

Cell Based Therapy Round Table - Call to Action

9:00 am – 10:00 am Conrad Ballroom

Stem cell transplantation in PD *

- Strategy based on hypothesis that DA neurons can be used to replace the depleted midbrain DA neurons
- Over the past 35 years, pre-clinical experiments and human trials provided proof of principle that grafted DA neurons can in principle
- a) survive transplantation,
- b) re-innervate the lesion in the midbrain
- c) improve symptoms.

Historical overview on human fetal \mathcal{P} transplantation in PD

- Early open-label trials in Europe and the US showed substantial clinical improvement in some patients receiving fetal cell transplants
- Interpretation of the functional improvements seen in these open-label studies has been questioned because placebo effects and/or natural history of some mild forms of PD

Clinical trials for Human fetal transplantation in PD failed



Denver-Columbia trial: improvement did not reach significance.

- Human fetal midbrain tissue was cultured for up to 4 weeks, less tissue was implanted than in the previous open-label trials, and no immunosuppressive treatment was given.
- In two patients who died after grafting, the number of surviving dopaminergic neurons in each putamen was less than half of what had previously been obtained in functional grafts in the open-label trials.
- <u>Tampa–Mount Sinai trial</u>: primary endpoint not met no significant group differences in motor scores at 24 months.
- Solid pieces of human fetal midbrain tissue from one or four donors were implanted.
- Immunosuppressive treatment, with cyclosporine only, was given for six months after surgery and patients were followed for two years.

Severe side-effects: graft-induced dyskinesia (GID)



- In both trials, a significant number of transplanted patients developed severe graftinduced dyskinesias persisted even after withdrawal of L-dopa medication.
- Such dyskinesias have also been observed in open-label studies.
- Side-effects appeared during the second year in the Denver–Columbia trial and after 6–12 months in the Tampa–Mount Sinai trial.

Extremely variable clinical outcome \mathcal{P} of transplantation

- Clinical improvement has been highly variable between different trials but also within groups of PD patients transplanted at the same center.
- In the Lund program (Sweden), some patients have shown an excellent response, with 40–60% improvement, whereas others have shown little or no benefit.

Long-term outcome of fetal transplants \mathcal{P} setback for transplantation in PD

- 8 patients from three groups who received human fetal midbrain tissue transplants 9-16 years earlier for PD.
- In two of the studies, the grafted midbrain neurons were found to have Parkinson's like pathology.
- Any benefits accrued from the transplanted tissue are temporary and the same pathology that drives the progression of PD affects the graft in a similar manner.
- Conclusion "the transplantation of dopamine neurons into human beings has not yet been optimized."

Summary of different stem cells for potential therapeutic applications





Human embryonic stem cells



- Tumor induction after transplantation
- •Cell survival in host brain, immunsuppression?
- •Standardized preparation of dopaminergic cells
- Ethical concerns

Human fetal neuronal precursor cells



Pitfalls and Concerns:

- •Cell survival in host brain, immunsuppression?
- •Standardized preparation of dopaminergic cells
- Ethical concerns

Human bone marrow cells for transplantation





Pitfalls and Concerns:

- •Cell survival in host brain
- •Standardized preparation of dopaminergic cells
- Long-term commitment to dopaminergic phenotype?



Innovative Approach for the Treatment of Parkinson's Disease



The principal goals of Transeuro are:



To show that the consistency and efficacy of dopaminergic cell replacement in Parkinson's disease can be improved by careful attention to tissue preparation and delivery, patient selection and immunosuppressive treatment





To show that dopaminergic cell replacement can be clinically efficacious in the absence of any troublesome off-state dyskinesias in clinical trials of fetal ventral mesencephalic transplants in patients with mild Parkinson's disease

To develop a protocol that can serve as a template for all future clinical trials in the cell therapy field including stem cell-based therapies and the ethical implications and ramifications of such work.

International Society for Stem Cell Research Patient Information

