SUMMARY OF THE INVENTION

The present invention relates to use of dengue antigen for the manufacture of a vaccine composition, wherein said vaccine composition is for use in a method of protecting a human subject against symptomatic dengue disease caused by dengue virus of any one of serotypes 1, 3 or 4 in a human subject aged 9-45 years old residing in a dengue endemic area, wherein said composition comprises:

(i) a dengue antigen selected from the group consisting of:
  (a) a live attenuated dengue virus;
  (b) an inactivated dengue virus;
  (c) a live attenuated or inactivated chimeric dengue virus;
  (d) a dengue virus-like particle (VLP); and
  (e) a combination of two or more of (a) to (d);

or

(ii) a nucleic acid construct or viral vector which is able to express in a human cell a dengue antigen which is a dengue VLP

and wherein said method results in a statistically significant reduction in the incidence or likelihood of symptomatic dengue disease caused by dengue virus of any one of serotypes 1, 3 or 4.

~~The present invention further relates to~~Also disclosed is the use of a vaccine composition of the present invention for the manufacture of a medicament for protecting a human subject against dengue disease.

~~The present invention further relates to~~Also disclosed is a method of protecting a human subject against dengue disease, wherein said method comprises administering to said human subject an effective amount of a composition according to the present invention.

Additionally, the present ~~invention relates to~~disclosure also disclose a kit comprising a composition according to the present invention and instructions for the use of said composition in a method of protecting a human subject against dengue disease."

Description of the Figure

Figure 1 illustrates the construction of the YF-VAX cDNA by RT-PCR and cloning

Definitions

The term "Dengue disease", as used herein, refers to the clinical symptoms exhibited by an individual following infection by any one of the four Dengue virus serotypes. Since 1970, clinical dengue has been classified according to World Health Organization guidelines as (i) dengue fever or (ii) dengue hemorrhagic fever (World Health Organization. Dengue hemorrhagic fever: Diagnosis, treatment, prevention and

CLAIMS

1. A vaccine composition for use in a method of protecting a human subject against dengue disease, wherein said composition comprises:

   (i) a dengue antigen selected from the group consisting of:
   - (a) a live attenuated dengue virus;
   - (b) an inactivated dengue virus;
   - (c) a live attenuated or inactivated chimeric dengue virus;
   - (d) a dengue virus-like particle (VLP); and
   - (e) a combination of two or more of (a) to (d);

   or

   (ii) a nucleic acid construct or viral vector which is able to express in a human cell a dengue antigen which is a dengue VLP.

2. A composition for use according to claim 1, wherein said human is 4-11 years of age.

3. A composition for use according to any preceding claim, wherein said subject resides in a dengue endemic area.

4. A composition for use according to any preceding claim, wherein said subject is flavivirus immune.

5. A composition for use according to any one of claims 1 to 4, wherein said subject is flavivirus naïve.

6. A composition for use in a method according to any preceding claim, wherein said method reduces the incidence or likelihood of dengue disease.

7. A composition for use in a method according to any preceding claim, wherein dengue disease is virologically-confirmed.

8. A composition for use in a method according to any preceding claim, wherein said dengue disease is caused by a dengue virus of serotype 1, serotype 3 or serotype 4.

9. A composition for use according to any preceding claim, wherein said method comprises administering said composition in multiple doses.

10. A composition for use according to claim 8, wherein said method comprises administering said composition in three or more doses.

11. A composition for use according to claim 8 or claim 9, wherein a first and a third dose are to be administered approximately twelve months apart.

12. A composition for use according to any one of claims 8 to 10, wherein said method comprises administering said composition in a first dose, a second dose and a third dose and wherein said second dose is to be administered about six months after said first dose and wherein said third dose is to be administered about twelve months after said first dose.

13. A composition for use according to any preceding claim, wherein said composition comprises a dengue antigen of serotype 1, a dengue antigen of serotype 2, a dengue antigen of serotype 3 and a dengue antigen of serotype 4.

14. A composition for use according to any preceding claim, wherein said composition comprises a live attenuated dengue virus or a live attenuated chimeric dengue virus.

15. A composition for use according to claim 13, wherein said dengue antigens of serotypes 1, 2, 3 and 4 are each independently selected from a live attenuated dengue virus or a live attenuated chimeric dengue virus.

16. A composition for use according to claim 15, wherein said dengue antigens of serotypes 1, 3 and 4 are each a live attenuated chimeric dengue virus and said dengue antigen of serotype 2 is selected from the group consisting of a live attenuated dengue virus and a live attenuated chimeric dengue virus, preferably a live attenuated dengue virus.

17. A composition for use according to claim 16, wherein said dengue antigen of serotype 2 is a live attenuated dengue virus which comprises a nucleic acid sequence having at least 90% sequence identity to the sequence as set forth in SEQ ID NO: 24.

18. A composition for use according to claim 15, wherein said dengue antigens of serotypes 1, 2, 3 and 4 are each a live attenuated chimeric dengue virus.

19. A composition for use according to any one of claims 1 to 18, wherein said composition comprises a live attenuated chimeric dengue virus.

20. A composition for use according to any preceding claim, wherein said chimeric dengue virus comprises one or more proteins from a dengue virus and one or more proteins from a different flavivirus.

21. A composition for use according to any one of claims 1 to 19, wherein said chimeric dengue virus comprises one or more proteins from a dengue virus of one serotype and one or more proteins from a dengue virus of a different serotype.

22. A composition for use according to claim 19 or 20, wherein the different flavivirus is a yellow fever virus.

23. A composition for use according to claim 21 or 22, wherein the yellow fever virus is strain YF17D.

24. A composition for use according to any one of claims 13 to 23, wherein said chimeric dengue virus comprises the prM-E sequence of a dengue virus.

25. A composition for use according to any one of claims 13 to 20 and 22 to 24, wherein the chimeric dengue virus comprises a yellow fever virus genome whose prM-E sequence has been substituted with the prM-E sequence of a dengue virus.

26. A composition for use according to any one of claims 13 to 25, wherein said composition comprises the prM-E sequences of CYD-1, CYD-2, CYD-3 and CYD-4.

27. A composition for use according to any one of claims 13 to 20 and 22 to 26, wherein said composition comprises CYD-1, CYD-2, CYD-3 and CYD-4.

28. A composition for use according to any one of claims 13 to 17, 19 to 20 and 22 to 25 and 21 to 25, wherein said composition comprises CYD-1, VDV-2, CYD-3 and CYD-4.

29. A composition for use according to any one of claims 13 to 28, wherein at least one serotype of said dengue virus is present in an amount of from about 10^3 to about 10^6 $CCID_{50}$.

30. A composition for use according to claims 13 to 28, wherein at least one serotype of said dengue virus is present in an amount of from about 10^3 to about 10^7 $CCID_{50}$.

31. A composition for use according to claim 27 or claim 29, wherein said composition comprises all four serotypes of dengue virus and each of said serotypes is present in an amount of from about 10^3 to about 10^6 $CCID_{50}$.

32. A composition for use according to claim 30, wherein said composition comprises all four serotypes of dengue virus and each of said serotypes is present in an amount of from about 10^3 to about 10^7 $CCID_{50}$.

33. A composition for use according to any one of claims 13 to 32, wherein at least one serotype of said dengue virus is present in an amount of about 10^5 $CCID_{50}$.

34. A composition for use according to any one of claims 13 to 32, wherein at least one serotype of said dengue virus is present in an amount of about 10^6 $CCID_{50}$.

35. A composition for use according to claim 31, wherein said composition comprises all four serotypes of dengue virus and each of said serotypes is present in an amount of about 10^5 $CCID_{50}$.

36. A composition for use according to claim 32, where said composition comprises all four serotypes of dengue virus and each of said serotypes is present in an amount of about 10^6 $CCID_{50}$.

37. A composition for use according to any preceding claim, wherein said composition is lyophilized.

38. A composition for use according to any preceding claim, wherein said method comprises administering said composition to said human subject via a subcutaneous route.

39. A composition for use according to any preceding claim, wherein said composition comprises a pharmaceutically acceptably carrier or excipient.

40. Use of an effective amount of a composition according to any one of claims 1 to 39 in the manufacture of a medicament for protecting a human subject against dengue disease.

41. A kit comprising a composition according to any one of claims 1 to 39 and instructions for the use of said composition in a method of protecting a human subject against dengue disease.

CLAIMS

1. Use of a dengue antigen for the manufacture of a vaccine composition, wherein said vaccine composition is for use in a method of protecting a human subject against symptomatic dengue disease caused by dengue virus of any one of serotypes 1, 3 or 4 in a human subject aged 9-45 years old residing in a dengue endemic area, wherein said composition comprises:

   (i) a dengue antigen selected from the group consisting of:
   - (a) a live attenuated dengue virus;
   - (b) an inactivated dengue virus;
   - (c) a live attenuated or inactivated chimeric dengue virus;
   - (d) a dengue virus-like particle (VLP); and
   - (e) a combination of two or more of (a) to (d);

   or

   (ii) a nucleic acid construct or viral vector which is able to express in a human cell a dengue antigen which is a dengue VLP

   and wherein said method results in a statistically significant reduction in the incidence or likelihood of symptomatic dengue disease caused by dengue virus of any one of serotypes 1, 3 or 4.

2. A use according to claim 1, wherein said human is 9-16 years of age.

3. A use according to any preceding claim, wherein said subject is flavivirus immune.

4. A use according to any one of claims 1 to 3, wherein said subject is flavivirus naïve.

5. A use in a method according to any preceding claim, wherein said method reduces the incidence or likelihood of dengue disease.

6. A use in a method according to any preceding claim, wherein dengue disease is virologically-confirmed.

7. A use according to any preceding claim, wherein said method comprises administering said composition in multiple doses.

8. A use according to claim 7, wherein said method comprises administering said composition in three or more doses.

9. A use according to claim 7 or claim 8, wherein a first and a third dose are to be administered approximately twelve months apart.

10. A use according to any one of claims 87 to 9, wherein said method comprises administering said composition in a first dose, a second dose and a third dose and wherein said second dose is to be administered about six months after said first dose and wherein said third dose is to be administered about twelve months after said first dose.

11. A use according to any preceding claim, wherein said composition comprises a dengue antigen of serotype 1, a dengue antigen of serotype 2, a dengue antigen of serotype 3 and a dengue antigen of serotype 4.

12. A use according to any preceding claim, wherein said composition comprises a live attenuated dengue virus or a live attenuated chimeric dengue virus.

13. A use according to claim 11, wherein said dengue antigens of serotypes 1, 2, 3 and 4 are each independently selected from a live attenuated dengue virus or a live attenuated chimeric dengue virus.

14. A use according to claim 13, wherein said dengue antigens of serotypes 1, 3 and 4 are each a live attenuated chimeric dengue virus and said dengue antigen of serotype 2 is selected from the group consisting of a live attenuated dengue virus and a live attenuated chimeric dengue virus, preferably a live attenuated dengue virus.

15. A use according to claim 14, wherein said dengue antigen of serotype 2 is a live attenuated dengue virus which comprises a nucleic acid sequence having at least 90% sequence identity to the sequence as set forth in SEQ ID NO: 24.

16. A use according to claim 11, wherein said dengue antigens of serotypes 1, 2, 3 and 4 are each a live attenuated chimeric dengue virus.

17. A use according to any one of claims 1 to 16, wherein said composition comprises a live attenuated chimeric dengue virus.

18. A use according to any preceding claim, wherein said chimeric dengue virus comprises one or more proteins from a dengue virus and one or more proteins from a different flavivirus.

19. A use according to any one of claims 1 to 17, wherein said chimeric dengue virus comprises one or more proteins from a dengue virus of one serotype and one or more proteins from a dengue virus of a different serotype.

20. A use according to claim 18, wherein the different flavivirus is a yellow fever virus.

21. A use according to claim 20, wherein the yellow fever virus is strain YF17D.

22. A use according to any one of claims 12 to 21, wherein said chimeric dengue virus comprises the prM-E sequence of a dengue virus.

23. A use according to any one of claims 12 to 18 and 20 to 22, wherein the chimeric dengue virus comprises a yellow fever virus genome whose prM-E sequence has been substituted with the prM-E sequence of a dengue virus.

24. A use according to any one of claims 11 to 23, wherein said composition comprises the prM-E sequences of CYD-1, CYD-2, CYD-3 and CYD-4.

25. A use according to any one of claims 11to 18 and 20 to 24, wherein said composition comprises CYD-1, CYD-2, CYD-3 and CYD-4.

26. A use according to any one of claims 11to 25 wherein at least one serotype of said dengue virus is present in an amount of from about 10^3 to about 10^6 $CCID_{50}$.

27. A use according to claims 11 to 25, wherein at least one serotype of said dengue virus is present in an amount of from about 10^3 to about 10^7 $CCID_{50}$.

28. A use according to claim 25 or claim 26, wherein said composition comprises all four serotypes of dengue virus and each of said serotypes is present in an amount of from about 10^3 to about 10^6 $CCID_{50}$.

29. A use according to claim 27, wherein said composition comprises all four serotypes of dengue virus and each of said serotypes is present in an amount of from about 10^3 to about 10^7 $CCID_{50}$.

30. A use according to any one of claims to 29, wherein at least one serotype of said dengue virus is present in an amount of about 10^5 $CCID_{50}$.

31. A use according to any one of claims 11 to 29, wherein at least one serotype of said dengue virus is present in an amount of about 10^6 $CCID_{50}$.

32. A use according to claim 28, wherein said composition comprises all four serotypes of dengue virus and each of said serotypes is present in an amount of about 10^5 $CCID_{50}$.

33. A use according to claim 29, where said composition comprises all four serotypes of dengue virus and each of said serotypes is present in an amount of about 10^6 $CCID_{50}$.

34. A use according to any preceding claim, wherein said composition is lyophilized.

35. A use according to any preceding claim, wherein said method comprises administering said composition to said human subject via a subcutaneous route.

36. A use according to any preceding claim, wherein said composition comprises a pharmaceutically acceptable carrier or excipient.