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## Developing nanoparticle-based molecular imaging probe for Alzheimer's disease-related enzymes

Alzheimer's disease (AD) has become a pandemic due to our nation's burgeoning aging population. A membrane embedded aspartyl protease complex with presenilin as the catalytic component- γ-secretase and β-site aspartyl cleaving enzyme (BACE1) or β-secretase are responsible for synergistic proteolytic cleavages of amyloid precursor protein (APP) and ultimate generation of amyloid Aβ peptides in AD patients' brain. Their inhibition and modulation have been proposed as therapeutic strategies for AD. Nevertheless, BACE1 knockout mice have phenotypes such as sensorimotor impairments, spatial memory deficits, and displayed seizures. On the other hand, lysosomal aspartyl protease- cathepsin D (CatD) is down regulated at both transcriptional and translational level and its processing is altered in AD fibroblasts. Thus, both BACE1 and CatD have been suggested as potential AD biomarkers. Hence, we intend to develop *in vivo* smart probes targeting BACE1 and CatD as they may be tools for the preclinical and even clinical development of AD therapy and diagnosis. To achieve this goal, we have created a multi-wavelength molecular imaging probe to report on the simultaneous activities of cathepsin D (CatD) and BACE1, and validated this probe with pure enzyme mixtures and cell lines. Magnetofluorescent nanoparticles (cross-linked dextran iron oxide nanoparticles or CLIO) served as a starting material. Peptide substrates containing a terminal near-infrared (NIR) fluorochrome (a fluorophore emitting at 688 nm for CatD or a fluorophore emitting at 775 nm for BACE1) were conjugated to the CLIO nanoparticles. The CatD substrate contained a phenylalanine-phenylalanine cleavage site more specific to CatD than BACE1. The BACE1 substrate contained the sequence surrounding the leucine-asparagine cleavage site of BACE1 found in APP, which is more specific to BACE1 than CatD. The nanoparticles were purified by gel filtration and their fluorescence intensities were determined using a fluorescence plate reader. The CatD nanoparticle demonstrated a 17-fold increase in fluorescence when incubated with CatD, approximately 3 times higher in fluorescence than BACE1. The BACE1 probe exhibited a 8-fold increase in fluorescence when incubated with BACE1, approximately 2 times higher in fluorescence than CatD. Probe specificity was also demonstrated in the human SH-SY5Y cells, in which the probe monitored enzymatic cleavage. In the SH-SY5Y cells, there was a 6-fold increase in CatD fluorescence as well as a 2-fold increase in BACE1 fluorescence. We conclude that this novel molecular imaging probe with a dual NIR fluorochrome can detect both BACE1 and CatD enzymatic activities selectively in either pure enzyme mixtures or cell lines, demonstrating its potential utility as a tool for development of AD therapy and diagnosis.

### Biography

Xudong Huang has completed his PhD from MIT and postdoctoral studies at Massachusetts General Hospital and Harvard Medical School. He is the Co-Director of Neurochemistry Lab, Psychiatry Department of Massachusetts General Hospital. He has published more than 90 papers in reputed journals. He is the Editor-in-Chief for International Journal of Biomedical Nanoscience and Nanotechnology, and has been serving as an editorial board member of repute.

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