

Renovación celular en el cerebro adulto



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ciberMed

TerCel
Red de Terapia Celular



BIOTECMED
ERI de Biotecnología i Biomedicina
Estructura de Recerca Interdisciplinar de
la Universitat de València



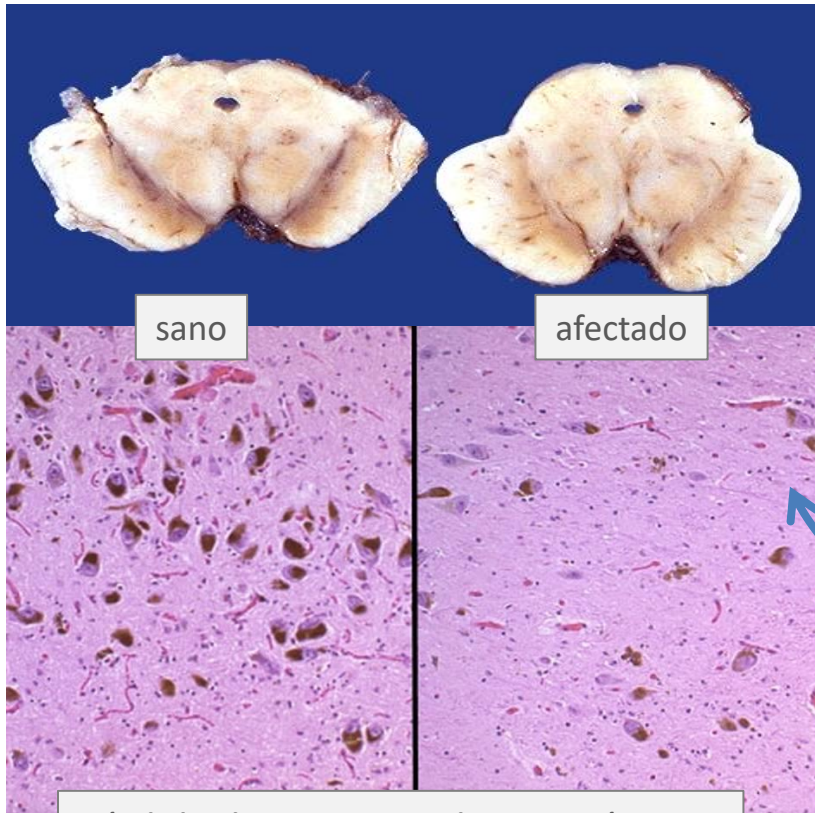
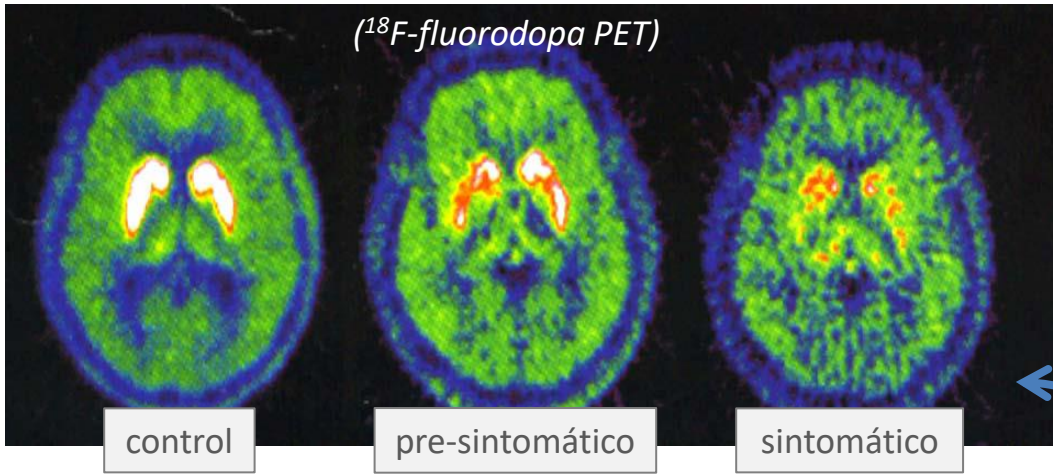
GENERALITAT VALENCIANA
CONSELLERIA D'EDUCACIÓ, CULTURA I ESPORT

**FUNDACIÓN
BOTÍN**

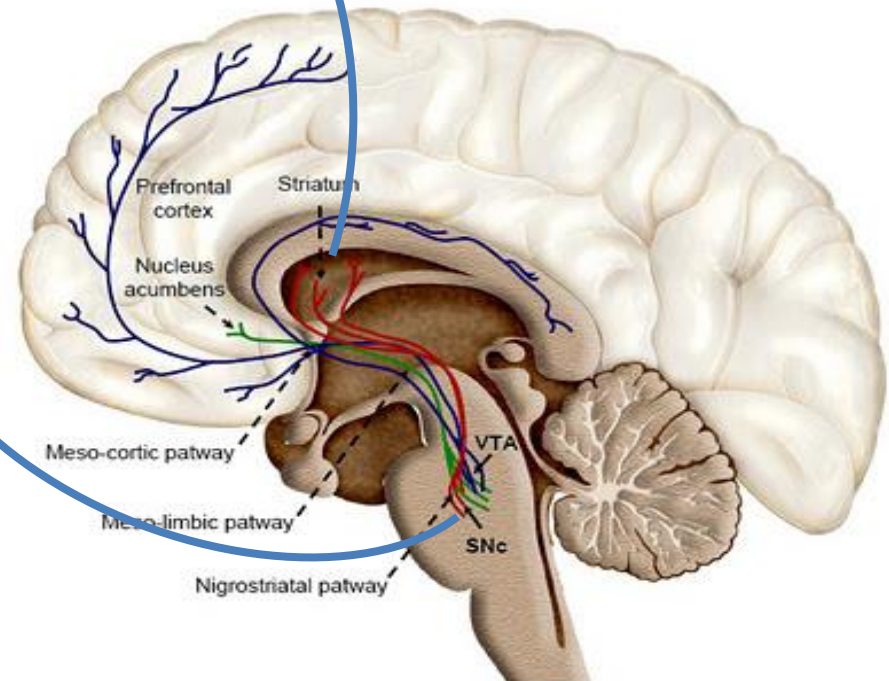
Renovación celular en el cerebro adulto

- Medicina regenerativa: ¿pueden nuestros cerebros acoger nuevas neuronas para recuperar situaciones de lesión o degeneración?
- Generación de nuevas neuronas: ¿ producen nuestros cerebros neuronas a lo largo de la vida de manera natural?

^{18}F -fluorodopa PET



Pérdida de neuronas dopaminérgicas





Estrategias terapéuticas en EP

¿Por qué terapia celular?

1- Neuroprotección: factores neurotróficos.

Sin embargo, el diagnóstico precoz no es posible: Falta de biomarcadores.

2- Restitución del déficit: fuente celular de liberación de dopamina o SUSTITUCIÓN NEURONAL.

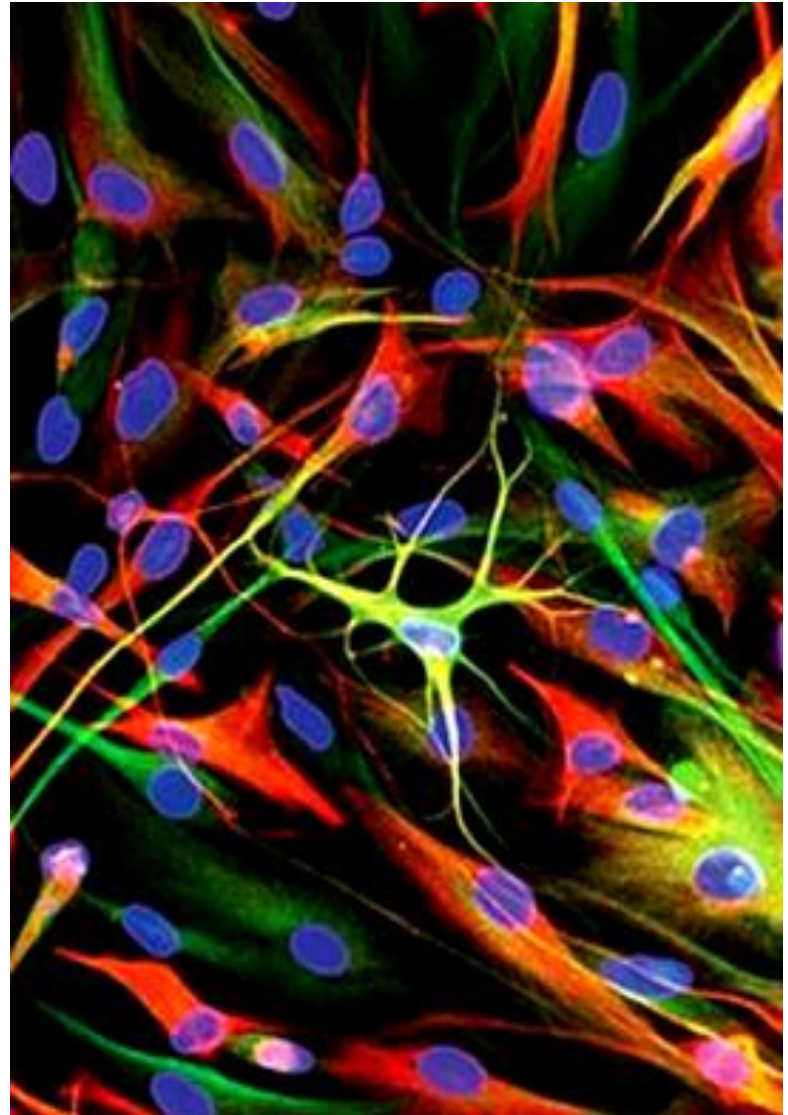
30 años de trasplantes en EP

- Primeros trasplantes tras los ensayos pre-clínicos: finales de los años 80 (Suecia, México, Inglaterra, EEUU, etc). Mejoría de los pacientes. Sin grupo placebo.
- Número bajo de trasplantes con técnicas quirúrgicas diferentes: dispersión de los datos. Prueba de seguridad y factibilidad.
- En 1993, se permite en EEUU que los Institutos Nacionales de Salud (NIH) financien este tipo de ensayos clínicos: primeros **ensayos doble-ciego**, con grupo placebo (controvertido). *Ensayos de Colorado y Tampa*.

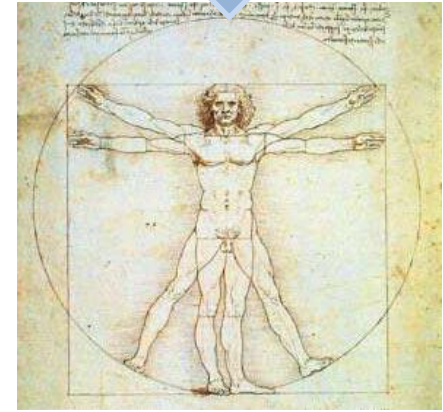
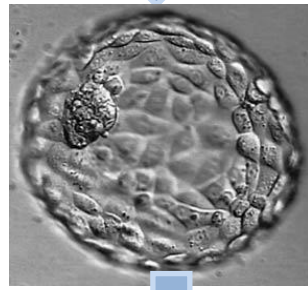
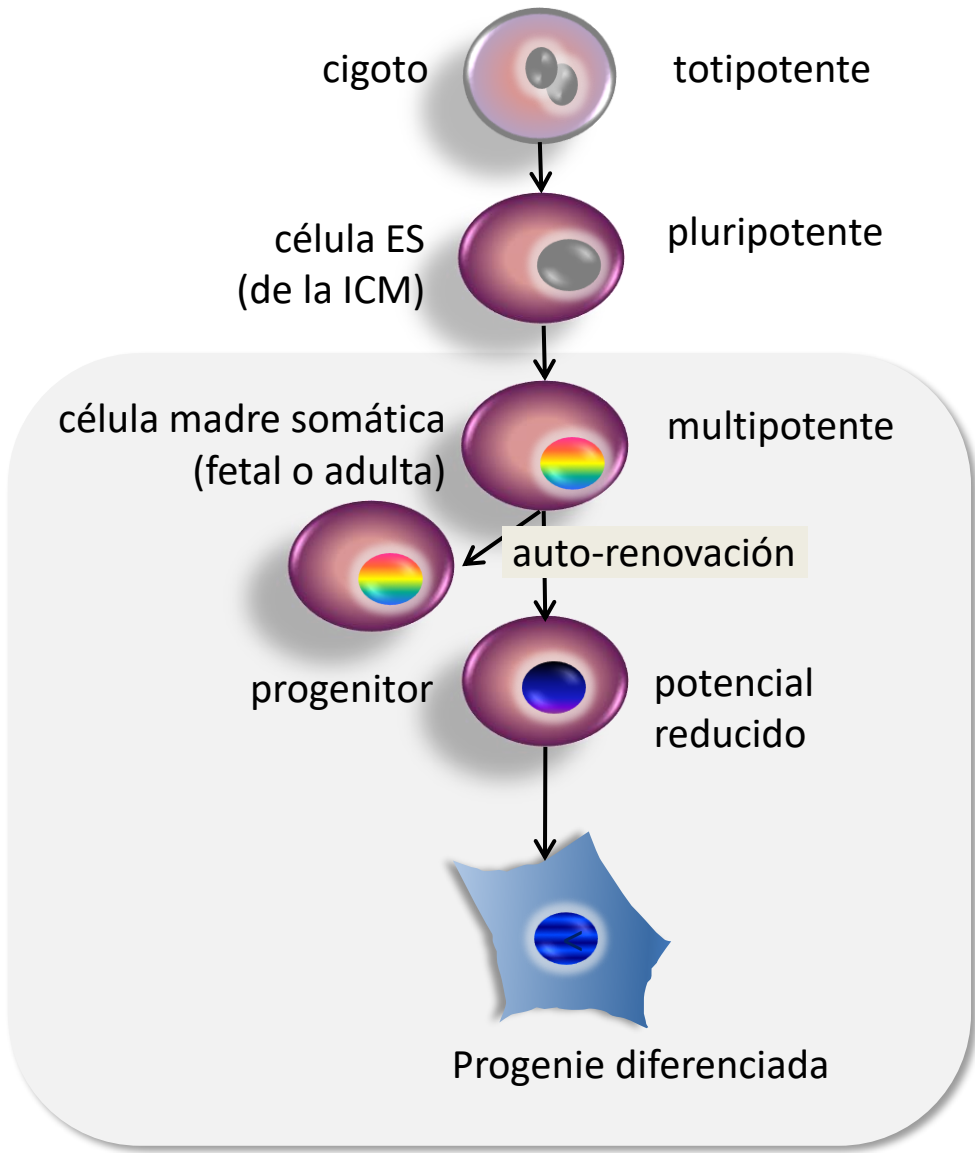
En lo que todos coinciden:

- Las neuronas trasplantadas sobreviven.
- No se necesita inmunosupresión.
- Mejoría, si hay buena producción de dopamina.

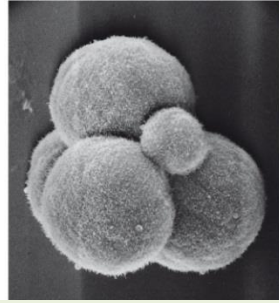
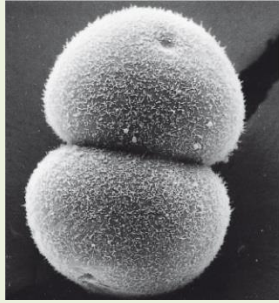
- Problemas:
 - Variabilidad celular: supervivencia, liberación de dopamina, crecimiento.
 - Rendimiento celular: 500.000 neuronas dopaminérgicas en la SN de una persona adulta. Aprox. 10.000 neuronas por feto sobreviven el proceso (4-6 fetos de 6-8 semanas por paciente trasplantado).
 - Necesidad de fuentes celulares alternativas.
 - **Células madre** de distintos orígenes: expandibles y con gran potencial de desarrollo.



potencial



cigoto

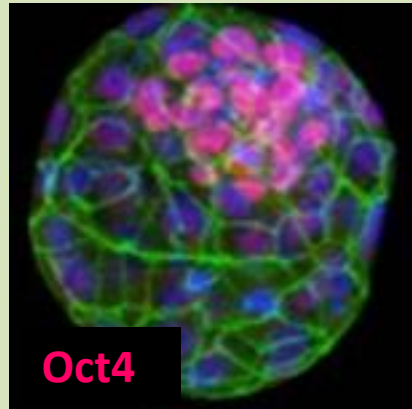


mórula

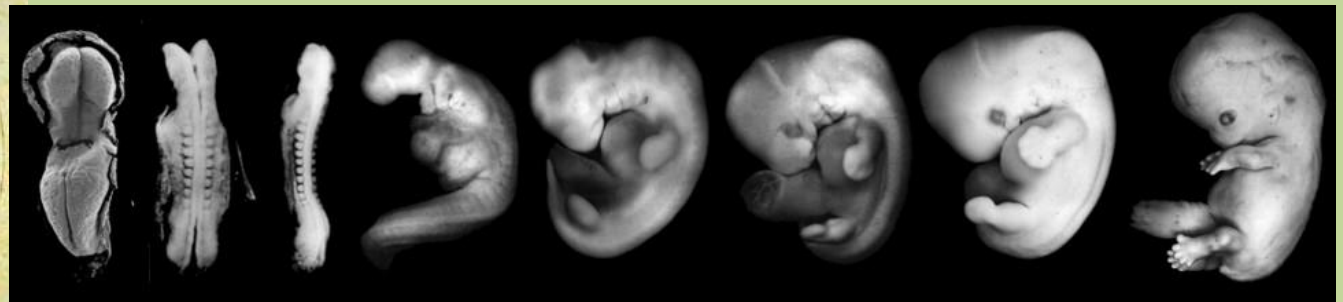
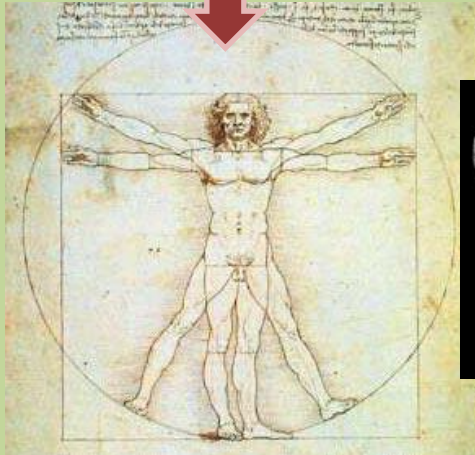
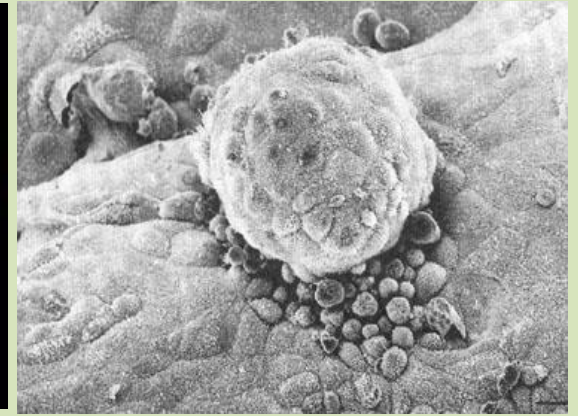


Blastocisto:

- Trofotodermo
- Masa celular interna

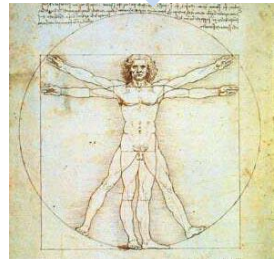
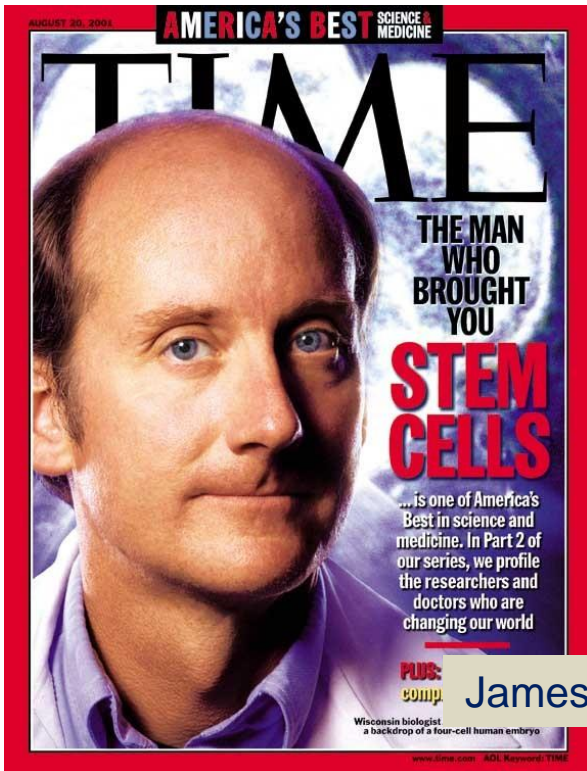
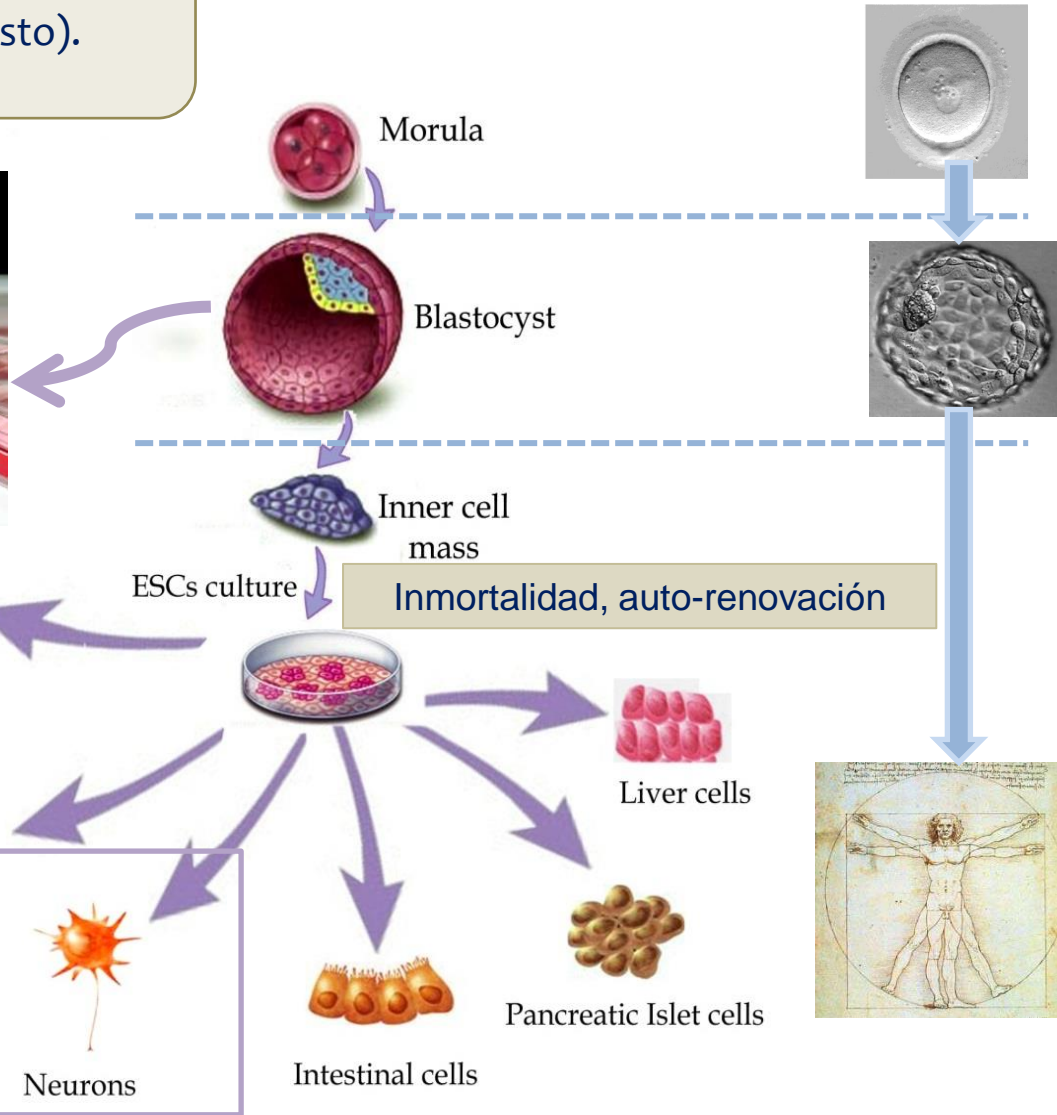


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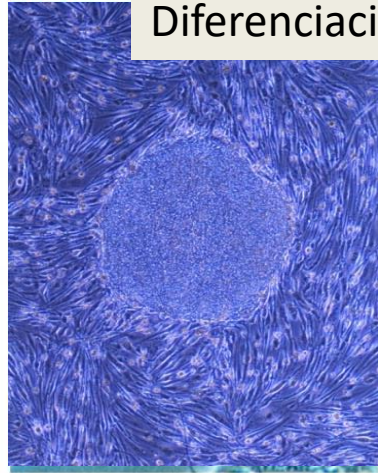
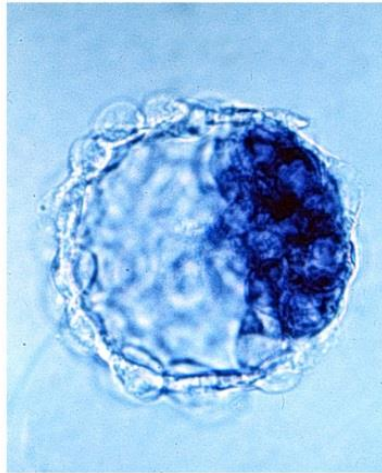


10^{14} células, >200 tipos distintos

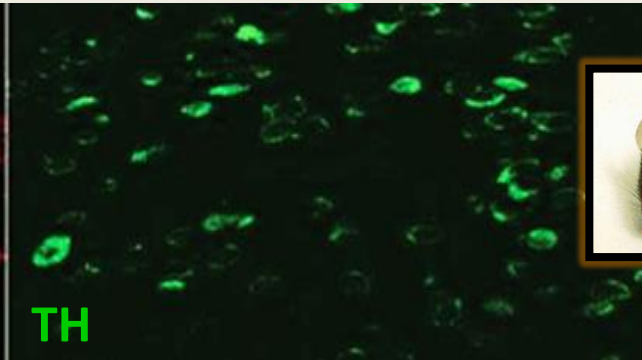
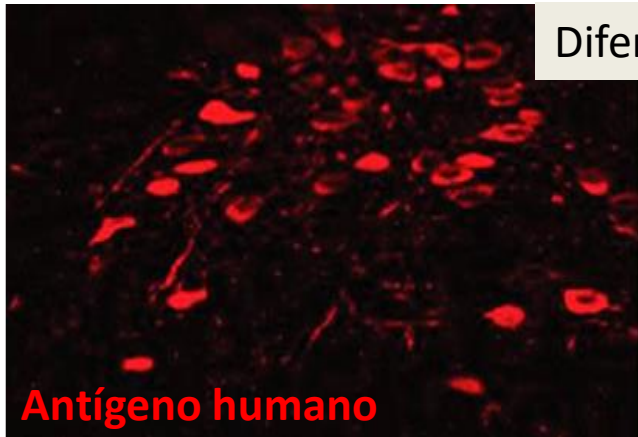
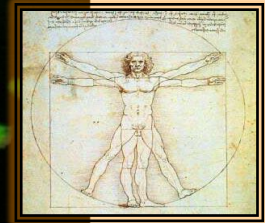
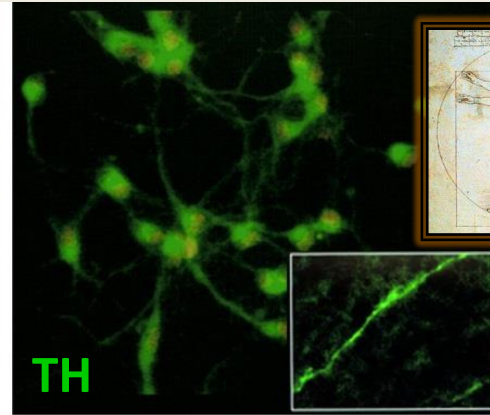
Células madre embrionarias humanas:
 pluripotentes; provienen de la masa celular interna
 de un embrión fecundado (estadio blastocisto).
 Propagación ilimitada.



Producción de neuronas dopaminérgicas *in vitro* para trasplante a partir de células pluripotentes. Se consigue un buen porcentaje de diferenciación y ya se han realizado “pruebas de concepto”. Pero, no se puede garantizar la seguridad.



Diferenciación dopaminérgica *in vitro*

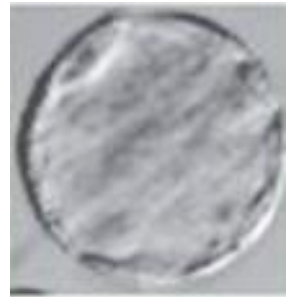
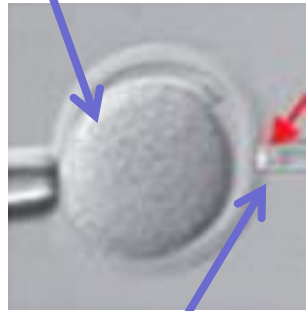
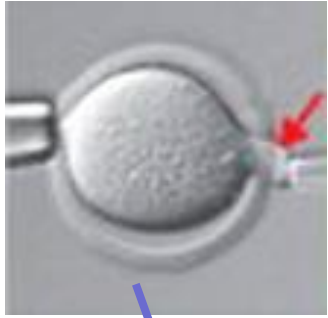


Diferenciación dopaminérgica *in vivo*



Transferencia nuclear somática: SCNT

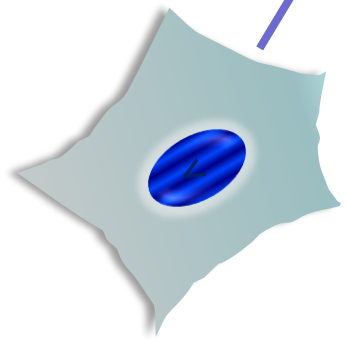
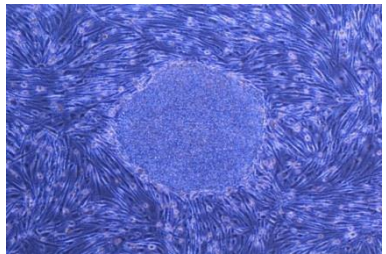
OOCITO ENUCLEADO



CLONACIÓN REPRODUCTIVA



CLONACIÓN TERAPÉUTICA



FIBROBLASTO DÉRMICO

AISLAMIENTO DE LAS CÉLULAS ES: idénticas genéticamente al individuo del que procede el núcleo

Transferencia nuclear (SCNT) en humanos



LETTERS

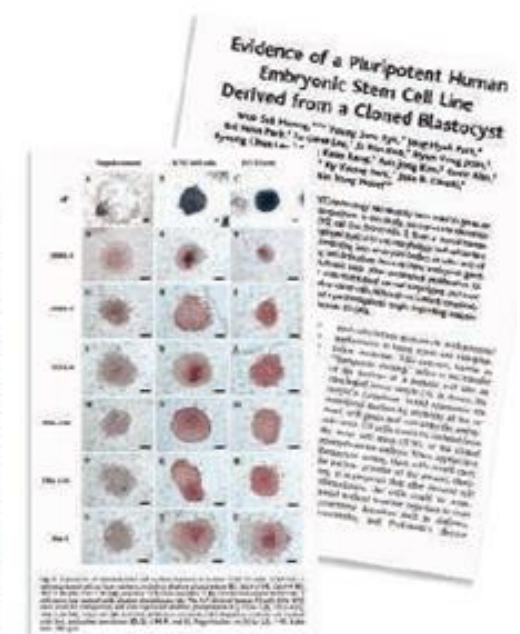
edited by Etta Kavanagh

Editorial Retraction

THE FINAL REPORT FROM THE INVESTIGATION COMMITTEE of Seoul National University (SNU) (1) has concluded that the authors of two papers published in *Science* (2, 3) have engaged in research misconduct and that the papers contain fabricated data. With regard to Hwang *et al.*, 2004 (2), the Investigation Committee reported that the data showing that DNA from human embryonic stem cell line NT-1 is identical to that of the donor are invalid because they are the result of fabrication, as is the evidence that NT-1 is a bona fide stem cell line. Further, the committee found that the claim in Hwang *et al.*, 2005 (3) that 11 patient-specific embryonic stem cells line were derived from cloned blastocysts is based on fabricated data. According to the report of the Investigation Committee, the laboratory “does not possess patient-specific stem cell lines or any scientific basis for claiming to have created one.” Because the final report of the SNU investigation indicated that a significant amount of the data presented in both papers is fabricated, the editors of *Science* feel that an immediate and unconditional retraction of both papers is needed. We therefore retract these two papers and advise the scientific community that the results reported in them are deemed to be invalid.

As we post this retraction, seven of the 15 authors of Hwang *et al.*, 2004 (2) have agreed to retract their paper. All of the authors of Hwang *et al.*, 2005 (3) have agreed to retract their paper.

Science regrets the time that the peer reviewers and others spent evaluating these papers as well as the time and resources that the scientific community may have spent trying to replicate these results.



2005 fraude en Korea:
Woo-Suk Hwang lab

DONALD KENNEDY

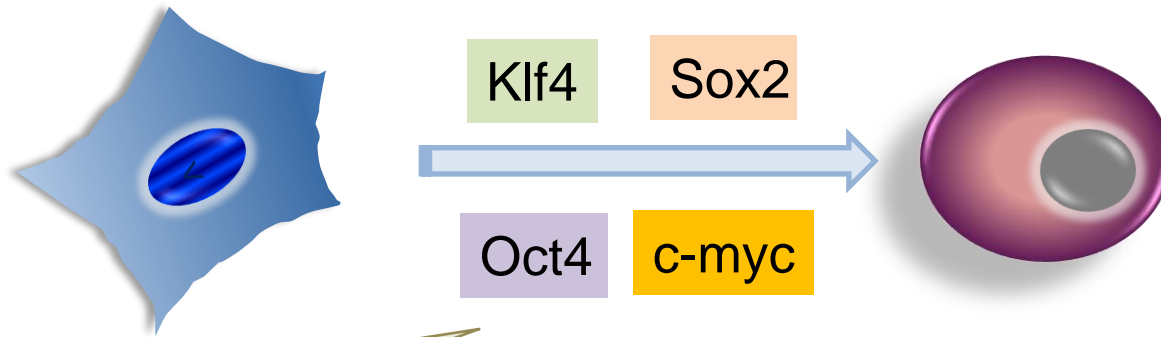
Editor-in-Chief



Shinya Yamanaka
2012

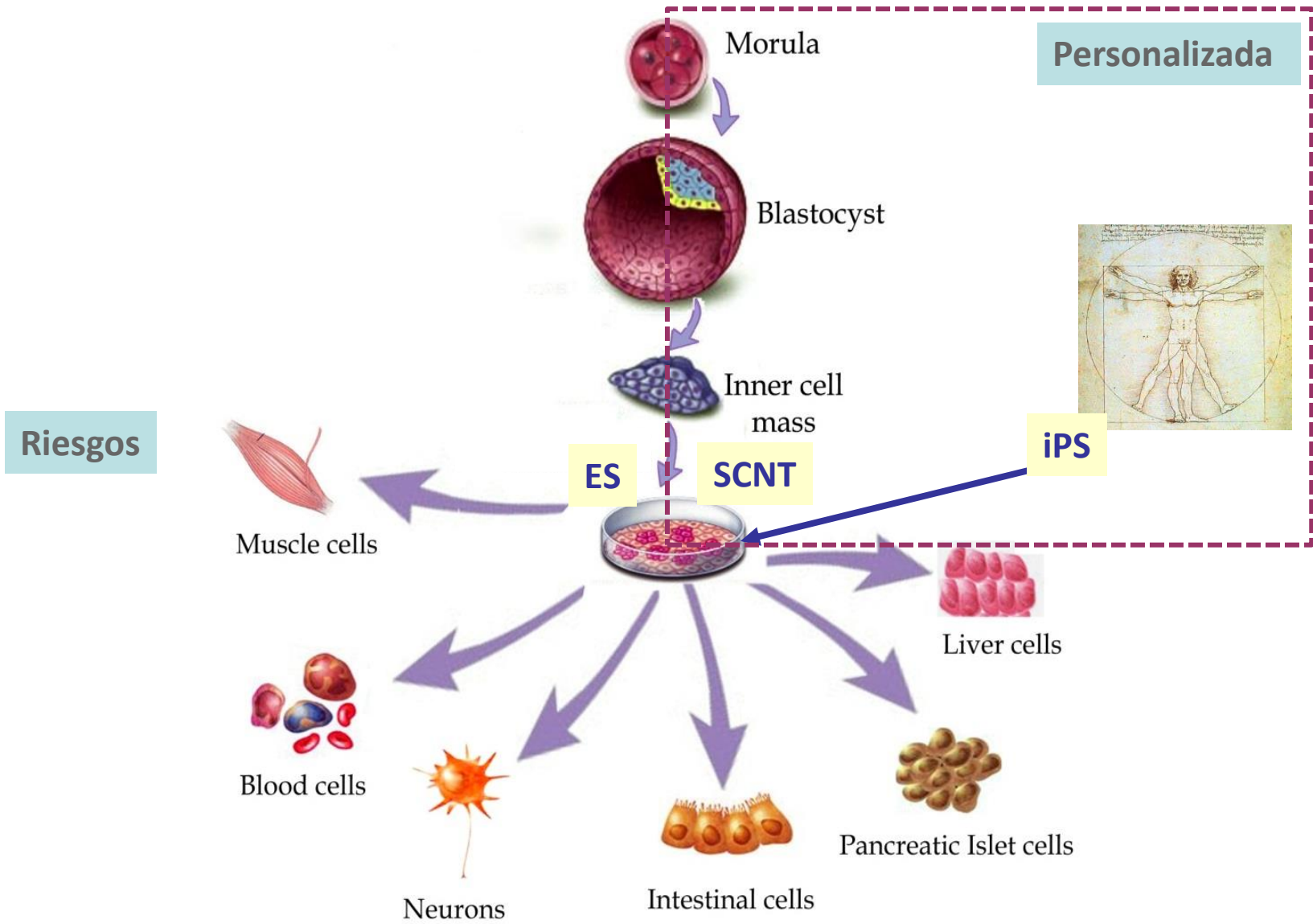


Células pluripotentes inducidas (iPS): enorme potencial, grandes limitaciones (bioseguridad). No rechazo.



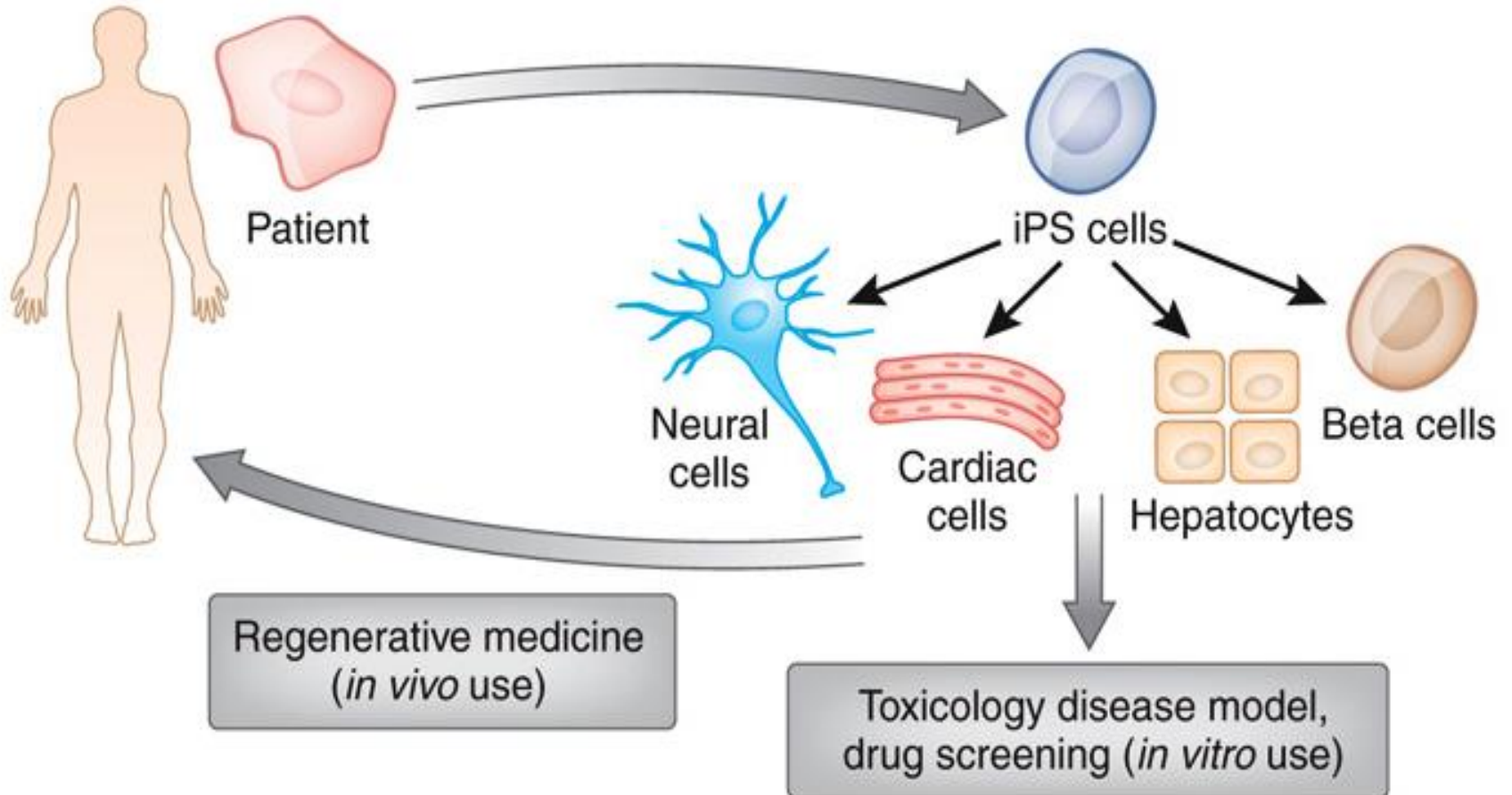
Reprogramación directa por un cóctel de factores de regulación de la pluripotencia

Células pluripotenciales para terapia

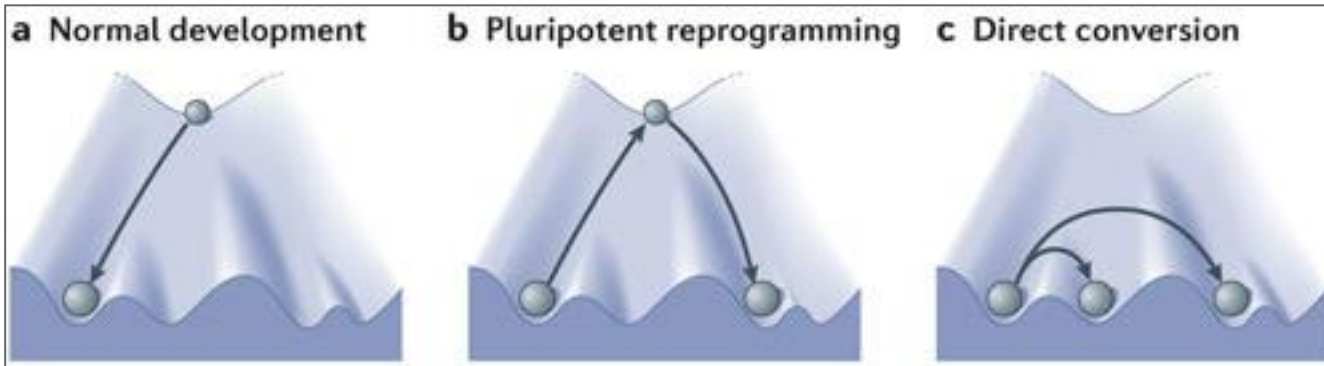
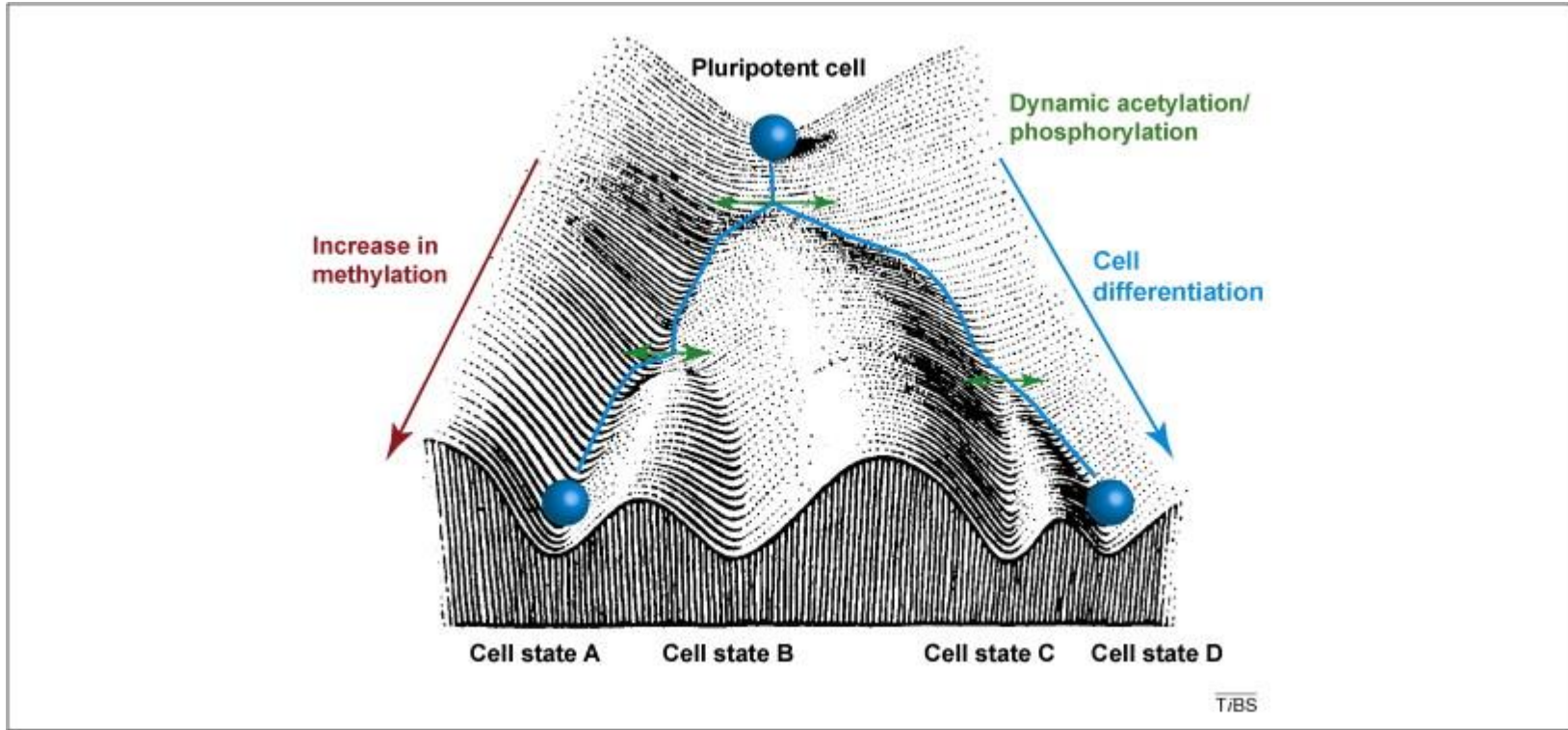


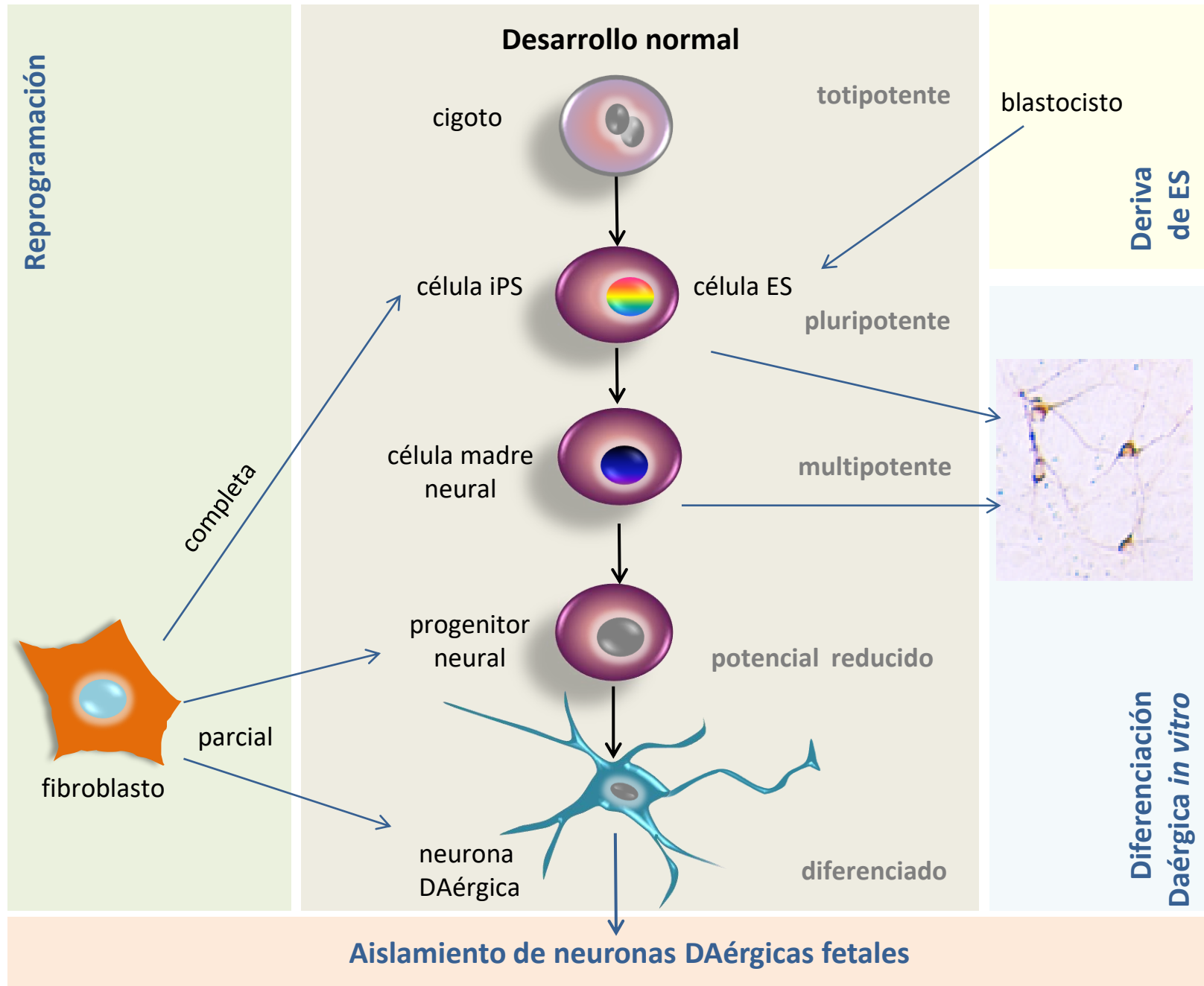


Las iPS ofrecen ventajas y despiertan el interés de las empresas farmacéuticas.



Concepto de reprogramación celular





ESTRATEGIAS DE LA TERAPIA CELULAR EN EL SISTEMA NERVIOSO

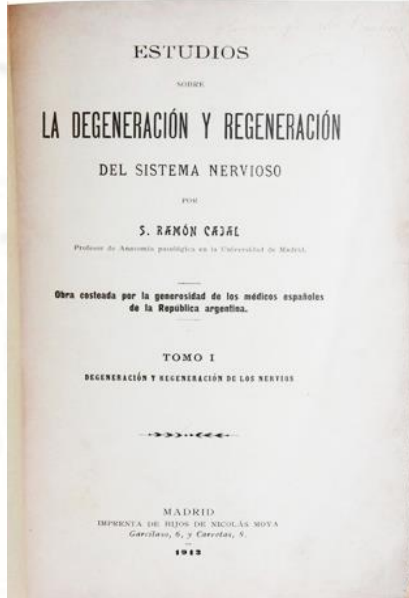
- Búsqueda de una fuente adecuada de células madre.
- Expansión *ex vivo* bajo condiciones reguladas.
- Diferenciación dirigida hacia tipos neuronales o gliales (ej: oligodendrocitos) específicos.
- Administración: intravenosa, intratecal, intraparenquimática (trasplante estereotáxico en regiones concretas).

ESTRATEGIAS DE LA TERAPIA CELULAR EN EL SISTEMA NERVIOSO

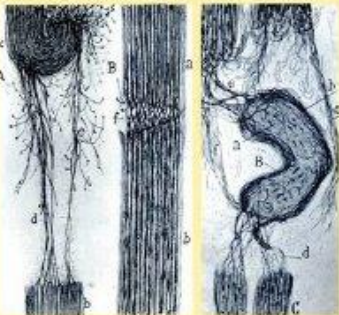
- RESTAURACIÓN CELULAR: PLURIPOTENTES O NEURALES.
- EFECTOS PARACRINOS: NEURALES, OTRAS.



○ Y...¿CUÁL ES LA CAPACIDAD DE NUESTRO PROPIO CEREBRO?



Cajal's Degeneration & Regeneration of the Nervous System



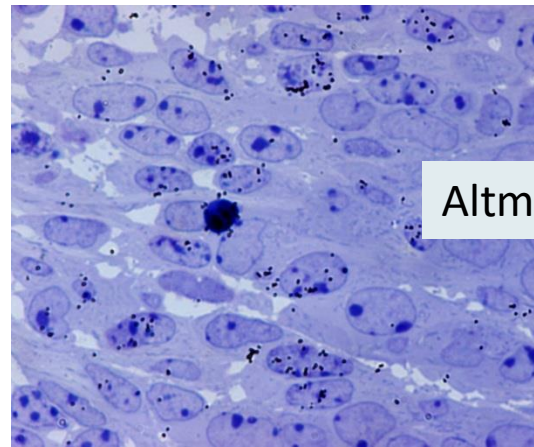
Translated by
Raoul M. May
Edited, with an introduction & Additional Translations by
Javier DeFelipe & Edward G. Jones

“...el aprendizaje hace que las células nerviosas existentes emitan o hagan crecer nuevas prolongaciones para reforzar sus conexiones con otras células nerviosas...”

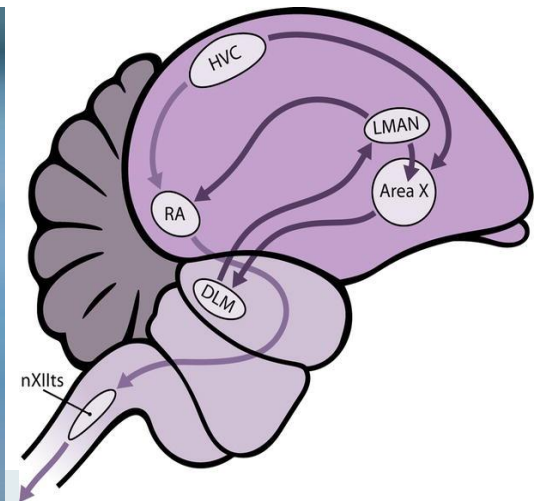
“Preciso es reconocer que, en los centros adultos, las vías nerviosas son algo fijo, acabado, inmutable. Todo puede morir, nada renacer”.

Santiago Ramón y Cajal, 1928

Se detecta proliferación en el cerebro adulto, mediante timidina tritiada



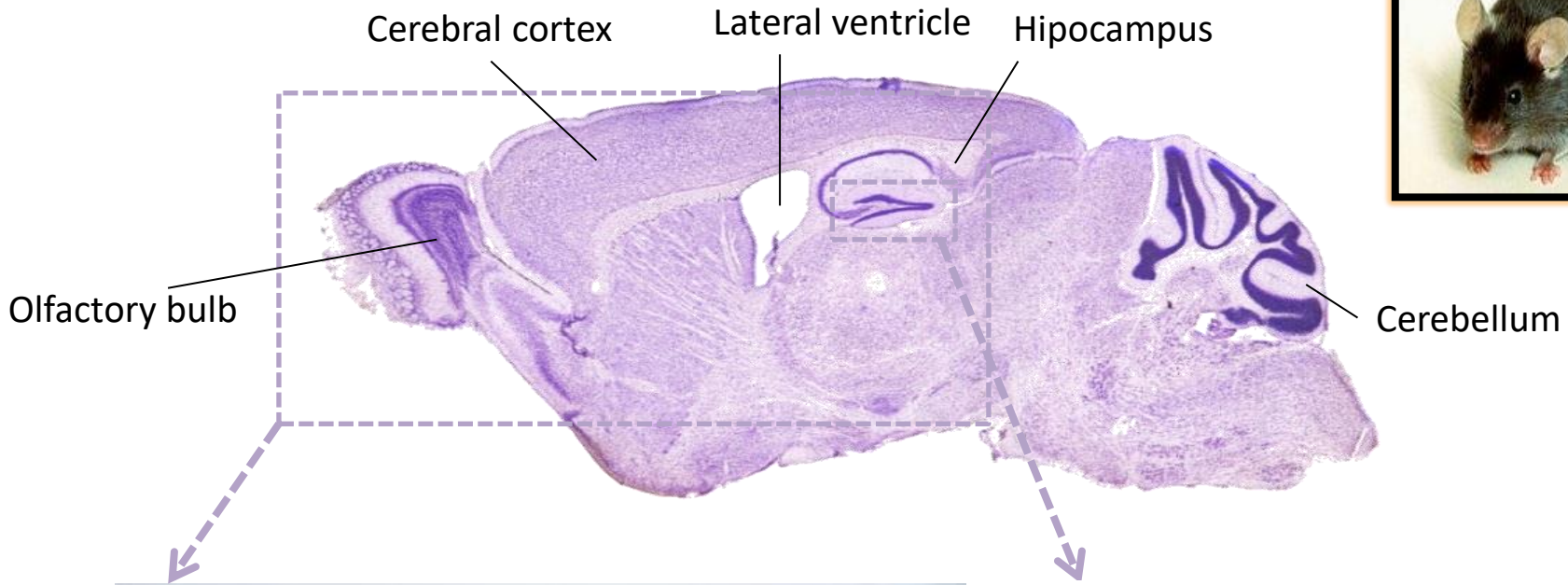
Altman y Bayer, 1960s



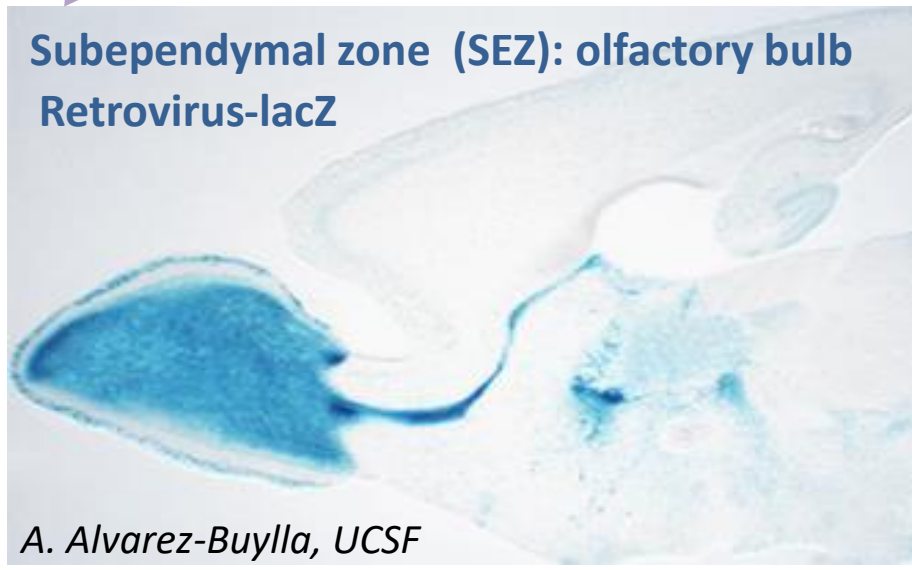
Neurons generated in the adult brain are recruited into functional circuits

Paton and Nottebohm

Science 7 September 1984: 1046-1048



Subependymal zone (SEZ): olfactory bulb
Retrovirus-lacZ

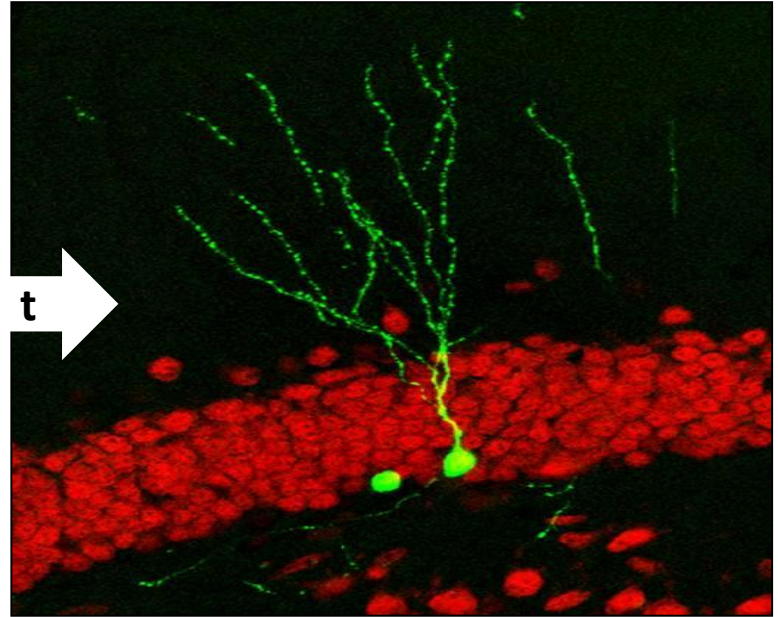
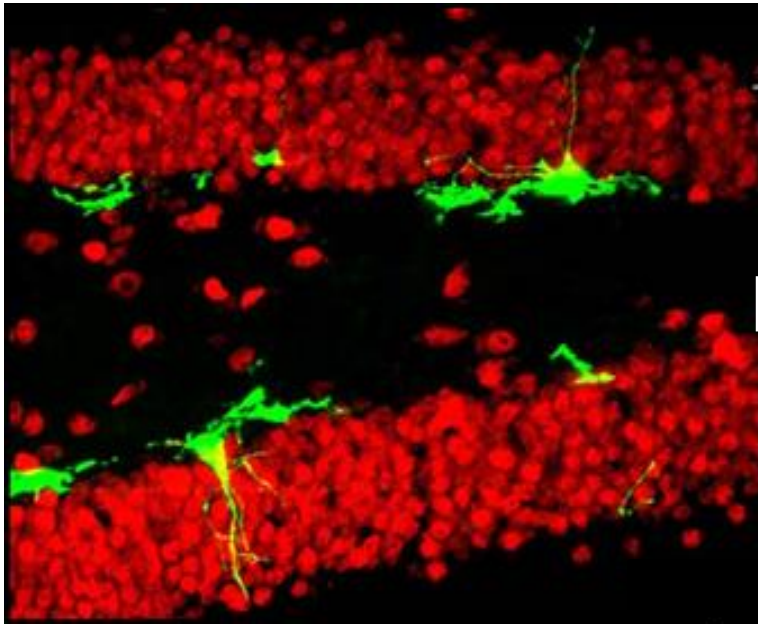
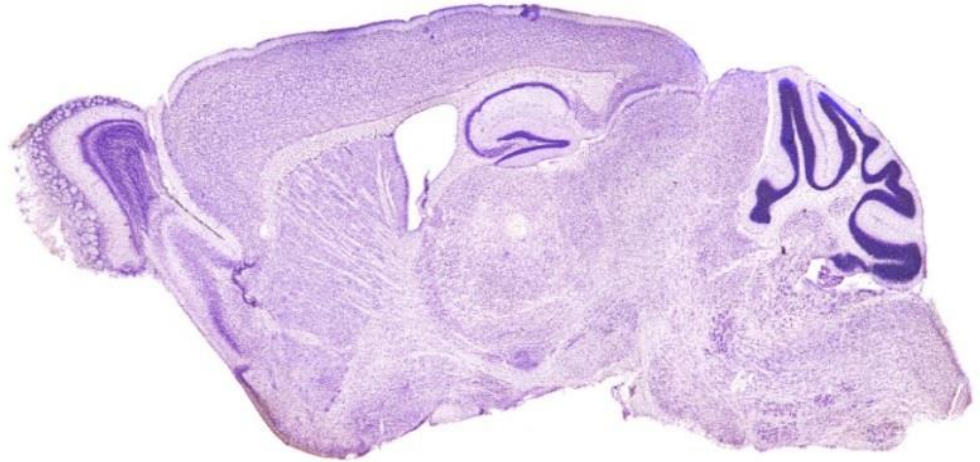


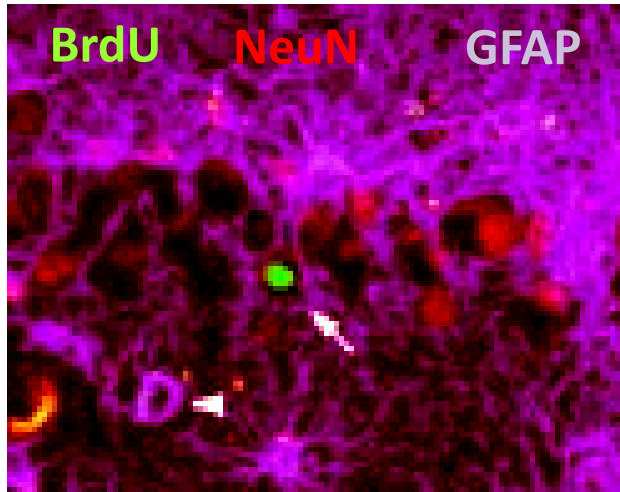
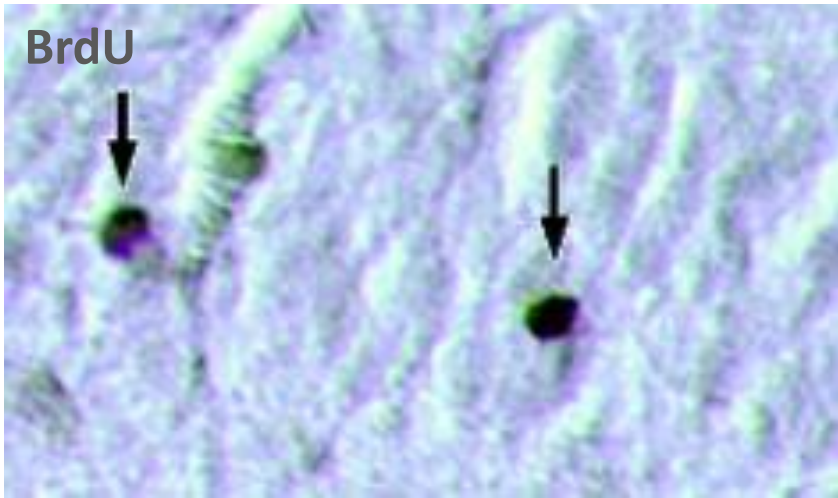
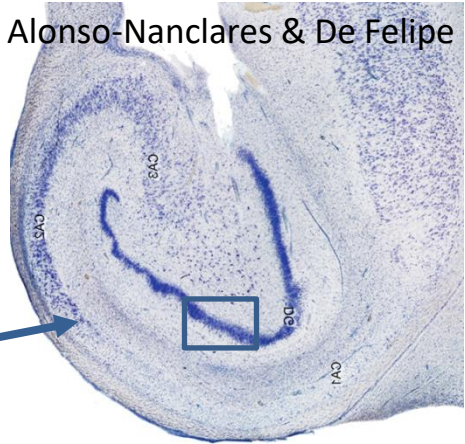
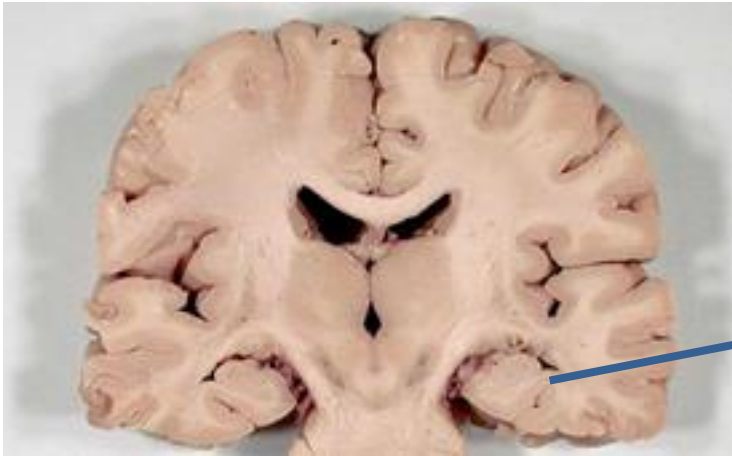
A. Alvarez-Buylla, UCSF

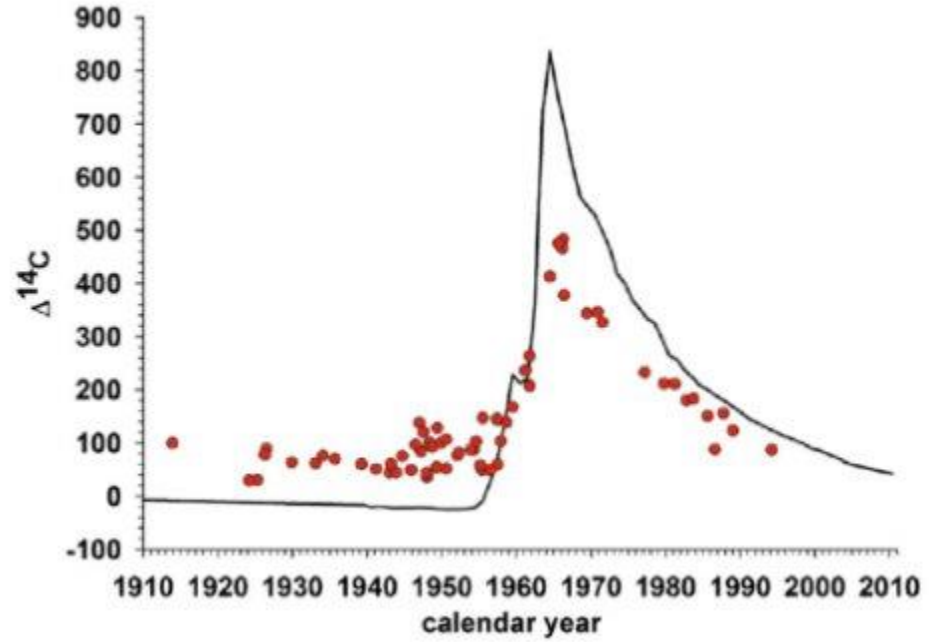
Subgranular zone (SGZ): dentate gyrus



S. Jessberger, BRI, Zurich



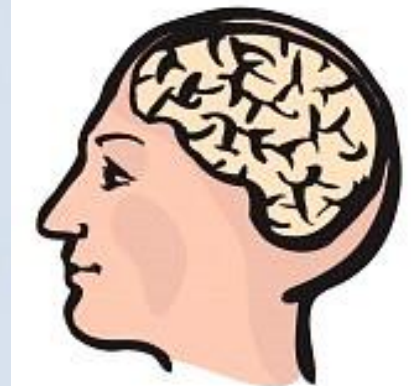


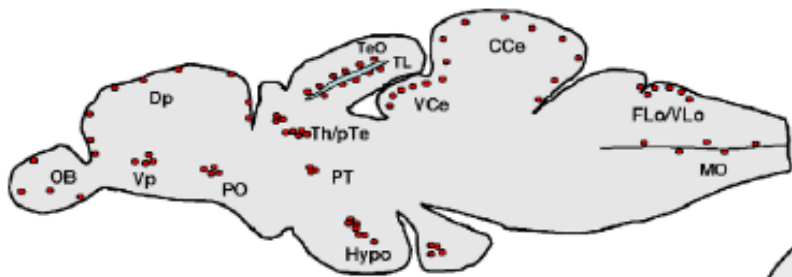
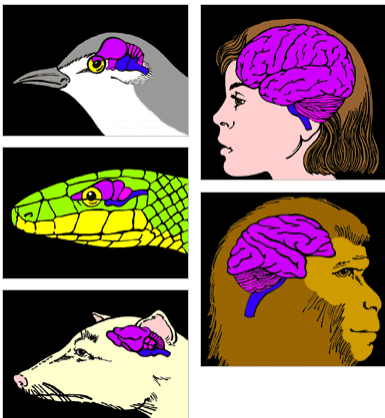


Active neurogenesis throughout adulthood

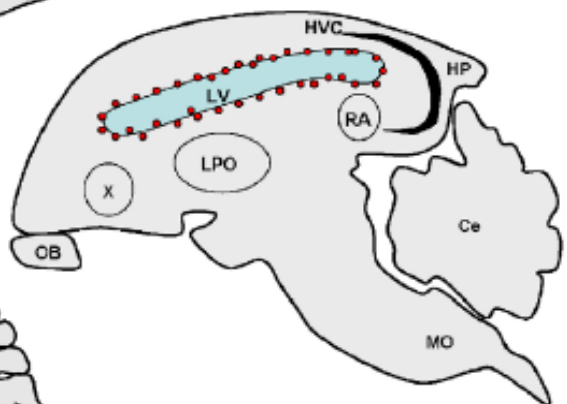


^{14}C

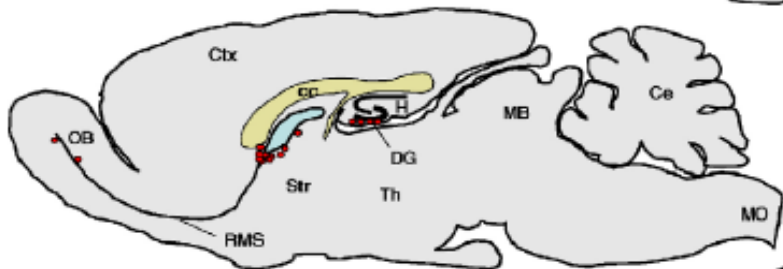




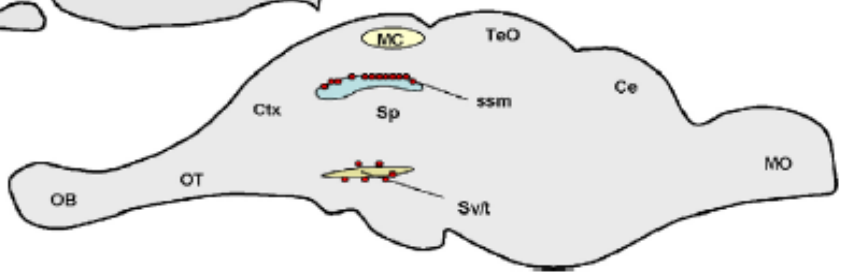
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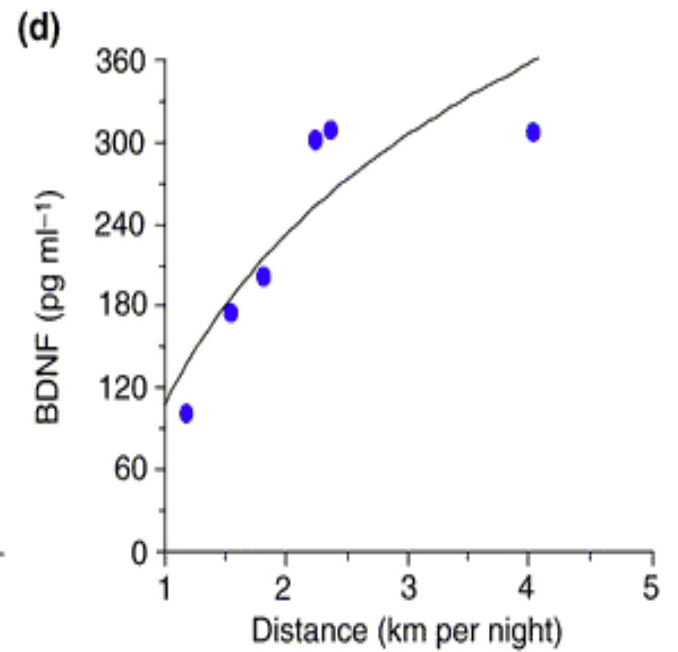
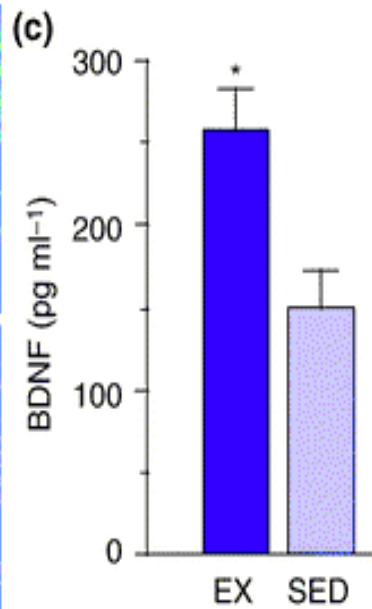
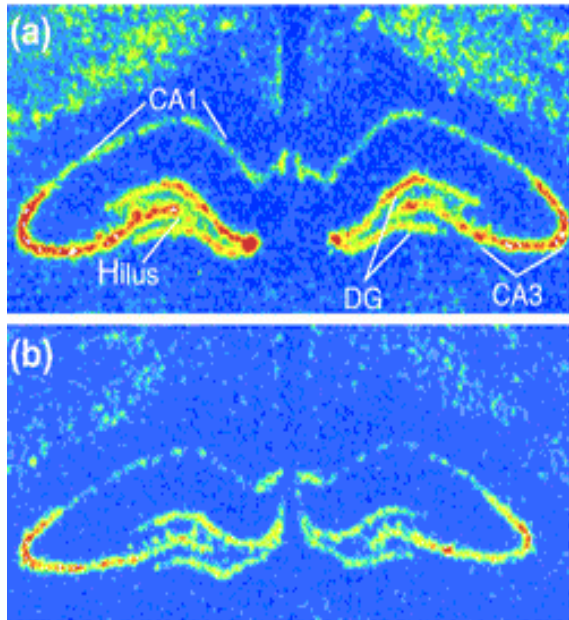
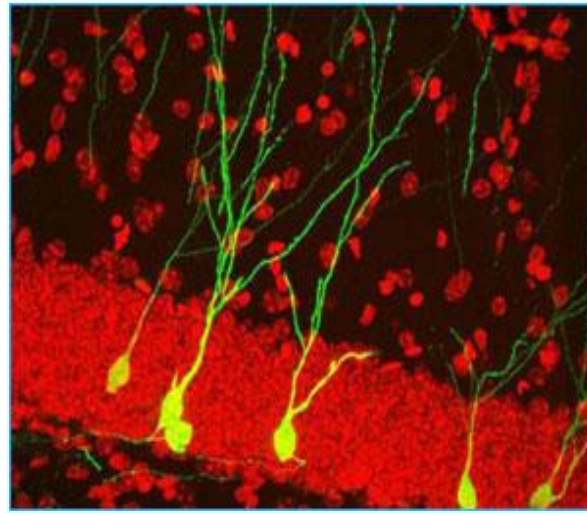
Roedor/humano

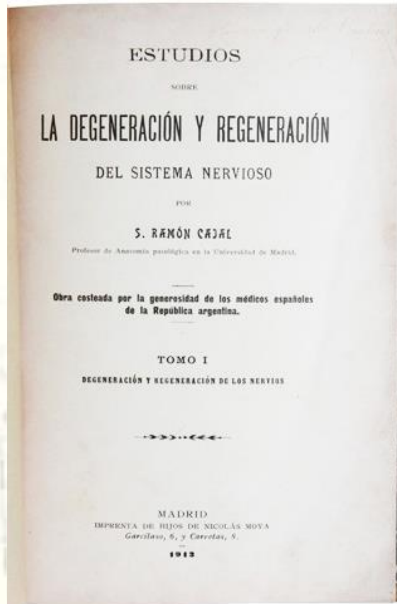


reptil

Neurogénesis postnatal/adulta

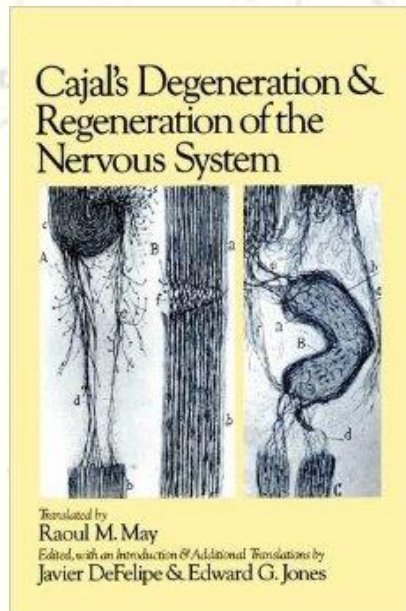
- Proceso de producción de nuevas neuronas en individuos maduros.
- En vertebrados, el grado de neurogénesis postnatal decrece con el incremento de la complejidad del cerebro.
- En el de los mamíferos se restringe a dos zonas neurogénicas concretas: la zona subventricular y la zona subgranular del hipocampo.
- Función desconocida.





“Preciso es reconocer que, en los centros adultos, las vías nerviosas son algo fijo, acabado, inmutable. Todo puede morir, nada renacer”.

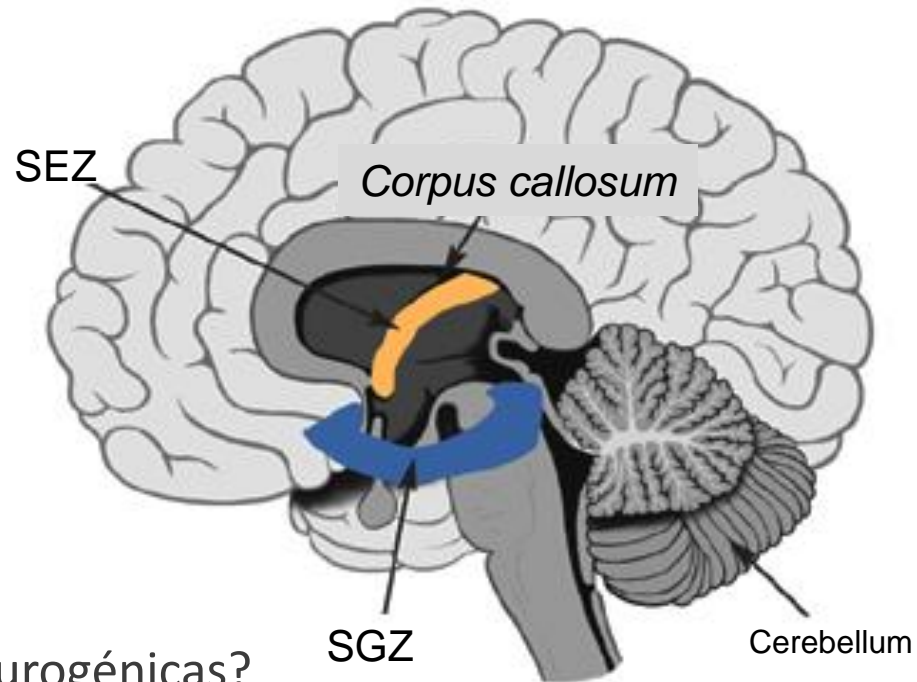
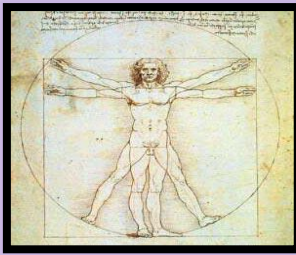
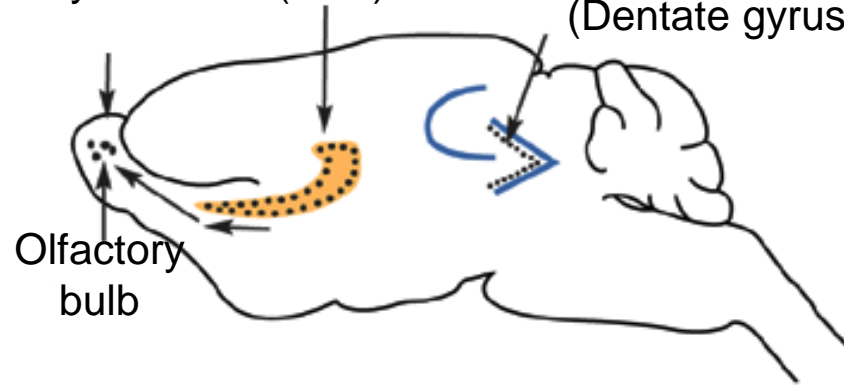
“...será tarea de la ciencia del futuro cambiar, si es posible, este duro decreto”.



Santiago Ramón y Cajal, 1928

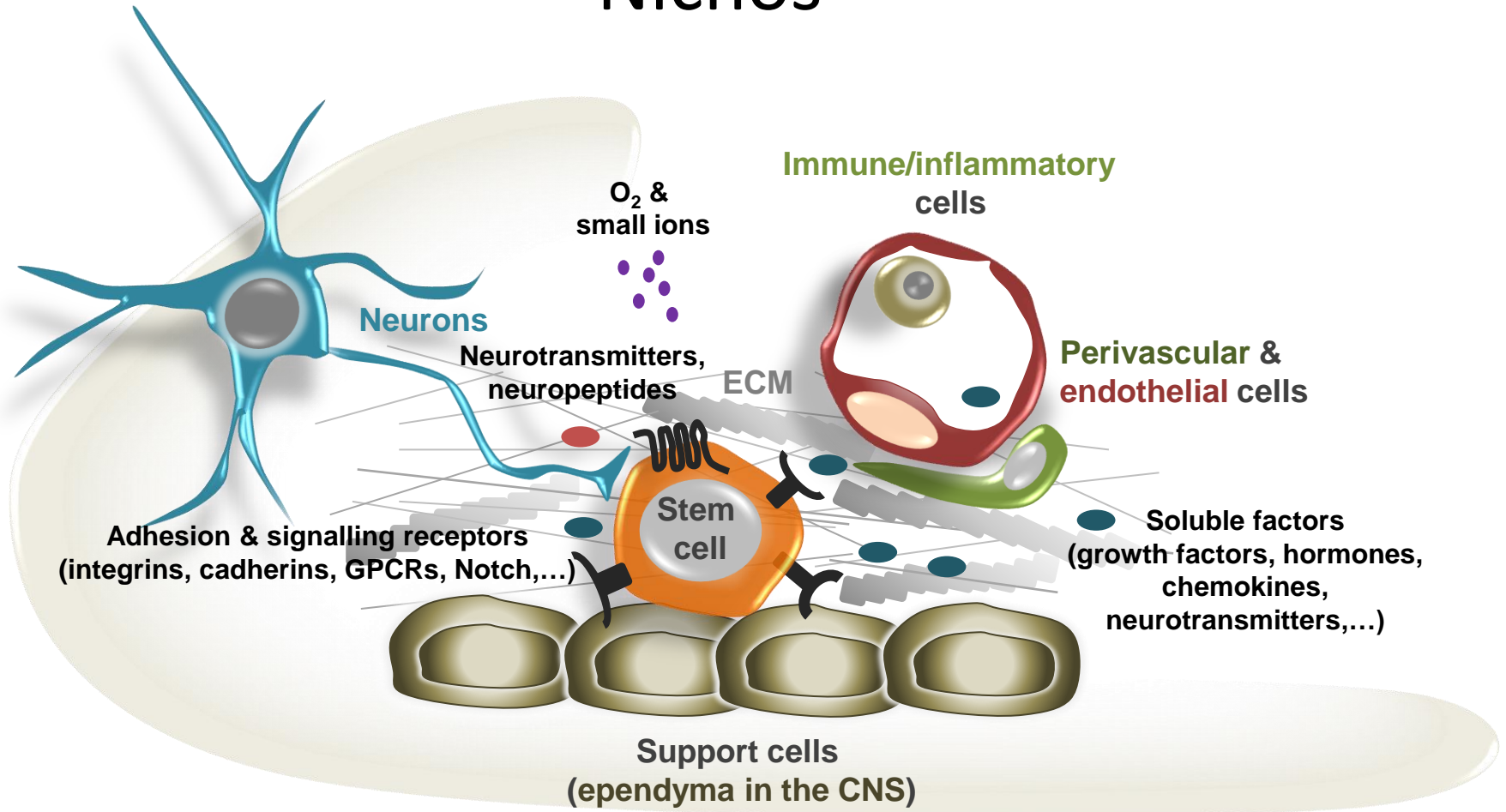
Ventricular-subventricular zone (V-SVZ) or Subependymal zone (SEZ)

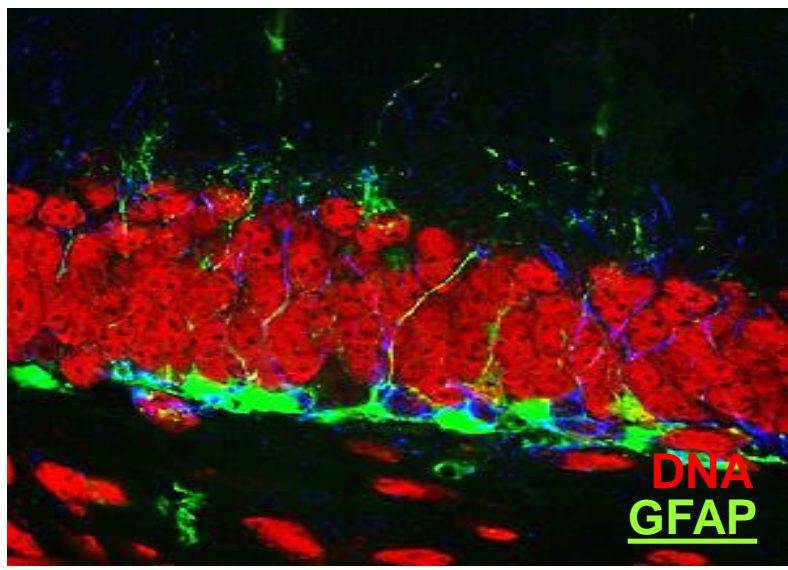
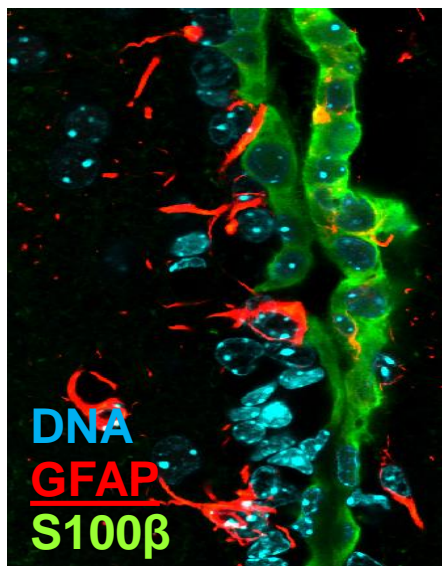
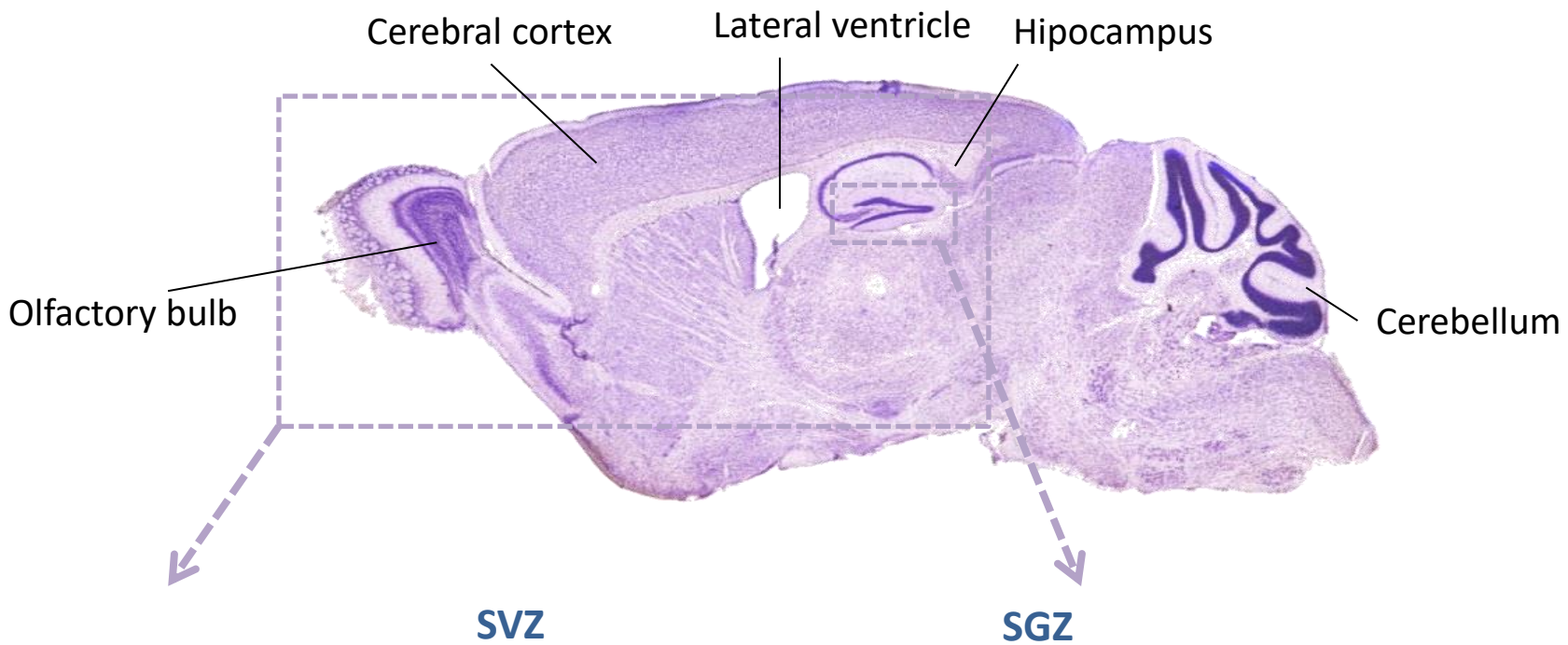
Subgranular zone (SGZ)
(Dentate gyrus)



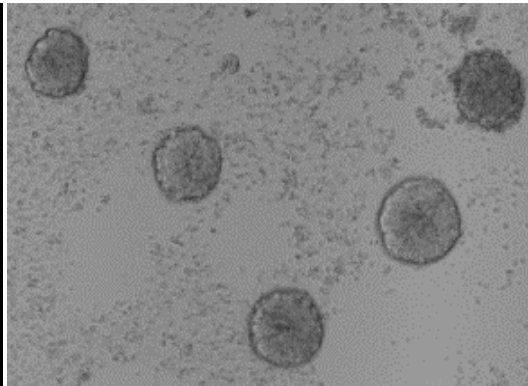
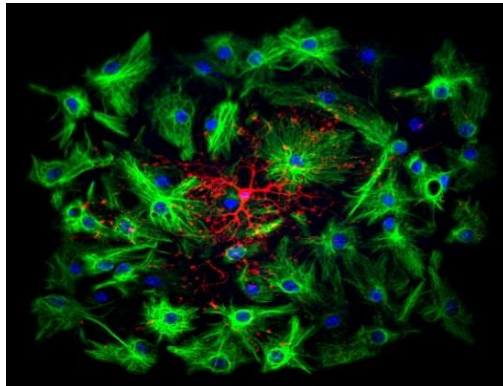
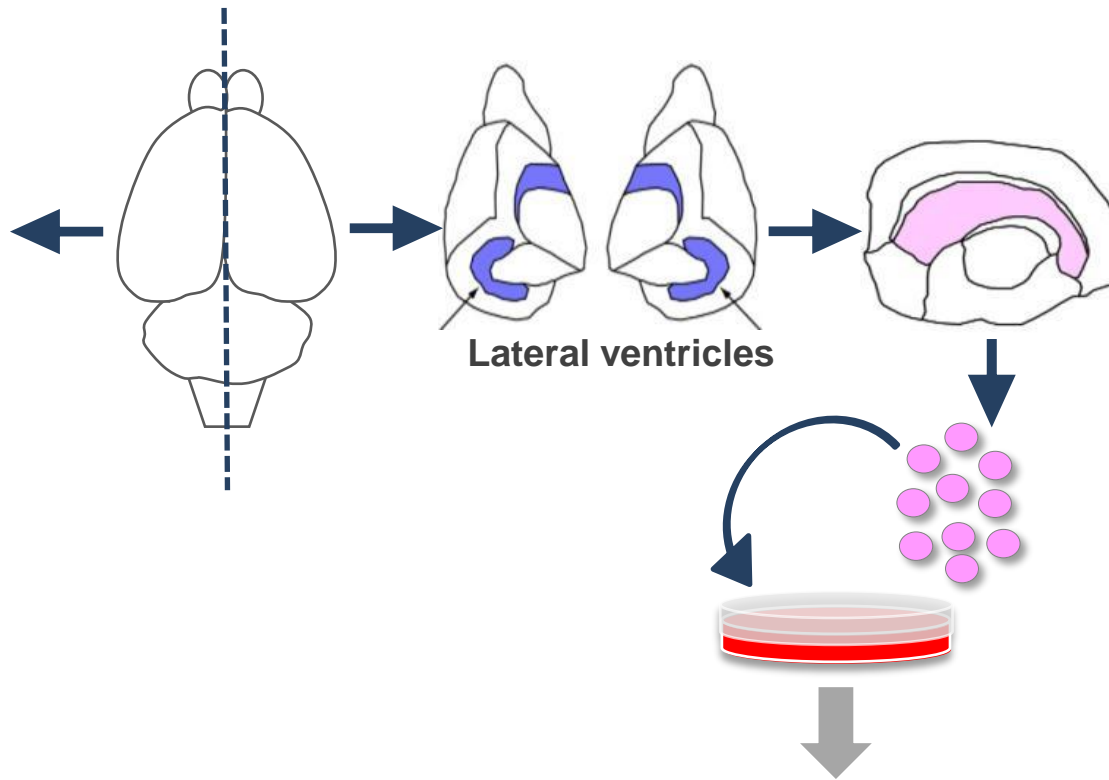
- ¿Por qué sólo dos zonas neurogénicas?
- Concepto de nicho neurogénico.

Nichos

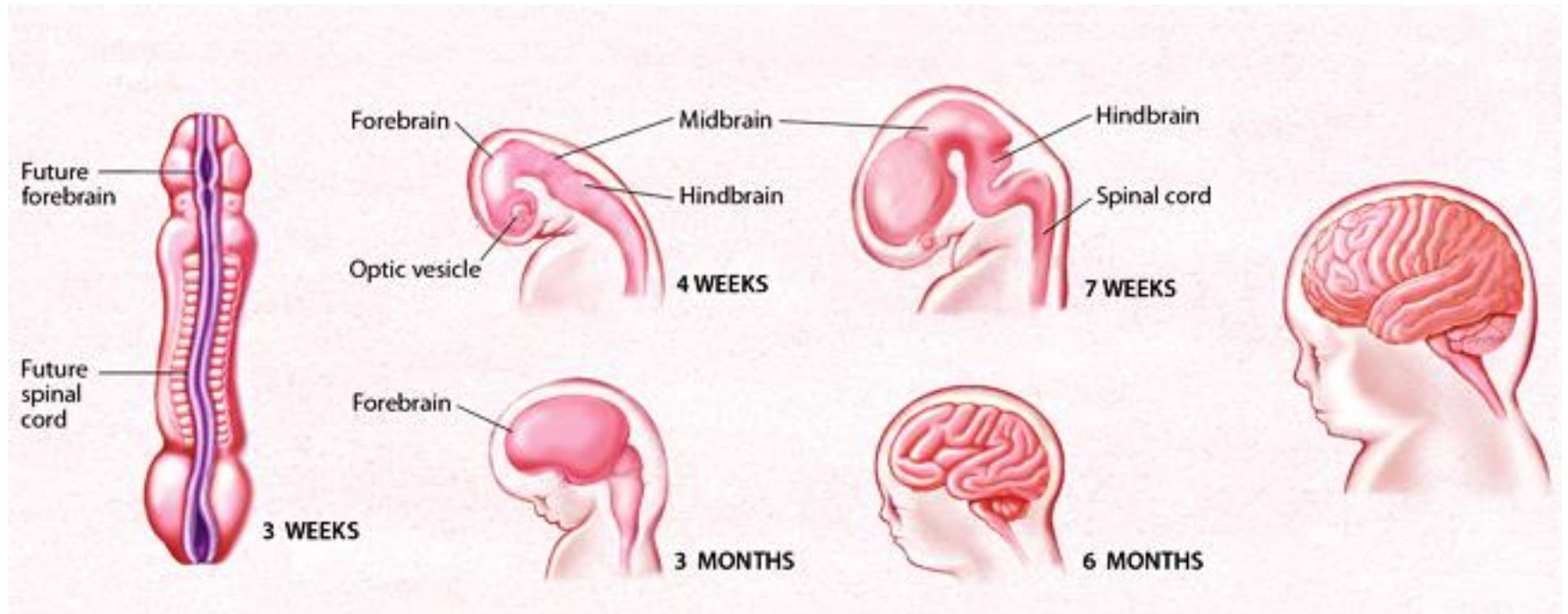




El ensayo de neuroesferas



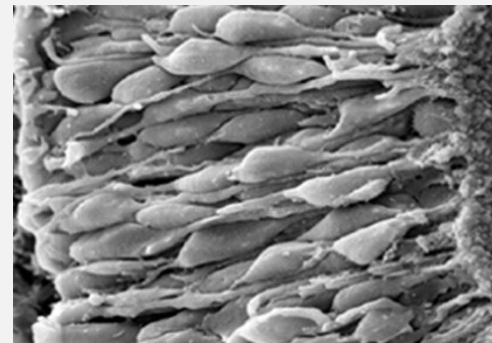
El proceso de neurogénesis: producción de neuronas



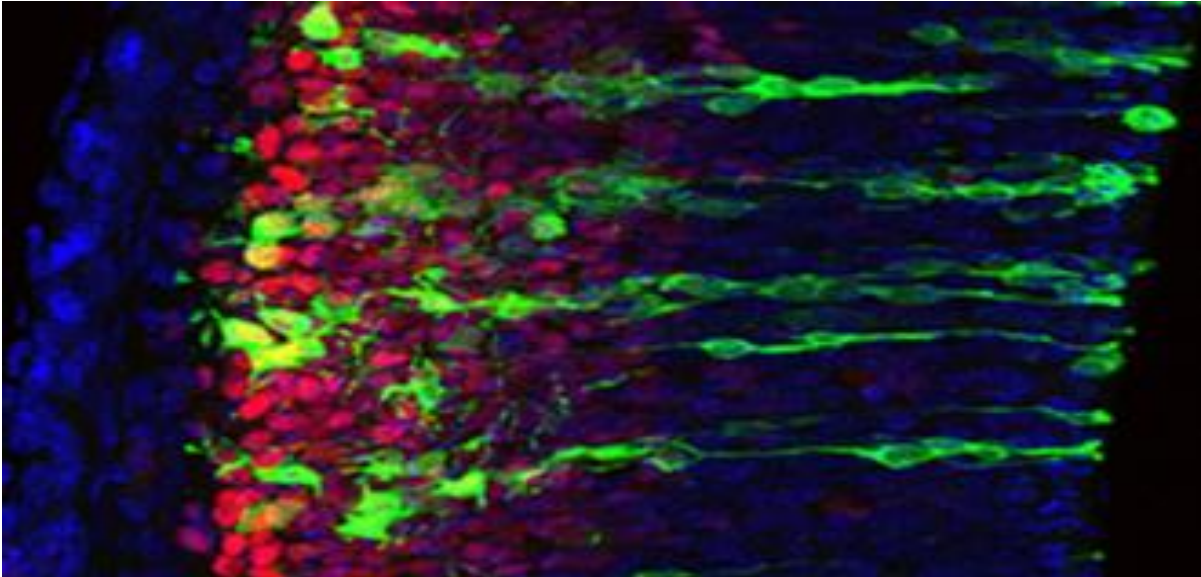
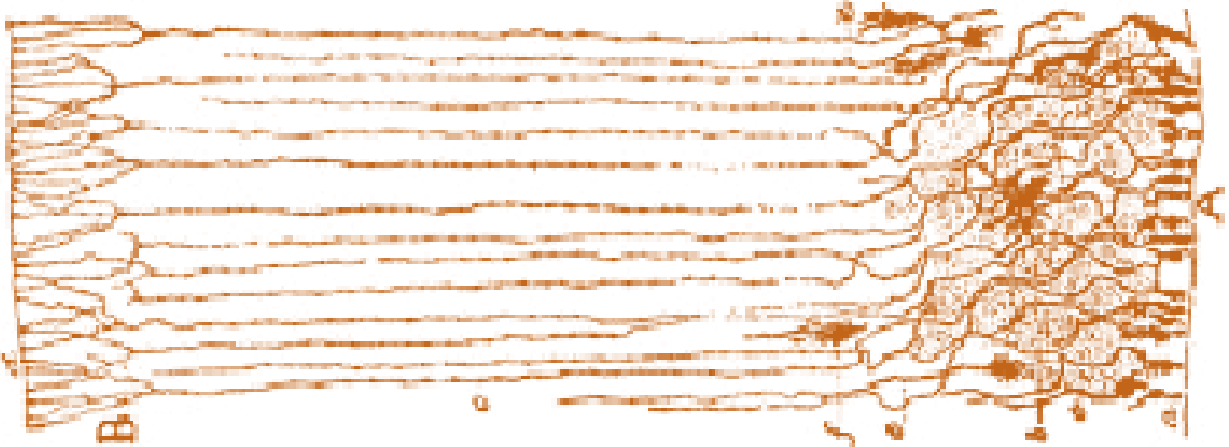
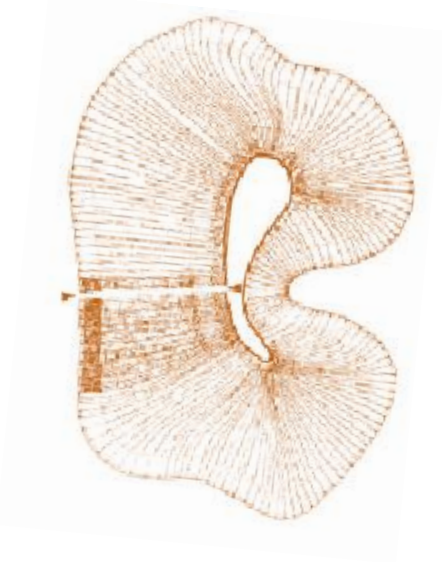
Neural tube



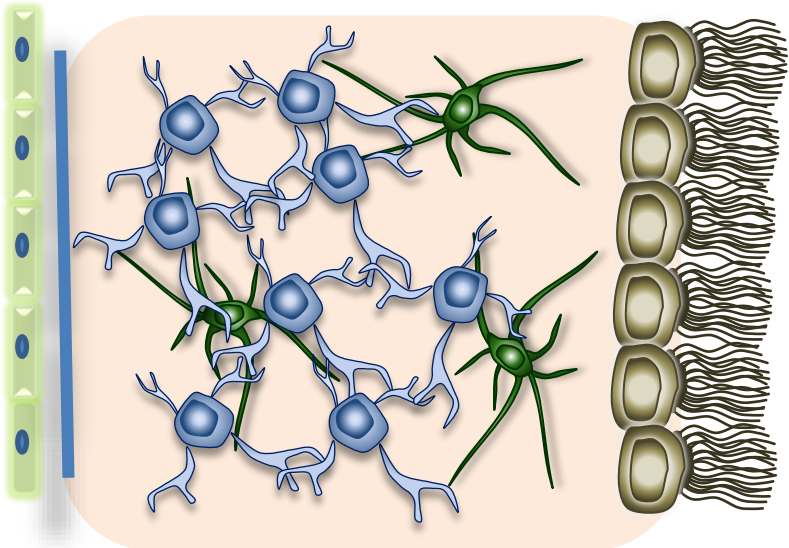
Neuroepithelium



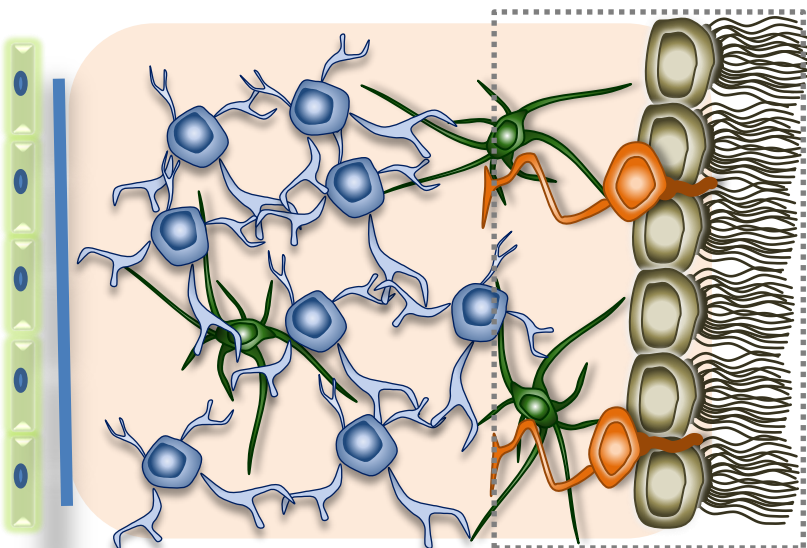
Glía radial



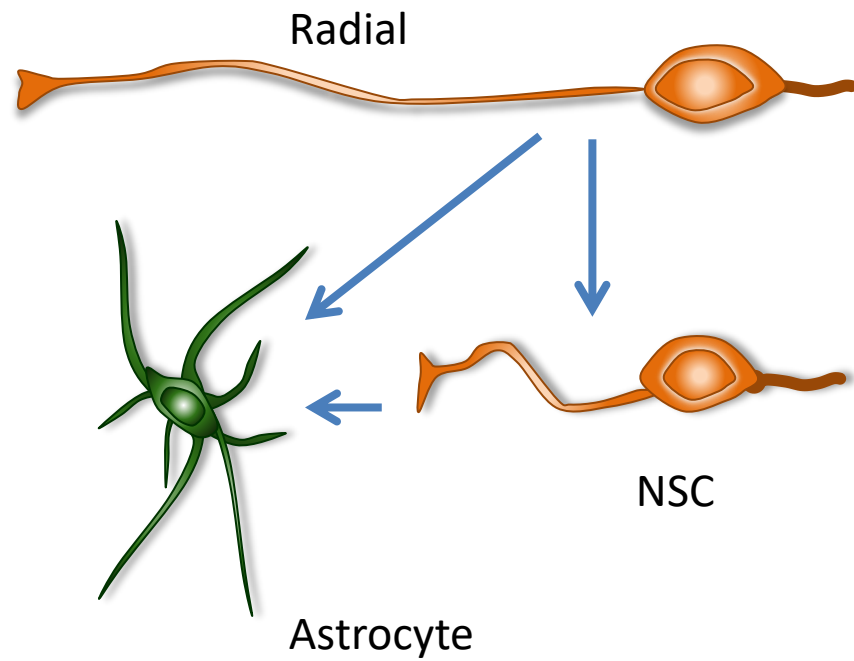
Non-neurogenic areas



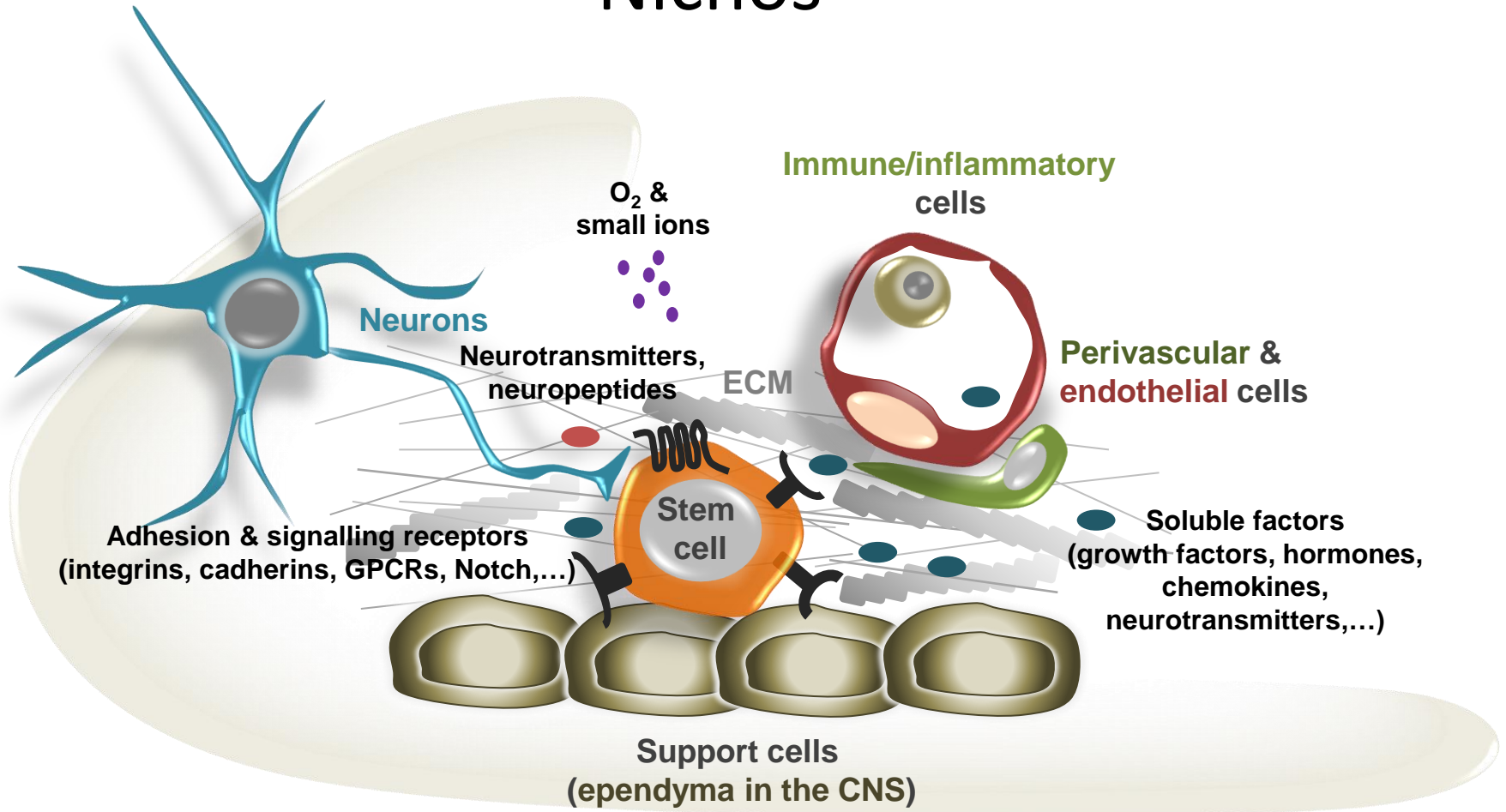
Neurogenic areas



El linaje glía radial-astrocito

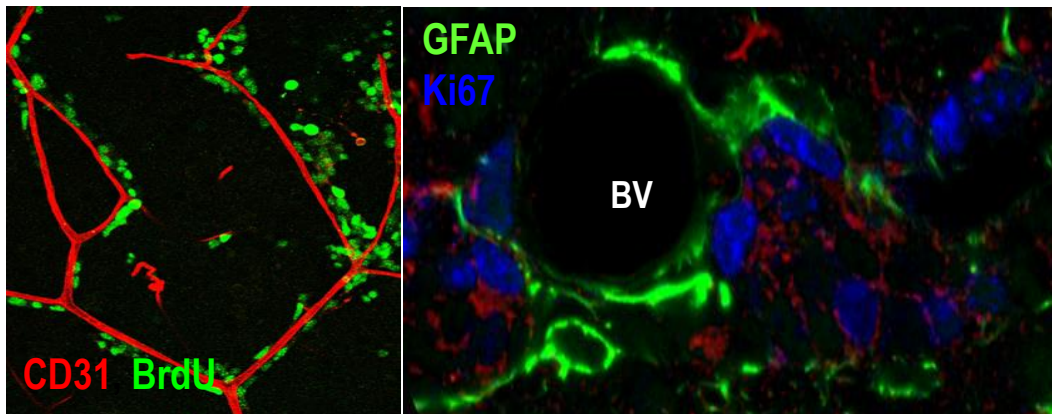
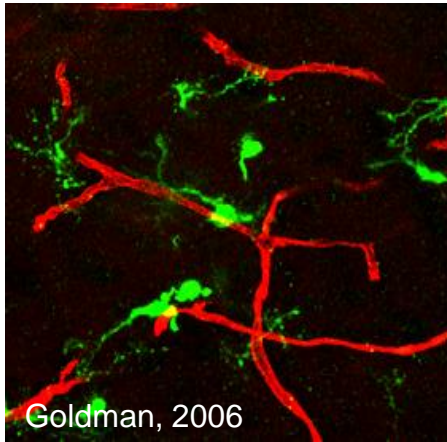
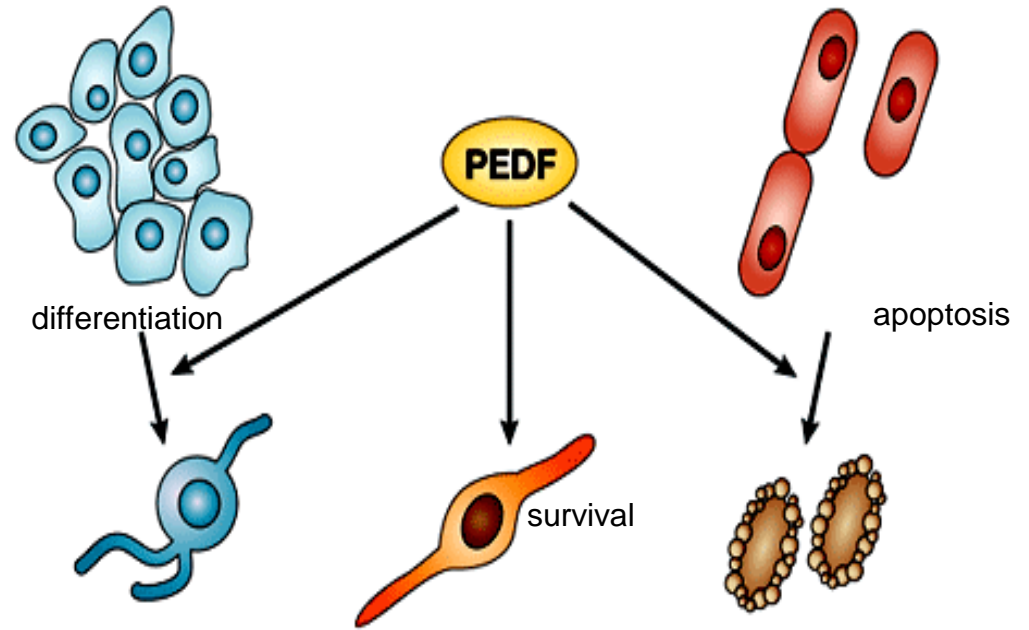


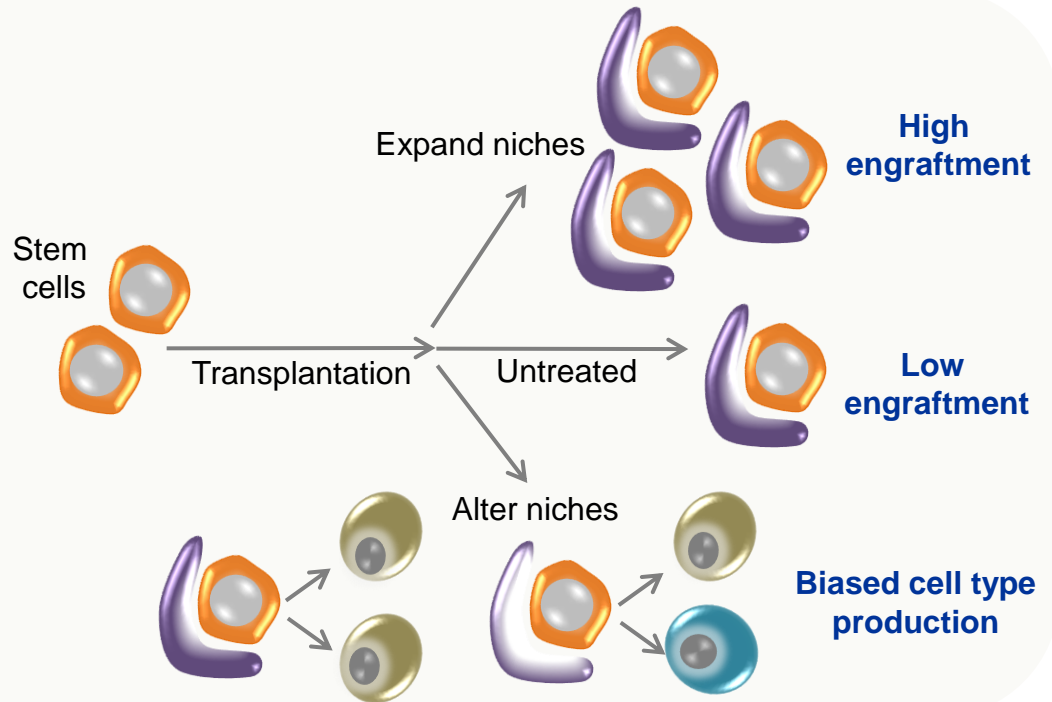
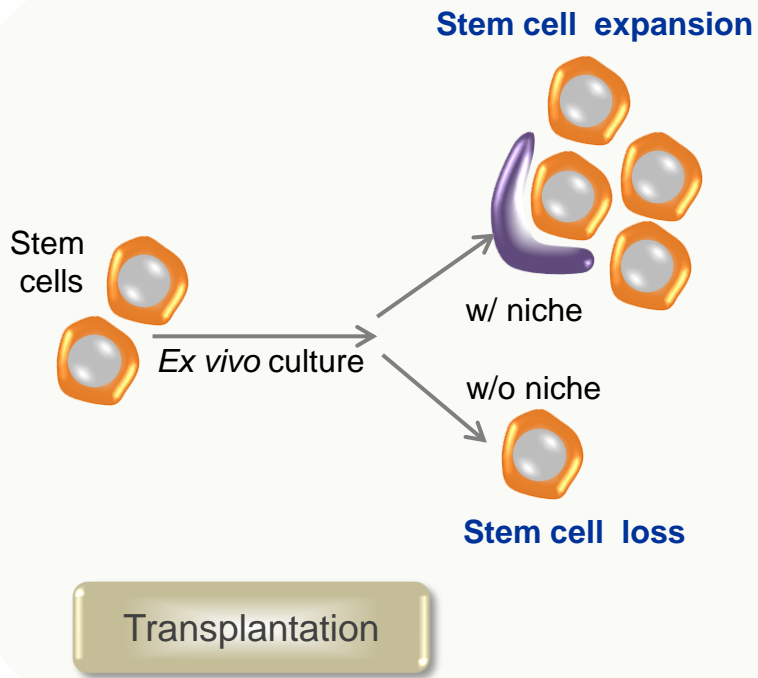
Nichos



Example of a factor that could be potentially used in stem cell cultures

- VEGF, erythropoietin, BDNF,...
- endothelial cells produce self-renewing molecules
- **Identification of PEDF: *Pigmented-Epithelium Derived Factor***





Embryonic stem cells



Blastocyst

Neural stem cells



Adult CNS



Fetal CNS

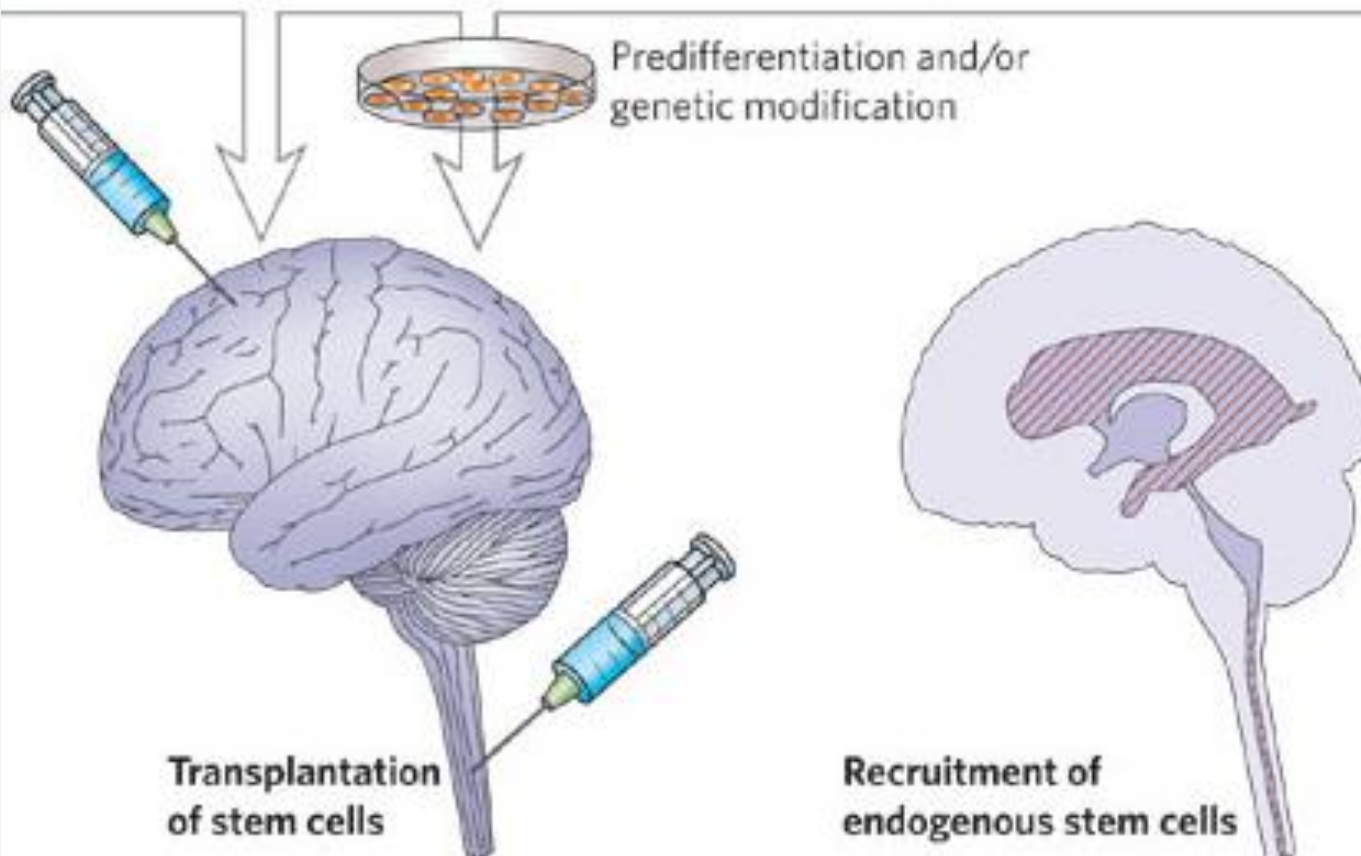
Other tissue stem cells



Bone marrow



Umbilical cord



Regeneration of Hippocampal Pyramidal Neurons after Ischemic Brain Injury by Recruitment of Endogenous Neural Progenitors

Hirofumi Nakatomi,^{1,2} Toshihiko Kuriu,⁴
Shigeo Okabe,^{4,5} Shin-ichi Yamamoto,^{1,3}
Osamu Hatano,⁶ Nobutaka Kawahara,²
Akira Tamura,⁷ Takaaki Kirino,²
and Masato Nakafuku^{1,5,8}

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⁶Department of Anatomy

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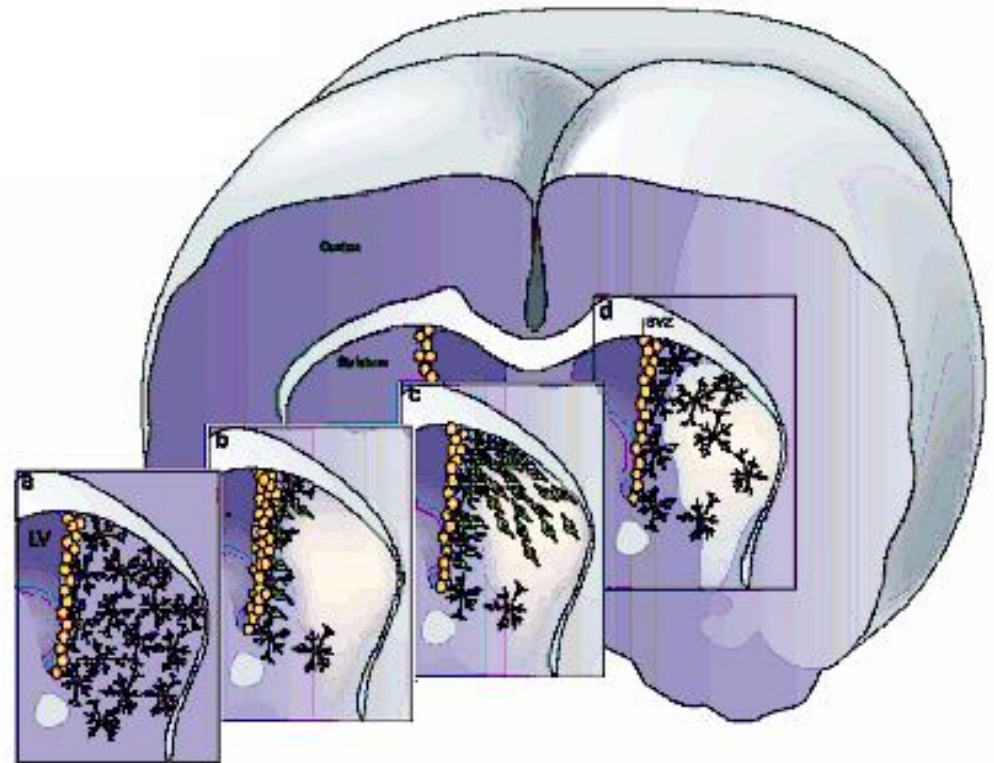
⁷Department of Neurosurgery

Teikyo University School of Medicine

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Japan



Endogenous NSCs respond to injury. i.e. ischemic

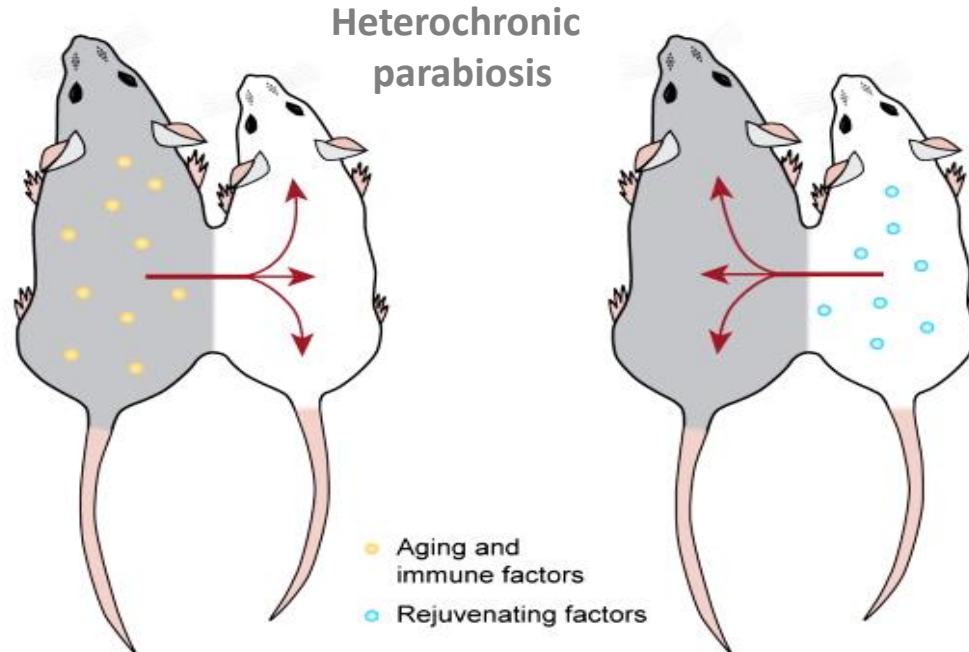
The systemic milieu is also part of the niche

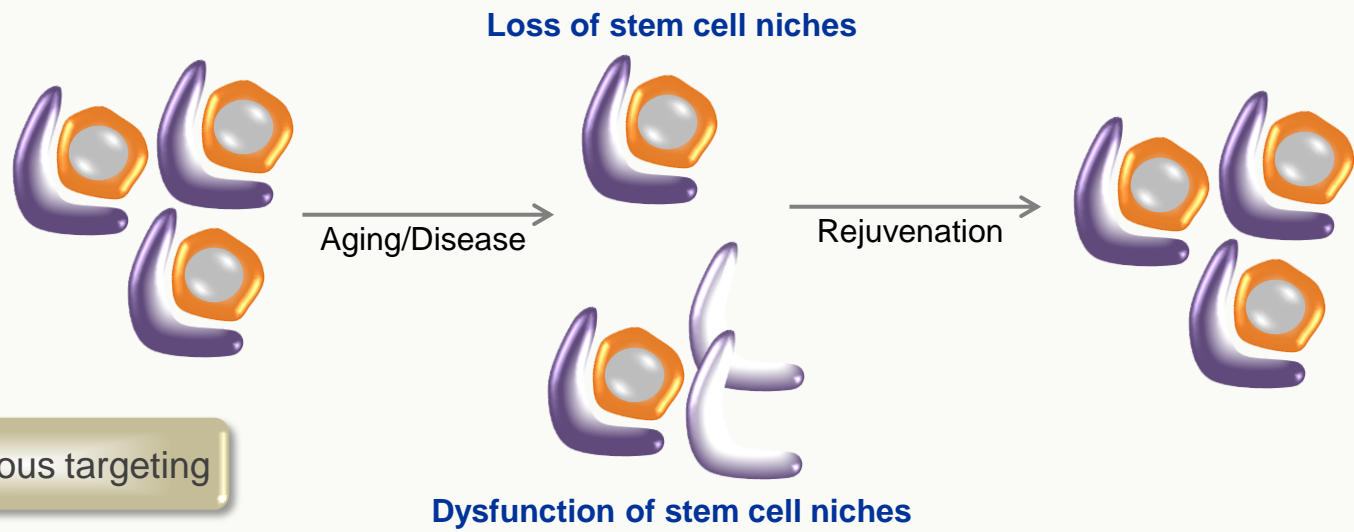
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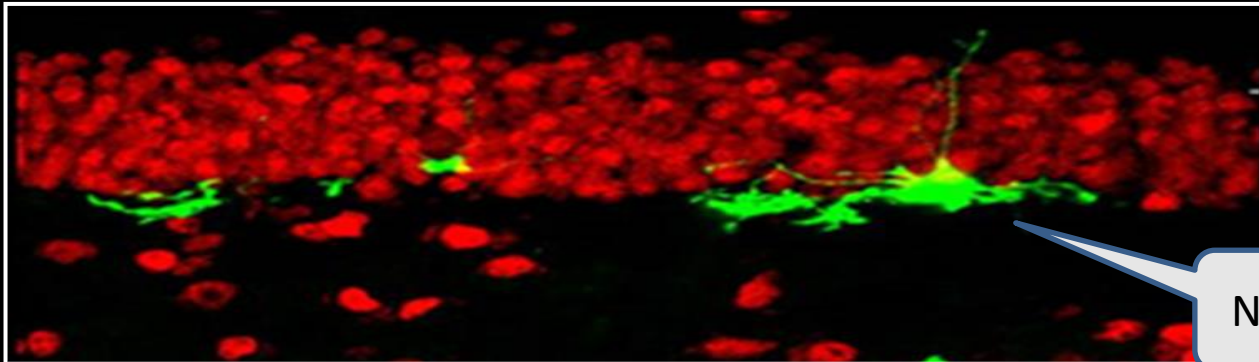
The ageing systemic milieu negatively regulates neurogenesis and cognitive function

Saul A. Villeda^{1,2}, Jian Luo¹, Kira I. Mosher^{1,2}, Bende Zou³, Markus Britschgi^{1†}, Gregor Bieri^{1,4}, Trisha M. Stan^{1,5}, Nina Fainberg¹, Zhaoping Ding^{1,5}, Alexander Eggel¹, Kurt M. Lucin¹, Eva Czirr¹, Jeong-Soo Park^{1†}, Sebastien Couillard-Després⁶, Ludwig Aigner⁶, Ge Li⁷, Elaine R. Peskind^{7,8}, Jeffrey A. Kaye⁹, Joseph F. Quinn⁹, Douglas R. Galasko¹⁰, Xinmin S. Xie³, Thomas A. Rando^{1,11,12} & Tony Wyss-Coray^{1,2,5,11}

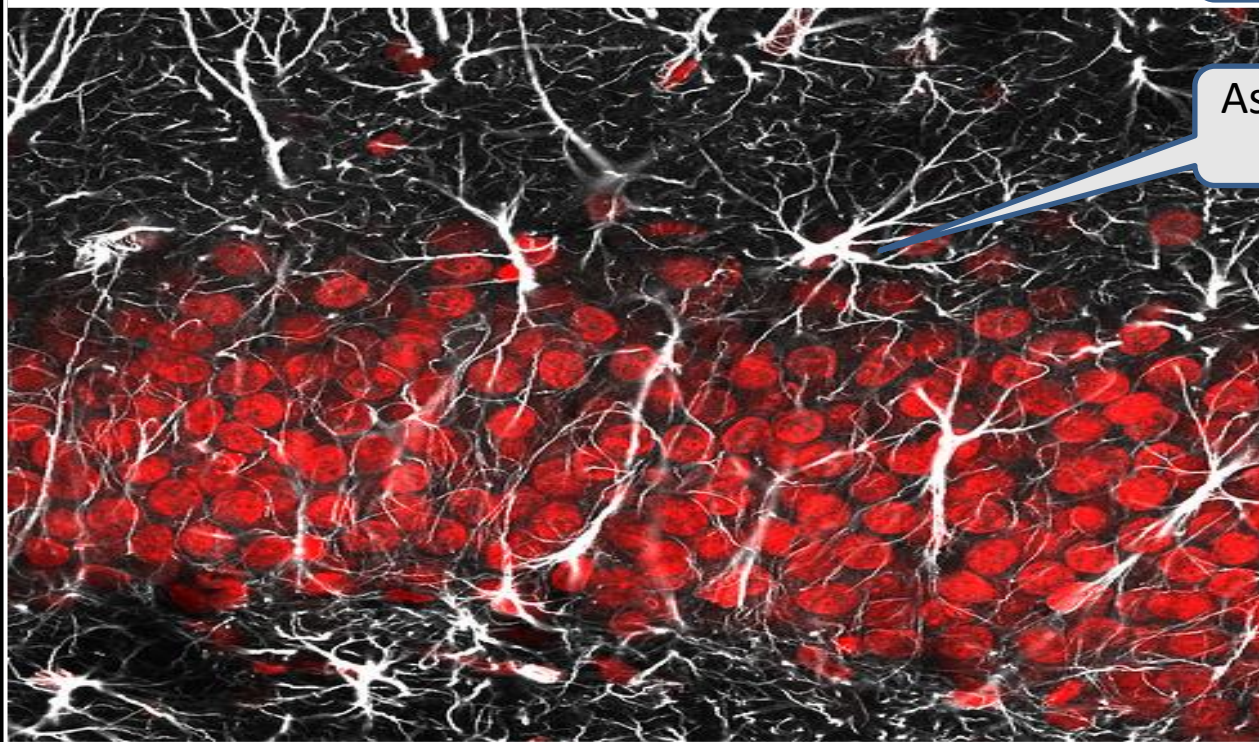




New concept: reactivation of astrocytes in different brain regions



NSCs in SGZ



Astrocytes in SGZ

Adult tissue-specific stem cells

