

# UPDATE ON WHAT'S NEW IN THE DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE: FROM AAIC 2018 TO THE PRESENT

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## DISCLOSURES

- CONSULTANT : ACADIA; ALKAHEST; ALLERGAN; AVANIR; AXOVANT; BIOXCEL; GE; GENENTECH; LUNDBECK; NOVARTIS; OTSUKA; ROCHE; TAKEDA
- RESEARCH SUPPORT : JANSSEN; GENENTECH/ROCHE; NIA
- SAFETY MONITORING COMMITTEE: ERYDEL; INTRA-CELLULAR THERAPIES; MERCK; NEWRON

# OBJECTIVES

- Update audience relative to major/promising research presented at the Alzheimer's Association International Conference (AAIC)-July 2018. Chicago
- 1)Role of hypertension as a modifiable risk factor
- 2)Exercise as a protective factor for developing MCI in patients with various cardiovascular risk-factors (The MYHAT Study- U. Pittsburgh)
- 3)Treatment with the monoclonal antibody BAN2401
- 4)Impact of estrogen on SCI post-menopausal women ; Reproductive history and risk of dementia
- 5)Photo-bio-modulation (PBM) and Transcranial Magnetic Stimulation (rTMS) as new treatment approaches
- 6)Use of young plasma infusion in advanced AD

## HIGHLIGHTS FROM AAIC- JULY 22-26, 2018- CHICAGO, USA

- SPRINT-MIND STUDY (Systolic Blood-Pressure Intervention Trial- Memory and Cognition IN Decreased Hypertension-Sub-study)
- NIH-funded, 4 yr study of >9,000 subjects at high risk for CVD. Looking at aggressive BP control (systolic BP of 120 mm or < vs 140 mm or <) and its impact on CV events/stroke/mortality and risk of MCI and all-cause dementia.
- 120 sites in US/Puerto Rico
- Age: 50 y/o or >; Mean age :68
- Results: Aggressive BP control reduced CV events and mortality & decreased MCI by 19%\* and dementia by 17% and 18% fewer WMH's
- “What’s good for the heart is good for the brain.”
- Published: JAMA: 1/2019

## Alzheimer's Association Funds 2 Year Extension of Study that Explores Intensive Blood Pressure Treatment on Dementia Risk (SPRINT MIND 2.0)

- SPRINT MIND study was terminated early due to success in preventing cardiovascular events.
- Early termination resulted in the duration of the trial not being long enough to assess impact on dementia.
- Further cognitive assessment of study participants may > additional cases of probable dementia to support a more definitive conclusion.

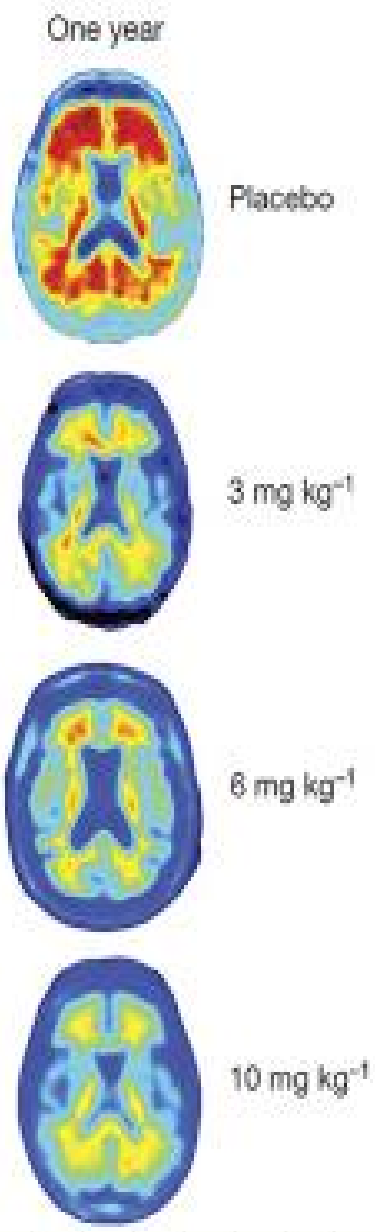
# “Cardiovascular Modifiers of the Association Between Exercise and Risk for Mild Cognitive Impairment :The MYHAT Study”

- 1,254 subjects with normal cognition (CDR=0) followed for progression to MCI (CDR=0.5)
  - Examined risk of MCI relative to total minutes of exercise/week ( 0 minutes vs 1-149 minutes vs 150+ minutes) in combination with CV risk factors: HTN; HLD; BMI; DM; smoking; CVA; CAD; alcohol; arrhythmia; CHF.
  - Results: 373 subjects developed MCI over 10 yrs. Adjusting for age, gender, education, a significant reduction in risk for MCI observed in : 150+ minutes exercise / week vs no exercise, for those w/o APOE4 or not smoking, but NOT in smokers or those with APOE4 genotype.
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- Ref: Hughes TF, Liu A, Sun Z, et al. Presented at AAIC, July 2018. Chicago
  - Reviewed in US Neurology by Grossberg GT: Fall, 2018.

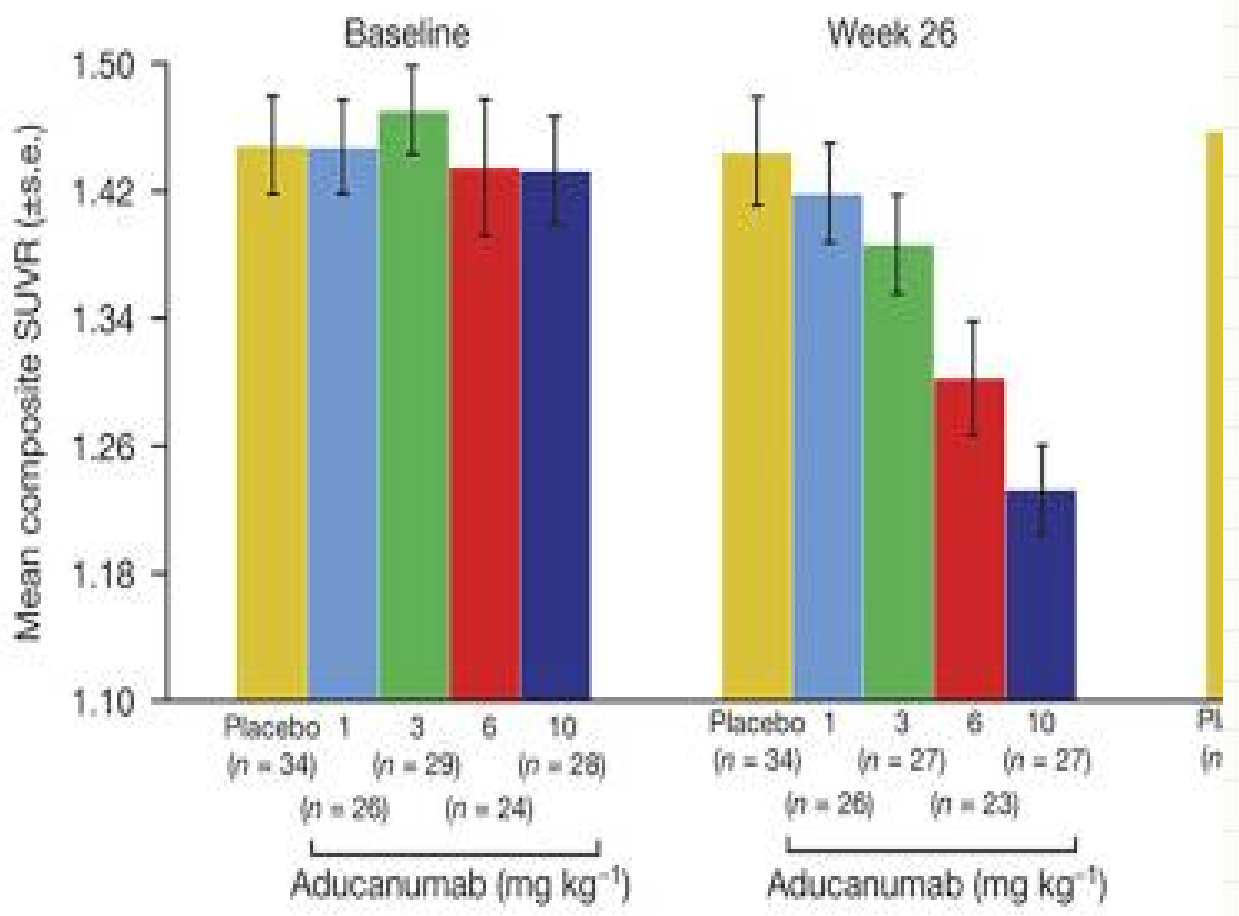


## BAN 2401 (EISAI/BIOGEN PHARMA)-MILD AD STUDY

- Monoclonal antibody (Binds soluble A Beta Protofibrils) to clear amyloid plaque and reduce cognitive decline
- 18 month, placebo- controlled study
- 800 subjects; MMSE 22-30
- Biweekly/monthly IV infusions (2.5, 5, 10mg/kg)
- Analyses at 12 & 18 months
- At 18 months: 81% converted to amyloid negative
- 30% reduction in rate of cognitive decline at 18 mos.
- Well-tolerated



**B**





# Estrogen Treatment in Young Postmenopausal Women with SCD Does Not Mitigate Anticholinergic Effects on Cognition

- Menopause is associated with Subjective Cognitive Decline (SCD) and older women are at greater risk for AD than men. ? Due to loss of protective effects of estrogen – estrogen can mitigate the adverse effects of anti-cholinergic drugs on cognition.
- This study from Vanderbilt looked at 56 early postmenopausal women (50-60yr)
- with SCD who were given 3 mos of 1mg estradiol daily vs placebo. Followed by a 4 day challenge with scopolamine (potent cholinergic blocker) vs placebo.

Results: All subjects performed worse with cholinergic challenge.

- Estrogen supplementation was not effective in mitigating the impact of anticholinergic drugs on cognitive performance.
- Ref: Conley CA [...]Newhouse PA. AAIC. Chicago. July, 2018.
- .

# Reproductive History and Dementia Risk

- Epidemiologic study (Kaiser Permanente) of ~15,000 women, 40-55 y/o
- Findings included:
  - Number of children: 3 or more children > 12% decreased dementia risk.
  - Number of miscarriages: 9% increased dementia risk/miscarriage
  - Age at 1<sup>st</sup> menstrual period (usually 13 y/o): if 16 y/o or later, 31% increased dementia risk.
  - Age at natural menopause (usually 47 y/o): if less than 45 y/o > 28% increased dementia risk.
  - Reproductive period (average 34 yrs): if 21-30 yrs, > 33% increased dementia risk.
- Study limitation: Based on self-reports, but suggests that greater/longer exposure to estrogen and/or other sex hormones may decrease dementia risk.
- Reviewed by: Grossberg GT: US Neurology, 2018.

## FEATURED RESEARCH SESSION : THE GLYMPHATIC SYSTEM

- + Recently detailed(2012) by Maiken Nedergaard, a Danish neuroscientist at the U. of Rochester
- + Like the body's lymphatic system, drains waste products,( including amyloid) but from the brain
- + In mouse models, > 50% of amyloid cleared by the Glymphatic System
- + In AD, the Glymphatic System goes awry >poor amyloid clearance
- + Potential new avenue of intervention

Ref: Iliff JJ, Wang M[...],Nedergaard M: Sci Transl Med, 2012.

## Poster: “A Pilot Clinical Trial of Trans-cranial and Intra-nasal Photobiomodulation (PBM) for Cognitive and Behavioral Function in AD”- Linda Chao, PhD- UCSF

- 8 adults, mean age = 78, with AD exposed to (PBM)- 20 minutes q 2days of low energy, near infra-red LED light trans-cranially & intra-nasally, for 12 weeks vs no exposure > statistically significant improvement on the ADAS-Cog (cognition) and the NPI (behavior).
- Also showed increased cerebral blood flow and increased connectivity of the brain’s default network.
- Newly initiated study in Canada and US will look at 228 patients with Mod-Severe AD (MMSE 8-20), at 8 sites exposed to PBM for 20 minutes, 6 days/wk for 24 weeks vs Sham PBM. Sponsored by Vielight, Inc. & the Canadian Centre for Aging and Brain Health Innovation. Ref: [Clinicaltrials.gov](http://Clinicaltrials.gov)
- PBM equipment available via internet for ~ \$1800.



## Poster: “ Effects of Transcranial Magnetic Stimulation (rTMS) on Cognitive Functions in Mild Cognitive Impairment (MCI)- A Systematic Review and Meta-analysis”

- Ying-hui Chu- U. of Arizona, Tucson
- Concluded: rTMS improves cognitive functions in MCI vs sham TMS
- Limitation: Studies are small and targeted brain regions varied
- Note: Brainsway TMS is now FDA approved for Depression and OCD
- SLU will be looking at Deep Magnetic Brain Stimulation (Brainsway Corp.) in AD and in PD (replace electrical brain stimulation?).





## “Young Blood Products: Emerging Treatment for AD”

- Using parabiosis, plasma transfusions of various neural growth factors, animal studies>positive impact of exposure to young blood products on neurogenesis and synaptic plasticity in the aging brain.
- Hippocampus and sub-ventricular zones mostly impacted.
- Hypothesis in AD: Re-activation of neural stem cells and remodeling of synaptic activity/enhanced neural plasticity may > enhanced neurogenesis and improved cognition.
- Alkahest Pharmaceuticals conducted safety study of young adult plasma infusions in AD> safe/well-tolerated
- We are working with Alkahest to conduct a pilot study(N=20) of young plasma infusion in patients with **advanced** AD (MMSE 0-10)

Ref: Khoury R, Ghossoub E. Neural Regen Res. 2018

# A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Tolerability of Pulsed GRF6019 Infusions in Subjects with Severe Alzheimer's Disease

- 20 subjects, 60-95 yrs., with Severe AD (MMSE-0-10); 2:1 randomization of GRF6019 infusions vs Placebo.
- Subjects reside in Long-Term Care facility
- 5 daily infusions during first week
- Total study duration – 9 wks
- Variety of pre-enrollment safety measures including EKG and Echocardiogram
- Efficacy measures: MMSE,SIB,ADCS-ADL-Severe, ADCS-CGIC+, NPI-NH
- Sponsor: Alkahest Pharmaceuticals San Carlos, CA.

# New Developments Since AAIC-2018

- Chronic Periodontitis Causing Alzheimer's Disease
- Blood-Brain Barrier Test May Predict Dementia
- Memantine as a Disease-Modifying Therapy in Alzheimer's Disease
- Education May Not Protect Against Dementia
- The Rise of Pseudomedicine for Dementia and Brain Health

# Porphyromonas Gingivalis In AD Brains: Evidence for Disease Causation and Treatment with Small Molecule Inhibitors

- . **Porphyromonas Gingivalis (PG)** is a key pathogen in chronic periodontitis
- . **PG** has been identified in the brains of AD patients, as have toxic proteases secreted by **PG**, called gingipains
- . Gingipain levels correlate with tau and ubiquitin pathology and oral **PG**
- . Infection in mice > brain colonization and increased A-Beta 1-42 production
- . Gingipains are also toxic in vitro and in vivo > weakening tau
- . Small molecules, which cross the blood-brain barrier have been developed, which inhibit gingipains.
- . Gingipain inhibition > decreased **PG** infection in the brain, blocked A-Beta production, decreased neuroinflammation, and rescued neurons in the hippocampus.
- . Gingipain inhibitors may be useful for treating **PG** brain colonization and neurodegeneration in Alzheimer's Disease.

Ref: Dominy SS...Potempa J: Sci. Adv. 2019



# Blood-Brain Barrier Breakdown is an Early Biomarker of Human Cognitive Dysfunction

- Researchers at USC enrolled 160 people with and w/o cognitive impairment and examined 2 markers involved in the breakdown of the blood-brain barrier (BBB).
- 1-Levels of platelet-derived growth-factor beta (PDGFRB). This protein is found in capillaries which maintain the BBB's integrity. Levels of soluble PDGFRB rise in CSF when BBB is compromised.
- 2- Integrity of BBB was tracked using a special MRI technique
- Results: Those with cognitive impairment had higher CSF levels of soluble PDGFRB in the CSF and greater breakdown of BBB in certain regions. These measures were independent of Beta amyloid and tau levels.
- These measures may pave the way for early diagnosis of AD and other causes of cognitive impairment.
- Ref: D'Orazio LM...Zlokovic BV. Nat Med.2019.



# N-methyl-D-aspartate Receptor (NMDAR)-Mediated Calcium Influx Connects Amyloid-Beta-Oligomers (ABO's) to Ectopic Neuronal Cell Cycle Re-entry In Alzheimer's Disease

- ABO's induce excess calcium entry into neurons via NMDA receptors, contributing to synaptic dysfunction.
- Using AD model mice, this study tested the hypothesis that ABO-stimulated calcium entry also drives neuronal cell-cycle re-entry(CCR), which is a prelude to neuronal death in AD.
- Results: In cultured neurons, ABO-stimulated CCR was blocked by NMDA receptor antagonists.
- Treatment of Tg2576 AD model mice with the NMDAR antagonist, memantine, prevented CCR and neuronal death.
- This study demonstrates a role for ABO-stimulated calcium influx via NMDAR and CCR in AD and suggests the use of memantine as a disease-modifying therapy for pre-symptomatic AD.
- Ref: Kodis EJ, et al: Alzheimer's & Dementia, 10/2018.

# Education and Cognitive Reserve In Old Age

- Study combined 1,239 subjects from the Rush Religious Orders Study of Older Clergy and 1,660 subjects from the Rush Memory and Aging Project (total n=2,899) in Chicago.
- Participants had a mean age of 78 at baseline, avg 16.3 yrs education, followed for avg of 8 yrs. 89% white; 74% women. All agreed to annual cognitive testing and brain autopsy at death.
- Three subgroups evolved; people who developed incident dementia(n=696), people who died and had neuropath examination (n=752), and people in both categories (n=405)
- Results: Across all participants, education was associated with initial level of cognition, but NOT with slower rates of cognitive decline. Of those who developed dementia, education was not linked to the onset or to a slower rate of linear cognitive decline.
- Ref:Wilson RS...Bennett DA: Neurology,2/2019.

# The Rise of Pseudomedicine for Dementia and Brain Health

- Patients with dementia and their families are targeted by practitioners and companies motivated by self-interest.
- Patients and caregivers encounter sophisticated techniques {and advertisements} that supply false “scientific” backing for brain health interventions.
- Physicians have an ethical mandate to protect patients who may be vulnerable to promotional materials.
- On a national level, we need to limit the claims of benefit for interventions lacking proven efficacy.
- Clinicians must distinguish testimony and cult science from quality medical research and explain when interventions may appear to represent pseudomedicine.
- Ref: Hellmuth J, Rabinovici GD, Miller BL: JAMA 1/2019.

# CONCLUSIONS

- AD is a complex brain disease
- Current FDA-approved treatments are symptomatic and may impact disease progression and improve QOL for patients and caregivers.
- There is growing evidence that lifestyle modification, including treatment of cardiovascular risk-factors such as hypertension, diabetes, hyperlipidemia and obesity; exercise; adopting a Mediterranean diet, may delay the onset/decrease the risk of AD
- We are close to FDA-approval of the first drug for treating agitation in AD and are becoming aware of the utility of non-pharmacologic approaches for BPSD
- We are making progress in moving toward an FDA-approved, disease-modifying therapy and are treating asymptomatic 'at-risk' individuals a decade or more before clinical symptoms (2 large studies at SLU)



**QUESTIONS?**