alzheimer's association®

Global Biomarkers Standardization Consortium (GBSC)
Teleconference Minutes
May 17, 2013

Participants:

Andreas Jeromin	Dean Hartley	Bob Umek
Paul Contestable	Meredith McNeil	Les Shaw
Guy Auclair	Randy Slemmens	Hugo Vanderstichele
Kina Hoglund	Holly Soares	Kendall Jensen
Moucun Yuan	June Kaplow	Kaj Blennow
Rand Jenkins	Erin Chambers	Diane Stephenson
Heather Snyder	Bob Dean	
Maria Carrillo	Hugh Salter	

1. **Update of progress each lab has made in the development of the 'substitute' or 'surrogate' matrix**

   Three of the laboratories provided an update on their progress to developing surrogate matrix:

   - Erin Chambers: tested calibration curves/ samples prepared in three formulations of artificial CSF surrogate matrices (as used by Waters, PPD and UPenn) verses standard addition in human CSF (similar to UGot); found there was small difference (6% overall) between the different conditions. This included multiple analysts, multiple days, frozen verses fresh and different instruments; the difference was consistently between 5-6% CV.
   - Rand Jenkins: completed a validation of the pentaplex method (AB1- 34, - 37, -38, -40, and -42); results were acceptable except for bench top thawed matrix stability in some human CSF lots. Apparent degradation was similar for all five amyloid analytes in affected lots (if instable, then all instable; if stable, then all stable).
   - Les Shaw: there has been lots of cross talk between each group, similar protocols although each lab uses a different surrogate matrix. Completed a detailed validation protocol with the final step a comparison of AD vs NC using the aliquots from the same AD and NC previously reported on in 2009. The ADs were pre-mortem CSFs collected by standard lp and were autopsy-based diagnoses and the NCs were age-matched living controls. Showed comparable performance to AlzBio3 and had an 89% accuracy (94% sensitivity, 85% specificity, 0.94 AUC) with Aβ42 assay using UPenn ADRC samples. Accuracy would be closer to 100% if young healthy NCs free of brain plaque burden are used as a control group. Not all immunoassays are compatible; may be possible to identify concordance at the fundamental level and provide a basis of harmonization of protocols.

2. **Update on the GBSC Round Robin program:**

   Les Shaw provided an update on the GBSC Round Robin program. To date, each laboratory received enough CSF to do three replications. The initial round had fairly consistent data across the four laboratories. These results showed that very good agreement was achieved across 4 labs each using a different surrogate matrix, 3 different mass spectrometry systems, and single-plex, triplex or pentaplex methods, and all used the same sample preparation protocol. Thus a good basis for the 4 labs to continue working collaboratively on the planned project to ultimately provide a reference material (CSF pool based) with Aβ1-42 values assigned by the 4 participating laboratories. More detailed update will be shared at the face-to-face meeting in Boston at AAIC.

3. **Update on the IFCC:**

   Kaj Blennow provided an update on the IFCC workgroup. They will be meeting May 20/21 in Milan to discuss next steps. An update will be given at the face-to-face meeting in Boston at AAIC. A brief summary of this update is included in attached PDF slides (1).

4. **Issues around AB stability:**

   Holly Soares and Rand Jenkins provided some updates regarding the issue of AB stability in CSF. The sample types evaluated by PPD to date have typically been obtained from commercial sources. Rand and team have noticed there may be a patient/donor age relationship. Samples from younger individuals appear to have much more protease activity and seem to be very unstable at room temperature; whereas, elderly samples appear much more stable. There was discussion around possible quality problems for commercial materials. The LC-MS lab group plans to investigate further using freshly collected and carefully handled clinical samples. This could be an important issue to continue to discuss, and an update will be provided for discussion during the face-to-face meeting.

5. **Highlights from recent Blood Biomarkers Meeting:**

   Andreas Jeromin provided update on the recent Blood Biomarker meeting, cosponsored by ADDF and the Alzheimer's Association in NYC in April. See the attached PDF summary slides (slides 2-4). Outcome from the discussion is that there is consensus around next steps. NOTE: Blood Based Biomarkers will convene as part of ISTAART professional interest area (PIA) during AAIC on Wednesday, July 17 at Westin Waterfront in the Otis Room.

6. **Future topics for discussion:**

   Topic suggestions for future discussion include strategies for assay harmonization/ globalization. The idea that as more analytical assays are developed, how will we globalize/ how will we compare. The idea of this discussion is to develop a framework or analytical strategy to align assays. There was a suggestion to define endpoints and what this type of discussion or effort would achieve; group agreed to revisit this idea on future teleconference.

   Also there was discussion around the need for consensus around first generation biomarkers. The group agreed this was a premature discussion and would be an on-going topic for consideration.

7. NEXT MEETING: Save the Date for AAIC Face-to-Face (Boston, MA) – July 13, 2013 at 5:30pm

IFCC Workgroup

- IFCC Workgroup – meeting in Milan, next week
  - Kaj Blennow, Chair
  - Henrik Zetterberg, Member
  - Anders Larsson, IFCC rep
  - Les Shaw, Member
  - Magdalena Korecka, Member
  - Ingid Zegers, Member
  - Piotr Lewczuk, Member
  - Rand Jenkins, Member
- Kaj – meeting with Gimpaolo Merlini, Italy from the IFCC Scientific Division
- Agenda for the CSF Workgroup includes updates/discussions:
  - How far we have come with the SRM mass spec methods
  - How far we have come with the reference materials
  - Round Robin Study
  - Commutability study
  - Next steps to establish the reference method(s)
  - Next steps to establish reference material

Developing Novel Blood-Based Biomarkers for Alzheimer's Disease Meeting

- Held on April 12th, 2013, in New York and co-sponsored by the Alzheimer's Association and Alzheimer's Drug Discovery Foundation (ADDF), co-chaired by Maria Carrillo, Howard Fillit and Mike Weiner
- Diverse and comprehensive overview of biomarker modalities and technologies with participation from academia and industry

Blood-Based Biomarkers for AD Meeting (continued)

- Emphasizing the importance of orthogonal technology assessment for biomarker verification, biological significance of identified biomarkers and clear identification of clinical utility/ “intended use”, for example identification of amyloid positive or at “risk” of becoming amyloid-positive subjects,
- Blood-based biomarker panel as “general” screening tool of the cognitively-impaired and patient enrichment tool for drug discovery trials
- Clinical utility/intended use influences study design or clinical sample selection

Blood-Based Biomarkers for AD Meeting (continued)

- Lessons learned from CSF biomarkers : need for standardization and agreement on minimal assay performance evaluation **and** data reported
- Most ß amyloids are for RUO only and fit-for-purpose for IVD/ pharmaceutical-use.
- Some emerging consensus of the potential of the 1-40/-12 ratio in blood as aid-in diagnostic biomarker
- Meeting Report in preparation
- The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) has established a Blood Based Biomarker Professional Interest Group to further promote synergy and collaboration and will convene at AAIC in Boston.