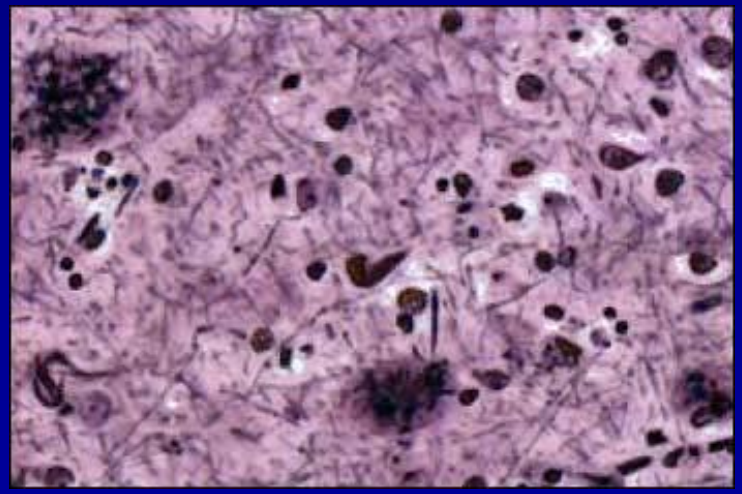
Why is there no treatment for dementia yet?

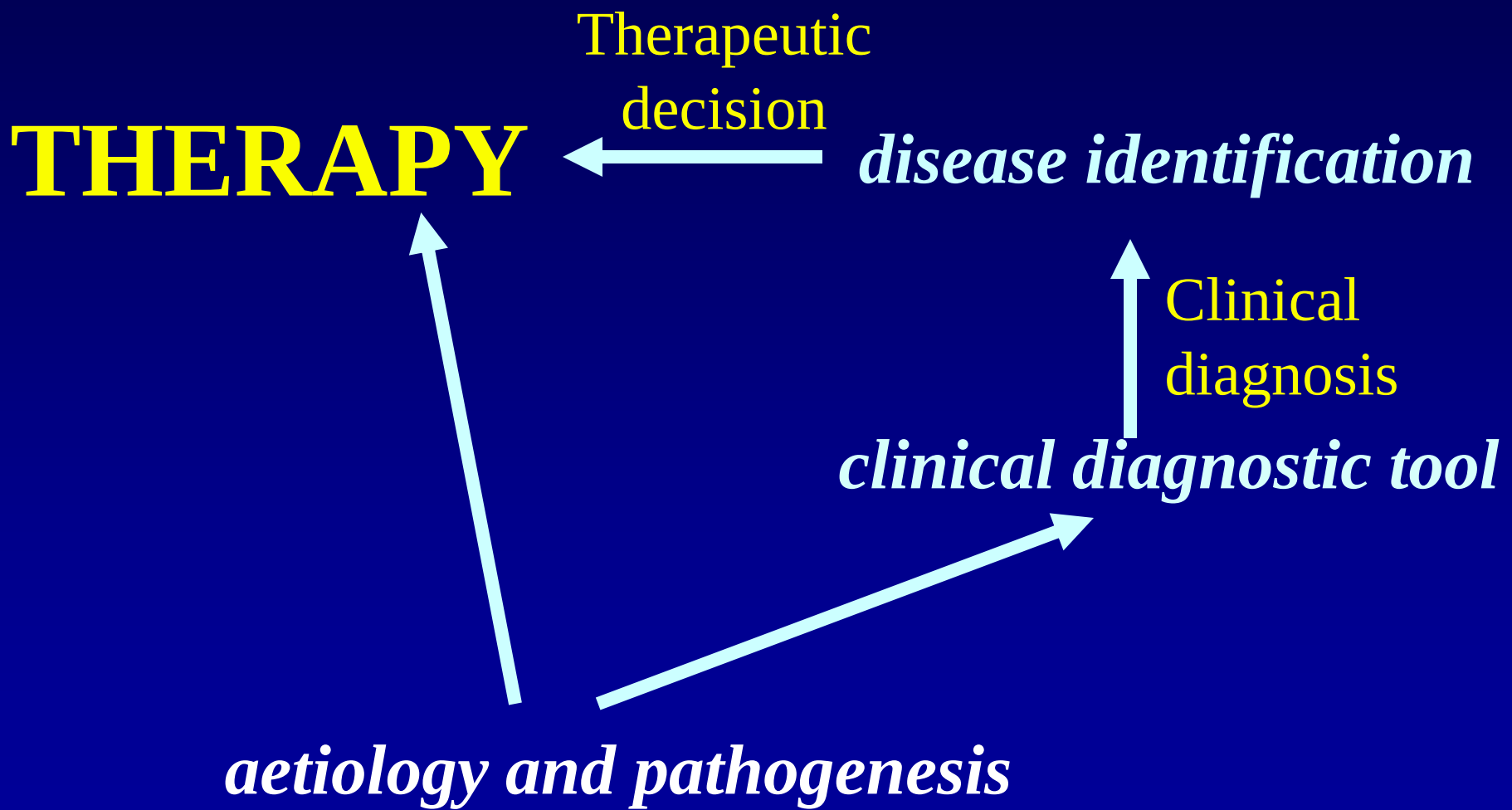
Dr. Zsuzsanna Nagy
University of Birmingham

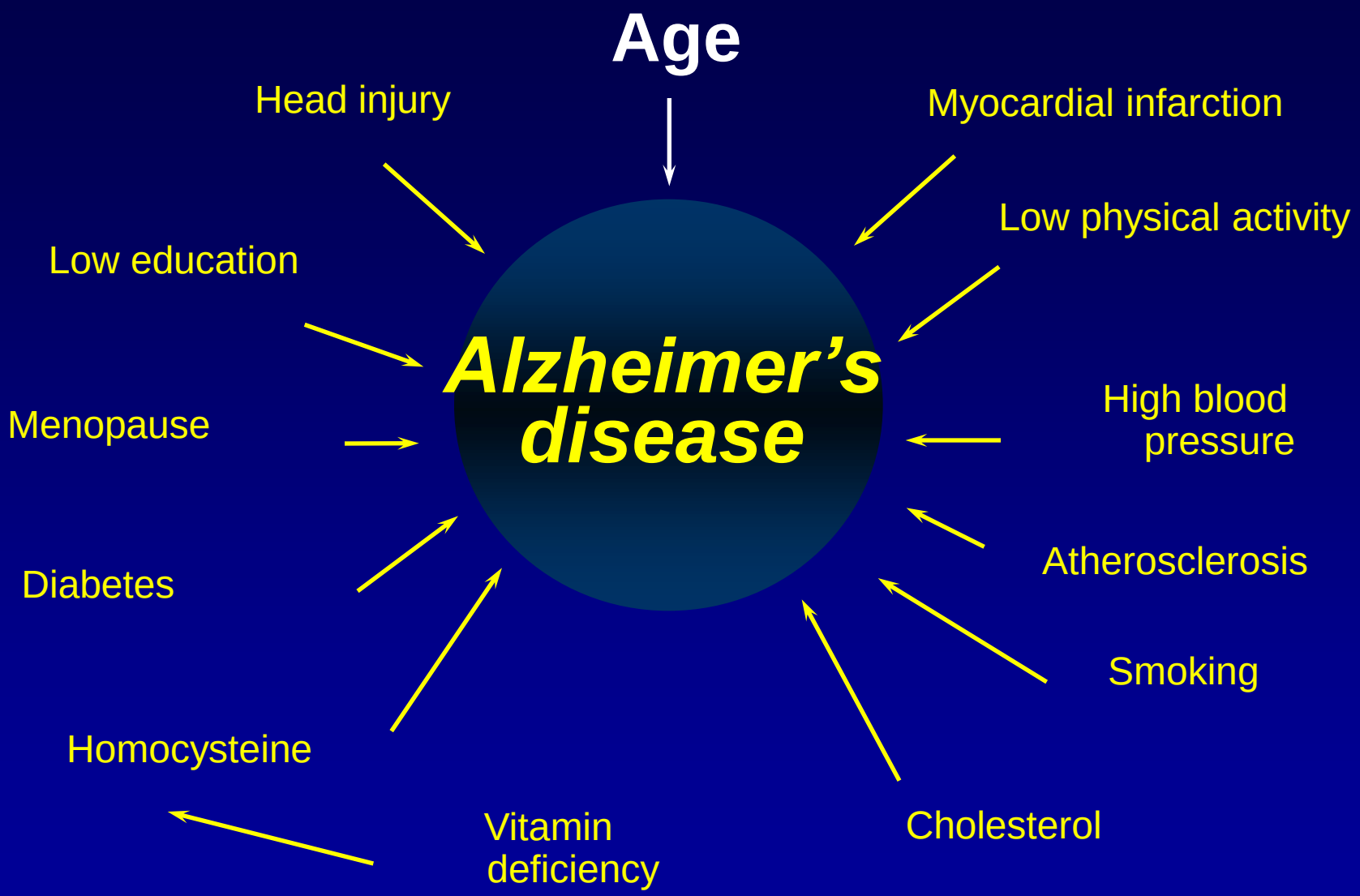
Alois Alzheimer

Auguste Deter

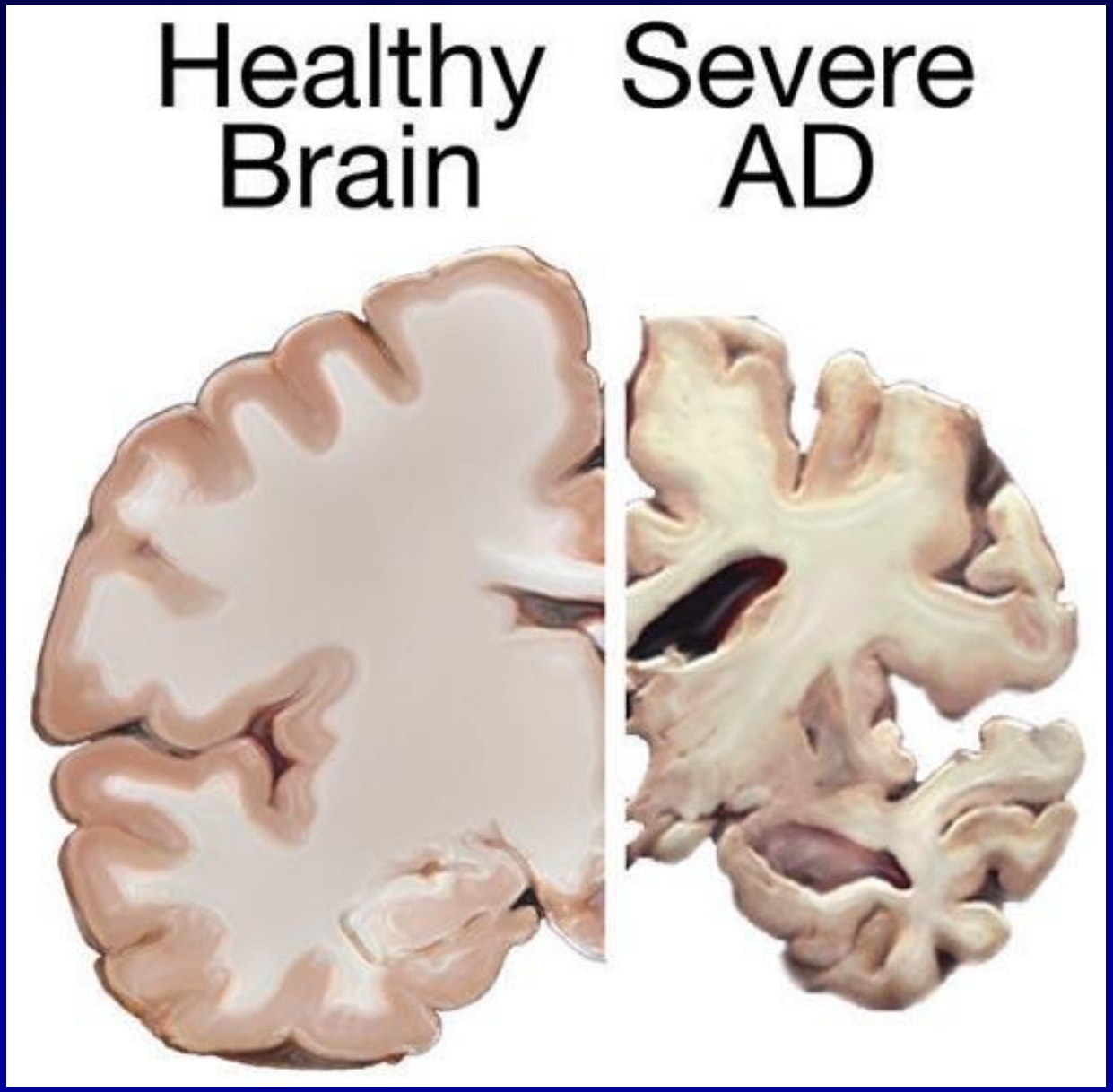


The challenge




Age
Head injury
Myocardial infarction
Low physical activity
Low education
Alzheimer's disease
Menopause
High blood pressure
Diabetes
Atherosclerosis
Smoking
Homocysteine
Vitamin deficiency
Cholesterol

Brain atrophy in Alzheimer's disease

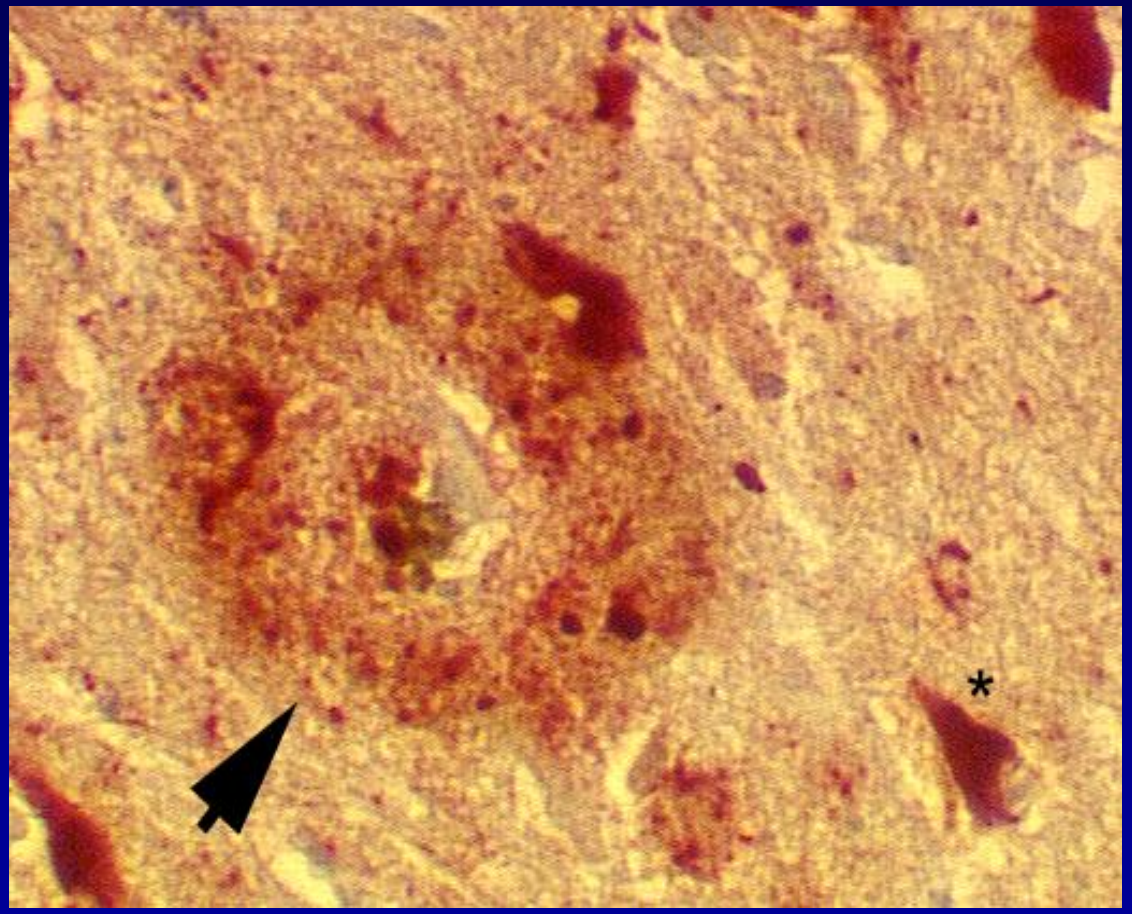


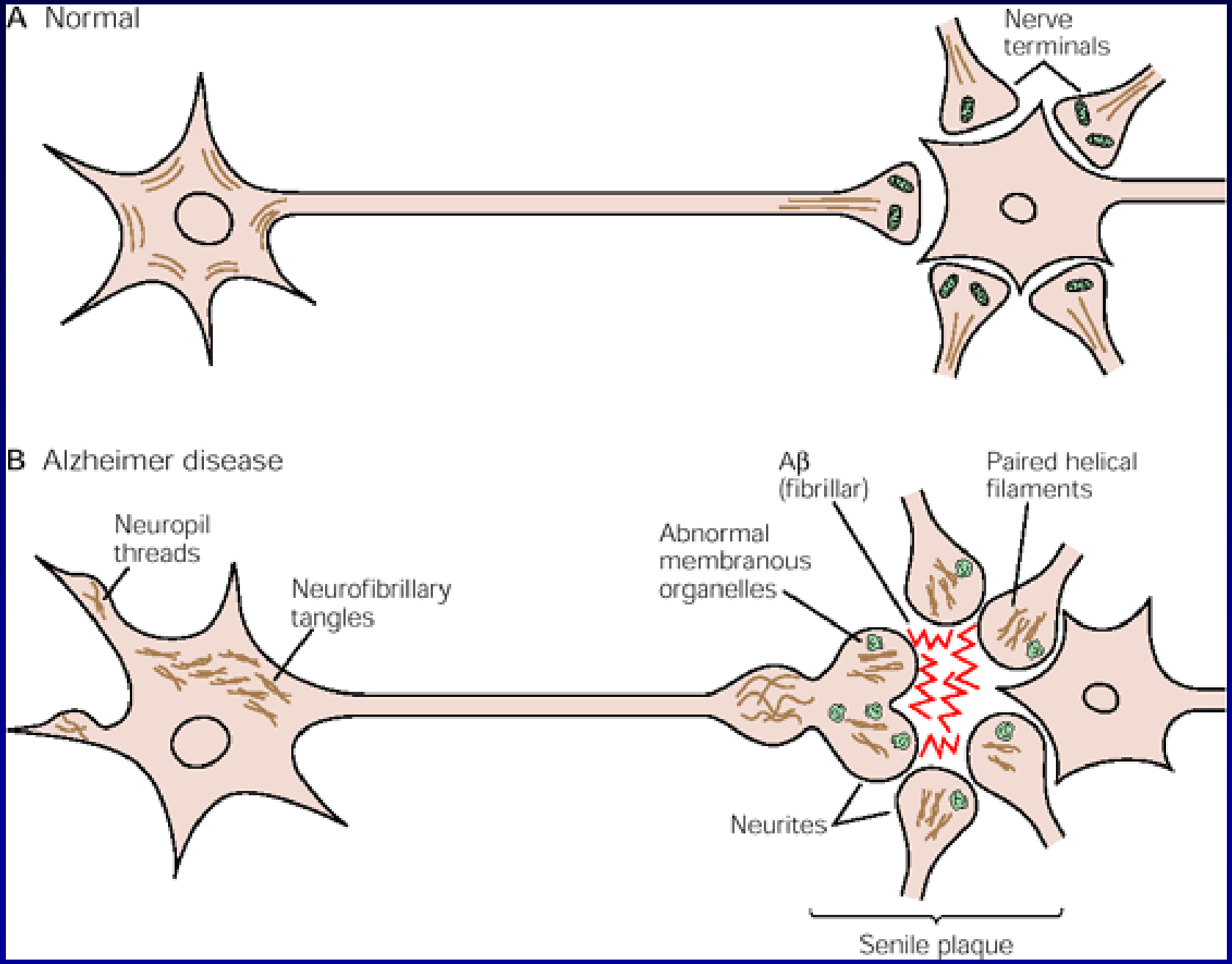
Alzheimer-type pathology

Immunohistochemistry

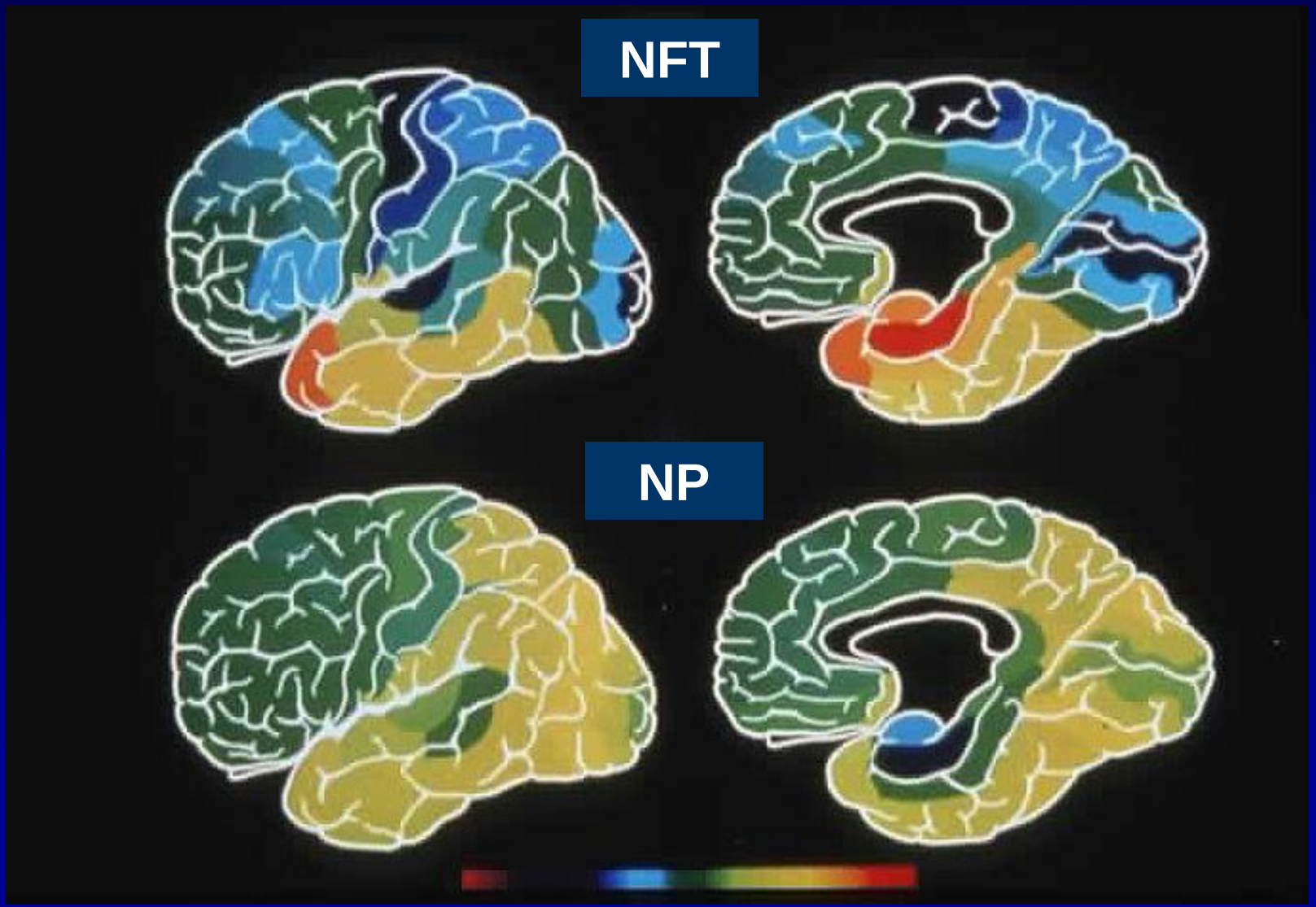
Brown: β-amyloid
Red: hyperphosphorylated tau

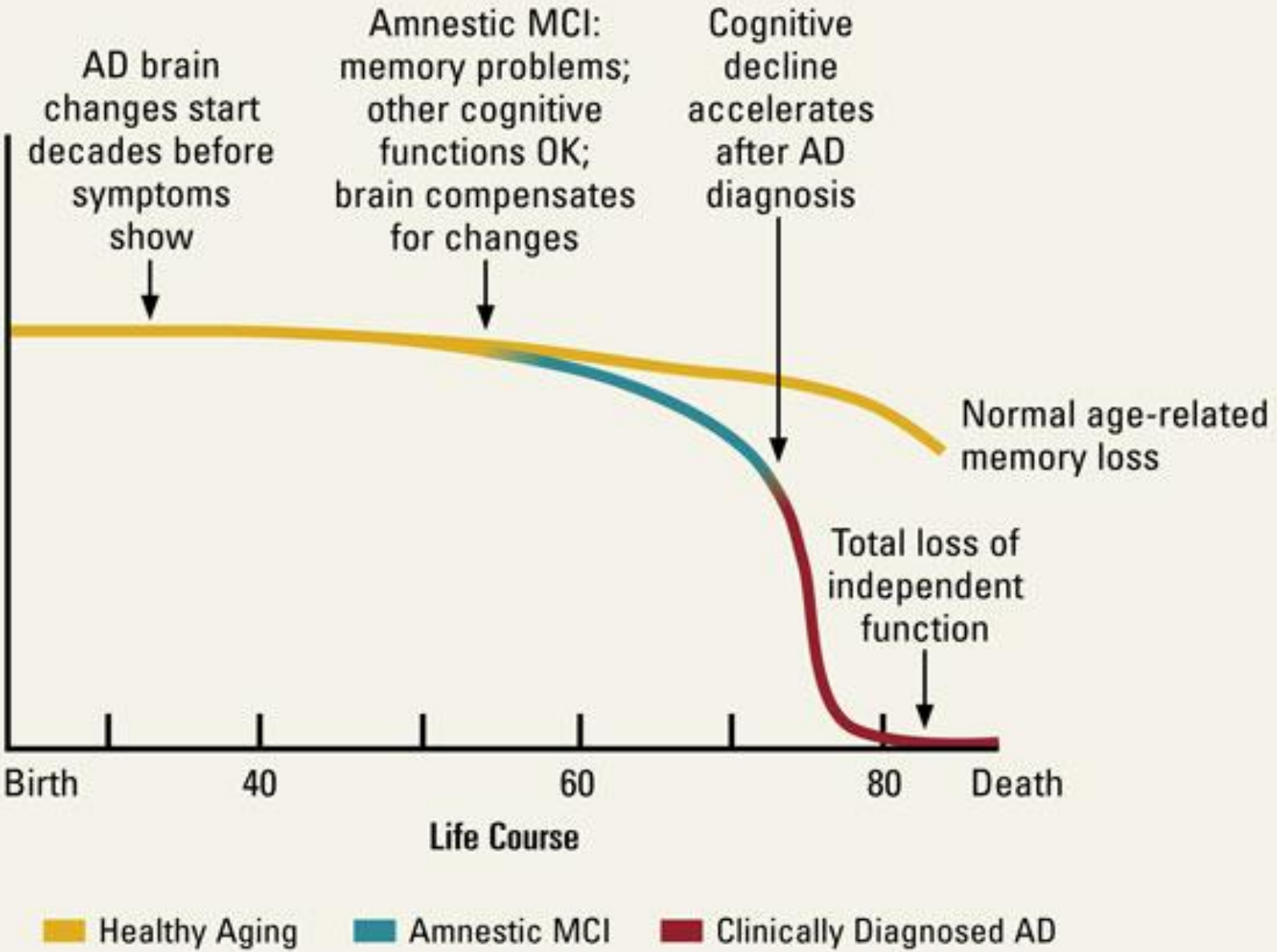
•Arrow: senile (neuritic) plaque
•Star: tangle

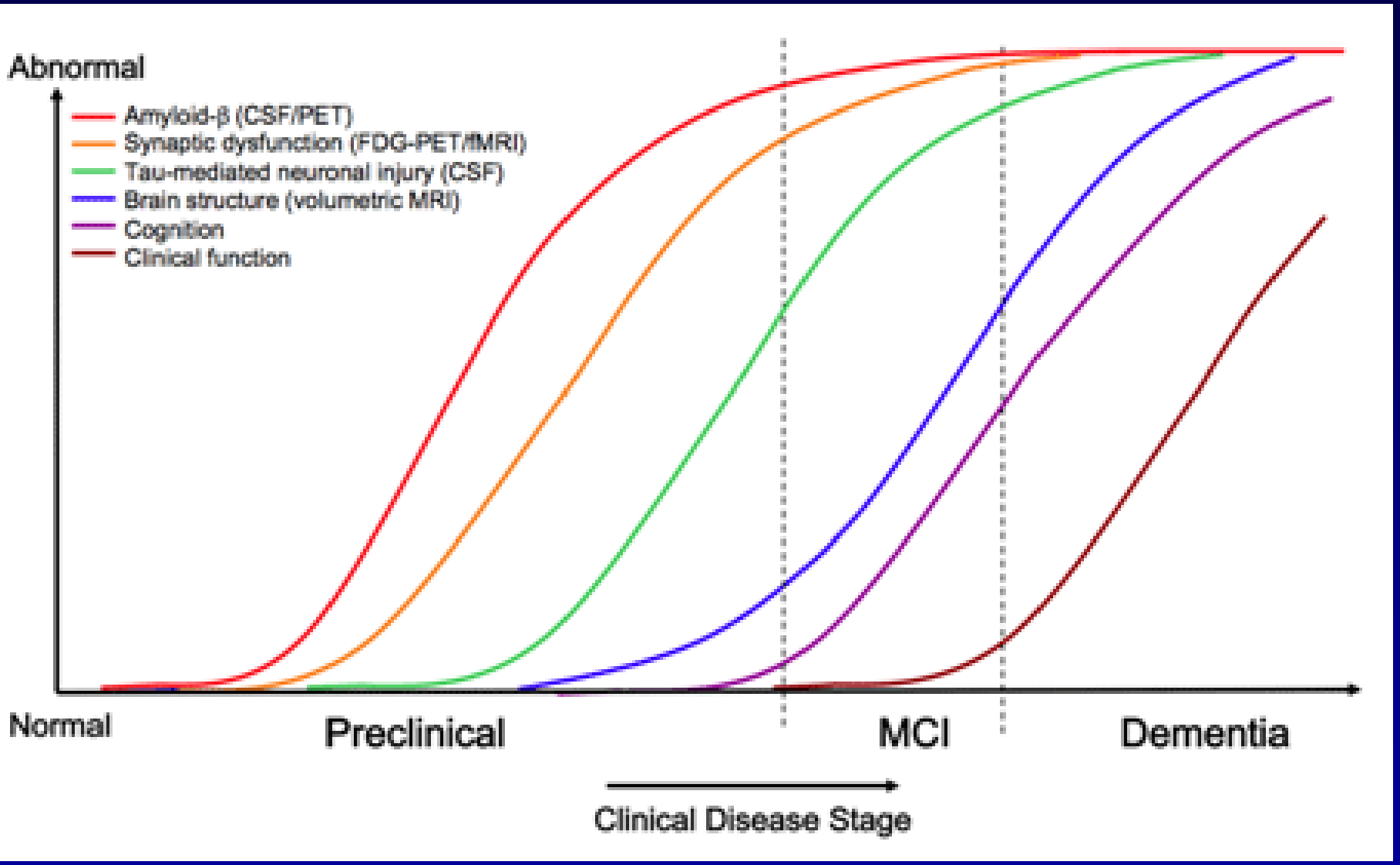



A Normal
Nerve terminals
B Alzheimer disease
Neuropil threads
Neurofibrillary tangles
Aβ (fibrillar)
Paired helical filaments
Abnormal membranous organelles
Neurites
Senile plaque

Distribution Of Tangles (NFT) & Plaques (NP) In AD The Brain




AD brain changes start decades before symptoms show
Amnestic MCI: memory problems; other cognitive functions OK; brain compensates for changes
Cognitive decline accelerates after AD diagnosis
Normal age-related memory loss
Total loss of independent function
Birth
40
60
80
Death
Life Course
Healthy Aging
Amnestic MCI
Clinically Diagnosed AD


Abnormal
Amyloid-β (CSF/PET)
Synaptic dysfunction (FDG-PET/fMRI)
Tau-mediated neuronal injury (CSF)
Brain structure (volumetric MRI)
Cognition
Clinical function
Normal
Preclinical
MCI
Dementia
Clinical Disease Stage

The pathogenesis of Alzheimer's disease

Genetic factors

Ageing

Environmental factor

?

?

?

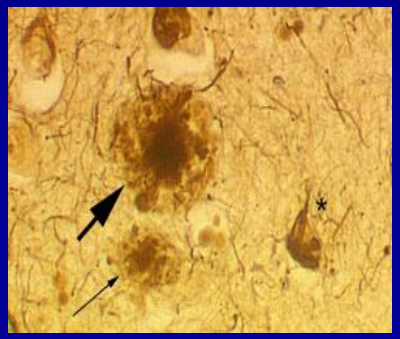
?

Metabolic abnormalities

?

Altered processing of APP

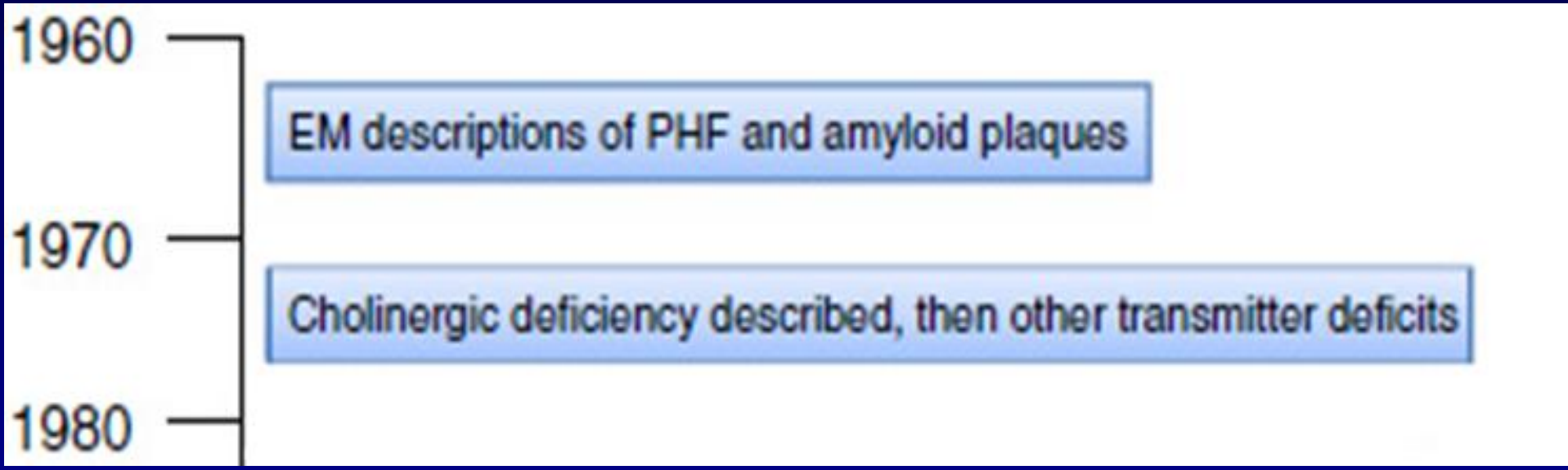
Destabilization of microtubules
Hyperphosphorylation of tau



Amyloid plaques

Tangles

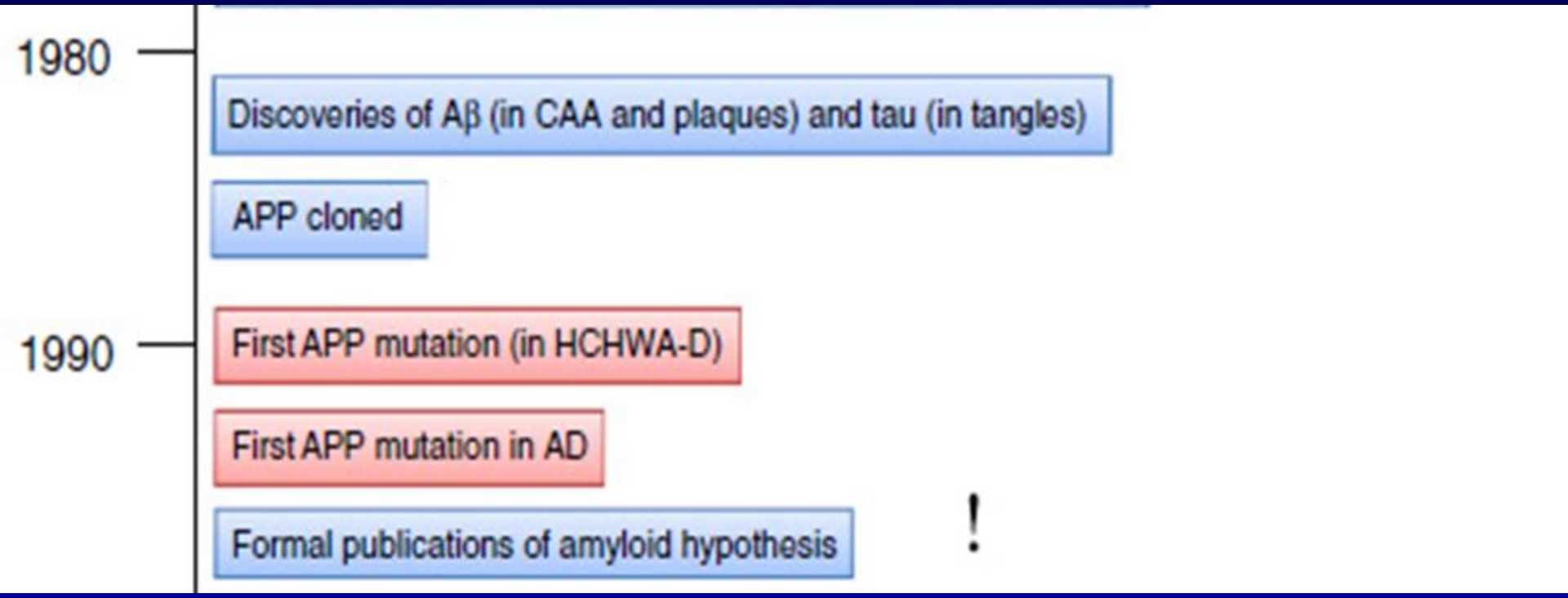
The first therapeutic attempt



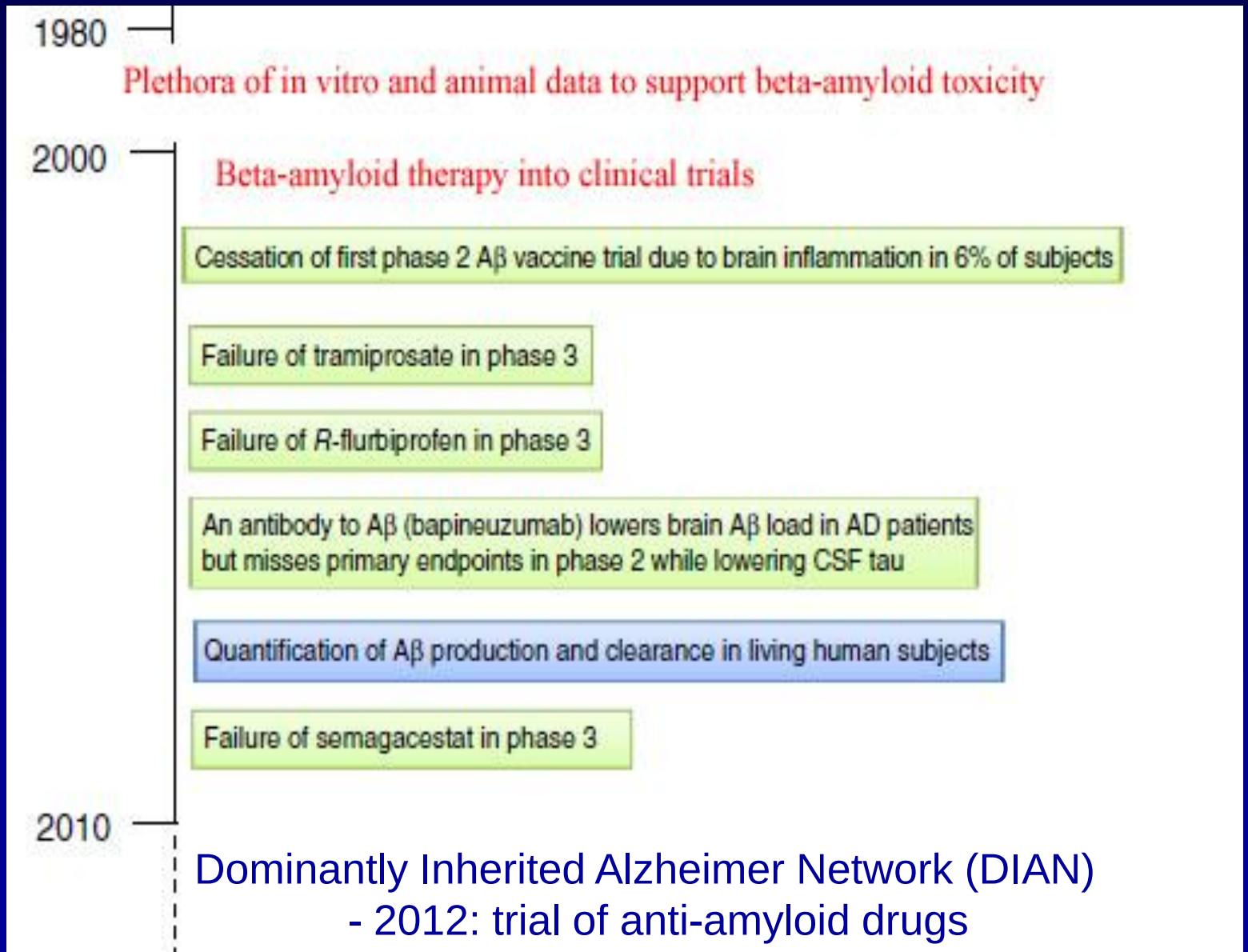
Anticholinesterase drugs – enhance cholinergic activity (Tacrin, Aricept)

- –Only symptomatic treatment
- –Modest, short-term effects

The revolution of the 80s



The aftermath of the revolution



The pathogenesis of Alzheimer's disease

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Environmental facto

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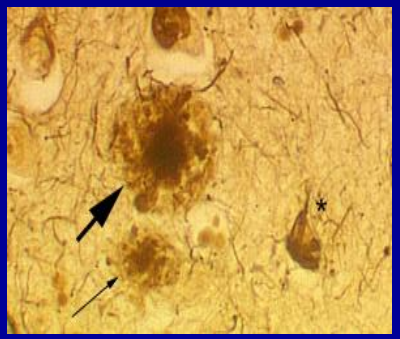


Amyloid plaques

Tangles

Pre-clinical proof of concept

- In vitro models

- In vivo models – transgenic animals
  - Amyloid based
  - Triple transgenic

Inadequate models of disease
  – inadequate targets
    – failure in clinic

Drug development and testing
What the regulator wants

- Symptomatic improvement – TOOLS?!
  - enhanced cognition
  - more autonomy
  - improvement in behavioural dysfunction.

Choice of tools

"No method for evaluation ….. emerged as the reference technique, … [therefore] the choice of assessment tools should remain open, provided that the rationale for their use is presented, and justified"

Disease modifying effects

"Up to now no clinical trial has led to a successful claim of disease modification in dementing conditions."

"….. a true disease modifying effect cannot be established conclusively based on clinical outcome data alone, …..

must be accompanied by strong supportive evidence from a biomarker programme. …. this is difficult to achieve without an adequately qualified and validated biomarker…."

Disease modifying effects

"Two-step approach"

- delay in the natural course of progression of the disease - clinical signs and symptoms
- convincing package of biological/neuroimaging data
  - delay in the progression of brain atrophy
- Mild/moderate dementia patients – too late for DMT!!!!!

Primary prevention

- reduce incidence

"Unfortunately trials so far have not given conclusive results… due to methodological reasons…"

- High baseline variability
- Heterogeneous populations
- Outcomes not sensitive to change
- Ceiling effects of assessment tools
- Rarity of proposed outcome, etc.
- Length of follow-up
- Timing in relation to possible dementia onset

Patient numbers required for trials

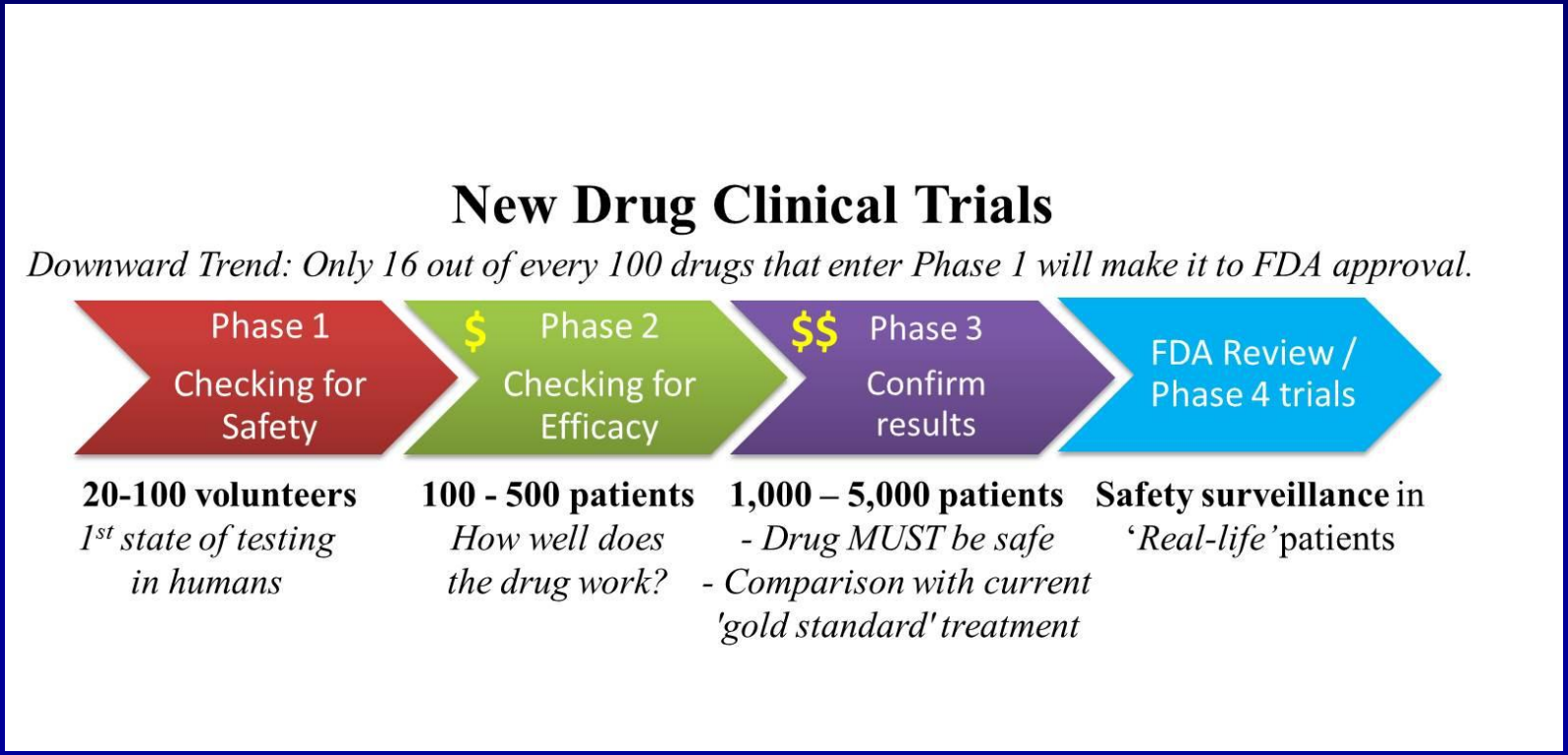
Withdrawal of patients – up to 27%!

- too complex trial protocol
- problems with informed consent

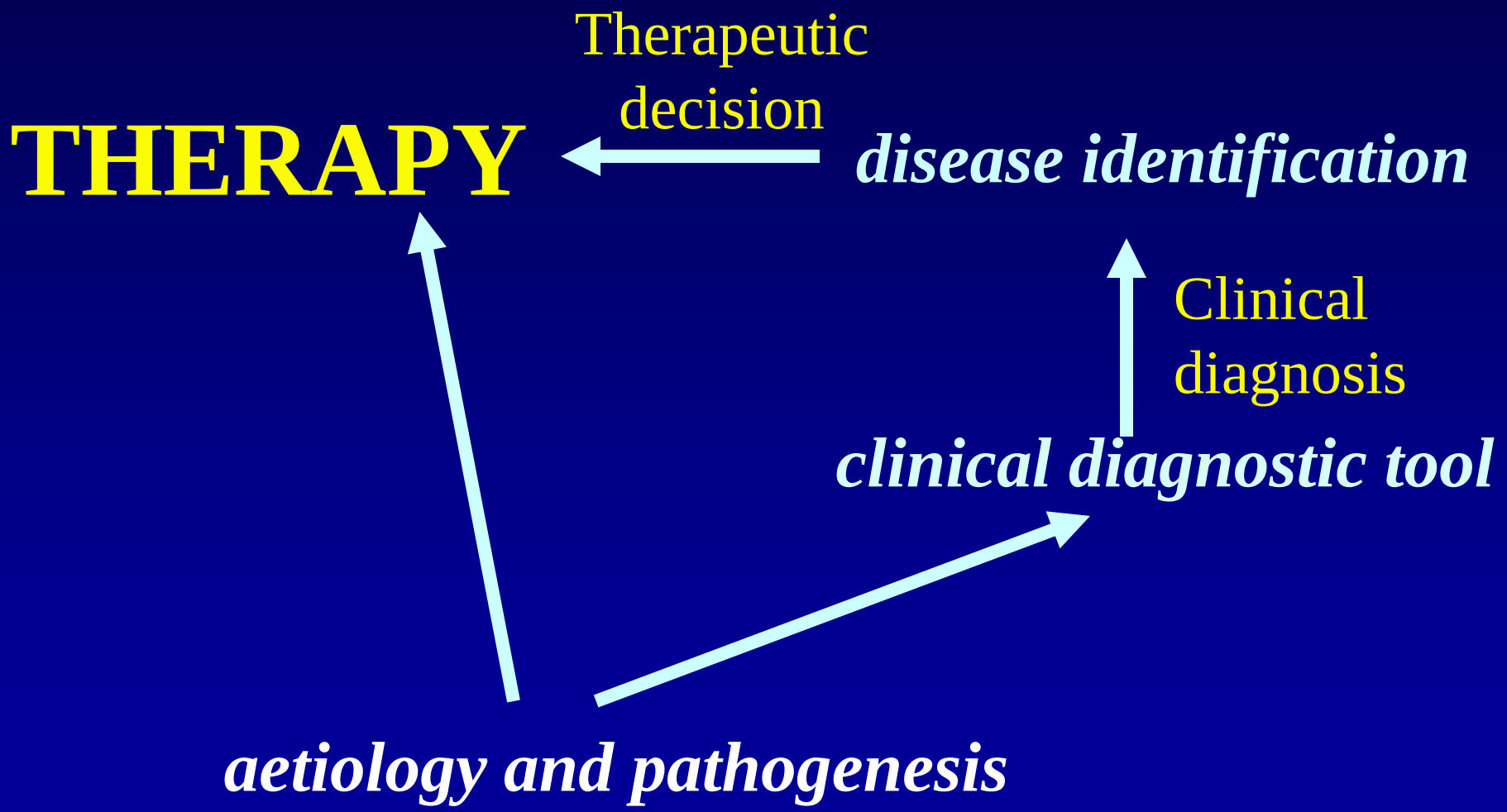
Trial costs

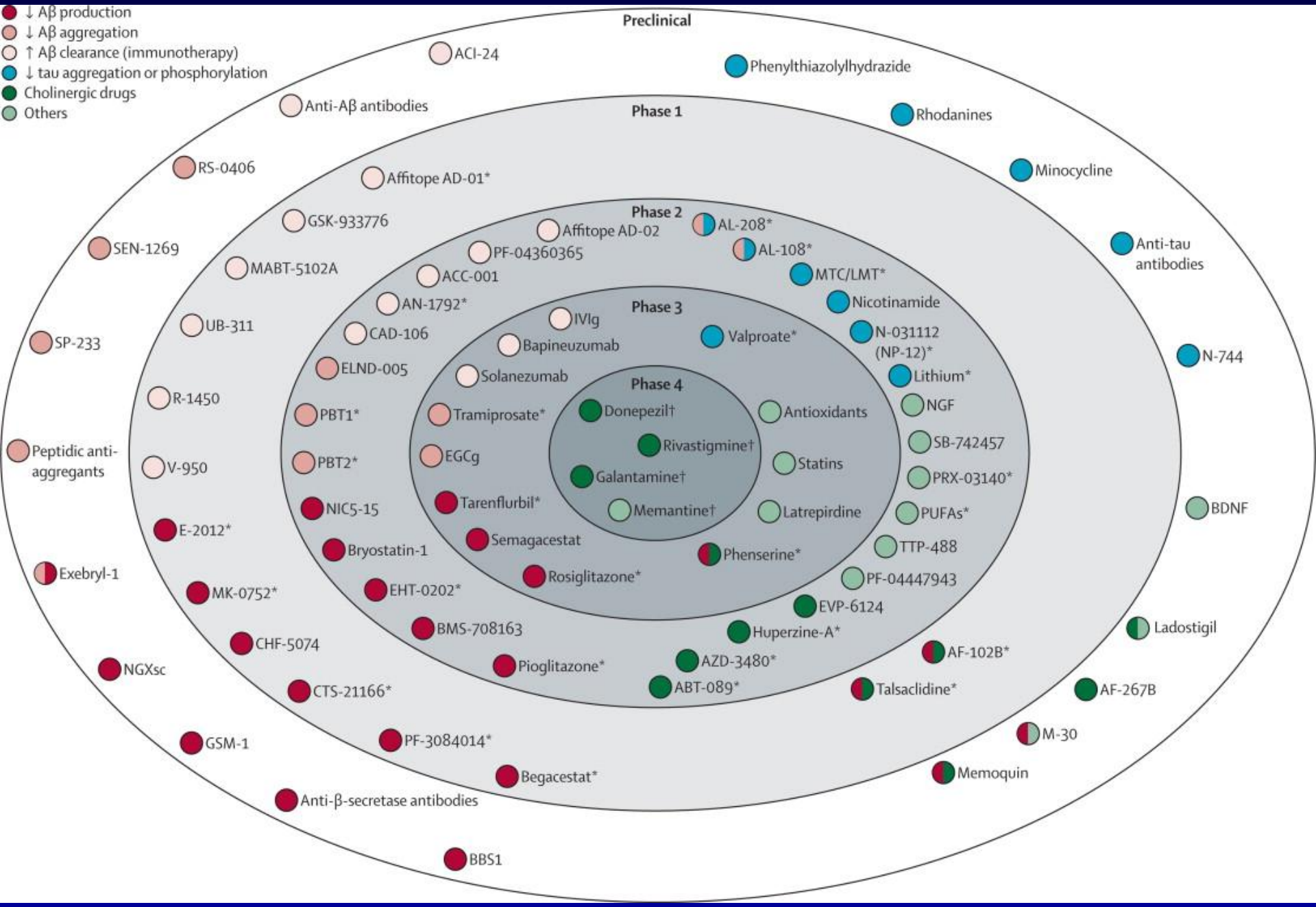
Easily >£5-10K/patient

~1000 patients (stratified, placebo/control with highly accurate diagnosis): >£5,000,000-£10,000,000



The challenge

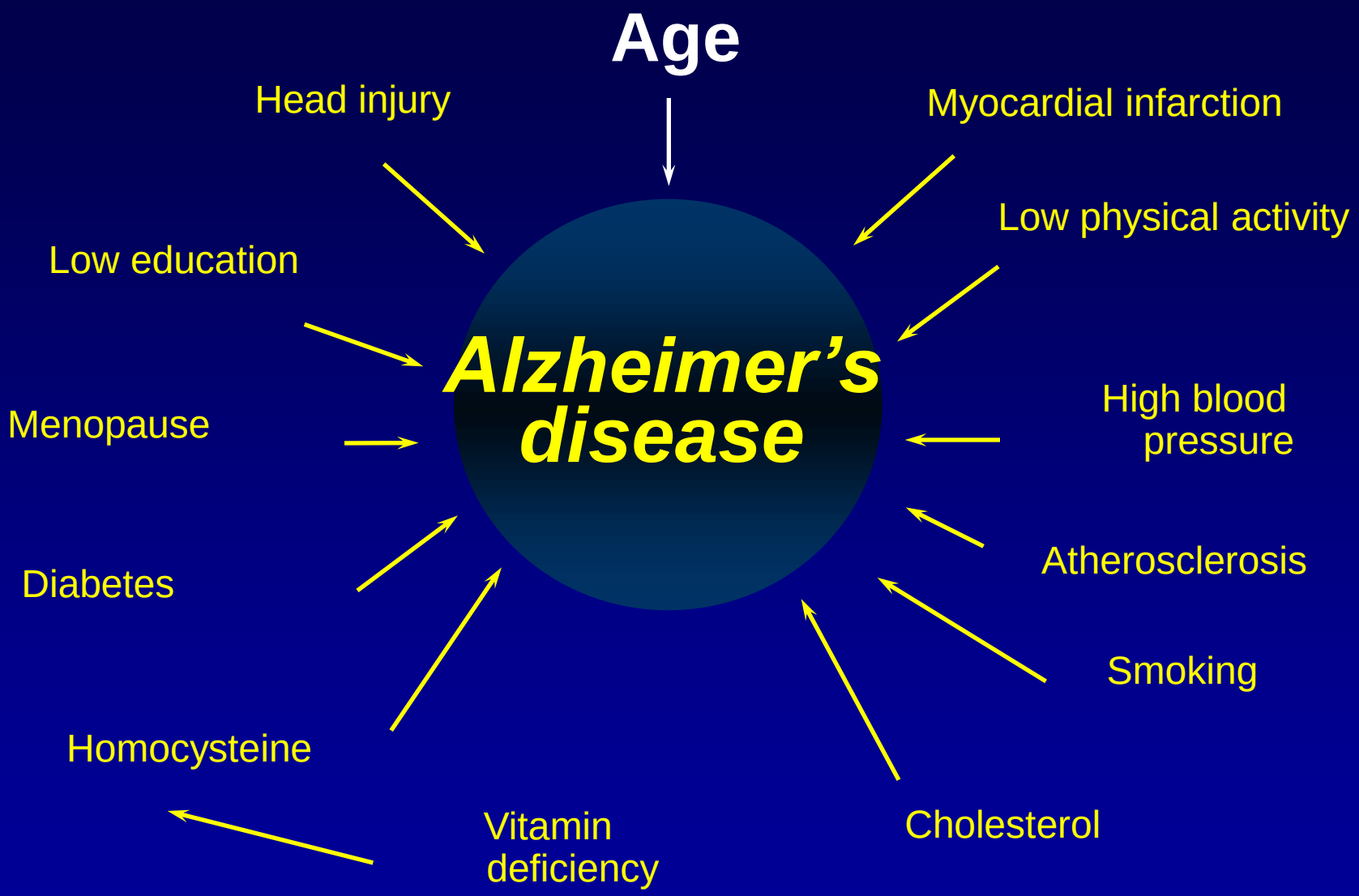



↓ Aβ production
↓ Aβ aggregation
↑ Aβ clearance (immunotherapy)
↓ tau aggregation or phosphorylation
Cholinergic drugs
Others
Preclinical
Phase 1
Phase 2
Phase 3
Phase 4
ACI-24
Phenylthiazolylhydrazide
Anti-Aβ antibodies
Rhodanines
RS-0406
Affitope AD-01*
Minocycline
GSK-933776
Affitope AD-02
AL-208*
SEN-1269
PF-04360365
AL-108*
Anti-tau antibodies
MABT-5102A
ACC-001
MTC/LMT*
AN-1792*
Nicotinamide
UB-311
IVIg
CAD-106
Valproate*
N-031112 (NP-12)*
SP-233
Bapineuzumab
N-744
ELND-005
Solanezumab
Lithium*
R-1450
Tramiprosate*
Donepezil†
Antioxidants
NGF
PBT1*
Rivastigmine†
SB-742457
Peptidic anti-aggregants
EGCg
Statins
PRX-03140*
PBT2*
Galantamine†
V-950
Tarenflurbil*
Memantine†
Latrepirdine
PUFAs*
BDNF
NIC5-15
E-2012*
Semagacestat
TTP-488
Bryostatin-1
Phenserine*
Exebryl-1
Rosiglitazone*
PF-04447943
MK-0752*
EHT-0202*
EVP-6124
BMS-708163
Huperzine-A*
Ladostigil
CHF-5074
AF-102B*
AZD-3480*
NGXsc
Pioglitazone*
ABT-089*
Talsaclidine*
AF-267B
CTS-21166*
M-30
GSM-1
PF-3084014*
Memoquin
Begacestat*
Anti-β-secretase antibodies
BBS1

Current solutions

reduce risk - prevention

symptomatic treatment


Age
Head injury
Myocardial infarction
Low physical activity
Low education
Alzheimer's disease
Menopause
High blood pressure
Atherosclerosis
Diabetes
Smoking
Homocysteine
Vitamin deficiency
Cholesterol

First and only successful primary prevention trial to date

No prior animal studies!

Reduction of a modifiable risk factor (homocysteine)

VITACOG: phase II trial

- MCI patients
- folate + B vitamins
- Endpoints
  - Neuroimaging
  - Cognitive measures