Neuroscience research in 2024: advances in blood biomarkers and brain omics

Substantial advancements in neuroscience research in 2024 have included the study of blood biomarkers for Alzheimer's disease and brain omics analyses with spatial context and cellular dynamics. Such advances will be instrumental in the development of diagnostic tools and therapeutic targets. Following US Food and Drug Administration approval of disease-modifying therapies targeting amyloid β for early Alzheimer's disease, there is an urgent need to identify appropriate patients for treatment and to monitor their responses. To date, detection of amyloid β pathology has relied on brain imaging techniques such as amyloid PET scans and on lumbar punctures to analyse CSF for amyloid β proteins. Although these approaches can detect brain pathology at early disease stages, blood-based biomarkers are emerging as accessible alternatives. Moreover, research has expanded the understanding of pathological mechanisms in Alzheimer's disease, beyond amyloid pathology, to explore molecular changes in neurons with spatial resolution and trajectories of cellular environments. This research has uncovered dysfunctions in biological processes such as impaired innate immunity, paving the way for innovative therapeutic strategies.

Biomarker measurements can be more sensitive than cognitive assessments in evaluating Alzheimer's disease. A prospective multicentre study by Jia and colleagues[1] provided compelling evidence for the necessity of biomarker detection in Alzheimer's disease diagnosis and management. In this study, cognitively healthy participants in China were enrolled and followed up for up to 20 years, of whom a subgroup were assessed for cognitive changes at 2-to-3-year intervals. A total of 648 participants developed Alzheimer's disease, and they were matched with 648 participants who had normal cognition, and their temporal trajectories of cognitive changes were assess via CSF biochemical markers, cognitive testing, and imaging. The study demonstrated changes in Alzheimer's disease-related biomarkers in CSF, including amyloid β42, amyloid β42/40, phosphorylated tau 181, total tau, and neurofilament light chain. Changes in CSF biomarkers could be detected up to 18 years before the clinical diagnosis. These findings emphasise the crucial role of biomarker measurements for early detection of Alzheimer's disease.

Although CSF biomarkers are sensitive for detecting Alzheimer's disease pathology, their invasive nature limits widespread implementation. By contrast, blood-based biomarker assays offer substantial advantages for clinical diagnosis. One prominent blood-based biomarker is phosphorylated tau 217 (p-tau217), which correlates strongly with brain amyloid pathology and has shown promise for early detection and monitoring of Alzheimer's disease.[2] In a notable prospective study, Palmqvist and colleagues[3] analysed blood samples from over 1200 older adults (aged 67–81 years) with cognitive symptoms, establishing a ratio of p-tau217 to non-p-tau (% p-tau217) in conjunction with the plasma amyloid β42/40 ratio. This blood test had a diagnostic accuracy of 88–92% in identifying Alzheimer's disease pathology across both primary and secondary care settings, substantially surpassing standard clinical evaluations (73% in specialty clinics and 61% in primary care).[3] In 2024, the Alzheimer's Association updated its diagnostic criteria to include plasma biomarkers, bridging the gap between research and clinical practice for Alzheimer's disease diagnosis and staging.[4]

A large-scale proteomic profiling study has identified over 300 blood proteins linked to the incidence of late-onset Alzheimer's disease,[5] with half of these associations influenced by *APOE4* genotypes, which is the strongest genetic risk factor for late-onset Alzheimer's disease. Recent work from our laboratory showed that measuring changes in specific blood proteins that are involved in Alzheimer's disease-related biological processes allows for comprehensive assessment of disease status.[6] We developed a blood-based biomarker assay chip that can measure concentrations of 21 Alzheimer's disease-associated blood proteins that are involved in biological pathways such as immune response, vascular function, and metabolism. This scoring system effectively classified Alzheimer's disease (area under the curve 0·941–0·987), mild cognitive impairment (0·843–0·895), and indicated amyloid pathology across populations of

Chinese and European descent. Notably, the assay examined changes across five biological processes and revealed ethnicity-specific dysregulations in Alzheimer's disease progression.

Brain omics analyses, such as single-nucleus RNA sequencing, spatial transcriptomics, and other transcriptomic techniques, have revolutionised research by enabling molecular analysis at cellular or spatial resolution. Investigators have developed comprehensive transcriptomic atlases of the human brain, revealing heterogenous cellular populations and their varying susceptibilities to Alzheimer's disease pathology. These studies have identified specific neurons and astrocytes linked to Alzheimer's disease pathological features, and region-specific glial inflammatory responses, enhancing understanding of the complex molecular characteristics of the disease.[7,8] Additionally, Gabitto and colleagues[9] integrated a multimodal cell atlas from the BRAIN Initiative by analysing cell types in the middle temporal gyrus of 84 donors with Alzheimer's disease of varying pathologies and outlining a pseudotime of Alzheimer's disease with two distinct phases: an early phase characterised by inflammatory responses; and a later phase marked by neuronal loss. Furthermore, Green and colleagues[10] analysed 1·65 million single-nucleus RNA sequencing profiles sampled from 437 individuals. Their study identified two trajectories of brain ageing, one of which leads to Alzheimer's disease dementia, and pinpointed key glial and neuronal subpopulations that drive amyloid β and tau pathologies. These findings highlight the power of single-nucleus RNA-sequencing in deciphering cellular mechanisms and underscore its potential in guiding targeted therapeutic strategies.

In conclusion, advancements in blood biomarkers research and brain omics technologies have enhanced our understanding of the biology of Alzheimer's disease. The knowledge from these advancements provides opportunities and foundations to ultimately develop better diagnostic tools and effective treatment strategies.

AKYF and NYI are inventors on a blood biomarker technology licensed by The Hong Kong University of Science and Technology to Cognitact. AKYF has served as a consultant for Cognitact with personal compensation.

*Amy K Y Fu, *Nancy Y Ip*
boip@ust.hk

Division of Life Science, Daniel and Mayce Yu Molecular Neuroscience Center, State Key Laboratory of Molecular Neuroscience, The Hong Kong University of Science and Technology, Hong Kong Special Administrative Region, China (AKYF, NYI); Hong Kong Center for Neurodegenerative Disease, InnoHK, Hong Kong Special Administrative Region, China (AKYF, NYI); Guangdong Provincial Key Laboratory of Brain Science, Disease and Drug Development, Shenzhen-Hong Kong Institute of Brain Science, HKUST Shenzhen Research Institute, Shenzhen, China (AKYF, NYI)

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