

## Neuronal exosome-derived human tau toxicity on recipient cells

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**A**lzheimer's disease (AD) is characterized by deposition of beta-amyloid as amyloid plaques and tau as neurofibrillary tangles. While the distribution of beta-amyloid is diffuse and does not correlate well with disease symptomatology, tau deposition follows progression in a synaptically connected pathway. Such progression is the basis of the Braack staging for the pathological diagnosis of AD, and correlate with the severity of patient symptoms. The disease progression suggests spreading of pathology from one area to another in the brain. Recently published work suggest that propagation of toxic protein tau can be mediated by exosomes. Exosomes belong to extracellular vesicles (EVs), which are released by the cells through the late endosomal pathway. We hypothesized that exosomes contain cargos which could mediate propagation of toxic proteins. We isolated exosomes derived from neuronally-differentiated, human induced pluripotent stem cells that expressed the repeat domain of tau P301L and V337M mutations (NiPSCs) and injected them into the wild-type mouse brain. We observed pathological changes including hyperphosphorylated tau, cell loss and blebbing of the dendrites in the recipient mouse neurons *in vivo*. The pathological tau also spread to other cortical and subcortical regions in both hemispheres. These results suggest that exosomes may regulate propagation of neurodegeneration, which may have implications for diagnostic and therapeutic potential.

### Recent Publications

1. Reilly P, Winston CN, Baron K, Trejo M, Rockenstein E, Akers JC, Kfoury N, Diamond M, Masliah E, Rissman RA, Yuan SH. "Novel human neuronal tau model exhibiting neurofibrillary tangles and transcellular propagation." *Neurobiology of Disease*. 106 (2017) 222-234
2. Winston, CN, Rockenstein EM, Adame A, Prikhodko O, Mishra P, Dave KN, Rissman RA\*, Yuan SH\*. "Exosome mediated propagation of human tau is toxic to recipient mouse neurons." Co-corresponding \*corresponding author. *J Alzheimers Dis*. 2019:67(2):541-553.

### Biography

Shauna Yuan, MD, is a board-certified neurologist who specializes in caring for patients with memory disorders and dementia, including Alzheimer's disease, Frontotemporal dementia, Lewy body dementia and Parkinson's dementia. An assistant professor in the UC San Diego School of Medicine, Dr. Yuan is a physician-scientist whose research focuses on Alzheimer's disease and neurodegenerative diseases using novel stem cell and animal models.

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