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Plasma Biomarkers of AD Emerging as Essential Tools for Drug Development: An EU/US CTAD Task Force Report

*R.J. Bateman[1], K. Blennow[2], R. Doody[3], S. Hendrix[4], S. Lovestone[5], S. Salloway[6], R. Schindler[7], M. Weiner[8], H. Zetterberg[2,9,10], P. Aisen[11], B. Vellas[12] and the EU/US CTAD Task Force**

* EU/US/CTAD TASK FORCE: Bjorn Aaris Gronning (Valby); Paul Aisen (San Diego); John Alam (Cambridge); Sandrine Andrieu (Toulouse), Randall Bateman (St. Louis); Monika Baudler (Basel); Joanne Bell (Wilmington); Kaj Blennow (Mölndal); Claudine Brisard (Blue Bell); Samantha Budd-Haeberlein (USA); Szofia Bullain (Basel); Marc Cantillon (Princeton) ; Maria Carrillo (Chicago); Gemma Clark (Princeton); Jeffrey Cummings (Las Vegas); Daniel Di Giusto (Basel); Rachelle Doody (Basel); Sanjay Dubé (Aliso Viejo); Michael Egan (North Wales); Howard Fillit (New York); Adam Fleisher (Philadelphia); Mark Forman (North Wales); Cecilia Gabriel-Gracia (Suresnes); Serge Gauthier (Montreal); Jeffrey Harris (South San Francisco); Suzanne Hendrix (Salt Lake City); Dave Henley (Titusville); David Hewitt (Blue Bell); Mads Hvenekilde (Basel); Takeshi Iwatsubo (Tokyo); Keith Johnson (Boston); Michael Keeley (South San Francisco); Gene Kinney (South San Francisco); Ricky Kurzman (Woodcliffe Lake); Valérie Legrand (Nanterre); Stefan Lind (Valby); Hong Liu-Seifert (Indianapolis); Simon Lovestone (Oxford); Johan Luthman (Woodcliffe); Annette Merdes (Munich); David Michelson (Cambridge); Mark Mintun (Philadelphia); José Luis Molinuevo (Barcelona); Susanne Ostrowitzki (South San Francisco); Anton Porsteinsson (Rochester); Martin Rabe (Woodcliffe Lake); Rema Raman (San Diego); Elena Ratti (Cambridge); Larisa Reyderman (Woodcliffe Lake); Gary Romano (Titusville); Ivana Rubino (Cambridge); Marwan Noel Sabbagh (Las Vegas); Stephen Salloway (Providence); Cristina Sampaio (Princeton); Rachel Schindler (New York); Peter Schüler (Langen); Dennis Selkoe (Boston); Eric Siemers (New York); John Sims (Indianapolis); Heather Snyder (Chicago); Georgina Spence (Galashiels); Bjorn Sperling (Valby); Reisa Sperling (Boston); Andrew Stephens (Berlin); Joyce Suhy (Newark); Gilles Tamagnan (New Haven); Edmond Teng (South San Francisco); Gary Tong (Valby); Jan Torleif Pedersen (Valby); Jacques Touchon (Montpellier); Bruno Vellas (Toulouse); Vissia Viglietta (Cambridge) ; Christian Von Hehn (Cambridge); Philipp Von Rosenstiel (Cambridge) ; Michael Weiner (San Francisco); Kathleen Welsh-Bohmer (Durham); Iris Wiesel (Basel); Haichen Yang (North Wales); Wagner Zago (South San Francisco); Beyhan Zaim (Woodcliffe Lake); Henrik Zetterberg (Mölndal)

1. Washington University School of Medicine, St. Louis, MO, USA; 2. Clinical Neurochemistry Laboratory, University of Gothenburg, Sahlgrenska University Hospital, Mölndal, Sweden; 3. Genentech/Roche, Basel, Switzerland; 4. Pentara Corporation, Salt Lake City, UT, USA; 5. Janssen Pharmaceuticals, Oxford, UK; 6. The Warren Alpert Medical School of Brown University, Providence RI, USA; 7. Schindler Neuroscience Consulting Group, New York NY, USA; 8. University of California, San Francisco, USA; 9. Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, United Kingdom; 10. UK Dementia Research Institute at UCL, London, United Kingdom; 11. Alzheimer's Therapeutic Research Institute (ATRI), Keck School of Medicine, University of Southern California, San Diego, CA, USA; 12. Gerontopole, INSERM U1027, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, Toulouse, France

Corresponding Author: Randall J. Bateman, Washington University School of Medicine, St. Louis, MO, USA, batemanr@wustl.edu

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Abstract

There is an urgent need to develop reliable and sensitive blood-based biomarkers of Alzheimer's disease (AD) that can be used for screening and to increase the efficiency of clinical trials. The European Union-North American Clinical Trials in Alzheimer's Disease Task Force (EU/US CTAD Task Force) discussed the current status of blood-based AD biomarker development at its 2018 annual meeting in Barcelona, Spain. Recent improvements in technologies to assess plasma levels of amyloid beta indicate that a single sample of blood could provide an accurate estimate of brain amyloid positivity. Plasma neurofilament light protein appears to provide a good marker of neurodegeneration, although not specific for AD. Plasma tau shows some promising results but weak or no correlation with CSF tau levels, which may reflect rapid clearance of tau in the bloodstream. Blood samples analyzed using -omics and other approaches are also in development and may provide important insight into disease mechanisms as well as biomarker profiles for disease prediction. To advance these technologies, international multidisciplinary, multi-stakeholder collaboration is essential.

Key words: Blood test, biomarker, Alzheimer's disease, plasma.

Introduction

Biomarkers of Alzheimer's disease (AD) are essential tools in drug development to assess and monitor the pharmacodynamic effects of compounds, demonstrate target engagement, aid in the selection of participants for drug trials, help in dose selection, and assess the efficacy of therapies (1, 2). Clinically, they can provide crucial diagnostic information and, when an effective treatment becomes available, they may also be useful as tools to personalize interventions according to stage and patient characteristics (3).

In the recently published National Institutes on Aging and Alzheimer's Association (NIA-AA) Research Framework, which defines AD biologically through the use of biomarkers, recognized AD biomarkers included cerebrospinal fluid (CSF) measures of amyloid-beta (Aβ) and tau, positron emission tomography (PET) assessment of amyloid and tau, and two other imaging measures: anatomic magnetic resonance imaging (MRI) and fluorodeoxyglucose PET (FDG-PET, a measure of brain metabolism) (4).

Despite their enormous promise in advancing the development of early and preventive treatments, there are challenges to using CSF and imaging biomarkers in diverse geographies globally, including rural areas within developed countries, and lower- and middle-income countries which have limited resources to fund these procedures (5). Many efforts worldwide are attempting to meet this challenge by developing blood-based biomarkers that could limit the number of people who require more expensive testing and would

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enable screening, aid clinical diagnosis, and allow for repeated sampling as possible pharmacodynamic markers in clinical trials (6). Recognizing the urgency of advancing the development of blood-based biomarkers for AD, the European Union-North American Clinical Trials in Alzheimer's Disease Task Force (EU/US CTAD Task Force) addressed this issue at its 2018 meeting in Barcelona, Spain. The Task Force provided a forum for investigators from the pharmaceutical and diagnostics industries to join researchers from academia and regulatory agencies in efforts to build consensus on the path forward in developing and bringing to market blood-based biomarker tests.

Many challenges have been encountered in efforts to identify reliable, sensitive, and specific biomarkers of AD in plasma or serum. The close and continuous contact of the brain with the CSF results in relatively high levels of specific molecules associated with brain disease, while much lower amounts exist in the bloodstream (6). Further complicating the measurement of plasma-based AD biomarkers are high levels of other proteins from peripheral organs in the blood and the presence of proteases that may degrade brain proteins.

Nonetheless, in recent years there have been dramatic improvements in highly sensitive and specific immunoassays and mass spectrometry-based assays used to assess plasma levels of molecules that could serve as biomarkers of AD and other types of neurodegeneration (7). These advances have increased optimism in the field regarding the use of blood-based biomarker "profiles" for diagnosis, prognosis, and disease progression monitoring (8). Blood-based biomarkers are also seen as an essential part of efforts to develop precision medicine approaches for AD (9, 10).

Plasma amyloid beta

Longitudinal studies in individuals with autosomal dominant forms of AD have shown that CSF levels of Aβ42 decline 25 years before expected symptom onset; and that amyloid plaques are detectable by PET imaging 15 years before expected symptom onset (11-13). Early attempts to measure Aβ peptides in plasma indicated that these tests had limited value as tools for diagnosis or prognosis (5), but these studies were based on comparing plasma Aβ in clinically diagnosed AD patients and cognitively unimpaired elderly, which, given the uncertainty of AD diagnosis and overlap in pathology, limits the chance to identify minor changes in biomarker levels, as compared with using brain amyloid positivity as the reference standard. High variability was attributed, in part, to a lack of standardized protocols and methods. In addition, plasma Aβ originates not only in the brain but also in other organs and tissues (14).

Recent improvements in the technologies used to assess plasma levels of Aβ have shown more promising results. For example, investigators at Washington University have demonstrated that the ratio of plasma Aβ42/40 provides a sensitive and reliable measure of amyloid status that predicts future conversion to positive amyloid PET independent of the time of day and correlates with CSF Aβ42/40 (15). Other studies in European memory clinics (16), the Swedish BioFINDER cross-sectional and ESTHER longitudinal cohorts (17, 18), the Australian Imaging, Biomarker and Lifestyle Flagship Study (AIBL) cohort (13), and the National Center for Geriatrics and Gerontology (NCGG) Hospital in Japan (19, 20) have also shown good correlations with amyloid PET.

While further studies are needed to validate plasma Aβ42/40 in comparison to CSF or PET, these encouraging results suggest that plasma Aβ42/40 can be used with a high degree of sensitivity and specificity to detect AD amyloid plaques in individuals before symptom onset, as well as in symptomatic individuals with unclear clinical diagnoses. For clinical use, a single sample of blood could provide a highly accurate estimate of who is amyloid positive and thus support the diagnosis of AD (15 20); while in clinical trials, a blood Aβ42/40 test could be used as a prescreening tool to identify who has or is at risk for AD and facilitate efficient and cost-efficient recruitment of participants, thus accelerating trials, lowering costs, and speeding drug discovery (15, 20). For example, it is estimated that more than 50% of amyloid PET scans could be avoided with blood-based screening for Aβ pathology in the brain.

Plasma tau

In CSF, total tau (T-tau) and phosphorylated tau (P-tau) have been well validated as biomarkers reflecting AD pathology (12). In the A/T/N classification system, P-tau is taken to represent the presence of tau pathology, including neurofibrillary tangles, while CSF T-tau more likely represents neuronal injury or neurodegeneration (21), although recent data on the kinetics of tau suggests that in AD, CSF tau may reflect increased neuronal secretion of tau in response to Aβ pathology, rather than neurodegeneration (22).

Several studies have reported that T-tau levels are also elevated in the plasma of people with AD, although there is substantial overlap between diagnostic groups (cognitively normal, MCI, AD) (23, 24). T-tau in CSF and plasma is elevated in other disorders involving substantial brain injury, such as Creutzfeldt-Jacob disease (CJD) (25, 26), stroke (27), cardiac arrest (28), and traumatic brain injury (29). P-tau181 levels are also elevated in AD dementia and show better associations with both Aβ and tau PET, suggesting greater specificity for AD pathology (4).

In regards to P-tau, a semi-sensitive assay for tau phosphorylated at threonine 181 (similar to the most-employed CSF test) with electrochemiluminescence detection has been developed (4). Using this assay,

plasma P-tau concentration was higher in AD dementia patients than controls. Plasma P-tau concentration was associated with both Aβ and tau PET, which is a promising result in need of replication.

The expression of tau is brain-enriched, but tau is also detectable at both mRNA and protein level in salivary glands and kidney (http://www.proteinatlas.org/ENSG00000186868-MAPT/tissue). This is an important potential confounder that may help explain the weak correlation of plasma with CSF tau. The weak correlation may also reflect rapid clearance of tau in the bloodstream (30, 31).

Neurofilament light (NFL)

Neurofilament light chain (NFL) is an intraneuronal protein and a component of the axonal cytoskeleton; thus, its presence in the CSF indicates neuronal damage or degeneration (32). In AD, CSF NFL concentrations increase in early stages of disease and increase over time as cognition declines and atrophy and white matter changes in the brain increase (33).

In a recent study comparing three analytical platforms for assessing NFL in serum, the single-molecule array (Simoa) method is emerging as more sensitive than conventional enzyme-linked immunosorbent assay (ELISA) or electroluminescence (ECL) (34). A large study in the ADNI population using the Simoa assay showed that plasma NFL correlates with CSF NFL as an indicator of neurodegeneration across the AD continuum, has diagnostic accuracy for AD dementia similar to that of CSF biomarkers, and is associated with cognitive decline and neuroimaging biomarkers of AD (35, 36). Similarly, in a study conducted in Germany using the Simoa method, plasma NFL concentrations were significantly higher in people with MCI and AD dementia compared to normal controls even after correcting for age (37). Plasma NFL concentrations were also inversely correlated with Mini Mental Status Examination (MMSE) scores, which suggests that unlike other CSF biomarkers of AD, increased NFL may indicate ongoing neurodegeneration and functional decline (37). These studies suggest that NFL may have potential for prognosis and monitoring of disease progression. A small study in patients with familial AD suggested that plasma NFL increases about 5 years prior to estimate onset, suggesting its utility as a screening tool (38), and a larger study in the Dominantly Inherited Alzheimer Network (DIAN) demonstrated serum NFL correlates with neurodegeneration and clinical decline and longitudinal change identifies mutations carriers 16 years before symptom onset (39, 40).

However, NFL is not specific for AD, but a general neuronal injury biomarker [for review, see (40)]. Knowledge about the usefulness of NFL as a biomarker for neurodegeneration emerged in large part from studies in multiple sclerosis, and it has also been used to assess CNS injury in HIV infection, frontotemporal dementia, amyotrophic lateral sclerosis (ALS), CJD, Parkinson's disease (PD) and other CNS disorders (35, 38, 41). One study in people with HIV infection suggested that plasma NFL may be useful to monitor downstream drug effects on the intensity of neurodegeneration (42). In patients with CJD, elevations of both tau and NFL in serum at baseline predict steeper increases over time (26). Studies in patients with multiple sclerosis also suggest a role for NFL as an indicator of treatment effectiveness (43, 44).

Differences in the preanalytic handling of serum samples was shown to significantly affect the measurement of NFL, pointing to the importance of standardized protocols for sample collection, storage, and transport (37).

Omics and other approaches

Blood samples are also useful for obtaining high-dimensional biomarker profiles using a combination of omics approaches, including genomics, transcriptomics, metabolomics, lipidomics, and proteomics. Advances in mass spectrometry have even enabled the molecular characterization of biological processes from single cells (45). These approaches enable the discovery of unknown unknowns and may also provide insight into molecular mechanisms that underlie diseases such as AD.

Different approaches may be used to harness the power of these technologies for omics studies (7). However, the choice of method may have substantial implications on what is found, and thus interpretation of omics studies must take into account the approach used. For example, Hye and colleagues used mass spectrometry and 2-D gel electrophoresis in a case-control approach comparing the plasma proteomes from elderly people with AD and normal elders (46). They found an elevation in complement factor H, and this finding was subsequently replicated in multiple studies. Using the same technology with an endophenotype approach in people with AD, where discovery was predicated on either hippocampal atrophy or speed of progression, these same investigators showed that elevations of plasma clusterin – an amyloid chaperone - was associated with both endophenotypes (47). This finding has also been widely replicated.

Now, the European Medical Information Framework – Multimodal Biomarker Discovery (EMIF-MBD) project is using an endophenotype approach to identify biomarkers (including plasma biomarkers) of pre-dementia AD. The endophenotypes selected for this multicenter study include amyloid positivity assessed by PET or CSF, MCI conversion to AD, and the rate of cognitive decline. First, they analyzed results from 10 years of studies using multiple omics approaches, which allowed them to identify 7 proteins predictive of amyloid positivity. Next, they used an aptamer capture array provided by SomaLogic to measure 4,600 plasma proteins simultaneously. A machine learning approach revealed

46 features (44 proteins plus ApoE status and age) that predicted amyloid positivity with an area under the curve (AUC) 0f .78, which indicates fair accuracy. Even in people with no signs of AD, the 46 features predicted preclinical AD with an AUC of .68, which is statistically significant. Although still in the exploratory phase and with nowhere near the accuracy of a well-targeted protein study such as CSF Aβ, tau, or plasma NFL, this approach may with further refinement enable screening of large populations to identify potential candidates for clinical studies targeting preclinical AD.

Conclusions

Studies completed in the last few years have produced substantial data supporting the further development and potential uses of blood-based biomarkers. Multiple groups have shown that plasma Aβ studies may be useful to predict brain amyloid status. If these results are confirmed, it is possible that a blood-based test of Aβ may ultimately enable screening of large populations to identify who is at risk for AD and start intervention before memory loss and brain damage. Yet while plasma Aβ assays using both mass spectrometry and immunoassay methods have shown promise in predicting brain amyloid levels measured by PET scanning, these studies need to be replicated in different populations to ensure that plasma assay methods are truly generalizable. Most studies have been conducted in patients without comorbidities, which might affect the ability of plasma Aβ to predict brain amyloid levels. In addition, large scale, longitudinal validation studies will be needed, and the usefulness of plasma Aβ markers to monitor disease progression in clinical trials will need to be determined (20). To help facilitate such studies, ADNI has huge numbers of coded and blinded plasma and CSF samples available upon request.

Plasma NFL has also been shown to be indicative of neurodegeneration in many populations, including in the DIAN population to measure progression, onset, and decline; as well as in sporadic AD. Current data are less supportive of the use of plasma tau as a useful biomarker for AD, at least using the current assay formats, which are based on N-terminal and mid-domain tau antibodies, although this remains a very active area of investigation. Proteomics appear to be useful primarily to search and find targets but may not be useful as inclusion criteria or outcome measures. Many other biomarkers are also being investigated, but thus far none has risen to the standards set by PET scans and CSF measures.

To advance development of plasma-based biomarkers for drug development and clinical use, much more work is also needed to develop the best methods for plasma collection, shipping and storage, and to determine the optimum approach to use all data – including genetic factors such as APOE, demographics such as age, and other analyses – to identify individuals at risk for development of AD. The Task Force concluded that global standardization and harmonization of preanalytical and analytical protocols will be necessary, which will require international multi-stakeholder collaboration (8, 48). Multiple public and private groups are now undertaking the important task of standardization and commercialization of plasma Aβ biomarkers. Round robins are planned in 2019 for plasma Aβ and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has recently initiated a project to create reference materials and a reference method for plasma and serum NfL.

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