

Name: Akhil Sharma  
PI Name: Anna Moszczynska

Email: akhilsharma@wayne.edu  
PI email: amosz@wayne.edu

## **Methamphetamine Neurotoxicity Does Not Contribute to Methamphetamine Use Disorder in Parkin Knockout Rats**

Akhil Sharma<sup>1</sup>, Rolando Garcia Milian<sup>2</sup>, TuKiet Lam<sup>3</sup>, and Anna Moszczynska<sup>1</sup>

<sup>1</sup>Pharmaceutical Sciences, Wayne State University; <sup>2</sup> Center for Biomedical Data Science, Yale University, <sup>3</sup>Discovery Proteomics Core, Yale University

There is no FDA-approved medication for methamphetamine (METH) use disorder. New therapeutic approaches are needed, especially for people who use METH heavily and are at high risk for overdose. In addition to being highly addictive, METH can cause neurodegeneration of nigrostriatal monoaminergic terminals when abused at high doses. People who heavily abuse METH suffer the most from METH abuse-related neuropsychological problems related to METH neurotoxic effects. We previously showed that *parkin* gene knockout (*Park2*<sup>-/-</sup>) rats self-administered more METH in an extended-access METH self-administration model of heavy METH abuse. As compulsive habitual METH abuse involves the dorsal striatum, we hypothesized that METH neurotoxicity in this brain area would contribute to the observed predisposition of *Park2*<sup>-/-</sup> rats to METH use disorder. Using the state-of-the art proteomics, we established that *parkin* knockout decreased striatal responses to oxidative stress as well as fatty acid and amino acid metabolism. Striatal electron transport chain enzymes showed deficits in selective subunits. However, higher than in controls METH intake in *parkin* knockout rats did not lead to higher METH neurotoxicity in the parkin-deficient striatum as compared to wild-type striatum. These results suggest that METH neurotoxicity does not contribute to higher METH intake by *Park2*<sup>-/-</sup> rats relative to the wild-types and that compulsive habitual METH abuse may be mediated by decreased energy metabolism in *Park2*<sup>-/-</sup> genotype.