

Renovación celular en el cerebro adulto

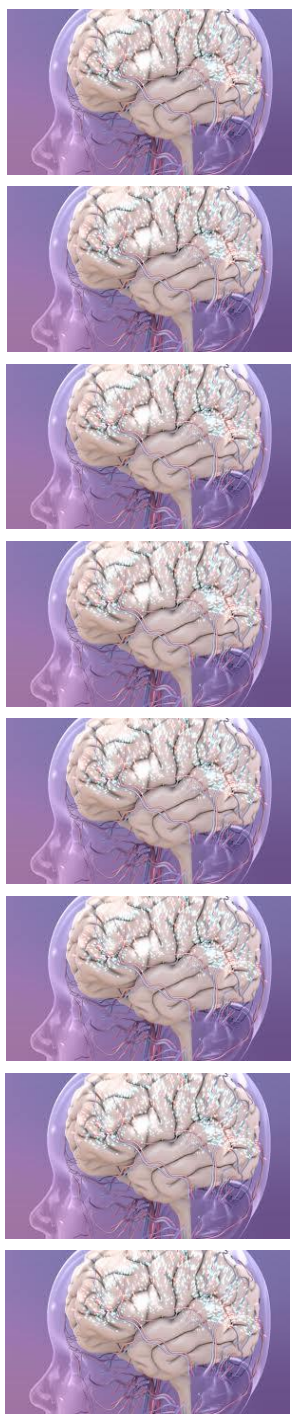


Isabel Fariñas

Isabel.farinas@uv.es

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?

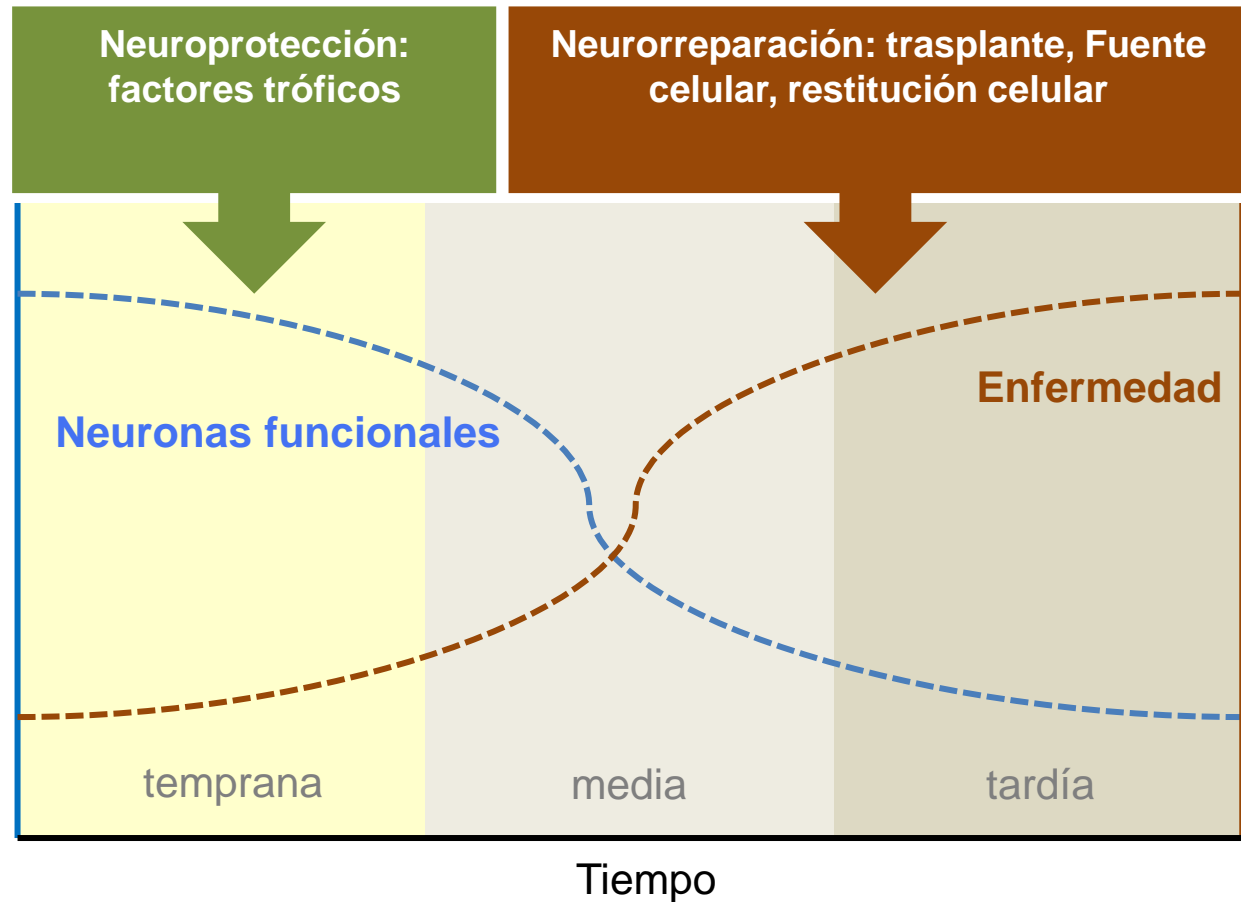


TERAPIA CELULAR EN EL SISTEMA NERVIOSO

- ENFERMEDADES NEURODEGENERATIVAS: PARKINSON, ALZHEIMER, HUNTINGTON, ELA.
- DESMIELINIZANTES, COMO ESCLEROSIS MÚLTIPLE (AUTOINMUNE).
- LESIONES: TRAUMÁTICAS (INCLUYENDO LESIONES MEDULARES) O ISQUÉMICAS (ICTUS).
- ENFERMEDADES NEUROLÓGICAS, ENFERMEDADES RARAS PEDIÁTRICAS,...

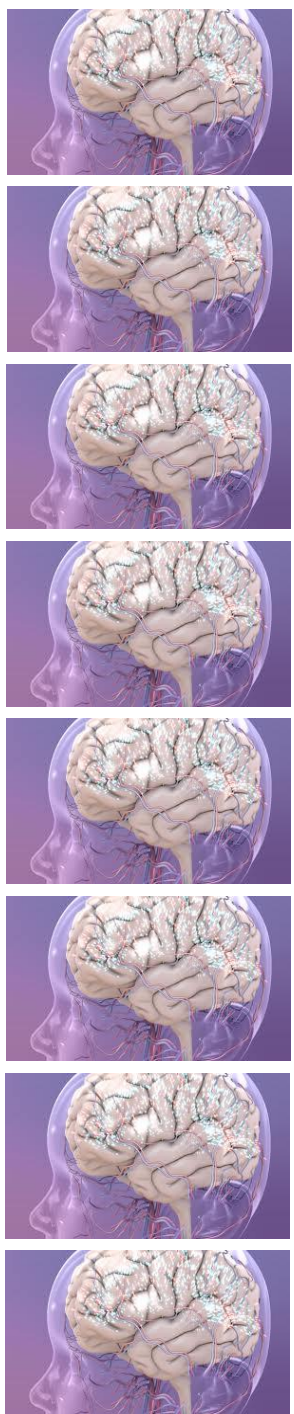
ESTRATEGIAS TERAPÉUTICAS PARA LA NEURODEGENERACIÓN

¿Por qué terapia celular?



FUENTES CELULARES

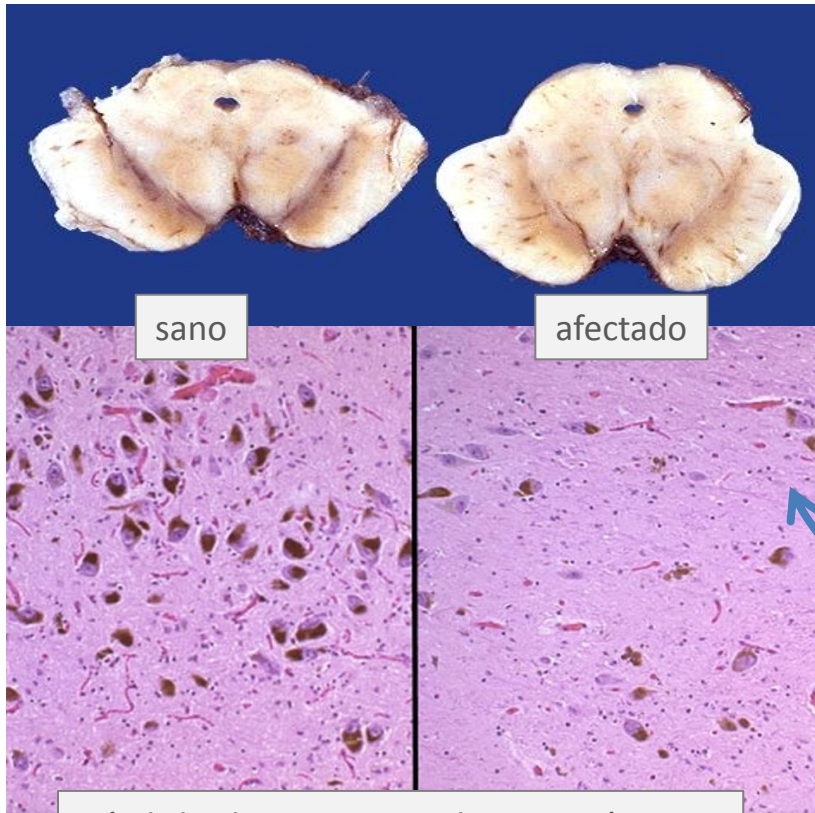
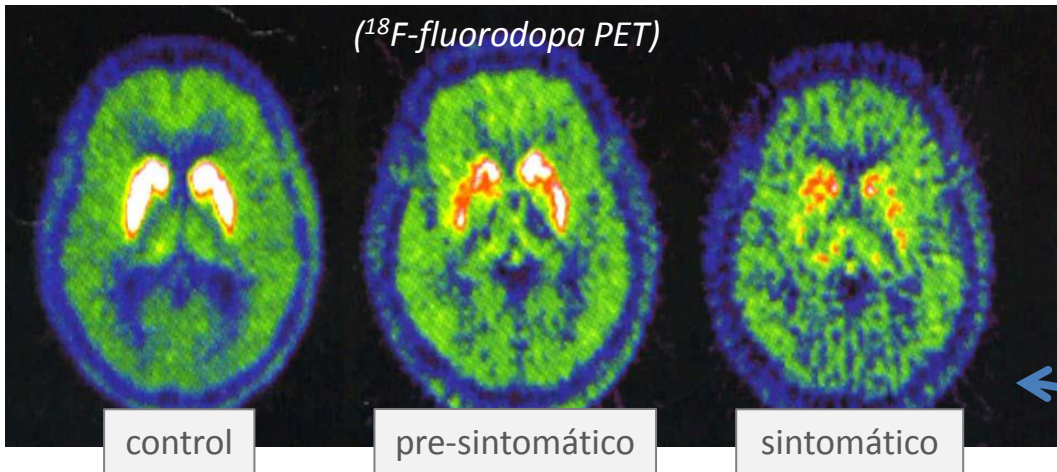
- Distintos tipos de células “stem” o “madres” (CM) de distintas partes de nuestro cuerpo o de distintos momentos de nuestra vida: fetales/adultas (específicas de tejido-órgano), embrionarias, iPS.



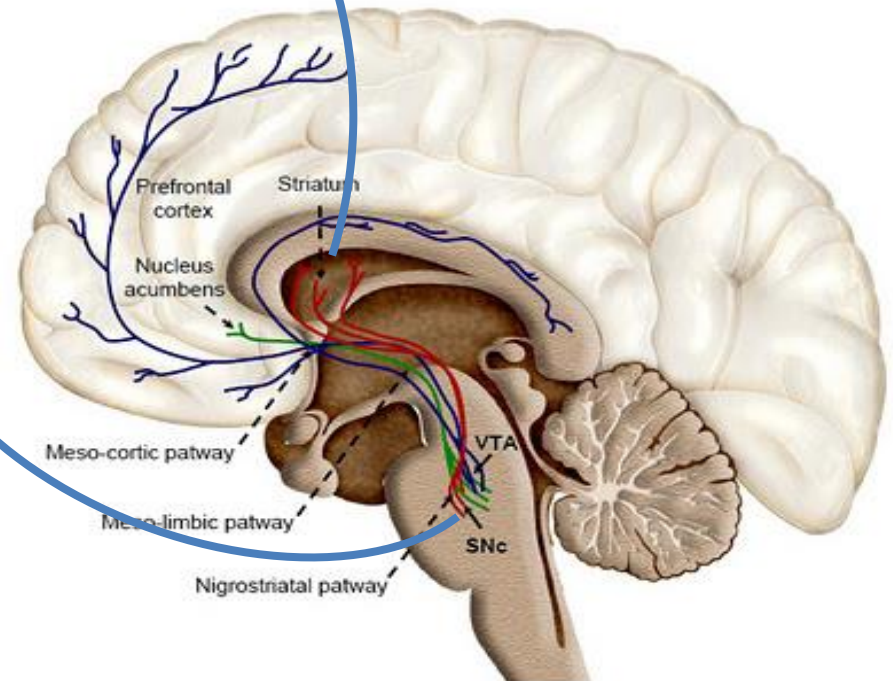
TERAPIAS CON CÉLULAS MADRE/TRONCALES

- Terapias “seguras”:
 - Sangre y sistema inmune: hematopoyesis.
 - Reparación de hueso, piel y córnea: injertos.
- Terapias “inciertas”:
 - El caso del sistema nervioso.

^{18}F -fluorodopa PET



Pérdida de neuronas dopaminérgicas



○ 30 AÑOS DE TRASPLANTES EN EP

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- Primeros trasplantes tras los ensayos pre-clínicos: finales de los años 80 (Suecia, Méjico, 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*.

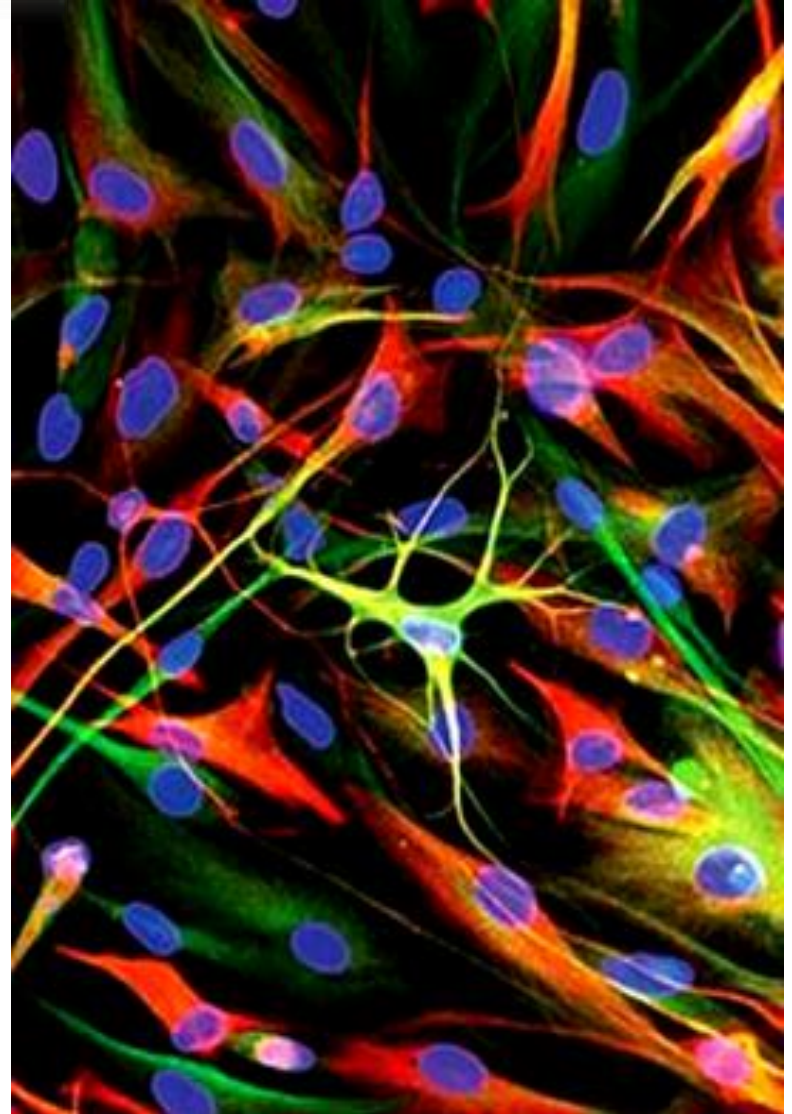
En lo que todos coinciden:

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

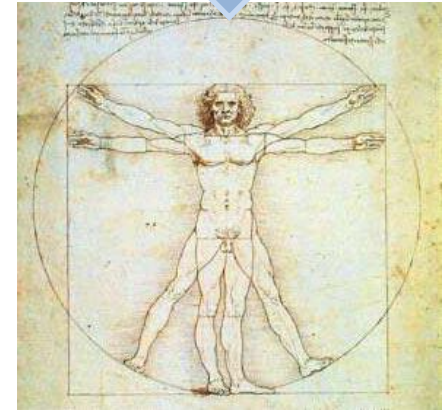
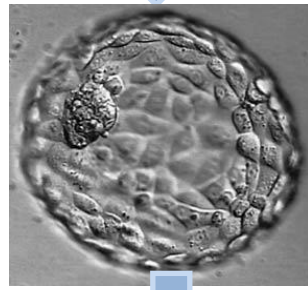
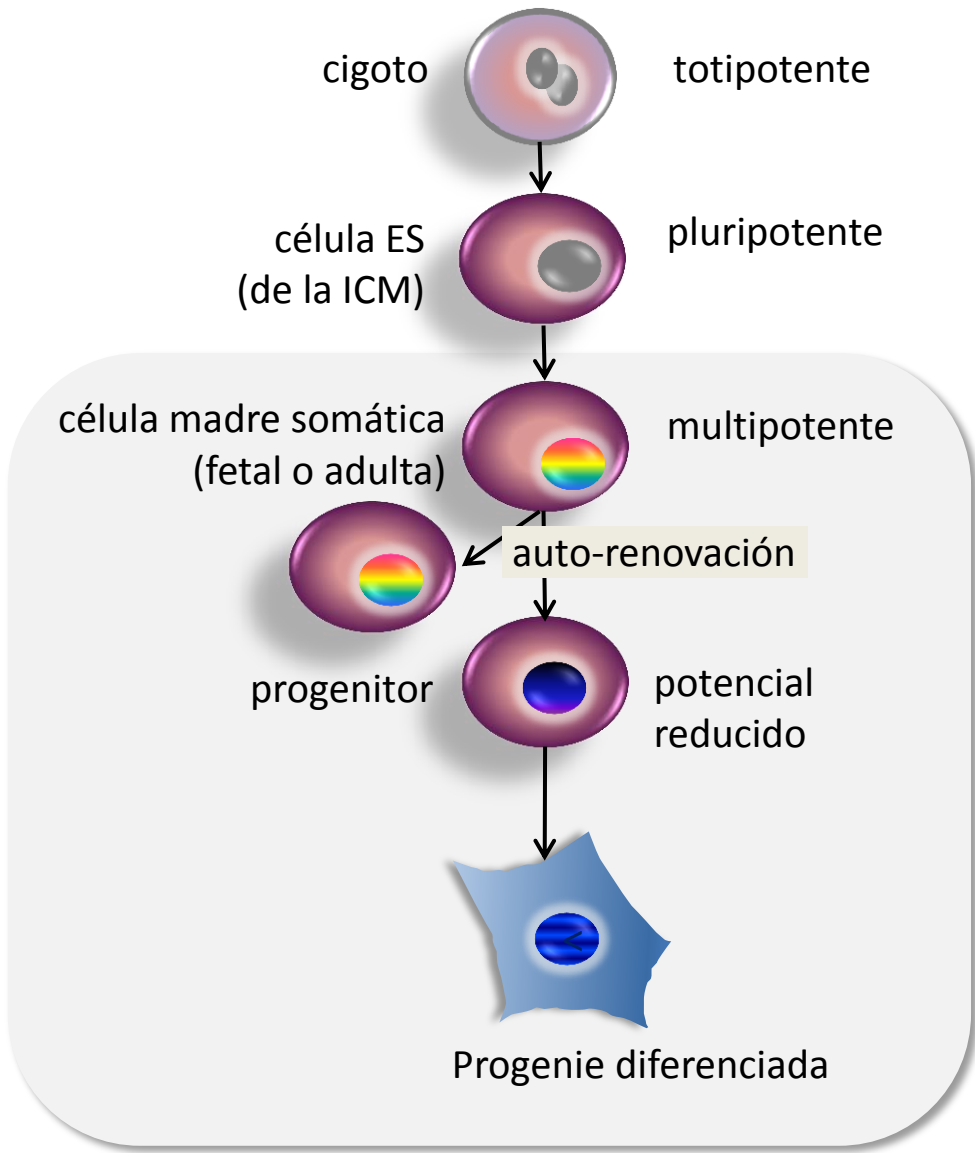
○ 25 AÑOS DE TRASPLANTES EN EP

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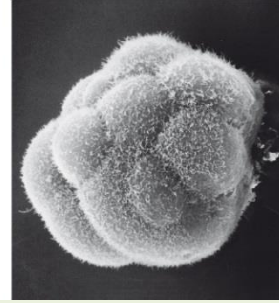
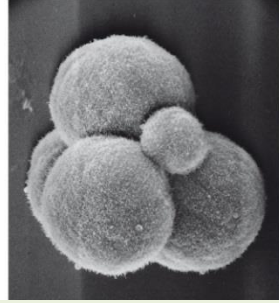
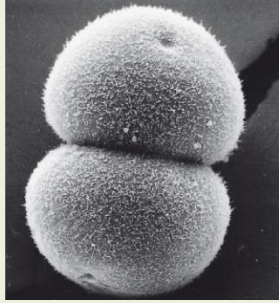
- Problemas:
 - Variabilidad celular: supervivencia, liberación de dopamina, crecimiento.
 - Rendimiento celular: 500.000 neuronas dopaminérgicas en la SN de una persona adulta. Aprox. 10.000 neuronas por feto sobreviven (4-6 fetos de 6-8 semanas por paciente trasplantado).
 - Necesidad de fuentes celulares alternativas.



potencial



cigoto

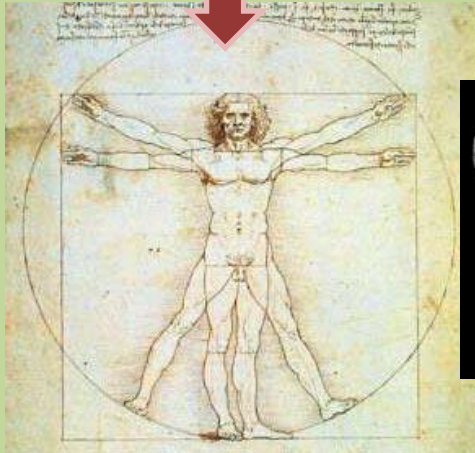
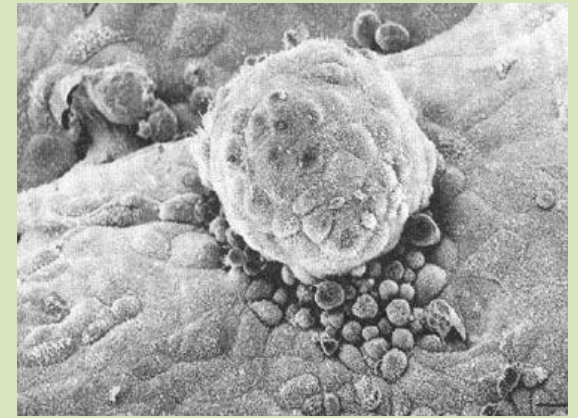
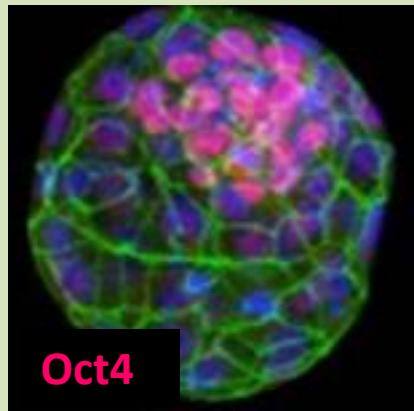


mórula



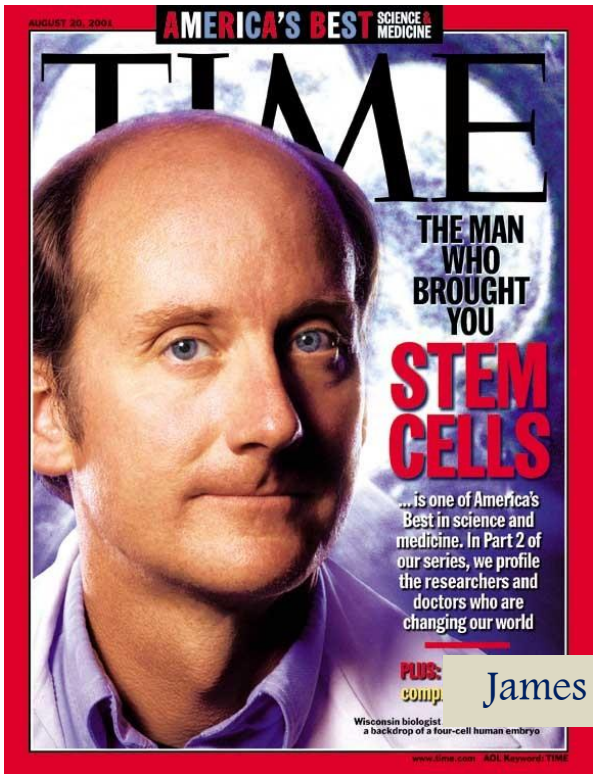
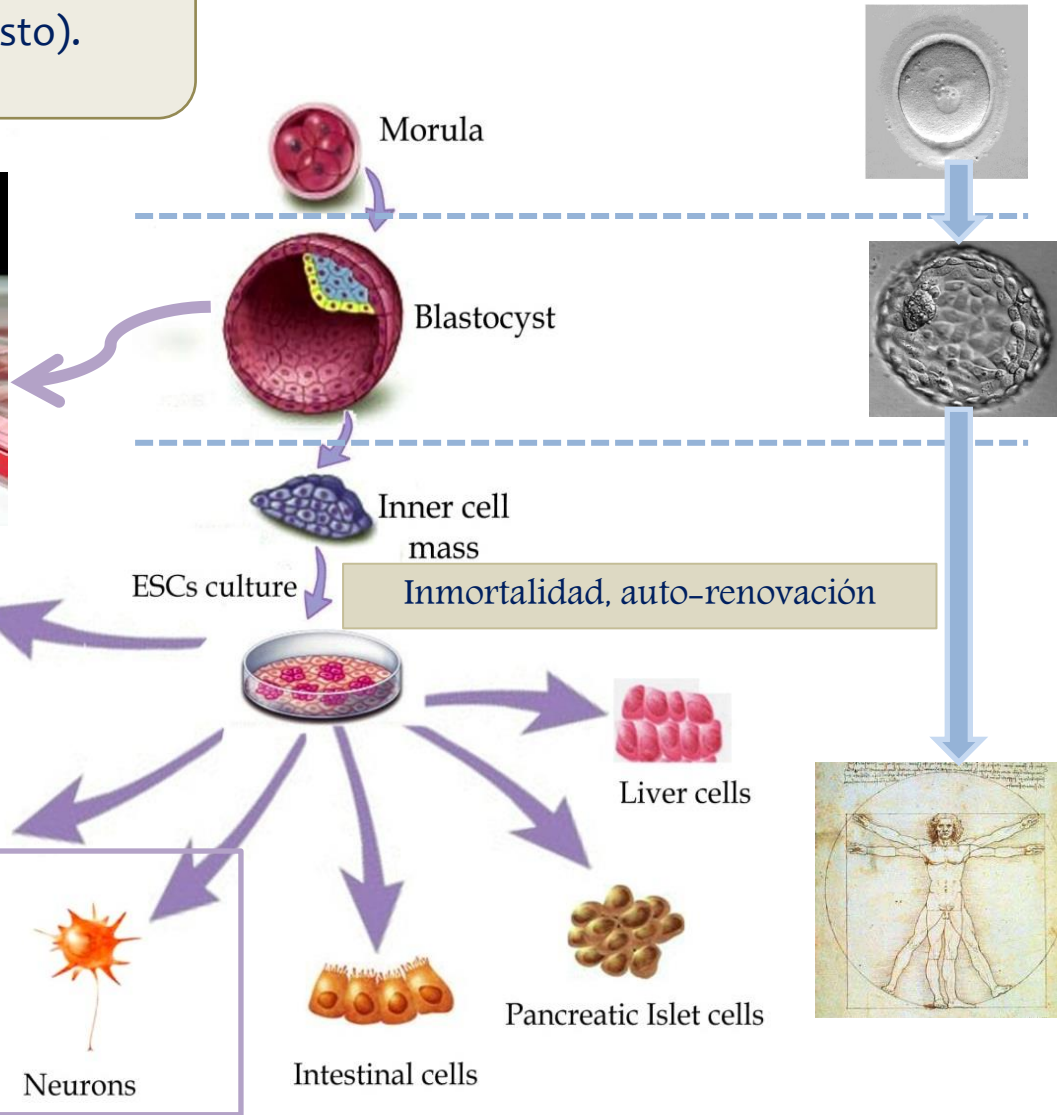
Blastocisto:

- TE
- ICM



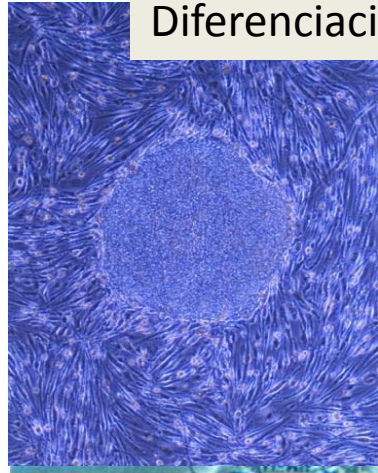
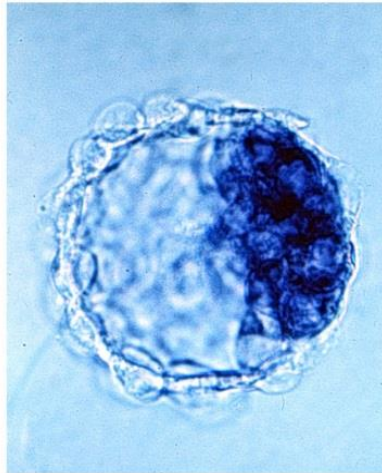
10^{14} células, >200 tipos distintos

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

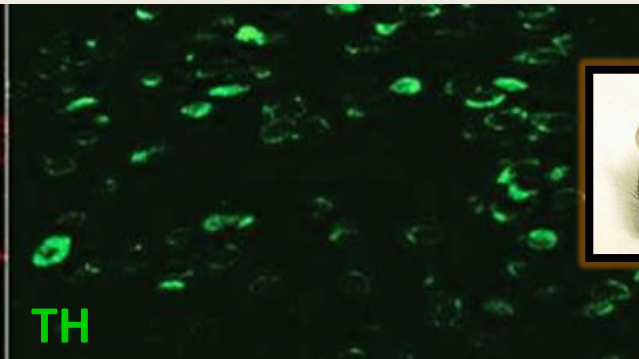
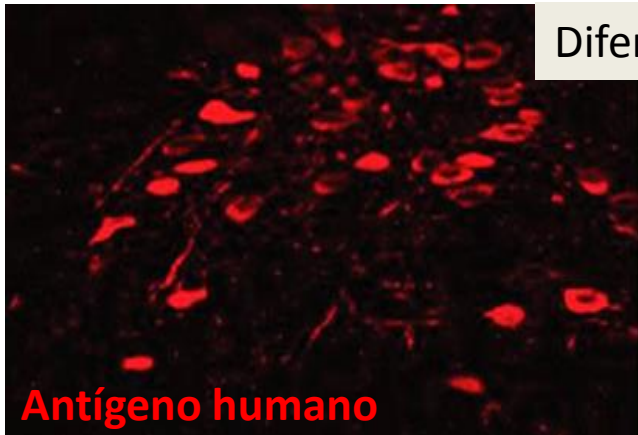
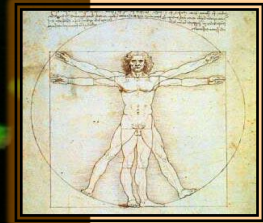
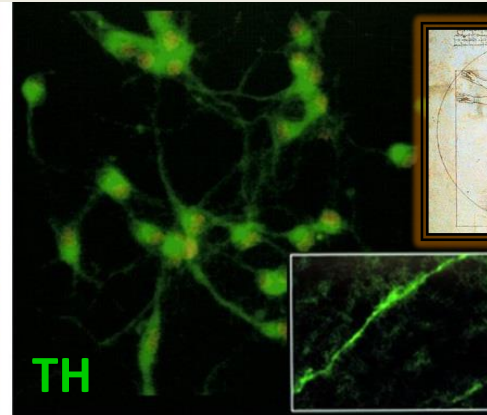


James Thomson

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*

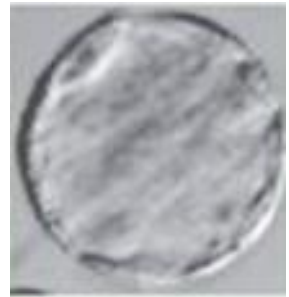
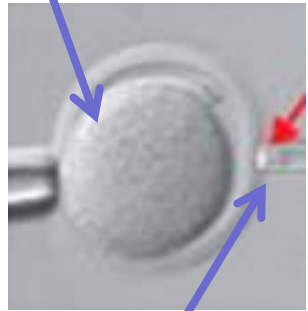
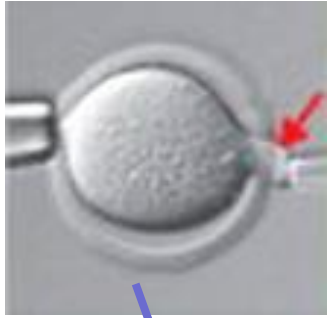


Diferenciación dopaminérgica *in vivo*



Transferencia nuclear somática: SCNT

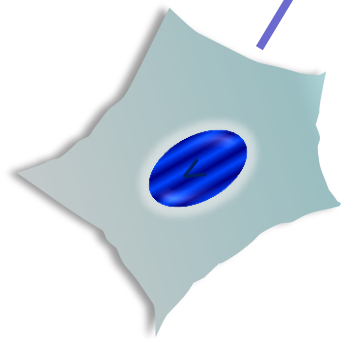
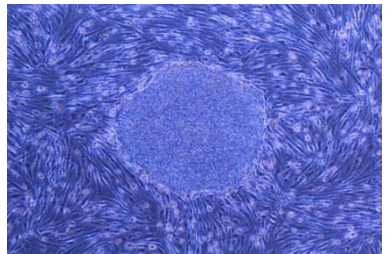
OOCITO ENUCLEADO



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

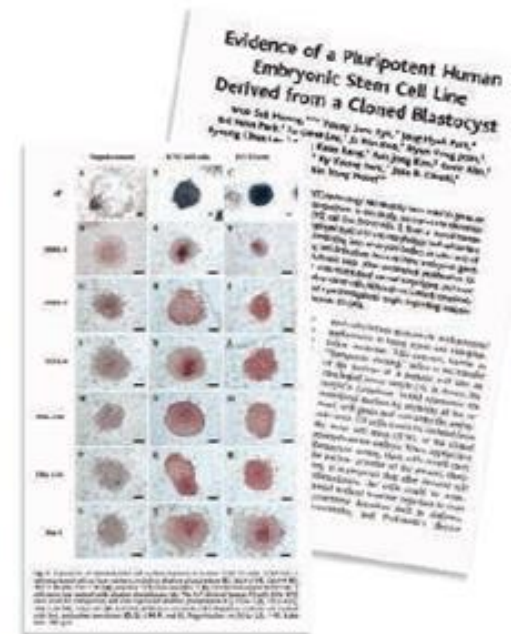
edited by Etta Kavanagh

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 cell lines 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

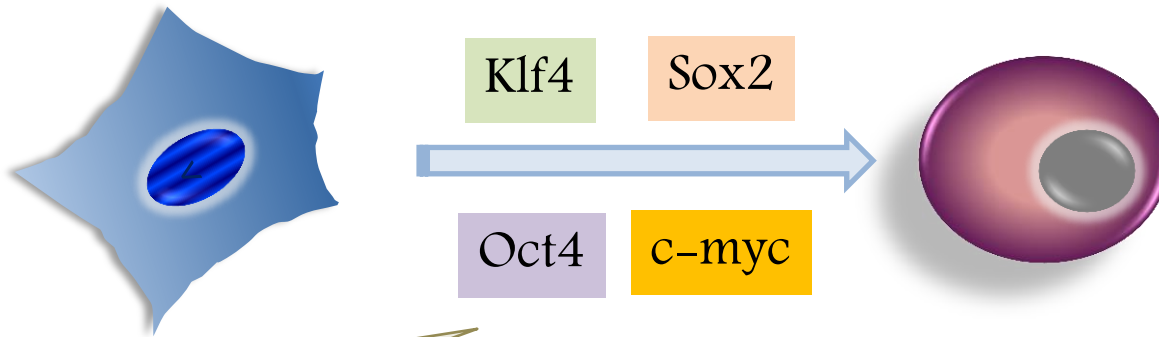
Editor-in-Chief



Shinya Yamanaka
2012

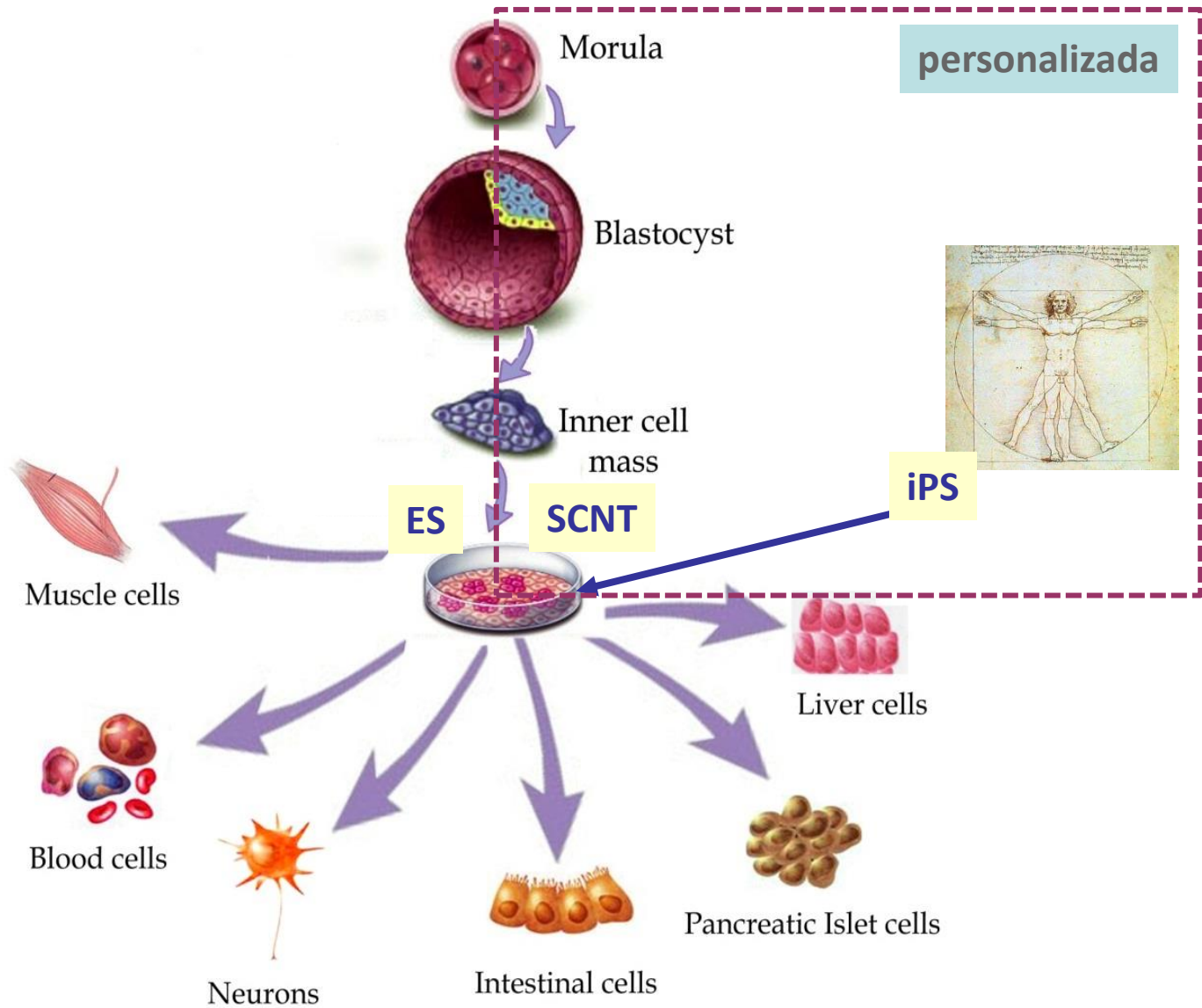


Células pluripotentes inducidas (iPS): enorme potencial, grandes limitaciones (bioseguridad). No rechazo.



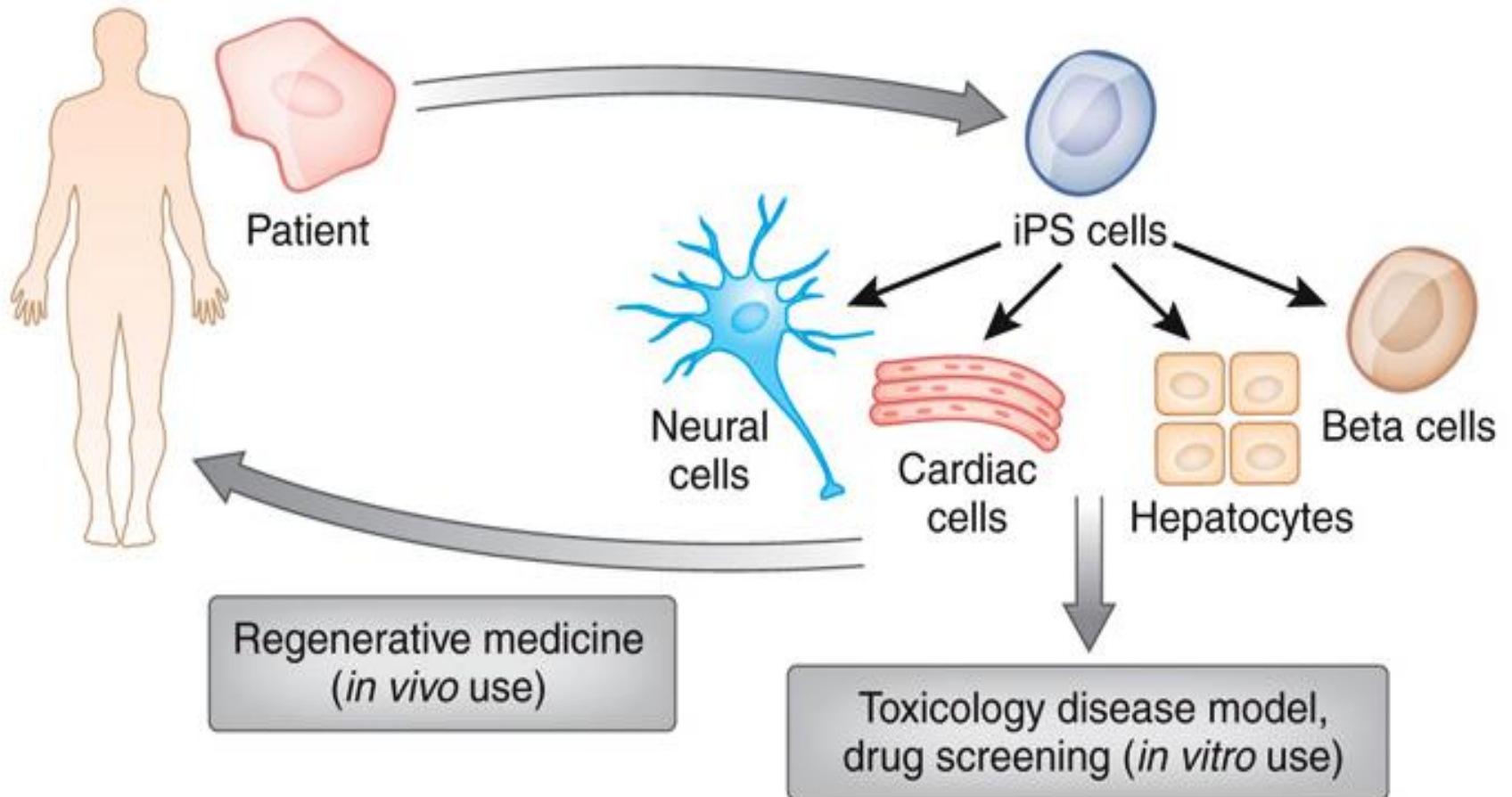
Reprogramación directa por un cóctel de factores de regulación de la pluripotencia

Células pluripotentes para terapia





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





FUENTES CELULARES

- Distintos tipos de células “stem” o “madres” (CM) de distintas partes de nuestro cuerpo o de distintos momentos de nuestra vida: fetales/adultas (específicas de tejido-órgano), embrionarias, iPS.
- Las CM adultas tienen un potencial limitado.
- Las células pluripotentes (ES o iPS) sí podrían generar tratamientos para un amplio rango de enfermedades. Sin embargo:
 - Tumorigénesis.
 - Ningún protocolo *in vitro* conduce a diferenciación completa.



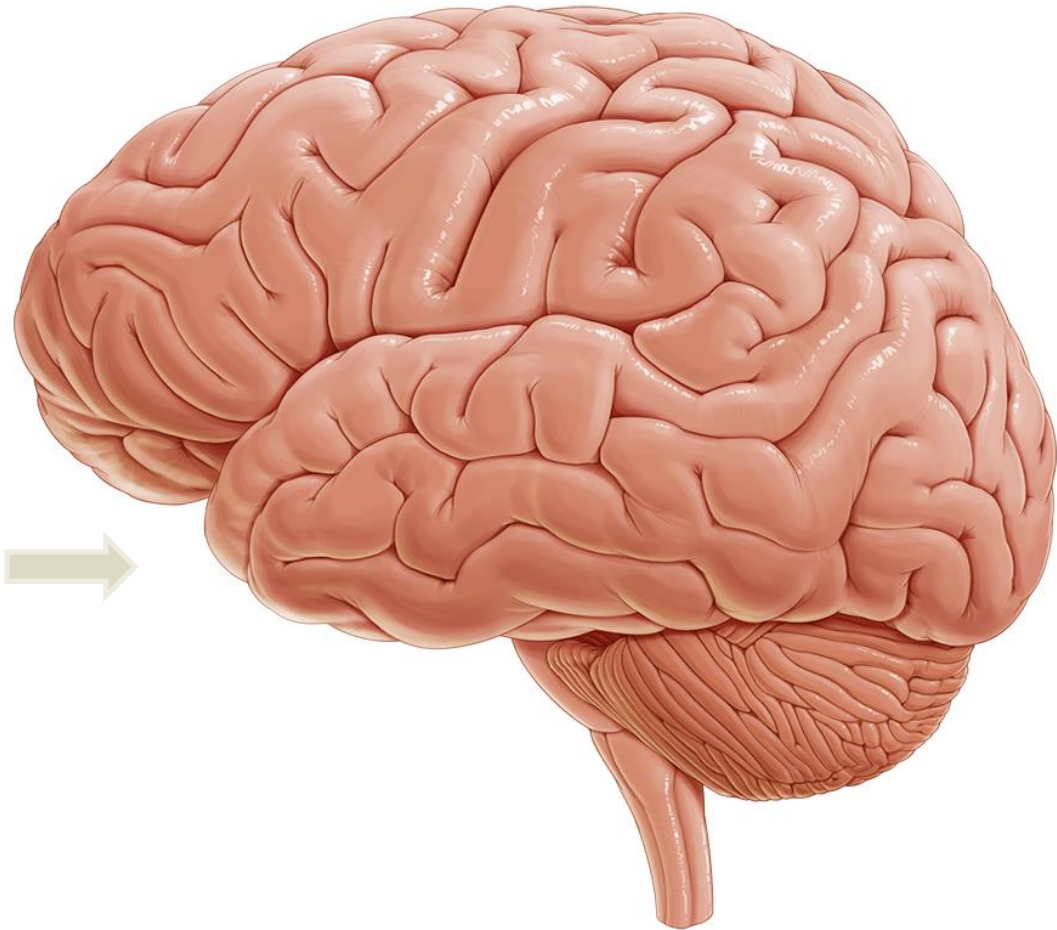
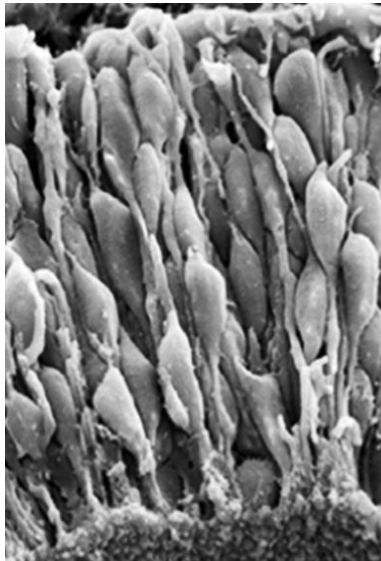
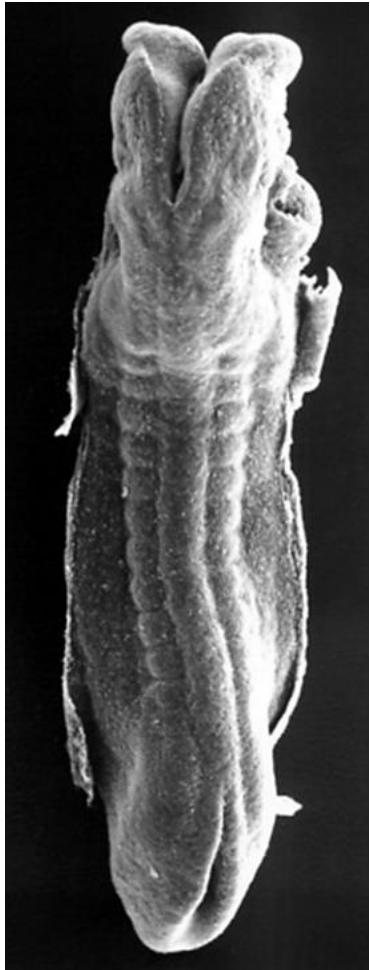


LA VÍA LÁCTEA

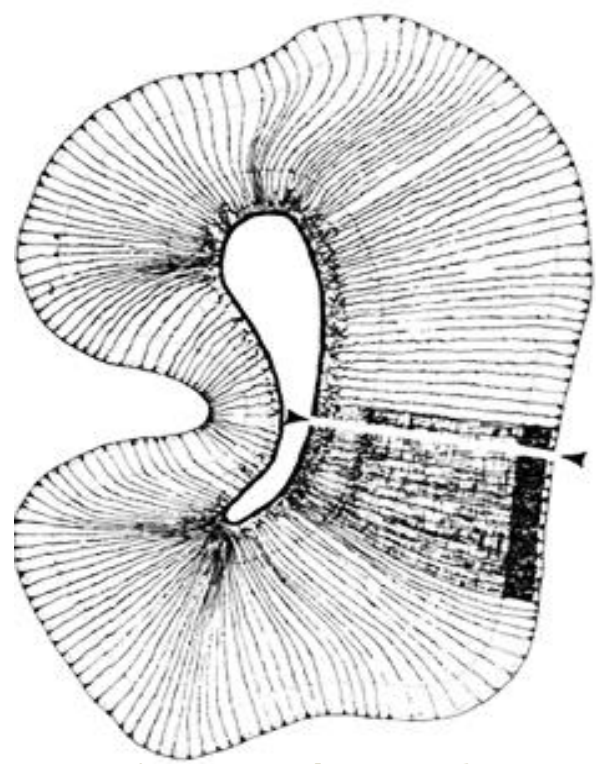
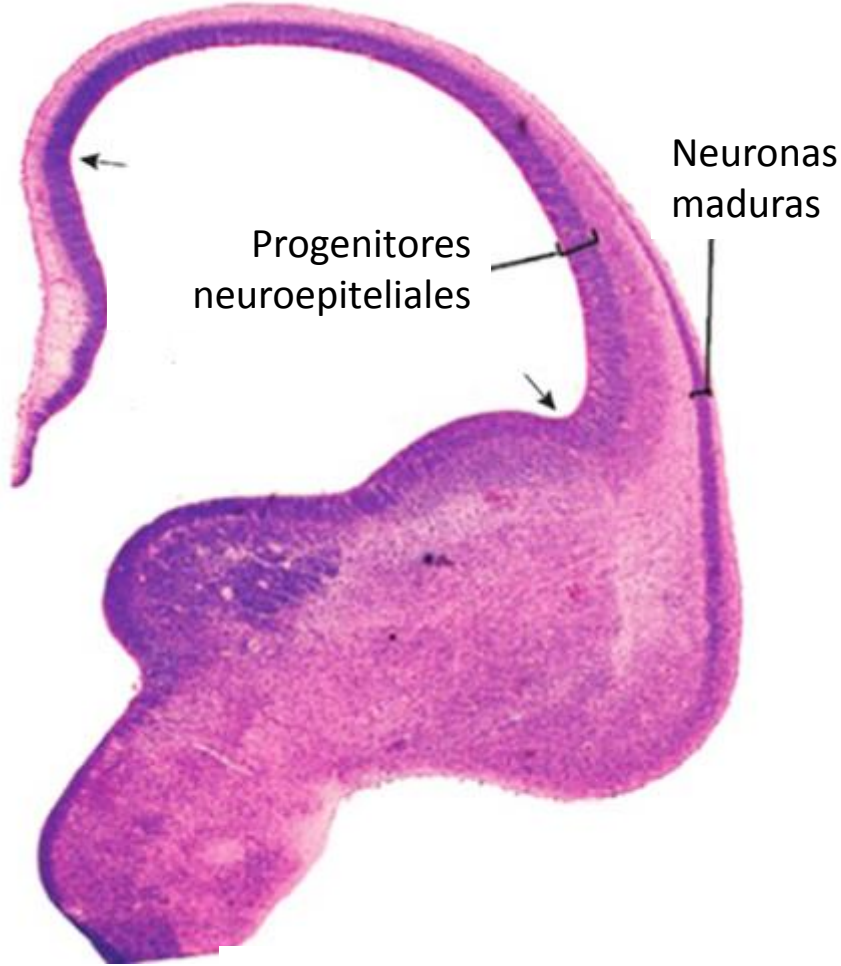
Trillón y medio de kilómetros
200.000 a 400.000 millones de
estrellas

NUUESTRO CEREBRO

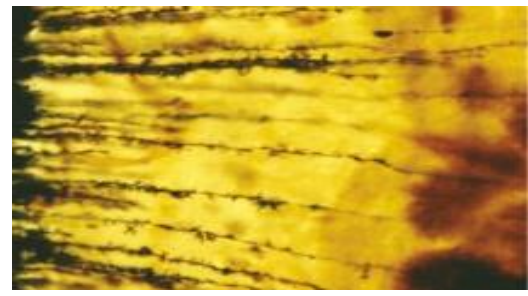
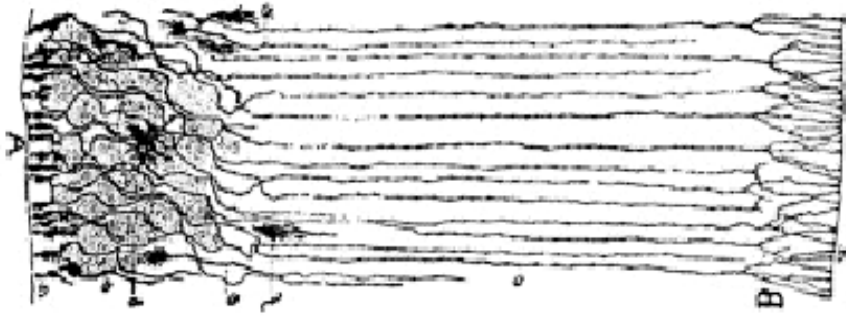
15 centímetros. 1,2-1,4 Kg
86.000 millones de neuronas
Cada neurona recibe alrededor de
10.000 sinapsis

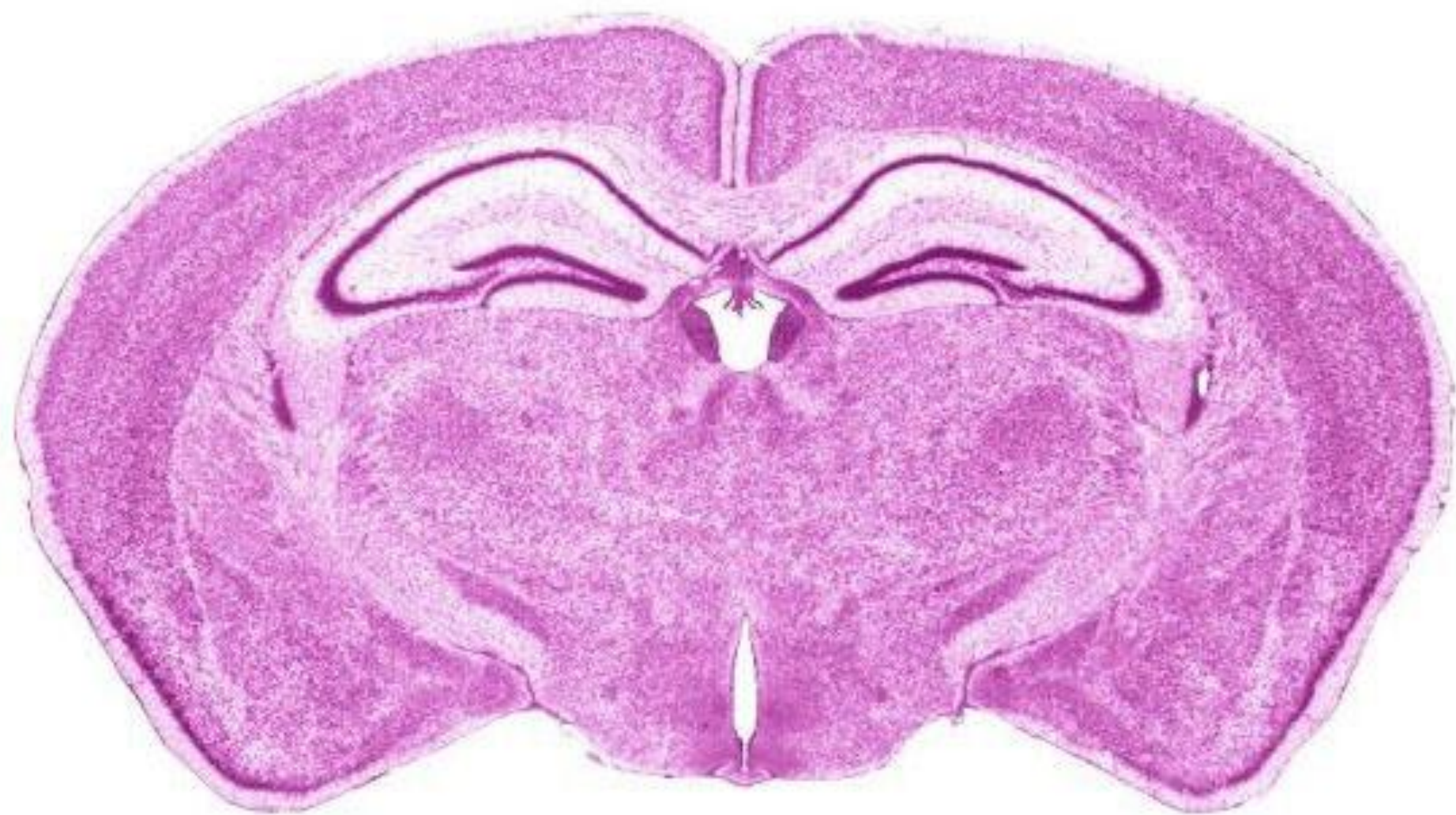


Progenitores neuroepiteliales

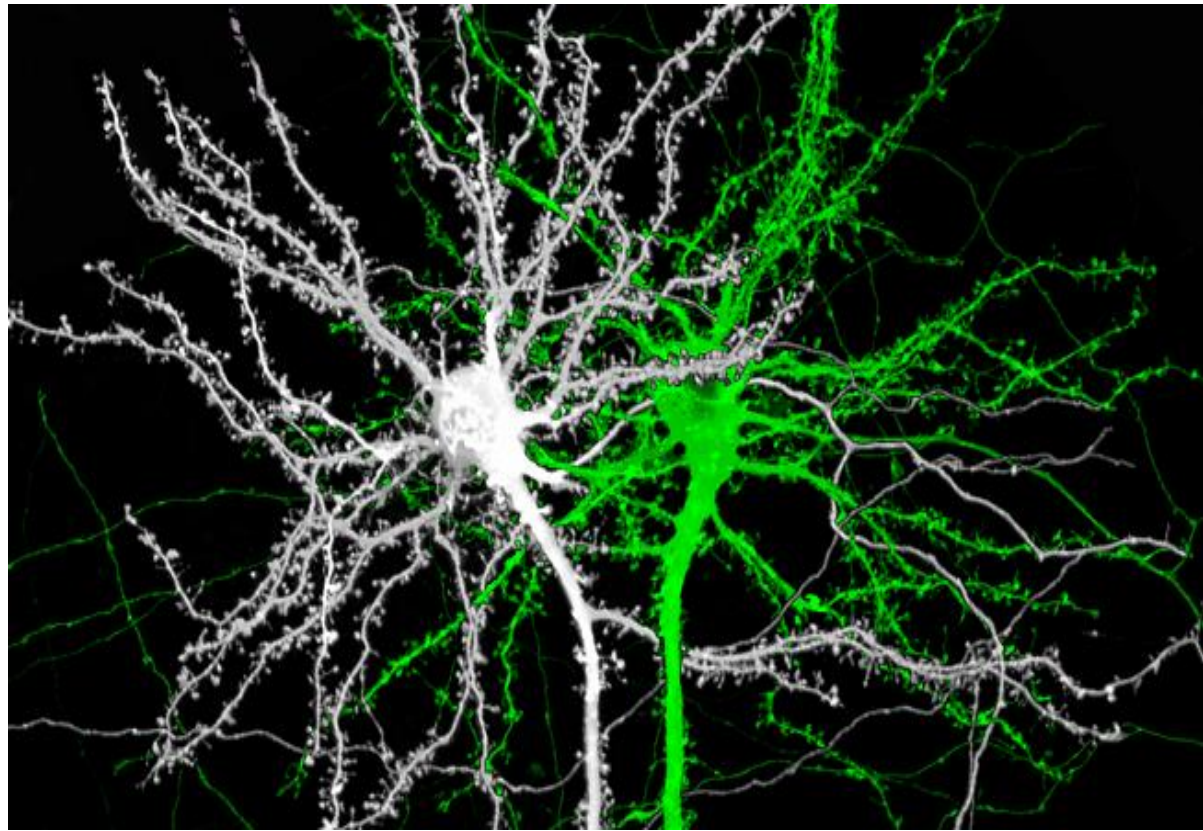


Santiago Ramón y Cajal



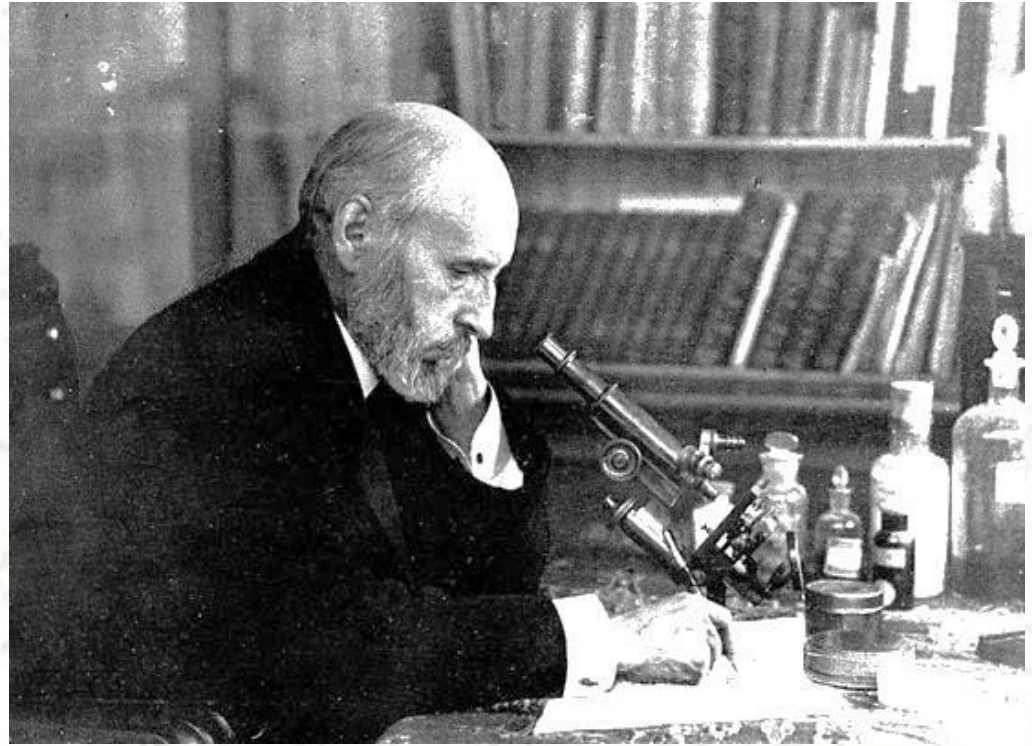


La **plasticidad neural** es la habilidad del cerebro de cambiar y adaptarse como resultado de la experiencia (aprender nuevas cosas, generar recuerdos,...)



Ventanas de oportunidad: periodos críticos

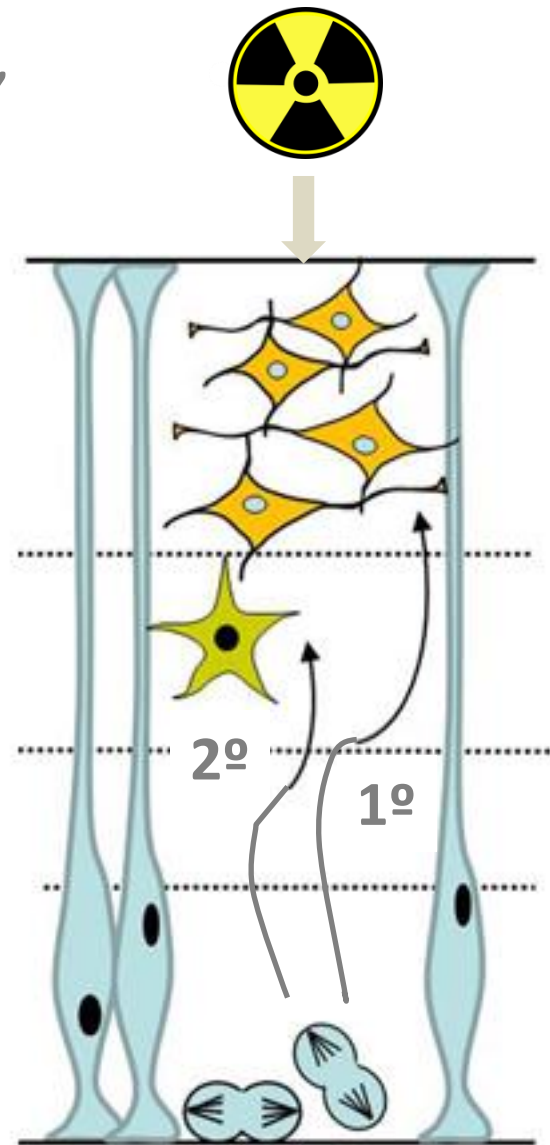
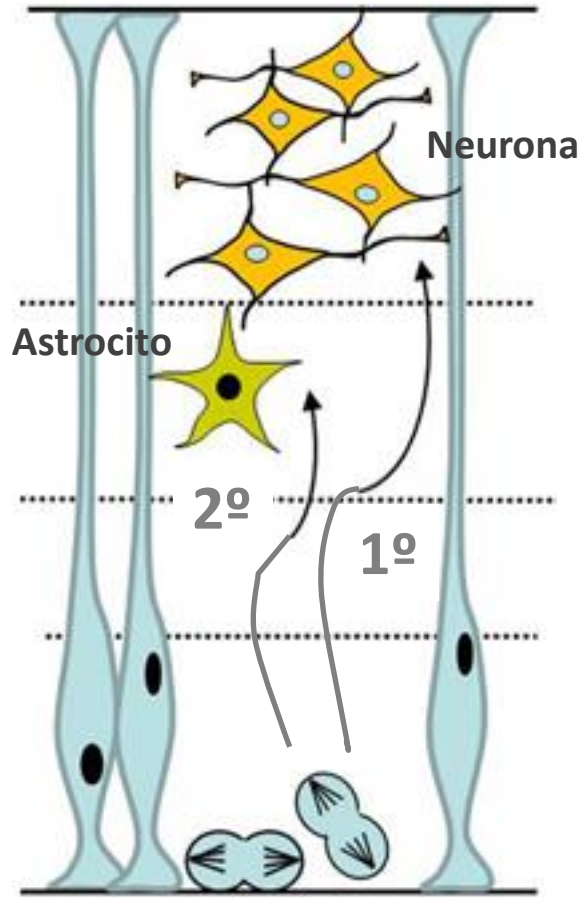
“...el aprendizaje hace que las células nerviosas existentes emitan o hagan crecer nuevas prolongaciones para reforzar sus conexiones con otras células nerviosas...”



“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

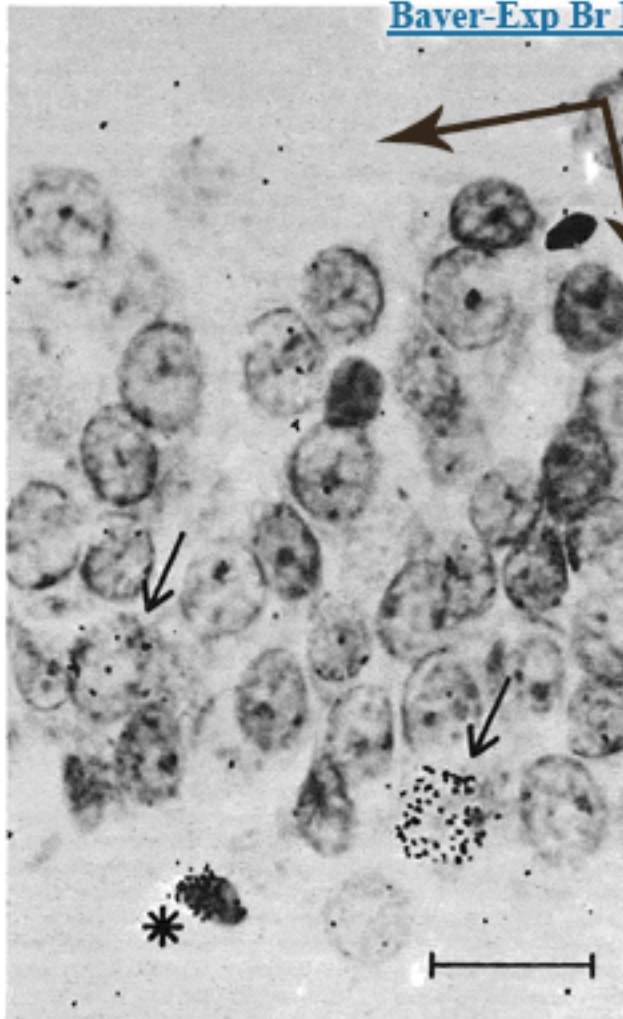
"Birthdating"





Se detecta proliferación en el cerebro adulto de roedores

[Bayer-Exp Br Res 1982.pdf](#)



These figures show that the dispersed germinal matrix in the adult dentate gyrus is a fragmentary scattering of small, dark cells in the dentate hilus (*fig. 3) called the **subgranular zone** (Altman & Bayer, 1975, see below)

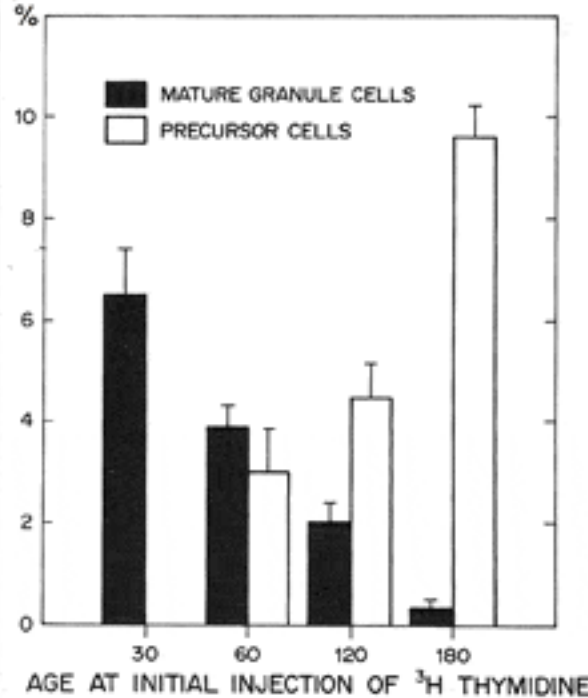
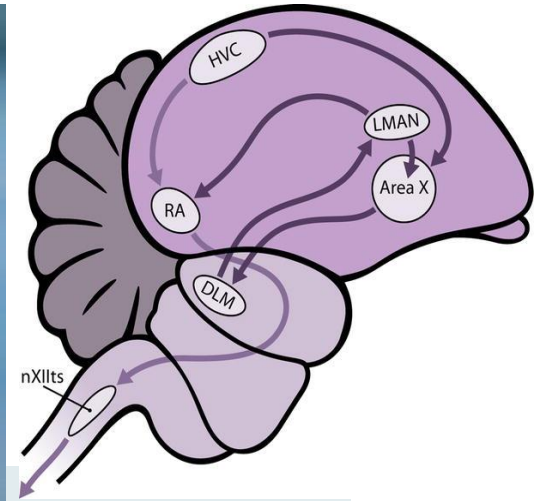


Fig. 4. Means (with standard deviations) of the proportion (labeled cells to total cells) of labeled mature granule cells (black bars) and labeled presumptive precursor cells (white bars) in animals aged 200 days after four consecutive daily injections of ³H-thymidine began of the days indicated. These data were collected from eight sagittal slices of the granular layer, four each at 1.0 mm and 3.8 mm lateral to the midline

Fig. 3. Labeled mature granule cells (arrows) and a labeled presumptive granule cell precursor (asterisk) in the granular layer endal limb in a rat given four injections of ³H-thymidine on 120-123 days of age and killed on 200 days of age

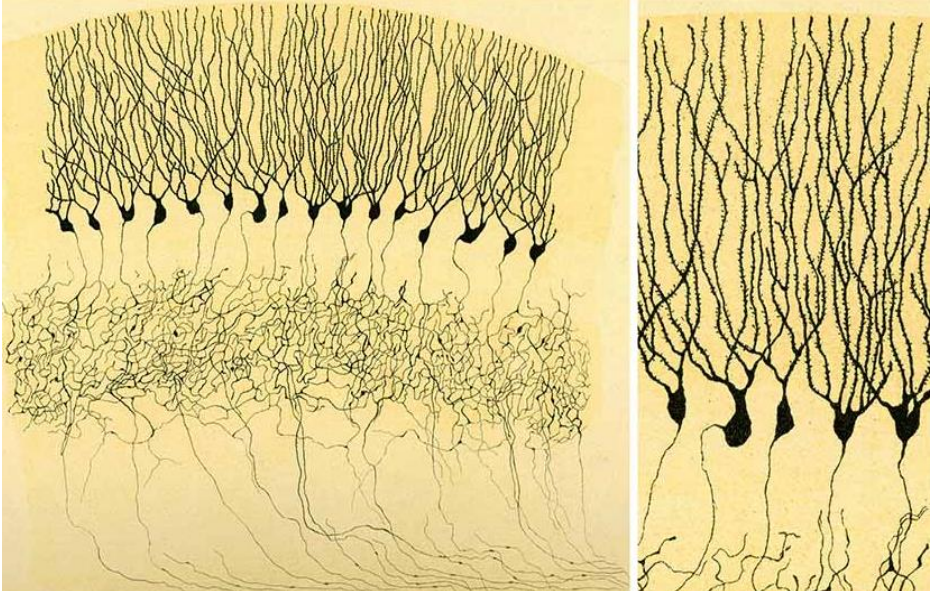
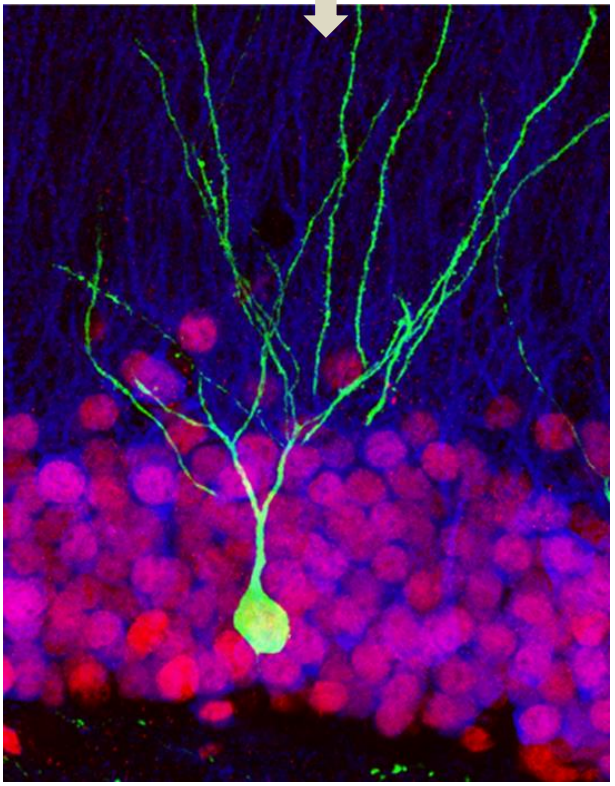
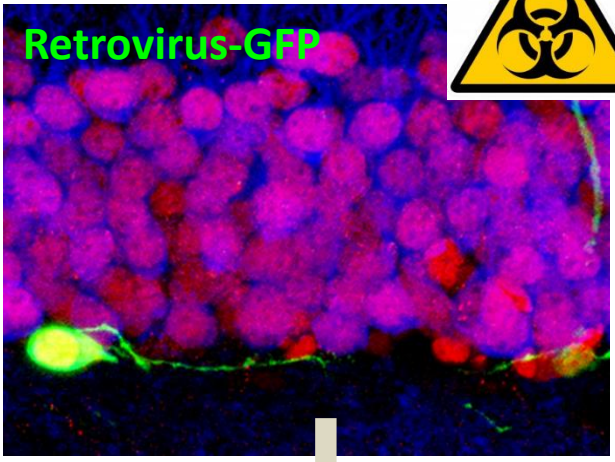
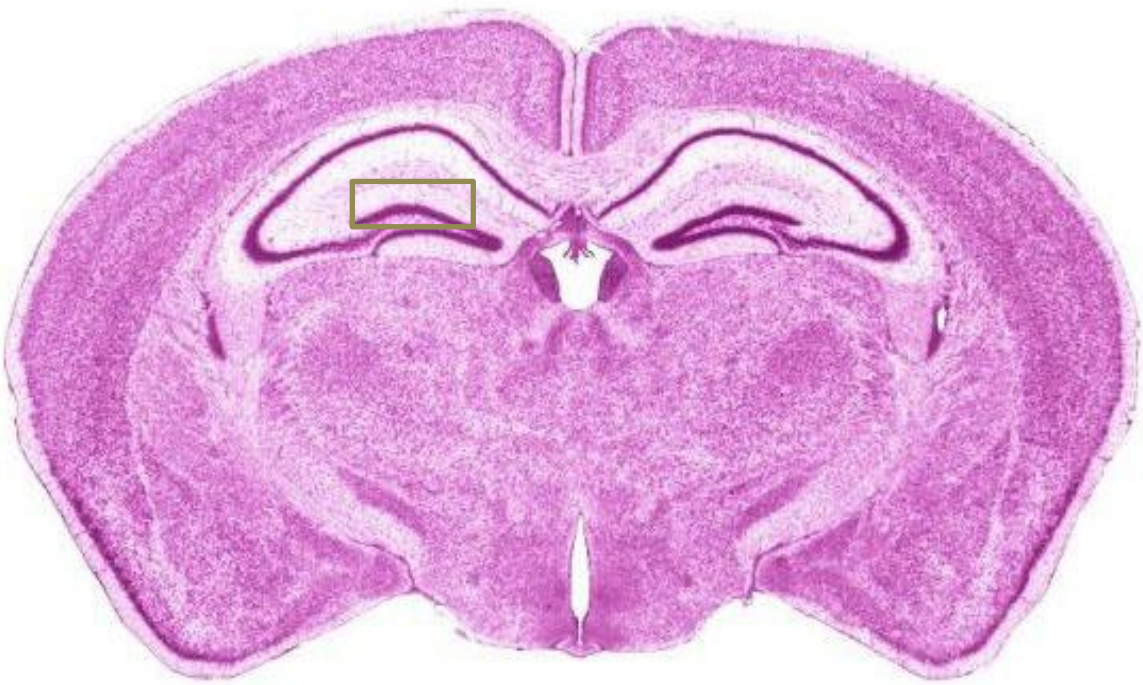




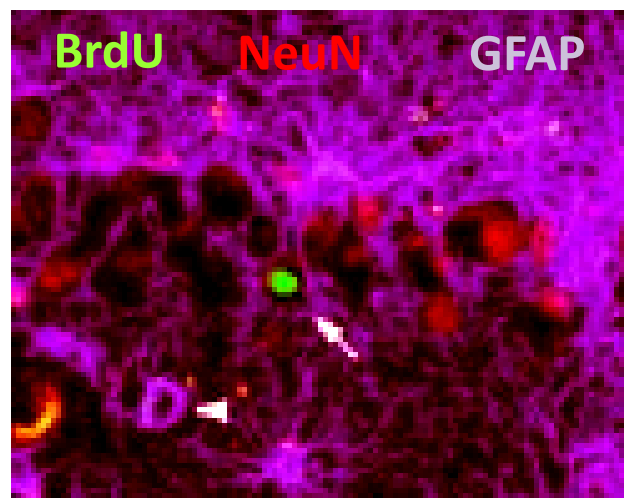
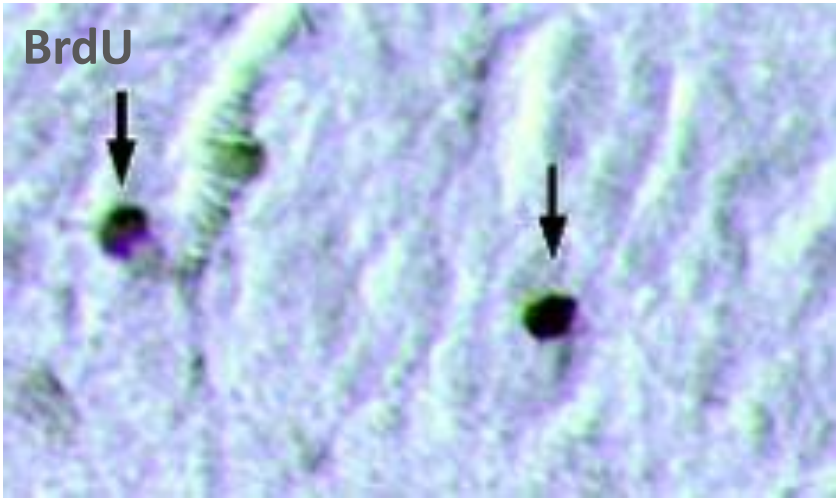
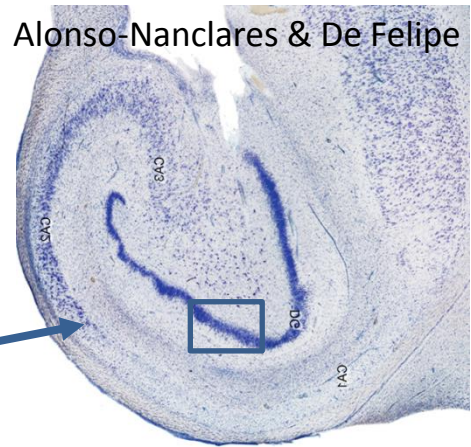
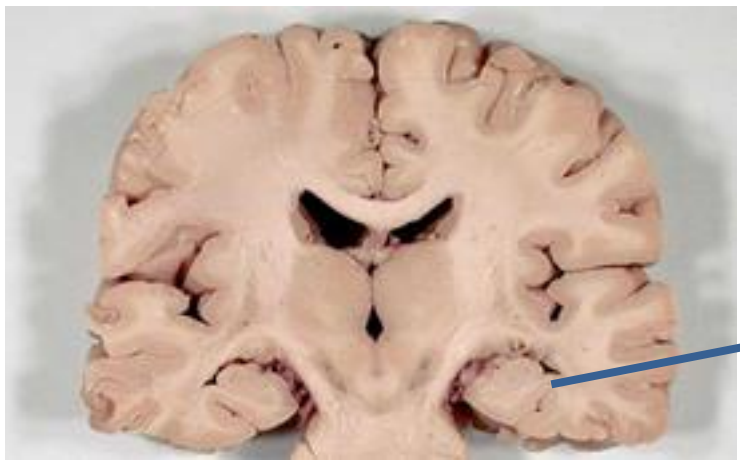
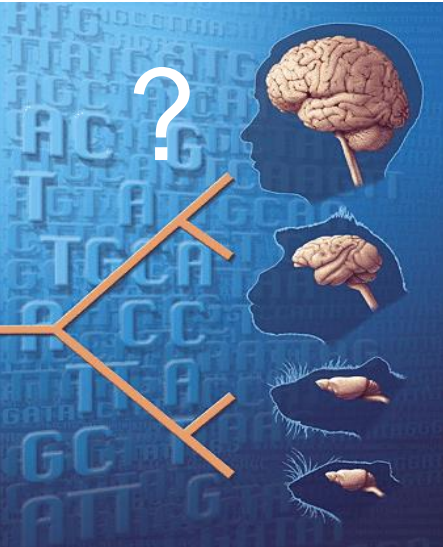
Neurons generated in the adult brain are recruited into functional circuits

Paton and Nottebohm

Science 7 September 1984: 1046-1048



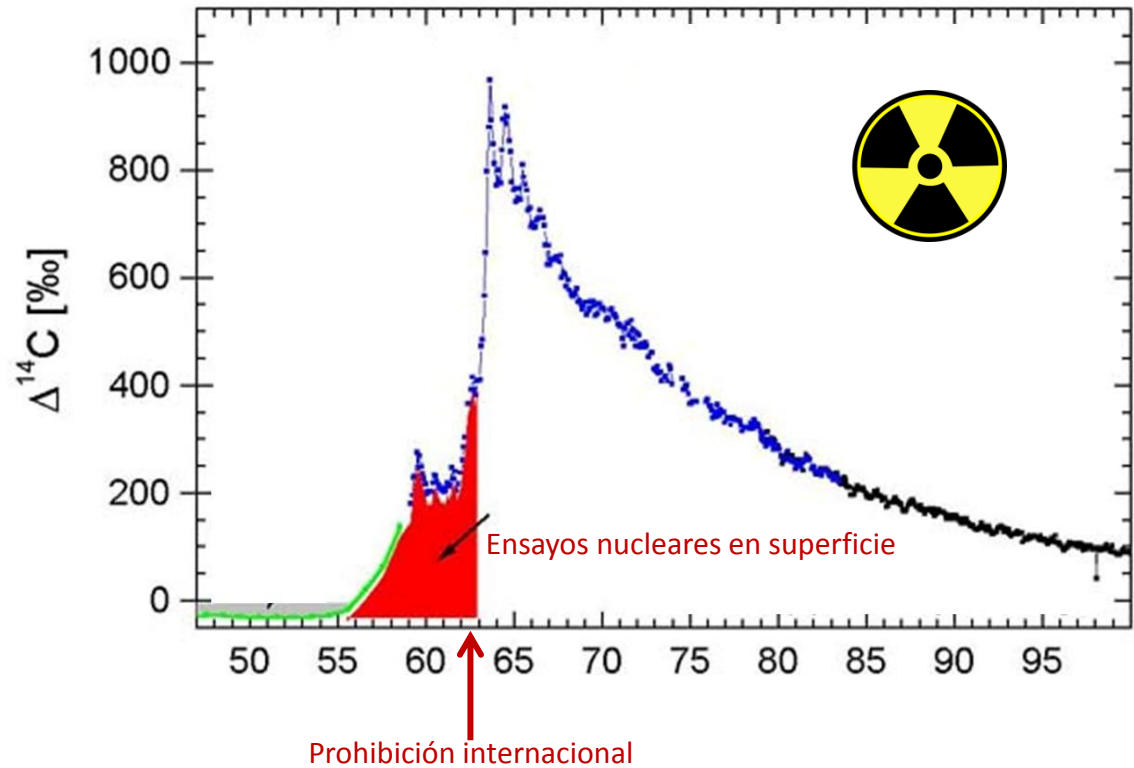
Santiago Ramón y Cajal



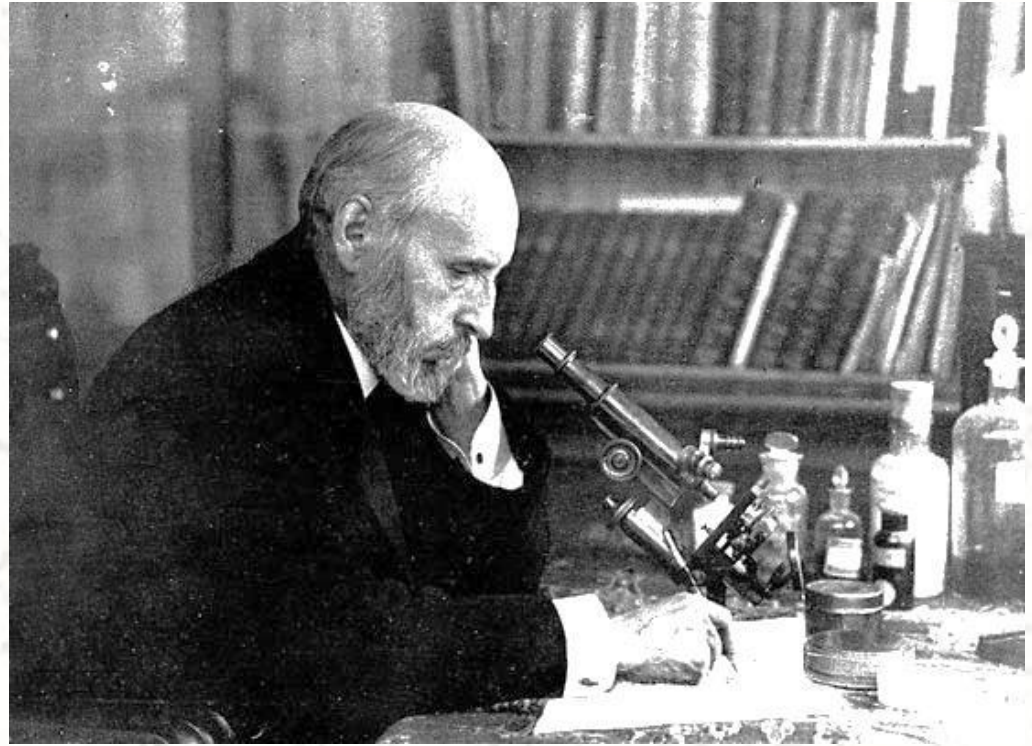
“Birthdating” en el ser humano



^{14}C en CO_2 atmosférico



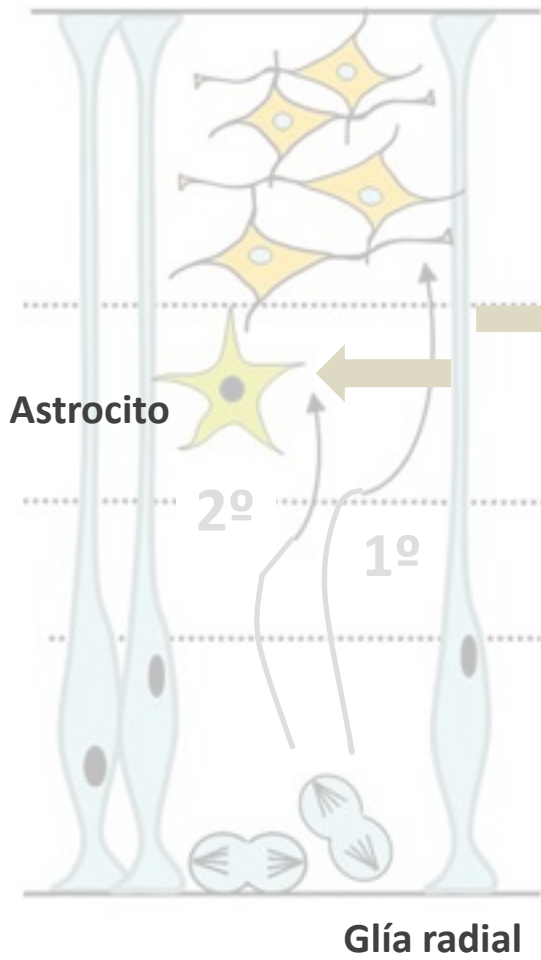
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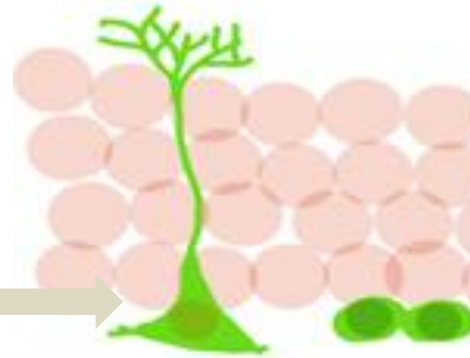
“Preciso es reconocer que, en los centros adultos, las vías nerviosas son algo fijo, acabado, inmutable. Todo puede morir, nada renacer”.

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

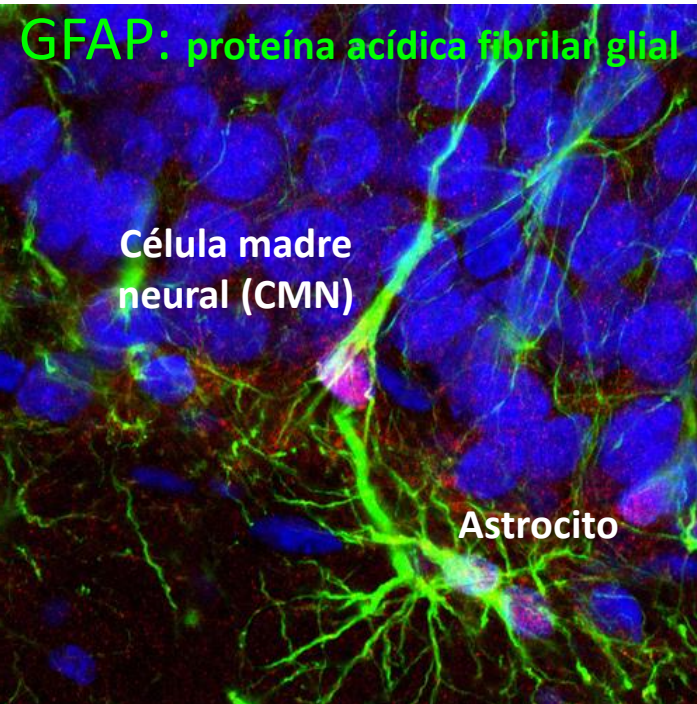
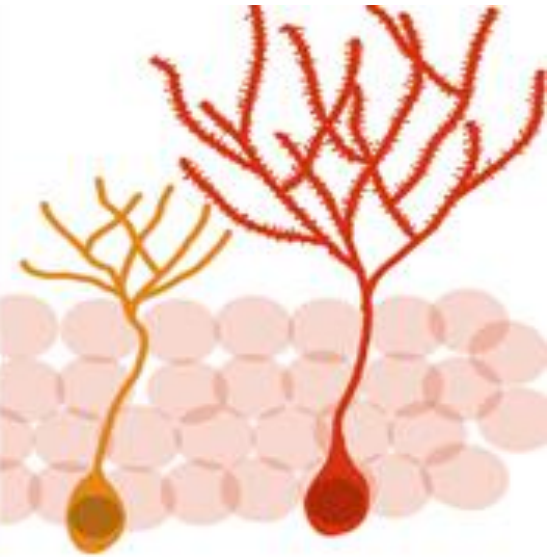
Santiago Ramón y Cajal, 1928

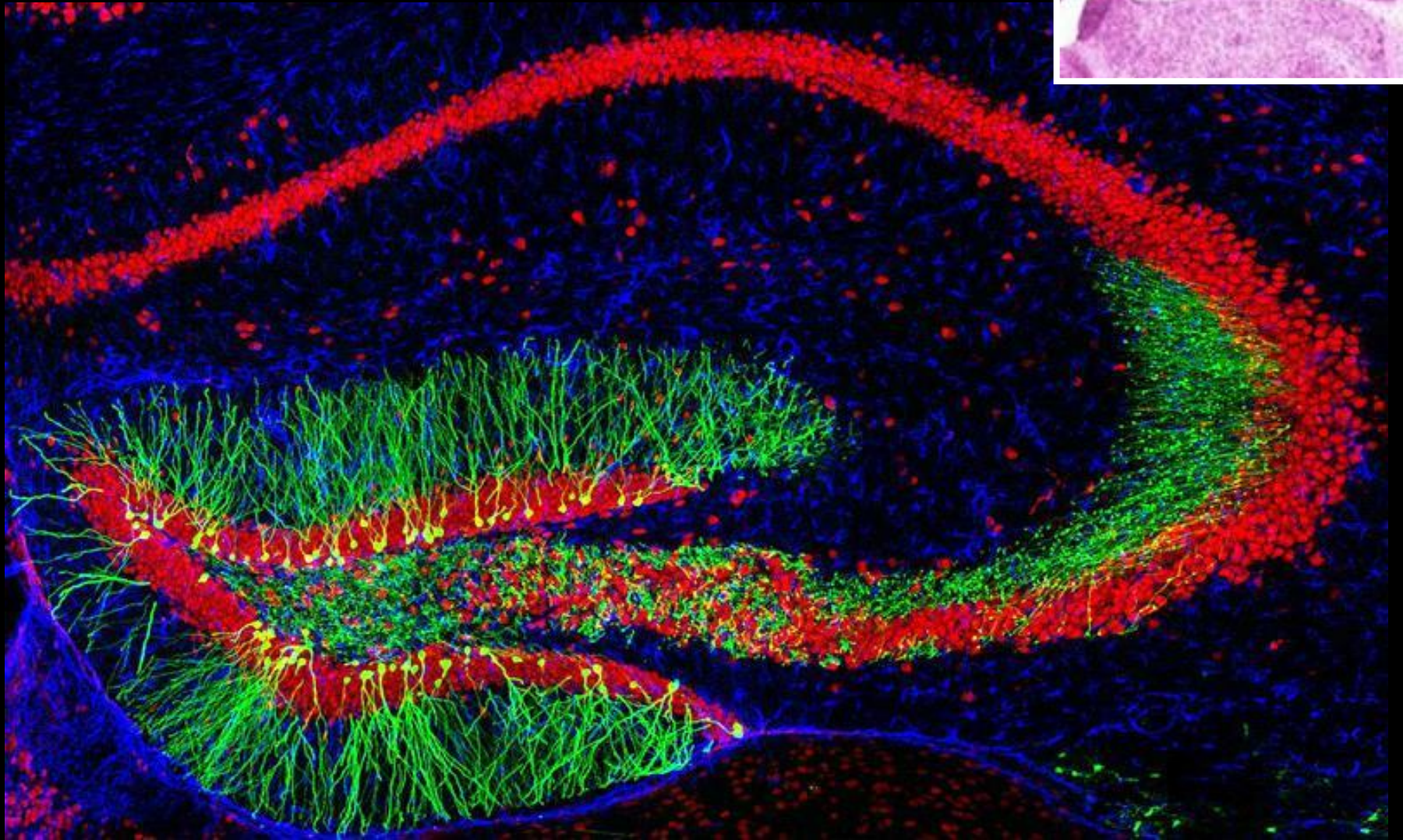


Célula madre neural (CMN)



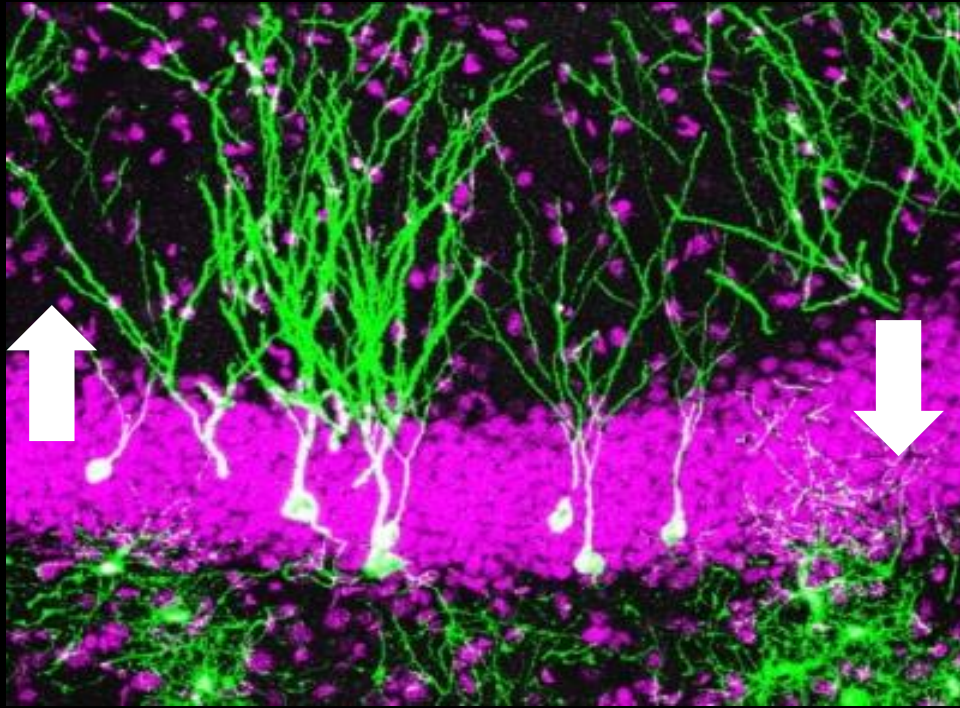
Neuron



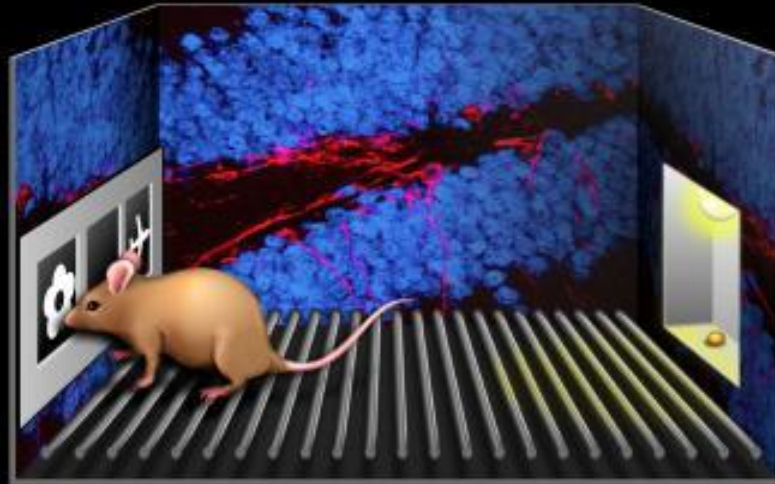




Ambientes
enriquecidos

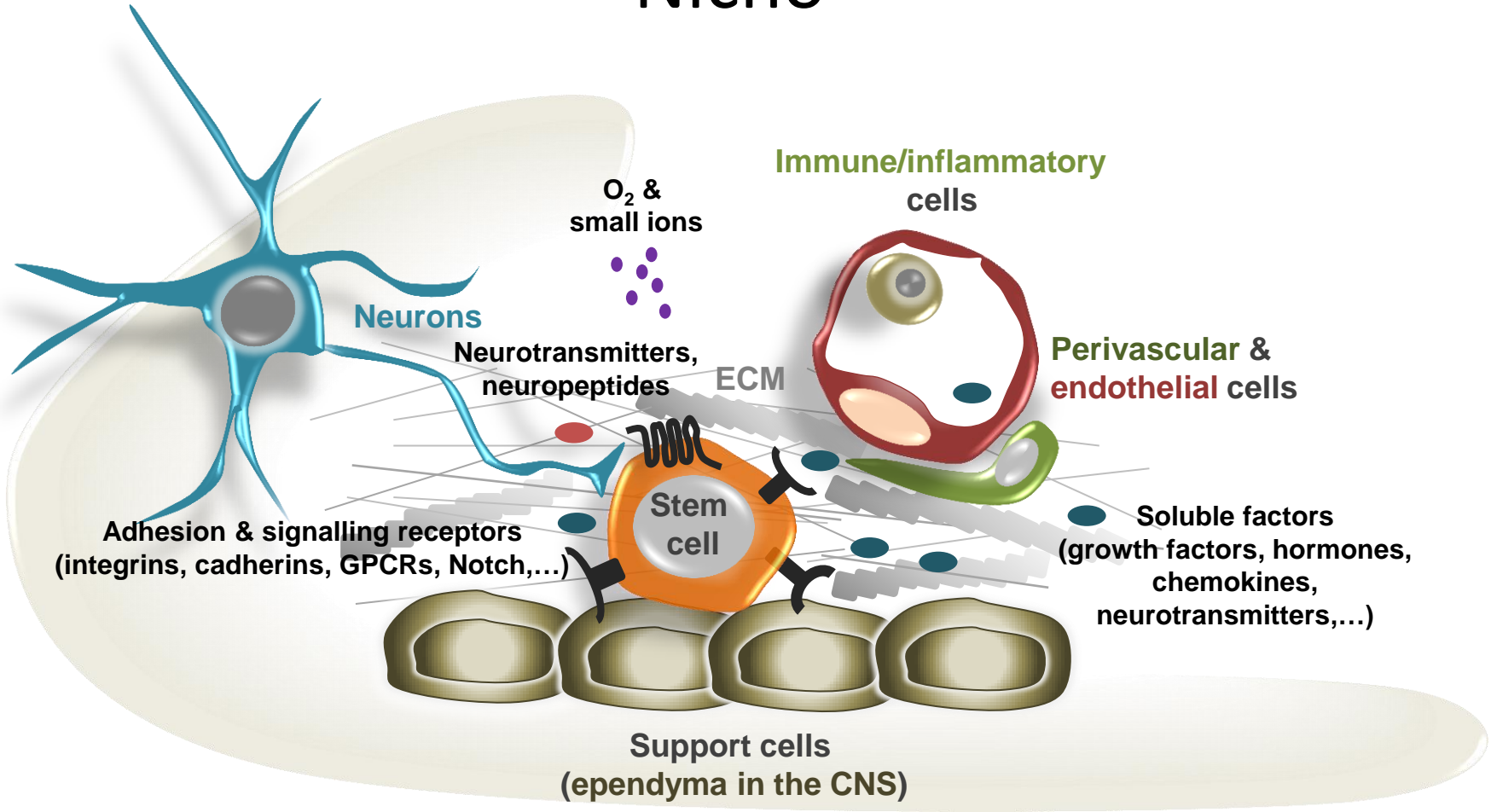


Edad

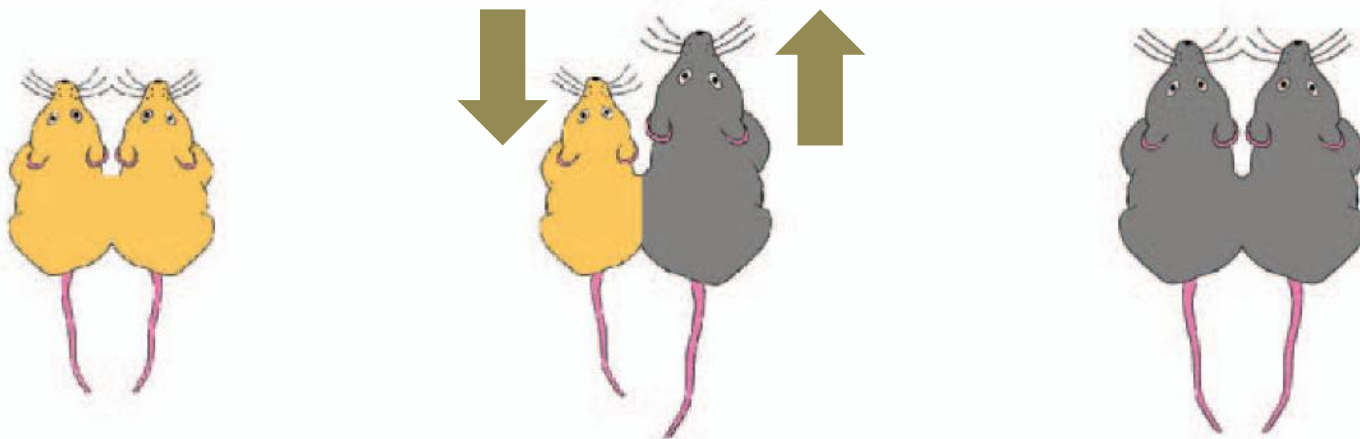
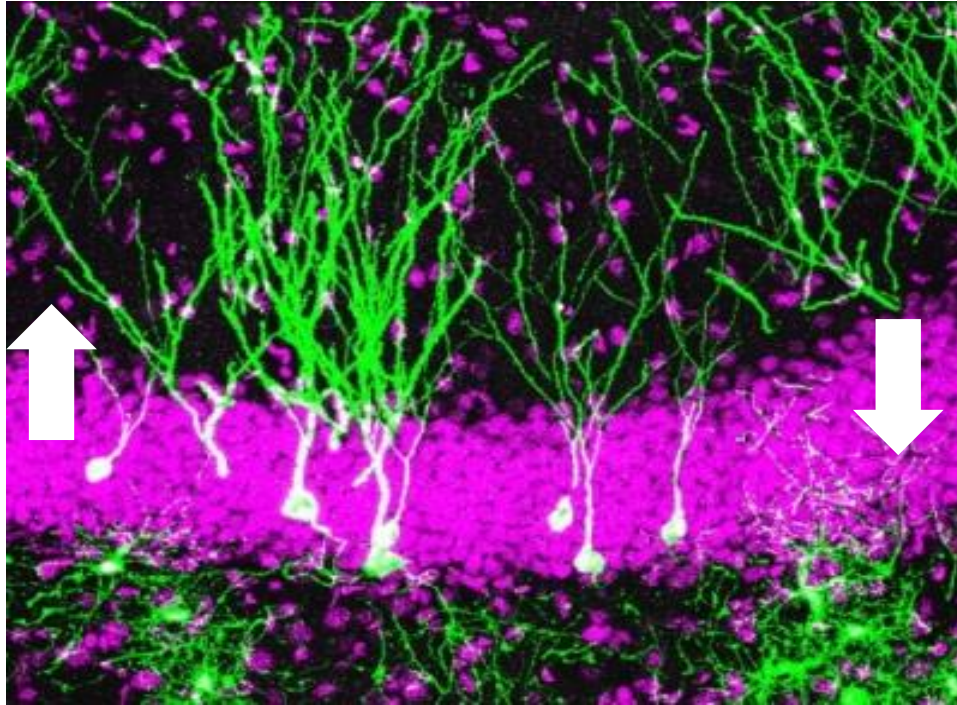


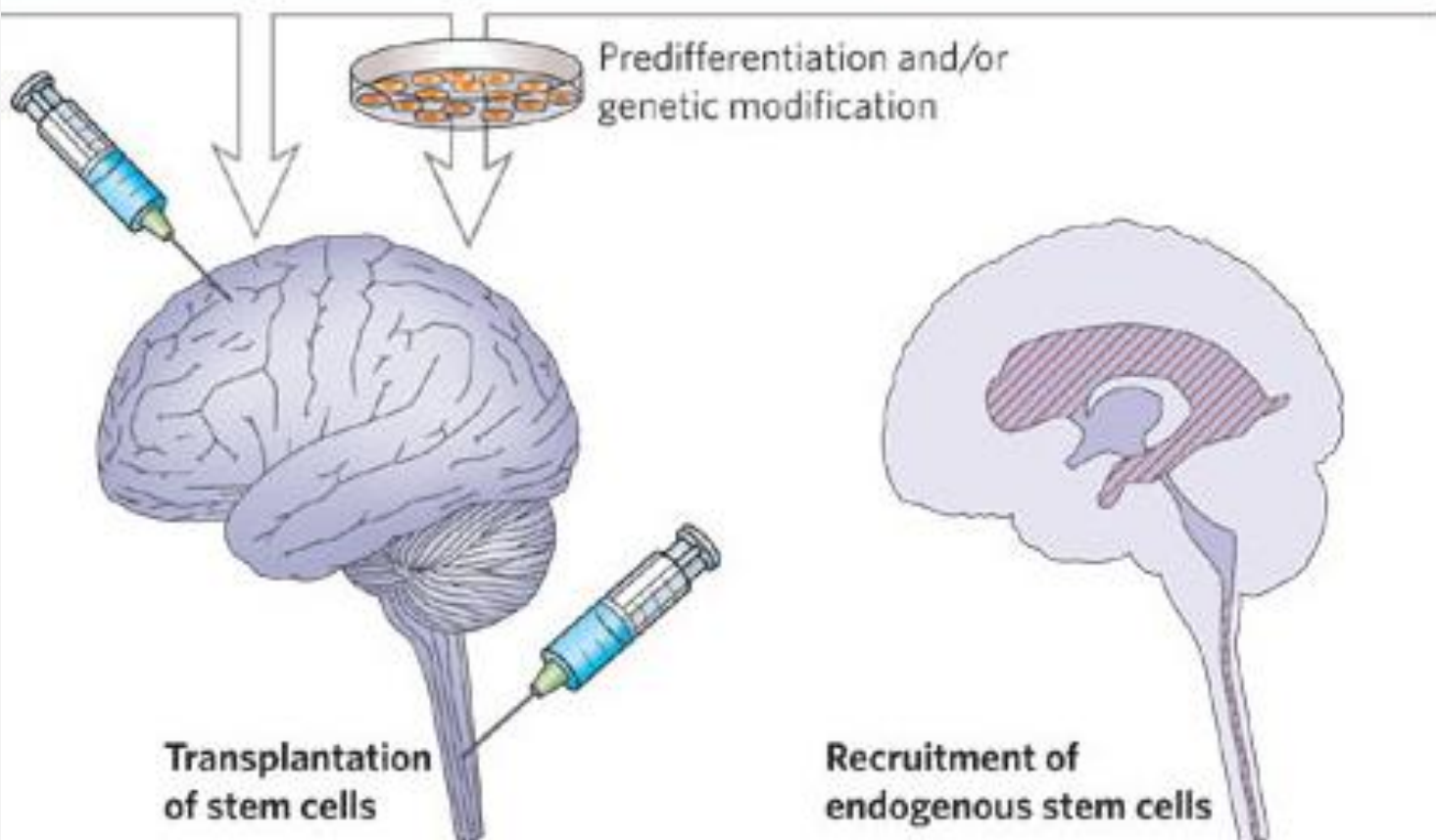
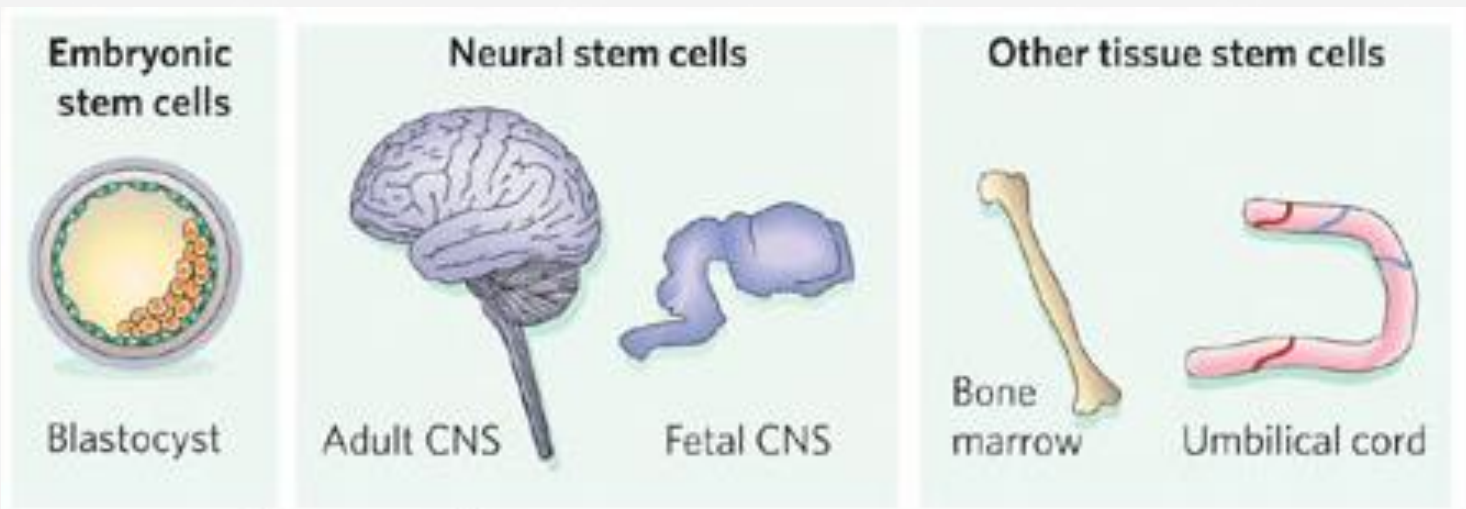
Discriminación de patrones y combinación de patrones

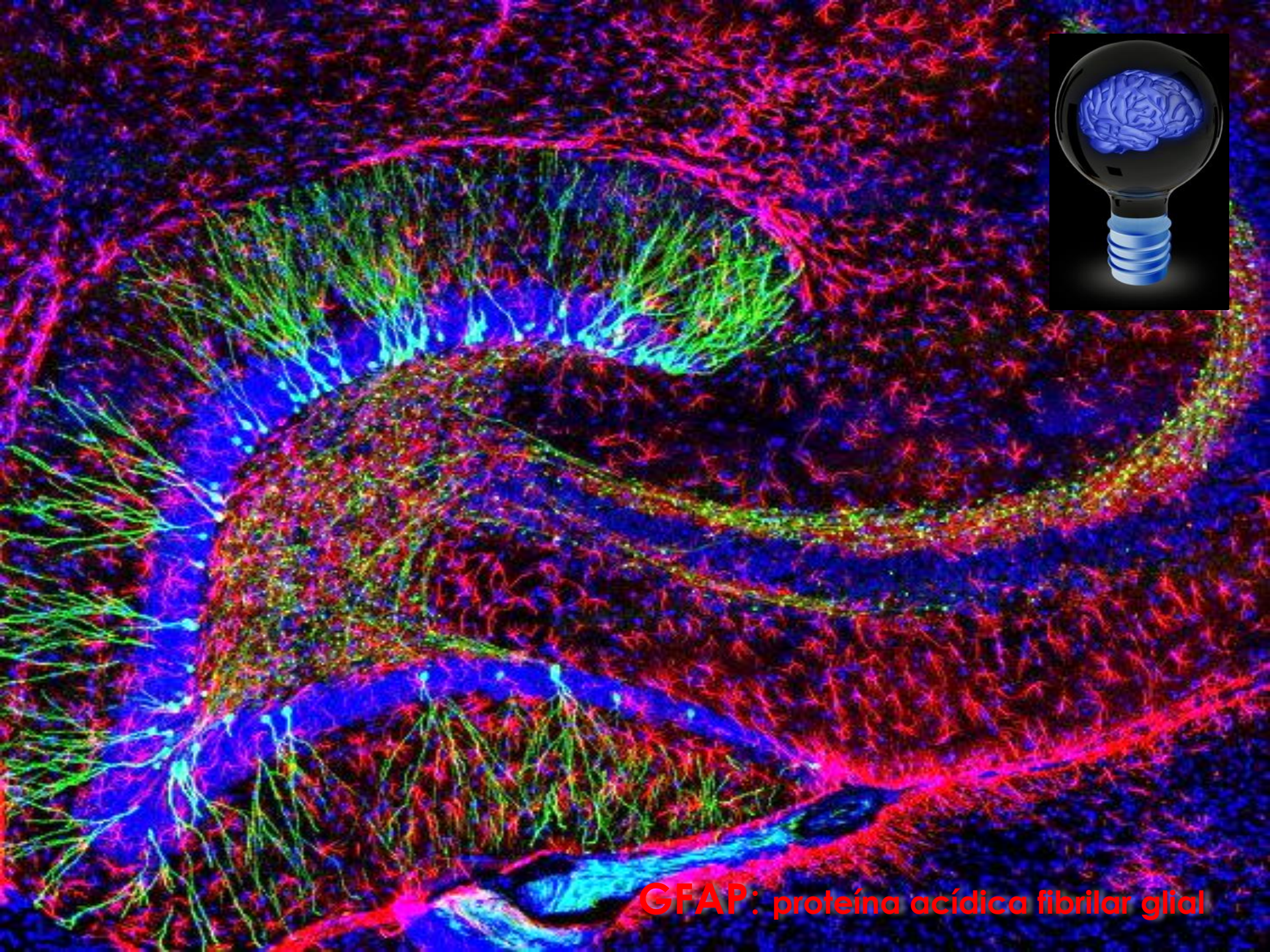
Nicho



Parabiosis

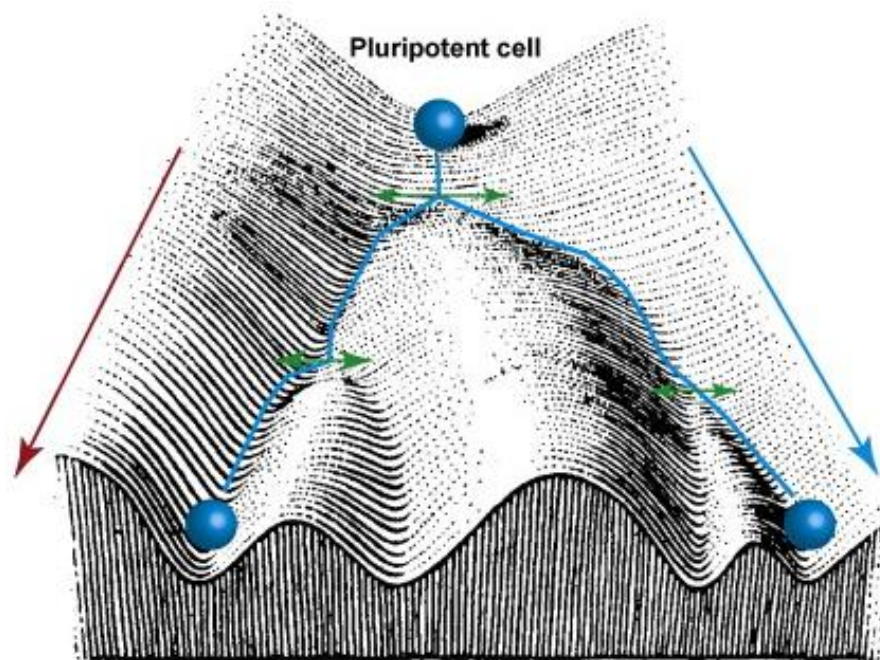
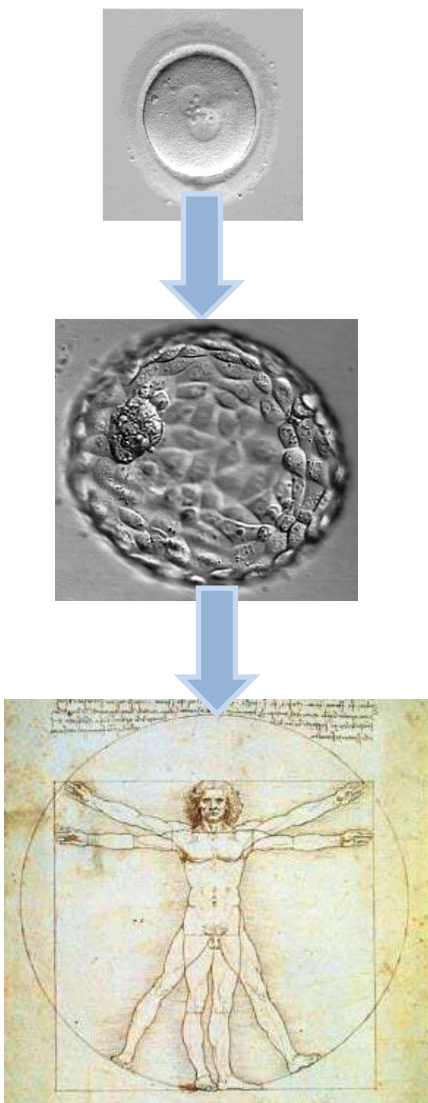




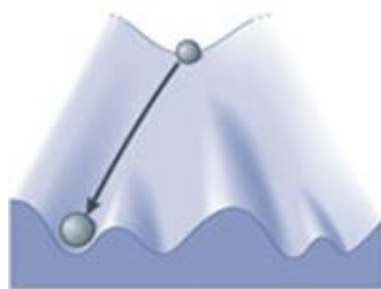


GFAP: proteína acídica fibrilar glial

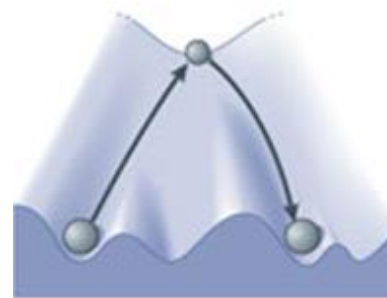
Conversión directa (reprogramación)



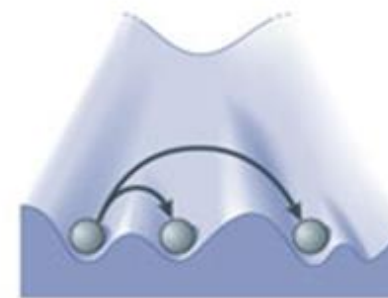
Conrad Hal Waddington



Desarrollo normal



Reprogramación a pluripotencia



Conversión directa

Shinja Yamanaka

Astrocitos:

- Respuesta a lesión
- Conversión directa

