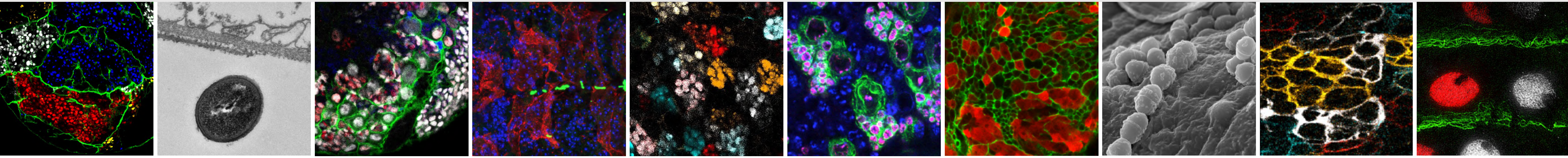
Structures and Signals
In the Neurogenic Niche



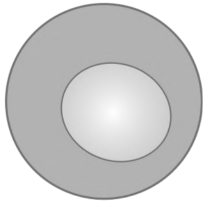
Pauline Spéder

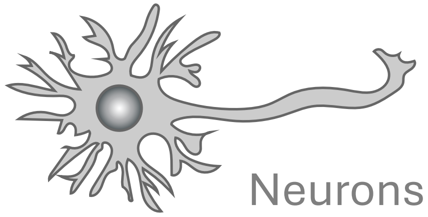
INSTITUT Pasteur

DSCB Developmental & Stem Cell Biology

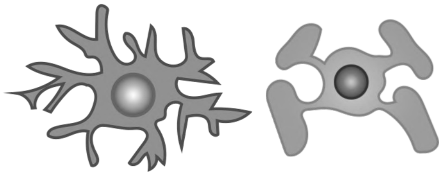
Stem cell → Progeny → Circuits → Behaviour

Neural
Stem/progenitor Cell
(NSC)

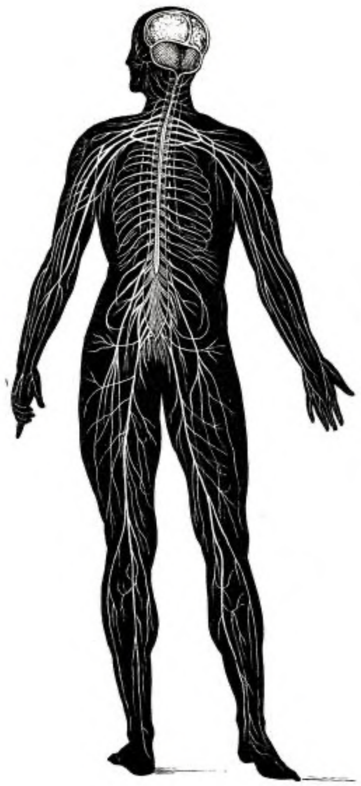




Neurons



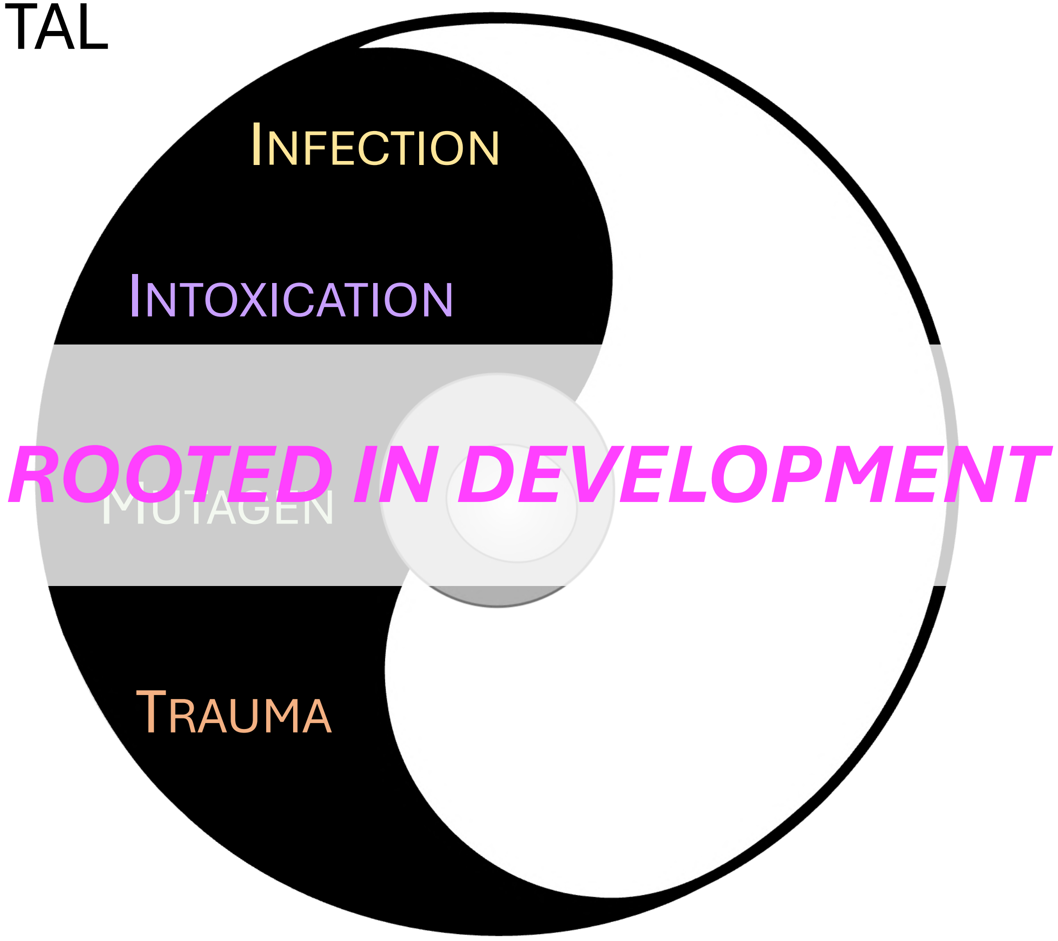
Glia



Neurodevelopmental disorders

Cancer

Mental health disorders



Prevention

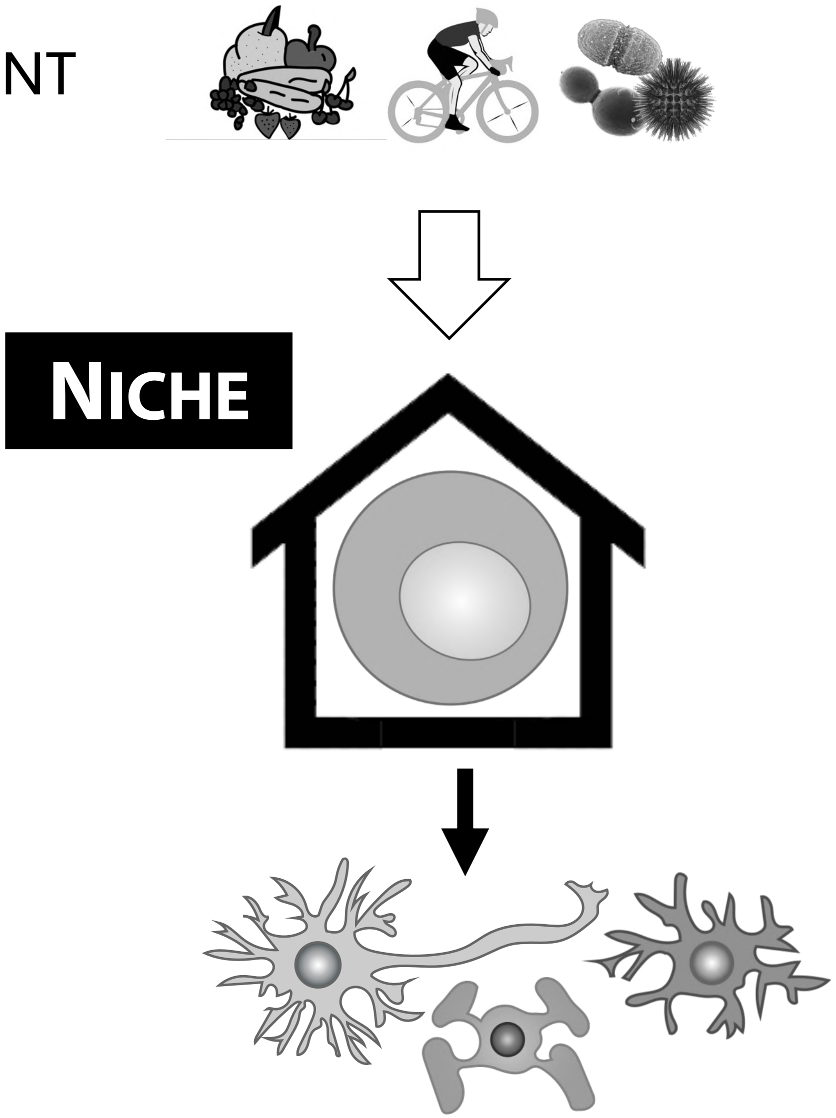
Repair

Regeneration

NSCs integrate several levels of information

EXTRINSIC
- ENVIRONMENT
- SYSTEMIC
- LOCAL

INTRINSIC



NEURODEVELOPMENT

What is a stem cell niche?

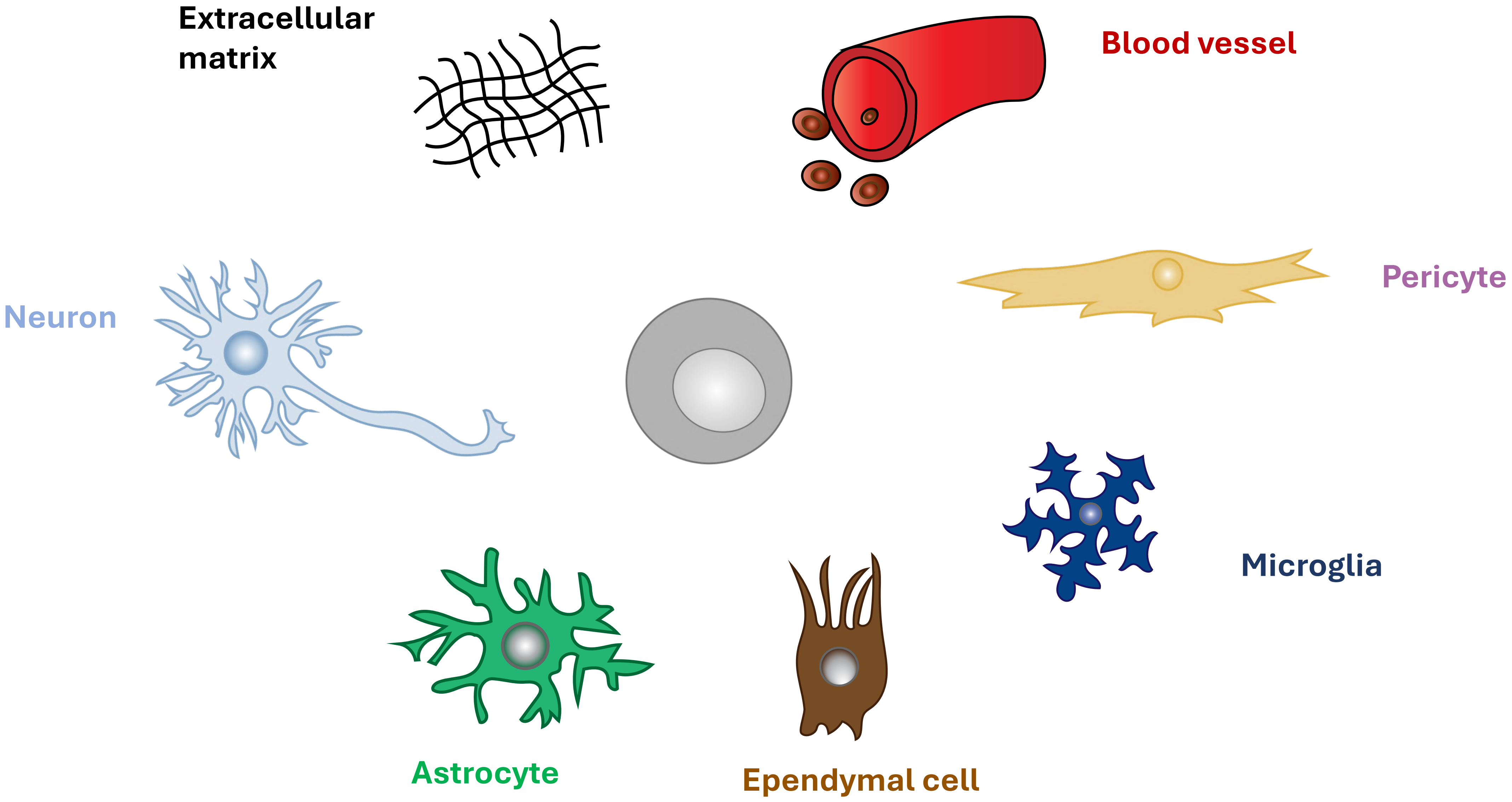
Where stem cells live

1. ENABLING stem cell functions

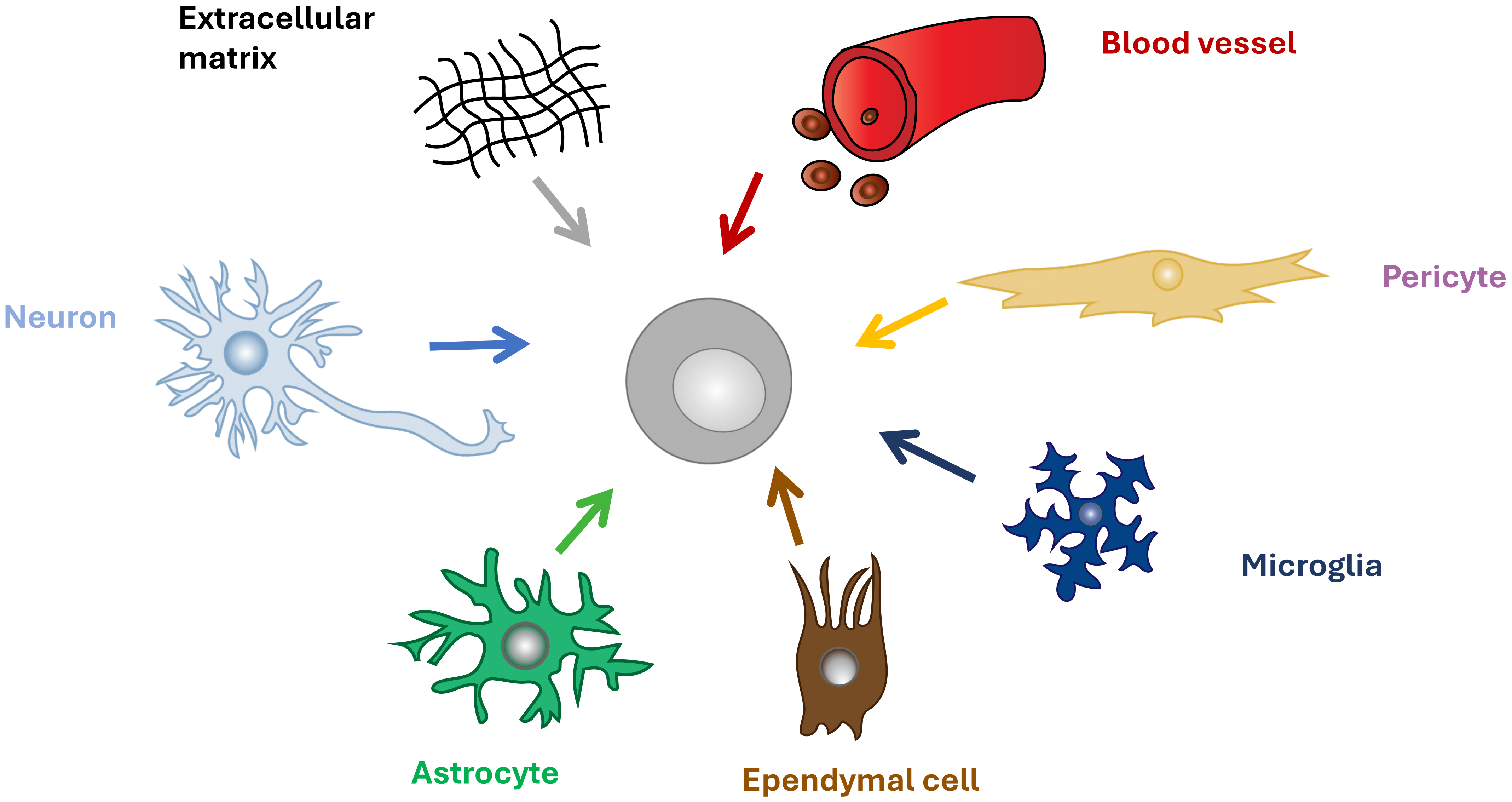
2. PURVEYING and CONVEYING INFORMATION to stem cells

- Great diversity of composition, shape and function
- *Often first defined in the adult*

The Neurogenic Niche is… 1. a complex microenvironment



The Neurogenic Niche is... 2. a signalling hub



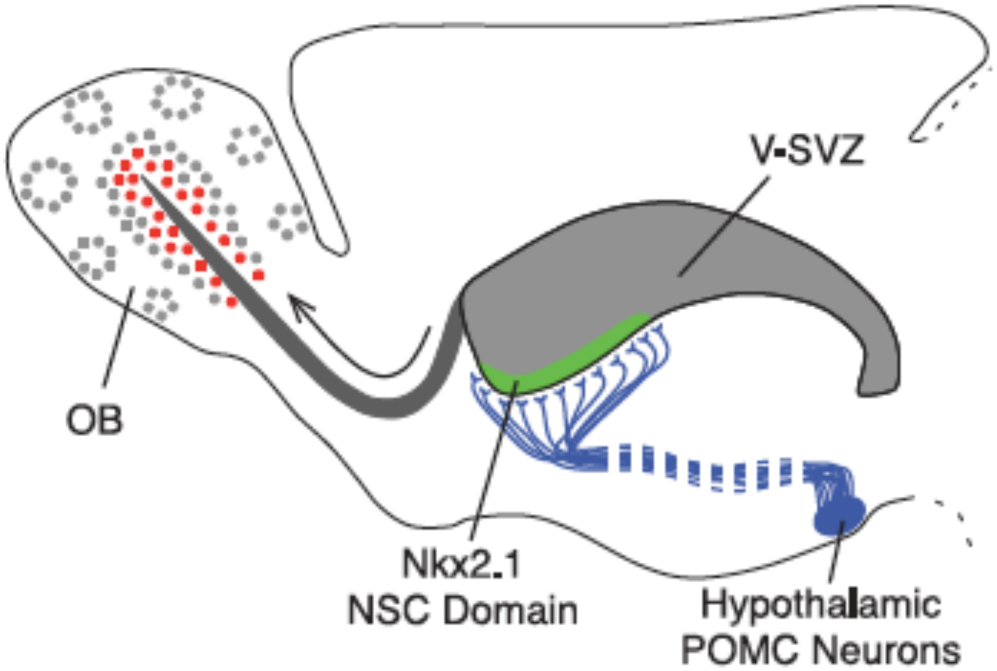
(NSCs integrate niche signals in health)

NEURODEVELOPMENT

Hypothalamic regulation of regionally distinct adult neural stem cells and neurogenesis

Alex Paul,[1,2] Zayna Chaker,[3] Fiona Doetsch[2,3]*

G



Paul et al., 2017

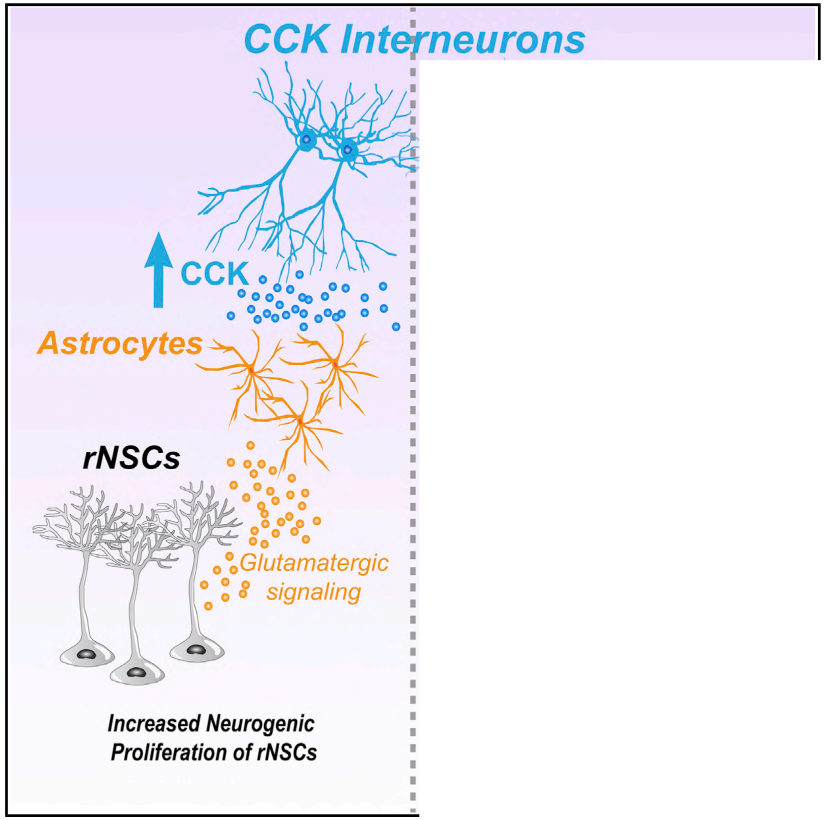
(NSCs integrate niche signals in health)

Neuron

Article

Neuropeptides Modulate Local Astrocytes to Regulate Adult Hippocampal Neural Stem Cells

Graphical Abstract



Authors

Brent Asrican, Josh Wooten, Ya-Dong Li, ..., Jessica Hu, Peng Jin, Juan Song

Correspondence

juansong@email.unc.edu

In Brief

Asrican et al. demonstrate that stimulating endogenous CCK neuropeptide release in adult dentate gyrus supports neurogenic proliferation of rNSCs through a dominant astrocyte-mediated glutamatergic signaling cascade. In contrast, reducing dentate CCK induced reactive astrocytes, decreased neurogenic proliferation of rNSCs, and upregulated genes involved in neuroinflammation.

Asrican et al., 2020

(NSCs integrate niche signals in disease)

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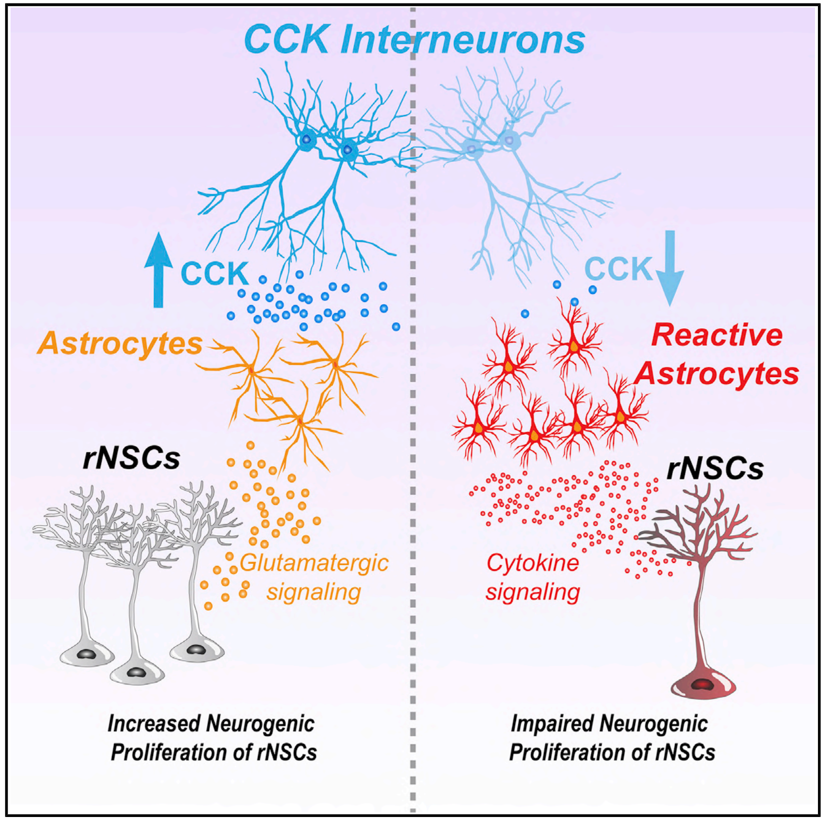

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Asrican et al., 2020

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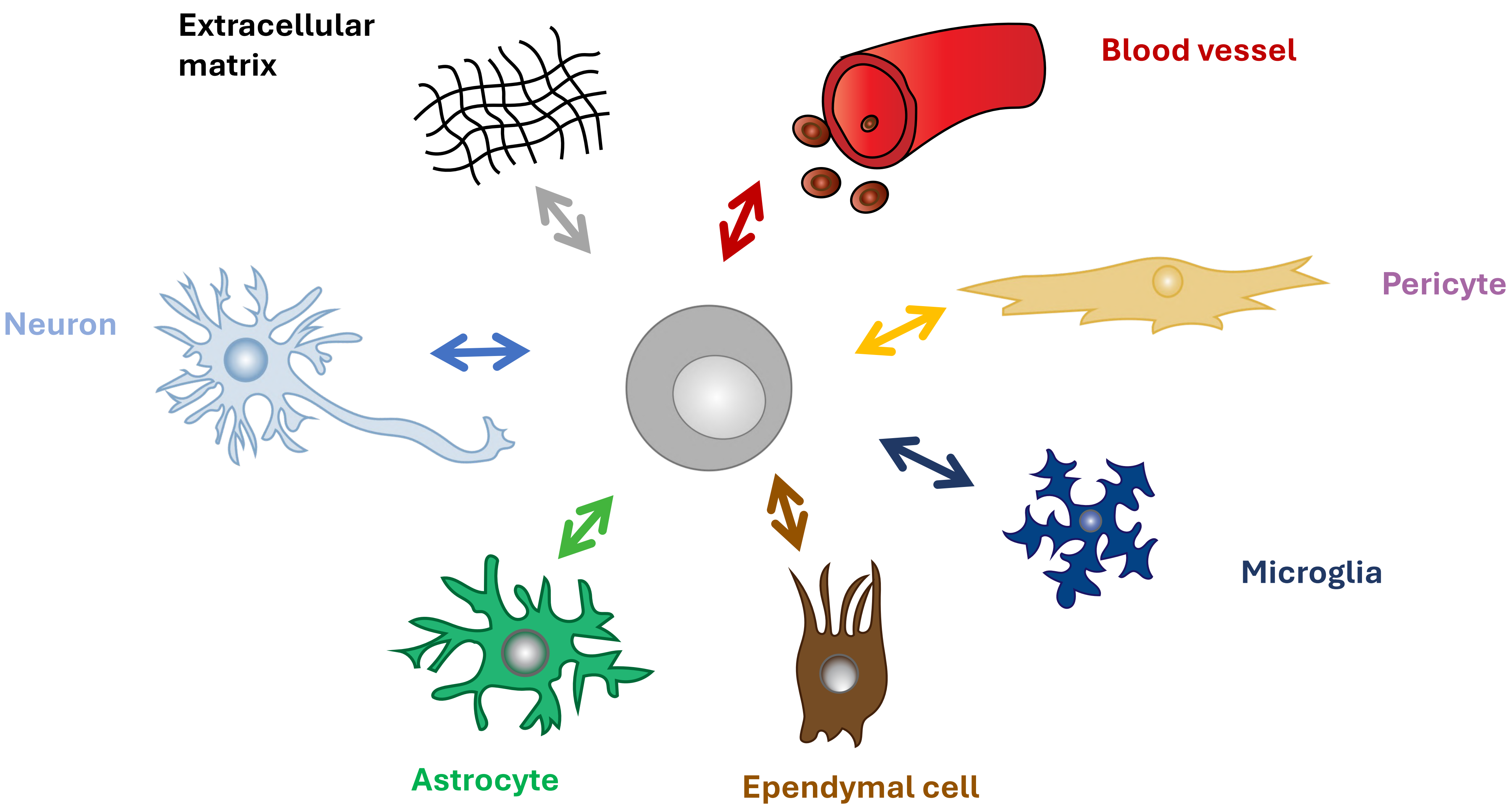
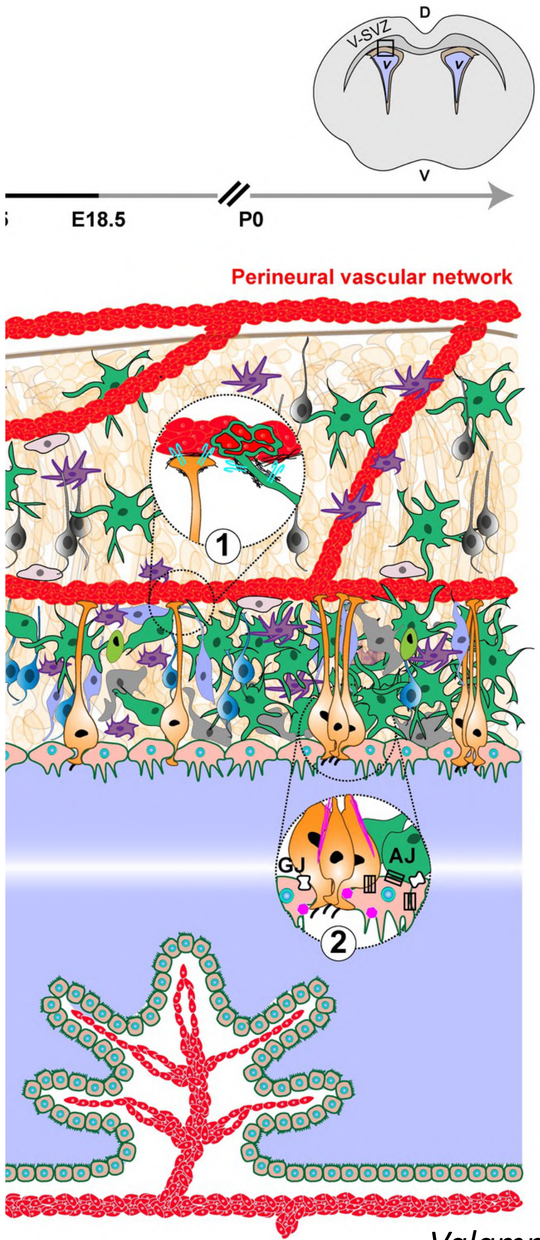
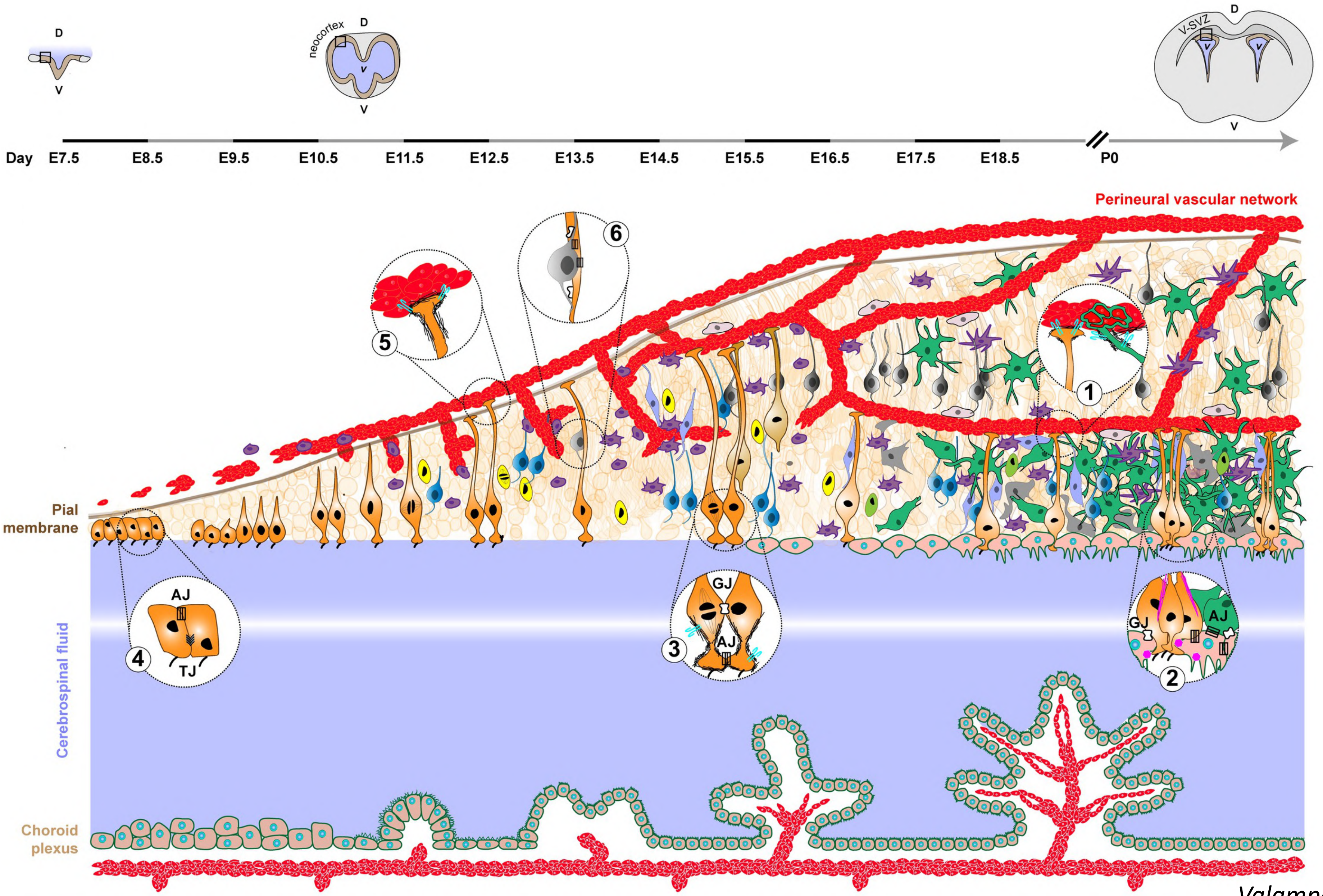


The Neurogenic Niche is... 3. a complex structure



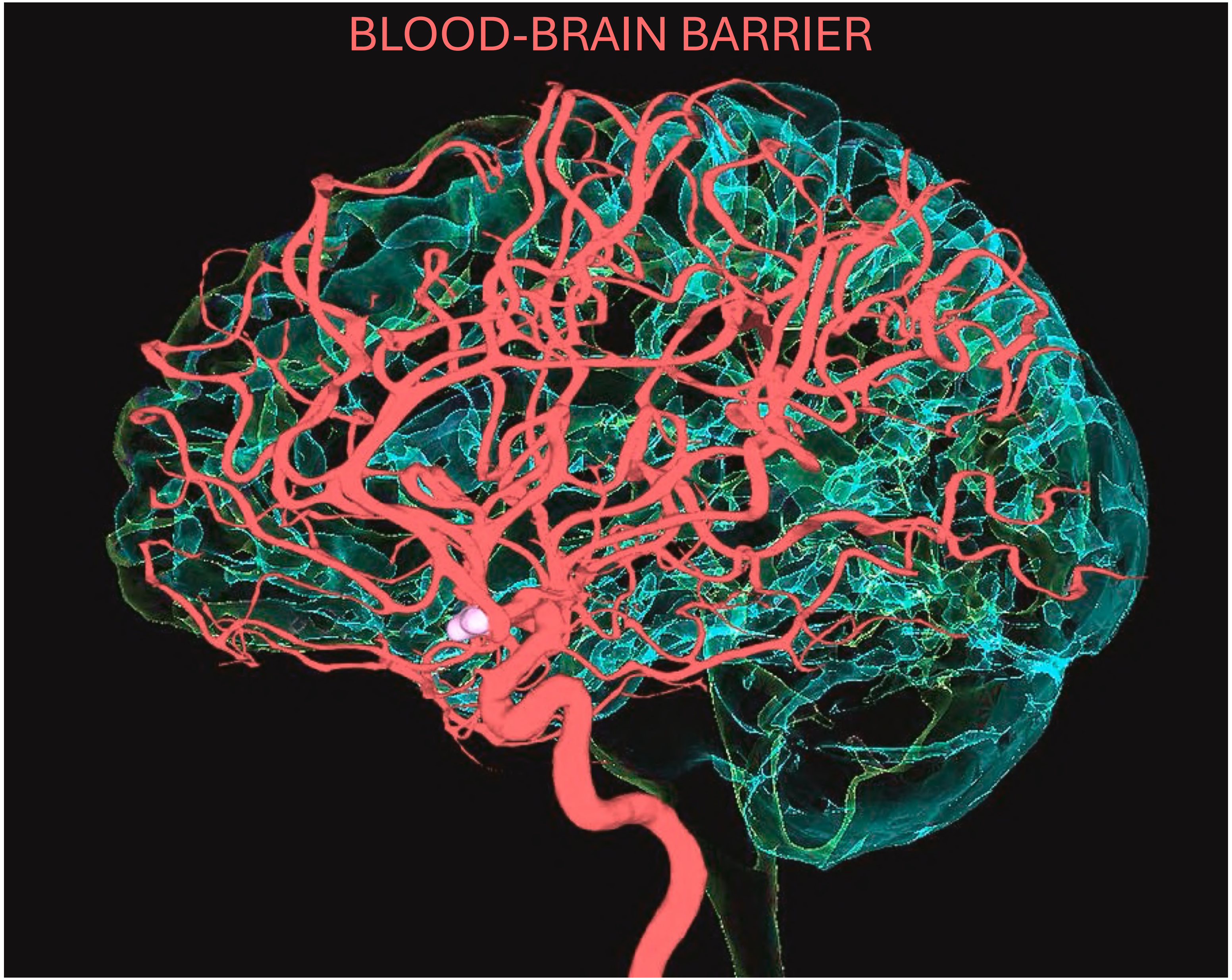
Valamparamban and Spéder, 2023

The Neurogenic Niche is... 4. built progressively

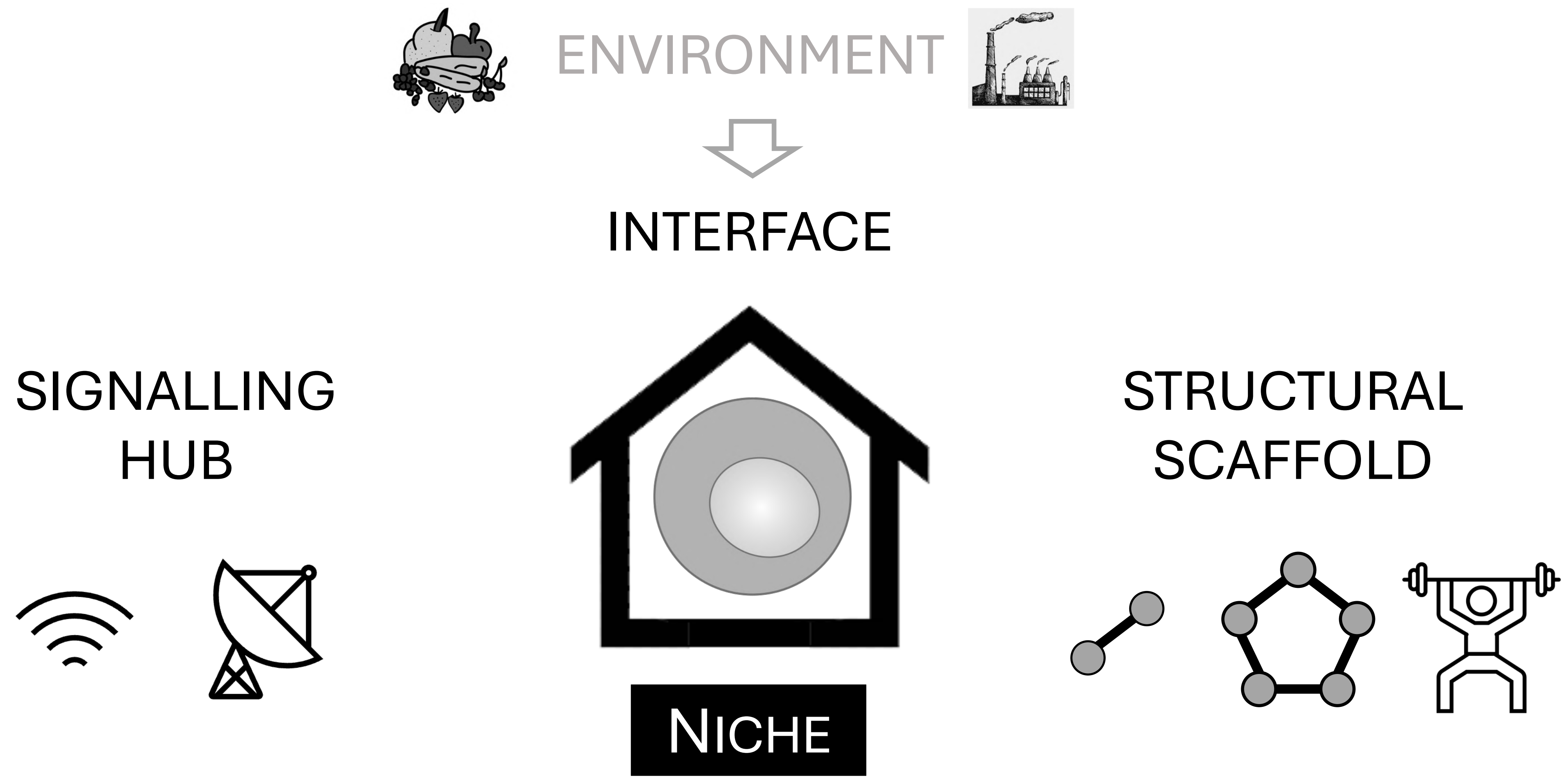


Valamparamban and Spéder, 2023

The neurogenic niche is …5. a sensor of changes



The neurogenic niche: signals meets structure

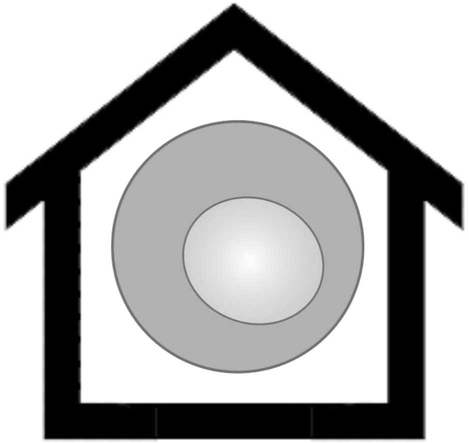


Our questions

1. Architecture

FORMATION & ROLES?

Single Community Population



NICHE

2. Perturbations

RESPONSES?

Protection Adaptation Pathological

Local Systemic Environmental

What would be a good model?

- Existence of bona fidae NSCs
- Existence of a niche: topology + function

In vivo

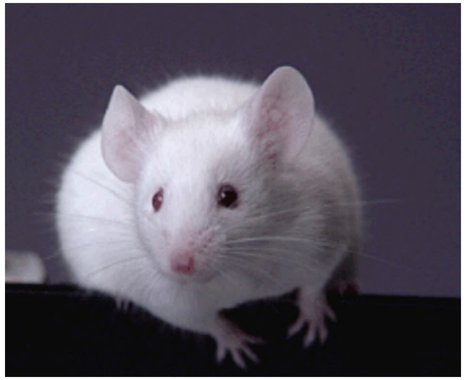
- Access to a living brain
- Identification, tracking and manipulation of cellular populations /individual cells precisely and independently

Accessibility Complexity Conservation Ethics

Drosophila melanogaster

Xenopus laevi

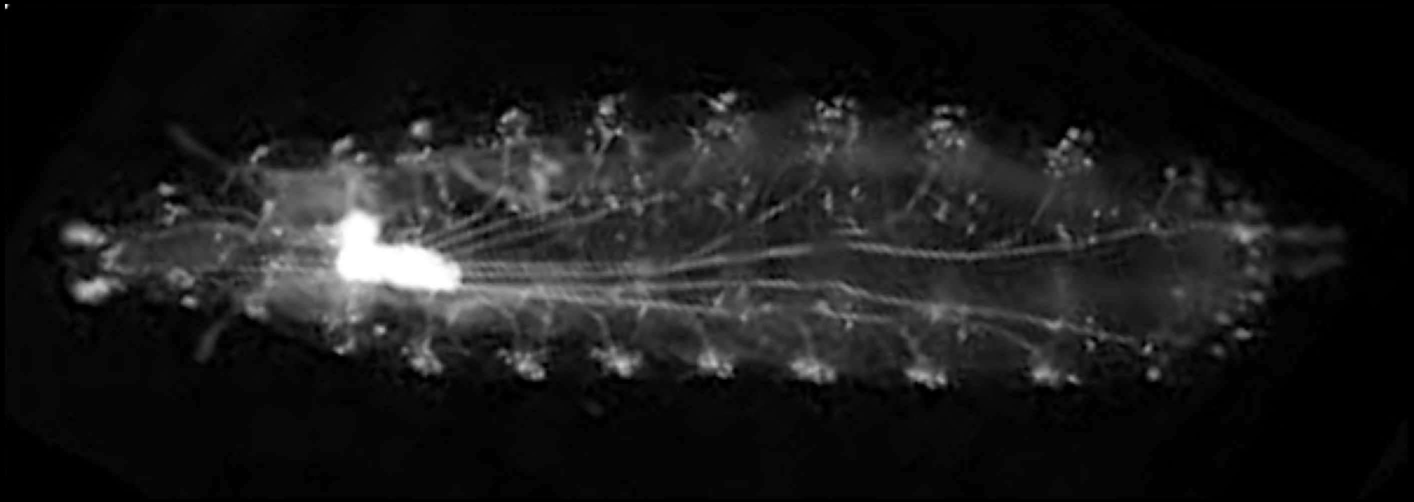
Danio rerio



Mus musculus

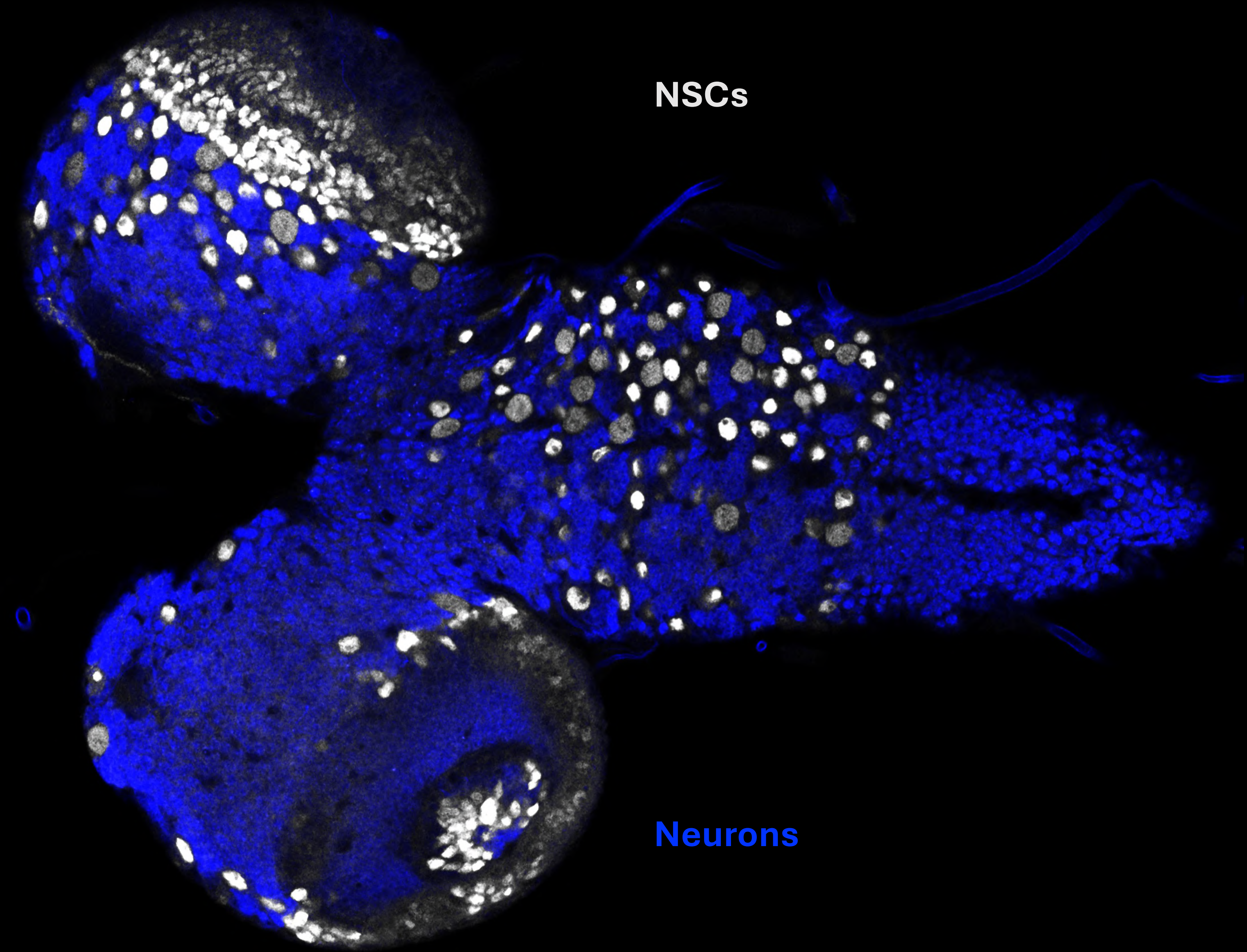
Callithrix jacchus

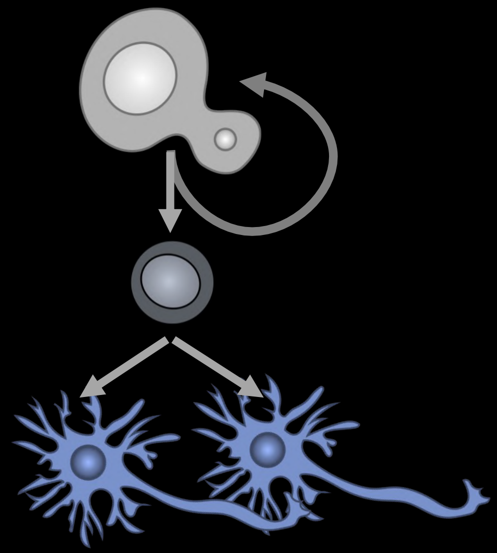
Drosophila larval brain



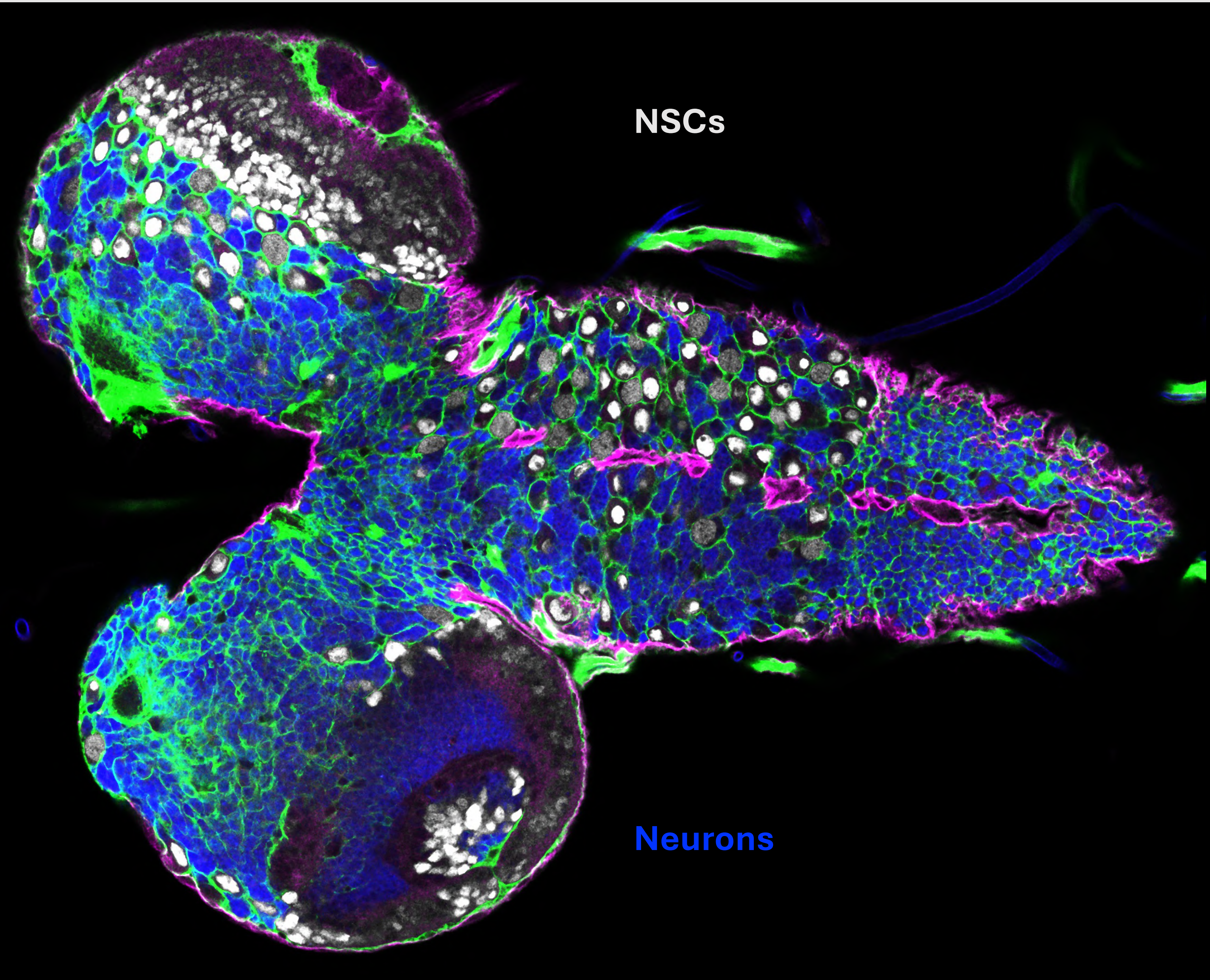
Credit: Balaji Iyengar

The neurogenic niche in the developing Drosophila brain





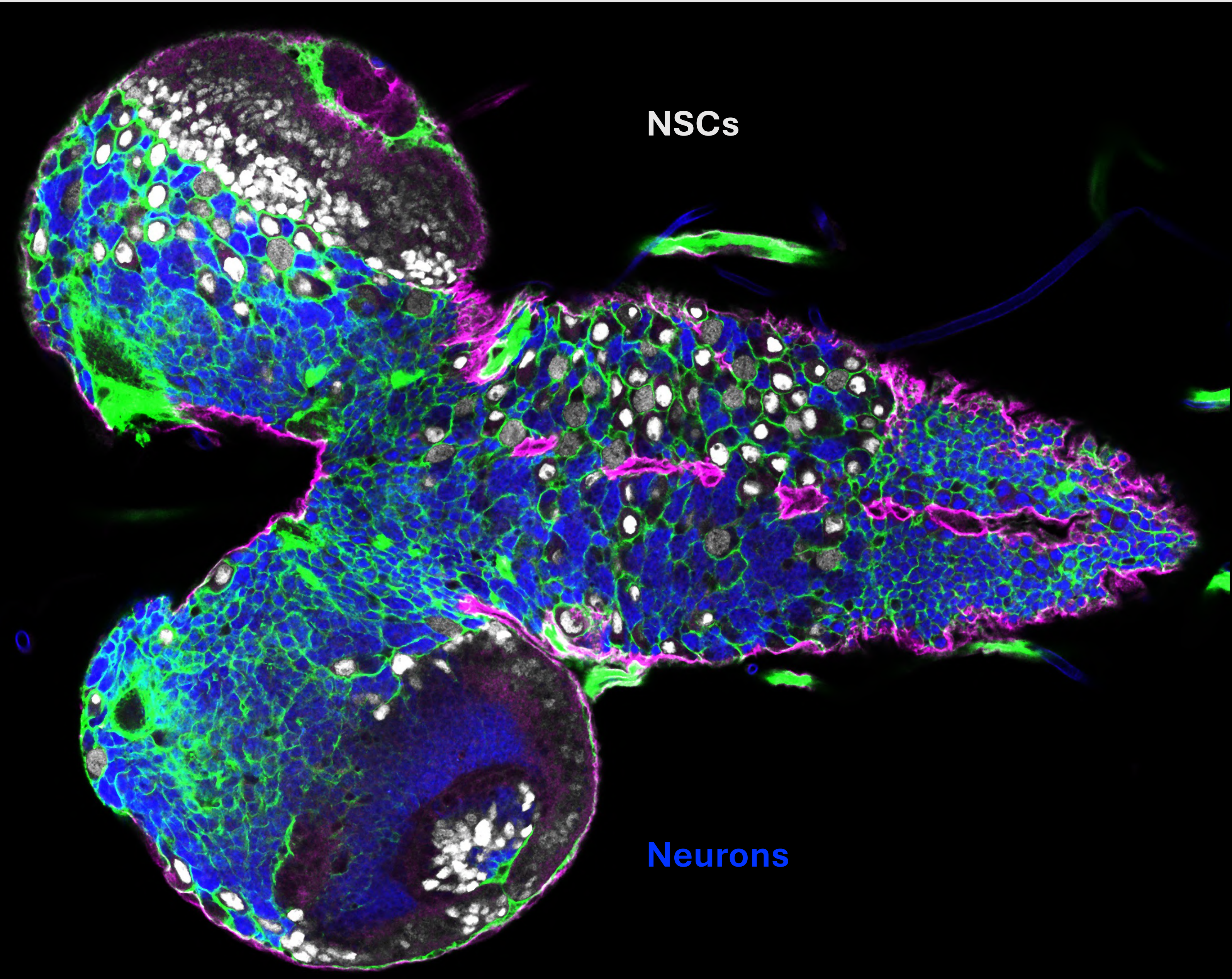
The neurogenic niche in the developing Drosophila brain



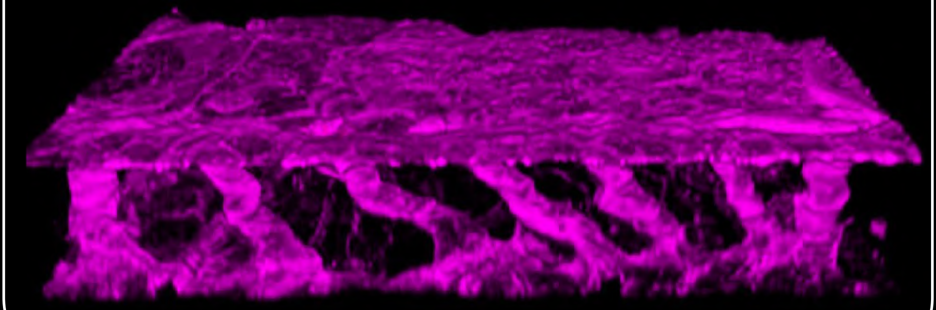
WELL-CHARACTERIZED NSCS

DEFINED NICHE

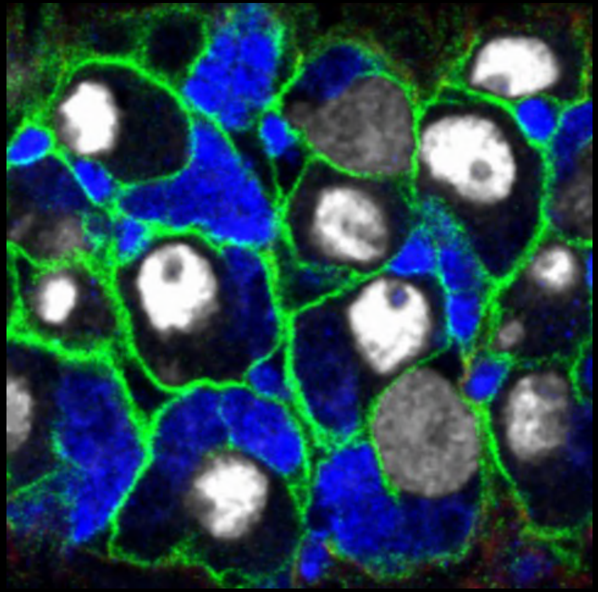
The neurogenic niche in the developing Drosophila brain



Blood –brain barrier

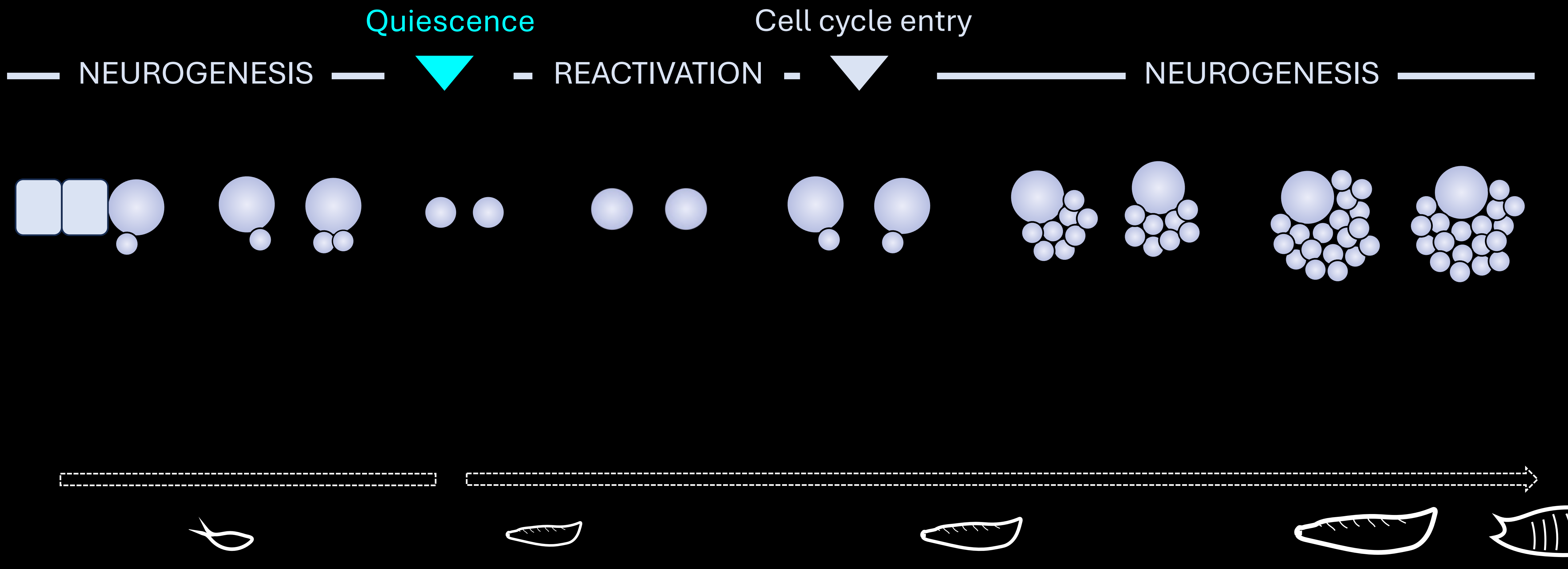


Cortex glia



How does the niche **form**?

Formation of the niche architecture is progressive



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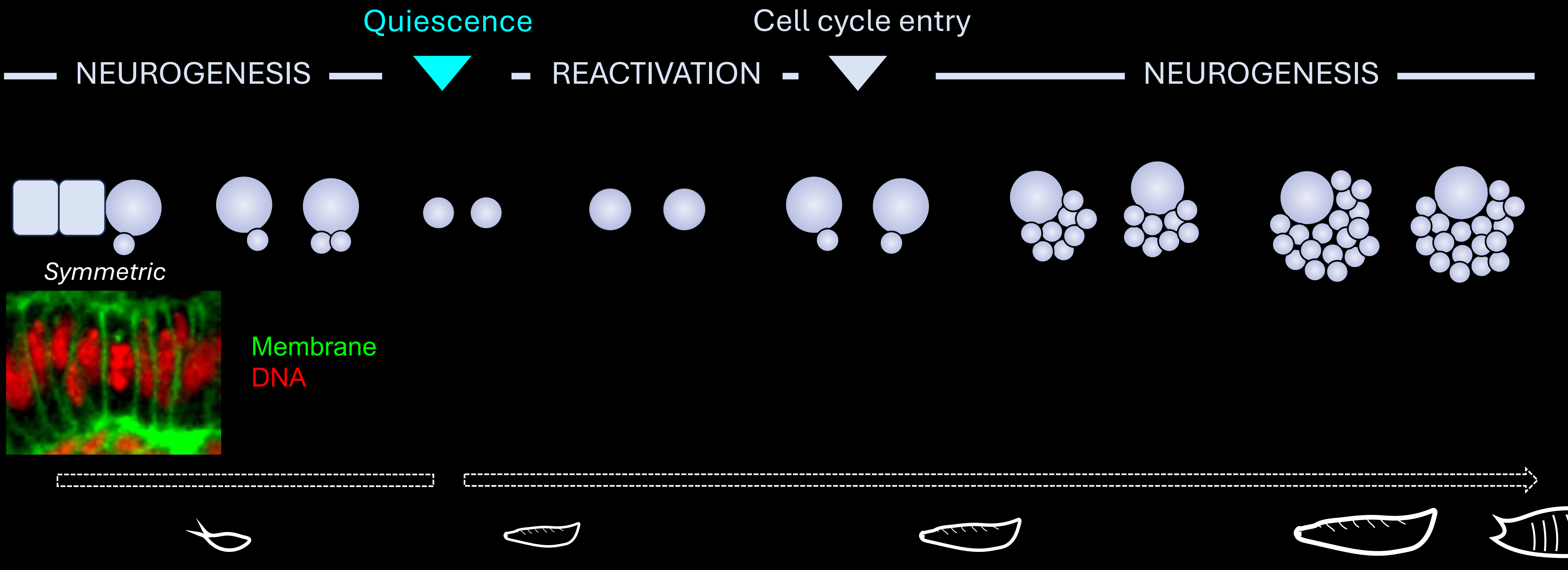

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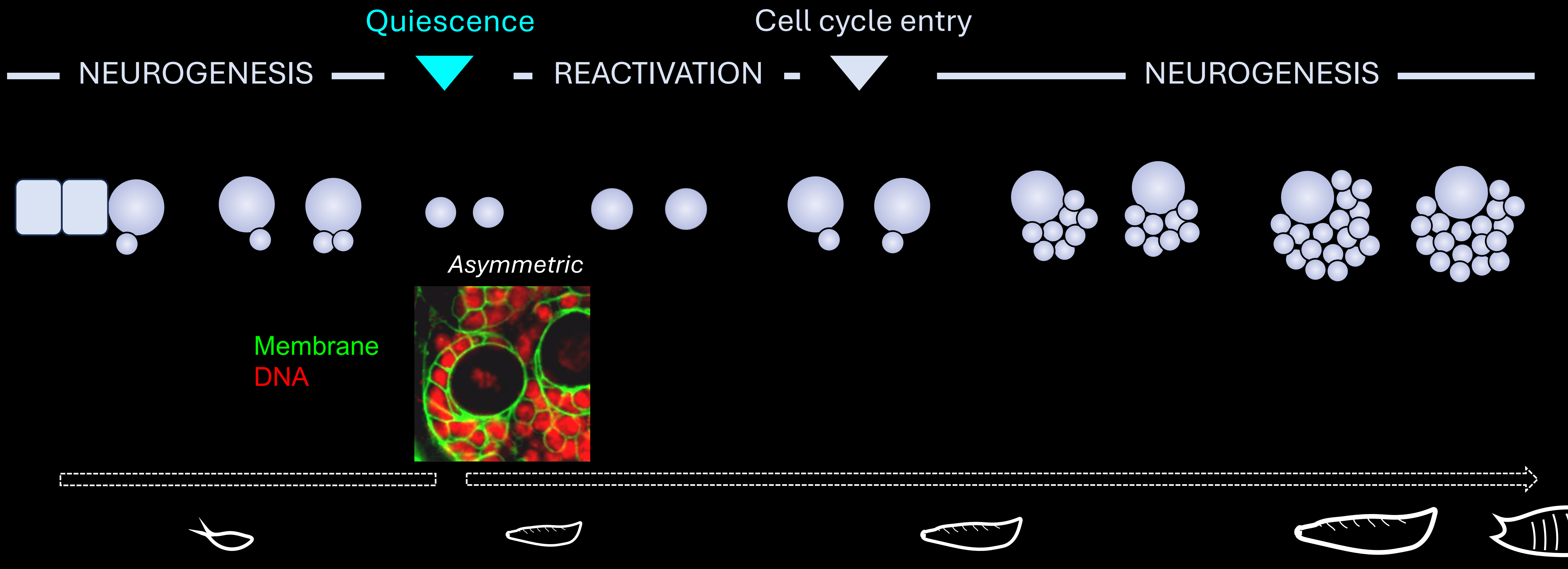

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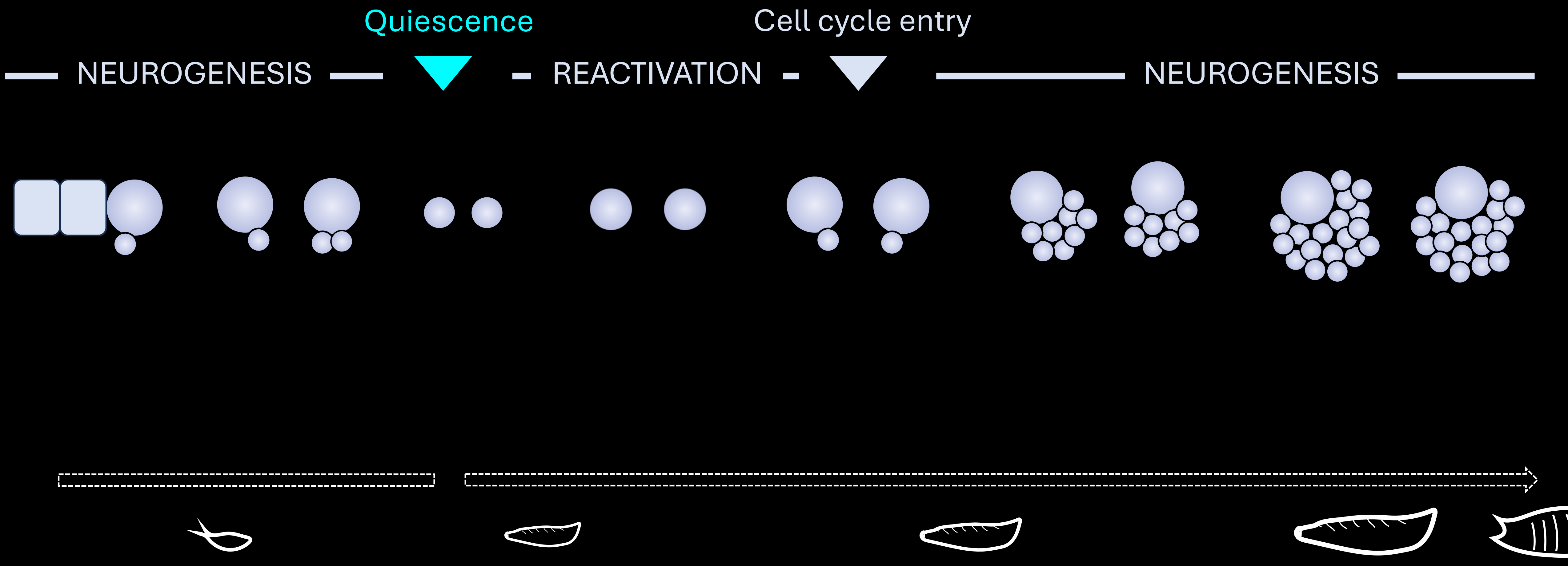

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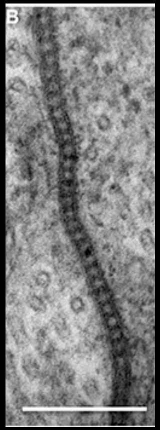
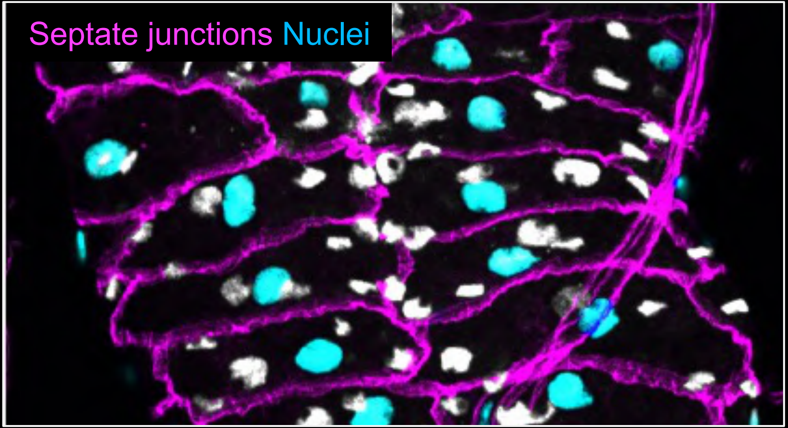
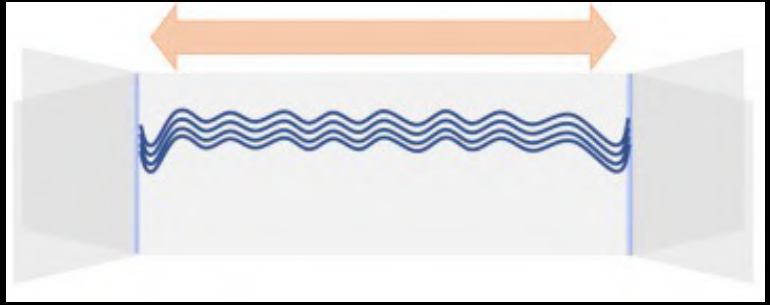
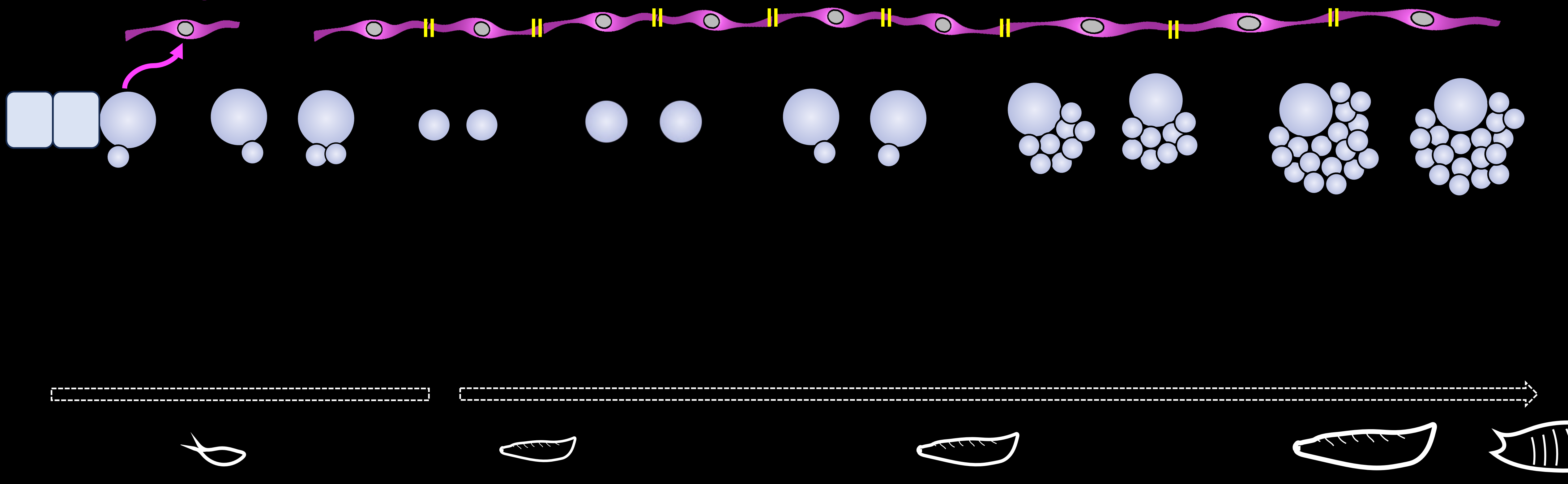






Babatz et al, 2018

Subperineurial glia



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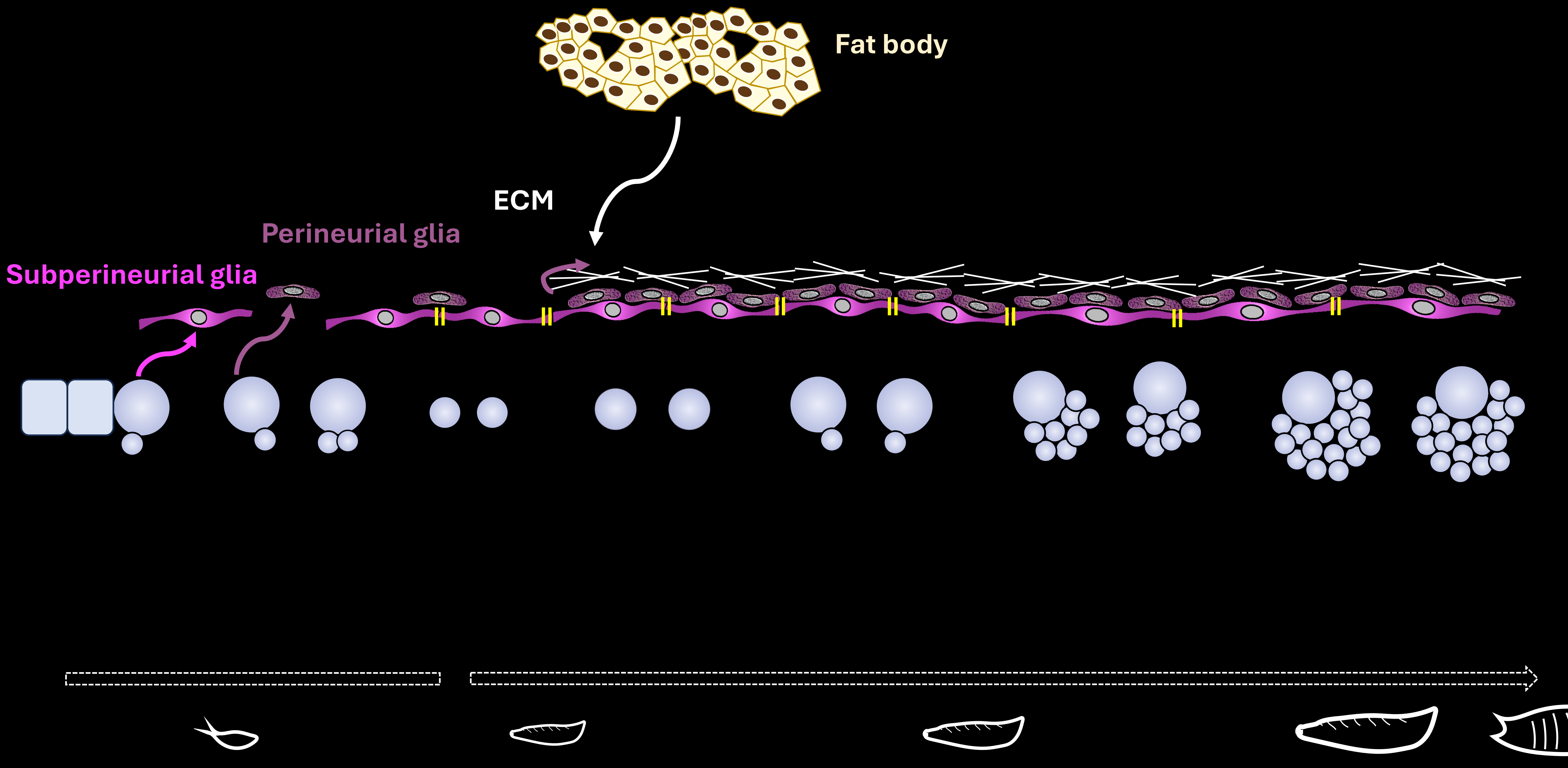

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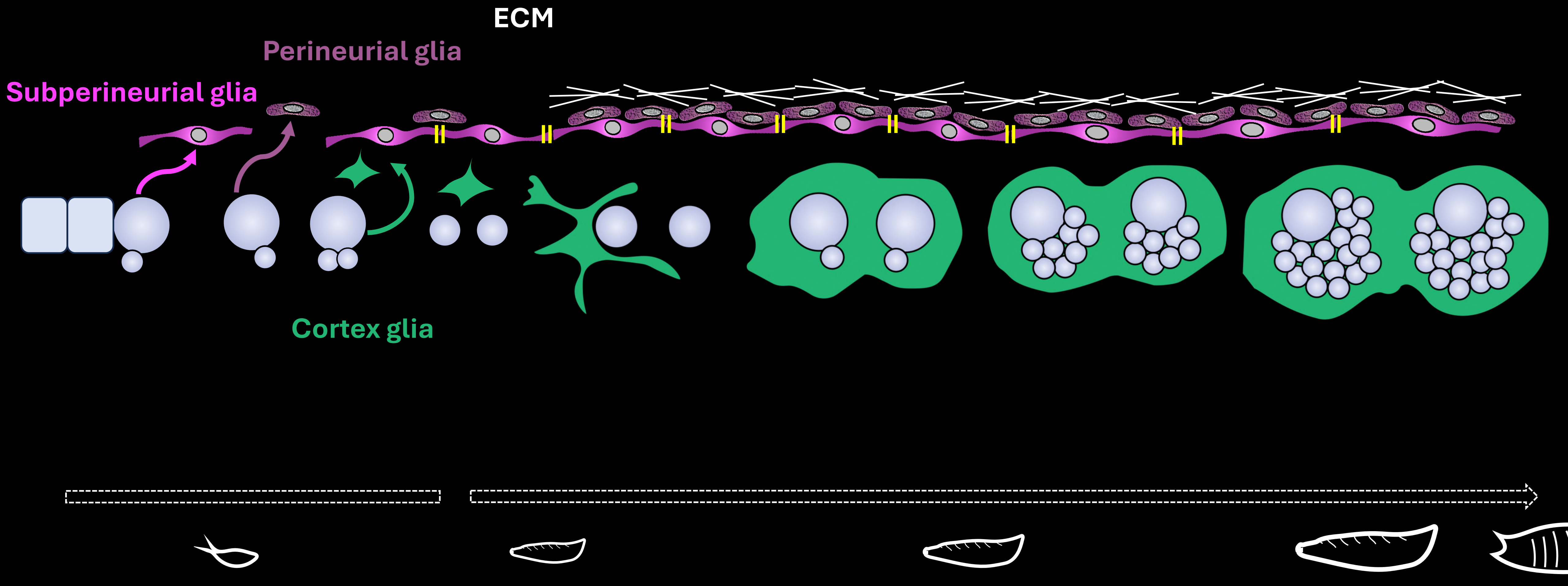

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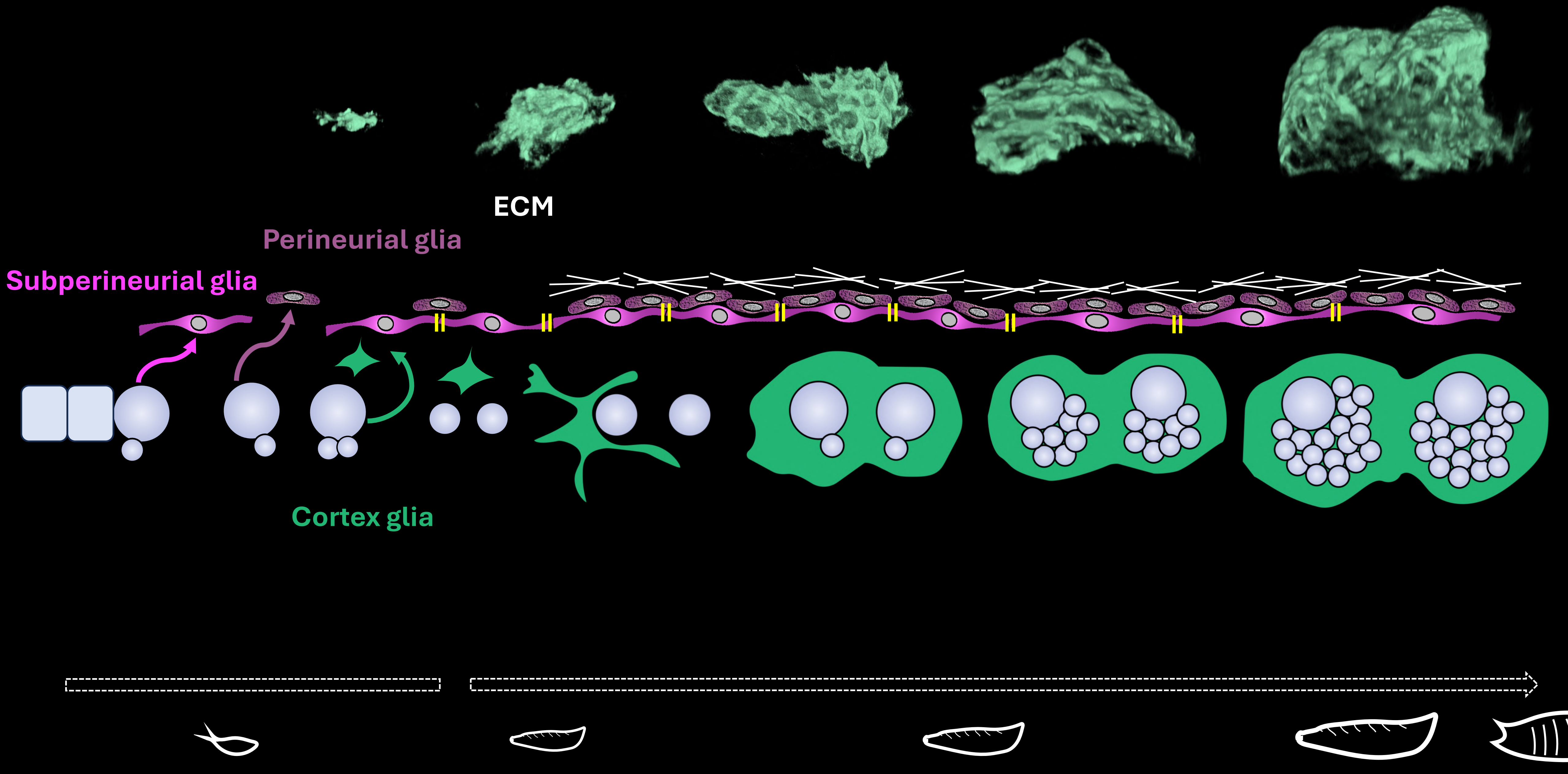
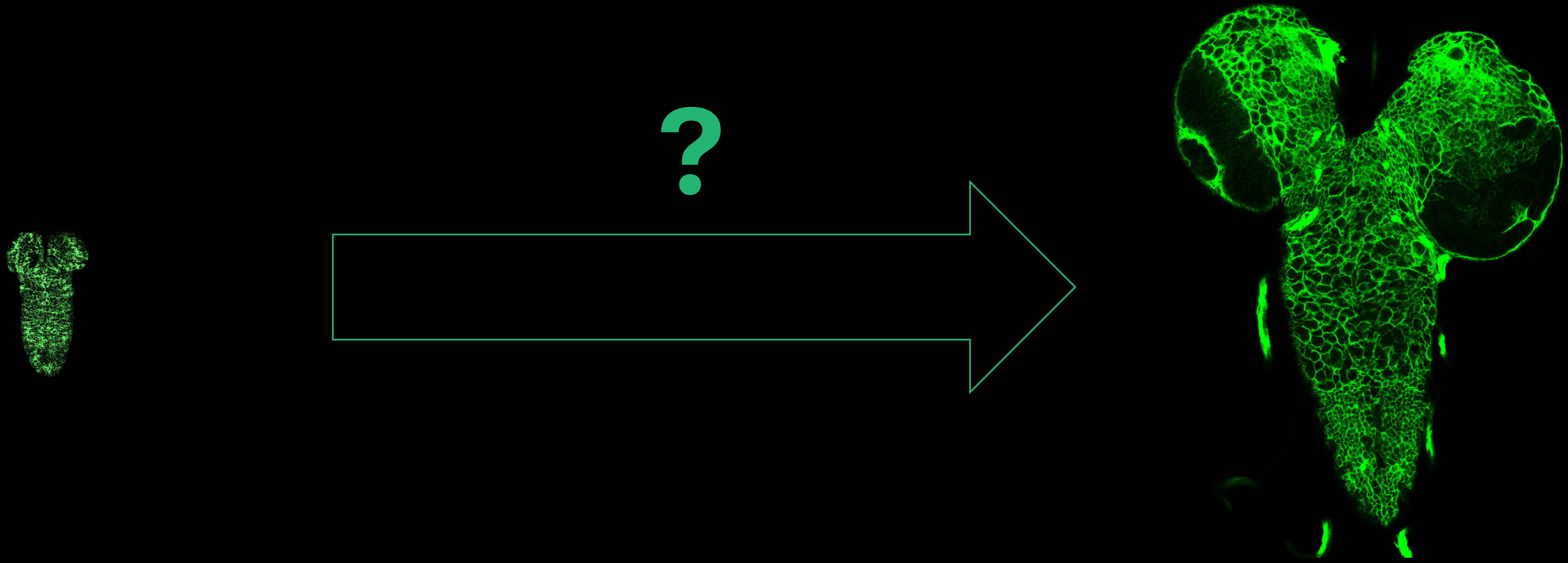
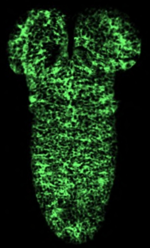
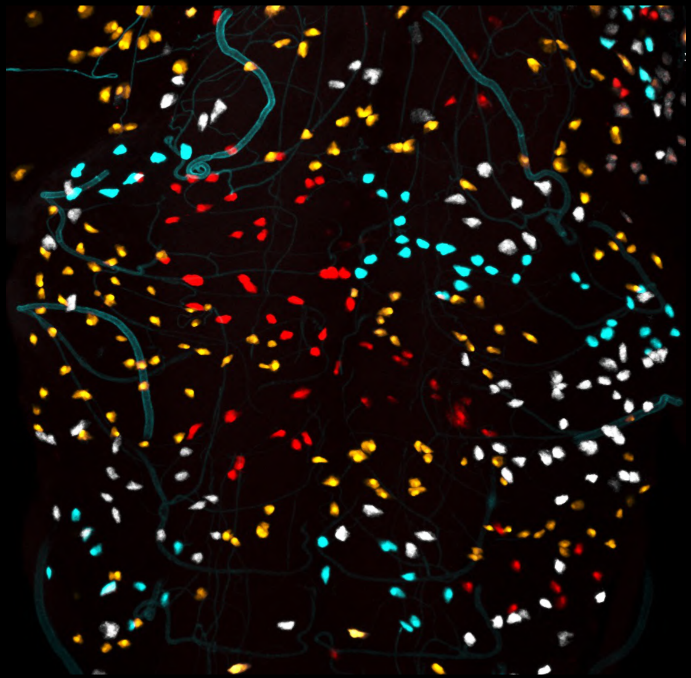


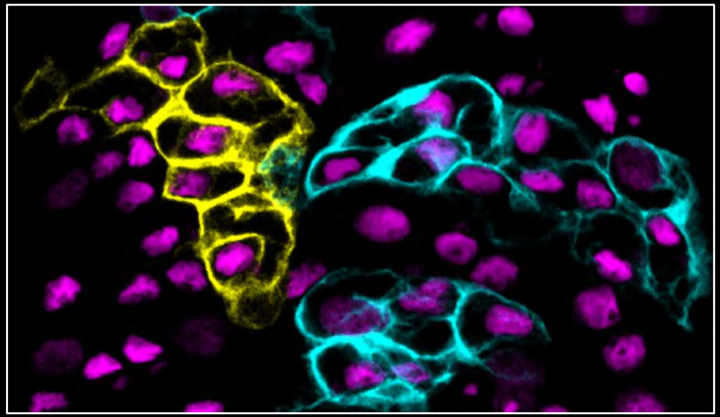


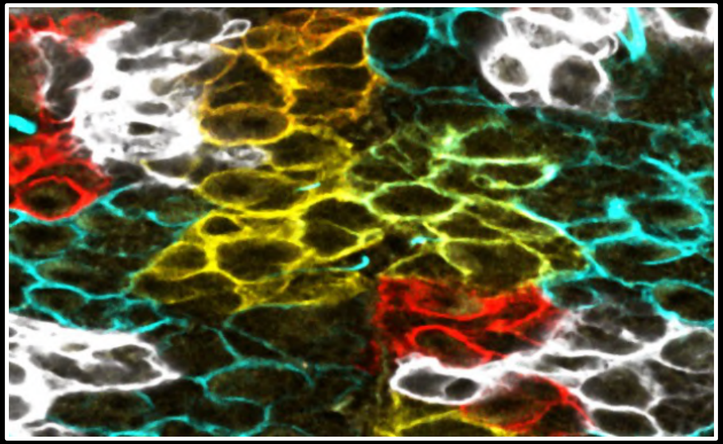
Clonal Amplification

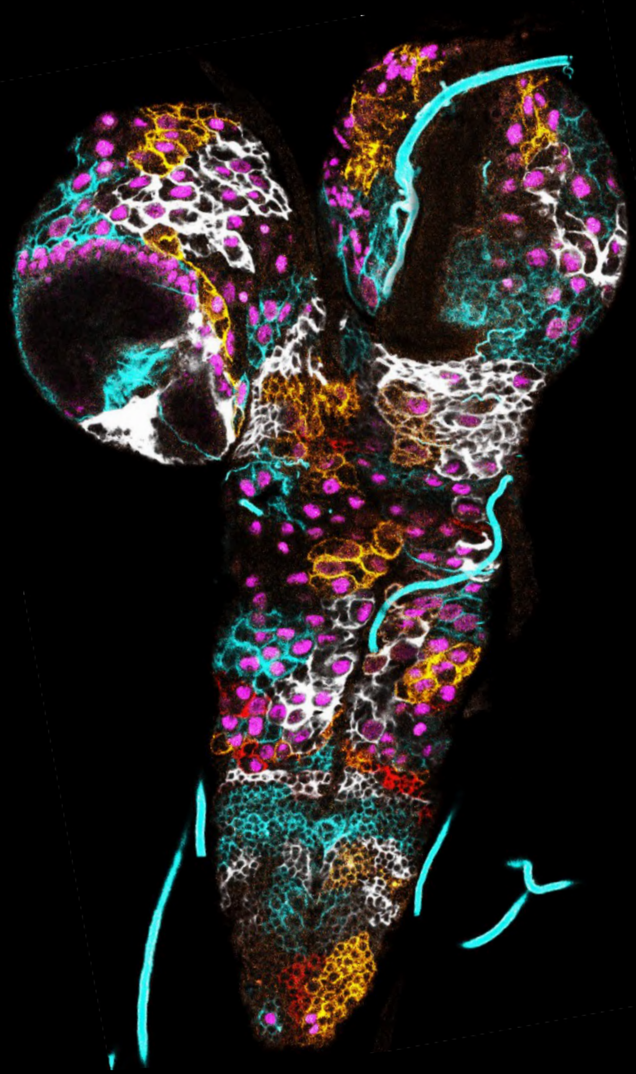




Tiling







Rujano et al., 2022

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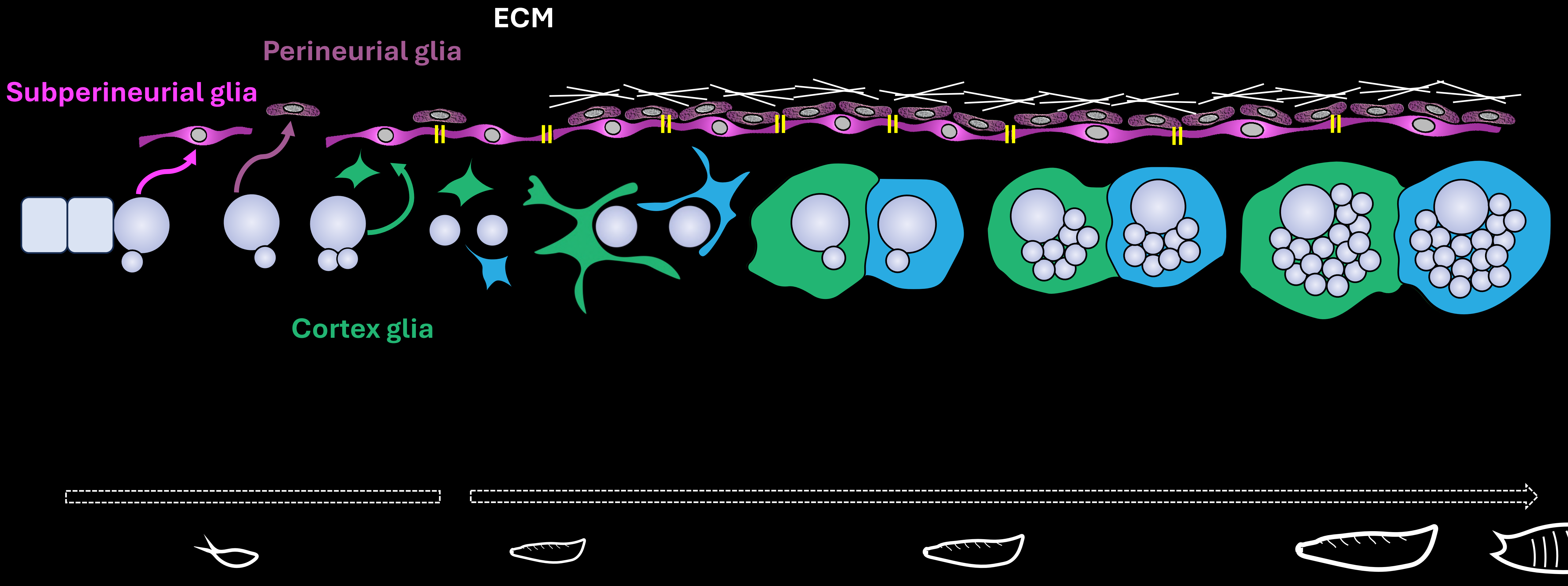

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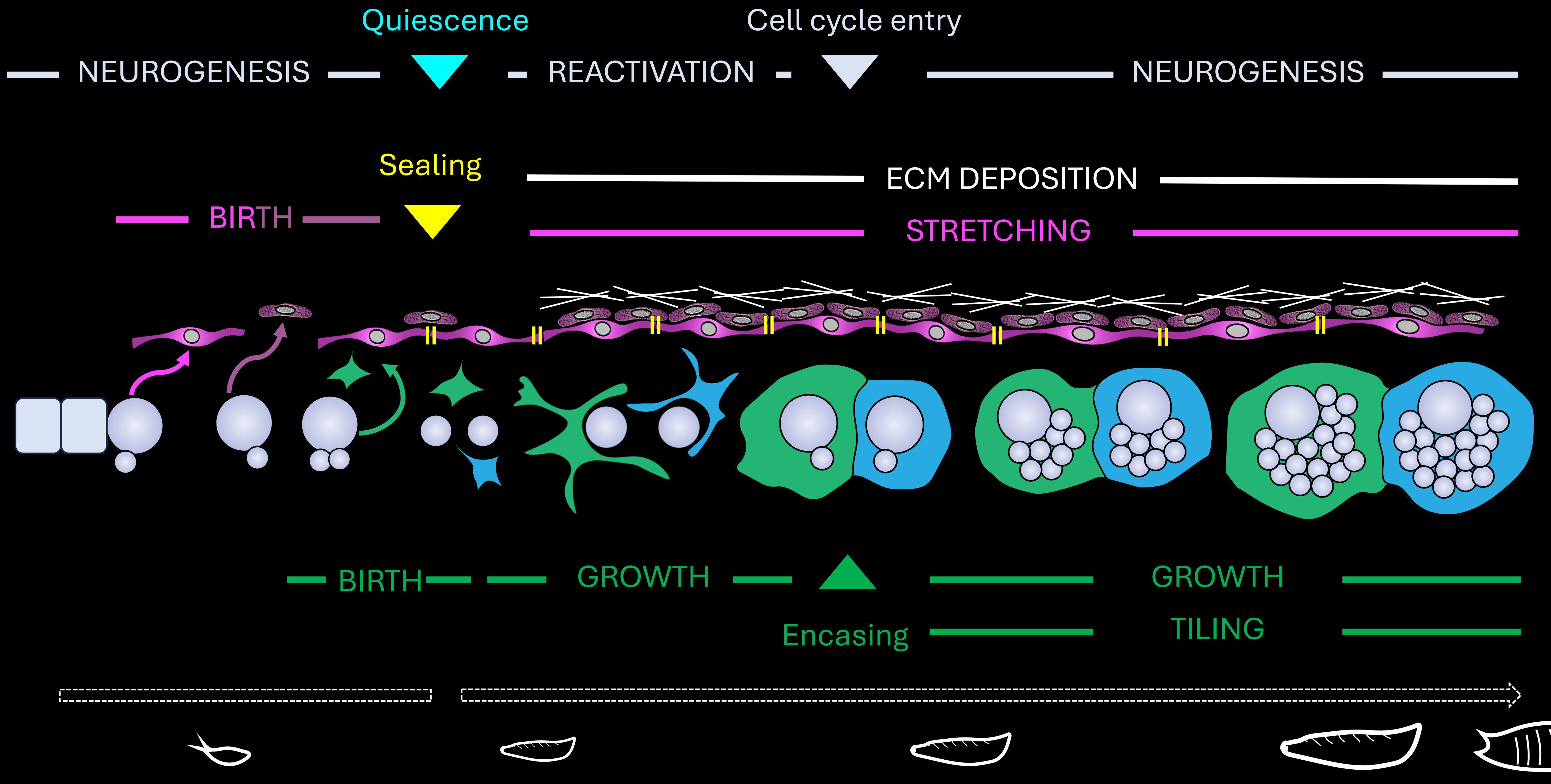

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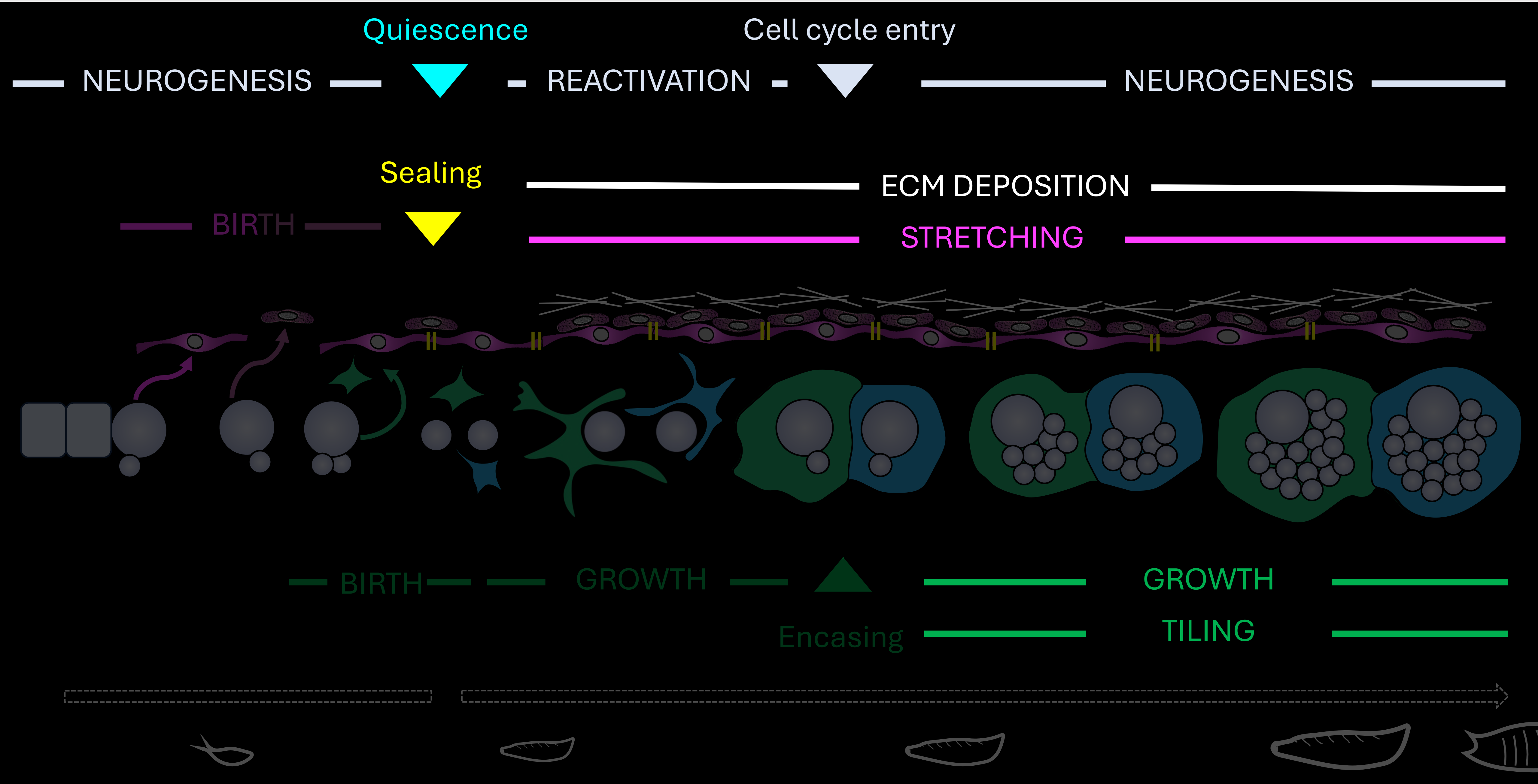
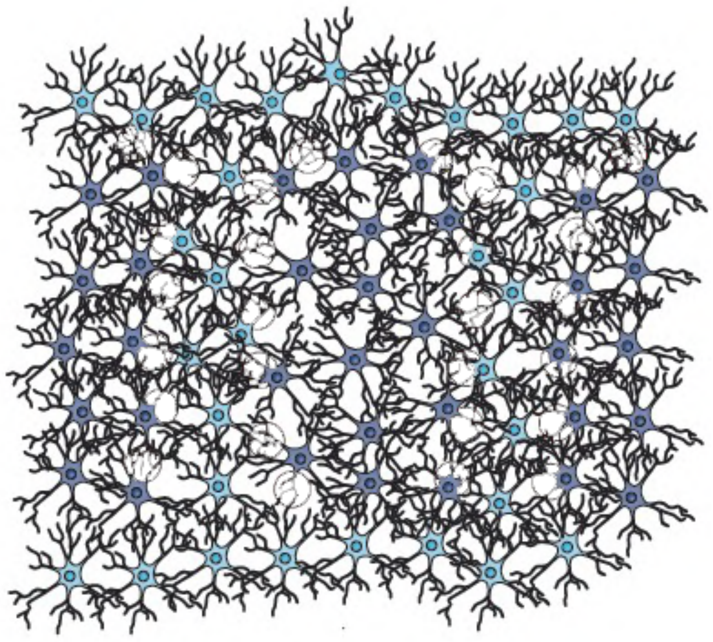
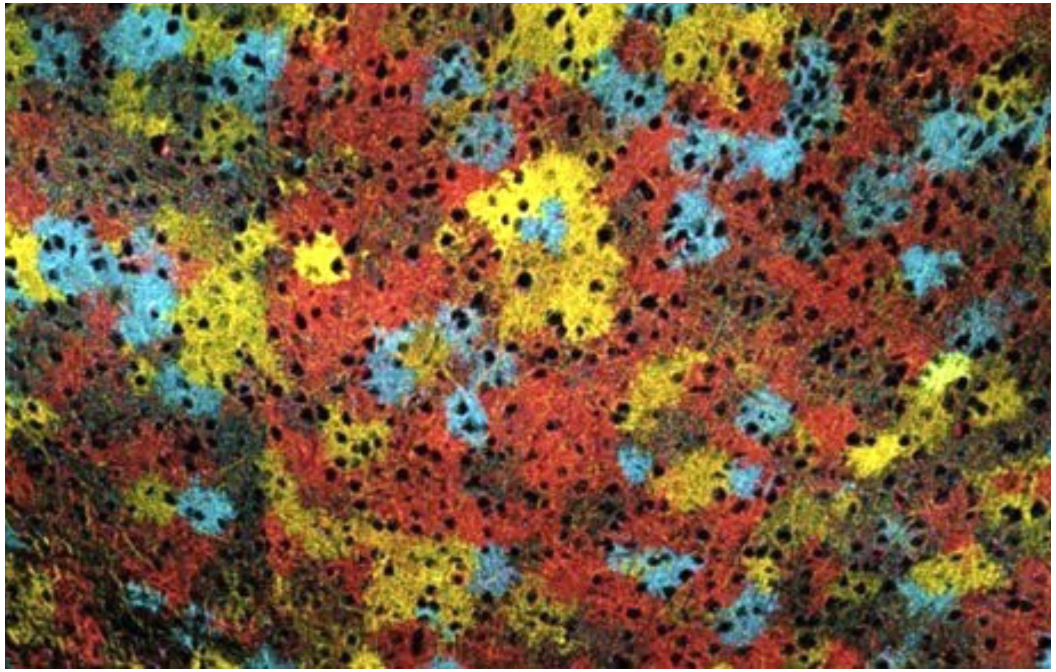


Far but not *SO* far

➢ **Formation of connected networks**



Giaume et al., 2010



Jean Livet

Far but not *SO* far

- **Ancestral glial blood-brain barrier**

GLIA 56:699–708 (2008)

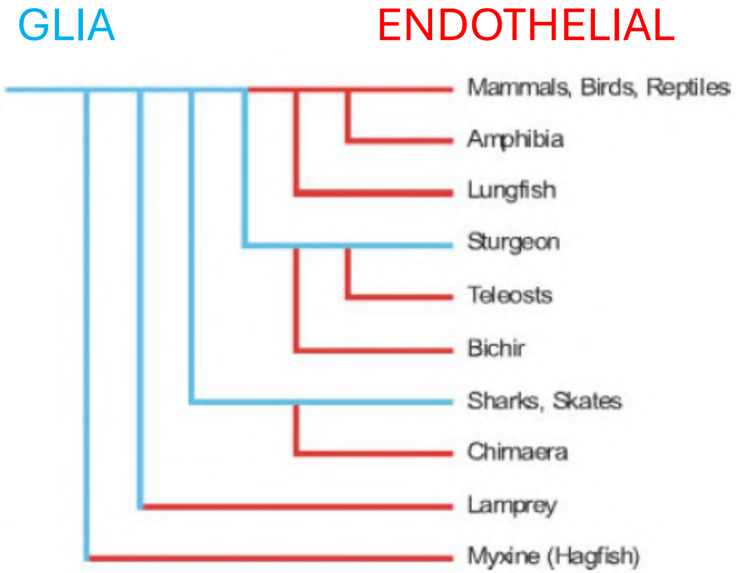
All Vertebrates Started Out with a Glial Blood-Brain Barrier 4–500 Million Years Ago

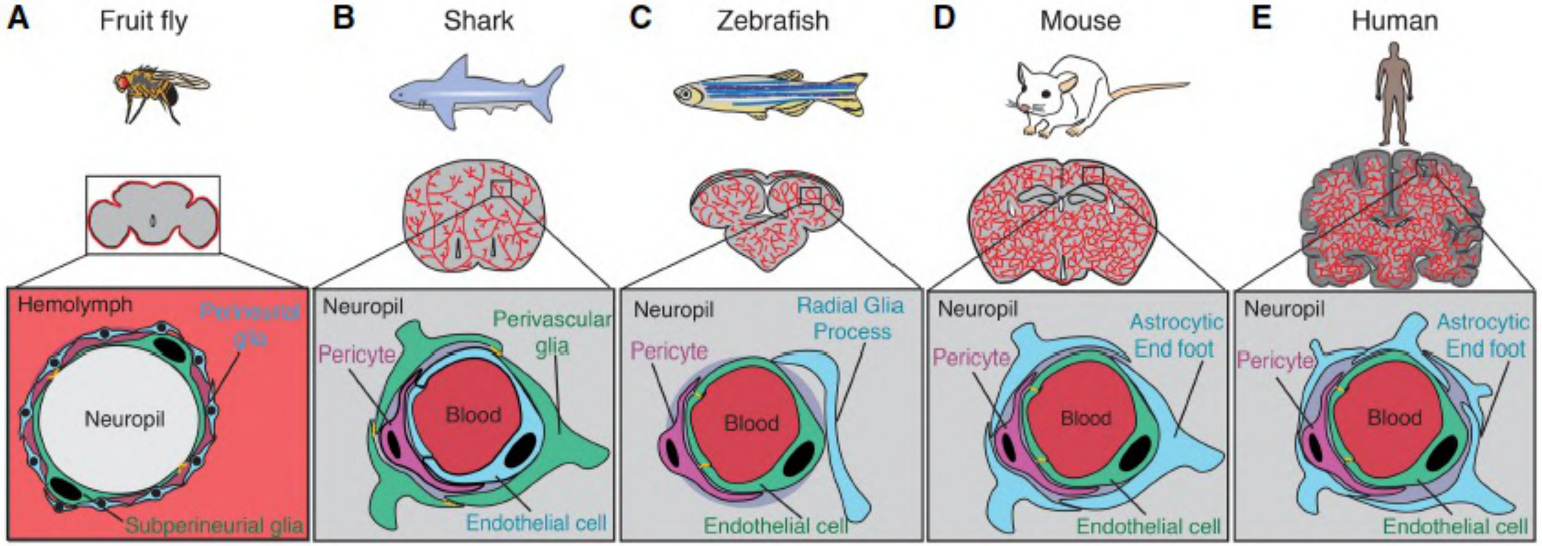
MAGNUS BUNDGAARD[1] AND N. JOAN ABBOTT[2*]
[1]*Department of Medical Physiology, University of Copenhagen, Panum Institute, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark*
[2]*Pharmaceutical Science Division, King's College London, London SE1 1UL, United Kingdom*

Bridging barriers: a comparative look at the blood–brain barrier across organisms

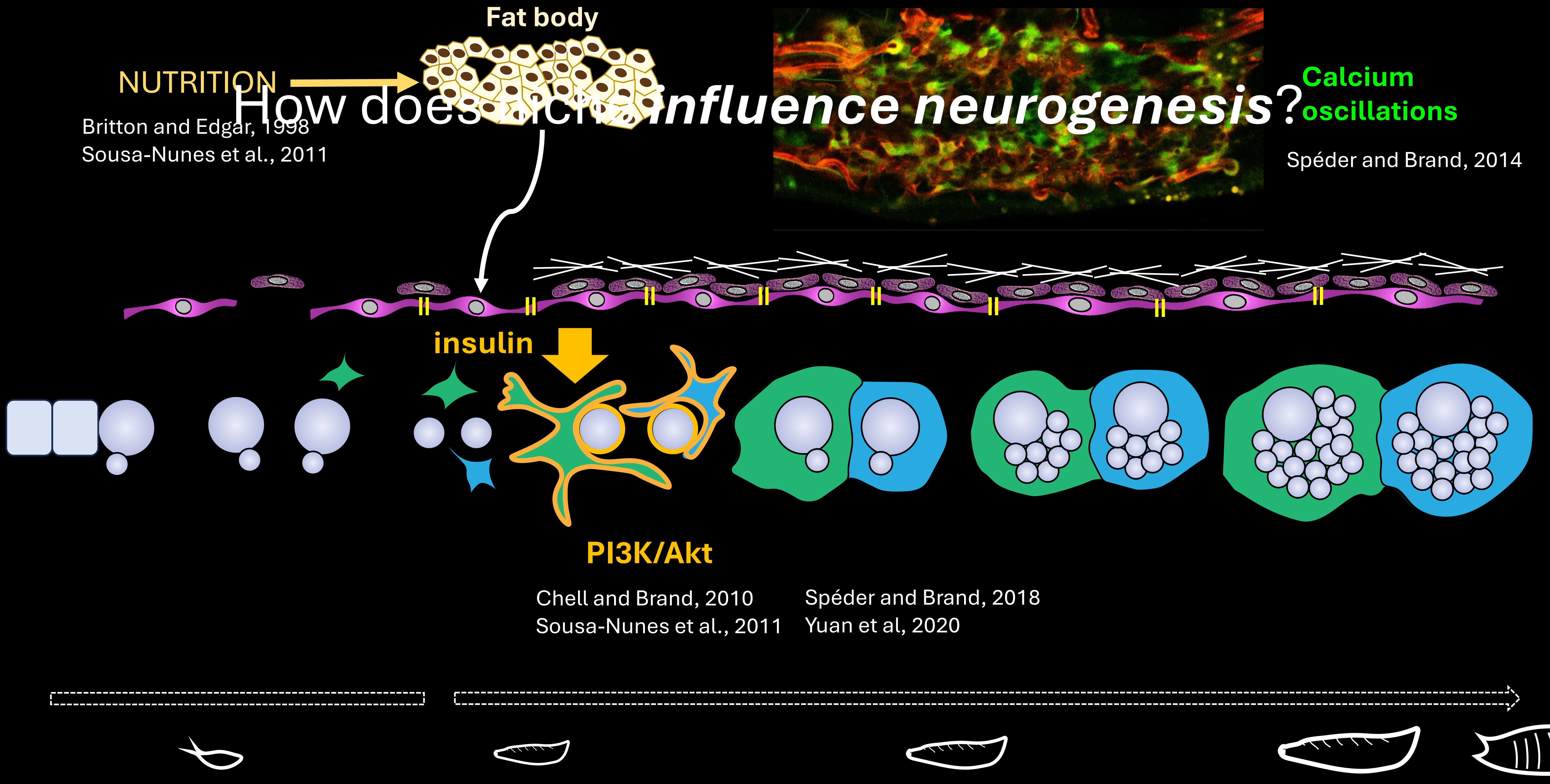
Natasha M. O'Brown,[1] Sarah J. Pfau,[1] and Chenghua Gu
Department of Neurobiology, Harvard Medical School, Boston, Massachusetts 02115, USA

GENES & DEVELOPMENT 32:466–478 Published by Cold Spring Harbor Laboratory Press; ISSN 0890-9369/18; www.genesdev.org

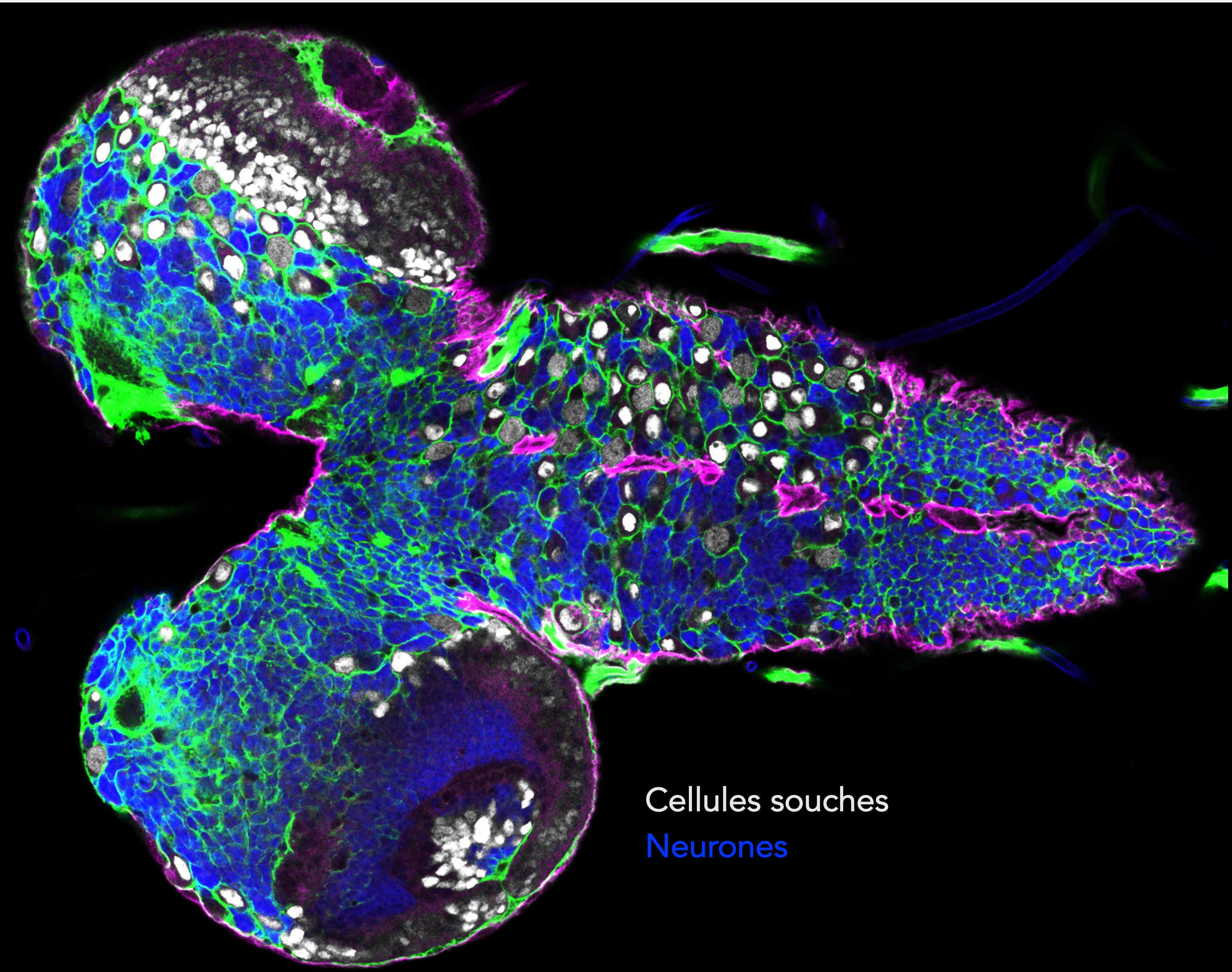




The Blood-Brain barrier controls NSC reactivation



The neurogenic niche in the developing Drosophila brain



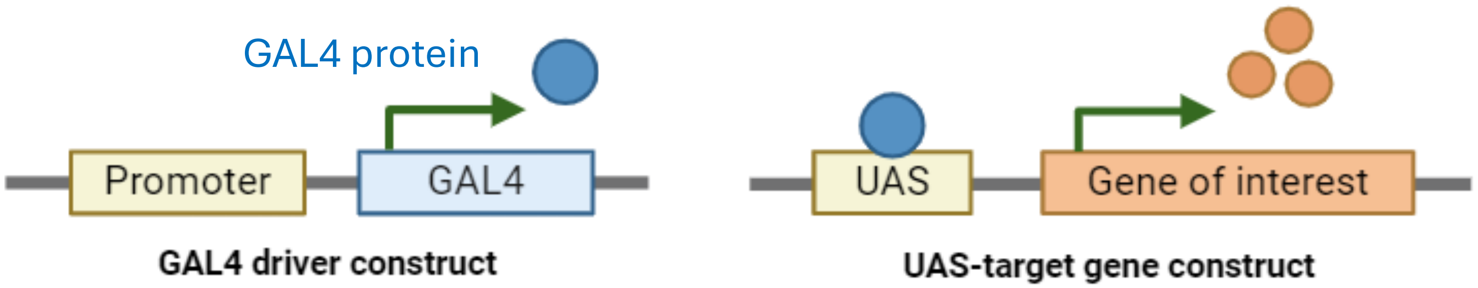
WELL-CHARACTERIZED NSCS

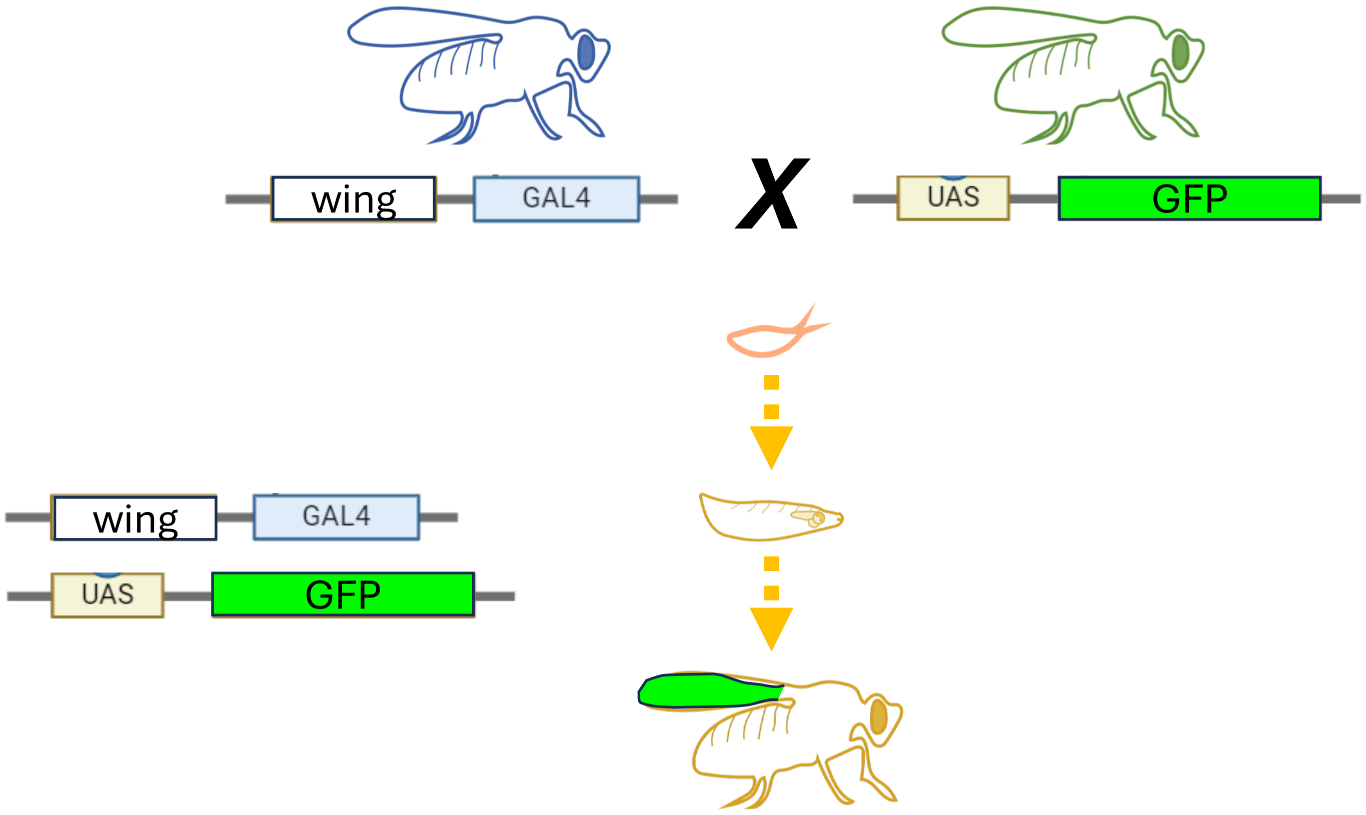
DEFINED NICHE

ACCESS TO ENVIRONMENT

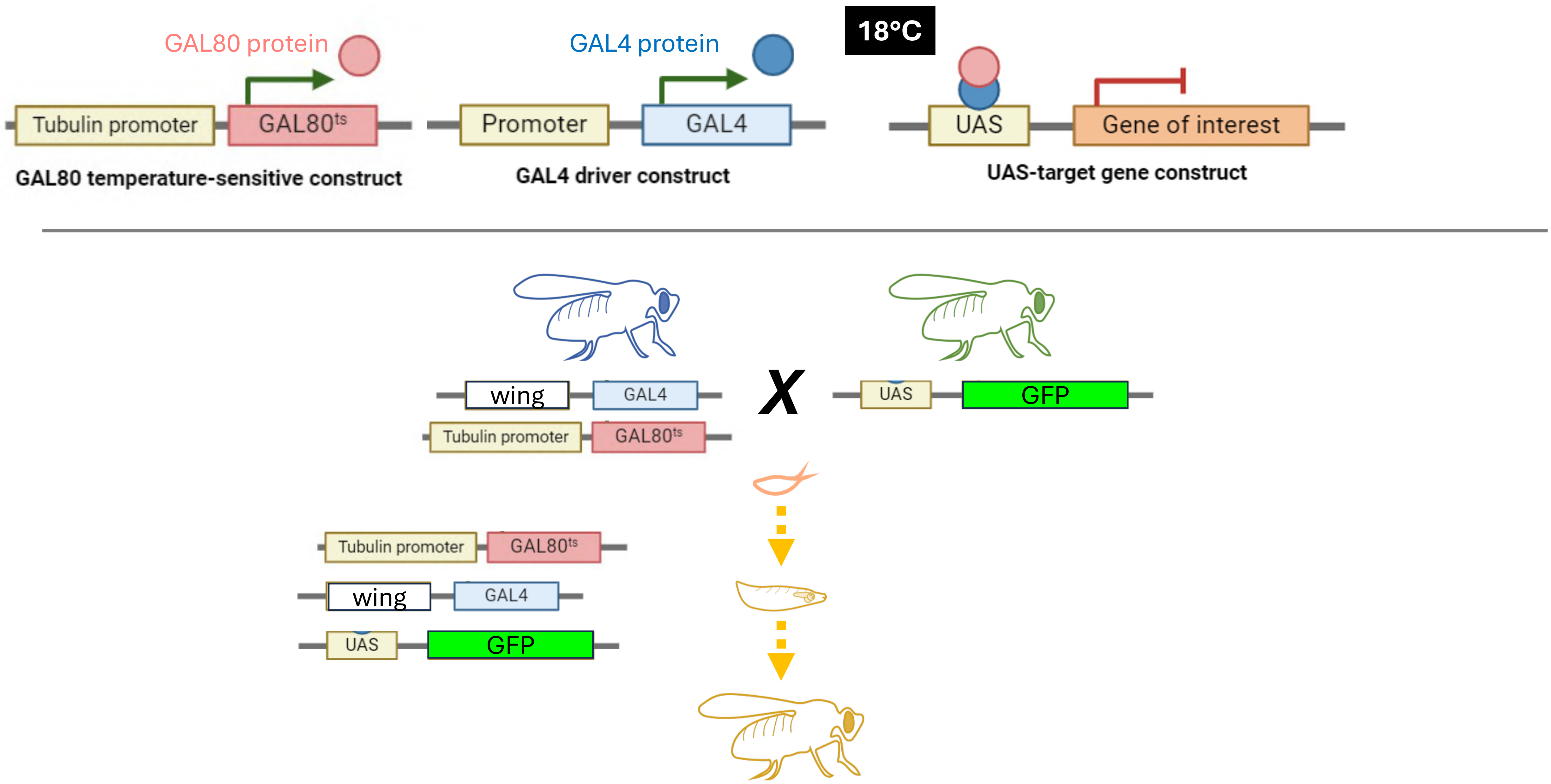
DROSOPHILA GENETICS

THE GAL4/UAS/GAL80^{ts} system in flies

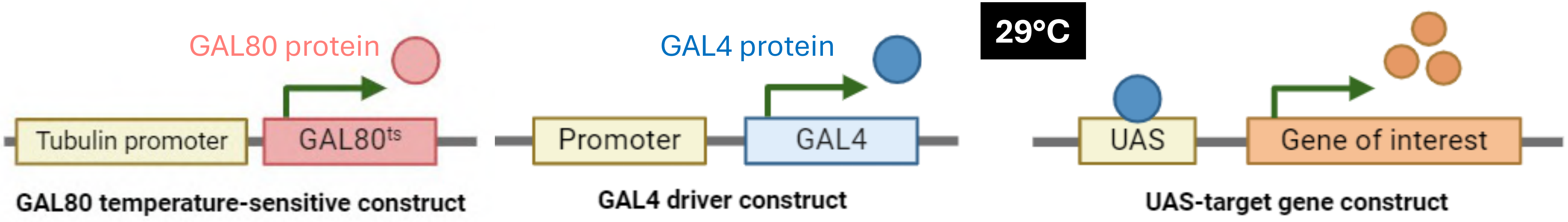


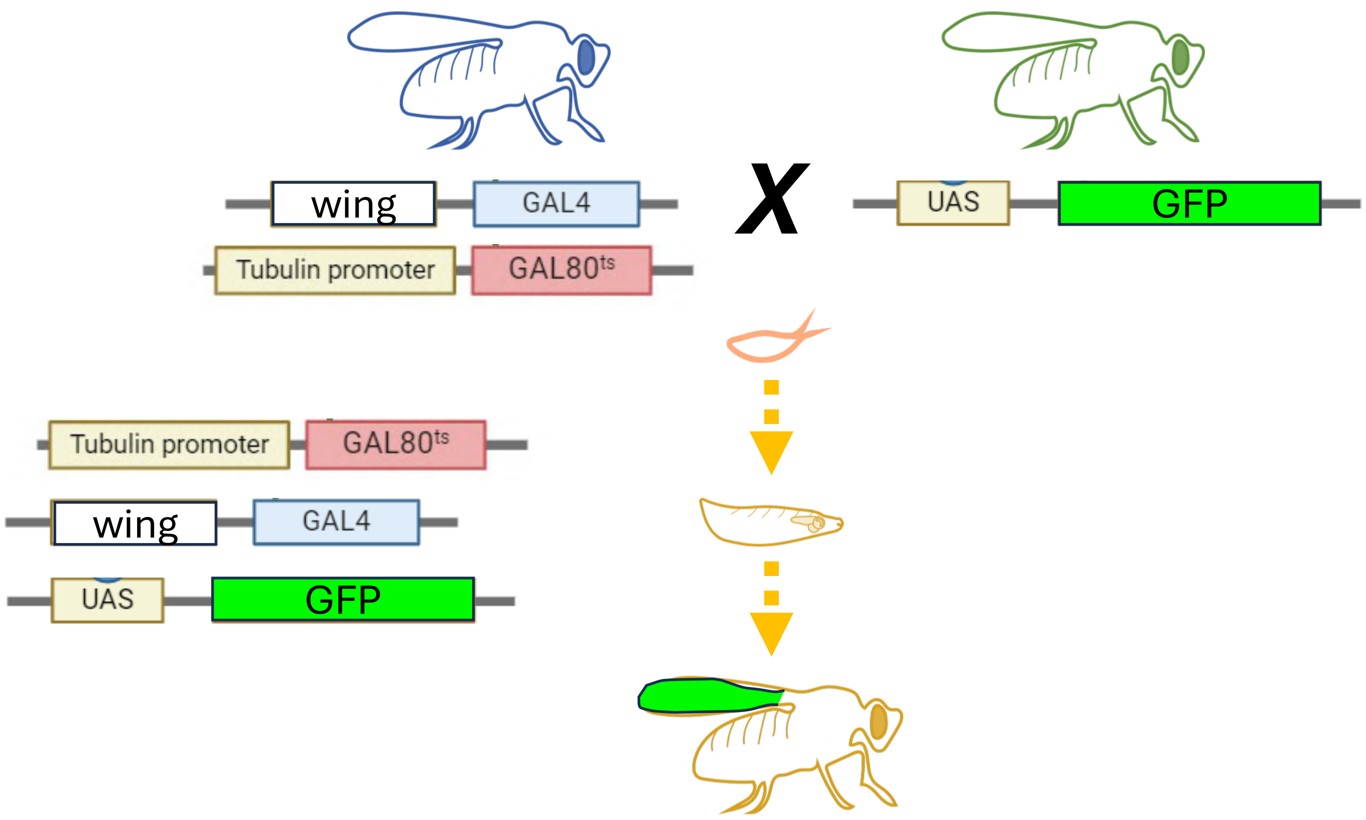


THE GAL4/UAS/GAL80^{ts} system in flies



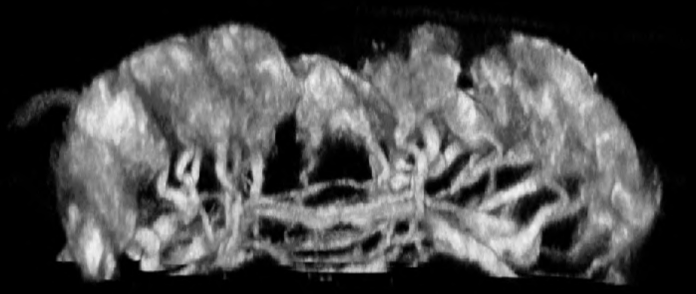
THE GAL4/UAS/GAL80^{ts} system in flies





1. STRUCTURE

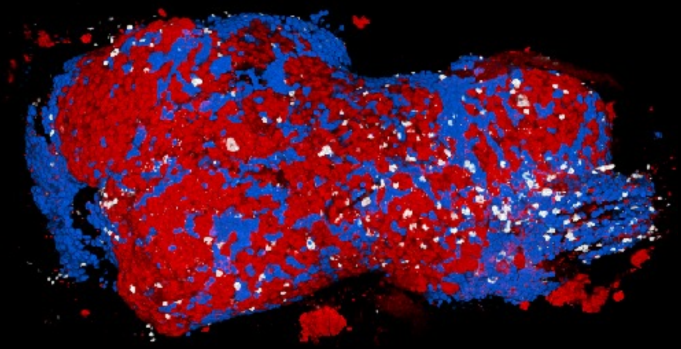
From development to behaviour



Complex genetics
Behaviour

3. TUMOUR

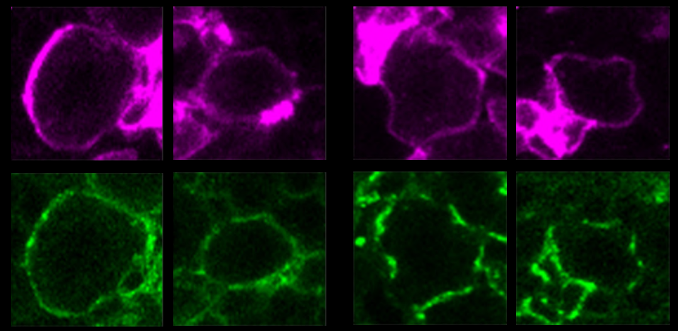
Host tissue resistance



Genetics
TaDa

2. MECHANICS

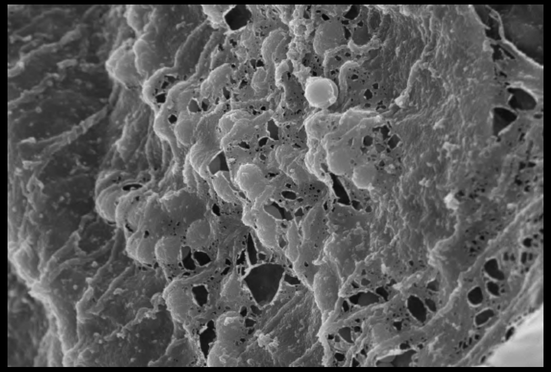
Keeping the balance



TaDa
Biophysics

4. INFECTION

Crossing the barrier



Explants

2. MECHANICS

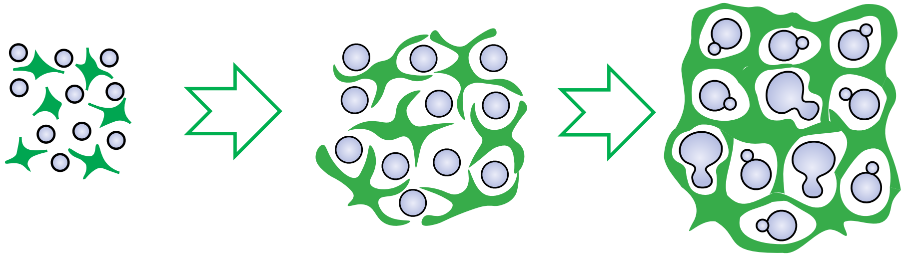
Keeping the balance

Anna Segú-Cristina

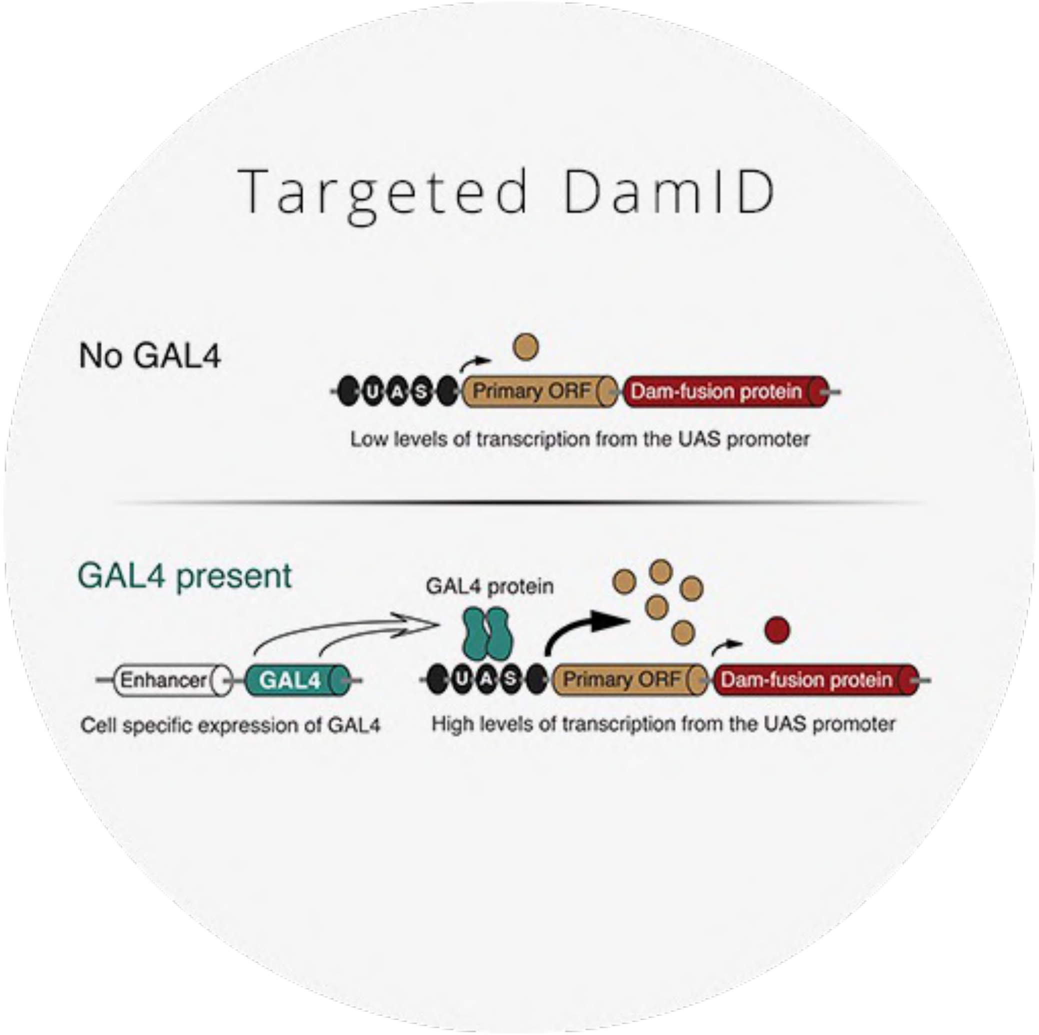
CG transcriptome over time identifies the immunoglobulin Dpr10

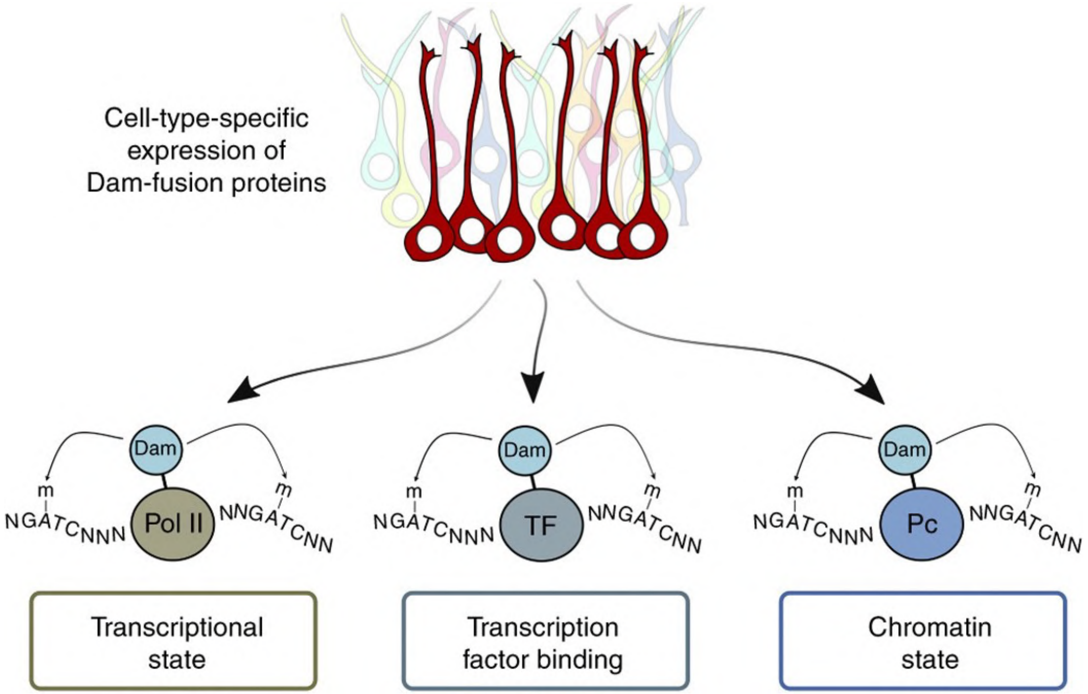
Targeted DamId (TaDa)

Southall et al., 2013



The Targeted DamID system





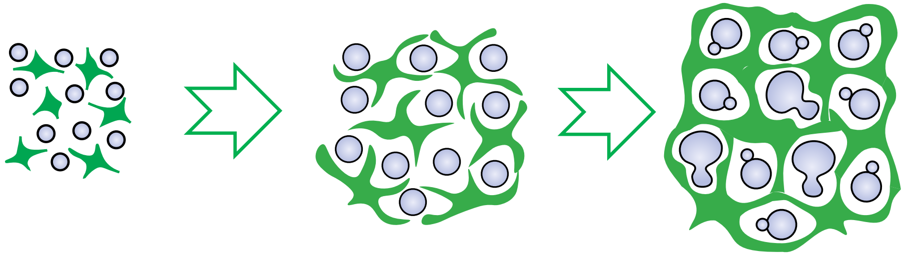
Andrea Brand lab

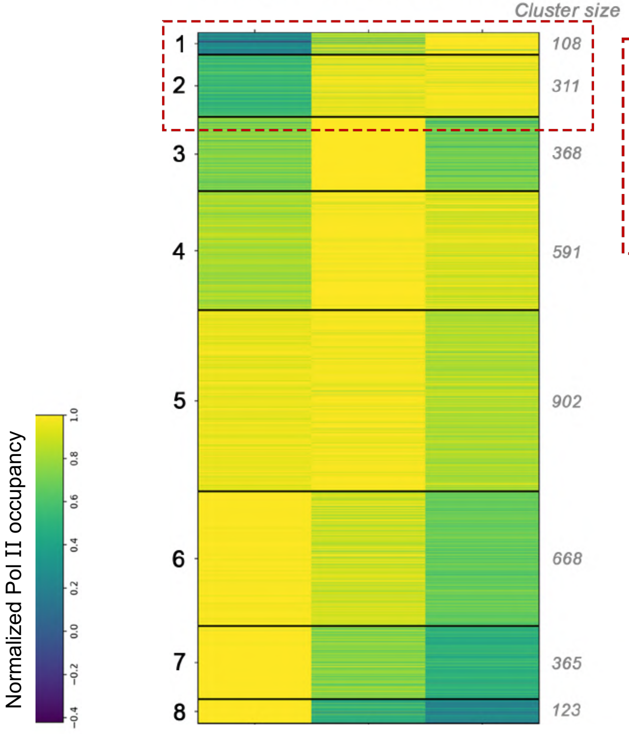
Tony D Southall et al. 2013

CG transcriptome over time identifies the immunoglobulin Dpr10

Targeted DamId (TaDa)

Southall et al., 2013

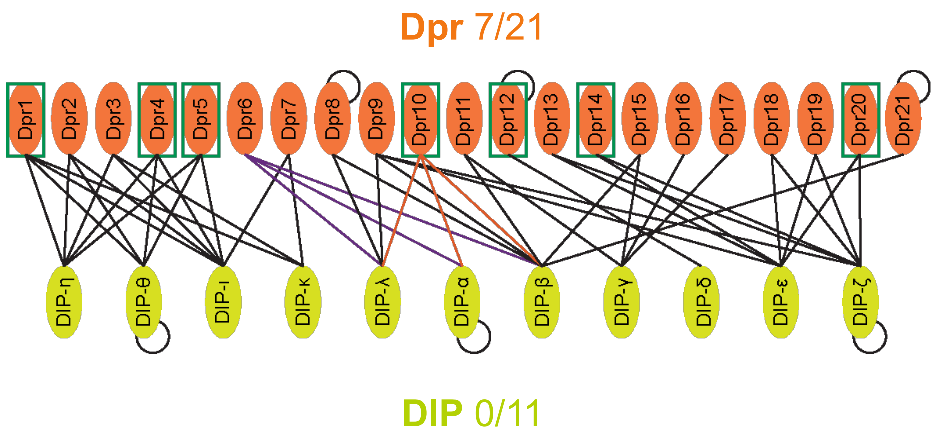


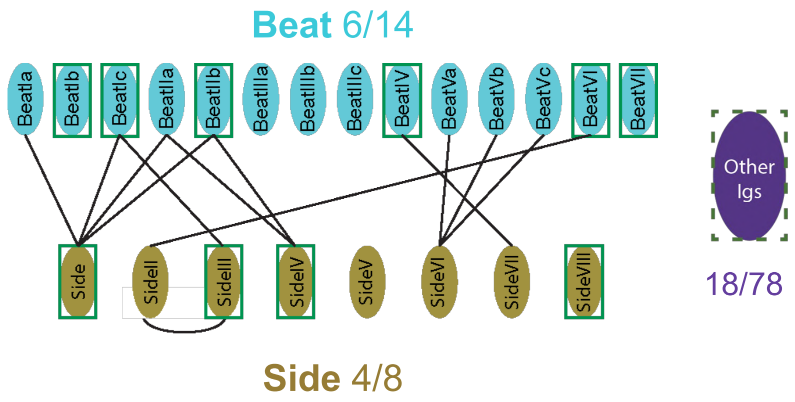


3436 genes (FDR < 0.01%)

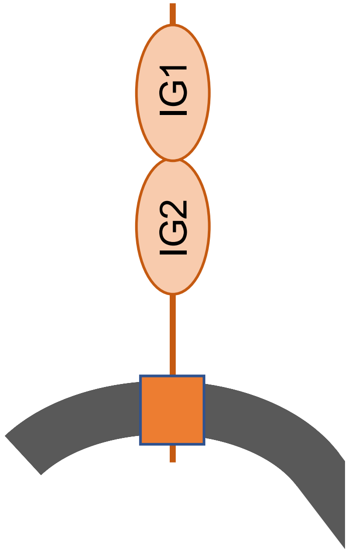
TOP ENRICHED GO TERMS
- Immunoglobulin (9.19)
- Transcription (2.98)
- Extracellular signalling (2.46)
- Homeobox (2.39)
- Ion transport (2.27)

Immunoglobulin superfamily

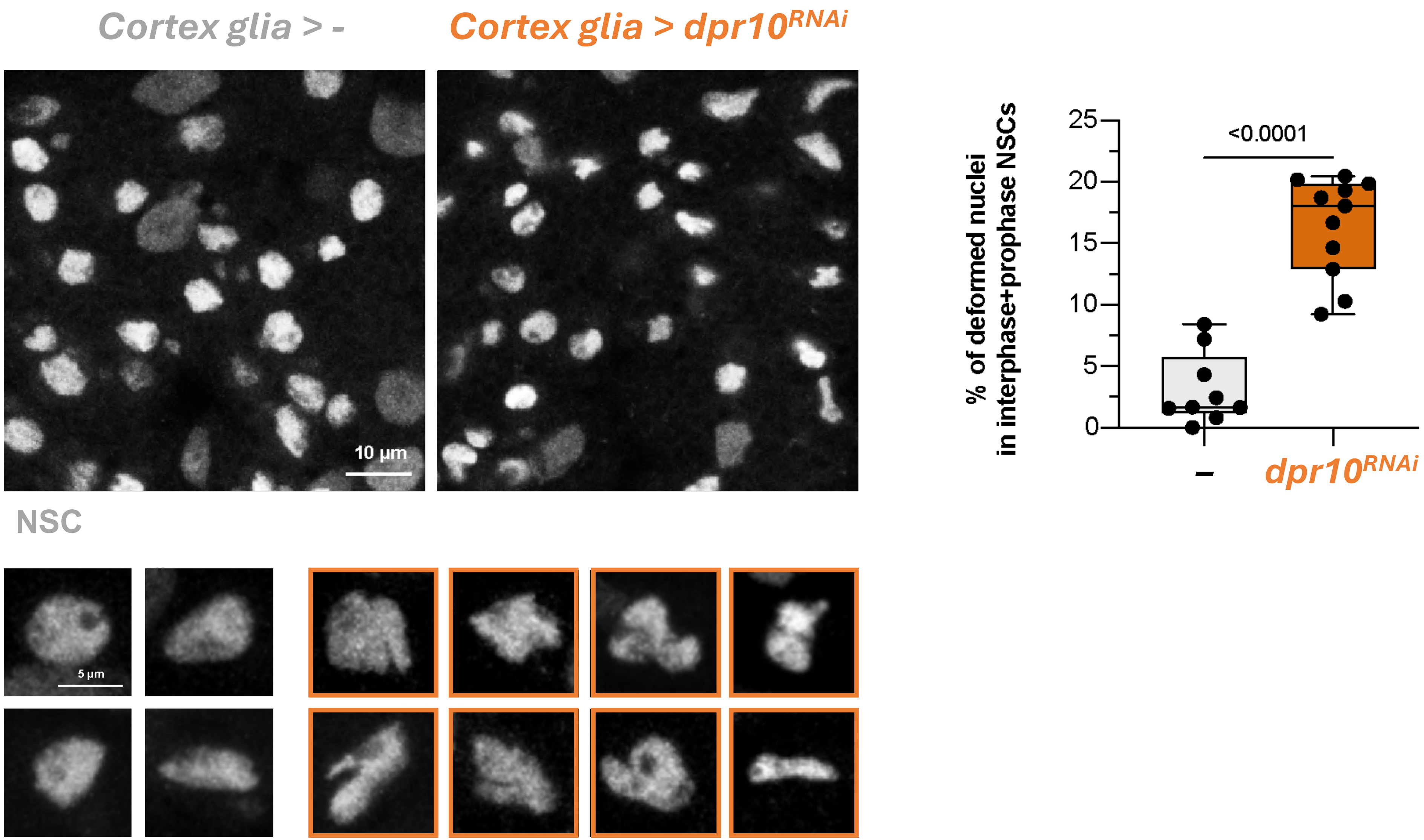




Dpr10

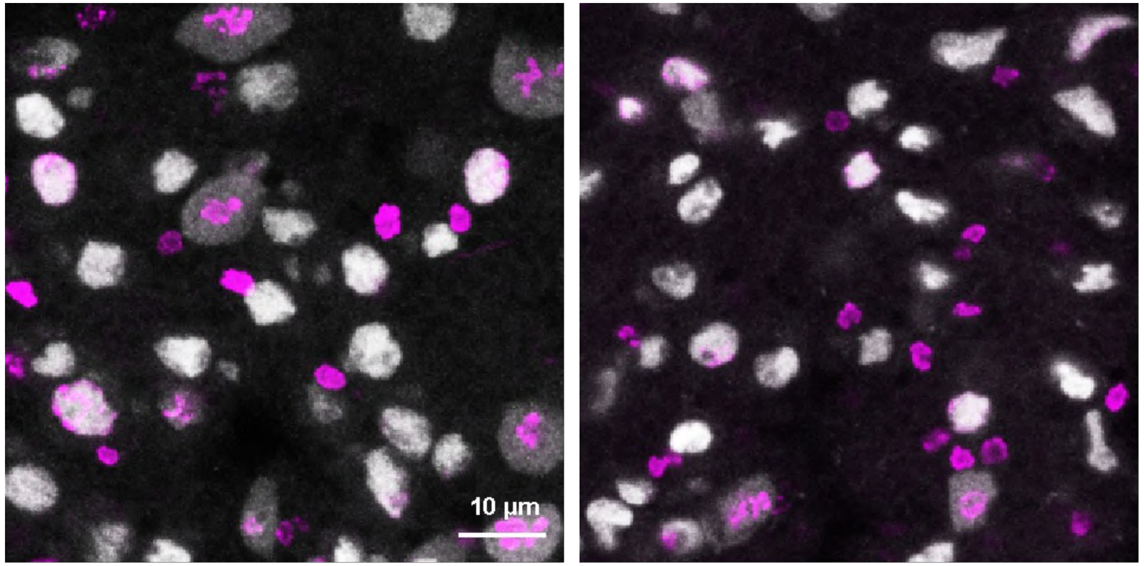


Dpr10 non-autonomously controls NSC nuclear shape

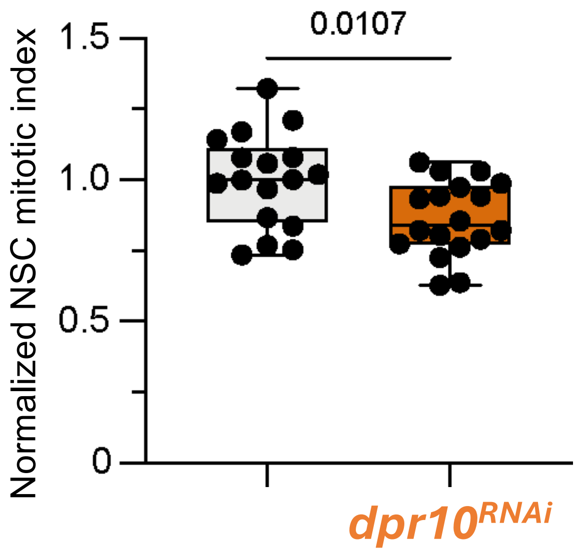


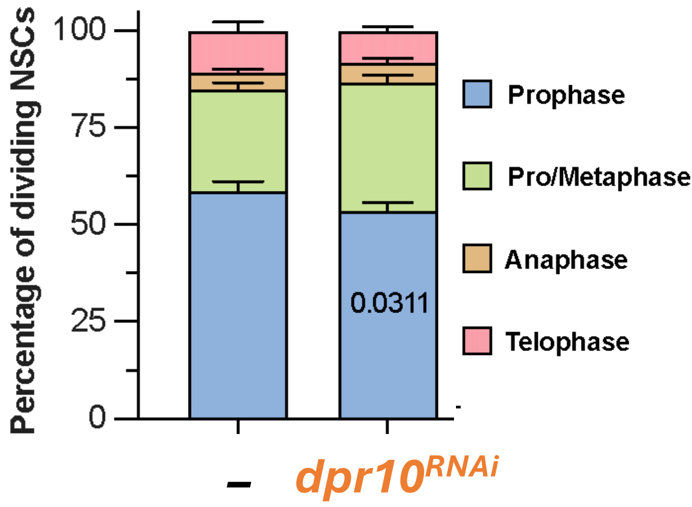
Dpr10 non-autonomously controls NSC nuclear shape and division

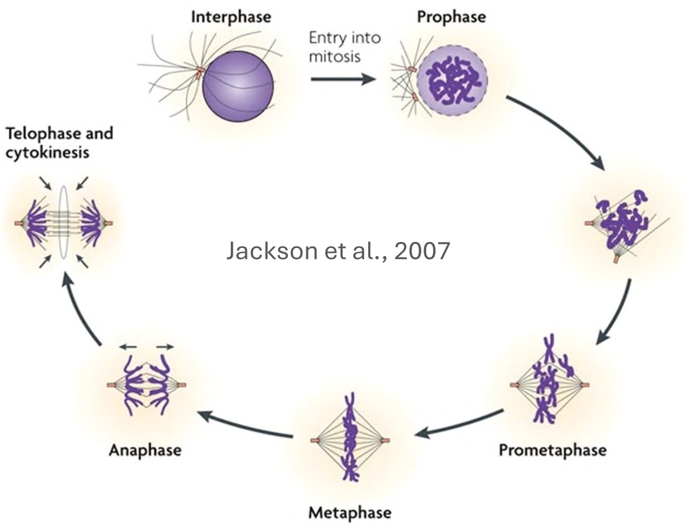
Cortex glia > - *Cortex glia > $dpr10^{RNAi}$*



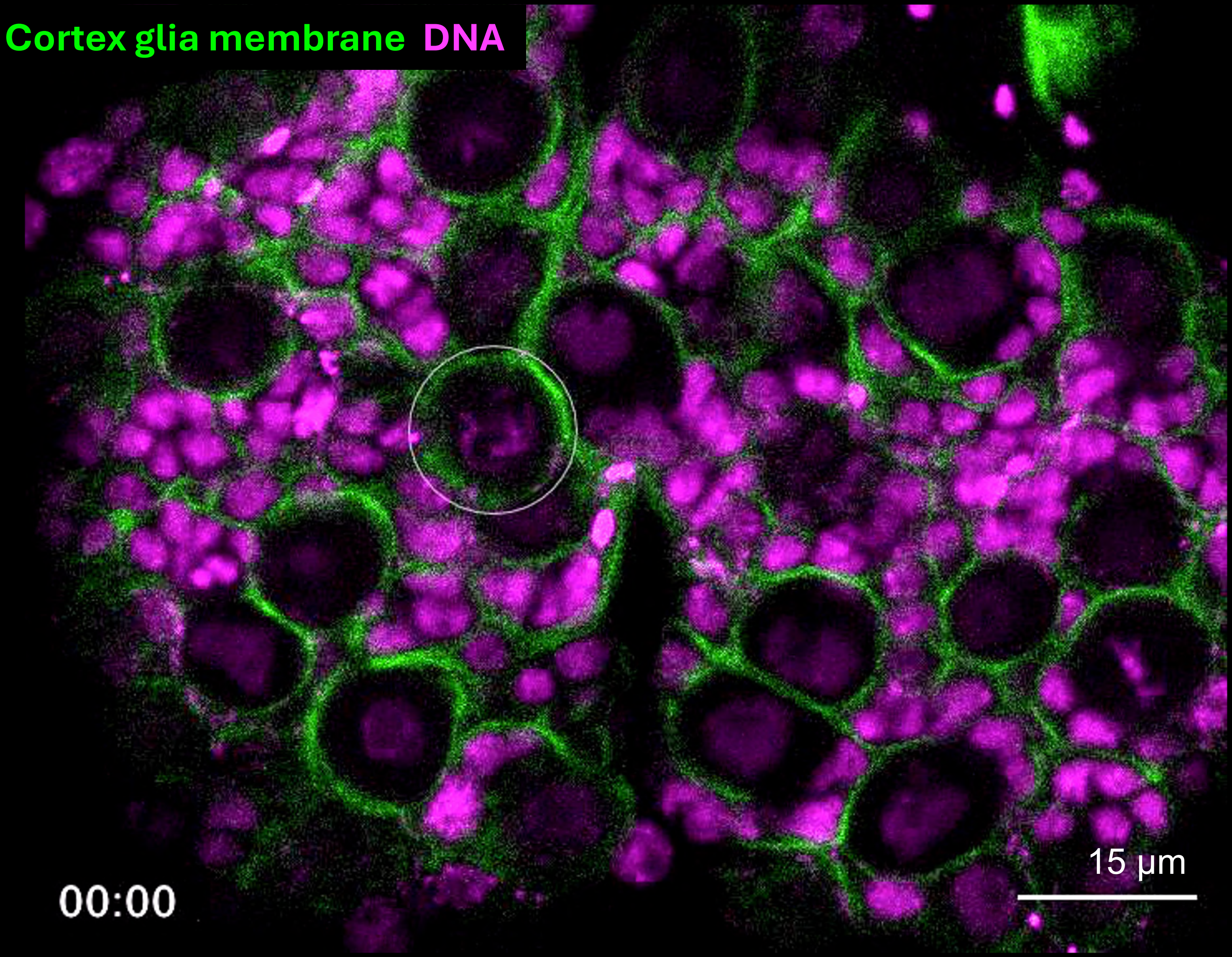
NSC PH3





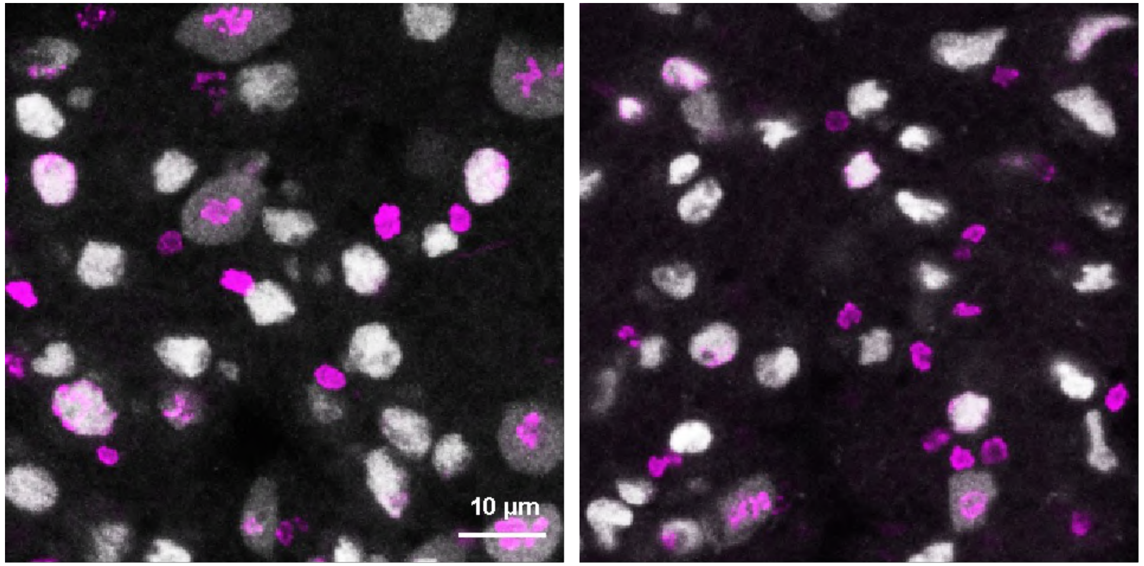


$CG > dpr10^{RNAi}$

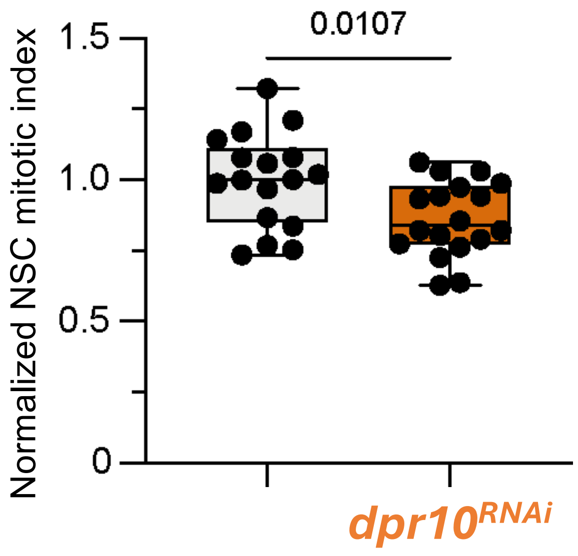


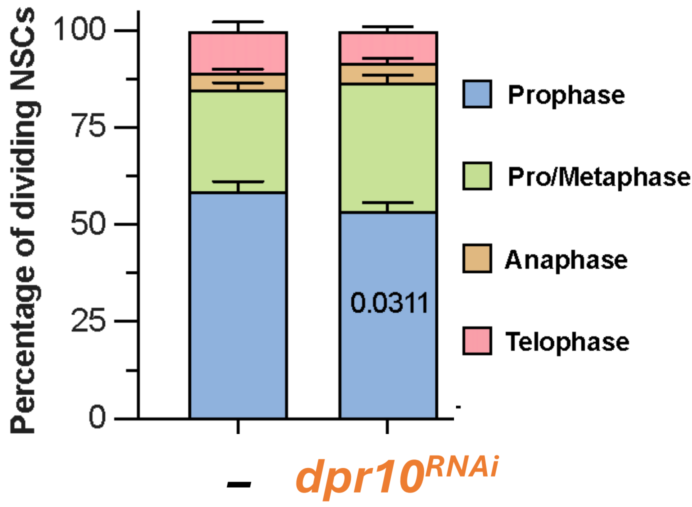
Dpr10 non-autonomously controls NSC nuclear shape and division

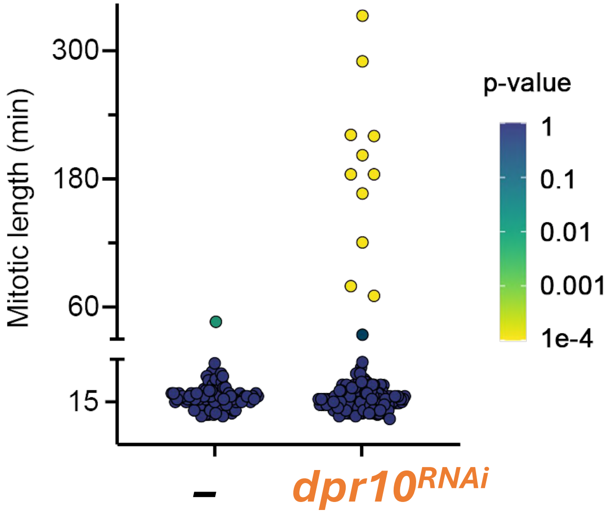
Cortex glia > -　　*Cortex glia > dpr10^{RNAi}*



NSC PH3



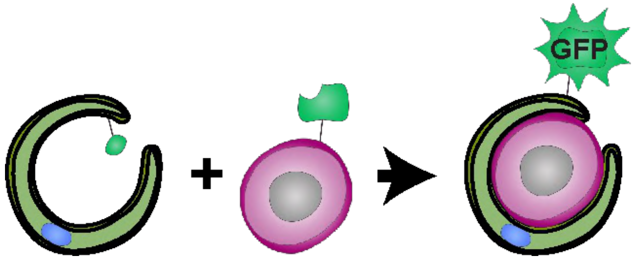




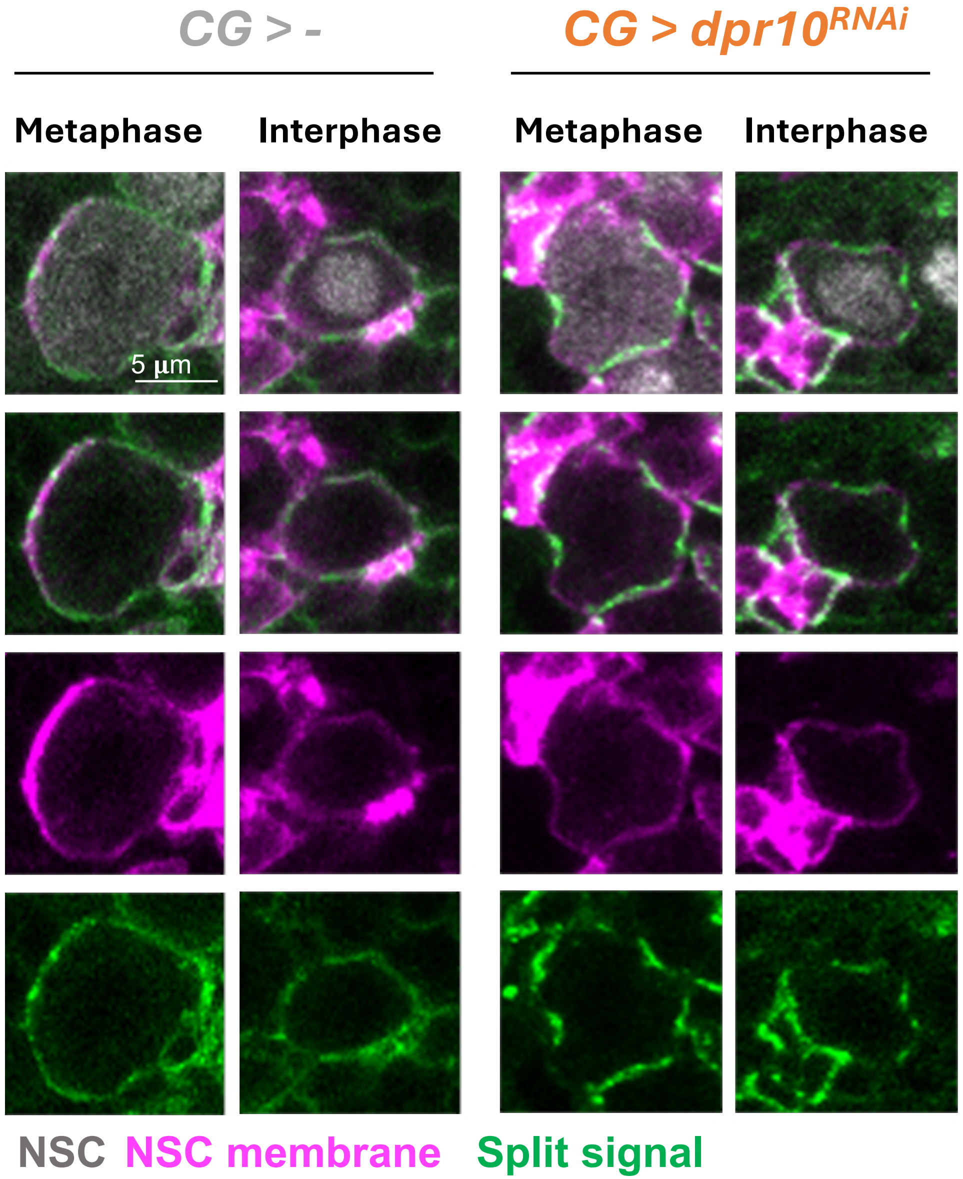
Dpr10 controls NSC-CG membrane interaction and geomtery

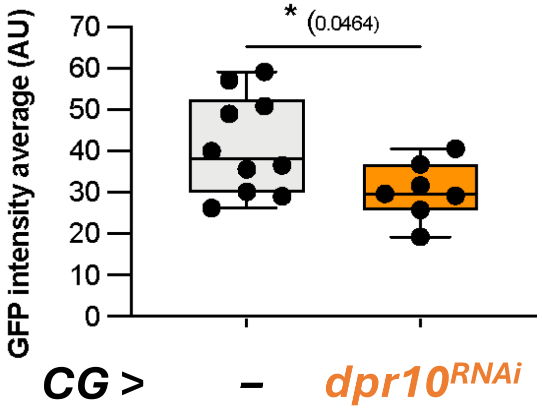
Spatial readout of membrane proximity

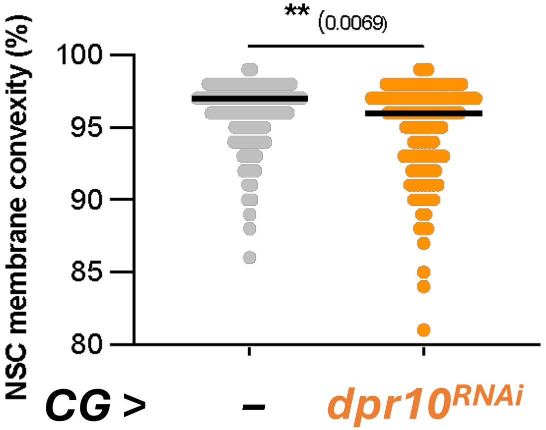
Split GFP tool

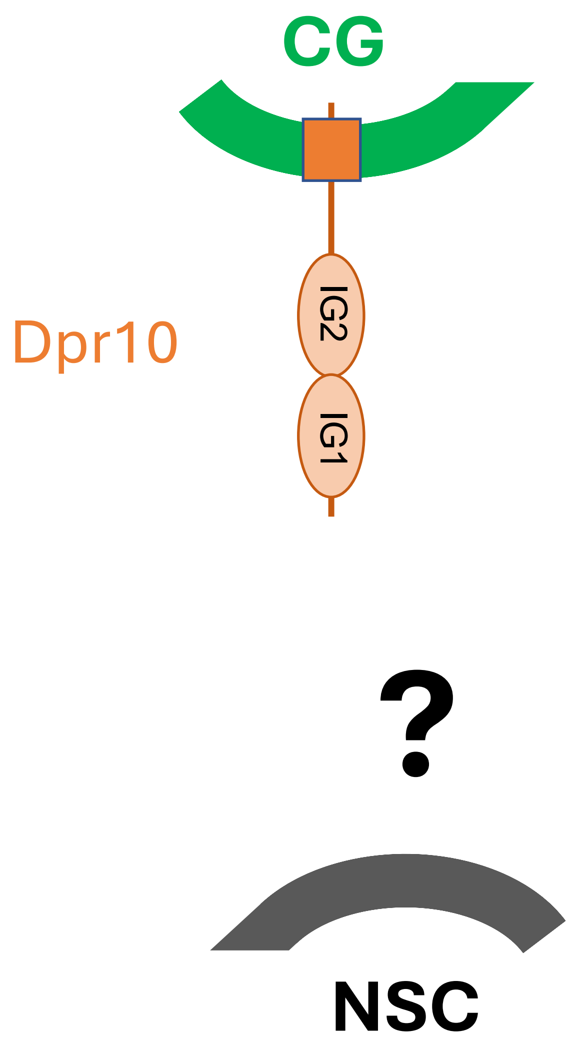


Cabantous et al., 2005
Feinberg et al., 2008



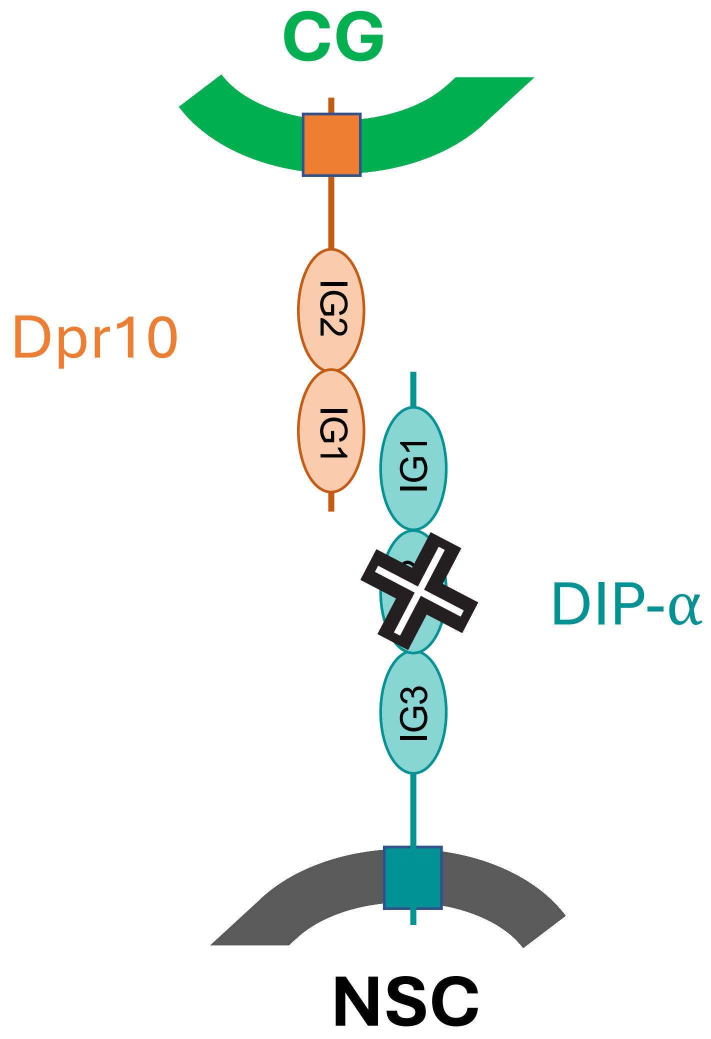





CG
Dpr10
IG2
IG1
?
NSC

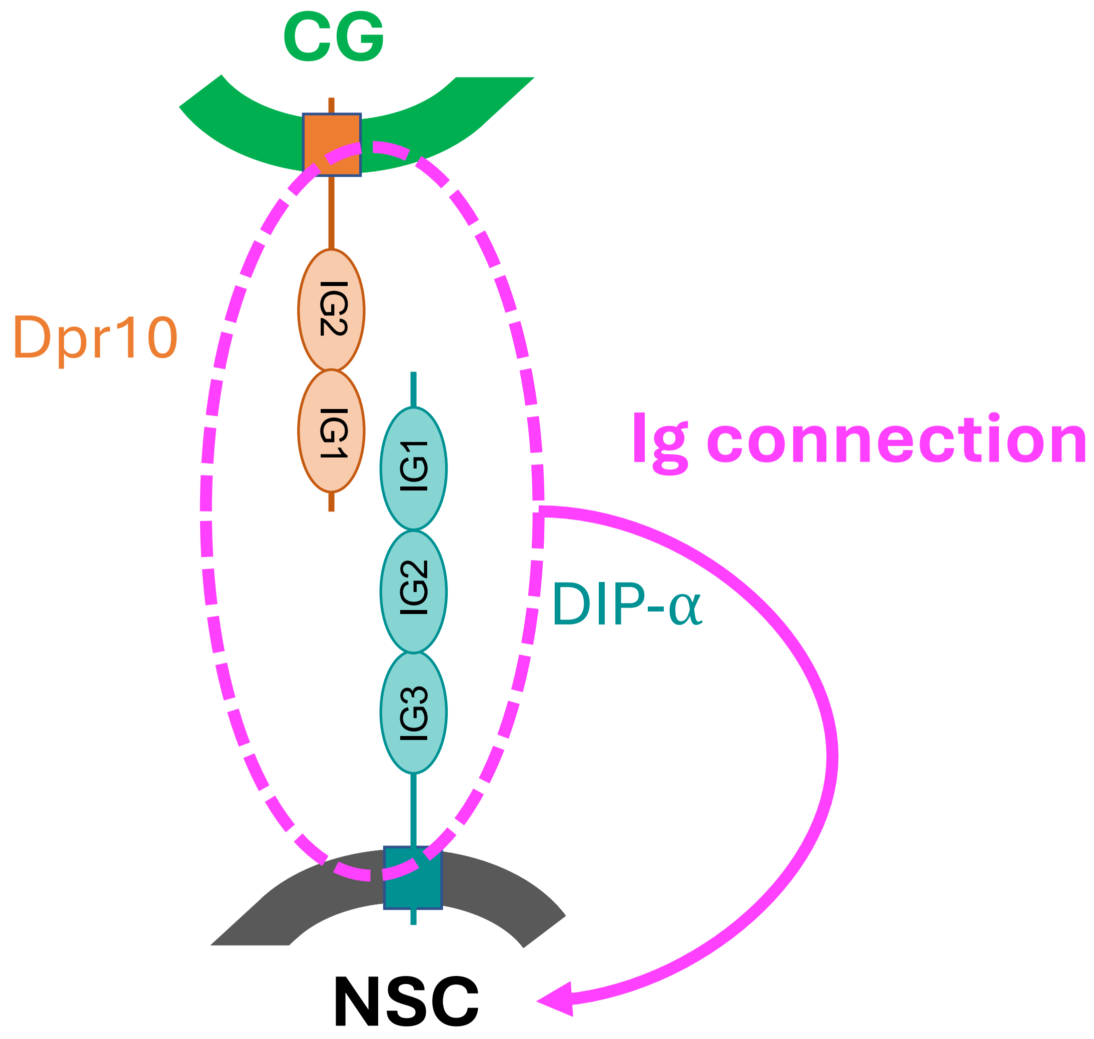
DIP-α is Dpr10 partner and mediator in NSCs

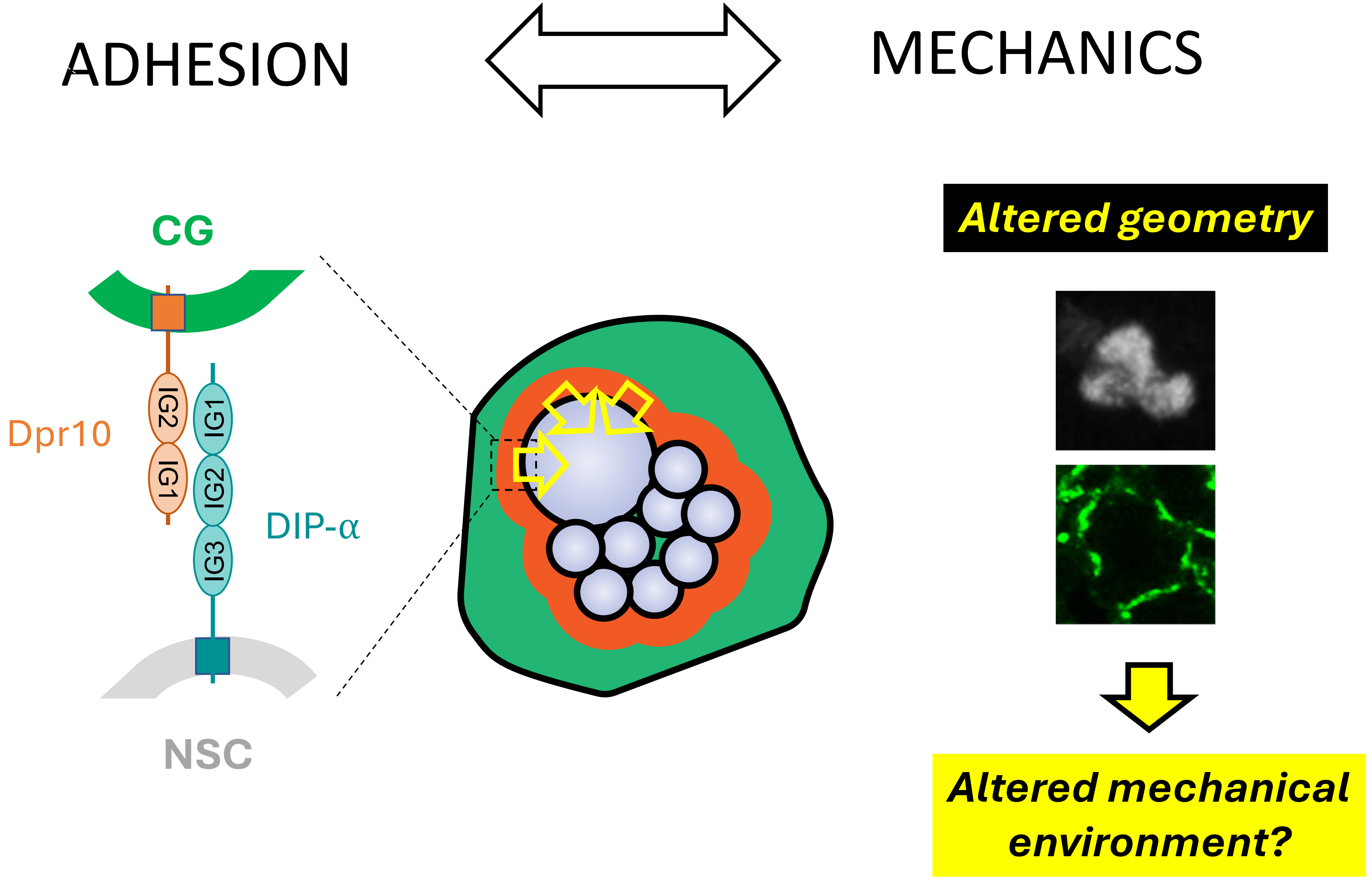
Nuclear deformation



Altered proliferation

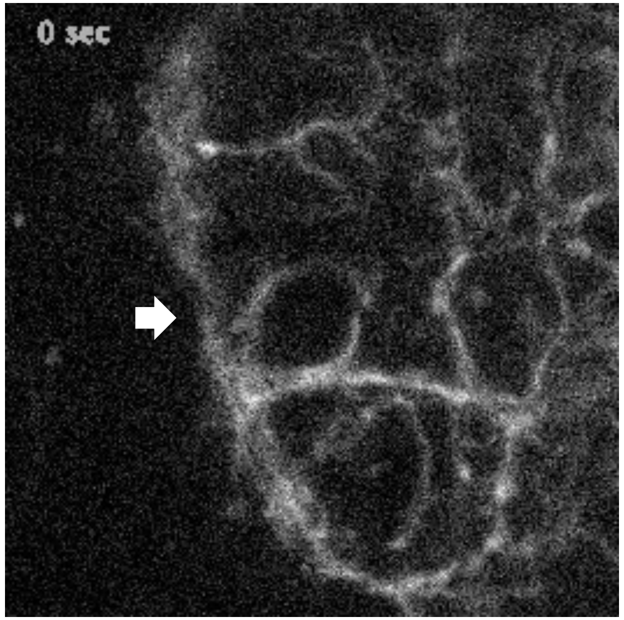
DIP-α is Dpr10 partner and mediator in NSCs




ADHESION
MECHANICS
CG
Dpr10
IG2
IG1
IG1
IG2
IG3
DIP-α
NSC
Altered geometry
Altered mechanical environment?

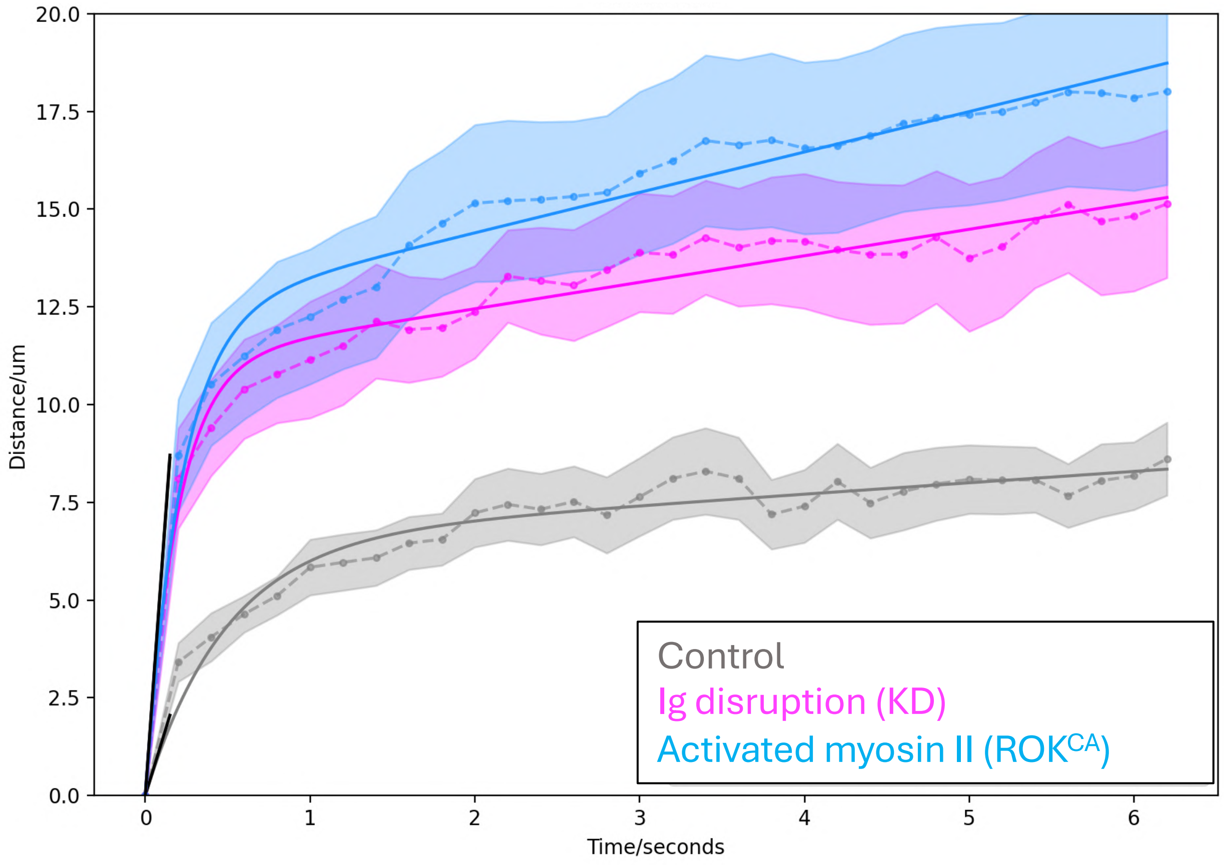
Ig disruption increases cortical tension in the CG

➢ *Assessment of cortical tension through mesure of relaxation after laser cut*



$$d(t) = (R/K)*(1 + M*K*t/R – \exp[-1*K*t])$$

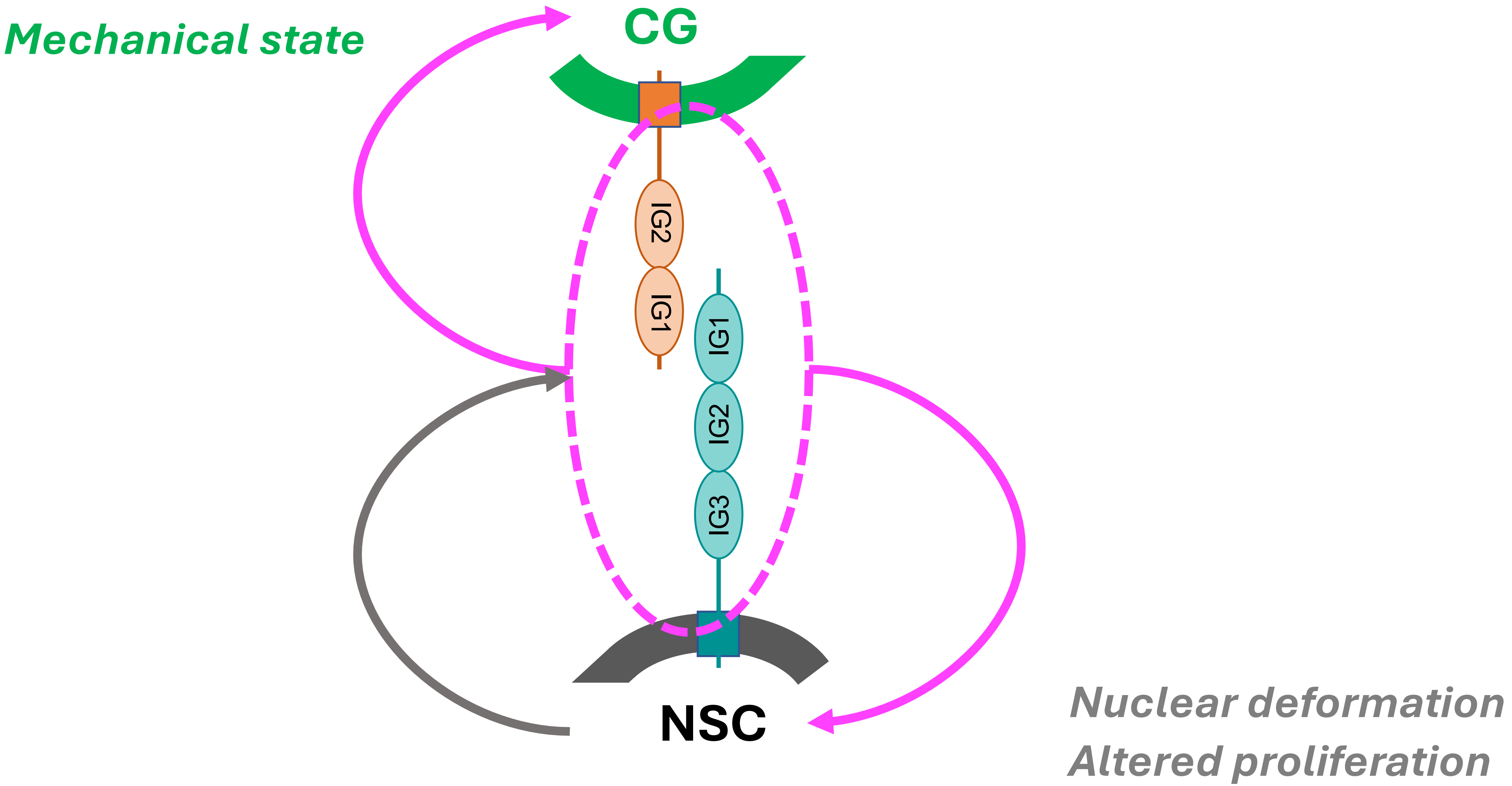
R = Initial recoil
K = elasticity



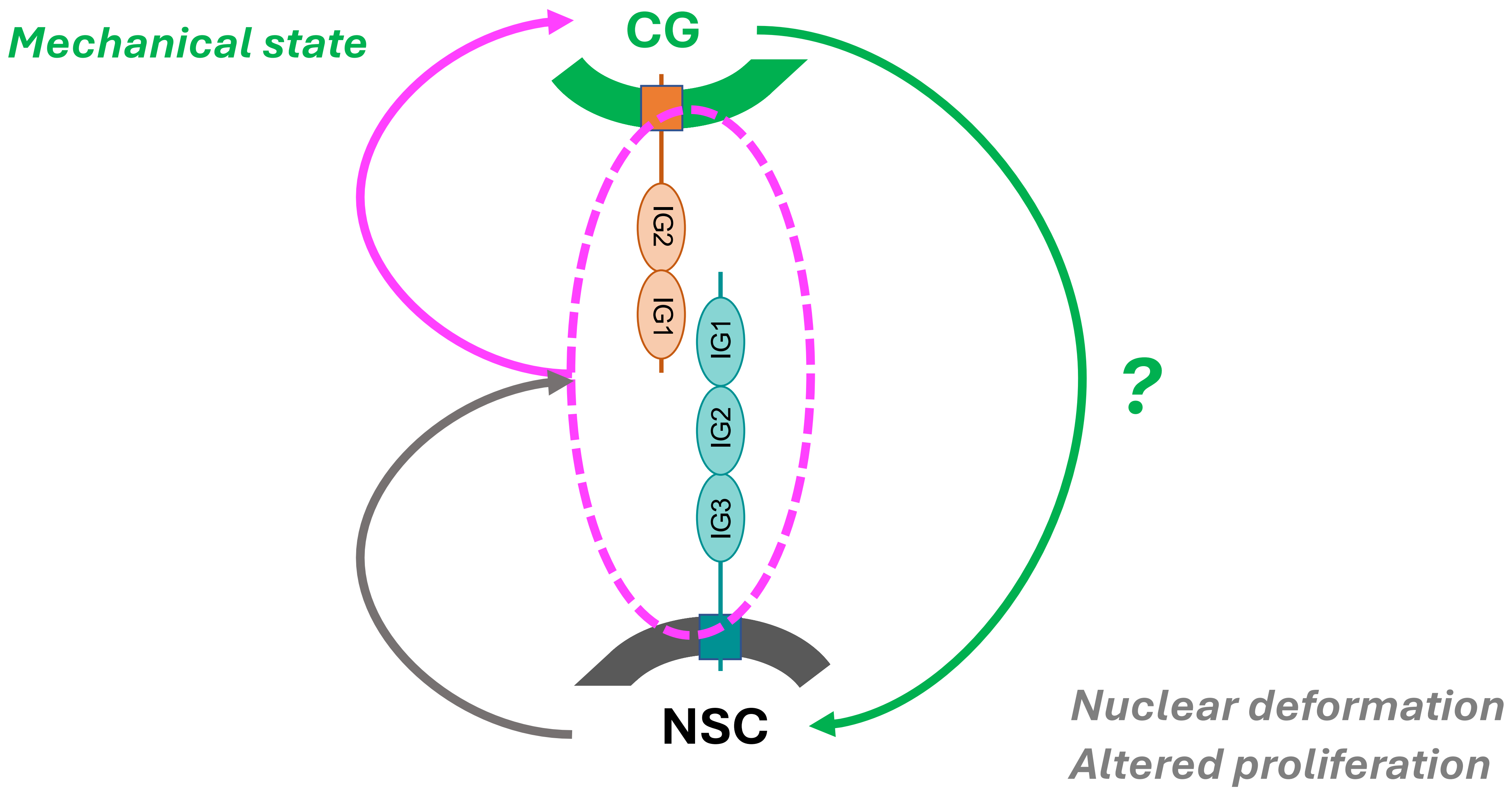
Initial gradient (d(t0))

Ctrl = 13.71	ROK^{CA} = 57.75	Ig KD = 58.28

Igs act as mechanoregulators in the CG



Igs act as mechanoregulators in the CG



Ig-controlled CG cortical tension is responsible for NSC phenotype

1. Increasing CG cortical tension (CG > ROK^{CA}) mimics Ig disruption

✓ *Altered NSC nuclear shape* ✓ *Altered NSC proliferation*

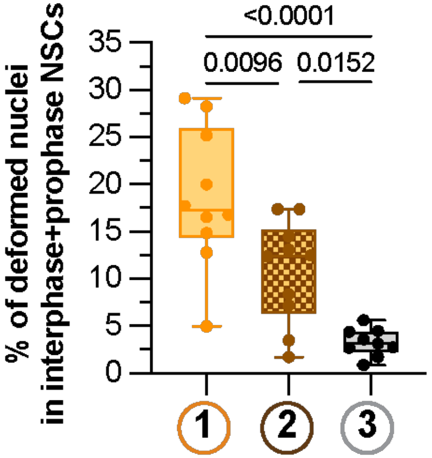
2. Decreasing CG cortical tension (CG > Rho^{DN}) rescues Ig disruption

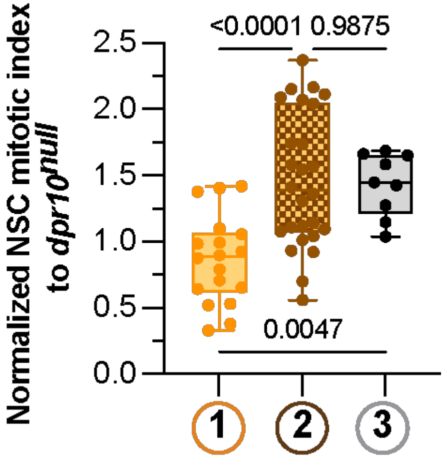
✓ *Rescued nuclear shape* ✓ *Rescued proliferation*

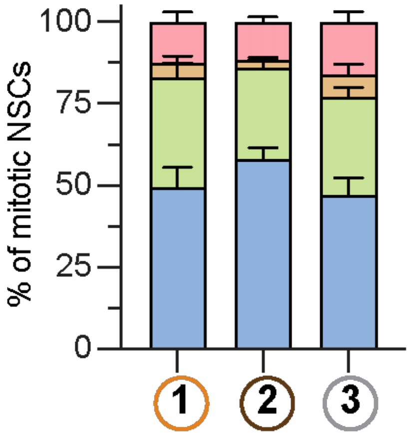
1 dpr10^{NULL}

2 dpr10^{NULL} + CG > Rho^{DN}

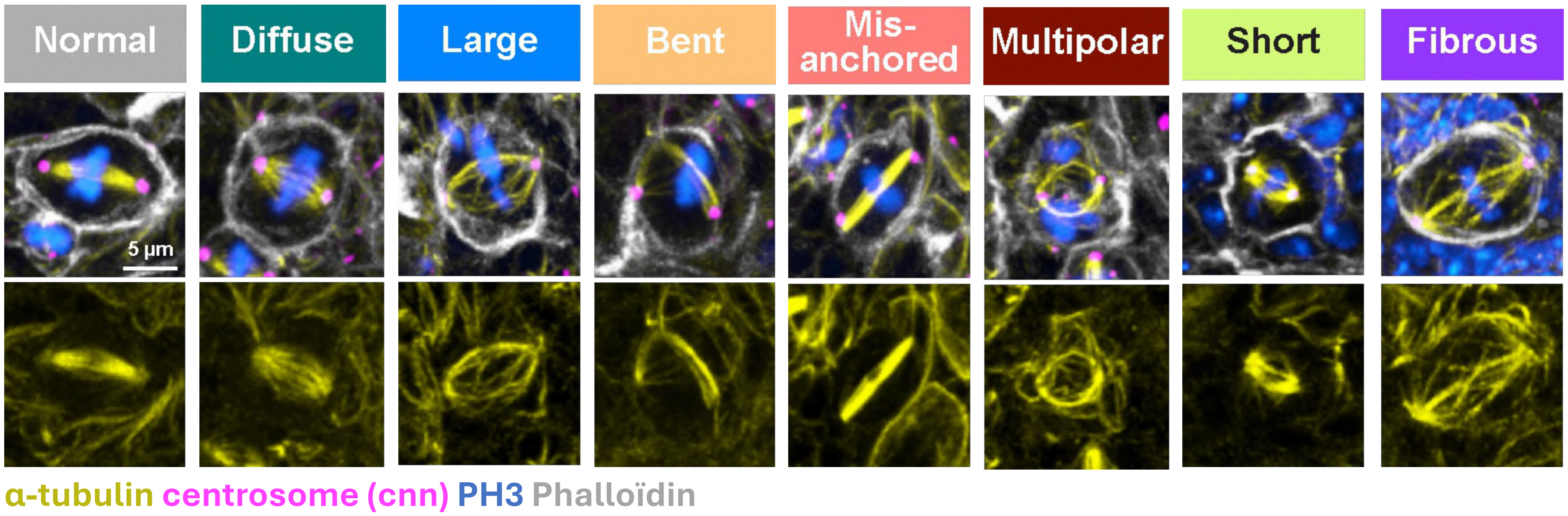
3 +/dpr10^{NULL}

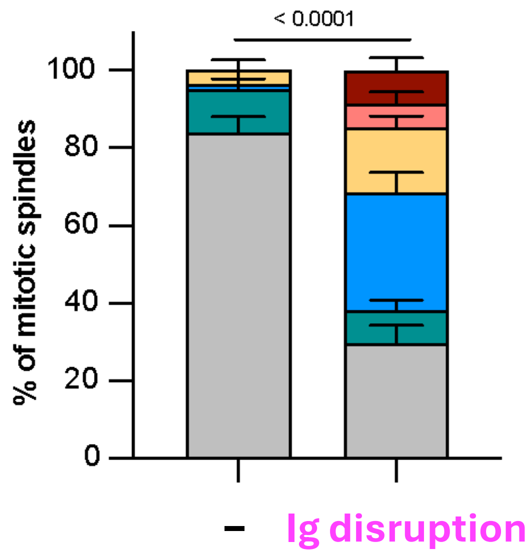






Defective niche mechanics lead to abnormal mitotic spindles in NSCs



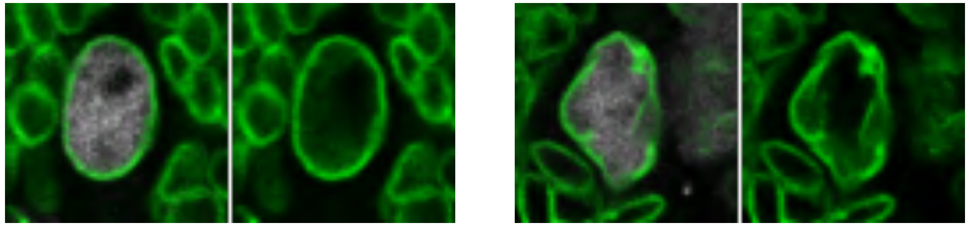


✓ ***Recapitulated under increased CG tensile forces***

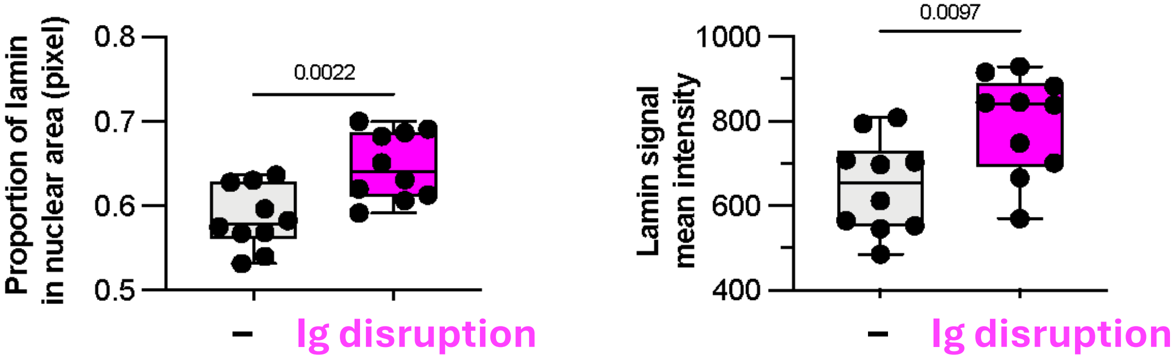
Defective niche mechanics increase lamin levels in NSCs

1. The nuclear lamina displays increased lamin content and folding

Control Ig disruption



NSC Lamin (B-type !)



✓ ***Recapitulated under increased CG tensile forces***

2. Lamin accumulation is causative of nuclear deformation

?

Nuclear phenotype ⟺ **Proliferative phenotype**

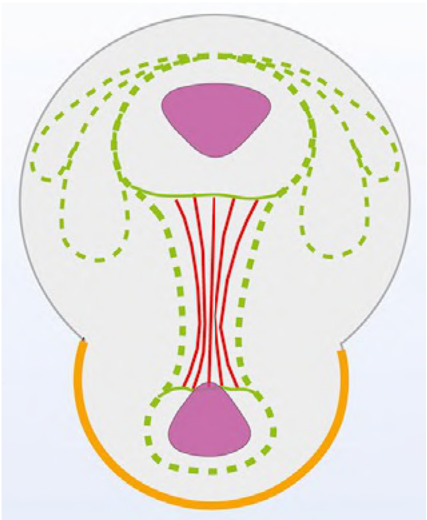
Lamin accumulation

Spindle deformation

?

Nuclear phenotype → **Proliferative phenotype**

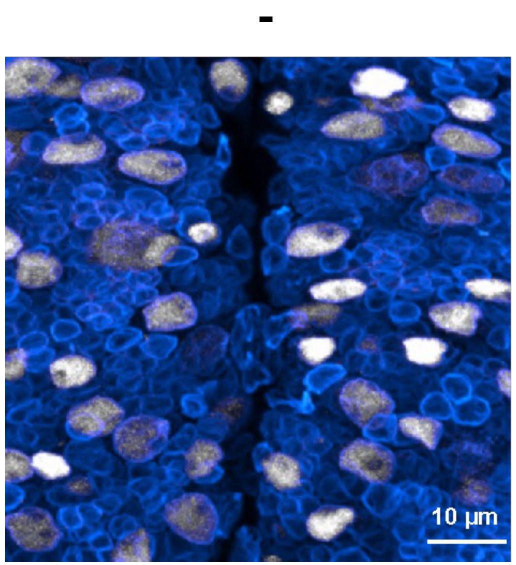
Lamin accumulation



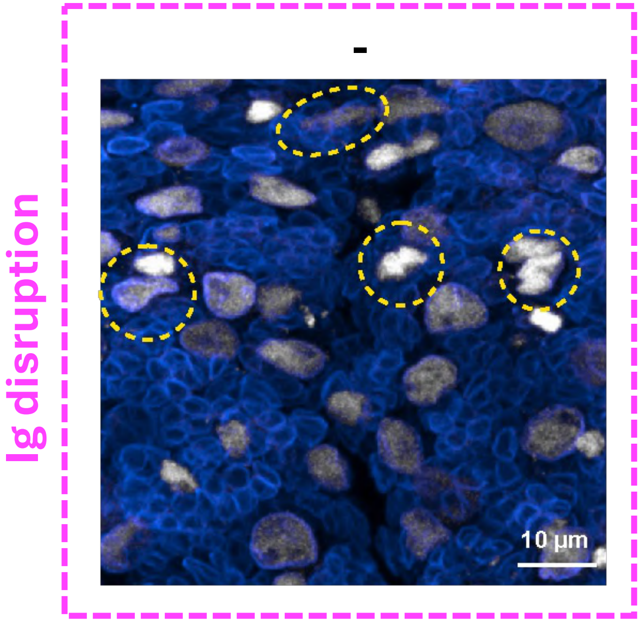
Roubinet et al, 2021

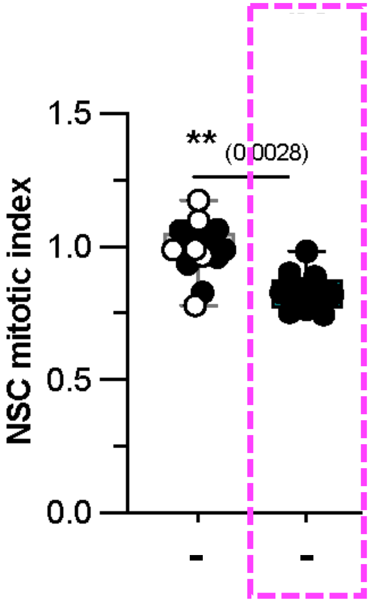
Spindle deformation

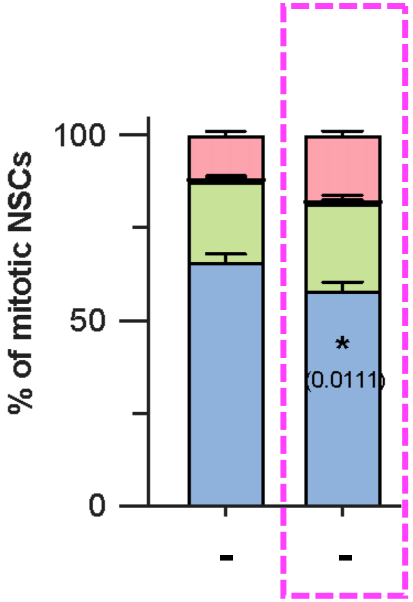
Lamin accumulation plays a protective role towards mitosis



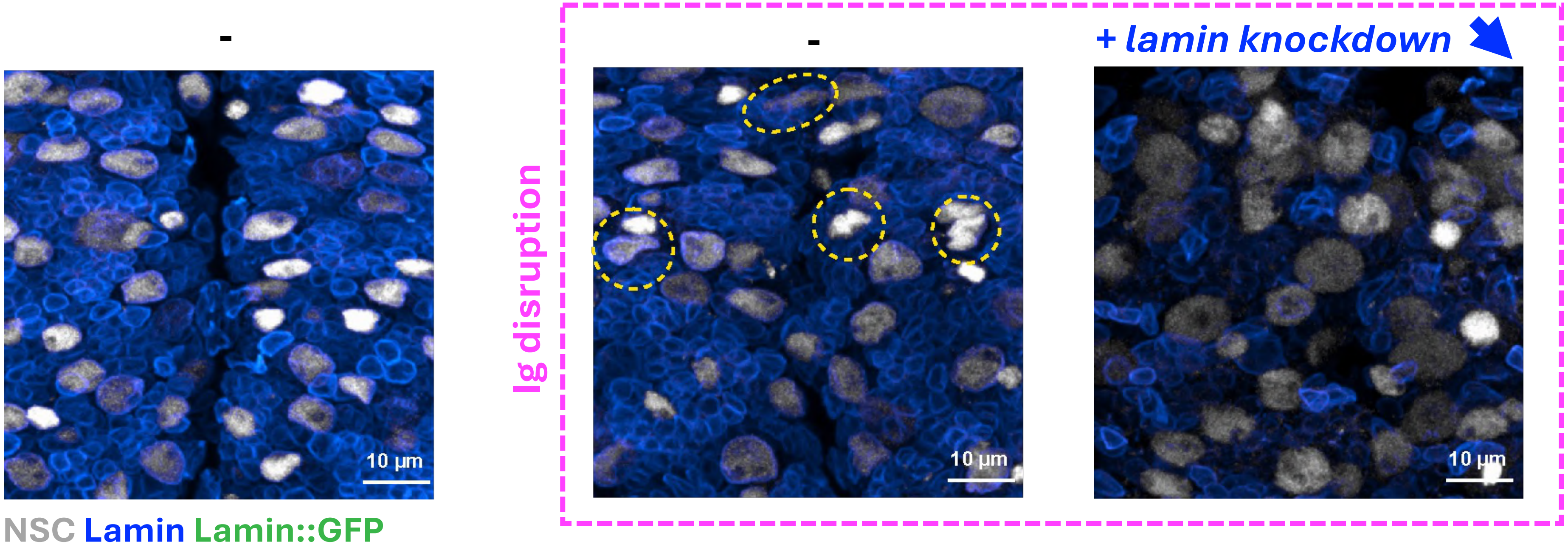
NSC Lamin Lamin::GFP

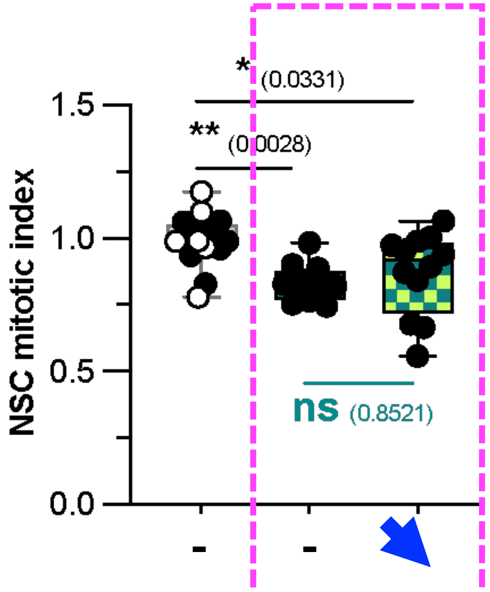


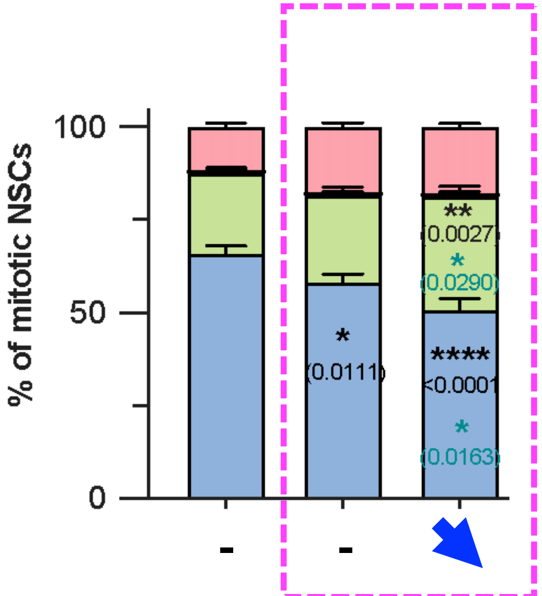




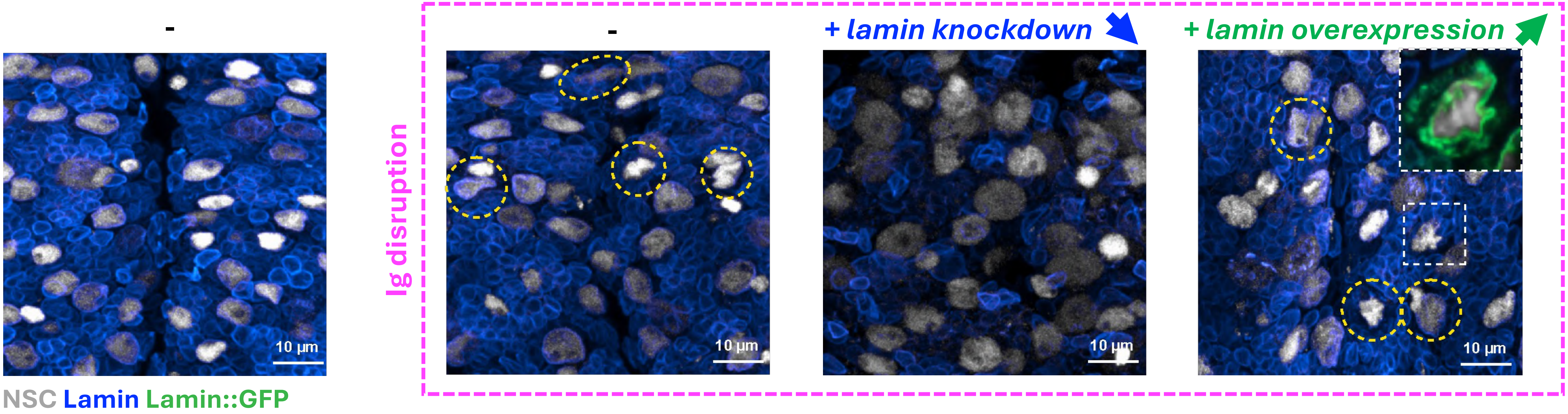
Lamin accumulation plays a protective role towards mitosis

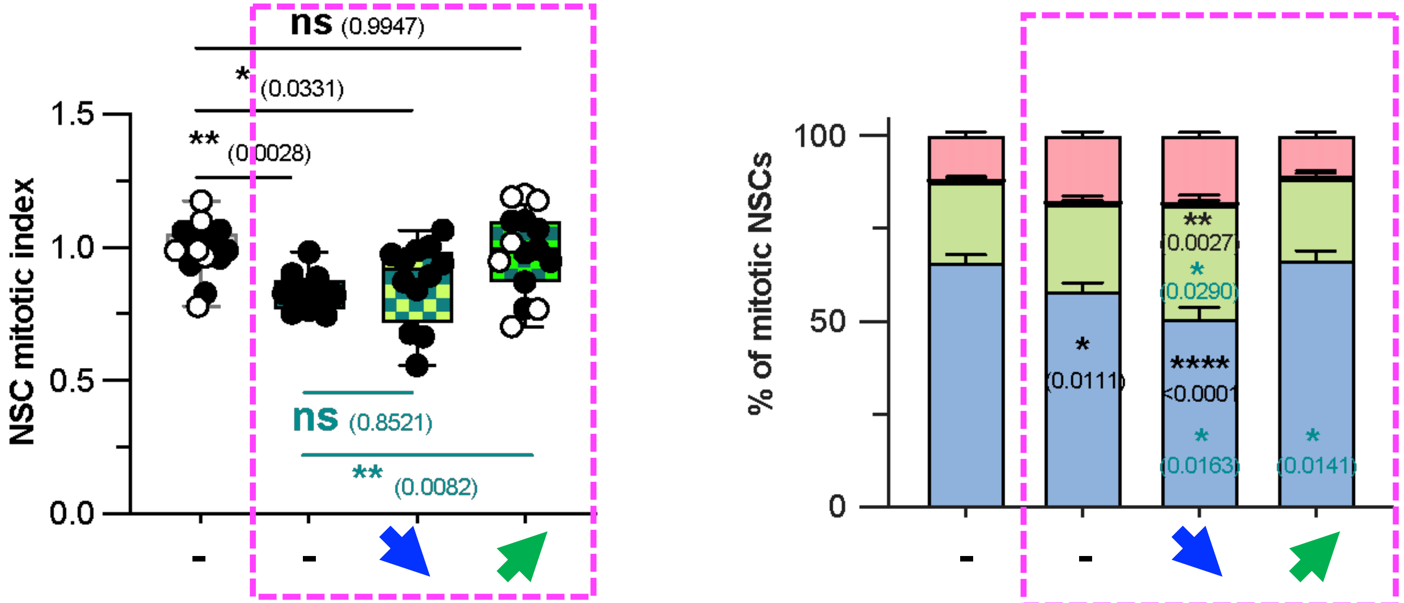






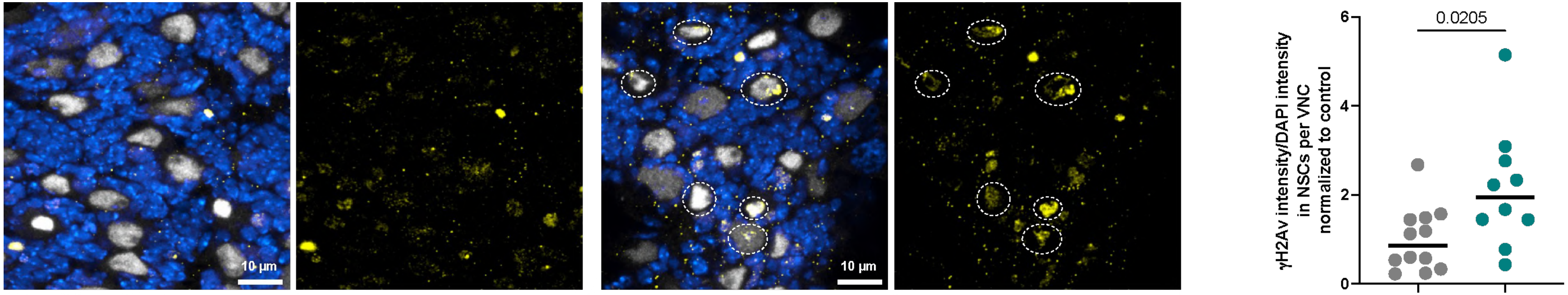
Lamin accumulation plays a protective role towards mitosis





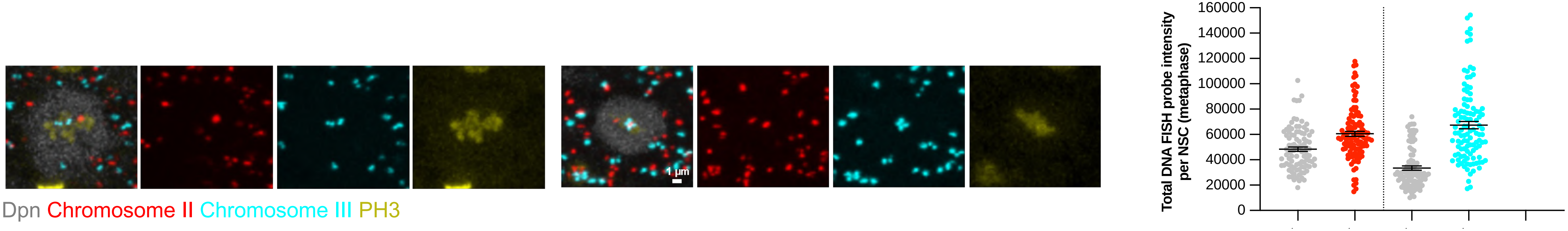
NSCs exhibit DNA alterations

- Increase in DNA damage



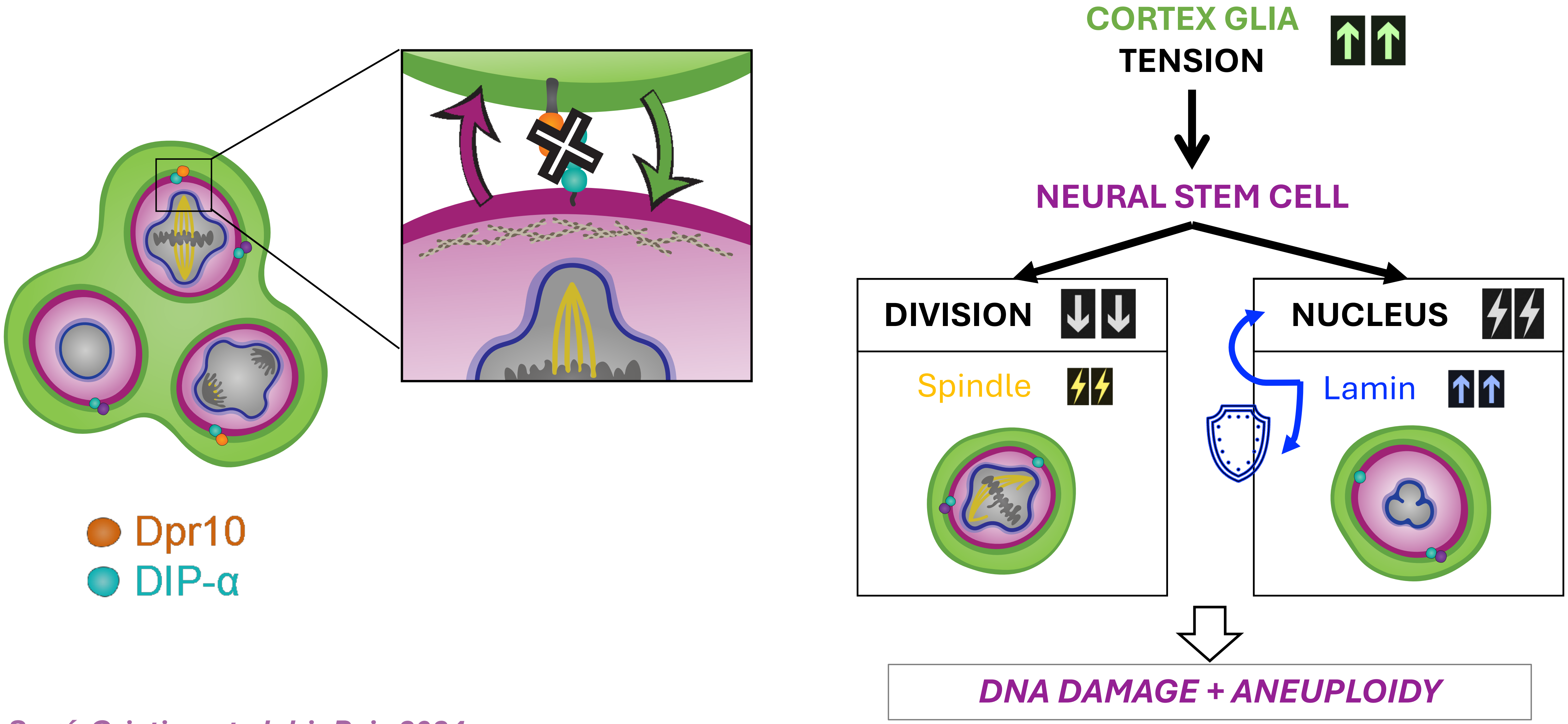
Dpn DAPI γH2Av

- Unbalanced DNA content



Dpn Chromosome II Chromosome III PH3

ADHESION-CONTROLLED FORCES IN THE NICHE GLIA REGULATE NEURAL STEM CELL PROLIFERATIVE FITNESS

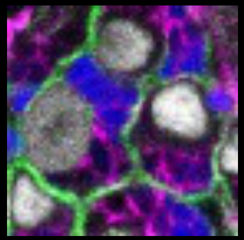


Segú-Cristina et al, bioRxiv 2024

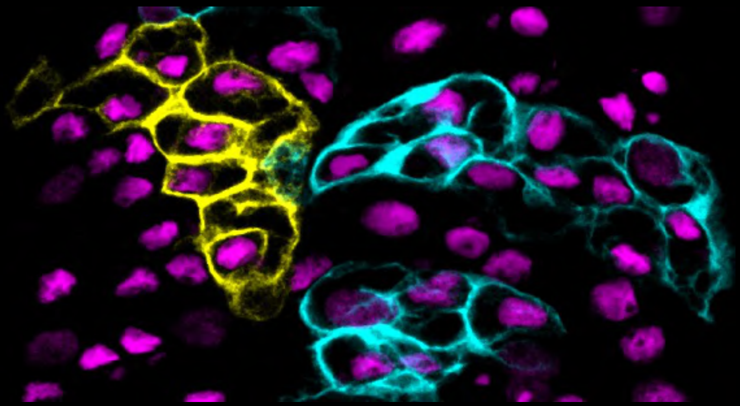
SCALES

SCALES

ARCHITECTURAL



Single



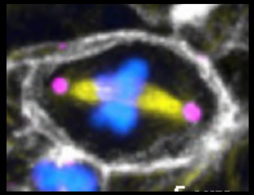
Community

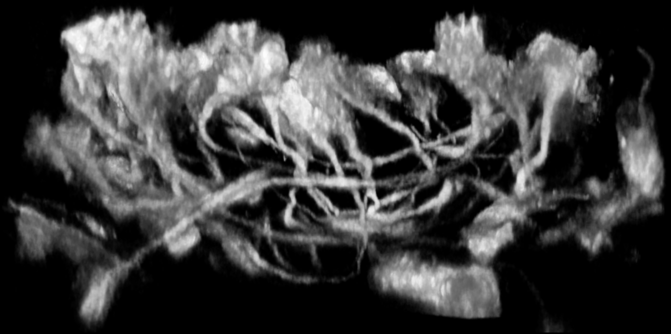
Population

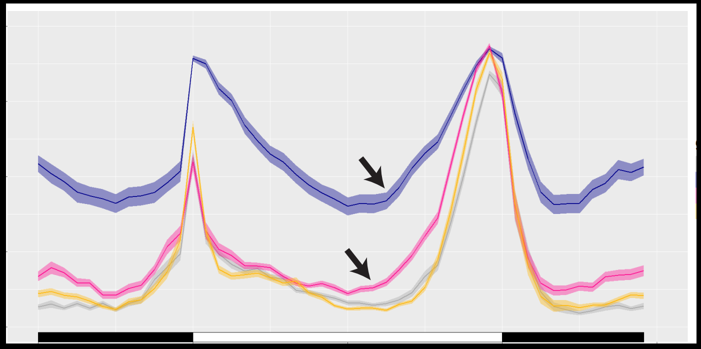
Scales

Architectural

Functional







NSC

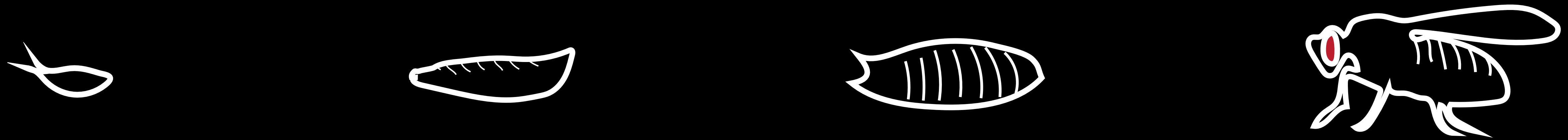
Neuron

Circuits

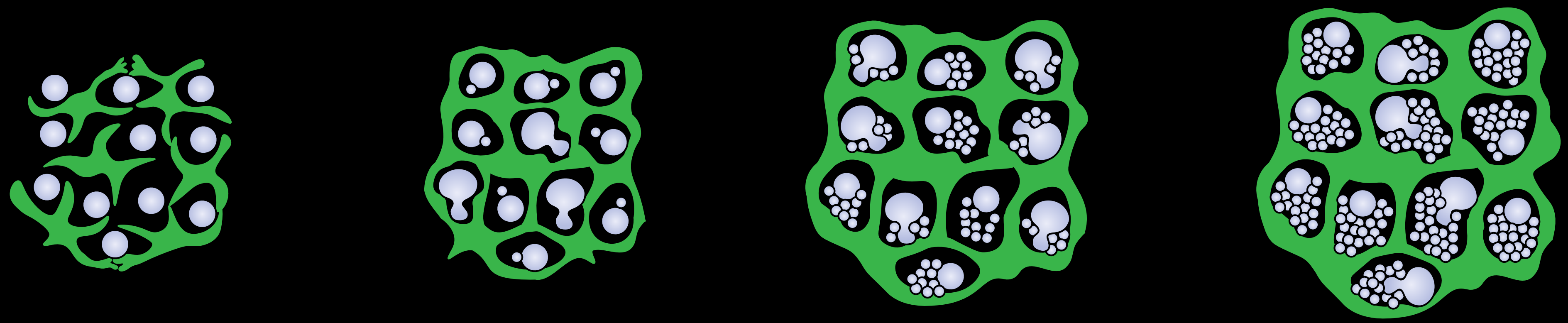
Behaviour

SCALES

ARCHITECTURAL FUNCTIONAL TIME



Embryo Larva Pupa Adult



Quiescence Reactivation Proliferation