Perspective

The case for widening the scope of Alzheimer's disease models and biomarkers

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ABSTRACT

Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder primarily associated with amyloid-beta and tau, but numerous other mechanisms, such as vascular injury, oxidative stress, mitochondrial dysfunction, and inflammation—among many others— also contribute but are comparatively less integrated into dominant research frameworks or biomarker classification systems. This paper builds on existing critiques of the amyloid-and tau-centric research paradigm by focusing on how this limited scope is reflected in both animal model usage and biomarker classification frameworks. While essential, many animal models chosen to investigate individual mechanisms fail to capture the full complexity of AD's pathology, limiting their ability to accurately model disease progression and translate findings to humans. In parallel, biomarker classification systems and therapeutic development remain largely centered on a narrow set of pathological features. Addressing these limitations requires a shift toward more comprehensive approaches, such as the combined use of complementary animal models, as well as the validation and integration of emerging multi-domain biomarker frameworks that incorporate diverse pathological processes. Such strategies may better capture disease heterogeneity and support biomarker-driven patient stratification, helping to link AD's diverse pathological processes to more targeted therapeutic approaches.

Alzheimer's Disease (AD) is a progressive neurodegenerative disease characterized by the accumulation of amyloid-beta peptides (Aβ) in the form of neuritic plaques and an increase in the hyperphosphorylation of tau protein resulting in bundles of neurofibrillary tangles, ultimately leading to cerebral atrophy.[1-2] AD is classified into two prominent types: familial (FAD) and sporadic (SAD). FAD often arises early and can be linked to well-known genetic mutations (APP, PSEN1, PSEN2, etc.), but it accounts for only 5-10% of cases.[3] In contrast, while SAD typically arises later in life and is associated with genetic factors that may increase the risk, such as the APOE e4 allele, it accounts for up to 95% of cases and has multiple pathways to its presentation.[3]

Over the past decade, the conceptualization of AD has evolved considerably. For example, advances in plasma biomarkers, such as phosphorylated tau isoforms, now allow for earlier and less invasive detection of AD pathologies.[4-5] Furthermore, updated classification systems emphasize the biological definition of AD over clinical symptomatology, allowing for a more individualized understanding of disease progression.[6-7] However, despite these key developments, significant challenges remain in translating this evolving framework into effective, widespread therapeutic strategies. These challenges are particularly rooted in the inherently heterogeneous nature of AD, as emerging systems-level and network-based models suggest that AD progression reflects dynamic interactions between various mechanistic pathways and selectively vulnerable neural networks, rather than isolated pathological processes.[8-10] This evolving perspective highlights the inherent difficulty in accurately modeling and designing AD therapeutics through traditional, reductionist approaches.

Accordingly, although many obstacles impede the development of more effective AD therapies, two key challenges are a) limitations with animal models and b) a persistently narrow scope within research and treatment conceptualization, as reflected in the continued focus of biomarkers and their classification. This opinion piece is informed by a targeted review of the literature, focusing on key studies related to AD pathophysiology, animal models, and biomarker development, with an emphasis on widely cited frameworks and representative examples rather than a systematic review.

From 1995-2010 alone, over 300 interventions were shown to reduce the neuropathy or cognitive deficits of AD in mouse models.[11] Despite these findings, translation to effective human therapies has remained limited.[12] This discrepancy is often attributed, at least in part, to challenges in translating findings from animal models—particularly rodents— to humans.[13-14] Animal models refer to non-human species used to study selected biological processes or diseases found in humans, either naturally occurring or transgenically engineered.[15] Because AD is a complex and heterogeneous disease that animals do not naturally replicate, AD models are most commonly transgenically engineered to express human AD mutations such as APP or PSEN1.[16] Historically, transgenic AD models have evolved from a reductionist approach that isolated a single pathological feature, such as amyloid, toward comprehensive models that incorporate both amyloid and tau— although reductionist approaches are often still used to interrogate individual mechanisms.[17]

However, while it might be expected that combining amyloid and tau would approximate the disease, even models incorporating both pathologies often fail to exhibit the

neurodegeneration characteristic of AD.[12,18] Furthermore, inserting aspects of the disease may have unintended effects that complicate interpretation. For instance, overexpressing the amyloid precursor protein (APP) gene results in elevated levels of other, non-related APP fragments that could have either neuroprotective or neurotoxic effects.[19]

As AD involves numerous interacting mechanisms ongoing throughout its progression, inserting the most prominent features at a given stage of development is unlikely to capture the full complexity of the disease and instead may represent only a partial model.[20-21] This challenge is particularly pronounced for SAD as it is not strongly related to specific mutations to the same degree as FAD and encompasses many possible pathways to a disease state, therefore making it inherently difficult to model.[16,22] Due to this, ongoing work includes the development of more sophisticated transgenic models and complementary human-derived systems, such as organoids, to better capture disease complexity.[23-24]

Despite these limitations, and acknowledging the ethical considerations inherent in animal research, current animal models remain essential for advancing our understanding of AD and developing effective treatments. Progress can be achieved by using the most complete pathological representation of AD possible, while focusing on specific components of disease progression to better understand how targeted interventions may translate to humans.[20] For example, studies in mice have shown that reducing Aβ is insufficient to rescue memory function once downstream processes are underway.[11] This finding was later confirmed in humans, contributing to the shift toward potential treatments targeting Aβ earlier in the disease pathogenesis.[25]

To this end, while it is a simplistic notion, this animal model-based roadblock could be partially mitigated by adopting a broader perspective in the choice of animal models. One step in this direction could involve using a reductionist tau-only or amyloid-only model in combination with a more pathologically comprehensive model, such as 3xTg mice—which exhibit both tau and Aβ pathology—in studies that are investigating solely tau- or amyloid-based mechanisms.[21,26] While tau- or amyloid-only models may allow for clearer mechanistic interrogation, the additional use of 3xTg mice may help determine how the effects being investigated manifest within a more accurate pathological environment. Therefore, this dual model approach allows a balance between mechanistic isolation and construct validity, providing greater insight into the interrogated mechanisms within a systems-level context than the use of either model alone. However, it must be acknowledged that implementing this approach at scale is constrained by the practical consideration of the associated cost and time to maintain multiple transgenic colonies and run parallel experiments. Furthermore, distributing limited resources across multiple models may reduce sample size, thereby decreasing statistical power and limiting the ability to detect significant effects. Regardless, a more integrative approach to model selection may help improve the contextualization and translational potential of preclinical findings, despite the practical limitations involved.

Regarding the scope of research and treatment, while Aβ and tau are the most well-known features of AD, other pathological mechanisms such as inflammation, immune dysregulation, vascular injury, oxidative stress, mitochondrial dysfunction, and calcium-mediated excitotoxicity also contribute but receive comparatively less attention.[27-32] Numerous studies have shown that AD is a multifactorial disease process with complex, bidirectional interactions and heterogeneity in pathology, genetics, and molecular mechanisms.[10,33-37] Importantly, these interactions between pathological mechanisms reflect systems-level dynamics. Therefore, perturbations in one aspect, such as vascular dysfunction, can propagate through interconnected molecular and cellular pathways to influence other processes, including neuroinflammation and synaptic dysfunction.[10] This perspective aligns with the framework of AD as a disorder of network degeneration, in which pathology within selectively vulnerable neural systems, such as the hippocampal-entorhinal memory network, leads to progressively altered widespread neural connectivity patterns.[8-9] Therefore, heterogeneity in clinical presentation may stem from differences in how these interacting molecular processes influence one another and how degeneration spreads across neural networks in individual patients, rather than from variation in any single pathological substrate.

Despite this, most disease modifying treatments focus primarily on amyloid, with relatively little investigation into other pathological substrates.[12,38-42] Furthermore, even though in preclinical studies the portfolio of targets for treatment is broader, the percentage of Aβ targeting therapies relative to all other approaches is almost double the percentage of that in clinical studies.[43-44] This comes despite it being well established that amyloid deposition alone does not cause the disease to reach the symptomatic stage without tau and other secondary pathologies contributing.[45-46] Therefore, although recent developments in the amyloid disease modifying therapies Lecanemab and Donanemab have shown promising results, combination therapies targeting multiple mechanisms will likely be necessary.[47-49]

This narrow focus is especially evident in the use of biomarkers for diagnosis and treatment. While biomarkers exist for many traditional AD substrates, there is a lack of them for many other critical aspects, such as mitochondrial injury or calcium-mediated excitotoxicity.[12,41-42] Consequently, only a subset of AD's components are monitored when assessing patient outcomes or progression. Given the individual variability in pathogenesis, and the fact that a patient's position on the pathogenic continuum greatly

determines their potential for treatment— as disease modifying therapies function best in early AD cases— this represents a significant limitation to effective treatment.[4-5,37,50-52]

This limited scope is best reflected in the National Institute on Aging and Alzheimer's Association (NIA-AA) A/T/N classification system, which categorizes AD based on three biomarkers: amyloid (A), tau (T), neurodegeneration (N).[53] Although there is significant heterogeneity among patients with the same clinical phenotype in terms of the degree, distribution, and progress of pathologies, the A/T/N system excludes other pathologies for which biomarkers currently exist.[28] Furthermore, considering most patients exhibit mixed pathologies, using this limited classification system complicates patient comparison.[43] For example, vascular disturbances can exacerbate Aβ and tau aggregation and therefore, may directly contribute to neurodegeneration.[54] Therefore, given that approximately 50-80% of aging and AD brains have varying degrees of vascular pathology, patients with the same A/T/N status may have vastly different underlying disease processes.[54-55]

One approach to addressing this limitation is the integration of emerging biomarker frameworks that capture multiple pathological mechanisms simultaneously to create a more comprehensive representation of disease state. For example, emerging multi-omic plasma biomarker panels could integrate a) proteomic markers of amyloid-β and phosphorylated tau, b) metabolomic signatures reflecting measures such as lipid dysregulation and oxidative stress (e.g. sphingolipids and N,N-dimethylglycine), and c) genomic risk scores capturing pathologic pathways such as inflammation (e.g. APOE-associated risk).[52, 56-57]

However, in contrast to the traditional A/T/N markers, these emerging multi-omic panels are less established and require a combination of multiple markers to generate a meaningful signal.[57-58] Therefore, these non-A/T/N markers are more difficult to standardize into a simple classification framework, which creates barriers to widespread adoption.[57-58] Regardless, machine learning-based clustering of this multidimensional plasma biomarker data in combination with imaging data has the potential to identify AD subtypes that more accurately reflect the underlying pathophysiology of individual patients.[58] By incorporating these diverse, comprehensive biomarkers into the classification system we may better capture the heterogeneity of the disease across patients. This approach has the potential to enable more accurate patient stratification based on their unique pathological signature, facilitating the eventual design of personalized treatment plans once the necessary combination of disease modifying therapies becomes available.[28] However, while this personalized approach using non-A/T/N biomarkers is conceptually promising, its routine implementation remains limited, as many non-A/T/N biomarkers still lack standardized thresholds and are not routinely available due to the cost of the necessary multi-omic assays and computational infrastructure.[59] Therefore, ongoing research into the development and validation of these panels is vital for facilitating their eventual clinical translation and integration into standardized diagnostic frameworks.

In conclusion, while the road to an effective treatment for AD remains complex, progress will depend on aligning research approaches with the multifactorial nature of the disease. Moving forward, AD research would greatly benefit from focusing on a) the combined use of reductionist and comprehensive models to allow isolated mechanisms to be properly contextualized and b) the validation and integration of emerging multi-omic biomarker panels into classification systems. By shifting to this comprehensive approach, AD research will be better positioned to translate mechanistic insight into therapies that target the heterogeneous nature of this disease.

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