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.
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

- **FRANCE**
  - Paris
  - ECRIN

- **GERMANY**
  - Freiburg

- **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?

BECAUSE IT WORKS BUT NEED TO..

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

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

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

EXPERIMENTAL WORK

Optimise the dissection and storage of tissue

Modelling and minimising the induction of Graft induced dyskinesias
TRANSEURO SCHEMA OF WORK OVER THE NEXT 5 YEARS

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

EXPERIMENTAL WORK

Optimise the dissection and storage of tissue

2010

Modelling and minimising the induction of Graft induced dyskinesias

2012

CLINICAL TRIALS

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
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

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

EXPERIMENTAL WORK

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

CLINICAL TRIALS

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
Two types of patient selection are discussed:

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

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

```
“Subtle” fronto-striatal cognitive impairment
but “LOCALISED” NIGRAL pathology

And earlier in disease course because...
```

---

Dementia

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.)

Olanow et al 2003
Factors affecting the clinical outcome after neural transplantation in Parkinson’s disease

Paola Piccini, Nicola Pavese, Peter Hagell, Jan Reimer, Anders Björklund, Wolfgang H. Oertel, Niall P. Quinn, David J. Brooks and Olle Lindvall

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

$^{18}$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 Levodopa induced dyskinesias.
- F–DOPA PET showing loss restricted to dorsal striatum.
TRANSEURO SCHEMA OF WORK OVER THE NEXT 5 YEARS

**EXPERIMENTAL WORK**

- Optimise the dissection and storage of tissue

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

- Modelling and minimising the induction of Graft induced dyskinesias

**CLINICAL TRIALS**

- 2010

- 2012

- 2014

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

- 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
SO NEED TO ENSURE GRAFTED MATERIAL IS EVENLY DISTRIBUTED ACROSS TRANSPLANTED STRIATUM using delivery system of Ivar Mendez
Patients with PD (n=150) followed every 6 months with longitudinal follow up.

Assessments:
- Motor including timed motor tasks;
- Cognitive inc CANTAB;
- Psychiatric;
- Imaging

Phase 1 study with 20 patients open label.

Second study with 60 patients double blind placebo.

But this study is dependent on data from the first trial and will be an iterative process.
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

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

Future stem cell based studies

Template for future novel therapies in PD

EXPERIMENTAL WORK

Optimise the dissection and storage of tissue

Modelling and minimising the induction of Graft induced dyskinesias

CLINICAL TRIALS

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

Future stem cell based studies