Regenerative Therapies: What is New?

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OVERVIEW

• Regenerative therapies in Parkinson’s disease: a brief survey
• Lessons learned from completed clinical trials
• A critical look at current efforts in developing regenerative therapeutics for Parkinson’s disease
• Future directions
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• Future directions
Neuroregeneration and PD

• Neurotrophic factor infusions
  • GDNF
  • RET signaling
  • Neurturin

• Gene therapy to program production of neurotrophic factors

• Current efforts in cell therapy
  • Cell replacement therapy
  • The regenerative secretome

Rationale for current dopamine cell replacement strategies

• Characteristic motor features arise largely due to loss of dopamine neurons from the substantia nigra

• Despite phenotypic and genetic heterogeneity, a common feature of PD is a clinical response to restoring striatal dopamine receptor stimulation

• Oral therapeutics provide insufficient long term benefit and can lead to motor complications of therapy

11C PE2i uptake in (A) control and (B) PD.  

Sarva and Henchcliffe - Restoring Function to Dopaminergic Neurons: Progress in the Development of Cell-Based Therapies for Parkinson's Disease. CNS Drugs (2020) 34:559-577
The Mainstay of Current Approaches


Figure 1. In the normal brain, DA neurons located in the substantia nigra send their axons to the striatum (i.e., the putamen and caudate nucleus). In the PD brain, the main pathology leading to motor symptoms is a degeneration of these neurons causing a loss of DA in the striatum. Transplantation of embryonic mesencephalic tissue, which is rich in DA neuroblasts, or of DA neuroblasts generated from stem cells aims to restore striatal dopaminergic innervation thereby alleviating PD symptoms.
Replacing Lost Cells: Running the Numbers

- The human substantia nigra contains about 500,000 dopamine containing neurons
- About 250,000 project to the putamen
- May not need to replace all these
  - individuals with PD don’t develop motor symptoms until at least 50% dopamine cells are lost
- <5-10% cells survived transplantation in early transplant studies

# Cell Sources for Transplant: Past

<table>
<thead>
<tr>
<th>Tissue source</th>
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| Human embryonic ventral mesencephalic (hEVM) tissue fragments/cell suspension - isolated by dissection at time of elective termination of pregnancy | Progenitor cells for A9 dopamine neurons  
Differentiate and functionally innervate striatum | Also contains serotonin neuron progenitors, vascular elements, other  
Needs evaluation for infectious agents                                                |
| Porcine EVM cell suspension                                                  | Same as human                                                                        | Same as human                                                                                |
| Adrenal medullary tissue fragments (autologous) - adrenalectomy at time of transplant | Neuroendocrine chromaffin cells proposed to function as a source of dopamine.        | Also neurotrophic effects?                                                                    |
| Carotid body cell aggregates (autologous) - Harvested surgically at time of transplant | Glomus cells are dopaminergic and release glial-derived neurotrophic factor (GDNF)  | Inconsistent content of DA cells/varying degrees of fibrosis.                                |
| Retinal pigment epithelial (RPE) cells on cross-linked porcine gelatin microcarriers (Spheramine®) - harvested from human eye post-mortem | Source of levodopa (melanin synthesis pathway)  
Do not make synapses                                                               | Neurotrophic effects?                                                                        |

Adapted from Sarva and Henchcliffe - Restoring Function to Dopaminergic Neurons: Progress in the Development of Cell-Based Therapies for Parkinson's Disease. CNS Drugs (2020) 34:559-577
## Cell Sources for Transplant: Present

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<td>Progenitor cells for A9 dopamine neurons Differentiate and functionally innervate striatum</td>
<td>See TRANSEURO clinical trial</td>
</tr>
<tr>
<td>Human parthenogenetic neural stem cells (NSCs)</td>
<td>Differentiate into dopamine neurons in animal models of PD. More likely neurotrophic support - BDNF and/or GDNF.</td>
<td>May differentiate into non-dopamine neurons and glia. Low immunogenicity.</td>
</tr>
<tr>
<td>Human induced pluripotent stem cells (hiPSC)</td>
<td>Expanded cells in culture may be synchronously differentiated to dopamine neuron precursors that will differentiate and integrate into host circuitry to deliver dopamine.</td>
<td>May be expanded as cell banks, facilitating a high degree of quality control and preclinical testing prior to transplant. Autologous approaches are in development.</td>
</tr>
<tr>
<td>- allogeneic hiPSC differentiated into dopamine neuron precursors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- autologous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human embryonic stem cells (hESC)</td>
<td>Expanded cells in culture may be synchronously differentiated to dopamine neuron precursors that will integrate into host circuitry when delivered to the striatum, and release dopamine at functional synapses.</td>
<td>May be expanded as cell banks, facilitating a high degree of quality control and preclinical testing prior to transplant. Not yet in clinical trials.</td>
</tr>
<tr>
<td>- allogeneic hESC differentiated into dopamine neuron precursors</td>
<td></td>
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OVERVIEW

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Allogeneic Transplants: Embryonic Ventral Mesencephalic Tissue Transplants for Parkinson’s disease

- **1970's**: Levodopa successful but with limitations and side effects. Other approaches including cell transplants considered.
- **1979**: Transplanted fVM provides new DA pathway innervation in rat model
- **1987**: First clinical trial in Sweden, with intra striatal transplantation of human fVM tissue in PD
- **1993**: Lifting of ban on fetal tissue research in the USA
- **2001-2003**: Publication of 2 NIH funded sham surgery controlled fVM transplant trials

**Figure 1.** Preparing for human fVM transplant trials in Parkinson’s disease
Early Attempts at VM Transplant

- Preclinical experiments demonstrated graft survival, dopamine release, and amelioration of motor deficits in 6OHDA-lesioned rat

- Transplant program using VM cell suspensions (begun in Lund Sweden)
  - 1987-1991, 4 patients with idiopathic PD received VM transplants, subsequently extended program

- several international programs were initiated

- overall open label studies were encouraging
  - clinical improvement
  - graft maintenance and function

- clinically meaningful improvement was not observed in all studies published

- within studies, there was a considerable variability that was incompletely understood

Variability in Early Open Label Studies

- VM cell suspension (4x 7-9wk), unilateral caudate-anterior putamen – mildly improved motor “off” at 6 months, n=2 (Lindvall)
- Modified protocol - VM cell suspension (4x 6-7wk), unilateral anterior and posterior putamen – moderately improved motor “off” (starting 6 weeks post-op), decreased “off” time, sustained over 3 years, 18F-DOPA uptake improved, n=2 (Lindvall, Peschanski)
- VM tissue fragments (1x 6-7wk), unilateral caudate and putamen, improved ADLs at 12 months, improved motor scores and decreased levodopa intake, n=7 (Freed)
- Cryopreserved VM tissue fragments (1x 5-9wk), unilateral caudate, mildly improved, n=3, 1 died 4 months post-op with MSA (Spencer)
- Solid VM tissue grafts (3-4x 6.5-9wk) bilateral posterior putamen, improved “off” scores and time, reduced dyskinesia at 6 months, improved 18FDOPA uptake (Olanow)

Randomized Controlled Clinical Trials

• Two sham-surgery controlled trials of VM cell transplant both failed to meet primary endpoints
  • Freed et al 2001
    • some clinical benefit in the subgroup of participants aged up to 60 years old at baseline, but not participants who were older
  • Olanow et al 2003
    • Who did better?
    • age-associated benefit was not observed
    • placebo effect and investigator bias in open label studies were highlighted as a possible reason for “failure”
• Both studies noted graft-induced dyskinesias (GID)
  • 15% at 3 years in the Freed study
  • 56% participants at 2 years in the Olanow study

Transplantation of tissue enriched in DA precursors: Early Studies, RCTs, and Reanalysis

• Preclinical experiments demonstrated graft survival, dopamine release, and amelioration of motor deficits

• Transplant program using VM cell suspensions
  • 1987-1991, 4 patients with idiopathic PD received VM transplants in Lund, subsequently extended program
  • clinical improvement
  • graft maintenance and function
  • but considerable variability that was incompletely understood

• Two sham-surgery controlled trials of VM cell transplant failed to meet primary endpoints

• identified subgroups with benefit
  • milder baseline disease
  • greater improvement after levodopa dose
  • “younger”

• graft-induced dyskinesia occurred in both trials

Bilateral VM transplantation to putamen

- Sham-surgery controlled, 40 participants
- No immunosuppression
Table 1. Base-Line Characteristics of Patients with Parkinson’s Disease.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N=40)</th>
<th>Sham-Surgery Group</th>
<th>Transplantation Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤60 yr (N=11)</td>
<td>&gt;60 yr (N=9)</td>
<td>≤60 yr (N=10)</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (48)</td>
<td>6 (55)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Male</td>
<td>21 (52)</td>
<td>5 (45)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>57±10</td>
<td>49±6</td>
<td>66±5</td>
</tr>
<tr>
<td>Duration of disease — yr</td>
<td>14±6</td>
<td>13±6</td>
<td>15±7</td>
</tr>
<tr>
<td>UPDRS score while on medication</td>
<td>22±14</td>
<td>16±6</td>
<td>30±15</td>
</tr>
<tr>
<td>UPDRS score while off medication</td>
<td>63±21</td>
<td>61±21</td>
<td>71±20</td>
</tr>
<tr>
<td>Improvement from “off” to “on” — %</td>
<td>65</td>
<td>74</td>
<td>58</td>
</tr>
<tr>
<td>Diary score</td>
<td>3.0±1.8</td>
<td>2.5±1.9</td>
<td>4.0±1.5</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. Higher scores on the Unified Parkinson’s Disease Rating Scale (UPDRS) and in the diary reflect more severe symptoms of Parkinson’s disease. The worst possible UPDRS score is 176, and the best score is 0. The worst possible diary score is 5, and the best score is 0.
Graft Survival up to 3 Years

2 subjects came to autopsy at 7 months and 3 years post transplant
- 7 months TH+ cells: 38,000 and 23,000 each side
- 3 years TH+ cells: 36,000 and 7,000 each side
- CD3+ and HLA Class II + staining present in tracks and perivascular areas

NO SYSTEMATIC LONG TERM FOLLOW-UP OF PD STATUS
Clinical and imaging outcomes at 17-18 years

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PDGRAFT-01</th>
<th>PDGRAFT-02</th>
<th>PDGRAFT-03</th>
<th>PDGRAFT-04</th>
<th>PDGRAFT-05</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>59</td>
<td>62</td>
<td>75</td>
<td>72</td>
<td>66</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Age of PD Onset, y</td>
<td>24</td>
<td>34</td>
<td>44</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>Transplant or Sham Surgery Date(s)</td>
<td>1997 / Sham</td>
<td>1998 / Graft</td>
<td>1997 / Graft</td>
<td>1997 / Graft</td>
<td>1998 / Graft</td>
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<tr>
<td>PD Duration at Transplant, y</td>
<td>17</td>
<td>12</td>
<td>13</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>PD Duration at Assessment, y</td>
<td>35</td>
<td>28</td>
<td>31</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Graft Age, y</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Subsequent Surgical Treatments</td>
<td>(B) STN DBS, 2009</td>
<td>(B) STN DBS, 2005 / (R) Pallidotomy, 2015</td>
<td>(L) STN DBS, 2004</td>
<td>(B) GPI DBS, 2007 &amp; 08</td>
<td>None</td>
</tr>
<tr>
<td>Current Medication Treatment: Levodopa Equivalent Daily Dose (mg)</td>
<td>300</td>
<td>480</td>
<td>855.5</td>
<td>1192</td>
<td>2550</td>
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<tr>
<td>Hoehn &amp; Yahr Stage</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Schwab &amp; England</td>
<td>70</td>
<td>90</td>
<td>50</td>
<td>80</td>
<td>40</td>
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<tr>
<td>Family History of PD</td>
<td>No</td>
<td>No</td>
<td>Maternal Aunt</td>
<td>Mother &amp; Maternal Uncle</td>
<td>Father</td>
</tr>
<tr>
<td>Genetic Status*</td>
<td>Negative</td>
<td>Negative</td>
<td>LRRK2 (G2019S)</td>
<td>LRRK2 (G2019S)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*Genetic testing by commercial panel. DNA sequencing only performed for LRRK2. Sequencing and MLPA applied for parkin, DJ-1, PINK1 and SNCA.

Henchcliffe et al (2016) Clinical and neuroimaging outcomes up to 18 years after fetal tissue transplant for Parkinson’s disease Mov Disord. 31 (suppl 2).
Long Term Outcomes: Motor Features


Risk of post-transplant “off” dyskinesias
15% study participants at 3 years (Freed et al 2001)
56% study participants at 2 years (Olanow et al 2003)

“Typical hole in the pants leg caused by groping hand movement in a patient with runaway off-medication dyskinesias.”

Parkinson’s Kinetigraph: PD Graft 02 - Severe dyskinesia appears to arise in the morning and persists for the rest of the day.
Very long term follow up on fVM transplant: Non-motor Symptoms

• Depression (2)
• Psychosis (1)
• Dopamine Dysregulation Syndrome (2)
• ICD (3)
• Urinary Incontinence (4)
• Orthostatic Hypotension (4)
• Cognitive Function: MoCA scores 25-27

• Neuropsychological testing: All scored in compromised range on measures of psychomotor speed; 3/4 scored well within normal limits on measures of higher cortical functioning, including attention, confrontation naming, new learning and delayed recall of word lists and stories
Porcine Embryonic Ventral Mesencephalic Cell Xenografts

• 12 patients with advanced PD,
• 12 million cells deposited in 3 tracks to unilateral putamen and caudate
• 6 cyclosporin/6 received cells pretreated with MHC class 1 monoclonal antibody F(ab’) fragment

• Total UPDRS “off” decreased by average 19% and 3 subjects achieved a 30% decrease (1 year)
• 5 improved 11% or less
• $^{18}$F-DOPA PET demonstrated no increase in uptake in the engrafted striatum
• Autopsy in 1 subject (7 months, PE, cyclosporine) showed extremely poor cell survival (est. 638 cells)

• Limited testing
• Why such poor cell survival?
  • risk of rejection and immunosuppression requirements need to be better understood
  • potential xenotic infections

Autologous Tissue Transplant from the Adrenal Medulla

- Unilateral transplant to putamen (Lindvall)
  - Improvements lasted 2 months
- Graft tissue fragments to lateral ventricle adjacent to caudate (Madrazo) in advanced PD
  - Patient 1: 35 yo, clinical improvement at 15 days, rigidity and akinesia "virtually disappeared" at 10 months, tremor reduced
  - Patient 2: 39 yo, clinical improvement at 6 days, "similar degree of improvement" at 3 months
- Varying outcomes in a number of small open label trials
- Multi-center study in the US found "substantial" post-op morbidity despite increased "on" time
  - United Parkinson Foundation Neurotransplantation Registry: 18% participants died with at least half attributable to transplant
    - "modest" motor off improvement

Carotid body - Autologous

- Source of dopaminergic cells vs GDNF
- Phase I/II open label clinical trial with 1-3 year follow up in
- N= 13 with advanced PD
- Harvesting/surgical implantation to bilateral putamen (caudate in 2)
- Primary outcome, UPDRS motor “off” score
  - 5-74% - improvement in 10/12 at 1 year
  - no GID
  - mean change 15 ± 21.5% (p=0.034)
- One patient had a highly fibrous carotid body - no benefit
- 18F-DOPA PET changes (n=7) subjects were not statistically significant
- 1 symptomatic lacunar infarct, 1 seizure resulting from haemorrhage next to a burr hole
- doubted feasibility and reliability

Human retinal pigment epithelial (RPE) cells/gelatin microcarriers

- Delivered on an excipient of cross-linked porcine gelatin microcarriers as Spheramine®
- Improve symptoms in rodent and non-human primate models of PD.
- Open label, single-center clinical trial was undertaken in n=6 subjects with advanced PD
  - post-commissural putamen contralateral to most affected side.
  - 48% improvement in UPDRS motor “off” score at 12 months
  - no SAEs related to the intervention
  - phase 2 multi-center, randomized, double blind controlled study in n=35 individuals vs n=36 sham
- 325,000 RPE cells per side
- no immunosuppression

RPE Cells/Gelatin Microcarriers: Outcomes

• UPDRS motor score “off” improved by \(-10.5 \pm 10.26\) (transplant) vs \(-10.1 \pm 12.26\) points sham (p=0.09).

• the study fail to demonstrate benefit,

• there were more deaths in the transplant versus sham procedure group (7 versus 2 respectively)

• 1 of these deemed possibly related to the surgery or cell

• suboptimal cell survival, based upon autopsy of a single individual at 6 months

Lessons Learned

• Strong preclinical data for potential cell sources, including MOA, is needed before clinical trials

• Common core approaches help compare across studies
  • e.g. CAPIT, use of registries or multi-center studies
  • Harmonizing approaches, as in the adrenal medullary transplant registry, allows comparison across centers to more efficiently determine outcomes

• Substantial variability in long term course needs to be captured by pre-planned long term follow up

• Variability in graft survival makes obtaining autopsy, whenever possible, critical

• There are gaps in understanding engrafted cell behavior, optimal delivery, immunosuppression in allogeneic transplants
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How Does New Stem Cell Technology Help?

- Cells are readily available and can be grown in almost unlimited numbers
- May be cryopreserved to store and transport as needed
- Testing for safety and efficiency is easier
- Possibility for matching donor cells immunologically
How are Cells for Transplant Produced?

- Source of highly pure dopamine nerve cells
- Readily available in the quantities needed
- Predicted lower risk of getting graft-induced dyskinesia
A Long Timeline - but a lot of progress

- 1998: Producing human embryonic stem cells
- 2004: Generating dopamine nerve cells from stem cells
- 2007: Generating dopamine nerve cells from human embryonic stem cells and iPSCs
- 2011: Discovery of human “iPSCs”
- 2014: Formation of international consortium: GForce-PD
- 2018: First patient grafted with matched cells - Kyoto
The “Kyoto” Clinical Trial

Fig. 2. Surgical procedure. The cells are transplanted into bilateral putamen through burr holes by using a stereotactic device.
The “New York/Boston” Clinical Trial

Personalized iPSC-Derived Dopamine Progenitor Cells for Parkinson’s Disease

Jeffrey S. Schweitzer, M.D., Ph.D., Bin Song, M.D., Ph.D., Todd M. Herrington, M.D., Ph.D., Tae-Yoon Park, Ph.D., Nayeon Lee, Ph.D., Sanghyeok Ko, Ph.D., Jeha Jeon, Ph.D., Young Cha, Ph.D., Kyungsang Kim, Ph.D., Quanzheng Li, Ph.D., Claire Henchcliffe, M.D., D.Phil., Michael Kaplitt, M.D., Ph.D., Carolyn Neff, M.D., Otto Rapalino, M.D., Hyemyung Seo, Ph.D., In-Hee Lee, Ph.D., Jisun Kim, Ph.D., Taewoo Kim, Ph.D., Gregory A. Petsko, D.Phil., Jerome Ritz, M.D., Bruce M. Cohen, M.D., Ph.D., Sek-Won Kong, M.D., Pierre Leblanc, Ph.D., Bob S. Carter, M.D., Ph.D., and Kwang-Soo Kim, Ph.D.
Neural Stem Cells (NSCs)

- Single center, open label, dose escalating clinical trial of human parthenogenetic neural stem cells in Australia (NCT02452723)
- Ascending doses of 30, 50, or 70 million cells (ISC-hpNSC®)
- Targeting bilateral caudate, putamen, and substantia nigra,
- Enrolment and procedures completed in early 2019
- Interim results presented with a published abstract containing an overview of data for 10 subjects transplanted
- 8 completed the 1-year study (with planned 5 year follow up)
- No SAEs related to the cell product, no tumors, no infections

NSCs Clinical Effects

- Dose-dependent improvement reported at 6 months on:
  - Hauser Motor Diary
  - PDQ-39
  - Clinical Global Impression scale
- Critical questions raised about incomplete understanding of the MOA
  - NSCs can differentiate to dopamine neurons in rodent and non-human primate models
  - recovery of dopaminergic inputs post-transplant is host-derived, not dopaminergic neuron replacement by engrafted cells
  - likely due to neurotrophic support to the host from the engrafted cells [67, 68].
- Other studies may aid in improving our understanding of the potential for such cells, such as a
  - new clinical trial targeting 50 individuals with severe PD in China (NCT03119636)
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Generation of Functional Human Embryonic Stem Cell-Derived Midbrain Dopamine Neurons

Efficient Derivation of Functional Floor Plate Tissue from Human Embryonic Stem Cells

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DOI 10.1016/j.stem.2010.03.001

LETTER

Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson’s disease

Sonja Kriks§,∥, Jae-Won Shin§,∥, Jinghua Piao§,∥, Yosif M. Ganat†,‡, Dustin R. Wakeman§, Zhong Xie§, Luis Carrillo-Reid§, Gordon Auyeung§,∥, Chris Antonacci§,∥, Amanda Bach§,∥, Lichuan Yang§,∥, M. Flint Beal§,∥, D. James Surmeier§,∥, Jeffrey H. Kordower§,∥, Viviane Tabar§,∥ & Lorenz Studer†,¶,*

doi:10.1038/nature10648
Dopamine neurons derived from human ES cells efficiently engraft in animal models of Parkinson’s disease

Sorina Kretz5,1,2, Jan Wen-Shin1,3,4, Angha Zha2,6,7, Yordi M. Canadú1,2, Dustin R. Walzmann1,2, Zhong Xie3,8, Luis Carrillo-Reid1, Gordon Ayre8,9,3, Chris Antonaci8,9, Amanda Buch1,2, Liuchuan Yang2, M. Fitch Reid1, D. James Sumerse1,2, Jeffrey H. Kordower1,2, Viviana Taller1,2 & Lorenzo Studer1,2,3
doi:10.1001/jneurosci.10848

Efficient Derivation of Functional Floor Plate Tissue from Human Embryonic Stem Cells

Christopher A. Passoa,1,2,4, Stuart M. Chambers,1 Gabeang Lee1,2, Mark J. Tonshoff3,2, and Lorenzo Studer1,2,4

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6Correspondence: christopher.pasa@nyserc.org (C.A.P.), studer@ucsf.org (L.S.)

Mouse (6OHDA)

Rhesus monkey (MPTP)

Fetal VM Human PD

HESC-DA MPTP RH-1

HESC-DA MPTP RH-2
Phase 1 Safety and Tolerability Study of MSK-DA01 Cell Therapy for Advanced Parkinson’s Disease

Inclusion Criteria:
• Age 60-76 years old
• Diagnosis of Parkinson’s Disease made between 5 to 15 years ago
• Taking levodopa, but with complications of therapy such as wearing off and/or dyskinesia
• Able to participate in all study visits and evaluations, including brain MRI and PET scan
• Existence of a study partner who may act as potential surrogate over long term for ongoing consent

ClinicalTrials.gov Identifier: NCT04802733
Autologous cell transplantation

• Overcomes burden and “unknowns” of immunogenicity

• iPSCs may be derived from an individual’s cells
  • skin fibroblasts
  • blood cells
  • fate programmed to become “authentic” midbrain dopamine neurons
  • survive robustly in preclinical models of PD
  • ameliorate motor deficits

• source iPSCs may be derived from patients themselves

Loring JF. Autologous Induced Pluripotent Stem Cell-Derived Neurons to Treat Parkinson’s Disease. Stem Cells Dev. 2018;27(14):958-9
Other Future Considerations

• Limitations of dopamine-focused therapeutics
• Spread of pathology
• Optimizing delivery
• Scaffolds and cell support
• Direct reprogramming
• Optimizing graft survival and function
• Opportunities for precision approaches/gene editing
Conclusions

• Intensive efforts are underway to develop an effective and competitive regenerative medicine approach
• The current focus is to restore nigrostriatal inputs that are lost in PD, and to relieve associated disabling symptoms
• Previous attempts have been hampered by limitations of the cell sources
• Stem cells provide the potential to overcome those limitations
• Cell therapies will face a broad competitive landscape
• Likely to be combined with other therapies
THANK YOU