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Research may provide missing link in search for Parkinson's disease therapeutics

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Parkinson's disease (PD), a chronic, progressive and devastating neurodegenerative motor disease affecting as many as one million Americans, is complex. Its causes likely include a combination of genetic, environmental and other lifestyle factors that influence gene expression. While progress has been made, a fundamental understanding of how the disease develops on the molecular level is still lacking, due in large part because there is no good way to model the disease. Research from the Buck Institute is poised to change that. Buck Institute faculty Xianmin Zeng, PhD, has derived 10 induced pluripotent stem cells (iPSC) lines from PD patients and is in the process of depositing those lines along with a wealth of related genomic information about them into an NIH-approved facility for use by the larger research community. Details about the iPSC lines will publish in *PLOS One* on Wednesday, May 18.

"We think this is the largest collection of patient-derived lines generated at an academic institute," said Zeng, who is also developing a stem cell replacement therapy for PD. "We believe the lines and the datasets we have generated from them will be a valuable resource for use in modeling PD and for the development of new therapeutics." Given the aging of the population and the fact that current therapies only address symptoms, the need for a relevant disease model for PD is urgent. Affected neurons cannot be obtained from PD patients (except for post-mortem tissue which has limited value) and Zeng says animal studies, while valuable often provide an inadequate representation of what occurs in human patients.

The iPSCs were made from skin cells donated by PD patients carrying the most common mutations linked to the disease: SNCA, LRRK2, PARK2 and GBA. Using an integration-free method which minimized genomic alteration, the cells were reprogrammed to behave like embryonic stem cells and then were coaxed into becoming dopaminergic neurons, the nerve cells affected in PD. Whole genome expression analysis was done at each stage of differentiation.

"This work combined with dozens of other control, isogenic and reporter iPSC lines developed by Dr. Zeng will enable researchers to model PD in a dish," said Brian Kennedy, PhD, Buck Institute President and CEO. "Her work, which we are extremely proud of, will help researchers dissect how genes interact with each other to cause PD, and assist scientists to better understand what experimental drugs are doing at the molecular level to decide what drugs to use based on mutations."

In addition to aiding drug development Zeng hopes the cell lines will also be used to develop biomarkers of PD that would enable the identification of patients at risk prior to the onset of the disease.

More information: Olga Momcilovic et al. Derivation, Characterization, and Neural Differentiation of Integration-Free Induced Pluripotent Stem Cell Lines from Parkinson's Disease Patients Carrying SNCA, LRRK2, PARK2, and GBA Mutations, *PLOS ONE* (2016). DOI: 10.1371/journal.pone.0154890

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