

# AAV-hAADC-2 for Parkinson's disease

A Phase 1 Open-label Safety Study of Intrastratial  
Infusion of Adeno-Associated Virus Encoding Human  
Aromatic L-Amino Acid Decarboxylase (AAV-hAADC-2)  
in Subjects with Advanced Parkinson's Disease  
[AAV-hAADC-2-003]

# Program Team

- **UCSF**

- **Principal Investigator:** Michael J. Aminoff, M.D., D. Sci.
- **Neurosurgeon:** Philip Starr, M.D., Ph.D.
- **Scientific Advisor:** Krys Bankiewicz, M.D., Ph.D.

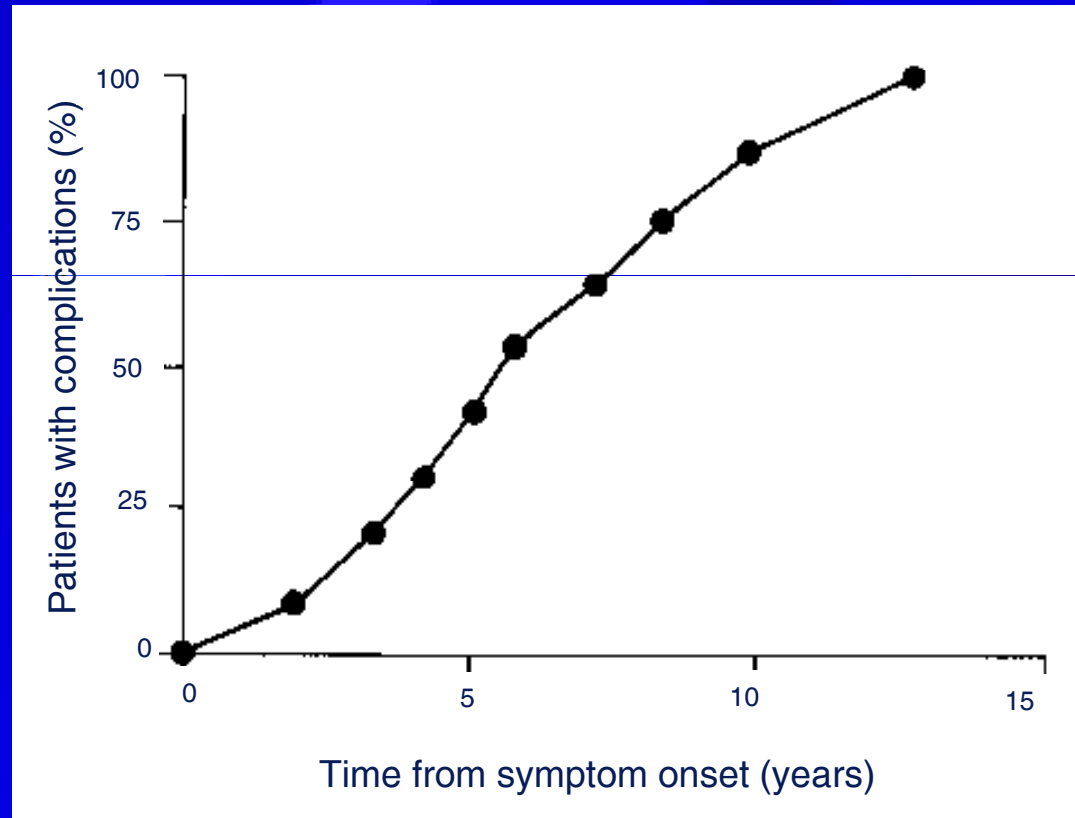
- **Lawrence Berkeley National Laboratory**

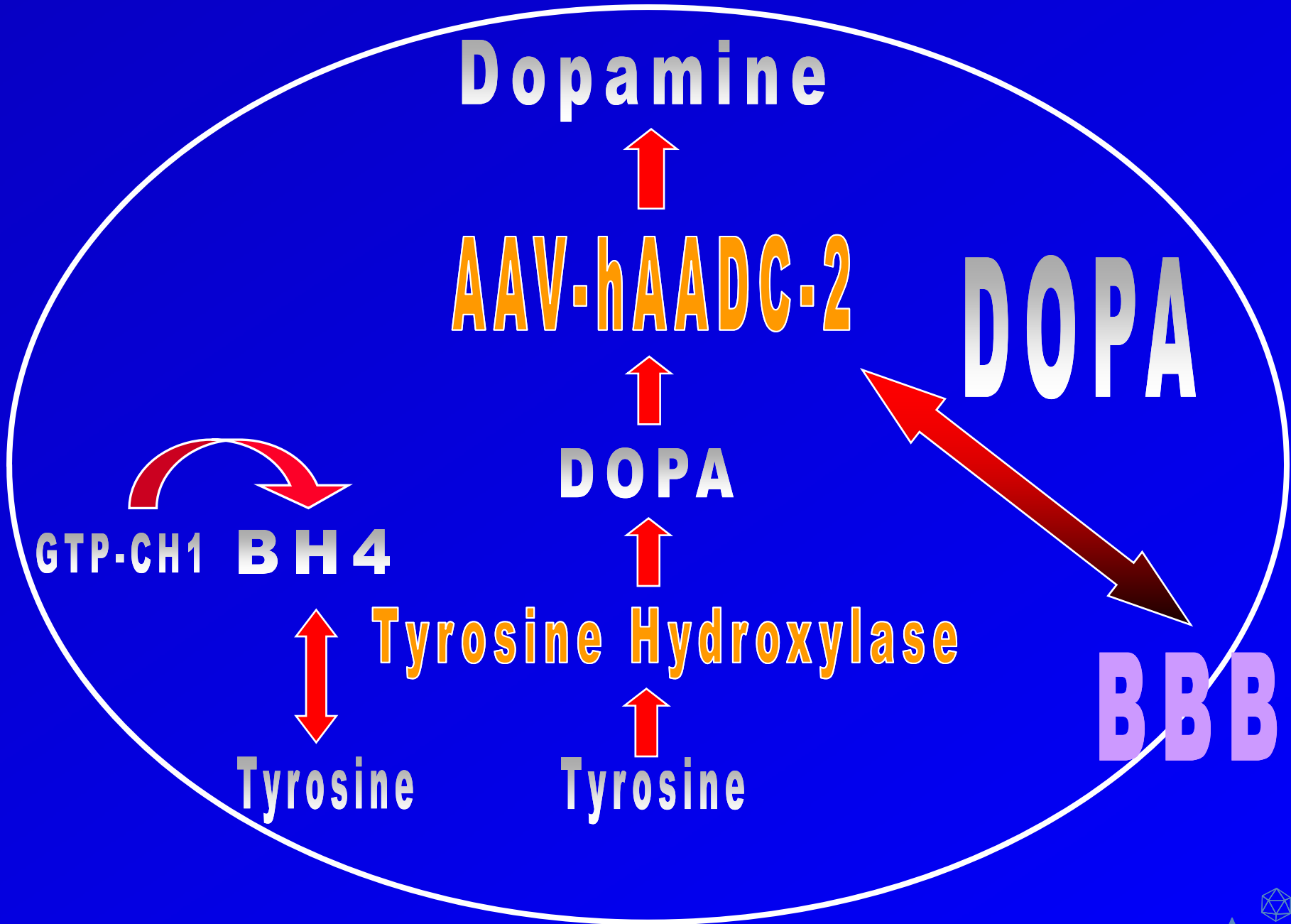
- **Neuroimaging:** Henry F. VanBrocklin, Ph.D.

- **Corporate Sponsor**

- Avigen, Inc.

# Complications of Levodopa Therapy in PD Patients





# Benefits of AADC Replacement

- Levodopa can enter the brain
- Unlike in rodents, in primates AADC limits levodopa to dopamine (DA) conversion
- Patients with early PD respond well to levodopa
- Patients with advanced PD do not respond well to levodopa
- Therapeutic window closes with progression of the disease
- Levels of striatal dopamine can be regulated by levodopa dosing
- Known mechanism: AADC transgene product is a “pro-drug”

# AAV-AADC Gene Transfer Safety in Preclinical Models

- **Striatal neurons express novel gene (AADC)**
  - D2 receptor expression evaluated by PET
  - Adverse effects evaluated by acute and chronic administration of levodopa
- **Unregulated extracellular dopamine, reduced DA storage, uptake and transport**
  - Dopamine serves as a local DA receptor agonist
- **Axonal transport of AADC**
  - No evidence of significant transport into cortex
  - Subcortical transport into areas affected by PD

A 3D blue cube is centered on a solid blue background. The cube is rendered with a slight perspective, showing its top, front-left, and front-right faces. The text 'Preclinical Data' is written in a bold, yellow, sans-serif font across the center of the front face of the cube.

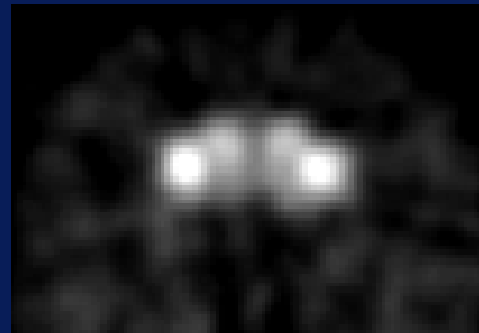
**Preclinical Data**

# Depletion of AADC in Parkinsonian NHPs

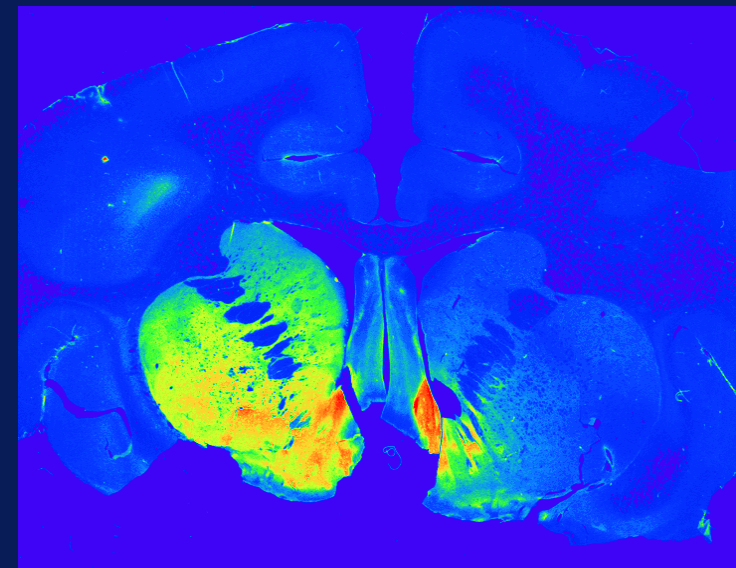
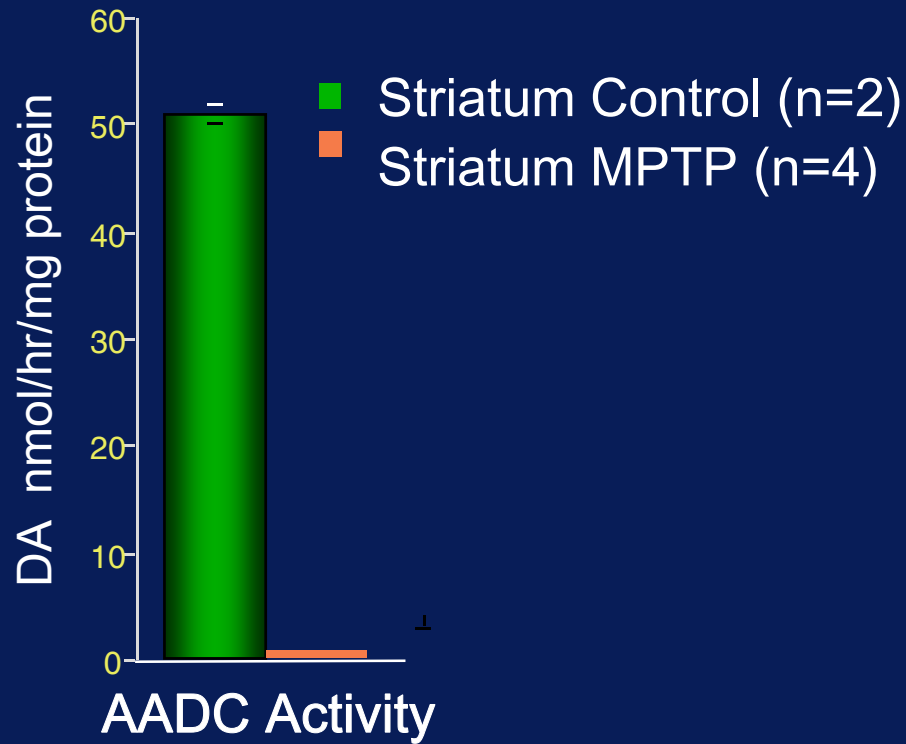
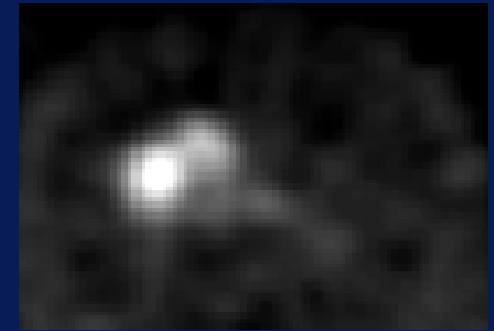
MRI



Normal - PET



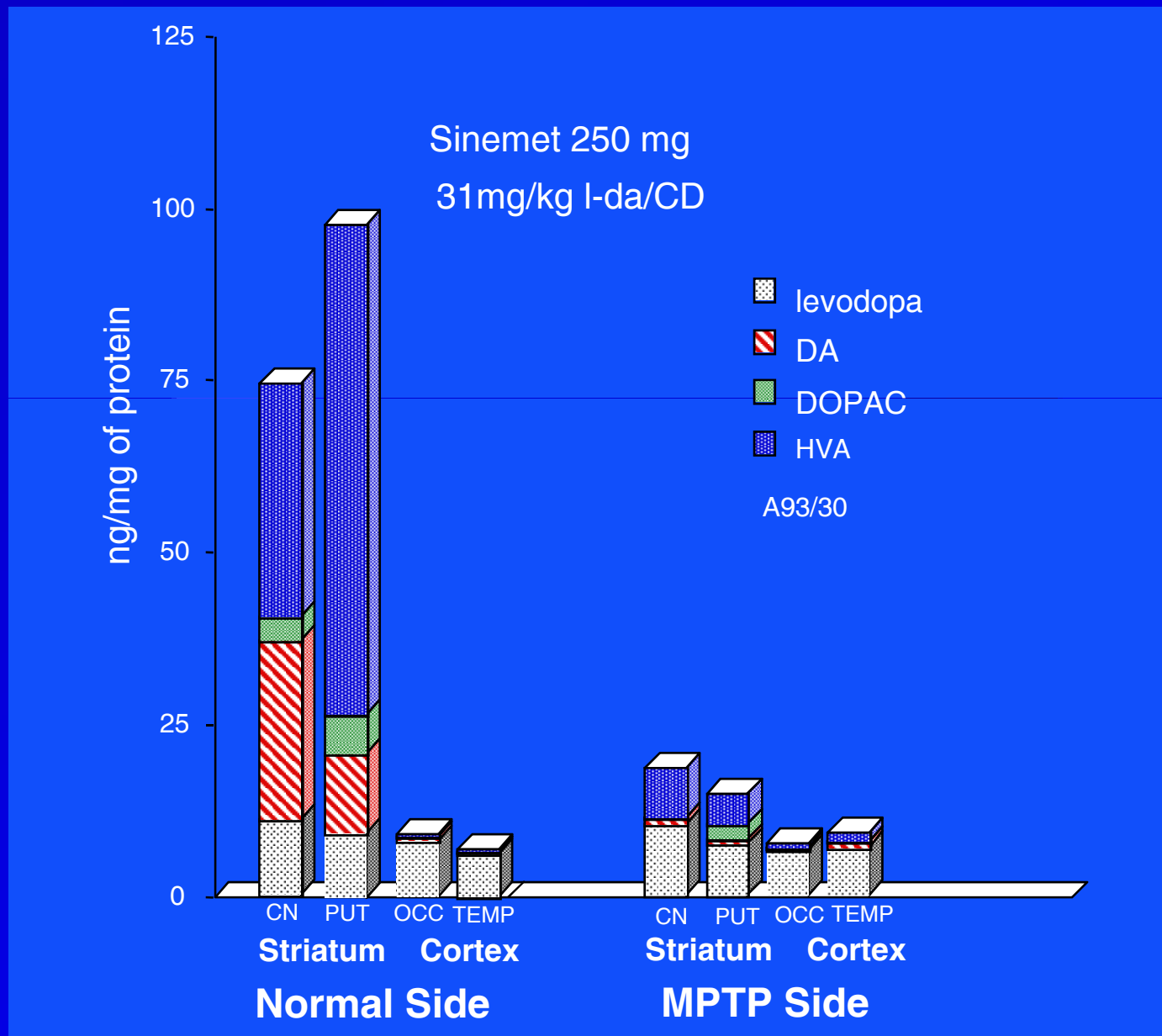
Hemi-PD - PET



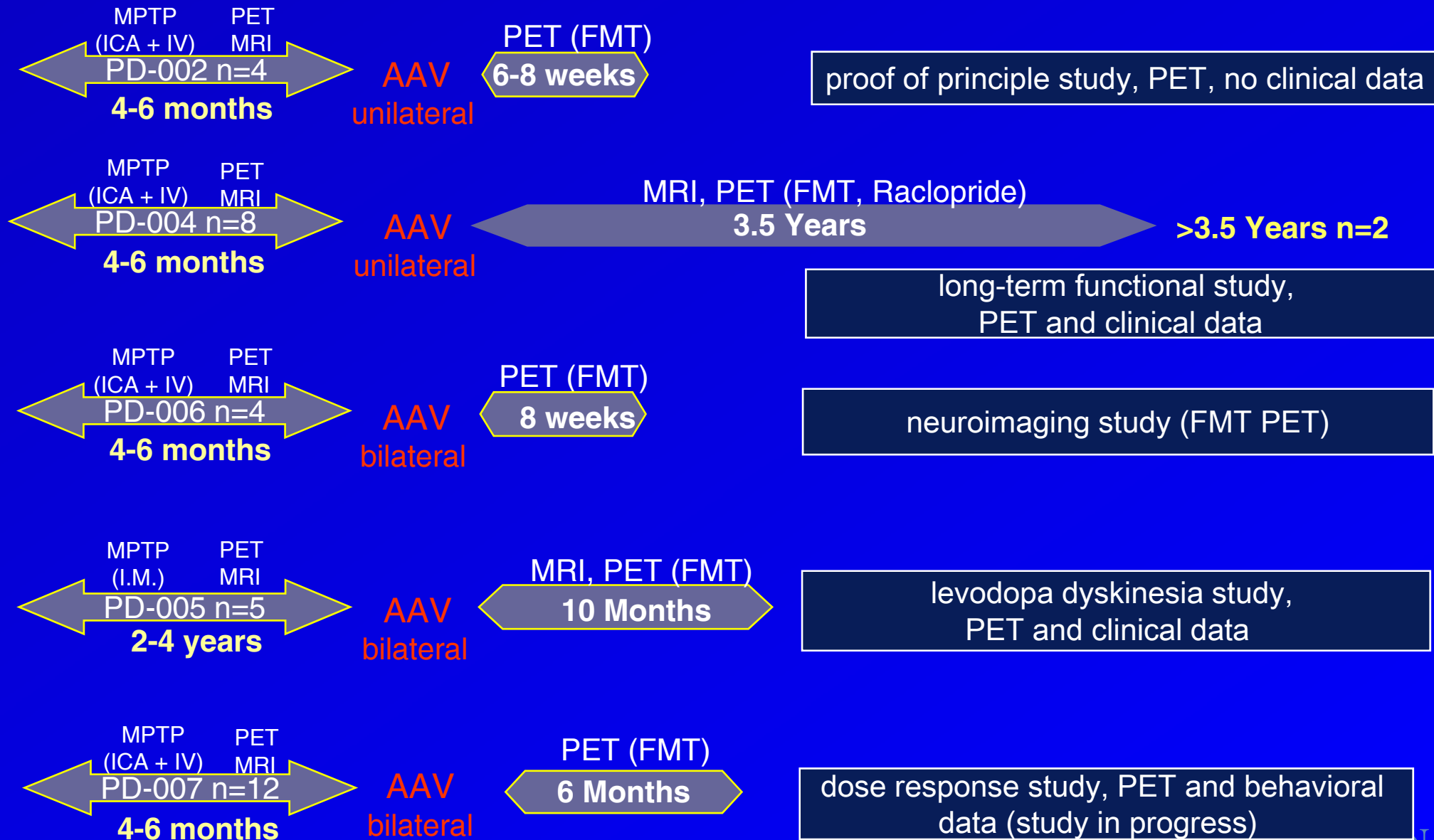
AADC immunoreactivity



# Poor Decarboxylation of Levodopa in PD NHPs

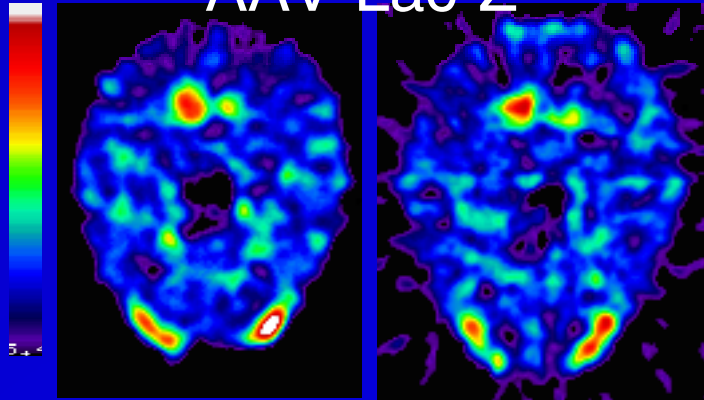


# Studies in PD Non-Human Primates



# AAV-AADC Restores AADC Activity in PD NHP (Study PD-002)

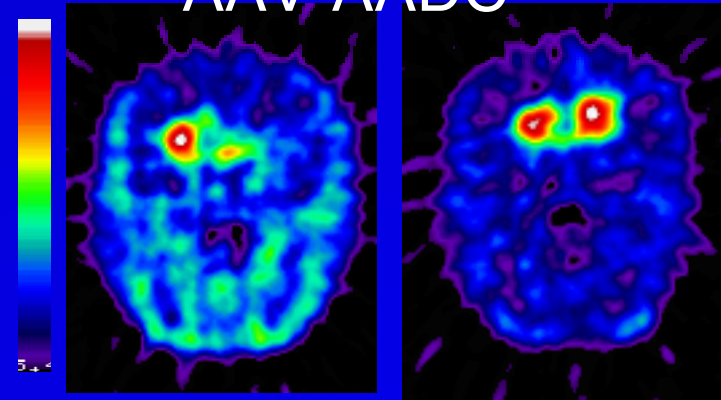
AAV-Lac-Z



pre

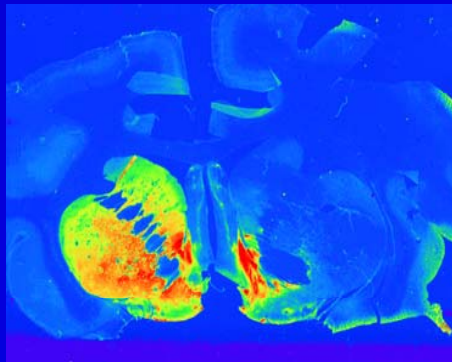
post

AAV-AADC

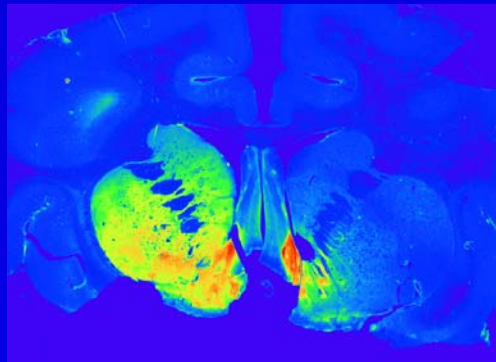


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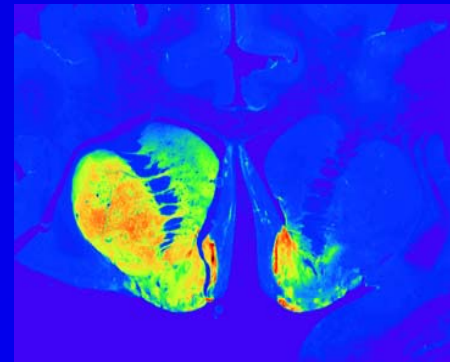
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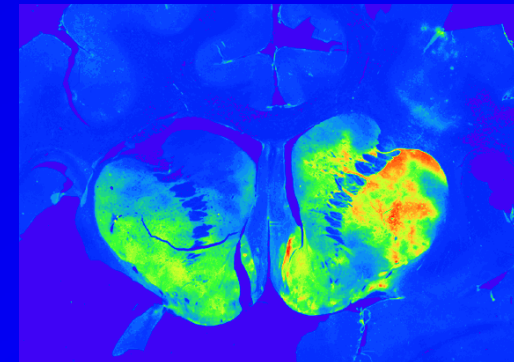
anti-TH



anti-AADC



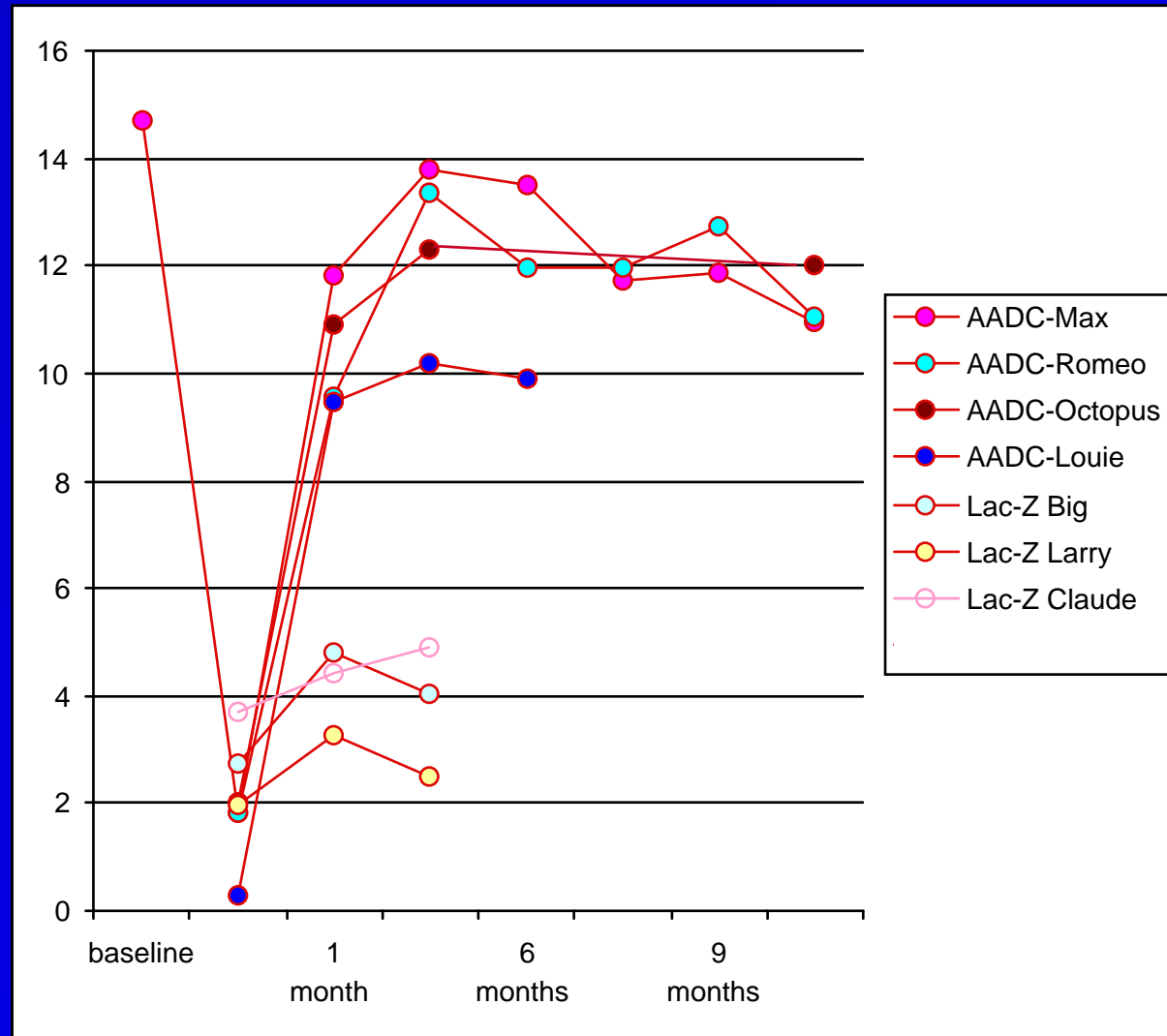
anti-TH



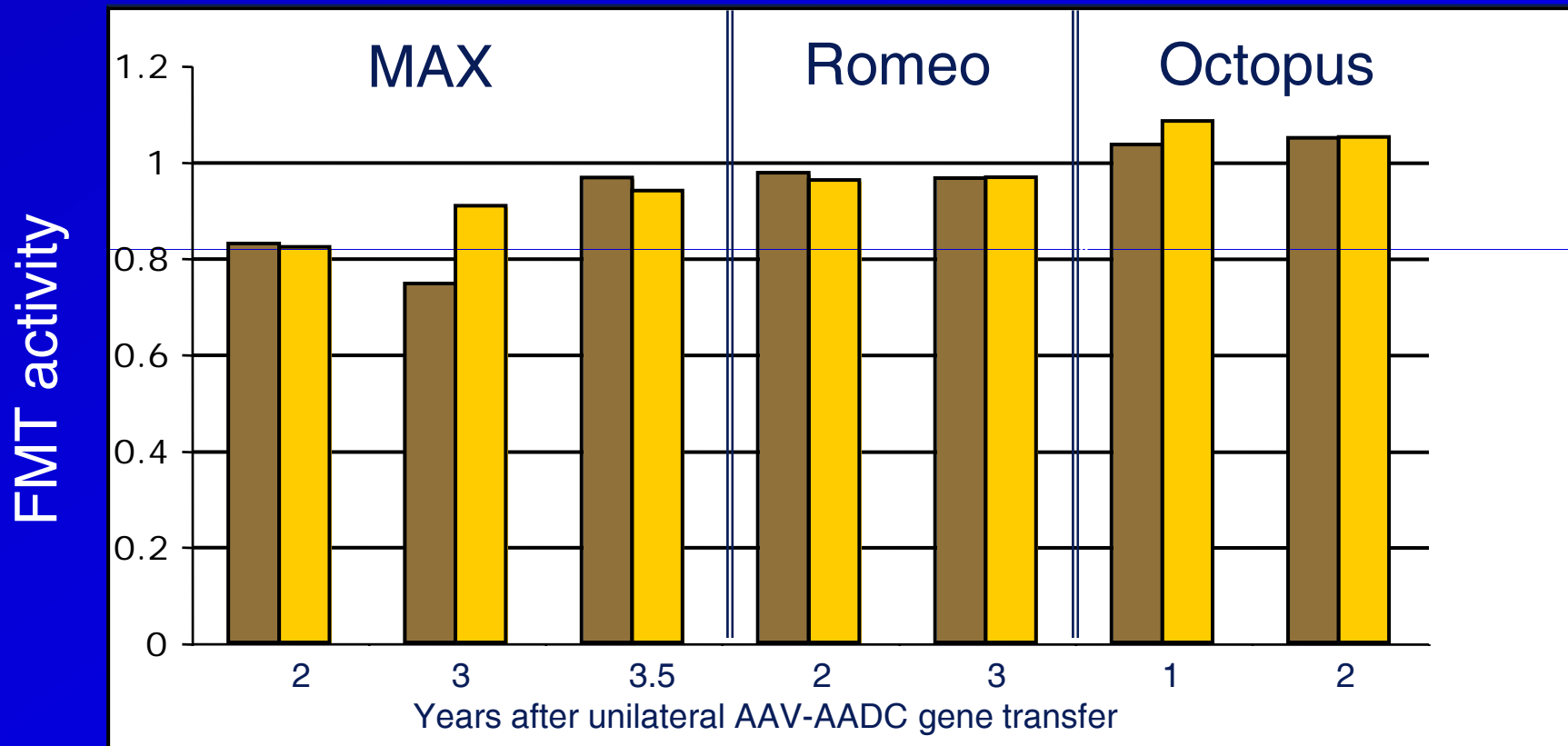
anti-AADC

# PET Following AAV-AADC Gene Transfer in MPTP-NHP (Ki values) (PD-004)

Ki



# No Evidence of Cortical AADC Activity by PET



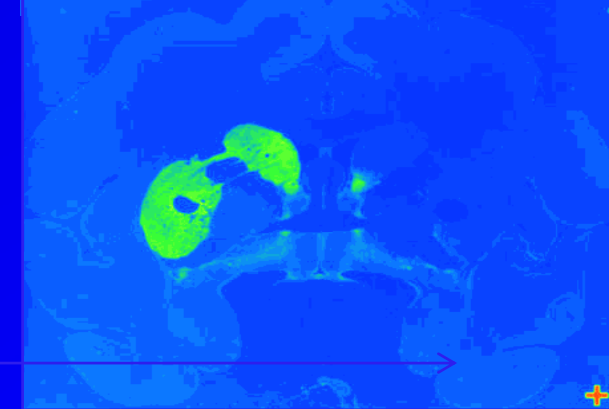
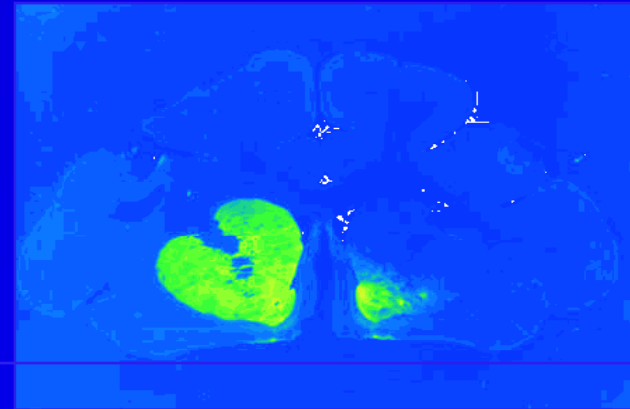
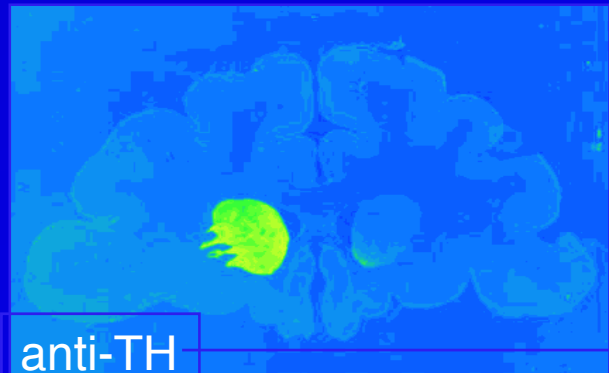
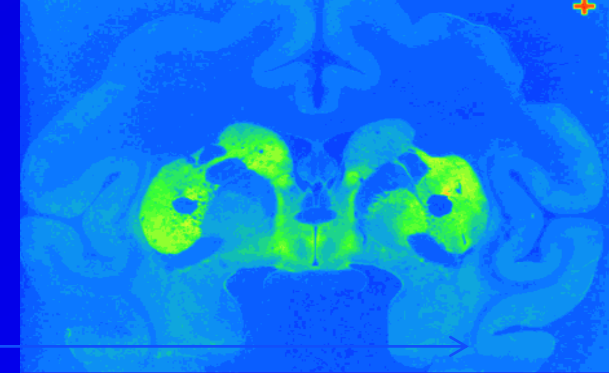
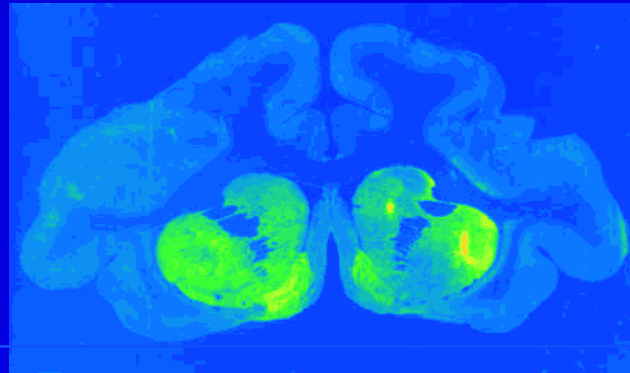
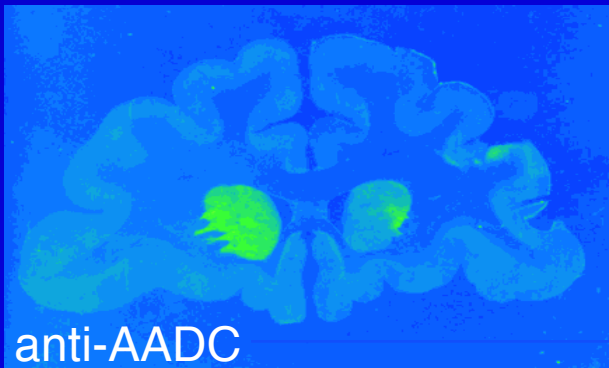
- left front/cortex
- right front/cortex + Striatal AADC

# FMT PET and Post-mortem Analysis after 3.5 Years

anterior

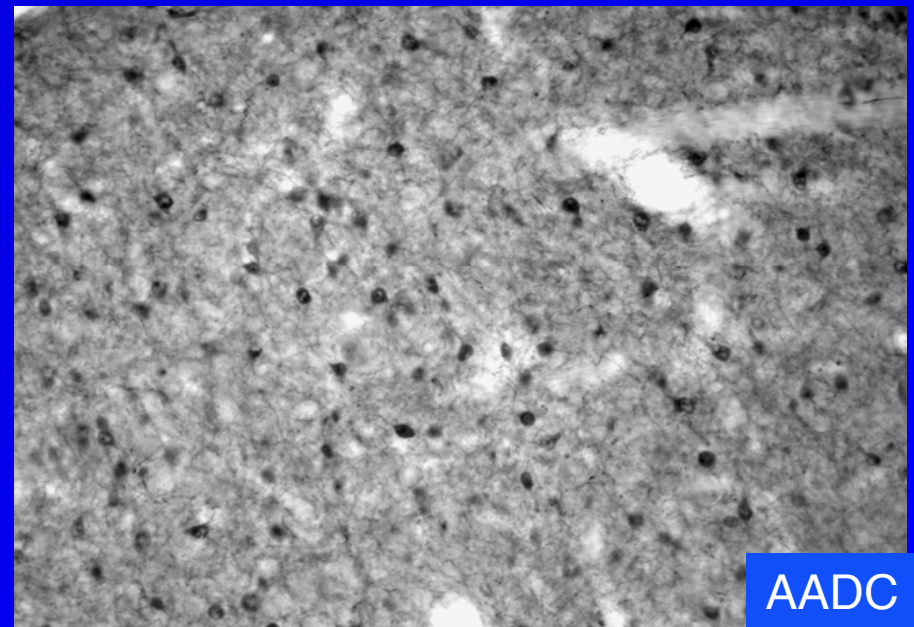
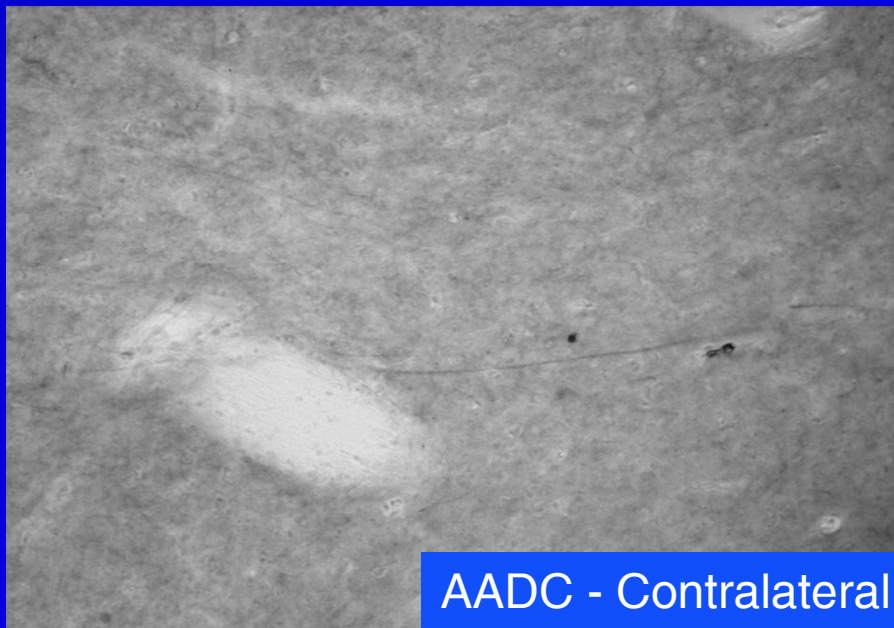
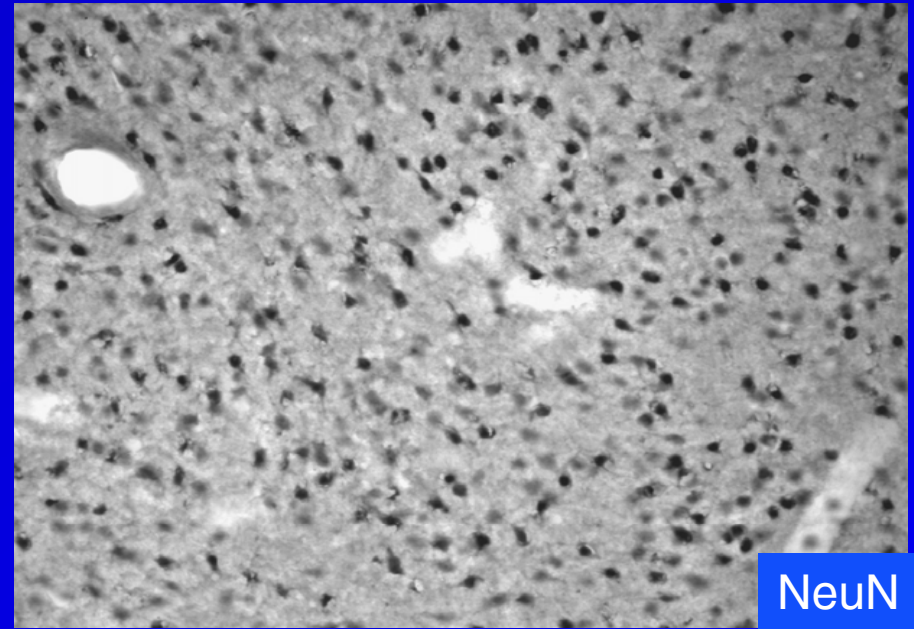
mid-striatum

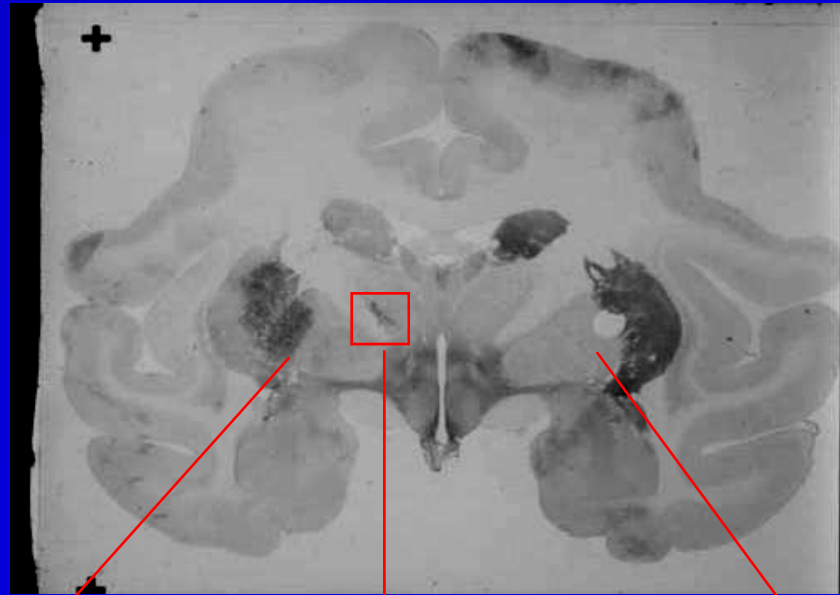
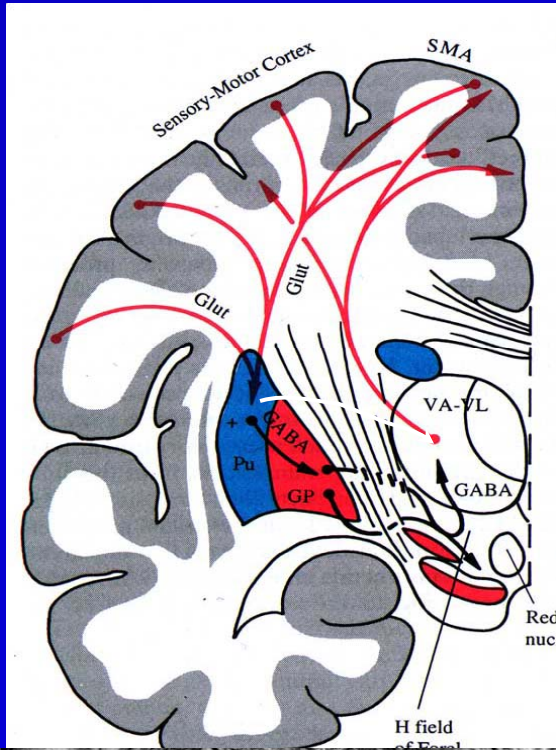
posterior



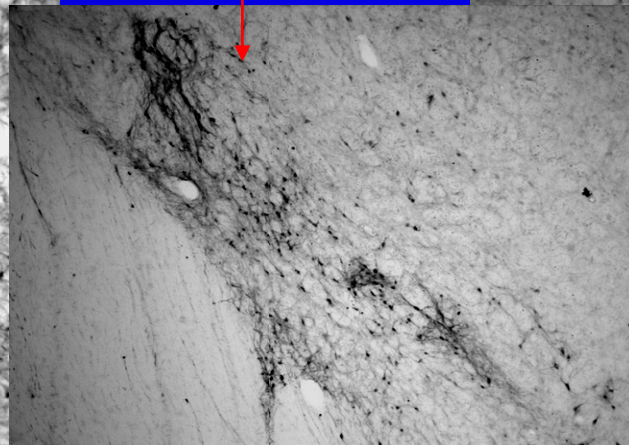
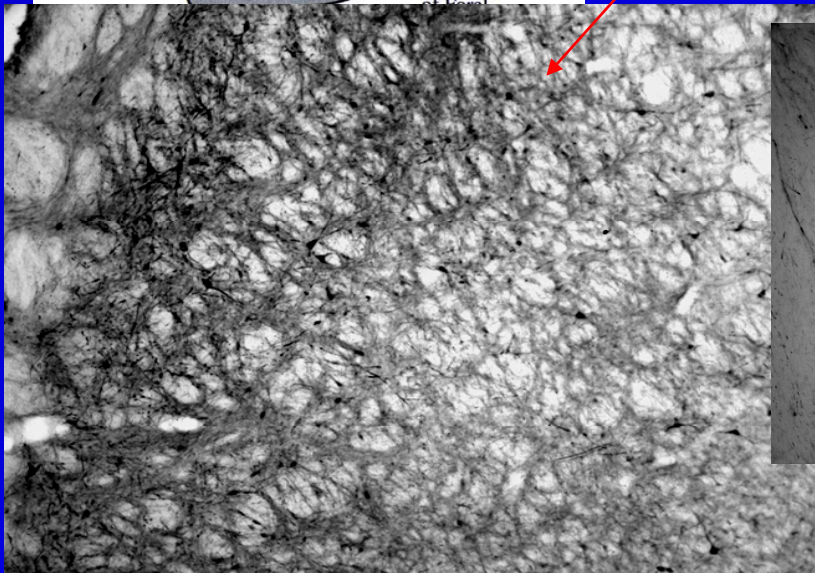


# Detection of AADC in the Putamen of PD NHP 3.5 Years after Gene Transfer



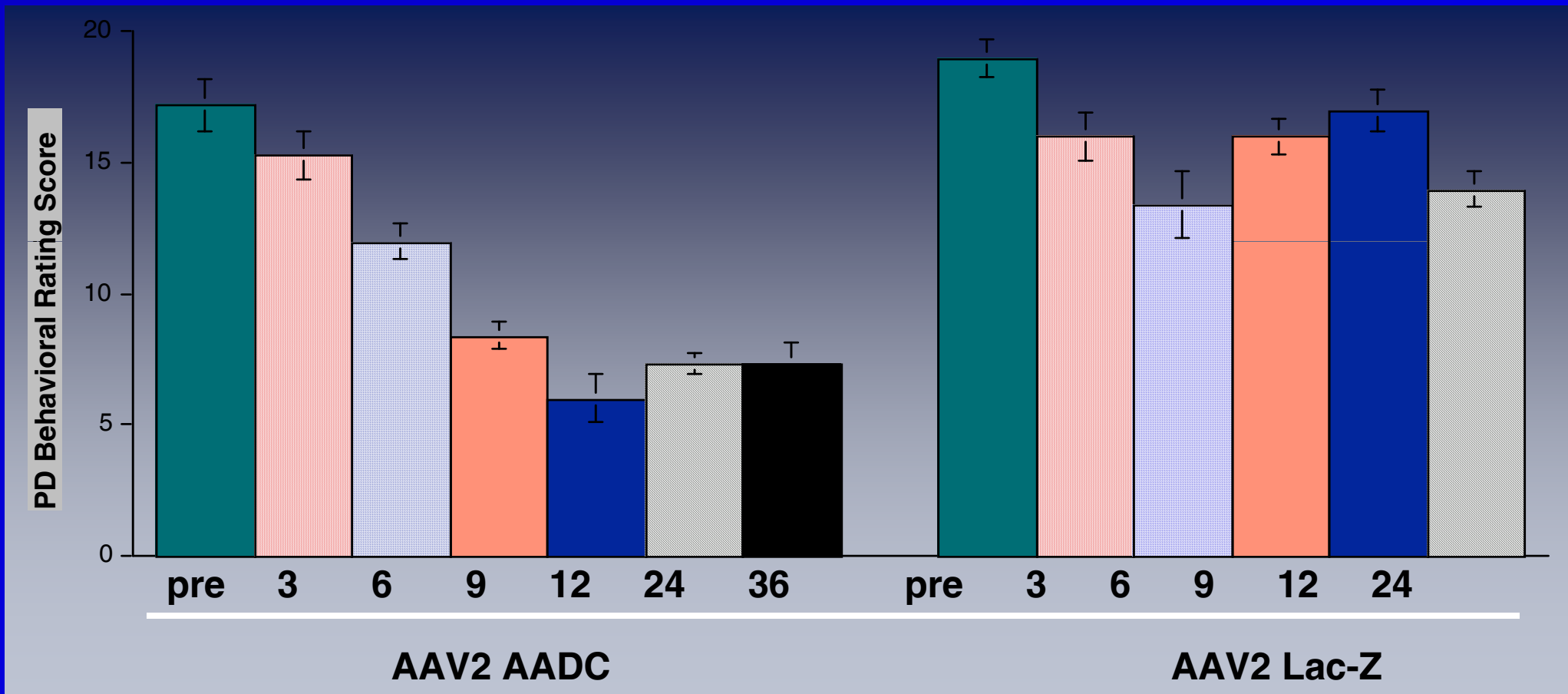


# AADC in Projection Sites from Striatum (3.5 years)



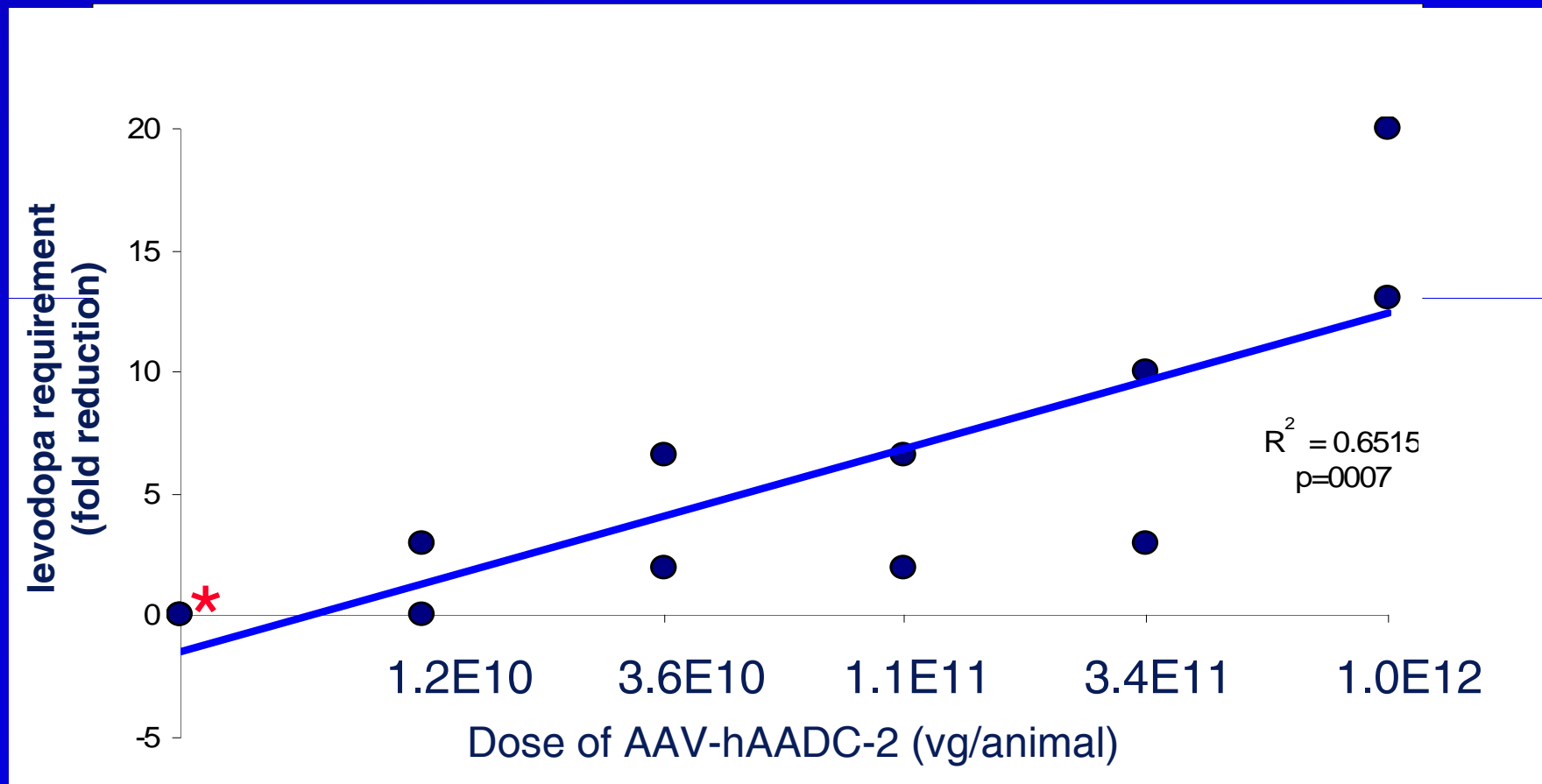


# Response to Sub-therapeutic Levodopa in PD NHP 36 Months After AAV-AADC Gene Transfer



levodopa 3 mg/kg IM.

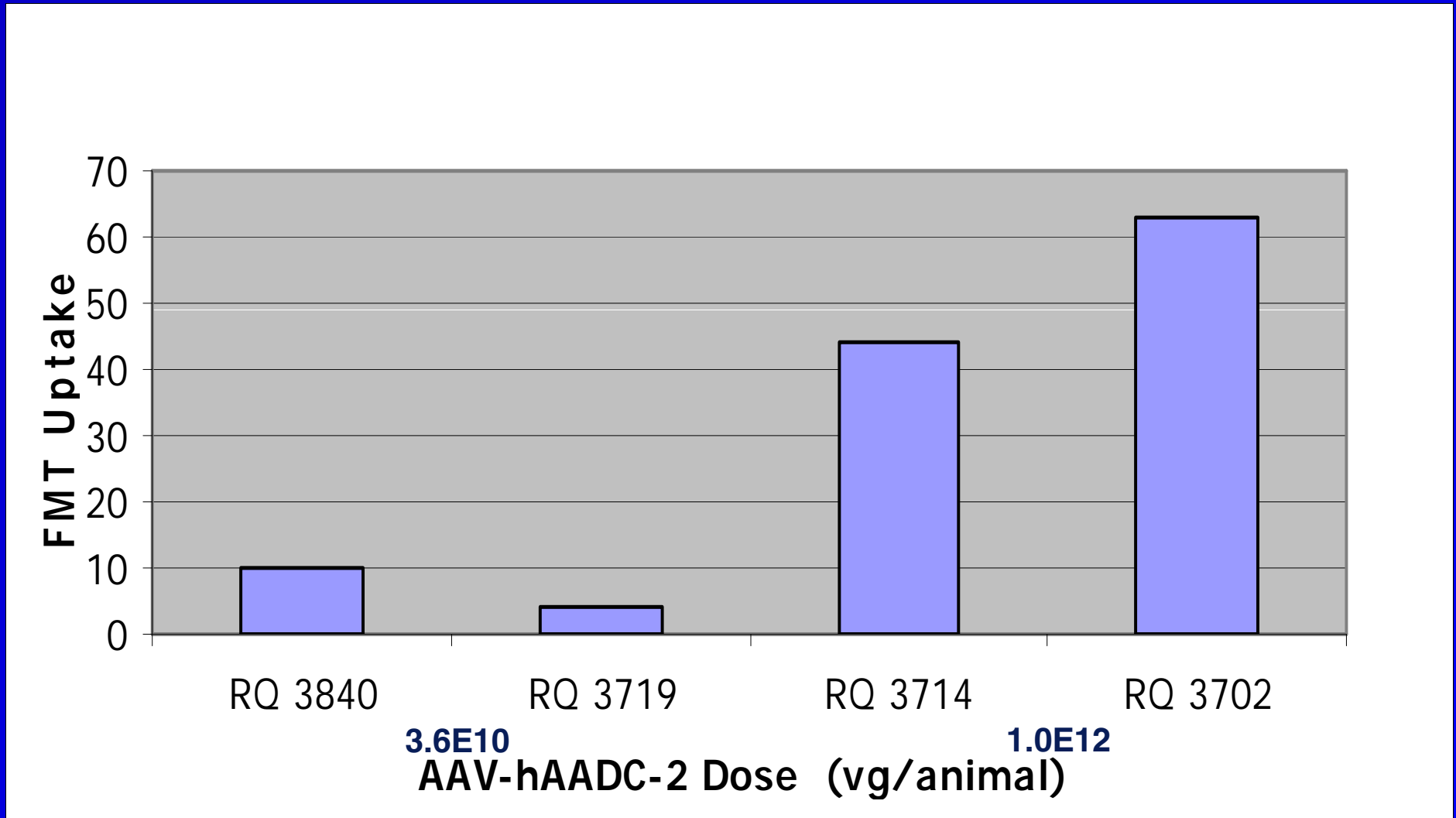
# Correlation Between Vector Dose and Reduction of Levodopa Required for Optimal Response



\*Control received 1.0E12 GFP

Study PD-007

# FMT PET Signal after Gene Transfer



Study PD-007

A 3D blue cube is centered on a solid blue background. The cube is rendered with a slight shadow and perspective. The text "Clinical Aspects" is written in a bold, yellow, sans-serif font across the front face of the cube.

# Clinical Aspects

# Advanced Parkinson's Disease

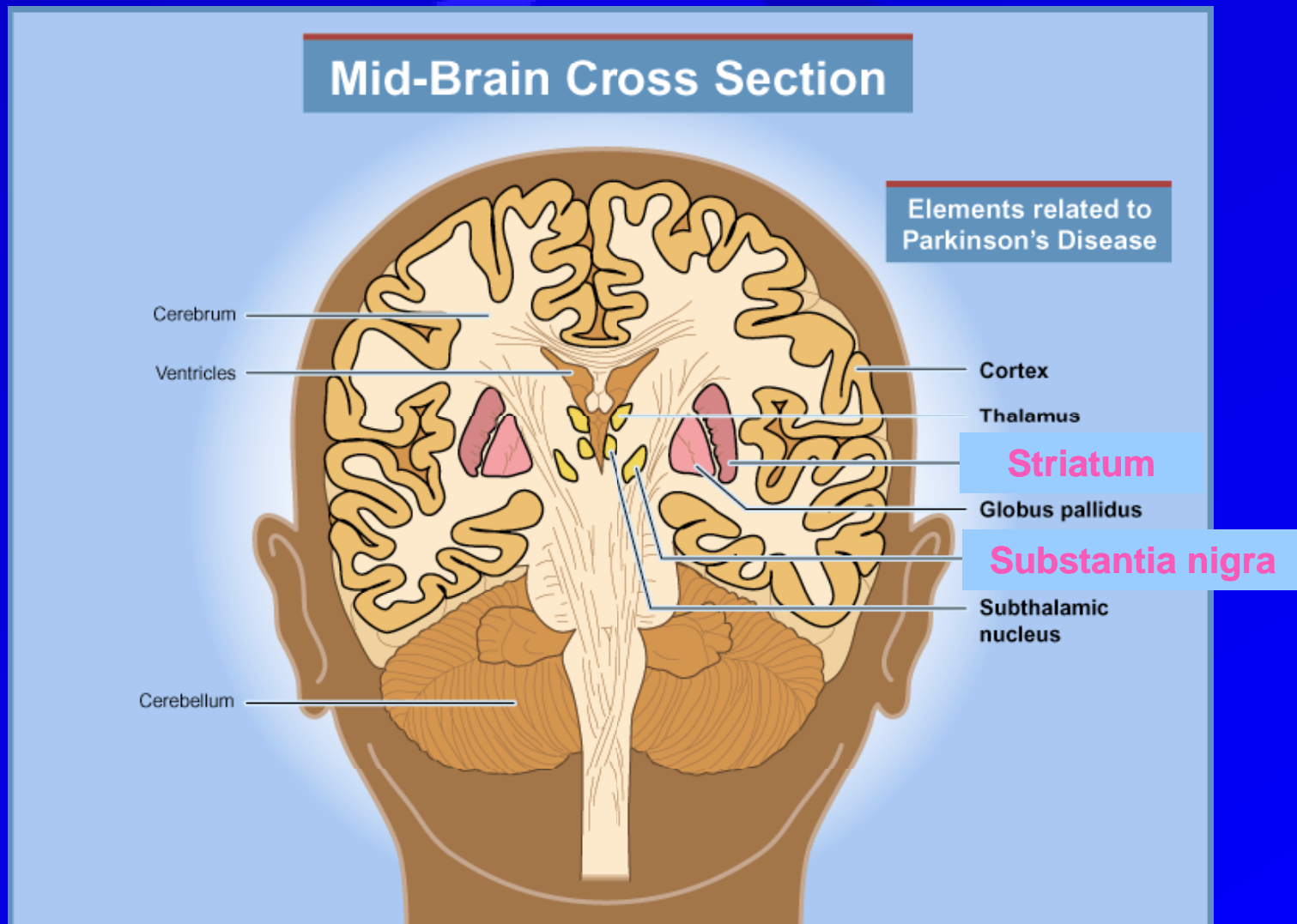
Age-related common neurodegenerative disorder resulting in a severe and profound loss of motor function and associated morbidity

## Major Symptoms

- **Tremor:** shaking of hands, feet and jaw
- **Rigidity:** resistance to movement
- **Bradykinesia:** slow movement
- **Postural Instability:** impaired balance and coordination
- **Dyskinesia:** side effect of levodopa therapy - involuntary uncontrollable movement

# Pathogenesis of PD

Degeneration of dopaminergic neurons projecting from the SN to the striatum results in a loss of striatal dopamine



# Current Treatments for PD

## Pharmacologic:

- **Replace dopamine (levodopa)**
- **Stimulate dopamine receptors (Dopamine receptor agonists)**
- **Block acetylcholine receptors (Amantadine)**
- **Enhance action of remaining dopamine (COMT and MAO-B inhibitors)**

# Current Treatments for PD (continued)

## Surgical:

- **Block output pathway (Pallidotomy; DBS)**
- **Deep Brain Stimulation (DBS):**
  - **Suppresses Parkinsonian symptoms in patients who have exhausted medical treatment**
  - **Intrinsically complex and expensive**
  - **Complication rate with hardware is high, requires multiple surgeries during patient lifetime**
  - **Average time to repeat operation 2-3 years**
  - **Expected survival post DBS 10-30 years**



# Parkinson's Disease

## *Patient Population*

- **Prevalence:** 1.2 million US, 1 million Europe
- **Incidence:** 50-60,000 new cases/year in the US
- **Demographic shift:** expect incidence to rise 2-4% per year over the next 30 years
- **Patient classes (Hoehn & Yahr)**
  - Mild to Moderate (I-III) 65%
  - Moderate to Severe (III-IV) 30%
  - End-stage (V) 5%

# Avigen's Gene Transfer for Advanced PD

- Direct bilateral infusion of AAV-hAADC-2 into striatum
- Manage subjects on levodopa therapy (dose adjustments if necessary)
- Safety assessments
- FMT PET analysis to assess expression
- UPDRS (Unified Parkinson's Disease Rating Scale) to evaluate safety and efficacy

# Clinical Study Design

- 9 -15 subjects, 3 dose groups; Advanced PD
- On levodopa but with variability in response
- Bilateral infusion:
  - 50  $\mu\text{L}/\text{site}$  x 2 sites/hemisphere
  - 200  $\mu\text{L}/\text{patient}$
- Starting dose
  - $2.5 \times 10^{11}$  vg/subject (pending confirmation from study #PD-007)
- Safety Assessments at 0.5, 1, 2, 3 & 6 months
  - UPDRS
  - Levodopa intake 9 -15 subjects, 3 dose groups; Advanced PD
- PET Scan

## Inclusion Criteria

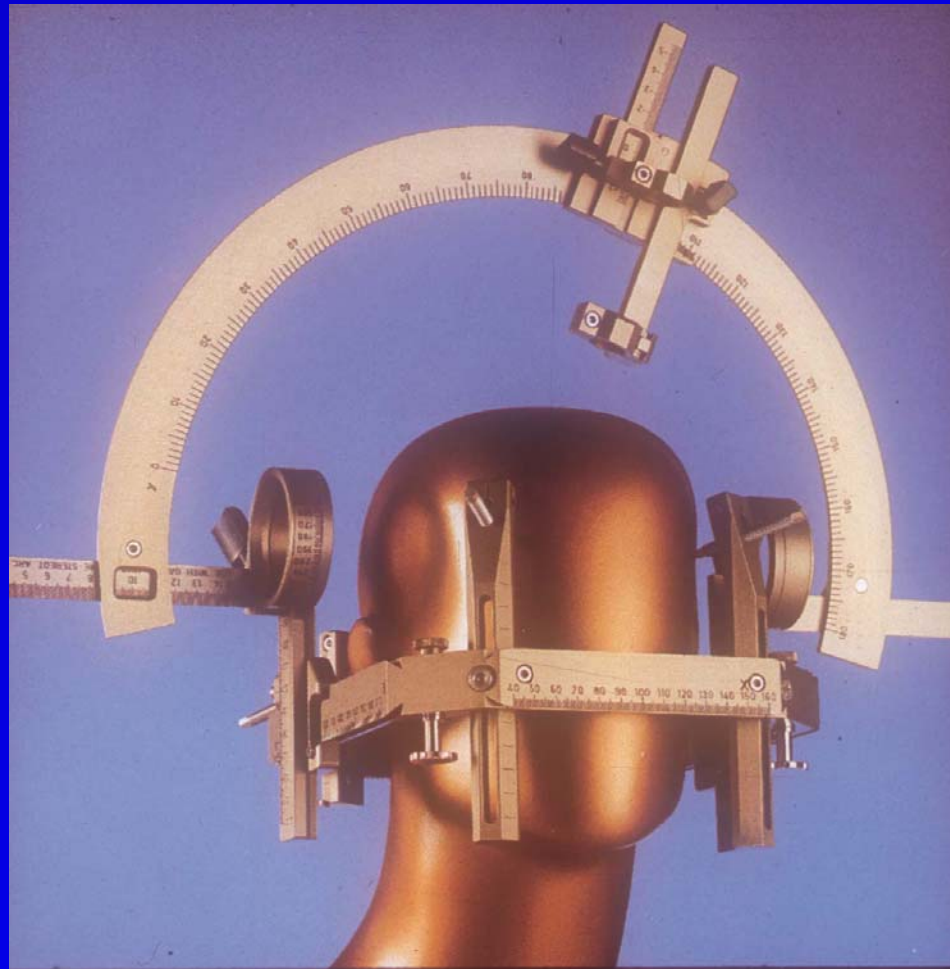
- Moderate to severe PD symptoms by Hoehn and Yahr staging (stage III to IV off medication at entry)
- Duration of levodopa therapy > 5 years
- Age at diagnosis >40
- Candidate for surgical intervention for Parkinson's disease because of intractable motor fluctuations not responsive to optimal medical therapy

## Exclusion Criteria

- Atypical PD
- Previous neurosurgery
- Dementia
- Significant co-morbidity
- Significant anti-AAV titer at screen

# Surgical Procedure

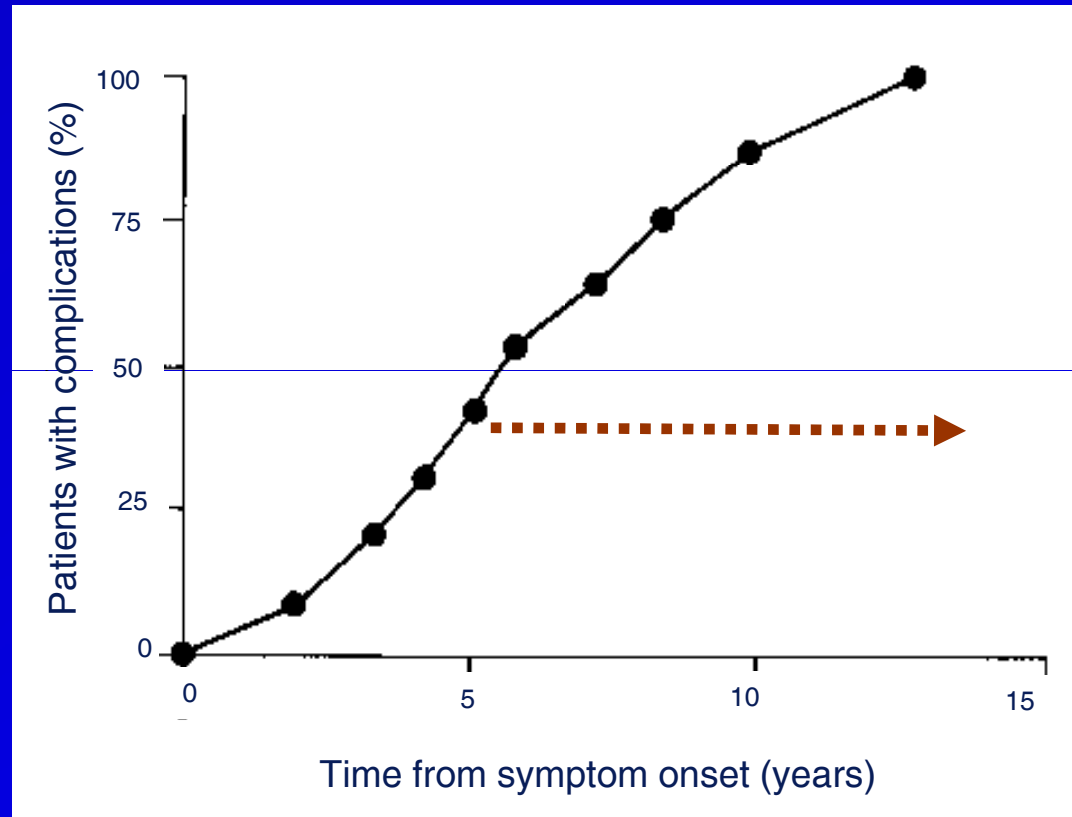
**Stereotaxy:** Use of an external coordinate system with a brain image to place a probe accurately through a small skull opening



# Risks of Surgery and Gene Transfer

- Surgery
  - Hemorrhagic stroke (DBS risk ~1.5%)
- Gene transfer
  - Enhanced sensitivity to runaway dyskinesias (surgical ablation globus pallidus or DBS); AADC placed into non-physiological tissue (not striatum); AADC transport could supply DA to other degenerating regions and other DA sensitive areas (GPI - surgical ablation; psychiatric effects - neuroleptic treatment)
  - Inflammatory reactions to vector
- Toxicity not detected in rat and NHP studies

# Goal of AAV-hAADC-2 Gene Transfer



Chase et al.