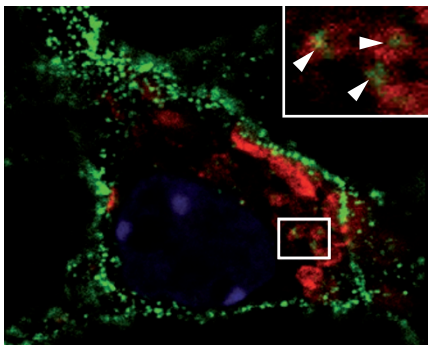
Nature Reviews Neurology **10**, 426 (2014); published online 8 July 2014; doi:10.1038/nrneurol.2014.119

PARKINSON DISEASE

A monoclonal antibody targeting misfolded α-synuclein has therapeutic potential in Parkinson disease

Over the past few years, evidence has emerged that misfolded α-synuclein —the main constituent of the Lewy bodies that accumulate in the brains of patients with Parkinson disease (PD) and related disorders—is transmitted between neurons in a 'prion-like' manner. In a study recently published in *Cell Reports*, a team led by Virginia Lee at the University of Pennsylvania School of Medicine found that propagation of α-synuclein pathology could be inhibited by a monoclonal antibody that specifically targets misfolded α-synuclein. In addition, this antibody ameliorated motor impairments in a mouse model of PD, suggesting potential therapeutic applications.



Confocal microscopy image of cultured primary mouse hippocampal neurons depicts synthetic α-synuclein pffs (green). Pffs are internalized in a neuron, as shown in the inset by colocalization with the lysosomal marker LAMP1 (red). Image courtesy of V. M. Y. Lee.

In vitro experiments show that synthetic α-synuclein preformed fibrils (pffs) are readily internalized by neurons, where they promote misfolding of endogenous α-synuclein. Using a three-chamber cell culture system in which axons and dendrites were the only points of contact between otherwise isolated populations of neurons, Lee and colleagues confirmed that α-synuclein pathology induced by pffs could spread from cell to cell.

The monoclonal antibody Syn303, which is specific for misfolded α-synuclein, was found to block uptake of pffs and propagation of α-synuclein pathology in cell culture. In a mouse model of sporadic PD, intraperitoneal injection of Syn303 led to a reduction of Lewy pathology and dopaminergic cell loss in the brain, and also improved various aspects of motor function, including motor coordination and grip strength.

"We believe that our models open up new opportunities for studying and treating PD, including the identification of new therapeutic targets," concludes Lee. "We plan to refine the immunotherapeutic approach by developing better monoclonal antibodies that have high affinity for α-synuclein pathology and not the normal protein."

Heather Wood

Original article Tran, H. T. *et al.* α-Synuclein immunotherapy blocks uptake and templated propagation of misfolded α-synuclein and neurodegeneration. *Cell Rep.* doi:10.1016/j.celrep.2014.05.033

© 2014 Macmillan Publishers Limited. All rights reserved