Update on "Subthalamic GAD Gene Therapy for Parkinson's Disease"

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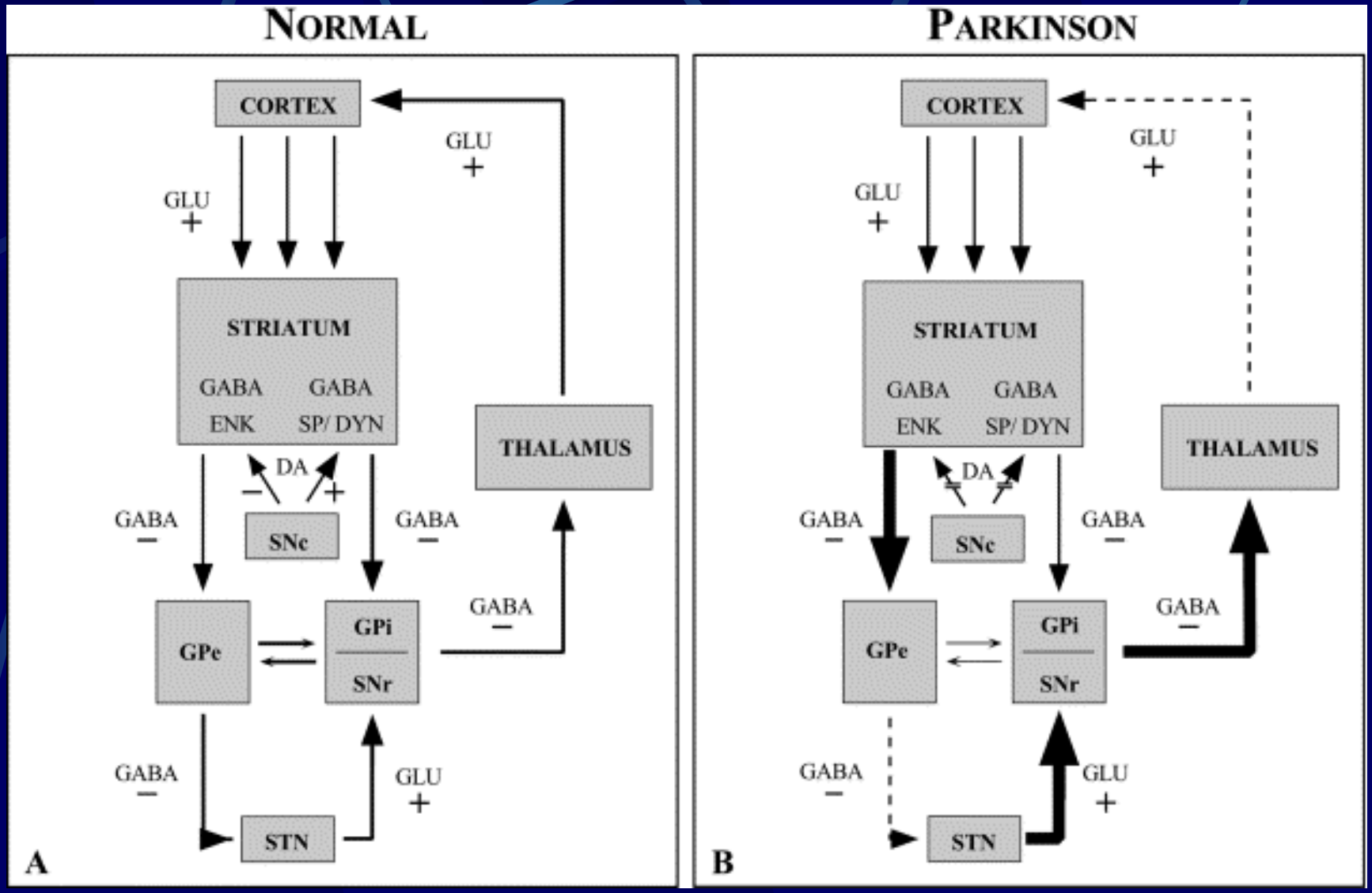
RAC Meeting, March 9, 2004

Study Overview

- Disease: Medically refractory Parkinson's Disease (PD)
- Vector: Adeno-associated virus (AAV)
- Gene: Glutamic acid decarboxylase (GAD)
- Vector Production Site: Univ. of Auckland and Neurologix
- Target: Human brain, subthalamic nucleus

Study Overview

- Study Design: Phase I, open-label dose-escalation investigator-initiated IND
- Funding Source: Corporate (Neurologix, Inc.)
- Clinical Sites: Weill-Cornell (Surgery), North Shore Hospital (Pre/Post-operative evaluations, imaging)
- Investigators: Matthew During, MD PhD (Co-PI, IND sponsor), Michael Kaplitt MD PhD (Co-PI, Surgeon), David Eidelberg MD (North Shore Co-PI, Neurologist), Andrew Feigin MD (North Shore Co-PI, Neurologist)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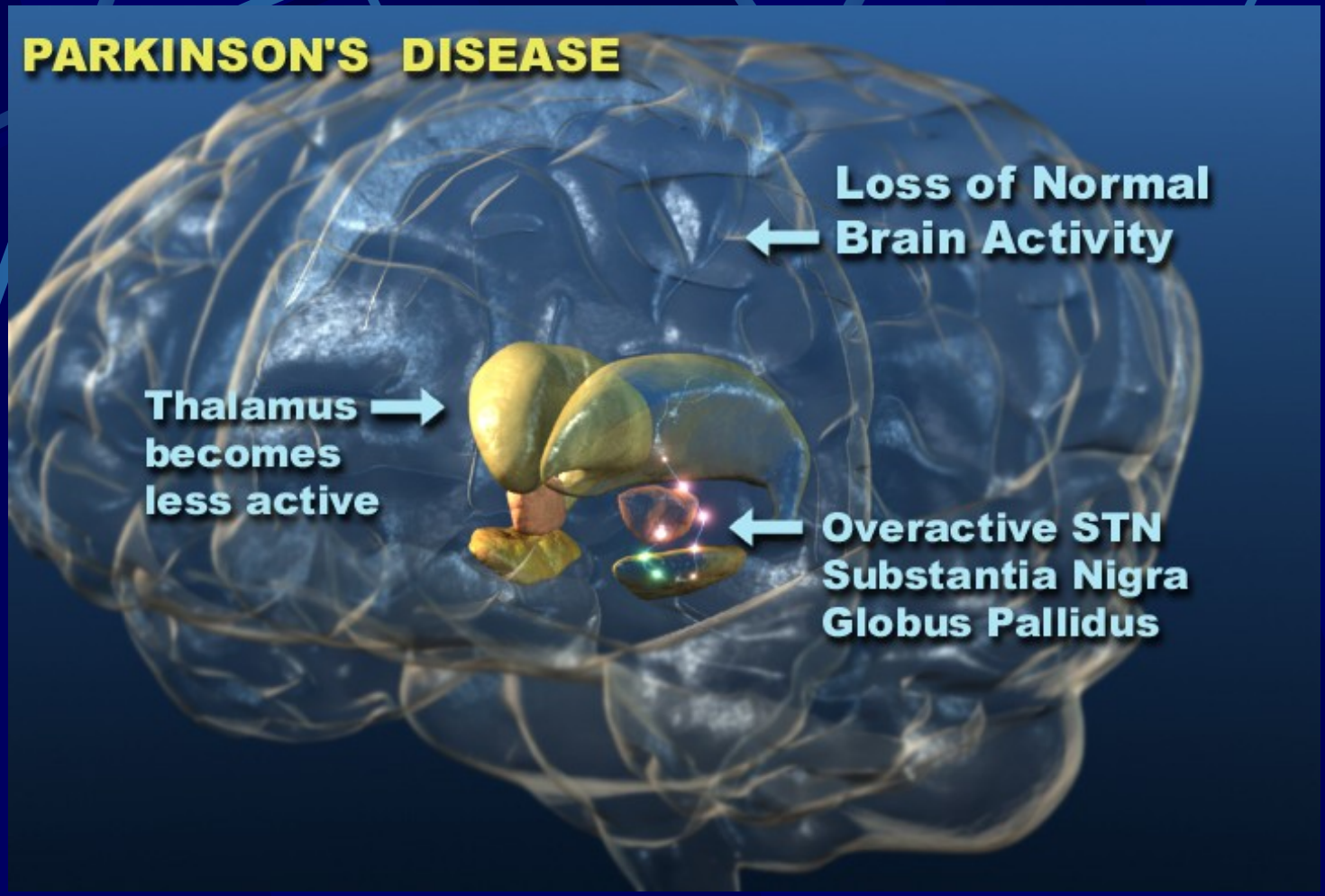
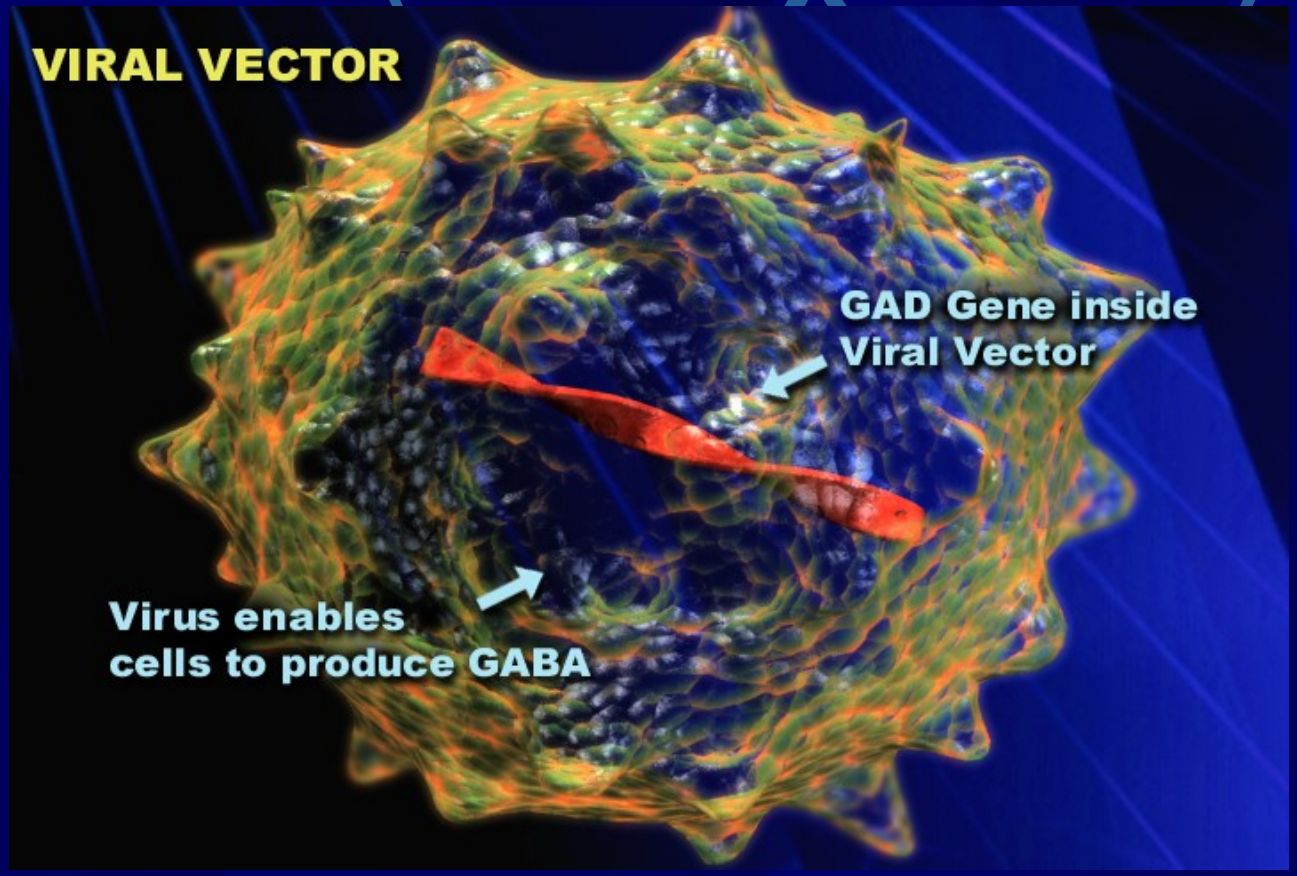
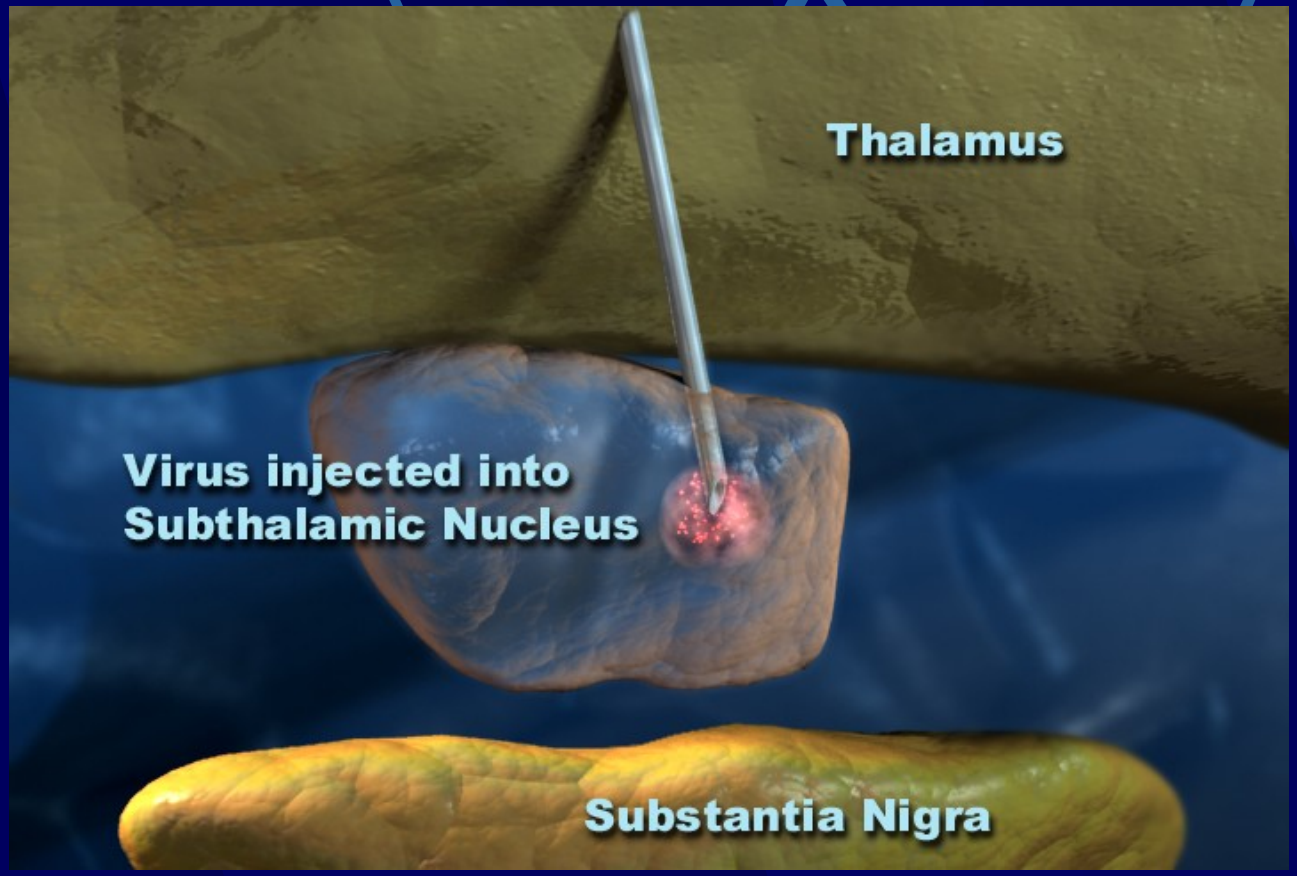
Delivery of GAD for Treatment of PD



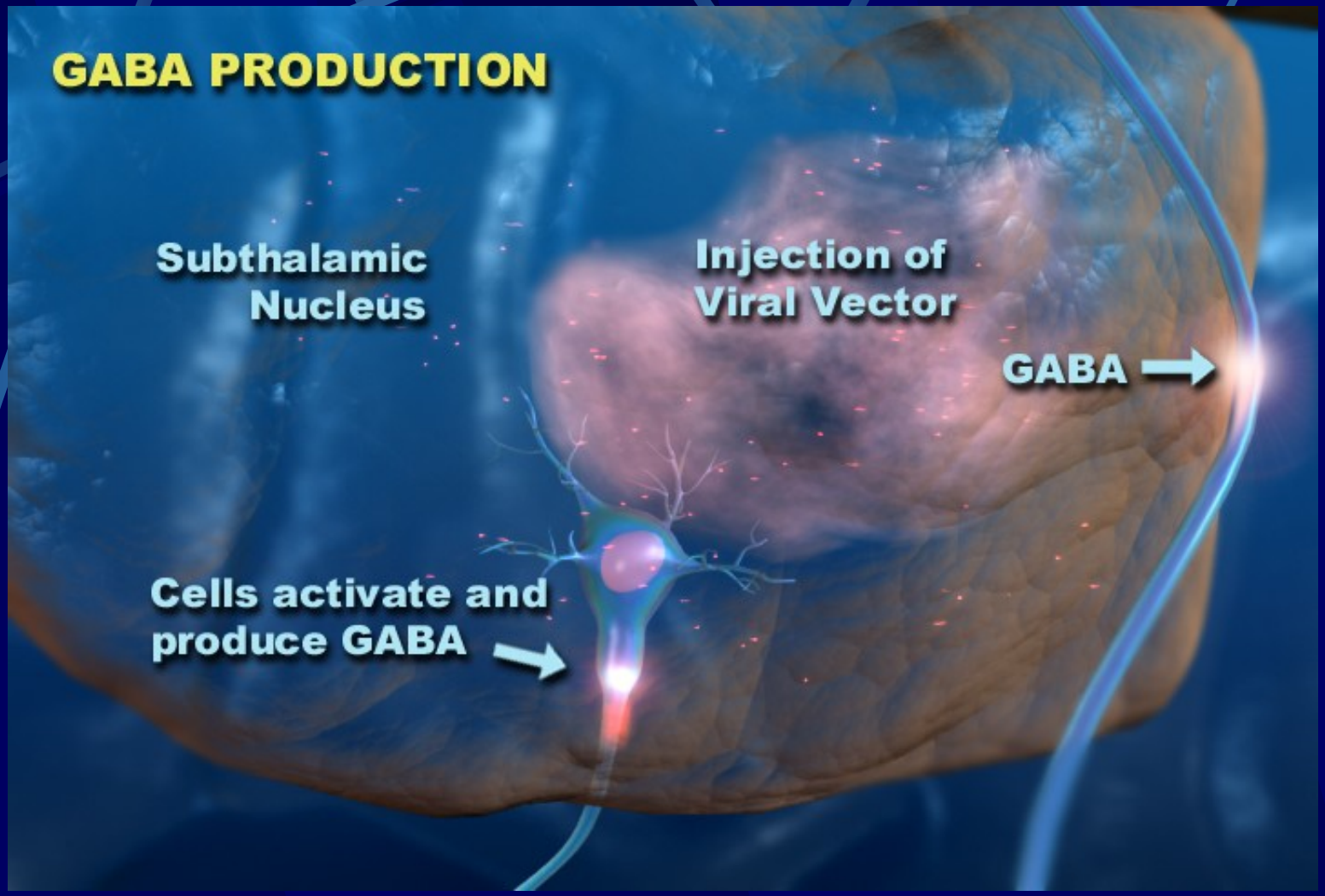
Delivery of GAD for Treatment of PD



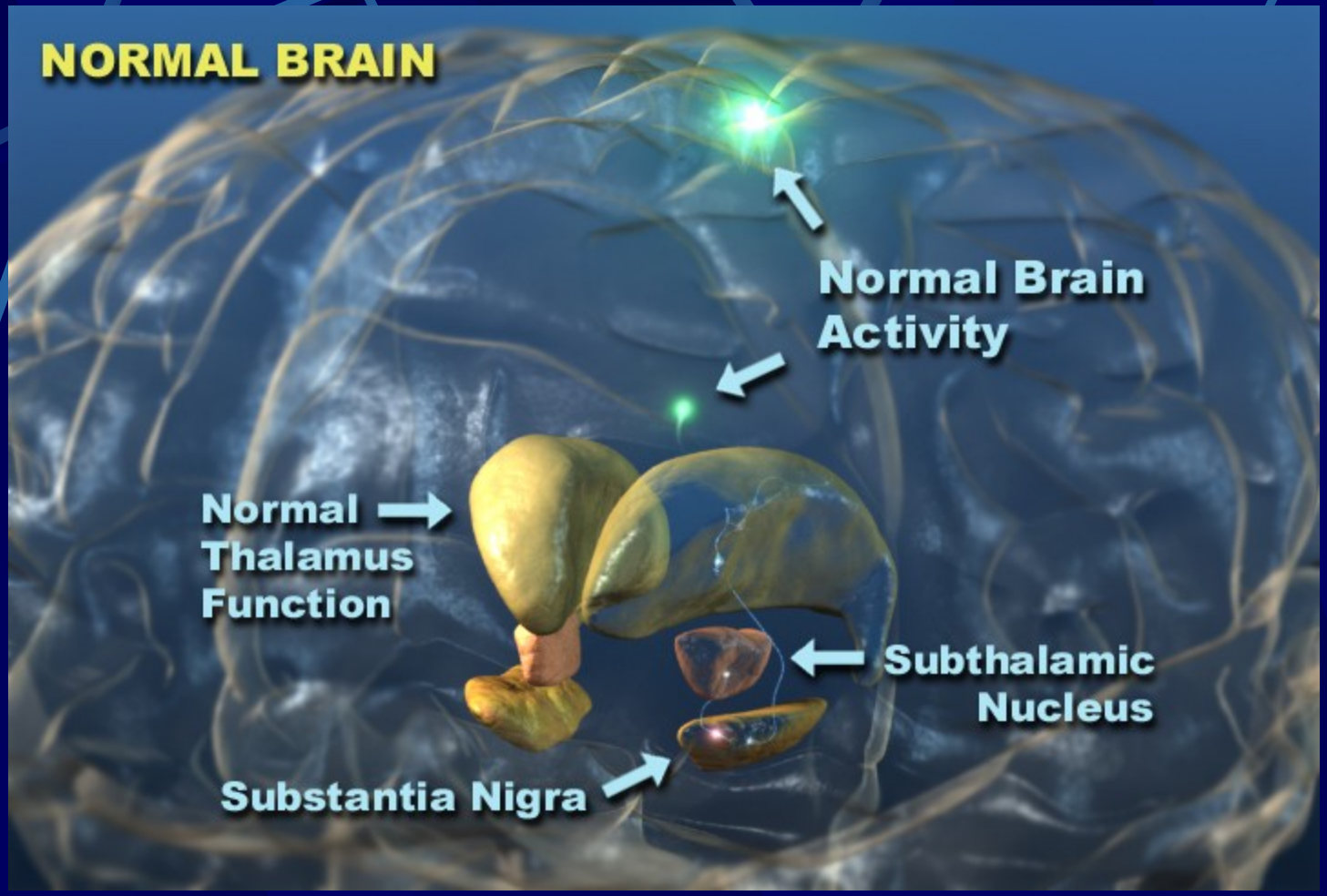
Delivery of GAD for Treatment of PD



Delivery of GAD for Treatment of PD



Delivery of GAD for Treatment of PD



AAV-GAD Gene Therapy for PD: Potential Advantages

- Standard neurosurgical target; well characterized
- Surgical proof of principle exists
- Wider range of therapeutic window
- Unanticipated adverse effect of GABA overproduction potentially controlled with rescue procedures
- If treatment fails, planned surgical target already mapped
- Hardware eliminated and potential for therapeutic improvement

Phase I AAV-GAD Gene Therapy for PD: Study Design

- Patients chosen from STN surgical candidates
- Unilateral injection for unilateral or asymmetric disease
- 4 patients enrolled at each of 3 doses; 35ul each of 10^{11}, $3x10^{11}$,10^{12}
- Core Assessments (CAPIT, UPDRS, etc..) and PET (FDG)

Regulatory Approval Process

- Recombinant DNA Advisory Committee (RAC) review June,2001
- U.S. FDA review completed and approval given August, 2002; product specification revised November, 2002; FDA release given January, 2003
- Weill Cornell IRB approval obtained September,2002; renewed Sept., 2003
- Weill Cornell Institutional Biosafety Committee (IBC) approval obtained May,2003
- North Shore University Hospital IRB approval obtained July, 2003; renewed March, 2003

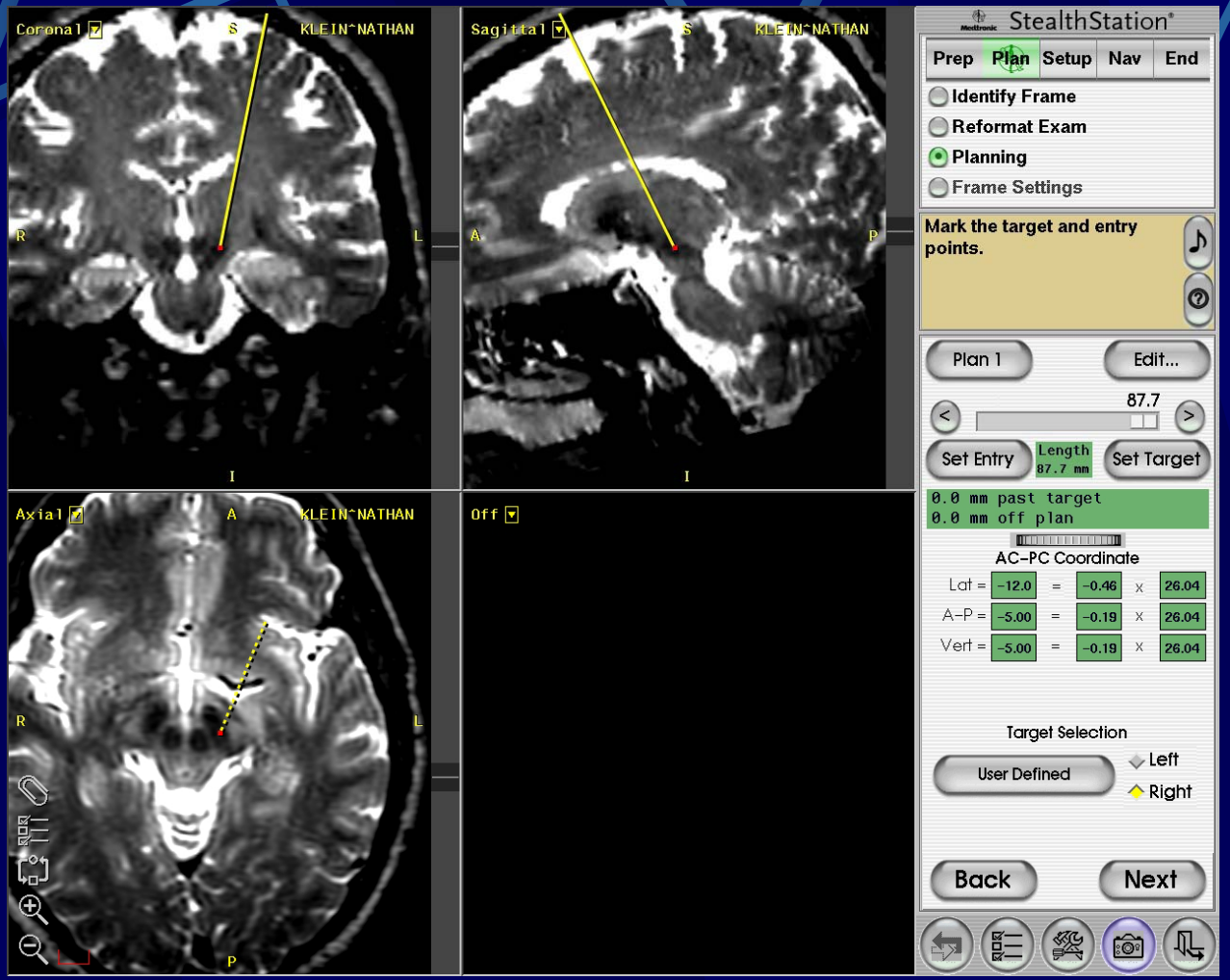
Conflict of Interest

- Kaplitt: Unpaid consultant to Neurologix; father officer and shareholder
  - Disclosed to FDA, institution, IRB, IBC and in consent form. Discussed in detail with each patient. Final patient entry and patient outcome determined by neurologists
- During: Paid consultant to Neurologix
  - Disclosed to FDA, institution, IRB, IBC and in consent form. Discussed in detail with each patient. No clinical role in study
- Eidelberg and Feigin: No conflict

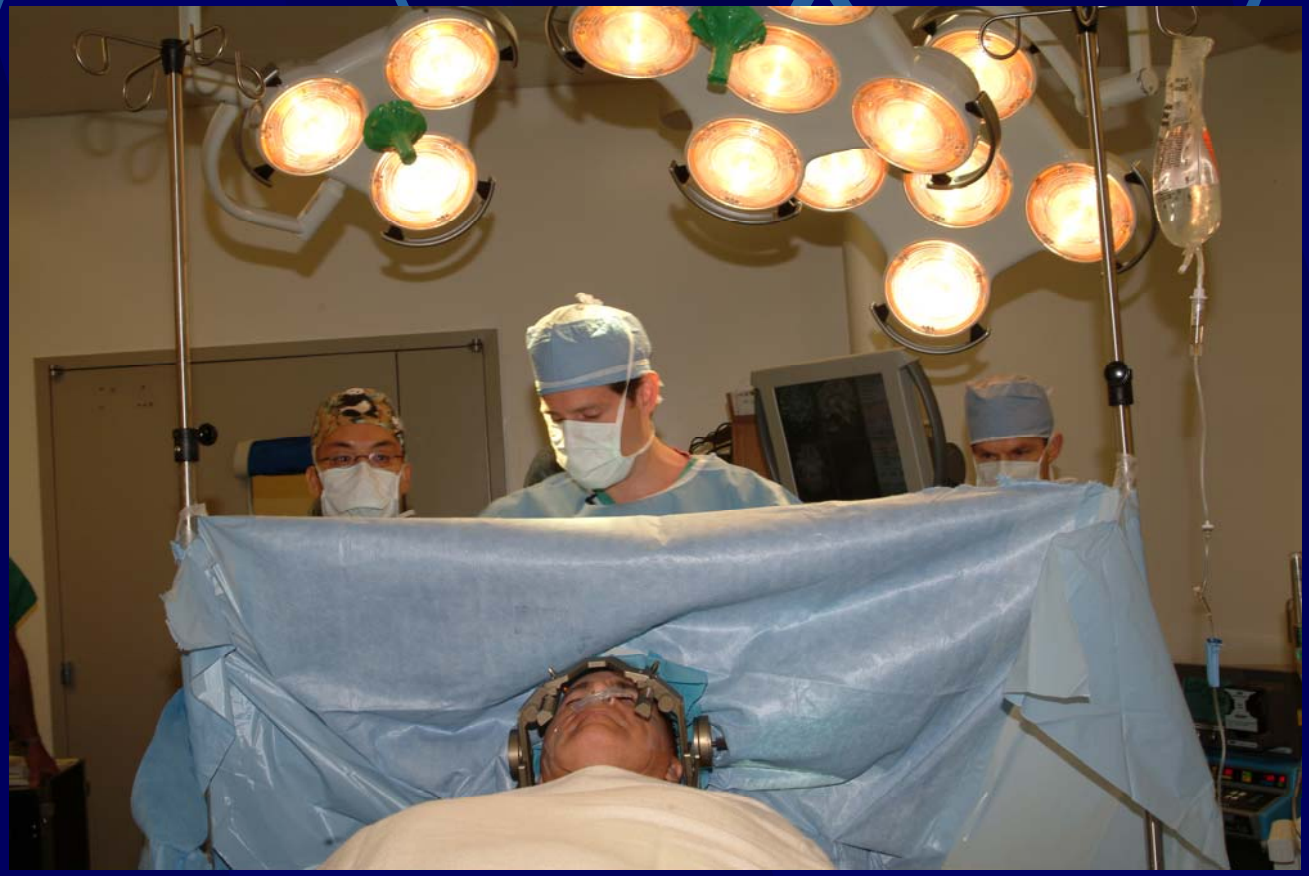
First Procedure

August 18, 2003

Preoperative Planning

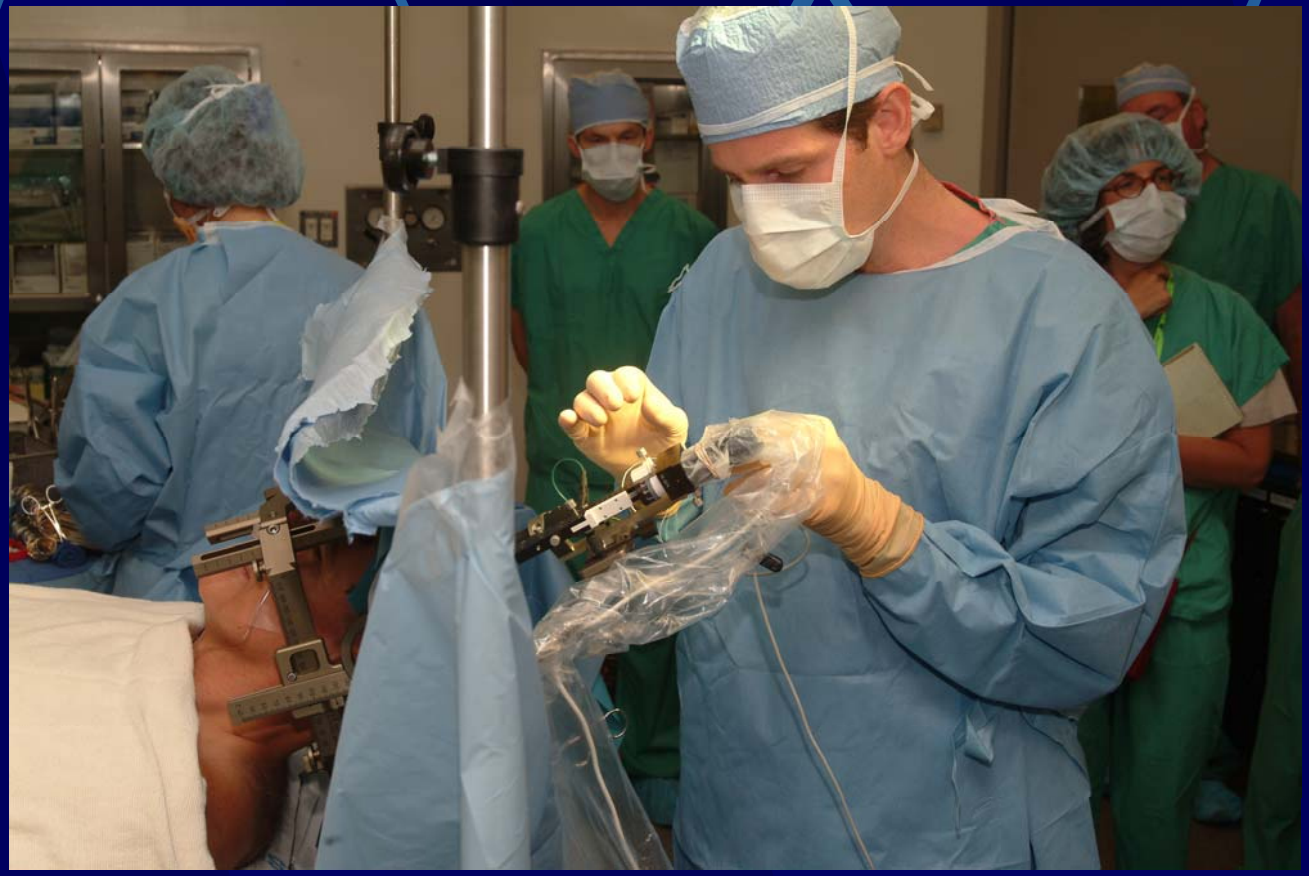


Intraoperative Setup



Microelectrode Recording

Microelectrode Recording



Microelectrode Recording

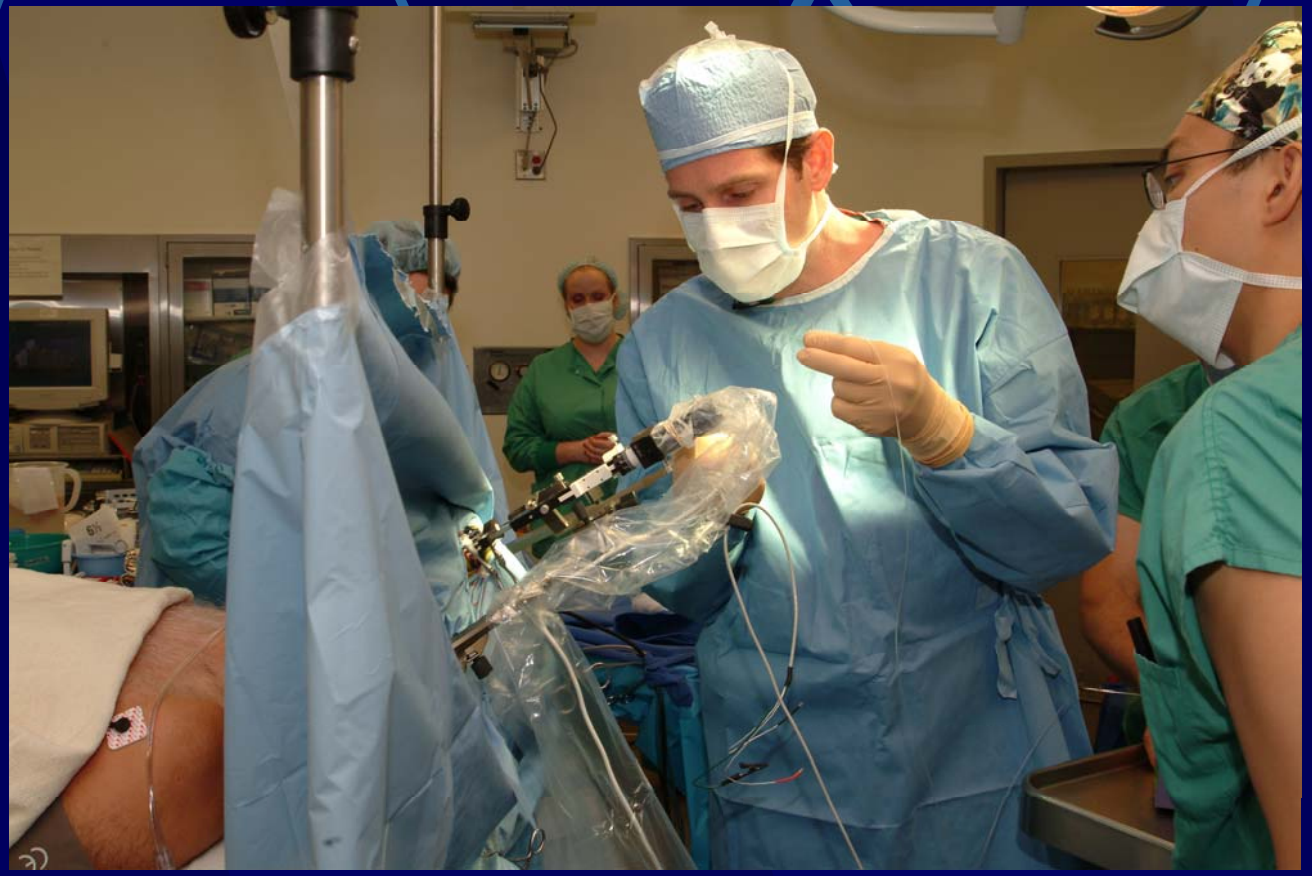
Microelectrode Recording

Infusion Catheter

AAVGAD Preparation

Preparation of Infusion System

Insertion of Catheter Into Brain Target



AAVGAD Infusion

Study Summary: Demographics

- 211 patients screened to date
- Men 145, Women 66
- Enrolled subjects: 5, Treated subjects: 4
- Ineligible Total: 112
  - Ineligible due to age: 88
  - Ineligible due to prior surgery: 10
  - Ineligible due to diagnosis: 14
- Remaining patients under consideration or did not follow-up

Enrolled Patients: Demographics

- Age range: 51-62
  - Entry criteria: 65 or younger
- Duration of Disease: 8-13 years
  - Entry criteria: Minimum 5 years
- Disability level (Hoehn and Yahr): 3 patient stage 3, one patient stage 4
  - Entry criteria: Stage 3
- 2 patients treated on dominant side (left)
- 2 patients treated on non-dominant side (1 right, 1 left)
- Current follow-up between 1 month and 7 months

Adverse Events

- No surgical complications
- All patients discharged on post-op day 2
- No fevers, no change in lab values
- No radiographic evidence of toxicity
- No study related adverse events
- One SAE unrelated to intervention reported: Patient with medication reduction 4 months after treatment worsened and required return of medication to previously stable level. Patient inappropriately admitted to hospital against opinion of neurology PI; discharged 12 hours later after given appropriate medication. Stable since. SAE reported due to hospitalization.

Process Issues for Discussion

- Release of working documents prior to final review
  - Initial RAC submission published without investigator knowledge despite substantial changes to final protocol after RAC review. Cause for some confusion among general public.