Candidate ADRD fluid biomarkers and their challenges and opportunities

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Disclosures

- Paid consultant Biohaven.
- Collaborator – Eli Lilly and InMune Bio
- Research funded by extramural grants from NIH (NIA and NINDS)
- Editor-in-Chief: Alzheimer's & Dementia

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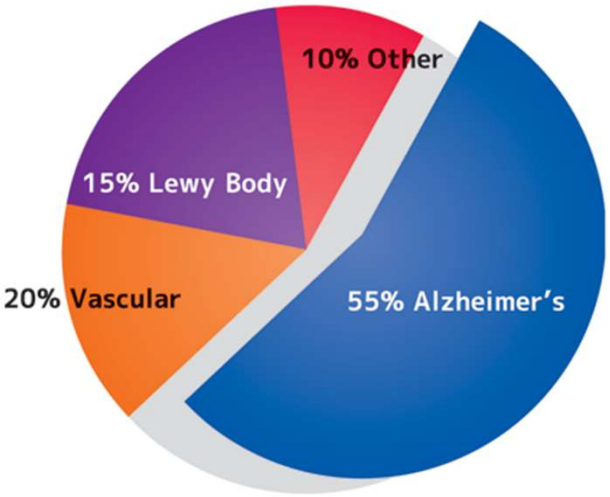
Reductionist view of dementia



- This is the traditional view of the dementia breakdown.
- Second most common cause of dementia is vascular dementia.
- This is not a true reflection of what we see in the brains of dementia patients.

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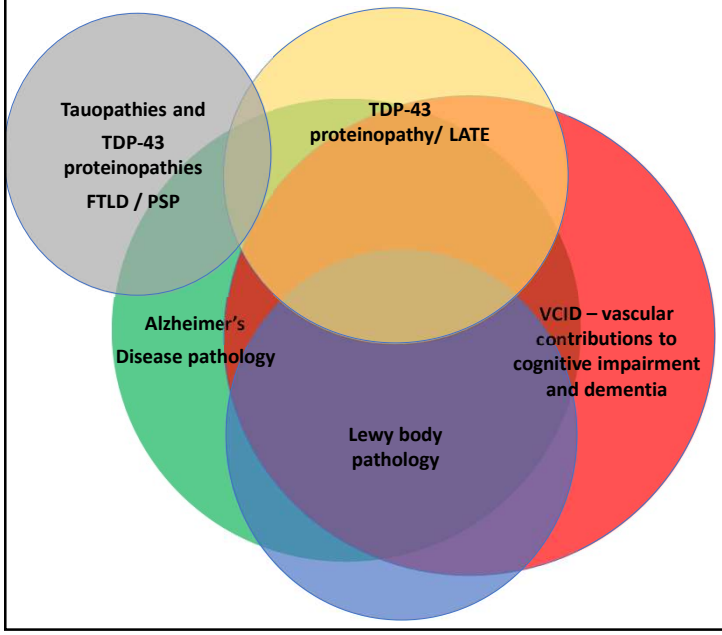
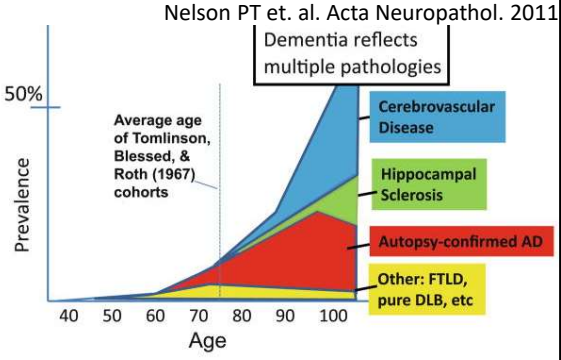
The real picture of dementia



Nelson PT et. al. Acta Neuropathol. 2011



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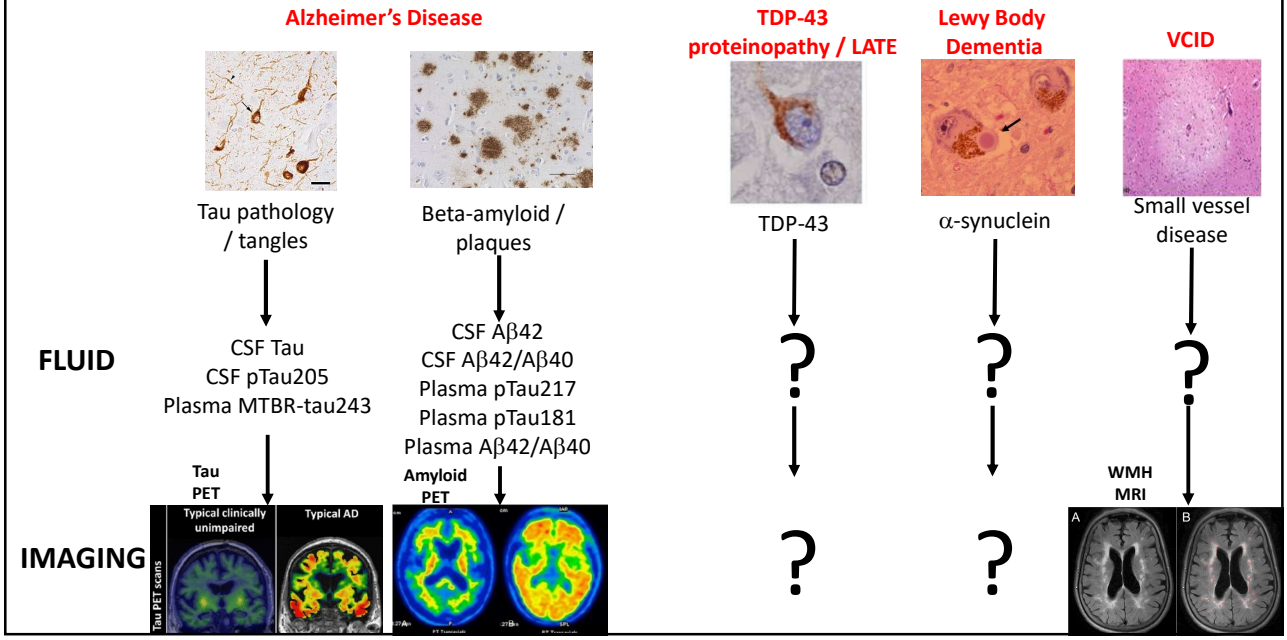
Current State of Biomarkers



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VCID, Inflammation, and the need for more sensitive biomarkers for these

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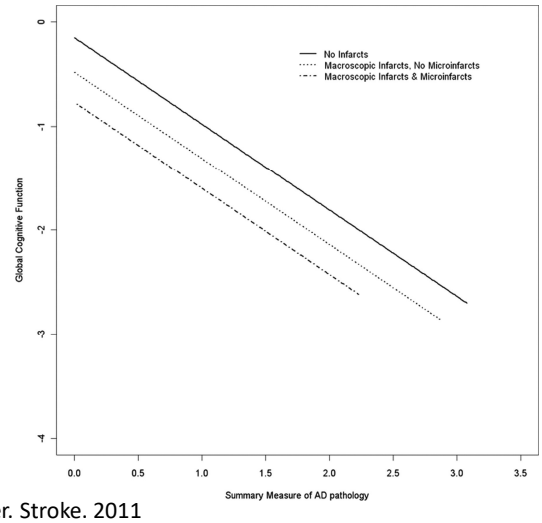
Why is it important to consider "Inflammation" and "Vascular" contributions

- Increasing evidence supports inflammation has a significant role to play in Alzheimer's disease:
  - Genetic risk factors from GWAS analyses identified key inflammation-related genetic SNPs in TREM2, CR1 and CD33.
  - IL6 is elevated in CSF and serum of AD patients.
- Cerebral small vessel disease has an additive effect on cognition when co-morbid with AD.



Arvanatakis……..Schneider. Stroke. 2011

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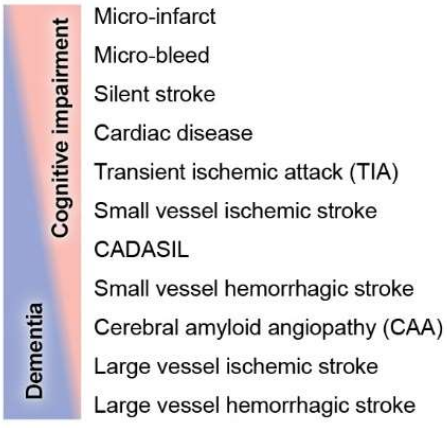
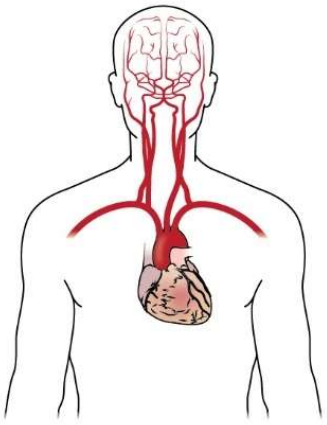
The challenge with vascular biomarkers

- VCID reflects varied vascular pathologies, and therefore mechanisms





Absolutely critical: Develop clinical outcomes & biomarker measures, and interventions, that match the targeted vascular injuries/disease.

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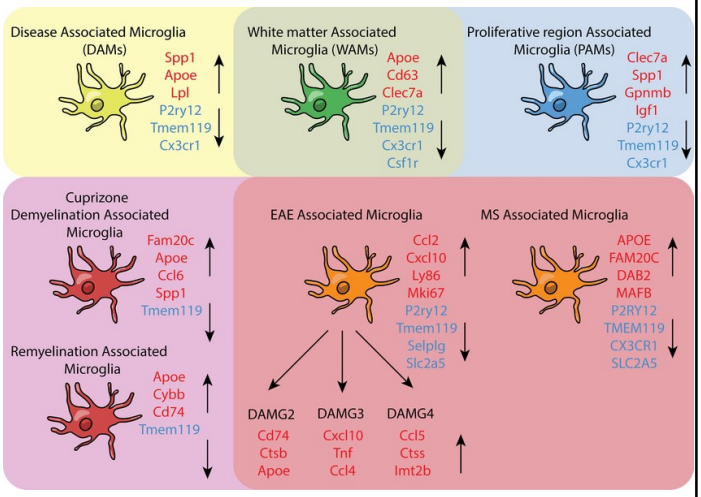
The challenge with adding "I"

- There are multiple states of microglial "activation".
- Mouse studies and limited human autopsy studies suggest some "states" are beneficial at early stages of disease but detrimental late in disease.
- GFAP and YKL-40, the front-runners of "inflammation" fluid biomarkers are astrocyte derived.
- Unclear what "state" these are associated with



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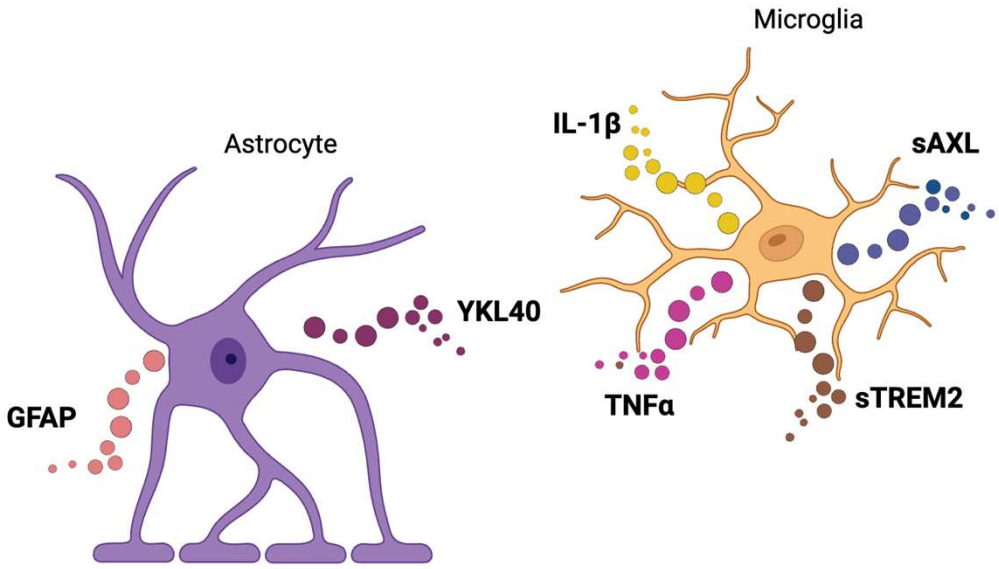
Potential fluid biomarkers of neuroinflammation



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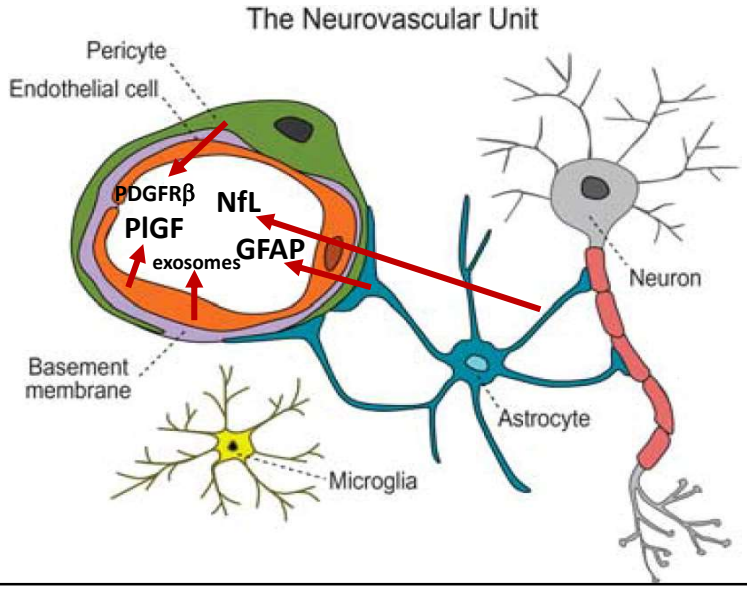
Potential fluid biomarkers of VCID



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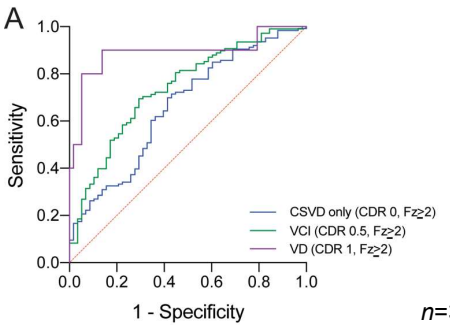
Plasma Placental Growth Factor may be Diagnostic for VCID

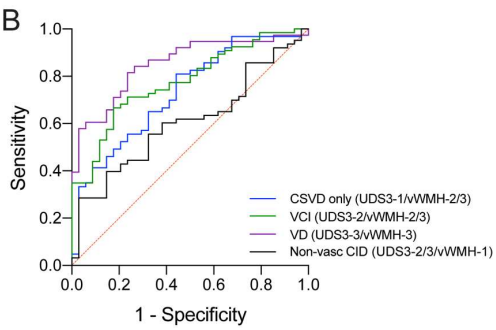
ROC Curves Using CDR/Fazekas



n=335

Diagnostic accuracy of Plasma PlGF:
- Vascular Dementia (CDR 1, Fazekas ≥2) = 0.89
- Vascular Cognitive Impairment (CDR 0.5, Fazekas ≥2) = 0.74

ROC Curves Using UDS3-EF/vWMH



n=335

Diagnostic accuracy of PIGF is retained using continuous clinical (UDS3) and radiographic (vWMH) measures:
- CSVD only = 0.73
- VCI = 0.78
- VD = 0.85
- Non-vasc CID = 0.61 (n.s.)

Hinman et al. *Alz & Dement 2023*

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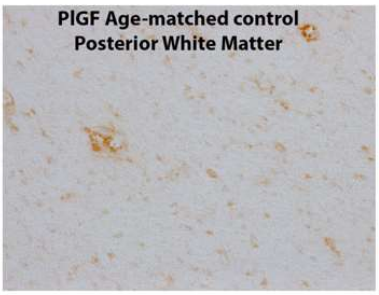
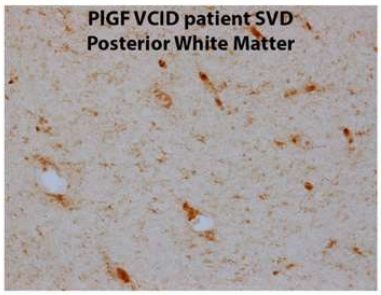
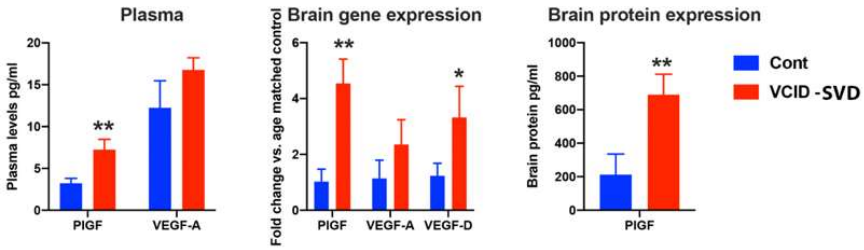
PlGF in the human brain





- N=12 / group matched for age, sex, and ApoE status



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Other ADRDs – DLB and LATE (α-synuclein and TDP-43)

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RT-Quic for detection of α-synuclein pathology

- Real-time quaking induced conversion (RT-QuIC) method, originally developed to diagnose prion diseases.
- Pathogenic protein can induce the conversion of a "normal" protein into a pathogenic one, where the former acts as a seed that promotes conversion and aggregation.
- By using CSF, if pathogenic proteins are present (in this case pathologic α-syn) they will convert "normal" a-synuclein into the pathogenic form.
- By breaking these assemblies up and then cycling them you can amplify the pathogenic protein, similarly to a PCR reaction.
- Thioflavin-T is included in the substrate mixture and it is the intensity of this signal that is read by a plate-reader.
- CSF or skin biopsy seems to be the most reliable tissue for RT-Quic.

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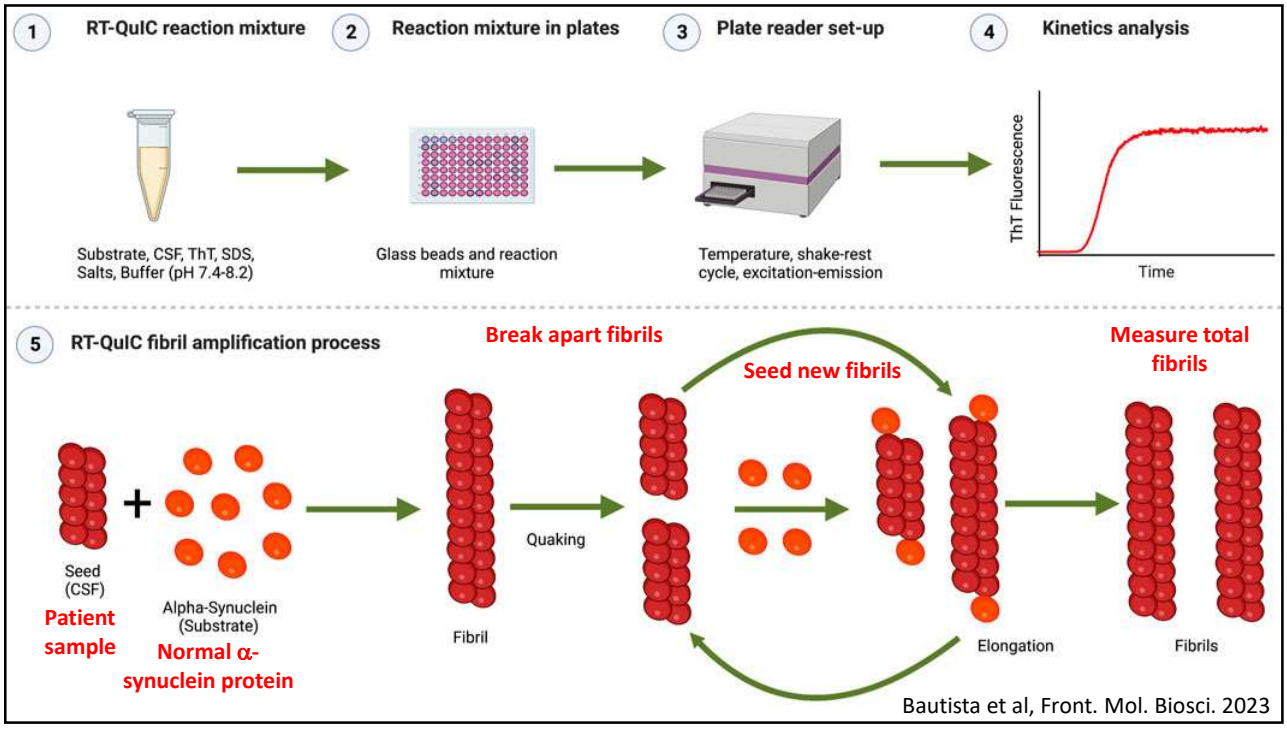

Bautista et al, Front. Mol. Biosci. 2023

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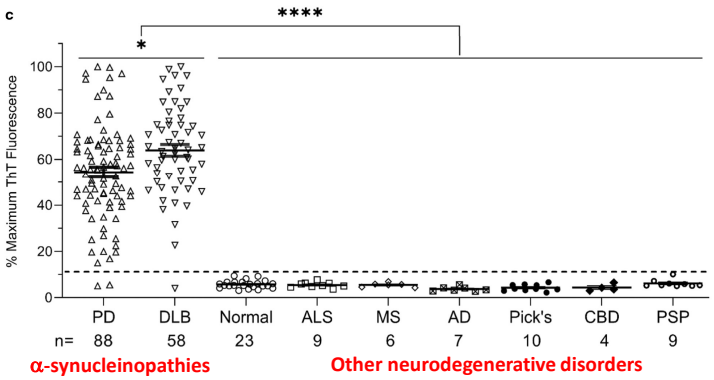
RT-Quic is specific and quite sensitive



- **Bargar et al, Acta Neuropath. Comm. 2021.**
- Showed that Parkinson's and Lewy body dementia patients have increased signal over age-matched controls and other neurodegenerative diseases.
- RT-Quic seems to be specific and sensitive, but does not appear to indicate disease severity.

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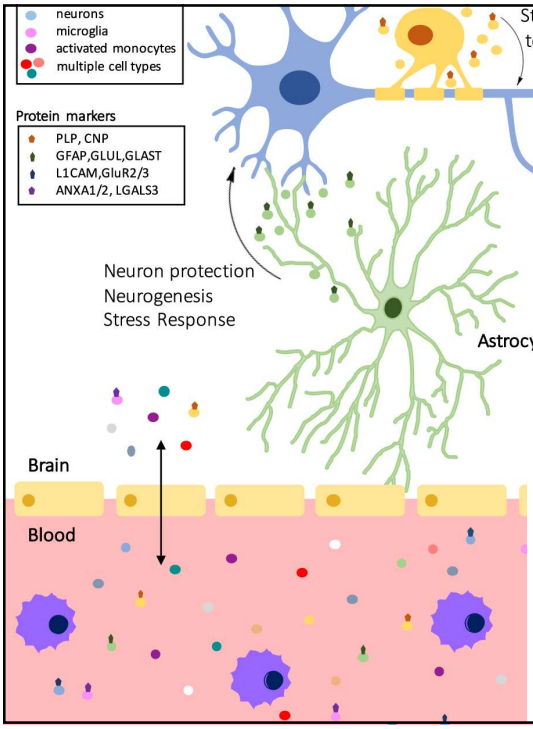

Are there biomarkers for TDP-43 proteinopathy?

- **Rissman et al, Alz Dement. 2022** examined extracellular vesicles from plasma of autopsy confirmed LATE-NC (limbic-predominant age-related TDP-43 encephalopathy – neuropathologic change) along with non-TDP-43 dementia cases and age-matched controls.
- Astrocyte-derived extracellular vesicles showed significantly elevated TDP-43 in LATE-NC cases compared to TDP-43 negative cases.
- Challenges with EVs as biomarkers include scalability and reproducibility.

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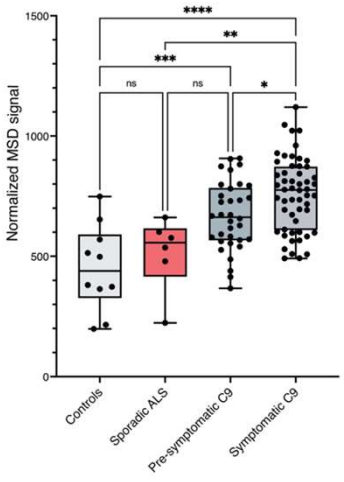
Candidate biomarker for TDP-43 proteinopathy



- TDP-43 normally minds to RNA regulating the translation of RNA to protein.
- Dysregulation of TDP-43 through aggregation and phosphorylation can lead to disruptions in protein translation and what are called “cryptic exon-encoded peptides”.
- Irwin et al have a paper in review that describes the detection of cryptic exon-encoded peptides in CSF of familial and sporadic ALS, which involved TDP-43.
- The authors found that cryptic HDGFL2 is elevated in CSF of all cases of ALS but significantly so in *C9ORF72* carriers.
- This biomarker could have relevance to LATE and FTLD-TDP.

Irwin et al, bioRxiv, 2023

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How to advance biomarker discovery for ADRDs

- Autopsy studies with matched antemortem biofluids.
- Mouse model and iPSC studies to identify fluid biomarkers that match specific subtypes of inflammation and cerebrovascular pathologies.
- We need “ground truth” for ADRDs, and while ideally this would be autopsies, that will not achieve the sample size required.
- PET ligands for TDP-43 aggregation and α-synuclein pathology would provide “ground truth” and significantly advance biomarker discovery for these ADRDs.
- Improved technologies to optimize brain-derived exosome approaches that will broaden the potential biomarkers that can be assessed.

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INDIANA UNIVERSITY
SCHOOL OF MEDICINE

Acknowledgements

IADRC

Wilcock laboratory

Erica Weekman PhD
Kate Foley PhD
Katelynn Krick
Sherika Johnson

Past Lab Members:
Katie Salmeron PhD
Brittani Price PhD
Courtney Kloske PhD
Tiffany L. Sudduth
Colin Rogers PhD
Alex Knoll PhD
Zachary Winder PhD
Charles Seaks PhD
Alex Linton PhD

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Liana Apostolova MD
Jared Brosch MD
Cristian Lasagna-Reeves PhD
Bruce Lamb PhD
Andy Saykin PhD
Adrian Oblak PhD
Paul Territo PhD
Shannon Risacher PhD

MODEL-AD
Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease

TREAT-AD
TaRget Enablement to Accelerate Therapy Development for AD

NIH National Institute on Aging

NIH National Institute of Neurological Disorders and Stroke

Collaborators
Ron DeMattos PhD: Eli Lilly – providing antibody for studies
Dave Morgan PhD: Michigan State
Carol Colton PhD: Duke Univ
Gareth Howell PhD – The Jackson Laboratory
Chris Norris PhD – Univ KY

Thank you to our research volunteers!

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