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Discovery may lead to a treatment to slow Parkinson's disease

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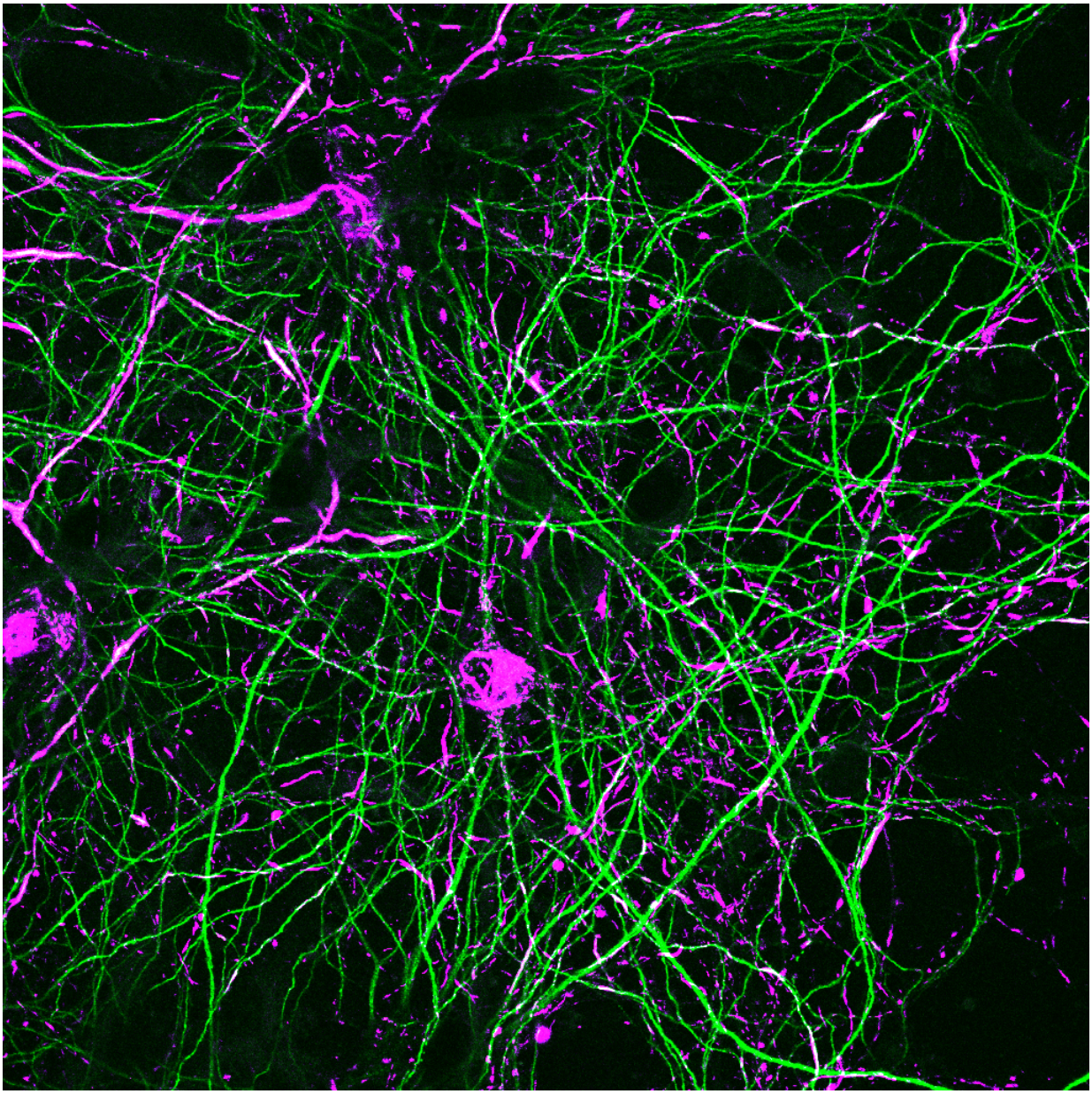

Primary hippocampal neurons from mice express G2019S-LRRK2. The neurons were treated with alpha-synuclein fibrils, and 18 days later immunofluorescence was performed. The magenta shows phospho-alpha-synuclein inclusions in the cell bodies and throughout the axons, which are visualized as green. Credit: UAB

Using a robust model for Parkinson's disease, University of Alabama at Birmingham researchers and colleagues have discovered an interaction in neurons that contributes to Parkinson's disease, and they have shown that drugs now under development may block the process.

The research team has shown that the most common genetic cause of Parkinson's disease—a mutant LRRK2 kinase enzyme—contributes to the formation of inclusions in neurons, resembling one of the hallmark pathologies seen in Parkinson's disease. These inclusions are made up of aggregated alpha synuclein protein, which—the research also shows—can be prevented from forming by using two LRRK2 kinase inhibitor drugs now being developed for clinical use.

The interaction between mutant LRRK2 kinase and alpha-synuclein "may uncover new mechanisms and targets for neuroprotection," the researchers write in a recent *Journal of Neuroscience* paper. "These results demonstrate that alpha-synuclein inclusion formation in neurons can be blocked and that novel therapeutic compounds targeting this process by inhibiting LRRK2 kinase activity may slow progression of Parkinson's disease-associated pathology."

The potential clinical applications for novel neuroprotection strategies in LRRK2-linked Parkinson's need to be tested in other preclinical models of Parkinson's disease, say the researchers, led by corresponding author Laura A. Volpicelli-Daley, Ph.D., and senior author Andrew B. West, Ph.D., Center for Neurodegeneration and Experimental Therapeutics,

UAB Department of Neurology.

"These data give us hope for the clinical potential of LRRK2 kinase inhibitors as effective therapies for Parkinson's disease," Volpicelli-Daley said. "The LRRK2 kinase inhibitors may inhibit the spread of pathologic alpha-synuclein, not only in patients with LRRK2 mutations, but in all Parkinson's disease patients. Future studies to validate the safety and efficacy of the LRRK2 inhibitors will be necessary before testing the inhibitors in human clinical trials."

Besides Parkinson's disease, alpha-synuclein also plays a central role in development of dementia with Lewy bodies and multiple system atrophy, and it is associated with Alzheimer's disease and other neurodegenerative disorders.

Research Details

The Parkinson's disease model developed by Volpicelli-Daley applies very low concentrations of pre-formed fibrils of alpha-synuclein to in vitro or in vivo neurons. This causes formation of modified alpha-synuclein inclusions that share morphology with those found in the Parkinson's disease brain after death.

They used this model to test the effects of neuron expression of the mutant LRRK2 ("lark two") kinase, G2019S-LRRK2, on the formation of the inclusion pathology.

They found that:

- G2019S-LRRK2 enhanced alpha-synuclein inclusions in primary hippocampal neurons from the hippocampus region of the brain, 18 days after fibril exposure, as compared with neurons that over-expressed normal LRRK2.

- The effects of G2019S-LRRK2 expression in the fibril-exposed neurons were lessened by very low concentrations of potent and selective preclinical drugs that inhibit LRRK2 kinase. This suggested that the kinase activity of G2019S-LRRK2, which adds a phosphate onto target proteins, underlies the faster formation of pathologic alpha-synuclein inclusions.
- G2019S-LRRK2 expression enhanced alpha-synuclein inclusion formation in dopamine neurons from the region of the brain called the substantia nigra pars compacta. The substantia nigra pars compacta is the area of the brain that dies in Parkinson's disease, so this experiment further supports a link between the G2019S-LRRK2 mutation and Parkinson's pathogenesis.

As a control, they used anti-sense oligonucleotides to knock down the expression endogenous alpha-synuclein in neurons that expressed G2019S-LRRK2, and this prevented formation of inclusions.

In fluorescence-recovery-after-photobleaching experiments, they found there was a larger pool of mobile alpha-synuclein, as opposed to membrane-bound alpha-synuclein, in neurons that expressed G2019S-LRRK2. Recent work by others has shown that mobile alpha-synuclein is prone to misfolding and aggregation, so the researchers hypothesize that the G2019S-LRRK2 mutation may contribute to Parkinson's susceptibility by boosting the amounts of mobile alpha-synuclein in neurons.

More information: L. A. Volpicelli-Daley et al, G2019S-LRRK2 Expression Augments -Synuclein Sequestration into Inclusions in Neurons, *Journal of Neuroscience* (2016). DOI: 10.1523/JNEUROSCI.3642-15.2016