Gene Therapy for Parkinson's Disease

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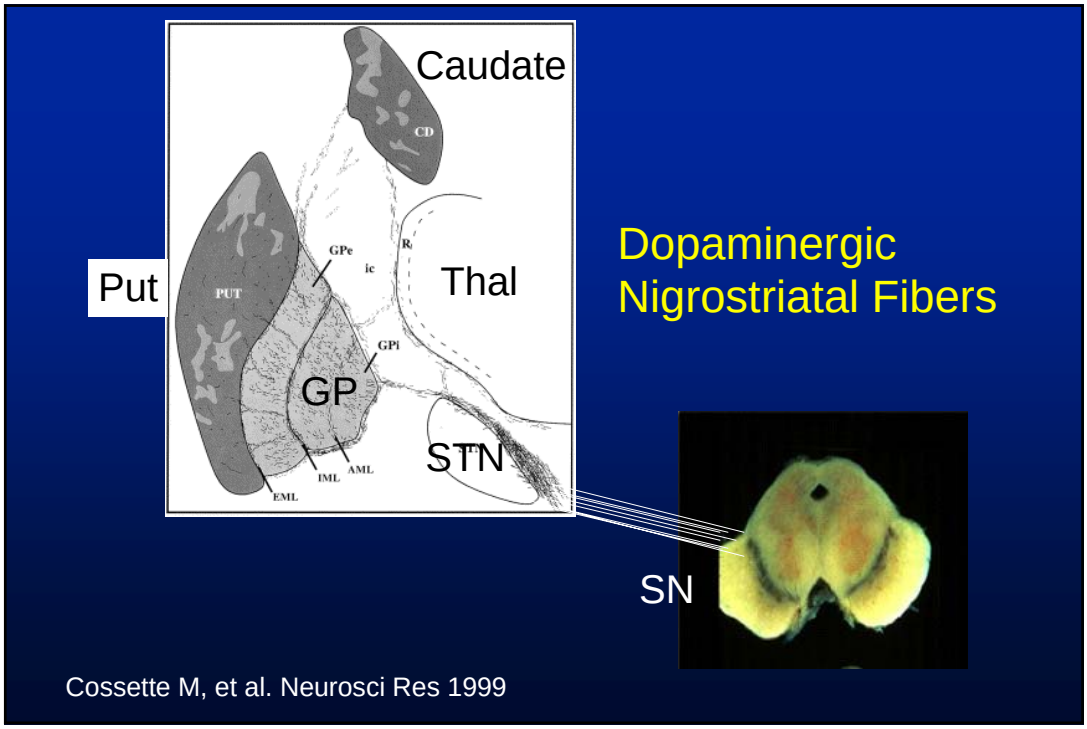
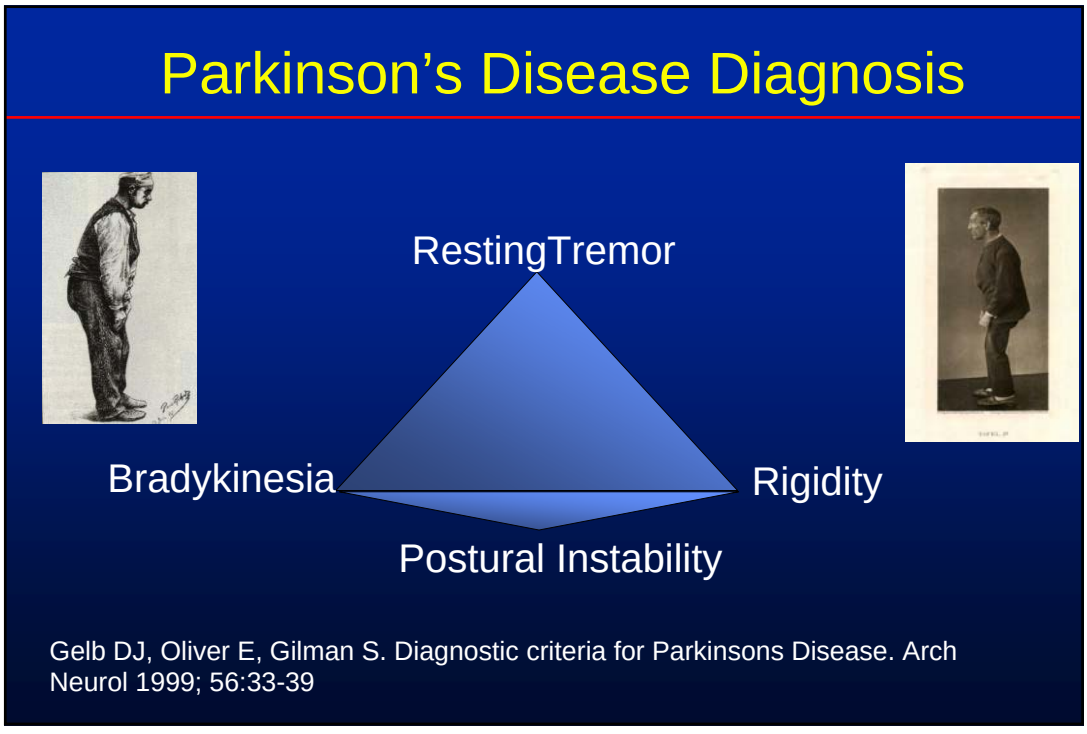
Objectives

- Discuss the outcomes of gene therapy clinical trials in Parkinson's disease.
- Define areas where future research is expected.





Why Gene Therapy for PD?

- Current Therapies are Symptomatic
- Amantadine / Anticholinergics
- MAO-B inhibitors
- Levodopa / Dopamine receptor agonist
- COMT inhibitors
- Deep brain stimulation
- Improve QOL, employment, motor symptoms
- Not effective for non-motor symptoms
- Not effective for balance & gait problems

Levodopa-induced Dyskinesia

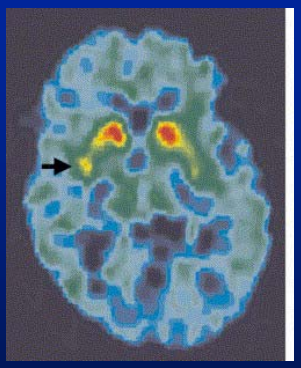
57 y/o man, PD x 11 yrs
"On" meds with dyskinesias

Limitations of Current Therapies

- Disease modifying?
- Non-physiologic
- Gold standard: Levodopa & motor complications
- Side effects: cognitive, behavioral
- Complex regimens
- Ineffective for non-motor symptoms, falling, freezing, gait
- DBS requires hardware maintenance and longitudinal programming

Dopaminergic Fetal Cell Transplantation: Disappointing

- Series of small, open-label trials
- 2 NIH-supported, double-blind, sham surgery controlled trials = negative results
- "Runaway" off-state dyskinesias
- Lewy pathology in transplants
- Issues: Pt selection, # of donor embryos, graft site, cell tissue preparation and source, immunosupression



Olanow CW et al. Ann Neurol 2003;54:403-14.
Freed CR et al. N Engl J Med 2001;344:710–719.
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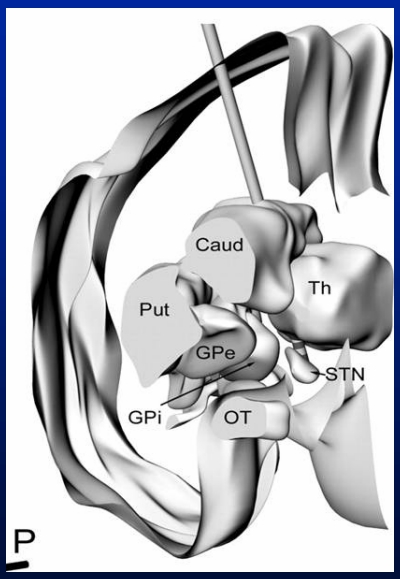
Basal Ganglia Anatomy

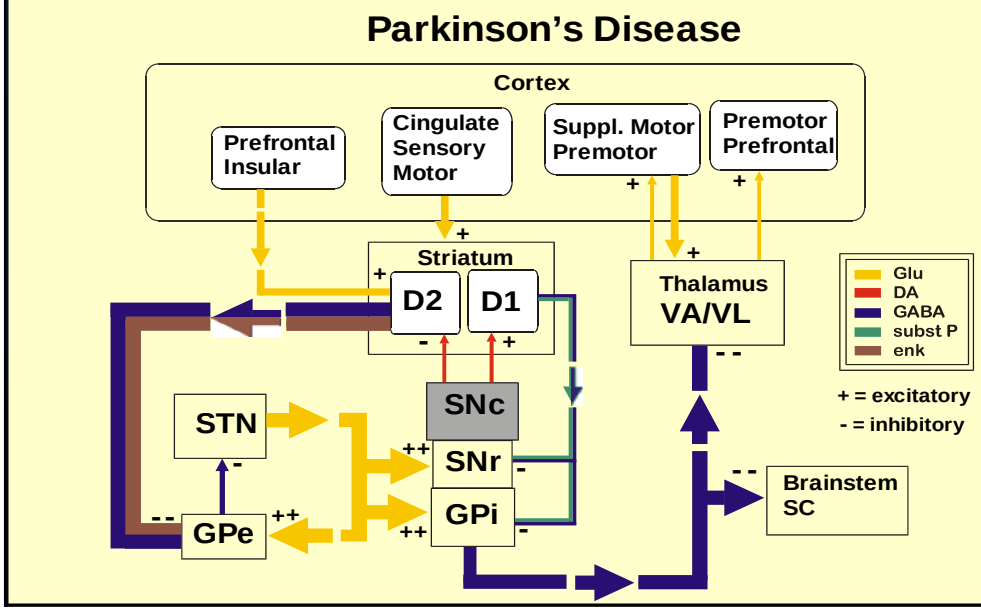


Miocinovic, S. et al. J Neurophysiol 2006;96:1569-1580.

Gene Therapy: Clinically-studied Approaches

- Restore basal ganglia activity
  - STN GAD
- Enhance synaptic dopamine
  - AADC
- Neurorestorative
  - GDNF analog: neuturin

Basal Ganglia in PD: Abnormal Functional Anatomy



Gene Therapy: Restoring Basal Ganglia Activity

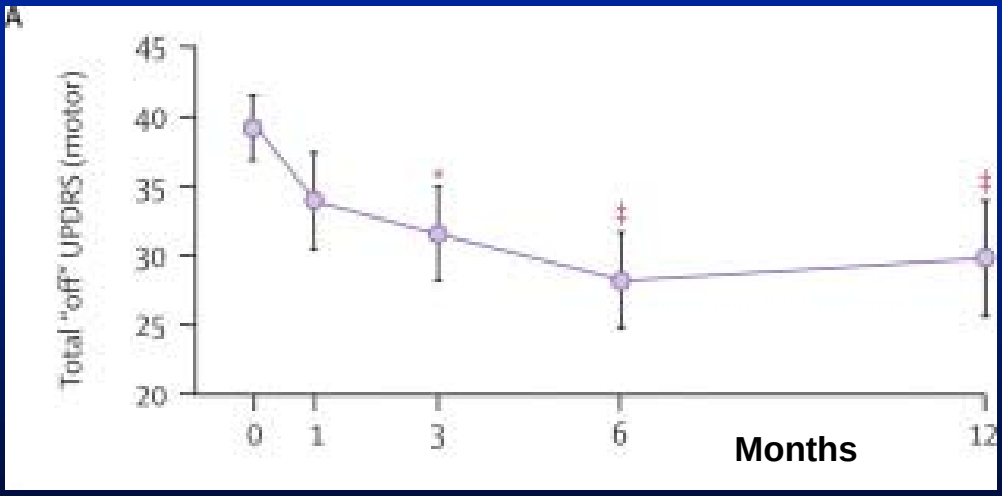
- Target: Subthalamic nucleus [STN]
- Glutamic acid decarboxylase [GAD] produces GABA
- Analogous to STN DBS but:
  - more physiologic?
  - no hardware
  - no programming
  - no hardware / electrical-related AEs

AAV2-*GAD* gene for PD: an open label, dose-escalation Phase I trial

- Glutamic acid decarboxylase
- AAV2-GAD 65/67 vector; unilateral STN delivery [50 μL]
- 12 month study; 3 doses
  - Low: 1×10^{11} viral genomes (vg)/mL
  - Med: 3×10^{11} vg/mL
  - High: 1×10^{12} vg/mL
- N=12 (11 men)
- Age: 58·2 ± 5·7 years
- PD 6-13 yrs, HY stage ≥3, levodopa motor complications

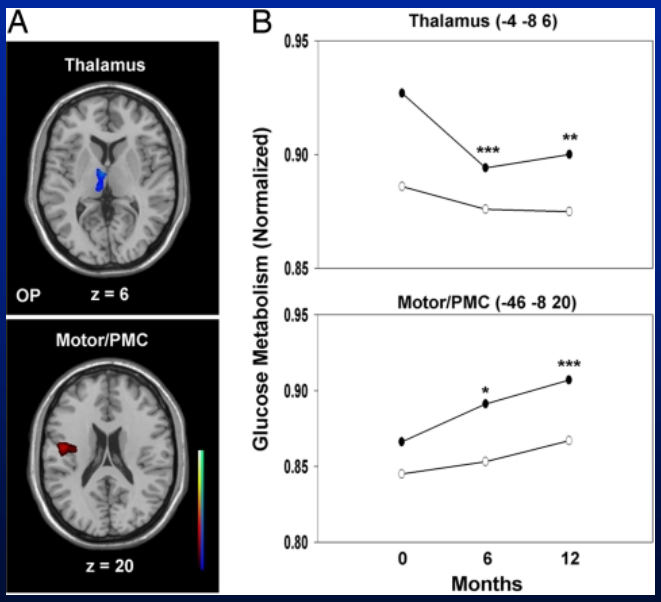
Kaplitt MG et al. Lancet 2007;369:2097-105.

AAV2-*GAD* gene for PD: Improvement in UPDRS



Kaplitt MG et al. Lancet 2007;369:2097-105.

AAV2-*GAD* gene: Changes in metabolic brain networks



Feigin A et al. PNAS 2007;104:19559-19564

AAV2-*GAD* gene for PD: Phase I results

- UPDRS "on" & "off" state: Improvement
- Functional imaging correlated to improvement
- ADL: Trend for improvement
- Dyskinesias: Trend for improvement
- PD meds: No change in doses
- No changes in anti-GAD 65 or 67 antibodies; IgA; IgM over time
- No study intervention related adverse events or unexpected neurological complications
  - 1-3+ years follow-up

Kaplitt MG et al. Lancet 2007;369:2097-105.

Gene Therapy: Clinically-studied Approaches

- Restore basal ganglia activity
  - STN GAD
- Enhance synaptic dopamine
  - AADC
- Neurorestorative
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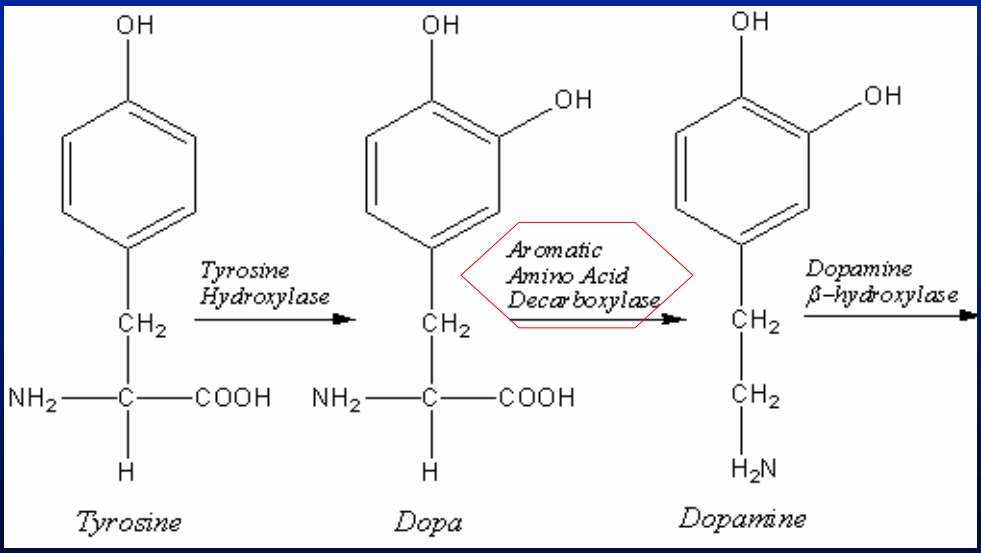
Levodopa conversion to Dopamine



Gene Therapy: Enhancing Synaptic Dopamine

- Target: Neurotransmitter augmentation
- Analogous to carbidopa but:
  - more physiologic
  - Less dependence on exogenous carbidopa
  - Still requires exogenous L-dopa

AAV2-*h*AADC gene therapy for PD: an open label Phase I trial

- Human aromatic L-amino acid decarboxylase
- AAV2-*h*AADC vector; bilateral delivery
  - postcommissural putamen
- 6 month study; dose = 9×10^{10} vg [200μL]
- N=5 (4 women)
- Mean age: 63 years
- Mean duration L-dopa therapy = 11 yrs
- Levodopa motor complications

Eberling JL et al. Neurology 2008;70:1980-983.

AAV2-*h*AADC gene for PD: Phase I results

- UPDRS "on" & "off" state: Improvement
- PET scan: increase in AADC putamen expression
- PD meds: Slight reduction [NS]
- No therapy related adverse events or unexpected neurological complications

Eberling JL et al. Neurology 2008;70:1980-983.

Gene Therapy: Clinically-studied Approaches

- Restore basal ganglia activity
  - STN GAD
- Enhance synaptic dopamine
  - AADC
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Intrastriatal GDNF infusions for PD

- 2 double-blinded, placebo-controlled trials = negative
  - Intracerebroventricular / intraputamenal infusion
  - Paresthesias, hyponatremia
  - No sig improvement despite increased 18F-dopa uptake in posterior putamen
- Adequate delivery / distribution / dose of GDNF throughout striatum?

Lang AE et al. Ann Neurol 2006;59:459-66.
Nutt JG. Neurology. 2003 Jan 14;60(1):69-73.

AAV2-neurturin gene (CERE-120) for PD: an open label Phase I trial

- Neurturin (*NRTN*) – natural GDNF analog
- AAV2-*NRTN* vector; bilateral intraputaminal delivery [80 μL total]
- 12 month study; 2 doses
  - Low: 1.3×10^{11} vg
  - High: 5.4×10^{11} vg
- N=12 (9 men)
- Age: 57 ± 8 years
- PD 11 ± 3.2 yrs, HY stage 3-4, levodopa motor complications

Marks WJ et al. Lancet Neurol 2008;7:400-08

AAV2-neurturin gene (CERE-120): Phase I results

- UPDRS “on” and “off” state: Improvement
- 18F-dopa PET scan: No change
- No therapy related adverse events or unexpected neurological complications
- No significant immune responses to neurturin
- Dose-related, transient elevation of anti-AAV2 antibodies

Marks WJ et al. Lancet Neurol 2008;7:400-08

Studies in Progress

- Phase I/II: Prosavin [Oxford BioMedica] lentivector. Intrastriatal [three genes: AADC, TH, GTP-cyclohydrolase 1]
- Phase II: STN AAV2-GAD [Neurologix, Inc]
- Phase II: CERE-120 [aav2-neurturin] [Ceregene]. Double-blind, sham surgery, controlled. Intraputaminal delivery.

www.clinicaltrials.gov

Unresolved Issues

- Vector profile, selection & technology
  - Viral, nonviral, insert size, tropism, pathogenicity, efficiency, long-term expression
- Transgene system [single, multiple]
- Vector dose
- Delivery site [putamen, STN]
- Transgene regulators / promoters
- Efficacy & safety superior to current therapies?
  - Motor & non-motor
- Patient selection & transgene product
  - Patient specific

Summary

- Safety: Phase I open label data
- Many unresolved issues
- Need for scientific rigor & replication
- Fullfillment of unmet needs?
  - Superior to current medical/surgical modalities?
- Neurorestorative or disease modifying?