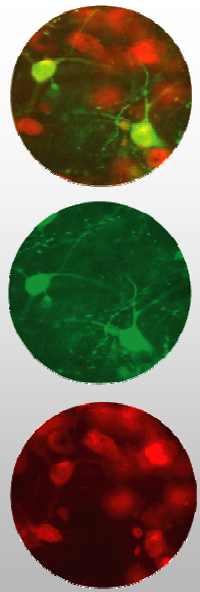


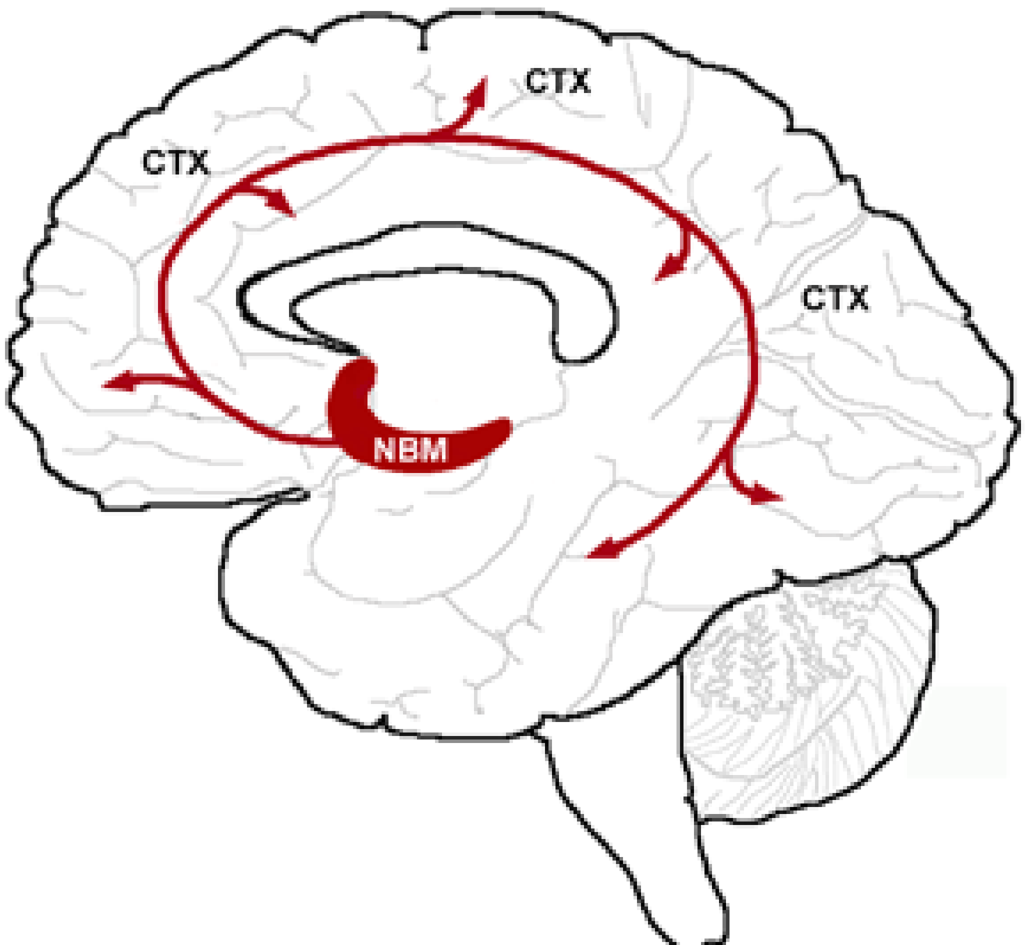
CERE-110 Nonclinical Studies

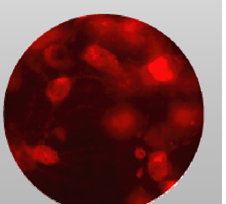
RAC Meeting

March 11, 2004

Raymond T. Bartus, Ph.D.
Vice President, Research & Development

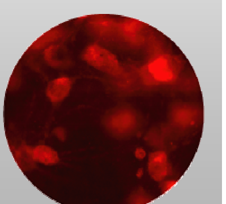
Basal Forebrain (Nucleus Basalis of Meynert) Cholinergic Degeneration and Alzheimer's Disease



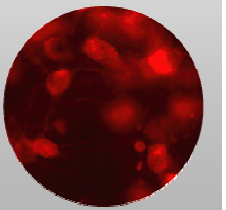


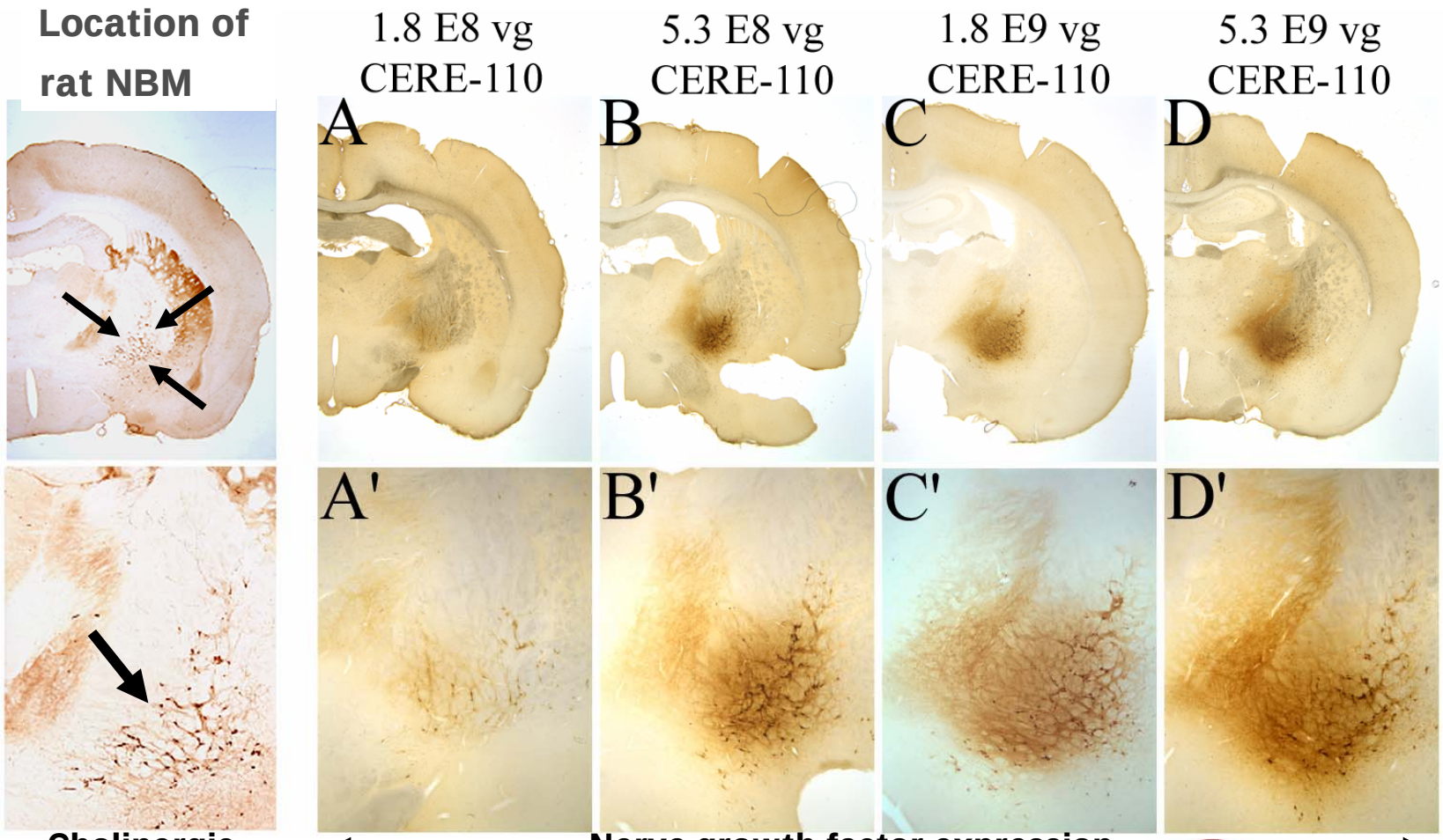
Overview of nonclinical studies with CERE-110

- **Expression of NGF delivered by CERE-110**
  - Orderly dose relationship
  - Restriction of NGF to targeted regions
  - Persistence of expression
- **Efficacy of NGF delivered by CERE-110**
  - Two conventional rat models of NGF bioactivity
  - Confirmed NGF bioactivity in non-human primate
- **Safety of CERE-110**
  - Multiple nonclinical safety/toxicology/biodistribution studies

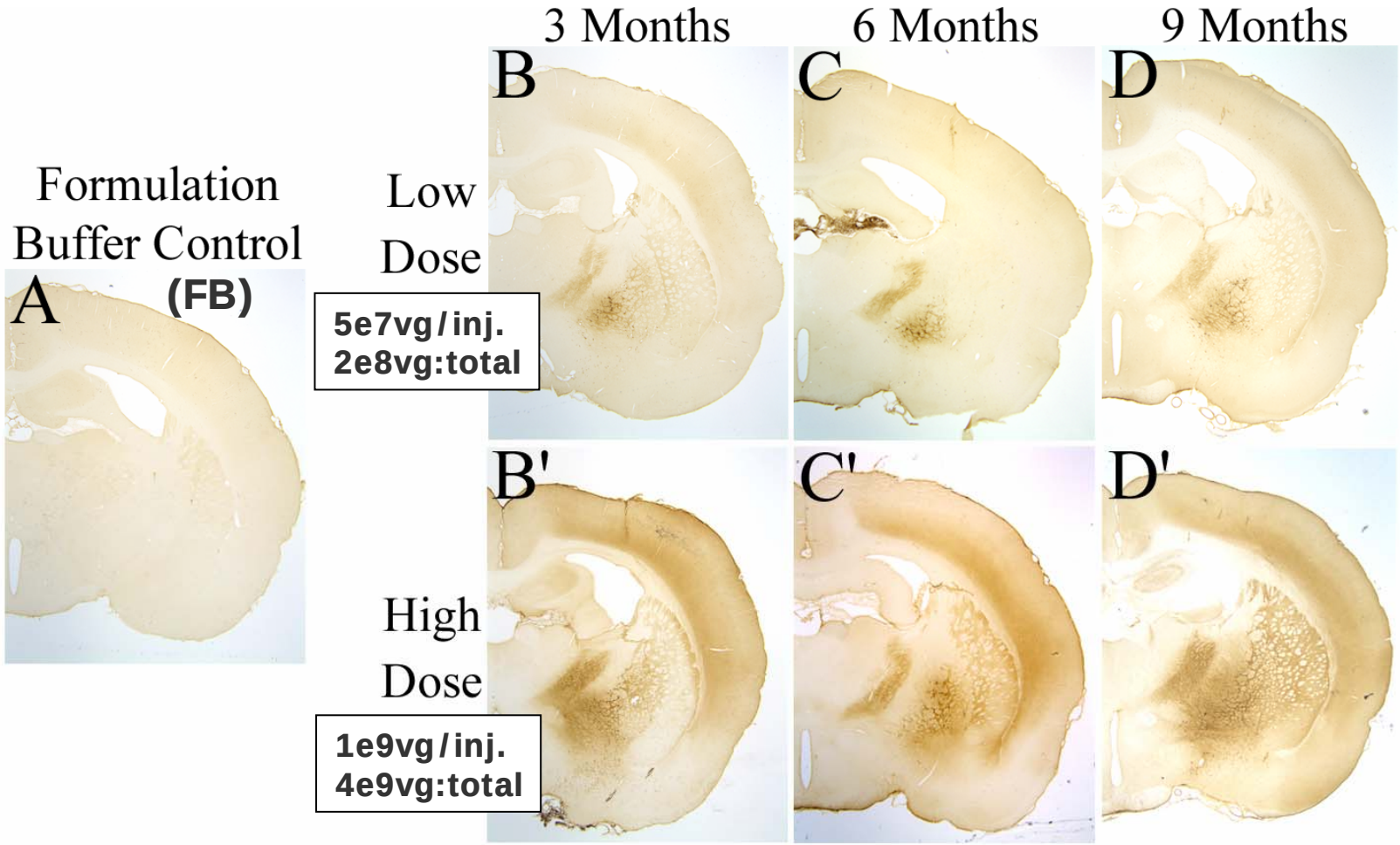


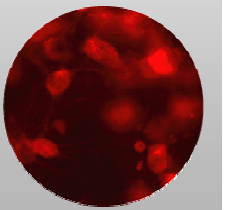
Orderly dose effect of CERE-110 on NGF expression





Persistence of NGF expression at 3, 6 and 9 months following CERE-110 delivery to the NBM





[additional data: persistent expression up to 12mos.]

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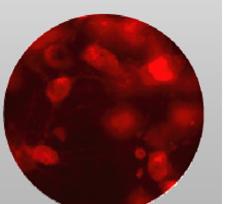
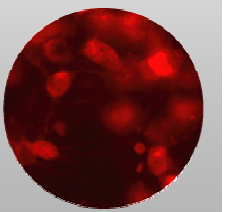
Safety/Toxicity Dose Multiples (compared on basis of relative brain weight)

	Human Dose A	Human Dose B
Rat Toxicology Studies (High Dose)	375 X lower	75 X lower
Monkey Toxicology Study (High Dose)	263 X lower	53 X lower

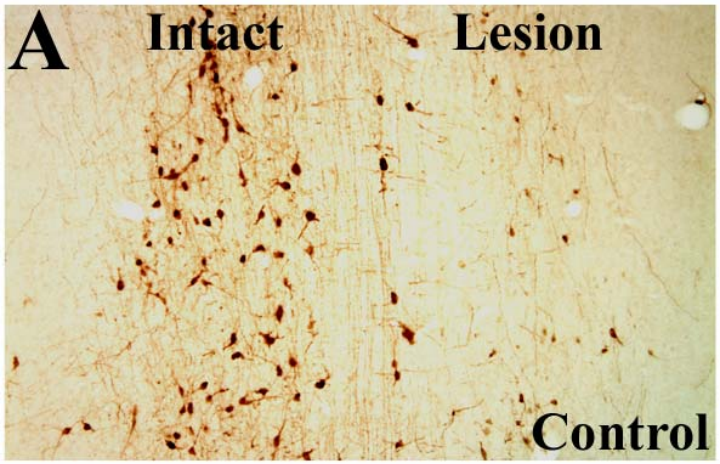


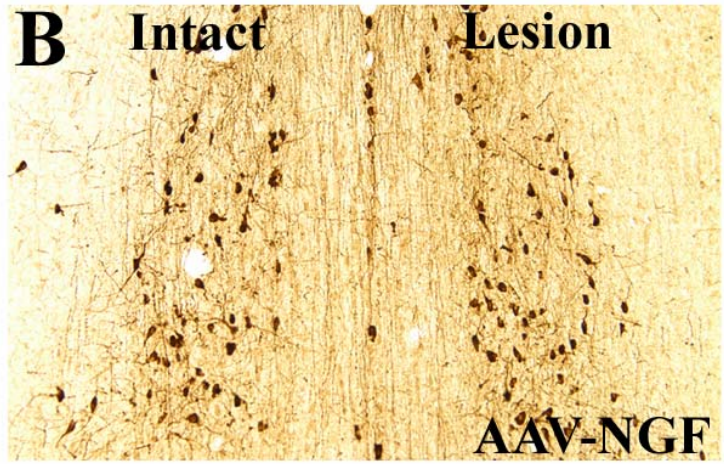
Rat Efficacy Studies

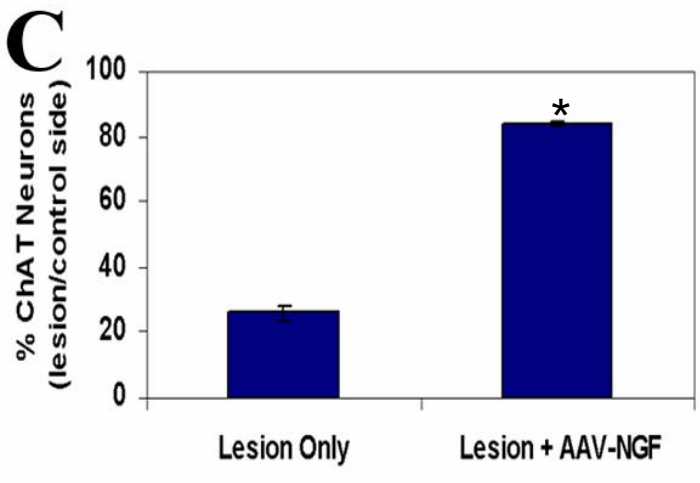
- Protection against cell death: Rat fimbria fornix transection model
  - "Gold standard" for testing in vivo activity of NGF and treatments to protect cholinergic neurons
- Improvement in neuronal vitality: Aged rat model of cholinergic degeneration
  - Exploits spontaneous degeneration of same cholinergic neurons we are targeting in Alzheimer's disease

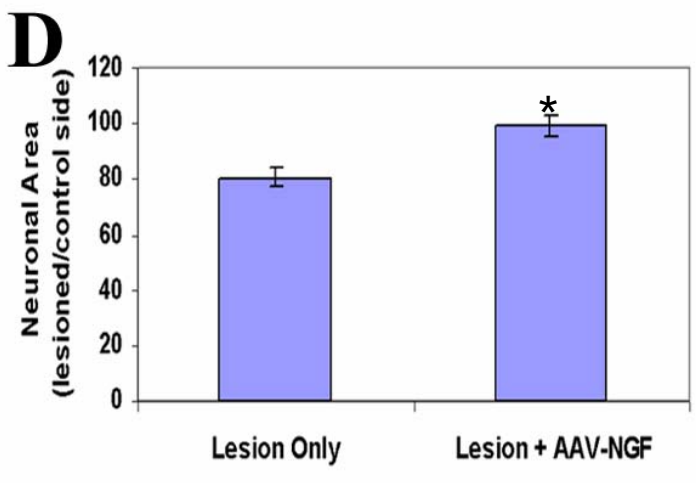


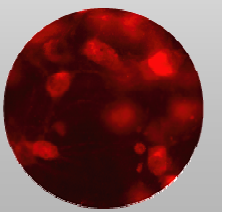
Neuroprotection of basal forebrain cholinergic neurons by AAV-NGF











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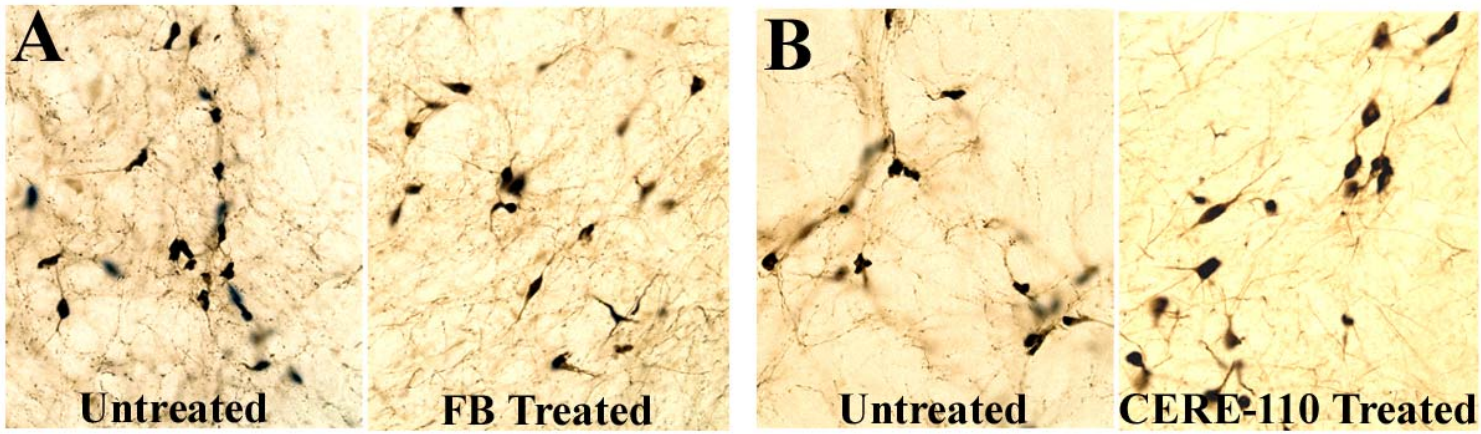
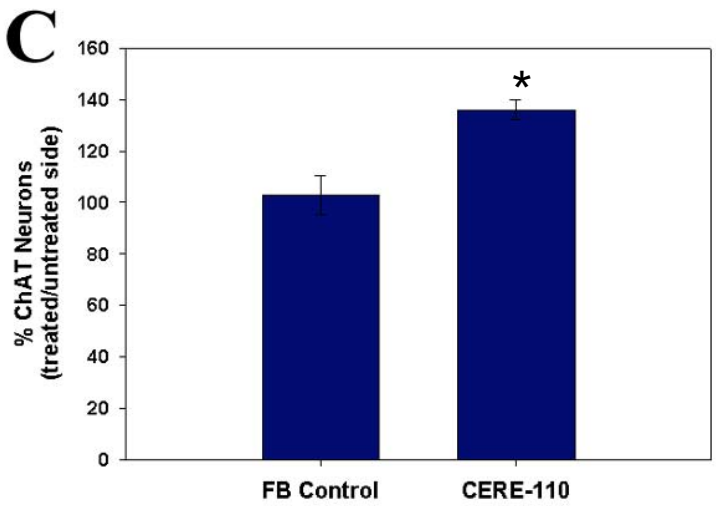
Restorative effects of CERE-110 on basal forebrain cholinergic neurons in aged rats





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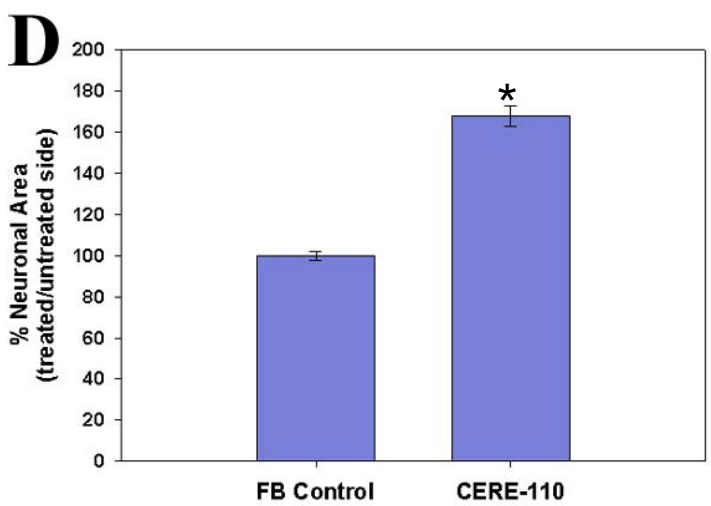

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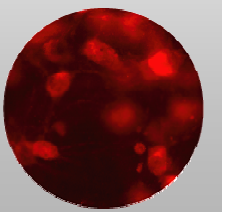

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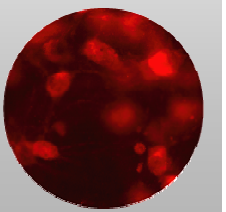
Nonclinical Safety/Toxicity Studies

Completed Studies:

- Rat Acute Toxicity & Biodistribution Study (CR-0302)
  - 2 doses: 3, 28, & 90 day time points
- Rat Long-term Expression & Neurotoxicity Study (CR-0301)
  - 2 doses: 3 & 6 month time points; in life 11 mos.
- Monkey Toxicity Study (CR-0304)
  - 3 doses: 3 month time point
- Aged Rat Efficacy/Toxicity Study (CR-0305)
  - 1 dose: 3 month time point

Ongoing Studies (to support future PhII trial):

- 9 & 12 Month Rat Long-term Expression/Neurotoxicity
- 1-year Monkey Toxicity Study (CR-0401)



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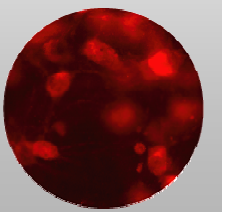
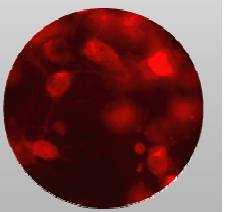
CERE-110 Biodistribution in Rats by Q-PCR (DNA)

- **Brain & CSF Samples**
  - All brain samples positive in a dose and time-dependent manner at 3, 28 & 90 days
  - ~95% of vector limited to injection site; >99% in brain
  - CSF: very low levels, in minority of rats, at high dose (only)
- **Non-target Organs & Fluids**
  - Extremely low levels (non-quantifiable) in spleen & cervical lymph nodes in minority of rats at high dose (only)
  - No distribution to gonads
  - All other tissues & fluids negative



Systemic Toxicity: Rats and Monkeys

- **Hematology & Serum Chemistry**
  - No clinically significant abnormalities up to 3 months in young rats, aged rats, and young monkeys
- **Organ Histopathology**
  - No abnormalities up to 3 months in young rats and monkeys
- **Immune Responses Human NGF or AAV2**
  - None detected in monkeys at 3 months
  - Weak (anti-human NGF) or moderate (anti-AAV2) in high dose rats only at 3, 6 and 9 months



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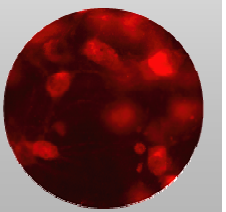
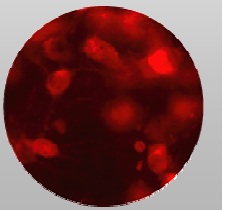
Neurological Toxicity

- **Brain Histopathology**
  - No abnormalities detected up to 6 months in young rats
  - None at 3 months in aged rats & young monkeys
- **Brain Inflammatory/Immune Markers (GFAP, CD45, CD68/ED1)**
  - No reactions detected up to 6 months in young rats
  - None at 3 months in aged rats & young monkeys
- **No Overt Neurological Effects**
  - Normal neurological exams up to 3 months in monkeys
  - Normal 'Functional Observation Battery' (FOB) up to 9 months in rats



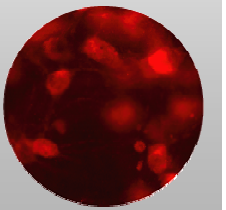
NGF-Related Side Effects

- No NGF detected in CSF
- No Weight Loss
- No Schwann Cell Hyperplasia or Axon Sprouting
- No Evidence of Pain



Summary: CERE-110 Nonclinical Safety/Tox Studies

- **No systemic toxicities**
- **No neurological toxicities**
- **No NGF-related side effects**
- **CERE-110 biodistribution primarily limited to brain with majority in brain limited to injection site**
- **Immune responses to human NGF or AAV2**
  - None in monkeys
  - Weak to moderate in high dose rats



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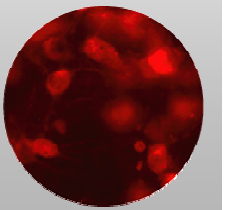
Overall Synopsis: CERE-110 Nonclinical Findings

- Dose-related NGF expression, persisting for 12 months (and likely beyond)
- Clear evidence of NGF bioactivity in cholinergic neurons
  - classic NGF neuroanatomical changes, including enhanced cell viability in two standard rodent models
- Confirmation of NGF bioactivity in primates
- Clean safety/tox profile (rats and primates)



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