Medications, Breakthroughs, and Therapies on the Horizon in Parkinson Disease

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Disclosures / Funding

- Disclosures
  - Research support from St. Jude / Abbott
- Funding
  - National Institutes of Health / NINDS
  - Parkinson Foundation

JOHNS HOPKINS
MEDICINE

Overview

- Future therapies for symptom management
- Future therapies to slow disease progression
- Recent breakthroughs that may lead to therapies

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- Future therapies to slow disease progression
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Future Therapies for Symptom Management

- Pharmacologic therapies
- Advances in DBS / brain lesioning

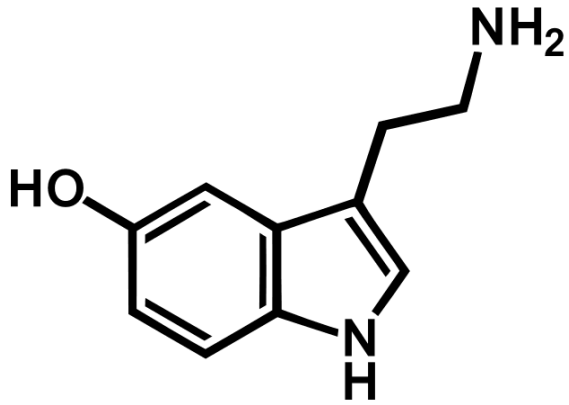
Adenosine 2A Antagonists

- Mechanism of caffeine
- Not effective for "off" time in Parkinson's
  - Istradefylline (Stacy et al. Neurology. 2008 70:2233)
  - Preladenant (Stocchi et al. Neurology. 20017 88:2196)
- Possibly effective: Tozadenant (Hauser et al. Lancet Neurol. 2014 13:767)
  - Reduced "off" time
  - More dyskinesia, nausea, dizziness
  - Currently in add-on trial for levodopa wearing-off

Serotonin Agents

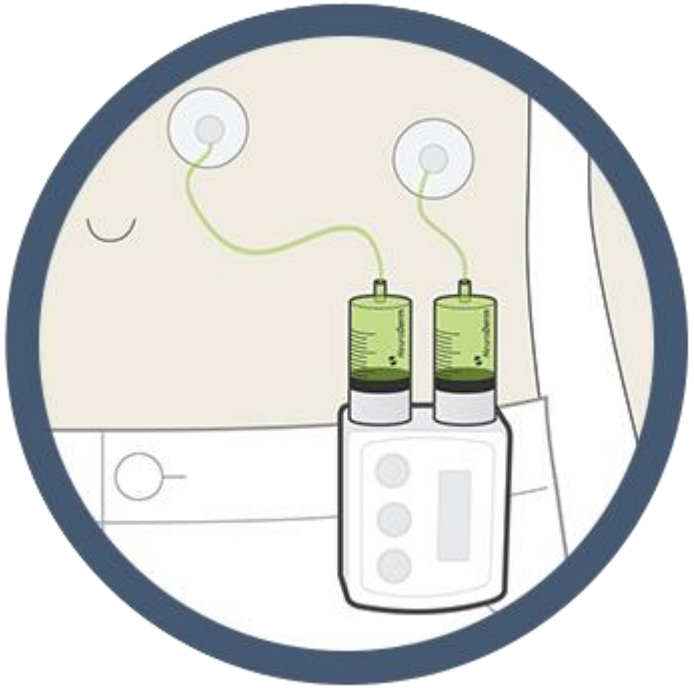
- Sarizotan failed to show benefit in PD

- Eltoprazine: 5-HT1a/b agonist (Paolone et al. Mov Dis. 2015 30:1728)
  - Prevents "experimental" dyskinesia from levodopa
  - Needs Phase III trial for efficacy



Continuous levodopa

- NeuroDerm ND0612H
  - Carbidopa/levodopa in solution
  - Continuous subcutaneous infusion
- Ongoing clinical trials



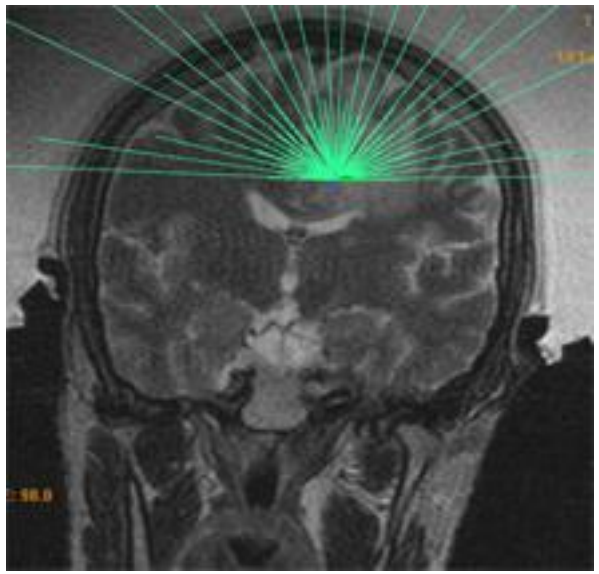
http://neuroderm.com/clinical-trials/ongoing-clinical-trials/

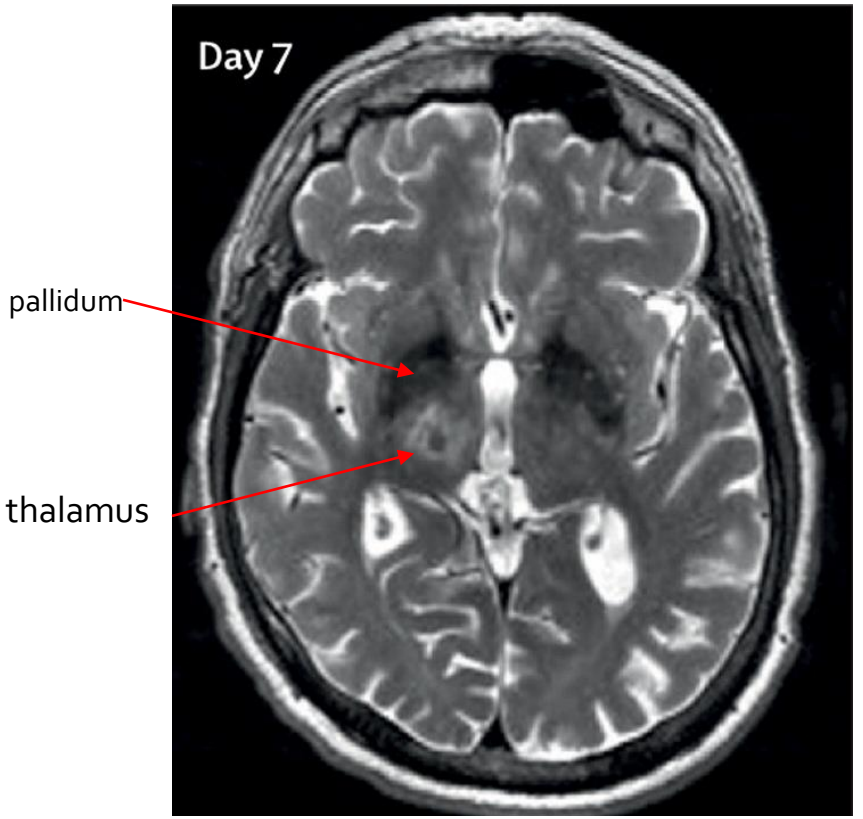
Future Therapies for Symptom Management

- Pharmacologic therapies
- Advances in DBS / surgical lesioning

MRI-guided Focused Ultrasound

- FDA-approved for essential tremor
- NOT approved for PD
  - Pallidotomy -> all PD symptoms
  - Thalamotomy -> mainly tremor

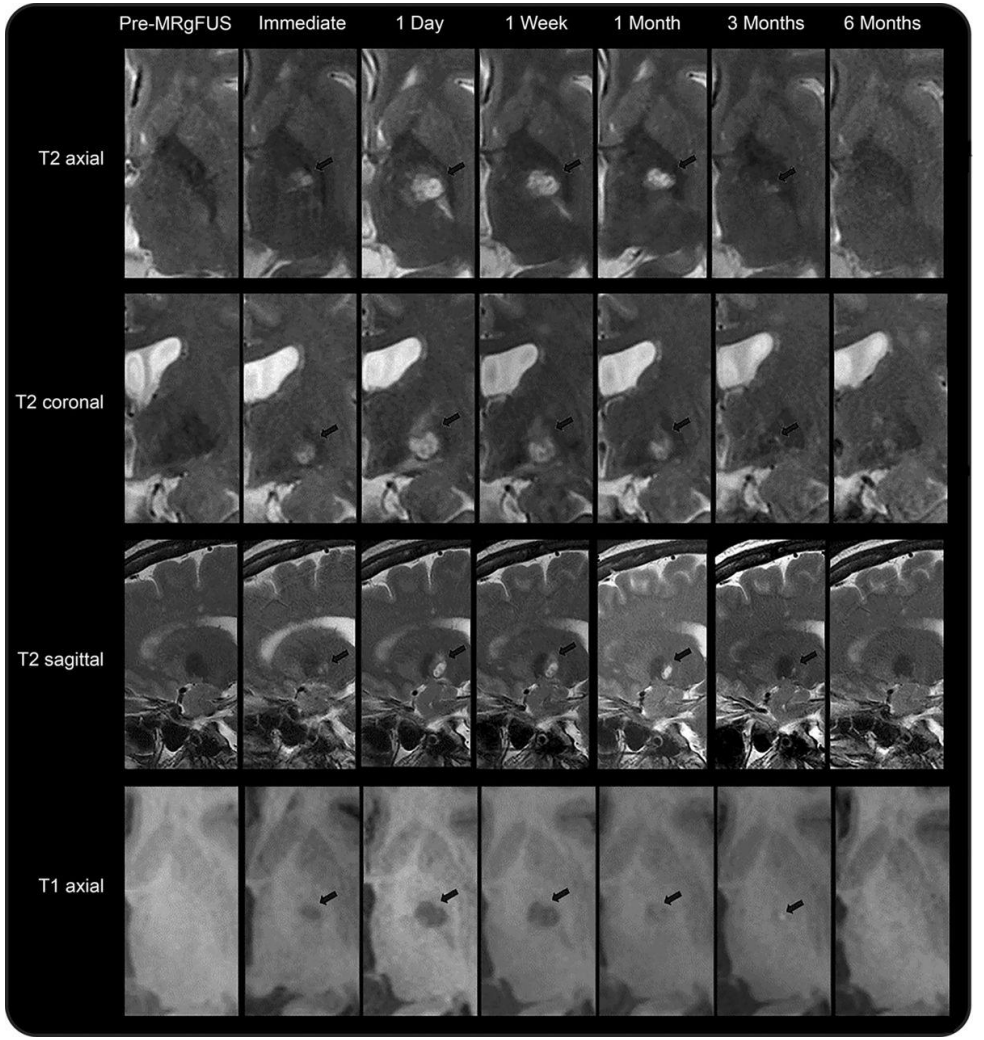




https://www.fusfoundation.org/newsletter-archive/941-fus-newsletter-volume-51

MRgFUS Pallidotomy in PD

- 1 patient
- 320 mm^3 ablated
- Bilateral PD
- UPDRS part III "off"
  - Baseline 31
  - 1 week -> 12
  - 1 month -> 12
  - 3 months -> 13
  - 6 months -> 14
- Current trial at University of Maryland
  - NCT03319485



Young Cheol Na et al. Neurology 2015;85:549-551

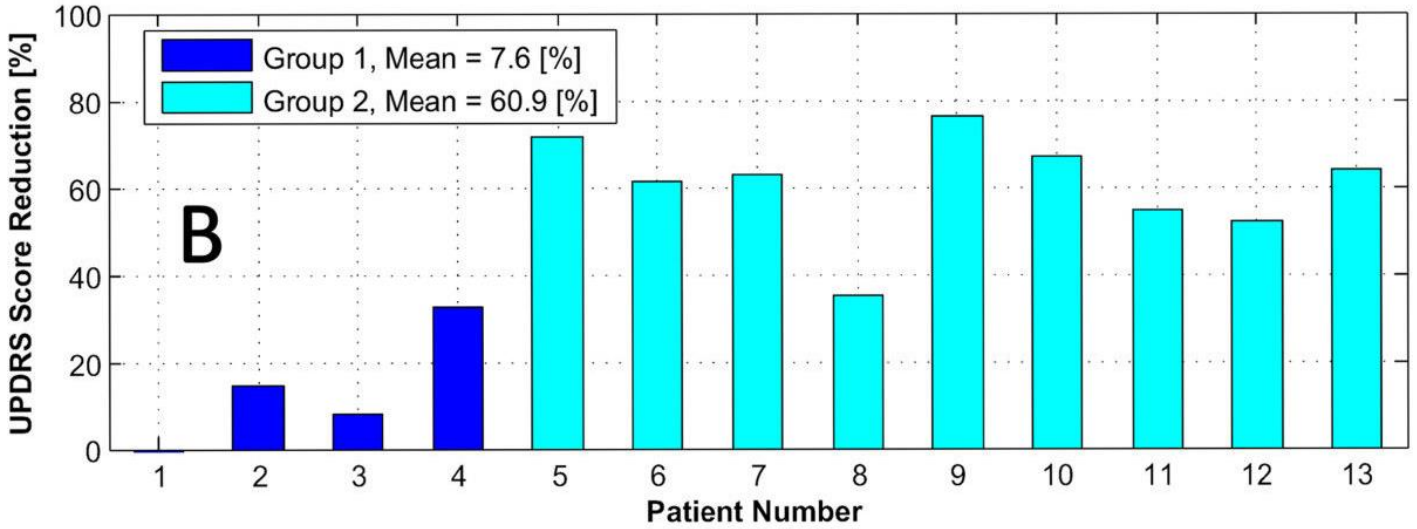
MRgFUS Thalamotomy

- 7 patients: moderate-severe PD tremor
- Tremor "abolished immediately"
- UPDRS reduced 50% 1 week later
- But…
  - Milder tremor reemerged in 3 of 7 patients
  - Detailed follow-up only given for 1 week
  - Short term side effects: headache (3), dizziness (2), vertigo (4)
  - Lasting side effects: reduced taste (1), unsteady feeling (1), gait imbalance (1)

Schlesinger et al. Park Dis. Pub Online 2015

MRgFUS Thalamotomy:

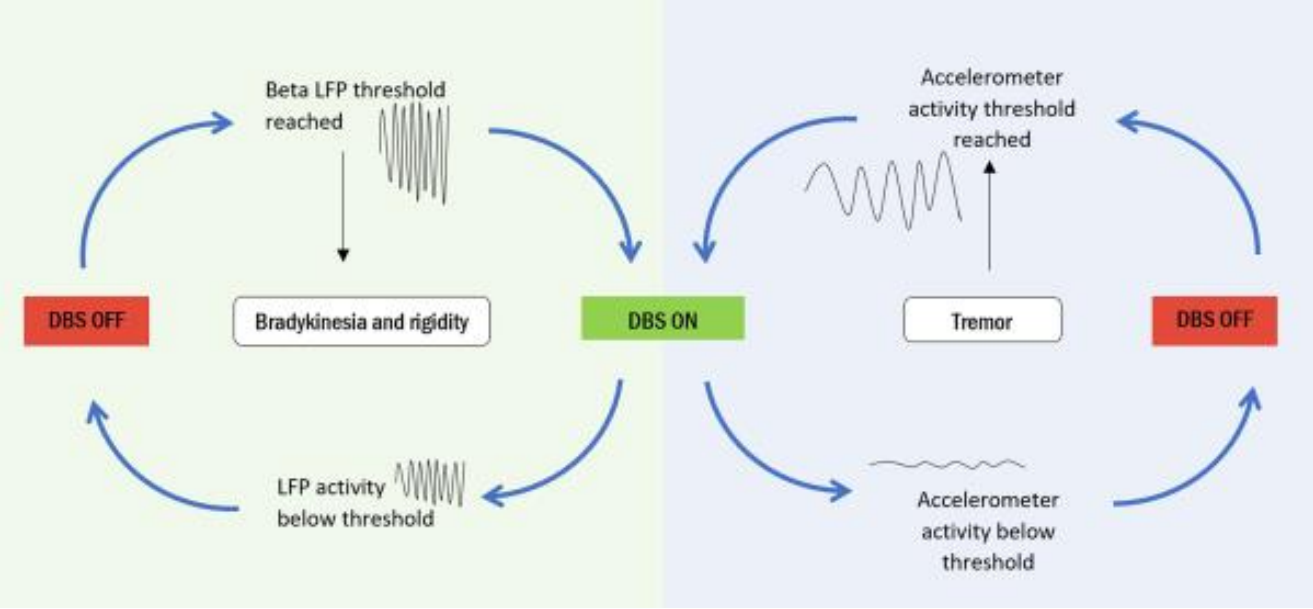
- 8 patients mostly tremor dominant
- Target: pallidothalamic tract
- UPDRS reduced 60.9% at 3 months
- No side effects



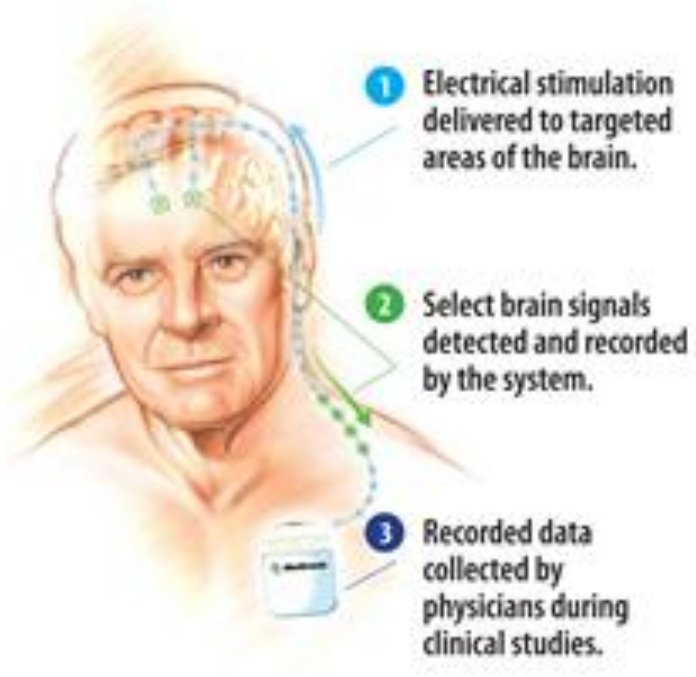
Magara et al. J Therap Ultras. 2014. 2:11

Closed-Loop Deep Brain Stimulation

Stimulation adapts to symptoms (tremor) or brain signals



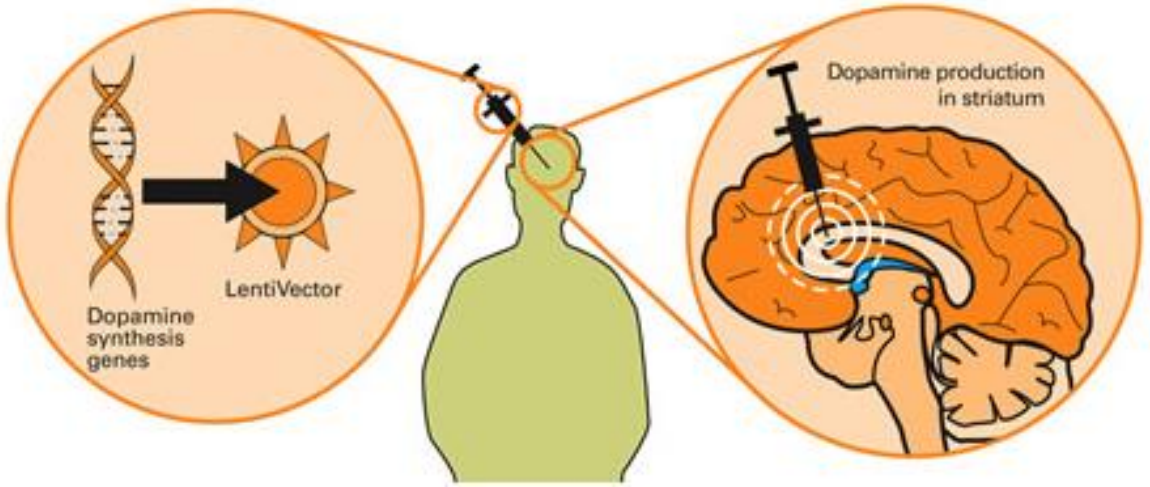
Meidahl et al. Mov Dis. 2017 32:810



https://medtronicmediacap.gcs-web.com/new-medtronic-deep-brain-stimulation-system-first-sense-and-record-brain-activity-while

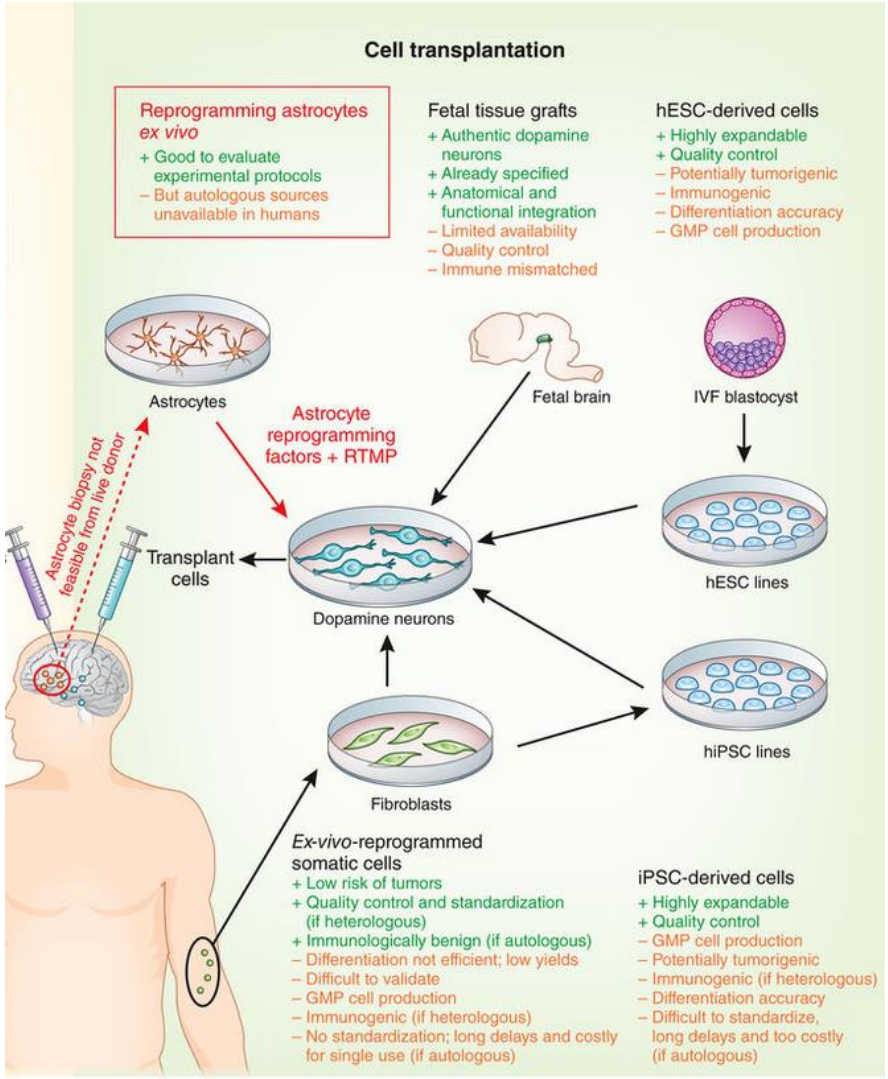
Gene Therapy

- Increasing dopamine production where it's needed
  - **AADC** → phase I promising (Voyager Therapeutics)
  - **AADC/TH/GCH** (Oxford biomedica) → Phase 1/2 trial with moderate improvement (Palfi et al. Lancet. 2014 383:1138)
  - **Glutamic acid decarboxylase**



"Stem Cell" Therapy

- Fetal ventral mesencephalon cells
- Embryonic stem cells
- Induced pluripotent stem cells
- Induced neurons



Dunnett et al. Nature Biotech. 2017. 35:426

"Stem Cell" Therapy

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- Induced pluripotent stem cells
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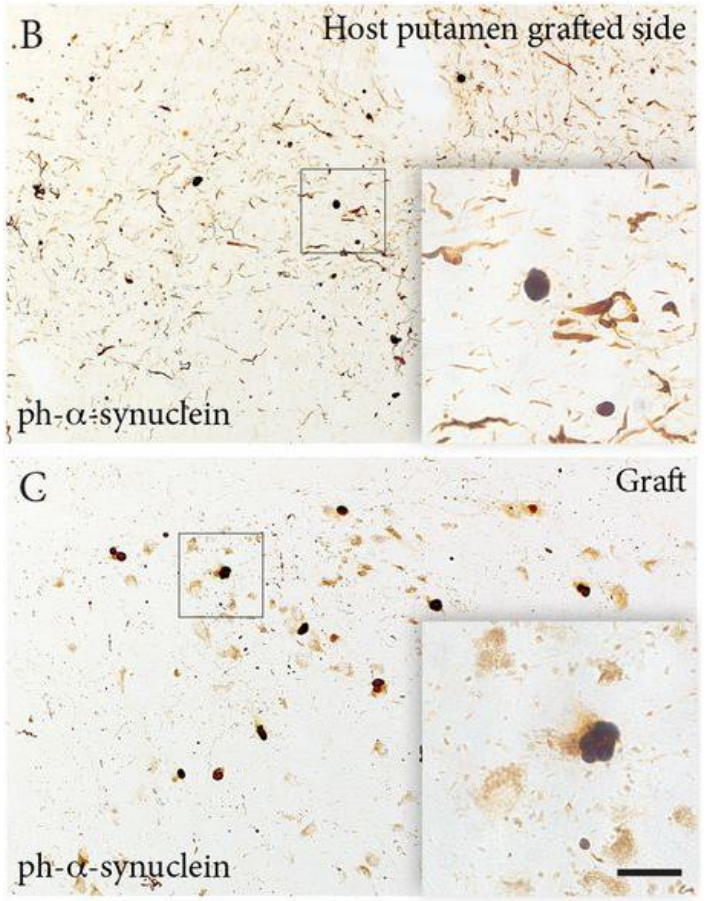
Why only *symptomatic and not a "cure"*?



Lewy bodies in grafted cells!

Li et al. PNAS. 2016 11:6544

"Stem Cell" Therapy

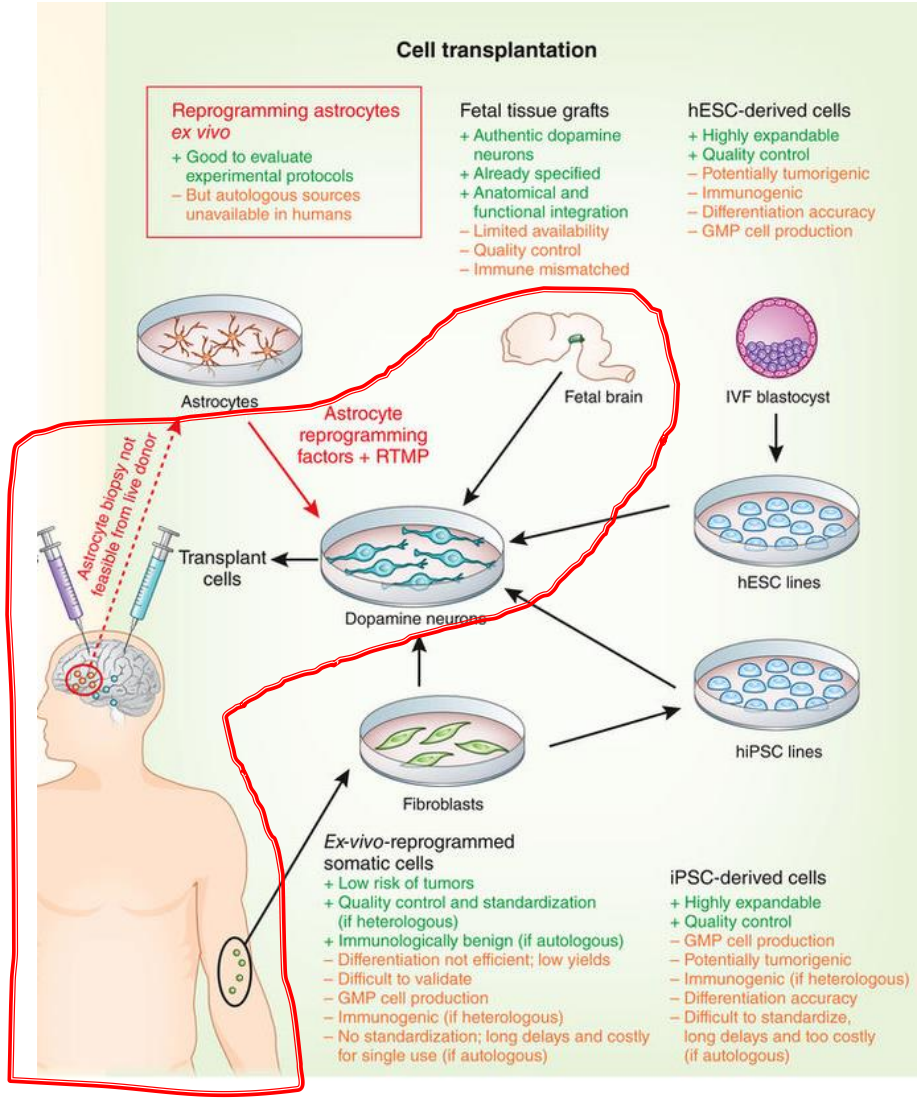
- Fetal ventral mesencephalon cells
- Embryonic stem cells
- Induced pluripotent stem cells
- Induced neurons

From another person and requires immunosuppression

From you but has your same Parkinson disease risk genes

"Stem Cell" Therapy

- Fetal ventral mesencephalon cells
  - 2 randomized trials -> no benefit (Freed et al. NEJM 2001; Olanow et al. Ann Neurol 2003)
  - New trial (TRANSNEURO) publication expected 2020
    - Cambridge, UK: NCT01898390



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Overview

- Future therapies for symptom management
- Future therapies to slow disease progression
- Recent breakthroughs that may lead to therapies

New treatments: two types

- Neuroprotective / disease-modifying
  - Slows underlying progression
  - Patient would NOT notice difference unless he/she had clone
- Symptomatic
  - Reduces symptoms day-to-day
  - Does not slow progression of underlying disease

Parkinson "neuroprotection"

TABLE 3. Summary of all of the previous clinical trials evaluating putative neuroprotective therapy for PD

		Study design				
Drug	Mechanism of action	Parallel arms (PA) versus delayed start (DS) versus futility study (FS)	Placebo (P) versus active arms only (A)	Washout period	Primary outcome(s)	Result
Selegiline	MAO-B inhibition; anti-apoptotic (GAPDH inhibition); antioxidant; other	PA	P	+ (Syndepar 2 months)[21]	Need for symptomatic treatment; change in UPDRS[9]	Positive[8,9,21]
Rasagiline	Ibid	DS	P	–	Change in UPDRS	Positive[26]
THC-346	Anti-apoptotic: GAPDH inhibition; no MAO-B inhibition effects	PA	P	–	Need for symptomatic treatment	Negative[10]
Pramipexole	Dopamine agonist, antiapoptotic	DS	P	–	Change in UPDRS	Negative[28]
Pramipexole	Dopamine agonist, antiapoptotic	PA	A	–	Surrogate imaging marker	Less change in striatal β-CIT with pramipexole versus levodopa[31]
Ropinirole	Dopamine agonist, antiapoptotic	PA	A	–	Surrogate imaging marker	Less change in striatal F-dops with ropinirdie versus levodopa[30]
Levodopa	Dopamine precursor; ? trophic	PA	P	+ (2 weeks; smaller subgroup had 4 weeks)	Change in UPDRS; surrogate imaging in subgroup	Positive for UPDRS; greater change in striatal β-CIT with levodopa versus placebo[22]
Tocopherol	Antioxidant	PA	P	–	Need for symptomatic treatment	Negative[8]

Lang et al., Mov Dis, 2013

Parkinson's "neuroprotection"

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CoQ10	Bioenergetic; antioxidant	PA	P	–	Change in UPDRS	Positive[43]
		FS	P	–	Change in UPDRS	Nonfutile[34]
		PA	P	–	Change in UPDRS	Negative: early termination - futile
Mitoquinone	Bioenergetic; antioxidant	PA	P	–	Change in UPDRS	Negative[44]
Creatine	Bioenergetic	FS	P	–	Change in UPDRS	Nonfutile[36]
CEP-1347	Antiapoptotic: mixed lineage kinase inhibitor	PA	P	–	Need for symptomatic treatment	Negative: early termination - futile[32]
Immunophilin	Antiapoptotic; ? trophic	FS	P	–	Change in UPDRS	Nonfutile[34]
		PA	P	–	Change in UPDRS	Negative[46]
GDNF	Trophic	PA	P	–	Change in UPDRS	Negative[47]
Pallroden	Trophic	PA	P	–	Surrogate imaging marker	Negative[48]
GM1 ganglioside	Stimulates recovery of damaged DA neurons	PA short term (16 weeks); open-label 5 y	NA	–	Change in UPDRS	Practically defined OFF scores at 5 y same or better than at baseline[49]
Riluzole	Glutamate antagonist	PA	P	–	Need for symptomatic treatment	Negative[45]
Minocycline	Anti-inflammatory	FS	P	–	Change in UPDRS	Nonfutile[35]

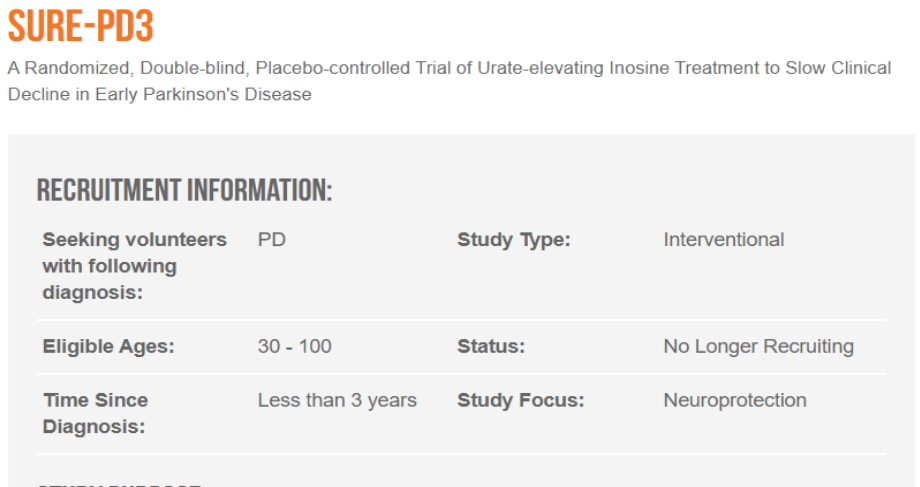
Lang et al., Mov Dis, 2013

Parkinson neuroprotection: Current Trials

- Isradipine – year 2.5 of 3 year phase III trial
- Elevating Urate – year 1.5 of 3 year phase III trial
- Nilotinib – Phase II trials enrolling
- Anti- α-synuclein therapies – Phase I-II trials
- GLP1-antagonists

Parkinson's "neuroprotection": SURE-PD

- Background: Human studies showed people with higher uric acid (usually "waste" excreted by kidneys) had lower incidence of Parkinson's disease
- **Inositol** can be used to increase uric acid in blood
- Goal of Study: does artificially increasing uric acid slow or prevent PD progression?
- Estimated end: 2020



SURE-PD3

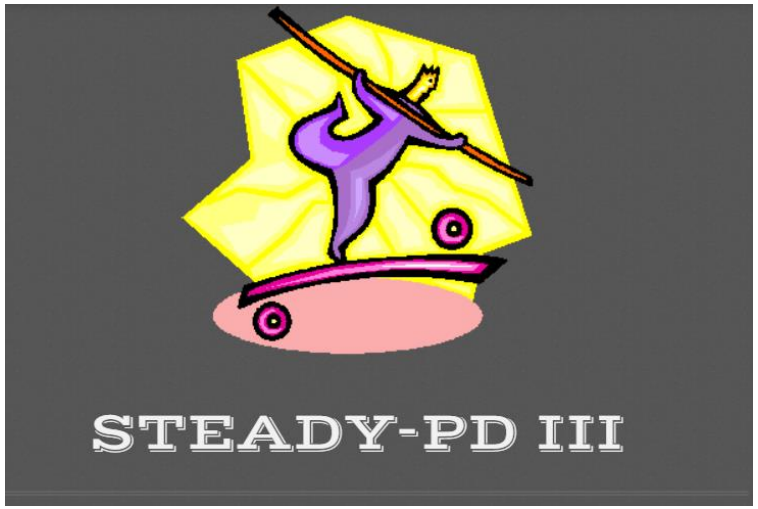
A Randomized, Double-blind, Placebo-controlled Trial of Urate-elevating Inosine Treatment to Slow Clinical Decline in Early Parkinson's Disease

RECRUITMENT INFORMATION:

Seeking volunteers with following diagnosis:	PD	**Study Type:**	Interventional
Eligible Ages:	30 - 100	**Status:**	No Longer Recruiting
Time Since Diagnosis:	Less than 3 years	**Study Focus:**	Neuroprotection

Parkinson's "neuroprotection": STEADY-PD III

- Background
  - It was found that people taking a certain type of blood pressure medication (Dihydropyridine calcium channel blockers) had a low incidence of developing Parkinson's disease
  - This medication slowed progression of Parkinson's brain pathology in animals with experimental Parkinson's disease
- Goal of Study: does taking **isradipine** slow or prevent progression of Parkinson's disease
- Estimated end: 2018 – early 2019
- Results 2019



Parkinson's "neuroprotection": Nilotinib

Cancer Drug That Mi
Alzheimer's Headed

March 15, 2017 · 12:29 PM ET
Heard on All Things Considered

JON HAMILTON

Cance
Dopamin
Parkinson's Symp
Early Study in Patients

JULY 18, 2016 BY MAGDALENA KEGEL IN NEWS.

STUDY: CANCER DRUG RESTORES BRAIN DOPAMINE, REDUCES TOXIC PROTEINS IN PARKINSON, DEMENTIA

Parkinson's "neuroprotection": Nilotinib

- In the lab
  - c-Abl protein acts to promote neurodegeneration in mouse model (Ko et al. PNAS 2010 107:16691)
  - c-Abl protein inhibitor, nilotinib (cancer therapy), protects dopamine-producing neurons in animal model (Karuppagounder et al. Sci Rep. 2014 4:4874)
  - Confirmed by another group: (Imam et al. PLoS One. 2013 8:e65129)
- In Humans
  - Nilotinib slowed progression in 12 persons with Parkinson disease or dementia with Lewy bodies (Pagan et al. J Park Dis. 2016 6:503)
    - Motor symptoms *improved* 3.6 points after 6 months on 300 mg nilotinib

Parkinson's "neuroprotection": Nilotinib

- Current studies:
- PD Nilotinib: Single-center phase II
  - Estimated completion date: 5/2020
  - https://clinicaltrials.gov/show/NCT02954978

ClinicalTrials.gov

- NILO-PD: Multi-center phase II
  - Cohort 1: 5 years or more (enrolling now)
  - Cohort 2: Under 3 years (enrolling in future)
  - Estimated completion date: 10/2020
  - https://clinicaltrials.gov/ct2/show/NCT03205488
  - www.michaeljfox.org

Parkinson's "neuroprotection": Exenatide

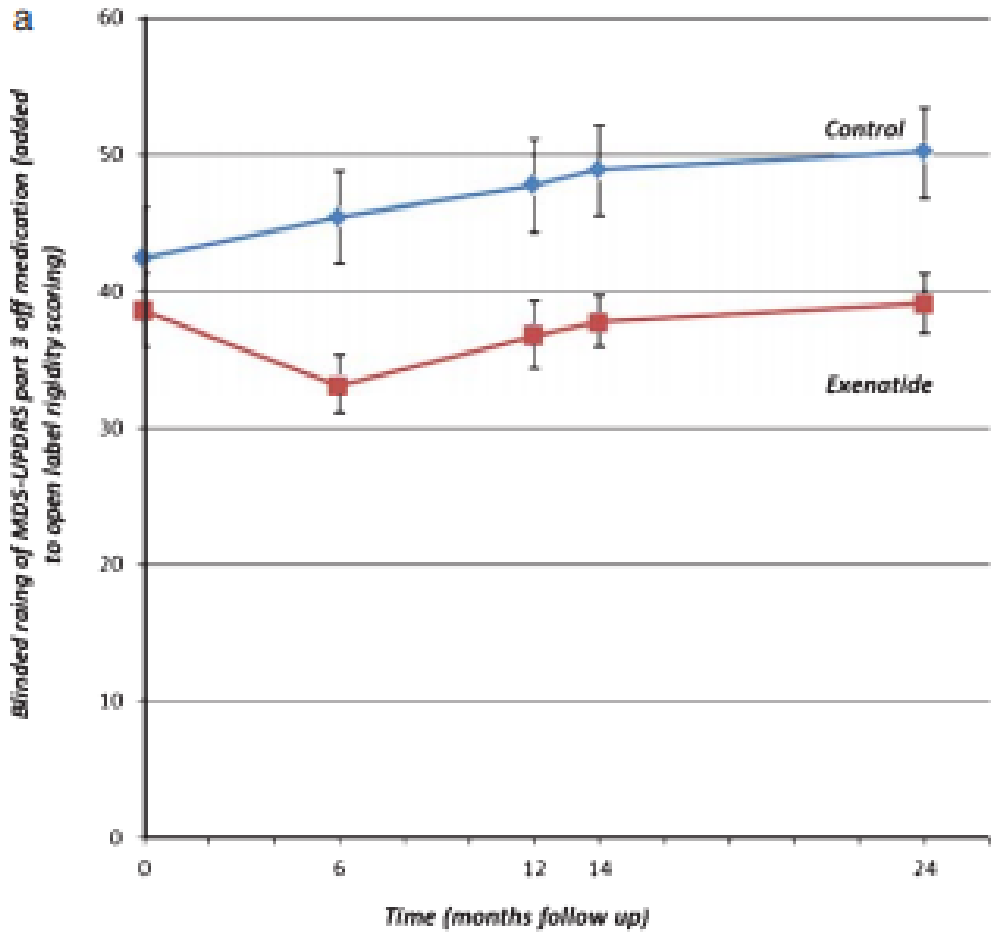
Lizard venom offers hope for Parkinson's disease patients

26 August 2010

Diabetes drug (Exenatide) found in lizard venom

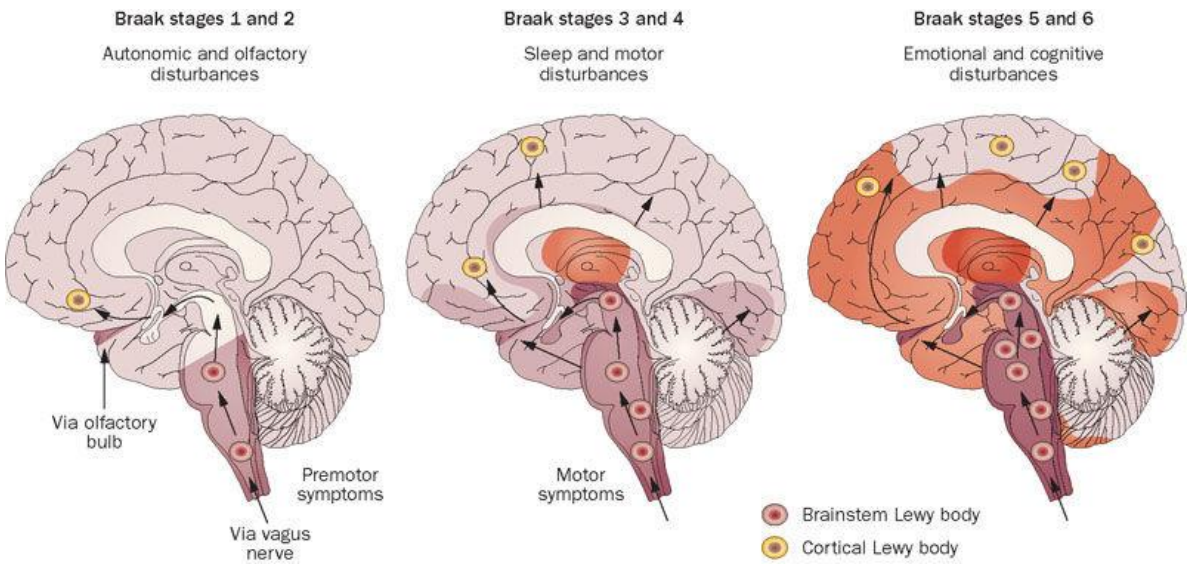
Parkinson's "neuroprotection": Exenatide

- Possible slowing of PD progression in early study (Aviles-Olmos et al. J Clin Invest 2013 123:2730)
- Slowed PD disease progression in phase II study (Athauda et al. Lancet. 2017 390:1664)
  - Increased dyskinesia -> levodopa reduced
  - Weight loss
- Promising because it is already on the market for diabetes
- Other GLP-1 inhibitors being tested



Parkinson's "neuroprotection": α -synuclein antibodies

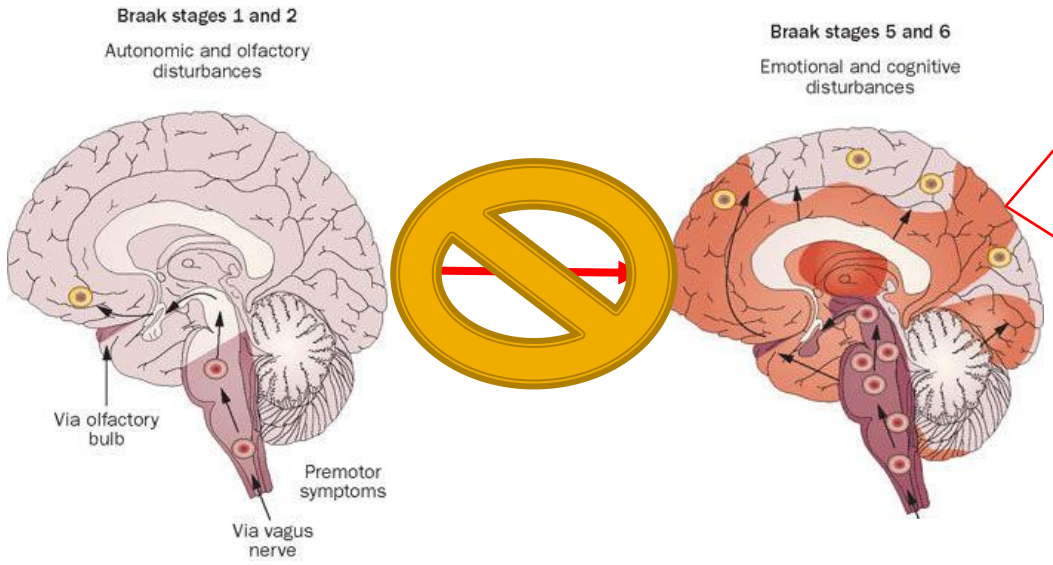
- Background
  - α-synuclein misfolds and clumps then accumulates in brain cells
  - Causes brain cells (neurons) to malfunction or die
  - Protein spreads from one cell to another, affecting more of the brain with time

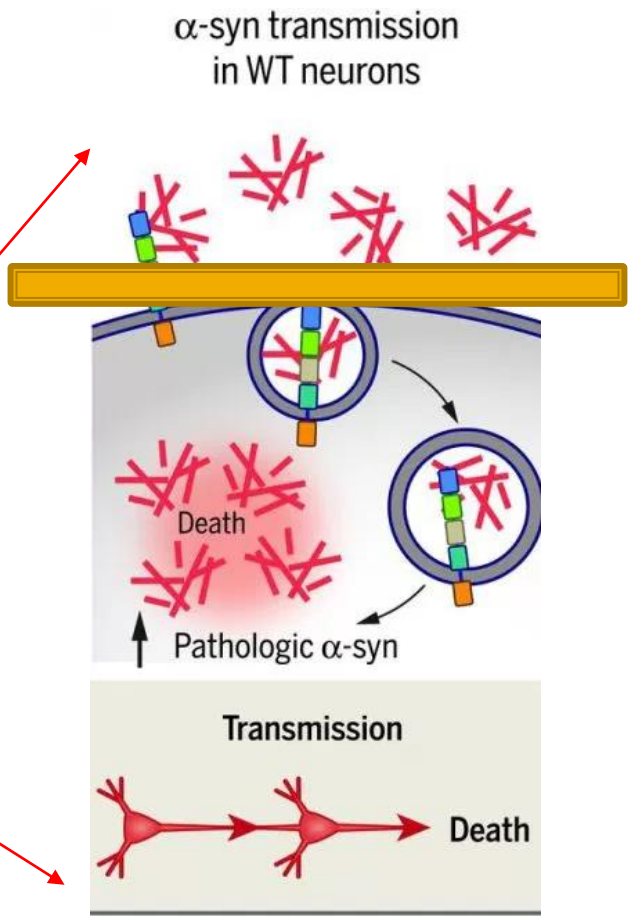


Doty. Nat Rev Neurol. 2012 8:329

Parkinson's "neuroprotection": α - synuclein antibodies

- Background
  - α-synuclein spreads from cell-to-cell
  - Stopping spread and clumping may slow or stop progression of PD





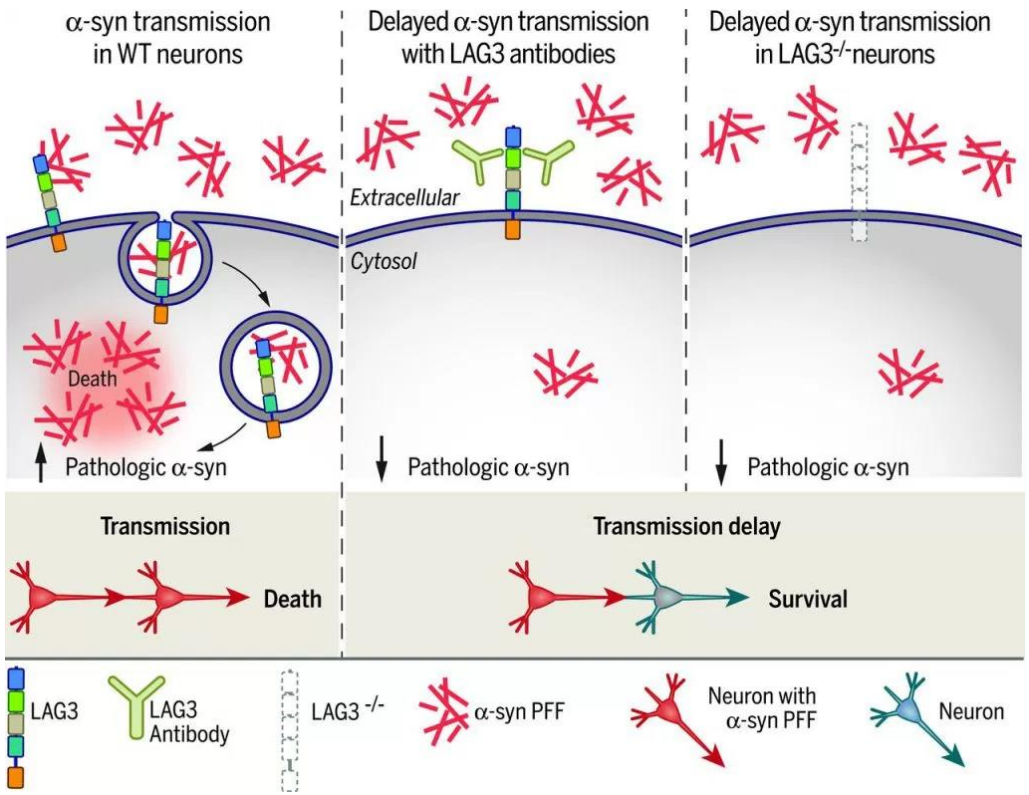
Mao et al. Science. 2016 353:1607

Parkinson's "neuroprotection": alpha-synuclein antibodies

- Current anti-alpha-synuclein trials
  - Prothena / Roche – antibody against α-synuclein (United States)
  - Biogen – antibody against α -synuclein (United States)
  - AFFiRiS – vaccinating against α -synuclein (like flu vaccine)
  - Neuropore / UCB – compound reducing clumping of α -synuclein

Parkinson's "neuroprotection": alpha-synuclein transmission

- Breakthrough!!
  - LAG3 identified as protein that allowed alpha-synuclein entry into cells

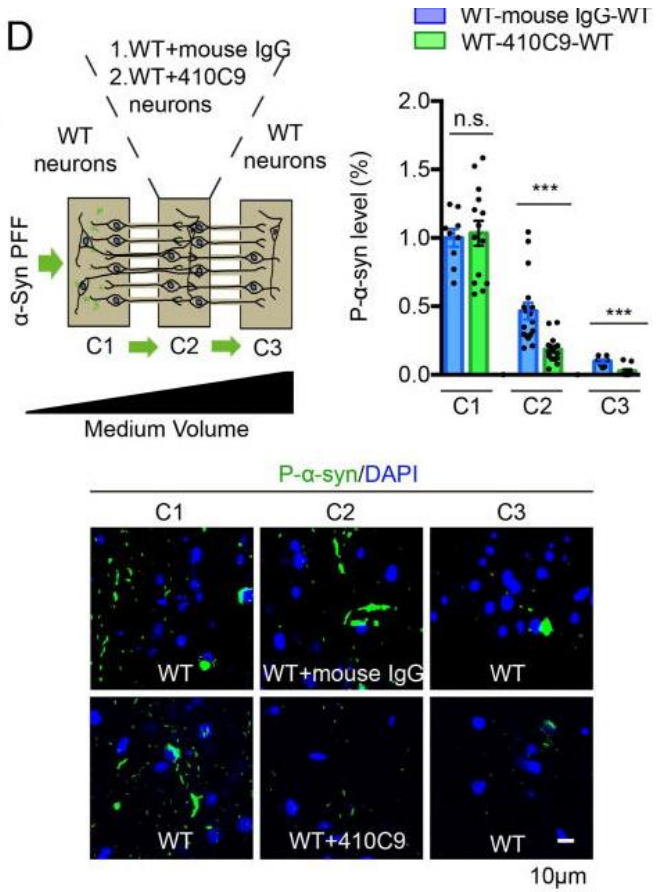


Mao et al. Science. 2016 353:1607

Lab of Drs. Ted and Valina Dawson at Johns Hopkins

Parkinson's "neuroprotection": alpha-synuclein transmission

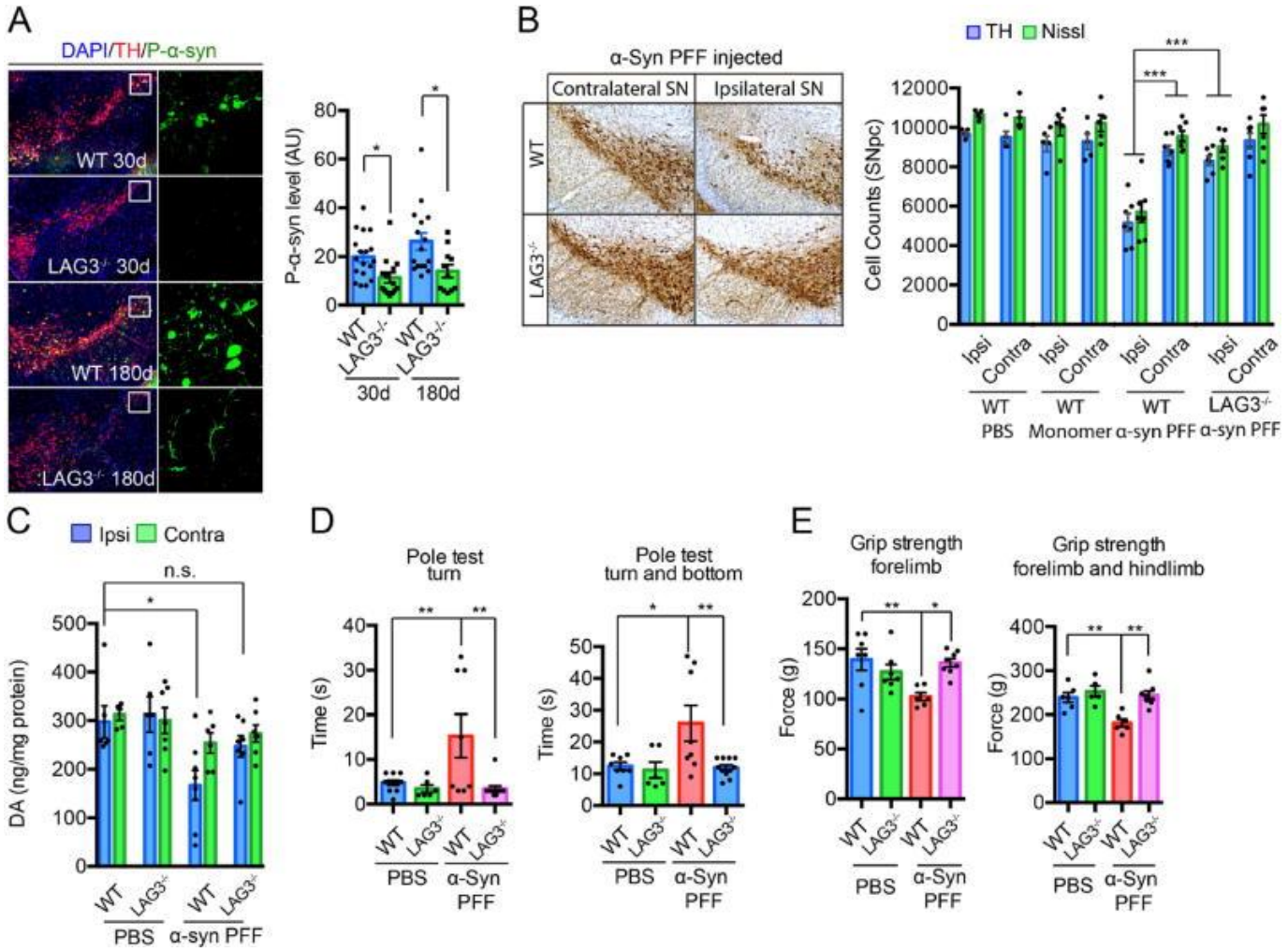
- Antibodies against LAG3 dramatically reduce transmission of alpha-synuclein protein in mice



Mao et al. Science. 2016 353:1607

Parkinson's "neuroprotection": alpha-synuclein transmission

- Removing LAG3:
  - Slows death of dopamine neurons in mouse PD
  - Preserves dopamine levels
  - Avoids symptoms of mouse PD



Mao et al. Science. 2016 353:1607

A more toxic form of α-synuclein

PNAS

Identification of a highly neurotoxic α-synuclein species inducing mitochondrial damage and mitophagy in Parkinson's disease

Diego Grassi[a,b], Shannon Howard[c], Minghai Zhou[a,b], Natalia Diaz-Perez[d], Nicolai T. Urban[e], Debbie Guerrero-Given[f], Naomi Kamasawa[f], Laura A. Volpicelli-Daley[g], Philip LoGrasso[c], and Corinne Ida Lasmézas[a,b,1]

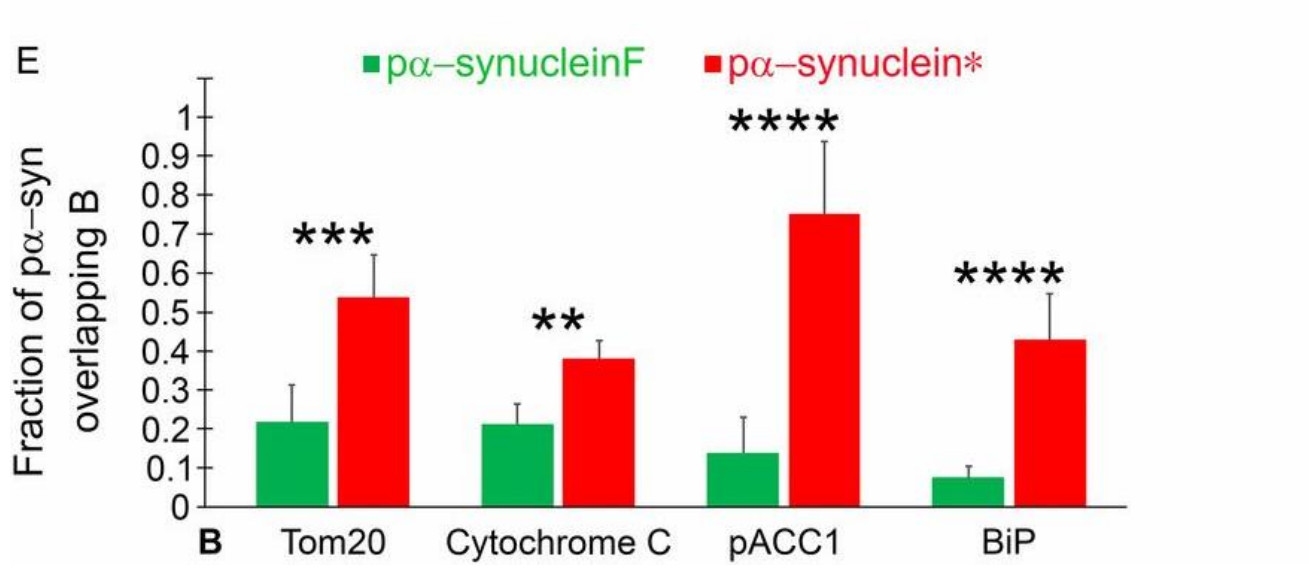
[a]Department of Immunology and Microbiology, Scripps Florida, The Scripps Research Institute, Jupiter, FL 33458; [b]Department of Neuroscience, Scripps Florida, The Scripps Research Institute, Jupiter, FL 33458; [c]Department of Molecular Medicine Scripps Florida, The Scripps Research Institute, Jupiter, FL 33458; [d]Private address, Palm Beach Gardens, FL 33418; [e]Light Microscopy Facility, Max Planck Florida Institute for Neuroscience, Jupiter, FL 33458; [f]Electron Microscopy Facility, Max Planck Florida Institute for Neuroscience, Jupiter, FL 33458; and [g]Center for Neurodegeneration and Experimental Therapeutics, University of Alabama at Birmingham, Birmingham, AL 35294

- Breakthrough!! -> more toxic form of α-synuclein
- Cells try to break-down the accumulating α-syn
- By product α-**s**ynuclein **t**runcated **a**damant and **r**eactive (pα-syn*) is formed

Grassi et al. PNAS. Published online Feb 2018

A more toxic form of α-synuclein

- pα-syn* is directly toxic to mitochondria



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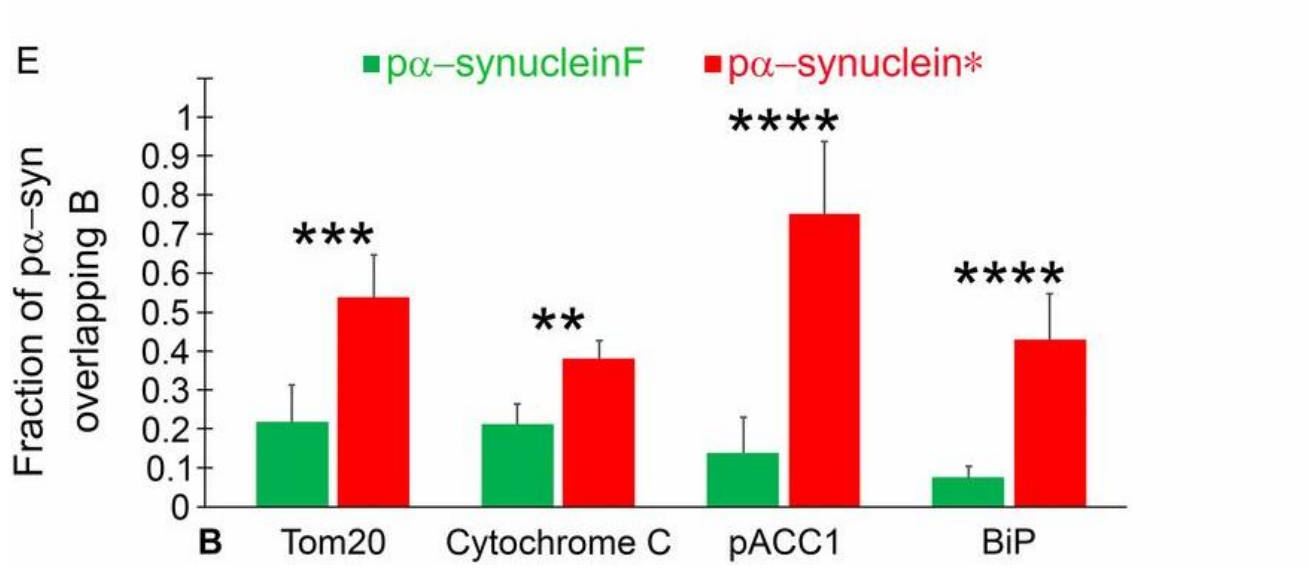
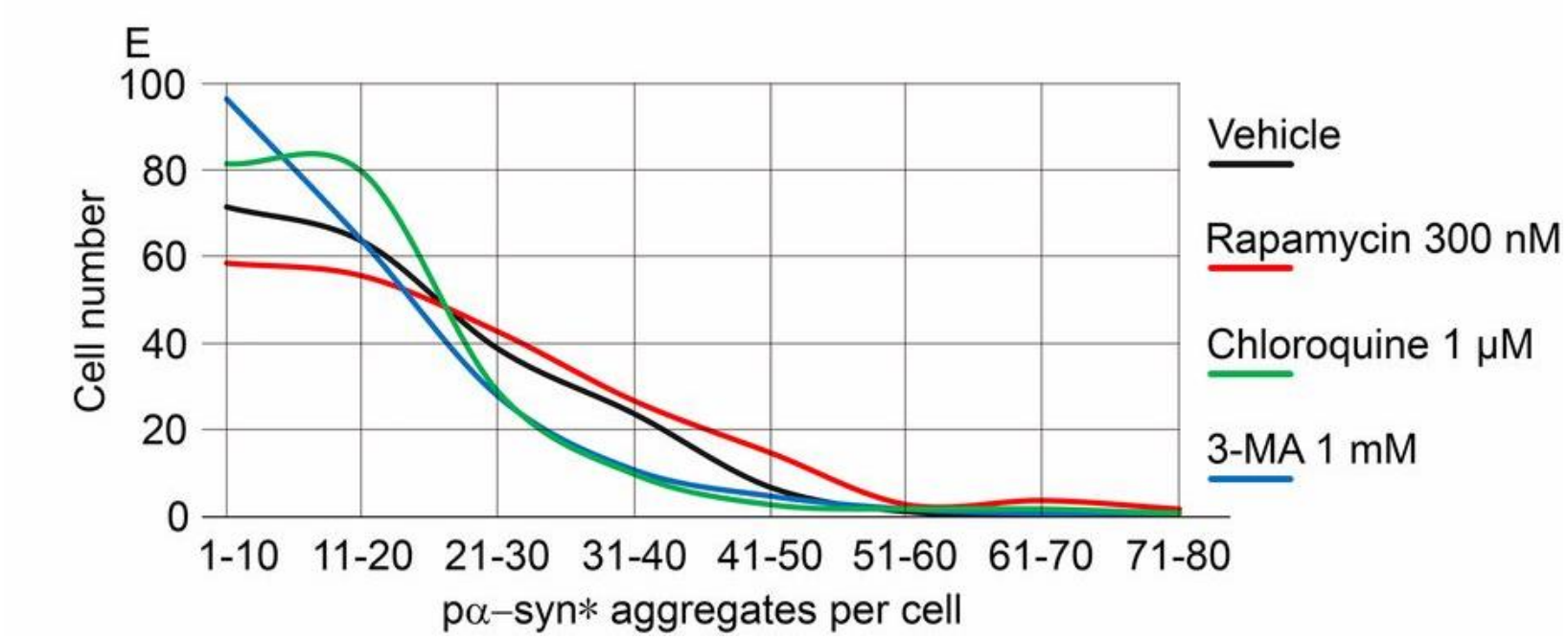


Grassi et al. PNAS. Published online Feb 2018

A more toxic form of α-synuclein

- Stopping breakdown of fibrillary pα-synF, reduces accumulation of pα-syn* (most toxic form)

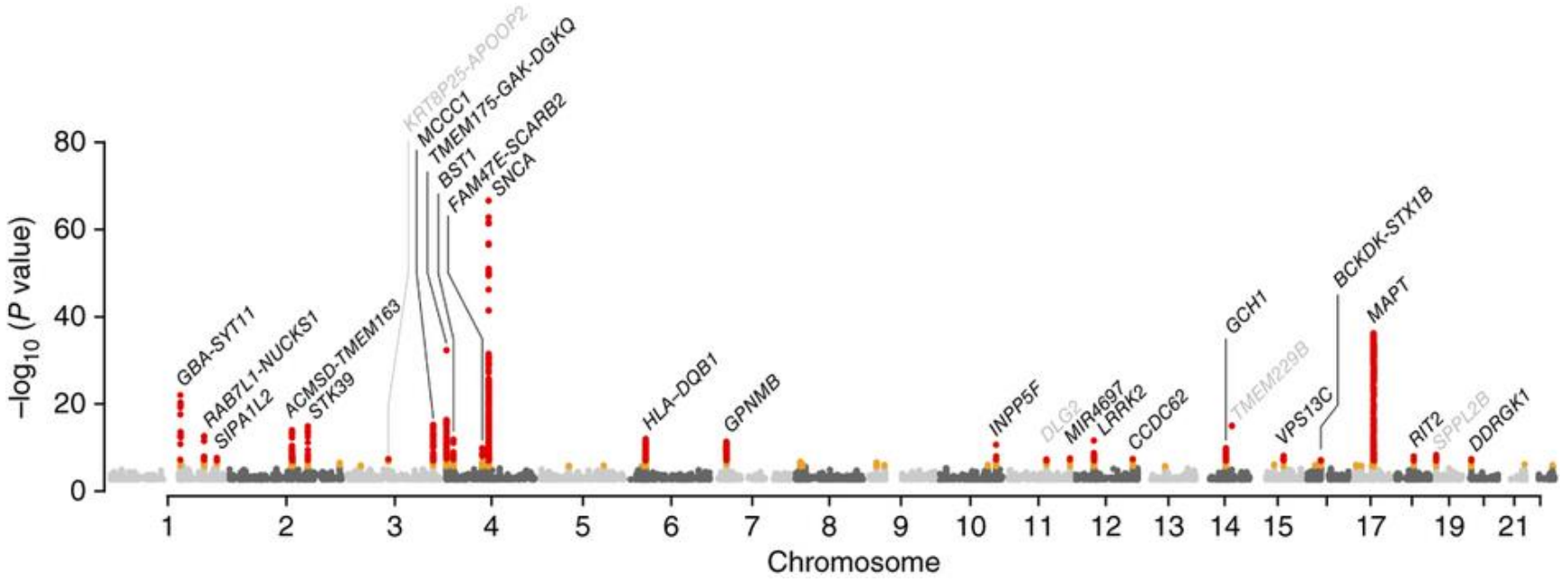


Grassi et al. PNAS. Published online Feb 2018

Approach to finding new treatments

- Define genes involved
- Explore biology of why gene mutations causes cell death
- Develop drugs to correct these deficits

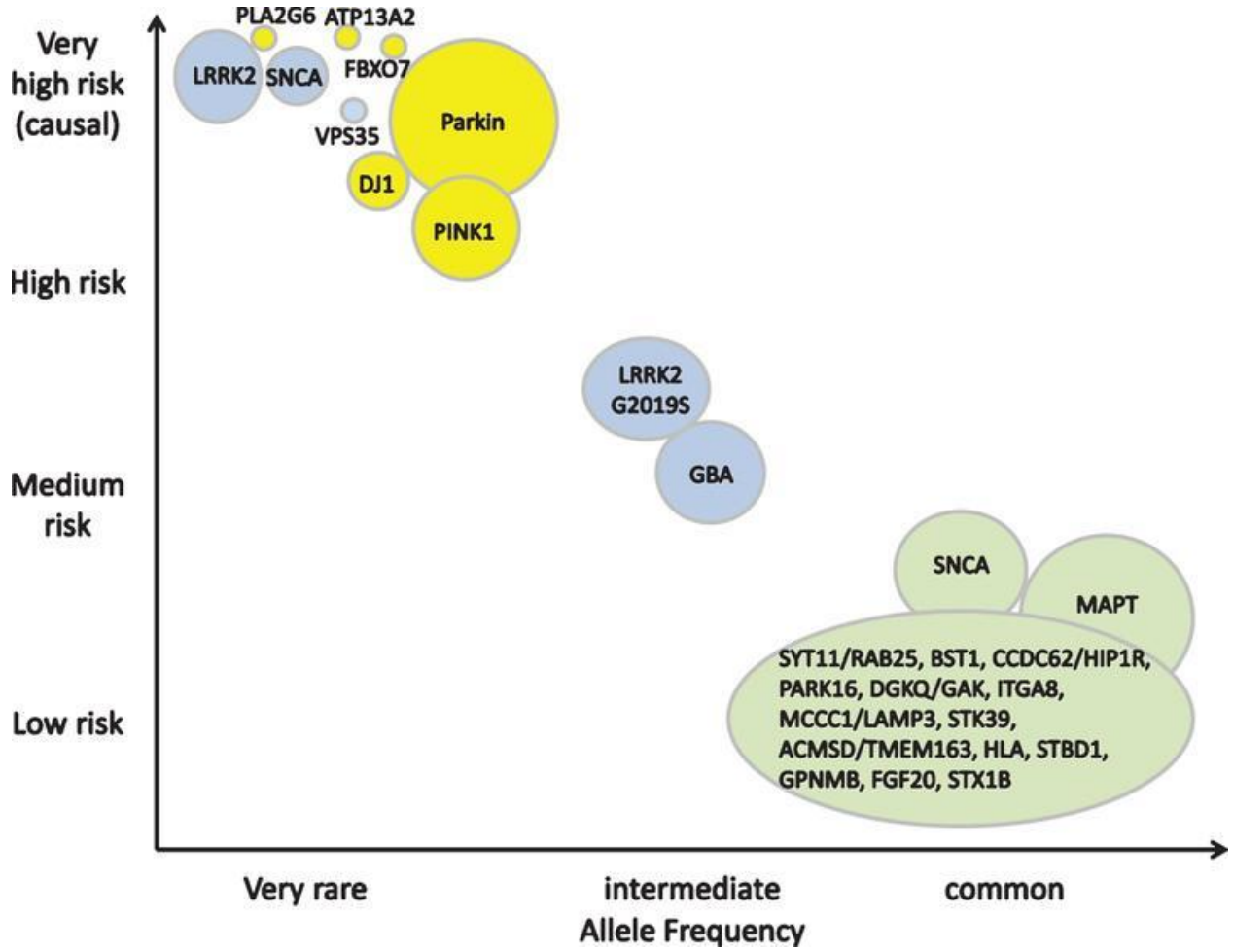
Genetics of Parkinson's disease



- Genomes of 13,700 PD patients and 95,282 controls compared
- 26 genes found to influence PD risk
- Risk is cumulative with the more genes you have

Nalls et al. Nat Genet. 2014 Sep;46(9):989-93

Genetics of Parkinson's disease



Journal of Parkinson's Disease

Questions?

- Need advice?
- PFNCA (parkinsonfoundation.org/)
- National Parkinson Foundation (NPF.org)
- Michael J. Fox Foundation (MJFF.org)
- Call **410-502-0133** ask for **Gigi**
  - Advice on referrals
  - Direct you to a local support group
  - Other questions

Thanks

PARKINSON FOUNDATION OF THE NATIONAL CAPITAL AREA

Parkinson's Foundation CENTER OF EXCELLENCE

NIH National Institute of Neurological Disorders and Stroke

Morris K. Udall Centers of Excellence for Parkinson's Disease Research

The Johns Hopkins Parkinson's Disease and Movement Disorders Center Team!

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