The appearance of dyskinesia, involuntary movements, represents a debilitating complication of levodopa (L-Dopa) therapy for Parkinson’s Disease (PD). Yet, L-Dopa remains the “gold standard” treatment for PD because it efficaciously ameliorates akinesia, bradykinesia and rigidity typical of PD. However, 80% of patients develop L-Dopa induced dyskinesia (LID) after 5 years of L-Dopa therapy, cutting short the effective window of L-Dopa therapy which is estimated to be 10 to 15 years for the majority of patients. The cardinal features of PD are caused by the relentlessly progressive degeneration of dopamine (DA) neurons of the midbrain. These neurons do not only communicate by dopamine, but also other cell signaling molecules, leaving open the possibility that drug induced imbalances between dopaminergic and other signaling modalities contribute to LID.

We discovered a novel signal transduction pathway originating from DA neurons. Antagonists of this pathway facilitate LID formation while agonists inhibit the formation of LID and ameliorate the display of established LID in murine and non human primate models of LID. In addition, agonists ameliorate motor habit formation, cognitive flexibility and compulsory deficits associated with L-Dopa therapy. We further established a discovery platform for the identification of targets downstream of this pathway with utility in basal ganglia diseases.

**APPLICATIONS**

- Agonists given as an adjuvant to L-Dopa are a novel pharmacological intervention that will
  a) block or reduce the formation and display of LID.
  b) ameliorate motor habit formation, cognitive flexibility and compulsory deficits.
- Use of a highly specific, scalable discovery- and validation- platform for the identification of novel drug targets downstream of our lead compounds for broadening compound base.

**ADVANTAGES**

- Drug intervention efficacious in
  a) Blocking the formation of LID when started with L-Dopa therapy.
  b) Ameliorating the display of established LID when given acutely with L-Dopa.
- Established discovery and validation platform for broadening compound structures starting with existing leads.
- Clear path to selective, PD and basal ganglia specific drug targets in same pathway to broaden compound base.

**MARKET**

The market for LID avoiding drugs could be foreseen as two folded:
1) In 2009 standard care cost for LID management was about $8000 per year per patient, indicating that drugs avoiding LID could thus be valued significantly higher.
2) An adjuvant strategy that would avoid LID will prolong the therapeutic window of L-Dopa from about 8 to possibly 15 years and therefore significantly increase, possibly double, the sale of L-Dopa, which reached 250 t and $101 billion worldwide in 2013 (Patil, 2013).

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