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at the Sanders-Brown Center on Aging

Advancements in AD treatment studies: "No one left behind"

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Disclosures

- **I will discuss research findings with unapproved implications for diagnosis and treatment of degenerative brain disease**
- **Contract Research: AbbVie, Alector, Biohaven, Esai, Lilly**
- **Funded by U01 AG010483, P30 AG028383, R01 HD064993, R01 AG038651, U01 AG024904, R01 AG061111, UH3 NS100606, R01 AG054130, R01 AG061848, R01 AG054029, R01 AG063689, R56 AG060608, R01 AG053798, U19 AG024904, R01 AG057187, R01 NS116058**

Your Tax Dollars at Work!

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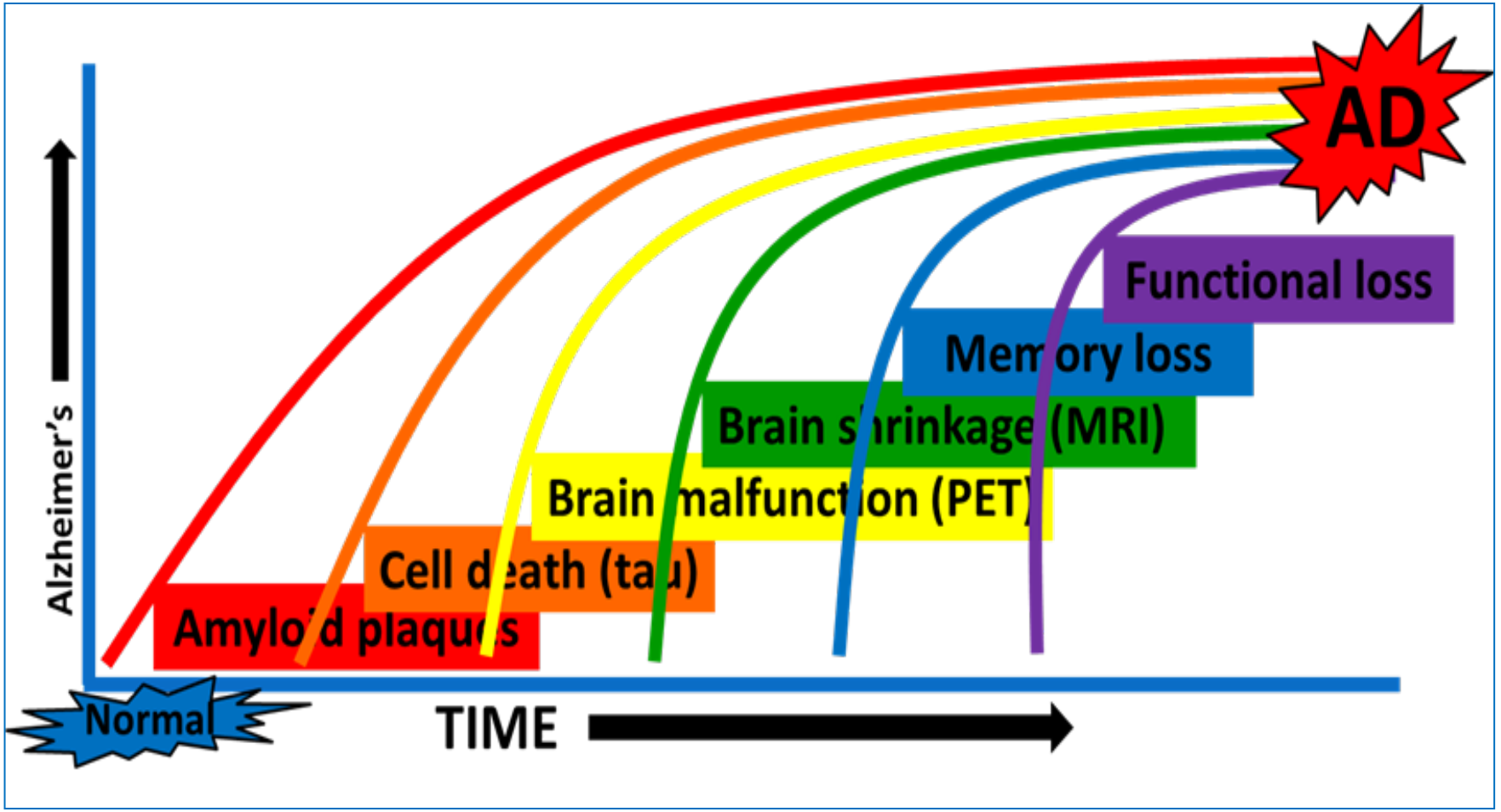
We have now figured out the major sequence of pathologic events responsible for AD…



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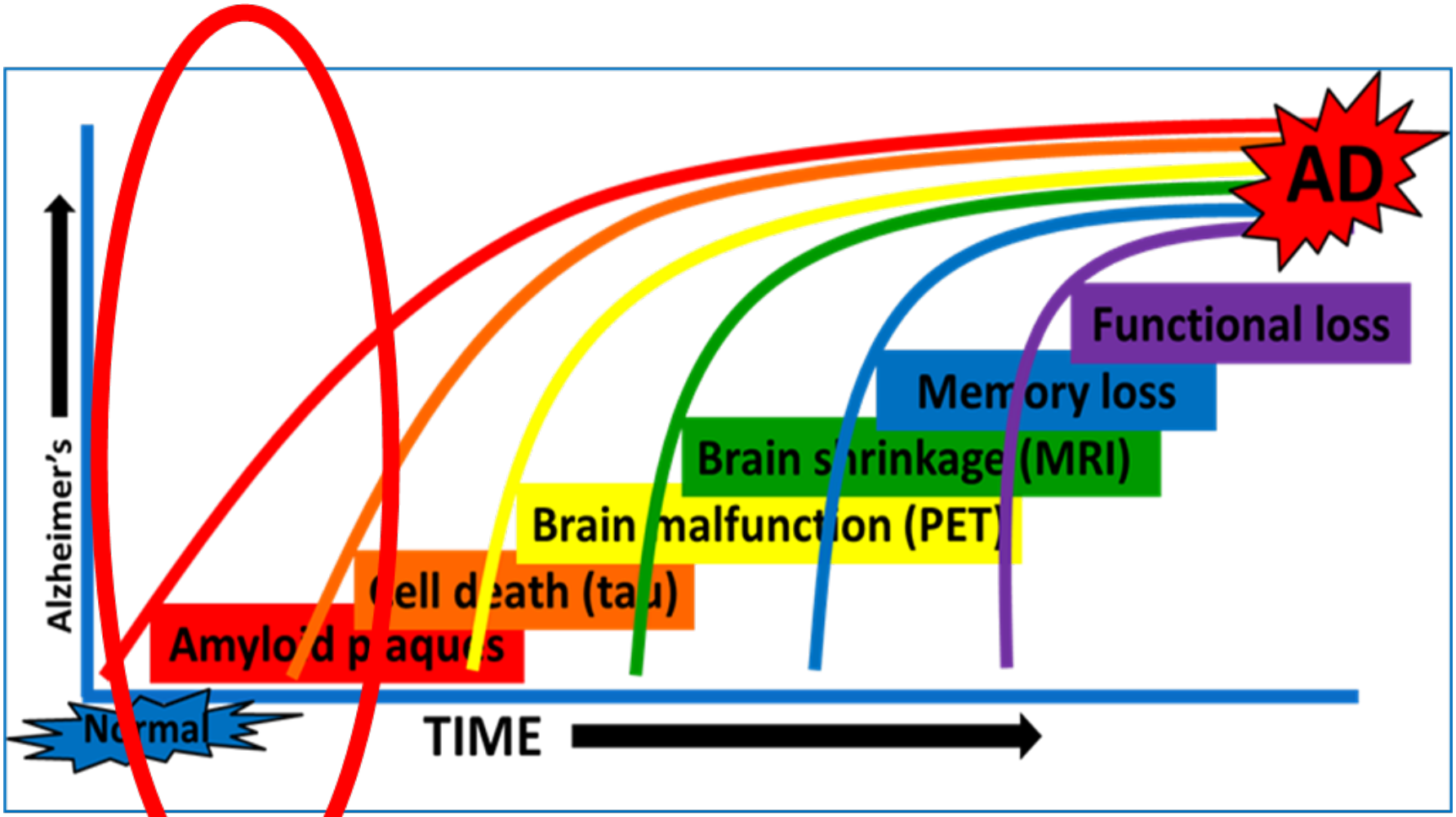
#1 Amyloid plaques



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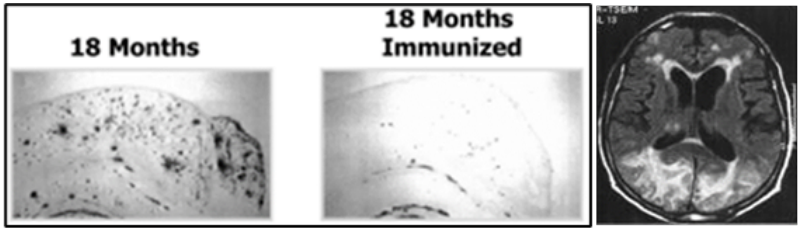
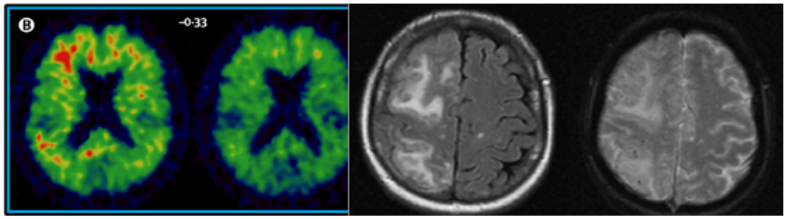
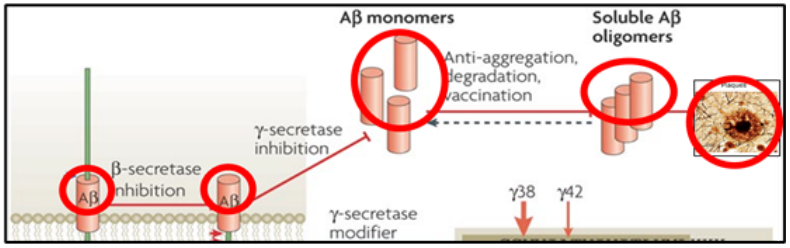
Aβ modulation: lessons learned & a path forward?

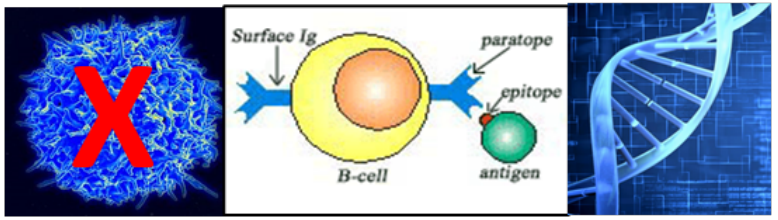
- Aβ vaccine trial halted
- Passive immunization has risk & won't stop late stage AD
- Antibody epitopes may matter
- Move to an earlier disease stage
- Safer vaccines on the way?







The A4 Study
Now is the time...



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Active vaccine progress?

- Vaccines are ideal
- Targeting prevention is optimal
- Older persons often have decreased immune responses
- Can we get this right?
- We think we can and are moving toward the day when we can protect everyone from AD!

Table 1. Examples of vaccine formulations currently being tested against Alzheimer's disease in animal models.

Vaccine formulation	Animal model tested	Reference
DNA vaccines		
pCMVE/MDC-3Aβ11-PADRE-C3d	C57BL/6 mice	Movsesyan et al. (23)
pVAX-3Aβ11-PADRE-Thep	Rhesus macaques	Evans et al. (24)
p(Aβ3-10)10-C3d-p28.3 + bupivacaine	B6C3-Tg mice	Guo et al. (25)
pVAX-6Aβ15-T-Hc/Hc-C	PDAPP^{V717I} mice	Yu et al. (26)
pN-3Aβ11-PADRE-Thep + electroporation	Rabbits	Ghochikyan et al. (27)
pCMVE/MDC-3Aβ11-PADRE + LT-IS	3xTg-AD mice	Davtyan et al. (29)
gL-Abx4-Fc-IL-4	B6C3-Tg mice, rabbits and cynomolgus monkeys	Matsumoto et al. (28)
Epitope/protein/VLP-based vaccines		
2Aβ$_{1-11}$-PADRE-MAP + QuilA	APP Tg 2576 mice	Petrushina et al. (30)
Adeno-10 × Aβ3-10 + CpG	B6C3-Tg mice	Li et al. (31)
2Aβ1-6-VLPQβ	APP24 mice	Wiessner et al. (32)
pDisplay-Aβ	APP23 mice	Bach et al. (33)
2Aβ1-11-PADRE-MAP + LT-IS	3xTg-AD mice	Davtyan et al. (29)
Prime-boost approach		
Aβ1-42 peptide prime/Aβ1-42 DNA + QuilA	B6SJLF1/J mice	Lambracht-Washington et al. (37)
AdenoPEDI-(Aβ1-6)1 prime/pCA-PEDI-(Aβ1-6)	C57BL/6J mice	Kim et al. (36)

- Over 14 new vaccines have been developed for AD that target amyloid
- All appear safe, but none (as of yet) produce high enough responses in aged persons

Alves RP, etal, Braz J Med Biol Res. 2014;47(6):438-444

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Passive immunization

- If you already have the disease, giving antibodies can really help!

- It works for COVID, and we have great data that such approaches may work in AD too!

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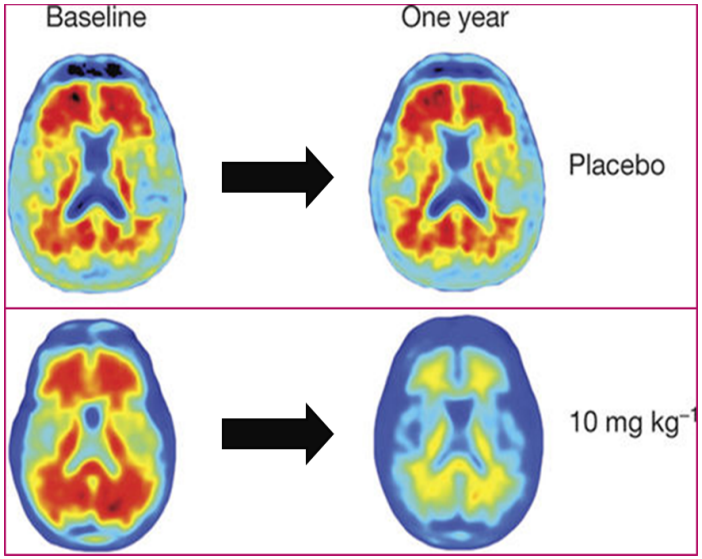
FDA approval for antibody infusions?

- ENGAGE and EMERGE, tested aducanumab in ~1600 mild AD patients
- The drug removed amyloid plaques from the brain
- The FDA concluded that benefits on slowing cognitive decline were inconclusive and the conditional approval requires an additional study
- ~41% subjects had brain swelling/stroke or bleeding in the brain and 25% of those had symptoms including worsening of cognitive decline



BIOMEDICINE

Doubts persist for claimed Alzheimer's drug

Once declared a failure, Biogen's antibody drug to be submitted for U.S. approval in 2020

By **Kelly Servick**

ast week, with trading in the company's stock halted for the widely anticipated

ties that suggest aducanumab helped trial participants retain some independence. "Those of us who know this disease well know what it means to lose yourself, slice

the high-dose group showed less cognitive decline than the placebo group, based on a standard dementia rating scale. But in ENGAGE, the high-dose group declined

http://science.sciencemag.org/content/366/6471/1298

Two other antibodies (maybe 3) are moving forward as well!

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Are these all the same medicines?

Let's think about how you might catch a rattlesnake?

- You could just grab it in the middle?
- Gives you a bigger target?
- But you might get bit and the rattle would attract others to attack?

- You could grab it by the rattle and tail?
- Keeps the rattle from attracting others to attack also?
- But you might get bit?

- Or you could grab it by the neck, right behind the head?
- Harder to do, but you can't get bit once you grab the snake?

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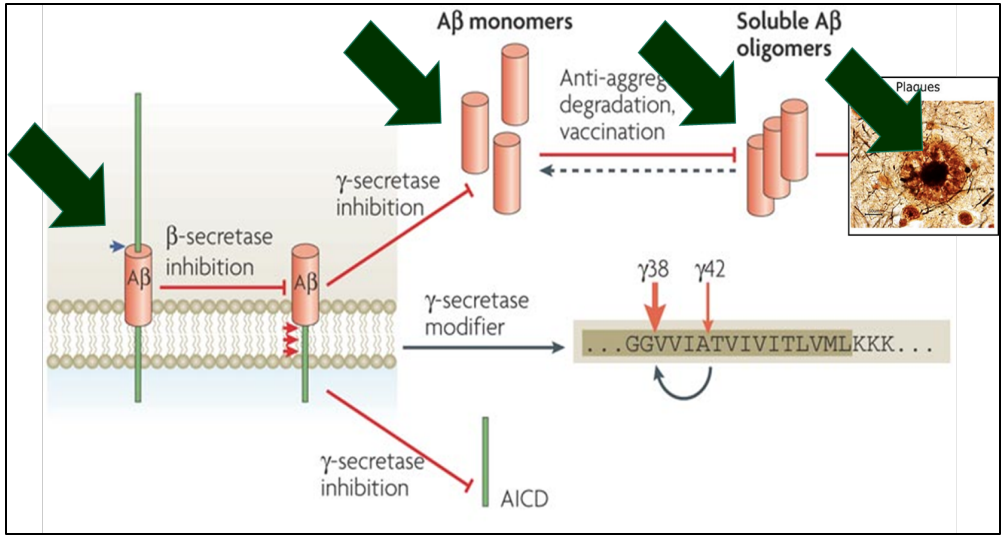
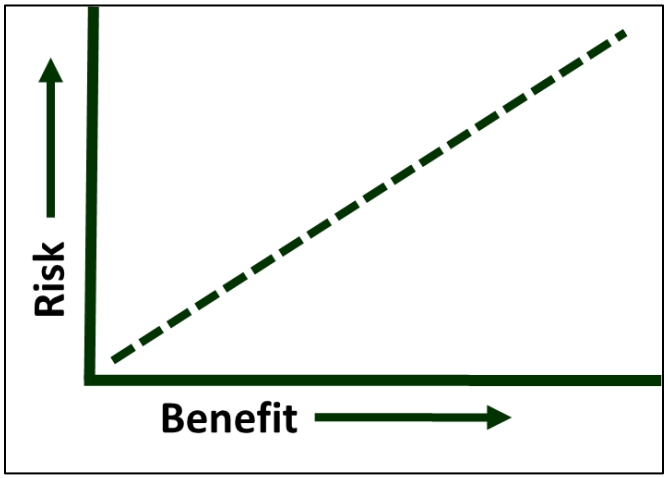
The antibodies "catch" amyloid in different ways



- They may recognize monomers (safest but least effective in removing plaques)
- They may recognize oligomers (increasing risk, but increasing benefit)
- They may recognize the plaque itself (highest risk, but most likely to remove plaques)

- **The higher the risk**
- **The higher the potential benefit**
- **Finding the right balance is critical for success**



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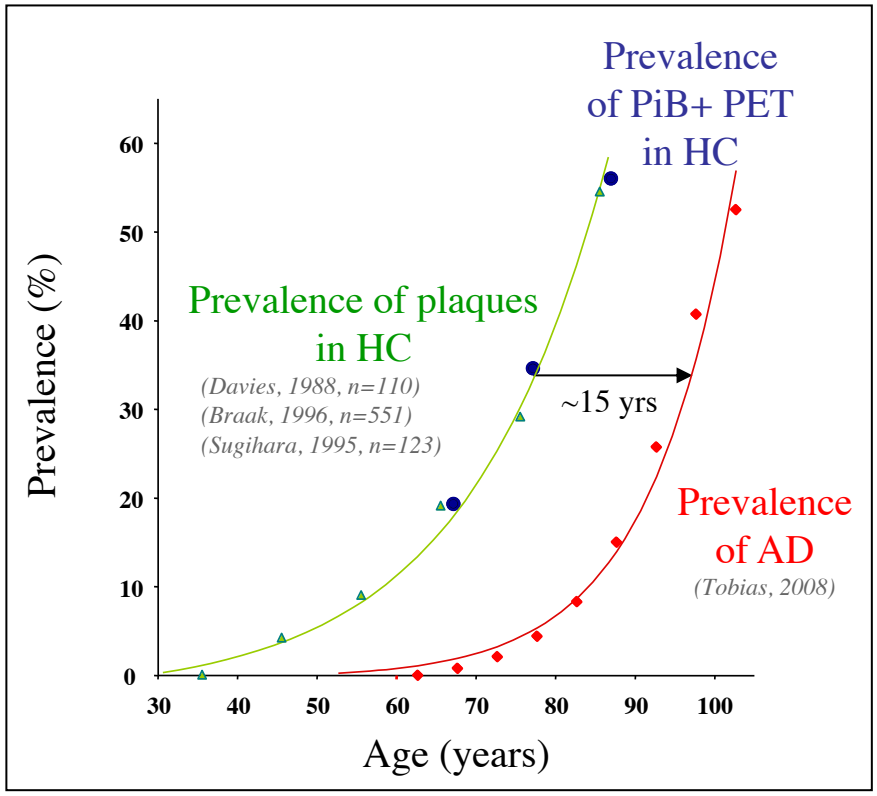
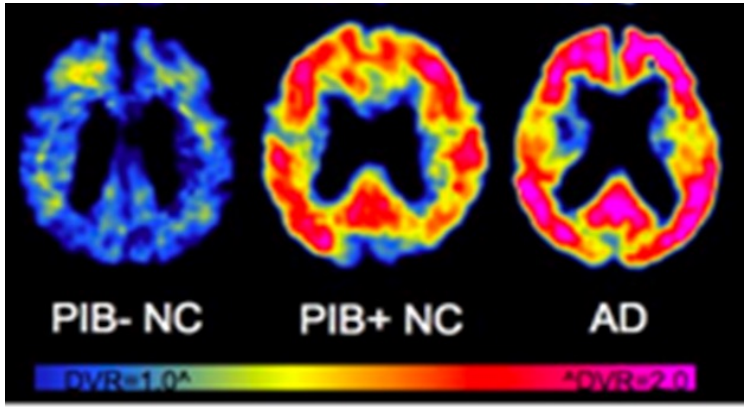
Preclinical Alzheimer's Disease (pAD)?



Rowe C et al *Neurobiology of Aging* 2010

- **Amyloid plaques are found in many asymptomatic persons**
- **Amyloid-PET allows us to see this in living persons**
- **Amyloid plaques occur ~15 years before clinical AD becomes evident**



Sperling, Johnson *NeuroMolecular Med* 2010

One out of every three persons over the age of 65 years has pAD

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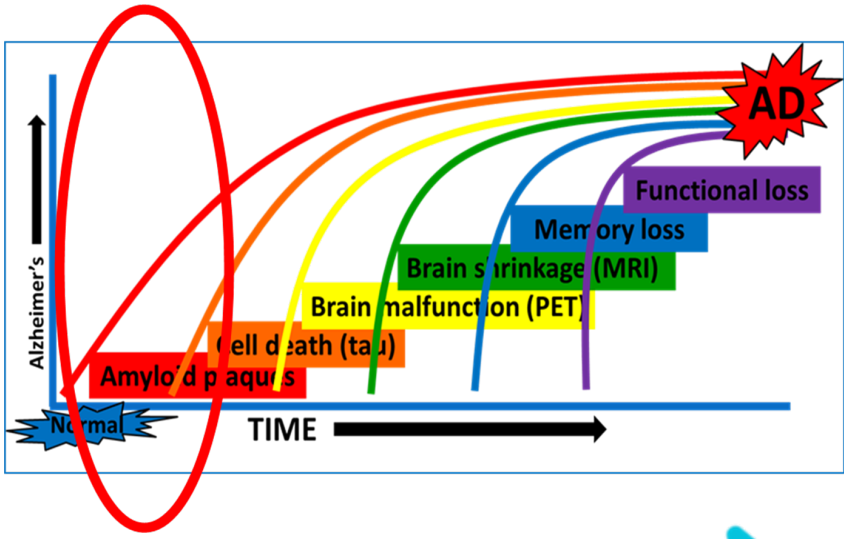
These drugs may work best prior to memory loss?

- These are critical studies in the field (NIH & UCI)
- A4 is ongoing and we should see results in the next 1-2 years
- AHEAD is enrolling now!
- "an ounce of prevention, is worth a pound of cure!"



AHEAD STUDY

The A4 Study
NOW IS THE TIME

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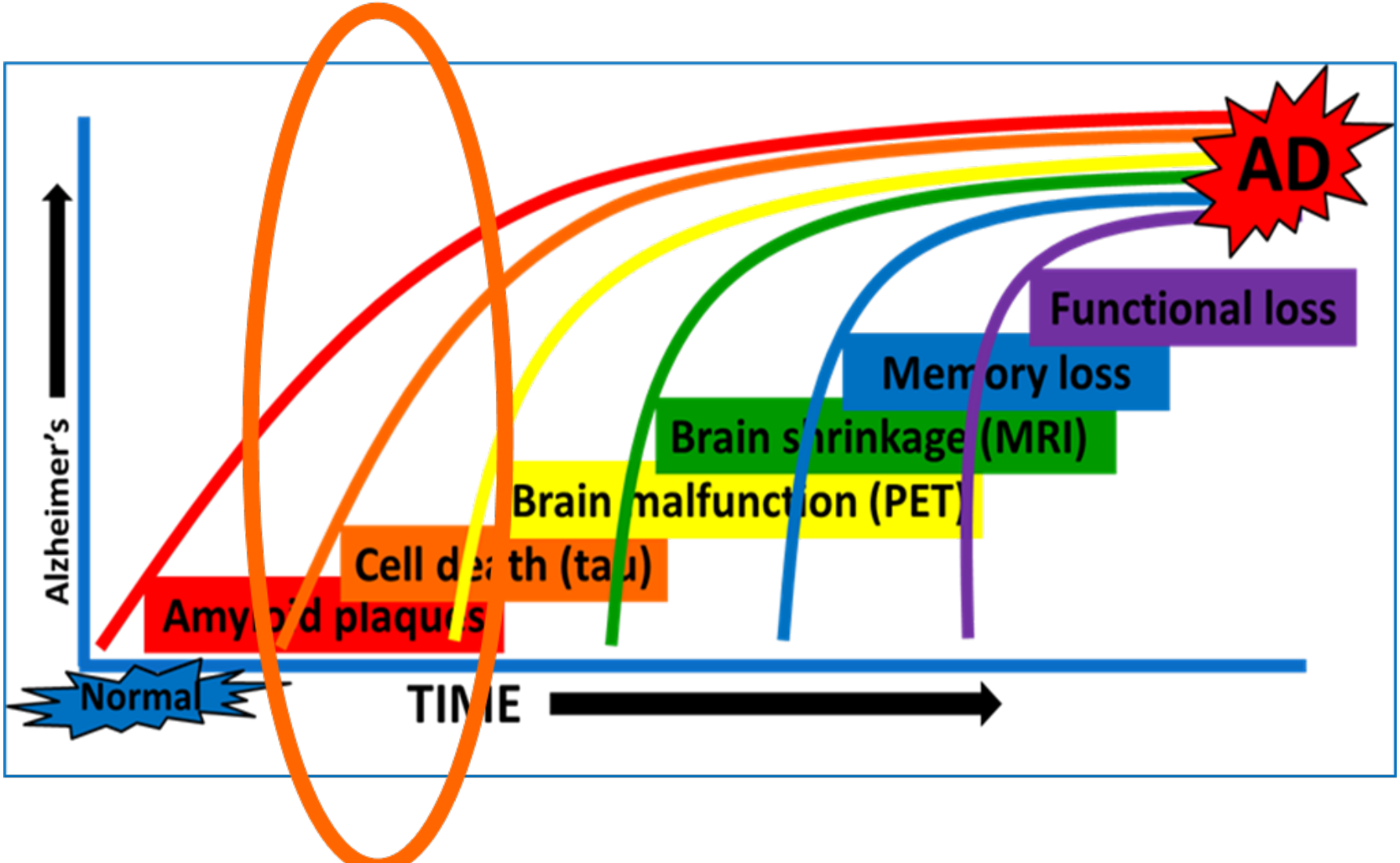
#2 Tau & tangles



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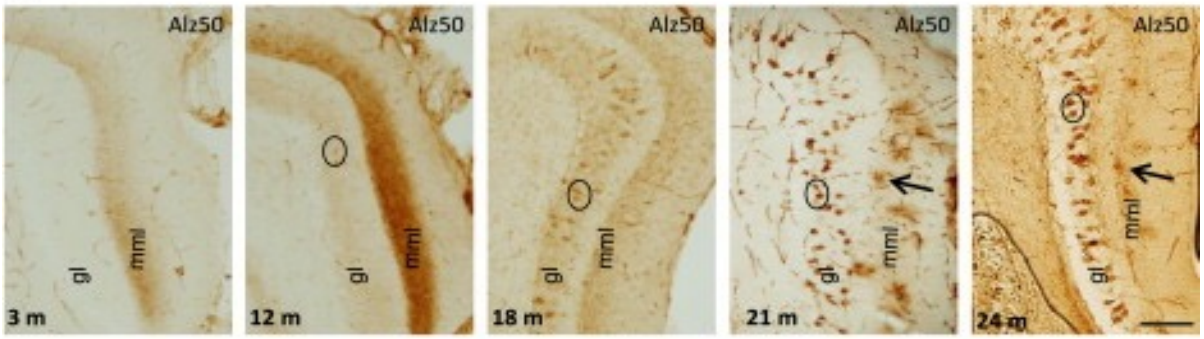
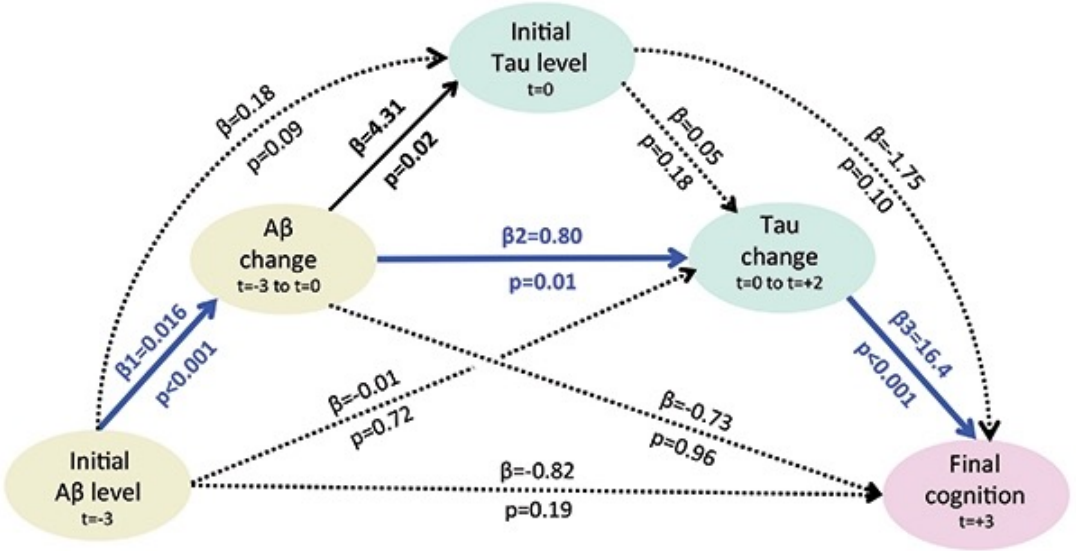
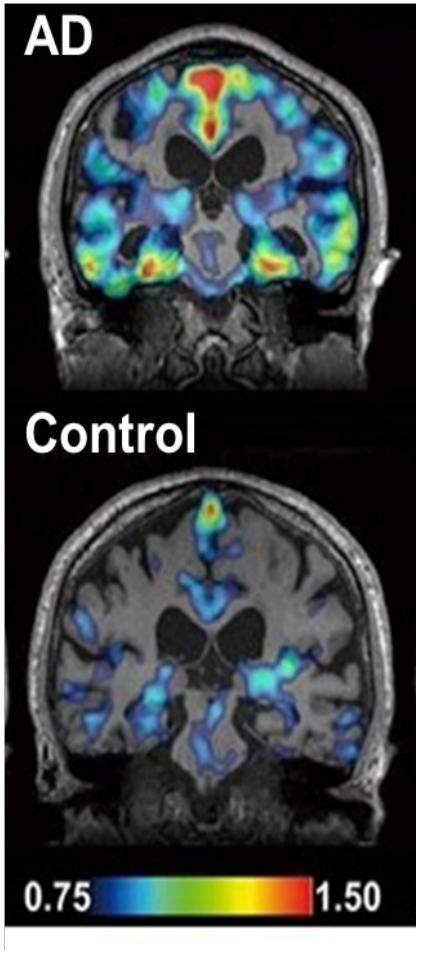
Tau/Neurofibrillary tangles spread from nerve cell to nerve cell



de Calignon et al.. Neuron. 2012 Feb 23:73(4):685-97: Liu et al.. PLoS One. 2012:7(2):e31302.





ADVISORY COUNCIL ON ALZHEIMER'S RESEARCH, CARE, AND SERVICES, http://aspe.hhs.gov/daltcp/napa/042914/Mtg12-Slides1.pdf

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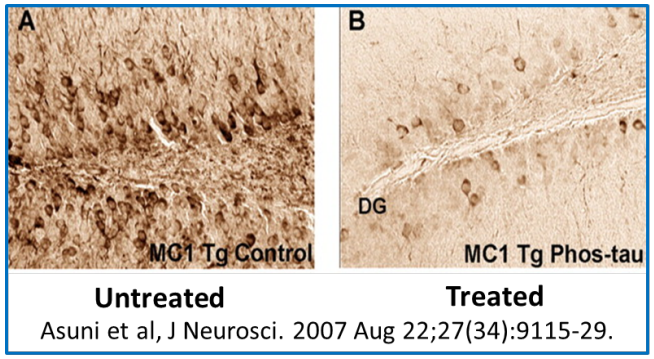
Targeting tau?



Asuni et al, J Neurosci. 2007 Aug 22;27(34):9115-29.

It works in mouseheimer's disease!

- 282 clinical trials of tau on clinical trials.gov, with 71 of these currently recruiting
- Yet several early Phase II studies have failed
  - Biogen TANGO, AbbVie AWARE, AC Immune (all n-terminal antibodies)
    - They all decreased CSF tau but no effect on tau-PET or clinical benefit
- Is this again a question of "catching rattlesnakes"?

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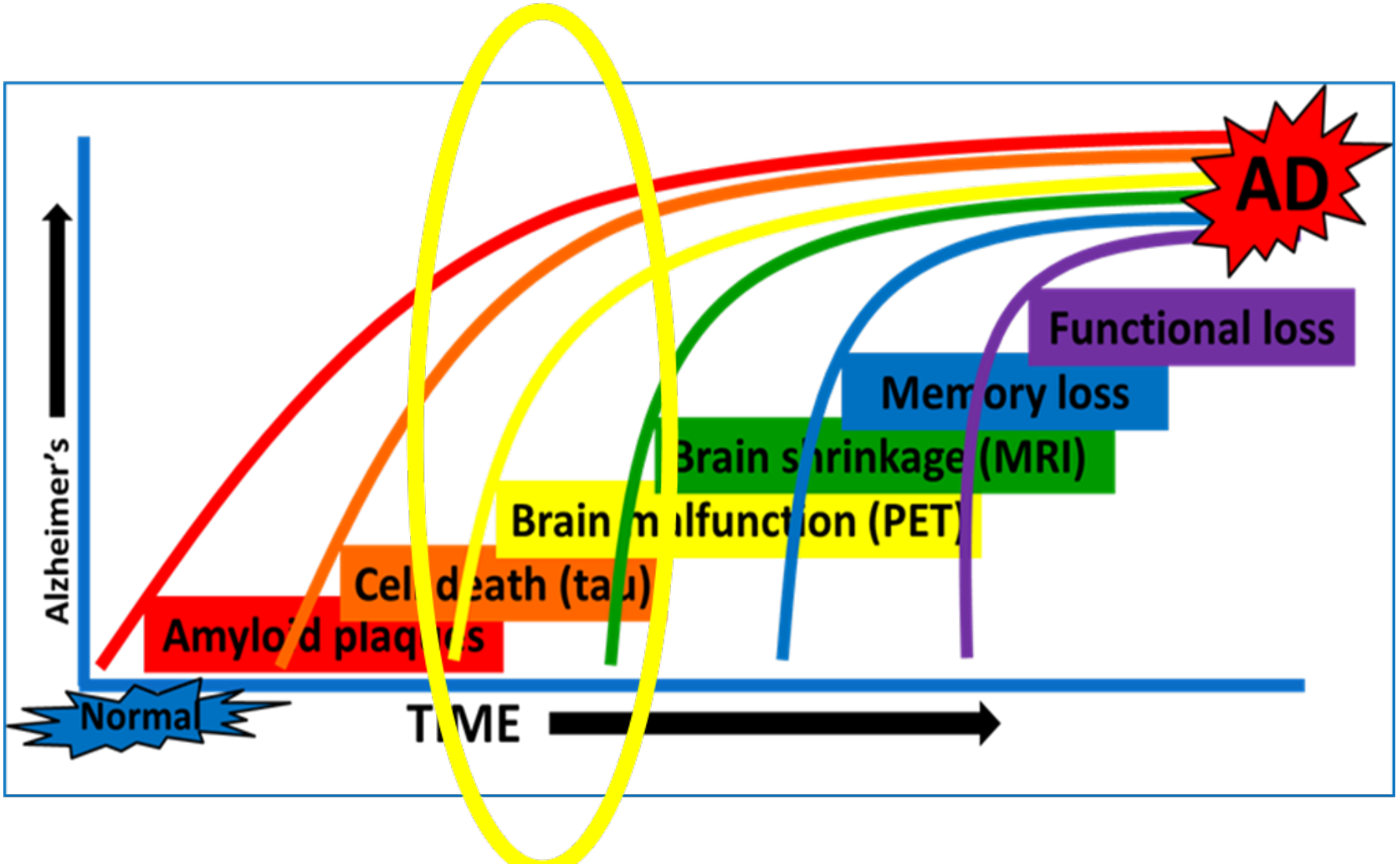
#3 Metabolic dysfunction



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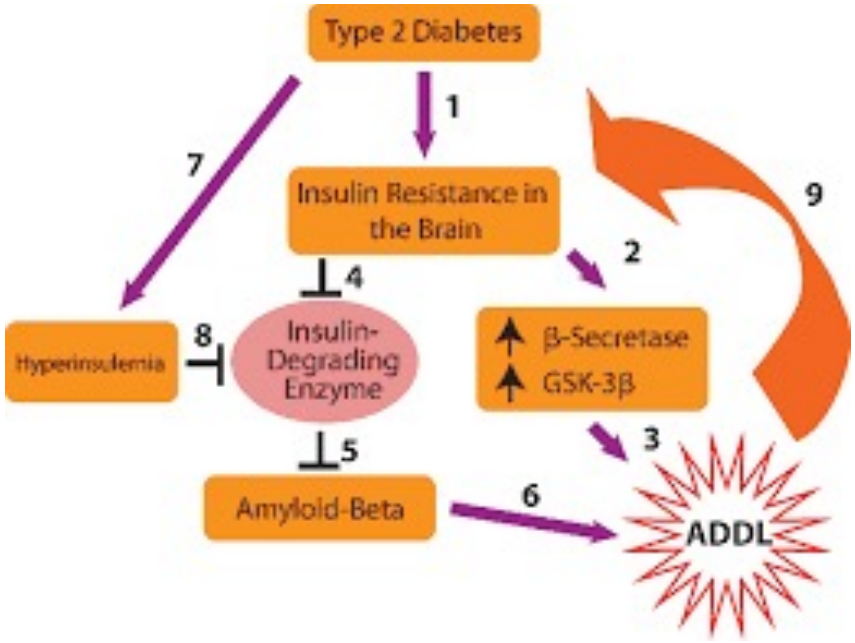
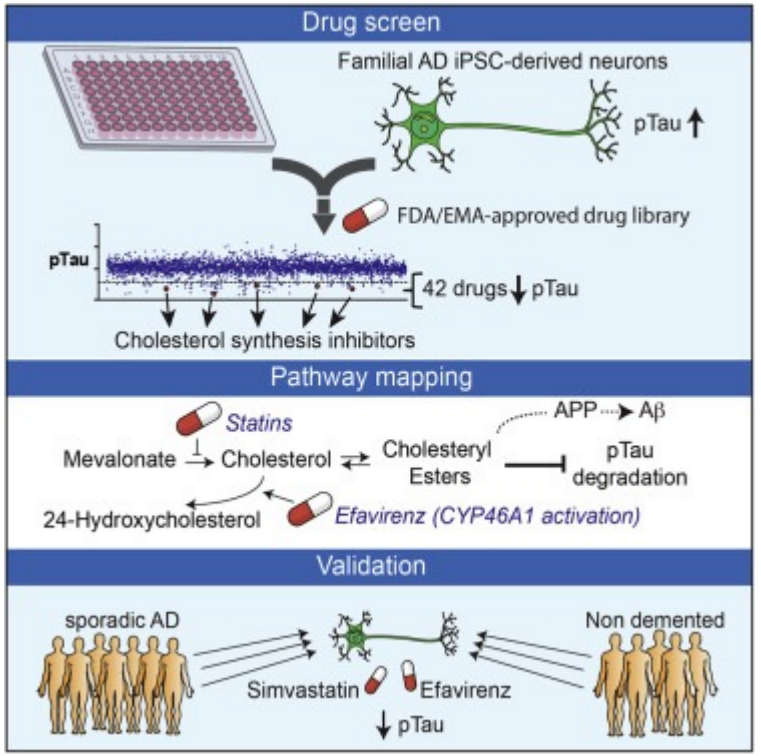
Metabolic malfunction



- Insulin resistance drives Aβ through negative effects on IDE (prevents clearance)
- Insulin resistance drives Aβ through activation of BACE (increases production)
- Insulin resistance drives tau pathology through GSK-3β hyperphosphorylation of tau

- Hypercholesterolemia may drive AD through dysregulation of metabolic pathways
- ApoE is the major AD risk gene for AD and functions as a regulator of lipid transport



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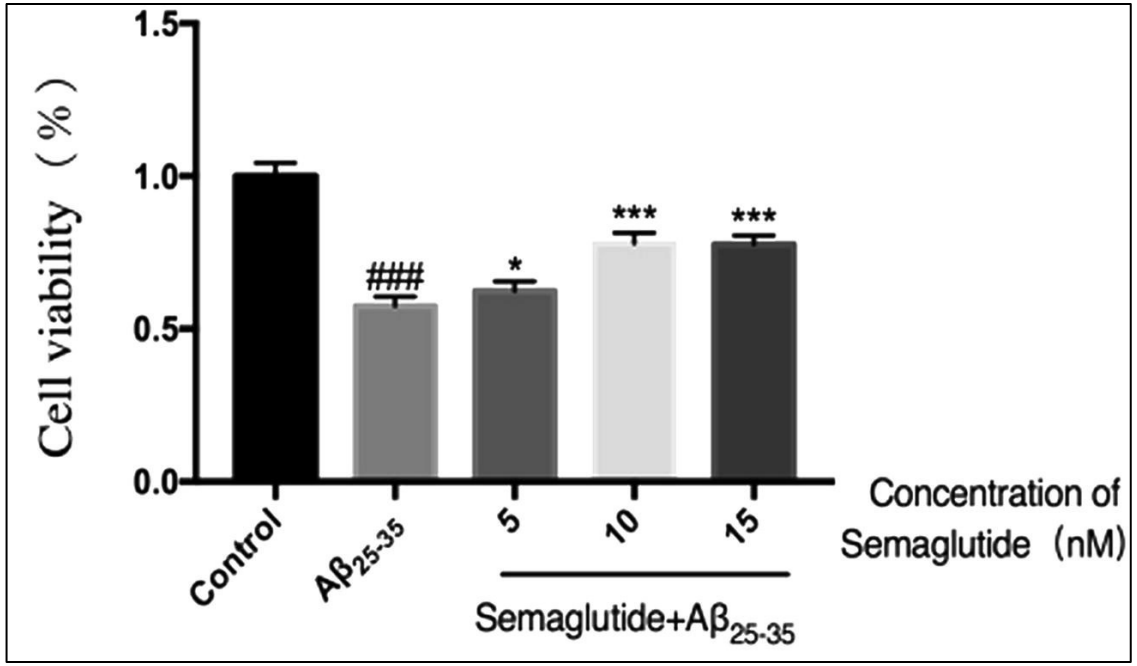
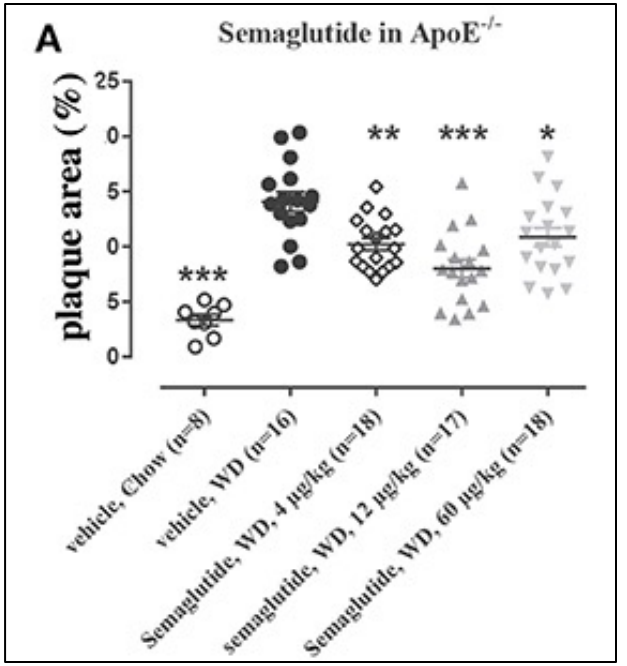
EVOKE



Chang et al., , 2020, J Clin Neurosci, 81, P234-239



Knudsen & Lau, 2019, Front. Endocrinol., 12

- **GLP-1 agonists increase insulin production**
- **Effects on brain insulin and AD pathology look promising**
- **Known cardiovascular risk reduction may also exert an effect on cerebrovascular disease**

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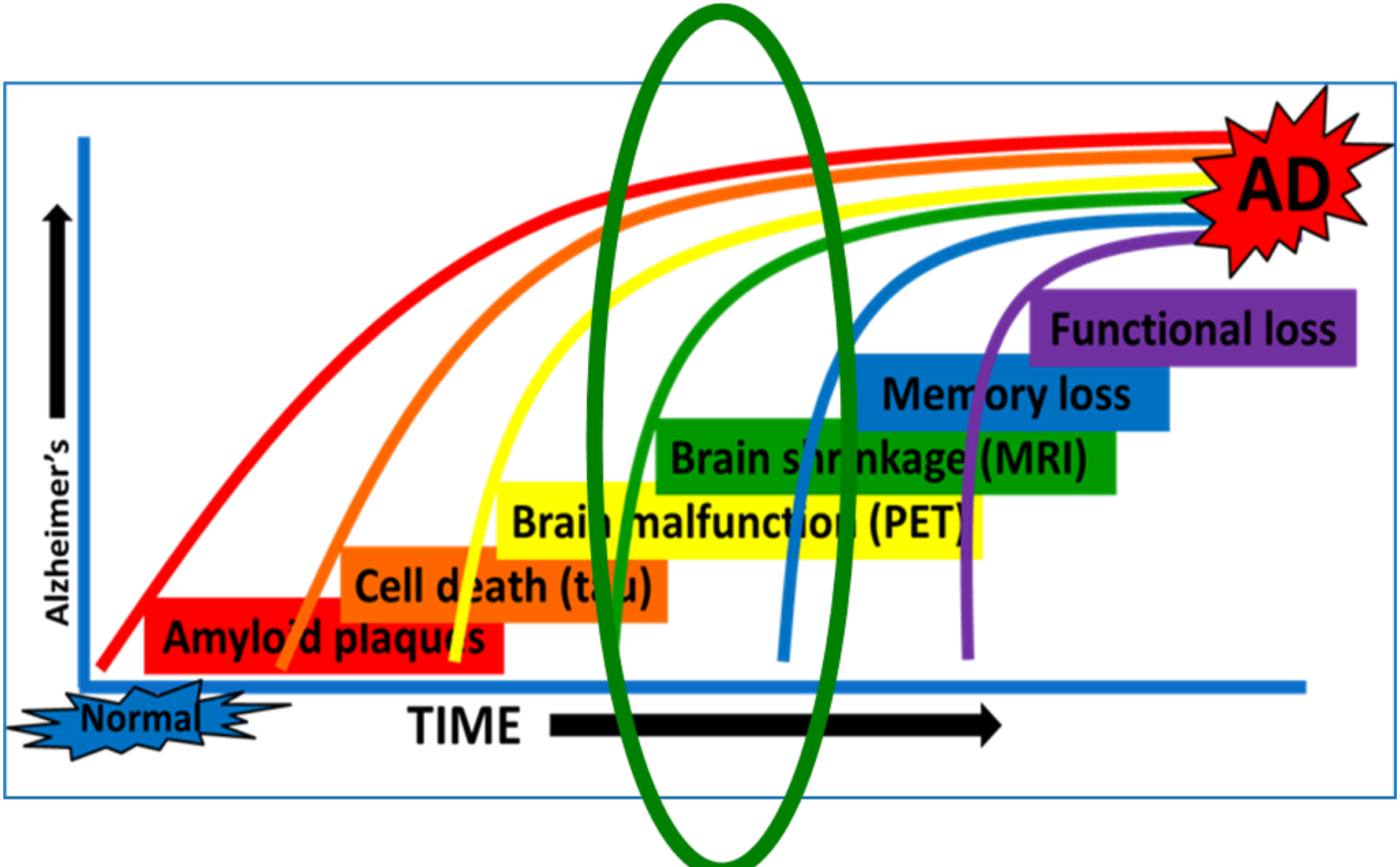
#4 Brain atrophy



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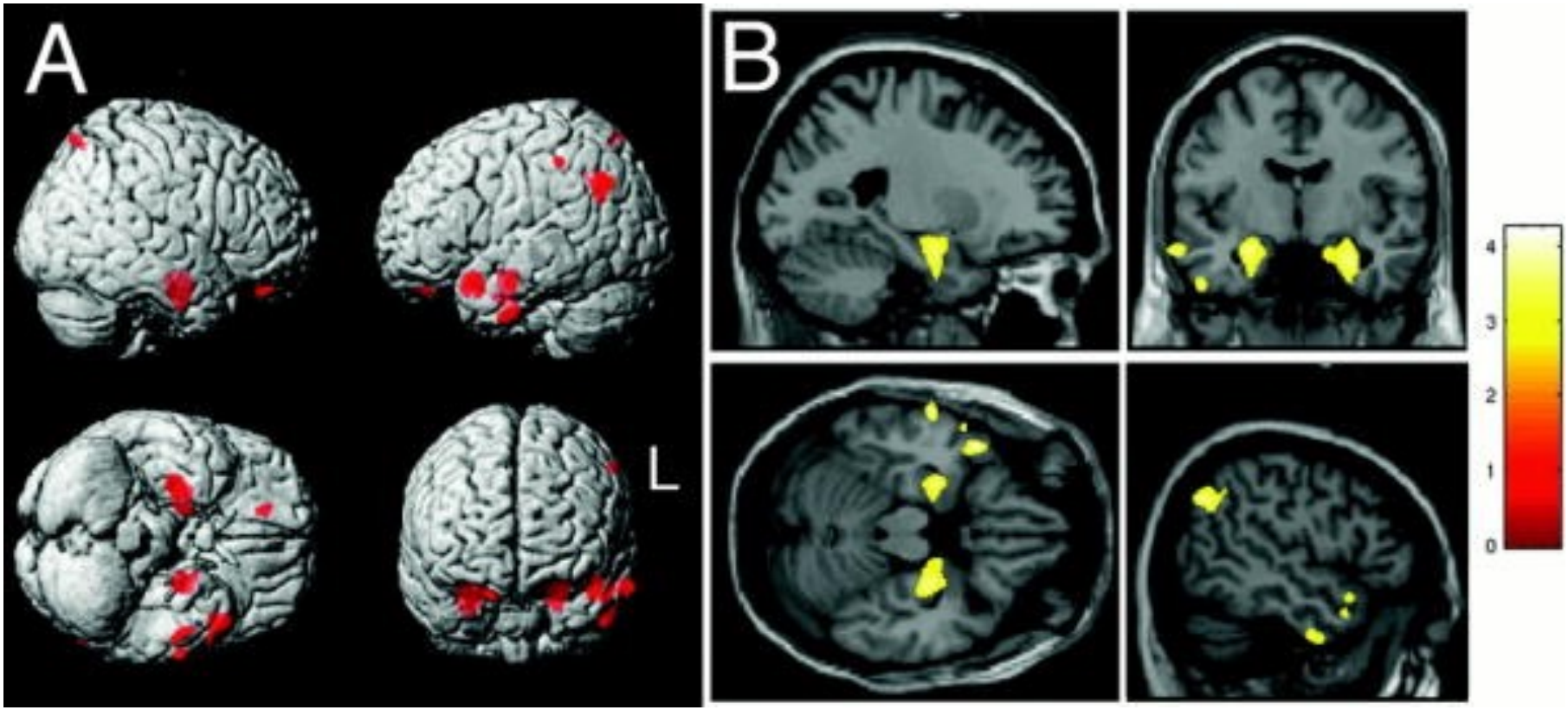
Structural MRI changes predict incipient AD 5 years before clinical cognitive decline



Smith et al, Neurology. 2007 Apr 17;68(16):1268-73.

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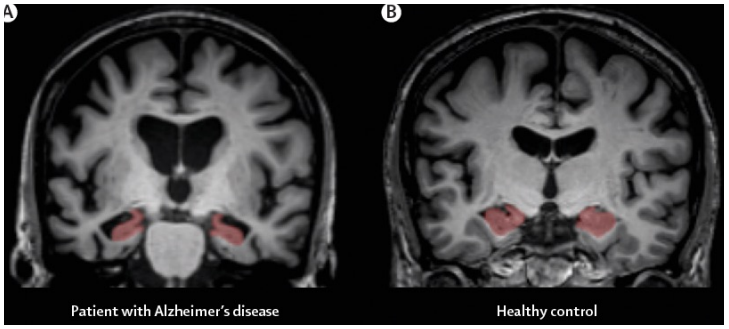
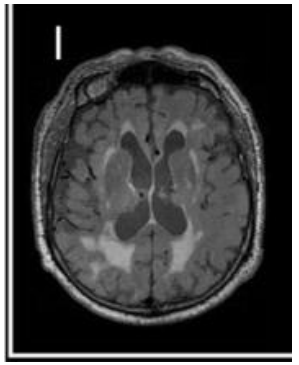
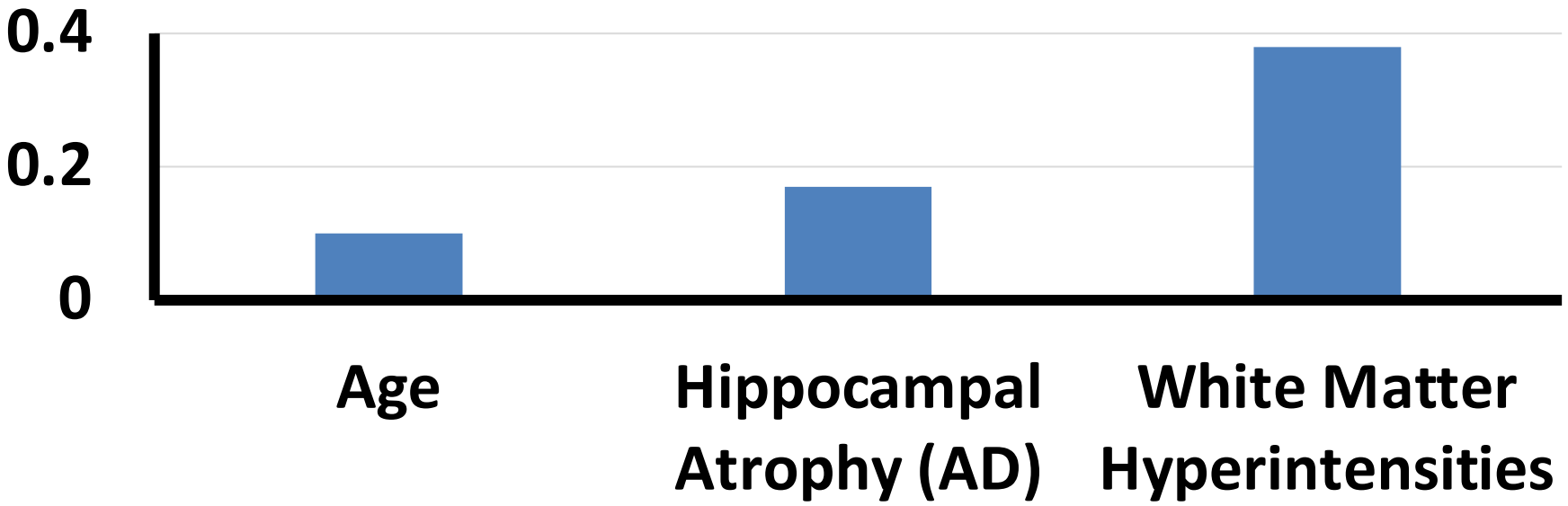
Brain atrophy in AD may be worsened by "hardening of the arteries"





Variance in Atrophy



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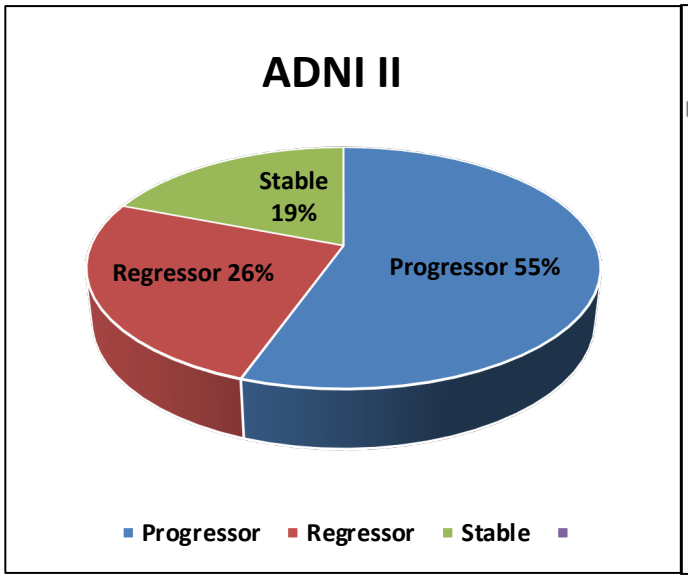
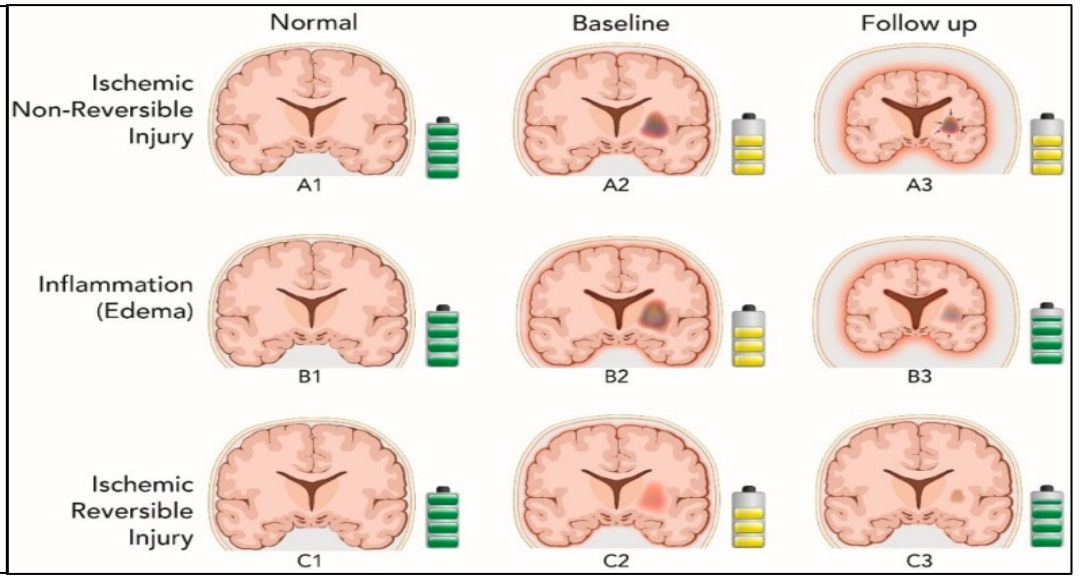
Vascular damage can heal and reverse!





- **Regression of WMH is a reality!**
- If it were due to contraction of irreversible ischemic injury or to resolution of inflammation, we would see associated atrophy.
- Instead, we see preservation of brain volume and improvement on cognitive scores, suggesting that such lesions are truly reversible

Al-Janabi et al., Brain Sci. 2019 Jul 19;9(7)

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SPRINT-MIND shows that controlling HTN can prevent MCI

QUESTION Does intensive blood pressure control compared with standard control reduce the occurrence of dementia?

CONCLUSION This randomized clinical trial of adults with hypertension found that intensive systolic blood pressure (SBP) control (target <120 mm Hg) did not significantly reduce the risk of probable dementia.

POPULATION

6029 Men
3332 Women

Adults aged ≥50 years with hypertension and without diabetes or stroke

Mean age: 68 years

LOCATIONS

102 US sites (including Puerto Rico)

INTERVENTIONS

9361 Patients randomized
8563 Patients analyzed
(≥1 cognitive assessment)

4278	4285
Intensive control (Target SBP <120 mm Hg)	Standard control (Target SBP <140 mm Hg)

Median treatment period, 3.3 years

PRIMARY OUTCOME

Occurrence of adjudicated probable dementia

SECONDARY OUTCOMES

Adjudicated mild cognitive impairment (MCI)

Composite outcome of MCI or probable dementia

FINDINGS

PRIMARY OUTCOME: Adjudicated probable dementia

Intensive control	Standard control
149 patients (7.2 cases/1000 person-years)	176 patients (8.6 cases/1000 person-years)

Hazard ratio: 0.83 (95% CI, 0.67-1.04)

SECONDARY OUTCOME: Adjudicated MCI

Intensive control	Standard control
287 patients (14.6 cases/1000 person-years)	353 patients (18.3 cases/1000 person-years)

Hazard ratio: 0.81 (95% CI, 0.69-0.95)

SECONDARY OUTCOME: Composite outcome

Intensive control	Standard control
402 patients (20.2 cases/1000 person-years)	469 patients (24.1 cases/1000 person-years)

Hazard ratio: 0.85 (95% CI, 0.74-0.97)

- **The HR for dementia did not improve with SBP≤120 mmHg**
- **The ARR was 0.015 for both MCI & the composite outcome with a NNT = 65**

Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. JAMA 2019;321:553-561.

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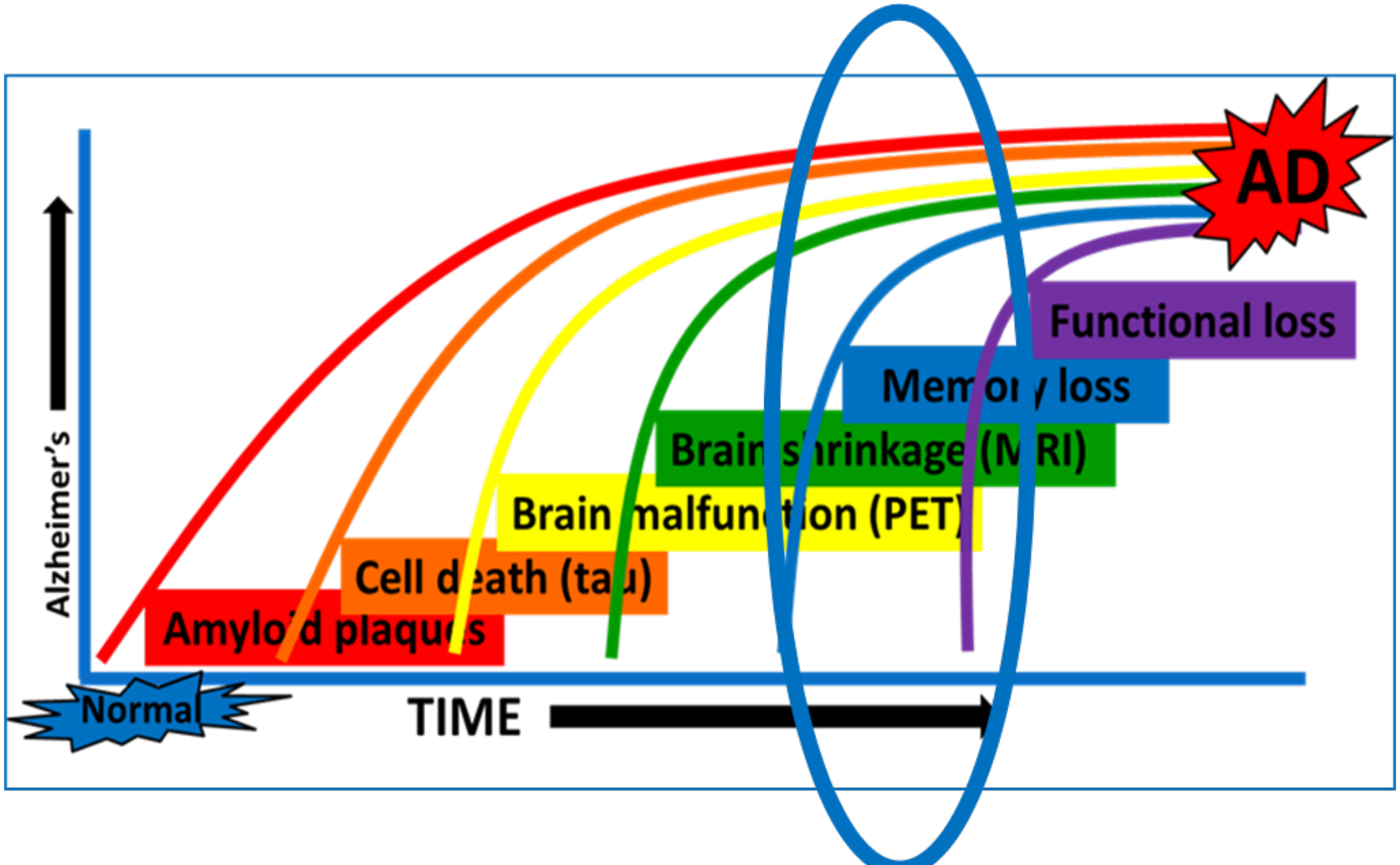
#5 Mild cognitive impairment



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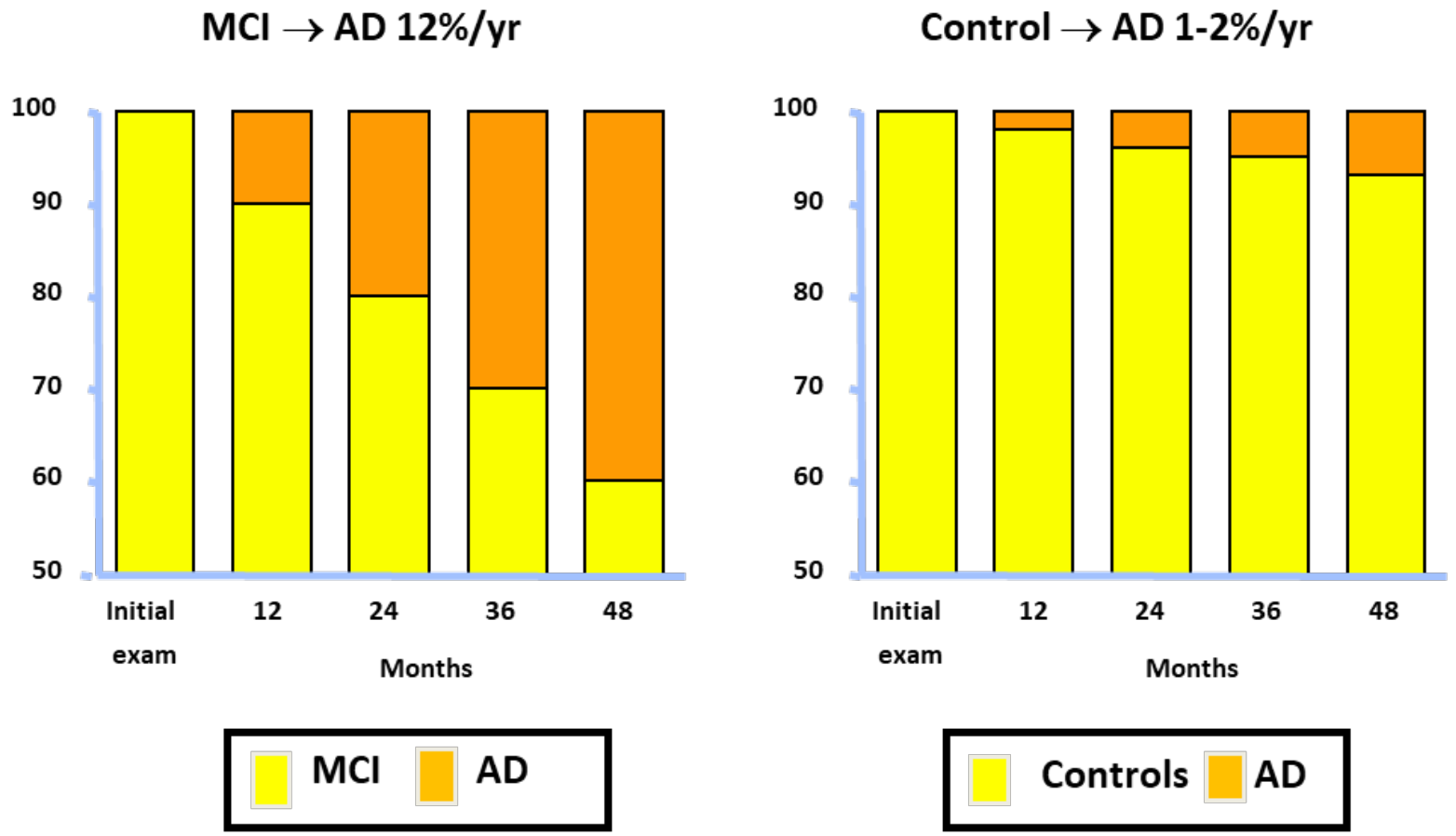
Mild Cognitive Impairment (MCI) predicts conversion to dementia



Petersen RC et al: Arch Neurol 56:303-308, 1999

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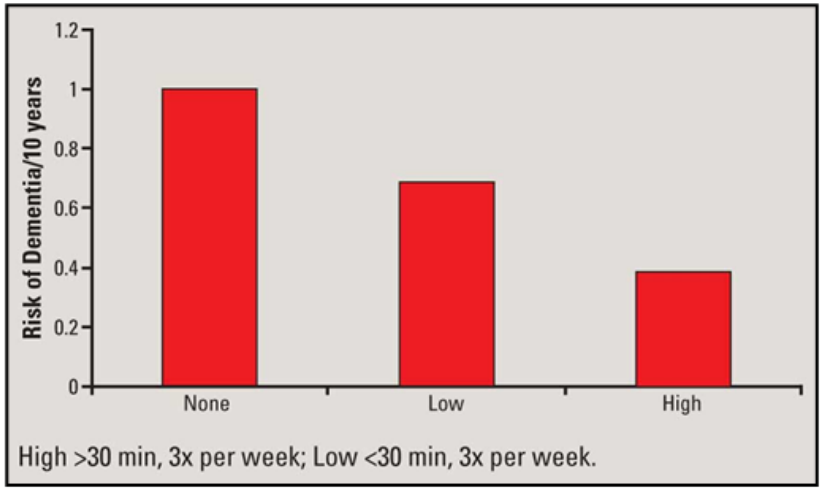
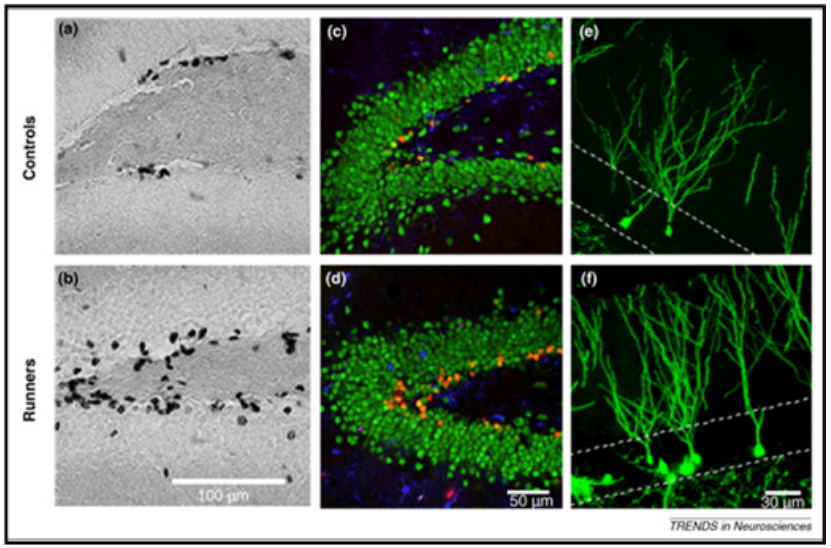
Will exercise help in MCI?



Cummings et al., Primary Psychiatry. 2008;15:2(suppl 1):1-24

Exercise reduces risk of dementia in a dose-dependent fashion!

BDNF released by exercise is like "Miracle-Grow" for your brain!



Lazarov et al, Trends Neurosci. 2010 Dec;33(12):569-79

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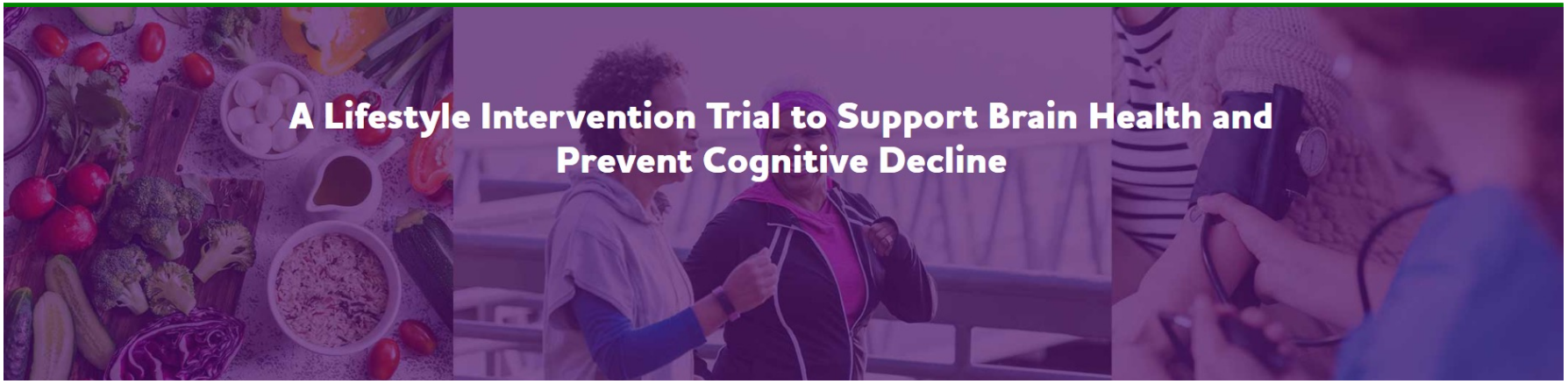
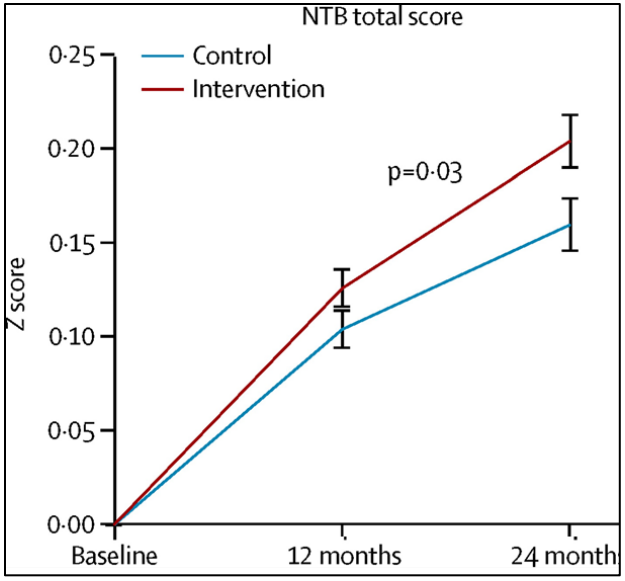
It's not just about drugs, It's also about lifestyle!



- **Based on the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)**
- **POINTER will explore combination therapy simultaneously targeting physical exercise, a healthy diet, cognitive stimulation, and self-monitoring of heart health risk factors**

U.S.POINTER
alzheimer's association



Ngandu et al., 2015, Lancet VOLUME 385, ISSUE 9984, P2255-2263

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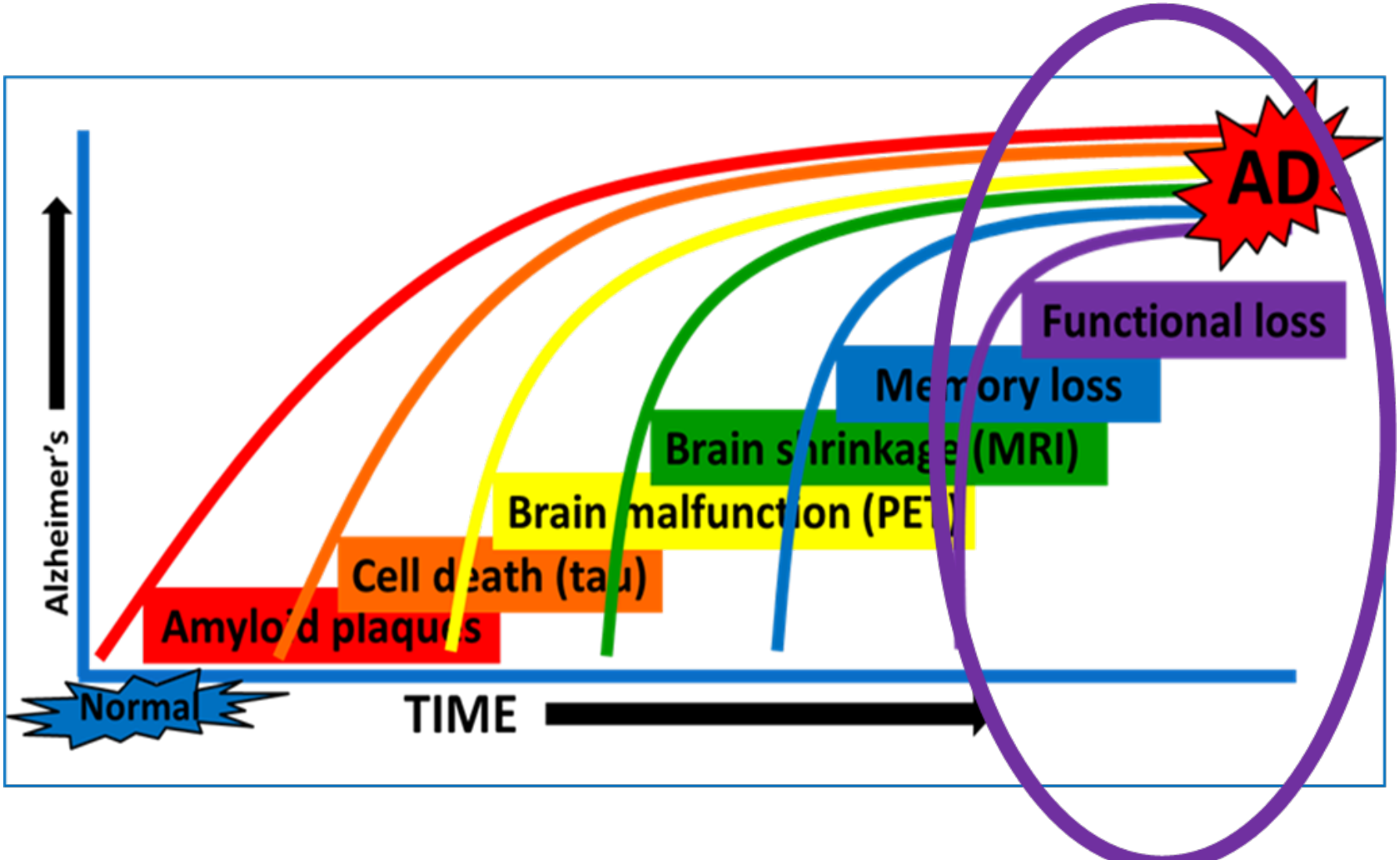
at the Sanders-Brown Center on Aging

#6 Alzheimer's disease



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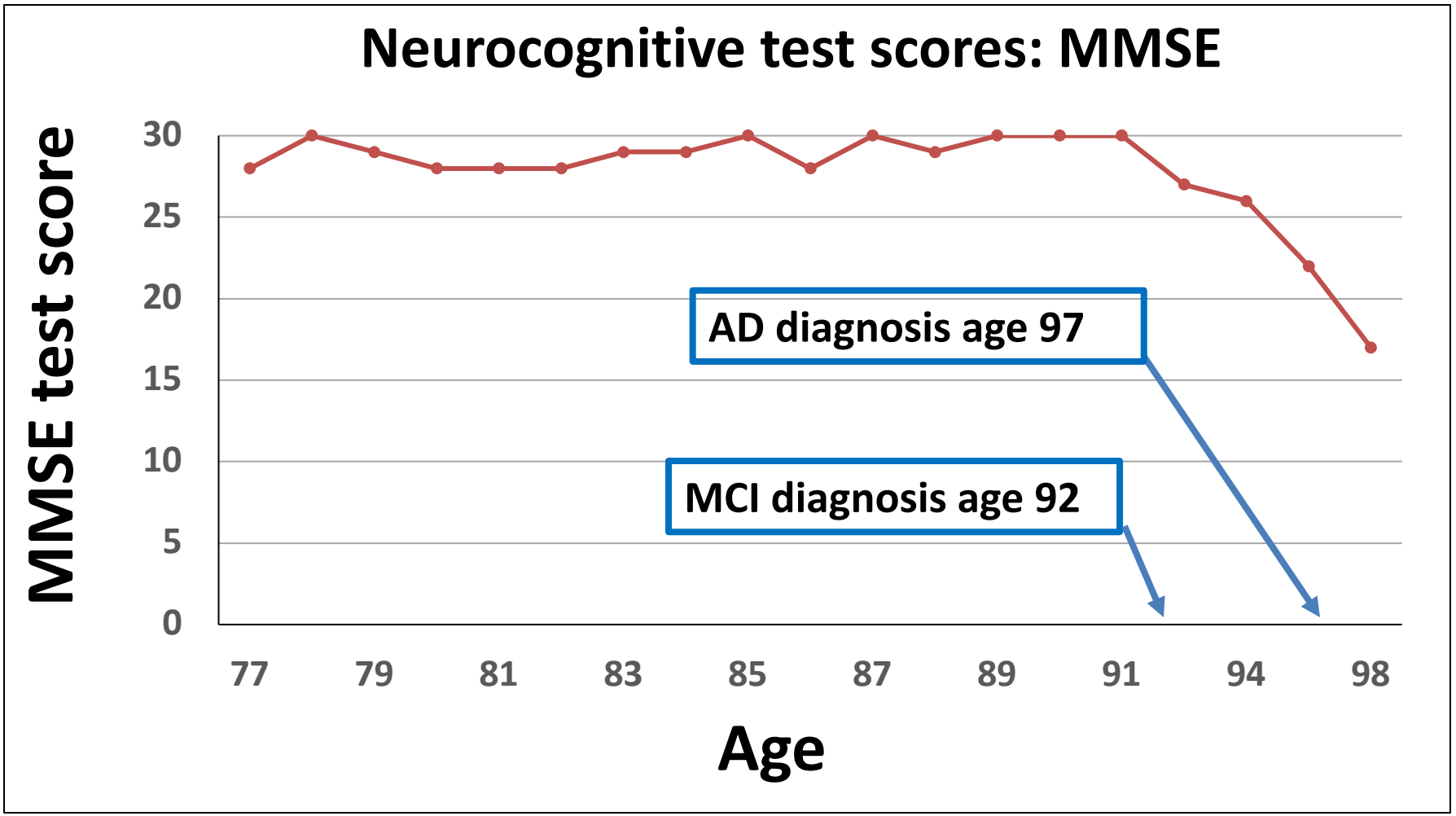
Case Report: Patient followed longitudinally (>20yrs) with neurocognitive testing, MRI, & autopsy



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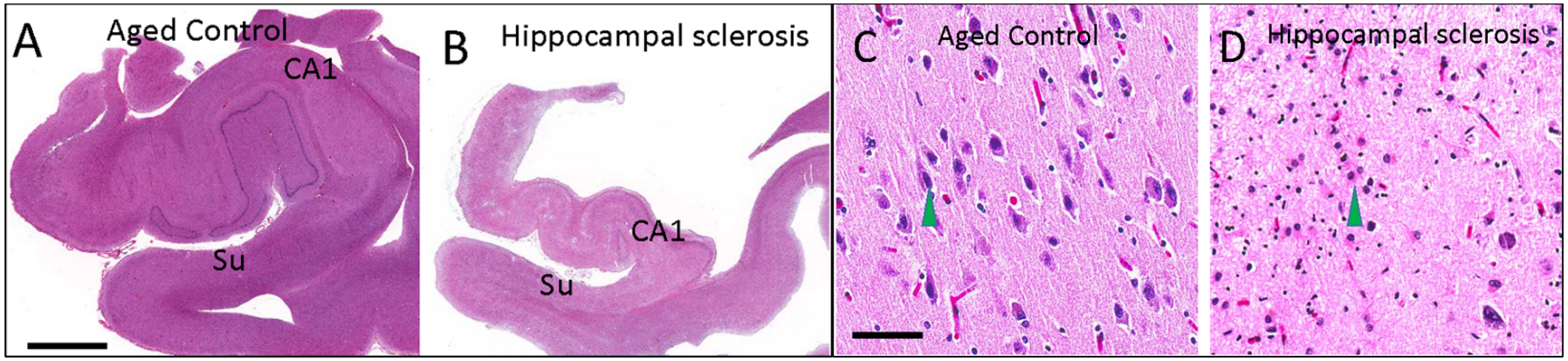
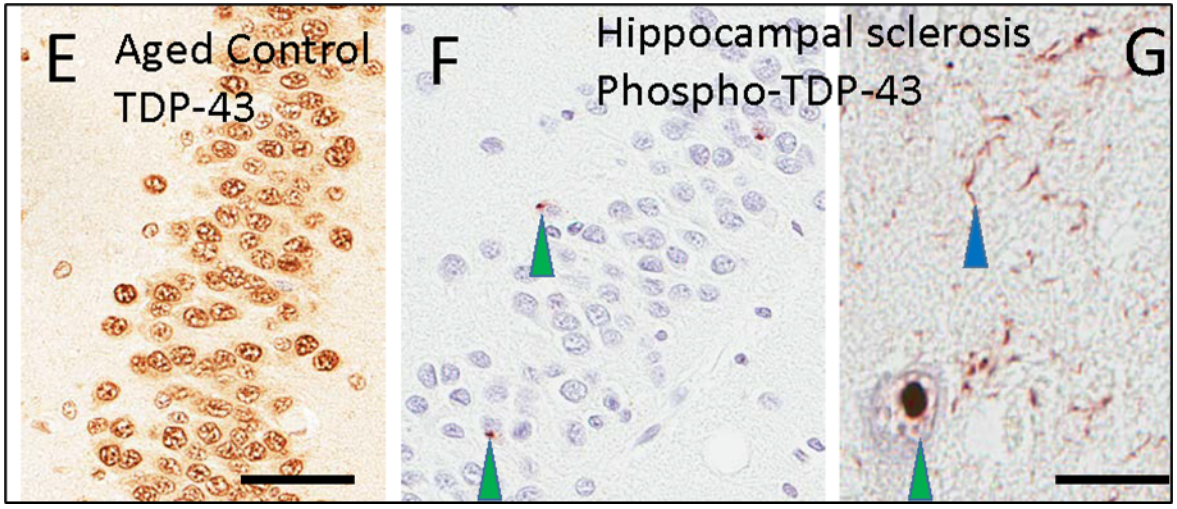
LATE





L = Late-onset

- **Usually > 80 years**

A = Age-related

- **Age is #1 risk**

T = TDP-43

- **Protein aggregate**

E = Encephalopathy

- **dementia**

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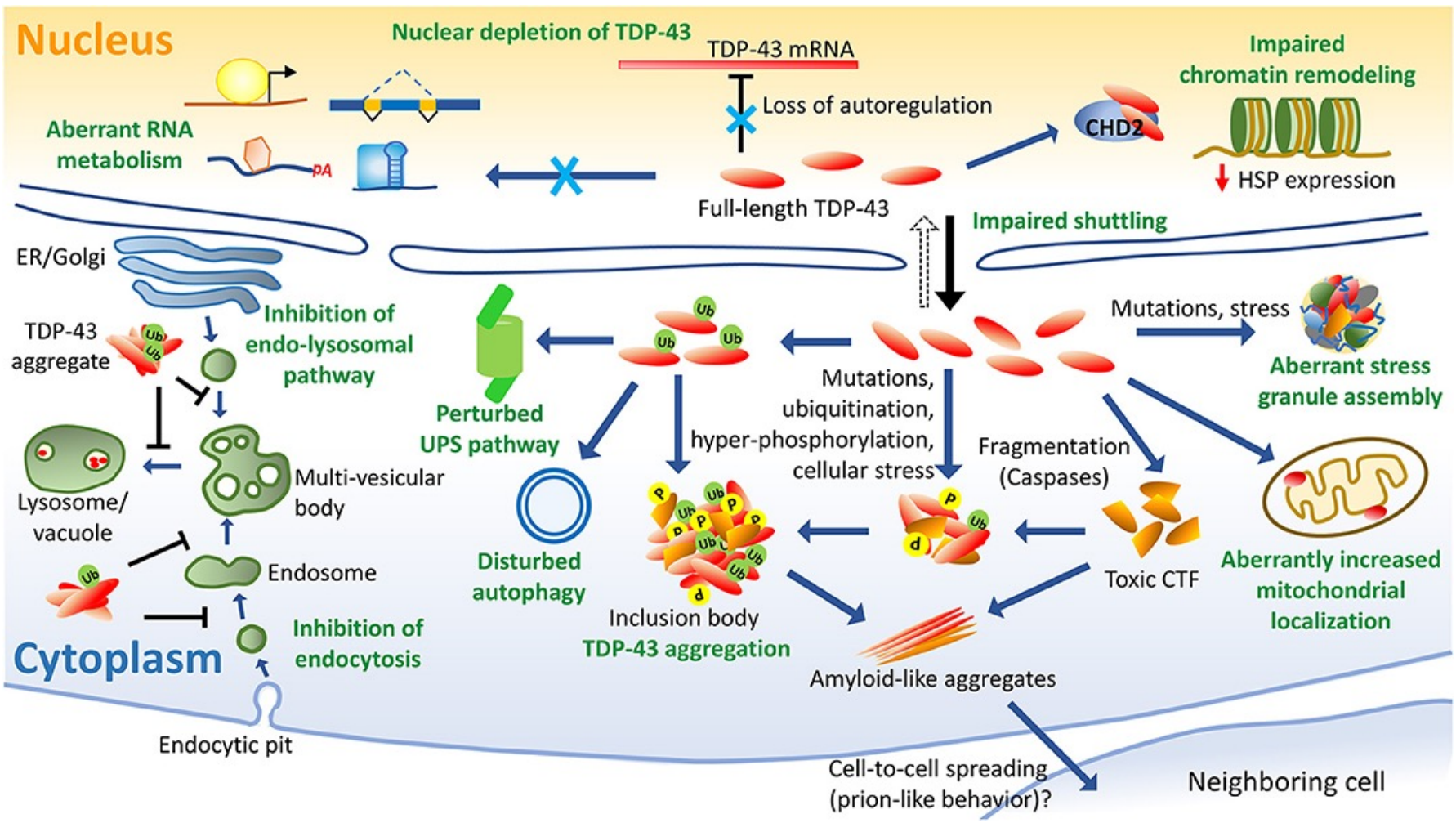
TDP43 relationships to dementia



Prasad et al., Front Mol Neurosci 2019

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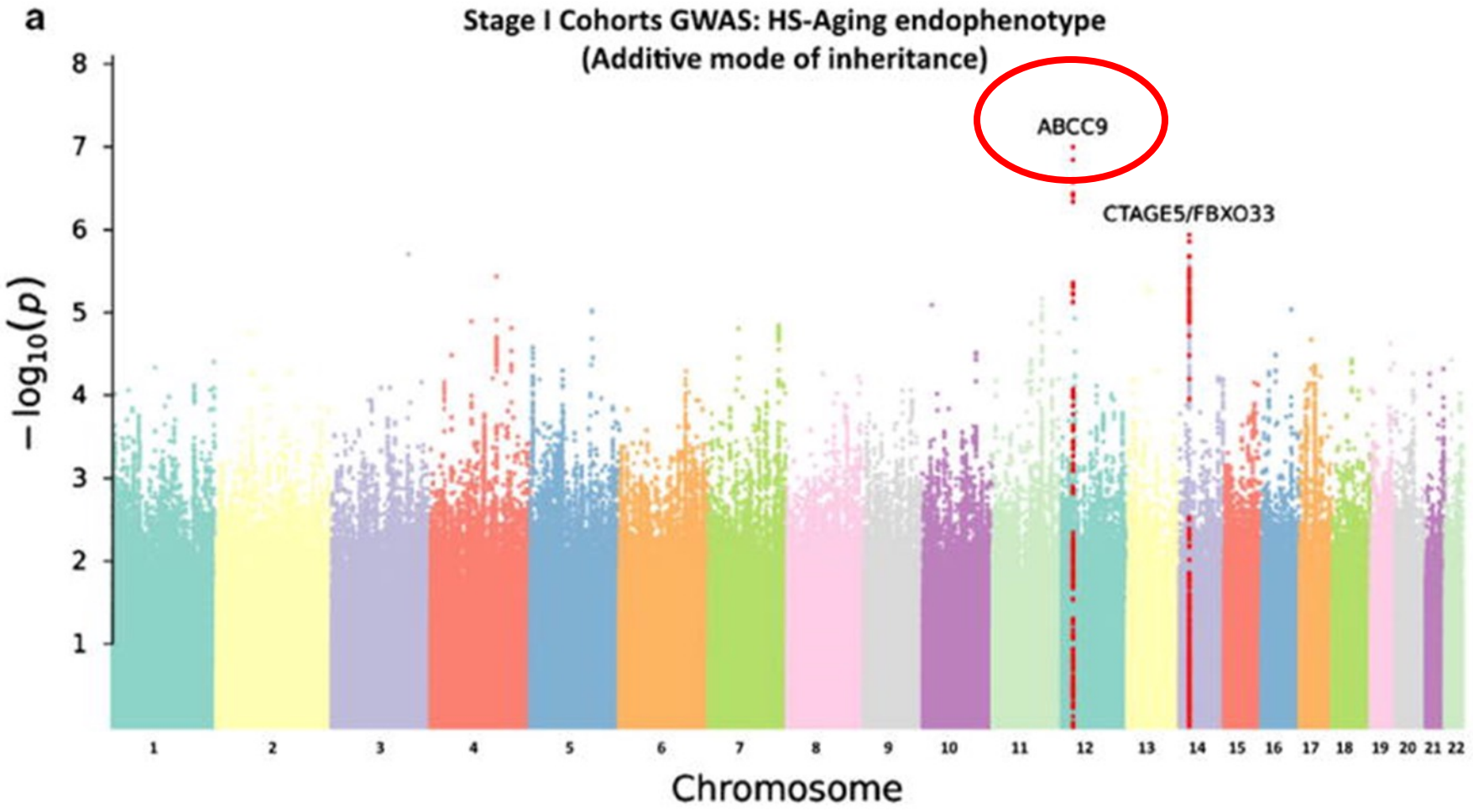
Genetic linkage to HS-aging?



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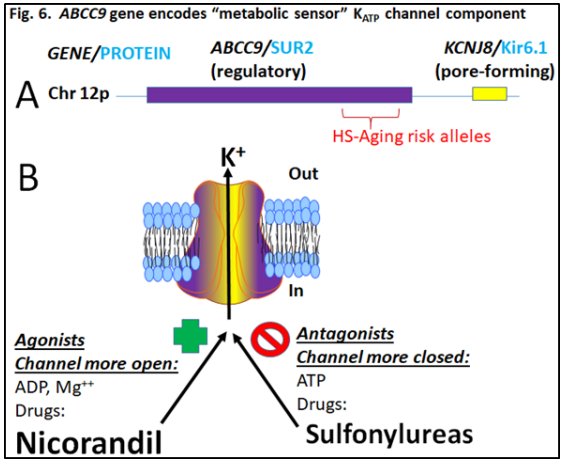
How can we stop these K+ channels?



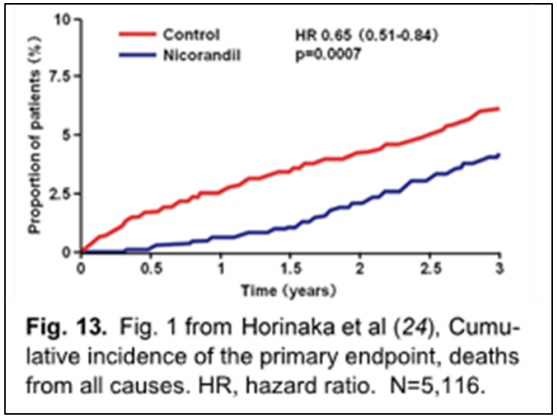
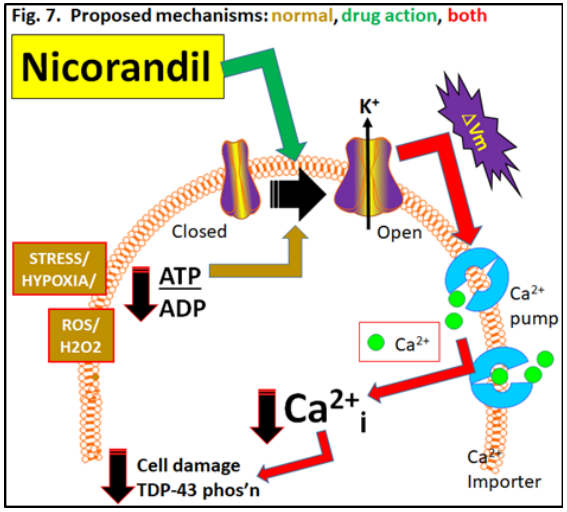


Fig. 13. Fig. 1 from Horinaka et al (*24*), Cumulative incidence of the primary endpoint, deaths from all causes. HR, hazard ratio. N=5,116.

Table 1. NACC cases (2010-2013) stratified by sulfonylurea drug use and eventual autopsy-proven HS-Aging pathology	**Sulfonylurea Use** (N=36)		**No Sulfonylurea Use** (N=588)	
	HS-Aging Pathology (n=11)	No HS-Aging Pathology (n=25)	HS-Aging Pathology (n=97)	No HS-Aging Pathology (n=491)
Age at death, years	88.7±4.8	90.8±4.3	91.2±4.3	90.9±4.4
Number of longitudinal evaluations	4.5±1.1	4.4±1.7	3.9±1.8	3.9±1.7
Estimated sulfonylurea exposure, years	3.4 (Range 0.5-6.2)	3.5 (Range 0.5-6.8)	N/A	N/A
Taking sulfonylurea at final evaluation, %	81.80%	72.00%	N/A	N/A



- **Nicorandil protects from death OR 0.65 [95% CI: 0.51-0.84]**
- **Sulfonylureas are linked to HS-aging OR 2.19 [95% CI: 1.04–4.63]**

Safety and Modulation of ABCC9 Pathways by Nicorandil for the Treatment of Hippocampal Sclerosis of Aging (SMArT-HS)
NIH R01AG061111 funded
ClinicalTrials.gov Identifier: NCT04120766

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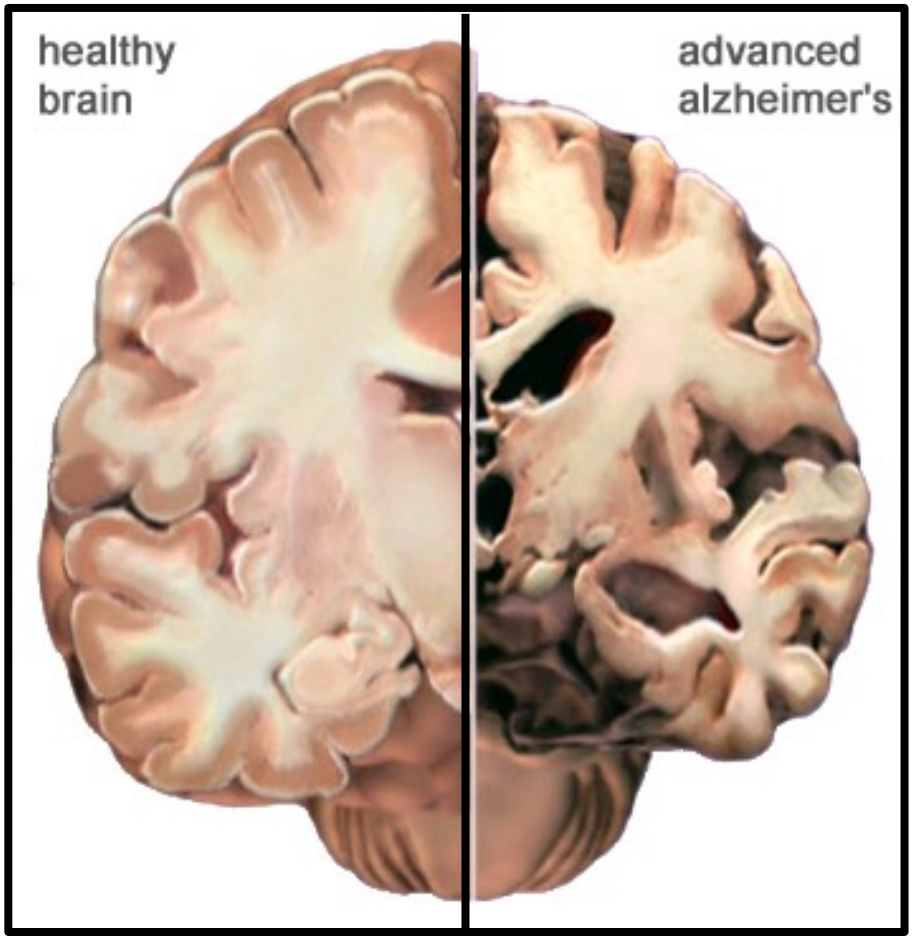
AD: a brain destroyed



- We can't fix a brain that is so damaged
- Reversing AD is many years in the future
- We may be able to slow or stop the disease at an earlier stage
- We may even be able to prevent AD within this very decade

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The end-stage of dementia…

- Joan is 82 years old and is in the end-stage of dementia
- She no longer walks, talks or engages in the world around her
- She frequently moans and grimaces as if she is in pain
- All we can do is keep her comfortable and be there for her as this disease slowly takes her life

- It's impossible to know what she is feeling…
- We can give her opiates and benzodiazepines to make her more comfortable, but then she is less aware and cannot even smile when her son gently kisses her forehead
- There must be more we can do?

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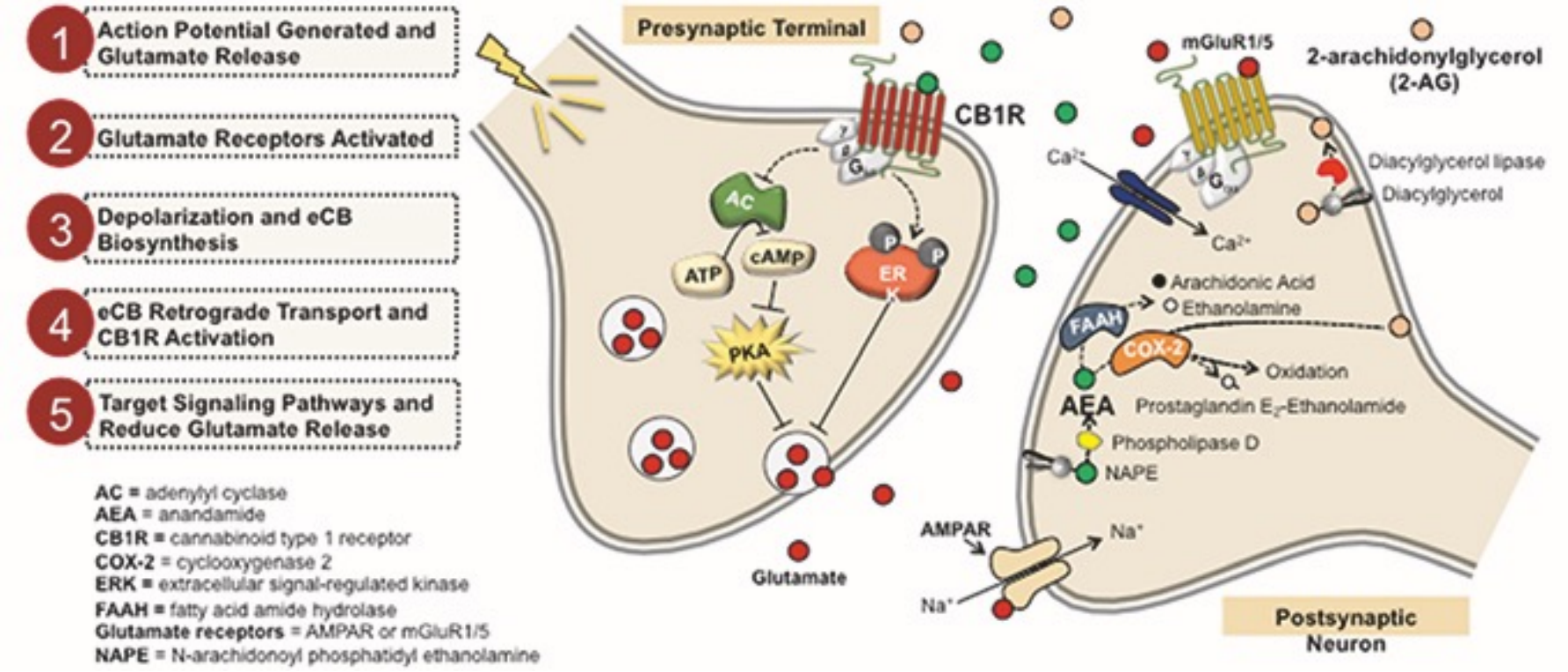
Cannabinoids?

Endocannabinoid signaling induces synaptic depression at excitatory synapses



https://www.medscape.org/viewarticle/884938_3

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LIBBY (Life's end Benefits of CannaBidol and TetrahYdrocannabinol (LiBBY) Trial)

ACTC ALZHEIMER'S CLINICAL TRIALS CONSORTIUM

- 12-week, phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study
- 150 hospice-eligible agitated AD patients from 15 USA sites over a 2-year period
- A total daily dose of 8 mg of THC and 400mg of CBD dissolved in digestible oil will be administered 3 times per day
- Following the 12-week randomized phase, all participants are eligible for a 6-month open-label extension

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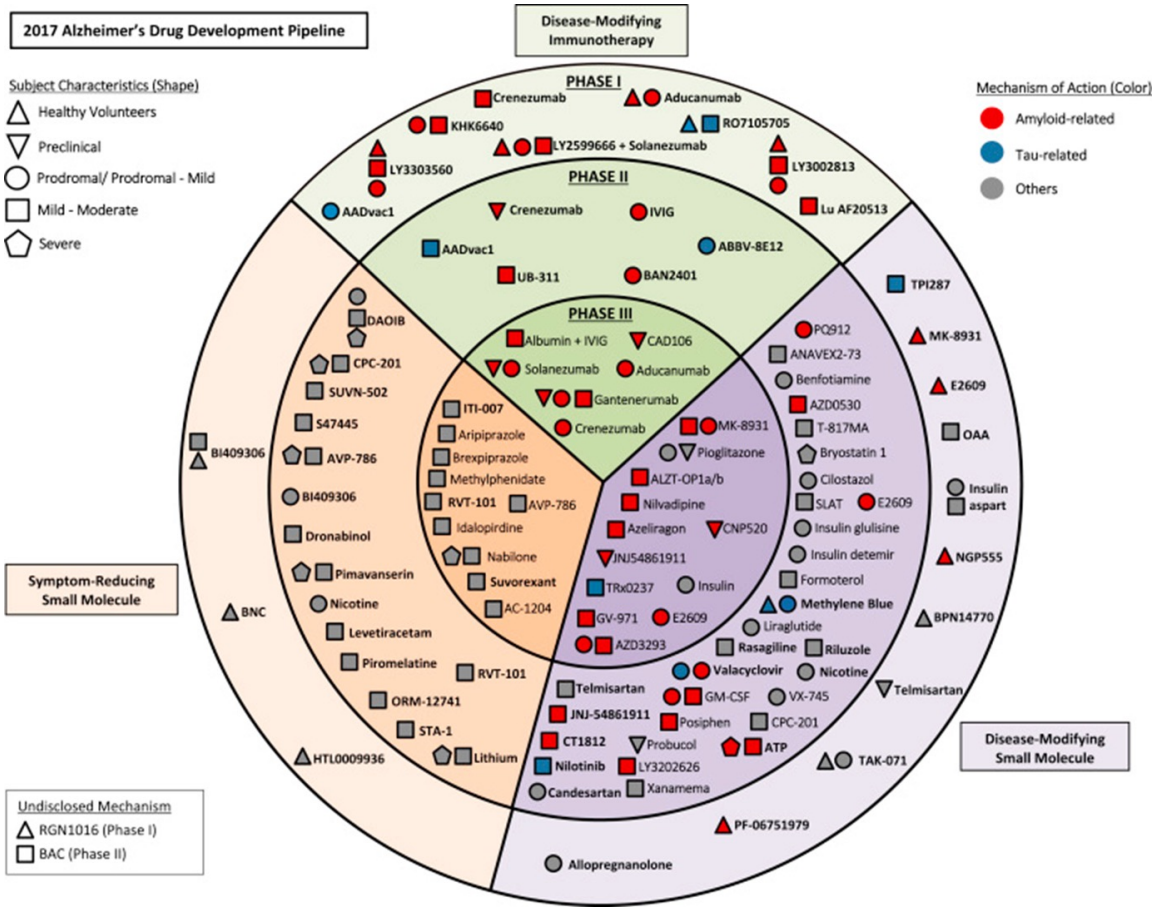
- **Why would you participate?**
- **To go beyond standard treatments rather than just rolling over and giving up!**
- **For the generations to come!**



Cummings et al., 2017