DEVELOPMENT OF NOVEL PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF MOTOR AND NON-MOTOR FEATURES OF PARKINSON'S DISEASE

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Introduction: Prolonged L-DOPA use leads to adverse motor side effects and fails to address cognitive impairments common in Parkinson's disease (PD). Phosphodiesterase 1 (PDE1) inhibitors, which act in brain circuits that mediate movement and cognition, represent a novel treatment for motor and non-motor features of the disease.

Aims: Intra-Cellular Therapies Inc (ITI) is developing novel PDE1 inhibitors with high potency (subnanomolar IC50) and selectivity for PDE1 (>2700 selective vs other PDE families) for treatment of motor and non-motor symptoms of PD.

Methods: IC200214, the development candidate, was tested for potentiation of L-DOPA motor effects in haloperidol- and reserpine-induced catalepsy assays and for effects on forelimb use in unilateral 6-OHDA-lesioned mice in the cylinder test. Memory was tested in the novel object recognition (NOR) model.

Results: IC200214 significantly reversed haloperidol-induced catalepsy with a minimal effective oral dose (MED) of ~0.3 mg/kg, without affecting basal locomotor activity, and potentiated effects of sub-threshold doses of L-DOPA to reverse reserpine-induced catalepsy and restore forelimb use in the cylinder test. IC200214 broadly enhanced memory performance in rats, improving memory acquisition, consolidation, and retrieval with an oral MED of ~0.1-0.3 mg/kg in NOR. IC200214 is effective in both catalepsy and NOR models at plasma free concentrations that approximate the IC50 for PDE1 inhibition.

Conclusions: PDE1 inhibitors may address motor disability and offer unique improvement in the cognitive impairments in PD that are not treated by available medications. IC200214 is a safe, orally-bioavailable compound advancing in preclinical development as a dose-sparing or stand-alone treatment for PD.