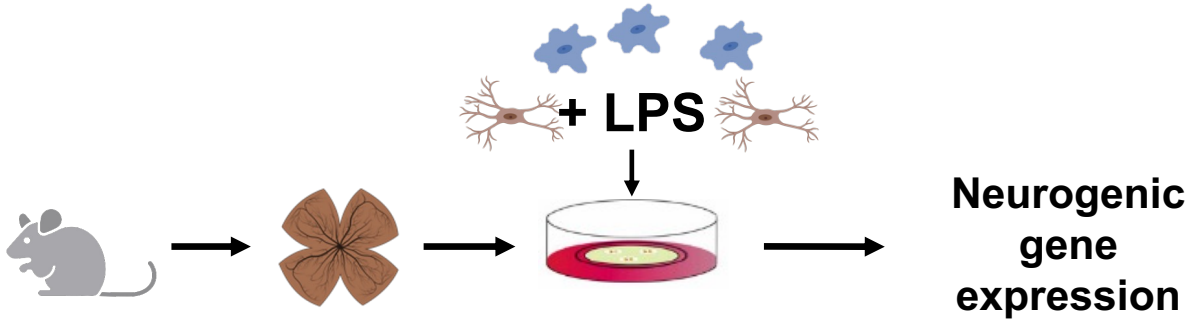
Microglia are necessary for YAP-dependent proliferative effects on Müller cells

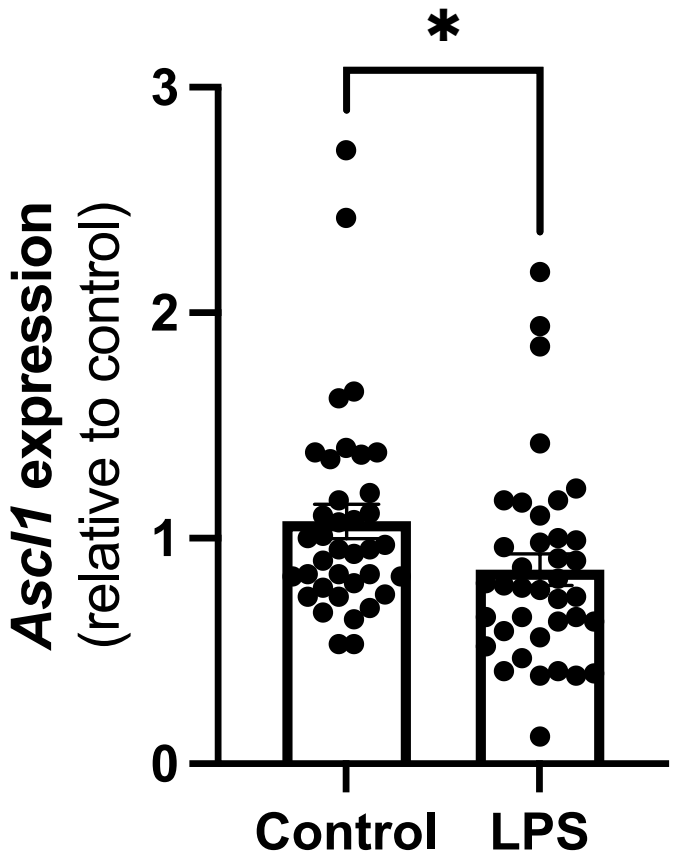




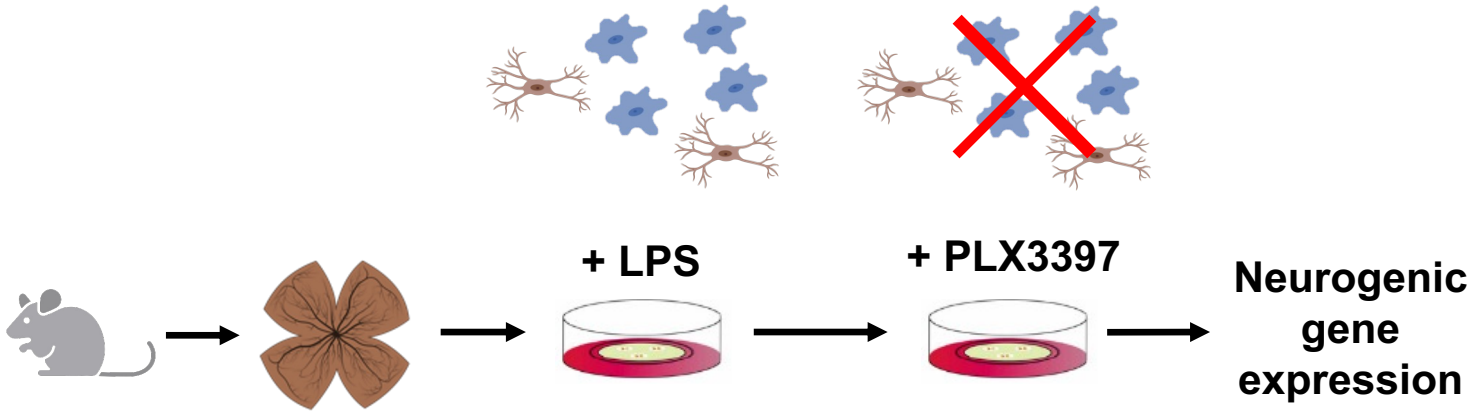
What about the neurogenic potential of LPS-induced proliferative Müller glia?

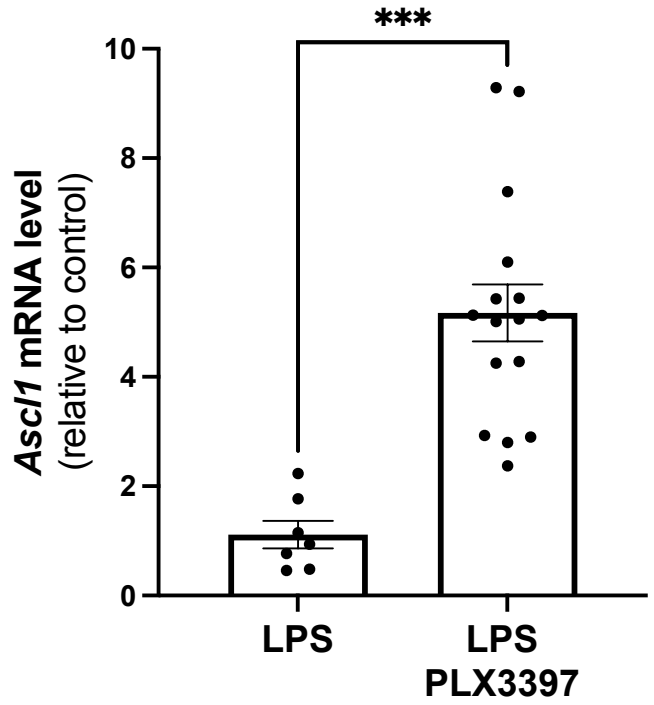
LPS-induced proliferative Müller cell are not neurogenic

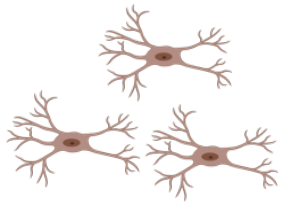




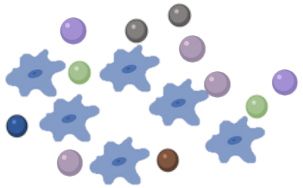
Ablation of microglia following an immune challenge triggers *Ascl1* expression





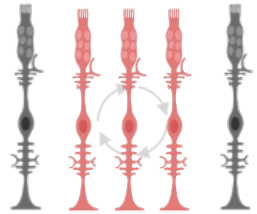


Microglia



Activated microglia

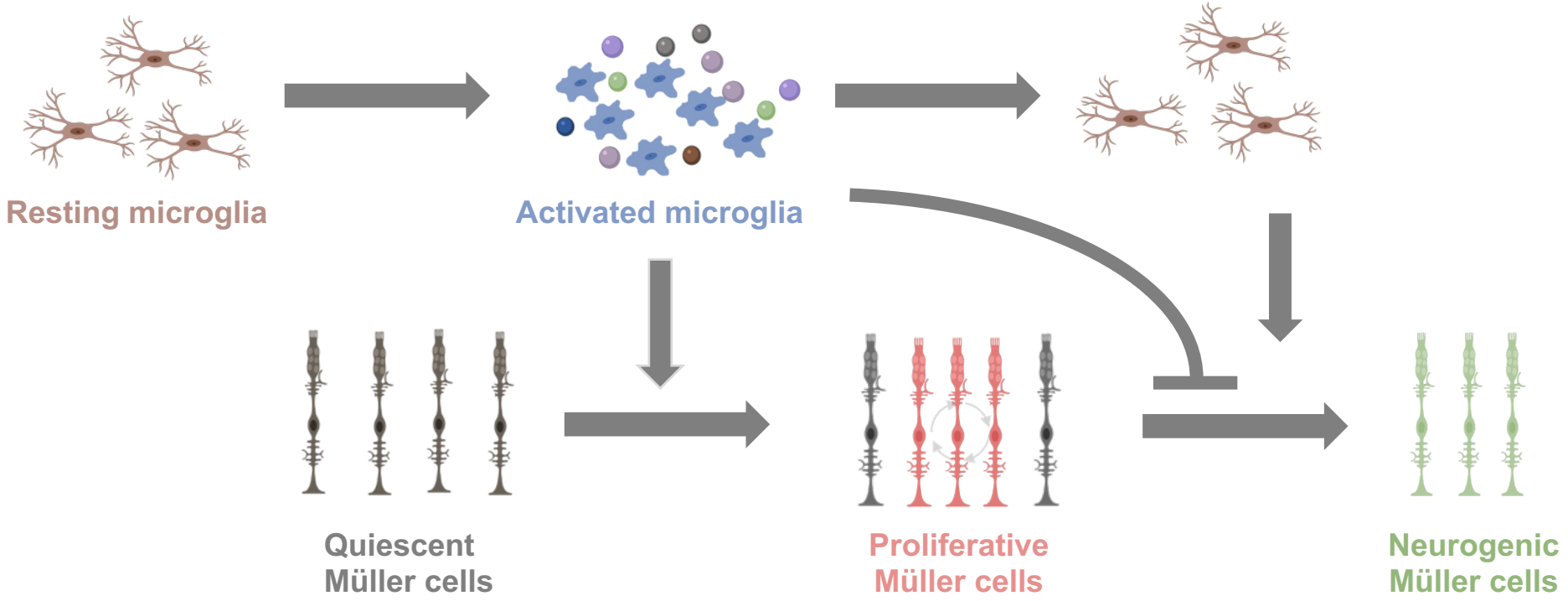
Quiescent
Müller cells

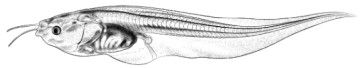


Proliferative
Müller cells

Neurogenic
Müller cells

Garcìa Garcìa, Science Advances 2024


Resting microglia
Activated microglia
Quiescent
Müller cells
Proliferative
Müller cells
Neurogenic
Müller cells



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