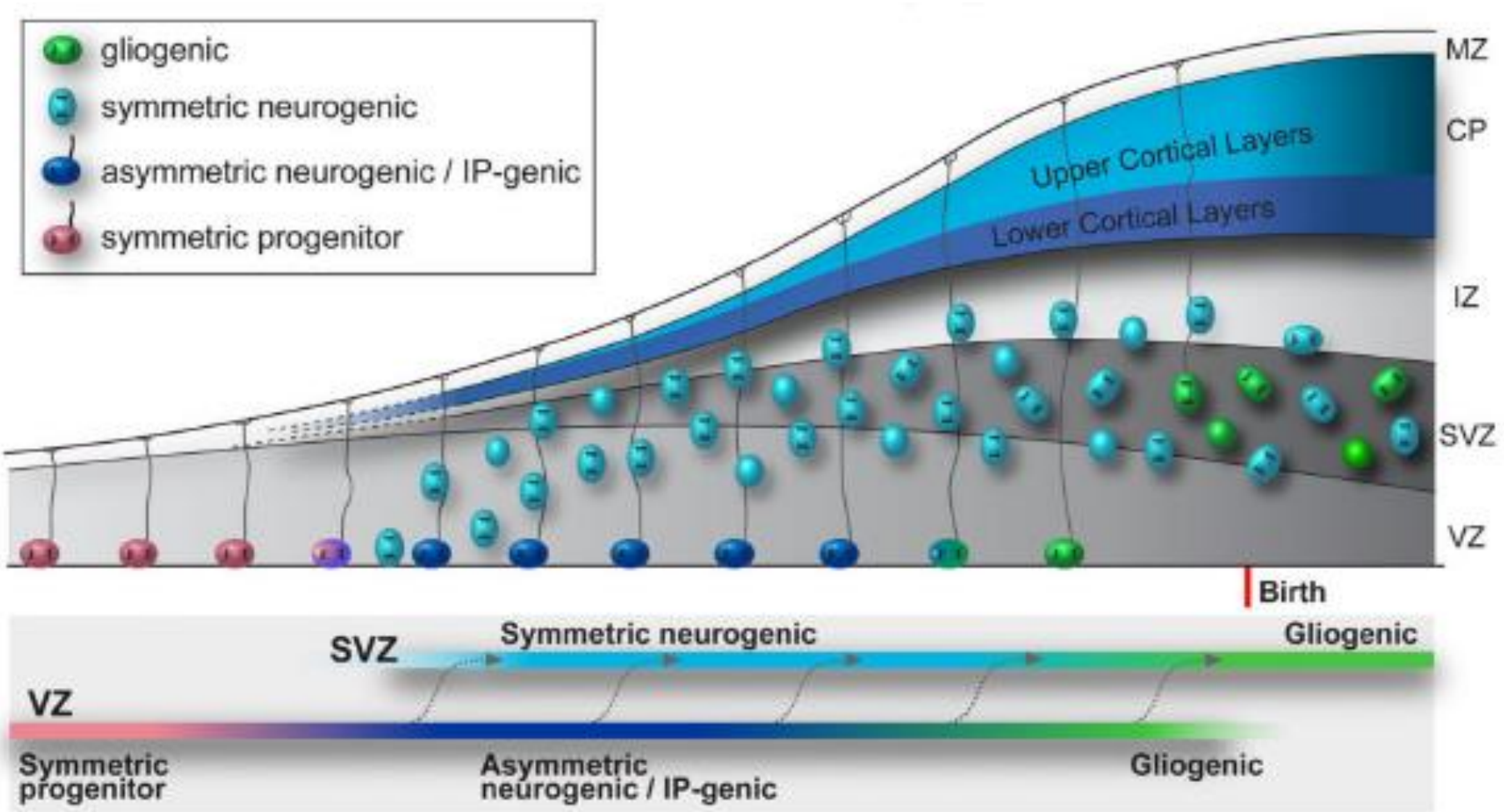
Idegsejtpótlás ős(?)sejtekkel - potenciális lehetőségek

A radiális glia leszármazásai (dorzális telencephalon)



IP: intermedier progenitor = bazális progenitor

Noctor et al *J Comp Neurol*. 2008 May 1; 508(1): 28–44.

Neurogenezis a felnőtt agyban

énekesmadarak:

high vocal center (striatum)

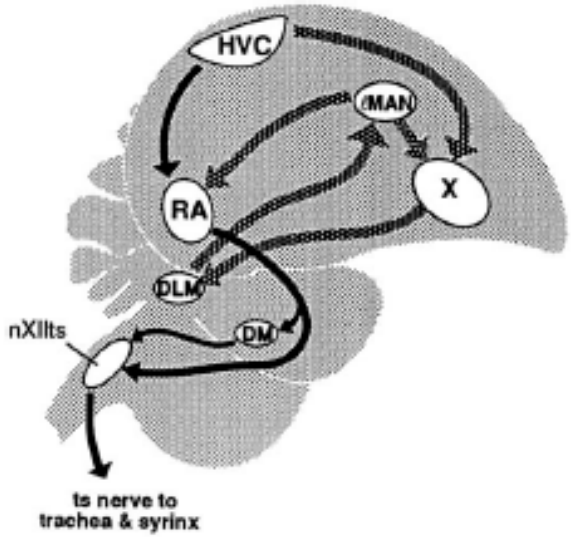
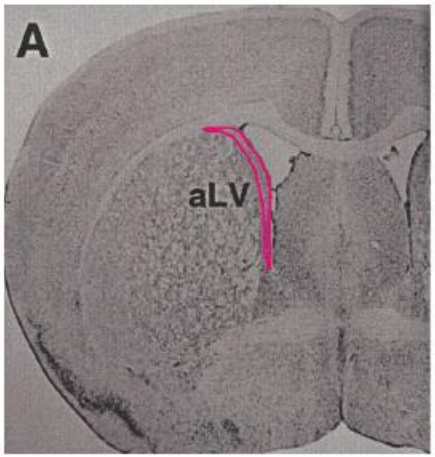


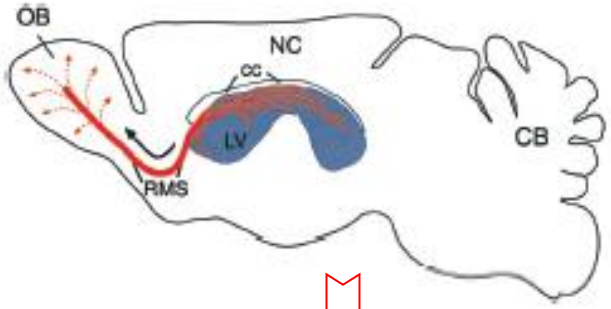
Figure 1. Sagittal section of oscine songbird's brain with schematic drawing of song system (Nottebohm, 1999), including some of the major nuclei and connecting pathways. The motor pathway necessary for production of learned song is shown by *black arrows*. The anterior forebrain pathway necessary for acquisition of learned song, but not for production, is shown by *stippled arrows*. Notice that the HVC is the source of both pathways. HVC neurons that project to the RA are replaceable; those that project to area X (*X*) are not replaceable. All the connections shown are ipsilateral. *lMAN*, Lateral magnocellular nucleus of anterior neostriatum; *DLM*, dorsolateral thalamic nucleus; *DM*, dorsomedial nucleus of the intercollicular complex; *nXIIts*, tracheosyringeal portion of the hypoglossal nucleus.

Nottebohm
J. Neurosci., 2002, 22(3):624-628

emlősök:

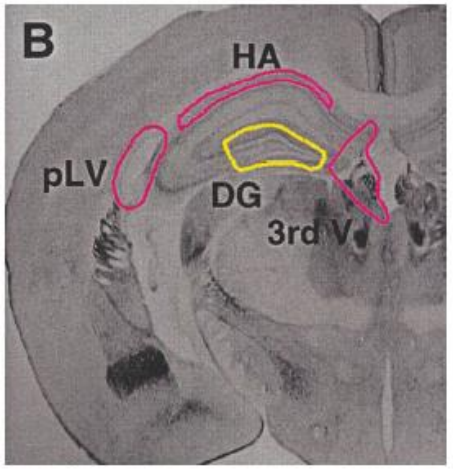
szubventrikuláris zóna (SVZ)





szaglógumó gátló GABAerg szemcsesejtek, dopaminerg periglomeruláris sejtek

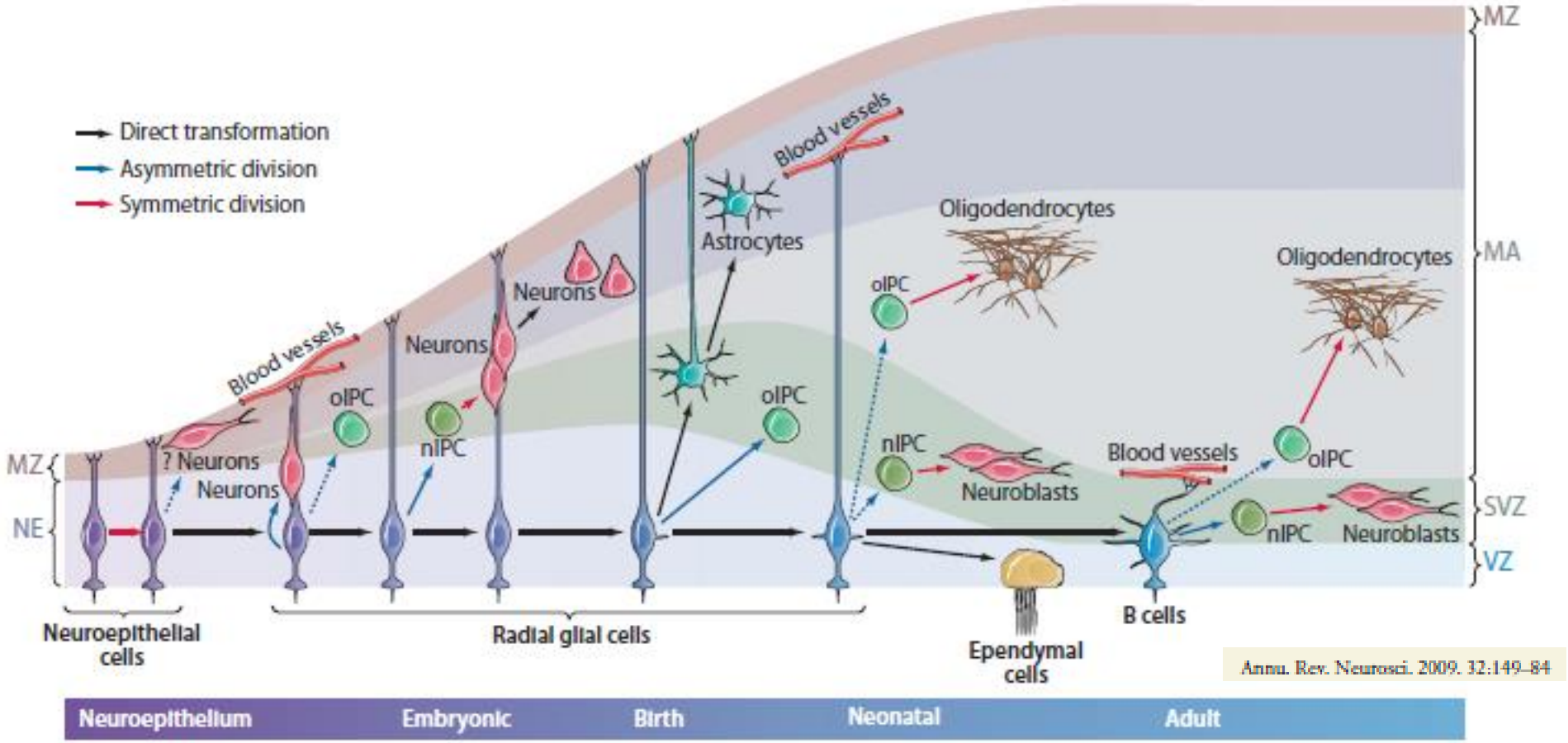
hippocampus gyrus dentatus (GD) szubgranuláris zóna (SGZ)



Alvarez-Buylla and Garcı´a-Verdugo
J. Neurosci., 2002, 22(3):629-634

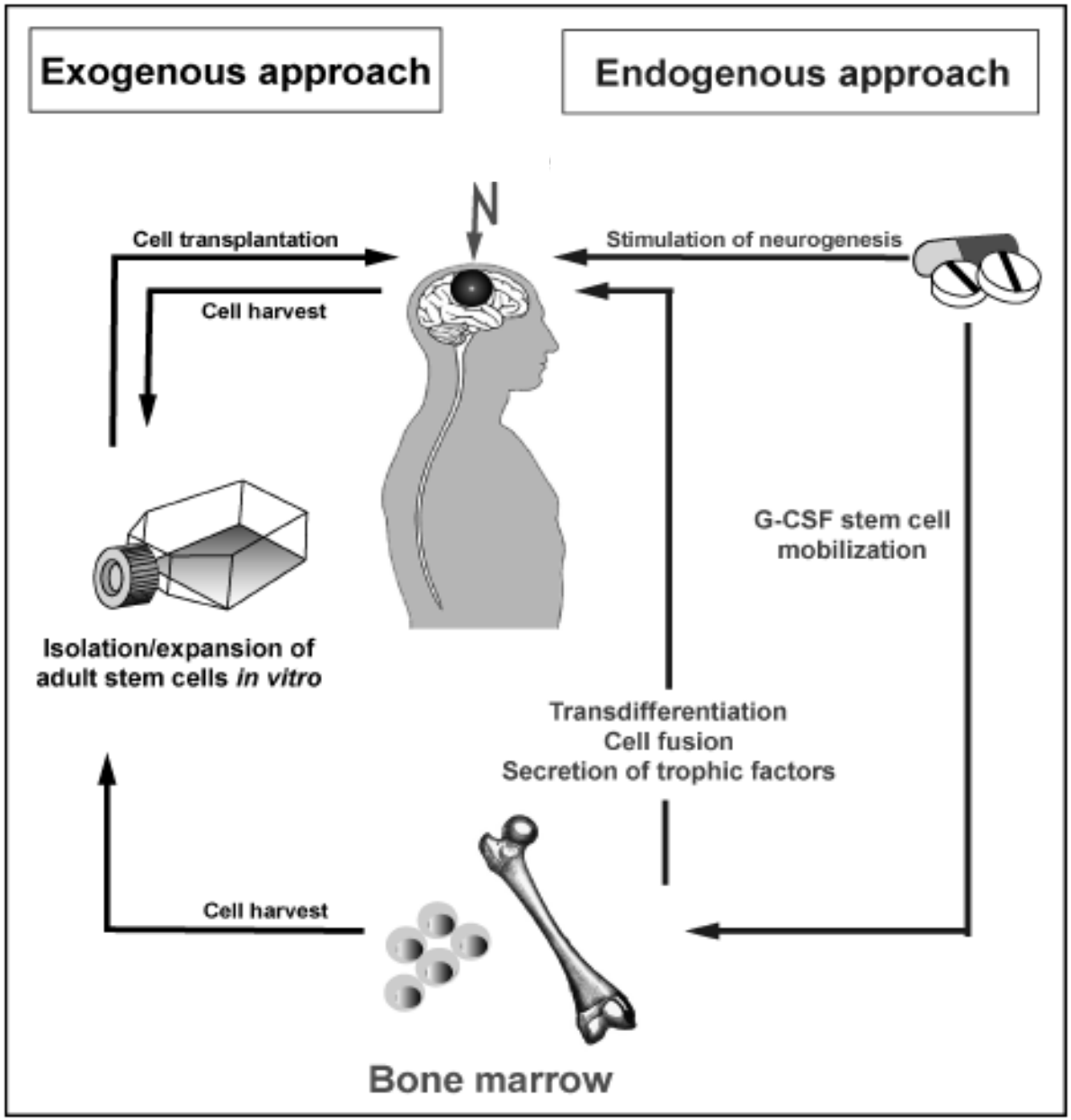
GD Glu-erg szemcsesejtek

A neurális őssejtek leszármazási sora

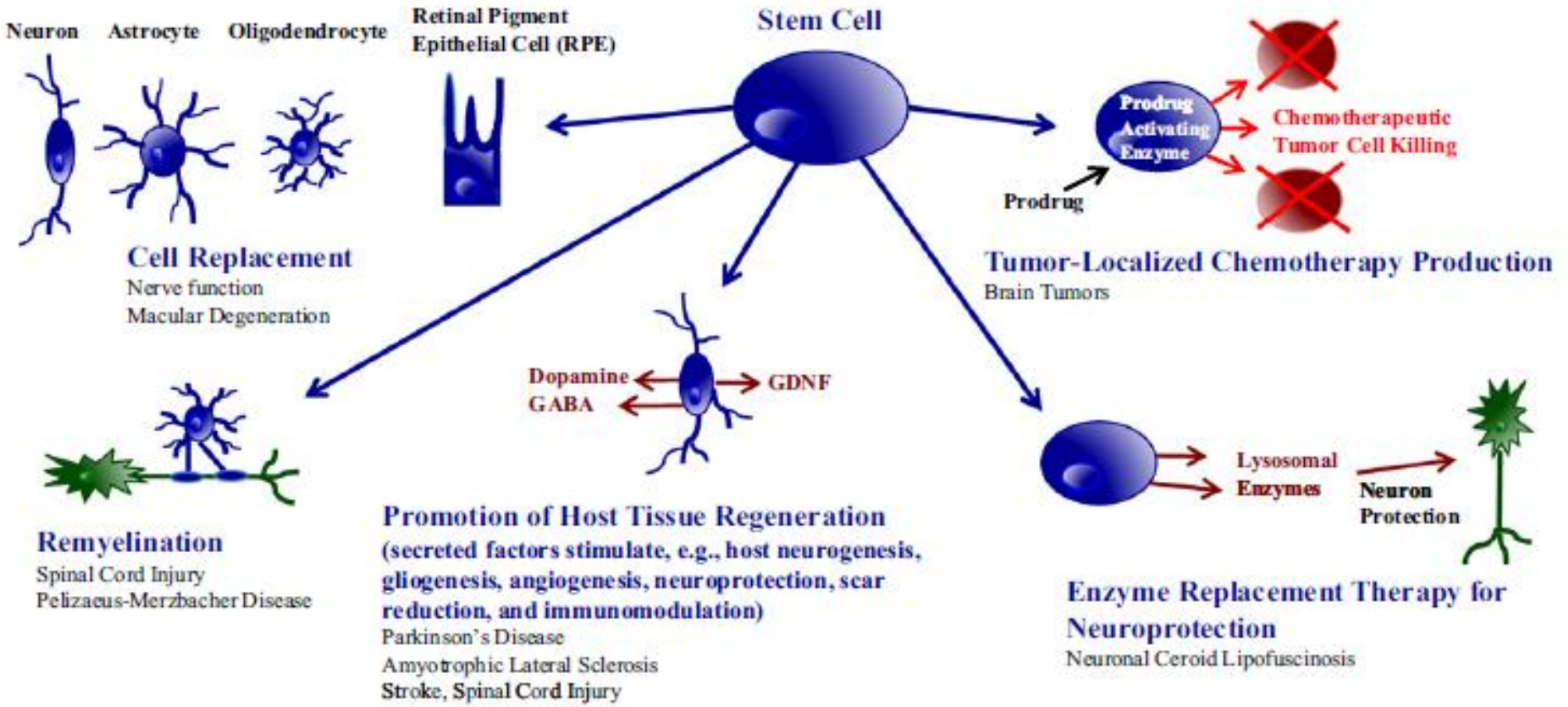


Solid arrows are supported by experimental evidence; dashed arrows are hypothetical. Colors depict symmetric, asymmetric, or direct transformation. IPC, intermediate progenitor cell; MA, mantle; MZ, marginal zone; NE, neuroepithelium; nIPC, neurogenic progenitor cell; oIPC, oligodendrocytic progenitor cell; RG, radial glia; SVZ, subventricular zone; VZ, ventricular zone.

Neurodegeneratív betegségek kezelése



Potenciális őssejt-terápiák a neurodegeneratív betegségek kezelésére



Translating Stem Cell Studies to the Clinic for CNS Repair: Current State of the Art and the Need for a Rosetta Stone

Neuron *70*, May 26, 2011 ©2011 Elsevier Inc. 597

Karen Aboody,[1] Alexandra Capela,[2] Nilofar Niazi,[3] Jeffrey H. Stern,[4] and Sally Temple[4,*]

Potenciális őssejt-terápiák a neurodegeneratív betegségek kezelésére

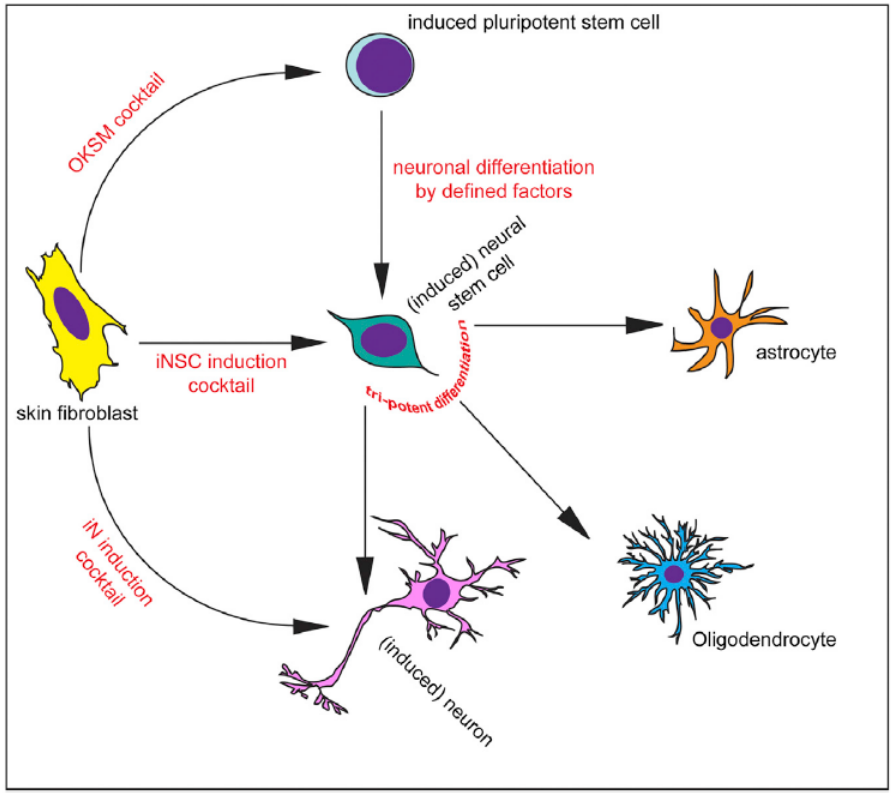


Table 1. A Summary of Human iPSC Differentiation Protocols toward Mature Neuronal Fates

Neuronal Subtypes	Key Components for Differentiation or Reprogramming	Efficiency	Duration	Reference
Glutamatergic neurons	hiPSC-derived EB formation followed by dissociated cultures in the absence of exogenous growth factors and serum	~85% from hiPSC to NPs; >60% from NP to neurons	~25 days to NPs with additional 5 weeks to the neuronal phenotype	Zeng et al., 2010
GABAergic neurons	Low levels of SHH and Wnts	~87%	5–6 weeks	Liu and Zhang, 2011
Cholinergic neurons	High level of SHH and low level of Wnts[a], BMP9, and NGF promote the yield	14%–38%	N/A	Liu and Zhang, 2011; Schnitzler et al., 2010
Dopaminergic neurons	Noggin and SB431542 followed by SHH and FGF8, then exposure to BDNF, AA, GDNF, TGFβ3, and cAMP	82% neural stem/ precursor induction	~19 days	Kriks et al., 2011
Motoneurons	Noggin and SB431542 followed by BDNF, AA, SHH, and RA	82% neural stem/ precursor induction	~19 days	Chambers et al., 2009
Serotoninergic neurons	Matrigel and noggin without EB formation or additional factors.	~80%	14 days	Shimada et al., 2012
NCSCs/Peripheral neurons	GSK-3β inhibitor and SB431542 /BDNF, GDNF, NT3, AA, cAMP	>90% from iPSCs to NCSCs; 70%–85% from NCSCs to neurons	~15 days from hiPSC to NCSCs; 12–14 days from NCSCs to peripheral neurons	Greber et al., 2011; Menendez et al., 2013

Abbreviations: EB, embryonic body; NPs, neural progenitors; SHH, sonic hedgehog; Wnt, wingless-int; BMP, bone morphogenetic protein; NGF, nerve growth factor; FGF8, fibroblast growth factor 8; BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor; TGFβ, transforming growth factor β; cAMP, cyclic AMP; AA, ascorbic acid; RA, retinoic acid, GSK-3β, glycogen synthase kinase-3 β; NCSCs, neural crest stem cell.
[a]The yield of cholinergic neurons is still very limited.

Table 2. A Summary of Directed Reprogramming Methods for the Generation of Human CNS Cell Phenotypes

Original Cells	Target Cells	Key Components for Differentiation or Reprogramming	Efficiency	Duration	Reference
Human fibroblasts	Glutamatergic/ GABAergic neurons	Ascl1, Brn2, Myt1l, Oligo2, Zic1	9%	2–3 weeks	Qiang et al., 2011
		miR-9/9*, miR-124, Ascl1, Myt1l, NeuroD2	N/A	6 weeks	Yoo et al., 2011
		Ascl1, Brn2, Myt1l, NeuroD1	4%	2–5 weeks	Pang et al., 2011
		Ascl1, Brn2, Myt1l	4%	2 weeks	Pfisterer et al., 2011
		Brn2, Myt1l, miR-124	4%–11%	2–3 weeks	Ambasudhan et al., 2011
	Dopaminergic neurons	Ascl1, LmX1a, Nurr1	3%–6%	2–3 weeks	Caiazzo et al., 2011
		Ascl1, Brn2, Myt1l, Lmx1a, FoxA2	5%–10%	3–4 weeks	Pfisterer et al., 2011
	Motoneurons	Ascl1, Brn2, Myt1l, NeuroD1, Lhx3, Hb9, Isl1, Ngn2	0.05%	4–5 weeks	Chatrchyan et al., 2011
	Neural stem cells	Sox2	N/A	1–2 weeks	Ring et al., 2012

Remodeling Neurodegeneration: Somatic Cell Reprogramming-Based Models of Adult Neurological Disorders

Neuron 78, June 19, 2013 ©2013 Elsevier Inc.

Az alapkutatástól az ipari alkalmazáig.....

Translation

	Basic Research	Preclinical	Human Trials Phase I	Human Trials Phases II/III
Description	➢ New findings related to neural stem cells and neural diseases and disorders ➢ Discoveries of new compounds ➢ Developing animal disease models ➢ Compound screening	➢ Toxicity and efficacy on more lab animals ➢ IND preparation process ➢ Clinical material manufacturing	➢ 20–80 subjects (fewer for rare diseases) ➢ The effect of treatment on the human body, delivery method, and dosage safety	➢ 100s to 1000s of subjects ➢ Test efficacy ➢ Avg. time 10 years and cost approximately $1 billion[3] from discovery to market
Status Overview	➢ Understanding of diseases is greater than ever before ➢ Driven by system of honors / grants / tenures ➢ Rewarded for publishing articles first—prohibiting ability to patent	➢ Lack of funding—start of "valley of death" ➢ Basic researchers lack the interest, incentive and know-how for the required developmental work after discovery is made	➢ Lack of funding—still the "valley of death" ➢ Require IP, transfer of which often becomes the bottleneck (academic tech transfer offices lack incentive to expedite or complete the process)	➢ Subject recruitment and retention time consuming and inefficient
Attrition Rate[1]	➢ 5 out of 5,000–10,000 [1] (<0.1%) of new compounds identified in the lab ultimately receive IND approval	➢ 17% of all IND applications approved (37% of in-licensed and 12% of self-originated applications[2])	➢ 20%[1] (33%[2] for in-licensed) of compounds granted FDA approval for marketing ➢ Approximately one-third[2] of the attrition is due to lack of funding	➢ 20%–30% of compounds entering phase II granted FDA approval for marketing

IND application to initiate human trials

NDA Review / Market

Figure 2. Drug Development Process Analysis

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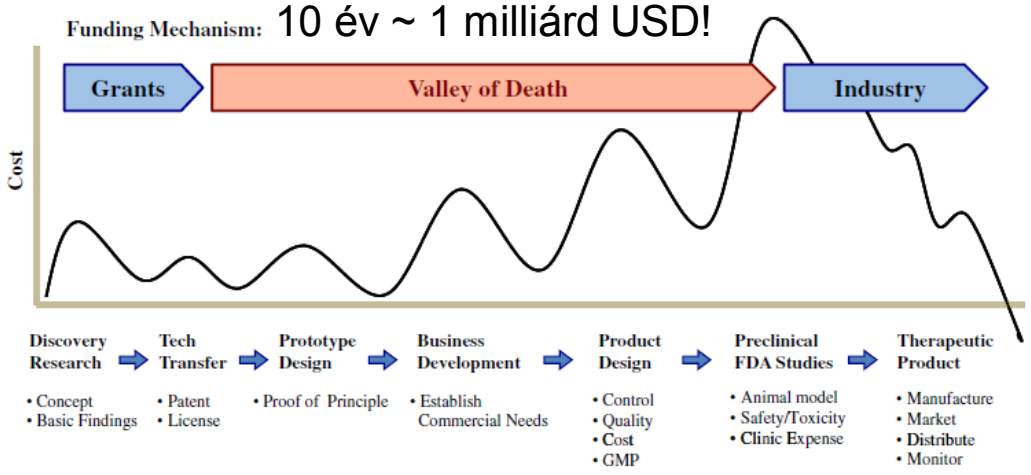


A klinikai tesztek

Translating Stem Cell Studies to the Clinic for CNS Repair: Current State of the Art and the Need for a Rosetta Stone

Karen Aboody,[1] Alexandra Capela,[2] Nilofar Niazi,[3] Jeffrey H. Stern,[4] and Sally Temple[4,*]

Identify Target Disease Indication

↓

Identify and Characterize Stem Cell Source

Isolate stem cells, process/expand to establish laboratory Resource Cell Bank for preclinical studies
Characterize and test genetic and functional stability, biodistribution, cell fate, nontumorigenicity, immunogenicity, and therapeutic efficacy in vitro and in vivo

↓

Produce cGMP Master (MCB) and Working Cell Banks (WCB) for Clinical Use

Establish cGMP Master and Working Cell Banks
Expand, characterize, and test for genetic and functional stability, adventitious agents
Finalize SOPs for product manufacture, release testing, viability, identity, and sterility testing
"IND-enabling" in vivo safety/toxicology studies using clinical cell lot

↓

Generate Clinical Protocol and Consent Form

Define study objectives, patient population, eligibility criteria, treatment plan, correlative studies, endpoints, data safety and monitoring plan

↓

Regulatory Submissions (for U.S.)

Pre-Investigational New Drug (IND) meeting with Food and Drug Administration (FDA) recommended
Cellular therapies regulated by Center for Biologics Evaluation and Research (CBER) within FDA)
Genetically modified cells require NIH Recombinant DNA Advisory Committee (RAC submission of Appendix M: "Points to consider in the design and submission of protocols for the transfer of recombinant DNA molecules into one or more human research participants")
Institutional Review Board (IRB), Institutional Biosafety Committee (IBC),
Stem Cell Research Oversight Committee (SCRO)
Formal IND Submission to FDA for acceptance to initiate clinical trial (30 days for FDA response)

IND Application Definition

A formal document composed of well-defined sections outlined in the Code of Federal Regulations Title 21 (21 CFR 312)—and includes:

1. **Form FDA 1571**
2. **Table of contents**
3. **Introductory statement**
4. **General investigational plan**
5. **Investigator's brochure**: describes the product broadly and summarizes data from all animal and human studies
6. **Protocols**: clinical study, investigator, facilities, and IRB information
7. **Product/chemistry, manufacturing, control (CMC)**: details product manufacturing and safety, quality, stability, and product release testing, etc.
8. **Pharmacology/toxicology**: study reports from all proof-of-concept efficacy and safety/toxicology studies
9. **Previous Human Experience; Other Relevant Information**: all requisite source documents

Detailed information on each part of the IND is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=312.

Clinical Trial Definitions

Phase 0: exploratory designation for first-in-human single subtherapeutic dose to gather preliminary data to speed up development (<20 patients)

Phase I: assessment of safety and dose finding in small patient cohorts

Phase II: assessment of therapeutic efficacy

Phase III: randomized, controlled multicenter trials of large numbers of patients for definitive assessment of therapeutic efficacy compared to standard of care

Phase IV: commercialization, postmarketing surveillance trial

Engedélyeztetés

FDA Home[3] Medical Devices[4] Databases[5]

CFR - Code of Federal Regulations Title 21

New Search

Help[6] | More About 21CFR[7]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D--DRUGS FOR HUMAN USE
PART 312 INVESTIGATIONAL NEW DRUG APPLICATION[8]

Subpart A--General Provisions

§ 312.1 - Scope.
§ 312.2 - Applicability.
§ 312.3 - Definitions and interpretations.
§ 312.6 - Labeling of an investigational new drug.
§ 312.7 - Promotion of investigational drugs.
§ 312.8 - Charging for investigational drugs under an IND.
§ 312.10 - Waivers.

Subpart B--Investigational New Drug Application (IND)

§ 312.20 - Requirement for an IND.
§ 312.21 - Phases of an investigation.
§ 312.22 - General principles of the IND submission.
§ 312.23 - IND content and format.
§ 312.30 - Protocol amendments.
§ 312.31 - Information amendments.
§ 312.32 - IND safety reporting.
§ 312.33 - Annual reports.
§ 312.38 - Withdrawal of an IND.

Subpart C--Administrative Actions

§ 312.40 - General requirements for use of an investigational new drug in a clinical investigation.
§ 312.41 - Comment and advice on an IND.
§ 312.42 - Clinical holds and requests for modification.
§ 312.44 - Termination.
§ 312.45 - Inactive status.
§ 312.47 - Meetings.
§ 312.48 - Dispute resolution.

Subpart D--Responsibilities of Sponsors and Investigators

§ 312.50 - General responsibilities of sponsors.
§ 312.52 - Transfer of obligations to a contract research organization.
§ 312.53 - Selecting investigators and monitors.
§ 312.54 - Emergency research under 50.24 of this chapter.
§ 312.55 - Informing investigators.
§ 312.56 - Review of ongoing investigations.
§ 312.57 - Recordkeeping and record retention.
§ 312.58 - Inspection of sponsor's records and reports.
§ 312.59 - Disposition of unused supply of investigational drug.
§ 312.60 - General responsibilities of investigators.
§ 312.61 - Control of the investigational drug.
§ 312.62 - Investigator recordkeeping and record retention.
§ 312.64 - Investigator reports.
§ 312.66 - Assurance of IRB review.
§ 312.68 - Inspection of investigator's records and reports.
§ 312.69 - Handling of controlled substances.
§ 312.70 - Disqualification of a clinical investigator.

Subpart E--Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

§ 312.80 - Purpose.
§ 312.81 - Scope.
§ 312.82 - Early consultation.
§ 312.83 - Treatment protocols.
§ 312.84 - Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.
§ 312.85 - Phase 4 studies.
§ 312.86 - Focused FDA regulatory research.
§ 312.87 - Active monitoring of conduct and evaluation of clinical trials.
§ 312.88 - Safeguards for patient safety.

Subpart F--Miscellaneous

§ 312.110 - Import and export requirements.
§ 312.120 - Foreign clinical studies not conducted under an IND.
§ 312.130 - Availability for public disclosure of data and information in an IND.
§ 312.140 - Address for correspondence.
§ 312.145 - Guidance documents.

Subpart G--Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

§ 312.160 - Drugs for investigational use in laboratory research animals or in vitro tests.

Subpart H [Reserved]

Subpart I--Expanded Access to Investigational Drugs for Treatment Use

§ 312.300 - General.
§ 312.305 - Requirements for all expanded access uses.
§ 312.310 - Individual patients, including for emergency use.
§ 312.315 - Intermediate-size patient populations.
§ 312.320 - Treatment IND or treatment protocol.

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.
Source: 52 FR 8831, Mar. 19, 1987, unless otherwise noted.

Engedélyeztetés

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Now Available for Public Comment: Notice of Proposed Rulemaking (NPRM) for FDAAA 801 and NIH Draft Reporting Policy fo

Trial record **1 of 1** for: Parkinson, iPS

Previous Study | Return to List | Next Study

Development of iPS From Donated Somatic Cells of Patients With Neurological Disease

This study is ongoing, but not recruiting participants.

Sponsor:
Hadassah Medical Organization

Information provided by (Responsible Party):
Hadassah Medical Organization

ClinicalTrials.gov Identifier:
NCT00874783

First received: April 2, 2009
Last updated: September 7, 2014
Last verified: September 2014
History of Changes

Full Text View | **Tabular View** | **No Study Results Posted** | Disclaimer | How to Read a Study Rec

Purpose

Human fibroblasts and possibly other human somatic cells may be reprogrammed into induced pluripotent stem (**iPS**) cell of transcription factors (1-5). The **iPS** cells seem to share many properties with human embryonic stem cells.

Induced pluripotent stem cells potentially may be useful in the future as an unlimited source of cells for transplantation.

The major goal of the project is to develop human **iPS** cells from cell cultures from skin biopsies or the patient's hair. The primarily for modeling diseases and drug discovery as well as basic research, and for developing the technology that may of **iPS** cells for future transplantation therapy. The **iPS** cells developed in the course of this application are not intended fc therapy. Future development of **iPS** cells for clinical transplantation therapies will be subjected to the appropriate authoriz regulatory committees.

Condition
Neurodegenerative Disorders

Study Type: Observational
Study Design: Observational Model: Case Control
Time Perspective: Prospective

Official Title: Derivation of Induced Pluripotent Stem Cells From Somatic Cells Donated by Patients With Neurological the Pathogenesis of the Disorders and Development of Novel Therapies

Endogén neurogenezis / repair fokozása

- sérülés hatására endogén neurogenezis -> célzott sejtvándorlás, sejtpótlás (?)

  - epilepszia
  - stroke

  } neurogenezis ⇧, új neuronok beépülése ⇧

  - Parkinson kór
  - Huntington kór

  } neurogenezis ⇩, új neuronok túlélése ⇩

  - Alzheimer kór

  } proliferációra és túlélére különböző hatás érvényesül

- SVZ progenitorok ált. „plasztikusabbak", mint az SGZ-ben: sérülés hatására neurogenezis -> célzott sejtvándorlás

Tissue engineering: hordozó felszínek + sejtek

beültetett sejtek túlélésének fokozása:

- 3D környezet
- mechanikai támogatás
- túlélést/differenciációt elősegítő faktorok

milyen a jó hordozó/váz felszín?

- kis méret: sztereotaxikus, lokalizált beadás, akár többször is
- biológiailag lebomló:
  - hidrogél (PEG, hialuronsav) *vs* in situ gélesedés
- biokompatibilis:
  - beültetés utáni reaktív gliózis kivédése (PLGA – poli(laktát-ko-glikolát)
  - makrofág/mikroglia és T-limfocita aktiváció – túl kis méret (1-30 um) fokozhatja, >30 um felett OK
  - gömb alak sokkal jobb, mint a hegyes / tűszerű
  - bomlási temékek se legyenek mérgezőek
- + felszín töltés, megfelelő hidrofil/hidrofobicitás

Tissue engineering: hordozó felszínek + sejtek

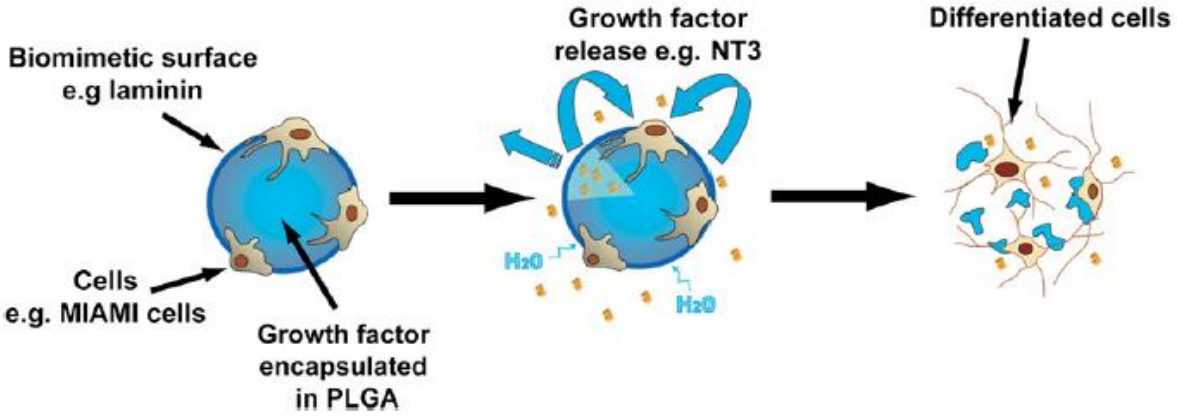
milyen a jó hordozó/váz felszín?

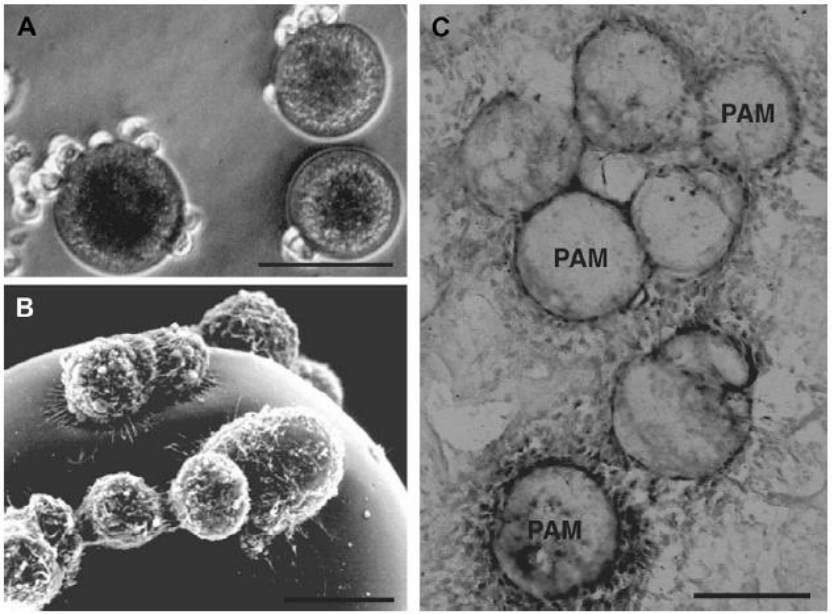
- külső / belső topográfia:
  - pórusok: gliasejtek bevándorlása, tápanyagellátás, vaszkularizáció
  - felszíni mintázat: sejtméretű a sejtek túlélését gátolja, a mikromintázat ált. segít
- mátrix elaszticitás:
  - lágy: neuronális
  - közepes: izom
  - kemény: csont

} differenciáció MSC sejtekből

stratégiák:

- sejtek belül („encapsulation") <-> sejtek a hordozók felszínén
- ECM bevonat
- farmakológiailag aktív hordozók

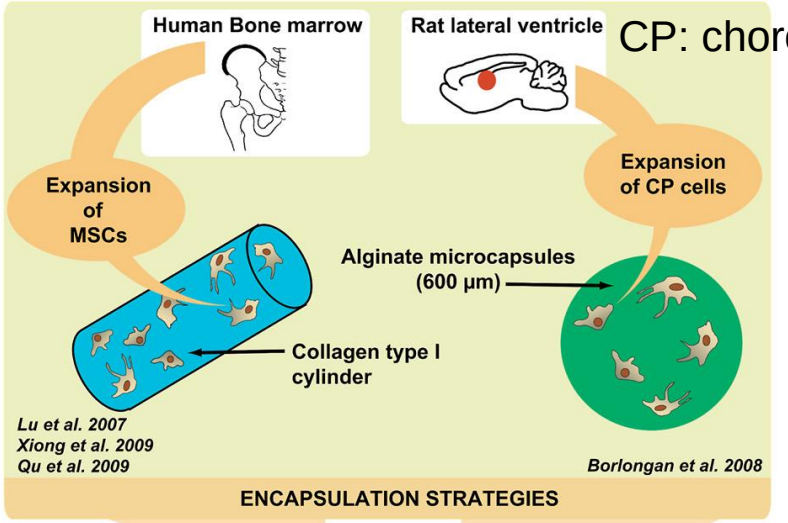




Adult cell therapy for brain neuronal damages and the role of tissue engineering

Gaëtan L-R. Delcroix [a,b], Paul C. Schiller [c,d], Jean-Pierre Benoit [a,b], Claudia N. Montero-Menei [a,b,*]

Biomaterials 31 (2010) 2105–2120



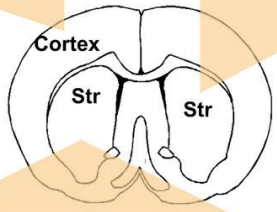
CP: choroid plexus

traumás agysérülés

TBI

HD

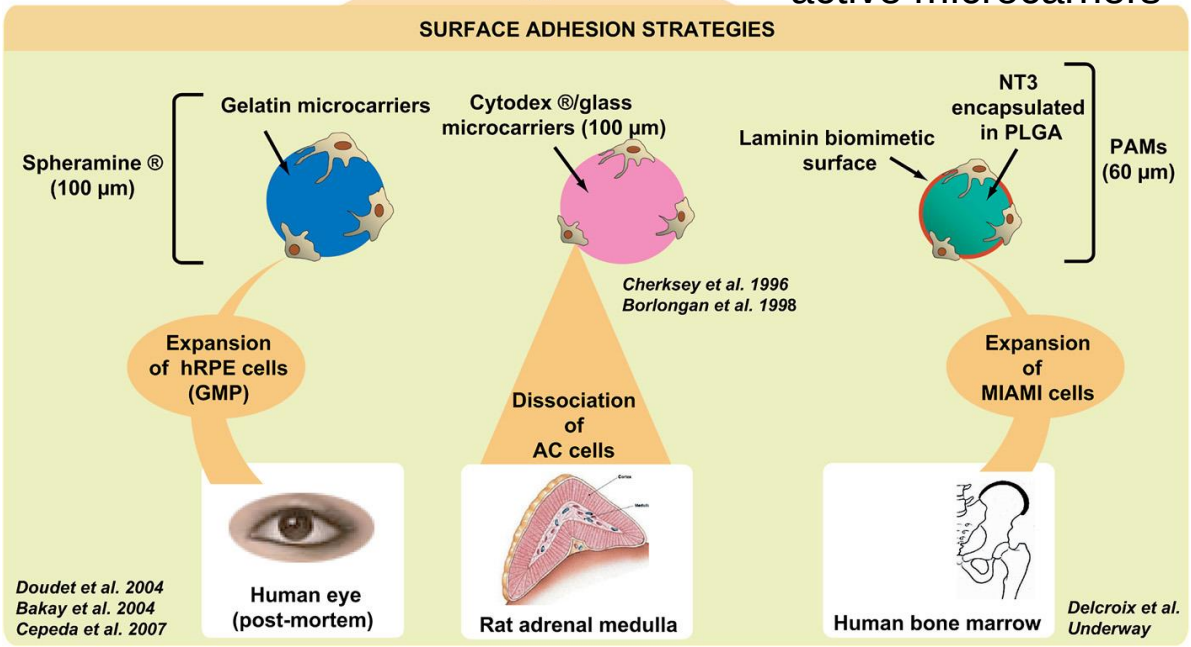
Huntington - kór



Parkinson - kór

PD

PAM: pharmacologically active microcarriers



MIAMI: marrow isolated adult multilineage inducible

hRPE: human retinal pigment epithelium

beültetett sejtek azonosítása

- post mortem nem elég...
- transzgén jelölések, reporter gének nem megengedettek humán kezelésnél
- SPIOs: superparamagnetic iron oxide particles – MRIvel in vivo is azonosítható jelölés
- nem csak a rövid, hanem a hosszú távú toxicitás is számít!

Parkinson kór

dopaminerg (DA) neuronok fejlődése:

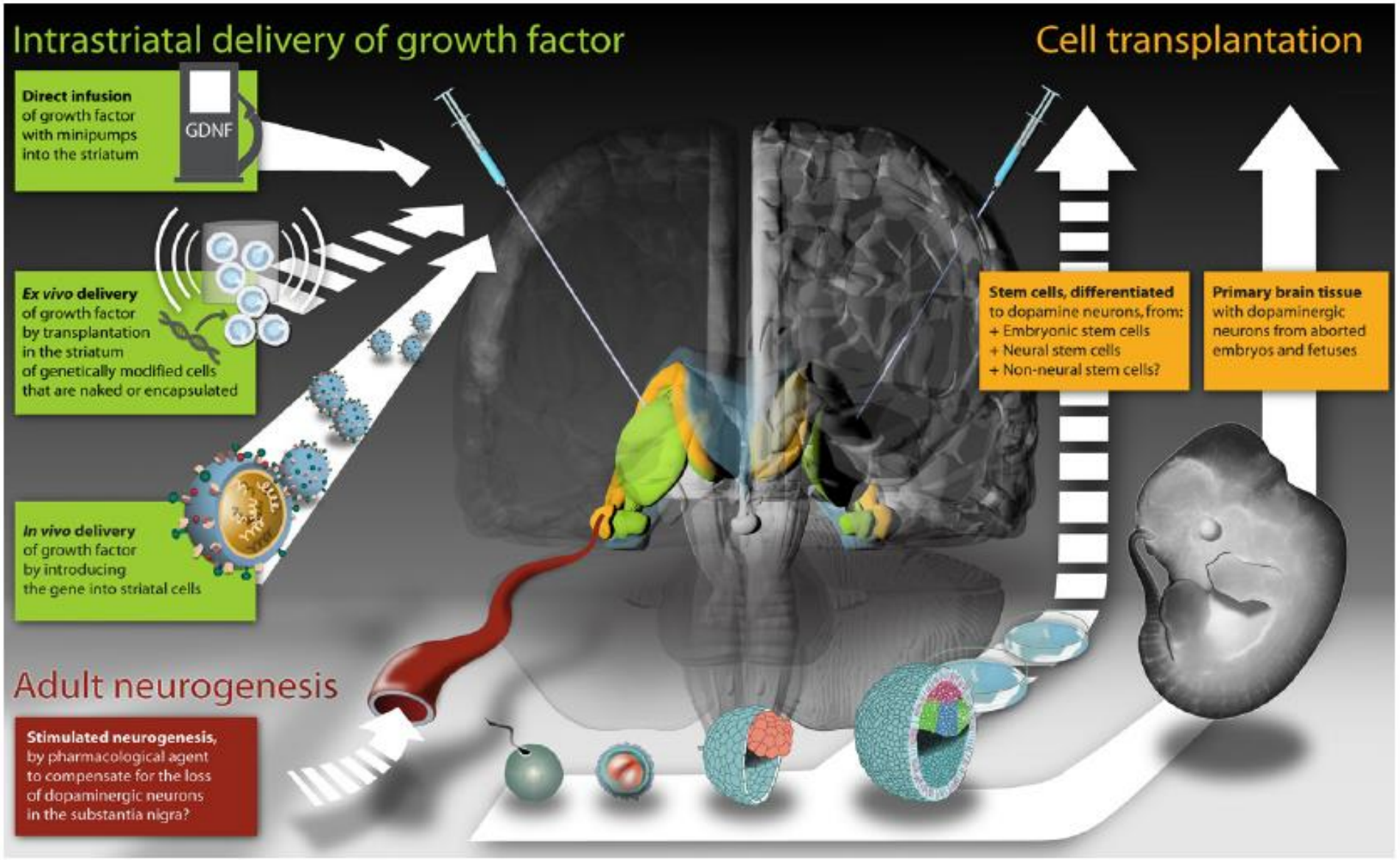
- egér E10 - E11,5; FGF-8 és Shh grádiens mentén (isthmus)
- E9: Nkx6.1+ sejtekben Shh indukálja a Lmx1a-t
- E9.5: Lmx1a -> Msx1 upreguláció -> Nkx6.1 expresszió a floor plate-ben lecsökken -> Ngn2 upreguláció: glia -> neuron sorsváltás
- E10: piális felszínre vándorlás; Nurr1 termelés, posztmitotikussá válás
- DA neuronok: En1, Lmx1b, Pitx3, TH expresszió
- E13: végső helyre vándorlás (subst. nigra, ventrális tegmentális area, retrorubral field, n. interfascicularis)

nigrostriatális dopaminerg neuronok pusztulása: tremor, mozgás-koordinációs zavar, dyskinézia...

cél:

- dopamin termelés, dopaminerg fenotípus kialakítása
- beilleszkedés
- reinnerváció
- tünetek csillapítása/megszüntetése
- hosszú távú túlélés

Parkinson kór - potenciális kezelési lehetőségek



Emerging restorative treatments for Parkinson's disease

Tomas Deierborg*, Denis Soulet, Laurent Roybon, Vanessa Hall, Patrik Brundin

Progress in Neurobiology 85 (2008) 407–432

Parkinson kór

1. embrionális mezencephalikus / felnőtt kromaffin / postmortem retina pigment epitelium dopaminerg sejtek beültetése (nem stem sejt!; posztmitotikus neuronok) - probléma:
    - sejtforrás,
    - sejtszám,
    - túlélés (>100000),
    - tisztítás (5-10%),
    - beültetés helye,
    - immunszupresszió,
    - betegség előrehaladottsága,
    - placebo,
    - stb

2. ES sejtek beültetése

A) ES sejtek közvetlen striatális beültetése

Björklund 2002 PNAS 99:2344-2349

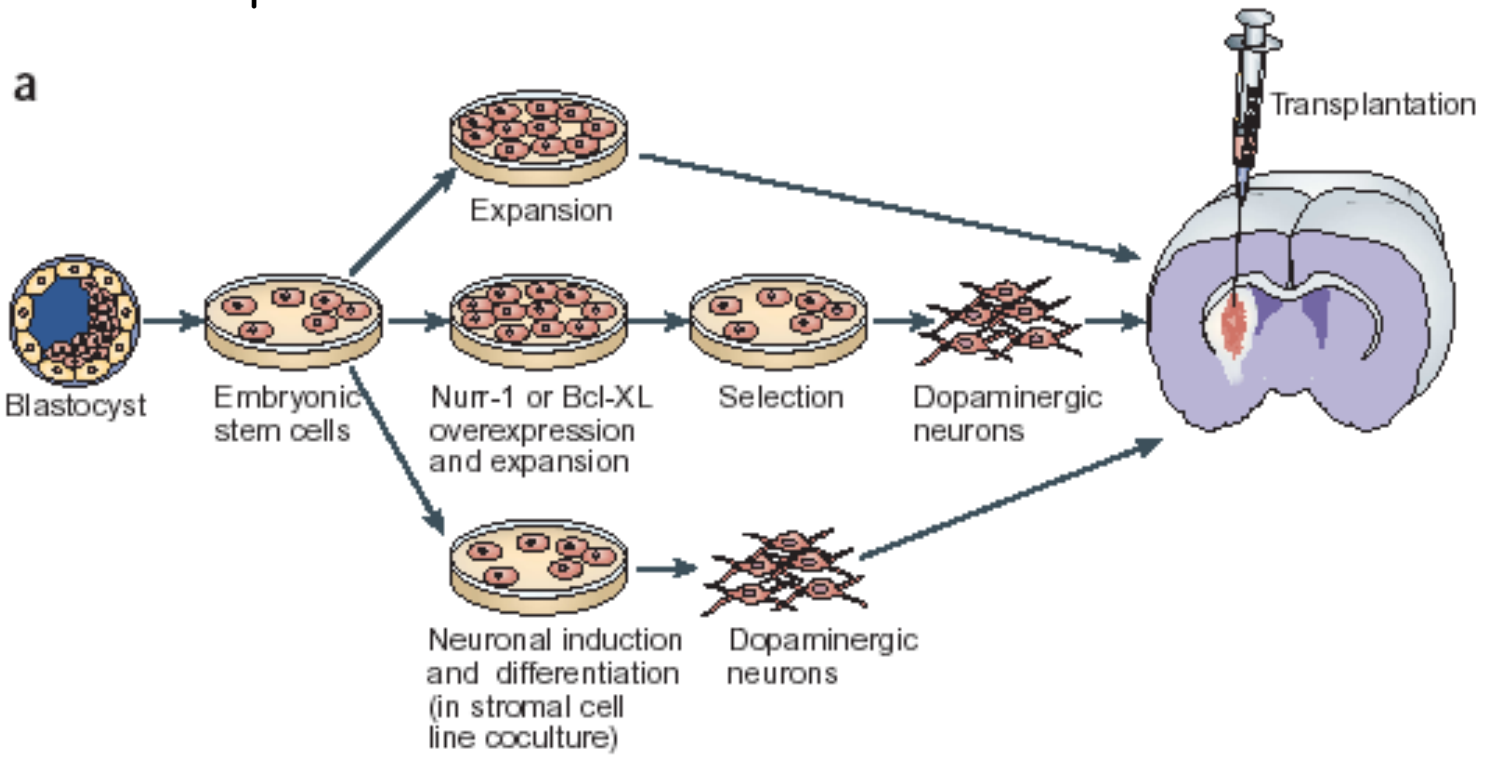
B) ES előzetes differenciáltatás: Nurr1 túltermeltetés

Kim 2002 Nature 418: 50-56

C) ES-sztromális sejt kokultúra

Kawasaki 2000 Neuron 28:31-40

„parakrin" diff. hatás



Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model

Lars M. **Björklund**, Rosario Sanchez-Pernaute, Sangmi Chung, Therese Andersson, Iris Yin Ching Chen, Kevin St. P. McNaught, Anna-Liisa Brownell, Bruce G. Jenkins, Claes Wahlestedt, Kwang-Soo Kim, and Ole Isacson

2002 PNAS 99:2344

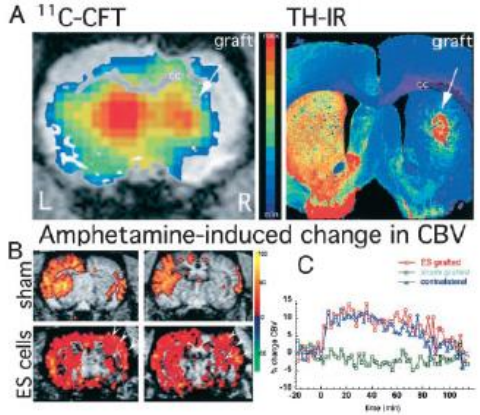
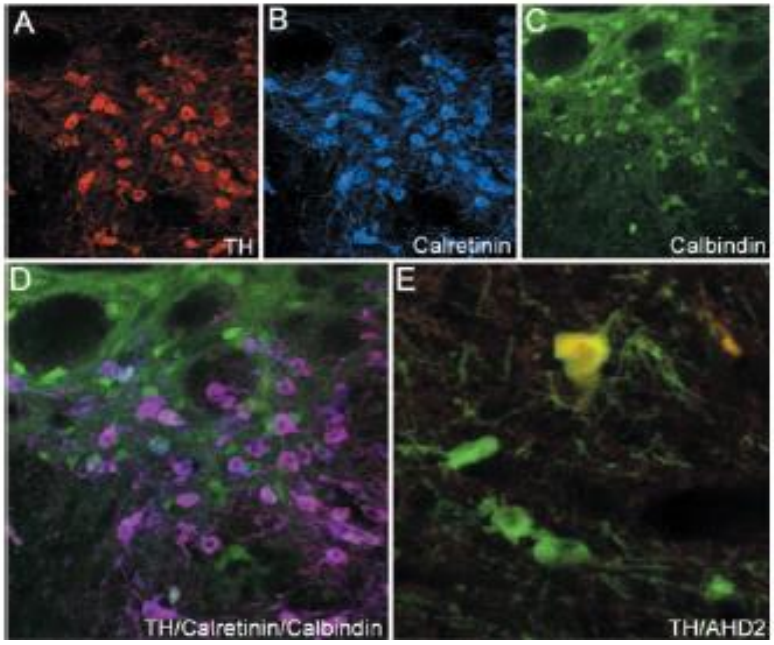


Fig. 4. (*A*) By using PET and the specific DAT ligand [^{11}C]CFT, we identified specific binding in the right grafted striatum, as shown in this brain slice (*A*, *Left*) acquired 26 min after injection of the ligand into the tail vein (acquisition time was 15 sec). Color-coded (activity) PET images were overlaid with MRI images for anatomical localization. The increase in [^{11}C]CFT binding in the right striatum was correlated with the postmortem presence of TH-immunoreactive (IR) neurons in the graft (*A*, *Right*). (*B*) Neuronal activation mediated by DA release in response to amphetamine (2 mg/kg) was restored in animals receiving ES grafts. Color-coded maps of the percentage of change in rCBV are shown at two striatal levels for control (*Upper*) and an ES cell-derived DA graft (*Lower*). A 6-OHDA lesion results in a complete absence of CBV response to amphetamine on striatum and cortex ipsilateral to the lesion (*Upper*). Recovery of signal change in motor and somatosensory cortex (arrows) and to a minor extent in the striatum was observed only in ES-grafted animals. (*C*) Graphic representation of signal changes over time in the same animal shown in *B*. The response on the grafted (red line) and normal (blue line) striata was similar in magnitude and time course, whereas no changes were observed in sham-grafted animals (green line). Baseline was collected for 10 min before and 10 min after monocrystalline iron oxide nanocolloid injection, and amphetamine was injected at time 0. cc, corpus callosum.



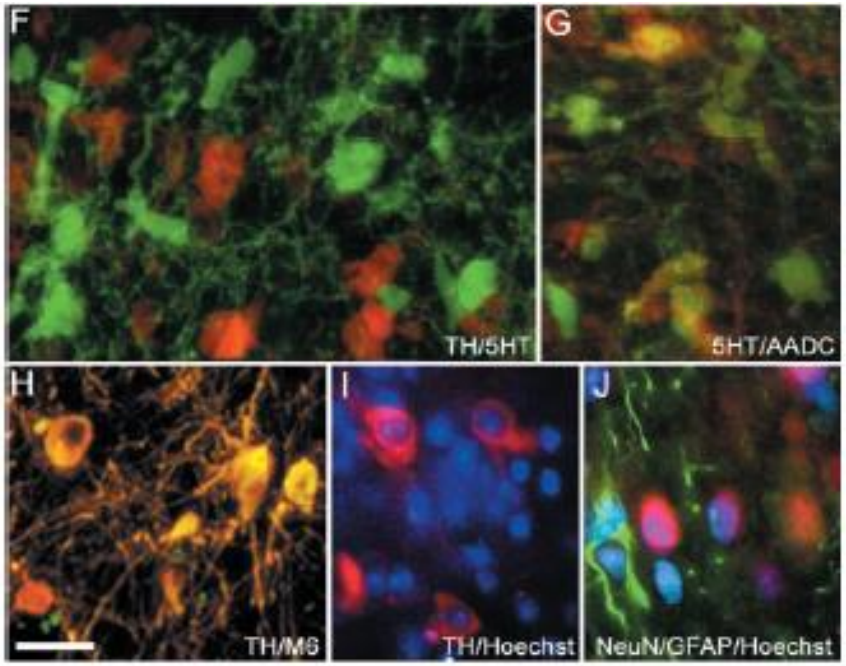
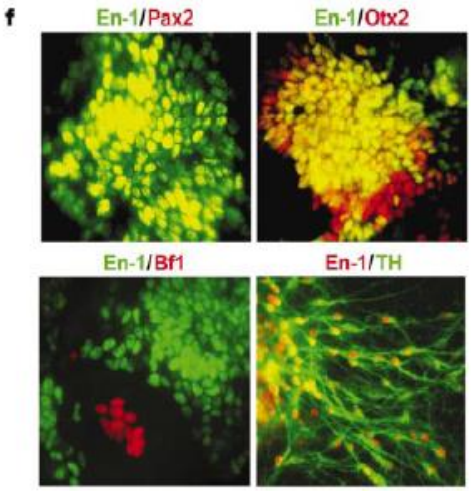


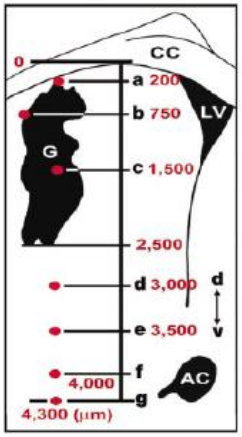
Fig. 2. Photomicrograph showing TH-positive neurons (*A* and *D*) coexpressing (*D*) typical midbrain DA neuron markers such as calretinin (*B* and *D*) and calbindin (*C* and *D*). TH-positive neurons (*E*, green) also coexpressed the A9 marker aldehyde dehydrogenase 2 (*E*, yellow coexpression). Numerous 5HT neurons were found in grafts (*F*, green), and 5HT neurons also coexpressed AADC (*G*, green, yellow coexpression with 5HT). Grafted mouse ES cell-derived DA neurons (*H*, yellow, and *I*, red) were identified by colabeling with mouse-specific antibodies, M6 (*H*, yellow coexpression with TH), or by mouse-specific intranuclear fluorescent inclusions after Hoechst staining (*I*, blue). Astrocytes (glial fibrillary acidic protein-positive, *J*, green) and neurons (NeuN-positive, *J*, red) show mouse intranuclear fluorescent inclusions (Hoechst, *J*, blue). (Scale bars: *A–C*, 100 μm; *D*, 67 μm; *E–J*, 20 μm.)

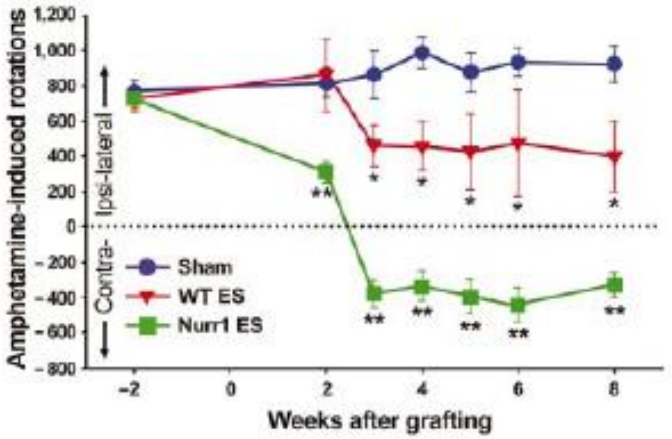
Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease

Jong-Hoon **Kim**, Jonathan M. Auerbach, Jose A. Rodriguez-Gomez, Ivan Velasco, Denise Gavin, Nadya Lumelsky, Sang-Hun Lee†, John Nguyen, Rosario Sanchez-Pernaute, Krys Bankiewicz & Ron McKay

Nature 2002 418:50-56.







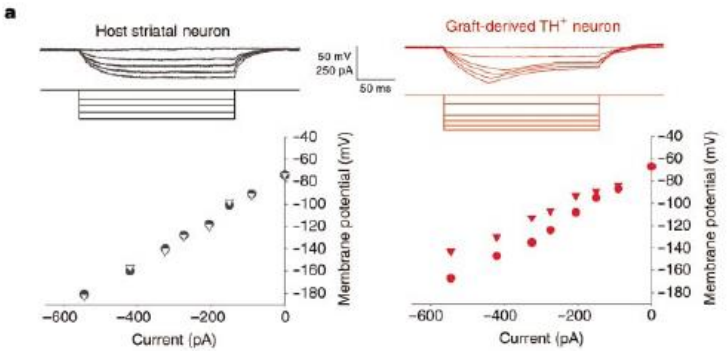
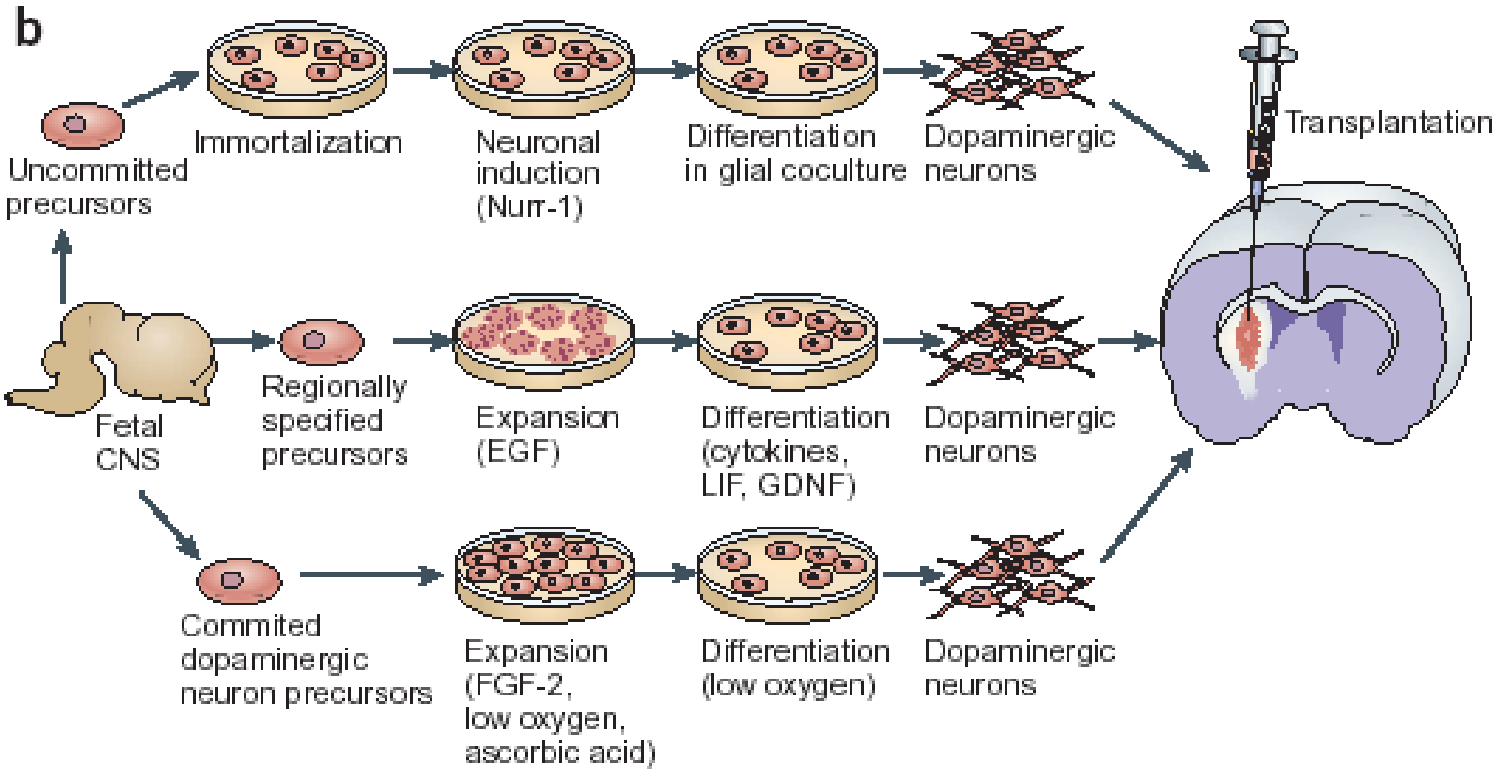


Figure 1 Properties of neural precursors derived from Nurr1 ES cells. **a**, Immunoblot analysis for transfected Nurr1 (HA), total Nurr1 and TH at the end of stage 4 and at day 8 of stage 5. **b**, Differentiation of Nurr1-transfected ES cells into TH^+ (red) and $serotonin^+$ (green) neurons at day 10 of stage 5. The proportion of TH^+ cells was greater than that in wild-type ES cells. **c**, Nurr1 overexpression was evaluated using anti-HA immunostaining (red) at stage 1. DAPI (4,6-diamidino-2-phenylindole), blue; TH, green. Inset, co-localization of Nurr1 with DAPI at higher magnification. **d**, Stage 4 cells were cultured in the presence of Shh (500 ng ml^{-1}) and FGF8 (100 ng ml^{-1}) with 20 ng ml^{-1} of FGF2 or FGF4 (5, 10 and 50 ng ml^{-1}) and immunostained with TH and serotonin at day 10 of stage 5. **e**, The yield of TH^+ and $serotonin^+$ neurons/ low power field (SEM from 40 different fields of view). **f**, Nurr1-expressing stage 4 cells show markers of midbrain precursors. $En\text{-}1^+$ immunoreactivity co-localizes with Pax2 and Otx2. In contrast, few $Bf1^+$ cells were positive for En-1. After differentiation at stage 5, most TH^+ neurons expressed the midbrain-specific marker En-1.

3. embrionális NSCs beültetése

A) embrionális NSCs, elkötelezetlen progenitor izolálás
immortalizálás, Nurr1 túltermeltetés, asztroglia kokultúra
Wagner 1999 Nat Biotechnol 17:653-659.

B) regionális izolálás, mezencefalikus progenitorok, növ-i faktorok, diff. hatás
Studer 1998 Nat Neurosci 1: 290-295



Parkinson kór

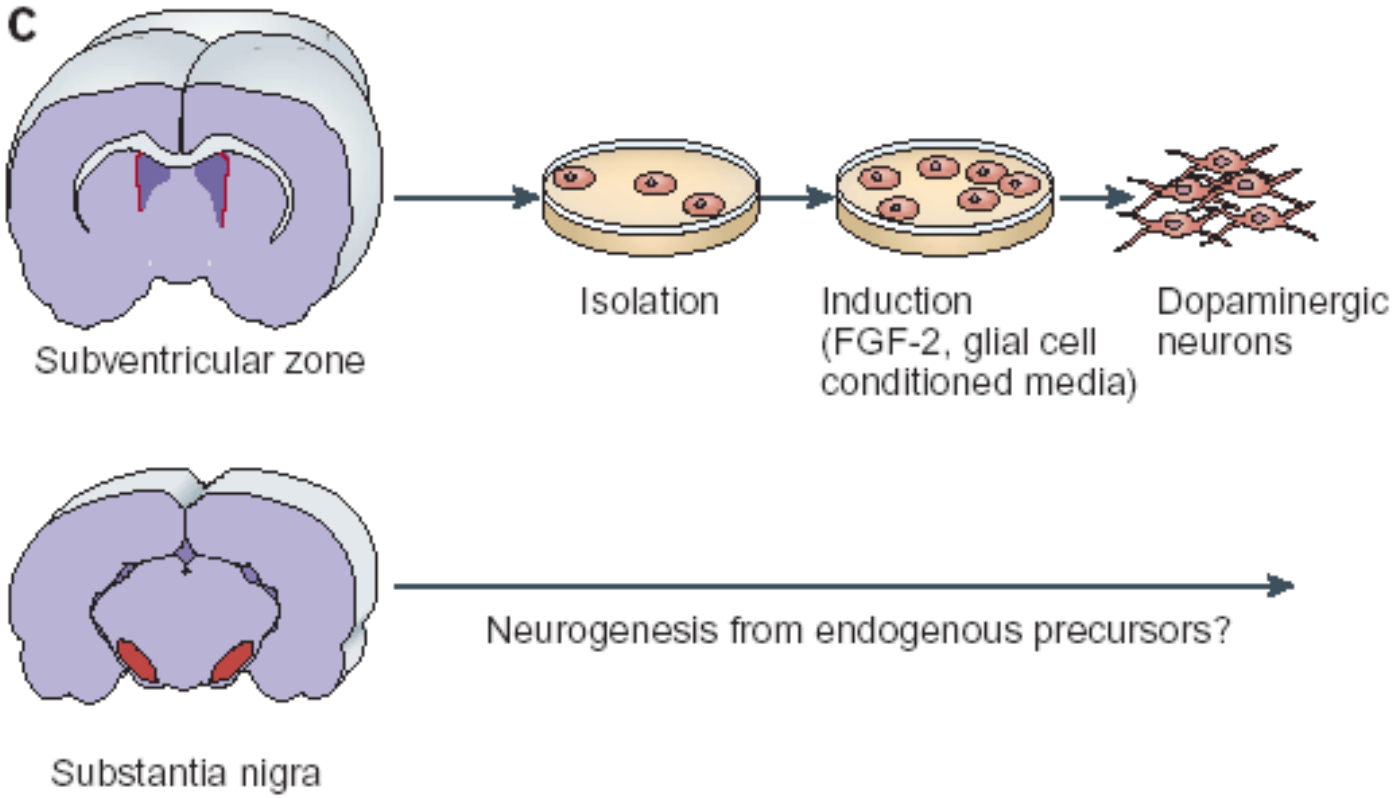
4. felnőtt NSCs beültetése

A) felnőtt NSCs ->

B) endogén NSC diff-ra késztetése ??

dopaminerg lézió után fokozott neurogenezis, de ezt mások kétlik

Zhao PNAS 2003 100:7925-7930



Parkinson kór

Therapeutic Microinjection of Autologous Adult Human Neural Stem Cells and Differentiated Neurons for Parkinson's Disease: Five-Year Post-Operative Outcome

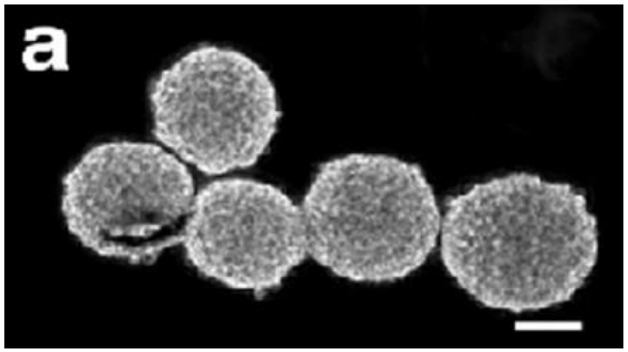
Michel F. Lévesque[1,2,3,*], Toomas Neuman[3] and Michael Rezak[2,4]

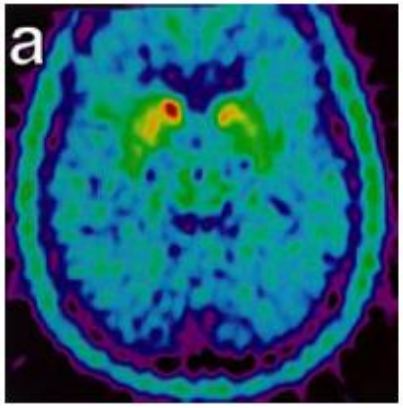
The Open Stem Cell Journal, 2009, *1*, 20-29

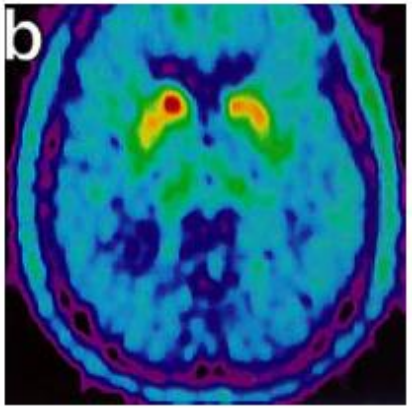
saját NSCs izolálás prefrontális/szubkortikális régióból (talamikus agytörzsi stimuláció); > 6 hónap neurosphere tenyésztés; 3 nap elő-differenciáltatás; 3 évig motoros javulás

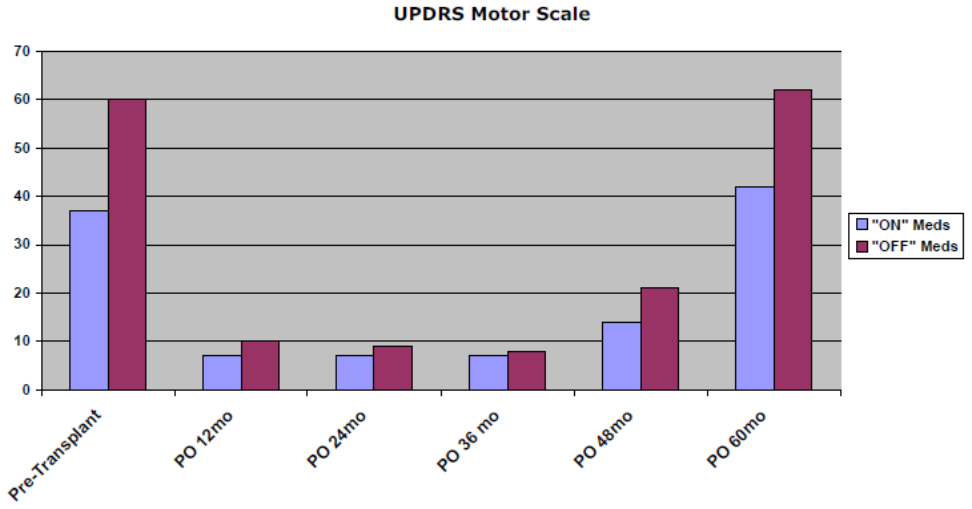
Table 2. **Characterization of Differentiated Neural Stem Cells Derived from AC2 Cell Line Prior to Implantation. Dopaminergic Cells, Dopamine Secretion at Baseline and After Stimulation Demonstrates Functionality *In Vitro*. A Large Proportion of GABAergic Cells is Represented with other Neuronal Phenotypes within the Injected Suspension**

Differentiated Neurons from AC2 Cell Line	35±6(%)
Tyrosine Hydroxylase(+) neurons	15±3(%)
DopaDecarboxylase (+)neurons	12±3(%)
Dopamine baseline secretion(pg/ml)	100±40
Dopamine secretion after stimulation (pg/ml)	350±82
GABA neurons	60±8(%)
Glutamate neurons	20±3(%)
Cholinergic neurons	2±1(%)
Glycine neurons	3±1(%)









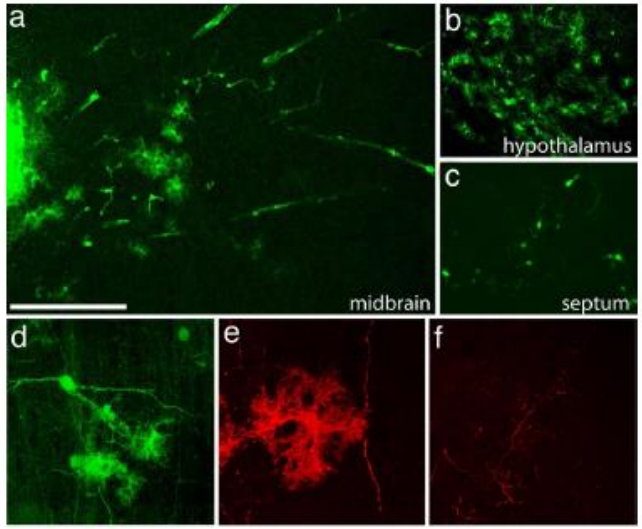
4. elődifferenciáltatott iPS beültetése

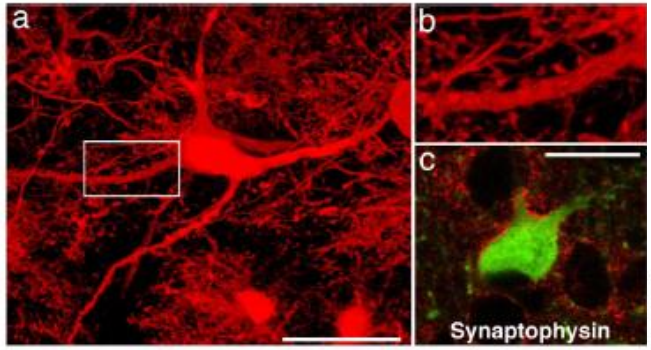
Parkinson kór

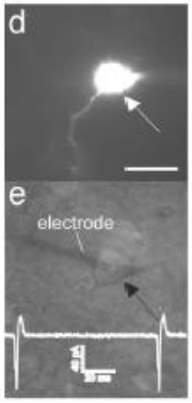
Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease

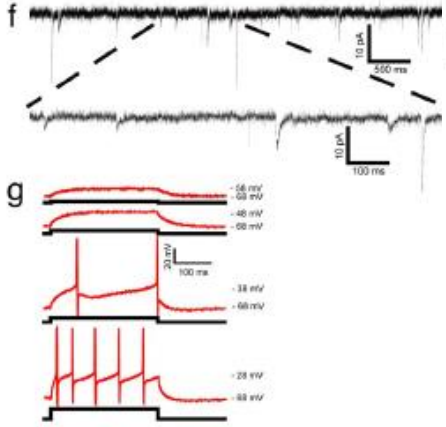
5856–5861 | PNAS | April 15, 2008 | vol. 105 | no. 15

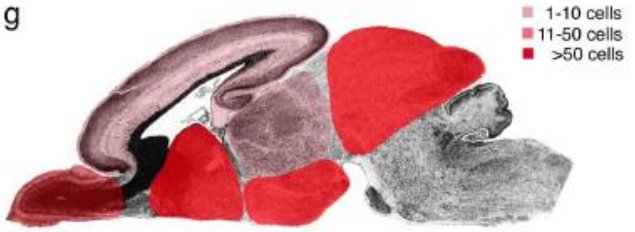
Marius Wernig*, Jian-Ping Zhao†, Jan Pruszak‡, Eva Hedlund‡, Dongdong Fu*, Frank Soldner*, Vania Broccoli§, Martha Constantine-Paton†, Ole Isacson‡, and Rudolf Jaenisch*¶‖

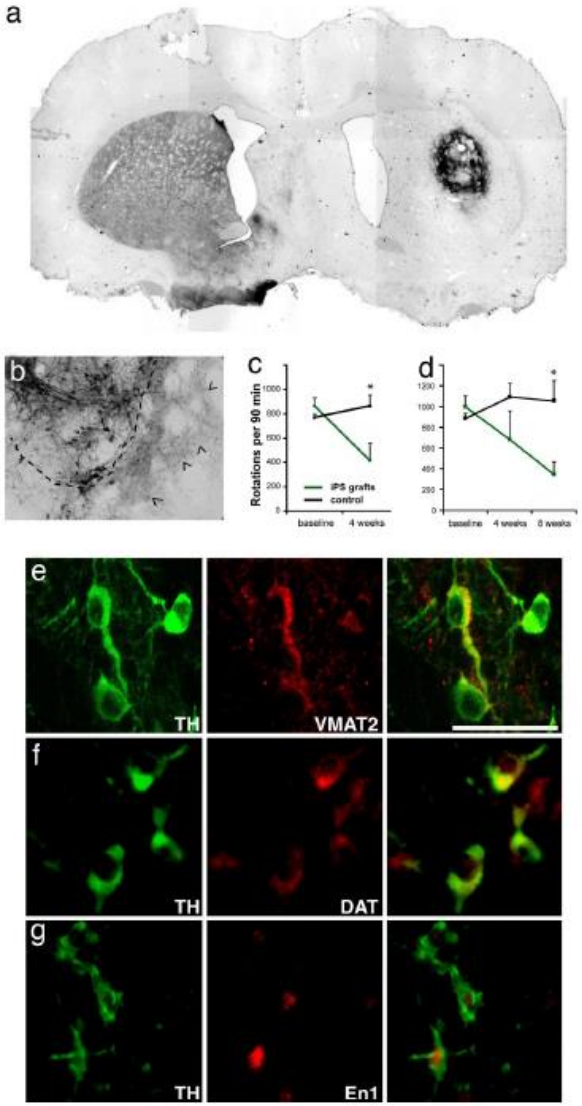












- „hagyományos" iPS gyártás, GFP jelölés, FGF2 előkezelés + Shh, FGF8 indukció
- embrionálisan funkcionális beilleszkedés
- felnőtt agyszövetben lokalizált túlélés, fenotípus javul

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

Parkinson kór

Cell 136, 964–977, March 6, 2009

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

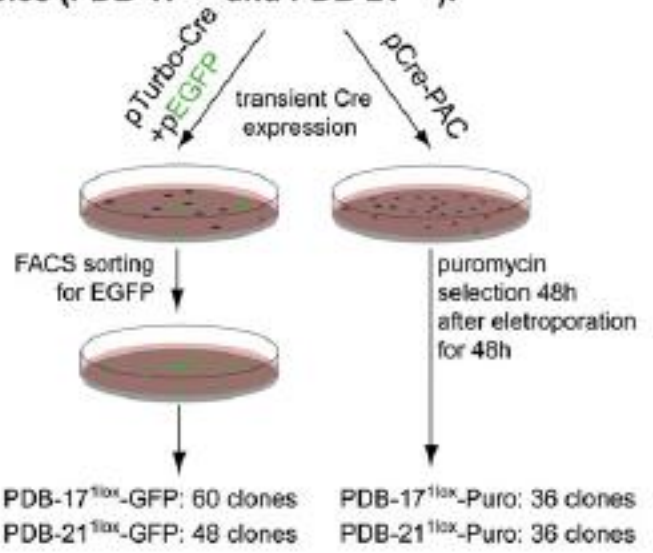
Table 1. Summary of hiPSCs Derived from Primary Fibroblasts

Parental Cell Line	Donor[a]	Age at Onset of PD	Age at Biopsy	Reprogramming Factors	Number of iPSC Clones Characterized	iPSC Clone ID
AG20443 (PDA)	Parkinson's disease patient, idopathic, male	NA	71	FUW-tetO 3 factors (OCT4, SOX2, KLF4)	2	PDA^{3F}-1, -5
AG20442 (PDB)	Parkinson's disease patient, idopathic, male	51	53	FUW-tetO 3 factors (OCT4, SOX2, KLF4)	5[b]	PDB^{3F}-1, -5, -8, -9, PDB^{3F}-d12
AG20442 (PDB)	Parkinson's disease patient, idopathic, male	51	53	FUW-tetO 4 factors (OCT4, SOX2, KLF4, c-MYC)	5[c]	PDB^{4F}-1, -2, -3, -4, -5
AG20446 (PDC)	Parkinson's disease patient, idopathic, male	50	57	FUW-tetO 3 factors (OCT4, SOX2, KLF4)	1	PDC^{3F}-1
AG20445 (PDD)	Parkinson's disease patient, idopathic, male	44	60	FUW-tetO 3 factors (OCT4, SOX2, KLF4)	3	PDD^{3F}-1, -4, -7
AG20445 (PDD)	Parkinson's disease patient, idopathic, male	44	60	FUW-tetO 4 factors (OCT4, SOX2, KLF4, c-MYC)	5	PDD^{4F}-1, -4, -5, -8, -9
AG08395 (PDE)	Parkinson's disease patient, idopathic, female	83	85	FUW-tetO 3 factors (OCT4, SOX2, KLF4)	2	PDE^{3F}-3, -4
GM01786	Dyskeratosis congenital carrier, female	–	30	FUW-tetO 3 factors (OCT4, SOX2, KLF4)	2	M^{3F}-1, -2
GM01660	Lesh-Nyhan carrier, female	–	11	FUW-tetO 3 factors (OCT4, SOX2, KLF4)	2[d]	A1, A6
MRC-5	male, embryonic fibroblasts			FUW-tetO 4 factors (OCT4, SOX2, KLF4, c-MYC)	2[d]	D1, D4

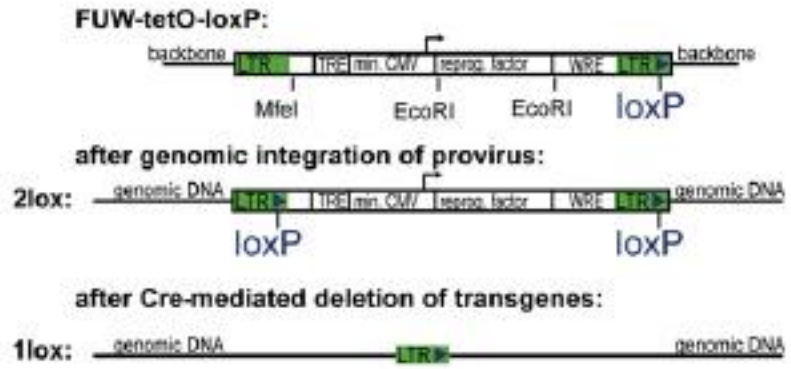
- in vitro dopaminerg neuronok
- retrovirális komponensek kivágása, szelekció

1. Generation of PDB^{2lox} iPSCs (n=24; efficiency ~ 0.005% of infected PDB fibroblasts):

2. Electroporation of 1*10^7 iPS cells of two iPS clones (PDB-17^{2lox} and PDB-21^{2lox}):



3. Southern blot analyis for transgene excision:
-48 out of 180 clones excised KLF4 (EcoRI digest)
-16 out of those 48 clones excised all copies of OCT4,SOX2 and KLF4 (XbaI and MfeI digest)

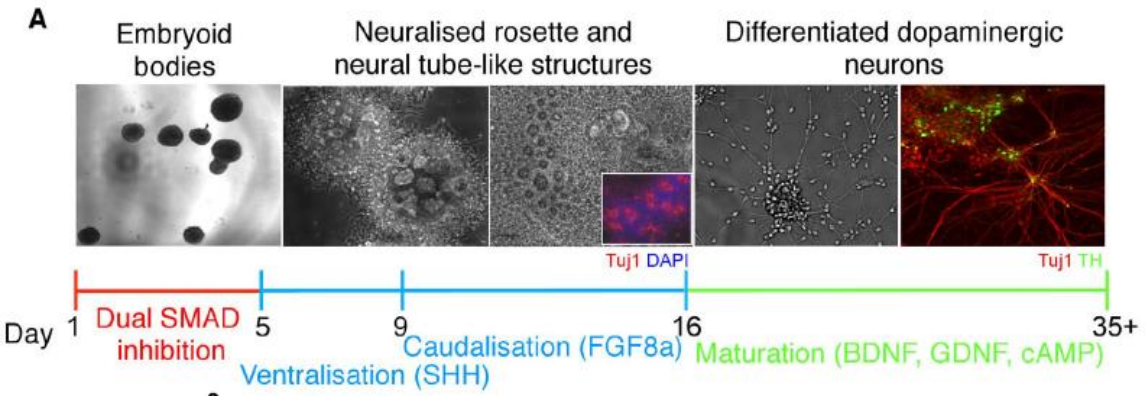


Physiological Characterisation of Human iPS-Derived Dopaminergic Neurons

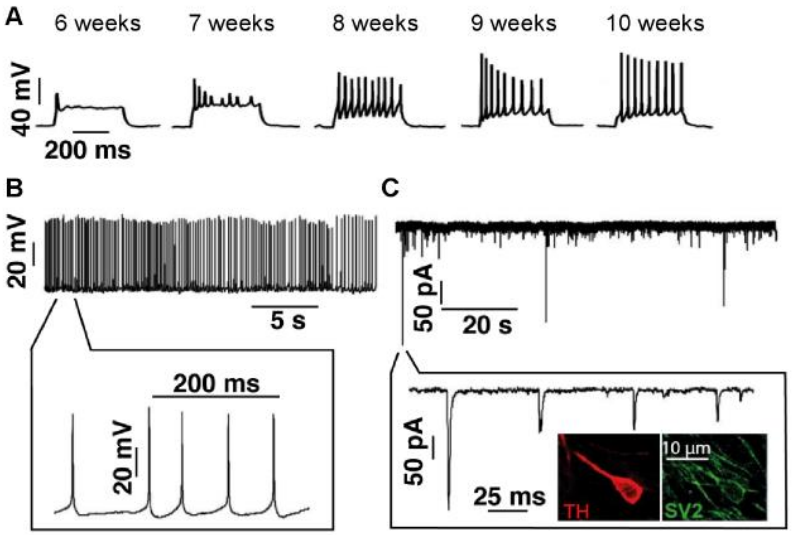
Parkinson kór

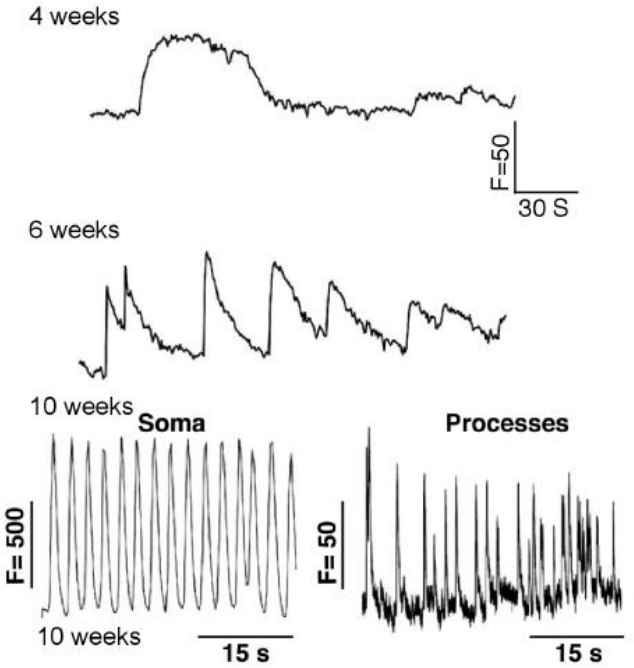
Elizabeth M. Hartfield[1,2¶], Michiko Yamasaki-Mann[1,2¶], Hugo J. Ribeiro Fernandes[1,2], Jane Vowles[1,3], William S. James[1,3], Sally A. Cowley[1,3], Richard Wade-Martins[1,2*]

PLOS ONE | www.plosone.org February 2014 | Volume 9 | Issue 2 | e87388



- OSKM + Nanog plazmid transzfekció
- dopaminerg differenciáltatás in vitro
- elektrofiziológiai, Ca image és DA release jellemzés





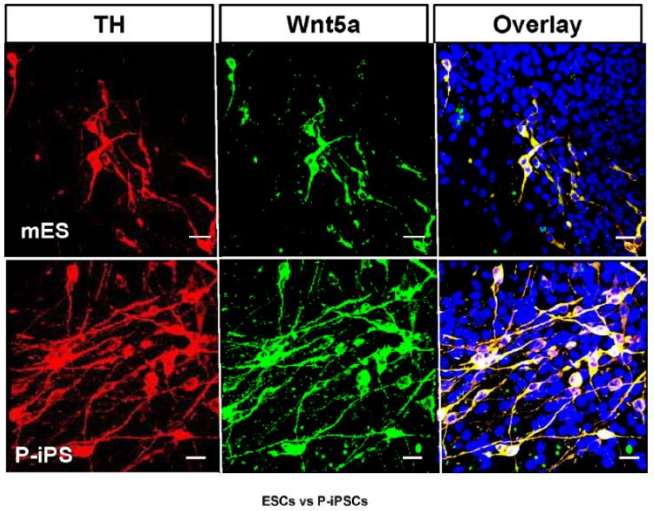
Parkinson kór

Comparative Study of Efficacy of Dopaminergic Neuron Differentiation between Embryonic Stem Cell and Protein-Based Induced Pluripotent Stem Cell

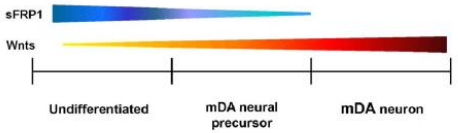
Yoo-Wook Kwon[1,2☯], Yeon-Ju Chung[1,2☯], Joonoh Kim[1,2], Ho-Jae Lee[1,2], Jihwan Park[3], Tae-Young Roh[3], Hyun-Jai Cho[1,2,5], Chang-Hwan Yoon[4], Bon-Kwon Koo[5], Hyo-Soo Kim[1,2,5,6*]

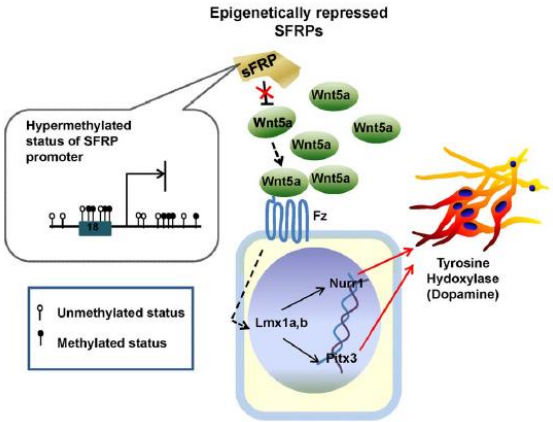
PLOS ONE | www.plosone.org
January 2014 | Volume 9 | Issue 1 | e85736

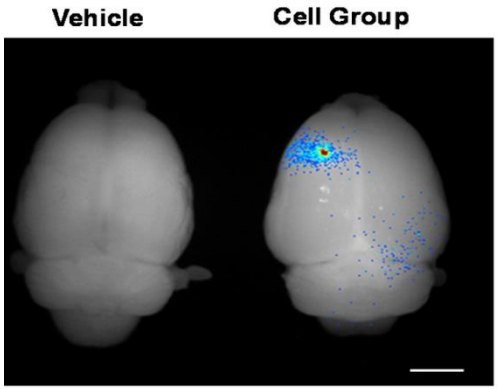
- egér ES sejtek és fibroblasztból készített P-iPSC (protein kivonat ES sejtekből) dopaminerg neuronok in vitro differenciáltatása az P-iPS sejteknél hatékonyabb
  - hipermetilált SFRP promoter – a represszált SFRP nem tudja a Wnt szignálutat gátolni - fokozottabb DA differenciációs irány/marker megjelenés
- az apomorfinnal kiváltott körözést a „parkinsonos" patkányokban (6-OHDA kezelés) mindkét sejt beültetése csökkentette (Neo-Stem fluoreszcens jelölés)

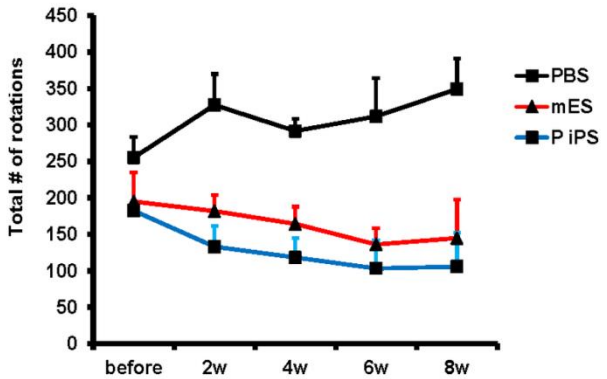


ESCs vs P-iPSCs









Parkinson kór

Gene	Mutations	iPSC-derived cells	Phenotype in human iPSC-derived cells	Use of isogenic & gene corrected iPSC	Drug testing	References
SNCA	Triplication of SNCA	Dopaminegic neurons	Double amount of alpha-synuclein protein	N/A	N/A	Devine *et al.* 2011
Parkin	Heterozygous deletions of exon 3 and exon 5/Homozygous deletion of exon 3	Dopaminergic neurons	Increased spontaneous dopamine release; Decreased dopamine uptake and dopamine transporter-binding sites; Elevated ROS by increasing MAO transcripts	Lentiviral expression of WT-parkin	N/A	Jiang *et al.* 2012
	Homozygous deletion of exon 2-4/Homozygous deletion of exon 6,7	Neural cells including dopaminergic neurons	Increased oxidative stress; Abnormal mitochondrial morphology and impaired mitochondrial homeostasis; Accumulation of alpha-synuclein protein	N/A	N/A	Imaizumi *et al.* 2012
PINK1	Q456X nonsense/V170G missense	Dopaminegic neurons	Impaired recruitment of PARKIN to mitochondria; Increased mitochondrial copy number; Up-regulation of PGC-1alpha	Lentiviral expression of wild-type PINK1	N/A	Seibler *et al.* 2011
	V170G missense	Dopaminegic neurons	Lack of Valinomycin-induced mitophagy	N/A	N/A	Rakovic *et al.* 2012
PINK1/LRRK2	Q456X nonsense (PINK1)/Heterozygous R1441C and homozygous G2019S mutation (LRRK2)	Neural cells including dopaminergic neurons	Production of reactive oxygen species (PINK1); Mitochondrial respiration (PINK1 and LRRK2); Proton leakage (PINK1); Intraneuronal movement of mitochondria (LRRK2)	N/A	Coenzyme Q10, rapamycin, or GW5074	Cooper *et al.* 2012
LRRK2	Homozygous G2019S mutation	Dopaminegic neurons	Increased expression of oxidative stress-response genes (HSPB1, NOX1, and MAOB) and alpha-synuclein protein; Sensitive to caspase-3 activation and cell death caused by hydrogen peroxide, MG-132, and 6-hydroxydopamine	N/A	N/A	Nguyen *et al.* 2011
	Homozygous G2019S mutation	Neural stem cells	Susceptibility to proteasomal stress; Passage-dependent deficiencies in nuclear-envelope organization; Clonal expansion and neuronal differentiation	Isogenic corrected LRRK2 iPSC/mtLRRK2 KI ESC	LRRK2-In-1	Liu *et al.* 2012a
	Heterozygous G2019S mutation	Dopaminegic neurons	Dysregulation of CPNE8, MAP7, UHRF2, ANXA1, and CADPS2; Increased extracellularsignal-regulated kinase 1/2 (ERK) phosphorylation; Increased expression of MAPT mRNA and TAU protein as well as Increased alpha-synuclei protein; Neurite outgrowth phenotype; Increased sensitivity to 6-Hydroxydopamine, rotenone and oxiditative stress	Isogenic corrected LRRK2 iPSC/mtLRRK2 KI iPSCs	LRRK2-IN1, PD0325901	Reinhardt *et al.* 2013
LRRK2/sporadic	G2019S mutation/Sporadic	Dopaminegic neurons	Increased accumulation of alpha-synuclein: Fewer and shorter neurites; Increased apototic cells; Abnormal autophagic clearance	N/A	N/A	Sanchez-Danes *et al.* 2012

Parkinson kór

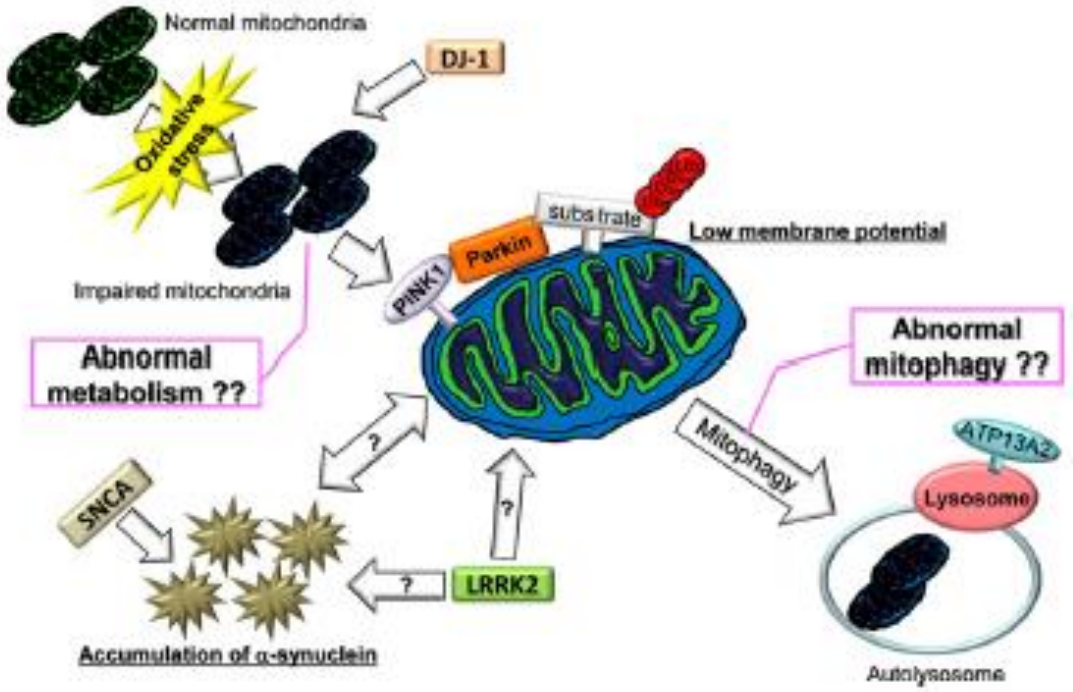


Fig. 3 Working model for familial Parkinson's disease (PD) risk factors: mediated mitochondrial quality control. Impaired mitochondria that have a low membrane potential develop as a result of increased oxidative stress and other factors. Mitochondrial quality is maintained by the familial PD factors PINK1 (PARK6) and PARKIN (PARK2). These factors pass into impaired mitochondria and guide the mitochondria toward degradation. DJ-1 (PARK7), another familial Parkinson's disease factor, is involved in a thioredoxin-mediated mechanism that protects mitochondria against oxidative stress, and a low mitochondrial membrane potential has been reported in LRRK2 mutants (PARK8). In addition, mutation of ATPase type 13A2 (ATP13A2, or PARK9), an H^+-ATPase involved in lysosomal acidification, causes abnormal lysosome function and abnormal protein degradation. On the other hand, α-synuclein oligomers cause mitochondrial impairment in familial PD (PARK1, 4) and are associated with a missense abnormality of the gene (SNCA) that encodes α-synuclein. In this case, a negative feedback loop is formed in which the mitochondrial impairment acts as a trigger for the formation of α-synuclein oligomers. These results strongly suggest that a breakdown of quality control in the impaired mitochondria plays a critical role in the onset of PD.

Parkinson kór

Study to Assess the Safety and Effects of Autologous Adipose-Derived Stromal in Patie Parkinson's Disease

This study is currently recruiting participants. (see Contacts and Locations)

Verified October 2013 by Ageless Regenerative Institute

Sponsor:
Ageless Regenerative Institute

Collaborator:
Instituto de Medicina Regenerativa, S.A. de C.V.

Information provided by (Responsible Party):
Ageless Regenerative Institute

ClinicalTrials.gov Identifier:
NCT01453803

First received: October 3, 201
Last updated: October 28, 20
Last verified: October 2013
History of Changes

Purpose

The intent of this clinical study is to answer the questions:

1. Is the proposed treatment safe
2. Is treatment effective in improving the disease pathology of patients with **Parkinson's** Disease and clinical outcom

Condition	Intervention
Parkinson's Disease	Procedure: Harvesting and Implantation of Adipose-Derived **Stem Cells**

Estimated Enrollment: 10
Study Start Date: May 2011
Estimated Study Completion Date: June 2015
Estimated Primary Completion Date: December 2014 (Final data collection date for primary outcome measure)

Intervention Details:

Procedure: Harvesting and Implantation of Adipose-Derived **Stem Cells**

The adipose tissue specimen will be collected from the patient's abdomen or applicable region using a liposuction car is transferred to the laboratory for separation of the adipose tissue-derived **stem cells**, which are then transferred for

Detailed Description:

This will be an open-label, non-randomized multi-center patient sponsored study of Adipose-Derived Stromal Cells (ASC) catheter delivery system. ASCs will be derived from the patient's adipose-derived tissue. Liposuction using local anesthes will be performed to collect the adipose tissue specimen for subsequent processing to isolate the stem cells. The cells wil into the Vertebral Artery and intravenously.

Eligibility

Ages Eligible for Study: 18 Years to 80 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

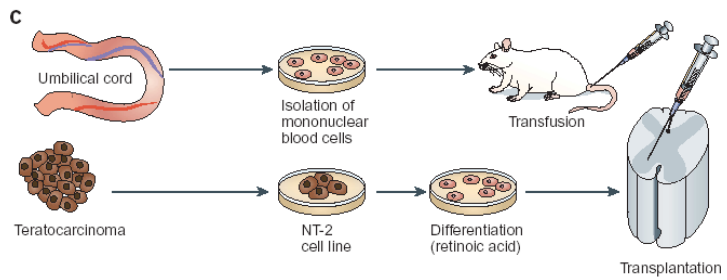
- Males and Females between Age 18 and 80 years.
- Patient with current diagnosis of PD with motor complications (as confirmed by neurologist) as per the standard criter
- Responsiveness to Levodopa or dopa agonist. This is defined as improvement between Off and On UPDRS by at lea UPDRS.
- PD of Stage 2.5, 3 & 4 of HOEHN & YAHR staging.
- Stable Parkinsonian medications for the 60 days prior to the surgical therapy.
- MRI not showing gross atrophy or any other pathology of brain.
- Patients with score less than 19 for the Montgomery-Asberg Rating Scale (MADRS) for Depression.
- NO Significant cognitive impairment.MMSE > 21.
- Up to date on all age and gender appropriate cancer screening per American Cancer Society

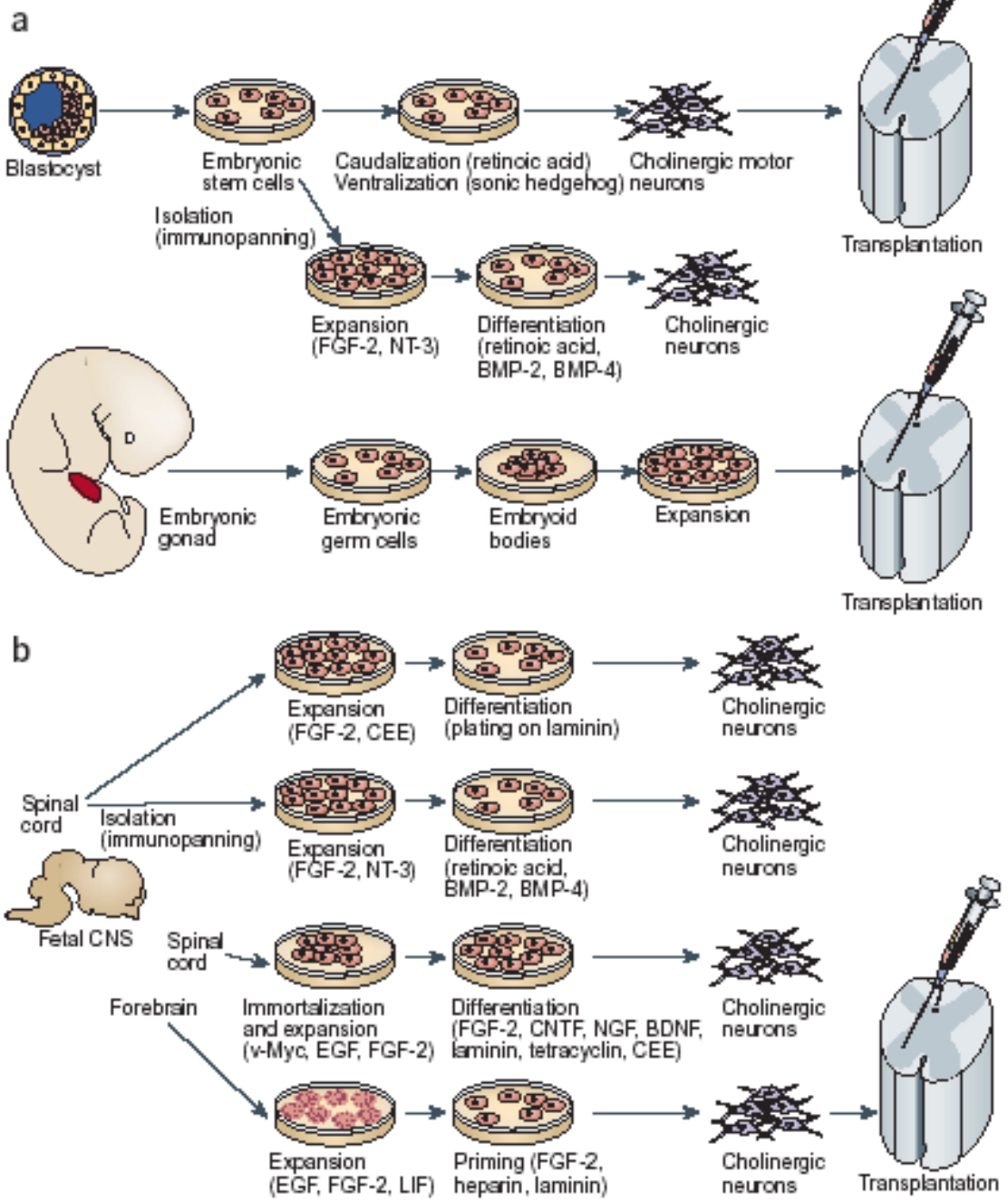
Exclusion Criteria:

- History of intracranial surgeries or implantation of a device for Parkinson's disease two years prior to treatment.
- History of psychiatric disorders like schizophrenia or psychotic disorders.
- History of other malignancy, with the exception of treated cutaneous squamous cell or basal cell carcinoma, within 5 y
- Contraindication for MRI
- Females who are pregnant or nursing or females of childbearing potential who are unwilling to maintain contraceptive the study
- Life expectancy < 6 months due to concomitant illnesses.
- Exposure to any investigational drug or procedure within 1 month prior to study entry or enrolled in a concurrent study results of this study.
- Active infectious disease. Patients known to have tested positive for HIV, HTLV, HBV, HCV, CMV (IgM > IgG) and/or s by an expert as to patient eligibility based on the patient's infectious status
- Any illness which, in the Investigator's judgement, will interfere with the patient's ability to comply with the protocol, cc or interfere with the interpretation of the study results
- Patients on chronic immunosuppressive transplant therapy
- Systolic blood pressure (supine) ≤90 mmHg;
- Resting heart rate > 100 bpm;
- Active clinical infection being treated by antibiotics within one week of enrollment.
- Known drug or alcohol dependence or any other factors which will interfere with the study conduct or interpretation of opinion of the investigator are not suitable to participate.
- History of cancer (other than non-melanoma skin cancer or in-situ cervical cancer) in the last two years.
- Unwilling and/or not able to give written informed consent.

ALS (amiotrofikus laterális szklerózis; Lou Gherig kór)

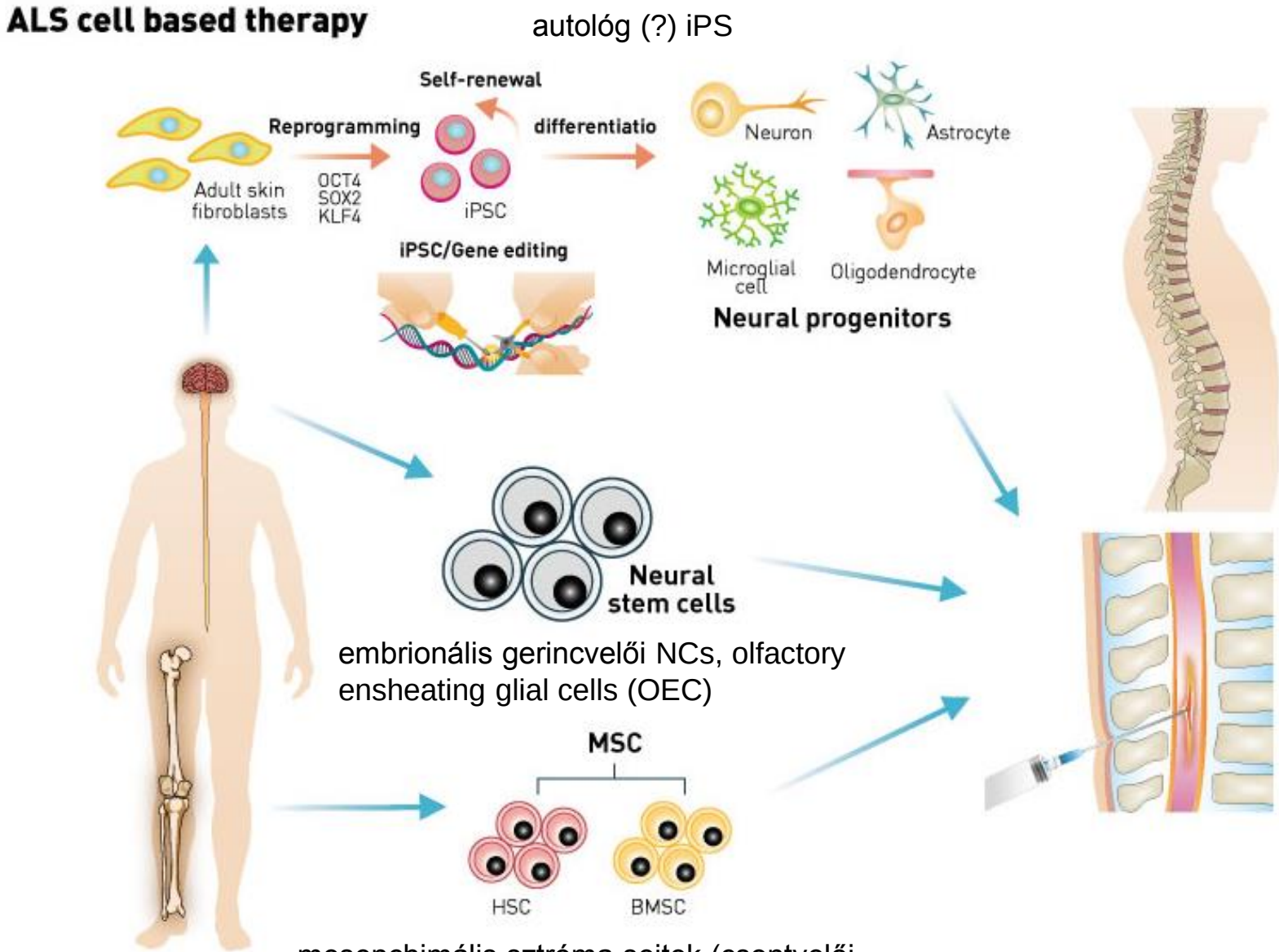
- kolinerg idegsejtek, főleg mozgatórendszer pusztulás - többféle mutáció (SOD-1, FUS, TDP-43...)
- wt glia környezetben jobban túlélnek a SOD1$^{-/-}$ neuronok: gliális vagy neuronális hatás?
- in vivo axonnövekedés: 1-3 mm/nap -> regenerációhoz min. hónapok kellenének!





Lindvall Nat Medicine 2004 10:S42-50

ALS (amiotrofikus laterális szklerózis; Lou Gherig kór)



Amyotrophic Lateral Sclerosis - Cell Based Therapy and Novel Therapeutic Development

http://dx.doi.org/10.5607/en.2014.23.3.207
Exp Neurobiol. 2014 Sep;23(3):207-214.

ALS (amiotrofikus laterális szklerózis; Lou Gherig kór)

Concise Review: Stem Cell Therapies for Amyotrophic Lateral Sclerosis: Recent Advances and Prospects for the Future

STEM CELLS *2014;32:1099–1109*

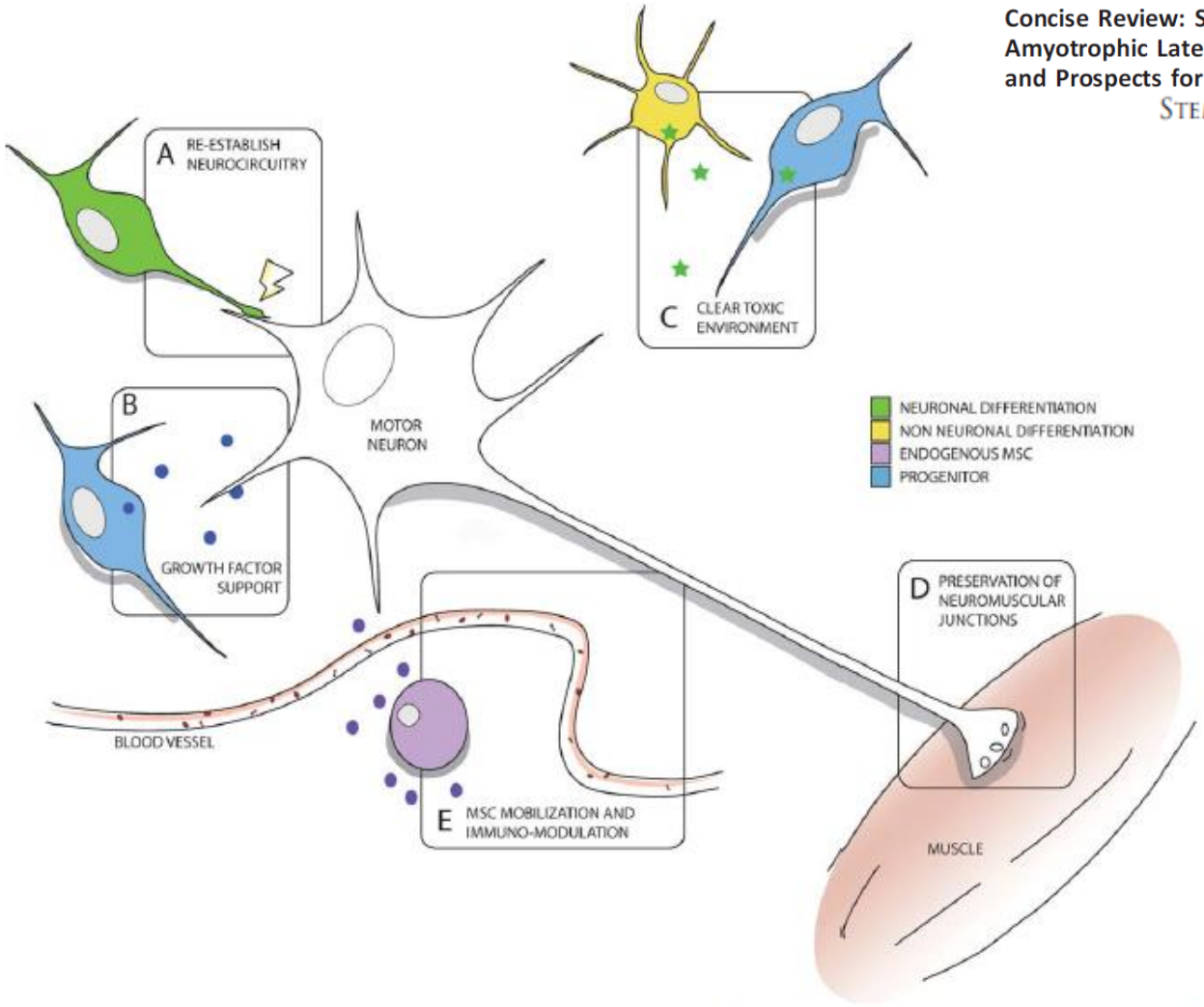


Figure 1. Potential mechanisms of stem cell efficacy in amyotrophic lateral sclerosis. In addition to motor neurons, multiple cell types within the motor neuron microenvironment play a role in disease pathogenesis; therefore, the delivery of stem cell-based therapies (blue) has the potential to provide support through many different mechanisms. Within the spinal cord, stem cells that differentiate into neurons (green) can synapse with existing motor neurons to re-establish or maintain neurocircuitry **(A)** as well as provide neurotrophic support **(B)**. Differentiation of stem cells into non-neuronal cell types (yellow) within the spinal cord microenvironment can also impact disease progression by providing neurotrophic support (B), and attenuating oligodendrocyte dysfunction and mitigating toxicity **(C)**. In the periphery, stem cell transplantation into muscle can provide critical support to maintain functional neuromuscular junctions **(D)**. Finally, the mobilization of endogenous MSCs from the bone marrow into the circulation can also induce immunomodulatory effects that attenuate inflammatory responses within the spinal cord via the production of cytokines and other anti-inflammatory mediators **(E)**. Abbreviation: MSC, mesenchymal stem cell.

ALS (amiotrofikus laterális szklerózis; Lou Gherig kór)

- klinikai Phase I teszt:
  - autológ csontvelői mesenchimális stem sejtek gv-i beültetése
  - biztonságos, kivitelezhető -> 10 betegből 2-nél a progresszió lassul

Intraspinal Neural Stem Cell Transplantation in Amyotrophic Lateral Sclerosis: Phase 1 Trial Outcomes

ANN NEUROL 2014;75:363–373

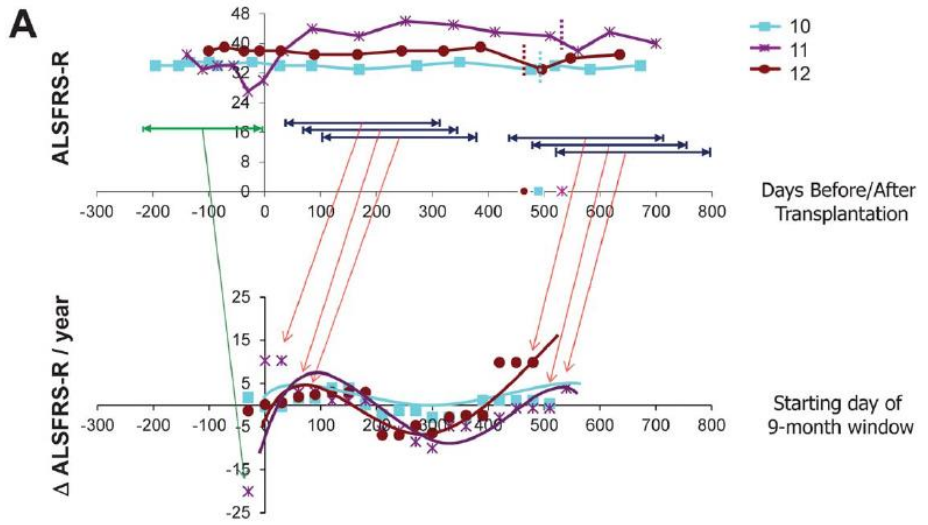


TABLE 1. Subject Demographics

Group	Surgery Details	Subject Number	Surgery Number	Subject Age at Surgery, yr	Disease Duration at Surgery, yr	Gender	Death, mo Postsurgery
A1	Nonambulatory	1	1	61.8	5.2	M	30
	unilateral	2	2	43.4	12.7	M	
	lumbar	3	3	51.1	2.1	M	13
A2	Nonambulatory	4	4	37.5	2	M	
	bilateral	5	5	66.3	2.2	M	19
	lumbar	6	6	55	2.2	M	9
B	Ambulatory	7	7	59	1.6	M	
	unilateral	8	8	41.1	5.6	M	
	lumbar	9	9	54.6	1.3	M	11
C/E	Ambulatory	10	10	48.9	11.6	M	
	bilateral		16	50.2	13		
	lumbar	11	11	39.3	1.6	M	
	and		18	40.7	3		
	unilateral	12	12	65.1	3	M	
	cervical		17	66.3	4.3		
D	Ambulatory	13	13	50.3	3.1[a]	M	20
	unilateral	14	14	54.3	1.8[a]	F	7
	cervical	15	15	35.2	1.7	F	

F = female; M = male.
[a]Subject demonstrated features of bulbar onset amyotrophic lateral sclerosis.

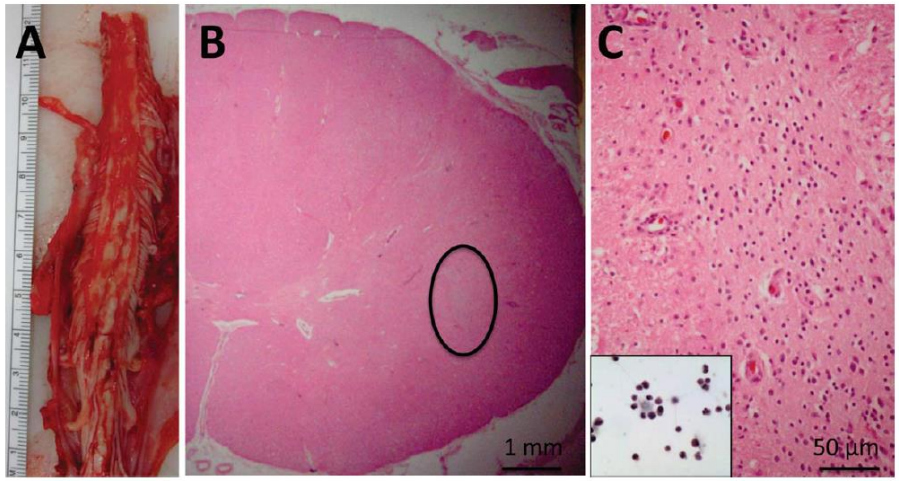
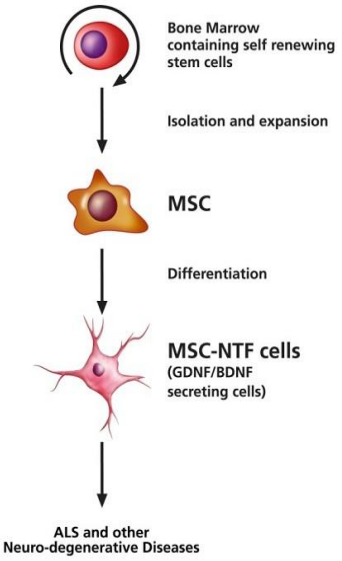


FIGURE 1: Neuropathological findings in Subject 14. (A) Gross image of cervical spinal cord at the time of autopsy. Serial sections through the region of transplantation did not demonstrate regions of cystic change, hemorrhage, or significant tissue disruption. (B) Representative cross section showing intact cord morphology using hematoxylin and eosin (H&E) staining. There is a nest of cells (circled) that are not intrinsic to the spinal cord, and do not stain with glial or neuronal markers (not shown). (C) Higher power of circled region in B showing the morphology of these cells, which is reminiscent of the morphology of the stem cells prior to transplantation (*inset*, H&E).

ALS (amiotrofikus laterális szklerózis; Lou Gherig kór)

- klinikai Phase IIa teszt (Izrael, 2012-2014)
- 2014 - USA: Phase II
- autológ csontvelői mesenchimális stem sejtek gv-i beültetése
- differenciáltatás GDNF / BDNF termelésre
- „NurOwn" sejtek



Home > Find Studies > Search Results > Study Record Detail

Text Size

Trial record **1 of 1** for: nct01051882

Previous Study | Return to List | Next Study

Autologous Cultured Mesenchymal Bone Marrow Stromal Cells Secreting Neurotrophic Factors (MSC-NTF), in ALS Patients.

This study is ongoing, but not recruiting participants.

Sponsor:
Hadassah Medical Organization

Collaborator:
Brainstorm Cell Therapeutics Ltd.

Information provided by (Responsible Party):
Hadassah Medical Organization

ClinicalTrials.gov Identifier:
NCT01051882

First received: January 17, 2010
Last updated: August 5, 2012
Last verified: August 2012
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The study will evaluate the safety, tolerability and therapeutic effects (preliminary efficacy) of injection of autologous cultured mesenchymal bone marrow stromal cells secreting neurotrophic factors (MSC-NTF), as a possible treatment for patients with Amyotrophic Lateral Sclerosis (ALS) at the early and progressive disease stages.

Condition	Intervention	Phase
Amyotrophic Lateral Sclerosis	Biological: MSC-NTF cells transplantation (i.m.) Biological: MSC-NTF cells transplantation (i.t.)	Phase 1 Phase 2

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Now Available for Public Comment: Notice of Proposed Rulemaking (NPRM) for FDAAA 801 and NIH Draft Reporting Policy for NIH-Funded Trials

Trial record **1 of 1** for: nurown stemcell

Previous Study | Return to List | Next Study

Phase 2, Randomized, Double Blind, Placebo Controlled Multicenter Study of Autologous MSC-NTF Cells in Patients With ALS (NurOwn)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2014 by Brainstorm-Cell Therapeutics

Sponsor:
Brainstorm-Cell Therapeutics

Information provided by (Responsible Party):
Brainstorm-Cell Therapeutics

ClinicalTrials.gov Identifier:
NCT02017912

First received: December 17, 2013
Last updated: November 27, 2014
Last verified: November 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

This is a multi-center, randomized, double blind, placebo controlled study to evaluate the safety and efficacy of autologous (self) transplantation of Neurotrophic factors-secreting Mesenchymal Stromal Cells (MSC-NTF, **NurOwn**™) in patients with ALS .

MSC-NTF cells are a novel cell-therapeutic approach which is expected to effectively deliver Neurotrophic factors, which are potent survival factors for neurons, directly to the site of damage.

Condition	Intervention	Phase
Amyotrophic Lateral Sclerosis (ALS)	Biological: Autologous MSC-NTF cells	Phase 2

ALS (amiotrofikus laterális szklerózis; Lou Gherig kór)

Biological Markers of Mesenchymal Stromal Cells as Predictors of Response to Autologous Stem Cell Transplantation in Patients With Amyotrophic Lateral Sclerosis: An Investigator-Initiated Trial and In Vivo Study

STEM CELLS 2014;32:2724–2731

- klinikai Phase II + in vivo tesztek:
  - autológ csontvelői mesenchimális stem sejt beültetése 2x
  - responder *vs* non-responder csoport 6 hónap után: in vitro VEGF, ANG (angiogenin), TGF-β magasabb szintje mellett nagyobb a betegekben a javulás , állatkísérletben jobb a túlélés

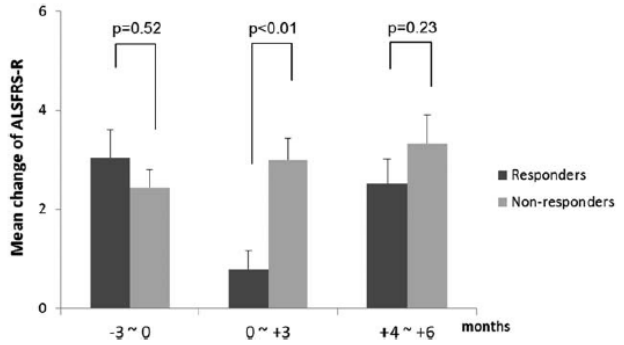


Figure 1. Difference in the mean change in ALSFRS-R scores between responders and nonresponders. Bars represent the standard error of the mean (Mann–Whitney *U*-test). Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-revised.

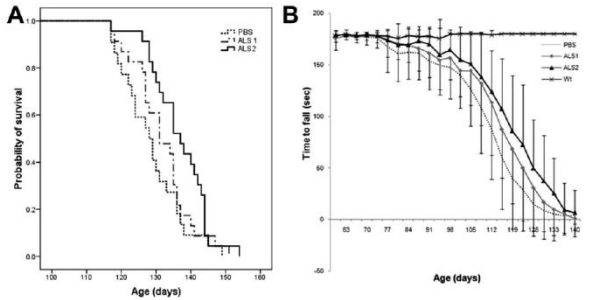


Figure 3. Effects of mesenchymal stromal cell (MSC) transplantation on survival time and rotarod performance. Survival time in the group that received MSCs isolated from responders was significantly longer (**A**) and the decline in rotarod performance was significantly slower (**B**) than in the phosphate-buffered saline group ($p = .030$ and $p < .01$, respectively). Abbreviations: ALS, amyotrophic lateral sclerosis; PBS, phosphate-buffered saline; Wt, wild type.

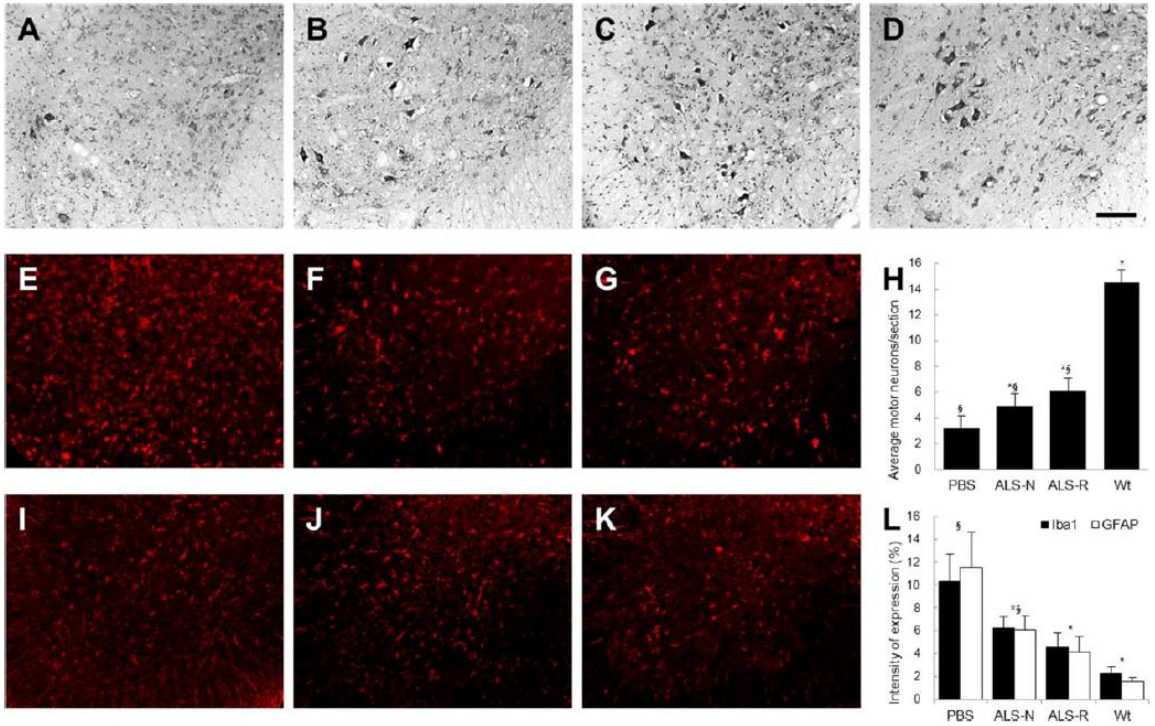


Figure 4. Motor neuron count and immunoreactivity for Iba1 and glial fibrillary acidic protein (GFAP) in the ventral horn of the spinal cord at 109 days. Number of motor neurons (MNs) in SOD1 mice **(A–C)** was significantly lower than in wild-type mice **(D)**. Mice that received mesenchymal stromal cells showed significantly slower MN loss **(H)**, fewer Iba1-immunoreactive-activated microglia **(E–G)**, and fewer GFAP-immunoreactive-activated astrocytes **(I–K)** than the phosphate-buffered saline (PBS) group **(L)**. *, $p < .05$ compared with the PBS group; §, $p < .05$ compared with the wild-type group. Scale bar = 100 μm. Abbreviations: ALS, amyotrophic lateral sclerosis; GFAP, glial fibrillary acidic protein; PBS, phosphate-buffered saline; Wt, wild type.

ALS (amiotrofikus laterális szklerózis; Lou Gherig kór)

- klinikai Phase I tesztek:

Stem Cells. 2012 Jun;30(6):1144-51. doi: 10.1002/stem.1079.

Lumbar intraspinal injection of neural stem cells in patients with amyotrophic lateral sclerosis: results of a phase I trial in 12 patients.

Glass JD, Boulis NM, Johe K, Rutkove SB, Federici T, Polak M, Kelly C, Feldman EL.
Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, USA. jglas03@emory.edu

NEURALSTEM INC.

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Neuralstem Cell Therapy for ALS

- **Product status**:
  - **U.S.:** NSI-566 Phase I Safety Trial completed: August 2012
  - **Mexico City:** NSI-566 Phase I / II Trial expected to commence in 4Q12
- **Mechanism of Action**: Rebuilding neural circuitry
- **Route of Administration**: Direct injections into the spinal cord

Neuralstem is seeking to treat the symptoms of ALS via transplantation of its NSI-566 human spinal cord stem cells (HSSCs) directly into the gray matter of the patient's spinal cord. In ALS, motor neurons die, leading to paralysis. In preclinical animal work, Neuralstem cells both made synaptic contact with the host motor neurons and expressed neurotrophic growth factors, which are protective of cells. View published papers here: 1, 2, 3.

Neuralstem initiated the first FDA-approved stem cell trial for ALS in January 2010, at Emory University. This Phase I safety trial, to evaluate the safety of the NSI-566 cells and surgical technique, was designed to enroll up to 18 patients. The Principal Investigator is Eva Feldman, MD, PhD, Director of the A. Alfred Taubman Medical Research Institute, Director of Research of the ALS Clinic at the University of Michigan Health System, and President of the American Neurological Association. The Site Investigator is Jonathan Glass, MD, Professor of Neurology, Emory School of Medicine and Director of the Emory ALS Center. The trial was awarded an Orphan Drug Designation by the FDA in February 2011.

Amyotrophic Lateral Sclerosis, also known as ALS or Lou Gehrig's disease, is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord, leading to complete paralysis, and eventually, death. According to the ALS Association, as many as 30,000 Americans have the disease, and about 5,600 people in the U.S. are diagnosed with ALS each year.

There is no cure.

Global Development Map

- 8 hetes humán gv-i NSC sejtvonal (NSI-566RSC) lumbáris / cervikális beültetése elődifferenciáltatás után
- uni- vagy bilaterális, 1-200000 sejt/alkalom, immunszuppresszió
- 1 páciensnél (12-ből) tünetek javulnak

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

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

29 AUGUST 2008 VOL 321 SCIENCE

ALS (amiotrofikus laterális szklerózis)

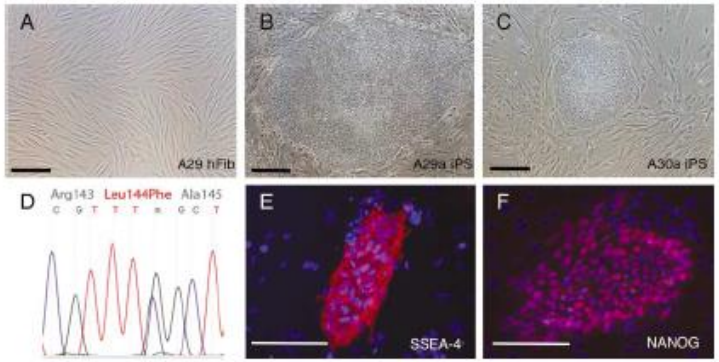


Fig. 1. iPS cells can be established from patient fibroblasts after biopsy. (**A**) Primary dermal fibroblasts (hFib, human fibroblasts) derived from an 82-year-old female ALS patient, A29. (**B**) iPS cells produced from patient A29. (**C**) iPS cells produced from a second patient, A30, sister to patient A29. (**D**) Direct sequencing of a PCR product from A29 iPS cells, confirming the presence of one copy of the dominant L144F *SOD1* allele. (**E** and **F**) SSEA-4 and NANOG protein expression in A29 iPS cells. Scale bars, 200 μm.

- 82 éves ALS betegből bőr-biopszia, iPS előállítás
- neuronális (motoneuron) in vitro differenciáltatás: RA és SHH

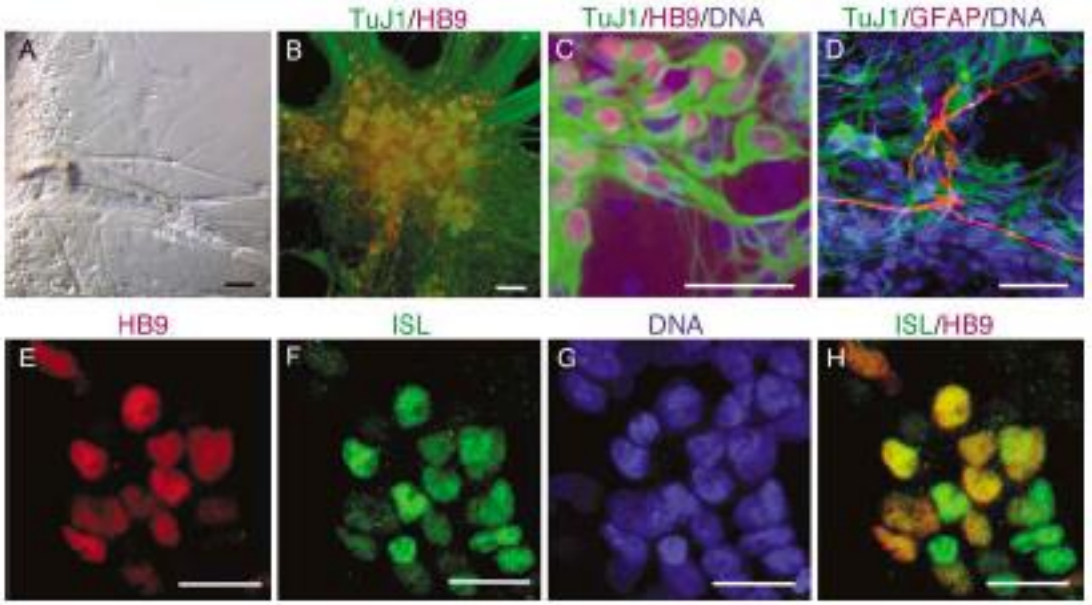


Fig. 4. iPS cells generated from ALS patients can be differentiated into motor neurons. A29b iPS cell EBs were patterned with RA and SHH, then plated on laminin, either whole (**A** and **B**) or after dissociation (**C** to **H**), and allowed to mature for 7 to 15 days. (**A**) Neuron-like outgrowths are visible from whole A29b patient-specific iPS cell EBs. (**B**) Extensive Tuj1-positive neuronal processes grow out from plated whole iPS EBs, which contain a high proportion of HB9-stained nuclei. (**C**) Neuronal identity of HB9-expressing cells is confirmed by high-magnification image of HB9 and Tuj1 coexpression in dissociated patient-specific motor neuron cultures. (**D**) GFAP-expressing glial cells can be found in addition to Tuj1-expressing neurons in differentiated patient-specific iPS cell cultures. [(**E**) to (**H**)] The motor neuron identity of HB9- and Tuj1-positive cells is confirmed by the coexpression of HB9 and ISL. HB9 (**E**) and ISL (**F**) localization is nuclear (**G**) and highly coincident (**H**). Scale bars, 100 μm [(**A**) to (**D**)], 75 μm [(**E**) to (**H**)].

ALS (amiotrofikus laterális szklerózis)

Amyotrophic Lateral Sclerosis (ALS) Tissue Donation Program

This study is currently recruiting participants. (see Contacts and Locations)

Verified May 2014 by Drexel University

Sponsor:
Drexel University College of Medicine

Collaborator:
MDA/**ALS** Center of Hope

Information provided by (Responsible Party):
Christine Barr, Drexel University

ClinicalTrials.gov Identifier:
NCT00716131

First received: July 14, 2008
Last updated: September 18, 2015
Last verified: May 2014
History of Changes

Purpose

Despite significant progress in the identification of mechanisms involved in motor neuron degeneration in **Amyotrophic Lateral Sclerosis** (**ALS**) and other motor system diseases, the actual pathogenesis and cause of these diseases remains unknown. Effective treatment of these diseases are dependent on the elucidation of their causes. The availability of diseased and control human tissues will be a critical resource for this research progress. . Samples of serum, spinal fluid, and urine from patients with motor system diseases can be used to study biochemical and genetic differences compared to tissues of neurologic disease controls and normal controls. Furthermore, the availability of autopsied CNS, PNS, as well as other tissues from patients with **ALS** or suspected **ALS** are useful for current and future research studies into the disease. Therefore, we propose to institute a Tissue Bank containing blood, urine, and cerebrospinal fluid donated from not only **ALS** and other motor neuron disease patients, but also those with other neurologic diseases and normals whose tissue can be used as controls. In addition there will be an autopsy band for post-mortem specimens of **ALS** and other motor neuron disease patients. Each specimen, whether from a living patient or autopsy will be de-identified and accompanied by a standard set of clinical information collected from the medical records in order that each specimen is characterized with the relevant clinical information to maximize the usefulness of the specimens.

Once established, this tissue bank will provide a resource in which a large number of samples will be readily available and expedite research by circumventing the delays in collecting specimens prospectively. These specimens will be used for research in the **ALS** Center of Hope at Drexel University College of Medicine and shared with any outside investigator with a valid IRB approved protocol.

Batten kór (neuronal ceroid lipofuscinosis; NCL)

- progresszív mentális és motoros leépülés, epilepszia, vakság: lizoszomális funkciózavar, neuronpusztulás

HuCNS-SC ® StemCells Inc. : klinikai I / IIa fázis terápia (FDA), 6 gyerek

- klonális, tisztított humán neuronális SC: beültetés után migráció, integráció, idegi és gliális differenciáció
- előrehaladott betegség, multifokális CNS beültetés, 12 hónapos immunszuppresszió és utánkövetés
- 2 dózis: $5x10^9$ és 10^{10} beültetett sejt; MRI vizsgálatok
- mellékhatás eddig "csak" immunszupresszió miatt, 1 haláleset

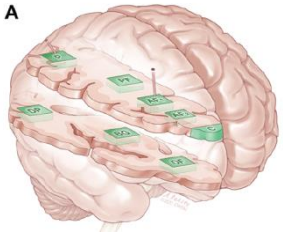
Classification of neuronal ceroid lipofuscinoses.

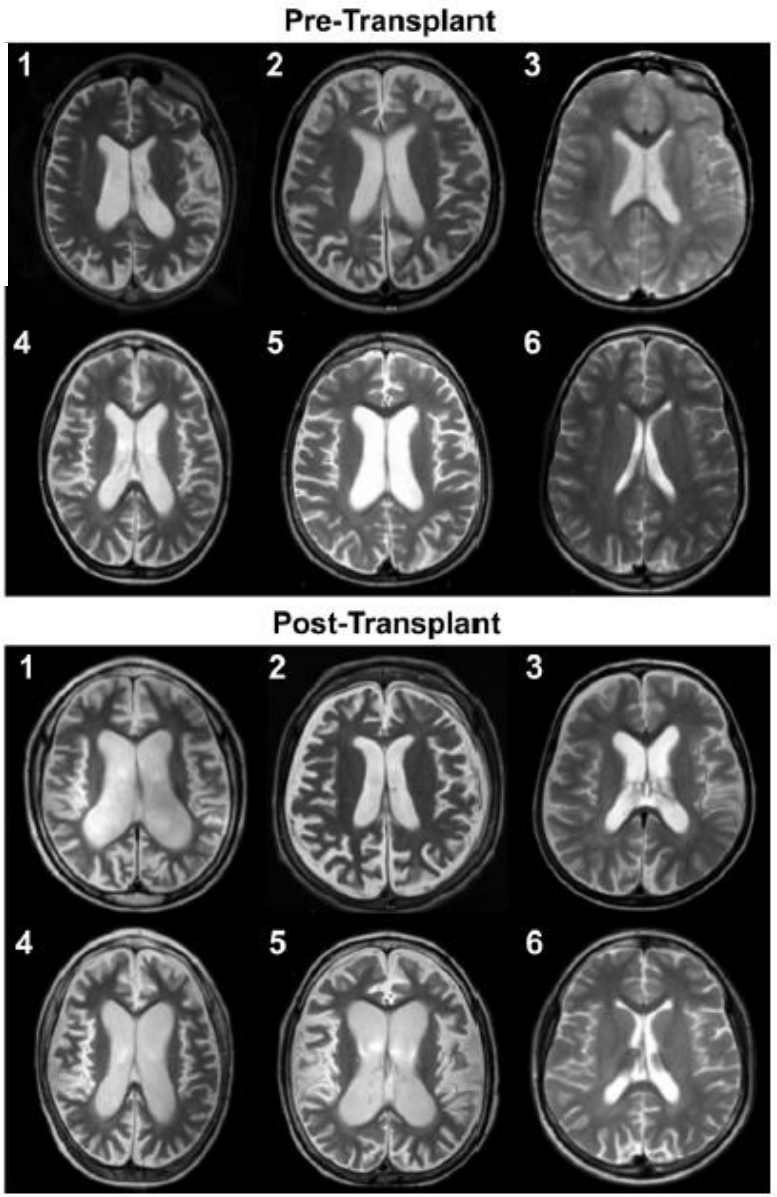
Age at manifestation	Designation	Chromosomal location	Product
Congenital or later	CLN10	11p15	CD[a]
Infantile or later	CLN1	1p32	PPT1[a]
Late infantile or later	CLN2	11p15	TPP1[a]
	CLN5	13q22	Partially soluble protein
	CLN6	15q21	Membrane protein
	CLN7	4q28	Membrane protein
	CLN8	8p23	Membrane protein
Juvenile	CLN3	16p12	Membrane protein
	CLN9		
Adult	CLN4		

[a] Lysosomal enzymes, CD, cathepsin D; PPT1, palmitoylprotein thioesterase 1; TPP1, tripeptidylpeptidase 1.

Batten kór (neuronal ceroid lipofuscinosis; NCL)

- multifokális beadás
- atrófia mértéke nem igazán változott...
- 2010-2015; még fiatalabb betegekkel – visszavonva





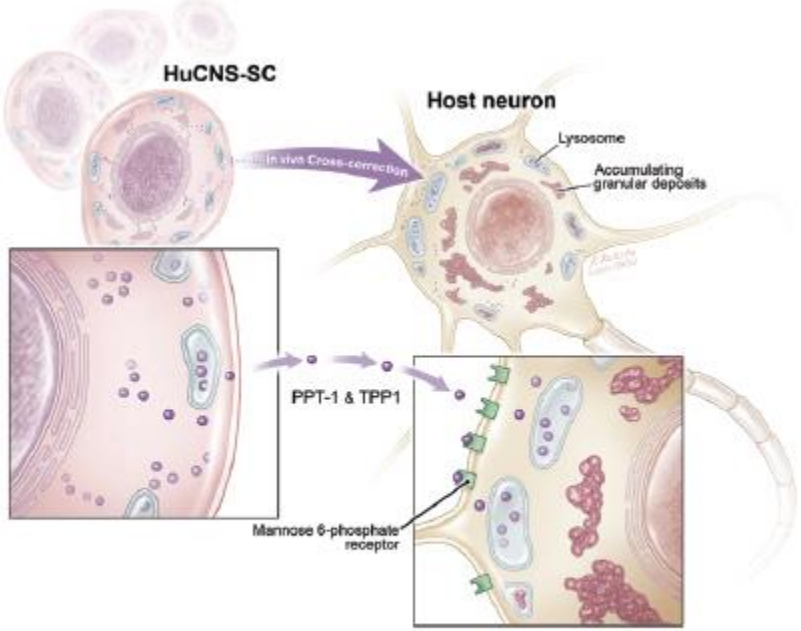


Fig. 1. Cross-correction of enzyme deficiency in vivo using HuCNS-SCs. Artist's conceptualization of cell-based cross-correction as a potential therapeutic strategy. With this experimental approach, PPT-1 and TPP1 are secreted by transplanted HuCNS-SCs and absorbed by host neurons through the mannose 6-phosphate receptor pathway. Cross-correction involves the uptake of these soluble enzymes, resulting in the reduction or stabilization of the accumulating harmful intracellular metabolites. Printed with permission from Andrew J. Rekito.

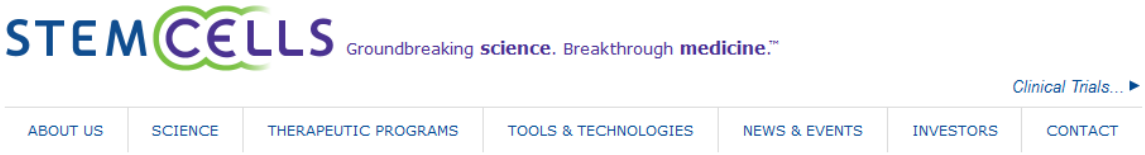
Central nervous system stem cell transplantation for children with neuronal ceroid lipofuscinosis

J Neurosurg: Pediatrics / April 12, 2013

Fig. 2. Magnetic resonance images pre– and post–HuCNS-SC transplantation. Representative T2-weighted axial MR images at the midventricular level for all patients at screening and 12 months (6 months in Case 2) after HuCNS-SC transplantation. Case numbers are in the *upper left corner* of each image. The progressive cerebral atrophy noted between the pre- and post-transplantation images is consistent with the stage of disease for each patient. The posttransplantation MR images did not reveal any delayed adverse reaction to the surgery or cell transplantation.

Pelizeaus-Merzbacher Disease (PMD)

- diszmielinizációs probléma: mielin hüvely nem épül fel -> nisztagmia, bénulás, mentális és fizikai problémák csecsemő kortól
- X kromoszómás, ált. PLP (proteolipid) gén duplikáció -> koleszterin hiány, mielin szintézis deficit
- embrionális huCNS-SCs multifokális beültetés a fehérállományba, csecsemő korban
- immunszuppresszió



Nat Med. 2012 Jul;18(7):1130-5.

Therapy of Pelizaeus-Merzbacher disease in mice by feeding a cholesterol-enriched diet.

Saher G, Rudolphi F, Corthals K, Ruhwedel T, Schmidt KF, Löwel S, Dibaj P, Barrette B, Möbius W, Nave KA.
Department of Neurogenetics, Max Planck Institute of Experimental Medicine, Göttingen, Germany. saher@em.mpg.de

- lehet, hogy a koleszterin-dús diéta is elegendő?
- köldökzsinór-vér transzplantáció: eddig 2 páciens, némi javulás

Duchenne izom-disztrófia (DMD)

- ált. disztrofin-disztroglikán rendszer károsodása
- DMD betegből iPS, ebben mesterséges humán kromoszómán (HAC; stabil episzóma) disztrofin gén bejuttatása (>2,4 Mb!)
- MMCT: microcell-mediated chromosome transfer

Complete Genetic Correction of iPS Cells From Duchenne Muscular Dystrophy

www.moleculartherapy.org vol. 18 no. 2, 386–393 feb. 2010

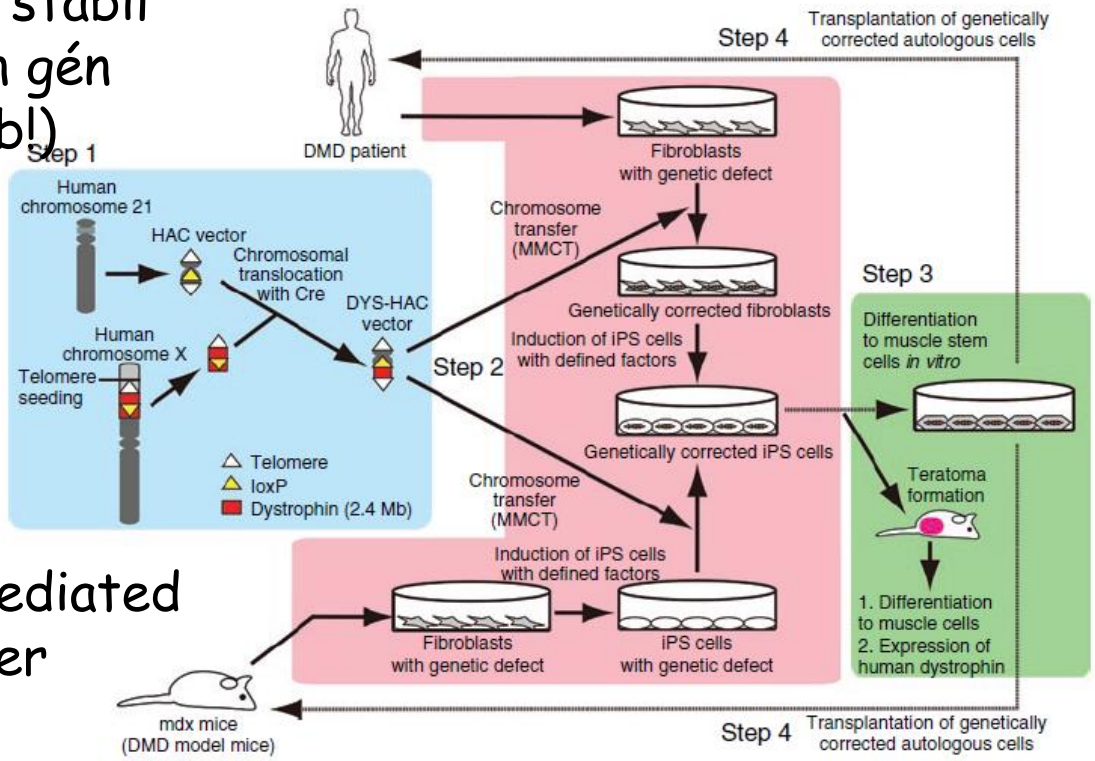
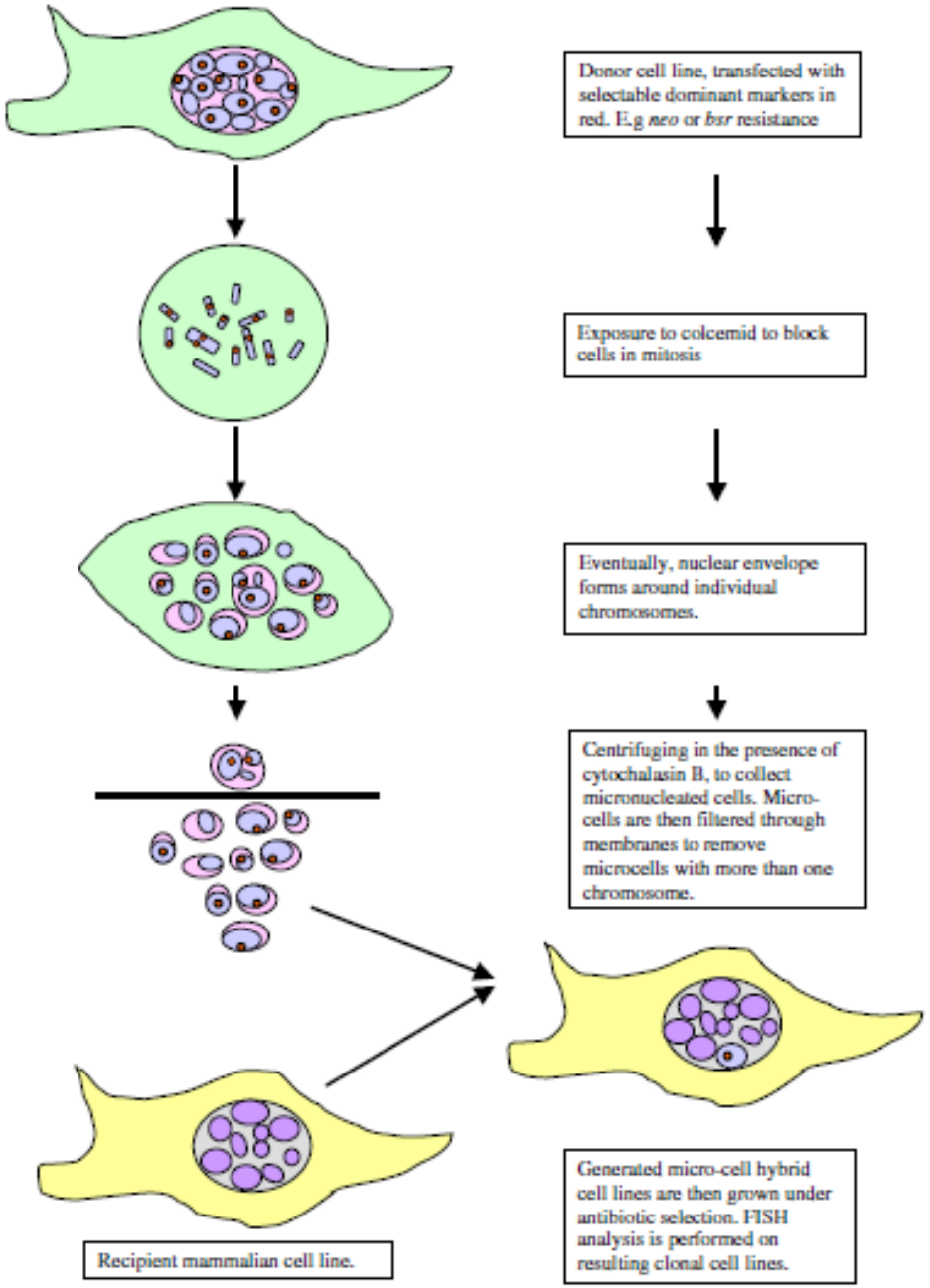


Figure 1 Schematic diagram of the HAC vector system for iPS cell–mediated gene therapy. Human dystrophin gene was cloned into a human chromosome 21–derived HAC vector using a combination of Cre-loxP-mediated chromosomal translocation and telomere-directed chromosomal truncation (Step 1, blue background). In Step 2 (pink background), mdx mice- or DMD patient–derived iPS cells were genetically restored by transfer of the DYS-HAC vector. The DYS-HAC was transferred to mdx-iPS cells directly. However, the DYS-HAC was transferred to DMD patient–derived fibroblasts via MMCT, as we failed to directly transfer the HAC into human iPS cells, then DMD-fibroblasts (DYS-HAC) were induced into iPS cells. Inability of MMCT into human iPS and embryonic stem cells is an unsolved issue. In Step 3 (green background), differentiation to muscle cells *in vivo* (teratoma formation) and expression of human dystrophin in muscle cells were confirmed. Step 4 represents the future and final goal of the transplantation of genetically corrected autologous cells by elegant differentiation and implantation technologies to come in a near future (dotted line). DMD, Duchenne muscular dystrophy; HAC, human artificial chromosome; iPS, induced pluripotent stem cells; Mb, megabase; MMCT, microcell-mediated chromosome transfer.

- MMCT: microcell-mediated chromosome transfer



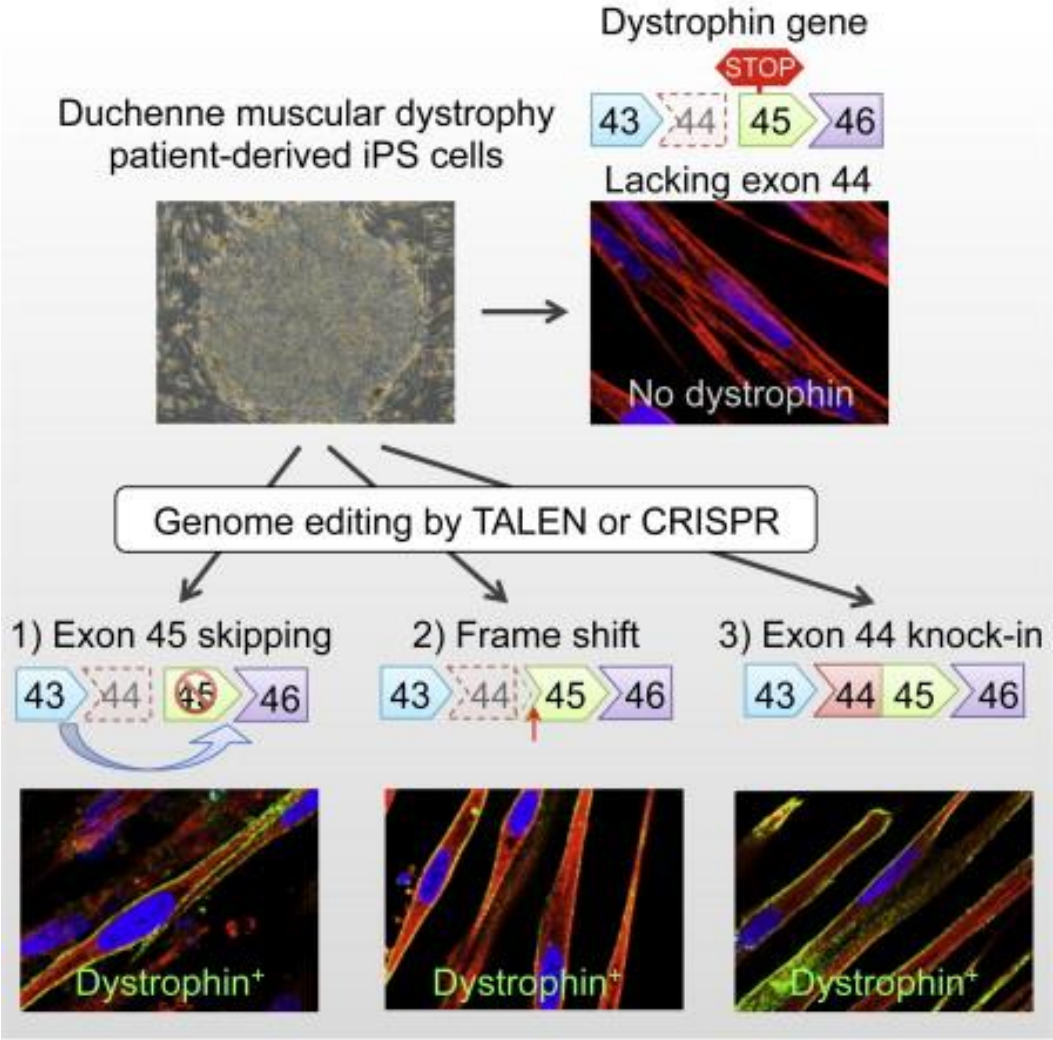
Karen J. Meaburn · Christopher N. Parris · Joanna M. Bridger

Chromosoma (2005) 114: 263–274
DOI 10.1007/s00412-005-0014-8

The manipulation of chromosomes by mankind: the uses of microcell-mediated chromosome transfer

Duchenne izom-disztrófia (DMD)

- spec. nucleázokkal irányított génkorrekció:
  - TALEN: transcription activator-like effector nuclease
  - CRISPR: clustered regularly interspaced short palindromic repeat (CRISPR)
  - Cas9: CRISPR associated 9 endonuclease systems
- iPS sejtekben 44. exonhiány génkorrekciója: nagy specificitás
- indukált izomsejtekben disztrofin-temelés



Precise Correction of the Dystrophin Gene in Duchenne Muscular Dystrophy Patient Induced Pluripotent Stem Cells by TALEN and CRISPR-Cas9

Stem Cell Reports | Vol. 4 | 1–12 | January 13, 2015

Duchenne izom-disztrófia (DMD)

ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Now Available for Public Comment: Notice of Proposed Rulemaking (NPRM) for FDAAA 801 and NIH Draft Reporting Policy for NIH-Funded Trials

10 studies found for: stem Cells AND muscular dystrophy
Modify this search | How to Use Search Results

List | By Topic | On a Map | Search Details

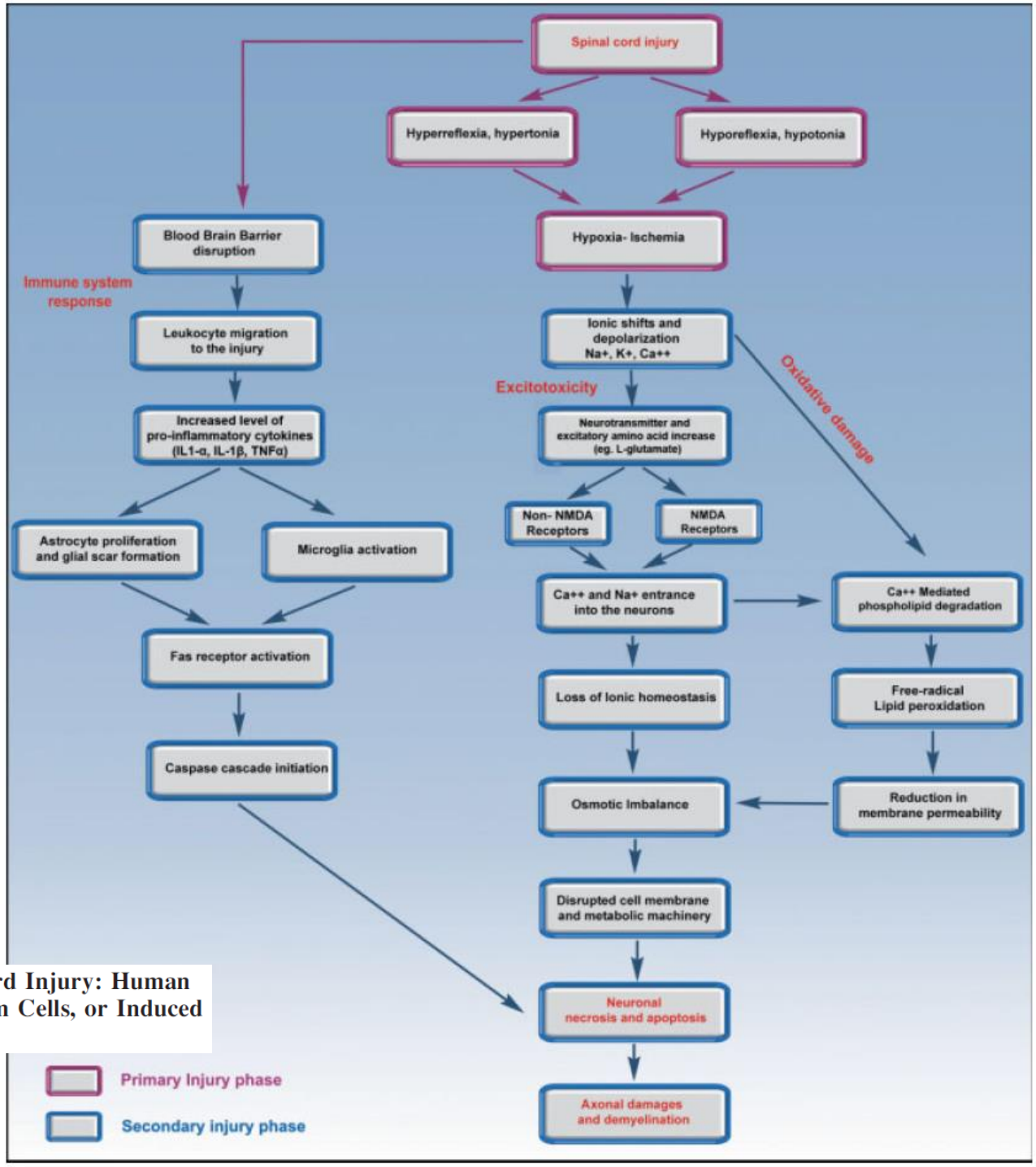
Show Display Options — Download — Subscribe to RSS

Include only open studies | Exclude studies with unknown status

Rank	Status	Study
1	Recruiting	Efficacy of Umbilical Cord Mesenchymal Stem Cells in Duchenne Muscular Dystrophy **Condition:** Duchenne Muscular Dystrophy **Intervention:** Biological: Umbilical Cord Mesenchymal Stem Cell
2	Enrolling by invitation	Allogeneic Human Umbilical Cord Mesenchymal Stem Cells for a Single Male Patient With Duchenne Muscular Dystrophy (DMD) **Condition:** Duchenne's Muscular Dystrophy **Intervention:** Biological: Umbilical Cord Mesenchymal Stem Cells
3	Unknown †	Safety and Efficacy of Umbilical Cord Mesenchymal Stem Cell Therapy for Patients With Duchenne Muscular Dystrophy **Condition:** Duchenne Muscular Dystrophy **Intervention:** Biological: human umbilical cord mesenchymal stem cells
4	Recruiting	Study Safety and Efficacy of Bone Marrow Derived Autologous Cells for the Treatment of Muscular Dystrophy. **Conditions:** Muscular Dystrophy; Duchenne Muscular Dystrophy **Intervention:** Biological: Stem Cell
5	Recruiting	Stem Cell Therapy in Duchenne Muscular Dystrophy **Condition:** Duchenne Muscular Dystrophy **Intervention:** Biological: Stem Cell
6	Recruiting	Stem Cell Therapy in Muscular Dystrophy **Condition:** Muscular Dystrophy **Intervention:** Biological: Stem Cell
7	Recruiting	Cell Therapy in Limb Girdle Muscular Dystrophy **Condition:** Limb Girdle Muscular Dystrophy **Intervention:** Biological: Stem Cell
8	Recruiting	Study Safety and Efficacy of BMMNC for the Patient With Duchenne Muscular Dystrophy **Conditions:** Muscular Dystrophy; Duchenne Muscular Dystrophy **Intervention:** Other: Intralesional/ Intravenous of Autologous Stem cells.
9	Completed	Stem Cell Therapy in Limb Girdle Muscular Dystrophy **Condition:** Limb Girdle Muscular Dystrophy **Intervention:** Biological: Autologous bone marrow mononuclear cell transplantation
10	Recruiting	Intramuscular Transplantation of Muscle Derived Stem Cell and Adipose Derived Mesenchymal Stem Cells in Patients With Facioscapulohumeral Dystrophy (FSHD) **Condition:** Dystrophy **Intervention:** Biological: Intramuscular injection

gerincvelői sérülés (SCI)

- elsődleges és másodlagos sérülések a periférián: a fő cél a neuronális nekrózis / excitotoxicitás és az oligodendroglia apoptózis kivédése

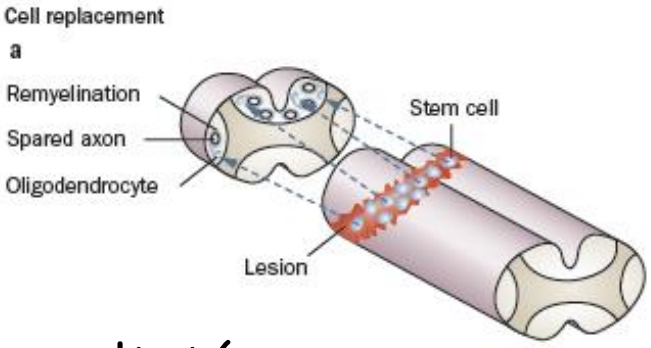


Challenges of Stem Cell Therapy for Spinal Cord Injury: Human Embryonic Stem Cells, Endogenous Neural Stem Cells, or Induced Pluripotent Stem Cells?

STEM CELLS 2010;28:93–99

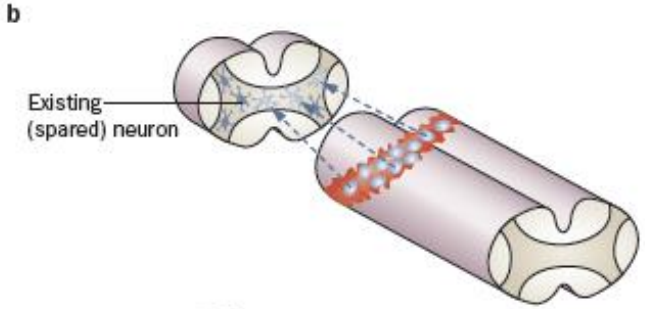
gerincvelői sérülés (SCI)

- sérült ideg- és gliasejtek pótlása
  - nincs neurogén zóna!

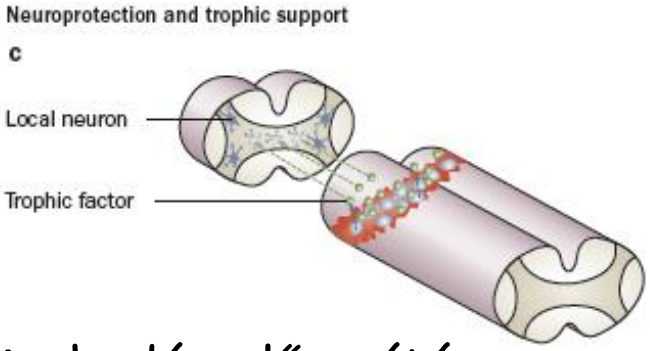


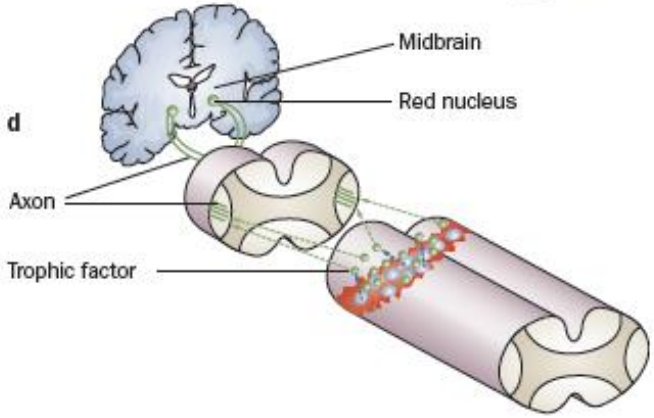
Stem cell therapies for spinal cord injury

Vibhu Sahni and John A
Nat. Rev. Neurol. 6, 363–372 (2010);

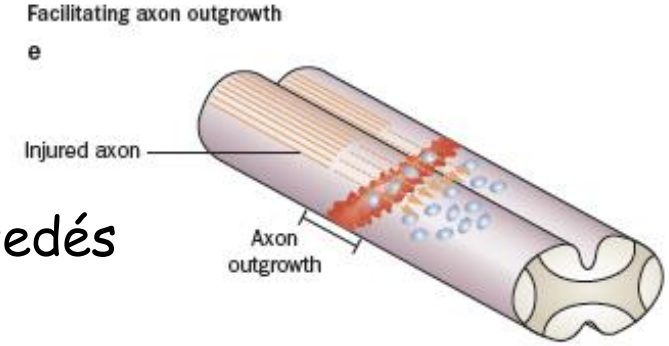


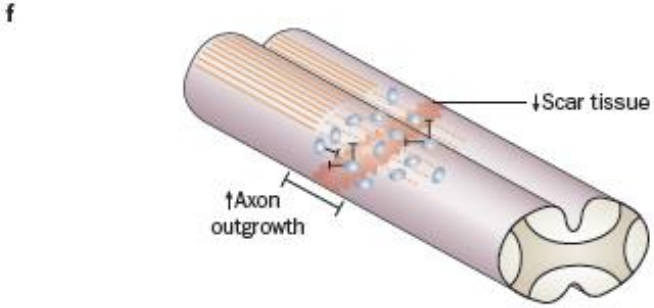
- trofikus faktorok termeltetése
  - lokálisan vagy a leszálló pályákra hatva





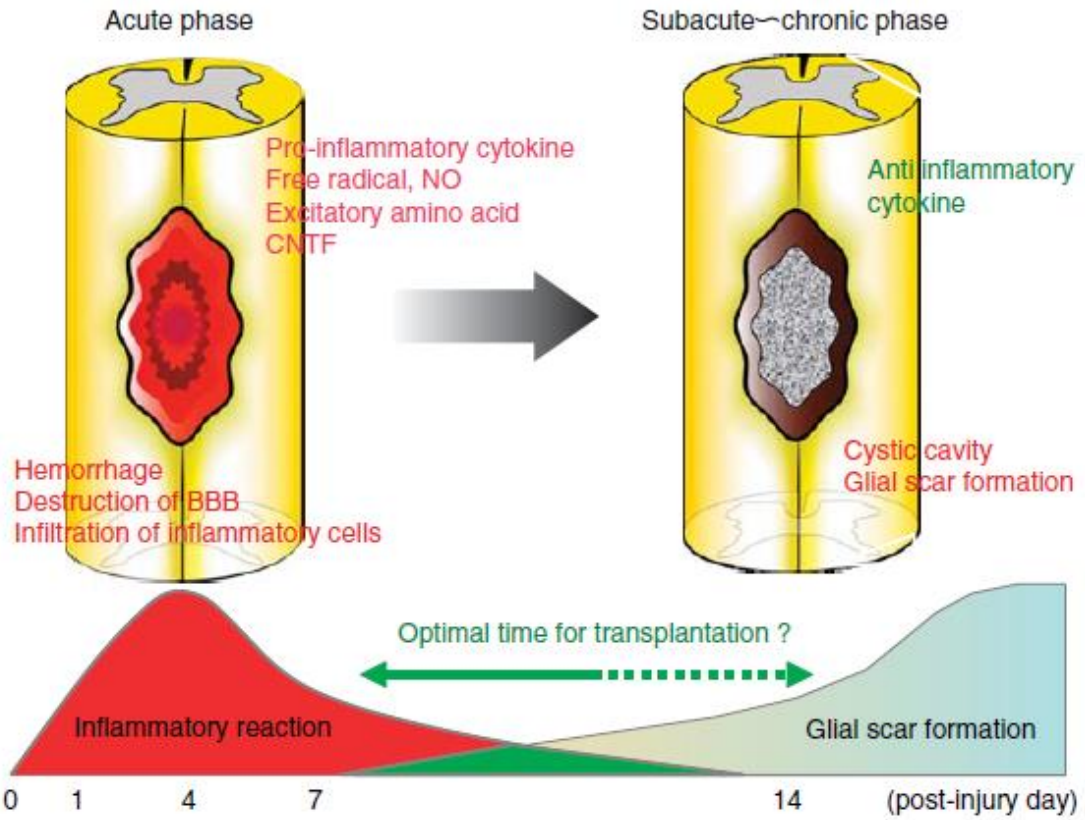
- axon regeneráció/növekedés elősegítése
  - axon átjutás elősegítése
  - gliózis és hegesedés kivédése





gerincvelői sérülés (SCI)

- limitált az optimális transzplantációs idő



Cell transplantation for spinal cord injury focusing on iPSCs

Masaya Nakamura†, Osahiko Tsuji, Satoshi Nori, Yoshiaki Toyama & Hideyuki Okano

10.1517/14712598.2012.681774 © 2012 Informa

Figure 1. Microenvironment of the injured spinal cord. Because the immediately post-traumatic microenvironment of the spinal cord is in an acute inflammatory stage, it is not favorable for the survival and differentiation of NS/PC transplants. On the other hand, in the chronic stage after injury, glial scars form in the injured site that inhibits the regeneration of neuronal axons. Thus, it is believed that the optimal timing of transplantation is 1 – 2 weeks after injury.

gerincvelői sérülés (SCI)

- klinikai Phase I tesztek:

  - HuESC, OPC beültetés 7-14 napon belül

Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitor Cell Transplants Remyelinate and Restore Locomotion after Spinal Cord Injury

4694 • The Journal of Neuroscience, May 11, 2005 • 25(19):4694–4705

  - HuCNS-Sc, beültetés 3-12 hónapon belül

gerincvelői sérülés (SCI)

- klinikai Phase I tesztek:

  - autológ csontvelői (mezenchimális) őssejtek

  - gyerekek

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Search for studies:

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Home > Find Studies > Search Results > Study Record Detail

Trial record **13 of 1221** for: spinal cord

◂ Previous Study | Return to List | Next Study ▸

Autologous Stem Cells for Spinal Cord Injury (SCI) in Children

This study is currently recruiting participants.

Verified October 2012 by Memorial Hermann Healthcare System

Sponsor:
James E.Baumgartner, MD

Collaborators:
The Institute for Rehabilitaion and Research Foundation
The University of Texas Health Science Center, Houston
M.D. Anderson Cancer Center
Baylor College of Medicine

Information provided by (Responsible Party):
James E.Baumgartner, MD, Memorial Hermann Healthcare System

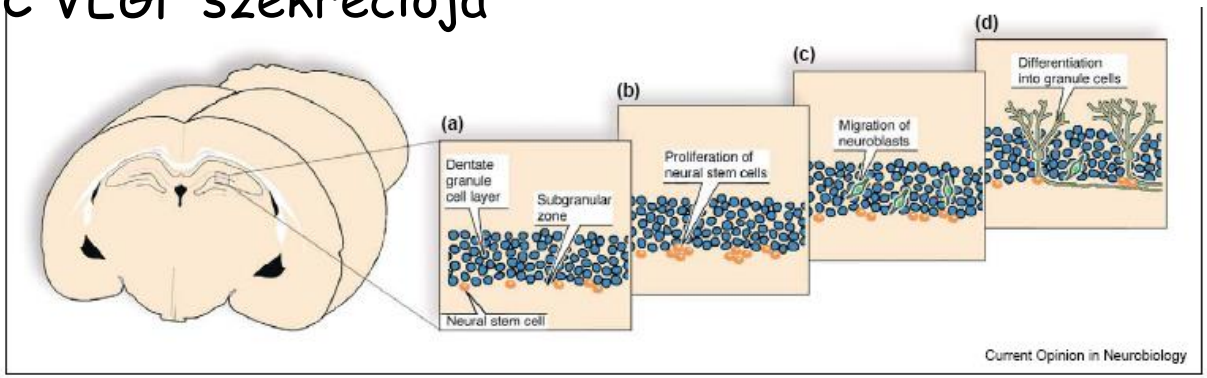
ClinicalTrials.gov Identifier:
NCT01328860

First received: April 1, 2011
Last updated: October 2, 2012
Last verified: October 2012
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Rec

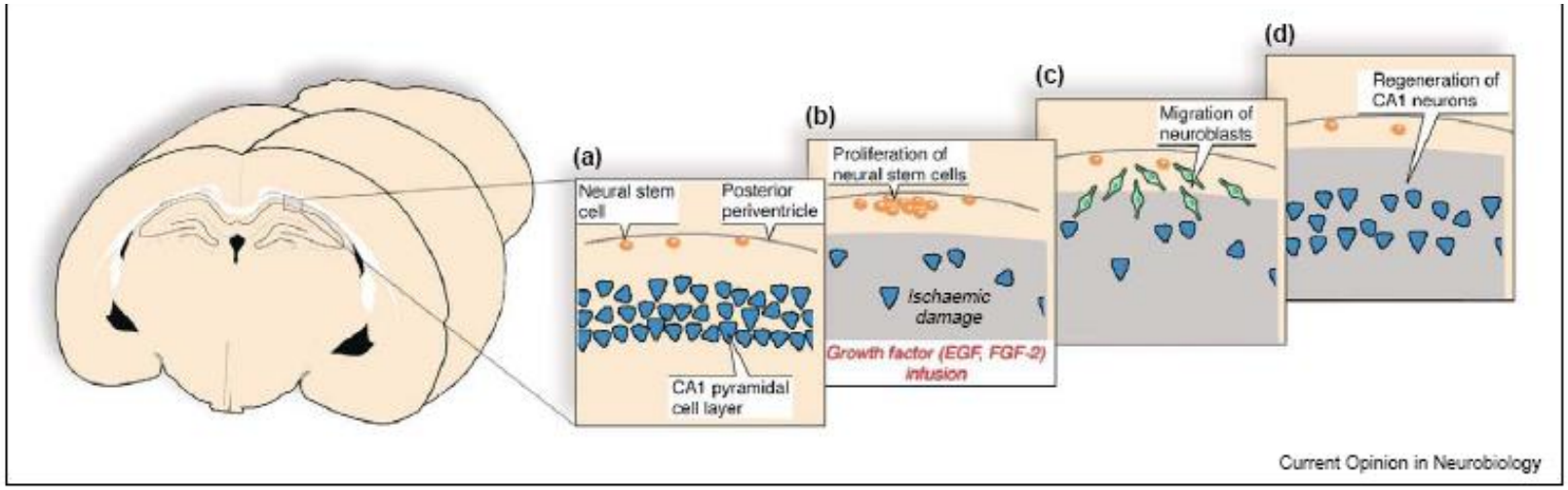
stroke (agyérelzáródás)

- lokális ischaemia (O_2- és tápanyaghiány)
- fokális sérülés ellenére kiterjedt, sokféle sejtet érintő sejpusztulás
- akut fázis:
  - serkentő NT, szabadgyökök, gyulladásmediátorok felszabadulása
    - mikroglia aktiváció, apoptózis: transzplantált sejtek túlélésére, endogén neurogenezisre káros
    - citokinek, növekedési faktorok: neurogenezis, differenciáció serkentése
- krónikus fázis:
  - hegszövet kialakulása miatt túlélés, differenciáció és innerváció nagyban gátolt
- angiogenezis lokálisan segíti a neurogenezist - vagy *vice versa*? SVZ neuroblast migráció / NPSC VEGF szekréciója
- sejtpótlás főleg a proliferatív területeken (cortexben sokkal kevésbé)

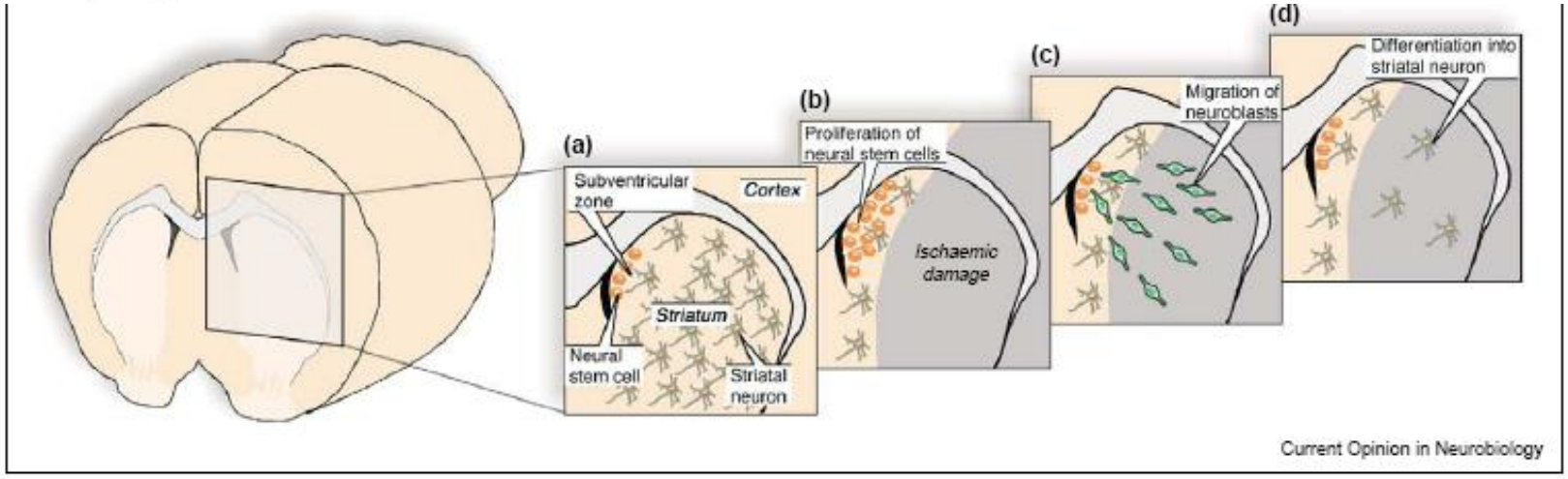


Schematic representation of neurogenesis in the dentate gyrus induced by global ischaemia and stroke. **(a)** Neural stem cells or progenitor cells reside in the subgranular zone. **(b)** Global ischaemia leads to increased proliferation of these cells. **(c)** Their progeny then migrate as neuroblasts inside the granule cell layer and **(d)** differentiate into granule cells.

stroke (agyérelzáródás)



Schematic representation of neurogenesis in the CA1 region following global ischaemia. **(a)** Neural stem or progenitor cells are located in posterior periventricle. **(b)** When a global ischaemic insult, which causes pronounced loss of CA1 pyramidal neurons, is followed by growth factor (FGF-2 and EGF) infusion there is proliferation of progenitors. **(c)** The generated neuroblasts then migrate to the CA1 region, **(d)** where they express neuronal markers. Some experimental evidence suggests that the new cells are functional neurons, have afferent and efferent connections, and contribute to recovery of cognitive function.



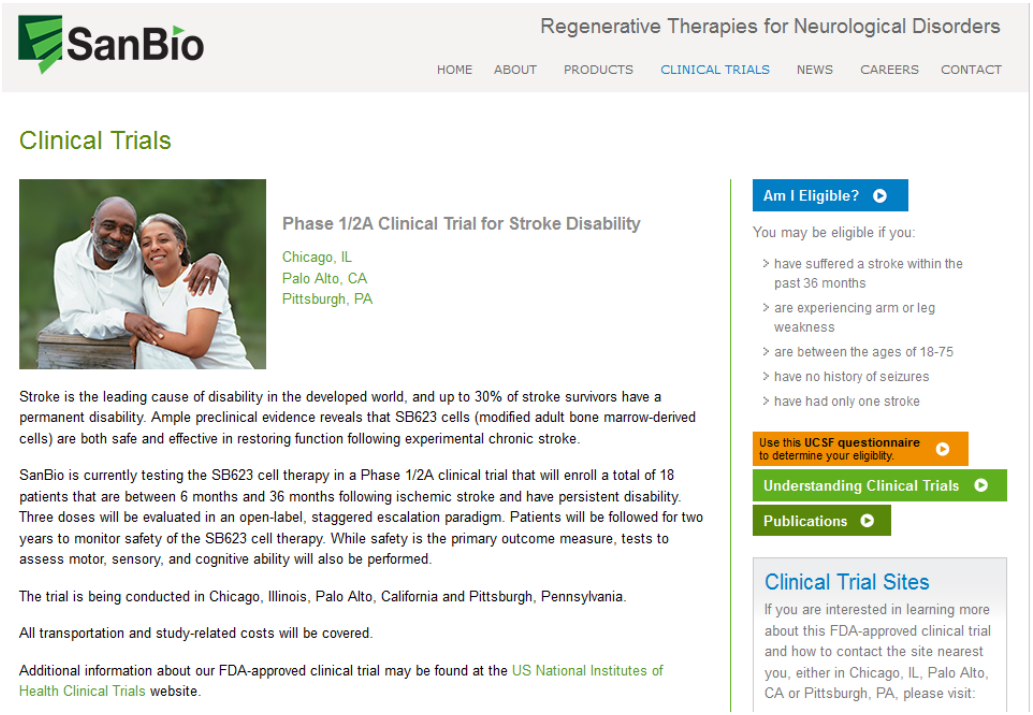
Schematic representation of stroke-induced neurogenesis in the striatum. **(a)** Neural stem or progenitor cells reside in subventricular zone. **(b)** Focal ischaemic insults which lead to pronounced loss of striatal and cortical neurons give rise to increased proliferation of progenitors. **(c)** Neuroblasts formed after and to some extent also before the stroke then migrate to the damaged part of the striatum, **(d)** where they express markers specific for striatal projection neurons.

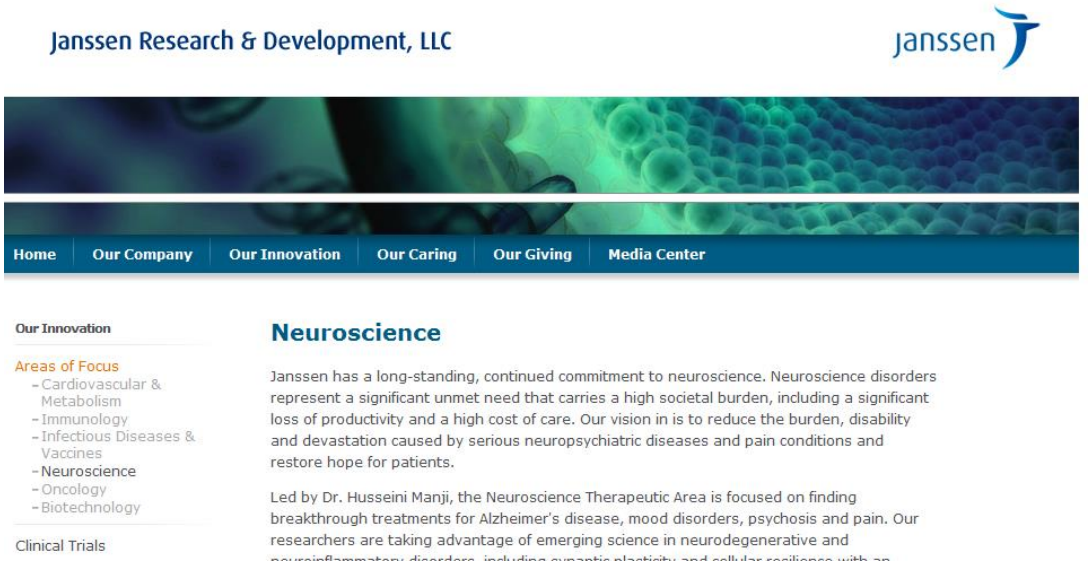
stroke (agyérelzáródás)

- az eredményt alapvetően befolyásolja:
  - a transzplantált sejttípus (főleg állatkísérlet)
    - embrionális és felnőtt NSCs (neural stem cell, neurosphere)
    - OECs (human olfactory ensheating cells/olfactory nerve fibroblasts)
    - ES sejtek: pl. hipoxiás prekondícionálás
    - immortalizált sejtvonalak (ált. neurális eredet)
    - hematopoetikus őssejtek (HSCs)
  - a sejtbeadás módja
    - intravaszkuláris
    - intraventrikuláris
    - intracerebrális (sérülés)
  - a sejtbeadás ideje a sérüléshez képest
  - szolubilis faktorok / növekedési faktorok, hormonok
    - GM-CSF (granulocyte colony stimulating factor); Glutamát...
    - EPO (erythropoetin)
    - IL10, VEGF, IGF-1....

stroke (agyérelzáródás)

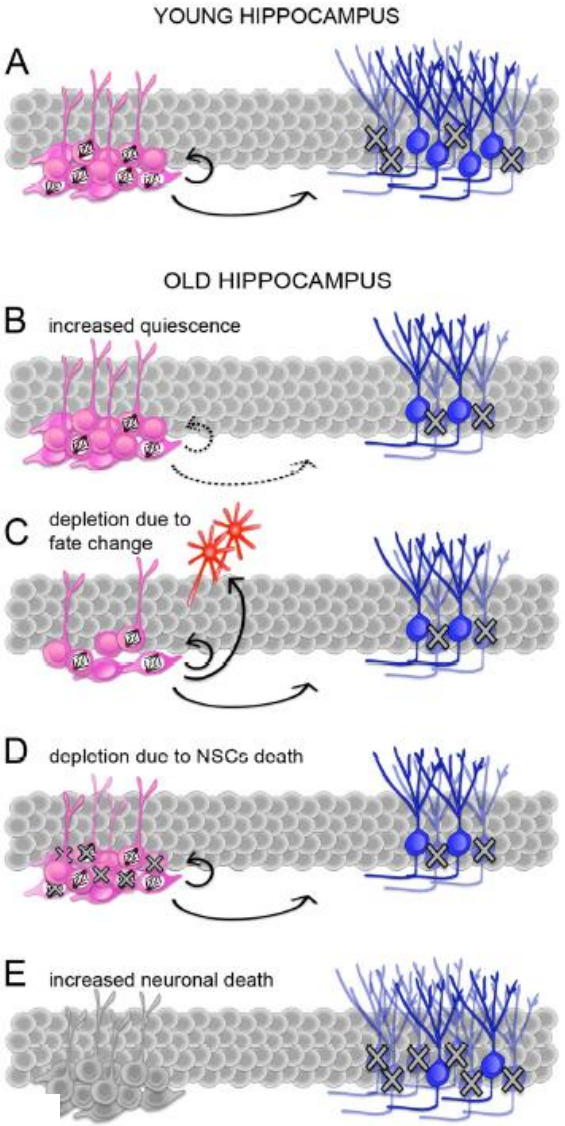
- Phase I / II klinikai tesztek:
  - SB623: felnőtt mesenchymal SCs transiently modified with Notch plasmid
  - intracerebrális beadás, min. 6 hónappal a stroke után - krónikus
  - intravénás injekció 1-5 nappal a stroke után - akut
  - köldökzsinór őssejtek





öregedés

- nem csak a neurogén zónákat érinti!
- fizikai aktivitás serkentő hatású
- táplálkozási szokások: mTOR gátlás -> őssejtek / prekurzorok öregedésének késleltetése



	FACTOR / STIMULUS	change during aging	effect on neurogenesis	correlation with cognitive function
systemic	hipoxic response	↓	↑	nd
	chemokines	↑	↓	✔
	CORT	↑	↓	✔
	IGF-1	↓	↑	✔
	FGF-2	↓	↑	nd
	VEGF	↓	↑	✔
	physical exercise	na	↑	✔
	enriched environment	na	△	✔
molecular	$p16^{INK4}$	↑	↓	nd
	$p19^{Arf}$	↑	↓	nd
	cyclinD1-2	↓	↑	nd
	cdk4/cyclinD1	nd	↑	nd
	cdk6	nd	↑	nd
	Bax	nd	△	nd

igure 2. Factors influencing neurogenesis luring aging. (From left to right) Factors and stimuli nfluencing neurogenesis, their physiological increase yellow arrows) or decrease (blue arrows) during ging, as well as effects on neurogenesis through, rimarily, a change in NSCs proliferation (arrows) or euronal survival (arrowhead) are indicated. Red ticks ndicate factors whose manipulation has been shown o correlate with cognitive function. nd=not letermined; na=not applicable.

Age-related cognitive decline: Can neural stem cells help us?

Benedetta Artegiani and Federico Calegari

AGING, March 2012, Vol. 4, No 3

Pharmacological Reprogramming of Fibroblasts into Neural Stem Cells by Signaling-Directed Transcriptional Activation

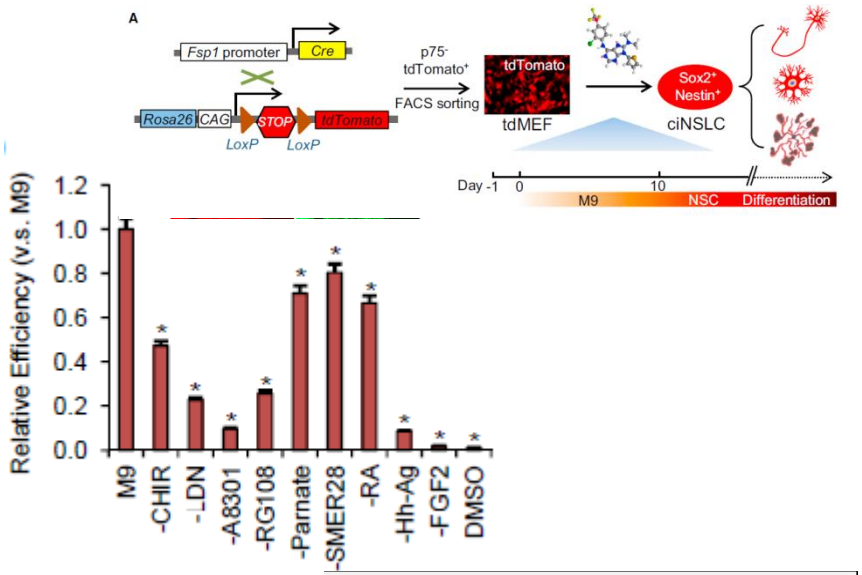
Cell Stem Cell *18*, 1–15, May 5, 2016

Mingliang Zhang,[1,2,9] Yuan-Hung Lin,[3,4] Yujiao Jennifer Sun,[7] Saiyong Zhu,[1,2,9,10] Jiashun Zheng,[8] Kai Liu,[1,2,9] Nan Cao,[1,2,9] Ke Li,[1,2,9] Yadong Huang,[2,3,5,6] and Sheng Ding[1,2,9,*]

- ciNSLCs: kémiailag indukált neural stem cell-like sejtek, virális vektorok nélkül
- egér embrionális fibroblaszt, FSP1-Cre: tdTomato jelöléssel (tdMEFs)
- M9: 9 faktor

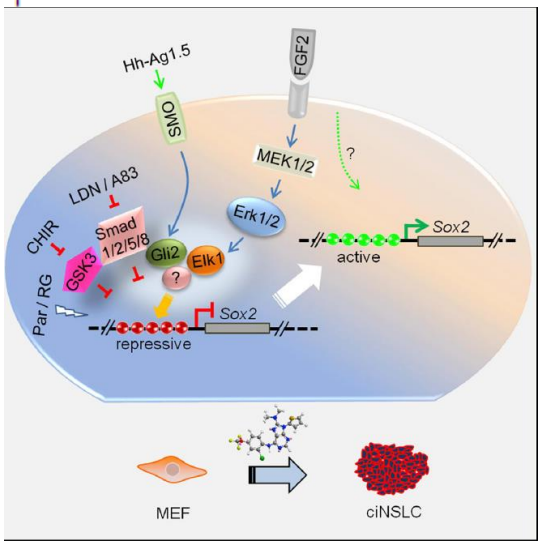
  - BMPR , TGFβ R gátlás -> mezodermális és endodermális fejlődés gátlása

  - GSK3 és Smo gátlás, bFGF serkentés, retinsav + DNS metiltarnszferáz és hiszton demetiláz gátlás, autofágia szabályozása -> neuronális indukció



- 6 napon belül MET, 10 napon belül >25% NSC ($Sox2^+/Nestin^+$)

- in vitro és in vivo neuron, asztroglia és oligodendroglia kialakítás



zombi-projekt....

Biotech Company Granted Ethical Permission To Attempt To Use Stem Cells To Reactivate The Brains Of The Dead

May 3, 2016 | by Robin Andrews

http://www.iflscience.com/brain/biotech-company-use-stem-cells-reactivate-brains-dead

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EGÉSZSÉG

Agyhalott emberek feltámasztására készülnek

http://www.origo.hu/egeszseg/20160504-agyhalal-agy-idegsejtek-neuronok-ujraelesztes.html

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ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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Trial record **1 of 1** for: bioquark

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Non-randomized, Open-labeled, Interventional, Single Group, Proof of Concept Study With Multi-modality Approach in Cases of Brain Death Due to Traumatic Brain Injury Having Diffuse Axonal Injury

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified April 2016 by Bioquark Inc.

Sponsor:
Bioquark Inc.

Collaborators:
Revita Life Sciences
Anupam Hospital

Information provided by (Responsible Party):
Bioquark Inc.

ClinicalTrials.gov Identifier:
NCT02742857

First received: April 6, 2016
Last updated: April 14, 2016
Last verified: April 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

This is the proof of concept study with multi-modality approach (using intra-thecal bioactive peptides, stem cells, laser and transcranial IV laser and Median Nerve stimulation as adjuvants) in cases of brain death due to traumatic brain injury having diffuse axonal injury to document possibility of reversal of brain death (BD).

Condition	Intervention	Phase
Brain Death	Biological: BQ-A Peptide Extract Biological: Mesenchymal Stem Cells Device: Transcranial Laser Therapy	Phase 1