

Gene Therapy for Parkinson's Disease

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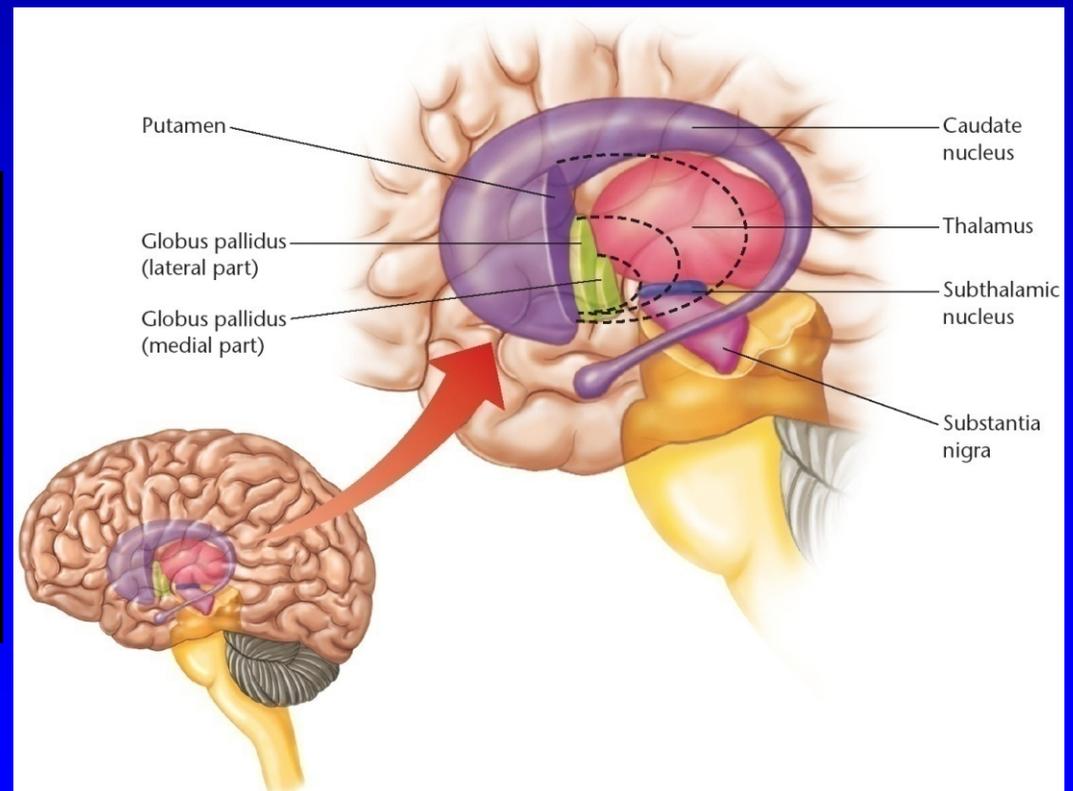
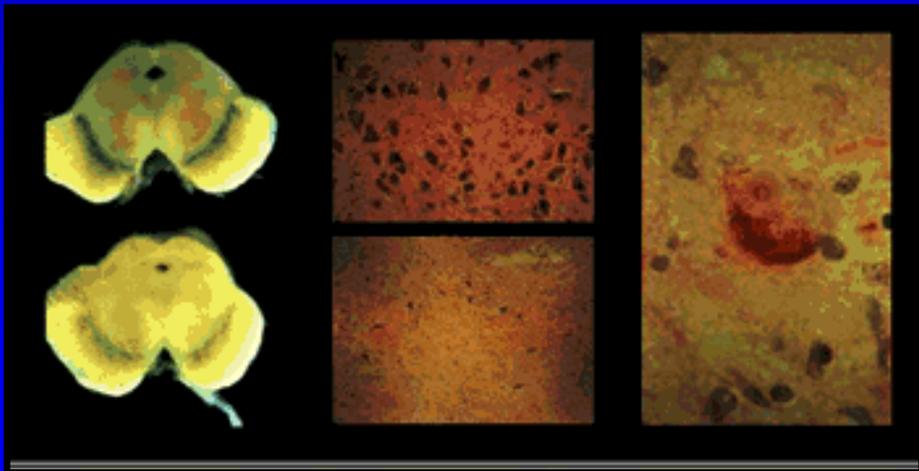
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Gene Therapy

- Techniques that make use of the body's own cells and genes to produce an effect that improves health or treats disease
 - "Replacing or repairing" a defective gene
 - OR
 - Using a gene to make a helpful protein

Parkinson's Disease

- A progressive neurodegenerative disorder of unknown cause; motor symptoms due to loss of neurons in substantia nigra



Treatment of PD

- Current treatments (pharmacological & surgical) mainly 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 (= growth 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.

Neurotrophic Factors

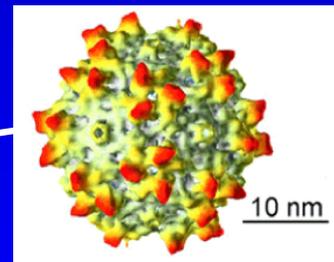
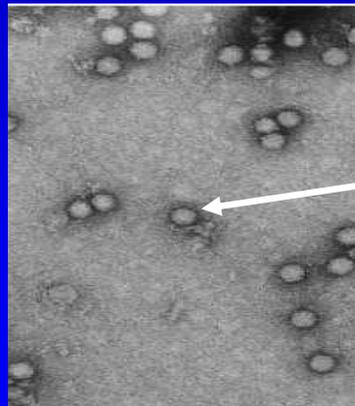
- Protein growth factors that regulate brain cell development
- Promote survival of neurons
- Counteract pathological cell death
- Neurturin is one of these

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

AAV Gene Transfer

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

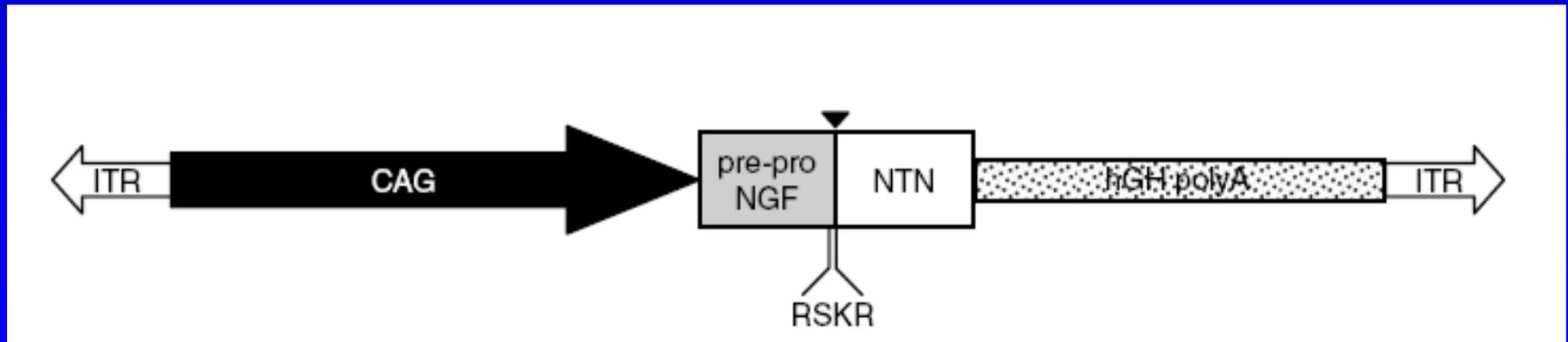


AAV: adeno-associated virus

Note: AAV is NOT biochemically or genetically related to adenovirus

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



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)

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

William J Marks Jr, Jill L Ostrem, Leonard Verhagen, Philip A Starr, Paul S Larson, Roy A E Bakay, Robin Taylor, Deborah A Cahn-Weiner, A Jon Stoessl, C Warren Olanow, Raymond T Bartus

Lancet Neurol 2008; 7: 400-08

Phase I Study Conclusions

- Delivery of a trophic factor via a viral vector to the human brain is feasible
- Bilateral intraputaminial 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
- Based on accumulating safety & tolerability data, coupled with the ongoing efficacy analyses, a Phase II controlled, multi-center study has been initiated

Phase II Study

- Prospective, multi-center, randomized, double-blind, controlled trial in 60 patients at 8 medical centers in the U.S.
- 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)

Phase II Study: Status

- Study completed enrollment in October 2007
- Results expected in early 2009

Other Gene Transfer Studies for PD

- AAV2-GAD into subthalamic nucleus
- AAV2-AADC into striatum

Conclusions

- More treatments for Parkinson's disease are available than ever before
 - Medications
 - Deep brain stimulation
 - Experimental treatments
- Gene therapy may provide an effective approach to deliver biological treatments to the brain