CCAD

Deciphering the Chemoproteomics and Chemotranscriptomics of Anti-Alzheimer Drugs for Novel Druggable Target Identification and Biomarkers Development

Multiomics and Big data integration can decipher the mode of action of drugs and possibly identify novel druggable targets as well as diagnostic or theragnostic-associated biomarkers. Alzheimer's disease (AD) is characterized by complex neuropathological processes driven by amyloid deposition, neurofibrillary degeneration, astrogliosis, and neuroinflammation. Ab peptides and Tau proteins, the respective components of amyloid deposits and neurofibrillary tangles, are believed to spread in a prion-like process from affected areas to interconnected brain regions. Drug development should ideally target the entire spectrum of AD pathophysiology rather than each process separately. We posit that protein aggregation and its neuroinflammatory and cognitive detrimental impacts can be targeted simultaneously by reinstating proper cellular/synaptic homeostasis with-out targeting specifically disease-associated aggregation-prone Ab peptides and Tau proteins. Through phenotypic drug screening, our laboratories have developed five different families of small drugs with anti-AD efficacy. Drug candidate Ezeprogind (AZP2006), which represses Ab1-x production and modulates autophagy, successfully completed a clinical phase IIa trial against progressive supranuclear palsy. Three further lead compounds mitigate in vivo both the amyloid and Tau pathologies as well as inflammation and cognitive deficits, hereinafter a drug-modifying paradigm. Based on solid preliminary results, our European Consortium team of experts in the field of AD, chemistry, prion-like propagation, neuroinflammation, big-data management and analysis, and biomarker development, we will pursue a highly innovative approach to identify molecular pathways that can be targeted for disease intervention. A combination of biorthogonal chemistry-based strategies, chemoproteomics, and cell-based assays will allow the characterization of the cellular drug target(s). Deep sequencing, spliceomics, single cell, spatial transcriptomics, Attack sequencing, miRNA epigenomics, and transcription factor footprinting will address the definition of the mode of action. We envision deciphering the drug-target mechanism of action which mitigates the AD-related lesional processes, including the cellular processes related to the seeding and prion-like propagation, changes in gene expression associated with cognitive improvements, and the drug's anti-neuroinflammatory properties. We will identify potential novel druggable target(s) and diagnostic or theragnostic biomarkers through Big data integrated analyses. This project will identify novel drug targets by characterizing modes of drug action toward aberrant protein deposition, neuroinflammatory processes, and cognitive benefits. Biomarkers, theragnostic markers, and potential druggable targets arising from multiomics big-data analyses might allow the repositioning of existing EMA-approved drugs to target AD.

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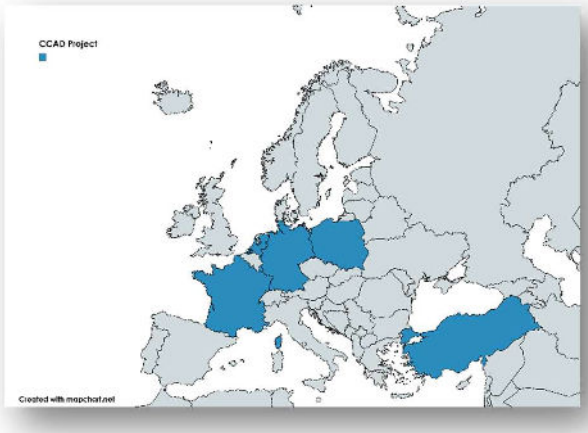

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