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Editorial

Introduction to special issue on Advances in blood-based biomarkers of Alzheimer's disease

Blood-based biomarkers related to Alzheimer's disease (AD) have significant potential to advance both the diagnostic and therapeutic processes and procedures related to this devastating disease. In light of this potential, a significant amount of work has been conducted in recent years. In fact a PubMed search (6/2016) using the terms "blood based biomarkers AND Alzheimer's disease" yielded 474 hits with an overwhelming 48% of these articles being published from 2013–2016. This special issue of *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* on Advances in blood-based biomarkers of Alzheimer's disease is intended to provide a broad-based snapshot regarding several aspects of the space. This special issue contains advancements in the space spanning newer technologies (e.g., exosome biomarkers) as well as progression in markers that have been more extensively studied (e.g., autoantibodies, apoJ). The special issue is broken down by categories that broadly correspond to a specific putative context of use (COU).

Blood-based biomarkers offer an excellent complementary information to well-established cerebrospinal fluid (CSF), imaging (MRI, PET, other) biomarkers for the establishment of multistage processes for diagnostic and therapeutic strategies, such as what has been of tremendous utility in other areas of medicine (e.g., cancer [1]). The intention of these blood-based biomarkers is to increase access to CSF, imaging, and other biomarker modalities as well as to provide novel information to enhance the scientific understanding of the complete biological dysfunction associated with AD and other neurological diseases.

This special issue has been conceptually divided into broadly defined categories beginning with methodological considerations, to a set of possible context of uses (COUs) and ends with a study highlighting ethnic considerations in this space of scientific investigation.

1. Methodological considerations

This issue begins with two manuscripts intended to provide an update and overview of novel methods as well as highlight areas of concern when comparing across platforms and tissue type. First, an overview of advancements in the area of novel ultrasensitive methods for detecting blood-based biomarkers is provided by Andreasson, Blennow, and Zetterberg [2]. This review describes single-molecule array (Sioma), single-molecule counting, proximity extension assay and MagQu platforms as well as provides examples of recent relevant publications using these methods in both the blood and CSF space. Next, O'Bryant et al. [3] conduct a follow-up study to the 2015 guidelines [4] project that directly compares biomarker assay results across different assay technologies as well as serum and plasma. This work highlights the concerns when making cross-study comparisons and generalizations when findings are based on serum versus plasma as well as different assay platforms or technologies. This work is directly relevant to the movement from biomarker discovery to locked-down methods for biomarker validation.

2. Understanding immune dysfunction in Alzheimer's disease

Next, a series of studies highlight the importance of immune dysregulation in AD. First, Guedes et al. examine blood-derived monocytes (BDMs) and monocyte-derived macrophages (MDMs) isolated from AD, mild cognitive impairment (MCI), and control subjects. These authors found that chemokine/chemokine receptor (CCL2/CCR2) axis and MDM-mediated phagocytosis of Aβ were altered. They also found alterations in triggering receptor expressed on myeloid cells 2 (TREM2) and expression of miRNAs. Together, this work provides additional support for dysfunction of the immune system in AD pathogenesis and may point toward a specific endophenotype of inflammatory dysfunction in AD. Next, Tampubolon [5] analyzed data from the English Longitudinal Study of Ageing, a nationally representative study of the older English population to determine if inflammation (CRP, fibrinogen) was associated with worsening of episodic memory. Multiple waves of data were analyzed, and results suggested that elevated inflammation was associated with poorer episodic memory, particularly among the oldest old (i.e., ≥75 years). Together, these studies continue to point toward the importance of immune dysregulation in AD and cognitive aging; however, they do

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not address whether this link is for a specific subset of individuals only or this effect is associated with a third variable of general worsening of health that is also related to cognitive aging. Despite this, this work supports the need for additional work in this area. It remains to be determined whether this line of work supports a potential COU of identification of specific patients most likely to benefit from targeted anti-inflammatory interventions.

3. Predicting conversion from MCI to AD or risk for incident AD or dementia

An important potential COU for AD biomarker science is the identification of risk for progression (e.g., progression from MCI to AD, risk for incident AD/dementia from normal cognition). Such biomarkers can potentially be useful for clinical trial design targeting specific populations with increased risk for imminent cognitive decline. Enrichment of these specific subjects into trials has the benefit of reducing the diluting effect of enrolling those subjects not likely to progress. This topic area begins with work by Winston and colleagues [6] examining the utility of neuronally derived exosomes (NDEs) in predicting conversion from MCI to dementia. Alterations in plasma NDE levels of p-tau, Aβ1-42, NRGN, and REST were found among AD and MCI cases that converted to AD when compared to stable MCI cases and normal controls. Additionally, when injected into the right hippocampus of wild-type (C57/BL6) mice, NDEs from MCI cases that converted to AD increased p-tau when compared to NDEs from normal controls and stable MCI cases. Next, Weinstein et al. [7] examine plasma clusterin from 1532 nondemented subjects of the Framingham Study Offspring cohort to determine how this putative biomarker predicts incident dementia and stroke. Among older adults, plasma clusterin was associated with significantly increased risk for dementia; however, plasma clusterin was related to a reduced risk of dementia and stroke among younger participants suggesting an age-effect when interpreting the predictive utility of this putative biomarker. These studies clearly support the potential use of blood-based biomarkers when considering the COU of predicting future risk. A next step would be to explicitly test this specific COU with these markers either in baseline samples from independent prospective studies (with direct application of specific cut-scores) or within new prospectively designed studies.

4. Identifying endophentoypes within AD

Recent work has begun to study the link between biomarker levels and specific clinically relevant outcomes (e.g., memory scores, structural MRI outcomes) [8]. In this issue, Bettcher et al. [9] study MCP-1 and eotaxin-1 levels among controls, MCI, and AD cases in relation to memory abilities as well as medial temporal lobe volumes. When both chemokines were elevated, memory scores were specifically poorer. Additionally, exploratory analyses suggested that these chemokine elevations were also associated with smaller left-medial temporal lobe volumes. Whether this work has potential to lead to a COU of identification of memory impairment remains unanswered; however, this work is illustrative of how specific clinically relevant outcomes (i.e., memory capacity, structural MRI biomarkers) can be used as outcome variables in blood-based biomarker work in addition to dichotomous outcomes of disease presence.

5. Blood biomarkers related to AD presence

The most studied COU for blood-based biomarkers in the AD space has been related to AD presence. In this issue, a series of publications are included that examine a broad range of biomarkers in relation to AD presence. First, Gupta et al. [10] examine baseline and 18-month follow-up plasma apoJ (aka clusterin) concentrations in the AIBL cohort. The authors found that apoJ levels were significantly higher among MCI and AD cases at both time points and were also correlated with standardized uptake value ratio PET amyloid levels and hippocampal volume. Next, DeMarshall et al. [11] find excellent accuracy in separating MCI from normal controls as well as AD using autoantibodies. Savica et al. [12] analyze plasma sphingolipid changes among autopsy-confirmed AD, Lewy Body Dementia (DLB), and control subjects. The authors found significant plasma ceramide alterations and monohexosylceramide alterations between dementia cases (AD and DLB) and controls suggesting that these biomarkers may have utility in identifying possible AD and/or DLB pathology. Next, Li et al. [13] analyze data from the Atherosclerosis Risk In Communities study in an attempt to cross-validate the cross-sectional detection of AD with plasma phospholipids found in a recently highly publicized article [14]. Among the 10 previously identified phospholipids altered in dementia, only alteration in PC aa C36:6 was associated with dementia prevalence in this independent cohort. The combined model of all phospholipids was not able to accurately classify dementia cases in this cross-sectional analysis. Finally, O'Bryant et al. [15] created the locked-down referent cohort for an AD blood screen intended for primary care use and demonstrated excellent positive and negative predictive values when compared to existing screening tests.

6. Considering ethnicity in AD blood biomarkers

Finally, Royall and Palmer [16] continue their efforts in understanding blood biomarkers related to their previously identified latent dementia phenotype "δ". Work from this collaborative group has previously demonstrated alterations in serum levels of thrombopoetin (THPO), which these authors found was significantly an ethnically equivalent homolog of δ but only for non-Hispanic whites. Although THPO has not been consistently related to AD status across studies or assay platforms, this work clearly demonstrates the

significant need to examine the impact of ethnicity on AD biomarkers, as has been shown the case for many biomarkers in other diseases (e.g., ethnic adjustments for eGFR levels). To move from discovery to clinic, the study of ethnic impact on biomarkers is a necessary and important step, which this work further supports.

When taken as a whole, this special issue reflects several significant advancements for the field of AD blood-based biomarkers. First, this work highlights novel techniques and methodological considerations of importance for progress of the field. When combined with the 2015 guidelines for pre-analytic processing, this work can greatly facilitate the identification of novel biomarkers as well as assist in moving from biomarker discovery to locked-down validation. Additionally contained within this special issue are advancements of newer technologies (ultrasensitive technologies, exosomes) as well as continued movement on previously studied methods and markers (autoantibodies, blood-based algorithm for AD screening). This special issue is intended to aid the reader in gaining an understanding of recent advancements in the space of AD blood-based biomarkers. The special issue reflects a substantial effort by DADM editor, Peter Snyder, as well as members of the Blood-Based Biomarker Professional Interest Area of the International Society to Advance Alzheimer's Research and Treatment and would not have been possible without their support.

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