2024 IMPACT CIRCLE

Project Title: Investigating Lactate as an Exercise Mimetic in *C. elegans* Models of Parkinson's Disease

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Unmet Need/Primary Question: Exercise has been shown to slow the progression of Parkinson's disease (PD.) However, the underlying mechanisms are not completely understood, specifically, how it may impact dysautonomia — dysregulation of the sympathetic and parasympathetic nervous systems, also known as the "flight-fight" and "rest-digest" states, which underly many symptoms present in PD such as gastrointestinal dysfunction and anxiety. Dysautonomia may result from the accumulation and spread of alpha-synuclein aggregates through the "gut-brain axis" or vagus nerve, but while exercise may be ameliorative, it is not always accessible for people with Parkinson's (PwPs.) As such, an exercise mimetic or supplement may be beneficial. Lactate is an exercise metabolite that is increased during stress response i.e. "flight-fight" mechanisms, and exerts many benefits that range from improved exercise performance to neuroprotection against proteotoxic stress, which was also recently supported by our own data in *C. elegans* models of PD. However, the benefit of lactate in the context of PD is not quite clear — on the one hand, lactate may protect neurons from alpha-synuclein proteotoxic stress, while on the other, increased lactate levels have been observed in cerebral spinal fluid (CSF) of PwPs. Here, we hope to better understand lactate's therapeutic potential for dysautonomia in Parkinson's.

Novel Hypothesis: We hypothesize that lactate behaves as an exercise mimetic involved in the upregulation of the "flight-fight" response, ultimately mitigating imbalances between "flight-fight" and "rest-digest" states.

Project Proposal: *C. elegans* exhibit a similar, albeit simpler, nervous system to mammals. We propose to study lactate's effect on "flight-fight" and "rest-digest" mechanisms in *C. elegans* models of PD to better understand lactate's therapeutic potential in mitigating dysautonomia.

Description of Potential Impact: Exploring lactate's relevance to the stress response system in the context of Parkinson's can provide more information about its viability as an exercise mimetic. We plan to begin our work in understanding the underlying mechanisms in *C. elegans* models of PD with future experiments in an N=1 clinical trial where lactate levels and stress response will be measured in a PwP undergoing an individualized exercise program.