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

Can we replace lost DA neurons?

Proof of Concept: Fetal Neurons in the 1990s

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

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

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

Wen Li, Elisabet Englund, Håkan Widner, Bengt Mattsson, Danielle van Westen, Jimmy Lätt, Stig Rehncrona, Patrik Brundin, Anders Björklund, Olle Lindvall, and Jia-Yi Li

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- 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- L-DOPA was withdrawn 2.5 yrs after TX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

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

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, Kit Wu, Clare Loane, Niall P. Quinn, David J. Brooks, Stig Rehncrona, Anders Bjorklund, Olle Lindvall, Paola Piccini

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

Science Translational Medicine (2) June 2010
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

Inner cell mass

Reprogramming factors

Pluripotent stem cells

Dermal fibroblasts

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:

- Pluripotent Stem Cell
- Neural Induction 9 Days
- Neural Stem Cell
- DA Induction 12-14 Days
- Early DA Neuron
- Maturation 20-25 Days
- Mature DA Neuron
TRANSEURO began 2015

Embryonic Stem Cells
- MSKCC – New York
- Lund University - Sweden

iPSCs
- CiRA–Kyoto
- TSRI/Scripps

Clinical Trials to start 2018 – 2020!

GFORCE Consortium for PD Cell Therapy

Blastocyst
Donor Cells
Pluripotent Stem Cells
Dopaminergic Progenitors

Fetal Ventral Mesencephalon

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

Our Rat Data

Lesioned side: No dopamine neurons

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
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!