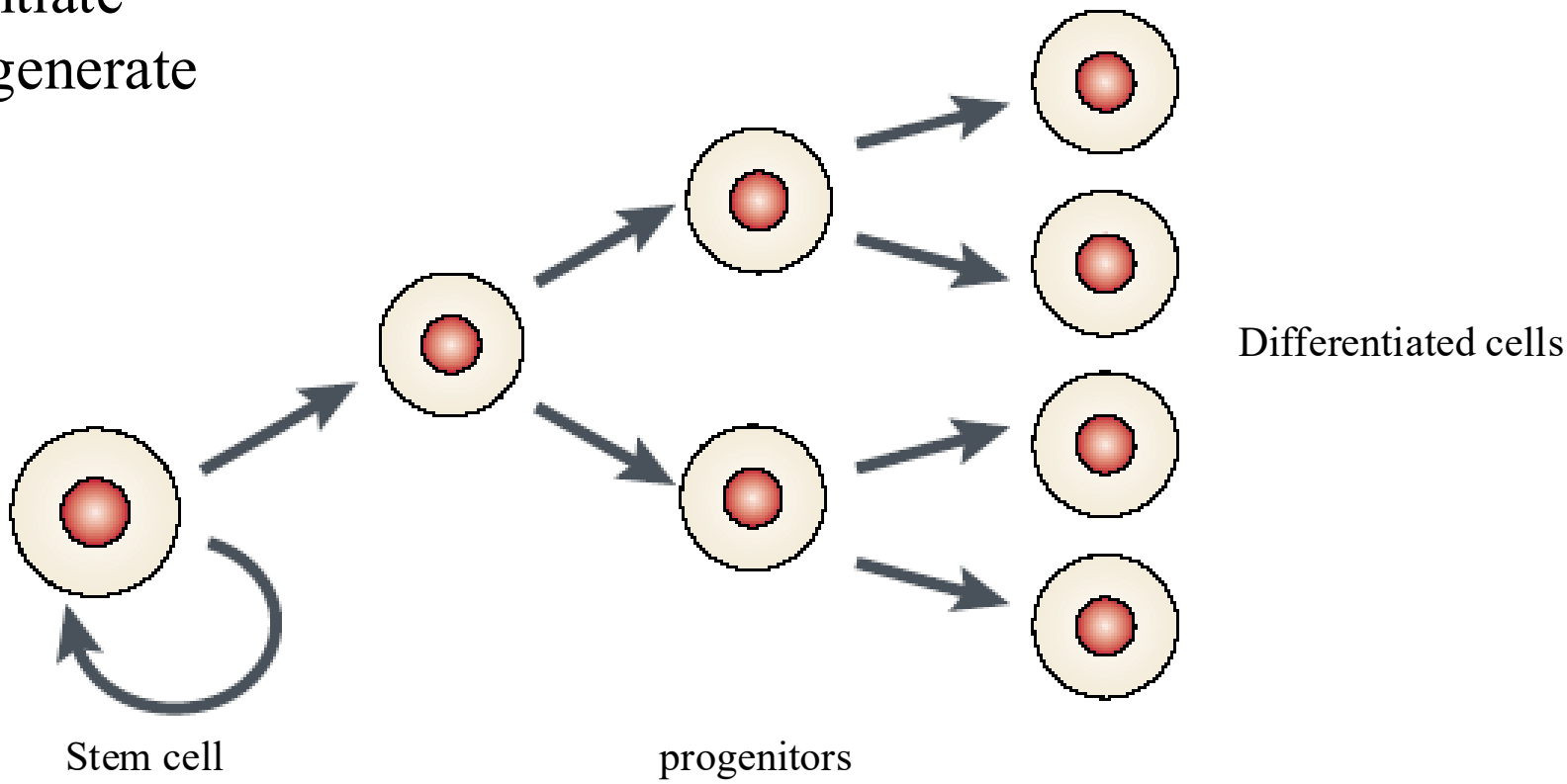
Un esperimento è una domanda che la scienza pone alla natura, ed una misurazione è la registrazione della risposta della Natura.
(Max Planck)

Stem cells properties

1 Differentiate
2. Self regenerate



History

~1900 self regenerating cell

1961 hemopoietic stem cell

1968 skeletal stem cells

1983 mouse ES

1997 Dolly the sheep (nuclear transfer)

1998 human ES

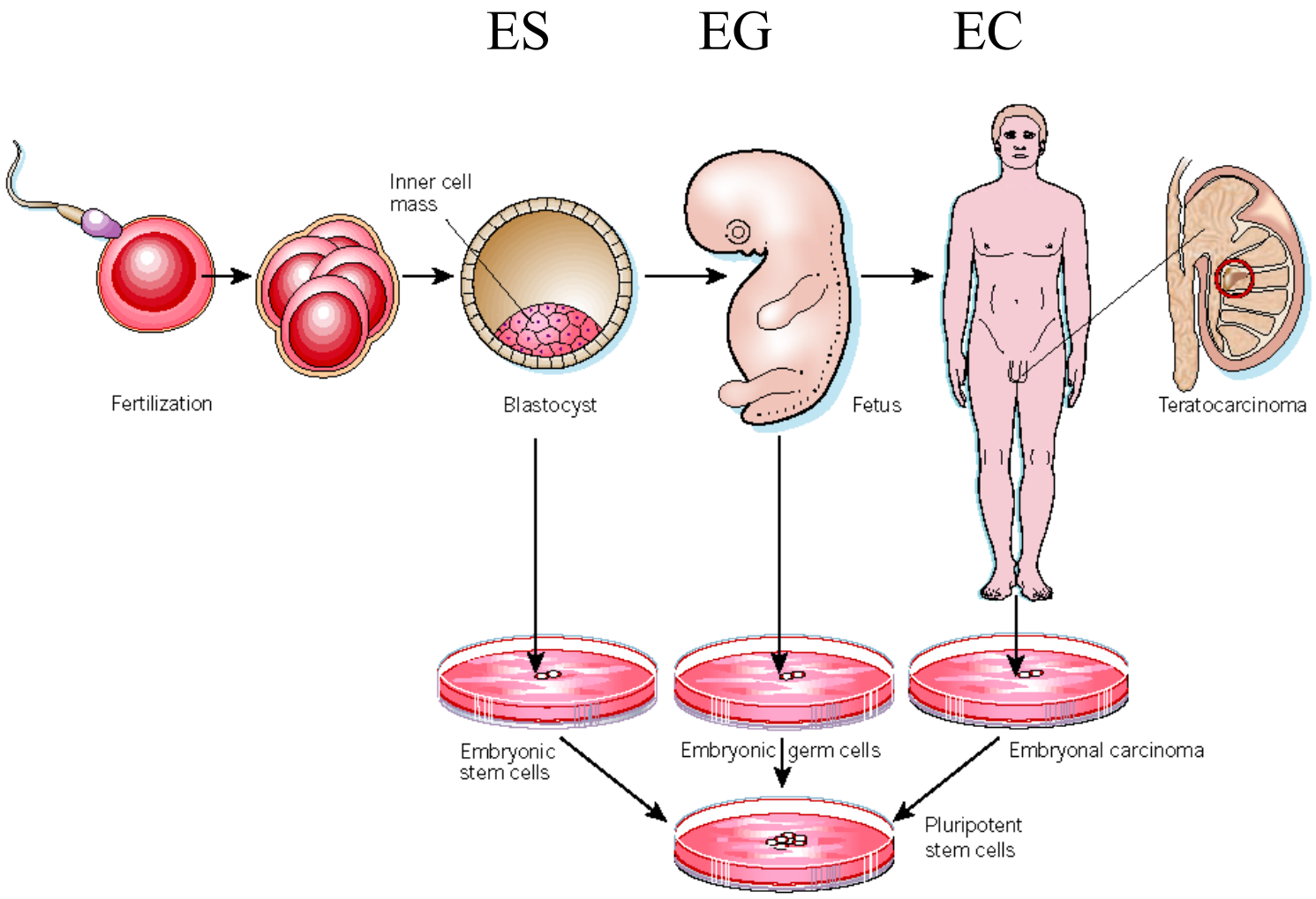
1999 adult stem cell

2006 IPS

Categories

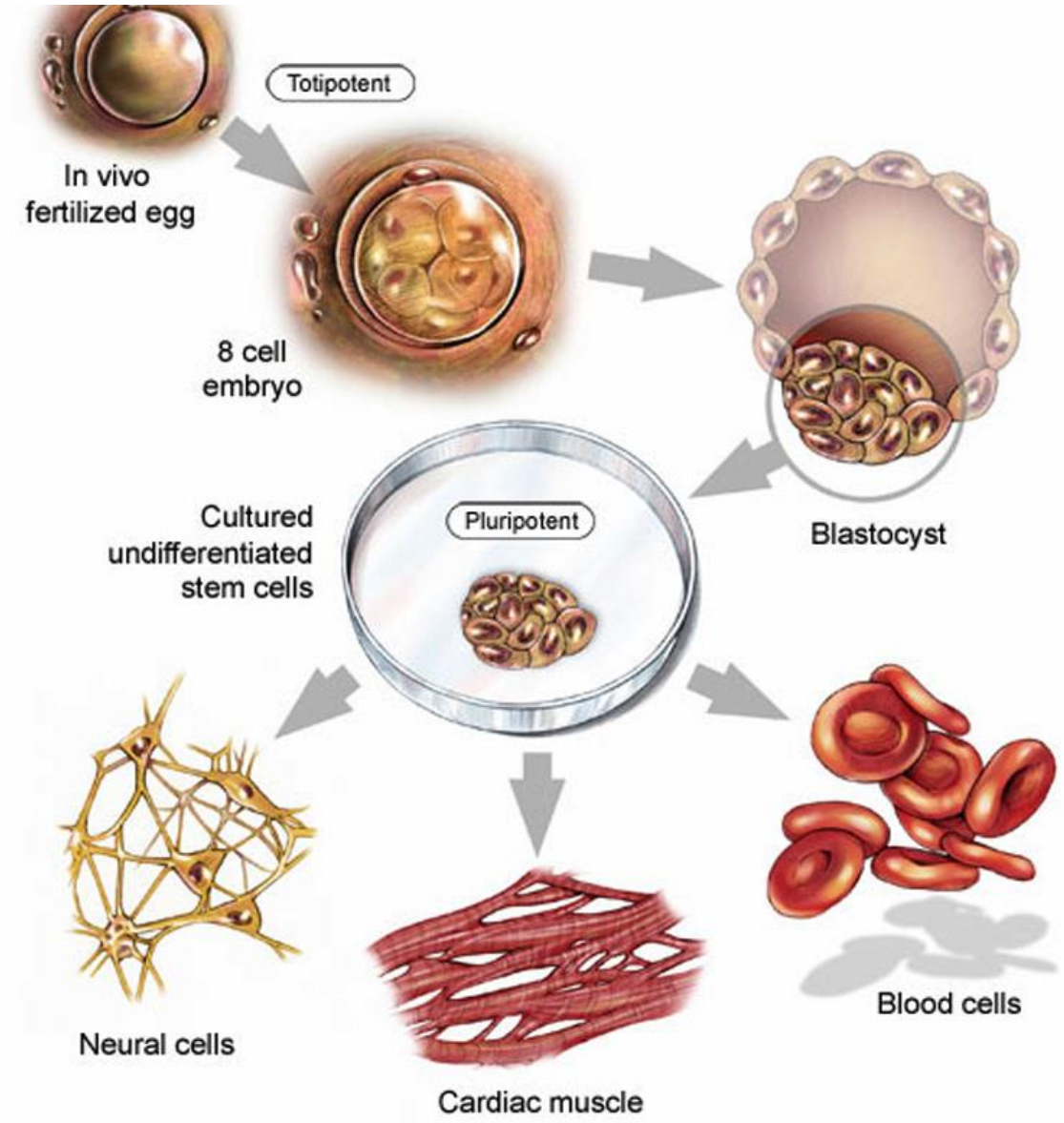
embryonic	ES
↓	EG (germ)
pluripotent	EC (carcinoma)
post-natal	hemopoietic
↓	epithelial
multipotent	skeletal
unipotent	……

ES origin

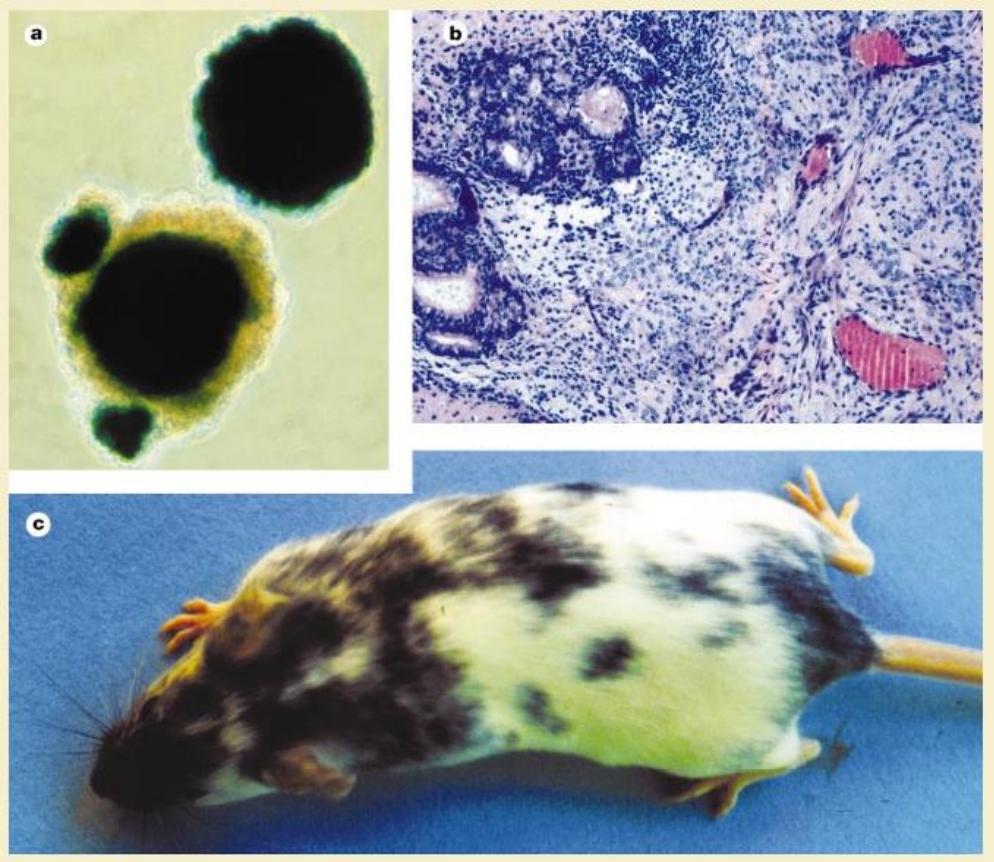


Teratocarcinoma: germ cell tumor

ES: in vitro differentiation



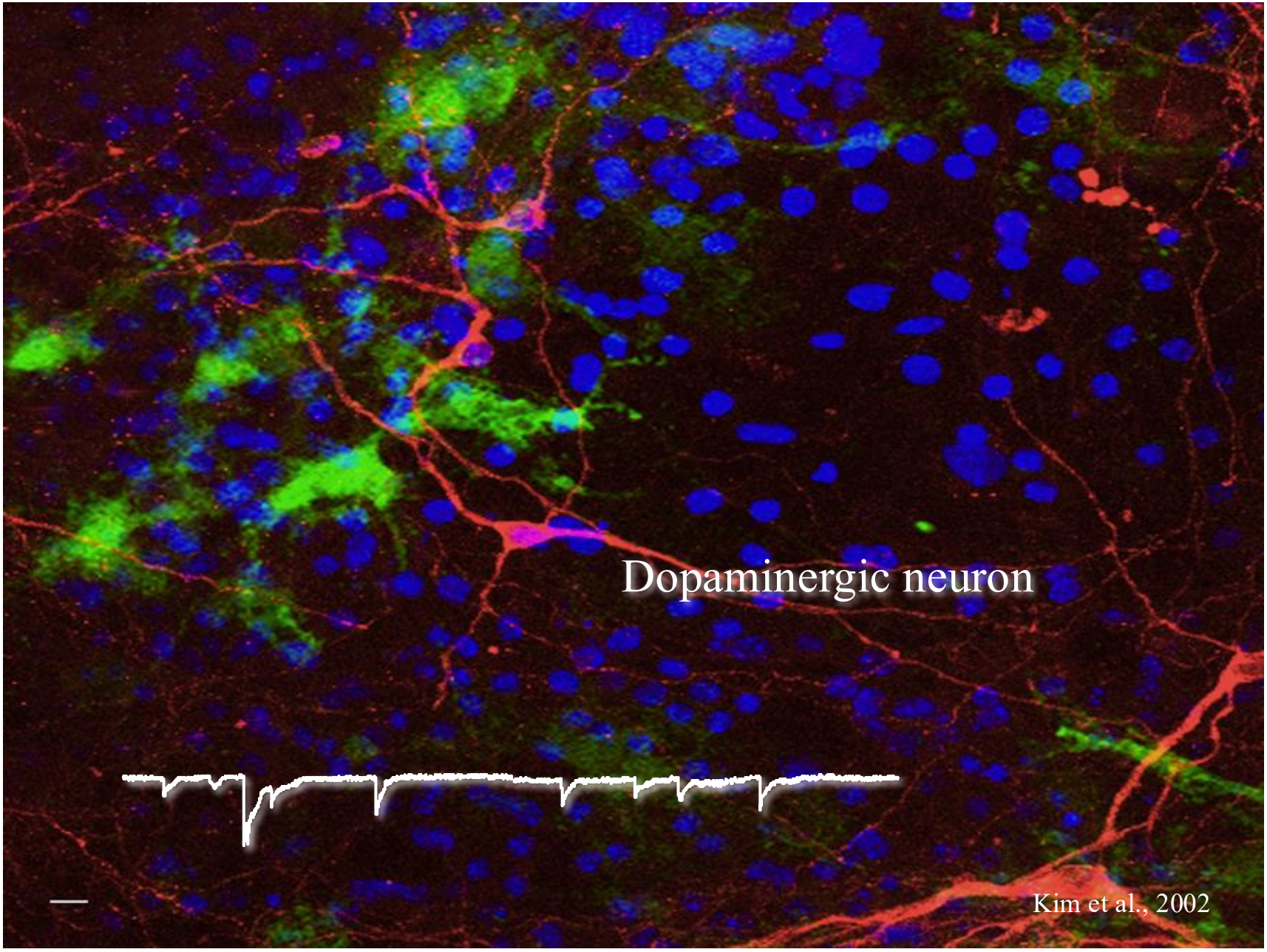
ES: in vivo differentiation



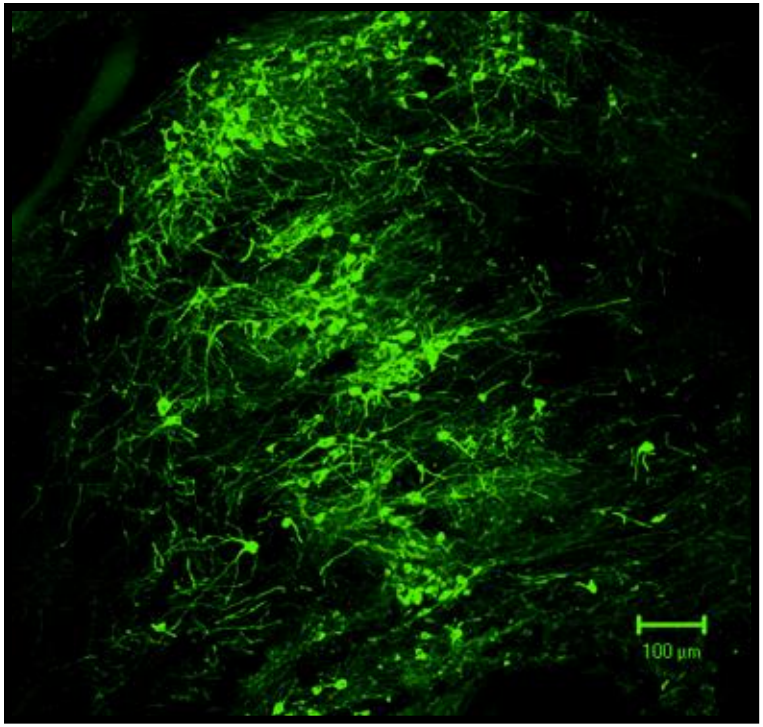
teratoma
(in mouse after transplantation)

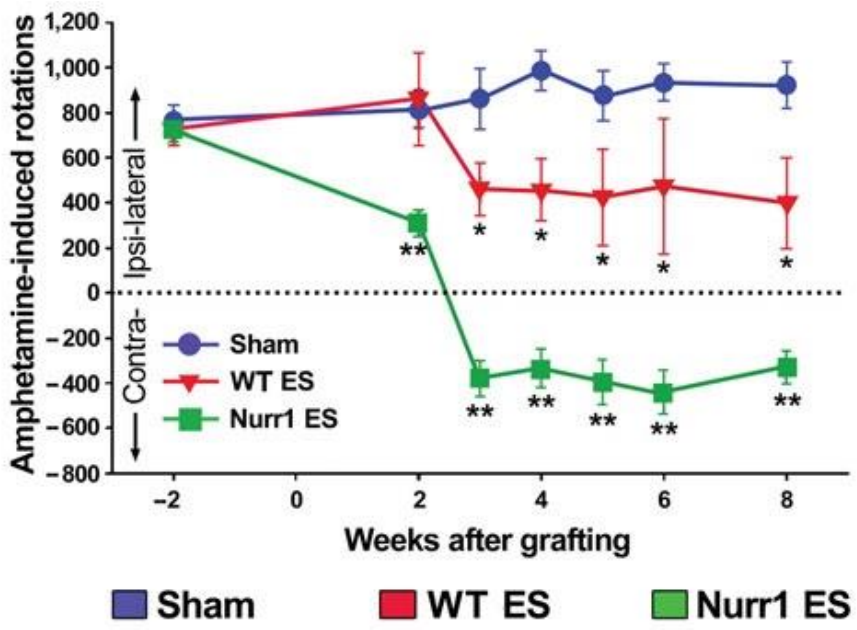
chimera
(implanted in the blastocyst)

Dopaminergic neurons from mouse ES differentiated in vitro



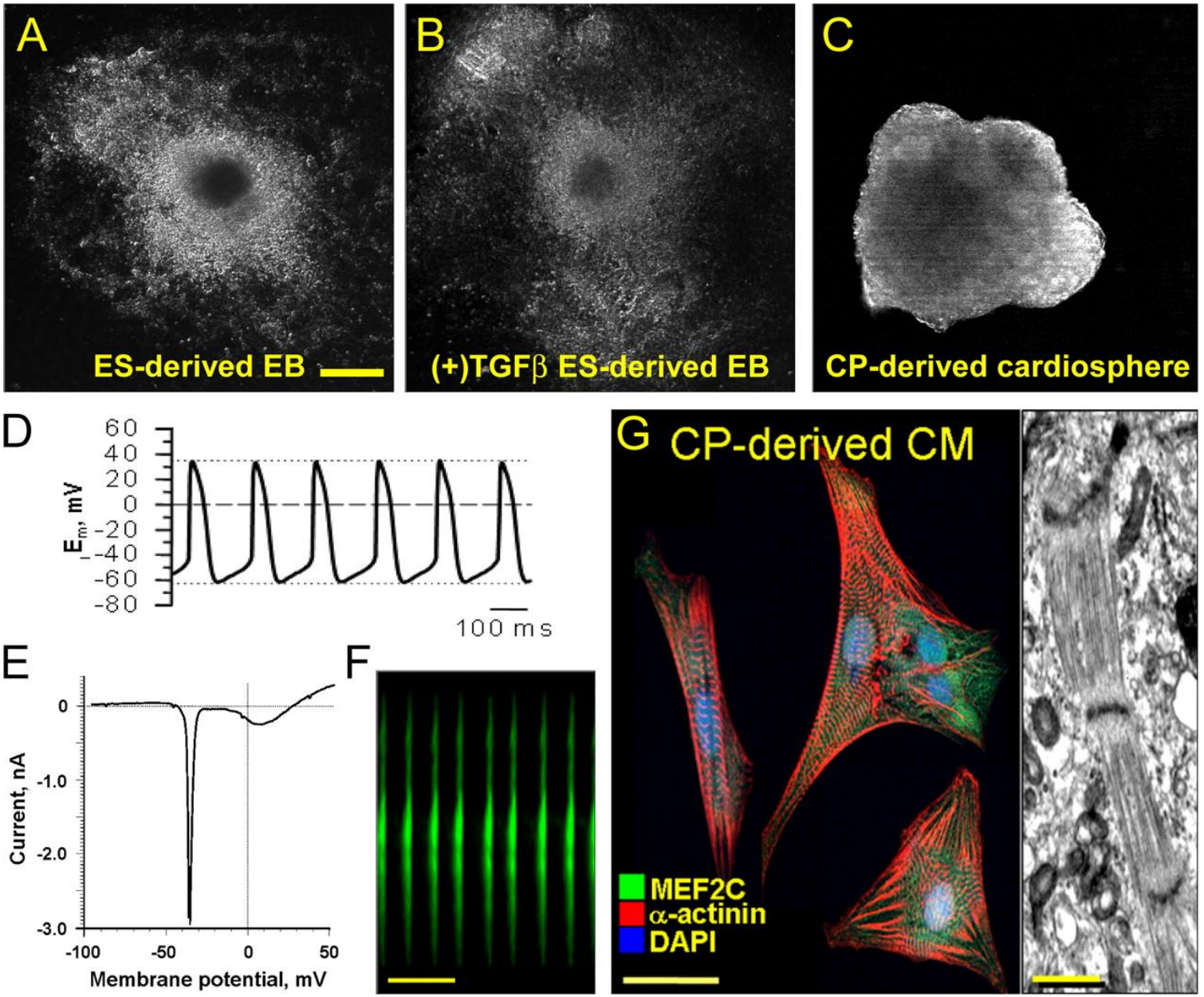
In vivo transplantation



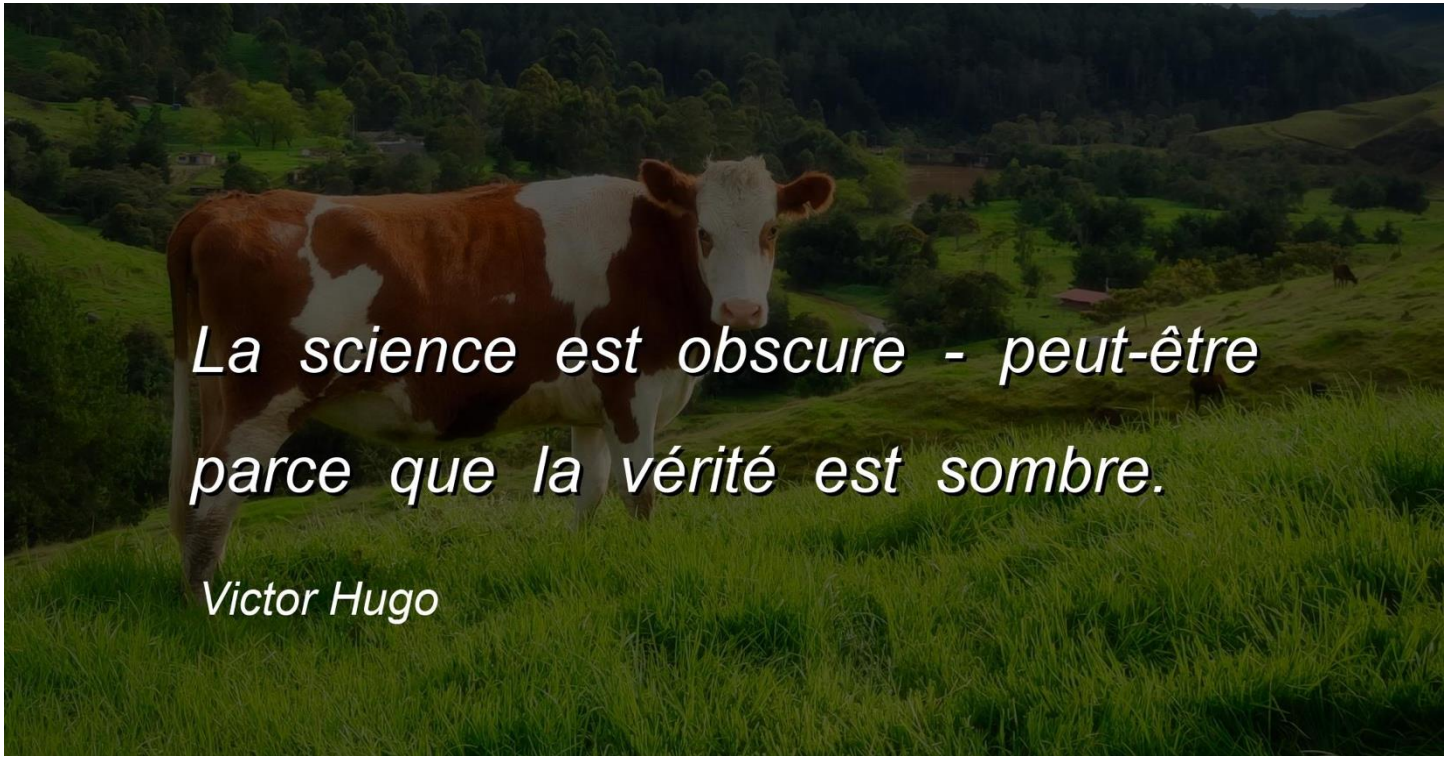


Kim et al., 2002 Nature ES murine

Cardiac cells from mouse ES



Behfar et al, 2007


La science est obscure - peut-être parce que la vérité est sombre.
Victor Hugo

“I have learned that the forest, humans and animals are interdependent, and if the forest is sick, then the animals will be sick, and animals will surely impact humans’ health too.”

Le **cellule staminali** sono cellule speciali con caratteristiche uniche che le distinguono dalle altre cellule dell'organismo. Le loro principali proprietà sono:

1. Auto-rinnovamento

•Possono dividersi indefinitamente mantenendo il loro stato indifferenziato.

•Questa capacità consente loro di rifornire continuamente il pool di staminali nel corpo.

2. Potenza (capacità di differenziarsi in altri tipi cellulari)

Le staminali possono essere classificate in base alla loro **potenza**, ovvero alla loro capacità di generare diversi tipi di cellule:

•**Totipotenti**: possono dare origine a tutti i tipi cellulari dell'organismo, inclusi quelli extraembrionali (es. cellule della placenta). Un esempio è lo zigote nelle prime fasi di sviluppo.

•**Pluripotenti**: possono differenziarsi in qualsiasi tipo cellulare derivato dai tre foglietti embrionali (ectoderma, mesoderma, endoderma). Un esempio sono le **cellule staminali embrionali (ESCs)**.

•**Multipotenti**: possono generare un numero limitato di tipi cellulari all'interno di un determinato tessuto o organo. Un esempio sono le **cellule staminali ematopoietiche**, che danno origine a tutte le cellule del sangue.

•**Oligopotenti**: possono differenziarsi in pochi tipi cellulari correlati (es. cellule staminali mieloidi, che danno origine a granulociti e monociti).

•**Unipotenti**: possono produrre un solo tipo di cellula, pur mantenendo la capacità di auto-rinnovarsi (es. cellule staminali muscolari o epiteliali).

3. Plasticità cellulare

•Alcune staminali possono **trasdifferenziarsi**, ossia trasformarsi in tipi cellulari diversi da quelli della loro normale linea di sviluppo.

•Questa caratteristica è sfruttata in medicina rigenerativa e nella ricerca sulle cellule staminali indotte **(iPSC - induced Pluripotent Stem Cells)**.

4. Sensibilità ai segnali ambientali

•Le cellule staminali rispondono a **fattori di crescita, segnali chimici e interazioni con la matrice extracellulare**, che ne regolano la proliferazione e il differenziamento.

•Questa caratteristica è fondamentale per il loro utilizzo in terapie cellulari e ingegneria tissutale.

5. Localizzazione specifica nel corpo (nicchie staminali)

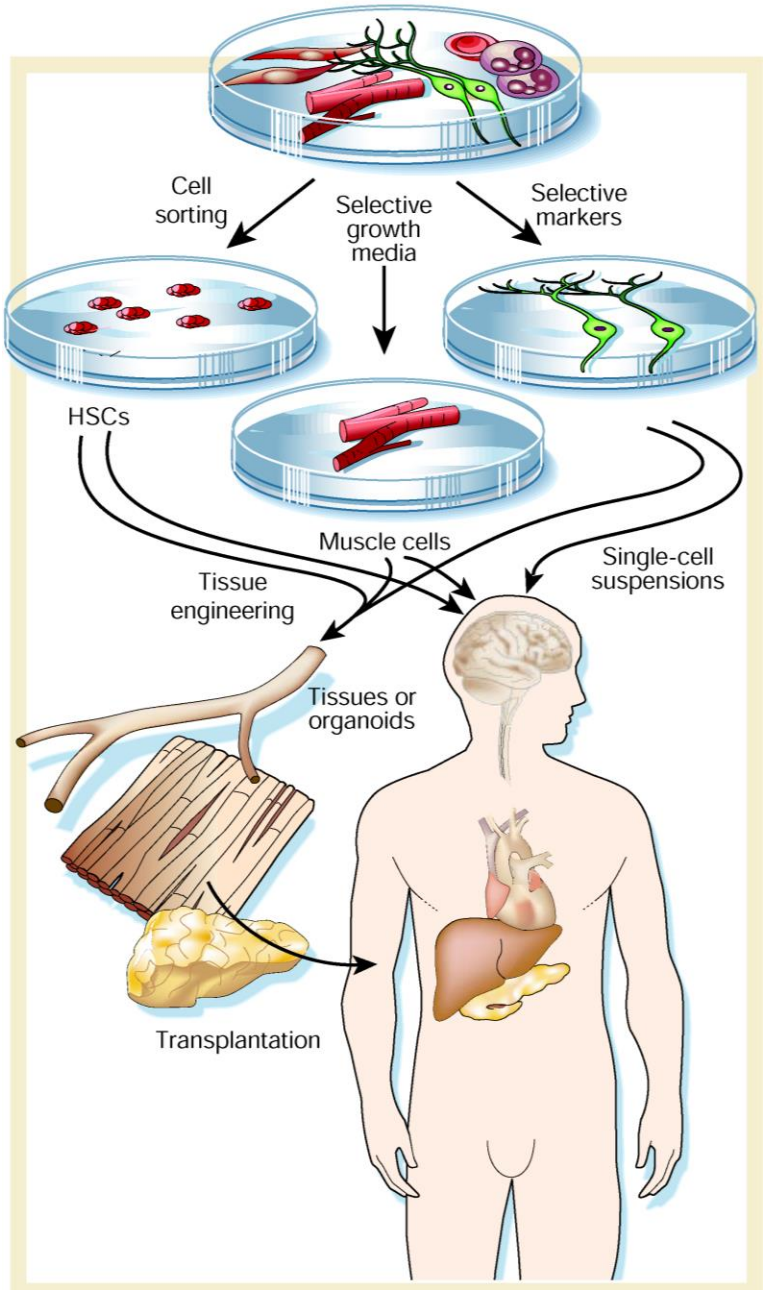
•Le cellule staminali adulte risiedono in specifiche **nicchie staminali**, ambienti protettivi che ne regolano l'attività e il mantenimento.

•Esempi di nicchie includono il **midollo osseo** (per le staminali ematopoietiche) e la **zona subventricolare del cervello** (per le staminali neurali).

Queste proprietà rendono le staminali fondamentali per lo sviluppo embrionale, il mantenimento dei tessuti adulti e le applicazioni terapeutiche, tra cui la **medicina rigenerativa, la terapia cellulare e la ricerca sulle malattie degenerative**.

Chat gpt 110225

ES: in therapy



ES: problems

A) Technical

manipulation

histocompatibility

……..

B) Bioethics

religion

laws

……..

Stem cells from human embryos

(Europe: 100.000 spare frozen embryos from FIVET)

Germany illegal

Great Britain legal

Italy illegal

Israel legal

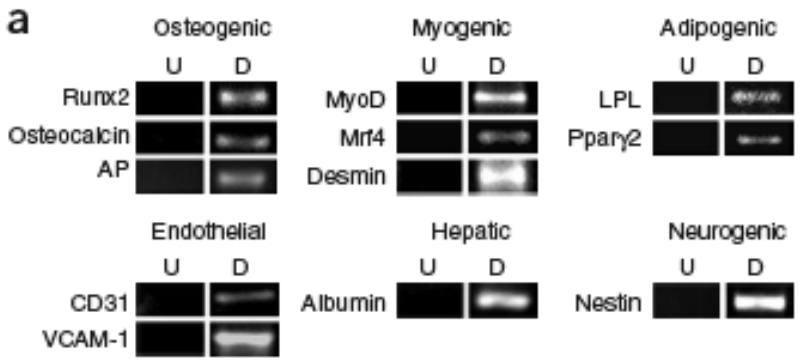
Napolitano Cattaneo 2013

USA Bush: illegal (cells derived before 9.08.2001)

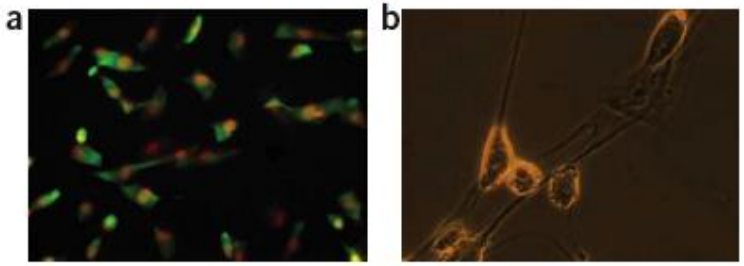
Obama: legal

(Executive Order 13505 - Removing Barriers to Responsible Scientific Research Involving Human Stem Cells - March 9, 2009)

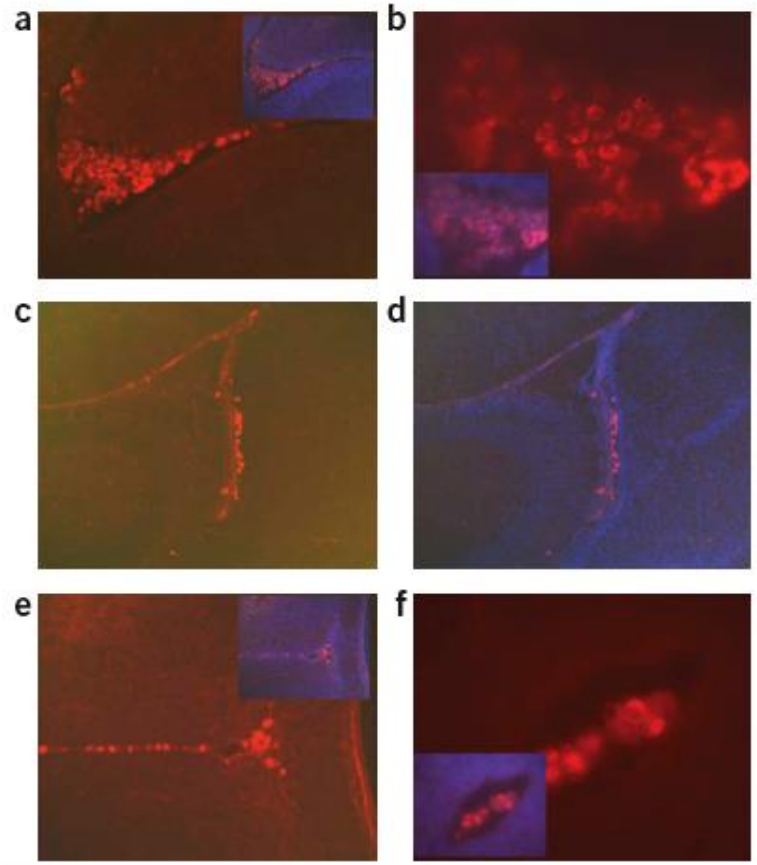
Amniotic fluid stem cells - *life in plastic is fantastic*



RT PCR for mRNA lineage specific



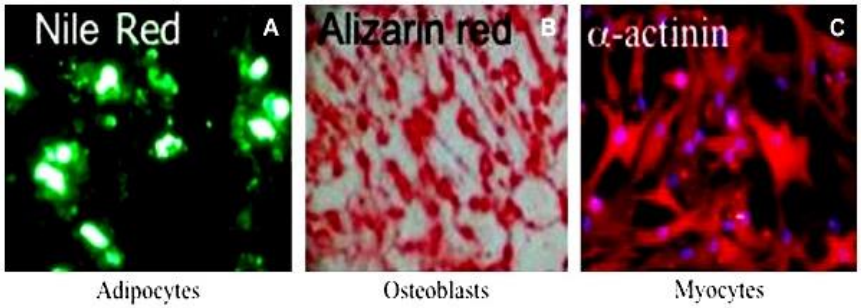
Neuron markers (nestin)



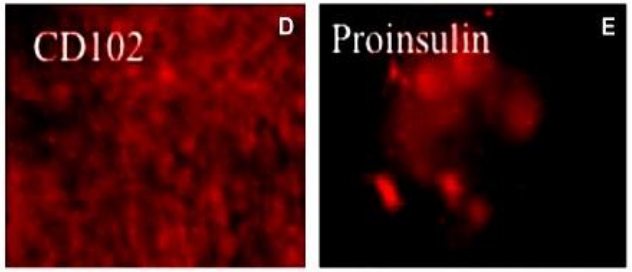
Mouse brain sections after implants of AFC: red hum mitoc

Coppi et al NBT 2007

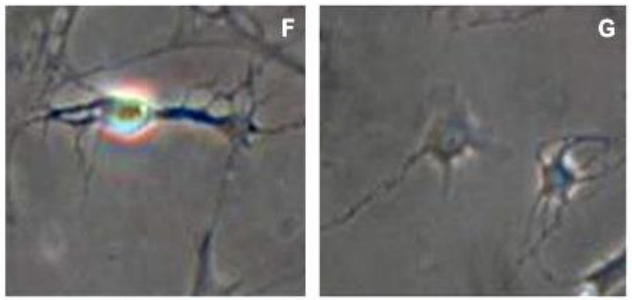
Umbilical cord blood cells (UCB)



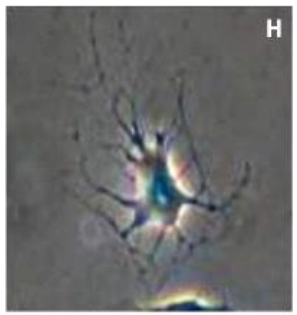
Adipocytes Osteoblasts Myocytes



Endothelium Hepato-pancreatic body



Neurons Astrocytes



- Hemopoietic cells

- Endothelial progenitors
- Mesenchymal progenitors
- Stem cells pluri/multipotent

Advantages:

•amount
•immunological “youth”
•banking

Van de Ven et al 2007

Post natal stem cells

Limited proliferation

Limited pluripotency

But……

How to isolate stem cells – localization of post natal stem cells

In regenerating tissues (blood and skin)

In low regenerating tissues (bone)

In non regenerating tissues (teeth, CNS)

How to isolate stem cells

- Antigen markers
- Efflux of the DNA binding dye Hoechst 33342

Best characterized adult stem cells: hematopoietic stem cells (HSC)- (Spangrude 1988)

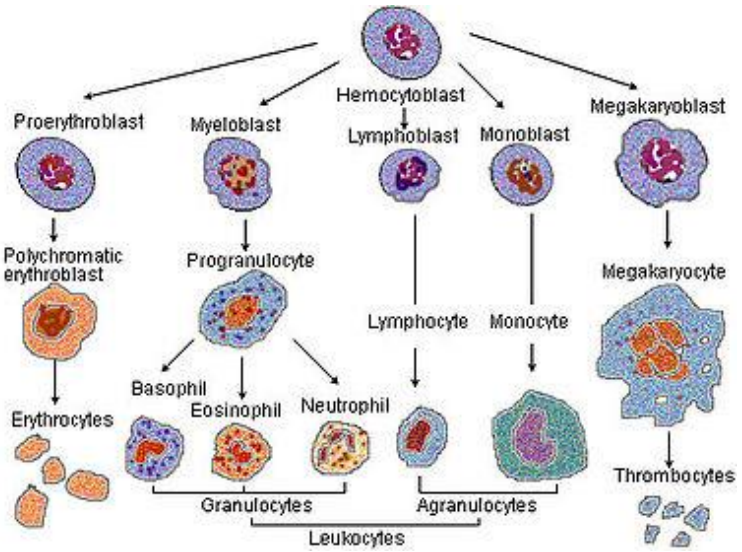
•Short term hematopoietic stem cells: 2 months

•Long term hematopoietic stem cells: greater than 6 months

•CD34+, enrichable on the basis of membrane markers 10000 -fold, 80% purity (and also marker negative selection)

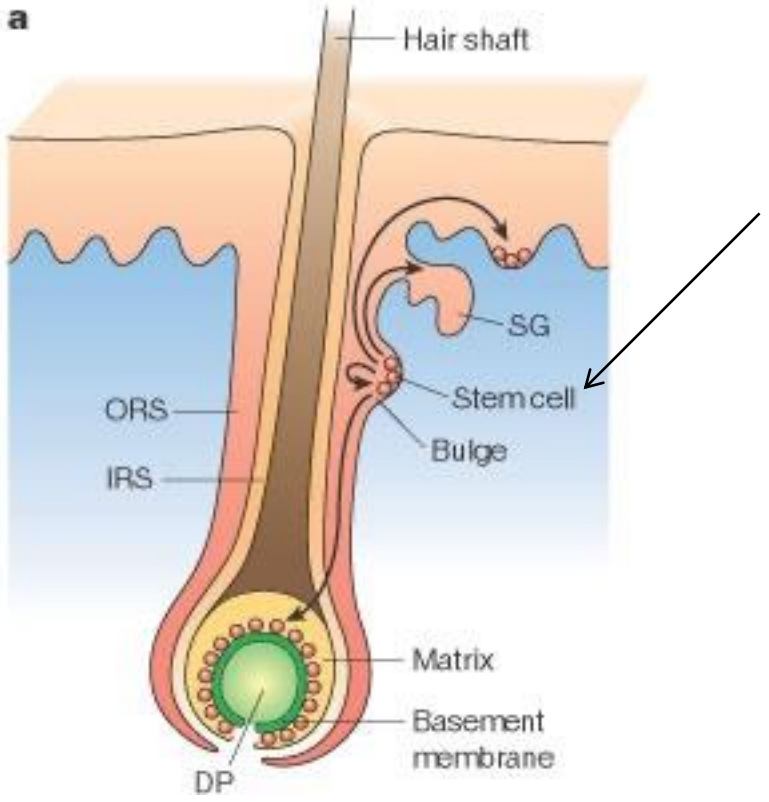
- **Mouse HSC :** $CD34^{lo/-}$, $SCA\text{-}1^{+}$, $Thy1.1^{+/lo}$, $CD38^{+}$, $C\text{-}kit^{+}$, lin^{-}
- **Human HSC :** $CD34^{+}$, $CD59^{+}$, $Thy1/CD90^{+}$, $CD38^{lo/-}$, $C\text{-}kit/CD117^{+}$, lin^{-}

•Can reconstitute **blood**



Stem cells for skin

- Hair follicles keratinocytes
- expressing keratin K5 and K14



Stem cells for skin

Michele De Luca

Hepatic stem cells

•Liver is an organ capable of extensive regeneration

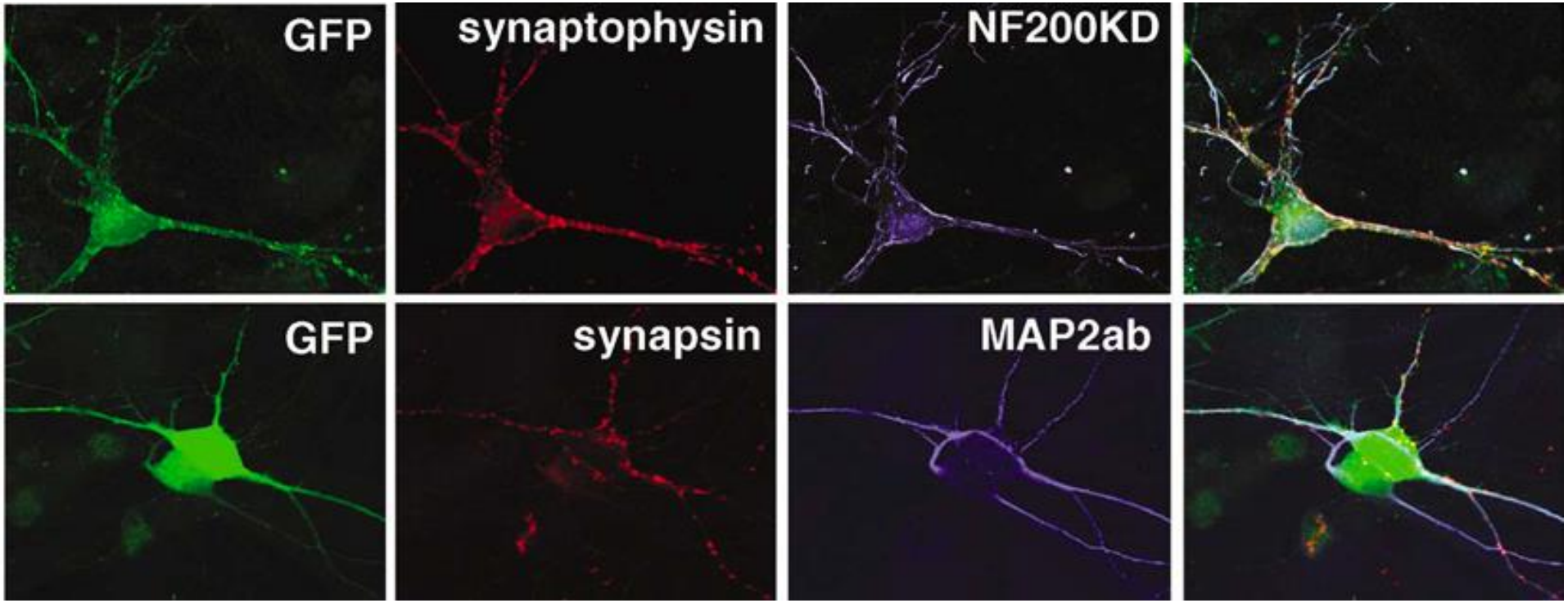
But

•The precise source of stem cells remains unclear (terminal bile ductules ?)

Neural stem cells

- Old studies in rats and songbirds (1969)
- More recent studies in mammals: neuronal progenitors exist, are capable of extensive cell division and self renewal
- Can be obtained by differential sedimentation on a gradient
- Available markers allow only 45 fold enrichment
- Neural progenitors can migrate and home to specific sites of damage or regeneration

Post natal neural cells



Song et al, 2002

Skeletal muscle stem cells

- Satellite cell: mononucleated cell ensheathed under the basal lamina that surrounds multinucleated muscle fibers (1961)

- Can be activated, induced to proliferate, and contribute to intact skeletal muscle fibers even after extensive tissue doublings

- Heterogeneous, no specific markers

- Are rapidly depleted in muscle of Duchenne patients