Adding the “I” and “V” to “ATN” Challenges and Opportunities

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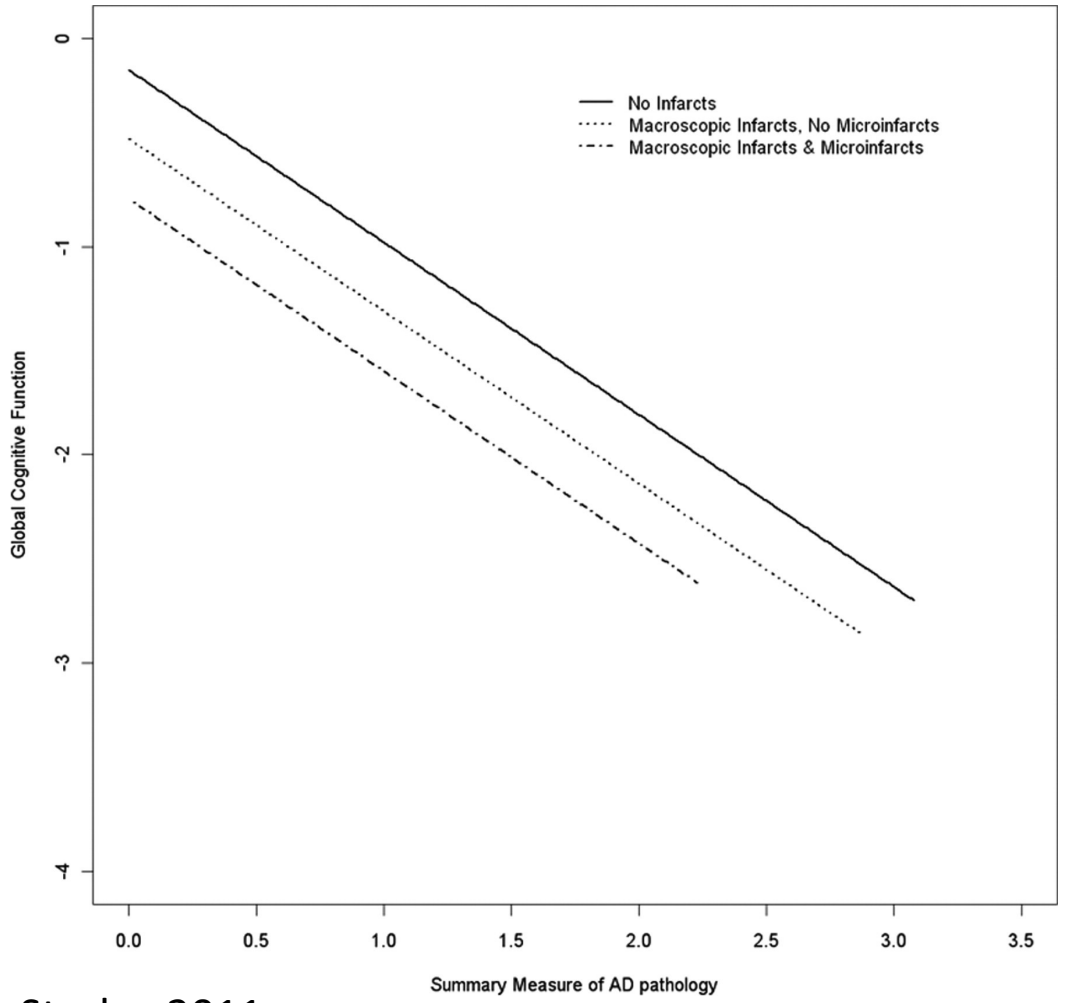
Disclosures

- Paid consultant Biohaven.
- Collaborator – Eli Lilly and InMune Bio

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

The challenge with adding “V”

- VCID reflects varied vascular pathologies, and therefore mechanisms

Cognitive impairment

Dementia

Micro-infarct

Micro-bleed

Silent stroke

Cardiac disease

Transient ischemic attack (TIA)

Small vessel ischemic stroke

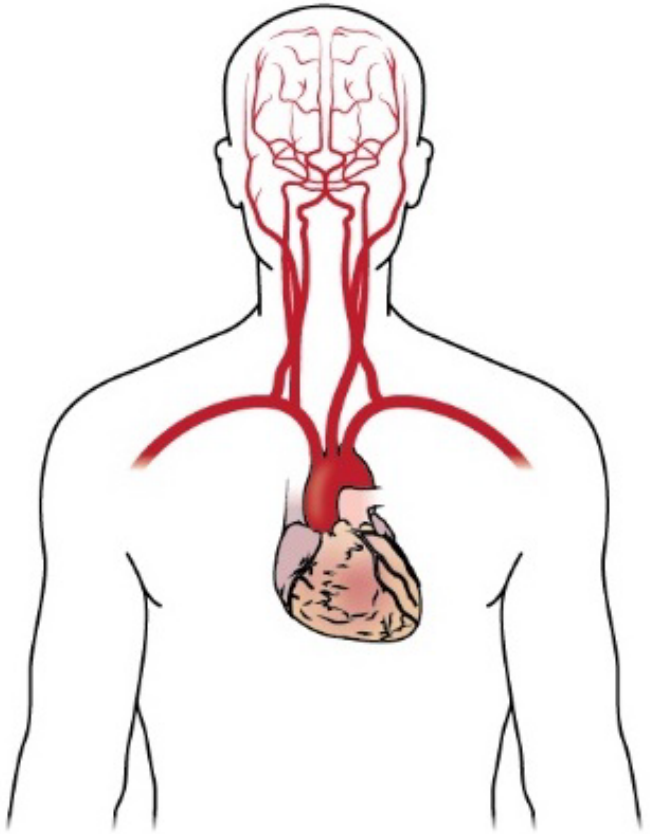
CADASIL

Small vessel hemorrhagic stroke

Cerebral amyloid angiopathy (CAA)

Large vessel ischemic stroke

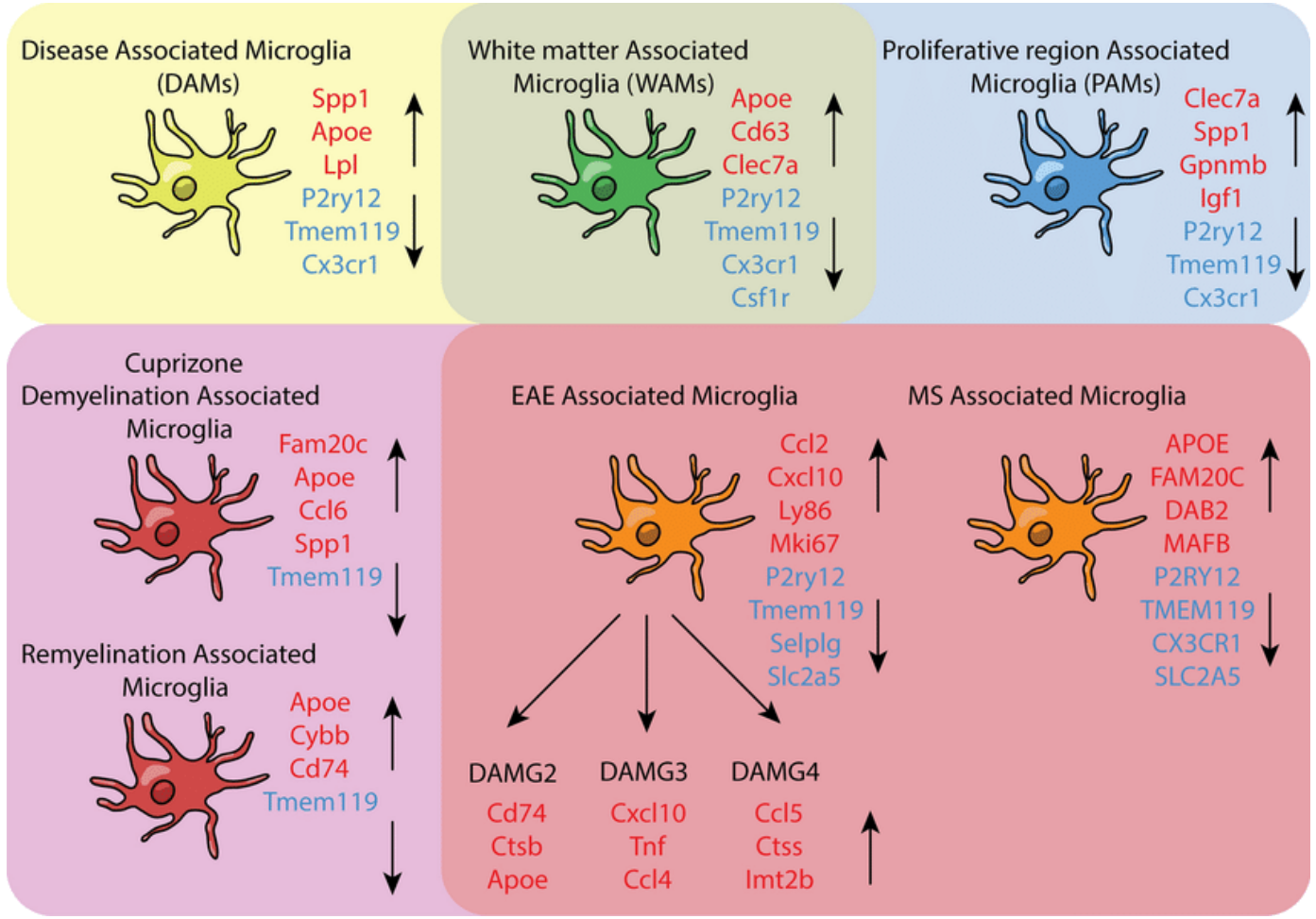
Large vessel hemorrhagic stroke



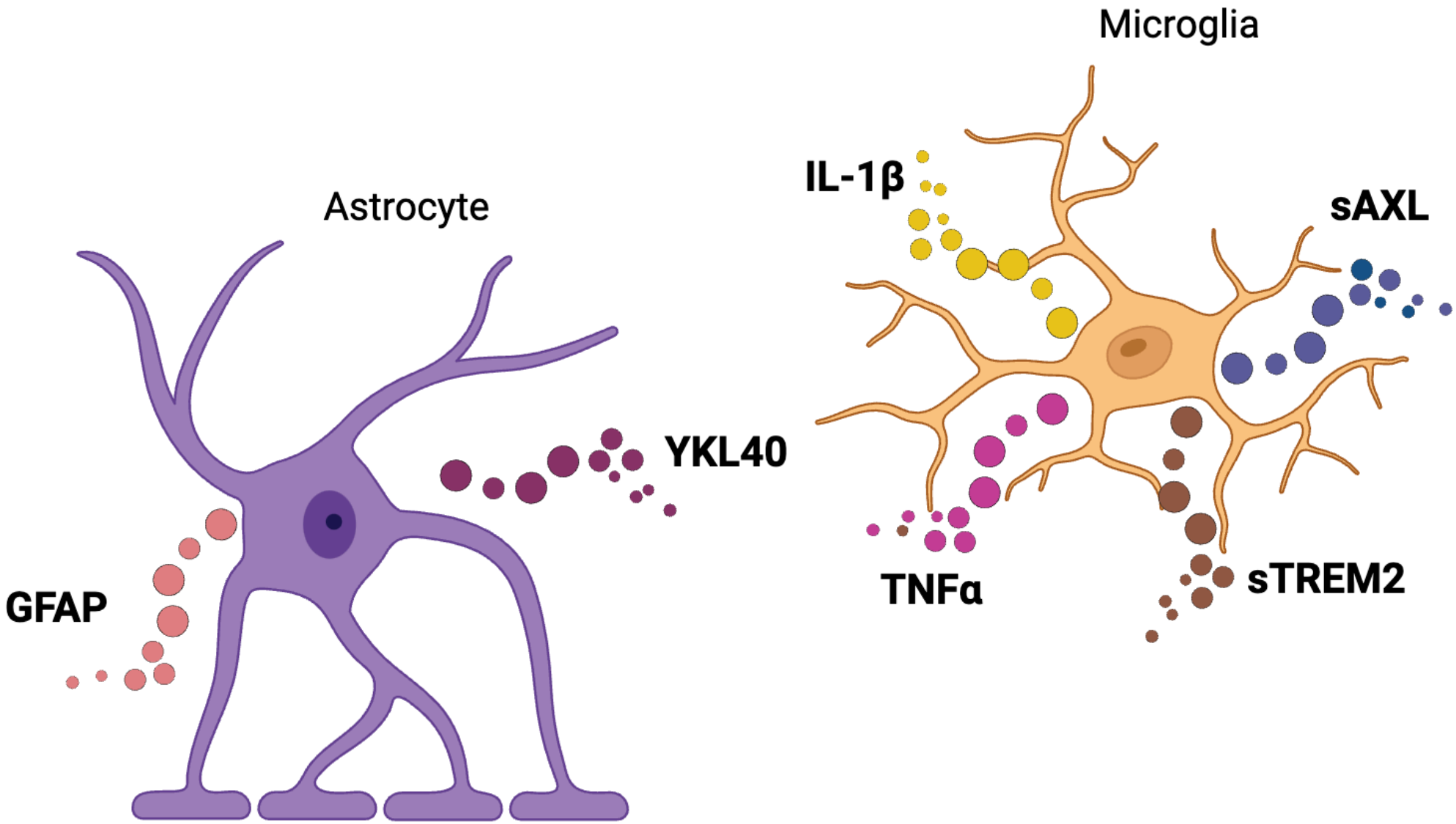
Absolutely critical: Develop clinical outcomes & biomarker measures, and interventions, that match the targeted vascular injuries/disease.

The challenge with adding “I”

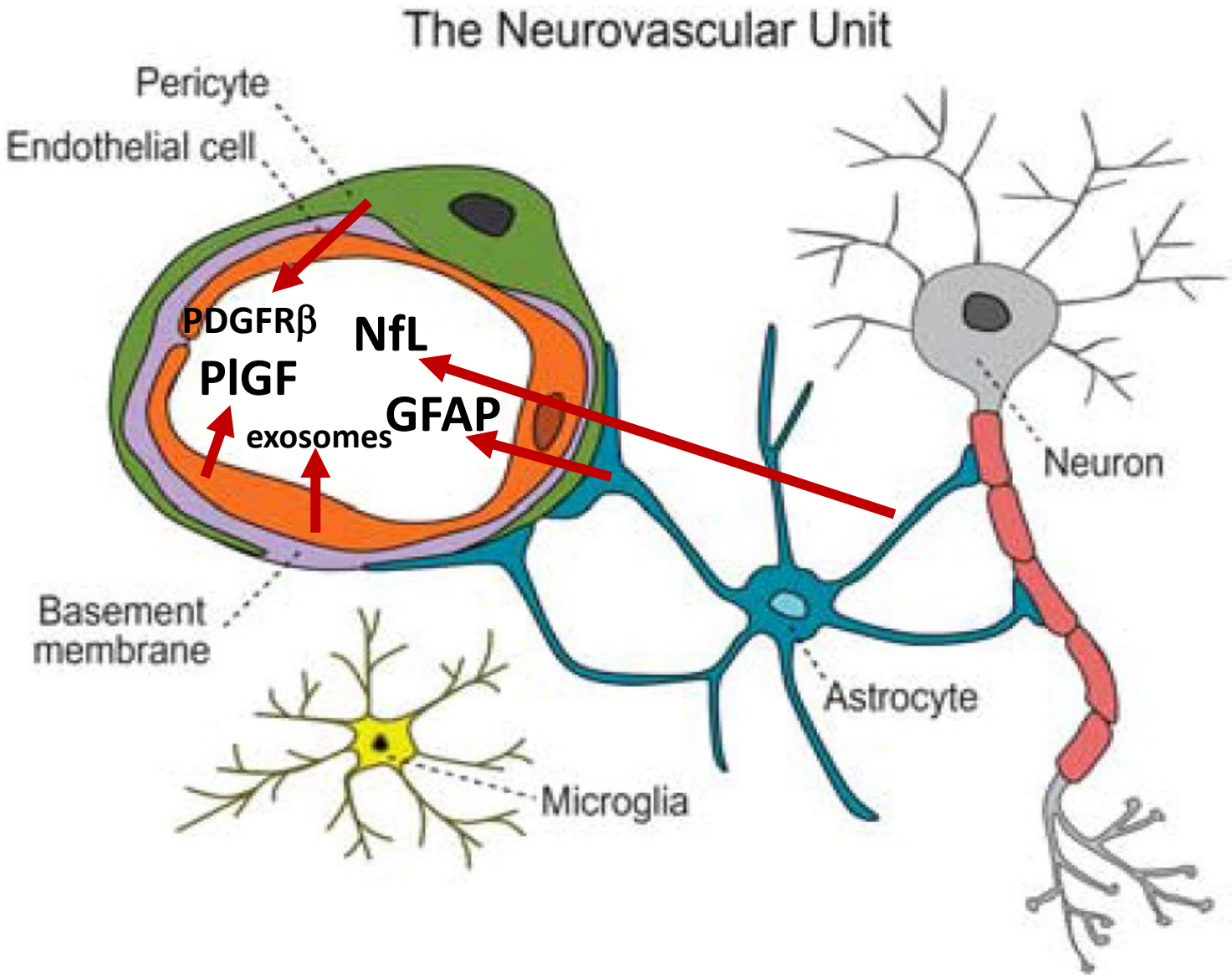
- There are multiple states of microglial “activation”.
- Mouse studies and limited human autopsy studies suggest some “states” are beneficial at early stages of disease but detrimental late in disease.
- GFAP and YKL-40, the front-runners of “inflammation” fluid biomarkers are astrocyte derived.
- Unclear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



Potential fluid biomarkers of neuroinflammation

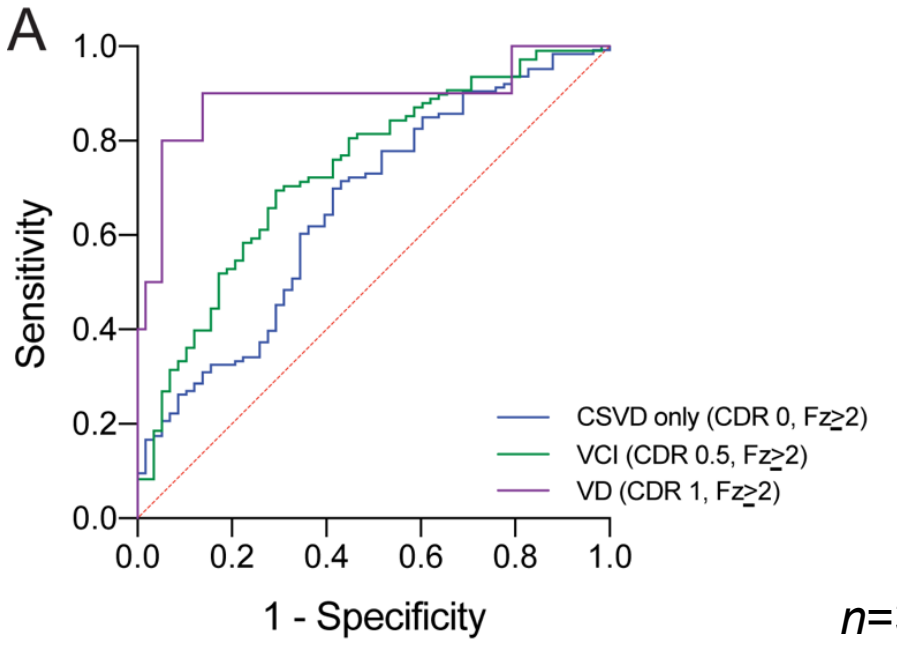


Potential fluid biomarkers of VCID



Plasma Placental Growth Factor may be Diagnostic for VCID

ROC Curves Using CDR/Fazekas

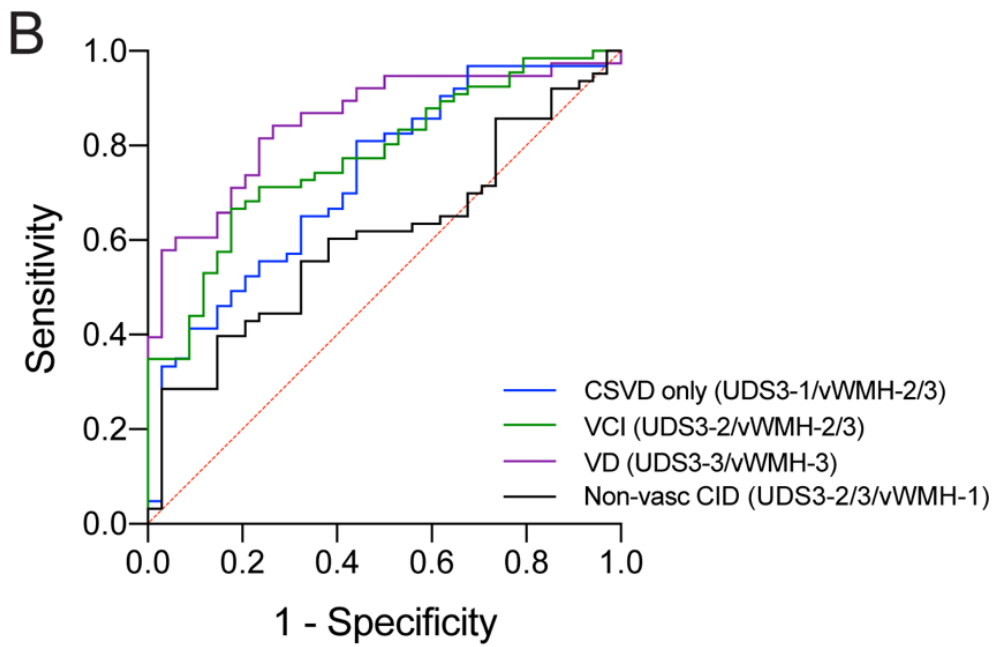


n=335

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



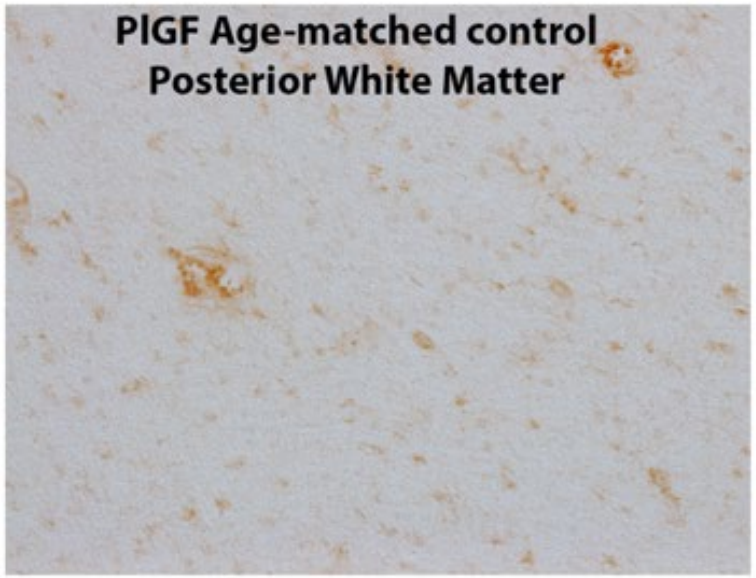
n=335

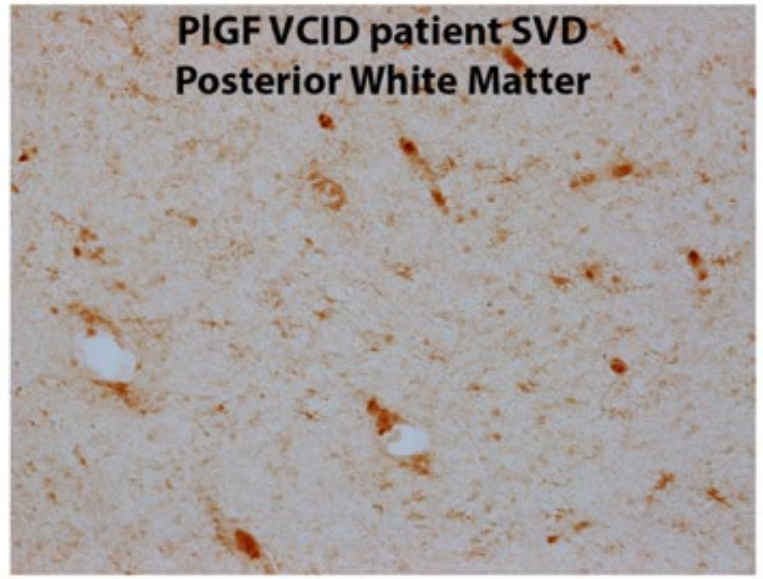
Diagnostic accuracy of PlGF is retained using continuous clinical (UDS3) and radiographic (vWMH) measures:

- CSVD only = 0.73
- VCI = 0.78
- VD = 0.85
- Non-vasc CID = 0.61 (n.s.)

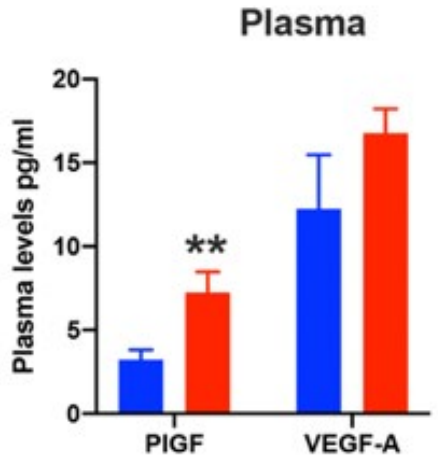
Hinman et al. *Alz & Dement 2023*

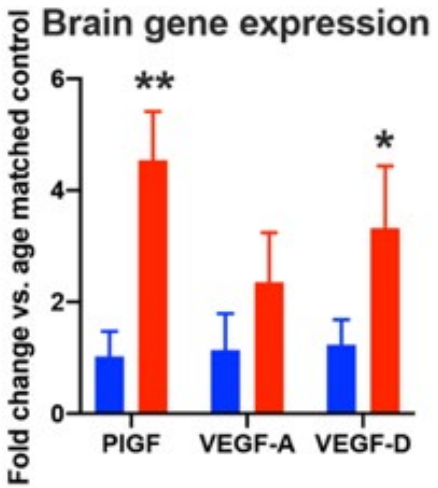
PlGF in the human brain

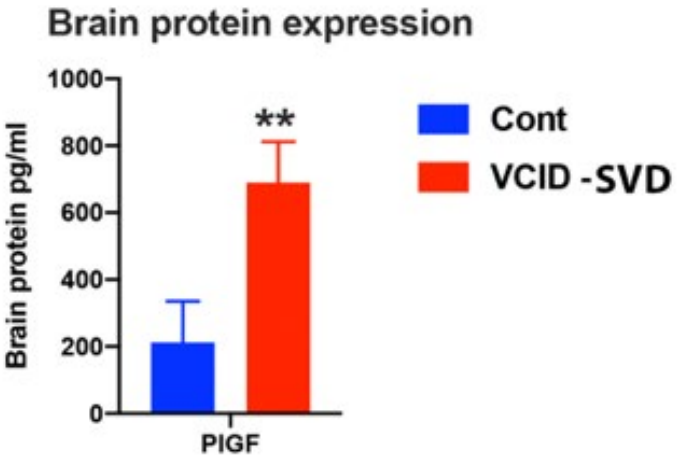




- N=12 / group matched for age, sex, and ApoE status







Solutions?

- Autopsy studies with matched antemortem biofluids.
- Mouse model and iPSC studies to identify fluid biomarkers that match specific subtypes of inflammation and cerebrovascular pathologies.
- Identification of CNS-derived fluid biomarkers of inflammation like GFAP and YKL-40.
- Improved technologies to optimize brain-derived exosome approaches that will broaden the potential biomarkers that can be assessed.
- Better PET ligands for glial reactivity.
- Better MRI sequences to detect small vessel pathologies.

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

IU Collaborators

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!