CLAIMS

1. A modified dengue virus, comprising

a recoded envelope (E) protein encoding sequence, or both the recoded envelope (E) protein encoding sequence and a recoded prM protein encoding sequence

in which the modified dengue virus is selected from serotype 1, serotype 2, serotype 3, or serotype 4, and

in which the recoded E protein encoding sequence has the E protein encoding sequence in SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12, or in which the recoded E protein encoding sequence has the E protein encoding sequence in SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12, with up to 15 nucleotide substitutions in the E protein encoding sequence.

2. A modified dengue virus according to Claim 1, in which the recoded E protein encoding sequence has the E protein encoding sequence in SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12.

3. A modified dengue virus according to Claim 1, in which the recoded E protein encoding sequence has the E protein encoding sequence in SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12, with up to 15 nucleotide substitutions in the E protein encoding sequence.

4. A modified dengue virus according to Claim 1, in which the modified dengue virus comprises a recoded sequence of SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12.

5. A modified dengue virus according to Claim 1, in which the recoded E protein encoding sequence is recoded from a parent E protein encoding sequence from DENV-1/VN/BID-V1774/2007 (SEQ ID NO: 1), DENV-2/NI/BID-V533/2005 (SEQ ID NO: 3), DENV-3/VE/BID-V2268/2008 (SEQ ID NO: 5), or DENV-4/US/BID-V2448/1999 (SEQ ID NO: 7).

6. A modified dengue virus according to any preceding claim, in which expression of the E protein or both the E protein and the prM protein are reduced compared to its parent dengue virus.

7. A modified dengue virus according to any preceding claim, in which the recoded E protein encoding sequence or both the recoded E-protein encoding sequence and the recoded prM-encoding sequence has a codon pair bias of less than -0.05.

8. A tetravalent dengue virus composition comprising: a modified dengue virus according to Claim 1 of serotype 1, a modified dengue virus according to Claim 1 of serotype 2, a modified dengue virus according to Claim 1 of serotype 3 and a modified dengue virus according to Claim 1 of serotype 4.

9. A tetravalent dengue virus composition according to Claim 8, in which the recoded E protein encoding sequence is recoded from a parent E protein encoding sequence of serotype 1 from DENV-1/VN/BID-V1774/2007 (SEQ ID NO: 1), a parent E protein encoding sequence of serotype 2 from DENV-2/NI/BID-V533/2005 (SEQ ID NO: 3), a parent E protein encoding sequence of serotype 3 from DENV-3/VE/BID-V2268/2008 (SEQ ID NO: 5), and a parent E protein encoding sequence of serotype 4 from DENV-4/US/BID-V2448/1999 (SEQ ID NO: 7).

10. A tetravalent dengue virus composition according to Claim 8 or 9, in which

the modified dengue virus according to Claim 1 of serotype 1 has a recoded E protein encoding sequence of the E protein encoding sequence in SEQ ID NO: 9 with up to 15 nucleic acid substitutions in the E protein encoding sequence,

the modified dengue virus according to Claim 1 of serotype 2 has a recoded E protein encoding sequence of the E protein encoding sequence in SEQ ID NO: 10 with up to 15 nucleic acid substitutions in the E protein encoding sequence,

the modified dengue virus according to Claim 1 of serotype 3 has a recoded E protein encoding sequence of the E protein encoding sequence in SEQ ID NO: 11 with up to 15 nucleic acid substitutions in the E protein encoding sequence, and

the modified dengue virus according to Claim 1 of serotype 4 has a recoded E protein encoding sequence of the E protein encoding sequence in SEQ ID NO: 12 with up to 15 nucleic acid substitutions in the E protein encoding sequence.

11. A tetravalent dengue virus composition according to Claim 8 or 9, in which

the modified dengue virus according to Claim 1 of serotype 1 has a recoded E protein encoding sequence of the E protein encoding sequence in SEQ ID NO: 9,

the modified dengue virus according to Claim 1 of serotype 2 has a recoded E protein encoding sequence of the E protein encoding sequence in SEQ ID NO: 10,

the modified dengue virus according to Claim 1 of serotype 3 has a recoded E protein encoding sequence of the E protein encoding sequence in SEQ ID NO: 11, and

the modified dengue virus according to Claim 1 of serotype 4 has a recoded E protein encoding sequence of the E protein encoding sequence in SEQ ID NO: 12.

12. A tetravalent dengue virus composition according to Claim 8 or 9, comprising modified dengue viruses having

a sequence of SEQ ID NO: 9 with up to 15 nucleic acid substitutions in its E protein encoding sequence,

a sequence of SEQ ID NO: 10 with up to 15 nucleic acid substitutions in its E protein encoding sequence,

a sequence of SEQ ID NO: 11 with up to 15 nucleic acid substitutions in its E protein encoding sequence, and

a sequence of SEQ ID NO: 12 with up to 15 nucleic acid substitutions in its E protein encoding sequence.

13. A tetravalent dengue virus composition according to Claim 8 or 9, comprising modified dengue viruses having sequences of SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12.

14. A dengue vaccine composition for inducing a protective immune response in a subject, comprising a modified dengue virus according to any of Claims 1 to 7, or a tetravalent dengue virus composition according to any of Claims 8 to 13, and a pharmaceutically acceptable excipient or carrier.

15. A modified dengue virus according to any of Claims 1 to 7 or a tetravalent dengue virus composition according to any of Claims 8 to 13 for use in a method of eliciting an immune response in a subject, in which an effective dose of a composition comprising the modified dengue virus is to be administered to a subject.

16. A modified dengue virus for use according to Claim 15 or a tetravalent dengue virus composition according to any of Claims 8 to 13, in which the immune response is a protective

immune response, and a prophylactically effective or therapeutically effective dose of a dengue vaccine composition according to Claim 14 is to be administered to the subject.

17. A modified dengue virus for use according to Claim 15 or a tetravalent dengue virus composition according to any of Claims 8 to 13, in which at least one adjuvant is to be further administered to the subject.

18. A modified dengue virus for use according to Claim 15 or a tetravalent dengue virus composition according to any of Claims 8 to 13, in which the immune response is cross-protective against a heterologous dengue virus.

19. A kit comprising:

(i) an attenuated dengue virus produced by a method other than codon-pair deoptimization or codon deoptimization, or increasing of CpG or UpA di-nucleotides and

(ii) a modified dengue virus according to any of Claims 1 to 7 or a composition according to any of Claims 8 to 13,

in which (i) and (ii) are formulated for separate or sequential administration as a prime dose and one or more boost doses to elicit an immune response in a subject.

20. A kit according to Claim 19, further comprising instructions for use, specifying that

a prime dose of (i) or (ii) is to be administered to the subject,

one or more boost dose of (i) or (ii) is to be administered to the subject;

in which at least the prime dose or the one or more boost dose is the modified dengue virus.

21. Use of:

(i) an attenuated dengue virus produced by a method other than codon-pair deoptimization or codon deoptimization, or increasing of CpG or UpA di-nucleotides and

(ii) a modified dengue virus according to any one of Claims 1 to 7 or a composition according to any one of Claims 8 to 13,

in the preparation of a medicament for protecting against viral infection and disease, in which

a prime dose of (i) or (ii) is to be administered to the subject,

one or more boost dose of (i) or (ii) is to be administered to the subject;

in which at least the prime dose or the one or more boost dose is the modified dengue virus.

22. A kit according to Claim 19 or use according to Claim 20 or 21, in which a first of the one or more boost dose is to be administered about 2 weeks after the prime dose.

23. A kit according to Claim 19 or 22 or use according to Claim 20, 21 or 22, in which (ii) comprises a composition according to any of Claims 8 to 13.

24. A method of making a modified dengue virus genome comprising:

obtaining a parent E protein encoding sequence of a parent dengue virus;

recoding the E protein encoding sequence to reduce protein expression,

in which the recoded envelope (E) protein encoding sequence has the E protein encoding sequence in SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12, **or** in which the recoded E protein encoding sequence has the E protein encoding sequence in SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12, with up to 15 nucleotide substitutions in the E protein encoding sequence, and

substituting the recoded envelope (E) protein encoding sequence into the parent dengue virus genome to make a modified dengue virus genome; whereby expression of the recoded envelope (E) protein encoding sequence is reduced compared to the parent virus, in which the parent E protein encoding sequence is from DENV-1/VN/BID-V1774/2007 (SEQ ID NO: 1), DENV-2/NI/BID-V533/2005 (SEQ ID NO: 3), DENV-3/VE/BID-V2268/2008 (SEQ ID NO: 5), or DENV-4/US/BID-V2448/1999 (SEQ ID NO: 7).

25. A tetravalent dengue virus composition according to any of Claims 8 to 13 for use in eliciting an immune response in a human subject.

26. A modified dengue virus according to any of Claims 1 to 7 for use in eliciting an immune response in a human subject.