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.