Clinical Results:

**Phase I Trial**

Ex Vivo Nerve Growth Factor Gene Therapy for Alzheimer’s Disease

- Cognitive Testing
- PET scans

(In press, Nature Medicine)

MLV vector transduced primary autologous fibroblasts, grafted into Nucleus Basalis
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Molecular/Cellular:
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Surgery:
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PET Studies:
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Conflict of Interest Statement: Mark Tuszyński, Armin Blesch, Jeffrey Kordower are scientific founders of Ceregene, Inc.
Growth Factor Premise:

Growth factors potently

- prevent death of responsive cell populations
- augment function of responsive cell populations

Potential for the treatment of progressive diseases of the nervous system
NGF Prevents Cholinergic Neuron Death in the Adult Primate Brain
Clinical Assessment Group

- 6 subjects: 5F, 1M who safely completed cell injection procedure
- Mean Age: 67.1 years (range 53-76 years at entry)
- Diagnosis of early, Probable Alzheimer’s disease
  - recruited at early disease stage to allow informed consent and to test potential for neuroprotection

- Dose escalation:
  - 1-2: 25 ul cells, right-NBM only (5 ul per site, 2.5x10^6 cells)
  - 3-4: 50 ul cells total, bilateral (5 ul per site, 5.0x10^6 cells)
  - 5-6: 100 ul cells total, bilateral (10 ul per site, 10x10^6 cells)
RESULTS:

Phase I Trial of Ex Vivo Gene Therapy for Alzheimer’s Disease: Cognitive Function

1. Mini-Mental Status Examination
   • 30 point scale; mean score = $20.7 \pm 2.0$ at time of treatment

2. ADAS-Cog
   • 70 point scale

Open small phase I trial
• no placebo controls
• no blinding
Mean MMSE Score

Mean MMSE

-12 mo  0 mo  3 mo  6 mo  9 mo  12 mo  18 mo  24 mo

+NGF
- 49% Reduction in Rate of Decline Over 2.2 Years
- Effect of Cholinesterase Inhibitors ~5%, for 3-6 Months
Annual Rate of Change in Mean ADAS-Cog Score

Mean ADAS-Cog Score

Worse

Better
Change in Mean ADAS-Cog Over Time

Annual Mean Rate of Decline

Better

Worse

Time Epochs

1-12mo 6-18mo 12-24mo
• Median Rate of Decline Over 2.2 yr Period = 4.4 pt/yr
RESULTS
Phase I Trial of Ex Vivo Gene Therapy for Alzheimer’s Disease: PET Imaging

1. 2-deoxy glucose uptake as reflection of metabolic activity
   • PET activity declines over time in AD

2. Serial PET scans in four subjects (bilaterally injected):
   • showed increased mean cortical PET activity after NGF delivery (p<0.05)
PET Scan Averages, 4 Bilaterally Treated Subjects

Scan 1

Scan 2

2-DG

P<0.05 Scan 2 vs. Scan 1
CONCLUSIONS:
Phase I Trial of Ex Vivo Gene Therapy for Alzheimer’s Disease:

1. **No adverse effects** related to the growth factor or the gene delivery system in the human brain using a non-regulated vector (2-4 yr period)

2. Significant increase in cortical activity by 2DG PET Scan

3. Cognitive analysis (in small, unblinded, non-controlled cohort) shows apparent reduction in rate of decline to an extent substantially exceeding effects of current AD therapies, providing rationale for a follow-up trial of AAV-NGF in AD
Phase I Trial of Ex Vivo Gene Therapy for Alzheimer’s Disease:

AAV-NGF gene delivery for AD
1. Genetically modified cells accurately located within brain
2. Cell survival and morphology consistent with previous non-human primate studies
Robust in vivo gene expression at 5 wk
“Trophic” Response to NGF in the AD Brain
Cholinergic Neurons in AD Express a Trophic Response to NGF

“Trophic” response in human AD

“Trophic” response in aged primate