Opportunities for inter-AD Center biofluid biomarker efforts.

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Multi-center biomarkers – why?

Biomarker research for AD and related disorders is burgeoning

The proposed A/T/N classification depends on biomarkers

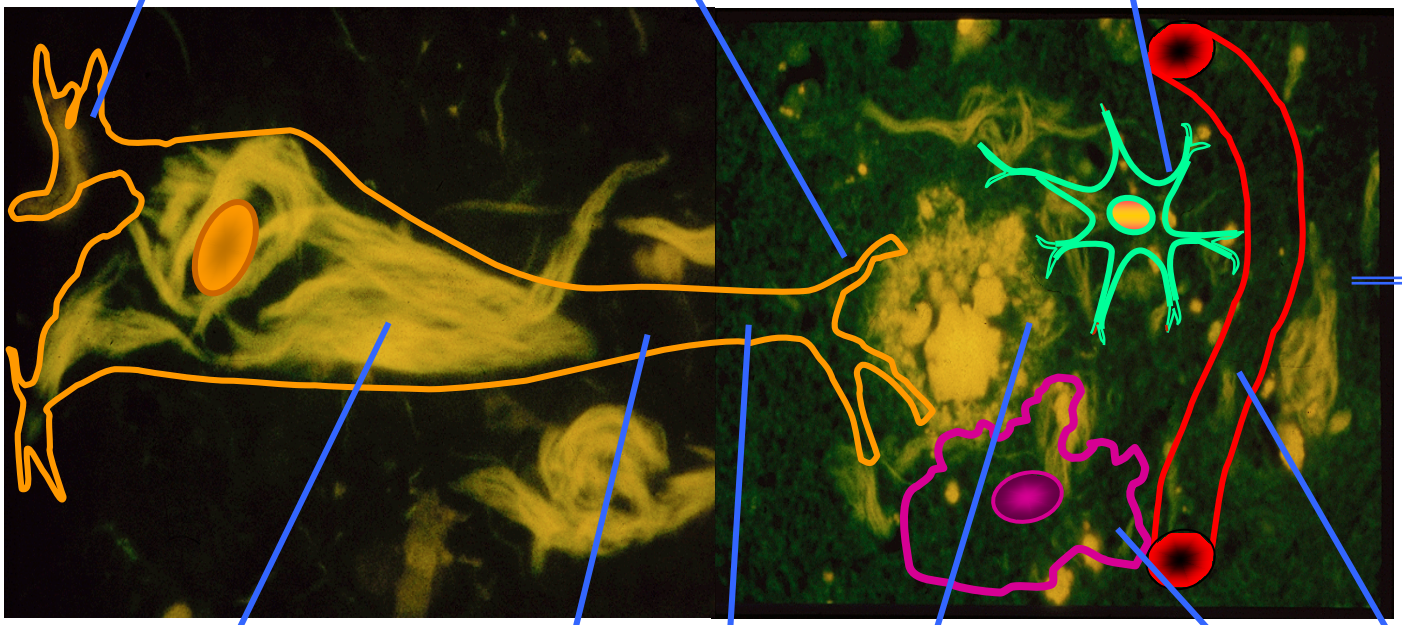
CSF:

- Better standardization of core biomarkers of Aβ42, tau and P-tau
- Refined pre-analytical procedures
- Novel CSF biomarkers paint a more detailed picture: microglial function, synaptic changes, vascular mechanisms …

Plasma and blood:

- Brain-specific proteins are detectable with ultrasensitive assays
- New opportunities e.g., miRNA, exosomes, epigenomics

Painting a more detailed biomarker picture



Neurogranin – dendritic Ca^{++} regulation / damage

SNAP25 - presynaptic

YKL40, S100b - astrocytes

proteomics
metabolomics
miRNA
exosomes

P-tau – tangle pathways

Tau – neuronal or axonal damage

NFL - axonal integrity

Aβ42
sAPP
Aβ38, 40

BBB: albumin ratio, MMPs

sTREM2 - microglia

How might an inter-AD Center effort contribute?

Many other groups are active

- European Centers and national efforts
  - ARUK cohorts; Swedish Biofinder Study; French, Netherlands, Belgian and and German multicenter studies
- ADNI; AIBL; DIAN
- Clinical trial consortia
- Single Center studies in USA
- AD-related Disorders:
  - PPMI, PDBP, Vascular Consortium, ARTFL

What is special about the AD Centers?

Many unique opportunities:

- Scale: 31 Centers, follow > 12,000 active subjects
- Standardization, deep phenotyping, longitudinal follow-up
- DNA analysis through ADGC
- Diversity: subjects, ethnicity; AD-related disorders
- Autopsy follow-up and available brain tissue
- Infrastructure and expertise

A kickstarter Project

Prospective CSF collection across interested AD Centers using a standard protocol, with analysis of Aβ42, tau and P-tau using an automated assay platform.

Test a clinically relevant workflow and develop/reassess diagnostic cutoffs

Establish a bank of CSF and plasma from these subjects

Survey of interested AD Centers

- Centers polled for interest, number of subjects they plan to subject to LPs in 1 year, and amount of additional CSF and plasma willing to bank
- 12 Center responses
- N = 500 prospective CSF samples estimated
- Interest in additional banking: ADC's agreed to banking of variable amounts of
  - plasma: most 2 mL, some 1 mL
  - CSF: most 1 mL, some 2 mL

Next steps for this prospective study

- Partnership for assay kits: Roche/Elecsys is agreeable
- Central laboratory: Les Shaw, U Penn
- LP kits, collection and aliquoting tubes: NCRAD to help coordinate and bank residual samples
- Data flow: CSF data returned to sites and to NACC
- Funding: Administrative Supplement to NACC

What about an inter-ADC plasma bank?

- If current AD Center subjects' plasma is banked over 12 months, this could create a repository with about 12,000 unique subjects.
- If prior AD Center subjects' plasma from autopsy-confirmed cases is banked, this could create a repository with > 4000 unique subjects
- NCRAD has capacity, expertise for training, standardization of banking, sample distribution for assay measurement
- Advisory committees for sample requests already exist
- Linkage to NACC, DNA and imaging data is feasible
- This would not impede each AD Center from conducting its own biomarker research