Other drugs such as anticholinergics and nicotinic acetylcholine receptor agonists may be useful but their efficacy for PD remains to be confirmed (7). Current research also focuses on neuroprotective treatments, but none of them provided evidence of improved degeneration. They target apoptosis (omigapil, CEP-1347), glutamate receptors, adenosine A2A receptor, calcium channels (isradipine), growth factors (GDNF), alpha-synuclein and inflammation (8).

Ongoing pharmaceutical research has shown a growing interest on gene therapy and neural transplantation (8).

WO 2009/133128, WO 2009/133141, WO 2009/133142, WO 2011/054759, WO 2009/068668, WO 2009/153291 disclose potential treatments for several neurodegenerative diseases, among which, PD.

PD remains so far an incurable disease and no effective disease-modifying treatment has been discovered yet. Therefore, current treatments aim at relieving symptoms and alleviate the slow progression of the disease.

SUMMARY ~~OF INVENTION~~

The present ~~invention~~ disclosure relates to new therapeutic methods and compositions for treating Parkinsonism. The ~~invention~~ disclosure stems, inter alia, from the identification of drug combinations which provide improved therapeutic effect and clinical benefit to subjects having Parkinsonism condition, particularly subjects having Parkinson's disease.

More particularly, an object of the ~~invention~~ disclosure relates to a composition for use in the treatment of Parkinsonism, particularly Parkinson's disease, comprising one, preferably at least two drugs selected from acamprosate, baclofen, cinacalcet, mexiletine, sulfisoxazole and torasemide, or a salt, prodrug, derivative of any chemical purity, or sustained-release formulation thereof.

A further object ~~of the invention~~ is a method for treating Parkinsonism, particularly Parkinson's disease, in a subject in need thereof, comprising administering to the subject at least two drugs selected from acamprosate, baclofen, cinacalcet,

mexiletine, sulfisoxazole and torasemide, or a salt, prodrug, derivative of any chemical purity, or sustained-release formulation thereof.

Preferred examples of drug combinations ~~for use in the invention~~ include, *e.g.*, baclofen and acamprosate, baclofen and cinacalcet, mexiletine and cinacalcet, torasemide and baclofen, or torasemide and sulfisoxazole. In a particular embodiment, the compositions and methods further comprise Levodopa.

The compositions ~~in the invention~~ may further comprise one or several pharmaceutically acceptable carrier(s) or excipient(s), and they may be administered repeatedly to the subject. Preferred compositions are administered orally. Moreover, the drugs may be formulated or administered together, separately or sequentially.

The ~~invention~~ disclosed compositions ~~is~~are suitable for treating Parkinsonism in any mammalian subject, particularly in a human subject, at any stage of the disease. The ~~invention~~ disclosure may be used *e.g.*, to retard the development of the disease, to reduce, delay or prevent tremor, hypokinesia (*e.g.*, bradykinesia, akinesia, rigidity) postural instability, and/or pain, and/or to increase survival.

One aspect of the invention relates to the use of a composition comprising acamprosate and baclofen or a salt, prodrug, derivative of any chemical purity, or sustained release formulation thereof, in the manufacture of a medicament for the treatment of parkinsonism.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Effect of cinacalcet and mexiletine combination therapy against glutamate toxicity on neuronal cortical cells. The glutamate intoxication is significantly prevented by the combination of cinacalcet (64 pM) and mexiletine (25.6 pM) whereas, at those concentrations, cinacalcet and mexiletine alone have no significant effect on intoxication. *: $p<0.001$, significantly different from glutamate intoxication; (ANOVA + Dunnett Post-Hoc test).

Figure 2: Effect of sulfisoxazole and torasemide combination therapy against glutamate toxicity on neuronal cortical cells. The glutamate intoxication is significantly prevented by the combination of sulfisoxazole (6.8 nM) and torasemide (400 nM) whereas, at those concentrations, sulfisoxazole and torasemide alone have no significant effect on intoxication.*: $p<0.001$, significantly different from glutamate intoxication; (ANOVA + Dunnett Post-Hoc test).