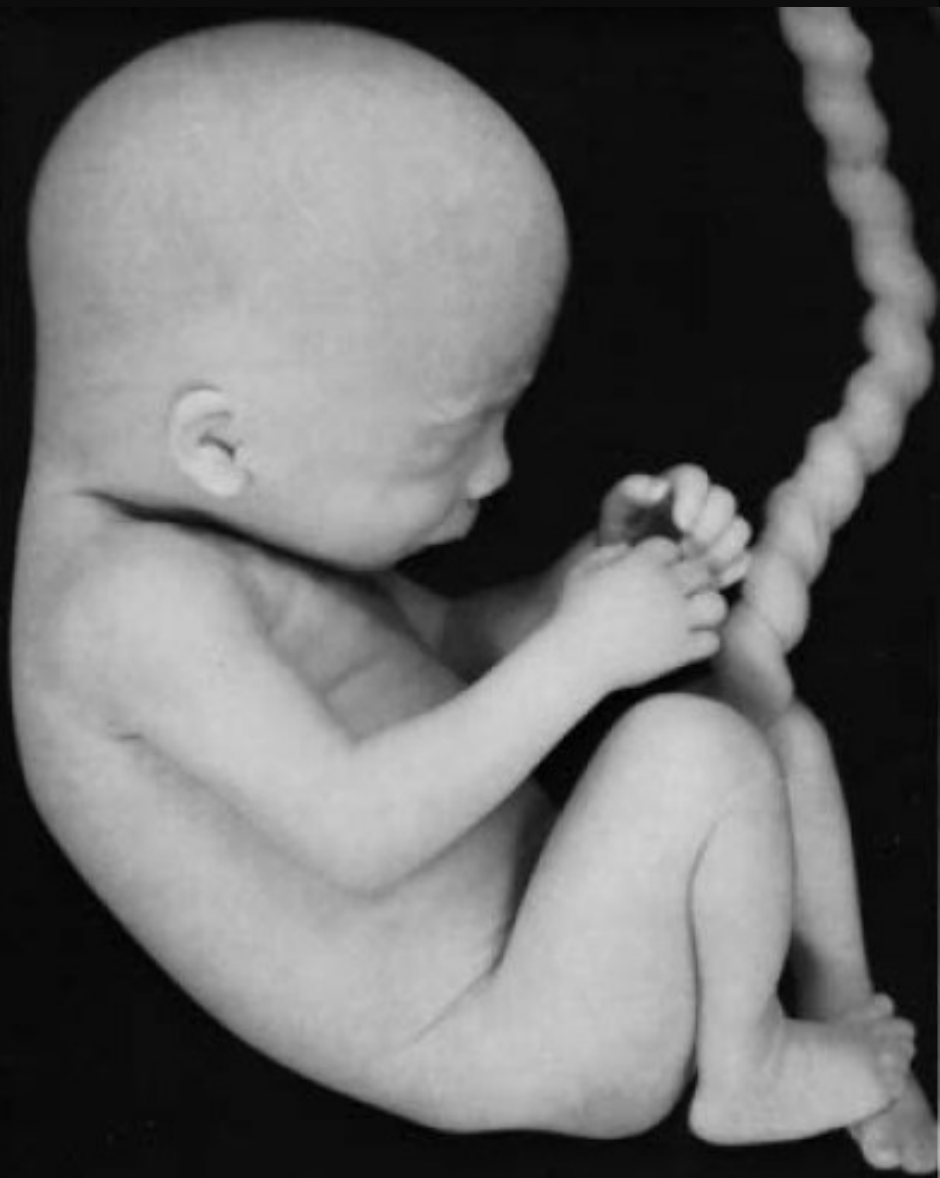
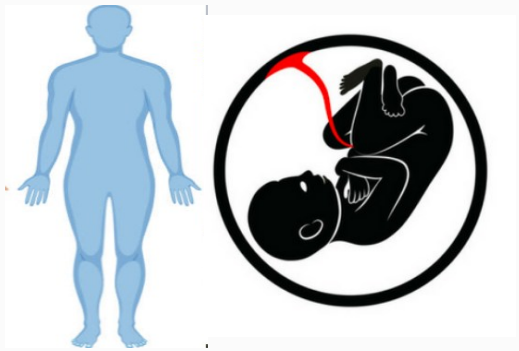
Βιολογία Βλαστοκυττάρων και Αναγέννησης

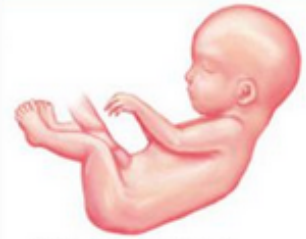


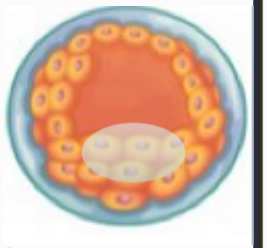
Γιατί τα ESC ;

Μ. Γρηγορίου 2025

Βλαστοκύτταρα: τύποι







όλους του σώματος

Απόγονοί τους διαφοροποιούνται σε **μερικούς κυτταρικούς τύπους** του σώματος

Πολυδύναμα ή ολιγοδύναμα

Απόγονοί τους διαφοροποιούνται σε **πολλούς κυτταρικούς τύπους** του σώματος

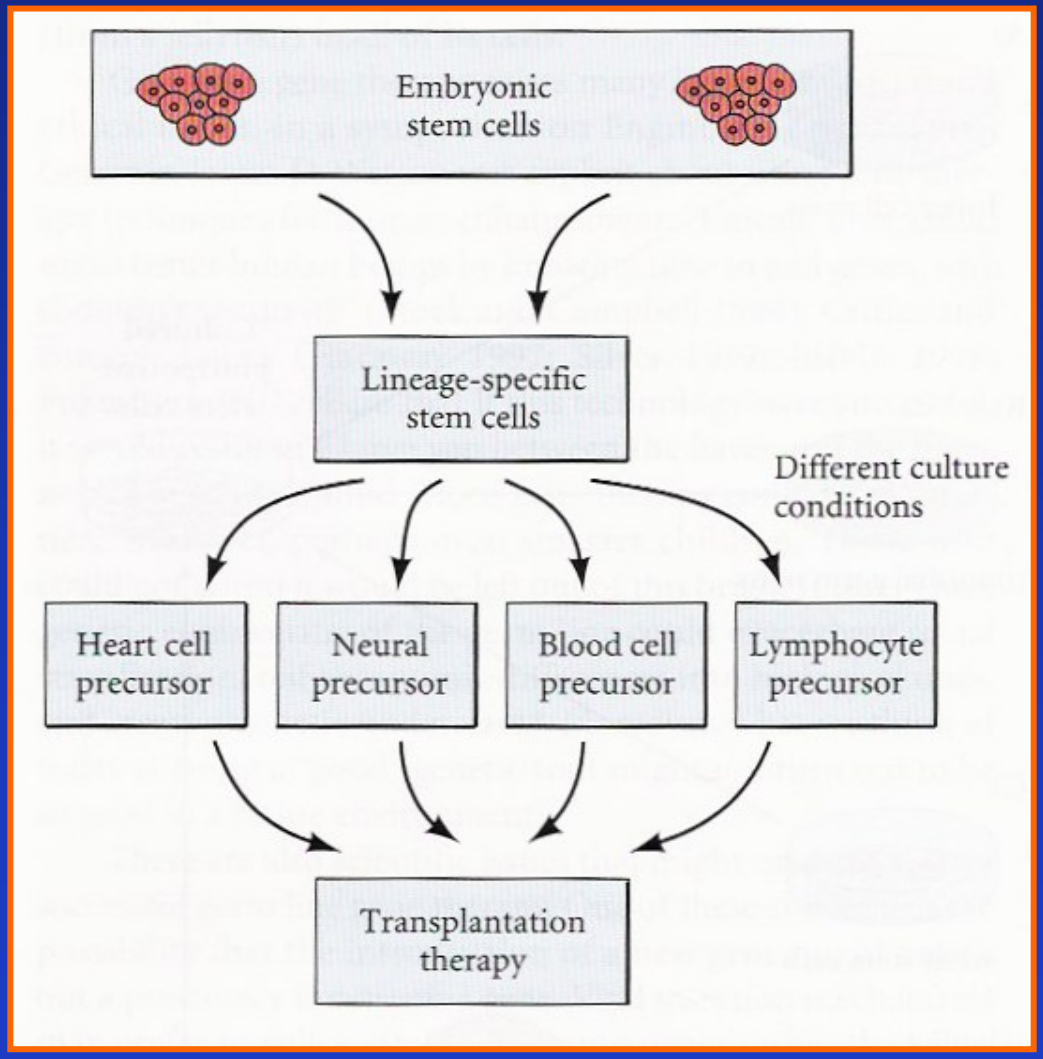
πολυδύναμα

Απόγονοί τους διαφοροποιούνται σε **όλους τους κυτταρικούς τύπους**

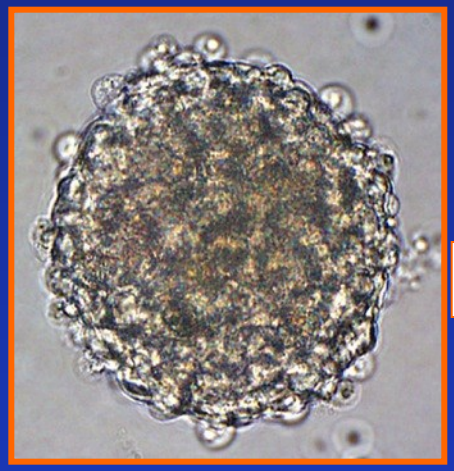
ολοδύναμα

Αυτοανανέωση – παραγωγή απογόνων που ανήκουν σε διαφορετικούς κυτταρικούς τύπους

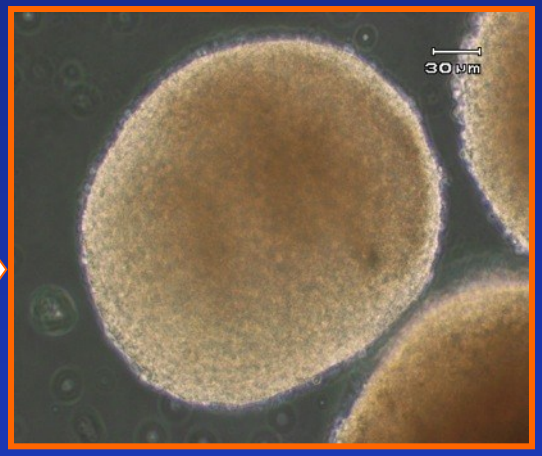
Τα ESC μπορούν κάτω από κατάλληλες συνθήκες να διαφοροποιηθούν in vitro σε διάφορους κυτταρικούς τύπους



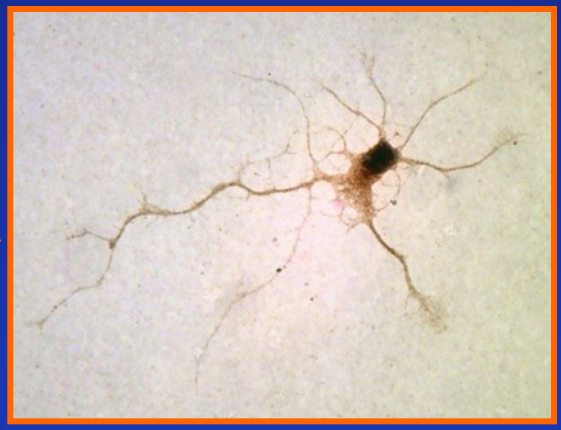
Τα ESC μπορούν κάτω από κατάλληλες συνθήκες να διαφοροποιηθούν *in vitro* σε διάφορους κυτταρικούς τύπους



ES

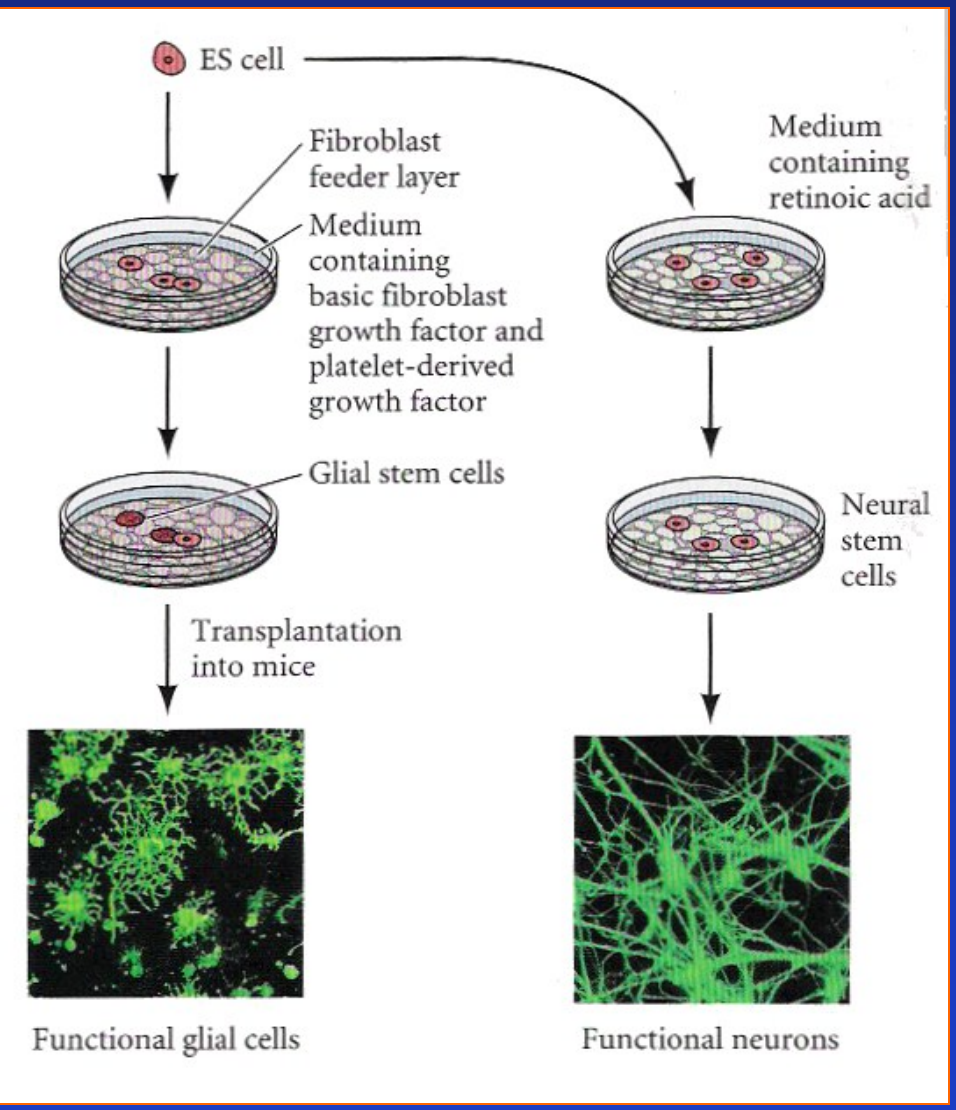


Νευροσφαιρίδια



Πρόδρομα ολιγοδενδροκύτταρα

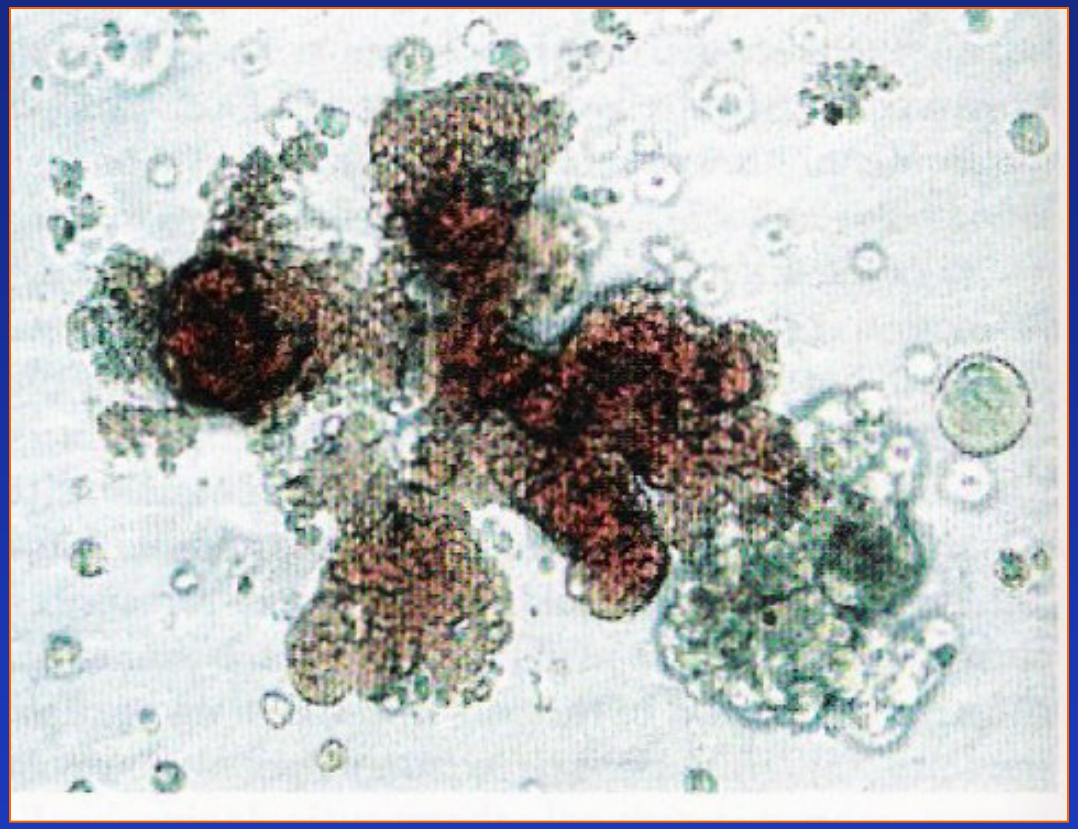
Τα ESC μπορούν κάτω από κατάλληλες συνθήκες να διαφοροποιηθούν *in vitro* σε διάφορους κυτταρικούς τύπους



Εμβρυϊκά βλαστοκύτταρα ποντικού μπορούν να καλλιεργηθούν και να διαφοροποιηθούν *in vitro* σε διάφορους κυτταρικούς τύπους.

Δίπλα: παρουσία bFGF και PDGF τα ES διαφοροποιούνται σε κύτταρα γλοίας ενώ παρουσία RA σε νευρώνες.

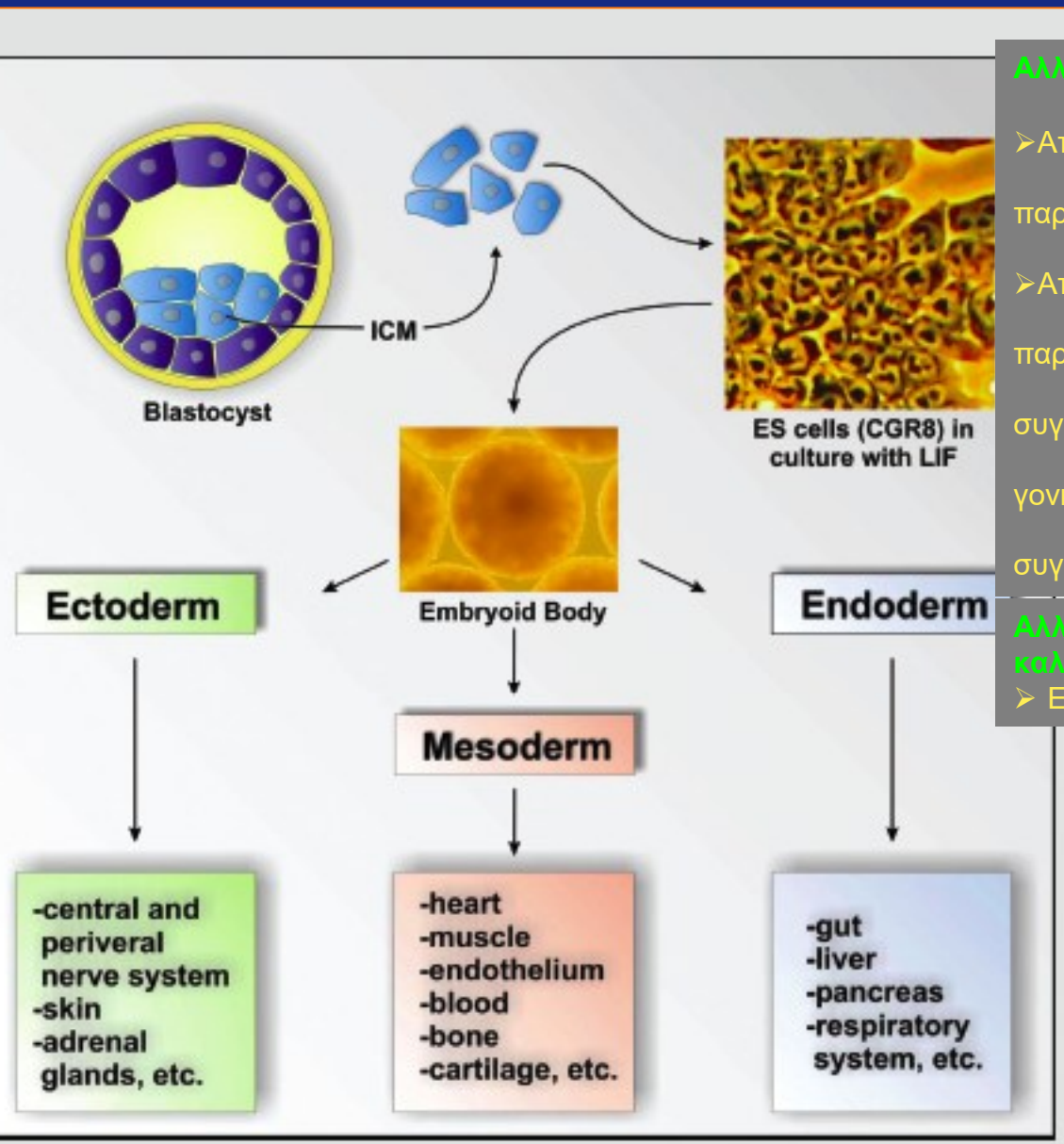
Τα ESC μπορούν κάτω από κατάλληλες συνθήκες να διαφοροποιηθούν *in vitro* σε διάφορους κυτταρικούς τύπους



Εμβρυϊκά βλαστοκύτταρα ανθρώπου μπορούν να καλλιεργηθούν και να διαφοροποιηθούν *in vitro* σε διάφορους κυτταρικούς τύπους.

Πάνω: Ανθρώπινα εμβρυϊκά βλαστοκύτταρα μπορούν να διαφοροποιηθούν σε κύτταρα του αίματος εάν καλλιεργηθούν πάνω σε μυελό των οστών ή ενδοθηλιακά κύτταρα ποντικού.

Διαφοροποίηση εμβρυϊκών βλαστικών κυττάρων- ΠΡΩΤΟΚΟΛΛΑ



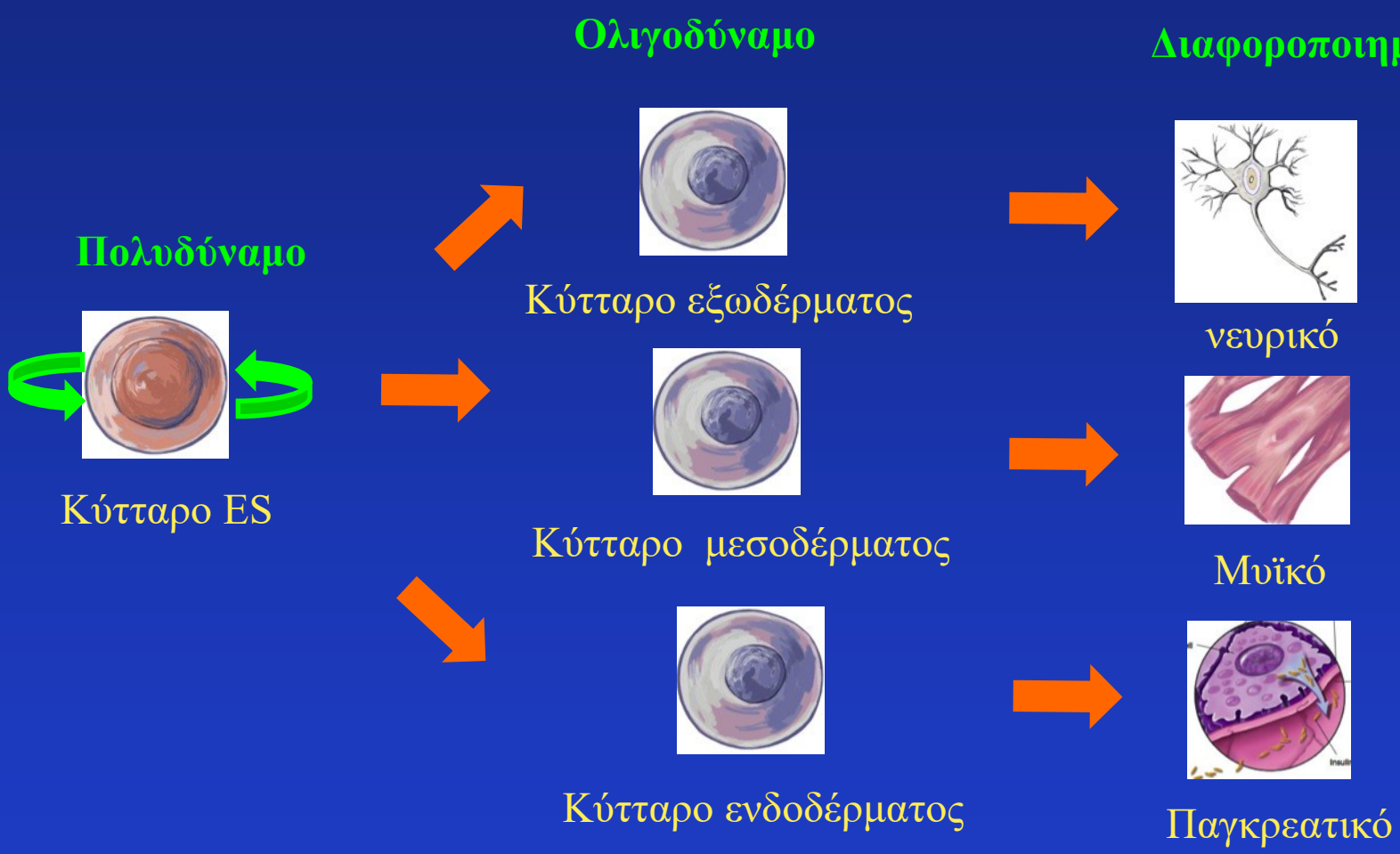
Αλλαγή των συνθηκών καλλιέργειας

- Απομάκρυνση από το θρεπτικό μέσον των διαχυτών παραγόντων που διατηρούν την πολυδυναμία
- Απομάκρυνση από το θρεπτικό μέσον των διαχυτών παραγόντων που προάγουν τη διαφοροποίηση προς συγκεκριμένη γενεαλογία ή Ενεργοποίηση/απενεργοποίηση γονιδίων που προάγουν τη διαφοροποίηση προς συγκεκριμένη γενεαλογία .

Αλλαγή της επιφάνειας ή/και του υποστρώματος καλλιέργειας

- Εμβρυϊκά σωμάτια

Τα ESC μπορούν κάτω από κατάλληλες συνθήκες να διαφοροποιηθούν *in vitro* σε διάφορους κυτταρικούς τύπους



Αξιοποίηση μονοπατιών –διαφοροποίηση ανάπτυξη

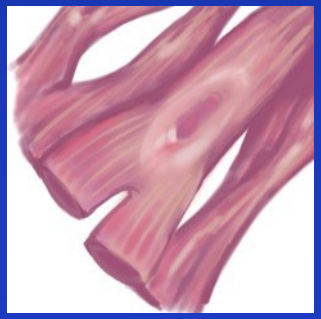
Shh

Πρόδρομο κυτταρο

Κινητικός νευρώνας

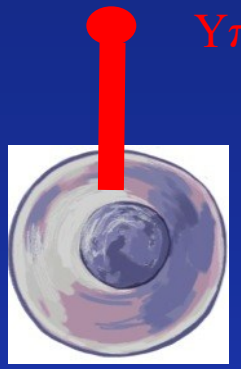
Activin/TGF-β

Πρόδρομο κυτταρο

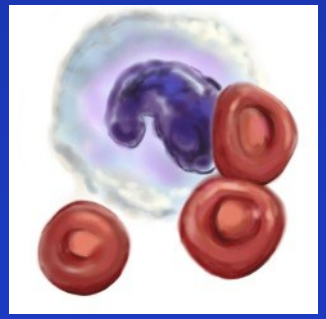


Κύτταρο του καρδιακού μυός

Erythropoietin (EPO)



Πρόδρομο κυτταρο



Ερυθροκύτταρο

Αξιοποίηση μορίων – διαφοροποίηση ανάπτυξη

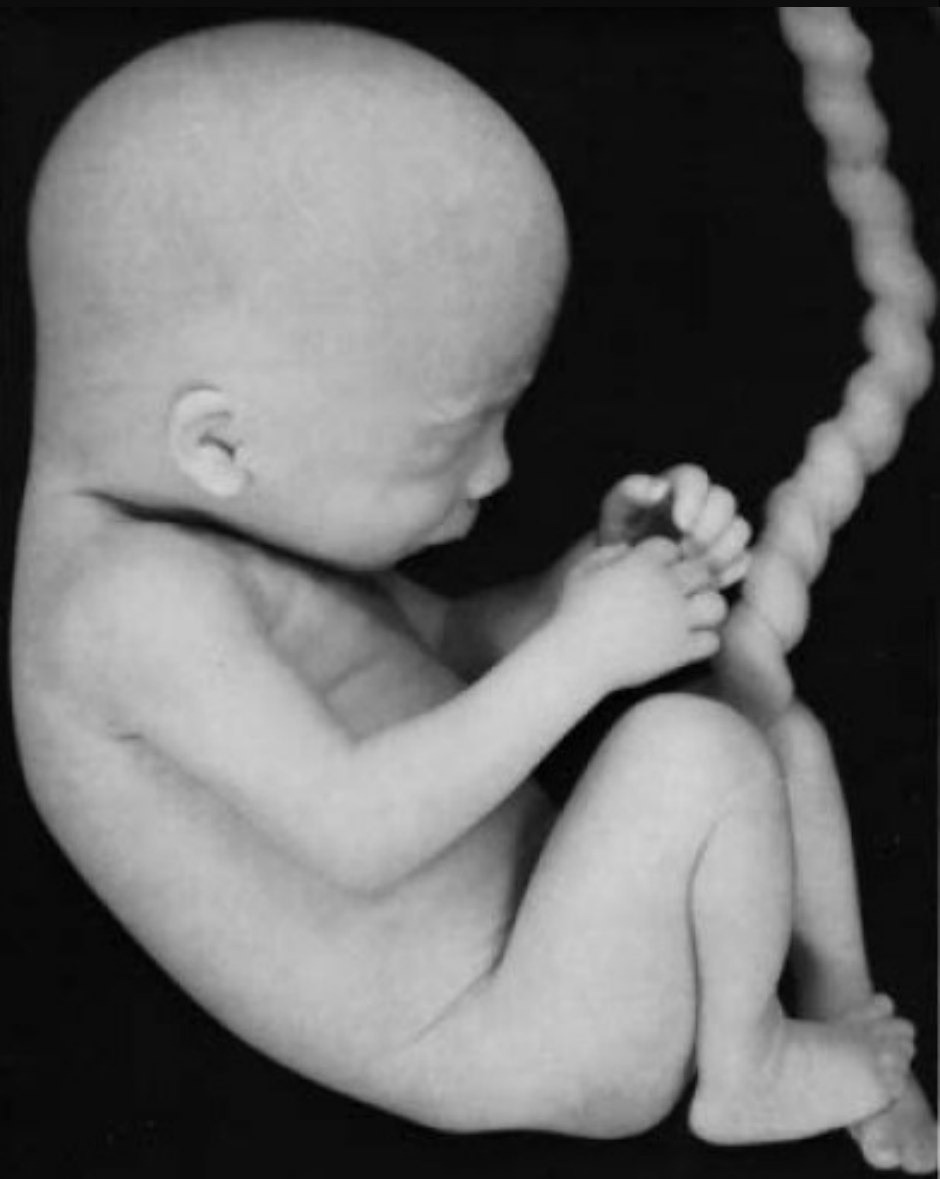
Διαμόλυνση με φορείς που φέρουν ένα ή παραπάνω γονίδια:

- Έκφραση ενός (ή παραπάνω) εξωγενούς γονιδίου που οδηγεί σε ένα συγκεκριμένο αναπτυξιακό μονοπάτι.
- Πολύ ακριβής και ελεγχόμενος τρόπος κατευθυνόμενης διαφοροποίησης.

Όμως.....

- Πρέπει να ξέρουμε με ακρίβεια τους μηχανισμούς που ενέχονται και τα συγκεκριμένα γονίδια που πρέπει να ενεργοποιηθούν.
- Το στάδιο της ενεργοποίησης = επιλογή της κατάλληλης χρονικής στιγμής για την έκφραση
- Το στάδιο της απενεργοποίησης = επιλογή της χρονικής στιγμής που θα σταματήσει η έκφραση του γονιδιου.

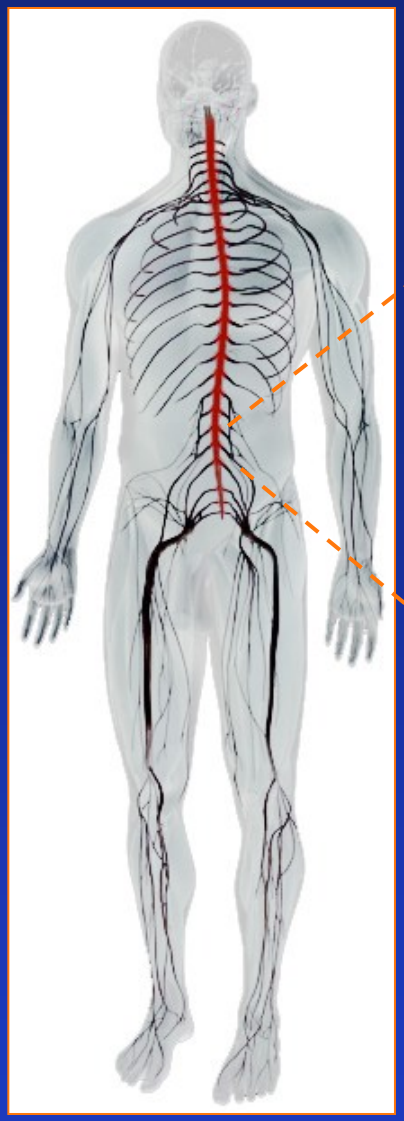
Βιολογία Βλαστοκυττάρων και Αναγέννησης

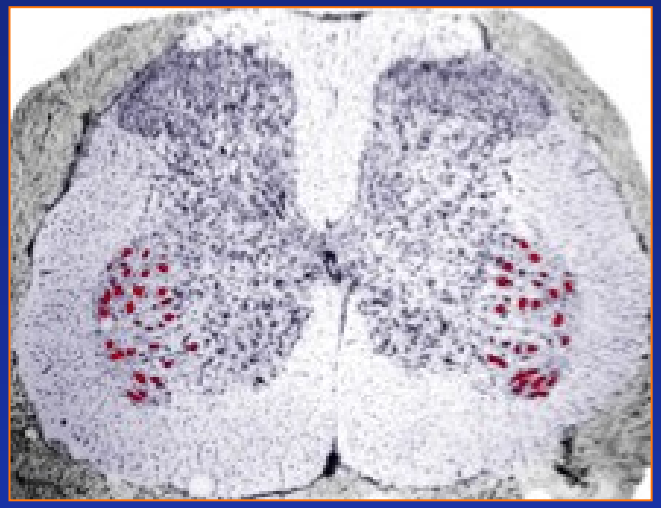


Jessel's saga

Μ. Γρηγορίου 2025

Κινητικοί νευρώνες και ασθένειες





Κινητικοί νευρώνες

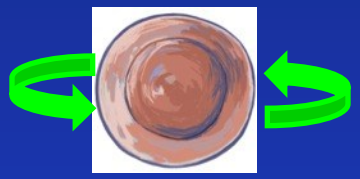
- Ένας ανά 10^6 κύτταρα του σώματος
- Στο κοιλιακό κέρας του νωτιαίου μυελού
- Κινήσεις των γραμμωτών μυών
- Διαφορετικοί υποτύποι για συγκεκριμένες ομάδες μυών (π.χ. Άκρων ή θωρακα

Ασθένειες που σχετίζονται με τους ΚΝ

- Παράλυση λόγω τραυματισμού του νωτιαίου μυελού
- Νωταία μυϊκή ατροφία
- Αμυοτροφική πλευρική (πλάγια) σκλήρυνση (ασθένεια Lou Gehrig ή ALS)

Κατευθυνόμενη διαφοροποίηση ESC σε κινητικούς νευρώνες

Πολυδύναμο



Κύτταρο ES

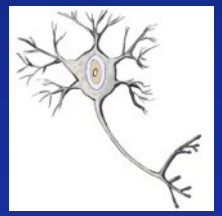
Ολιγοδύναμο

Κύτταρο εξωδέρματος

Κύτταρο μεσοδέρματος

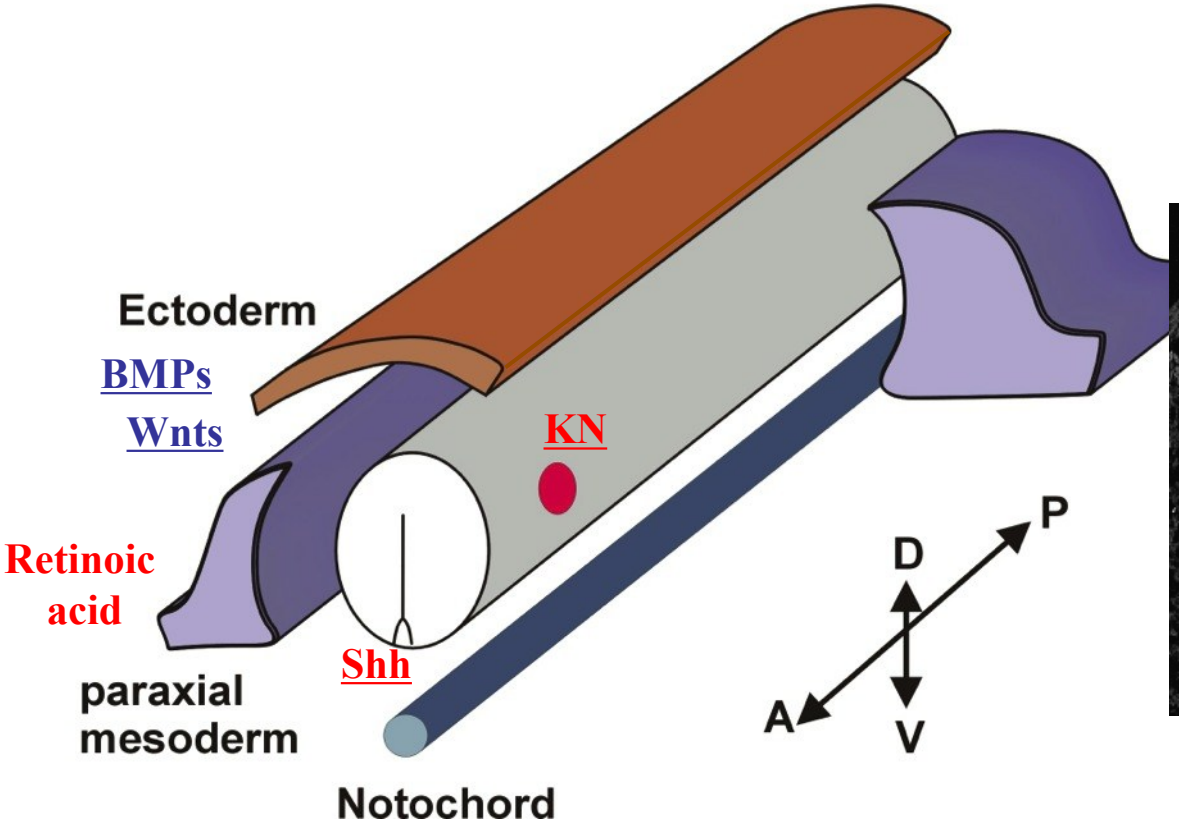
Κύτταρο ενδοδέρματος

Διαφοροποιημένο

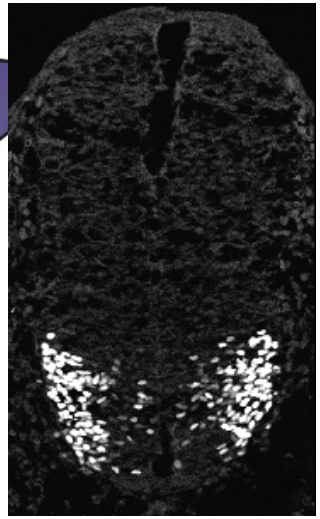


νευρικό

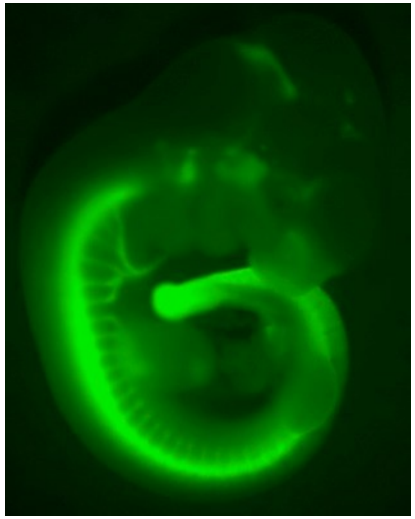
Η διαφοροποίηση των κινητικών νευρώνων εξαρτάται από την παρουσία σηματοδοτικών μορίων



Hb9



Hb9::eGFP



Cell, Vol. 73, 673–686, May 21, 1993, Copyright © 1993 by Cell Press

Control of Cell Pattern in the Neural Tube: Motor Neuron Induction by Diffusible Factors from Notochord and Floor Plate

Toshiya Yamada,* Samuel L. Pfaff,* Thomas Edlund,† and Thomas M. Jessell*

Summary

The identity of cell types generated along the dorsoventral axis of the neural tube depends on inductive signals that derive from both mesodermal and neural cells. To define the nature of these signals, we have analyzed the differentiation of cells in neural plate explants. Motor neurons and neural crest cells differentiate in vitro from appropriate regions of the neural plate, indicating that the specification of cell fate along the dorsoventral axis of the neural tube begins at the neural plate stage. Motor neuron differentiation can be induced by a diffusible factor that derives initially from the notochord and later from floor plate cells. By contrast, floor plate induction requires contact with the notochord. Thus, the identity and patterning of neural cell types appear to involve distinct contact-mediated and diffusible signals from the notochord and floor plate.

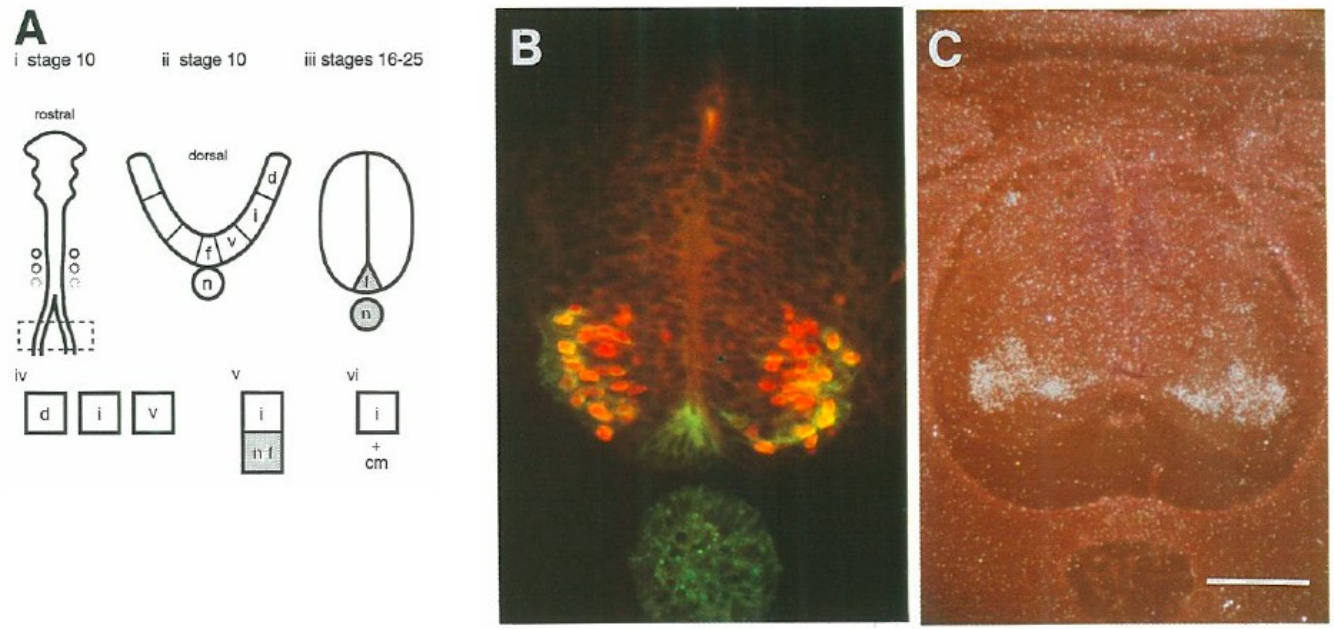


Figure 1. In Vitro Induction Assay and Expression of Markers Used to Detect Motor Neuron Differentiation

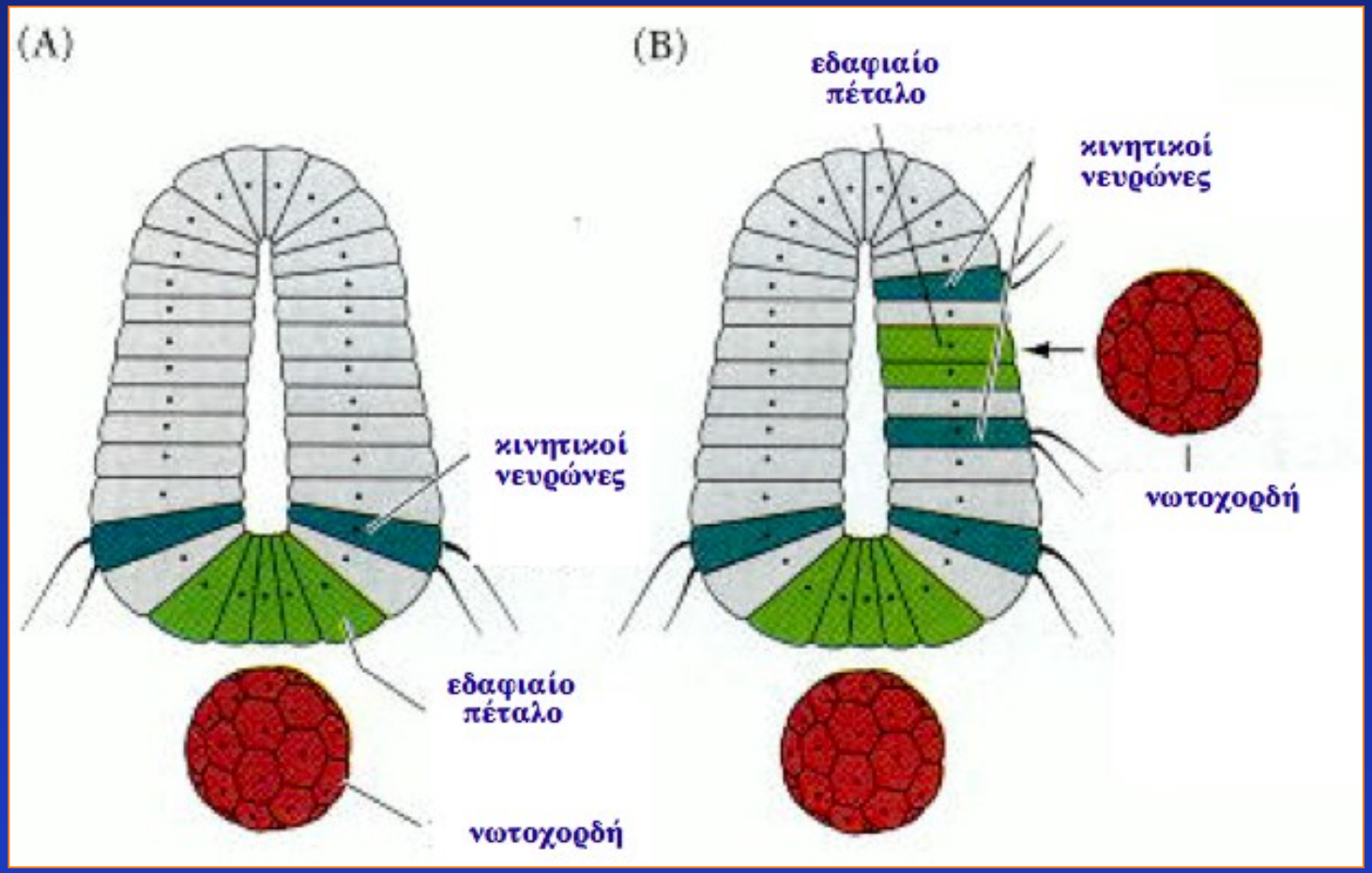
(A) (Diagram i) A dorsal view of the neural plate and neural tube of a stage 10 chick embryo showing the position and rostrocaudal extent (300–350 μm) of the region of neural plate isolated for induction assays. (Diagram ii) Transverse section showing the neural plate and the dorsal (d), intermediate (i), and ventral (v) regions used in in vitro assays. The fate of cells in the ventral midline region (f) was not examined. (Diagram iii) Inducing tissue was isolated from stage 10–17 notochord (n) and from stage 10–25 and stage 10–26 floor plate (f). (Diagram iv) To determine the degree of commitment of cells in the neural plate, dorsal (d), intermediate (i), and ventral neural plate (v) explants were grown separately in collagen gels. (Diagrams v and vi) For induction assays, intermediate neural plate explants (i) were grown in contact with notochord (n) or floor plate (f) explants (diagram v) or in the presence of notochord- or floor plate–conditioned medium (cm) (diagram vi). For details see Experimental Procedures.

(B) Coexpression of SC1 and Islet-1 by embryonic spinal motor neurons in a transverse section of stage 16–17 chick spinal cord. SC1 (green label) is expressed by motor neurons and also by floor plate cells and the notochord. Islet-1 expression (red label) is restricted to motor neurons at this stage of spinal cord development.

(C) Dark-field micrograph showing the localization of ChAT mRNA by in situ hybridization histochemistry in a section of a stage 26 chick embryo. Hybridization is detected over cells in the motor column but not over other cells in the spinal cord.

Scale bar: (B), 60 μm; (C), 250 μm.

Διαφοροποίηση του νευρικού σωλήνα κατά μήκος του ραχιοκοιλιαίου άξονα



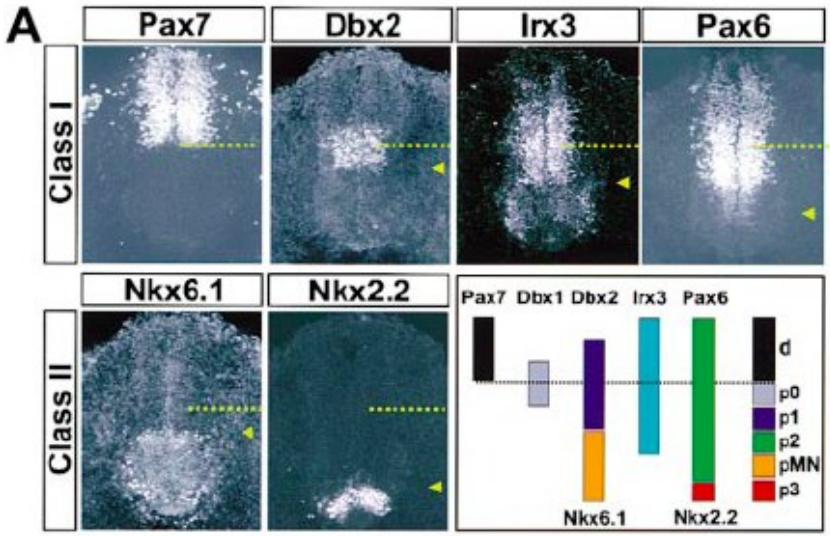
Μεταμόσχευση της **νωτοχορδής** έχει ως αποτέλεσμα την επαγωγή εκτοπικού **εδαφιαίου πεταλου** και εκτοπικών **κινητικών νευρώνων.** Το ίδιο αποτέλεσμα έχει και η μεταμόσχευση κυττάρων COS που εκφράζουν shh.

Cell, Vol. 101, 435–445, May 12, 2000, Copyright ©2000 by Cell Press

A Homeodomain Protein Code Specifies Progenitor Cell Identity and Neuronal Fate in the Ventral Neural Tube

Summary

Distinct classes of neurons are generated at defined positions in the ventral neural tube in response to a gradient of Sonic Hedgehog (Shh) activity. A set of homeodomain transcription factors expressed by neural progenitors act as intermediaries in Shh-dependent neural patterning. These homeodomain factors fall into two classes: class I proteins are repressed by Shh and class II proteins require Shh signaling for their expression. The profile of class I and class II protein expression defines five progenitor domains, each of which generates a distinct class of postmitotic neurons. Cross-repressive interactions between class I and class II proteins appear to refine and maintain these progenitor domains. The combinatorial expression of three of these proteins—Nkx6.1, Nkx2.2, and Irx3—specifies the identity of three classes of neurons generated in the ventral third of the neural tube.



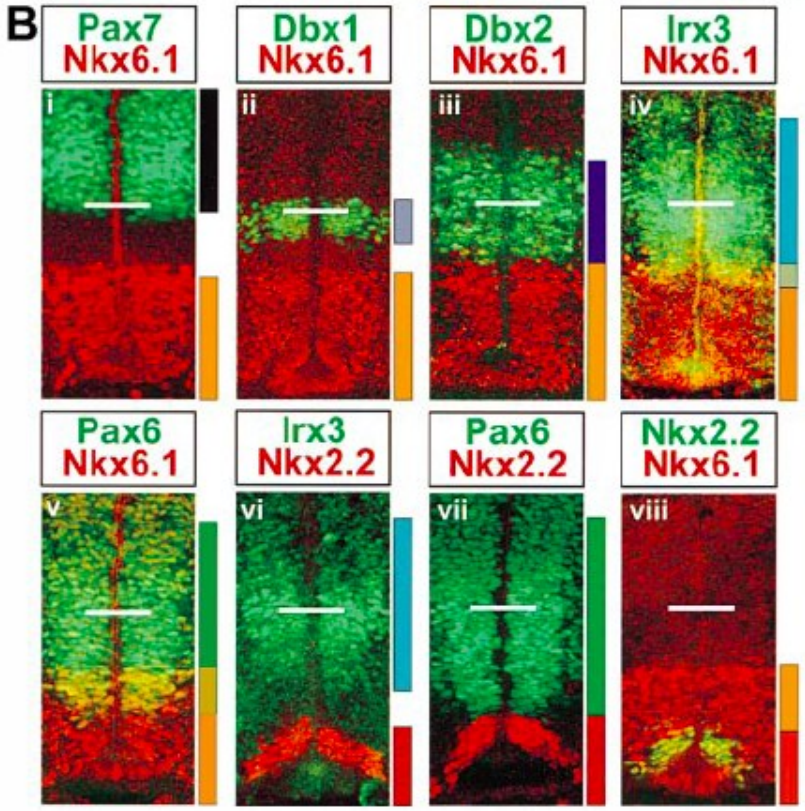
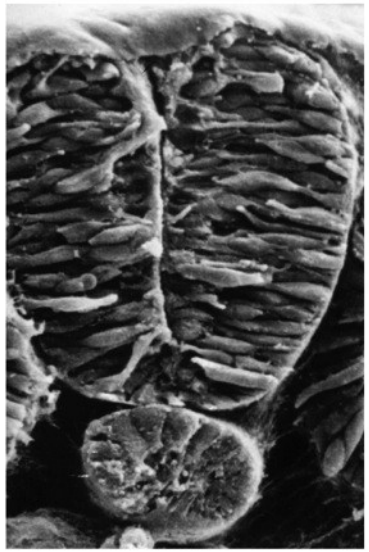


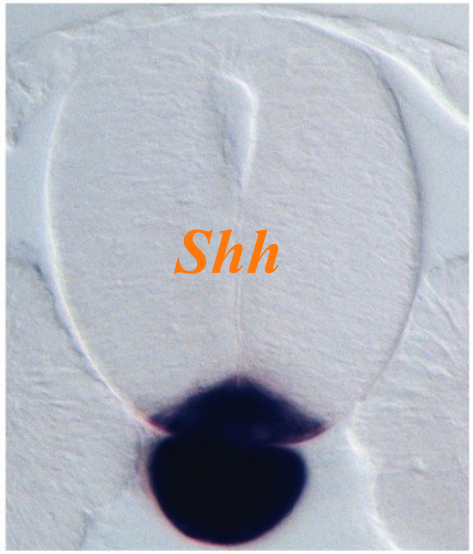
Figure 1. Homedomain Proteins Define Five Ventral Progenitor Domains

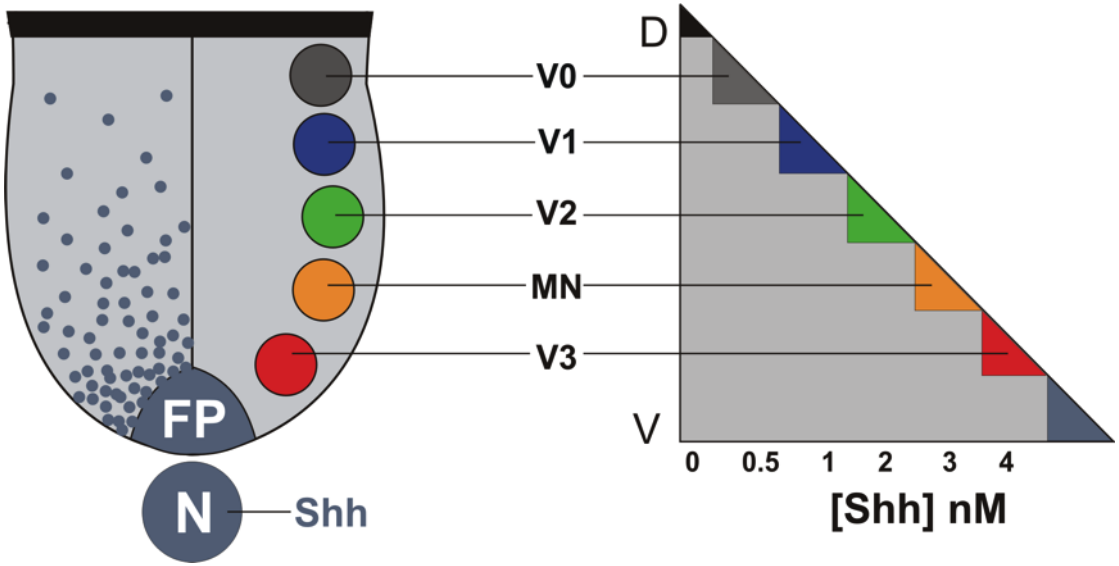
(A) Localization of homeodomain proteins in the neural tube of HH stage 20 chick embryos. Class I proteins (Pax7, Dbx2, Irx3, and Pax6) have different ventral boundaries (yellow arrowheads). Class II proteins (Nkx6.1 and Nkx2.2) have different dorsal boundaries (yellow arrowheads). The dorsoventral (DV) boundaries of the neural tubes are indicated by dotted lines. Composite of expression domains shown in (B), p = progenitor domain.

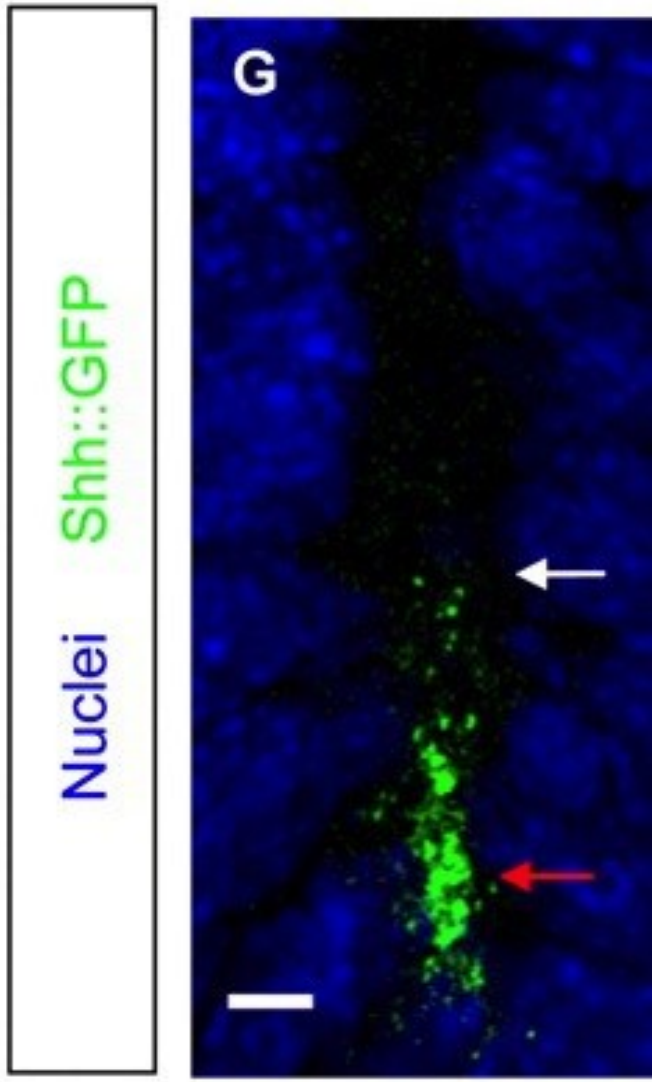
(B) The combinatorial expression of class I and class II proteins defines five ventral progenitor domains. Images show protein expression in the neural tube of HH stage 22 chick embryos.

Διαφοροποίηση κινητικών νευρώνων









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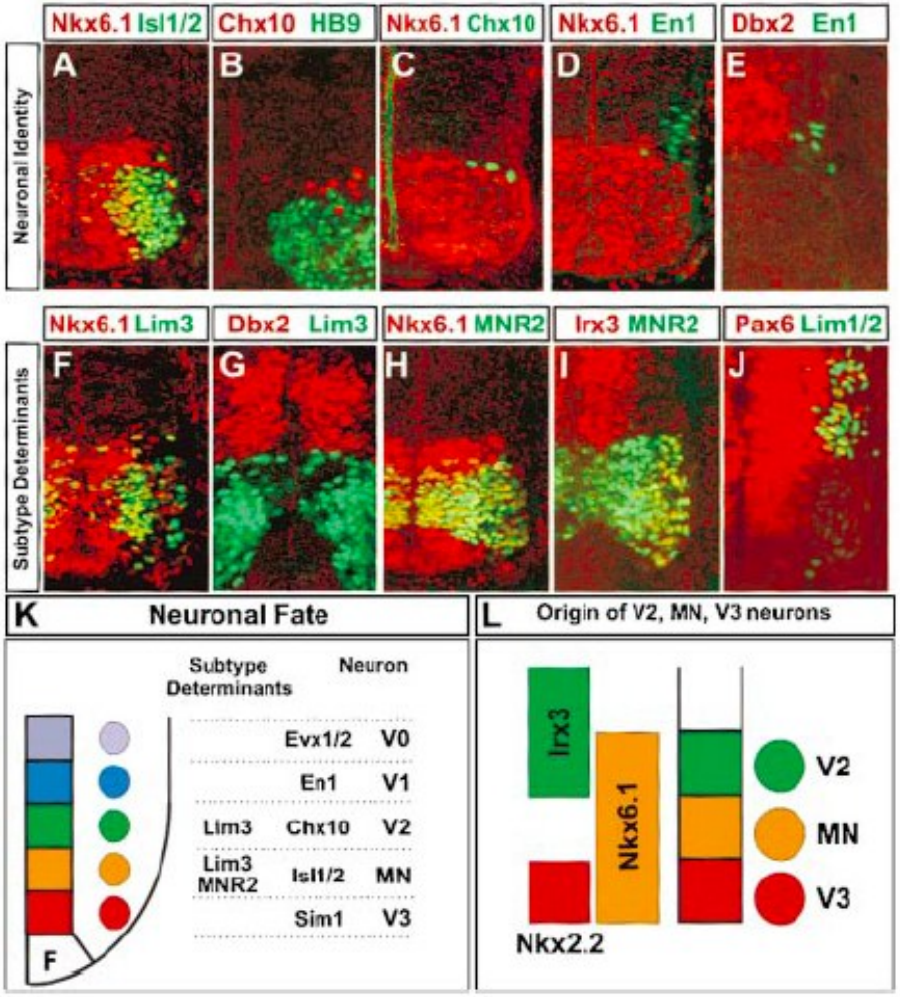


Figure 4. Each Progenitor Domain Generates a Distinct Neuronal Subtype

(A–E) Relationship between class I and class II proteins and neuronal markers. The domain of Nkx6.1 expression encompasses Isl1/2 MNs (A) and Chx10 V2 neurons (C) but is positioned ventral to En1 V1 neurons (D). Chx10 V2 neurons are generated dorsal to HB9 MNs (B). En1 V1 neurons are generated at the ventral extent of the Dbx2 domain (E). Images from HH stage 22–24 embryos.

(F–J) Relationship between class I and class II proteins and neuronal subtype determinants. The domain of Nkx6.1 expression encompasses the domain of generation of Lim3 (F) and MNR2 cells (H). Lim3 cells are positioned ventral to the domain of Dbx2 expression (G). MNR2 cells are positioned ventral to the domain of Irx3 expression (I). Lim1/2 cells derive from Pax6 progenitors (J).

(K) The relationship between progenitor domain identity and neuronal fate.

(L) The progenitor homeodomain code within the three ventral-most domains of neurogenesis.

Cell, Vol. 101, 435–445, May 12, 2000, Copyright ©2000 by Cell Press

A Homeodomain Protein Code Specifies Progenitor Cell Identity and Neuronal Fate in the Ventral Neural Tube

Summary

Distinct classes of neurons are generated at defined positions in the ventral neural tube in response to a gradient of Sonic Hedgehog (Shh) activity. A set of homeodomain transcription factors expressed by neural progenitors act as intermediaries in Shh-dependent neural patterning. These homeodomain factors fall into two classes: class I proteins are repressed by Shh and class II proteins require Shh signaling for their expression. The profile of class I and class II protein expression defines five progenitor domains, each of which generates a distinct class of postmitotic neurons. Cross-repressive interactions between class I and class II proteins appear to refine and maintain these progenitor domains. The combinatorial expression of three of these proteins—Nkx6.1, Nkx2.2, and Irx3—specifies the identity of three classes of neurons generated in the ventral third of the neural tube.

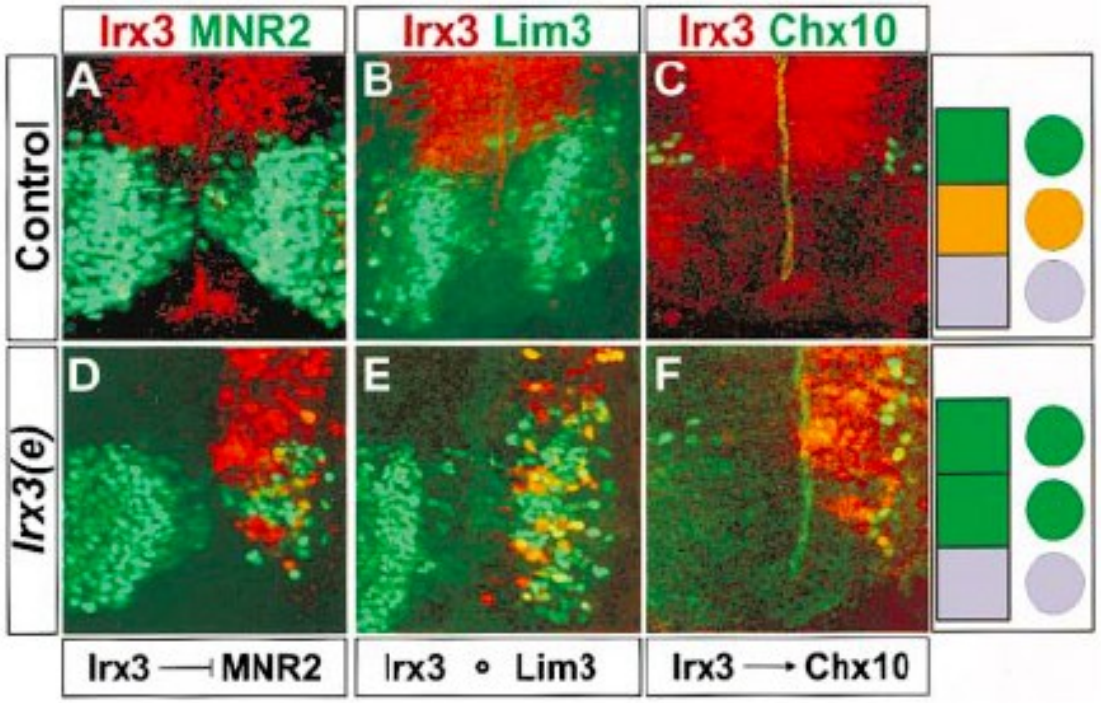
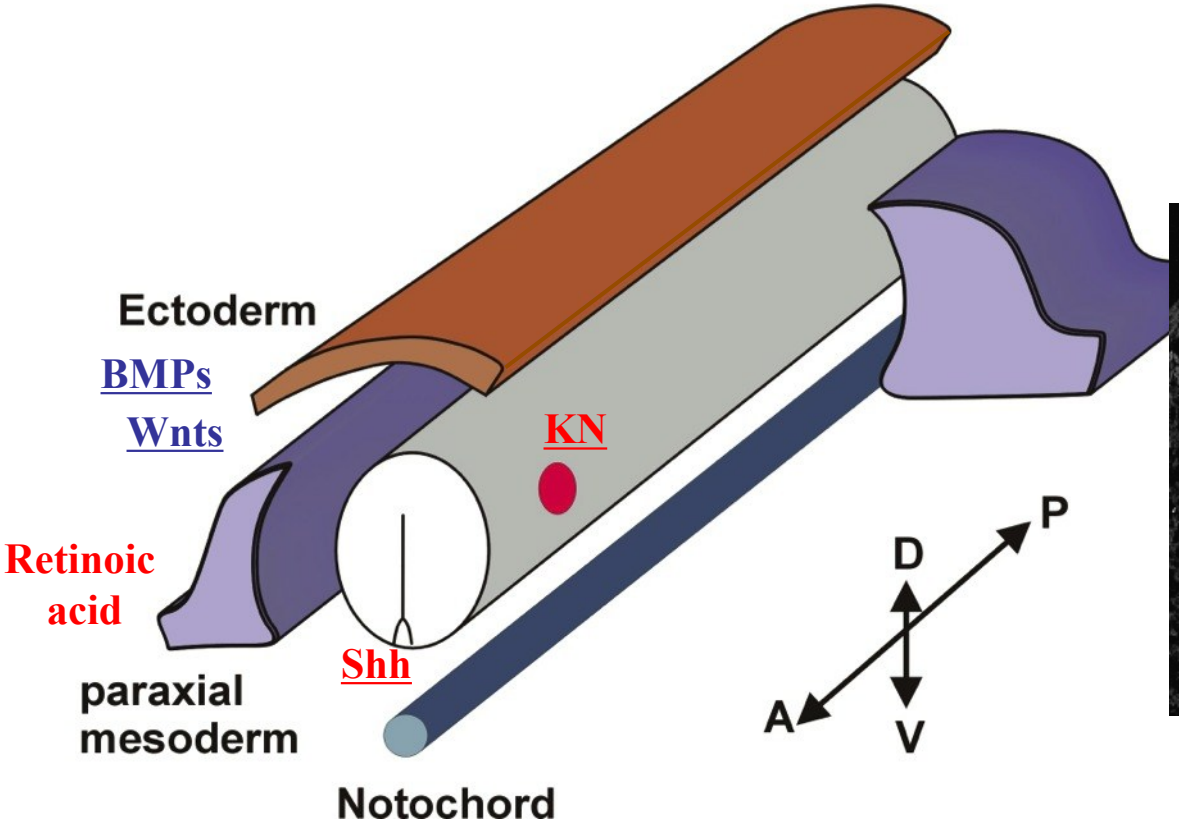


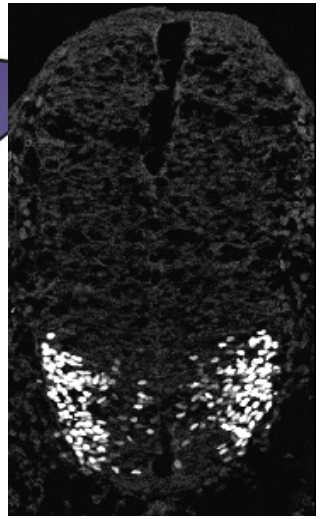
Figure 6. Irx3 Represses Motor Neuron Generation and Induces V2 Neurons

(A) The ventral limit of Irx3 expression corresponds to the dorsal extent of MNR2+ cells in control embryos. Progenitor cells in the ventral-most domain of Irx3 expression give rise to V2 neurons that express Lim3 (B) and Chx10 (C). **After ventral misexpression of Irx3 by electroporation** there is no change in the pattern of Lim3 expression (E) but MNR21 cells are repressed (D) and Chx10+ V2 neurons differentiation, extending findings that Nkx2.2 activity are generated within the pMN domain (F). Images representative of 10 experiments.

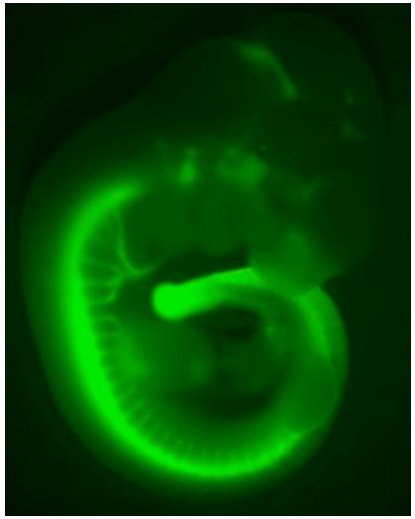
Η διαφοροποίηση των κινητικών νευρώνων εξαρτάται από την παρουσία σηματοδοτικών μορίων



Hb9



Hb9::eGFP



Cell, Vol. 97, 903–915, June 25, 1999, Copyright ©1999 by Cell Press

A Sonic Hedgehog–Independent, Retinoid-Activated Pathway of Neurogenesis in the Ventral Spinal Cord

Alessandra Pierani,* Susan Brenner-Morton,*
Chin Chiang,† and Thomas M. Jessell*‡

Summary

Sonic hedgehog (Shh) is thought to control the generation of motor neurons and interneurons in the ventral CNS. We show here that a Shh-independent pathway of interneuron generation also operates in the ventral spinal cord. Evidence for this parallel pathway emerged from an analysis of the induction of ventral progenitors that express the Dbx homeodomain proteins and of Evx1/2 (V0) and En1 (V1) neurons. Shh signaling is sufficient to induce Dbx cells and V0 and V1 neurons but is not required for their generation in vitro or in vivo. Retinoids appear to mediate this parallel pathway. These findings reveal an unanticipated Shh-independent signaling pathway that controls progenitor cell identity and interneuron diversity in the ventral spinal cord.

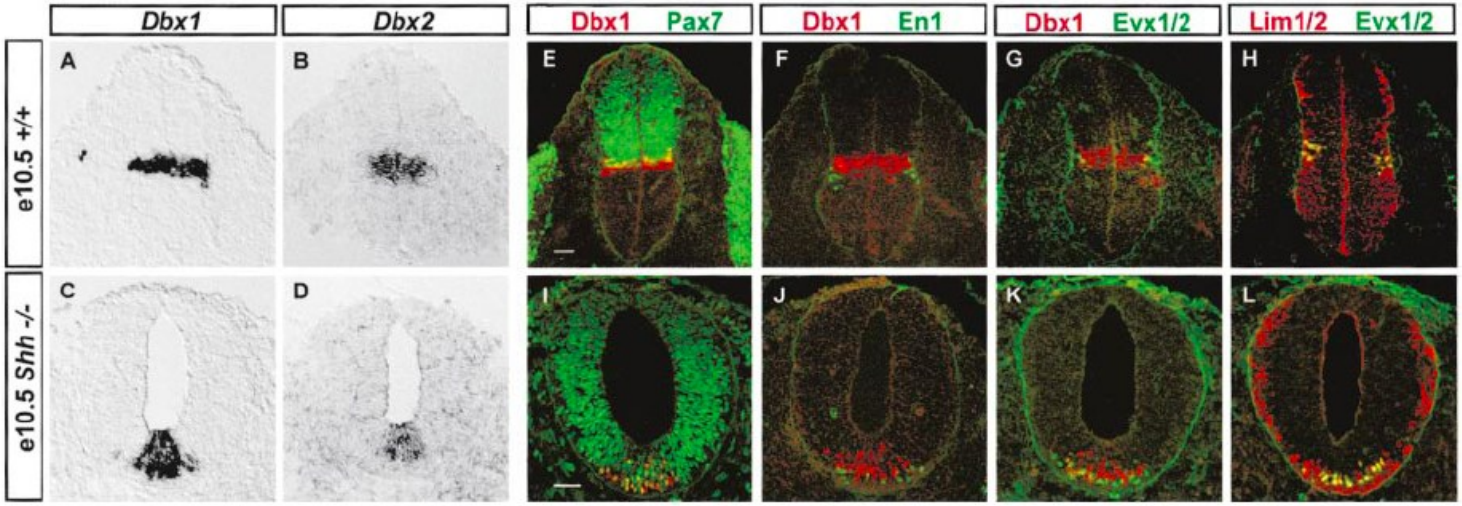


Figure 4. Generation of *Dbx* Progenitors and Evx1/2 (V0) and En1 (V1) Neurons in $Shh^{-/-}$ Embryos

(A–D) *Dbx1* and *Dbx2* expression in E10.5 $Shh^{-/-}$ mice. In contrast to wild-type embryos (A and B), in $Shh^{-/-}$ embryos (C and D) expression of both genes is restricted to the ventral midline of the spinal cord. *Dbx1* and *Dbx2* expression was also detected at caudal hindbrain levels at E9.5 (not shown).

(E–L) Localization of Dbx1, Pax7, En1, and Evx1/2 in E10.5 wild-type (E–H) and $Shh^{-/-}$ (I–L) embryos. (E and I) Pax7 expression in wild-type and $Shh^{-/-}$ embryos. Ventral midline progenitors express low or negligible Pax7 levels. (F and J) Dbx1 expression (red) and En1 neurons (green) in $Shh^{-/-}$ embryos. In $Shh^{-/-}$ mutants, the number of En1 neurons was lower than the number of Evx1/2 neurons. (G and K) Dbx1 expression (red) and Evx1/2 neurons (green) in $Shh^{-/-}$ embryos. (H and L) Evx1/2 neurons in $Shh^{-/-}$ embryos coexpress Lim1/2.

Scale bar, 40 μm.

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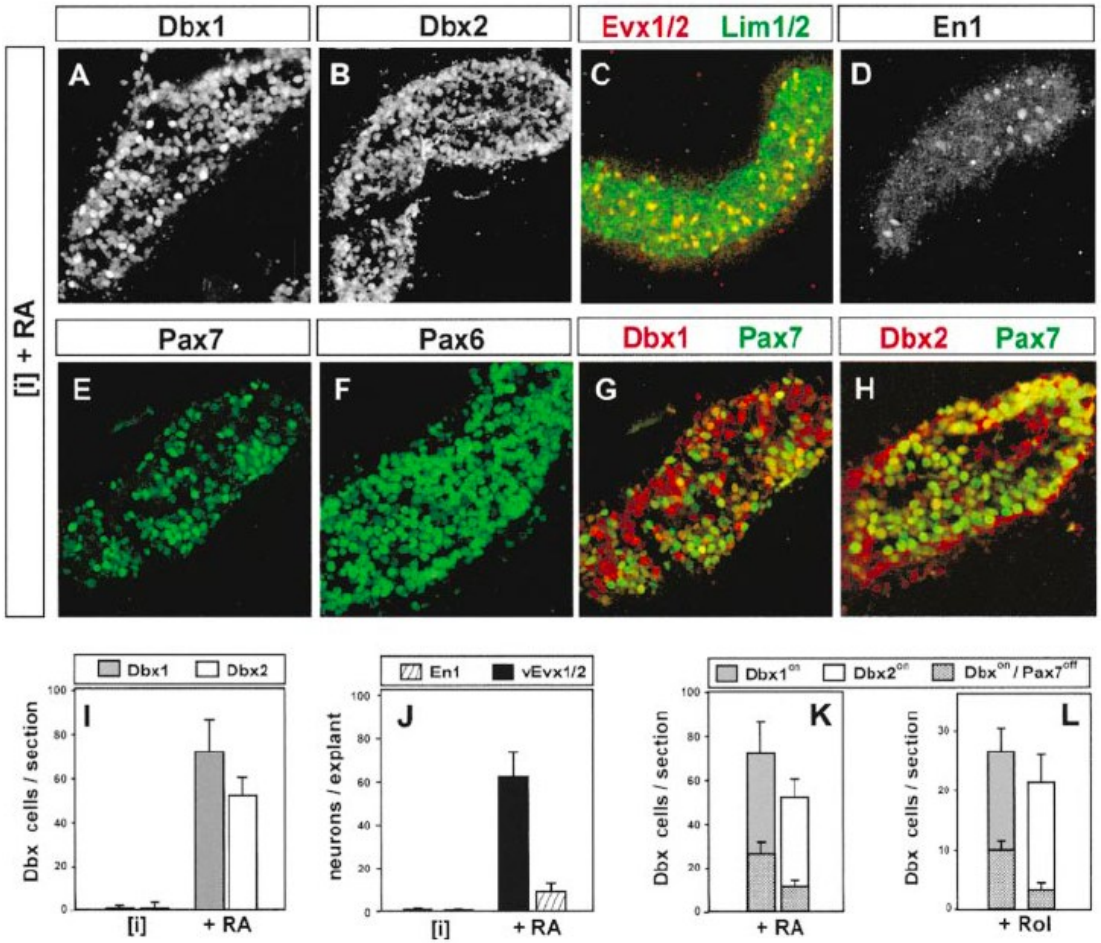


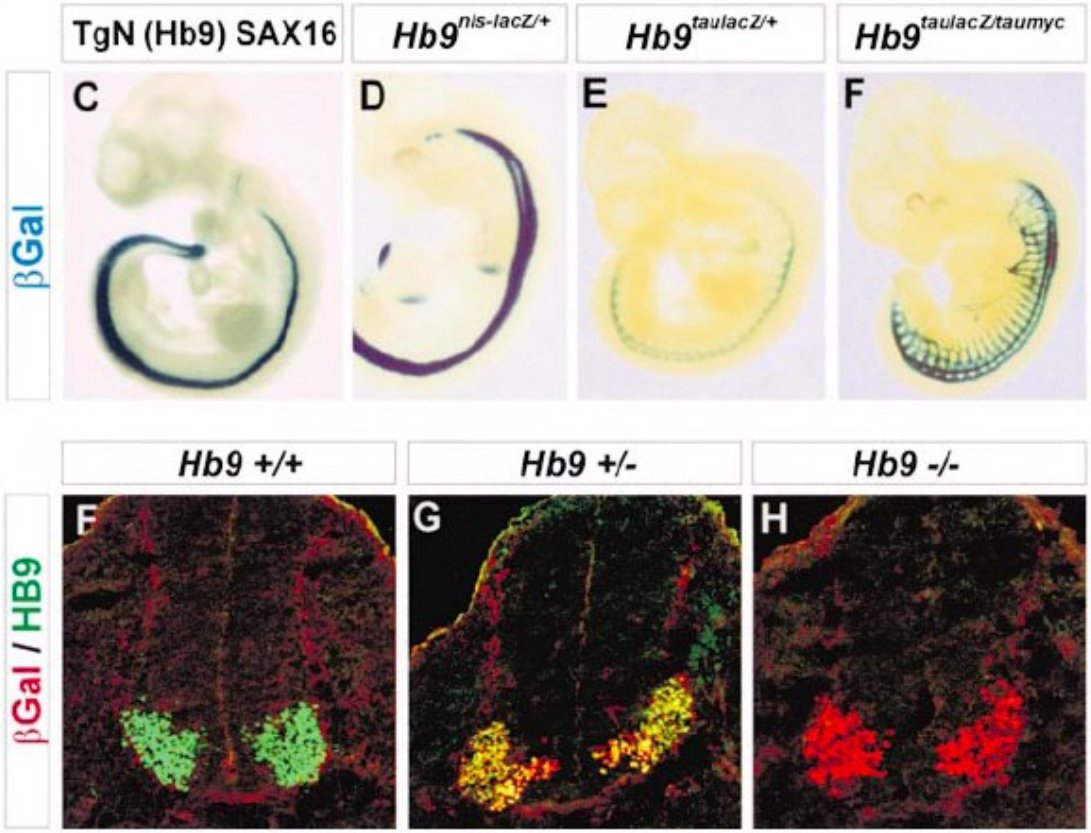
Figure 5. Retinoids Induce Dbx Expression and V0 and V1 Neurons

(A and B) Induction of Dbx1 (A) and Dbx2 (B) expression by RA (100 nM). Similar results were obtained with Rol (1 mM). Induction of Dbx1 and Dbx2 expression was obtained at the same threshold concentration of RA (appx 5 nM, not shown). (C and D) Generation of Evx1/2, Lim1/2 neurons (C) and En1 neurons (D) by RA (100 nM). (E) Absence of Pax7 expression from many cells in [i] explants incubated with RA (100 nM). (F) Expression of Pax6 in [i] explants incubated with RA (100 nM). (G) Many Dbx1 cells lack Pax7 expression in [i] explants incubated with RA (100 nM). (H) A smaller fraction of Dbx2 cells lack Pax7 expression in [i] explants incubated with RA (100 nM). (I) Induction of Dbx1 and Dbx2 cells by RA (100 nM). (J) Induction of En1 and vEvx1/2 neurons by RA (100 nM). En1 (hatched) and vEvx1/2 (black) neurons/explant, mean 6 SEM, n 5 7–10 explants. (K and L) Fraction of Pax7off Dbx cells in [i] explants incubated with RA (100 nM) (K) or Rol (1 mM) (L). Dbx1 (gray), Dbx2 (white), and Dbxon,Pax7off (cross-hatched) cells per section. Values in (I), (K), and (L) show mean 6 SEM, n 5 4–10 sections.

Neuron, Vol. 23, 659–674, August, 1999, Copyright ©1999 by Cell Press

Requirement for the Homeobox Gene *Hb9* in the Consolidation of Motor Neuron Identity

Silvia Arber,† Barbara Han, Monica Mendelsohn, Michael Smith, Thomas M. Jessell,* and Shanthini Sockanathan†



Summary

The homeobox gene *Hb9*, like its close relative *MNR2*, is expressed selectively by motor neurons (MNs) in the developing vertebrate CNS. In embryonic chick spinal cord, the ectopic expression of *MNR2* or *Hb9* is sufficient to trigger MN differentiation and to repress the differentiation of an adjacent population of V2 interneurons. Here, we provide genetic evidence that *Hb9* has an essential role in MN differentiation. In mice lacking *Hb9* function, MNs are generated on schedule and in normal numbers but transiently acquire molecular features of V2 interneurons. The aberrant specification of MN identity is associated with defects in the migration of MNs, the emergence of the subtype identities of MNs, and the projection of motor axons. These findings show that HB9 has an essential function in consolidating the identity of postmitotic MNs.

(C) E10 transgenic embryo (TgN(*Hb9*)SAX16) labeled for β-gal expression.
(D) E11.5 $Hb9^{nlslacZ/+}$ embryo. The staining in the developing limbs corresponds to the region of the zone of polarizing activity (zpa).
(E and F) β-gal staining of E11.5 $Hb9^{taulacZ/+}$ (E) and compound mutant $Hb9^{taulacZ/taumyc}$ (F) embryos. In the presence of one allele of *taulacZ*, the staining intensity in the compound homozygote is ~5-fold higher than in the heterozygote. Embryos were processed for the same incubation time.
(F) Expression of HB9 in the spinal cord of E10.5 wild-type embryos.
(G) Coincidence of expression of HB9 protein (green) and nlsLacZ (β-gal) (red) in E10.5 $Hb9^{nlslacZ/+}$ spinal cord.
(H) Absence of HB9 protein in the spinal cord of E10.5 $Hb9^{nlslacZ/nlslacZ}$ embryos.

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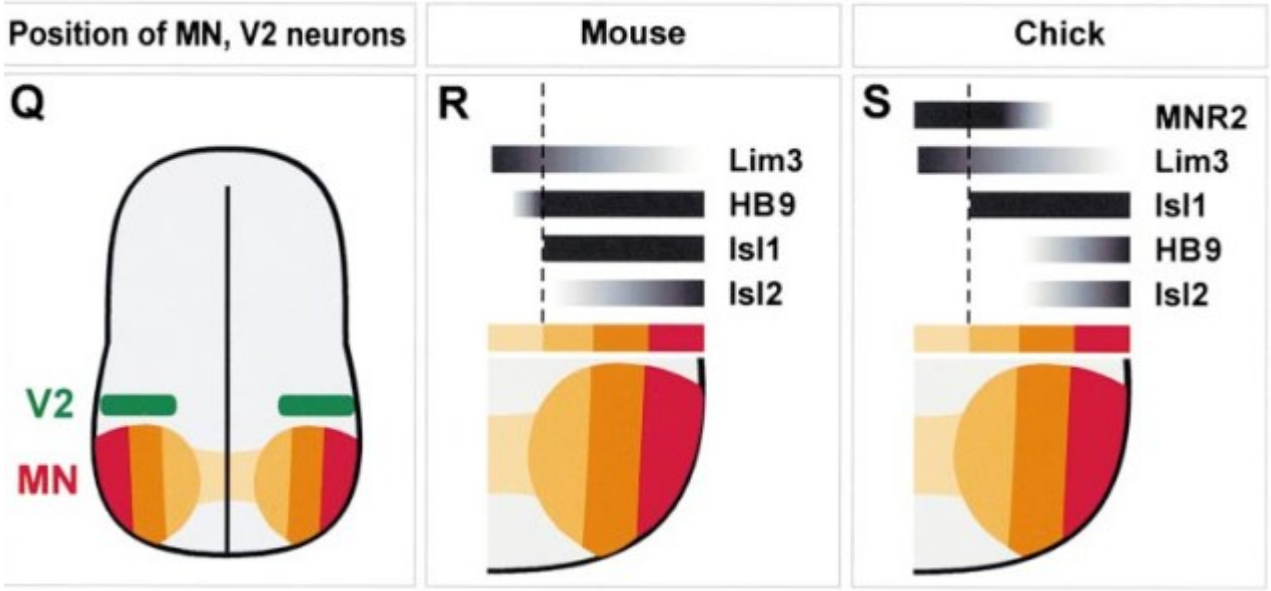
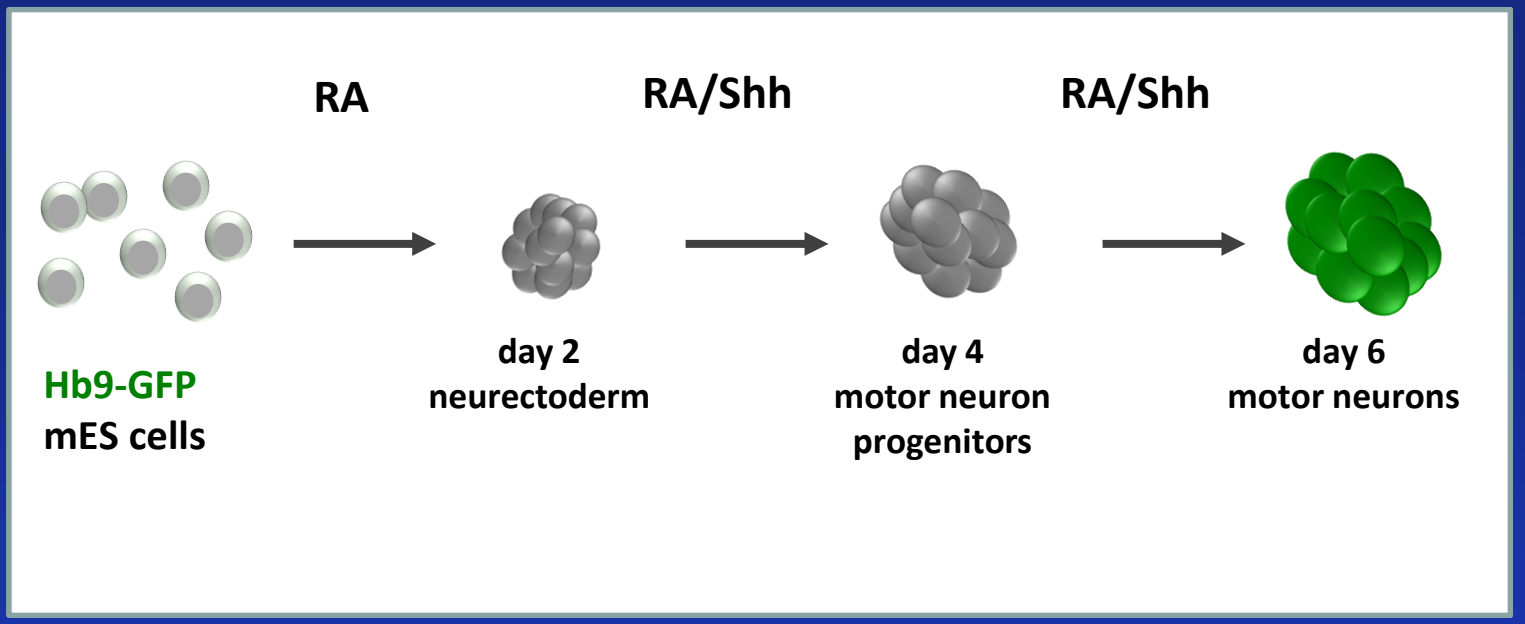
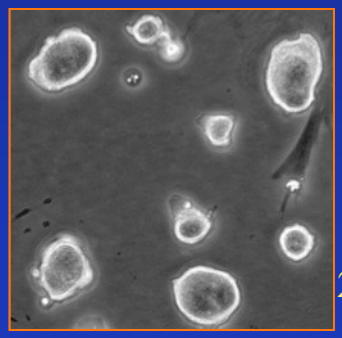


(Q) The position of generation of MNs and V2 interneurons.
(R and S) Diagrams indicating the temporal profile of expression of HB9 in the early differentiation of mouse (R) and chick (S) spinal MNs, assessed by expression of homeodomain transcription factors. The sequential stages in the conversion of MN progenitors into postmitotic MNs in chick are based on the data of Tanabe et al. (1998). Dashed vertical line indicates approximate time of cell cycle exit.

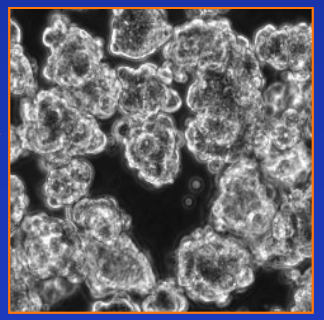
Κατευθυνόμενη διαφοροποίηση mESC σε κινητικούς νευρώνες





ESC

2 μέρες

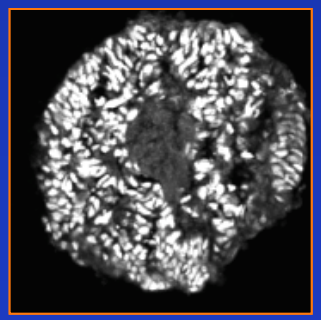


Νευροεξώδερμα

2 μέρες

1 nM αγωνιστή Shh
(~3 nM Shh)

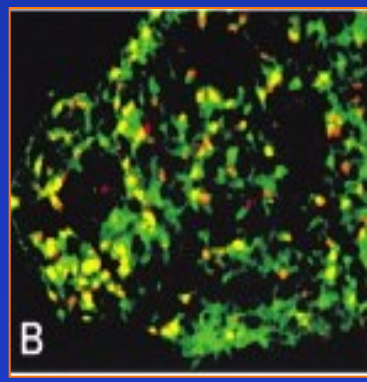
Olig2



Πρόδρομοι ΚΝ

2 μέρες

GFP Hb9



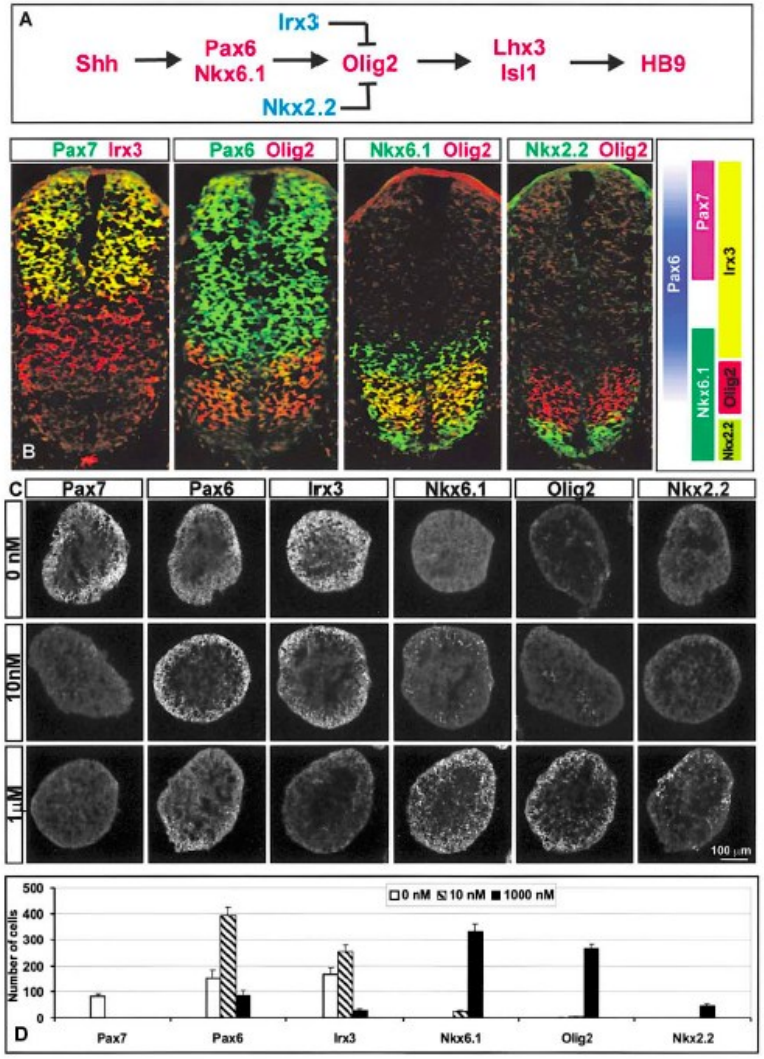
Κινητικοί νευρώνες

Witcherle et al., Cell (2002)

Cell, Vol. 110, 385–397, August 9, 2002, Copyright ©2002 by Cell Press

Directed Differentiation of Embryonic Stem Cells into Motor Neurons

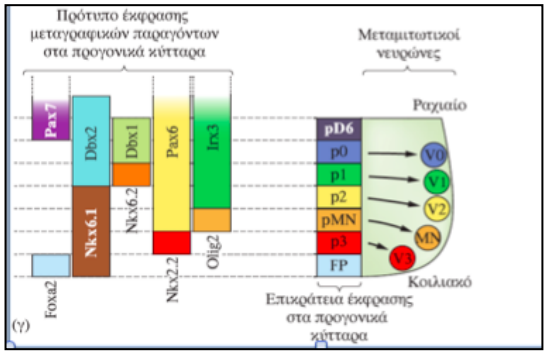
Hynek Wichterle,[1] Ivo Lieberam,[1]
Jeffery A. Porter,[2] and Thomas M. Jessell[1,3]



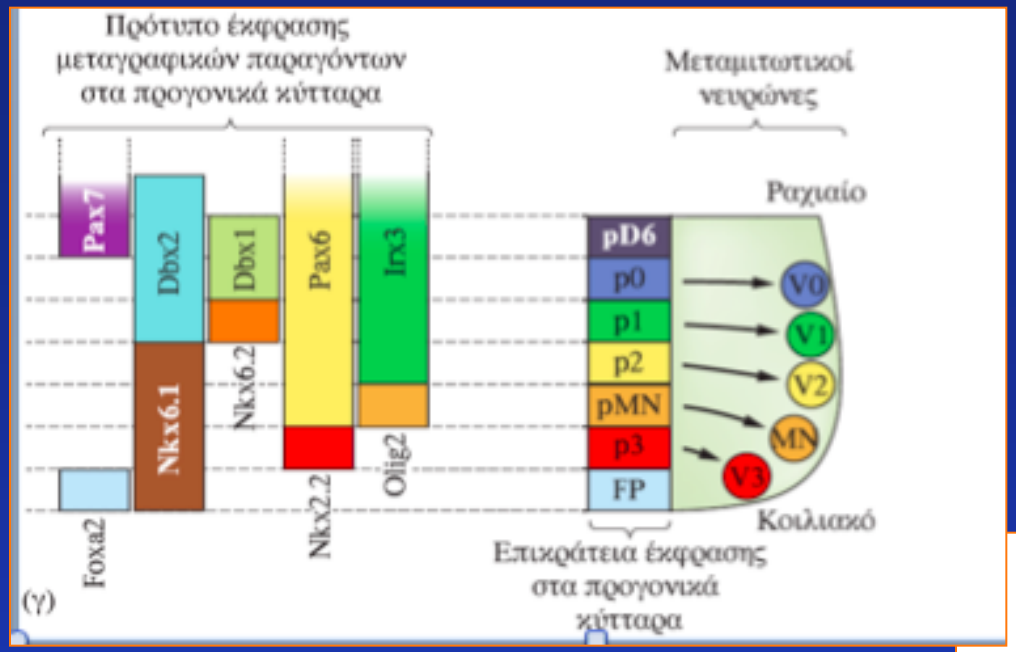
Summary

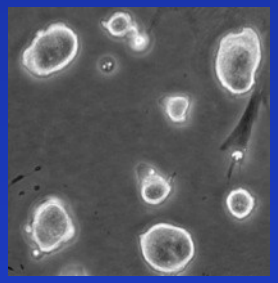
Inductive signals and transcription factors involved in motor neuron generation have been identified, raising the question of whether these developmental insights can be used to direct stem cells to a motor neuron fate. We show that developmentally relevant signaling factors can induce mouse embryonic stem (ES) cells to differentiate into spinal progenitor cells, and subsequently into motor neurons, through a pathway recapitulating that used in vivo. ES cell-derived motor neurons can populate the embryonic spinal cord, extend axons, and form synapses with target muscles. Thus, inductive signals involved in normal pathways of neurogenesis can direct ES cells to form specific classes of CNS neurons.

Figure 2. Hedgehog-Dependent Ventralization of Neural Progenitor Cells in Embryoid Bodies(A) Shh-activated transcriptional pathway of spinal MN generation. Proteins that promote and inhibit MN generation are shown in red and blue, respectively. (B) Expression of HD and bHLH proteins in the caudal neural tube of E9.5 mouse embryos. Progenitors in the domain giving rise to MNs express Olig2, Nkx6.1, and low levels of Pax6.(C) Transcription factor expression in ES cell-derived EBs grown for 3 days in the presence of RA (2 μM) alone, and with 10 nM or 1 μM Hh-Ag1.3.(D) Quantitation of transcription factor expression in EBs in the presence of RA and Hh-Ag1.3. Mean +/- SEM, number of cells per section from eight EBs assayed.



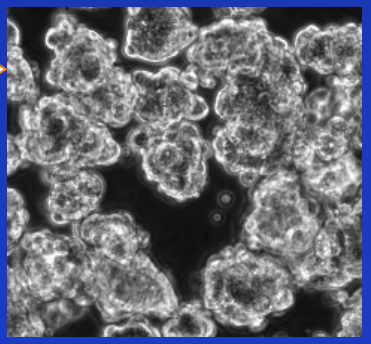
Κατευθυνόμενη διαφοροποίηση mESC σε κινητικούς νευρώνες





ESC

2 μέρες

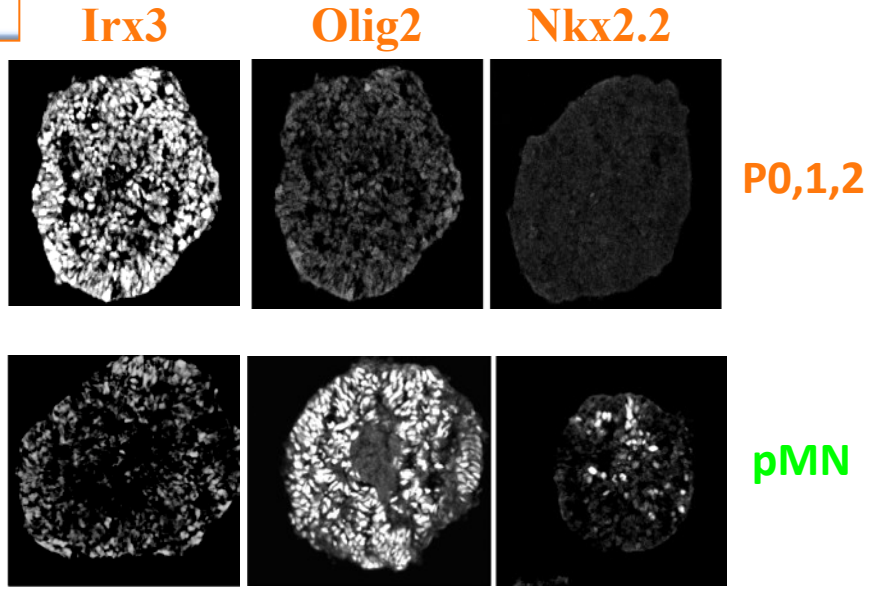


Νευροεξώδερμα

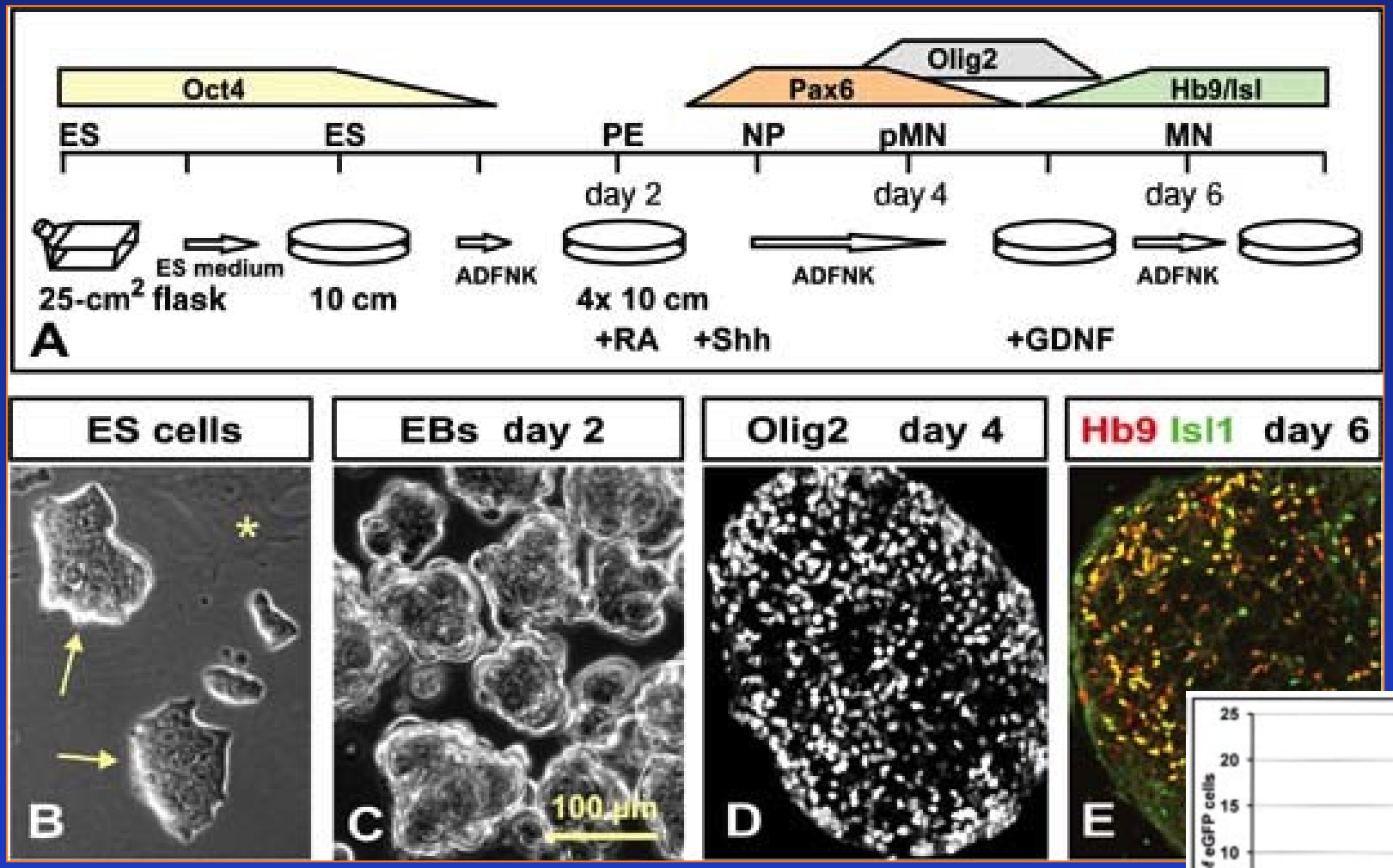
Αγωνιστής 10 nM Shh

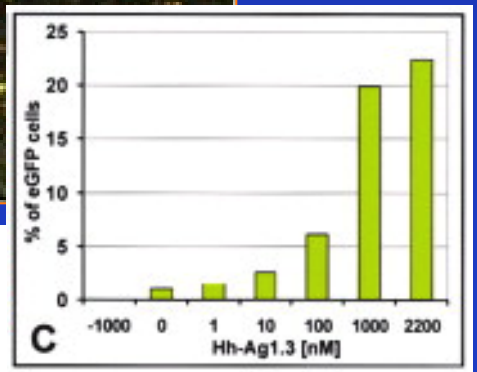
2 μέρες

Αγωνιστής 1 μM Shh



Βελτιωμένο πρωτόκολλο διαφοροποίησης κινητικών νευρώνων





(C) Quantitation of eGFP⁺ MNs in EBs grown for 5 days with RA and Hh-Ag1.3 (0 to 2.2 μM). The point marked as −1000 refers to EBs grown with 1 μM Hh-Ag1.3, but without RA.

Witcherle and Pelzo Current Protocols (2009)

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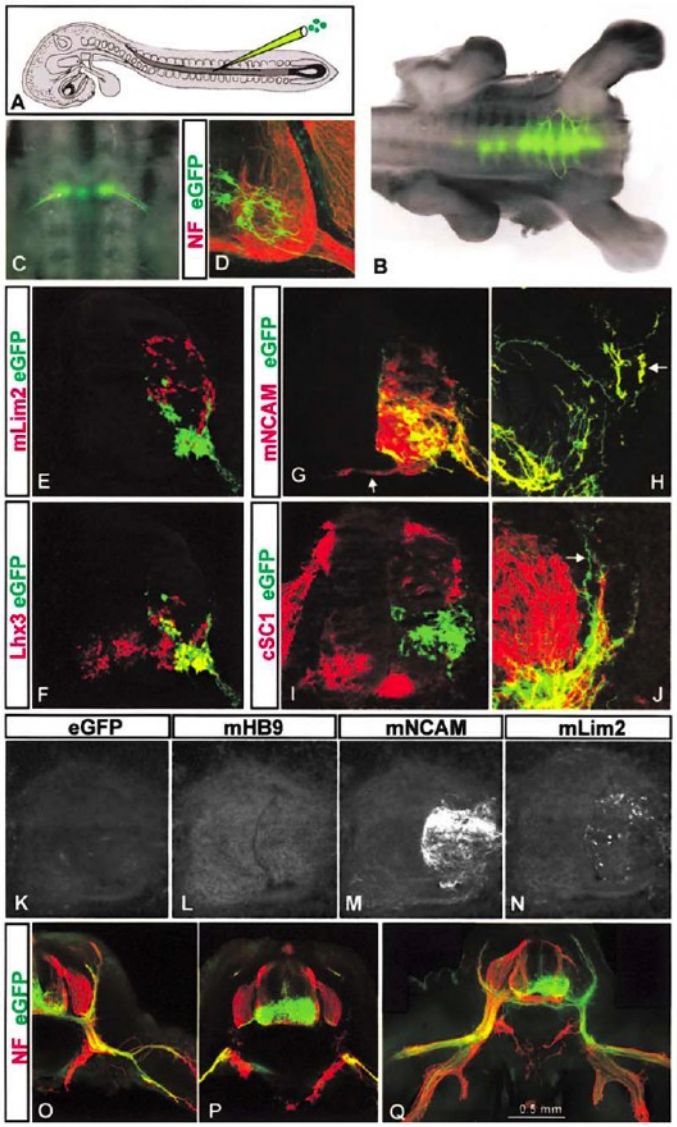
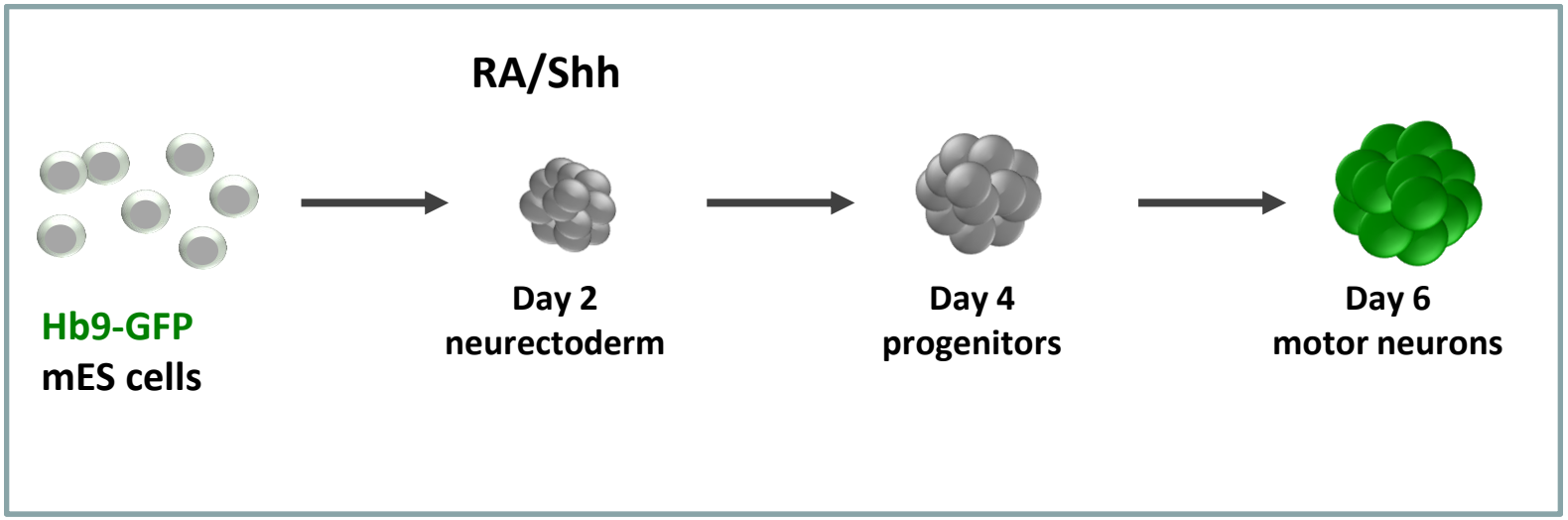
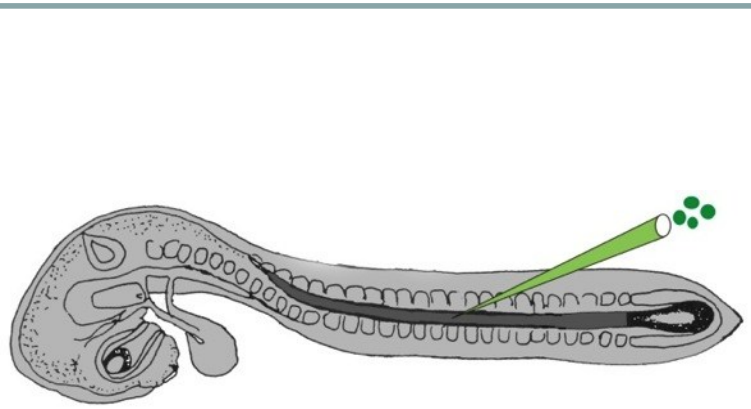
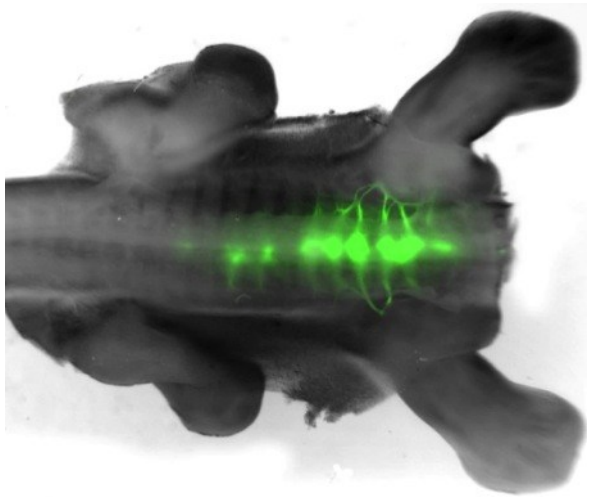


Figure 7. Integration of Transplanted ES Cell-Derived Motor Neurons into the Spinal Cord In Vivo
(A) Implantation of HBG3 ES cell-derived MNenriched EBs into stage 15–17 chick spinal cord. (B) Bright-field/fluorescence image showing eGFP MNs in thoracic and lumbar spinal cord, assayed at stage 27 (ventral view). (C and D) Location of FACS-sorted ES-cell derived eGFP MNs in thoracic spinal cord, assayed at stage 27. eGFP MNs are clustered in the ventral spinal cord (D). (E–J) Transverse sections through stage 27 chick spinal cord at rostral cervical levels after transplantation of MN-enriched EBs. MNs are concentrated in the ventral spinal cord and are segregated from transplanted interneurons, labeled by a mouse-specific Lim2 antibody (E). Many ES cell-derived MNs coexpress eGFP and Lhx3 (F). ES cell-derived MNs (G) and axons (arrow, H) are labeled by rodent-specific anti-NCAM antibody, but do not express the chick MN marker protein SC1 (I and J). eGFP, NCAM axons cross the floor plate but do not project out of the spinal cord (arrows, G and H). (K–N) Transverse sections of thoracic spinal cord at stage 27, after grafting EBs grown with RA (2 M) and anti-Hh antibody (5E1, 30 g/ml). No mouse-derived MNs were detected either by eGFP (K) or by a mousespecific anti-HB9 antibody (L). In contrast, many mouse-derived NCAM (M) and Lim2 (N) interneurons are present. (O–Q) Transverse sections through stage 27 spinal cord at thoracic (O and P) and lumbar (Q) levels after grafting MN-enriched EBs. eGFP MNs are concentrated in the ventral spinal cord. Ectopic eGFP MNs are located within the lumen of the spinal cord. eGFP axons exit the spinal cord primarily via the ventral root and project along nerve branches that supply axial (O–Q), body wall (O and P), and dorsal and ventral limb (Q) muscles. The pathway of axons is detected by neurofilament (NF) expression. eGFP axons are not detected in motor nerves that project to sympathetic neuronal targets.

Μεταμόσχευση κινητικών νευρώνων μετά από κατευθυνόμενη διαφοροποίηση

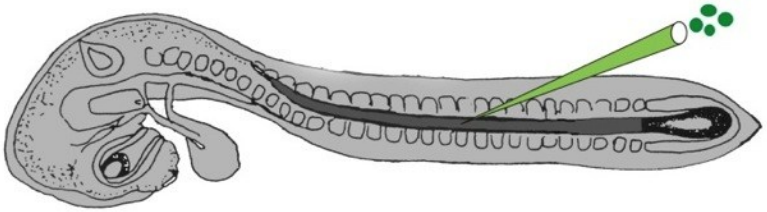


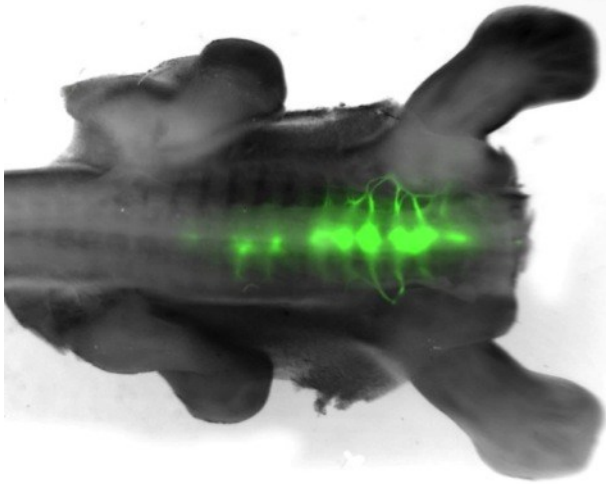




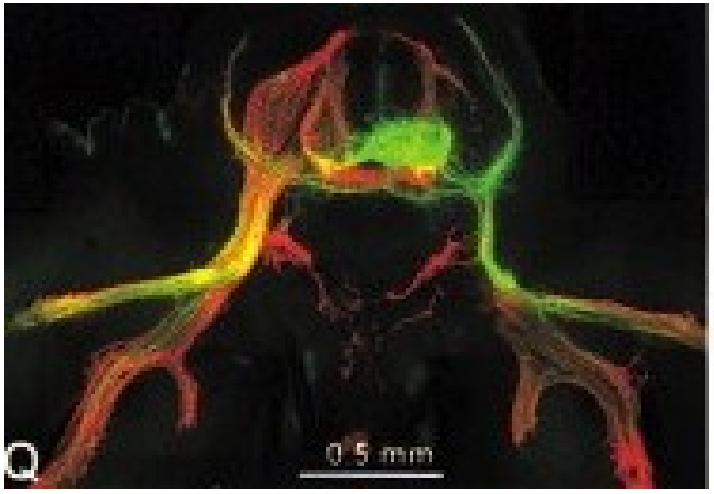
Μεταμόσχευση κινητικών νευρώνων μετά από κατευθυνόμενη διαφοροποίηση

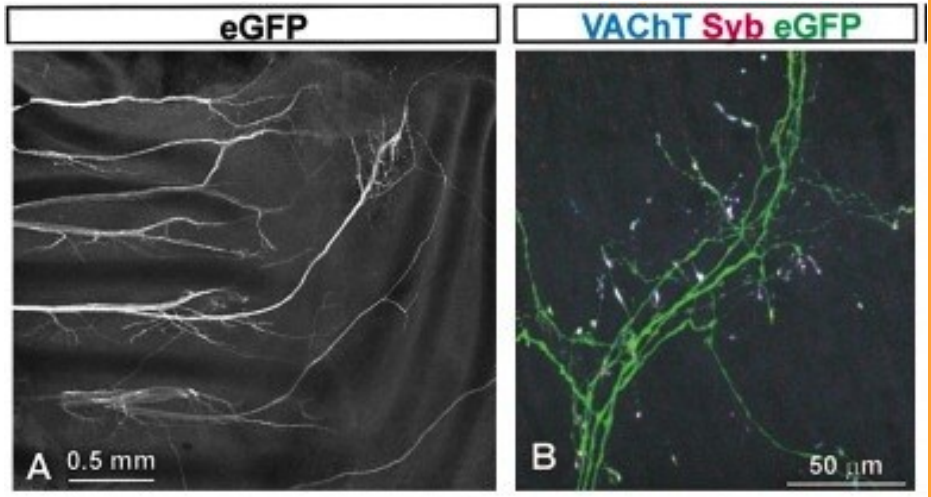
Ένεση των διαφοροποιημένων in vitro ΚΝ (ποντικού) σε έμβρυο όρνιθας



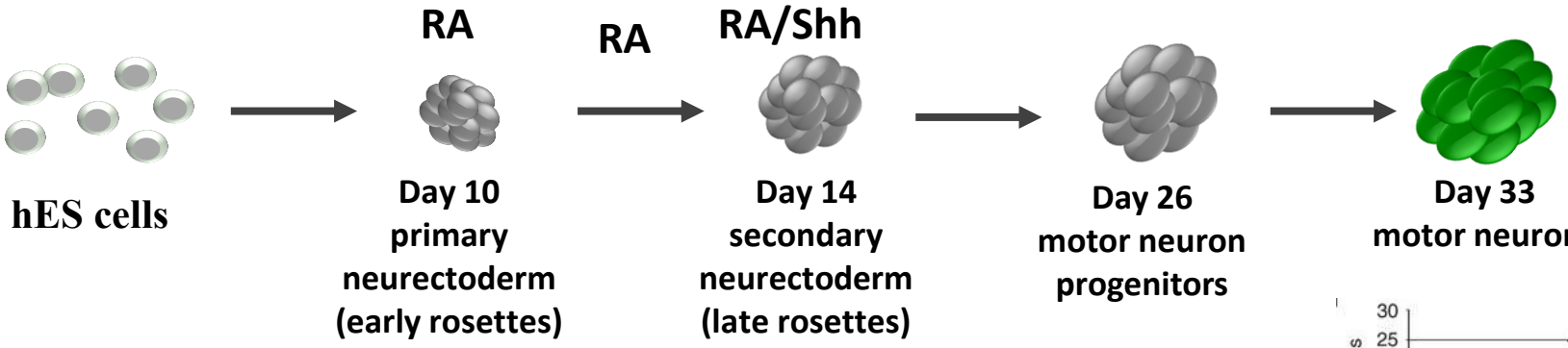


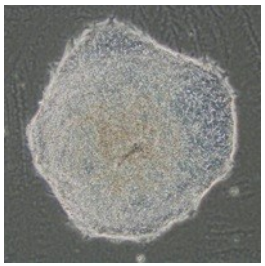
Οι νευρώνες επιβιώνουν και νευρώνουν μύες





Κατευθυνόμενη διαφοροποίηση hESC σε κινητικούς νευρώνες

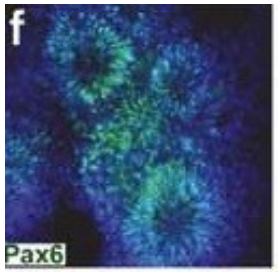




hES

10 μέρες

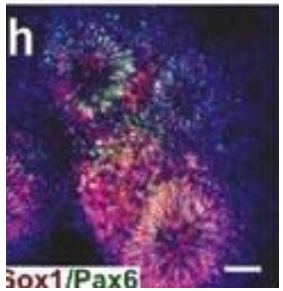
RA



Πρωιμες ροζέττες

RA

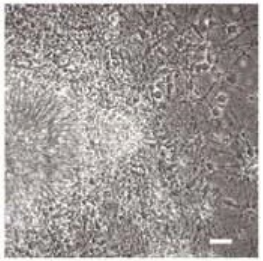
4 μέρες



Όψιμες ροζέττες

12 μέρες

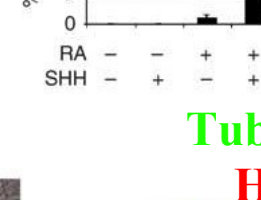
1 νM Shh agc + RA



Πρόδρομοι KN

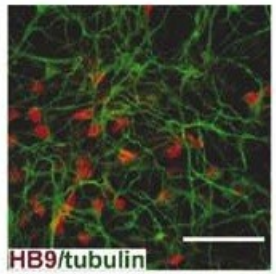
7 μέρες

1 νM Shh agonist + RA



Tubulin

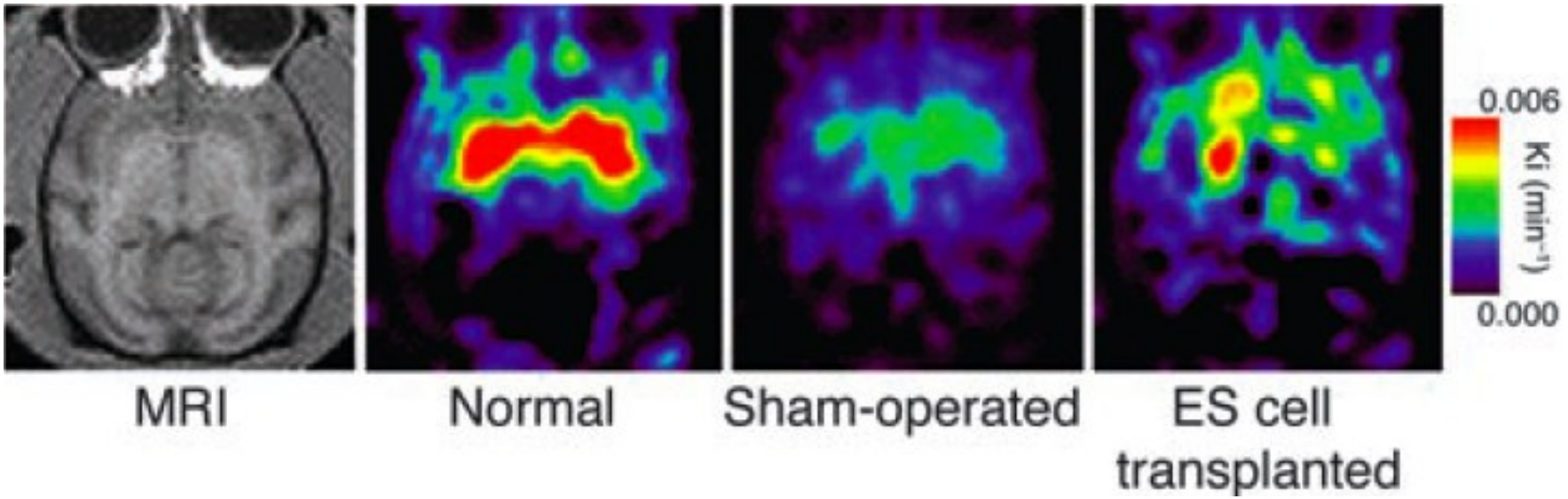
Hb9



KN

Li et al., Nature Neuroscience (2005)

Μεταμόσχευση διαφοροποιημένων ES

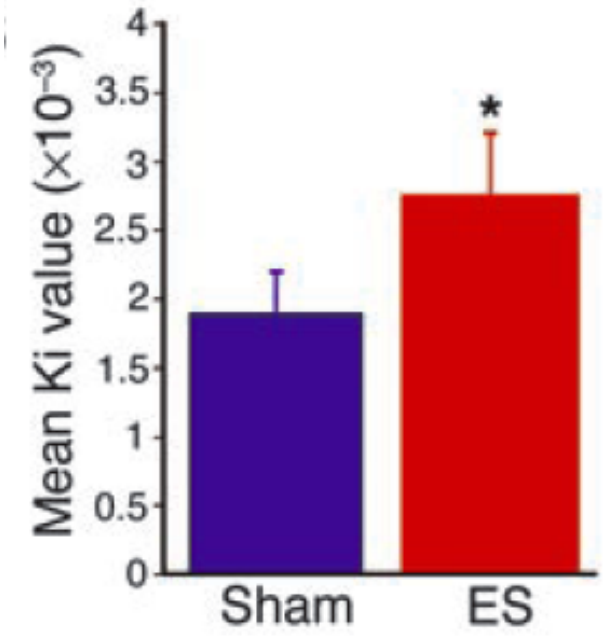


- Η συμπεριφορά των ζώων μετά τη μεταμόσχευση βελτιώνεται.

Κινητικότητα

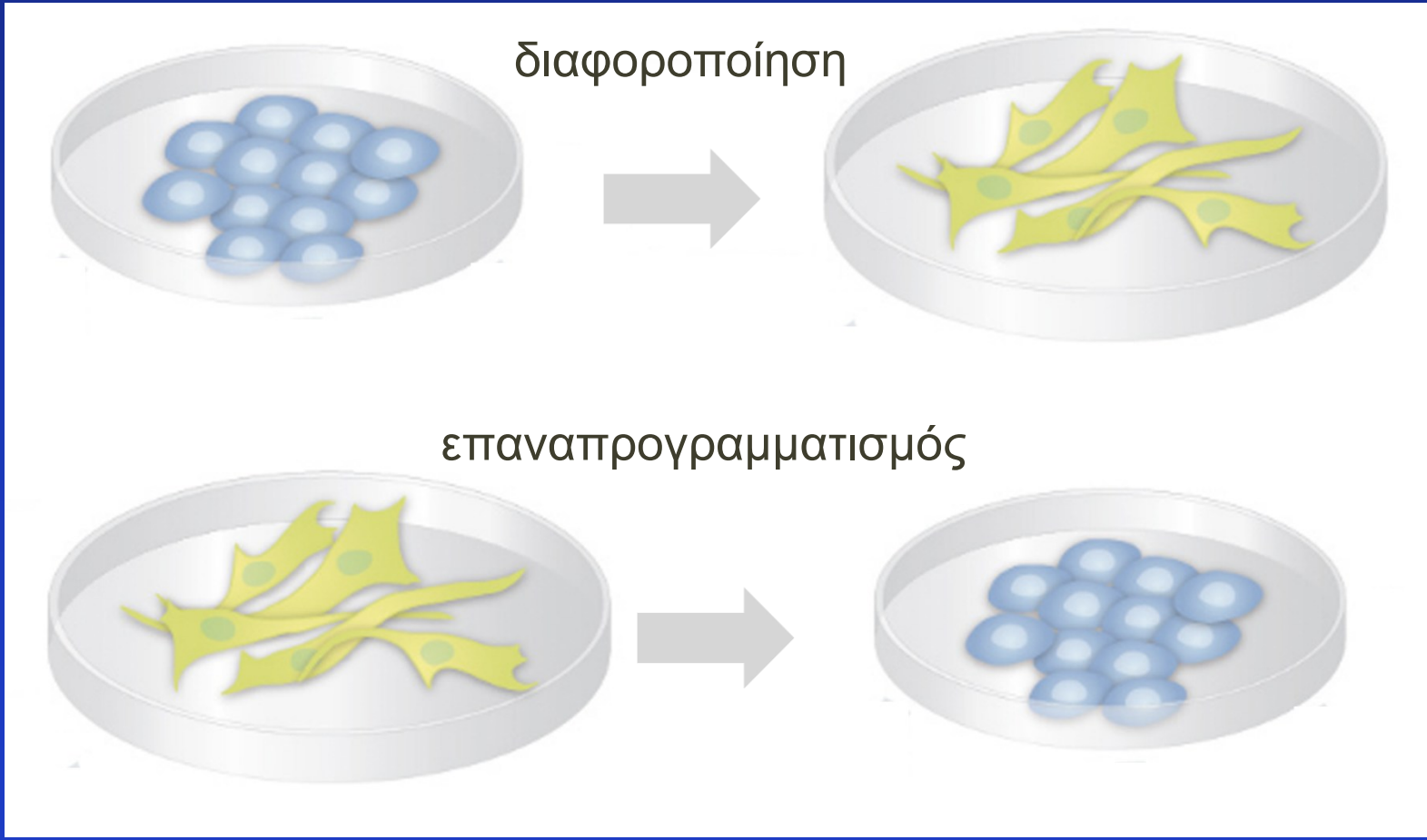
Στάση

Τρεμώδεις κινήσεις κεφαλής



Όμως....

- Ηθικοί λόγοι
- Απόρριψη απο τον δότη



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

Kazutoshi Takahashi[1] **and Shinya Yamanaka**[1,2,*]
[1] Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
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DOI 10.1016/j.cell.2006.07.024

SUMMARY

Differentiated cells can be reprogrammed to an embryonic-like state by transfer of nuclear contents into oocytes or by fusion with embryonic stem (ES) cells. Little is known about factors that induce this reprogramming. Here, we demonstrate induction of pluripotent stem cells from mouse embryonic or adult fibroblasts by introducing four factors, Oct3/4, Sox2, c-Myc, and Klf4, under ES cell culture conditions. Unexpectedly, Nanog was dispensable. These cells, which we designated iPS (induced pluripotent stem) cells, exhibit the morphology and growth properties of ES cells and express ES cell marker genes. Subcutaneous transplantation of iPS cells into nude mice resulted in tumors containing a variety of tissues from all three germ layers. Following injection into blastocysts, iPS cells contributed to mouse embryonic development. These data demonstrate that pluripotent stem cells can be directly generated from fibroblast cultures by the addition of only a few defined factors.

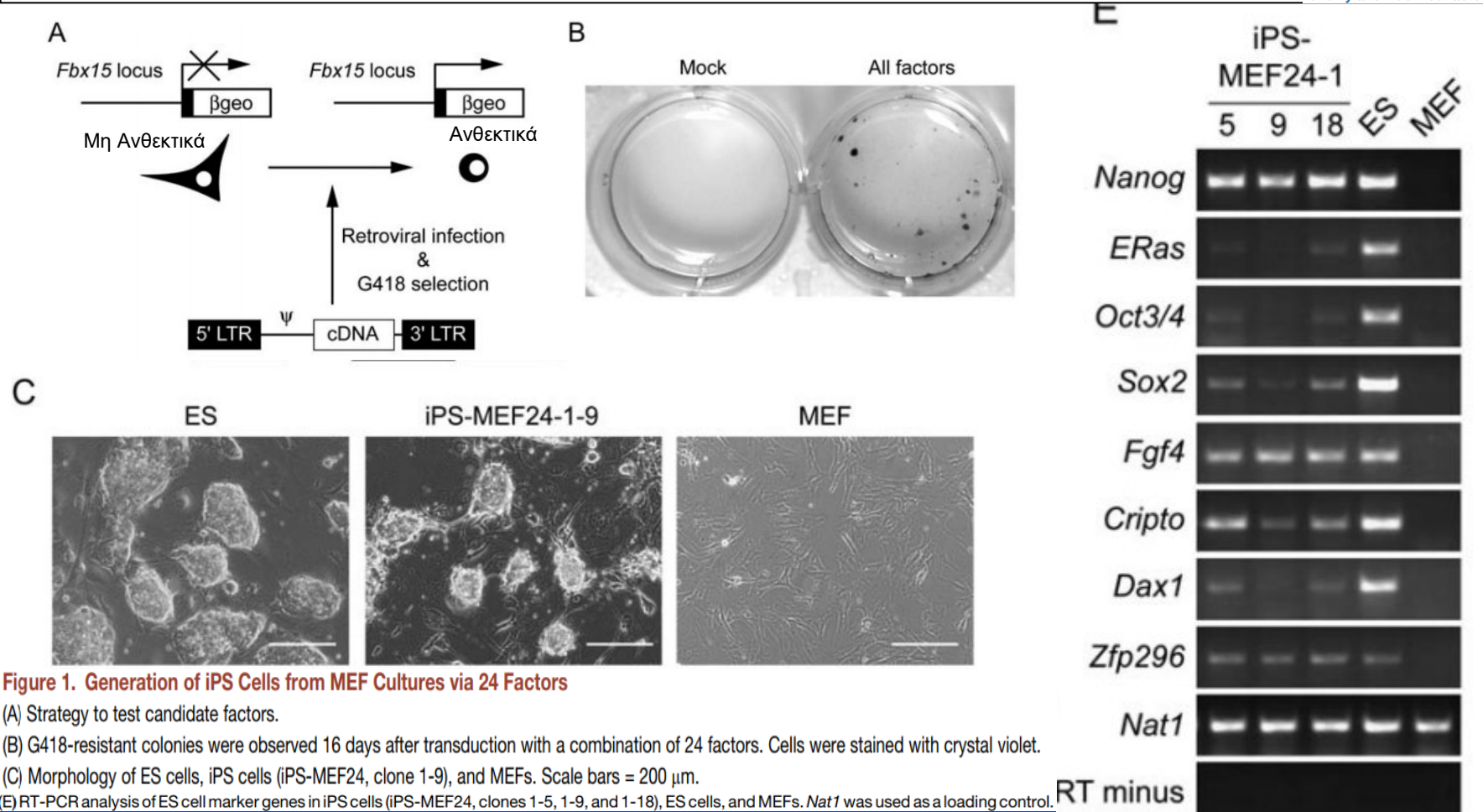


Figure 1. Generation of iPS Cells from MEF Cultures via 24 Factors

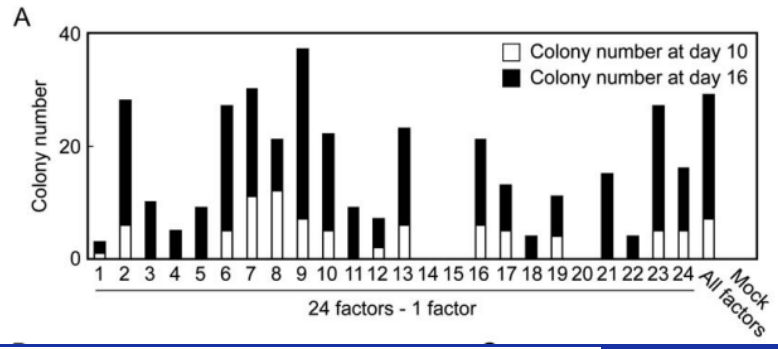
(A) Strategy to test candidate factors.

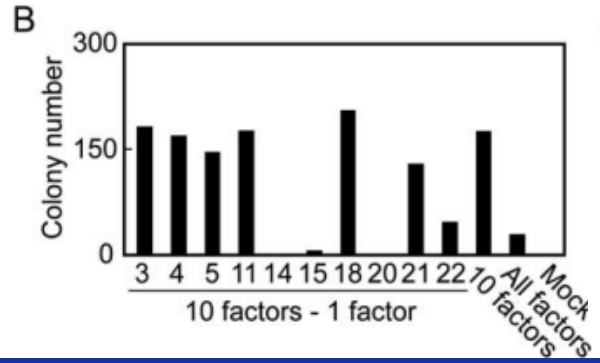
(B) G418-resistant colonies were observed 16 days after transduction with a combination of 24 factors. Cells were stained with crystal violet.

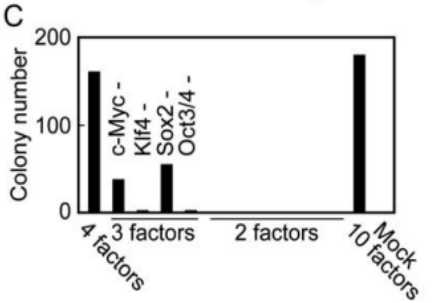
(C) Morphology of ES cells, iPS cells (iPS-MEF24, clone 1-9), and MEFs. Scale bars = 200 μm.

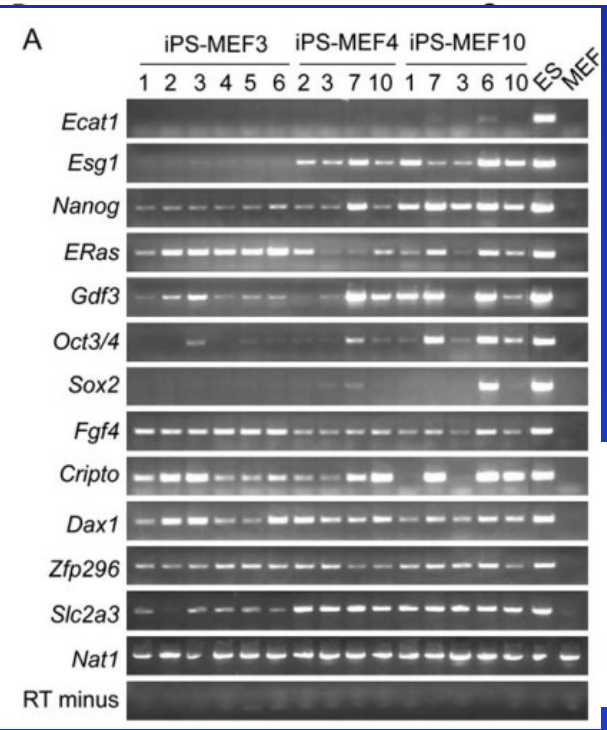
(E) RT-PCR analysis of ES cell marker genes in iPS cells (iPS-MEF24, clones 1-5, 1-9, and 1-18), ES cells, and MEFs. *Nat1* was used as a loading control.

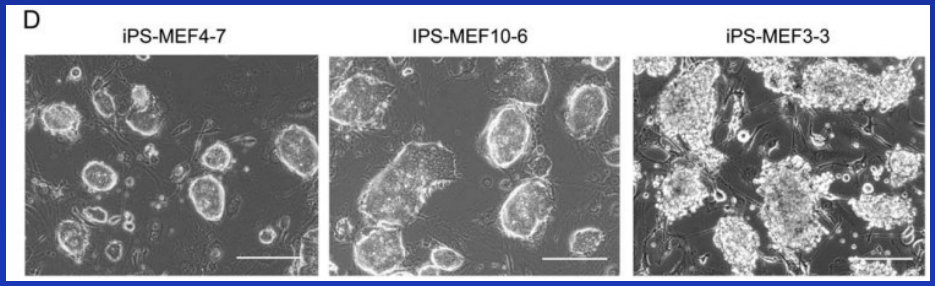
Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors











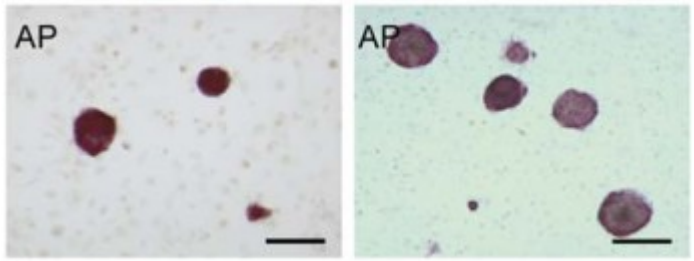
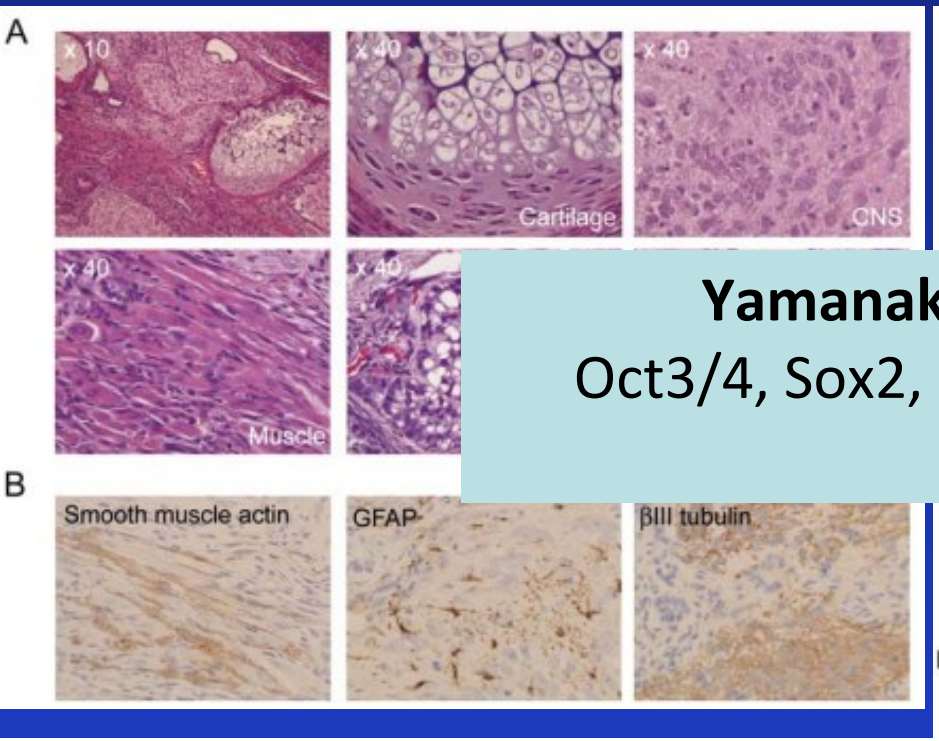


Figure 2. Narrowing down the Candidate Factors
(A) Effect of the removal of individual factors from the pool of 24 transduced factors on the formation of G418-resistant colonies. Fbx15bgeo/bgeo MEFs were transduced with the indicated factors and selected with G418 for 10 days (white columns) or 16 days (black columns).
(B) Effect of the removal of individual factors from the selected 10 factors on the formation of G418-resistant colonies 16 days after transduction.
(D) Morphologies of iPS-MEF4 (clone 7), iPS-MEF10 (clone 6), and iPS-MEF3 (clone 3). Scale bars = 200 mm.

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

Yamanaka factors:
Oct3/4, Sox2, c-Myc and Klf4



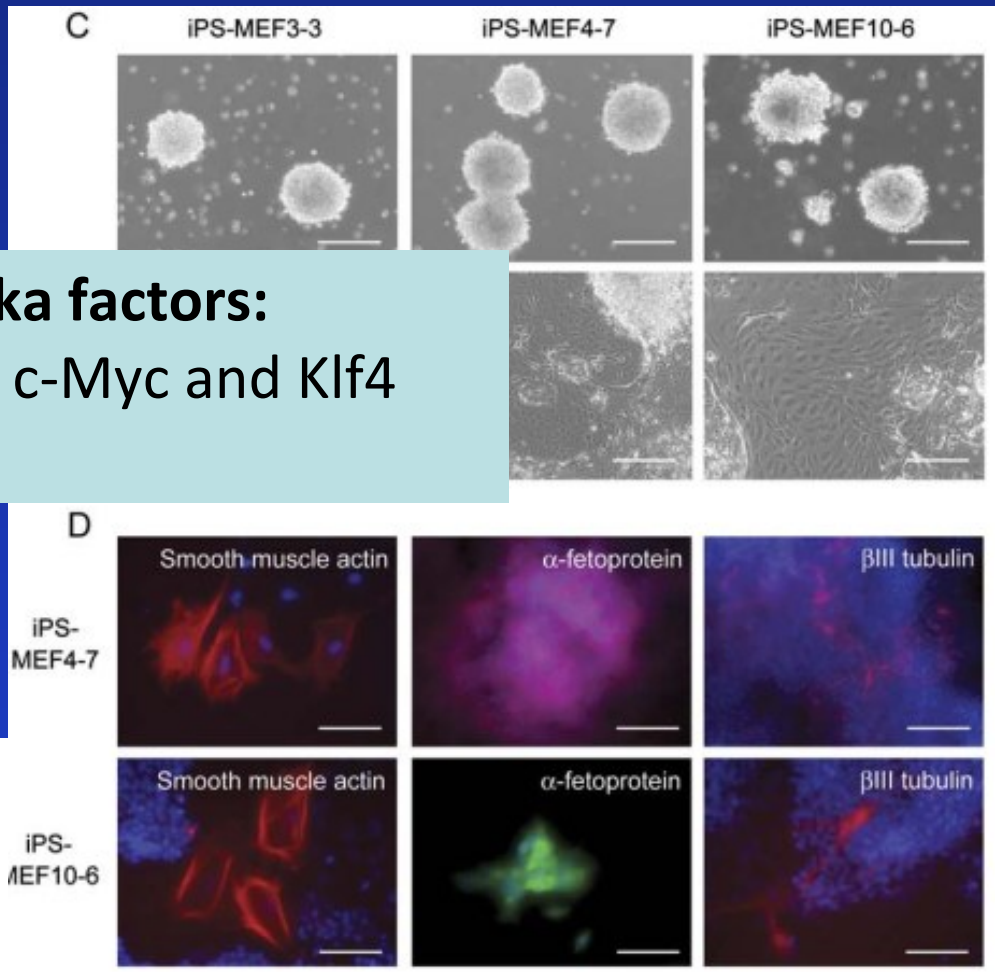
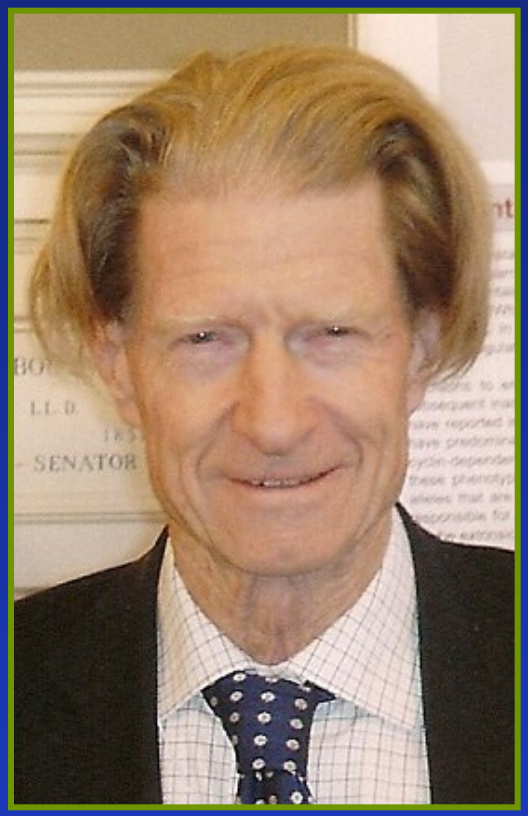
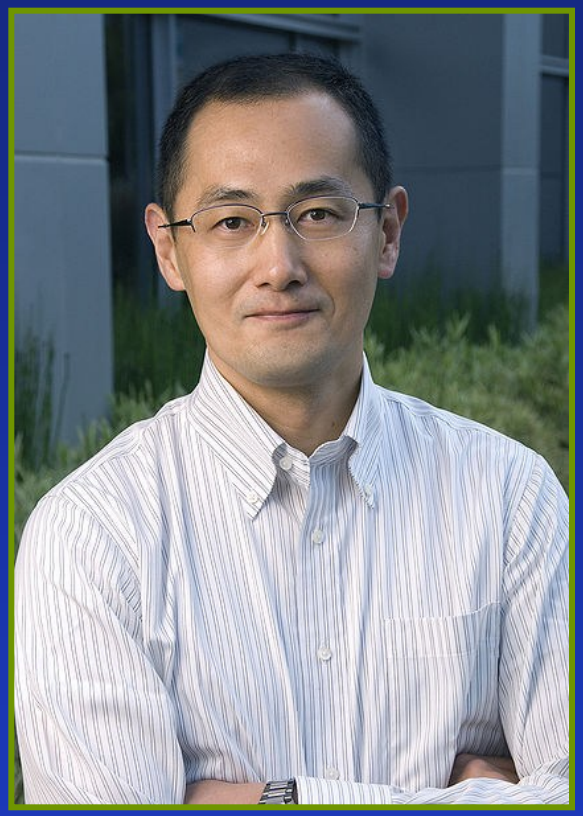


Figure 5. Pluripotency of iPS Cells Derived from MEFs
(A) Various tissues present in teratomas derived from iPS-MEF4-7 cells. (B) Immunostaining confirming differentiation into neural tissues and muscles in teratomas derived from iPS-MEF4-7. (C) In vitro embryoid body formation (upper row) and differentiation (lower row). Scale bars = 200 mm. (D) Immunostaining confirming in vitro differentiation into all three germ layers. Scale bars = 100 mm. Secondary antibodies were labeled with Cy3 (red), except for a-fetoprotein in iPSMEF10-6, with which Alexa 488 (green) was used.

2012 Nobel Prize in Medicine





J. Gurdon
Department of Zoology, University of Cambridge

S. Yamanaka
Institute of Cardiovascular Disease, San Francisco

"revolutionized our understanding of how cells & organisms develop"

Κυτταρικές θεραπείες η πρώτη απόπειρα έγινε πριν από περίπου 68 χρόνια!

The NEW ENGLAND JOURNAL of MEDICINE

INTRAVENOUS INFUSION OF BONE MARROW IN PATIENTS RECEIVING RADIATION AND CHEMOTHERAPY*

E. Donnall Thomas, M.D.,† Harry L. Lochte, Jr., M.D.,‡ Wan Ching Lu, Ph.D.,§ and Joseph W. Ferrebee, M.D.¶

Cooperstown, New York, and Boston, Massachusetts

Κυτταρικές θεραπείες χαρακτηρισμός πληθυσμού

RADIATION RESEARCH 14, 213-222 (1961)

A Direct Measurement of the Radiation Sensitivity of Normal Mouse Bone Marrow Cells[1]

J. E. TILL AND E. A. McCULLOCH

Department of Medical Biophysics, University of Toronto, and the Divisions of Biological Research and Physics of the Ontario Cancer Institute, Toronto, Ontario

Κυτταρικές θεραπείες η πρώτη αλλογενής μεταμόσχευση μυελού των οστών..

THE LANCET

Volume 292, Issue 7583, 28 December 1968, Pages 1366–1369

Originally published as Volume 2, Issue 7583

IMMUNOLOGICAL RECONSTITUTION OF SEX-LINKED LYMPHOPENIC IMMUNOLOGICAL DEFICIENCY

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Κυτταρικές θεραπείες η πρώτη μεταμόσχευση κυττάρων ομφαλοπλακουντιακού αίματος ..

The NEW ENGLAND JOURNAL of MEDICINE

Originally published: N Engl J Med. 1989 Oct 26;321(17):1174-8. pmid: 2571931

Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling

Eliane Gluckman[1], Hal E. Broxmeyer[2], Arleen D. Auerbach[3], Henry S. Friedman[4], Gordon W. Douglas[5], Agnes Devergie[1], Helene Esperou[1], Dominique Thierry[6], Gerard Socie[1], Pierre Lehn[1], Scott Cooper[2], Denis English[2], Joanne Kurtzberg[4], Judith Bard[7], and Edward A. Boyse[7]

Σε αυτές οι κυτταρικές θεραπείες χρησιμοποιούνται βλαστοκύτταρα (πριν από τον όρο) αλλά αυτά είναι σωματικά βλαστοκύτταρα !

ES και κυτταρικές θεραπείες

Κυτταρικές θεραπείες βασιζόμενες στα ES

- ✓ Μεταμόσχευση **διαφοροποιημένων** κυττάρων τα οποία προέρχονται από βλαστοκύτταρα. Στην περίπτωση αυτή τα βλαστοκύτταρα αναπτύσσονται στο εργαστήριο, διαφοροποιούνται προς συγκεκριμένο κυτταρικό τύπο και ακολουθεί μεταμόσχευσή τους (π.χ. διαφοροποίηση νευρώνων που παράγουν ντοπαμίνη για τη θεραπεία της νόσου Parkinson). Τα βλαστοκύτταρα ενδέχεται να είναι εμβρυϊκής (ή σωματικής προέλευσης) και ιδανικά του ίδιου του ασθενούς ώστε να μην ανακύπτουν προβλήματα με τη συμβατότητα (εξατομικευμένη θεραπευτική προσέγγιση).

- ✓ Μεταμόσχευση **μη διαφοροποιημένων** βλαστοκυττάρων: Σε ορισμένες περιπτώσεις, πιθανόν να είναι δυνατή ή/και απαραίτητη η απευθείας χορήγηση βλαστοκυττάρων στον ασθενή, ούτως ώστε να είναι δυνατός ο αποικισμός στο σωστό σημείο του σώματος και η συνεχής διαφοροποίηση στον επιθυμητό τύπο κυττάρων.

ES και κυτταρικές θεραπείες

Κυτταρικές θεραπείες βασιζόμενες στα ES

Για να προχωρήσουν χρειάζεται από πλευράς βασικής έρευνας

- ✓ Γνώση των μηχανισμών που ρυθμίζουν την ανάπτυξη, και τη διαφοροποίηση των βλαστοκυττάρων.
- ✓ Διασφάλιση της βιωσιμότητας αλλά και της λειτουργικότητας των κυττάρων για μεγάλο χρονικό διάστημα μετά από τη μεταμόσχευση

ES και κυτταρικές θεραπείες

Προβλήματα στην εφαρμογή

➢ Στα περισσότερα πρωτόκολλα διαφοροποίησης, τα κύτταρα που μας ενδιαφέρουν είναι ένα ποσοστό του συνολικού πληθυσμού. Προκειμένου να ξεπεραστεί αυτό το πρόβλημα ακολουθούνται διάφορες προσεγγίσεις:

α) Απομόνωση των κυττάρων με τη βοήθεια αντισωμάτων που εκφράζονται στον πληθυσμό που μας ενδιαφέρει (πχ. Μαγνητικά σφαιρίδια ή FACS)

β) Γενετικά τροποποιημένα κύτταρα ES στα οποία ένας δείκτης εκφράζεται κάτω από τον έλεγχο ενός ιστοειδικού υποκινητή – ο δείκτης επιτρέπει την ταυτοποίηση - απομόνωση του πληθυσμού π.χ με χρήση αντισωμάτων. Ακόμα ο δείκτης μπορεί να κωδικοποιεί ανθεκτικότητα σε αντιβιοτικό.

Αυτή η προσέγγιση δεν είναι πολύ επιθυμητή.

ES και κυτταρικές θεραπείες

Προβλήματα στην εφαρμογή.

Καρκινογένεση

➢Τα μη διαφοροποιημένα ES προκαλούν τερατώματα, οπότε θα πρέπει να εξασφαλιστεί με κάποιο τρόπο η μεταμόσχευση διαφοροποιημένων κυττάρων και μόνο.

α) Οι προηγούμενες προσεγγίσεις

β) Αρνητική επιλογή για έκφραση δεικτών πολυδυναμίας

γ) Γενετική τροποποίηση των ES ώστε σε περίπτωση προβλήματος τα μη διαφοροποιημένα κύτταρα να πεθαίνουν.

Απόρριψη μοσχεύματος - τα ES εκφράζουν υψηλά επίπεδα αντιγόνων ιστοσυμβατότητας

α) Αντικατάσταση του συμπλέγματος ιστοσυμβατότητας

β) Ένθεση μορίων που προάγουν την ανοσοκαταστολή π.χ. Fas ligand.

γ) Δημιουργία αδρανοποιητικών μεταλλάξεων για μόρια που ενέχονται στην απόρριψη όπως ο CD40 ligand.

δ) Custom tailored ES.

ES και κυτταρικές θεραπείες

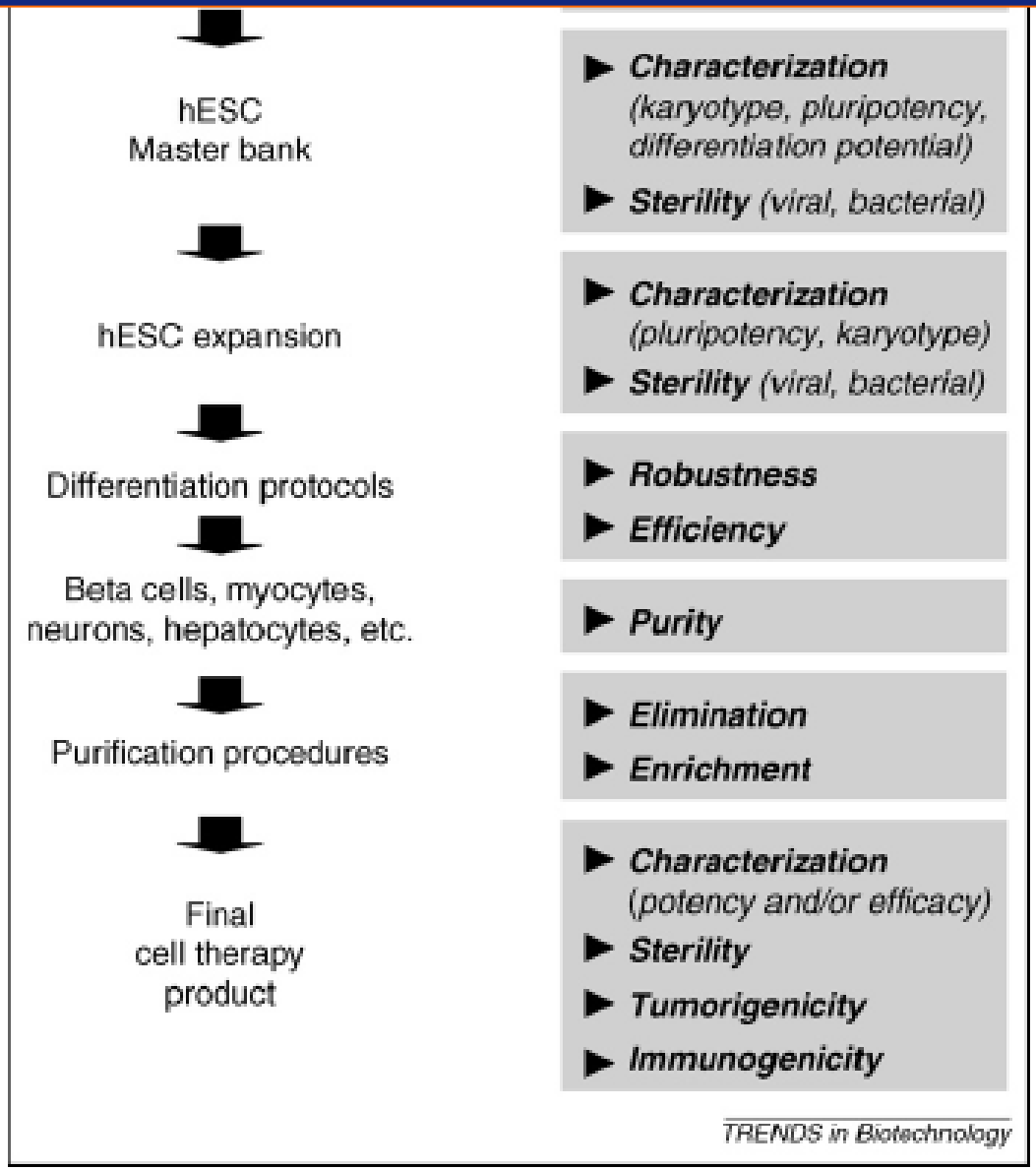


Figure 1. Outline of a general strategy to generate a clinically compliant hESC product. Each step of the procedure is depicted, and all critical issues are highlighted in grey boxes. For details, see text 'General strategy to develop a clinically compliant cell therapy product from hESC'. Abbreviations: cGMP, current Good Manufacturing Practice; IRB, Institutional Review Board.

ES και κυτταρικές θεραπείες

Table 1. Overview of methods to eliminate unwanted cells and/or enrich for the desired cell type

Selection Method	Principle	Advantages	Disadvantages	Example
(a) Positive selection				
Genetically engineered hESC	Transfection with a fusion gene consisting of a desired tissue-specific promoter driving a resistance gene	Stringent selection, many examples for proof-of-principle in mESC	Genetic manipulation introduces another level of complexity – regulatory concerns	α-cardiac myosin heavy chain promoter driving a neomycin resistance gene for cardiomyocyte enrichment from mESC
Selection by specific ectopic marker expression	Purification of the desired cell type with antibodies against specific cell surface markers	Highly stringent selection for clinical use	Antibody specificity is crucial, costs	FACS or MACS® sorting of $CD34^+$ human hematopoetic progenitor cells
Purification on physical properties	Separation of cells by density gradient centrifugation or differences in cell	Easy to perform, inexpensive,fast	Low specificity and low yields of enrichment	Enrichment of cardiomyocytes derived from hESC
(c) General manipulation				
Mitotical inactivation of the cell therapy product	Mitomycin C treatment blocks mitosis of the entire cell population	Easy to perform, inexpensive	Effects on the desired cell population unclear (e.g. integration into host tissue, long term survival)	ES cells differentiated to dopamine neurons and treated with Mitomycin C were in rodents and primates
Inducing differentiation of the remaining undifferentiated cells	Extended differentiation or an additional differentiation step by chemical induction to deplete remaining hESC (e.g. by retinoic acid)	Easy to perform, inexpensive	Efficiency of differentiation critical; undesired cell types are generated and might need to be removed	Unproven concept, but prolonged *in vitro* differentiation was shown to reduce teratoma formation

ES και κυτταρικές θεραπείες

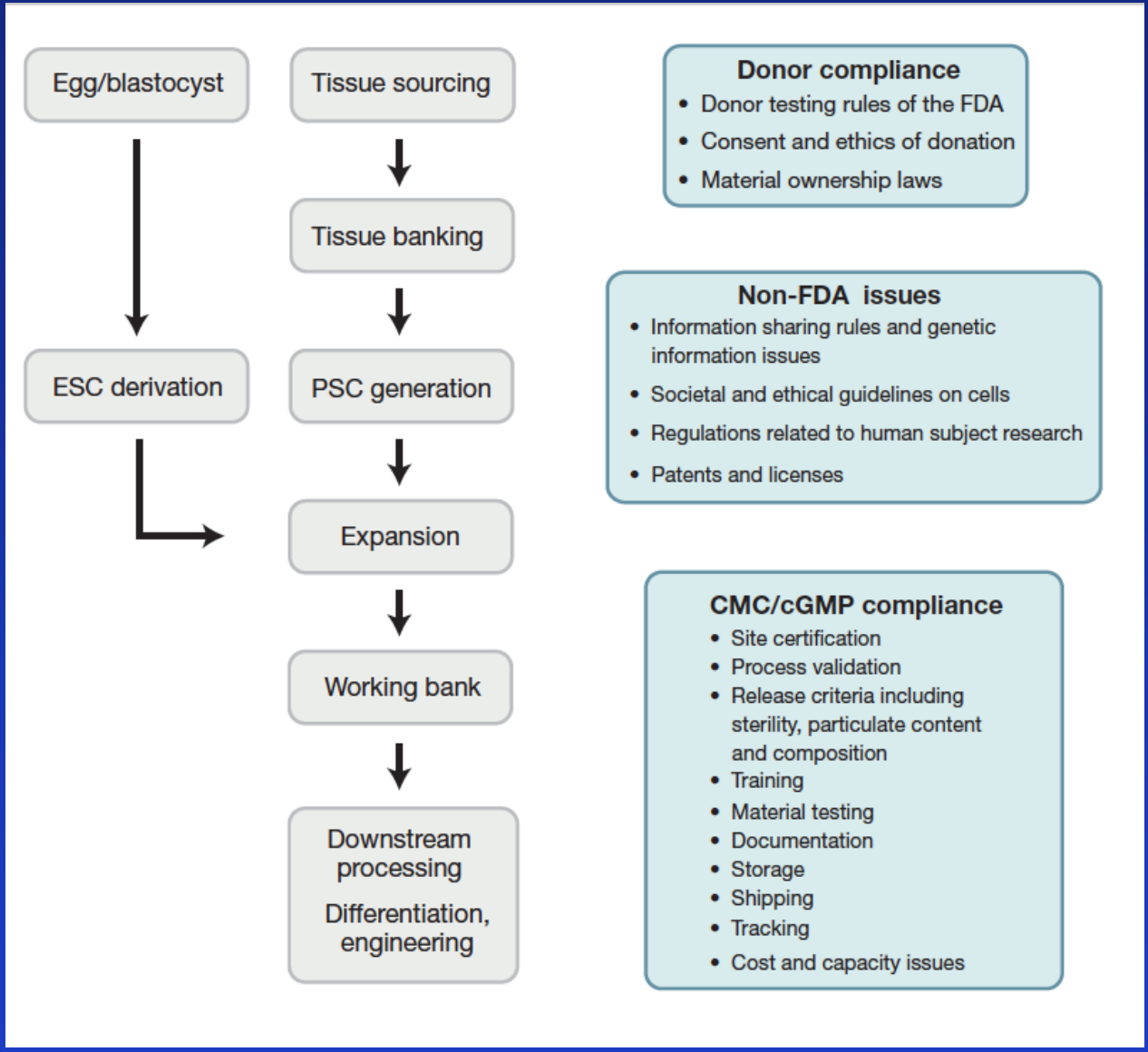
(b) Negative selection				
Genetically engineered hESC	Transfection with a fusion gene consisting of an undesired phenotype-specific promoter (e.g. *Oct-4*) driving a suicide gene	Highly selective elimination of undifferentiated, potentially harmful cells	Genetic manipulation introduces another level of complexity – regulatory concerns	Cell ablation by thymidine kinase expression in a non-selective manner
Selection on specific ectopic marker expression	Removal of the undesired cell type with antibodies against specific cell surface markers	Highly selective elimination of undifferentiated, potentially harmful cells	Ensuring high sensitivity, costs	Use of well-characterized hESC surface antigens such as SSEA-4 and TRA-60, to remove pluripotent cells
Targeted elimination by cytotoxic antibodies	Incubation with antibodies targeting and eliminating only undifferentiated cells	Highly selective (depending on the antibody), simple to perform, no additional steps involved	Ensuring high sensitivity, costs	Use of new, cell death-related hESC-specific epitopes
Purification on physical properties	Separation of cells by density gradient centrifugation or by differences in cell adherence	Easy to perform, inexpensive, fast	Low specificity and low yields of enrichment	Undifferentiated cells eliminated by discontinuous gradient centrifugation
Elimination of pluripotent cells by cytotoxic drugs	Undifferentiated cells with high proliferation rate targeted by drugs (e.g. nucleoside analogues)	Easy to perform, inexpensive, fast	Only applicable to finally differentiated cell populations, dormant stem cells not targeted	Ceramide analogues induce apoptosis in pluripotent cells

ES και κυτταρικές θεραπείες – Κλινικές δοκιμές

Phase I	Phase II	Phase III	Phase IV
Safety	Efficacy	Confirm Safety/ Efficacy	Post-approval Trials
-First dosing in humans -carried out in healthy volunteers or patients if no other effective treatments are available -Goals: -pharmokinetics -safety profile -signs of expected pharmacology	-many compounds fail at this stage (fail to demonstrate the anticipated effect or they are not well tolerated)	-Final testing stage before registration -usually randomized, placebo controlled and often using an active comparator (eg. Current standard of care)	-further trials are conducted after market approval for a number of reasons: -ongoing safety monitoring -address a specific regulatory issue
20-100 patients	10's to 100's patients	100's-1000's patients	

ES και κυτταρικές θεραπείες – Κλινικές δοκιμές

The manufacturing process for PSC-based therapies. Multiple **regulatory**, **ethical** and **business** issues must be considered (right). The figure excludes issues related to evaluation of cell therapies in clinical trials.



nature biotechnology volume 32 NUMBER 8 AUGUST 2014

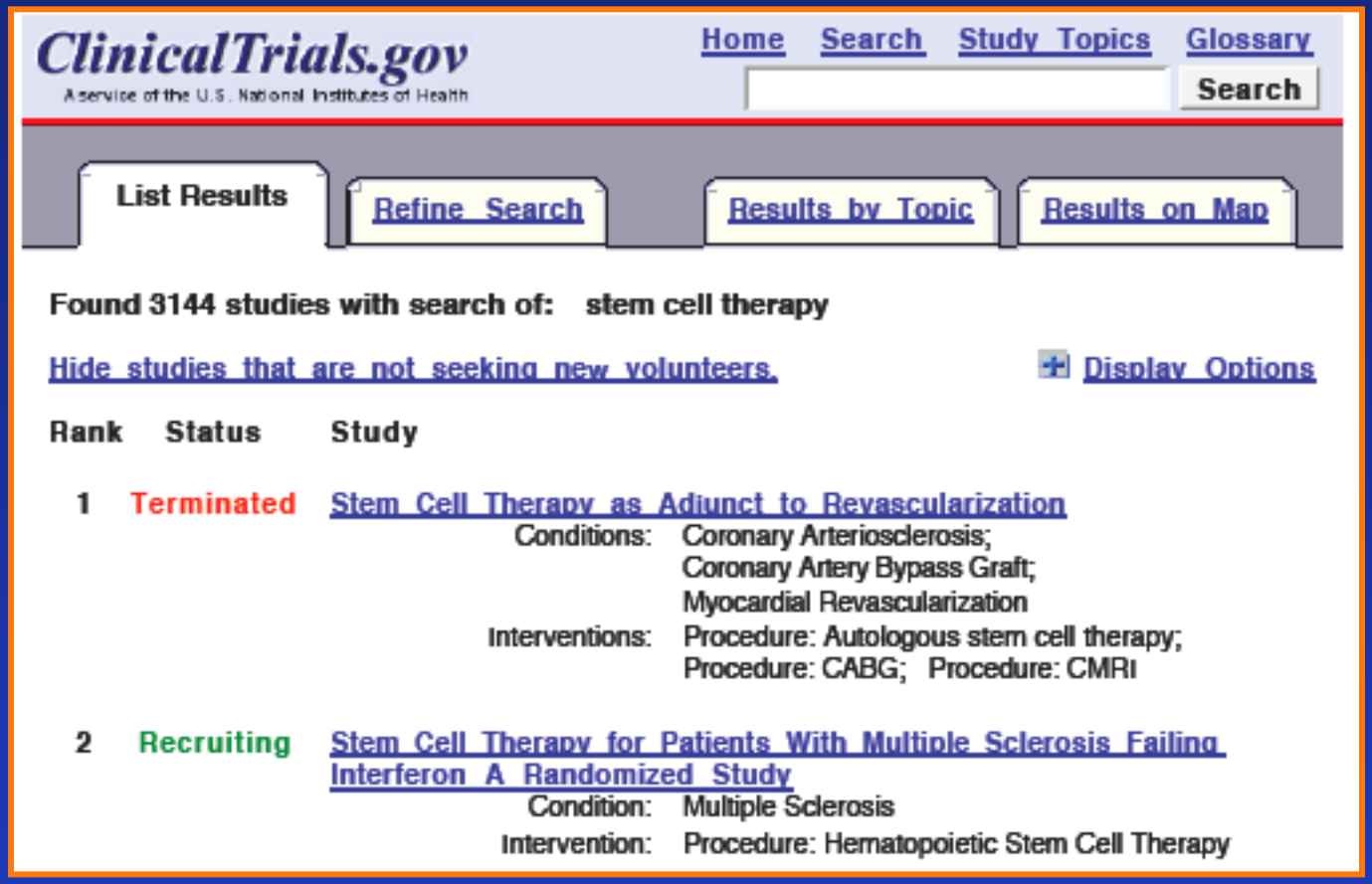
The Washington Post

FDA OKs 1st Embryonic Stem Cell Trial

By Steven Reinberg
HealthDay Reporter
Friday, January 23, 2009; 12:00 AM

FRIDAY, Jan. 23 (HealthDay News) -- The first human trial using embryonic stem cells as a medical treatment has been approved by the U.S. Food and Drug Administration.

ES και κυτταρικές θεραπείες



Οι περισσότερες από τις κλινικές δοκιμές αφορούν δοκιμές με βλαστοκύτταρα ενηλίκου (μυελός)

Η πρώτη κλινική δοκιμή στη Geron

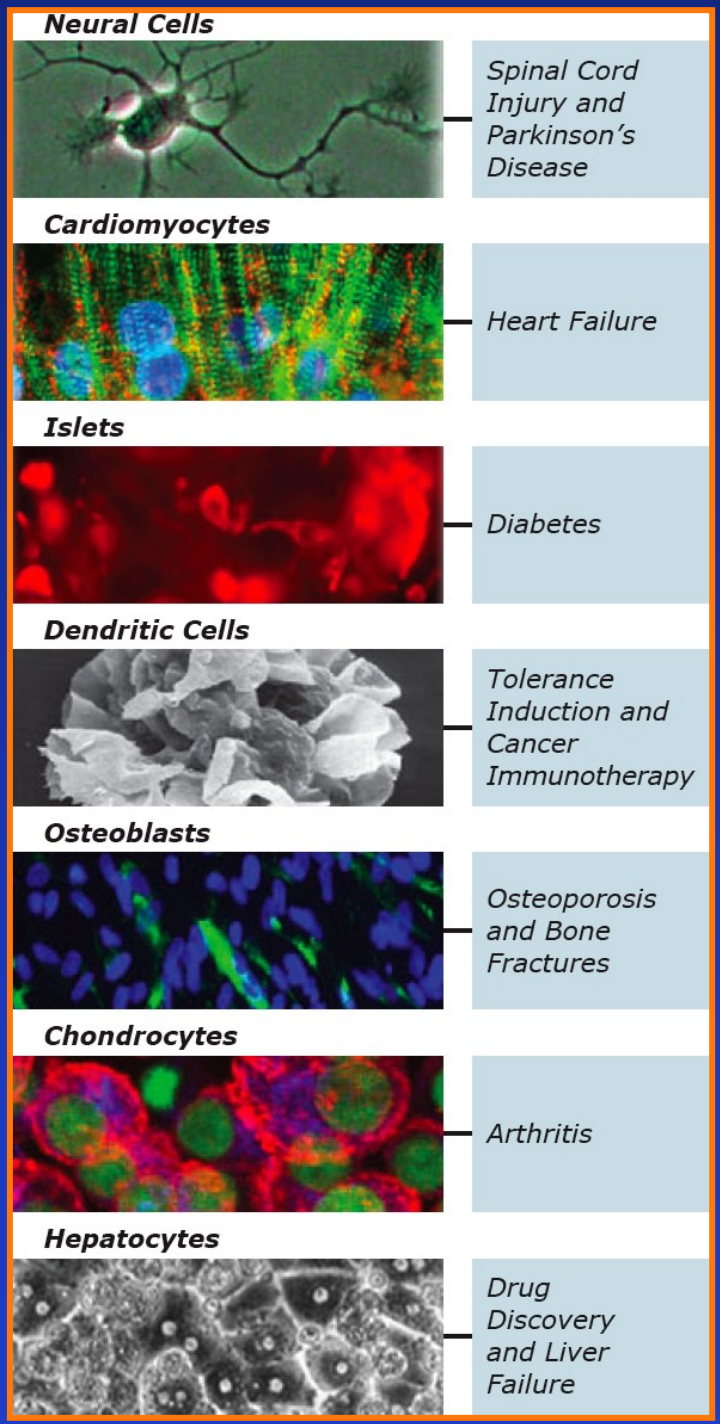
1. Τα κύτταρα

The hESCs with which Geron works were derived from surplus in vitro fertilized embryos originally created as part of an in vitro fertilization (IVF) procedure. The embryos, which would otherwise have been destroyed, were 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. 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.

Undifferentiated hESCs under carefully defined conditions, enabling them to be numerically expanded to form large cell banks (hundreds of vials of frozen undifferentiated hESCs) that serve as uniform starting material for manufacturing procedures that convert the undifferentiated hESCs into large numbers of functional therapeutic cells.

Η πρώτη κλινική δοκιμή στη Geron

Τα hESCs της Geron σύμφωνα με την εταιρεία έχουν διαφοροποιηθεί με επιτυχία προς



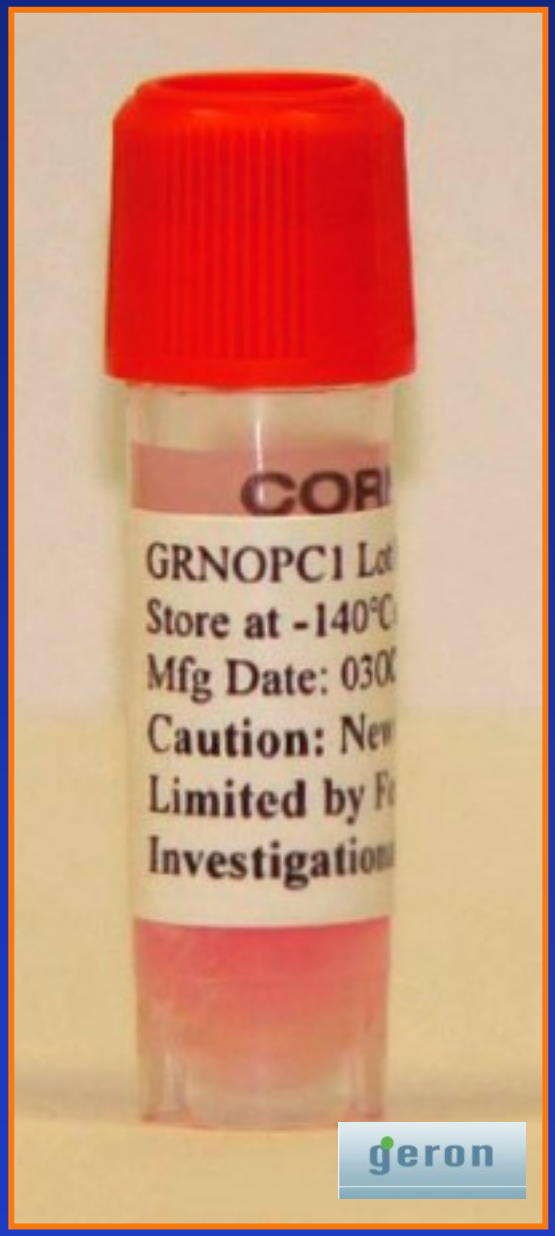
Η πρώτη κλινική δοκιμή στη Geron

2. Τα GRNOPC1 (το προϊόν)

- ✓ GRNOPC1 is a population of living cells containing oligodendrocyte progenitor cells (OPC).

- ✓ Oligodendrocytes:
  1. produce myelin
  2. produce neurotrophic factors to support the maintenance of nerve cells.

- ✓ Oligodendrocytes are lost in spinal cord injury, resulting in myelin and neuronal loss that cause paralysis in many patients with spinal cord injuries.



Safety Study of GRNOPC1 in Spinal Cord Injury

This study is currently recruiting participants.
Verified by Geron Corporation, March 2011

First Received: October 6, 2010 Last Updated: March 8, 2011 History of Changes

Sponsor:	Geron Corporation
Information provided by:	Geron Corporation
ClinicalTrials.gov Identifier:	NCT01217008

Purpose

The purpose of the study is to evaluate the safety of GRNOPC1 administered at a single time-point between 7 and 14 days post injury, inclusive, to patients with neurologically complete spinal cord injuries (SCI).

Condition	Intervention	Phase
Spinal Cord Injury	Biological: GRNOPC1	Phase I

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Control: Uncontrolled
Endpoint Classification: Safety Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Phase 1 Safety Study of GRNOPC1 in Patients With Neurologically Complete, Subacute, Spinal Cord Injury

Resource links provided by NLM:

MedlinePlus related topics: Spinal Cord Injuries

U.S. FDA Resources

Η πρώτη κλινική δοκιμή στη Geron

Further study details as provided by Geron Corporation:

Primary Outcome Measures:

- Safety [Time Frame: One year] [Designated as safety issue: Yes]

  The primary endpoint is safety, as measured by the frequency and severity of adverse events within 1 year (365 days) of GRNOPC1 injection that are related to GRNOPC1, the injection procedure used to administer GRNOPC1, and/or the concomitant immunosuppression administered.

Secondary Outcome Measures:

- Neurological function [Time Frame: One year]
  [Designated as safety issue: Yes]

  The secondary endpoint is neurological function as measured by sensory scores and lower extremity motor scores on International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) examinations.

Estimated Enrollment:	10
Study Start Date:	October 2010
Estimated Study Completion Date:	October 2012
Estimated Primary Completion Date:	October 2012 (Final data collection date for primary outcome measure)

Eligibility

Ages Eligible for Study:	18 Years to 65 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Major Inclusion Criteria:

- Neurologically complete, traumatic SCI (ASIA Impairment Scale A), zone of partial preservation < 5 levels
- Last fully preserved neurological level from T-3 through T-10
- From 18 through 65 years of age at time of injury
- Single spinal cord lesion
- Informed consent for this protocol and the companion long term follow-up protocol must be provided and documented (i.e., signed informed consent forms) no later than 11 days following injury
- Able to participate in an elective surgical procedure to inject GRNOPC1 7-14 days following SCI

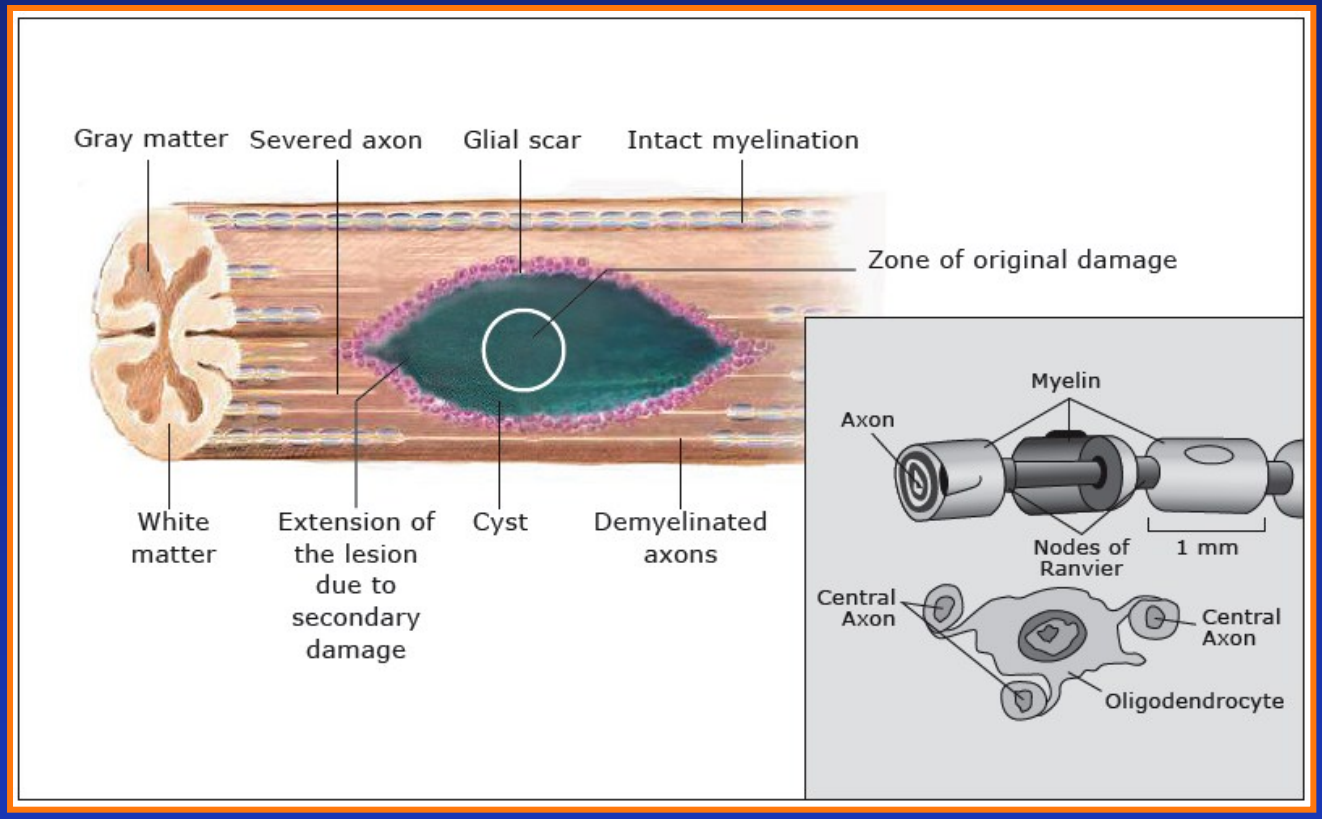
Major Exclusion Criteria:

- SCI due to penetrating trauma
- Traumatic anatomical transection or laceration of the spinal cord
- Any concomitant injury or pre-existing condition that interferes with the performance, interpretation or validity of neurological examinations
- Inability to communicate effectively with neurological examiner
- Significant organ damage or systemic disease that would create an unacceptable risk for surgery or immunosuppression
- History of any malignancy
- Pregnant or nursing women
- Body mass index (BMI) > 35 or weight > 300 lbs.
- Active participation in another experimental procedure/intervention

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01217008

Η πρώτη κλινική δοκιμή στη Geron

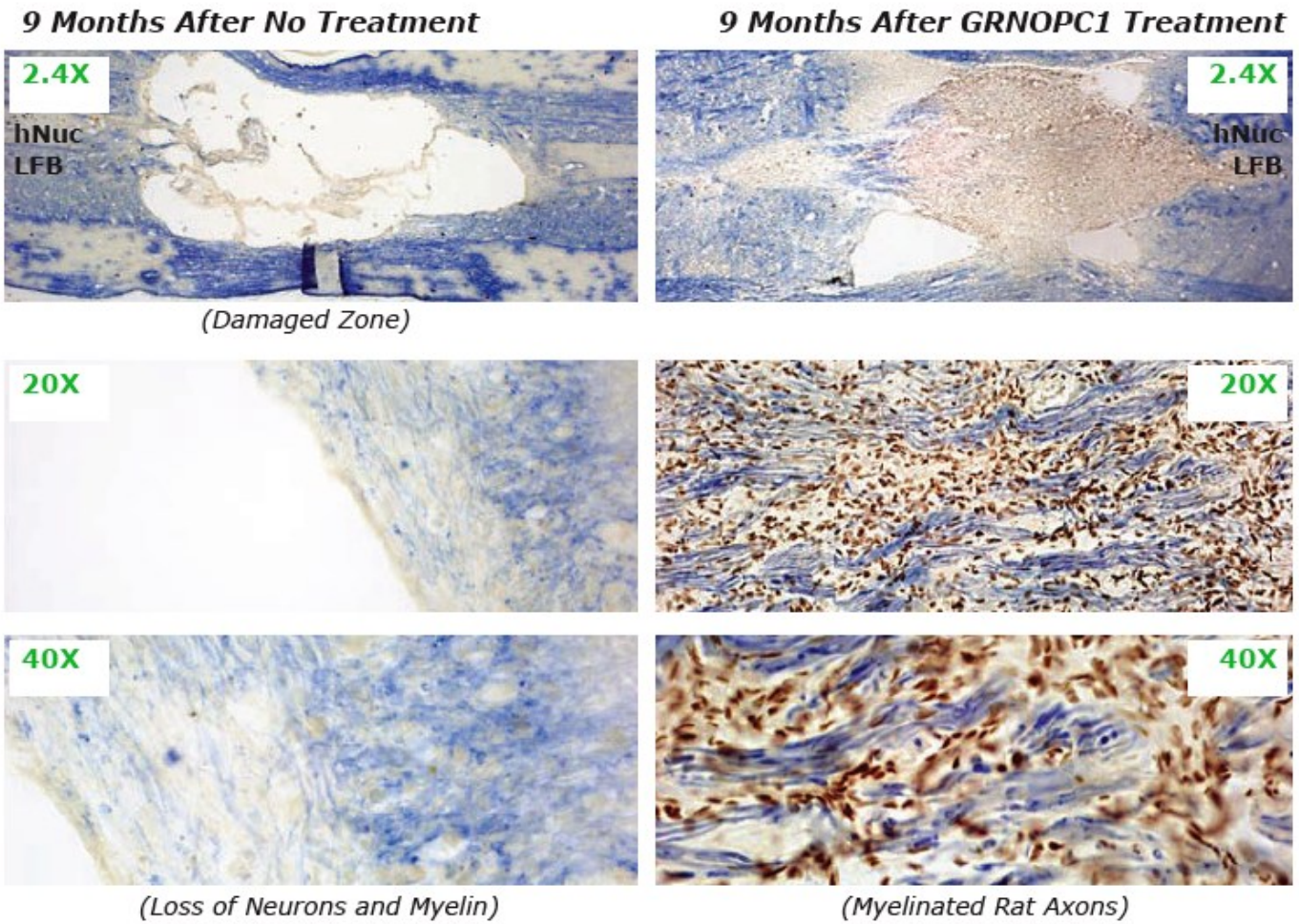


3. Πριν τη δοκιμή

Προκλινικές δοκιμές σε ζώα.
(Stem Cells and Development, Vol. 15, 2006)

- ✓ Το σύστημα που χρησιμοποιήθηκε περιέλάμβανε τη δημιουργία τραυματισμού στο νωτιαίο μυελό των αρουραίων και στη συνέχεια μεταμόσχευση των GRNOPC1 και μελέτη της κινητικής συμπεριφοράς των ζώων μετά τη μεταμόσχευση

Η πρώτη κλινική δοκιμή στη Geron



Στα ζώα καταγράφηκε επιβίωση των μεταμοσχευμένων κυττάρων, πολλαπλασιασμός, μετανάστευση των κυττάρων και κάλυψη της περιοχής της βλάβης.

Η συμπεριφορά των ζώων σε σχέση με τα control ήταν βελτιωμένη.

Journal of Neuroscience, Vol. 25, May 2005

Η πρώτη κλινική δοκιμή στη Geron

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Journal of Neuroscience, Vol. 25, May 2005

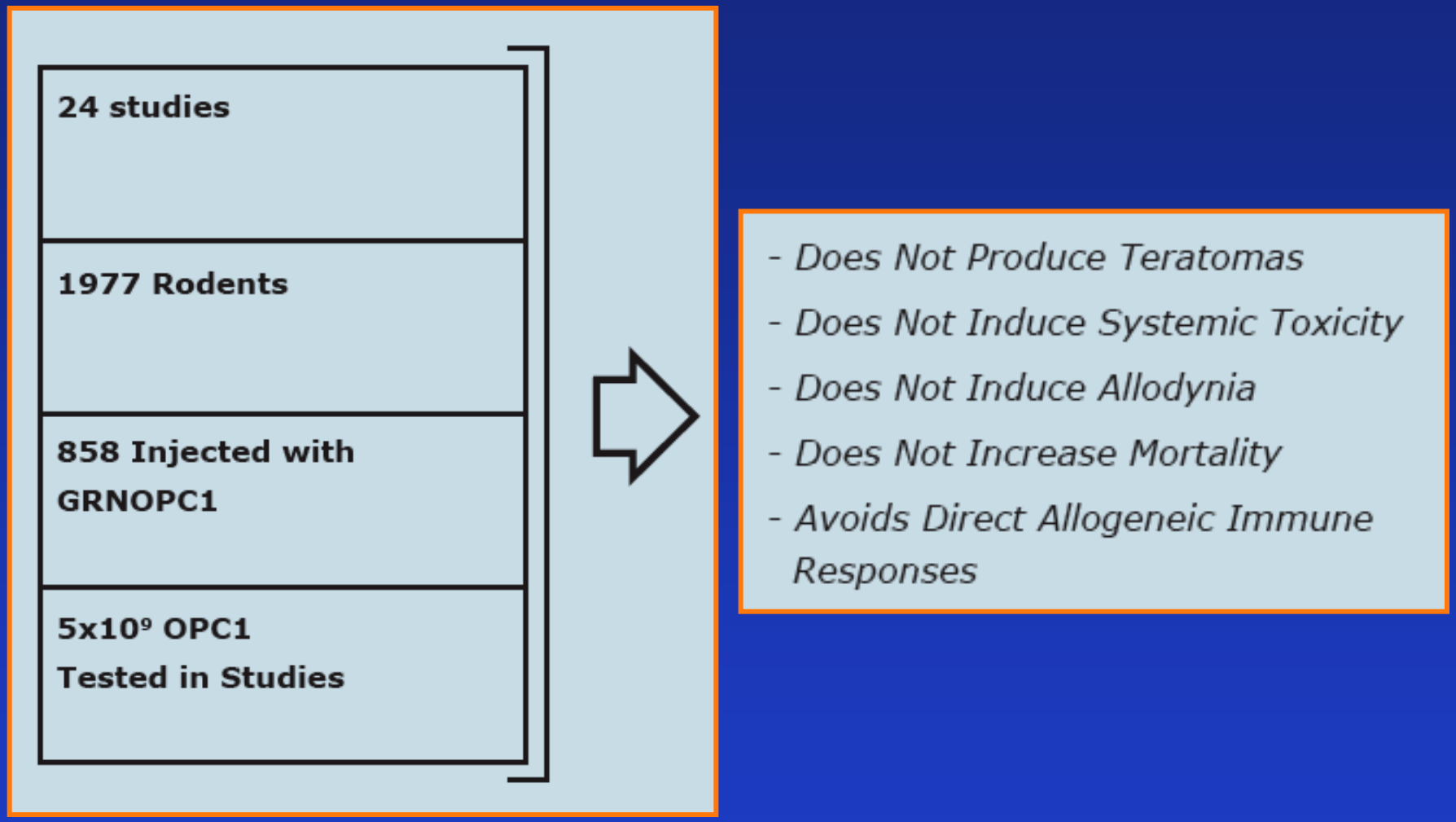
Η πρώτη κλινική δοκιμή στη Geron

3. Πριν τη δοκιμή

Δοκιμές ασφάλειας

- ✓ 24 separate studies in rats and mice that required more than five billion GRNOPC1 cells. The IND application (Investigational New Drug) contained more than 21,000 pages of data from the animal and in vitro testing of the cells to ensure the highest possible degree of safety of the product before initiating human clinical trials.

Η πρώτη κλινική δοκιμή στη Geron



3. Πριν τη δοκιμή

Δοκιμές ασφάλειας

Journal of Neuroimmunology, Vol. 192, 2007

ES και κυτταρικές θεραπείες

Conclusions from IND-Enabling Nonclinical Studies

24 studies

1977 Rodents

858 Injected with GRNOPC1

5x10⁹ OPC1 Tested in Studies

GRNOPC1

- *Survives in the Injured Spinal Cord*
- *Induces Myelination*
- *Produces Neurotrophic Factors*
- *Reduces Parenchymal Cavitation*
- *Improves Locomotor Activity*
- *Predominantly Neural Cell Types Observed*
- *Non-Neural Differentiated Cell Types Observed in Some Animals*
- *Does Not Produce Teratomas*
- *Does Not Induce Systemic Toxicity*
- *Does Not Induce Allodynia*
- *Does Not Increase Mortality*
- *Avoids Direct Allogeneic Immune Responses*

ES και κυτταρικές θεραπείες

5. Το προφίλ της δοκιμής

- ✓ Σκοπός της δοκιμής (Φάση Ι) είναι να δοκιμαστεί η ασφάλεια της προσέγγισης
- ✓ Σε επόμενη φάση θα δοκιμαστεί η αποτελεσματικότητα της προσέγγισης
- ✓ ASIA grade A injured **patients** with a thoracic injury resulting in a neurological level of T3 to T10. 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.

- ✓ In mice GRNOPC1 injections are ineffective if administered more than three months after the injury due to the scarring that occurs in the injured cord as part of the inflammatory response to spinal cord injury.

ES και κυτταρικές θεραπείες

5. Το προφίλ της δοκιμής

- ✓ GRNOPC1 will be injected by qualified, trained spine surgeons seven to 14 days postinjury to patients who give informed consent and also have appropriate laboratory, physical and radiographic characteristics that verify the location and severity of the injury.
- ✓ Testing will be administered before and after the injection of GRNOPC1 at specified time points for one year after the injection to monitor safety parameters. The secondary endpoint of efficacy will use similar testing for evidence of any 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.**

ES και κυτταρικές θεραπείες

6. Η παραγωγή

- ✓ GRNOPC1 is produced under current Good Manufacturing Practices (cGMP) in Geron's qualified manufacturing facilities.The GRNOPC1 manufacturing process in Geron's clean room suites has been inspected and licensed by the state of California.
- ✓ The manufacturing process consists of three stages:

  1) numerical expansion of undifferentiated hESCs obtained from the qualified H1 hESC master cell bank,

  2) differentiation of the expanded hESCs into GRNOPC1, and

  3) harvest, formulation, fill and cryopreservation of the GRNOPC1 drug product.
- ✓ Sequential addition of biologicals and growth factors to induce the expansion and progressive differentiation of undifferentiated hESCs into the GRNOPC1 drug product.

ES και κυτταρικές θεραπείες

6. Η παραγωγή

- ✓ A significant portion of each manufacturing run of GRNOPC1 is retained and subjected to extensive quality control testing to ensure the identity, sterility, viability and cellular composition of each manufacturing run before the product is released to the sites for clinical use. GRNOPC1 product that has passed all such specifications and has been released is available for the approved clinical trial.
- ✓ The current production scale is sufficient to supply all clinical trial needs.
- ✓ 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.

ES και κυτταρικές θεραπείες

6. Οι πατέντες

- ✓ The production and commercialization of GRNOPC1 is protected by three separate patent estates owned by or exclusively licensed to Geron. Geron funded the work at the University of Wisconsin-Madison that led to the original derivation of hESCs.
- ✓ Geron maintains an exclusive license to the issued fundamental WARF patents covering hESCs for the production of neural cells, cardiomyocytes and pancreatic islets for therapeutic applications.
- ✓ Additionally, the GRNOPC1 product is protected by an exclusive license to Geron from the University of California covering technology developed in a research collaboration between Geron and the University of California scientists that led to the discovery of the method to produce oligodendrocyte progenitors from hESCs.
- ✓ Finally, the product is protected by an expanding patent estate of pending and issued patents owned by Geron covering novel technologies for undifferentiated hESC expansion, scalable cell manufacturing methods and the production of specific therapeutic cell preparations.

ES και κυτταρικές θεραπείες

6. Η εξέλιξη της προκλινικής δοκιμής

- ✓ In one of the preclinical expansion studies, a higher frequency of animals developed cysts in the injury site than had been seen in numerous foregoing preclinical studies with clinical grade GRNOPC1, including the IND-enabling studies.

- ✓ Notification of the FDA are the findings from this animal study : **the trial was put on clinical hold in August 2009**. As part of ongoing work to optimize GRNOPC1 manufacturing and product release, **new candidate markers and assays have been developed. Data from studies using the new markers were submitted to the FDA**.

“Stem cells were God’s will”

Ο Timothy J. Atchison ήταν ο πρώτος ασθενής που εντάχθηκε σε κλινική δοκιμή με κύτταρα που είχαν διαφοροποιηθεί από ESC

ES και κυτταρικές θεραπείες

6. Η εξέλιξη της προκλινικής δοκιμής

✓ 11/10/2010 (Reuters)

- U.S. doctors have begun treating the first patient to receive human embryonic stem cells, but details of the patient enrolled in the landmark clinical trial are being kept confidential, Geron Corp said on Monday.

"Geron, whose shares were up 6.4 percent on the Nasdaq late on Monday afternoon, has the first U.S. Food and Drug Administration license to use the controversial cells to treat people, in this case patients with new spinal cord injuries. It is the first publicly known use of human embryonic stem cells in people."

✓ Παράλληλα την ίδια εποχή δίνεται και η άδεια για δοκιμές με βλαστοκύτταρα ενηλίκου

✓ Το 2013 η Geron πούλησε όλα της τα δικαιώματα σε άλλη εταιρεία .....

στην Asterias Biotherapeutics, Inc.


ASTERIAS
BIOTHERAPEUTICS

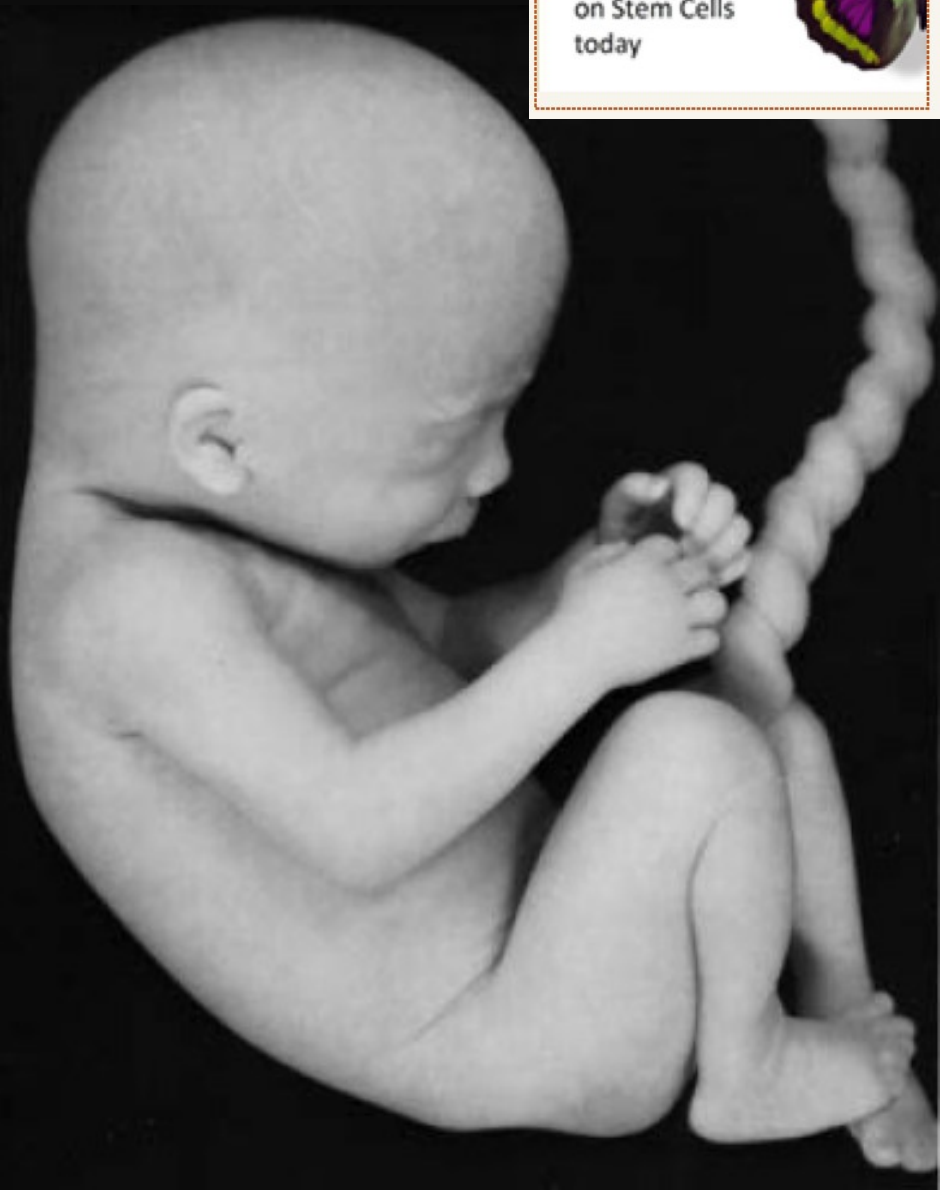
Η κλινική δοκιμή της Stem Cells Inc.

- Τα **παιδιά με νόσο Batten εμφανίζουν** πολλαπλές νευρολογικές αναπηρίες, όπως σοβαρές κινητικές, γνωστικές, ακουστικές και οπτικές αναπηρίες – πεθαίνουν γύρω στα 20 (τουλάχιστον 8 γονίδια).
- Δεν υπάρχουν θεραπείες
- Η Stem Cells Inc πραγματοποίησε μια κλινική μελέτη φάσης I με μεταμόσχευση **σε 6 παιδιά** απομονωμένων νευρικών βλαστοκυττάρων, HuCNS-SC® από εμβρυϊκά βλαστοκύτταρα.
- Τα HuCNS-SC χορηγήθηκαν χειρουργικά σε πολλά σημεία σε δόσεις μέχρι 10^9
- Στενή παρακολούθηση για 12 μήνες και μετά για 4 χρόνια - μόνο τρία παιδιά επιβίωσαν και παρακολουθούνται ακόμα..
- Στα παιδιά που απεβίωσαν έγιναν νεκροτομές που έδειξαν ότι τα μεταμοσχευμένα κύτταρα είχαν μεταναστεύσει και διαφοροποιηθεί η αιτία του θανάτου τους δεν συσχετίστηκε με τη θεραπεία αλλά με την ασθένεια αυτή καθαυτή.


FORTUNE


TIME100


Stem Cells
Top 50 most influential people on Stem Cells today



Lanza's saga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2011 Calendar

Η επιτυχημένη δοκιμή της Advanced Stem Cell

Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies

Steven D Schwartz, Carl D Regillo, Byron L Lam, Dean Eliott, Philip J Rosenfeld, Ninel Z Gregori, Jean-Pierre Hubschman, Janet L Davis, Gad Heilwell, Marc Spirn, Joseph Maguire, Roger Gay, Jane Bateman, Rosaleen M Ostrick, Debra Morris, Matthew Vincent, Eddy Anglade, Lucian V Del Priore, Robert Lanza

Stem Cell Reports

Article

OPEN ACCESS

Treatment of Macular Degeneration Using Embryonic Stem Cell-Derived Retinal Pigment Epithelium: Preliminary Results in Asian Patients

Won Kyung Song,[1,*] Kyung-Mi Park,[2] Hyun-Ju Kim,[2] Jae Ho Lee,[3] Jinjung Choi,[4] So Young Chong,[5] Sung Han Shim,[6] Lucian V. Del Priore,[7] and Robert Lanza[8,*]

CLONING AND STEM CELLS
Volume 6, Number 3, 2004

Derivation and Comparative Assessment of Retinal Pigment Epithelium from Human Embryonic Stem Cells Using Transcriptomics

IRINA KLIMANSKAYA,[1] JASON HIPP,[2] KOUROUS A. REZAI,[3] MICHAEL WEST,[1] ANTHONY ATALA,[2] and ROBERT LANZA[1,2]

Human stem-cell derivatives are likely to play an important role in the future of regenerative medicine. Evaluation and comparison to their *in vivo* counterparts is critical for assessment of their therapeutic potential. Transcriptomics was used to compare a new differentiation derivative of human embryonic stem (hES) cells—retinal pigment epithelium (RPE)—to human fetal RPE. Several hES cell lines were differentiated into putative RPE, which expressed RPE-specific molecular markers and was capable of phagocytosis, an important RPE function. Isolated hES cell–derived RPE was able to transdifferentiate into cells of neuronal lineage and redifferentiate into RPE-like cells through multiple passages (>30 Population doublings). Gene expression profiling demonstrated their higher similarity to primary RPE tissue than of existing human RPE cell lines D407 and ARPE-19, which has been shown to attenuate loss of visual function in animals. This is the first report of the isolation and characterization of putative RPE cells from hES cells, as well as the first application of transcriptomics to assess embryonic stem-cell derivatives and their *in vivo* counterparts—a "differentiomics" outlook. We describe for the first time, a differentiation system that does not require coculture with animal cells or factors, thus allowing the production of zoonoses-free RPE cells suitable for subretinal transplantation in patients with retinal degenerative diseases. With the further development of therapeutic cloning, or the creation of the banks of homozygous human leucocyte antigen (HLA) hES cells using parthenogenesis, RPE lines could be generated to overcome the problem of immune rejection and could be one of the nearest term applications of stem-cell technology.

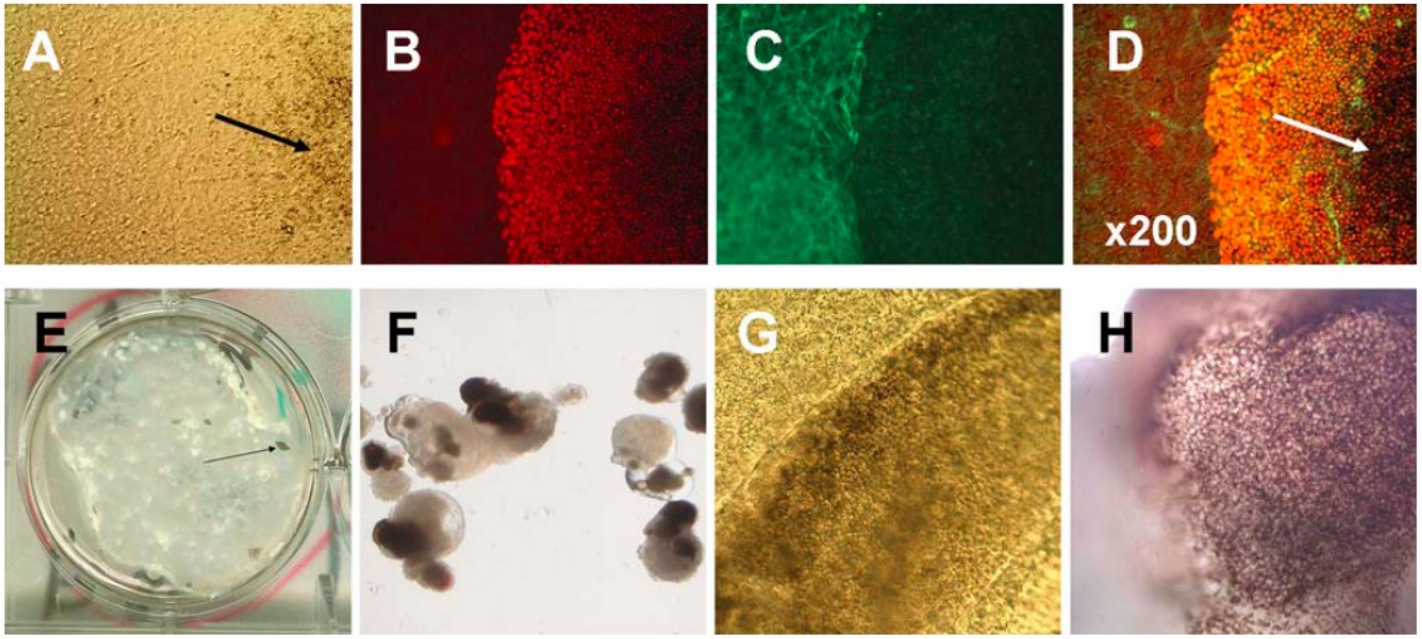

FIG. 1. Appearance of clusters of pigmented epithelial cells in spontaneously differentiating human embryonic stem (hES) cells. (**A–D**) Differentiating adherent hES cells. (**A–D**) Appearance of pigmented epithelial cells, surrounded by pax6 and tubulin β III-positive cells; note that both pax6 and tubulin β III staining is gradually decreased or lost toward the center of such cluster; (arrows in A and D). Original magnification, × 200. Arrows point to the pigmented center of the cluster. (**E**) A well of a 4-well plate scanned, no original magnification. Arrows point to a "freckle"—a cluster of pigmented cells forming on a cell culture plate of differentiation hES cells. (**F**) Differentiating embryoid bodies (EBs) with pigmented regions, original magnification × 30. (**G** and **H**) A cluster of pigmented epithelial cells in 4 weeks old adherent culture of hES cells, original magnification × 200; (**H**) A pigmented region of a differentiating EB, original magnification × 400.

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Volume 6, Number 3, 2004

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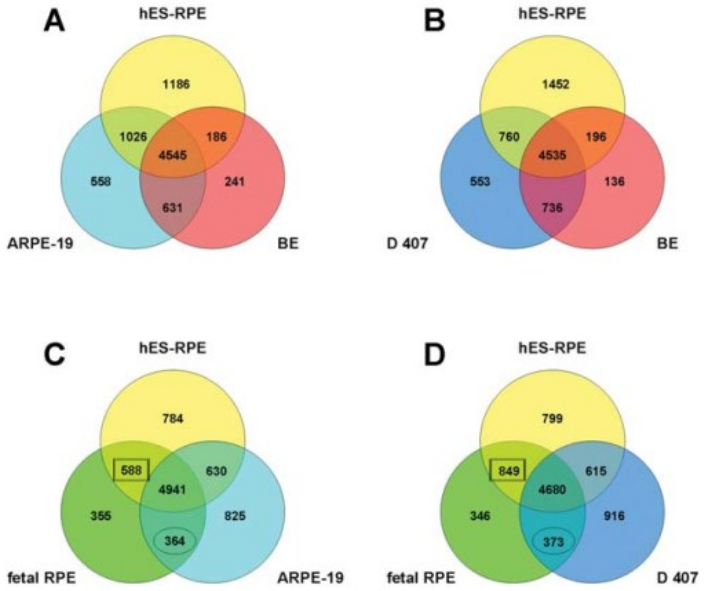

FIG. 4. Venn diagram comparisons of retinal pigment epithelium (RPE) lines. The Venn diagrams demonstrate the transcriptional relationships between human embryonic stem (hES)–RPE and other known RPE cell lines. While ignoring the genes expressed in all three cell types, note the intersections of each Venn diagram because they allow for comparisons of hES-RPE to other RPE cell lines, such as ARPE-19, D407, or feRPE, which serve as positive controls, and bronchial epithelium (BE serves as a negative control. Comparing these intersections to one another, allows one to quantifiably assess the quality of RPE derived from hES. (**A**) Transcriptional similarity of hES-RPE to ARPE-19 (with 1026 genes in common) and BE (186 genes in common). (**B**) Although D407 has a similar number of transcripts in common with hES-RPE and BE (760 and 736, respectively) hES-RPE cells (C and D) have a greater transcriptional identity to *in vivo*–derived RPE relative to ARPE-19 (588, square frame, versus 364, oval frame, genes, see Fig. 4C) and to D407 (849, square frame, versus 373, oval frame, genes, see Fig. 4D).

CLONING AND STEM CELLS
Volume 8, Number 3, 2006

Human Embryonic Stem Cell–Derived Cells Rescue Visual Function in Dystrophic RCS Rats

RAYMOND D. LUND,[1] SHAOMEI WANG,[1] IRINA KLIMANSKAYA,[2] TOBY HOLMES,[1] REBECA RAMOS-KELSEY,[2] BIN LU,[1] SERGEJ GIRMAN,[1] N. BISCHOFF,[1] YVES SAUVÉ,[3] and ROBERT LANZA[2]

Embryonic stem cells promise to provide a well-characterized and reproducible source of replacement tissue for human clinical studies. An early potential application of this technology is the use of retinal pigment epithelium (RPE) for the treatment of retinal degenerative diseases such as macular degeneration. Here we show the reproducible generation of RPE (67 passageable cultures established from 18 different hES cell lines); batches of RPE derived from NIH-approved hES cells (H9) were tested and shown capable of extensive photoreceptor rescue in an animal model of retinal disease, the Royal College of Surgeons (RCS) rat, in which photoreceptor loss is caused by a defect in the adjacent retinal pigment epithelium. Improvement in visual performance was 100% over untreated controls (spatial acuity was approximately 70% that of normal nondystrophic rats) without evidence of untoward pathology. The use of somatic cell nuclear transfer (SCNT) and/or the creation of banks of reduced complexity human leucocyte antigen (HLA) hES-RPE lines could minimize or eliminate the need for immunosuppressive drugs and/or immunomodulatory protocols.

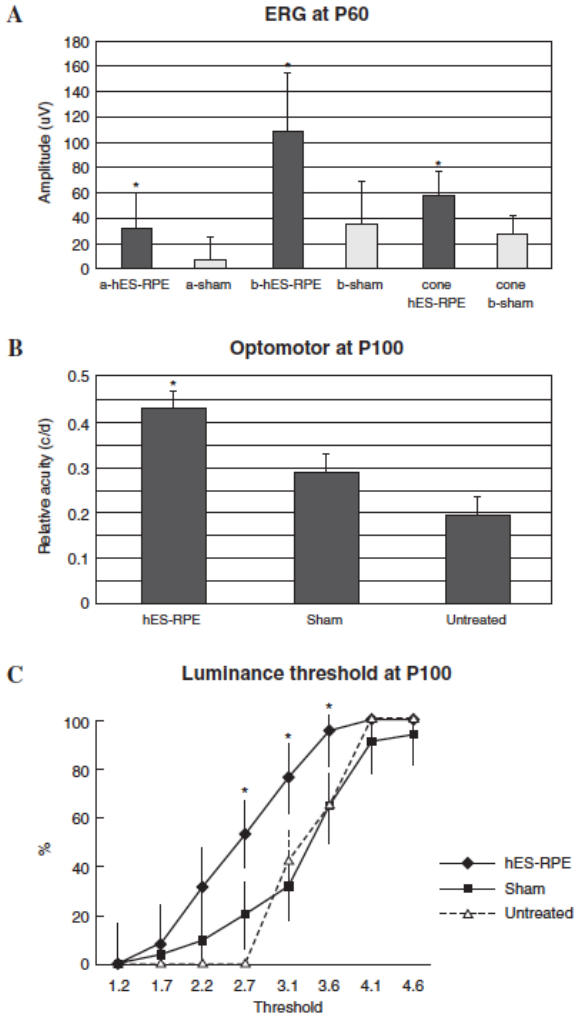

FIG. 3. Functional assessment of human embryonic stem cell (hES)–derived retinal pigment epithelium (RPE) after subretinal transplantation in Royal College of Surgeons (RCS) rats. (**A**) hES-RPE grafted animals achieved significantly better responses over sham controls ($p < 0.05$, *t*-test) for a-wave (31 ± 27 vs. 6 ± 17 μV), b-wave (108 ± 46 μV vs. 36 ± 33 μV) and cone b-wave (57 ± 19 vs. 28 ± 13 μV). (**B**) The relative acuity as measured by the optomotor system shows that the hES-RPE treated eyes perform significantly better than the medium treated and untreated eyes ($p < 0.05$, *t*-test), giving approximately 50% and 100% improvement in visual acuity over the sham and untreated controls, respectively. Non-dystrophic untreated eyes give readings of 0.53–0.6 cycles/degree (**c/d**). (**C**) Luminance threshold responses recorded across the superior colliculus, each curve (average ± SEM) shows the percent of retinal area (*y*-axis) where the visual threshold is less than the corresponding value on the *x*-axis (log units, relative to background illumination 0.02 cd/m^2). Asterisks show the points where the curves for grafted and sham-operated eyes are statistically different (*t*-test, $p < 0.05$). The curves show that 52% of the area of the superior colliculus (SC) in grafted animals gave thresholds of 2.7 log units and against shams in which approximately 18% gave thresholds of 2.7 log units.

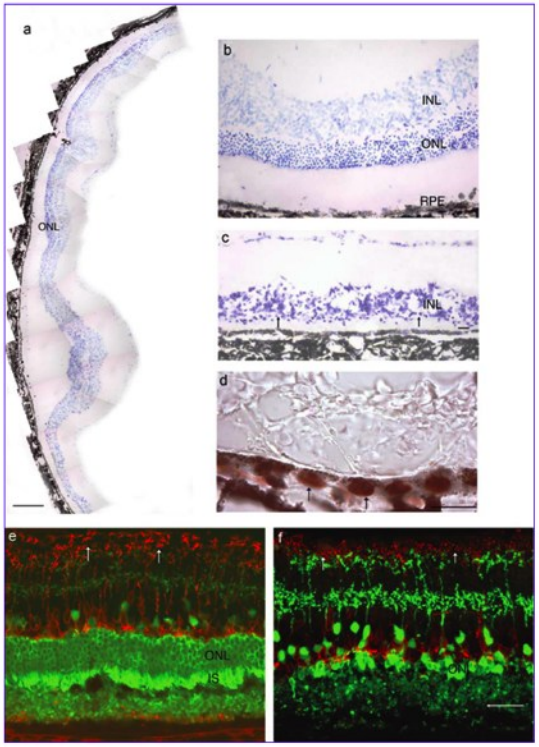

FIG. 4. Anatomical rescue of photoreceptors after transplantation of human embryonic stem cell (hES)–derived retinal pigment epithelium (RPE). (**a–c**) Retinal sections at P100 stained with cresyl violet: extensive photoreceptor rescue with hES-RPE graft (**a**); high-power image of the rescued outer nuclear layer (ONL), which is 5–7 cells deep (**b**); distant from graft, the ONL is reduced to a single layer (**c**). (**d**) grafted retina section stained with human nuclear marker (arrows indicate positively stained donor cells). (**e,f**) Confocal microscopic images of retinal sections double stained with recoverin (green) and PKCa (red): graft protected area (**e**) had several layers of ONL with inner segments, rod bipolar cells have denser terminals, whereas at area distant from graft (**f**), there is only a single layer of ONL, and the rod bipolar cell terminals are reduced in density. Scale bar 200 m (**a**), 20 m (**b–f**).

STEM CELLS 2009;27:2126–2135

Long-Term Safety and Function of RPE from Human Embryonic Stem Cells in Preclinical Models of Macular Degeneration

BIN LU,[a] CHRISTOPHER MALCUIT,[b] SHAOMEI WANG,[a] SERGEJ GIRMAN,[a] PETER FRANCIS,[a] LINDA LEMIEUX,[b] ROBERT LANZA,[b] RAYMOND LUND[a]

ABSTRACT

Assessments of safety and efficacy are crucial before human ESC (hESC) therapies can move into the clinic. Two important early potential hESC applications are the use of retinal pigment epithelium (RPE) for the treatment of age-related macular degeneration and Stargardt disease, an untreatable form of macular dystrophy that leads to early-onset blindness. Here we show long-term functional rescue using hESC-derived RPE in both the RCS rat and Elov14 mouse, which are animal models of retinal degeneration and Stargardt, respectively. Good Manufacturing Practice-compliant hESC-RPE survived subretinal transplantation in RCS rats for prolonged periods (>220 days). The cells sustained visual function and photoreceptor integrity in a dose-dependent fashion without teratoma formation or untoward pathological reactions. Near-normal functional measurements were recorded at >60 days survival in RCS rats. To further address safety concerns, a Good Laboratory Practice-compliant study was carried out in the NIH III immune-deficient mouse model. Long-term data (spanning the life of the animals) showed no gross or microscopic evidence of teratoma/tumor formation after subretinal hESC-RPE transplantation. These results suggest that hESCs could serve as a potentially safe and inexhaustible source of RPE for the efficacious treatment of a range of retinal degenerative diseases. STEM CELLS 2009;27:2126–2135

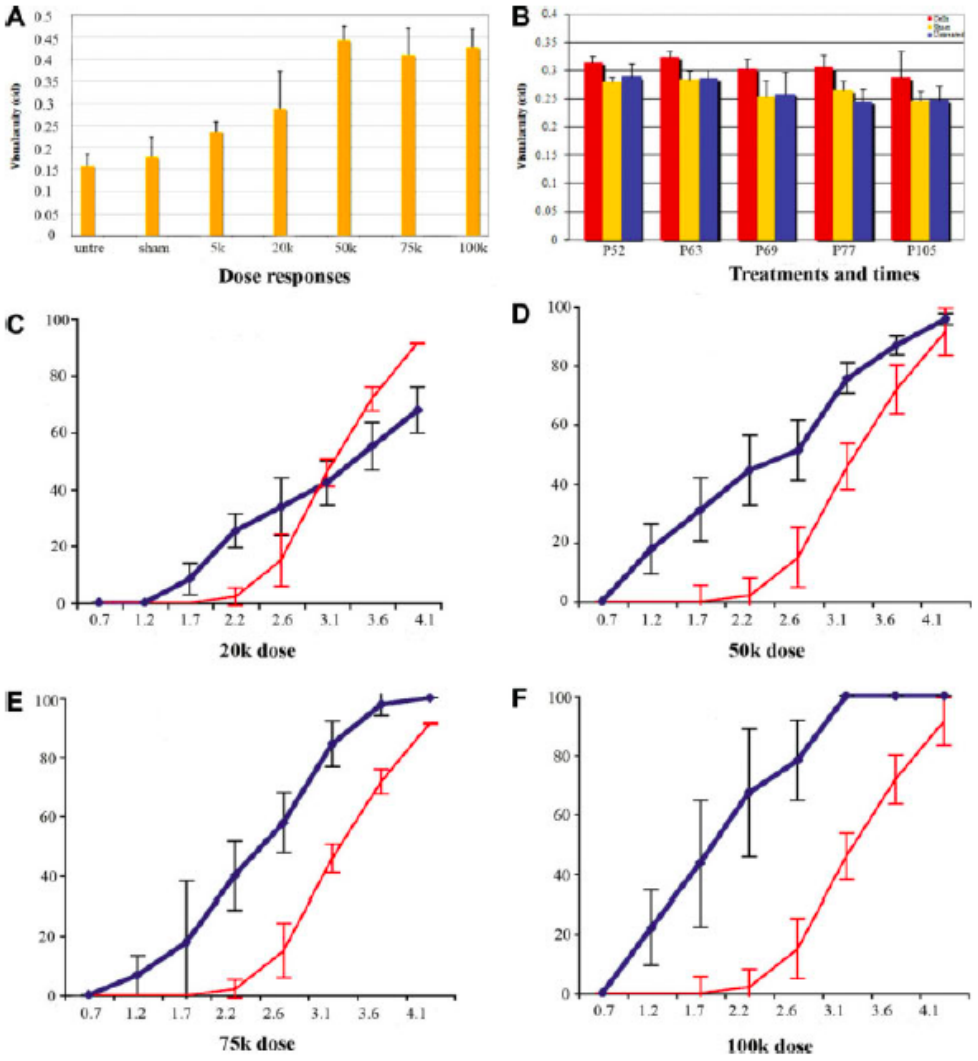

Figure 4. (A): Visual acuity as measured by the optomotor response shows that animals treated with 5,000, 20,000, 50,000, 75,000, and 100,000 cells performed significantly better than those with sham injection and untreated controls ($p < .01$) at P90 days. The best performers gave a figure of 0.563 c/d (compared with 0.6 c/d in normal rat). It is interesting to note that the difference among the groups of 50,000, 75,000, and 100,000 is not significant ($p > .05$). (B): Visual acuity tested in Elovl4 mice at several time points after subretinal injection of human ESC-retinal pigment epithelium showed that cell-injected animals performed significantly better than medium-injected and untreated controls ($p < .05$). The best performers had a figure of 0.32 c/d at P63 (compared with 0.35 c/d in normal mice), whereas control animals had a figure of 0.28 c/d. (C–F): Luminance threshold responses recorded across the superior colliculus (SC); each curve (average SEM) shows the percent of retinal area (y-axis) where the visual threshold is less than the corresponding value at x-axis (log units, relative to background illumination 0.02 cd/m2). Cell-injected groups are significantly better than controls: the curves showed that 28% of the area in the SC in animals with the 20,000 dose (C) 45% with the 50,000 dose (D); 40% with the 75,000 dose (E); and only 3% in medium control had thresholds of 2.2 log units. The 100,000 in F seemed better, but the variance is rather high. Blue lines, cell-treated; red lines, medium control. Abbreviation: c/d, cycles/degree.

Stem Cell Reports | Vol. 4 | 860–872 | May 12, 2015 |

Treatment of Macular Degeneration Using Embryonic Stem Cell-Derived Retinal Pigment Epithelium: Preliminary Results in Asian Patients

Won Kyung Song,[1,*] Kyung-Mi Park,[2] Hyun-Ju Kim,[2] Jae Ho Lee,[3] Jinjung Choi,[4] So Young Chong,[5] Sung Han Shim,[6] Lucian V. Del Priore,[7] and Robert Lanza[8,*]

Embryonic stem cells hold great promise for various diseases because of their unlimited capacity for self-renewal and ability to differentiate into any cell type in the body. However, despite over 3 decades of research, there have been no reports on the safety and potential efficacy of pluripotent stem cell progeny in Asian patients with any disease. Here, we report the safety and tolerability of subretinal transplantation of human embryonic-stem-cell (hESC)-derived retinal pigment epithelium in four Asian patients: two with dry age-related macular degeneration and two with Stargardt macular dystrophy. They were followed for 1 year. There was no evidence of adverse proliferation, tumorigenicity, ectopic tissue formation, or other serious safety issues related to the transplanted cells. Visual acuity improved 9–19 letters in three patients and remained stable (+1 letter) in one patient. The results confirmed that hESC-derived cells could serve as a potentially safe new source for regenerative medicine.

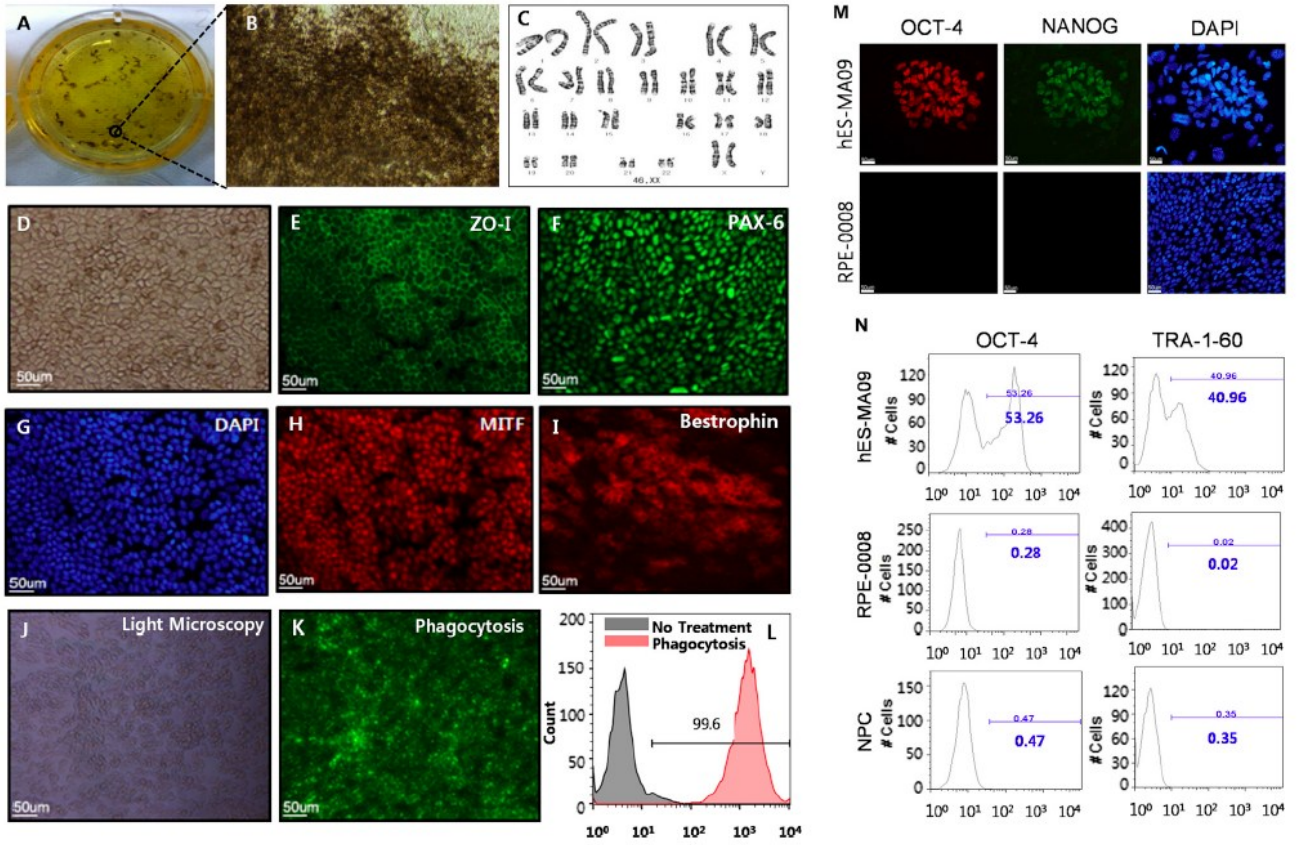

Figure 1. Characterization of the Clinical Product: Identity, Potency, and Purity (A) RPE clusters were obtained by culturing an embryoid body attached to a six-well plate for about 8 weeks. (B) The cells at the edge of the pigmented cluster displayed typical morphology of hRPE with hypo-pigmentation of the leading edge. (C) A normal female karyotype (46XX) is shown. (D) A confluent cobblestone monolayer was observed via Hoffman modulation contrast microscopy. (E and F) Cells were positive for ZO-1 (E) and PAX-6 (F). (G and H) DAPI staining in (G) was used to identify the location of the nuclei corresponding to ZO-1 (in E) and MITF (H) at the same time. ZO-1 and MITF were double stained in one sample. (I) Mature RPE cells were recognized with anti-Bestrophin. (J–L) Phagocytosis assay results were shown. Fluorescence microscopy image and FACS analyses of the differentiated hESC-derived RPE cells demonstrate that most of the cells (99.6%) were phagocytized with the fluorescent-labeled particles. (M and N) Purity was assessed by the absence of hESCs of the final product by immunocytochemical staining for OCT-4 and NANOG (M) and FACS analysis demonstrating the absence of OCT-4 and TRA-1-60 (N). Scale bars, 50 mm.

Η επιτυχημένη δοκιμή της Advanced Stem Cell

- Δύο μελέτες φάσης I/II για να αξιολογηθεί η ασφάλεια και η ανοχή κυττάρων του επιθηλίου του αμφιβληστροειδούς τα οποία έχουν διαφοροποιηθεί από ESC και μεταμοσχεύθηκαν σε ασθενείς με εκφύλιση ωχράς κηλίδας λόγω ηλικίας ή λόγω της ασθένειας Stargardt.
- Η ασθένεια Stargardt αποτελεί την πιο κοινότυπη μορφή κληρονομικής εκφύλισης της ωχράς (κεντρικό τμήμα του αμφιβληστροειδούς) σε ασθενείς κάτω των 20 ετών – 1/10000 στις ΗΠΑ και γίνεται αντιληπτή στην παιδική ηλικία και προοδευτικά οδηγεί σε τύφλωση.
- Συνολικά 18 ασθενείς 9 και 9
- Μεταμόσχευση 50000 ή 100000 ή 150000 κυττάρων
- Συχνή παρακολούθηση με εξετάσεις για 22 μήνες.

www.thelancet.com Published online October 15, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61376-3

Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies

Steven D Schwartz, Carl D Regillo, Byron L Lam, Dean Eliott, Philip J Rosenfeld, Ninel Z Gregori, Jean-Pierre Hubschman, Janet L Davis, Gad Heilwell, Marc Spirn, Joseph Maguire, Roger Gay, Jane Bateman, Rosaleen M Ostrick, Debra Morris, Matthew Vincent, Eddy Anglade, Lucian V Del Priore, Robert Lanza

Summary

Background Since they were first derived more than three decades ago, embryonic stem cells have been proposed as a source of replacement cells in regenerative medicine, but their plasticity and unlimited capacity for self-renewal raises concerns about their safety, including tumour formation ability, potential immune rejection, and the risk of differentiating into unwanted cell types. We report the medium-term to long-term safety of cells derived from human embryonic stem cells (hESC) transplanted into patients.

Methods In the USA, two prospective phase 1/2 studies were done to assess the primary endpoints safety and tolerability of subretinal transplantation of hESC-derived retinal pigment epithelium in nine patients with Stargardt's macular dystrophy (age >18 years) and nine with atrophic age-related macular degeneration (age >55 years). Three dose cohorts (50 000, 100 000, and 150 000 cells) were treated for each eye disorder. Transplanted patients were followed up for a median of 22 months by use of serial systemic, ophthalmic, and imaging examinations. The studies are registered with ClinicalTrials.gov, numbers NCT01345006 (Stargardt's macular dystrophy) and NCT01344993 (age-related macular degeneration).

Findings There was no evidence of adverse proliferation, rejection, or serious ocular or systemic safety issues related to the transplanted tissue. Adverse events were associated with vitreoretinal surgery and immunosuppression. 13 (72%) of 18 patients had patches of increasing subretinal pigmentation consistent with transplanted retinal pigment epithelium. Best-corrected visual acuity, monitored as part of the safety protocol, improved in ten eyes, improved or remained the same in seven eyes, and decreased by more than ten letters in one eye, whereas the untreated fellow eyes did not show similar improvements in visual acuity. Vision-related quality-of-life measures increased for general and peripheral vision, and near and distance activities, improving by 16–25 points 3–12 months after transplantation in patients with atrophic age-related macular degeneration and 8–20 points in patients with Stargardt's macular dystrophy.

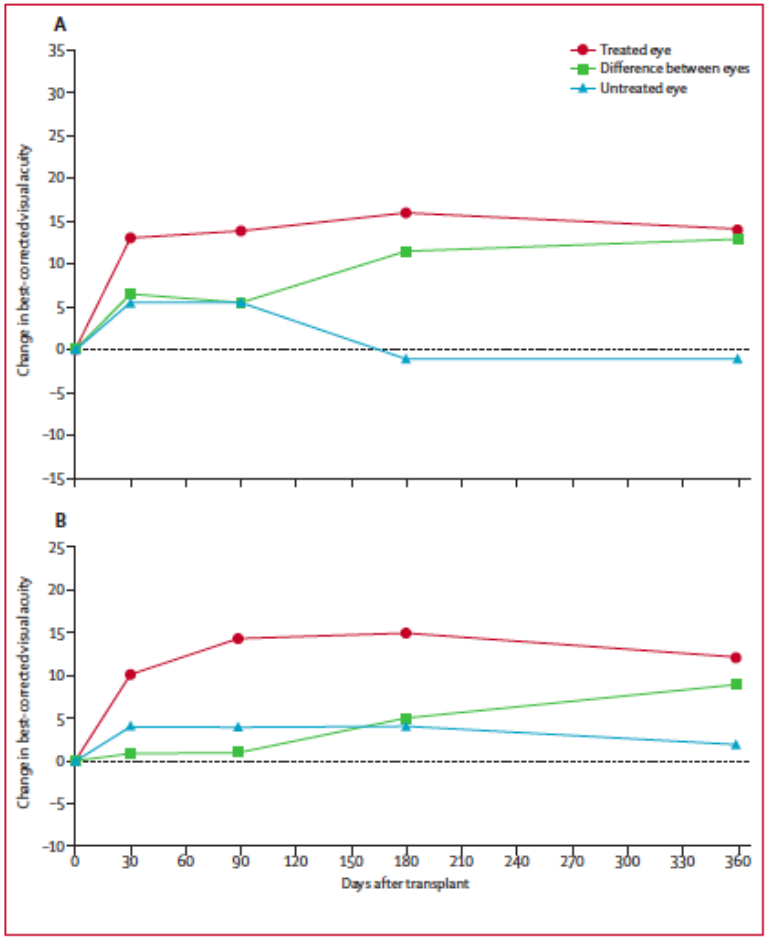

Figure 3: **Change from baseline in best-corrected visual acuity in patients with age-related macular degeneration (A) and Stargardt's macular dystrophy (B)**
Median change in best-corrected visual acuity was expressed as number of letters read on the Early Treatment of Diabetic Retinopathy Study visual acuity chart in patients with age-related macular degeneration (A) and Stargardt's macular dystrophy (B). Red lines show treated eyes and blue lines show untreated eyes of patients during the fi rst year after transplantation of the cells derived from human embryonic stem cells. Green lines show the difference between the treated and untreated eyes. Patients who underwent cataract surgery after transplantation are not included in the graph. There was a signifi cant diff erence in the letters read in transplanted eyes of patients with age-related macular degeneration versus non-transplanted controls at 12 months (median 14 letters *vs* –1 letter; p=0ÅE0117). There was an increase in letters read in transplanted eyes of patients with Stargardt's macular dystrophy versus non-transplanted controls at 12 months (median 12 letters *vs* two letters, although the sample size was too small to allow reliable calculation of the Wilcoxon signed-rank test).

.....δημοσιότητα...

HEALTH MEDICINE

TIME

Stem Cells Allow Nearly Blind Patients to See

First UK patient receives stem cell treatment to cure loss of vision

theguardian

CBSNEWS

First patient receives stem cell treatment for blindness

The New York Times

Study Backs Use of Stem Cells in Retinas

Harvard Stem Cell Lab Signs Two Major Partnerships to Bring Stem Cell Therapies for Diabetes to Life

April 2015

Cell *159*, 428–439, October 9, 2014

Generation of Functional Human Pancreatic β Cells In Vitro

Felicia W. Pagliuca,[1,3] Jeffrey R. Millman,[1,3] Mads Gürtler,[1,3] Michael Segel,[1] Alana Van Dervort,[1] Jennifer Hyoje Ryu,[1] Quinn P. Peterson,[1] Dale Greiner,[2] and Douglas A. Melton[1,*]

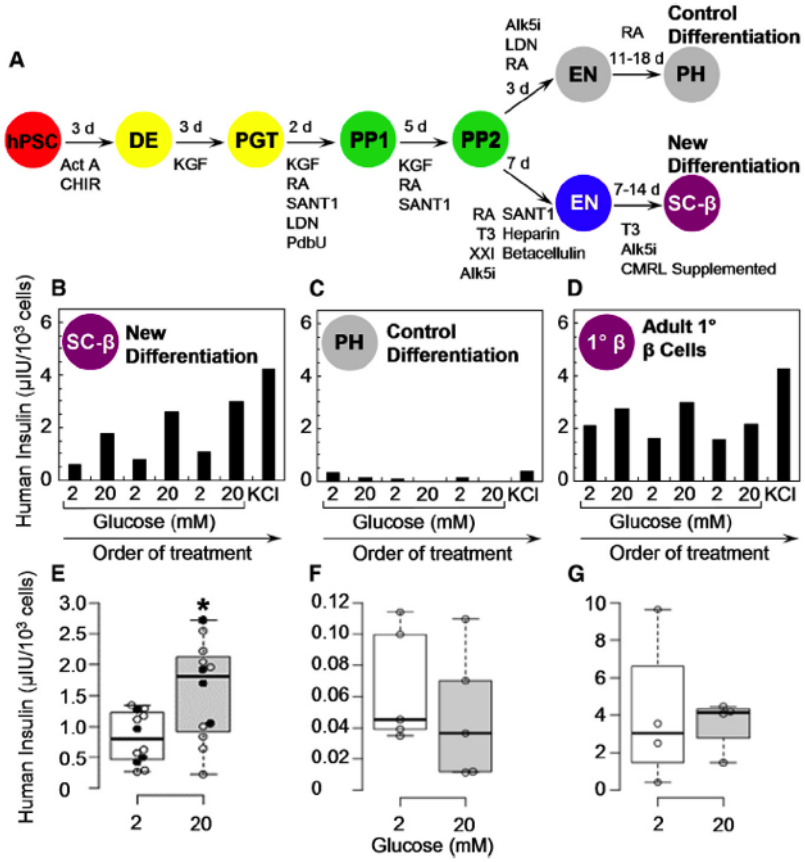

Figure 1. SC-β Cells Generated In Vitro Secrete Insulin in Response to Multiple Sequential High-Glucose Challenges like Primary Human β Cells

(A) Schematic of directed differentiation from hPSC into INS+ cells via new or previously published control differentiations.

(B–D) Representative ELISA measurements of secreted human insulin from HUES8 SC-β cells (B), PH cells (C), and primary β (1°β) cells (D) challenged sequentially with 2, 20, 2, 20, 2, and 20 mM glucose, with a 30 min incubation for each concentration (see Experimental Procedures). After sequential low/high-glucose challenges, cells were depolarized with 30 mM KCl.

(E–G) Box and whisker plots of secreted human insulin from different biological batches of HUES8 (open circles) and hiPSC SC-β (black circles) cells (E; n = 12), biological batches of PH cells (F; n = 5), and primary β cells (G; n = 4). Each circle is the average value for all sequential challenges with 2 mM or 20 mM glucose in a batch. Insulin secretion at 20 mM ranged 0.23–2.7 μIU/10^3 cells for SC-β cells and 1.5–4.5 μIU/10^3 cells for human islets, and the stimulation index ranged 0.4–4.1 for SC-β cells and 0.6–4.8 for primary adult. The thick horizontal line indicates the median.

See also Figures S1 and S2A and Table S1. *$p < 0.05$ when comparing insulin secretion at 20 mM versus 2 mM with paired t test. Act A, activin A; CHIR, CHIR99021, a GSK3α/β inhibitor; KGF, keratinocyte growth factor or FGF family member 7; RA, retinoic acid; SANT1, sonic hedgehog pathway antagonist; LDN, LDN193189, a BMP type 1 receptor inhibitor; PdbU, Phorbol 12,13-dibutyrate, a protein kinase C activator; Alk5i, Alk5 receptor inhibitor II; T3, triiodothyronine, a thyroid hormone; XXI, γ-secretase inhibitor; Betacellulin, EGF family member.

Semma Therapeutics
AstraZeneca
Harvard Stem Cell Institute
Novartis

.....και άλλες δοκιμές

Paul Laikind. Ph.D, President and Chief Executive Officer, ViaCyte. (Source: ViaCyte)

Embryonic Stem Cells in Trial for Diabetes

Thu, 10/16/2014 - 11:44am

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Working Toward a Cure in Diabetes: Partnering with BetaLogics

BetaLogics is a division of Janssen Research & Development, one of the Johnson & Johnson Family of Companies based in New Jersey. The BetaLogics venture is focused on a transformational stem cell therapy to treat diabetes and eliminate a need for exogenous insulin, with the goal of revolutionizing the way patients and physicians manage insulin-requiring diabetes. Moreover, the intent is to change diabetes management from palliative to curative, i.e. treat the underlying cause of the disease instead of treating symptoms of a degenerative process. To that end, BetaLogics is developing an integrated therapeutic product that incorporates a pancreatic precursor cell in an implantable device.

…..και άλλες δοκιμές από δύο εταιρείες..

Paul Laikind. Ph.D, President and Chief Executive Officer, ViaCyte. (Source: ViaCyte)

Embryonic Stem Cells in Trial for Diabetes

Thu, 10/16/2014 - 11:44am

VIACYTE Regenerating Health™

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UPDATED: J&J goes all in with ViaCyte, hands over BetaLogics assets in hunt for diabetes cure

by *John Carroll* | Feb 4, 2016 8:34am

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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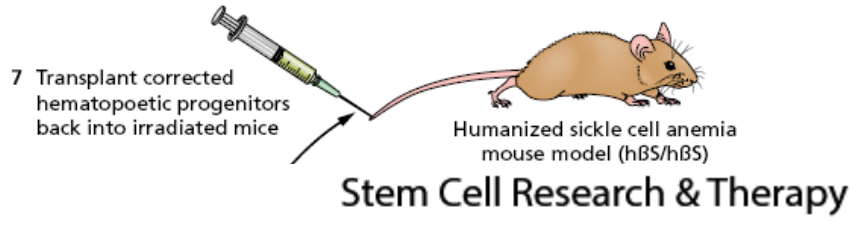
Εξατομικευμένες θεραπείες – iPS?

A model experiment to cure mice of sickle cell disease. The mice have humanized hemoglobin β genes carrying the sickle cell a i g h a C c t r grafted with the iPS which colonize the bone marrow and form blood.



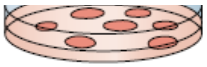
Stem Cell Research & Therapy

Kumar and Tanwar *Stem Cell Research & Therapy* (2024) 15:487
https://doi.org/10.1186/s13287-024-04036-0

LETTER Open Access

World's first: stem cell therapy reverses diabetes

Dinesh Kumar[1*] and Rajni Tanwar[1]



h β A, normal allele;
h β S, sickle cell allele.

Hanna *et al. Science*2007; 318: 1920 – 1923,

Clinical trials 2020

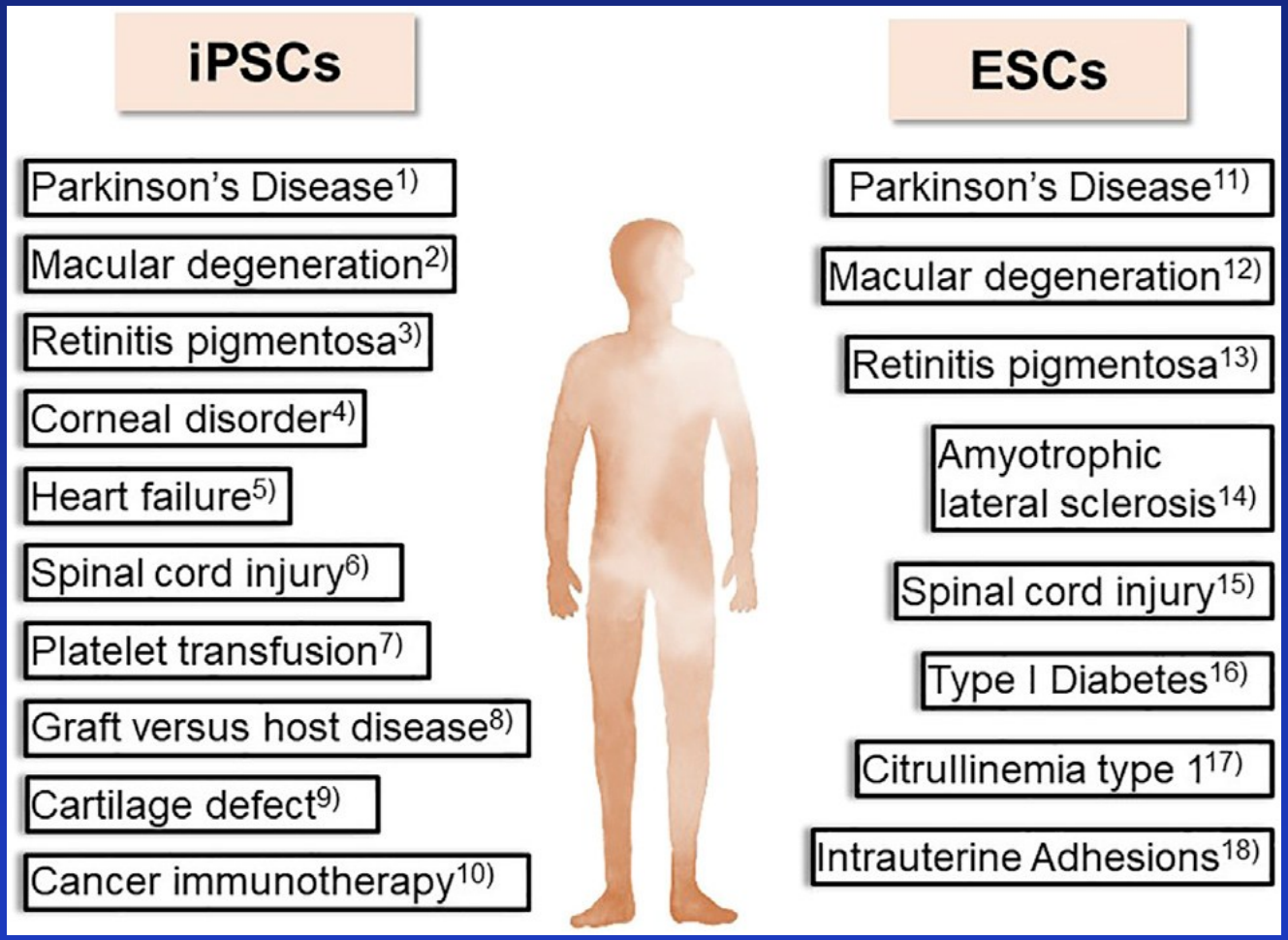


Figure 1. Clinical Trials for Cell Therapies Using PSCs
Shown are clinical trials that use hiPSC or hESC and are found in UMIN Clinical Trials Registry (https://www.umin.ac.jp/ctr/index.htm) or ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) as of Septermber, 2020.

https://doi.org/10.1016/j.stem.2020.09.014

•16 April 2025

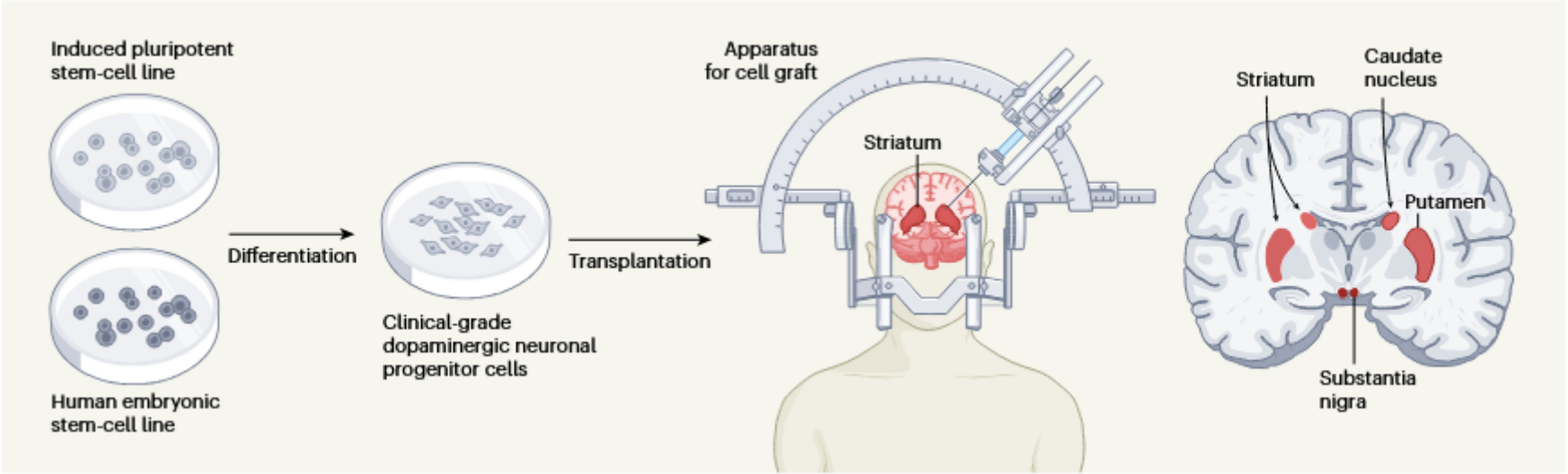
News & views

Regenerative medicine

Safety test for Parkinson's disease stem-cell therapy

Hideyuki Okano

Transplanting dopamine-releasing neurons into the brain is a promising regenerative therapy for Parkinson's disease. Two clinical trials show that it is safe, but more evidence is needed to prove its effectiveness.



Clinical Trial Tests Novel Stem-Cell Treatment for Parkinson's Disease

Mar 6, 2025 — 7 minute read

Patient Care | Innovation | Gene & Cell Therapy | Brain & Nervous System Conditions | Research

- **Phase 1 trial reprograms patient's own stem cells to replace dopamine neurons in the brain**
- **Work is born out of three decades of preclinical research led by McLean Hospital and Ole Isacson**
- **First-of-its-kind trial has treated three-of-six participants who will be tracked for more than a year**

Πρωτοβουλίες

GMP Banking of Human Pluripotent Stem Cells: A US and UK perspective

Elsa Abranches[a,*], Sofia Spyrou[a], Tenneille Ludwig[b]

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[b] WiCell Research Institute, 504 S. Rosa Rd Suite 101, Madison, WI, 53719, USA

https://doi.org/10.1016/j.scr.2020.101805

Stem Cell Network

Jon Draper[a], Cate Murray[b,*]

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[b] Executive Director, Stem Cell Network at the Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

https://doi.org/10.1016/j.scr.2020.101890

The German stem cell network GSCN - a nationwide network with many tasks

Stefanie Mahler, Daniel Besser*

German Stem Cell Network (GSCN), c/o Max Delbrück Center, Robert-Rössle-Str. 10, 13125 Berlin, Germany

https://doi.org/10.1016/j.scr.2019.101672

Kyoto hESC cell resource for regenerative medicine

Eihachiro Kawase*, Kei Takada, Hirofumi Suemori

Division of Clinical Basis for ES Cell Research, Center for Human ES Cell Research, Institute for Frontier Life and Medical Sciences, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

https://doi.org/10.1016/j.scr.2020.102020

Overview of iPS Cell Stock Project

Center for iPS Cell Research and Application, Kyoto University
CiRA

iPS cell outpatients (Kyoto University Hospital) etc.

Obtaining of consent, testing, blood tests

CiRA・Facility for iPS Cell Therapy(FiT)

Generation and evaluation of iPS cells

CiRA・FiT

iPS cell stock for use in regenerative medicine

Distribution

Transplan-tation

Generation of differentiated cells for transplantation

medical-related enterprises

Research institutions

Ωστόσο...

Article

Genome-wide Screen for Culture Adaptation and Tumorigenicity-Related Genes in Human Pluripotent Stem Cells

Human pluripotent stem cells recurrently acquire and expand dominant negative P53 mutations

Florian T. Merkle[1,2,3,4*†], Sulagna Ghosh[1,2,3,4*], Nolan Kamitaki[3,5,6], Jana Mitchell[1,2,3,4], Yishai Avior[7], Curtis Mello[3,5,6], Seva Kashin[3,5,6], Shila Mekhoubad[1,2,4†], Dusko Ilic[8], Maura Charlton[1,2,3,4], Genevieve Saphier[1,3,4], Robert E. Handsaker[3,5,6], Giulio Genovese[3,5,6], Shiran Bar[7], Nissim Benvenisty[7], Steven A. McCarroll[3,5,6] & Kevin Eggan[1,2,3,4]

Review

iPS-Cell Technology and the Problem of Genetic Instability—Can It Ever Be Safe for Clinical Use?

J. Clin. Med. 2019, 8, 288; doi:10.3390/jcm8030288 iScience 11, 398–408, January 25, 2019 doi:10.1038/nature22312

CellPress
OPEN ACCESS

Cell Stem Cell

Review

Pluripotent stem-cell-derived therapies in clinical trial: A 2025 update

Agnete Kirkeby,[1,2,*] Heather Main,[3] and Melissa Carpenter[4,*]
[1]Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW) and Department of Neuroscience, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark
[2]Department of Experimental Medical Sciences, Wallenberg Center for Molecular Medicine (WCMM) and Lund Stem Cell Center, Lund University, 221 84 Lund, Sweden
[3]HOYA Consulting (ReGenMed Solutions), Stockholm, Sweden
[4]Carpenter Consulting Corporation, Washington, USA
*Correspondence: agnete.kirkeby@sund.ku.dk or agnete.kirkeby@med.lu.se (A.K.), melissa@carpentergroupstrategy.com (M.C.)
https://doi.org/10.1016/j.stem.2024.12.005

SUMMARY

Since the first derivation of human pluripotent stem cells (hPSCs) 27 years ago, technologies to control their differentiation and manufacturing have advanced immensely, enabling increasing numbers of clinical trials with hPSC-derived products. Here, we review the landscape of interventional hPSC trials worldwide, highlighting available data on clinical safety and efficacy. As of December 2024, we identify 115 clinical trials with regulatory approval, testing 83 hPSC products. The majority of trials are targeting eye, central nervous system, and cancer. To date, more than 1,200 patients have been dosed with hPSC products, accumulating to >10^{11} clinically administered cells, so far showing no generalizable safety concerns.

Cell Stem Cell
Review

CellPress
OPEN ACCESS

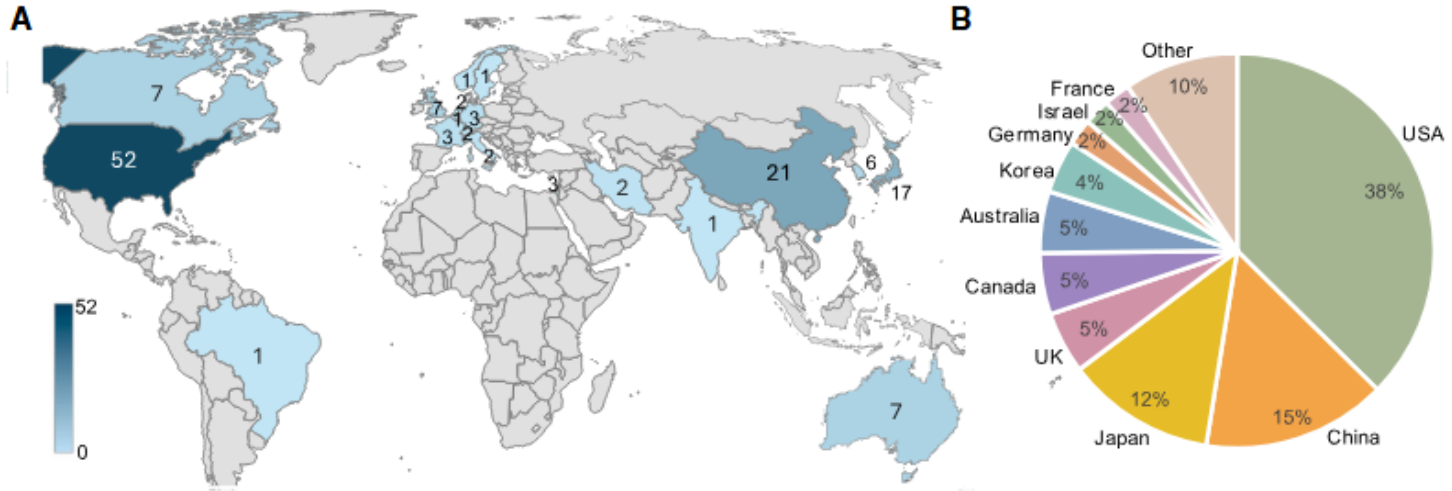


Figure 1. Distribution of hPSC trials per country

(A) Overview of number of hPSC clinical trials per country. The numbers indicate the countries' involvement in a trial as a trial site, and a trial with multiple sites in different countries will therefore be counted several times on the map. A trial with several sites within the same country is counted as just one trial. Chart made with Excel, Bing Maps.

(B) Pie chart showing fraction of hPSC clinical trial sites distributed per country.

EU approved products (2018)

List of ATMPs approved by the EMA **ATPM = Advanced Therapy Medicinal Products= Stem /Gene therapy**

Name	Developer	Indication	Approval date	Status
Alofisel	TiGenix	Perianal fistulas in Crohn's disease	March 2018	Approved
Spherox	CO.DON	Cartilage defects in the knee	May 2017	Approved
Zalmoxis	MolMed	Stem cell transplantation in high-risk blood cancer	June 2016	Approved
Strimvelis	GSK	ADA-SCID	April 2016	Approved
Imlygic	Amgen	Melanoma	October 2015	Approved
Holoclar	Chiesi	Severe limbal stem cell deficiency in the eye	March 2015	Approved
Provenge	Dendreon	Metastatic prostate cancer	October 2013	Withdrawn in 2015
MACI	Vericel	Cartilage defects in the knee	July 2013	Withdrawn in 2014
Glybera	uniQure	Lipoprotein lipase deficiency (LPLD)	November 2012	Withdrawn in 2017
Chondrocelect	TiGenix	Cartilage defects	November 2009	Withdrawn in 2016

With drawn 2020

With drawn 2022

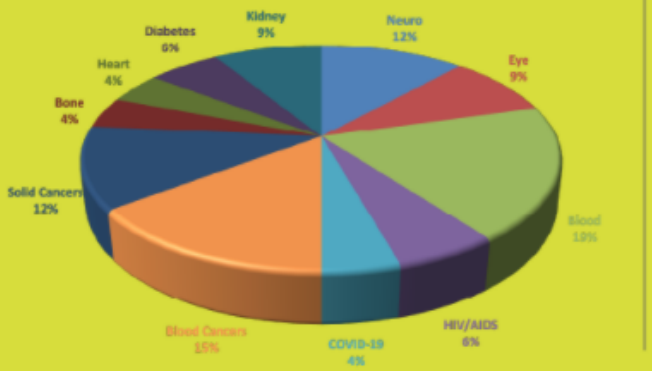
non autologous

Εγκεκριμένα προϊόντα FDA (2018)

Currently, the only stem cell treatments approved by the Food and Drug Administration (FDA) are products that treat certain

CIRM-FUNDED CLINICAL TRIALS:

DISEASE AREAS:



LEARN MORE:

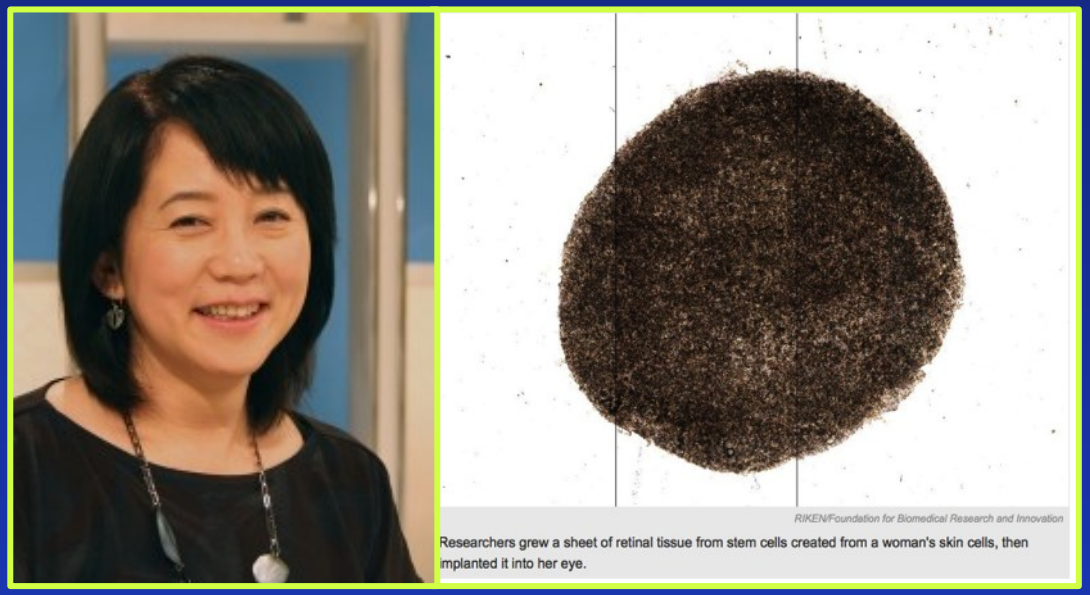
Read our CIRM-Funded Trials brochure

2021 μόνο ένα Ινστιτούτο!

However a large number of trials are on the way…

A complete list @ clinicaltrials.gov.

Clinical trial iPS



RIKEN/Foundation for Biomedical Research and Innovation

Researchers grew a sheet of retinal tissue from stem cells created from a woman's skin cells, then implanted it into her eye.

"This project could not have existed without the late Yoshiki Sasai's research, which led the way to differentiating retinal tissue from stem cells."

Kurimoto – surgeon performed the transplantation

"I cannot imagine any regulatory agency permitting such a trial without years of extensive pre-clinical testing,"
Robert Lanza

12 September 2014

Clinical trial iPS

RIKEN suspends first clinical trial involving induced pluripotent stem cells

Ken Garber

Nature Biotechnology **33**, 890–891 (2015) | doi:10.1038/nbt0915-890
Published online 08 September 2015

- Mutations in the second patient's iPSCs: three single nucleotide variations (SNVs) and three copy-number variants (CNVs) were present that were not detectable in the patient's original fibroblasts. It is not definitely known whether the reprogramming process induced the iPSC abnormalities, although iPSCs often acquire mutations and epigenetic and chromosomal changes in culture (*Nature* **471**, 46–47, 2012).
- The RIKEN group has now revised its AMD trial protocol to use allogeneic cells.
- Efforts for an iPS biobank covering the needs of Japan
- CiRA (Center for iPS cells Research and Application- Yamanaka Head

Clinical trials

Table 2 – The two different transplantation strategies used for ES and iPS cell derived RPE for AMD patients

Investigator/company	Starting cells	Immune status	Transplantation vehicle	Clinical stage
1. Transient dosing strategy				
I. Advanced Cell Technology (ACT)	ESCs	Allogeneic	Cell suspension	Phase I/IIa completed
I. Cell-cure-neurosciences (Eyal Banin & Bejamin Reubinoff, HMC)	ESCs	Allogeneic	Cell suspension	IND approved, Phase I initiated
2. Permanent implantation strategy				
I. Pfizer, London (Pete Coffey, UCL)	ESCs	Allogeneic	Polyester scaffold	IND approved, Phase I initiated
I. PI - Mark Humayun (USC), Co-PIs - Dennis Clegg (UCSB) & David Hinton (USC) (CIRM, USA)	ESCs	Allogeneic	Paralene scaffold	IND approved, Phase I initiated
I. Masayo Takahashi (RIKEN, Japan)	Fibroblasts-derived iPSCs	Autologous	RPE sheet, no scaffold	First patient transplanted, study halted
I. Kapil Bharti & Sheldon Miller (NEI, NIH, USA)	CD34+ cell-derived iPSCs	Autologous	Biodegradable scaffold	Performing IND-enabling studies

Abbreviations: AMD – Age-related Macular Degeneration; **ESC** – Embryonic Stem Cells; **IND** – Investigational New Drug; **iPSC** – Induced Pluripotent Stem Cells; **RPE** – Retinal Pigment Epithelium.
Clinical Groups Affiliations: UCL – University College London; **USC** – University of Southern California; **UCSB** – University of California Santa Barbara; **HMC** – Hadassah Medical Center; **NEI** – National Eye Institute; **NIH** – National Institutes of Health.

http://dx.doi.org/10.1016/j.brainres.2015.12.011

Clinical trials in the eye

Table 1 Selected pluripotent stem cell transplantation trials in the eye

Institution	Investigator	Indication	Cell source	Stage
Ocata Therapeutics, Marlborough, Massachusetts	Steven Schwartz	AMD, Stargardt macular dystrophy	ESC	Phase 1 complete
RIKEN	Masayo Takahashi	AMD	iPSC	Phase 1
University College London; Pfizer, New York	Peter Coffey	AMD	ESC	Phase 1 approved, enrollment pending
University of California Santa Barbara; Caltech, Pasadena; City of Hope, Duarte, California	Dennis Clegg, Mark Humayun	AMD	ESC	Phase 1 approved, enrollment pending
National Eye Institute, National Institutes of Health	Kapil Bharti	AMD	iPSC	Preclinical

AMD, age-related macular degeneration.

Ευρώπη

2015 ¨Europe approves Holoclar®, the first stem cell-based medicinal product!

In February 2015, Holoclar was the first stem cell-based medicine to receive authorization for commercial use throughout the European Union. Injury to the eye can destroy limbal stem cells (LSCs) leading to loss of vision as the cornea is invaded by conjunctival cells. Holoclar uses a patient's own LSCs from the unaffected eye to form a graft grown outside the body. Graft transplantation into the injured eye restores the LSC population allowing a normal transparent corneal surface to be regenerated. This is a significant development in the field of regenerative medicine no other stem cell therapy has demonstrated sufficient quality standards and clinical successes to achieve authorization status.

2010 LARGE-SCALE SUCCESS

An individual with a spinal-cord injury becomes the first person to receive a therapy derived from embryonic stem cells. A large study the same year reports that stem cells harvested from patients' healthy cornea tissue can be grown in the lab and transplanted into the damaged corneas to restore eyesight.

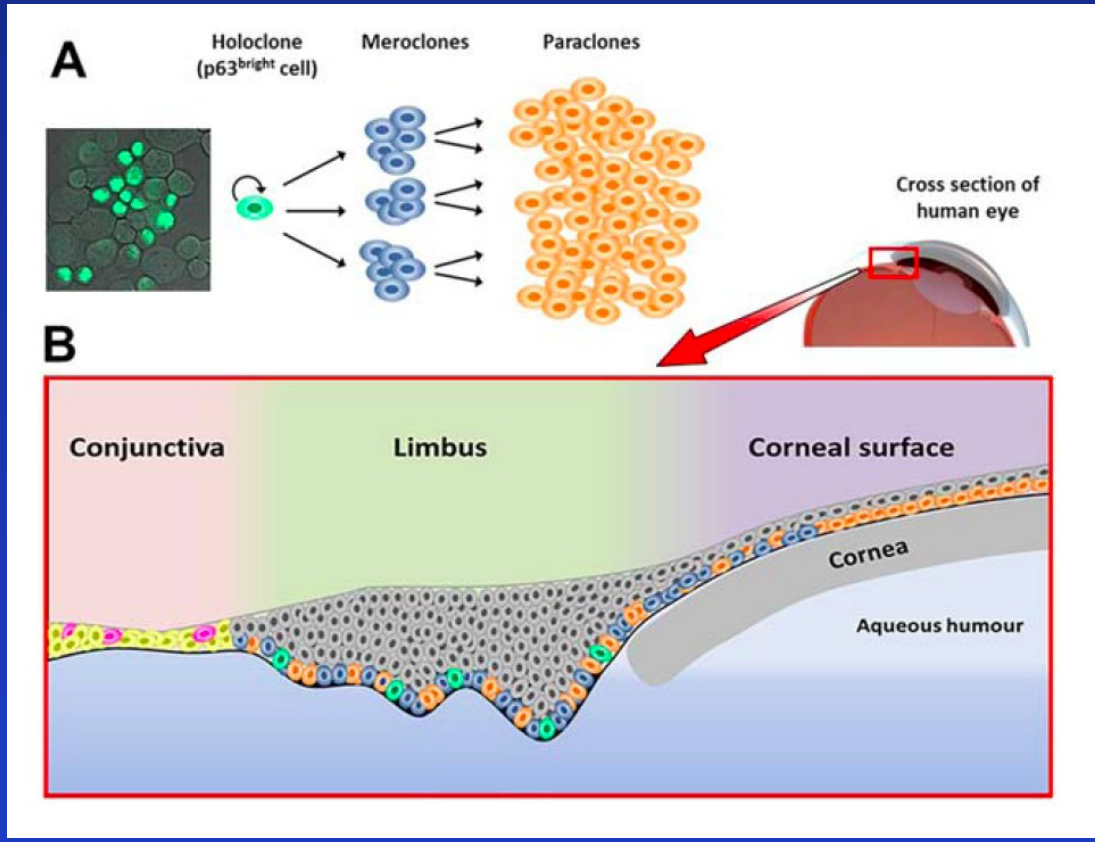
2015 FIRST TO MARKET

The Europe Commission approves the sale of Holoclar to treat people with severely damaged corneas. It is the first stem-cell therapy to reach the market.

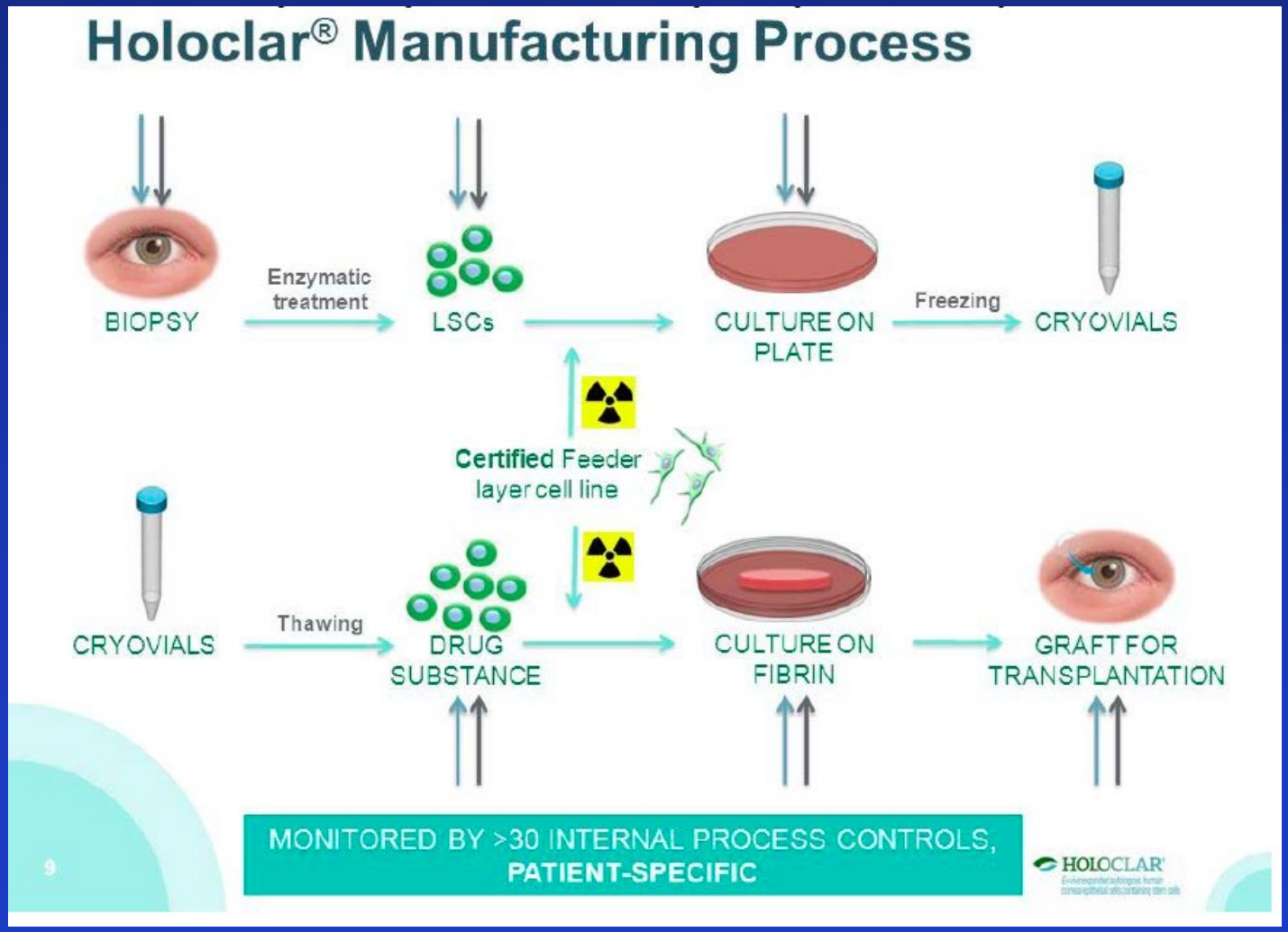
Holoclar®

The role of clonogenic keratinocytes in generation andrenewal of the corneal epithelium. (A): The holoclone differentiation process from highly proliferative self-renew in gholoclones to transiently amplifying cells (meroclones and paraclones). A confocal microscopy image of holoclone stem cells is on the left showing high expression of DNp63a, an isoform of the p63 transcription factor.

Due to this characteristic, these cells are also referred to asp63 bright cells. (B): Stem cells from (A) in their ocular context. Holoclones, meroclones, and paraclones are found in the basal layer of the limbus with holoclones having the least abundance (10%–15%).The basal layer of the cornea is populated by meroclones and paraclones at the periphery, and only paraclones in the central cornea. All suprabasal layers of the limbus and corneal surface contain terminally differentiated cells which have no capacity for self-renewal or proliferation (shown in gray). The conjunctival surface is composed of epithelial cells (yellow) and a low proportion of goblet cells (magenta) that are interspersed throughout.

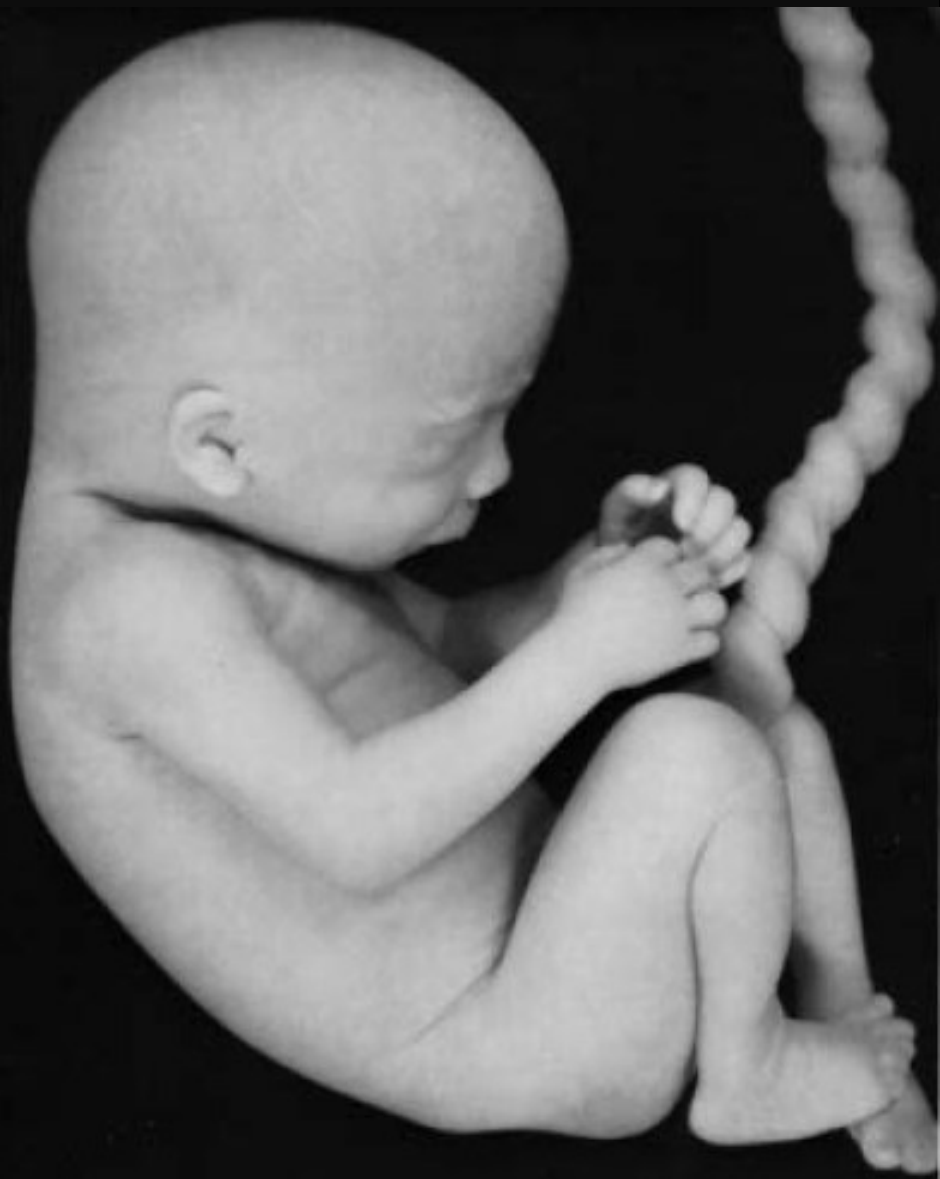


2015 ¨Europe approves Holoclar®, the first stem cell-based medicinal product!
Επιθηλιακά βλαστοκύτταρα κερατοειδούς



Βιολογία Βλαστοκυττάρων και Αναγέννησης

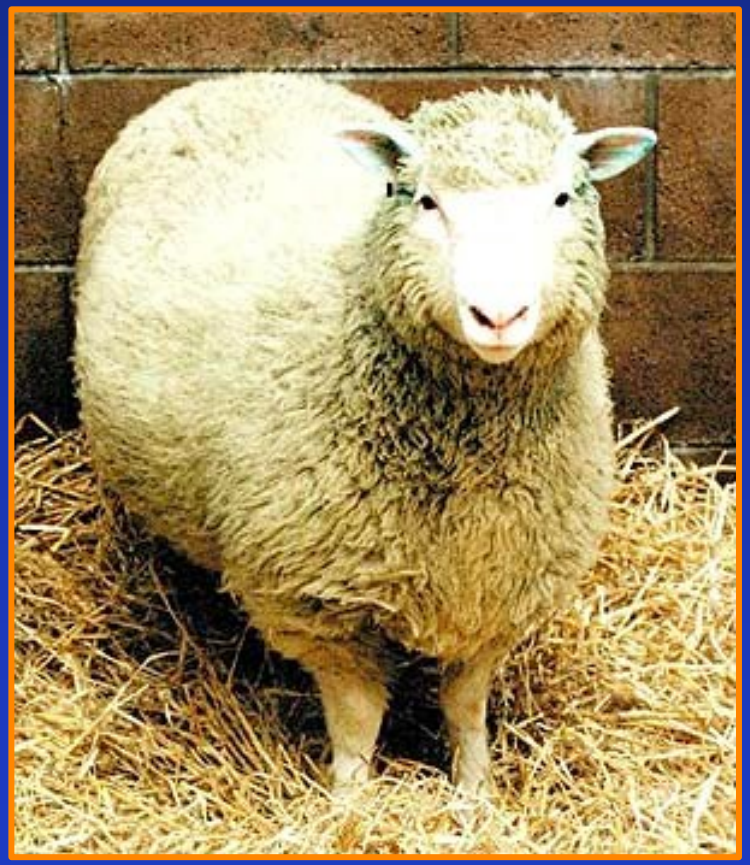
Ηθικά και νομοθετικά ζητήματα και θεραπείες βλαστοκυττάρων



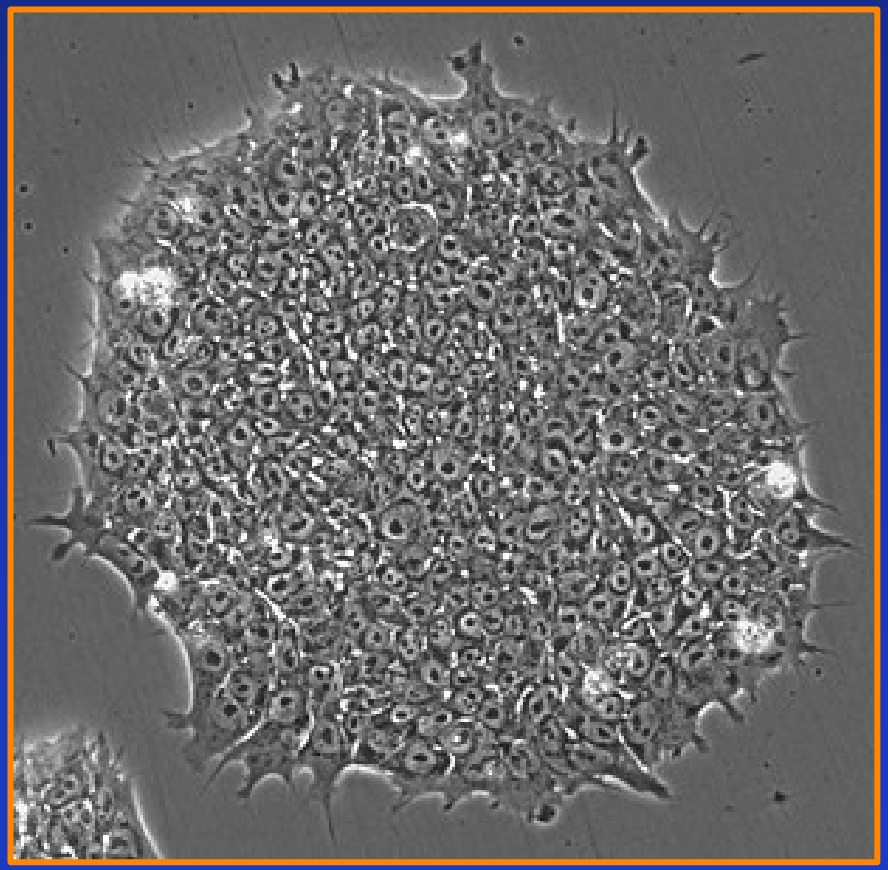
Μ. Γρηγορίου 2025

Βλαστοκύτταρα & κοινωνία

Η κλωνοποίηση της Dolly και η δημιουργία των ESC ανέδειξαν έναν προβληματισμό...



Dolly, 1996 nuclear transfer



hES from spare human blastocysts, 1998

Βλαστοκύτταρα & κοινωνία

- Η κοινωνία δυσκολεύεται να ακολουθήσει τους ταχείς ρυθμούς προόδου της επιστήμης μας...
- Διαφορετικές χώρες, θρησκείες και αντιλήψεις.....
- Ακόμα και μεταξύ των επιστημόνων οι απόψεις για πολλά από τα θέματα που εγείρονται είναι διαφορετικές.

- Οι φορείς που διαμορφώνουν τα νομοθετικά πλαίσια πρέπει να καταλήγουν σε ρυθμίσεις που να είναι ευρέως αποδεκτές από την κοινωνία – αυτό δεν είναι πάντα απλό π.χ στις ΗΠΑ από πολιτεία σε πολιτεία οι ρυθμίσεις είναι διαφορετικές.
- Φορείς που εκπροσωπούν ασθενείς έχουν συμβουλευτικό ρόλο.
- Λόγω των δυνατοτήτων για ανάπτυξη θεραπευτικών προσεγγίσεων πρέπει να λαμβάνονται υπόψη και οικονομικές παράμετροι.
- Η εμπλοκή του ιδιωτικού τομέα πρέπει να ρυθμίζεται επίσης...

Βλαστοκύτταρα & κοινωνία

- Η διαμάχη για τα βλαστοκύτταρα έχει τις ρίζες της στη διαμάχη των αμβλώσεων.
- Αφού τα ESC προέρχονται από έμβρυα που πρέπει να καταστραφούν...
- Παράλληλα οι φόβοι για κλωνοποίηση του ανθρώπου θέτουν μια σειρά άλλων προβληματισμών σε σχέση με το ποιο είναι το όριο στην έρευνα...

Βέβαια...

- Εμβρυϊκοί ιστοί έχουν χρησιμοποιηθεί σε ΗΠΑ και Ευρώπη για ερευνητικούς σκοπούς από το 1930. Για παράδειγμαα για την ανάπτυξη του εμβολίου *polio* (Nobel Prize in Medicine 1954) ή στην Parkinson στις αρχές της δεκαετίας 90 (έγιναν και κάποιες κλινικές δοκιμές ασφάλειας που σταμάτησαν)

Δείτε το βίντεο... Ethics, scince & stem cells (link στο eclass)

The duty to prevent/alleviate suffering
vs
the duty to respect the human life/personhood

- The embryo has full moral status from fertilization.

Development is continuous process - an embryo does not *currently* have the characteristics of a person, but it *will become* a person therefore it should be given the respect and dignity of a person.

An embryo before implantation in the uterus does not have the psychological, emotional or physical characteristics that are associated with being a person. We can use it for the benefit of patients who are persons. The embryo cannot live outside the mother- it *could* potentially become a person however before becoming one it should not be treated as if it *were* a person. Twins can arrise during the first days of gestation

- The embryo has no moral status at all.

Embryos are parts of their mother's body until they have developed enough to live independently. Property of the mother (parents).

Using embryonic stem cells out of an early embryo, we prevent the embryo from becoming as it is normal and programmed to a human being.

The duty to prevent/alleviate suffering
vs
the duty to respect the human life

- Increasing status of the embryo status as it develops.

Stages of development with different status: before implantation, before nervous system appearence (primitive streak), 25th week- the baby can survive if born prematurely and birth. More than half of fertilized eggs are normally lost due to natural causes. using some embryos in stem cell research should not worry us either.

The life that an embryo lives has a value to the embryo. prior to neural tissue formation- a person who has lost nerve cells for example in a stroke has not become less human.

- A cut-off point at 14 days after fertilization- appearence of the neural tissue.

After the 14th day twins cannot form. The embryo has no central nervous system and hence no senses (essential the same as taking organs from brain dead patients).

The life that an embryo lives has a value to the embryo. prior to neural tissue formation- a person who has lost nerve cells for example in a stroke has not become less human.

Should research on hES be allowed?

Can public entities use tax payers' money to fund research on hES ? ... Scope of research?

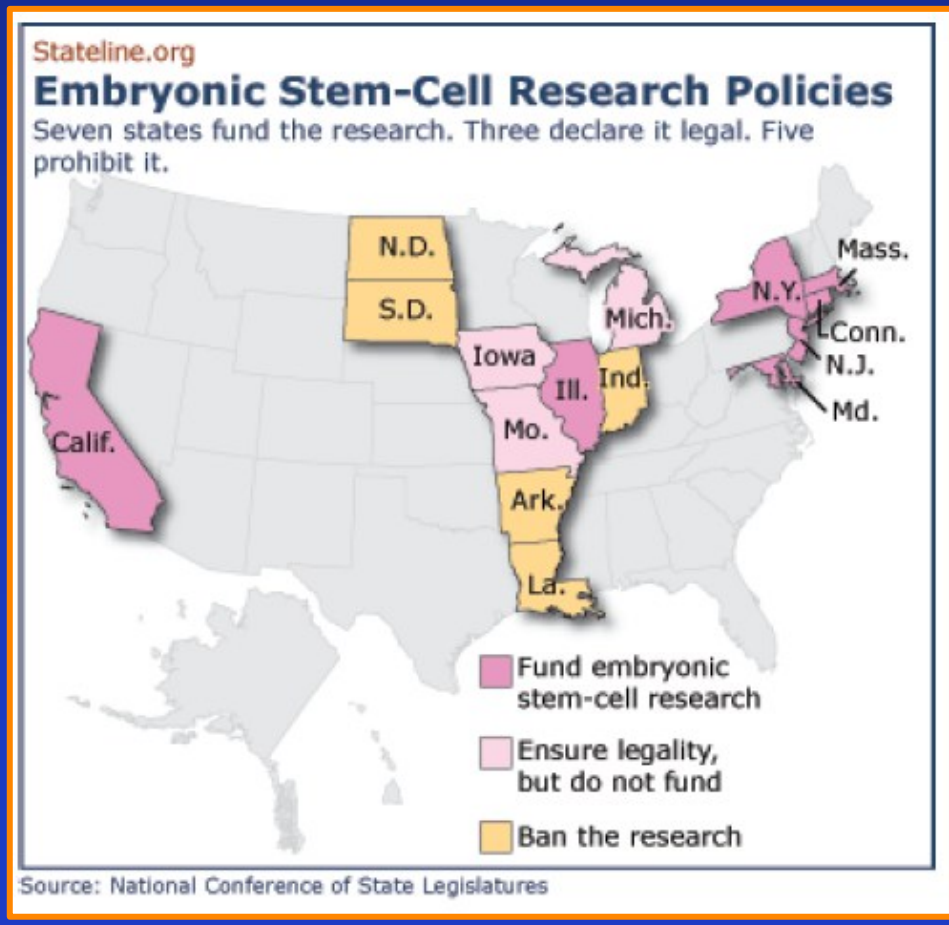
What about private companies? Patents?

Should these issues be regulated at the national, European or international level? Is the latter feasible?

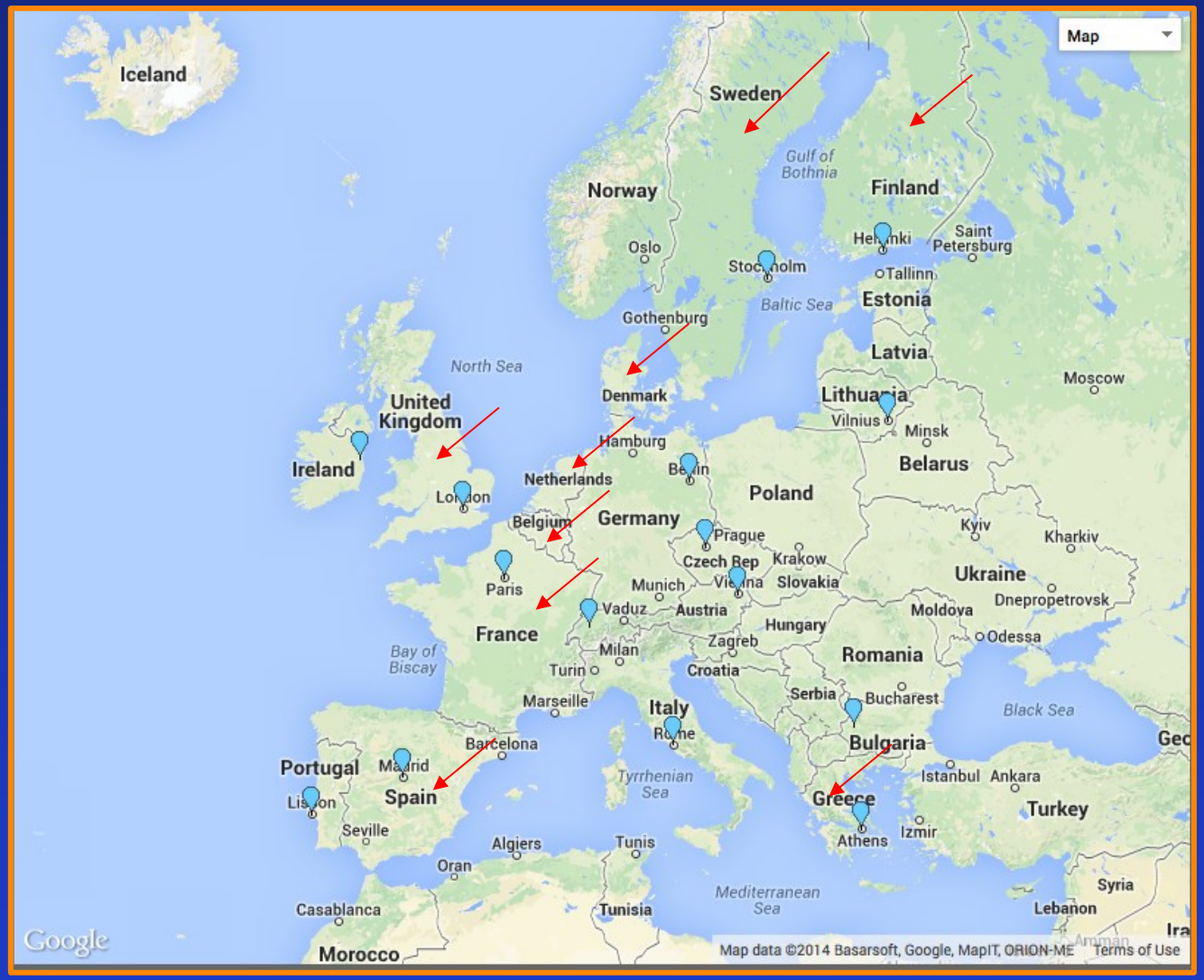
What are the consequencies for the economy of the country?

The regulations... USA

- In USA these regulations apply for the federal funding, not for private funding.
- Several states have started stem cell funding programs following Bush's guidelines: California ($3 billion bond- public ballot to decide) establishment of the California Institute for Regenerative Medicine. New York – NYSTEM ($600 million/year).
- Different states have different legislation



The regulations Europe



Not all European countries have regulations

The regulations UK

- UK is the leading country in stem cell research (many scientists moved to UK from USA following Bush restrictions.
- UK Stem Cell Bank was established in 2004. $4.7 billion invested- all embryonic cell lines generated in UK is stored in the Bank.
- The use of embryos in stem cell research is carried out only with a liscence. Liscences are granted only if the Human Fertilization and Embryology Regulations are satisfied that any proposed use of embryos is absolutely necessary for the purposes of the research (Human Fertilisation and Embryology Authority).
- Licensed only on embryos created *in vitro:* embryos. Most embryos used in UK are embryos initially created for IVF. These embryos*, if donated with the full consent of the parents*, can be used for research.
- Licensed research can only on embryos *up to 14 days,* cloning is prohibited.
- Several regulatory bodies depending on the type of research - *UK Stem Cell Tool Kit* is e a reference tool for those who wish to develop a programme of human stem cell research and manufacture, including clinical applications.

The regulations- Greece

- Embryonic stem cells can be derived from surplus IVF embryos, for medical and research purposes.
- Human reproductive cloning is prohibited.
- Embryos can be frozen and stored for up to five years, then they are either destroyed or used for therapeutic /research purposes.
- Fertilized eggs that have not been frozen should be destroyed 14 days following fertilization.
- The Hellenic National Bioethics Commission as of 1999 advises and issues opinions on medical and scientific issues that may have implications for human health and society.
- The National Transplantation Organization oversees the transplantation of organs and tissues under law 3984/2011.

The international Society for Stem Cell Research

- "The International Society for Stem Cell Research (ISSCR) is an independent, nonprofit organization established to promote and foster the exchange and dissemination of information and ideas relating to stem cells, to encourage the general field of research involving stem cells and to promote professional and public education in all areas of stem cell research and application"
- More than 4000 members mainly scientists, A "task force" – leading scientists
- An annual meeting, publications etc.
- An **influential Ethics and Public Policy Committee** (Prof. Kimmelman- Mc Gill)

Κυτταρικές θεραπείες βλαστοκυττάρων χωρίς επιστημονικά δεδομένα...

- Πάνω από 200 κλινικές στην Κίνα παρέχουν κυτταρικές θεραπείες διαφόρων ειδών...
- Μεχρι το 2009 στην Κίνα δεν υπήρχε καν πλαίσιο και έτσι θεραπείες που βασίζονταν σε ελάχιστα δεδομένα ή ήταν καθαρή απάτη παρέχονταν από ιδιωτικούς φορείς.
- Και σε άλλες αναπτυσσόμενες χώρες παρόμοια φαινόμενα

Ινδία...

Μεξικό,

Ρωσία

Τουρκία .. Και αλλού

Illustration by David Simonds

Κυτταρικές θεραπείες βλαστοκυττάρων χωρίς επιστημονικά δεδομένα... και στην Ευρώπη

FIG. 2. Casualties and controversies with unproven stem cell based therapies in Europe.

Italy	Germany	Hungary
• 72-year-old man affected by Parkinson's disease died in 2009 after autologous stem cell injection by an Italian doctor (now Stamina's scientific director – see main text) in a clinic located in the Republic of San Marino. • Family members suspect the death is directly linked to the procedure, but doctor claims the patient died for other causes. The case has not yet been decided by Italian courts, but gave rise to an investigation [105].	• XCell, a German clinical center charging patients for injections of autologous bone marrow-derived cell, closed in 2011 after the death of a 18-month-old Romanian child following cell-injections in the brain. [12,106]. • xCell has now moved from Germany and operates in Lebanon and India as Cell4health [107].	• In July 2009 Hungarian police detained four individuals suspected of providing illegal stem cell treatments using cells from embryos or aborted fetuses [108]. • The alleged treatments were administered in a private clinic in Budapest for a cost of about 20,000 €. For cell preparation, the clinic relied on a private stem cell research institute.

Κυτταρικές θεραπείες βλαστοκυττάρων χωρίς επιστημονικά δεδομένα... και στην Ευρώπη

Stem cell doctor forced to close his clinic after child's death is back in business

The boss behind Europe's largest stem cell clinic, which was shut down following the death of a child in its care, is back in business working in partnership with a British laboratory.

Philippines Investigating 3 Politician Deaths Allegedly From Stem Cells in Germany

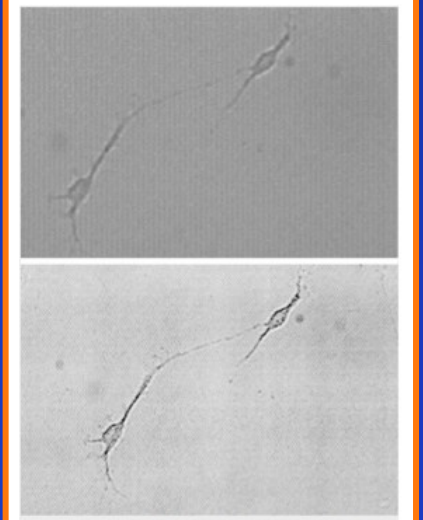
Posted on **June 23, 2013**

Κυτταρικές θεραπείες βλαστοκυττάρων χωρίς επιστημονικά δεδομένα... και στην Ευρώπη

Η περίπτωση της εταιρείας Stamina που κατόρθωσε να εντάξει μια κυτταρική της θεραπεία βλαστοκυττάρων στο Σύστημα Υγείας και όταν αποδείχθηκε ότι πρόκειται για απάτη και σταμάτησε... Έγιναν διαδηλώσεις!

Don't market stem-cell products ahead of proof

The controversy over an unproven stem-cell therapy in Italy highlights the dangers of doing translational medicine in reverse, argues **Paolo Bianco.**



Davide Vannoni, US patent No. 12/964,941 (top); Ref. 1

The micrograph in Figure 3 from Vannoni's 2010 US patent application (top) and Figure 2b from the 2003 Russian and Ukranian paper.

Κυτταρικές θεραπείες βλαστοκυττάρων χωρίς να... και στην Ευρώπη

Stranger bequeaths fortune to prominent neuroscientist

Elena Cattaneo is a relentless campaigner against the misuse of science.

Alison Abbott

22 June 2016

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Tania/A3/Contrasto/eyevine

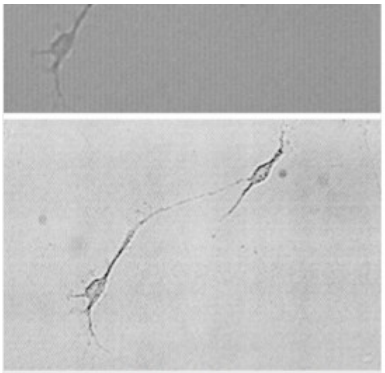
Senator-for-life Elena Cattaneo worked to stop use of unproven stem cell therapies.

Cattaneo, who is based at the University of Milan, is no ordinary researcher. In 2013, then-president Giorgio Napolitano appointed her a senator-for-life in recognition of her activities in promoting science. One of her most famous achievements, made with a handful of colleagues, was a successful two-year battle **to stop the Stamina Foundation in Brescia from administering unproven stem-cell therapies**.

κειται για απάτη και

em-cell products ahead of proof

The controversy over an unproven stem-cell therapy in Italy highlights the dangers of doing translational medicine in reverse, argues **Paolo Bianco**.

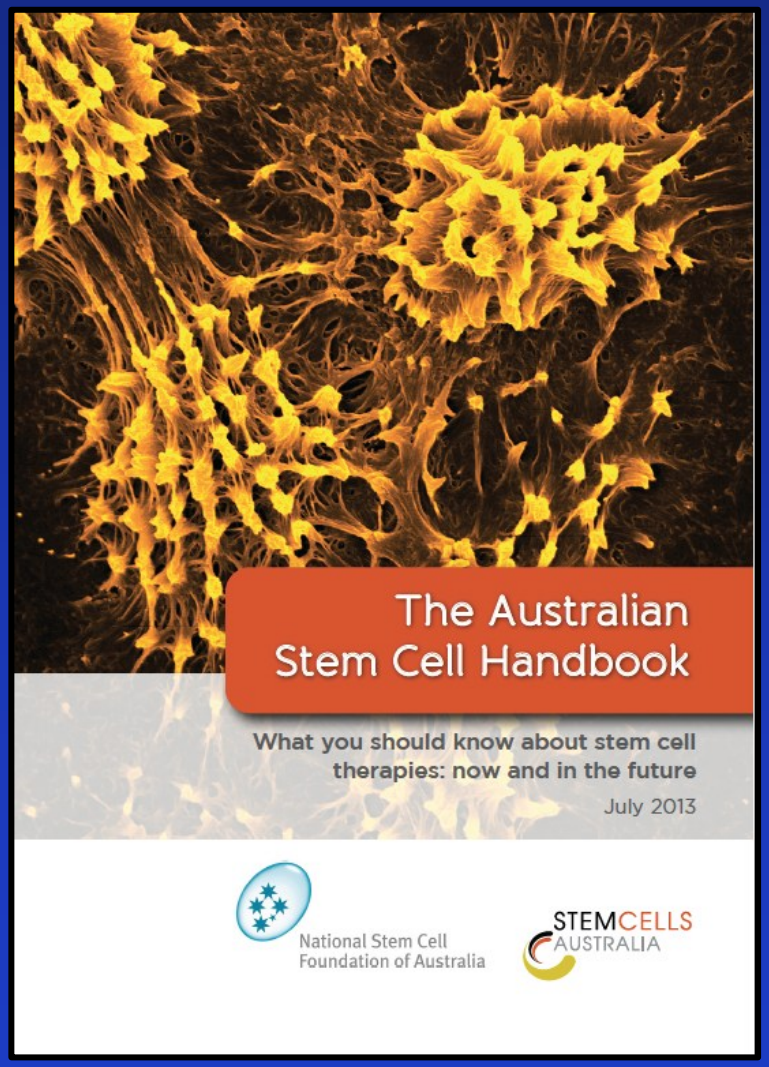


Davide Vannoni, US patent No. 12/964,941 (top); Ref. 1

The micrograph in Figure 3 from Vannoni's 2010 US patent application (top) and Figure 2b from the 2003 Russian and Ukranian paper.

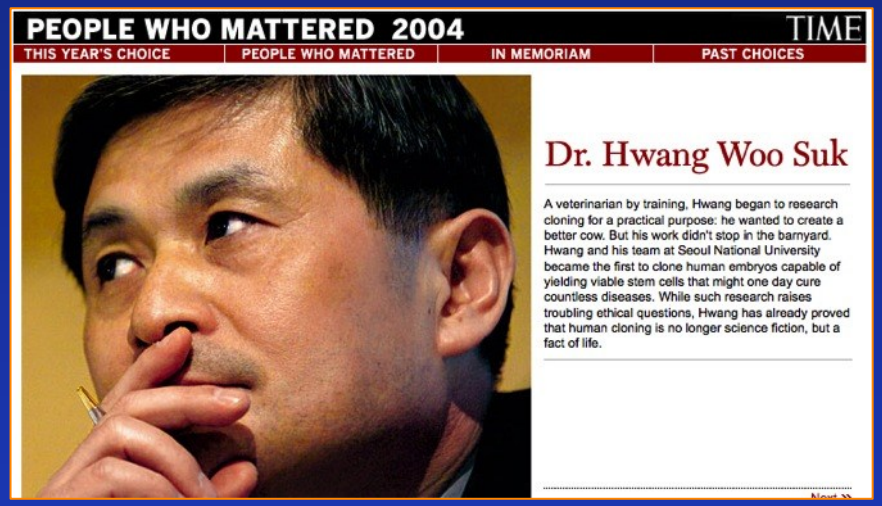
Κυτταρικές θεραπείες βλαστοκυττάρων χωρίς επιστημονικά δεδομένα..

Πολλές χώρες αλλά και επιστημονικοί φορείς έχουν αναλάβει το έργο της πληροφόρησης του κοινού ώστε να προστατευθεί από τέτοια φαινόμενα.



Scientific ethics…….

South Korea invested in stem cell research in late 1990's



Hwang Woo-suk claimed to have achieved human cloning by somatic nucleus transfer in 2004 and also to have generated hES lines from the cloned embryos. the embryo was to be used for stem cell harvesting. In 2006 they reported that they had a protocol that uses less eggs to produce hESCs. In 2006, both of these claims were shown to be fraudulent.

Concerns were raised about the egg donation process (185 eggs) as well as about his two Science papers. It was later shown that both papers were fabricated and were retracted.

Hwang lost his job, and in 2009 was sentenced to two years in prison. He was found guilty of buying human eggs and of embezzling US$700,000) of government money.

Hwang has rebuilt his carreer .

Hwang WS et al. (2004) Science 303 (5664): 1669–74. doi:10.1126/science.1094515. PMID 14963337. (Retracted)
Hwang WS et al. (2005). "Patient-specific embryonic stem cells derived from human SCNT blastocysts". Science 308 (5729): 1777–83 (Retracted)
Nature 461, 1035 (2009)

..και στην Αμερική!

Home / News & Opinion

Journals Retract 13 Papers from Heart Stem Cell Lab

It's the latest fallout from an investigation by Harvard and Brigham and Women's into work overseen by Piero Anversa.

Dec 14, 2018
KERRY GRENS

The cardiac stem cell field has had a rough
only have scientists piled up evidence th
exist, but one of the leading proponents of th
papers retracted.

the hospital agreed to a $10 million settlement with the U.S. government over allegations Anversa and two colleagues' work had been used to fraudulently obtain federal funding.

Home / News & Opinion

The Lancet Retracts Cardiac Stem Cell Clinical Trial Paper

The publication of the SCIPIO trial is among many by Piero Anversa's lab that Harvard Medical School flagged for fraudulent data.

Mar 14, 2019
KERRY GRENS

Update (March 15): The Lancet *sent* The Scientist *the retraction notice, which states that the data from Harvard "cannot be held to be reliable." The editors note that they believe the clinical work conducted in Louisville was done "in good faith."*

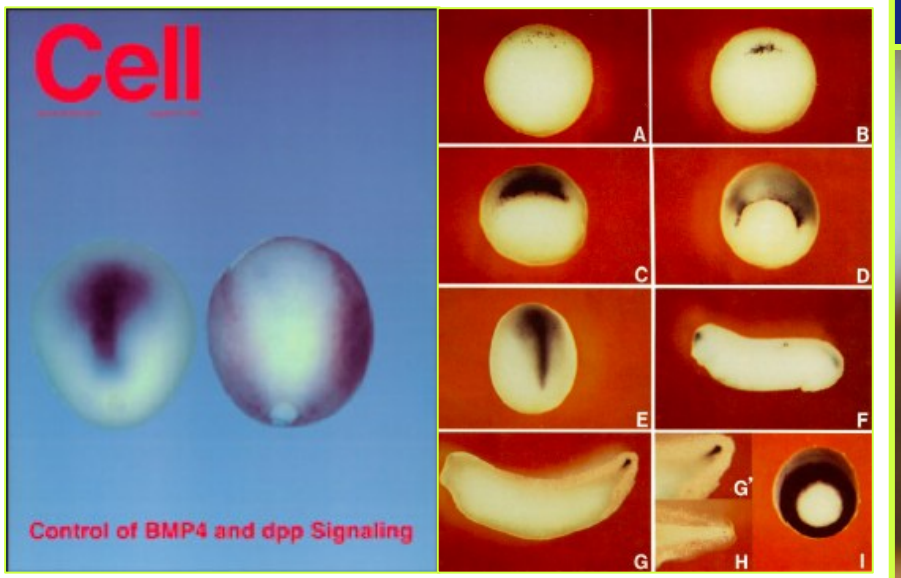
ABOVE: © ISTOCK.COM, NOCTILUXX

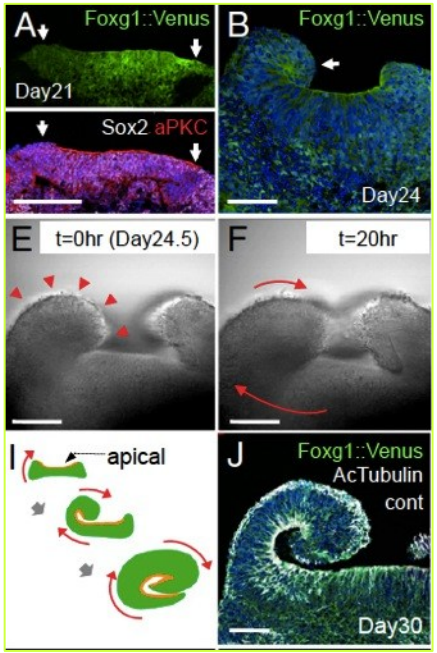
Since 2014, a paper in *The Lancet* describing the results of a clinical trial using supposed cardiac stem cells has sat with an editors' expression of concern looming over it. Now, the journal has retracted the paper—the 16th retraction for Piero Anversa, formerly of Harvard Medical School and Brigham and Women's Hospital.

The Scientist could not locate a retraction notice, and the press office at *The Lancet* did not immediately respond to a request for information. (We sent the message after business hours in the UK, and will update this post once we hear back.)

In October, Harvard Medical School and Brigham and Women's Hospital determined that 31 papers from the Anversa lab ought to be retracted. By *Retraction Watch*'s reporting, it's not clear whether the 2011 paper in *The Lancet* was among the 31, but the expression of concern came about because the institutions gave the journal a heads up that they were investigating the "integrity of certain data" in the paper, the editors wrote at the time.

Scientific ethics…….





Stimulus-triggered fate conversion of somatic cells into pluripotency

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Bidirectional developmental potential in reprogrammed cells with acquired pluripotency

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- In many countries cord blood banking has emerged within a regulatory vacuum- started around 1995.
- Over 1 million Cord Blood Units (CBUs) in private banks, 600.000 in the 54 public banks (2013).
- Problems regarding property– mother / child or children. In private banks the type of contract may refer only to the child or to all siblings of a family.
- Common law does not recognise property rights in human tissues.
- The case of *Moore v. Regents of the University of California,* 793 P.2d 479 (Cal.1990), *cert denied* 499 U.S. 936 (1991) is the first case on this issue, though not related to stem cells.
- However in the past years there is a growing concern on this issue, as cell therapies based either in CB cells or other types of stem cells may become available.
- PXE (a non-profit organisation incorporated by a patient advocacy group, individuals affected by pseudoxanthoma elasticum, a genetic disorder causing calcification of elastic tissues), Cure Autism Now and the Juvenile Diabetes Research Foundation- coordinate and fund research labs, provide tissues etc. Contracts with the labs they fund is entitled to retain ownership rights in any patent application arising from the research.

Moore vs. Regents of the Univ. of California

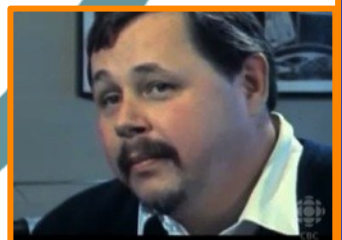
Facts of the Case

- Landmark case heard in the Supreme Court of California (highest court in State of California)
- Appealed from the Court of Appeal which held that Moore had property rights to maintain the cause of action for conversion
- The first common law authority to address whether a living person can claim property rights to separated biological materials

TIMELINE

- 1976 - Moore signed a written consent authorising the removal of his spleen
  - Moore provided samples of blood, blood serum, skin and bone marrow
- 1983 - Moore was asked to sign a consent form in continuing research, refused to do so
- 1984 - Regents were granted a patent which included methods for using the cell-line to product lymphokines
  - Cell-line had a commercial value of US$3 billion over a six-year period

1990 The California Supreme Court ruled that a hospital patient's discarded blood and tissue samples are not his personal property and that individuals do not have rights to a



Greanpeace vs. Brüstle Patent

- In 2004, Greenpeace filed a lawsuit against the German scientist Oliver Brüstle at the German patent court.
- A patent on isolated and purified neural progenitor cells it was granted by the patent office. The progenitor cells were derived from embryonic stem cells.
- The establishment of the hES line is prohibited in Germany but the import is not- the pattent was in accordance with German law.
- Greapeace claimed that " use of human embryos for industrial or commercial purposes " constitutes a breach of *ordre public (public policy)* and thus precludes patentability"
- 2006 the German Federal Patents Court justified Greanpeace partially, any cell or tissue no matter how distantly related to a human embryo cannot be patented.
- Brüstle appealed at the German Federal Court of Justice on the basis that every action was according to the German Stem Cell Ac, which he claimed was ignored by the German Federal Patents Court .

Greanpeace vs. Brüstle Patent

- the German Federal Court of Justice held a pretrial session and then adressed the European Court of Justice (ECJ). The German Patent Act is literally implemented from the European Directive 98 / 44 (Biopatent Directive). ECJ justified Greanpeace

A Summation of the Findings from the ECJ

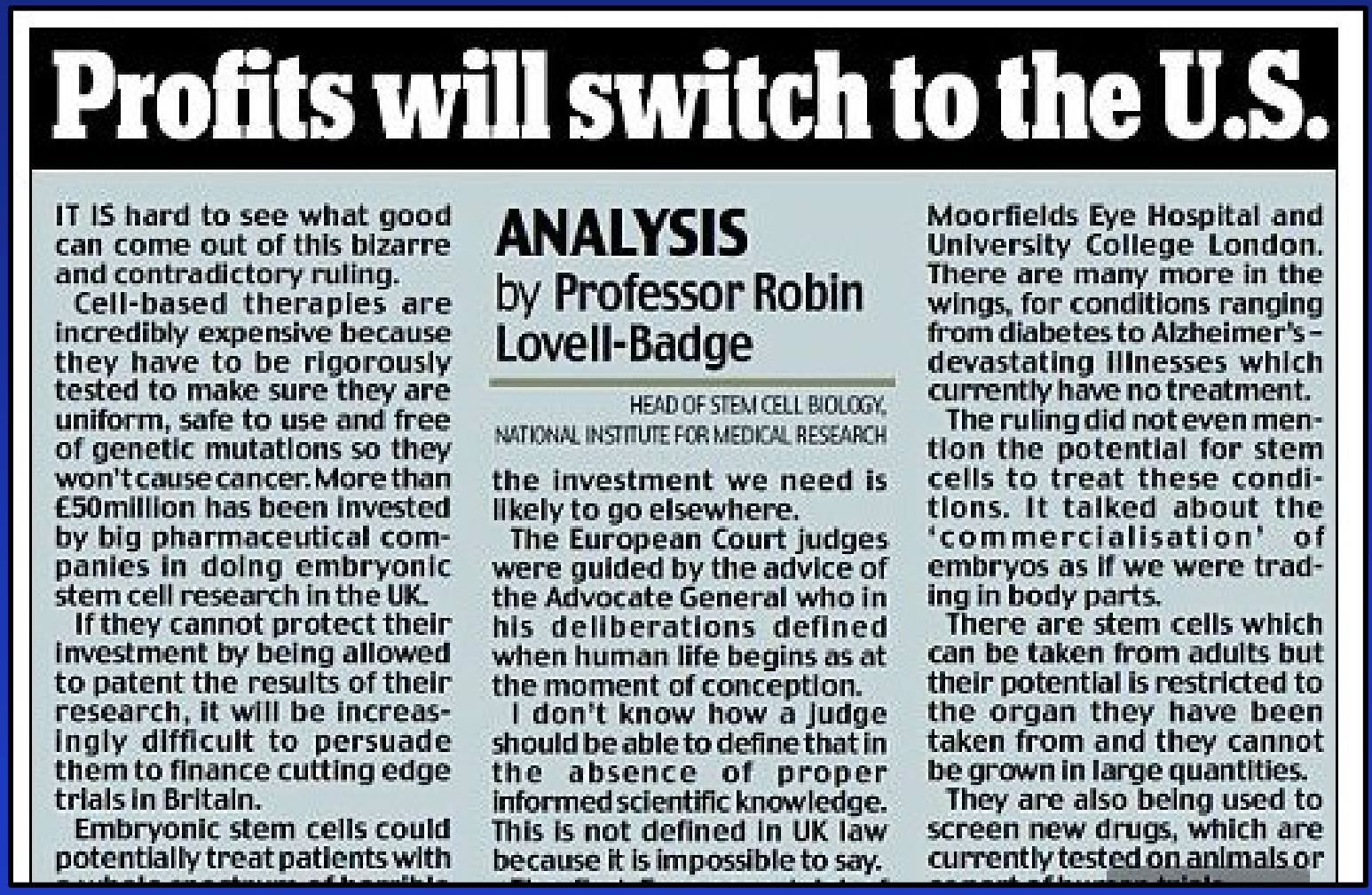
- A uniform and very broad concept of "embryo" defined for patent law.
- Embryo defined as each human egg cell from the stage of fertilization onward.
- Every invention regarding a process that includes the prior destruction of embryos, or their use as source material, represents an industrial or commercial use.
- Is immaterial whether the process refers to human embryos.
- Using embryos for research purposes is an industrial or commercial use and leads to exclusion of patentability.

Complaints from the European sientific community

- "'This is a devastating decision which will stop stem cell therapies use in medicine. The potential to treat disabling and life threatening disease commonly using stem cells will not be realised in Europe" Prof. Peter Coffey.

- 'This unfortunate decision by the Court leaves scientists in a ridiculous position. We are funded to do research for the public good, yet prevented from taking our discoveries to the marketplace where they could be developed into new medicines.' Prof Austin Smith

Greanpeace vs. Brüstle Patent



Profits will switch to the U.S.

IT IS hard to see what good can come out of this bizarre and contradictory ruling.

Cell-based therapies are incredibly expensive because they have to be rigorously tested to make sure they are uniform, safe to use and free of genetic mutations so they won't cause cancer. More than £50million has been invested by big pharmaceutical companies in doing embryonic stem cell research in the UK.

If they cannot protect their investment by being allowed to patent the results of their research, it will be increasingly difficult to persuade them to finance cutting edge trials in Britain.

Embryonic stem cells could potentially treat patients with

ANALYSIS
by Professor Robin Lovell-Badge

HEAD OF STEM CELL BIOLOGY, NATIONAL INSTITUTE FOR MEDICAL RESEARCH

the investment we need is likely to go elsewhere.

The European Court judges were guided by the advice of the Advocate General who in his deliberations defined when human life begins as at the moment of conception.

I don't know how a judge should be able to define that in the absence of proper informed scientific knowledge. This is not defined in UK law because it is impossible to say.

Moorfields Eye Hospital and University College London. There are many more in the wings, for conditions ranging from diabetes to Alzheimer's – devastating illnesses which currently have no treatment.

The ruling did not even mention the potential for stem cells to treat these conditions. It talked about the 'commercialisation' of embryos as if we were trading in body parts.

There are stem cells which can be taken from adults but their potential is restricted to the organ they have been taken from and they cannot be grown in large quantities.

They are also being used to screen new drugs, which are currently tested on animals or

The 13 judges of the European Court of justice were unanimous