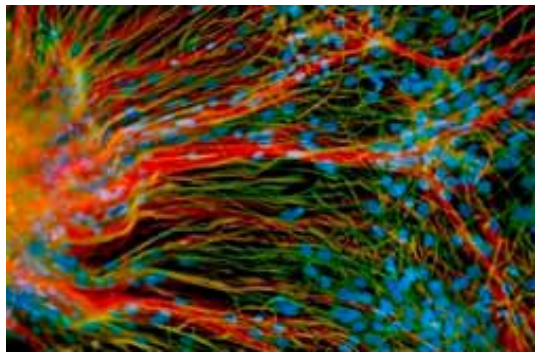
# WHAT GOES WRONG IN PARKINSON'S DISEASE and WHAT CAN WE DO ABOUT IT? Some thoughts...



**Roger Barker**

Cambridge Centre
for Brain Repair
and
Department of Neurology
Cambridge CB2 2PY, UK
rab46@hermes.cam.ac.uk

# To begin at the beginning....

1817- James Parkinson describes the disease that Charcot named after him

1912- Friedrich Lewy describes inclusion body pathology

1960s- Loss of dopamine as core pathological event in PD is first described with successful treatment of patients with L-dopa

**1990s- Alpha-synuclein is linked to**

*Science 27 June 1997:*
*Vol. 276 no. 5321 pp. 2045-2047*
*MH Polymeropoulos et al-*
**Mutation in the α-Synuclein Gene Identified in Families with Parkinson's Disease**

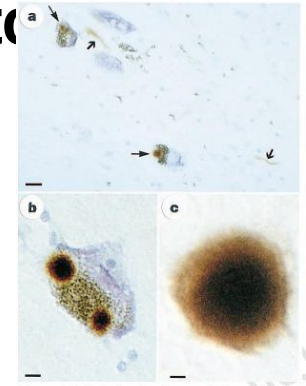



**Figure 1** Substantia nigra from patients with Parkinson's disease (from the MRC Cambridge Brain Bank) immunostained for α-synuclein. **a,** Two pigmented nerve cells, each containing an α-synuclein-positive Lewy body (thin arrows). Lewy neurites (thick arrows) are also immunopositive. Scale bar, 20 μm. **b,** A pigmented nerve cell with two α-synuclein-positive Lewy bodies. Scale bar, 8 μm. **c,** α-Synuclein-positive, extracellular Lewy body. Scale bar, 4 μm.

## α-Synuclein in Lewy bodies

**Maria Grazia Spillantini**
*Medical Research Council Centre for Brain Repair and Department of Neurology, University of Cambridge, Robinson Way, Cambridge CB2 2PY, UK*
**Marie Luise Schmidt**
**Virginia M.-Y. Lee**
**John Q. Trojanowski**
*Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-4283, USA*
**Ross Jakes, Michel Goedert**
*Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK*

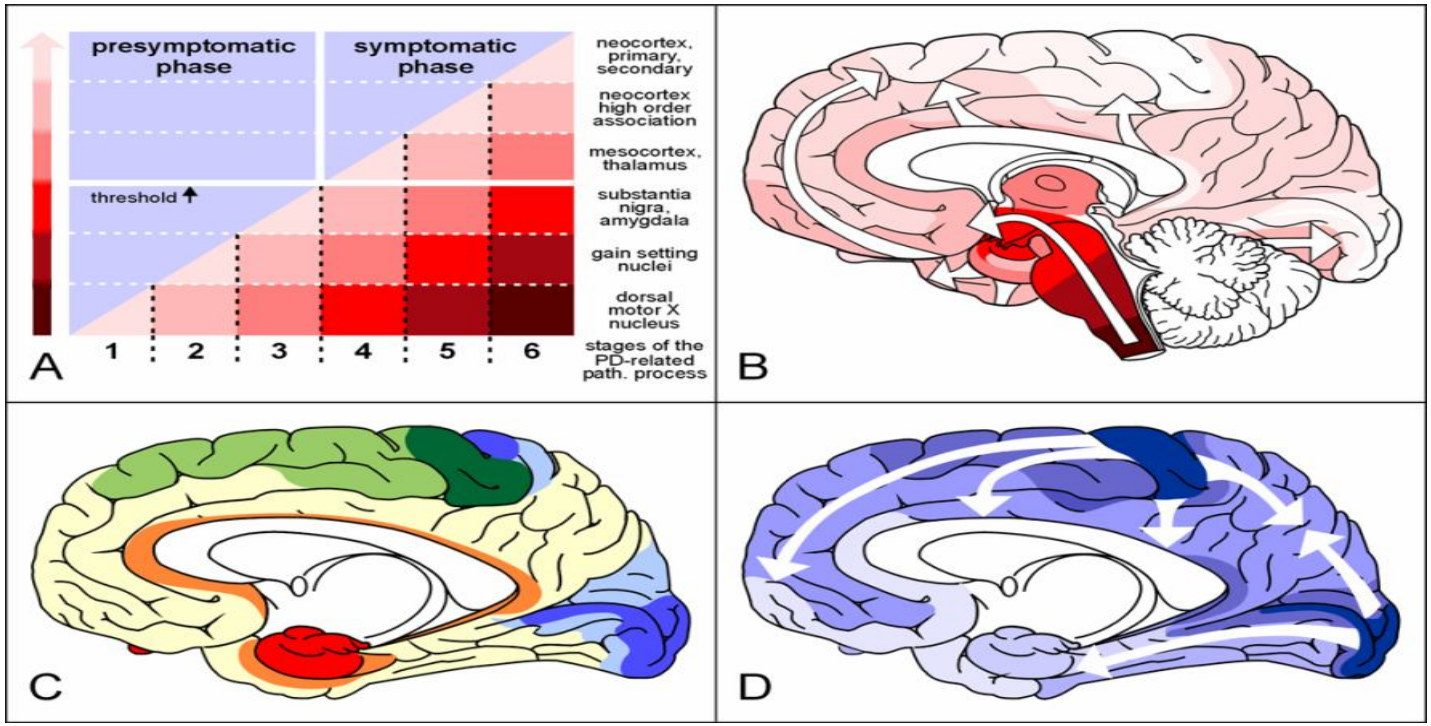
NATURE | VOL 388 | 28 AUGUST 1997

# THE EVOLUTION OF A NEW HYPOTHESIS about PD

1817- James Parkinson describes the disease that Charcot named after him
1912- Friedrich Lewy describes inclusion body pathology
1960s- Loss of dopamine as core pathological event in PD is first described with successful treatment of patients with L-dopa
1990s- Alpha-synuclein is linked to PD
**2003- Heiko Braak classification of PD pathology and concept of non-motor/prodromal disease**

Heiko Braak · Estifanos Ghebremedhin · Udo Rüb ·
Hansjürgen Bratzke · Kelly Del Tredici

# Stages in the development of Parkinson's disease-related pathology




**NOW RECOGNISED THAT PD PATIENTS HAVE A RANGE OF NON-MOTOR FEATURES INCLUDING: AFFECTIVE; AUTONOMIC; SLEEP; ENTERIC; and COGNITIVE DEFICITS... AND SOME OR ALL OF THESE START AT OR BEFORE MOTOR DISEASE ONSET..Pre PD**

Postuma RB et al (2009)
**Idiopathic REM sleep behavior disorder in the transition to degenerative disease.**

Since 2004, we have been conducting a prospective study of idiopathic RBD patients…Of 67 patients, 6 developed PD and eleven developed dementia.

Claassen DO et al (2010) **REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century.**

**Results: Clinical criteria were met by 27 patients who experienced isolated RBD for at least 15 years before evolving into PD, PD dementia (PDD), DLB, or MSA**. The interval between RBD and subsequent neurologic syndrome ranged up to 50 years, with the median interval 25 years.

# THE EVOLUTION OF A NEW HYPOTHESIS about PD

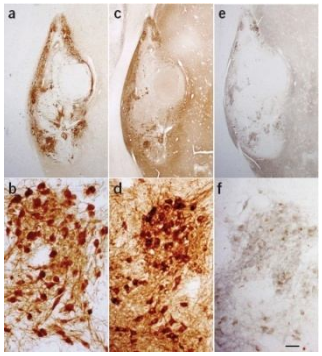
1817- James Parkinson describes the disease that Charcot named after him
1912- Friedrich Lewy describes inclusion body pathology
1960s- Loss of dopamine as core pathological event in PD is first described with successful treatment of patients with L-dopa
1990s- Alpha-synuclein is linked to PD
2003- Heiko Braak classification of PD pathology and concept of non-motor/prodromal disease
**2008- Synuclein pathology in fetal neural grafts**

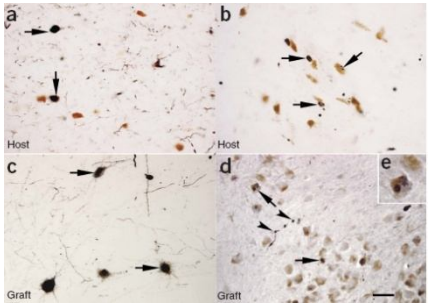
BRIEF COMMUNICATIONS

nature medicine

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

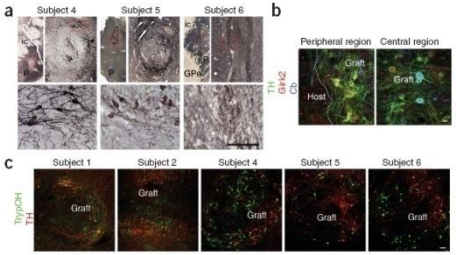
Jeffrey H Kordower[1], Yaping Chu[1], Robert A Hauser[2], Thomas B Freeman[3] & C Warren Olanow[4]

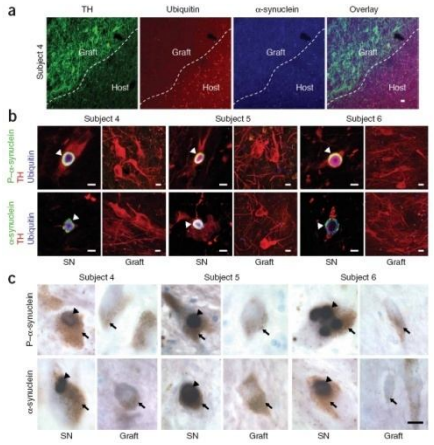





# Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years

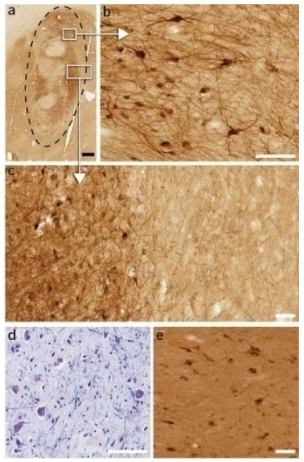
Ivar Mendez[1,6], Angel Viñuela[2,6], Arnar Astradsson[2], Karim Mukhida[1], Penelope Hallett[2], Harold Robertson[1], Travis Tierney[2,3], Renn Holness[1], Alain Dagher[4], John Q Trojanowski[5] & Ole Isacson[2]

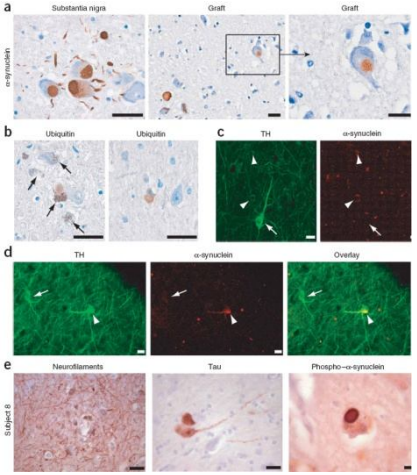



# Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation

Jia-Yi Li[1], Elisabet Englund[2], Janice L Holton[3], Denis Soulet[1], Peter Hagell[4], Andrew J Lees[3], Tammaryn Lashley[3], Niall P Quinn[5], Stig Rehncrona[6], Anders Björklund[7], Håkan Widner[4], Tamas Revesz[3,9], Olle Lindvall[4,8,9] & Patrik Brundin[1,9]



# THE EVOLUTION OF A NEW HYPOTHESIS about PD

1817- James Parkinson describes the disease that Charcot named after him
1912- Friedrich Lewy describes inclusion body pathology
1960s- Loss of dopamine as core pathological event in PD is first described with successful treatment of patients with L-dopa
1990s- Alpha-synuclein is linked to PD
2003- Heiko Braak classification of PD pathology and concept of non-motor/prodromal disease
2008- Synuclein pathology in fetal neural grafts
**2009- PD as a prion (i.e. mad cow disease) disorder?**

PNAS 2009; August 4th; 106:12571-12572

## Is Parkinson's disease a prion disorder?

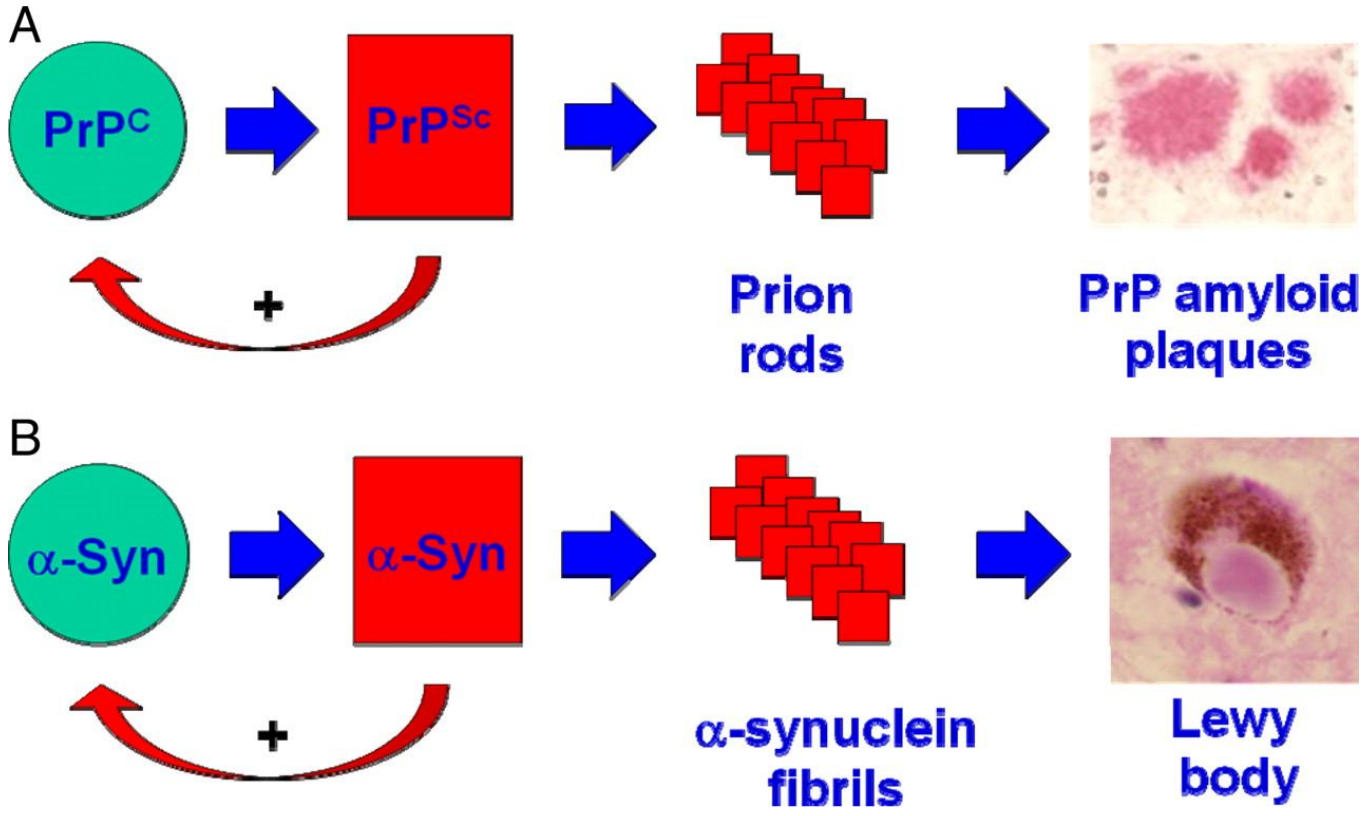
C. Warren Olanow[a,1] and Stanley B. Prusiner[b]
[a]Departments of Neurology and Neuroscience, Mount Sinai School of Medicine, New York, NY 10029; and [b]Institute for Neurodegenerative Diseases and Department of Neurology, University of California, San Francisco, CA 94143

PNAS 2009; August 4th; 106:12571-12572

# Is Parkinson's disease a prion disorder?

C. Warren Olanow[a,1] and Stanley B. Prusiner[b]
[a]Departments of Neurology and Neuroscience, Mount Sinai School of Medicine, New York, NY 10029; and [b]Institute for Neurodegenerative Diseases and Department of Neurology, University of California, San Francisco, CA 94143

## Schematic illustration demonstrating similarities in the relationships between the PrPC protein and prion diseases, and the α-synuclein protein and Parkinson's disease



# Many studies have now shown that proteins associated with neurodegenerative disorders can spread from cell to cell and this includes alpha-synuclein both in transplants of fetal brain tissue ..

Research article

## α-Synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells

Christian Hansen,[1] Elodie Angot,[1] Ann-Louise Bergström,[2] Jennifer A. Steiner,[1] Laura Pieri,[2] Gesine Paul,[1] Tiago F. Outeiro,[4,5] Ronald Melki,[3] Pekka Kallunki,[2] Karina Fog,[2] Jia-Yi Li,[1] and Patrik Brundin[1]

[1]Neuronal Survival Unit, Wallenberg Neuroscience Center, Lund University, Lund, Sweden. [2]H. Lundbeck A/S, Valby, Denmark. [3]Laboratoire d'Enzymologie et Biochimie Structurales, CNRS, Gif-sur-Yvette, France. [4]Cell and Molecular Neuroscience Unit, Instituto de Medicina Molecular, Lisbon, Portugal. [5]Instituto de Fisiologia, Faculdade de Medicina de Lisboa, Universidade de Lisboa, Lisbon, Portugal.

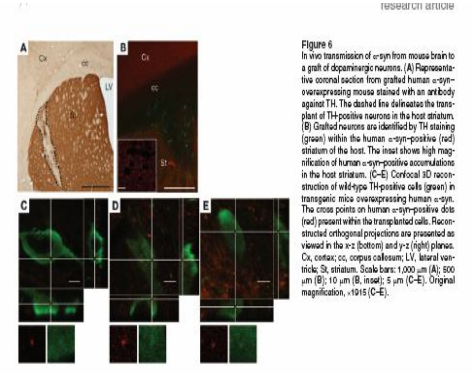


Figure 6
In vivo transmission of α-syn from mouse brain to a graft of dopaminergic neurons. (A) Representative coronal section from grafted human α-syn–overexpressing mouse stained with an antibody against TH. The dashed line delineates the transplant of TH-positive neurons in the host striatum. (B) Grafted neurons are identified by TH staining (green) within the human α-syn–positive (red) striatum of the host. The inset shows high magnification of human α-syn–positive accumulations in the host striatum. (C–E) Confocal 3D reconstruction of wild-type TH-positive cells (green) in transgenic mice overexpressing human α-syn. The cross points on human α-syn–positive dots (red) present within the transplanted cells. Reconstructed orthogonal projections are presented as viewed in the x-z (bottom) and y-z (right) planes. Cx, cortex; cc, corpus callosum; LV, lateral ventricle; St, striatum. Scale bars: 1,000 μm (A); 500 μm (B); 10 μm (B, inset); 5 μm (C–E). Original magnification, ×1915 (C–E).

Neuron
Article

## Exogenous α-Synuclein Fibrils Induce Lewy Body Pathology Leading to Synaptic Dysfunction and Neuron Death

Laura A. Volpicelli-Daley,[1] Kelvin C. Luk,[1] Tapan P. Patel,[2] Selcuk A. Tanik,[1] Dawn M. Riddle,[1] Anna Stieber,[1] David F. Meaney,[2] John Q. Trojanowski,[1] and Virginia M.-Y. Lee[1,*]
[1]Department of Pathology and Laboratory Medicine, Institute on Aging and Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA
[2]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, USA
*Correspondence: vmylee@upenn.edu
DOI 10.1016/j.neuron.2011.08.033

**..and our own in vitro work has shown..**

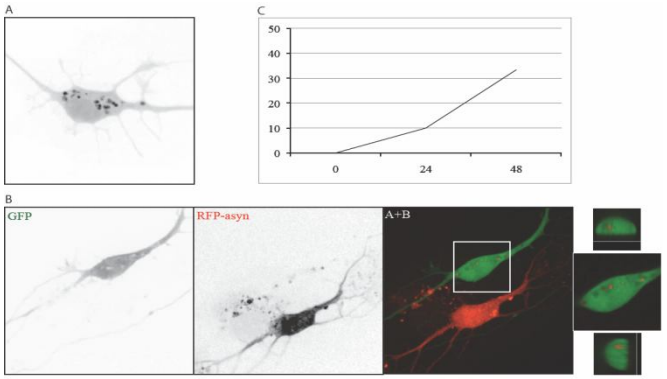



**Figure 4. Overexpression of RFP-tagged a-synuclein leads to aggregate formation and spreading in neurons.**
**A.** Confocal micrograph of neurons expressing RFP-tagged a-synuclein for 3 days. **B.** Confocal micrograph of neurons expressing RFP-tagged a-synuclein co-culture with GFP-expressing neurons **C.** Percentage of GFP-expressing neurons containing RFP-tagged a-synuclein aggregates.

## Rotenone model:

- Progressive accumulation of alpha-synuclein within enteric nervous system and peripheral centres of intestinal innervation
- Three month intragastric administration of rotenone causes alpha-synuclein accumulation in substantia nigra, accompanied by minor cell loss and rotarod deficit.

## I. Effects of PD-related mitochondrial toxin rotenone on aggregation of alpha-synuclein within enteric nervous system

Tissue collection

5mg/kg rotenone via stomach gavage

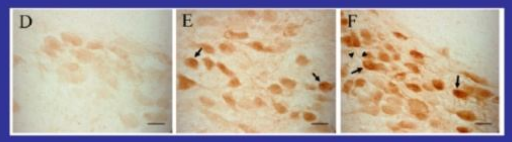
start

1.5 months treatment

3 months treatment

## Effects of oral rotenone on CNS alpha-synuclein – parasympathetic centre of enteric innervation

Dorsal motor nucleus of vagus



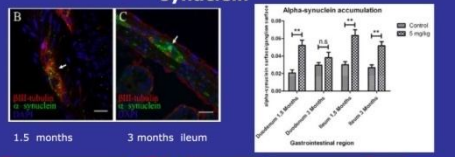

control

1.5 months treatment

3 months treatment

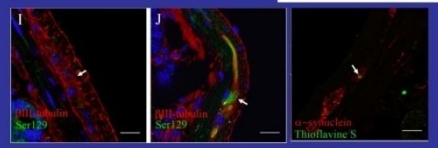
Pan-Montojo et al., 2010

## Effects of oral rotenone on enteric alpha-synuclein




1.5 months

3 months ileum

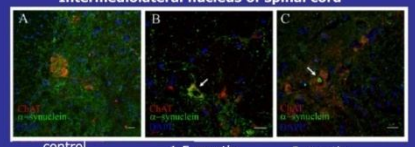



control

3 months treatment

## Effects of oral rotenone on CNS alpha-synuclein – sympathetic centres of enteric innervation

Intermediolateral nucleus of spinal cord



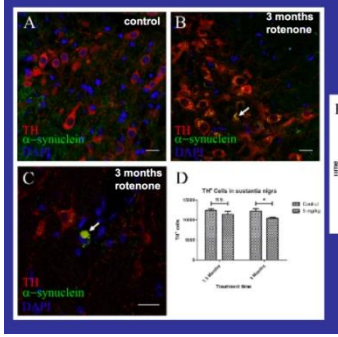

control

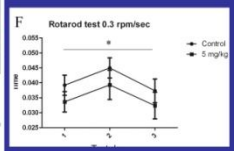
1.5 months treatment

3 months treatment

Pan-Montojo et al., 2010

## Effects of oral rotenone on alpha-synuclein in substantia nigra

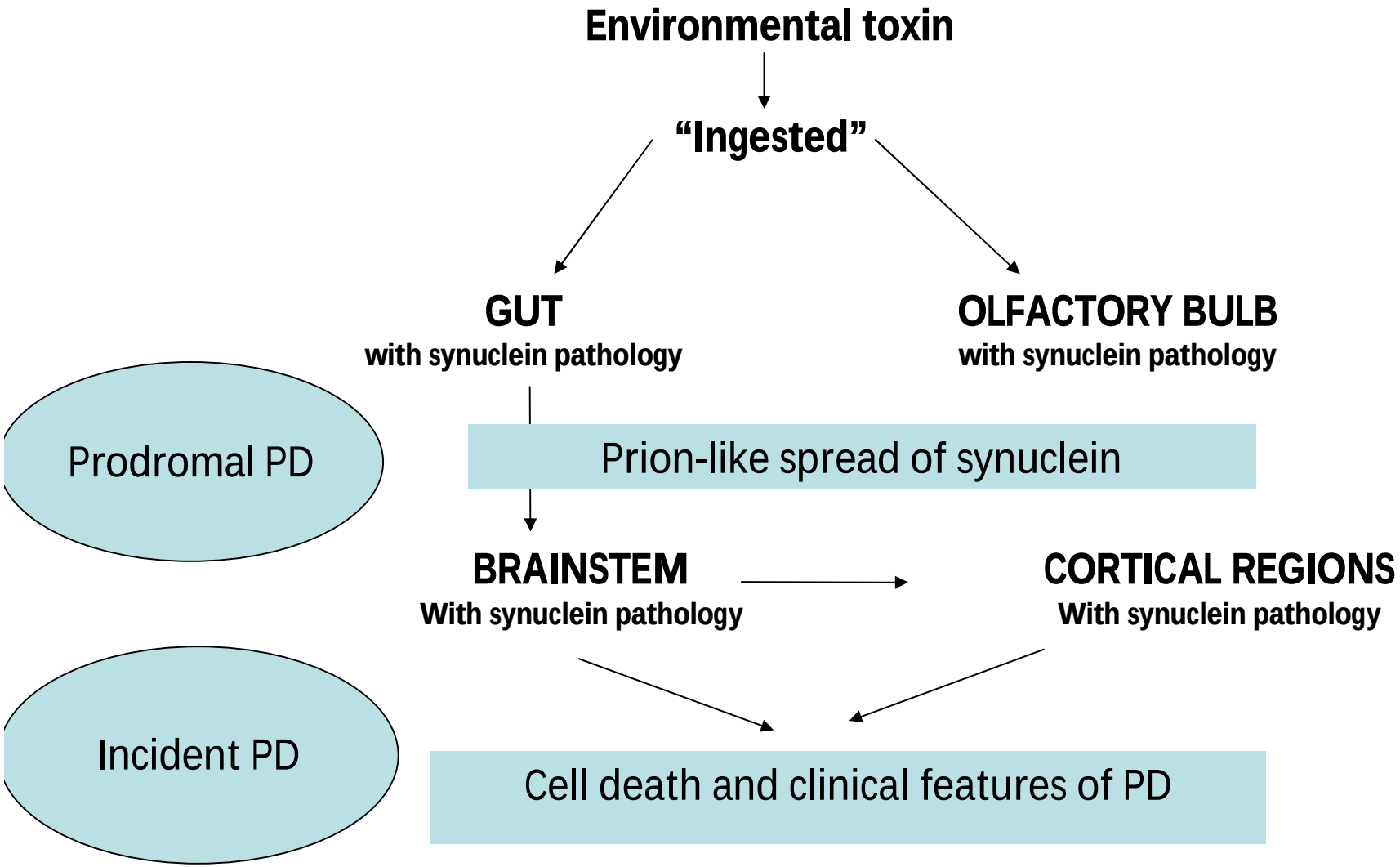


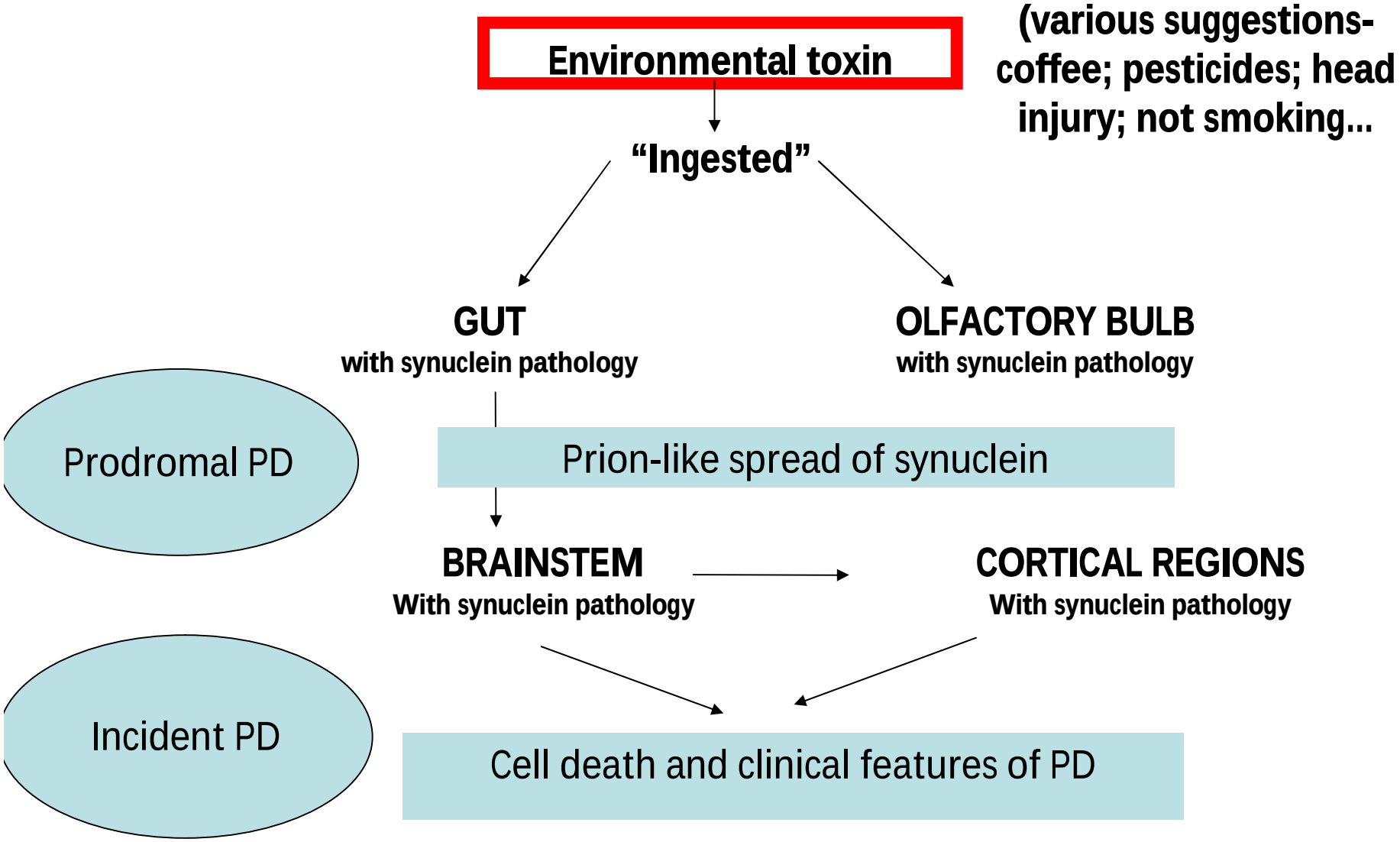

Pan-Montojo et al., 2010

**..and there is Lewy body pathology in GIT possibly ahead of overt motor disease (reviewed in Lebouvier et al 2009);**

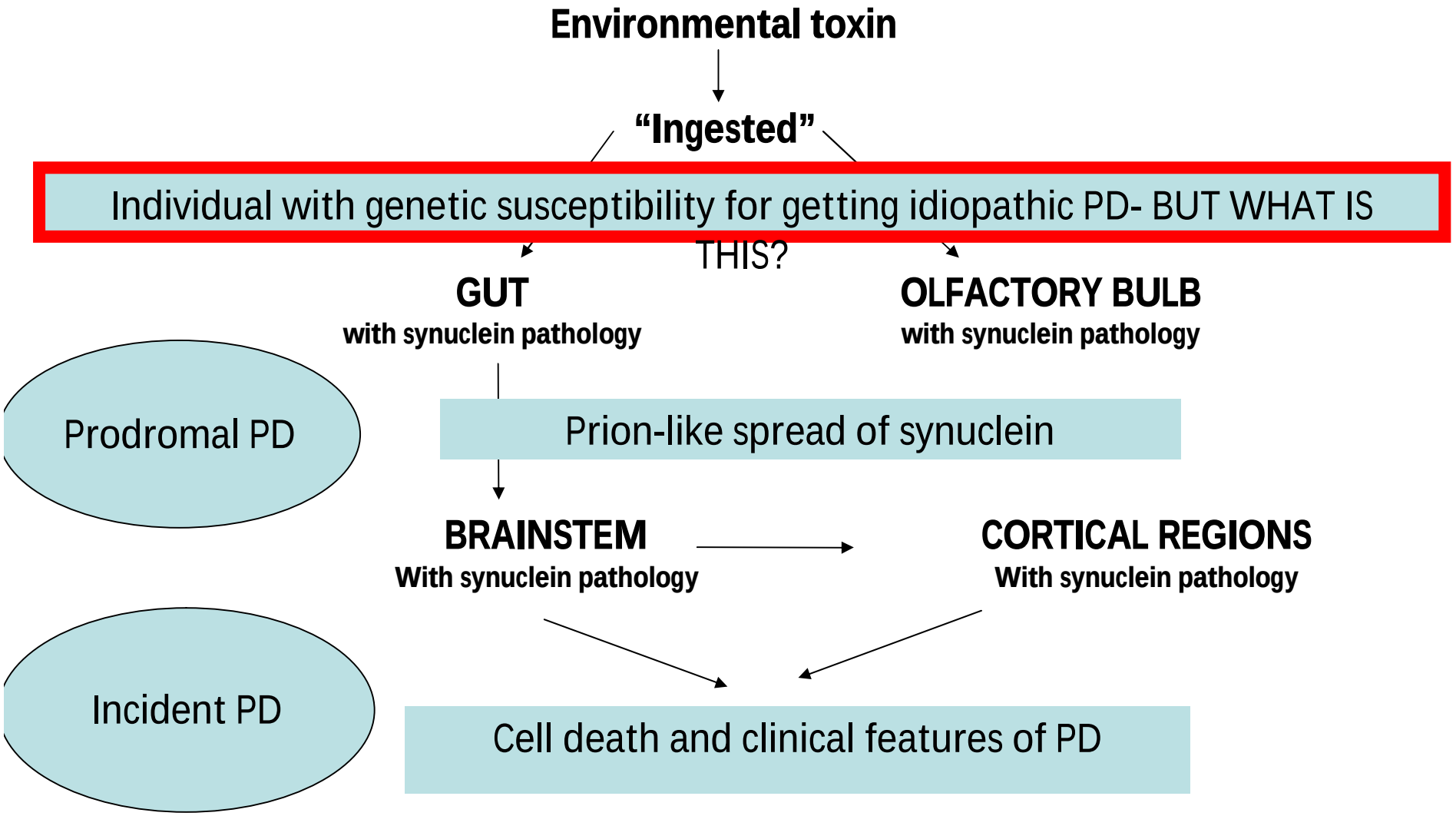
# THE EVOLUTION OF A NEW HYPOTHESIS about PD



# THE EVOLUTION OF A NEW HYPOTHESIS about PD



# THE EVOLUTION OF A NEW HYPOTHESIS about PD



# Recent Genome Wide Association Studies (GWAS) have been published which look at all genes linked to PD...

nature genetics

Genome-wide association study reveals genetic risk underlying Parkinson's disease

nature genetics

Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease

**PD patients= 1713**
**Controls= 3978**
**Tau and synuclein**

**PD patients= 2011**
**Controls= 18381**
**NEW loci 1q15 and 4p15; synuclein and ?LRRK2**

## Genome-Wide Association Study Confirms SNPs in *SNCA* and the *MAPT* Region as Common Risk Factors for Parkinson Disease

Todd L. Edwards[1,2], William K. Scott[1], Cherylyn Almonte[1], Amber Burt[1], Eric H. Powell[1], Gary W. Beecham[1], Liyong Wang[1], Stephan Züchner[1], Ioanna Konidari[1], Gaofeng Wang[1], Carlos Singer[4], Fatta Nahab[4], Burton Scott[5], Jeffrey M. Stajich[5], Margaret Pericak-Vance[1], Jonathan Haines[3], Jeffery M. Vance[1] and Eden R. Martin[1,*]

[1]*John P. Hussman Institute for Human Genomics and the Dr. John T. Macdonald Foundation Department of Human Genetics, Miller School of Medicine, University of Miami, FL*
[2]*Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Vanderbilt University, TN*
[3]*Center for Human Genetics Research, Vanderbilt University Medical Center, Vanderbilt University, TN*
[4]*Department of Neurology, Miller School of Medicine, University of Miami, FL*
[5]*Department of Medicine, Duke University Medical Center, Duke University, NC*

**PD patients= 1752**
**Controls= 1748**
**Tau and synuclein**

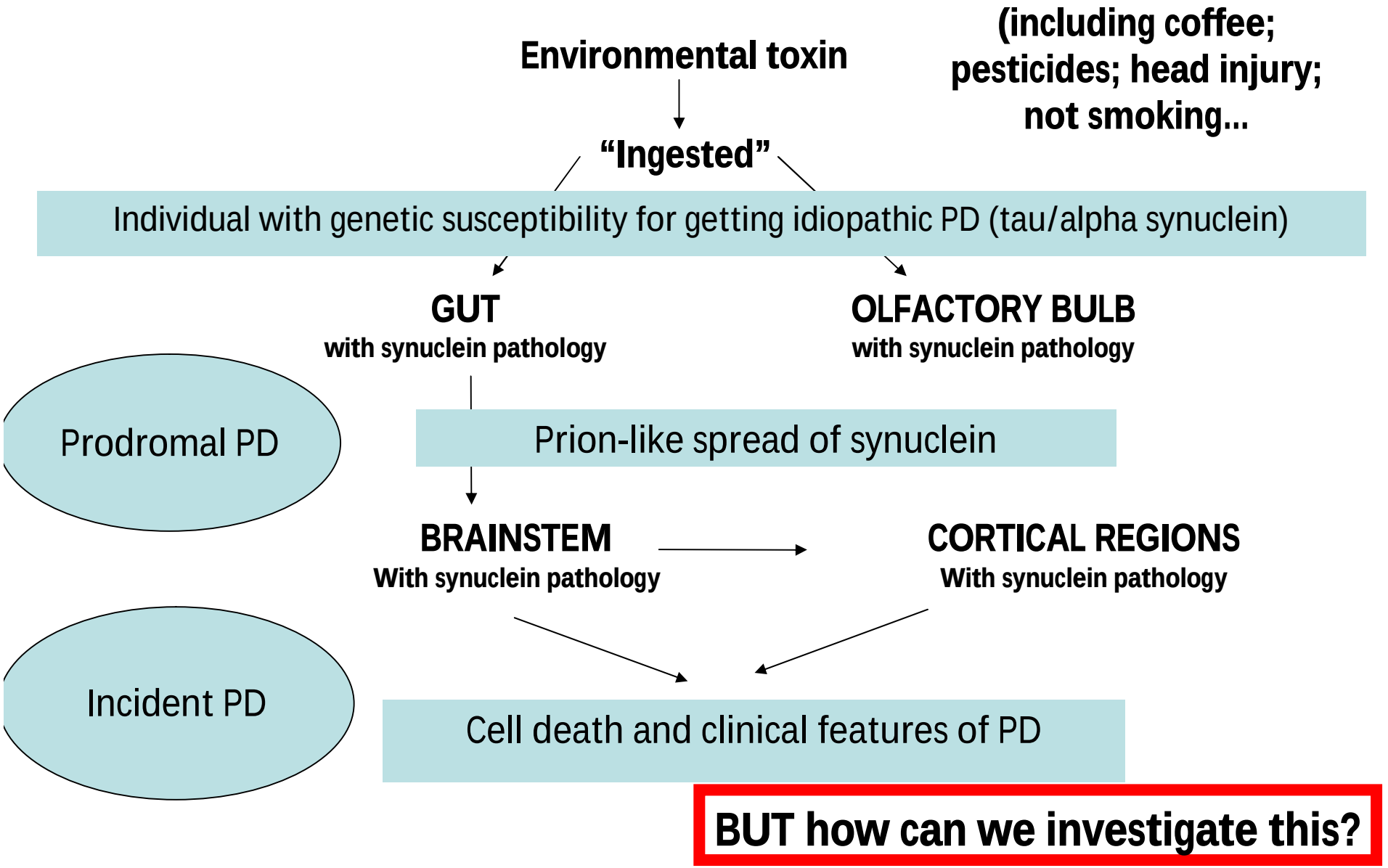
**OVERALL the genetic risk factors are:**

## Summary

**Background** Genome-wide association studies (GWAS) for Parkinson's disease have linked two loci (*MAPT* and *SNCA*) to risk of Parkinson's disease. We aimed to identify novel risk loci for Parkinson's disease.

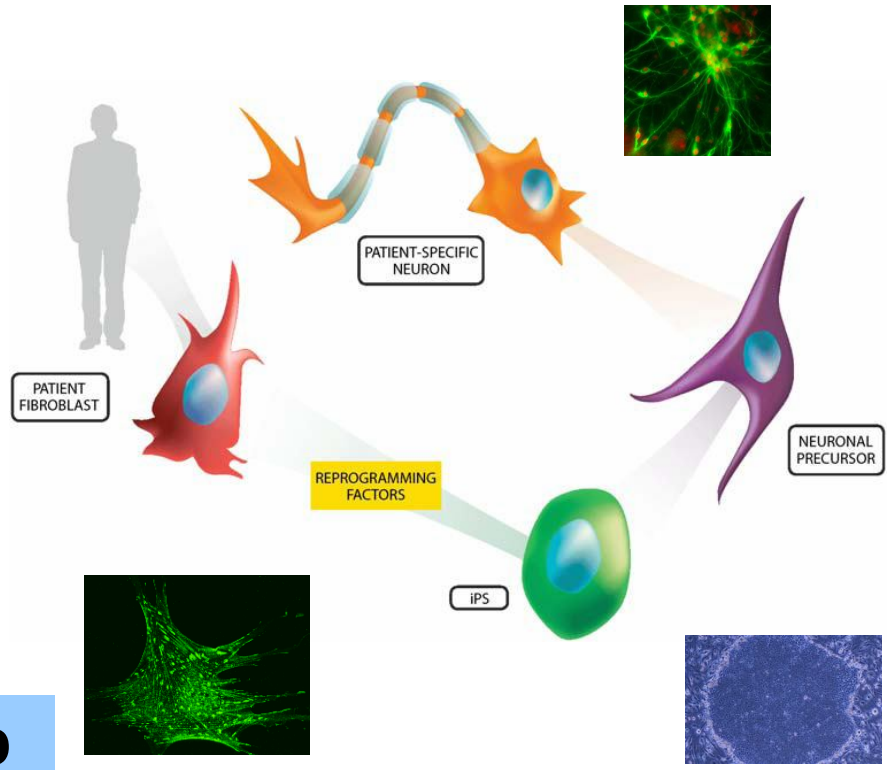
*Lancet* 2011; 377: 641–49
Published Online
February 2, 2011

# THE EVOLUTION OF A NEW HYPOTHESIS about PD




**BUT how can we investigate this?**

**A NEW TECHNOLOGY- The ability to make induced Pluripotent Stem Cells (iPS cells) from mice then man**



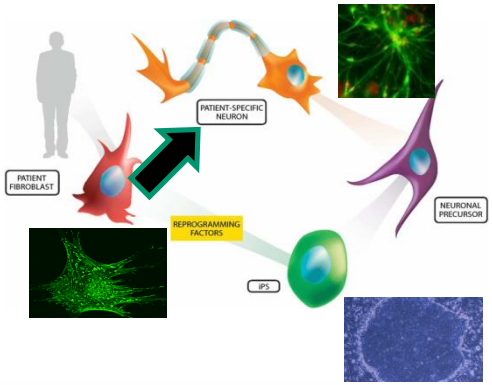

**..and iPS cells can be made to turn into DA neurons which work in animal models of PD..**

**..and now can even directly turn skin cells into DA neurons which work in animal models of PD..**

**2010**

## Direct conversion of fibroblasts to functional neurons by defined factors

Thomas Vierbuchen[1,2], Austin Ostermeier[1,2], Zhiping P. Pang[3], Yuko Kokubu[1], Thomas C. Südhof[3,4] & Marius Wernig[1,2]




**2011**

PNAS

## Direct conversion of human fibroblasts to dopaminergic neurons

Ulrich Pfisterer[1], Agnete Kirkeby[1], Olof Torper[1], James Wood, Jenny Nelander, Audrey Dufour, Anders Björklund, Olle Lindvall, Johan Jakobsson, and Malin Parmar[2]

Departments of Experimental Medical Science and Clinical Sciences, Wallenberg Neuroscience Center, and Lund Stem Cell Center, Lund University, SE-221 84 Lund, Sweden

Edited* by Fred H. Gage, The Salk Institute, San Diego, CA, and approved May 13, 2011 (received for review March 31, 2011)

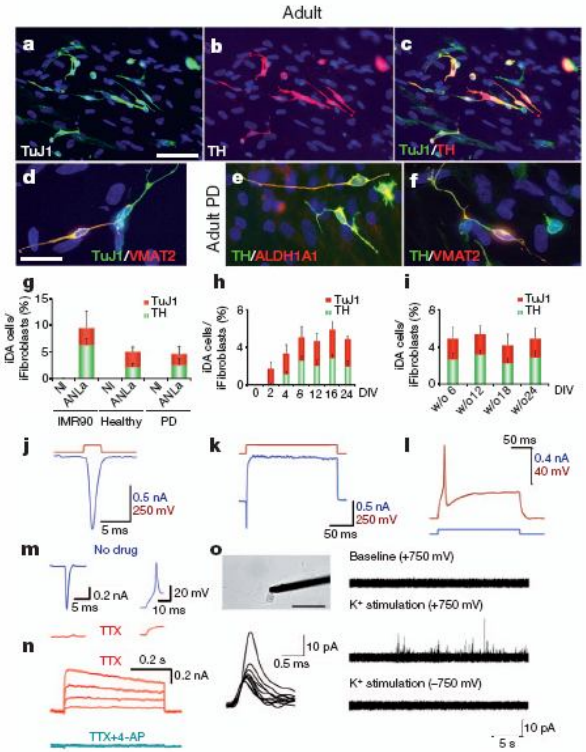



Figure 4 | Characterization of human fibroblasts reprogrammed into iDA cells. a–f, Fibroblasts from a healthy donor (a–d) and a Parkinson's disease (PD)

LETTER

doi:10.1038/nature10284

## Direct generation of functional dopaminergic neurons from mouse and human fibroblasts

Massimiliano Caiazzo[1], Maria Teresa Dell'Anno[1]*, Elena Dvoretskova[2]*, Dejan Lazarevic[3,4], Stefano Taverna[2], Damiana Leo[2], Tatyana D. Sotnikova[2], Andrea Menegon[5], Paola Roncaglia[4], Giorgia Colciago[1], Giovanni Russo[2], Piero Carninci[6], Gianni Pezzoli[7], Raul R. Gainetdinov[2], Stefano Gustincich[4,8], Alexander Dityatev[2] & Vania Broccoli[1]

Cell

## Directed Conversion of Alzheimer's Disease Patient Skin Fibroblasts into Functional Neurons

Liang Qiang,[1,3] Ryousuke Fujita,[1,3] Toru Yamashita,[1,3] Sergio Angulo,[2,3] Herve Rhinn,[1] David Rhee,[1] Claudia Doege,[1] Lily Chau,[1] Laetitia Aubry,[1] William B. Vanti,[1] Herman Moreno,[2] and Asa Abeliovich[1,*]

**..which not only can be used to study disease but drug screening..**

Vol 457|15 January 2009|doi:10.1038/nature07677 nature

ARTICLES

# Induced pluripotent stem cells from a spinal muscular atrophy patient

Allison D. Ebert[1,2], Junying Yu[3], Ferrill F. Rose Jr[4], Virginia B. Mattis[4], Christian L. Lorson[4], James A. Thomson[2,3,5] & Clive N. Svendsen[1,2,5,6]

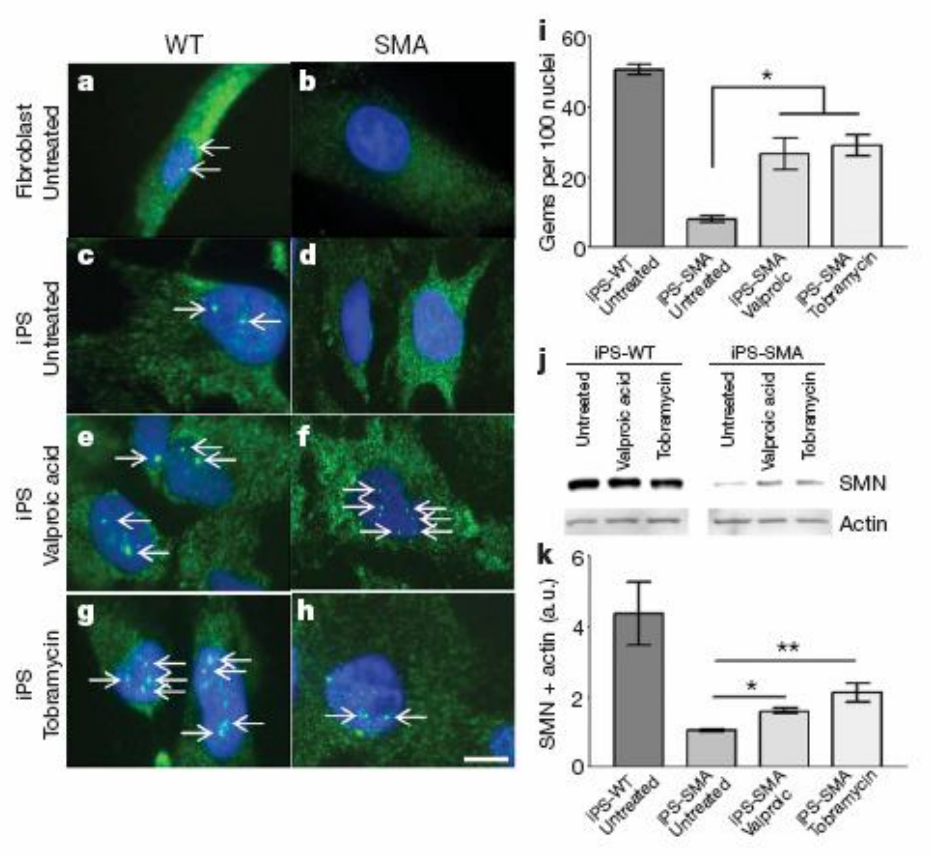
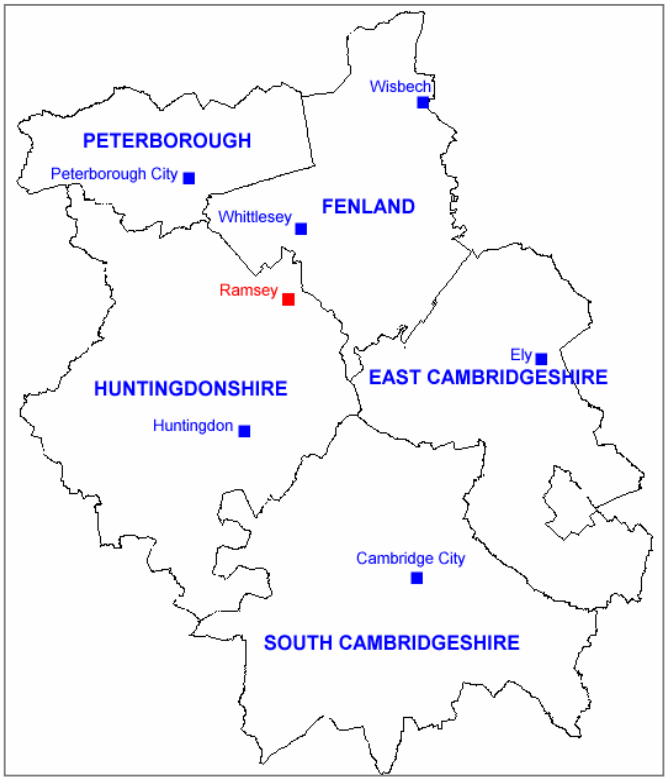


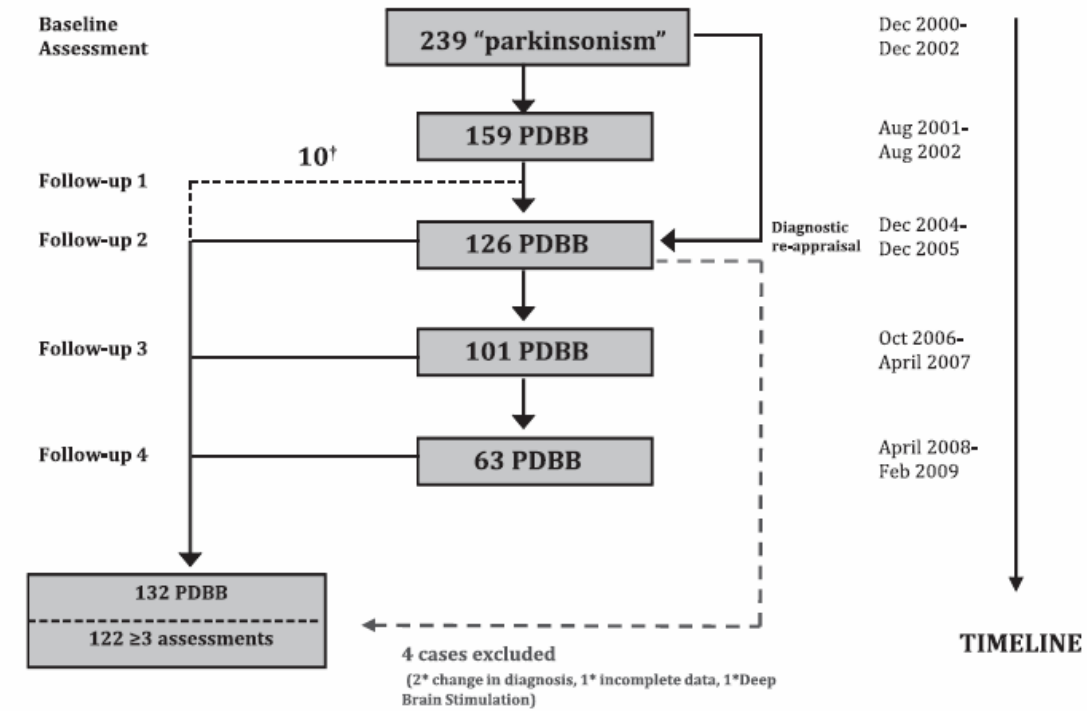

**Figure 4 | iPS-WT and iPS-SMA cells increase SMN protein in response to drug treatment.** **a–d**, Untreated Fib-WT and iPS-WT cells show nuclear

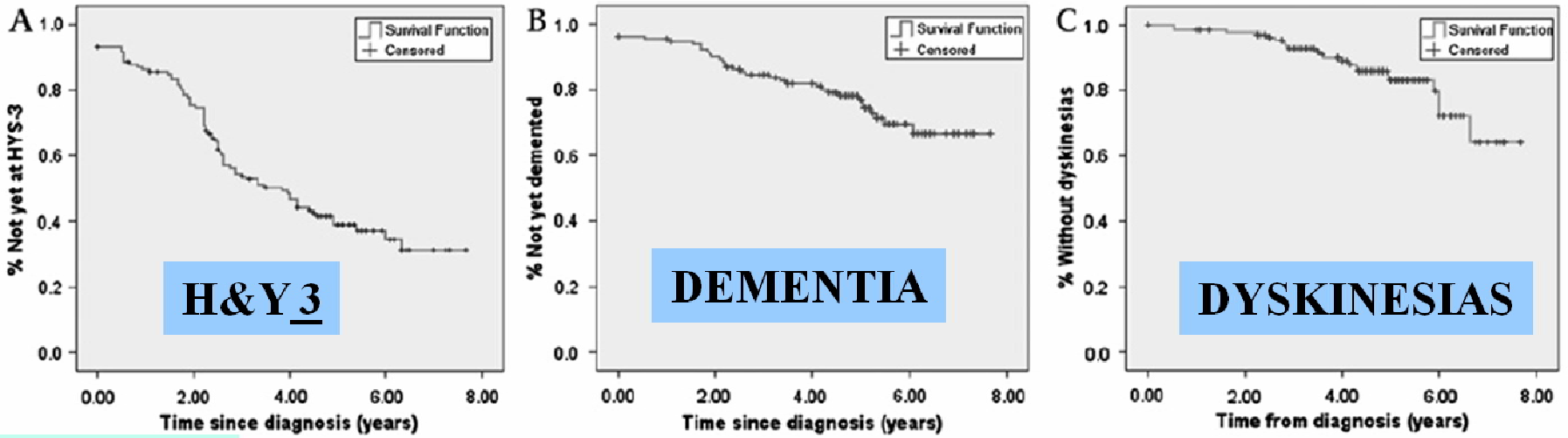
**BUT are all patients the same?**

# NO… The CamPaIGN study
# [Now being replicated PICNICS-ICICLE study]



# THE NATURAL HISTORY OF TREATED PARKINSON'S DISEASE




*Evans et al JNNP 2011*

# The two types of idiopathic PD?

**Younger patient with normal thinking**

"Subtle" complex cognitive impairments

but "LOCALISED" NIGRAL pathology

**Older patients with some problems in thinking as evidenced by poor semantic fluency and pentagon drawing**

Posterior cortical impairment and "WIDESPREAD" pathology throughout CNS with accelerated LB formation

↓

**Early PDD**

Foltynie et al Brain 2004; Williams- Gray CH et al, J.Neurosci.2007; Brain 2007, Brain 2009; Goris et al. Ann.Neurol. 2007; Evans et al JNNP 2011

# The two types of idiopathic PD?

**Younger patient with normal thinking**

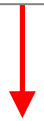
"Subtle" fronto-striatal cognitive impairment

but "LOCALISED" NIGRAL pathology

**DA CELL THERAPIES and GROWTH FACTOR TREATMENTS for DA CELLS may ONLY work for this type of PD patient**

**Older patients with some problems in thinking as evidenced by poor semantic fluency and pentagon drawing**

Posterior cortical impairment and "WIDESPREAD" pathology throughout CNS with accelerated LB formation



**Early PDD**

**DISEASE MODIFYING THERAPIES?**

Foltynie et al Brain 2004; Williams- Gray CH et al, J.Neurosci.2007; Brain 2007, Brain 2009; Goris et al. Ann.Neurol. 2007; Evans et al JNNP 2011

# The two types of idiopathic PD?

**Younger patient with normal thinking**

"Subtle" fronto-striatal cognitive impairment

but "LOCALISED" NIGRAL pathology

**DA CELL THERAPIES and GROWTH FACTOR TREATMENTS for DA CELLS may ONLY work for this type of PD patient**

**Older patients with some problems in thinking as evidenced by poor semantic fluency and pentagon drawing**

Posterior cortical impairment and "WIDESPREAD" pathology throughout CNS with accelerated LB formation

**Early PDD**

**DISEASE MODIFYING THERAPIES?**

Foltynie et al Brain 2004; Williams- Gray CH et al, J.Neurosci.2007; Brain 2007, Brain 2009; Goris et al. Ann.Neurol. 2007; Evans et al JNNP 2011

# The development of fetal dopamine (VM) cell therapies for PD

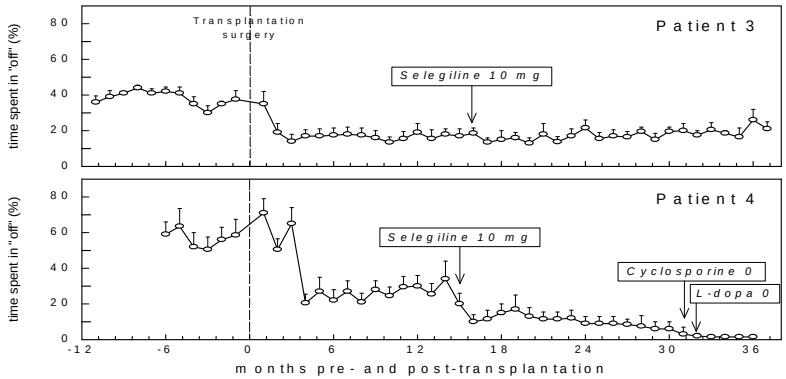
1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998

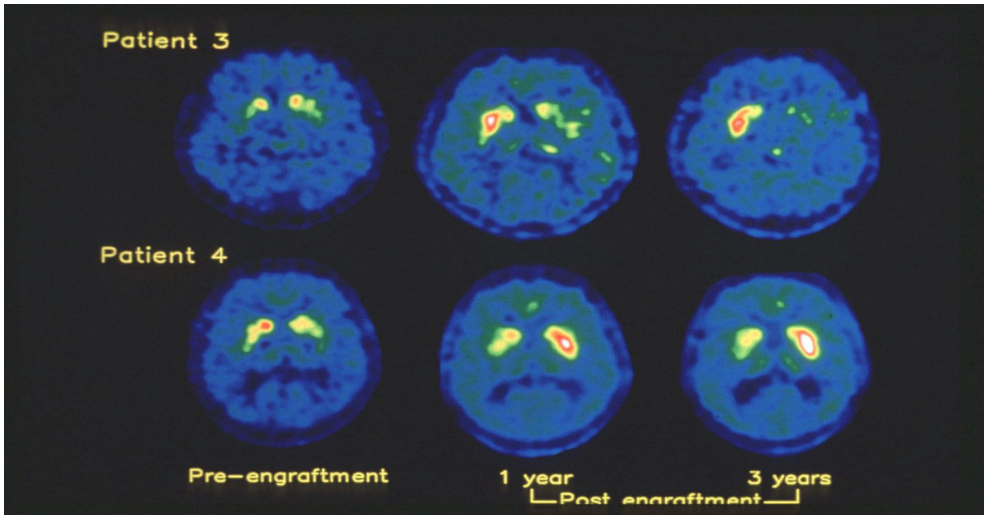
Development of fetal VM transplants in animal models of PD experimentally

1st patients with advanced PD treated with fetal VM grafts

~50 patients grafted with VM tissue using an open label approach

**INITIAL TRIAL SHOWED A MAIN CLINICAL EFFECT BUT NOT IN ALL CASES...**



1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

Double blind placebo control trials with N=40 and 34

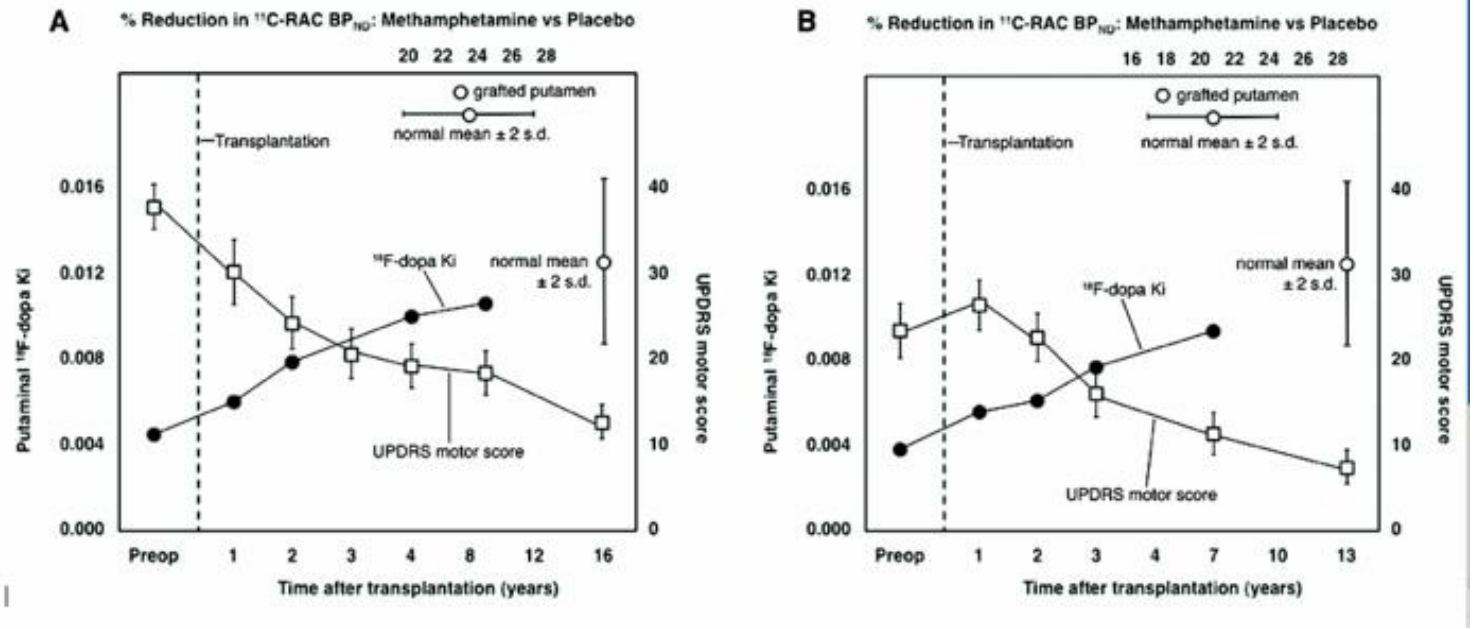
NIH

Open label study in Halifax, Canada;N=10

**NEW "BIG" TRIAL SHOWED NO SIGNIFICANT MAIN CLINICAL EFFECT ..... WITH PROBLEMS OF GIDS**

**SO WHERE NEXT?**

**YET STILL FROM OLD STUDIES BEST OUTCOME SHOWS**



1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

Double blind placebo control trials with N=40 and 34

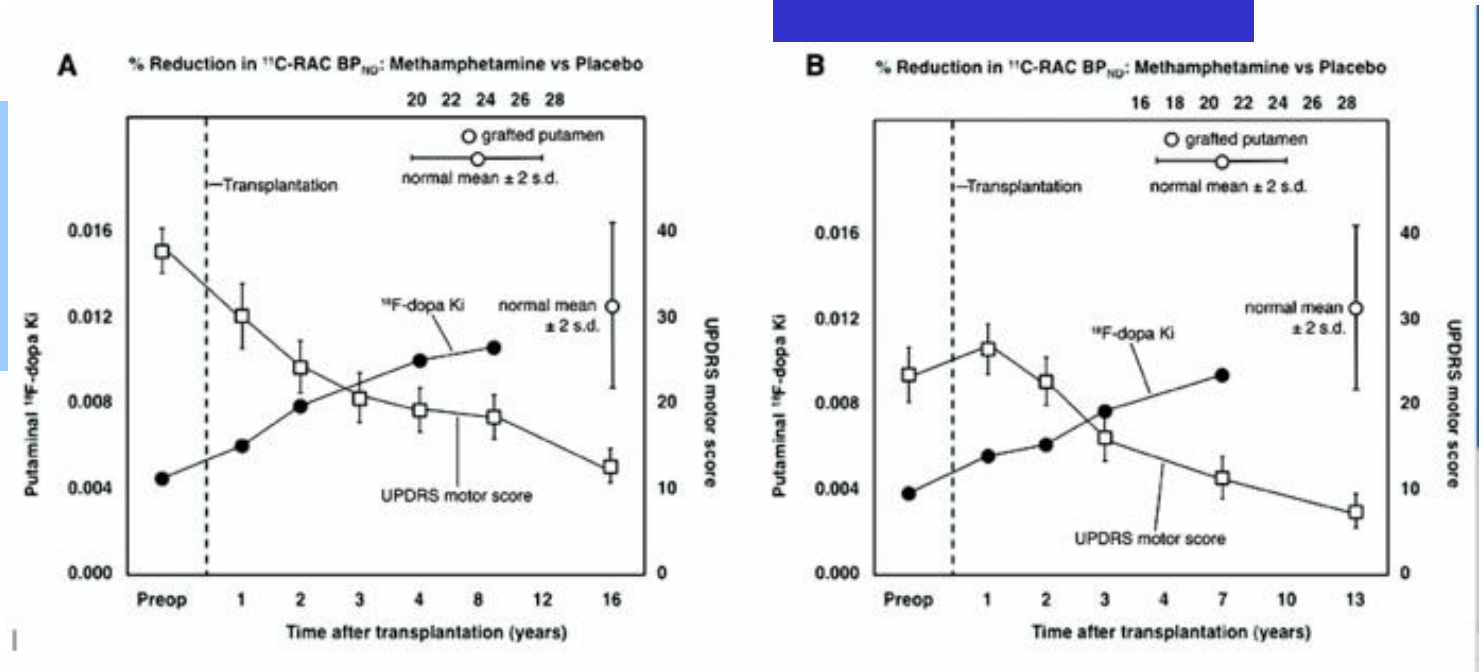
NIH

Open label study in Halifax, Canada;N=10

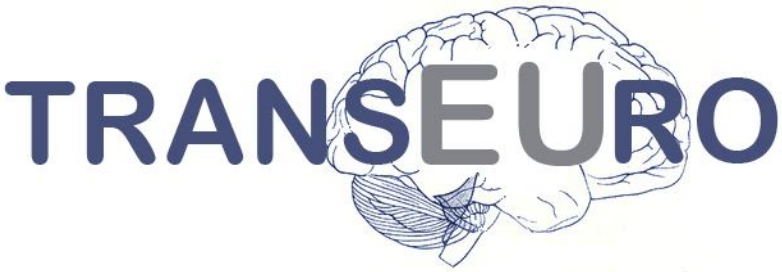
NEW "BIG" TRIAL SHOWED NO SIGNIFICANT MAIN CLINICAL EFFECT ..... WITH PROBLEMS OF GIDS

SO WHERE NEXT?

YET STILL FROM OLD STUDIES BEST OUTCOME SHOWS




TRANSEURO


1. To establish and conduct a small open label study of fetal ventral mesencephalic transplants to patients with early PD;

2. To establish and conduct a larger double blind placebo controlled study of fetal ventral mesencephalic transplants to patients with early PD using imitation surgery and best medical therapy.

## THE CRITICAL ISSUES TO ACHIEVE THIS.

1.PATIENT SELECTION
2.TISSUE COMPOSITION
3.TISSUE PLACEMENT
4.TRIAL DESIGN AND END POINTS

# The two types of idiopathic PD?

**Younger patient with normal semantic fluency and pentagon drawing but may have subtle executive deficits at PRESENTATION**

"Subtle" fronto-striatal cognitive impairment

but "LOCALISED" NIGRAL pathology

**DA CELL THERAPIES and GROWTH FACTOR TREATMENTS for DA CELLS may ONLY work for this type of PD patient**

**Older patients with MCI at presentation as evidenced by poor semantic fluency and pentagon drawing**

Posterior cortical impairment and "WIDESPREAD" pathology throughout CNS with accelerated LB formation

↓

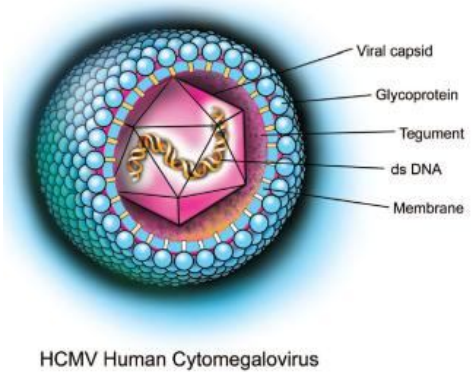
**Early PDD**

**DISEASE MODIFYING THERAPIES?**

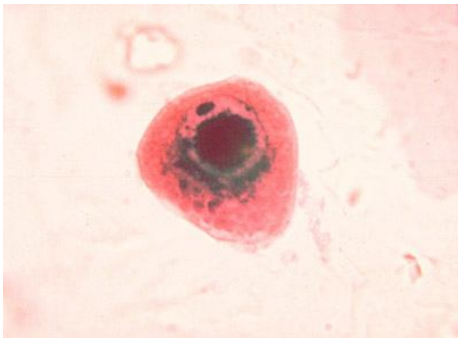
Foltynie et al Brain 2004; Williams- Gray CH et al, J.Neurosci.2007; Brain 2007, Brain 2009; Goris et al. Ann.Neurol. 2007; Evans et al JNNP 2011

# A NOVEL APPROACH.... using something that naturally is found -the HUMAN Cytomegalovirus (HCMV)...

- It codes for a pro-life product called β2.7 which is the single most abundant transcript during infection ;
- And this works to keep cell happy and in a good energetic state

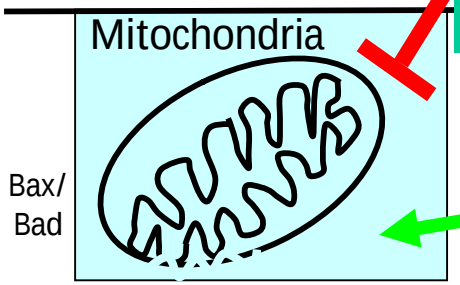



HCMV Human Cytomegalovirus



*HCMV β2.7**

*(Intrinsic pathway)*




*Cellular stress signals*

Mitochondrial outer membrane permeability

Cytochrome C

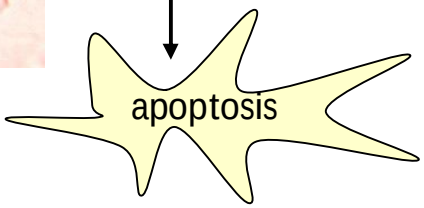
Caspase 9/Apaf-1 (Apoptosome)

Caspase cascade

AIF/EndoG

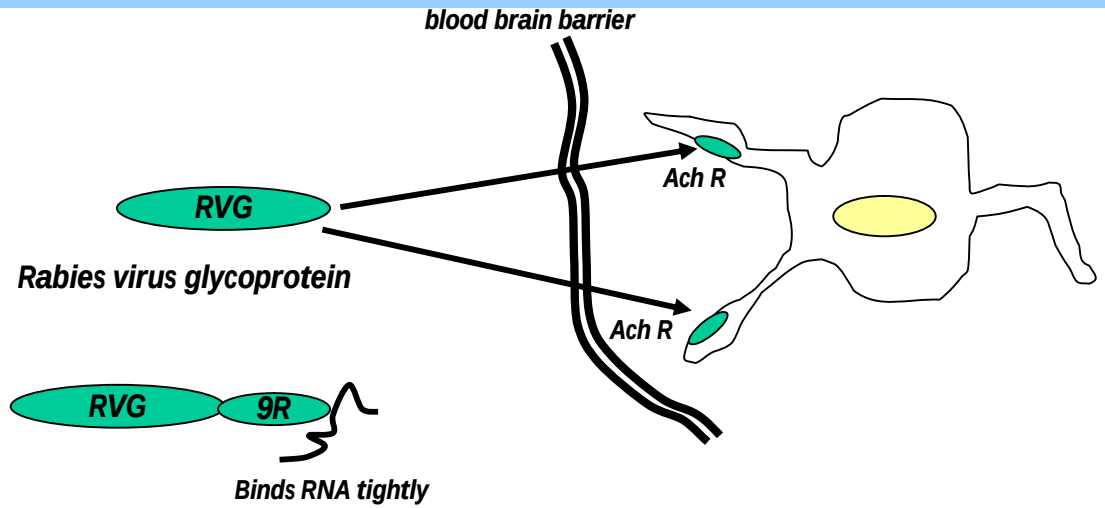
caspase independent

*HCMV UL37 ( vMIA)*



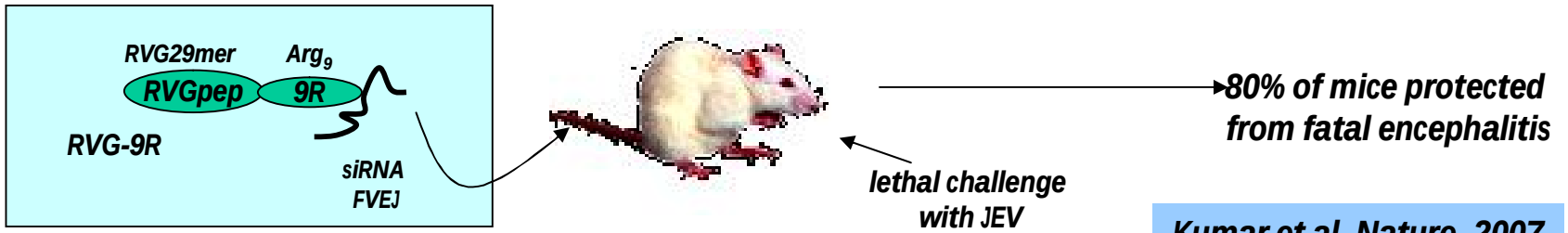

**BUT IF THIS THERAPY IS TO BE USED FOR PD NEED TO GET IT INTO BRAIN....another naturally occurring virus can help us here!!**

# ...the Rabies virus glycoprotein peptide which can transport proteins etc into the brain




-no evidence of any immune response to it


*specific knock-down of GFP expression In brain*




*80% of mice protected from fatal encephalitis*

*lethal challenge with JEV*

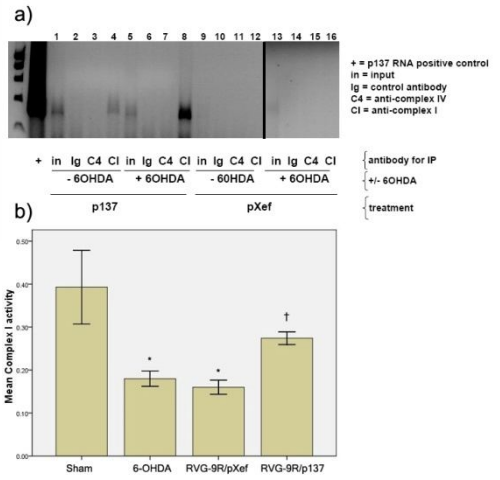
*Kumar et al, Nature, 2007*

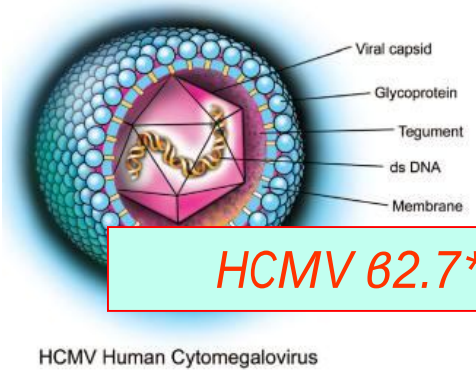
Published December 19, 2011
JEM



# A novel neuroprotective therapy for Parkinson's disease using a viral noncoding RNA that protects mitochondrial Complex I activity

Wei-Li Kuan,[1,2] Emma Poole,[3] Michael Fletcher,[4] Sharon Karniely,[3] Pam Tyers,[1,2] Mark Wills,[3] Roger A. Barker,[1,2] and John H. Sinclair[3]

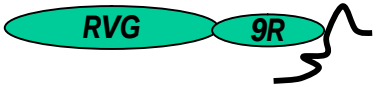



HCMV 82.7*

HCMV Human Cytomegalovirus

+




**Animal with a lesion already to its dopamine cells**

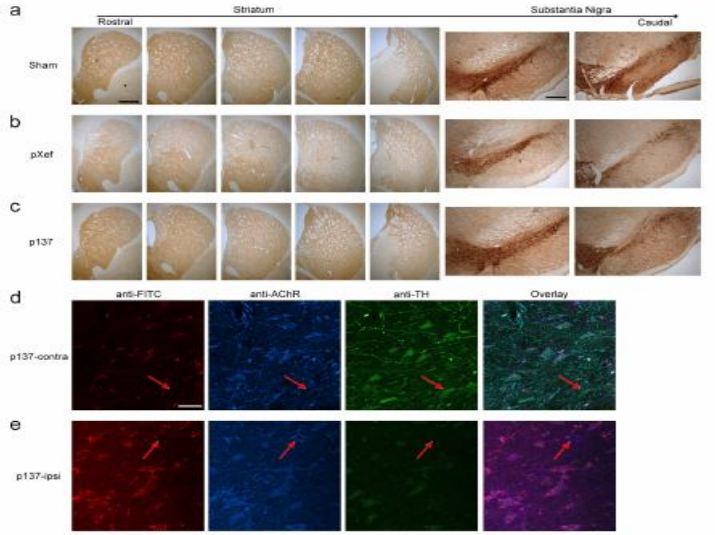



Figure 3. Intravenous delivery of RVG9R–p137 attenuates the loss of dopaminergic expression in a progressive rat model of PD, and the expression of FITC-tagged p137 colocalized with AChR and TH-expressing cells in the nigra. (a–c) Representative pictures of the rostrocaudal

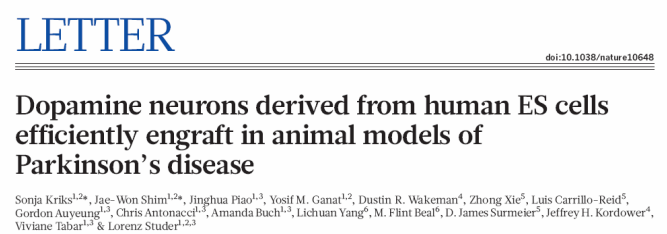
**RESCUE CELLS THAT WOULD NORMALLY BE LOST TO LESION!!**

# WHAT GOES WRONG IN PARKINSON'S DISEASE and WHAT CAN WE DO ABOUT IT? In one type of PD...

**DA CELL THERAPIES and GROWTH FACTOR TREATMENTS**

**Environmental toxin**

**"Ingested"**



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

Individual with genetic susceptibility for getting idiopathic PD

**GUT**
**with synuclein pathology**

**OLFACTORY BULB**
**with synuclein pathology**

Prodromal PD

Prion-like spread of synuclein

**BRAINSTEM**
**With synuclein pathology**

**CORTICAL REGIONS**
**With synuclein pathology**

Incident PD

Cell death and clinical features of PD

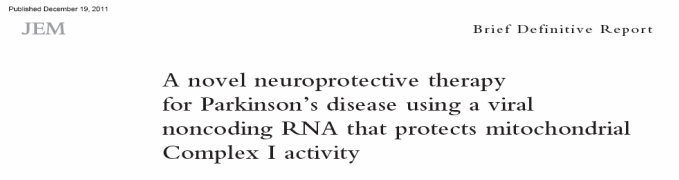
**More BENIGN form of PD..in younger patients with less gait or thinking problems..**

# WHAT GOES WRONG IN PARKINSON'S DISEASE and WHAT CAN WE DO ABOUT IT? In the other type of PD..

**DISEASE MODIFYING THERAPIES?**

**Environmental toxin**

**"Ingested"**




Individual with genetic susceptibility for getting idiopathic PD

**GUT**
**with synuclein pathology**

**OLFACTORY BULB**
**with synuclein pathology**

Prodromal PD

Prion-like spread of synuclein

**BRAINSTEM**
**With synuclein pathology**

**CORTICAL REGIONS**
**With synuclein pathology**

Incident PD

Cell death and clinical features of PD

**More MALIGNANT form of PD- In older PD patients with more significant walking and thinking problems at disease onset**

# THE TEAM involved with this PD work over the years includes..

Our work is supported by: MRC; PDS; Cure PD; and Wellcome Trust


Richard Armstrong
Claire Clelland
Minee Choi
Jonathan Evans
Carrie Hurelbrink
Meena Jain
Wei-Li Kuan
Rocio Laguna Goya
Sarah Mason
Andy Michell
Grainne O'Keefe
Wendy Phillips
Pam Tyers
Caroline Williams-Gray

**Main Collaborations in PD:**

Professor Trevor Robbins; Maria Grazia Spillantini; Adrian Owen; Maeve Caldwell; Carol Brayne; James Rowe; David Grainger; Roger Carpenter; Stephen Sawcer; Alastair Compston; John Sinclair (Cambridge)
Professor David Burn and Patrick Chinnery (Newcastle)
Professor David Brooks, Dr Paola Piccini (Hammersmith Hospital)
Dr Daniel Weinberger (USA)