WHAT CLAIMED IS:

1. A modified dengue virus, comprising

a recoded prM protein, a recoded envelope (E) protein, or both,

wherein the recoded prM protein has a reduced codon pair bias compared to its parent prM protein encoding sequence, or has at least 5 codons substituted with synonymous codons less frequently used, or has an increased number of CpG or UpA di-nucleotides compared its parent prM protein encoding sequence, and

wherein the recoded E protein has a reduced codon pair bias compared to its parent E protein encoding sequence, or has at least 5 codons substituted with synonymous codons less frequently, or has an increased number of CpG or UpA di-nucleotides compared its parent E protein encoding sequence.

2. The modified dengue virus of claim 1, wherein expression of the prM protein or E protein or both are reduced compared to its parent dengue virus.

3. The modified dengue virus of claim 1, wherein the recoded prM protein has a reduced codon pair bias compared to its parent prM protein encoding sequence.

4. The modified dengue virus of claim 1, wherein the recoded prM protein has at least 5 codons substituted with synonymous codons less frequently used.

5. The modified dengue virus of claim 1, wherein the recoded prM protein has an increased number of CpG or UpA di-nucleotides compared its parent prM protein encoding sequence.

6. The modified dengue virus of claim 1, wherein the recoded E protein has a reduced codon pair bias compared to its parent E protein encoding sequence.

7. The modified dengue virus of claim 1, wherein the recoded E protein has at least 5 codons substituted with synonymous codons less frequently used.

8. The modified dengue virus of claim 1, wherein the recoded E protein has an increased number of CpG or UpA di-nucleotides compared its parent E protein encoding sequence.

9. The modified dengue virus of claim 1, wherein each of the recoded prM or E protein-encoding sequence has a codon pair bias of less than -0.05.

10. The modified dengue virus of claim 1, wherein the codon pair bias of each of the recoded prM or E protein-encoding sequence is reduced by at least 0.05.

11. The modified dengue virus of claim 1, wherein the modified dengue virus is selected from type 1, type 2, type 3, type 4 or a combination thereof.

12. The modified dengue virus of claim 1, where the modified dengue virus is a modified tetravalent dengue virus.

13. A dengue vaccine composition for inducing a protective immune response in a subject, comprising a modified dengue virus of any one of claims 1-12, and a pharmaceutically acceptable excipient or carrier.

14. A method of eliciting an immune response in a subject, comprising: administering to the subject an effective dose of a composition comprising a modified dengue virus of any of claims 1-12.

15. The method of claim 14, wherein the immune response is a protective immune response, and a prophylactically effective or therapeutically effective dose of a vaccine composition of claims is administered.

16. The method of claim 14, further comprising administering to the subject at least one adjuvant.

17. The method of claim 14, wherein the immune response is cross-protective against a heterologous dengue virus.

18. A method of eliciting an immune response in a subject in need thereof, comprising:

administering a prime dose 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, or (ii) a modified dengue virus comprising a recoded prM protein, a recoded envelope (E) protein, or both, wherein the recoded prM protein has a reduced codon pair bias compared to its parent prM protein encoding sequence, or has at least 5 codons substituted with synonymous codons less frequently used, or has an increased number of CpG or UpA di-nucleotides compared its parent prM protein encoding sequence, and wherein the recoded E protein has a reduced codon pair bias compared to its parent E protein encoding sequence, or has at least 5 codons substituted with synonymous codons less frequently, or has an increased number of CpG or UpA di-nucleotides compared its parent E protein encoding sequence; and

administering one or more boost dose of (i) the attenuated dengue virus produced by methods other than codon-pair deoptimization or codon deoptimization, or increasing of CpG or UpA di-nucleotides, or (ii) the modified dengue virus to the subject in need thereof, wherein at least the prime dose or the one or more boost dose is the modified dengue virus.

19. The method of claim 18, wherein a first of the one or more boost dose is administered about 2 weeks after the prime dose.

20. The method of claim 18, wherein expression of the prM protein or E protein or both are reduced compared to its parent dengue virus.

21. The method of claim 18, wherein the recoded prM protein has a reduced codon pair bias compared to its parent prM protein encoding sequence.

22. The method of claim 18, wherein the recoded prM protein has at least 5 codons substituted with synonymous codons less frequently used.

23. The method of claim 18, wherein the recoded prM protein has an increased number of CpG or UpA di-nucleotides compared its parent prM protein encoding sequence.

24. The method of claim 18, wherein the recoded E protein has a reduced codon pair bias compared to its parent E protein encoding sequence.

25. The method of claim 18, wherein the recoded E protein has at least 5 codons substituted with synonymous codons less frequently used.

26. The method of claim 18, wherein the recoded E protein has an increased number of CpG or UpA di-nucleotides compared its parent E protein encoding sequence.

27. The method of claim 18, wherein each of the recoded prM or E protein-encoding sequence has a codon pair bias of less than -0.05.

28. The method of claim 18, wherein the codon pair bias of each of the recoded prM or E protein-encoding sequence is reduced by at least 0.05.

29. The method of claim 18, wherein the modified dengue virus is selected from type 1, type 2, type 3, type 4 or a combination thereof.

30. The method of claim 18, where the modified dengue virus is a modified tetravalent dengue virus.

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

obtaining a nucleotide sequence encoding the envelope protein of a dengue virus;

recoding the envelope encoding nucleotide sequence to reduce protein expression, and

substituting a nucleic acid having the recoded envelope-encoding nucleotide sequence into a parent dengue virus genome to make a modified dengue virus genome; whereby expression of the recoded envelope-encoding nucleotide sequence is reduced compared to the parent virus.

CLAIMS

1. A modified Zika virus in which expression of viral proteins is reduced compared to a parent virus, in which the reduction in expression is the result of recoding the envelope (E), or prM region, or the nonstructural protein 3 (NS3) region or both the E and NS3 regions.

2. A modified Zika virus according to Claim 1, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by reducing the codon pair bias or codon usage bias of the protein-encoding sequence.

3. A modified Zika virus according to Claim 2, in which reducing the codon-pair bias comprises identifying a codon pair in the parent protein-encoding sequence having a codon-pair score that can be reduced, and reducing the codon-pair bias by substituting the codon pair with a codon pair that has a lower codon-pair score.

4. A modified Zika virus according to Claim 2, in which reducing the codon-pair bias comprises rearranging the codons of a parent protein-encoding sequence.

5. A modified Zika virus according to Claim 1, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by increasing the number of CpG or UpA di-nucleotides compared to a parent virus.

6. A modified Zika virus according to Claim 1, in which each of the recoded E/prM protein-encoding sequence and the recoded NS3 protein-encoding sequence have a codon pair bias less than, -0.05, −0.1, or less than −0.2, or less than −0.3, or less than −0.4.

7. A modified Zika virus according to Claim 1, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by replacing one or more codons with synonymous codons that are less frequent in the host.

8. A Zika vaccine composition for inducing a protective immune response in a subject, comprising a modified virus according to any preceding claim.

9. Use of a modified virus according to any of Claims 1 to 7 in the manufacture of a medicament for eliciting a protective immune response in a subject, in which preferably a prophylactically or therapeutically effective dose of a vaccine composition comprising the modified virus is to be administered to a subject.

10. Use according to Claim 9, in which at least one adjuvant is to be further administered to the subject.

11. Use according to Claim 9, in which the immune response is cross-protective against a heterologous Zika virus.

12. A method of making a modified Zika virus genome comprising:

obtaining the nucleotide sequence encoding the envelope protein of a Zika virus and the nucleotide sequence encoding the nonstructural 3 proteins of a Zika virus;

recoding the envelope encoding nucleotide sequence to reduce protein expression and recoding the nonstructural protein 3-encoding nucleotide sequence to reduce protein expression, and

substituting a nucleic acid having the recoded envelope-encoding nucleotide sequence and a nucleic acid having the recoded nonstructural protein 3-encoding nucleotide sequence into a parent Zika virus genome to make a modified Zika virus genome; whereby expression of the recoded envelope-encoding nucleotide sequence and expression of the recoded nonstructural protein 3-encoding nucleotide sequence is reduced compared to the parent virus.

13. A modified Flavivirus virus in which expression of viral proteins is reduced compared to a parent virus, in which the reduction in expression is the result of recoding the envelope (E), or prM region, or the nonstructural protein 3 (NS3) region or both the E and NS3 regions.

14. A modified Flavivirus virus according to Claim 13, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by reducing the codon pair bias or codon usage bias of the protein-encoding sequence.

15. A modified Flavivirus virus according to Claim 14, in which reducing the codon-pair bias comprises identifying a codon pair in the parent protein-encoding sequence having a codon-pair score that can be reduced, and reducing the codon-pair bias by substituting the codon pair with a codon pair that has a lower codon-pair score.

16. A modified Flavivirus virus according to Claim 14, in which reducing the codon-pair bias comprises rearranging the codons of a parent protein-encoding sequence.

17. A modified Flavivirus virus according to Claim 13, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by increasing the number of CpG or UpA di nucleotides compared to a parent virus.

18. A modified Flavivirus virus according to Claim 13, in which each of the recoded E/prM protein-encoding sequence and the recoded NS3 protein-encoding sequence have a codon pair bias less than, -0.05, −0.1, or less than −0.2, or less than −0.3, or less than −0.4.

19. A modified Flavivirus virus according to Claim 13, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by replacing one or more codons with synonymous codons that are less frequent in the viral host.

20. A modified Flavivirus virus according to Claim 13, in which the parent virus is a Flavivirus selected from the group consisting of dengue fever virus, West Nile virus, yellow fever virus, Japanese encephalitis virus, Spondweni virus, Saint Louis encephalitis virus, and Powassan virus.

21. A modified Flavivirus virus according to Claim 13, in which the parent virus is a natural isolate.

22. A modified Flavivirus virus according to Claim 13, in which the parent virus is a mutant of a natural isolate.

23. A Flavivirus vaccine composition for inducing a protective immune response in a subject, which comprises a modified virus according to any of Claims 13 to 22.

24. Use of a modified virus according to any of Claims 13 to 22 in the manufacture of a medicament for eliciting a protective immune response in a subject, in which preferably a prophylactically or therapeutically effective dose of a vaccine composition comprising the modified virus is to be administered to the subject.

25. Use according to Claim 24, in which at least one adjuvant is to be further administered to the subject.

26. Use according to Claim 24, in which the immune response is cross-protective against a heterologous Flavivirus virus.

27. A method of making a modified Flavivirus virus genome comprising:

obtaining the nucleotide sequence encoding the envelope protein of a Flavivirus virus and the nucleotide sequence encoding the nonstructural 3 proteins of a Flavivirus virus;

recoding the envelope encoding nucleotide sequence to reduce protein expression and recoding the nonstructural protein 3-encoding nucleotide sequence to reduce protein expression, and

substituting a nucleic acid having the recoded envelope-encoding nucleotide sequence and a nucleic acid having the recoded nonstructural protein 3-encoding nucleotide sequence into a parent Flavivirus virus genome to make a modified Flavivirus virus genome; whereby expression of the recoded envelope-encoding nucleotide sequence and expression of the recoded nonstructural protein 3-encoding nucleotide sequence is reduced compared to the parent virus.

28. Use of an attenuated Flavivirus produced by a method other than codon-pair deoptimization or a modified Flavivirus in which expression of viral proteins is reduced compared to a parent virus, in which the reduction in expression is the result of recoding the envelope (E), or prM region, or the nonstructural protein 3 (NS3) region or both the E and NS3 regions in the manufacture of a medicament for eliciting an immune response in a subject in need thereof,

in which the attenuated Flavivirus by methods other than codon-pair deoptimization or the modified Flavivirus is to be administered to the subject in need thereof as a prime dose;

in which the attenuated Flavivirus by methods other than codon-pair deoptimization or the modified Flavivirus to be administered to the subject in need thereof as one or more boost doses; and

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

29. Use according to Claim 28, in which a first of the one or more boost dose is to be administered about 2 weeks after the prime dose.

30. Use according to Claim 28, in which the Flavivirus is a Zika virus.

31. Use according to Claim 28, in which the Flavivirus is selected from the group consisting of dengue fever virus, West Nile virus, yellow fever virus, Japanese encephalitis virus, Spondweni virus, Saint Louis encephalitis virus, and Powassan virus.

32. Use according to Claim 28, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by reducing the codon pair bias or codon usage bias of the protein-encoding sequence.

33. Use according to Claim 28, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by increasing the number of CpG or UpA di nucleotides compared to a parent virus.

34. Use according to Claim 28, in which reducing the codon-pair bias comprises identifying a codon pair in the parent protein-encoding sequence having a codon-pair score that can be reduced, and reducing the codon-pair bias by substituting the codon pair with a codon pair that has a lower codon-pair score.

35. Use according to Claim 28, in which reducing the codon-pair bias comprises rearranging the codons of a parent protein-encoding sequence.

36. Use according to Claim 28, in which each of the recoded E/prM protein-encoding sequence and the recoded NS3 protein-encoding sequence have a codon pair bias less than, -0.05, −0.1, or less than −0.2, or less than −0.3, or less than −0.4.

37. Use according to Claim 28, in which one or both of the E protein-encoding sequence and the NS3 protein-encoding sequence are recoded by replacing one or more codons with synonymous codons that are less frequent in the viral host.