Editorial

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Turning Point towards Blood Biomarker-Guided Targeted Therapy for Precision Medicine in Alzheimer's Disease

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Biological markers play an increasingly important role in several contexts-of-use (COU) which go beyond consolidated outcome, such as in screening and diagnostic purposes, and include predictive responses, prognostic information (i.e., the likely outcome of an untreated disease), and pure exploratory data to address unresolved scientific questions and discover novel surrogate endpoints (1).

Recently, a novel integrated partnership model to advance the field of biomarker development from discovery to clinical translation has been proposed. The Food and Drug Administration (FDA)/NIH Biomarker Working Group (FDA-NIH Biomarker Working Group) released the Biomarkers, EndpointS, and other Tools (BEST) Resource to define several terms and concepts, with special reference to analytical validation, candidate surrogate endpoints, clinical benefits, and for the term "biomarker" itself. A biomarker is defined as a "characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or response to an exposure or intervention, including therapeutic interventions. A biomarker is not an assessment of how an individual feels, functions, or survives". Accordingly, the following distinct biomarker categories have been recommended: I) susceptibility/risk biomarkers, II) diagnostic biomarkers, III) monitoring biomarkers, IV) prognostic biomarkers, V) predictive biomarkers, VI) pharmacodynamic/response biomarkers, and VII) safety biomarkers (2).

In pharmaceutical companies, academic settings and biotech laboratories, biomarkers have been increasingly introduced to re-engineer drug development, ultimately enabling a better standardization and facilitating quality control (1).

Indeed, biomarkers serve as decisive tools to improve and inform all phases of drug Research & Development programs, including the implementation of diagnostic assays – such as microarrays for gene fingerprinting – or therapeutic compounds from the proof-of pharmacology (PoP, see below) to the identification process of true biological outcomes and until regulatory agency authorization. This development is facilitated by advances in the understanding of the molecular pathophysiology of diseases, along with progress in high-throughput and high-content technologies combined with powerful computational and statistical modeling (1, 3, 4).

The confirmation that the tested compound is capable of hitting the target is the major challenge associated with stepwise drug development. In addition, a correct quantification of the magnitude of active molecule-target engagement is paramount. Valid biomarkers should reflect all of the three standardized key steps within PoP investigations for putative disease-modifying therapies: I) alteration of the pathophysiological mechanism(s) following the active molecule-target interaction (i.e., target engagement); II) modifications of disease pathophysiology towards the physiological condition; III) improvement of clinical course upon target engagement and pathomechanistic alterations (1, 3, 4).

Specifically: I) pharmacodynamic biomarkers should demonstrate target engagement, dose selection, and treatment response; II) pharmacokinetic biomarkers are aimed at measuring drug absorption, distribution, metabolization, and excretion; and III) toxicity biomarkers should chart and predict adverse events (1, 3, 4).

Biomarkers assist enhanced trial design and early drug development by optimizing surrogate endpoints thus accelerating regulatory decision-making, with respect to "go/no-go" decisions, prioritization of compounds within a company pipeline, and drug repositioning. Biomarkers may significantly accelerate the overall drug development process (1, 3, 4). Biomarkers that are part of drug development programs have commercial value for several reasons. For example, biomarkers reflecting the magnitude of target engagement may serve as diagnostic tools for early detection of a given disease (provided that

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the target is differentially expressed between health and disease) (5, 6). Conversely, biomarkers that quantitatively reflect mechanistic effects can be validated as diagnostic tests to inform treatment modalities, from exploratory biomarkers to surrogate biomarkers (5, 6). There is a multi-phase program for the biomarker development process, encompassing a structured cycle of cross-validation steps and COU identification, from academic biomarker discovery to pharmaceutical industry validation. Thus, it has become clear that the integration of biomarker data in clinical trials can simultaneously address a broad range of crucial questions related to several COU, accelerating the duration of a drug trial (1, 5, 6).

Within the multiple clinical COU, biomarkers are increasingly reaching and transforming clinical practice, since they can support the identification of individuals likely to respond to a given drug (predictive outcome measures) and likely to experience adverse drug effects (safety outcome measures) (1, 5, 6). In these two COU, biomarkers can be used to disclose predictive molecular signatures mapping out both disease progression and rate of therapeutic response. In the areas of oncology and immunology, biomarker-guided patient selection and stratification are already validated clinical practices where the individual molecular profiling allows the optimization of targeted treatments (1, 5, 6).

Indeed, oncologists and immunologists already successfully treat several phenotypes of cancer with differential cytology, histology, topography, and clinical manifestation – with the same drugs targeting shared molecular pathways (7).

Unfortunately, the clear-cut distinction among biomarkers proposed by the BEST Resource is challenging to be implemented across the biomarker spectrum in AD.

Precise discrimination among different biomarker categories, however, is essential to develop targeted treatments and prevention strategies. There is an urgent need for biomarker-guided investigations in early disease stages, such as in asymptomatic individuals at risk for AD.

Cerebrospinal fluid (CSF) and neuroimaging (positron emission tomography [PET] and/or magnetic resonance imaging [MRI]) biomarkers of AD are primarily used in academic expert clinical research centers and not accessible and feasible for global primary care centers. Consequently, increasing efforts have been devoted to the identification and validation of innovative blood/plasma-based biomarkers that reflect primary pathophysiological processes associated with neurodegenerative diseases (ND) including AD. Different biomolecules – including proteins/peptides, nucleic acids, lipids, and other metabolites – can be quantified in plasma/serum or blood cellular compartments (red blood cells, leukocytes, and platelets) (1, 4). Blood-based biomarkers offer significant advantages over traditional CSF and neuroimaging biomarkers, including minimal invasiveness, increased accessibility, decreased direct and indirect costs, as well as reduced time and resource utilization (1, 4). Ultimately, the advantages associated with the implementation of blood-based biomarkers would be invaluable for a number of different COU.

Blood-based AD biomarkers are characterized by a degree of heterogeneity and influencing factors (including varying ranges of different protein concentrations, isoforms, post-translational modifications, and numerous metabolic products) which reflect the inherent complexity of the blood (1, 4, 6). Accordingly, a number of different molecular systems and pathways can be investigated through blood-based assays. Its close proximity and interaction with all different body tissues and organs makes it a reliable holistic source of objective biological information for a variety of physiological and pathophysiological clinical applications. The blood reflects direct and indirect alterations originating in the central nervous system, particularly when the blood-brain or blood-cerebrospinal fluid barriers are compromised (8–10). Blood-based biomarker candidates have excellent potential to be routinely and widely analyzed both in a primary care setting and in the community. Repeated blood sampling is feasible even in elderly subjects and frail patients. There is increasing optimism that blood-based tests for AD diagnosis will soon be widely available, inexpensive and easy-to-implement (4, 11).

Blood (plasma/serum) is undoubtedly the most relevant biological matrix for use in exploratory proteomic studies (4, 11). Alterations of protein blood composition are frequently the result of pathophysiological mechanisms and external stimuli. From a methodological standpoint, proteomics is one of the founding methods of the systems biology paradigm and allows the systems-level depiction of all proteins in a living organism (based on sequence, localization, abundance, post-translational modifications, and biomolecular interactions) (4, 11). However, due to the complexity of the cellular proteome and the low abundance of many physiologically relevant proteins, proteomics presents substantial challenges. As the aberrant molecular pathways typical for the AD brain are well interconnected, an exploratory, global, integrative approach is crucial to elucidate the etiology and pathophysiology of AD at a complex network level. Evolving blood biomarker panels appear most suitable to gain a system-wide perspective of AD across multilevel systems from subcellular detrimental signals to related abnormal neural network oscillations (4, 11).

Traditionally, the molecular basis of AD has been explored through an a priori approach focused on biological candidates (informed by currently prevailing pathogenetic hypotheses) (4, 11). This mono-mechanistic approach fails to capture the full pathophysiological complexity of AD across stages from upstream

to downstream mechanism and does not support complementary therapeutic advances (4, 11). Unbiased, exploratory systems biology has been introduced as a means to circumvent these hypothesis-driven theoretical limitations. An integrative, interdisciplinary framework was achieved through the development of theoretically unbiased quantitative high-throughput "omics" platforms – including genomics/epigenomics, transcriptomics, miRNomics, proteomics/peptidomics, and metabolomics/lipidomics (4, 11). These exploratory methods can be applied at multiple system levels, from subcellular compartments to the whole organism. As a result, a comprehensive and accurate profile of the complex dynamics of molecular systems can be obtained. This prerequisite to systems biology is the integrative analysis, harmonization, and validation of multimodal big data generating novel, unbiased hypotheses on the pathophysiology of the disease (4, 11).

The promising field of discovery and development of biomarkers for AD in peripheral blood/plasma is steadily advancing. Numerous studies investigated the existence of a characteristic molecular "AD profile" (or molecular "signature"), i.e., a specific set of blood (plasma/serum) molecules that may be diagnostically useful for the entirety of diagnosed AD patients. Since most of AD is a complex polygenic disease, with differential profiles and magnitudes of expression of diverging and converging cellular and molecular pathways across affected individuals at various time points, this hope for a magic unifying "signature for all" maybe as disappointing as the quest for a "magic-bullet" therapy for all at all stages (4, 11, 12).

However, there is growing optimism regarding the use of blood-based biomarkers in AD reflecting various relevant and common pathophysiological mechanisms, supported by increasing evidence that core AD markers – including amyloid beta (Aβ) peptides and proteins associated with inflammatory pathways – are not brain-specific but can be detected in the blood and track the progression of pathophysiology (e.g. amyloidogenesis, neurodegeneration and/or inflammation) (4, 11).

There will not be a single blood-based diagnostic or prognostic biomarker. However, a systems-based "combinatorial strategy", based on a multi-staged diagnostic process and the combined assessment of blood- and non-blood-based biomarkers (e.g., neuroimaging markers), is more realistic. Different clusters or sets of biomarkers will be identified for various COU, including: I) supporting AD diagnosis, II) predicting conversion from preclinical stages to mild cognitive impairment and finally to AD dementia, and III) monitoring disease progression.

The field is currently in an ever accelerating dynamic process to identify and validate blood-derived biomarkers for early detection, diagnosis and prognosis of AD. Supporting the international Alzheimer Precision Medicine Initiative (APMI) and its evolving cohort program (APMI-CP) (4, 11, 13), the Blood-Based Biomarker Interest Group (BBBIG) has been established with the objective to provide global standards and best practices for the appraisal of blood-based biomarkers. A Professional Interest Area focused on Blood Based Biomarkers (BBB-PIA) – integrated in the Alzheimer's Association's International Society to Advance Alzheimer's Research and Treatment (ISTAART) – has been created to support the harmonization process of preanalytical and analytical protocols and emphasize the need for a biorepository of clinical reference samples enabling the assessment of clinical performance (1).

International collaborations between academia, public-private partners and industry are certainly crucial to accelerate the development, co-development and qualification of blood-based biomarkers, ultimately avoiding the substantial drawbacks associated with CSF and brain imaging approaches. Blood-based biomarkers have not yet been fully standardized for research and clinical use in AD. Current research programs and multi-disciplinary collaborations have mostly reached academic discovery-stage. Therefore, the field will need to address the missing development issues in focused industry partnerships (1, 3). We strongly believe that blood-based biomarker discovery and development must be an inherent part of drug discovery and development programs throughout all stages from preclinical to clinical in a consequent co-development process that allows objective go/no-go decisions (1, 3). Traditionally, this has not been achieved with very negative consequences for decision making within AD drug development programs (14).

The Alzheimer's Association ISTAART BBB-PIA is a sustaining collaborative initiative to accelerate the progress in the field of AD blood biomarkers; specific goals include the identification and validation of reliable and inexpensive blood-based biomarkers for diagnosing AD and monitoring its progression (4, 11).

Only a fraction of all dynamic protein alterations occurring under different pathophysiological conditions can be explored through current proteomic technologies. However, novel strategies are expected to allow the identification of post-translational modifications and the inspection of the "hidden proteome" in the blood (4, 11). The standardization of a comprehensive matrix of blood-based AD biomarkers will represent a milestone in the implementation of precision medicine for treating and preventing AD and other neurodegenerative diseases (ND). Previous studies have shown the clinical utility of neuroproteomics for identifying novel biomarkers of ND in an unbiased fashion (i.e., not informed by current pathophysiological mechanisms). For instance, neuroproteomics has allowed identifying the prominent role of neuroinflammation in the pathophysiology of AD and other ND. This led to the hypothesis that neuroinflammatory mechanisms are critical for AD pathogenesis, at least in a subset of individuals. In this

pathophysiological subgroup, the role of Aβ peptides, tau protein, and α-synuclein may be less prominent than originally expected. There may be a multi-stage diagnostic scenario in which blood-based biomarker tests would be the entry point preceding the use of CSF analysis, MRI and PET imaging; further profiling (i.e. genomic) steps may be implemented as part of multi-model interventions targeted to specific patient subgroups (4, 11).

In the near future, biomarker-driven algorithms will support the classification of individuals defining distinct biological-functional stages of AD. This has been achieved in different medical specialties using validated staging systems. For instance, the consolidated TMN system is routinely used for cancer staging, providing prognostic evaluation, supporting the selection of appropriate therapeutic options and providing objective biological inclusion criteria for clinical trials. Genetic mutations and blood concentrations of specific bioproducts are currently used as prognostic or predictive markers for drug efficacy and / or toxicity, guiding the clinical decision-making process including initiation or termination of molecular targeted therapies. Clinically established biomarkers are KRAS as well as the HER2genotype, the blood count of circulating tumor cells, and the blood concentrations of CEA, CA19-9, beta-tubulin, beta2 microglobulin, estrogen receptor, epidermal growth factor receptor, among many others.

During the last decade, large-scale exploratory blood-based biomarker studies indicate pathophysiological commonalities between AD and several oncological / immunological diseases regarding genetic-epigenetic factors, signaling pathways, and protein expression profiles.

Therefore, successful cross-trans-fertilization between the advanced medical research fields, including oncology and immunology, and neurology and neurodegenerative diseases, presents unique opportunities to open new therapeutic discovery and development perspectives for AD (4, 6, 11, 15). Biomarker-driven animal studies are increasingly enhancing drug repositioning programs. Several approved anti-cancer and immunopathy compounds have been investigated in AD. For instance, Sarcatinib is a small molecule currently studied in several types of cancers and also in AD. Sarcatinib inhibits both the Src family Fyn kinase and Bcr-Abl tyrosine-kinase, involved in the pathway of tau hyperphosphorylation and tau / Aβ induced toxicity. Another example is Vorinostat, an approved compound used for cutaneous T cell lymphoma (4). It is a small molecule acting as an epigenetic inhibitor of class I histone deacetylases, whose overactivation is associated to aberrant microglia activity, insulin resistance, and sustained epigenetic post-translational modifications of Aβ (4).

In perspective, we are approaching the turning point of a fundamental paradigm shift in Neuroscience drug discovery and development, based on comprehensive genomic and multi-modal blood-based biomarker profiling. We are leaving classical traditional clinical Neurology with a descriptive focus on late-stage clinical phenotypes towards a new age of molecular pathway-driven therapeutic interventions for major brain diseases demonstrating pathophysiological commonalities.

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