S100B Protein in Neurological Disorders, J Pak Med Assoc Vol. 61, No. 3, March 2011, which is incorporated herein by reference.

Ultra-low doses of antibodies to S-100 protein have been shown to have anxiolytic, anti-asthenic, anti-aggressive, stress-protective, anti-hypoxic, anti-ischemic, neuroprotective and nootropic activity. *See* Castagne V. et al., *Antibodies to S100 proteins have anxiolytic-like activity at ultra-low doses in the adult rat*, J Pharm Pharmacol. 2008, 60(3):309-16; Epstein O. I., *Antibodies to calcium-binding S100B protein block the conditioning of long-term sensitization in the terrestrial snail,* Pharmacol Biochem Behav., 2009, 94(1):37-42; Voronina T.A. et al., Chapter 8. *Antibodies to S-100 protein in anxiety-depressive disorders in experimental and clinical conditions. In "Animal models in biological psychiatry",* Ed. Kalueff A.V. N-Y, "Nova Science Publishers, Inc.", 2006, pp. 137-152, all of which are incorporated herein by reference.

The present invention is directed to a combination pharmaceutical composition and methods of its use in treatment of functional disorders of gastrointestinal tract, including irritated bowel syndrome and disorders of the motor-evacuator function.

The solution to the existing problem is presented in form of a combination pharmaceutical composition for treatment and prophylaxis of diseases or conditions of functional etiology of the gastrointestinal tract which comprises activated-potentiated form of antibodies, to histamine activated-potentiated form of antibodies to tumor necrosis factor alpha (TNF-α) and activated-potentiated form of antibodies to brain-specific protein S-100.

SUMMARY

In one aspect, the present disclosure~~invention~~ provides a combination pharmaceutical composition comprising a) an activated-potentiated form of an antibody to S-100 protein, b) an activated-potentiated form of an antibody to histamine, and c) an activated-potentiated form of an antibody to TNF-alpha. In an embodiment, the combination pharmaceutical composition further comprises a solid carrier, wherein said activated-potentiated form an antibody to S-100 protein, said activated-potentiated form of an antibody to

histamine, and said activated-potentiated form of an antibody to TNF-alpha are impregnated onto said solid carrier. In a variant, the combination pharmaceutical composition is in the form of a tablet.

Preferably, the combination pharmaceutical composition includes said activated-potentiated form of an antibody to S-100 protein is in the form of a mixture of C12, C30, and C200 homeopathic dilutions. It is specifically contemplated that said mixture of C12, C30, and C200 homeopathic dilutions is impregnated onto a solid carrier.

Preferably, the combination pharmaceutical composition includes said activated-potentiated form of an antibody to histamine is in the form of a mixture of C12, C30, and C200 homeopathic dilutions. It is specifically contemplated that said mixture of C12, C30, and C200 homeopathic dilutions is impregnated onto a solid carrier.

Preferably, the combination pharmaceutical composition includes said activated-potentiated form of an antibody to TNF-alpha is in the form of a mixture of C12, C30, and C200 homeopathic dilutions. It is specifically contemplated that said mixture of C12, C30, and C200 homeopathic dilutions is impregnated onto a solid carrier.

The activated-potentiated form of an antibody to histamine may be a monoclonal, polyclonal or natural antibody. It is specifically contemplated that the activated-potentiated form of an antibody to histamine is a polyclonal antibody. The activated-potentiated form of an antibody to S-100 protein may be a monoclonal, polyclonal or natural antibody. It is specifically contemplated that the activated-potentiated form of an antibody to S-100 protein is a polyclonal antibody. The activated-potentiated form of an antibody to TNF-alpha may be a monoclonal, polyclonal or natural antibody. It is specifically contemplated that the activated-potentiated form of an antibody to TNF-alpha is a polyclonal antibody. The present disclosure~~invention~~ provides activated-potentiated forms of antibodies to antigen(s) having sequences described in the specification and claimed in the appended claims.

In a variant, the combination pharmaceutical composition includes activated-potentiated form of an antibody to histamine prepared by successive centesimal dilutions coupled with shaking of every dilution. In a variant, the combination pharmaceutical composition includes activated-potentiated form of an antibody to S-100

protein prepared by successive centesimal dilutions coupled with shaking of every dilution. In a variant, the combination pharmaceutical composition includes activated-potentiated form of an antibody to TNF-alpha prepared by successive centesimal dilutions coupled with shaking of every dilution. Vertical shaking is specifically contemplated.

In another embodiment~~aspect~~, the present disclosure~~invention~~ provides a method of treating a disease or condition of functional etiology of the gastrointestinal tract, said method comprising administering to a patient in need thereof a) an activated-potentiated form of an antibody to histamine, b) an activated-potentiated form of an antibody to S-100 protein and c) an activated-potentiated form of an antibody to TNF-alpha. Preferably, the activated-potentiated form of an antibody to a histamine, the activated-potentiated form of an antibody to S-100 protein and the activated-potentiated form of an antibody to TNF-alpha are administered in the form of combined pharmaceutical composition.

It is contemplated that said disease or condition of functional etiology of the gastrointestinal tract is psychosomatic in nature. Preferably, said disease or condition of functional etiology of the gastrointestinal tract is irritable bowel syndrome. It is contemplated that said disease or condition of functional etiology of the gastrointestinal tract is abdominal pain. It is contemplated that said disease or condition of functional etiology of the gastrointestinal tract is diarrhea. It is contemplated that said disease or condition of functional etiology of the gastrointestinal tract is constipation. It is contemplated that said disease or condition of functional etiology of the gastrointestinal tract is a distortion in the motor-evacuatory function of the gastrointestinal tract.

In an embodiment, the combination pharmaceutical composition is administered in the form of a solid oral dosage form which comprises a pharmaceutically acceptable carrier and said activated-potentiated form of an antibody to histamine impregnated onto said carrier, said activated-potentiated form of an antibody to S-100 protein impregnated onto said carrier, and said activated-potentiated form of an antibody to TNF-alpha impregnated onto said carrier. In a variant, said solid oral dosage form is a tablet. Variants and embodiments are provided.

In accordance with the method embodimentaspect of the present disclosureinvention, the combination pharmaceutical composition may be administered in one to two unit dosage forms, each of the dosage form being administered from once daily to four times daily. In a variant, the combination pharmaceutical composition is administered twice daily, each administration consisting of two oral dosage form. In a variant, the combination pharmaceutical composition is administered in one to two unit dosage forms, each of the dosage forms being administered twice daily. All variants and embodiments described with respect to the composition embodimentaspect of the present disclosureinvention may be used with the method embodimentaspect of the present disclosureinvention. With respect to the method embodimentaspect of the present disclosureinvention, it is specifically contemplated that the administration of the combination of the present disclosureinvention may be accompanied by statistically significant reduction HADS score in the representative population of patients.

Co-administration of the combination pharmaceutical composition with an additional active ingredient is specifically contemplated. In a variant, the additional active ingredient is approved for treatment of irritable bowel syndrome. Variants and embodiments are contemplated.

DETAILED DESCRIPTION

The invention is defined with reference to the appended claims. With respect to the claims, the glossary that follows provides the relevant definitions.

The term "antibody" as used herein shall mean an immunoglobulin that specifically binds to, and is thereby defined as complementary with, a particular spatial and polar organization of another molecule. Antibodies as recited in the claims may include a complete immunoglobulin or fragment thereof, may be natural, polyclonal or monoclonal, and may include various classes and isotypes, such as IgA, IgD, IgE, IgG1, IgG2a, IgG2b and IgG3, IgM, etc. Fragments thereof may include Fab, Fv and $F(ab')_2$, Fab', and the like. The singular "antibody" includes plural "antibodies."

The term "activated-potentiated form" or "potentiated form" respectively, with respect to antibodies recited herein is used to denote a product of homeopathic potentization of any initial solution of antibodies. "Homeopathic potentization" denotes the use of methods of homeopathy to impart homeopathic potency to an initial solution

What is claimed is:

1. A combination pharmaceutical composition comprising a) an activated-potentiated form of an antibody to S-100 protein, b) an activated-potentiated form of an antibody to histamine, and c) an activated-potentiated form of an antibody to TNF-alpha.

2. The combination pharmaceutical composition of claim 1, which further comprises a solid carrier, wherein said activated-potentiated form an antibody to S-100 protein, said activated-potentiated form of an antibody to histamine, and said activated-potentiated form of an antibody to TNF-alpha are impregnated onto said solid carrier.

3. The combination pharmaceutical composition of claim 2, which is in the form of a tablet.

4. The combination pharmaceutical composition of claims 1, wherein said activated-potentiated form of an antibody to S-100 protein is in the form of a mixture of C12, C30, and C200 homeopathic dilutions.

5. The combination pharmaceutical composition of claim 4, wherein said mixture of C12, C30, and C200 homeopathic dilutions is impregnated onto a solid carrier.

6. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to histamine is in the form of a mixture of C12, C30, and C200 homeopathic dilutions.

7. The combination pharmaceutical composition of claim 6, wherein said mixture of C12, C30, and C200 homeopathic dilutions is impregnated onto a solid carrier.

8. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to TNF-alpha is in the form of a mixture of C12, C30, and C200 homeopathic dilutions.

9. The combination pharmaceutical composition of claim 8, wherein said mixture of C12, C30, and C200 homeopathic dilutions is impregnated onto a solid carrier.

10. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to histamine is a monoclonal, polyclonal or natural antibody.

11. The combination pharmaceutical composition of claim 10, wherein the activated-potentiated form of an antibody to histamine is a polyclonal antibody.

12. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to S-100 protein is a monoclonal, polyclonal or natural antibody.

13. The combination pharmaceutical composition of claim 12, wherein the activated-potentiated form of an antibody to S-100 protein is a polyclonal antibody.

14. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to TNF-alpha is a monoclonal, polyclonal or natural antibody.

15. The combination pharmaceutical composition of claim 14, wherein the activated-potentiated form of an antibody to TNF-alpha is a polyclonal antibody.

16. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to a TNF-alpha is to the entire molecule of TNF-alpha having SEQ ID NO. 1.

17. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to a TNF-alpha is to a fragment of TNF-alpha having sequences selected from group consisting of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, and SEQ ID NO. 12.

18. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to protein S-100 is an antibody to bovine S-100 protein.

19. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to protein S-100 is to the entire S-100 protein having SEQ ID NO 13.

20. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to protein S-100 is to the entire S-100 protein having SEQ ID NO 16.

21. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated forms of an antibody are prepared by successive centesimal dilutions coupled with shaking of every dilution.

22. A method of treating a disease or condition of functional etiology of the gastrointestinal tract, said method comprising administering to a patient in need thereof, substantially at the same time a) an activated-potentiated form of an antibody to histamine, b) an activated-potentiated form of an antibody to S-100 protein and c) an activated-potentiated form of an antibody to TNF-alpha.

23. The method of claim 22, wherein said activated-potentiated form of an antibody to histamine, said activated-potentiated form of an antibody to S-100 protein and said activated-potentiated form of an antibody to TNF-alpha are administered in the form of a combined pharmaceutical composition.

24. The method of claim 23, wherein said disease or condition of functional etiology of the gastrointestinal tract is psychosomatic in nature.

25. The method of claim 23, wherein said disease or condition of functional etiology of the gastrointestinal tract is irritable bowel syndrome.

26. The method of claim 23, wherein said disease or condition of functional etiology of the gastrointestinal tract is abdominal pain.

27. The method of claim 23, wherein said disease or condition of functional etiology of the gastrointestinal tract is diarrhea.

28. The method of claim 23, wherein said disease or condition of functional etiology of the gastrointestinal tract is constipation.

29. The method of claim 23, wherein said disease or condition of functional etiology of the gastrointestinal tract is a distortion in the motor-evacuatory function of the gastrointestinal tract.

30. The method of claim 23, wherein said combination pharmaceutical composition is administered in the form of a solid oral dosage form comprising a pharmaceutically acceptable carrier and said activated-potentiated form of an antibody to a histamine impregnated onto said carrier, said activated-potentiated form of an antibody to S-100 protein impregnated onto said carrier, and said activated-potentiated form of an antibody to TNF-alpha impregnated onto said carrier.

31. The method of claim 30, wherein said solid oral dosage form is a tablet.

32. The method of claim 30, wherein said carrier is lactose or isomalt.

33. The method of claim 31, wherein said combination pharmaceutical composition is administered in one to two unit dosage forms, each of the dosage form being administered from once daily to four times daily.

34. The method of claim 33, wherein said combination pharmaceutical composition is administered twice daily, each administration consisting of two oral dosage form.

35. The method of claim 33, wherein said combination pharmaceutical composition is administered in one to two unit dosage forms, each of the dosage forms being administered twice daily.

36. The method of claims 23 or 30, wherein said activated-potentiated form of an antibody to a S-100 protein is in the form of a mixture of C12, C30, and C200 homeopathic dilutions.

37. The method of claim 23 or 30, wherein said activated-potentiated form of an antibody to histamine is in the form of a mixture of C12, C30, and C200 homeopathic dilutions.

38. The method of claim 23 or 30, wherein said activated-potentiated form of an antibody to TNF-alpha is in the form of a mixture of C12, C30, and C200 homeopathic dilutions.

39. The method of claim 23 or 30, wherein each of said activated-potentiated forms of an antibody is selected from the group consisting of a monoclonal, polyclonal and natural antibody.

40. The method of claim 39, wherein each of said activated-potentiated forms of an antibody is a polyclonal antibody.

41. The method of claim 23, wherein the activated-potentiated form of an antibody to a TNF-alpha is to the entire molecule of TNF-alpha having SEQ ID NO: 1.

42. The method of claim 23, wherein the activated-potentiated form of an antibody to a TNF-alpha is to a fragment of TNF-alpha having sequences selected from group consisting of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, and SEQ ID NO. 12.

43. The method of claim 23, wherein the activated-potentiated form of an antibody to protein S-100 of brain of a bull.

44. The method of claim 23, wherein the activated-potentiated form of an antibody to protein S-100 is to the entire S-100 protein having SEQ ID NO 13.

45. The method of claim 24, wherein the activated-potentiated form of an antibody to protein S-100 is to the entire S-100 protein having SEQ ID NO 16.

46. The method of claim 24, wherein each of said activated-potentiated forms of an antibody is prepared by successive centesimal dilutions coupled with shaking of every dilution.

47. The method of claims 23, 24, 25, 26, 27, 28 or 29, wherein said administration is accompanied by statistically significant reduction HADS score in the representative population of said patients.

48. The method of claim 23, further comprising co-administration of said combination pharmaceutical composition with an additional active ingredient suitable for treatment of disorders or conditions of gastrointestinal tract.

49. The method of claim 48, wherein said additional active ingredient is approved for treatment of irritable bowel syndrome.

50. The method of claim 48, wherein said additional active ingredient is selected from the group consisting of 5-HT3 antagonists, 5-HT4 antagonists, mixed 5-HT4 agonist/5-HT3 antagonists, opioid agents, CRH receptor antagonists, chloride channel activators, CCK antagonists, neurokinin antagonists, antidepressants, antispasmodics, anticholinergics/antimuscarinic agents, direct smooth muscle relaxing agents, antidiarrheals, benzodiazepines, proton pump inhibitors, and antibiotics.

51. The method of claim 25, wherein said irritable bowel syndrome is characterized predominantly by abdominal pain and flatulence.

52. The method of claim 25, wherein said irritable bowel syndrome is characterized predominantly by diarrhea.

53. The method of claim 26, wherein said irritable bowel syndrome is characterized predominantly by constipation.

54. A pharmaceutical composition for use in treating a patient suffering from a disease or condition of functional etiology of the gastrointestinal tract, said composition having been obtained by providing a) an activated-potentiated form of an antibody to histamine, b) an activated-potentiated form of an antibody to S-100 protein and c) an activated-potentiated form of an antibody to TNF-alpha, each prepared by consecutive repeated dilution and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

55. The pharmaceutical composition of claim 54, wherein said disease or condition of functional etiology of the gastrointestinal tract is irritable bowel syndrome.

56. The pharmaceutical composition of claim 55, wherein said irritable bowel syndrome is characterized predominantly by abdominal pain and flatulence.

57. The pharmaceutical composition of claim 55, wherein said irritable bowel syndrome is characterized predominantly by diarrhea.

58. The pharmaceutical composition of claim 55, wherein said irritable bowel syndrome is characterized predominantly by constipation.

59. The pharmaceutical composition of claim 54, wherein each of said activated-potentiated forms of antibody is a mixture of C12, C30, and C200 homeopathic dilutions.

What is claimed is:

1. A combination pharmaceutical composition comprising a) an activated-potentiated form of an antibody to S-100 protein, b) an activated-potentiated form of an antibody to histamine, and c) an activated-potentiated form of an antibody to TNF-alpha.

2. The combination pharmaceutical composition of claim 1, which further comprises a solid carrier, wherein said activated-potentiated form an antibody to S-100 protein, said activated-potentiated form of an antibody to histamine, and said activated-potentiated form of an antibody to TNF-alpha are impregnated onto said solid carrier.

3. The combination pharmaceutical composition of claim 2, which is in the form of a tablet.

4. The combination pharmaceutical composition of claims 1, wherein said activated-potentiated form of an antibody to S-100 protein is in the form of a mixture of C12, C30, and C200 homeopathic dilutions.

5. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to histamine is in the form of a mixture of C12, C30, and C200 homeopathic dilutions.

6. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to TNF-alpha is in the form of a mixture of C12, C30, and C200 homeopathic dilutions.

7. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to histamine is a monoclonal or polyclonal antibody.

8. The combination pharmaceutical composition of claim 7, wherein the activated-potentiated form of an antibody to histamine is a polyclonal antibody.

9. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to S-100 protein is a monoclonal or polyclonal antibody.

10. The combination pharmaceutical composition of claim 9, wherein the activated-potentiated form of an antibody to S-100 protein is a polyclonal antibody.

11. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to TNF-alpha is a monoclonal or polyclonal antibody.

12. The combination pharmaceutical composition of claim 11, wherein the activated-potentiated form of an antibody to TNF-alpha is a polyclonal antibody.

13. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to a TNF-alpha is to the entire molecule of TNF-alpha having SEQ ID NO. 1.

14. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to a TNF-alpha is to a fragment of TNF-alpha having a sequence selected from group consisting of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, and SEQ ID NO. 12.

15. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to protein S-100 is an antibody to bovine S-100 protein.

16. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to protein S-100 is to the entire S-100 protein having SEQ ID NO 13.

17. The combination pharmaceutical composition of claim 1, wherein the activated-potentiated form of an antibody to protein S-100 is to the entire S-100 protein having SEQ ID NO 16.

18. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated forms of an antibody are prepared by successive centesimal dilutions coupled with shaking of every dilution.

19. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to S-100, said activated-potentiated form of an antibody to histamine, and said activated-potentiated form of an antibody to TNF-alpha are impregnated onto a solid carrier.