Expert Briefings
Parkinson's Foundation

WELCOME TO EXPERT BRIEFINGS

Understanding Gene and Cell-Based Therapies in Parkinson's

- The program will begin at the top of the hour
- Meeting attendees will be muted and off video

Better Lives. Together.

Expert Briefings
Parkinson's Foundation

James Beck, PhD
Chief Scientific Officer, Parkinson's Foundation

Roger Barker, BA, MBBS, MRCP, PhD
Professor, University of Cambridge

Better Lives. Together.

Our Mission

The Parkinson's Foundation makes life better for people with Parkinson's disease by improving care and advancing research toward a cure. In everything we do, we build on the energy, experience and passion of our global Parkinson's community.

We have everything you need to live better with Parkinson's.

Our Goals

To help our global community live better with Parkinson's, we pursue **three goals:**

- **Improve care for everyone with Parkinson's**
- **Advance research toward a cure**
- **Empower and educate our global community**

Your Parkinson's community across the globe

22 countries represented around the world today:

- United States of America
- Canada
- Germany
- United Kingdom
- France
- India
- Mexico
- Puerto Rico
- Italy
- Switzerland
- Austria
- Norway
- Mauritius
- Pakistan
- New Zealand
- Thailand
- Australia
- Spain
- Colombia
- Finland
- Israel
- Taiwan

Poll: Getting to Know You

What best describes your connection to Parkinson's disease?

- Person with PD
- Spouse/Partner
- Parent has/had PD
- Other family
- Healthcare Professional
- Physician/Clinician
- Scientist/Researcher
- Nurse/Nurse Practitioner
- Other

Today's Sponsors

PD Health @ Home is presented by

Prevail THERAPEUTICS

A Wholly Owned Subsidiary of Eli Lilly and Company

Light of Day Foundation

whose generosity has made this programming possible.

For Your Convenience

Recording

Expert Briefings are recorded and archived on
www.Parkinson.org/ExpertBriefings

Meet Your Expert

Roger Barker, BA, MBBS, MRCP, PhD

- Professor of Neurology
- University of Cambridge

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Expert Briefings
Parkinson's Foundation

GENE AND CELL THERAPIES FOR PARKINSON'S DISEASE

WHERE ARE WE IN ALL THIS?

Roger Barker

John van Geest Centre for Brain Repair,
Wellcome- MRC Cambridge Stem Cell Institute &
Department of Neurology
University of Cambridge, UK
rab46@cam.ac.uk

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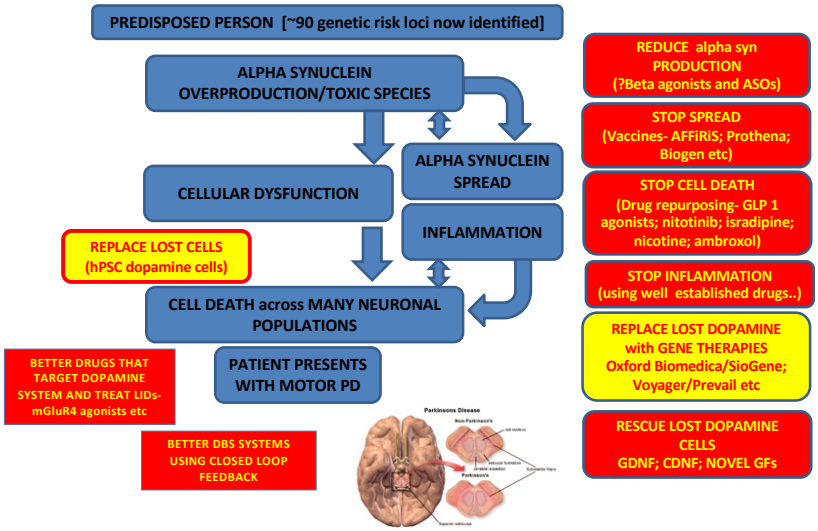
Disclosures

- Roger Barker currently advises the following companies on gene and cell-based therapies for Parkinson's disease: Aspen Neurosciences, Bayer, Transine Therapeutics Ltd and Novo Nordisk
- Roger Barker works with UCB on patient-related outcomes in early Parkinson's disease and M J Fox Foundation on patient risk-benefits for advanced therapies
- Roger Barker receives funding from EU, NIHR, MRC, Wellcome, Rosetrees Trust, Cure Parkinsons, MJFox Foundation and Aligning Science Across Parkinson's
- Roger Barker receives royalties from Wiley-Springer

NOVEL THERAPEUTIC STRATEGY

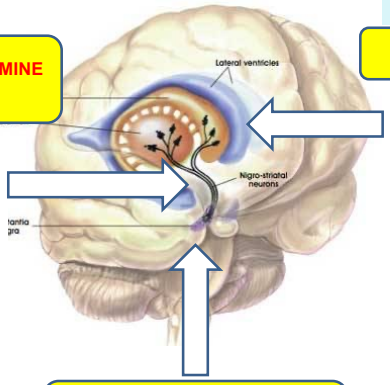


GENE THERAPIES FOR PARKINSON'S DISEASE

Parkinson's Foundation

RESCUE/REGROW DOPAMINE SYSTEM

CEREGENE
NEURTURIN GENE THERAPYY
BAYER
GDNF GENE THERAPY



REPLACE LOST DOPAMINE

OXFORD BIOMEDICA/AXOVANT/SIOGENE THERAPIES
PROSAVIN/OXB 102 GENE THERAPY

VOYAGER
AADC GENE THERAPY

RESCUE DYING CELLS

PREVAIL
GCASE GENE THERAPY
NysnoBio
PARKIN replacement in -/- patients or boost in iPD

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GENE THERAPIES FOR PARKINSON'S DISEASE

Parkinson's Foundation

RESCUE/REGROW DOPAMINE SYSTEM

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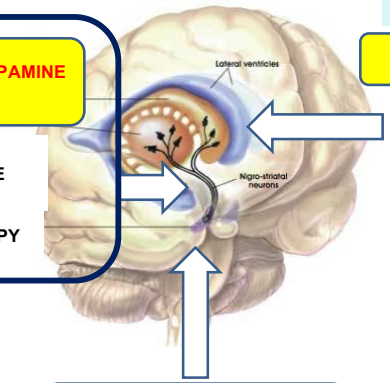

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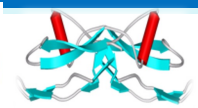
NEURTURIN/GDNF GENE THERAPIES FOR PARKINSON'S DISEASE- DOPAMINE REGROWTH

REPORTS

GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons



LF Lin, DH Doherty, JD Lile, S Bektesh, F Collins

+ Author Affiliations

Science 21 May 1993:
Vol. 260, Issue 5111, pp. 1130-1132
DOI: 10.1126/science.8493557

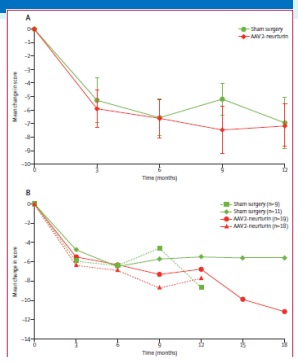
Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial

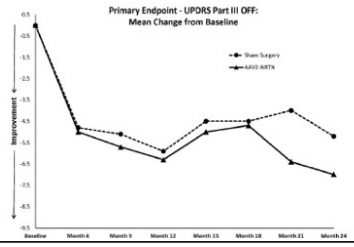
William J Marks Jr*, Raymond T Bartus*, Joao Siffert, Charles S Davis, Andres Lozano, Nicholas Boulis, Jerrold Vitek, Mark Stacy, Dennis Turner, Leonard Verhagen, Roy Bakay, Raymond Watts, Barton Guthrie, Joseph Jankovic, Richard Simpson, Michele Tagliati, Ron Alterman, Matthew Stern, Gordon Baltuch, Philip A Starr, Paul S Larson, Jill L Ostrem, John Nutt, Karl Kieburtz, Jeffrey H Kordower, C Warren Olanow*

RESEARCH ARTICLE

Gene Delivery of Neurturin to Putamen and Substantia Nigra in Parkinson Disease: A Double-Blind, Randomized, Controlled Trial

C. Warren Olanow, MD,[1] Raymond T. Bartus, PhD,[2] Tiffany L. Baumann, BS,[3] Stewart Factor, DO,[4] Nicholas Boulis, MD,[5] Mark Stacy, MD,[6] Dennis A. Turner, MD,[7] William Marks, MD,[8] Paul Larson, MD,[8] Phillip A. Starr, MD, PhD,[8] Joseph Jankovic, MD,[9] Richard Simpson, MD,[10] Ray Watts, MD,[11] Barton Guthrie, MD,[12] Kathleen Poston, MD,[13] Jaimie M. Henderson, MD,[14] Matthew Stern, MD,[15] Gordon Baltuch, MD,[16] Christopher G. Goetz, MD,[17] Christopher Herzog, PhD,[18] Jeffrey H. Kordower, PhD,[17] Ron Alterman, MD,[19] Andres M. Lozano, MD, PhD,[20] and Anthony E. Lang, MD[21]





ALSO SIMILAR REULTS WITH GDNF INFUSIONS..SO WHERE NEXT

RECOMMEND that going forward GDNF is given in EARLY disease

and also need to optimize serotype of gene being used, volume and dose given to ensure coverage of target structure..but still activity in this field..

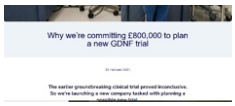
Journal of Parkinson's Disease 10 (2020) 875–881
DOI 10.3233/JPD-202004
IOS Press

875

Review Article

GDNF and Parkinson's Disease: Where Next? A Summary from a Recent Workshop

Roger A. Barker[a,*], Anders Björklund[b], Don M. Gash[c], Alan Whone[d], Amber Van Laar[e], Jeffrey H. Kordower[f], Krystof Bankiewicz[g], Karl Kieburtz[h], Matt Saarma[i], Sigrid Boonsa[j], Henri J. Huttunen[k,l], Adrian P. Kells[c], Massimo S. Fiandaca[g], A. Jon Stoessl[j], David Eidelberg[m], Howard Federoff[n], Merja H. Voutilainen[l], David T. Dexter[o], Jamie Eberling[g], Patrik Brundin[p], Lyndsey Isaacs[q], Leah Mursaleen[a,r], Eros Bresolin[s], Camille Carroll[t], Alasdair Coles[u], Brian Fiske[g], Helen Matthews[v], Cédric Lange[w], Richard K. Wyse[x], Simon Stott[y] and Anthony E. Lang[a,*]



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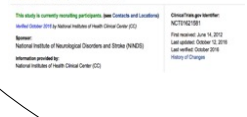

Gene Therapy Studies Underway in Parkinson Disease

June 15, 2021

Victoria Johnson

Bayer provided an update on their phase 1 and 1b studies of dopaminergic neurons and GDNF gene therapy,

0 5 10 15 Time in years

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GENE THERAPIES FOR PARKINSON'S DISEASE

Parkinson's Foundation

RESCUE/REGROW DOPAMINE SYSTEM

CEREGENE
NEURTURIN GENE THERAPYY
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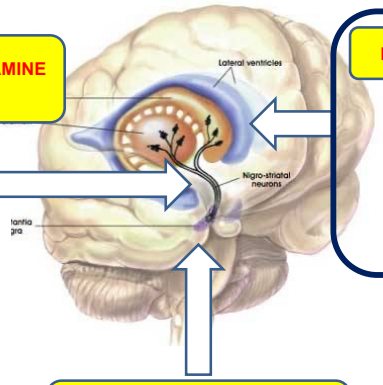

REPLACE LOST DOPAMINE

OXFORD BIOMEDICA/AXOVANT/SIOGENE THERAPIES
PROSAVIN/OXB 102 GENE THERAPY

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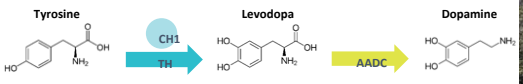
PARKIN replacement in -/- patients or boost in iPD

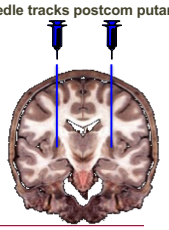
PROSAVIN/OXB 102 GENE THERAPIES FOR PARKINSON'S DISEASE-DOPAMINE REPLACEMENT

Parkinson's Foundation

ProSavin ® - A Lenti-TH-AADC-CH1



needle tracks postcom putamen

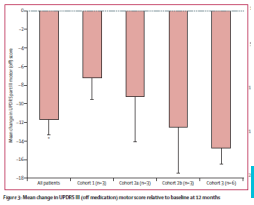


- 15 Patients with 3 different doses of ProSavin ®
- 2 severe adverse event totally unrelated to Prosavin
  - No dyskinesia in OFF states
  - Nb exacerbations of uncontrolled dyskinesia in ON states

Palfi et al. Lancet 2014

Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson's disease: a dose escalation, open-label, phase 1/2 trial

Stéphane Palfi, Jean Marc Gurruchaga, G Scott Ralph*, Helene Lepetit*, Sonia Lavisse, Philip C Buttery, Colin Watts, James Miskin, Michelle Kelleher, Sarah Deeley, Hirokazu Iwamura, Jean Pascal Lefaucheur, Claire Thiriez, Gilles Fenelon, Cherry Lucas, Pierre Brugières, Inanna Gabriel, Kou Abhay, Xavier Drouot, Naoki Tani, Aurelie Kas , Bijan Ghaleh, Philippe Le Corvoisier, Patrice Dolphin, David P Breen, Sarah Mason, Natalie Valle Guzman, Nicholas D Mazarakis, Pippa A Radcliffe, Richard Harrop, Susan M Kingsman, Olivier Rascol, Stuart Naylor, Roger A Barker, Philippe Hantraye, Philippe Remy, Pierre Cesaro, Kyriacos A Mitrophanous*



Cohort	1 (1x dose)	2 (2x dose)	3 (2x dose)	4 (5x dose)
Improvement in UPDRS Part III "OFF" score[1]	✓	✓	✓	✓
Average reduction in L-DOPA equivalent therapy	✓	✓	✓	✓
Improvement in UPDRS Part III "ON" score[2]	×	×	✓	✓
Reduction in PET[3] signal (i.e. increase in dopamine provision)	×	×	×	✓

LED on to a new trial; SUNRISE-PD: Phase 1/2 Open-label, Single-arm Dose Escalation Study

Parkinson's Foundation

SID GENE THERAPIES

Cohort 3
2.7 x 10^7 TU*
1800 µL total infusion volume

Cohort 2
9.0 x 10^6 TU*
600 µL total infusion volume

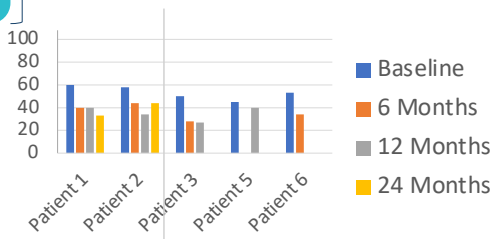
12 Month data reported

Cohort 1
2.6 x 10^6 TU*
600 µL total infusion volume

Observed Score

*Target dose

Improvement Shown by a Decrease in UPDRS Part III OFF Score of 14 to 27 Points in Cohort 1 at Month 24, and 5 to 23 Points in Cohort 2 at Month 12



Cohort 1 **Cohort 2***

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Phase I safety trial of hAADC gene therapy for Parkinson's disease

Parkinson's Foundation

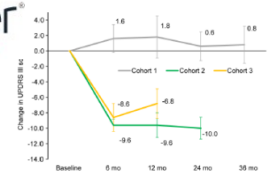
Ann Neurol 2019

SEARCH ARTICLE

Magnetic Resonance Imaging–Guided Phase 1 Trial of Putaminal *AADC* Gene Therapy for Parkinson's Disease

Chadwick W. Christine, MD,[1] Krystof S. Bankiewicz, MD,[2] Amber D. Van Laar, MD,[3] R. Mark Richardson, MD,[4] Bernard Ravina, MD,[5a] Adrian P. Kells, PhD,[5b] Brendon Boot, MBBS,[5c] Alastair J. Martin, PhD,[6] John Nutt, MD,[7] Marin E. Thompson, MS,[2] and Paul S. Larson, MD[2]

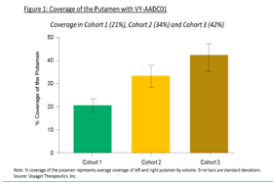
Voyager THERAPEUTICS

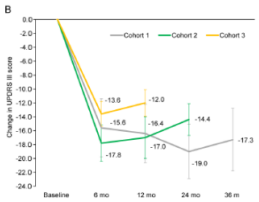


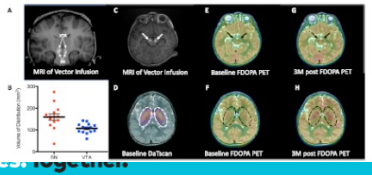
Nat Comm 2021

ARTICLE OPEN

Gene therapy for aromatic L-amino acid decarboxylase deficiency by MR-guided direct delivery of AAV2-AADC to midbrain dopaminergic neurons







OVERALL dopamine gene therapies have been shown to hold promise but remain unproven at present and investment in them is poor at present.

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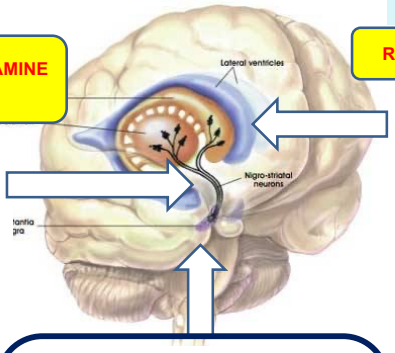
GENE THERAPIES FOR PARKINSON'S DISEASE

Parkinson's Foundation

RESCUE/REGROW DOPAMINE SYSTEM

CEREGENE
NEURTURIN GENE THERAPYY
BAYER
GDNF GENE THERAPYY



REPLACE LOST DOPAMINE

OXFORD BIOMEDICA/AXOVANT/SIOGENE THERAPIES
PROSAVIN/OXB 102 GENE THERAPY

VOYAGER
AADC GENE THERAPY

RESCUE DYING CELLS

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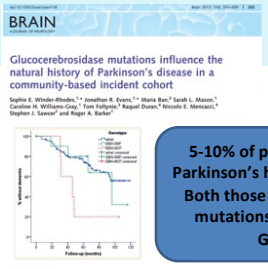
A NEW APPROACH USING GCase GENE THERAPY

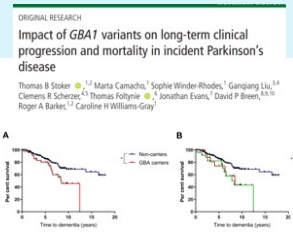
Parkinson's Foundation

2013


BRAIN

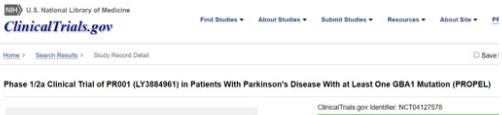
Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort

2020

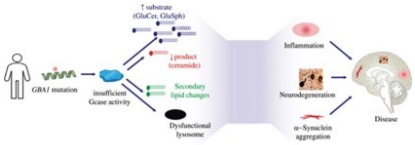

ORIGINAL RESEARCH

Impact of *GBA1* variants on long-term clinical progression and mortality in incident Parkinson's disease

5-10% of people with "sporadic" Parkinson's have a GBA 1 mutations; Both those with and without GBA mutations are said to have low GCase activity


ClinicalTrials.gov

Phase 1/2a Clinical Trial of PR001 (LY3884961) in Patients With Parkinson's Disease With at Least One GBA1 Mutation (PROPEL)



- Phase 1/2a, multicenter, open-label, ascending dose, first in-human study that will evaluate the safety of intracisternal LY3884961 administration in moderate GBA1 mutation PD patients.
- Two dose level cohorts of LY3884961 are planned with some immunosuppression
- The duration of the study is 5 years.
- During the first year, patients will be evaluated for the effect of LY3884961 on safety, tolerability, immunogenicity, biomarkers, and clinical efficacy measures.
- Patients will continue to be followed for an additional 4 years to continue to monitor safety as well as selected biomarker and efficacy measures.

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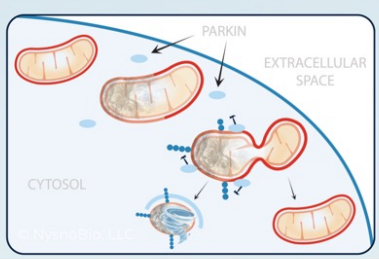
A NEW APPROACH USING PARKIN GENE THERAPY



1 - Damaged mitochondria recruit active Parkin

2 - Parkin then ubiquitinates specific proteins

3 - Ubiquitinated proteins signal synthesis of autophagosome

4 - Damaged portions of mitochondria are segregated and degraded

STEP 1

Replace PARKIN in Genetic Patients

- Parkin -/- early onset patients
- Clearly defined population and disease
- High chance to show clinical benefit for motoric deficit

STEP 2

Boost PARKIN Expression in Non-Genetic Patients

- Young Onset Parkinson's Disease (YOPD) patients of *non-genetic etiology*
- Later-onset, sporadic PD population
- Show benefit in larger, more heterogeneous population

Gene Therapy	Indication	Engineering	In Vivo POC	IND
NB001	Parkin PD	→	→	Q1-2024
NB001	Idiopathic PD, AD, ALS, Mitochondrial Disorders, Aging, and Lifespan	→		

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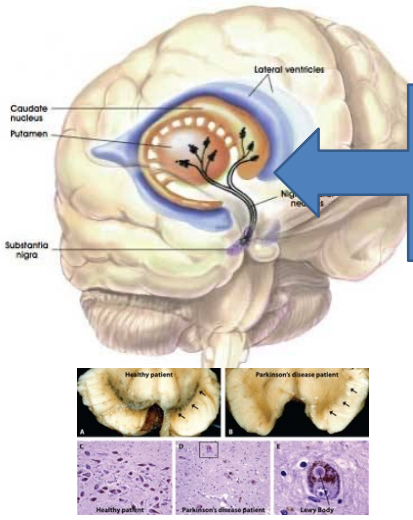
THE RATIONALE FOR DOPAMINE CELL REPLACEMENT



REPLACE A9 DOPAMINE NEURONS THROUGH NEURAL TRANSPLANT

- **IT WILL AVOID THE OFF TARGET EFFECTS OF DOPAMINERGIC DRUGS AS THERAPY IS TARGETED TO SITE OF DOPAMINE LOSS**
- **IT WILL REMOVE PROBLEMS OF LONG TERM DRUG TREATMENT OF PD AS DOPAMINE WILL BE RELEASED SYNAPTICALLY IN STRIATUM**

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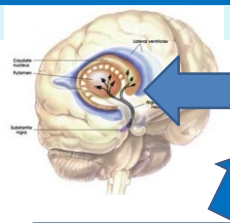
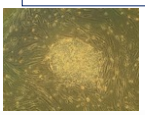
CELL THERAPIES FOR PARKINSON'S DISEASE

Parkinson's Foundation



REPLACE A9 DOPAMINE NEURONS THROUGH NEURAL TRANSPLANT

HUMAN FETAL DOPAMINE CELL THERAPIES



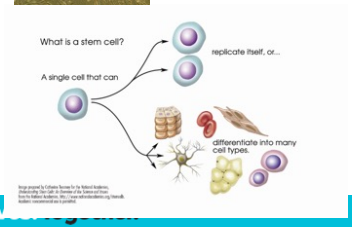
EMBRYONIC STEM CELL SOURCES

HUMAN STEM CELL DERIVED DOPAMINE CELL THERAPIES

ALLOGENEIC

- BLUEROCK THERAPEUTICS/BAYER H9 ES CELL LINE
- STEM-PD RC17 ES CELL LINE
- NOVO NORDISK (TRANSCEND STUDY) RC17 ES CELL LINE

INDUCED STEM CELL SOURCES



ALLOGENEIC

- CIRA IN JAPAN
- ARIZONA STATE UNIVERISTY IN PKN PATIENTS
- ?FCDI IN CHICAGO

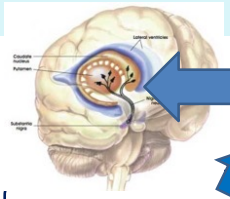
AUTOLOGOUS

- ASPEN NEUROSCIENCE
- MGH/HMS

Better Liv

CELL THERAPIES FOR PARKINSON'S DISEASE

Parkinson's Foundation



REPLACE A9 DOPAMINE NEURONS THROUGH NEURAL TRANSPLANT

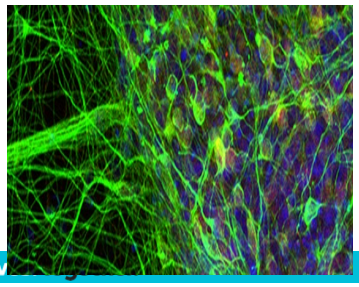
HUMAN FETAL DOPAMINE CELL THERAPIES

EMBRYONIC STEM CELL SOURCES

HUMAN STEM CELL DERIVED DOPAMINE CELL THERAPIES

ALLOGENEIC

- BLUEROCK THERAPUTICS/BAYER H9 ES CELL LINE
- STEM-PD RC17 ES CELL LINE
- NOVO NORDISK (TRANSCEND STUDY) RC17 ES CELL LINE



INDUCED STEM CELL SOURCES

ALLOGENEIC

- CIRA IN JAPAN
- ARIZONA STATE UNIVERISTY IN PARKIN PATIENTS
- ?FCDI IN CHICAGO

AUTOLOGOUS

- ASPEN NEUROSCIENCE
- MGH/HMS

Better Liv

CELL BASED THERAPIES FOR PARKINSON'S DISEASE
THE STORY WITH FETAL VENTRAL MESENCEPHALIC TISSUE

Parkinson's Foundation

LONG TERM CLINICAL BENEFITS

Case Report/Case Series

Long-term Clinical Outcome of Fetal Cell Transplantation for Parkinson Disease
Two Case Reports

Zinovia Kefalopoulou, MD, PhD; Marios Politis, MD, PhD; Paola Piccini, MD, PhD, FRCP; Niccolo Mencacci, MD; Kailash Bhatia, MD, PhD; Marjan Jahanshahi, PhD; Håkan Widner, MD, PhD; Stig Rehncrona, MD, PhD; Patrik Brundin, MD, PhD; Anders Björklund, PhD; Olle Lindvall, MD, PhD; Patricia Limousin, MD, PhD;

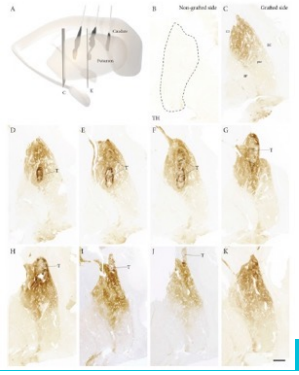
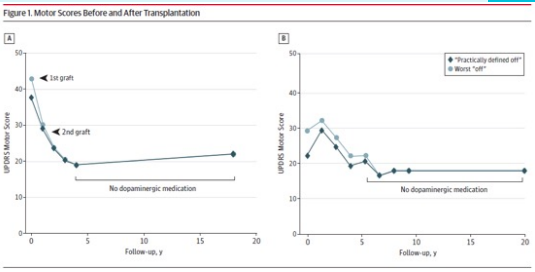


Figure 1. Motor Scores Before and After Transplantation



LONG TERM SURVIVAL

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

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

BUT NOT ALL STUDIES SHOWED THIS…

CELL BASED THERAPIES FOR PARKINSON'S DISEASE
THE NEGATIVE NIH STUDIES FETAL VENTRAL MESENCEPHALIC TISSUE

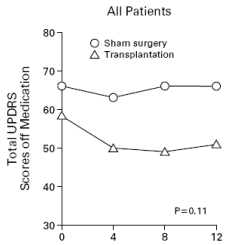
Parkinson's Foundation

The New England Journal of Medicine

TRANSPLANTATION OF EMBRYONIC DOPAMINE NEURONS FOR SEVERE PARKINSON'S DISEASE

Curt R. Freed, M.D., Paul E. Greene, M.D., Robert E. Breeze, M.D., Wei-Yann Tsai, Ph.D., William DuMouchel, Ph.D., Richard Kao, Sandra Dillon, R.N., Howard Winfield, R.N., Sharon Culver, N.P., John Q. Trojanowski, M.D., Ph.D., David Eidelberg, M.D., and Stanley Fahn, M.D.

RESULT
No significant benefit at 1 year using global rating scale;
Graft induced dyskinesias (GIDs) seen in 15% of patients



EXPEDITED PUBLICATION

A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease

C. Warren Olanow, MD,[1] Christopher G. Goetz, MD,[2] Jeffrey H. Kordower, PhD,[2] A. Jon Stoessl, MD,[3] Vesna Sossi, PhD,[3] Mitchell F. Brin, MD,[4] Kathleen M. Shannon, MD,[4] G. Michael Nauert, MD,[4] Daniel P. Perl, MD,[5] James Godbold, PhD,[6] and Thomas B. Freeman, MD[6]

RESULT
No significant benefit at 2 year using UPDRS defined off;
GIDs seen in 54% of patients

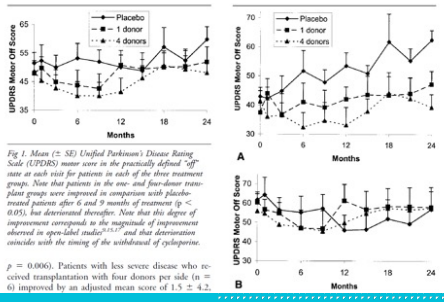


Fig 1. Mean (± SE) Unified Parkinson's Disease Rating Scale (UPDRS) motor score in the practically defined "off" state at each visit for patients in each of the three treatment groups. Note that patients in the one- and four-donor transplant groups were improved in comparison with placebo-treated patients after 6 and 9 months of treatment (p < 0.05), but deteriorated thereafter. Note that this degree of improvement corresponds to the magnitude of improvement observed in open-label studies[2,13,17] and that deterioration coincides with the timing of the withdrawal of cyclosporine.

$p = 0.006$). Patients with less severe disease who received transplantation with four donors per side (n = 6) improved by an adjusted mean score of 1.5 ± 4.2,

CELL BASED THERAPIES FOR PARKINSON'S DISEASE
A RECONCILIATION OF THE DATA

Parkinson's Foundation

Fetal dopaminergic transplantation trials and the future of neural grafting in Parkinson's disease

Roger A Barker, Jessica Barrett, Sarah L Mason, Anders Björklund

Lancet Neurol 2013; 12: 84–91 Clinical use of allografts of fetal ventral mesencephalic tissue as a treatment to replace dopaminergic neurons in

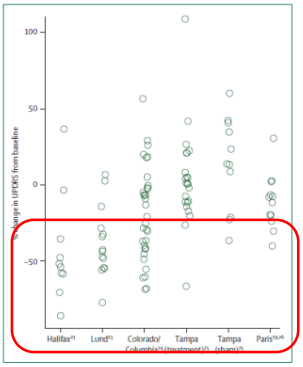


Figure 1: Change in UPDRS score for patients enrolled in ventral mesencephalic transplant trials

.. IDENTIFIED 4 KEY FACTORS LINKED TO BETTER PATIENT OUTCOMES

1. Younger/less advanced patients;
2. Better tissue prep and implantation;
3. Longer duration of immunosuppression
4. Longer follow up

TRANSEURO

Better Lives. Together.

CELL BASED THERAPIES FOR PARKINSON'S DISEASE
THE TRANSEURO TRIAL

Parkinson's Foundation

TRANSEURO

2015 2018

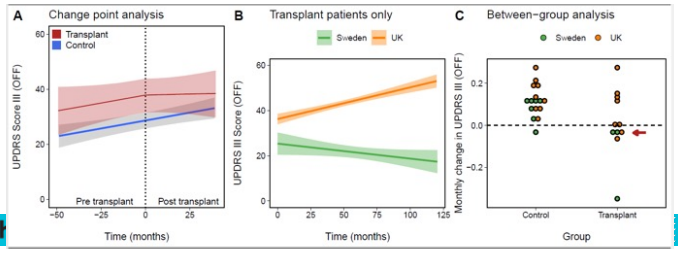
ONE INCOMPLETE TRANSPLANT TRIAL

2021

- 11/14 GRAFTED;
- 14 MATCHED and NOT GRAFTED but FOLLOWED WITH PET;
- 100+ FOLLOWED CLINICALLY;

3 YEAR PRIMARY END POINT (UPDRS OFF) ; Many secondary end points

CONCLUSION:
NO MAJOR BENEFIT but
?DOSING
?DEVICE…
..and fundamentally…..



Better Lives. Togeth

CELL BASED THERAPIES FOR PARKINSON'S DISEASE
THE TRANSEURO TRIAL

Parkinson's Foundation

2010

TRANSEURO

ONE INCOMPLETE TRANSPLANT TRIAL

2015 2018 2021

OPTIMISED PATIENT SELECTION
Patients <65 years old;
<10 years duration;
Cognitively normal;
Minimal or no LIDs;
From an observational cohort of >100

STANDARDISED TISSUE PREPARATION with a cell suspension made from AT LEAST 3 VM per side

OPTIMAL GRAFTING PROCEDURE:
DELIVERY OF TISSUE USING 5-7 TRACTS TO POST PUTAMEN;
"REHNCRONA" INSTRUMENT FOR GRAFTING.

- **11/14 GRAFTED;**
- **14 MATCHED and NOT GRAFTED but FOLLOWED WITH PET;**
- **100+ FOLLOWED CLINICALLY;**

3 YEAR PRIMARY END POINT (UPDRS OFF) ; Many secondary end points

LOGISTICALLY NOT VIABLE

Table 1 | The timetable of transplants and the reasons why planned surgeries were cancelled

	2015	2016	2017	2018*	Total
Theater slots	30	62	31	5	128
Completed procedures	7	9	4	1	21
Cancelled (due to)	23	53	27	4	107
Tissue supply	15	44	24	4	87
Tissue viability	1				1
Scheduling issues	2	6	3		11
Instruments	3				3
GMP airflow	2				2
Localization queries		2			2
Oncology case		1			1

Twenty-one transplant surgeries were completed across the two sites. This included ten bilateral grafts that were done sequentially (that is, at two different surgical operations), and one patient elected not to have a second transplant after their unilateral surgery. *Final procedure March 2018

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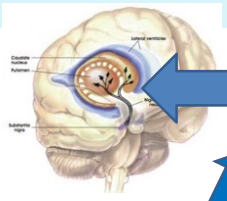
CELL THERAPIES FOR PARKINSON'S DISEASE

Parkinson's Foundation



REPLACE A9 DOPAMINE NEURONS THROUGH NEURAL TRANSPLANT

HUMAN FETAL DOPAMINE CELL THERAPIES

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RC17 ES CELL LINE

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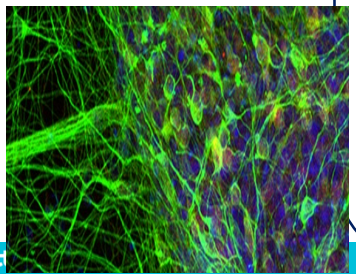

INDUCED STEM CELL SOURCES

ALLOGENEIC

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- **ARIZONA STATE UNIVERISTY IN PKN PATIENTS**
- **?FCDI IN CHICAGO**

AUTOLOGOUS

- **ASPEN NEUROSCIENCE**
- **MGH/HMS**

Bet

BUT CAN WE MAKE MIDBRAIN DAn from hPSCs?

Parkinson's Foundation

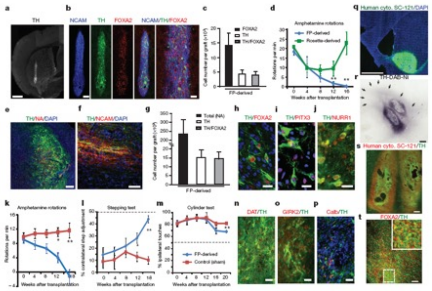
2011-2012

LETTER

doi:10.1038/nature10648

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

Sonja Kriks[1,2]*, Jae-Won Shim[1,3]*, Jinghua Piao[1,2], Yosif M. Ganat[1,2], Dustin R. Wakeman[4], Zhong Xie[5], Luis Carrillo-Reid[1], Gordon Auyeung[1,2], Chris Antonacci[1,2], Amanda Buch[1,2], Lichuan Yang[6], M. Flint Beal[6], D. James Surmeier[5], Jeffrey H. Kordower[4], Viviane Tabar[1,2] & Lorenz Studer[1,2,3]

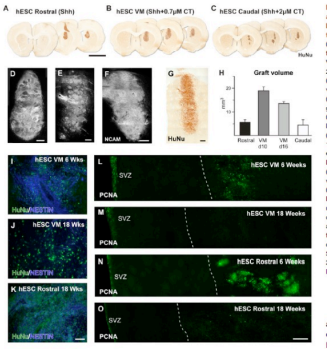


Cell Reports

Article

Generation of Regionally Specified Neural Progenitors and Functional Neurons from Human Embryonic Stem Cells under Defined Conditions

Agnete Kirkeby,[1,2,4] Shane Grealish,[1,4] Daniel A. Wolf,[1,2] Jenny Nelander,[1,2] James Wood,[2,3] Martin Lundblad,[1] Olle Lindvall,[2,3] and Malin Parmar[1,2,*]



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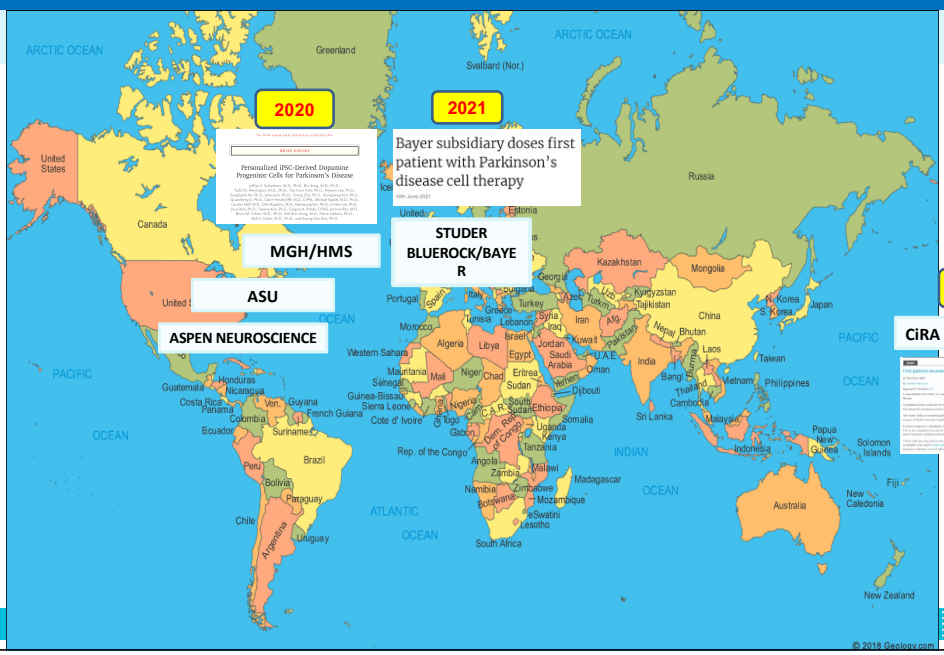
STEM CELL BASED THERAPIES FOR PARKINSON'S DISEASE

Parkinson's Foundation



2020

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

MGH/HMS

ASU

ASPEN NEUROSCIENCE

2021

Bayer subsidiary doses first patient with Parkinson's disease cell therapy

19th June 2021

STUDER BLUEROCK/BAYER

2018

CiRA

First patient receives stem cell transplant in Parkinson's trial

ONLY PUBLISHED STEM CELL TRIAL IN PD

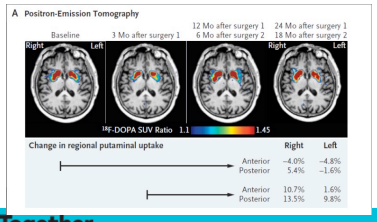
..and N=1 AUTOLOGOUS iPSC derived dopamine cells

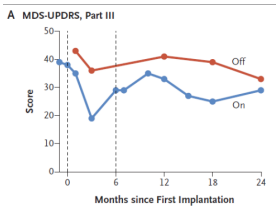
The NEW ENGLAND JOURNAL of MEDICINE

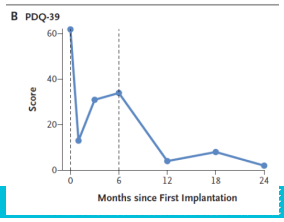
BRIEF REPORT

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.







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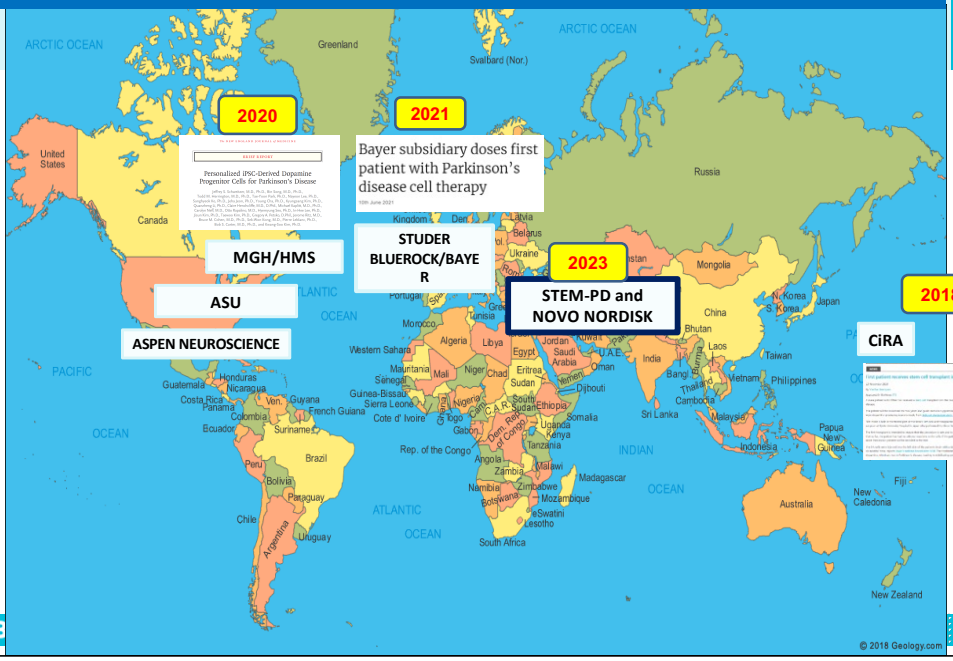
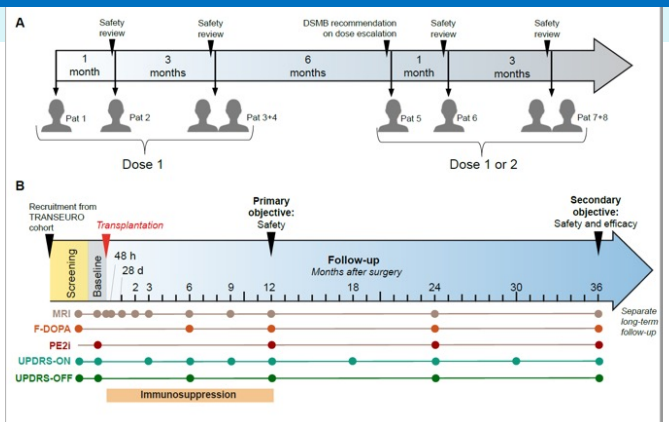
STEM CELL BASED THERAPIES FOR PARKINSON'S DISEASE



OUR STEM-PD TRIAL



Primary objective

To assess the **safety, tolerability** and **feasibility** of intraputamenal transplantation of the STEM-PD product in patients with moderate PD.

Secondary objectives

To evaluate the **course** and **efficacy** on **clinical features** following intraputamenal transplantation of the STEM-PD product in patients with moderate PD.

To assess the **survival of DA cells** following transplantation of the STEM-PD product in patients with moderate PD using **PET imaging**.

To determine the **safety** and **clinical efficacy between doses** (if dose escalation is undertaken) of the STEM-PD product, including assessment of whether there is a **dose response effect**.

DOPAMINE CELL THERAPIES have shown proof of concept …stem cell derived dopamine cells now being trialled- results awaited

Better

AND IN THE FUTURE- Direct reprogramming..

ARTICLES

nature biotechnology

Induction of functional dopamine neurons from human astrocytes *in vitro* and mouse astrocytes in a Parkinson's disease model

Pia Rivetti di Val Cervo[1], Roman A Romanov[2,3], Giada Spigolon[3], Débora Masini[3], Elisa Martín-Montañez[1,4], Enrique M Toledo[1], Gioele La Manno[1], Michael Feyder[5], Christian Pifl[6], Yi-Han Ng[1], Sara Padrell Sánchez[1], Sten Linnarsson[1], Marius Wernig[5], Tibor Harkany[2,3], Gilberto Fisone[3] & Ernest Arenas[1]

Article

Reversing a model of Parkinson's disease with in situ converted nigral neurons

https://doi.org/10.1038/s41586-020-2388-4
Received: 12 November 2018
Accepted: 13 May 2020

Hao Qian[1], Xinjiang Kang[2,3], Jing Hu[1,4], Dongyang Zhang[4], Zhengyu Liang[1], Fan Meng[1], Xuan Zhang[1], Yuanchao Xue[1,4], Roy Maimon[1,5], Steven F. Dowdy[1], Neal K. Devaraj[4], Zhuan Zhou[3], William C. Mobley[3], Don W. Cleveland[1,3] & Xiang-Dong Fu[1,2]✉

Cell

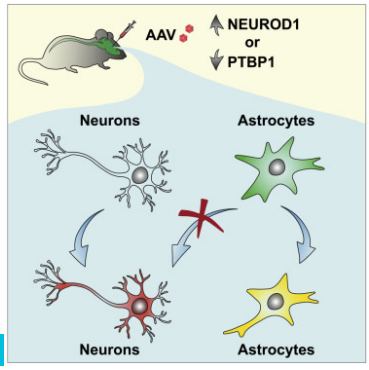
CellPress

Article

Revisiting astrocyte to neuron conversion with lineage tracing *in vivo*

Lei-Lei Wang,[1,2,7] Carolina Serrano,[1,2] Xiaoling Zhong,[1] Shuaipeng Ma,[1] Yuhua Zou,[1] and Chun-Li Zhang[1,2,*]
[1]Department of Molecular Biology and Hamon Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
[7]These authors contributed equally
[*]Lead contact
*Correspondence: lei.lei.wang@utsouthwestern.edu (L.-L.W.), chun-li.zhang@utsouthwestern.edu (C.-L.Z.)
https://doi.org/10.1016/j.cell.2021.09.005

In situ reprogramming of astrocytes to nigral dopaminergic neurogenesis is currently not that efficient…



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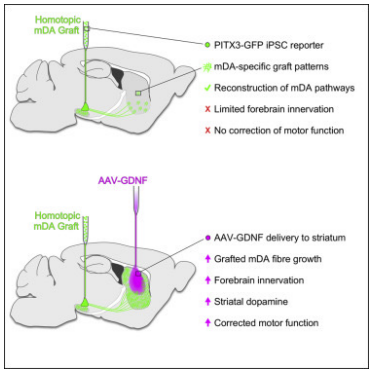
AND IN THE FUTURE- Combined therapies..

Article

A combined cell and gene therapy approach for homotopic reconstruction of midbrain dopamine pathways using human pluripotent stem cells

Niamh Moriarty,[1] Carlos W. Gantner,[1,2] Cameron P.J. Hunt,[1] Charlotte M. Ermine,[1] Stefano Frausin,[1] Serena Viventi,[1] Dmitry A. Ovchinnikov,[1] Deniz Kirik,[2,3] Clare L. Parish,[1,4,*] and Lachlan H. Thompson[1,4,5,*]

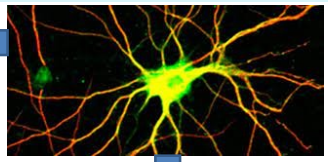


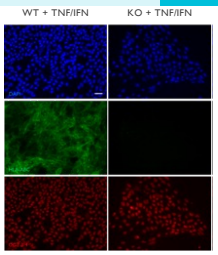
- **A PITX3-eGFP iPSC line reveals patterns of mDA neuron growth from stem cell grafts**
- **mDA neurons in homotopic grafts target nuclei not well innervated by ectopic grafts**
- **Forebrain GDNF facilitates robust striatal innervation by homotopic mDA grafts**

Combined therapies may prove very useful but bring with it some significant regulatory issues..

AND IN THE FUTURE- Engineered cell products..

Make alpha synuclein KO stem cells to prevent disease spreading to transplant





BRIEF COMMUNICATIONS

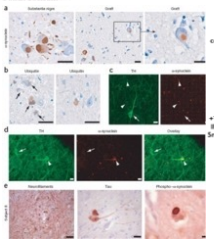
Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease

Jeffrey H Kordower[1], Yaping Chu[1], Robert A Hauser[2], Thomas B Freeman[2] & C Warren Olanow[3]

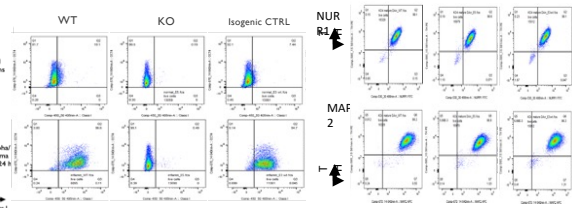
nature medicine

Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation

Jia-Yi Li[1], Elisabet Englund[2], Janice L Holton[3], Denis Soulet[1], Peter Hagell[4], Andrew J Lees[3], Tamamaryn Lashley[3], Niall P Quinn[3], Stig Rehncrona[4], Anders Björklund[5], Håkan Widner[4], Tamas Revesz[3,6], Olle Lindvall[1,6,9] & Patrik Brundin[1,9]



Make cells less immunogenic by knocking out MHC…



Gene editing could be done and may be useful but unclear whether it is really needed

CONCLUSIONS

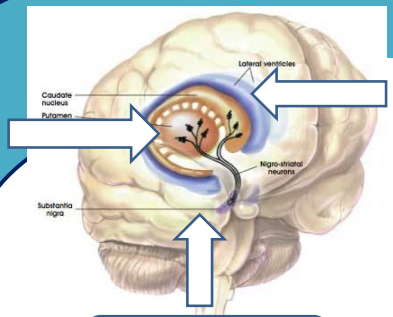
RESCUE/REGROW DOPAMINE SYSTEM

SOME INTEREST WITH GDNF GENE THERAPY STILL ONGOING and also PROTEIN INFUSIONS

REPLACE LOST DOPAMINE

NO REAL INTEREST CURRENTLY IN THIS USING A GENE THERAPY APPROACH but

MUCH INTEREST IN DOING THIS USING DOPAMINE NEURONS MADE FROM STEM CELLS- TRIALS ONGOING



RESCUE DYING CELLS

STARTING TO BE INVESTIGATED WITH GENE THERAPIES

MAJOR AREA OF WORK WITH DRUGS AND SMALL MOLECULES

Better Lives. Together.

ULTIMATELY COULD BRING THEM ALL TOGETHER

The Barker/Williams-Gray Lab

STEM-PD

COLLABORATORS in this WORK:

CAMBRIDGE; Phil Buttery, Rob Morris, Amy Evans, Bronwen Harry, Emma Cutting, Ruwani Wijeeyikoon, Tagore Nakorchai, Danielle Daft, Shaline Fazel and STEM PD team

LUND; Malin Parmar; Agnete Kirkeby; Anders Bjorklund plus STEM-PD team

OTHERS; TRANSEURO; GFORCE-PD; NSCReconstruct; Stephane Palfi; Tom Foltynie; Paola Piccini

This work has been supported by:

MRC; Cure Parkinson's Trust; Rosetrees Trust; NIHR; Wellcome; and EU FP7/H2020 programmes.

John Van Geest Centre for Brain Repair

wellcome-MRC cambridge stem cell institute

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2023 Expert Briefings

Expert Briefings
Parkinson's Foundation

Wednesday, March 8

Parkinson's & Medications – What's New
Tanya Simuni, MD

Wednesday, April 12

A Balancing Act – Freezing and Fall Prevention in Parkinson's
Colum MacKinnon, PhD

Wednesday, May 10

Understanding Gene and Cell-Based Therapies in Parkinson's
Roger Barker, MD

Wednesday, September 13

Parkinson's Disease & the Bladder
Abhimanyu Mahajan, MD, MHS

Wednesday, October 11

Parkinson's & the Gut-Brain Connection
Carley Rusch, MS, RDN, LDN

Wednesday, November 8

Do You See What I See? Hallucinations & Delusions in Parkinson's
Megan E. Gomez, PhD

Register at **Parkinson.org/ExpertBriefings**

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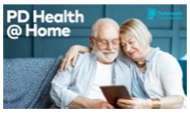
Resources and Support

Aware in Care
Parkinson.org/AwareInCare

PD Library
Parkinson.org/PDLibrary



PD Health @ Home
Parkinson.org/PDHealth

Resources and Support Continued

Podcast: Substantial Matters
Parkinson.org/Podcast

Professional Education
Parkinson.org/ProfessionalEducation

PD Generation
Parkinson.org/PDGeneration

We're Here For You

Parkinson's Foundation

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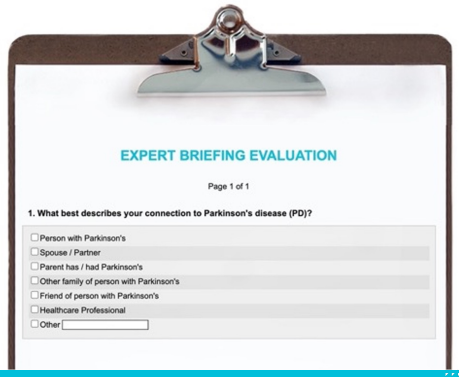
Before You Go…

Parkinson's Foundation

Your feedback is important to us!
Please complete the evaluation after the close of this webinar.



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