I. Welcome

Christopher Weber

- Registration is open for the Tau 2022 Global Conference to be held virtually on February 22-23, 2022.
- AAIC will be held both in-person in San Diego, CA USA and online on July 31-August 4, 2022.
- The SABB manuscript has been published and is available online.

II. pTau Round Robin Updates

Henrik Zetterberg

- The round robin study will look at plasma p-tau181, p-tau217 and p-tau231 using all available p-tau methods that are sensitive enough to work on plasma. Sample collection is underway to obtain 40 paired large volume plasma and CSF samples (20 CSF AD biomarker-positive, 20 CSF AD biomarker-negative).
- This study will also include candidate reference materials consisting of plasma spiked at 3 different concentrations with either GSK3β Tau, or CSF.
- Strengths and slopes of correlations in CSF and plasma will be examined as well as fold change between AD and non-AD samples and candidate reference materials.
- The study received funding from the Alzheimer's Association and there are 12 confirmed labs and those interested in being involved can contact henrik.zetterberg@gu.se.

III. SABB Workgroup

Charlotte Teunissen

- This study investigates the effects of common pre-analytical sample handling variations on AD-related blood-based biomarker levels. The initial and SOP was published in Alzheimer's & Dementia.
- The follow on Pre-Analytics Next study is funded by the Alzheimer’s Association and will continue to refine the recommended workflow with the addition of p-tau assays, and the use of AD samples in addition to healthy controls to meet the pTau measurement ranges.
- The following areas will be the focus in this study: Extension and refining of samples and conditions, Effect of fasting status, Effect of long-term storage at -80°C, Effect of one-time freezing of samples compared to no freezing and short-term, intra-person variability.
- Please email Mariam Gouda (m.m.t.e.e.gouda@amsterdamumc.nl) with questions or interest in participating in sample analysis.
IV. Reference Materials Workgroup

- Since the last update to the GBSC membership, the Workgroup will use the CSF samples provided and tested in the AA QC program to analyze and monitor on performance of the EuroImmun, Fujirebio and Roche assays.
- The IFCC Working Group for Neuro biomarkers is a standardization initiative that came out of the Reference Materials Workgroup. This group met in December 2021 to update on four new reference materials that they are working on:
  - A commutability study between 8 existing NfL assays was done and the correlation between the assays was quite good. This work is ongoing as they found that NfL in plasma and serum did not respond the same.
  - Final analysis for a CSF Aβ 1-40 reference measurement procedure is ongoing. Once published the work will be re-submitted for review and certification.
  - Three reference measurement procedures for total tau in CSF are under investigation (at University of Pennsylvania, University of Gothenburg and LNE). A round robin did show some differences between methods that will need to be explained before moving forward.
  - A commutability study for tau immunoassays will be coming in the next few months and initial steps towards standardization for p-tau plasma have begun.

V. Prediction of future Alzheimer’s disease dementia using plasma phospho-tau combined with other accessible measures

- Several high impact studies published in 2020 regarding plasma p-tau (217, 181) showing an impressive fold change in AD dementia (increase 7-10 times compared to controls in p-tau 217). Further, a gradual increase in p-tau levels as individuals become closer to dementia stage, providing a potentially predictive value for AD dementia.
- In this study, the aim was to examine which accessible measures could be combined with plasma biomarkers for prediction of future AD dementia within 4 years in patients with SCD and MCI.
- The Swedish bioFINDER cohort (n=340) and ADNI participants (validation cohort; n=543) were used for this study. A combination of variables that provided a balance between model complexity and accuracy were selected. A combination of APOE and p-tau 217 plasma biomarkers with memory and execution provided an AUC of 0.91 for progression to AD dementia within 4 years. This combination also had an AUC of 0.94 for 6-year conversion and similar accuracies between SCD and MCI populations. There was no significant difference when using CSF instead of plasma biomarkers. This algorithm is available for research purposes (http://predictAD.app)
- The ADetect study (BioFINDER Primary Care) is an ongoing validation of the algorithm in primary care units. Pilot quality analyses have occurred and plasma sample analysis is ongoing.

VI. Detection of Alzheimer’s disease with amyloid PET/plasma

- For this study, 1,780 plasma samples representing 1,085 individuals was sent to C2N to run on their high precision mass spectrometry assay. Plasma samples were matched to CSF collected at the same visit that was analyzed on Lumipulse assays. Using the C2N assay, there was a high concordance of plasma Aβ42/Aβ40 with CSF Aβ42/Aβ40 (ROC AUC 0.88) and a high Amyloid Probability Score (APS; ROC AUC of 0.92). Similarly, there was high concordance with amyloid PET status (ROC AUC 0.82) and high APS (ROC AUC 0.92).
Recent work has focused on predicting symptom onset in sporadic AD with Amyloid PET. Amyloid burden as measured by PET can be used as a clock for preclinical AD. Jack, et al Neurology 2013 showed that the number of years accumulating amyloid can be estimated based on Amyloid PET score. Though individuals start to accumulate amyloid at different ages, the rate of amyloid accumulation is consistent. Can this amyloid clock be used to figure out when people are going to develop dementia?

- 180 individuals were used to align clinical trajectories to predict symptom onset. The study found in a sub-cohort that the age of symptom onset and tipping point of amyloid accumulation are highly correlated ($R^2=0.84$).
- The amyloid clock algorithm has been published and is purposefully flexible to allow for multiple types of biomarkers. The algorithm works best with highly sensitive, precise measures of brain amyloidosis that change consistently across individuals.

VII. Discussion

All Moderator: Henrik Zetterberg

- In response to a question on potential fluid biomarkers that could potentially be used as a ‘clock’, Dr. Schindler discussed that among the CSF biomarkers, according to the algorithm, Aβ 42/40 works well and p-tau works but does have some variability between individuals. Even among individuals who are Amyloid PET- exhibit quite a bit of variability in CSF biomarker levels. Perhaps tau PET would be good ‘clock’ for symptomatic AD.
- Dr. Schindler addressed a question on the idea that amyloid PET does not correlate well with cognitive change. In comparing those who are symptomatic and asymptomatic, amyloid PET is not a good predictor because amyloid plateaus and does not correlate well with symptoms. To this end, the clock stops working once there is symptom onset. Dr. Schindler also discussed the thought that amyloid plaques influence a cascade that in turn leads to cognitive symptoms rather than amyloid causing the symptoms themselves. This could explain cognitive symptoms continue to decline while plaques do not change.
- When asked about a ‘clock’ for symptom onset, Dr. Palmqvist explained that using CSF Aβ 42/40 does not seem to be a good predictor of onset of cognitive symptoms as it is more of a binary state (between abnormal and normal).
- In terms of lifestyle and AD, though certain lifestyle factors have potential to delay the onset of disease, the consistent trajectories seen across individuals of amyloid accumulation seem to reach a tipping point where accumulation is high enough that symptom onset cannot be modified. Dr. Schindler believes that there will be certain factors that modify the relationship between amyloid tipping point and symptom onset that are yet to be uncovered, but our own power is limited against this disease.
- There was a suggestion to discuss GFAP as an amyloid marker and potential standardized studies on future meetings.