International patent application n° PCT/EP2008/066468 describes compositions for the treatment of the Charcot-Marie-Tooth disease which comprise at least two compounds selected from the group of multiple drug candidates.

Summary of invention

The purpose of the present invention is to provide new therapeutic combinations for treating CMT and related disorders. The ~~invention~~disclosure thus relates to compositions and methods for treating CMT and related disorders, in particular toxic neuropathy and amyotrophic lateral sclerosis, using particular drug combinations.

An ~~object~~embodiment of this ~~invention~~disclosure more specifically relates to a composition comprising Baclofen, Sorbitol and a compound selected from Pilocarpine, Methimazole, Mifepristone, Naltrexone, Rapamycine, Flurbiprofen and Ketoprofen, salts or prodrugs thereof, for simultaneous, separate or sequential administration to a mammalian subject.

A particular ~~object~~embodiment of the present ~~invention~~disclosure relates to a composition comprising Baclofen, Sorbitol and Naltrexone, for simultaneous, separate or sequential administration to a mammalian subject.

Another ~~object of the invention~~embodiment relates to a composition comprising (a) rapamycin, (b) mifepristone or naltrexone, and (c) a PMP22 modulator, for simultaneous, separate or sequential administration to a mammalian subject.

In a particular embodiment, the PMP22 modulator is selected from Acetazolamide, Albuterol, Amiloride, Aminoglutethimide, Amiodarone, Aztreonam, Baclofen, Balsalazide, Betaine, Bethanechol, Bicalutamide, Bromocriptine, Bumetanide, Buspirone, Carbachol, Carbamazepine, Carbimazole, Cevimeline, Ciprofloxacin, Clonidine, Curcumin, Cyclosporine A, Diazepam, Diclofenac, Dinoprostone, Disulfiram, D-Sorbitol, Dutasteride, Estradiol, Exemestane, Felbamate, Fenofibrate, Finasteride, Flumazenil, Flunitrazepam, Flurbiprofen, Furosemide, Gabapentin, Galantamine, Haloperidol, Ibuprofen, Isoproterenol, Ketoconazole, Ketoprofen, L-

carnitine, Liothyronine (T3), Lithium, Losartan, Loxapine, Meloxicam, Metaproterenol, Metaraminol, Metformin, Methacholine, Methimazole, Methylergonovine, Metoprolol, Metyrapone, Miconazole, Mifepristone, Nadolol, Naloxone, Naltrexone; Norfloxacin, Pentazocine, Phenoxybenzamine, Phenylbutyrate, Pilocarpine, Pioglitazone, Prazosin, Propylthiouracil, Raloxifene, Rapamycin, Rifampin, Simvastatin, Spironolactone, Tacrolimus, Tamoxifen, Trehalose, Trilostane, Valproic acid, salts or prodrugs thereof.

Another ~~object of this invention~~embodiment is a composition comprising Rapamycin and mifepristone, for simultaneous, separate or sequential administration to a mammalian subject.

A further ~~object of this invention~~embodiment is a composition as disclosed above further comprising one or several pharmaceutically acceptable excipients or carriers (i.e., a pharmaceutical composition).

Another ~~object of the present invention~~embodiment relates to a composition as disclosed above for treating CMT or a related disorder.

A further ~~object of this invention~~embodiment relates to the use of a combination of compounds as disclosed above for the manufacture of a medicament for the treatment of CMT or a related disorder.

A further ~~object of this invention~~embodiment is a method for treating CMT or a related disorder, the method comprising administering to a subject in need thereof an effective amount of a composition as defined above.

A further ~~object of this invention~~embodiment is a method of preparing a pharmaceutical composition, the method comprising mixing the above compounds in an appropriate excipient or carrier.

A more specific ~~object of this invention~~embodiment is a method of treating CMT1a in a subject, the method comprising administering to the subject in need thereof an effective amount of a compound or combination of compounds as disclosed above.

A further specific ~~object of this invention~~embodiment is a method of treating toxic neuropathy in a subject, the method comprising administering to the subject in need thereof an effective amount of a compound or combination of compounds as disclosed above.

A further specific ~~object of this invention~~embodiment is a method of treating ALS in a subject, the method comprising administering to the subject in need thereof an effective amount of a compound or combination of compounds as disclosed above.

Any of the various uses or methods of treatment disclosed herein can also include an optional step of diagnosing a patient as having CMT or a related disorder, particularly CMT1A, or identifying an individual as at risk of developing CMT or a related disorder, particularly CMT1A.

In this regard, a further ~~object of this invention~~embodiment is a method of treating CMT, particularly CMT1a, the method comprising (1) assessing whether a subject has CMT, particularly CMT1a and (2) treating the subject having CMT, particularly CMT1a with an effective amount of a combination of compounds as described above. Determining whether a subject has CMT, particularly CMT1a, can be done by various tests known per se in the art, such as DNA assays.

The ~~invention~~disclosure may be used for treating CMT or a related disorder in any mammalian subject, particularly human subjects, more preferably CMT1a.

In one aspect of the disclosure, there is provided a composition comprising baclofen, D-sorbitol and naltrexone, salts, enantiomers, or racemates thereof, for simultaneous, separate or sequential administration to a mammalian subject.

In another aspect, there is provided the use of the composition as defined above, in the manufacture of a medicament for the treatment of Charcot Marie Tooth ("CMT") disease, a toxic neuropathy or Amyotrophic Lateral Sclerosis ("ALS") in a mammalian subject.

In another aspect, there is provided the use of Baclofen, D-sorbitol and naltrexone, salts, enantiomers, or racemates thereof in the manufacture of a medicament for the treatment of CMT disease, a toxic neuropathy or ALS in a mammalian subject, said medicament being formulated for simultaneous, separate or sequential administration.

Legend to the figures

Figure 1. Synergistic effect of drug combination, dose 1: effect of **A)** Mix7 (dose 1, day 10), **B)** d-Sorbitol (SRB, 500 µM, day 10), **C)** (R/S)-Baclofen (BCL, 5 µM, day 10) and **D)** Naltrexone (NTX, 5 µM, day 10) on MBP expression. *:$p<0.05$: