

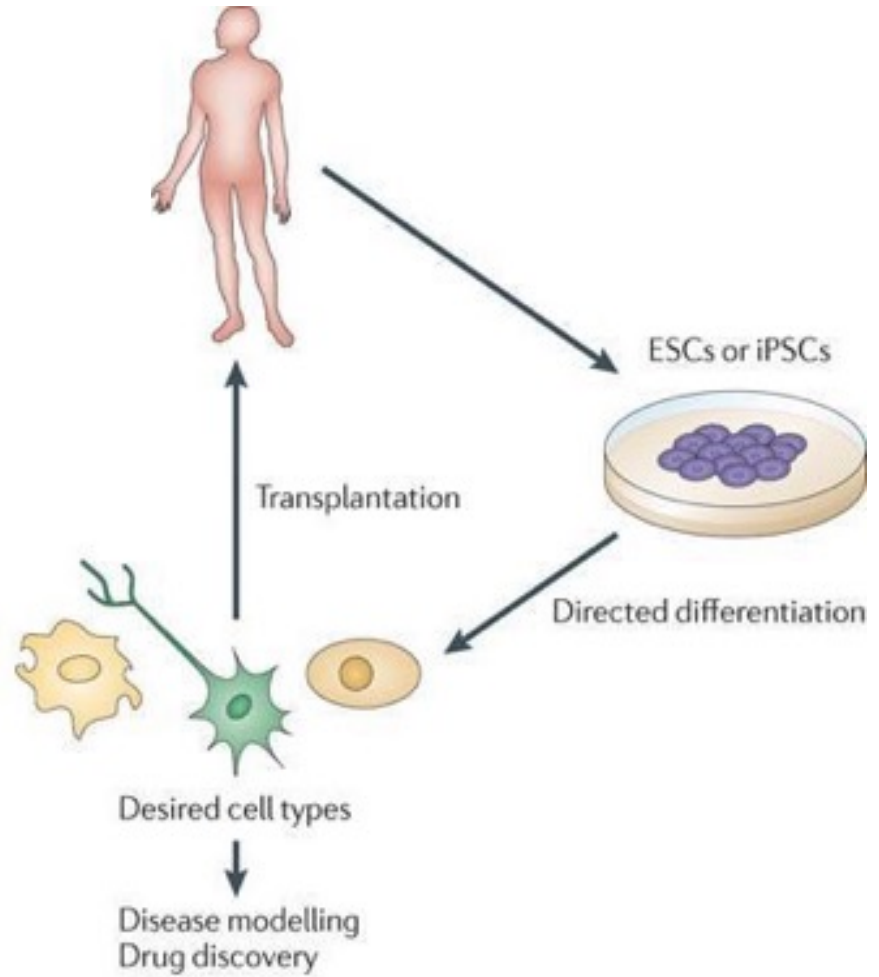
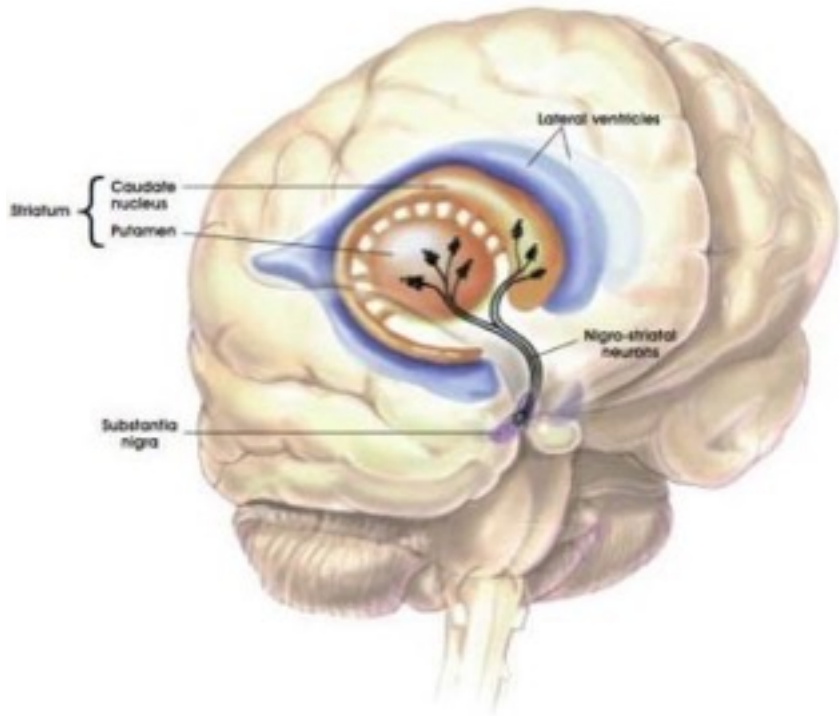
# The New News in Stem Cell Research

## Andrés Bratt-Leal, PhD

12/1/2017



# Cell Therapy and Parkinson's Disease



- Very specific neural degeneration
- >50% of DA neurons are gone by diagnosis
- 1 million in the USA, 15k in San Diego County
- No disease modifying treatment available

Nature Reviews | **Genetics**

Cohen and Melton. Nature Reviews Genetics 12, 243-252 (April 2011)

## Can we replace lost DA neurons?

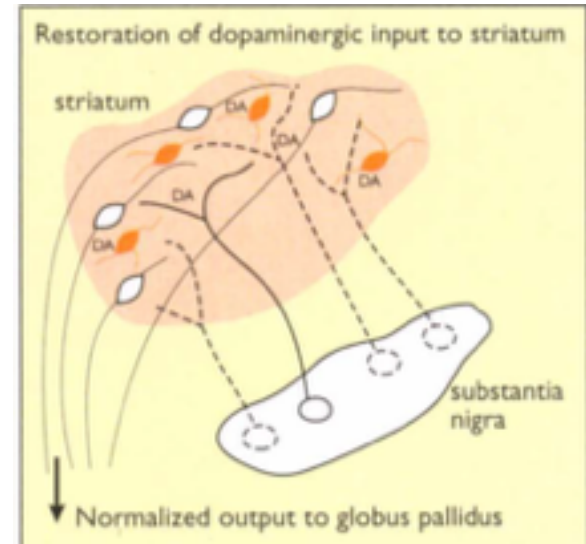
# Proof of Concept: Fetal Neurons in the 1990s

Colorado: Curt Freed: 1994-1999 (NIH)

- Double blind clinical trial with fetal neuron transplantation, 40 PD patients

• Outcomes:

- Long-term reduction of PD symptoms
- No Change
- Dyskinesia in nearly 15%



## HealthlineNews

Healthline — Healthline News — Transplanted Brain Cells Survive, Thrive in Parkinson's Patients

### Transplanted Brain Cells Survive, Thrive in Parkinson's Patients

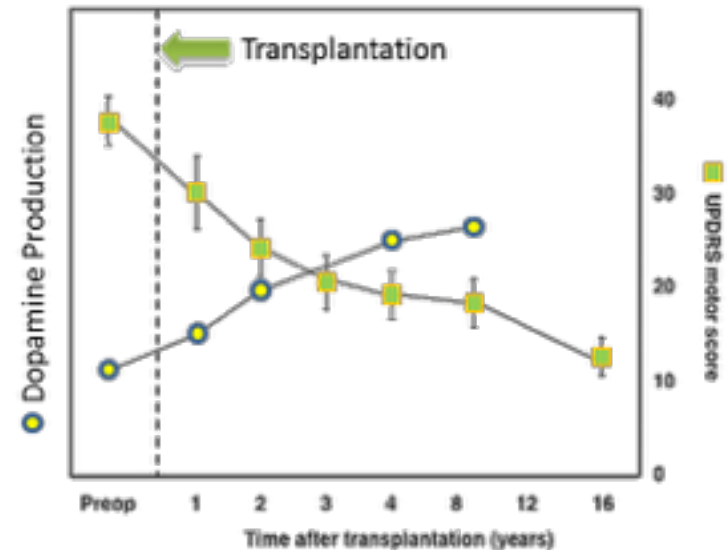
Cells in the fetal brain that produce the chemical dopamine can be transplanted into Parkinson's patients to keep their symptoms at bay for many years.

Written by Alexa Severson | Published on June 5, 2014



Transplanting fetal dopamine cells into the brains of patients with Parkinson's disease may be the key to treating the illness, according to a study published this week in [Cell Reports](#).

Researchers at Harvard-affiliated McLean Hospital found that these cells remained healthy and functional in patients with Parkinson's

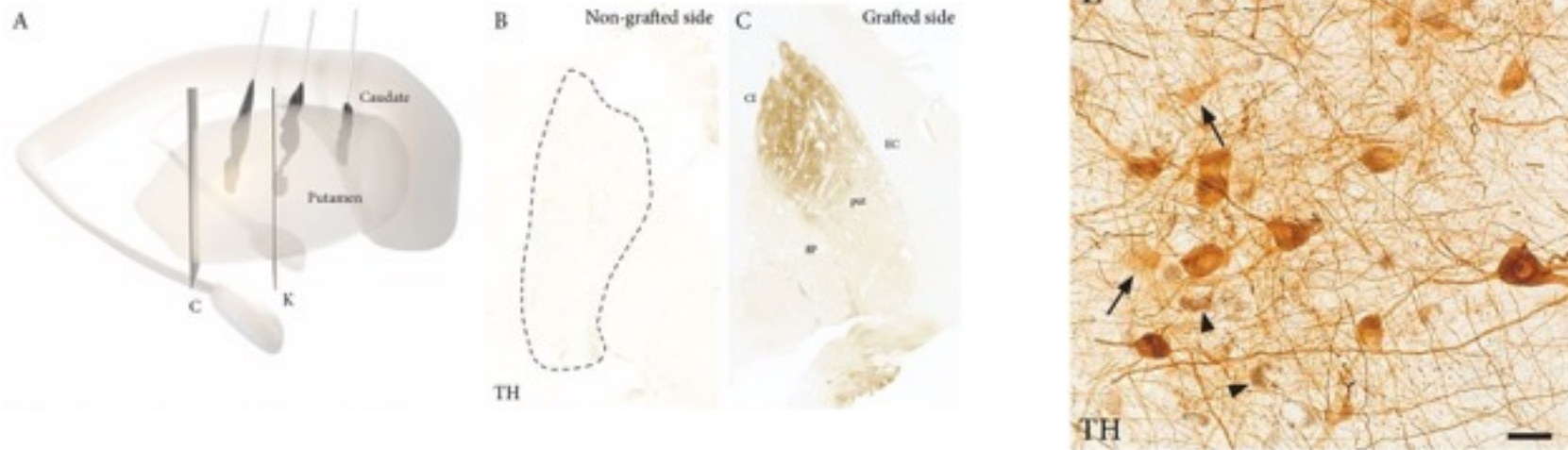


Freed CR, et al. *New Eng. J. of Med.* 344(10), 710-719 (2001)  
Isacson and Breakefield. *Nature Med.* 3, 964-969 (1997).

# Extensive graft-derived dopaminergic innervation is maintained 24 years after transplantation in the degenerating parkinsonian brain

Wen Li<sup>a</sup>, Elisabet Englund<sup>b</sup>, Håkan Widner<sup>c</sup>, Bengt Mattsson<sup>d</sup>, Danielle van Westen<sup>e</sup>, Jimmy Lätt<sup>e</sup>, Stig Rehnström<sup>f</sup>, Patrik Brundin<sup>g</sup>, Anders Björklund<sup>d,1,2</sup>, Olle Lindvall<sup>c,h,1,2</sup>, and Jia-Yi Li<sup>a,1,2</sup>

<sup>a</sup>Neural Plasticity and Repair Unit, Wallenberg Neuroscience Center, Department of Experimental Medical Science, Lund University, 221 84 Lund, Sweden; <sup>b</sup>Division of Oncology and Pathology, Lund University Hospital, 221 85 Lund, Sweden; <sup>c</sup>Division of Neurology, Lund University Hospital, 221 85 Lund, Sweden; <sup>d</sup>Neurobiology Unit, Wallenberg Neuroscience Center, Department of Experimental Medical Science, Lund University, 221 84 Lund, Sweden; <sup>e</sup>Center for Medical Imaging and Physiology, Lund University Hospital, 221 85 Lund, Sweden; <sup>f</sup>Division of Neurosurgery, Lund University Hospital, 221 85 Lund, Sweden; <sup>g</sup>Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, MI 49503; and <sup>h</sup>Lund Stem Cell Center, Lund University Hospital, 221 84 Lund, Sweden



- 42,000 surviving dopaminergic neurons from transplant
- L-DOPA was withdrawn 2.5 yrs after TX
- 12 years after TX L-DOPA was reintroduced and patient responded well until year 14
- Graft related motor improvement persisted through year 18

# Lewy Body Pathology in Grafted Neurons

Journal of Parkinson's Disease 1 (2011) 83–92  
DOI 10.1215/2019-2010-11000  
IOS Press

## Signs of Degeneration in 12–22-Year Old Grafts of Mesencephalic Dopamine Neurons in Patients with Parkinson's Disease

Zuzanna Kurowska<sup>a,b</sup>, Elisabet Englund<sup>c</sup>, Håkan Widner<sup>d</sup>, Olie Lindvall<sup>a,1</sup> and Jia-Yi Li<sup>a,b,c,1</sup>  
and Patrik Brundin<sup>a,1</sup>

<sup>a</sup>Neuro  
<sup>b</sup>Neuro  
<sup>c</sup>Depa  
<sup>d</sup>Divit  
<sup>e</sup>Labo  
Land

In 12- to 22 year old transplants 1-5% of transplanted neurons had Lewy Body Pathology

### Cell Reports Report

## Long-Term Health of Dopaminergic Neuron Transplants in Parkinson's Disease Patients

Penelope J. Hallett,<sup>1</sup> Oliver Cooper,<sup>1</sup> Damaso Sadi,<sup>2</sup> Harold Robertson,<sup>2</sup> Ivar Mendez,<sup>2</sup> and Ole Isacson<sup>1,2</sup>

<sup>1</sup>Neuroregeneration Research Institute, Harvard University and McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA

<sup>2</sup>Division of Neurosurgery, Department of Anatomy and Neurobiology, and Department of Pharmacology, Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, NS B3H 3A7, Canada

\*Correspondence: [isacson@rms.harvard.edu](mailto:isacson@rms.harvard.edu)

<http://dx.doi.org/10.1016/j.celrep.2014.05.027>

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

Others did not find Lewy bodies

In a more recent 24 year old transplant, 12% of neurons had Lewy Body pathology. Patient had widespread Lewy body pathology throughout the brain. Evidence suggests post-synaptic degeneration was responsible for loss of effectiveness

# Lessons Learned

- Quality control issues:
  - Multiple fetuses used
  - Fetal tissue viability varies
  - Variable numbers & types of brain cells
- Unpredicted adverse outcome: dyskinesia
- Complex legal and ethical landscape associated with the use of aborted fetuses

## **Serotonergic Neurons Mediate Dyskinesia Side Effects in Parkinson's Patients with Neural Transplants**

**Marios Politis,<sup>1,2\*</sup> Kit Wu,<sup>1,2</sup> Clare Loane,<sup>1,2</sup> Niall P. Quinn,<sup>3</sup> David J. Brooks,<sup>1,2</sup> Stig Rehncrona,<sup>4</sup> Anders Bjorklund,<sup>5</sup> Olle Lindvall,<sup>6,7</sup> Paola Piccini<sup>1,2</sup>**

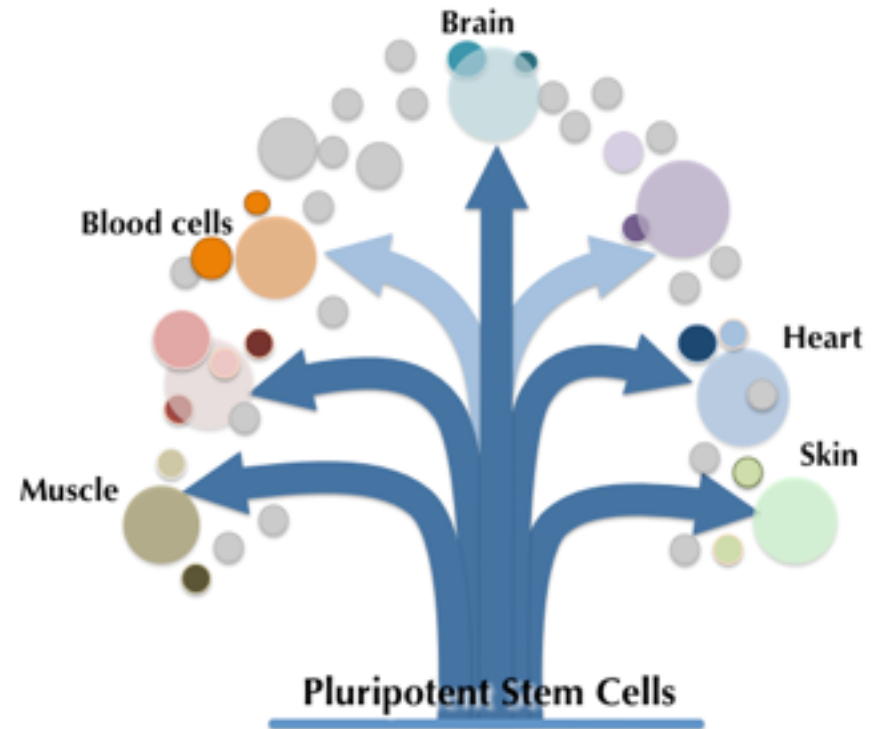
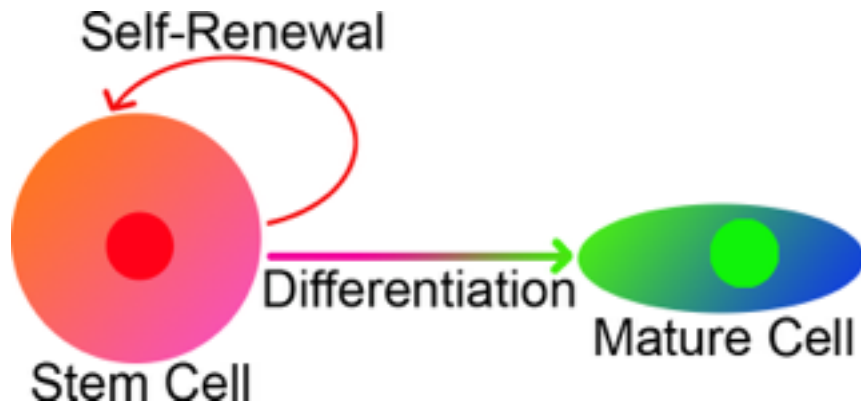
(Published 30 June 2010; Volume 2 Issue 38 38ra46)

Science Translational Medicine (2) June 2010

# Stem Cells

Stem cells have the ability to:

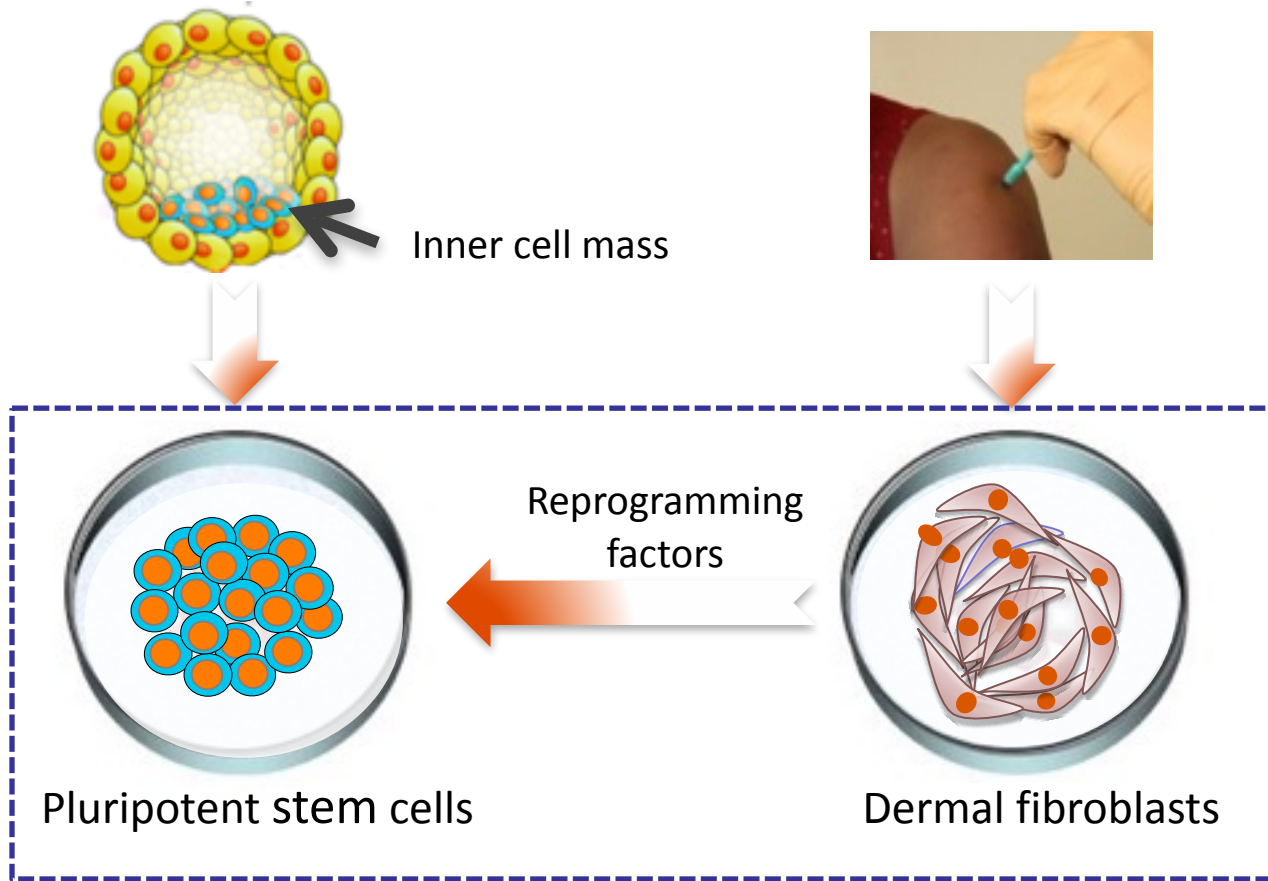
1. divide to make copies of themselves
2. give rise to specialized cells.



# Sources of Pluripotent Stem Cells

Discarded embryos from in vitro fertilization procedures

Skin biopsies from volunteers

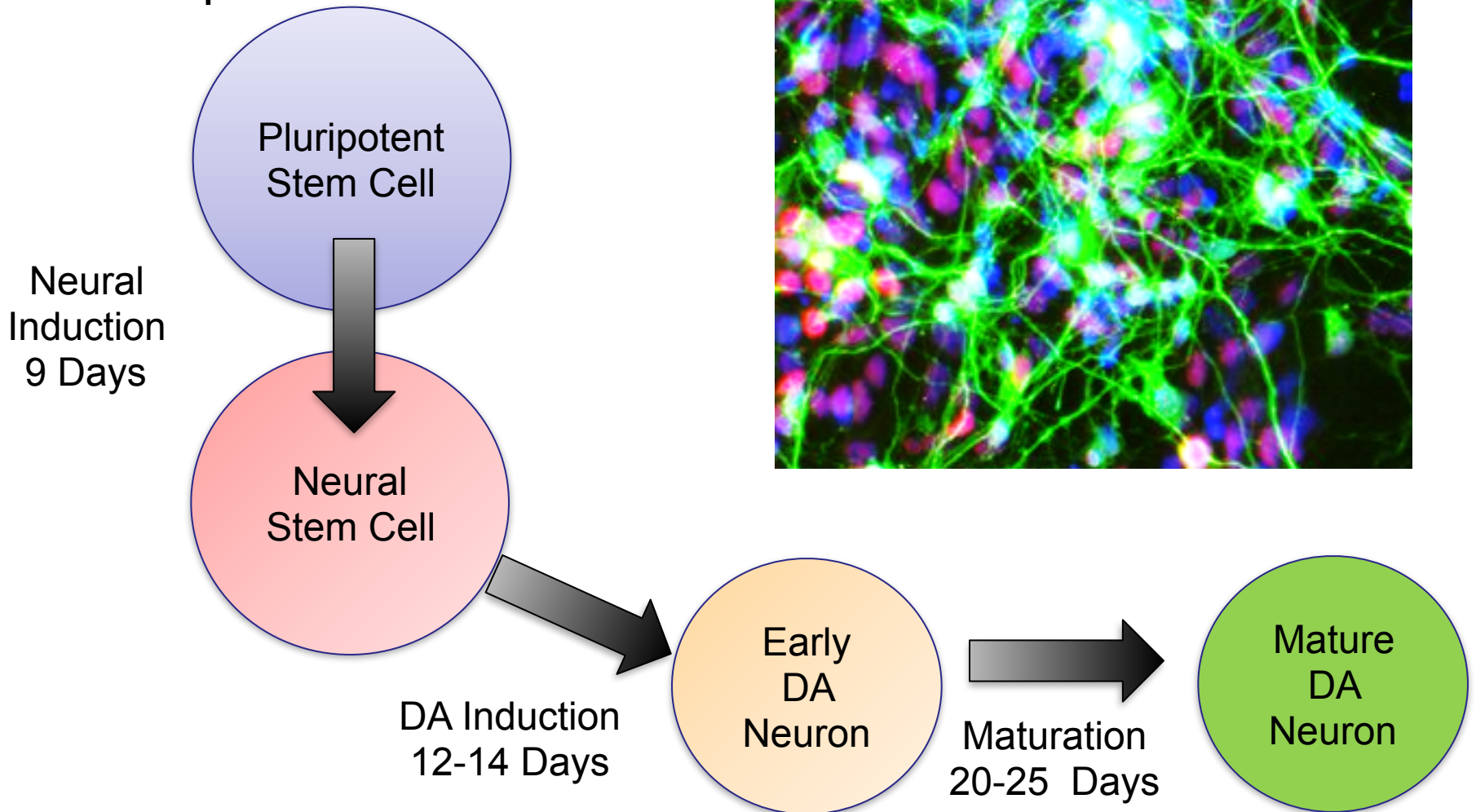


Shinya Yamanaka, MD, PhD – Winner of 2012 Nobel Prize in Physiology or Medicine for Cellular Reprogramming



# Dopamine Neuron Production

- Reproducible Protocol
- Guide the cells through development:



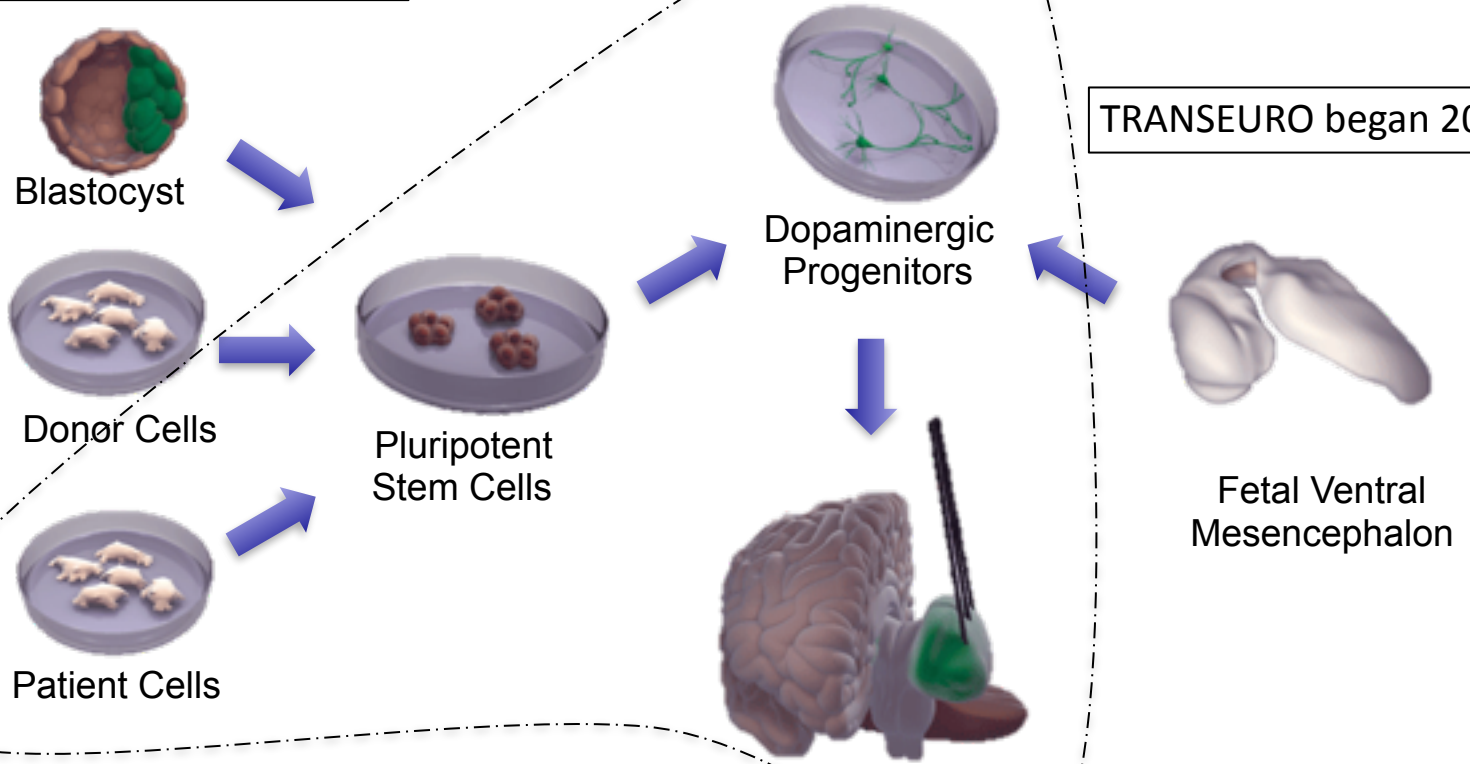
# GFORCE Consortium for PD Cell Therapy

Embryonic Stem Cells

- MSKCC – New York
- Lund University - Sweden

iPSCs

- CiRA–Kyoto
- TSRI/Scripps



TRANSEURO began 2015

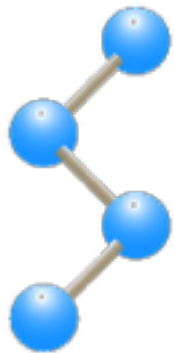
**Clinical Trials to start 2018 – 2020!**

Summit For Stem Cell Project  
Patient Specific Neuron Replacement

# Collaborative Research: Scientists & Community

Goal: To use our patient's own cells to treat their disease.

- Community outreach
- Lab tours and seminars



THE  
SCRIPPS  
RESEARCH  
INSTITUTE



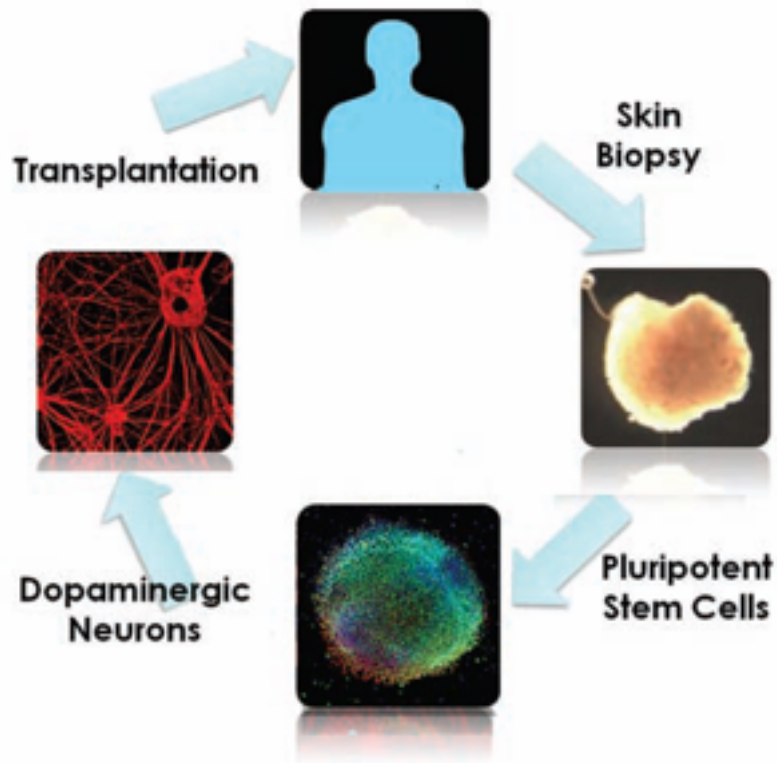
Scripps

SUMMIT FOR  
STEM CELL  
VICTORY OVER PARKINSON'S

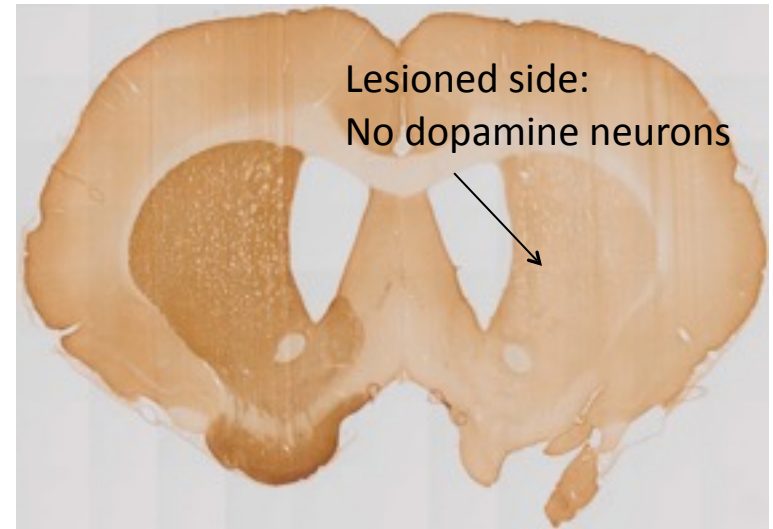


# Study Design

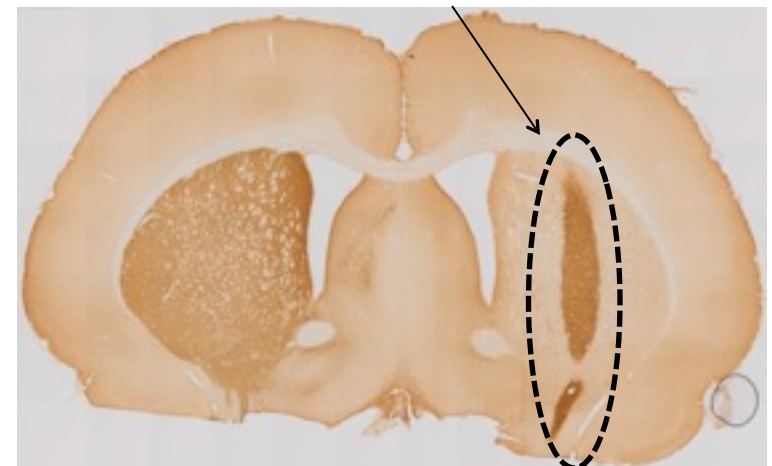
We want to replace the lost neurons in Parkinson's disease new ones made from the patient's own skin



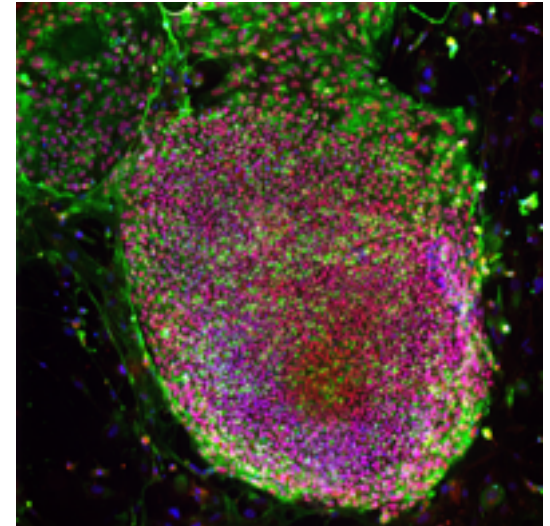
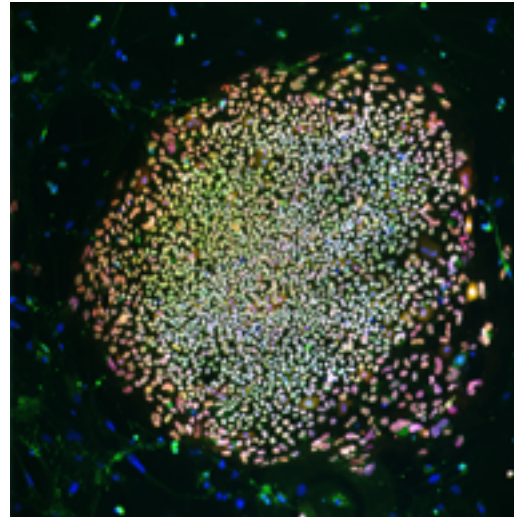
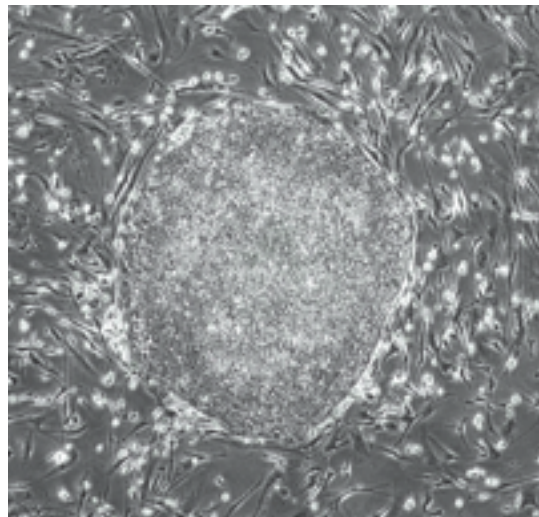
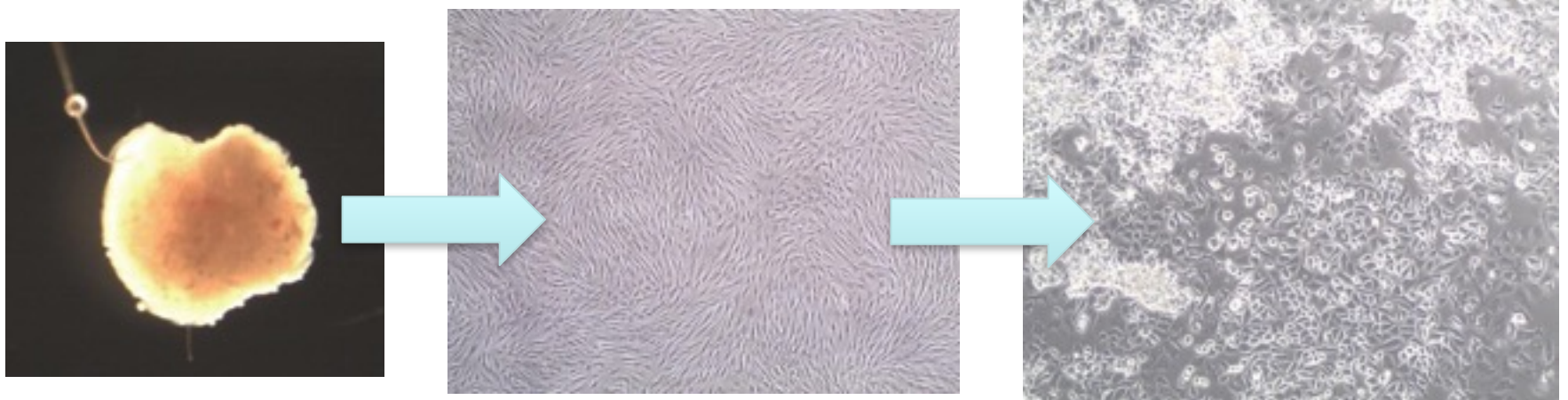
## Our Rat Data



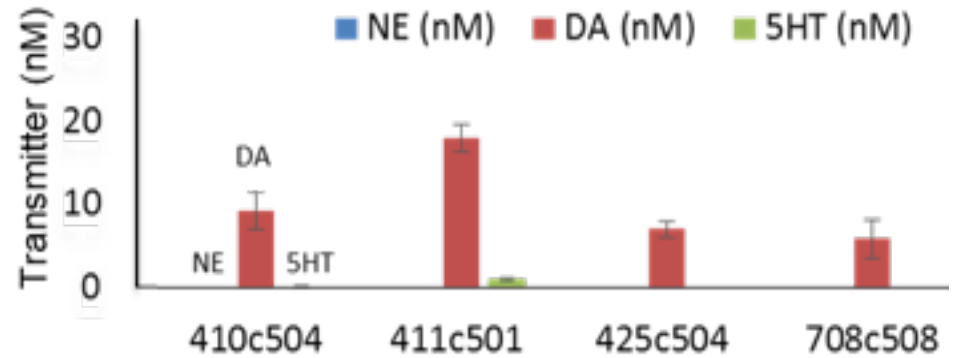
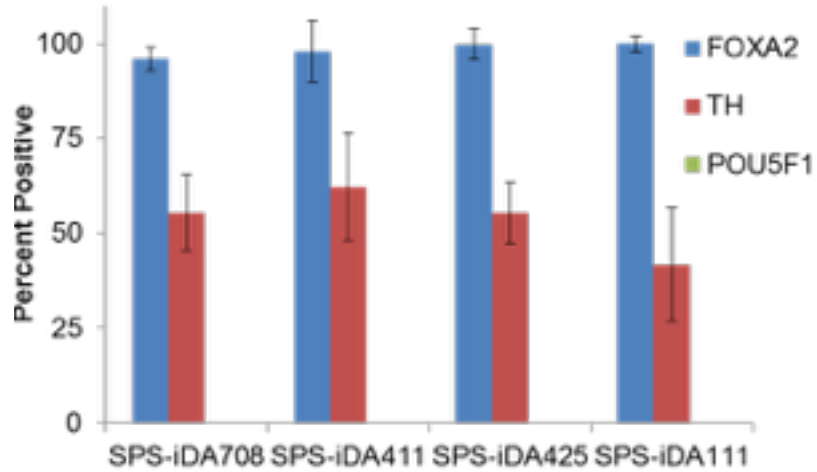
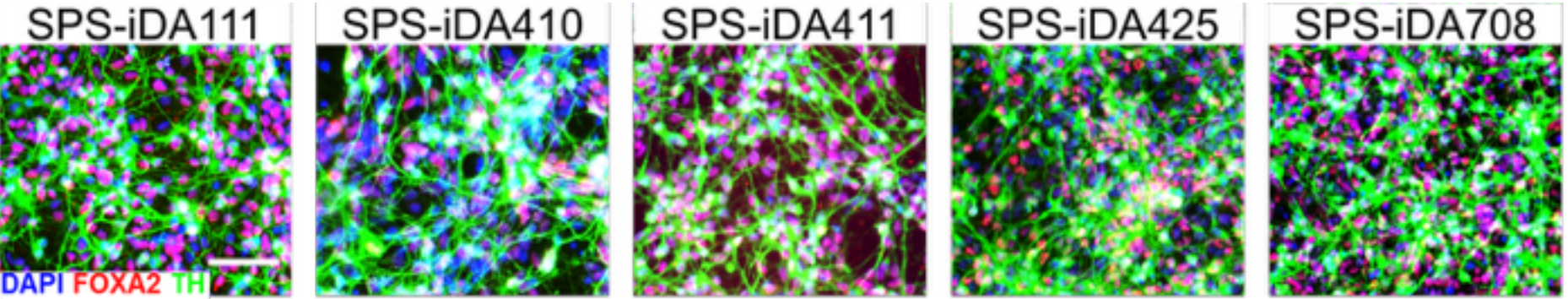
Injected patient neurons survive and produce dopamine



# First Patient-Specific iPSCs : 2012



# Dopamine Neuron Production

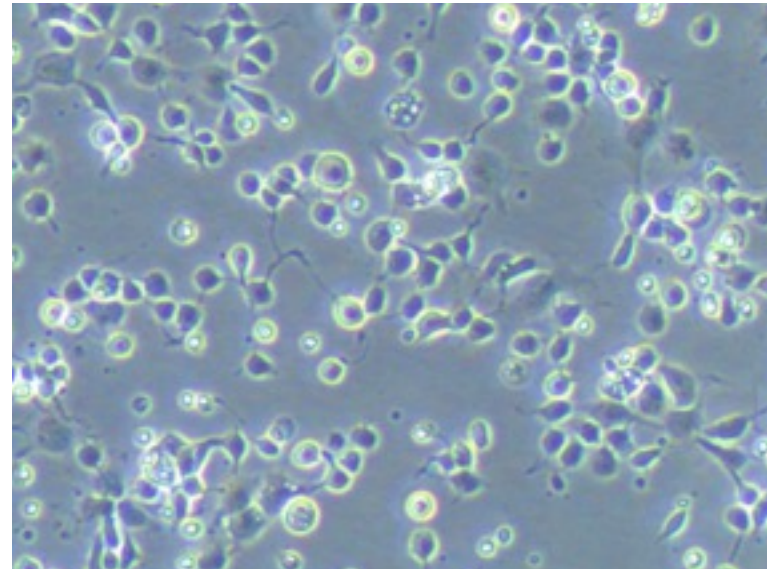


# Cell Cryopreservation

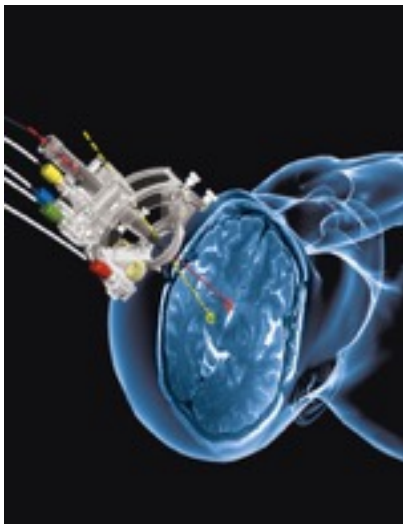
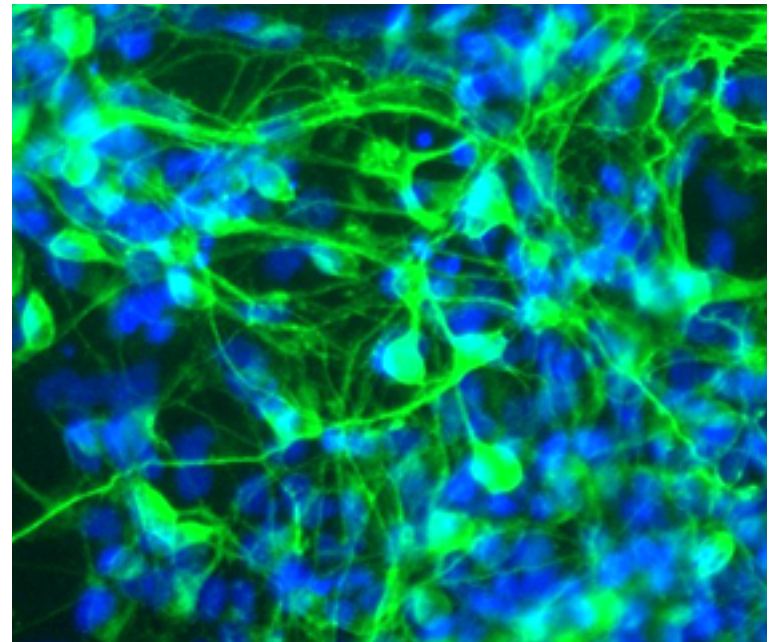
Cells are thawed and directly injected



1 day after thaw

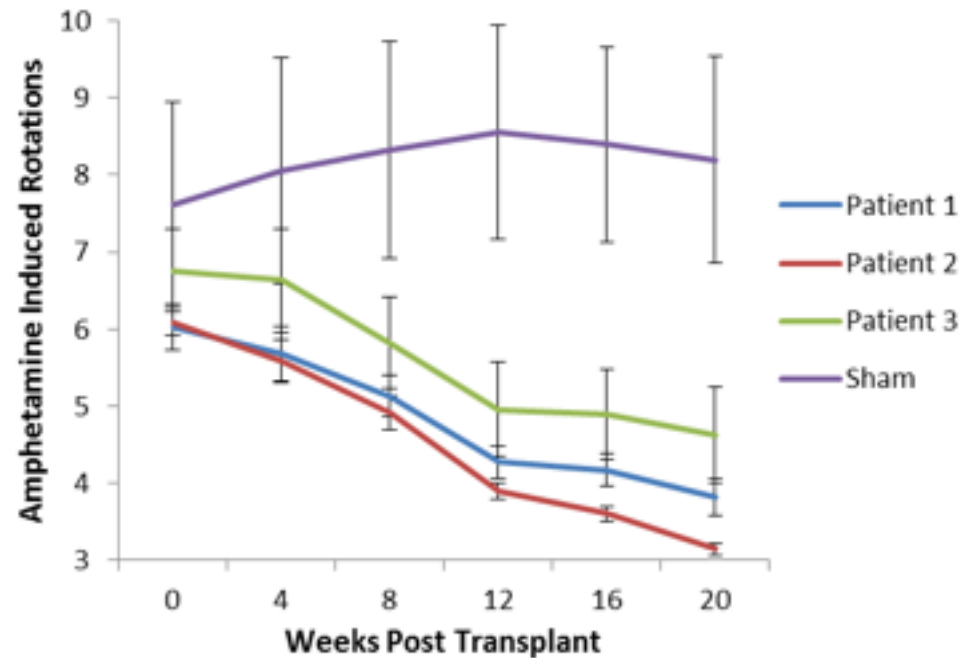


5 days after thaw



Intraoperative  
MRI allows for  
precision  
targeting and  
minimizes risk

# Patient Cells Cause Recovery in Rat Model



9 month safety study in rats using neurons from 4 patients is complete and does not show any safety concerns



# Steps to FDA Approval

- 1) Cell Manufacturing – City of Hope
  - Produce Clinical Grade Cells
- 2) IND-Enabling Animal Studies
  - 9 months after Pre-IND
- 3) Clinical Protocol Development

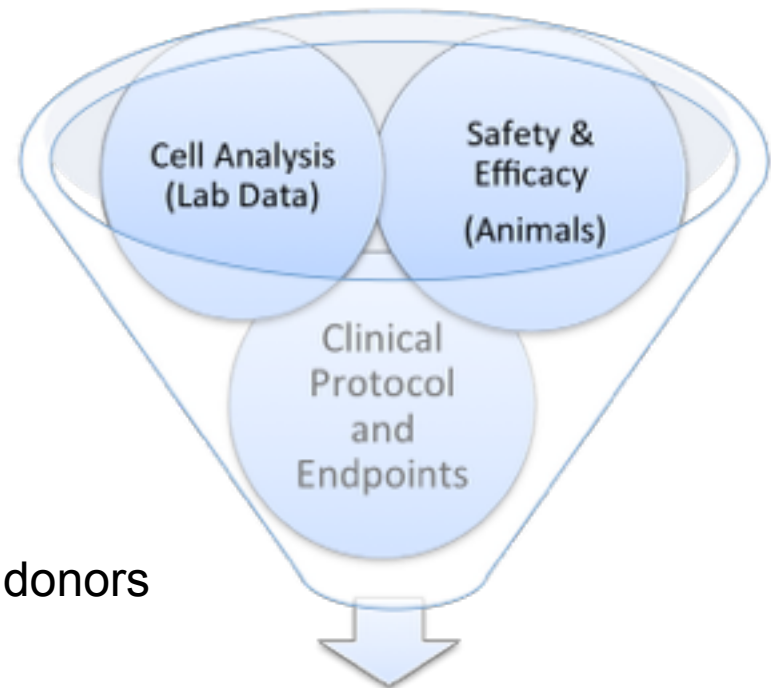
## Funding Support

Summit: ~\$3 million since 2011 from over 2,000 donors

CIRM: \$2.5 million in 2017

National Stem Cell Foundation: \$250k in 2017

Scripps Clinic Medical Group: \$45k since 2013



## FDA Approval

Feb 2016

2019

Implant



Pre-pre IND

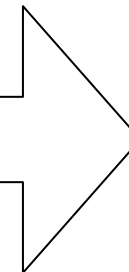


Pre IND

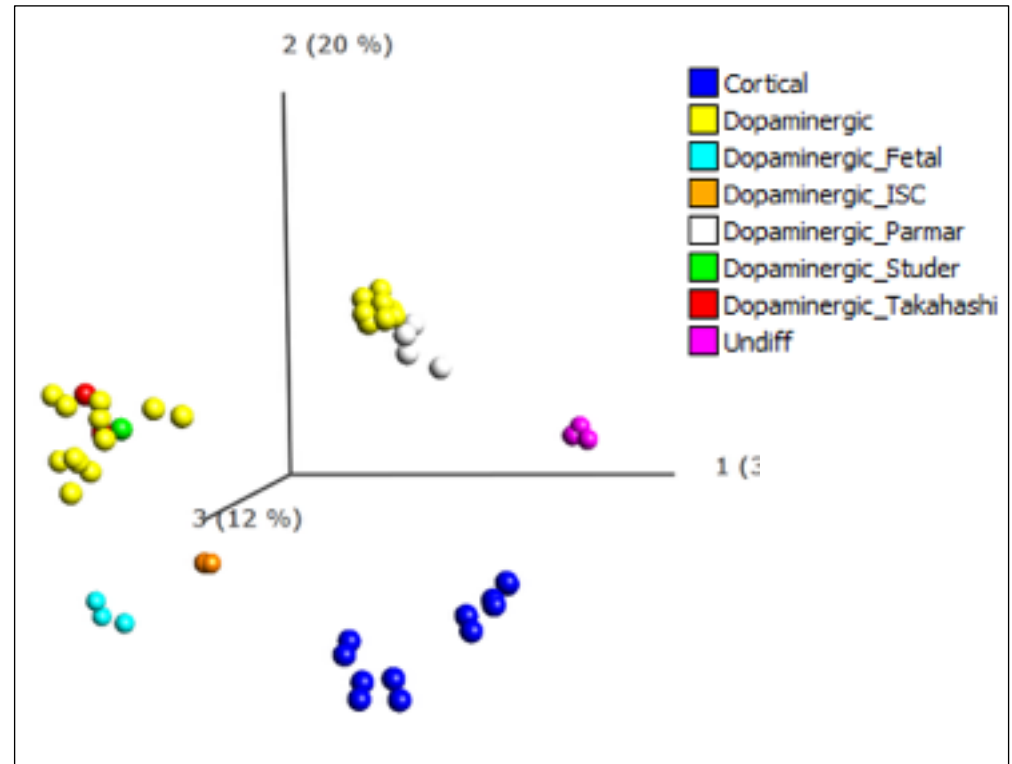
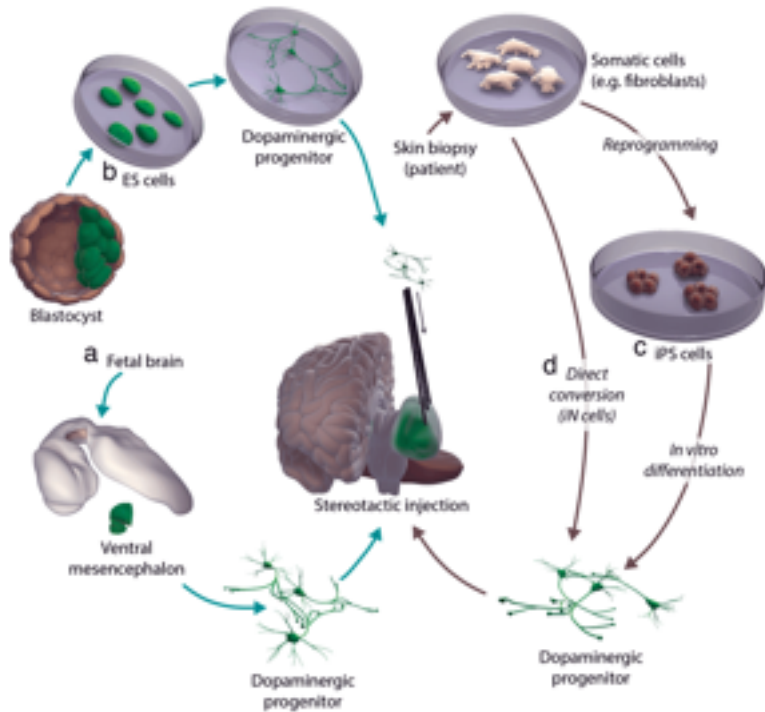


IND

Q1 2018



# Cell Therapy Landscape for PD



GFORCE-PD groups are all using high quality cells which are virtually identical

# Future of Cell Therapy

- Our project could be the first to use patient's own iPSCs with FDA approval
- Other projects are using pluripotent derivatives now:
  - Macular Degeneration
  - Spinal Cord Injury
  - Diabetes
- Future research in the pipeline
  - Multiple Sclerosis
  - Alzheimer's Disease
  - Heart Disease

Thank you!