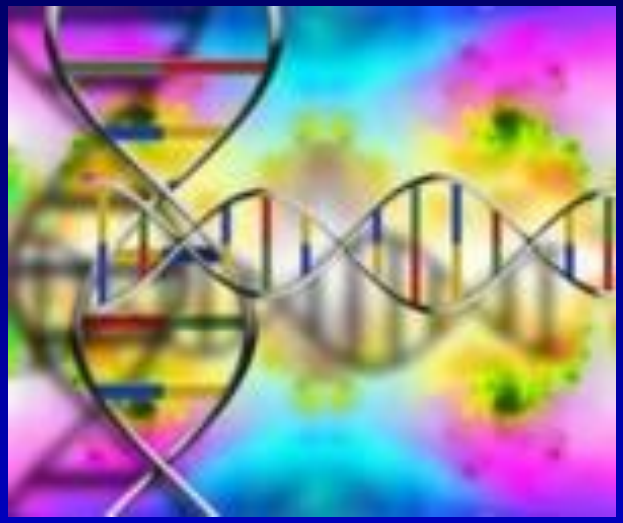

Advances in Gene Therapy for Parkinson's Disease

VA EES Educational Seminar
July 2011

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Gene Therapy

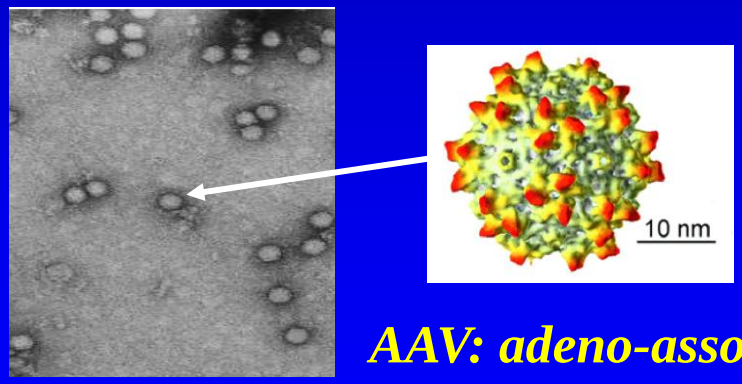
- Techniques that make use of genes to produce an effect that improves health or treats disease
  - "Replacing or repairing" a defective gene
  - Using a gene to make a helpful protein

Gene Therapy for PD

- A potentially attractive means of targeting anatomic loci disrupted by the pathophysiology of Parkinson's disease and delivering a gene to make a therapeutic protein
  - STN—key basal ganglia output nucleus displaying excessive excitatory activity and aberrant neural physiology → inhibit activity via expression of glutamic acid decarboxylase (GAD) to synthesize inhibitory neurotransmitter GABA
  - Putamen—site of diminished dopamine release due to degeneration of nigral neurons → provide putamenal neurons the ability to produce dopamine via expression of aromatic acid decarboxylase (AADC)
  - Nigrostriatum—principal dysfunctional pathway in PD → improve function and protect via expression of trophic factor (e.g., neurturin)

AAV Gene Transfer

- Adeno-associated virus type 2 (AAV-2)
  - Viral vector with demonstrated robust & safe long-term expression in the brain



AAV: adeno-associated virus

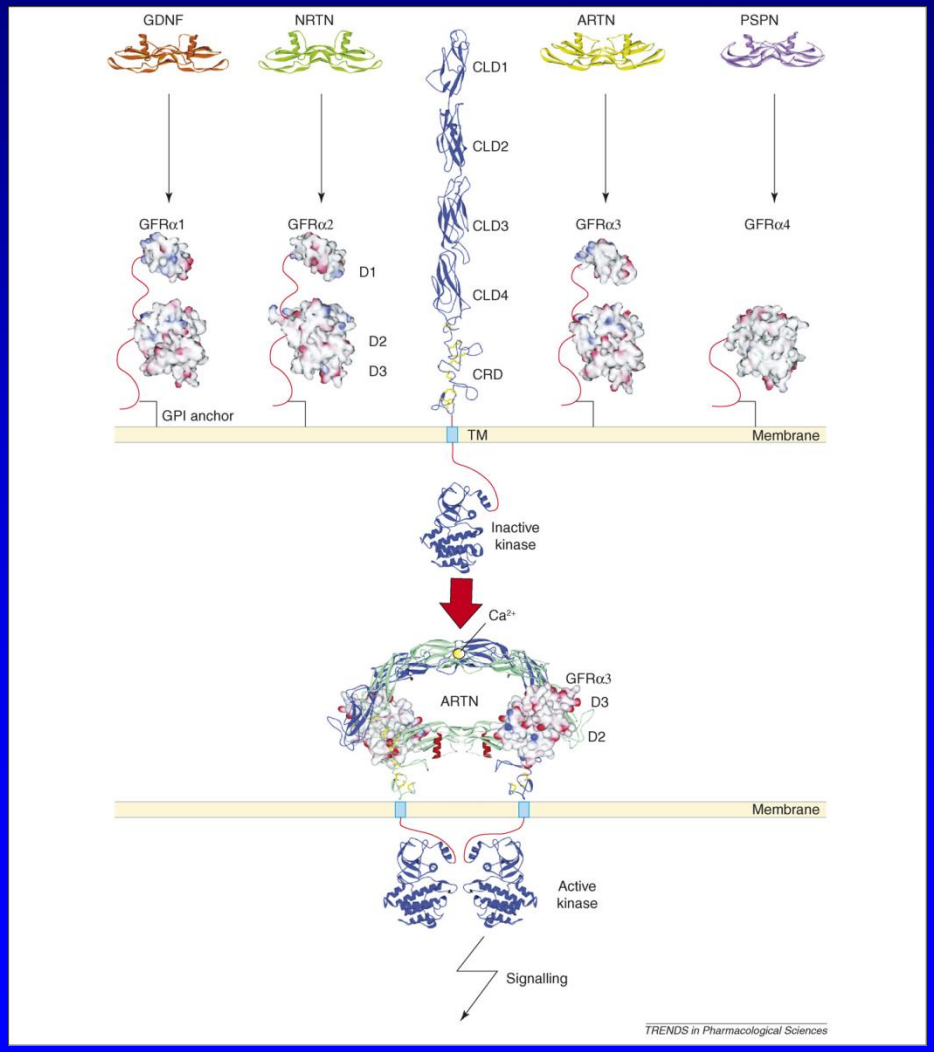
Note: AAV is NOT biochemically or genetically related to adenovirus

Neurotrophic Factor Gene Therapy

- Current treatments (pharmacological & surgical) only suppress symptoms
- There is an urgent need for treatments that improve the function of degenerating dopaminergic neurons and slow, halt, or reverse their degeneration
- Delivery of a trophic factor to the nigrostriatal system may be an effective approach to achieve this goal
- Gene delivery of a trophic factor provides the means to selectively target the factor to the desired site in a sustained fashion.

Neurturin (NTN or NRTN)

- Naturally occurring analog of GDNF; both signal through Ret transmembrane protein kinase
- Supports survival & enhances function of dopaminergic cells *in vitro*
- Prevents degeneration of nigrostriatal neurons & improves function in animal models of PD

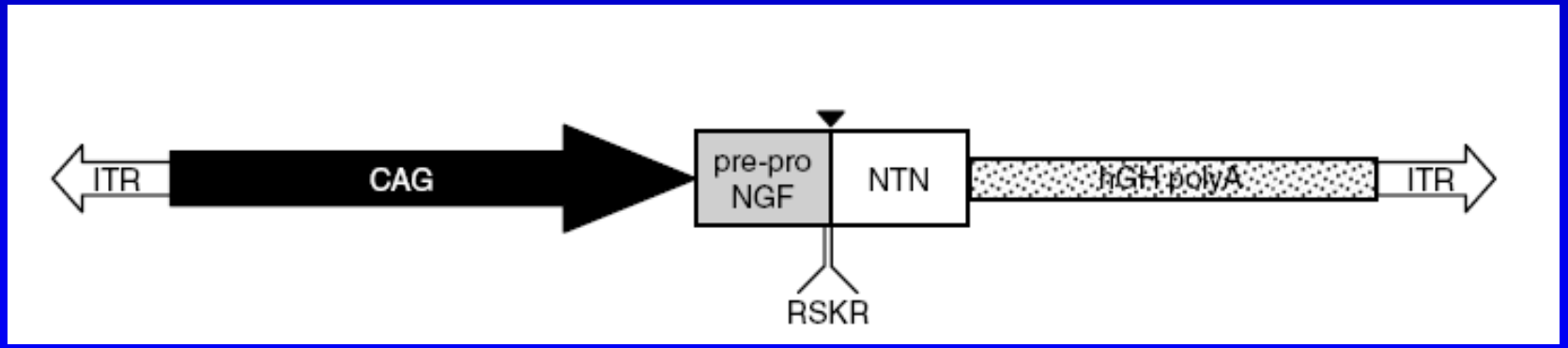


Delivery of Trophic Factors

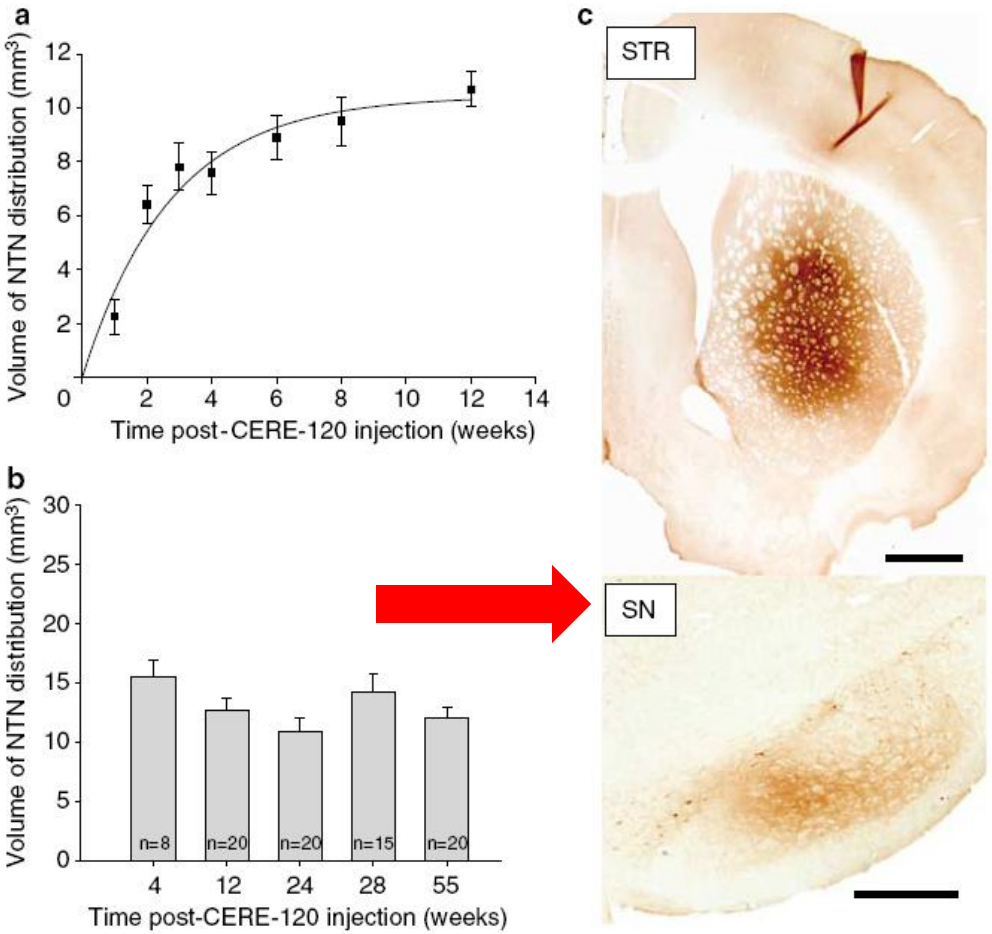
- To achieve desired effect, need
  - Targeted delivery
  - Ability to prevent spread to unwanted areas
  - Sustained delivery
- Past attempts (GDNF) suboptimal: intraventricular, point source with implanted catheter
- Gene transfer may provide method of obtaining desired delivery

CERE-120

- CERE-120 (AAV2-NTN)
  - Genetically engineered, replication-defective AAV vector into which the DNA coding sequences required to express human neurturin (NTN) have been inserted



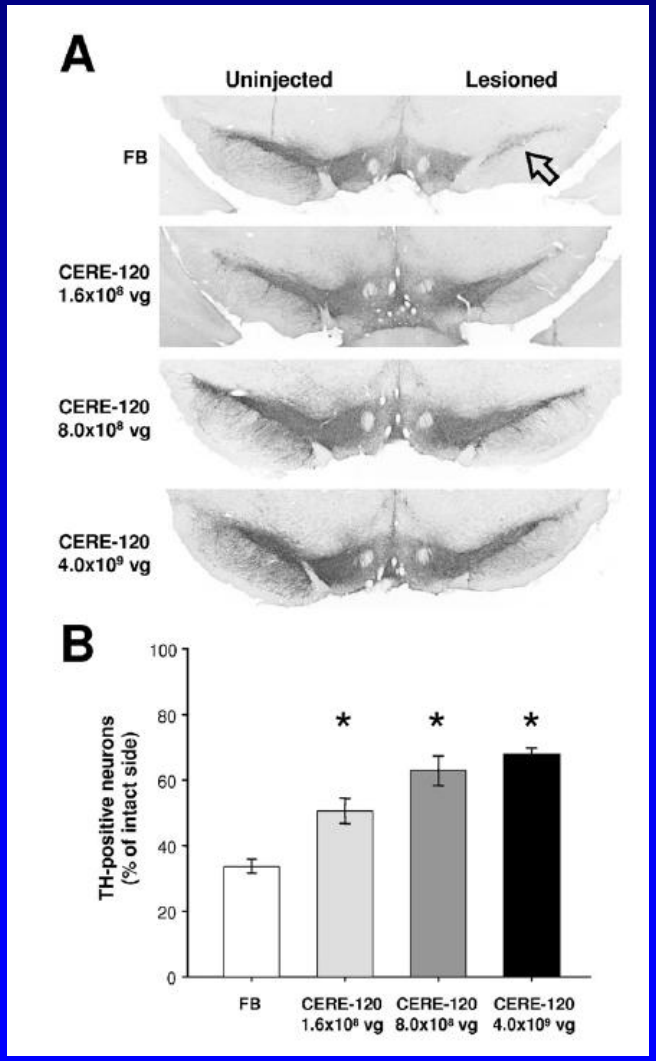
NTN Expression Following CERE-120 Striatal Injection in Rat



- NTN rapidly expressed, reaches steady state at 4 weeks, is sustained up to 12 months
- NTN signal restricted to striatum & substantia nigra

Gasmi et al., 2007

CERE-120 Provides Dose-Related Neuroprotection of Nigral Neurons Following Striatal Injection in 6-OHDA Rat Model

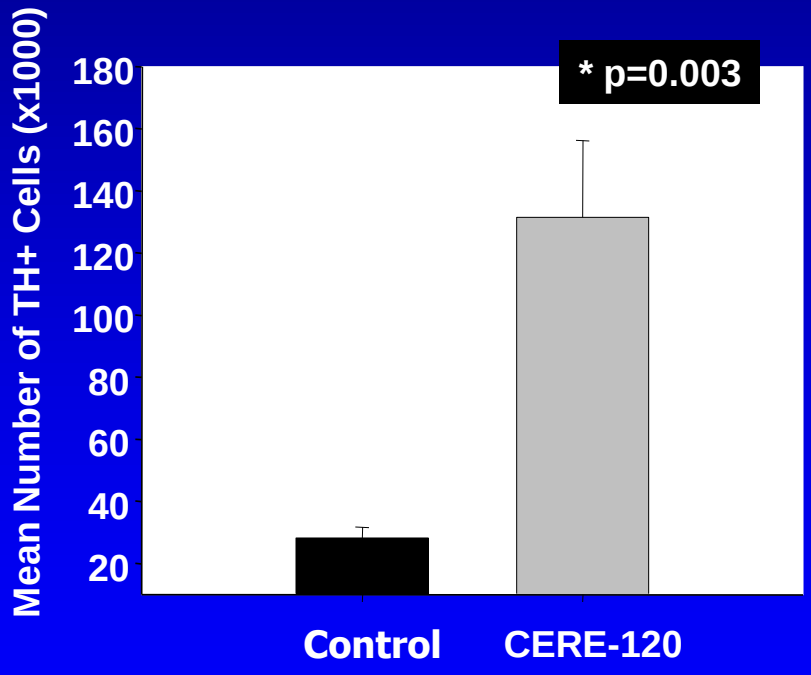


Gasmi et al., 2007

Nigrostriatal Delivery of CERE-120 Promotes Significant Increase in Dopaminergic (TH+) Cells in the Nigra in the MPTP Model of PD

MPTP

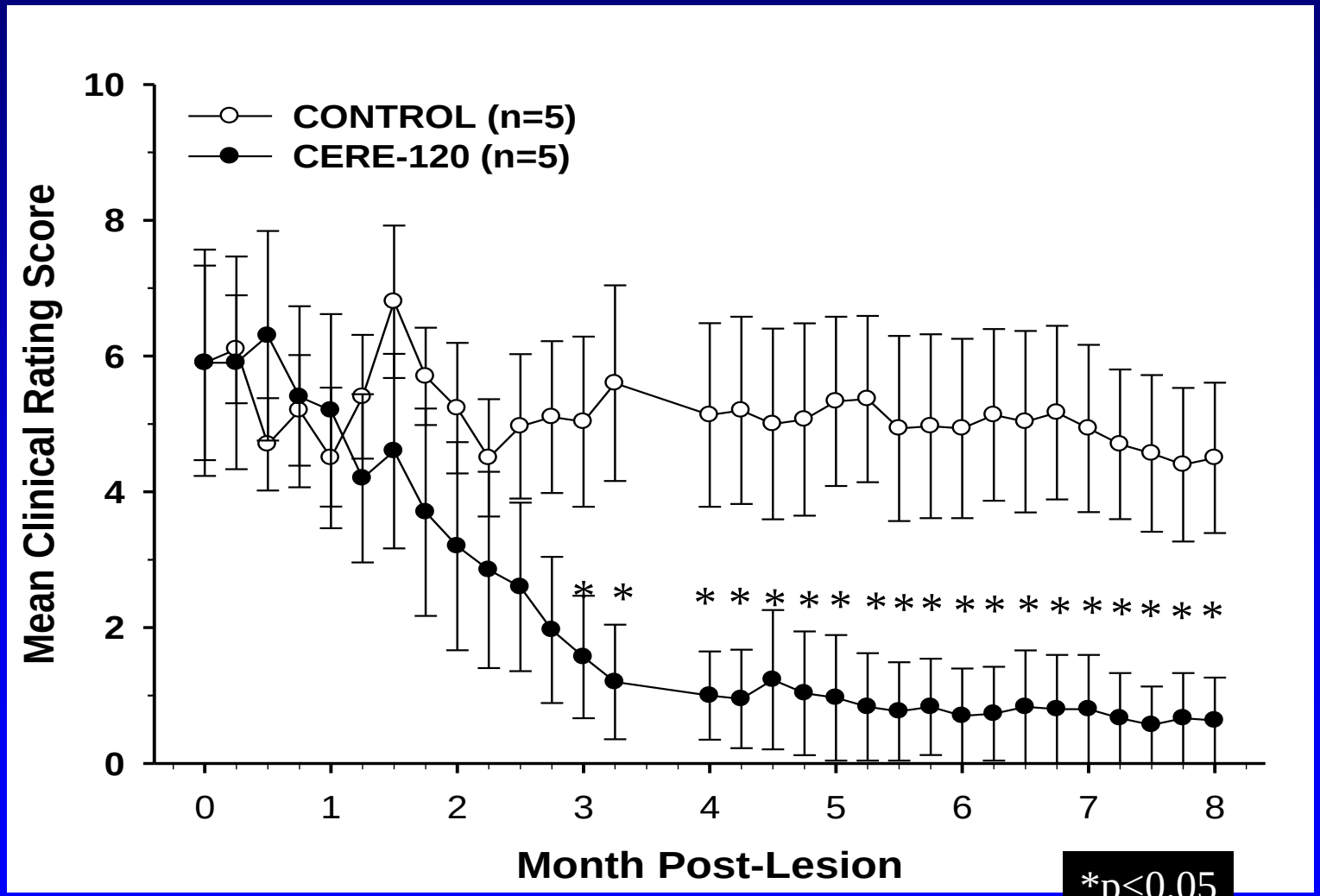
MPTP + CERE-120



Kordower et al., 2006

CERE-120 injected 4 days after MPTP injection

CERE-120 Produces Sustained Motor Improvement in MPTP Primate Model



*p<0.05

Kordower et al., 2006

Phase I Study

Demonstrate the safety, tolerability, & potential efficacy of Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN] (CERE-120) delivered intraputaminally to treat Parkinson's disease (PD)

Sponsored by Ceregene, Inc. (San Diego)

Collaborators

- UCSF
  - Jill L. Ostrem, MD
  - Graham A. Glass, MD
  - Philip A. Starr, MD, PhD
  - Paul S. Larson, MD
  - Robin Taylor, RN, FNP
  - Deborah Cahn-Weiner, PhD
- Rush Medical Center
  - Leonard Verhagen, MD, PhD
  - Roy A. E. Bakay, MD
- University of British Columbia
  - A. Jon Stoessl, MD
- Ceregene, Inc.
  - Raymond T. Bartus, PhD

Study Design/Methods

- First in humans, Phase I study to investigate safety, tolerability, & potential efficacy of CERE-120 delivered intraputaminally in patients with Parkinson's disease
- Approved by FDA, NIH RAC, IBCs, IRBs
- 12 patients: H&Y Stage 3-4 with motor fluctuations
  - 6 patients (4 UCSF, 2 Rush): low dose (1.3×10^{11} vg)
  - 6 patients (4 UCSF, 2 Rush): high dose (5.4×10^{11} vg)
- First patient dosed June 30, 2005
- Final patient dosed March 1, 2006
- Report published in May 2008 *Lancet Neurology*

Inclusion/Exclusion Criteria

Inclusion

- Bilateral idiopathic PD with motor fluctuations despite adequate antiparkinsonian therapy
- PD for at least 5 years
- Age 35-75
- Non-pregnant females
- H&Y 3 or 4 in off condition
- UDPRS off motor score of > 30
- Average off time of at least 3 hours
- Stable dose of PD medications
- Medically able to undergo surgery

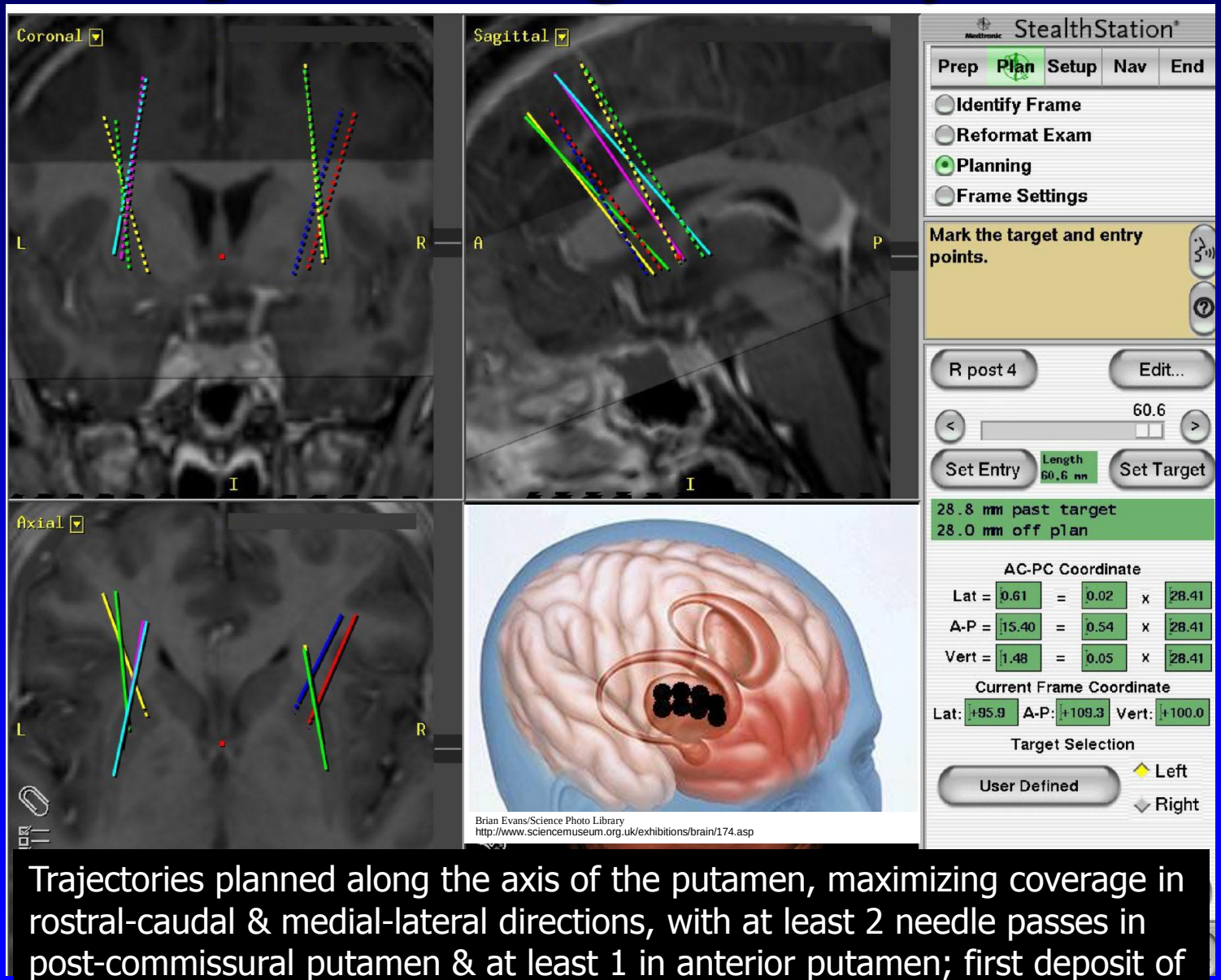
Exclusion

- Medical, psychiatric, or lab abnormality posing safety risk
- Tx of PD by intracranial surgery or implantation of a device.
- Abnormal MRI of the brain
- < 25 on the Folstein MMSE
- Chemotherapy, cytotoxic therapy, or immunotherapy within 6 weeks
- Vaccinations within 30 days
- History of drug or alcohol abuse
- Treatment with nonantiparkinsonian agents (e.g., neuroleptics) that may affect symptoms within 60 days
- Hx of prior gene transfer therapy
- Treatment with investigational agent within 60 days

Study Design/Methods

- Baseline data (30 days prior to dosing)
  - UPDRS & timed tests (off- & on-meds), physical exam, lab tests, brain MRI, ^{18}F Dopa-PET scan, QoL measures, neurocognitive battery
- Dosing procedure
  - Frame-based MRI stereotaxy with computer-assisted trajectory planning
  - 4 injections x 2 deposits each per hemisphere through burr holes under heavy sedation or anesthesia
  - 4-6 hour procedure
  - Hospitalization x 2 days
- Follow-up (weekly x 1 month, then monthly x 3 months, then quarterly; annual follow-up for life)

Example of Surgical Trajectories



Trajectories planned along the axis of the putamen, maximizing coverage in rostral-caudal & medial-lateral directions, with at least 2 needle passes in post-commissural putamen & at least 1 in anterior putamen; first deposit of 5 μl at terminus of trajectory, second deposit 4mm superior

Primary Outcome: Adverse Events

- No serious adverse events have occurred
- No clinically significant adverse changes in physical exam, neurological status, or laboratory values have occurred
- A variety of non-serious, transient adverse events have occurred

Safety and tolerability of intraputaminal delivery of CERE-120 (adeno-associated virus serotype 2–neurturin) to patients with idiopathic Parkinson's disease: an open-label, phase I trial

Marks et al., *Lancet Neurology* 2008

Phase I Study Conclusions

- Delivery of a trophic factor via a viral vector to the human brain is feasible
- Bilateral intraputaminal injection of CERE-120 in 12 patients with moderate to advanced PD has resulted in no serious adverse events to date
- ~36% mean improvement in off-med UPDRS motor scores observed ($p<0.001$), with sustained response at 12 months
- No consistent changes in Fluorodopa PET scans
- Based on accumulating safety & tolerability data, coupled with the ongoing efficacy analyses, a Phase II controlled, multi-center study was initiated

Phase II Study

- Prospective, multi-center, randomized, double-blind, controlled trial in 58 patients at 9 medical centers
- 2 : 1 active : sham surgery
- High dose CERE-120; partial burr hole sham
- Primary outcome measure: change in off-med UPDRS motor score from baseline at 12 months
- After 12 months of blinded study, sham patients can receive active treatment (if safety & efficacy established)
- Study completed enrollment October 2007; 1-year follow-up of final subject occurred in October 2008

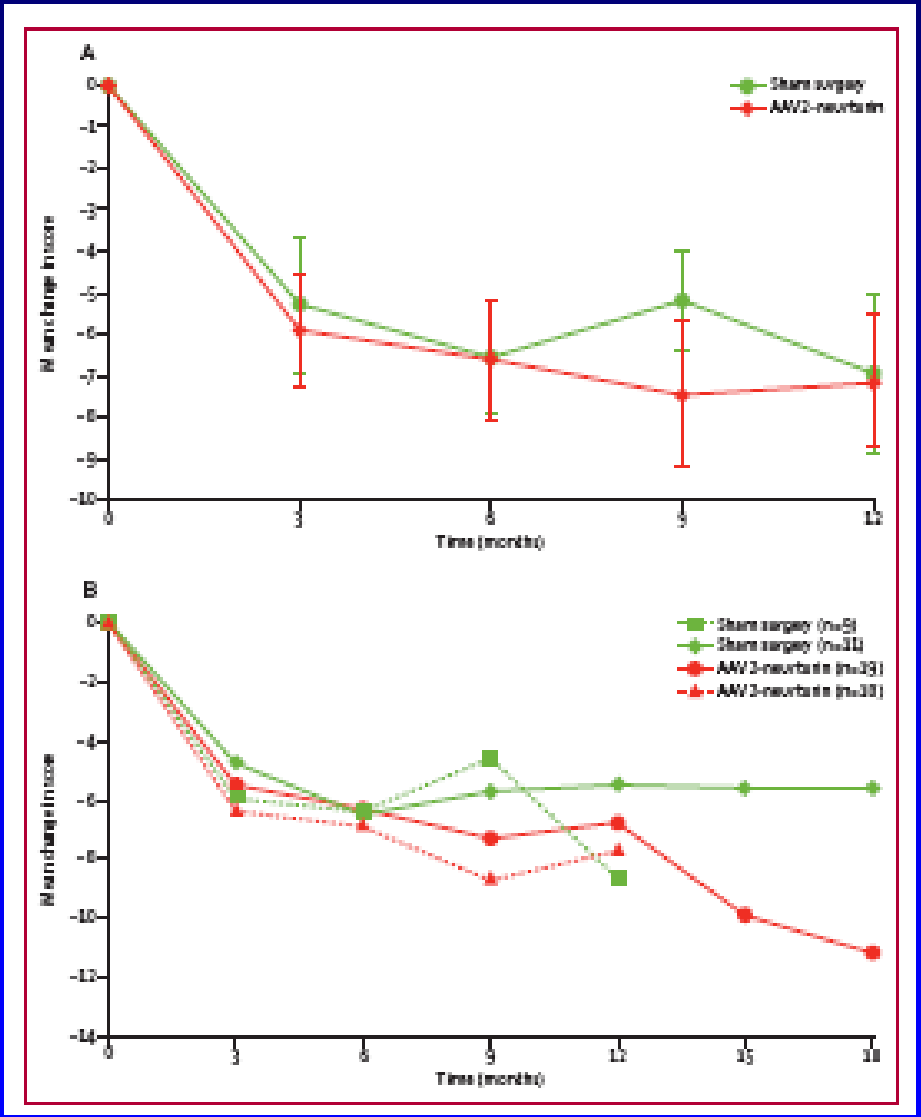
Phase II Study Results

- No significant difference in change in off-med motor score for active vs. sham at 12 months
- Pre-specified analysis in patients with 15-18 months of blinded evaluation showed modest (but significant) improvements in off-med UPDRS motor score and other secondary measures in those receiving CERE-120; no measures favored sham
- Treatment well tolerated

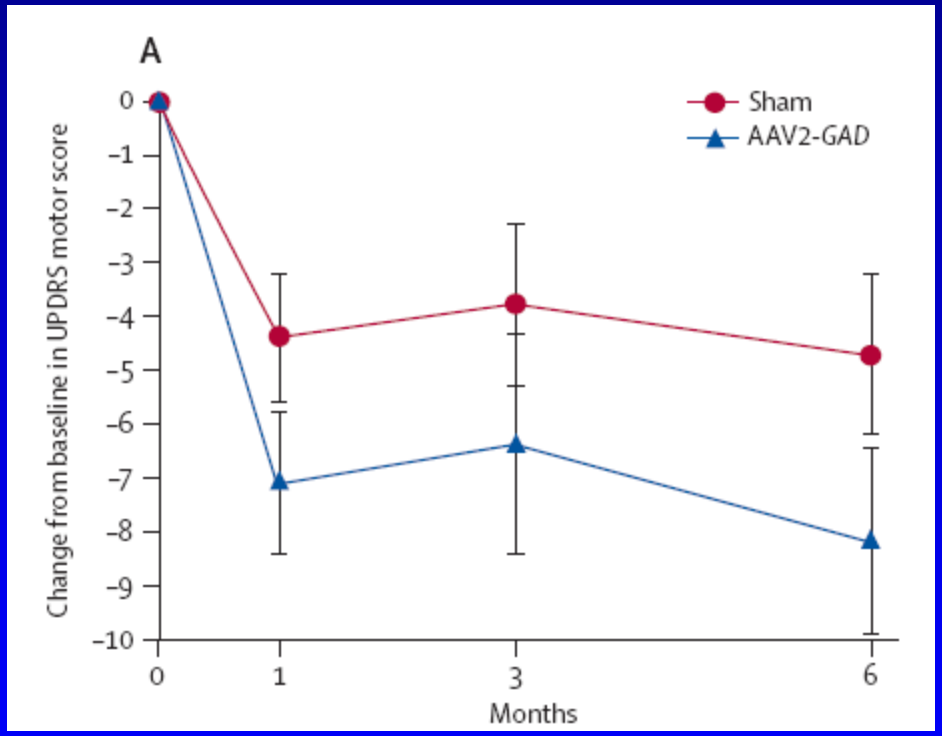
Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial

Marks et al., *Lancet Neurology* 2010

Phase II Study Results



AAV2-*GAD* gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial



LeWitt et al., *Lancet Neurology* 2011

Conclusions

- Gene therapy may provide an effective approach to deliver biological treatments to the brain
- Preliminary data using AAV2 to deliver DNA encoding GAD, AADC, and Neurturin promising
- Phase II AAV2-GAD trial demonstrated benefit
- Phase II AAV2-Neurturin study failed to demonstrate robust superiority of treatment over control in short-term follow-up (autopsy data shows neurturin failed to reach substantia nigra); new protocol underway includes higher dose in putamen and addition of direct nigral target

Question & Answers

Thank You