Parkinson Disease Treatment Research Pipeline

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NINDS, NIH

Disclosures

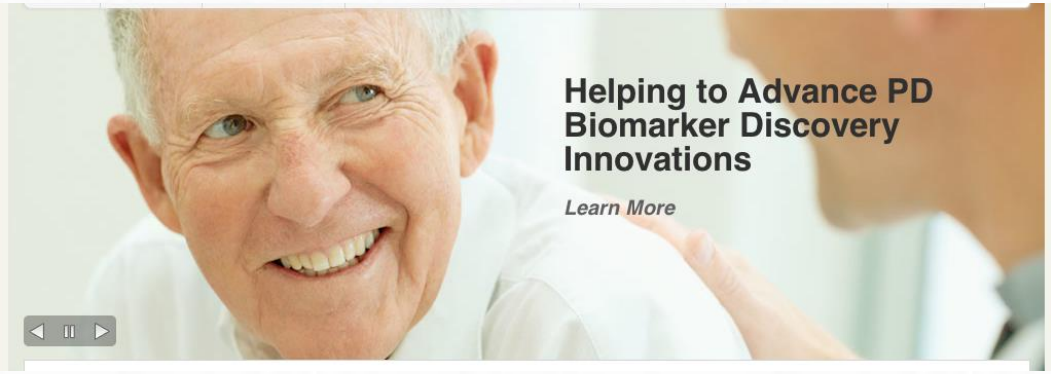
I receive payments from MAPMG for clinical work and from Elsevier, inc. for editorial work.

I have worked on research projects sponsored by Medtronic, inc., BCN Peptides Llc, and Allergan, inc.

Major Needs in the PD and Movement Disorders Field

- Reliable diagnosis and biomarkers
- Pre-symptomatic diagnosis and risk profiling
- Therapy guidance and improved symptomatic therapies
- Disease-modifying or curative therapies

The Search for Biomarkers



The NINDS Parkinson's disease biomarkers program

Liana S. Rosenthal MD[1,*], Daniel Drake PhD[2], Roy N. Alcalay MD, MS[3], Debra Babcock MD, PhD[4], F. DuBois Bowman PhD[2], Alice Chen-Plotkin MD[5], Ted M. Dawson MD, PhD[1,6], Richard B. Dewey Jr. MD[7], Dwight C. German PhD[8], Xuemei Huang MD, PhD[9], Barry Landin BS[10], Matthew McAuliffe PhD[10], Vladislav A. Petyuk PhD[11], Clemens R. Scherzer MD[12], Coryse St. Hillaire-Clarke PhD[4], Beth-Anne Sieber PhD[4], Margaret Sutherland PhD[4], Chi Tarn PhD[13], Andrew West PhD[14], David Vaillancourt PhD[15], Jing Zhang MD, PhD[16], Katrina Gwinn MD[4] and on behalf of the PDBP consortium

Article first published online: 7 OCT 2015

Issue

PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

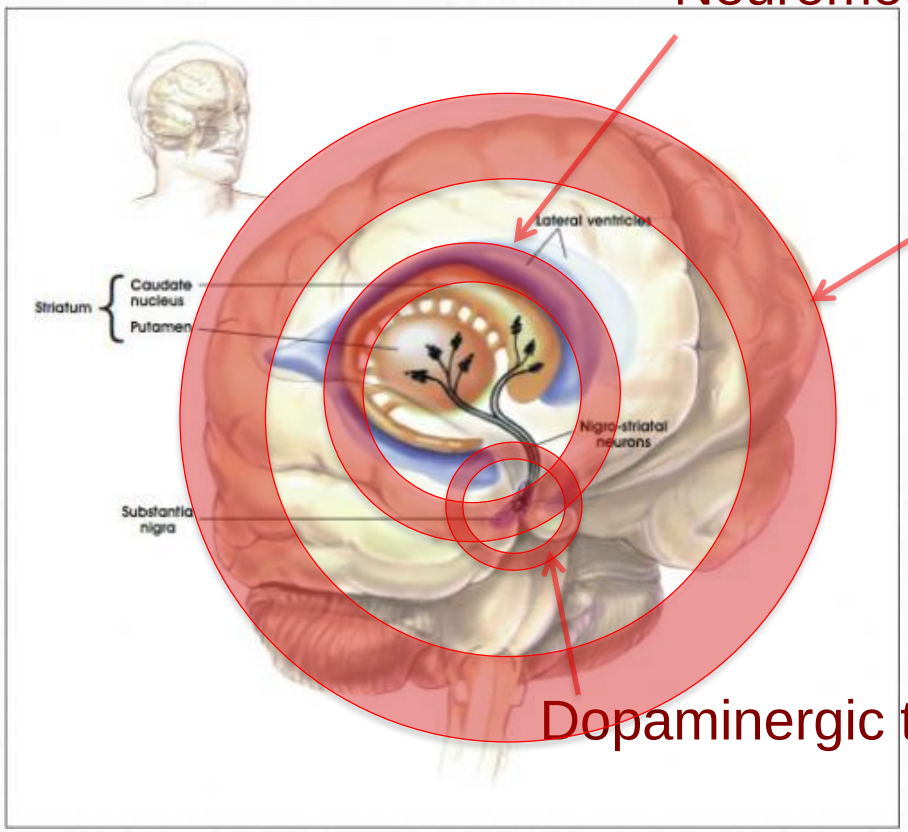
Therapy Research

- Symptomatic therapy
  - Drug therapy
    - Dopaminergic
    - Non-dopaminergic (and peripheral-acting)
  - Surgical and neuromodulation therapy
  - Other non-pharmacologic, non-invasive therapies
- Disease-modifying therapy

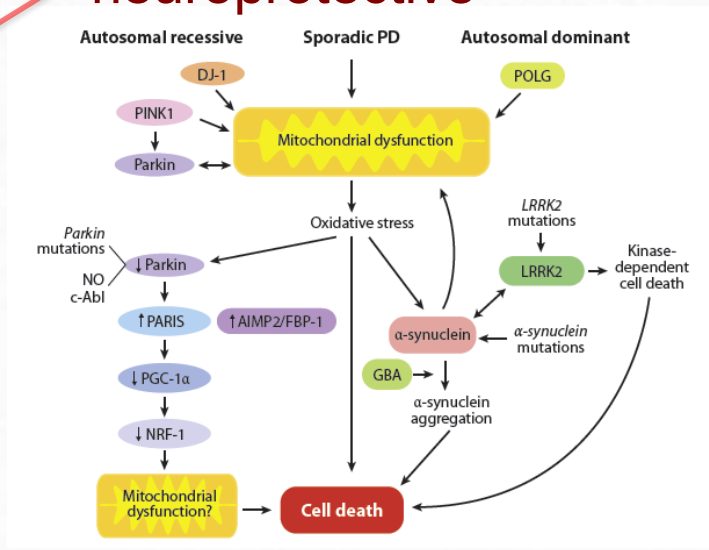
Therapy Research

Neuromodulation

Disease modifying/
neuroprotective



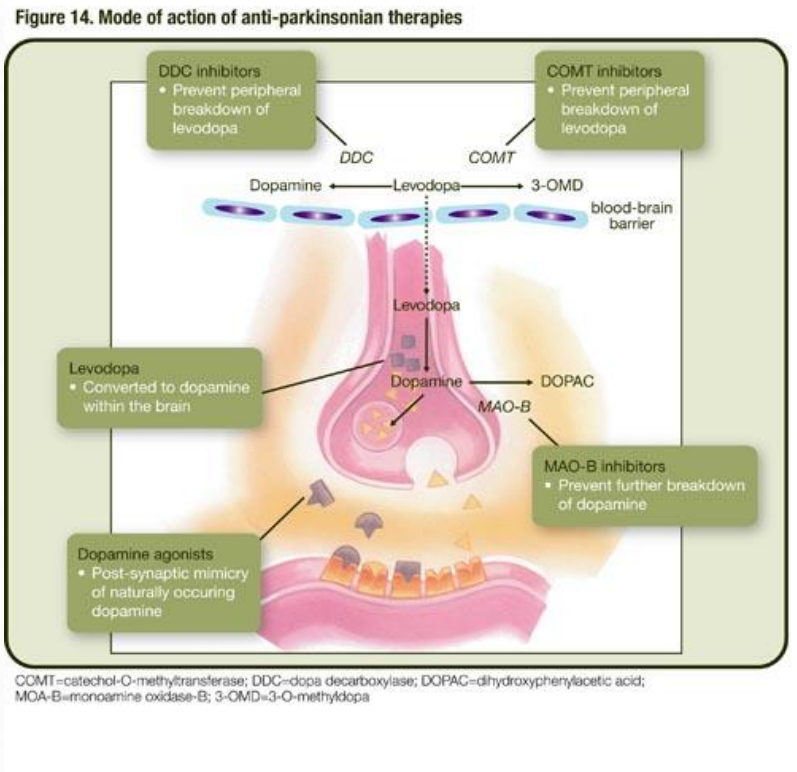
Cozzens, Dis Mon 2007



Martin I et al. Annu Rev Genomics Hum Genet. 2010

Dopaminergic therapy

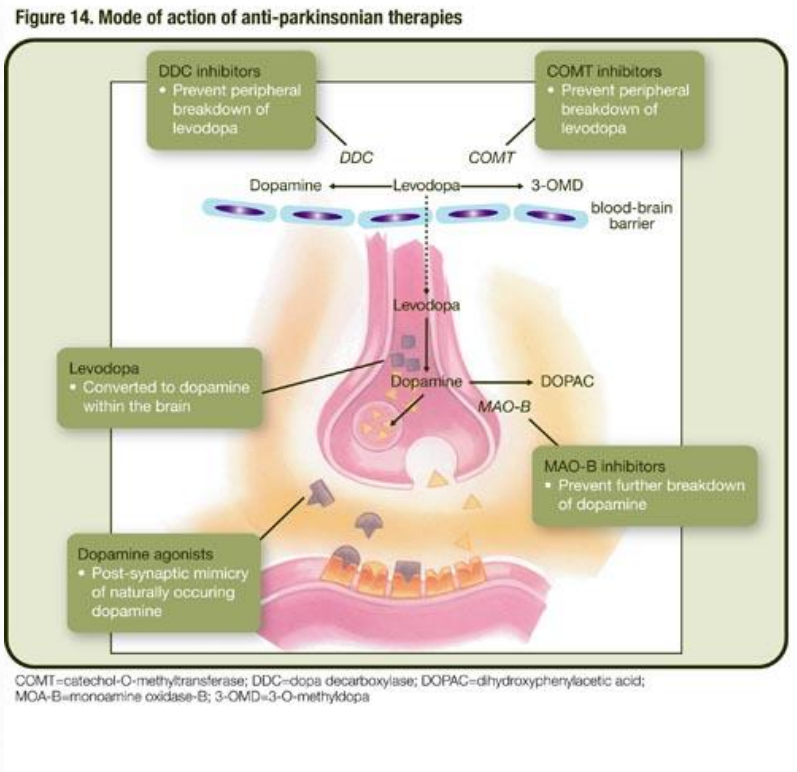
Current Symptomatic Treatment



Levodopa:
Carbidopa/Levodopa; Sinemet®; Rytary®: Provides the missing dopamine, combined with COMT inhibition. Side effects: dyskinesia; nausea

DA agonists: Pramipexole – Mirapex®; Ropinirole – Requip®; Rotigotine – Neupro® etc. Mimic the effects of dopamine by activating the same receptors. Side-effects: psychiatric; sleep-related

Current Symptomatic Treatment

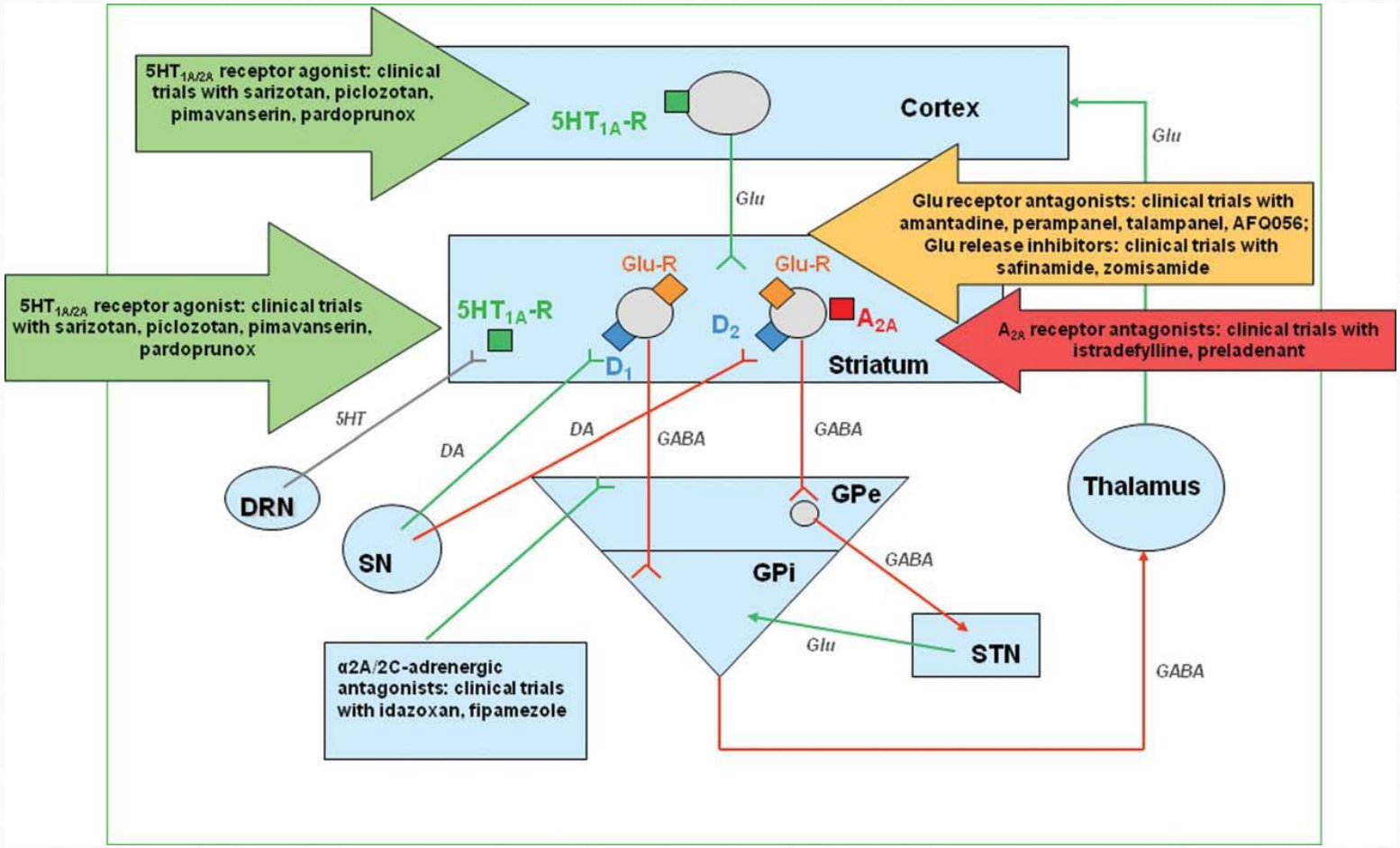


Anticholinergics: Trihexyphenidyl – Artane® etc: Act on the cholinergic system, for tremor. Side-effects: cognitive slowing

MAO-inhibitors: Rasagiline – Azilect®; Selegiline – Zelapar® etc.: prevent break-down of dopamine. Studied for disease-modifying effect. Side-effects: concern for interaction with anti-depressants

Amantadine – Symmetrel®: unclear mechanism of action. Can help dyskinesia. Side-effects: cognitive slowing

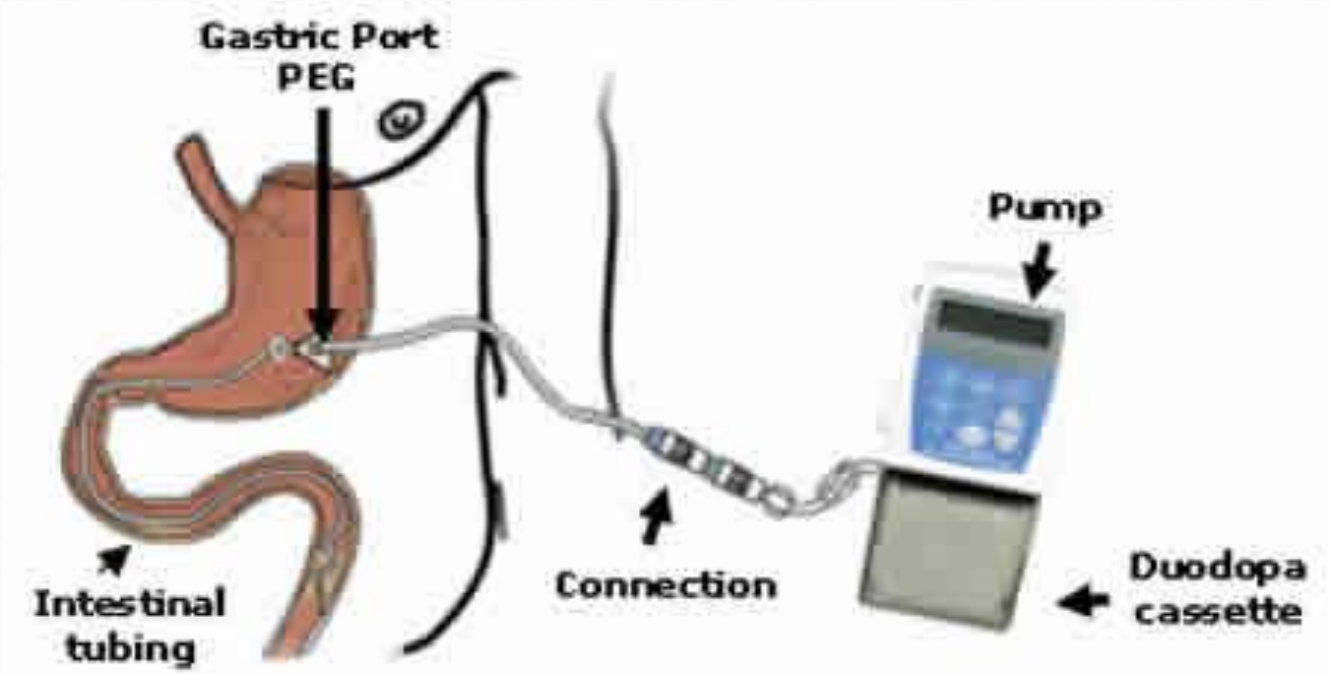
Non-Dopaminergic Symptomatic Therapy



Rascol O et al. Mov Disord 2011

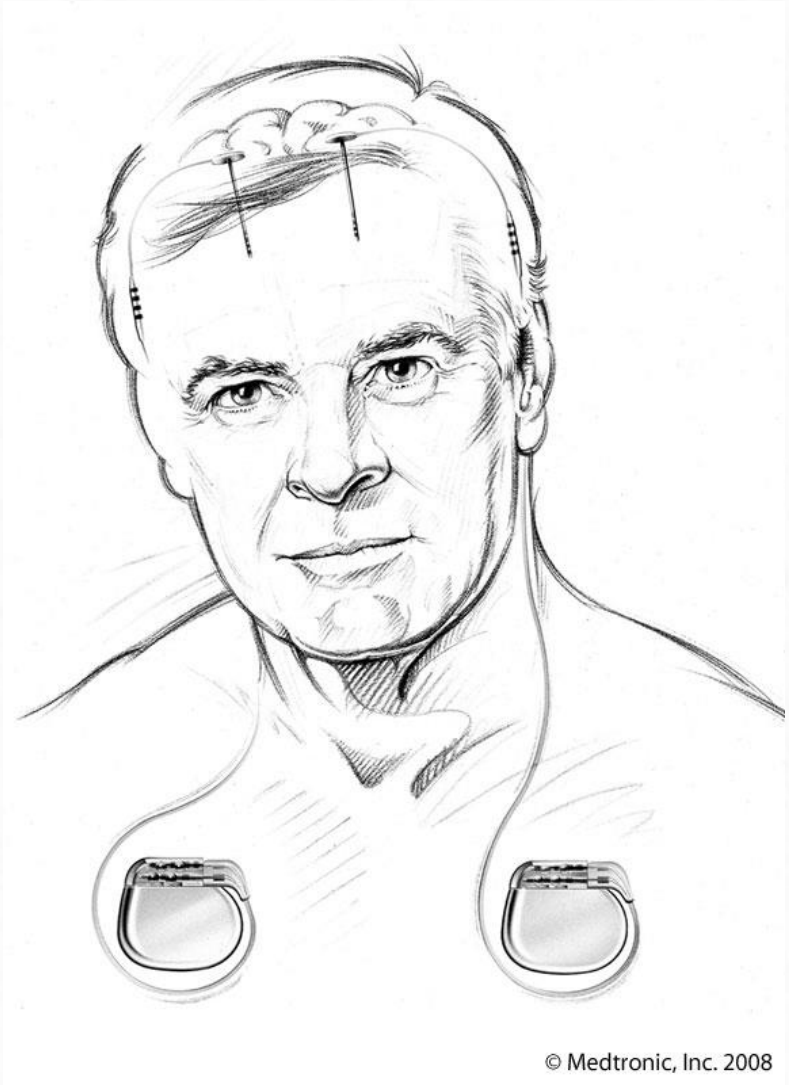
Symptomatic continuous dopaminergic therapy: Duodopa

- Uses a pump to deliver the medication into the intestine



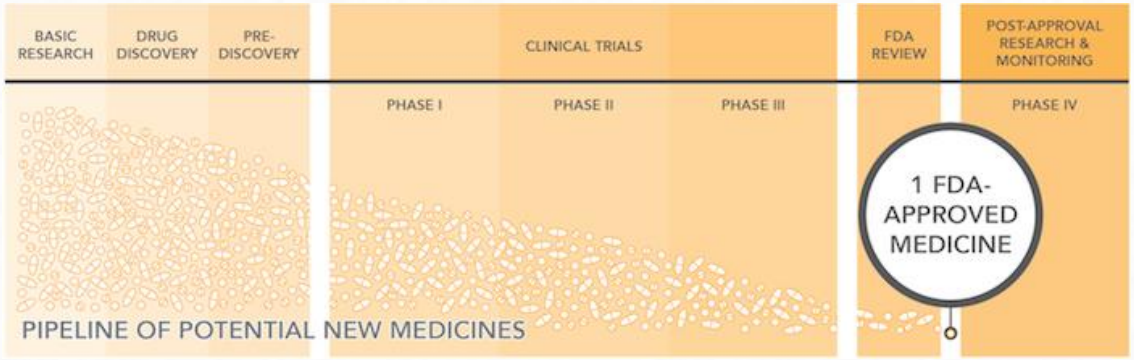
- Recently approved in the US.
- Has similar goals to DBS, but different and possibly more frequent side-effects

Surgery: Deep Brain Stimulation.



- Delivers external current patterns that override and replace the abnormal ones
- These propagate through the brain circuits in both directions
- Overall consequence is a new regular activity, locked to stimulation in a complex way, resulting in reduction in cardinal PD symptoms of bradykinesia, rigidity and tremor

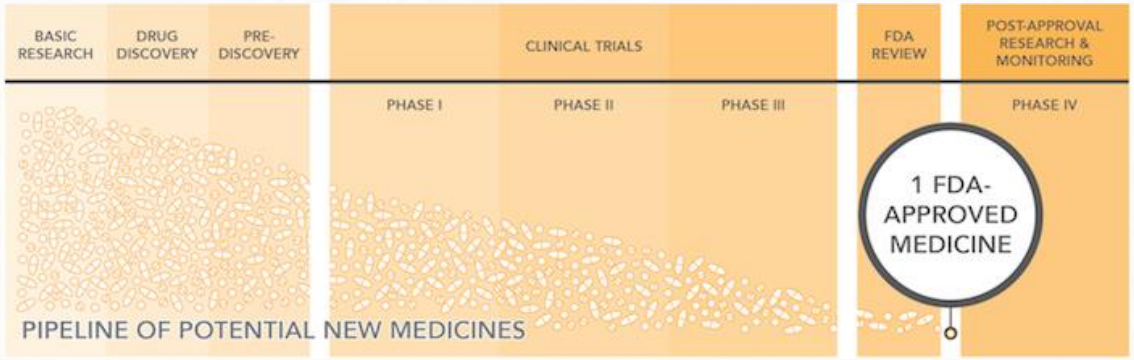
Therapy Development Pipeline



Recent successes:

- Rytary: dopaminergic symptomatic therapy, L-DOPA with extended efficacy
- Duopa: dopaminergic symptomatic therapy, surgical delivery of continuous dopaminergic stimulation
- Pimavanserin (Nuplazid): non-dopaminergic symptomatic therapy, first drug approved for PD psychosis

Therapy Development Pipeline

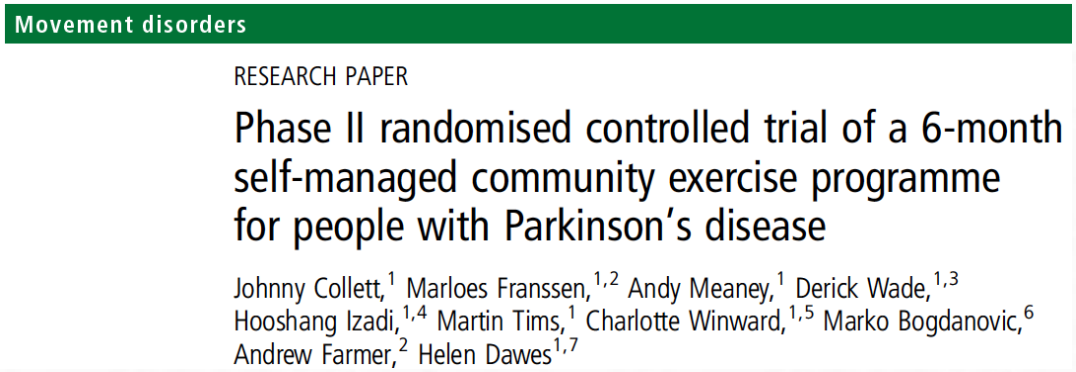


Recent successes:

- Droxidopa (Northera): Peripheral-acting dopaminergic for orthostatic hypotension
- Safinamide (Xadago): dopaminergic symptomatic (MAO inhibitor). Approved on 3/21/2017!

Symptomatic Therapy, Non-Pharmacologic: Exercise and PT

Multiple lines of evidence for benefit



Movement disorders

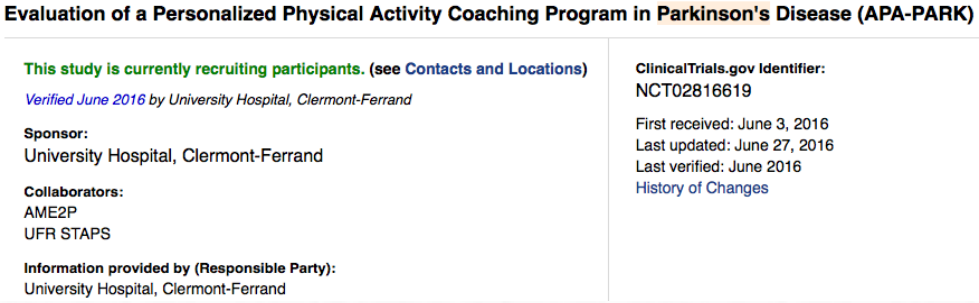
RESEARCH PAPER

Phase II randomised controlled trial of a 6-month self-managed community exercise programme for people with Parkinson's disease

Johnny Collett,[1] Marloes Franssen,[1,2] Andy Meaney,[1] Derick Wade,[1,3] Hooshang Izadi,[1,4] Martin Tims,[1] Charlotte Winward,[1,5] Marko Bogdanovic,[6] Andrew Farmer,[2] Helen Dawes[1,7]

JNNP 03/2017

Several on-going studies



Evaluation of a Personalized Physical Activity Coaching Program in Parkinson's Disease (APA-PARK)

This study is currently recruiting participants. (see Contacts and Locations)

Verified June 2016 by University Hospital, Clermont-Ferrand

Sponsor:
University Hospital, Clermont-Ferrand

Collaborators:
AME2P
UFR STAPS

Information provided by (Responsible Party):
University Hospital, Clermont-Ferrand

ClinicalTrials.gov Identifier:
NCT02816619

First received: June 3, 2016
Last updated: June 27, 2016
Last verified: June 2016
History of Changes

Rhythmic Auditory Stimulation Optimalization for Gait Improvement in Parkinson's Disease - BeatPark Study (BeatPark)

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2016 by University Hospital, Montpellier

Sponsor:
University Hospital, Montpellier

Collaborator:
Université Montpellier

Information provided by (Responsible Party):
University Hospital, Montpellier

ClinicalTrials.gov Identifier:
NCT02438124

First received: April 30, 2015
Last updated: January 7, 2016
Last verified: January 2016
History of Changes

Symptomatic Non-Dopaminergic Therapy: SAGE-127

SAGE-127 is a GABA-A receptor modulator, studied for treatment of tremor

A Study to Evaluate SAGE-217 in Patients With Parkinson's Disease of Moderate Severity

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2017 by Sage Therapeutics

Sponsor:
Sage Therapeutics

Information provided by (Responsible Party):
Sage Therapeutics

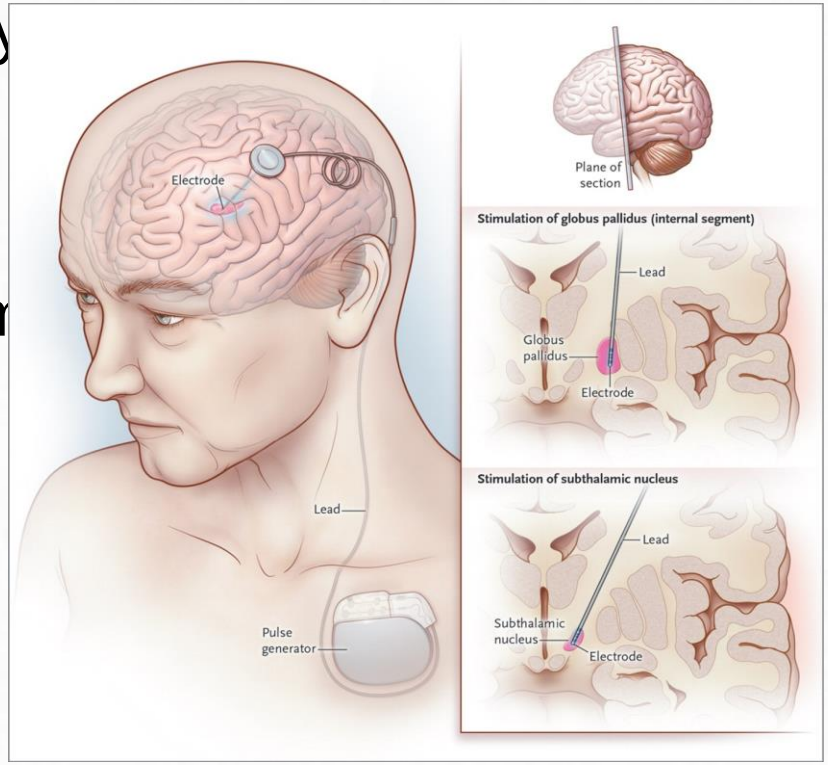
ClinicalTrials.gov Identifier:
NCT03000569

First received: November 28, 2016
Last updated: March 1, 2017
Last verified: March 2017
History of Changes

Early phase trials in progress

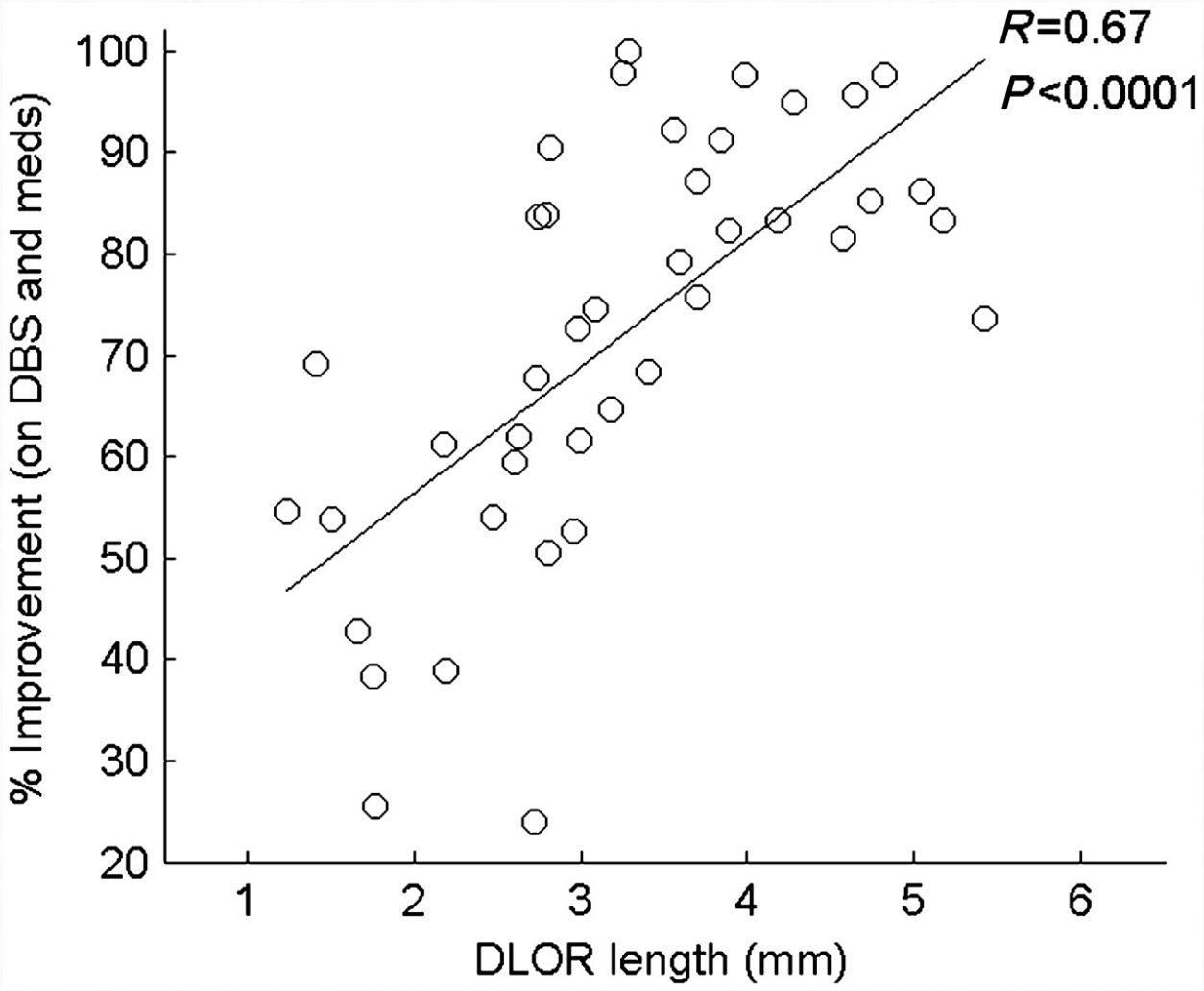
Deep Brain Stimulation
Major Current Directions
(no pun intended)

- Tailoring therapy to abnormal electrical activity
- Constant current, new delivery paradigms
- Current steering
- Understanding the mechanism action
- Guiding programming
- New targets



Okun NEJM 2012

The spatial extent of STN β oscillations predicts the outcome of STN DBS



Zaidel A et al. Brain 2010;133:2007-2021

Courtesy of Dr Mark Hallett

BRAIN A JOURNAL OF NEUROLOGY

Beta-HFO PAC Could Predict Efficacy

Neurobiology of Disease

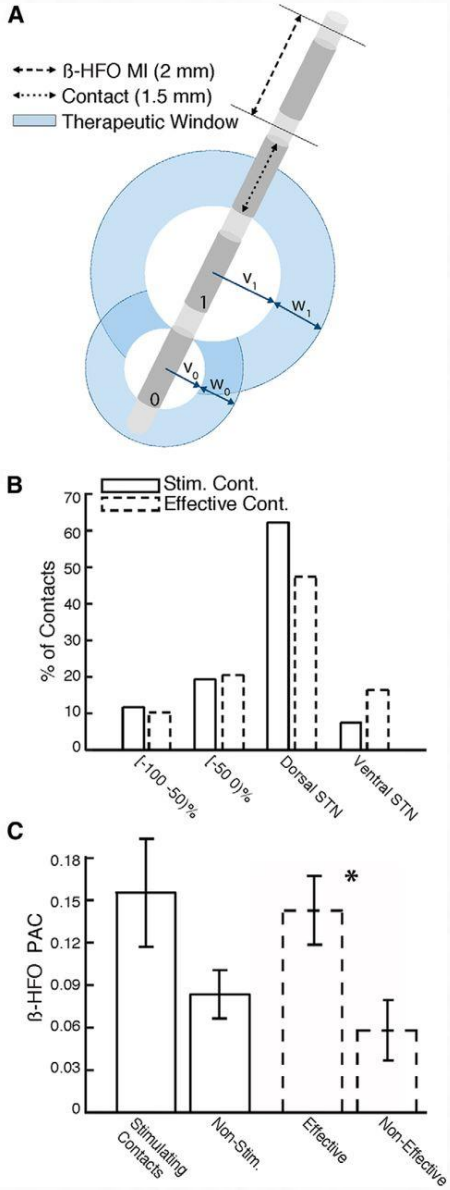
Beta-Coupled High-Frequency Activity and Beta-Locked Neuronal Spiking in the Subthalamic Nucleus of Parkinson's Disease

Andrew I. Yang[1], Nora Vanegas[2,3], Codrin Lungu[2], and Kareem A. Zaghloul[1]

+ Show Affiliations

Author contributions: A.I.Y. and K.A.Z. designed research; A.I.Y., N.V., C.L., and K.A.Z. performed research; A.I.Y., N.V., and K.A.Z. analyzed data; A.I.Y., N.V., C.L., and K.A.Z. wrote the paper.

The Journal of Neuroscience, 17 September 2014, 34(38): 12816-12827; doi: 10.1523/JNEUROSCI.1895-14.2014

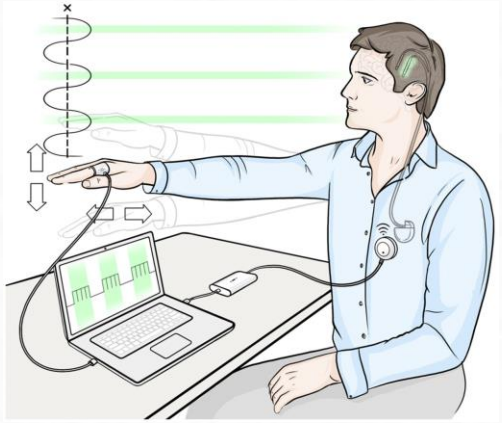


doi:10.1093/brain/aww286 BRAIN 2017: 140; 132–145 | 132

BRAIN
A JOURNAL OF NEUROLOGY

Stimulating at the right time: phase-specific deep brain stimulation

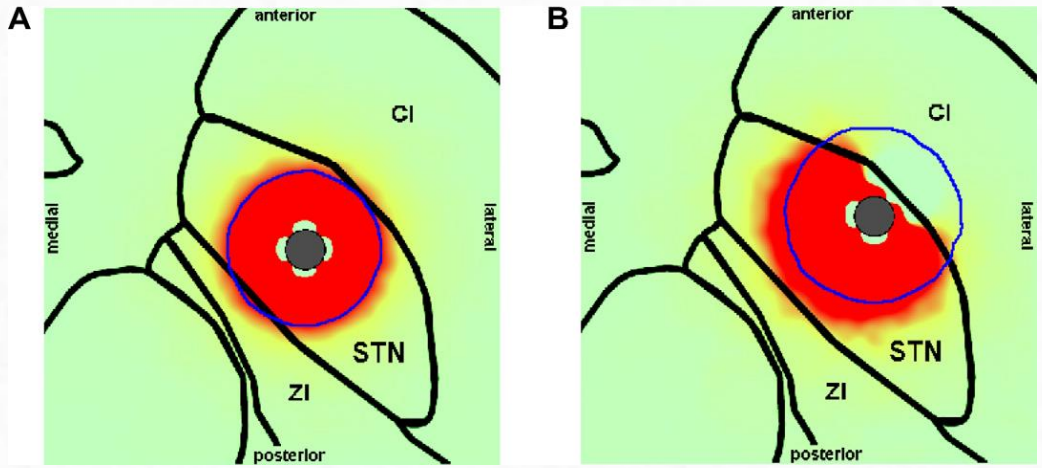
Hayriye Cagnan,[1,2,3] David Pedrosa,[2,3] Simon Little,[1] Alek Pogosyan,[2,3] Binith Cheeran,[2] Tipu Aziz,[2] Alexander Green,[2] James Fitzgerald,[2] Thomas Foltynie,[1] Patricia Limousin,[1] Ludvic Zrinzo,[1] Marwan Hariz,[1] Karl J. Friston,[1] Timothy Denison[4] and Peter Brown[2,3]



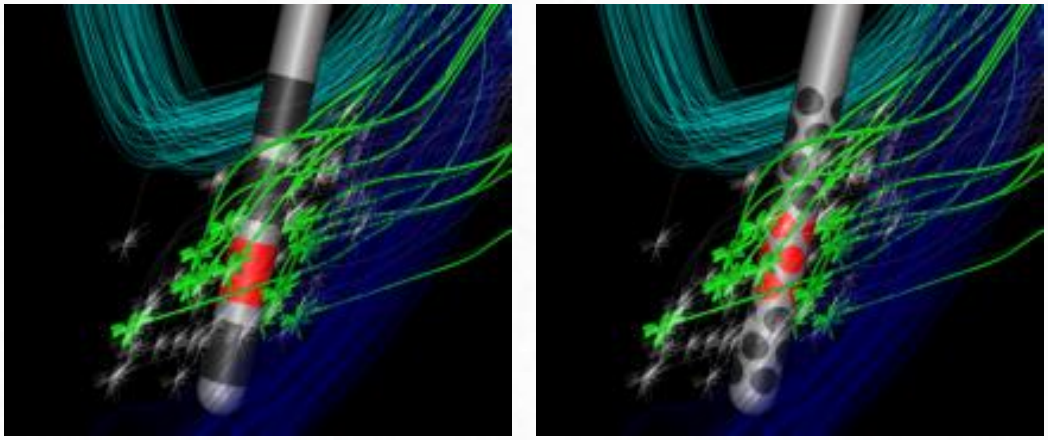
Stimulation locked to specific phase of tremor oscillation is more efficient than continuous stimulation

Current Steering

Uses DBS array electrodes in place of the cylindrical electrodes currently in use; allows targeting the VTA in cardinal directions

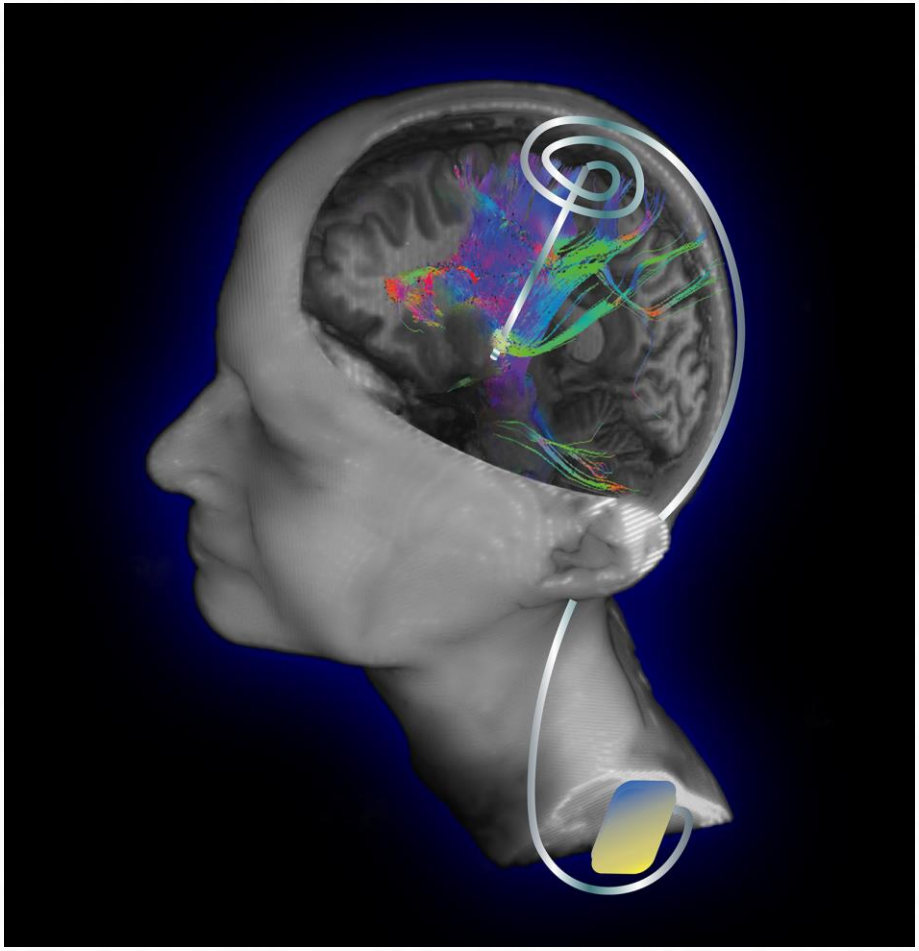


Martens et al., Clin. Neurophysiol. 2011



Lead design constantly evolving

Using DTI Imaging to Study DBS Effects and Refine Therapeutic Paradigms

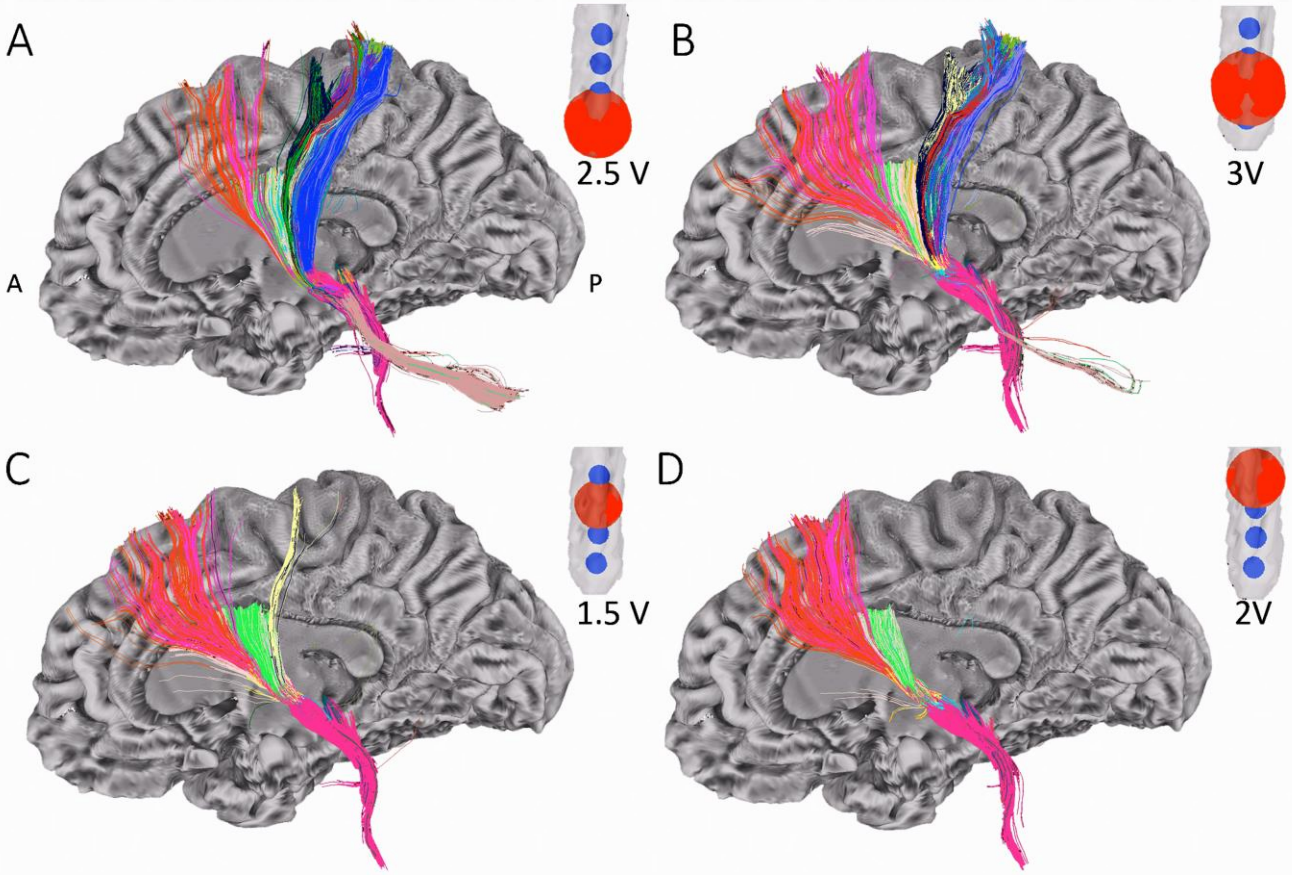


Tractography Patterns of Subthalamic Nucleus Deep Brain Stimulation.

Vanegas-Arroyave N, Lauro P, Huang L, Hallett M, Horovitz S, Zaghloul K, Lungu C. Brain 2016

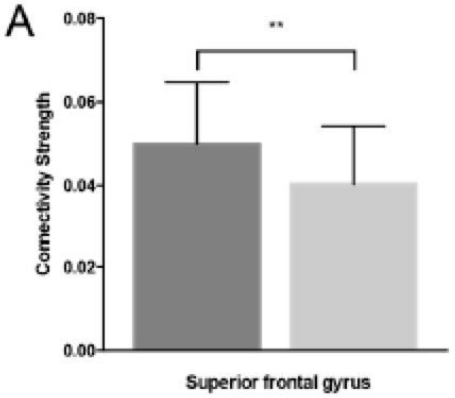
Individual Tractographic Patterns

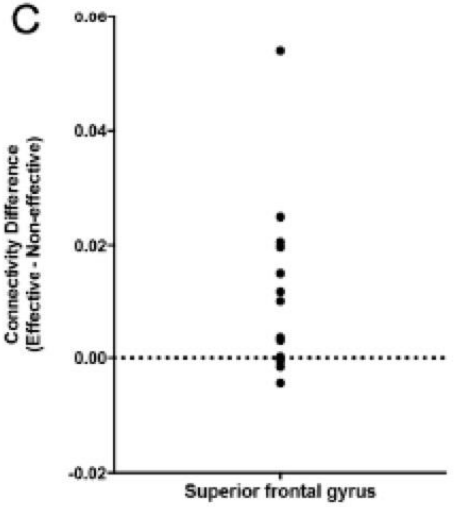
Different tractographic patterns of effective and non-effective contacts on an example lead

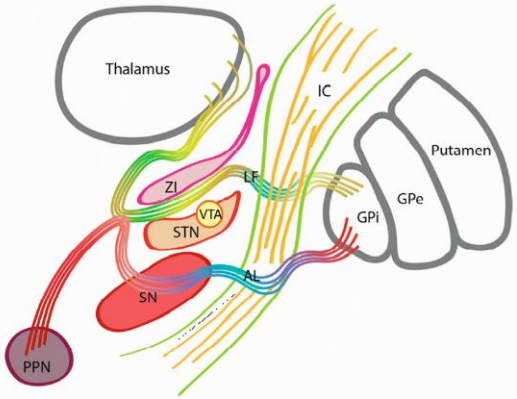


Results Summary and Significance

- SFG, thalamus connectivity associate with effective contacts, discriminant power 0.89, 0.80 respectively
- Potential for pre-programming identification of effective contacts
- This likely represents activation of hyperdirect pathway and pallidothalamic fibers respectively

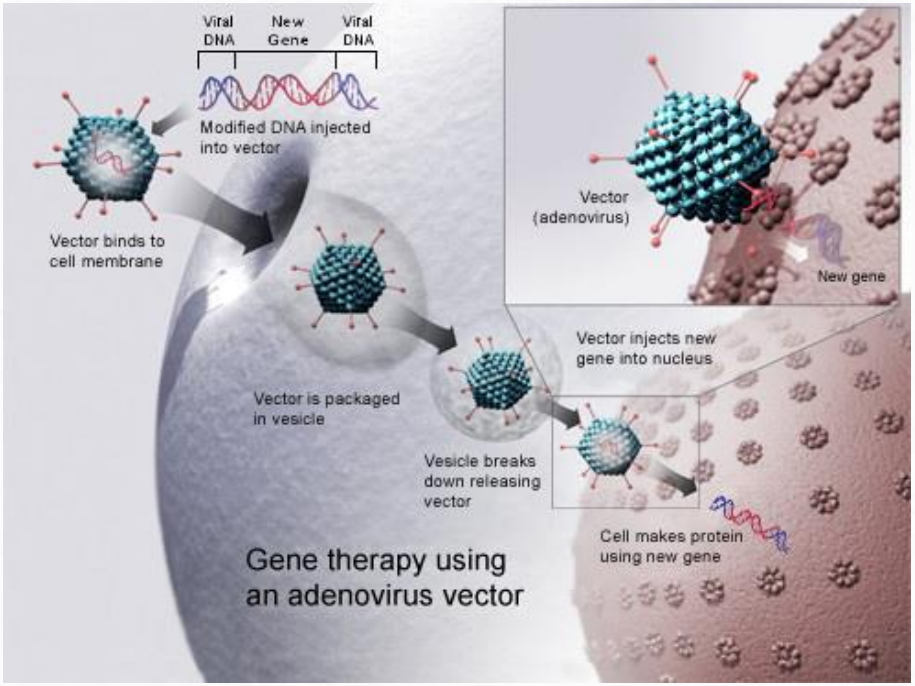




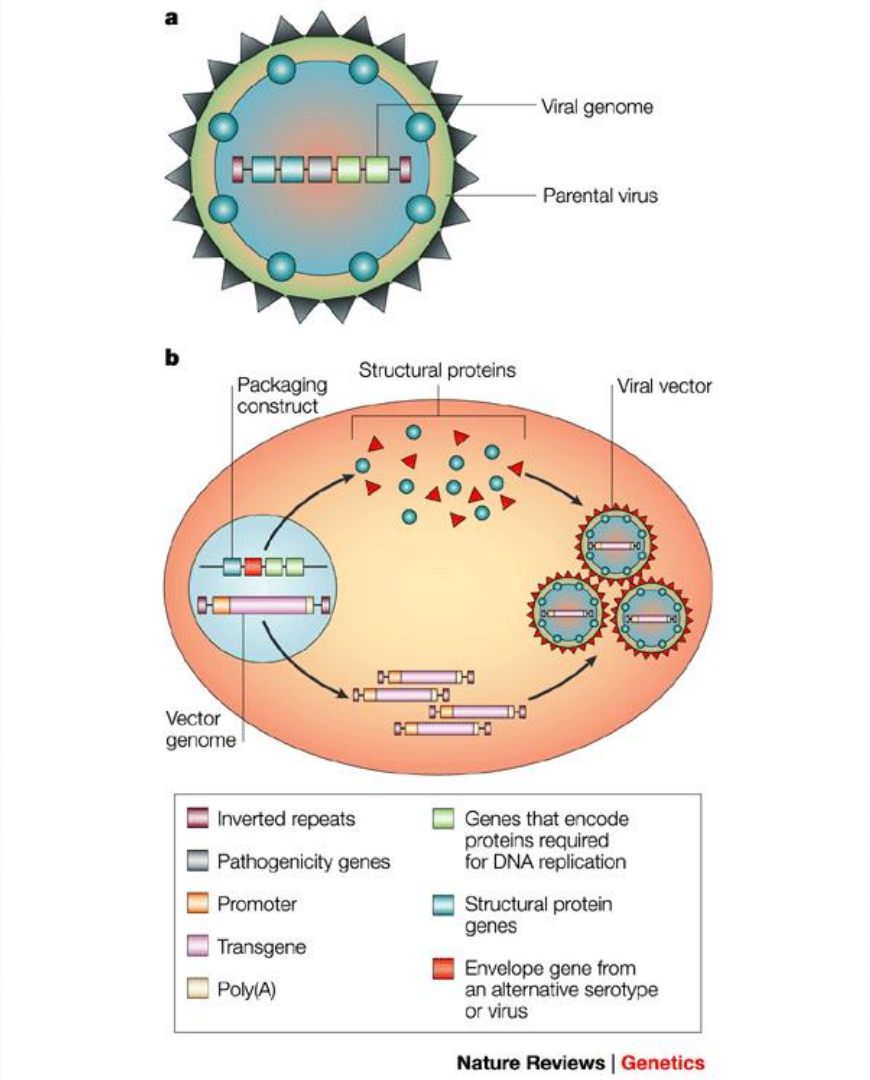


Viral Vector Gene Therapy

Surgically delivered constructs

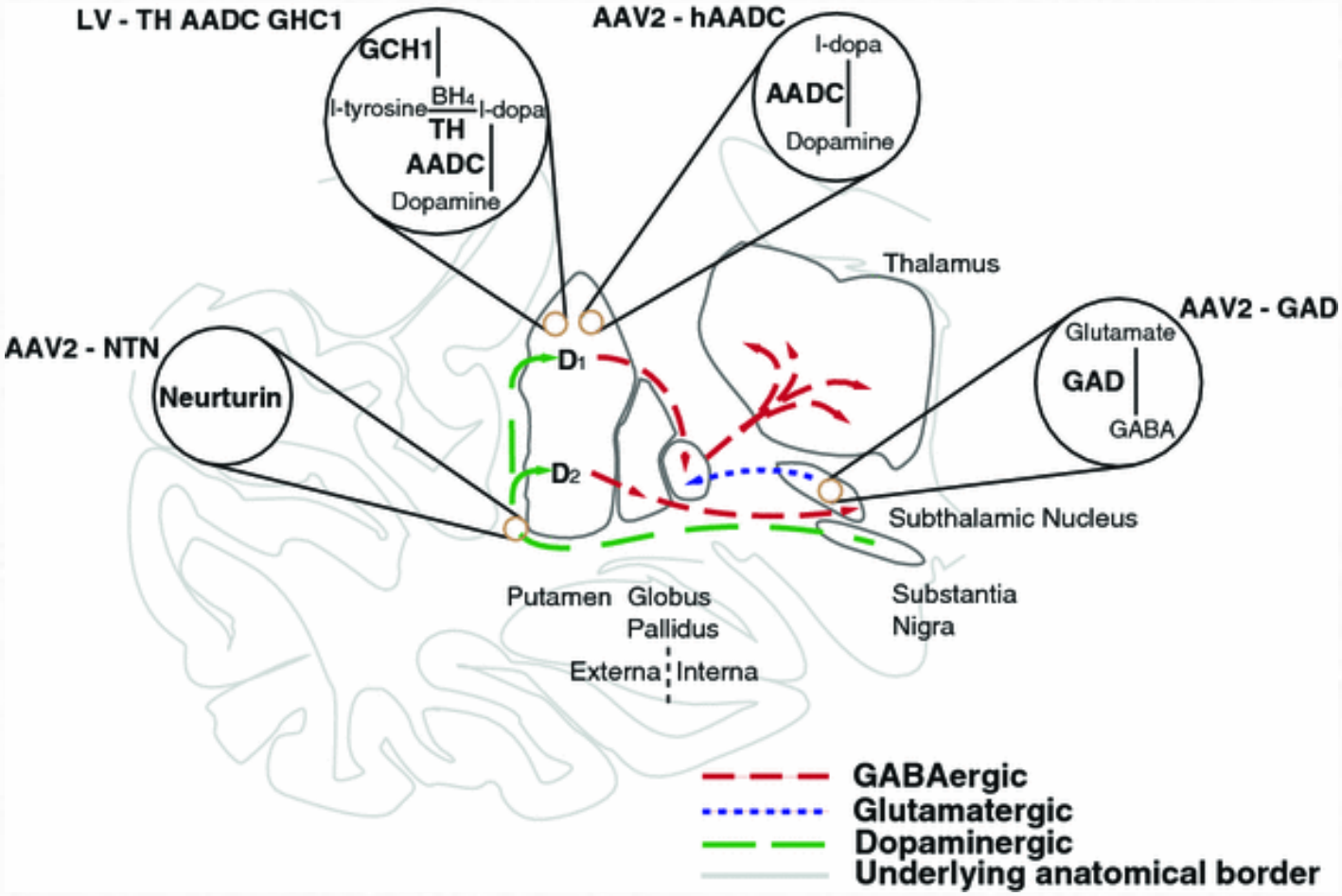


NLM public domain



Thomas et al Nat Rev Genetics 2003

Relevant PD Pathogenic Pathways Including Symptomatic Approaches



Berry and Foltynie, J Neurol 2011

Symptomatic Gene Therapy: ProSavin Trial

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 Iwamuro, 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*

Interpretation **ProSavin was safe and well tolerated in patients with advanced Parkinson's disease. Improvement in motor behaviour was observed in all patients.**

Symptomatic Gene Therapy: AAV2-AADC Trial

AADC Gene Therapy for Parkinson's Disease

This study is currently recruiting participants. (see Contacts and Locations)

Verified February 2015 by University of California, San Francisco

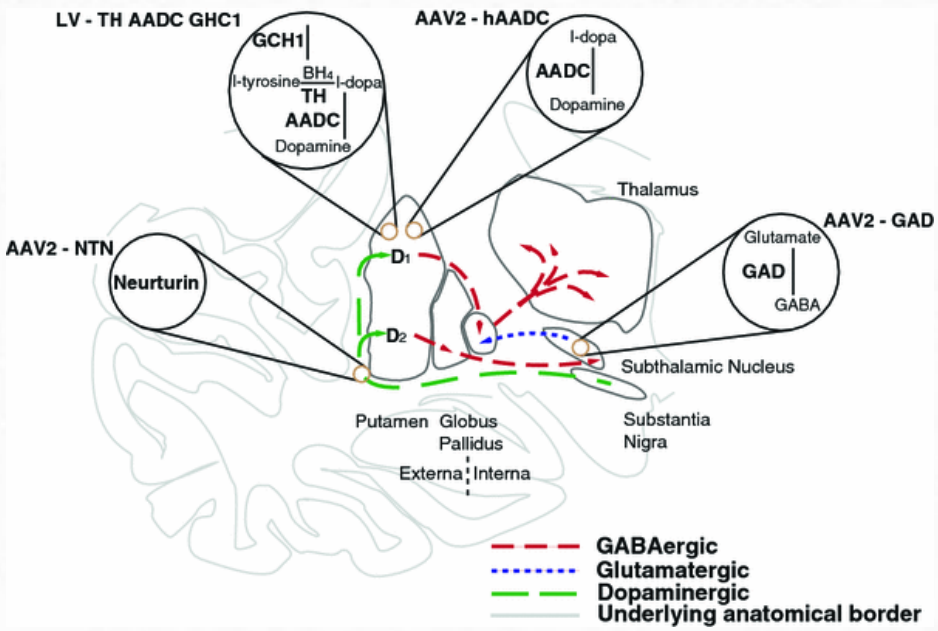
Sponsor:
Krystof Bankiewicz

Collaborator:
Oregon Health and Science University

Information provided by (Responsible Party):
Krystof Bankiewicz, University of California, San Francisco

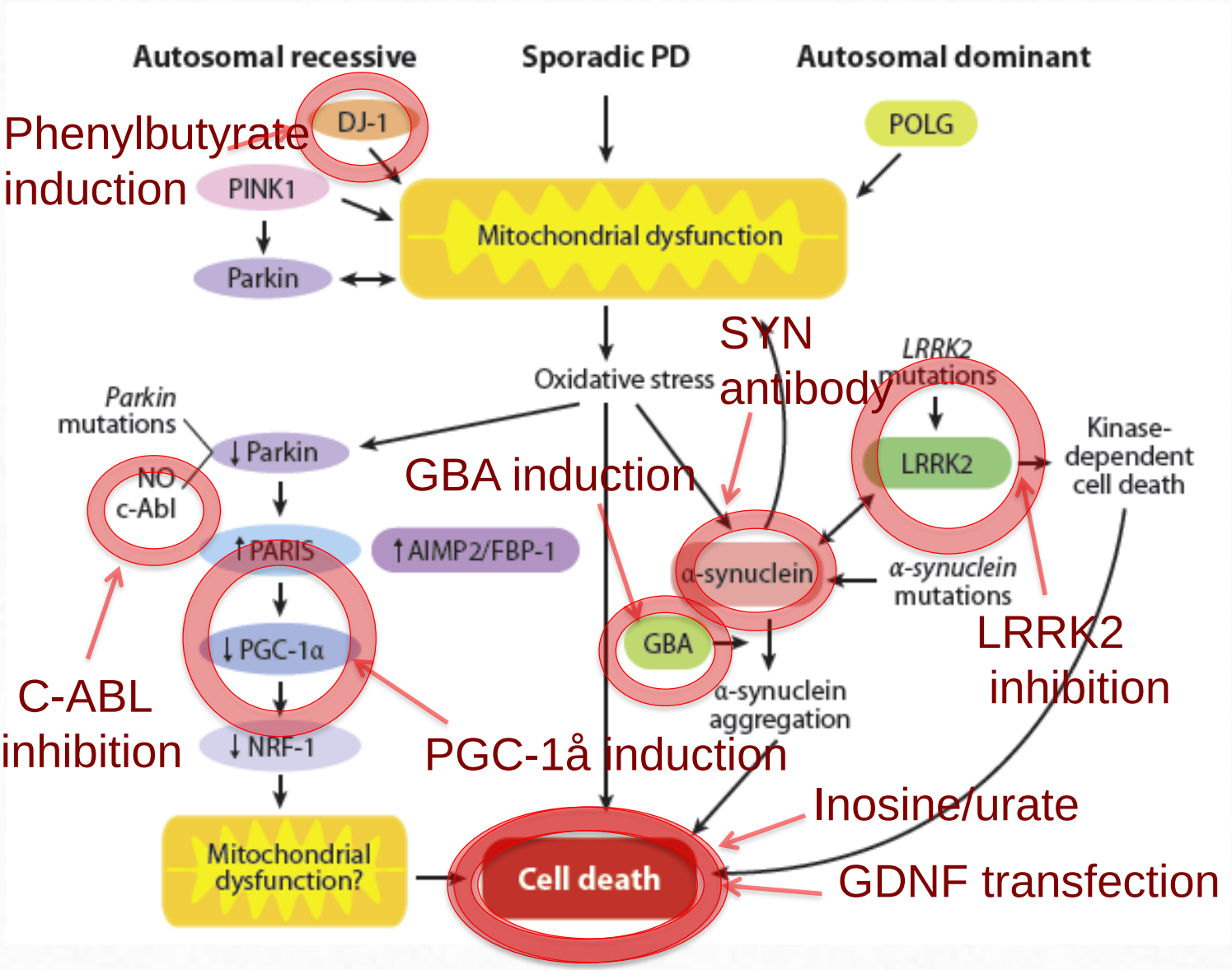
ClinicalTrials.gov Identifier:
NCT01973543

First received: October 25, 2013
Last updated: February 12, 2015
Last verified: February 2015
History of Changes



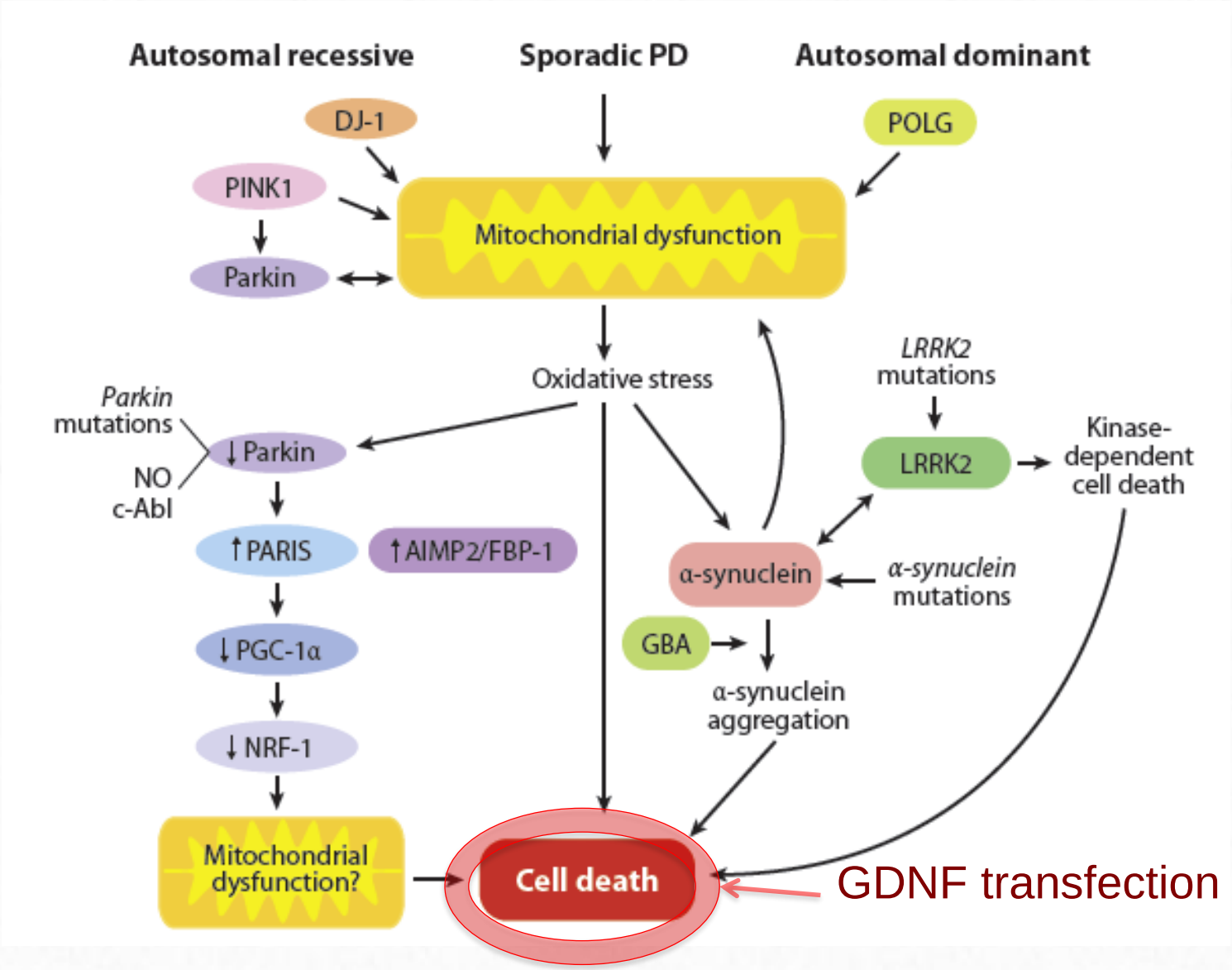
- Uses a similar delivery method to the NIH GDNF study
- Ongoing

Molecular-Targeted Therapy



Martin I et al. Annu Rev Genomics Hum Genet. 2010

Molecular-Targeted Therapy



Martin I et al. Annu Rev Genomics Hum Genet. 2010

Potential Disease-Modifying Therapy: GDNF

One of several known NTFs, which mediate neuronal survival (Aron and Klein, Trends Neuroci 2011)

Isolated from the B49 cell line based on its ability to promote the survival of embryonic DA neurons in vitro

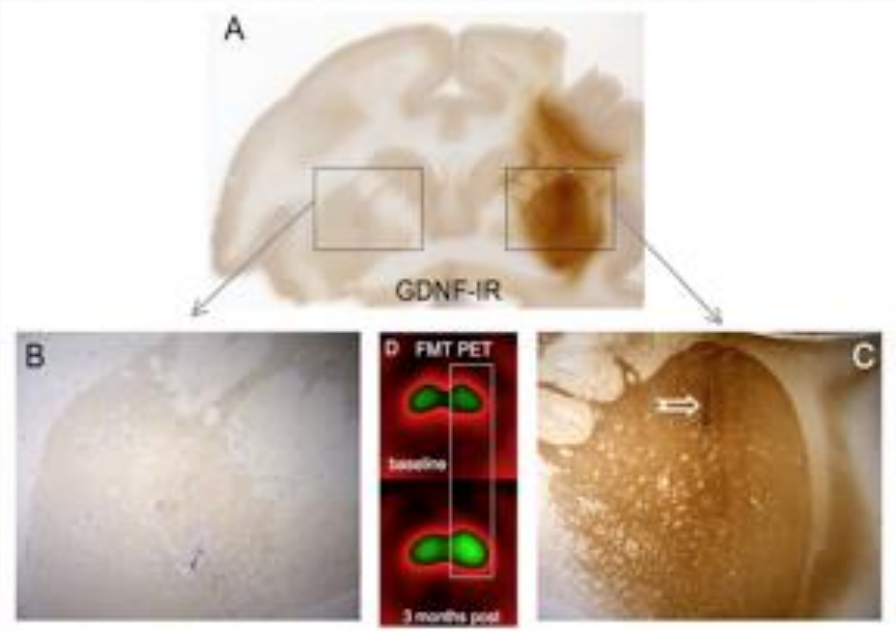
Proposed neuroprotective/neurorestorative therapy in PD

Neurturin (NTN) shares functional homology and a physiologic action pathway – but diffusivity is limited

Both are part of the GDNF family of ligands (GFLs)

GDNF pre-clinical data

GDNF has been shown to be neuroprotective, to encourage neuronal fiber outgrowth, and to improve motor function when delivered into the cerebral ventricles or directly into the striatum or nigra in both rodent and primate models of PD (reviewed in Rangasamy SB et al, Prog Brain Res. 2010)



Courtesy of Dr Russell Lonser

Cere 120 Trial

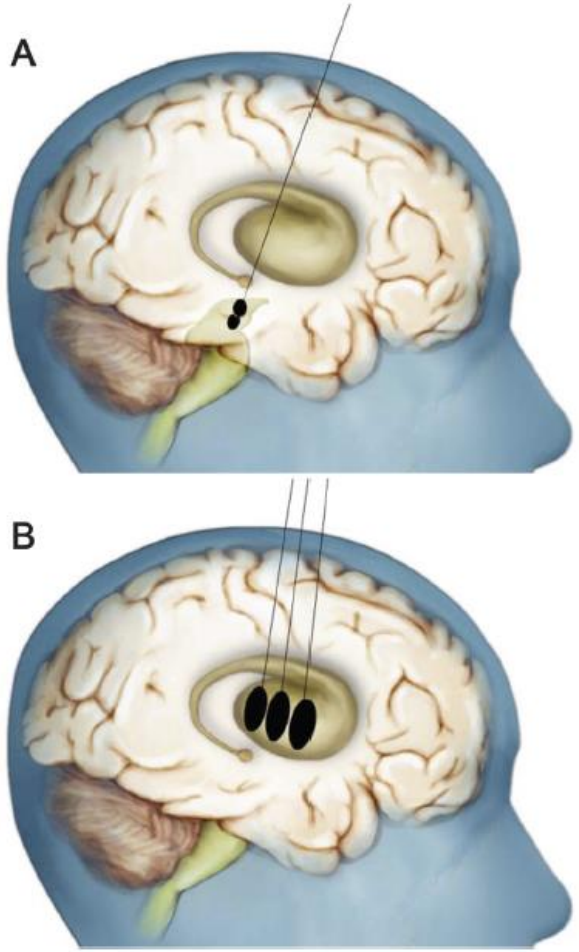
Neurology®

Safety/feasibility of targeting the substantia nigra with AAV2-neurturin in Parkinson patients

Raymond T. Bartus, Tiffany L. Baumann, Joao Siffert, et al.

Neurology; Published online before print April 10, 2013;
DOI 10.1212/WNL.0b013e3182904faa

Figure Artist's rendition of the dosing scheme employed to bilaterally target the substantia nigra and putamen with AAV2-NRTN (CERE-120)



GDNF Early Clinical Data and Next Steps

- 4 GDNF and 2 NTN trials conducted so far
- Variable efficacy, limited primarily by the efficacy of drug delivery
- New trial ongoing at the NIH, intramural – extramural collaboration
- Convention-enhanced delivery of AAV2-GDNF allows much better distribution of the gene product to the striatum
- 4 sequential dosing cohorts planned

GDNF Trial at the NIH

Two dosing cohorts completed

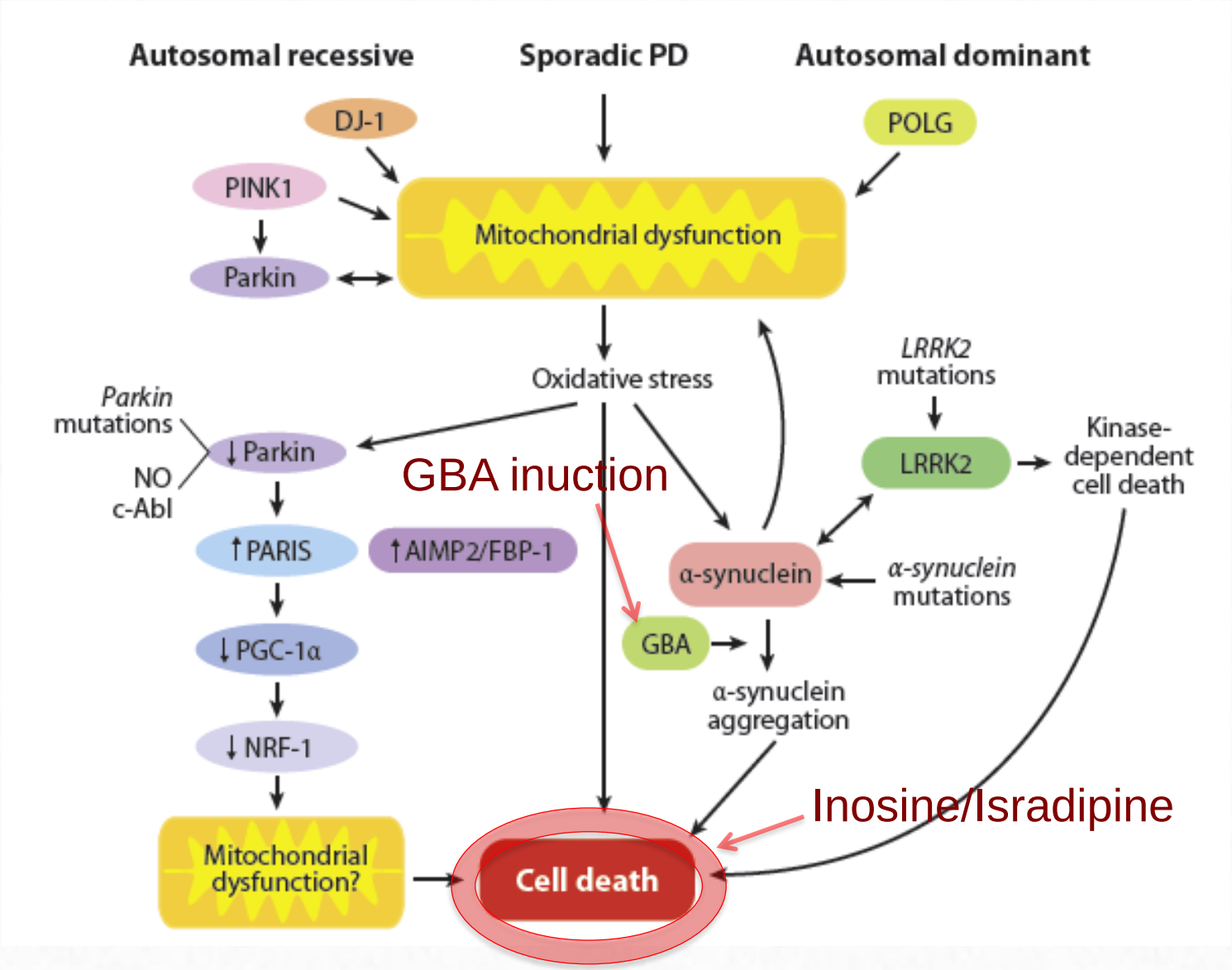
No significant problems reported

Proceeding per protocol

Still recruiting and looking for candidates

Safety data very good, potentially encouraging other preliminary data

Molecular-Targeted Therapy



Martin I et al. Annu Rev Genomics Hum Genet. 2010

Potential Disease-Modifying Therapy: Inosine

Inosine to Increase Serum and Cerebrospinal Fluid Urate in Parkinson Disease

A Randomized Clinical Trial FREE

The Parkinson Study Group SURE-PD Investigators

JAMA Neurol. 2014;71(2):141-150. doi:10.1001/jamaneurol.2013.5528.

Inosine is a precursor of urate, shown to be neuroprotective in vivo and animal models

Phase 3 trial of inosine for Parkinson's disease CCC

Schwarzschild, Michael A.

Massachusetts General Hospital, Boston, MA, United States

Potential Disease-Modifying Therapy: Isradipine

Movement Disorders

Official Journal of the International Parkinson and Movement Disorder Society

Explore this journal >

Research Article

Phase II safety, tolerability, and dose selection study of isradipine as a potential disease-modifying intervention in early Parkinson's disease (STEADY-PD)

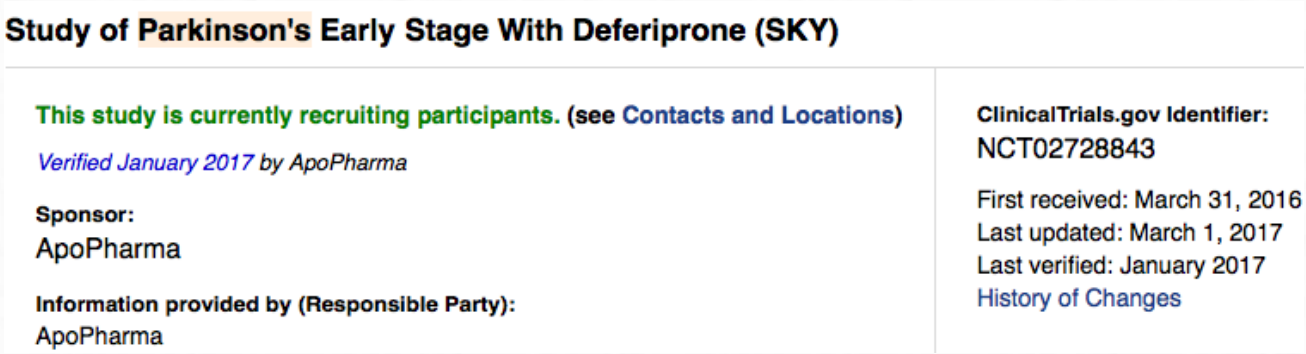
Parkinson Study Group

First published: 30 September 2013 Full publication history

Isradipine is a calcium channel blocker, shown to protect nigral dopaminergic cell in vitro.

STEADY-PD III phase III multicenter trial on-going

Potential Disease-Modifying Therapy: Deferiprone



Study of Parkinson's Early Stage With Deferiprone (SKY)

This study is currently recruiting participants. (see Contacts and Locations)

Verified January 2017 by ApoPharma

Sponsor:
ApoPharma

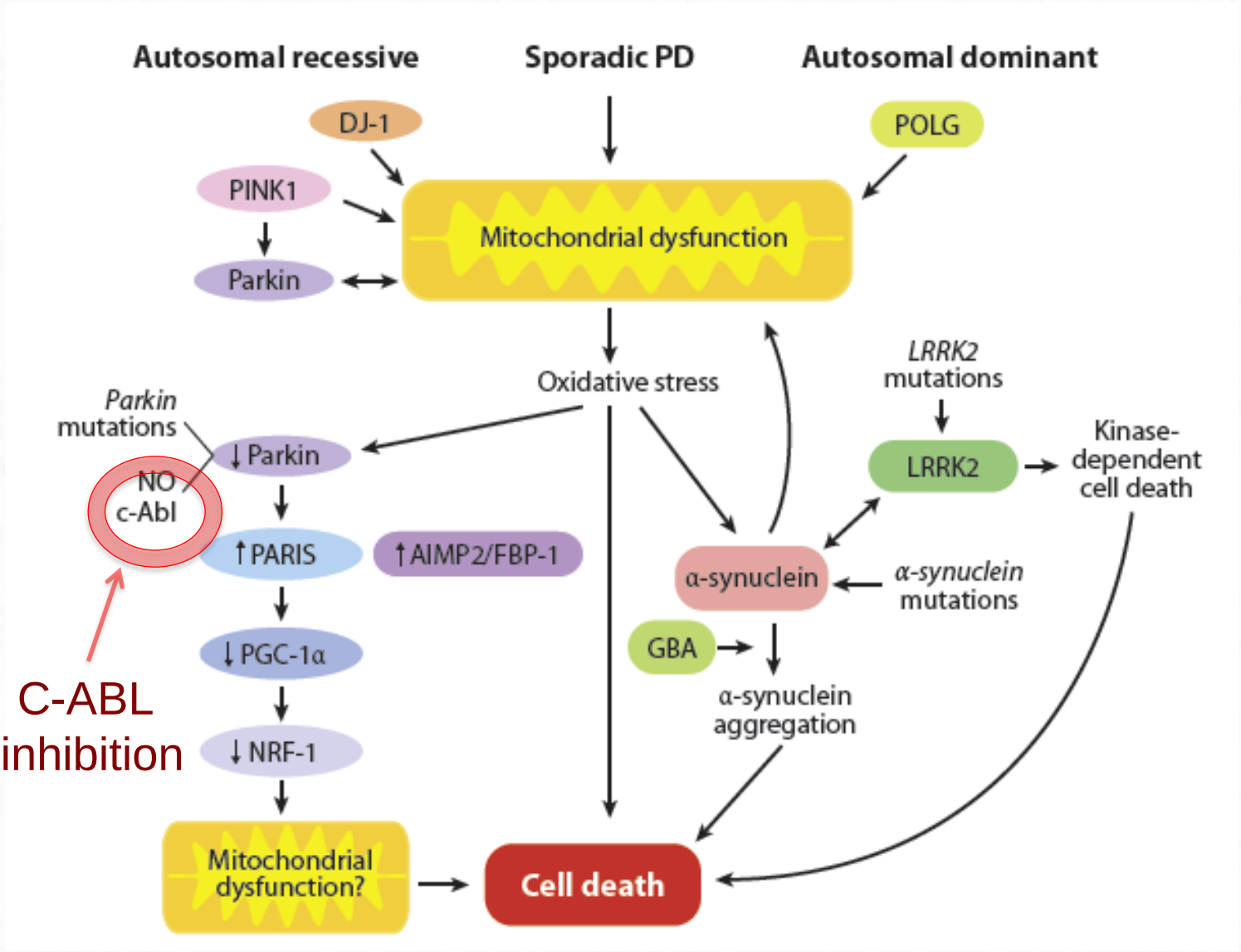
Information provided by (Responsible Party):
ApoPharma

ClinicalTrials.gov Identifier:
NCT02728843

First received: March 31, 2016
Last updated: March 1, 2017
Last verified: January 2017
History of Changes

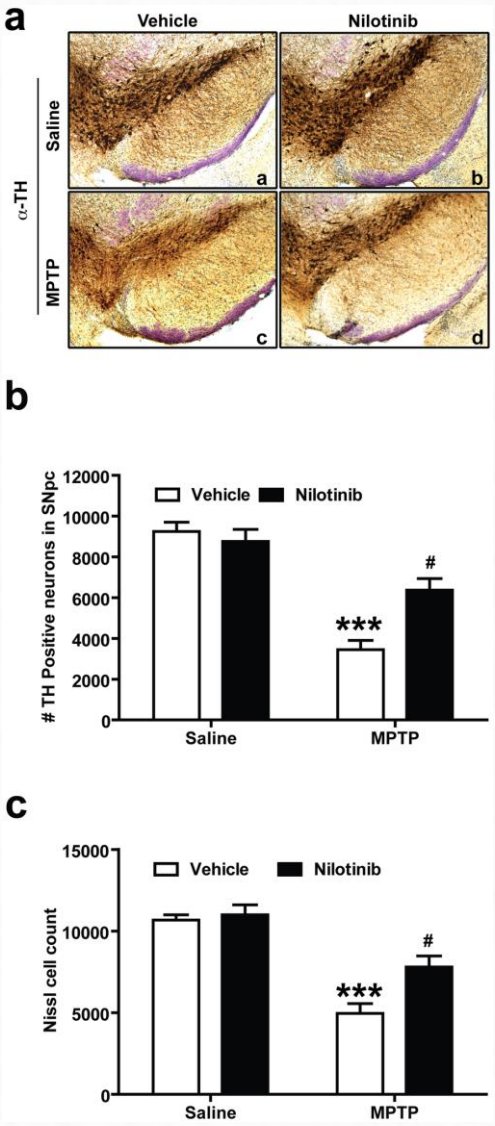
Deferiprone is an iron chelator, targeting abnormal iron accumulation and mitochondrial dysfunction in the substantia nigra.

Molecular-Targeted Therapy

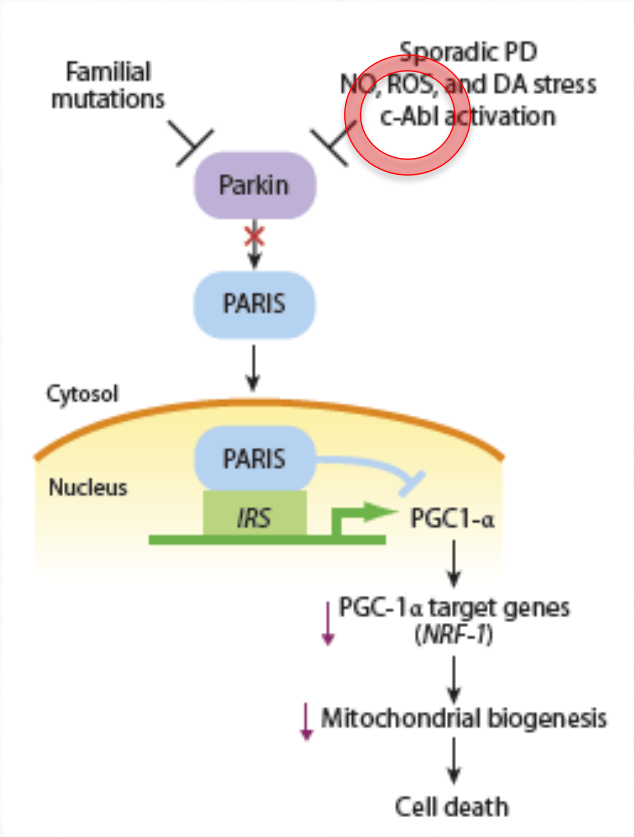


Martin I et al. Annu Rev Genomics Hum Genet. 2010

C-ABL as target



Karuppagounder
Sci Rep 2014

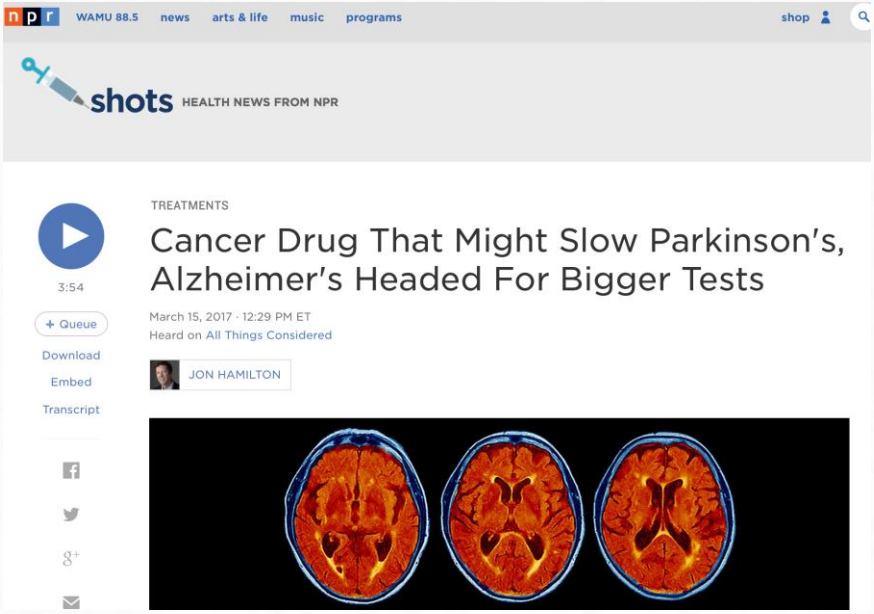


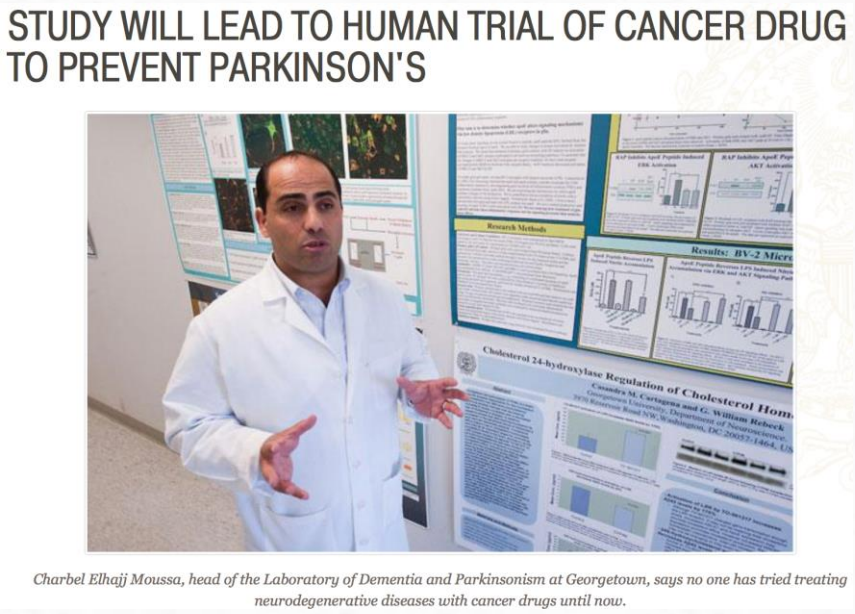
Martin I et al. Annu Rev
Genomics Hum Genet. 2011

- C-ABL inhibits Parkin's protective effect
- C-ABL KO protects against MPTP-induced loss of DA neurons as dose nilotinib

C-ABL as target

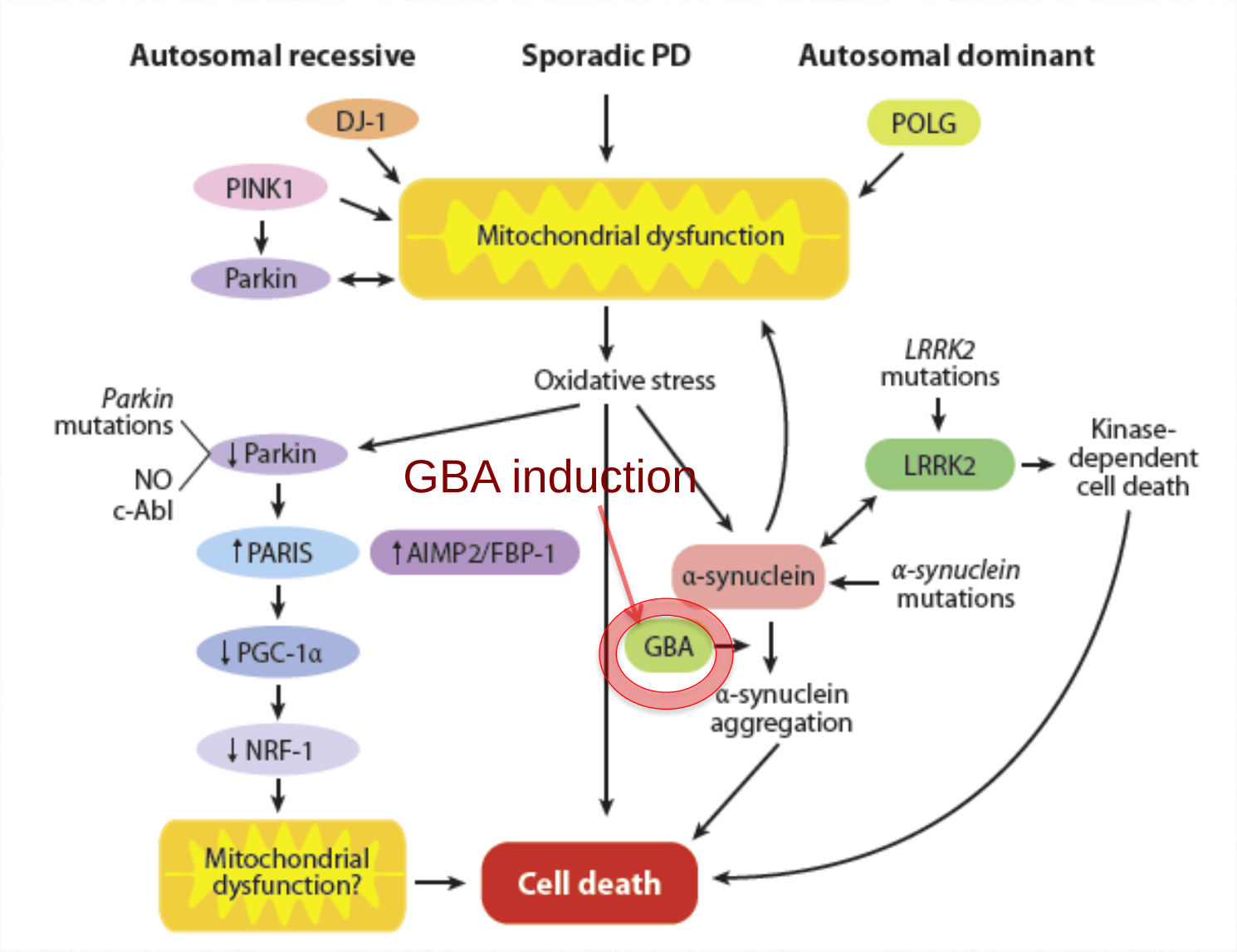
- C-ABL inhibitors exist and can be delivered systemically
- Studies in progress





Charbel Elhajj Moussa, head of the Laboratory of Dementia and Parkinsonism at Georgetown, says no one has tried treating neurodegenerative diseases with cancer drugs until now.

Molecular-Targeted Therapy



Martin I et al. Annu Rev Genomics Hum Genet. 2010

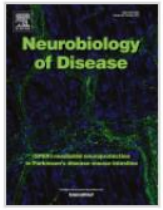
Targeting GBA

- GBA mutations are the most common genetic risk factor for PD, associated with reduced GCase activity

ELSEVIER

Neurobiology of Disease

Volume 82, October 2015, Pages 495–503



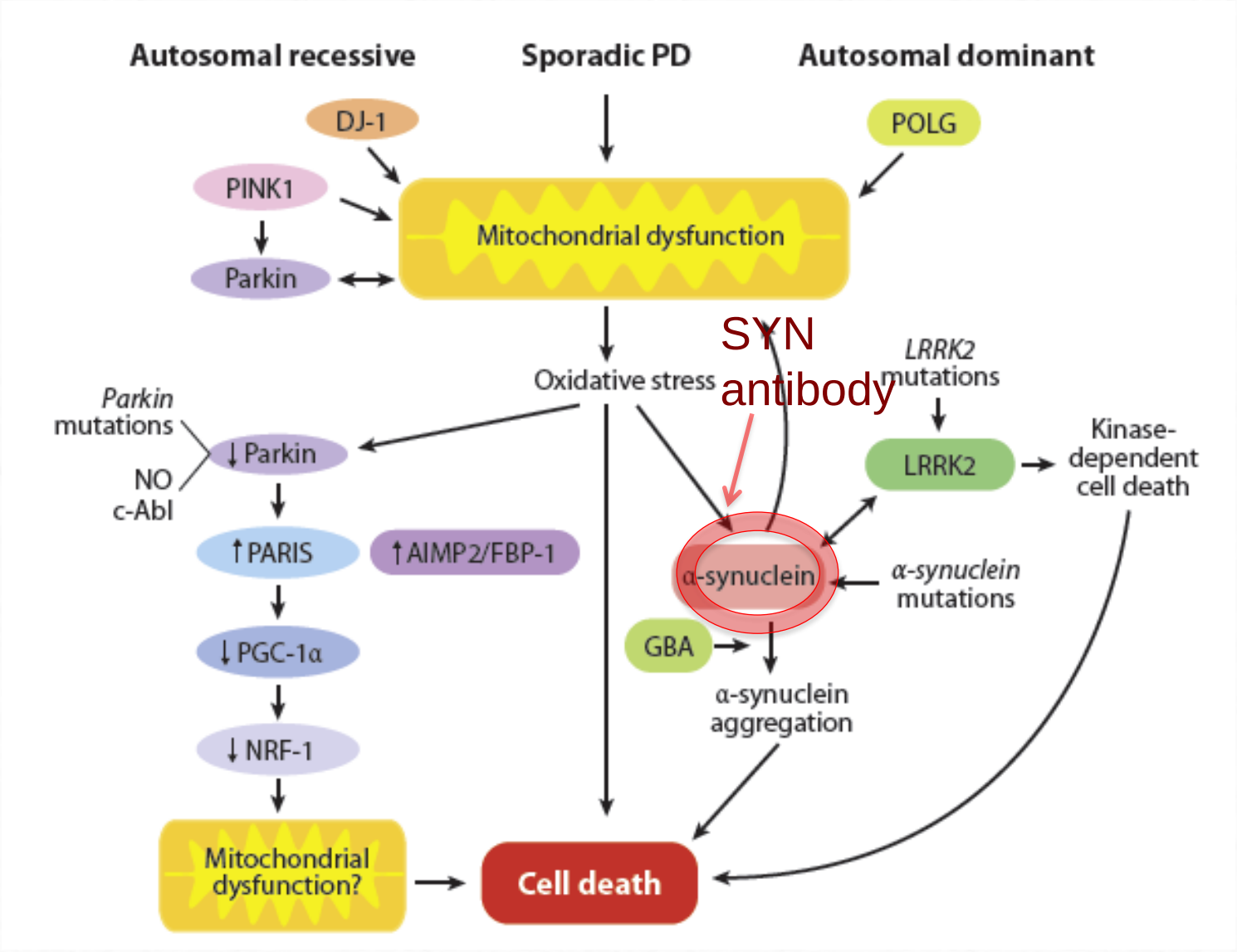
Glucocerebrosidase gene therapy prevents α-synucleinopathy of midbrain dopamine neurons

Emily M. Rocha[a, 1], Gaynor A. Smith[a, 1], Eric Park[b], Hongmei Cao[b], Eilish Brown[b], Melissa A. Hayes[a], Jonathan Beagan[a], Jesse R. McLean[a], Sarah C. Izen[a], Eduardo Perez-Torres[a], Penelope J. Hallett[a], , Ole Isacson[a], ,

Rocha, Neurobiol Dis 2015

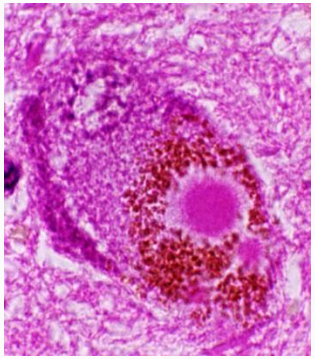
- AAV-GBA gene delivery prevented α-synuclein-mediated degeneration of nigrostriatal dopamine neurons

Molecular-Targeted Therapy



Martin I et al. Annu Rev Genomics Hum Genet. 2010

Targeting Synuclein



First-in-Human Assessment of PRX002, an Anti–α-Synuclein Monoclonal Antibody, in Healthy Volunteers

Dale B. Schenk, PhD,[1†] Martin Koller, MD, MPH,[1] Daniel K. Ness, DVM, PhD,[1] Sue G. Griffith, MD, PhD, MRCP,[2] Michael Grundman, MD, MPH,[3,4] Wagner Zago, PhD,[1] Jay Soto, BS,[1] George Atiee, MD,[5] Susanne Ostrowitzki, MD, PhD,[6] and Gene G. Kinney, PhD[1*]

Mov Disord 03/2017

The study in healthy volunteers showed safety and good immunogenicity. Further studies, as well as complementary approaches, are in progress.

Where to Find Information

https://clinicaltrials.gov

https://www.nih.gov/health-information/nih-clinical-research-trials-you/finding-clinical-trial

https://foxtrialfinder.michaeljfox.org

More Studies Are Needed

"Human clinical trials start in six months.
Sooner if we run out of mice."

Summary and Conclusions

- Biomarkers remain an important focus, with slow but steady progress. Genetic markers may be the key to presymptomatic diagnosis. Instrumented assessments can provide useful *targeted* information

- New techniques can refine old therapies, like DBS

- Targeting specific pathogenic pathways may yield disease-modifying or curative therapies

Thanks

- NIH HMCS:
  - Mark Hallett
  - Silvina Horovitz
  - Sule Tinaz
  - Elaine Considine
- NIH SNB:
  - Kareem Zaghloul
  - John Heiss
  - Russell Lonser
- PDMD Center:
  - Steve Grill
- Holy Cross Hospital
  - Zach Levine
- MAPMG:
  - Ejaz Shamim
- NIH
  - Barbara Karp
  - Katharine Alter
- NLM/Emory
  - Bona Kim
- NINDS Leadership
  - Walter Koroshetz
  - Alan Koretsky
  - Avi Nath
- PFNCA
- UCI/ Georgetown:
  - Howard Federoff
  - Massimo Fiandaca
- NIH PD Clinic:
  - Beverly McElroy
  - Mae Brooks
  - Nora Vanegas
  - Omar Ahmad
  - Peter Lauro
  - Ling Huang
  - Sana Zahir
- NIH Neurogenetics
  - Andy Singleton
  - Mike Nalls
- NHLBI
  - Michael Sack
- GW:
  - Pritha Ghosh