

# Review of Parkinson's disease trials that did not include a sham neurosurgical arm: Fetal Cell Transplantation Trials for Parkinson's Disease

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Neuronal Survival Unit

[www.med.lu.se/expmed/nesu](http://www.med.lu.se/expmed/nesu)

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Sham Neurosurgical Procedures in Clinical Trials  
for Neurodegenerative Diseases:  
Scientific and Ethical Considerations

June 30 - July 1, 2010

Bethesda, USA, June 30th - July 1st, 2010

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# Disclosures

Co-founder of biotech company

Parkcell AB

(skin-derived cells for grafting in Parkinson's disease)

## **Declaration of potential conflicts of interest:**

### **Commercial interests**

Patent holder – ciclosporin for acute and neurodegenerative disorders

Senior Advisor and shareholder Neurovive AB, for ciclosporin

### **Advisory Boards or similar expert committees (current)**

Actelion AG, Zurich, Lundbeck AB Sweden, MedaiLink A/S,

### **Advisory Boards or similar expert committees (previous – non active)**

Orion Pharma Global, Orion Pharma Sweden, Boehringer+Ingelheim AB, Lundbeck, GSK , Medtronic

### **Ongoing clinical trials:**

NeuroNova AB, and Medtronic Inc for growth factor infusion in PD; Abbot AB, Duodopa Health Economy;

Michael J Fox Foundation and Psychogenics Inc, Anti-dyskinetic drugs; Lundbeck A/S observational study

Astra Zeneca AB, safety committee

### **Previous clinical trials**

Orion Pharma , Boehringer+Ingelheim AB, Lundbeck, GSK , Medtronic, Abbot, Neurosearch/ACResearch

### **Academically driven trials (non-commercial funding)**

Biomarker for Parkinson's disease and related disorders, fMRI in Huntington's Disease

TransEuro – neural tissue transplantation, Gene therapy in Parkinson's disease (planning phase)

### **Participation in sponsored events**

Boehringer+Ingelheim, GSK, Medtronic, Solvay, Orion Pharma, Lundbeck, UCB/Schwarz,

Roche, Sandoz, Astra Zeneca, Actelion

### **Previous Transplantation trials**

Member of the original group of 5 that translated neural tissue grafting to clinical trials

Responsible for: Immunosuppression and patient evaluation

MPTP-cases

Member of the CAPIT committee – core assessment programme for intracerebral transplantation and

CAPSIT – core assessment programme for surgical interventions and transplantation (EU-funded)

# NIH questions

- What factors were considered in deciding not to include a sham neurosurgical arm?
- What were the ethical considerations, and how did these impact the study design?
- What questions can be answered in the absence of a sham arm?
- Are there questions that can be answered only with the inclusion of a sham neurosurgical arm?
- Given the results of the subsequent trials, would you design the study differently to answer your original study questions?

# Overview of open label trials

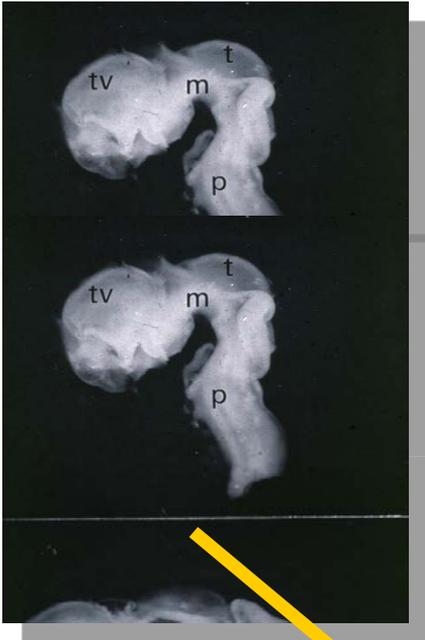
- Over 300 patients in several centers worldwide
- A minority reported in the scientific literature
- At least 40 original papers published in 1988-2010

# Themes for today's talk

- Overview of open label trials
- Lessons learnt from open label trials
- Ethical considerations

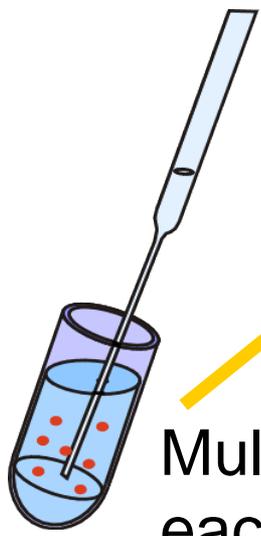
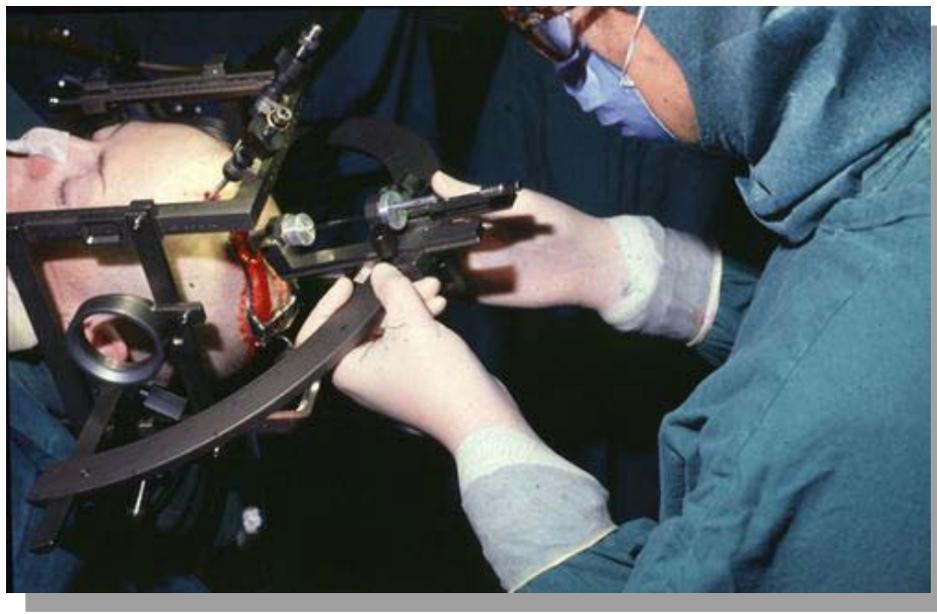


# 18 patients grafted in 1987-1999



Human donor tissue

Uni- or bilateral grafts in immunosuppressed patients



Multiple donors for each side of brain



# First formal report of success

**Grafts of Fetal Dopamine Neurons Survive and  
Improve Motor Function in Parkinson's Disease**  
**Science 1990**

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OLLE LINDVALL,\* PATRIK BRUNDIN, HÅKAN WIDNER, STIG REHNCRONA,  
BJÖRN GUSTAVII, RICHARD FRACKOWIAK, KLAUS L. LEENDERS, GUY SAWLE,  
JOHN C. ROTHWELL, C. DAVID MARSDEN, ANDERS BJÖRKLUND

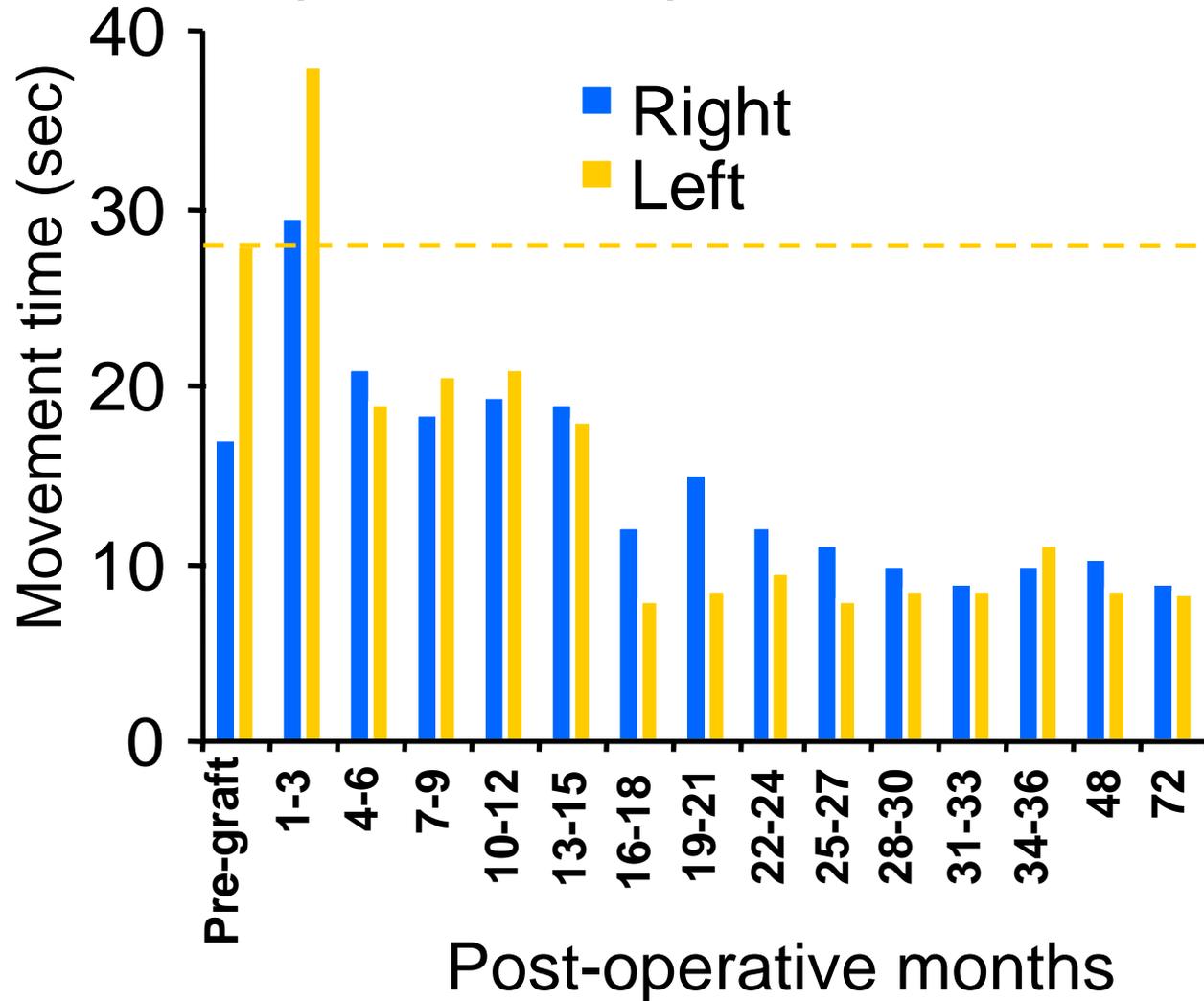
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Unilateral graft

Exploratory study with multiple  
outcome measures

# Timed test in Patient 4 (unilateral graft)

20 pronation/supinations with hand



**Graft effect, placebo  
effect or observer  
bias?**

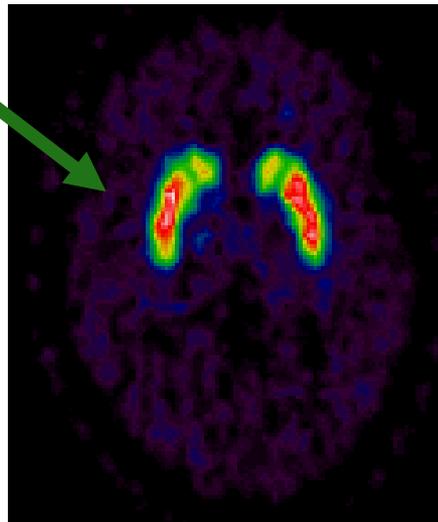
# Dopamine release from nigral transplants visualized *in vivo* in a Parkinson's patient

Nature Neuroscience 1999

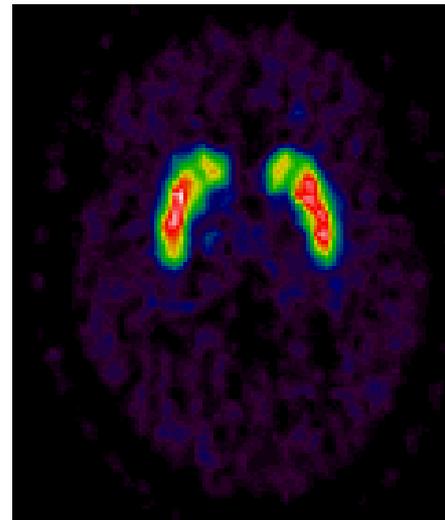
Paola Piccini<sup>1</sup>, David J. Brooks<sup>1</sup>, Anders Björklund<sup>2</sup>, Roger N. Gunn<sup>1</sup>, Paul M. Grasby<sup>1</sup>, Ornella Rimoldi<sup>1</sup>, Patrik Brundin<sup>3</sup>, Peter Hagell<sup>4,5</sup>, Stig Rehncrona<sup>6</sup>, Håkan Widner<sup>3,5</sup> and Olle Lindvall<sup>4,5</sup>

[<sup>11</sup>C]-Raclopride (D2) binding

Unilateral  
graft



Patient 4

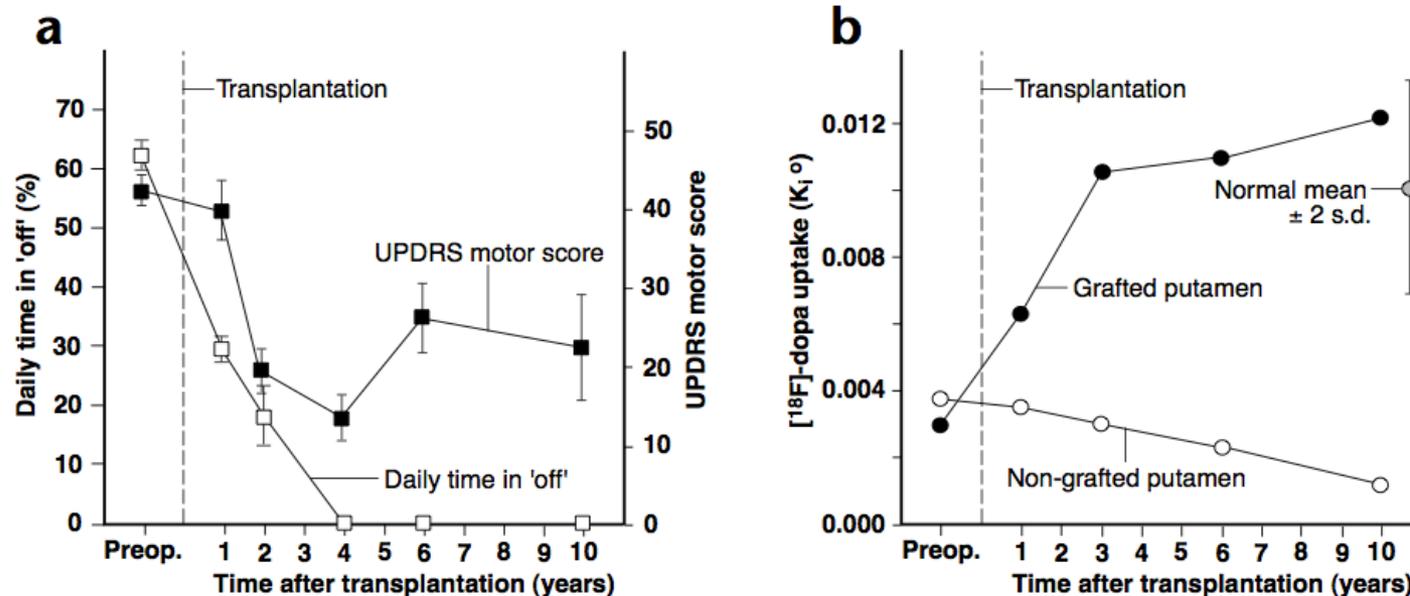


Normal subject

# Dopamine release from nigral transplants visualized *in vivo* in a Parkinson's patient

Nature Neuroscience 1999

Paola Piccini<sup>1</sup>, David J. Brooks<sup>1</sup>, Anders Björklund<sup>2</sup>, Roger N. Gunn<sup>1</sup>, Paul M. Grasby<sup>1</sup>, Ornella Rimoldi<sup>1</sup>, Patrik Brundin<sup>3</sup>, Peter Hagell<sup>4,5</sup>, Stig Rehncrona<sup>6</sup>, Håkan Widner<sup>3,5</sup> and Olle Lindvall<sup>4,5</sup>

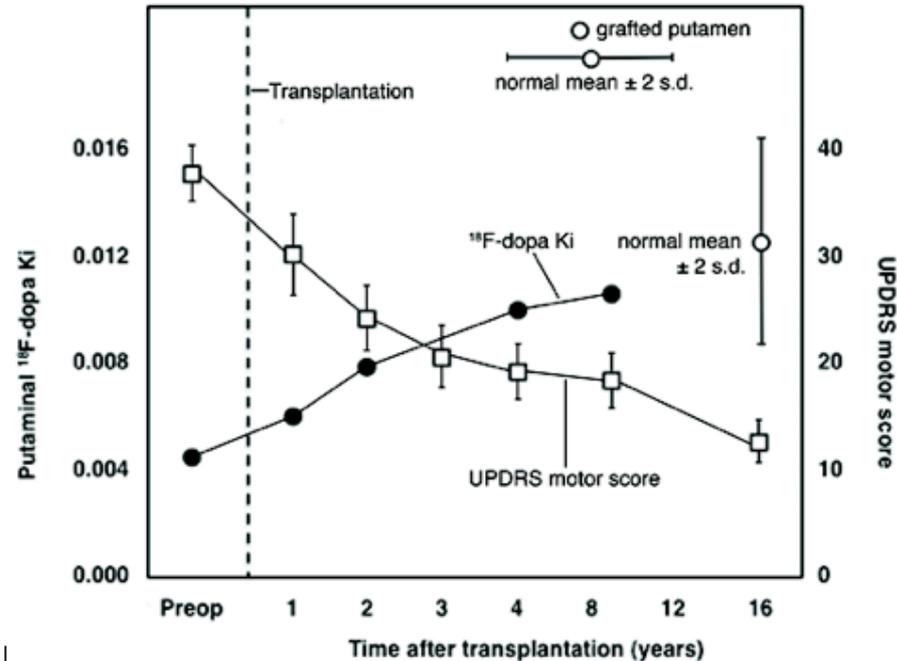


Effect even at 10 years post-surgery

# "Very" long-term outcome

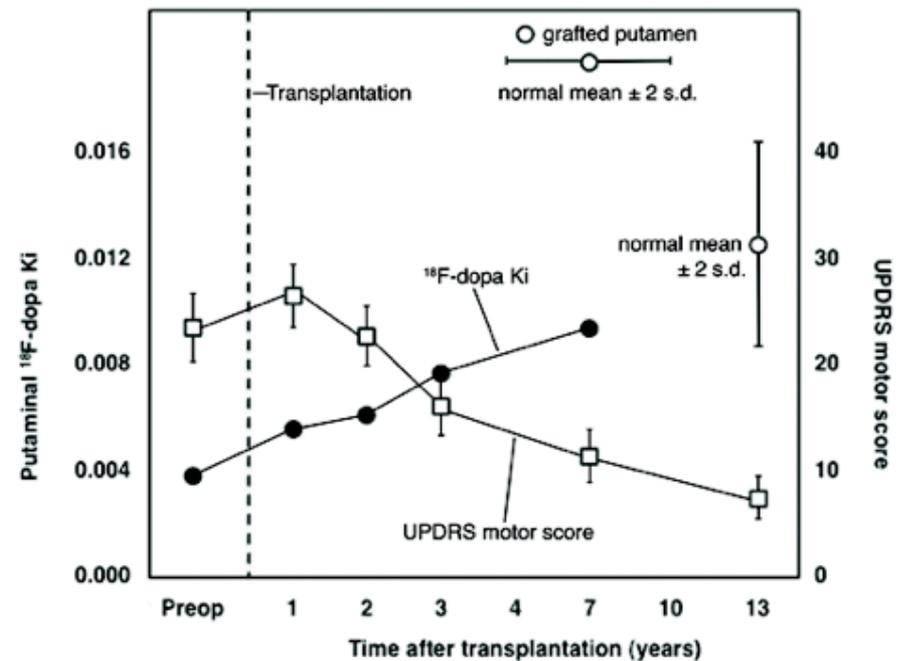
**A** % Reduction in  $^{11}\text{C}$ -RAC BP<sub>ND</sub>: Methamphetamine vs Placebo

20 22 24 26 28



**B** % Reduction in  $^{11}\text{C}$ -RAC BP<sub>ND</sub>: Methamphetamine vs Placebo

16 18 20 22 24 26 28



Published online today (Politis et al, 2010)

Placebo effect unlikely

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- Lessons learnt from open label trials
- Ethical considerations



# Lessons learnt from open label trials - 1

- Safety and tolerability (graft-related dyskinesias)
- Long delay before signs of improvement
- Improvement beyond one decade (including objective timed tests)

# Lessons learnt from open label trials - 2

- Brain imaging changes (unilateral grafts highly informative)
- Histological evidence for survival of grafted dopamine neurons
- Late development of Parkinson-like pathology in grafted neurons

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# Ethical issues 1986 did not consider a sham surgery arm

8. Etisk frågeställning (konkretisera Din egen värdering av den etiska problematiken).

Är det etiskt riktigt att använda nervceller tagna från foster, som aborterats helt oberoende av transplantationsverksamheten, för att utveckla en behandlingsmetod som skulle kunna hjälpa en stor grupp svårt sjuka Parkinson patienter? Uppläggningsen av Forskningsprojektet avser att följa de provisoriska etiska riktlinjer för användning av vävnad från foster i transplantationsverksamhet som antagits av läkar-sällskapets delegation för medicinsk etik (se Bilaga 1).

Ethical discussions focused on fetal tissue

Published by the **American Association for the Advancement of Science (AAAS)**, *Science* serves its readers as a forum for the presentation and discussion of important issues related to the advancement of science, including the presentation of minority or conflicting points of view, rather than by publishing only material on which a consensus has been reached. Accordingly, all articles published in *Science*—including editorials, news and comment, and book reviews—are signed and reflect the individual views of the authors and not official points of view adopted by the AAAS or the institutions with which the authors are affiliated.

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## NIH Neural Transplantation Funding

We view with considerable interest the funding of a program of neural transplantation recently announced by the National Institute of Neurological Diseases and Stroke (NINDS) of the National Institutes of Health (NIH). This is an encouraging development in support of an increasingly vigorous field of scientific endeavor.

The \$4.5-million NIH-NINDS grant is the first major award since the federal ban on fetal tissue research was lifted. It sup-

the outcome is unlikely to determine the optimal procedure for clinical application of neural transplantation as a treatment for Parkinson's disease.

The scientific community is acutely aware of the manifold difficulties in determining and developing an effective neural transplantation therapy. We earnestly plead that, in addition to the above study, NIH will also be seeking to explore other grafting protocols at the same time.

*Håkan Widner\**

*Department of Neurology,*

*University Hospital, S-221 85 Lund, Sweden*

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single center is to be assessed. Since transplantation techniques are still at an early stage of development, the optimal methods of tissue procurement, graft preparation, and implantation are not yet established. Consequently the results and implications

## Alloimmunization to Prevent AIDS?

In a recent letter, "Alloimmunization as an AIDS vaccine" (8 Oct., p. 161), Gene M.

**At what stage is a surgical technique sufficiently developed to merit testing in a randomized controlled trial?**