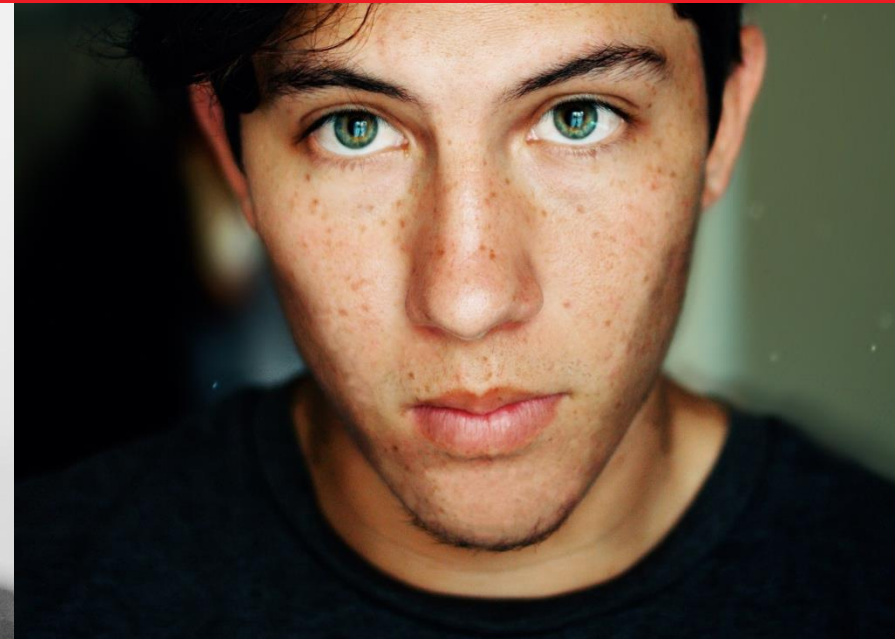
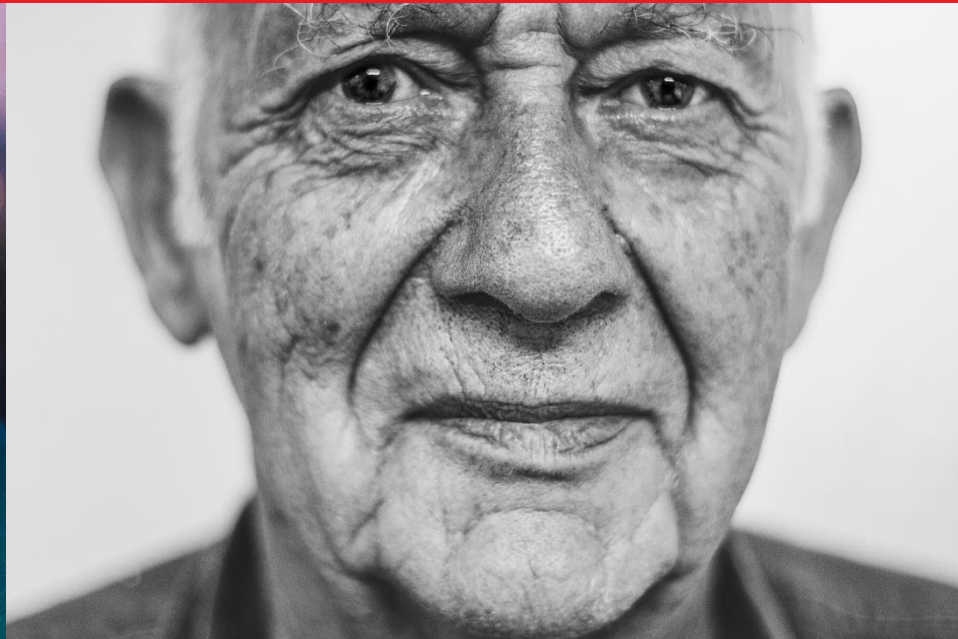
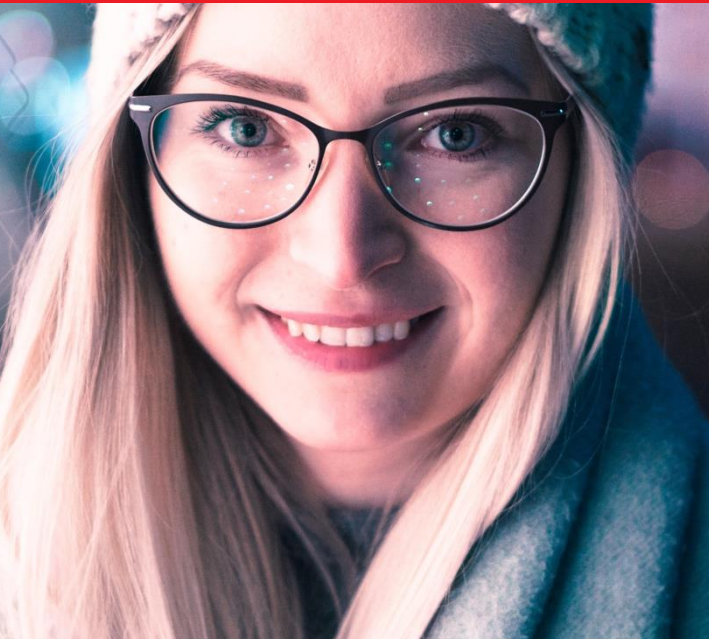


Interpreting Recent Results in AD Drug Development



Stephen Salloway, MD, MS

Disclosures and Acknowledgements

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2. Alzheimer's Association-Part The Cloud Program, US POINTER
3. Fain Family Foundation, Joukowsky Family Foundation, Winter Family, Rhode Island Foundation, Goodman Family Foundation, Global Alzheimer Platform Foundation

Speakers Bureau: None

Clinical Trials:

Lilly, Biogen, Genentech, Avid, Roche, Eisai, Novartis,

Consultant:

Lilly, Biogen, Roche, Genentech, Eisai, Novartis

I own no stocks or equity in any pharmaceutical company and have no patents or royalties.

Lecture Outline

- Personal reflections on building a global AD research network and advances in AD biomarkers
- Discuss recent clinical trial results and emerging therapeutic targets to achieve meaningful impact on QOL





Building the Alzheimer's Army



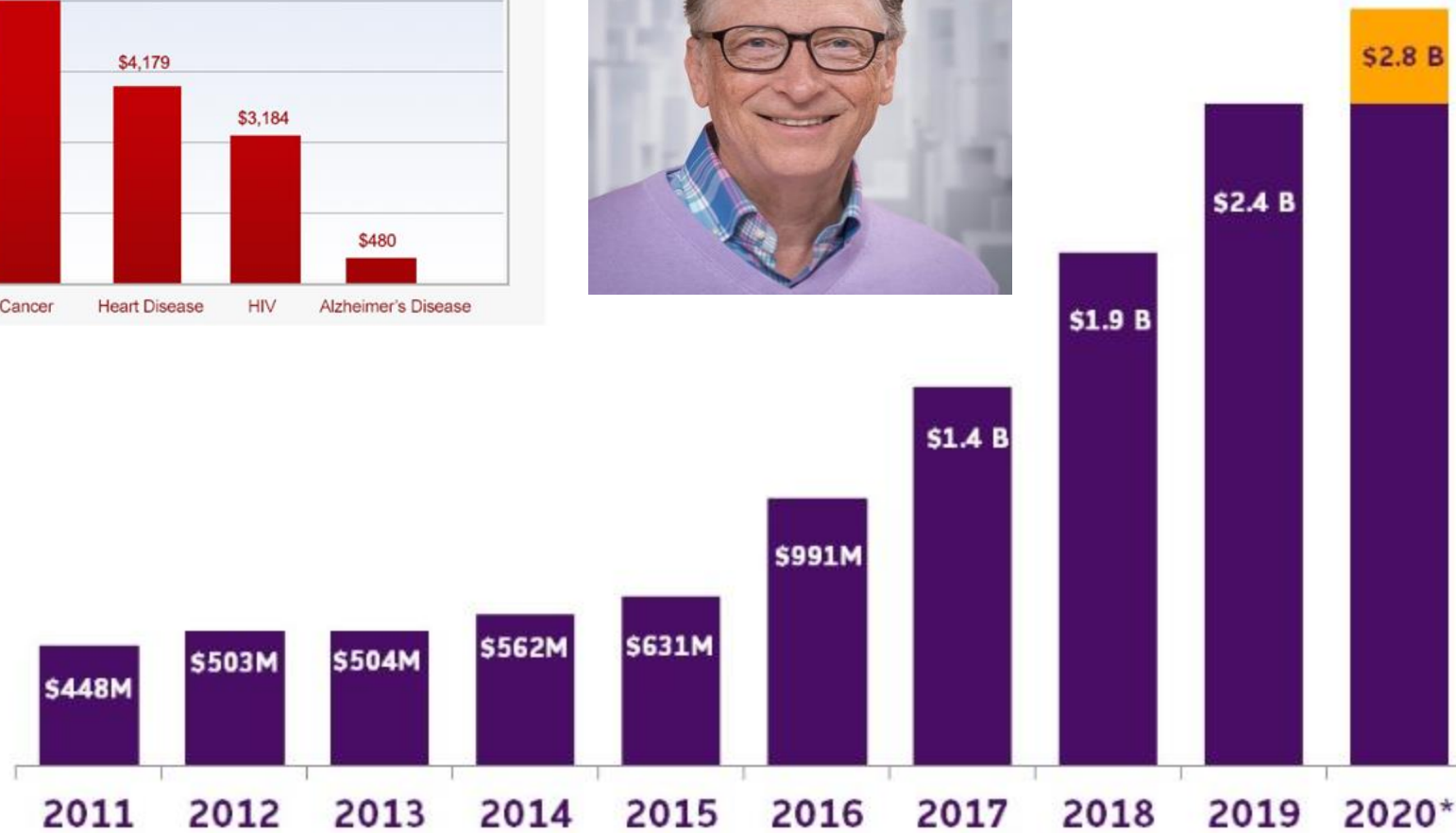
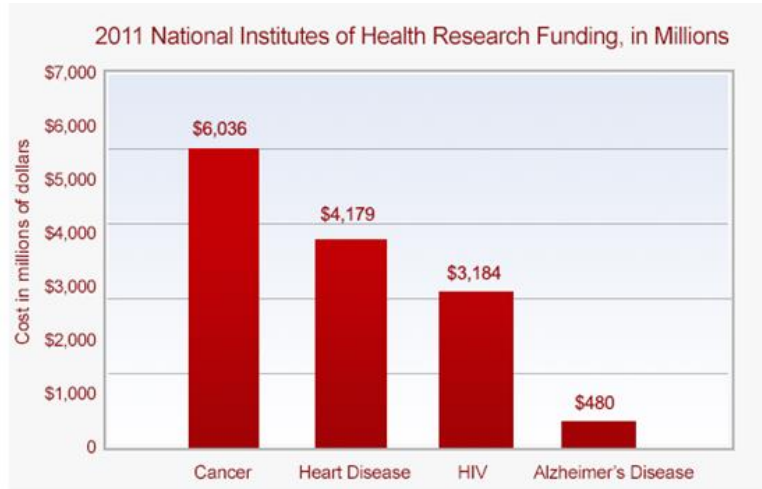


Building a Global Research Network



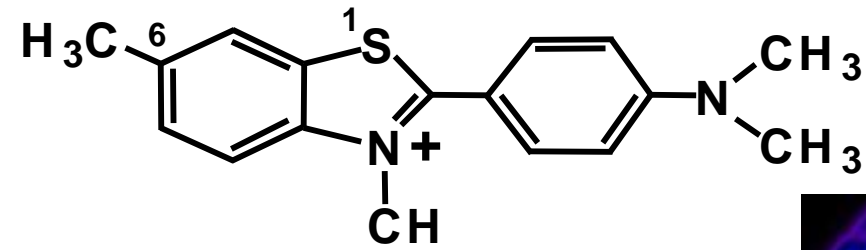
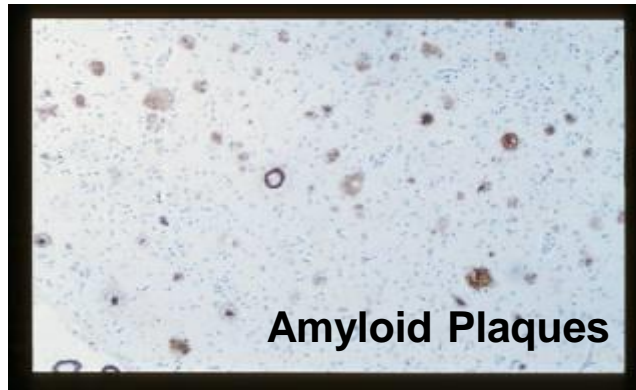
ADNI, DIAN, ACTC, GAP, LEADS, EPAD

Increase in NIH Funding for Alzheimer's Research

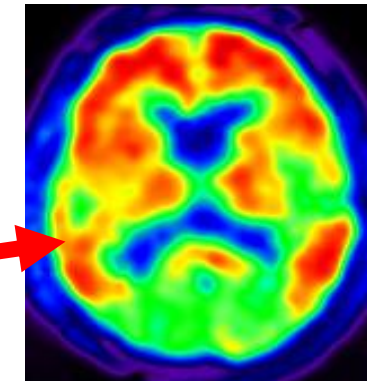


*FY2020 number includes pending \$350 million increase proposed by Senate appropriators

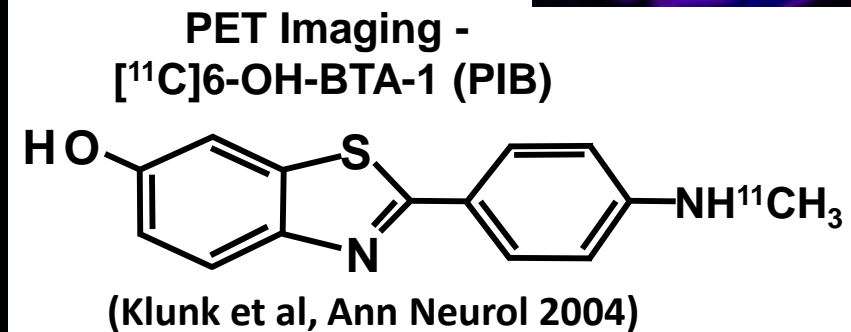
Advances in Molecular Brain Imaging



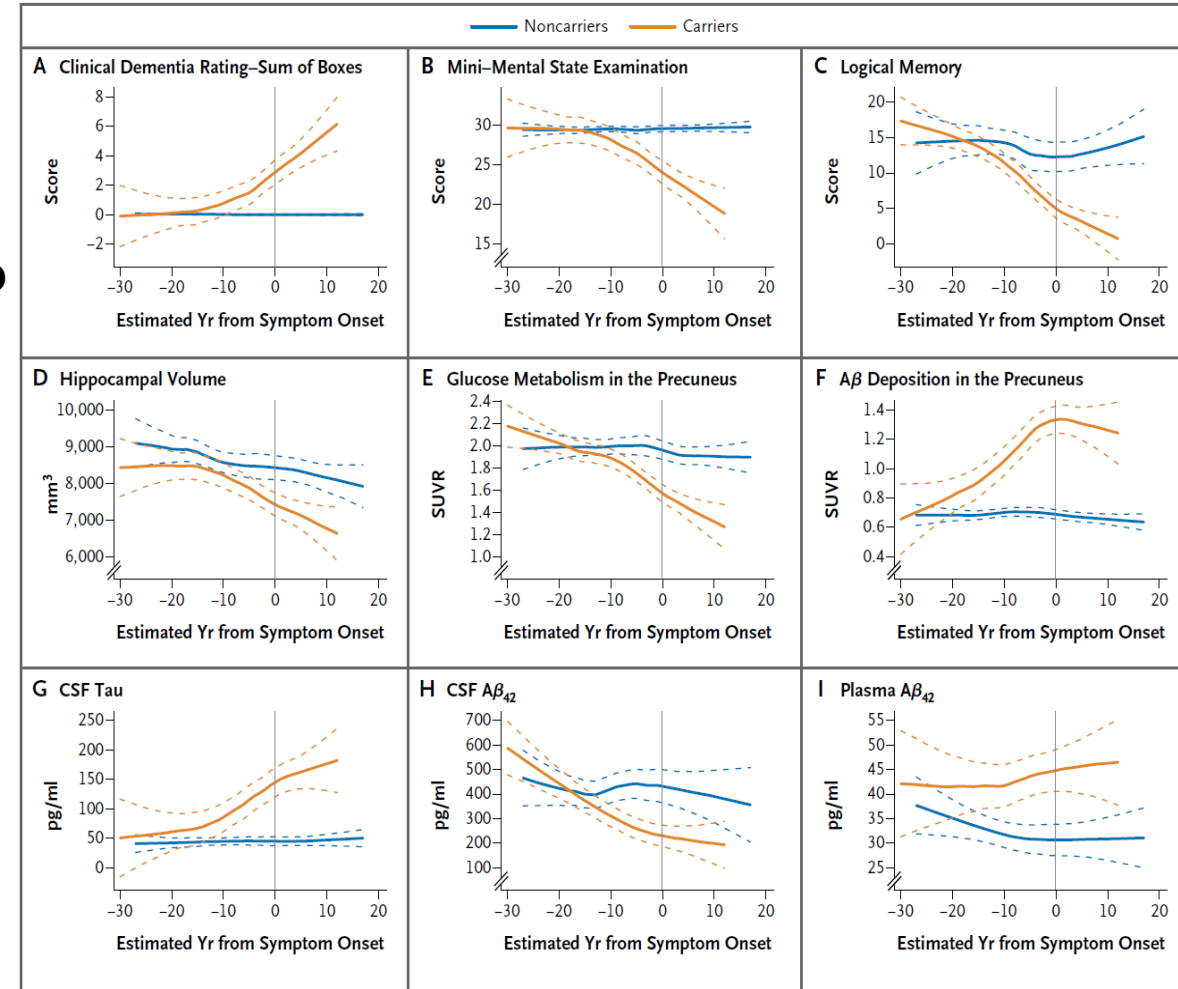
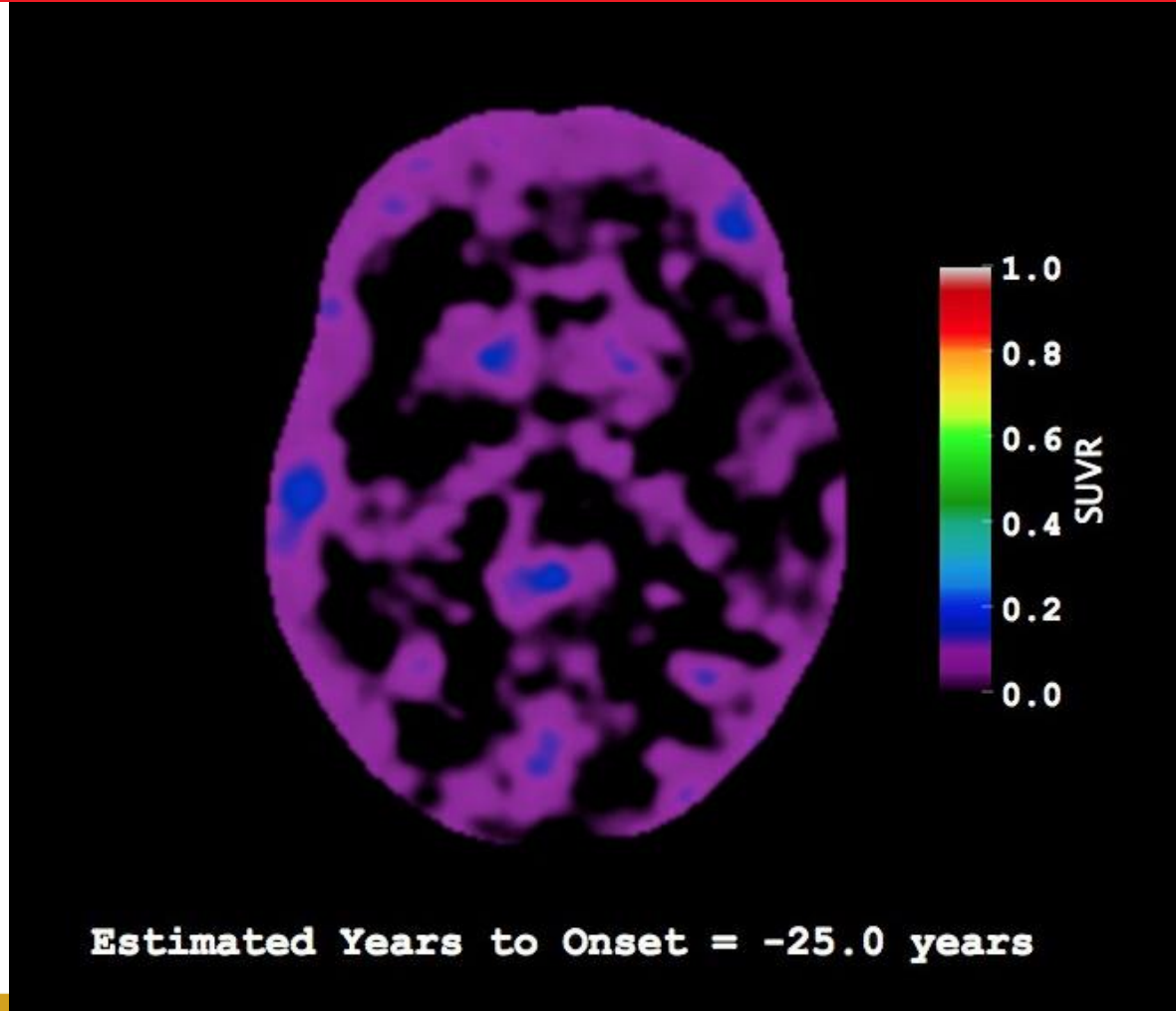
Histology - Thioflavin T



Courtesy of William Jagust



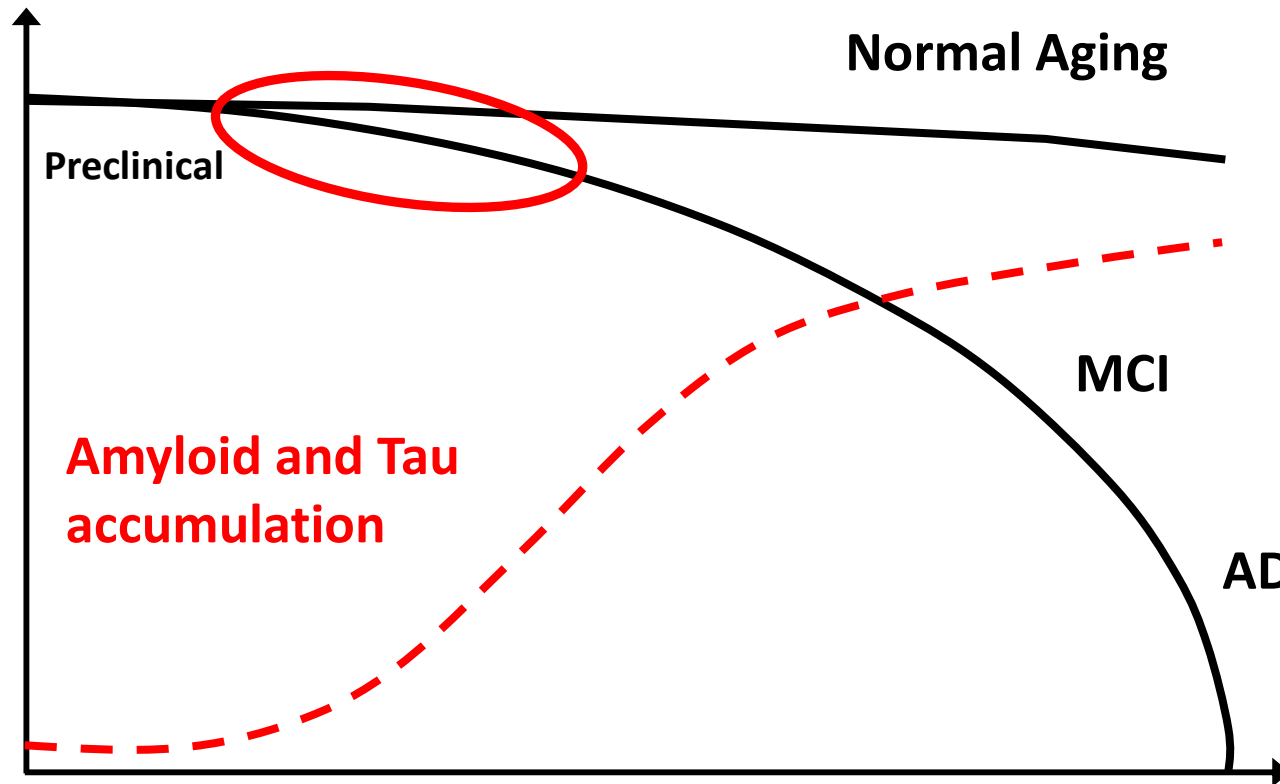
Plaque build up begins early



Amyloid PET IDEAS Study

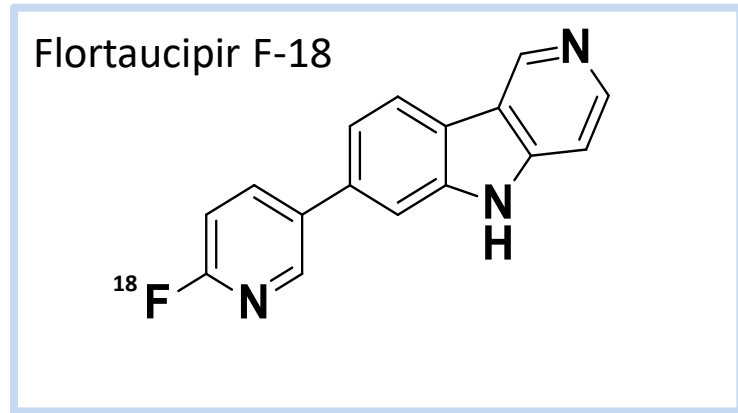
- Recruitment of 16,008 participants with 11,409 amyloid PET scans
- Change in diagnosis from AD to non-AD 25.1% and from non-AD to AD 10.5%
- Change in management in 60.2% in MCI and 63.5% with dementia
- Amyloid PET is clinically meaningful but is not covered and rarely used in practice

Opening the Era of Alzheimer's Prevention Research

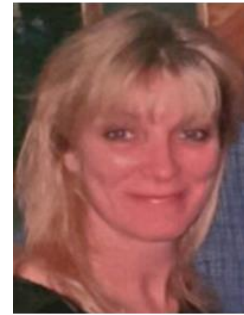


70% of people get good news that they are at lower risk on amyloid PET

Tau PET as a Diagnostic, Prognostic and Outcome Measure



AKA [¹⁸F]AV-1451, [¹⁸F]T807



Brain Section from Alzheimer's Patient



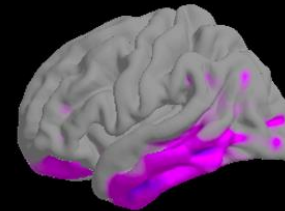
Flortaucipir F-18
Autoradiography



Tau Pathology
With AT8 Antibody

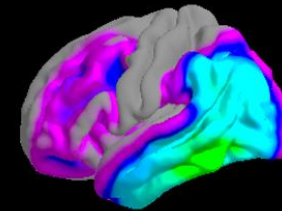
Summed PET images from AV-1451-A05 (Exploratory) Phase 2

Old Cognitively Normal
Controls *Amyloid Positive*



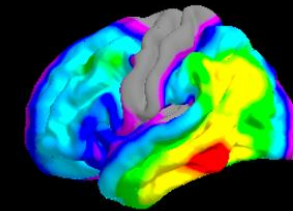
N=5

Mild Cognitive Impairment
Amyloid Positive



N=46

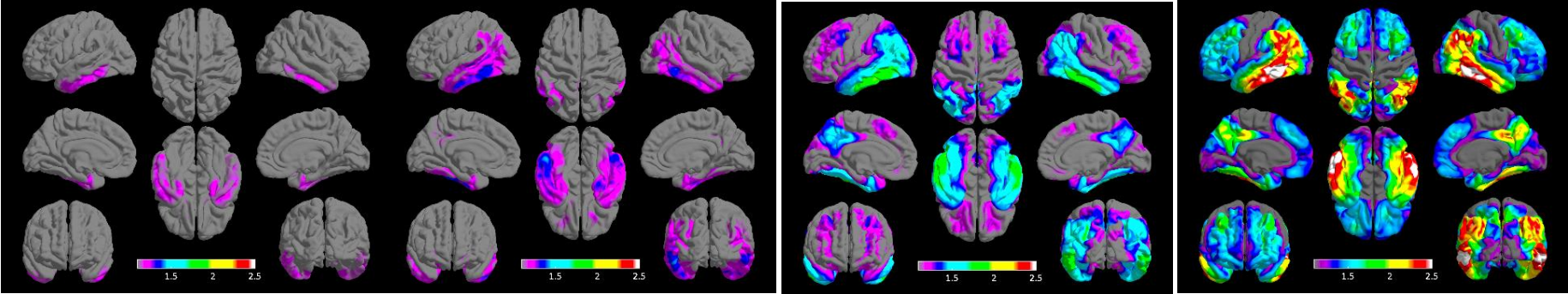
Mild to Moderate AD
Amyloid Positive



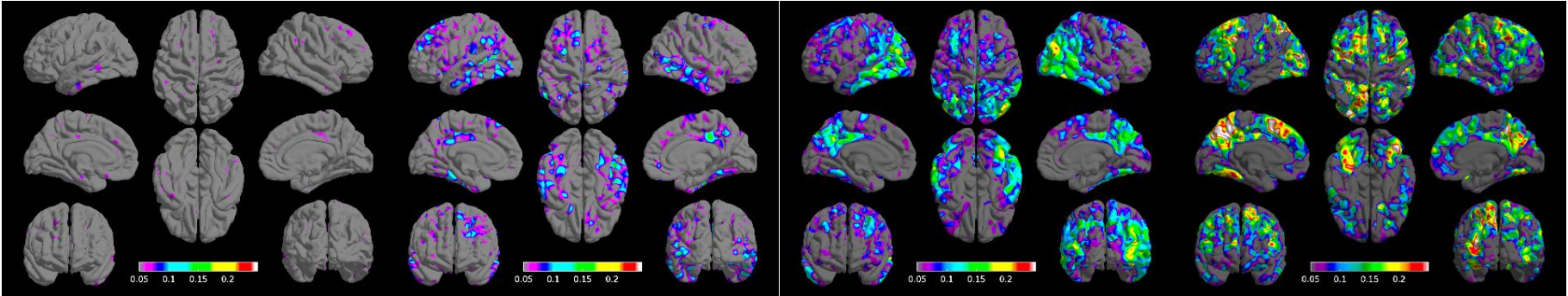
N=32

Baseline Tau PET is Associated with Accumulation of Tau and Rate of Cognitive Decline

Baseline Tau



Δ Tau



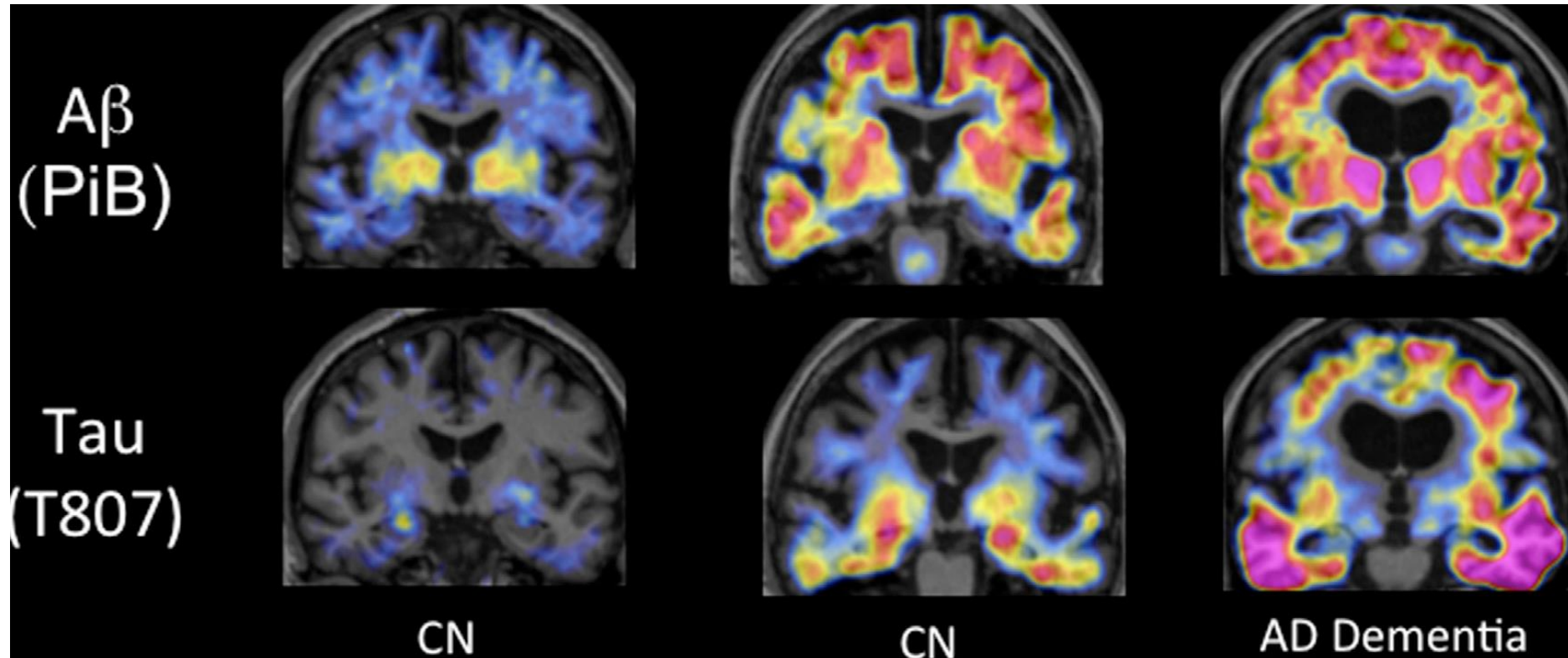
1st Quartile
Very low tau

2nd Quartile
Low tau

3rd Quartile
Intermediate tau

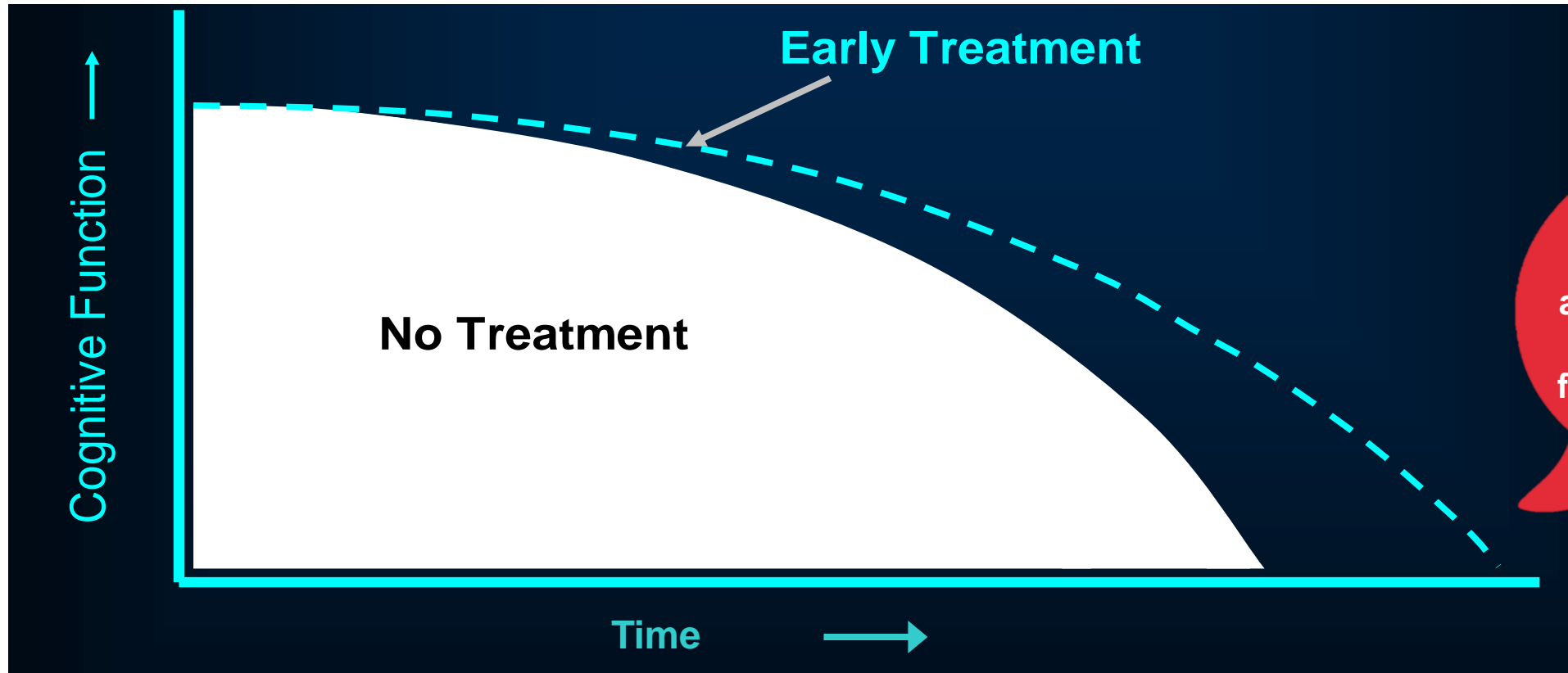
4th Quartile
High tau

Biomarkers for Staging AD



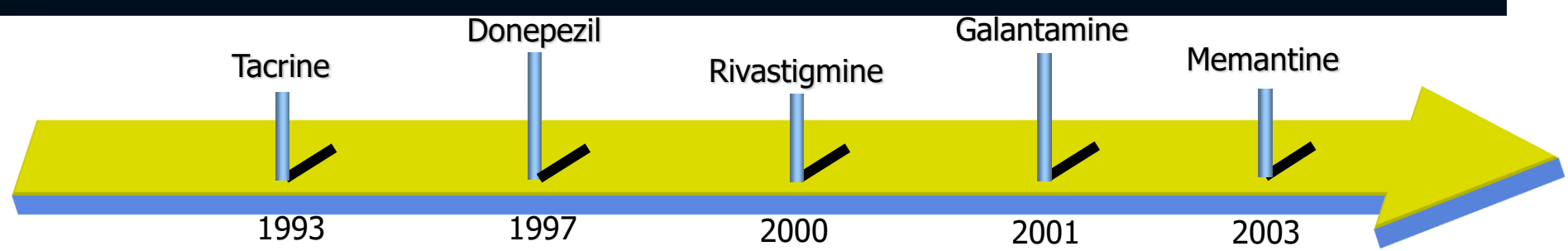
Sperling, Neuron 2014
Jack Alz and Dementia 2018

FDA Approved Drugs for AD



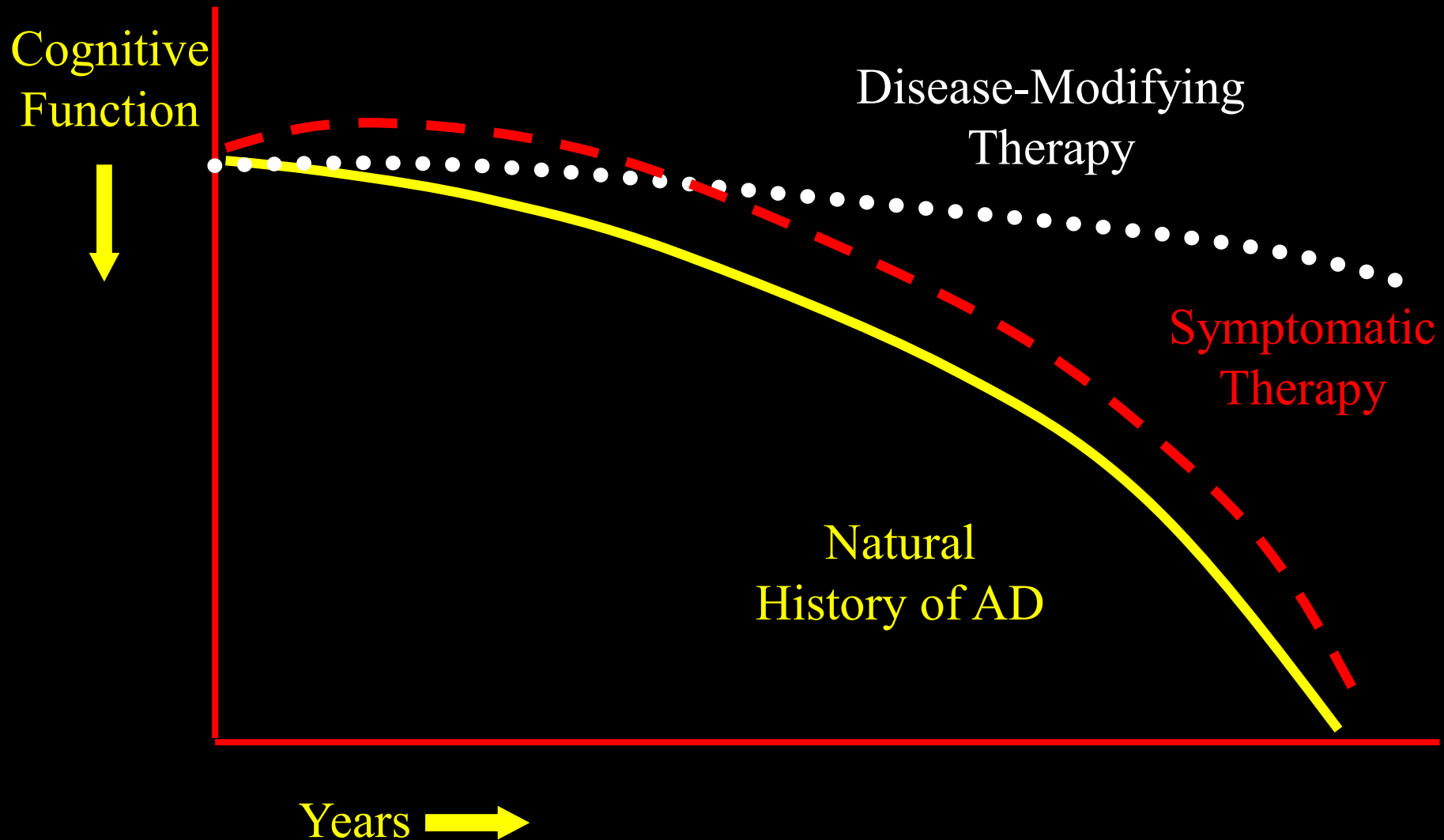
BREAKING NEWS

Oligomannate
GV-971
approved by the
Chinese FDA
for mild-mod AD
on 11/2/2019

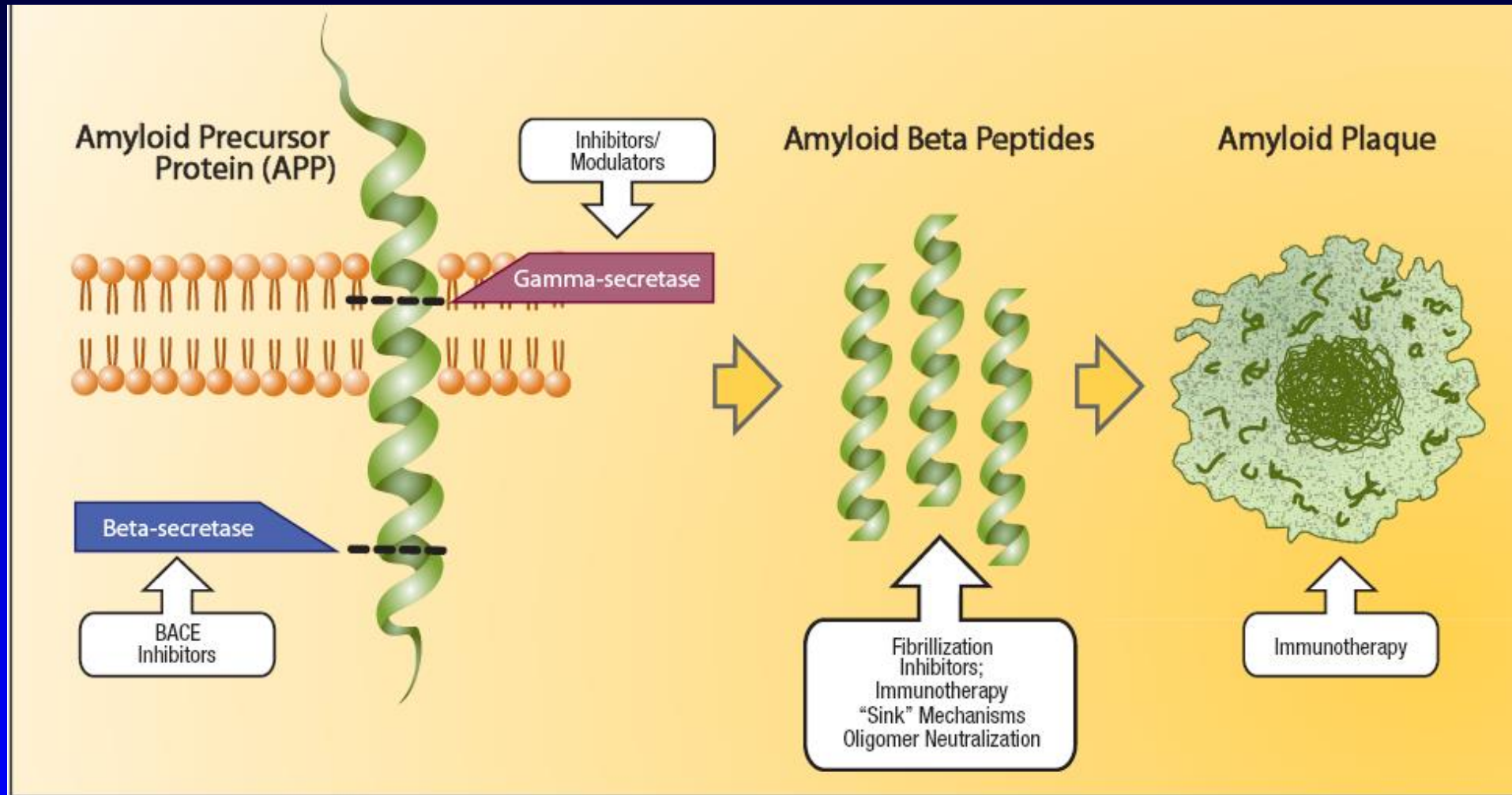


Courtesy N.Relkin

Moving Toward Disease Modification



Treatments Targeting Amyloid Beta



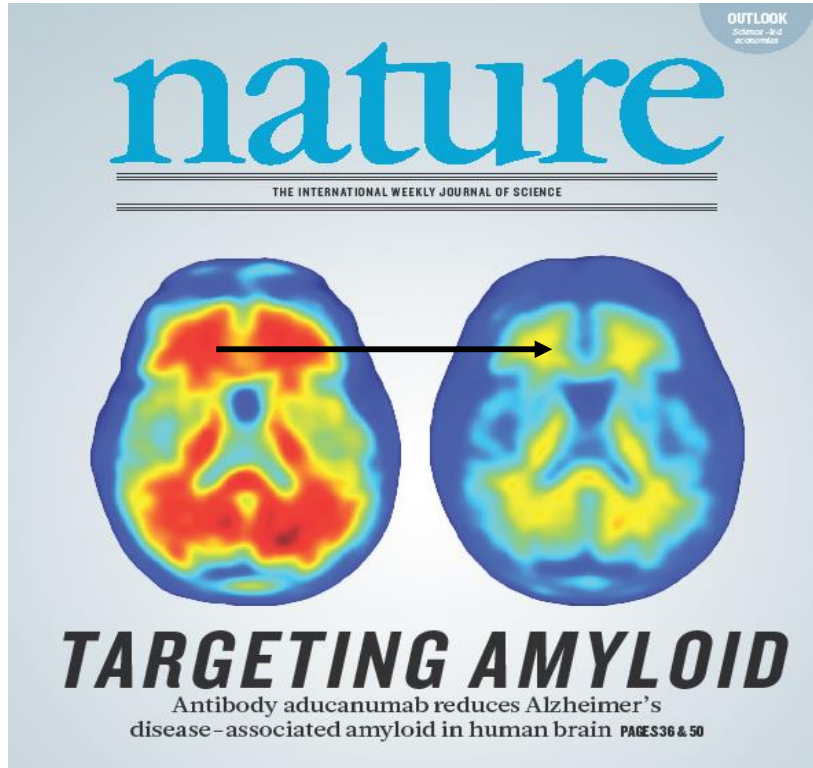
BACE Inhibitor Trials

- Appealing mechanism with good lowering of CSF ABeta42 with promise for primary and secondary prevention
- 4 BACEi produced cognitive worsening and a 5th lacked efficacy
- ? mechanism and duration of cognitive worsening, on or off-target
- Excellent collaborative response to analyzing, sharing and presenting data

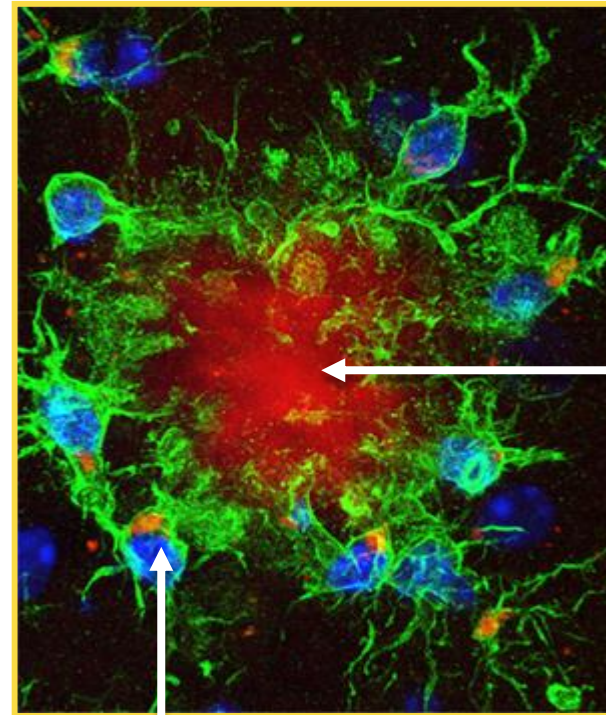
Anti-Amyloid Antibody Trials for Mild-Mod Dementia and MCI

- Bapineuzumab-Salloway, NEJM 2014
- Solanezumab-Doody, NEJM 2014, Honig, NEJM 2018
- Crenezumab-Cummings, Neurology 2018, Salloway, Alz Res and Ther 2018
- Gantenerumab-Ostrowitski, Alz Res and Ther 2017
- 20% had negative amyloid PET in Bapi and Sola
- Dosing limited by amyloid-related imaging abnormalities (ARIA)
- Evidence from phase 2 not compelling
- Disease stage may be too advanced to benefit from this approach

Aducanumab for Early AD



Sevigny, Nature 2016



Senile plaque
amyloid core

Activated
Microglia

Inside One Couple’s Experimental Treatment to Battle Alzheimer’s Disease

TIME

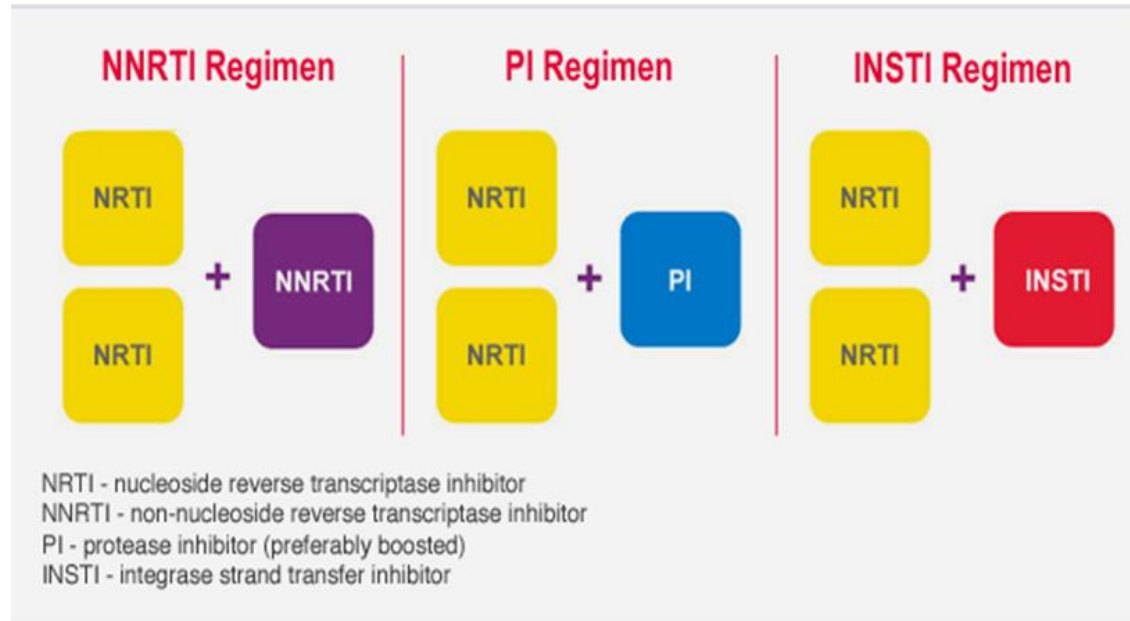


Aducanumab, BAN2401 and Gantenerumab

- Dose matters
- Substantial dose-related amyloid lowering
- ARIA appears to be manageable
- Signals of efficacy in PRIME, BAN phase 2 and EMERGE
- ? Duration needed, can change in aPET help guide Rx, ? maintenance
- Responder analysis
- If sufficiently +, good first step for combination, would lead to coverage and use of amyloid PET

Goal: Develop Treatments that Meaningfully Impact QOL

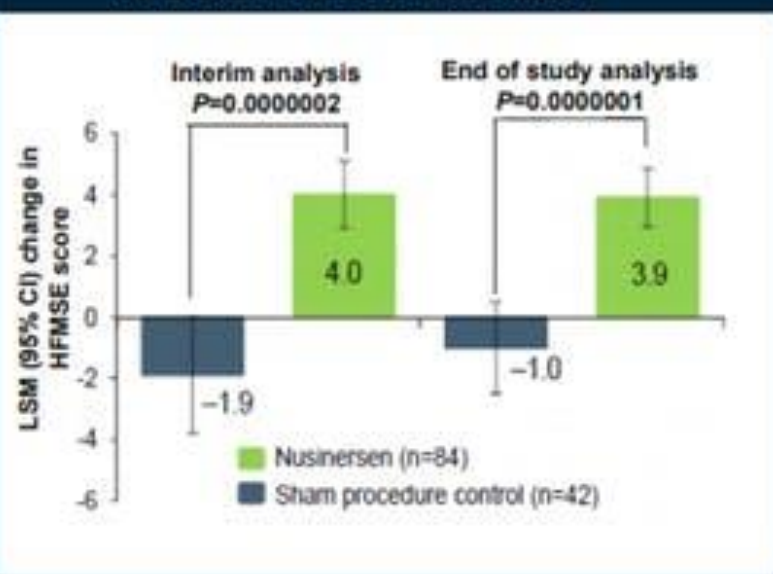
Combination Treatment for HIV



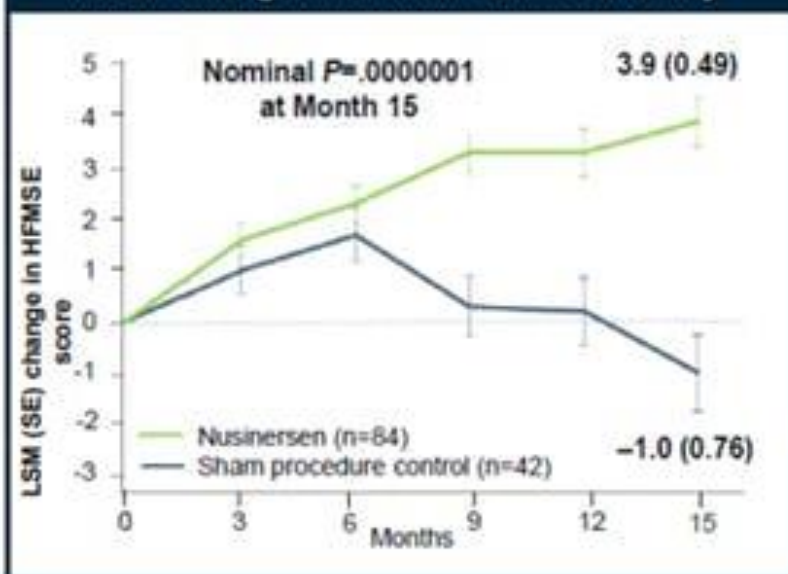
End of Study CHERISH Results Demonstrate Benefit in Patients with Later-onset SMA

SPINRAZA-treated children achieved statistically significant and clinically meaningful improvements in motor function

Primary endpoint: change from baseline to Month 15 in HFMSE score^a



End of study analysis
Mean change over time at end of study^a



SPINRAZA demonstrated a favorable safety profile

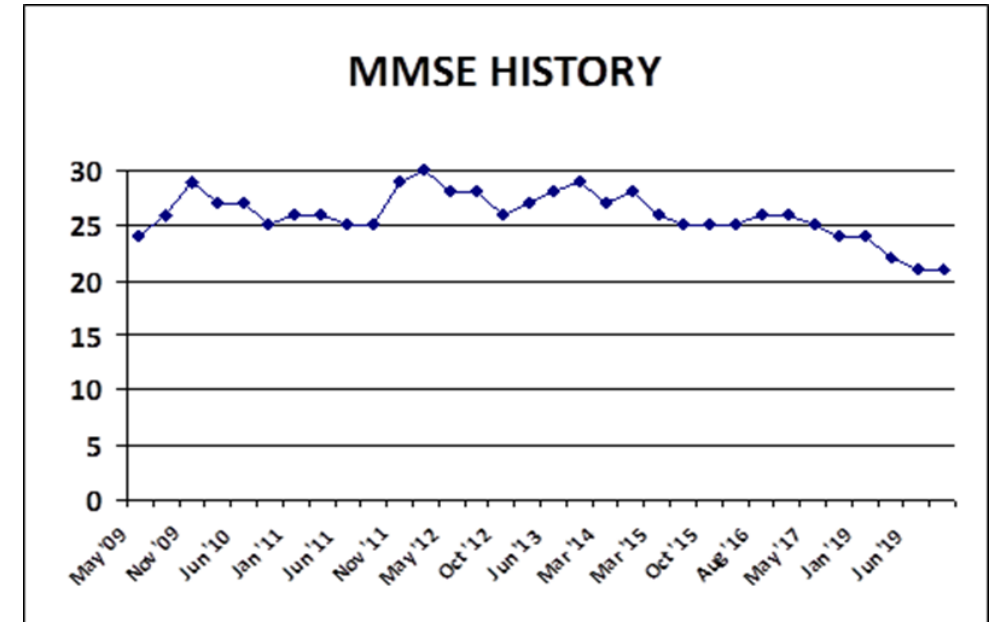


HFMSE = Hammersmith Functional Motor Scale Expanded; LSM = least-squares mean; ^aFrom baseline to Month 15. Interim analysis: observed: sham procedure control, n=19; nusinersen, n=35; imputed: sham procedure control, n=23; nusinersen n=49. End of study analysis: observed: sham procedure control, n=34; nusinersen, n=66; imputed: sham procedure control n=8, nusinersen n=18.

Mercuri E, et al. Efficacy and Safety of Nusinersen in Children With Later-Onset Spinal Muscular Atrophy (SMA): End of Study Results From the Phase 3 CHERISH Study. Presented at: 69th Annual American Academy of Neurology Meeting; April 22-28, 2017; Boston, MA.

78 year old with gradual cognitive and functional decline

- Initial stage MCI due to AD-amyloid PET elevated, ApoE3,4
- Treated with donepezil
- Enrolled in a DB anti-amyloid monoclonal antibody trial including open treatment for 4 years
- His wife reports that his cognitive symptoms and daily functioning have been relatively stable



Milestones in AD Prevention Research

- Recruitment of the Generation, Columbian, DIAN and A4 cohorts
 - ▣ 481 ApoE4 homozygotes and 1,145 mostly heterozygotes
- Pioneering AD platform trials and prevention registries
- Going earlier-A3,4-5 and DIAN Primary Prevention
- Multi-modal lifestyle intervention
 - ▣ FINGER, POINTER and Worldwide FINGERS

U.S. POINTER Trial



Does a recipe that combines lifestyle interventions prevent or delay cognitive decline in larger population?

THE LANCET

35%

Global Dementia
May be Preventable



Physical Exercise



Nutritional Counseling
& Modification



Cognitive &
Social Stimulation



Improved
Self-Management of
Health Status

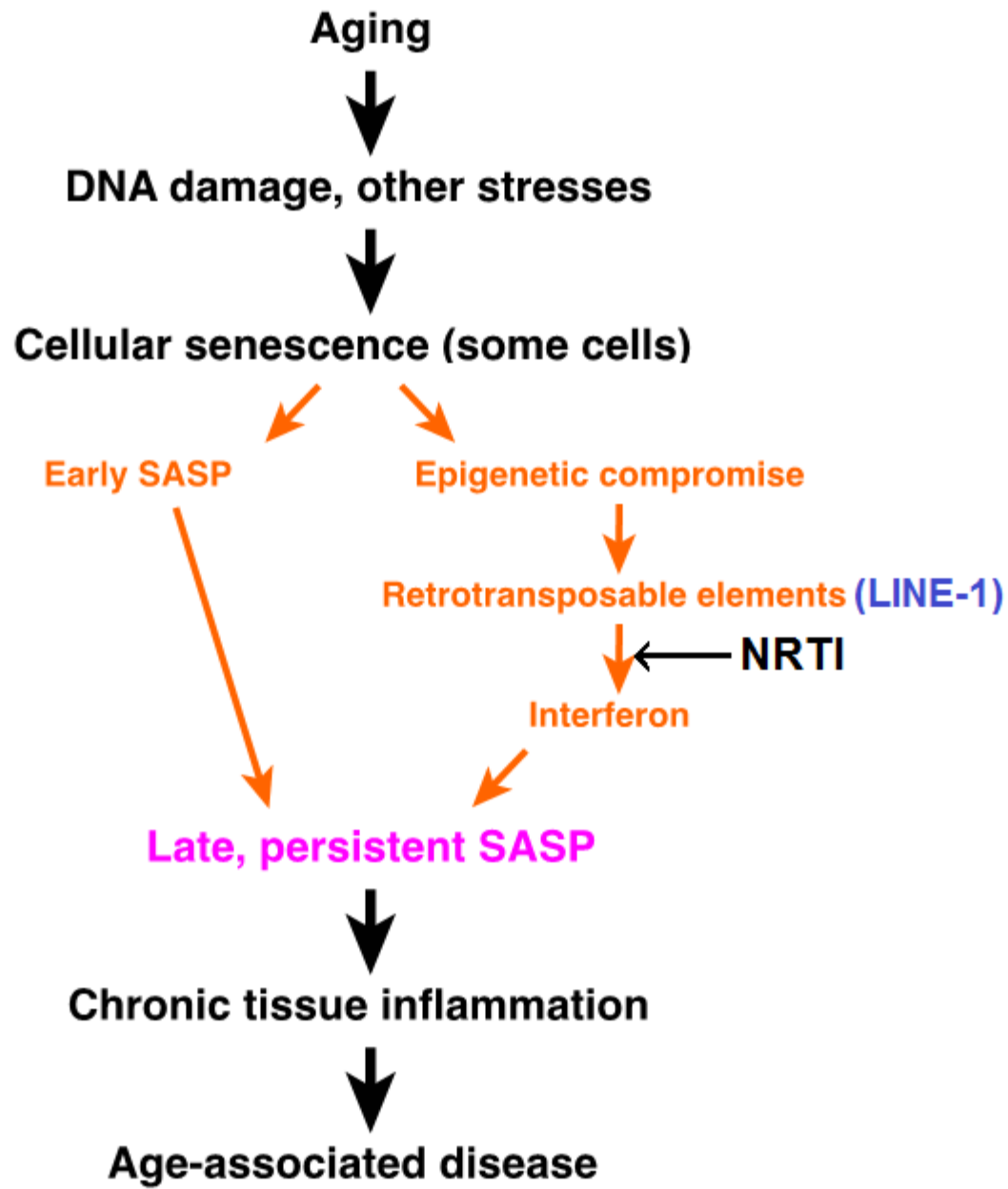
Emerging Targets and Discovery Science

- Tau-based treatments
- Gene modifying
 - ASO, viral gene transfer, gene editing
- Targeting mechanisms of cellular aging
 - Inflammation, epigenetics, autophagy and mitochondria
- Blood biomarkers
- Combination Rx



PART THE CLOUD

alzheimer's 
association



Supporting Research Careers of Young Investigators



What Will It Take to Succeed?

- Testing anti-amyloid drugs earlier in the disease
- Discovery science, combination treatment
- Platform trials
- Public-private partnerships with strong collaboration and data sharing
- Broad public engagement
- Establishing efficacy for a disease modifying target and building on this foundation