






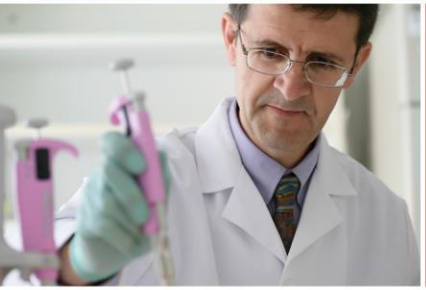


2024 Spring ADRC Meeting

October 15-17, 2024, Boston, MA

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NIH National Institute on Aging DESIGNATED Alzheimer's Disease Research Center

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Disclosures

- I have received grants from NIA/NIH, Department of Veterans Affairs, State of Wisconsin, and UW-Madison to support my research program

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- UW-Madison has received grants from pharmaceutical companies for me to serve as a site PI to conduct treatment trials involving patients with MCI and dementia
- I have no conflicts of interest for this presentation

Overarching Scientific Theme

Biomarkers of non-AD Coexisting Pathologies

- The scientific themes permeate many sessions of this 2-day meeting
- Theme aligned with the Spring ADRC meeting that focused on TDP-43

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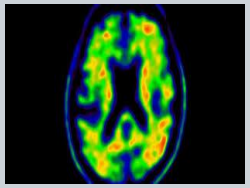
Advances in AD/ADRD Research with Relevance to Coexisting Non-AD Pathologies



Neuroimaging and fluid biomarkers of AD/ADRD

- Plasma biomarkers of amyloid and tau deposition
- Plasma markers of neuroinflammation, neurodegeneration
- Dried blood spots
- SAA and skin biopsy for phosphorylated α synuclein
- Neuronally derived extracellular vesicle α syn as a serum marker
- Detection of TDP-43 splicing loss of function by cryptic exon epitopes

Prevention and treatment of AD and ADRD

- FDA approval of monoclonal antibodies (MABs) for MCI and early AD
- Active trials of MABs targeting preclinical stages of AD
- Behavioral and lifestyle interventions
- Antisense oligonucleotides to inhibit TDP-43 aggregation
- Therapies targeting α synuclein aggregation, degradation, clearance

Diversifying ADRC cohorts and enhancing inclusion in clinical trials

- Major NIA-supported efforts to diversify research cohorts and trials

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Advances in AD/ADRD Research with Relevance to Coexisting Non-AD Pathologies

Role of social exposome in AD/ADRD pathobiology

- Area Deprivation Index
- Neighborhood Atlas
- SDOH and their effects on risk and resilience to AD/ADRD

Early diagnosis of AD/ADRD

- Fluid biomarkers – TDP-43 levels in extracellular vesicles
- Digital biomarkers
- Remote cognitive testing and data collection
- EUREKA Challenge – prediction of dementia in marginalized populations through inclusive algorithms from large datasets

Patient care and caregiving research

- IMPACT Collaboratory – pragmatic trials for people living with dementia

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Neuronal Alpha Synuclein Disease

Neuronal α synuclein disease (NSD) defined by the presence of pathological n-αsyn irrespective of any specific clinical syndrome

Persons with n-αsyn are at risk for dopaminergic neuronal dysfunction

Clinical syndromes of NSD include motor syndrome (Parkinson's disease), cognitive syndromes (Lewy body disease), neuropsychiatric symptoms, sleep disorder (REM disorder) or autonomic symptoms (Multiple System Atrophy)

Alpha synuclein aggregates perturb dopaminergic transmission and induce presynaptic and postsynaptic dysfunction

Immune response to α synuclein misfolding contributes to disease progression

Fluid biomarkers and novel treatments are being developed for NSDs

Simuni et al. Lancet Neurol 2024;23: 178-190

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Preliminary Pilot SAA Study

- Study involved **424 largely CU (89%) participants** with CSF p-tau181 and Aβ42/40 ratio

Goals:

1) Characterize synSAA- (S-) and synSAA+ (S+) people in terms of AD CSF biomarkers (ptau181, aβ42/40)
2) Relationship to markers of neurodegeneration and neuroinflammation in CSF (i.e., Nfl, neurogranin, GFAP, sTREM2 and YKL40
3) Does S+ impact cognitive trajectories?

- SAA performed by Amprion

Preliminary Findings:

- Significant overlap between AD and S biomarker positivity in a mostly CU cohort
  - 12% S+ overall increases to 20% among people who were also T+
- S+ more likely to be impaired
- 80% of S+ were CU at LP;
  - Suggests it is feasible to detect S+ among CU
- Some evidence for an association between S+ and cognitive decline on 1 of 4 tests (non-episodic memory test)

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Scientific Presentations

A) Pathology Validation of AD Biomarkers

Speaker – Renaud La Joie, PhD
UCSF ADRC

Renaud La Joie

B) Significance of Diversifying ADRC Cohorts

Speaker - Rosie Curiel Cid, PhD
Florida ADRC

Rosie Curiel Cid

Scientific Presentation & Panel Session

C) Pathology Validation of AD Biomarkers

Speaker – Kathleen Poston, MD, MS
Stanford ADRC

Kathleen Poston

D) Plenary Session

Panel Chair: Gil Rabinovici, MD

Gil Rabinovici, MD

Ganesh Babulal, PhD

Astrid Suchy-Dicey, PhD

Edward Lee, MD, PhD