

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.

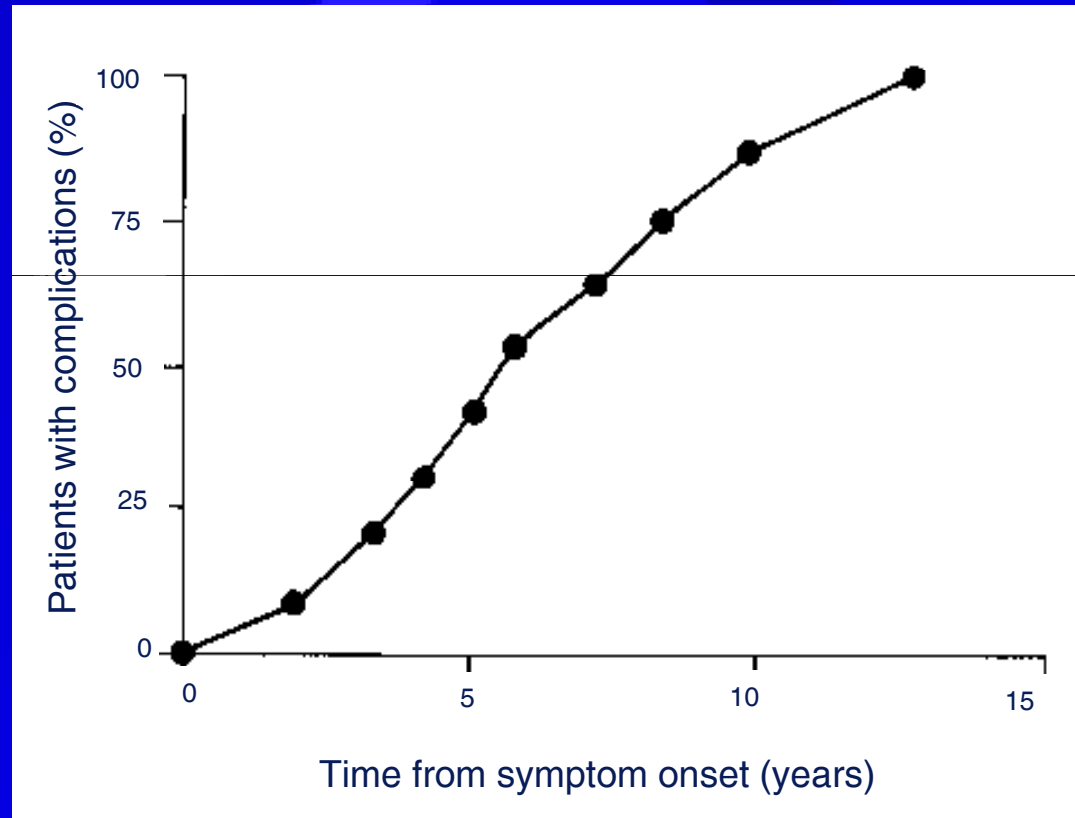
- **Lawrence Berkeley National Laboratory**

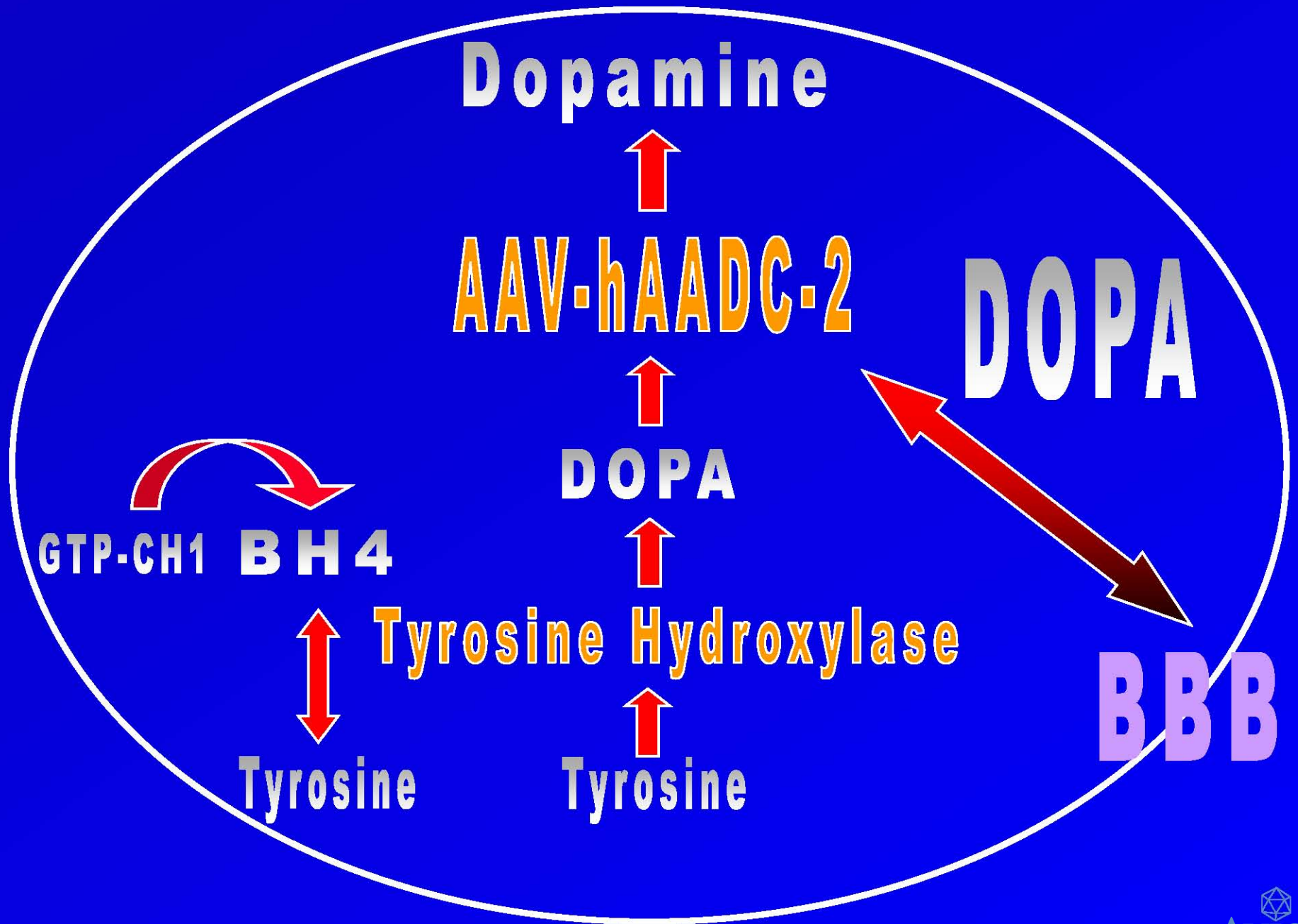
- **Neuroimaging:** Henry F. VanBrocklin, Ph.D.

- **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 shadow and highlights to give it a three-dimensional appearance. The text "Preclinical Data" is written in a bold, yellow, sans-serif font across the front face of the cube.

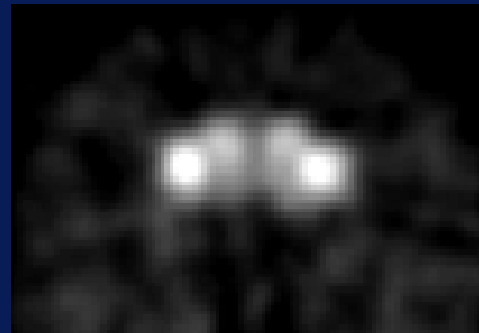
Preclinical Data

Depletion of AADC in Parkinsonian NHPs

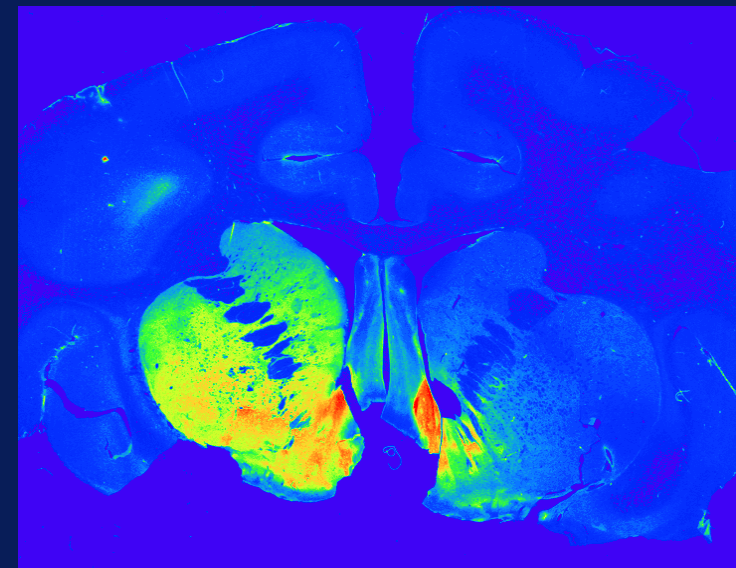
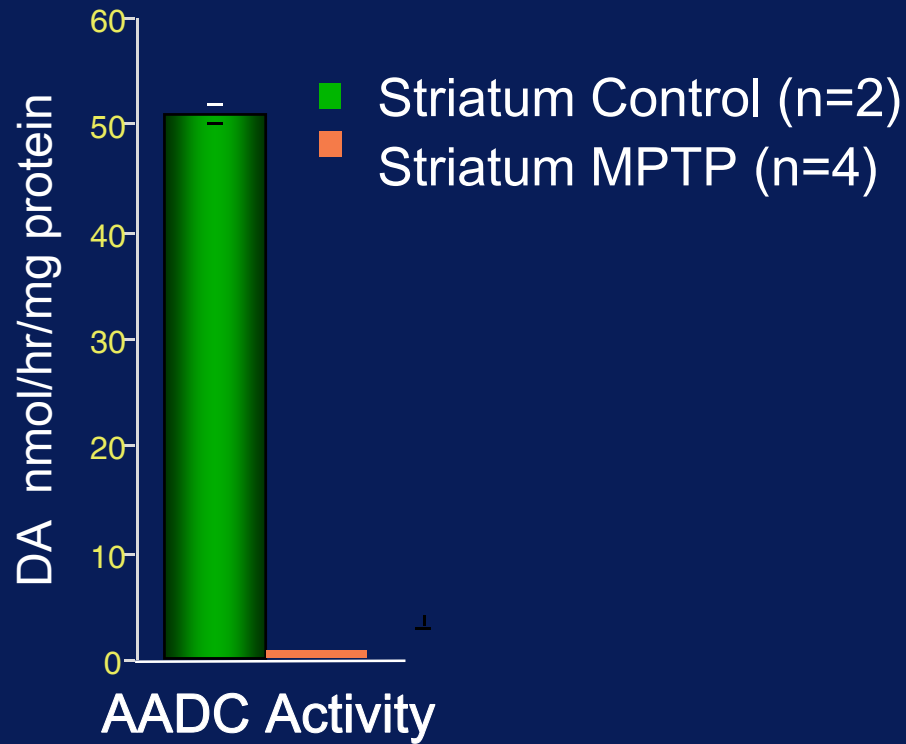
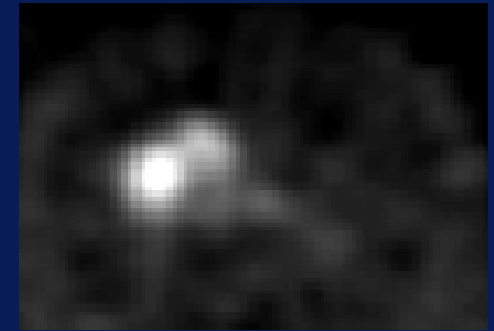
MRI



Normal - PET

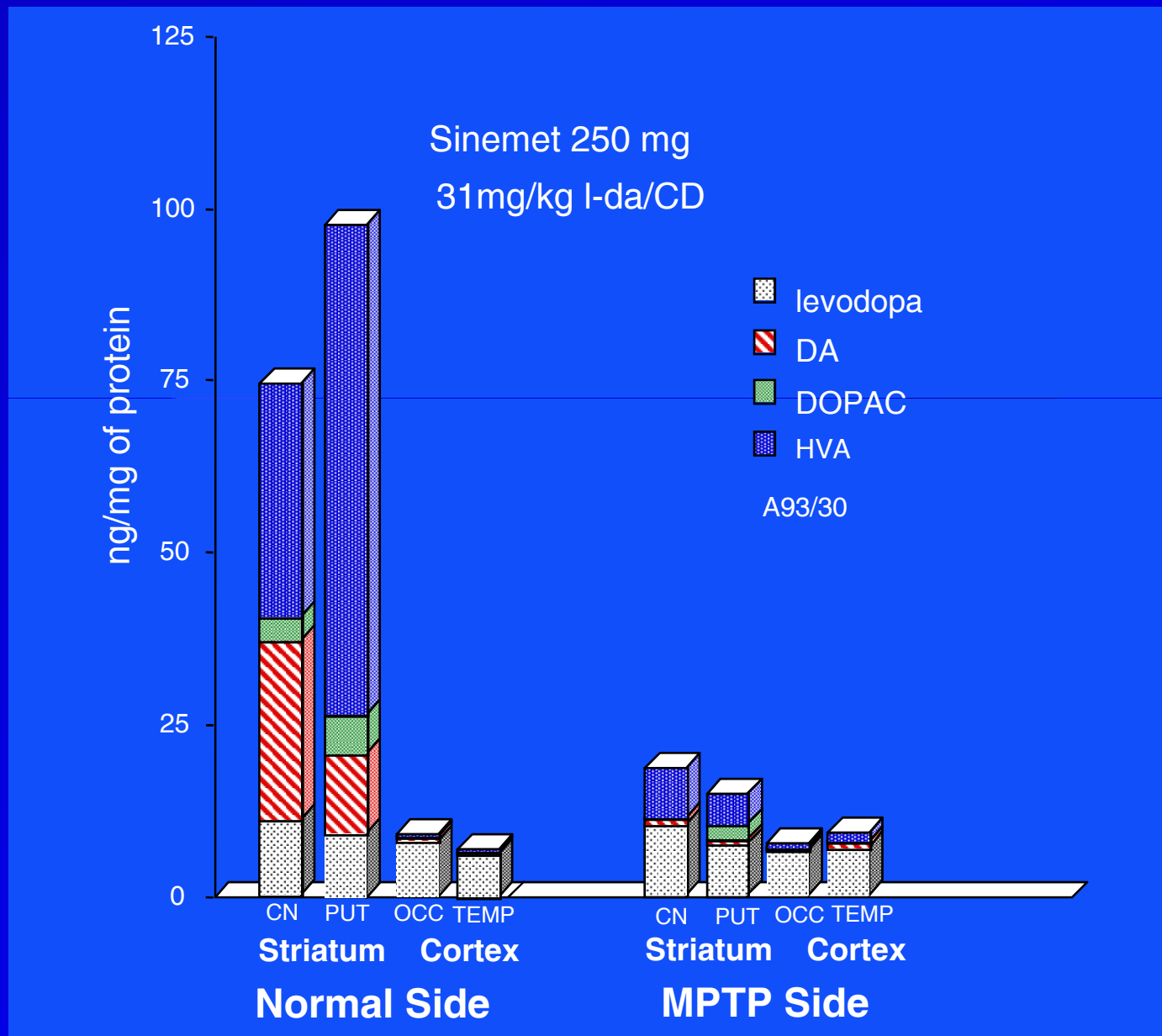


Hemi-PD - PET

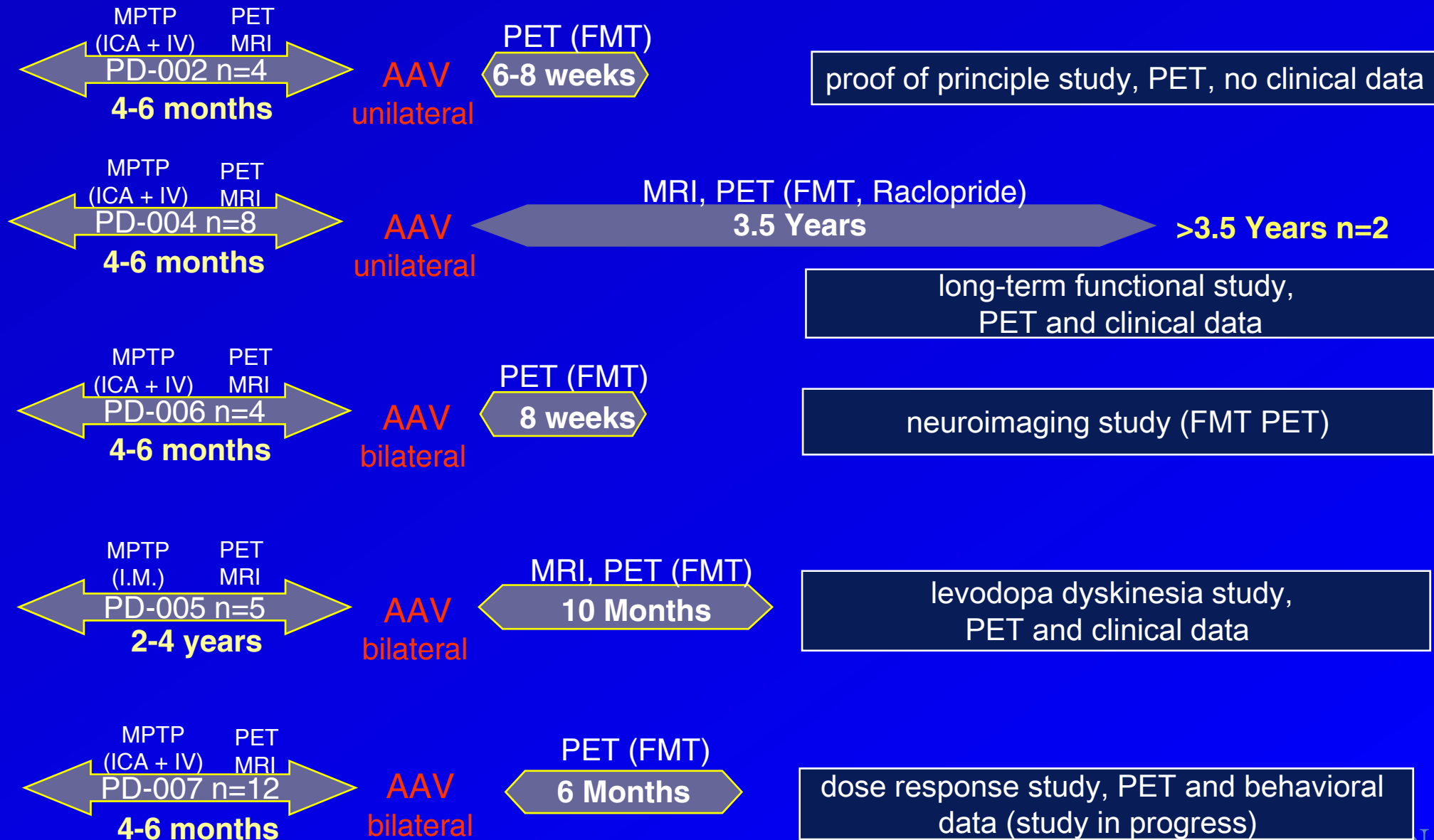


AADC immunoreactivity

Poor Decarboxylation of Levodopa in PD NHPs

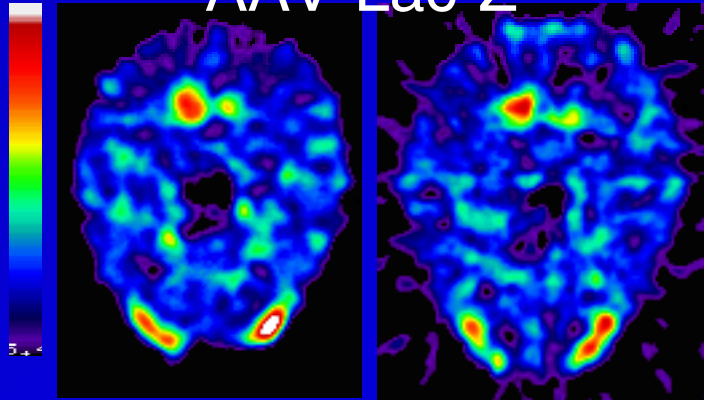


Studies in PD Non-Human Primates



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

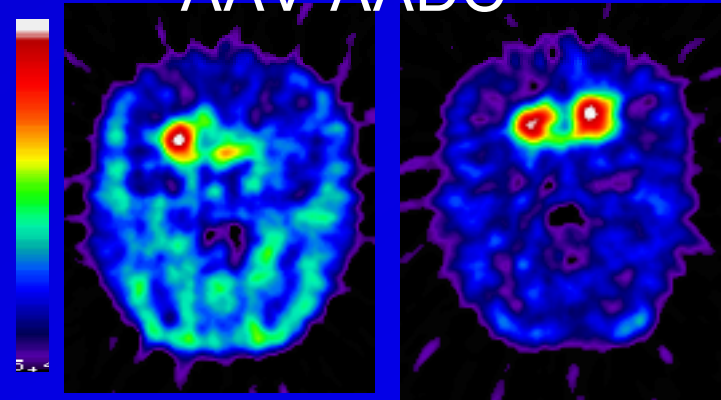
AAV-Lac-Z



pre

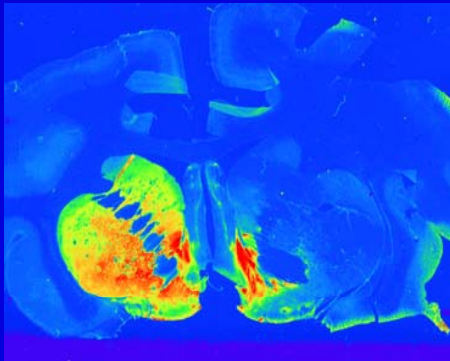
post

AAV-AADC

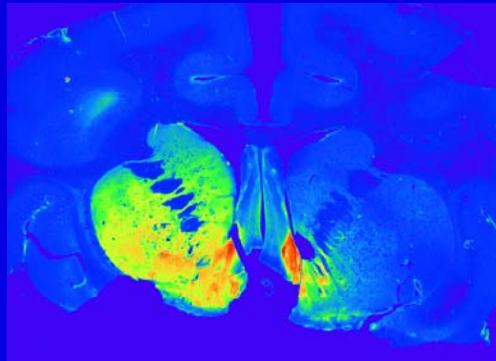


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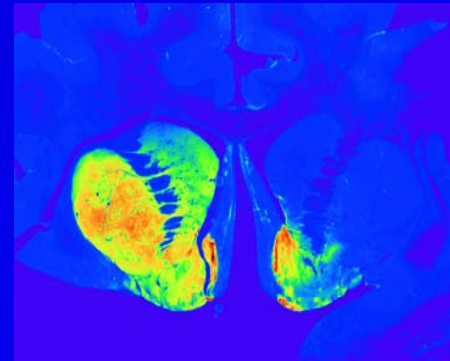
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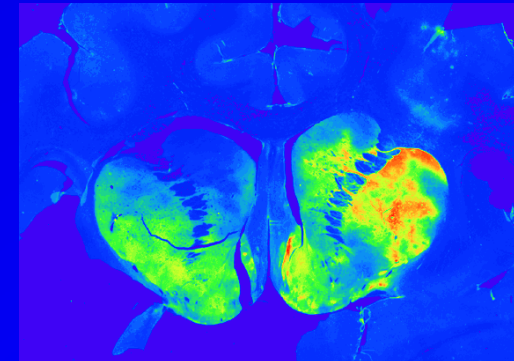
anti-TH



anti-AADC



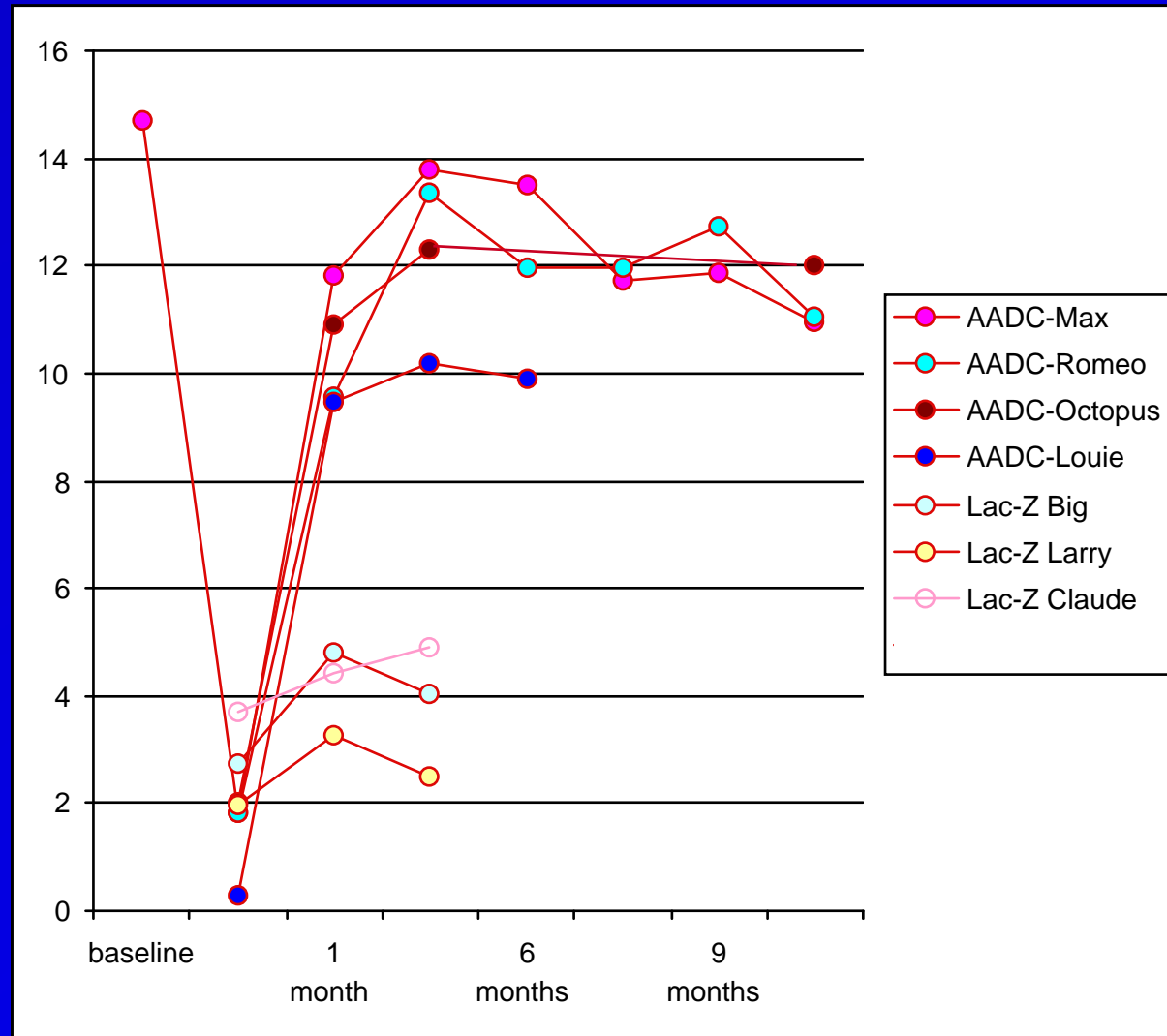
anti-TH



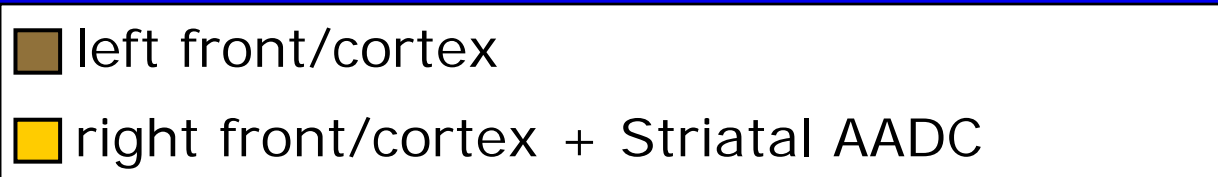
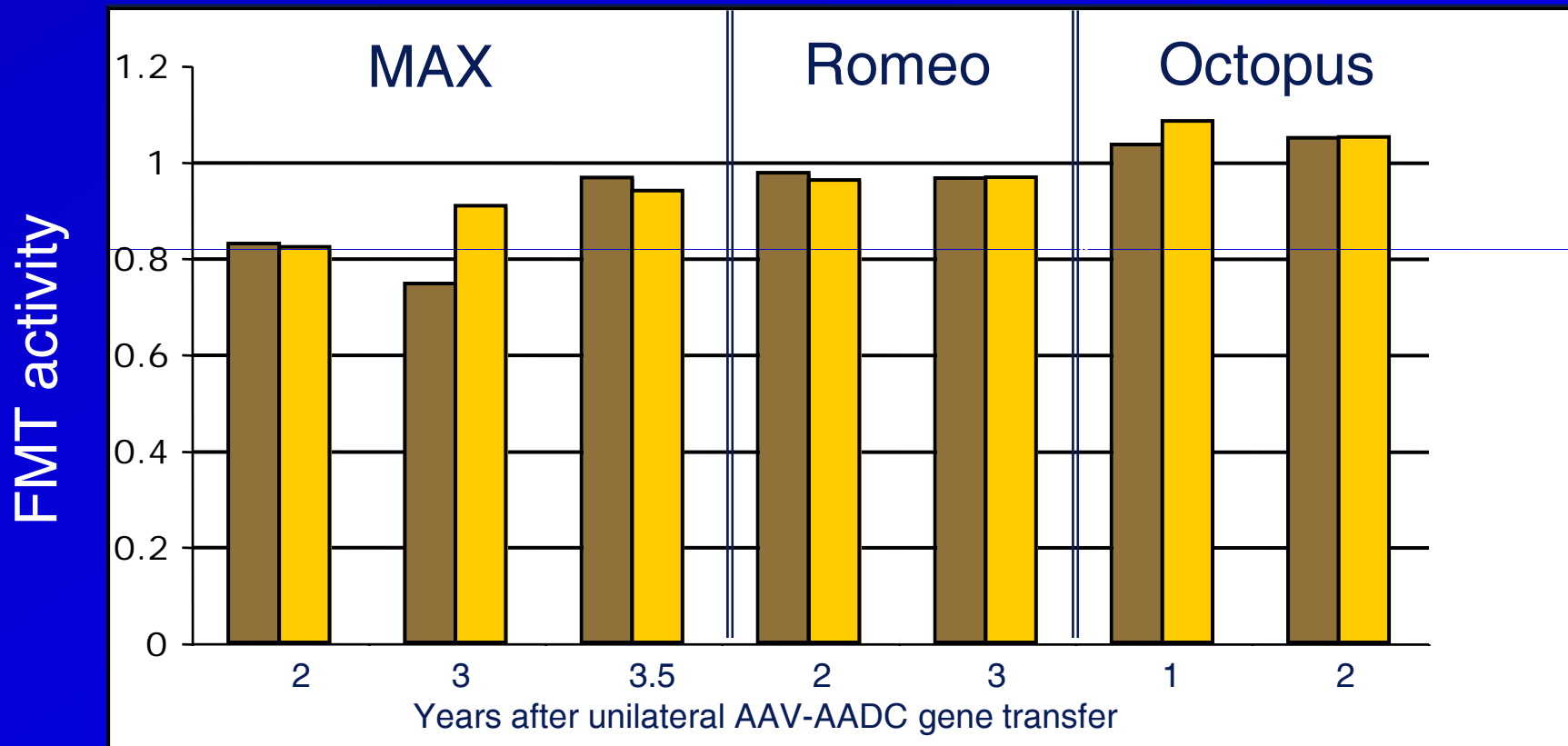
anti-AADC

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

Ki



No Evidence of Cortical AADC Activity by PET

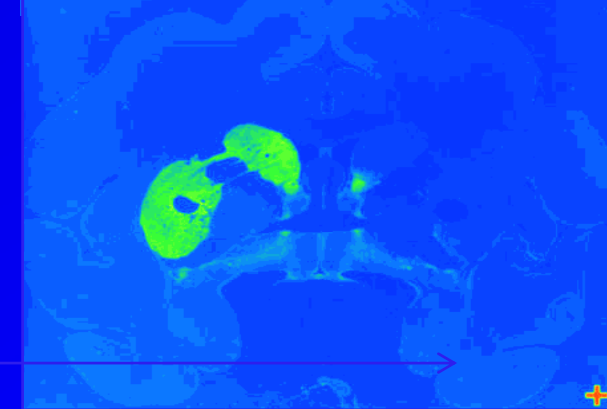
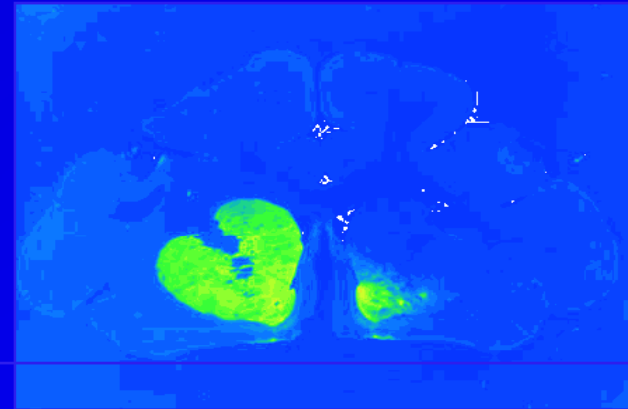
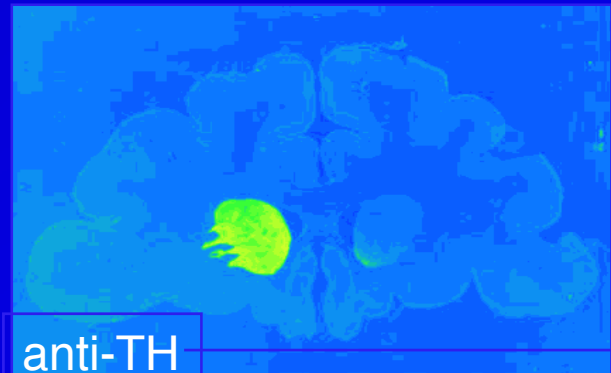
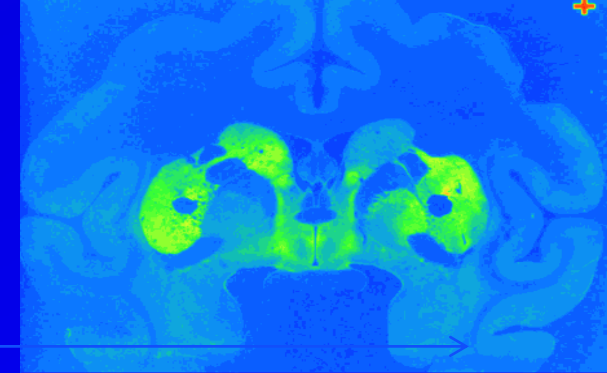
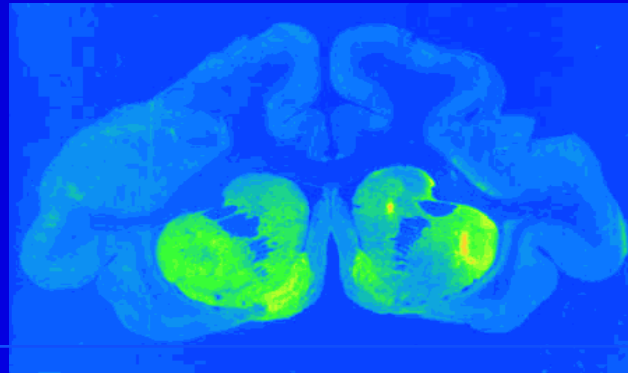
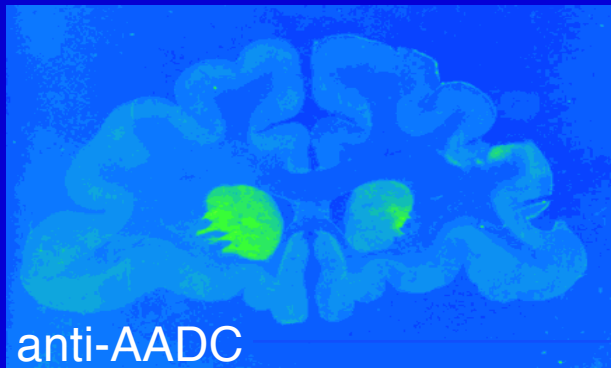


FMT PET and Post-mortem Analysis after 3.5 Years

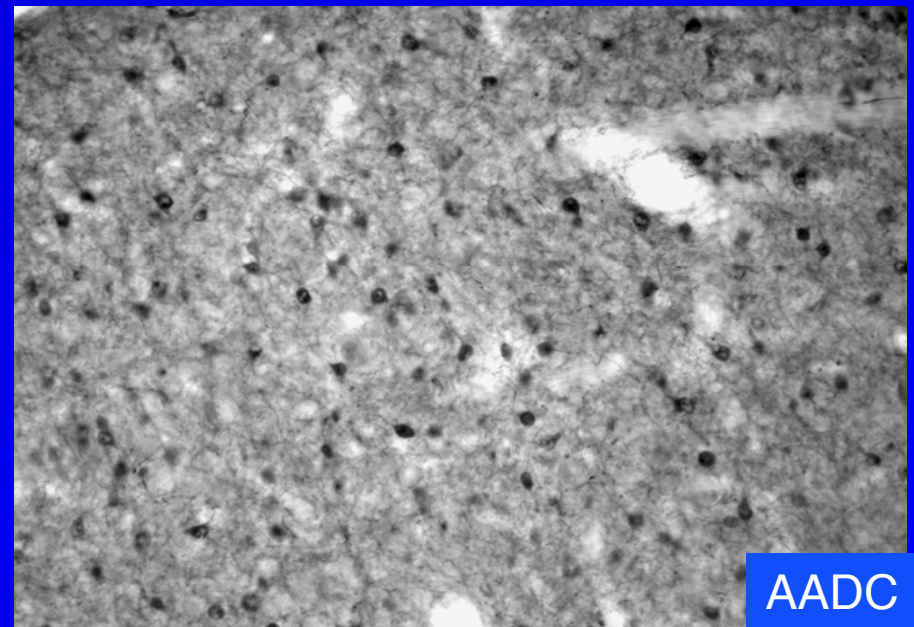
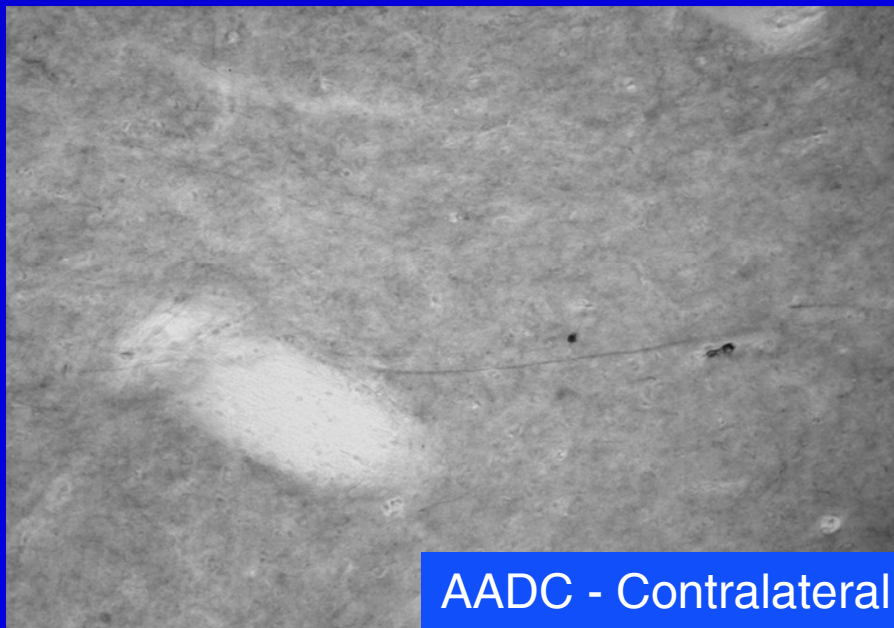
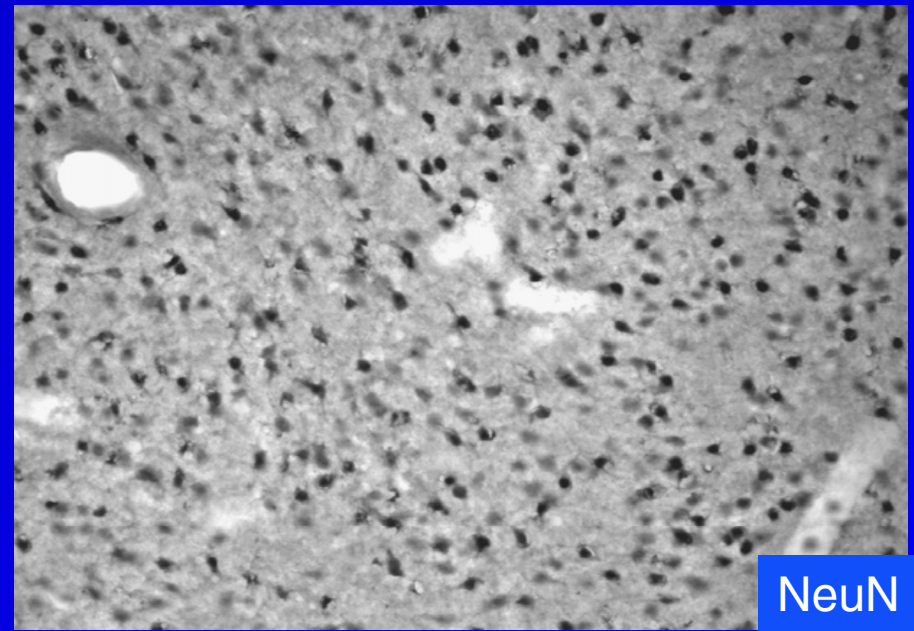
anterior

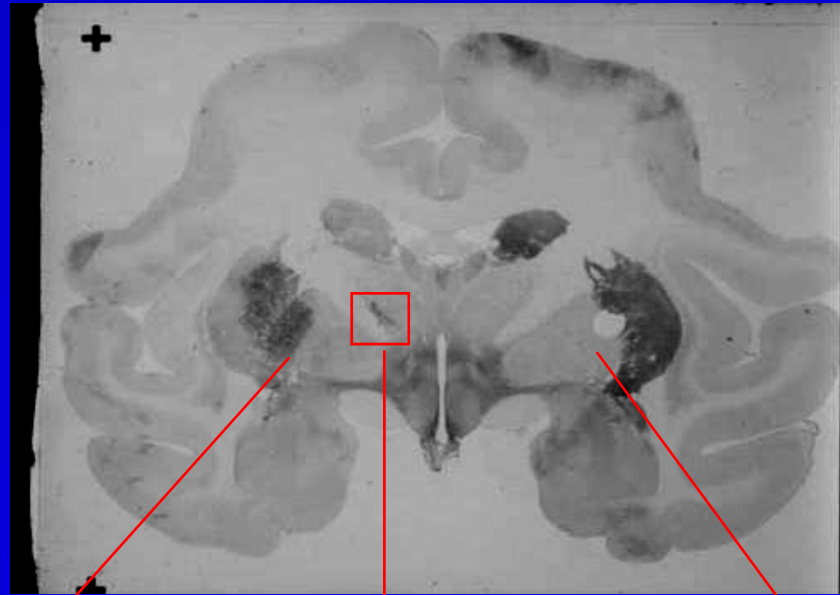
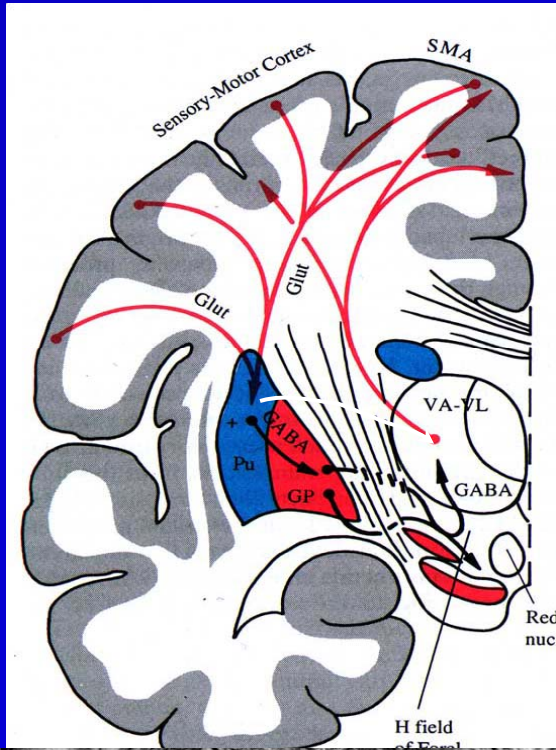
mid-striatum

posterior

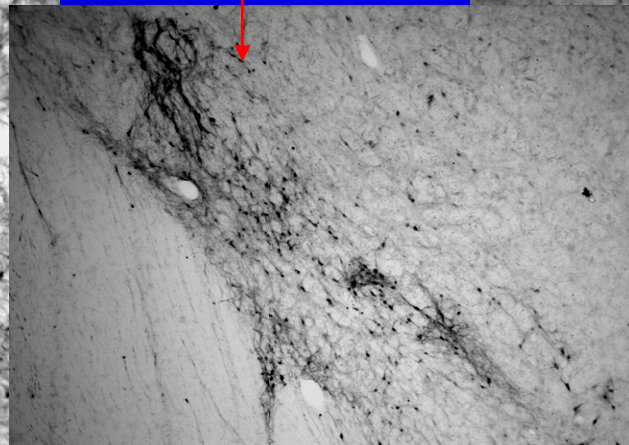
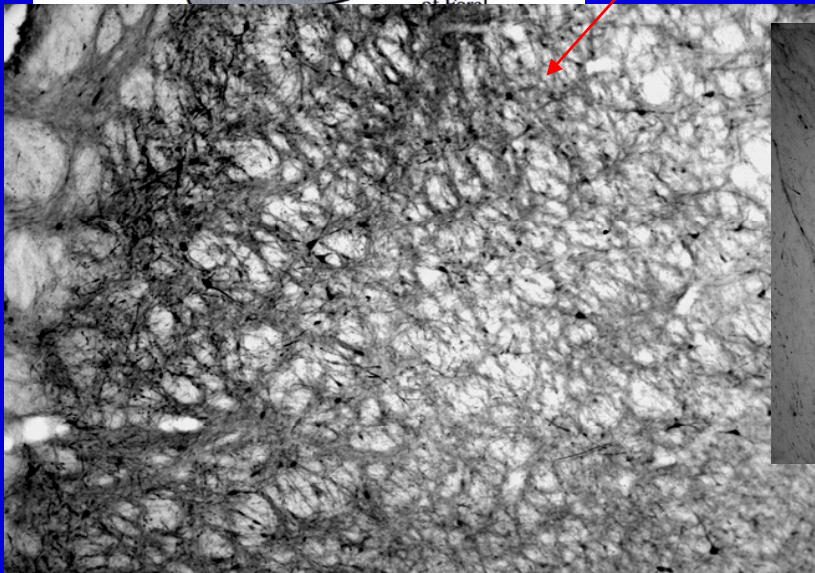


Detection of AADC in the Putamen of PD NHP 3.5 Years after Gene Transfer

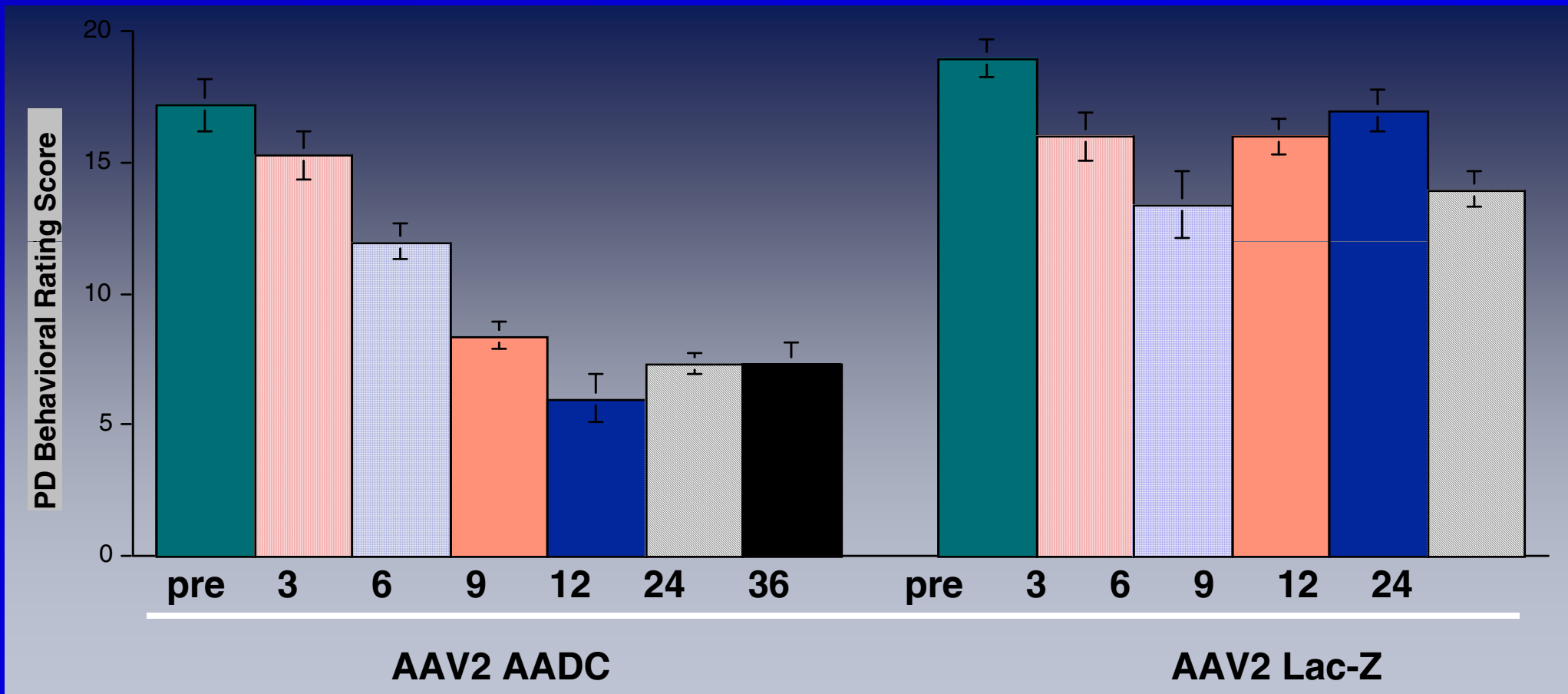




AADC in Projection Sites from Striatum (3.5 years)

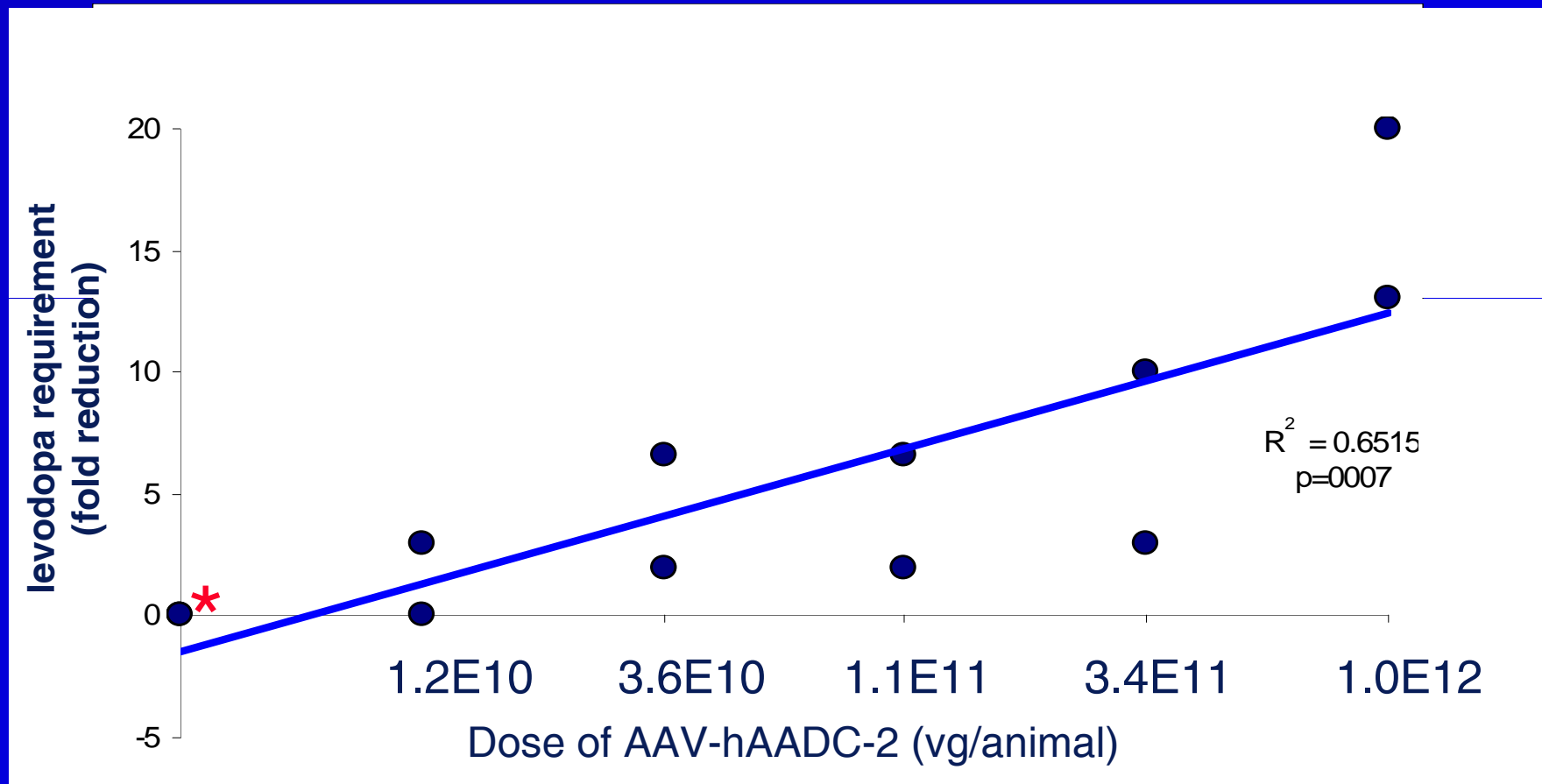


Response to Sub-therapeutic Levodopa in PD NHP 36 Months After AAV-AADC Gene Transfer



levodopa 3 mg/kg IM.

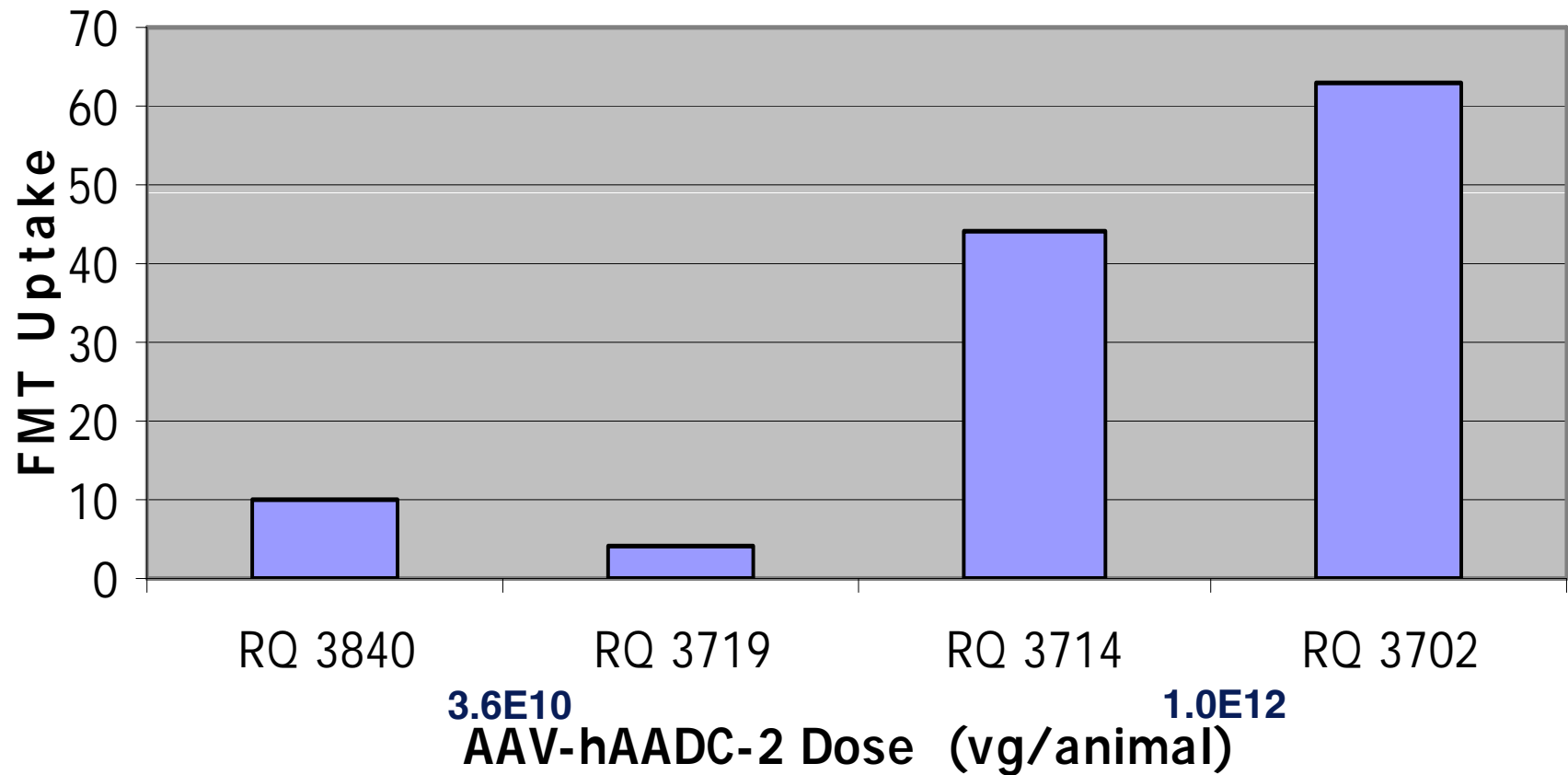
Correlation Between Vector Dose and Reduction of Levodopa Required for Optimal Response



*Control received 1.0E12 GFP

Study PD-007

FMT PET Signal after Gene Transfer



Study PD-007

Clinical Aspects

Advanced Parkinson's Disease

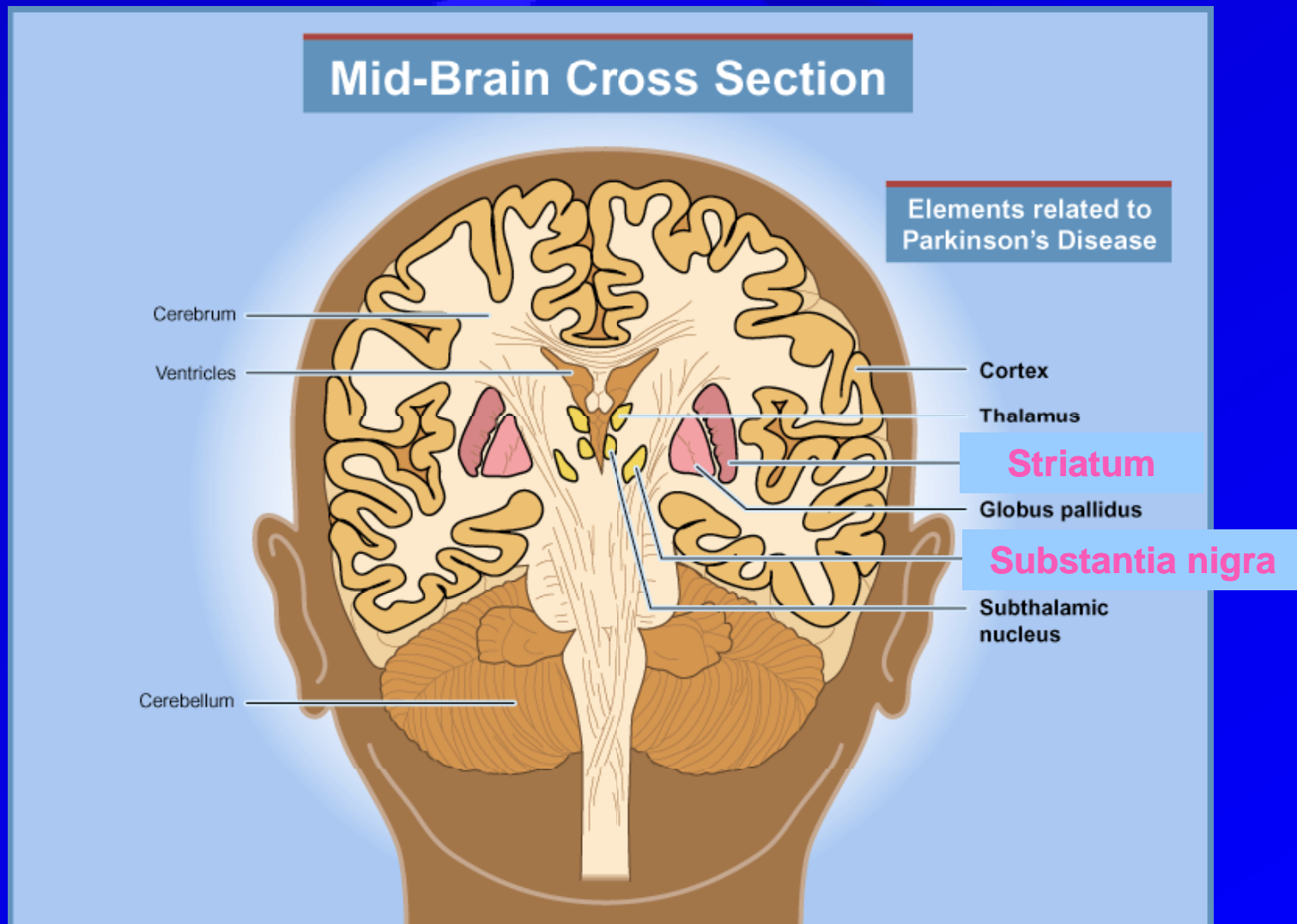
Age-related common neurodegenerative disorder resulting in a severe and profound loss of motor function and associated morbidity

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 μL /site x 2 sites/hemisphere
 - 200 μL /patient
- Starting dose
 - 2.5×10^{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

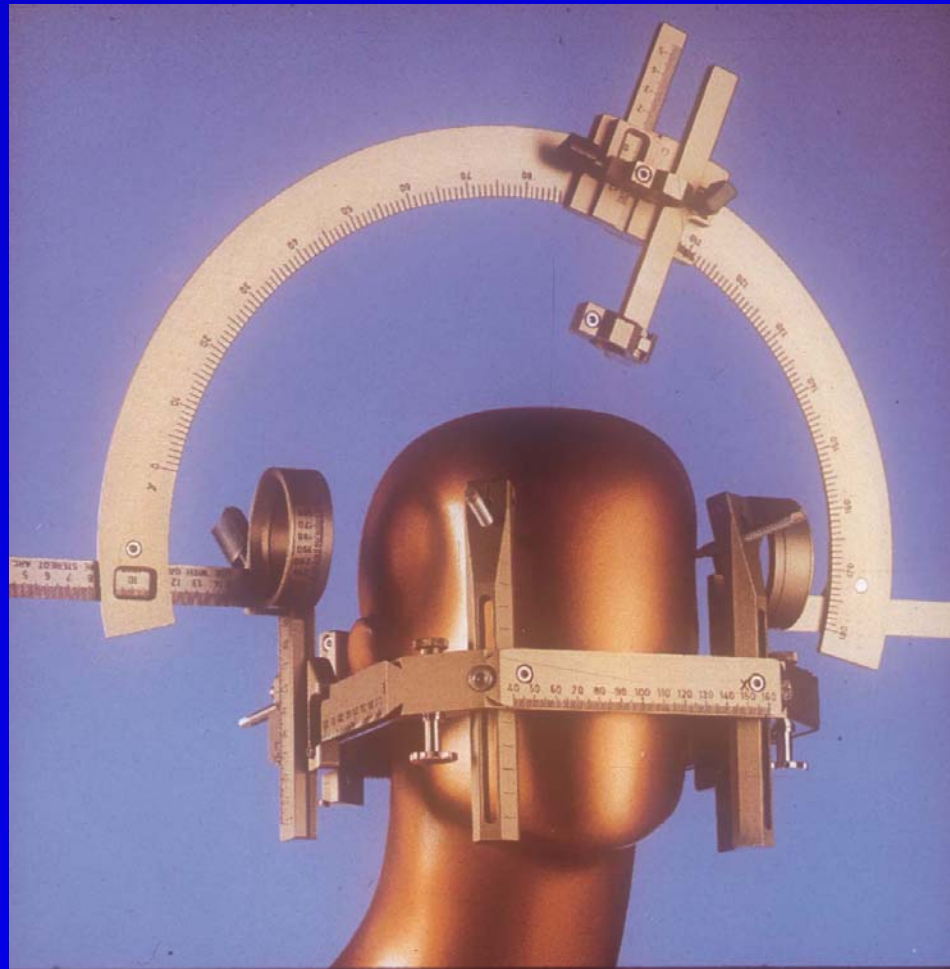
- Moderate to severe PD symptoms by Hoehn and Yahr staging (stage III to IV off medication at entry)
- Duration of levodopa therapy > 5 years
- Age at diagnosis >40
- Candidate for surgical intervention for Parkinson's disease because of intractable motor fluctuations not responsive to optimal medical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

Exclusion Criteria

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

Surgical Procedure

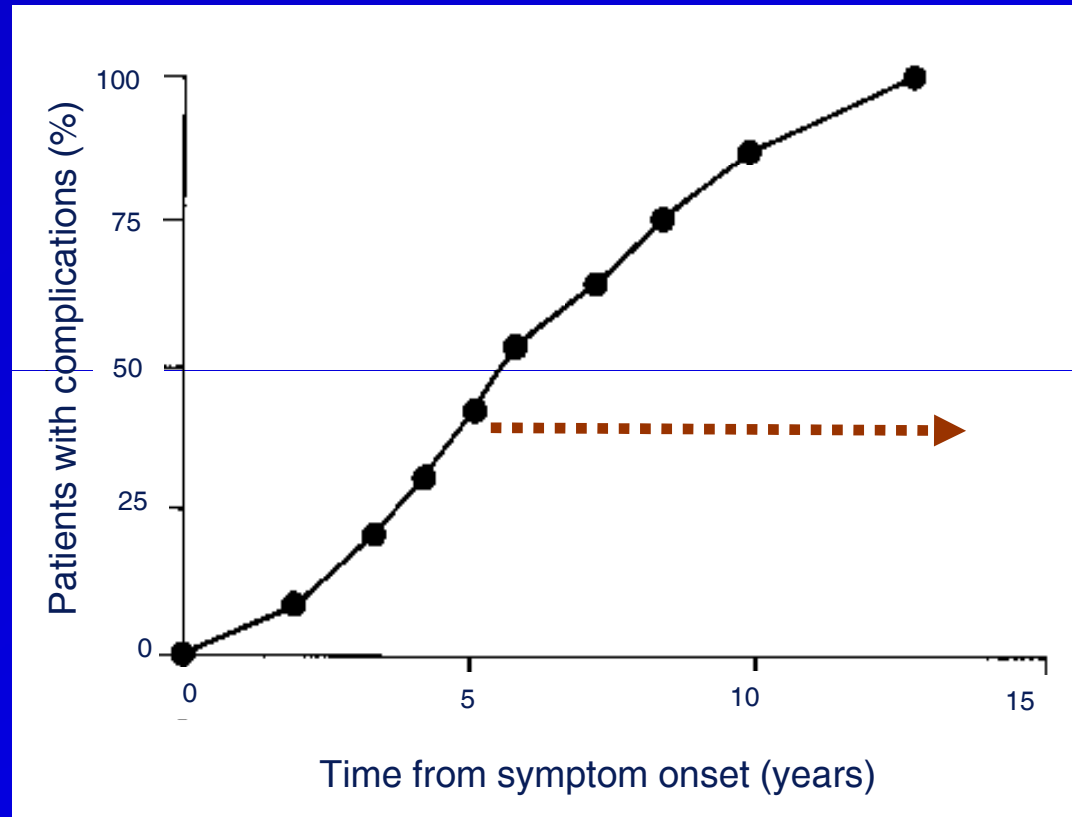
Stereotaxy: Use of an external coordinate system with a brain image to place a probe accurately through a small skull opening



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.