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Review - Part of the Special Issue: Alzheimer's Disease – Amyloid, Tau and Beyond

Perspective on future role of biological markers in clinical therapy trials of Alzheimer's disease: A long-range point of view beyond 2020

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ABSTRACT

Recent advances in understanding the molecular mechanisms underlying various paths toward the pathogenesis of Alzheimer's disease (AD) has begun to provide new insight for interventions to modify disease progression. The evolving knowledge gained from multidisciplinary basic research has begun to identify new concepts for treatments and distinct classes of therapeutic targets; as well as putative disease-modifying compounds that are now being tested in clinical trials.

There is a mounting consensus that such disease modifying compounds and/or interventions are more likely to be effectively administered as early as possible in the cascade of pathogenic processes preceding and underlying the clinical expression of AD. The budding sentiment is that "treatments" need to be applied before various molecular mechanisms converge into an irreversible pathway leading to morphological, metabolic and functional alterations that characterize the pathophysiology of AD. In light

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of this, biological indicators of pathophysiological mechanisms are desired to chart and detect AD throughout the asymptomatic early molecular stages into the prodromal and early dementia phase.

A major conceptual development in the clinical AD research field was the recent proposal of new diagnostic criteria, which specifically incorporate the use of biomarkers as defining criteria for preclinical stages of AD. This paradigm shift in AD definition, conceptualization, operationalization, detection and diagnosis represents novel fundamental opportunities for the modification of interventional trial designs.

This perspective summarizes not only present knowledge regarding biological markers but also unresolved questions on the status of surrogate indicators for detection of the disease in asymptomatic people and diagnosis of AD.

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1. Introduction

Sporadic Alzheimer's disease (AD) is currently conceptualized as a multifactorial neurodegenerative disease transitioning later through a prodromal cognitive stage into a late-stage dementia syndrome. This initially clinically "silent" multi-dimensional disease cascade chronically, non-linear progressively unfolds through the emergence and probably at some point convergence of a yet not fully understood and characterized parallelized and/or interrelated array of molecular mechanisms and signaling pathways. For many decades, the definite diagnosis of AD has relied on the *postmortem* detection of senile plaques (SPs) and neurofibrillary tangles (NFTs). There, these historic hallmark neuropathological lesions have been extensively studied. Their molecular constituents have been isolated (intracellular aggregation of tau protein and extracellular accumulation of amyloid beta (Aβ) peptide). The neuropathology is now better understood in terms of amyloid and tau pathology – as a consequence Aβ and tau assays having secondarily been developed and validated during the last two decades to provide first "core feasible" cerebrospinal fluid (CSF) biomarkers. The stereotyped progression of tau [1] and Aβ pathology [2] in the brain has been described and is the basis of the new National Institute on Aging and the Alzheimer's Association neuropathological criteria [3]. The amyloid cascade hypothesis, relying on the observation that all the mutations causing early-onset AD involve genes that alter Aβ production, has generated a theory emphasizing the central relevance of the amyloidogenic cascade and the Aβ peptide. As a consequence, many treatment trials in AD have been aimed at altering the abnormal production, accumulation and deposition Aβ. The optimism that reducing Aβ accumulation and/or