

EARLY DETECTION OF TAU ACETYLATION USING ULTRA-HIGH AFFINITY ANTIBODIES

<https://neurodegenerationresearch.eu/survey/early-detection-of-tau-acetylation-using-ultra-high-affinity-antibodies/>

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USA

Title of project or programme

EARLY DETECTION OF TAU ACETYLATION USING ULTRA-HIGH AFFINITY ANTIBODIES

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NIH (NIA)

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01/09/2016

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Research Abstract

Project Summary Acetylation of tau is a recently identified mechanism critical in the initial stages of pathology mediated by tau. Initial results show that tau acetylation occurs early on in disease progression, reduces tau turnover, and promotes aggregation of phosphorylated tau. Therefore, early detection of tau acetylation and monitoring its synergy with tau phosphorylation is a promising route to identifying the mechanism underlying tauopathies. However, existing methods to detect this critical modification have relied on polyclonal antibodies, which have

poorly characterized binding properties. In this proposal, we hypothesize that enhancing the sensitivity of detecting acetylated tau would dramatically improve our ability to study the initial stages of tau mediated pathology. However, yielding high affinity and specificity antibodies against specific protein modification sites is challenging. This requires enhancing antibody affinity while preventing unwanted cross reactivity towards similar binding sites. Even though numerous methods have been developed to screen antibody sequences to quantify and engineer affinity, methods to optimize antibody specificity based on measurement of cross reactivity are virtually non-existent. To address this problem, a novel antibody screening approach based on quantitative measure of antibody specificity will be developed. The proposed high-throughput screening approach will enable simultaneous optimization of antibody specificity and affinity. Using this approach, ultra- high affinity monoclonal antibodies against key acetylation sites specific to AD patients will be generated. The specific aims during this project period are 1) Identifying acetylated tau binding antibodies by screening recombinant antibody libraries, 2) optimizing specificity and affinity of the antibodies through directed evolution, and 3) validation of the antibodies using tissue samples from mouse models and Alzheimer's disease patients. The outcomes of this project will be high quality monoclonal antibodies targeting acetylated tau. If successful, the project will enable early detection of acetylated tau, which has enormous impact on basic biological investigations and novel therapeutic development in tau mediated neurodegeneration.

Further information available at:

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