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Translational Contract Research

Parkinson's disease – Primate model of dyskinesia

Available for use in both new (marmoset) and old-world (macaque) primates, MPTP induces degeneration of dopaminergic neurons in the substantia nigra which translates to a behavioural impairment similar to that observed in people with Parkinson's disease. Repeated administration of L-DOPA induces dyskinesia and other motor complications, recapitulating what is seen in the clinic.

Well characterised primate model of L-DOPA-induced dyskinesia

Excellent face validity allows application of modified clinical rating scales

Highly predictive of Phase II clinical efficacy

Rapid evaluation of test compounds

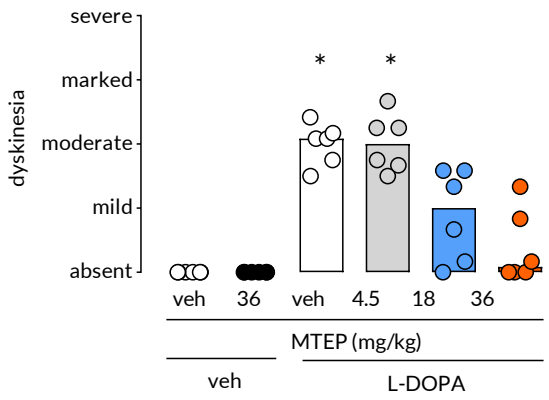
Model overview

Marmosets or macaques, previously rendered parkinsonian by MPTP administration, are administered twice-daily L-DOPA (25 mg/kg/day *p.o.*) over a 12-week period until the development of dyskinesia. Stable and robust dyskinesia can be maintained over several years by regular administration of L-DOPA. The model can be applied to examine effects of treatment on the development of dyskinesia or dyskinesia once established.

Model highly predictive of Phase II clinical efficacy

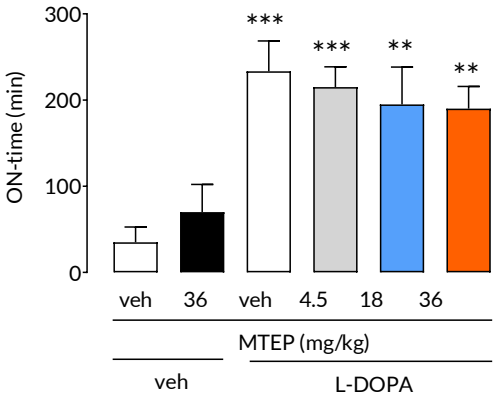
Several compound classes evaluated in the MPTP primate model of dyskinesia have also been tested in Phase II clinical studies. The dyskinetic MPTP primate has excellent face and predictive validity for treating dyskinesia and has been instrumental in the development of several approaches that are currently used to treat motor complications in PD.

Compound class	NHP	Phase II
NMDA receptor antagonists	Yes	Yes
mGlu5 NAMs	Yes	Yes
AMPA antagonists	Yes	Yes
alpha adrenergic antagonists	Yes	Yes
5-HT1A agonists	Yes	Yes
5-HT1B/D antagonists	Yes	Yes
5-HT2A antagonists/inverse agonists	Yes	Yes
mu opioid antagonists	Yes	N/A
alpha 7 nicotinic agonists	Yes	N/A
beta 2 nicotinic agonists	Yes	N/A
SV2A	Yes	No



L-DOPA-induced dyskinesia can be reversed by pharmacological intervention. L-DOPA-induced dyskinesia can be reversed by a wide range of pharmacological interventions. In this example MTEP, an negative allosteric modulator at the mGluR5 receptor, dose-dependently reduces L-DOPA induced dyskinesia.

Effect of test compounds on dyskinesia and parkinsonian symptoms can be assessed simultaneously. It is critical that compounds that reduce L-DOPA induced dyskinesia do so without reducing the anti-parkinsonian benefits of L-DOPA. The primate model of dyskinesia allows the assessment of the effect of test compounds on both dyskinesia and parkinsonian symptoms in the same animal, thus providing a strong go/ no-go decision for continued development.



Experimental readouts

Behavioural - Behavioural assessments include the monkey parkinsonian disability (mPDRS) rating scale and dyskinesia rating scale (NHPDysRs), the primate equivalents of the clinical rating scales used to assess disability and dyskinesia in PD patients. Additional behavioural endpoints include home-cage activity, observation-cage activity and fine motor control.

Post-mortem – Generally, dyskinetic macaques are used to evaluate the effect of test compounds on dyskinesia. This endpoint is highly translatable into Phase II clinical studies. If required, post mortem analyses can include striatal dopamine and dopamine transporter and the number of number of tyrosine-hydroxylase positive cells in the substantia nigra. Additional post-mortem measures can be incorporated at the request of the client.

Imaging - We offer both MRI and PET imaging that allows longitudinal measurement of markers of dopaminergic function and metabolism.

Pharmacokinetics, safety and blood chemistry - Can be incorporated into all studies. Blood and CSF can be sampled throughout the study and functional observational battery and blood chemistry can be used to assess off-target effects and adverse effects.

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