Fetal Cell Transplantation For PD Trials with a Sham Neurosurgical Arm

C. Warren Olanow, MD, FRCPC
Professor of Neurology and Neuroscience
Chairman Emeritus, Department of Neurology
Mount Sinai School of Medicine
New York, NY
Conflict of Interest

- Consultant
  - Teva/Lundbeck
  - Novartis/Orion
  - Abbot/Solvay
  - Merck/Schering Plough
  - Ceregene
  - Pharm2B
  - GSK

- Stock/Options
  - Ceregene
  - Clintrex
Double Blind Sham-Controlled Trials of Dopaminergic Transplantation in PD

- Fetal nigral transplantation
  - Freed et al, NEJM
- Fetal nigral transplantation
  - Olanow et al, Ann Neurol
- Fetal porcine nigral transplantation
  - Unpublished
- Spheroids (retinal pigmented epithelial cells)
  - Unpublished
## Open Label vs Double Blind Trials

### Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Open Label Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal nigral (Freed)</td>
<td>Positive</td>
</tr>
<tr>
<td>Fetal nigral (Olanow)</td>
<td>Positive</td>
</tr>
<tr>
<td>Fetal porcine nigral</td>
<td>Positive</td>
</tr>
<tr>
<td>Spheramine</td>
<td>Positive</td>
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## Open Label vs Double Blind Trials

### Efficacy

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<thead>
<tr>
<th></th>
<th>Open Label Trials</th>
<th>Double-Blind Trials</th>
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<tbody>
<tr>
<td>Fetal nigral (Freed)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
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<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Fetal Nigral Transplant – Open Study
% Improvement in Total UPDRS “OFF”

Hauser et al, Arch Neurol, 1999
Fetal Nigral Transplant Open Label Study  FD-PET Studies

Pre-Transplant  Post-Transplant
TH Staining of Transplanted and Non-Transplanted Regions of Striatum

Non-Transplanted Region

Transplanted Region

Kordower et al, NEJM 1995
Fetal Nigral transplant Study

$\Delta$ UPDRS Motor Off ± SE

Baseline Adjusted Mean Change in UPDRS Motor Off

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>1 Donor</th>
<th>4 Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change</td>
<td>9.4</td>
<td>3.5</td>
<td>-0.72</td>
</tr>
<tr>
<td>Overall P value</td>
<td>P = 0.240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 donor vs placebo</td>
<td>P = 0.334</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 donors vs placebo</td>
<td>P = 0.096</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 donors vs 1 donor</td>
<td>P = 0.479</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Olanow et al, Ann Neurol 2003
Porcine Fetal Nigral Transplantation
Open Label Trial

% Improvement in Total UPDRS Score

Months Post Transplant

n = 10
Spheramine
Mean UPDRS Motor Scores

UPSRS Mean Motor Scores

ON
OFF

Baseline 6 12 18 24

Months Post Treatment

Watts et al
# Open Label vs Double Blind Trials

## Adverse Events

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Fetal nigral</td>
<td></td>
</tr>
<tr>
<td>Off-med dyskinesia</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Fetal nigral porcine</td>
<td></td>
</tr>
<tr>
<td>Toxic encephalopathy</td>
<td>Not Reported</td>
</tr>
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<td>Spheramine</td>
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<td>Venous infarction</td>
<td>Not Reported</td>
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# Open Label vs Double Blind Trials
## Adverse Events

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<th>Double blind trials</th>
</tr>
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<tr>
<td>Fetal nigral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Off-med dyskinesia</td>
<td>Not Reported</td>
<td>Up to 56% of cases</td>
</tr>
<tr>
<td>Fetal nigral porcine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic encephalopathy</td>
<td>Not Reported</td>
<td>1 case</td>
</tr>
<tr>
<td>Spheramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous infarction</td>
<td>Not Reported</td>
<td>Multiple cases</td>
</tr>
</tbody>
</table>
Off-Medication Dyskinesia – Off State

# 34
24-month visit
OFF meds
NIH Specified Issues

- Factors We Considered in Deciding to Include a Placebo Arm
- Safety Assessments
- Ethical Considerations
- Would you design Trial Differently
- Did studies fail because of type II error
Use of placebo surgery in a controlled trial of a cellular-based therapy for Parkinson’s disease

Freeman TB, Vawter DE, Leaverton PE, Godbold JH, Hauser RA, Goetz CG, Olanow CW

New Eng J Med 1999; 341: 988-992
Factors Considered in Inclusion of Placebo Arm

- Unreliability of open label studies
  - Placebo
  - Physician bias

- Feasibility of performing double blind, sham-controlled, surgical trials
  - Perform surgery at remote site
  - Script surgical procedure
  - Anesthesia for all patients
  - Partial thickness burr hole
  - Separate treating and evaluating investigators
  - Independent, neurology/neurosurgery team to manage complications
Factors to consider in double blind placebo controlled surgical trial

- Study must address an important question
- There must be evidence to suggest that the intervention is effective
- Risk:reward ratio must be acceptable
- Efforts should be made to minimize risks for sham-treated patients
- Procedures must be in place to "blind" both subjects and investigators
- Study design should be sufficiently rigorous to assure that it will answer the research question

Olanow, Arch Neurol, 2004
Factors to consider in justifying double blind placebo controlled surgical trial

- Informed consent must be rigorously addressed
  - Informed consent should clearly identify all of the risks of participation in the study.
  - Subjects should fully understand the purpose, procedures, risks, and benefits of the trial, and must be advised of alternative therapies.
  - Informed consent must be approved by IRB and appropriate regulatory agencies

- Ethicist was active member of steering committee

Olanow, Arch Neurol, 2004
How Did Sham Arm Help in Efficacy Assessments

- Demonstrated lack of efficacy of the transplant protocol that we employed
  - Suggested open label assessments compromised by effects of placebo and physician bias
- Without double blind studies, these procedure might now be widely performed based on the results of open label studies
How Did Sham Arm Help in Safety Assessments

- Identified adverse events not reported in open label trials
  - Fetal nigral transplant - Off medication Dyskinesia
  - Fetal porcine nigral transplant – toxic encephalopathy
  - Spheramine – venous infarction

- No clinically significant adverse events related to surgical or experimental intervention reported in placebo patients who underwent a sham-control procedure
Did studies fail because of Type II Error

- Type II error unlikely because, In comparison to Open label trials
  - Entry criteria were the same
  - Transplant protocol was the same
  - Variability at baseline was no greater
  - Sample size was larger
Future Phase II/III Transplant Trials

- Would use double blind sham-controlled trial
- Younger patients
- Milder patients
- Patients with relatively pure dopamine lesion – avoid patients with clinically significant non-dopaminergic problems (e.g. dementia and postural instability)
- Immunosuppression throughout duration of trial
Future Phase I Transplant Trials

- Larger sample size (approx 12)
- Staged recruitment (2 pts at a time)
- Randomized control group
  - Best medical treatment or DBS
- Blinded evaluators
  - Separate from treatment investigator
  - Gown patients to mask surgical procedure
  - Blinded randomized video assessment
The double-blind placebo controlled trial is the “gold standard” for the assessment of a new intervention.
Physicians must demand the same high standards of science for new operations as we do for new medicines. The alternative is uncontrolled human experimentation...

David A. Grimes, 1993
The methods to assess surgical technologies are well accepted and widely available; what remains to be seen is whether we as a profession have the moral courage to use them.

David A. Grimes, 1993