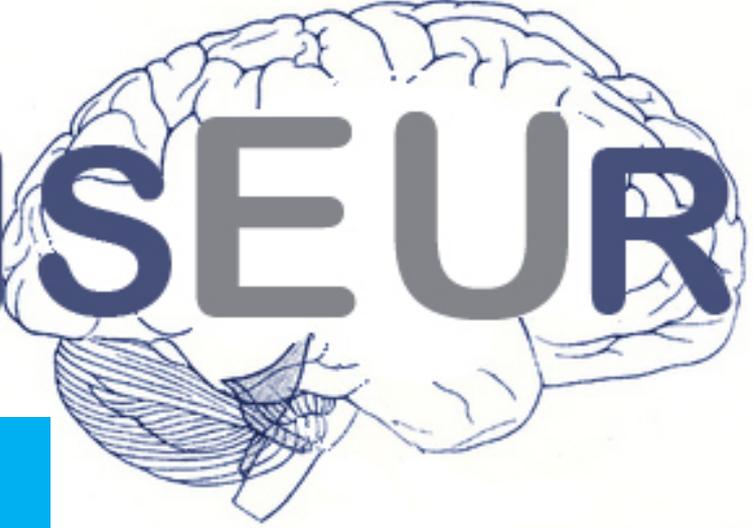


# TRANSEURO



Neural Transplantation in  
the treatment of patients  
with Parkinson's Disease

Dr Roger A Barker  
University of Cambridge, UK

**Financial Disclosure:** I sit on an advisory board of Teva-Lundbeck; I have also advised and received honorariums from Solvay; GSK; Eli-Lilly; and Pfizer. I receive grant support from Parkinson's UK; EU FP7 programme; NIHR; Michael J Fox Foundation, ARC and MRC. I receive royalties from Springer; Wiley and Cambridge University Press.

# Background TRANSEURO

- ▶ EU Seventh Framework Programme
- ▶ 5 years funding
- ▶ 13 partners involved from across Europe

## NORTH AMERICA

New York  
(Fahn/Eidelberg)  
Tampa (Freeman)  
Halifax and Harvard  
(Mendez/  
Robertson/  
Isacson)

UK  
Cambridge;  
Cardiff;  
London (Imperial; UCL)  
**CAMBRIDGE COGNITION  
INVITROGEN**

SWEDEN  
Lund

GERMANY  
Freiburg  
**INOMED**

FRANCE  
Paris  
**ECRIN**

AUSTRIA  
Vienna



**INSERM; Help with Trial ethics etc**

**DANDO & COLUCCI : Management of grant/consortium**

**Scientific Advisory board: Yoav Ben Shlomo; Andrew Lees; Clive Svendsen; Jeff Kordower**

**Ethical committee: Herbert Gottweiss; Ruth Chadwick; Alasdair Coles; Jasper Bovenberg**

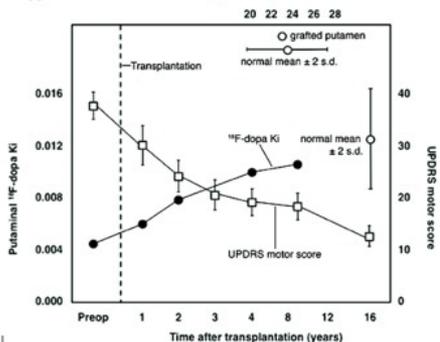
**Trial Monitoring Committee: Werner Poewe; Eduardo Tolosa; Gilles Defer; Marc Levivier**

## The history of TRANSEURO:

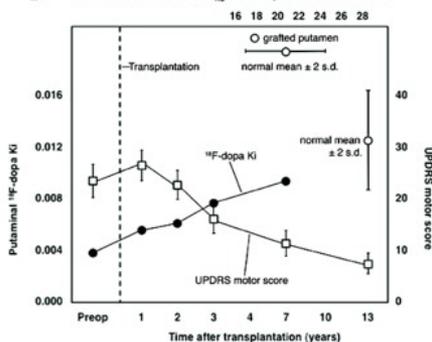
- Late 1980s/1990s- Open label studies of VM grafting in patients with PD showed efficacy.
  - 2001 and 2003- Two double blind VM transplant trials in PD fail primary end points and in addition many patients developed GIDs.
  - MORATORIUM ON FURTHER TRIALS whilst a re-examination of the field was undertaken.
  - NECTAR 2005- Discussion with Anders on relaunching the work.
  - May 2006- first of many workshops discussing available VM transplant trial data and way forward.
  - 2006-2009- PDS supported meetings of International working group on Cell therapies for PD.
  - December 2008- FP7 bid TRANSEURO submitted.
  - April 2009- TRANSEURO awarded.
  - January 2010- TRANSEURO starts.
- 

# WHY DO A NEW TRIAL?

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



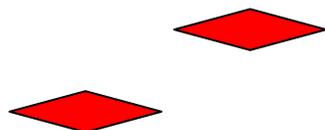
B % Reduction in  $^{11}\text{C}$ -RAC BP<sub>ND</sub>: Methamphetamine vs Placebo



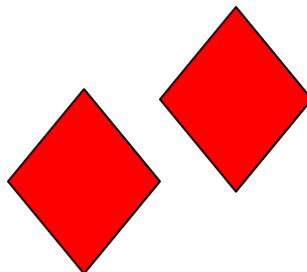
BECAUSE IT WORKS BUT NEED TO..

TO OPTIMISE THE PROCESS OF CELL DELIVERY TO MAKE GRAFTING EFFECTS MORE CONSISTENT.

Big effect with small variance then n can be small



Big effect with large variance then when n is small highly likely to have a Type II error



AVOID or MINIMISE GRAFT INDUCED DYSKINESIAS

AND DEVELOP A PROCESS TO FACILITATE STEM CELL DELIVERY AS A THERAPEUTIC OPTION IN THE CLINIC..

1. To establish and conduct a small open label study of fetal ventral mesencephalic transplants to patients with early PD;
2. To establish and conduct a larger double blind placebo controlled study of fetal ventral mesencephalic transplants to patients with early PD using imitation surgery and best medical therapy;

# TRANSEURO SCHEMA OF WORK OVER THE NEXT 5 YEARS

## CLINICAL TRIALS

Optimise the dissection and storage of tissue

2010

Patient selection:  
Younger;  
<10 years duration;  
Minimal LIDs;

2012

Open label study  
N=20  
2 years with safety  
end-point

2014

Double blind  
placebo control study  
comparing  
transplants in patients  
with early PD  
and  
best medical therapy  
versus  
imitation surgery and  
best medical therapy  
(N=60)

ASSUMING THAT FIRST TRIAL  
HAS GIVEN DATA FOR  
POWER CALCULATION THAT  
CAN BE USED TO DESIGN THIS  
NEW STUDY ADEQUATELY

Modelling and  
minimising  
the induction of  
Graft induced  
dyskinesias

EXPERIMENTAL WORK

# TRANSEURO SCHEMA OF WORK OVER THE NEXT 5 YEARS

## CLINICAL TRIALS

Optimise the dissection and storage of tissue

2010

Patient selection:  
Younger;  
<10 years duration;  
Minimal LIDs;

2012

Open label study  
N=20  
2 years with safety  
end-point

2014

Double blind  
placebo control study  
comparing  
transplants in patients  
with early PD  
and  
best medical therapy  
versus  
imitation surgery and  
best medical therapy  
(N=60)

ASSUMING THAT FIRST TRIAL  
HAS GIVEN DATA FOR  
POWER CALCULATION THAT  
CAN BE USED TO DESIGN THIS  
NEW STUDY ADEQUATELY

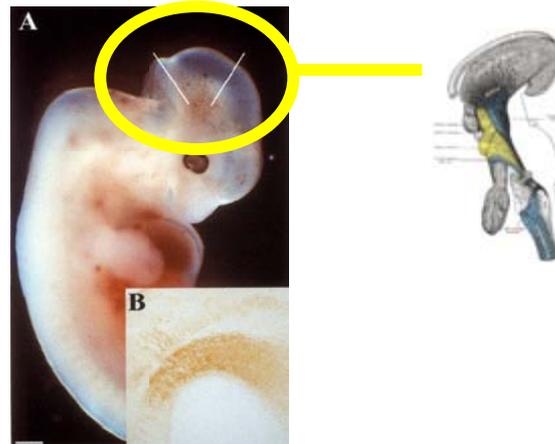
Modelling and  
minimising  
the induction of  
Graft induced  
dyskinesias

EXPERIMENTAL WORK

# 1. TISSUE PREPARATION

NEED TO OPTIMISE THE NUMBER OF SURVIVING NIGRAL DOPAMINE CELLS by:

- Using "right" number of fetuses;
- Consistent preparation of tissue with defined dissection;
- Minimising the immune reaction to that tissue through adequate immunotherapy



DEFINE ROLE OF NON-NIGRAL CELLS AND/OR MINIMISE THEIR NUMBERS IN THE VM GRAFT, especially with respect to:

- 5HT neurons- a role in GIDs;
- Other neurons +/- glia

SO NEED TO ENSURE ENOUGH FETAL MATERIAL CAN BE ADEQUATELY PREPARED (sTOP v mTOP tissue; Dissection defined; Storage defined with GMP reagents and maximal hibernation period for tissue etc), and MAINTAINED POST GRAFTING (Immunosuppression of adequate duration)

# TRANSEURO SCHEMA OF WORK OVER THE NEXT 5 YEARS

## CLINICAL TRIALS

Optimise the dissection and storage of tissue

2010

Patient selection:  
Younger;  
<10 years duration;  
Minimal LIDs;

2012

Open label study  
N=20  
2 years with safety  
end-point

2014

Double blind  
placebo control study  
comparing  
transplants in patients  
with early PD  
and  
best medical therapy  
versus  
imitation surgery and  
best medical therapy  
(N=60)

ASSUMING THAT FIRST TRIAL  
HAS GIVEN DATA FOR  
POWER CALCULATION THAT  
CAN BE USED TO DESIGN THIS  
NEW STUDY ADEQUATELY

Modelling and  
minimising  
the induction of  
Graft induced  
dyskinesias

EXPERIMENTAL WORK

## 2. PATIENT SELECTION- choose right "subtype" of disease at right stage of disease

Young; non PIGD; Normal semantic fluency; good pentagon drawing but may have subtle executive deficits at PRESENTATION

"Subtle" fronto-striatal cognitive impairment but "LOCALISED" NIGRAL pathology

..and earlier in disease course because...

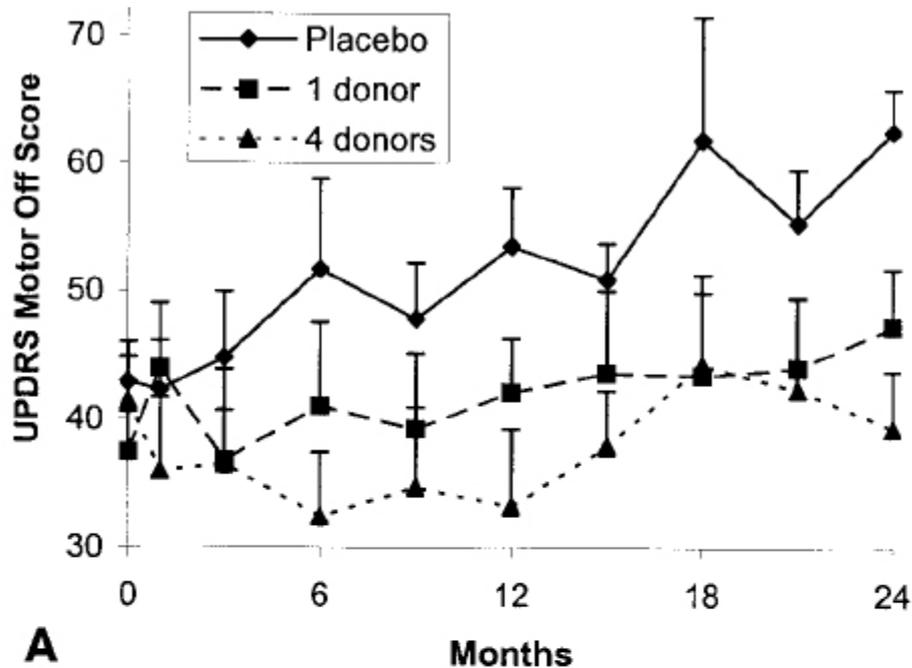
Old; PIGD; Poor semantic fluency; poor pentagon drawing at PRESENTATION with specific tau haplotype +/-synuclein polymorphism

Posterior cortical impairment and "WIDESPREAD" pathology throughout CNS with accelerated LB formation



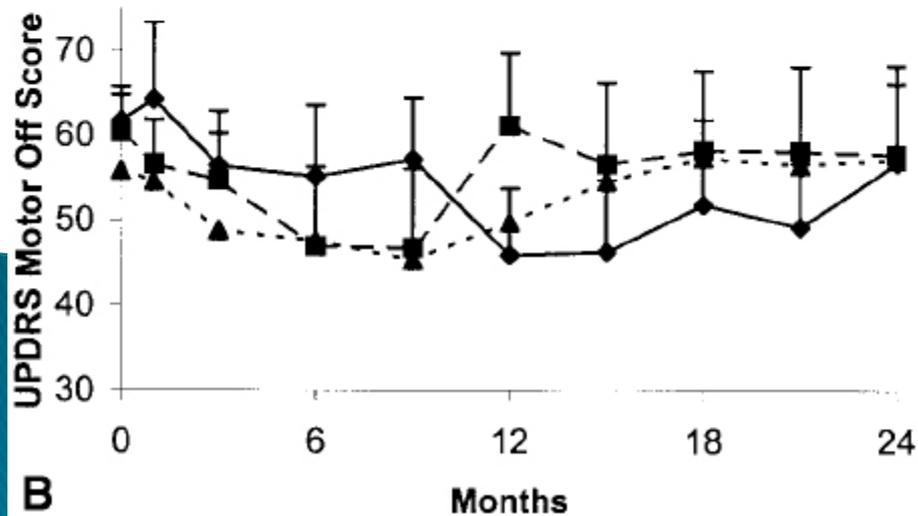
Dementia

Foltynie et al Brain 2004; Williams- Gray CH et al, J.Neurosci.2007; Brain 2007, Brain 2009; Goris et al. Ann.Neurol. 2007



UPDRS "off"score of <49  
(overall treatment effect;  
 $p < 0.006$ )

And experimentally  
"GIDs" only seen in  
animals that have  
been primed with  
LIDs...AND..



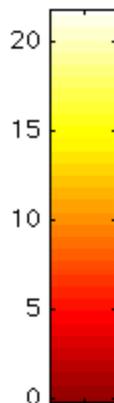
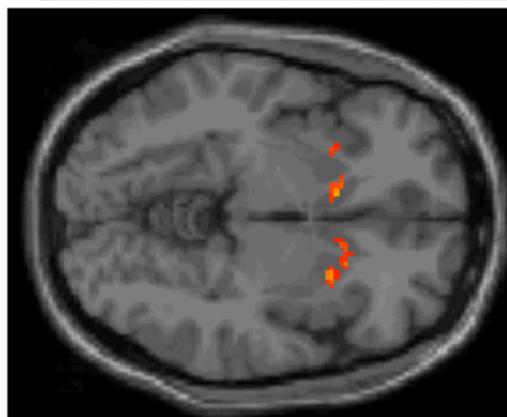
UPDRS "off"score of >49  
(overall treatment effect;  
n.s.)

# Factors affecting the clinical outcome after neural transplantation in Parkinson's disease

Paola Piccini,<sup>1</sup> Nicola Pavese,<sup>1</sup> Peter Hagell,<sup>3,4</sup> Jan Reimer,<sup>3</sup> Anders Björklund,<sup>5</sup> Wolfgang H. Oertel,<sup>6</sup> Niall P. Quinn,<sup>2</sup> David J. Brooks<sup>1</sup> and Olle Lindvall<sup>3</sup>



**Those patients who did least well following fetal VM transplants had dopaminergic denervation involving ventral striatum at baseline**

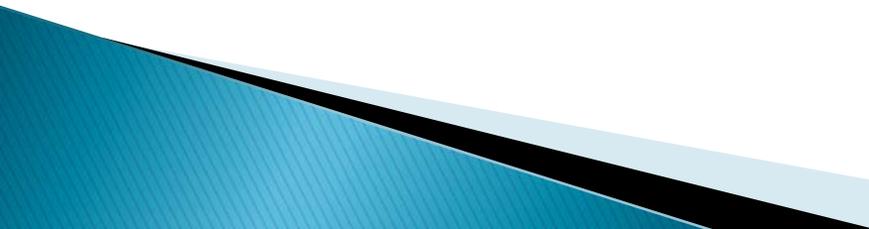


**AND EARLIER IN DISEASE COURSE BEFORE STRIATAL DOPAMINE PATHOLOGY IS TOO EXTENSIVE**

→ <sup>18</sup>F-dopa uptake reductions in ventral striatum and midbrain

Brain. 2005

# Inclusion Criteria

- ▶ PD as defined using PDSUKBB criteria.
  - ▶ Disease duration  $\geq 2$  years and  $\leq 10$  years.
  - ▶ Aged  $\geq 30$  years and  $\leq 65$  years at the time of recruitment.
  - ▶ Hoehn & Yahr stage 2.5 or better when 'on'.
  - ▶ Treatment is allowed but must NOT have significant Levo-dopa induced dyskinesias.
  - ▶ F-DOPA PET showing loss restricted to dorsal striatum
- 

# TRANSEURO SCHEMA OF WORK OVER THE NEXT 5 YEARS

## CLINICAL TRIALS

Optimise the dissection and storage of tissue

2010

Patient selection:  
Younger;  
<10 years duration;  
Minimal LIDs;

2012

Open label study  
N=20  
2 years with safety  
end-point

2014

Double blind  
placebo control study  
comparing  
transplants in patients  
with early PD  
and  
best medical therapy  
versus  
imitation surgery and  
best medical therapy  
(N=60)

ASSUMING THAT FIRST TRIAL  
HAS GIVEN DATA FOR  
POWER CALCULATION THAT  
CAN BE USED TO DESIGN THIS  
NEW STUDY ADEQUATELY

Modelling and  
minimising  
the induction of  
Graft induced  
dyskinesias

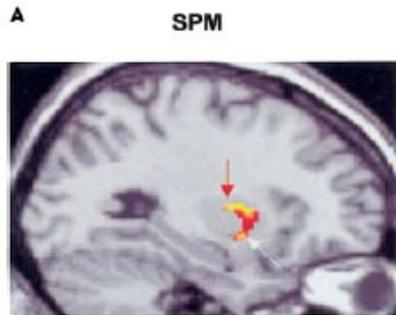
EXPERIMENTAL WORK

# 3. TISSUE DELIVERY

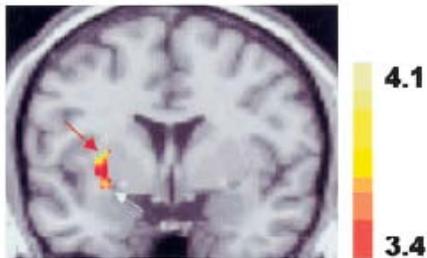
## Dyskinesia after Fetal Cell Transplantation for Parkinsonism: A PET Study

Yilong Ma, PhD,<sup>1,2</sup> Andrew Feigin, MD,<sup>1,2</sup> Vijay Dhawan, PhD,<sup>1,2</sup> Masafumi Fukuda, MD,<sup>1</sup> Qiuhu Shi, PhD,<sup>3</sup> Paul Greene, MD,<sup>4</sup> Robert Breeze, MD,<sup>5</sup> Stanley Fahn, MD,<sup>4</sup> Curt Freed, MD,<sup>6</sup> and David Eidelberg, MD<sup>1,2</sup>

**SO NEED TO ENSURE GRAFTED MATERIAL IS EVENLY DISTRIBUTED ACROSS TRANSPLANTED STRIATUM using delivery system of Ivar Mendez**

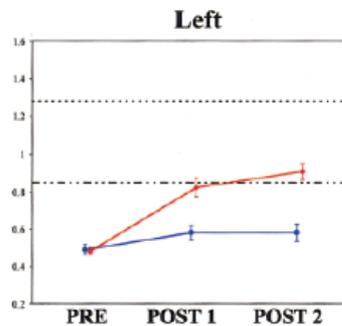


**x = - 28 mm**

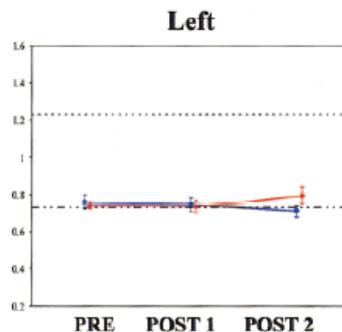
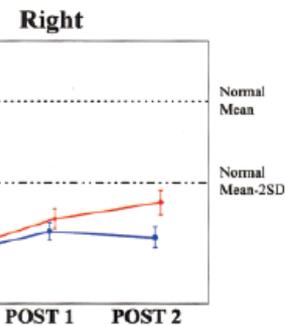


**y = 2 mm**

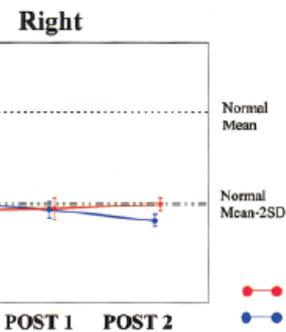
**p < 0.001 (corrected)**



**Putamen**



**Caudate**



● DYS (+) n=5  
● DYS (-) n=12

Patients with PD (n=150) followed every 6 months  
With  
LONGITUDINAL FOLLOW UP

Phase 1 study with  
20 patients  
OPEN LABEL

Second study with  
60 patients  
DOUBLE BLIND  
PLACEBO

**ASSESSMENTS:**

**MOTOR** including timed motor tasks;  
**COGNITIVE** inc CANTAB;  
**PSYCHIATRIC**;  
**IMAGING**

**BUT THIS STUDY IS  
DEPENDENT ON DATA  
FROM THE FIRST TRIAL  
AND WILL BE AN  
ITERATIVE PROCESS**

# PLANNED SECOND STUDY...dependent on outcome of first open label study..

## Primary Outcome

- ▶ The change in motor UPDRS in a defined "OFF" period at 2 years. Off being defined as receiving no DA therapy for 24 hours prior to assessment or longer in the case of long acting dopamine agonists.

## Secondary Outcome

- ▶ Safety and feasibility as assessed using standard surgical, neurological, psychiatric and psychometric testing including the incidence and severity of "off"/ graft induced dyskinesias
- ▶ The number of patients with dyskinesias (including troublesome and graft induced dyskinesias) at 2 years post intervention.
- ▶ Number of patients on L-dopa therapy at 2 years.
- ▶ The amount of off time 2 years after surgical intervention.
- ▶ Quality of life as assessed by PDQ-39 and calculated "overall outcome changes" 2 years after surgical intervention.
- ▶ Changes in F-DOPA PET scanning in grafted patients 2 years post grafting
- ▶ Changes in cognitive and affective deficits along with novel tests from WP2 in grafted patients 2 years post grafting.

# TRANSEURO SCHEMA OF WORK OVER THE NEXT 5 YEARS

## CLINICAL TRIALS

Optimise the dissection and storage of tissue

2010

Patient selection:  
Younger;  
<10 years duration;  
Minimal LIDs;

2012

Open label study  
N=20  
2 years with safety  
end-point

2014

Double blind  
placebo control study  
comparing  
transplants in patients  
with early PD  
and  
best medical therapy  
versus  
imitation surgery and  
best medical therapy  
(N=60)

ASSUMING THAT FIRST TRIAL  
HAS GIVEN DATA FOR  
POWER CALCULATION THAT  
CAN BE USED TO DESIGN THIS  
NEW STUDY ADEQUATELY

Modelling and  
minimising  
the induction of  
Graft induced  
dyskinesias

EXPERIMENTAL WORK

Template for future  
novel therapies in PD

Future stem cell  
based  
studies