

## **The link between purine metabolism and Parkinson's Disease**

Fatemeh Seifar, MD, Principal Investigator; H. A. Jinnah MD, PhD, Co-Principal Investigator

Purines are important components of DNA, ATP, GTP and are crucial for cell function and energy consumption. Cells use two main pathways to metabolize purines: *de novo* purine synthesis and recycling. Uric acid (UA) is the end-product of purine metabolism and is linked to incidence and progression of Parkinson's disease (PD). The link between low UA and PD is quite strong and reproducible, however, the biological mechanism linking UA to PD is still undiscovered. Since UA level is closely linked to purine metabolic pathway, low UA could be due to lower purine production in PD. This project is aimed to discover the link between purines metabolism and PD. We will use human derived induced pluripotent stem cells (iPSC)s to develop an in vitro model of dopamine neurons, the most relevant cells to PD. We will measure purine pools in PD neurons relative to controls (aim 1) to determine whether low UA is due to low purine production. The results may show low purines or the opposite, but even if the levels of purines were normal, this doesn't refute the low capacity to produce purines due to downstream and compensatory pathways. So, we will measure the expression of key enzymes in purine pathway (aim 2). Then, we will challenge purine metabolism to see how PD neurons respond to high purine demands (aim 3). Our findings will provide clues to determine the biological mechanisms that link low UA to PD.

## **Cortical activity underlying impaired reactive and anticipatory postural control in Parkinson's disease**

Lena H. Ting, PhD, Principal Investigator; Michael Borich, DPT, PhD, Co-Principal Investigator; J Lucas McKay, PhD, MSCR, Co-Investigator; Svyetlana Miocinovic, MD PhD, Co-Investigator

Interactions between balance and cognitive impairments in older adults with and without Parkinson's disease (PD) lead to reduced mobility and falls, through unknown mechanisms. Our recent work showed that cognitive set-shifting impairment is associated with fall history in older adults with and without PD – even after controlling for overall cognitive impairment. We have developed expertise using high-resolution scalp electroencephalography (EEG) during reactive balance perturbations, revealing a number of associations between evoked cortical activity to cognitive set shifting and dual-task interference in older adults with and without PD. Here, we seek to identify cortical mechanisms underlying cognitive-motor interactions in more ecologically-relevant standing balance conditions that support upper-limb motor tasks. These are the first experiments we propose on our newly-acquired KinArm End-Point Lab™, a graspable robot that monitors and manipulates location of the hand in 2-dimensional space during standing or sitting. We will record EEG activity while participants stand and hold the hand within a target or reach to a target. In **Aim 1**, we will compare cortical activity during reactive versus anticipatory postural control in older adults (HOA) and older adults with PD. In **Aim 2**, we will test the hypothesis that cortical activity related to error assessment will be greater as the consequences of perturbations increase, and that this relationship will be impaired in PD. In **Aim 3**, we will compare spatiotemporal cortical activity during cognitive dual-task conditions using a robotic Trail Making Test (a test of cognitive set-shifting), conducted in the standing position in PD vs HOA. If successful, we will develop an initial set of instrumented tests to precisely and objectively probe cognitive-motor impairments in PD during coordinated upper and lower limb movements, time-locked to spatiotemporal cortical activity. We anticipate this research to lead to a number of externally-funded clinical and neurophysiological studies of PD pathophysiology and treatment.