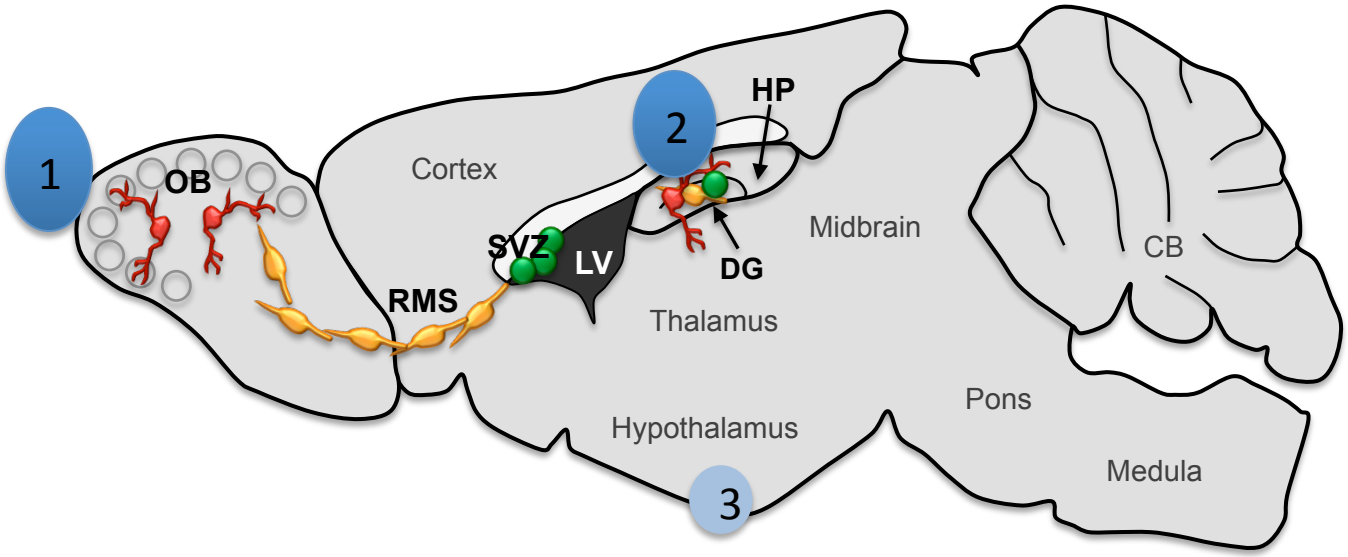
Main sites of Adult Neurogenesis in the rodent brain (physiological conditions)



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

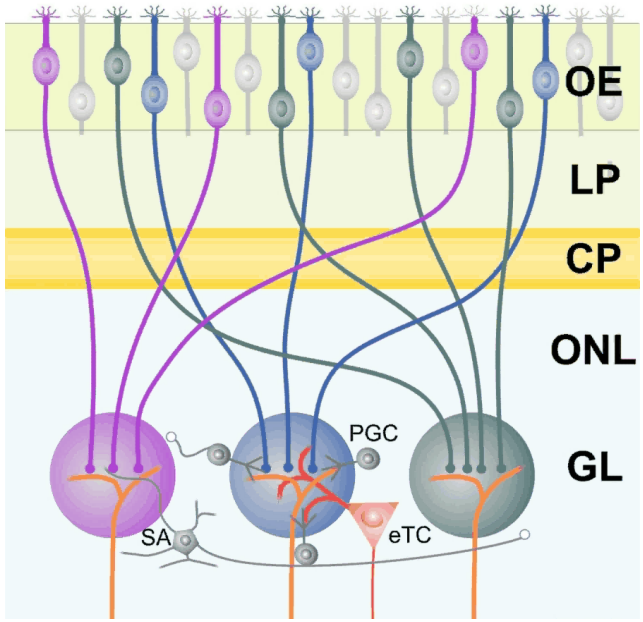
Adult neurogenesis recapitulates the complete process of neuronal development in a mature CNS environment, from proliferation and neuronal fate specification of NPCs, through differentiation, migration and targeting of neurons, to synaptic integration and survival of new neurons

The olfactory bulb

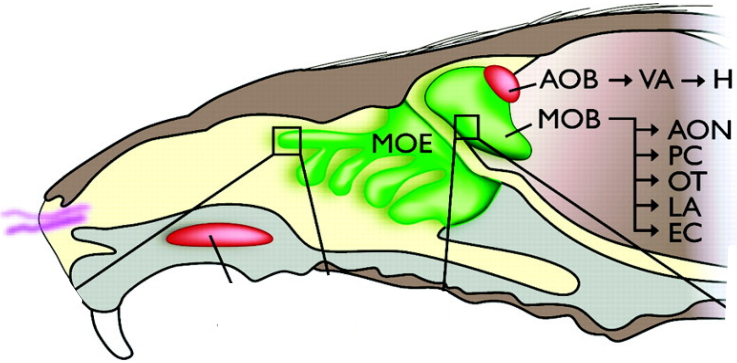
the first brain region involved in the **processing of olfactory information**

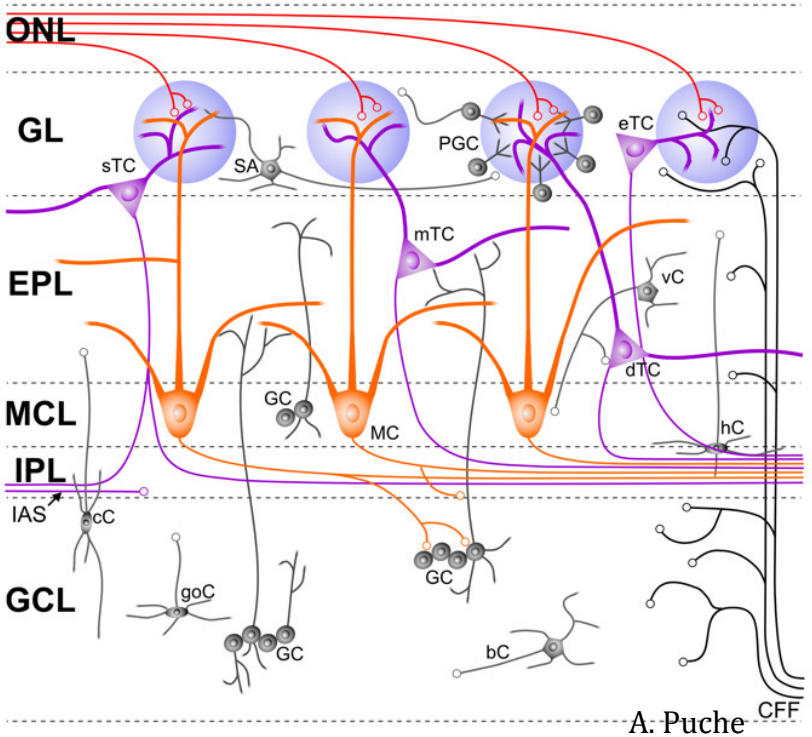
MOE

MOB



courtesy of A. Puche





A. Puche

Lledo et al., Physiol Rev 2004

Olfactory bulb neurogenesis

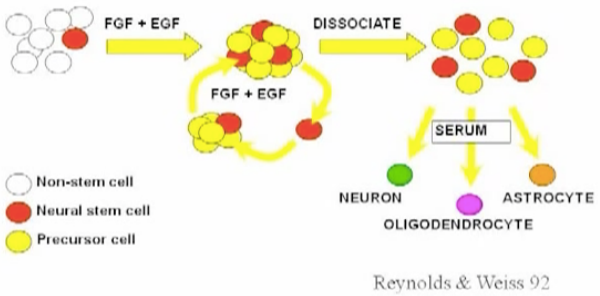
a long story….

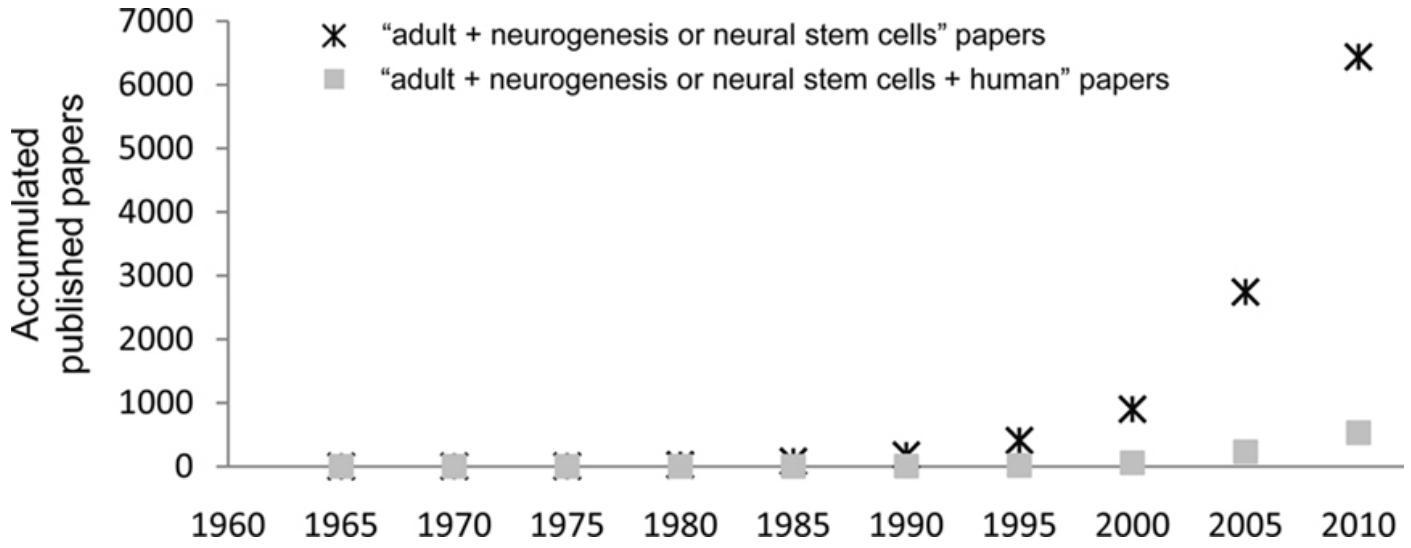
Altman J.
Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb.
J. Comp Neurol. 1969

Luskin MB
Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. Neuron. 1993

Lois C, Alvarez-Buylla A.
Long-distance neuronal migration in the adult mammalian brain. Science, 1994

Morshead CM, Reynolds BA, Craig CG, McBurney MW,Staines WA, Morassutti DJ, Weiss S, and **van der Kooy D**. Neural stem cells in the adult mammalian forebrain: a relatively quiescent subpopulation of subependymal cells. Neuron, 1994

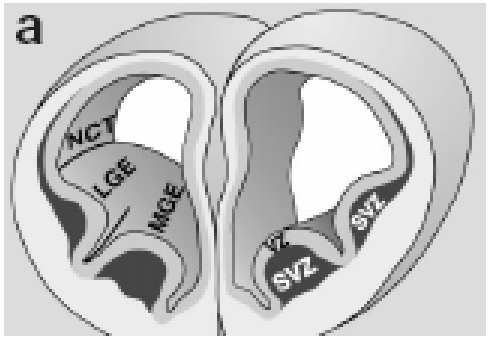




Published papers on adult neurogenesis per quinquennium. The graph shows the accumulated papers published from 1960 onward, searched in PubMed with the search terms "adult" AND ("neurogenesis" OR "stem cells"). The asterisks show the total number of papers, and the filled squares show those papers with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

Sierra et al. Front. Neurosci. 2011

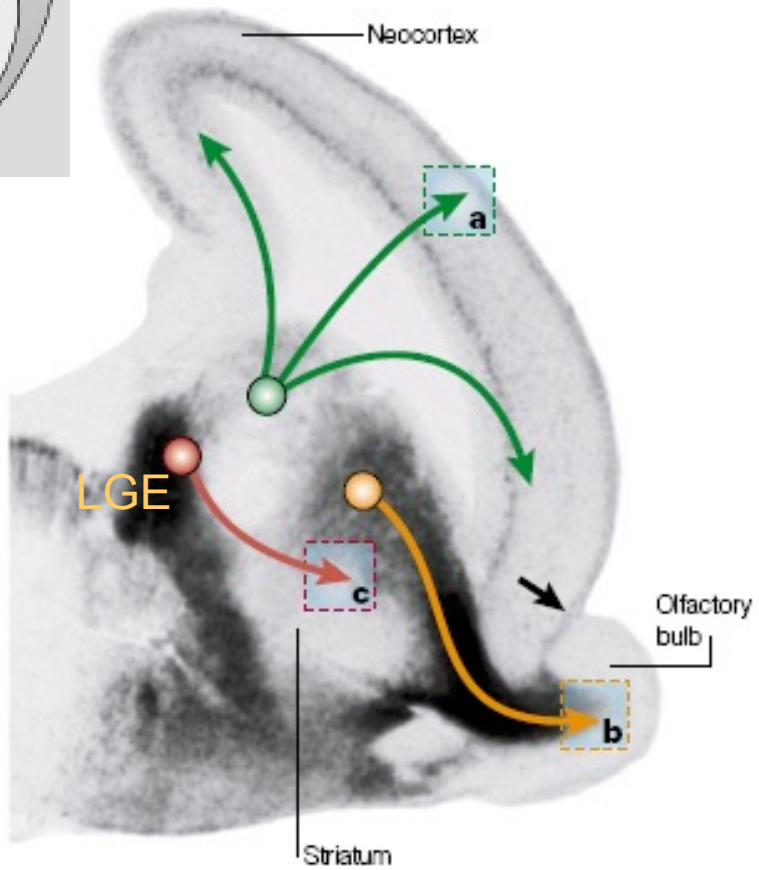
Embryonic development of olfactory bulb interneurons



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

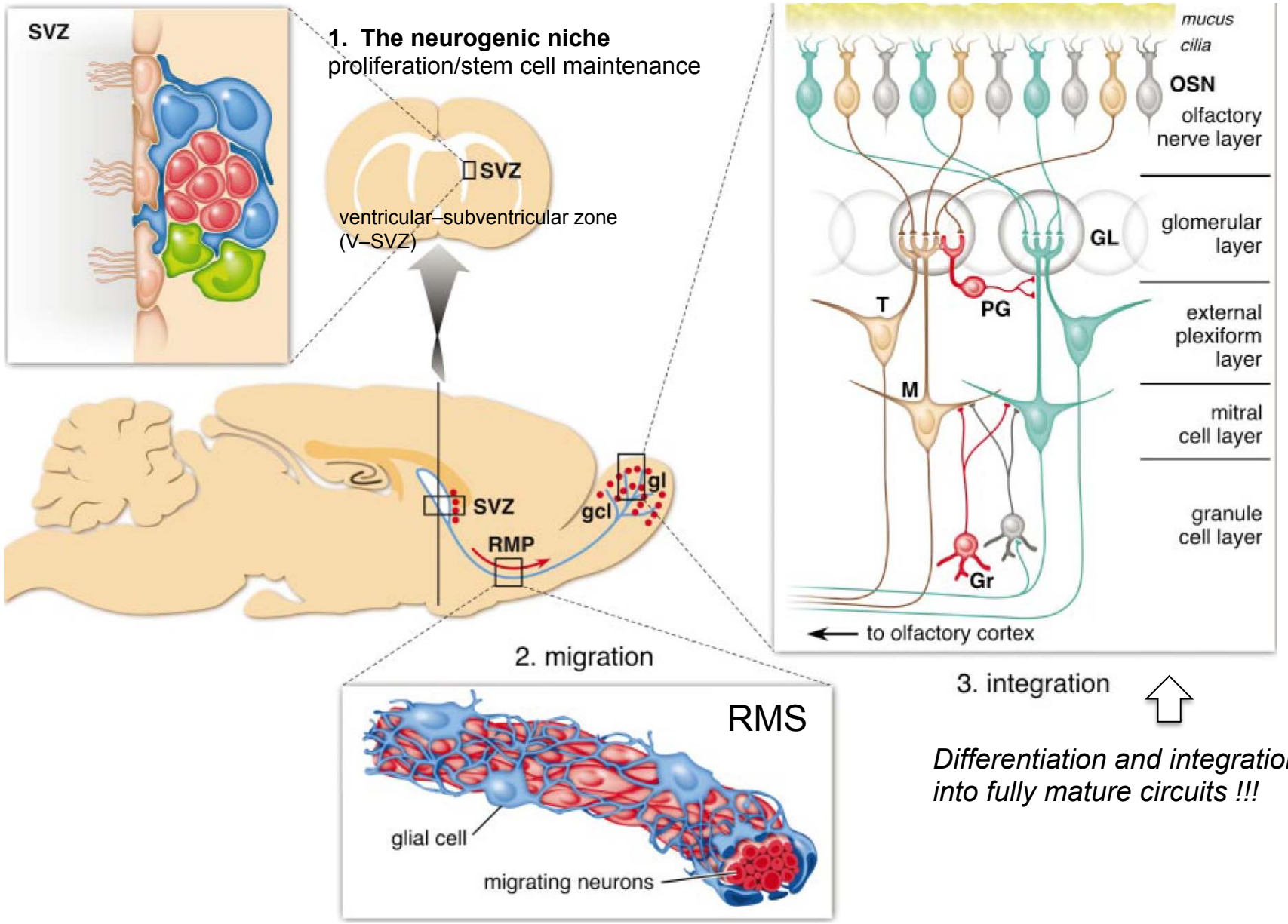
Peack of interneuron neurogenesis

Adult life

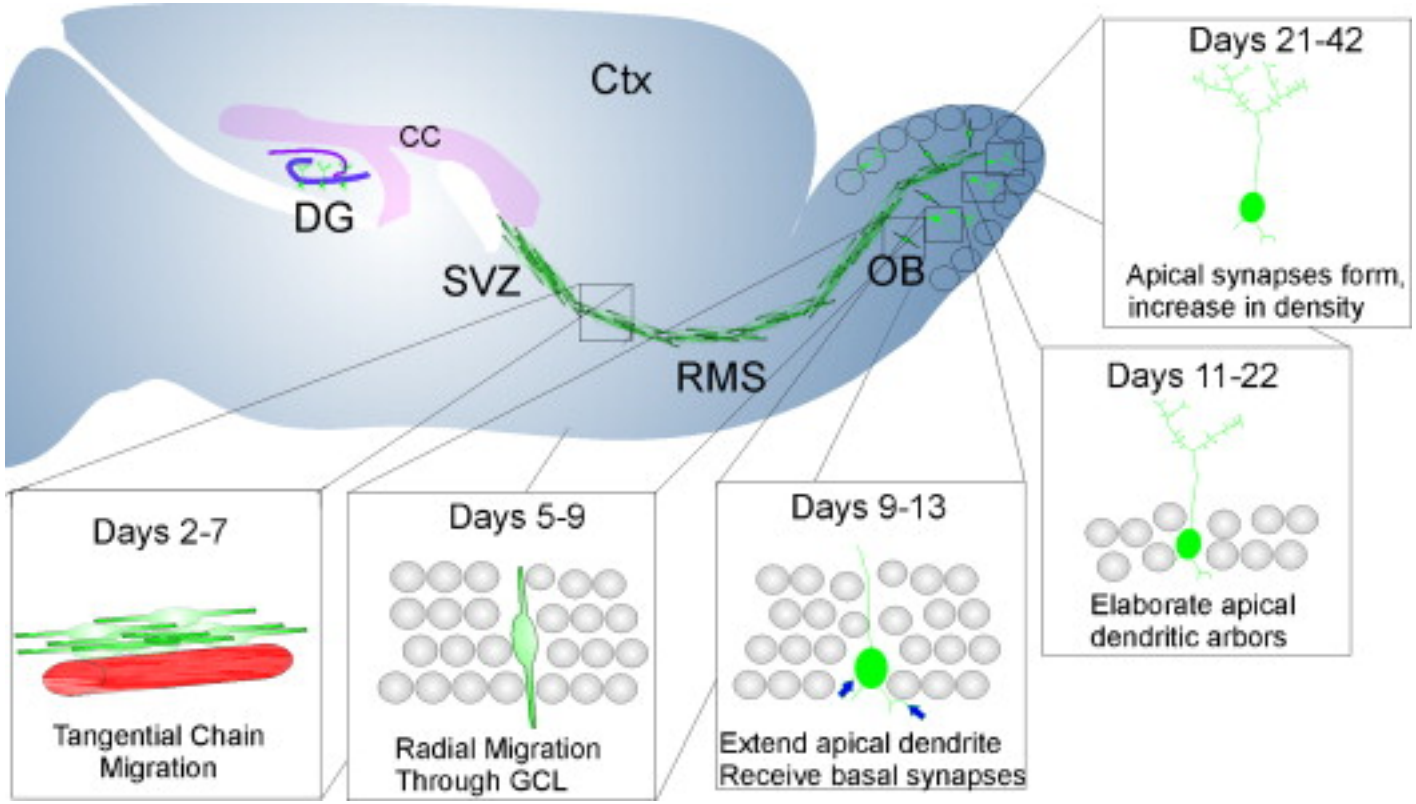
Continuos neurogenesis

Marin and Rubenstein, Nature Reviews Neuroscience 2001

Adult olfactory bulb neurogenesis

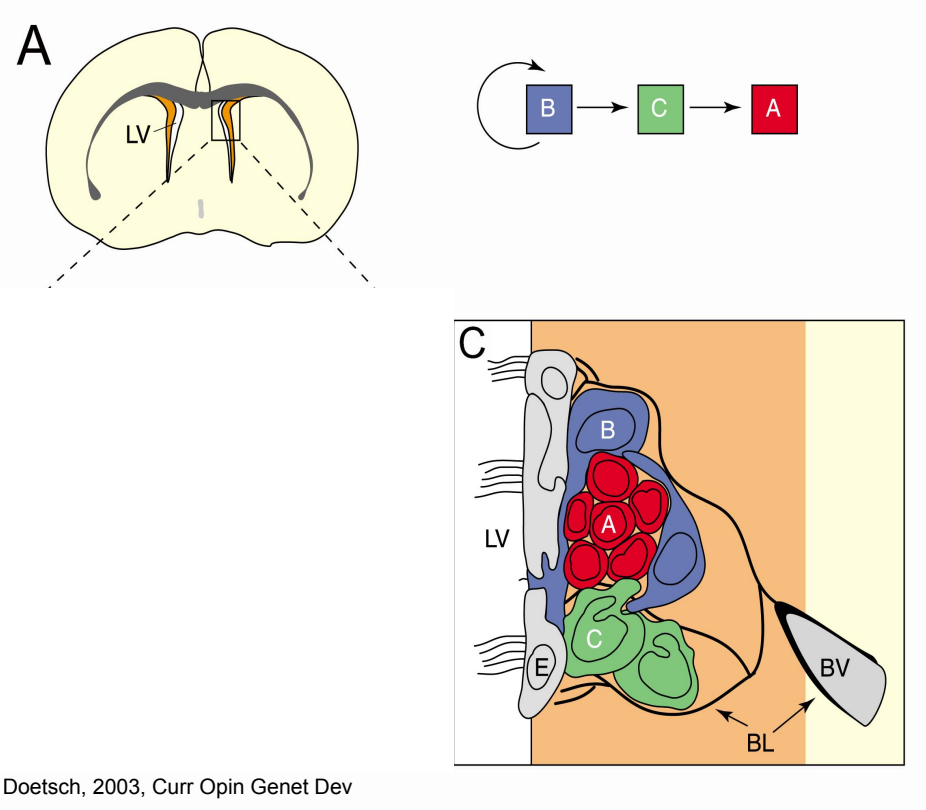


Differentiation and integration into fully mature circuits !!!



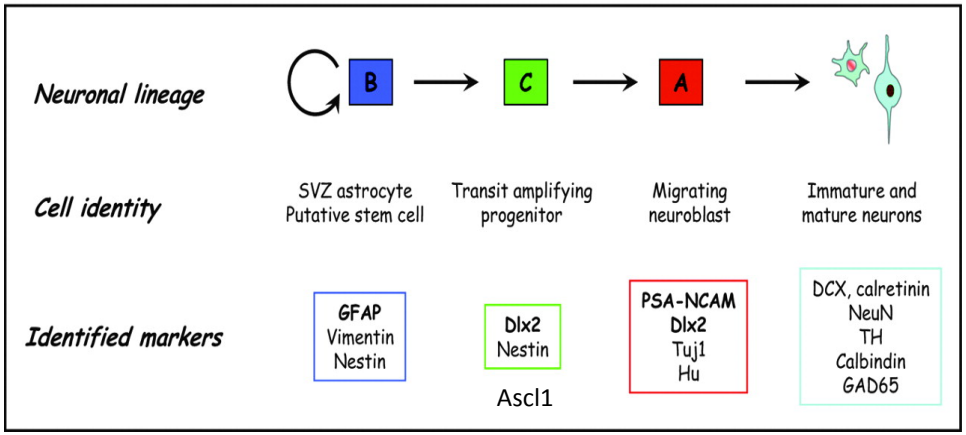
Whitman and Greer 2009

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

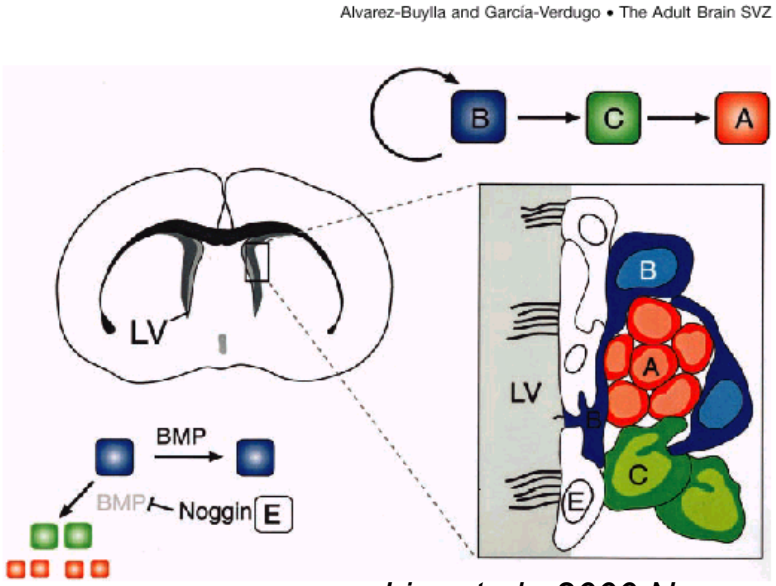
Bénédicte Menn,[1] Jose Manuel Garcia-Verdugo,[2] Cynthia Yaschine,[1] Oscar Gonzalez-Perez,[1] David Rowitch,[3] and Arturo Alvarez-Buylla[1]

[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

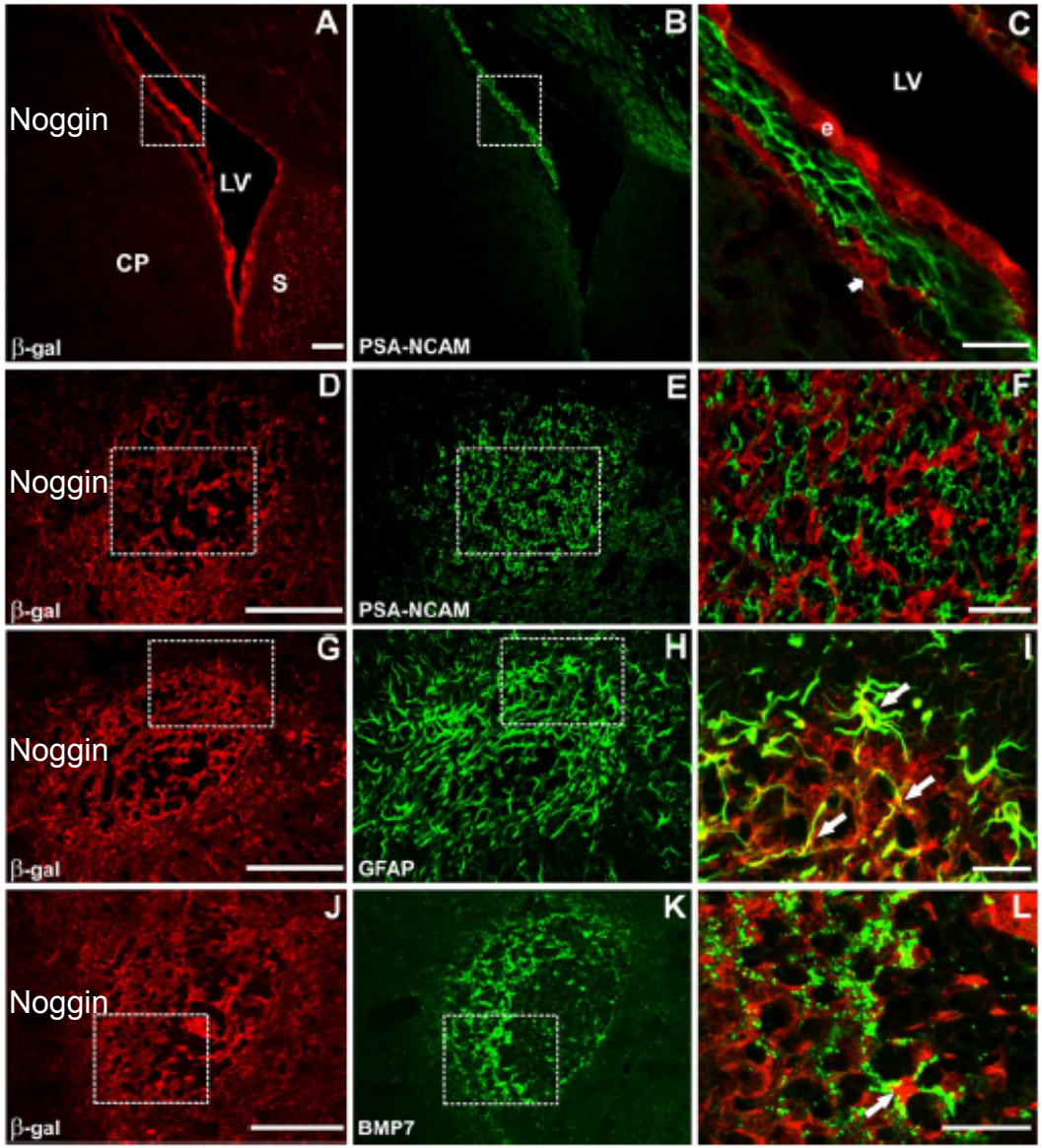
Astrocytes production has been reported in injured brain

migrate into corpus callosum, striatum, and fimbria fornix

Neurogenic niche in the SVZ



Lim et al., 2000 Neuron



Peretto et al., 2004 Neuroscience

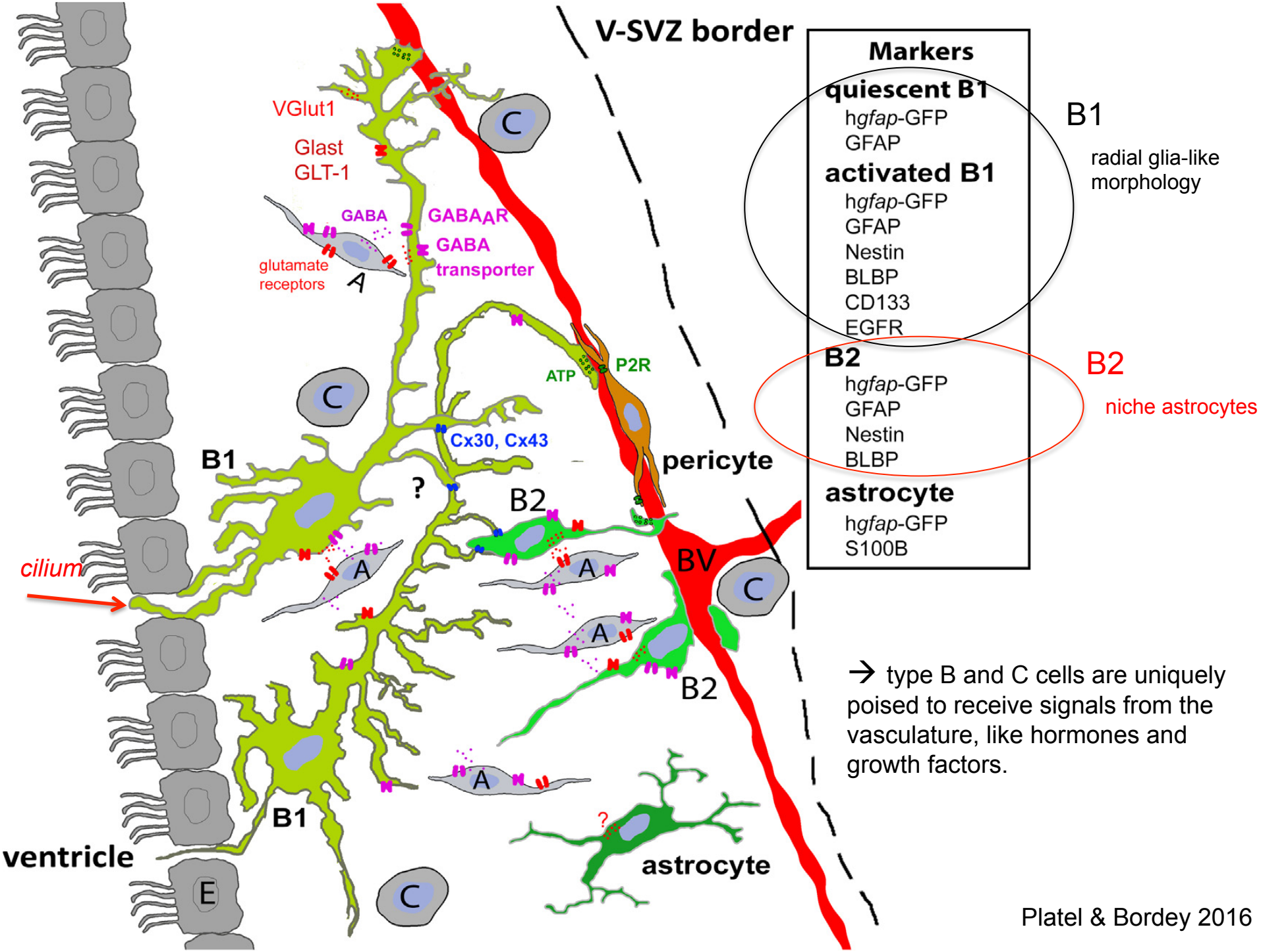
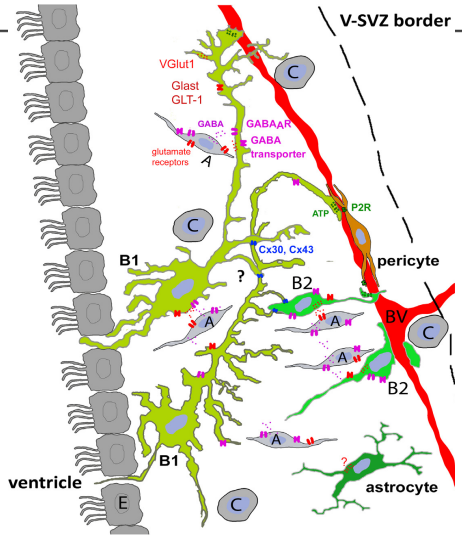

V-SVZ border
Markers
quiescent B1
hgfap-GFP
GFAP
activated B1
hgfap-GFP
GFAP
Nestin
BLBP
CD133
EGFR
B2
hgfap-GFP
GFAP
Nestin
BLBP
astrocyte
hgfap-GFP
S100B
B1
radial glia-like morphology
B2
niche astrocytes
VGlut1
Glast
GLT-1
GABA
GABA$_A$R
GABA transporter
glutamate receptors
ATP
P2R
Cx30, Cx43
pericyte
cilium
B1
B2
BV
B2
B1
ventricle
astrocyte
C
A
E
?
→ type B and C cells are uniquely poised to receive signals from the vasculature, like hormones and growth factors.
Platel & Bordey 2016

Table 1. Anatomical, antigenic, and neurophysiological properties of V–SVZ cells

Type	Subtype		Morphology	Location	Markers	Glutamate related marker	GABA related marker
V–SVZ astrocytes	Type B1	Overall Type B1	Fusiform	Attached to the ventricle and blood vessels Cell body in V–SVZ	GFAP + CD133 +/- Nestin +/- Cx43; Cx30 hgfap-GFP BLBP +/-	GLAST GLT-1 VGlut1 Glutamate mGluR1–5	GAT4 $GABA_AR$
		Quiescent	"	"	GFAP + CD133 +/-	?	?
		Activated	"	"	GFAP +; Nestin + EGFR + CD133 + hgfap-GFP BLBP	?	?
	Type B2		Intermediate fusiform/stellate	Periphery of the V–SVZ, not in contact with the ependymal layer	GFAP +; BLBP + Nestin + Cx43 +; Cx30? hgfap-GFP	GLAST; GLT-1 VGlut1 ? Glutamate mGluR1–5 ?	GAT4 $GABA_AR$
	Other astrocytes		Stellate	No specific location	hgfap-GFP +/- S100B +; GFAP? Cx43 ?; Cx30?	?	?
Type C			Larger, more spherical than type B	Core SVZ	Mash1 +; EGFR + Lex +; Dlx2 + BLBP +/-	?	?
Type A			Bipolar elongated	Core SVZ	DCX +; Tuj1 + PSA-NCAM +	NMDA-R Kainate-R AMPA-R mGluR	GAT1 VGAT $GABA_AR$ GABA
Ependymal cells			Cubic	Border of the ventricle	S100B +; CD24 + Nestin +; Cx43 + CD133 (cilia) +	–	–

+/- indicates that the marker is not expressed in all the population.



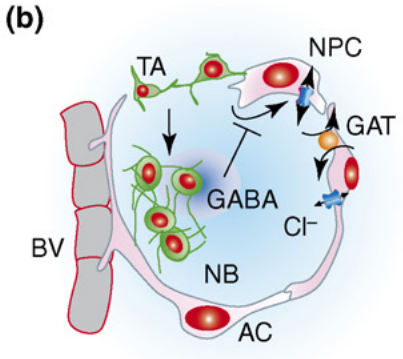
!!!→ always use a combination of markers to identify the quiescent vs activated V–SVZ NPCs

Nature Neurosci 2005

Nonsynaptic GABA signaling in postnatal subventricular zone controls proliferation of GFAP-expressing progenitors

Xiuxin Liu[1], Qin Wang[1], Tarik F Haydar[2] & Angélique Bordey[1]

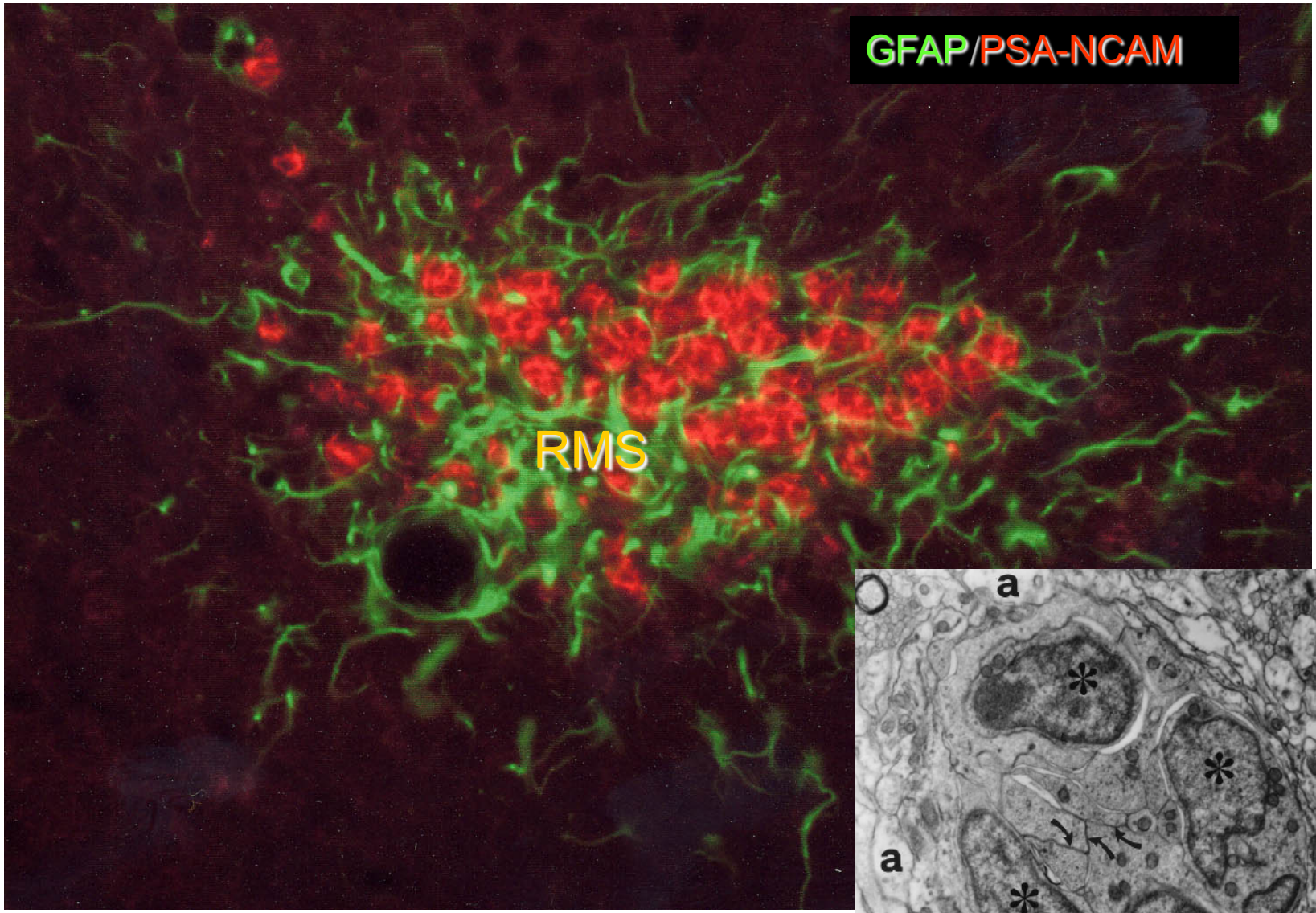
In the postnatal subventricular zone (SVZ), local cues or signaling molecules released from neuroblasts limit the proliferation of glial fibrillary acidic protein (GFAP)-expressing progenitors thought to be stem cells. However, signals between SVZ cells have not been identified. We show that depolarization of neuroblasts induces nonsynaptic SNARE-independent $GABA_A$ receptor currents in GFAP-expressing cells, the time course of which depends on GABA uptake in acute mouse slices. We found that $GABA_A$ receptors are tonically activated in GFAP-expressing cells, consistent with the presence of spontaneous depolarizations in neuroblasts that are sufficient to induce GABA release. These data demonstrate the existence of nonsynaptic GABAergic signaling between neuroblasts and GFAP-expressing cells. Furthermore, we show that $GABA_A$ receptor activation in GFAP-expressing cells limits their progression through the cell cycle. Thus, as GFAP-expressing cells generate neuroblasts, GABA released from neuroblasts provides a feedback mechanism to control the proliferation of GFAP-expressing progenitors by activating $GABA_A$ receptors.

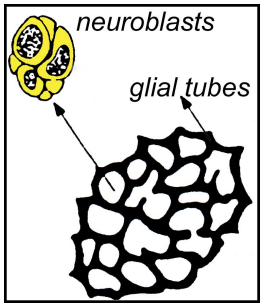


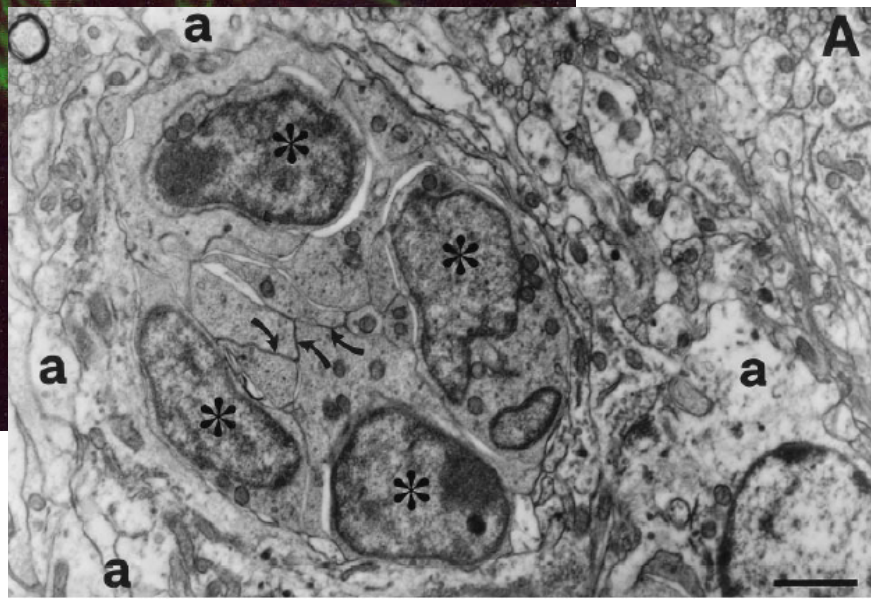
→ Cell–cell interactions in the adult SVZ.
GABA released from neuroblasts (NB) negatively regulates the proliferation of NPCs.

→ GABA is a key player regulating multiple steps of adult neurogenesis

SVZ-neuroblasts migration (tangential migration-glial tubes)



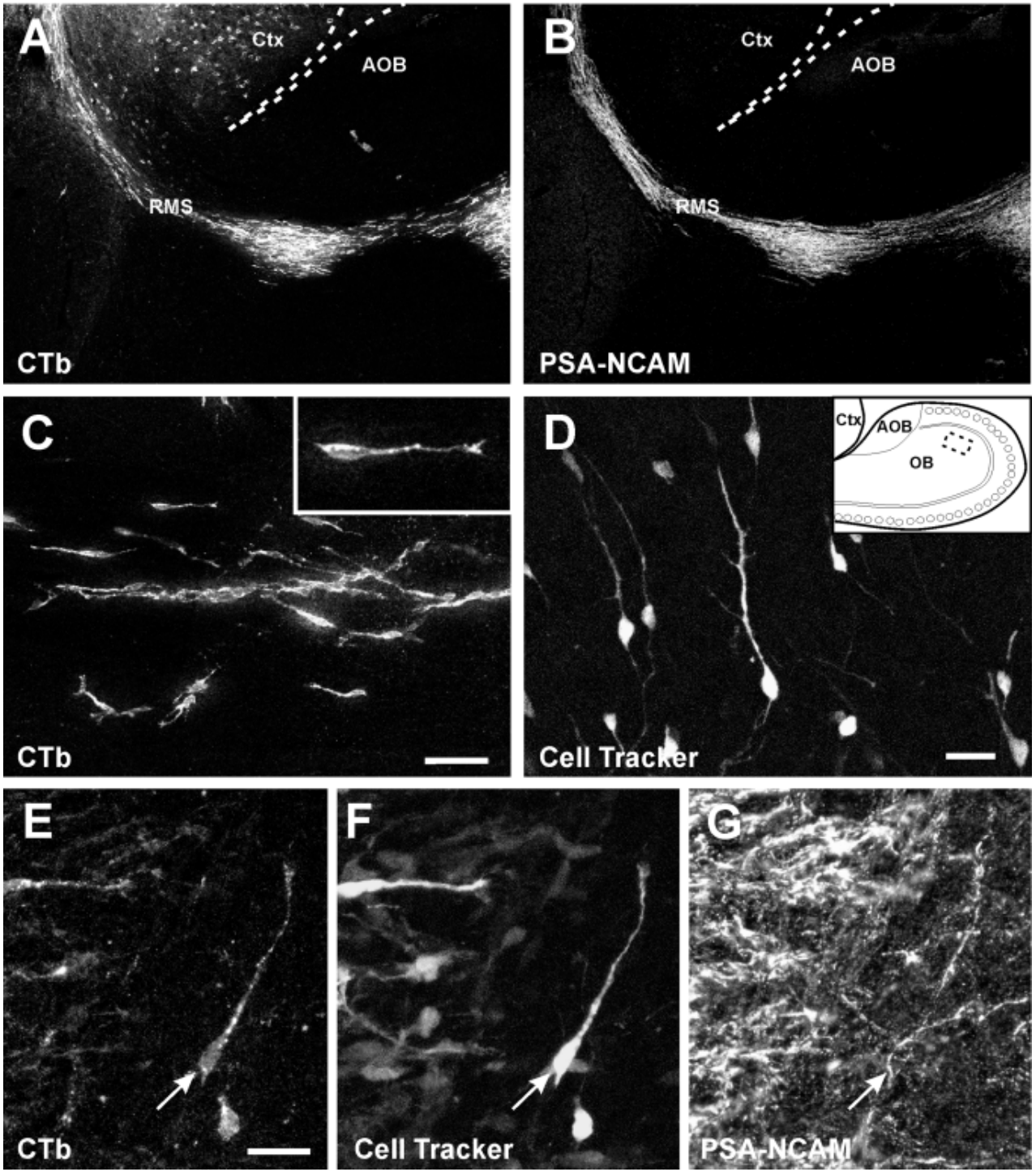




Peretto et al., 1997 Brain Res Bull

MOUSE *Lois and Alvarez Buylla, 1996 Science*

Stereotaxic injection
of fluorescent dyes:
Ctb
Cell tracker green



Unique Neuronal Tracers Show Migration and Differentiation of SVZ Progenitors in Organotypic Slices

S. De Marchis,[1] A. Fasolo,[1] M. Shipley, [2] A. Puche[2]

[1] Department of Human and Animal Biology, University of Torino, 10123 Torino, Italy

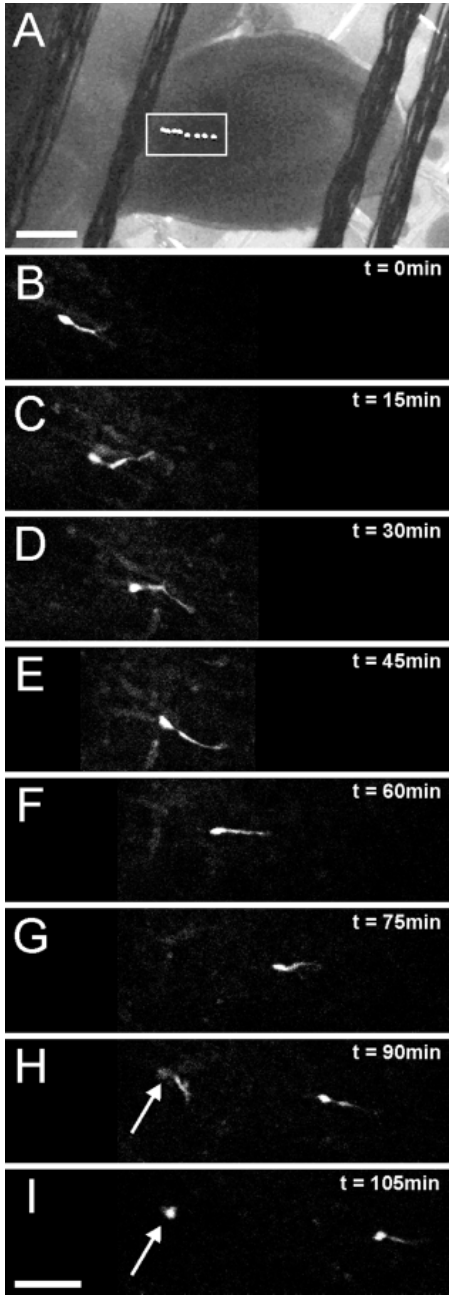
[2] Department of Anatomy and Neurobiology, University of Maryland, School of Medicine, Rm. 222, 685 W. Baltimore, Baltimore, Maryland 21201

Received 20 June 2001; accepted 15 August 2001

ABSTRACT: Continual neurogenesis in the subventricular zone (SVZ) of postnatal and adult mammalian forebrain has been well documented, but the mechanisms underlying cell migration and differentiation in this region are poorly understood. We have developed novel *in vivo* and *in vitro* methods to investigate these processes. Using stereotaxic injections of a variety of tracers/tracker [Cholera Toxin β subunit (CTb-), Fluorogold (FG), and Cell Tracker Green (CTG)], we could efficiently label SVZ cells. Over several days, labeled cells migrate along the rostral migratory stream (RMS) to their final differentiation site in the olfactory bulb (OB). The compatibility of these tracers/trackers with immunohistochemistry allows for cell labeling with multiple dyes (e.g., CTb and CTG) and/or specific cell antigens. To investigate the dynamics of migration we labeled SVZ progenitor cells with small injections of CTG and monitored the movements of individual cells in fresh parasagittal brain slices over several hours using time-lapse confocal microscopy. Our observations suggest that tangential cell migration along the RMS occurs more rapidly than radial cell migration into the OB granule cell layer. To investigate migration over longer time periods, we developed an *in vitro* organotypic slice in which labeled SVZ progenitors migrate along the RMS and differentiate within the OB. The phenotypic characteristics of these cells *in vitro* were equivalent to those observed *in vivo*. Taken together, these methods provide useful tools investigating cell migration and differentiation in a preparation that maintains the anatomical organization of the RMS. © 2001 John Wiley & Sons, Inc.

J Neurobiol 49: 326–338, 2001

Keywords: subventricular zone; subependymal layer; olfactory bulb; cell migration; cell differenetiation; organotypic culture



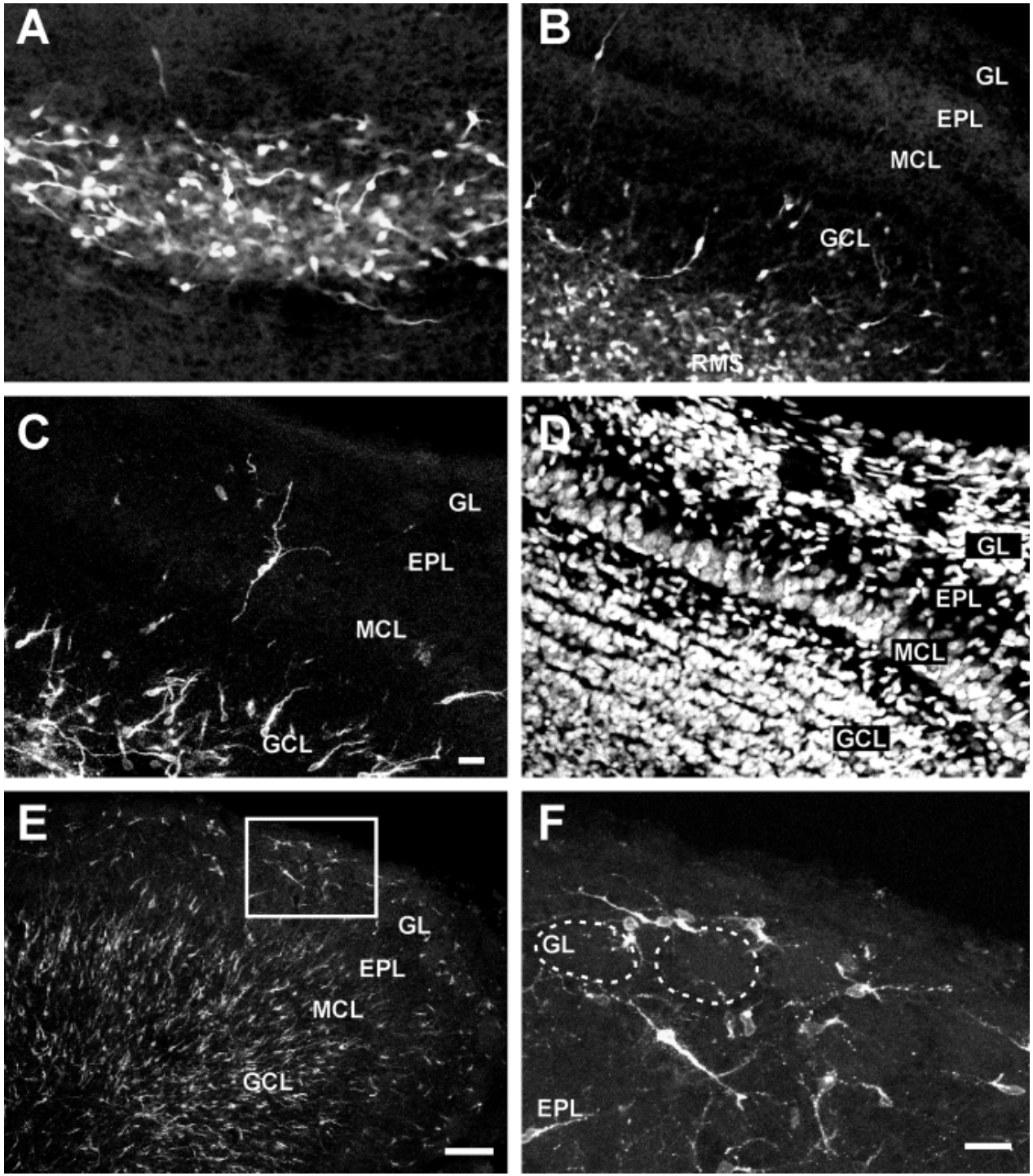
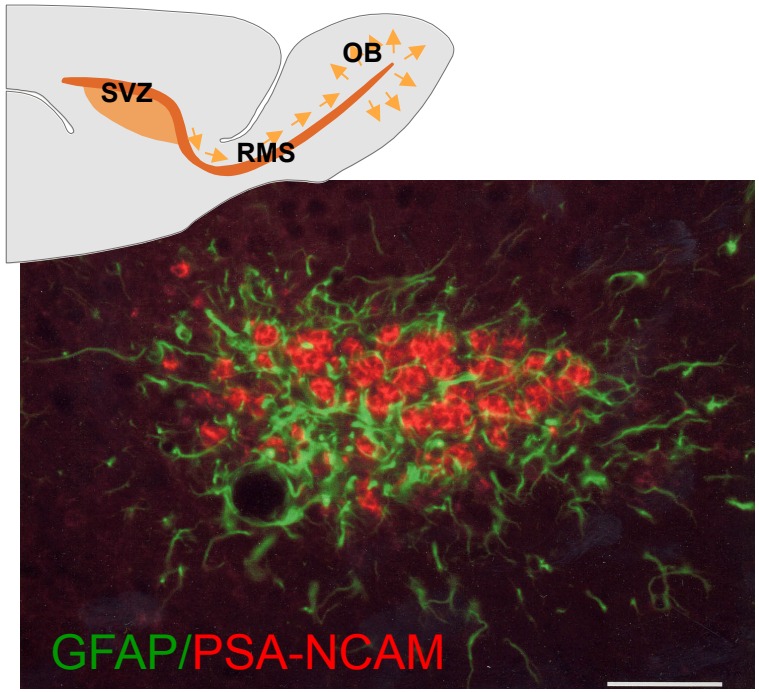
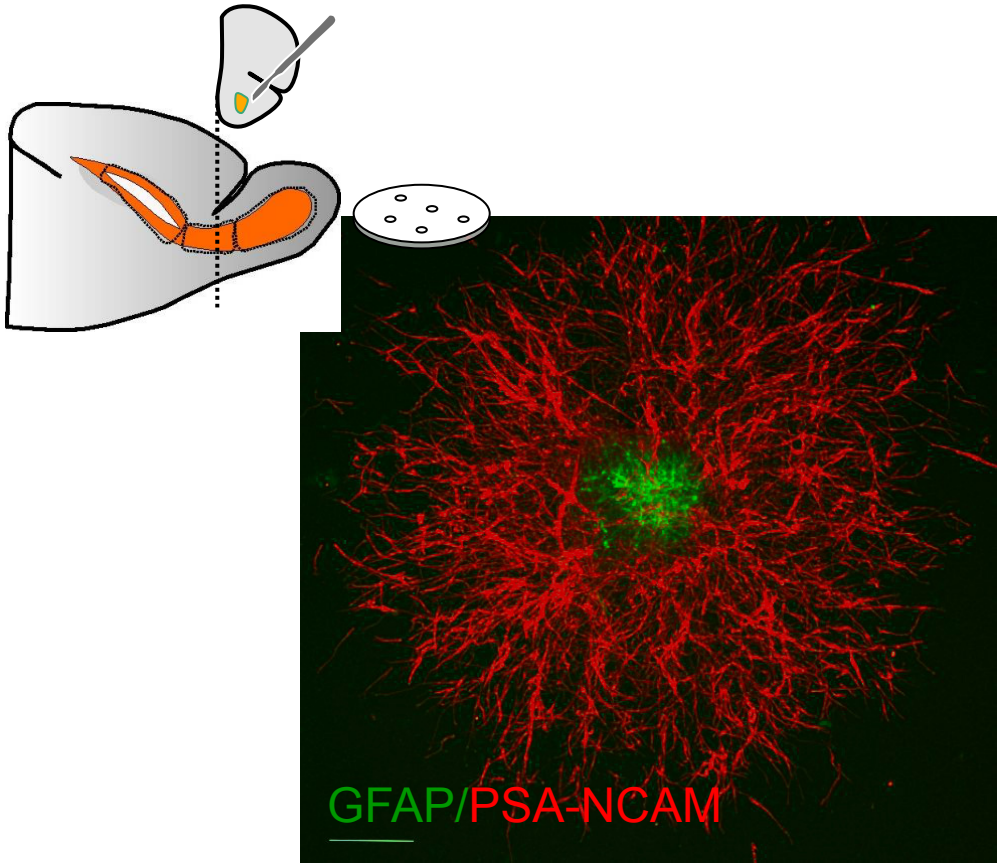


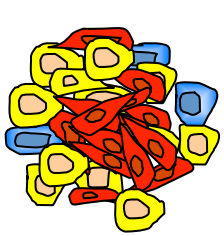
Figure 2 Parasagittal sections of the forebrain of newborn mice 1–2 (A,B), 3–4 (C,D), and 6 (E,F) days postinjection.

(A) Numerous CTb labeled cells migrating in the rostral migratory stream 1–2 days post injection.
(B) In the olfactory bulb of a 1–2-daypost injection animal, only a few scattered cells have left the RMS and entered the granule cell layer.
(C) At 3–4 days postinjection labeled cells are present throughout the granule cell layer and scattered cells are present in the external plexiform and glomerular layers.
(D) Nuclear counterstaining of the same section in (C) showing the position of the bulb layers.
(E) Six days postinjection; labeled cells are distributed widely throughout the bulb.
(F) Higher magnification of the insert in (F) showing dye-labeled juxtaglomerular neurons.

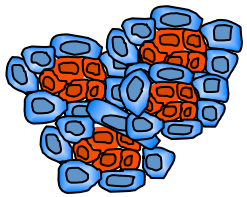
Neuronal migration in the RMS





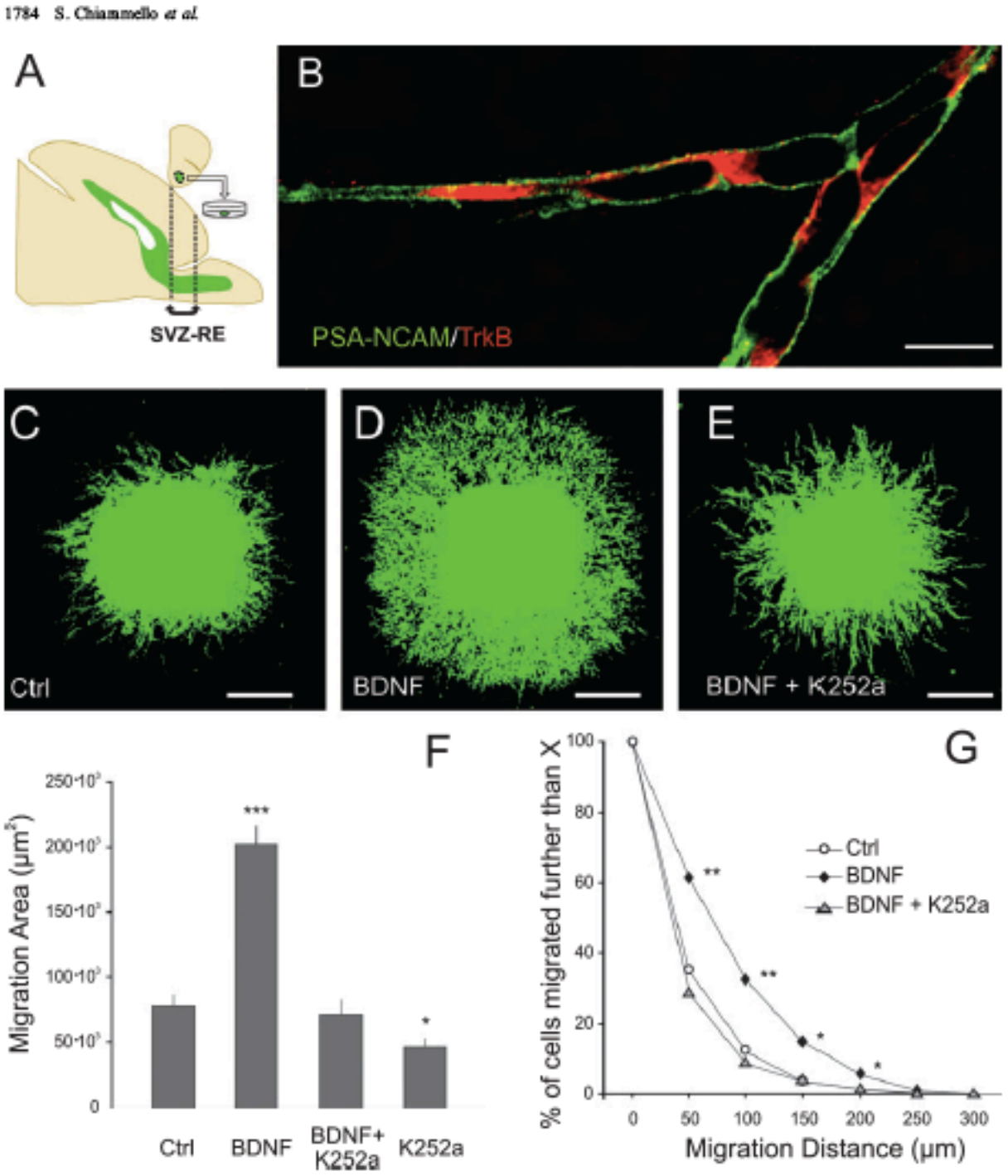


P5



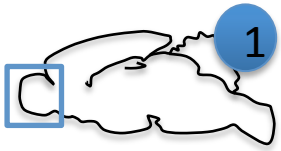
adult

Tissue explants
In vitro assay

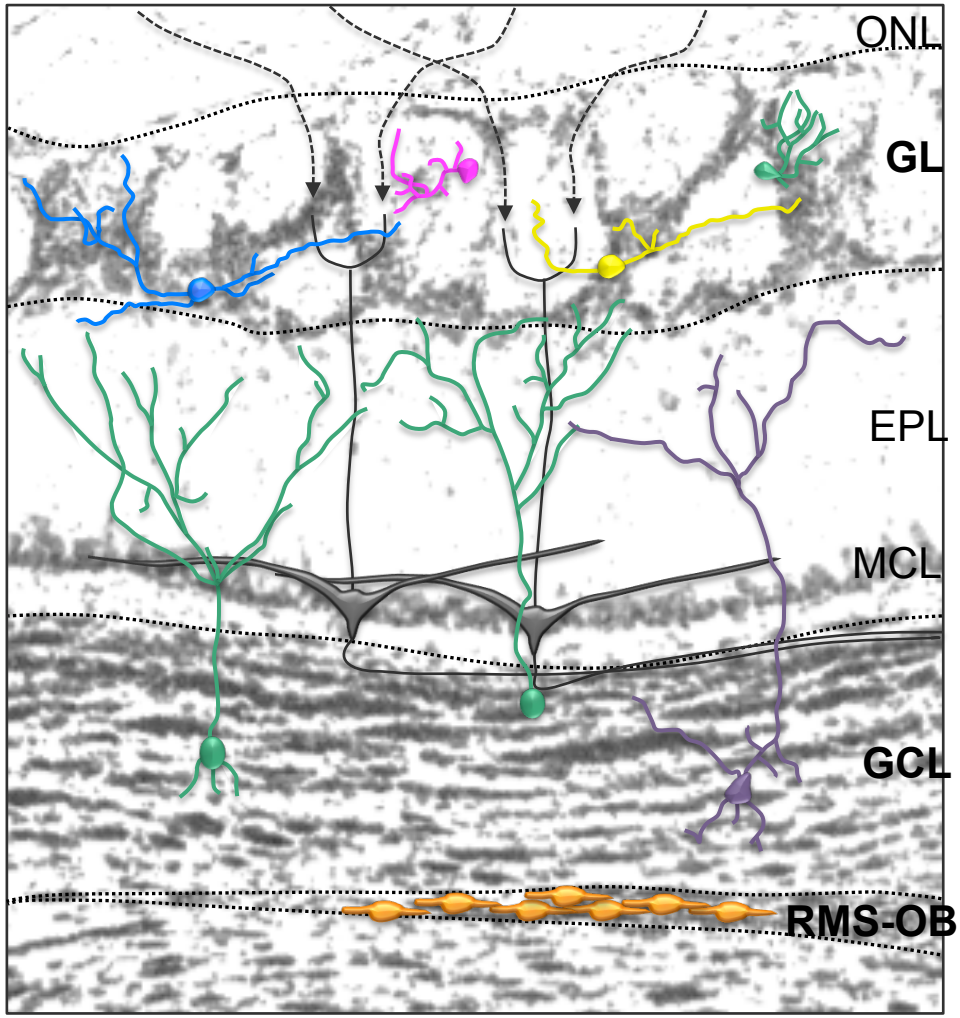


Chiaramello et al., EJN 2007

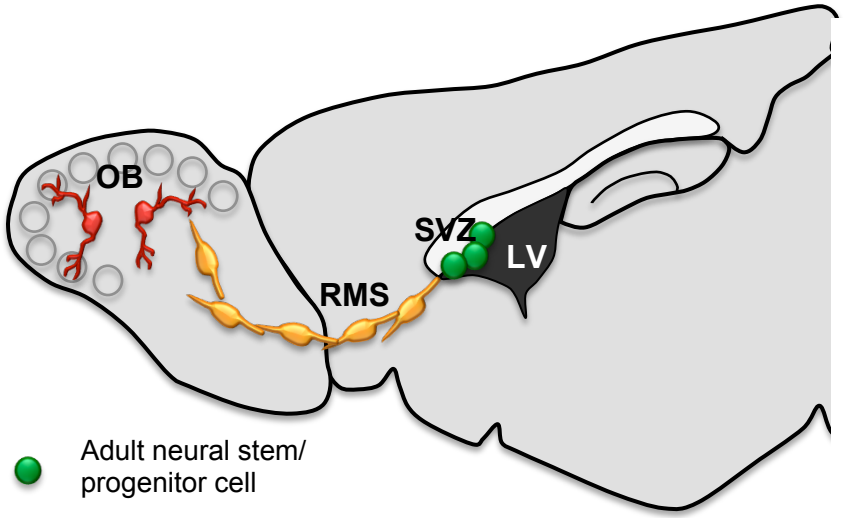
Generation of cellular diversity in the OB



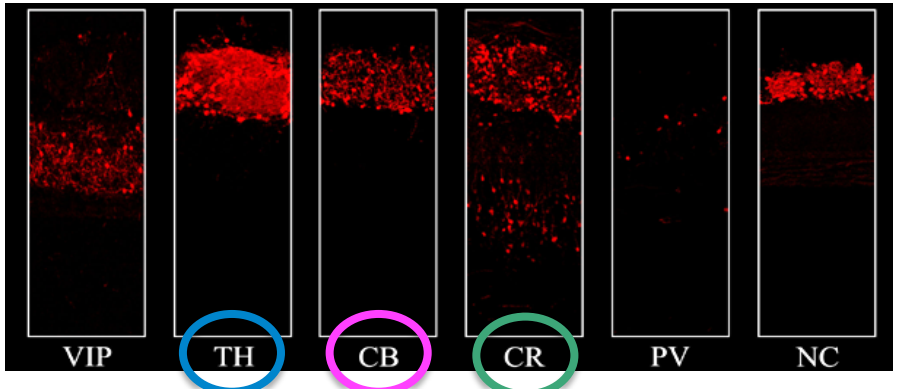
INIBITORY GABAERGIC INTERNEURONS



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



Neurochemical phenotypes of OB GABAergic interneurons



Development/Plasticity/Repair

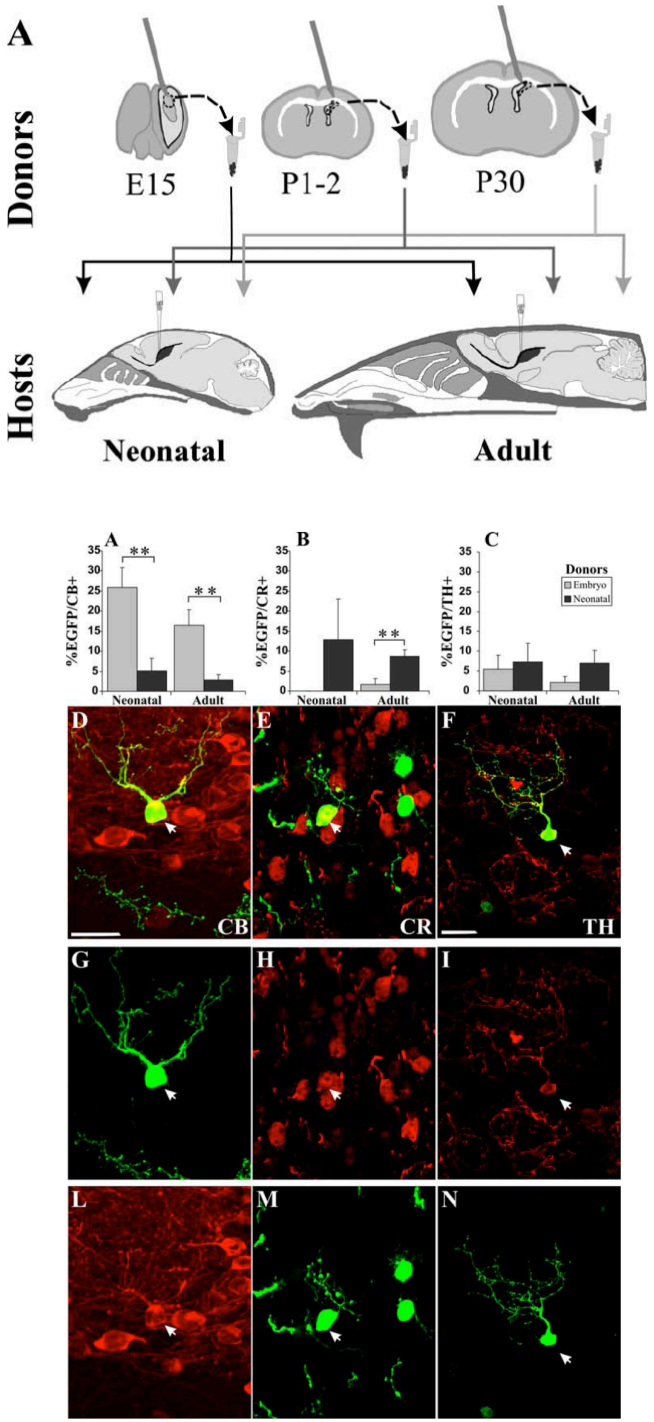
Generation of Distinct Types of Periglomerular Olfactory Bulb Interneurons during Development and in Adult Mice: Implication for Intrinsic Properties of the Subventricular Zone Progenitor Population

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.

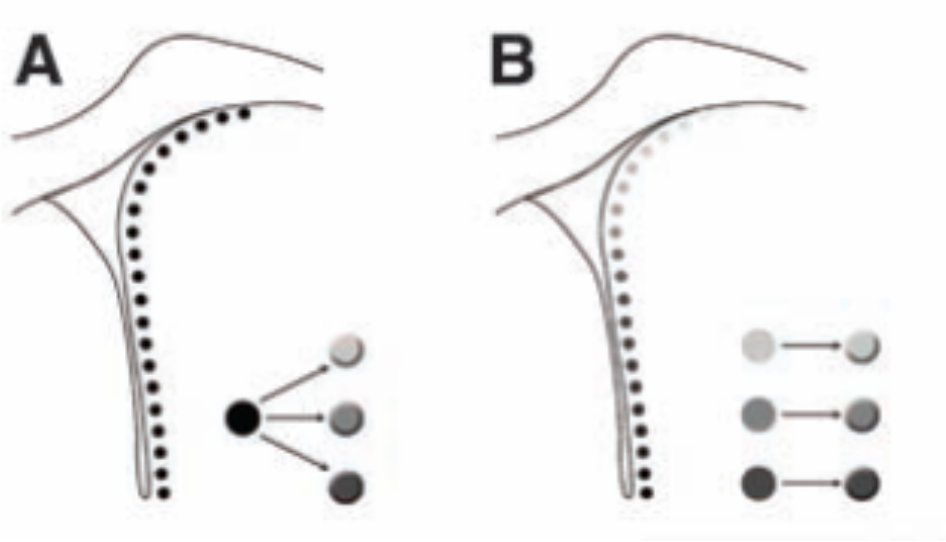
Key words: olfactory bulb; subventricular zone; transplantation; periglomerular cell; specification; neurogenesis



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

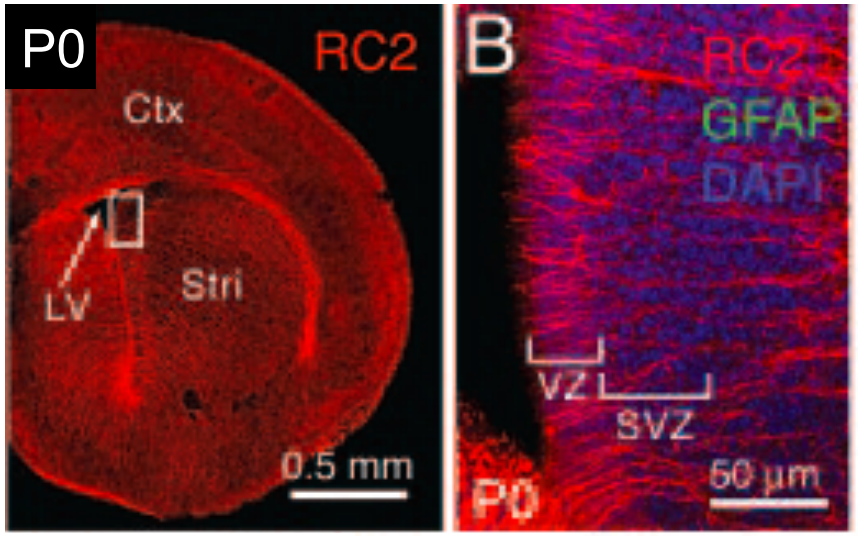
Model of SVZ stem cell potential

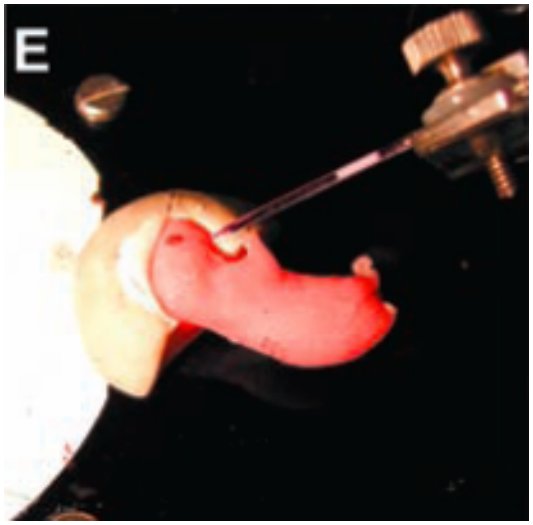


Equivalent stem cells generate multiple neuron types

OR

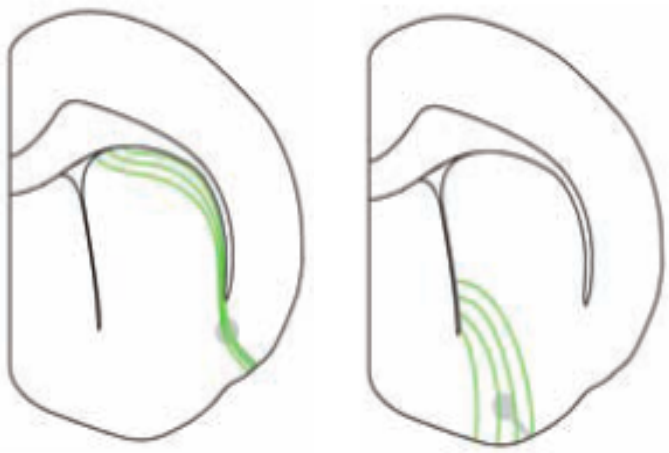
Different stem cells generate specific neuron types





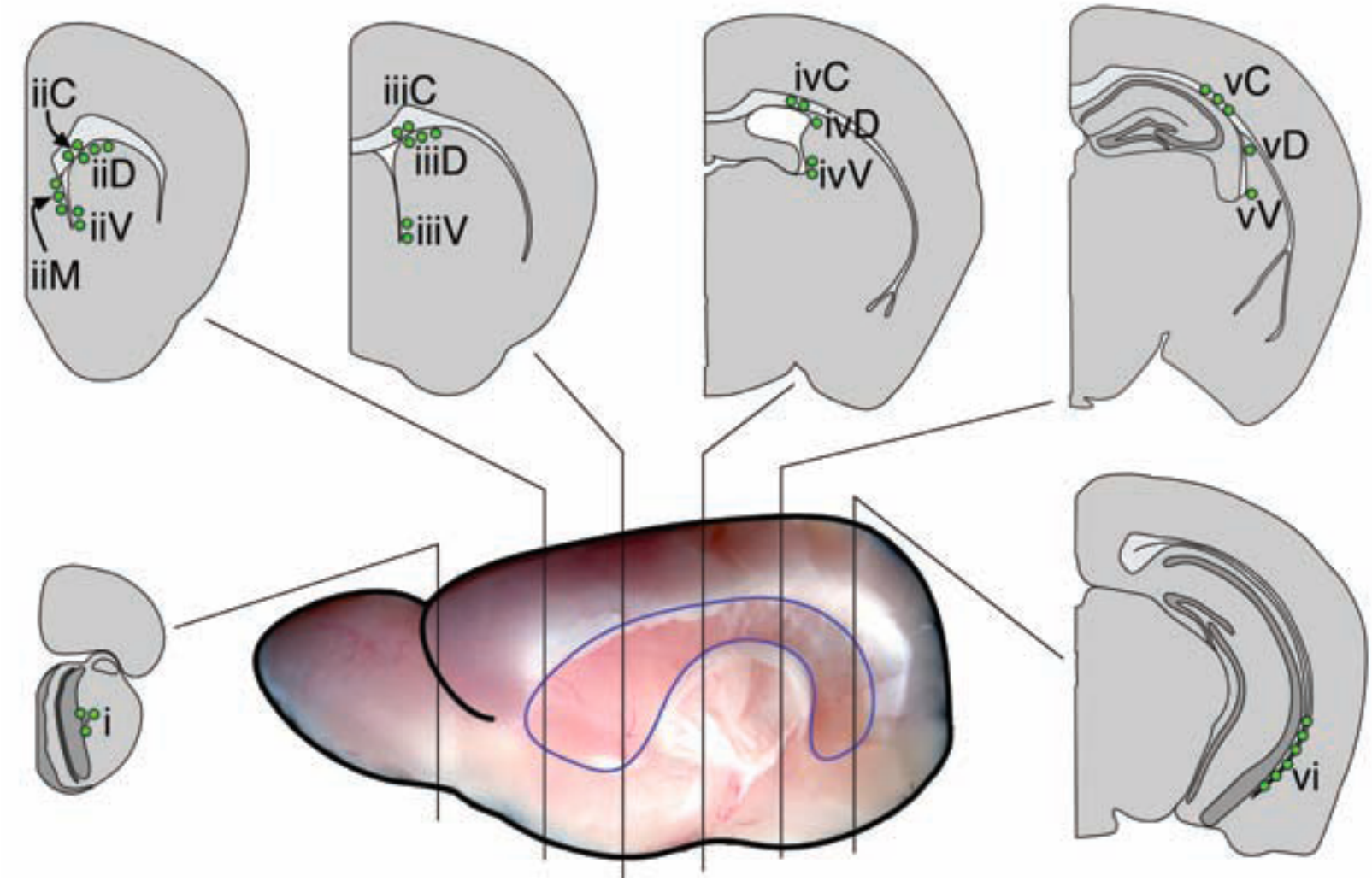
(Merkle et al., 2004)

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

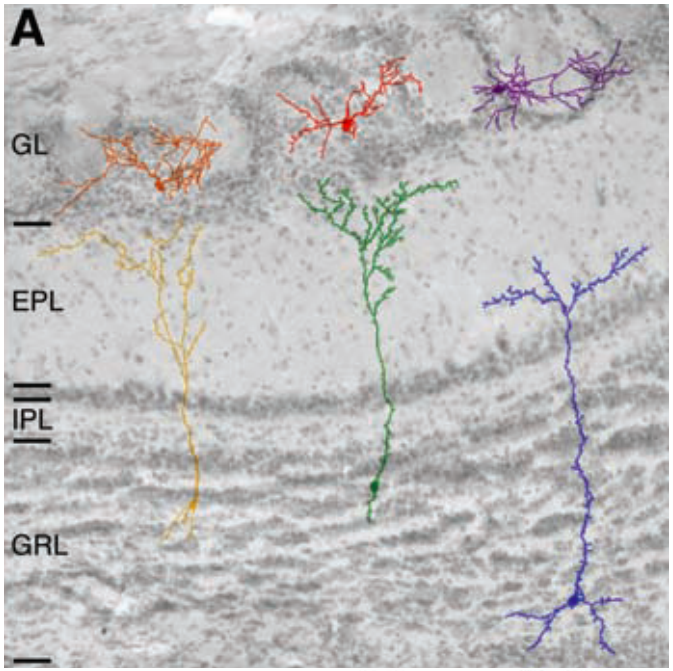


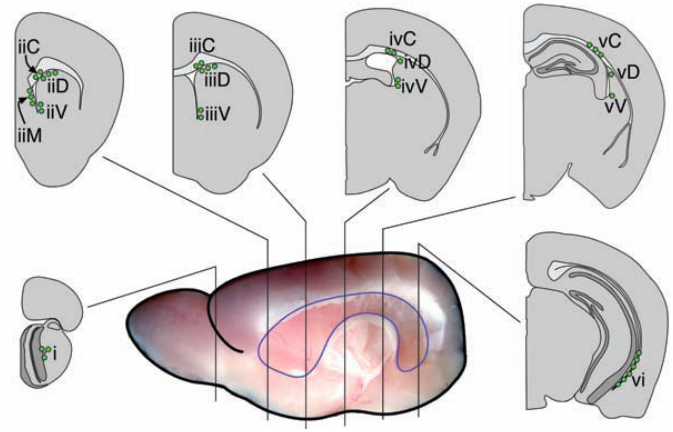
RGCs have a unique morphology that allows them to be targeted specifically

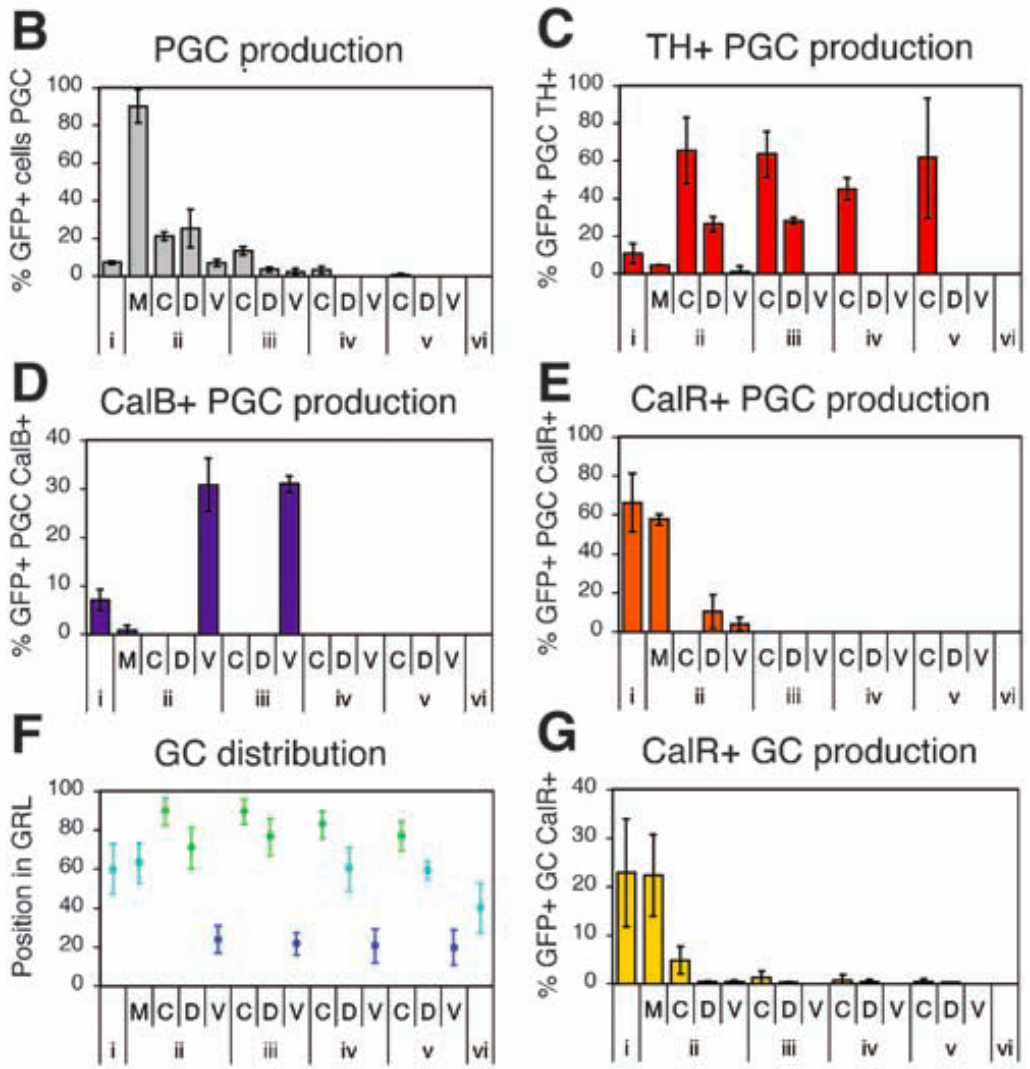
Adenovirus expressing Cre recombinase (Ad:Cre) injected into green fluorescent protein (GFP) reporter (Z/EG) mice, infected radial glia and their progeny become permanently labeled with GFP



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





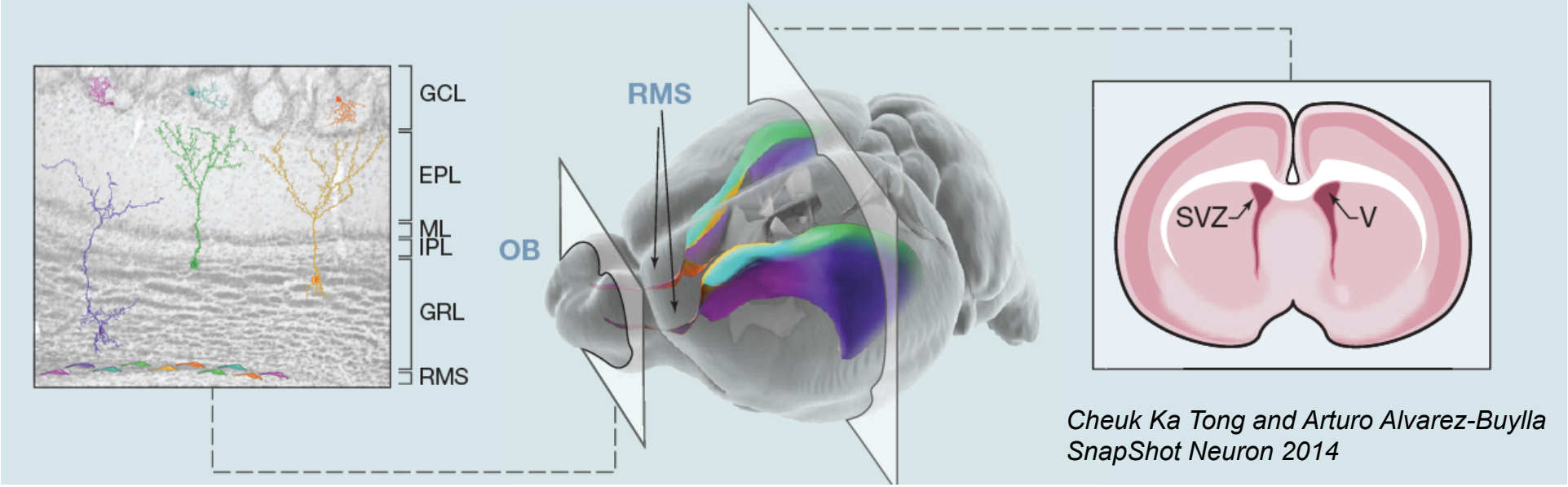


NSC are regionally specified in both the neonatal and adult SVZ

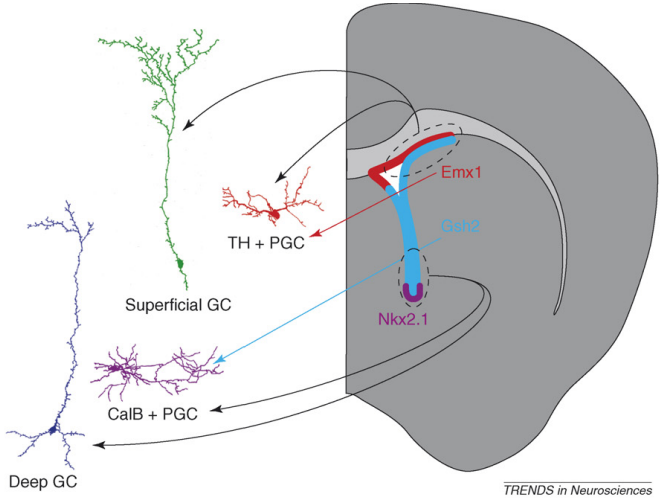
→different types of OB interneurons are derived from different locations in the SVZ

The olfactory bulb

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



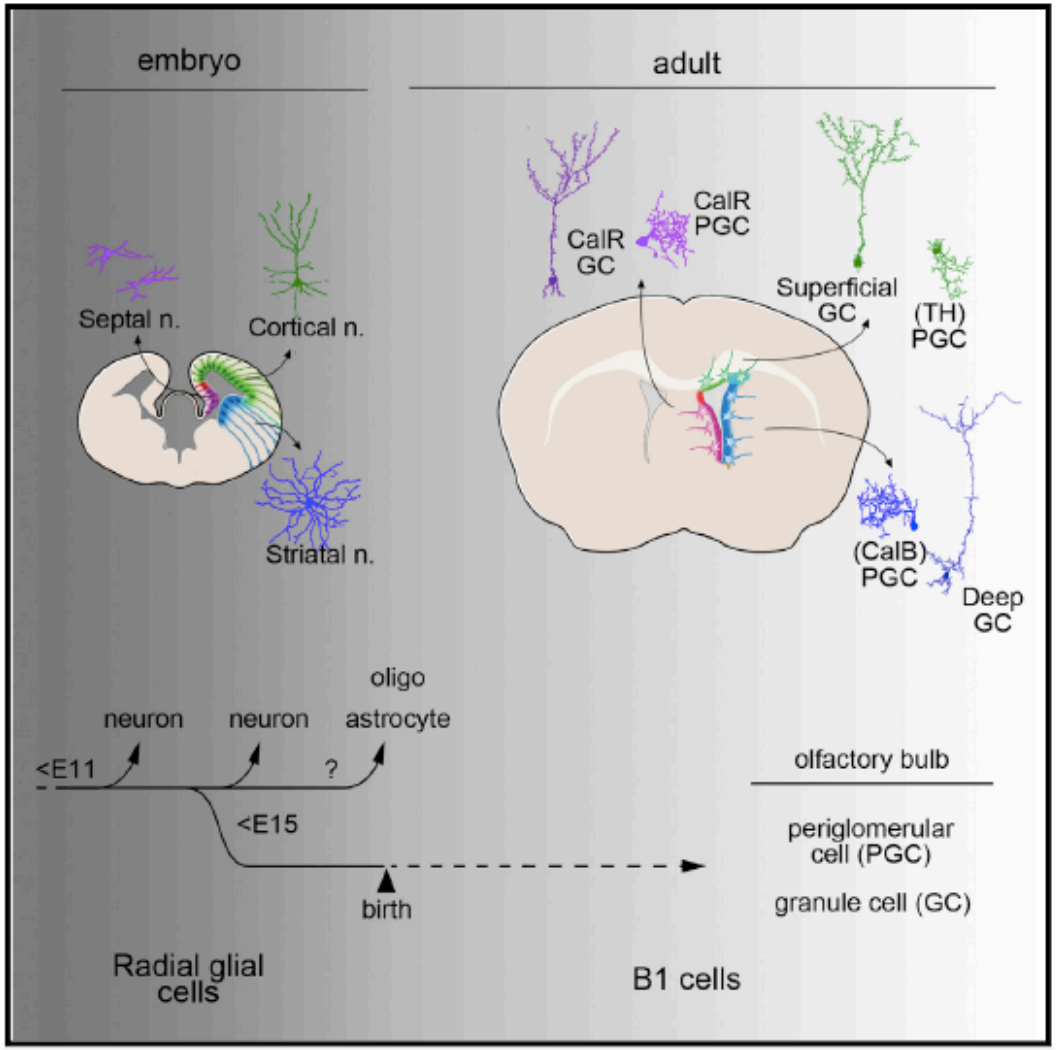
Cheuk Ka Tong and Arturo Alvarez-Buylla
SnapShot Neuron 2014



Cell 2015

Embryonic Origin of Postnatal Neural Stem Cells

Graphical Abstract



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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.