Study Shows Promise for LRRK2 Inhibitor Approach to Parkinson's

Research is focusing on the LRRK2 gene as a means of neuroprotection.

BY MICHAEL J. FOX FOUNDATION STAFF

A recently published study funded by The Michael J. Fox Foundation and using MJFF research tools showed two avenues through which inhibiting the function of the protein LRRK2 may help treat Parkinson's. The paper from the laboratory led by Andrew West, PhD, from the University of Alabama at Birmingham, appears in the *Proceedings of the National Academy of Sciences.*

Mutations in the LRRK2 gene are the greatest known genetic cause of PD, accounting for one to two percent of all cases of PD and more in certain ethnic populations. Mutations appear to heighten activity of the LRRK2 protein. Therefore, development of LRRK2 inhibitors is a priority of the Foundation.

"LRRK2 is one of our most promising areas of research toward a therapy to stop or slow the progression of Parkinson's, and MJFF has established a roadmap to learn more about this target and build the infrastructure to accelerate discovery and drug development," said Marco Baptista, PhD, MJFF associate director of research programs.

Part of the Foundation's LRRK2 roadmap is the creation of research tools such as pre-clinical models and antibodies important to hasten the development of future therapeutics. The LRRK2 knockout pre-clinical model is bred without the LRRK2 gene, which can mimic the effects of a LRRK2 inhibitor drug.

Dr. West and his team studied both the LRRK2 knockout model and a wild-type model (typical form) when they introduced an excess of the protein alpha-synuclein. Parkinson's is marked by clumps of alpha-synuclein in brain cells, which leads to cell death. The scientists compared the effects of too much alpha-synuclein in a LRRK2 knockout and a control model.

They found cell loss from the excess alpha-synuclein in the wild-type model but not in the LRRK2 knockout, meaning inhibiting LRRK2 could protect from neurodegeneration. Using new antibodies developed by MJFF, Dr. West also found that LRRK2 was highly expressed in cells that responded to injury, leading to another hypothesis that inhibiting LRRK2 may help alleviate a specific type of inflammation. To test this hypothesis, they also introduced an inflammatory agent into both models and found, again, that the wild-type model experienced cell loss while the LRRK2 knockout did not.

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Often tests of LRRK2 inhibitors use models with LRRK2 gene mutations. Since this study compared only knockout and wild-type models, its findings suggest LRRK2 inhibition may also benefit people who have PD but no LRRK2 mutations (the majority of PD patients).

"This broadens the window of those who might be helped by this therapeutic approach beyond only those with a LRRK2 mutation," said Dr. West. "Seeing protection in this study gave us the green light to attempt and copy the symptomatic results pharmacologically, to help find a drug that we can bring to clinical trial." ■

Adapted from the Michael J. Fox Foundation website: michaeljfox.org.