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.

Dopaminergic Nigrostriatal Fibers

Put

Caudate

Thal

GP

STN

SN

Caudate

Parkinson’s Disease Diagnosis

Resting Tremor

Bradykinesia

Postural Instability

Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinsons Disease. Arch Neurol 1999; 56:33-39
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, immunosuppression

Basal Ganglia Anatomy

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: $1\times10^{11}$ viral genomes (vg)/mL
  – Med: $3\times10^{11}$ vg/mL
  – High: $1\times10^{12}$ vg/mL
• N=12 (11 men)
• Age: 58±2 ± 5·7 years
• PD 6-13 yrs, HY stage ≥3, levodopa motor complications


AAV2-GAD gene for PD: Improvement in UPDRS

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

Gene Therapy: Clinically-studied Approaches

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

Levodopa conversion to Dopamine

1. Tyrosine $\rightarrow$ Dopa $\rightarrow$ Dopamine

   - Tyrosine $\rightarrow$ Dopa: Tyrosine Hydroxylase
   - Dopa $\rightarrow$ Dopamine: Aromatic Amino Acid Decarboxylase
   - Dopamine $\rightarrow$ Dopamine: Dopamine $\beta$-Hydroxylase
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-hAADC gene therapy for PD: an open label Phase I trial

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

AAV2-hAADC 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


Gene Therapy: Clinically-studied Approaches

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


**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: $1.3 \times 10^{11}$ vg
  - High: $5.4 \times 10^{11}$ vg
- N=12 (9 men)
- Age: $57 \pm 8$ years
- PD $11 \pm 3.2$ 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 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
- Fulfillment of unmet needs?
  - Superior to current medical/surgical modalities?
- Neurorestorative or disease modifying?