MY RETURN TO CELL REPLACEMENT: WHAT IS THE PROMISE WHAT ARE THE CHALLENGES

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Fetal Nigral Transplantation
Graft-Striatal Interface and normal morphology
Fetal Nigral Transplant Study
Mean UPDRS Motor Off Score by Visit
Who sees Lewy Bodies in Grafts? Everyone who really looks

Li et al., Nature Medicine, 2009
Grafts of dopamine cells placed into the striatum with viral over-expression of alpha synuclein

Note the physical segregation of the graft (brown) and gene delivery (black)
A small percentage (5%) of grafted neurons retrogradely transported host-derived alpha synuclein
Case 2

PD changes in grafted neurons occur that are analogous to what is seen within nigral neurons in PD.
DBS
Beyond Nine Years of Continuous Subthalamic Nucleus Deep Brain Stimulation in Parkinson’s Disease

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ABSTRACT: Deep brain stimulation of the subthalamic nucleus is an effective treatment for advanced Parkinson’s disease. The benefits of bilateral subthalamic stimulation are well documented, and some studies reported outcomes with a follow-up of 5 to 6 years; nevertheless, few data are available beyond 5 years. We report a long-term prospective evaluation of 14 consecutive parkinsonian patients, treated by bilateral subthalamic stimulation for at least 9 years. Motor symptoms, activity of daily living, and motor complications were evaluated by means of the Unified Parkinson’s Disease Rating Scale, while cognition and mood were assessed with a specific neuropsychological test battery; medication intake, stimulation parameters, comorbidity, and adverse events were also recorded. Patients were evaluated before surgery and at 1, 5, and ≥9 years after surgery. At last follow-up, deep brain stimulation significantly improved the motor score by 42% compared to baseline, whereas activities of daily living were no longer improved; there was a 39% reduction in the dosage of dopaminergic drugs and a 59% improvement of L-dopa-related motor complications. The neuropsychological assessment showed that 4 patients (29%) developed a significant cognitive decline over the follow-up period. These results indicate a persistent effect of deep brain stimulation of the subthalamic nucleus on the cardinal motor symptoms in advanced Parkinson’s disease patients in the long-term; however, a worsening of patients’ disability, mainly due to disease progression, was observed. © 2011 Movement Disorder Society

Key Words: Parkinson’s disease; deep brain stimulation; subthalamic nucleus; long-term follow-up
Do We Need Cell Replacement?

• The major unmet needs in PD are not levodopa-responsive motor deficits but levodopa non-responsive motor deficits (e.g. gait disturbance) and non-motor PD (e.g. depression, dementia, constipation, sleep disturbance). There is no reason to believe these symptoms would benefit from DA cell replacement.

• The patient population that would benefit from DA cell replacement is the same one that would benefit from DBS.

• The symptoms that would benefit from cell replacement are the same ones that would benefit from DBS (levodopa responsive symptoms).

• There is no evidence that the graft would be neuroprotective
AAV2-Neurturin (Cere-120) reverses parkinsonian signs in MPTP-Treated monkeys

![Graph showing the comparison of Mean Clinical Rating Score between CONTROL (n=5) and AAV-NTN (n=5) groups over 10 months. The graph indicates a statistically significant difference (*p<0.01-0.05) between the two groups from Month 3 onwards.](image)
Preservation of striatal dopamine by AAV2-Neurturin
Preservation of TH-ir nigral perikarya by AAV2-neurturin
Targeting Nigrostriatal Neurons With AAV-2 NTN

AAV2-NTN injected into terminal fields (putamen)

NTN-induced upregulation of DA terminals which induce clinical benefit

NTN expressed in putamen and transported to cell bodies in nigra to induce activation of repair genes
Change From Baseline in UPDRS (Part III) Motor Score “off” (Blinded data; N=30)

- ANCOVA model with a main effect for treatment group and baseline UPDRS Part III motor score in the practically defined off condition as covariate. Note: at 18 mos, 14 subjects have scores; therefore 16 subjects: LOCF

* p=0.025*
Cere-120-2-Right
NTN Staining in Putamen of PD Patient Following AAV2-NTN Gene Delivery

Bartus et al, Mov Disord 2011
Table 1

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Optical density of TH-ir putamenal neurons as a function of disease duration
Axonal Transport Defects in PD

Chu et al., Brain 2012
Targeting Nigrostriatal Neurons With AAV2-NTN in PD

- AAV2-NTN injected into terminal fields (putamen)
- Robust enhancement of DA axons and enhanced clinical benefit
- AAV2-NTN injected directly into SNc
Synuclein staining

Parkinson disease

Crohn’s disease

Control
Which PD cases get synuclein? All of them!!
Alpha synuclein

Parkinson’s

A

B

Nitro-tyrosine

Ulcerative Colitis

C

D

Aged-Matched Control

E

F
Case study

- 85-y/o woman
- Psychotic depression 2002 → ECT
- MCI
- Rest tremor 2/2010

- Colonic polyp biopsied 2005.

Shannon et al. Movement Disorders, 2012
Intestinal permeability in PD

24-hour sucralose excretion

*p=.013
LH-PCR PD gut microbiota
Induced Pluripotent Stem (iPS) Cells

- Transient expression of POU5F1, MYC, KLF4, SOX2
- Epigenetic reprogramming
- Selection of iPS cells?
- In vitro or in vivo differentiation?
- Drug or genetic screens
- Cellular studies (disease in vitro)
- Transplantation studies (disease in vivo)

iPS Cells + ESC

- Mesoderm (Middle Layer)
- Endoderm (Internal Layer)
- Ectoderm (External Layer)

- Cardiac Muscle
- Tubule Cell of the Kidney
- Smooth Muscle (In Gut)
- Lung Cell (Arenular Cell)
- Pancreatic Cell
- Skin Cells of Epidermis
- Neuron Cell
- Pigment Cell

Nat Med
Nat Meth
Sigma-Aldrich
PD-Patient Derived iPS-DA Neurons Reduce Motor Asymmetry in PD Rats

Hargus et al., PNAS 2010
FP-Derived Human DA Neurons in PD Monkey (3-Month)
ESC-Derived Human Dopamine Neurons in PD Monkey

Transplanted HESC-DA cell Retain Midbrain Morphology in MPTP Rhesus Monkey
Transplanted HESC-DA Cells Are Similar to Fetal VM Dopaminergic Phenotype
Transplanted HESC-DA Cells Express Midbrain Specific Transcription Factor FoxA2
FP-Derived Human DA Neurons in PD Monkey (3-Month)

Transplanted Human Cells Survive and Project Fibers in MPTP Rhesus Monkey
ESC-Derived Human Dopamine Neurons in PD Monkey

Transplanted Neurons Retain Dopaminergic Characteristics Up to 3-Months
Transplanted HESC-DA Cells Induce Host Immune Reaction in MPTP Rhesus Monkey
AGED MONKEYS AS A MODEL OF EARLY PD
Amphetamine-induced rotational behavior in rats of varying age and lesion duration after implantation of DA neuron grafts.

Representative ventral mesencephalic tissue grafts in rats of varying age and lesion duration.

**a**

- **Stochastic interaction between multiple factors**
- **PD (accelerated DA loss)**
- **Threshold for PD**

**b**

- **DA neuron dysfunction and death**
- **UPS dysfunction**
- **Unknown factors**
- **DA metabolism**
- **Compensatory mechanisms**
- **Inflammation**
- **Mitochondrial damage**
- **Oxidative and nitrative stress**

**Accelerants**
- Genetic predispositions
- Environmental toxins
- Cellular predispositions
- Prenatal infections
- Unknown factors
So where does cell replacement fit in the field of experimental therapeutics?

- Stem cell transplantations ultimate utility for PD may be a proof of principle for their ultimate use in other scenarios such as non-levodopa responsive and non-motor PD or in other neurodegenerative diseases (Huntington’s disease??).

- Great strides have been made in the viability and appropriate phenotypic expression of grafted cells but the need to improve the pace and extent of fiber outgrowth remains.

The absence of a need to rely on the host system may put cell replacement in a competitive advantage when compared to gene therapy and trophic factor approaches that replay in the presence of a viable host system.
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