Alzheimer Clinical Trials: History and Lessons

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Disclosures

Dr. Cummings has provided consultation to Acadia, Avanir, Axsome, BiOasis, Biogen, Boehinger-Ingelheim, Bracket, Eisai, Genentech, Lilly, Lundbeck, Medavante, QR, Resverlogix, Roche, and Samus pharmaceutical and assessment companies.

Dr. Cummings has stock options in Prana, Neurokos, ADAMAS, MedAvante, QR pharma.

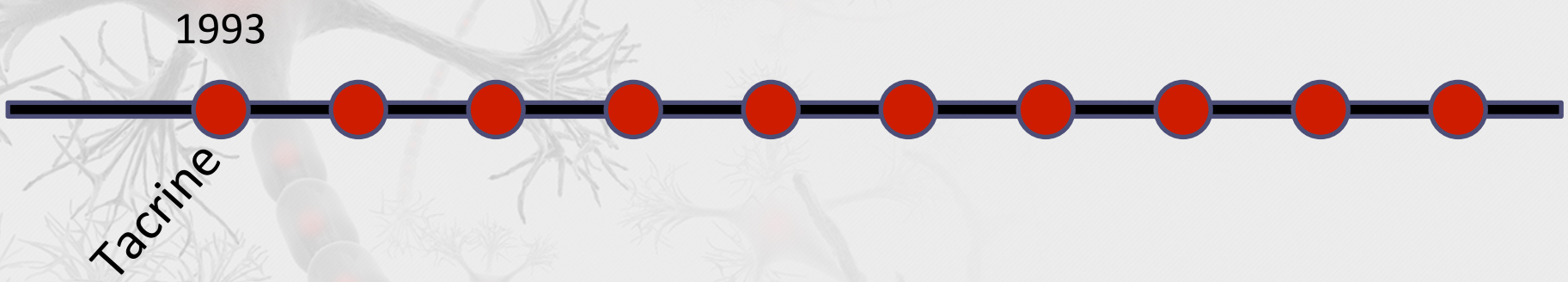
Dr. Cummings owns the copyright of the Neuropsychiatric Inventory.

This lecture will include reference to unapproved medications

AD Clinical Trials: History and Lessons

- Idiosyncratic history of influential agents
- Cholinesterase inhibitors and memantine
- Monoclonal antibodies
- Small molecules
- Progressive refinement of trials
- Lessons

AD Clinical Trials: History and Lessons



Tacrine: The Breakthrough Agent

ORIGINAL ARTICLE FREE PREVIEW ARCHIVE

Oral Tetrahydroaminoacridine in Long-Term Treatment of Senile Dementia, Alzheimer Type

William Koopmans Summers, M.D., Lawrence Victor Majovski, Ph.D., Gary Martin Marsh, Ph.D., Kenneth Tachiki, Ph.D., and Arthur Kling, M.D.

NEJM 1986; 315: 1241-1245

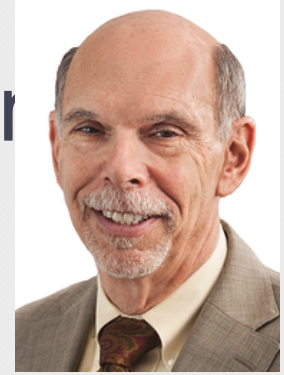
- Marked improvement reported
- Unknown instruments
- Poor trial methods
- “Lost” records
- Patient advocacy led to follow-on trials

Tacrine: The Breakthrough Agen

Volume 327 OCTOBER 29, 1992 Number 18

A DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER STUDY OF TACRINE FOR ALZHEIMER'S DISEASE

Kenneth L. Davis, M.D., Leon J. Thal, M.D., Elkan R. Gamzu, Ph.D., Charles S. Davis, Ph.D., Robert F. Woolson, Ph.D., Stephen I. Gracon, Ph.D., David A. Drachman, M.D., Lon S. Schneider, M.D., Peter J. Whitehouse, M.D., Ph.D., Toni M. Hoover, Ph.D., John C. Morris, M.D., Claudia H. Kawas, M.D., David S. Knopman, M.D., Nancy L. Earl, M.D., Vinod Kumar, M.D., Rachelle S. Doody, M.D., and the Tacrine Collaborative Study Group*



NEJM 1992;
327: 1253-1259

A Controlled Trial of Tacrine in Alzheimer's Disease

Martin Farlow, MD; Stephen I. Gracon, DVM; Linda A. Hershey, MD; et al

JAMA. 1992;268(18):2523-2529. doi:10.1001/jama.1992.03490180055026

JAMA 1992;
268: 2523-2529

Tacrine: The Breakthrough Agent

- Defined many of the assessments and design still used now
- Cognitive outcome
  - AD Assessment Scale – cognitive subscale (ADAS-cog[1])
- Global outcome
  - Clinical Global Impression of Change (CGIC)
- Behavioral outcome
  - ADAS-noncog[1]
- Study entry
  - MMSE 10-26

[1]Rosen W; Mohs R, Davis K. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984; 141: 1356-1364

Tacrine: The Breakthrough Agent

- Approved by the FDA, 1993
- Paul Leber, head of Neurology Division of FDA
- Draft guidelines (1990)
  - Symptomatic and "definitive" treatments
  - Dual outcomes:
    - Core: cognition plus
    - Measures of clinical meaningfulness: global or functional
  - Placebo comparison ("internal control" vs historical controls)

Guidelines for the Clinical Evaluation of Antidementia Drugs

First Draft

November 8, 1990

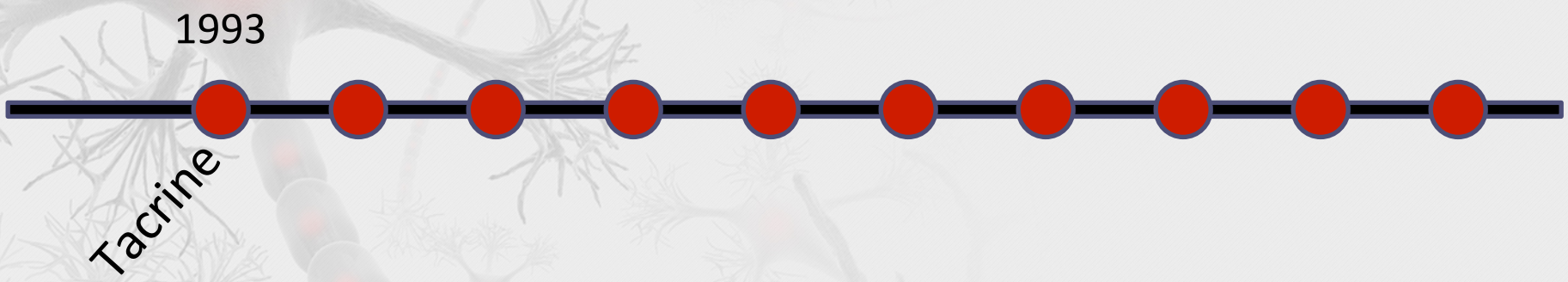
Prepared by Paul Leber, M.D.

Leber P. Guidelines for the Clinical Evaluation of antiDementia Drugs (1990 draft).

Tacrine: The Breakthrough Agent

Alzheimer's disease is treatable!

AD Clinical Trials: History and Lessons



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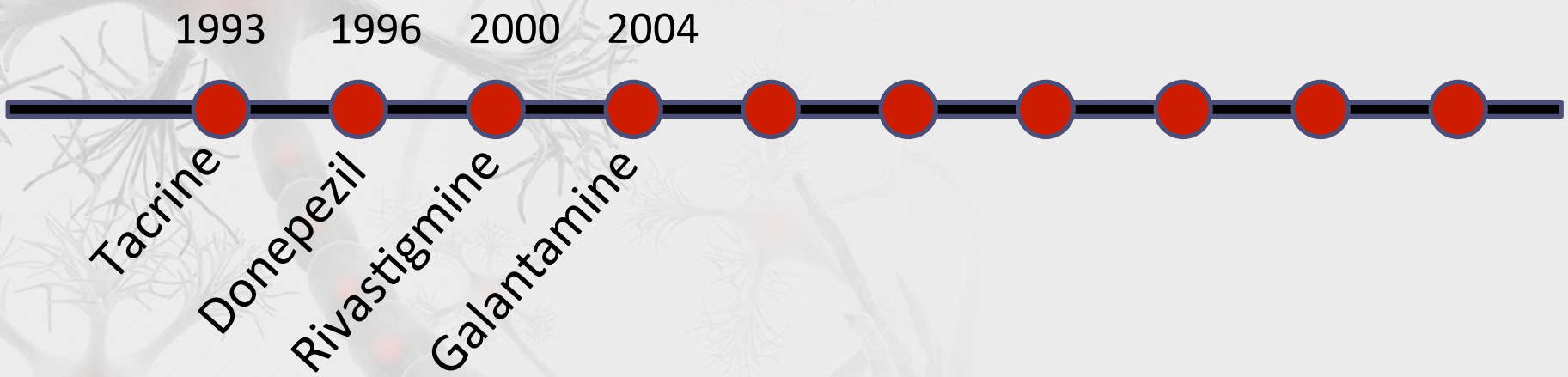


Cholinesterase Inhibitors

- Donepezil (Aricept)[1]
  - 5, 10 mg (1996)
  - High dose (23 mg); 2010
- Rivastigmine (Exelon)[2]
  - Oral form; 3 mg, 4.5 mg, 6 mg (2000)
  - Patch (transdermal formulation)(2007)
  - High dose (13.3 mg) patch (2012)
- Galantamine (Reminyl [2004] → Razadyne [2005])[3]
- Mild, moderate and severe (donepezil, rivastigmine) AD dementia

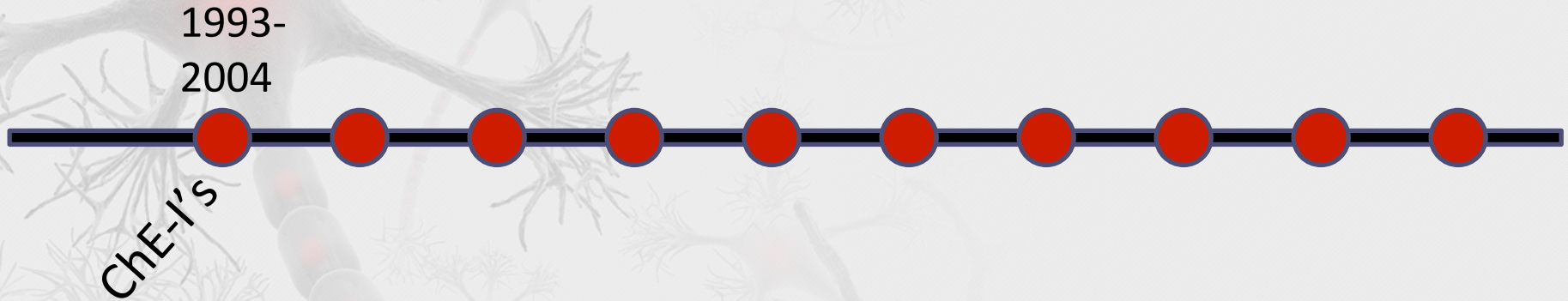
[1]Rogers S, et al. Neurol 1998; 50: 1360145; [2]Rosler M, et al. BMJ 1999; 318: 633-638;
[3]Wilcock G, et al. BMJ 2000; 321: 1445-1449

Cholinergic Casualties and Catastrophes

- Cholinesterase inhibitors
  - Physostigmine; short half life[1]
  - Metrifonate; respiratory paralysis[2,3]
- Muscarinic agonists
  - Syncope (xanomeline[4])
- Nicotinic agonists
  - Promising in some trials
  - Outcomes inconsistent[5]
- ***Not all cholinergic approaches succeeded***

[1]Beller S, et al. Psychopharm 1985; 87: 147-151; [2]Lopez-Arrieta J, Schneider L. Cochrane Database Syst Rev 2006; 19: CD003155; [3]Cummings J, et al. Neurology 1998; 50: 1214-1221; [4]Bodick N et al. Arch Neurol 1997; 54: 465-473
[5]Florian H, et al. J Alz Dis 2016; 51: 1237-1247

AD Clinical Trials: History and Lessons



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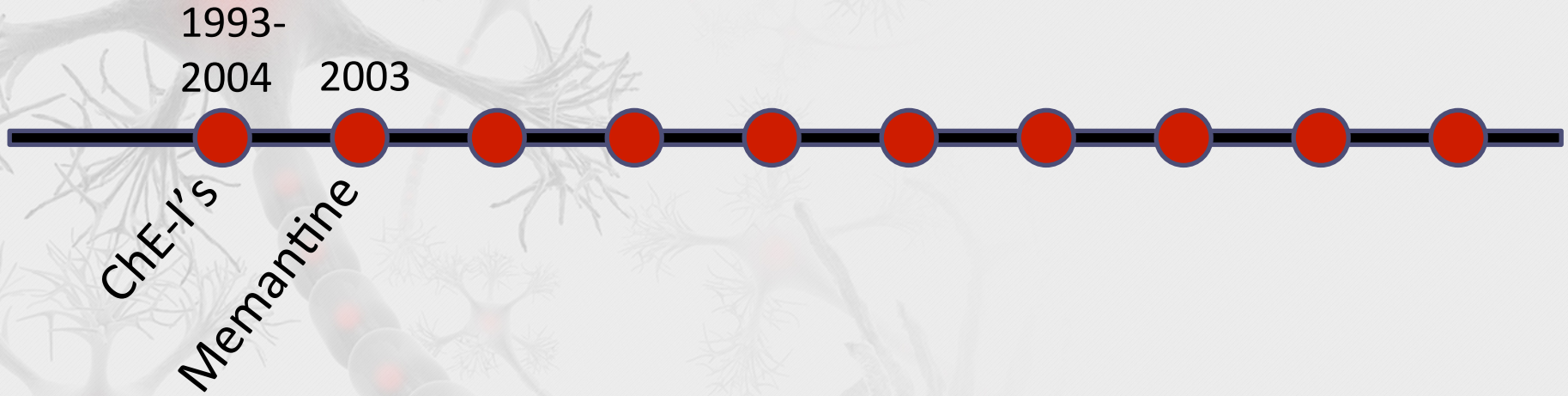
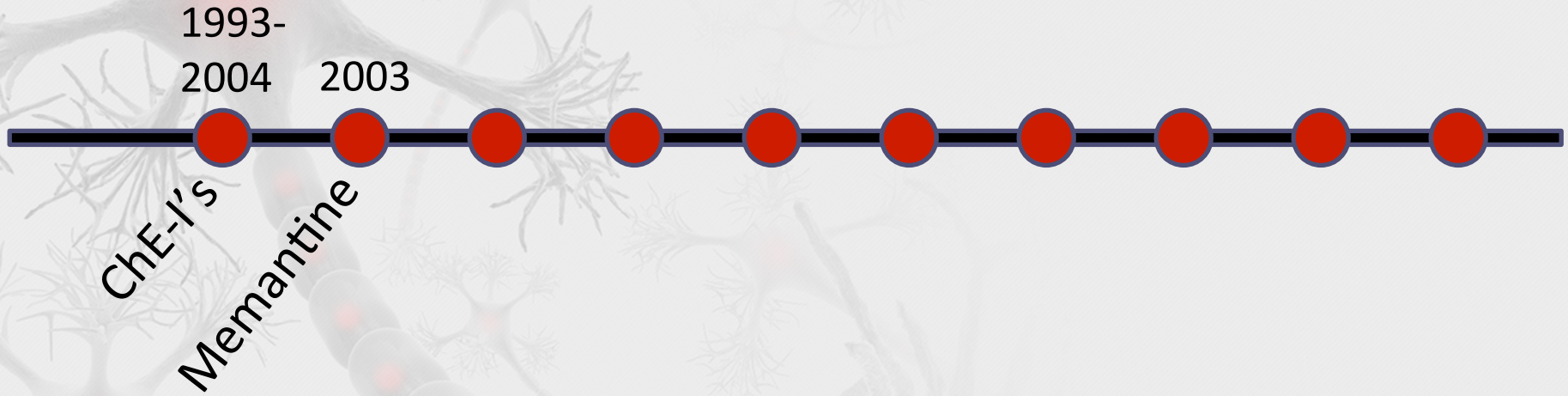


Memantine

- N-methyl-d-aspartate inhibitor
- Monotherapy[1] and add-on therapy[2]
- Moderate to severe AD
- Used in conjunction with cholinesterase inhibitors
- ***Add-on treatment to standard-of-care is the trial norm established by memantine***

[1]Reisberg B et al. New Engl J Med 2003; 348: 1333-1341; [2]Tariot P et al. JAMA 2004; 291: 317-324

AD Clinical Trials: History and Lessons



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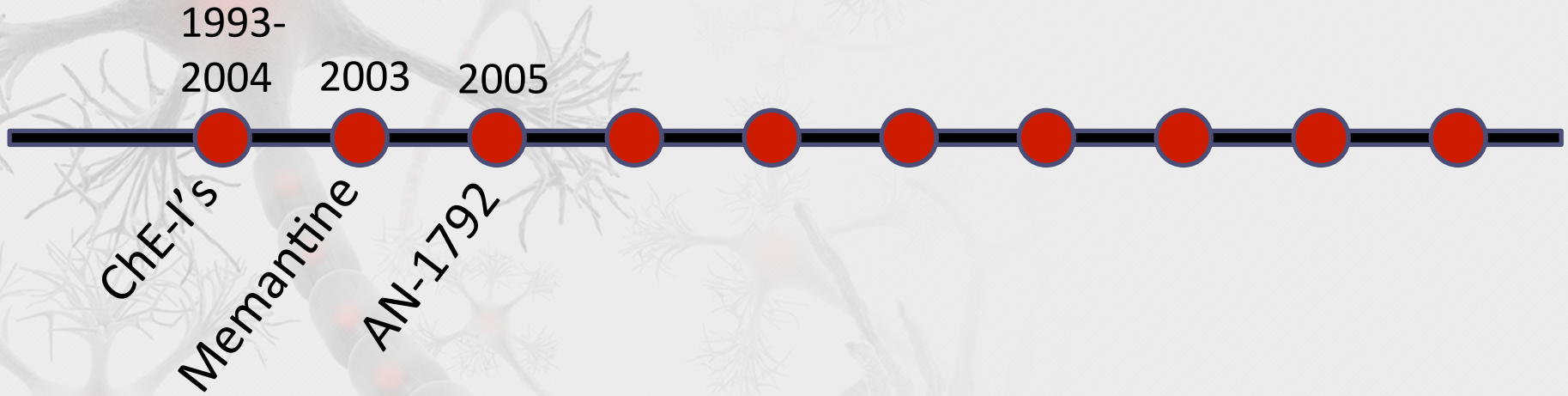


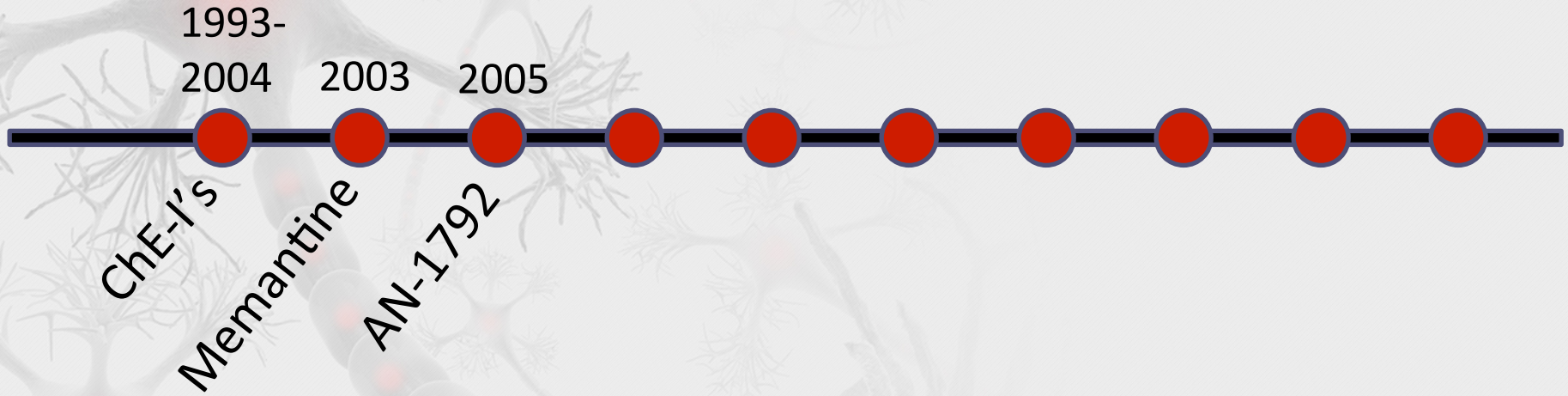
AN 1792

- Amyloid beta protein (Aβ) vaccine
- Based on APP animal model of AD[1]
- Clinical trial[2]
  - First major disease-modification trial
  - First immunotherapy trial
  - Antibodies generated
  - 6% developed meningoencephalitis
  - No consistent clinical benefit

Dale Schenk, PhD

[1]Schenk D, et al. Nature 1999; 400: 173-177; [2]Gilman S, et al. Neurology 2005; 64: 1553-1562

AD Clinical Trials: History and Lessons



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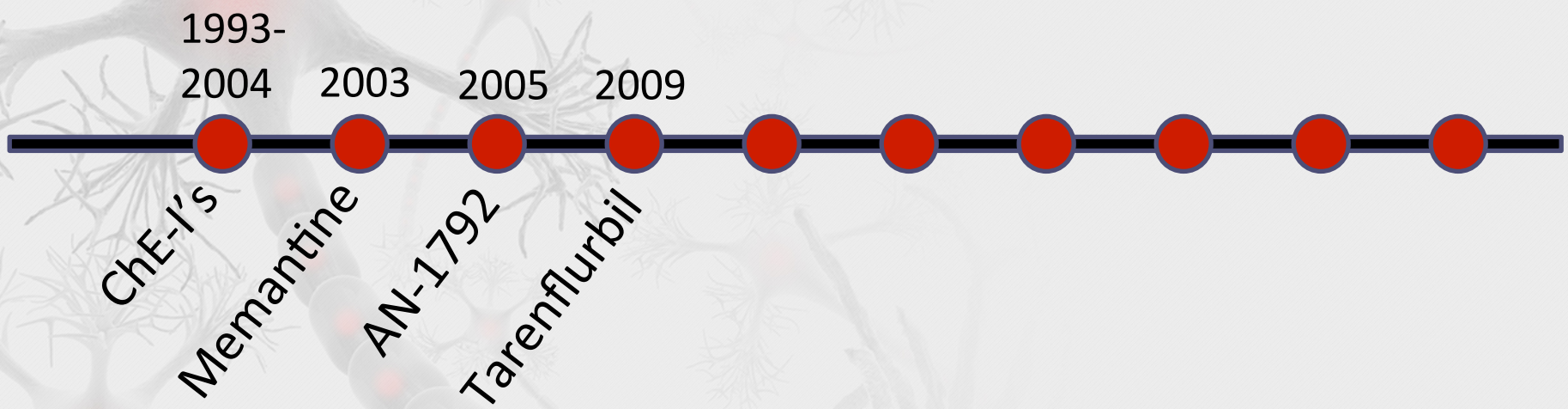
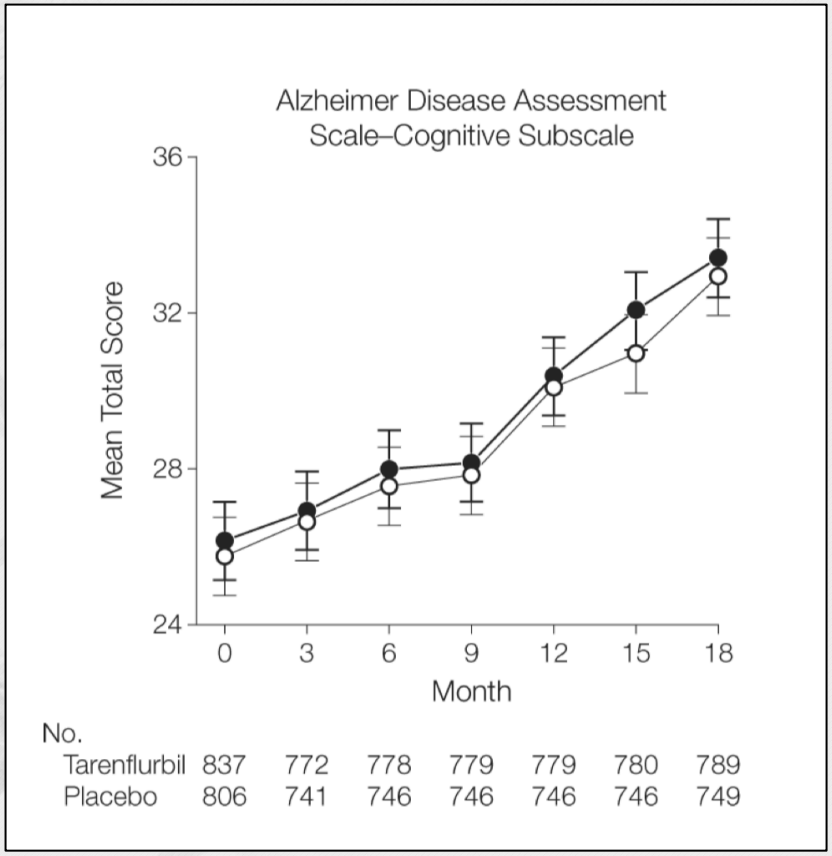


Tarenflurbil (R-flurbuprofen)[1]

- R enantiomer of ibuprofen (reduced anti-inflammatory effects and NSAIDs-related side effects)
- Gamma-secretase modulator; reduced brain amyloid in animal models



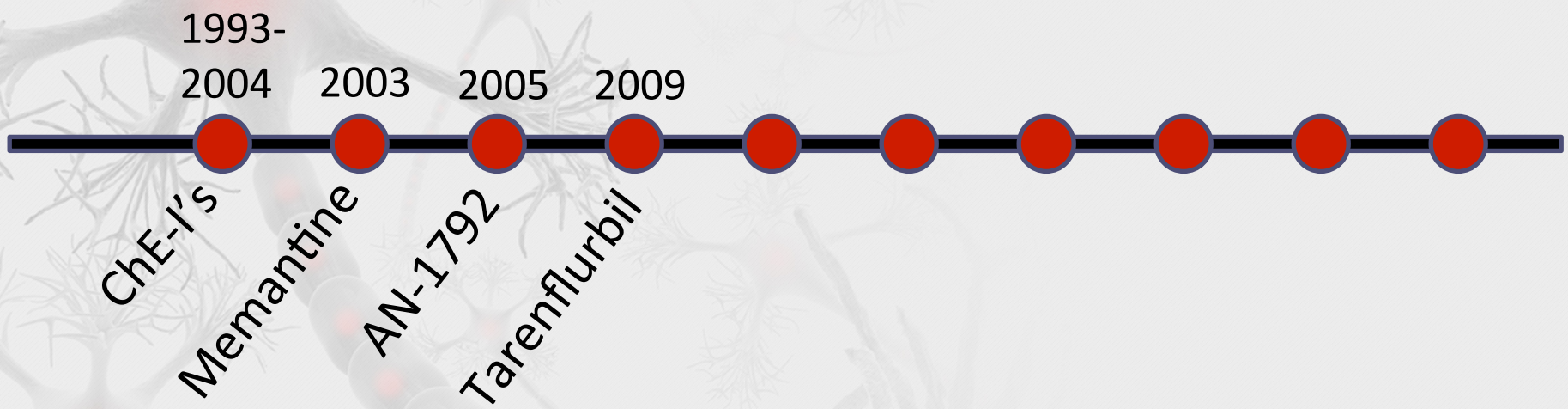
[1]Green R, et al, JAMA 2009; 302: 2557-2564

Tarenflurbil (R-flurbuprofen)[1]

- ***Target engagement not shown in humans***
- ***Brain penetration poor in humans***
- ***Dose-response not explored in humans***
- ***Phase 2 trial negative; subgroup analysis guided Phase 3***
  - ***Mild patients***
  - ***High serum levels***

[1]Green R, et al, JAMA 2009; 302: 2557-2564

AD Clinical Trials: History and Lessons



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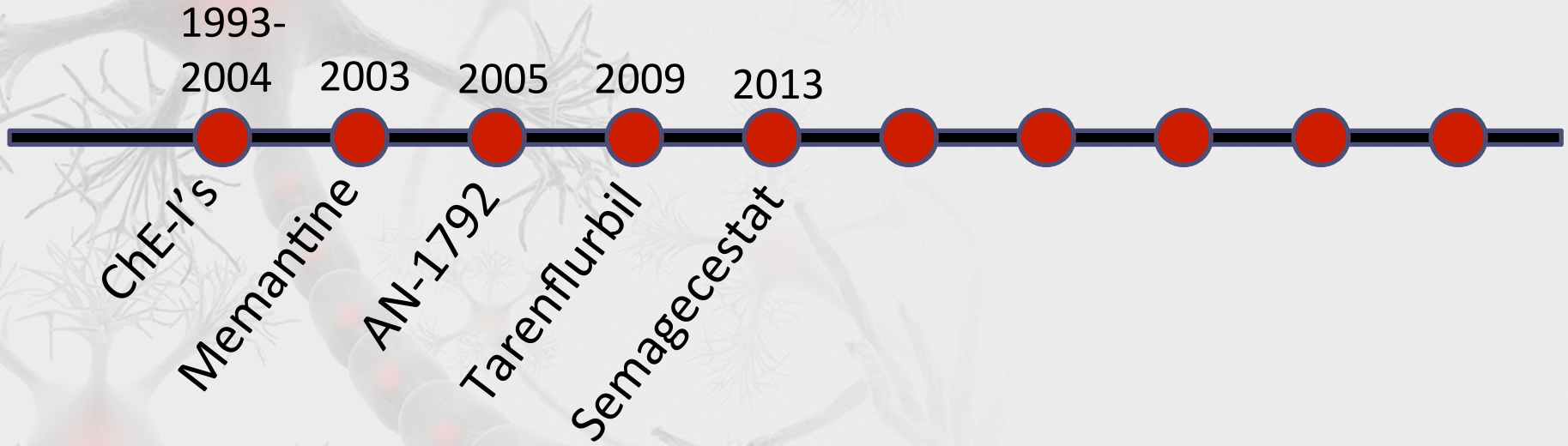
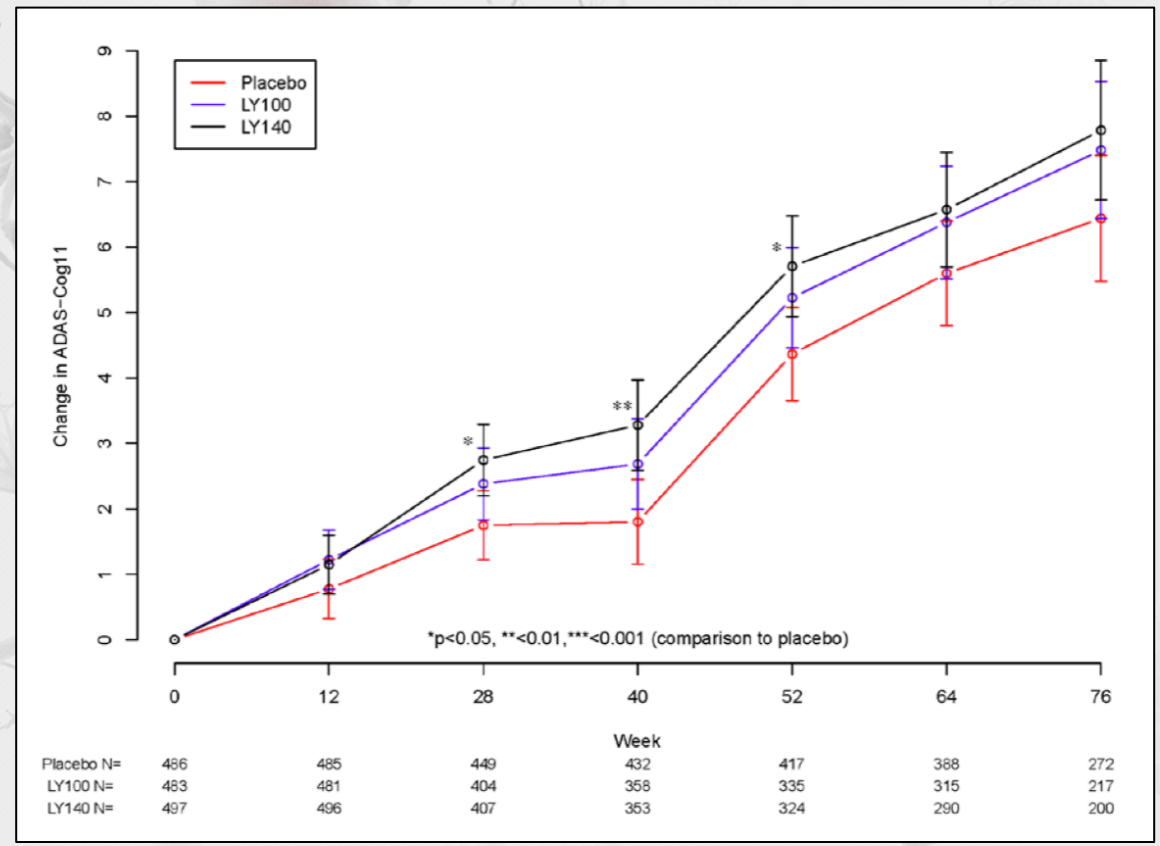


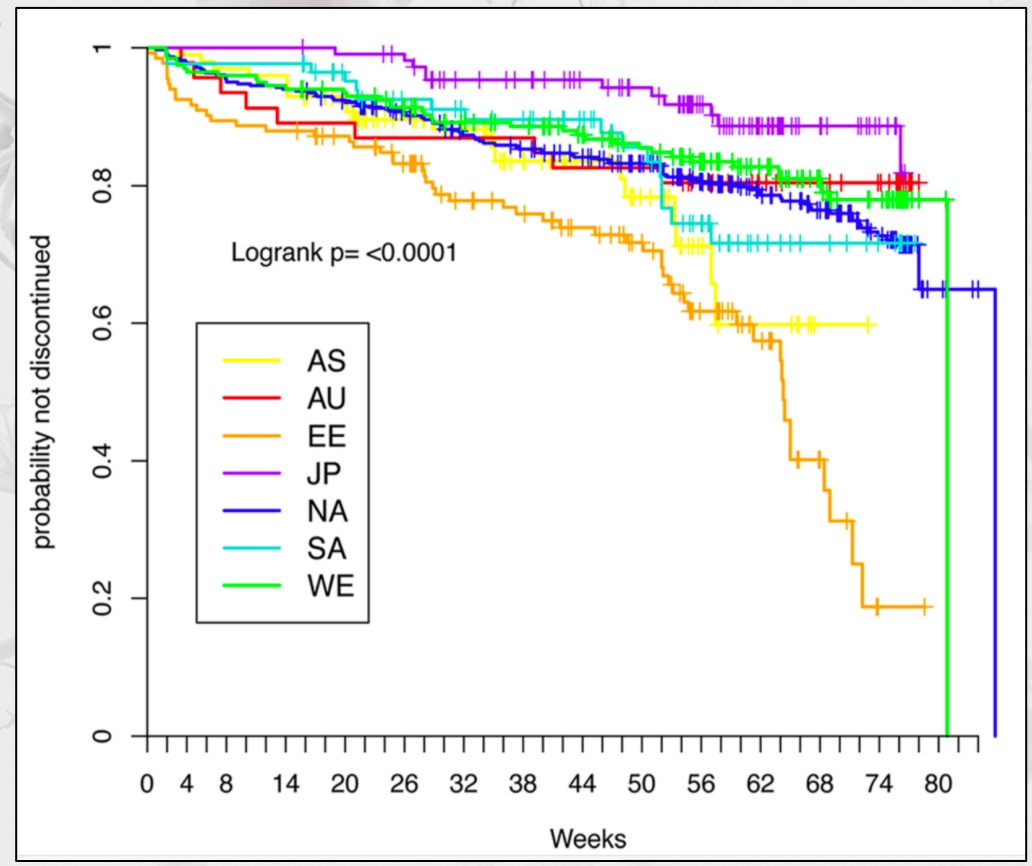
Semagecestat



- Gamma-secretase inhibitor
- Mild-moderate AD
- No biological confirmation of dx
- Worsened cognition
- Worsened function
- Skin cancer in treatment group

Doody R, et al. NEJM 2013; 369: 341-350

Semagecestat

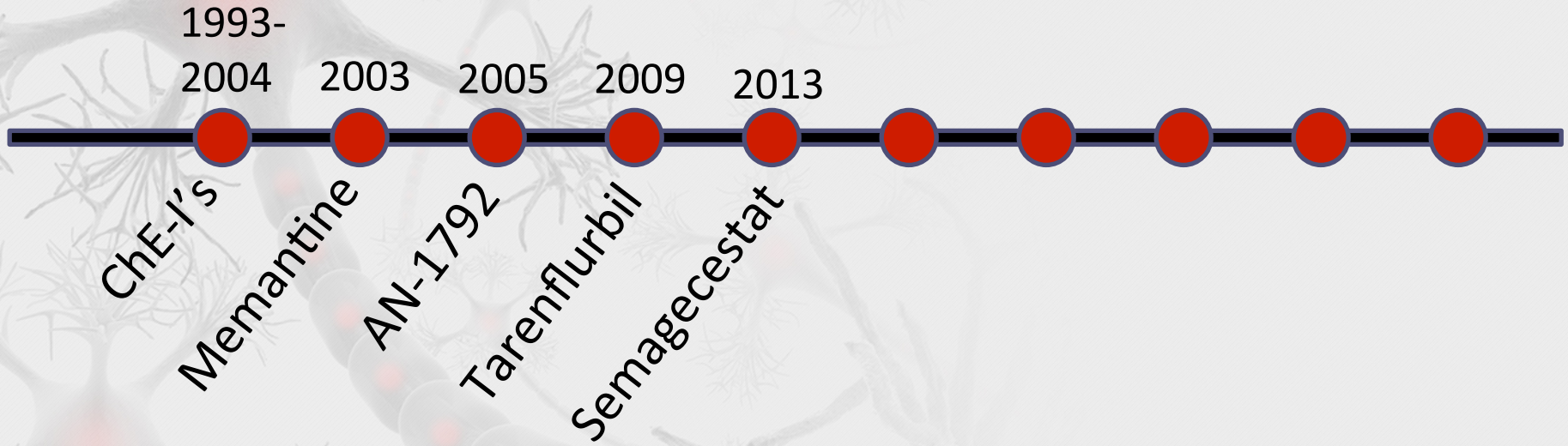


Time to discontinuation (retention)

- Differs by global region
- Japan – highly likely to stay in study
- Eastern Europe – high discontinuation rate
- Creates heterogeneity in data
- Heterogeneity in rate of decline, adverse events, etc

Grill J, et al. Alz Res & Therapy 2015:7:39

AD Clinical Trials: History and Lessons



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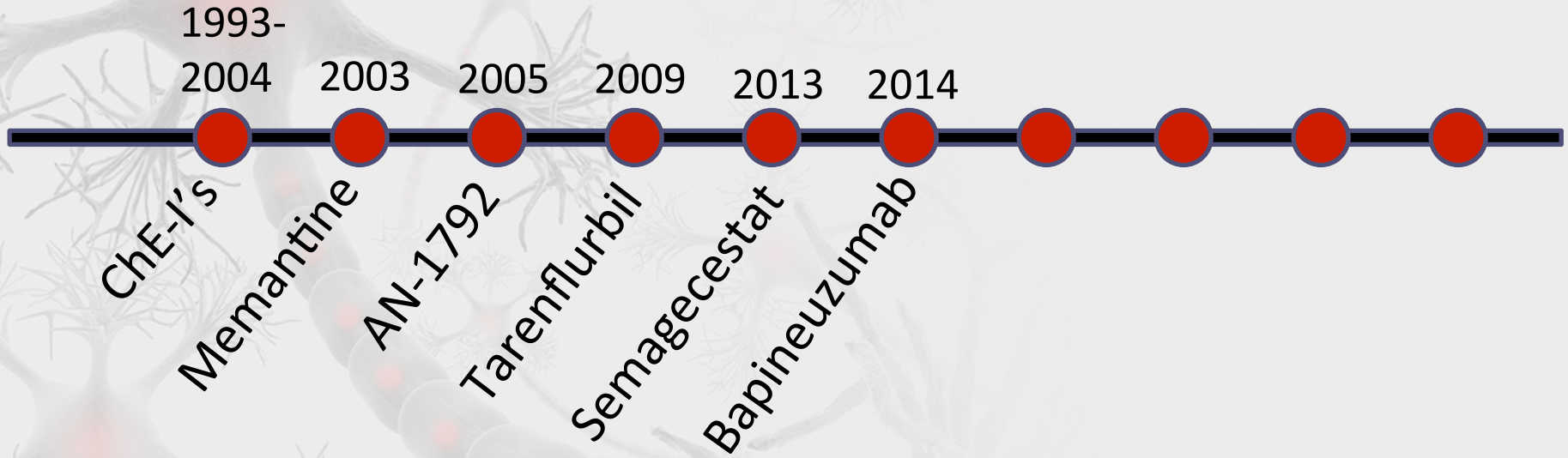
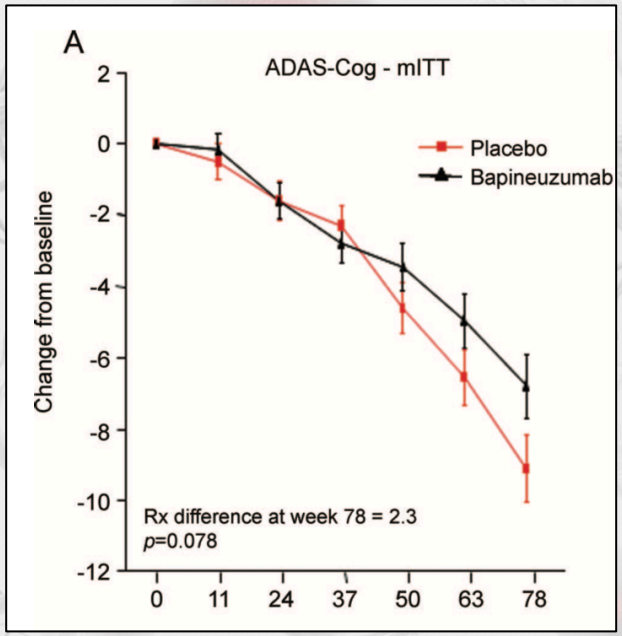


Bapineuzumab

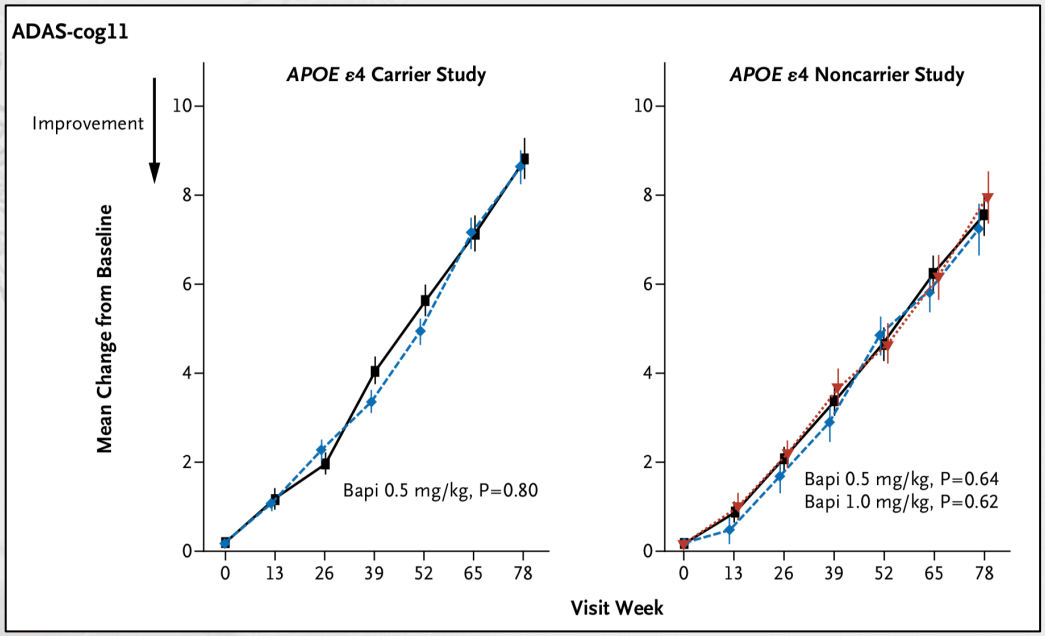
- Vaccine (AN1792) caused encephalitis
- Monoclonal antibodies represented a more focused type of immunotherapy
- Bapineuzumab represented the next step in immunotherapy
  - Phase 2 showed no effect on ADAS-cog[1]
  - Post hoc analysis suggested benefit in ApoE-4 noncarriers
  - P3 showed no benefit in carriers or non-carriers[2]
  - Mild-to-moderate AD; dx not confirmed biologically

[1]Salloway S, et al. Neurology 2009; 73: 2061-2070; [2]Salloway S, et al. 2914; 370: 322-333

Bapineuzumab



Phase 2: Nonsignificant[1]



Phase 3: Nonsignificant[2]

[1]Salloway S, et al. Neurology 2009; 73: 2061-2070; [2]Salloway S, et al. 2914; 370: 322-333

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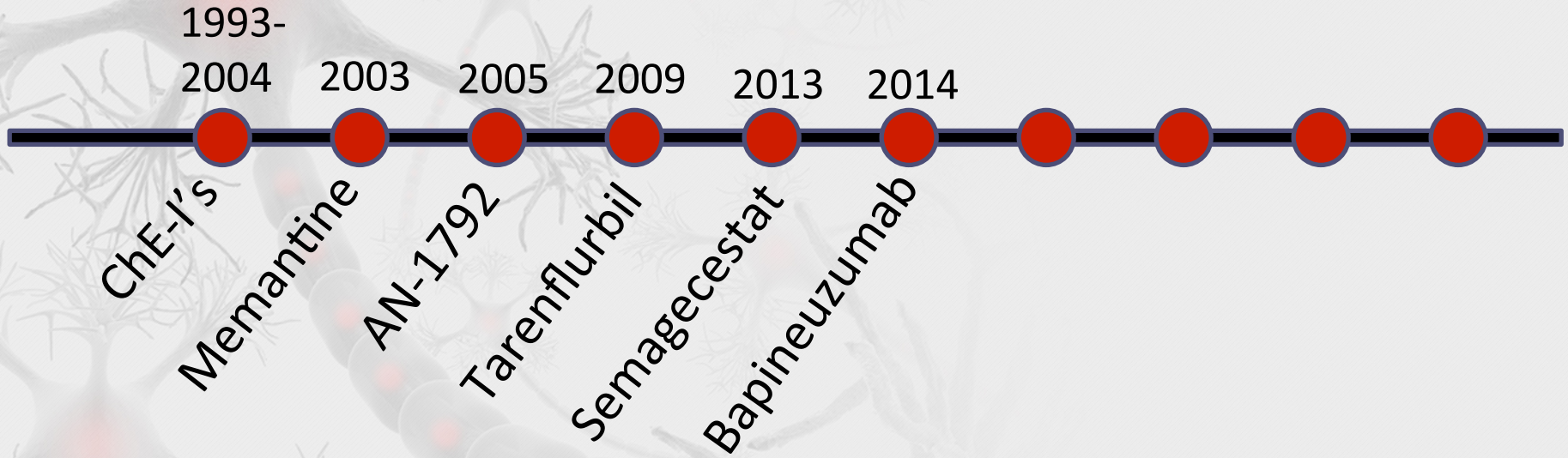

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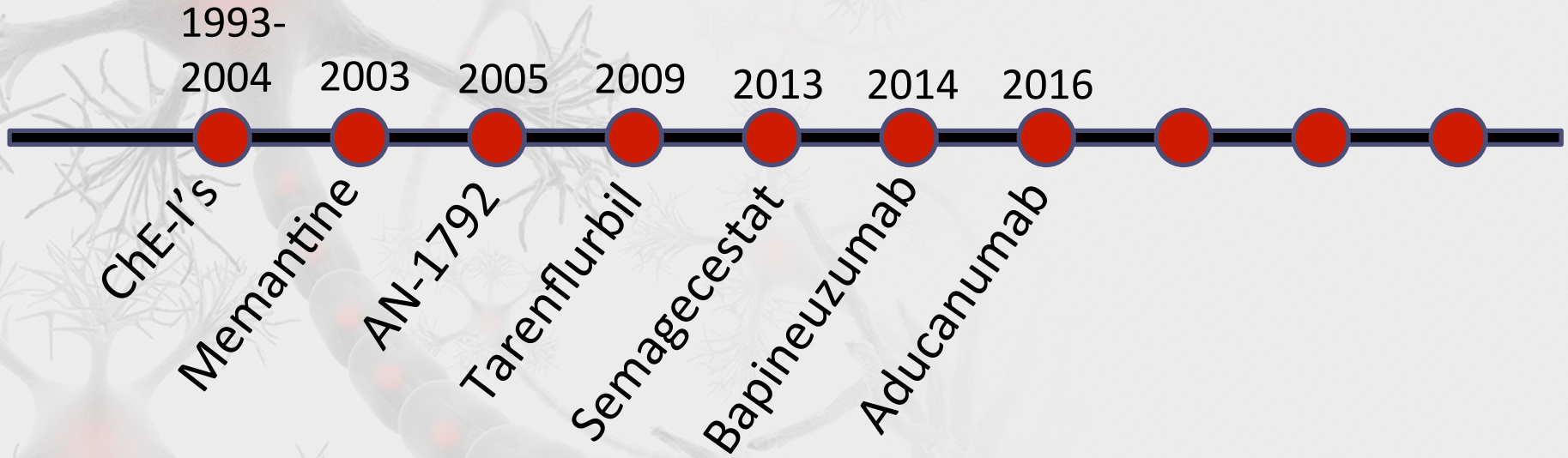
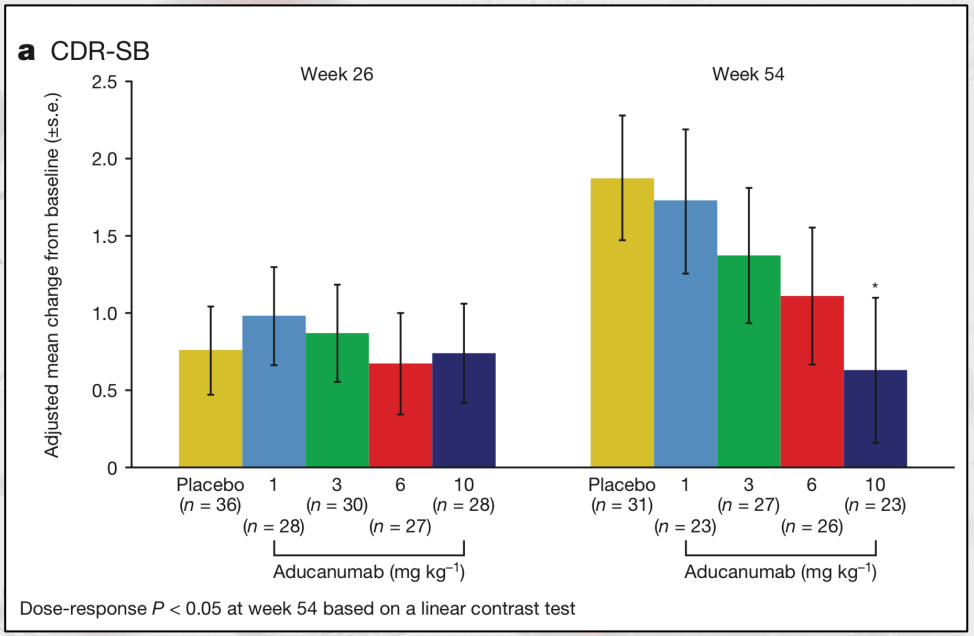
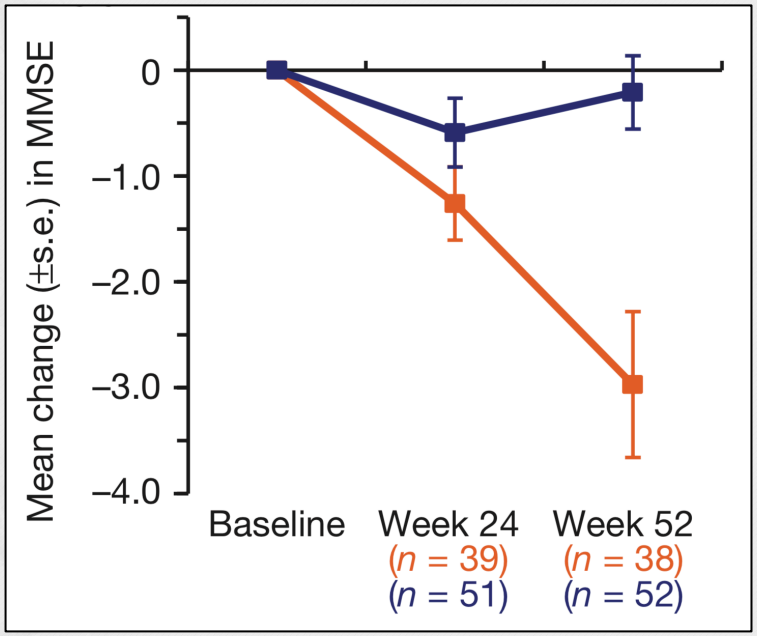


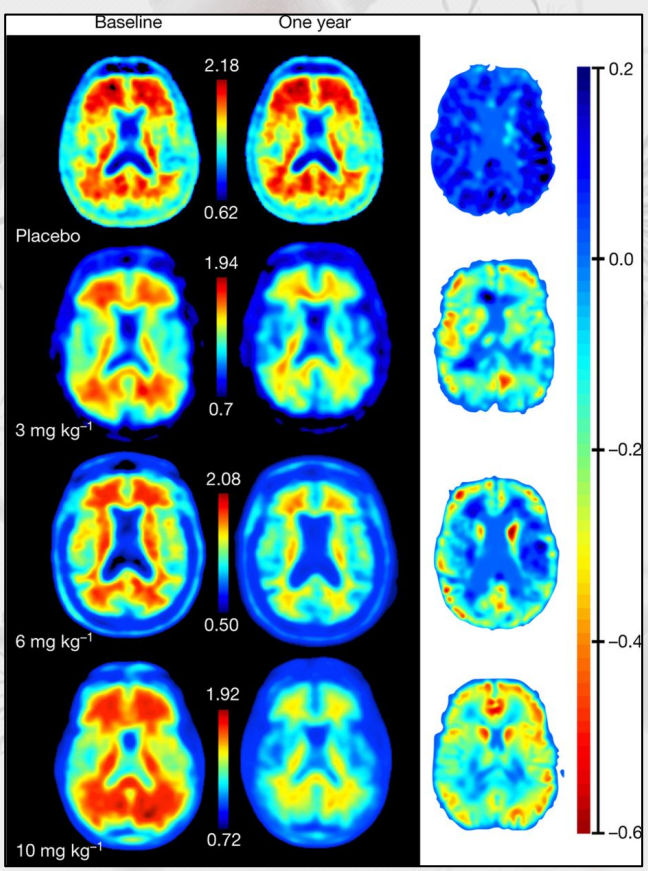
Aducanumab





Sevigny J et al. Nature 2016; 537: 50-58

Aducanumab



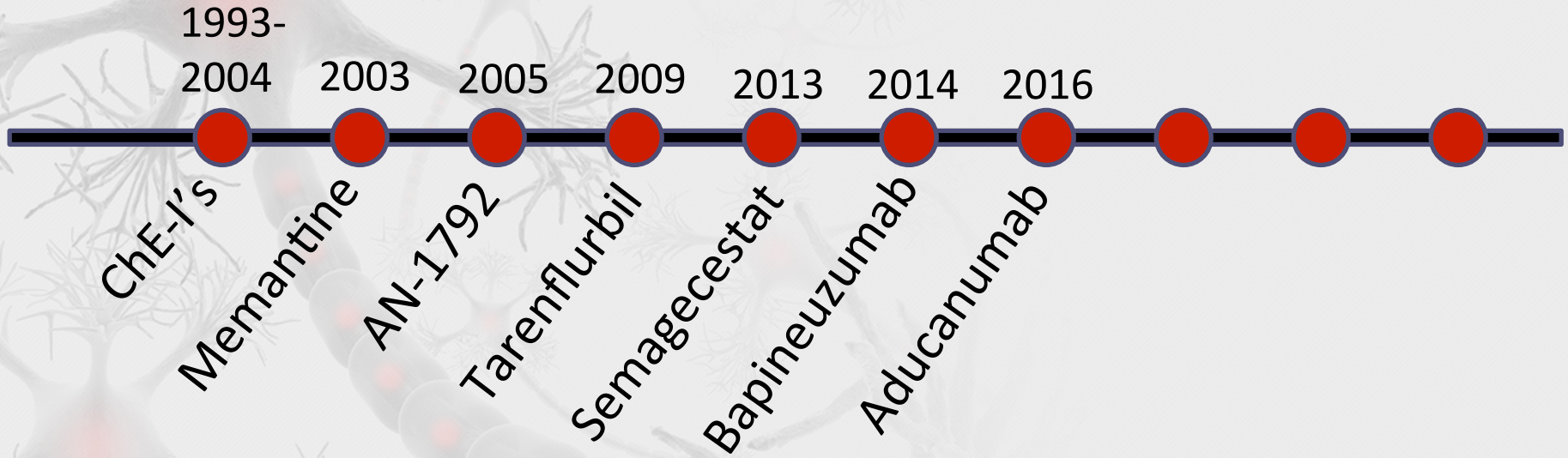
- Removed amyloid plaque
- Reduced cognitive decline on CDR, MMSE (not NTB)
- Prodromal AD and mild AD dementia
- Biologically confirmed (PET)
- Phase 2 (165 patients)
- High rate of ARIA

Sevigny J et al. Nature 2016; 537: 50-58

Aducanumab: Phase I/ Phase III Differences

Feature	PRIME	ENGAGE	EMERGE
N	197 (planned)	1350 (+ 255)	1350 (+255)
Countries	US only	US + 13 countries	US + 12 countries
Prodromal AD	MMSE 24-30 CDR 0.5 FCSRT $\leq$27	MMSE 24-30 CDR 0.5	MMSE 24-30 CDR 0.5
Mild AD dementia	MMSE 20-26 CDR 0.5 or 1	Not included	Not included
Cohorts	9 (drug w pbo)	3 (2 doses, pbo)	3 (2 doses, pbo)
Duration	52 weeks	78 weeks	78 weeks
Primary outcome	Safety	CDR-sb	CDR-sb
Secondary outcome	Amyloid imaging	MMSE ADAS-cog ADCS-ADL (MCI)	MMSE ADAS-cog ADCS-ADL (MCI)

AD Clinical Trials: History and Lessons



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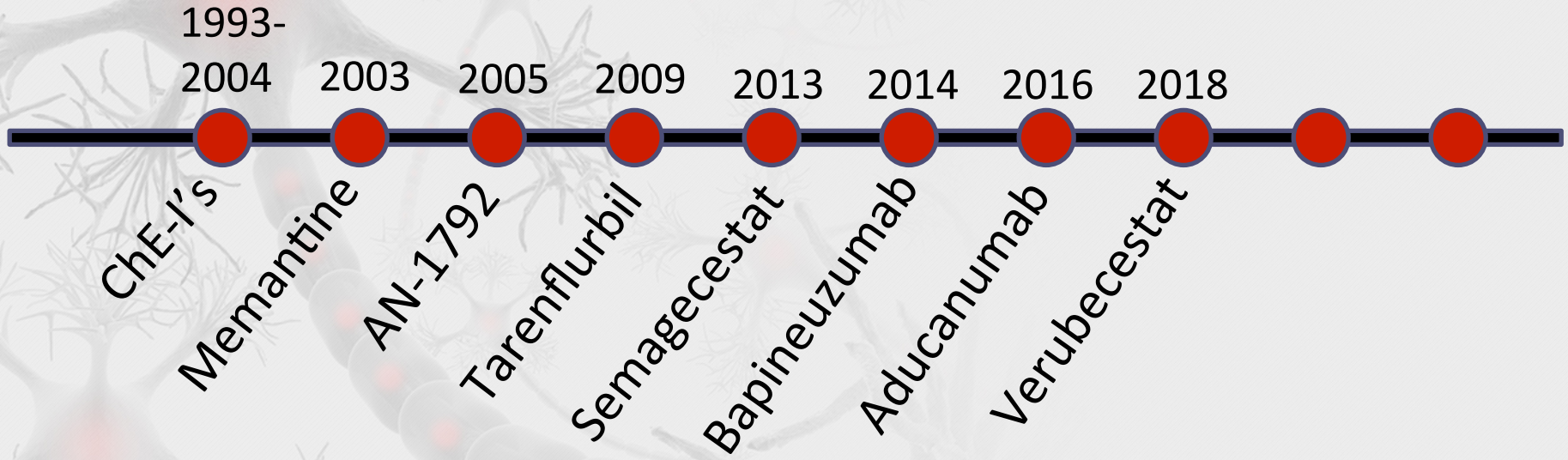
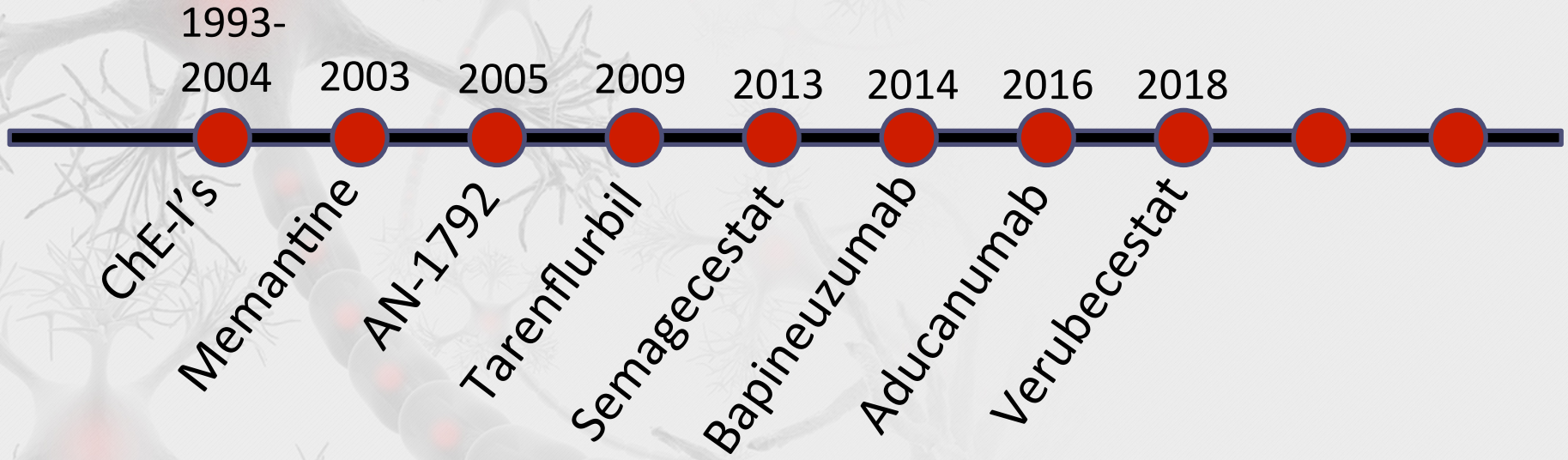


Verubecestat

- Beta amyloid precursor protein cleavage enzyme (BACE) inhibitor
- 1958 patients in trial
- Mild-moderate AD
- Dx not biologically confirmed
- Reduced CSF Aβ 65-90%
  - Effective pharmacology
- No cognitive benefit (terminated for futility)

Egan M, et al. NEJM 2018; 378; 1691-1703

AD Clinical Trials: History and Lessons



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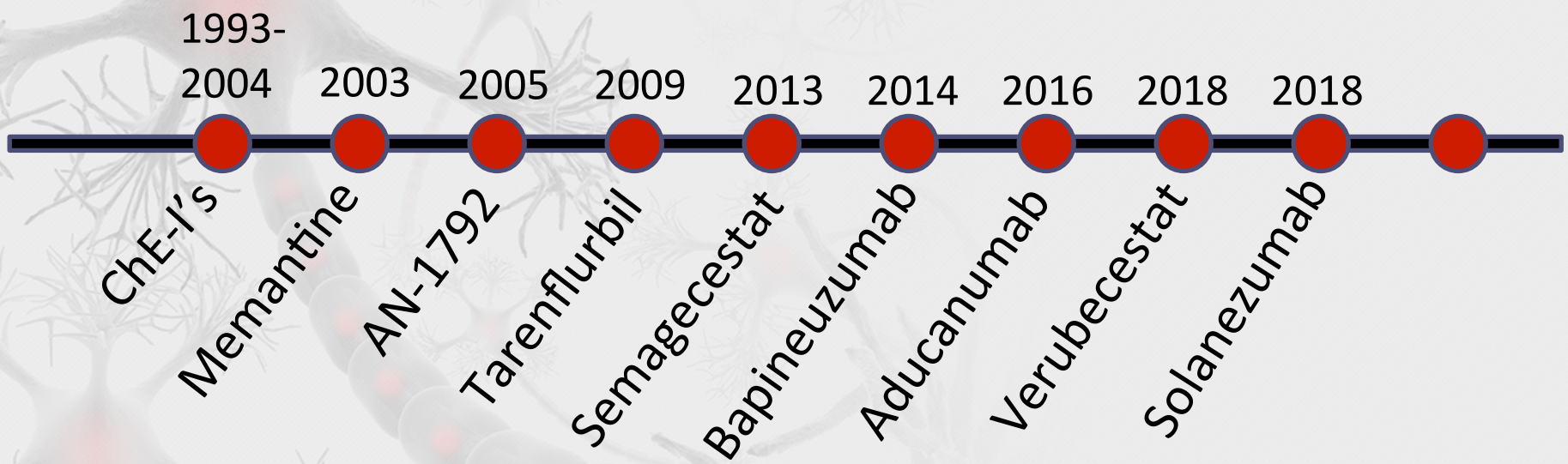
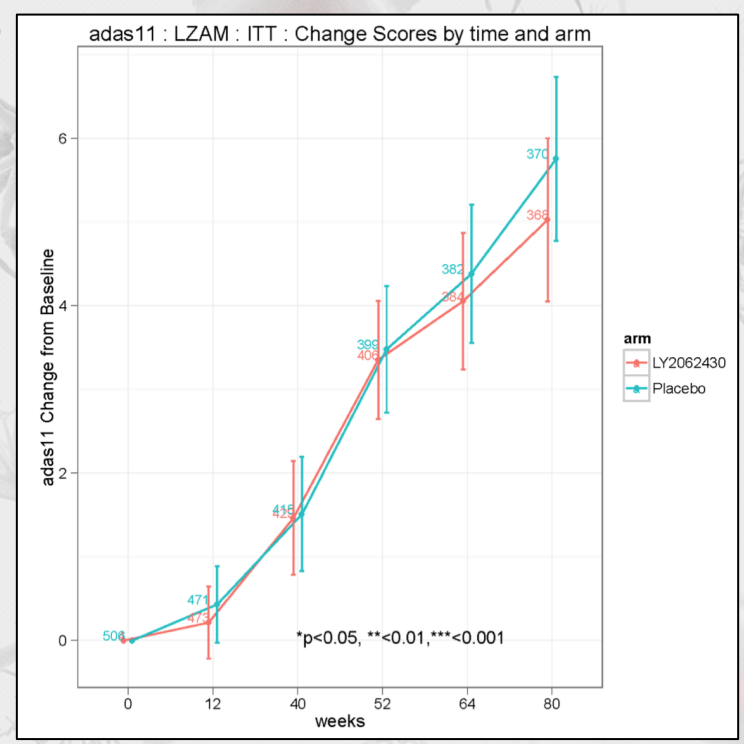
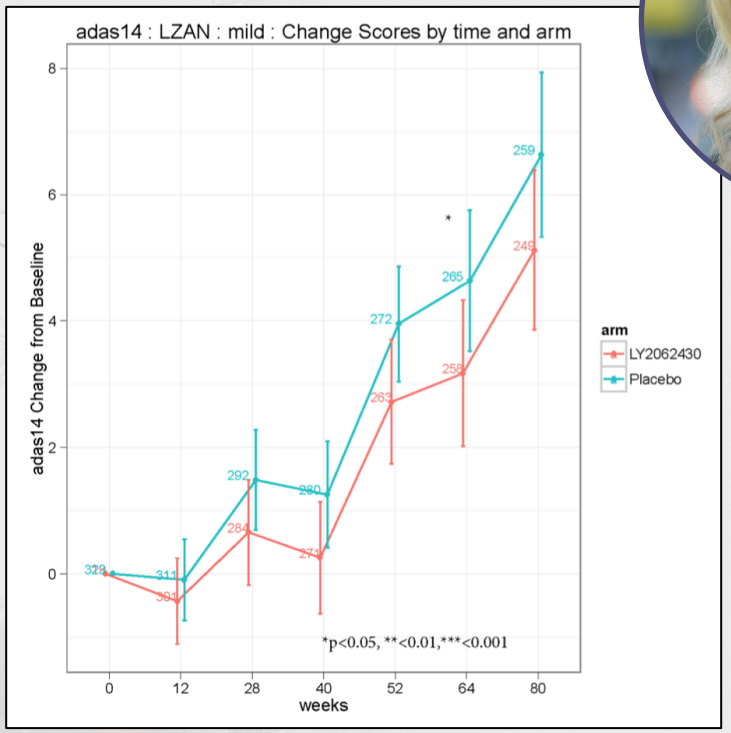


Solanezumab



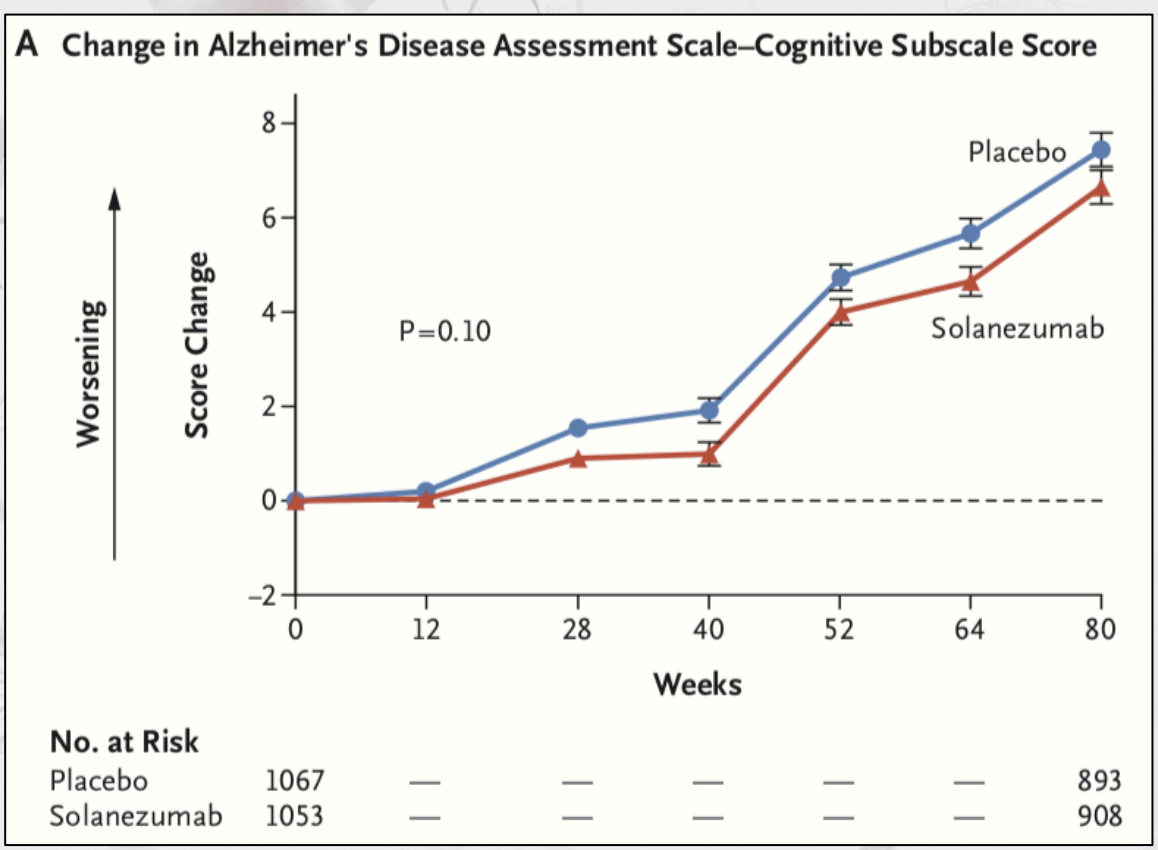


Rachelle Doody

- Post hoc
- Improved in mild AD

Doody R, et al. NEJM 2014; 370: 311-321

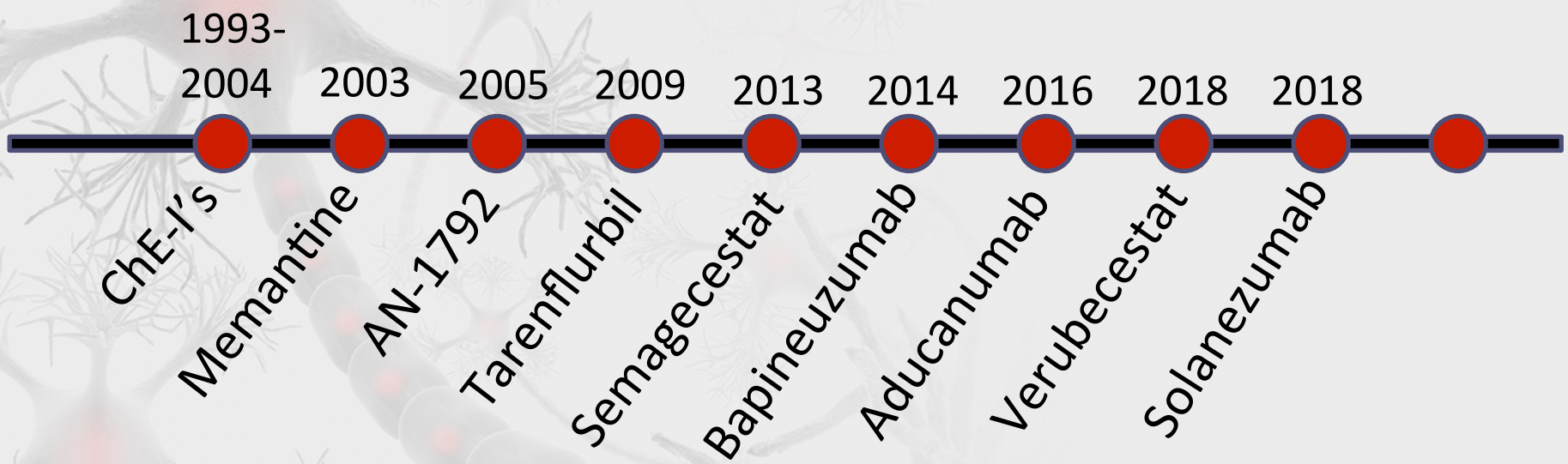
Solanezumab



- Mild AD only
- Dx biologically confirmed (CSF or PET)
- No benefit

Honig L, et al. NEJM 2018; 378: 321-330.

AD Clinical Trials: History and Lessons



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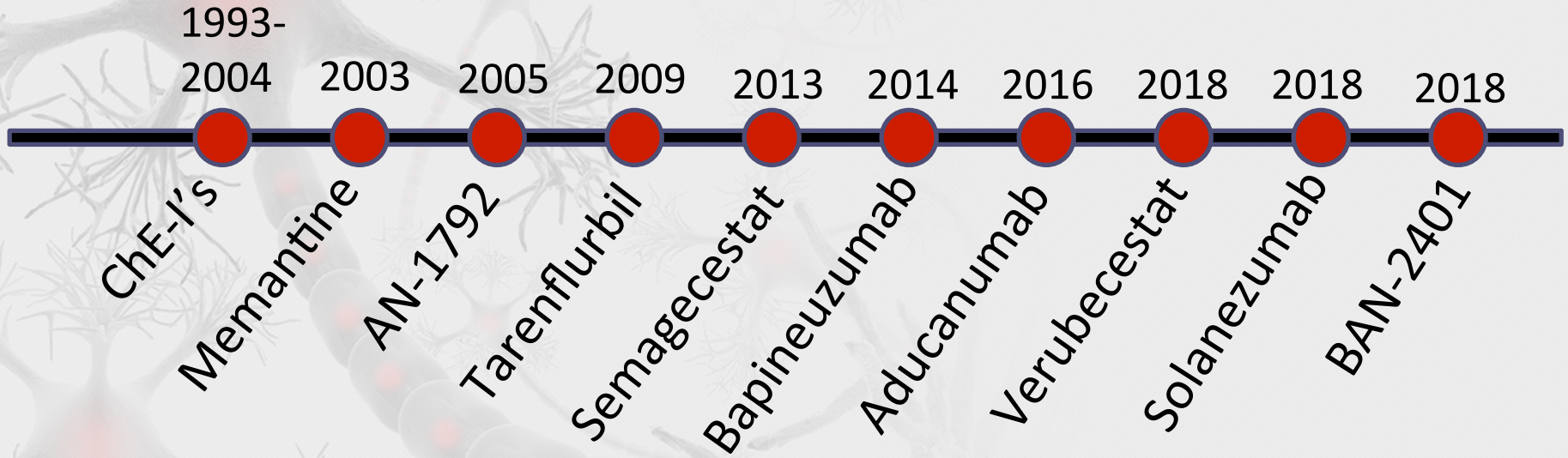
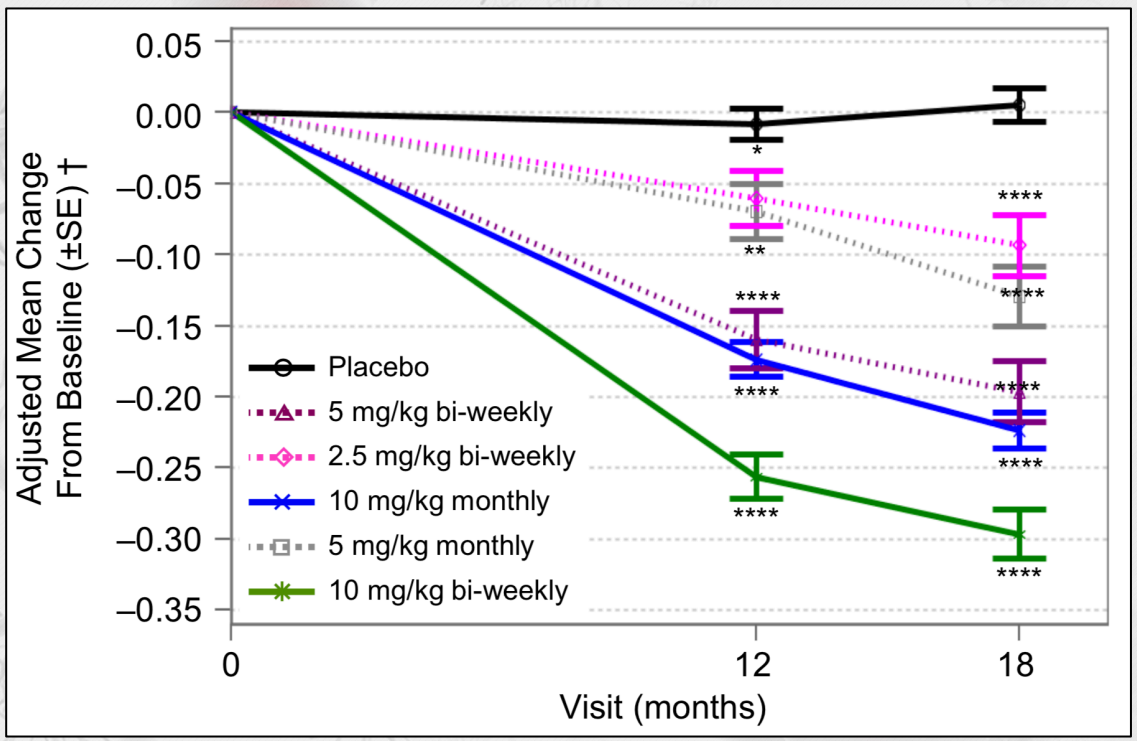


BAN-2401[1]

- Monoclonal antibody
- Prefibrillar amyloid target epitope
- Prodromal AD and mild AD dementia
- Dx biologically confirmed
- Phase 2
- 856 randomized
- Adaptive design
- ADCOMS[2]; novel primary outcome
- Irregular randomization of ApoE-4 carriers

[1]Kramer L, et al. AAIC, 2018; [2]Wang J, et al. JNNP 2016; 87: 993-999

BAN-2401

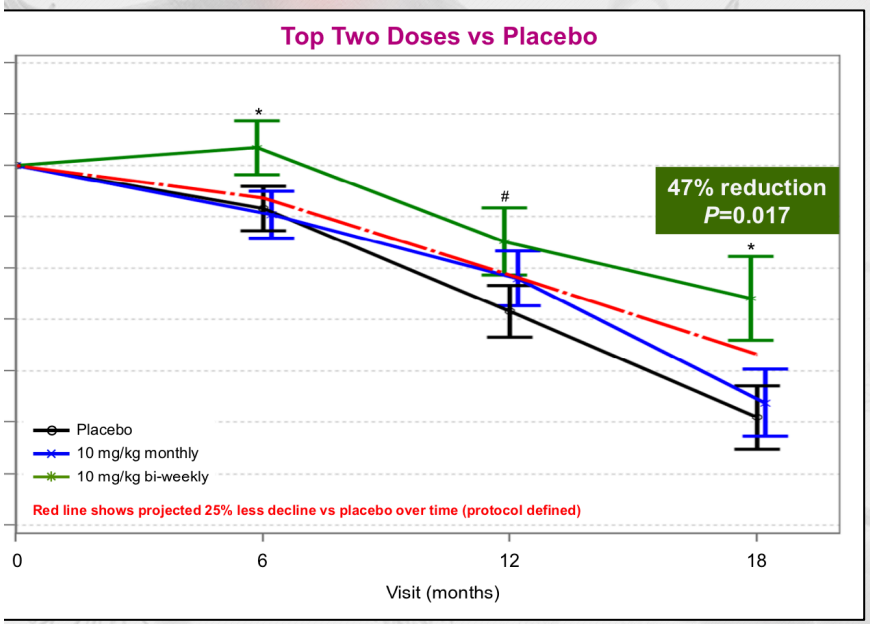


Kramer L, et al. AAIC, 2018

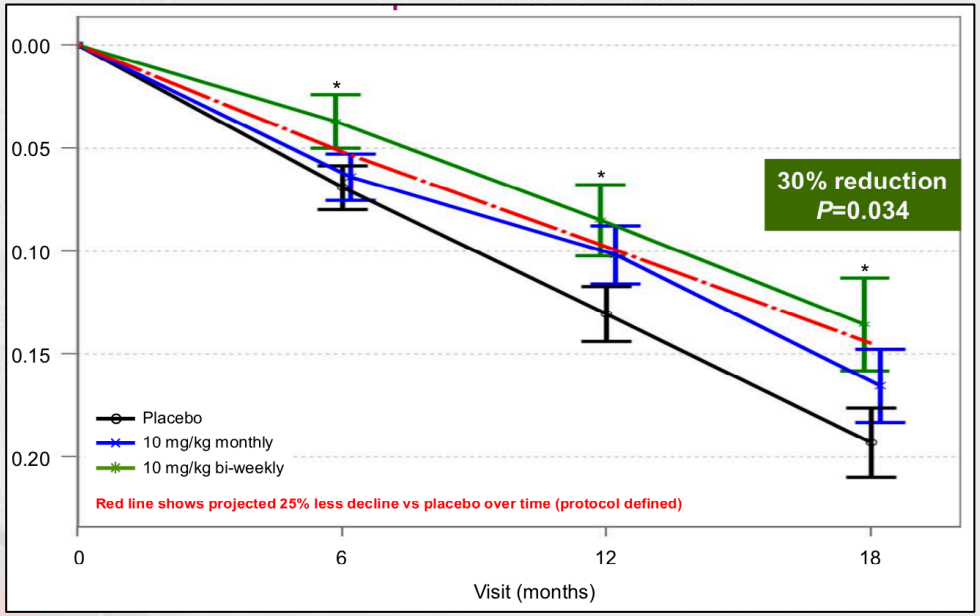
- Amyloid PET SUVR
- 81% converted from visual + to visual (-) on amyloid PET
- Low rate of ARIA

BAN-2401

ADCOMS[1]



ADAS-cog

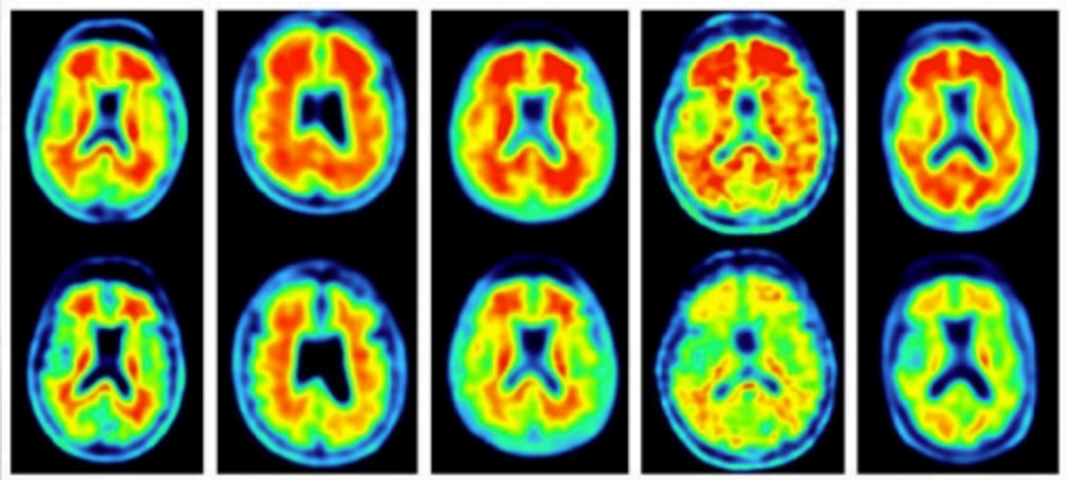


Kramer L, et al. AAIC, 2018

[1]Wang J, et al. JNNP 2016; 87: 993-999

Monoclonal Antibodies

- Solanezumab in prevention trial of cognitively normal amyloid positive individuals (A4)
- Gantanerumab[1]
- Crenezumab[2]



Amyloid reduction with gantenerumab

[1]Ostrowitzki S, et al. Alz Res Therapy 2017; 9: 95; [2]Cummings J, et al. Neurology 2018; 90: e1889-1897

AD Clinical Trials: History and Lessons

- This is hard work!
- Progressive improvement in understanding biology, developing therapies, conducting trials
- Animals may not predict efficacy or safety (AN1792; tarenflurbil)
- Brain penetration, dose, and target engagement must solved in Phase 2 (tarenflurbil)
- Post hoc sub-group findings are a poor basis for Phase 3 (bapineuzumab, solanezumab)

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AD Clinical Trials: History and Lessons

- Biological confirmation of diagnosis to insure the presence of the target pathology
- Global trials introduce heterogeneity of data
- Drugs may make patients worse (semagecestat)
- Treating earlier in disease may have benefit (aducanumab, BAN-2401; not solanezumab)
- New trial tools are emerging (BAN-2401)

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THANK YOU