DOES ADENOSINE A\textsubscript{2A} RECEPTOR ANTAGONISM IMPACT LONG-TERM OUTCOME IN PARKINSON’S DISEASE? ASSESSMENT OF SCH 412348 IN A MOUSE MODEL OF PROGRESSIVE DOPAMINE DEPLETION

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Introduction: Adenosine A\textsubscript{2A} receptor antagonists are acutely efficacious in animal models of Parkinsonian motor deficits, and show palliative improvements in Parkinson’s disease patients. It is currently unclear whether A\textsubscript{2A} antagonism has disease-modifying benefits, partly due to lack of appropriate preclinical models. A recent study suggested that chronic A\textsubscript{2A} inhibition delayed locomotor decline in MitoPark mice, a model of progressive dopamine depletion (Marcellino et al., Neurobiol. Dis, 40:460, 2010). We examined whether the consequences of A\textsubscript{2A} inhibition persist after drug withdrawal in this model.

Aim: To determine if the A\textsubscript{2A} receptor antagonist SCH 412348 shows symptomatic and disease-modifying benefit in MitoPark mice.

Methods: MitoPark mice were treated with SCH 412348 (1 or 3 mg/kg, PO, QD) or vehicle from 10 to 16 weeks of age (from onset of motor symptoms). Littermate wildtype mice received vehicle. To assess acute effects on motor behaviors, open field locomotion, rotarod and hindlimb bradykinesia were assayed 1h post-compound at 2-week intervals. After dosing was discontinued, behaviors were re-assessed at 2 and 9 days off-drug.

Results: MitoPark mice showed progressive declines in motor activities over time. SCH 412348 dose-dependently improved all parameters. After compound was discontinued, significant improvements in locomotor activities persisted at 2 d off-drug (1 and 3 mg/kg) and 9d off-drug (3 mg/kg).

Conclusion: Persistence of locomotion improvements in MitoPark mice >1 week after SCH412348 withdrawal may reflect an influence of A\textsubscript{2A}-R antagonism on the rate of disease progression in this model. We are currently examining whether pathologic changes in post-mortem brain support this hypothesis.