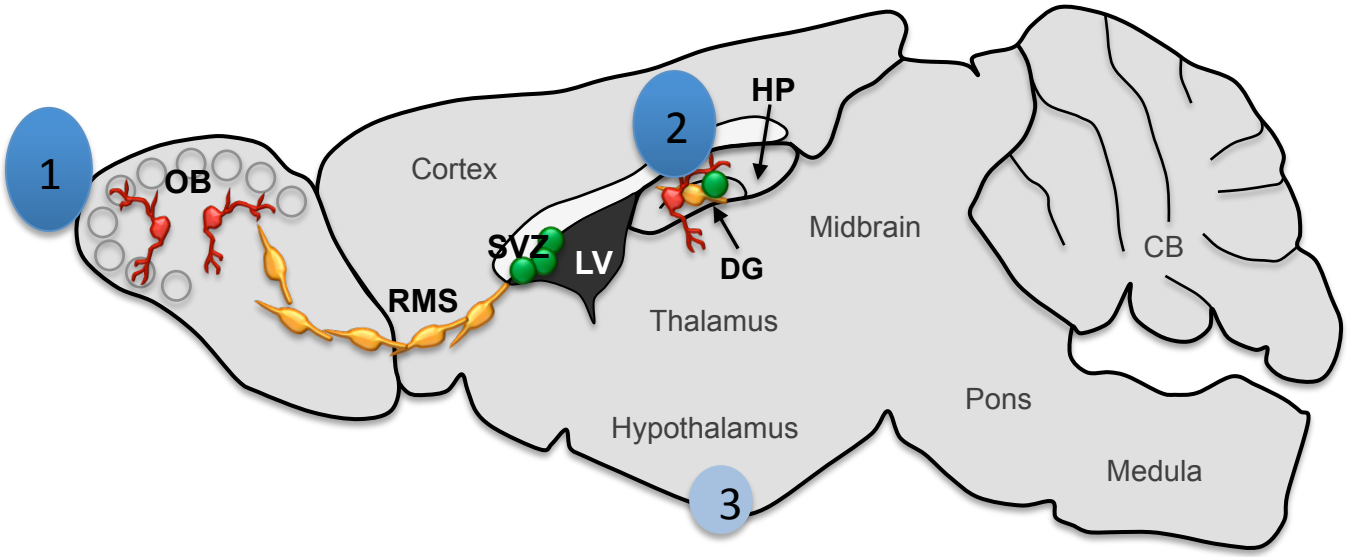
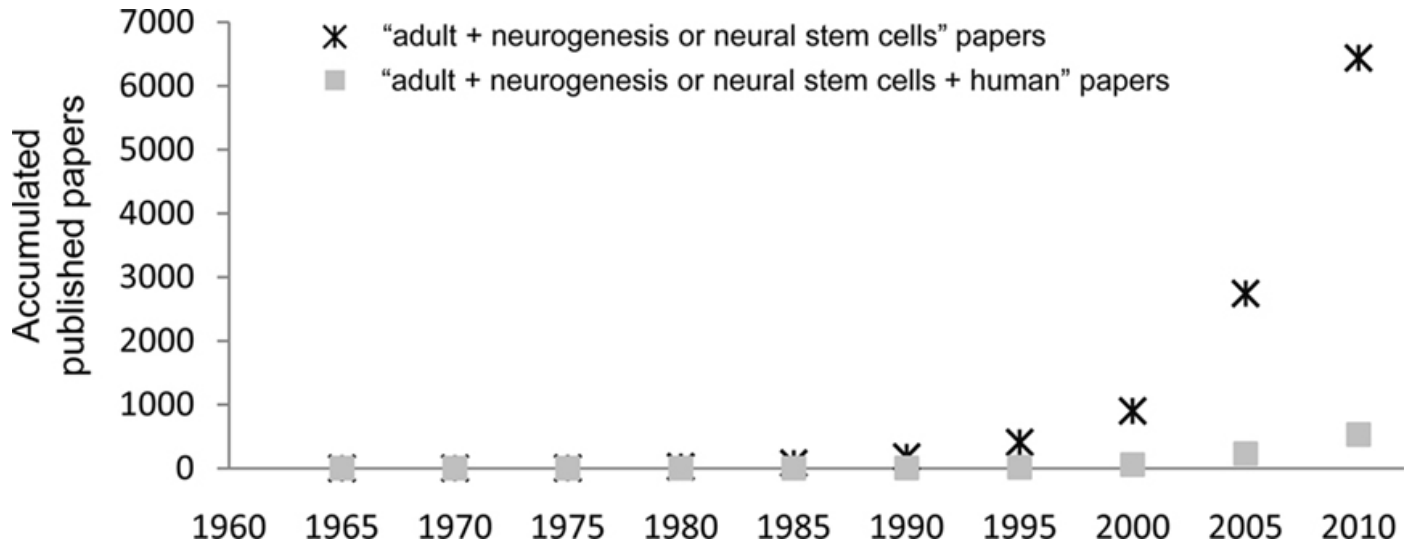
Main sites of Adult Neurogenesis in the rodent brain (physiological conditions)



Active neurogenesis= a process that **generates functional neurons** from neural progenitor and/or stem cells (NPCs), occurs throughout life in discrete brain regions of all mammals, including humans

Adult neurogenesis recapitulates the complete process of neuronal development in a mature CNS environment (proliferation - fate specification of NPCs – migration – differentiation and targeting of neuron - synaptic integration – survival of new neurons)

9213 -June 2018



Published papers on adult neurogenesis per quinquennium. The graph shows the accumulated papers published from 1960 onward, searched in PubMed with the search terms "adult" AND ("neurogenesis" OR "stem cells"). The asterisks show the total number of papers, and the filled squares show those papers with the term "human" in their title.

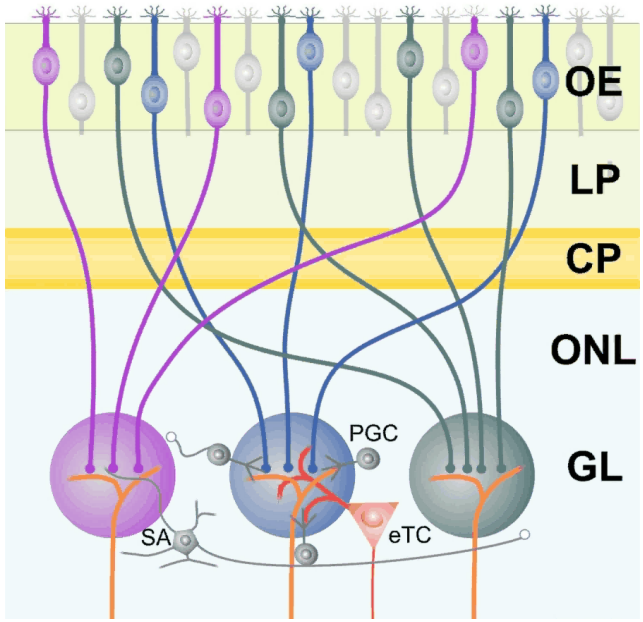
Sierra et al. Front. Neurosci. 2011

The olfactory bulb

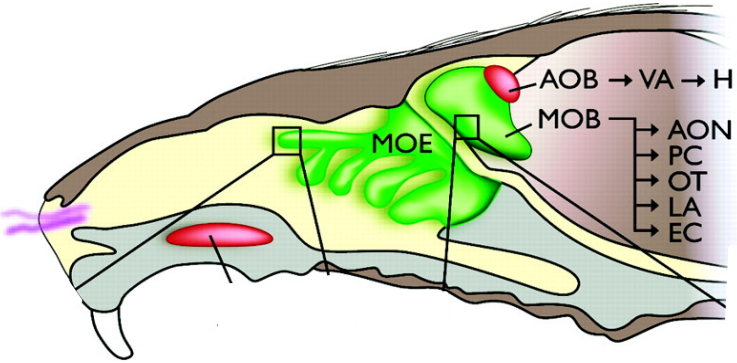
the first brain region involved in the **processing of olfactory information**

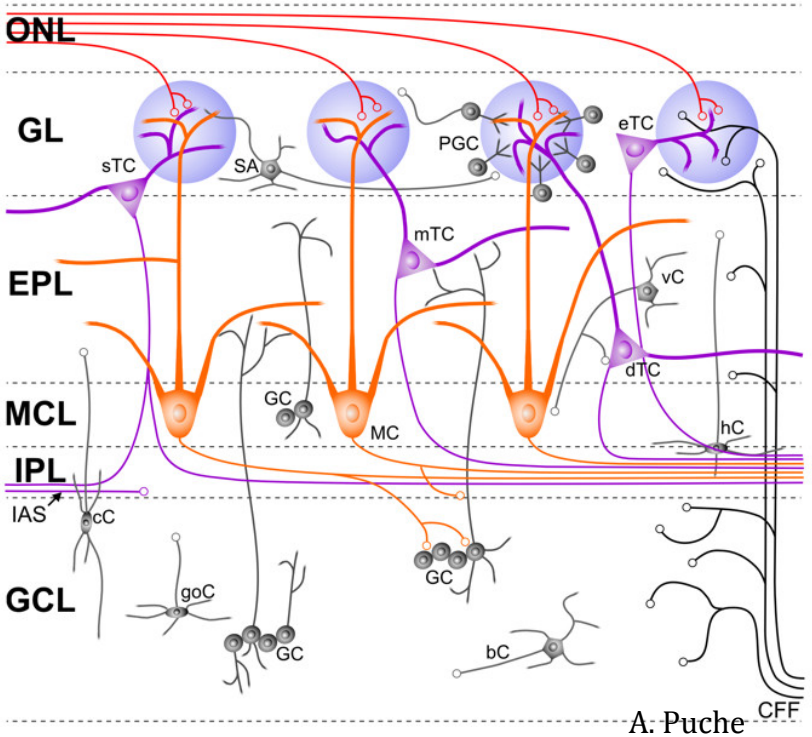
MOE

MOB



courtesy of A. Puche

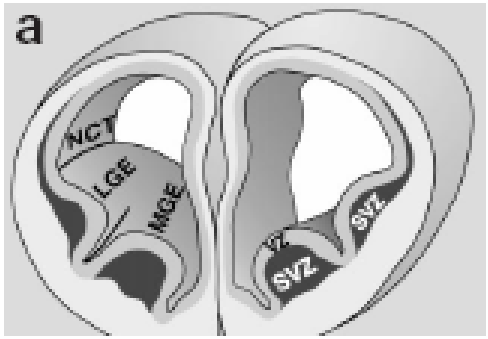




A. Puche

Lledo et al., Physiol Rev 2004

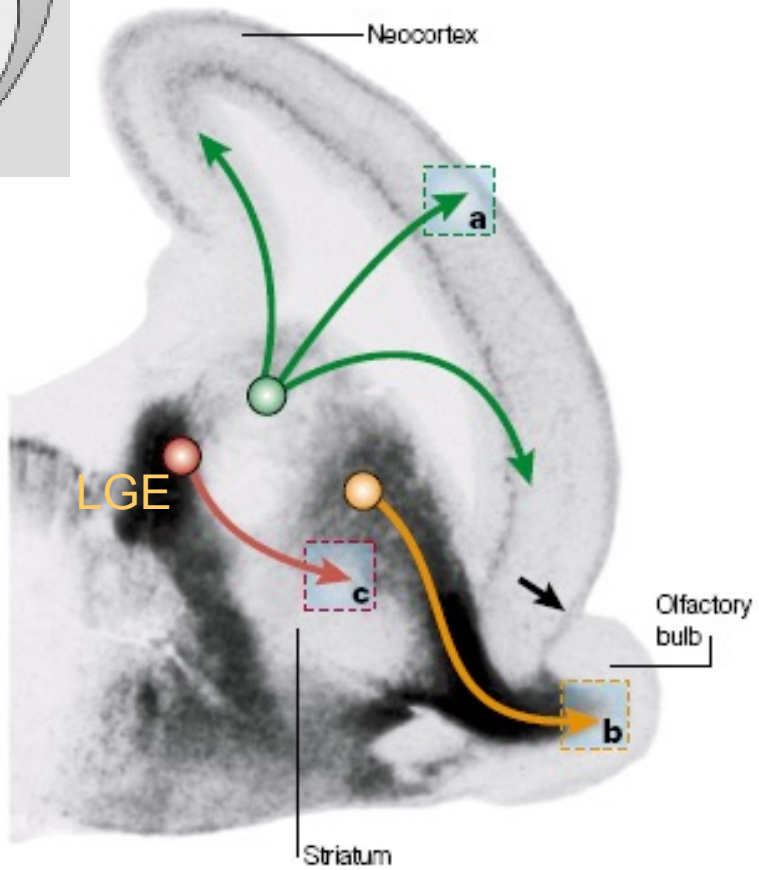
Embryonic development of olfactory bulb interneurons



Mice OB

Embryonic development (E12-E18)

1. Formation of output neurons from local progenitors
2. Migration of interneuron precursors from LGE
3. Beginning at embryonic day 17, olfactory sensory neurons expressing the same OR gene converge onto the same glomerulus



Early postnatal development

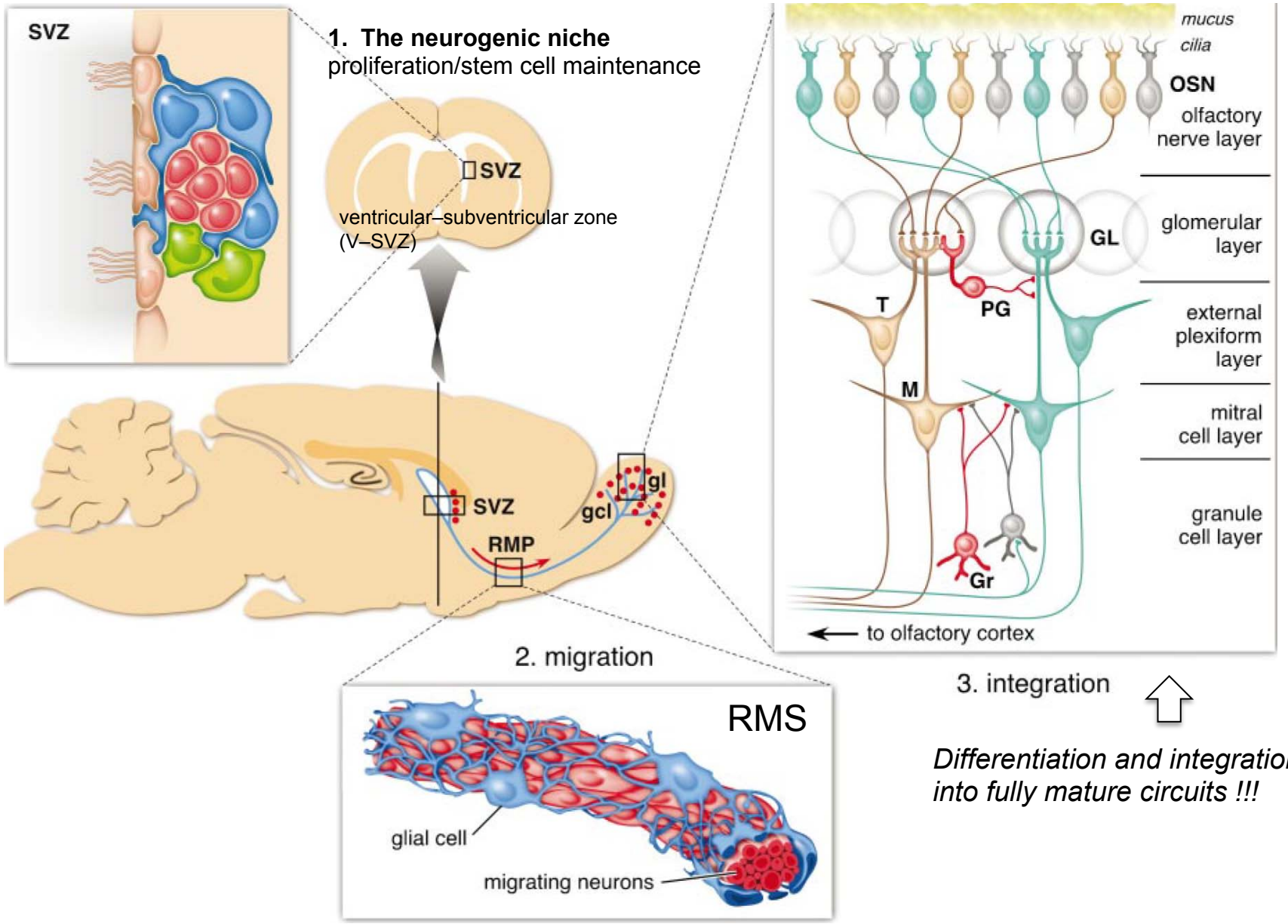
Peack of interneuron neurogenesis

Adult life

Continuos neurogenesis

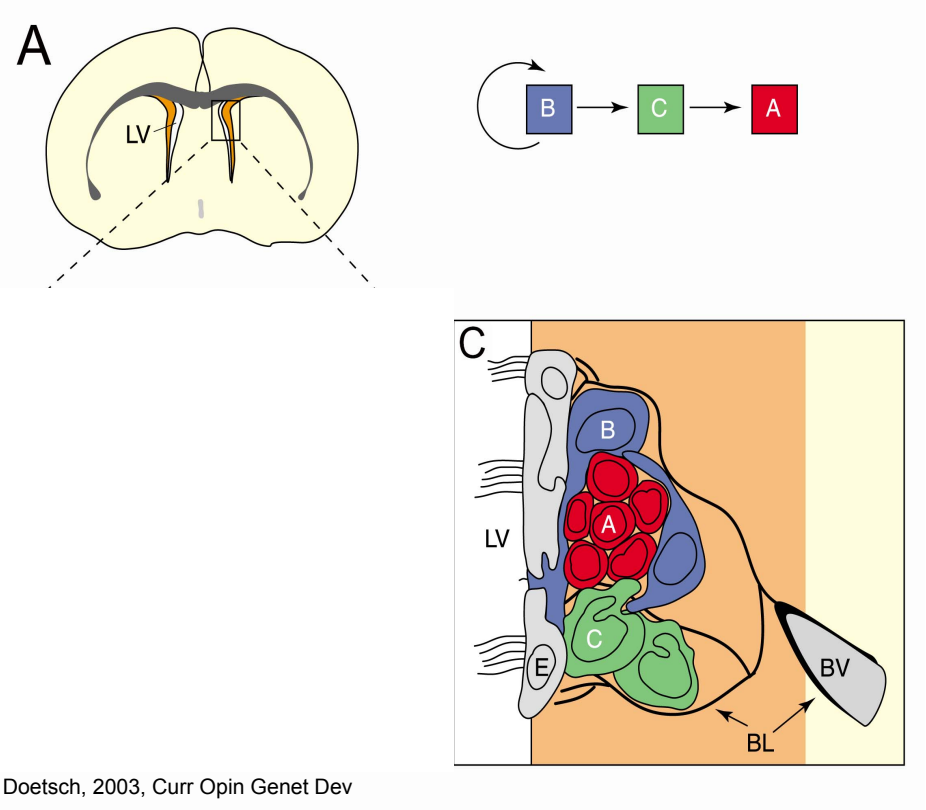
Marin and Rubenstein, Nature Reviews Neuroscience 2001

Adult olfactory bulb neurogenesis



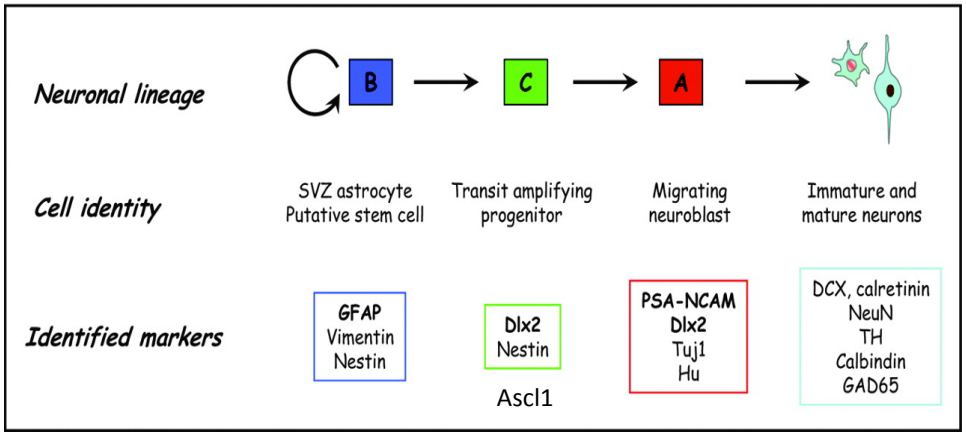
Differentiation and integration into fully mature circuits !!!

1. The SVZ neurogenic niche



Doetsch, 2003, Curr Opin Genet Dev

- Adult neural progenitor cells share many features of astrocytes



SVZ stem cells can also generate oligodendrocytes in vitro- in vivo also generate a small number of nonmyelinating NG2-positive OPCs and mature myelinating oligodendrocytes.

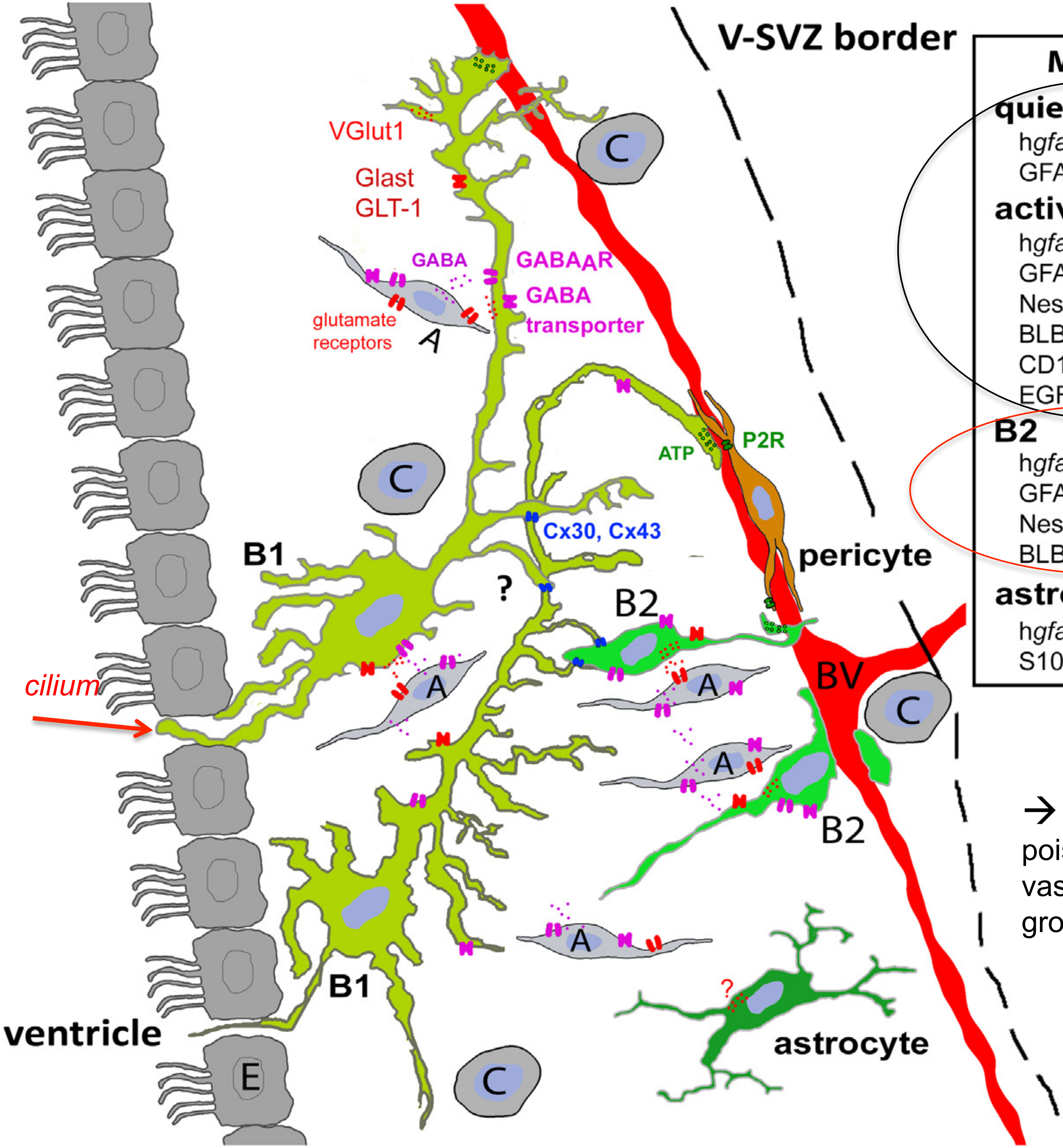
Origin of Oligodendrocytes in the Subventricular Zone of the Adult Brain

Bénédicte Menn,[1] Jose Manuel Garcia-Verdugo,[2] Cynthia Yaschine,[1] Oscar Gonzalez-Perez,[1] David Rowitch,[3] and Arturo Alvarez-Buylla[1]

[1]Department of Neurosurgery and Developmental and Stem Cell Biology Program, University of California at San Francisco, San Francisco, California 94143, [2]University of Valencia, 46010 Valencia, Spain, and [3]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115

Astrocytes production has been reported in injured brain

migrate into corpus callosum, striatum, and fimbria fornix



Markers

quiescent B1
- *hgfap*-GFP
- GFAP

activated B1
- *hgfap*-GFP
- GFAP
- Nestin
- BLBP
- CD133
- EGFR

B2
- *hgfap*-GFP
- GFAP
- Nestin
- BLBP

astrocyte
- *hgfap*-GFP
- S100B

B1

radial glia-like morphology

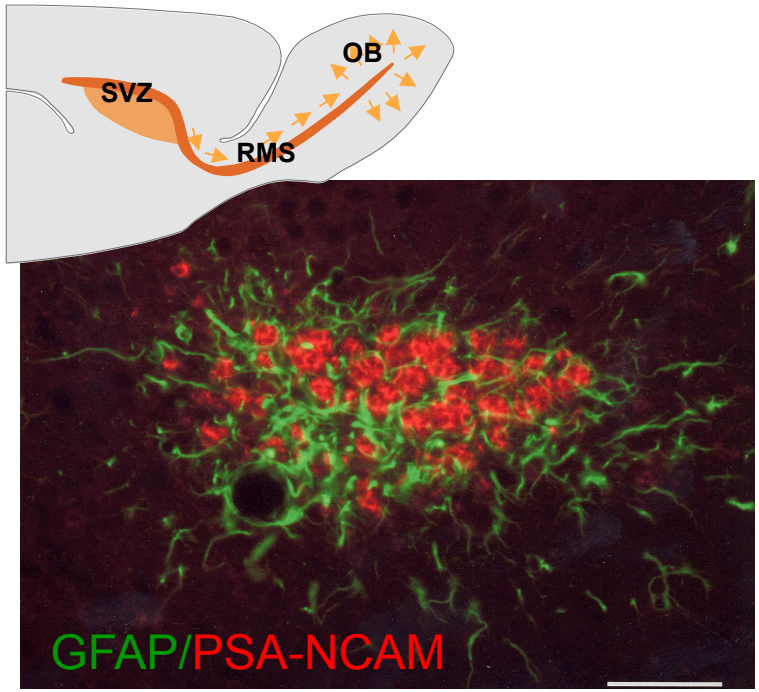
B2

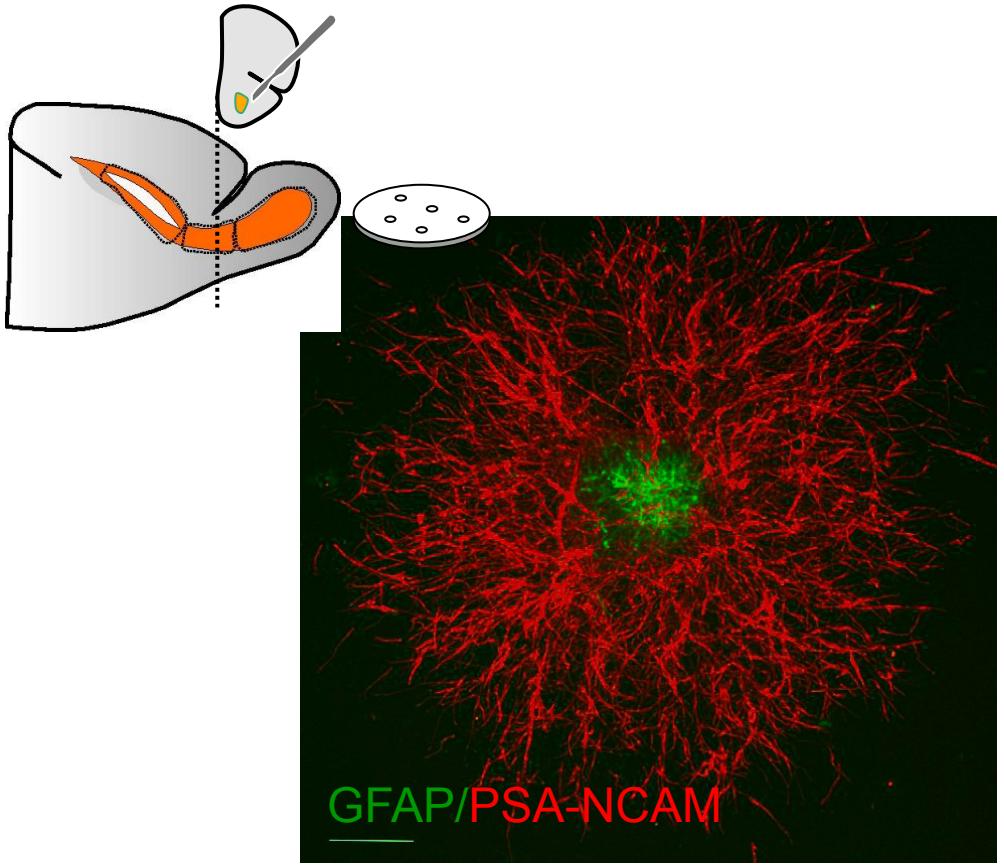
niche astrocytes

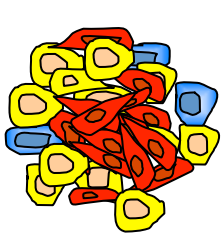
→ type B and C cells are uniquely poised to receive signals from the vasculature, like hormones and growth factors.

Platel & Bordey 2016

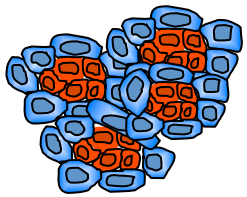
Neuronal migration in the RMS





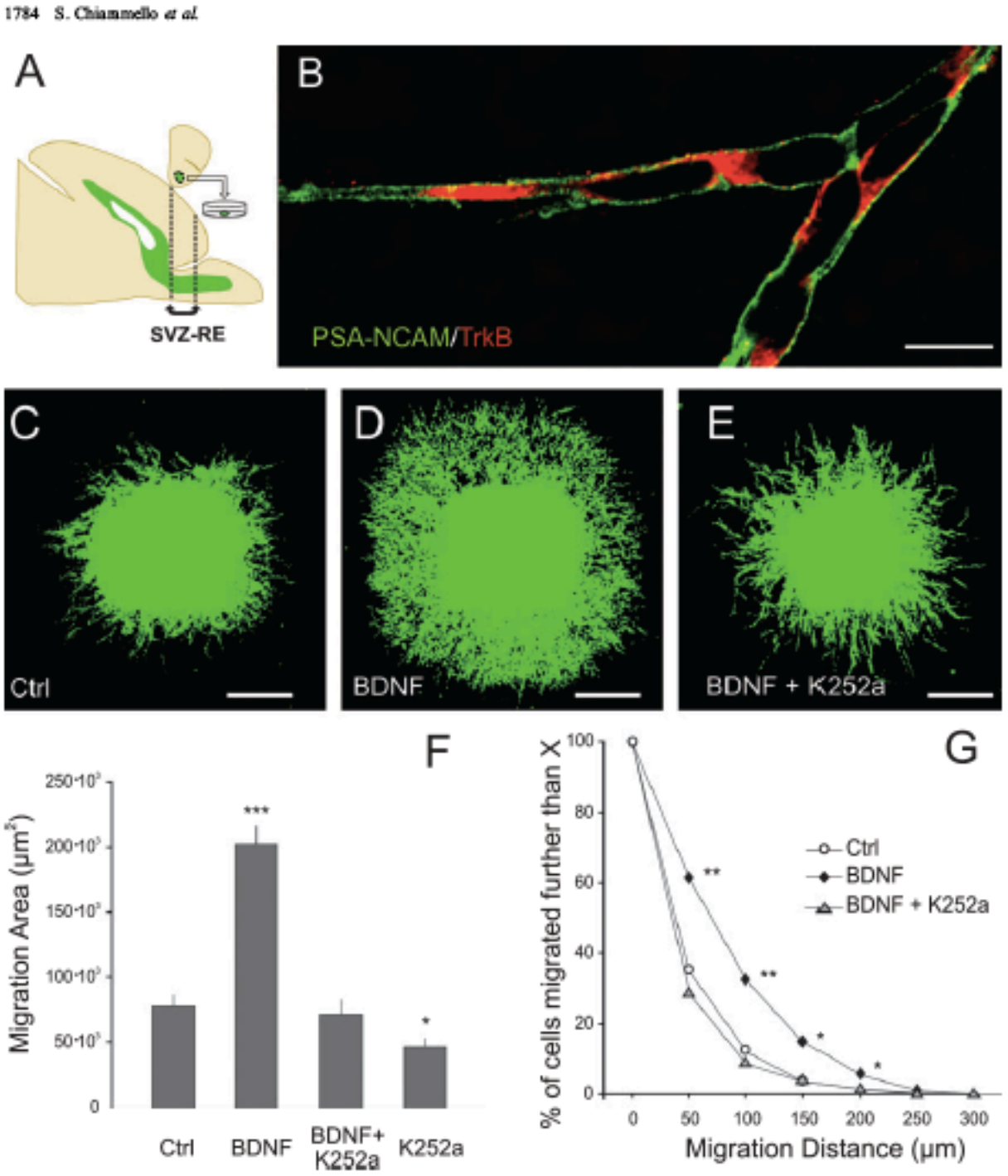


P5



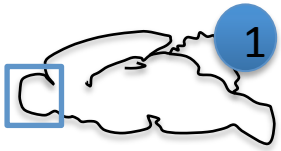
adult

Tissue explants
In vitro assay

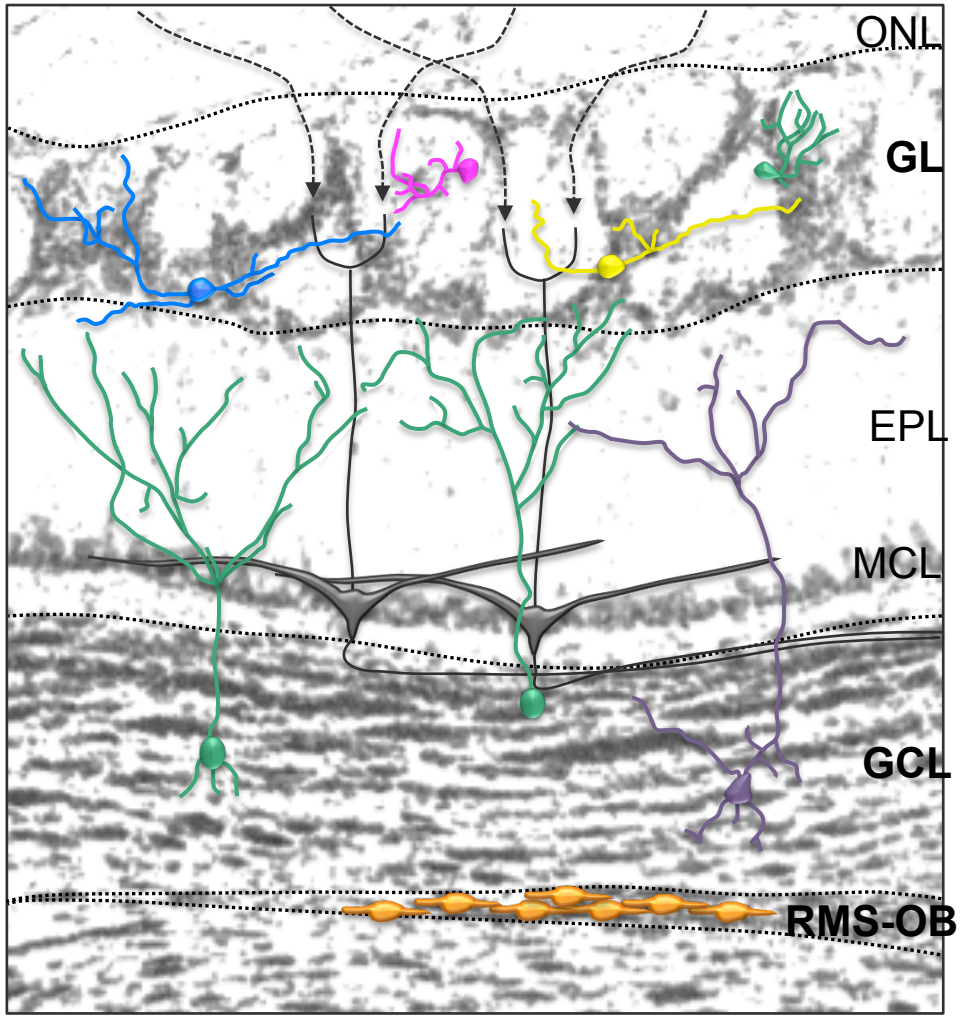


Chiaramello et al., EJN 2007

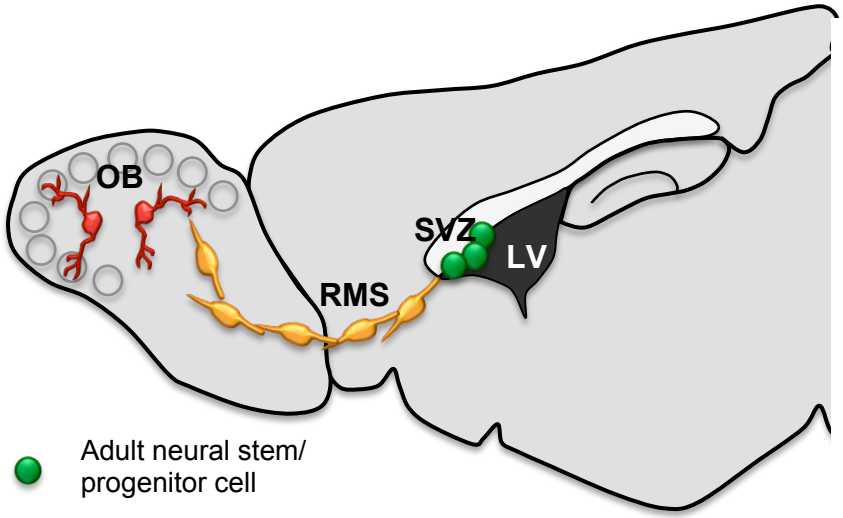
Generation of cellular diversity in the OB



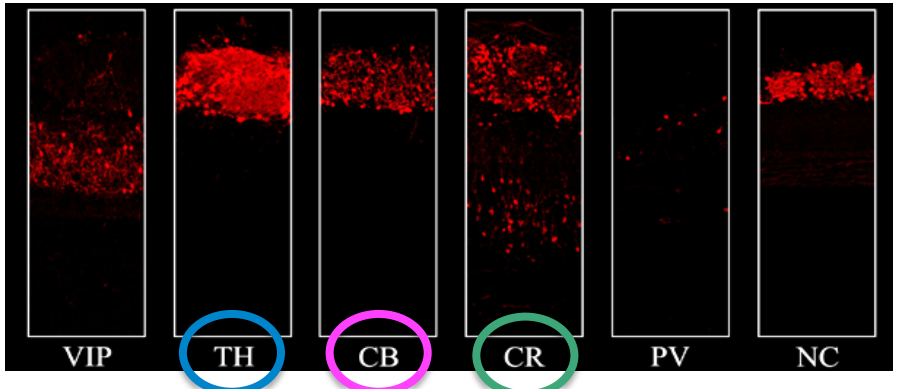
INIBITORY GABAERGIC INTERNEURONS



GL, glomerular layer; **GCL**, granule cell layer



Neurochemical phenotypes of OB GABAergic interneurons



Development/Plasticity/Repair

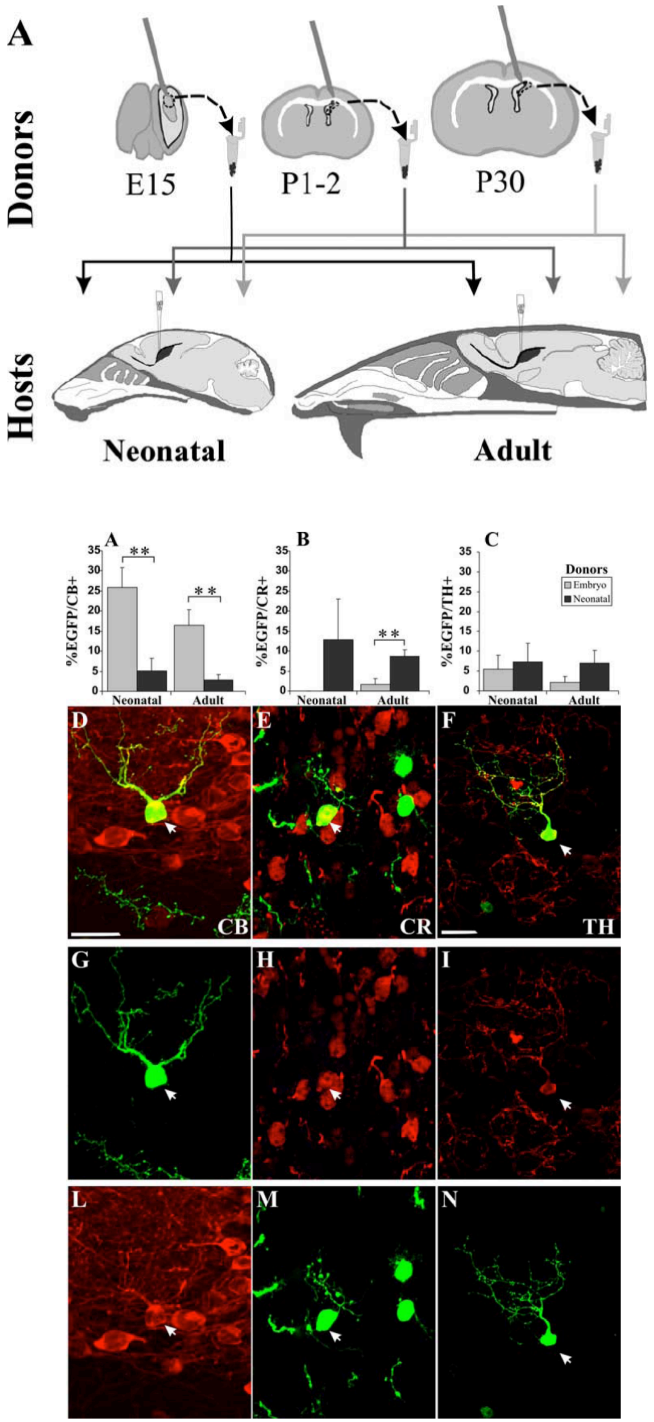
Generation of Distinct Types of Periglomerular Olfactory Bulb Interneurons during Development and in Adult Mice: Implication for Intrinsic Properties of the Subventricular Zone Progenitor Population

Silvia De Marchis,[1] Serena Bovetti,[1,2]* Barbara Carletti,[3]* Yi-Chun Hsieh,[2] Donatella Garzotto,[1] Paolo Peretto,[1] Aldo Fasolo,[1] Adam C. Puche,[2] and Ferdinando Rossi[3]

[1]Department of Animal and Human Biology, University of Turin, I-10123 Turin, Italy, [2]Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, Maryland 21201, and [3]Department of Neuroscience, University of Turin, I-10125 Turin, Italy

The subventricular zone (SVZ) of the lateral ventricle develops from residual progenitors of the embryonic lateral ganglionic eminence (LGE) and maintains neurogenic activity throughout life. Precursors from LGE/SVZ migrate to the olfactory bulb (OB) where they differentiate into local interneurons, principally in the granule layer and glomerular layer (GL). By *in situ* dye labeling, we show that neonatal and adult SVZ progenitors differentially contribute to neurochemically distinct types of periglomerular interneurons in the GL. Namely, calbindin-positive periglomerular cells are preferentially generated during early life, whereas calretinin- and tyrosine hydroxylase-expressing neurons are mainly produced at later ages. Furthermore, homochronic/heterochronic transplantation demonstrates that progenitor cells isolated from the LGE or SVZ at different stages (embryonic day 15 and postnatal days 2 and 30) engraft into the SVZ of neonatal or adult mice, migrate to the OB, and differentiate into local interneurons, including granule and periglomerular cells as well as other types of interneurons. The total number of integrated cells and the relative proportion of granule or periglomerular neurons change, according to the donor age, whereas they are weakly influenced by the recipient age. Analysis of the neurochemical phenotypes acquired by transplanted cells in the GL shows that donor cells of different ages also differentiate according to their origin, regardless of the host age. This suggests that progenitor cells at different ontogenetic stages are intrinsically directed toward specific lineages. Neurogenic processes occurring during development and in adult OB are not equivalent and produce different types of periglomerular interneurons as a consequence of intrinsic properties of the SVZ progenitors.

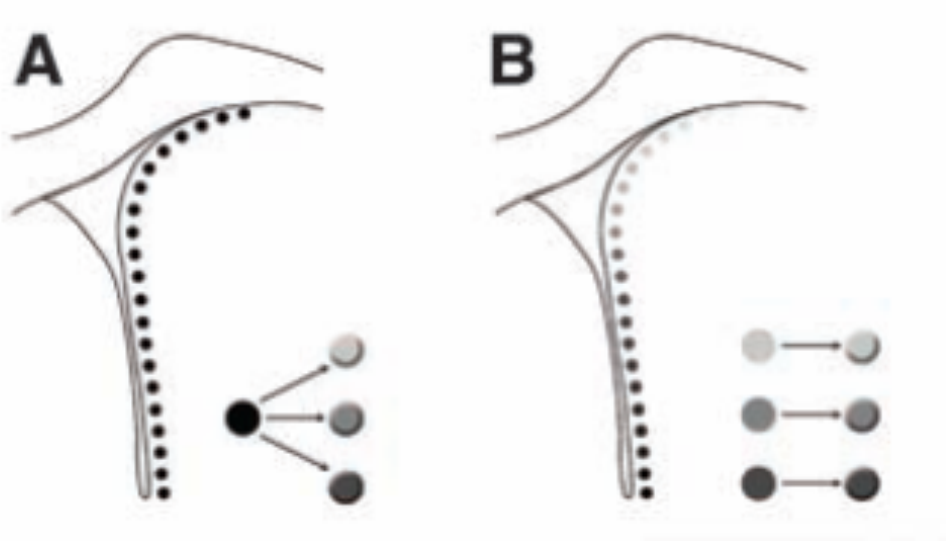
Key words: olfactory bulb; subventricular zone; transplantation; periglomerular cell; specification; neurogenesis



Science
AAAS

Mosaic Organization of Neural Stem Cells in the Adult Brain
Florian T. Merkle, *et al.*
Science **317**, 381 (2007);
DOI: 10.1126/science.1144914

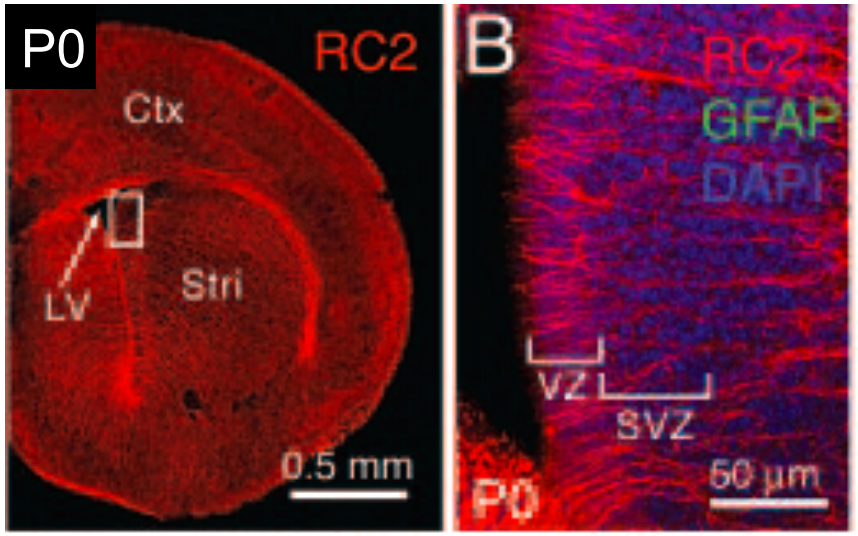
Model of SVZ stem cell potential

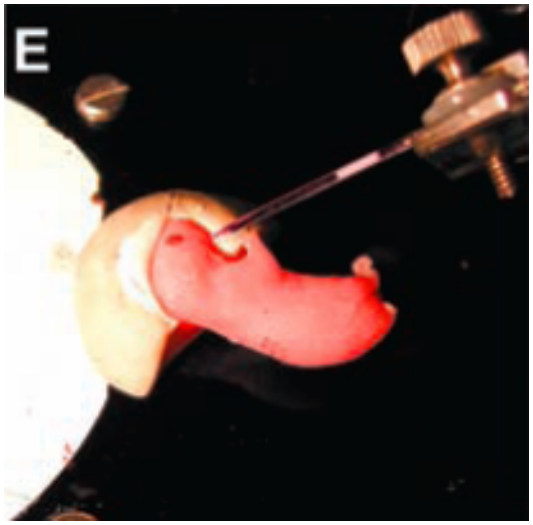


Equivalent stem cells generate multiple neuron types

OR

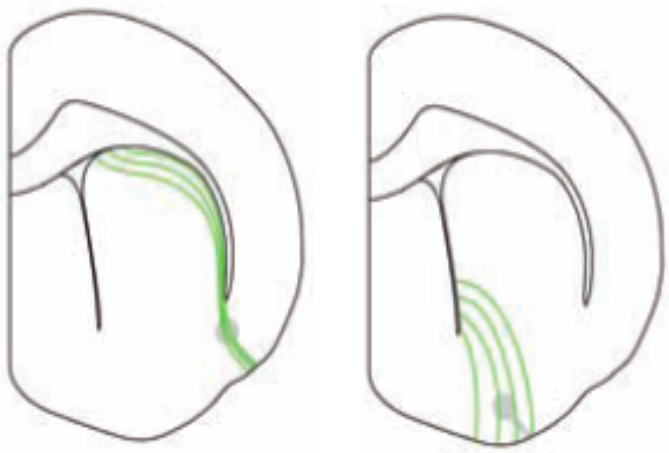
Different stem cells generate specific neuron types





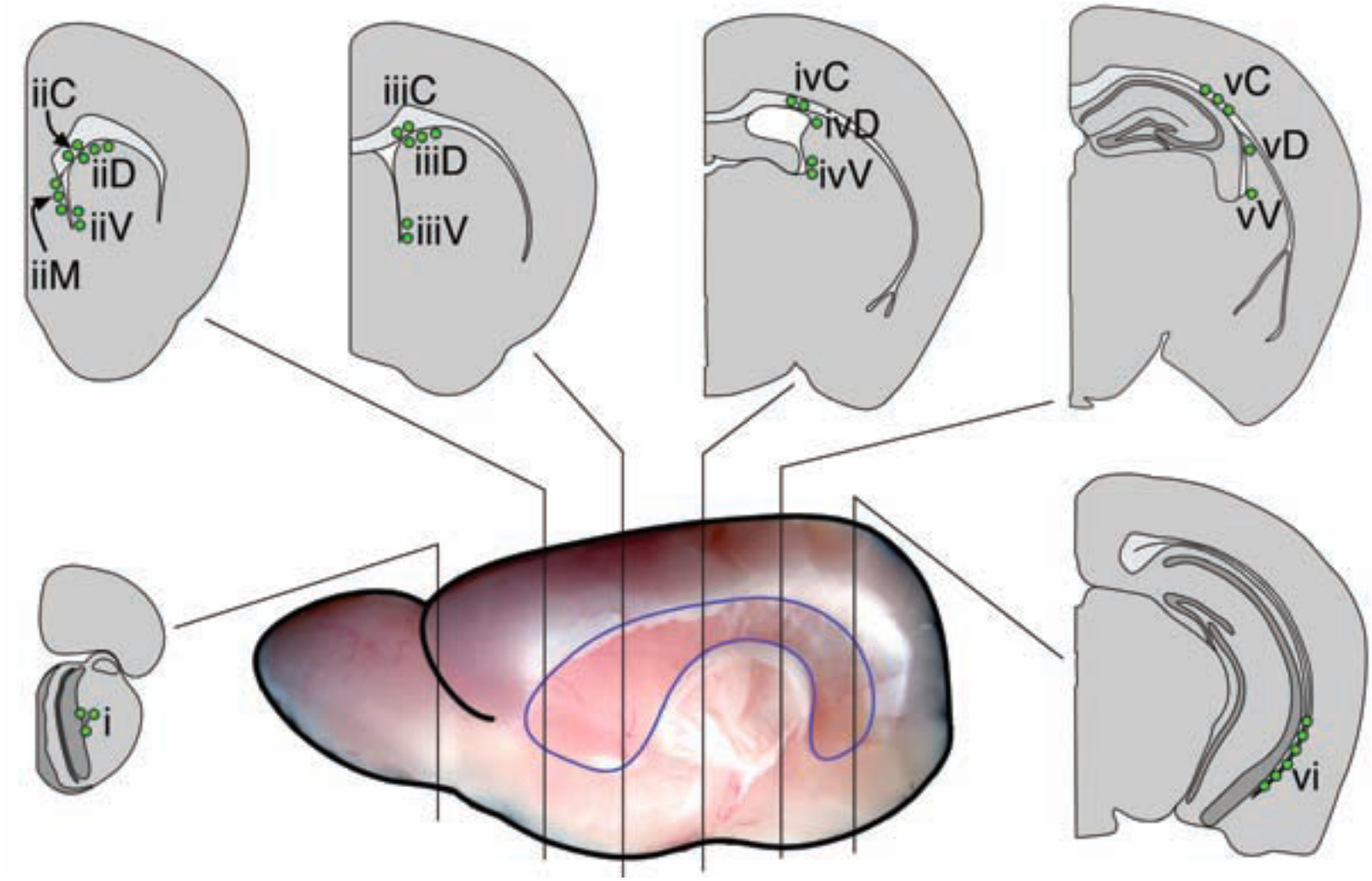
(Merkle et al., 2004)

Adult neural stem cells are derived from radial glia present in the neonatal (P0) mouse brain

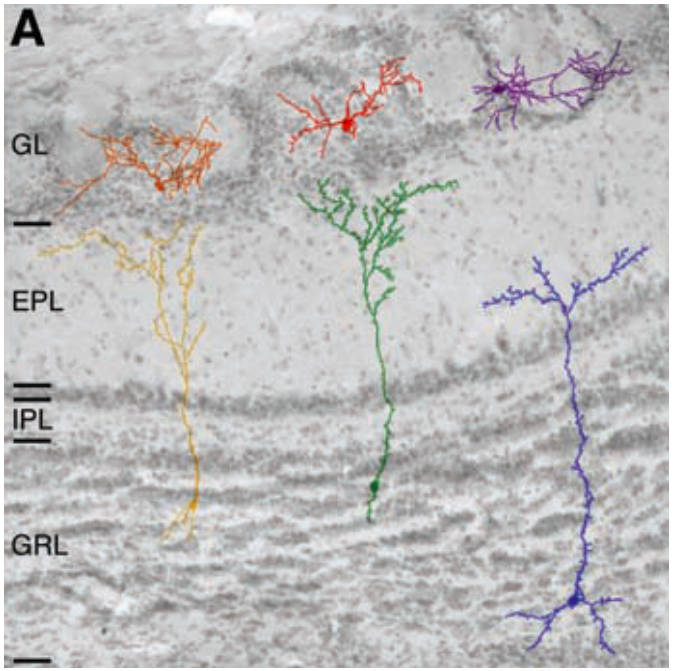


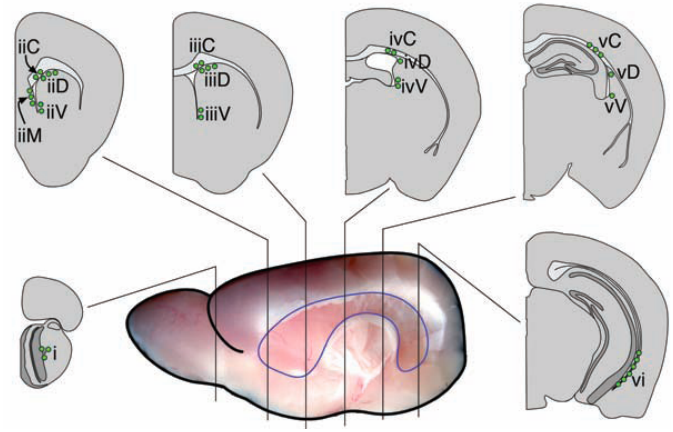
RGCs have a unique morphology that allows them to be targeted specifically

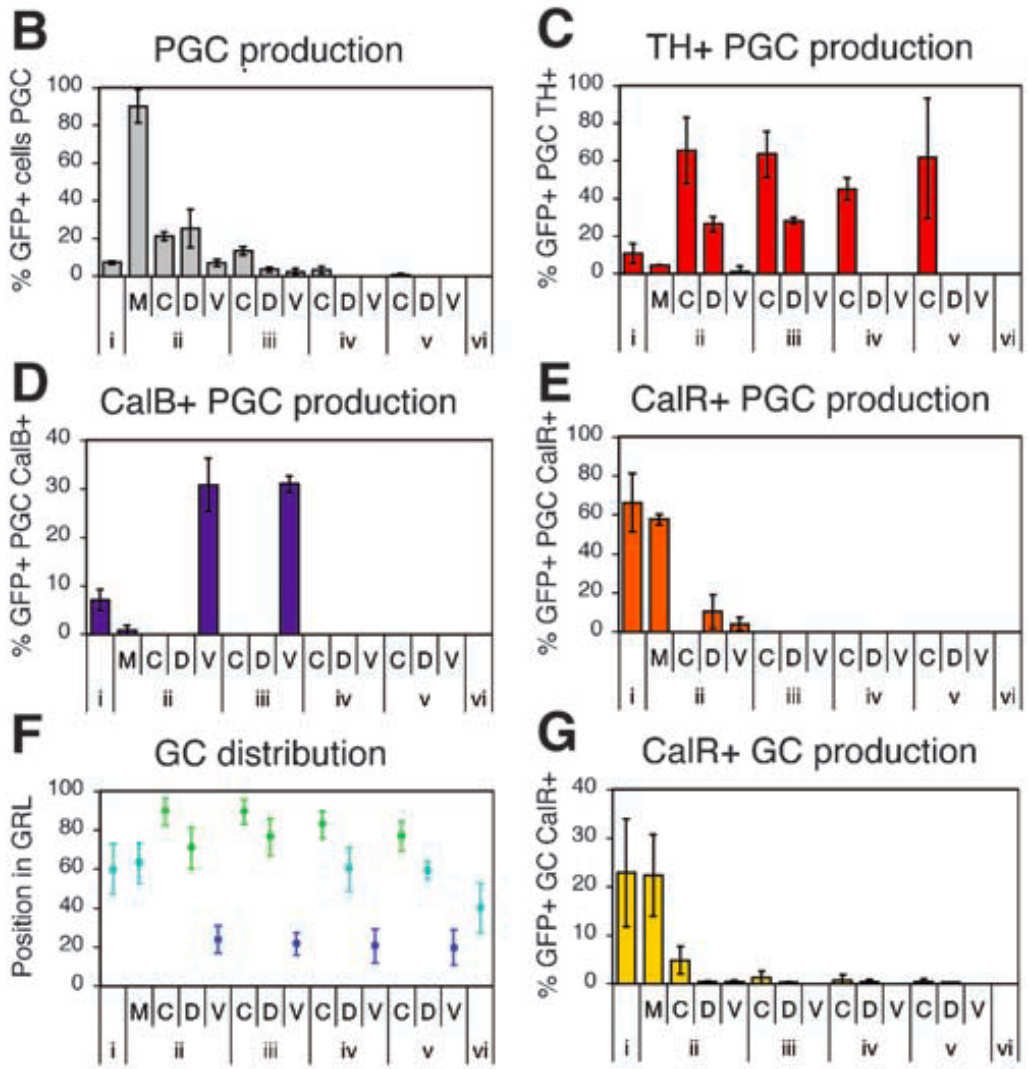
Adenovirus expressing Cre recombinase (Ad:Cre) injected into green fluorescent protein (GFP) reporter (Z/EG) mice, infected radial glia and their progeny become permanently labeled with GFP



Specific target of radial glia and of adult SVZ stem cells they generate





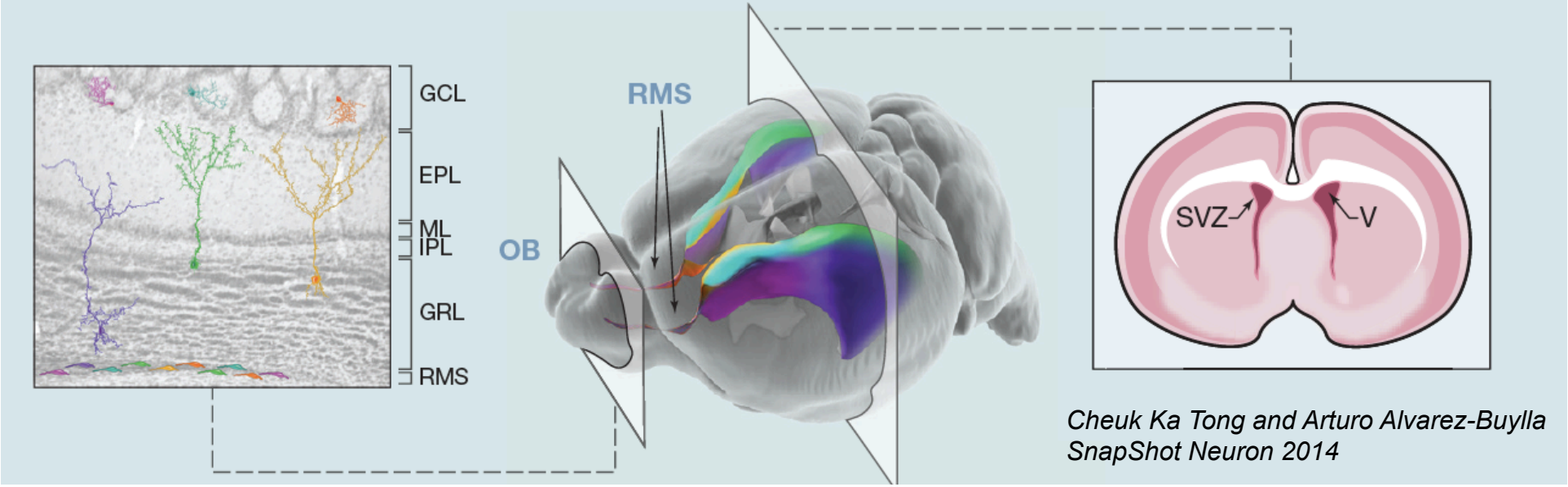


NSC are regionally specified in both the neonatal and adult SVZ

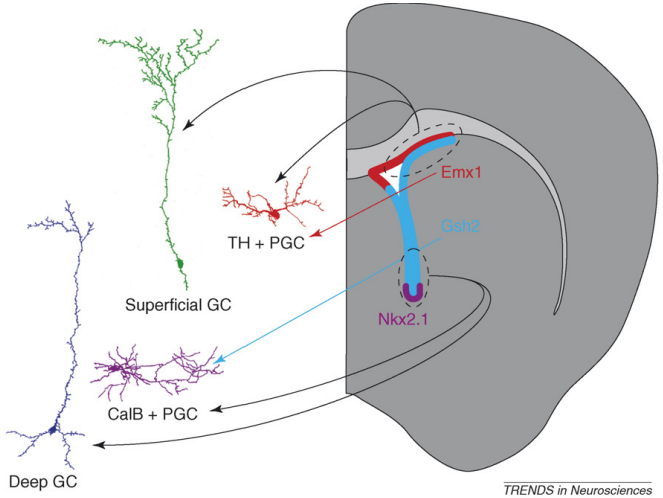
→different types of OB interneurons are derived from different locations in the SVZ

The olfactory bulb

A mosaic of early specified neural stem/progenitor cells contribute to the different OB interneurons phenotype



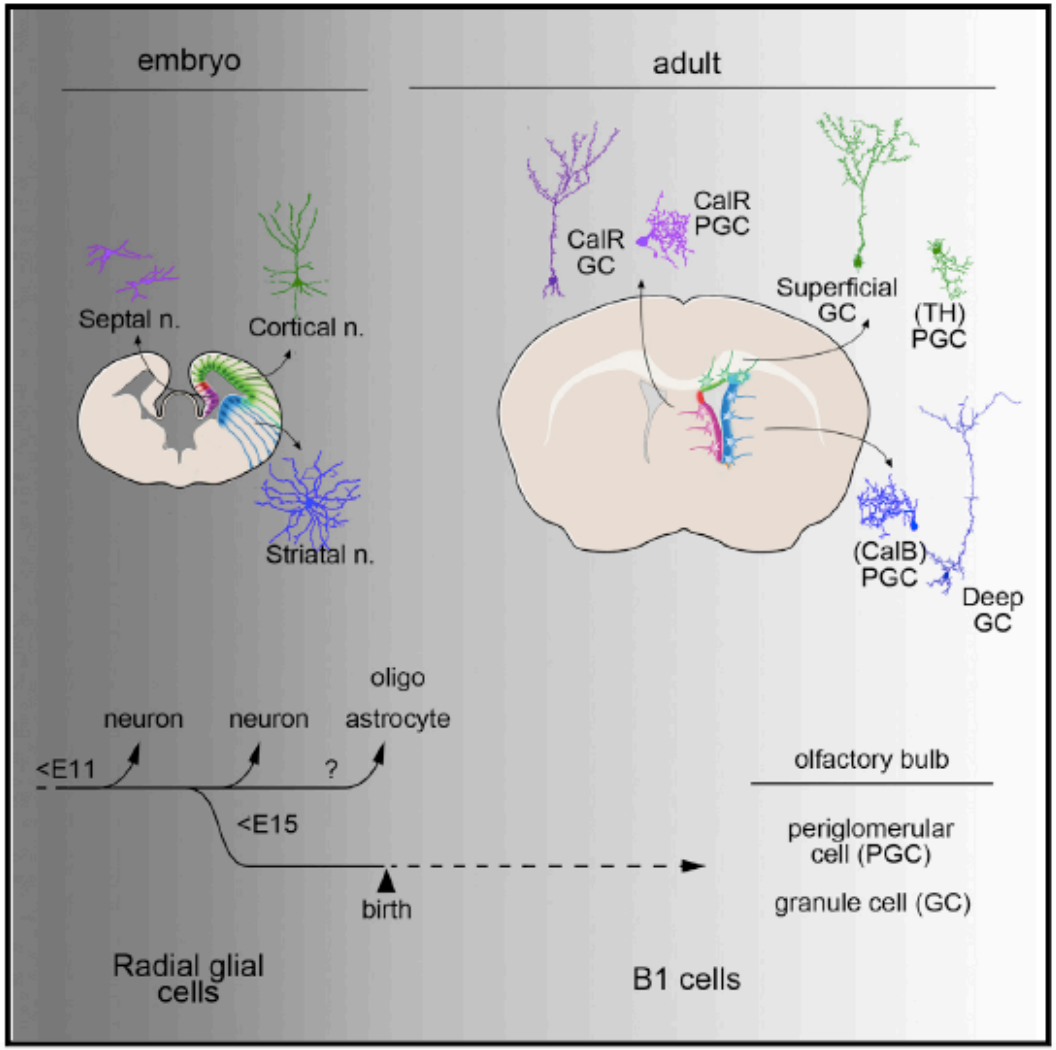
Cheuk Ka Tong and Arturo Alvarez-Buylla
SnapShot Neuron 2014



Cell 2015

Embryonic Origin of Postnatal Neural Stem Cells

Graphical Abstract



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Correspondence

abuylla@stemcell.ucsf.edu

In Brief

Postnatal neural stem cells become regionally specified early in embryonic development and remain largely quiescent until reactivation.

The embryonic progenitors of B1 cells are produced during mid-fetal development (E13.5–E15.5) and remained relatively quiescent until they were reactivated in post-natal life.