NS201B: Basic Concepts for Cellular and Developmental Neuroscience

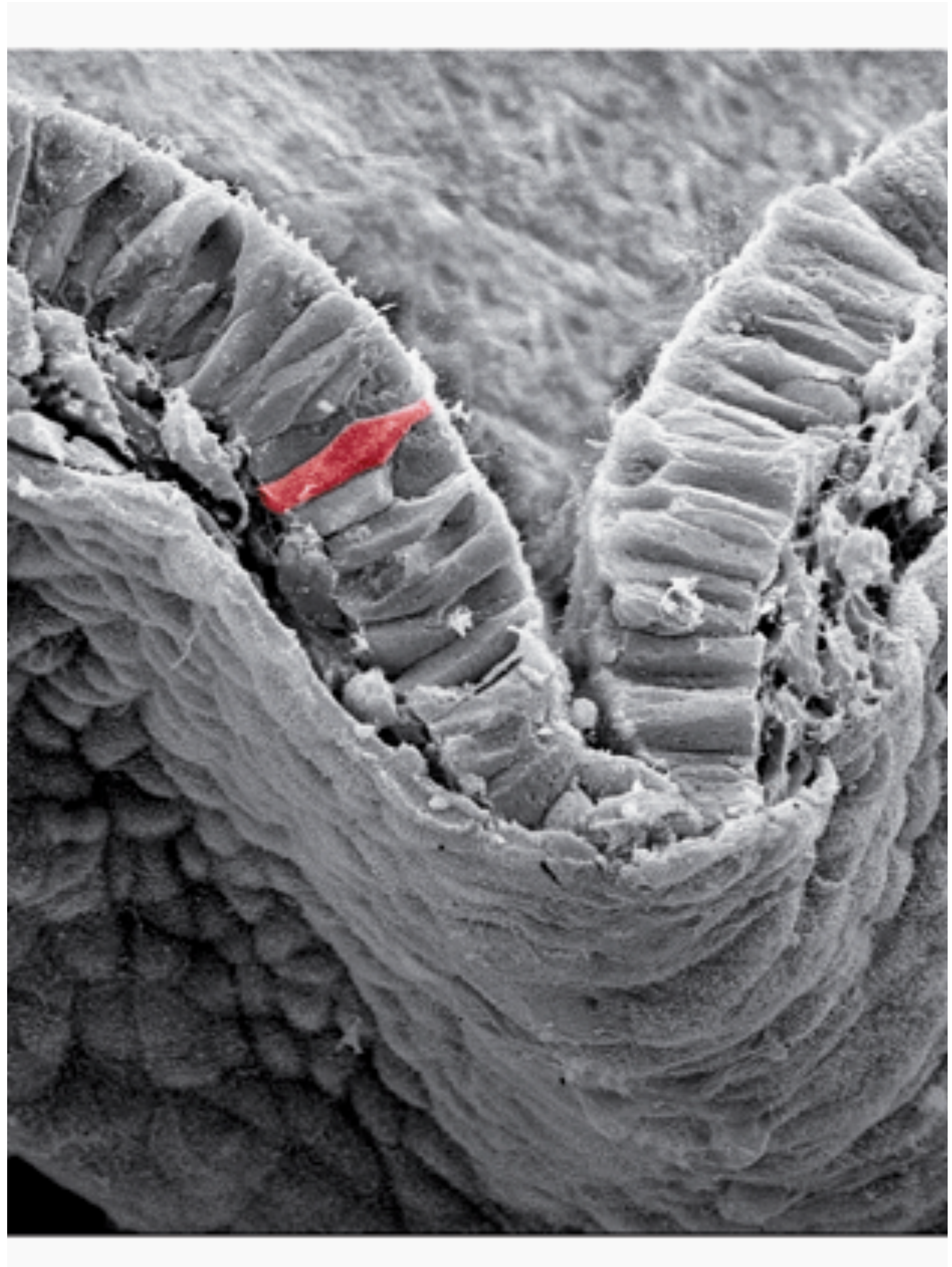
December 16 2016 • UCSF Neuroscience Program

Cortical Development III; NSCs and Migration

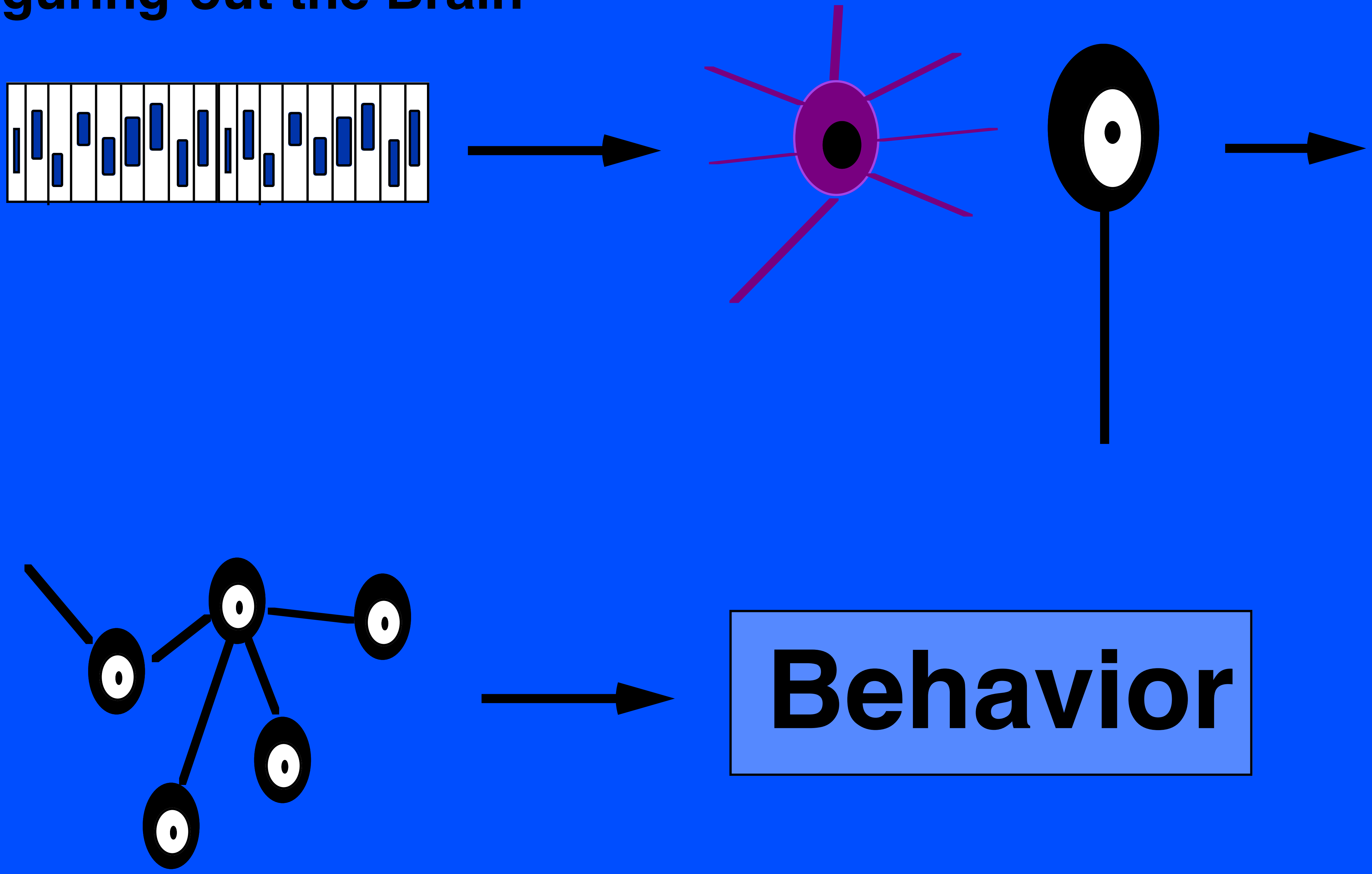
Which cells are the NSCs in the Brain; and how they change through development?

Why and how young neurons and glia cells migrate, often very long distances?

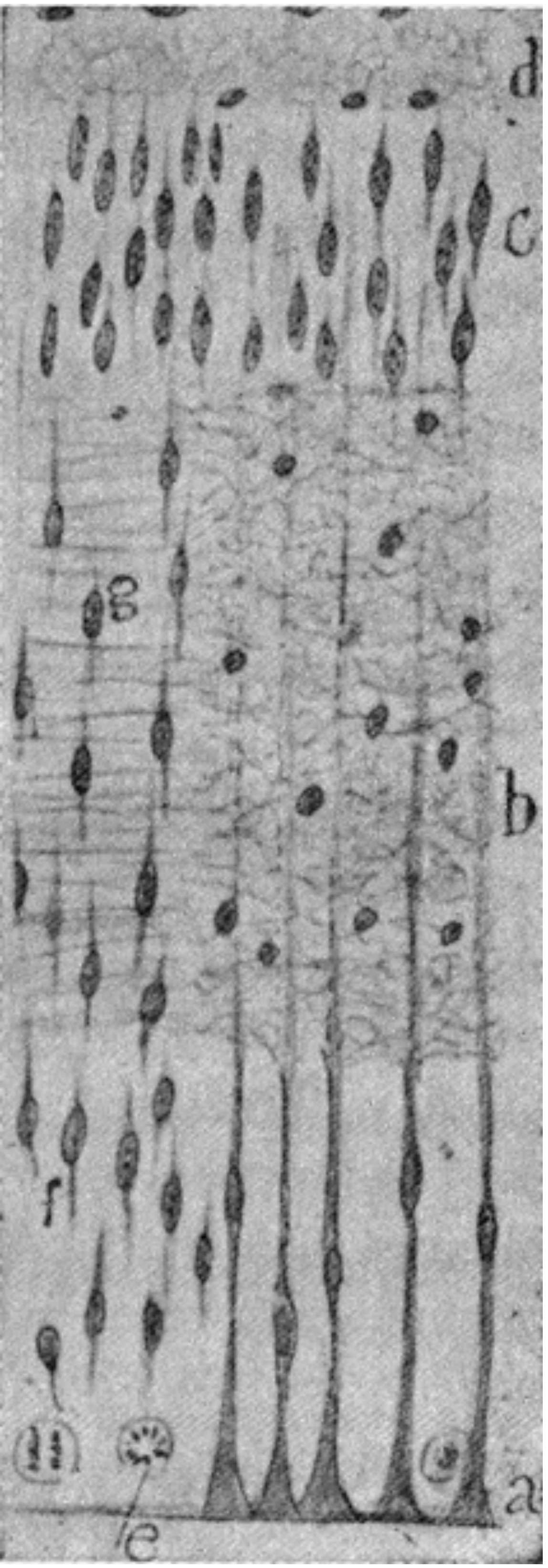
Brain Complexity Originates in a Simple Neuroepithelium



An Understanding of Neural Development will be Key to Figuring-out the Brain



Facts or Interpretations?



•**Virchov (1846)** Glia, the connective tissue of the brain; neuroglia develops from mesoderm

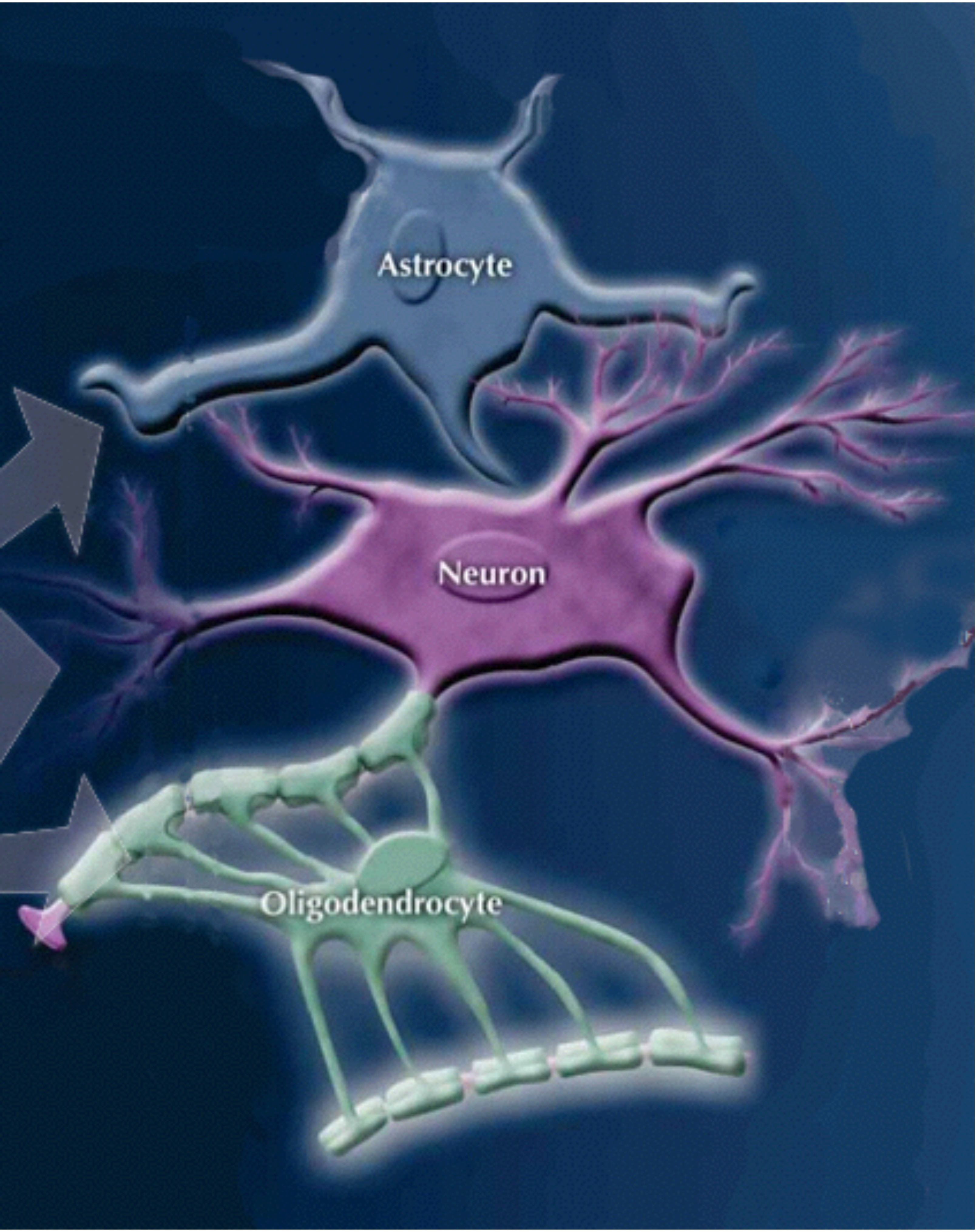
•**His (1889)** Neuroglia is derived from the neuroectoderm, from ***spongioblast***

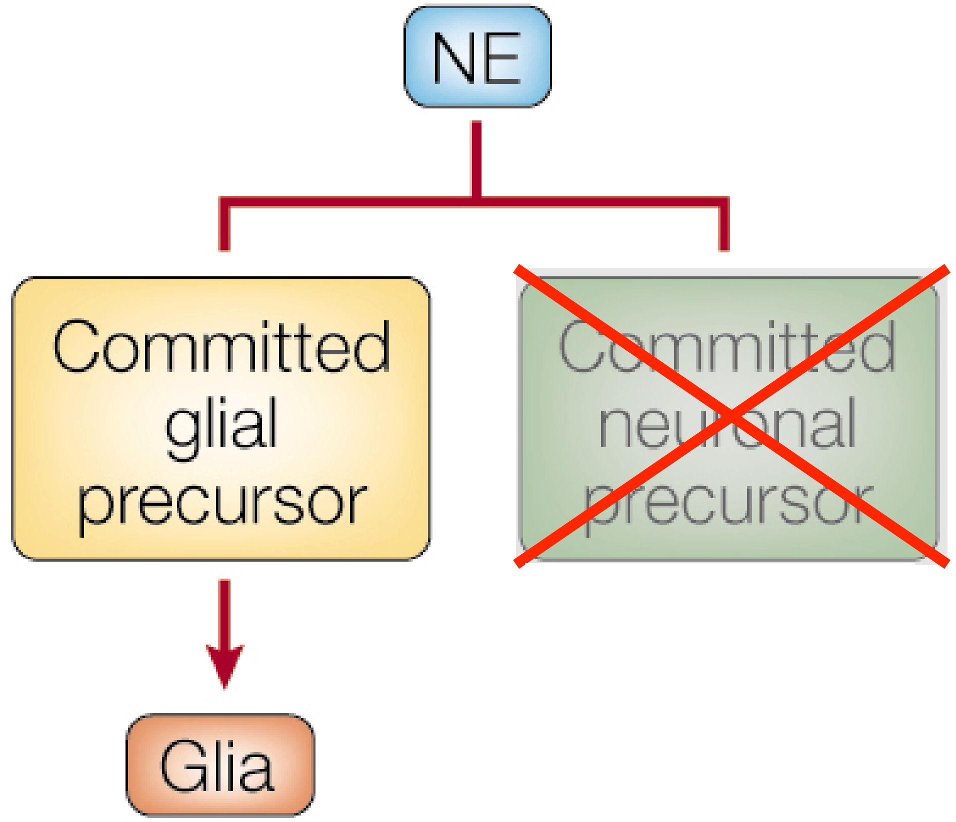
•**Koelliker (1890)** / **Lenhossék (1893)** / **Cajal (1894)** Transformation of spongioblasts into astrocytes in mammals

•**Eng (1971) / Bignami (1972)** GFAP a marker for differentiated astrocytes

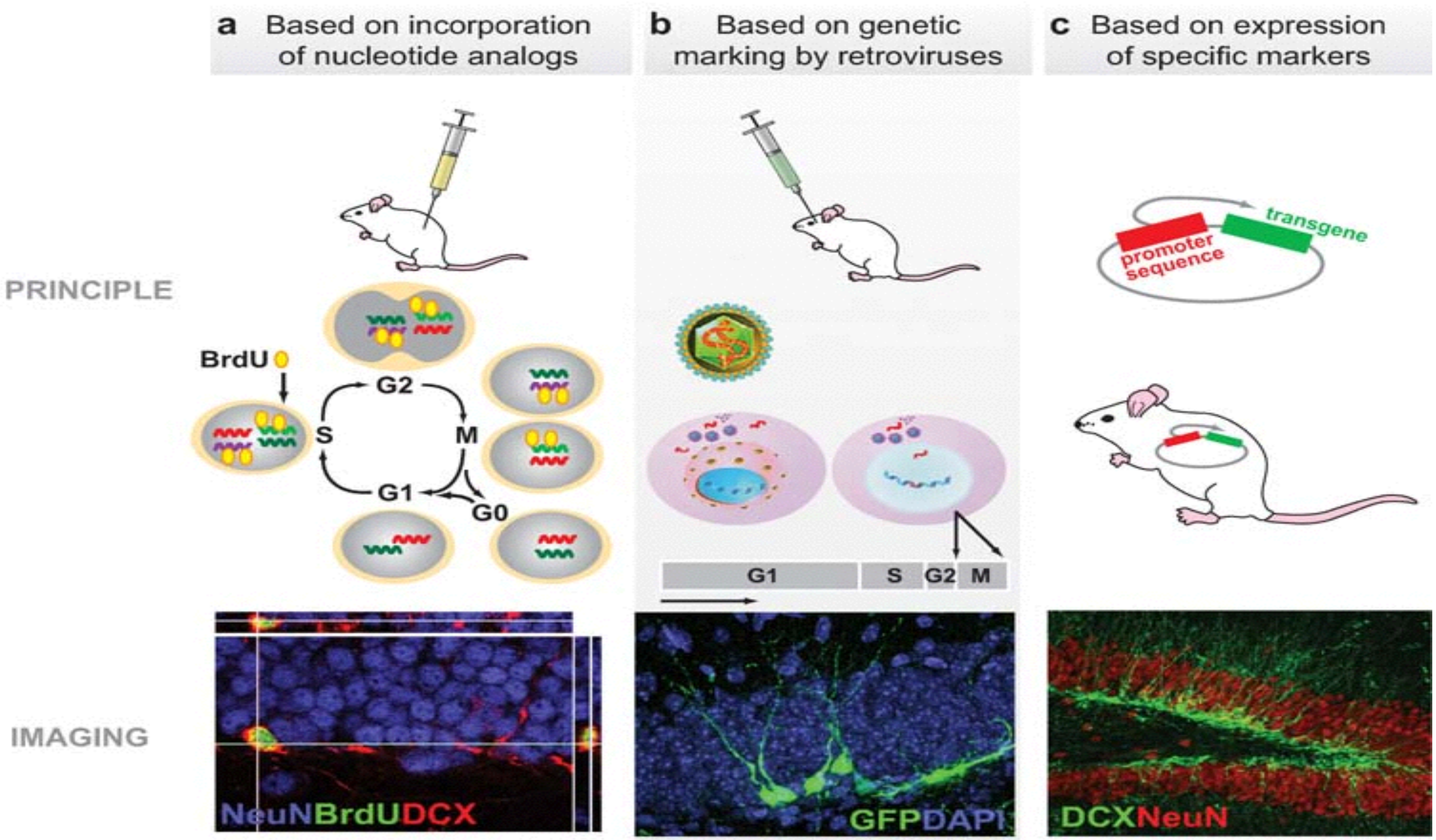
•**Schmechel, D.E. and Rakic, P. (1979).** Arrested proliferation of radial glial during neurogenesis.

•**Levitt, Cooper and Rakic (1981)** Coexistance of neuronal and glial precursors in the VZ


Astrocyte
Neuron
Oligodendrocyte


NE
Committed glial precursor
Committed neuronal precursor
Glia

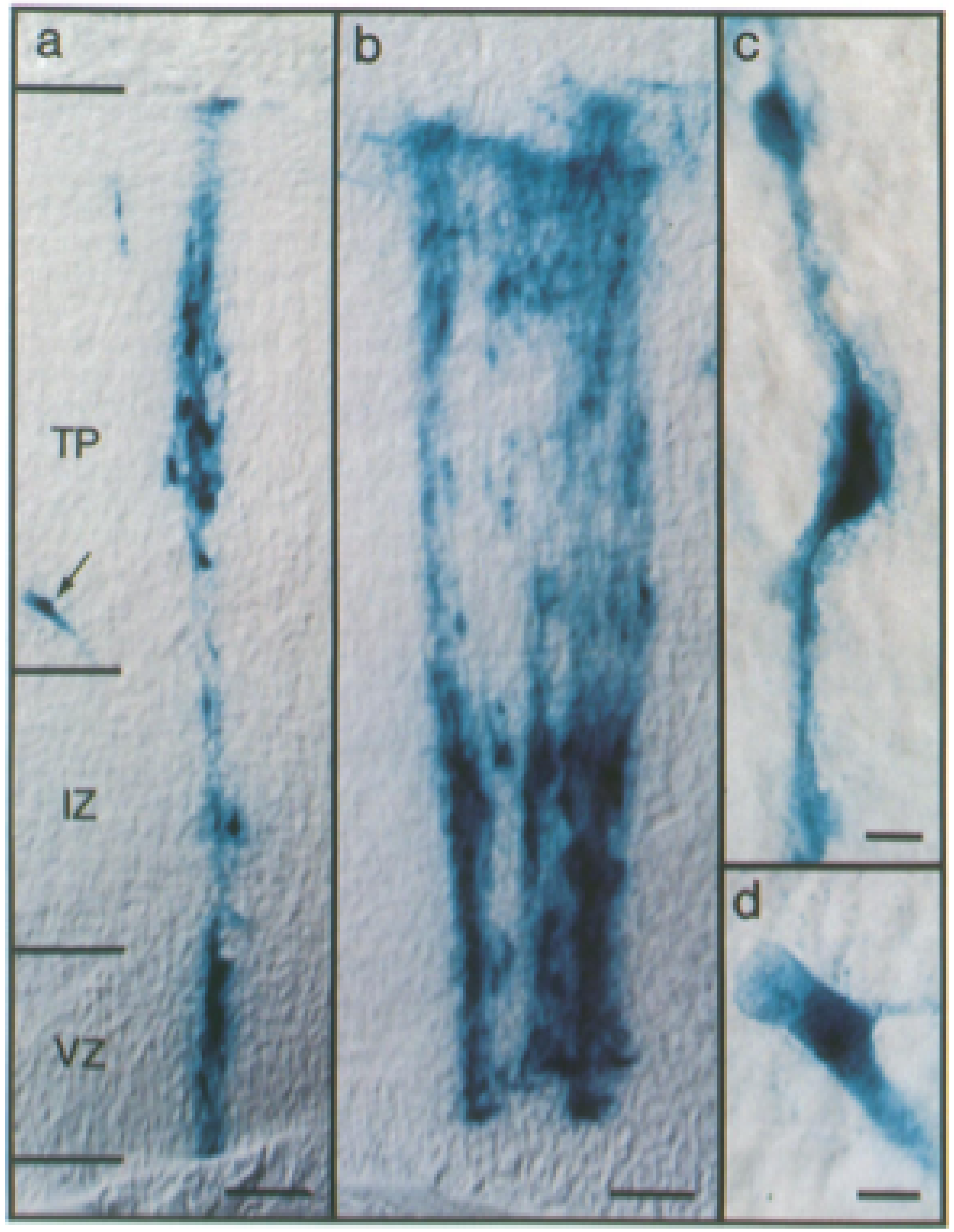
Methods to Study Progenitors

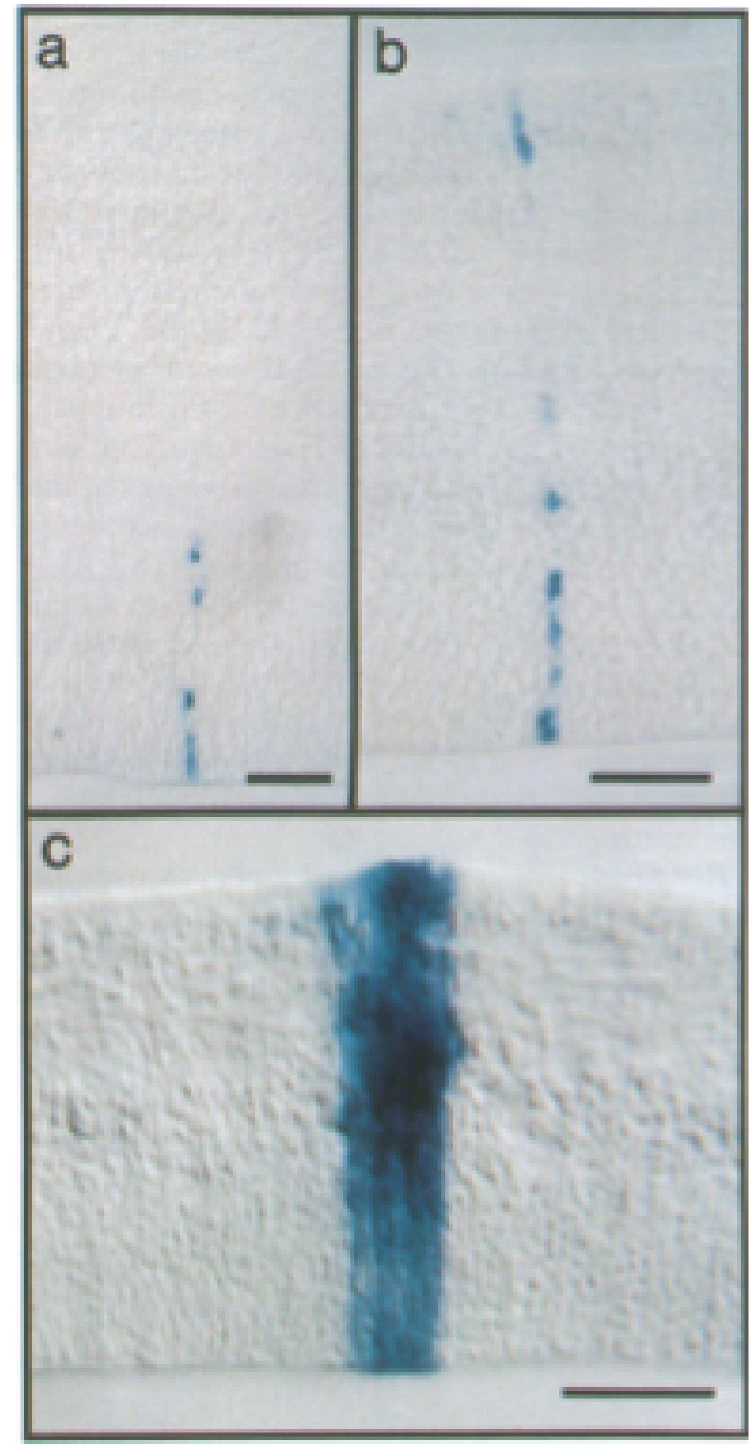


	a	b	c
Birth dating	good	good	poor
Tracing	permanent	permanent	transient / permanent
Cell Population	whole population	limited cells	whole population
Visualization	fixation / processing	direct	processing / direct
Morphology	nuclear	whole cell	cellular / whole cell
Concerns	DNA repair	invasive	specificity

Ming, G and Song, H. 2005
Annu. Rev. Neurosci. 28: 223–50

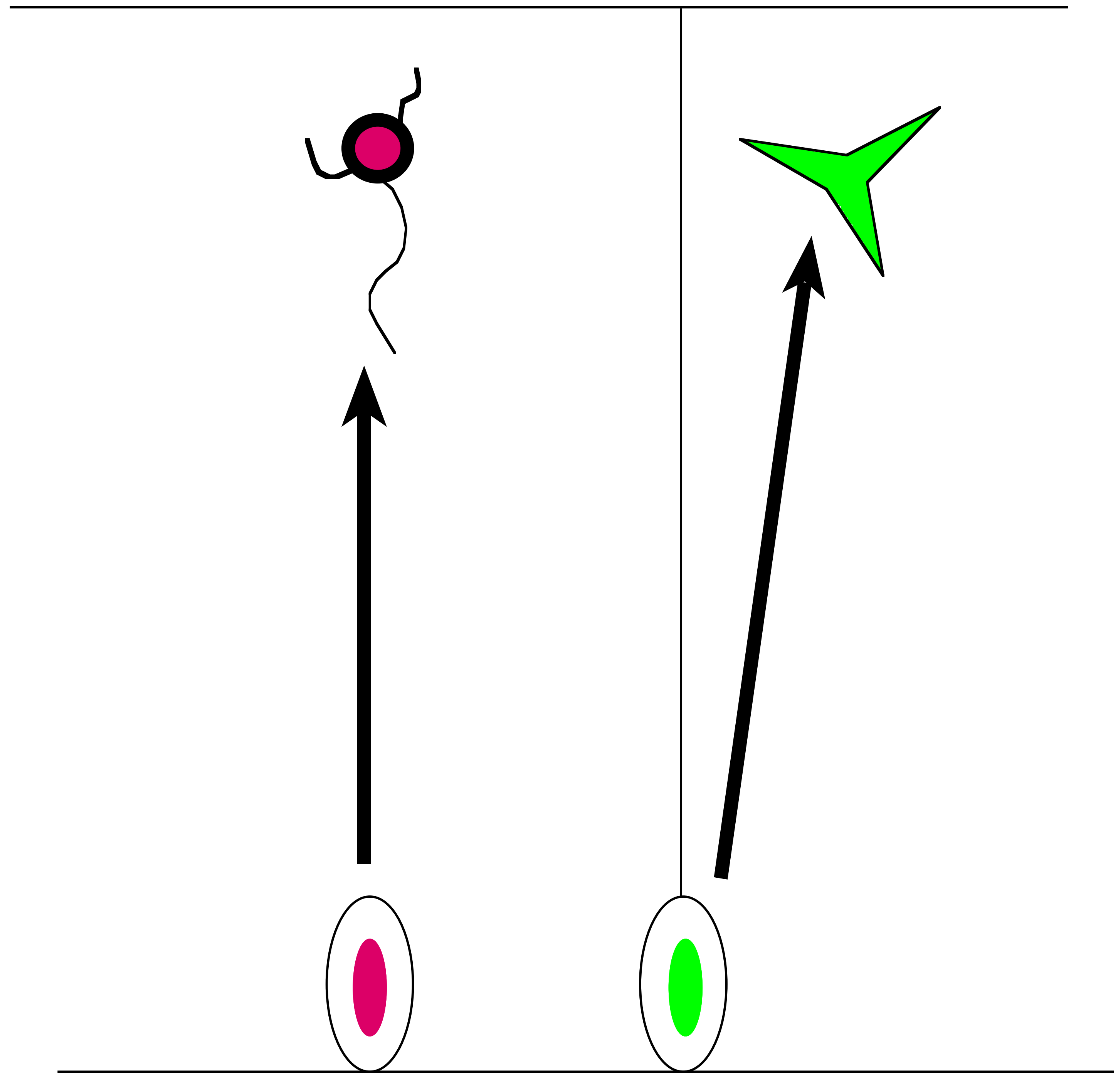
Retroviral Injection, Chick Optic Tectum



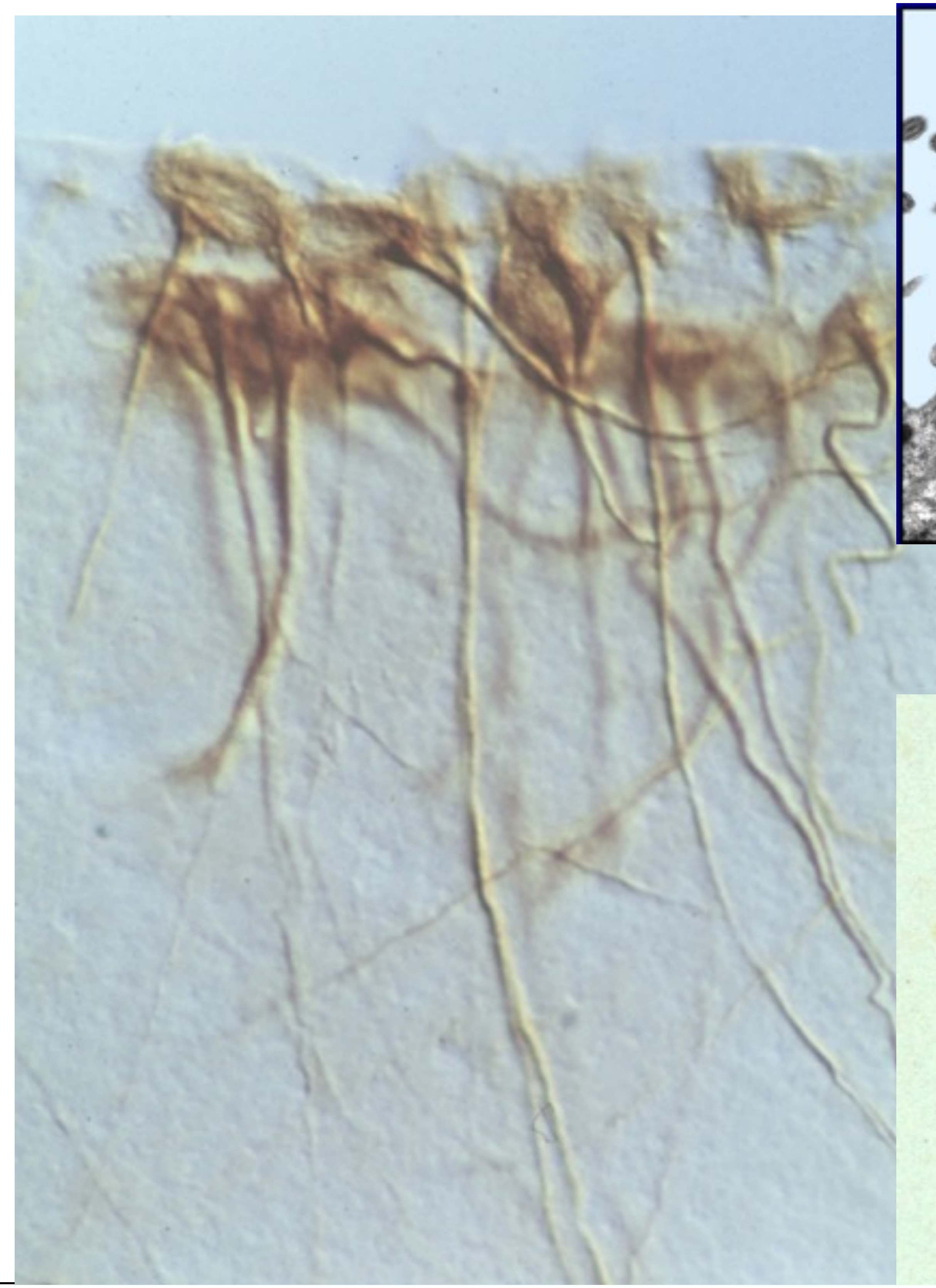


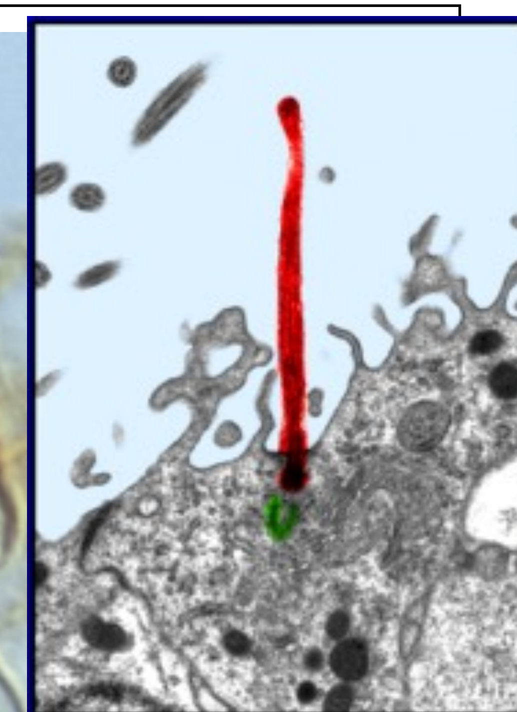
GRAY, GLOVER, MAJORSO, SANES, PNSA(1988)

Historical Misinterpretation

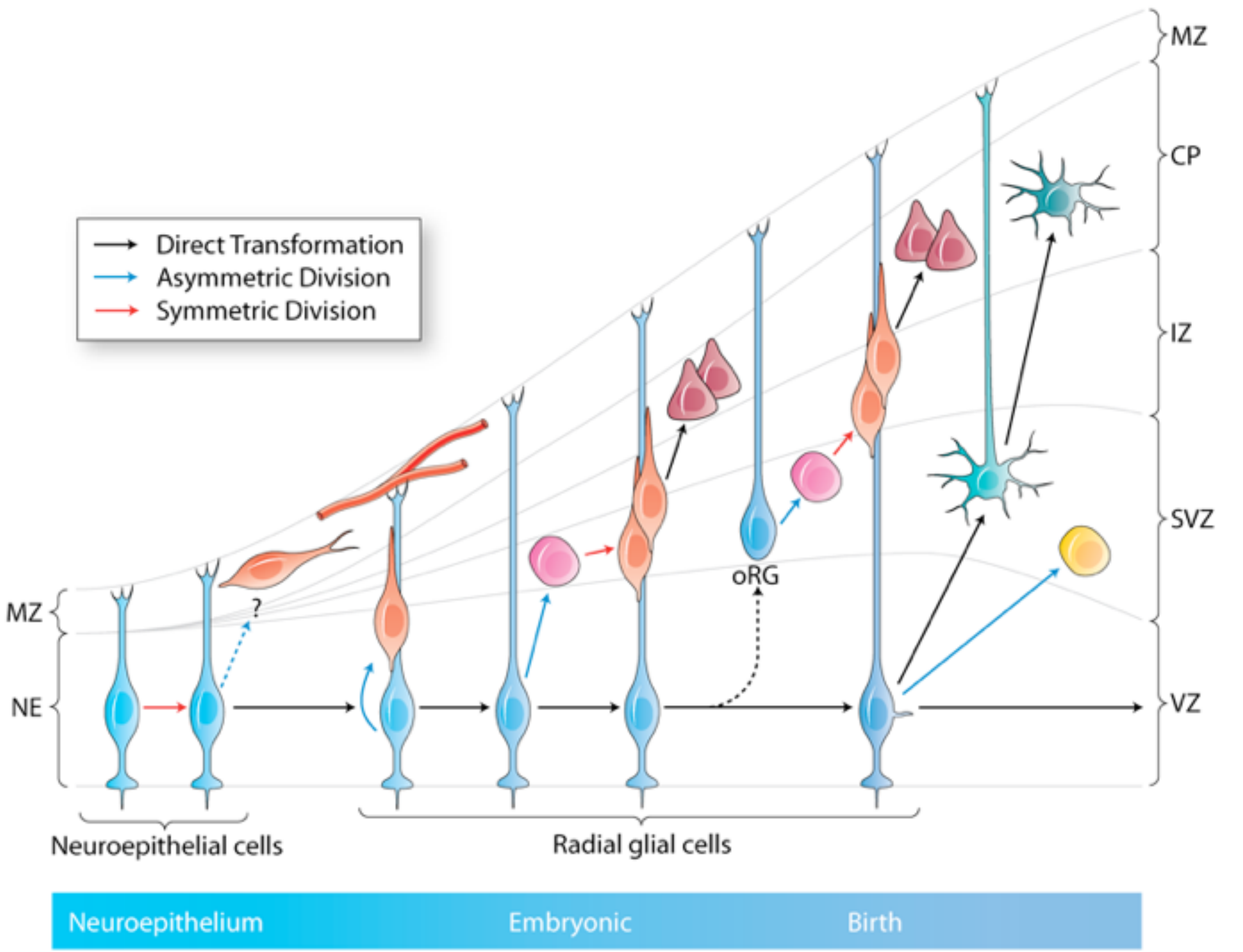


Radial Glia are Progenitors of New Neurons; Primary Cilia

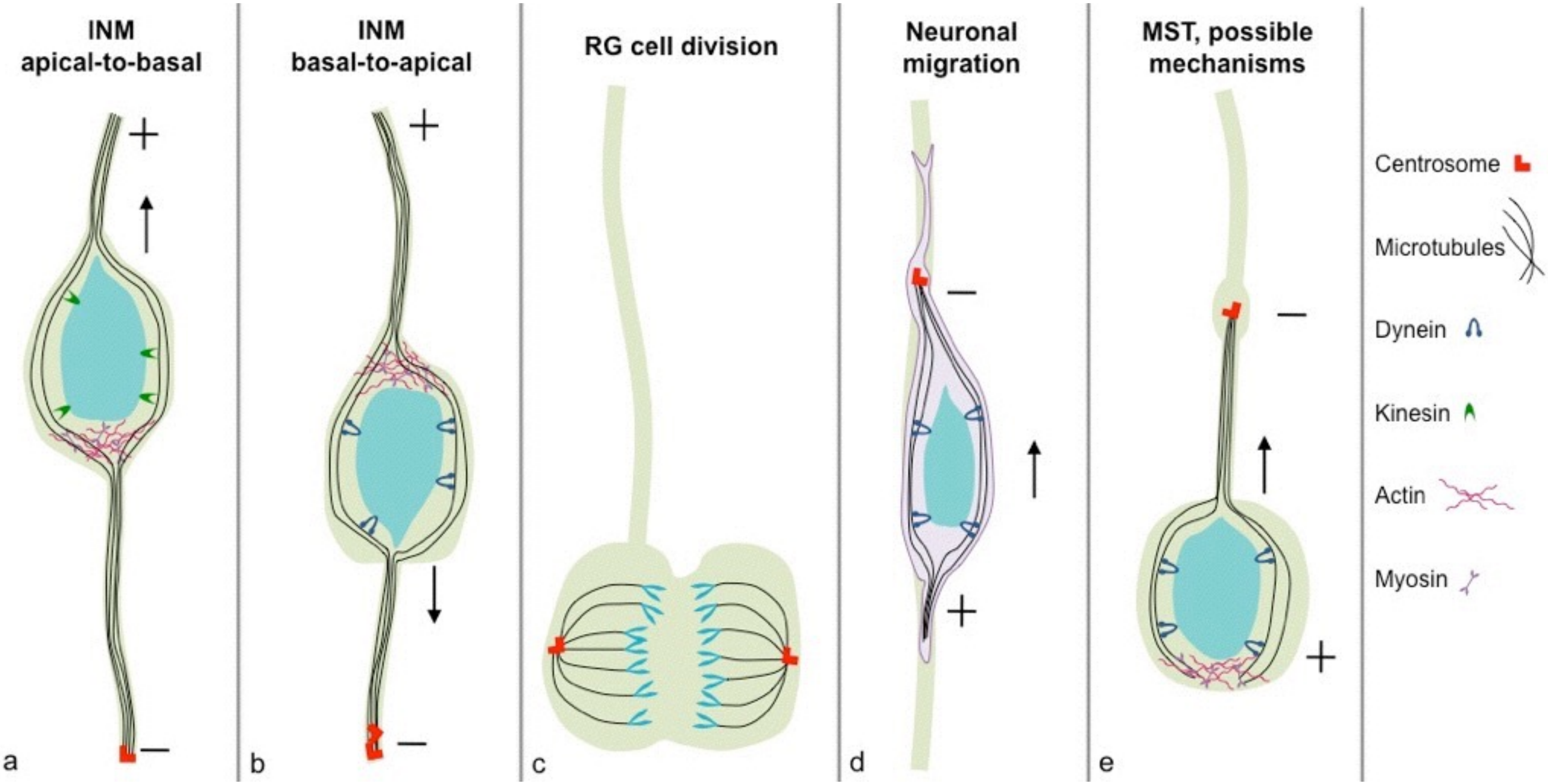




RG and ORG in the Development of Cortex



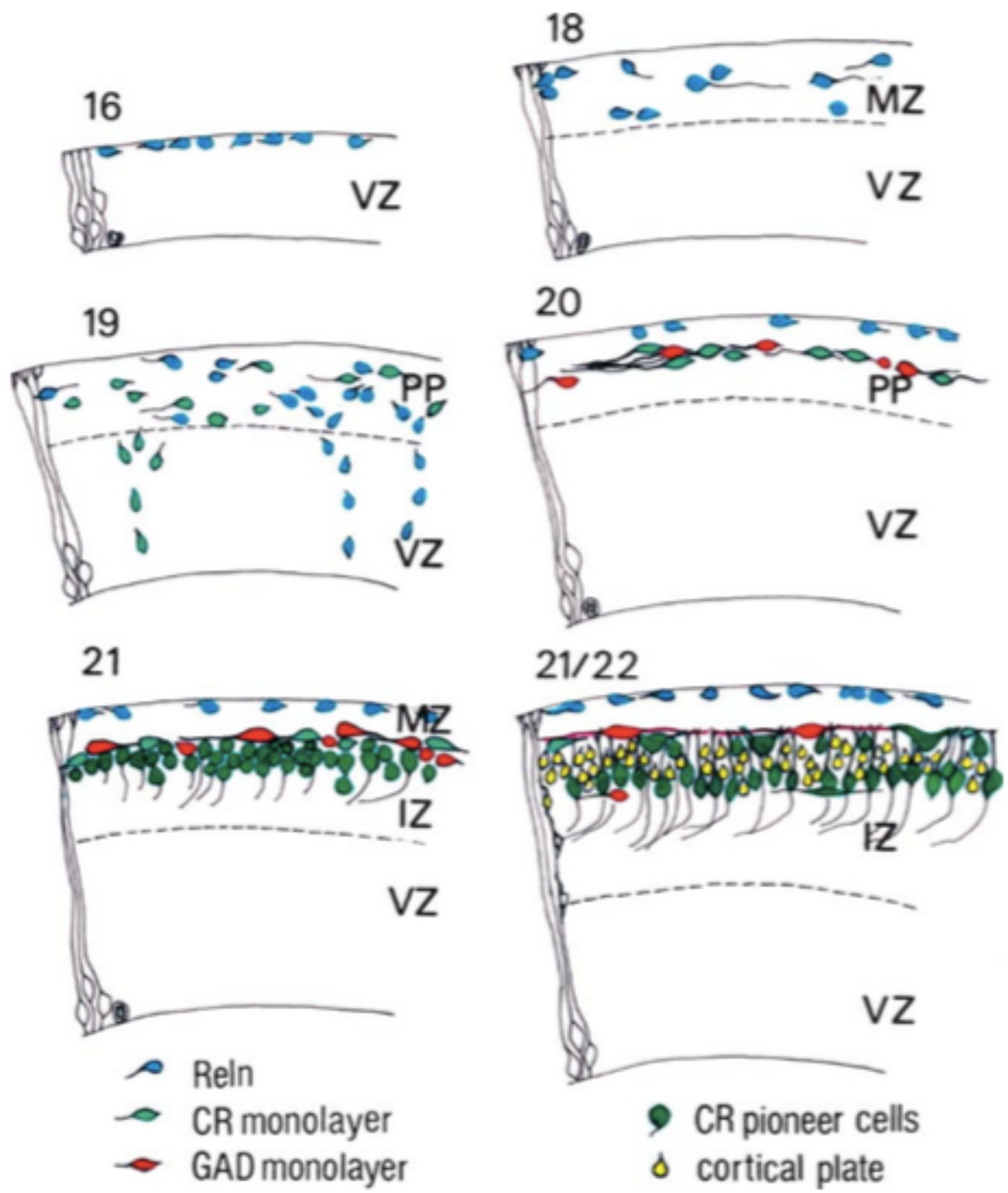
Celullar Motility Essential to Build the Brain



LaMonica BE, et al., Curr Opin Neurobiol (2012), doi:10.1016/ j.conb.2012.03.006

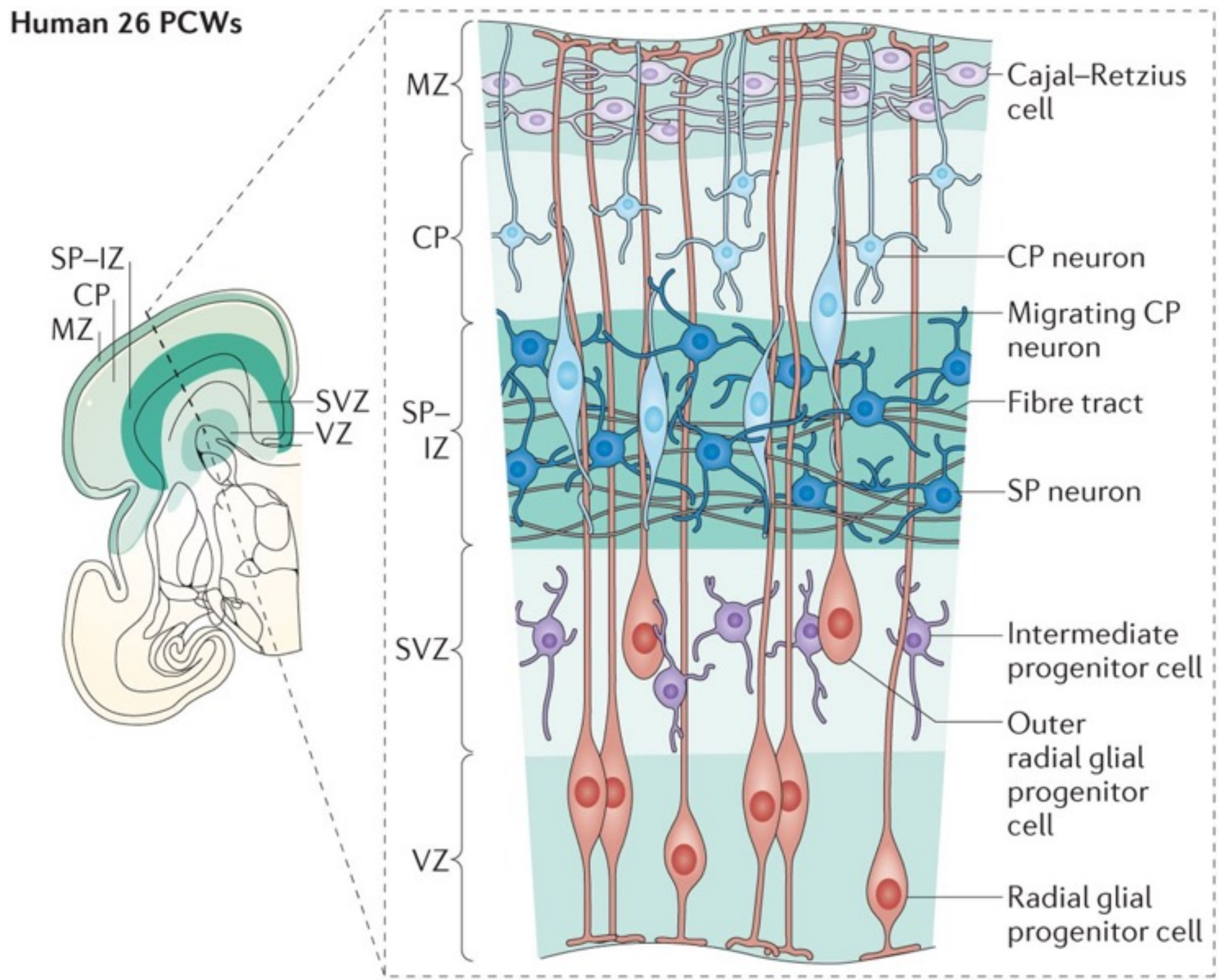
Very Early Migrations

Early Events in the Formation of the Pre Plate; More than just Cajal-Retzius Cells.



G. Meyer (2007); Advances in Anatomy Embryology and Cell Biology 189

Compartments of the Developing Human Cerebral Cortex

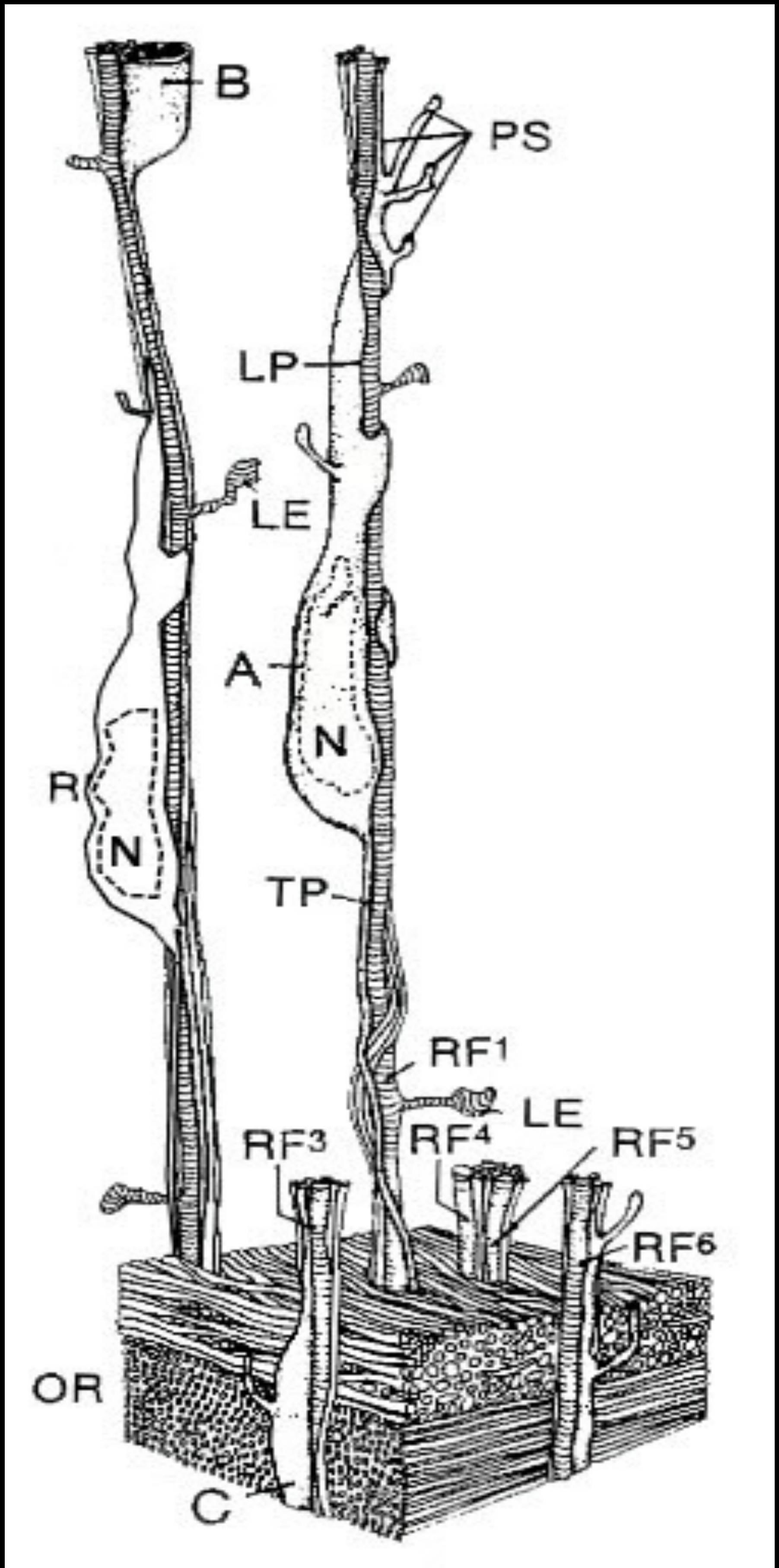


Nature Reviews | Neuroscience

Hoerder-Suabedissen& Zoltán Molnár (2015) doi:10.1038/nrn3915

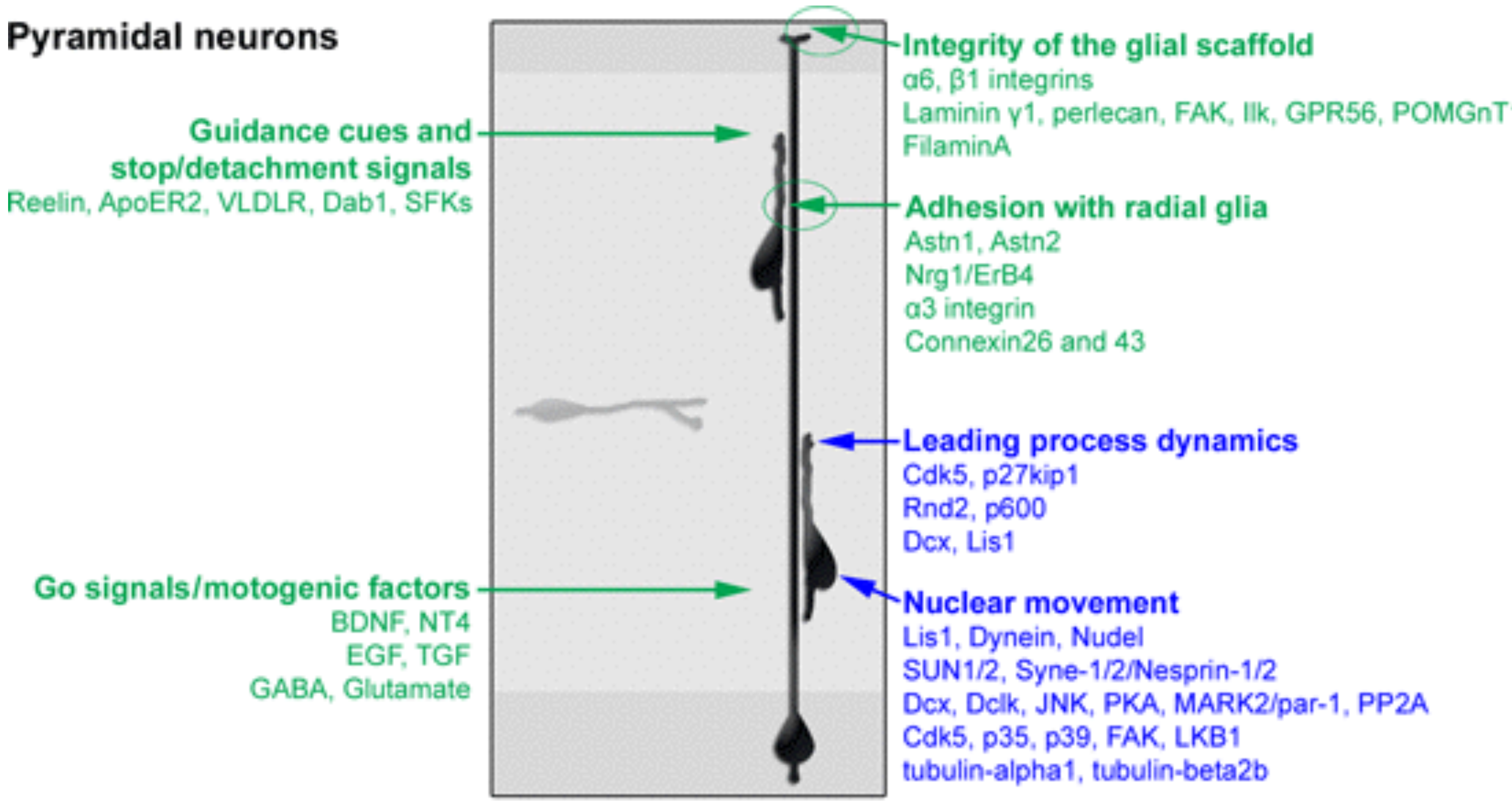
Radial Migration

• Radial Glial Fibers as Guides for Neuronal Migration

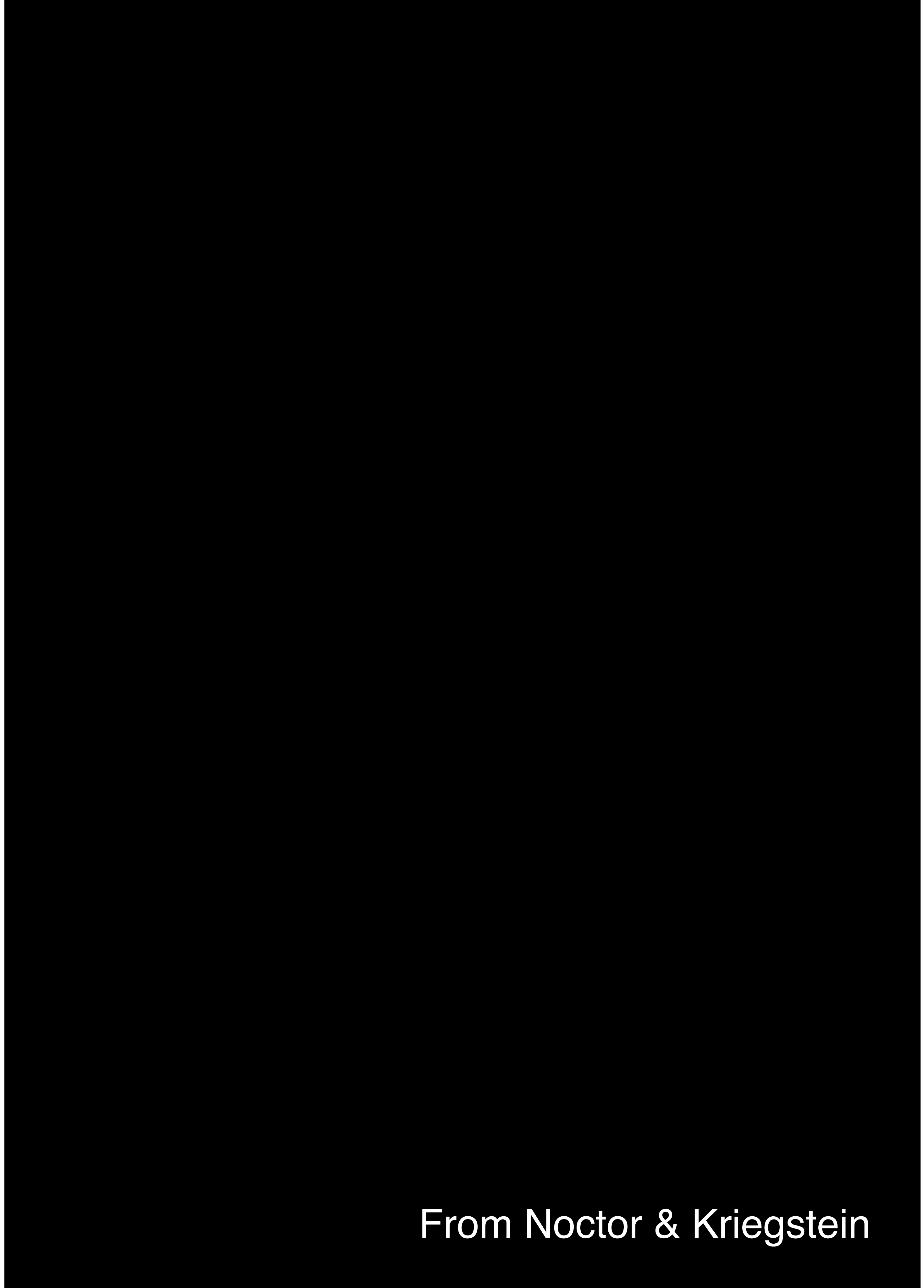


Rakic, 1972

Molecular Control of Radial Neuronal Migration

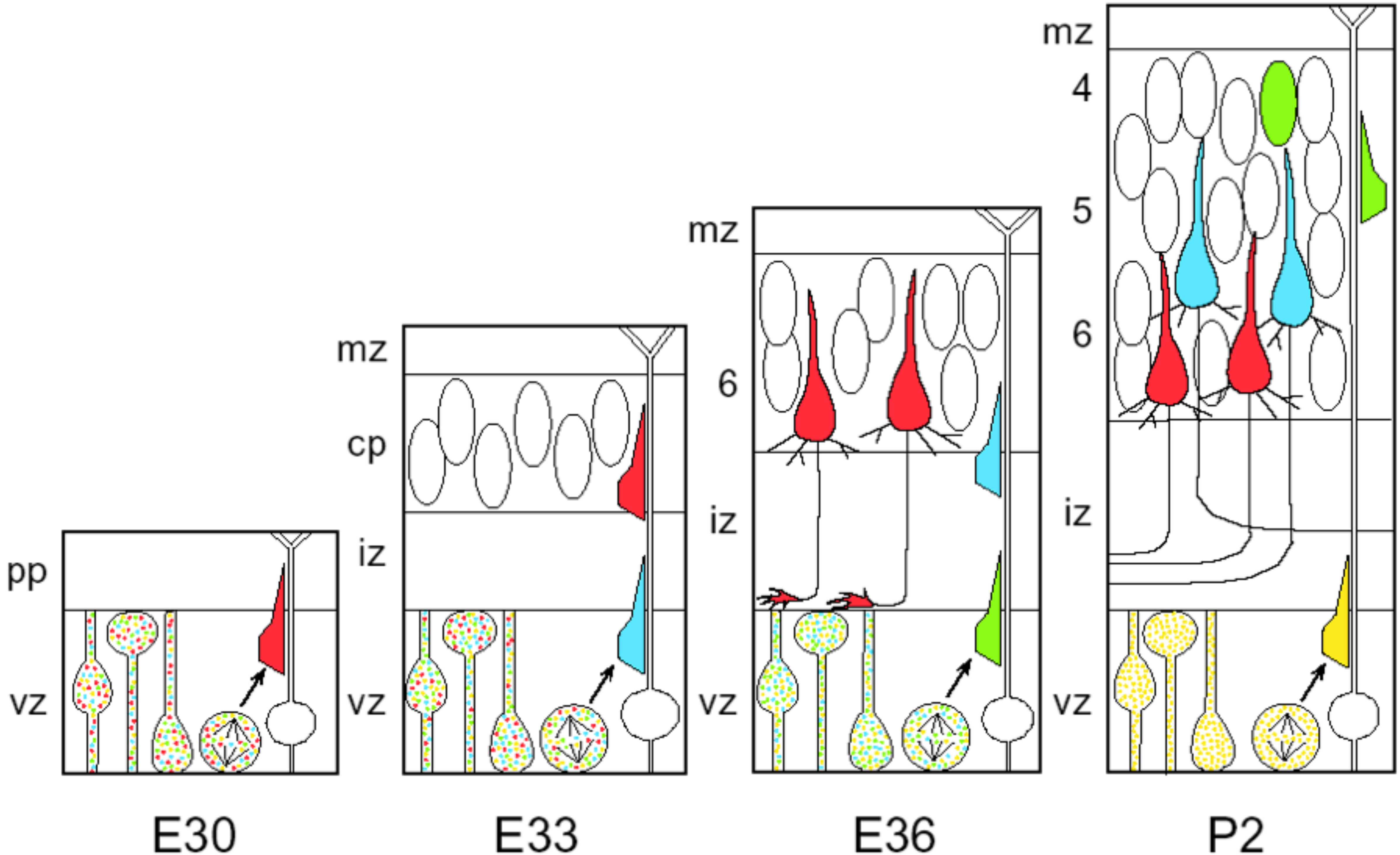


Manent et al, EJN 2011



From Noctor & Kriegstein

Sequential Addition of Neurons During Development



Angievine & Sidman (1962) **Rakic (1974)** **McConnell et al. (1995-2000)**

Tangential Migration

- MGE migration

- SVZ-OB migration

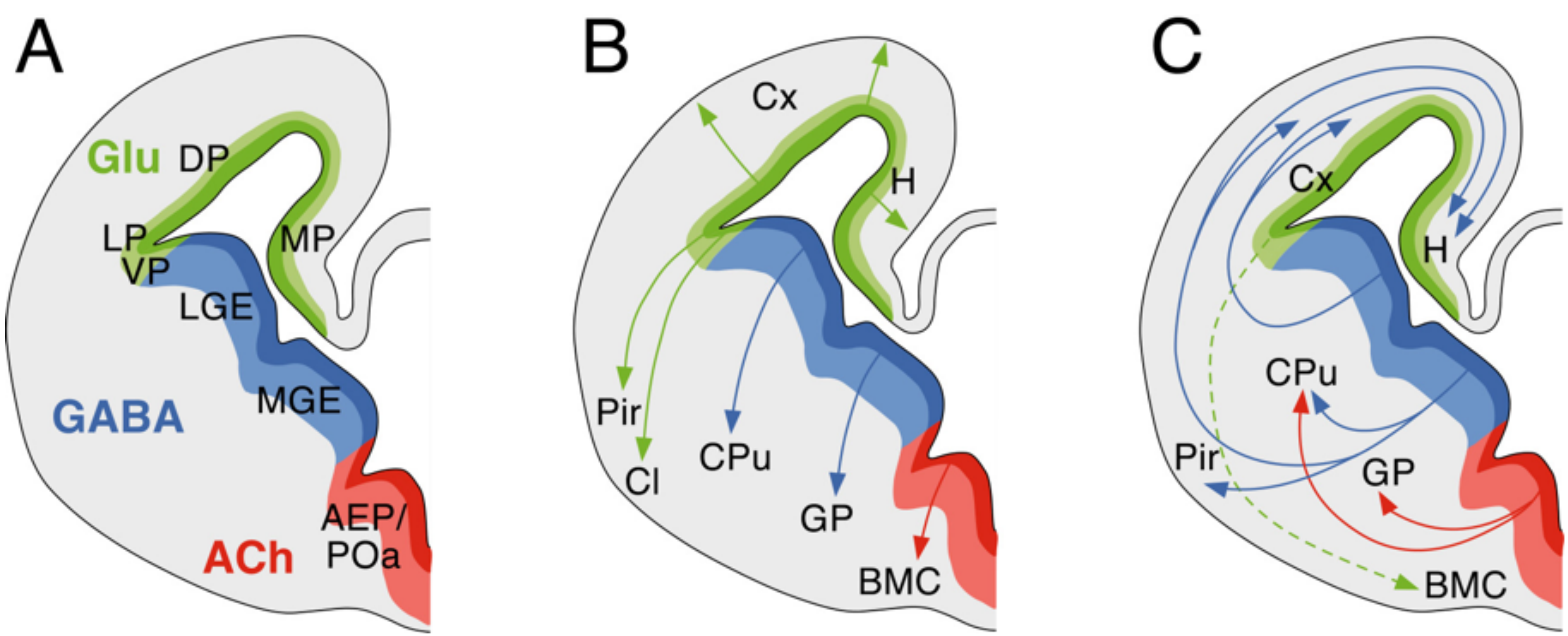
- Massive Tangential Migration in early Postnatal Human Brain

REGIONAL SPECIFICATION, RADIAL & TANGENTIAL MIGRATORY PATHS

Regional Specification Generates Domains That Produce Neurons That Make Primarily Glutamate, GABA Or Acetylcholine

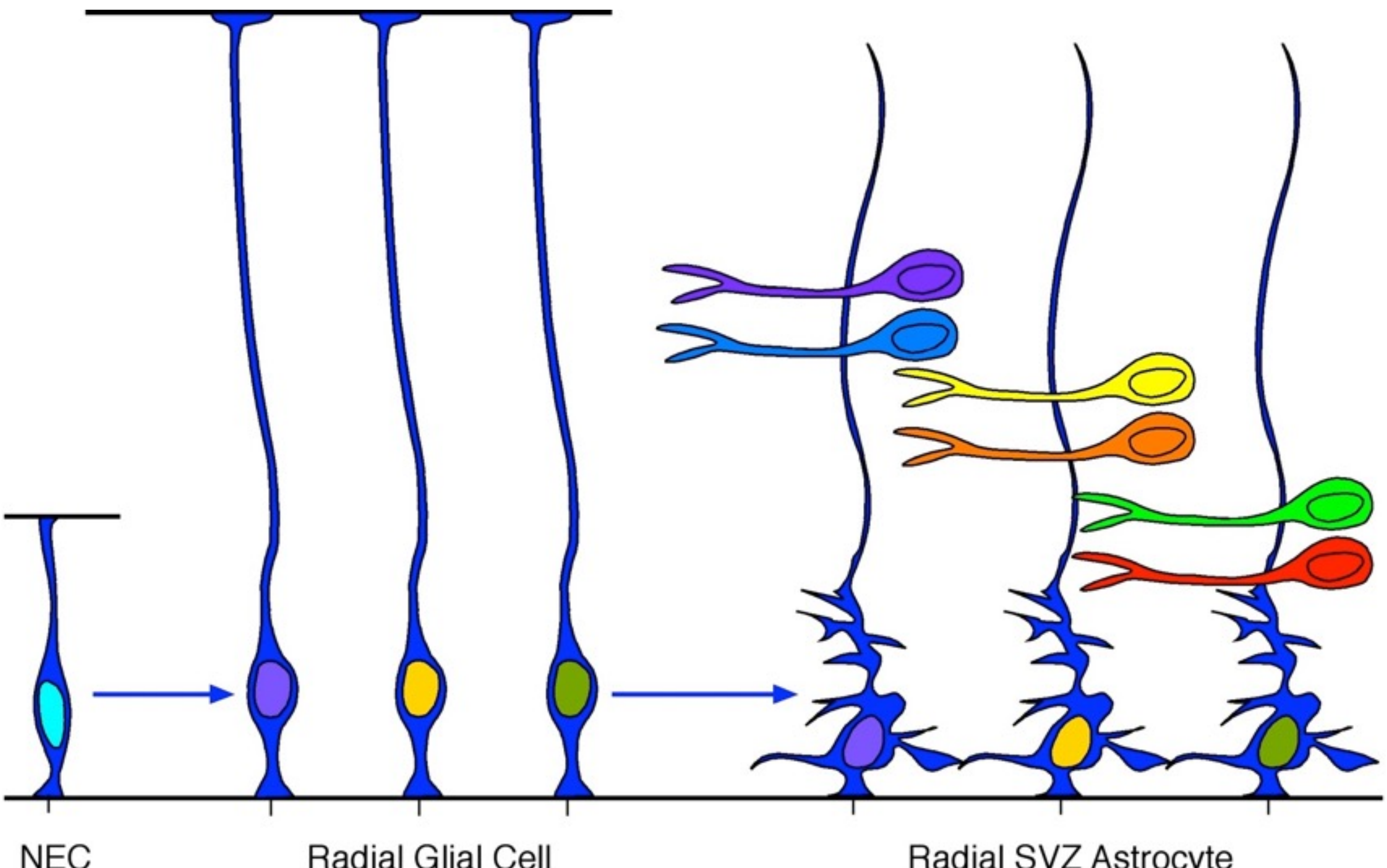
Radial Migration of Projection Neurons

Tangential Migration of Local Circuit Neurons

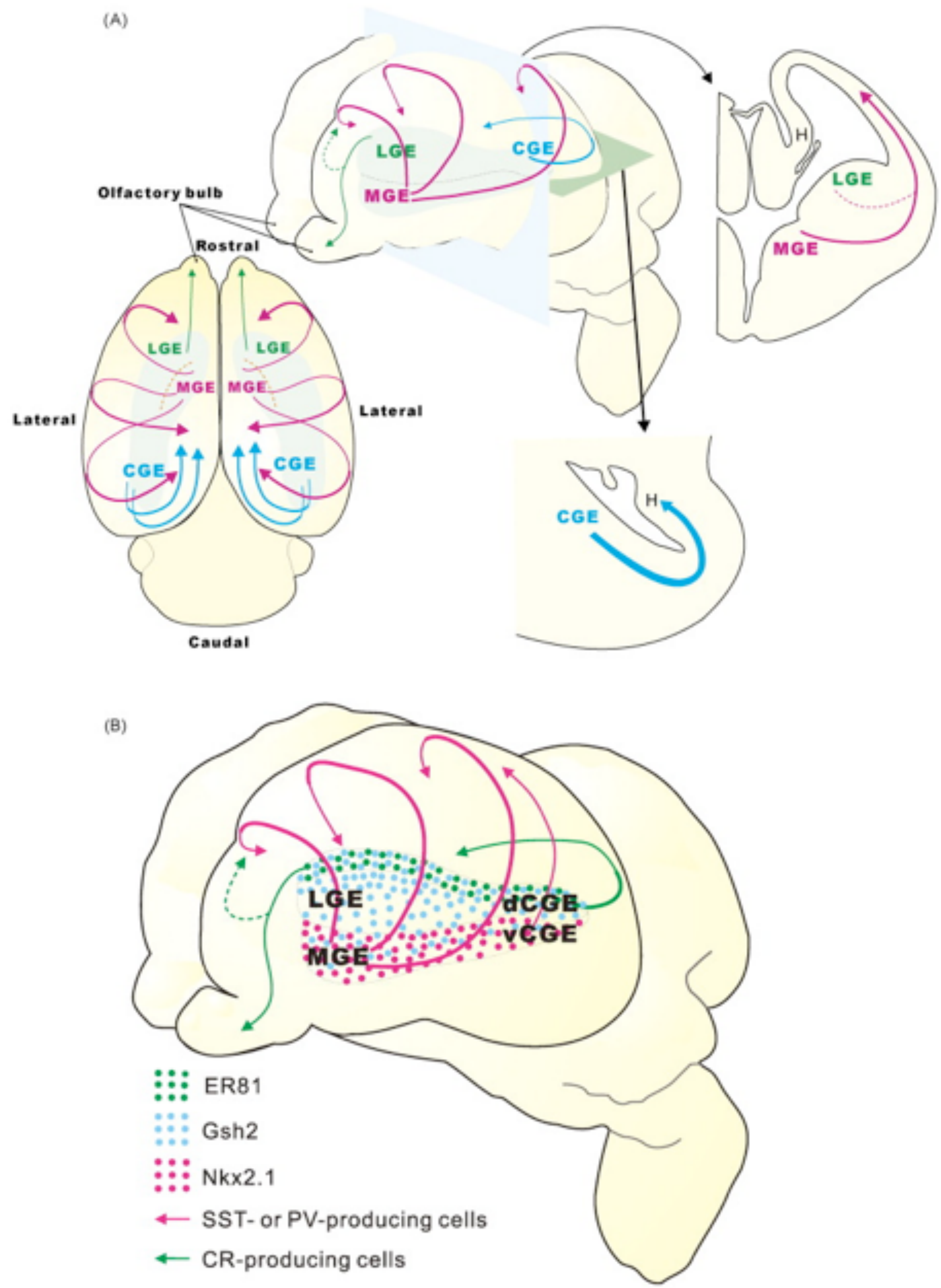


Marin and Rubenstein, Nature Neuroscience Reviews, 2001

Neuronal Final Destination Radially Uncoupled from Birth Location.
A NEED FOR ANOTHER FORM OF MIGRATION:
Tangential Migration

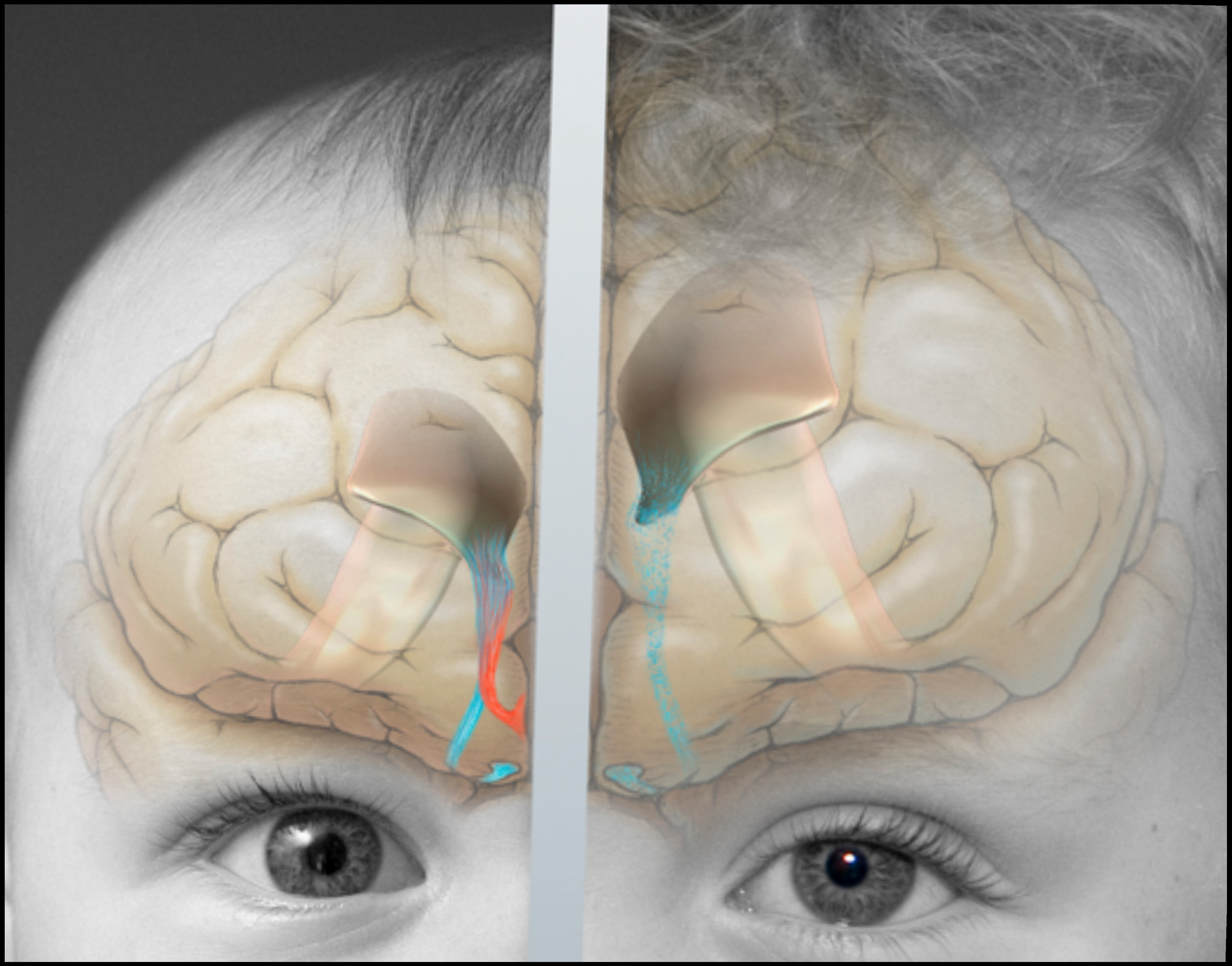


• Routes on Interneuron Migration from MGE into Cortex



Morimoto and Nakajima (2007)

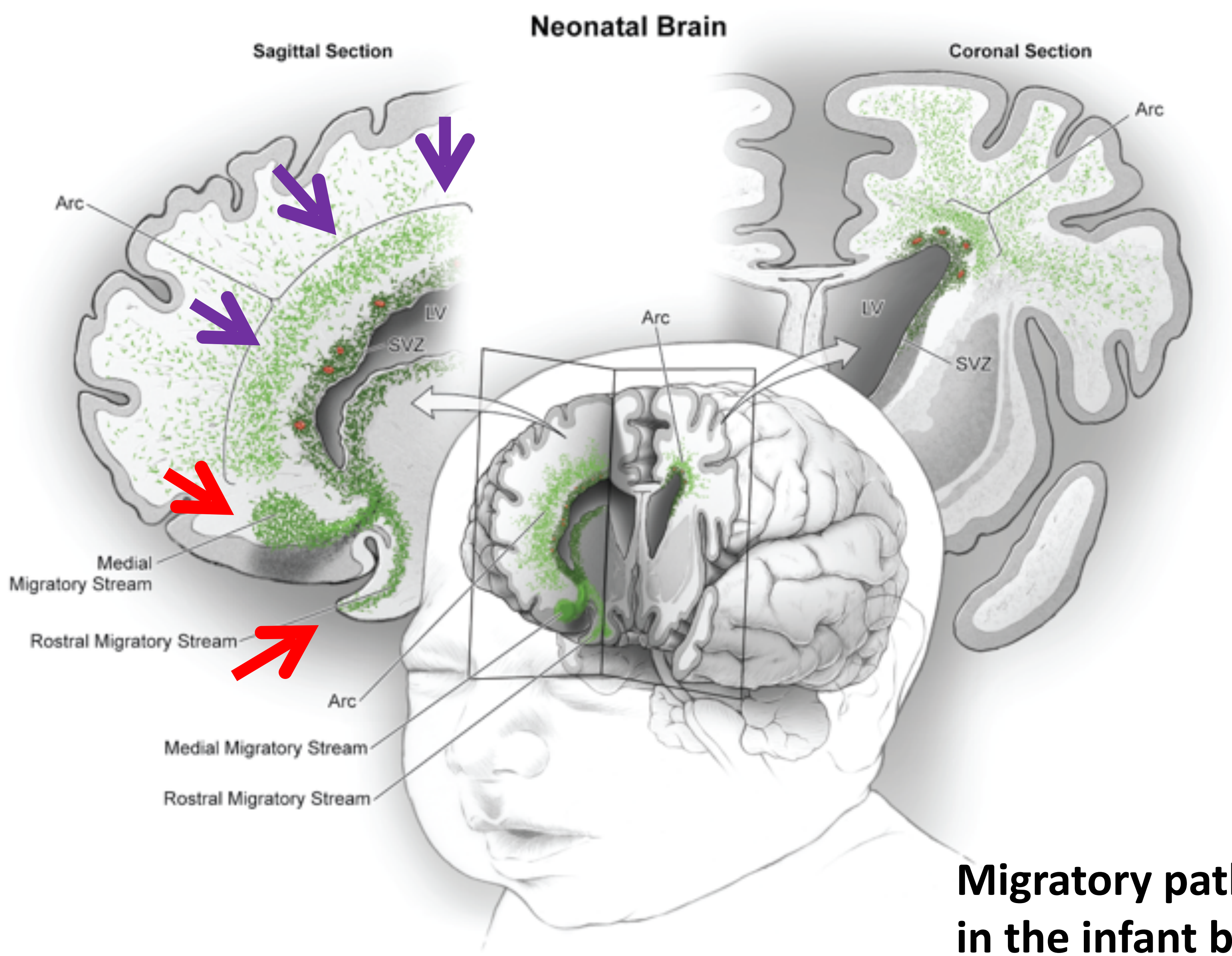
Tangential migrations in the infant human brain



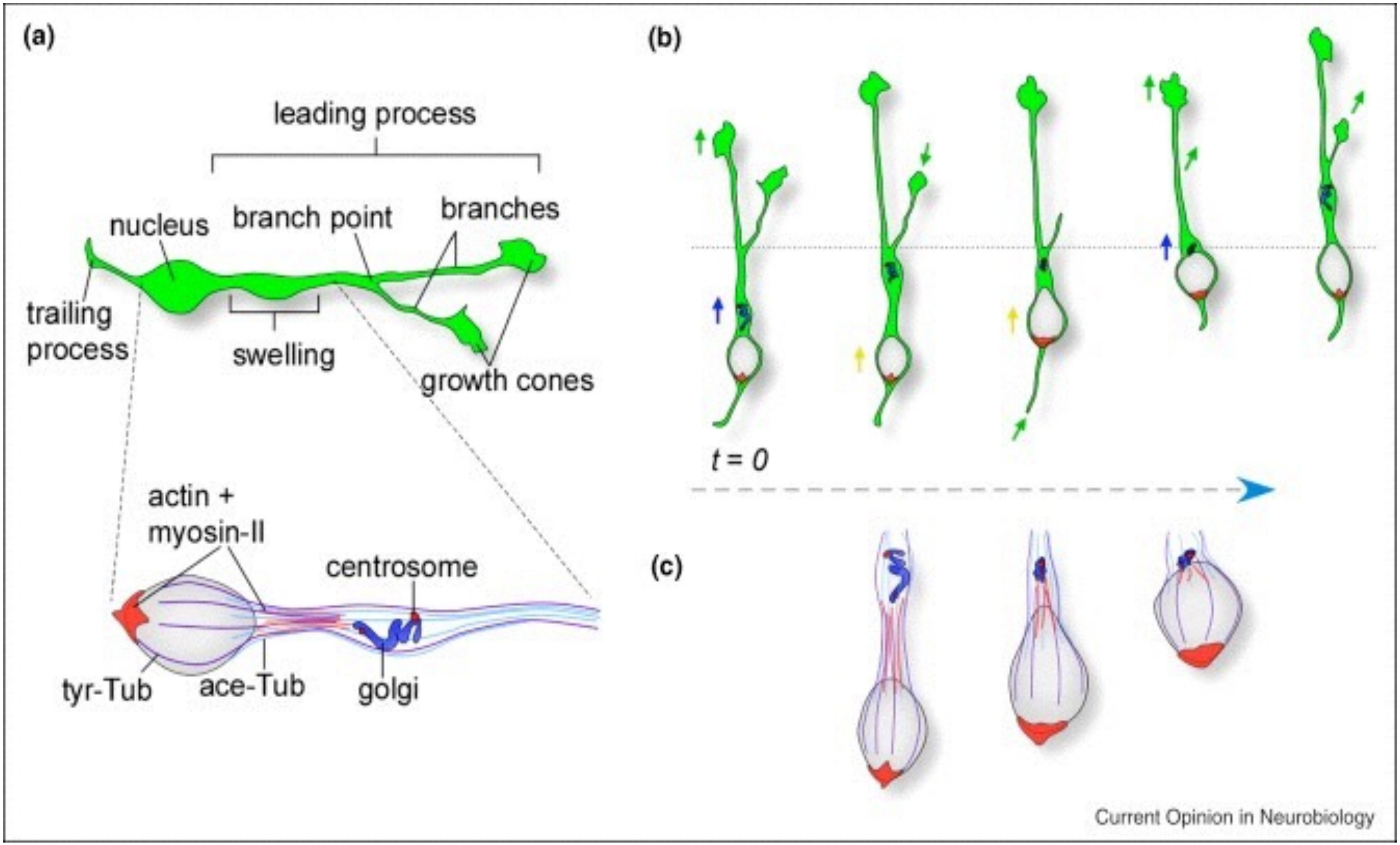
Sanai et al, Nature 2011

The Arc: A major migratory stream of DCX+ cells in the postnatal human brain

- target the **cingulate and frontal cortices.**
- have **an interneuron identity and subpallial origin**.
- precedes change in interneuron subtype composition --NPY, SST, and CR populations

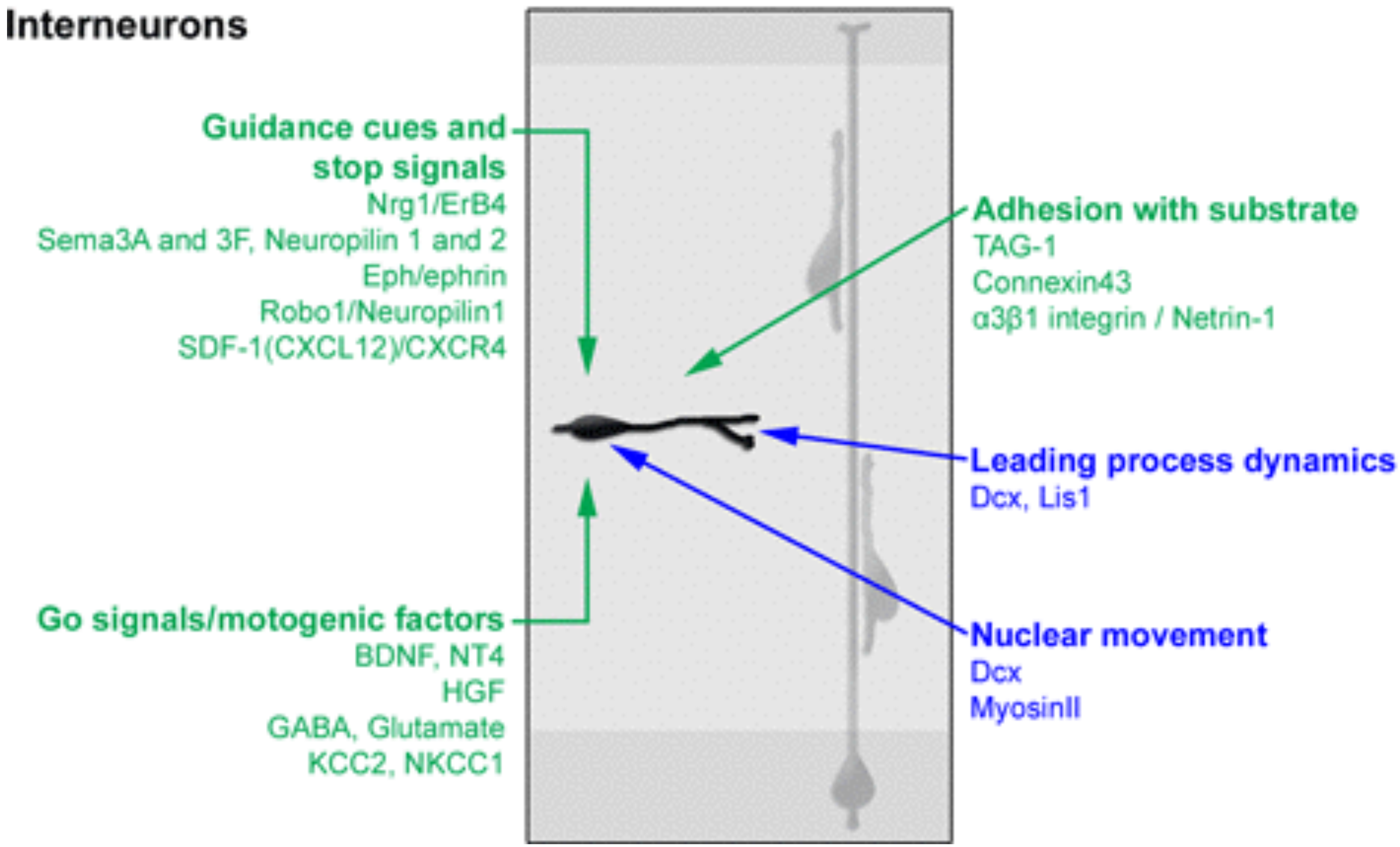


Migratory pathways for neurons in the infant brain



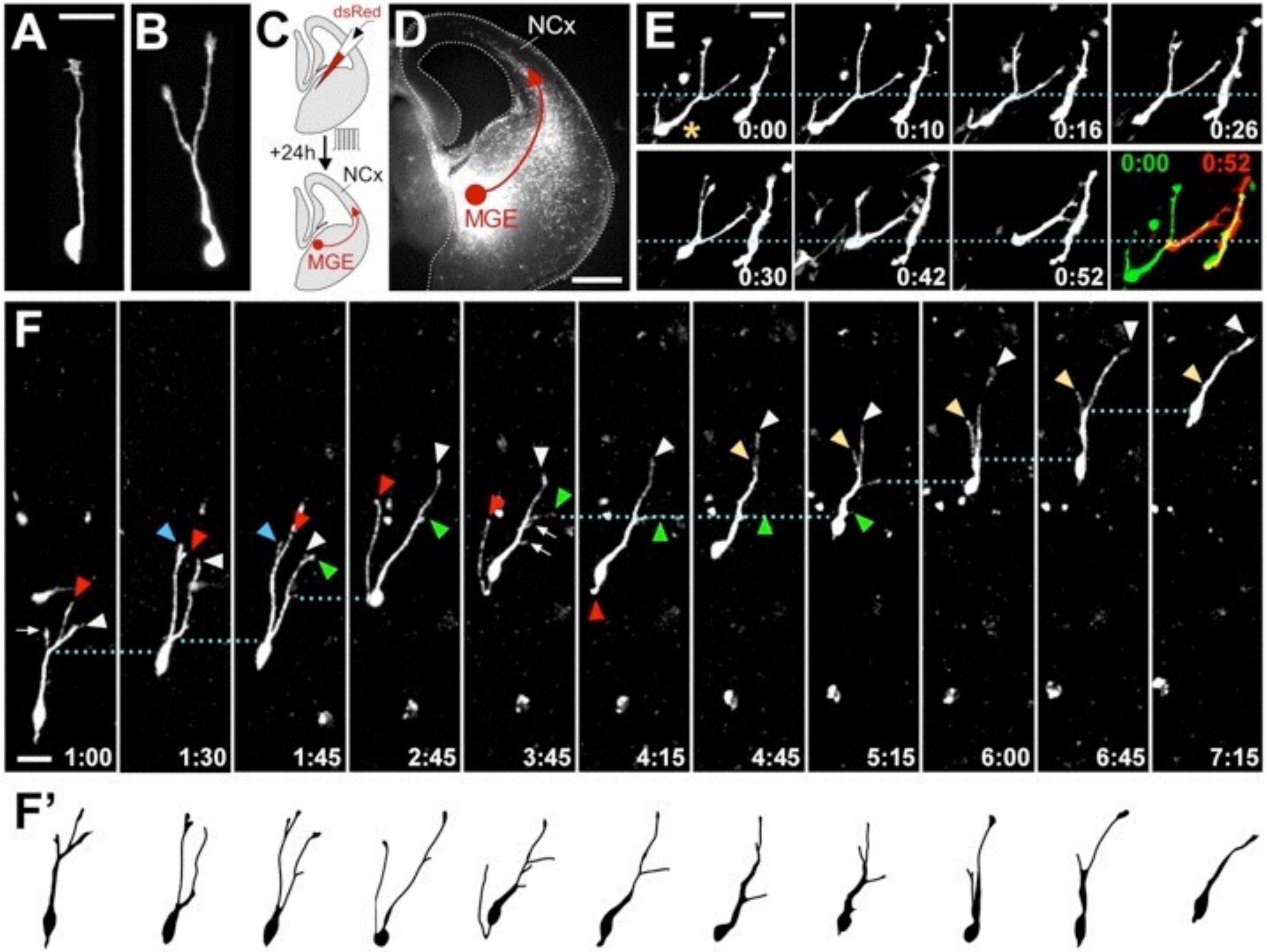
Valiente & Marín, Current Opinion in Neurobiology 2010. http://dx.doi.org/10.1016/j.conb.2009.12.003

Molecular Control of Tangential Neuronal Migration



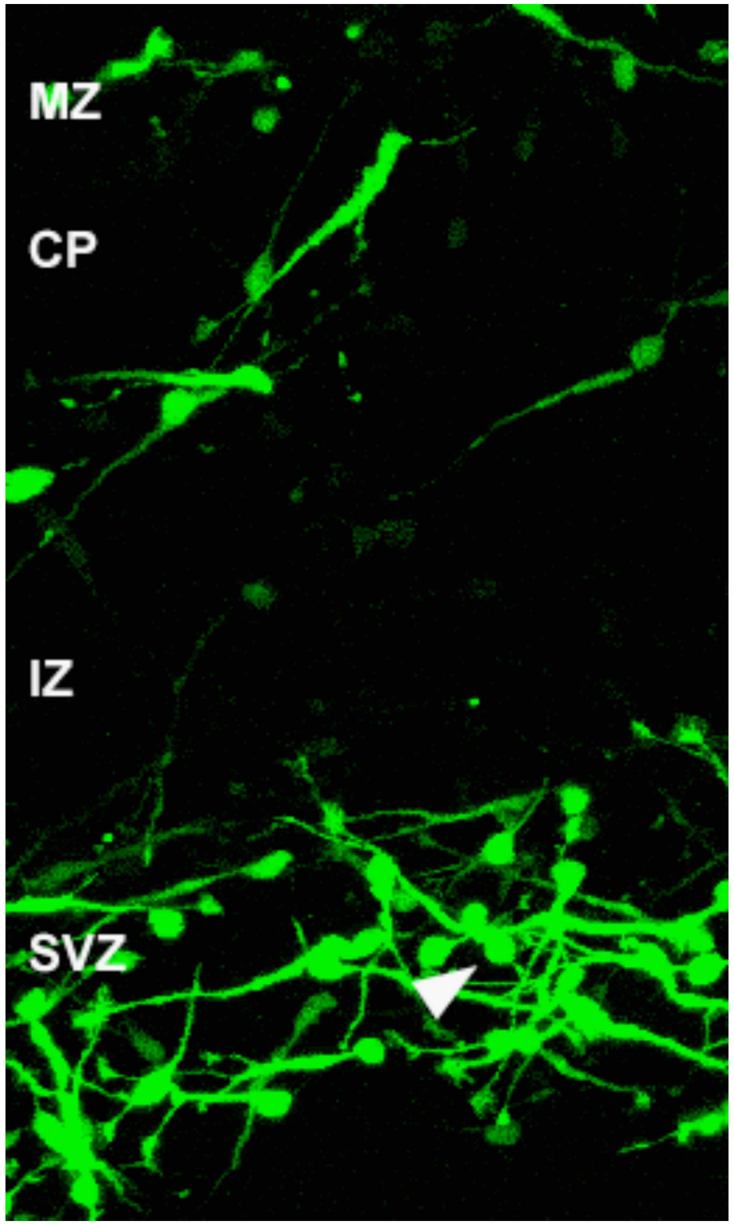
Manent et al, EJN 2011

Stereotyped dynamic behavior of tangentially migrating interneurons



Martini, F. J. et al. Development 2009;136:41-50

Branched Leading Process; a Mechanism of Steering



Gad65-GFP; Changing directions involves making new branches and nucleokinesis into the angled branch.

Movie 4. Branch dynamics in migrating neurons rapidly changing direction. An E16.5 Gad65-Gfp interneuron migrating through the cortical plate in a slice culture. Images were acquired every 6 minutes. The total duration of the movie is 2:18 hours. This cell (arrowhead) changes its orientation by means of a wide leading process bifurcation angle (75°; arrow).

Telencephalic Interneurons

•Multiple interneuron subtypes in cortex, OB and striatum.

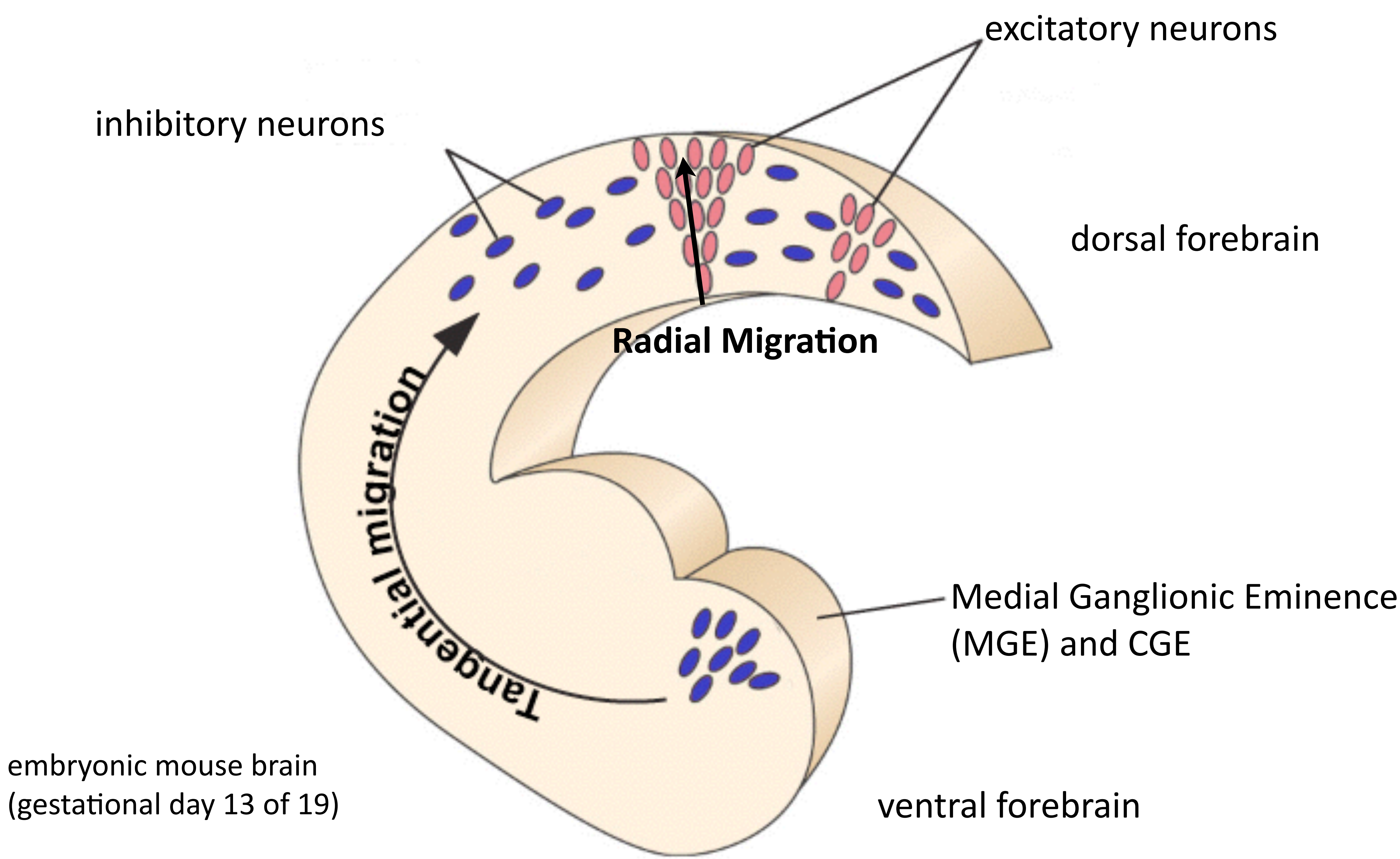
•Most contains GABA (gamma-aminobutyric acid).

•GABA interneurons can be further subdivided:
- Ca++ binding proteins(calbindin, calretinin and parvalbumin)
- neuropeptides (eg, neuropeptide Y).

•Not all interneurons are GABAergic:
- dopamine
- acetylcholine

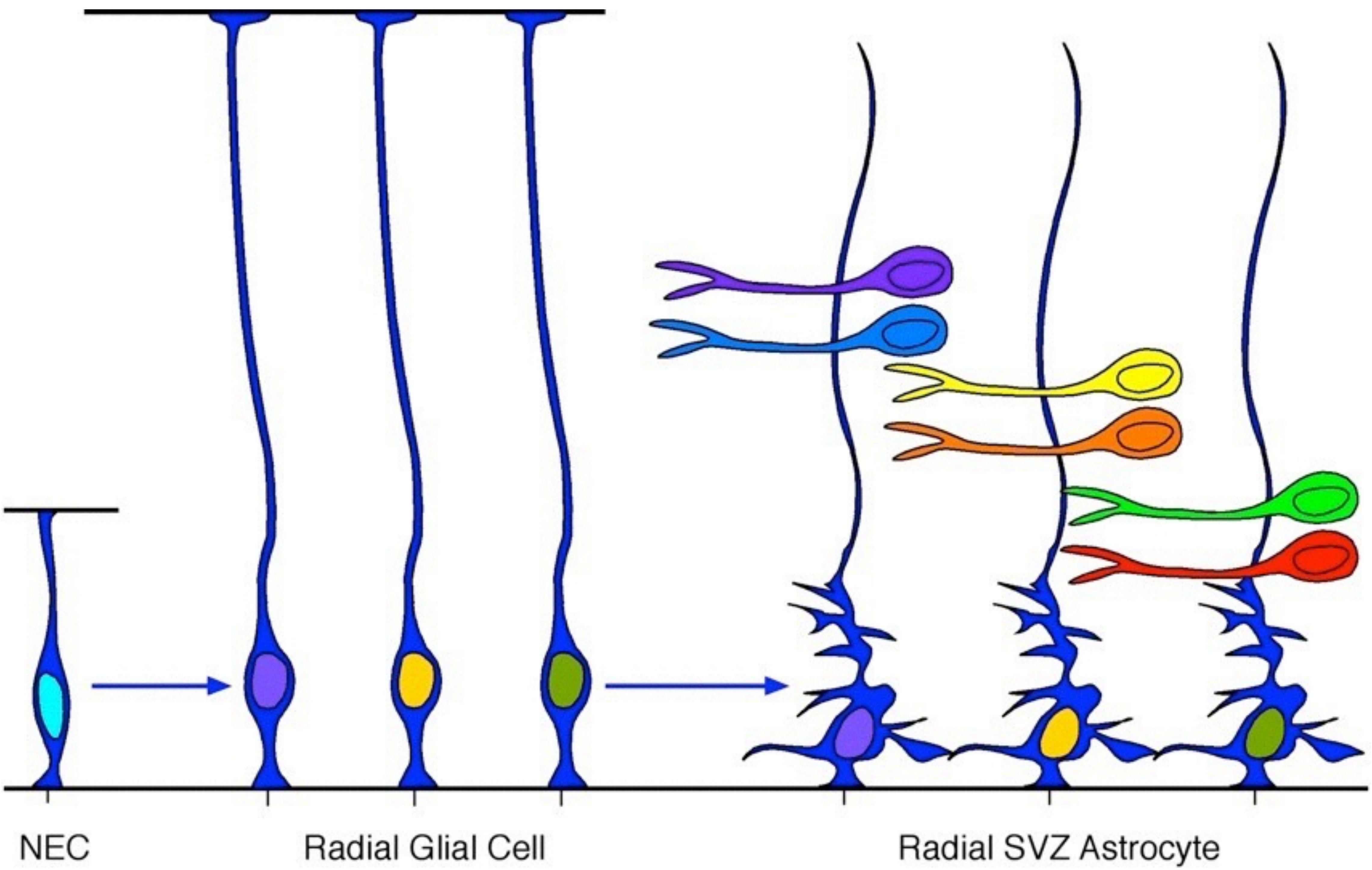
• Not all GABA neurons are interneurons.

Radial and Tangential migration: deployment of different classes of forebrain neurons: Radial for excitatory and Tangential for inhibitory neurons.

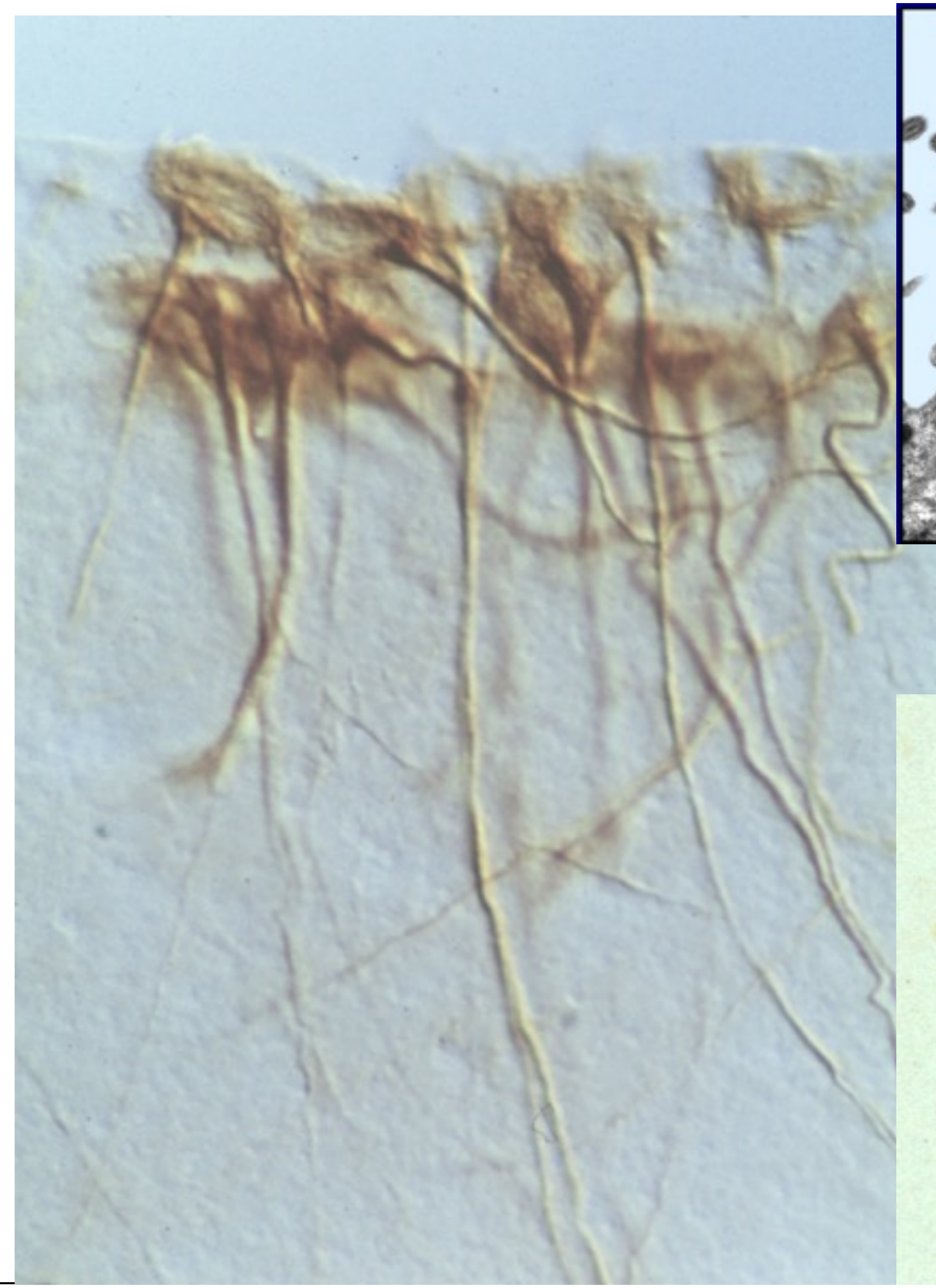


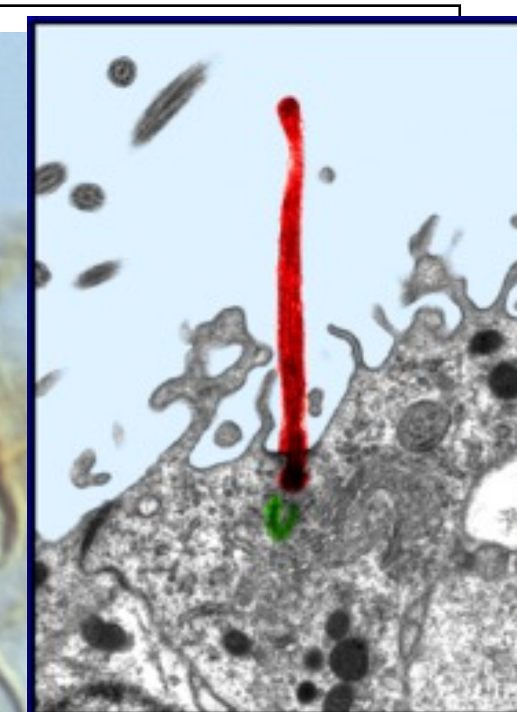
(figure: Sanes et al., 2006)

• Progenitors are Contained within Unique Domains and Tangentially Fixed. Tangential Migration.



Radial Glia are Progenitors of New Neurons; Primary Cilia

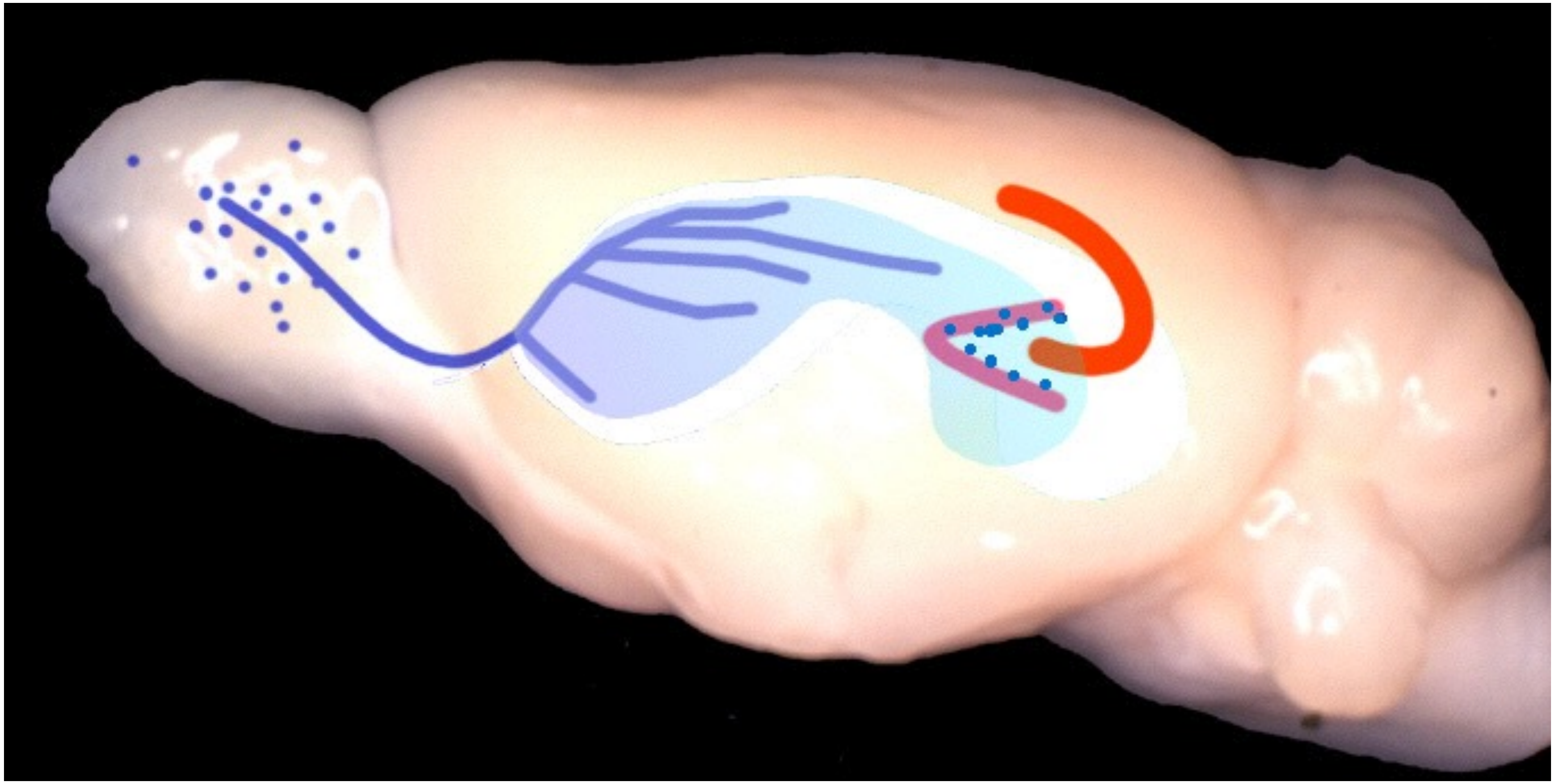




Neurogenesis Continues in the Adult Mammalian Brain

- If Radial Glia disappear during Development, which cells function as adult NSCs in mammals?

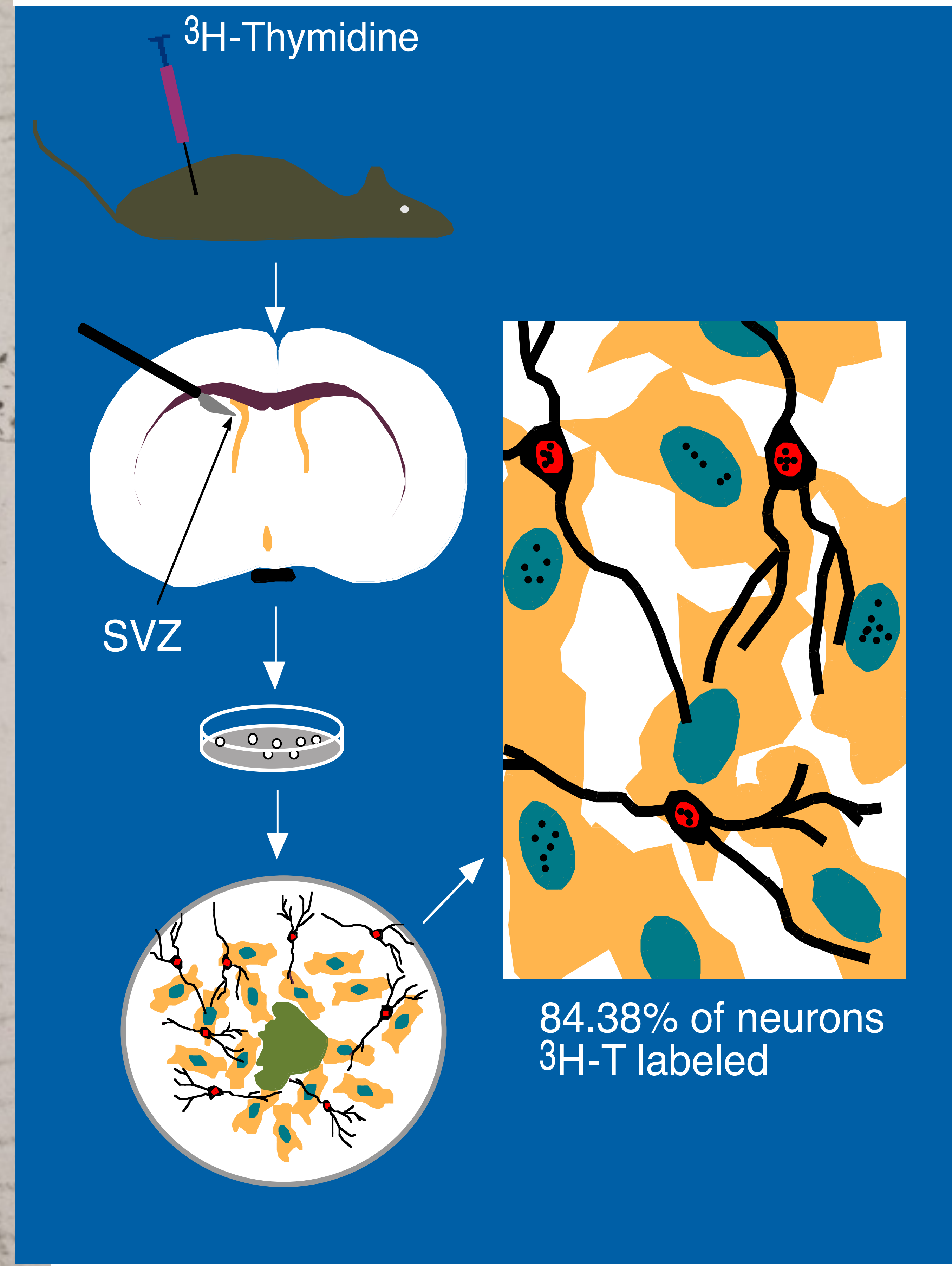
Neurogenesis in the Adult Mammalian Brain



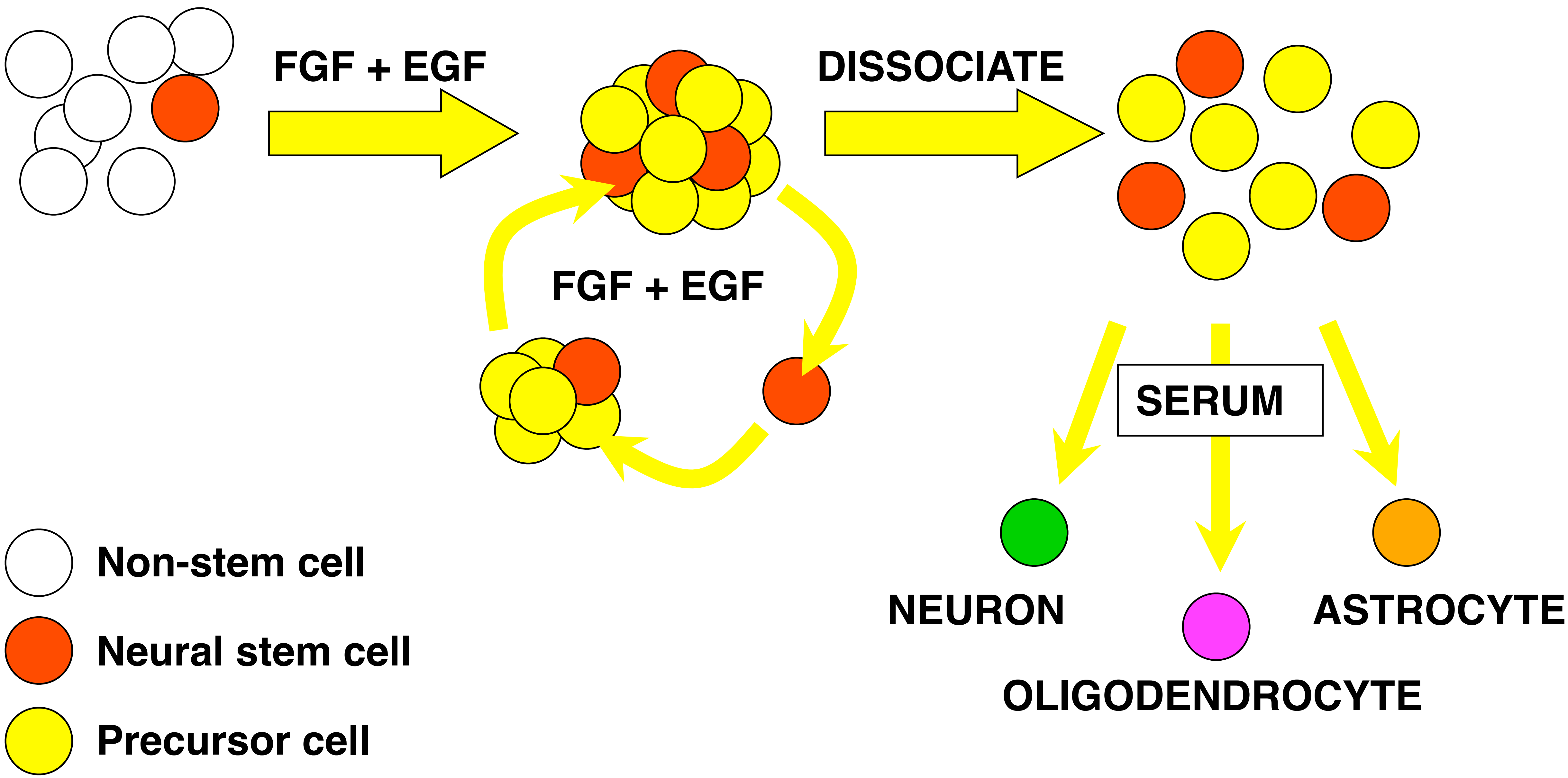
Joseph Altman

Dividing SVZ cells can give rise to Neurons and Glia

I. Smart 1961

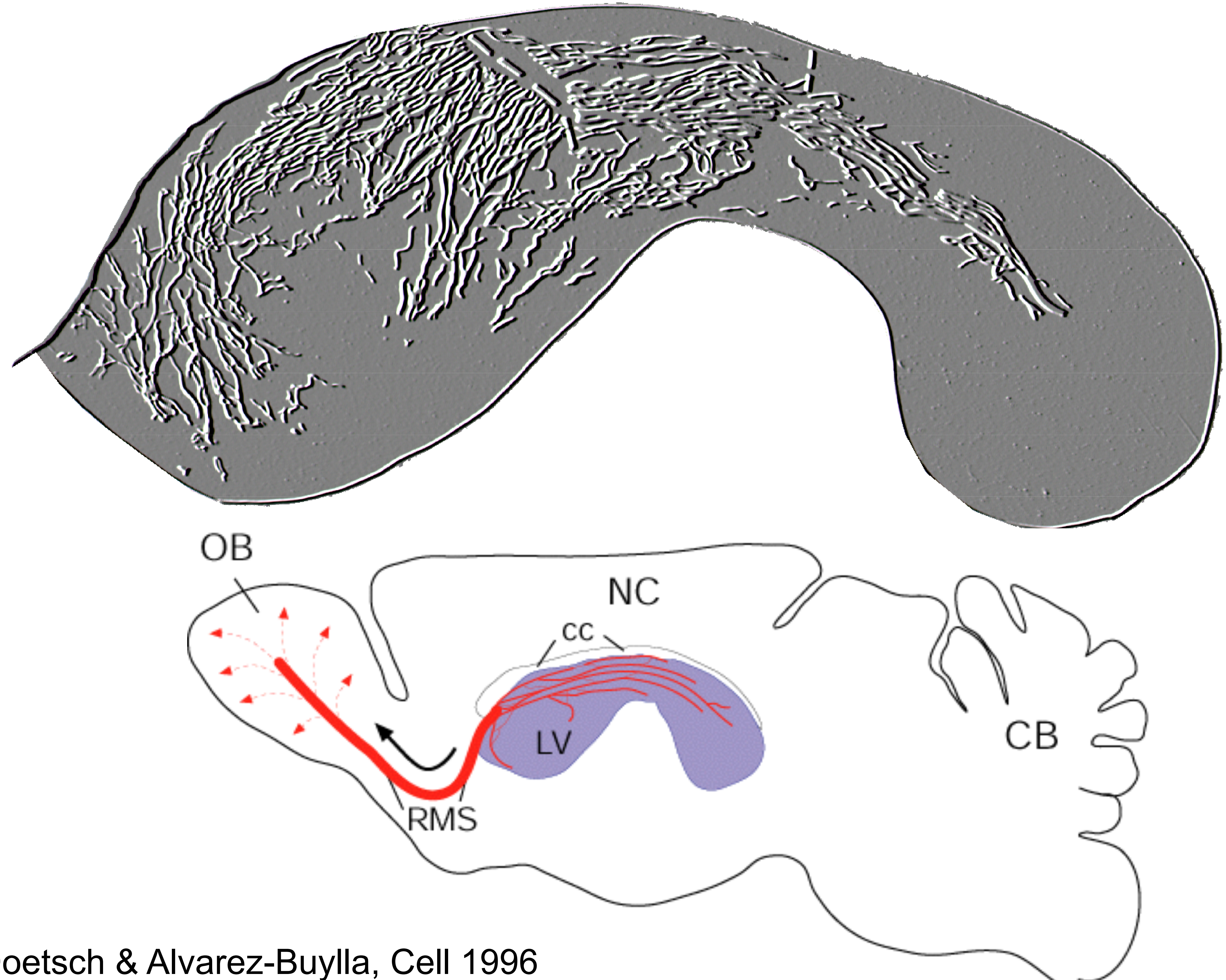


Identifying Self-Renewal and Multipotency

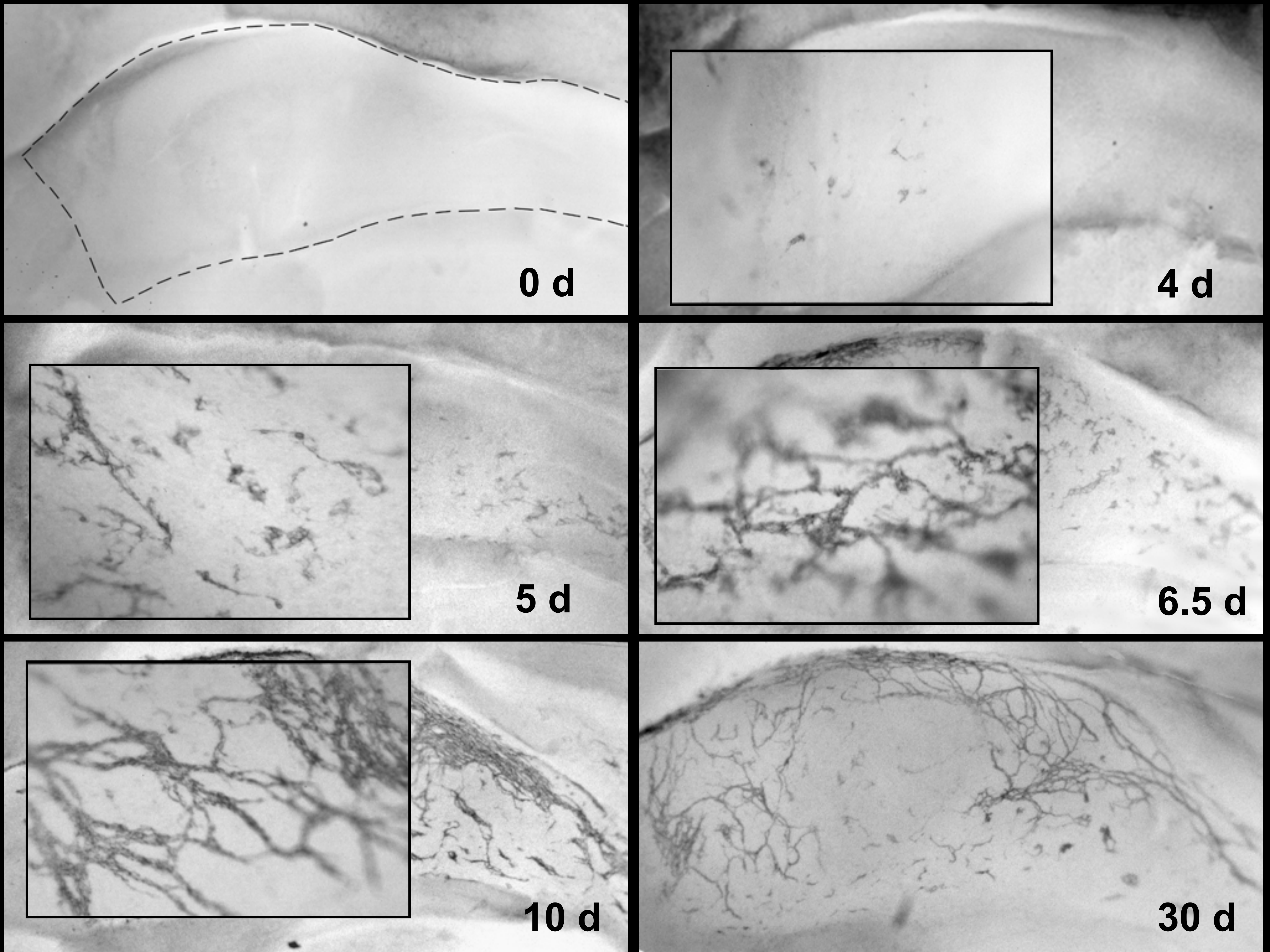


Reynolds and Weiss 1996

The V-SVZ Contains the Major Repository of NSCs in the Adult Brain

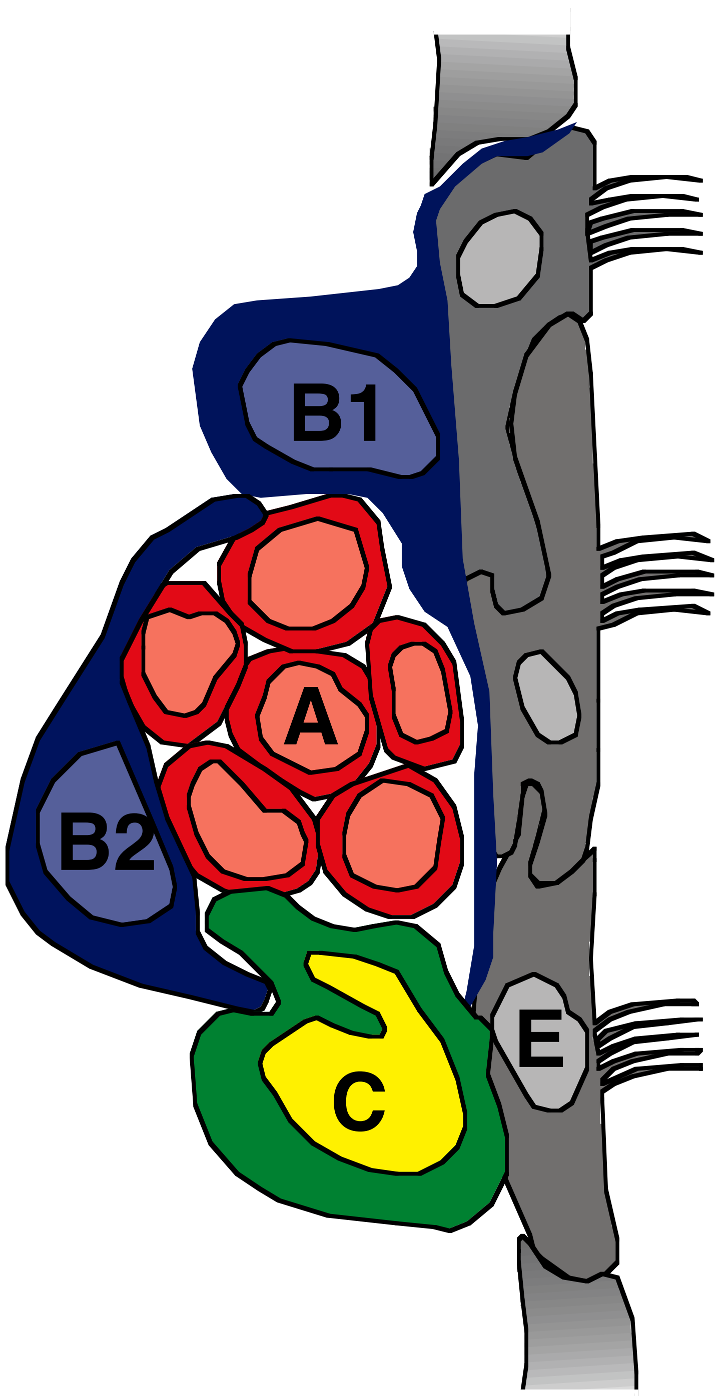


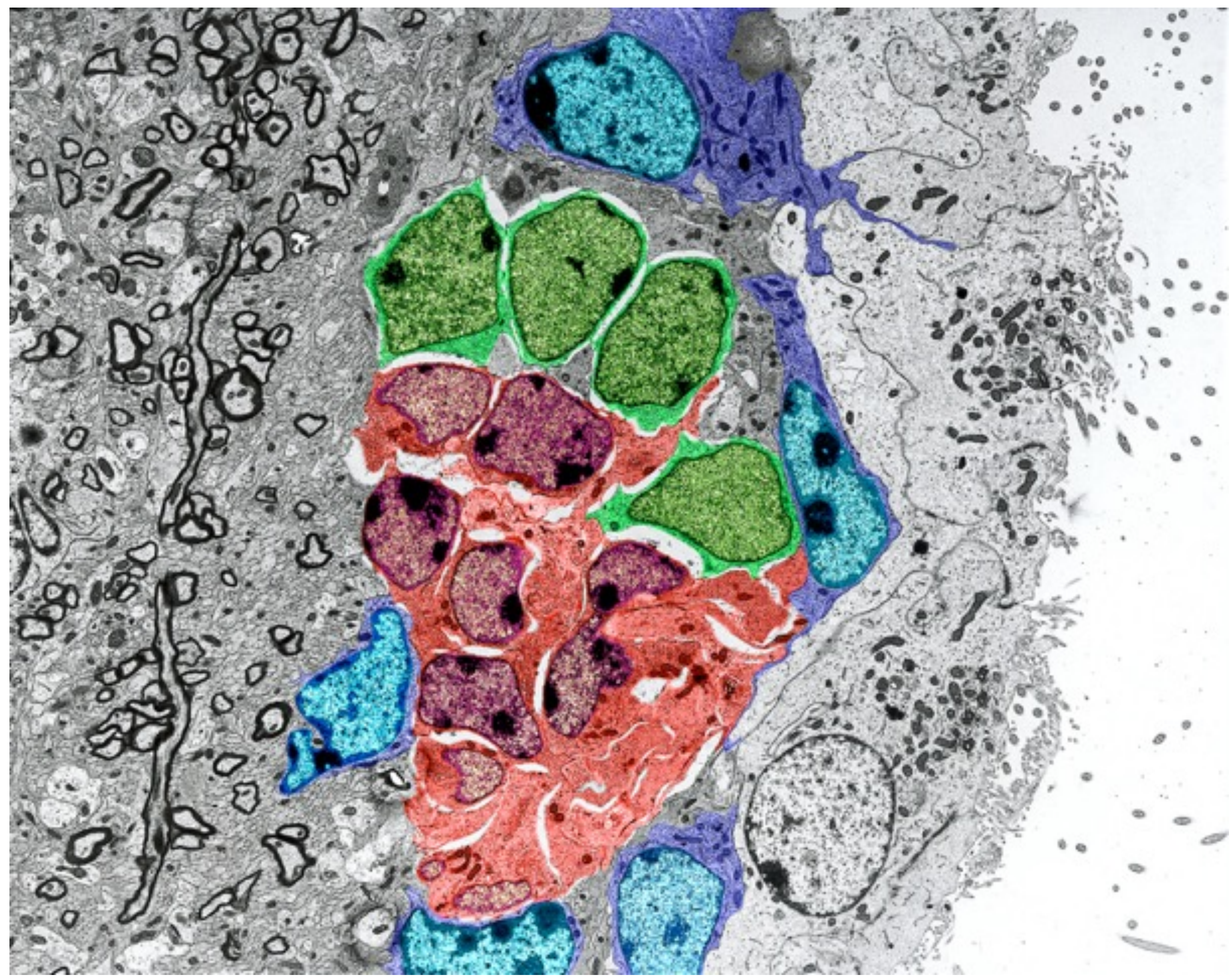
Doetsch & Alvarez-Buylla, Cell 1996



0 d
4 d
5 d
6.5 d
10 d
30 d

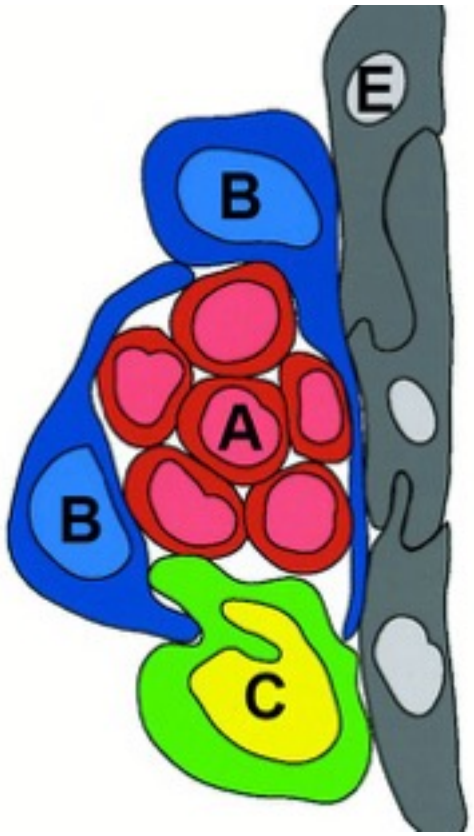
Identification of Neural Stem Cells in Adult Mammals

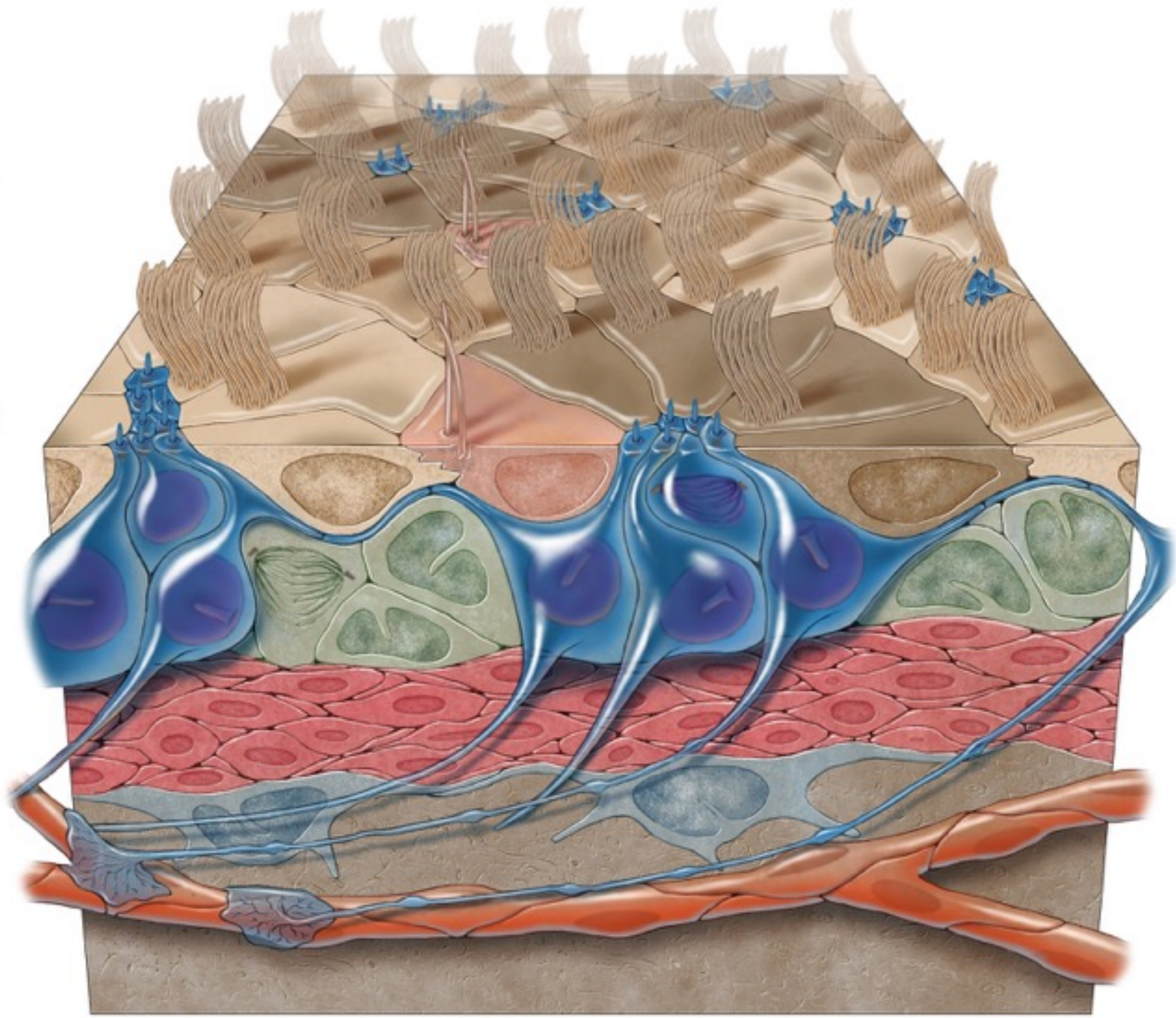




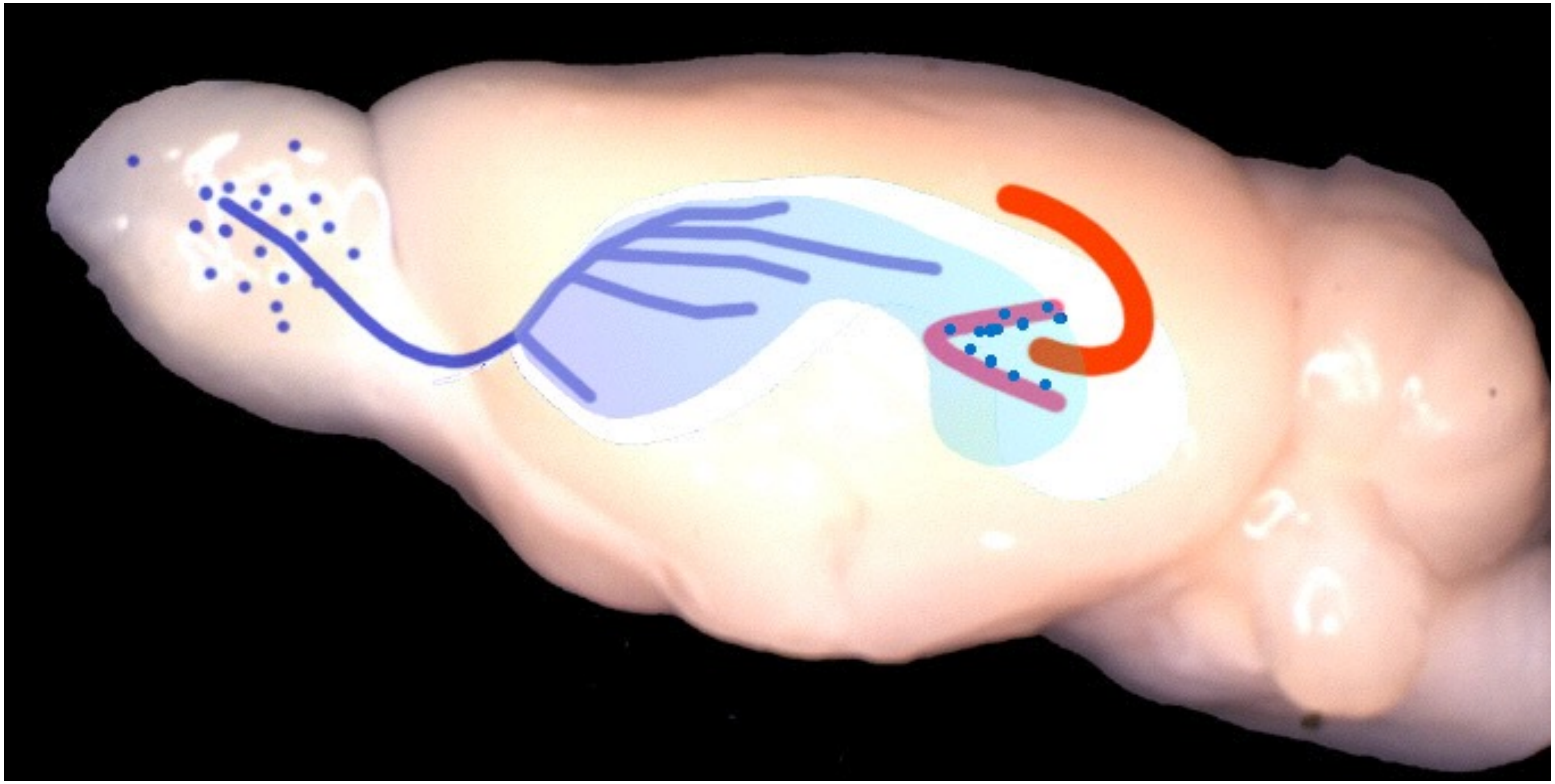
Doetsch et al, Cell 1999

Niche Interactions of Adult Neural Stem Cells



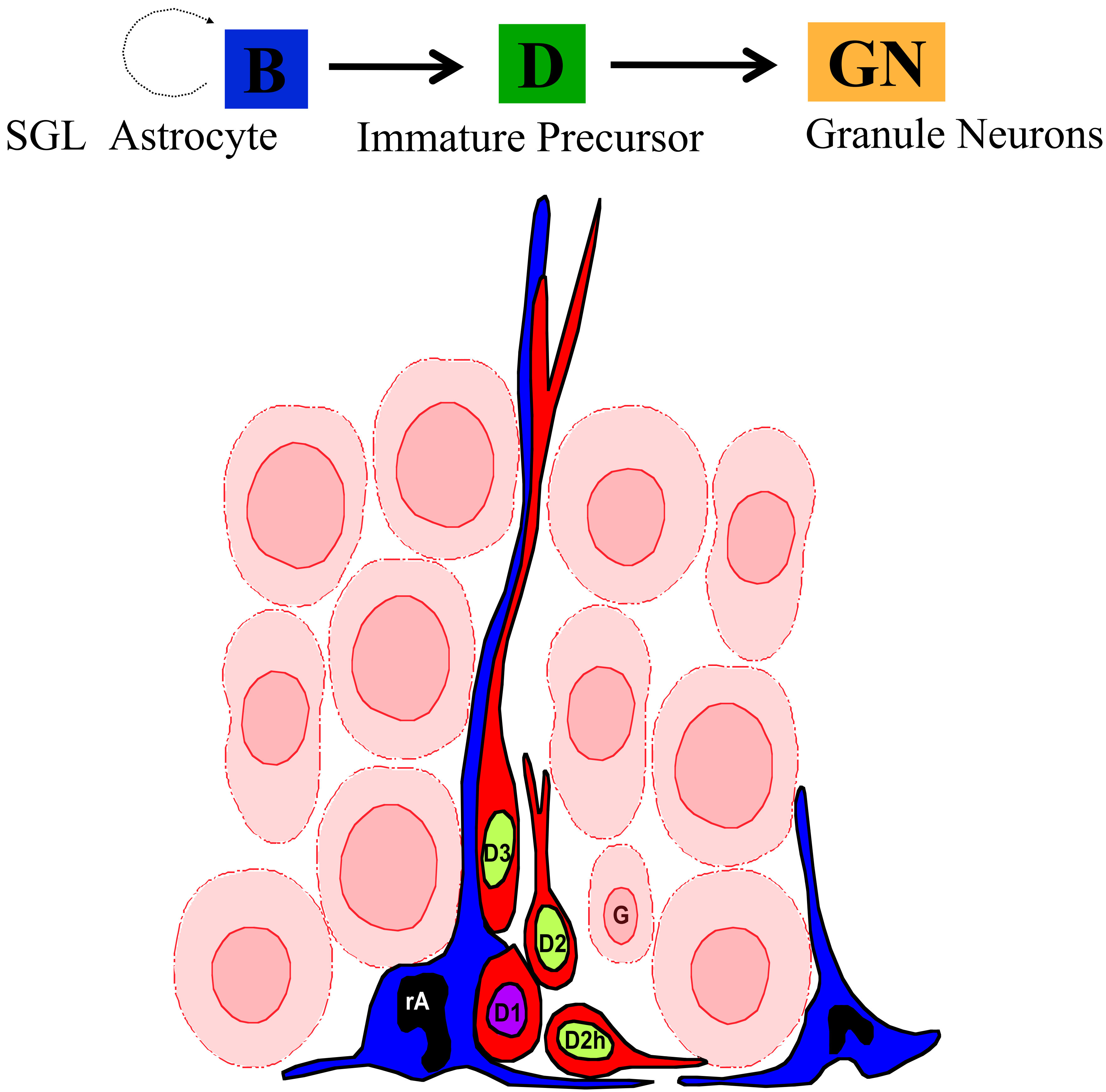


Neurogenesis in the Adult Mammalian Brain

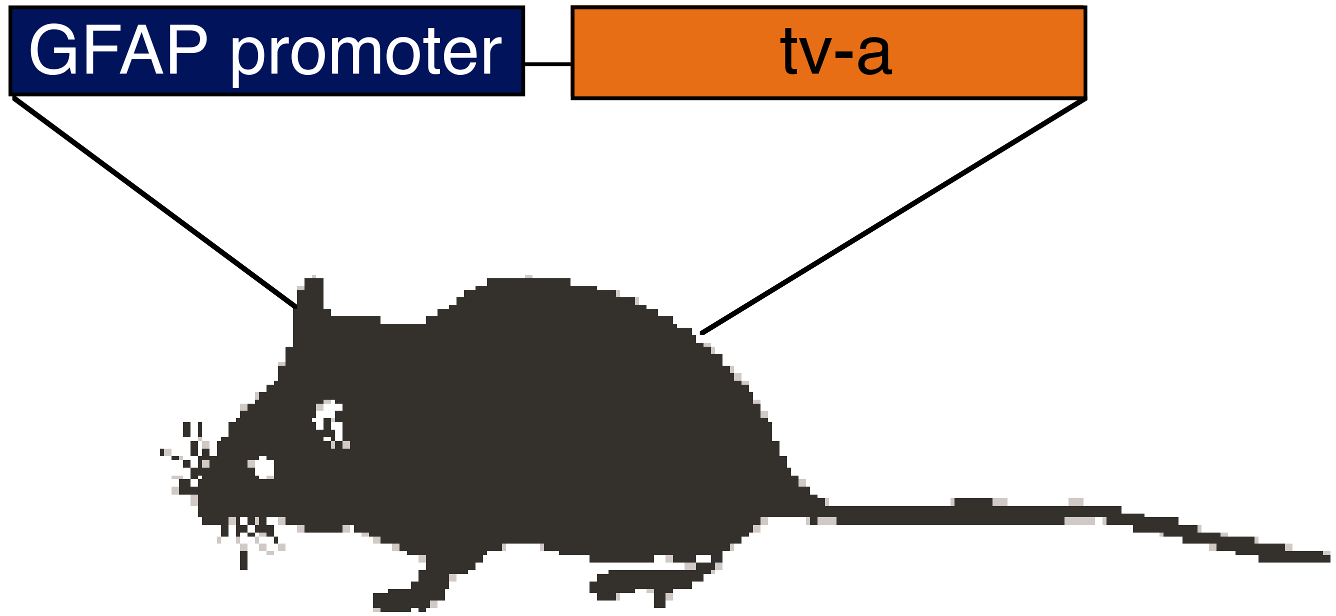


Joseph Altman

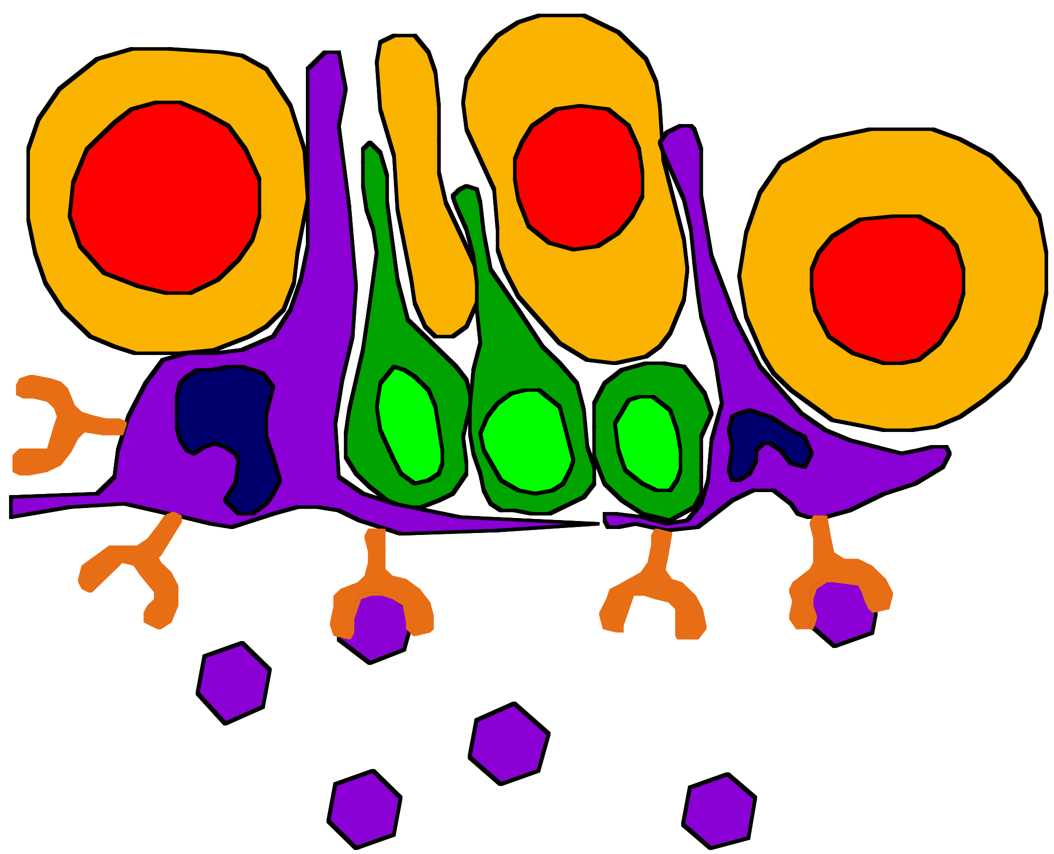
Identification of Neural Stem Cells in Adult Hippocampus



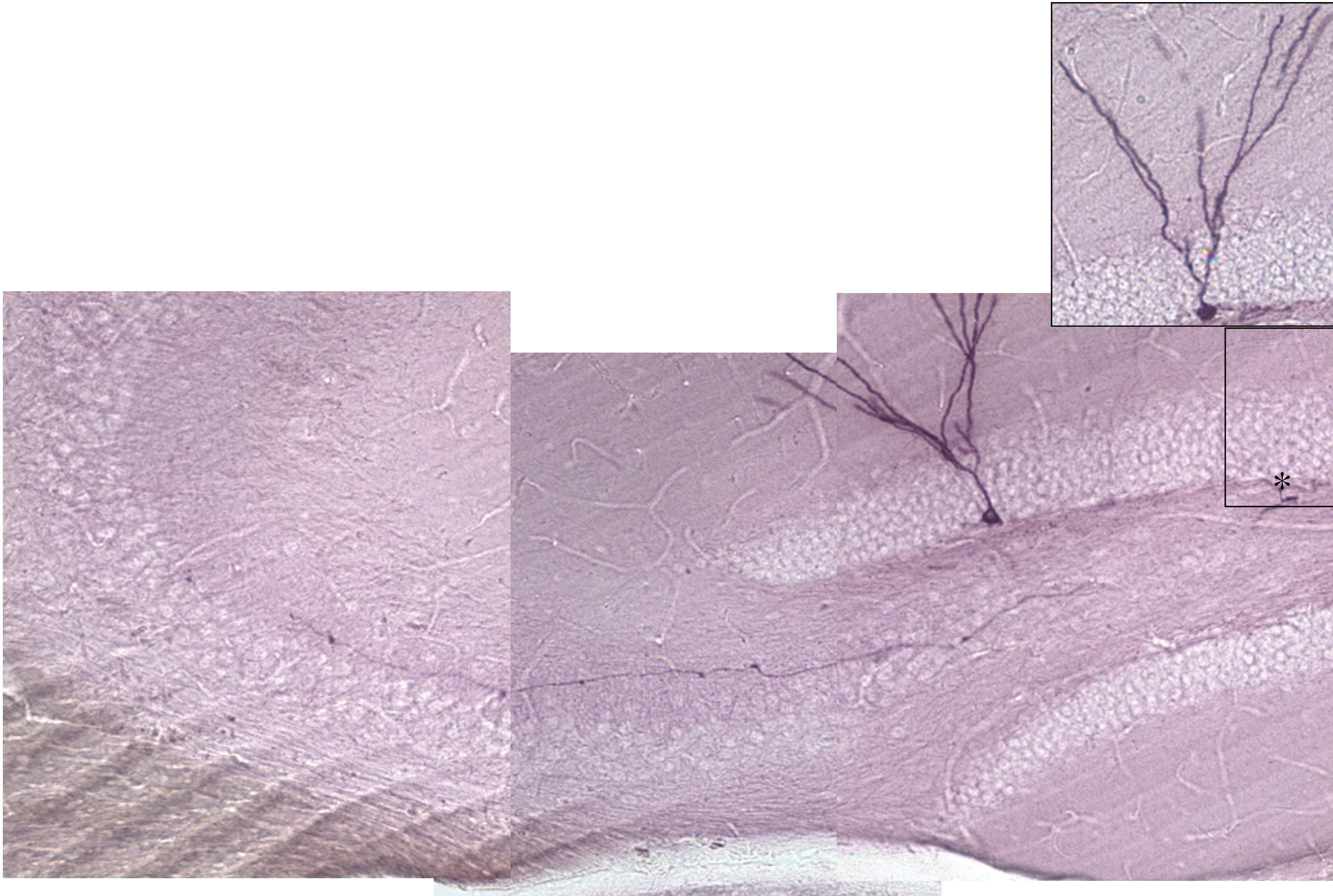
Strategy to Label the Primary Neuronal Progenitors.



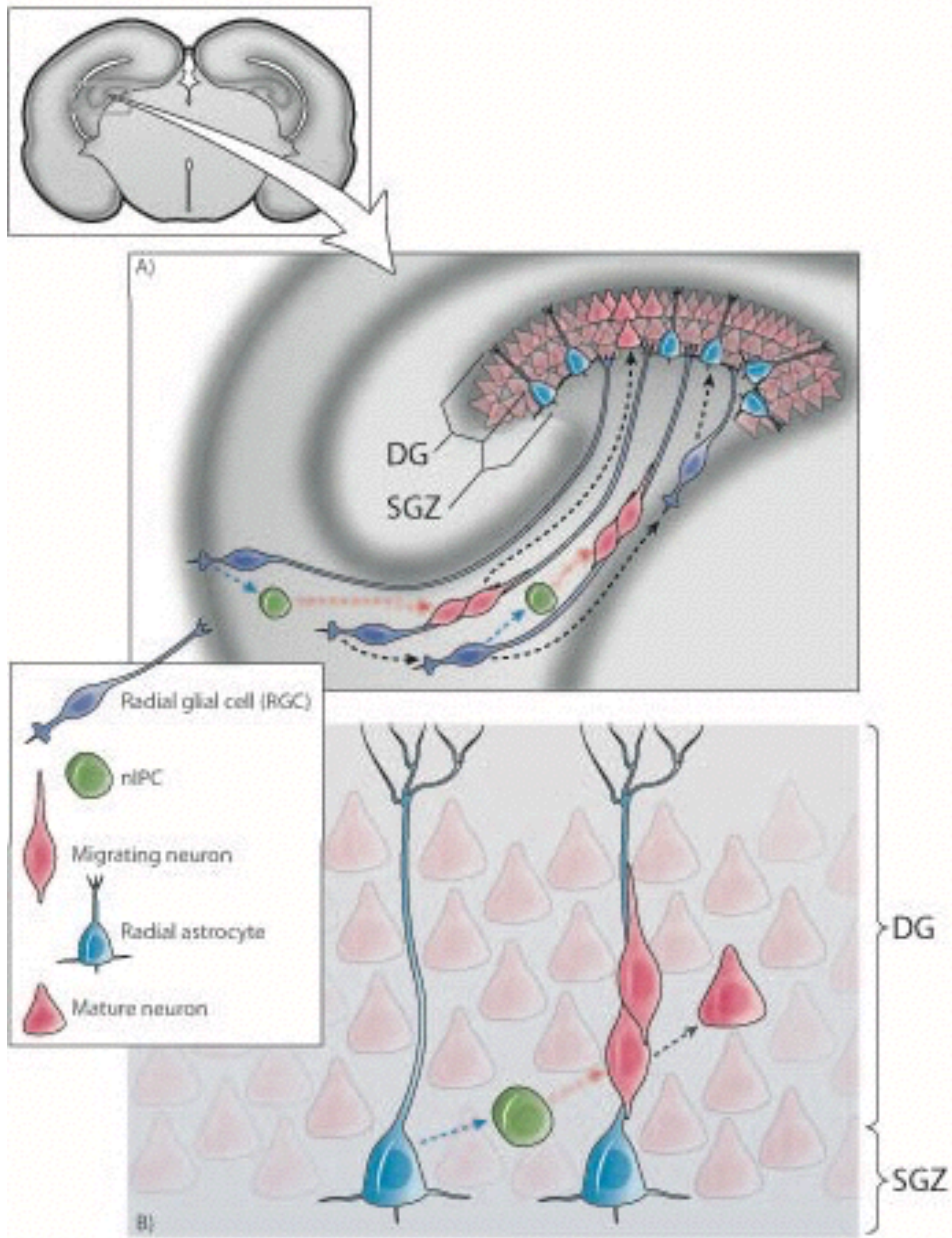
Holland EC and Varmus HE (1998)



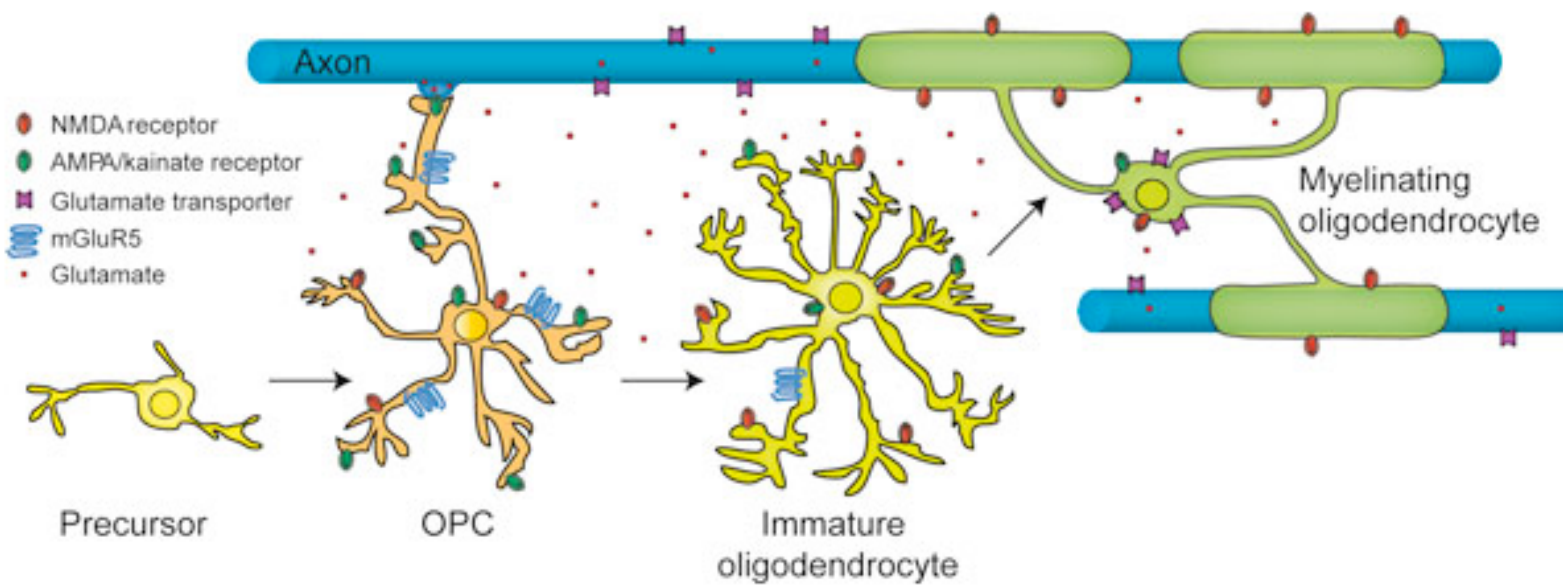
New Neurons Derived from GFAP+ Astrocytes



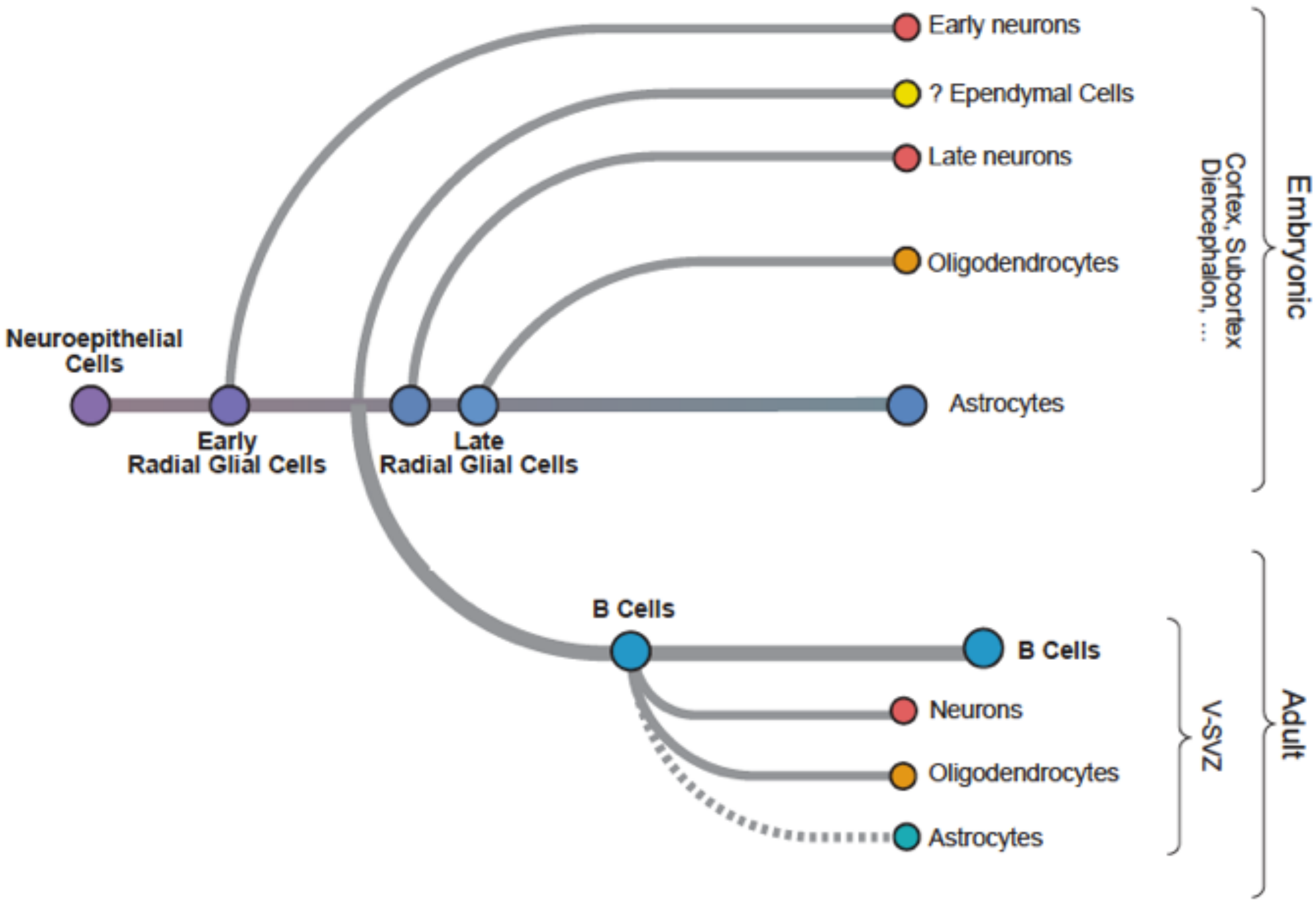
NSCs in Hippocampus also Contain Primary Cilia



A Third Population of Adult Progenitors



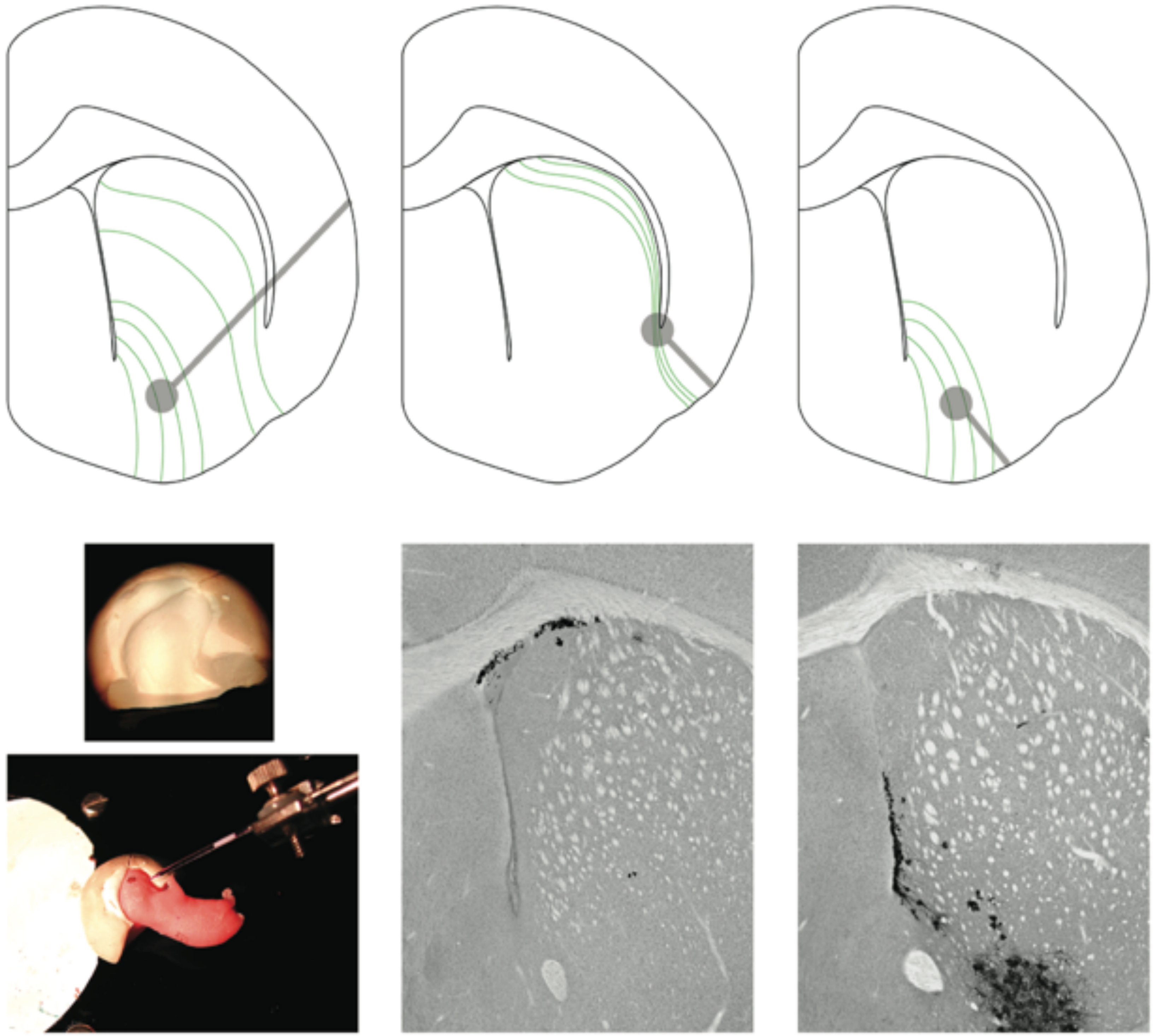
Separate origins of adult NSCs



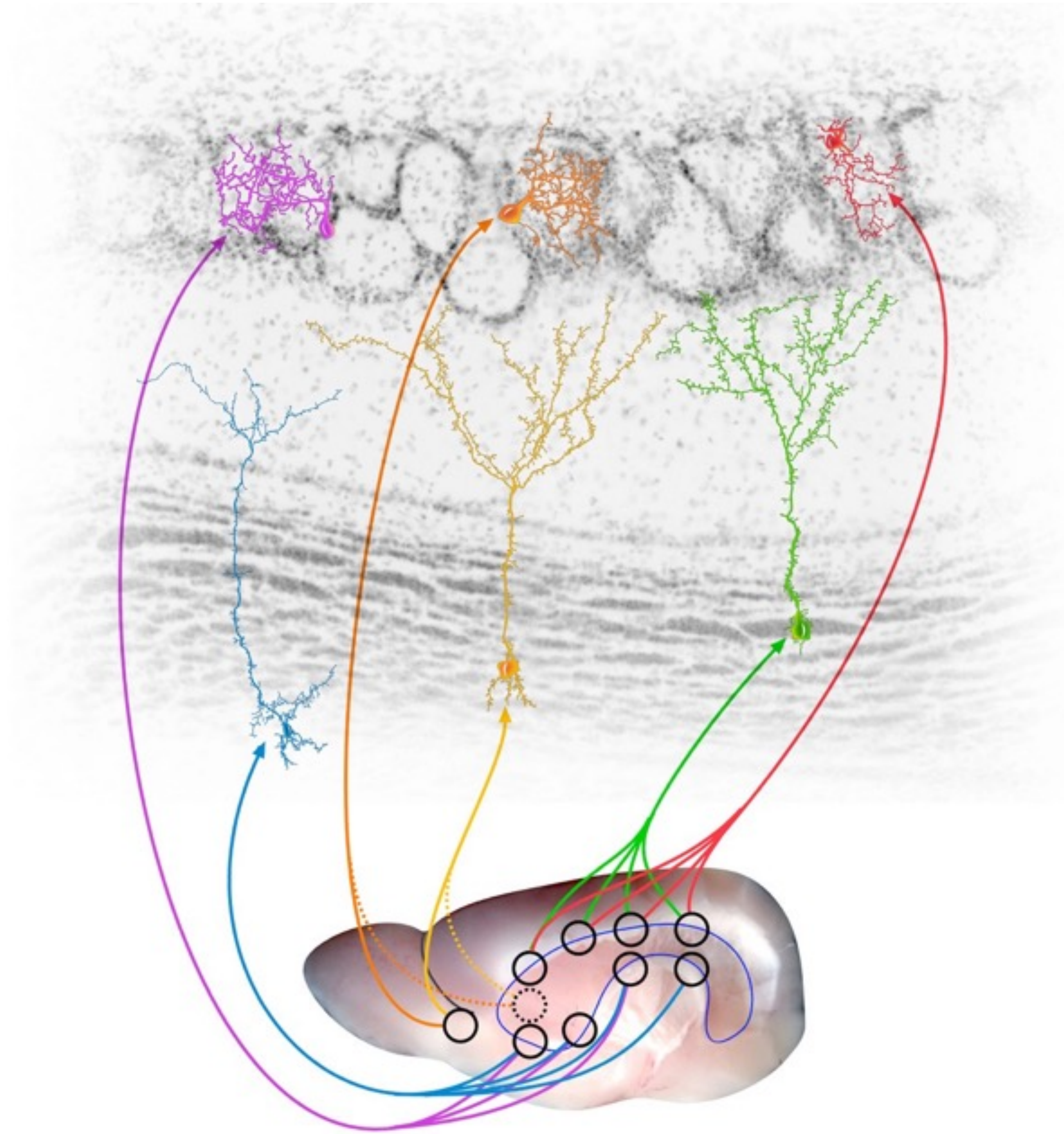
- Postnatal and fetal forebrain NSCs share common progenitors in the early embryo, but these two lineages diverge between P13.5 - P15.5.

Fuentealba et al; 2015

Regional Labeling of Radial Glia NSCs



Regional Specification of Neural Stem Cells in the Adult Brain



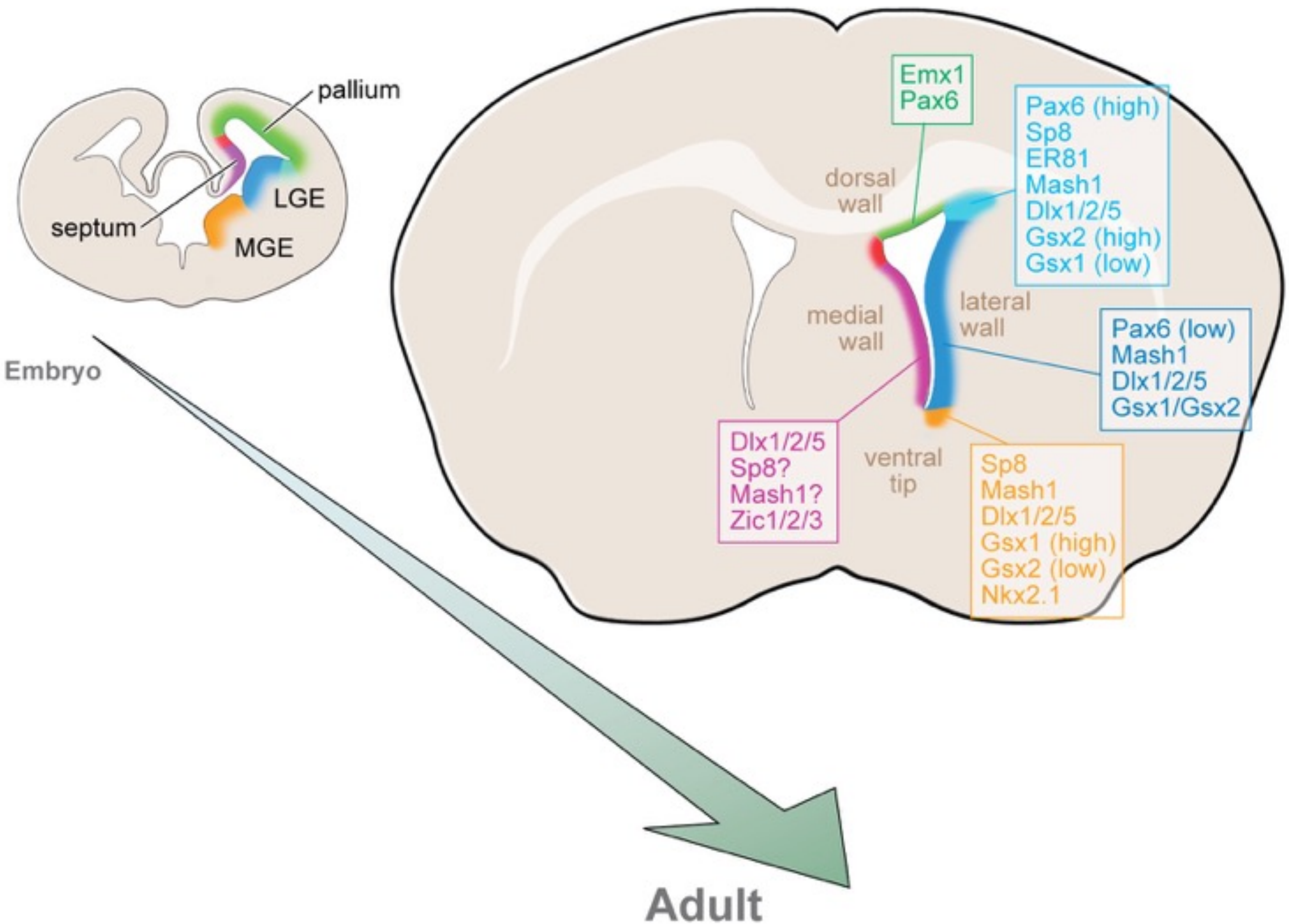
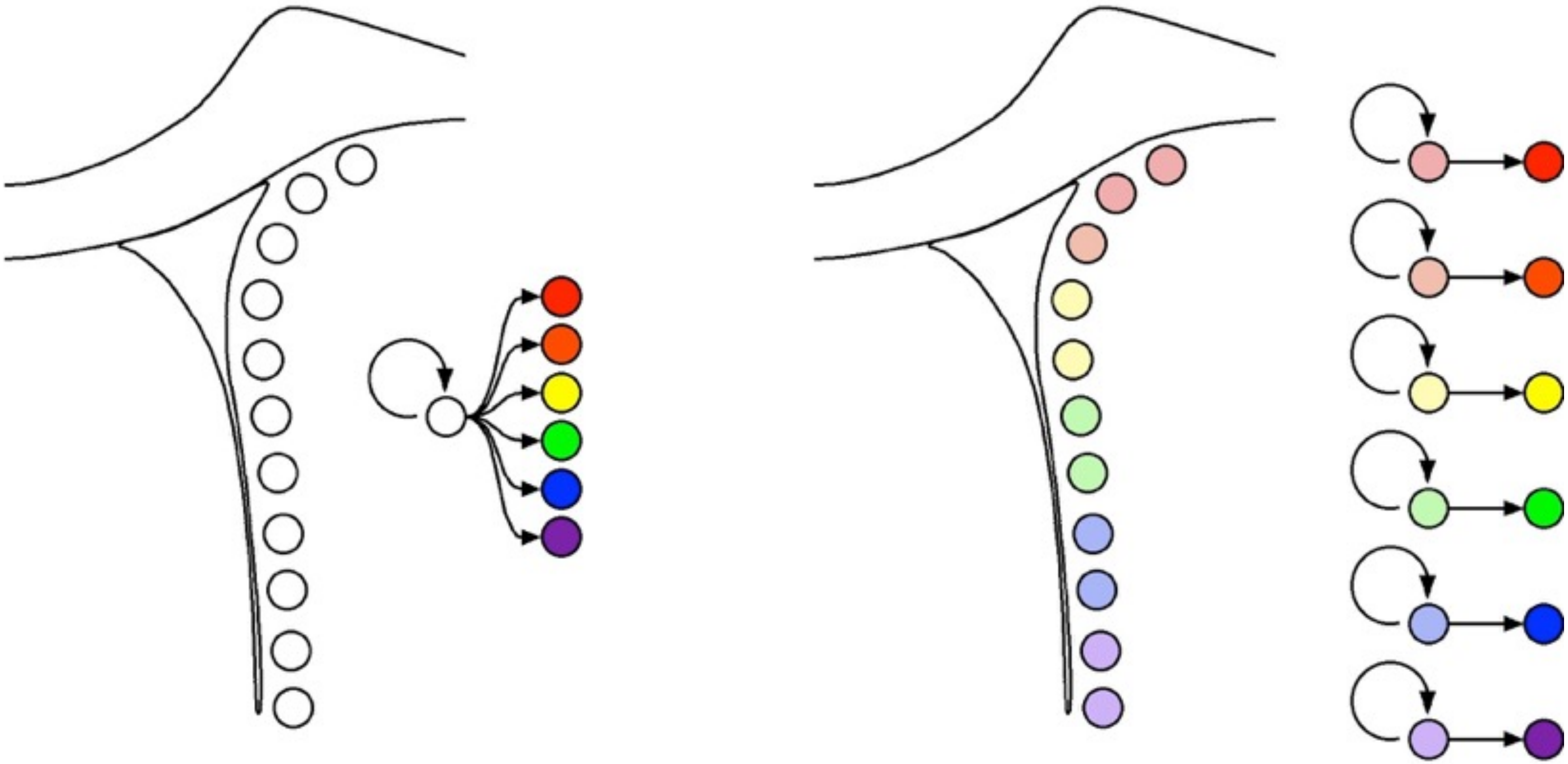
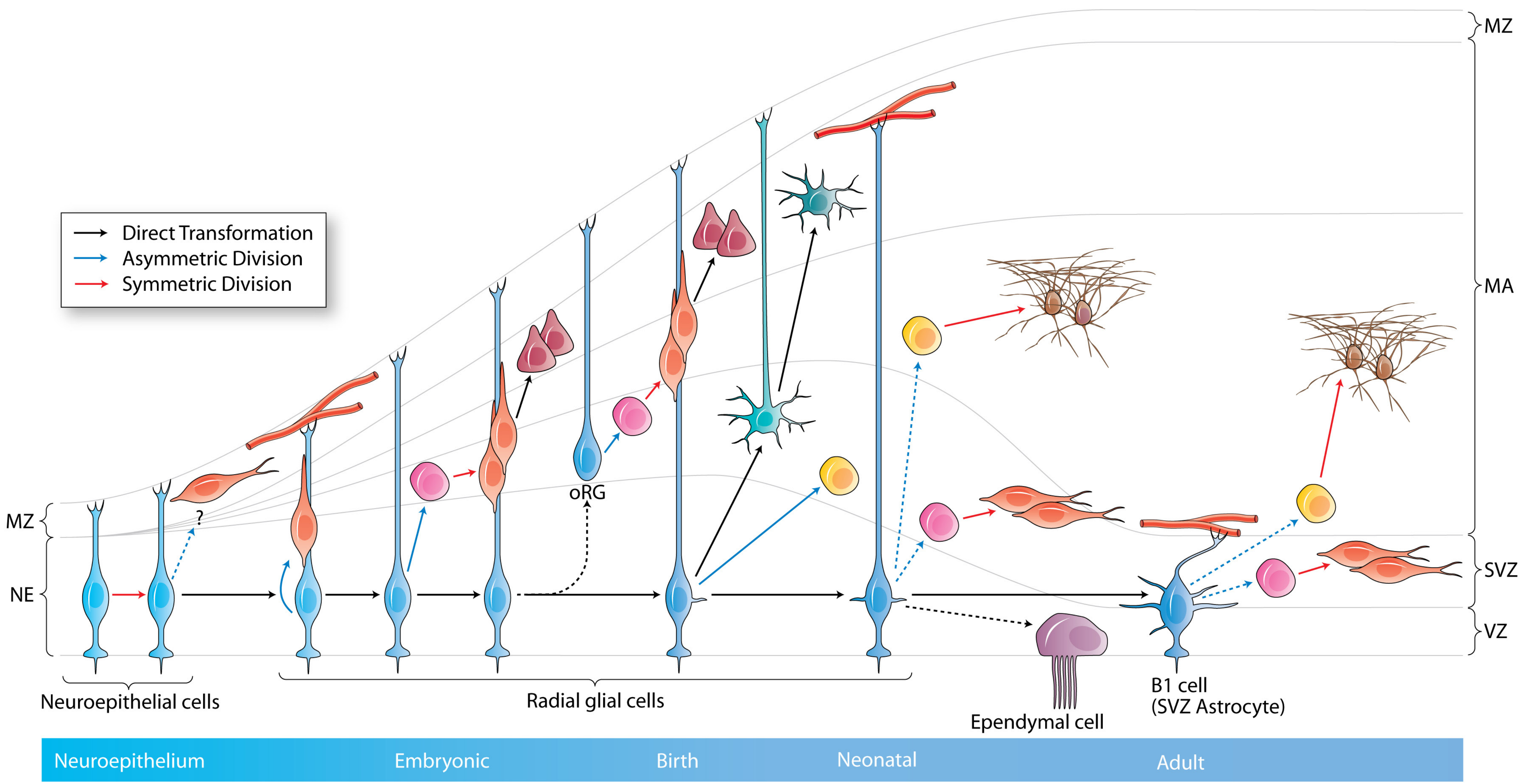


Figure 2
Alvarez-Bullya, Merkle and Fuentealba

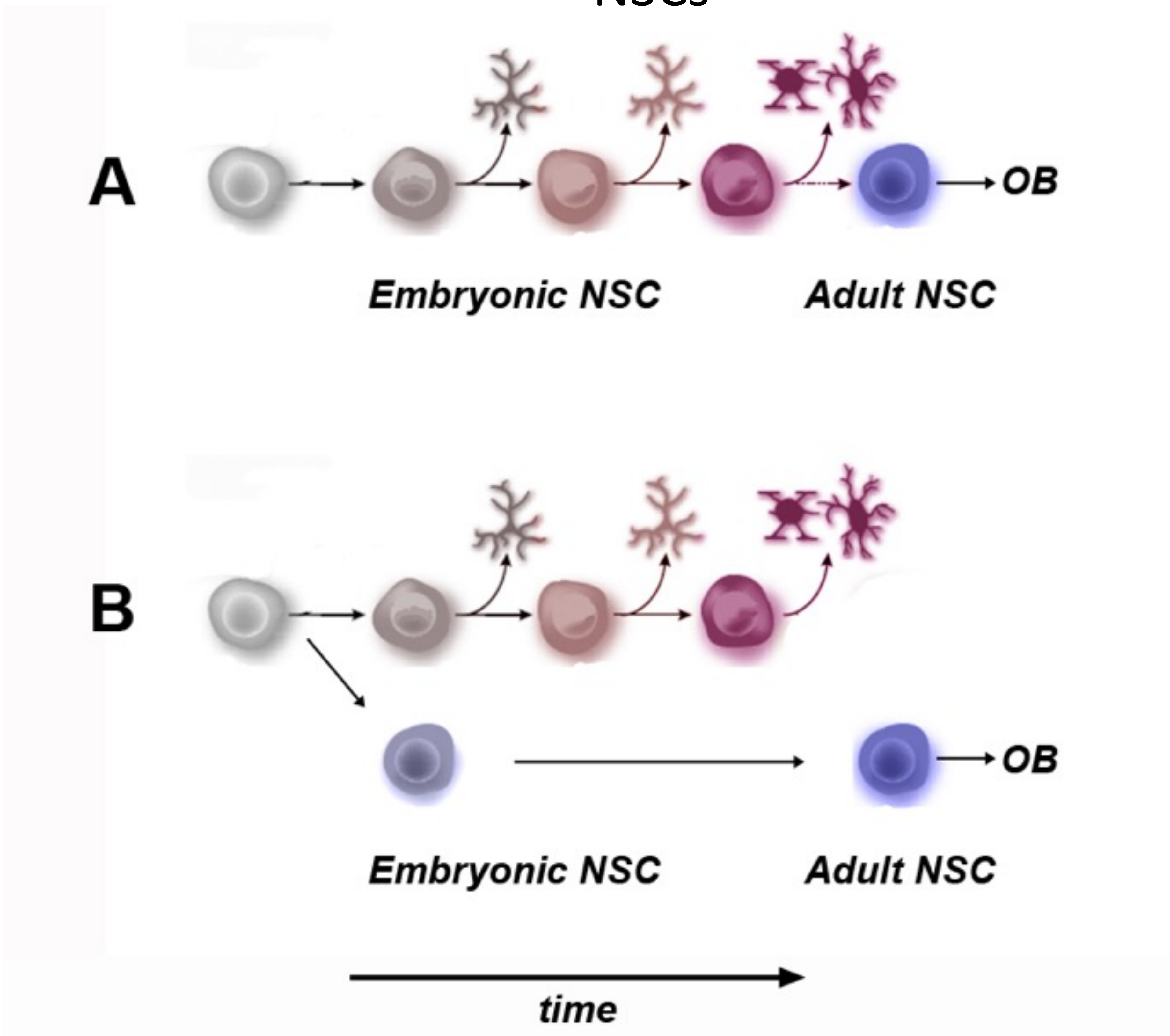
Models of NSC potential



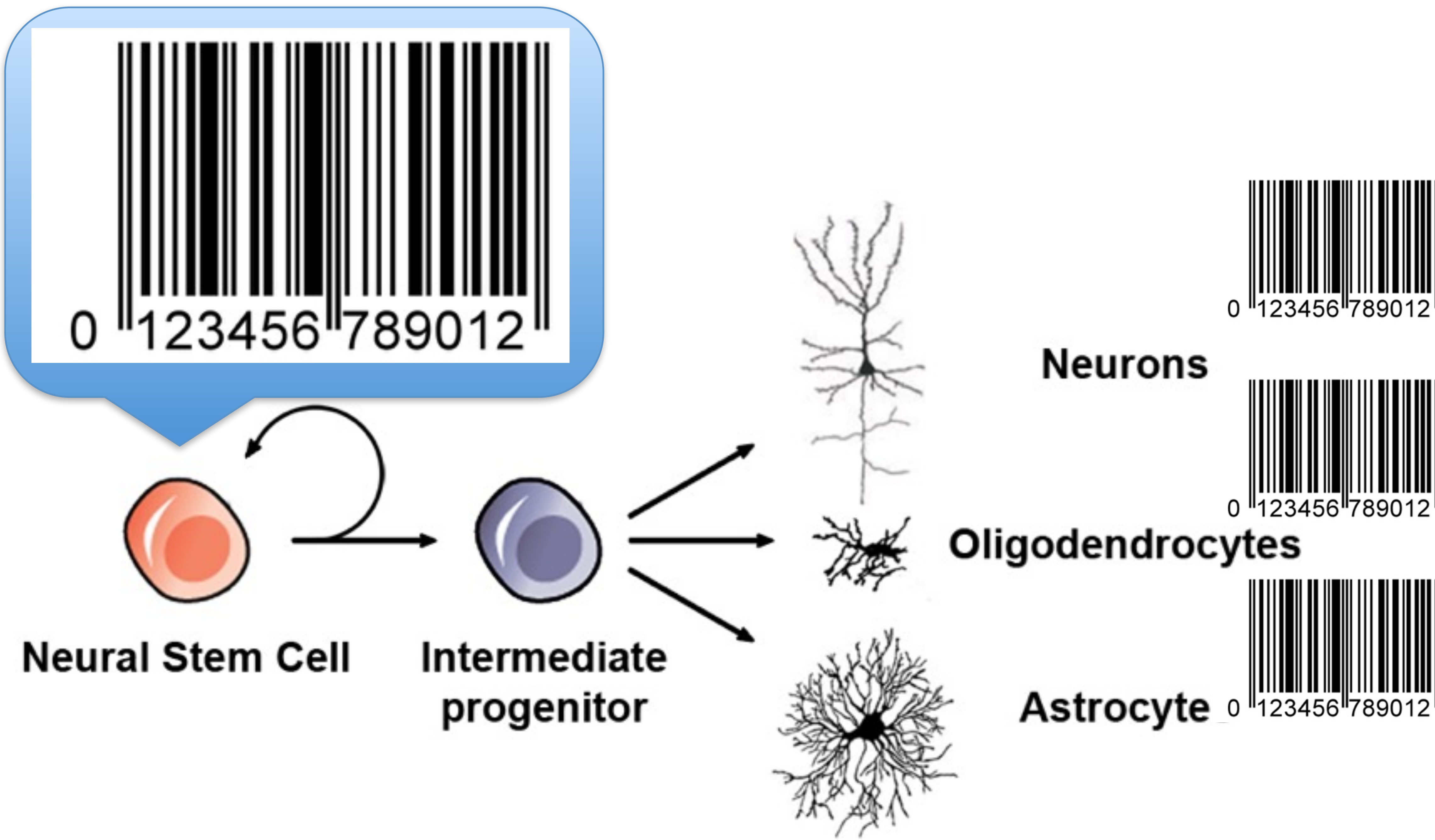
Neural Progenitor Lineage from Embryo to Adult



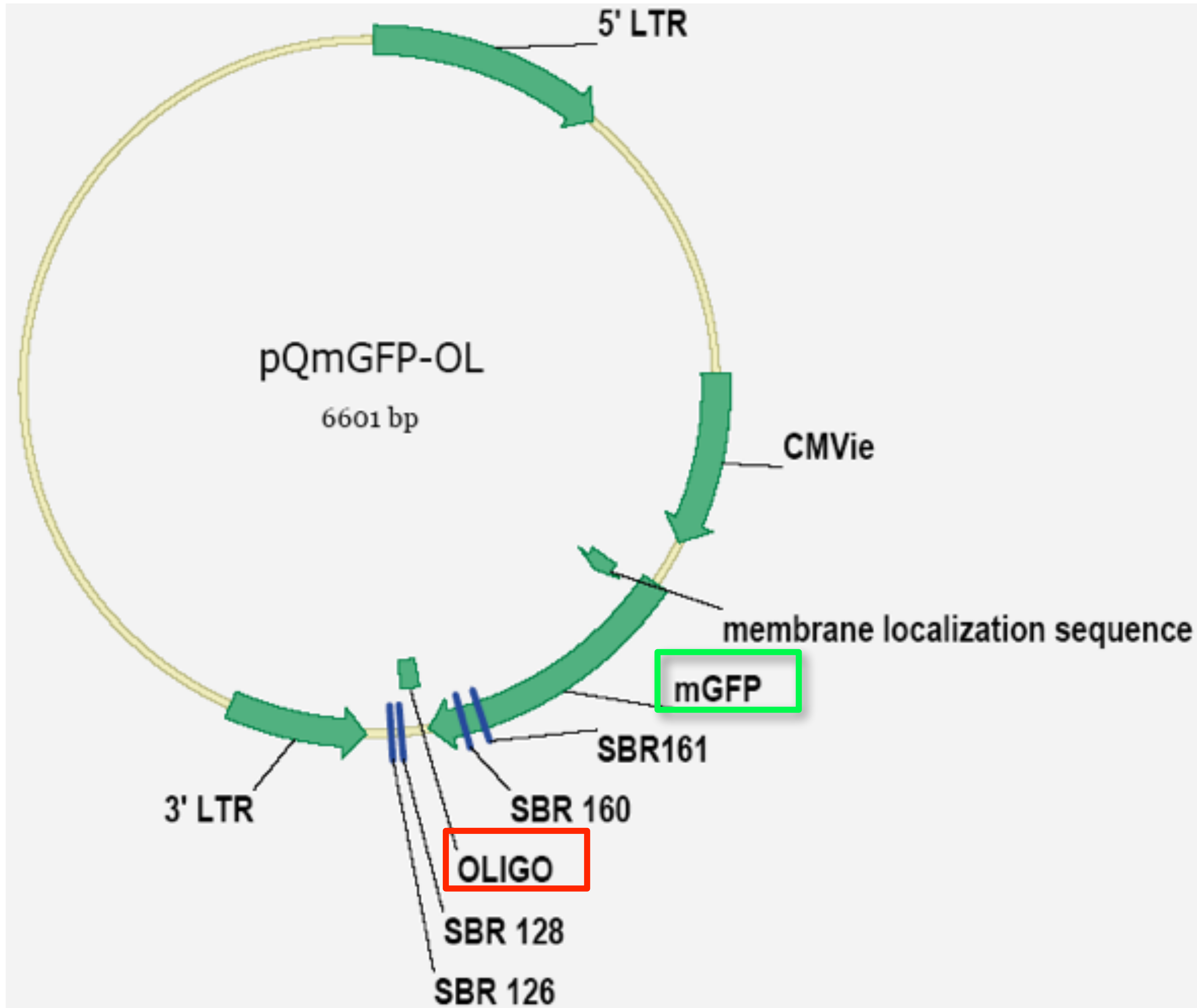
Alternative hypotheses that may explain the origins of adult NSCs



Tracing individual progenitors in vivo



Identifying *sibling relationships* of individual GFP^{+}-cells



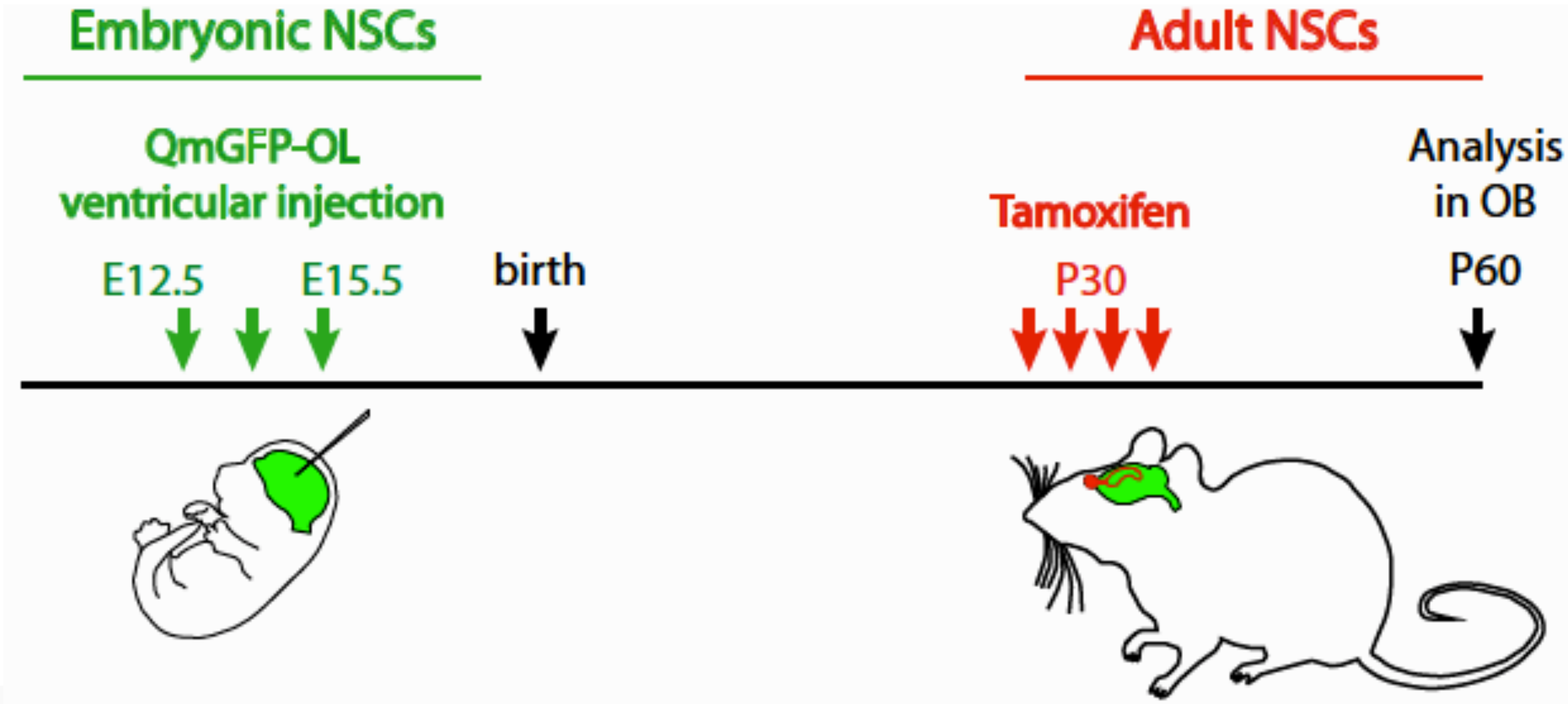
...TAGAT *CACACACACACACACACACACACA* GTAGAT...
GTGTGTGTGTGTGTGTGTGTGTGT

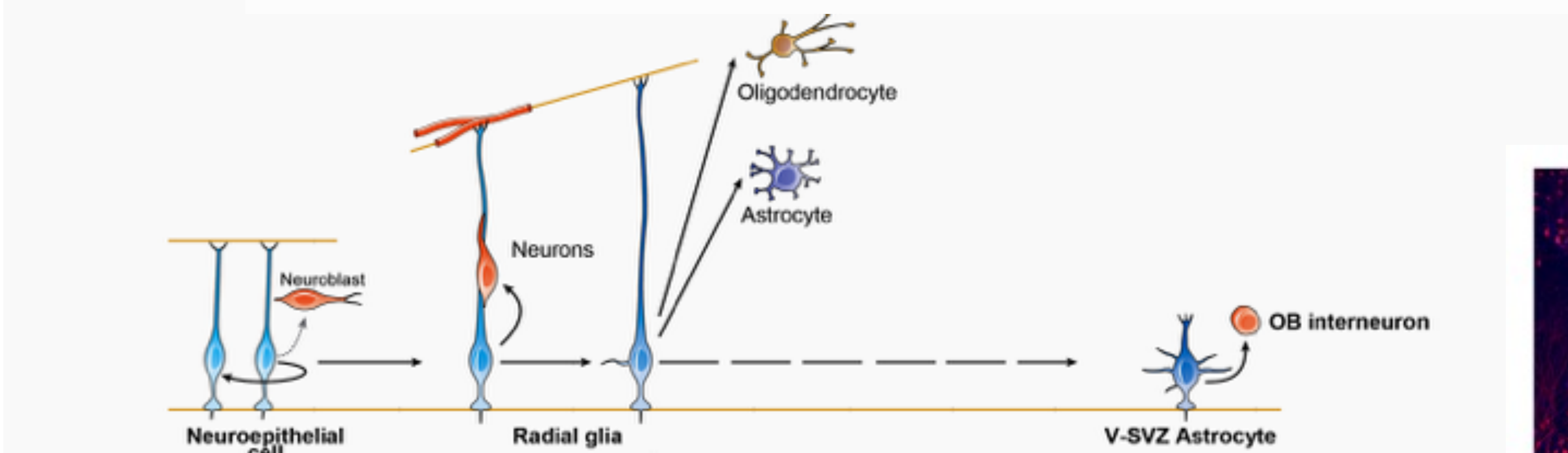
With: Connie Cepko &
Santiago Rompani

Q-mGFP-oligo library: "barcode" complexity = 10^7 (actual 10^5)

Tracing INDIVIDUAL embryonic NSCs into adulthood

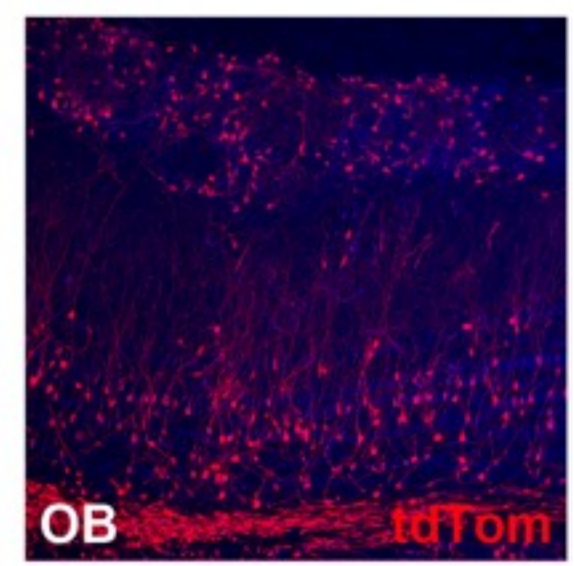
in NestinCre-ER; Ai14 mouse (Amelia J. Eisch UT SMC)

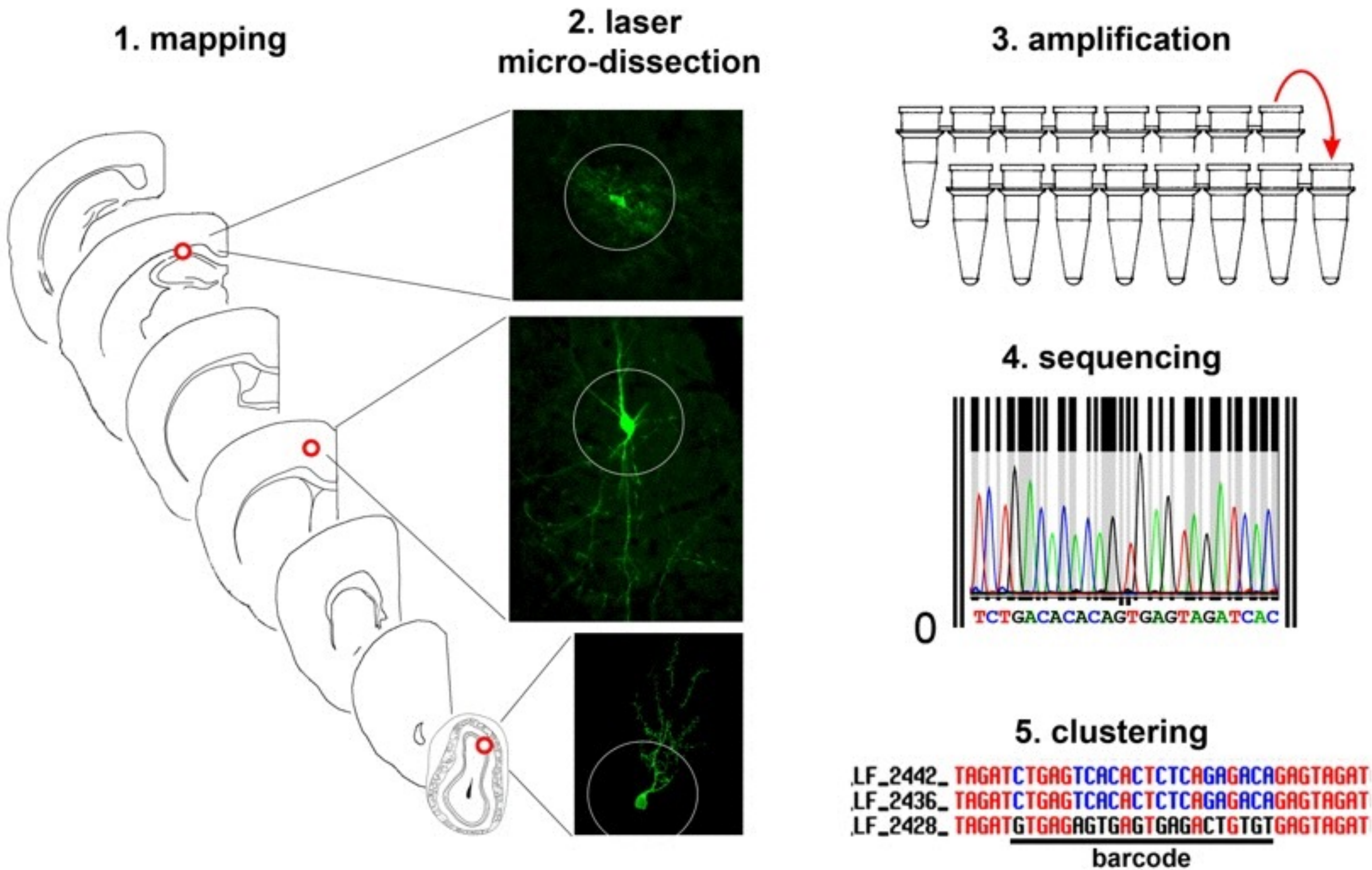




QmGFP labeled

tdTomato labeled

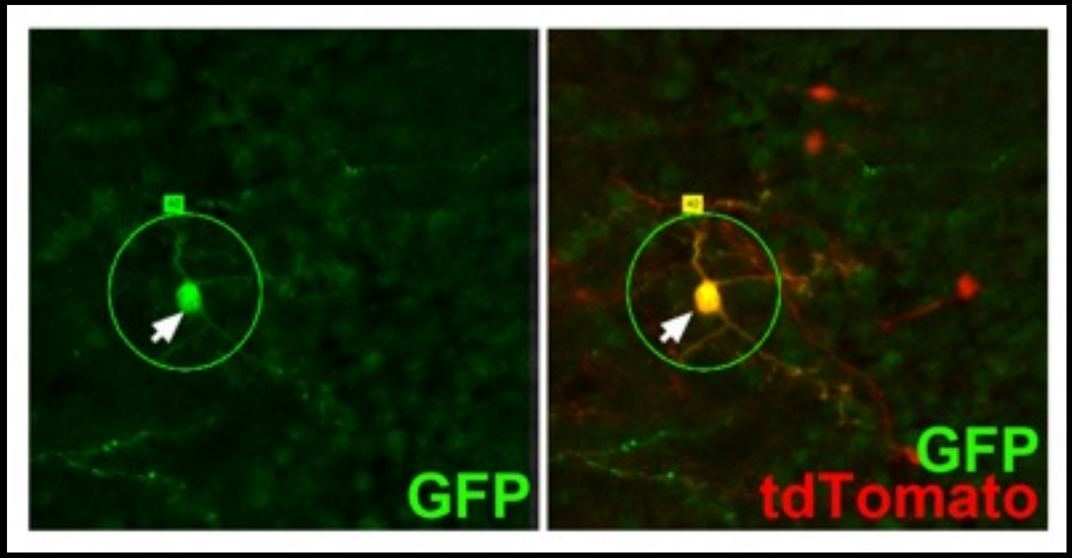




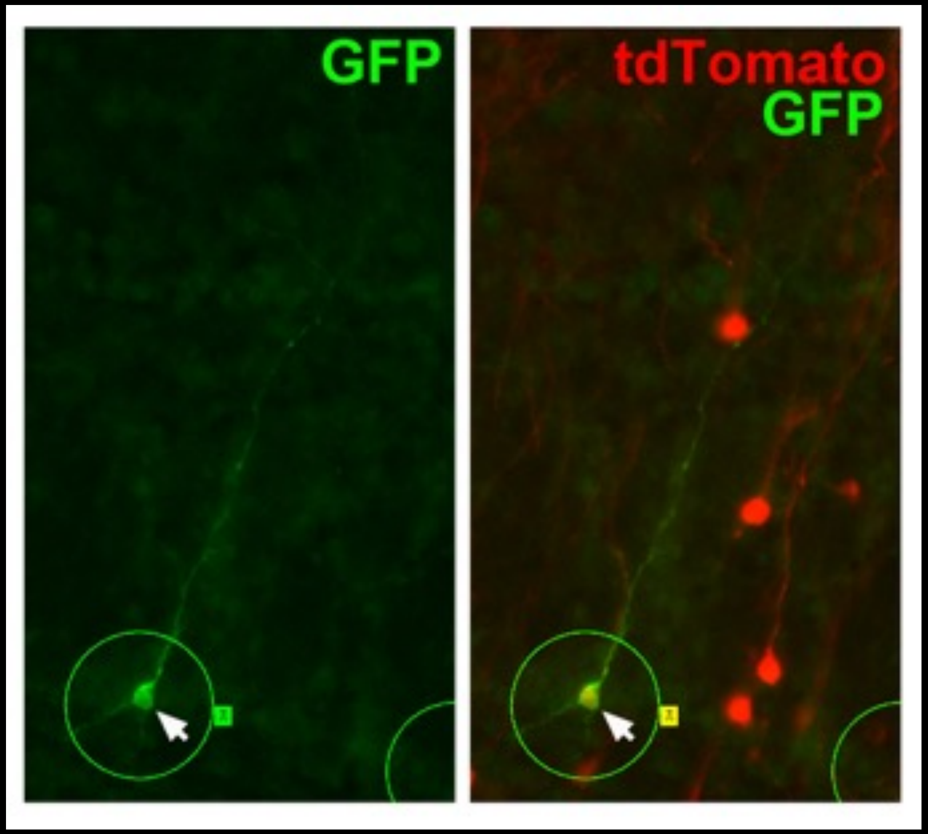
1. mapping
2. laser micro-dissection
3. amplification
4. sequencing
TCTGACACACAGTGAGTAGATCAC
0
5. clustering
LF_2442_ TAGATCTGAGTCACACTCTCAGAGACAGAGTAGAT
LF_2436_ TAGATCTGAGTCACACTCTCAGAGACAGAGTAGAT
LF_2428_ TAGATGTGAGAGTGAGTGAGACTGTGTGAGTAGAT
barcode

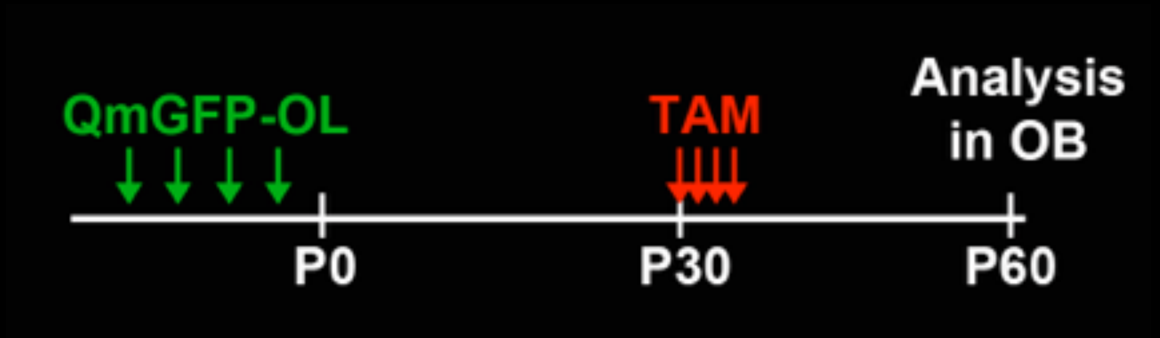
Tracing of Embryonic NSCs into Adulthood
Adult GFP+-tdTomato+-OB neurons

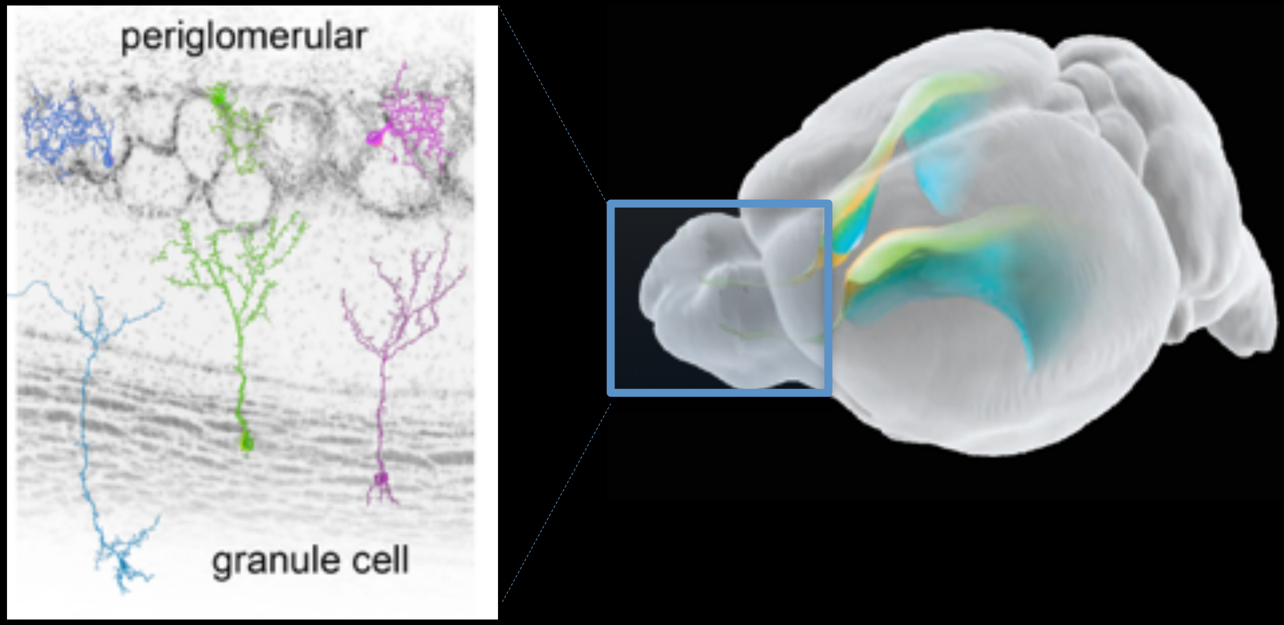
Periglomerular neurons



Granule neurons







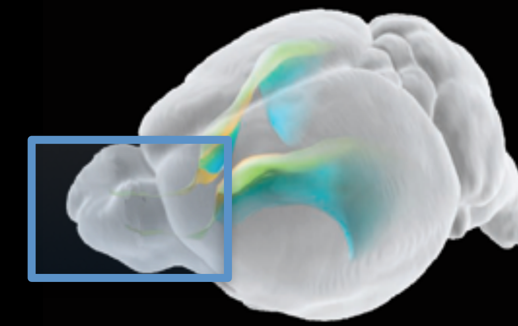
Olfactory bulb

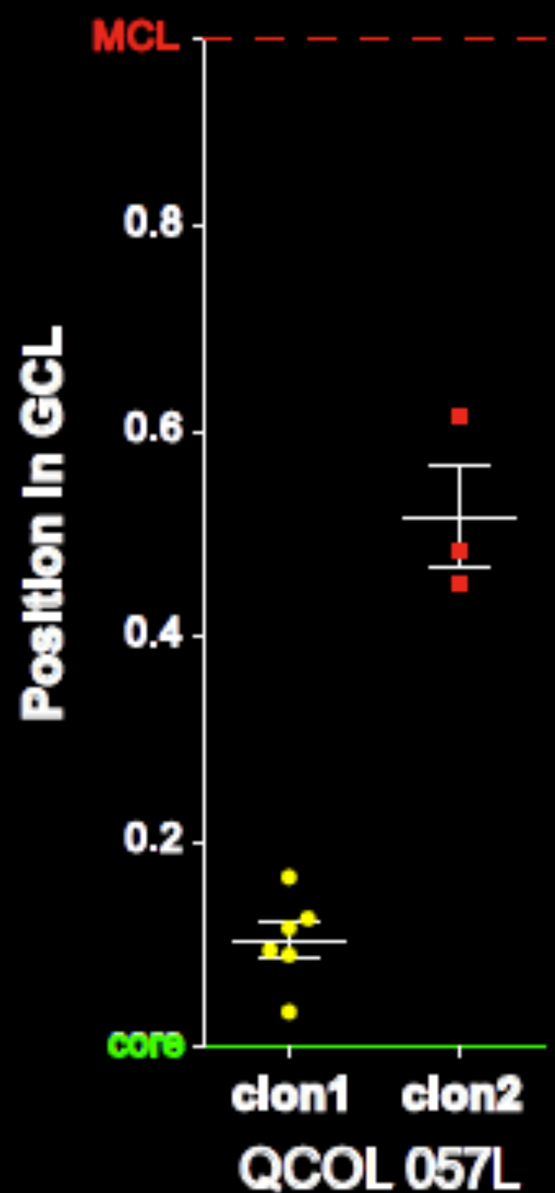
QmGFP-OL injected from E11.5 to E15.5

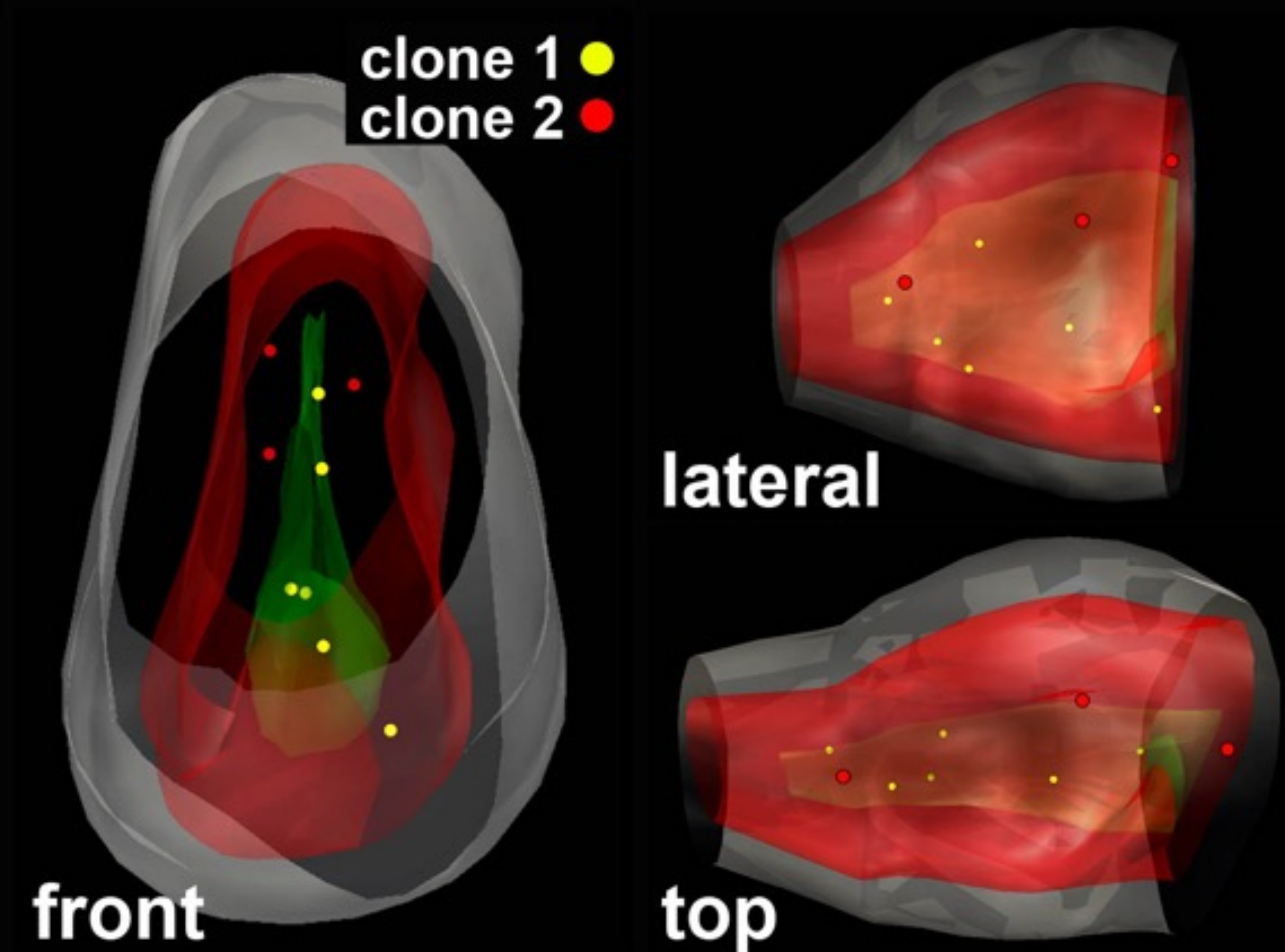
Adult-generated neurons (specified clones)

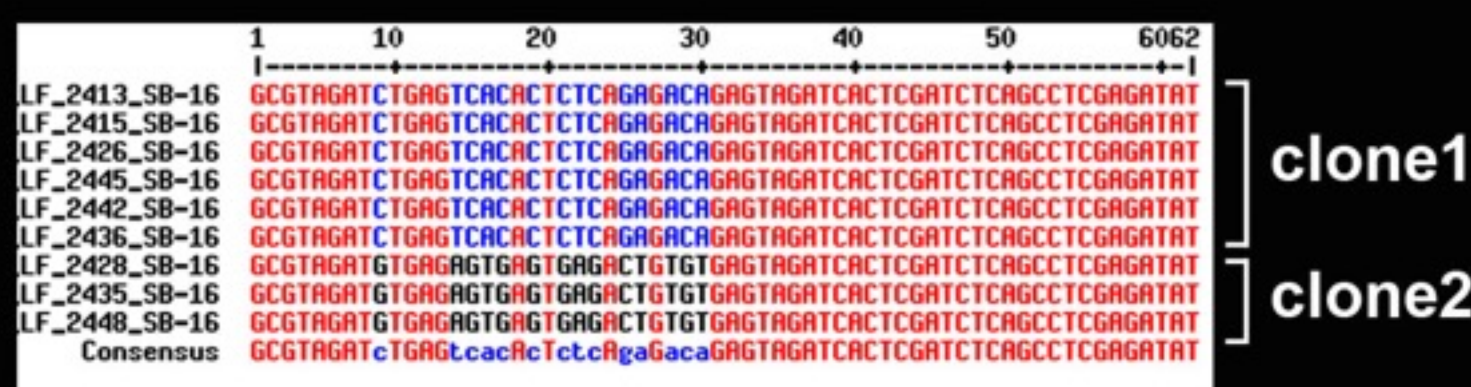
QmGFP-OL injected at E13.5

with Neurolucida v10

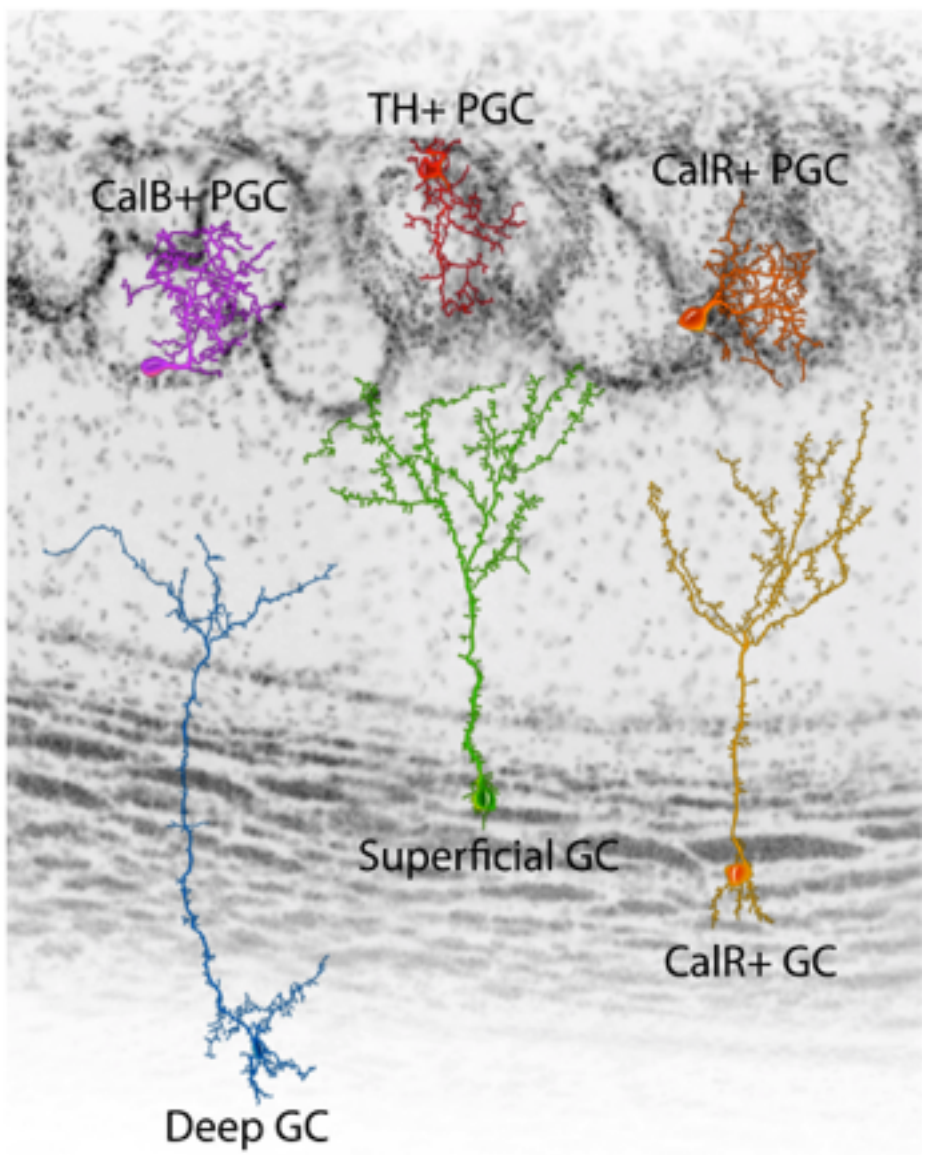


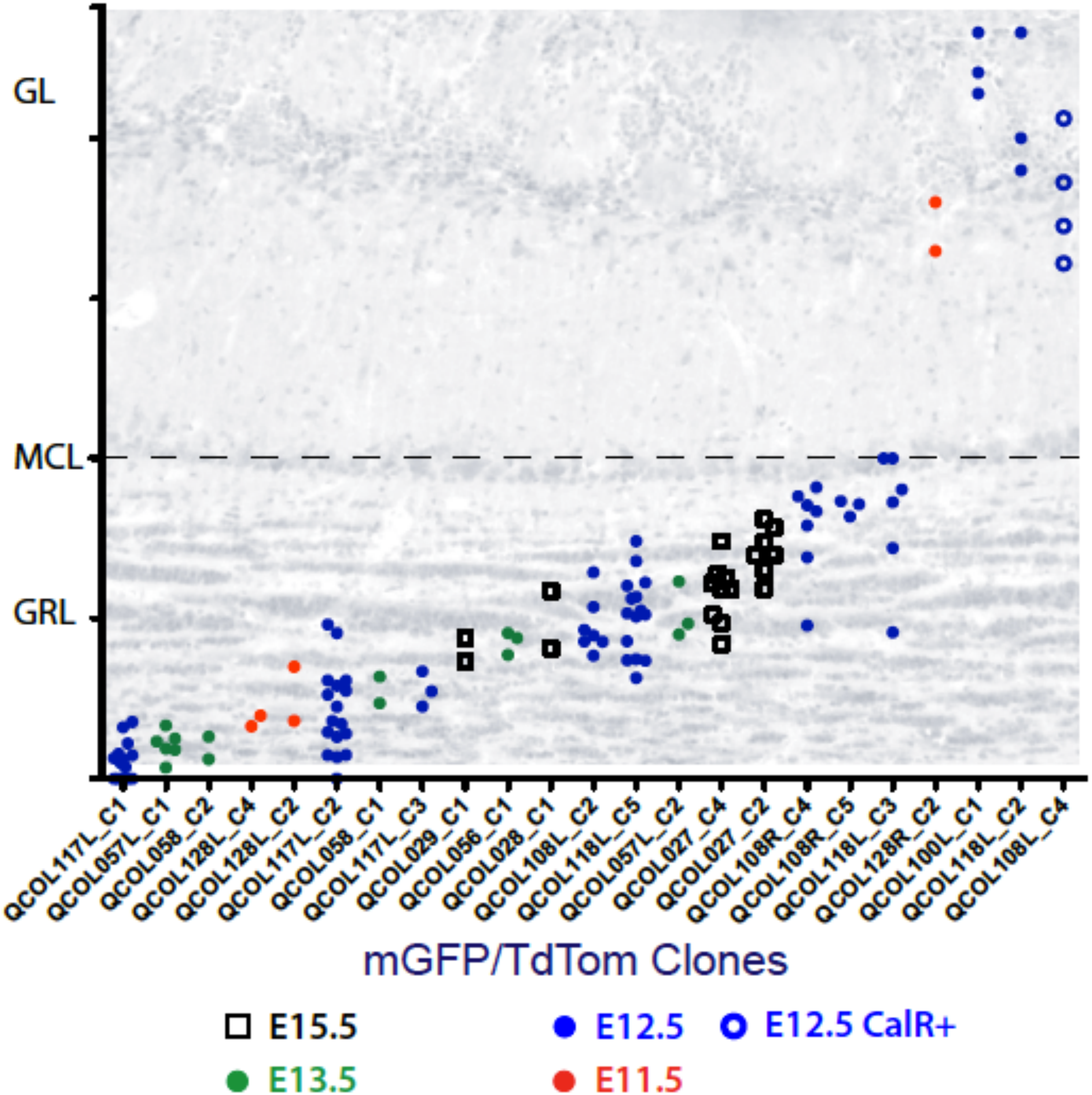




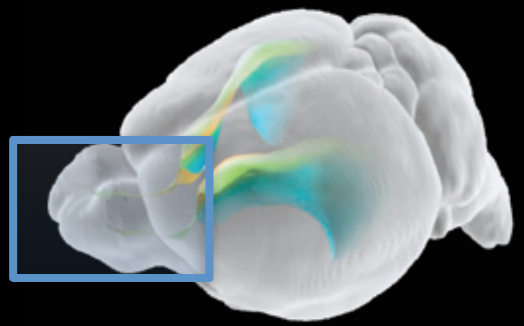


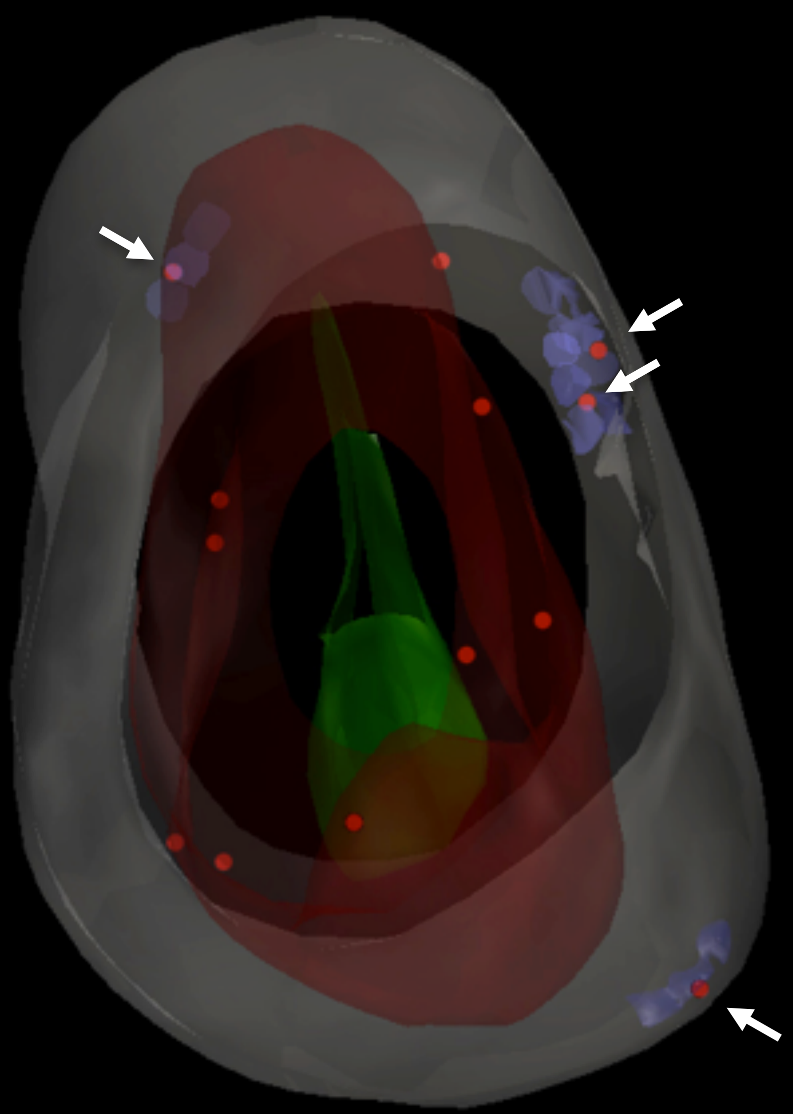
Adult-generated neurons are finely specified (as early as E11.5)

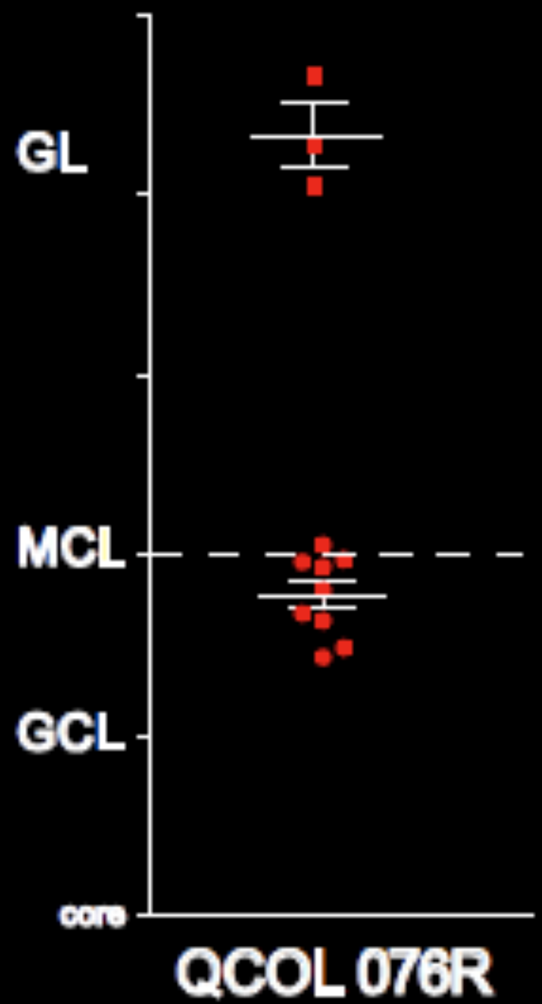


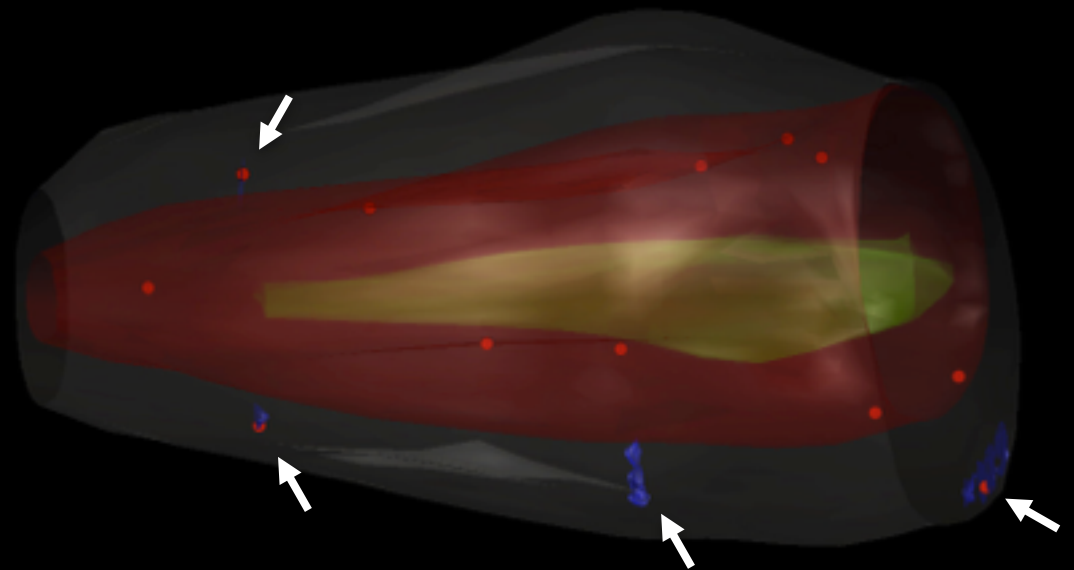


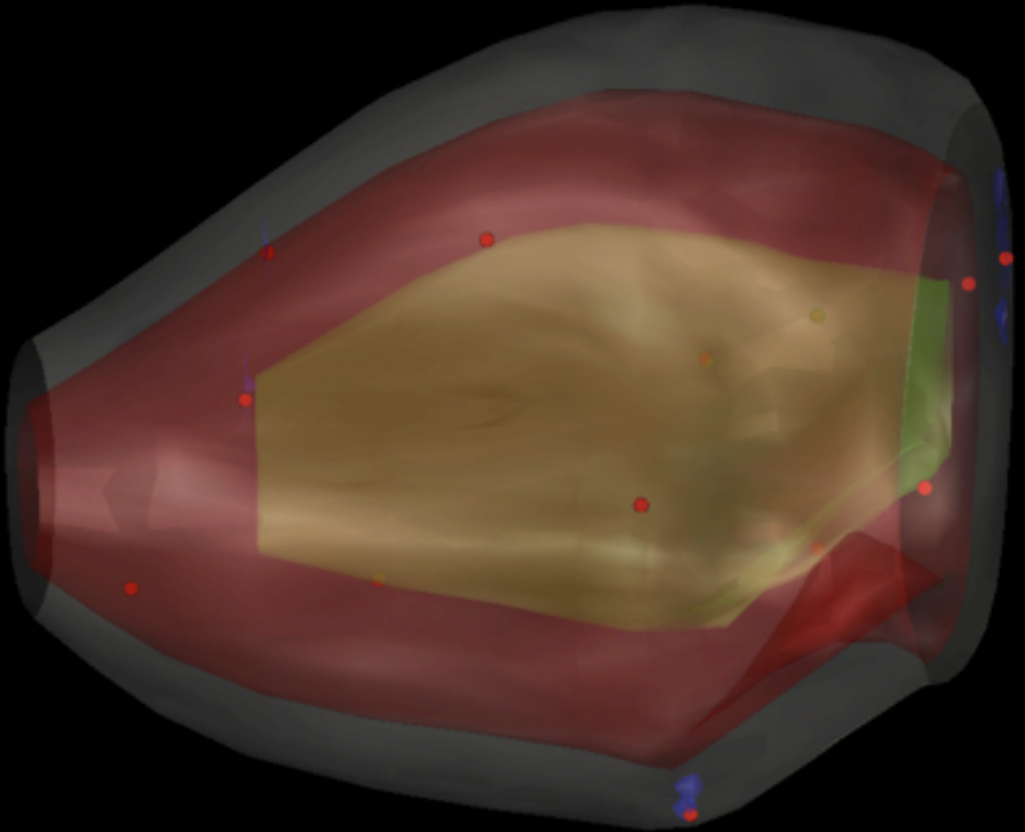
Adult-generated neurons (mixed clones)









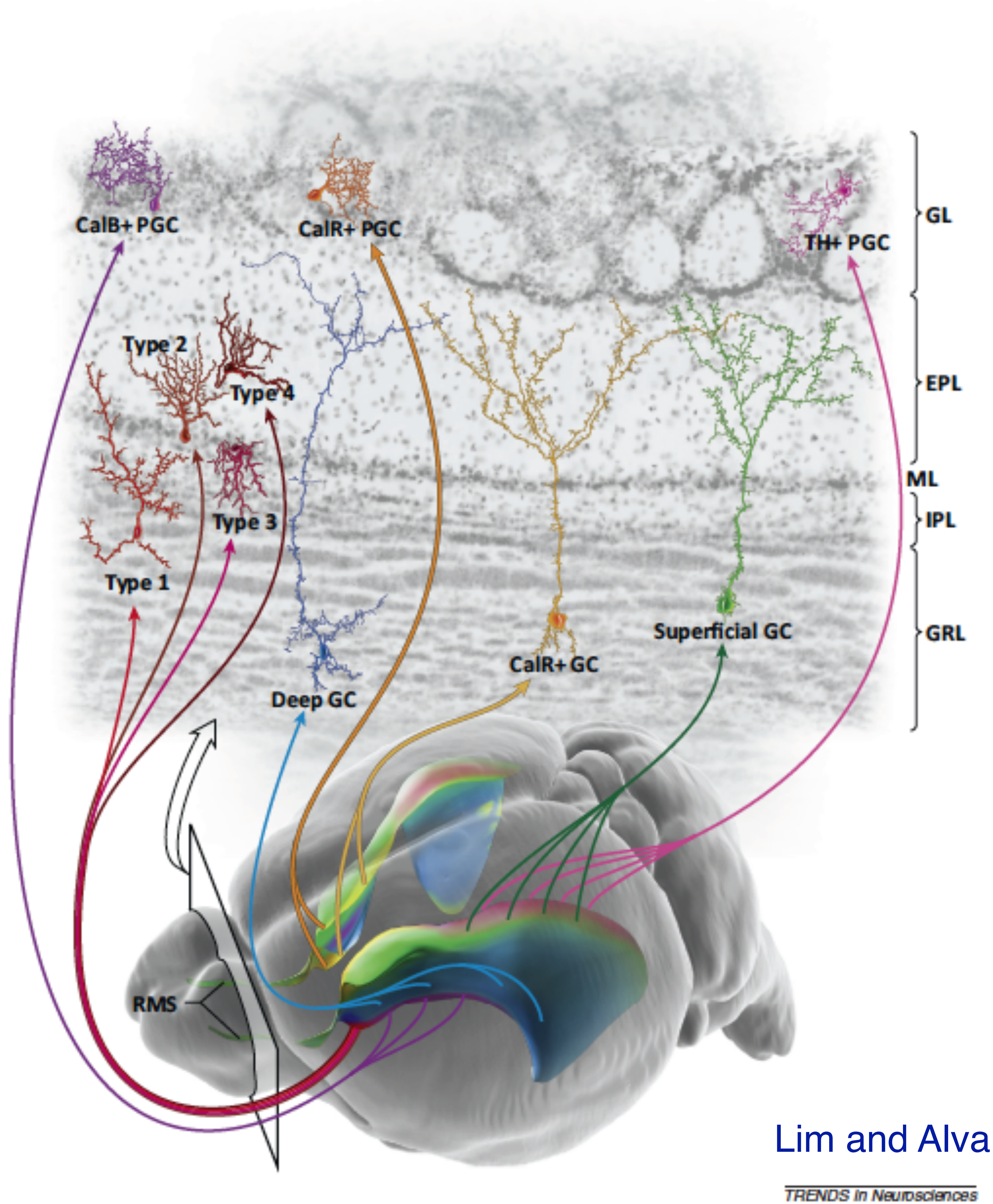


QmGFP-OL injected at E13.5

with Neurolucida v10

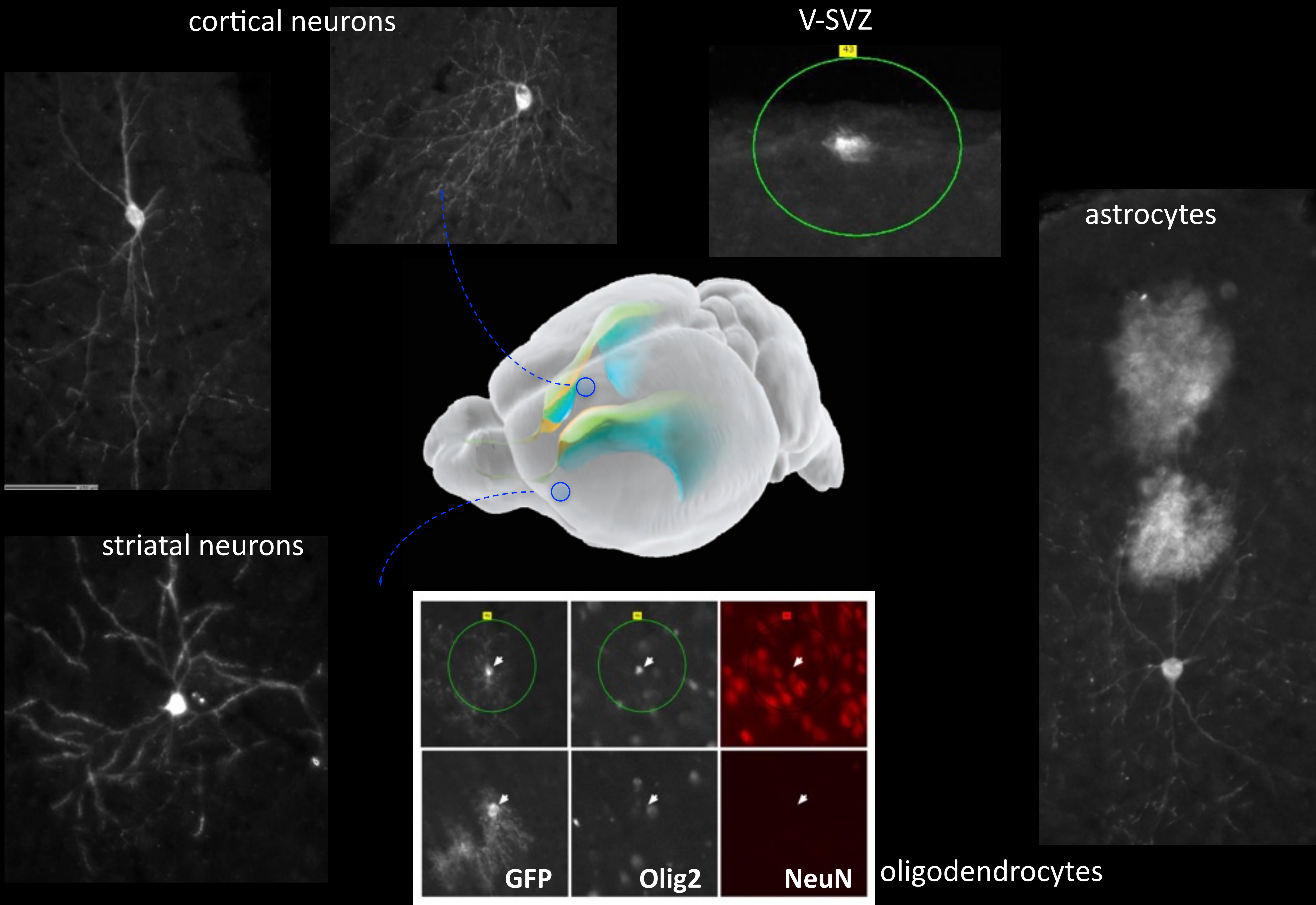
- Postnatal neural stem cells (NSC) become regionally-specified very early development.

Fuentealba et al., 2015

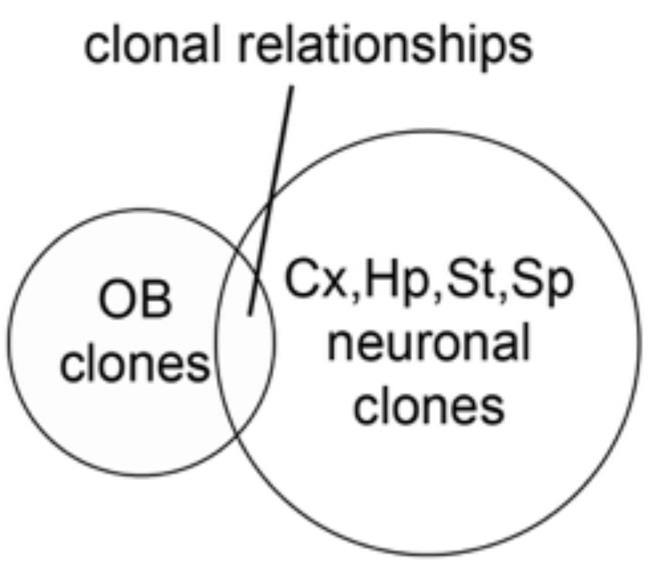


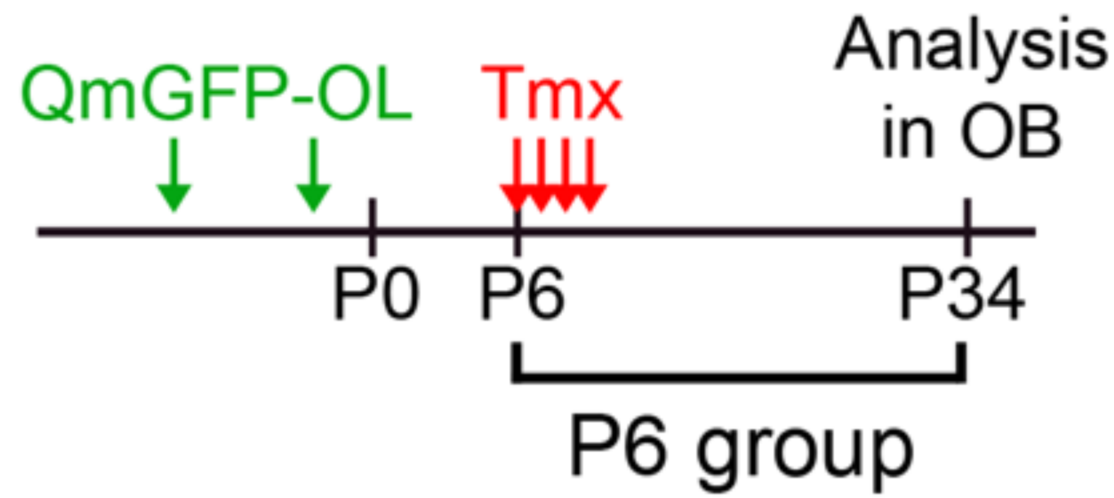
Lim and Alvarez-Buylla, 2014

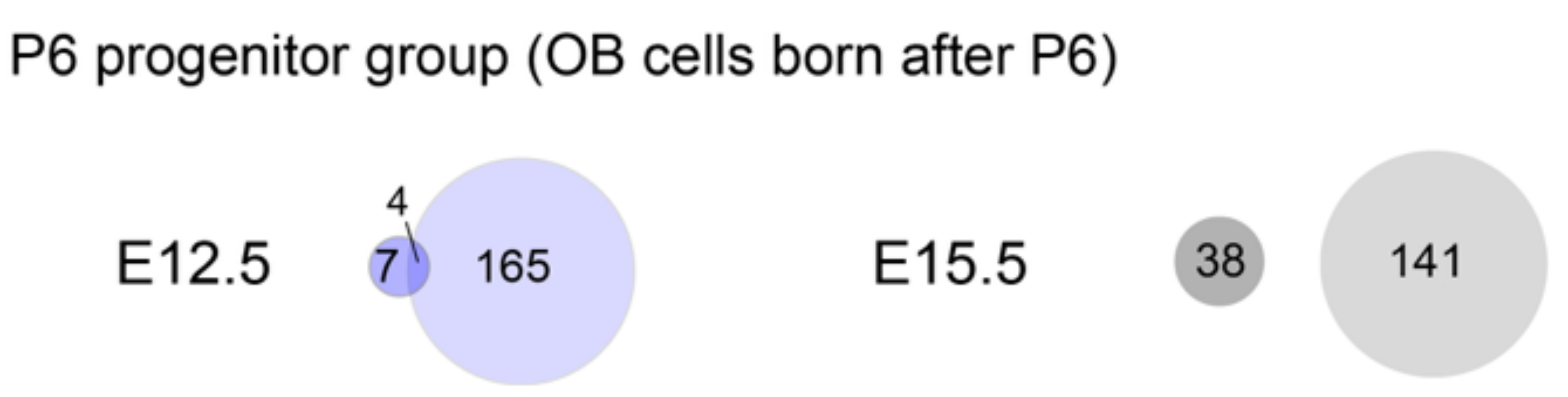
Tracing of embryonic NSCs into adulthood
GFP+-cells in the forebrain



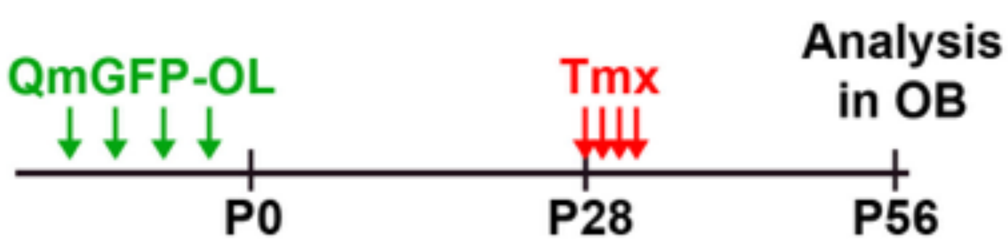
Born After P6 (GFP+ Ai14+)—Lineage relationship Between Neurons in the OB and other Forebrain Regions

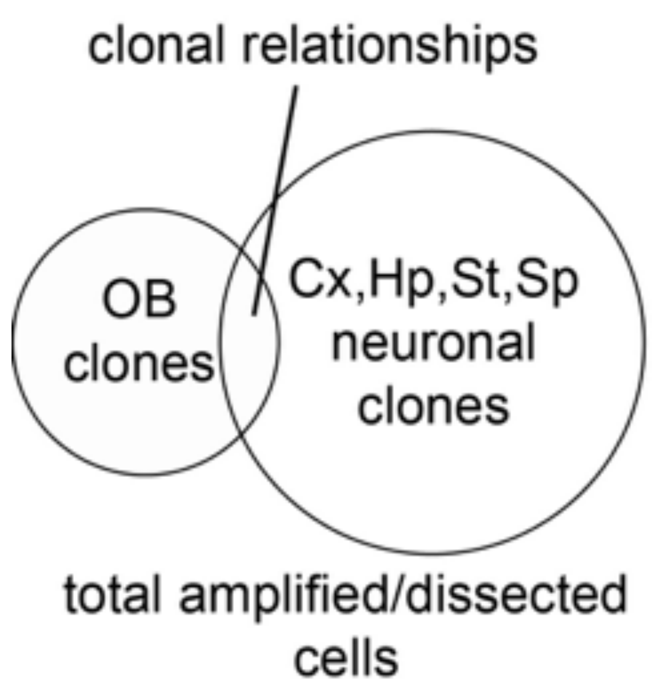


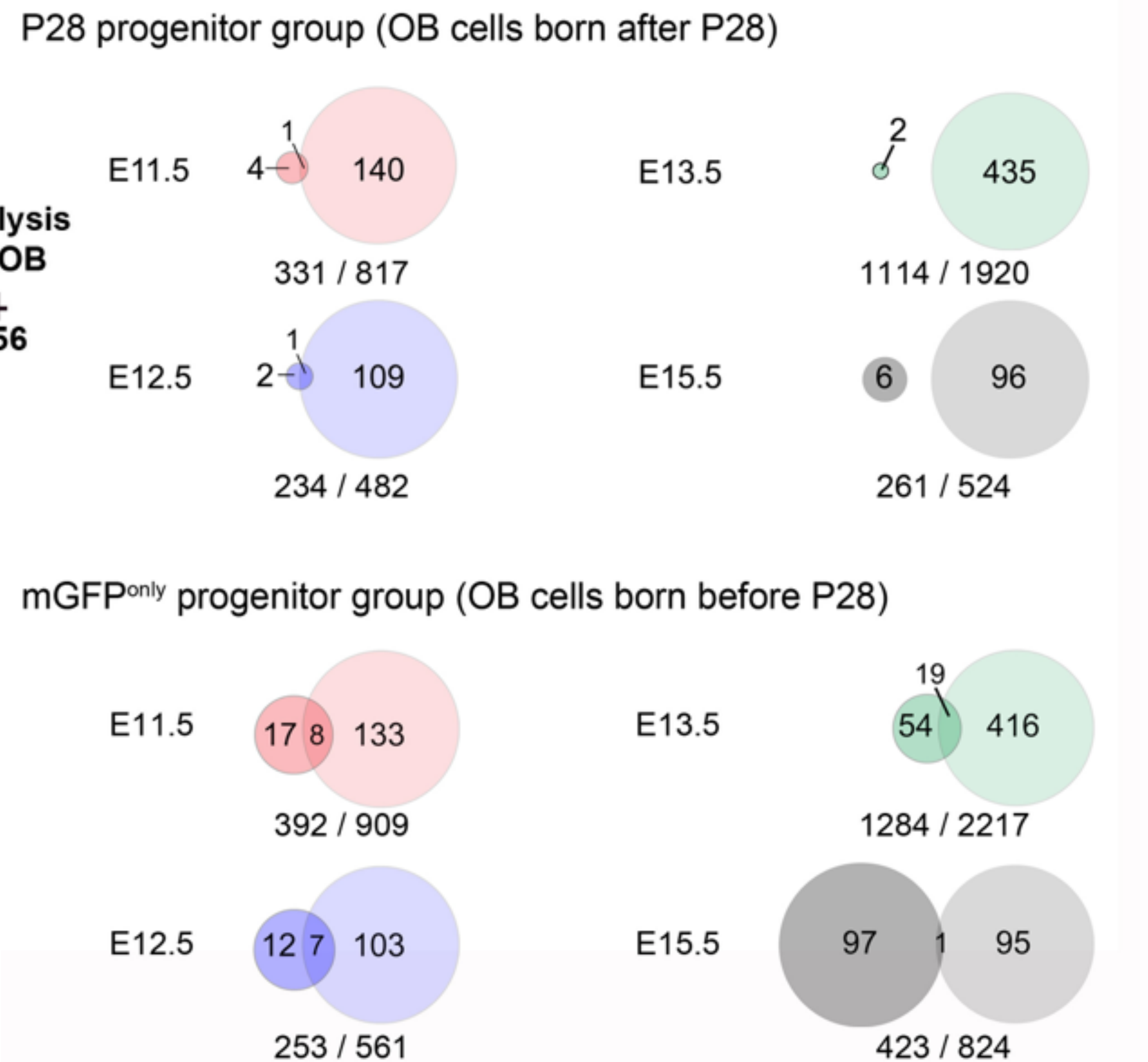




Lineage Relationship Between Neurons in the OB and other Forebrain Regions: After or Before P28



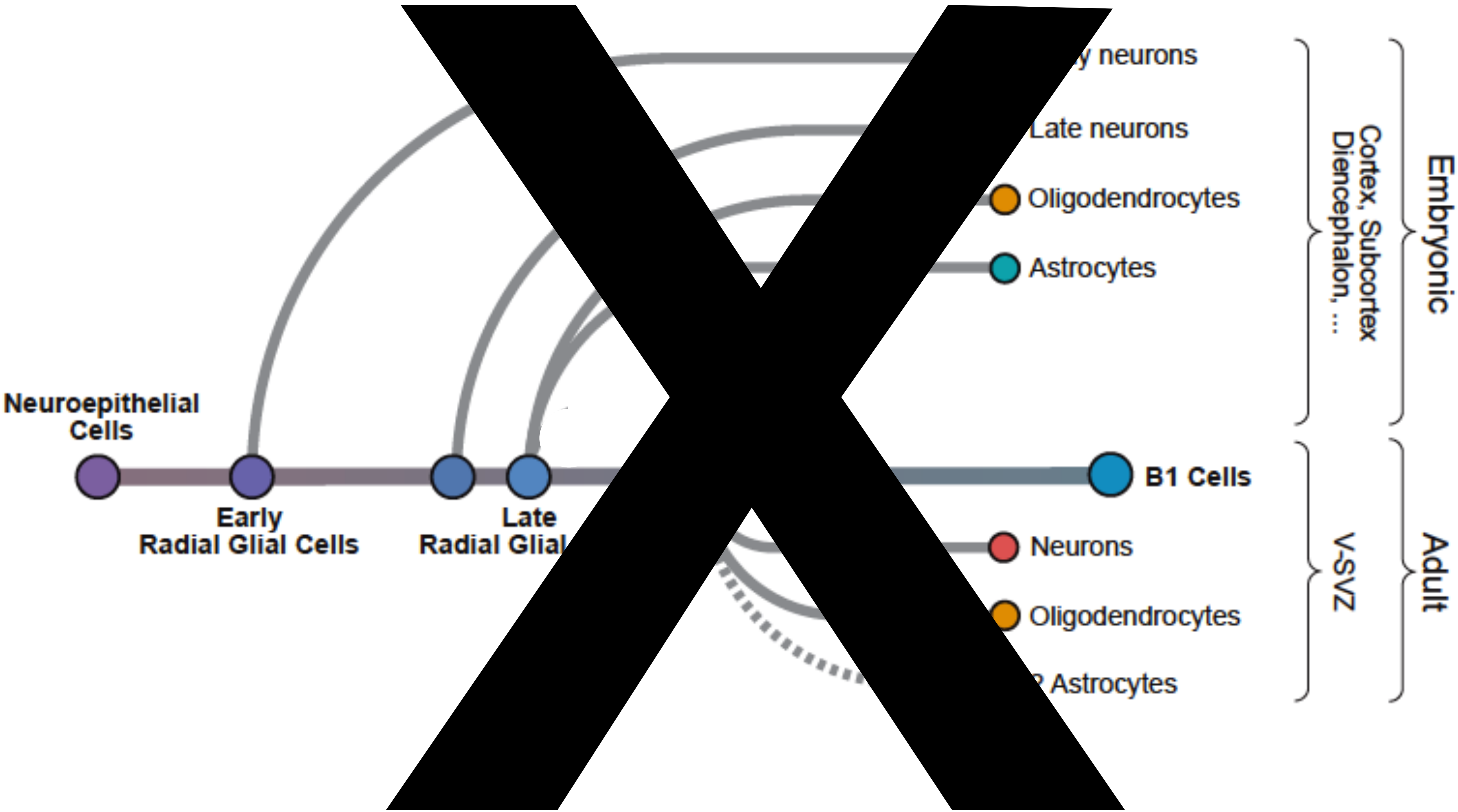




- Postnatal and fetal forebrain NSCs share common progenitors in the early embryo, but these two lineages diverge between P13.5 - P15.5.

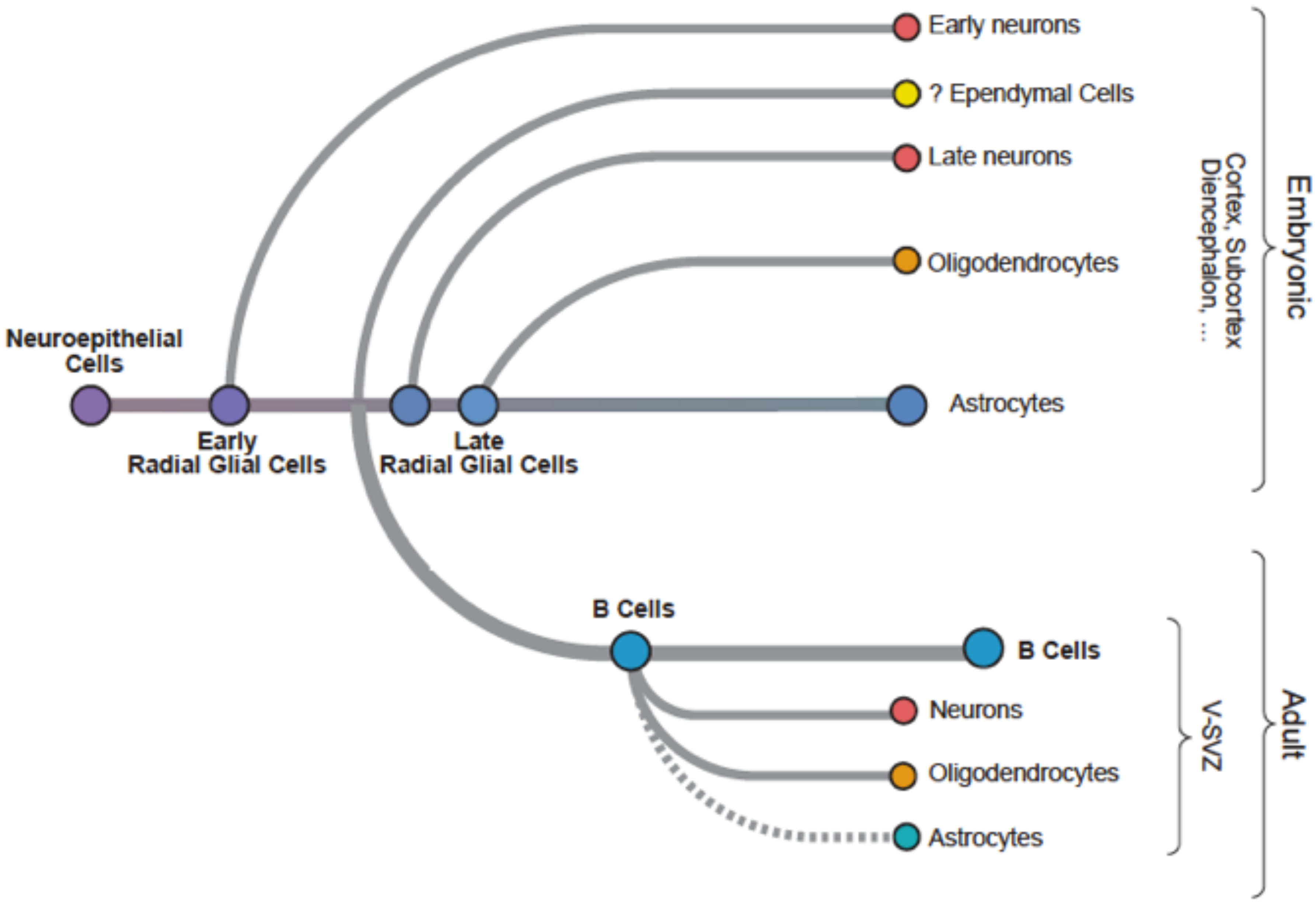
Fuentealba et al., 2015

The NSC lineage in development



Alvarez-Buylla et al., 2001.
Kriegstein and Alvarez-Buylla, 2009.

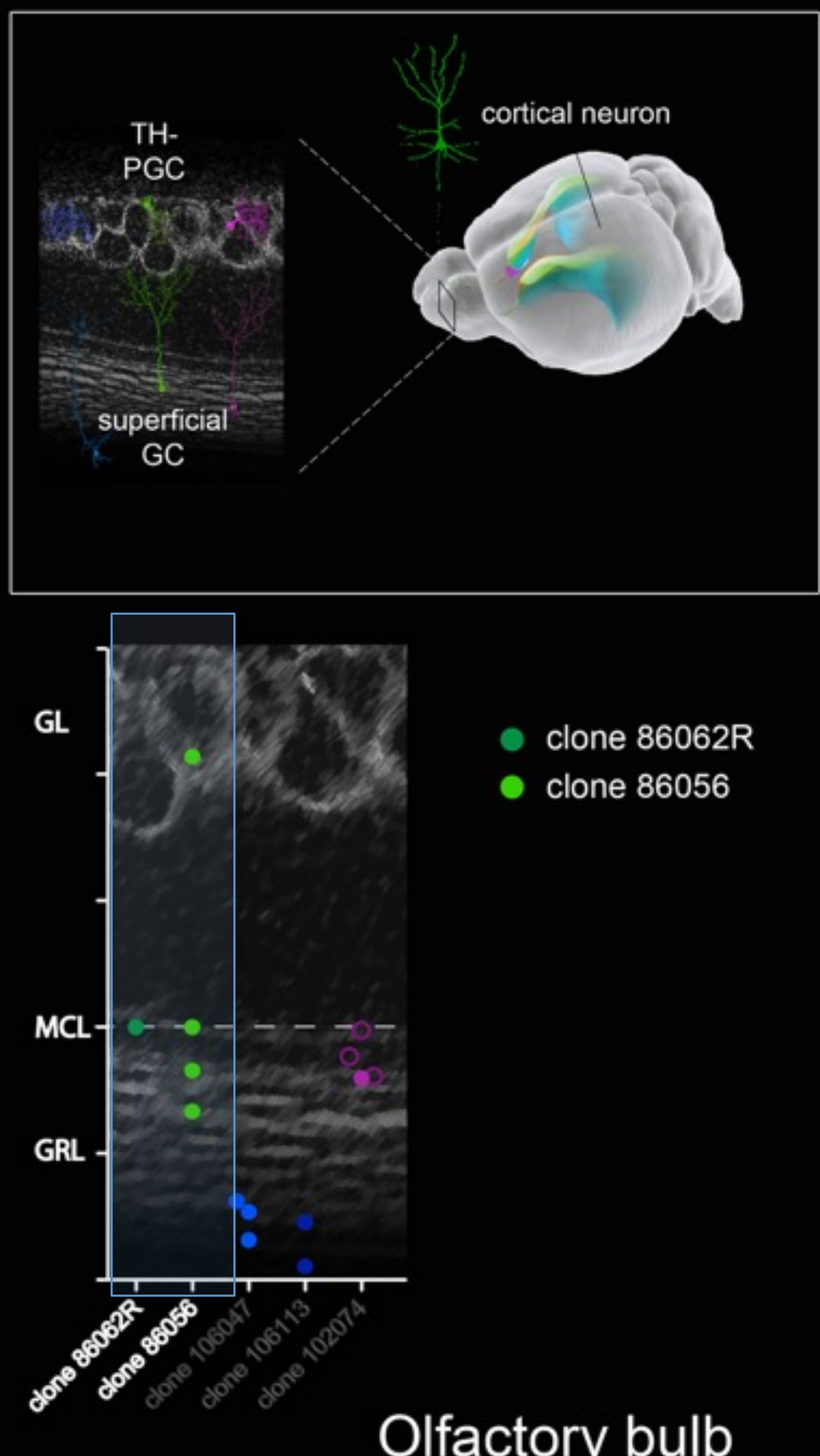
Separate origins of adult NSCs

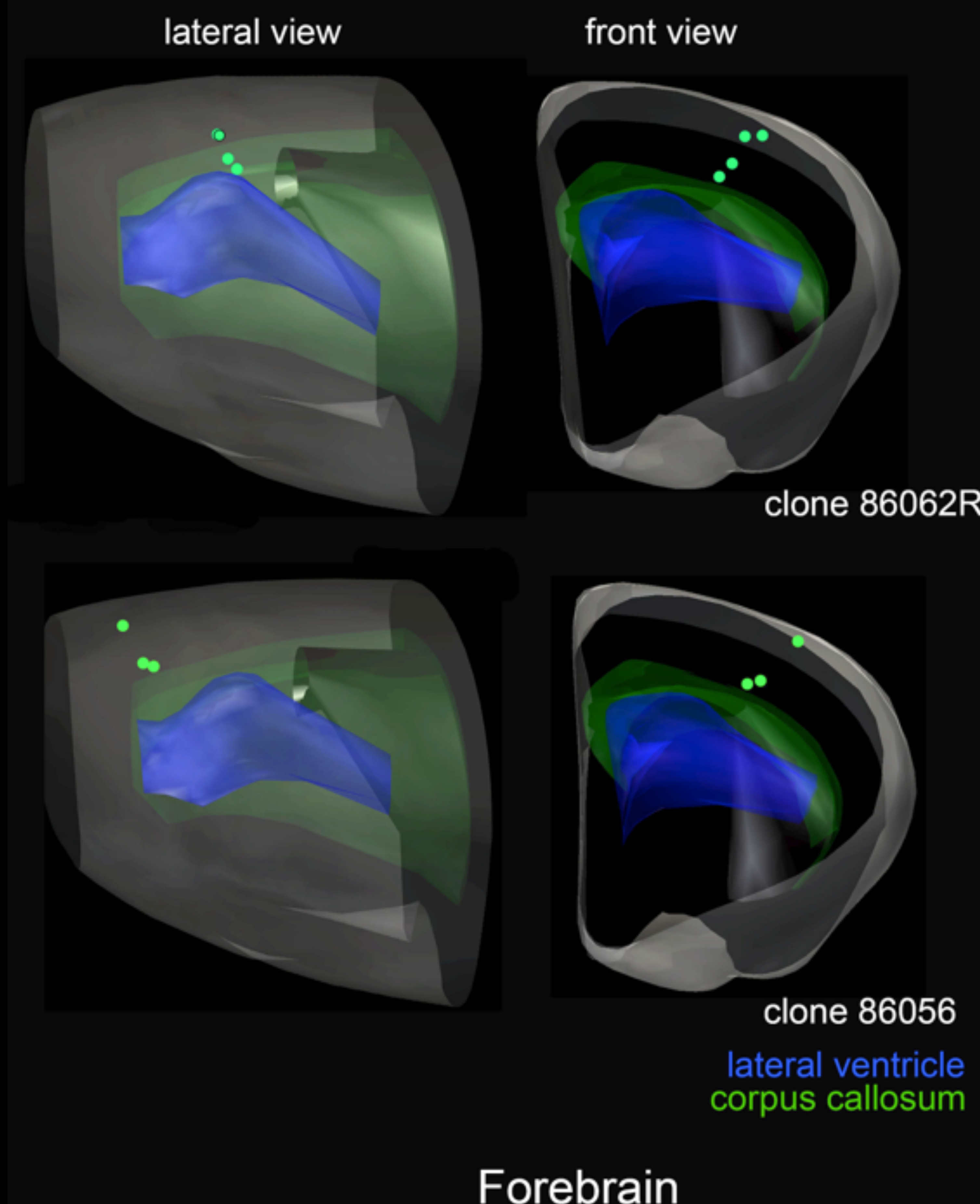


- Postnatal and fetal forebrain NSCs share common progenitors in the early embryo, but these two lineages diverge between P13.5 - P15.5.

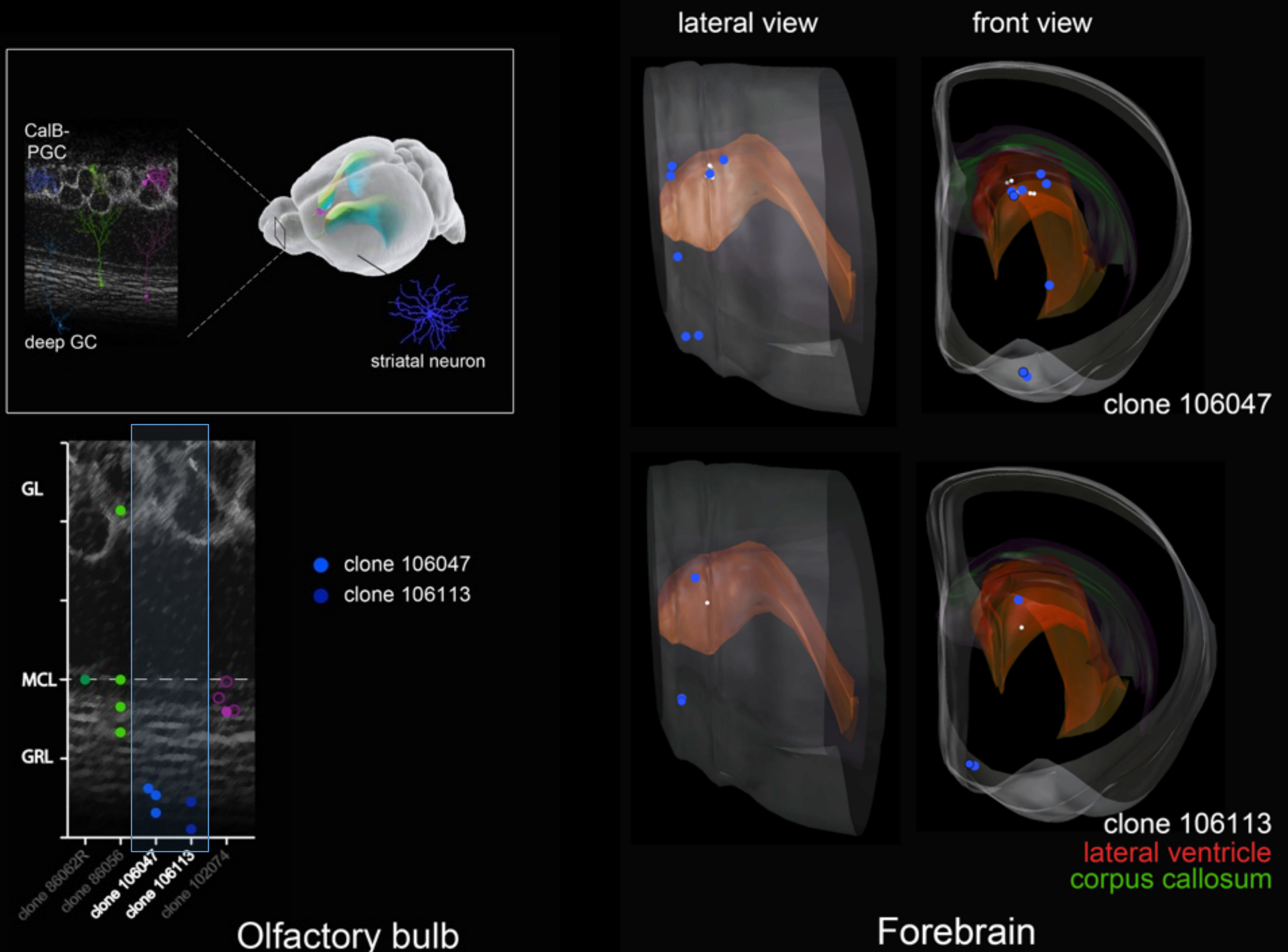
Fuentealba et al; 2015

Sibling relationships between cortical/superficial GC neurons

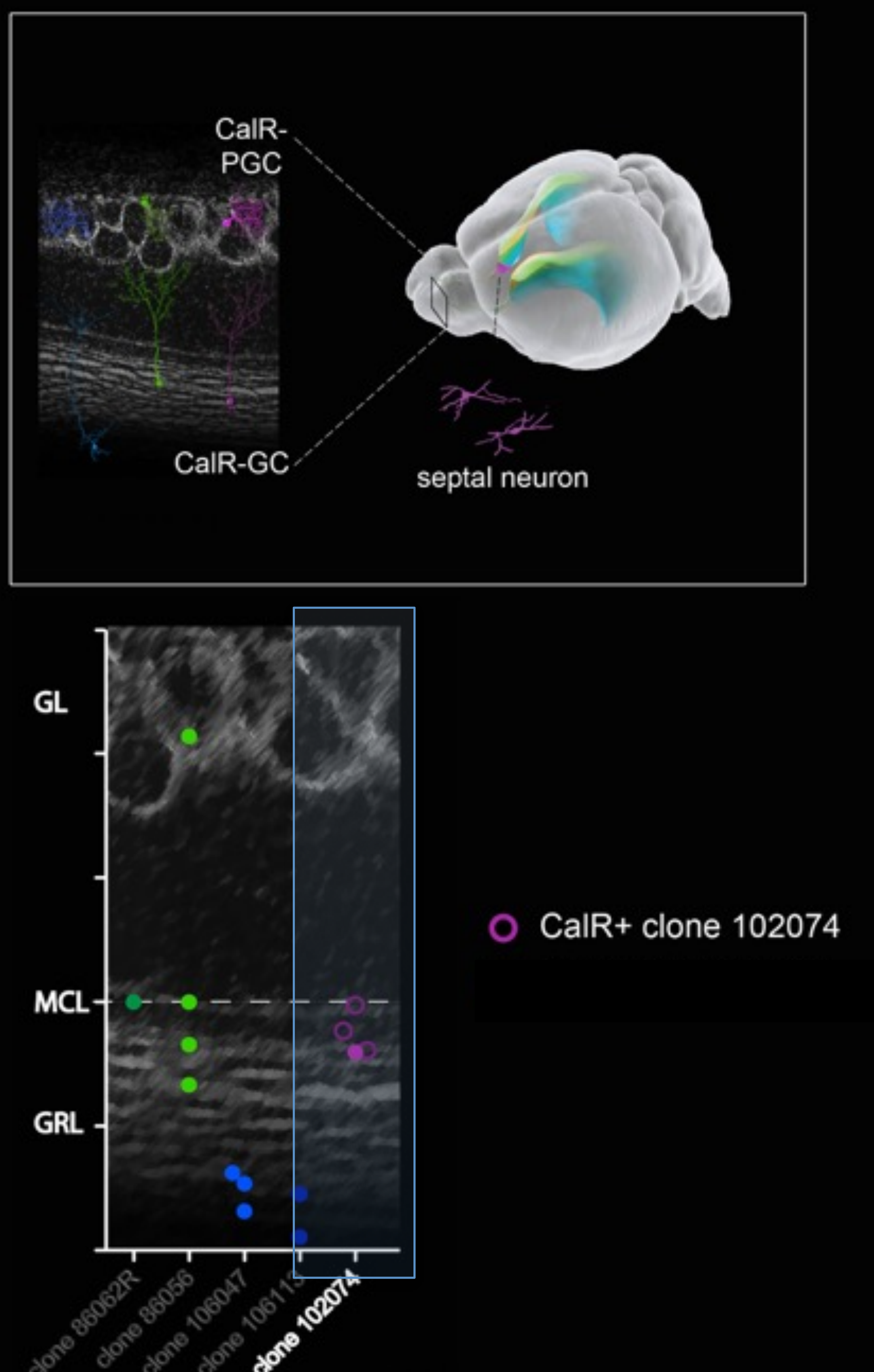




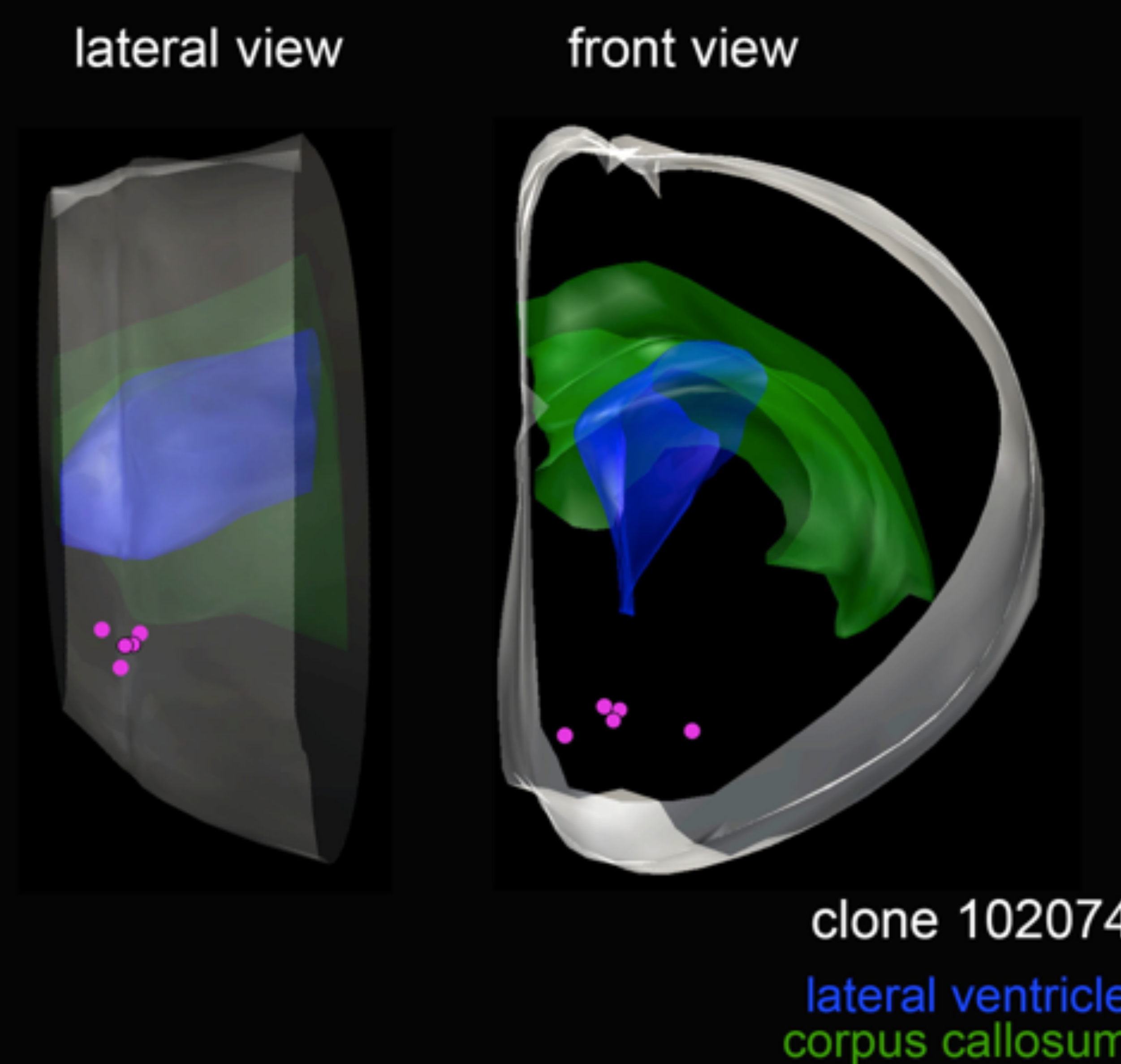
Sibling relationships between striatal/deep GC neurons



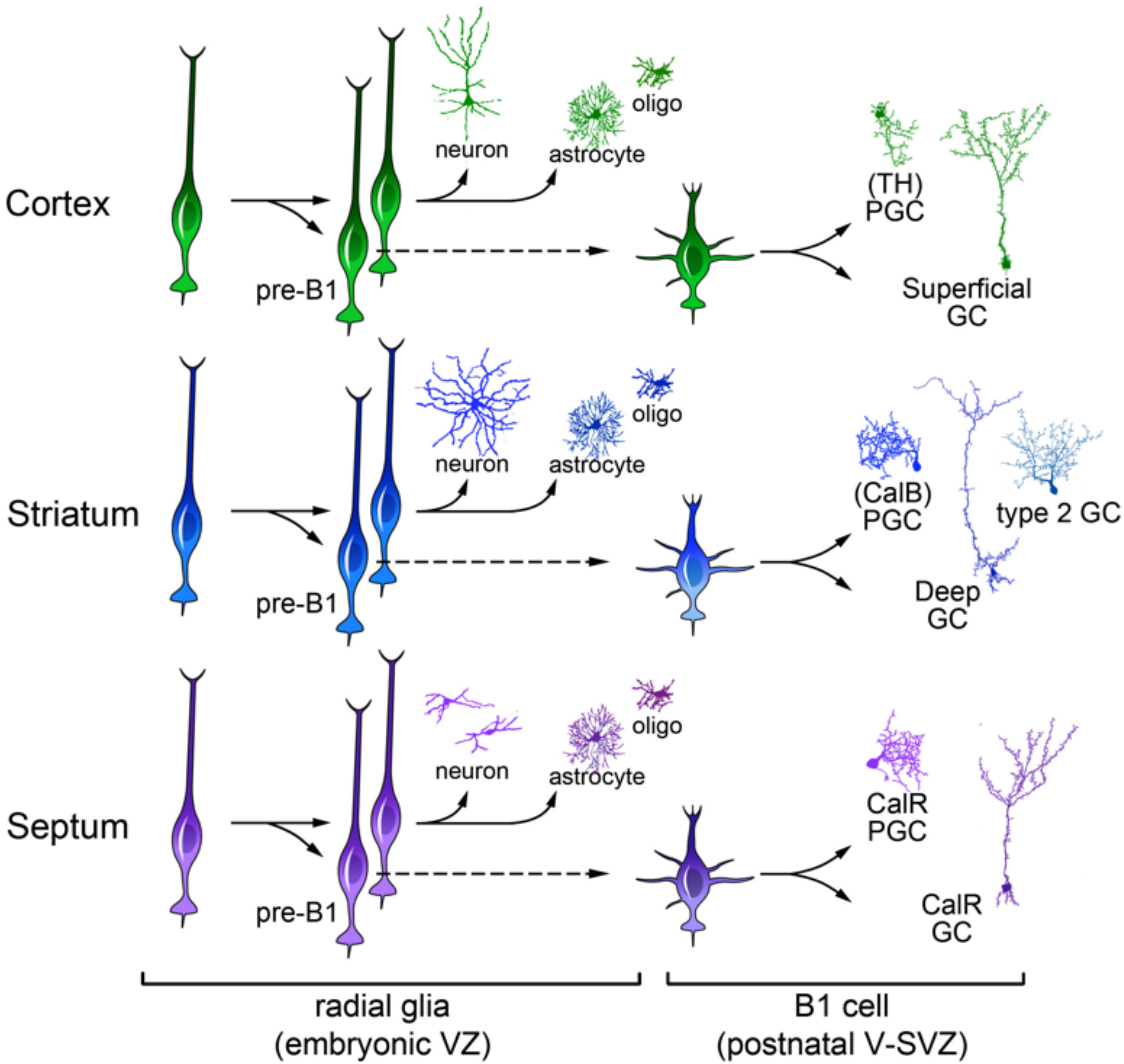
Sibling relationships between septal/CalR^{+} GC neurons



Olfactory bulb



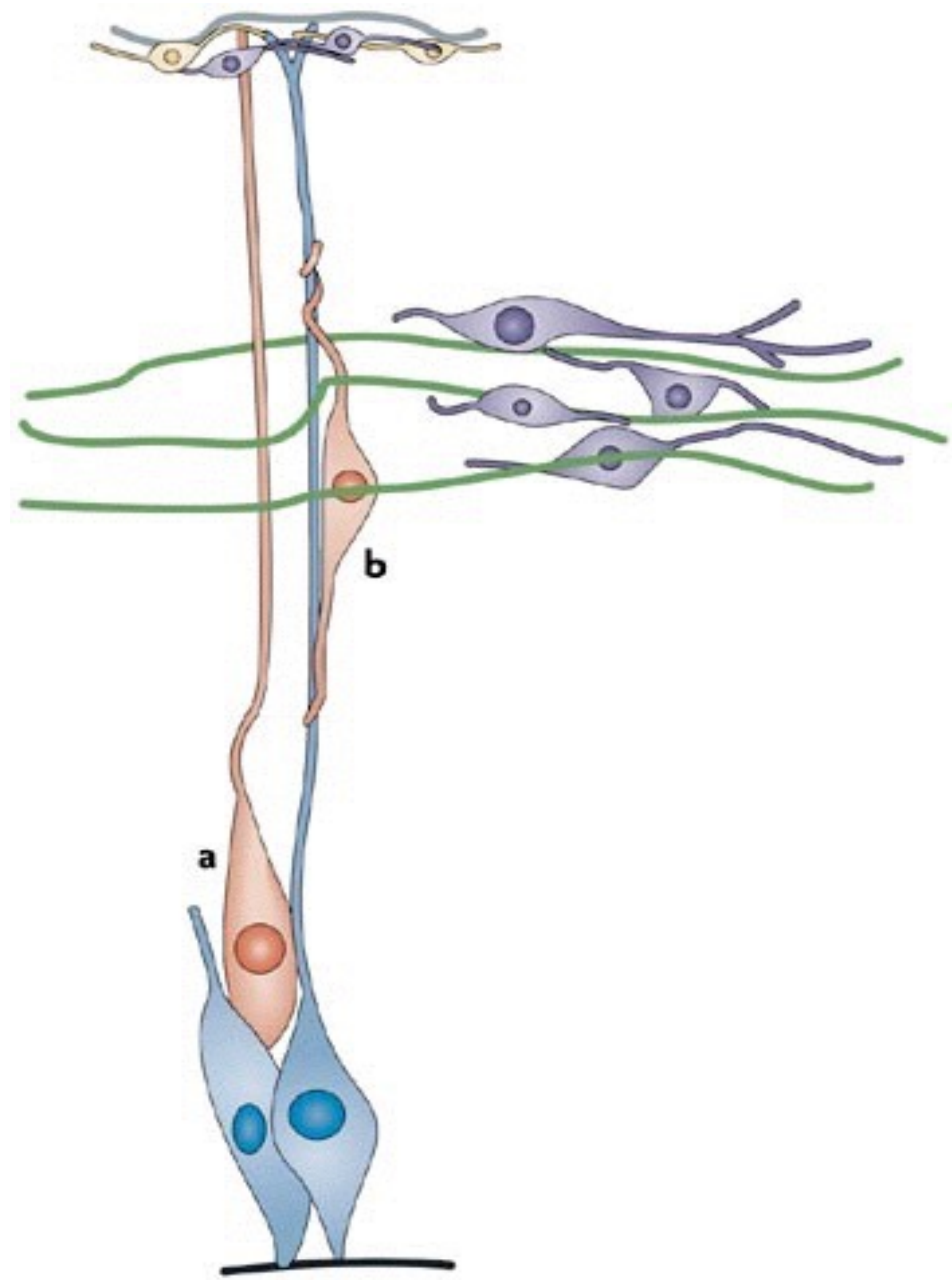
Forebrain


Cortex
Striatum
Septum
pre-B1
pre-B1
pre-B1
neuron
astrocyte
oligo
neuron
astrocyte
oligo
neuron
astrocyte
oligo
(TH)
PGC
Superficial
GC
(CalB)
PGC
type 2 GC
Deep
GC
CalR
PGC
CalR
GC
radial glia
(embryonic VZ)
B1 cell
(postnatal V-SVZ)

- Neuronal Migration: Two basic orientations.

- Radial

- Tangential



Ghashghaei *et al. Nature Reviews Neuroscience* 2007

Nature Reviews | Neuroscience