Adult neural stem cells and neurogenesis

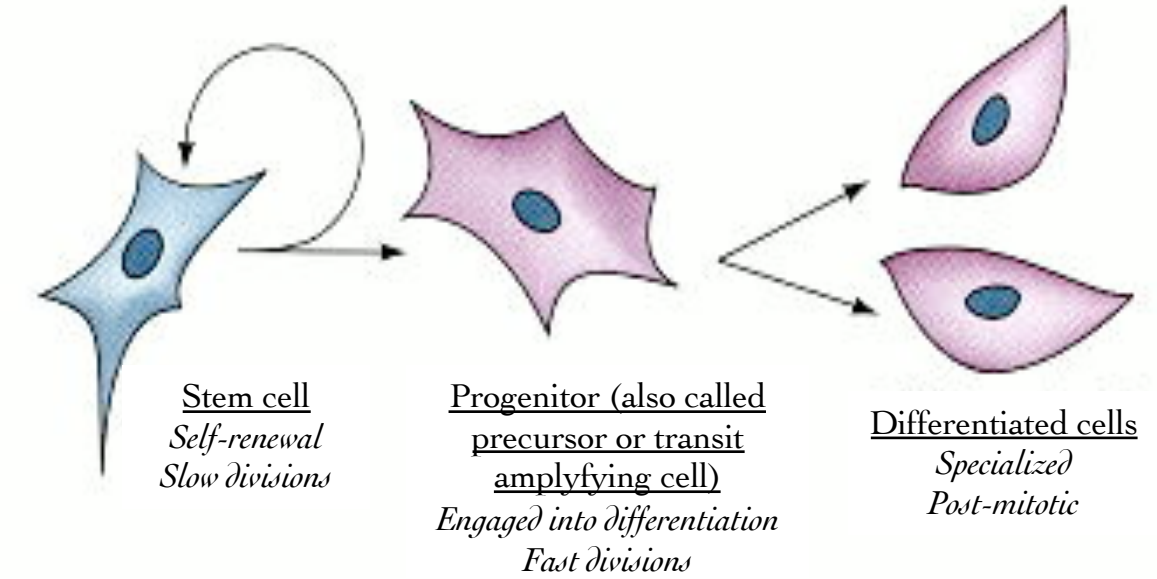
Morgane Locker
CNRS UMR 9197 Neuro-PSI

morgane.locker@universite-paris-saclay.fr
Cours Master 2 GCD/SCN

Stem versus progenitor cells

✓ Stem cells are undifferentiated cells with two properties: **self-renewal** ability and **potency** to generate one or more cell types

✓ Two possibilities upon division: to generate 2 stem cells (symetric division) or to generate 1 stem cell and 1 progenitor cell (asymetric division) that will irreversibly engage into the differentiation process.



✓ **Differentiation**: Process allowing for the progressive acquisition of specialized functions

Presentation plan :
A focus on mammalian adult NSCs

1- Neurogenesis in the adult mammalian brain

2- What is the nature of mammalian brain NSCs?

3- What is the origin of mammalian brain NSCs?

4- How do these cells function?

5- What is known about human neural stem cells?

6- What is the function of adult neurogenesis?

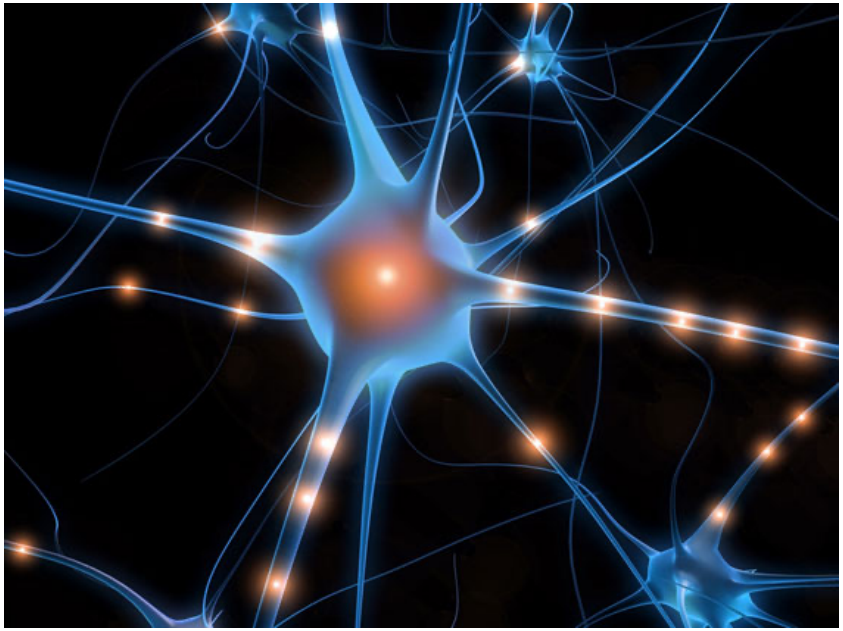
7- Brain regeneration in mammals

Informations on NSC behaviour in non-mammalian vertebrate species in Muriel Perron's conference (*Xenopus* retina).

1-Neural stem cells in the adult brain?

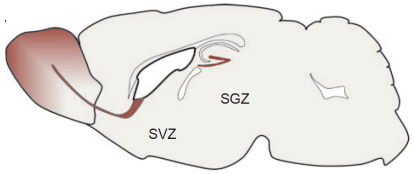
"We are born with a certain number of brain cells which decrease with age. Everything must die in the brain or spinal cord - nothing can regenerate."

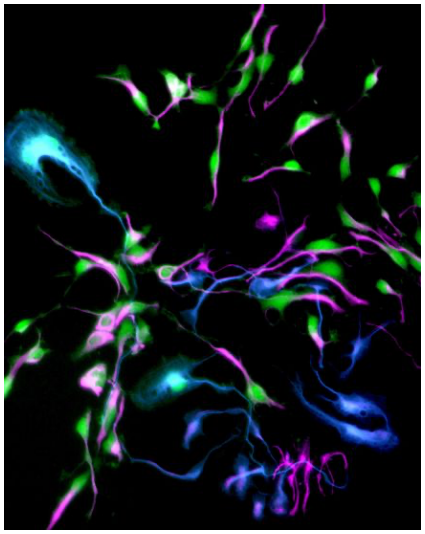
Ramon y Cajal 1902



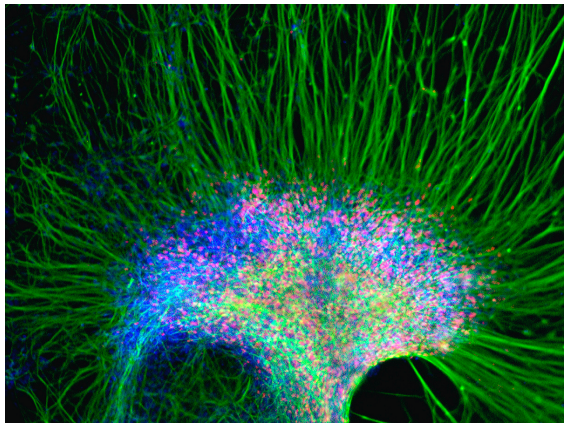
Adult neurogenesis?

- *1993* Discovery of neurogenic regions in the adult mammalian brain

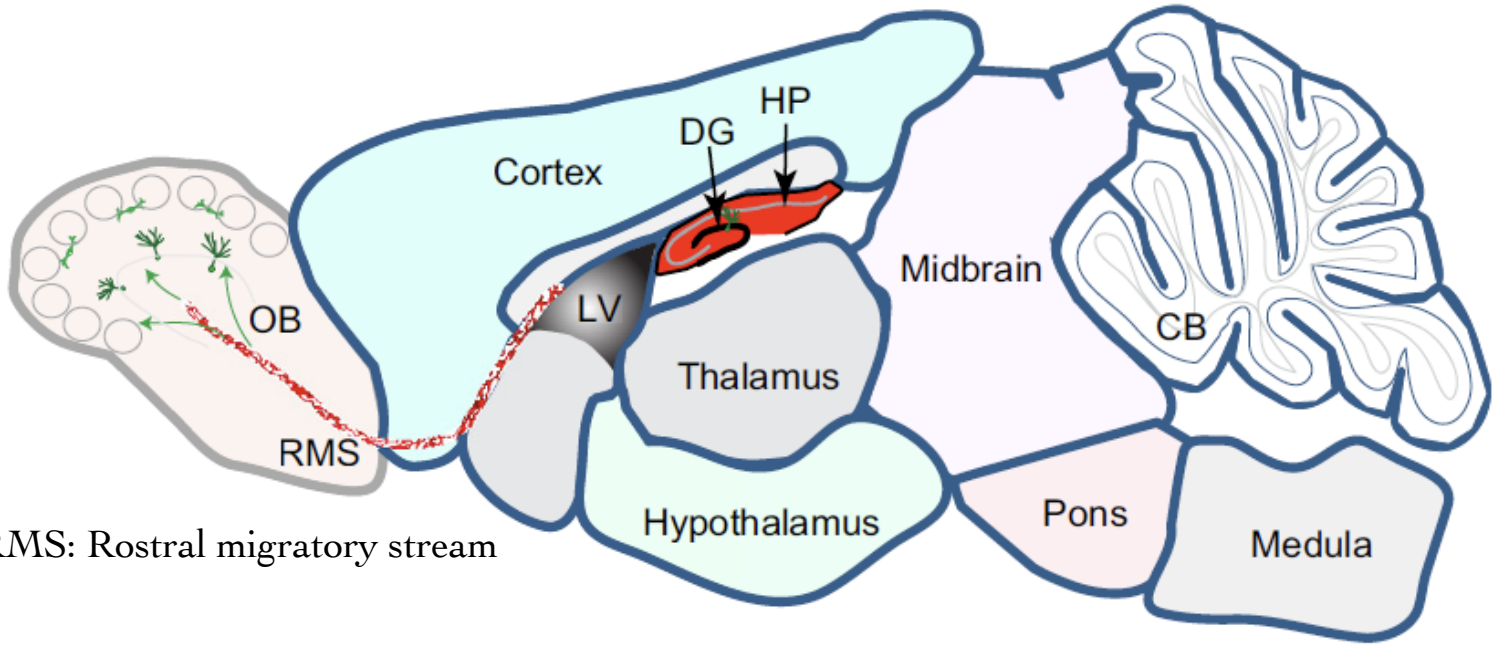




- 1996 First evidence for cells with multipotency and self-renewing capacity in the adult mammalian brain



Locations of NSCs in the adult mammalian brain?

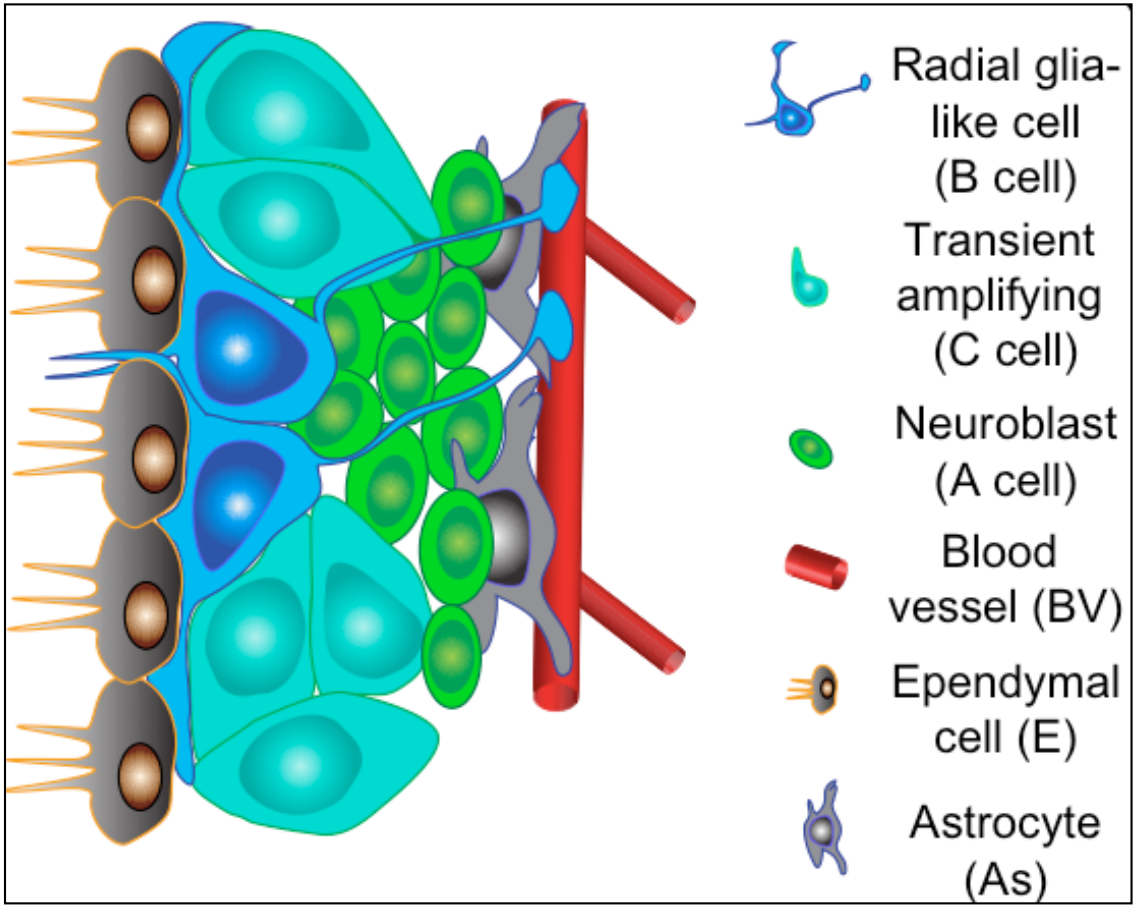


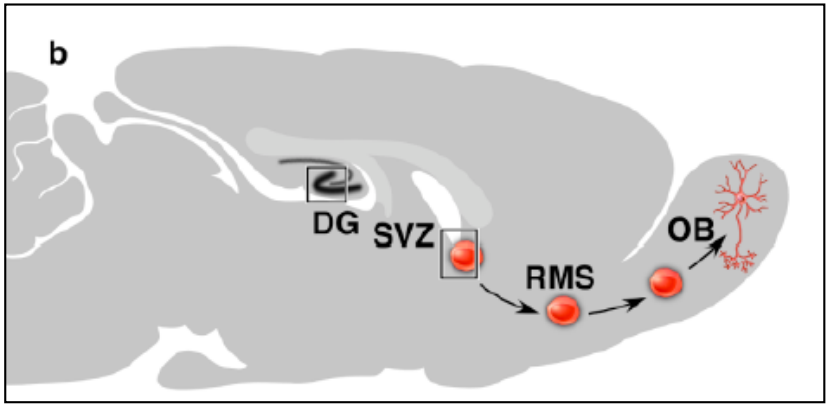
RMS: Rostral migratory stream

- Main regions with continuous neurogenesis:
  - *Olfactory bulb*
  - *Hippocampus*
- Main regions containing adult neural stem cells:
  - *Subventricular zone of the forebrain lateral ventricles*
  - *Dentate gyrus*

Ming & Song 2011

Neural stem cells of the Subventricular Zone (SVZ)



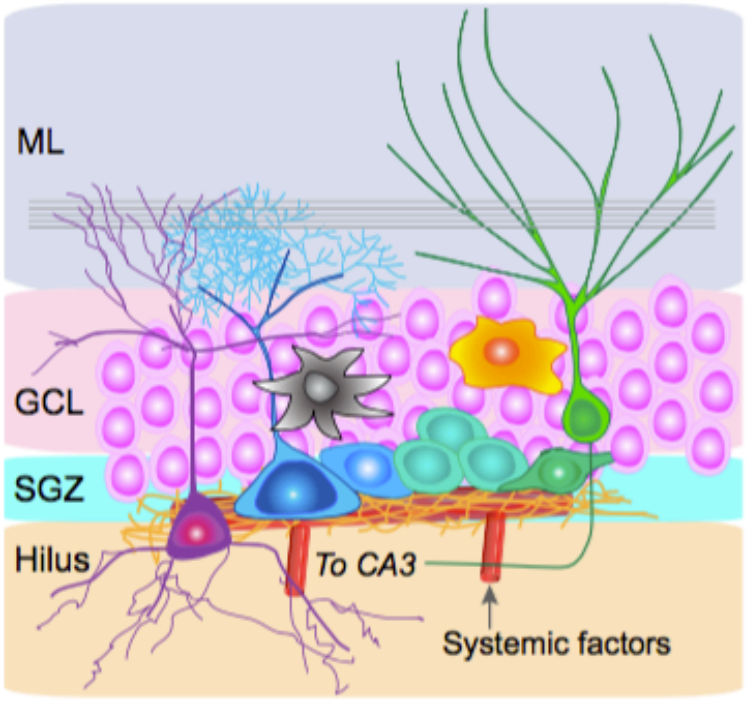


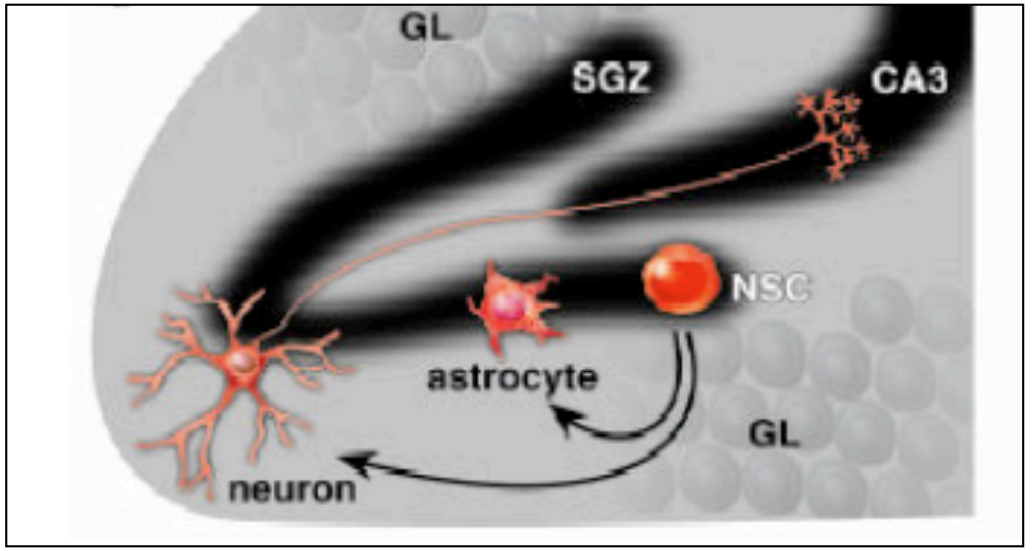
✓ About 30 000 new neuronal precursors are produced every day and migrate to the olfactory bulb towards the RMS

✓ 50% of these new neurons die within two months

Taupin et Gage, 2002; Galli et al, 2003; Ming & Song 2011

Neural stem cells of the Hippocampus subgranular zone (SGZ)





✓ Each day, 9 000 neurons are produced in the dentate gyrus of the hippocampus (local differentiation)

✓ 60% of newly generated neurons die

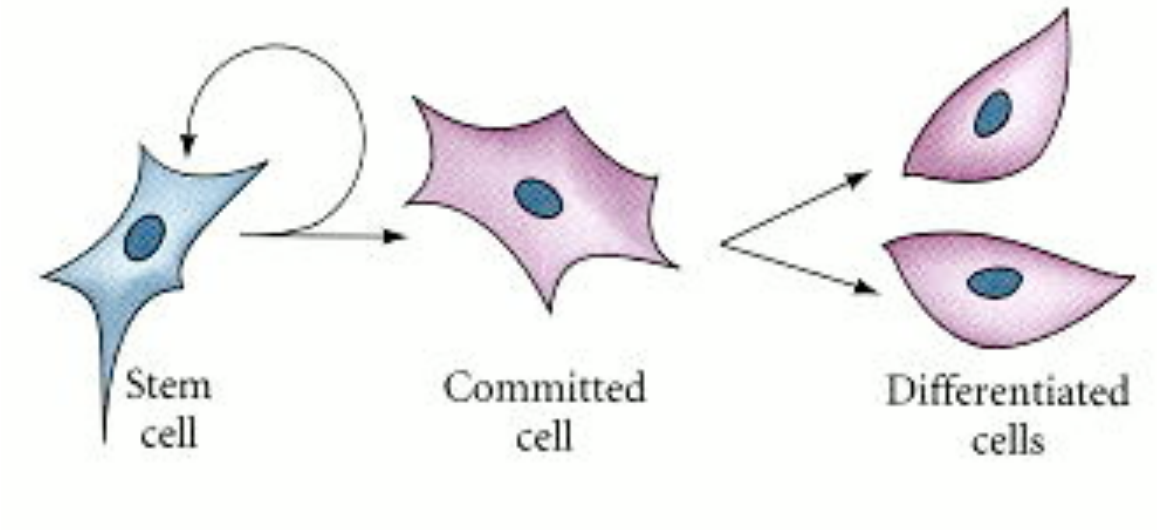
Taupin et Gage, 2002; Galli et al, 2003; Ming & Song 2011

2- Nature of brain NSCs?

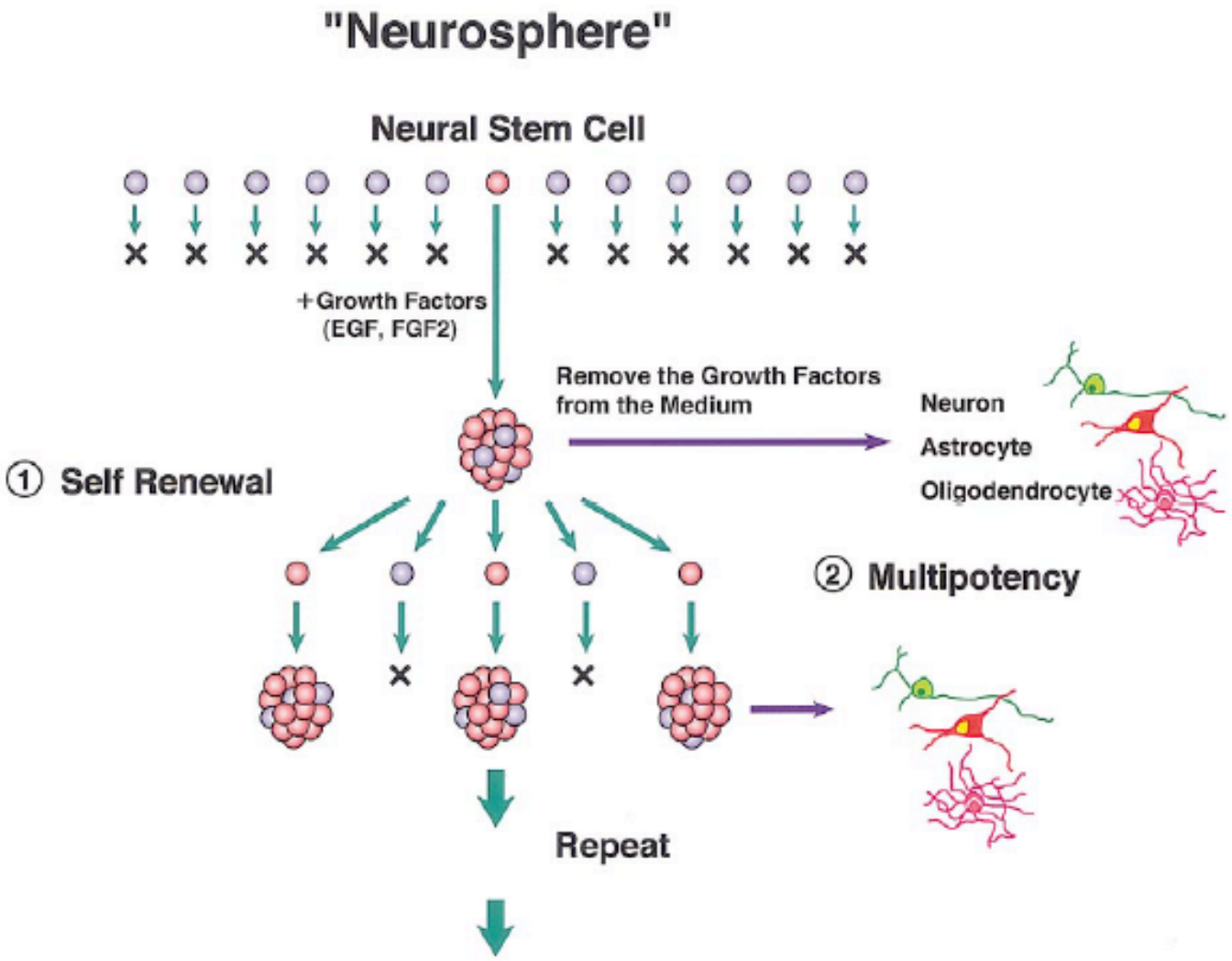
How to determine which cells are stem cells?

Expected properties:

Multipotency – self renewal – slow cell cycle kinetics or quiescence

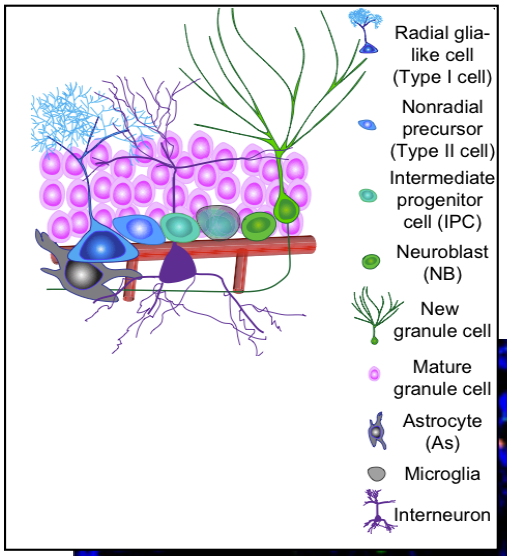


An *ex vivo* test for self-renewal and multipotency

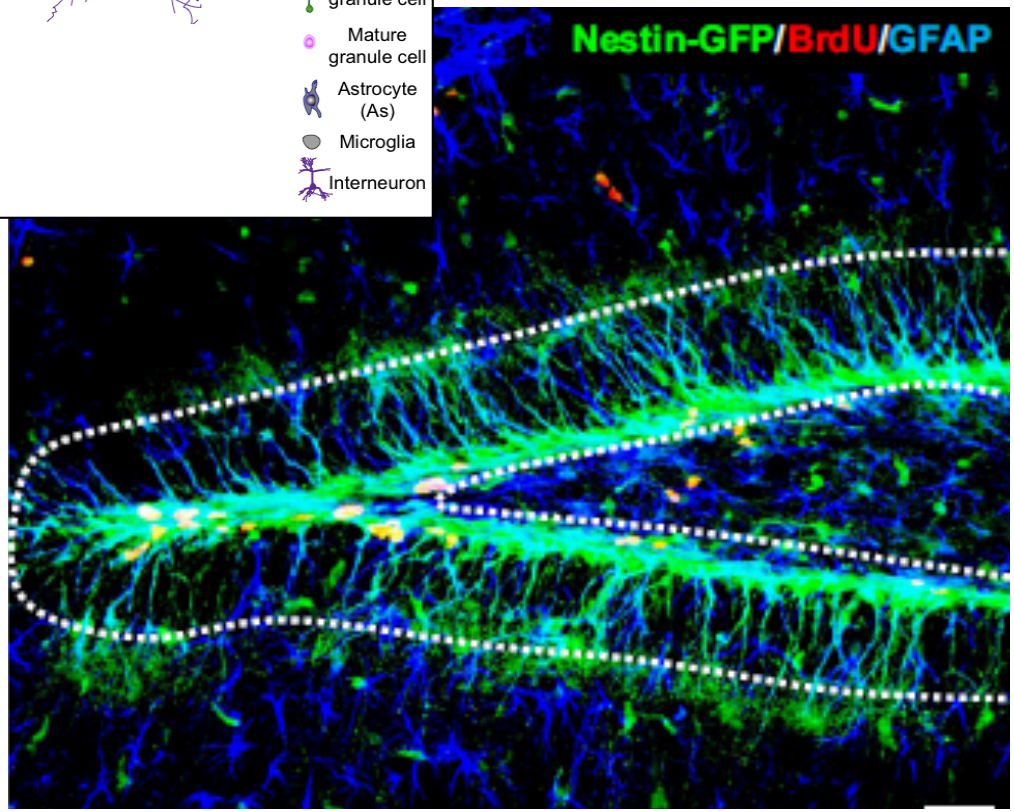


Okano, 2002

How dividing Cell Populations can be distinguished?
The cell cycle kinetics criteria (e.g. in DG)



Nestin-GFP mice (n = 4; age 2 months) received three injections of BrdU (150 mg/kg) at 3 hr intervals and were sacrificed 1 hr after the last injection.



Careful: mixture of really quiescent cells and slow dividing cells

Stem cells

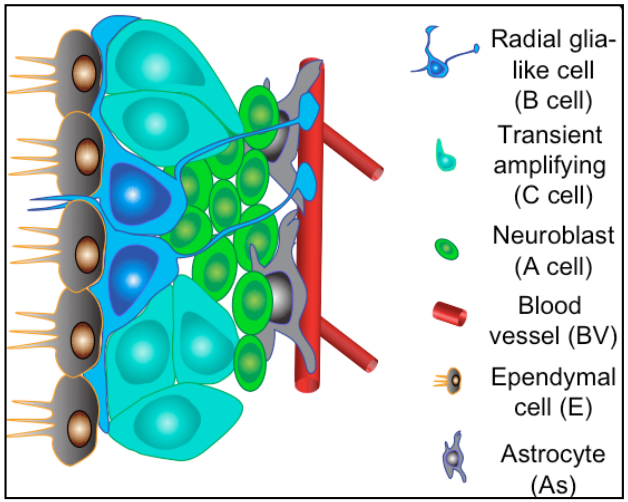
- long GFAP$^+$ process extending from the SGZ toward the molecular layer and ramifying there – rare (less than 10% of the proliferative population)
- low levels of proliferation (2-5% of these cells incorporate BrdU upon pulse labeling)

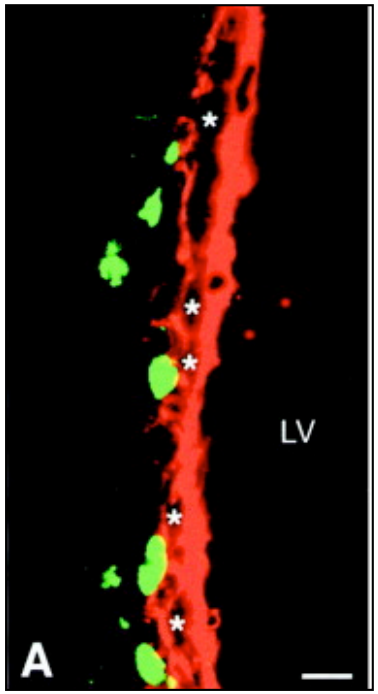
Amplifying neural progenitors

- round or oval cells, devoid of a long GFAP$^+$ radial process
- high levels of proliferation (10%–20% of these cells incorporate BrdU upon pulse labeling)

Encinas et al., Cell Stem Cell 2011

How dividing Cell Populations can be distinguished?
The cell cycle kinetics criteria (e.g. in SVZ)

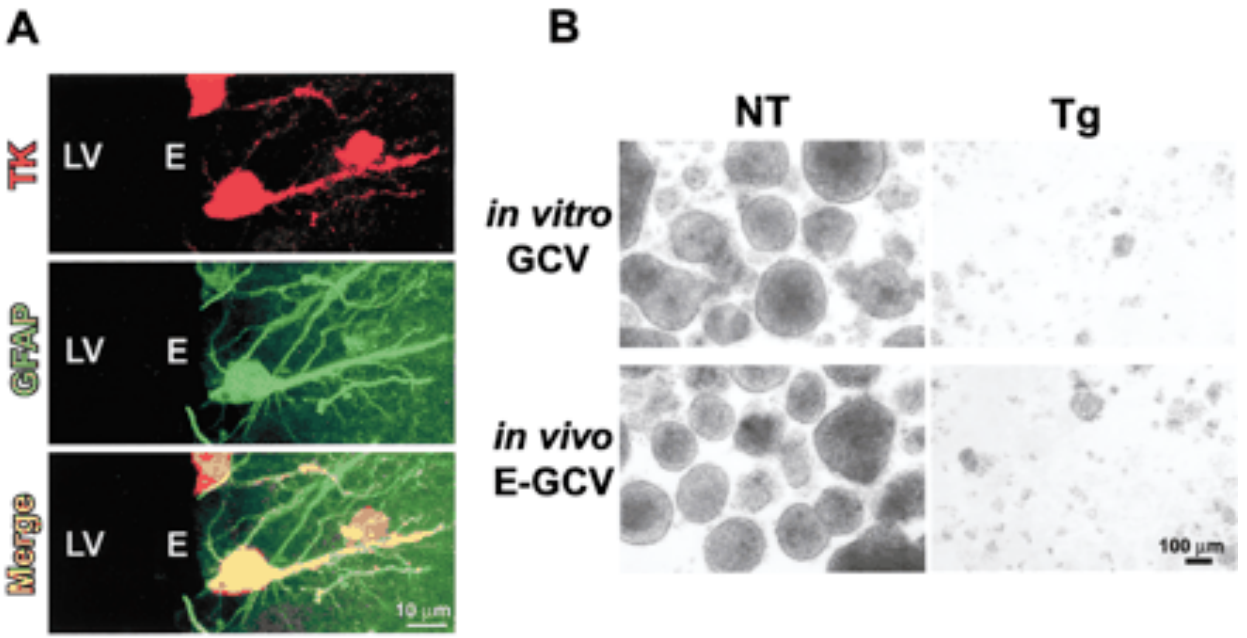




Type B astrocyte-like cells are the only label-retaining cells in the adult SVZ
= Stem cells

Doetsch et al., Cell 1999

How can we assess stemness?
The self-renewal and multipotency criteria

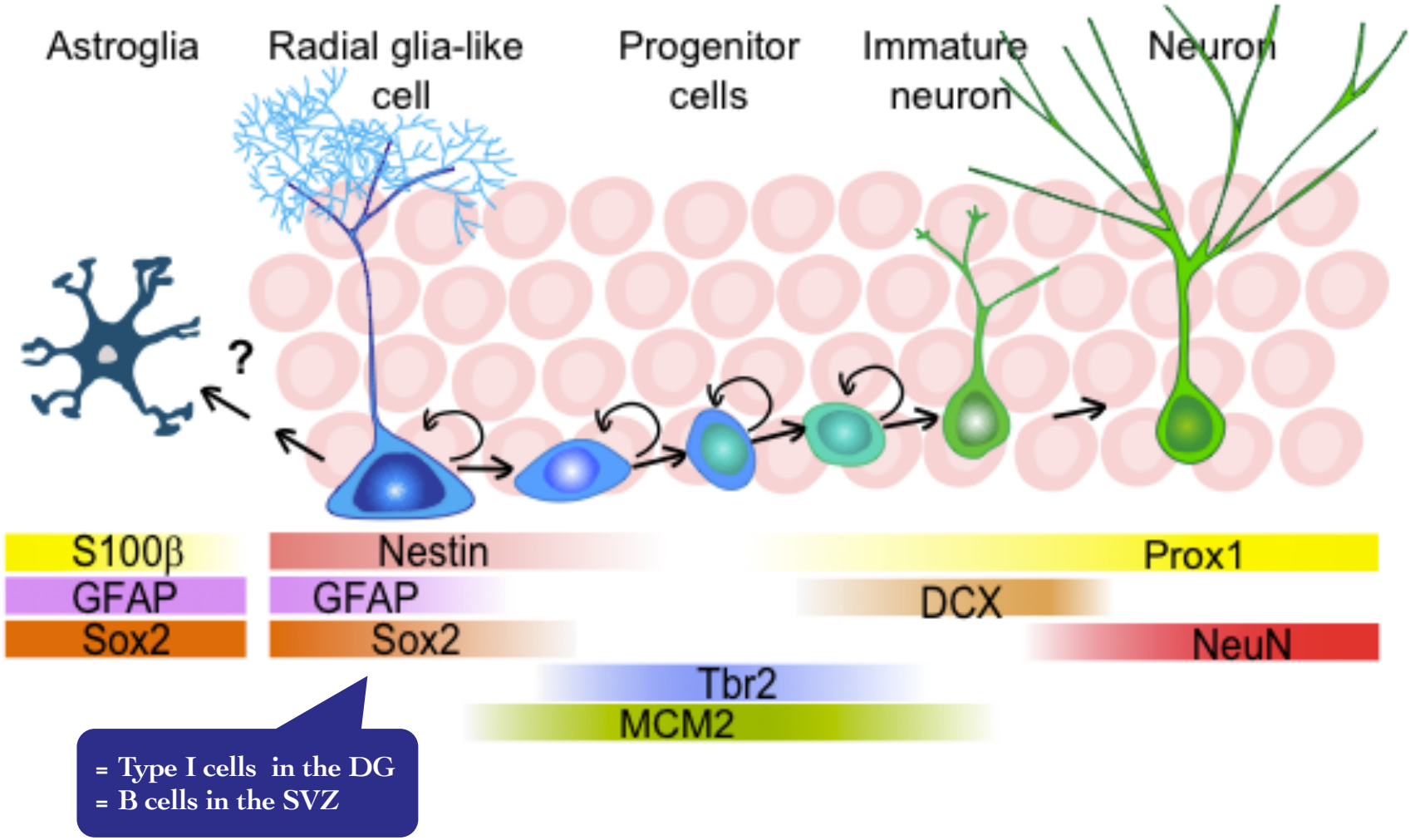


Primary cultures from GFAP-TK transgenic mice exposed or not to ganciclovir (GCV)

Genetic ablation of GFAP-expressing cells from the SGZ *in vitro* or *in vivo* abolishes the ability to derive NSCs from adult SVZ

Imura et al., J neurosciences 2003

Proposed cellular sequence: example of the dentate gyrus



Bonaguidi et al., Cell 2011

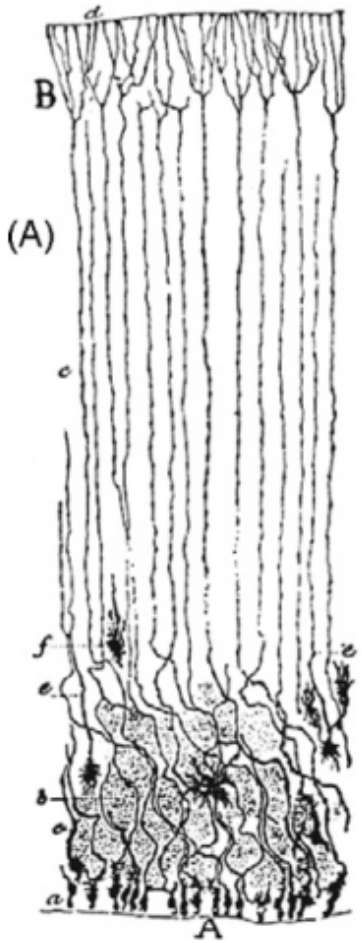
Careful: Common Markers of the NSC Lineage Are Often Shared by Different Cell Types in the Lineage and Niche.

	Niche elements		NSC lineage			
	Ependymal cell	Niche astrocyte	qNSC	aNSC	TAC	Neuroblast
GFAP	-	+	+	+	-	-
GLAST	-	+	+	+	+/-	-
CD133	+	-	+	+	-	-
Nestin	+	-	-	+	+/-	+/-
EGFR	-	-	-	+	+	-
ASCL1	-	-	-	+/-	+	-
S100β	+	+	-	-	-	-

Shaker et al. WIREs Dev Biol 2016

3- Lineage of adult NSCs?

What is radial glia?



✓ Specialized cells in the developing nervous system of all vertebrates, bipolar-shaped, polarized and characterized by long radial processes

✓ Several characteristics typical of astrocytes

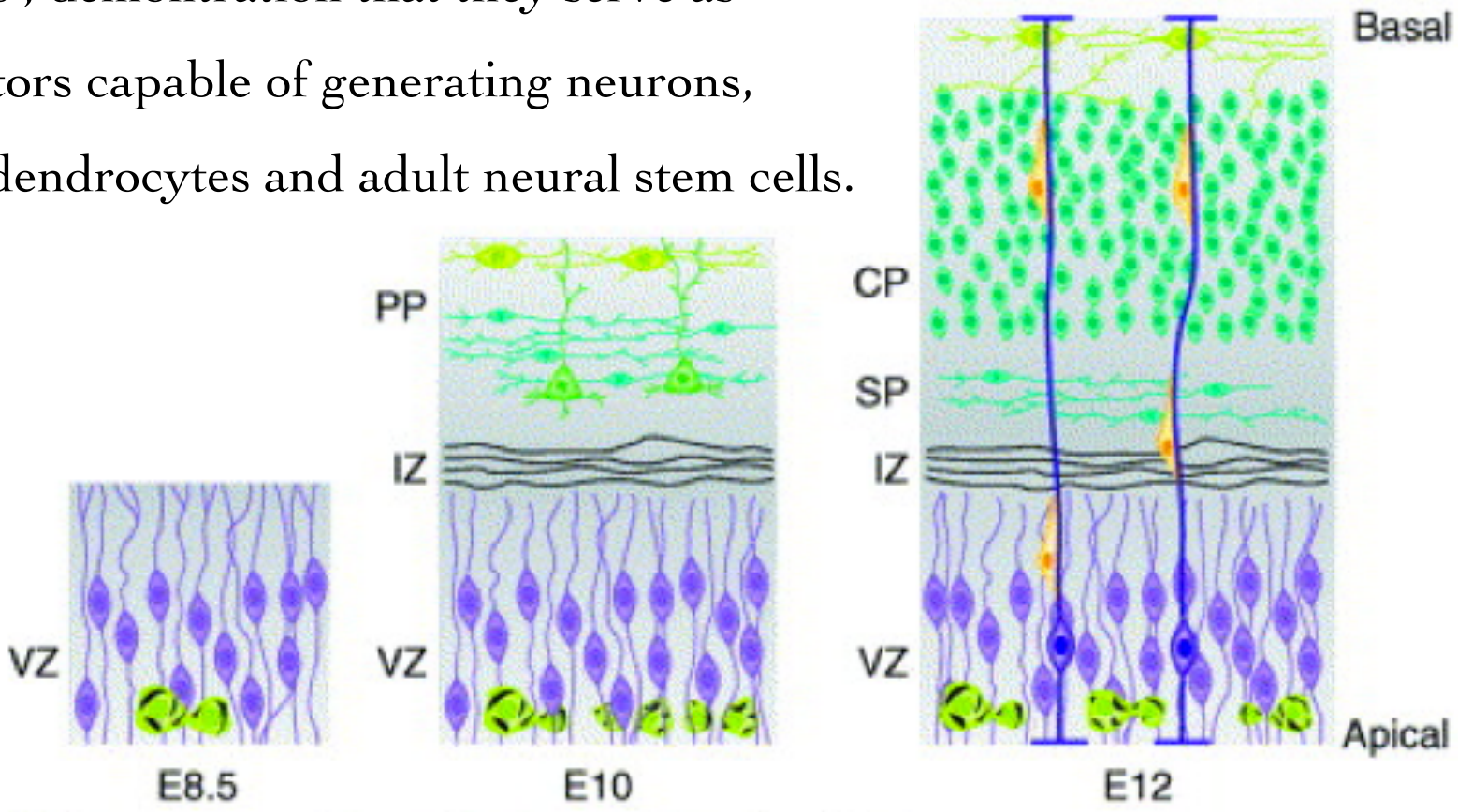
✓ Transient cell type during mammalian embryogenesis (persists however at specific locations in the mature CNS; e.g. Müller cells in the retina or Bergmann cells in the cerebellum) (SEE MURIEL PERRON'S CONFERENCE FOR MÜLLER CELLS)

✓ Persistence in the brain of several non-mammalian vertebrates

What is radial glia function?

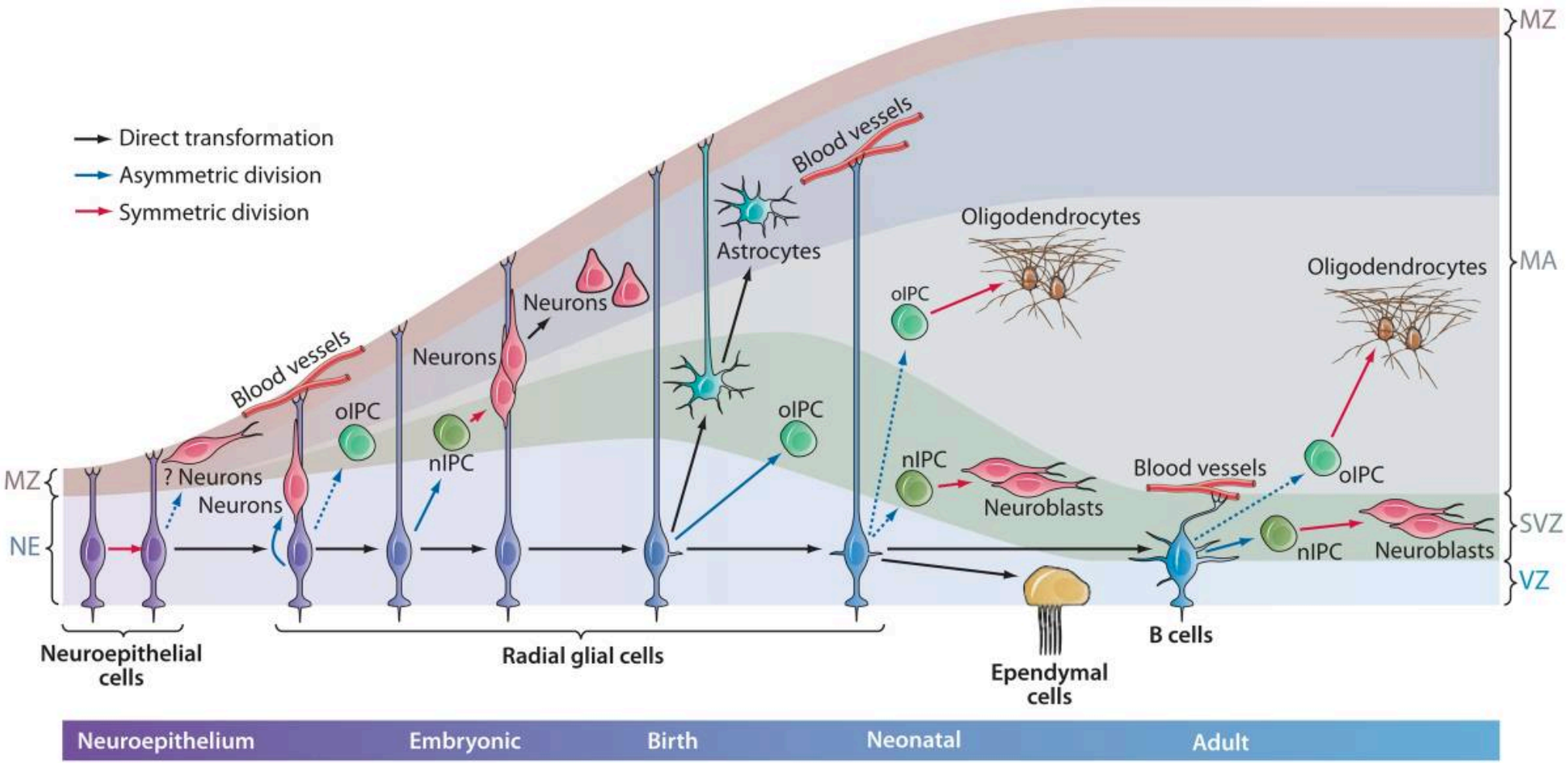
✓ Guiding the radial migration of newborn neurons from the ventricular zone to the mantle regions.

✓ In the 2000s , demontration that they serve as primary progenitors capable of generating neurons, astrocytes, oligodendrocytes and adult neural stem cells.



Campbell & Götz, Trends in Neurosciences 2002

The "developmental continuum" view of neural progenitors in mammals



Kriegstein & Alvarez Buylla 2009

Markers shared by neuroepithelial, radial glial and neural stem cells

	Neuroepithelial cells	Radial Glia (early)	Radial Glia (late)	Mammalian aNSCs (Astrocyte-like stem cells)
GFAP	-	-/+	+	+++
GLAST	-	++	++	++
Glutamine synthetase	-	-	+	++
S100-β	-	-	+	+
Nestin	+++	+++	+++	+++
Vimentin	-	+	++	+++
BLBP	++	+++	+++	++
Sox2	+++	+++	+++	++
ZO-1	+	-	-	-
aPKC	+	+	+	ND

From Alessandro Brombin thesis; adapted from Götz et al. 2015

4- How do these NSC behave?

Do NSCs have a continuous activity?

Are they multipotent?

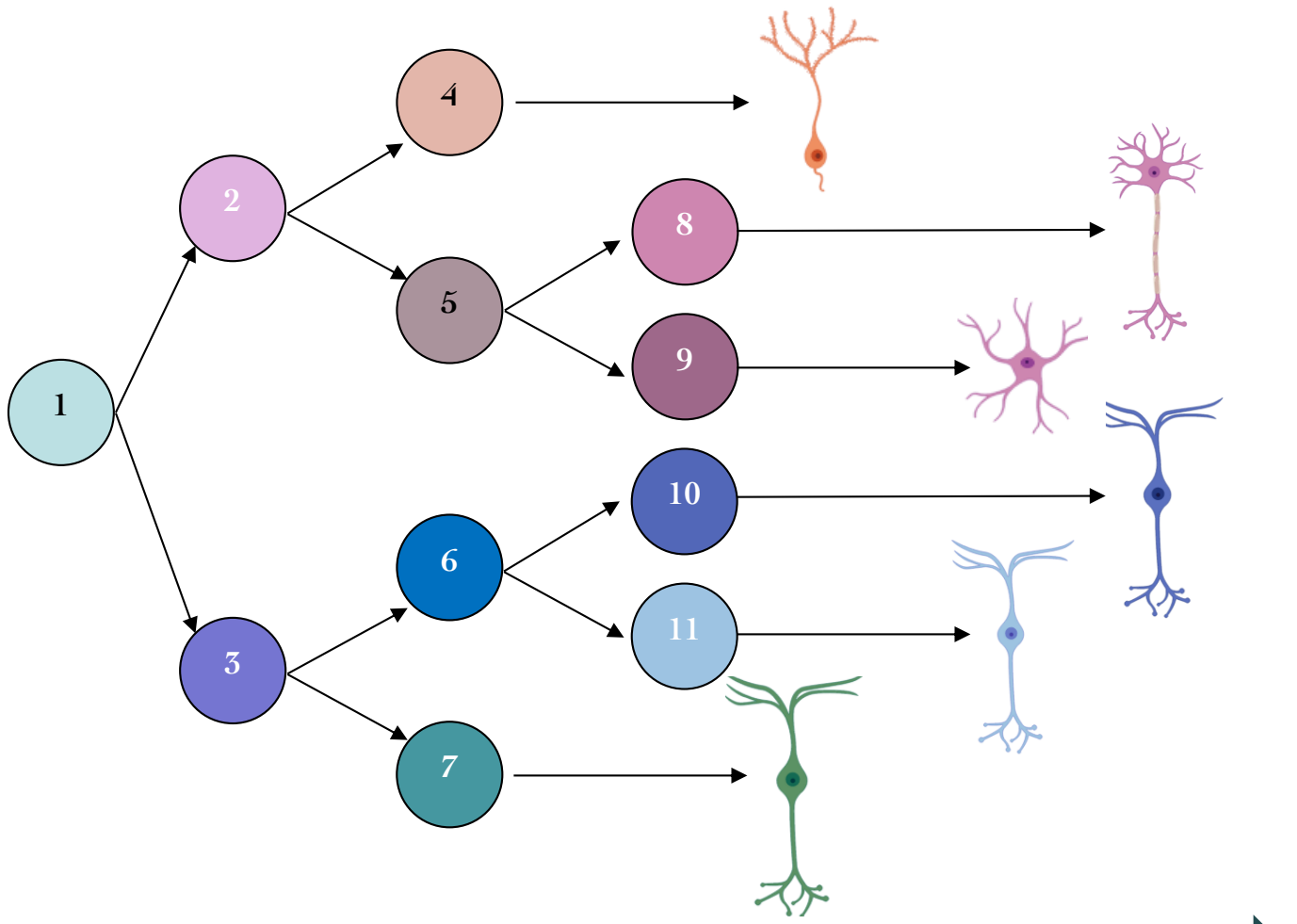
What is their division mode?

Do they constitute a homogenous population?

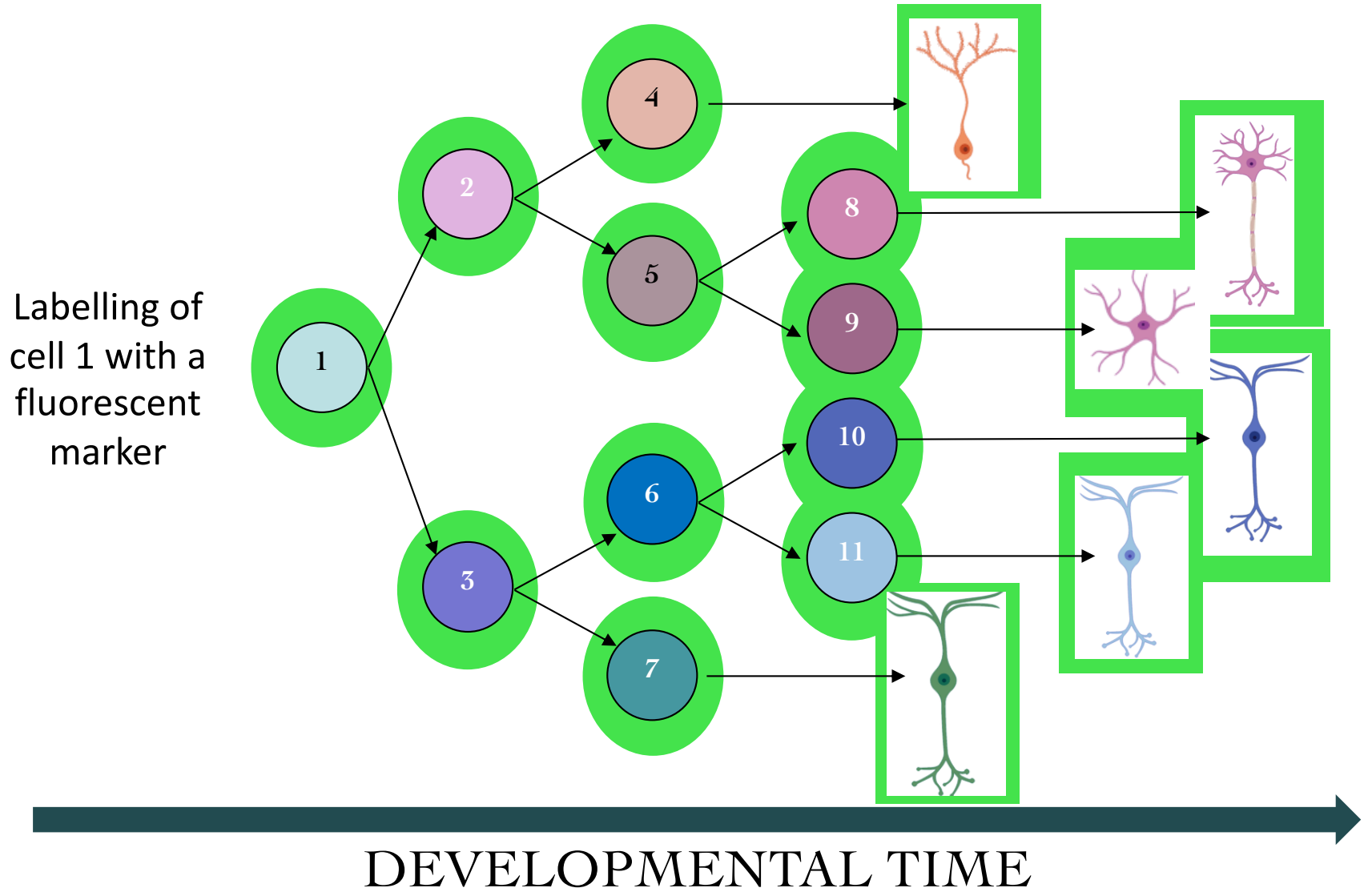
Need to follow them clonally to answer some of these questions

Basic principle of a lineage tracing experiment

Labelling of cell 1 with a fluorescent marker

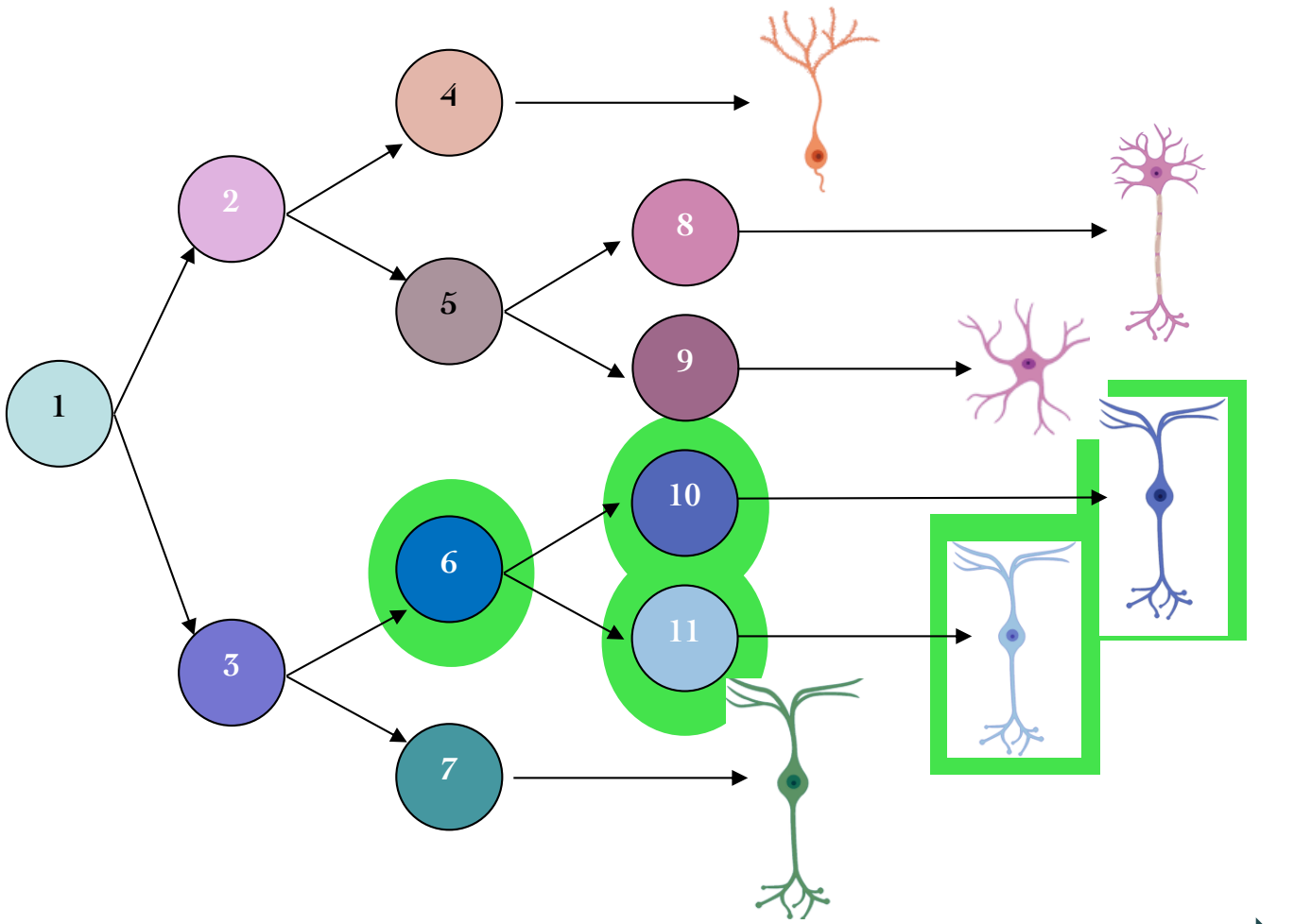


Basic principle of a lineage tracing experiment



Basic principle of a lineage tracing experiment

Labelling of cell 6 with a fluorescent marker



Basic principle of a lineage tracing experiment

Basic principle of a lineage tracing experiment

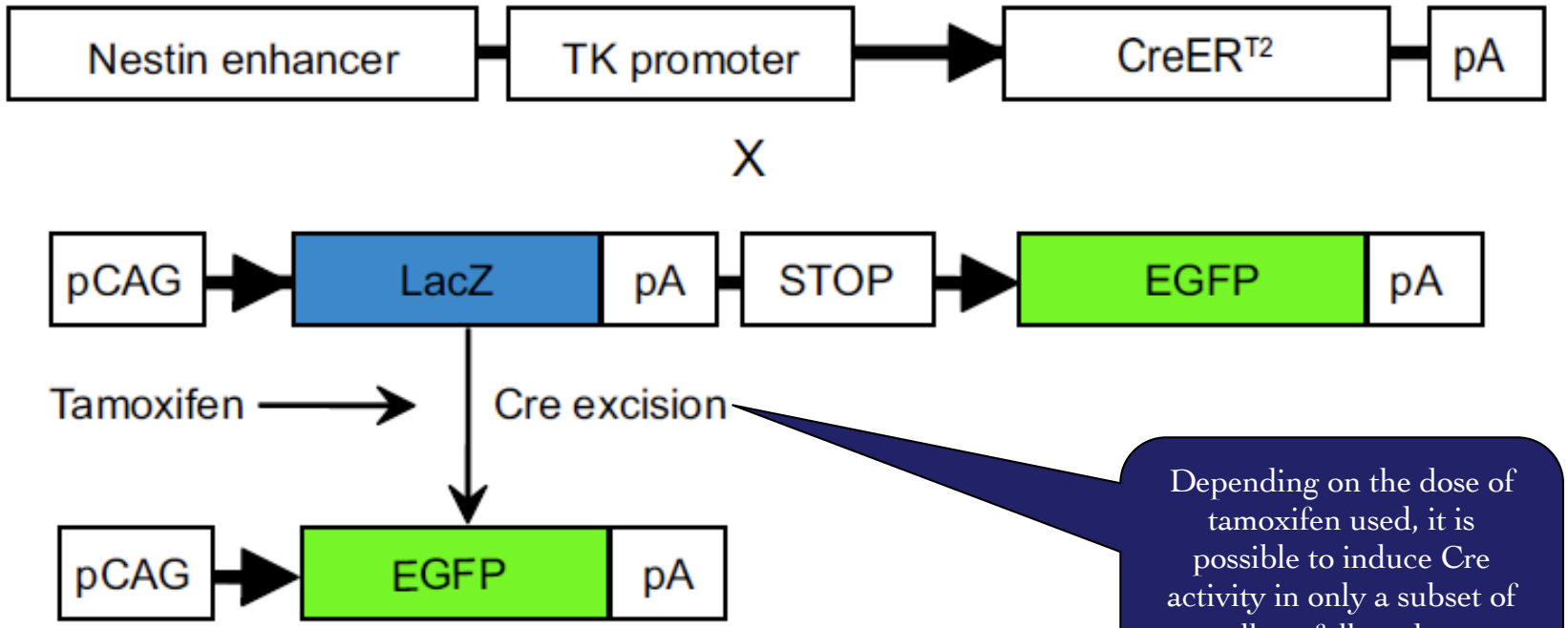
IF I WANT TO TRACE THE LINEAGE OF A GIVEN CELL TYPE AT A GIVEN DEVELOPMENTAL TIME, I NEED A TOOL TO LABEL THE MOTHER CELL I WISH TO FOLLOW.

Mouse trangenic strain expressing LacZ in all cells but not EGFP

CRE-expressing transgene delivery in specific cell types or crossing with a mouse line expressing an inducible CRE under the control a specific promoter

How can NSCs be followed clonally?

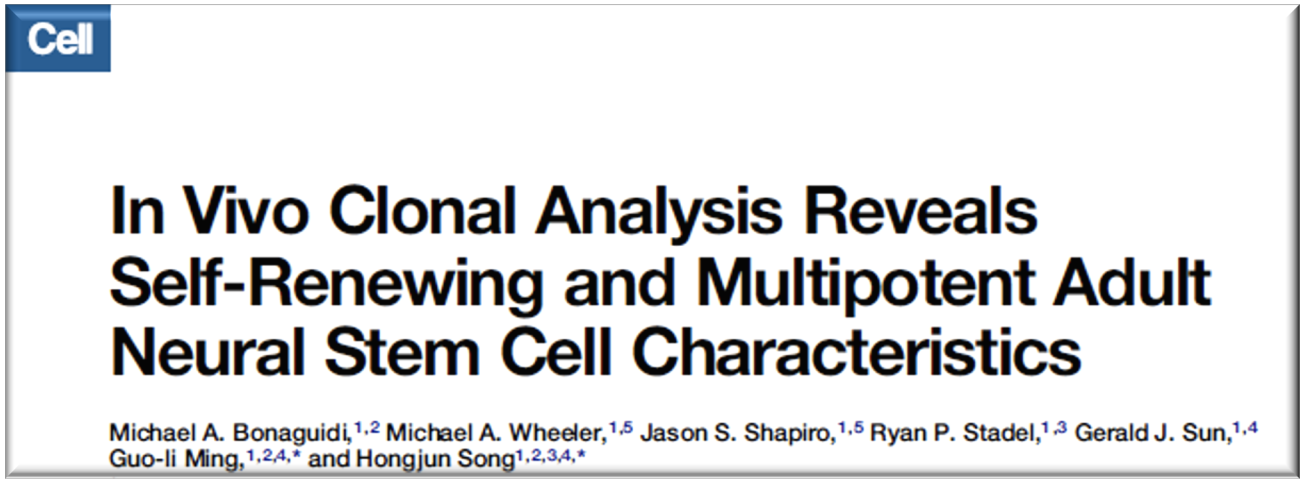
Example of A Genetic Sparse Marking Strategy for *In Vivo* Analysis of Individual Nestin+ Radial Glia-like Neural Precursors in the Adult Mouse Dentate Gyrus



Nestin-positive cells and their progeny are permanently labelled with EGFP

Bonaguidi et al., Cell 2011

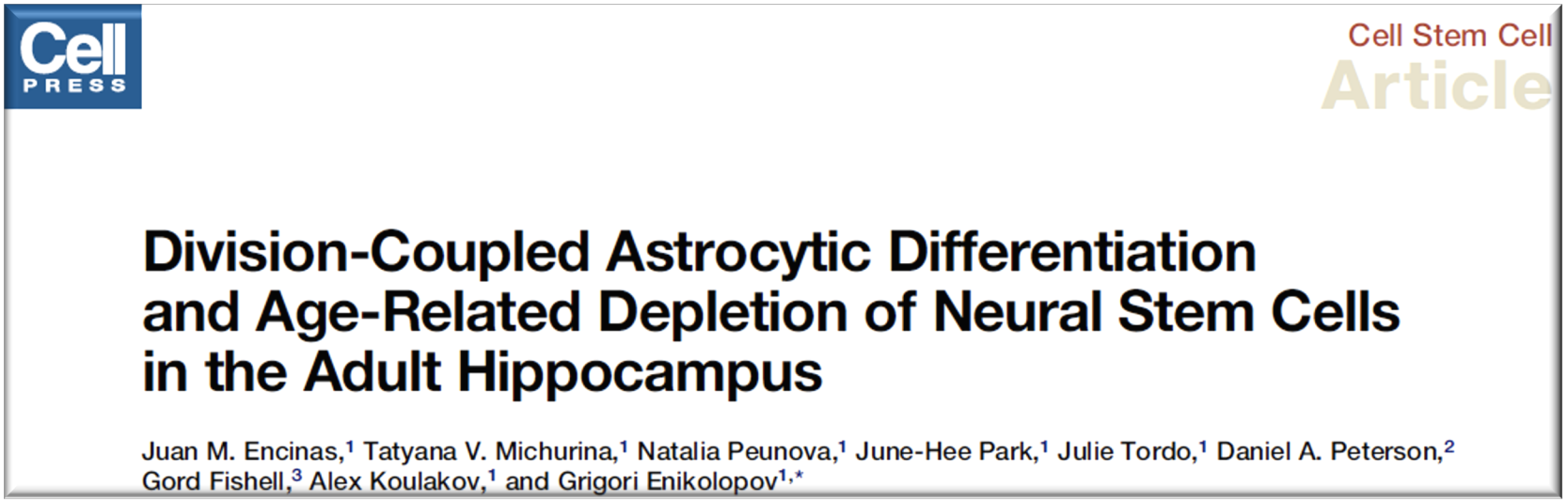
Mammalian NSC division mode: an ongoing debate...



Cell

In Vivo Clonal Analysis Reveals Self-Renewing and Multipotent Adult Neural Stem Cell Characteristics

Michael A. Bonaguidi,[1,2] Michael A. Wheeler,[1,5] Jason S. Shapiro,[1,5] Ryan P. Stadel,[1,3] Gerald J. Sun,[1,4] Guo-li Ming,[1,2,4,*] and Hongjun Song[1,2,3,4,*]



Cell PRESS

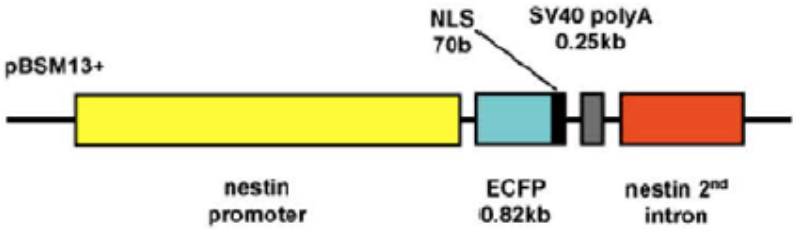
Cell Stem Cell

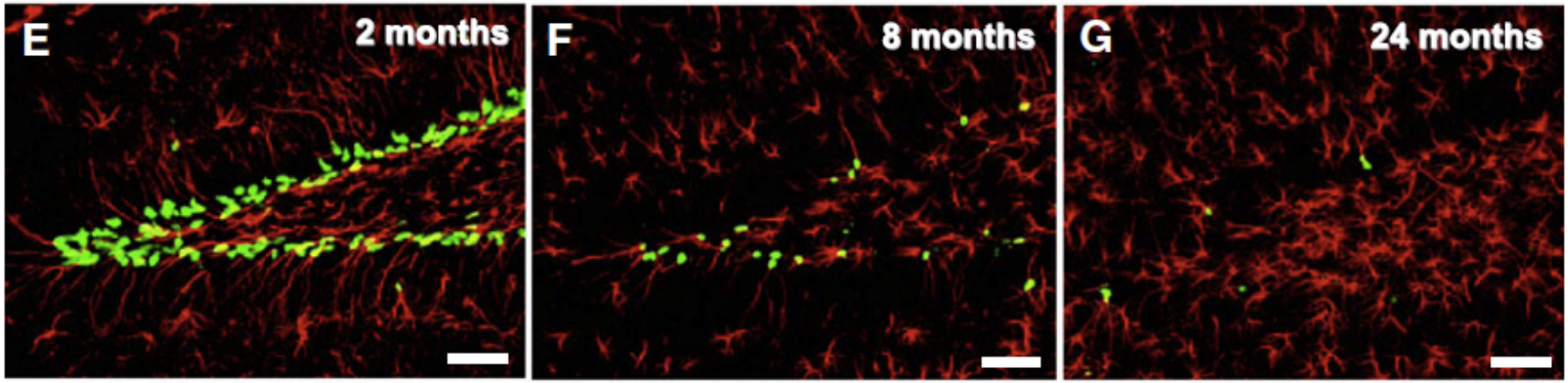
Article

Division-Coupled Astrocytic Differentiation and Age-Related Depletion of Neural Stem Cells in the Adult Hippocampus

Juan M. Encinas,[1] Tatyana V. Michurina,[1] Natalia Peunova,[1] June-Hee Park,[1] Julie Tordo,[1] Daniel A. Peterson,[2] Gord Fishell,[3] Alex Koulakov,[1] and Grigori Enikolopov[1,*]

The number of QNPs shows age-dependent decrease



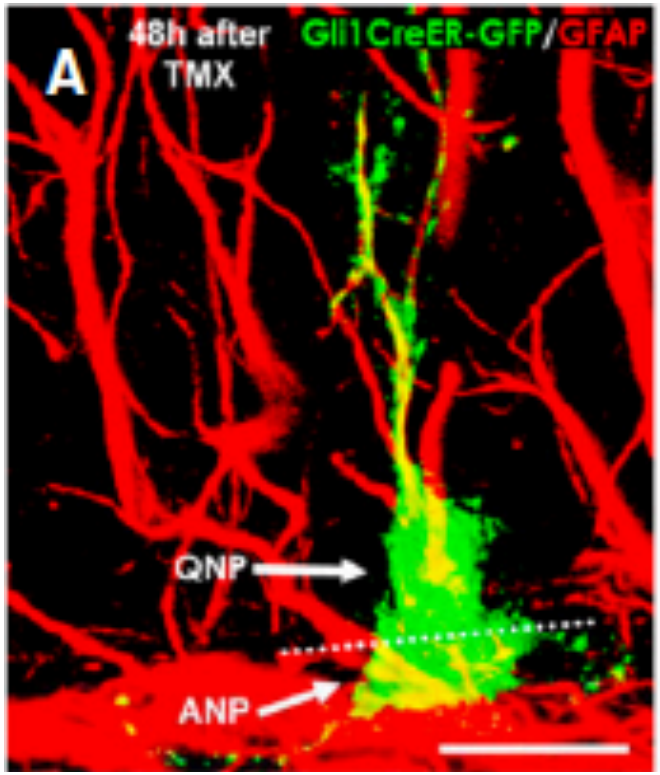


!!!!! Nestin does not label quiescent NSCs !!!!

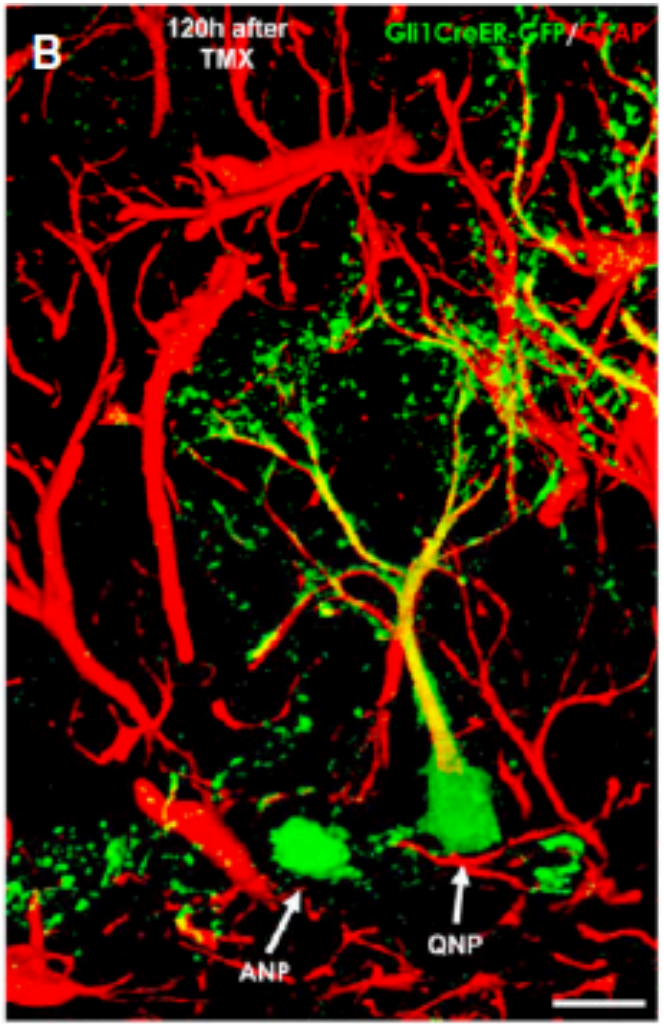
Encinas et al., Cell Stem Cell 2011

QNPs undergo asymetric cell divisions only to produce ANPs

NB: In Gli1-CreER animals, GFP is expressed exclusively in QNPs 12–18 hr after tamoxifen induction



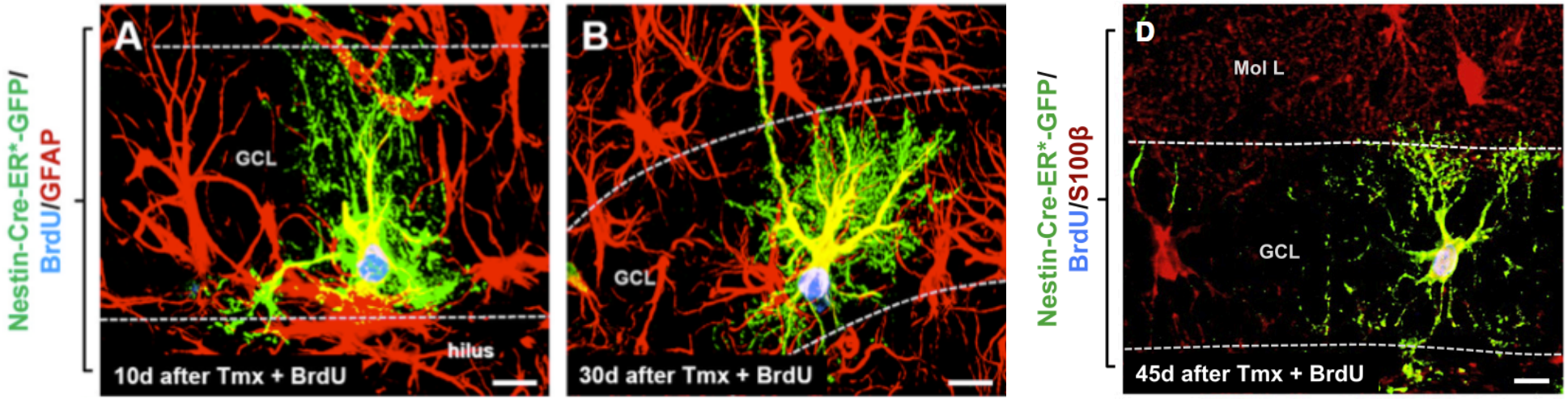
Later (48 hrs after the induction), asymmetrically dividing QNPs giving rise to ANPs can be observed

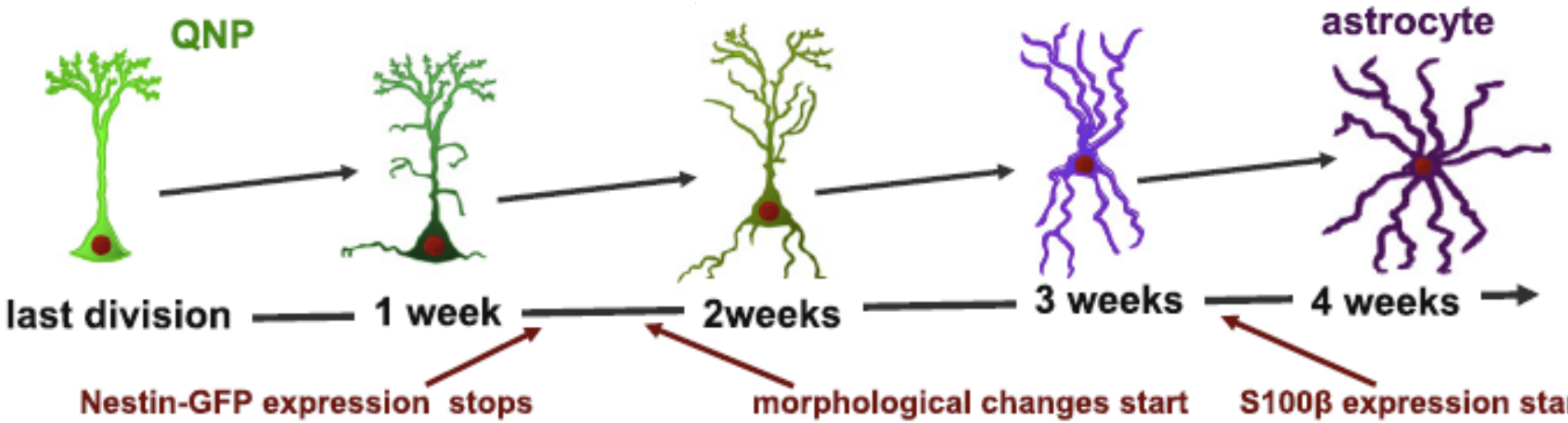


(120 hrs after the induction), separate ANPs can be identified.

Encinas et al., Cell Stem Cell 2011

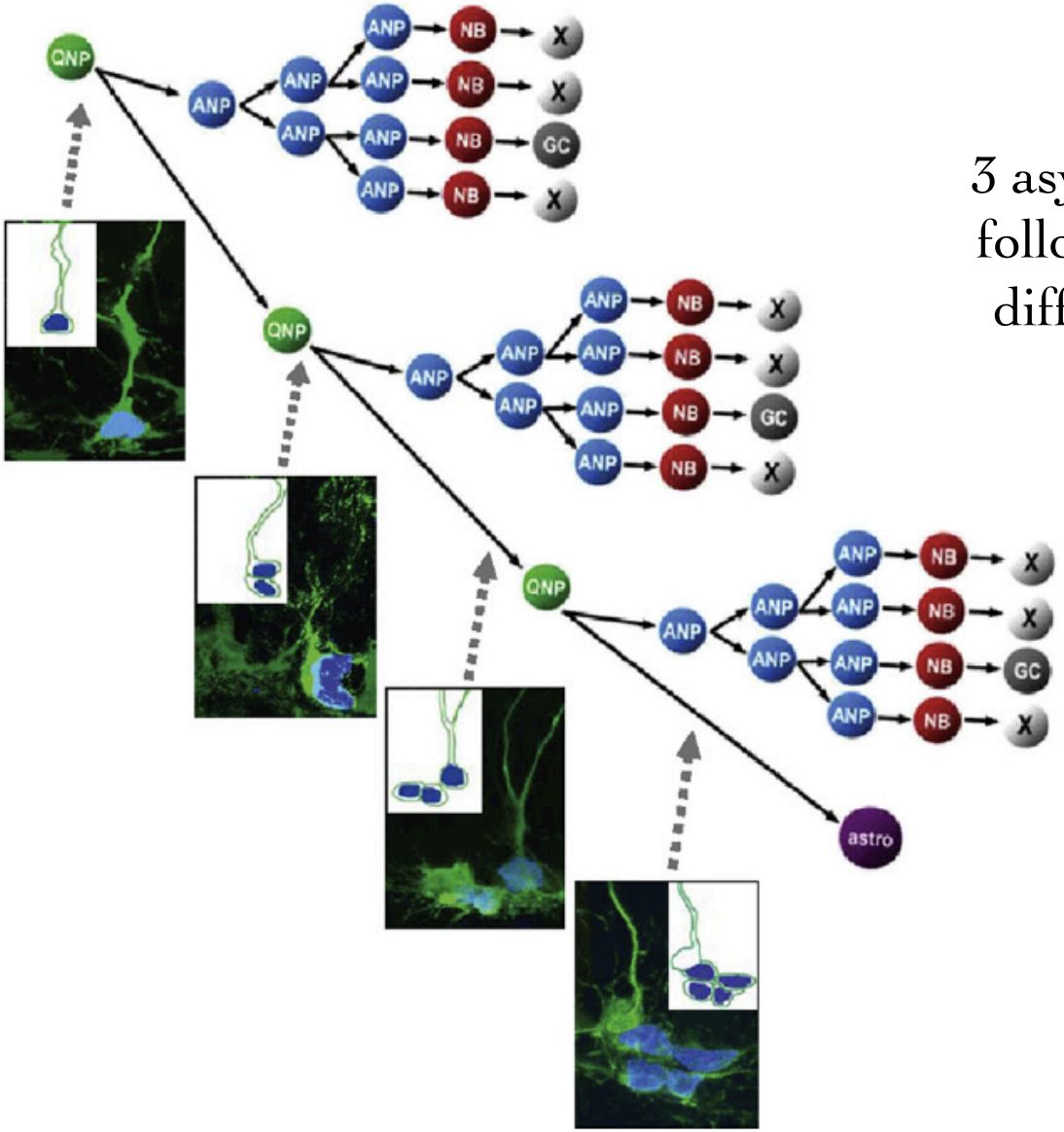
QNPs undergo division-coupled astrocytic differentiation





Encinas et al., Cell Stem Cell 2011

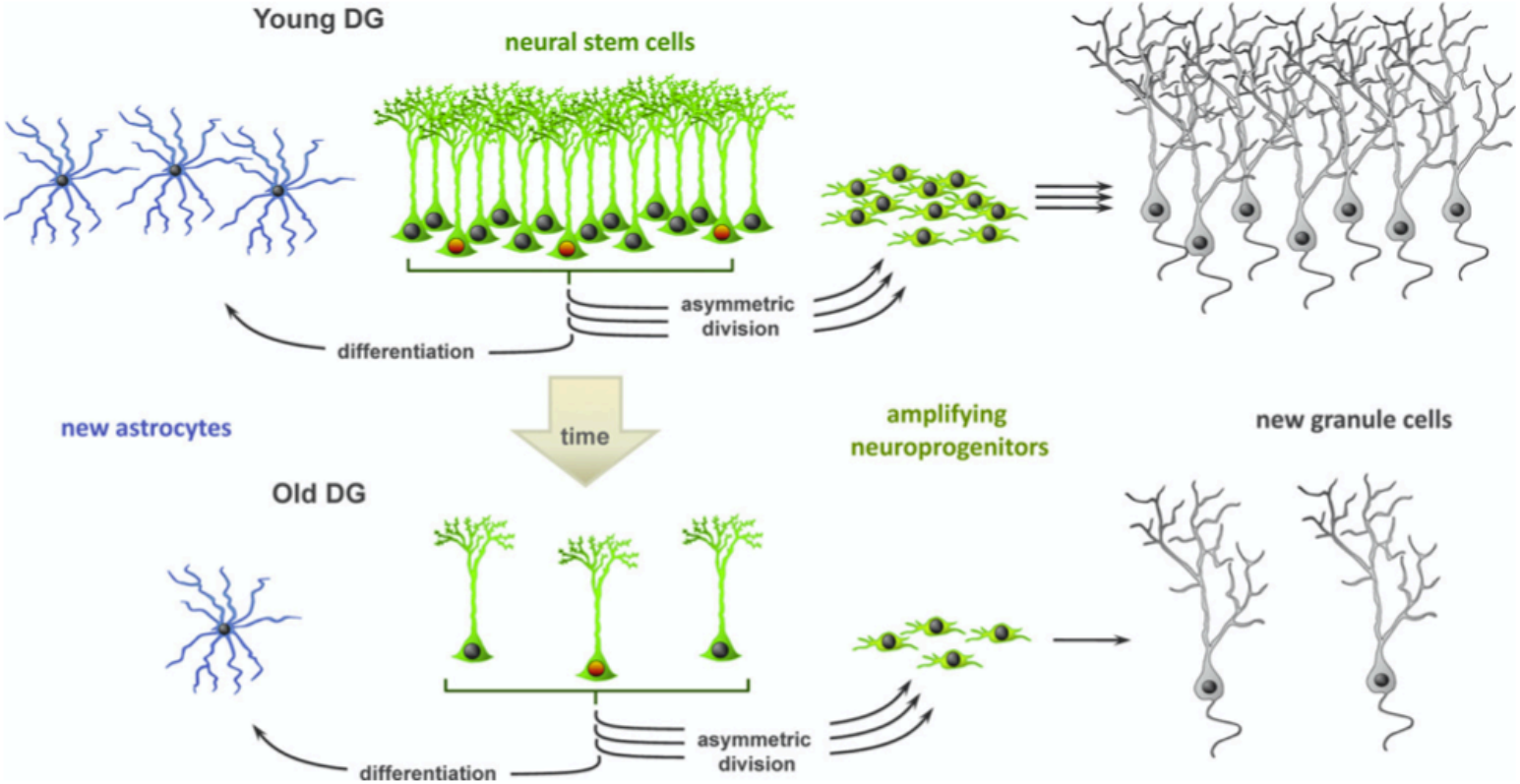
Scheme of divisions and death of stem cells and their progeny in the DG



3 asymetrical divisions followed by astrocytic differentiation of the stem cells

Encinas et al., Cell Stem Cell 2011

Neural stem cell deforestation as the main force driving the age-related decline in adult hippocampal neurogenesis?

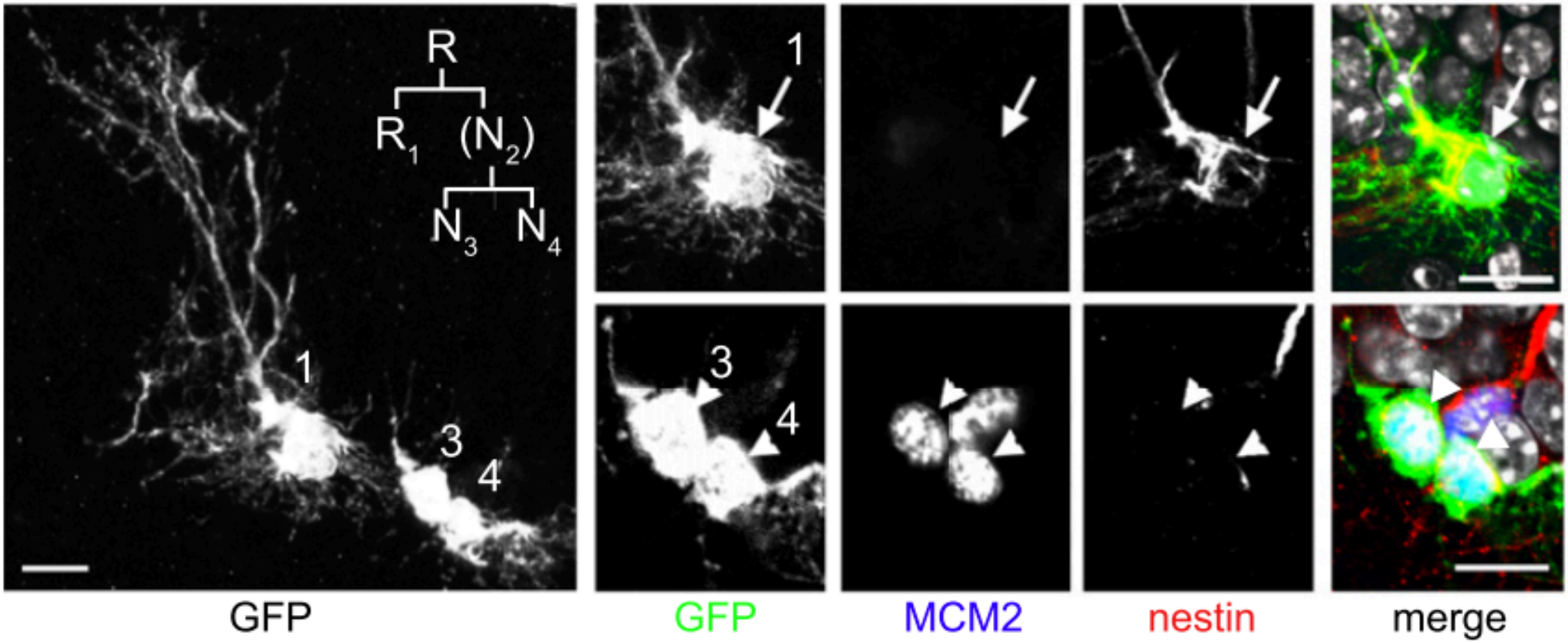


!!!!! Whether aging depletes the NSC pools (through their terminal differentiation) or hasten the transition between quiescence and activation is still an ongoing debate!!!!

Encinas & Sierra., Behavioural brain research 2012

Encinas model in question...

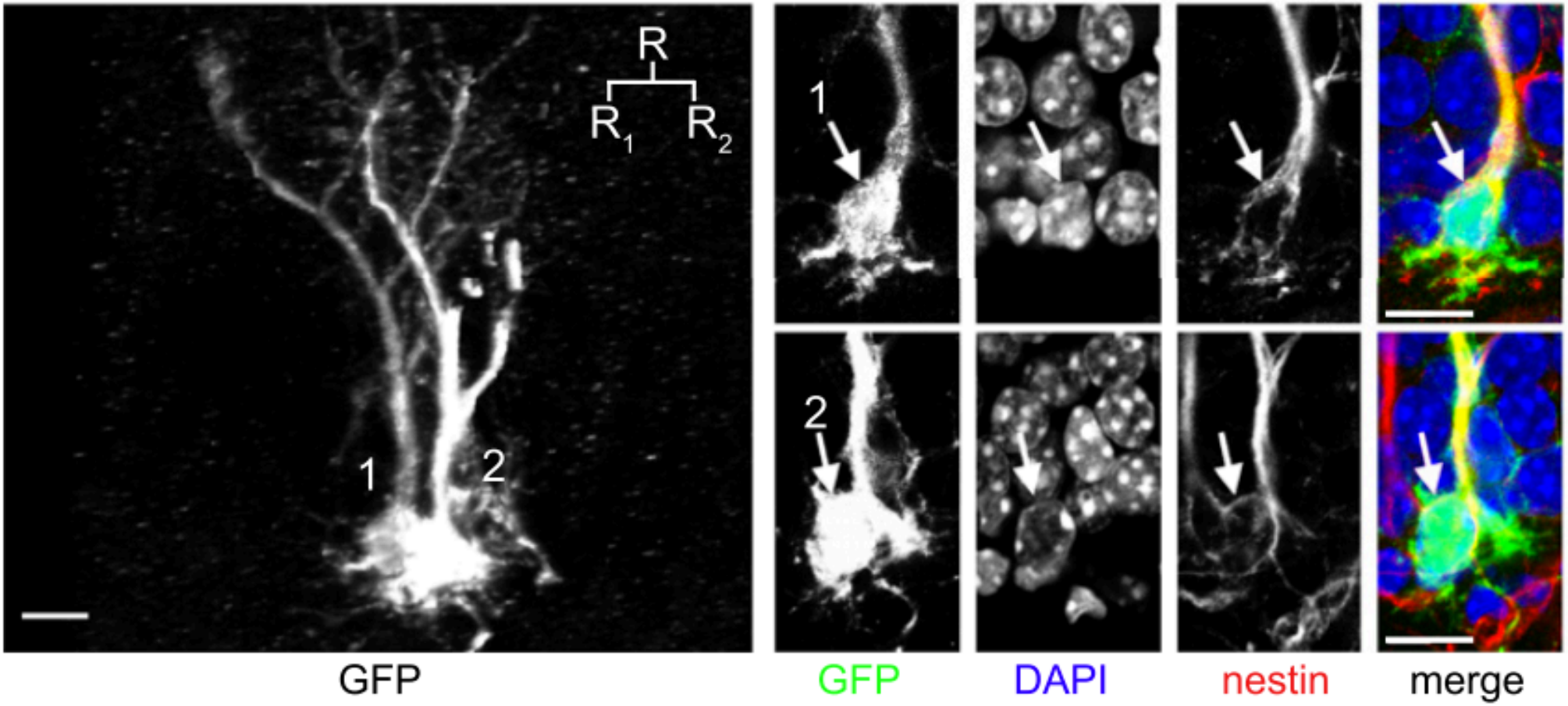
→ Visualisation of asymetric cell divisions



Bonaguidi et al., Cell 2011

Encinas model in question...

→ Visualisation of **symetric** cell divisions **as well**



Bonaguidi et al., Cell 2011

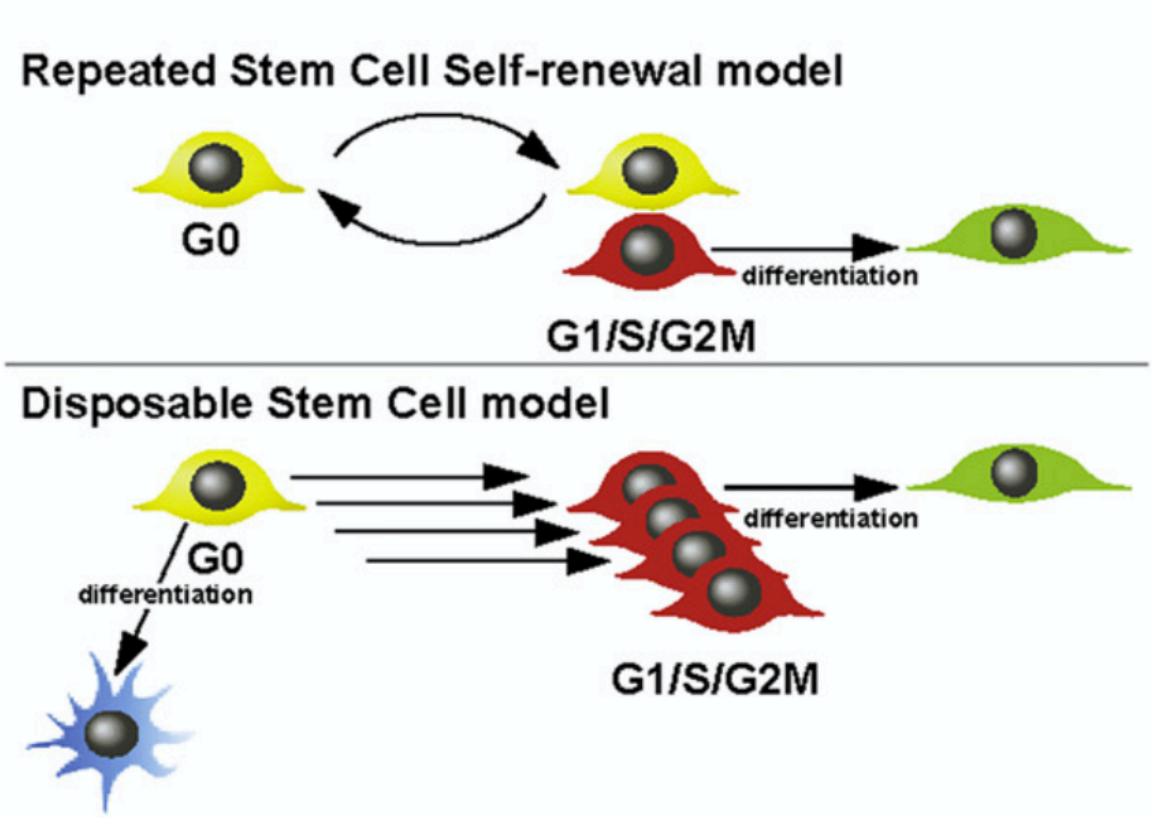
Two Views of Adult Neurogenesis

Bonaguidi Cell 2011

In the conventional « **repeated stem cell self-renewal » model (left), a quiescent stem cell is activated, undergoes an asymmetric division, produces a progeny that eventually differentiates, and returns to the quiescent state to be activated again several times** until the death of this stem cell or of the organism.

Encinas Cell 2011

In the « **disposable stem cell » model, a stem cell is quiescent for the entire postnatal life, is activated, undergoes several rapid asymmetric divisions producing progeny, and quits the pool of stem cells by differentiation** (in this case into an astrocyte).



NOT THE SAME GENETIC TOOLS, NOT THE SAME AGE/STRAIN OF MICE ANALYSED…

Kempermann, 2011

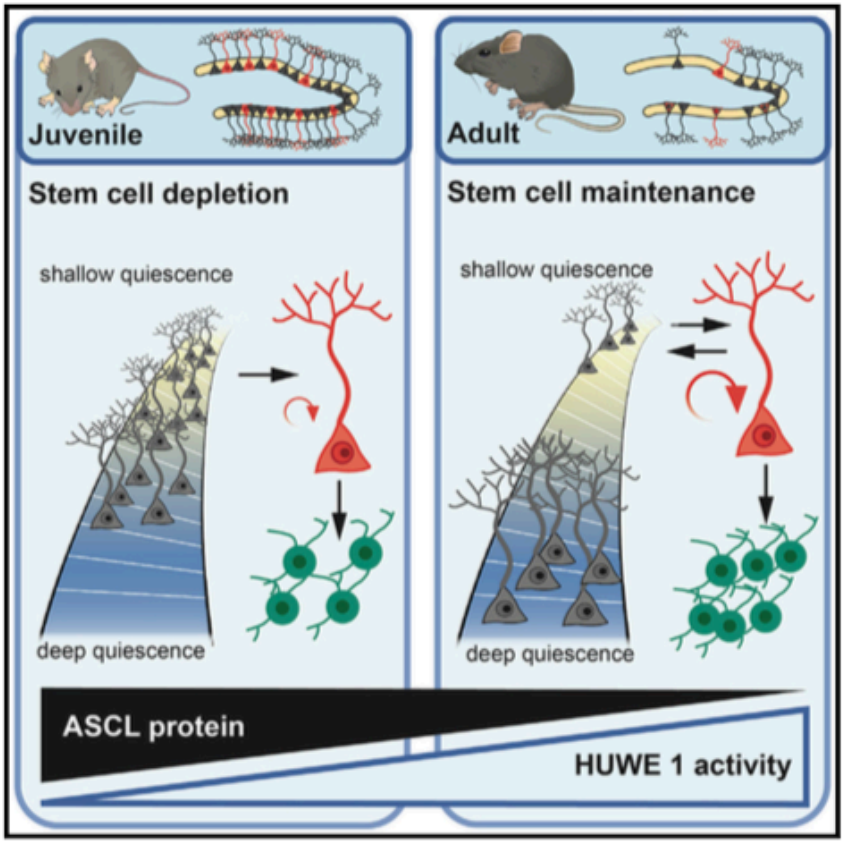
Reconciliation of the 2 models ?

Article

Cell Stem Cell

Coordinated changes in cellular behavior ensure the lifelong maintenance of the hippocampal stem cell population

Graphical Abstract



Authors

Lachlan Harris, Piero Rigo, Thomas Stiehl, ..., Noelia Urbán, Anna Marciniak-Czochra, François Guillemot

Correspondence

francois.guillemot@crick.ac.uk

In Brief

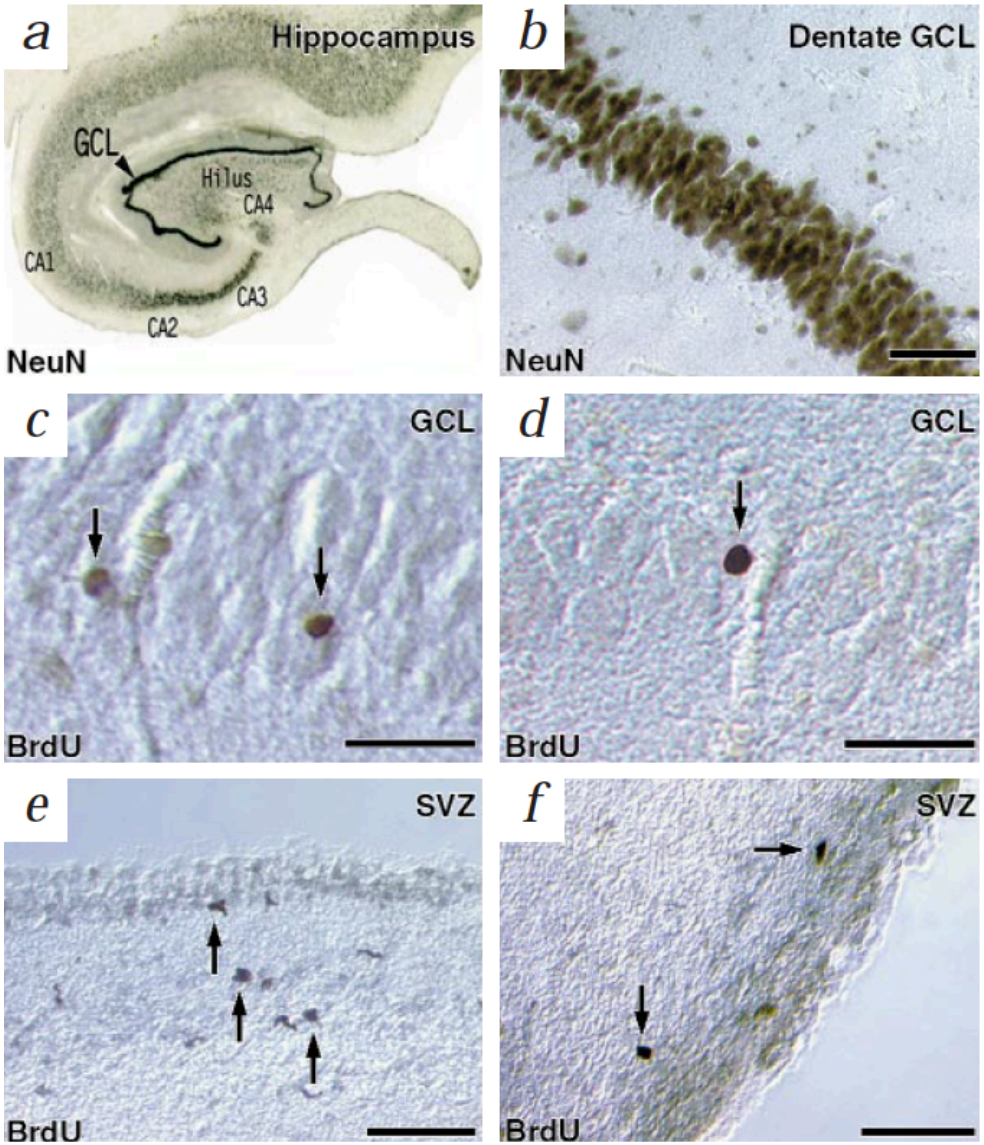
Harris et al. show that multiple cellular changes work in concert during early life to preserve the hippocampal stem cell population throughout adulthood in mice. In particular, more proliferating stem cells return to quiescence instead of differentiating. The changes are coordinated by increasing degradation of the pro-activation factor ASCL1.

5- What is known about human neural stem cells?

Neurogenesis in the adult human hippocampus

PETER S. ERIKSSON[1,4], EKATERINA PERFILIEVA[1], THOMAS BJÖRK-ERIKSSON[2], ANN-MARIE ALBORN[1], CLAES NORDBORG[3], DANIEL A. PETERSON[4] & FRED H. GAGE[4]

Do we find proliferative cells in the human brain?



→ Human brain tissue was obtained postmortem from patients who had been treated with the thymidine analog, bromodeoxyuridine (BrdU), that labels DNA during the S phase.

ERIKSSON et al., 1998

Do we find proliferative cells in the human brain?

→ This study by Eriksson et al., 1998, provided the only direct evidence to date for adult neurogenesis in humans, although it did not enable researchers to assess the number of new neurons generated or the dynamics of this process.

What the bomb said about the brain...

Cell PRESS

Neuron
Report
2012

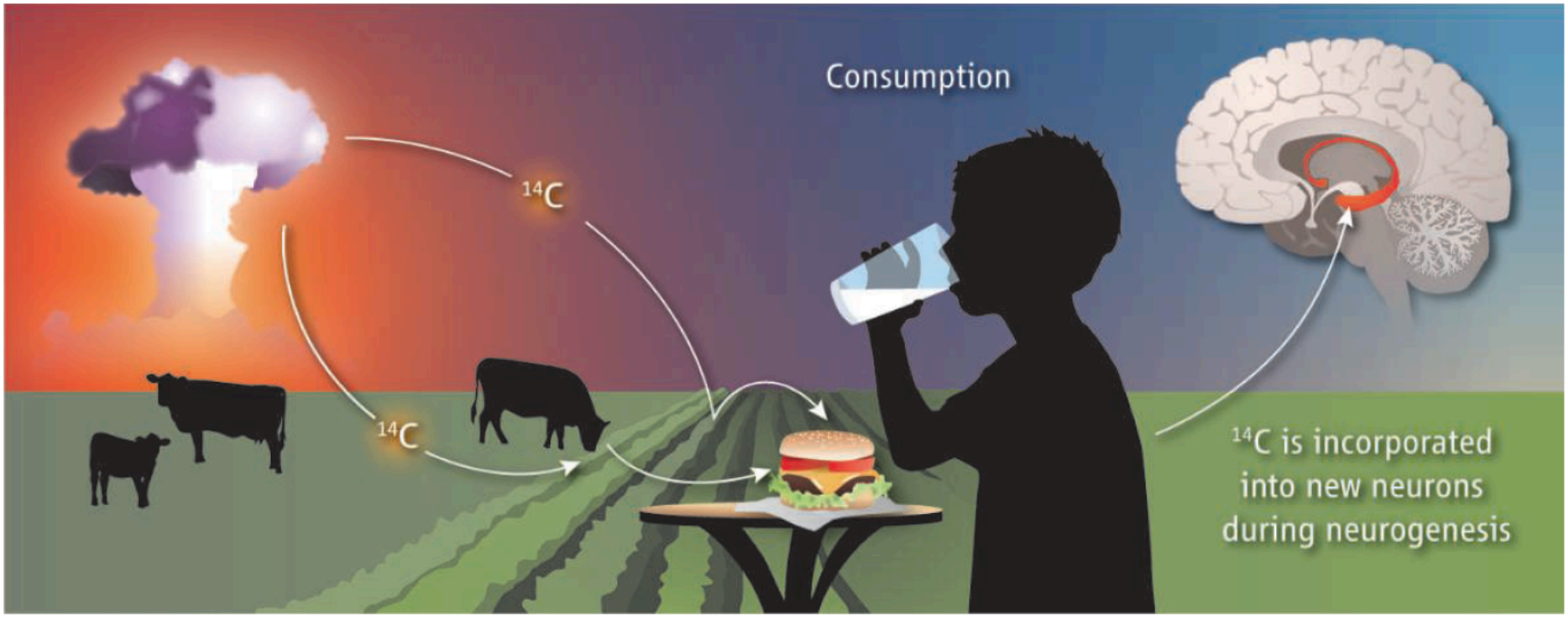
The Age of Olfactory Bulb Neurons in Humans

Olaf Bergmann,[1] Jakob Liebl,[4] Samuel Bernard,[5] Kanar Alkass,[2] Maggie S.Y. Yeung,[1] Peter Steier,[4] Walter Kutschera,[4] Lars Johnson,[3] Mikael Landén,[3,6] Henrik Druid,[2] Kirsty L. Spalding,[1,*] and Jonas Frisén[1,*]

[1]Department of Cell and Molecular Biology
[2]Department of Oncology-Pathology
[3]Division of Psychiatry, Department of Clinical Neuroscience
Karolinska Institute, SE-17177 Stockholm, Sweden
[4]University of Vienna, Faculty of Physics – Isotope Research, AT-1090 Vienna, Austria
[5]Institut Camille Jordan, CNRS UMR 5208, University of Lyon, FR-69622 Villeurbanne, France
[6]Institute of Neuroscience and Physiology, Sahlgrenska Academy at Gothenburg University, SE-40530 Gothenburg, Sweden
*Correspondence: kirsty.spalding@ki.se (K.L.S.), jonas.frisen@ki.se (J.F.)
DOI 10.1016/j.neuron.2012.03.030

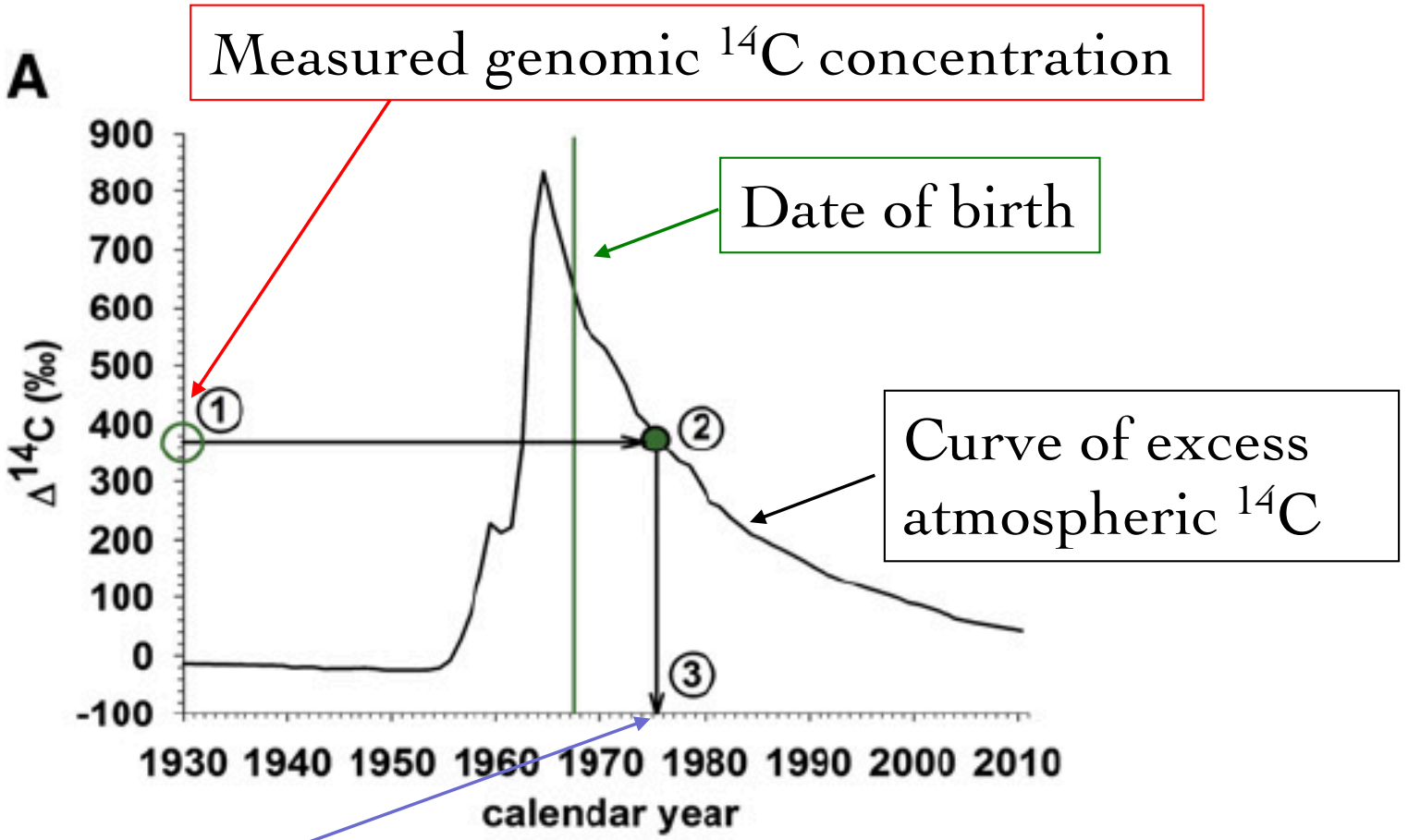
What the bomb said about the brain…

✓ Atmospheric ^{14}C that was released during nuclear bomb tests between 1945 and 1963 has been incorporated into the DNA of dividing cells, providing a time-stamp.



Kempermann, 2013

Strategy to establish cell age by ^{14}C dating



Bergmann, 2012

Limited Neurogenesis in the Adult Human Olfactory Bulb

- We cannot exclude that there may be low-grade turnover of neurons, but at a constant rate, the annual turnover would be around 0.008%.

- That corresponds to <1% of neurons being exchanged after 100 years.

- It has been estimated that up to 50% of olfactory bulb neurons are exchanged annually in rodents.

Bergmann, 2012

Limited Neurogenesis in the Adult Human Olfactory Bulb

There is very limited, if any, postnatal neurogenesis in the human olfactory bulb.

---> This identifies a fundamental difference in the plasticity of the human brain compared to other mammals.

Bergmann, 2012

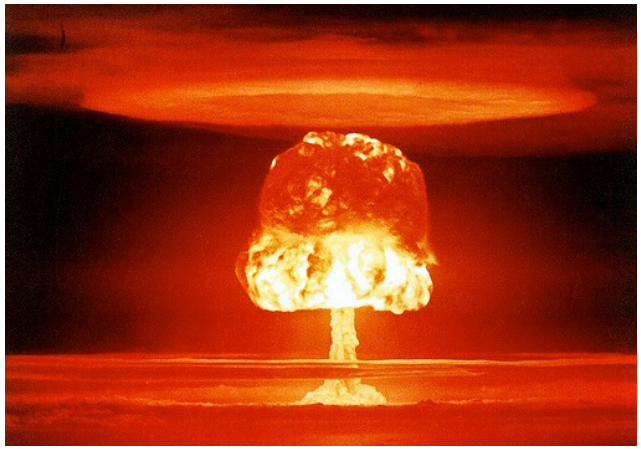
What about hippocampal neurogenesis?

Cell

Juin 2013

Dynamics of Hippocampal Neurogenesis in Adult Humans

Kirsty L. Spalding,[1,8] Olaf Bergmann,[1,8] Kanar Alkass,[1,2] Samuel Bernard,[3] Mehran Salehpour,[4] Hagen B. Huttner,[1,5] Emil Boström,[1] Isabelle Westerlund,[1] Céline Vial,[3] Bruce A. Buchholz,[6] Göran Possnert,[4] Deborah C. Mash,[7] Henrik Druid,[2] and Jonas Frisén[1,*]

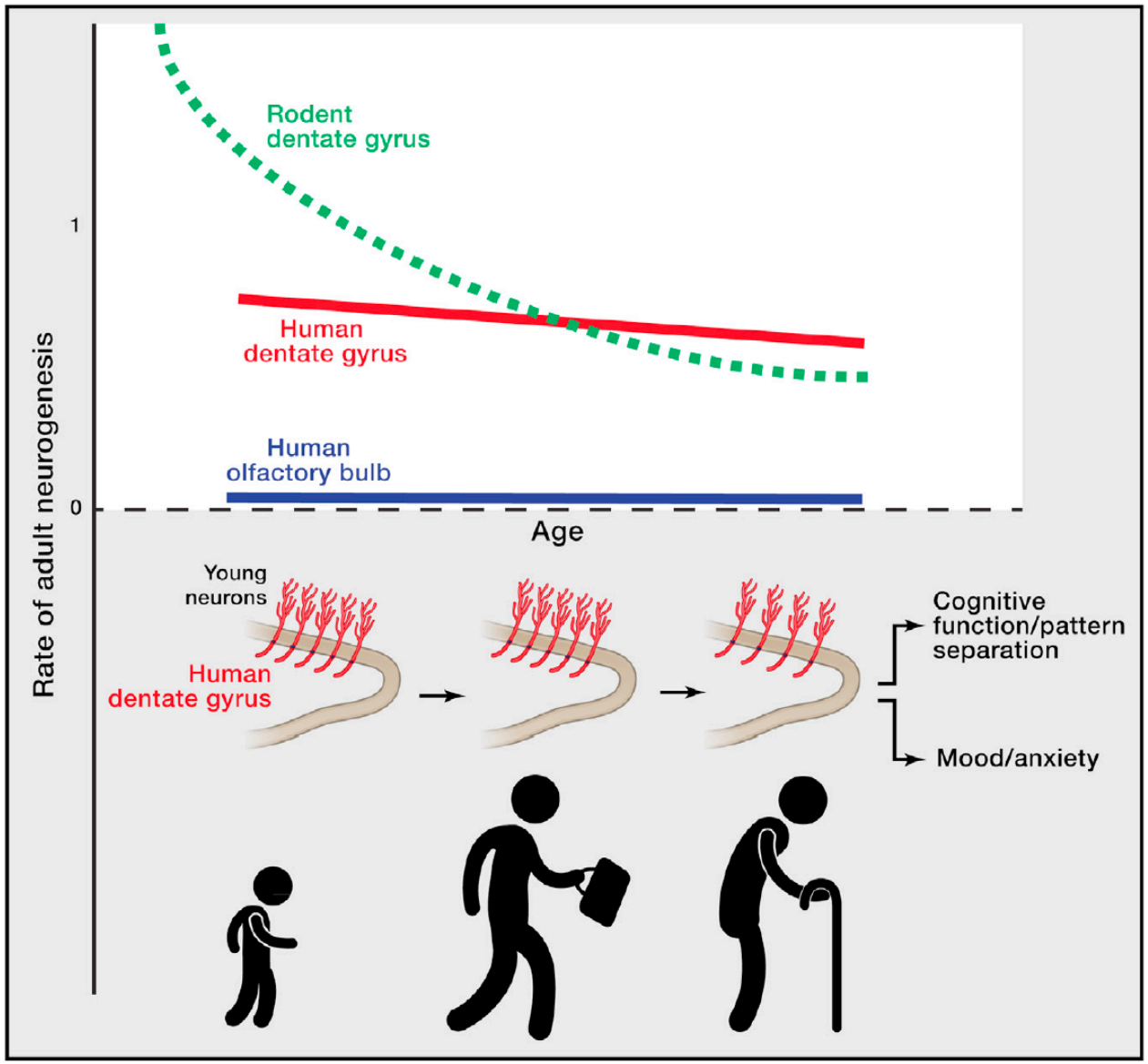


Evidence for continued neurogenesis into adulthood at rates that suggest it may play a significant role in humans

This retrospective carbon dating approach proves that there is substantial production of new neurons in the adult human brain throughout life.

- One third of adult hippocampal neurons are turning over.
- 700 new neurons are added in each hippocampus per day, corresponding to an annual turnover of 1.75% of the neurons within the renewing fraction
- This turnover rate was not significantly different between men and women and declined only modestly with age.

Evidence for continued neurogenesis into adulthood at rates that suggest it may play a significant role in humans



Kheirbek and Hen, 2013

Adult hippocampal neurogenesis in questions...

LETTER Nature 2018

doi:10.1038/nature25975

Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults

Shawn F. Sorrells[1,2*], Mercedes F. Paredes[1,3*], Arantxa Cebrian-Silla[4], Kadellyn Sandoval[1,3], Dashi Qi[5], Kevin W. Kelley[1], David James[1], Simone Mayer[1,3], Julia Chang[6], Kurtis I. Auguste[2], Edward F. Chang[2], Antonio J. Gutierrez[7], Arnold R. Kriegstein[1,3], Gary W. Mathern[8,9], Michael C. Oldham[1,2], Eric J. Huang[10], Jose Manuel Garcia-Verdugo[4], Zhengang Yang[5] & Arturo Alvarez-Buylla[1,2]

Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease

Nature Med 2019

Elena P. Moreno-Jiménez[1,2,3,6], Miguel Flor-García[1,2,3,6], Julia Terreros-Roncal[1,2,3,6], Alberto Rábano[4], Fabio Cafini[5], Noemí Pallas-Bazarra[1,3], Jesús Ávila[1,3] and María Llorens-Martín[1,2,3*]

Based on immunofluorescence labelling of diverse markers on post-mortem tissues

6- Adult neurogenesis: what for?

Replacement of neuronal cell loss?

Probably not, as by the age of 25, the number of neurons starts to decline (at least 100 000 neurons lost per day)…

Role in cognitive function, memory, behaviour, pathological disorders…?

Regulation by environmental cues such as diet, exercice, learning, pathologies…)?

Effect of adult-born neuron depletion on animal's cognitive ability

→ Accumulating evidence suggests that adult-born hippocampal neurons do make contributions to learning and memory (SEE ROSELINE POIRIER'S CONFERENCE)

→ Fundamental question largely unresolved: how a small number of generated neurons contribute to brain function modulation?

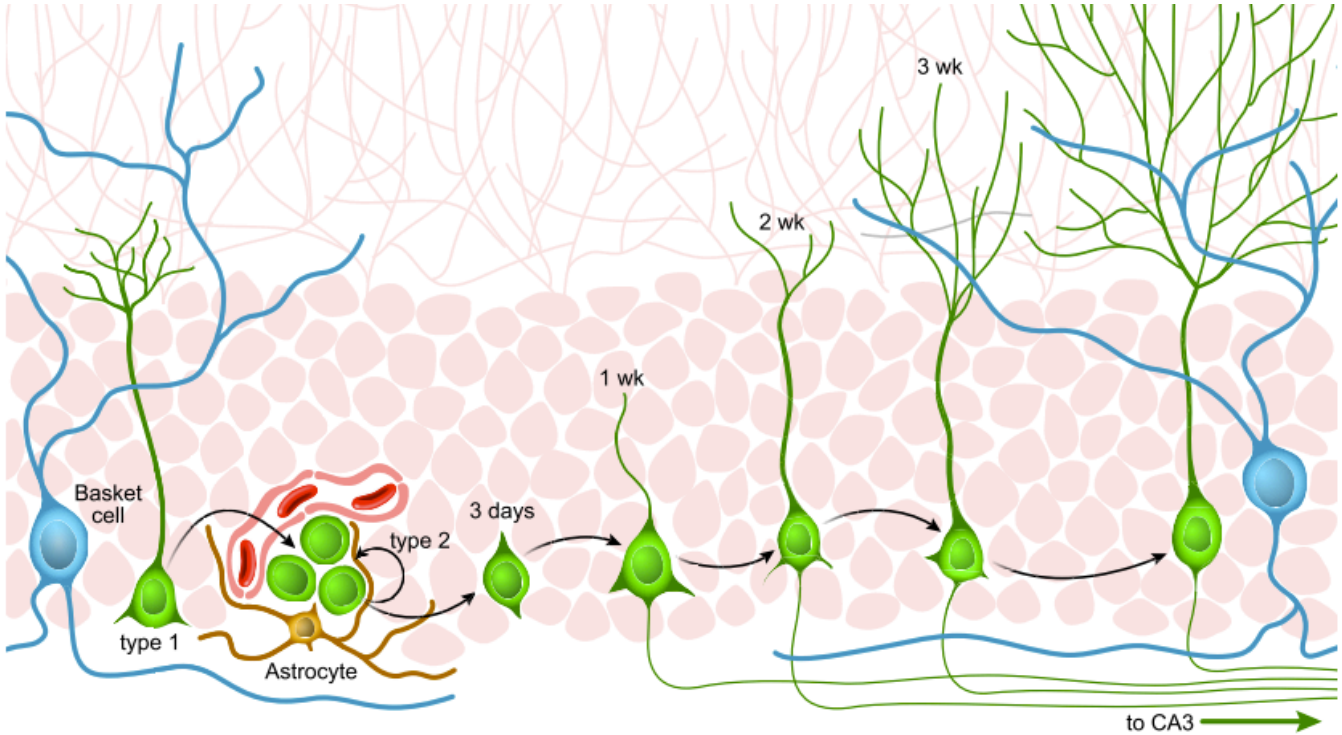
SCIENCE 2023

NEUROGENESIS

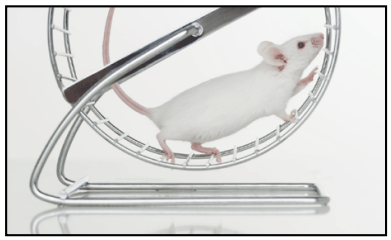
Pregnancy-responsive pools of adult neural stem cells for transient neurogenesis in mothers

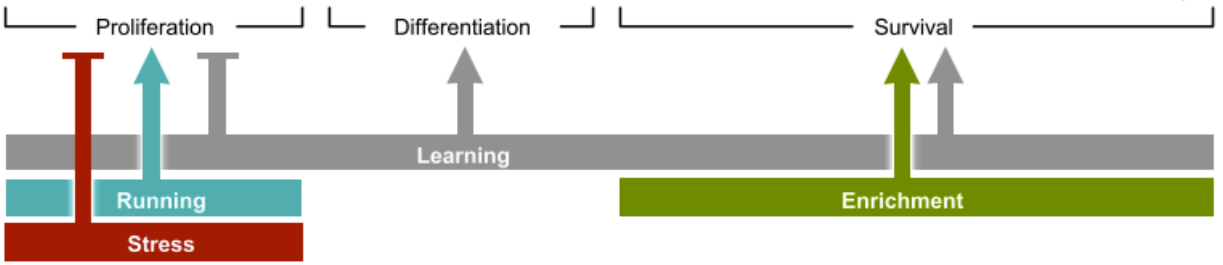
Zayna Chaker[1]†, Corina Segalada[1]†, Jonas A. Kretz[2], Ilhan E. Acar[2], Ana C. Delgado[1], Valerie Crotet[1], Andreas E. Moor[2], Fiona Doetsch[1]*

Which factors favors adult neurogenesis?



Running wheel





Enriched environment

Aimone et al., Physiological Review 2014

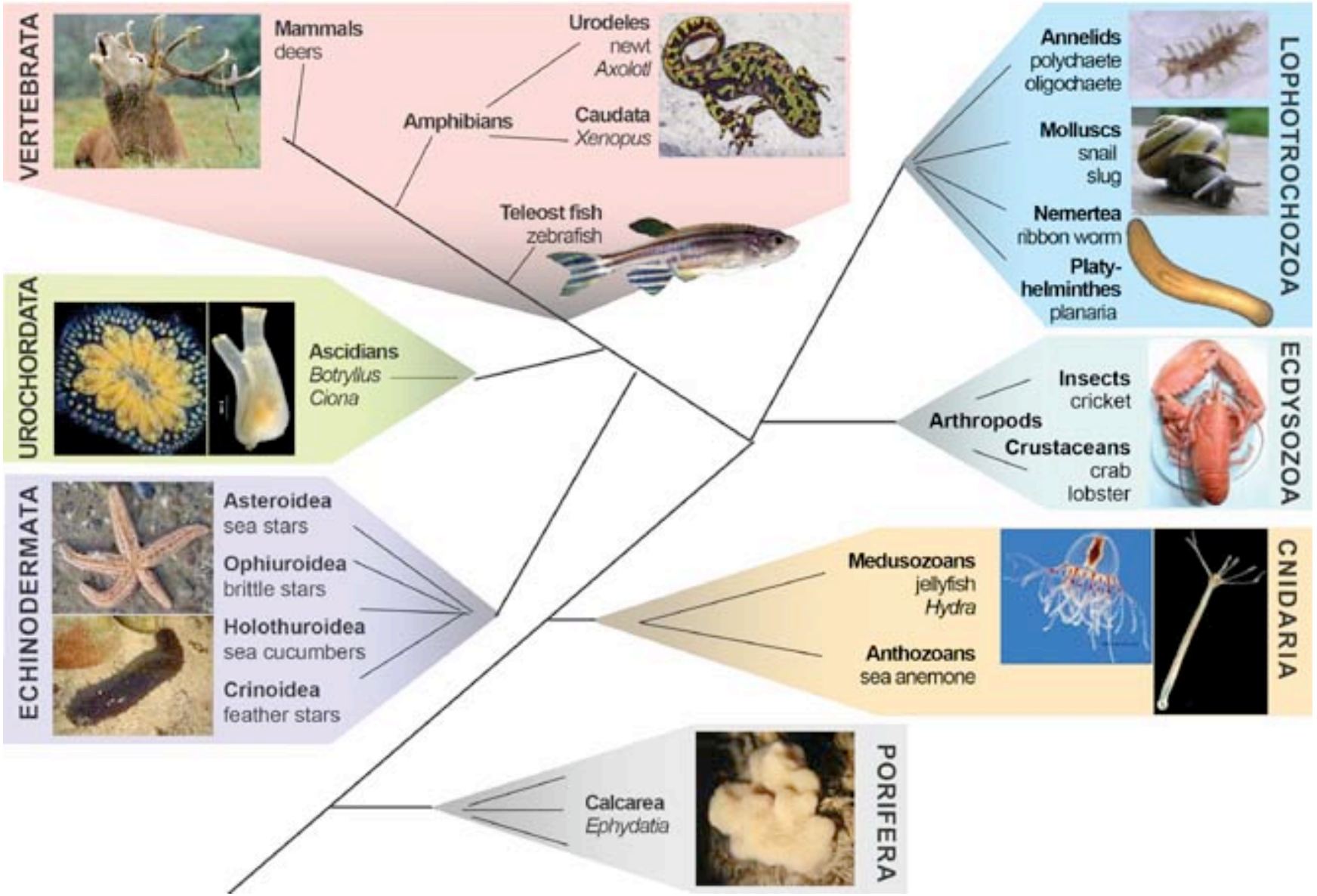
Neural stem cells and brain repair?

Do mammalian NSCs have regenerative capacities?

Might cells outside the neurogenic niches be involved ?

What is the efficiency of regenerative processes in the mammalian brain?

Phylogenetic tree of the animal species exhibiting a regenerative potential after injury



Adult neurogenesis and neuronal regeneration across vertebrate species

TABLE 1. Summary of adult neurogenesis and neuronal regeneration across vertebrate species

	Fish		Urodeles		Anurans		Reptiles		Birds		Mammals	
	N	R	N	R	N	R	N	R	N	R	N	R
Telencephalon	+	+	+	+	+	–	+	+	+	S	+	–
Mesencephalon	+	?	–	+	+/–	–						
Cerebellum	+	+	?	?	?	?	(+)	?	–	–	–	–
Spinal cord	+	+	+	+	–	–	–	–	–	–	–	–
Spinal nerves		+		+		+		+		–		–
Retina	+	+	+	+	+	–	–	–	–	–	–	–
Optic nerve		+		+		+		+		–		–
Olfactory system*	+	+	+	+	+	–	+	+	+	?	+	S
Olfactory nerve		+		+		?		+		+		+
Hair cells**			+	+		?	?	+	$+^{(v)}$	+	–	$S^{(v)}$
Vestibular nerve		+		?		+/–		?		+/–		+/–

N, neurogenesis; R, regeneration. *Neurogenesis both in the olfactory bulb and olfactory epithelium; **neurogenesis/regeneration known to occur in hair cells (from vestibular or auditory neuroepithelia and/or lateral line). ?, Lack of/insufficient information available; +, reported only in some species; +/–, not full functional recovery; S, subset of neurons following chemical lesion; $S^{(v)}$, subset of neurons (vestibular, but not cochlear sensory neurons).

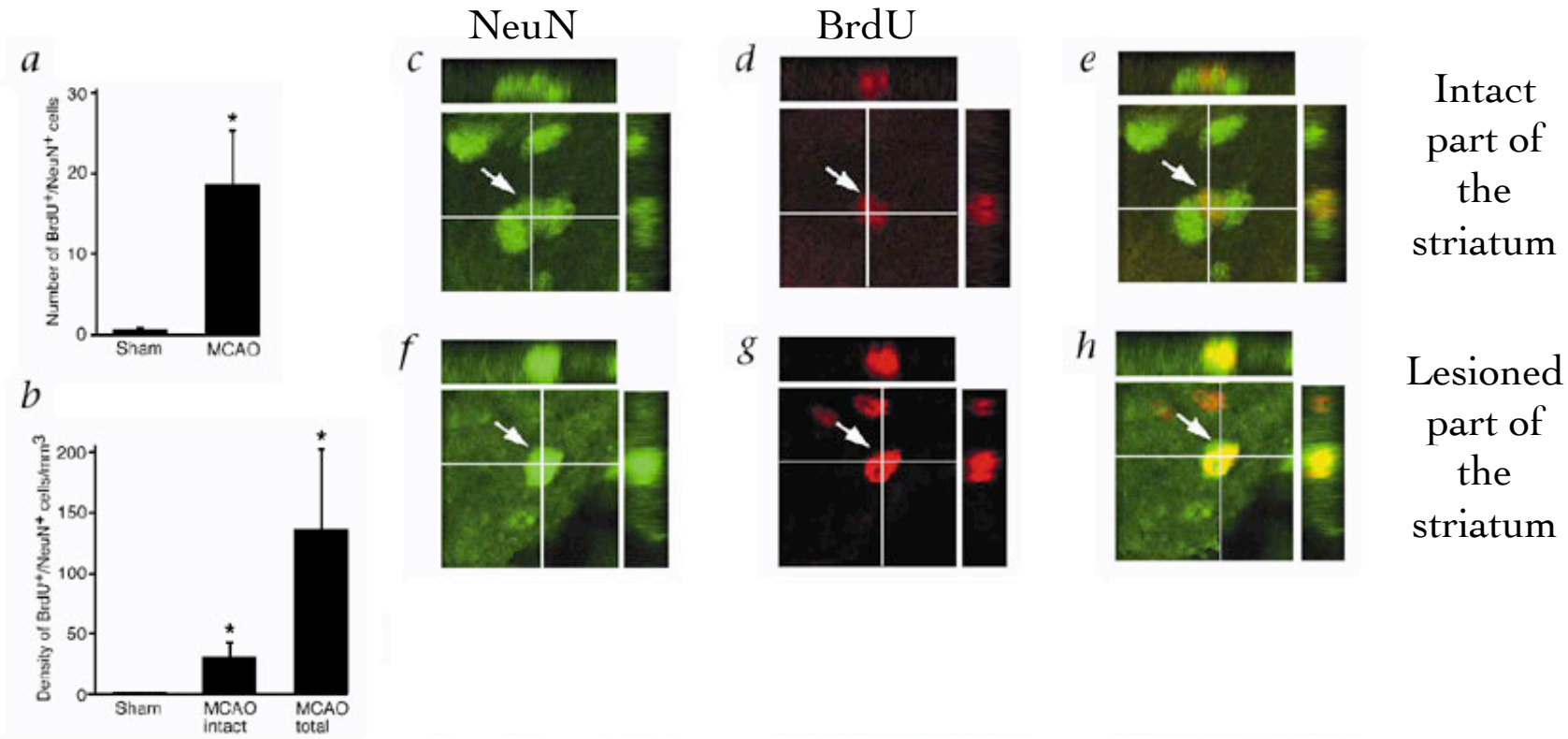
Ferreti, European J Neuroscience 2011

Neuronal replacement from endogenous NSCs in the adult brain?

✓ Animal models for stroke (MCAO = middle cerebral artery occlusion)

✓ Leads to massive neuronal degeneration in the striatum and parietal cortex

✓ Observation of neurogenesis in the striatum

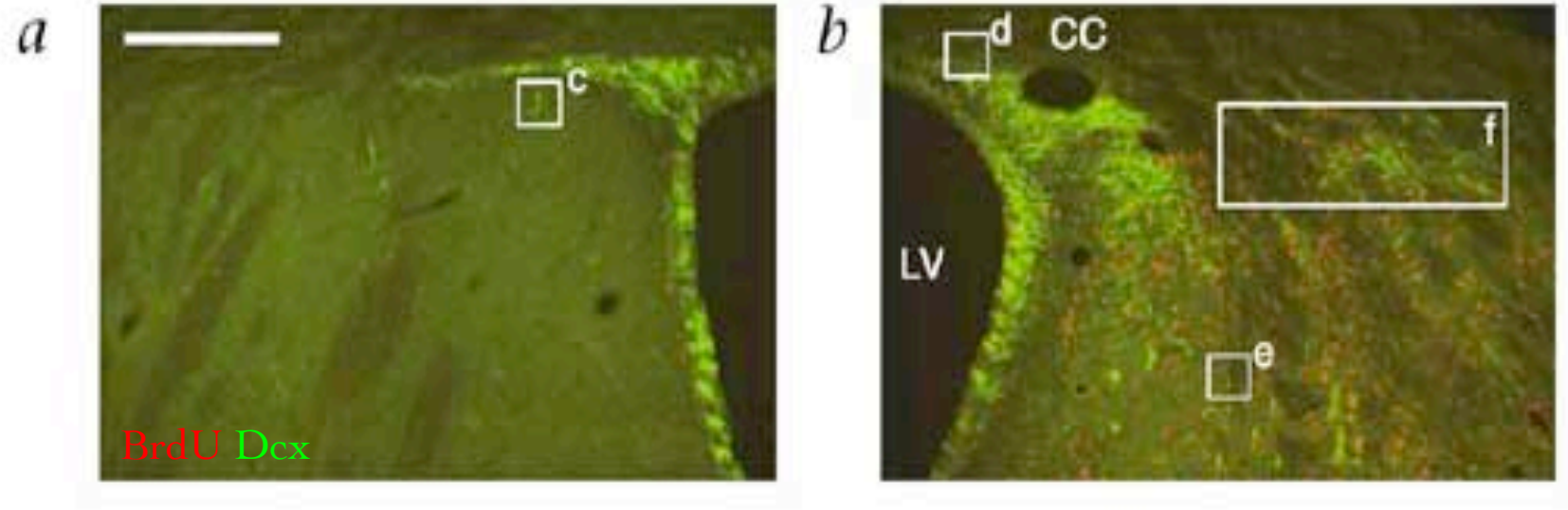


Arvidsson et al., Nature Medecine, 2002

Neuronal replacement from endogenous NSCs in the adult brain?

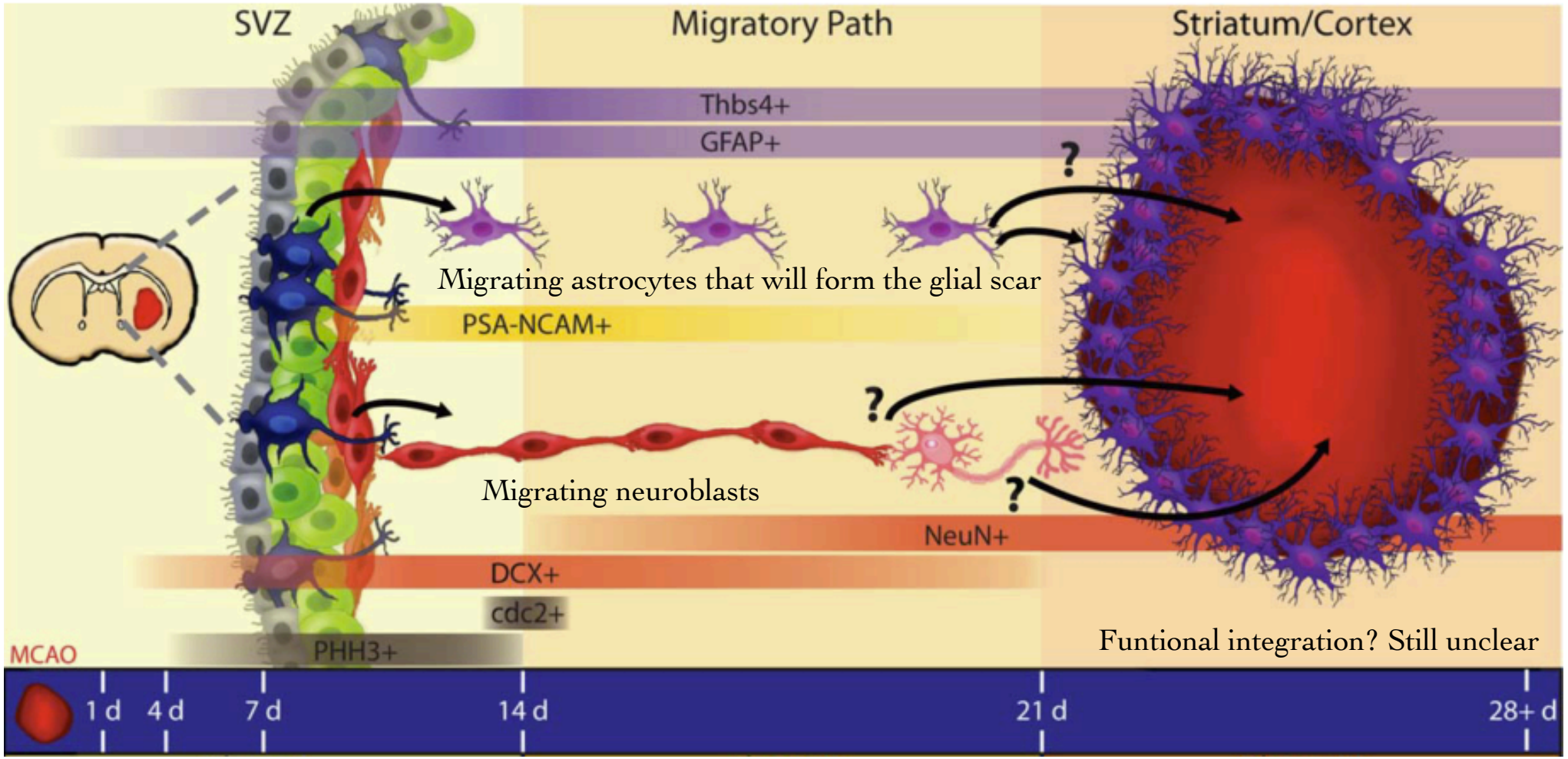
Contralateral to MCAO

Ipsilateral to MCAO



✓ Migrating neuroblasts from the SVZ are rerouted towards the striatum (f)

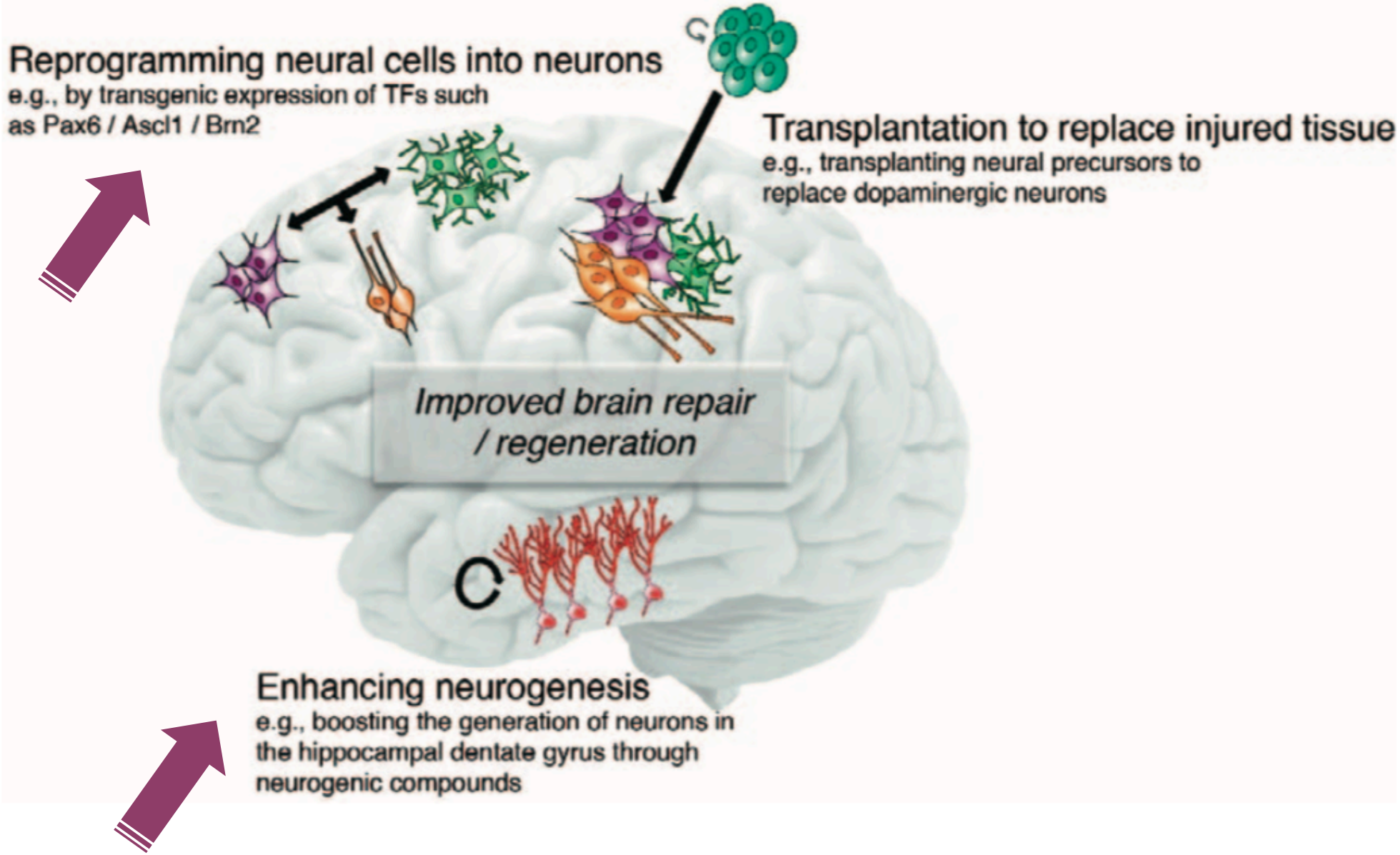
Neuronal replacement from endogenous NSCs in the adult brain?



- 80% of newly generated neurons die.
- Only 0,2% of dead neurons are replaced

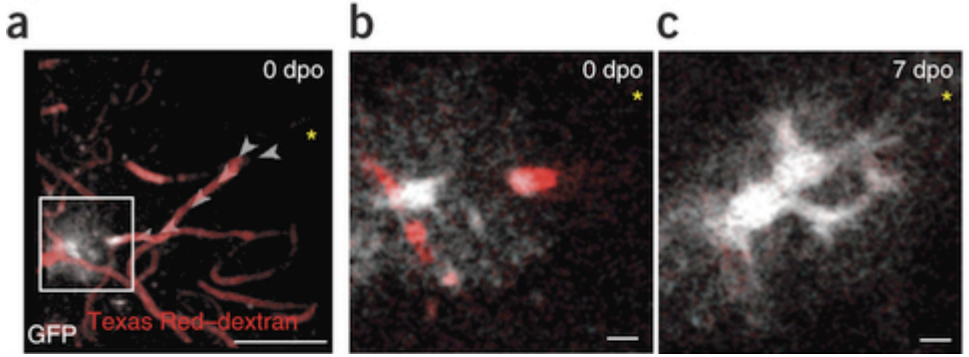
Grégoire et al., Glia 2015

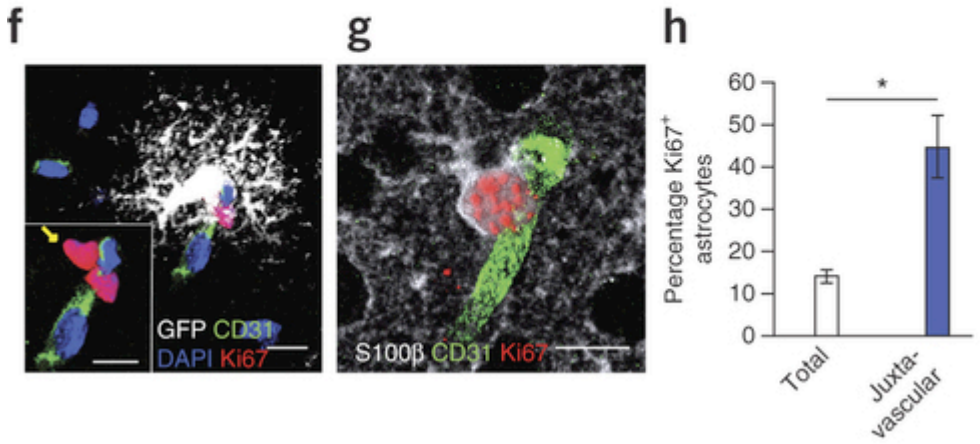
STRATEGIES FOR REGENERATIVE MEDICINE OF THE BRAIN



Jessberger Transfus Med Hemother 2016

Glial cell potential outside the neurogenic niche after acute injury



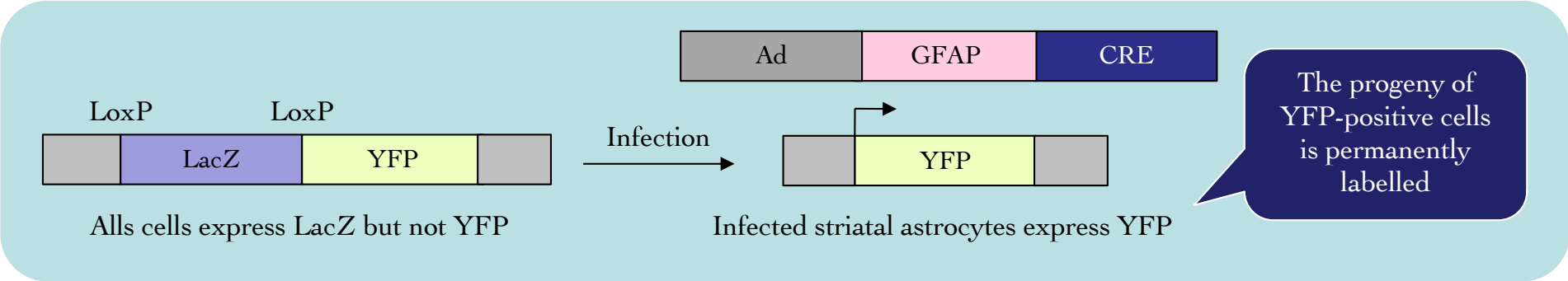


✓ Live imaging of GFP-labeled astrocytes in the adult mouse cerebral cortex over several weeks after acute injury reveals contact with blood vessels

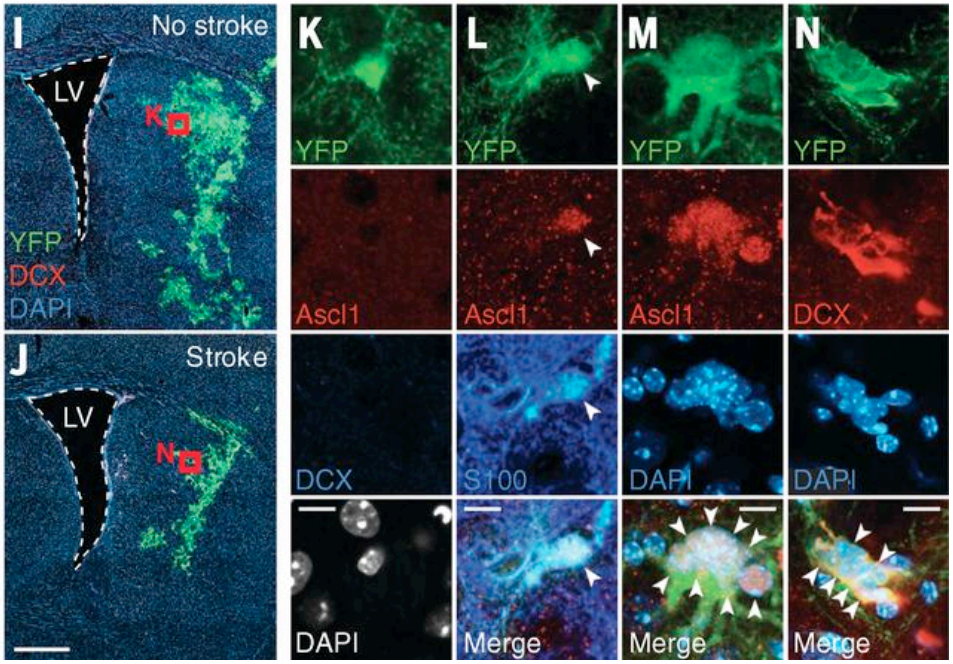
✓ A subset of astrocytes located at juxtavascular sites proliferate (importance of the niche!)

Bardehle et al., Nature Neuroscience 2013

Glial cell potential outside the neurogenic niche



I,K: No stroke J,L-N: Stroke



✓ Evidence for astrocyte-derived neuroblast production in the striatum after a stroke

✓ Use of of an Adeno-GFAP-Cre virus with astrocyte-specific Cre expression injected in the striatum to avoid labelling of migrating SVZ cells

Magnusson et al., Science 2014

Glial cell potential outside the neurogenic niche

✓ In addition to astrocytes, ependymal cells and NG2-Glia can also proliferate at injury sites and re-express RGC markers, Nestin or the reprogramming/neurogenic factor Ascl1

✓ *Note: Also abundant proliferation of microglial cells, the resident macrophages that act as the first and main form of active immune defence in the CNS*

	Normal function	**Proliferation in physiological conditions**	**Proliferation after CNS injury**	**Neurosphere formation after injury**	***In vivo* neurogenic potential after injury (without delivery of exogenous factors)**
Astrocytes	Neuronal support/regulation, brain homeostasis…	NO	A subset YES (15-40%)	YES in the brain (5% of brain reactive astrocytes) NO in the spinal cord	Highly limited. Reported in the striatum but not in the cortex or spinal cord.
Ependymal cells	Line the ventricular system, secrete & circulate cerebrospinal fluid	Very limited (generates new ependymal cells)	A subset YES	YES (at least those from SVZ & spinal cord)	Highly limited. Reported generation of neuroblasts after stroke in the forebrain. Astrocyte generation for scar formation upon spinal cord injury.
NG2-Glia	Oligodendrocyte precursors	YES	YES (more)	YES	Highly limited and still controversial. Oligodendrocyte generation (mostly studied for their repair potential in demyelinating diseases).

Glial-driven cellular therapy in the mammalian brain: dream or reality? The limited neurogenic potential of reactive glial cells

Could any of the above glial progenitors actually be used to replace the lost neurons?

✓ PROBLEM 1 : Global lineage restriction towards gliogenesis is observed *in vivo*, which is most probably be due to a **neurogenic-inhibitory local environment** (even grafted neuroblasts from SVZ revert to gliogenesis)

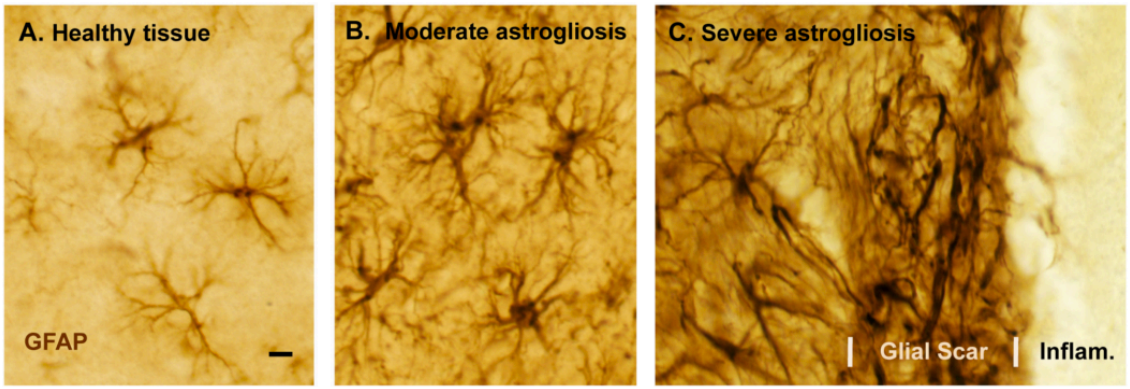
Future directions: characterization of the neurogenic niche molecular nature / pursuing the identification of local inhibitory cues…

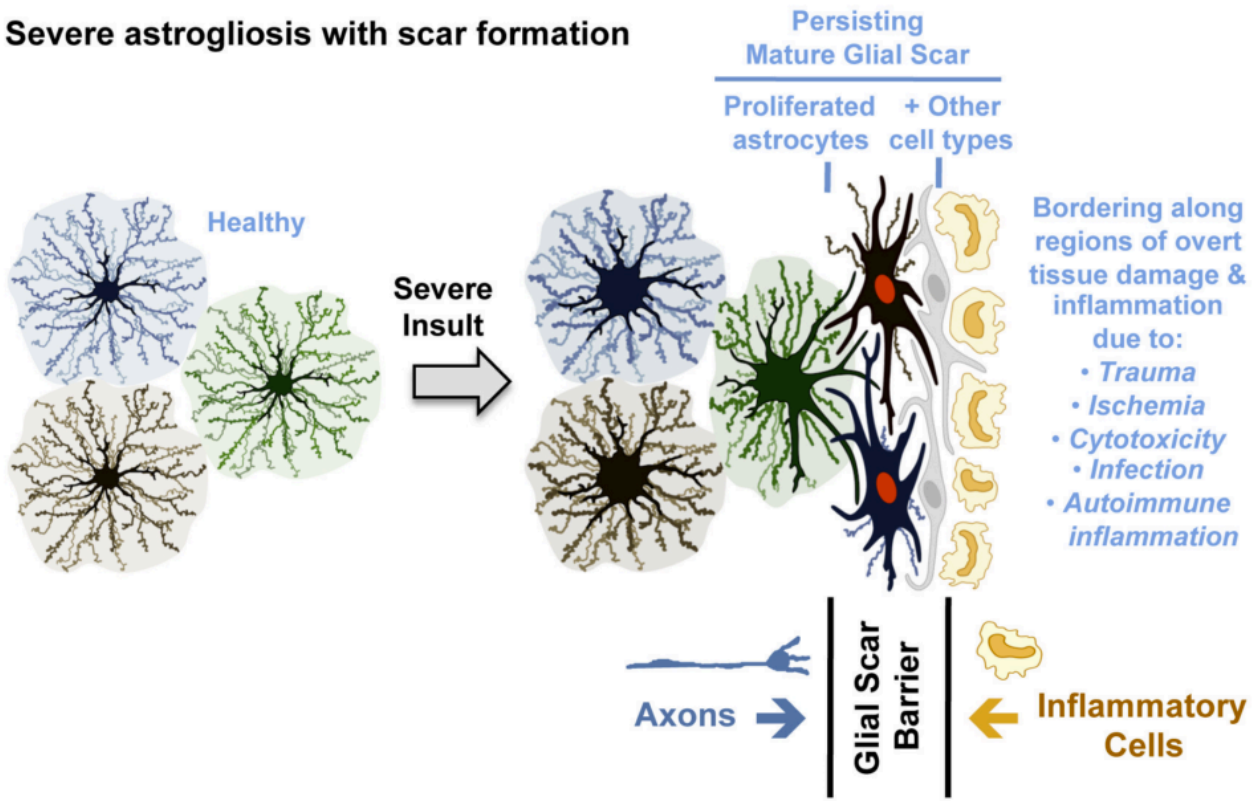
✓ PROBLEM 2 : Injury promotes partial reprogramming of reactive glial cells into neural progenitors but **neuronal maturation is still incomplete** (even when reprogramming factors such as Sox2 are artificially expressed) + despite their plasticity, **glial cells are locally highly heterogenous** + **regional specifity in their response**

Future directions: transcriptomic and epigenomic comparisons may help understanding what's missing…

Dimou & Götz, Glia 2014

Glial-driven cellular therapy in the mammalian brain: dream or reality?
Reactive astrogliosis: beneficial and adverse effects





✓ Beneficial: Blood-brain barrier repair, neural protection, restricton of inflammatory cell spreading and infection…

✓ Detrimental: inhibition of axon regeneration, neurotoxicity, inflammation or chronic pain…

Sofroniew, Trends in Neuroscience 2009

Glial-driven cellular therapy in the mammalian brain: dream or reality? The limited survival (& integration?) of newly produced neurons

Especially after brain injury, the number of the originally elicited neurons profoundly decreases over weeks with few of them surviving. But is longer survival and successful integration of new neurons into the adult brain parenchyma at all possible?

✓ YES in conditions when reactive gliosis is limited (e.g. mild lesion with scarless wound healing in zebrafish)

Future directions: understand which reactive glial subtypes create an adverse environment for survival of new neurons and best utilize these to turn them into neurons by neurogenic fate determinants.

Dimou & Götz, Glia 2014