Alzheimer's & Dementia 13 (2017) 45-58

Alzheimer's & Dementia

Perspective

Blood-based biomarkers in Alzheimer disease: Current state of the science and a novel collaborative paradigm for advancing from discovery to clinic

Sid E. O'Bryant[a,*], Michelle M. Mielke[b,c], Robert A. Rissman[d], Simone Lista[e,f], Hugo Vanderstichele[g], Henrik Zetterberg[h,i], Piotr Lewczuk[j,k], Holly Posner[l], James Hall[a], Leigh Johnson[a], Yiu-Lian Fong[m], Johan Luthman[n], Andreas Jeromin[o], Richard Batrla-Utermann[p], Alcibiades Villarreal[q], Gabrielle Britton[q], Peter J. Snyder[r], Kim Henriksen[s], Paula Grammas[t], Veer Gupta[u], Ralph Martins[u], Harald Hampel[e,f], and the Biofluid Based Biomarker Professional Interest Area

[a]*Institute for Healthy Aging, University of North Texas Health Science Center, Fort Worth, TX, USA*
[b]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*
[c]*Department of Health Science Research, Mayo Clinic, Rochester, MN, USA*
[d]*Alzheimer's Disease Cooperative Study, Department of Neurosciences, UCSD School of Medicine, La Jolla, CA, USA*
[e]*AXA Research Fund and UPMC Chair, Paris, France*
[f]*Department de Neurologie, Institut de la Memorie et de la Maladie d'Alzheimer (IM2A) et Institut du Cerveau et du la Moelle epiniere (ICM), Hospital de la Pitie-Salpetriere, Sorbonne Universites, Universite Pierre et Marie Curie, Paris, France*
[g]*ADx NeuroSciences NV, Ghent, Belgium*
[h]*Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gotenburg, Molndal, Sweden*
[i]*UCL Institute of Neurology, London, UK*
[j]*Department of Psychiatry and Psychotherapy, Universitätsklinikum Erlangen and Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany*
[k]*Department of Neurodegeneration Diagnostics, Medical University of Bialystok, Bialystok, Poland*
[l]*Pfizer, Inc., New York, USA*
[m]*Johnson & Johnson, London Innovation Center, London, UK*
[n]*Neuroscience Clinical Development, Clinical Neuroscience Eisai, Woodcliff Lake, NJ, USA*
[o]*Quanterix Corporation, Lexington, MA, USA*
[p]*Roche Diagnostics International Ltd., Rotkreuz, Switzerland*
[q]*Centro de Neurociencias y Unidad de Investigacion Clinica, Instituto de Investigaciones Cientificas y Servicios de Alta Tecnologia (INDICASAT AIP), Ciudad del Saber, Panama, Panama*
[r]*Department of Neurology, Rhode Island Hospital and Alpert Medical School of Brown University, Providence, RI, USA*
[s]*Neurodegenerative Diseases, Nordic Bioscience Biomarkers and Research, Herlev, Denmark*
[t]*George and Anne Ryan Institute for Neuroscience, University of Rhode Island, RI, USA*
[u]*Faculty of Health, Engineering and Sciences, Center of Excellence for Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, WA, Australia*

Abstract The last decade has seen a substantial increase in research focused on the identification of blood-based biomarkers that have utility in Alzheimer's disease (AD). Blood-based biomarkers have significant advantages of being time- and cost-efficient as well as reduced invasiveness and increased patient acceptance. Despite these advantages and increased research efforts, the field has been hampered by lack of reproducibility and an unclear path for moving basic discovery toward clinical utilization. Here we reviewed the recent literature on blood-based biomarkers in AD to provide a current state of the art. In addition, a collaborative model is proposed that leverages academic and industry strengths to facilitate the field in moving past discovery only work and toward clinical

*Corresponding author. Tel.: +1-817-735-2963; Fax: +1-817-735-0628.
E-mail address: sid.obryant@unthsc.edu

http://dx.doi.org/10.1016/j.jalz.2016.09.014

use. Key resources are provided. This new public-private partnership model is intended to circumvent the traditional handoff model and provide a clear and useful paradigm for the advancement of biomarker science in AD and other neurodegenerative diseases.

Keywords: Alzheimer's disease; Biomarker; Blood; Diagnosis; Cerebrospinal fluid; Imaging; Diagnosis; Context of use

1. Current state of the science

There has been a significant amount of research focused on the identification of blood-based biomarkers that have utility in Alzheimer's disease (AD) or other neurologic disorders [1–4]. Blood-based biomarkers have important advantages of being cost- and time-effective, compared with the collection of cerebrospinal fluid (CSF) or neuroimaging, while simultaneously being feasible at the population level [4,5]. Therefore, blood-based biomarkers can serve as the first step in a multistage process [2,5,6] similar to the procedures used in other disease states (e.g., cancer, cardiovascular disease, and infectious disease). Given the insidious nature of AD, this multistep approach can aid in the detection of disease as early as possible. Acknowledging that peripheral biomarkers (blood or otherwise) of brain disorders are more difficult to identify and lockdown, there are many potential contexts of use (COUs) for blood-based AD biomarkers, including, but not limited to, primary care screening, diagnostics, predictive risk (i.e., risk for incident AD, risk for progression from mild cognitive impairment [MCI] to AD), disease monitoring, stratification into clinical trials, and pharmacodynamic or treatment response monitoring (positive or adverse). Multiple international working groups have provided overviews of the landscape, potential uses, and challenges for blood-based AD biomarkers [1,2,7]. Because those reviews/perspectives were published, there has been significant movement in the field, including a recent special issue of Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring focused specifically on advances in blood-based biomarkers of AD [3]. Here, we discuss additional recent advances in the field.

1.1. Methodological considerations

One key advancement produced by the international professional interest area on blood-based biomarkers was the generation of the first-ever guidelines for preanalytic processing of specimens [8]. This initial effort was the result of a tremendous work spanning industry and academic investigators from across the globe. It provided a basic set of preanalytic processing variables to be followed (and refined) and a minimum set of information that should be provided within publications to allow for appropriately designed cross-validation efforts. More recently, this workgroup published data comparing biomarkers from the same blood draw (person, date, and time) across assay platforms and blood fraction (serum and plasma) [9]. Results indicated that individual markers, although often statistically significantly correlated, may share minimal variance across the platform or tissue indicating that direct comparisons are regularly not possible. Differences in the concentration for specific analytes on different technological platforms can be because of a number of things including (1) calibrators, (2) neat biological samples or different dilutions may not have the same immunoreactivity with the antibodies included, (3) differences in antibodies, and (4) differences in overall sensitivity and reliability of the instrument. In addition, the use of different assay design can impact findings [10]. Together, this work clearly demonstrated methodological factors that must be considered when comparing across studies, cohorts, and biorepositories. Andreasson et al. [11] provided an update and overview of ultrasensitive technologies to measure AD-related biomarkers in blood and CSF. Although still early in the process, these novel assay technologies have the capacity to detect very low levels of markers that may be of significant advantage when seeking to move from research grade to "pharmaceutical-grade" kits in future attempts to take research use only methods toward laboratory developed tests (LDTs) and in vitro diagnostics (IVDs) [12,13]. As evident from the continued progress of the Global Biomarkers Standardization Consortium of CSF biomarkers, the blood-based biomarker field will need to address additional methodological barriers to produce clinically useful and applicable biomarkers.

1.2. Blood biomarkers of AD risk

An important potential COU for blood-based AD biomarker science is the identification of individuals at greatest risk, which can take several forms: (1) risk of incident cognitive impairment and AD, (2) risk of progressing from MCI to AD, and (3) risk for rapid progression within AD. Biomarkers related to these specific COUs have tremendous potential for clinical intervention trials aimed at preventing AD, halting progression from MCI, and slowing progression among patients with manifest AD. Enrichment of these specific subjects into trials has the benefit of reducing the diluting effect of enrolling those subjects not likely to progress. Indeed, an important potential of AD blood biomarkers could be to increase the likelihood of subjects being positive on more expensive (e.g., positron emission tomography [PET] imaging) or invasive (lumbar