Scientists design a potential drug compound that attacks Parkinson's disease on two fronts

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Scientists from the Florida campus of The Scripps Research Institute (TSRI) have found a compound that could counter Parkinson's disease in two ways at once.

In a new study published recently online ahead of print by the journal *ACS Chemical Biology*, the scientists describe a "dual inhibitor"- two compounds in a single molecule— that attacks a pair of proteins closely associated with development of Parkinson's disease.

"In general, these two enzymes amplify the effect of each other," said team leader Phil LoGrasso, a TSRI professor who has been a pioneer in the development of JNK inhibitors for the treatment of neurodegenerative diseases. "What we were looking for is a high-affinity, high-selectivity treatment that is additive or synergistic in its effect—a one-two punch."

That could be what they found.

This new dual inhibitor attacks two enzymes—the leucine-rich repeat kinase 2 (LRRK2) and the c-jun-N-terminal kinase (JNK)—pronounced "junk." Genetic testing of several thousand Parkinson's patients has shown that mutations in the LRRK2 gene increase the risk of Parkinson's disease, while JNK has been shown to play an important role in neuron (nerve cell) survival in a range of neurodegenerative diseases.

As such, they have become highly viable targets for drugs to treat disorders such as Parkinson's disease.

A dual inhibitor ultimately would be preferred over separate individual JNK and LRRK2 inhibitors because a combination molecule would eliminate complications of drug-drug interactions and the need to optimize individual inhibitor doses for efficacy, the study noted.

Now the team's new dual inhibitor will need to be optimized for potency, high selectivity (which reduces off-target side effects) and bioavailability so it can be tested in animal models of Parkinson's disease.

More information: "A Small Molecule Bidentate-Binding Dual Inhibitor Probe of the LRRK2 and JNK Kinases," pubs.acs.org/doi/abs/10.1021/cb3006165

Provided by The Scripps Research Institute

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