

WHAT IS CLAIMED IS:

1. A modified HCV E2 ectodomain polypeptide, comprising an engineered E2 ectodomain sequence that contains at least one modification selected from (a) a truncation in the VR2 disordered region and (b) a deletion in the β -sandwich loop
5 connecting β sheets 6 and 7 of the β -sandwich domain.
2. The modified HCV E2 ectodomain polypeptide of claim 1, wherein the engineered E2 ectodomain sequence comprises SEQ ID NO:4, a conservatively modified variant or a substantially identical sequence thereof.
3. The modified HCV E2 ectodomain polypeptide of claim 2, wherein
10 truncation of the VR2 disordered region comprises replacing residues 41-61 of SEQ ID NO:4, CPERLASCSSGCWHYPPRPC (SEQ ID NO:6), with CPERASGHYPPRPC (SEQ ID NO:10).
4. The modified HCV E2 ectodomain polypeptide of claim 2, wherein truncation of the VR2 disordered region comprises replacing residues 41-61 of SEQ ID
15 NO:4, CPERLASCSSGCWHYPPRPC (SEQ ID NO:6), with a sequence set forth in CXXXXXXHYPPRPC (SEQ ID NO:8) or CXXXXXHYPPRPC (SEQ ID NO:9), wherein X is any amino acid residue.
5. The modified HCV E2 ectodomain polypeptide of claim 4, wherein XXXXXX in SEQ ID NO:8 is QNWDEP (SEQ ID NO:11), KVNIDP (SEQ ID NO:12),
20 EKVEEL (SEQ ID NO:13), PDENMK (SEQ ID NO:14), or KREEKM (SEQ ID NO:15).
6. The modified HCV E2 ectodomain polypeptide of claim 4, wherein XXXXX in SEQ ID NO:9 is PKTEV (SEQ ID NO:16), KRVDI (SEQ ID NO:17), PSDMV (SEQ ID NO:18), PNEEE (SEQ ID NO:19), or KKEIR (SEQ ID NO:20).
7. The modified HCV E2 ectodomain polypeptide of claim 2, wherein
25 deletion of the β -sandwich loop sequence (SEQ ID NO:21) comprises deletion of one or more residues that form the tip of the β -sandwich loop.
8. The modified HCV E2 ectodomain polypeptide of claim 7, wherein residues that form the tip of the β -sandwich loop are residues 543-546 from SEQ ID NO:4.

9. The modified HCV E2 ectodomain polypeptide of claim 7, wherein residues 543-546 from SEQ ID NO:4, RRPL (SEQ ID NO:22), are deleted.

10. The modified HCV E2 ectodomain polypeptide of claim 1, comprising both truncation in the VR2 disordered region and deletion in the β -sandwich loop.

5 11. The modified HCV E2 ectodomain polypeptide of claim 10, comprising an amino acid sequence as set forth in any one of SEQ ID NOs:26-38, a conservatively modified variant or a substantially identical sequence thereof.

12. A polynucleotide encoding the modified HCV E2 ectodomain polypeptide of claim 1.

10 13. A pharmaceutical composition, comprising the modified HCV E2 ectodomain polypeptide of claim 1, and a pharmaceutically acceptable carrier.

14. A vaccine composition, comprising a modified HCV E2 ectodomain polypeptide of claim 1 that is displayed on the surface of a self-assembling nanoparticle.

15 15. The vaccine composition of claim 14, wherein C-terminus of the modified HCV E2 ectodomain polypeptide is fused to the N-terminus of subunit of the self-assembling nanoparticle via a linker sequence.

16. The vaccine composition of claim 15, wherein the linker sequence comprises (GGGGS)₂ (SEQ ID NO:42).

20 17. The vaccine composition of claim 14, wherein the modified HCV E2 ectodomain polypeptide comprises an amino acid sequence as set forth in any one of SEQ ID NOs:26-38, a conservatively modified variant or a substantially identical sequence thereof.

25 18. The vaccine composition of claim 14, wherein subunit of the self-assembling nanoparticle comprises the polypeptide as shown in SEQ ID NO:39 (E2p), SEQ ID NO:40 (I3-01), or SEQ ID NO:41 (ferritin), a conservatively modified variant or a substantially identical sequence thereof.

19. A polynucleotide, encoding a fusion protein comprising a modified HCV E2 ectodomain polypeptide of claim 1 and a self-assembling nanoparticle subunit,

wherein the modified HCV E2 ectodomain polypeptide is fused at its C-terminus to the N-terminus of the self-assembling nanoparticle subunit.

20. A pharmaceutical composition, comprising the vaccine composition of claim 14, and a pharmaceutically acceptable carrier.

5 **21.** A method of treating or preventing HCV infection in a subject, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of the vaccine composition of claim 14, thereby treating or preventing HCV infection in the subject.

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