Neuropathology Contributions to Clinical Trials and Drug Development: A Trialist's View

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Disclosures

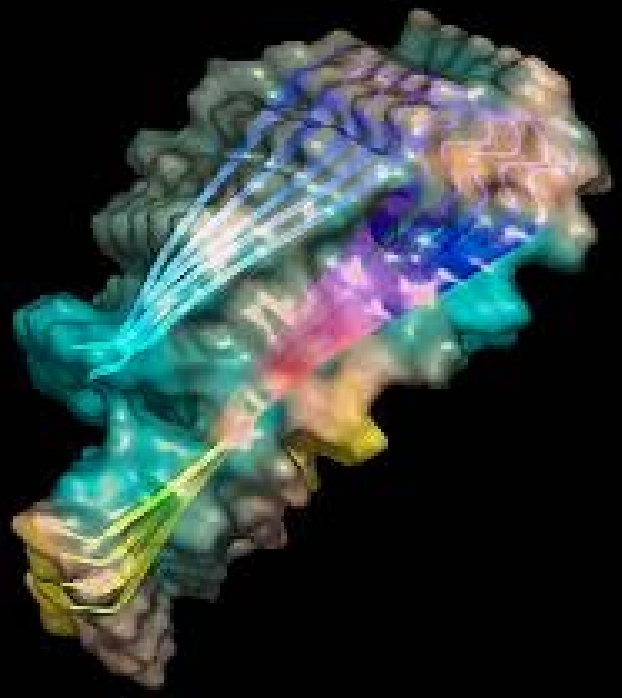
- Dr. Cummings has provided consultation to Abbott, Acadia, Adamas, Astellas, Avanir, Bayer, BMS, Eisai, EnVivo, ExonHit, Janssen, Forest, Genentech, GSK, Myriad, Lundbeck, Neurokos, Novartis, Merz, Pfizer, Prana, Sanofi-Aventis, Signum and Takeda pharmaceutical companies.
- Dr. Cummings has provided consultation to MedAvante, Neurotrax, and UBC assessment companies.
- Dr. Cummings owns the copyright of the Neuropsychiatric Inventory
- Dr. Cummings has stock options in Prana, Neurokos, ADAMAS, Medavante

Cleveland Clinic Lou Ruvo Center for Brain Health

LRCBH; Folded Architecture

Frank Gehry, architect

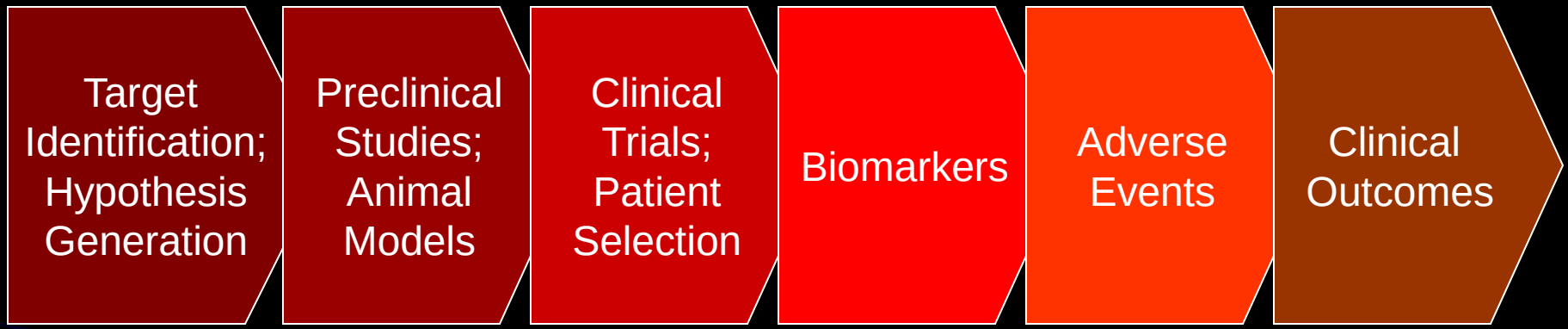
Misfolded Amyloid Protein



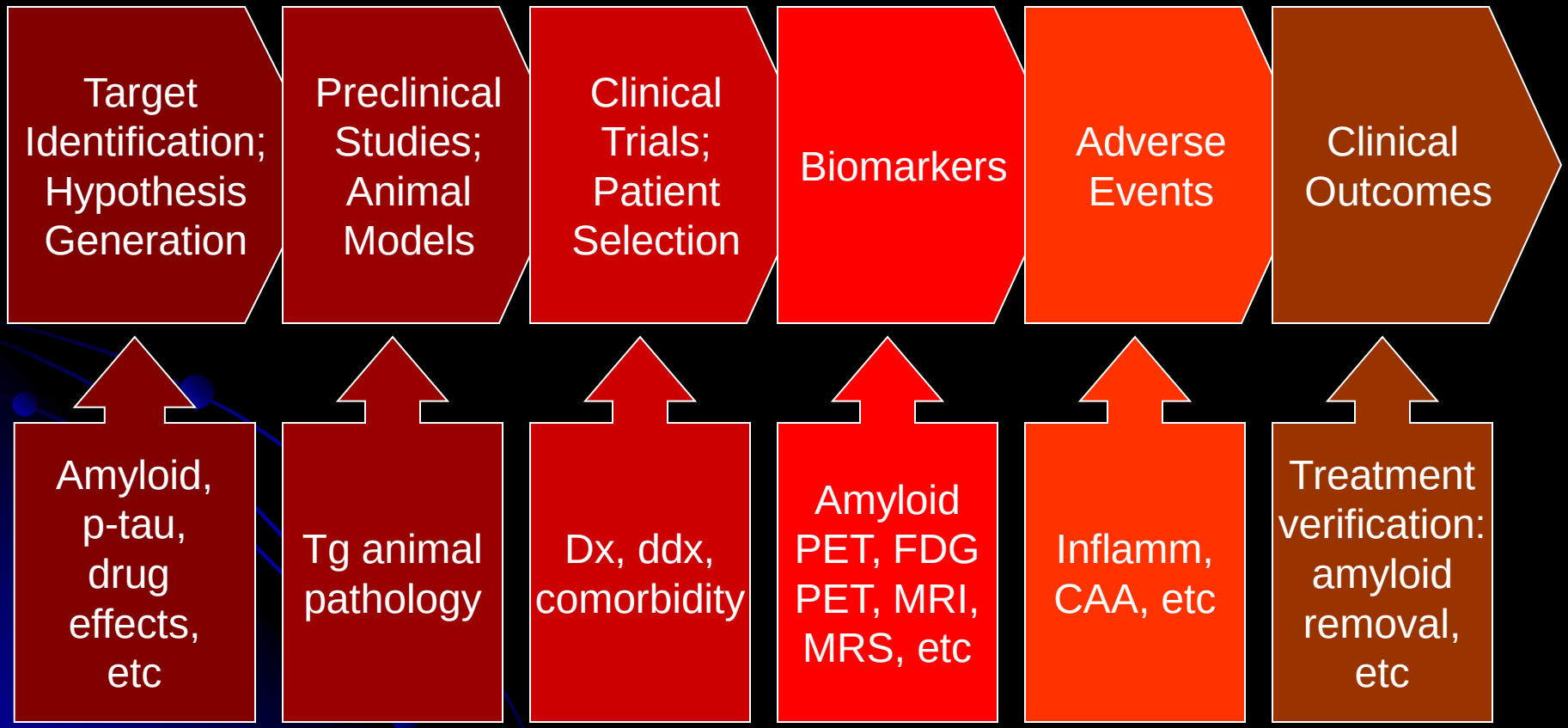
Neuropathology Contributions to Clinical Trials

- Target validation
- Animal model pathology
- Patient selection
- Biomarkers
- Adverse events
- Verification of drug effect
- Hypothesis generation of drug effects
- Emphasis on morphologic and histopathology

Stages of Drug Development and Neuropathology Relationships



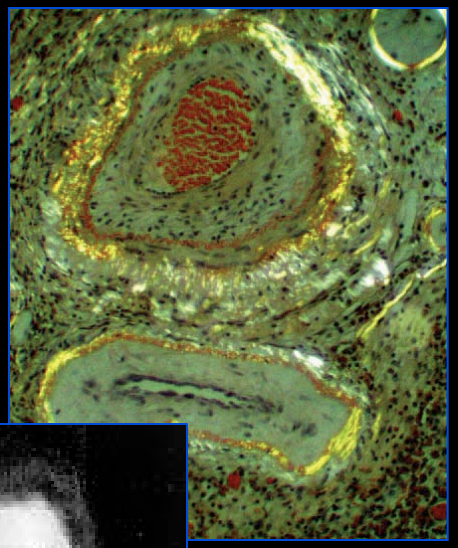
Stages of Drug Development and Neuropathology Relationships



Neuropathology Contributions to Clinical Trials: Target Validation

- Amyloid protein in vessels
  - George Glenner, 1984
- Amyoid protein in plaques (AD, DS)
  - Wong, Glenner (1985)
- Hyperphosphoylated tau in NF tangles
  - Iqbal, 1974

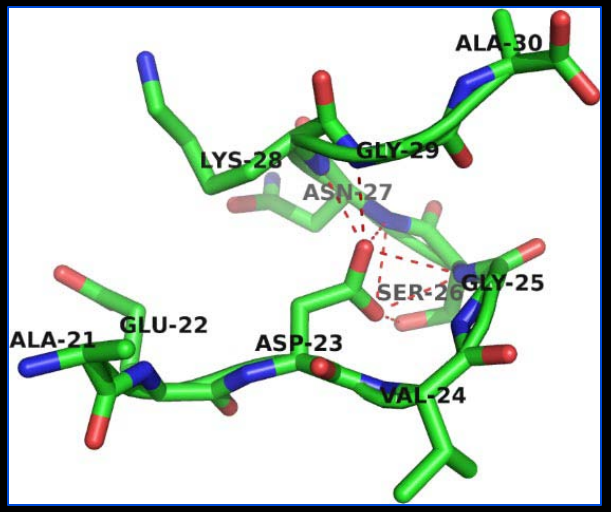
CAA

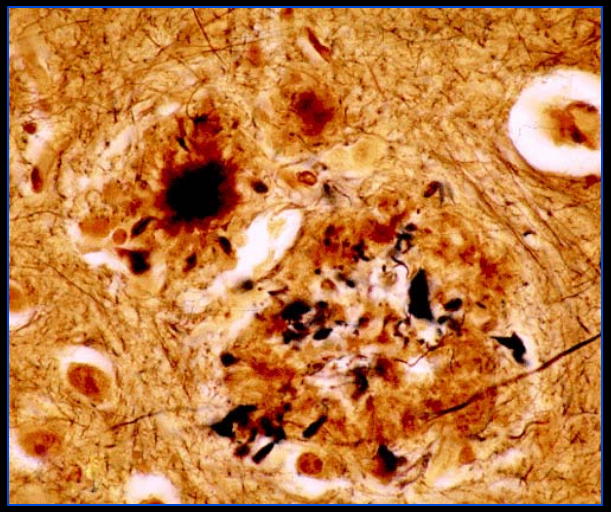


Glenners

Amyloid-Based Clinical Trials

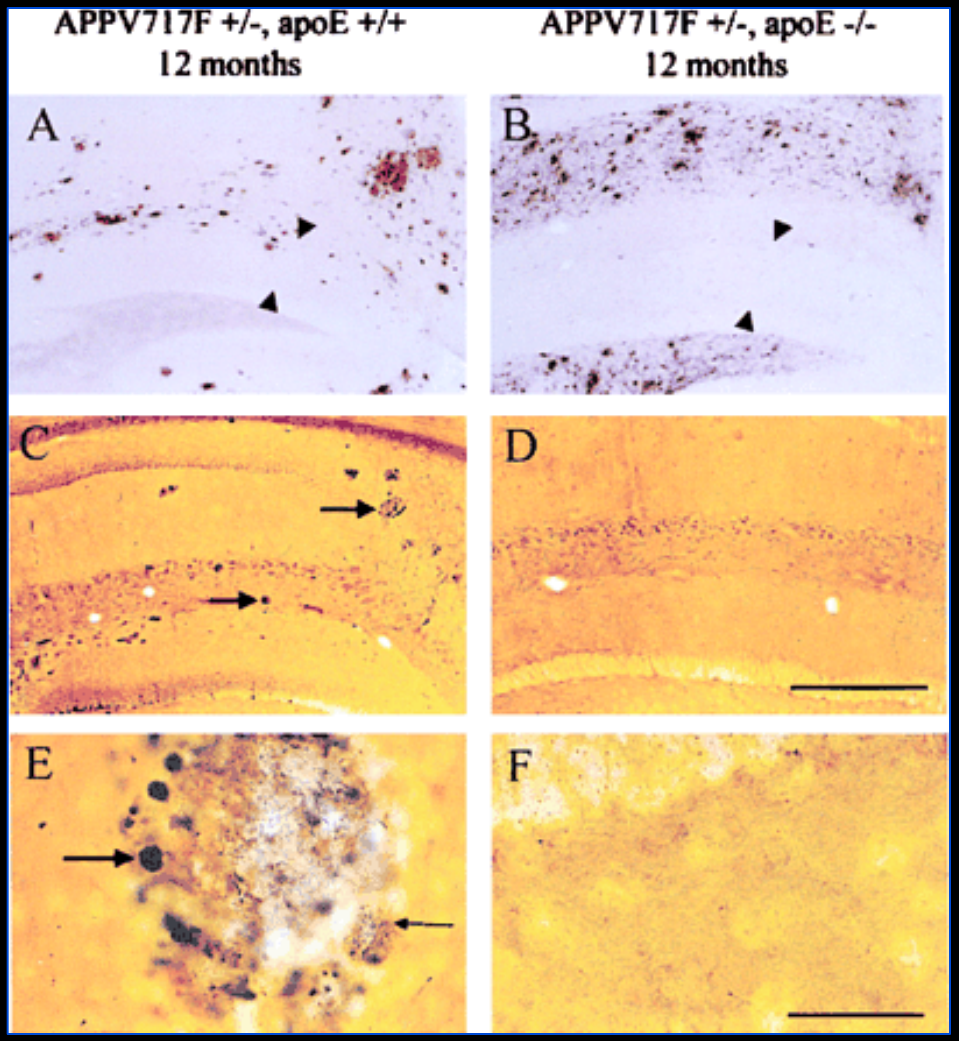
- Immunotherapies
- Beta-secretase inhibitors
- Gamma-secretase inhibitors
- Alpha secretase enhancers
- Aggregation inhibiting agents
- BBB agents (inhibit import; facilitate export)
- Degradation enhancers





Neuropathology Contributions to Clinical Trials: Animal Models

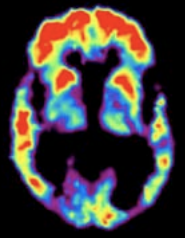
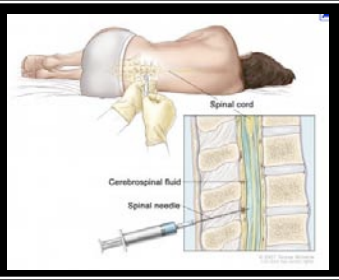
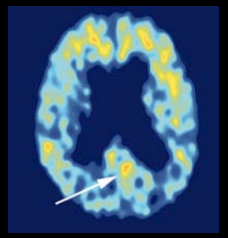
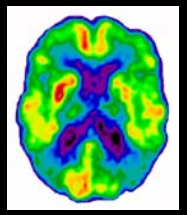
- APP transgenics
- APP/PS1 2x tg
- APP/PS1/tau 3x tg
- Arctic mutations
- Effect of e4
- Tau mutants
- Tau knockouts
- Time effects
- Microhemorrhages



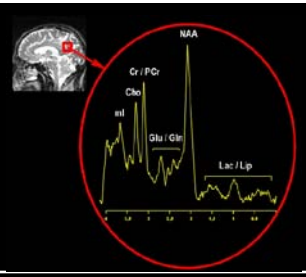
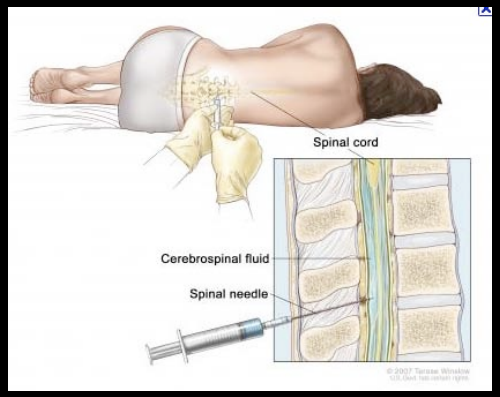
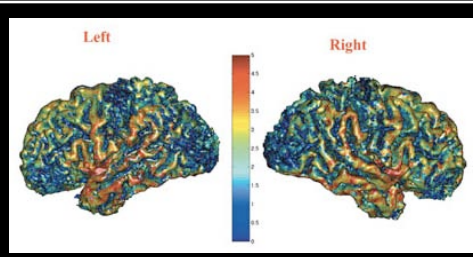
Neuropathology Contributions to Clinical Trials: Patient Selection

- Clinical-pathological correlations in AD diagnosis and differential diagnosis
  - Exclude non-AD dementias
- Exclude comorbid condition
  - Cerebrovascular disease
  - Microhemorrhages in immunotherapy trials

Neuropathology Contributions to Clinical Trials: Biomarkers

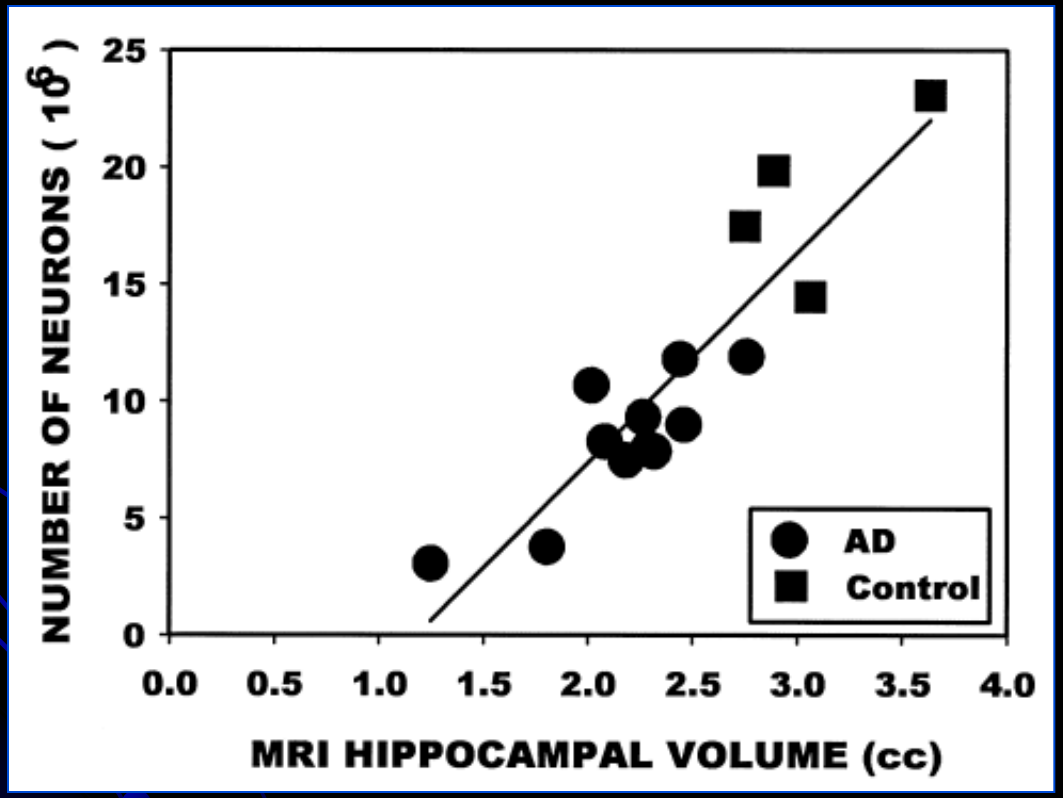
Neuritic and diffuse plaques	Amyloid imaging	
Neuritic and diffuse plaques	Decreased CSF A-beta 42	
Neurofibrillary tangles	FDDNP	
Synaptic pathology	FDG PET	

Neuropathology Contributions to Clinical Trials: Biomarkers

Cell loss (NAA content)	MRS	
Cell loss	CSF total tau	
Extracellular NFTs	CSF p-tau	
Neurodegeneration; cell loss	MRI atrophy; cortical thinning	

Neuropathology Contributions to Clinical Trials: Biomarkers

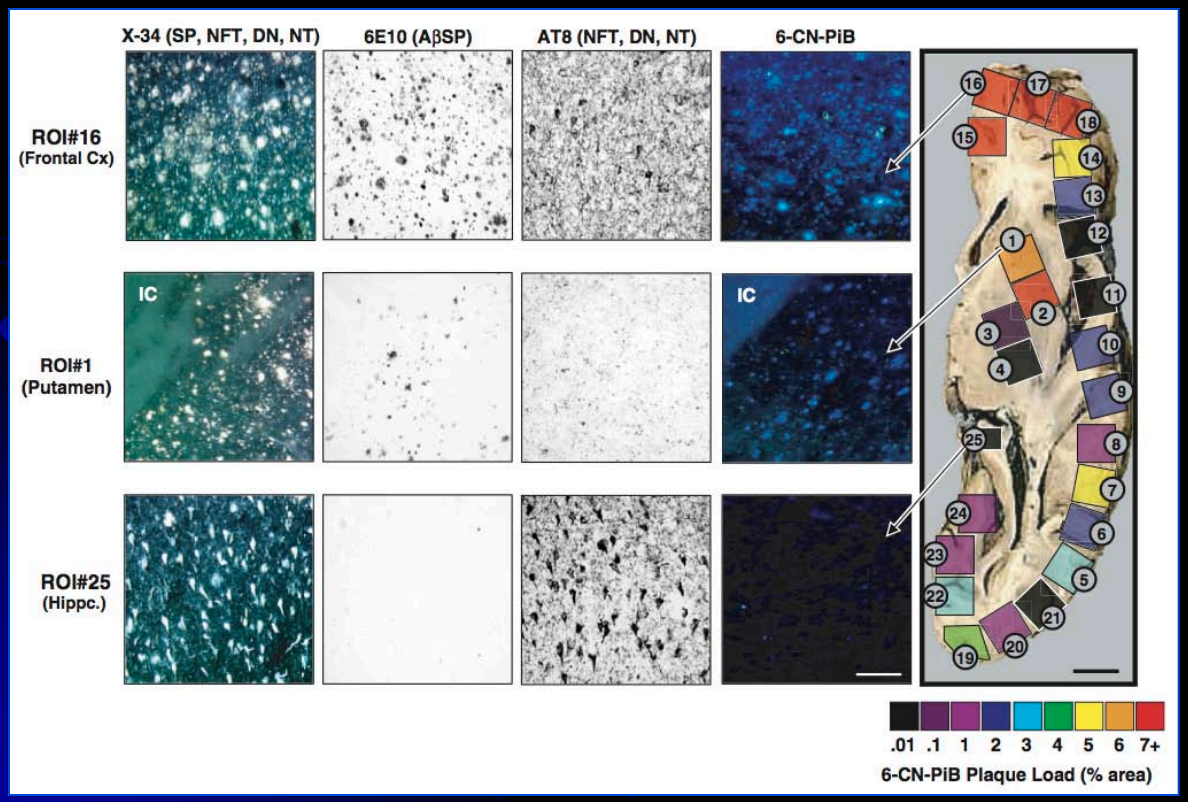
- Cell loss correlates with MRI atrophy

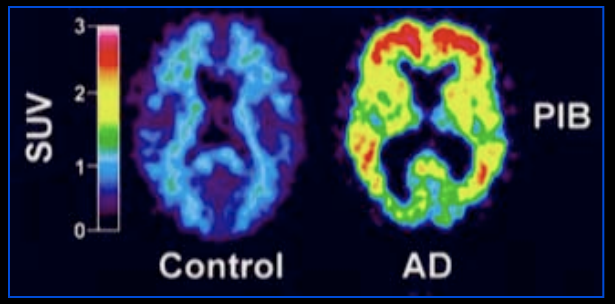


Bobinski M et al. Neurosci 2000; 95: 721-725

Neuropathology Contributions to Clinical Trials: Amyloid Imaging

- PIB binds to fibrillar amyloid: neuritic plaques and diffuse plaques



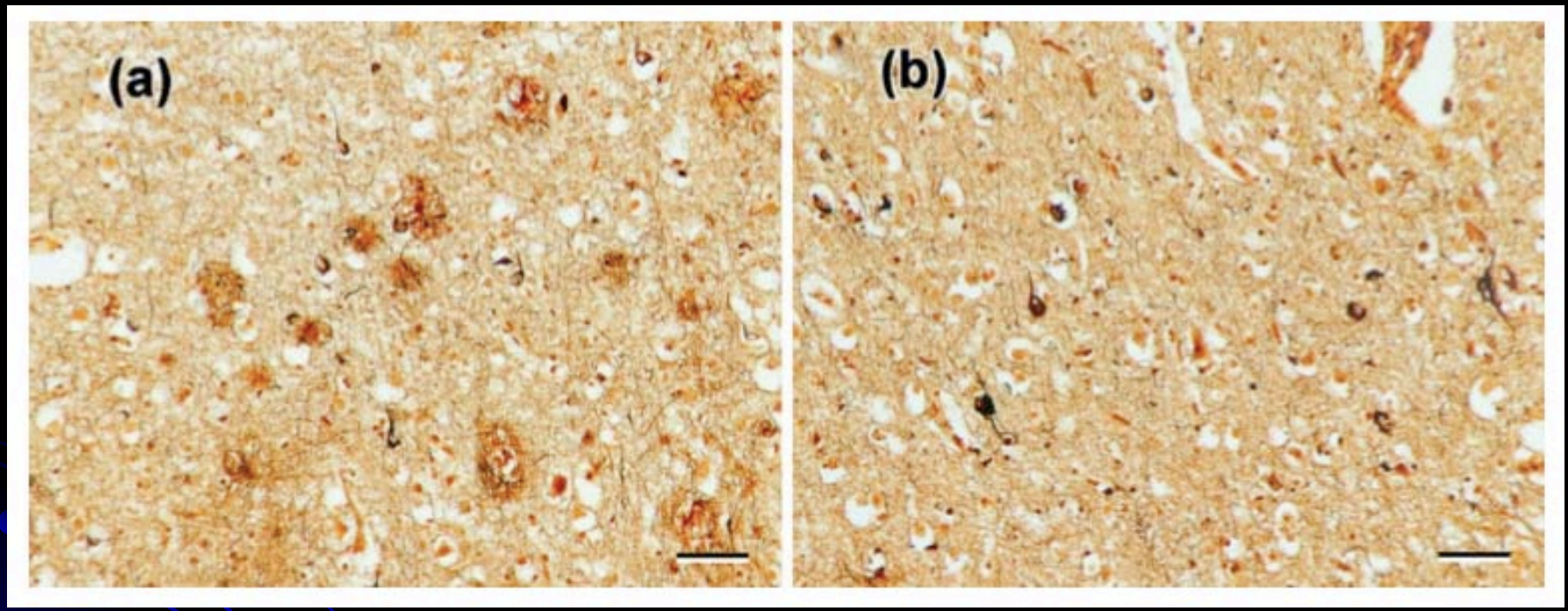


(Ikonomovic MD, et al. Brain 2008; 131: 1630-1645)

Neuropathology Contributions to Clinical Trials: Treatment Verification

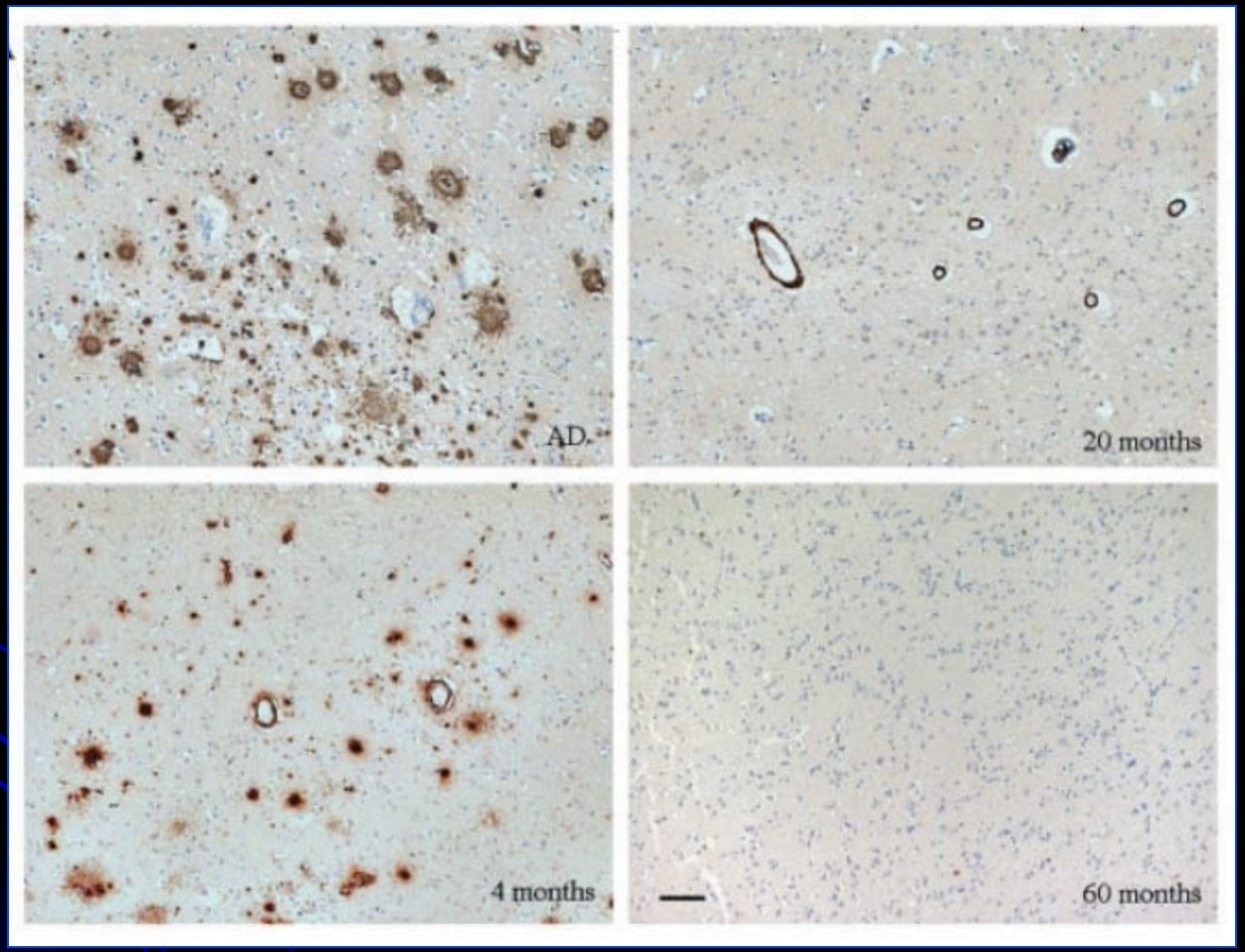
- AN 1792
  - Plaque removal
  - Increase in congophilic angiopathy (at least early in the course of treatment)
  - No change in neurofibrillary tangles
  - Reduction in neuritic dystrophy
  - Encephalitis features

AN 1792: Neuropathology Provides Insight into Drug Activity



Weller RO et al. Acta Neuropath 2009 (on line)

Evolution of Cerebral Angiopathy Following AN1792 Vaccination



(Broche D et al. Brain 2008)

Neuropathologic Correlations with Clinical Trial Measures

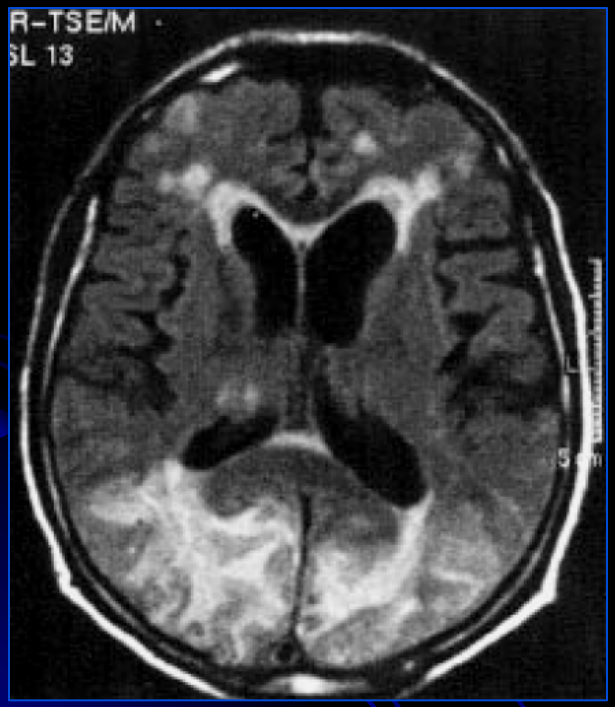
Trial Instrument	Neuritic Plaques	Braak Stage	Total Neuropath Burden
MMSE	-0.29 (0.0001)	-.35 (0.0001)	-0.39 (0.0001)
Logical memory	-0.39 (0.0001)	-0.50 (0.0001)	-.54 (0.0001)
FAQ	0.54 (0.0001)	0.56 (0.0001)	0.56 (0.0001)
NPI-Q	0.16 (0.04)	0.43 (0.0001)	0.36 (0.0001)
CDR-sb	0.54 (0.0001)	0.63 (0.0001)	0.64 (0.0001)

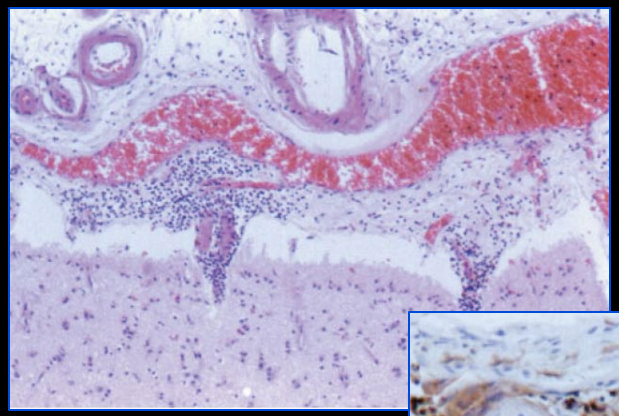
CDR0sb – Clinical Dementia Rating sum of the boxes; FAQ – Functional Activity Questionnaire; NPI-Q – Neuropsychiatric Inventory Questionnaire

Cummings JL et al. ICAD 2010

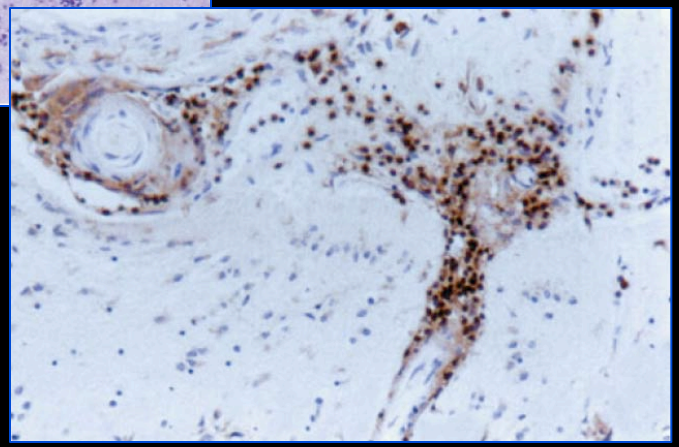
Neuropathology Contributions to Clinical Trials: Adverse Events

- Encephalitis in the AN 1792 trials





Encephalitis with T-cell infiltration



Orgogozo Jm et al. Neurology 2003; 61: 46-54; Nicoll JAR et al, Nature Med 2003; 4: 448-452

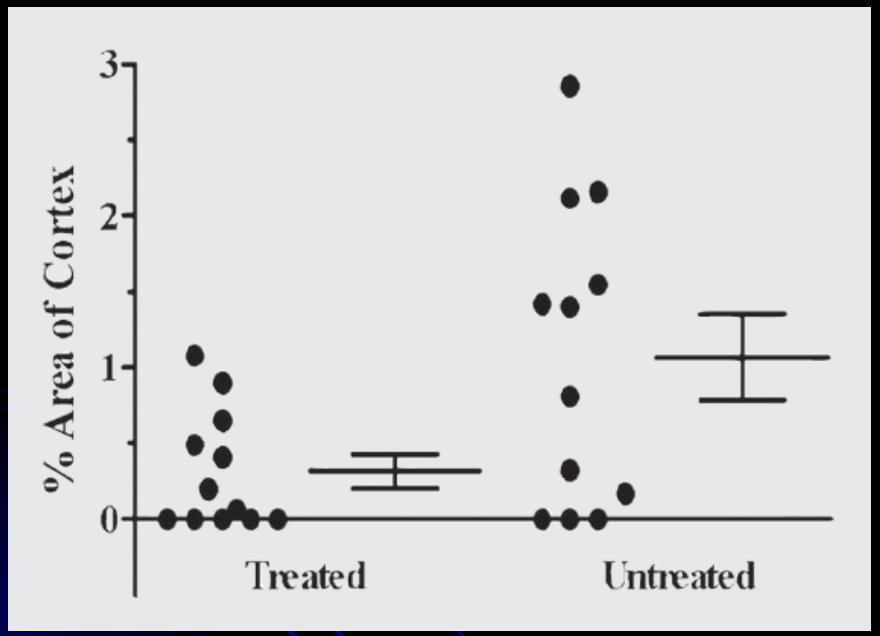
Treatment-Related Observations

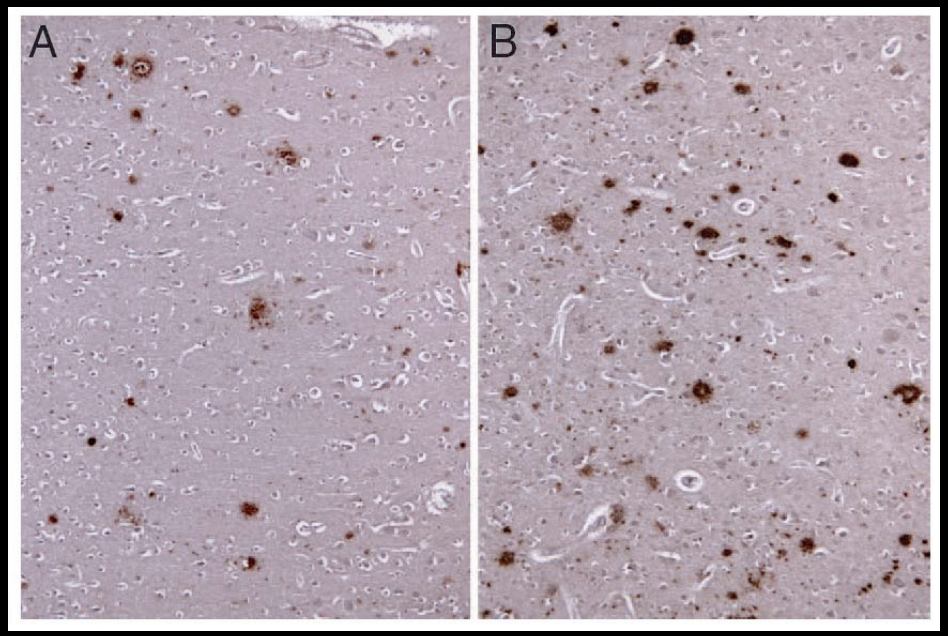
- The following pathology observations have been reported in relation to treatment
- These are not based on comparison of treatment and placebo groups in trials and are subject to bias

Treatment-Related Observations

- Reduced plaque burden in DLB patients treated with cholinesterase inhibitors
- Increased plaque burden with chronic anticholinergic therapy
- Reduced plaque burden in patients treated with statins
- Other

Cholinesterase Inhibitors May Reduce Aß in DLB

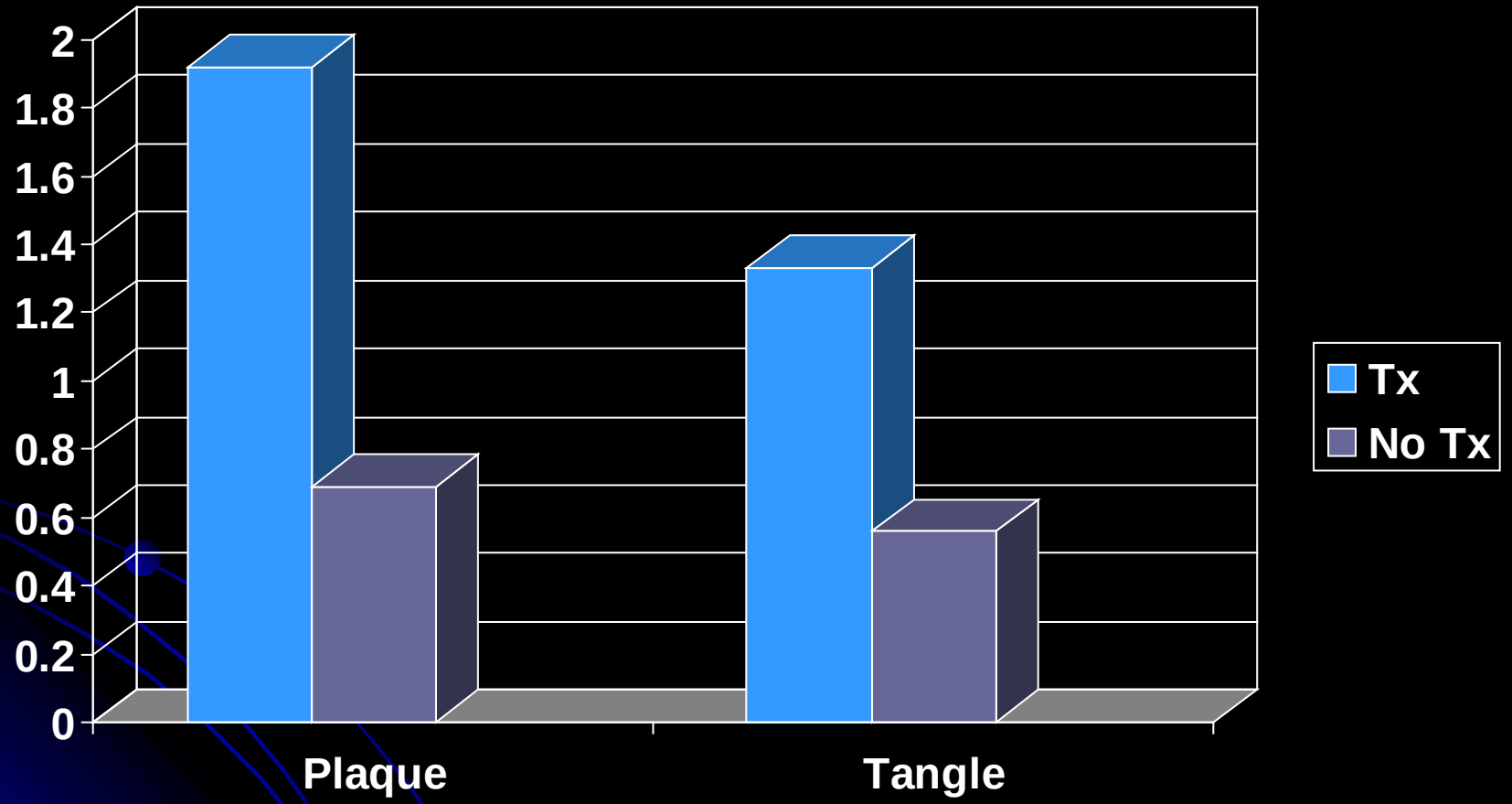




With ChE-I Without ChE-I

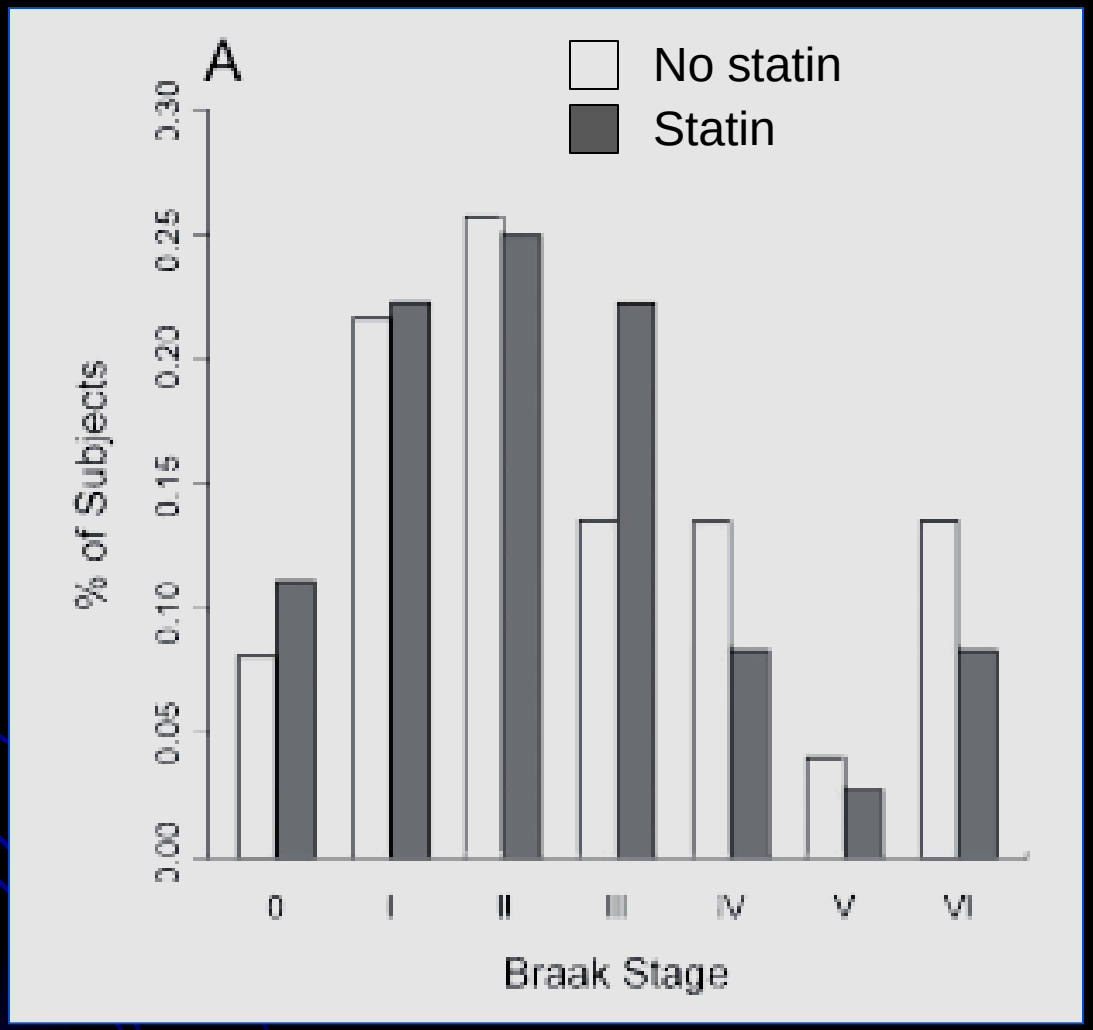
Ballard CG et al. Neurol 2007; 68: 1726-1729

Anticholinergic Treatment Has Been Associated with Increased Plaque and Tangle Burden



Perry EK et al. Ann Neurol 2003; 54: 235-238

Statins May Reduce Tangle Burden



Li G et al. Neurol 2007; 69: 878-885

Neuropathology Contributions to Clinical Trials: Critical Importance

- Neuropathology studies are critical to better understand the neurobiological effects of disease-modifying therapies
  - Type
  - Magnitude
  - Sequence
  - Relationships
    - Biomarkers
    - Clinical outcomes
  - Adverse events