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The sterile controversy on the amyloid cascade hypothesis

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HIGHLIGHTS

- There is a growing debate on the role of Aβ in the pathogenesis of AD.
- A "one-fits-all" approach (based on a single biomarker/process) is inadequate for AD.
- There is the need to overcome the traditional paradigms of "standalone-diseases".
- A multidimensional modeling of biomarkers may have important implications.

Abstract

In these last years, several phase III randomized controlled trials testing promising candidates sharing **Aβ** depots as target of their action have failed, despite showing some reductions of the brain **Aβ** charge. The announcements of the negative results have heated the discussion in the field and divided the scientific community between the defenders versus the opponents of the **Aβ** theory. In the present article, we discuss the limits of these drastic, opposite positions and we propose a novel approach to Alzheimer's disease (AD). In particular, a "one-fits-all" approach where a single biomarker/process is able to explain the clinical manifestation seems inadequate for AD (as for other conditions of old age). Accordingly, there is an urgent need to overcome the traditional paradigms of "standalone-diseases" (requiring unimodal interventions) in favor of more comprehensive and multidimensional approaches. **Specifically, promoting biomarker modeling procedures based on multivariate statistical methodologies may have important implications and advantages in the field of AD and other neurodegenerative diseases.**

Keywords: Alzheimer's disease; amyloid; randomized controlled trials; aging; biomarkers.

Several phase III randomized controlled trials testing promising candidates sharing **Aβ** depots as target of their action have recently failed, despite showing some reductions of the brain **Aβ** charge[1]. The announcements of the negative results have heated the discussion in the field and divided the scientific community between the defenders versus the opponents of the amyloid theory. On one side, remaining convinced of the pivotal/causal role of **Aβ** in the pathogenesis of AD[2,3], some researchers have attributed the failure of trials (considered only as "temporary setbacks"[2]) to the characteristics of the sample populations, the dosing of the compounds, and/or molecular specificities of the targets/mechanisms. They still firmly support the design and conduction of further research on anti-**Aβ** treatments, usually proposing the anticipation of

interventions to milder/prodromal stages of the disease. On the other hand, there is a growing feeling that both research and industry have been over-reliant on **Aβ** to both define AD and develop treatments against it. For some critics, the disappointing findings coming from the recent trials inevitably confirm the non-centrality of **Aβ** in the pathophysiological processes leading to AD[4]. Consistently, they solicit at redirecting attention towards other mechanisms and pathways (e.g., tau, neuroinflammation, cell cycle and oxidative stress), **despite the scarcity of defined and validated targets.**

In our opinion, both reactions are understandable but rather drastic. Taken separately, they do not adequately interpret the results of the negative trials, potentially affecting future research in the field. It is not a matter to choosing whether embracing or rejecting the amyloid cascade hypothesis. Also thanks to these studies, we do know now that AD is an extremely complex condition, much more perhaps than what we thought. As all the age-related diseases, it is determined by multiple, simultaneous, and interacting pathophysiological processes, which make difficult to reduce everything to a single hypothesis or model. Based on recent evidence, it is increasingly being considered as a nosological "umbrella" covering multiple and heterogeneous conditions. This relevant complexity characterizes also the presenile variants, whose pathophysiology and phenotypic manifestations are not fully explained by an individual pathological process (i.e., **Aβ** deposition), even if predominant. Accordingly, a "one-fits-all" approach where a single biomarker/process is able to explain the clinical manifestation seems simply inadequate for AD (as for other conditions of old age). Under this perspective, models simultaneously considering multiple biomarkers for understanding the intricate biological background of age-related conditions have already been proposed[5]. **The adoption of multivariate statistical methodologies may support a fundamental shift to a multidimensional modeling of complementary biomarkers. These methods may consent to properly capture the**

heterogeneity of neurodegeneration and the underlying pathophysiology by merging the information obtained from different sources of variability (e.g., circulating biomolecules, clinical parameters, imaging findings, genetic traits)[5]. In this regard, principal component analysis (PCA), analysis of variance (ANOVA) - simultaneous component analysis (ASCA), multilevel simultaneous component analysis (MSCA), and partial least squares - discriminant analysis (PLS-DA), are few example of statistical approaches that are increasingly considered for exploring biomarkers for age-related conditions[5,6].

In conclusion, there is an urgent need to overcome the traditional paradigms of "standalone-diseases" (requiring unimodal interventions) in favor of more comprehensive and multidimensional approaches. The adoption of such novel methodology (valid for both the clinical and research settings) may lead to 1) a wiser consideration of past negative experiences for better informing future activities, 2) the development of person-tailored and function-driven interventions, and 3) avoid sterile barricades and divisions in the scientific community. **Aβ** remains a cornerstone of AD pathology. However, it should not be overcharged of responsibility but considered as only a piece of the complex puzzle of AD. Solving the whole picture only looking at it might simply be unrealistic.

Conflicts of interest

The Authors have no competing interests to disclose for the present study.

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