Dynamic Metal-Enhanced Fluorescence Microarray for ultrasensitive detection of Neurodegenerative Disease Biomarkers

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Neurodegenerative diseases (NDDs) have become a healthcare challenge in ageing societies worldwide.[1] The key to effective disease management lies in the detection of NDDs at early phases when appropriate treatments are available to slow down NDD progression. However, current NDD diagnosis based on clinical symptoms and brain imaging commonly occurs at post-symptomatic stages and cannot predict disease onsets. The slow turnaround and prohibitive costs of brain imaging create a major barrier for their routine uses in NDD screening and monitoring. Biomarkers such as amyloid beta, tau proteins, and neurofilament light-polypeptide have been used for an unbiased classification of NDD pathophysiology. While biomarkers are identified in cerebrospinal fluid, NDD biomarkers are also present in blood plasma albeit at much lower concentrations.[2] However, conventional bioassays such as enzyme-linked immunosorbent assay (ELISA) have a detection limit of picomolar ranges. Hence, there is an urgent need to develop innovative technologies for ultrasensitive detection of protein biomarkers in blood plasma.

Microarrays have been widely used in high-throughput analysis of molecular biomarkers. However, conventional microarray assays usually suffer from low sensitivity due to slow molecular diffusion and intrinsic low emission efficiency of fluorophores.[3] In this study, we developed a dynamic metal-enhanced fluorescence microarray assay platform for ultrasensitive detection of NDD biomarkers in blood plasma. The platform is fundamentally based on two core technologies established by our team recently: (1) Magnetic nanochains (MNCs) for assay improvement by eliminating diffusion limitation;[4,5] (2) Metal-enhanced fluorescence (MEF) nanoprobes for signal enhancement.[6] The MNCs undergo synchronous rotation in response to a rotating magnetic field, making them ideal nanomixers to promote fast mixing and analyte transport. We developed a MEF-based nanoplatform by employing gold nanorods as plasmonic substrates and biotinylated proteins as the spacer and linker to anchor fluorescent probes and specific antibody for ultrasensitive high-throughput detection of NDD biomarkers ((Aβ40, Aβ42 and pTau231)). We demonstrated that the dynamic mixing and fluorescence enhancement of our approach can improve the sensitivity by 2-3 order in comparison with conventional microarray assays.

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