Fluid Biomarkers of Cerebrovascular Disease
The Need for Specificity

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White Matter Hyperintensities Are a Core Feature of Alzheimer’s Disease: Evidence from the Dominantly Inherited Alzheimer Network

How to get specific but not invasive?

“You will feel a thing.”
Cells secret vesicles: extra-cellular vesicles
Extracellular Vesicles Are Diverse: Exosomes 30-150 nm

Electron Micrograph

NTA: count and size
What if we could isolate specific sub-populations?
WMH and the diversity of underlying molecular-cellular dysregulations
Case-Control Design

- Consecutive sample total 26 subjects high versus no WMH
- Functionally / cognitively normal older adults
- CDR=0; MMSE >27
- Imaging, blood draw, cognitive testing, neurological exam and history
- Platelet-poor plasma prepared for EDE extraction
Series of Immunoprecipitations

1. All exosomes
2. IP: EDE
3. re-IP: EDE
Classical Complement Pathway

![Graphs showing C1q and C3b levels in control and VD groups with significant p-values.](image)

Elahi et al., 2019
Host Defense / Complement Regulatory

CD59  p=0.003

![Graph showing CD59 levels in Control and VD groups.](image)
Complement Factors Associated with Cognition and SBP

R² .6
β .7
p = .0008

R² .4
β .7
p = .003
Conclusions

• Secreted biomarkers lack specificity; need for “gold-standards”
• Exosomes: enhanced specificity; ?sensitivity remains to be determined
• Potential for diagnostic classification; ?Risk stratification
• Potential for mechanistic studies of multi-cellular dysfunction (NVU)
• Changes in molecular concentrations may reflect cellular loss of molecules or compensatory upregulation
Study participants and families

UCSF MAC
Hillblom Aging Network

Bruce Miller
Joel Kramer and team
Edward Goetzl
Charlie DeCarli and IDeA Lab
Howie Rosen & Lab
Katerina Akassoglou & Lab
Gil Rabinovici and Lab
Marie Altendahl and Daniel Bennett
Anna Karydas and Will Rivera
Conversion from MCI to AD: ADE complement factor elevation

Winston et al., 2019