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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Conflict of Interest Statement: Mark Tuszynski, Armin Blesch, Jeffrey Kordower are scientific founders of Ceregene, Inc.

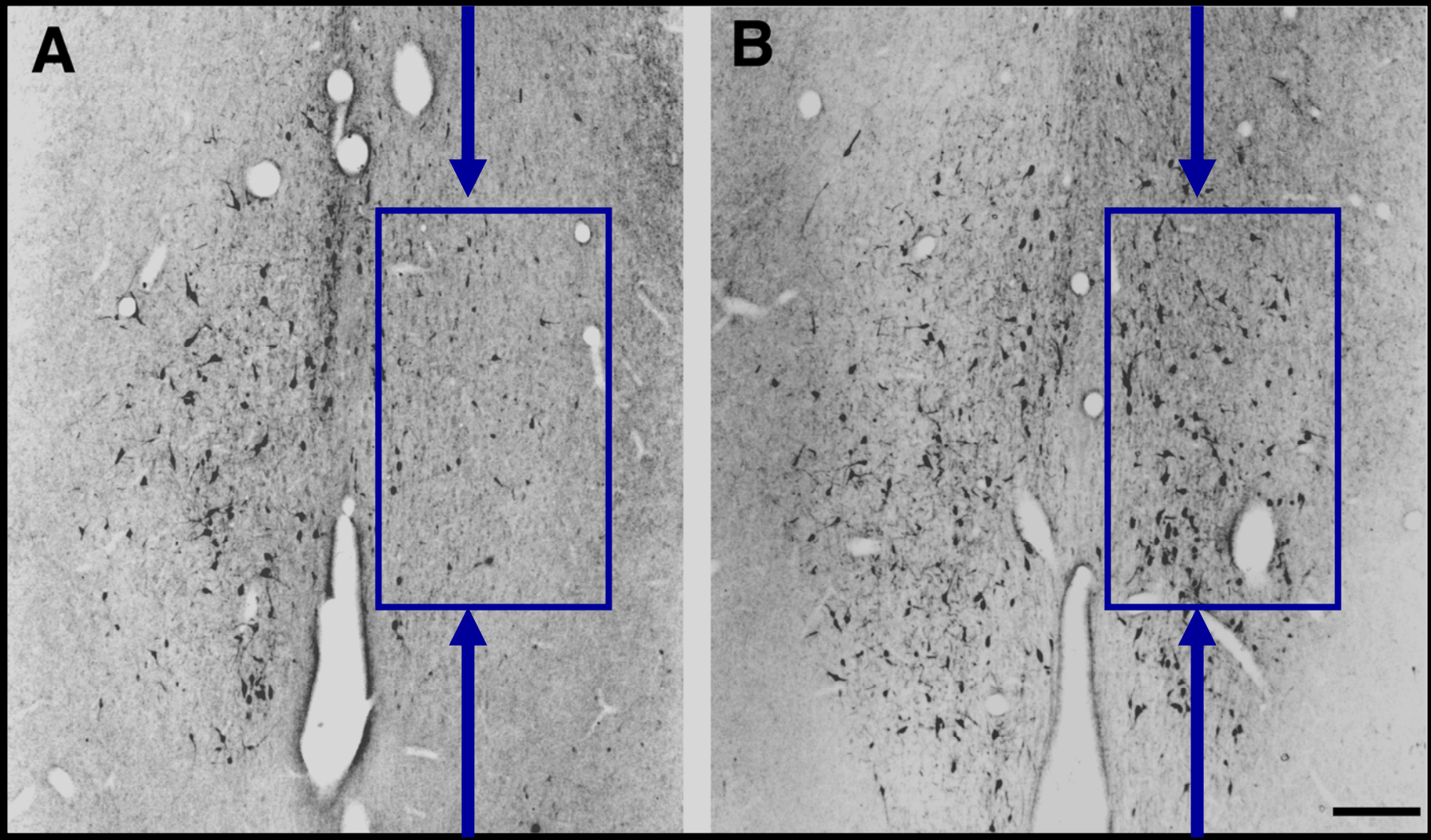
Growth Factor Premise:

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

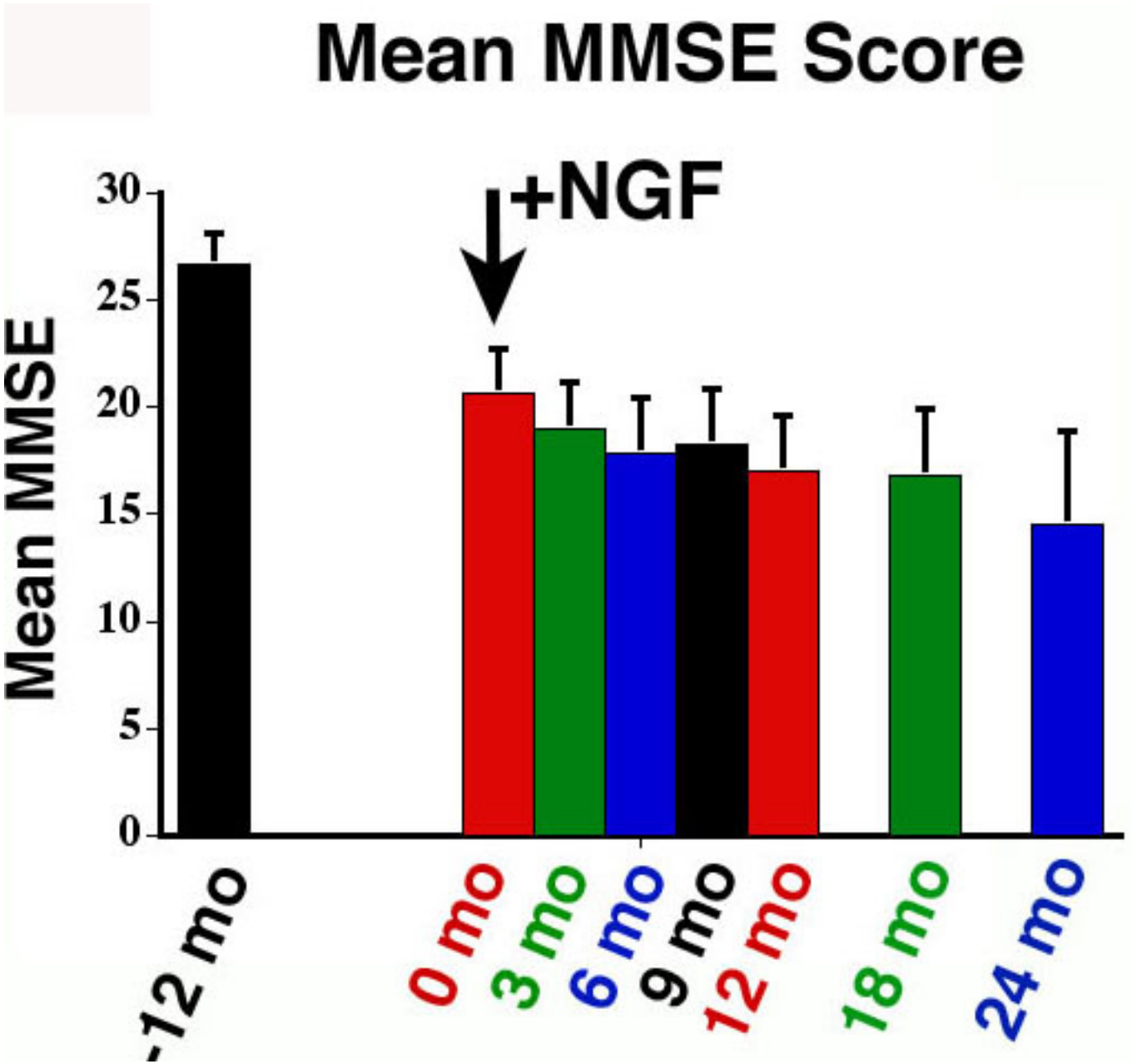
- **6 subjects: 5F, 1M who safely completed cell injection procedure**
- **Mean Age: 67.1 years (range 53-76 years at entry)**
- **Diagnosis of early, Probable Alzheimer's disease**
  - **recruited at early disease stage to allow informed consent and to test potential for *neuroprotection***
- **Dose escalation:**
  - 1-2: 25 ul cells, **right**-NBM only (5 ul per site, 2.5×10^6cells)
  - 3-4: 50 ul cells total, **bilateral** (5 ul per site, 5.0×10^6cells)
  - 5-6: 100 ul cells total, **bilateral** (10 ul per site, 10×10^6cells)

RESULTS:

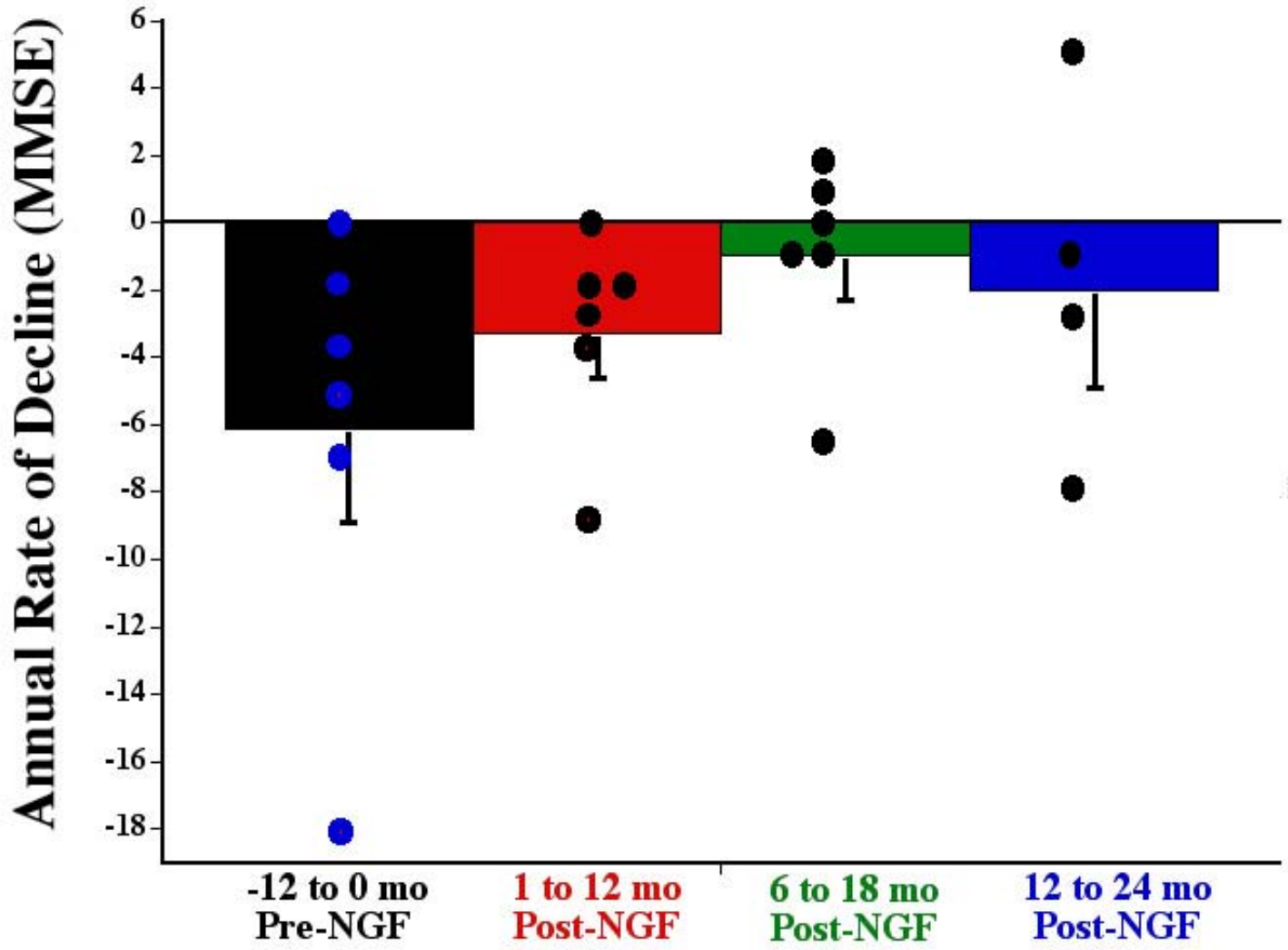
Phase I Trial of Ex Vivo Gene Therapy for Alzheimer's Disease: Cognitive Function

1. Mini-Mental Status Examination
   - 30 point scale; mean score = **20.7 ± 2.0** at time of treatment
2. ADAS-Cog
   - 70 point scale

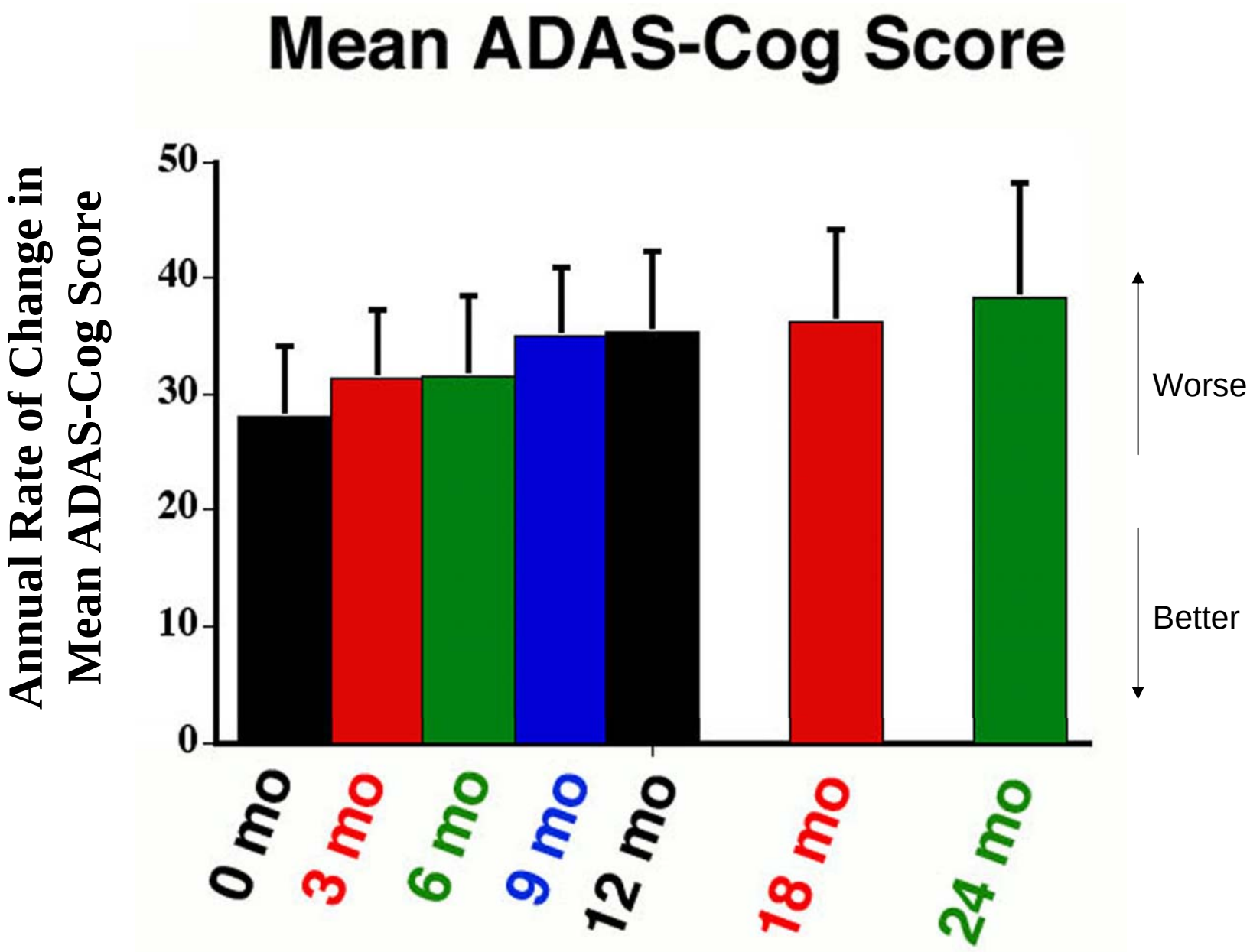
Open small phase I trial
- no placebo controls
- no blinding

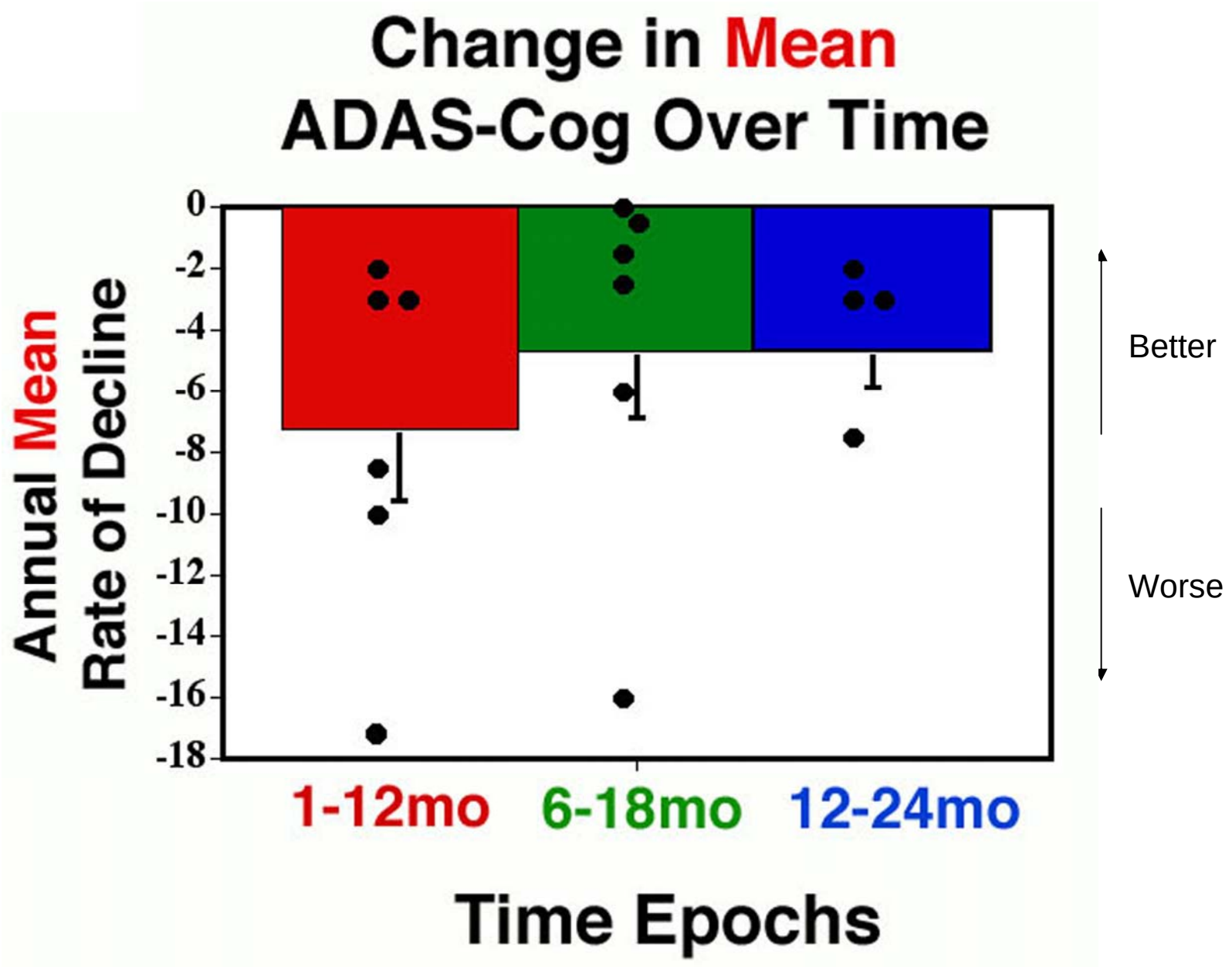

Mean MMSE Score
+NGF
Mean MMSE
30
25
20
15
10
5
0
-12 mo
0 mo
3 mo
6 mo
9 mo
12 mo
18 mo
24 mo

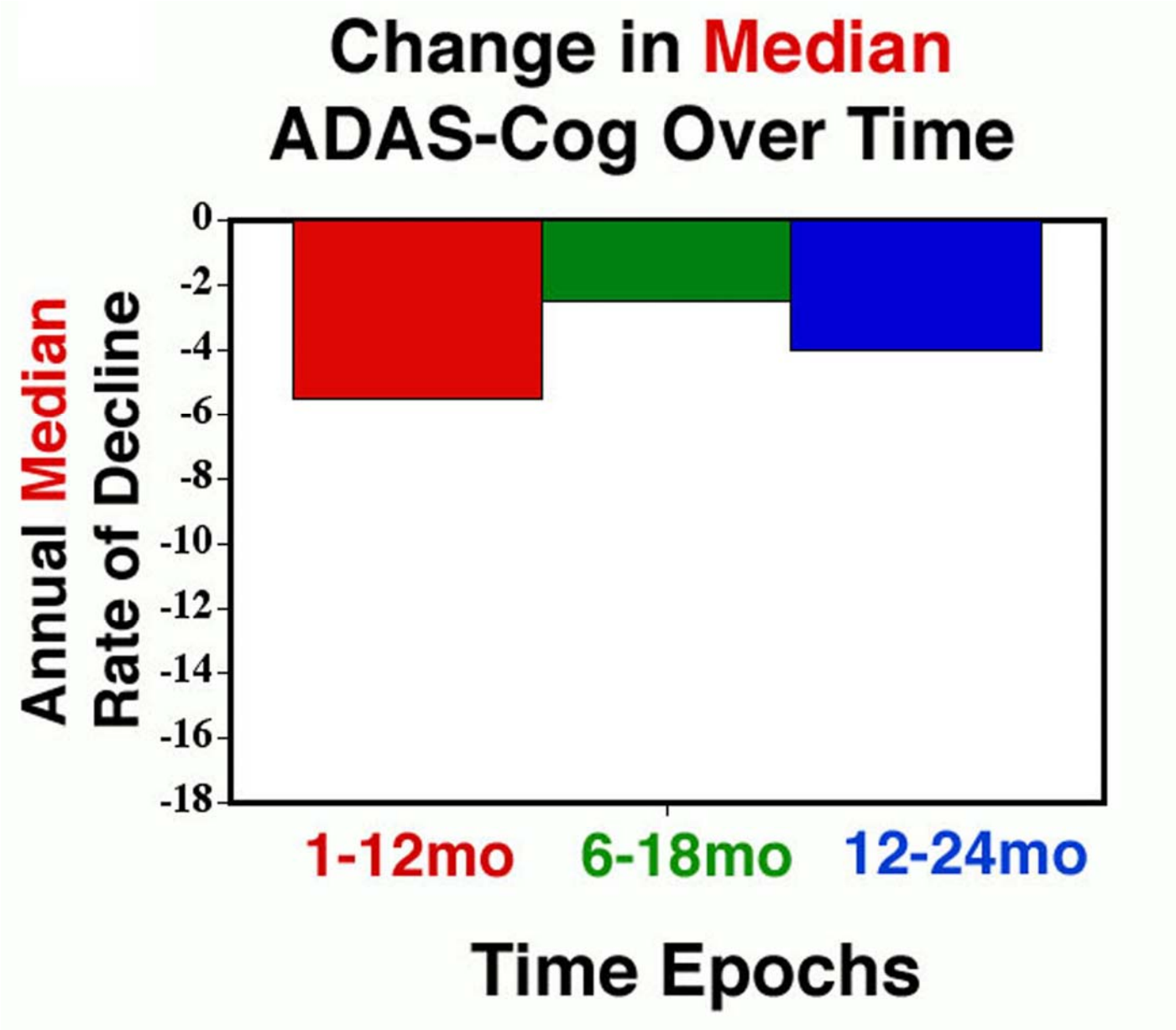
Change in Mean MMSE Over Time



- 49% Reduction in Rate of Decline Over 2.2 Years
- Effect of Cholinesterase Inhibitors ~5%, for 3-6 Months


Mean ADAS-Cog Score
Annual Rate of Change in Mean ADAS-Cog Score
50
40
30
20
10
0
0 mo
3 mo
6 mo
9 mo
12 mo
18 mo
24 mo
Worse
Better


Change in Mean
ADAS-Cog Over Time
Annual Mean
Rate of Decline
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
1-12mo
6-18mo
12-24mo
Time Epochs
Better
Worse



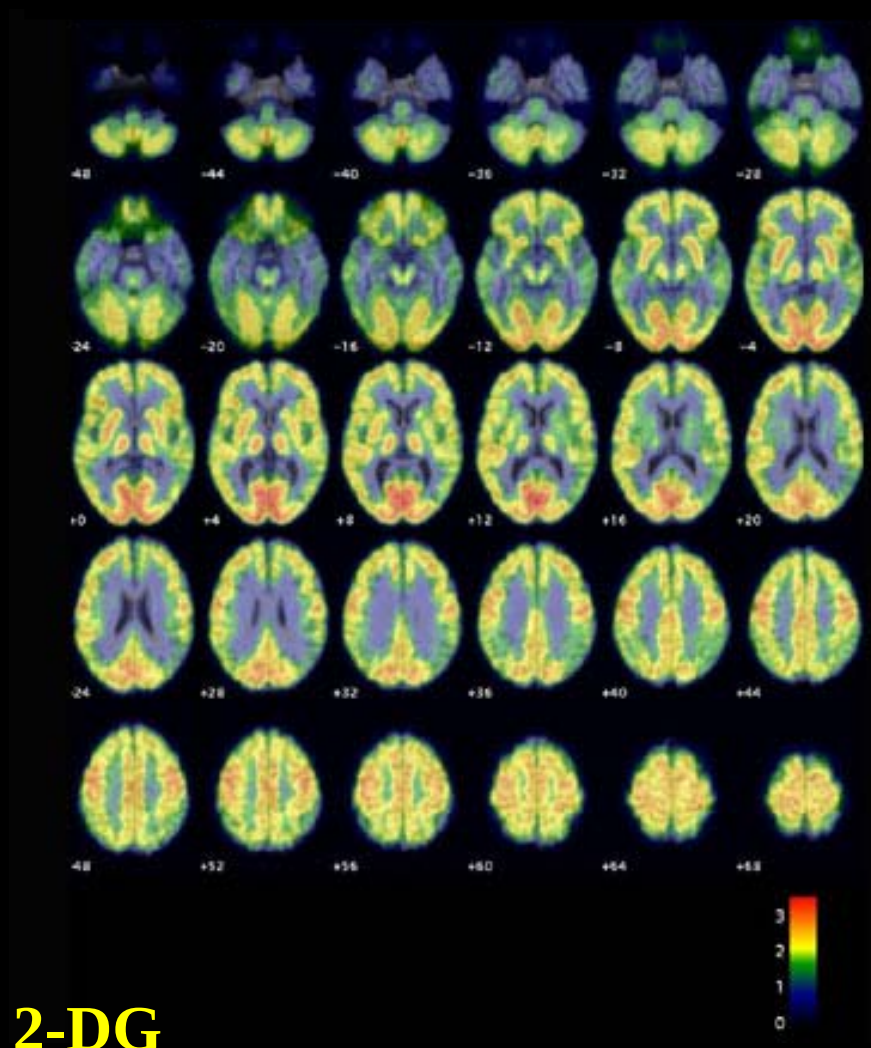
- **Median Rate of Decline Over 2.2 yr Period = 4.4 pt/yr**

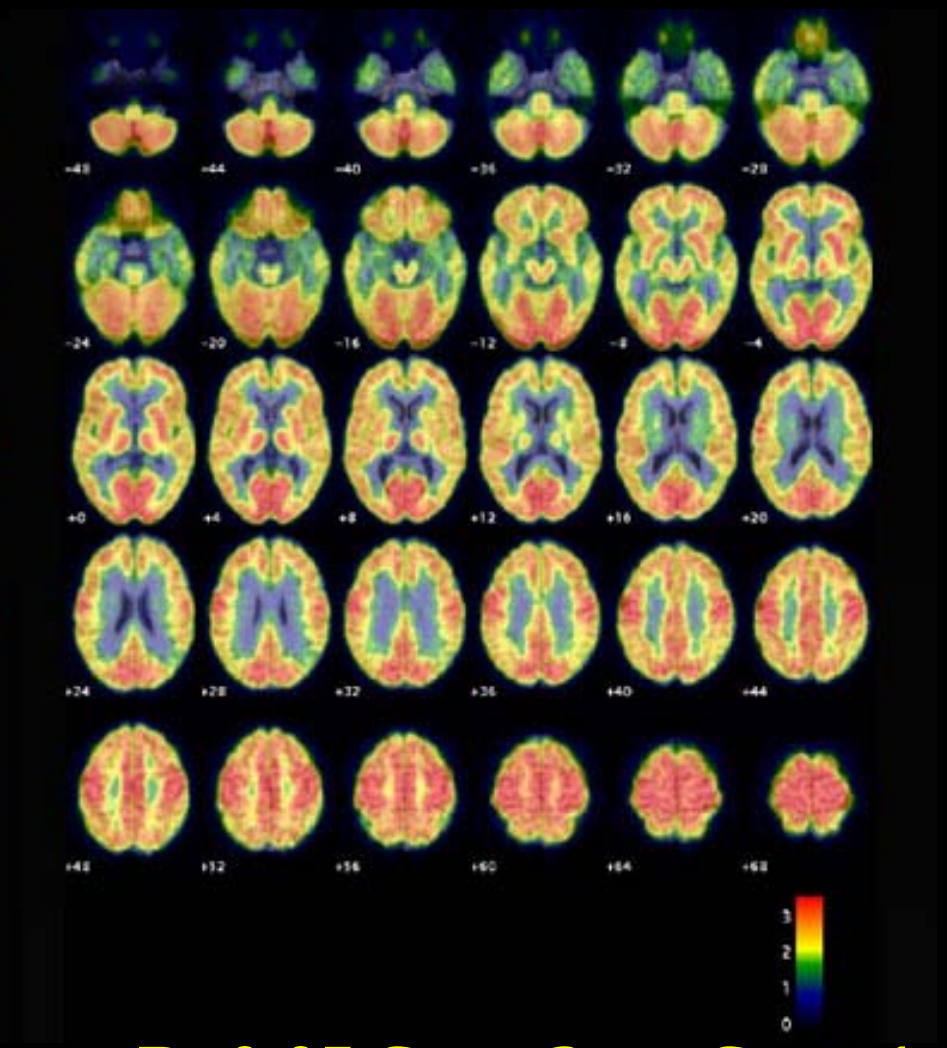
RESULTS

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





2-DG

P<0.05 Scan 2 vs. Scan 1

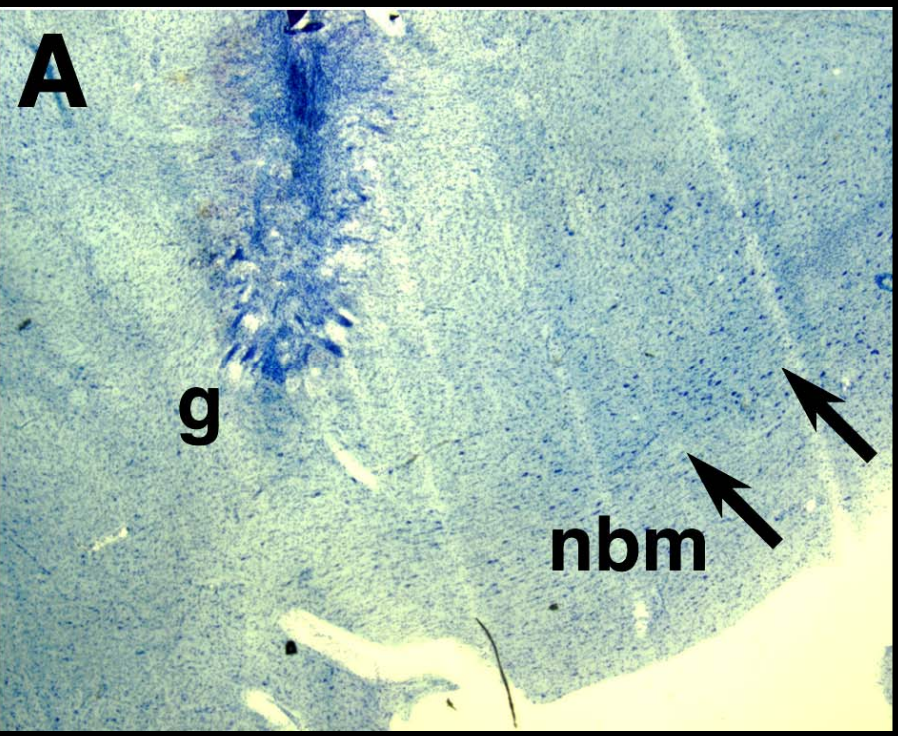
CONCLUSIONS:

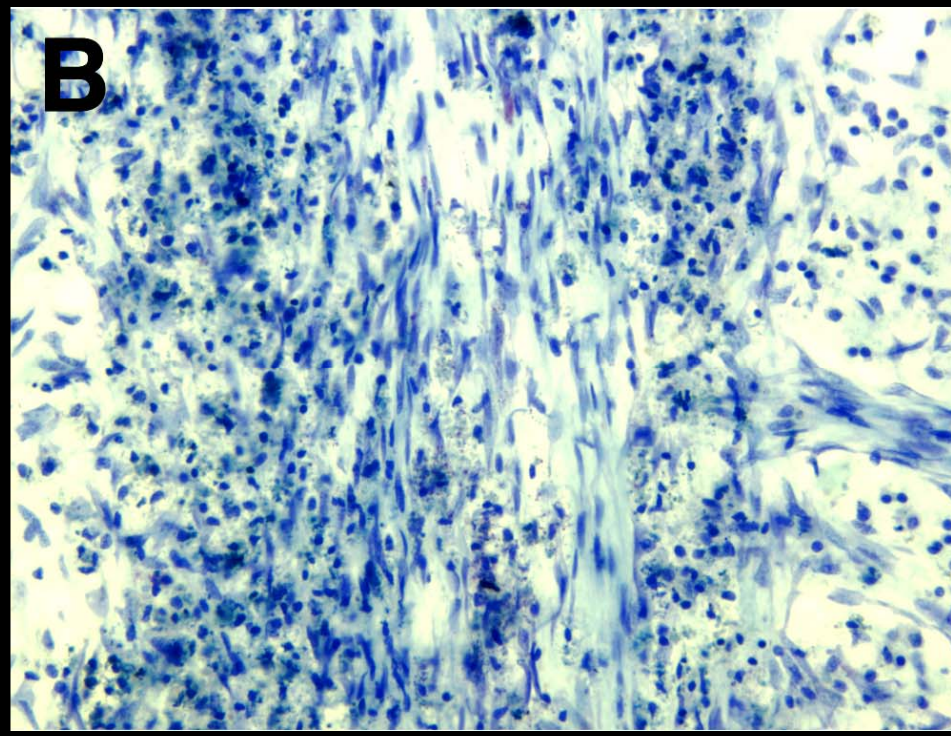
Phase I Trial of Ex Vivo Gene Therapy for Alzheimer's Disease:

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

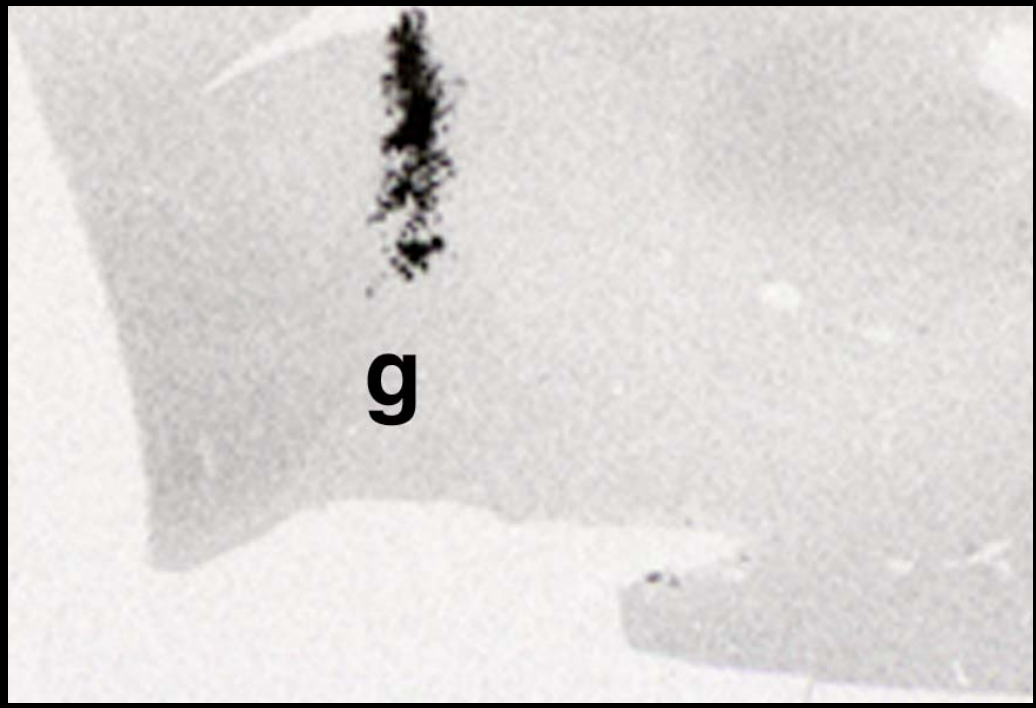
Phase I Trial of Ex Vivo Gene Therapy for Alzheimer's Disease:

AAV-NGF gene delivery for AD



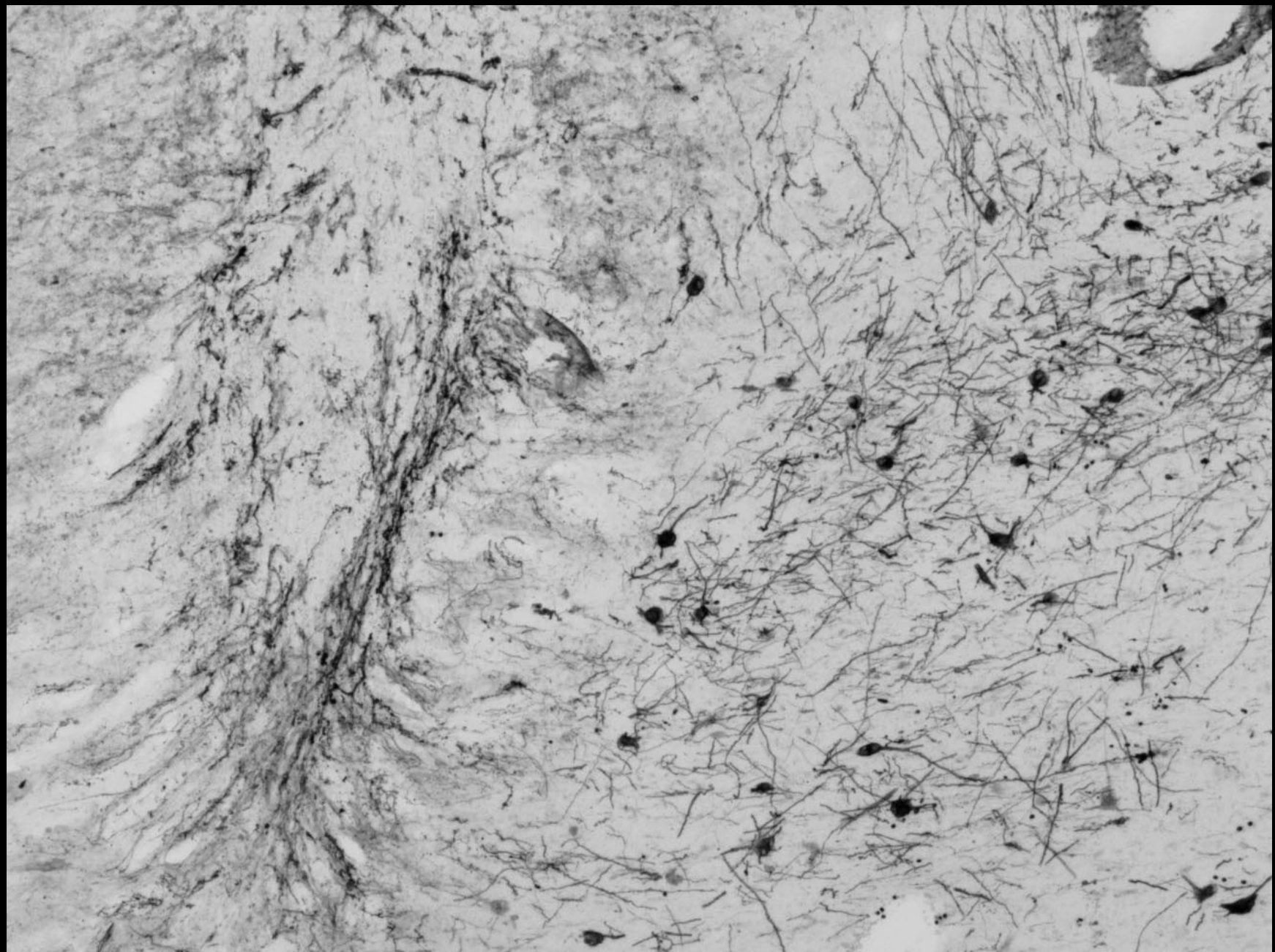


1. Genetically modified cells accurately located within brain
2. Cell survival and morphology consistent with previous non-human primate studies



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