Pregunta básica

Qué célula madre utilizar?

Células madre

Células con capacidad de:

- autoperpetuarse (prolongada o ilimitada)
- diferenciarse a distintos tipos celulares

Tipos:

Embrionarias

Adultas

- hematopoyéticas
- epiteliales
- músculo cardíaco
- hígado
- páncreas
- sistema nervioso

Reprogramadas

Células madre embrionales

Ventaja

Alta plasticidad: fuente potencial de cualquier célula

Desventajas

Feeder layer
Comportamiento en cultivo muy variable.
Tumorigénicas
Respuesta inmunológica al trasplante

Debate ético: fuente celular

Células madre adultas

Ventajas

Larga experiencia en células madre hematopoyéticas
Sin evidencias de tumorigenicidad
Sin debate ético

Rechazo poco probable (autotrasplante)

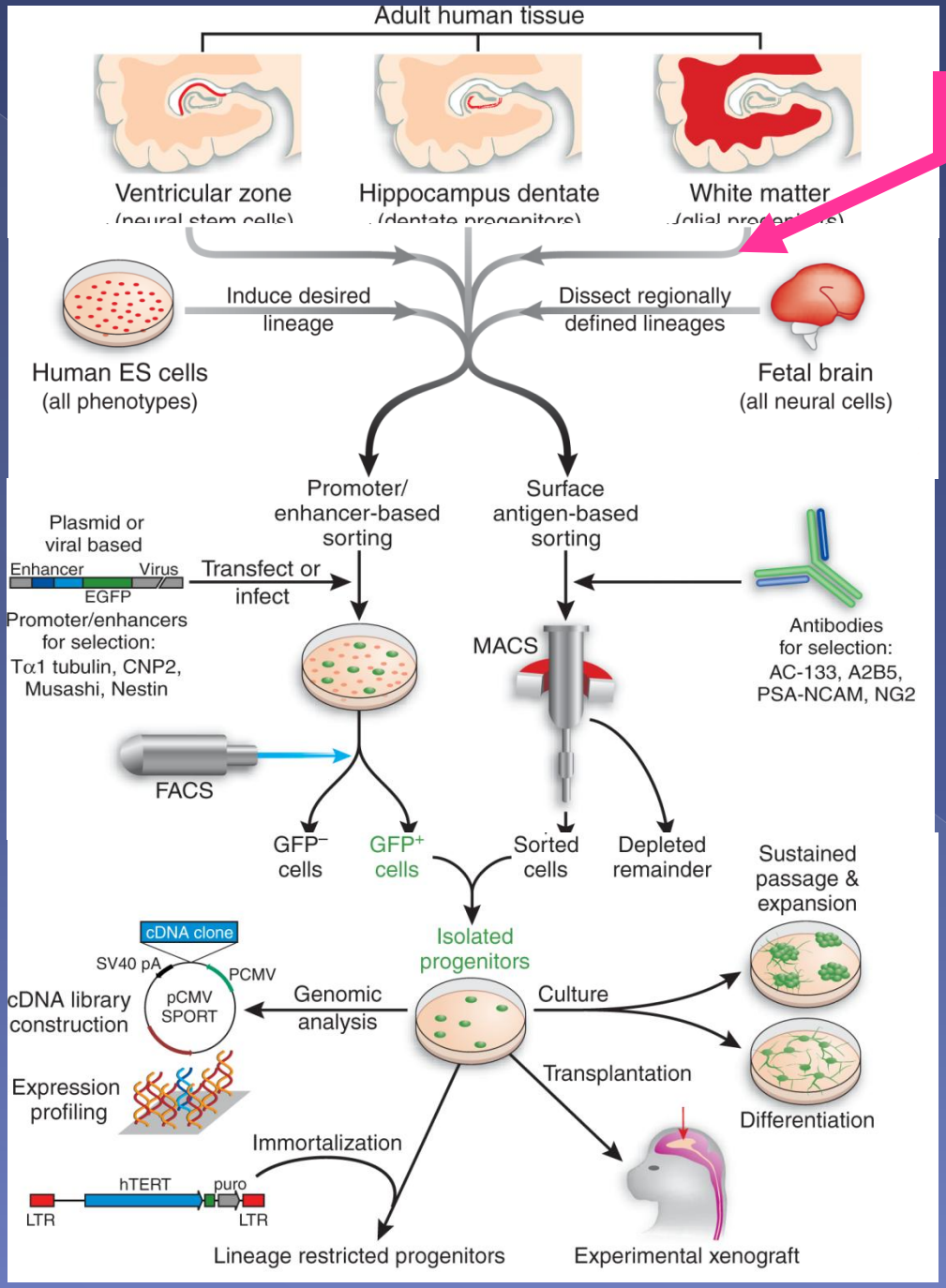
Desventajas

Menor plasticidad- *específicas de linaje*

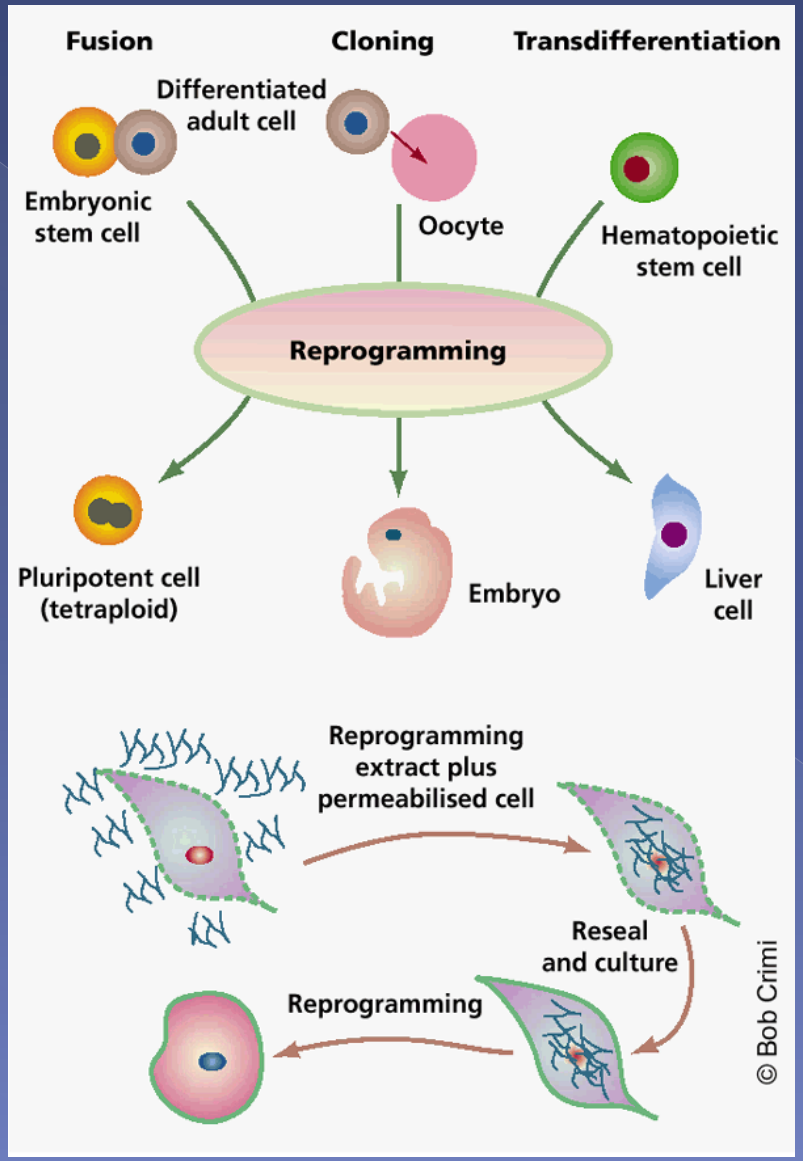
Baja homogeneidad de la muestra
Dificil acceso (neurales)
Baja eficiencia de diferenciación (neurales)

Células madre reprogramadas

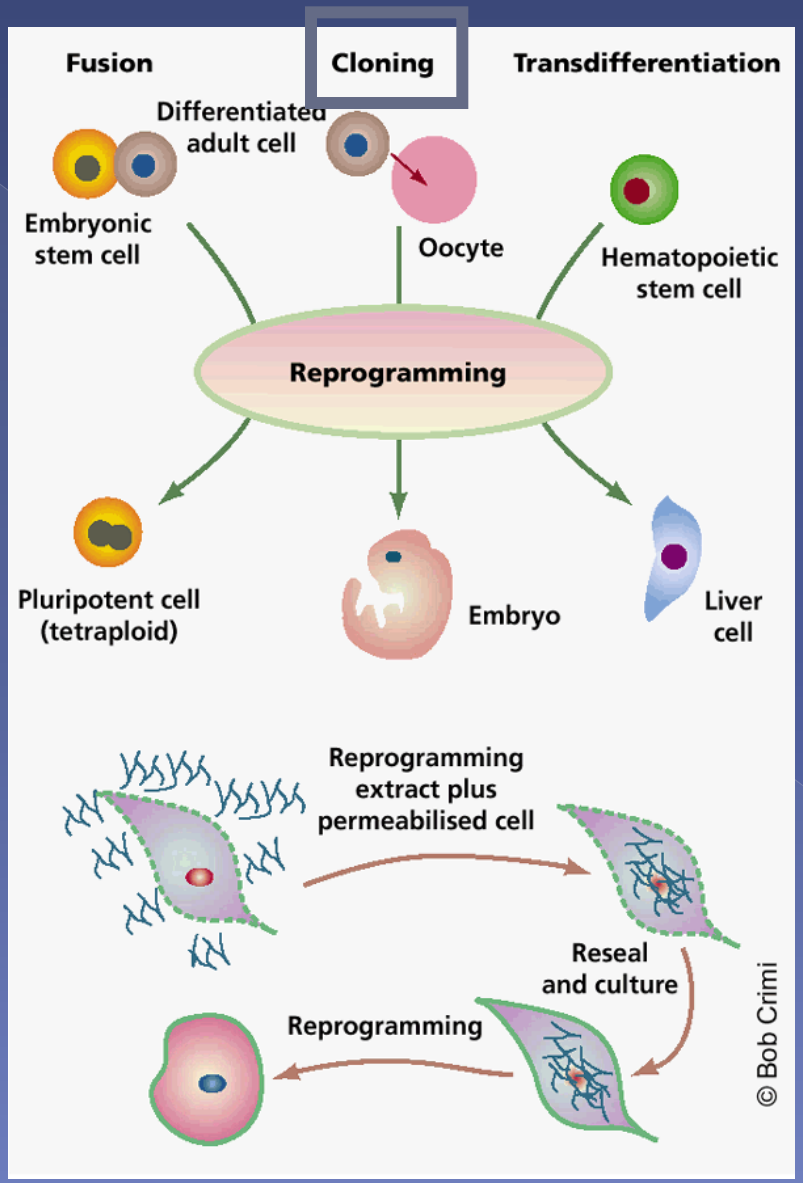
Reprogramación



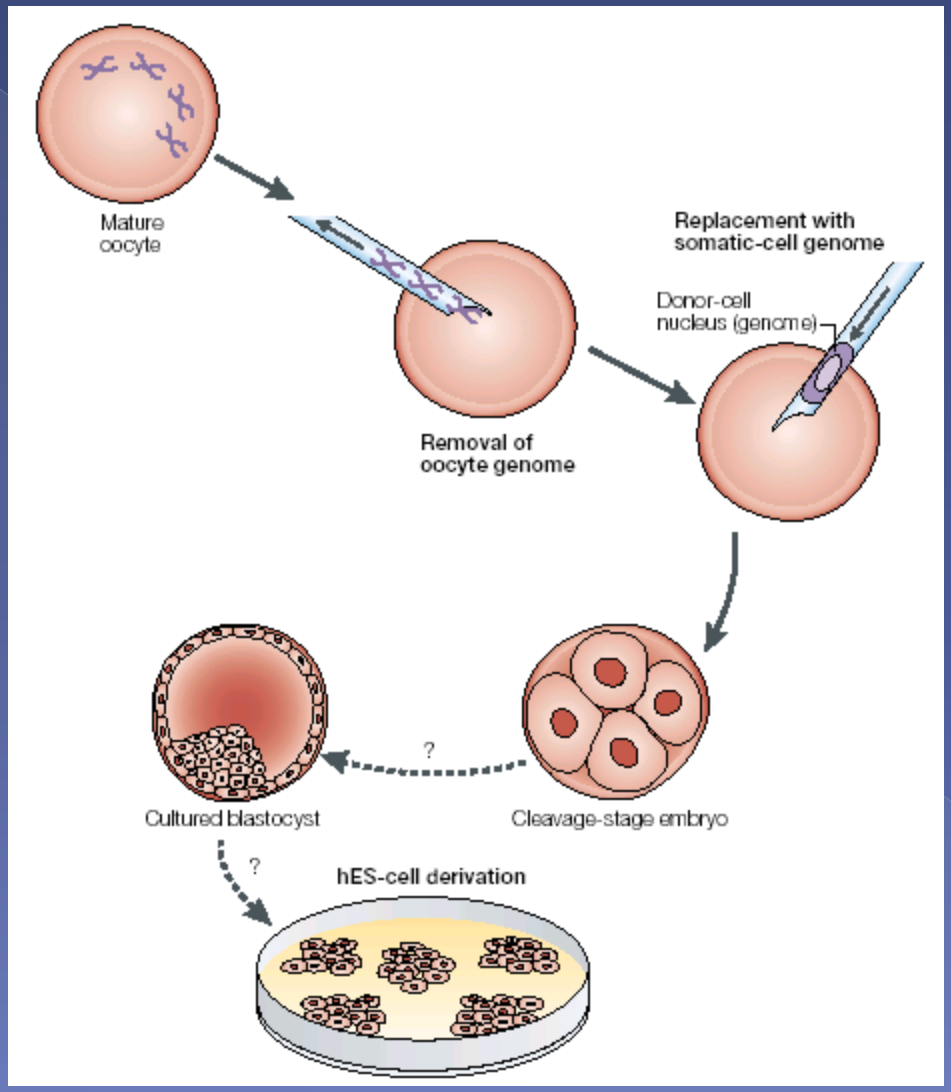
Reprogramación



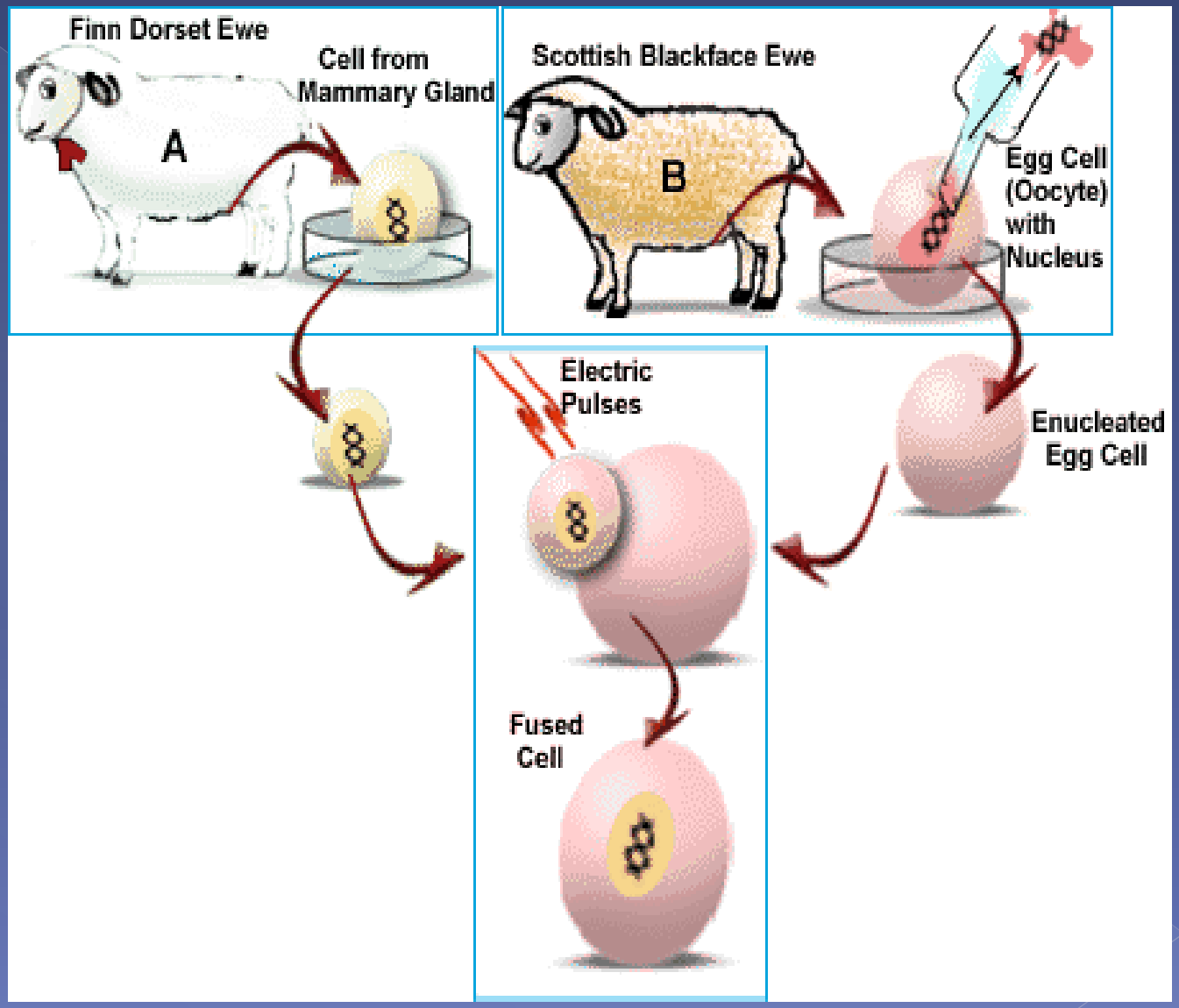
Reprogramación



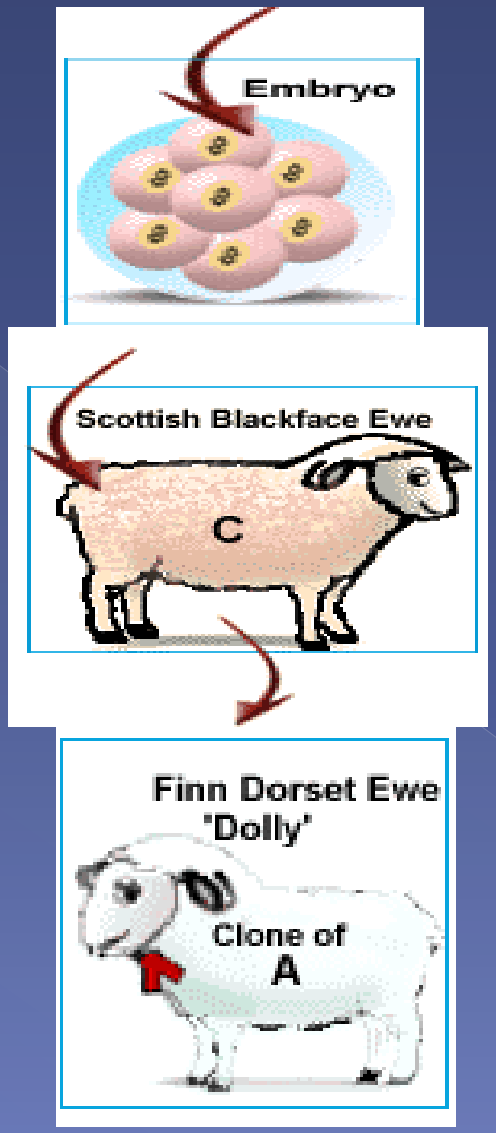
Clonación


Mature
oocyte
Removal of
oocyte genome
Replacement with
somatic-cell genome
Donor-cell
nucleus (genome)
?
Cultured blastocyst
Cleavage-stage embryo
?
hES-cell derivation

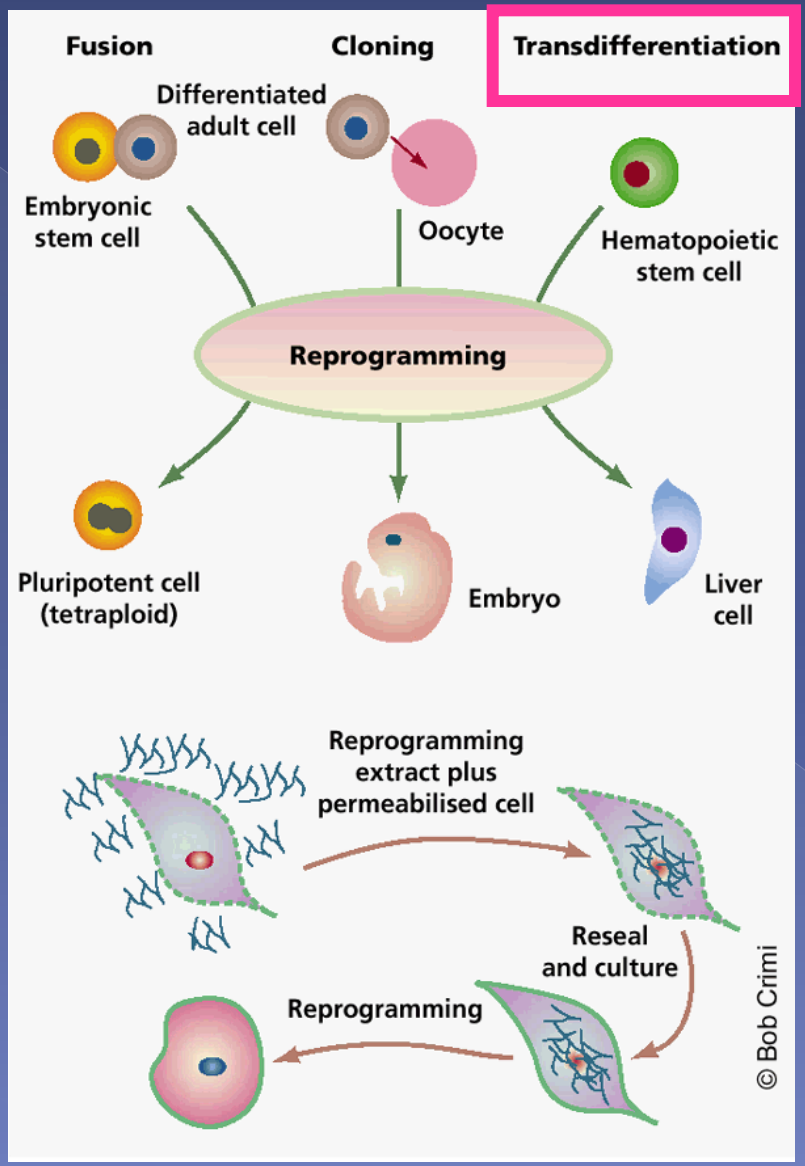
Clonado de Dolly



Clonado de Dolly



Reprogramación



Transdiferenciación

Capacidad de una célula de un linaje de diferenciarse a células de otro linaje

Transdiferenciación

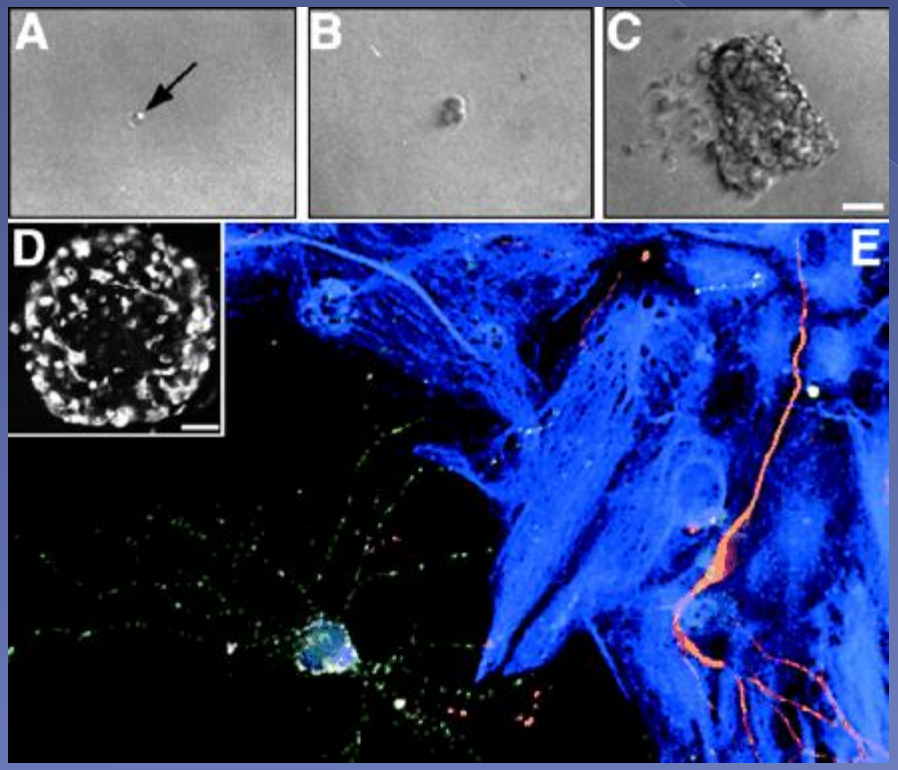
Table 1
Transdifferentiation of adult stem cells

Tissue of origin	Newly formed tissue	References
Bone marrow		
Unfractionated	Brain	[72,73]
	Kidney	[79,80]
	Skeletal muscle	[113]
Mesenchymal/	Brain	[71]
stromal	Bone	[63,64]
	Fat	[66]
	Heart	[67–69]
HSC	Liver, lung, skin, gastro-intestinal tract	[77]
MAPC	Brain, retina, lung, heart, skeletal muscle,	
	liver, intestine, kidney, spleen, bone marrow, blood and skin	[84]
Brain	Heart, skeletal muscle, kidney, stomach, intestine, liver	[87]
	Blood	[85,86]
	Blood	[94,95]
Skeletal muscle	Heart	[99]
Liver	Bile duct	[97]
Fat	Pancreas	[98]
Skin	Bone, skeletal muscle	[101,102]
Pancreas	Fat, brain, muscle	[103]
	Liver	[100]

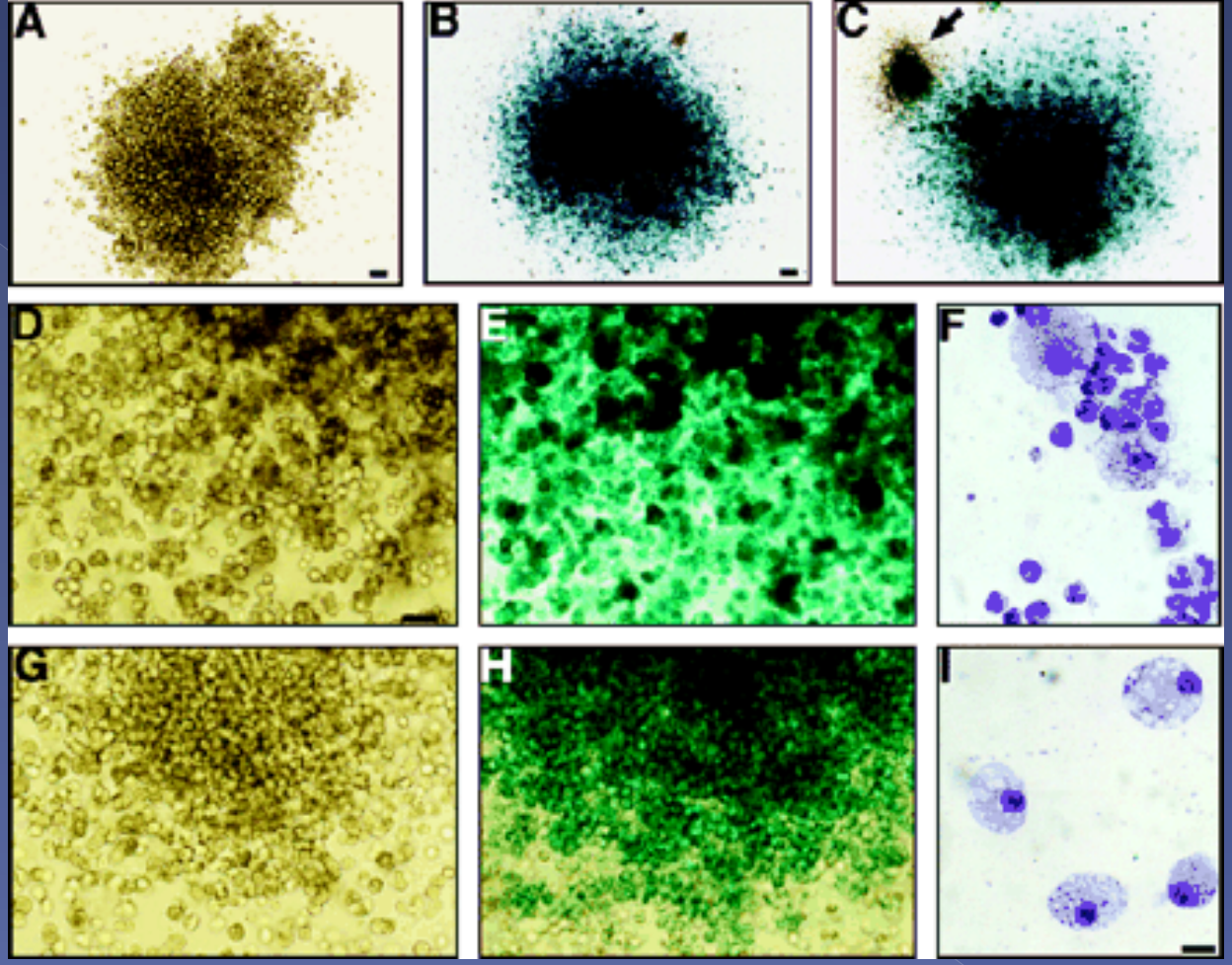
HSC, hematopoietic stem cells; MAPC, multipotent adult progenitor cell.

Transdiferenciación

When the brain turns into blood
Vescovi, Science,1999



A: single ROSA26 NSC
B: 1 day
C: 8 days
D: neuroesfera (nestin+?)
E: neurons (red), astroglia (blue), oligos (green)



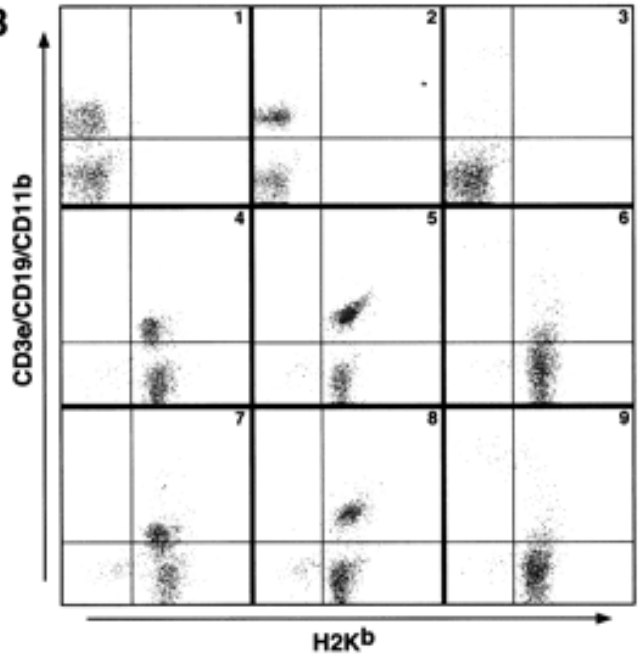
A. BM from Balb/c
B. BM from Balb/c transplanted
C. Idem B
D + F. macrophage+ granulocytes
E. D + betagal
G + I. macrophages
H. G + beta gal

5 to 12 months after transplantatio
to sub-irradiated animals.

A

% H-2K^b	Balb/c	ROSA 26	EBSS	Bone Marrow	Adult NSCs	Embryonic NSCs
Peripheral Blood	2.35±0.40	94.2±1.13	1.68±0.43	56.7±12.6	43.1±6.87	43.9±6.98
Spleen	0.92±0.15	97.3±1.03	1.68±0.44	95.3±2.45	65.4±23.5	60.7±11.0
Bone Marrow	2.26±0.55	42.3±4.09	1.59±0.51	38.8±2.48	35.8±10.0	40.4±6.61
CD3e/H-2K^b	0.52±0.08	33.0±5.16	0.77±0.05	31.9±2.62	28.1±14.2	9.86±4.69
CD11b/H-2K^b	0.47±0.09	30.0±2.24	0.43±0.02	14.5±3.85	14.9±10.9	19.5±6.88
CD19/H-2K^b	0.57±0.08	51.0±1.90	0.59±0.07	56.2±2.50	26.8±11.7	31.8±1.38

B



CD3: T cells
CD11: myeloid cells
CD19: B cells

H-2kb= ROSA

Engraftment: 22 weeks post-transplant

From Marrow to Brain: Expression of Neuronal Phenotypes in Adult Mice

Timothy R. Brazelton, Fabio M. V. Rossi, Gilmor I. Keshet, Helen M. Blau*

Table 2. Number and location of individual bone marrow–derived CNS cells. Sections from five mice were stained with a single antibody to a cellular marker and were analyzed by laser scanning confocal microscopy. "Cells per section" indicates the average number of neurons, astrocytes, or microglial cells analyzed (±SD) in each coronal olfactory bulb section using antibodies specific to proteins for each cell type analyzed. The average number of neurons per OB section was determined using NeuN staining and was used to estimate neurons evaluated for NF-H staining. SAL, superficial axon layer; EPL, external plexiform layer; and IPL, internal plexiform layer.

	Neurons		Astrocytes	Microglia
	NeuN$^+$	NF-H$^+$	GFAP$^+$	F4/80
Mice analyzed	5	4	4	3
Sections analyzed	8	4	4	3
Cells per section	10,400 (± 600)		2000 (± 200)	550 (± 50)
GFP$^+$ cells per OB layer from all sections analyzed				
Total	165	128	0	510
Layer				
SAL	105	66	0	312
Glomerular layer	30	41	0	114
EPL	14	10	0	56
Mitral cell layer	4	0	0	7
IPL	0	0	0	8
Granule layer	12	11	0	13

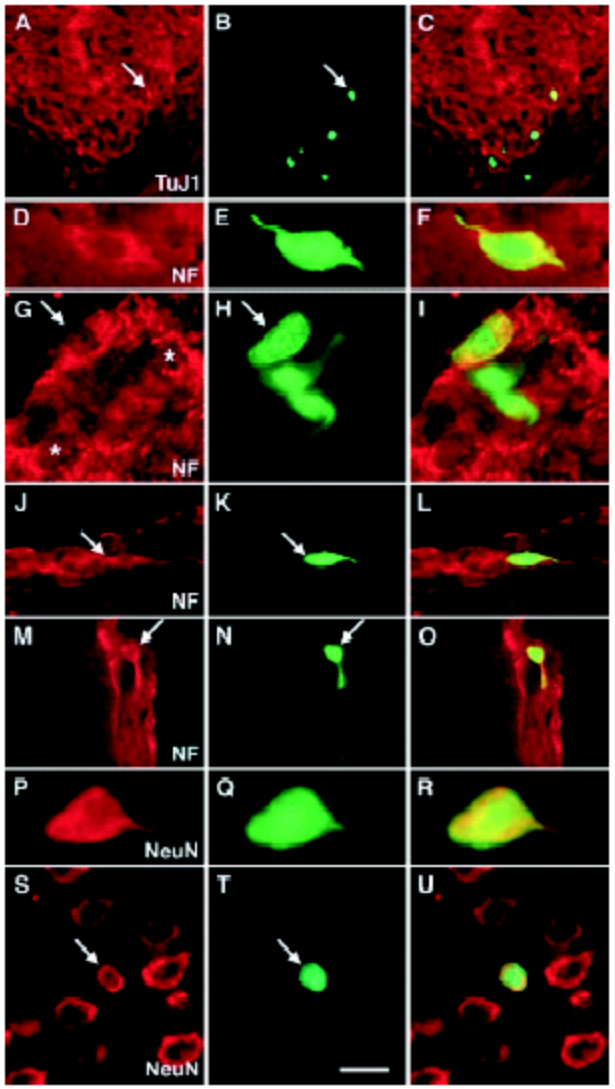


Fig. 2. Laser scanning confocal microscopic analysis of GFP$^+$ cells derived from bone marrow in adult brain sections. Marrow-derived cells (green in all images) from adult mice expressed neuronal-specific proteins. Morphological nomenclature is as described in Table 1. (A to C) A marrow-derived cell (arrow) expressing class III β-tubulin (TuJ1; red) in a group of five marrow-derived cells. (D to F) Cell with spindle morphology and a small extension expressing 200-kD neurofilament (NF-H; red). (G to I) Cell with oval morphology (arrow) expressing NF-H (red) next to two marrow-derived cells lacking expression of NF-H. Nuclear outlines (*) of non-marrow-derived neurons expressing NF-H (red) are visible. (J to L) A cell with triangular morphology (arrow) with a small extension expressing NF-H (red) in an olfactory bulb layer containing NF-H expressed by both marrow-derived cells and native neurons. (M to O) Cell with triangular morphology (arrow) with a small extension expressing NF-H (red) in the superficial axonal layer. (P to R) Prototypical triangular cell with a small extension expressing NeuN (red) which is known to be nuclear and perinuclear in the cell body (33). (S to U) Bone marrow–derived cell (arrow) expressing NeuN (red) in layer 2/3 of the parietal cortex. Left panels [(A), (D), (G), (J), (M), (P), and (S)], expression of neuron-specific proteins (TuJ1, NF, or NeuN); middle panels [(B), (E), (H), (K), (N), (Q), and (T)], GFP$^+$ marrow-derived cells in CNS; right panels [(C), (F), (I), (L), (R), (O), and (U)], colocalization of markers in left and middle panels. Scale bar in (T) corresponds to 31 μm for (A) through (C), 7.5 μm for (D) through (F), 10 μm for (G) through (I), 20 μm for (J) through (L), 18 μm for (M) through (O), 6 μm for (P) through (R), and 14 μm for (S) through (U). TuJ1, class III β-tubulin; NF, 200-kD neurofilament, NF-H.

nature cell biology

ARTICLES

Stable reprogrammed heterokaryons form spontaneously in Purkinje neurons after bone marrow transplant

James M. Weimann[1,2], Clas B. Johansson[1], Angelica Trejo[1] and Helen M. Blau[1,2]

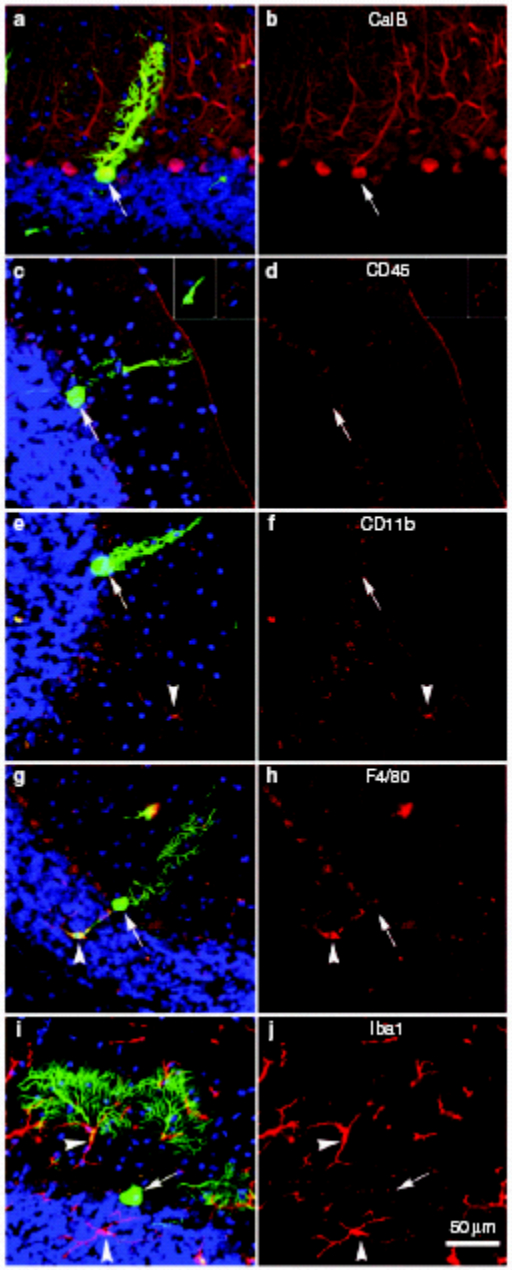
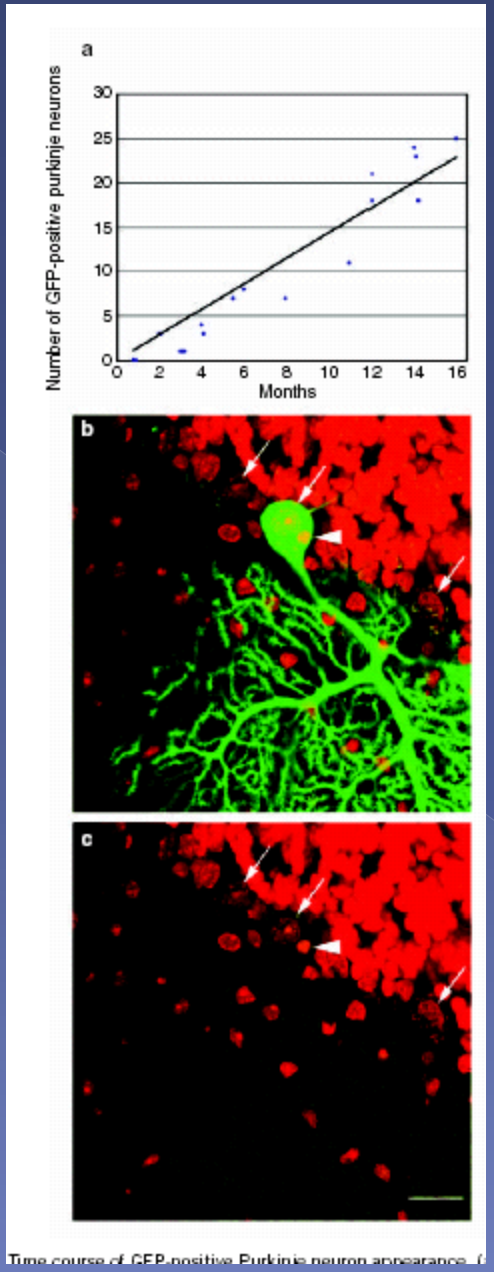


Figure 2 Marker expression in GFP-positive Purkinje neurons. Immunohistochemistry with specific antibodies demonstrates the presence of Purkinje-specific markers, but not marrow markers. (a, b) Calbindin, a



Time course of GFP-positive Purkinje neuron appearance. (

Figure 3 Time course of GFP-positive Purkinje neuron appearance. (a) Mice were bone-marrow-transplanted at two months of age and cerebella were collected and analysed at various times. The number of GFP-positive Purkinje cells increased in a linear manner over time, with a linear regression of 0.92. One animal analysed at 18 months had a higher than expected number of cells ($n = 60$) that may reflect some aspect of the ageing process. This one data point was not included in the graph. (b, c) All of the GFP-positive Purkinje cells observed contained two nuclei. This Purkinje cell has a distinctive dendritic tree with many synaptic spines and an axon exiting the soma at the left. One of the two nuclei in the cell is compact (arrowhead) and is the putative BMD nucleus. The other nucleus has dispersed chromatin similar to other Purkinje neurons (arrows). In 752 control Purkinje neurons from transplanted and normal mice, no binucleated cells were observed. Scale bar represents 20 μm.

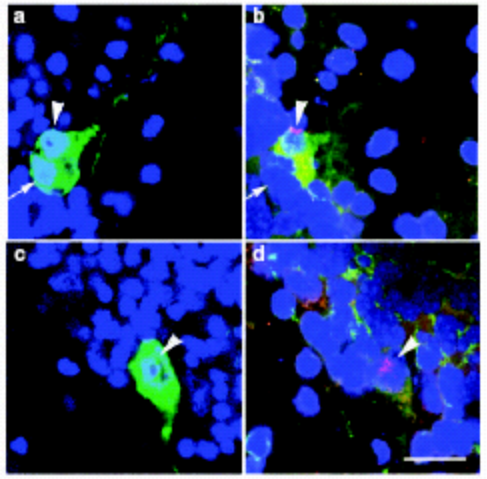


Figure 4 Fusion of a male BMDC to a female Purkinje neuron. (a) A Texas-Red-labelled Y chromosome probe was used to detect donor-derived male nuclei by FISH. A single 1-mm confocal optical section through a 12-mm section of a GFP-positive Purkinje cell containing two nuclei. (b) After protease digestion and hybridization, it is evident that the top nucleus (arrowhead) has a Y chromosome and is donor-derived. Note that some displacement of the nuclei occurs through digestion and *in situ* processing. (c) Another double-nuclei GFP-positive cell. The host nucleus in d is beneath the male donor-derived nucleus shown in c (arrowhead). The host nucleus visible in d does not possess a Y chromosome. Scale bar represents 20 μm.

Fusion causes confusion

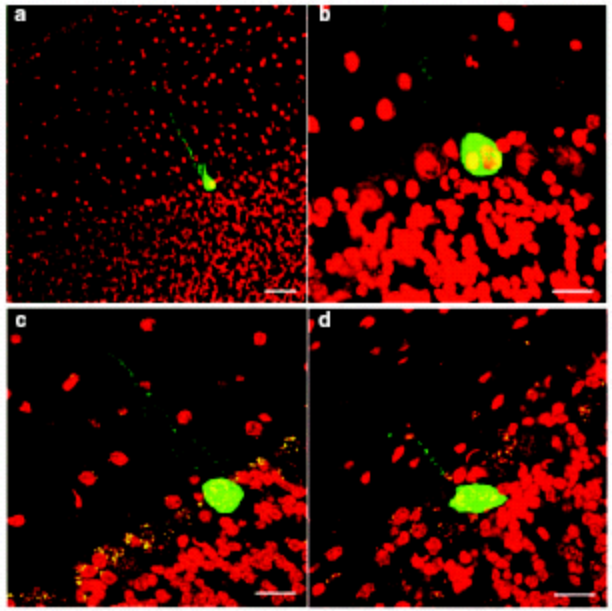
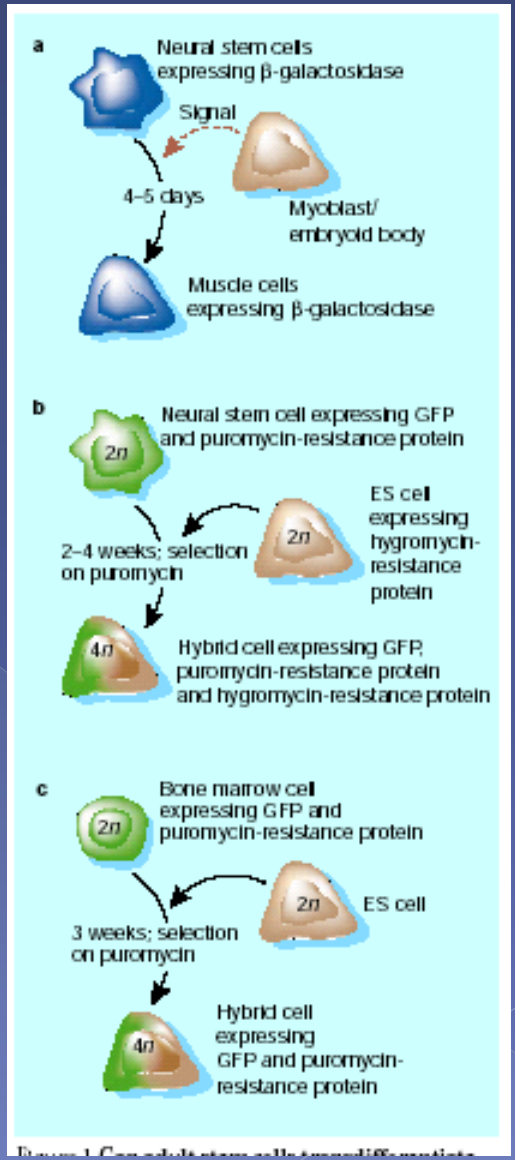


Figure 7 Evidence for reprogramming of BMDCs after fusion to Purkinje neurons. (a) Low-power image of L7-*GFP* bone-marrow-derived Purkinje neuron with the soma in the PCL and a dendrite extending into the ML. (b–d) High-power images of three L7-GFP bone-marrow-derived Purkinje neurons. All eight of the L7-GFP neurons had double nuclei. In all images, Green represents GFP and Red represents To-Pro3. Scale bar represents 50 μm in a and 20 μm in b–d.



Bone marrow cells regenerate infarcted myocardium

Donald Orlic†, Jan Kajstura*, Stefano Chimenti*, Igor Jakoniuk*, Stacie M. Anderson†, Baosheng Li*, James Pickel‡, Ronald McKay‡, Bernardo Nadal-Ginard*, David M. Bodine†, Annarosa Leri* & Piero Anversa*

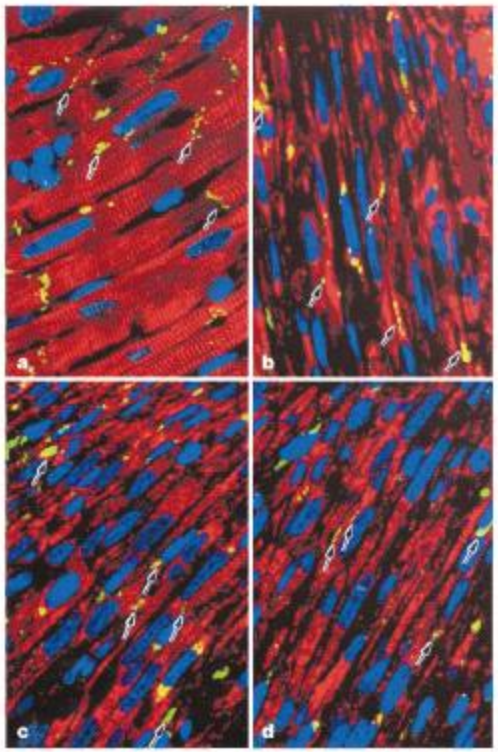


Figure 4 Myocardial repair and connexin 43. **a**, Border zone; **b**–**d**, regenerating myocardium. Shown are connexin 43 (yellow–green; arrows indicate contacts betwe myocytes) and α-sarcomeric actin (red), and PI-stained nuclei (blue). Original magnification, ×500 (**a**), ×800 (**b**–**d**).

68 11% newly formed myocardium

Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts

Charles E. Murry[1], Mark H. Soonpaa[2], Hans Reinecke[1], Hidehiro Nakajima[2], Hisako O. Nakajima[2], Michael Rubart[2], Kishore B. S. Pasumarthi[2,4], Jitka Ismail Virag[1], Stephen H. Bartelmez[3], Veronica Poppa[1], Gillian Bradford[2], Joshua D. Dowell[2], David A. Williams[2,4] & Loren J. Field[2]

[1] *Department of Pathology, Box 357470, Room D-514 HSB, University of Washington, Seattle, Washington 98195, USA*
[2] *Wells Center for Pediatric Research, Indiana University, 1044 West Walnut Street, R4 Bldg, Room W376, Indianapolis 46202-5225, USA*
[3] *Department of Pathobiology, University of Washington, Seattle, Washington 98195, USA*

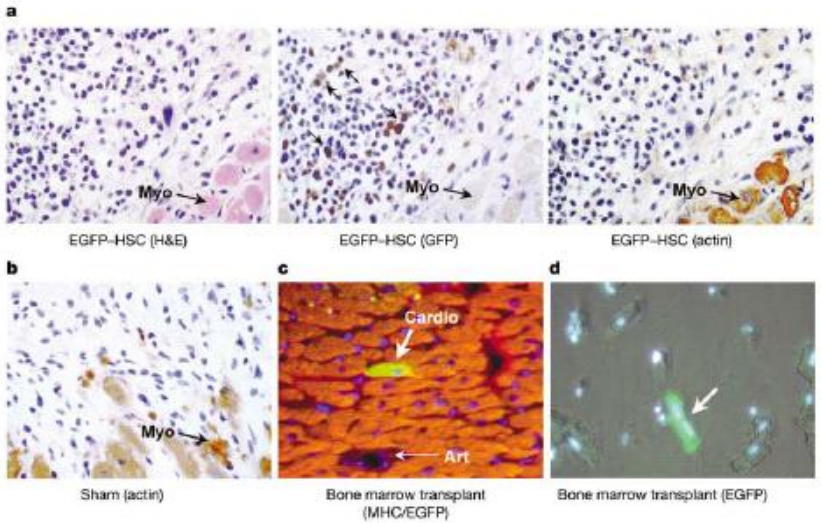


Figure 2 Absence of cardiac differentiation of HSCs after direct injection into infarcts, contrasted with rare transdifferentiation after bone marrow transplantation. β-Act–EGFP mice were cell donors. **a**, Left panel: haematoxylin- and eosin-stained section showing junction of host myocardium (Myo) with granulation tissue of 1-week-old, HSC-injected (EGFP–HSC) infarct. Granulation tissue contains numerous granulocytes and mononuclear inflammatory cells. Middle panel: serial section from the same heart immunostained for EGFP (brown), showing numerous $EGFP^+$ cells dispersed throughout granulation tissue (arrows). Host myocardium (Myo) is unstained. Right panel: serial section from the same heart immunostained for sarcomeric actin (brown). Host myocardium (Myo) is strongly stained, but no sarcomeric actin is present in the region containing EGFP-expressing cells. **b**, Sham-injected heart 1 week after infarction stained for sarcomeric actin (brown). Myocardium (Myo) at infarct border stains strongly, but infarct granulation tissue is negative. **c**, Histological detection of a rare $EGFP^+$ cardiomyocyte (Cardio; yellow) in the peri-infarct region after bone marrow transplantation, shown by immunostaining for α-myosin heavy chain (red) and EGFP (green). Approximately 2–4 such cells were identified per heart. A small arteriole (Art) is unstained. **d**, Rare transdifferentiation event after bone marrow transplantation detected in enzymatically dispersed cardiomyocytes. A single rod-shaped cardiomyocyte contains EGFP (arrow), while multiple other cardiomyocytes are negative.

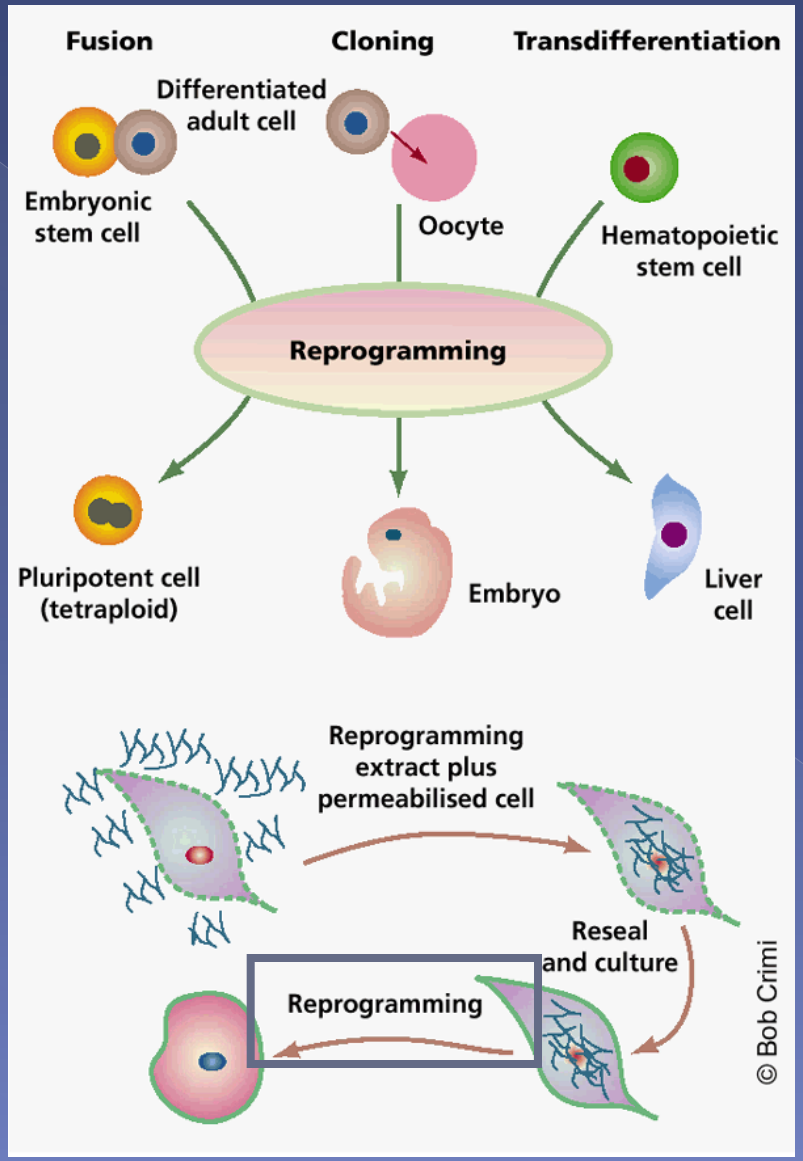
Transdiff= 1/100.000

Table 1 **Summary of intracardiac HSC transplantation data**

Donor cell genotype	Haematopoietic stem cell used	Heart injury	Number of cells transplanted	Graft age at death (days)	Cardiomyogenic events per graft
MHC-nLAC	Lin^- c-kit^+	MI	100,000	14–28	0/42
	Lin^- c-kit^+	Cautery	100,000	7–28	0/26
	Lin^- c-kit^+ $Sca\text{-}1^+$	Cautery	31,000–75,000	7–36	0/11
	Lin^- c-kit^+ $Sca\text{-}1^+$	None	40,000–65,000	1–119	0/9
	Lin^- c-kit^- $Sca\text{-}1^+$	Cautery	17,000–25,000	7–36	0/11
	Lin^- c-kit^- $Sca\text{-}1^+$	None	7,000–37,000	1–119	0/9
MHC-EGFP	Lin^- c-kit^+	MI	100,000	14	0/10
β-Act-EGFP	Lin^- c-kit^+	MI	50,000	7–14	0/27

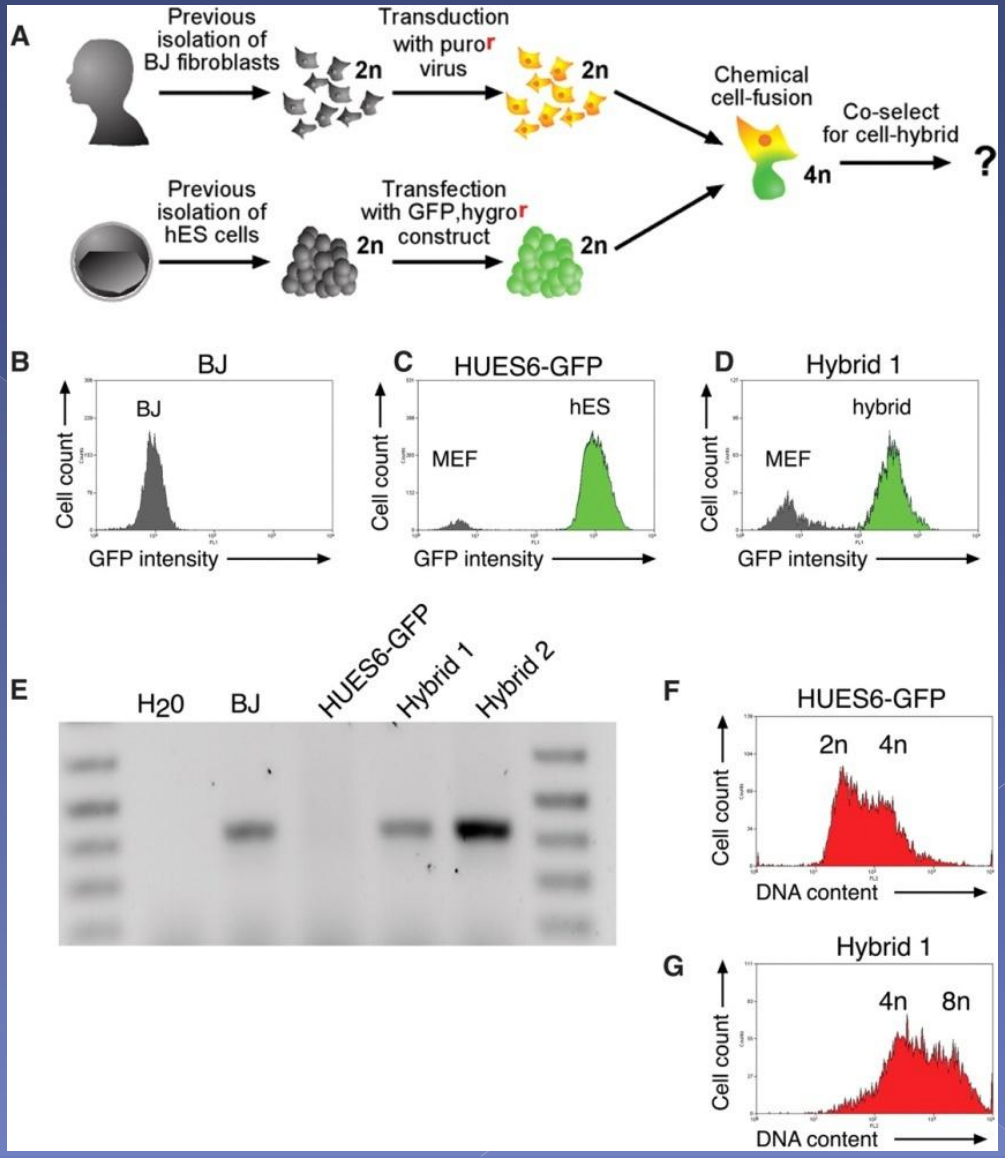
MI, myocardial infarct.

Reprogramación



Cellular Reprogramming

- Cell-cell fusion experiments suggest that the ES cell dominate the hybrid cell phenotype. (Clarke and Frisen, *Science* 2000; Terada and Scott *Nature* 2002; Ying and Smith *Nature* 2002; Cowan and Eggan *Science* 2005).
- The hybrid ES cells possess all properties of pluripotent stem cells – including teratoma formation, self-renewal, yet contains a cell nucleus from an exogenous cells.



Cell

Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] **and Shinya Yamanaka**[1,2,*]
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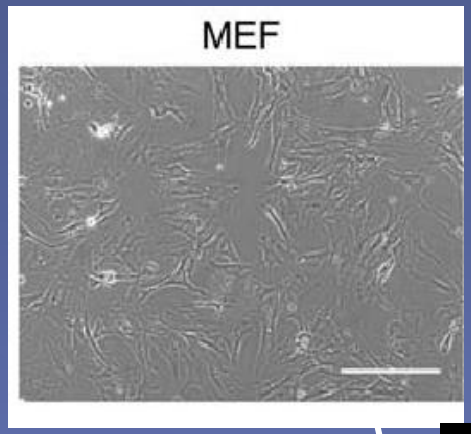
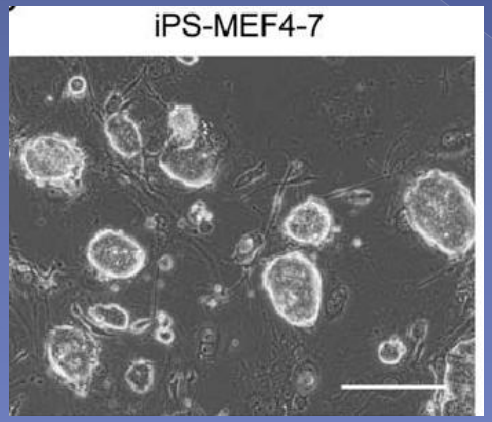
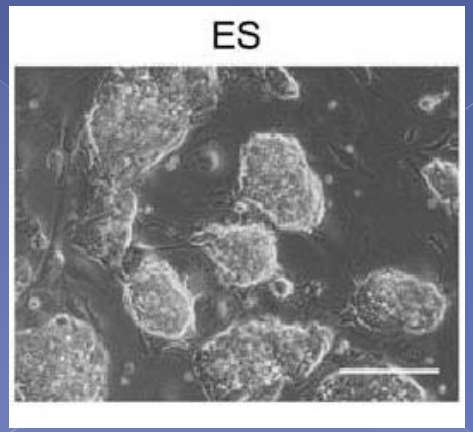
DOI 10.1016/j.cell.2006.07.024

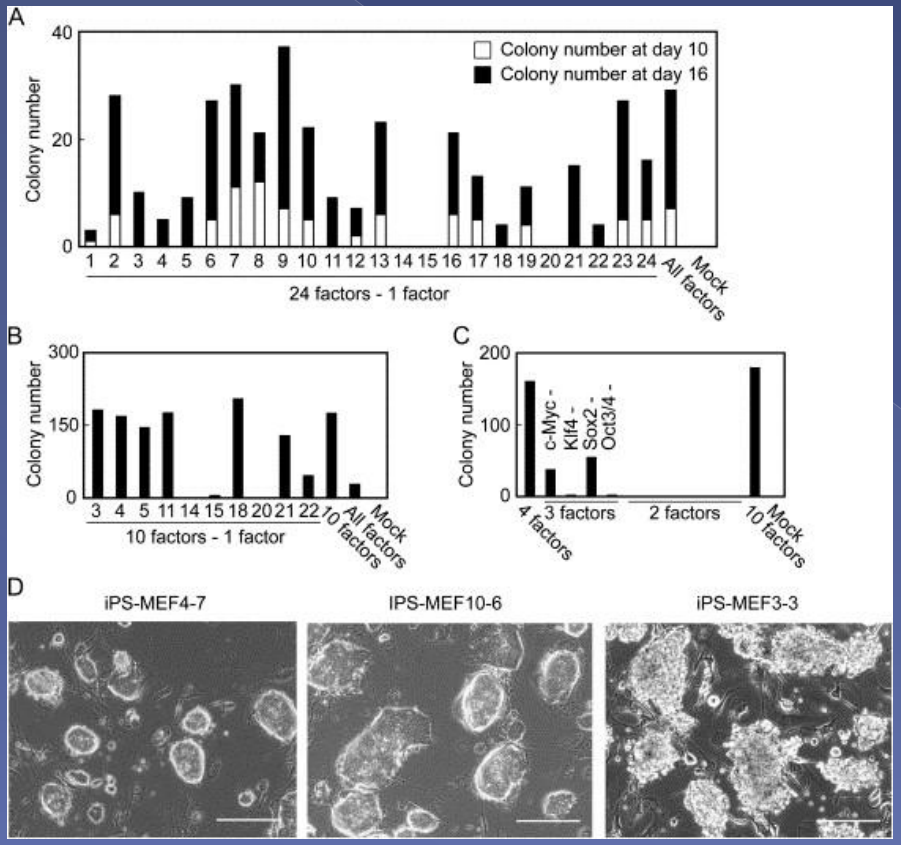


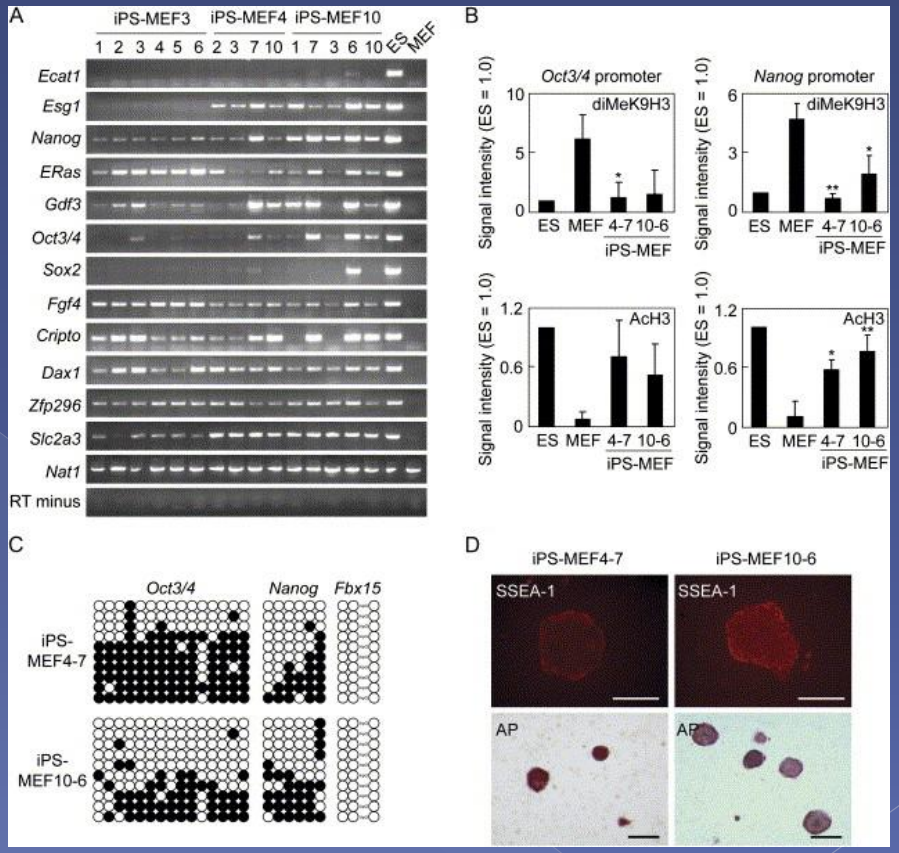
Oct3/4
Sox2
c-Myc
Klf4

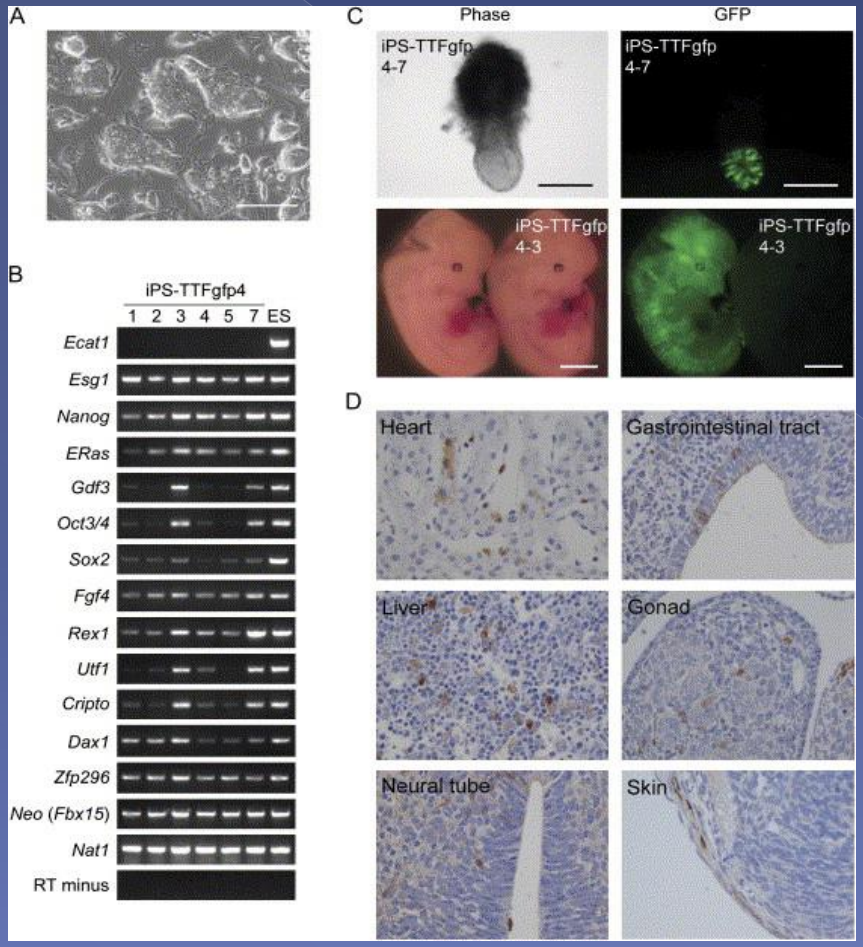
24 candidate factors:
Ecat1, Dpp5(Esg1), Fbx015, Nanog, ERas, Dnmt3l, Ecat8, Gdf3, Sox15, Dppa4, Dppa2, Fthl17, Sall4, Oct4, Sox2, Rex1, Utf1, Tcl1, Dppa3, Klf4, b-cat, cMyc, Stat3, Grb2

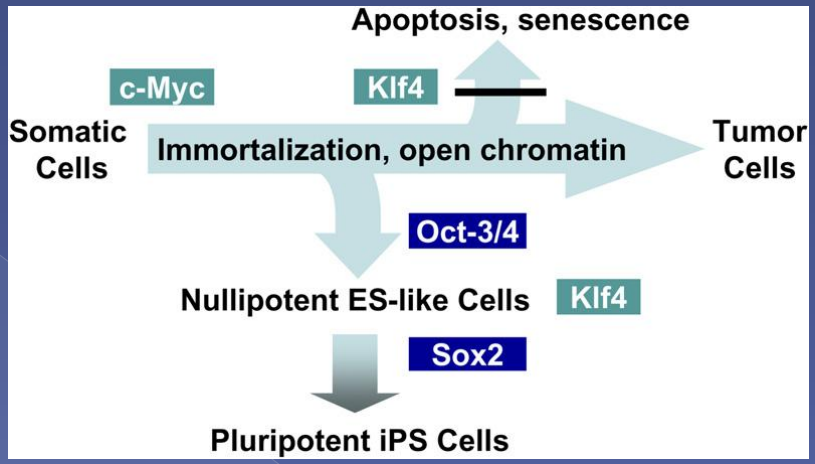





A
Colony number
Colony number at day 10
Colony number at day 16
24 factors - 1 factor
All factors
Mock
B
Colony number
10 factors - 1 factor
C
Colony number
c-Myc -
Klf4 -
Sox2 -
Oct3/4 -
4 factors
3 factors
2 factors
10 factors
D
iPS-MEF4-7
IPS-MEF10-6
iPS-MEF3-3


A
iPS-MEF3
iPS-MEF4
iPS-MEF10
ES
MEF
Ecat1
Esg1
Nanog
ERas
Gdf3
Oct3/4
Sox2
Fgf4
Cripto
Dax1
Zfp296
Slc2a3
Nat1
RT minus
B
Oct3/4 promoter
Nanog promoter
diMeK9H3
AcH3
Signal intensity (ES = 1.0)
ES MEF 4-7 10-6
iPS-MEF
C
Oct3/4
Nanog
Fbx15
iPS-MEF4-7
iPS-MEF10-6
D
iPS-MEF4-7
iPS-MEF10-6
SSEA-1
AP


A
B
iPS-TTFgfp4
1 2 3 4 5 7 ES
Ecat1
Esg1
Nanog
ERas
Gdf3
Oct3/4
Sox2
Fgf4
Rex1
Utf1
Cripto
Dax1
Zfp296
Neo (Fbx15)
Nat1
RT minus
C
Phase
GFP
iPS-TTFgfp 4-7
iPS-TTFgfp 4-3
D
Heart
Gastrointestinal tract
Liver
Gonad
Neural tube
Skin


Apoptosis, senescence
c-Myc
Klf4
Somatic Cells
Immortalization, open chromatin
Tumor Cells
Oct-3/4
Nullipotent ES-like Cells
Klf4
Sox2
Pluripotent iPS Cells

Cell

Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]

Cell

Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

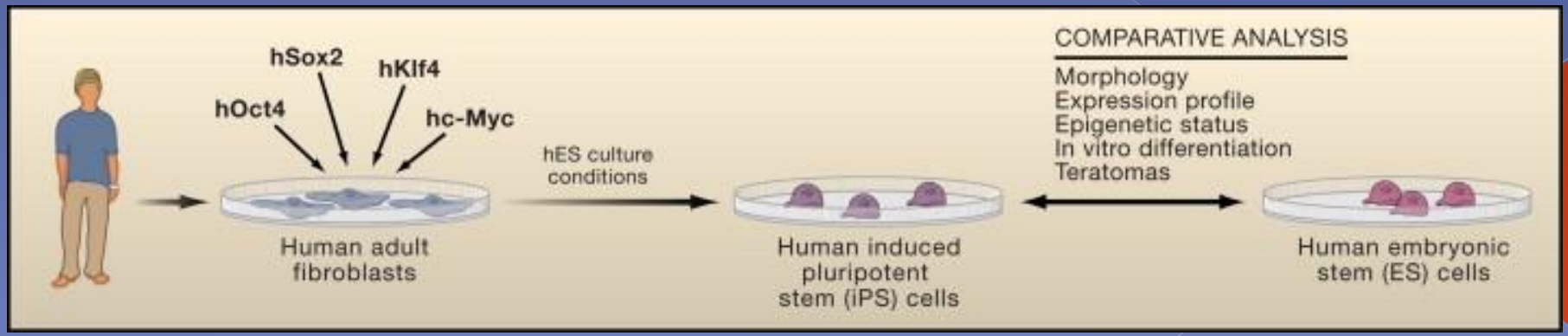
Kazutoshi Takahashi,[1] Koji Tanabe,[1] Mari Ohnuki,[1] Megumi Narita,[1,2] Tomoko Ichisaka,[1,2] Kiichiro Tomoda,[3] and Shinya Yamanaka[1,2,3,4,*]

SCIENCE VOL 318 21

2007 - Human

Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells

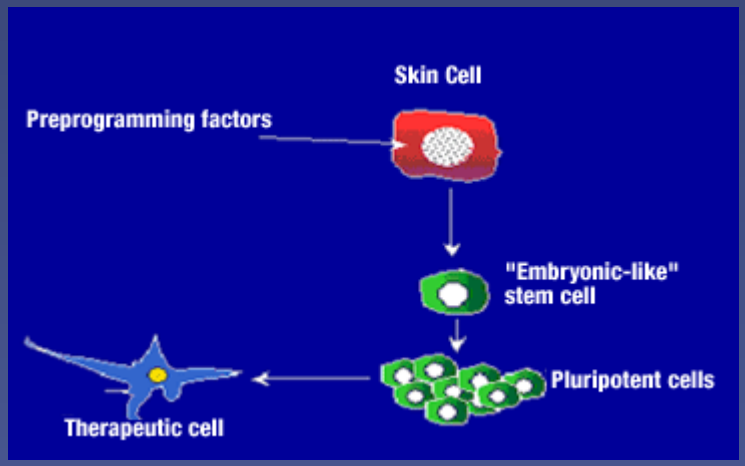
Junying Yu,[1,2*] Maxim A. Vodyanik,[2] Kim Smuga-Otto,[1,2] Jessica Antosiewicz-Bourget,[1,2] Jennifer L. Frane,[1] Shulan Tian,[3] Jeff Nie,[3] Gudrun A. Jonsdottir,[3] Victor Ruotti,[3] Ron Stewart,[3] Igor I. Slukvin,[2,4] James A. Thomson[1,2,5*]



Reprogramación células adultas

Nanog

Lin28

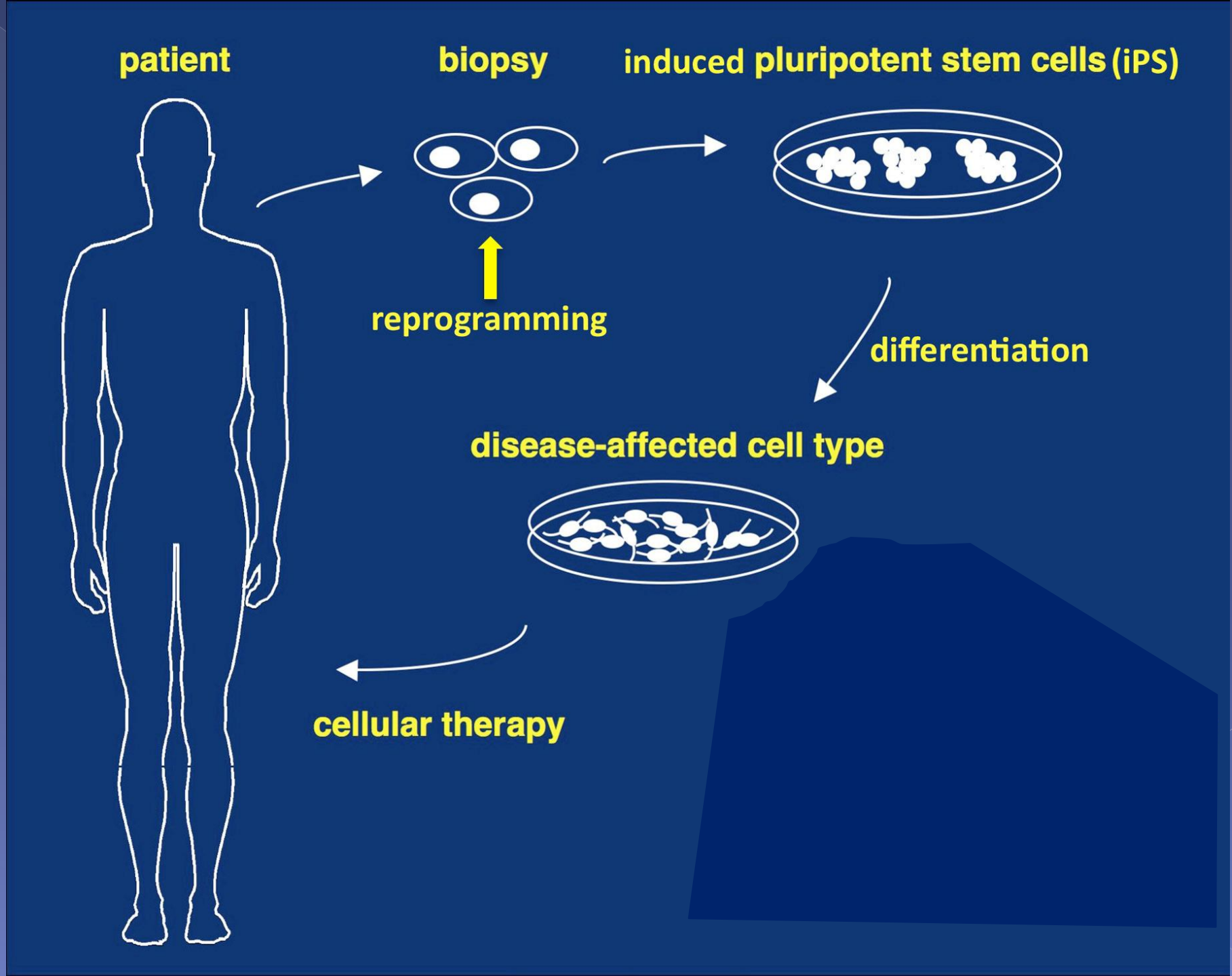


VENTAJAS

Pluripotentes
Fácil acceso
Sin dilemas éticos
Rechazo poco probable
Modelos in vitro de enfermedades

DESVENTAJAS

Tumorigenicidad
Baja eficiencia
Carga genética del paciente


patient
biopsy
induced pluripotent stem cells (iPS)
reprogramming
differentiation
disease-affected cell type
cellular therapy

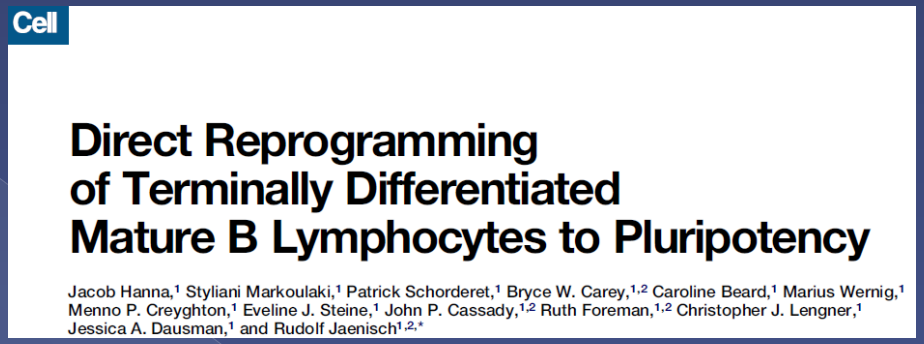
iPS cells generation in patient fibroblasts

- Parkinson's disease (Wernig and Jaenisch, 2008, Maehr and Melton PNAS 2009).
- Amyopathic Lateral Sclerosis, (Dimos and Eggan Science 2008)
- Type I diabetes (Maehr and Melton PNAS 2009)
- ADA-SCID, SBDS, Gaucher disease, Duchenne and Becker Muscular dystrophin, Parkinson's disease, Huntington disease, JDM, Down syndrome, Lesch-Nyhan syndrome. (Park and Daley Cell 2008).

iPS cells generation from other cell types

- Blood cells (Loh and Daley 2009). B-cells (Hanna and Jaenisch Cell 2008)
- Blood stem cells (Emiinli and Hochedlinger Nat Genet 2009)
- Pancreatic β-cells (Stadtfeld and Hochedlinger Cell Stem Cell2008)
- Hepatic and gastric endoderm (Aoi and Yamanaka Science 2008)
- Neural stem cells (Kim and Scholar, Nature 2008)

Other tissues: blood.

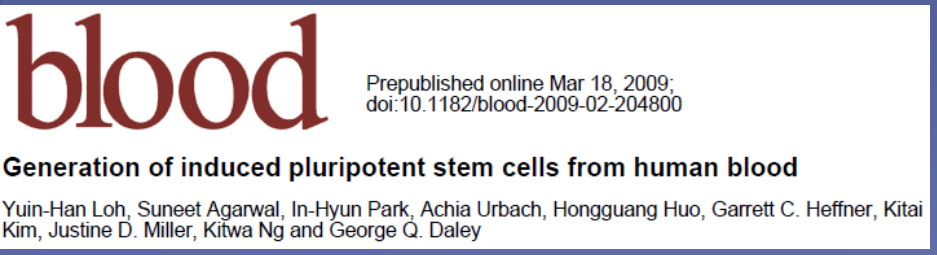

Cell

Direct Reprogramming of Terminally Differentiated Mature B Lymphocytes to Pluripotency

Jacob Hanna,[1] Styliani Markoulaki,[1] Patrick Schorderet,[1] Bryce W. Carey,[1,2] Caroline Beard,[1] Marius Wernig,[1] Menno P. Creyghton,[1] Eveline J. Steine,[1] John P. Cassady,[1,2] Ruth Foreman,[1,2] Christopher J. Lengner,[1] Jessica A. Dausman,[1] and Rudolf Jaenisch[1,2,*]

Human mobilized cells- CD34^{+}

2009 – Human Blood CD34

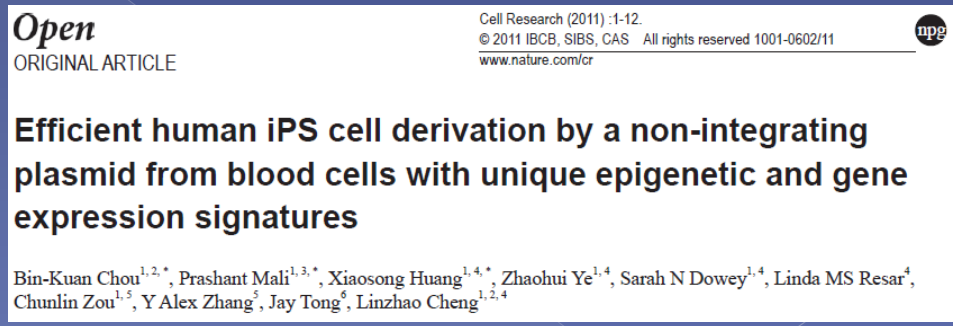

blood

Prepublished online Mar 18, 2009;
doi:10.1182/blood-2009-02-204800

Generation of induced pluripotent stem cells from human blood

Yuin-Han Loh, Suneet Agarwal, In-Hyun Park, Achia Urbach, Hongguang Huo, Garrett C. Heffner, Kitai Kim, Justine D. Miller, Kitwa Ng and George Q. Daley

2011 - Human Blood CD34


Open

ORIGINAL ARTICLE

Cell Research (2011) :1-12.

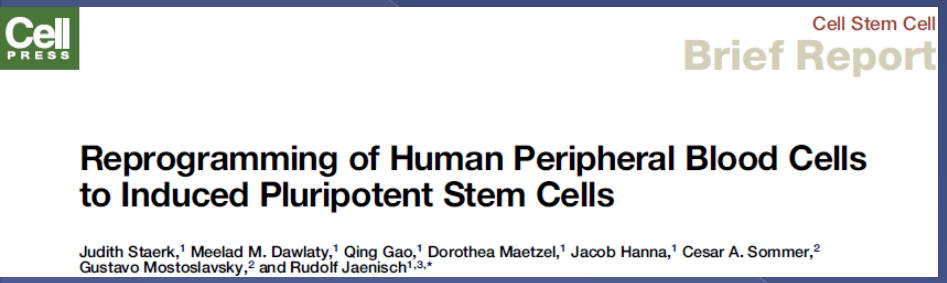
www.nature.com/cr

Efficient human iPS cell derivation by a non-integrating plasmid from blood cells with unique epigenetic and gene expression signatures

Bin-Kuan Chou[1, 2, *], Prashant Mali[1, 3, *], Xiaosong Huang[1, 4, *], Zhaohui Ye[1, 4], Sarah N Dowey[1, 4], Linda MS Resar[4], Chunlin Zou[1, 5], Y Alex Zhang[5], Jay Tong[6], Linzhao Cheng[1, 2, 4]

Peripheral Blood
T Cells - Ficoll

2010 – T Cells



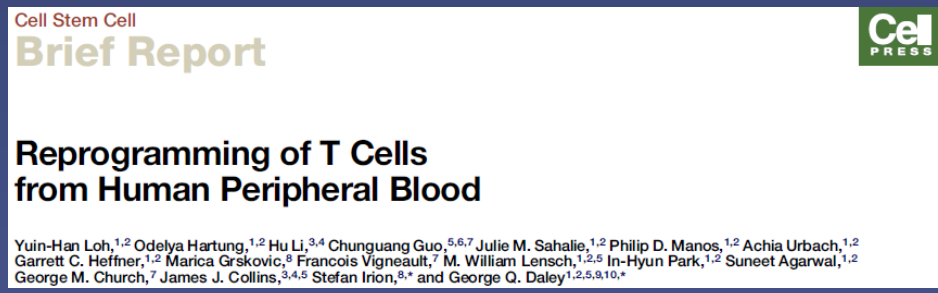
Cell Stem Cell

Brief Report

Reprogramming of Human Peripheral Blood Cells to Induced Pluripotent Stem Cells

Judith Staerk,[1] Meelad M. Dawlaty,[1] Qing Gao,[1] Dorothea Maetzel,[1] Jacob Hanna,[1] Cesar A. Sommer,[2] Gustavo Mostoslavsky,[2] and Rudolf Jaenisch[1,3,*]

2010 – T Cells and CD 34+

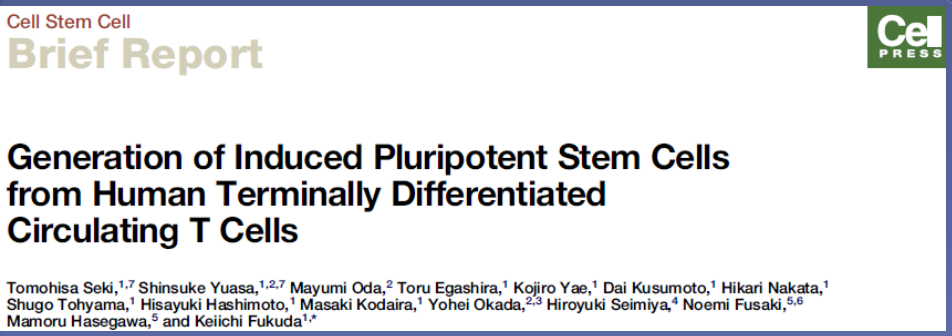


Cell Stem Cell

Brief Report

Reprogramming of T Cells from Human Peripheral Blood

Yuin-Han Loh,[1,2] Odelya Hartung,[1,2] Hu Li,[3,4] Chunguang Guo,[5,6,7] Julie M. Sahalie,[1,2] Philip D. Manos,[1,2] Achia Urbach,[1,2] Garrett C. Heffner,[1,2] Marica Grskovic,[8] Francois Vigneault,[7] M. William Lensch,[1,2,5] In-Hyun Park,[1,2] Suneet Agarwal,[1,2] George M. Church,[7] James J. Collins,[3,4,5] Stefan Irion,[8,*] and George Q. Daley[1,2,5,9,10,*]



Cell Stem Cell

Brief Report

Generation of Induced Pluripotent Stem Cells from Human Terminally Differentiated Circulating T Cells

Tomohisa Seki,[1,7] Shinsuke Yuasa,[1,2,7] Mayumi Oda,[2] Toru Egashira,[1] Kojiro Yae,[1] Dai Kusumoto,[1] Hikari Nakata,[1] Shugo Tohyama,[1] Hisayuki Hashimoto,[1] Masaki Kodaira,[1] Yohei Okada,[2,3] Hiroyuki Seimiya,[4] Noemi Fusaki,[5,6] Mamoru Hasegawa,[5] and Keiichi Fukuda[1,*]

Developments toward the "safer" iPS generation

Reduced number of transcription factor use:

- No myc: Nakagawa and Yamanaka, Nat Biotechnol 2008, Wernig and Jaenisch, Cell Stem Cell 2009
- No Sox2: by adding GSK-3 inhibitor, Zhou and Ding, Stem cell 2009, in neural stem cell, Kim and Scholer Nature 2008
- No Klf4/myc, by addition of Valproic acid : Huangfu and Melton, Nat Biotech 2008
- No Myc and Sox2, by addition of BIX01294 and PD0325901 (Zhou and Ding, Cell Stem Cell 2008).
- Klf4 only by adding Kenpaullone (Lyssiotis and Jaenisch, PNAS 2009)

Specific pathways:

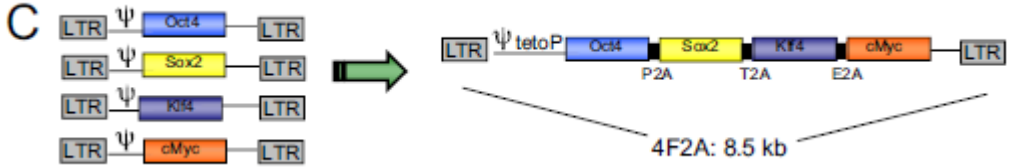
- TGFb inhibitor replace Sox2 and cMyc and induce Nanog (Maherali and Hochedlinger, Curr Biol 2009, Ichida and Eggan 2009)
- p53 inhibition augments iPS efficiency (Hong and Yamanaka, Nature 2009,Utikal and Hochedlinger Nature 2009, Marion and Blastco Nature 2009, Li and Serrano Nature 2009, Kawamura and Belmonte 2009)
- Hypoxia – Yoshida and Yamanaka Cell Stem Cell 2009
- WNT signaling stimulates reprogramming efficiency (Marsonm, Jaenisch Cell Stem Cell 2008)

Better vectors:

- Drug Inducible vectors: Wernig and Jaenisch, Nat Biotechnol 2008, Hockemeyer and Jaenisch, Cell Stem Cell 2008
- Non-integrating vectors : adenovirus in hepatocyte (Stadtfeld and Hochedlinger Science 2008)
- Self-inactivating vectors: Piggy Bac (Yusa and Bradley, Nat Methods 2009)
- multi-cistronic vectors: single lentiviral cassette (Carey and Jaenisch, PNAS 2009, Sommer and Mostoslavsky, Stem Cell 2009)
- Vector free (episome Yu and Thomson, Science 2009; direct transfection Okita and Yamanaka Science 2008)
- Direct protein induction: poly arginine modification of recombinant protein (Zhou and Ding, Cell Stem Cell 2009),

Reprogramming of murine and human somatic cells using a single polycistronic vector

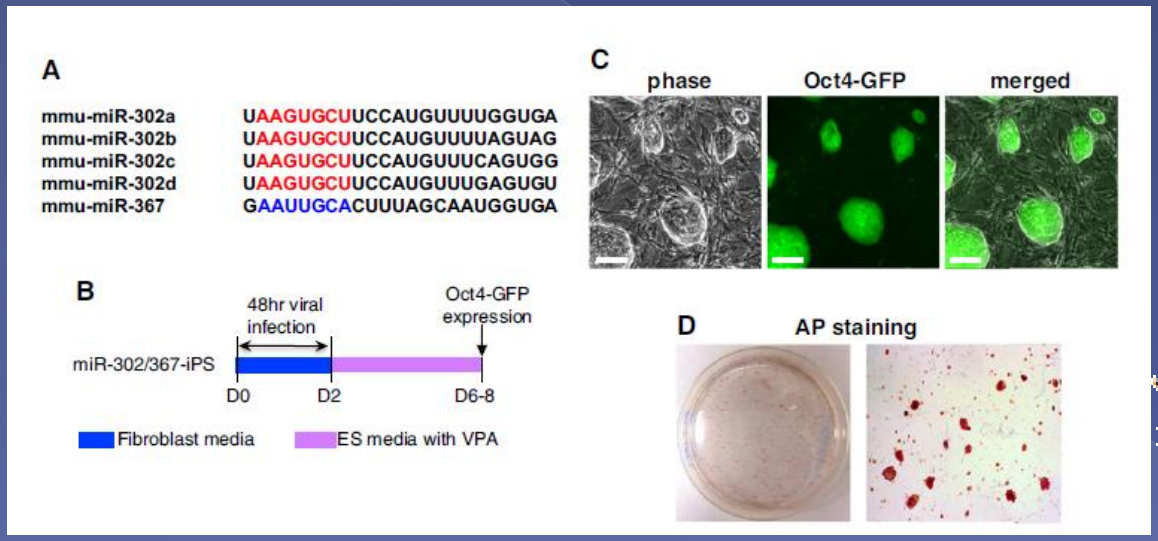
Bryce W. Carey[a,b], Styliani Markoulaki[a], Jacob Hanna[a], Kris Saha[a], Qing Gao[a], Maisam Mitalipova[a,1], and Rudolf Jaenisch[a,b,1]

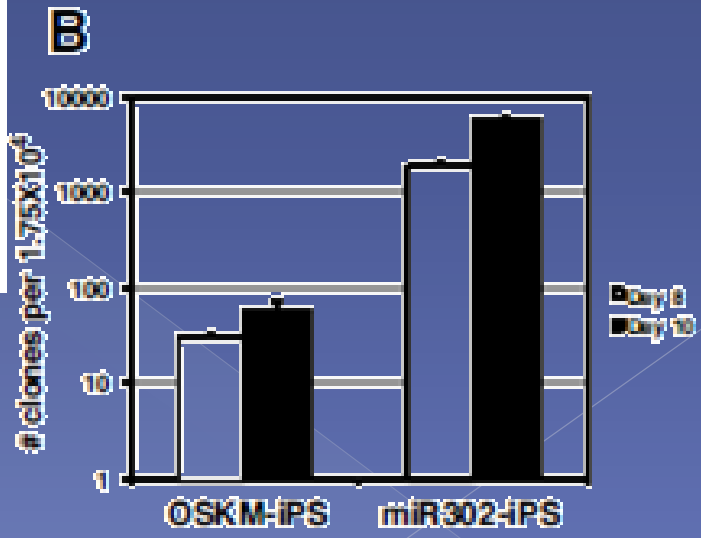


Highly Efficient miRNA-Mediated Reprogramming of Mouse and Human Somatic Cells to Pluripotency

Frederick Anokye-Danso,[1] Chinmay M. Trivedi,[2] Denise Juhr,[5] Mudit Gupta,[2] Zheng Cui,[1] Ying Tian,[1] Yuzhen Zhang,[1] Wenli Yang,[1,4] Peter J. Gruber,[3,4,5] Jonathan A. Epstein,[1,2,3,4] and Edward E. Morrisey[1,2,3,4,*]

2011

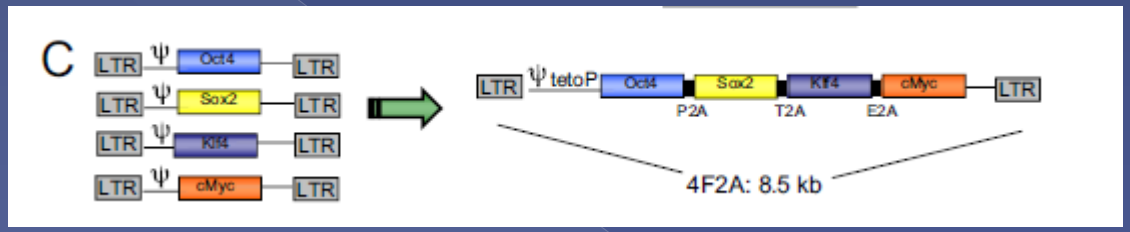




Easier hiPSCs

Reprogramming of murine and human somatic cells using a single polycistronic vector

Bryce W. Carey[a,b], Styliani Markoulaki[a], Jacob Hanna[a], Kris Saha[a], Qing Gao[a], Maisam Mitalipova[a,1], and Rudolf Jaenisch[a,b,1]



Safer hiPSCs – no c-Myc

Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts

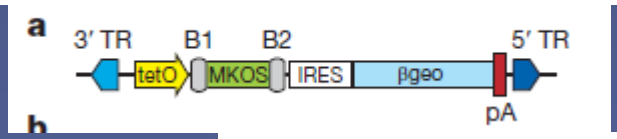
Masato Nakagawa[1,5], Michiyo Koyanagi[1,5], Koji Tanabe[1], Kazutoshi Takahashi[1], Tomoko Ichisaka[1,2], Takashi Aoi[1], Keisuke Okita[1], Yuji Mochiduki[1], Nanako Takizawa[1] & Shinya Yamanaka[1,2,3,4]

Safer hiPSCs – no integration

piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells

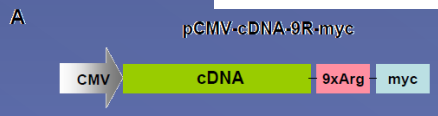
Knut Woltjen[1], Iacovos P. Michael[1,2], Paria Mohseni[1,2], Ridham Desai[1,2], Maria Mileikovsky[1], Riikka Hämäläinen[1], Rebecca Cowling[1], Wei Wang[3], Pentao Liu[3], Marina Gertsenstein[1], Keisuke Kaji[4], Hoon-Ki Sung[1] & Andras Nagy[1,2]

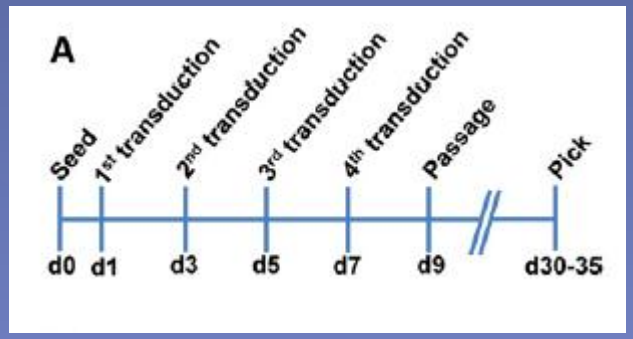
2009



Cell Stem Cell
Brief Report

Generation of Induced Pluripotent Stem Cells Using Recombinant Proteins



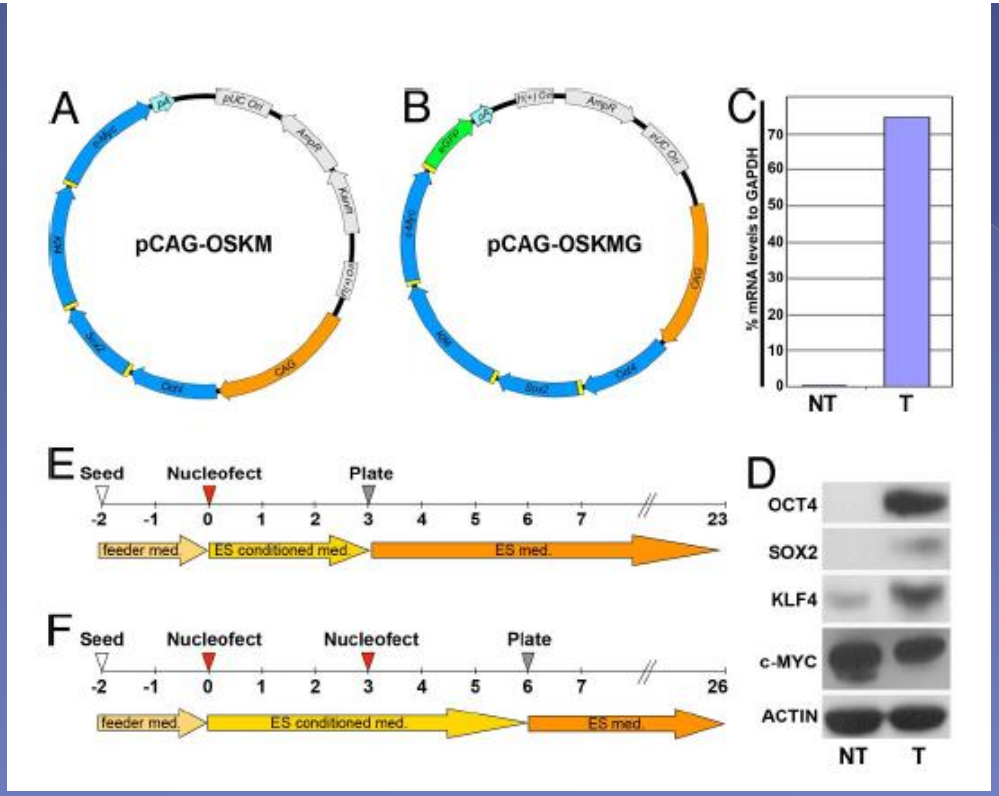


Safer hiPSCs – no integration

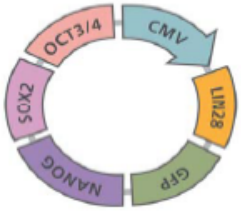
Generation of mouse-induced pluripotent stem cells by transient expression of a single nonviral polycistronic vector

Federico Gonzalez[a], Montserrat Barragan Monasterio[a], Gustavo Tiscornia[a], Nuria Montserrat Pulido[a], Rita Vassena[a], Laura Batlle Morera[a], Ignasi Rodriguez Piza[a], and Juan Carlos Izpisua Belmonte[a,b,1]

2009



STEMcircles™ Protocol



as per Nature Methods paper using human adipose stem cells and human fibroblasts

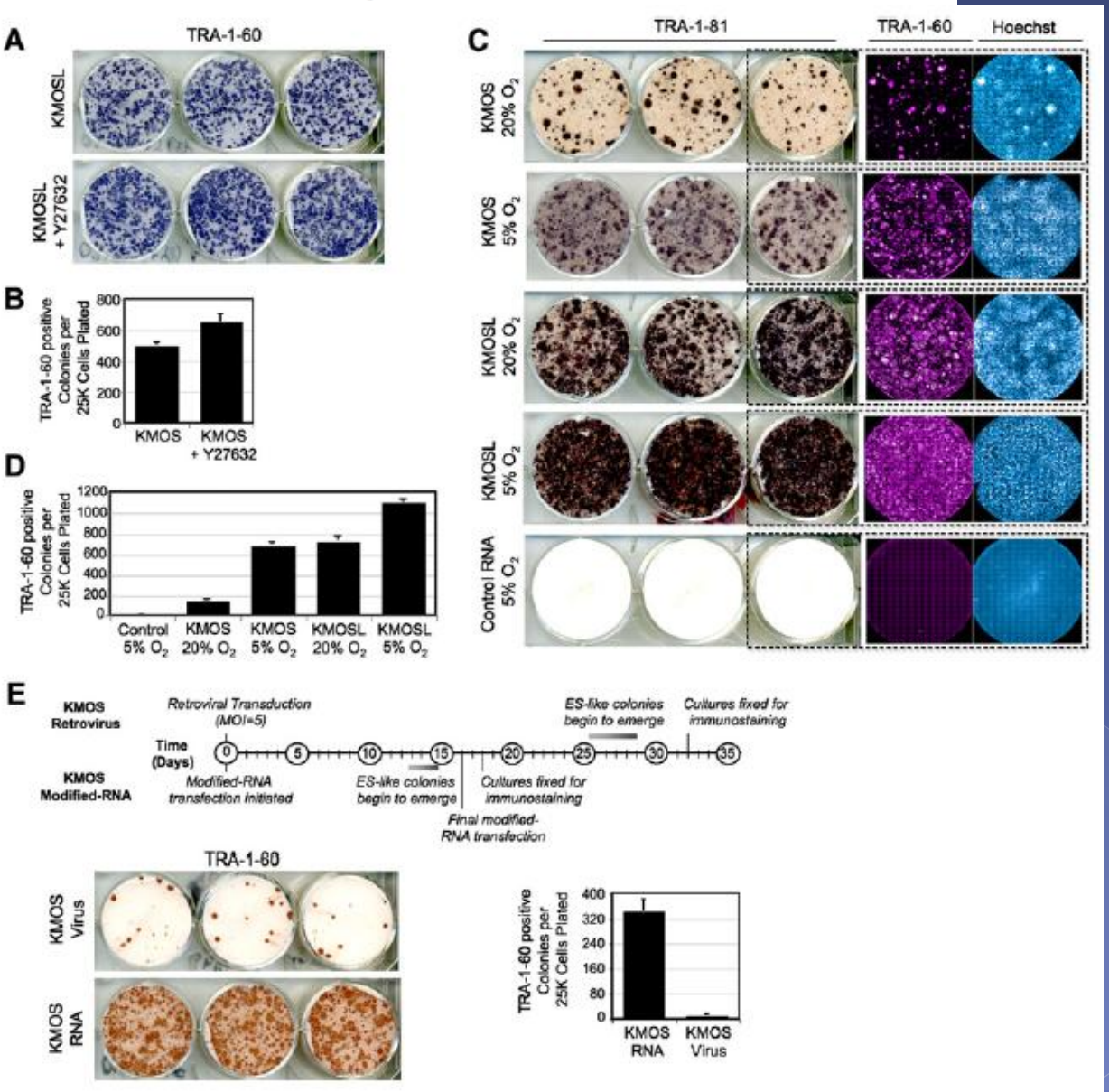
Nature Methods, 7:197-199, Jia et al., 2010,

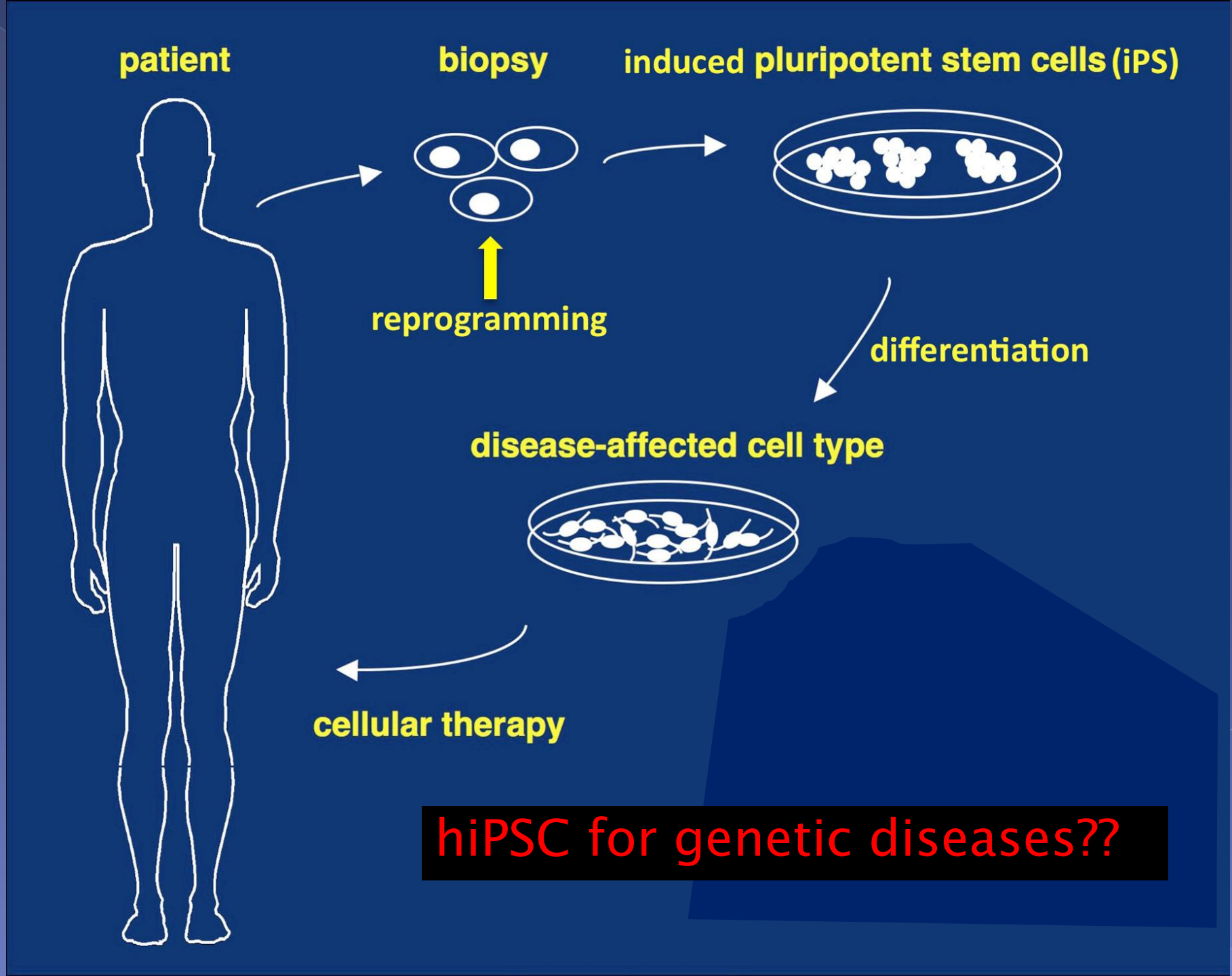
"A non-viral minicircle vector for deriving human IPS cells."

Day 0	• Start with ~**10 x 10^6** hADSCs/or fibroblasts • Transfect/electroporate **5ug** STEMcircles™-LGNSO per 1x 10^6 cells using Amaxa U-023 program • Plate in 10x 10cm dishes (at 1 x 10^6/plate) for 72 hours DMEM/F12 + 10% serum
Day 3	• GFP sort (approx 10% efficiency) • Replate at 0.5 x 10^5-1 x 10^6 cells/well on mouse embryonic fibroblast feeders (MEFs) on gelatin-coated plates in 20% KSR/ KO-DMEM
Day 4	• Re-transfect with 5ug/well using Lipofectamine 2000, media change after 6 h to remove Lipofectamine 2000.
Day 6	• Re-transfect with 5ug/well using Lipofectamine 2000, media change after 6 h to remove Lipofectamine 2000. • Next media change is at Day 8.
Day 10	• Switch media to **mTeSR™1** on the same plate of MEFs. Do not passage or split until ready to pick reprogrammed colonies. • Media change every other day after this.
Day 18-28	• Observe morphology and pick hiPSC colonies when >1000 cells in size & replate on Matrigel™ and in **mTeSR®1** for expansion and characterization. • Reprogrammed colonies should exhibit characteristics of pluripotent cells such as prominent nucleoli and high nucleus to cytoplasm ration.

Safer hiPSCs – no integration

Highly Efficient Reprogramming to Pluripotency and Directed Differentiation of Human Cells with Synthetic Modified mRNA




patient
biopsy
induced pluripotent stem cells (iPS)
reprogramming
differentiation
disease-affected cell type
cellular therapy
hiPSC for genetic diseases??

2007

Treatment of Sickle Cell Anemia Mouse Model with iPS Cells Generated from Autologous Skin

Jacob Hanna,[1] Marius Wernig,[1] Styliani Markoulaki,[1] Chiao-Wang Sun,[2] Alexander Meissner,[1] John P. Cassady,[1,3] Caroline Beard,[1] Tobias Brambrink,[1] Li-Chen Wu,[2] Tim M. Townes,[2]* Rudolf Jaenisch[1,3]*

A

S/hβS iPS line #3 established

Disease-corrected haematopoietic progenitors from Fanconi anaemia induced pluripotent stem cells

Ángel Raya[1,2,3], Ignasi Rodríguez-Pizà[1], Guillermo Guenechea[4,5], Rita Vassena[1], Susana Navarro[4,5], María José Barrero[1], Antonella Consiglio[1,6], Maria Castellà[5,7], Paula Río[4,5], Eduard Sleep[1,3], Federico González[1], Gustavo Tiscornia[1], Elena Garreta[1,3], Trond Aasen[1,3], Anna Veiga[1], Inder M. Verma[8], Jordi Surrallés[5,7], Juan Bueren[4,5] & Juan Carlos Izpisúa Belmonte[1,9]

Genetic correction and analysis of induced pluripotent stem cells from a patient with gyrate atrophy

Sara E. Howden[a,b,c], Athurva Gore[d], Zhe Li[d], Ho-Lim Fung[d], Benjamin S. Nisler[e], Jeff Nie[a], Goukai Chen[a,b,c], Brian E. McIntosh[a,b,c], Daniel R. Gulbranson[a,b,c], Nicole R. Diol[a,b,c], Seth M. Taapken[e], David T. Vereide[a,b,c], Karen Dyer Montgomery[e], Kun Zhang[d], David M. Gamm[f], and James A. Thomson[a,b,c,g,1]

Terapias regenerativas con células madre

Preguntas básicas

Qué célula madre?

EMBRIONARIA

ADULTA

REPROGRAMADA

hiPSC as a DISEASE MODEL

Resource

Cell

Disease-Specific Induced Pluripotent Stem Cells

In-Hyun Park,[1,7] Natasha Arora,[1,7] Hongguang Huo,[1,7] Nimet Maherali,[2,3,7] Tim Ahfeldt,[2,5,7] Akiko Shimamura,[4] M. William Lensch,[1,7,9] Chad Cowan,[2,6,7] Konrad Hochedlinger,[2,7] and George Q. Daley[1,7,8,9,*]

2008

Induced Pluripotent Stem Cells Generated from Patients with ALS Can Be Differentiated into Motor Neurons

John T. Dimos,[1*] Kit T. Rodolfa,[1,2*] Kathy K. Niakan,[1] Laurin M. Weisenthal,[1] Hiroshi Mitsumoto,[3,4] Wendy Chung,[4,5] Gist F. Croft,[4,6] Genevieve Saphier,[1] Rudy Leibel,[5] Robin Goland,[7] Hynek Wichterle,[4,6] Christopher E. Henderson,[4,6] Kevin Eggan[1]†

Cell

Resource

Parkinson's Disease Patient-Derived Induced Pluripotent Stem Cells Free of Viral Reprogramming Factors

Frank Soldner,[1,4] Dirk Hockemeyer,[1,4] Caroline Beard,[1] Qing Gao,[1] George W. Bell,[1] Elizabeth G. Cook,[1] Gunnar Hargus,[3] Alexandra Blak,[3] Oliver Cooper,[3] Maisam Mitalipova,[1] Ole Isacson,[3] and Rudolf Jaenisch[1,2,*]

ARTICLES

Induced pluripotent stem cells from a spinal muscular atrophy patient

Allison D. Ebert[1,2], Junying Yu[3], Ferrill F. Rose Jr[4], Virginia B. Mattis[4], Christian L. Lorson[4], James A. Thomson[2,3,5] & Clive N. Svendsen[1,2,5,6]

nature Vol 461|17 September 2009|doi:10.1038/nature08320

LETTERS

Modelling pathogenesis and treatment of familial dysautonomia using patient-specific iPSCs

Gabsang Lee[1], Eirini P. Papapetrou[2], Hyesoo Kim[1], Stuart M. Chambers[1], Mark J. Tomishima[1,2,3], Christopher A. Fasano[1], Yosif M. Ganat[1,6], Jayanthi Menon[4], Fumiko Shimizu[4], Agnes Viale[5], Viviane Tabar[2,4], Michel Sadelain[2] & Lorenz Studer[1,2,4]

iPS cells generation in patient fibroblasts

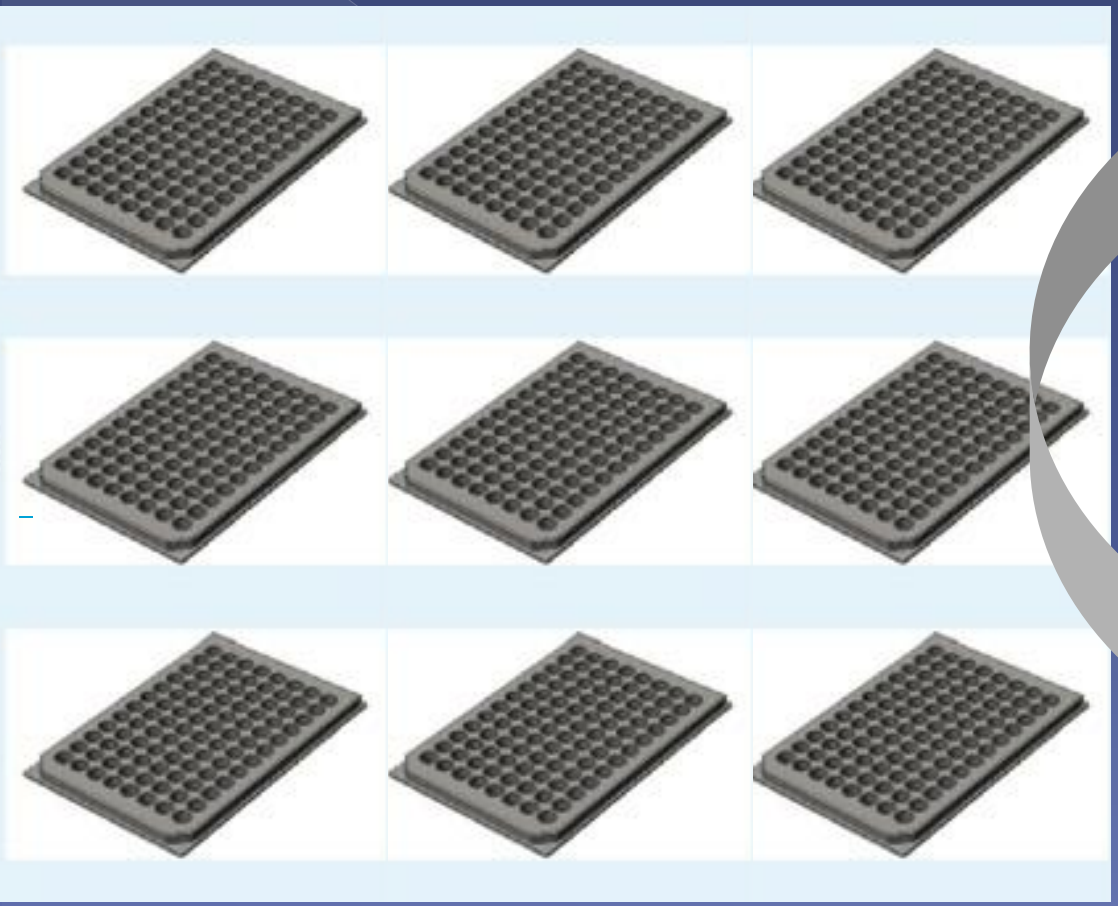
- Parkinson's disease (Wernig and Jaenisch, 2008, Maehr and Melton PNAS 2009).
- Amyopathic Lateral Sclerosis, (Dimos and Eggan Science 2008)
- Type I diabetes (Maehr and Melton PNAS 2009)
- ADA-SCID, SBDS, Gaucher disease, Duchenne and Becker Muscular dystrophin, Parkinson's disease, Huntington disease, JDM, Down syndrome, Lesch-Nyhan syndrome. (Park and Daley Cell 2008).

Gold rush of hiPSCs

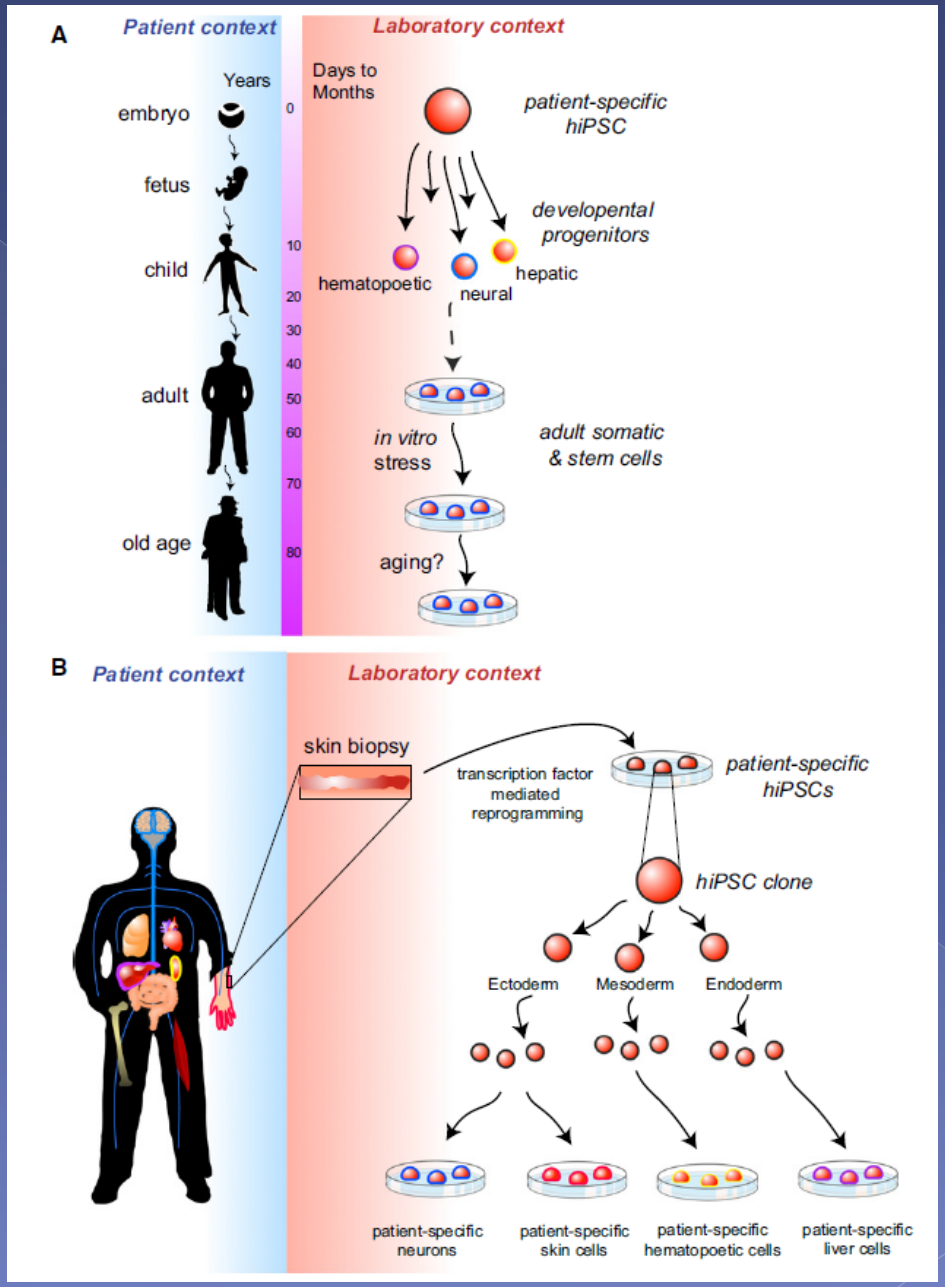
Table 1 Selected companies focused on the commercialization of iPS cells

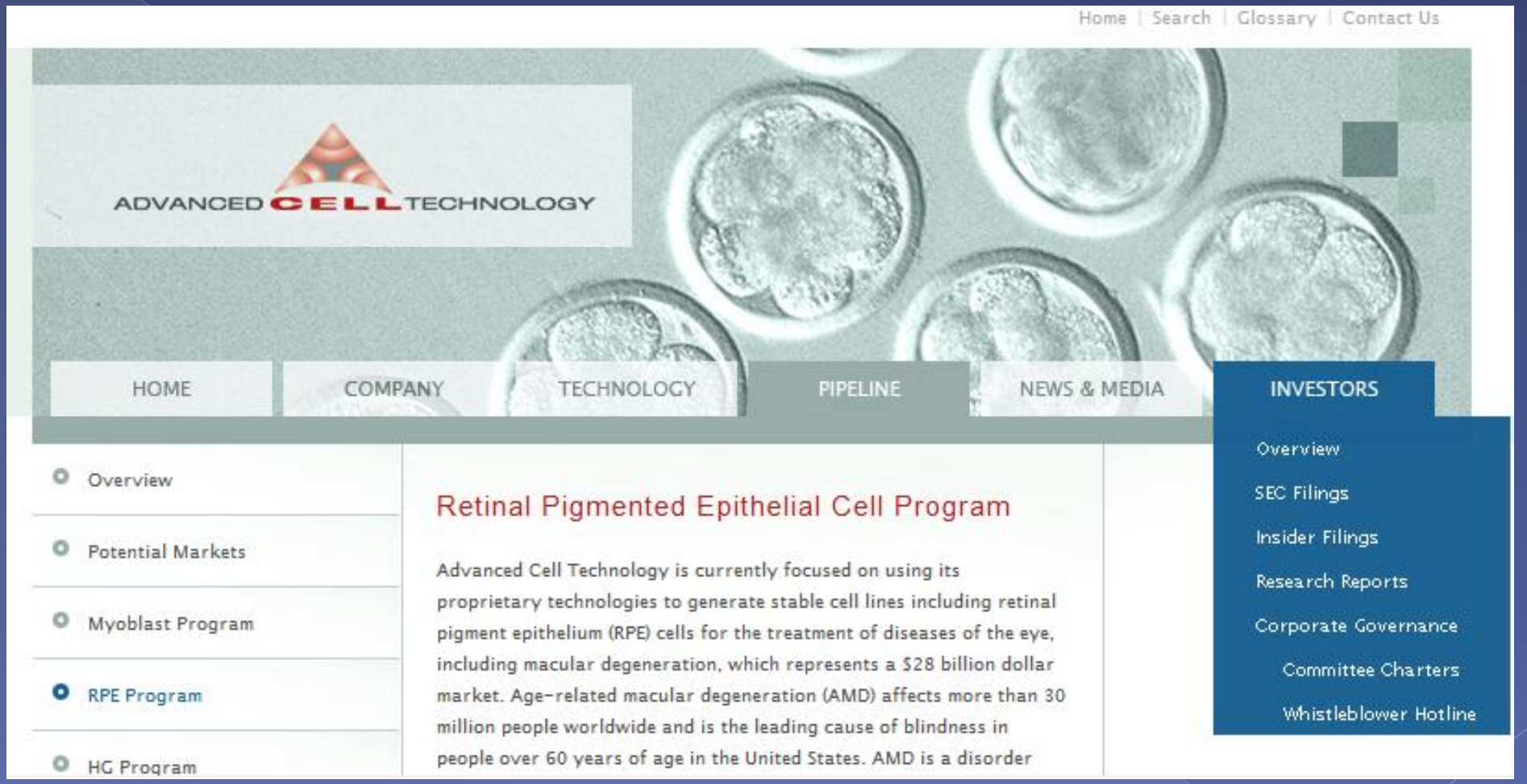
Company	Date founded	Intellectual capital	Venture capital	Focus
Cellular Dynamics International	2004	Founders: James Thomson, Craig January, Timothy Kamp, Igor Slukvin Recent hire: Junying Yu	$18 million Tactics II Stem Cell Ventures, Tactics II Ventures and Wisconsin Alumni Research Foundation	Cardiotoxicity modeling and iPS cell–derived products; industrializing production of iPS cells and cell-based tools
Fate Therapeutics	2007	Founders: Philip Beachy, Sheng Ding, Rudolf Jaenisch, Randall Moon, David Scadden, Leonard Zon	$22.5 million ARCH, Polaris and Venrock	Adult and iPS cell–based therapies; finding small molecules or biologics to guide cell fate to produce therapeutics
iPierian	2009	Scientific advisers include: George Daley, Kevin Eggan, Corey Goodman, Konrad Hochedlinger, Douglas Melton, Lee Rubin, Deepak Srivastava Recent hire: John Dimos	$31.5 million Kleiner Perkins Caufield & Byers, Highland Capital Partners, MPM Capital and FinTech Global Capital	iPS cell–based drug discovery research
Stemgent	2008	Scientific advisers include: Sheng Ding, Rudolf Jaenisch, Gordon Keller, Robert Langer, Douglas Melton, Lee Rubin, Bob Weinberg, Leonard Zon	$14 million HealthCare Ventures, Morgenthaler Ventures	Tools and reagents for iPS and other stem cell research

In Vitro Farmacogenomics

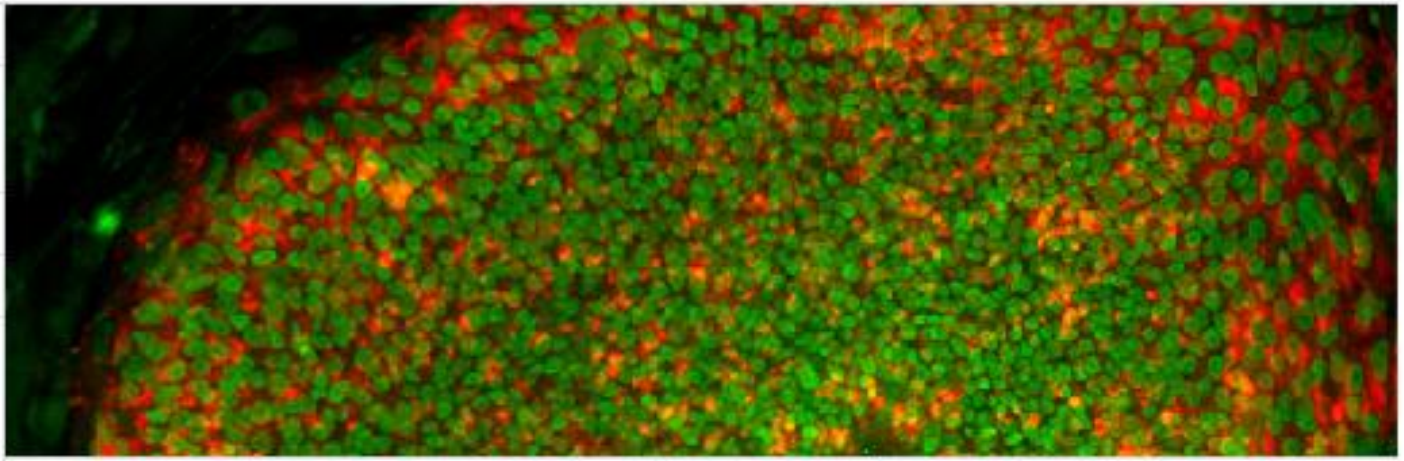


Disease model - challenges




Home | Search | Glossary | Contact Us
ADVANCED CELL TECHNOLOGY
HOME
COMPANY
TECHNOLOGY
PIPELINE
NEWS & MEDIA
INVESTORS
Overview
Potential Markets
Myoblast Program
RPE Program
HG Program
Retinal Pigmented Epithelial Cell Program
Advanced Cell Technology is currently focused on using its proprietary technologies to generate stable cell lines including retinal pigment epithelium (RPE) cells for the treatment of diseases of the eye, including macular degeneration, which represents a $28 billion dollar market. Age-related macular degeneration (AMD) affects more than 30 million people worldwide and is the leading cause of blindness in people over 60 years of age in the United States. AMD is a disorder
Overview
SEC Filings
Insider Filings
Research Reports
Corporate Governance
Committee Charters
Whistleblower Hotline

Overview
Stem Cell Engineering
Cell Encapsulation
Drug Discovery
Resources & Links



Novocell uses directed differentiation to engineer human embryonic stem cells (hESCs) and generate therapeutic cell types. Novocell is a world leader and the first company to engineer hESCs into definitive endoderm, the gatekeeper cells that differentiate into the pancreas, liver and other cells, tissues and organs.

The company is currently developing insulin-producing cells from hESCs and expects to be able to produce large quantities of safe and functional islet cells to treat insulin-dependent type 1 and type 2 diabetics.

geron

visionary therapeutics

recent publications

Nature Reviews Cancer
8:167-179, March 2008

Nature Biotechnology
25:1015-1024, Sept. 2007

news

1/23/2009
Geron Receives FDA Clearance to Begin World's First Human Clinical Trial of Embryonic Stem Cell-Based Therapy...more ⇢

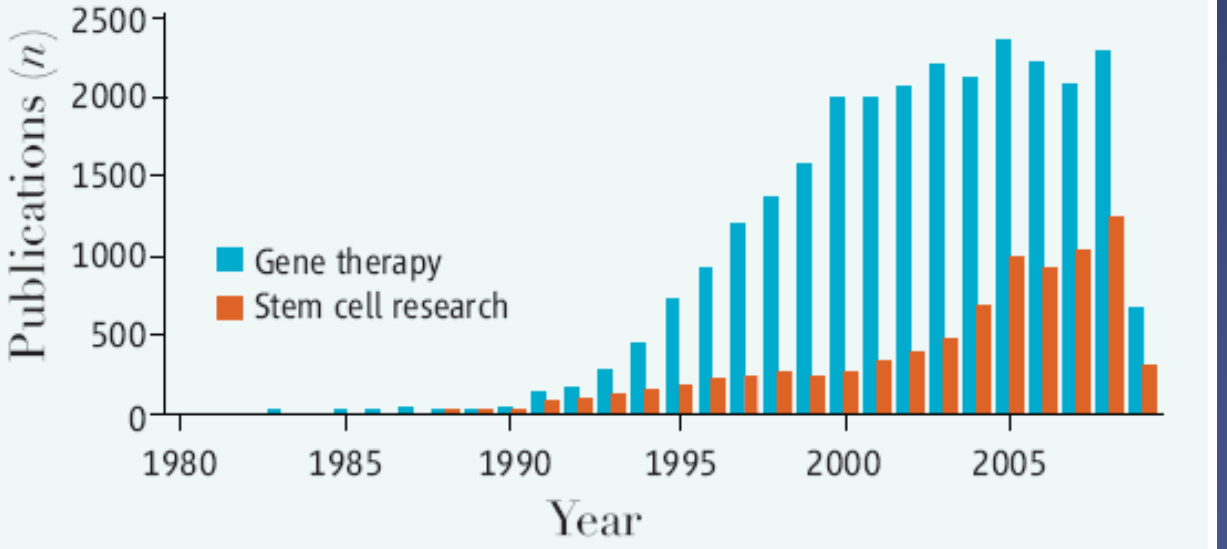
12/8/2008
Geron Presents Interim Clinical Data On Its Telomerase Inhibitor Drug Trial In Patients With Multiple Myeloma...more ⇢

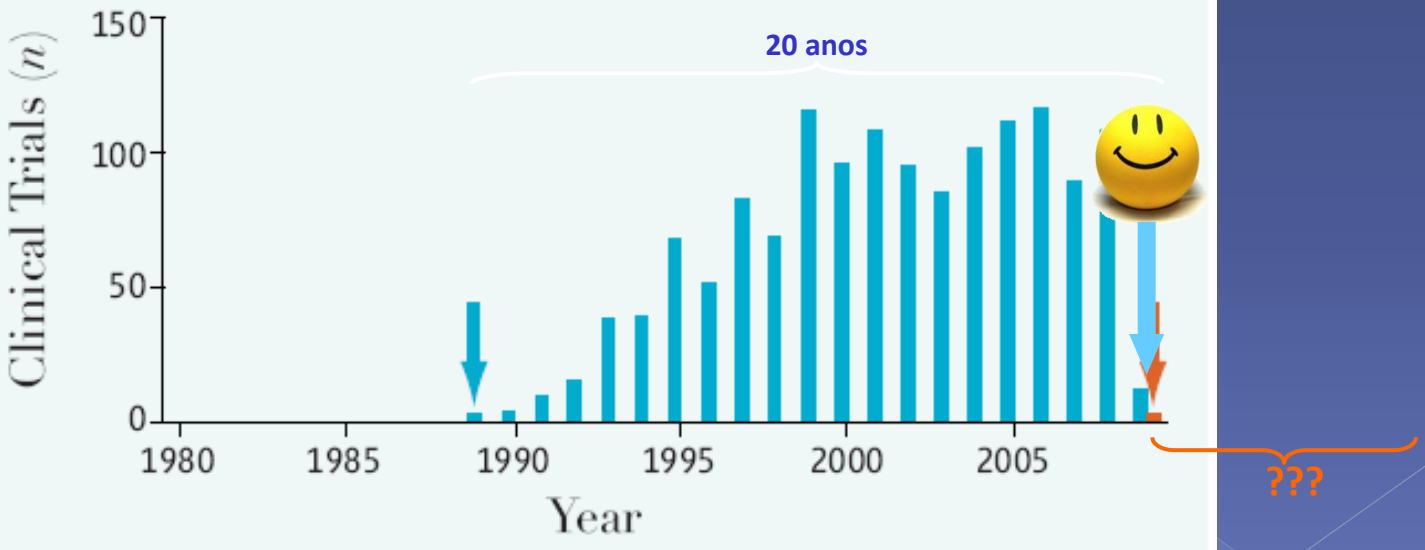
events

January 23, 2009, 6:00 am PT / 9:00 am ET
Geron Discusses FDA Clearance for World's First Human Clinical Trial of Embryonic Stem Cell-Based Therapy, Menlo Park, CA
Click here to access the webcast⇢

Uncommon Medicine / Unlimited Potential

Geron is developing first-in-class biopharmaceuticals for the treatment of cancer and chronic degenerative diseases, including spinal cord injury, heart failure and diabetes. The company is advancing an anti-cancer drug and a cancer vaccine that target the enzyme telomerase through multiple clinical trials. Geron is also the world leader in the development of human embryonic stem (hESC) cell-based therapeutics. The company has received FDA clearance to begin the world's first human clinical trial of a hESC-based therapy: GRNOPC1 for acute spinal cord injury.

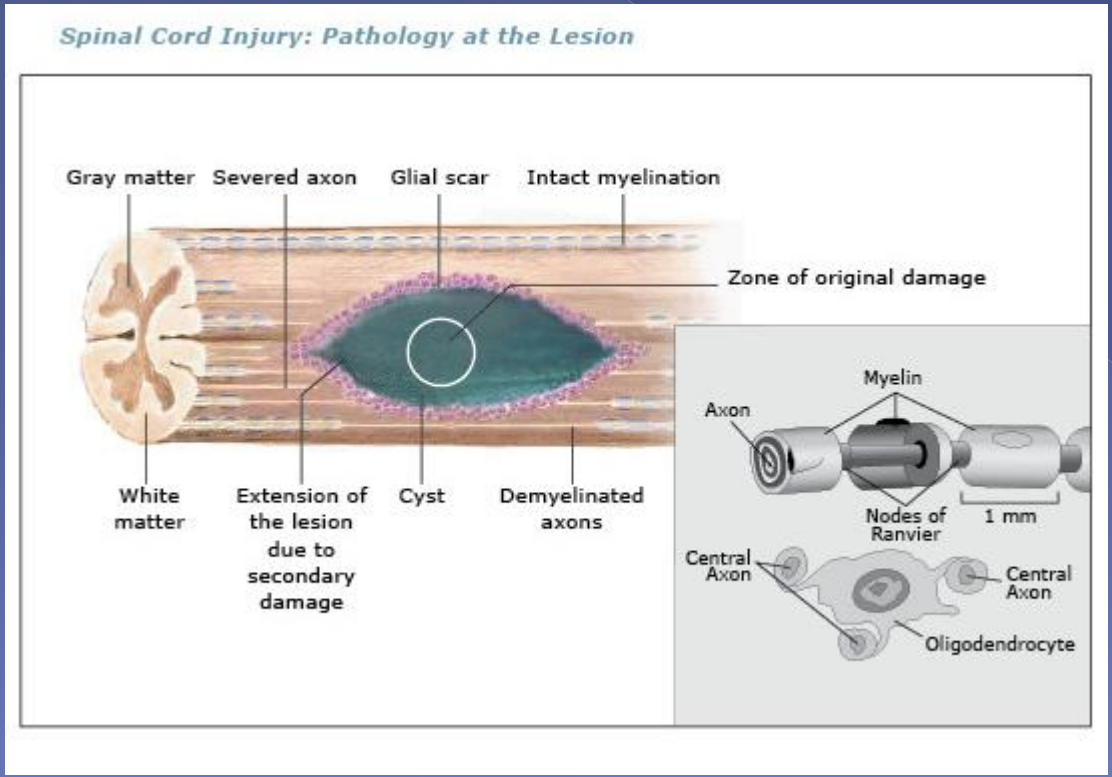




SCIENCE VOL 324 8 MAY 2009

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

The disease
SPINAL CORD INJURY



Associated with inflammation
Loss of neural connection
Loss of oligodendrocytes

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

The cells

Human embryonic stem cells (hESCs) derived from surplus *in vitro* fertilized embryos

Donated for research by the parental donors under informed consent.

The hESC line that is used to produce GRNOPC1 is the H1 line which was derived before August 9, 2001. GRNOPC1 is a population of living cells **containing** oligodendrocyte progenitor cells (OPC).

Studies using this line qualify for U.S. federal research funding, although no federal funding was received for the development of the product or to support the clinical trial.

The existing qualified H1 master cell bank of undifferentiated hESCs could potentially supply sufficient starting material for GRNOPC1 manufacturing to commercially supply the entire spinal cord injury market in the United States for more than 20 years.

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

Preclinical studies

Spinal cord- partially injured animals received either no treatment, control cells or media, or one injection of GRNOPC1 within seven days after injury

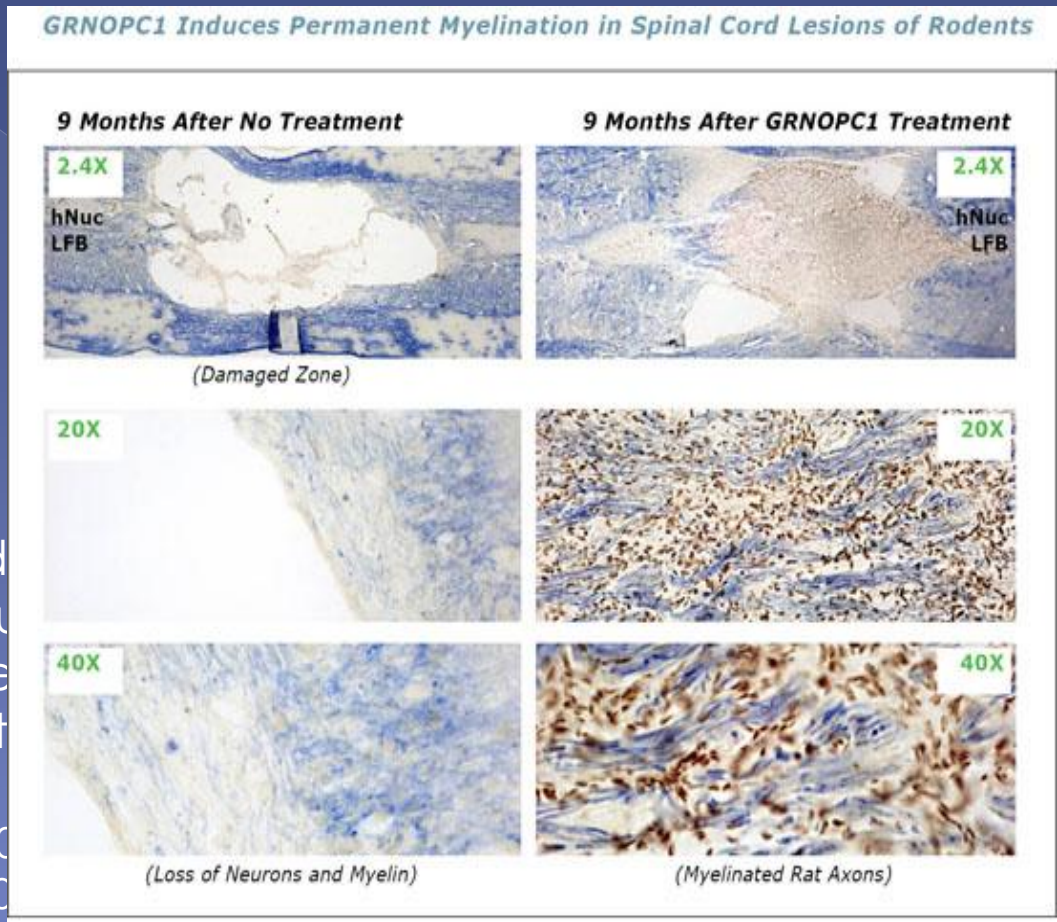
Improved:

1. Hind limb locomotor control
2. Paw placement
3. Stride length
4. Remyelination of axons
5. in the injury site
6. Axonal survival and sprouting

Benefits seen up to 9 months after treatment

Treatment *ineffective* if administered *more than three months* after the inju due to the scarring that occurs in the injured cord as part of the inflammat response to spinal cord injury.

Journal of Neuroscience, Vol. 25, May 200
Stem Cells and Development, Vol. 15, 200



Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

Preclinical TOXICITY studies

IND (Investigational New Drug) application:

24 separate studies in rats and mice
21,000 pages of data from the animal and *in vitro* testing of the cells

Absence of Teratoma Formation
Uninjured and spinal cord-injured animals were studied for **up to 12 months** after a
single injection of clinical grade GRNOPC1.
No teratomas were found in any animal injected in the spinal cord with clinical grade GRNOPC1.
Positive control animals in which teratomas were found included animals that received undifferentiated hESCs or GRNOPC1 preparations that were intentionally contaminated
with at least 5% of live, undifferentiated hESCs.

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

Preclinical TOXICITY studies

Acute or chronic systemic toxicity

No significant systemic toxicity was found:
Multiple hematology, clinical chemistry, urinalysis, and gross and microscopic pathology tests were performed on the spinal cord-injured rats that received GRNOPC1.

GRNOPC1 was not detected outside of the central nervous system in spinal cord-injected animals.
In some animals, human non-neural differentiated cell types were observed in the injury site, which did not lead to adverse consequences.

No evidence of allodynia (pain induced by normally non-noxious stimuli) was detected.
Control and GRNOPC1-treated animals were tested for abnormal behavioral responses to cold and mechanical stimuli placed at, above or below the area of injury.

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

Immunological studies

In vitro studies were performed to test human allogeneic antibody, T cell and NK cell responses to GRNOPC1.
GRNOPC1 was incubated with serum and cell samples from normal healthy volunteers and analyzed for either GRNOPC1 lysis or T cell proliferation.
GRNOPC1 does not have major susceptibility to direct humoral or cell-mediated alloimmune attack.

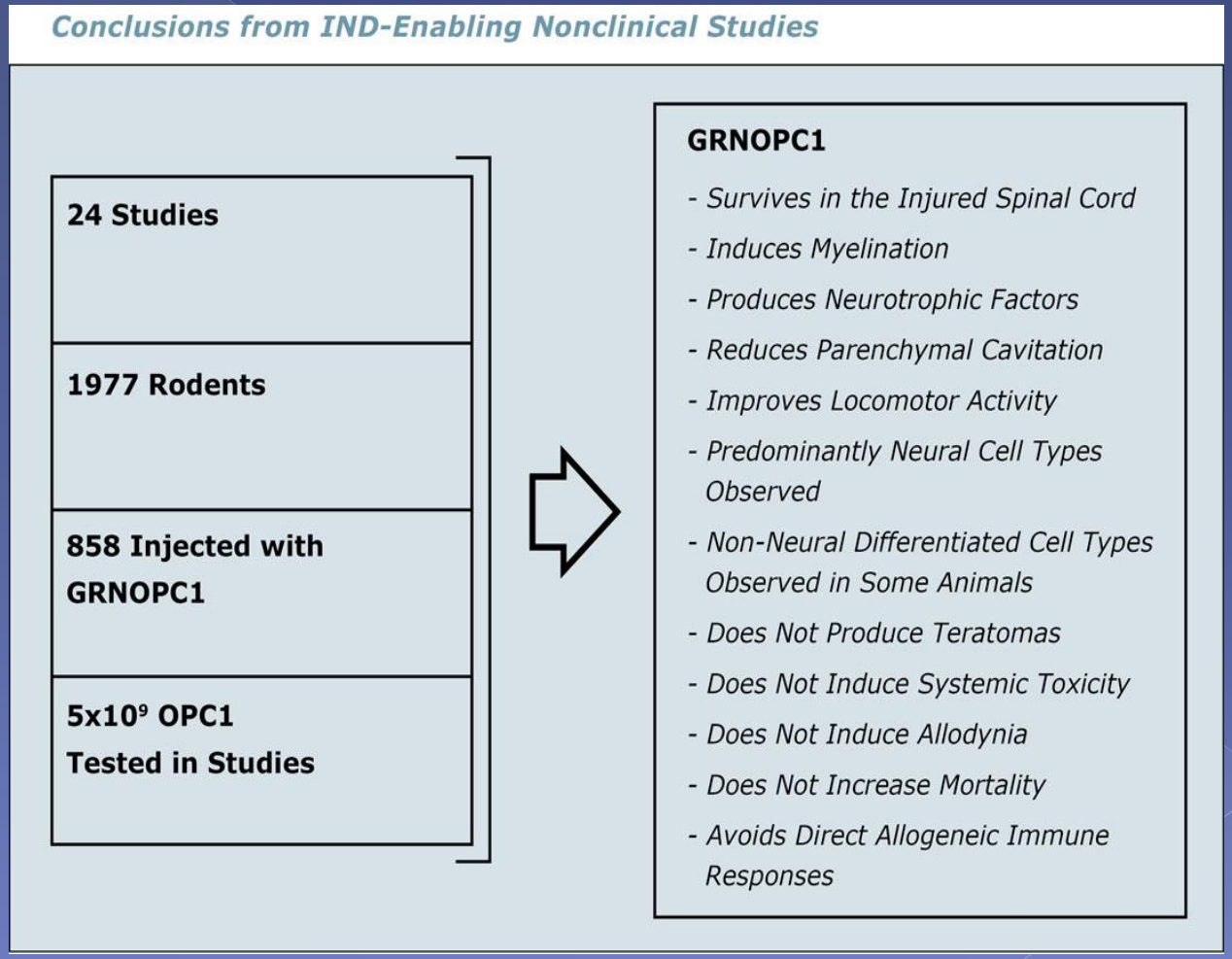
These results serve as the rationale for short-term administration of **low-dose immunosuppression** in the clinical protocol.

***Journal of Neuroimmunology*, Vol. 192, 2007**

No in vivo data?

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

Preclinical studies- Summary



Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

The FDA-approved clinical study is a Phase I multi-center trial designed to assess the safety and tolerability of GRNOPC1 in patients with complete ASIA (American Spinal Injury Association) grade A thoracic spinal cord injuries.

ASIA grading scale - grade A: most severe with complete loss of locomotor and sensory activity below the site of the injury. Most such patients do not recover function or respond significantly to physical therapy.

The therapeutic protocol is also limited to subjects with subacute injuries - injuries that can be treated with GRNOPC1 within seven to 14 days after the injury (more than 3 months> too late).

The primary endpoint of the study is safety

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

The primary endpoint of the study is safety

Standardized physical examinations and neurological testing will be administered before and after the injection of GRNOPC1 at specified time points for one year after the injection

The secondary endpoint of efficacy: return of sensory function or lower extremity motor function for one year after injection of GRNOPC1.

Subjects will be immune-suppressed from the time of injection with low-dose tacrolimus for 46 days, at which time the immune suppression will be tapered and withdrawn at 60 days.

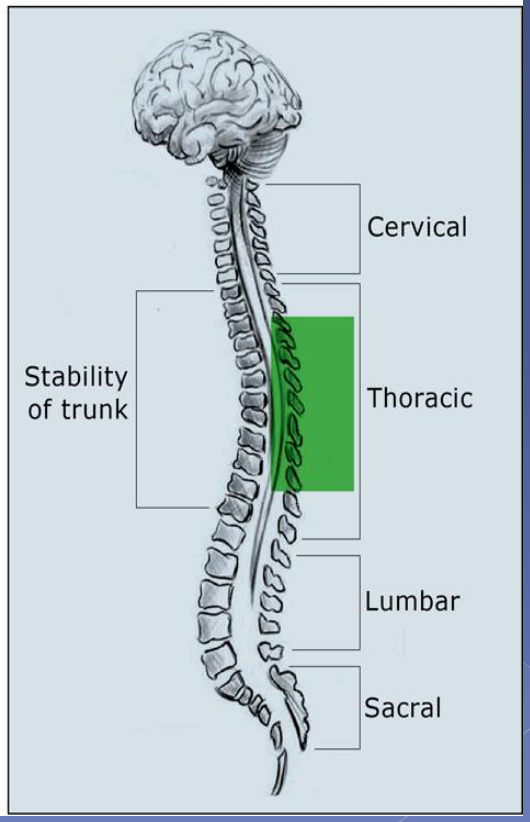
Subjects will be monitored for a total of **15 years** after they are administered GRNOPC1.

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

Clinical- Summary

GRNOPC1 Phase 1 Multi-Center Spinal Cord Injury Trial

- **Open Label Trial**
- **Subacute, Functionally Complete Spinal Cord Injury with a Neurological Level of T3 to T10**
- **2x10^6 Cells**
- **Transplant 7-14 Days Post Injury**
- **Temporary Immunosuppression with Low Dose Tacrolimus**
- **Primary Endpoint: Safety**
  - *Neurological*
  - *Overall*
- **Secondary Endpoint: Efficacy**
  - *ASIA Sensory Score*
  - *Lower Extremity Motor Score*



Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

Public reactions

Political

"I think this approval is directly tied to the change in administration," said Robert N
the chairman of California's $3 billion stem cell research program. He said he thou
Bush administration had pressured the F.D.A. to delay the trial.
F.D.A. denies this statement.

Scientific

"It would be a disaster, a nightmare, if we ran into …. problems in this very first trial," said Dr. John A. Kessler, the chairman of neurology and director of the stem cell institute at Northwestern University.
Dr. Kessler, whose own daughter was paralyzed from the waist down in a skiing accident, said he thought Geron's therapy was not the ideal candidate for the first trial. He said results showing the therapy worked in **moderately injured animals** might not apply to more seriously injured people.

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

Public reactions

Scientific

"We really want the best trial to be done for this first trial, and this might not be it," Dr. Kessler said.

The main safety concern is that if raw embryonic cells are put into the body, they can form **tumors.** Even though most such tumors do not spread like other cancers, any unwanted growth in the spinal cord can further damage nerves.

"It's not ready for prime time, at least not in my mind, until we can be assured that the transplanted stem cells have completely lost the capacity for tumorogenicity," said Dr. Steven Goldman, chairman of neurology at the University of Rochester. He was a member a committee convened by the F.D.A. last April to examine the safety aspects of trials using therapies from embryonic stem cells.

Clinical Trial
Human embryonic –derived oligodendrocytes for spinal cord injury

Geron, which was formed in 1990 as an antiaging company, is still in the development stage and is not yet profitable, having lost about $500 million since its inception. Besides working on stem cells, it is testing drugs for cancer that influence telomeres, the caps on the ends of chromosomes that help control the aging of cells. Geron's market value is about $400 million.

Annual Direct Expenditures in the U.S. for Selected Diseases

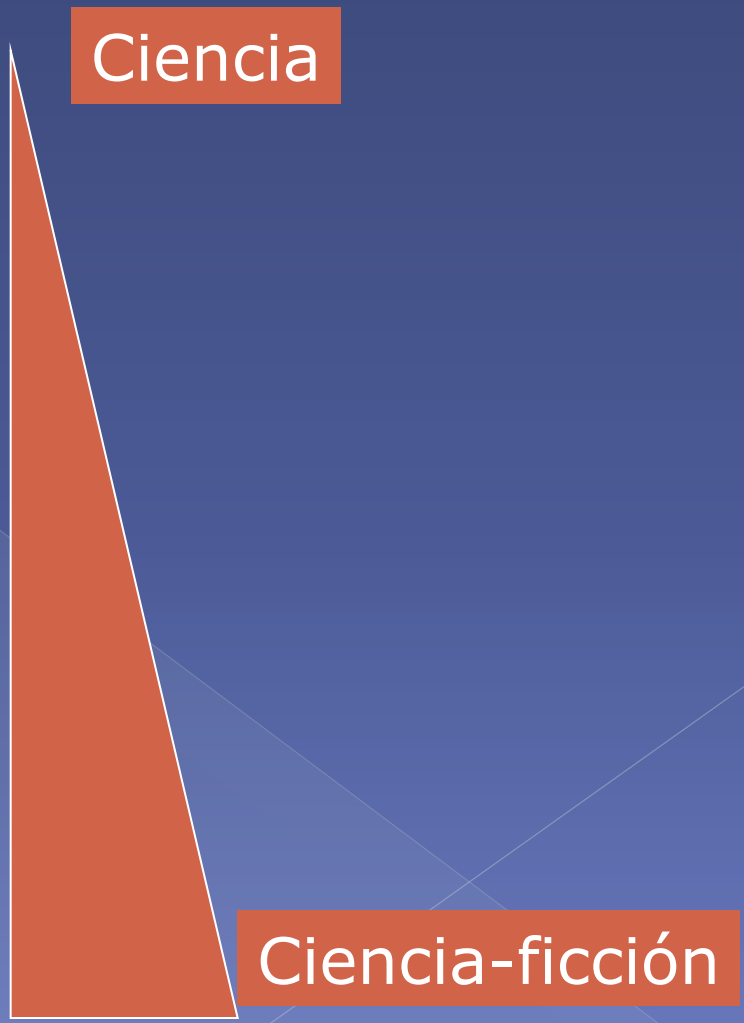
Diseases	Expenditures
Diabetes	$45,000,000,000[1]
Alzheimer's	$100,000,000,000[2]
Stroke	$30,000,000,000[3]
Chronic Liver Disease	$25,000,000,000[4]
Spinal Cord Injury	$10,000,000,000[5]
Parkinson's Disease	$6,500,000,000[6]

Terapias regenerativas con células madre

Enfermedades de la sangre

Enfermedades cardíacas

Enfermedades neurodegenerativas



Turismo de célula madre

Stem-cell experts raise concerns about medical tourism

Stem-cell therapies are emerging as a growing area of medical tourism, even while research is still in its early stages. The trend is causing concern among experts. Eliza Barclay investigates.

Stem-cell experts are worried that some doctors in developing countries are treating patients with adult stem cells without waiting for clinical trials to validate the safety of using them for health problems.

In treatments using adult stem cells, the cells are injected into the blood, the lumbar region, or damaged tissue. The only treatments using adult stem cells that are proven by trials are for blood disorders, bone marrow transplantation, and rare immune deficiencies. Current clinical trials are mostly focused on heart disease.

The International Society for Stem Cell Research (ISSCR), in late 2008, released guidelines for patients who are seeking stem-cell treatments from unlicensed doctors overseas in increasing numbers. The guidelines insist that all treatments must be expertly evaluated with independent oversight. They also advocate for an informed consent process to provide patients with information about stem-cell-based treatments, and transparency in reporting of trial results.

therapy for multiple sclerosis, he says that many patients do not want to wait. "This area is going to progress a lot in the next 10–15 years, but a lot of patients need therapeutic help now and want to go through with the procedure", Brenes says. "Our doctors explain to the patients that they are undergoing a fairly safe procedure."

> "There are many doctors tapping into the public's sense of stem cells' potential to cure..."

But many stem-cell experts are worried that doctors like Brenes are proceeding recklessly by doing unproven therapies that may have negative consequences for patients. "There are many doctors tapping into the public's sense of stem cells' potential to cure in countries with looser medical regulations", said Sean Morrison, director of the University of Michigan Center for Stem Cell Biology, and treasurer of ISSCR. "But the details of stem-cell treatment are much more complicated."

cell treatment in Russia may have contributed to the growth of brain tumours.

In the February issue of *PLoS Medicine*, Israeli researchers from Sheba Medical Center in Tel Aviv detailed the first case of a human brain tumour related to neural stem-cell therapy. The patient, a young Israeli boy with a rare degenerative brain disease, ataxia telangiectasia, received several injections of fetal neural stem cells at a clinic in Moscow beginning in 2001. According to Gideon Rechavi, one of the study's investigators, he and other doctors at Sheba who had attended to the boy in Tel Aviv advised the family not to travel to Moscow for the treatment.

In 2005, the boy's brain was scanned in Tel Aviv because of recurring headaches, revealing abnormal growths in his brain and spinal cord. Later studies showed that the tumour was of nonhost origin indicating it was probably derived from the transplanted neural stem cells, according to *PLoS Medicine*.

www.thelancet.com Vol 373 March 14, 2009

POLICYFORUM

MEDICINE

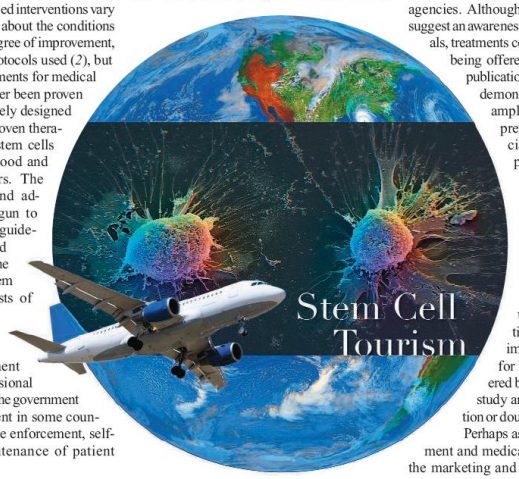
Monitoring and Regulating Offshore Stem Cell Clinics

Unverified medical treatments based on stem cells are proliferating and need oversight.

Sorapop Kiatpongsan[1,2,3] and Douglas Sipp[4,5]*

Traveling to another country in the hope of finding a stem cell–based treatment for a disease—"stem cell tourism"—has been the object of intense scrutiny in recent years, following reports of charlatanry, baseless claims, and adverse medical events (*1*). Providers of stem cell–based interventions vary widely in their assertions about the conditions that can be treated, the degree of improvement, and the cell types and protocols used (*2*), but there are many advertisements for medical procedures that have never been proven efficacious in appropriately designed clinical trials. To date, proven therapeutic applications for stem cells have been mainly for blood and immunological disorders. The scientific community and advocacy groups have begun to respond by formulating guidelines for physicians and scientists engaged in the clinical translation of stem cell research (*3*) and lists of questions for prospective patients to ask when considering an experimental stem cell treatment (*3*, *4*). Inaction and occasional complicity on the part of the government and medical establishment in some countries, however, have made enforcement, self-policing, and the maintenance of patient trust problematic.

that can legally be made by providers or to relegate them to operating outside of their borders. The possibility of operating extraterritorially has meant that unapproved treatments could be had by those willing to travel abroad, but in the great majority of instances, this has



IBRIMAGES; PLANE: ISTOCKPHOTO; (STEM CELLS) PETER ARNOLD, INC./ALAMY

Netherlands (*9*), and Ireland (*10*); others have been forced out of business (*11*) or prevented from opening by negative publicity (*12*, *13*).

Successful clinics that remain in business are sometimes supported by local medical associations, governments, and regulatory agencies. Although the company Web sites suggest an awareness of the need for clinical trials, treatments costing $20,000 or more are being offered in the absence of prior publication of peer-reviewed studies demonstrating efficacy. For example, TheraVitae has an impressive list of Thai physicians, including the current presidents of the Thai Heart Association and the Thai Atherosclerosis Society (*14*), and recognition from the Davos-based World Economic Forum as a 2006 Technology Pioneer (*15*). However, the peer-reviewed article listed by the company as "accreditation" for its therapeutic regime of adult stem cell therapy for heart disease was considered by the authors to be a safety study and did not use randomization or double-blind controls (*16*, *17*). Perhaps as important as the government and medical establishment links are the marketing and patient recruitment stra-

TREATABLE CONDITIONS

Beike has already considerable experience with certain conditions. Below is a list of diseases and conditions we currently offer treatment for.

Neurological Disorders:

- Alexander Syndrome
- Alzheimer's disease
- Ataxia
  - Cerebellar ataxia
  - Hereditary ataxias
    - Spinocerebellar ataxia
    - Friedreich ataxia
  - Acquired ataxia (caused by Spinocerebellar atrophy or Degeneration, Olivoponto cerebellar atrophy, etc.)
- Autism Spectrum Disorders
  - Autism
  - Rett Syndrome
- Disseminated Encephalomyelitis (Sequelae)
- Agenesis of the Corpus Callosum/Aicardi Syndrome
- Brown-Sequard syndrome
- Central Cord Syndrome
- Central Pain Syndrome
- Central Pontine Myelinolysis
- Cerebellar Hypoplasia
- Cerebral Atrophy
- Chiari Malformation
- Cerebral Palsy
- Charcot-Marie-Tooth disease
- Chronic Inflammatory Demyelinating Polyneuropathy
- Down Syndrome
- Encephalopathy
- Encephalitis (Sequelae)
- Early Infantile Epileptic Encephalopathy (Ohtahara Syndrome)
- Glycogen Storage Disease Type II (Pompe Disease)
- Guillain-Barr Syndrome
- Huntington's Disease
- Kennedy's Disease (X-Linked Spinal and Bulbar Muscular Atrophy)
- Landau-Kleffner Syndrome (Acquired Epileptiform Aphasia)
- Lissencephaly
- Leber's hereditary optic neuropathy
- Meningitis (Sequelae)
- Motor Neuron Disease
  - Amyotrophic Lateral Sclerosis
  - Primary Lateral Sclerosis
  - Spinal Muscular Atrophy
- Microcephaly
- Multisystem Atrophy
- Multiple Sclerosis
- Muscular Dystrophy
  - Becker's Muscular Dystrophy
  - Duchenne Muscular Dystrophy
  - Progressive Muscular Dystrophy
- Myoclonic Encephalopathy of Infants
- Myopathy
- Neuronal Ceroid lipofuscinosis
- Neurotoxicity
- Optic Nerve Disorders
  - Optic Nerve Hypoplasia
  - Optic Atrophy
  - Damage to the Optic Nerve
  - Ischemic Optic Neuropathy
- Parkinson's Syndrome
- Peripheral nerve injury
- Perisylvian Syndrome
- Persistent Vegetative State
- Polymicrogyria
- Post-polio Syndrome
- Schizencephaly
- Septo-Optic Dysplasia
- Spastic Tetraparesis
- Spina Bifida
- Spinal Cord Injury
- Stroke
- Traumatic Brain Injury (Sequelae)
- West Nile Meningitis or Encephalitis
- West Syndrome (Infantile Spasms)
- William's Syndrome

Heart Conditions:

- Cardiomyopathy
- Chronic Heart Failure
- Myocardial Infarction (Sequelae)

Other Disorders:

- Alopecia, Arthritis, Autoimmune Disease, Chronic Renal Failure, Diabetic Foot, Diabetes Mellitus, Femoral Head Necrosis, Leber's Congenital Amaurosis, Liver Cirrhosis, Glaucoma, Graft Versus Host disease, Lower Limb Ischemia, Osteopetrosis, Peripheral Vascular Disease, Retinitis Pigmentosa, Retinopathy of Prematurity, Sensorineural Hearing Loss

Beike Biotech, China

Las terapias con células madre no son inocuas

OPEN ACCESS Freely available online

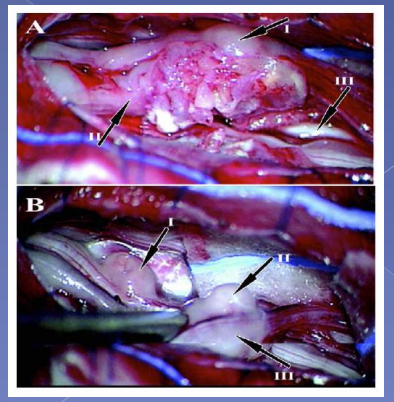
PLOS MEDICINE

Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient

Ninette Amariglio[1,2], Abraham Hirshberg[3], Bernd W. Scheithauer[4], Yoram Cohen[1], Ron Loewenthal[5], Luba Trakhtenbrot[2], Nurit Paz[1], Maya Koren-Michowitz[2], Dalia Waldman[6], Leonor Leider-Trejo[7], Amos Toren[6], Shlomi Constantini[8], Gideon Rechavi[1,6*]

1 Cancer Research Center, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel, **2** Institute of Hematology, Sheba Medical Center, Tel Hashomer, Israel, **3** Department of Oral Pathology, School of Dental Medicine, Tel Aviv University, Tel-Aviv, Israel, **4** Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, United States of America, **5** Tissue Typing Laboratory, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel, **6** Department of Pediatric Hemato-Oncology, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel, **7** Institute of Pathology, Tel-Aviv Medical Center, Tel-Aviv, Israel, **8** Pediatric Neurosurgery, Dana Children's Hospital, Tel-Aviv Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel

February 2009 | Volume 6 | Issue 2 | e1000029



Angiomyeloproliferative Lesions Following Autologous Stem Cell Therapy

Duangpen Thirabanjasak,* Kavirach Tantiwongse,† and Paul Scott Thorner*‡§

Departments of *Pathology and †Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; ‡Division of Pathology, Hospital for Sick Children, Toronto, Canada; and §Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

J Am Soc Nephrol 21: ●●●–●●●, 2010. doi: 10.1681/ASN.2009111156

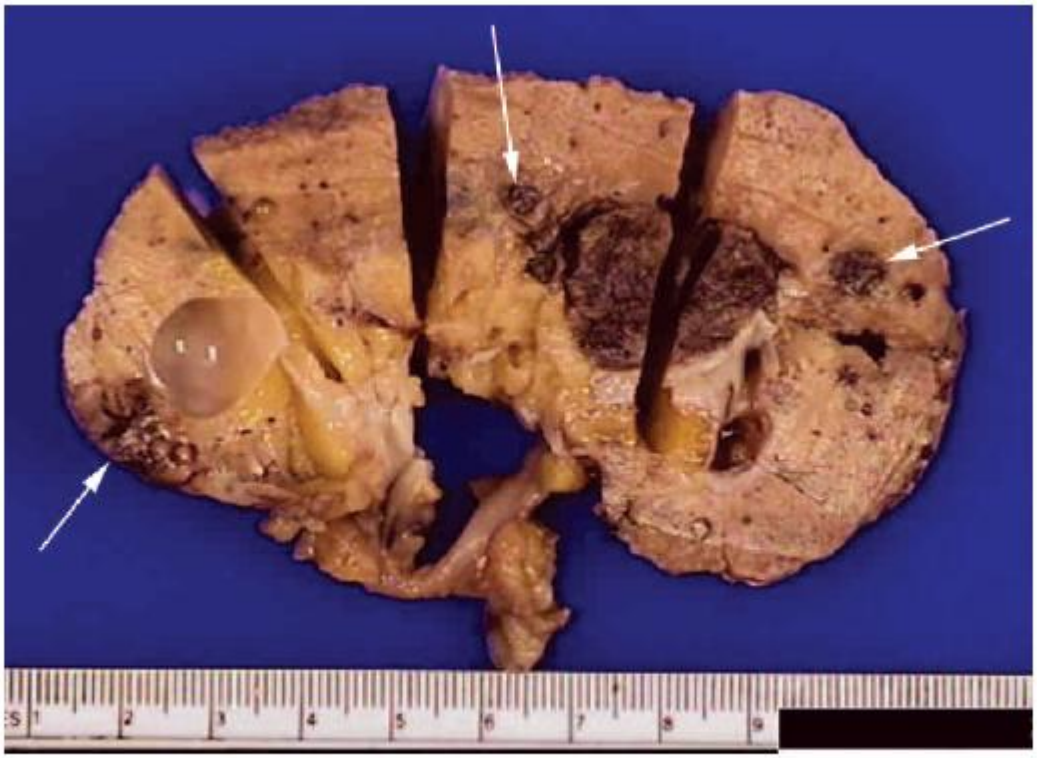


Figure 1. Macroscopic appearance of resected kidney. A solid hemorrhagic mass is present in the renal sinus, external to which is atrophic renal parenchyma. In addition, three similar smaller lesions are present (arrows), separate from the main lesion.

No existe evidencia experimental en modelos animales que sustenten estudios clínicos de terapias regenerativas para enfermedades neurológicas utilizando células madre hematopoyéticas

La fusión causa confusión y algunos la aprovechan

NUEVO ENSAYO CLÍNICO UTILIZANDO CÉLULAS MADRE:

GRATUITO

AUTORIZADO POR EL INCUCAI

Terapias regenerativas con células madre en Argentina

Comisión Asesora en células madre y terapias regenerativas

Objetivo: ASESORAMIENTO/INVESTIGACIÓN/DIFUSIÓN

Presidente: Min. Lino Barañao

Coordinadora: Fabiana Arzuaga - H. Cámara de Diputados de la Nación

Miembros:

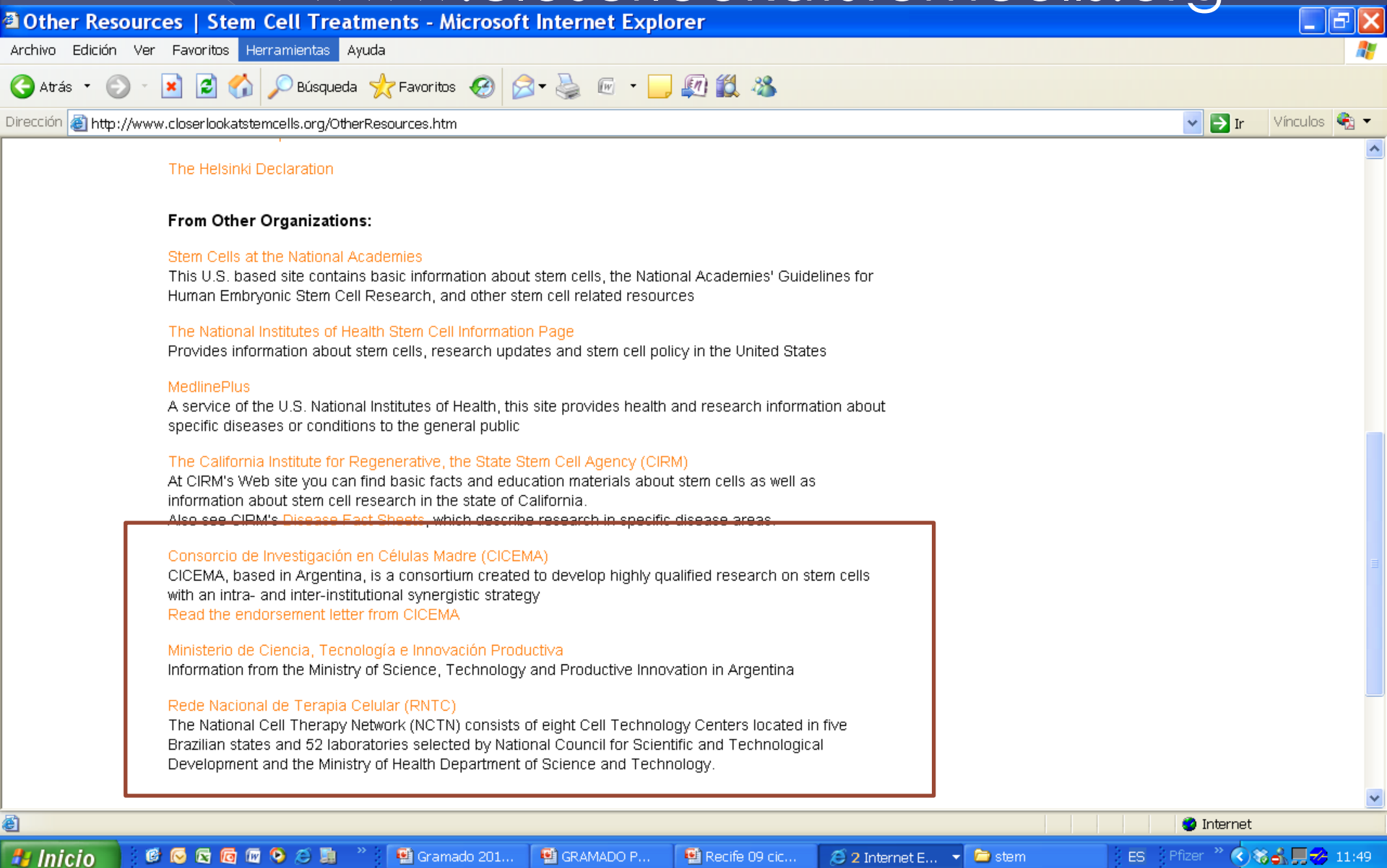
Pablo Argibay- Hospital Italiano-CONICET
Salvador Bergel- UBA
Roberto Coco -FECUNDITAS
Ana del Pozo- Hospital Garrahan
Gustavo Kusminsky- Hospital Austral
Florencia Luna-CONICET-FLACSO
Jorge Peralta- INCUCAI-UBA
Fernando Pitossi –Instituto Leloir-CONICET
Osvaldo Podhajcer-Instituto Leloir-CONICET
Patricia Saidón- Hospital Ramos Mejía
Martín Seoane- (ANMAT)
Gustavo Sevlever –FLENI
Susana Sommer – UBA

http://www.mincyt.gov.ar

ISSCR TASK FORCE
www.closerlookatstemcells.org

ISSCR TASK FORCE

www.closerlookatstemcells.org



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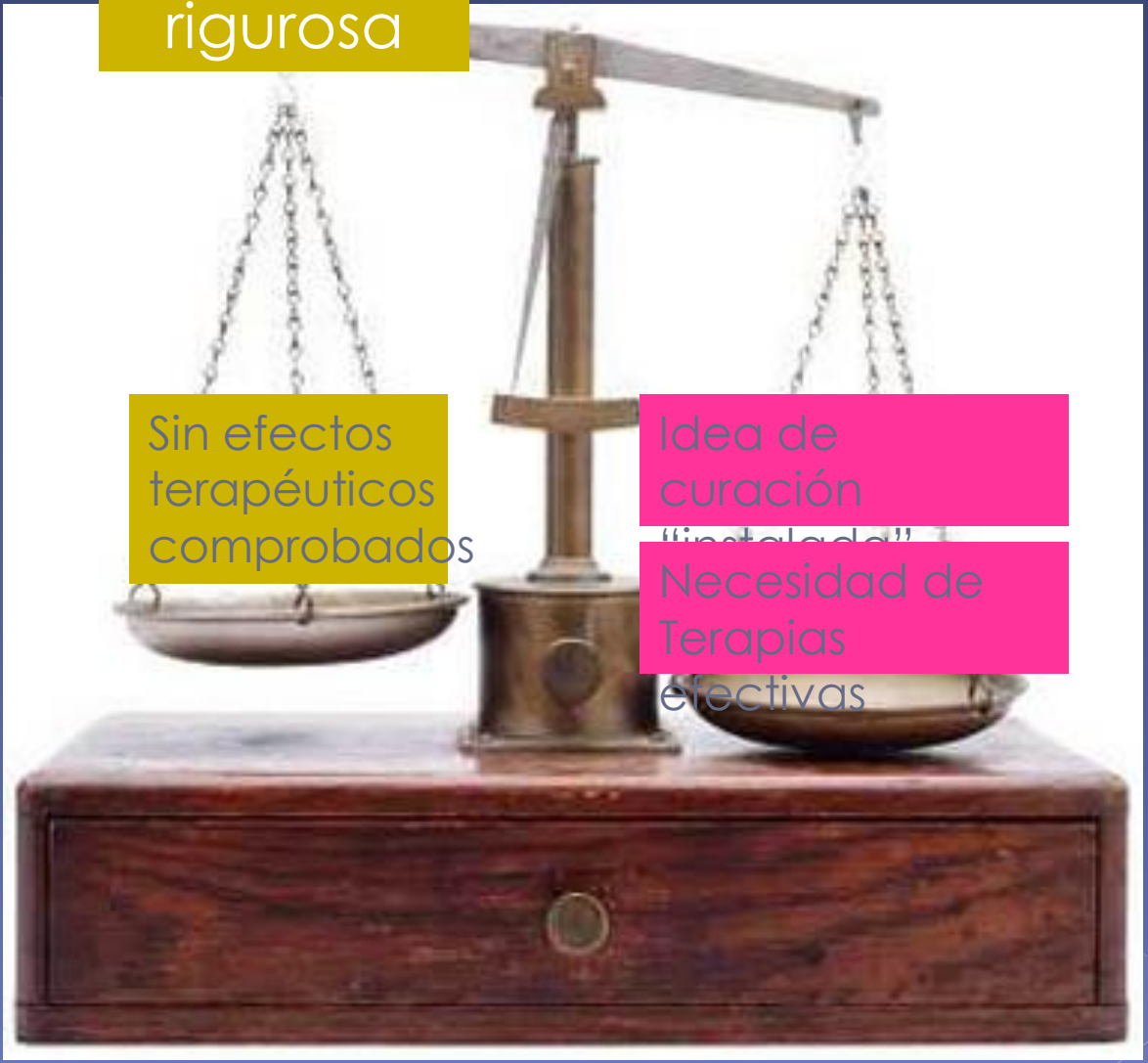
Visión

Información rigurosa



Visión


Alta potencialidad
Información rigurosa
Efectos terapéuticos comprobados
Idea de cura instalada
Necesidad de Terapias efectivas