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Review

Precision pharmacology for Alzheimer's disease

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ABSTRACT

The complex multifactorial nature of polygenic Alzheimer's disease (AD) presents significant challenges for drug development. AD pathophysiology is progressing in a non-linear dynamic fashion across multiple systems levels – from molecules to organ systems – and through adaptation, to compensation, and decompensation to systems failure. Adaptation and compensation maintain homeostasis: a dynamic *equilibrium*

Abbreviations: $A\beta_{1-42}$, 42-amino acid-long Aβ peptide; AD, Alzheimer's disease; ADAPT, Alzheimer's Disease Anti-Inflammatory Prevention Trial; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living; ADCS-PACC, Alzheimer's Disease Cooperative Study-Preclinical Alzheimer Cognitive Composite; AMS, Academy of Medical Sciences; APMI, Alzheimer Precision Medicine Initiative; APMI-CP, Alzheimer Precision Medicine Initiative Cohort Program; APOE, apolipoprotein E; APP, amyloid precursor protein; BACE1, β-site amyloid precursor protein cleaving enzyme; CD33, cluster of differentiation 33; CDER, Center for Drug Evaluation and Research; CDER/FDA, Center for Drug Evaluation and Research at the Food and Drug Administration; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; CNS, central nervous system; CPC, clinicopathological correlations; CSF, cerebrospinal fluid; EC50, half maximal effective concentration; fAD, familial AD; FDA, Food and Drug Administration; ^{18}F-FDG-PET, ^{18}F-2-fluoro-2-deoxy-D-glucose; GWAS, genome-wide association studies; HEK293, human embryonic kidney 293; HMDB, Human Metabolome Database; IAPP, islet amyloid polypeptide; IL-1β, interleukin-1-beta; IL-6, interleukin-6; LOAD, late-onset AD; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MS, mass spectrometry; MTD, maximum tolerated dose; NF-κβ, nuclear factor kappa-light-chain-enhancer of activated B cells; NSAIDs, non-steroidal anti-inflammatory drugs; PD, pharmacodynamic; PET, Positron emission tomography; PK, pharmacokinetic; PM, Precision Medicine; PMI, U.S. Precision Medicine Initiative; PP, Precision Pharmacology; PPAR-γ, peroxisome proliferator-activated receptor-γ; PSEN-1, presenilin-1; PSEN-2, presenilin-2; sIL-6RC, IL-6 receptor complex; SILK, stable isotope labelling kinetics; SNPs, single nucleotide polymorphism; TACE, TNFα converting enzyme; TDP-43, transactive response DNA-binding protein 43; TGF-β, transforming growth factor-beta; TNF-, αtumor necrosis factor-alpha; TNFRs, TNF receptors; TREM2, triggering receptor expressed on myeloid cells 2; UPS, ubiquitin/proteasome system.

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resulting from the dynamic non-linear interaction between genome, epigenome, and environment. An individual vulnerability to stressors exists on the basis of individual triggers, drivers, and thresholds accounting for the initiation and failure of adaptive and compensatory responses. Consequently, the distinct pattern of AD pathophysiology in space and time must be investigated on the basis of the individual biological makeup. This requires the implementation of systems biology and neurophysiology to facilitate Precision Medicine (PM) and Precision Pharmacology (PP).

The regulation of several processes at multiple levels of complexity from gene expression to cellular cycle to tissue repair and system-wide network activation has different time delays (temporal scale) according to the affected systems (spatial scale). The initial failure might originate and occur at every level potentially affecting the whole dynamic interrelated systems within an organism. Unraveling the spatial and temporal dynamics of non-linear pathophysiological mechanisms across the *continuum* of hierarchical self-organized systems levels and from systems homeostasis to systems failure is key to understand AD. Measuring and, possibly, controlling space- and time-scaled adaptive and compensatory responses occurring during AD will represent a crucial step to achieve the capacity to substantially modify the disease course and progression at the best suitable timepoints, thus counteracting disrupting critical pathophysiological inputs. This approach will provide the conceptual basis for effective disease-modifying pathway-based targeted therapies.

PP is based on an exploratory and integrative strategy to complex diseases such as brain proteinopathies including AD, aimed at identifying simultaneous aberrant molecular pathways and predicting their temporal impact on the systems levels. The depiction of pathway-based molecular signatures of complex diseases contributes to the accurate and mechanistic stratification of distinct subcohorts of individuals at the earliest compensatory stage when treatment intervention may reverse, stop, or delay the disease. In addition, individualized drug selection may optimize treatment safety by decreasing risk and amplitude of side effects and adverse reactions.

From a methodological point of view, comprehensive "omics"-based biomarkers will guide the exploration of spatio-temporal systems-wide morpho-functional shifts along the *continuum* of AD pathophysiology, from adaptation to irreversible failure.

The Alzheimer Precision Medicine Initiative (APMI) and the APMI cohort program (APMI-CP) have commenced to facilitate a paradigm shift towards effective drug discovery and development in AD.

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