WO2009133128, WO2009133141, WO2009133142 and WO2011054759 disclose drug combinations for use in the treatment of AD.

Despite active research in this area, there is still a need for alternative or improved efficient therapies for neurological disorders and, in particular, neurological disorders which are related to glutamate and/or amyloid beta toxicity. The present invention provides new treatments for such neurological diseases of the central nervous system (CNS) and the peripheral nervous system (PNS).

SUMMARY ~~OF INVENTION~~

It is an object of the present ~~invention~~disclosure to provide new therapeutic methods and compositions for treating neurological disorders. More particularly, the ~~invention~~disclosure relates to compositions and methods for treating neurological disorders related to glutamate and/or amyloid beta toxicity, based on a combination of Baclofen and Acamprosate.

The ~~invention~~disclosure stems, inter alia, from the unexpected discovery, by the inventors, that the combination of Baclofen and Acamprosate provides substantial and unexpected benefit to patients with Alzheimer's disease. Moreover, the inventors have surprisingly discovered that this combination provides substantial and unexpected protection of neuronal cells against various injuries encountered in neurological disorders including glutamate toxicity. Thus, this combination of Baclofen and Acamprosate constitutes an efficient treatment for patients suffering from, predisposed to, or suspected to suffer from neurological disorders.

An object of this ~~invention~~disclosure therefore relates to compositions comprising a combination Baclofen and Acamprosate, for use in the treatment of a neurological disorder, particularly AD and related disorders, Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease (PD), neuropathies (for instance neuropathic pain or alcoholic neuropathy), alcoholism or alcohol withdrawal, Huntington's disease (HD) and spinal cord injury.

In one aspect, there is provided the use of a composition comprising Baclofen and Acamprosate, or pharmaceutically acceptable salts thereof, for the manufacture of a medicament for treating Alzheimer's disease or a related disease selected from senile dementia of AD type (SDAT), Lewis body dementia, mild cognitive impairment (MCI) and age-associated memory impairment (AAMI).

In another aspect, there is provided the use of Baclofen, or a pharmaceutically acceptable salt thereof, in combination with at least Acamprosate, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating Alzheimer's disease or a related disease selected from senile dementia of AD type (SDAT), Lewis body dementia, mild cognitive impairment (MCI) and age-associated memory impairment (AAMI).

In another aspect, there is provided the use of Baclofen, or a pharmaceutically acceptable salt thereof, in combination with at least Acamprosate, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for improving cognitive symptoms in a subject suffering from, predisposed to, or suspected to suffer from Alzheimer's disease.

In another aspect, there is provided the use of Baclofen, or a pharmaceutically acceptable salt thereof, in combination with at least Acamprosate, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for protecting neuronal cells against amyloid beta and/or glutamate toxicity, in a subject suffering from, predisposed to, or suspected to suffer from Alzheimer's disease.

In another aspect, there is provided a composition comprising Baclofen, Acamprosate and Donepezil, or pharmaceutically acceptable salts thereof.

In another aspect, there is provided a composition comprising Baclofen and Acamprosate, or pharmaceutically acceptable salts thereof, for use as a medicament.

The composition of the ~~invention~~disclosure may contain Baclofen and Acamprosate as the only active ingredients. Alternatively, the compositions may comprise additional active

ingredient(s). In this regard, a further object of this ~~invention~~disclosure relates to a composition comprising a combination of Baclofen, Acamprosate, and at least one third compound selected from Sulfisoxazole, Methimazole, Prilocaine, Dyphylline, Quinacrine, Carbenoxolone, Aminocaproic acid, Cabergoline, Diethylcarbamazine, Cinacalcet, Cinnarizine, Eplerenone, Fenoldopam, Leflunomide, Levosimendan, Sulodexide, Terbinafine, Zonisamide, Etomidate, Phenformin, Trimetazidine, Mexiletine, Ifenprodil, Moxifloxacin, Bromocriptine or Torasemide, for use in the treatment of neurological disorders in a subject in need thereof.

As it will be further disclosed in the present application, the compounds in a combinatorial therapy of the ~~invention~~disclosure may be administered simultaneously, separately, sequentially and/or repeatedly to the subject.

The ~~invention~~disclosure also relates to any pharmaceutical composition *per se* comprising a combination of at least two compounds as defined above.

The compositions of the ~~invention~~disclosure typically further comprise one or several pharmaceutically acceptable excipients or carriers. Also, the compounds as used in the present ~~invention~~disclosure may be in the form of a salt, hydrate, ester, ether, acid, amide, racemate, or isomer. They may also be in the form of sustained-release formulations. Prodrugs or derivatives of the compounds may be used as well.

In a preferred embodiment, the compound is used as such or in the form a salt, hydrate, ester, ether or sustained release form thereof. A particularly preferred salt for use in the present ~~invention~~disclosure is Acamprosate calcium.

In another preferred embodiment, a prodrug or derivative is used.

A further object of this ~~invention~~disclosure is a method of preparing a pharmaceutical composition, the method comprising mixing Baclofen and Acamprosate, in a pharmaceutically acceptable excipient or carrier.

Another object of this ~~invention~~disclosure relates to a method for treating a neurological disorder in a mammalian subject in need thereof, preferably a human subject in need

thereof, the method comprising administering to said subject an effective amount of a combination of the ~~invention~~disclosure.

A further object of this ~~invention~~disclosure relates to a method for treating Alzheimer or a related disorder in a mammalian subject in need thereof, preferably a human subject in need thereof, the method comprising administering to said subject an effective amount of a combination of the ~~invention~~disclosure.

A preferred object of this ~~invention~~disclosure relates to a method for treating a neurological disorder in a mammalian subject in need thereof, preferably a human subject in need thereof, the method comprising simultaneously, separately or sequentially administering to said subject an effective amount of Baclofen and Acamprosate.

A more preferred object of this ~~invention~~disclosure relates to a method for treating Alzheimer or a related disorder in a mammalian subject in need thereof, preferably a human subject in need thereof, the method comprising simultaneously, separately or sequentially administering to said subject an effective amount of Baclofen and Acamprosate.

The ~~invention~~disclosure may be used for treating a neurological disorder in any mammalian subject, preferably in any human subject, at any stage of the disease. As will be disclosed in the examples, the compositions of the ~~invention~~disclosure are able to ameliorate the pathological condition of said subjects.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Validation of the experimental model of human βamyloid's toxicity on endothelial cells used for drug screening. One hour of VEGF pre-treatment at 10nM significantly protected the capillary network from this amyloid injury (+70% of capillary network compared to amyloid intoxication).

Figure 2: Effect of Baclofen (BCL) and Acamprosate (ACP) combination therapy on the total length of capillary network in beta-amyloid intoxicated HBMEC cultures. The human amyloid peptide ($A\beta_{1-42}$ 2.5μM) produces a significant intoxication, above 40%, compared to vehicle-treated cells. This intoxication is significantly prevented by the

15. Use of Baclofen, or a pharmaceutically acceptable salt thereof, in combination with at least Acamprosate, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for protecting neuronal cells against amyloid beta and/or glutamate toxicity, in a subject suffering from, predisposed to, or suspected to suffer from Alzheimer's disease.

16. A composition comprising Baclofen, Acamprosate and Donepezil, or pharmaceutically acceptable salts thereof.

17. The use of claim 11, wherein the dose of Acamprosate is comprised between 1 and 400 mg/day, preferably between 1 and 200 mg/day.

18. The use of claim 17, wherein the dose of Acamprosate is comprised between 1 and 50 mg/day.

19. A composition comprising Baclofen and Acamprosate, or pharmaceutically acceptable salts thereof, for use as a medicament~~in treating Alzheimer's disease or a related disease selected from senile dementia of AD type (SDAT), Lewis body dementia, mild cognitive impairment (MCI) and age-associated memory impairment (AAMI)~~.

20. Baclofen, or a pharmaceutically acceptable salt thereof, in combination with at least Acamprosate, or a pharmaceutically acceptable salt thereof, for use in treating Alzheimer's disease or a related disease selected from senile dementia of AD type (SDAT), Lewis body dementia, mild cognitive impairment (MCI) and age-associated memory impairment (AAMI).

21. Baclofen, or a pharmaceutically acceptable salt thereof, in combination with at least Acamprosate, or a pharmaceutically acceptable salt thereof, for use in improving cognitive symptoms in a subject suffering from, predisposed to, or suspected to suffer from Alzheimer's disease.

22. Baclofen, or a pharmaceutically acceptable salt thereof, in combination with at least Acamprosate, or a pharmaceutically acceptable salt thereof, for use in protecting neuronal cells against amyloid beta and/or glutamate toxicity, in a subject suffering from, predisposed to, or suspected to suffer from Alzheimer's disease.