alzheimer's association®

the compassion to care, the leadership to conquer

Global Biomarkers Standardization Consortium (GBSC)

Webinar Minutes

March 3, 2017

Time: 10:00 am ET / 9:00 am CT / 7:00 am PT / 3:00 pm Europe

Co-Chairs: Henrik Zetterberg, Kaj Blennow, Charlotte Teunissen

Facilitator: Jim Hendrix, Alzheimer's Association

Welcome/Introduction - Jim Hendrix

Jim Hendrix welcomed all participants to the meeting and reviewed the agenda. Bob Umek of MSD was originally scheduled to speak but had a last minute scheduling conflict and was not able to participate in the meeting.

Update Abeta1-40 reference method application – Josef Pannee

Josef provided an update on progress with the development of the $A\beta_{1-40}$ reference method utilizing mass spectrometry (MS). The use of MS has several advantages:

1. MS allows for the use of stable isotopes as internal standards. These standards have the same amino acid composition as the analytes of interest only differing by the mass of the isotopes. In the case of $A\beta_{1-40}$, the internal standard has ^{15}N instead of ^{14}N so the standard has a slightly higher molecular weight. An antibody would not be able to detect the MW difference between the endogenous and the standard material.
2. No antibodies are needed for detection.
3. MS allows for different sample pre-treatments which might not be compatible with other methods. MS is highly specific in terms of the isolation of the analytes and fragments.

- The reference method for $A\beta_{1-40}$ will be used to determine the concentration of the peptide in CSF. Once the concentration of the analyte has been precisely determined, aliquots of the reference material can be sent to different labs to calibrate their instruments and harmonize the results.
- The pretreatment and sample preparation methods as well as the LC column are the same methods used in the $A\beta_{1-42}$ method. The method is not a high throughput but is useful for generating reference material.
- Results show that the method is very linear with 40,000 pg/mL the upper limit of quantification. The relative errors <15% with data collected daily over 5 days. The precision of the method has been evaluated at both high and low concentrations. The precision measured within the same day is 4.1% (high

conc.) and 3.4% (low conc.). Intermediate precision is around 6% as measured over 5 days in both concentrations.

- CSF sample stability of $A\beta_{1-40}$ was shown to be good for up to 5 freeze / thaw cycles. Different storage temperatures were evaluated ranging from -80^{o} C to +7^{o} C for 1 week. The temperature of -80^{o} C is preferred but -20^{o} C seems to be acceptable. These results are similar to $A\beta_{1-42}$ with a 15% +/- range.

Next Steps:

- They have not gone to multisite testing yet. Kaj reported that a ring trial is being planned and is hoped to be launched with 4-5 centers within 6 months.
- It was proposed that Ingrid Zegers could begin work on certified reference material of $A\beta_{1-40}$ reference material in addition to her efforts on $A\beta_{1-42}$.

Update of LP Video - Charlotte Teunissen

- The LP video developed by Charlotte and presented at the GBSC F2F meeting in Toronto has nearly been accepted by the on-line journal Alzheimer's &Dementia: Diagnosis, Assessment & Disease Monitoring. The video will be posted on-line with the publication of LP recommendations.
- A patient friendly video is also in development and should be ready to be shown at AAIC.

Company Briefs on novel assay development:

- **Quanterix - Andreas Jeromin**
  - Andreas described the Quanterix to aggressively pursue partnerships.
  - He presented the Quanterix pipeline of neurology biomarker assays for CSF, both currently available and those that are in development.
  - They are developing a 4-plex assay for TBI to be used in acute brain injury.
  - They are also developing a neurogranin and c-neurogranin assay for AD.
  - They are also working on blood biomarkers but currently don't have clinical data.
  - Andreas also proposed some future directions for the GBSC to consider.

- **ADx – Hugo Vanderstichele**
  - ADx is focused on generation of monoclonal antibodies for development of (IVD) assays on different technology platforms for proteins with a link to hallmarks/pharma targets of the disease.
  - They have antibodies available for Aβ (42-, 40-, 38-, 1-, x-), Tau (Tau, p-TAU181P, p-TAU231P), neurofilament ((p) NF-H), Synapse proteins (Neurogranin TruncP75, BACE-1, synuclein), and Apo lipoproteins (ApoE, ApoE4). Many other antibodies are in development, including efforts in blood.
  - Partnerships are done in function of the technology.

Update on AAIC 2017, London – Jim Hendrix

- There will be another Fluid Biomarkers Workshop at AAIC 2017 similar in scope to the Workshop held at AAIC 2016 in Toronto. In addition to Kaj and Henrik, the speakers will include Bob Dean – Lilly; Piotr Lewczuk – U. Erlangen-Nurnburg; Sid O'Bryant – U. North Texas; Markus Otto – U. of Ulm; Elaine Peskind – U. of Washington; Jonathan Schott – U. College London. The Workshop will be held on Friday, July 14 prior to the start of AAIC.
- The GBSC Face-To-Face Meeting will be held on July 15 and will be a similar format to past years. The agenda will be published several weeks prior to the meeting.

Next Meeting:

Face-to-Face on July 15, 2017 in London