SUMMARY ~~OF THE INVENTION~~

In one aspect, the present disclosure relates to a Use of a vaccine composition in the manufacture of a medicament for protecting a human subject against symptomatic dengue disease, 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, wherein said dengue antigens are each independently selected from the group consisting of:

a live attenuated dengue virus

and a live attenuated chimeric dengue virus and wherein said live attenuated chimeric dengue virus;

is a recipient flavivirus in which the genetic backbone has been modified by exchanging the sequences encoding the prM and E proteins by the corresponding sequences of a dengue virus.

The present ~~invention~~ disclosure relates to 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.

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

The present ~~invention~~disclosure further relates to 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~~disclosure.

Additionally, the present ~~invention~~disclosure relates to a kit comprising a composition according to the present ~~invention~~disclosure 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

CLAIMS

1. ~~A~~ Use of a vaccine composition in the manufacture of a medicament for ~~use in a method of~~ protecting a human subject against symptomatic dengue disease, wherein said composition comprises:

   ~~(i)~~ 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, wherein said dengue antigens are each independently selected from the group consisting of:

   ~~(a)~~ a live attenuated dengue virus~~;~~

   ~~(b) an inactivated dengue virus;~~

   ~~(c)~~ and a live attenuated chimeric dengue virus and wherein said 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)~~ is a recipient flavivirus in ~~nucleic acid construct or viral vector~~ which the genetic backbone has been modified by exchanging the sequences encoding the prM and E proteins by the corresponding sequences of a dengue virus~~is able to express in a human cell a dengue antigen which is a dengue VLP~~.

2. ~~A composition for~~ A use according to claim 1, wherein said human is ~~4-11~~9-45 years of age.

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

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.~~ medicament results in a statistically significant reduction in ~~A composition for use in a method according to any preceding claim, wherein said method reduces~~ the incidence or likelihood of symptomatic virologically-confirmed dengue disease.

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

~~8.~~5. ~~A composition for use in a method~~ use according to any preceding claim, wherein said dengue disease is caused by a dengue virus of serotype 1, serotype 3 or serotype 4.

~~9.~~6. ~~A composition for~~ use according to any preceding claim, wherein said ~~method comprises administering said~~ composition is to be administered in multiple doses.

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

7. A ~~composition for~~ use according to claim ~~8 or claim 9~~6, wherein said composition is to be administered in two doses~~a first and a third dose are to be administered approximately twelve months apart~~.

8. A use according to claim 7, wherein said doses are to be administered three or six months apart.

~~11.~~9. A use according to claim 6, wherein said composition is to be administered in three or more doses.

~~12.~~10. A ~~composition for~~ use according to ~~any one of claims 8 to 10~~claim 9, wherein ~~said method comprises administering~~ said composition is to be administered 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.~~11. ~~A composition for use according to claim 13, wherein said~~ dengue antigens of serotypes 1, ~~2,~~ 3 and 4 are each a live attenuated chimeric dengue virus and said dengue antigen of serotype 2 is ~~independently~~ selected from the group consisting of a live attenuated dengue virus ~~or~~ and a live attenuated chimeric dengue virus.

~~16.~~12. A ~~composition for~~ use according to ~~claim 15~~any preceding claim, 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, and wherein said live attenuated chimeric dengue viruses are each a recipient flavivirus in which the genetic backbone has been modified by exchanging the sequences encoding the prM and E proteins by the corresponding sequences of a dengue virus and wherein said recipient flavivirus is selected from the group consisting of a yellow fever virus and a dengue virus ~~preferably a live attenuated dengue virus~~.

~~17.~~13. A ~~composition for~~ use according ~~to claim 16~~to any preceding claim, wherein said dengue antigens of serotypes 1, 3 and 4 are each a live attenuated chimeric dengue virus and 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.~~14. A ~~composition for~~ use according to any one of claims 1 to 12~~claim 15~~, wherein said dengue antigens of serotypes 1, 2, 3 and 4 are each a live attenuated chimeric dengue virus.

~~19.~~15. ~~composition for~~ use according to any one of claims 1 to ~~18~~14, wherein said composition comprises a live attenuated chimeric dengue virus.

16. A ~~composition for~~ use according to any ~~preceding claim~~one of claims 1 to 15, wherein said live attenuated chimeric dengue virus ~~comprises one or more~~is a recipient flavivirus in which the genetic backbone has been modified by exchanging the sequences encoding the prM and E proteins by the corresponding sequences of ~~from~~ a dengue virus and said recipient flavivirus is selected from the group consisting of a yellow fever virus and a dengue virus ~~one or more proteins from a different flavivirus~~.

~~20.~~17. A use according to any one of claims 1 to 16, wherein said live attenuated chimeric dengue virus is a recipient flavivirus in which the genetic backbone has been modified by exchanging the sequences encoding the prM and E proteins by the corresponding sequences of a dengue virus and said recipient flavivirus is a yellow fever virus.

~~21.~~18. ~~composition for~~ use according to any one of claims 1 to ~~19~~16, 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.~~ ~~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.~~19. ~~A composition for use according to any one of claims 13 to 25~~1 to 18, wherein said composition comprises the prM-E sequences of CYD-1, CYD-2, CYD-3 and CYD-4.

~~27.~~20. A ~~composition for~~ use according to any one of claims ~~13 to 20 and 22 to 26~~1 to 17 and 19, 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. 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 any one of claims 1 to 39.~~

~~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.~~