Dopamine 2016
Vienna, 5–8 September 2016

**MEETING ABSTRACT**

**A11.4**
Dissecting the role of functional selectivity of dopamine D₃ receptor agonists in L-DOPA-induced dyskinesia and Parkinson’s disease
Wei Xu¹, Courtney Marshall¹, Courtney Williams², Jay Schneider² and Sandhya Kortagere¹,*

¹Drexel University College of Medicine, Philadelphia, PA, United States of America; ²Thomas Jefferson University College of Medicine, Philadelphia, PA, United States of America

The dopamine D₃ receptor (D₃R) has been suggested to play a critical role in the etiology of both Parkinson’s disease (PD) and levodopa (L-DOPA)-induced dyskinesia (LID). Several dopaminergic agents including L-DOPA have been used as therapeutic agents for Parkinson’s disease with limited success for therapy. We have recently designed a class of atypical D₃R agonists (SK609 and SK608) with functional selectivity to G protein-dependent, but β-arrestin-independent signaling features. In addition, these atypical agonists do not induce desensitization of D₃Rs but induce dose- and time-dependent internalization of D₃Rs over-expressed in CHO cells. These results are in complete contrast with the signaling properties of other known D₃R agonists such as dopamine and PD128907, which induce desensitization but not internalization of D₃Rs. D₃Rs are only known to undergo pharmacological sequestration in response to these known D₃R agonists. Our compounds improved motor impairments associated with PD-like symptoms in a 6-OHDA induced hemiparkinson rat model of PD. SK609 and SK608 demonstrated synergistic effects with L-DOPA in improving the motor symptoms in the MPTP-induced non-human primate model of PD. In rodents, chronic treatment of SK609 or SK608 did not induce abnormal involuntary movements (AIMs) but significantly reduced AIMs induced by L-DOPA when used adjuvantly with L-DOPA. Our results suggest that the internalization of D₃Rs induced by SK608 contributes to the re-sensitization of D₃R signaling and receptor trafficking which may explain its novel therapeutic efficacy observed in alleviating the symptoms of PD in rodent and non-human primate models and LID in a rodent PD model.

*Submitting author e-mail: sandhya.kortagere@drexelmed.edu