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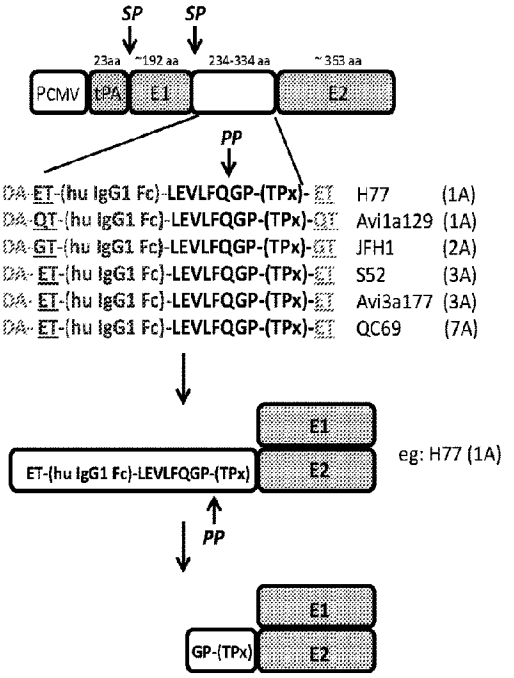
(54) Titre : COMPOSITIONS IMMUNOGENES A BASE DU VIRUS DE L'HEPATITE C ET PROCEDES D'UTILISATION
(54) Title: HEPATITIS C VIRUS IMMUNOGENIC COMPOSITIONS AND METHODS OF USE THEREOF



(57) Abrégé/Abstract:
The present disclosure provides heterodimeric polypeptides comprising: 1) a variant hepatitis C virus (HCV) E2 polypeptide and an HCV El polypeptide; 2) a variant HCV El polypeptide and an HCV E2 polypeptide; or 3) a variant HCV El polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide and/or the HCV El polypeptide comprises one or more T cell epitopes, present in an HCV polypeptide other than an HCV El polypeptide or an HCV E2 polypeptide. The present disclosure provides nucleic acids encoding a polyprotein that includes El and variant E2, E2 and variant El, or variant E2 and variant El. The present disclosure provides a method of producing an E1/E2 heterodimer of the present disclosure. The present disclosure provides a method of inducing an immune response in an individual. The present disclosure provides variant E2 polypeptides and variant E1 polypeptides; and nucleic acids encoding same.

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(54) **Title**: HEPATITIS C VIRUS IMMUNOGENIC COMPOSITIONS AND METHODS OF USE THEREOF

(57) **Abstract**: The present disclosure provides heterodimeric polypeptides comprising: 1) a variant hepatitis C virus (HCV) E2 polypeptide and an HCV El polypeptide; 2) a variant HCV El polypeptide and an HCV E2 polypeptide; or 3) a variant HCV El polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide and/or the HCV El polypeptide comprises one or more T cell epitopes, present in an HCV polypeptide other than an HCV El polypeptide or an HCV E2 polypeptide. The present disclosure provides nucleic acids encoding a polyprotein that includes El and variant E2, E2 and variant El, or variant E2 and variant El. The present disclosure provides a method of producing an E1/E2 heterodimer of the present disclosure. The present disclosure provides a method of inducing an immune response in an individual. The present disclosure provides variant E2 polypeptides and variant E1 polypeptides; and nucleic acids encoding same.

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CONTENANT LES PAGES 1 À 176

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HEPATITIS C VIRUS IMMUNOGENIC COMPOSITIONS AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/189,657, filed July 7, 2015.

SEQUENCE LISTING PROVIDED AS A TEXT FILE

[0002] A Sequence Listing is provided herewith as a text file, "UALB-027WO_Sequence_Listing_ST25.txt" created on July 5, 2016 and having a size of 933 KB.

INTRODUCTION

[0003] Hepatitis C virus (HCV) is a blood-borne pathogen that is estimated to infect 150-200 million people worldwide. Infection by HCV may be non-symptomatic, and can be cleared by patients, sometimes without medical intervention. However, the majority of patients develop a chronic HCV infection, which may lead to liver inflammation, scarring, and even to liver failure or liver cancer. In the United States alone, over 3 million people have a chronic infection.

[0004] The HCV virion contains a positive-sense single stranded RNA genome of about 9.5 kb. The genome encodes a single polyprotein of 3,010 to 3,030 amino acids. The structural proteins comprise a core protein forming the viral nucleocapsid and two envelope glycoproteins, E1 and E2.

[0005] A vaccine based on the recombinant envelope glycoproteins (rE1E2) from a single genotype 1a strain (HCV-1) protected chimpanzees from chronic infection following homologous and heterologous genotype 1a (gt1a) viral challenge (reviewed in Houghton, M Immunol Rev 2011). Antisera from the immunized chimpanzees were shown to exhibit *in vitro* cross-neutralizing activity (Meunier et al. (2011) *J. Infect. Dis.* 204:1186). A phase I clinical trial was conducted in human volunteers with a similar antigen (Frey et al. (2010) *Vaccine* 28:6367). Antisera from selected vaccinated individuals were similarly capable of neutralizing chimeric cell culture-derived viruses (HCVcc) expressing the structural proteins of strains representing all 7 major HCV genotypes *in vitro* (Law et al. (2013) *PLoS One* 8:e59776) and to be able to compete with the binding of numerous discrete monoclonal antibodies with broad cross-neutralising activities (Wong et al. (2014) *J. Virol.* 88:14278).

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[0006] There is a need in the art for compositions and methods for inducing immune responses to HCV.

SUMMARY

[0007] The present disclosure provides heterodimeric polypeptides comprising a variant hepatitis C virus (HCV) E2 polypeptide and an HCV E1 polypeptide, or comprising a variant HCV E1 polypeptide and an HCV E2 polypeptide, or comprising a variant HCV E1 polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide and/or the variant HCV E1 polypeptide comprises one or more T cell epitopes, e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide. The present disclosure provides nucleic acids encoding a polyprotein that includes E1 and variant E2, or that includes E2 and variant E1, or that includes variant E2 and variant E1. The present disclosure provides a method of producing an E1/E2 heterodimer of the present disclosure. The present disclosure provides a method of inducing an immune response in an individual. The present disclosure provides variant E2 polypeptides and variant E1 polypeptides; and nucleic acids encoding the variant polypeptides.

[0008] The present disclosure provides a heterodimeric polypeptide comprising: a) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising a T-cell epitope present in an HCV protein other than E1 and E2; and b) an HCV E1 polypeptide. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in one or more of: a) an HCV non-structural polypeptide-3 (NS3) polypeptide; b) an HCV non-structural polypeptide-2 (NS2) polypeptide; c) an HCV non-structural polypeptide-4A (NS4A) polypeptide; d) an HCV non-structural polypeptide-4B (NS4B) polypeptide; e) an HCV non-structural polypeptide-5A (NS5A) polypeptide; f) an HCV non-structural polypeptide-5B (NS5B) polypeptide; g) an HCV core polypeptide; and h) an HCV p7 polypeptide. In some cases, a) the HCV E2 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7; and b) the HCV E1 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7. In some cases, the HCV E2 polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%,at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an E2 polypeptide depicted in one of FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B. In some cases, the

heterologous polypeptide has a length of from about 10 amino acids to about 3000 amino acids. In some cases the heterologous polypeptide has a length of from about 10 amino acids to about 100 amino acids. In some cases the heterologous polypeptide comprises one or more T cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD ALMTGFTGDFDSVIDCN (SEQ ID NO:3). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYR GLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4). In some cases, the variant HCV E2 polypeptide comprises, in order from N-terminus to C-terminus: i) the heterologous polypeptide; and ii) the HCV E2 polypeptide. In some cases, the variant HCV E2 polypeptide comprises, in order from N-terminus to C-terminus: i) the HCV E2 polypeptide; and ii) the heterologous polypeptide. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) CRM197. In some cases, the E2 polypeptide and/or the E1 polypeptide lacks a C-terminal transmembrane domain. In some cases, the modified HCV E2 polypeptide and the HCV E1 polypeptide are derived from an HCV of the same genotype. In some cases, the modified HCV E2 polypeptide and the HCV E1 polypeptide are derived from an HCV of different genotypes. In some cases, the HCV E1 polypeptide comprises an amino acid sequence having at least 20% amino acid

sequence identity to an E1 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B.

[0009] The present disclosure provides a nucleic acid comprising nucleotide sequences encoding any one of the heterodimeric polypeptides as described above or elsewhere herein. In some cases, the nucleotide sequence encoding the variant HCV E2 polypeptide and the nucleotide sequence encoding the HCV E1 polypeptide are operably linked to a promoter. The present disclosure provides a recombinant expression vector comprising the nucleic acid.

[0010] The present disclosure provides a heterodimeric polypeptide comprising: a) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising a T-cell epitope present in an HCV protein other than E1 and E2; and b) an HCV E2 polypeptide. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in one or more of: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS-4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; and h) an HCV p7 polypeptide. In some cases, a) the HCV E2 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7; and b) the HCV E1 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7. In some cases, the HCV E1 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E1 polypeptide depicted in one of FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B. In some cases, the heterologous polypeptide has a length of from about 10 amino acids to about 3000 amino acids. In some cases, the heterologous polypeptide has a length of from about 10 amino acids to about 100 amino acids. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2). In some cases, the heterologous polypeptide comprises an amino acid

sequence having at least 20% amino acid sequence identity to the following amino acid sequence:
KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD ALMTGFTGDFDSVIDCN (SEQ ID NO:3). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence:
VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYR GLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4). In some cases, the variant HCV E1 polypeptide comprises, in order from N-terminus to C-terminus: i) the heterologous polypeptide; and ii) the HCV E1 polypeptide. In some cases, the variant HCV E1 polypeptide comprises, in order from N-terminus to C-terminus: i) the HCV E1 polypeptide; and ii) the heterologous polypeptide. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) CRM197. In some cases, the E2 polypeptide and/or the E1 polypeptide lacks a C-terminal transmembrane domain. In some cases, the modified HCV E2 polypeptide and the HCV E1 polypeptide are derived from an HCV of the same genotype. In some cases, the modified HCV E2 polypeptide and the HCV E1 polypeptide are derived from an HCV of different genotypes. In some cases, the HCV E2 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E2 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B.

[0011] The present disclosure provides nucleic acid comprising nucleotide sequences encoding any one of the heterodimeric polypeptides described above or elsewhere herein. In some cases, the nucleotide sequence encoding the variant HCV E2 polypeptide and the nucleotide sequence encoding the HCV E1 polypeptide are operably linked to a promoter. The present disclosure provides a recombinant expression vector comprising the nucleic acid.

[0012] The present disclosure provides a heterodimeric polypeptide comprising: a) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a first heterologous polypeptide comprising a T-cell epitope present in an HCV protein other than E1 and E2; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii)

a second heterologous polypeptide comprising a T-cell epitope present in an HCV protein other than E1 and E2. In some cases, the first and the second heterologous polypeptides comprise one or more T cell epitopes present in one or more of: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS-4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; and h) an HCV p7 polypeptide. In some cases, a) the HCV E2 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7; and b) the HCV E1 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7. In some cases, the HCV E1 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E1 polypeptide depicted in one of FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B. In some cases, each of the first and the second heterologous polypeptide independently has a length of from about 10 amino acids to about 3000 amino acids. In some cases, each of the first and the second heterologous polypeptide independently has a length of from about 10 amino acids to about 100 amino acids. In some cases, the first and/or the second heterologous polypeptide comprises one or more T cell epitopes present in an HCV NS3 polypeptide. In some cases, the first and/or the second heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1). In some cases, the first and/or the second heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2). In some cases, the first and/or the second heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD ALMTGFTGDFDSVIDCN (SEQ ID NO:3). In some cases, the first and/or the second heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYR GLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4). In some cases, the variant HCV E1 polypeptide comprises, in order from N-

terminus to C-terminus: i) the heterologous polypeptide; and ii) the HCV E1 polypeptide, and wherein the variant HCV E2 polypeptide comprises, in order from N-terminus to C-terminus: i) the heterologous polypeptide; and ii) the HCV E2 polypeptide. In some cases, the variant HCV E1 polypeptide comprises, in order from N-terminus to C-terminus: i) the HCV E1 polypeptide; and ii) the heterologous polypeptide, and wherein the variant HCV E2 polypeptide comprises, in order from N-terminus to C-terminus: i) the HCV E2 polypeptide; and ii) the heterologous polypeptide. In some cases, the first and/or the second heterologous polypeptide comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) CRM197. In some cases, the E2 polypeptide and/or the E1 polypeptide lacks a C-terminal transmembrane domain. In some cases, the modified HCV E2 polypeptide and the HCV E1 polypeptide are derived from an HCV of the same genotype. In some cases, the modified HCV E2 polypeptide and the HCV E1 polypeptide are derived from an HCV of different genotypes. In some cases, the HCV E2 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E2 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B.

[0013] The present disclosure provides a nucleic acid comprising nucleotide sequences encoding any one of the heterodimeric polypeptides described above or elsewhere herein. In some cases, the nucleotide sequence encoding the variant HCV E2 polypeptide and the nucleotide sequence encoding the HCV E1 polypeptide are operably linked to a promoter. The present disclosure provides a recombinant expression vector comprising the nucleic acid.

[0014] The present disclosure provides a composition comprising: a) a heterodimeric polypeptide as described above or elsewhere herein; and b) a pharmaceutically acceptable excipient. In some cases, the pharmaceutically acceptable excipient comprises an adjuvant. In some cases, the adjuvant is MF59, alum, poly(DL-lactide co-glycolide), a CpG oligonucleotide, or keyhole limpet hemocyanin.

[0015] The present disclosure provides a nucleic acid comprising a nucleotide sequence encoding an HCV E1-E2 polyprotein comprising: a) an HCV E1 polypeptide; b) an HCV E2 polypeptide; and c) a heterologous polypeptide that comprises one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an

HCV E2 polypeptide. In some cases, the HCV E1 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E1 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B. In some cases, the HCV E2 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7. In some cases, the HCV E2 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E2 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B. In some cases, the HCV E2 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7. In some cases, the HCV E2 polypeptide and the HCV E1 polypeptide are of the same genotype. In some cases, the HCV E2 polypeptide and the HCV E1 polypeptide are of different genotypes. In some cases, the heterologous polypeptide has a length of from about 10 amino acids to about 3000 amino acids. In some cases, the heterologous polypeptide has a length of from about 10 amino acids to about 100 amino acids. In some cases, the E1-E2 polyprotein comprises, in order from N-terminus to C-terminus: i) the HCV E1 polypeptide; ii) the heterologous polypeptide; and iii) the HCV E2 polypeptide. In some cases, the E1-E2 polyprotein comprises, in order from N-terminus to C-terminus: i) the HCV E1 polypeptide; ii) the HCV E2 polypeptide; and iii) the heterologous polypeptide. In some cases, the E1-E2 polyprotein comprises, in order from N-terminus to C-terminus: i) the heterologous polypeptide; ii) the HCV E1 polypeptide; and iii) the HCV E2 polypeptide. In some cases, the E1-E2 polyprotein comprises, in order from N-terminus to C-terminus: i) the HCV E1 polypeptide; ii) the heterologous polypeptide; and iii) the HCV E2 polypeptide. In some cases, the nucleic acid comprises a nucleotide sequence encoding an immunoglobulin Fc polypeptide. In some cases, the polypeptide encoded by the nucleic acid comprises, in order from N-terminus to C-terminus: i) the E1 polypeptide; ii) the Fc polypeptide; iii) the heterologous polypeptide; and iv) the HCV E2 polypeptide. In some cases, the polypeptide encoded by the nucleic acid comprises a proteolytically cleavable linker interposed between the Fc polypeptide and the heterologous polypeptide. In some cases, the polypeptide encoded by the nucleic acid comprises, in order from N-terminus to C-terminus: i) the E1 polypeptide; ii) the Fc polypeptide; iii) the HCV E2 polypeptide; and iv) the heterologous polypeptide. In some cases, a proteolytically cleavable linker is interposed between the Fc polypeptide and the HCV E2 polypeptide. In some cases, a) the proteolytically cleavable linker comprises the sequence LEVLFQGP (SEQ ID

NO:5), wherein cleavage occurs between the glutamine and the glycine; b) the proteolytically cleavable linker comprises the sequence ENLYTQS (SEQ ID NO:6), wherein cleavage occurs between the glutamine and the serine; c) the proteolytically cleavable linker comprises the sequence DDDDK (SEQ ID NO:7), wherein cleavage occurs immediately C-terminal to the lysine residue; or d) the proteolytically cleavable linker comprises the sequence LVPR (SEQ ID NO:8). In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in one or more of: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; and h) an HCV p7 polypeptide. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) CRM197. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD ALMTGFTGDFDSVIDCN (SEQ ID NO:3). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYR GLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4).

[0016] The present disclosure provides a recombinant expression vector comprising a nucleic acid as described above or elsewhere herein. In some cases, the nucleotide sequence is

operably linked to a promoter. In some cases, the promoter is functional in a eukaryotic cell. The present disclosure provides a genetically modified *in vitro* host cell comprising a nucleic acid as described above or elsewhere herein, or the recombinant vector. In some cases, the host cell is a eukaryotic cell. In some cases, the host cell is a mammalian cell.

[0017] The present disclosure provides a method of making a variant HCV E1-E2 heterodimer, the method comprising: a) contacting a lysate of a genetically modified host cell described above, or elsewhere herein, with an Fc-binding polypeptide immobilized on an insoluble support, wherein the encoded HCV E1-E2 heterodimer comprises an Fc polypeptide, and wherein the HCV E1-E2 heterodimer present in the lysate binds to the immobilized Fc-binding polypeptide, generating an immobilized HCV E1-E2 heterodimer; and b) contacting the immobilized HCV E1-E2 heterodimer with an enzyme that cleaves the proteolytic cleavage site interposed between the Fc polypeptide and the heterologous polypeptide, thereby releasing the variant HCV E1-E2 heterodimer. In some cases, the released variant HCV E1-E2 heterodimer is at least 50% pure. In some cases, the Fc binding polypeptide is Protein A, Protein G, or a Protein A/G fusion. In some cases, a) the proteolytically cleavable linker comprises the sequence LEVLFQGP (SEQ ID NO:5), wherein cleavage occurs between the glutamine and the glycine; b) the proteolytically cleavable linker comprises the sequence ENLYTQS (SEQ ID NO:6), wherein cleavage occurs between the glutamine and the serine; c) the proteolytically cleavable linker comprises the sequence DDDDK (SEQ ID NO:7), wherein cleavage occurs immediately C-terminal to the lysine residue; or d) the proteolytically cleavable linker comprises the sequence LVPR (SEQ ID NO:8). In some cases, the enzyme is human rhinovirus 3C protease, a tobacco etch virus protease, an enterokinase, or thrombin. In some cases, the method further comprises subjecting a composition comprising the released HCV E1-E2 heterodimer to hydroxyapatite chromatography. Hydroxyapatite chromatography can be carried out as described in, e.g., Mazzocca et al. (2005) *J. Biol. Chem.* 280:11329.

[0018] The present disclosure provides a variant HCV E2 polypeptide comprising: a) an HCV E2 polypeptide; and b) a heterologous polypeptide that comprises one or more T cell epitopes present in an HCV protein other than E1 and E2. In some cases, the HCV E2 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7. In some cases, the HCV

E2 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E2 polypeptide depicted in one of FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B. In some cases, the heterologous polypeptide has a length of from about 10 amino acids to about 3000 amino acids. In some cases, the heterologous polypeptide has a length of from about 10 amino acids to about 100 amino acids. In some cases, wherein the heterologous polypeptide comprises one or more T cell epitopes present in one or more of: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS-4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; and h) an HCV p7 polypeptide. In some cases, the HCV E2 polypeptide lacks a C-terminal transmembrane domain. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) CRM197. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD ALMTGFTGDFDSVIDCN (SEQ ID NO:3). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYR GLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4). In some cases, the variant HCV E2 polypeptide comprises, in order from N-terminus to C-terminus: i) the heterologous polypeptide; and ii) the HCV E2 polypeptide. In some cases, the varian HCV E2 polypeptide comprises, in order from N-

terminus to C-terminus: i) the HCV E2 polypeptide; and ii) the heterologous polypeptide. In some cases, the variant HCV E2 polypeptide comprises an immunoglobulin Fc polypeptide. In some cases, the variant HCV E2 polypeptide comprises, in order from N-terminus to C-terminus: i) the Fc polypeptide; ii) the heterologous polypeptide; and iii) the HCV E2 polypeptide. In some cases, the variant HCV E2 polypeptide comprises a proteolytic cleavage site interposed between the Fc polypeptide and the heterologous polypeptide. In some cases, the proteolytic cleavage site comprises the sequence LEVLFQGP (SEQ ID NO:5), wherein cleavage occurs between the glutamine and the glycine.

[0019] The present disclosure provides a variant HCV E1 polypeptide comprising: a) an HCV E1 polypeptide; and b) a heterologous polypeptide that comprises one or more T cell epitopes. In some cases, the HCV E1 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7. In some cases, the HCV E1 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E1 polypeptide depicted in one of FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B. In some cases, the heterologous polypeptide has a length of from about 10 amino acids to about 3000 amino acids. In some cases, the heterologous polypeptide has a length of from about 10 amino acids to about 100 amino acids. In some cases, the HCV E1 polypeptide lacks a transmembrane domain. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in one or more of: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS-4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; and h) an HCV p7 polypeptide. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) CRM197. In some cases, the heterologous polypeptide comprises one or more T cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG

(SEQ ID NO:2). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence:
KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD ALMTGFTGDFDSVIDCN (SEQ ID NO:3). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the following amino acid sequence:
VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYR GLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4). In some cases, the variant HCV E1 polypeptide comprises, in order from N-terminus to C-terminus: i) the heterologous polypeptide; and ii) the HCV E1 polypeptide. In some cases, the variant HCV E1 polypeptide comprises, in order from N-terminus to C-terminus: i) the HCV E1 polypeptide; and ii) the heterologous polypeptide. In some cases, the variant HCV E1 polypeptide comprises an immunoglobulin Fc polypeptide. In some cases, the variant HCV E1 polypeptide comprises, in order from N-terminus to C-terminus: i) the Fc polypeptide; ii) the heterologous polypeptide; and iii) the HCV E1 polypeptide. In some cases, the variant HCV E1 polypeptide comprises a proteolytic cleavage site interposed between the Fc polypeptide and the heterologous polypeptide. In some cases, the proteolytic cleavage site comprises the sequence LEVLFQGP (SEQ ID NO:5), wherein cleavage occurs between the glutamine and the glycine.

[0020] The present disclosure nucleic acid comprising a nucleotide sequence encoding a variant HCV E2 polypeptide as described above or elsewhere herein, or a variant HCV E1 polypeptide as described above or elsewhere herein. The present disclosure provides a recombinant expression vector comprising the nucleic acid. In some cases, the nucleotide sequence is operably linked to a promoter. In some cases, the promoter is functional in a eukaryotic cell. The present disclosure provides a genetically modified *in vitro* host cell comprising a nucleic acid as described above or elsewhere herein, or a recombinant vector as described above or elsewhere herein. In some cases, the host cell is a eukaryotic cell. In some cases, the host cell is a mammalian cell.

[0021] The present disclosure provides a method of inducing an immune response in an individual, the method comprising administering to the individual an effective amount of

a heterodimeric polypeptide as described above or elsewhere herein, or a composition as described above or elsewhere herein. The present disclosure provides a method of inducing an immune response in an individual, the method comprising administering to the individual an effective amount of a nucleic acid as described above or elsewhere herein.

[0022] The present disclosure provides a method of inducing an immune response in an individual, the method comprising administering to the individual an effective amount of a recombinant expression vector as described above or elsewhere herein. In some cases, the recombinant expression vector is a recombinant modified vaccinia Ankara vector. In some cases, the recombinant expression vector is a recombinant replication-defective adenovirus. In some cases, administration of the recombinant expression vector is by intramuscular administration. In some cases, administration of the recombinant expression vector is by subcutaneous administration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1A-1C provide an amino acid sequence alignment of examples of the core-E1-E2 coding regions of a HCV genotype 1 virus, specifically representative HCV 1A, 1B and 1C genotypes. Genbank database sequences for the coding region core-E1-E2 were aligned using Geneious software v5.6.4. Numbering of amino acids is according to strain NP_671941 (H77). Consensus: SEQ ID NO:74; AVI1a129: SEQ ID NO:75; NP_671491 (H77): SEQ ID NO:76; EU155269: SEQ ID NO:77; EU781810: SEQ ID NO:78; EU781771: SEQ ID NO:79; AB250610: SEQ ID NO:80; EU781752: SEQ ID NO:81; EU781759: SEQ ID NO:82; EF407439: SEQ ID NO:83; EF407427: SEQ ID NO:84; EU362905: SEQ ID NO:85; EF407413: SEQ ID NO:86; EU781808: SEQ ID NO:87; EU78170: SEQ ID NO:88; AJ238799 (Con1): SEQ ID NO:89; AAK97744: SEQ ID NO:90; AF139594: SEQ ID NO:91; AF176573: SEQ ID NO:92; BAA19625: SEQ ID NO:93; BAA25076: SEQ ID NO:94; BAC54896: SEQ ID NO:95; BAD91386: SEQ ID NO:96; BAF46764: SEQ ID NO:97; BAG30950: SEQ ID NO:98; CAB41951: SEQ ID NO:99; AAK95832: SEQ ID NO:100; AAT69968: SEQ ID NO:101; and BAA03581: SEQ ID NO:102.

[0024] FIG. 2A-2C provide an alignment of amino acid sequences of the core-E1-E2 coding region of representative HCV 2A and HCV2B subtypes. Genbank database sequences for the coding region core-E1-E2 were aligned using Geneious software v5.6.4. The amino acid numbering depicted is in accordance to the common HCV strains: ABO47639 (JFH1) and HPCJ8G-J8 (J8) for HCV2A and HCV2B, respectively. AB047639 (JFH1): SEQ ID NO:103; AB047645: SEQ

ID NO:104; AF169003: SEQ ID NO:105; AF169005: SEQ ID NO:106; AF238482: SEQ ID NO:107; AY746460: SEQ ID NO:108; HPCPOLP: SEQ ID NO:109; NC_009823: SEQ ID NO:110; HPCJ8G HC-J8: SEQ ID NO:111; AB030907: SEQ ID NO:112; AY232730: SEQ ID NO:113; AY232747: SEQ ID NO:114; and DQ430817: SEQ ID NO:115.

[0025] FIG. 3A-3C provide an amino acid sequence alignment of the core-E1-E2 coding region for representative HCV 3A, 3B and 3K genotypes. Genbank database sequences for the coding region core-E1-E2 were aligned using Geneious software v5.6.4. Consensus: SEQ ID NO:116; AVI3a177: SEQ ID NO:117; ADF97232(S52): SEQ ID NO:118; YP_0014696: SEQ ID NO:119; CAA54244: SEQ ID NO:120; AAC03058: SEQ ID NO:121; AAY29642: SEQ ID NO:122; ABD85062: SEQ ID NO:123; ABD85063: SEQ ID NO:124; ABD97104: SEQ ID NO:125; BAA06044: SEQ ID NO:126; BAA08372: SEQ ID NO:127; and BAA09890: SEQ ID NO:128.

[0026] FIG. 4A-4B provide an amino acid sequence of the core-E1-E2 coding region for HCV genotype 7a. Amino acid sequence for the coding region core-E1-E2 of genotype 7a (isolate QC69; Genbank: ABN05226.1; SEQ ID NO:129) is shown according to the numbering scheme of the reference strain, NP_671941 (H77).

[0027] FIG. 5A-5B present schematic representations of Fc-tagged and untagged E1E2 expression constructs and polypeptide processing. FIG. 5A depicts a schematic representation of an Fc-tagged E1E2 expression construct and polypeptide processing. SP denotes signal peptidase cleavage site. PP denotes cleavage site for precision protease. TPx denotes the addition of a polytope (a polypeptide comprising T-cell epitope(s)) to the E1E2 polypeptide at the N-terminus of E2. SEQ ID NO:5. FIG. 5B depicts a schematic representation of an un-tagged E1E2 expression construct and polypeptide processing.

[0028] FIG. 6A-6B depict an alignment of Fc-tagged E1-E2 polypeptide, with and without a polytope (TPx) for H77 (GenBank NP_671941) and Alberta isolate Avi1a129 (genotype 1A). AVI1a129: SEQ ID NO:130; AVI1a129TP29: SEQ ID NO:131; AVI1a29TP52: SEQ ID NO:132; AVI1a129TP100: SEQ ID NO:133; H77: SEQ ID NO:134; H77 TP29: SEQ ID NO:135; H77 TP52: SEQ ID NO:136; H77 TP100: SEQ ID NO:137.

[0029] FIG. 7A-7B depict an alignment of Fc-tagged E1-E2 polypeptide, with and without a polytope (TPx) for S52 (GenBank ADF97232.1) and Alberta isolate Avi3a177 (genotype 3A). S52: SEQ ID NO:138; S52 TP29: SEQ ID NO:139; S52 TP52: SEQ ID NO:140; S52 TP100: SEQ ID NO:141; AVI3a177: SEQ ID NO:142; AVI3a177 TP29: SEQ ID NO:143; AVI3a177 TP52: SEQ ID NO:144; AVI3a177 TP100: SEQ ID NO:145.

[0030] FIG. 8A-8B depict purification of an E1E2 heterodimer from CHO cell extracts expressing Fc-tagged E1E2.

[0031] FIG. 9A-9C provide amino acid sequences of immunoglobulin Fc regions (SEQ ID NOs:146-153).

[0032] FIG. 10 presents Table 1, which provides conserved regions based on conserved CD4 epitopes ($CD4^+$ T cell epitopes) (SEQ ID NOs:154-164).

[0033] FIG. 11 presents Table 2, which provides the number of located HCV $CD8^+$ T cell epitopes and anchor positions for common human leukocyte antigen (HLA)-I Alleles in the United States.

[0034] FIG. 12 presents Table 3, which provides conserved regions based on conserved CD8 epitopes ($CD8^+$ T cell epitopes) (SEQ ID NOs:165-174).

[0035] FIG. 13A-13B provide a list of CD4 and CD8 epitopes that are conserved amond HCV genotypes 1a, 1b, 2a, 2b, and 3.

[0036] FIG. 14A-14D provide amino acid sequences of examples of T-cell polytopes ("TP"). The start and end amino acids are based on the sequence designated "Consensus" in FIG. 16A-16L. The T-cell epitopes contained within each TP are provided; the T-cell epitope designations correspond to those presented in FIG. 15A-15N (SEQ ID NOs:175-184).

[0037] FIG. 15A-15N provide consensus amino acid sequences of HCV polypeptides; and depict the locations of T-cell epitopes (SEQ ID NO:185).

[0038] FIG. 16A-16L provide consensus amino acid sequences of HCV polypeptides (SEQ ID NOs:186-197).

DEFINITIONS

[0039] The term "hepatitis C virus" ("HCV"), as used herein, refers to any one of a number of different genotypes and isolates of hepatitis C virus. Thus, "HCV" encompasses any of a number of genotypes, subtypes, or quasispecies, of HCV, including, e.g., genotype 1, 2, 3, 4, 6, 7, etc. and subtypes (e.g., 1a, 1b, 2a, 2b, 3a, 4a, 4c, etc.), and quasispecies. Representative HCV genotypes and isolates include: the "Chiron" isolate HCV-1, H77, J6, Con1, isolate 1, BK, EC1, EC10, HC-J2, HC-J5; HC-J6, HC-J7, HC-J8, HC-JT, HCT18, HCT27, HCV-476, HCV-KF, "Hunan", "Japanese", "Taiwan", TH, type 1, type 1a, H77 type 1b, type 1c, type 1d, type 1e, type 1f, type 10, type 2, type 2a, type 2b, type 2c, type 2d, type 2f, type 3, type 3a, type 3b, type 3g, type 4, type 4a, type 4c, type 4d, type 4f, type 4h, type 4k, type 5, type 5a, type 6 and type 6a.

[0040] The terms "individual," "host," "subject," and "patient" are used interchangeably herein, and refer to a mammal, including, but not limited to, non-human primates (e.g., simians), equines (e.g., horses), and humans.

[0041] As used herein, the term "isolated," in reference to a polypeptide, refers to a polypeptide that is in an environment different from that in which the polypeptide naturally occurs. An isolated polypeptide can be purified. By "purified" is meant a compound of interest (e.g., a polypeptide) has been separated from components that accompany it in nature. "Purified" can also be used to refer to a polypeptide separated from components that can accompany it during production of the polypeptide (e.g., during synthesis in vitro, etc.). In some embodiments, a polypeptide (or a mixture of polypeptides) is substantially pure when the polypeptide (or mixture of polypeptides) is at least 60% or at least 75% by weight free from organic molecules with which it is naturally associated or with which it is associated during production. In some embodiments, the polypeptide is from 30% to 60% pure. In some embodiments, the polypeptide (or mixture of polypeptides) is at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, by weight, pure. For example, in some embodiments, an E1 or an E2 polypeptide (or a mixture of E1 and E2 polypeptides) is substantially pure when the E1 or E2 polypeptide (or mixture of E1 and E2 polypeptides) is at least 60% or at least 75% by weight free from organic molecules with which the polypeptide(s) is naturally associated or with which it is associated during production. In some embodiments, the E1 or E2 polypeptide (or mixture of E1 and E2 polypeptides) is at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, by weight, pure. In some embodiments, where a composition comprises an E2 polypeptide, the E2 polypeptide is at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, by weight, pure. In some embodiments, where a composition comprises an E1/E2 heterodimeric complex polypeptide, the E1/E2 heterodimeric complex polypeptide is at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, by weight, pure. In some embodiments, where a composition comprises an E1/variant E2 heterodimeric complex polypeptide, the E1/variant E2 heterodimeric complex polypeptides are at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, by weight, pure. In some embodiments, where a composition comprises a variant E1/E2 heterodimeric complex polypeptide, the variant E1/E2 heterodimeric complex polypeptides are at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, by weight, pure. In some embodiments, where a composition comprises a variant E1/variant E2 heterodimeric complex polypeptide, the variant E1/variant E2 heterodimeric complex polypeptides are at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, by weight, pure. In some embodiments, where a composition comprises a variant E1 polypeptide, the variant E1 polypeptide is at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, by weight, pure. In some embodiments, where a composition comprises a variant E2 polypeptide, the variant E2

polypeptide is at least 60%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%, by weight, pure.

[0042] The terms "polynucleotide" and "nucleic acid," used interchangeably herein, refer to a polymeric form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. Thus, this term includes, but is not limited to, single-, double-, or multi-stranded DNA or RNA, genomic DNA, cDNA, DNA-RNA hybrids, or a polymer comprising purine and pyrimidine bases or other natural, chemically or biochemically modified, non-natural, or derivatized nucleotide bases. In some cases, a polynucleotide is RNA. In some cases, a polynucleotide is DNA. A "polynucleotide" includes a nucleic acid that is incorporated into a viral vector or a bacterial vector.

[0043] The terms "peptide," "polypeptide," and "protein" are used interchangeably herein, and refer to a polymeric form of amino acids of any length, which can include coded and non-coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified peptide backbones. The term "polypeptide" includes glycosylated polypeptides.

[0044] The term "heterologous" refers to two components that are defined by structures derived from different sources. For example, where "heterologous" is used in the context of a polypeptide, where the polypeptide includes operably linked amino acid sequences that can be derived from one or more different polypeptides, e.g., amino acid sequences that are not operably linked to the polypeptide in nature.

[0045] Before the present invention is further described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0046] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0047] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described.

[0048] It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a variant HCV E2 polypeptide" includes a plurality of such polypeptides and reference to "the HCV E1 polypeptide" includes reference to one or more HCV E1 polypeptides and equivalents thereof known to those skilled in the art, and so forth. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

[0049] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the invention are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed. In addition, all sub-combinations of the various embodiments and elements thereof are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

[0050] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

DETAILED DESCRIPTION

[0051] T cell responses and antibody responses to HCV can be protective against HCV infection. The present disclosure provides heterodimeric polypeptides comprising: 1) a variant hepatitis C virus (HCV) E2 polypeptide and an HCV E1 polypeptide; 2) a variant HCV E1 polypeptide and an

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HCV E2 polypeptide; and 3) a variant HCV E1 polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide and/or or the HCV E1 polypeptide comprises a heterologous polypeptide comprising one or more T cell epitopes, e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide, where the one or more T-cell epitopes are referred to as a "polytope." Inclusion of T cell epitopes provides for a more robust T-cell response to HCV, including cytotoxic $CD8^+$ T-cell responses to HCV-infected cells, and $CD4^+$ T helper responses. Enhanced $CD4^+$ responses may also result in a higher titer of neutralizing anti-E1/E2 antibodies to HCV. Such T-cell responses and antibody titers can provide a protective response against HCV infection. The T-cell epitopes that are included within the polytope can include conserved T-cell epitopes and/or immunodominant T-cell epitopes. It was found that inclusion, in an HCV E2 polypeptide, of a heterologous polypeptide comprising a polytope (one or more T-cell epitopes) allows formation of an E1/E2 heterodimer. A purification scheme was devised, which provides for ease of production of E1/E2 heterodimers (where one or both of the E1 and E2 polypeptides comprises a heterologous polypeptide comprising one or more T-cell epitopes), and which provides for highly purified E1/E2 heterodimers using a scaleable vaccine manufacturing level process.

[0052] E1/E2 heterodimers of the present disclosure provide improvements to previously-described vaccine candidates by 1) eliciting higher levels of HCV-specific $CD4^+$ T helper responses, which are known to contribute to protection against HCV infection; 2) eliciting higher levels of HCV-specific $CD8^+$ cytotoxic T cell responses, which are known to contribute to protection against HCV infection; and 3) via the inclusion of extra CD4+ T helper epitopes, leading to higher titers of HCV neutralizing antibodies which are also known to be associated with protection against HCV infection.

[0053] A variant E2 polypeptide, also referred to as an "E2 fusion polypeptide," comprises an HCV E2 polypeptide and a heterologous polypeptide, where the heterologous polypeptide is also referred to as a "fusion partner." The heterologous polypeptide is covalently linked to the HCV E2 polypeptide. A variant E1 polypeptide, also referred to as an "E1 fusion polypeptide," comprises an HCV E1 polypeptide and a heterologous polypeptide, where the heterologous polypeptide is also referred to as a "fusion partner." The heterologous polypeptide is covalently linked to the HCV E1 polypeptide. The heterologous polypeptide ("fusion partner") comprises one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2

polypeptide. The heterologous polypeptide can be fused to the N-terminus or the C-terminus of the HCV E1 or HCV E2 polypeptide.

[0054] The present disclosure provides heterodimeric polypeptides comprising a variant HCV E2 polypeptide and an HCV E1 polypeptide, or comprising a variant HCV E1 polypeptide and an HCV E2 polypeptide, or compriing a variant HCV E1 polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide and/or the HCV E1 polypeptide comprises a heterologous polypeptide comprising one or more T cell epitopes, e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide. The present disclosure provides nucleic acids encoding a polyprotein that includes E1 and variant E2, or that includes E2 and variant E1, or that includes variant E2 and variant E1. The present disclosure provides a method of producing an E1/E2 heterodimer of the present disclosure. The present disclosure also provides variant E2 polypeptides and variant E1 polypeptides; and nucleic acids encoding the variant polypeptides. The present disclosure provides a method of inducing an immune response in an individual. The present disclosure provides a method of inducing an immune response (e.g., a protective immune response) to HCV antigens in an individual. The present disclosure provides a method of inducing a protective immune response to one or more HCV genotypes in an individual. In some cases, the HCV E2 polypeptide is an HCV E2 ectodomain polypeptide. In some cases, the HCV E2 polypeptide is a full-length HCV E2 polypeptide. In some cases, the HCV E1 polypeptide is an HCV E1 ectodomain polypeptide. In some cases, the HCV E1 polypeptide is a full-length HCV E1 polypeptide.

[0055] The present disclosure provides heterodimeric polypeptides comprising: a) a variant HCV E2 polypeptide and an HCV E1 polypeptide; b) a variant HCV E1 polypeptide and an HCV E2 polypeptide; or c) a variant HCV E1 polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide or the HCV E1 polypeptide comprises one or more T cell epitopes, e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide. The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV non-structural polypeptide-3 (NS3) polypeptide; b) an HCV non-structural polypeptide-2 (NS2) polypeptide; c) an HCV non-structural polypeptide-4A (NS4A) polypeptide; d) an HCV non-structural polypeptide-4B (NS4B) polypeptide; e) an HCV non-structural polypeptide-5A (NS5A) polypeptide; f) an HCV non-structural polypeptide-5B (NS5B) polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present

in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein. Thus, in some cases, a variant HCV E1 polypeptide or variant HCV E2 polypeptide of an E1/E2 heterodimer of the present disclosure includes: a) an HCV E1 polypeptide or an HCV E2 polypeptide; and b) a heterologous polypeptide that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein.

[0056] In some cases, a heterodimeric polypeptide of the present disclosure includes: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide). The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein. In some cases, a variant HCV E2 polypeptide of an E1/E2 heterodimer of the present disclosure includes: a) an HCV E2 polypeptide; and b) a heterologous polypeptide that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein

[0057] In some cases, a heterodimeric polypeptide of the present disclosure includes: a) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide); and b) an HCV E2 polypeptide. The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an

HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein. In some cases, a variant HCV E1 polypeptide of an E1/E2 heterodimer of the present disclosure includes: a) an HCV E1 polypeptide; and b) a heterologous polypeptide that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein.

[0058] In some cases, a heterodimeric polypeptide of the present disclosure includes: a) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide); and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide). The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein. In some cases, a variant HCV E2 and a variant HCV E1 polypeptide of an E1/E2 heterodimer of the present disclosure includes: 1) a) an HCV E2 polypeptide; and b) a heterologous polypeptide that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein; and 2) a) an HCV E1 polypeptide; and b) a heterologous polypeptide

that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein.

[0059] As noted above, the present disclosure provides heterodimeric polypeptides comprising: a) a variant HCV E2 polypeptide and an HCV E1 polypeptide; b) a variant HCV E1 polypeptide and an HCV E2 polypeptide; or c) a variant HCV E1 polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide or the HCV E1 polypeptide comprises one or more T cell epitopes, e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide. The presence of the one or more T-cell epitopes (e.g., one or more T-cell epitopes conserved among the hepacivirus genus; e.g., one or more immunodominant T-cell epitopes) provides for a more robust cellular immune response (e.g., a $CD4^+$ and/or a $CD8^+$ immune response) to HCV than a wild-type HCV E1/E2 heterodimer. For example, the addition of the one or more T-cell epitopes provides for a more robust $CD4^+$ helper and $CD8^+$ cytotoxic T cell response to HCV than a wild-type HCV E1/E2 heterodimer, and provides greater T helper activity to promote stronger antibody responses to the E1/E2 heterodimer. These features provide for superior HCV vaccine antigens.

[0060] The present disclosure provides variant HCV E2 polypeptides, and variant HCV E1 polypeptides. A variant E2 polypeptide of the present disclosure heterodimerizes with an HCV E1 polypeptide. A variant E1 polypeptide of the present disclosure heterodimerizes with an HCV E2 polypeptide. The heterodimer, or a polynucleotide(s) comprising a nucleotide sequence encoding the heterodimer, can be used to induce an immune response against HCV in an individual. For example, the heterodimer, or a polynucleotide(s) comprising a nucleotide sequence encoding the heterodimer, can be used to induce a protective immune response against HCV in an individual. In some cases, the heterodimer, or a polynucleotide(s) comprising a nucleotide sequence encoding the heterodimer, can be used to induce a protective immune response against HCV of more than one genotype.

[0061] Suitable T-cell epitopes (e.g., one or more conserved T-cell epitopes; e.g., one or more immunodominant T-cell epitopes) are described in detail below; and in the Figures. Suitable T-cell epitopes can be identified using the methods described in the Examples section, or using any other method that identifies conserved T-cell epitiopes or immunodominant T-cell epitopes.

[0062] In some cases, a heterologous polypeptide present in a variant E1 polypeptide or a variant E2 polypeptide described herein, where the heterologous polypeptide comprises one or more T-cell

epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide, comprises: a) two or more (2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10) T cell epitopes of an HCV NS3 polypeptide; b) two or more (2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10) T cell epitopes of an HCV NS2 polypeptide; c) two or more (2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10) T cell epitopes of an HCV NS4A polypeptide; d) two or more (2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10) T cell epitopes of an HCV NS4B polypeptide; e) two or more (2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10) T cell epitopes of an HCV NS5A polypeptide; f) two or more (2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10) T cell epitopes of an HCV NS5B polypeptide; g) two or more (2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10) T cell epitopes of an HCV core polypeptide; h) two or more (2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10) T cell epitopes of an HCV p7 polypeptide; i) one or more T-cell epitopes of an HCV NS3 polypeptide and one or more T-cell epitopes of an HCV NS2 polypeptide; j) one or more T-cell epitopes of an HCV NS3 polypeptide and one or more T-cell epitopes of an HCV NS4B polypeptide; k) one or more T-cell epitopes of an HCV NS3 polypeptide and one or more T-cell epitopes of an HCV NS5A polypeptide; l) one or more T-cell epitopes of an HCV NS3 polypeptide and one or more T-cell epitopes of an HCV NS5B polypeptide; m) one or more T-cell epitopes of an HCV NS3 polypeptide and one or more T-cell epitopes of an HCV core polypeptide; n) one or more T-cell epitopes of an HCV NS3 polypeptide, one or more T-cell epitopes of an HCV NS2 polypeptide, and one or more T-cell epitopes of an HCV core polypeptide; o) one or more T-cell epitopes of an HCV NS3 polypeptide, one or more T-cell epitopes of an HCV NS2 polypeptide, and one or more T-cell epitopes of an HCV NS4B polypeptide; or p) one or more T-cell epitopes of an HCV NS3 polypeptide, one or more T-cell epitopes of an HCV NS2 polypeptide, and one or more T-cell epitopes of an HCV NS5A polypeptide. Other combinations are possible and are contemplated by the present disclosure.

[0063] In some cases, a variant E2 polypeptide and/or a variant E1 polypeptide comprises a heterologous polypeptide comprising a polytope that comprises: 1) a contiguous NS3-NS4a polypeptide in which the NS3-encoded serine protease is rendered inactive by mutation of any one of the catalytic triad amino acids (H,D,S); 2) a contiguous NS3-NS4a –NS4a polypeptide in which the NS3-encoded serine protease is rendered inactive by mutation of any one of the catalytic triad amino acids (H,D,S); 3) a contiguous NS3-NS4a-NS4a-NS5a polypeptide in which the NS3-encoded serine protease is rendered inactive by mutation of any one of the catalytic triad amino acids (H,D,S); or 4) a contiguous NS3-NS4a-NS4a-NS5a-NS5a polypeptide in which the NS3-encoded serine protease is rendered inactive by mutation of any one of the catalytic triad amino acids (H,D,S) and the NS5b-encoded RNA polymerase is

rendered inactive by mutation of any residues in the GDD motif that is required for polymerase activity.

[0064] In some cases, a linker can be interposed between the heterologous polypeptide ("polytope") and the HCV E1 or HCV E2 polypeptide. The linker peptide may have any of a variety of amino acid sequences. A linker can be a peptide of between about 6 and about 40 amino acids in length, or between about 6 and about 25 amino acids in length. These linkers can be produced by using synthetic, linker-encoding oligonucleotides to couple the proteins. Peptide linkers allowing a degree of flexibility can be used. The linking peptides may have virtually any amino acid sequence, bearing in mind that suitable linkers will have a sequence that results in a generally flexible peptide. The use of small amino acids, such as glycine and alanine, are of use in creating a flexible peptide. The creation of such sequences is routine to those of skill in the art.

[0065] Suitable linkers can be readily selected and can be of any of a suitable of different lengths, such as from 1 amino acid (e.g., Gly, Ala, or Ser) to 20 amino acids, from 2 amino acids to 15 amino acids, from 3 amino acids to 12 amino acids, including 4 amino acids to 10 amino acids, 5 amino acids to 9 amino acids, 6 amino acids to 8 amino acids, or 7 amino acids to 8 amino acids, and may be 1, 2, 3, 4, 5, 6, or 7 amino acids.

[0066] Exemplary flexible linkers include glycine polymers $(G)_n$, glycine-serine polymers (including, for example, $(GS)_n$, $(GSGGS)_n$ (SEQ ID NO:55) and $(GGGS)_n$ (SEQ ID NO:56), where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers known in the art. Glycine and glycine-serine polymers are of interest since both of these amino acids are relatively unstructured, and therefore may serve as a neutral tether between components. Glycine polymers are of particular interest since glycine accesses significantly more phi-psi space than even alanine, and is much less restricted than residues with longer side chains (see Scheraga, *Rev. Computational Chem.* 11173-142 (1992)). Exemplary flexible linkers include, but are not limited to, GGSG (SEQ ID NO:57), GGSGG (SEQ ID NO:58), GSGSG (SEQ ID NO:59), GSGGG (SEQ ID NO:60), GGGSG (SEQ ID NO:61), GSSSG (SEQ ID NO:62), and the like. The ordinarily skilled artisan will recognize that design of a peptide conjugated to any elements described above can include linkers that are all or partially flexible, such that the linker can include a flexible linker as well as one or more portions that confer less flexible structure.

I. E1/E2 HETERODIMERS

[0067] The present disclosure provides heterodimeric polypeptides comprising: a) a variant HCV E2 polypeptide and an HCV E1 polypeptide; b) a variant HCV E1 polypeptide and an HCV E2 polypeptide; or c) a variant HCV E1 polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide or the HCV E1 polypeptide comprises one or more T cell epitopes,

e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide.

[0068] An E1/E2 heterodimer of the present disclosure, or a nucleic acid(s) (e.g., one or more recombinant expression vectors; an mRNA molecule(s); a DNA molecule(s)) comprising a nucleotide sequence encoding the E1/E2 heterodimer, can be used to induce an immune response to HCV in an individual. The nucleic acid may be in the form of DNA or RNA, or may be complexed with a polymer such as poly-lactic-co-glycolide (PLG) or liposomal formulations or may be inserted into a viral vaccine vector or bacterial vaccine vectors. Nucleic acid vaccines are feasible using either viral or bacterial vectors to deliver the nucleic acids encoding vaccine antigens or by delivering the encoding DNA or RNA into an immunogenic vaccine formulation (Deering et al. (2014) *Expert Opin Drug Deliv.* 11(6):885-99).

IA. E1E2 heterodimers comprising HCV E1 and a variant HCV E2

[0069] The present disclosure provides an E1/E2 heterodimer, where the E1/E2 heterodimer comprises: a) a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide comprises: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T-cell epitopes not present in an HCV E1 or an HCV E2 polypeptide; e.g., one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 or an HCV E2 polypeptide); and b) an HCV E1 polypeptide. Thus, in some cases, a heterodimeric polypeptide of the present disclosure includes: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide). The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein. The heterologous polypeptide is also referred to as a "polytope."

[0070] An E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes), when administered to an individual in need thereof, induces an immune response in the individual to one or more HCV genotypes. An E1/E2 heterodimer of the present disclosure, when

administered to an individual in need thereof, induces an immune response in the individual to one or more HCV genotypes, where the immune response is greater than the immune response induced by administration of an HCV E1/E2 heterodimer comprising a wild-type E1 and a wild-type E2 polypeptide or an E2 polypeptide lacking the polytope.

[0071] For example, in some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes), when administered to an individual in need thereof, induces cytotoxic T lymphocytes (CTLs) specific for HCV, where the number of HCV-specific CTLs induced is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 7.5-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold, or more than 100-fold, higher than the number of HCV-specific CTLs induced by administration of an HCV E1/E2 heterodimer comprising a wild-type E1 and a wild-type E2 polypeptide or an E2 polypeptide lacking the polytope.

[0072] In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces production of HCV-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual, where the number of HCV-specific $CD4^+$ T cells and $CD8^+$ T cells is increased, such that the percent of the total peripheral blood T cells (i.e., the total number of $CD4^+$ T cells + $CD8^+$ T cells in the peripheral blood) that are HCV-specific $CD4^+$ T cells and $CD8^+$ T cells is from 0.05% to 10% (e.g., from 0.05% to 0.1%, from 0.1% to 0.5%, from 0.5% to 1%, from 1% to 2%, from 2% to 5%, or from 5% to 10%). The number of HCV-specific $CD4^+$ T cells and $CD8^+$ T cells in a control individual (e.g., an individual not infected with HCV) not treated with the E1/E2 heterodimer would be undetectable.

[0073] For example, in some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more HCV NS3 T-cell epitopes), when administered to an individual in need thereof, induces production of HCV NS3-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual, where the number of HCV NS3-specific $CD4^+$ T cells and $CD8^+$ T cells is increased, such that the percent of the total peripheral blood T cells (i.e., the total number of $CD4^+$ T cells + $CD8^+$ T cells in the peripheral blood) that are HCV NS3-specific $CD4^+$ T cells and $CD8^+$ T cells is from 0.05% to

10% (e.g., from 0.05% to 0.1%, from 0.1% to 0.5%, from 0.5% to 1%, from 1% to 2%, from 2% to 5%, or from 5% to 10%). The number of HCV NS3-specific $CD4^+$ T cells and $CD8^+$ T cells in a control individual (e.g., an individual not infected with HCV) not treated with the E1/E2 heterodimer would be undetectable.

[0074] In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, increases the number of HCV E1/E2-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 7.5-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold, or more than 100-fold, compared to the number of HCV E1/E2-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual induced by administration of an E1/E2 heterodimer comprising a wild-type E1 polypeptide and a wild-type E2 polypeptide, or an E2 polypeptide lacking the polytope, or compared to the number of HCV E1/E2-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual before administration of the E1/E2 heterodimer of the present disclosure.

[0075] As another example, in some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces helper T lymphocytes (e.g., $CD4^+$ T cells) specific for HCV, where the number of HCV-specific helper T cells induced is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 7.5-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold, or more than 100-fold, higher than the number of HCV-specific helper T cells induced by administration of an E1/E2 heterodimer comprising a wild-type E1 polypeptide and a wild-type E2 polypeptide, or an E2 polypeptide lacking the polytope, or compared to the number of HCV-specific helper T cells in the individual before administration of the E1/E2 heterodimer of the present disclosure.

[0076] In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes

present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces antibody specific for HCV (e.g., anti-E1/E2 antibody), where the level of HCV-specific antibody induced is at least at high as the level of HCV-specific antibody induced by administration of an E1/E2 heterodimer comprising a wild-type E1 polypeptide and a wild-type E2 polypeptide, or an E2 polypeptide lacking the polytope.

[0077] In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces antibody specific for HCV (e.g., anti-E1/E2 antibody), where the level of HCV-specific antibody induced is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 7.5-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold, or more than 100-fold, higher than the level of HCV-specific antibody induced by administration of an E1/E2 heterodimer comprising a wild-type E1 polypeptide and a wild-type E2 polypeptide, or an E2 polypeptide lacking the polytope.

[0078] An E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response (e.g., a cellular immune response) in the individual to one or more HCV genotypes. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 1. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 2. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2

polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 3. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 1 and HCV genotype 3. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 1, HCV genotype 2, and HCV genotype 3. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 1, HCV genotype 2, HCV genotype 3, and HCV genotype 7. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to 1, 2, 3, 4, 5, 6, or all, of HCV genotype 1, HCV genotype 2, HCV genotype 3, HCV genotype 4, HCV genotype 5, HCV genotype 6, and HCV genotype 7. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 1, HCV genotype 2, HCV genotype 3, HCV genotype 4, HCV genotype 5, HCV genotype 6, and HCV genotype 7.

Variant E2

[0079] As noted above, a variant E2 polypeptide of an HCV E1/E2 heterodimer of the present disclosure comprises: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes (e.g., one or more T-cell epitopes not present in an HCV E1 or an HCV E2 polypeptide; e.g., one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 or an HCV E2 polypeptide). In some cases, the variant HCV E2 polypeptide comprises, in order from amino terminus (N-terminus) to carboxyl terminus (C-terminus): i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes. In some cases, the variant HCV E2 polypeptide comprises, in order from N-terminus to C-terminus: i) a heterologous polypeptide comprising one or more T cell epitopes; and ii) an HCV E2 polypeptide.

[0080] In some cases, a variant E2 polypeptide of an HCV E1/E2 heterodimer of the present disclosure comprises from 1 to 10 amino acids at the N-terminus of the variant E2 polypeptide, which 1 to 10 amino acids are part of a cleavable linker that remains following cleavage of a polyprotein precursor, as described below. For example, where the cleavable linker comprises the amino acid sequence LEVLFQGP (SEQ ID NO:5), the variant E2 polypeptide can comprise Gly-Pro residues at the N-terminus of the polypeptide, e.g., as depicted in FIG. 5A.

E2

[0081] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can have a length of from about 200 amino acids (aa) to about 250 aa, from about 250 aa to about 275 aa, from about 275 aa to about 300 aa, from about 300 aa to about 325 aa, from about 325 aa to about 350 aa, or from about 350 aa to about 365 aa. In some cases, an HCV E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure is an HCV E2 ectodomain polypeptide. In some cases, an HCV E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure is a full-length HCV E2 polypeptide.

[0082] In FIG. 1A-AC, the amino acid sequence of E2 is amino acid 384 to amino acid 746. In FIG. 2A-2B, the amino acid sequence of E2 is amino acid 384 to amino acid 751. In FIG. 3A-3C, the amino acid sequence of E2 is amino acid 385 to amino acid 754. In FIG. 4A-4B, the amino acid sequence of E2 is amino acid 384 to amino acid 750. As used herein, an "E2 polypeptide" includes a precursor E2 protein, including the signal sequence; includes a mature E2 polypeptide which lacks this sequence; and includes an E2 polypeptide with a heterologous signal sequence. An E2 polypeptide can include a C-terminal membrane anchor sequence which occurs at approximately amino acid positions 715-730 and may extend as far as approximately amino acid residue 746 (see, Lin et al., J. Virol. (1994) 68:5063-5073).

[0083] In some cases, a E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure lacks a portion of its C-terminal region, e.g., from about amino acid 715 to the C-terminus; from about amino acid 625 to the C-terminus; from about amino acid 661 to the C-terminus; from about amino acid 655 to the C-terminus; from about amino acid 500 to the C-terminus, where the amino acid numbering is with reference to the numbering in FIG. 1A-1C. See, e.g., U.S. Patent No. 6,521,423.

[0084] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%,at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, or FIG. 4A-4B. An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 75%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, or FIG. 4A-4B.

[0085] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1 can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1A can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence

identified as 1A and depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1B can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence identified as 1B and depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1C can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence identified as 1C and depicted in FIG. 1A-1C.

[0086] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 2A-2C. For example, an E2 polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-751 of an amino acid sequence depicted in FIG. 2A-2C. For example, an E2 polypeptide of genotype 2A can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-751 of the "consensus" amino acid sequence depicted in FIG. 2A-2C. For example, an E2 polypeptide of genotype 2B can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-751 of the "consensus" amino acid sequence depicted in FIG. 2A-2C.

[0087] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3 can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of an amino acid sequence depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3A can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of an amino acid sequence identified as 3A and depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3B can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of the amino acid sequence identified as 3B and depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3K can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of the amino acid sequence identified as 3K and depicted in FIG. 3A-3C.

[0088] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence of the E2 polypeptide

depicted in FIG. 4A-4B. For example, an E2 polypeptide of genotype 7A can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-750 of the amino acid sequence depicted in FIG. 4A-4B.

Heterologous polypeptide

[0089] In some cases, the heterologous polypeptide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10 (e.g., from 10 to 15, from 15 to 20, from 20 to 25, or from 25 to 30, or more than 30), T cell epitopes. T-cell epitopes are epitopes that, when presented with a major histocompatibility complex (MHC) (e.g., a human leukocyte antigen (HLA)) Class I or MHC Class II molecule, are recognized and bound by a T-cell receptor (TCR) present on a T cell surface. T-cell epitopes include epitopes recognized by cytotoxic T cells (e.g., $CD8^+$ T cells), and epitopes recognized by helper T cells (e.g., $CD4^+$ T cells).

[0090] The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein. A suitable source of T-cell epitopes non-toxic mutants of toxins, where the mutants are referred to as "cross-reactive material (CRM)." Other examples of strong T helper epitopes are diphtheria toxoid, tetanus toxoid, meningococcal outer membrane protein, or mutant diphtheria protein CRM197 (see, e.g.: http://www(dot)medscape(dot)com/viewarticle/431127).

[0091] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS3 T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS3 T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS3 T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS3 T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS3 $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS3 $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS3 $CD8^+$ T-cell epitope. In some cases, the

heterologous polypeptide comprises 2 or more HCV-NS3 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS3 $CD4^+$ T cell epitope and at least one HCV-NS3 $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS3 $CD4^+$ T-cell epitopes and 2 or more HCV-NS3 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS3 $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS3 $CD8^+$ T-cell epitopes.

[0092] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS2 T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS2 T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS2 T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS2 T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS2 $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS2 $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS2 $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS2 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS2 $CD4^+$ T cell epitope and at least one HCV-NS2 $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS2 $CD4^+$ T-cell epitopes and 2 or more HCV-NS2 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS2 $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS2 $CD8^+$ T-cell epitopes.

[0093] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS4A T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS4A T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS4A T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS4A T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS4A $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS4A $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS4A $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS4A $CD8^+$ T-cell epitopes. In

some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS4A $CD4^+$ T cell epitope and at least one HCV-NS4A $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS4A $CD4^+$ T-cell epitopes and 2 or more HCV-NS4A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS4A $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS4A $CD8^+$ T-cell epitopes.

[0094] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS5A T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5A T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS5A T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS5A T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5A $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5A $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5A $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS5A $CD4^+$ T cell epitope and at least one HCV-NS5A $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS5A $CD4^+$ T-cell epitopes and 2 or more HCV-NS5A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS5A $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS5A $CD8^+$ T-cell epitopes.

[0095] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS5B T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5B T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS5B T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS5B T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5B $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5B $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5B $CD8^+$ T-cell epitope. In some

cases, the heterologous polypeptide comprises 2 or more HCV-NS5B $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS5B $CD4^+$ T cell epitope and at least one HCV-NS5B $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS5B $CD4^+$ T-cell epitopes and 2 or more HCV-NS5B $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS5B $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS5B $CD8^+$ T-cell epitopes.

[0096] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-core T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-core T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-core T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-core T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-core $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-core $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-core $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-core $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-core $CD4^+$ T cell epitope and at least one HCV-core $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-core $CD4^+$ T-cell epitopes and 2 or more HCV-core $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-core $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-core $CD8^+$ T-cell epitopes.

[0097] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-p7 T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-p7 T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-p7 T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-p7 T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-p7 $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-core $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-p7 $CD8^+$ T-cell epitope. In some cases, the

heterologous polypeptide comprises 2 or more HCV-p7 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-p7 $CD4^+$ T cell epitope and at least one HCV-p7 $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-p7 $CD4^+$ T-cell epitopes and 2 or more HCV-p7 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-p7 $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-p7 $CD8^+$ T-cell epitopes.

[0098] In some cases, the heterologous polypeptide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, or 63, of the T-cell epitopes set out in Fig. 13A-13B. In some cases, the heterologous polypeptide comprises from 1 to 3, from 3 to 5, from 5 to 10, from 10 to 15, from 15 to 20, from 20 to 25, or from 25 to 30 of the T-cell epitopes set out in Fig. 13A-13B. For example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, and NS3-11 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-7, and NS2-8 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, NS3-5, and NS3-11 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated Core-1, Core-2, Core-3, Core-4, Core-5, Core-6, Core-7, Core-8, Core-9, Core-10, Core-11, Core-12, Core-13, Core-14, Core-16, Core-17, Core-18, Core-19, Core-20, Core-21, and Core-22 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-4, NS2-5, NS2-6, NS2-7, NS2-8, NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in

Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, and NS4b-10 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, NS4b-10, NS5a-1, NS5a-2, NS5b-1, and NS5b-2 in Fig. 13A-13B and Fig. 15A-15N. In some cases, the T-cell epitopes are contiguous. In some cases, any two T-cell epitopes are separated by linkers (e.g., a linker having a length of from 1 amino acid to about 50 amino acids, e.g., from 1 amino acid to 5 amino acids (aa), from 5 aa to 10 aa, from 10 aa to 15 aa, from 15 aa to 20 aa, from 20 aa to 25 aa, from 25 aa to 30 aa, from 30 aa to 40 aa, or from 40 aa to 50 aa).

[0099] In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1 and 2. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1 and 3. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1, 2, and 3. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1, 2, 3, and 7. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1-7.

[00100] The heterologous polypeptide can have a length of from about 10 amino acids to about 2000 amino acids; e.g., the heterologous polypeptide can have a length of from 10 amino acids (aa) to 15 aa, from 15 aa to 20 aa, from 20 aa to 25 aa, from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 800 aa. The heterologous polypeptide can have a length of from about 25 amino acids to about 2000 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50

aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 500 aa, from 500 aa to 600 aa, from 600 aa to 700 aa, from 700 aa to 800 aa, from 800 aa to 900 aa, from 900 aa to 1000 aa, from 1000 aa to 1100 aa, from 1100 aa to 1200 aa, from 1200 aa to 1300 aa, from 1300 aa to 1400 aa, from 1400 aa to 1500 aa, from 1500 aa to 1600 aa, from 1600 aa to 1700 aa, from 1700 aa to 1800 aa, from 1800 aa to 1900 aa, or from 1900 aa to 2000 aa. The heterologous polypeptide can have a length of from about 25 amino acids to about 3000 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 500 aa, from 500 aa to 600 aa, from 600 aa to 700 aa, from 700 aa to 800 aa, from 800 aa to 900 aa, from 900 aa to 1000 aa, from 1000 aa to 1100 aa, from 1100 aa to 1200 aa, from 1200 aa to 1300 aa, from 1300 aa to 1400 aa, from 1400 aa to 1500 aa, from 1500 aa to 1600 aa, from 1600 aa to 1700 aa, from 1700 aa to 1800 aa, from 1800 aa to 1900 aa, from 1900 aa to 2000 aa, from 2000 aa to 2250 aa, from 2250 aa to 2500 aa, from 2500 aa to 2750 aa, or from 2750 aa to 3000 aa.

[00101] The heterologous polypeptide can have a length of from about 25 amino acids to about 800 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 800 aa. The heterologous polypeptide can have a length of from about 25 amino acids to about 400 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, or from 350 aa to 400 aa. The heterologous polypeptide can have a length of 25 amino acids (aa), 26 aa, 27 aa, 28 aa, 29 aa, 30 aa, 31 aa, 32 aa, 33 aa, 34 aa, 35 aa, 36 aa, 37 aa, 38 aa, 39 aa, 40 aa, 41 aa, 42 aa, 43 aa, 44 aa, 45 aa, 46 aa, 47 aa, 48 aa, 49 aa, or 50 aa. The heterologous polypeptide can have a length of from about 100 amino acids (aa) to 800 aa, e.g., from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 800 aa. The heterologous polypeptide can have a length of from 25 aa to 30 aa. The heterologous polypeptide can have a length of from 30 aa to 40 aa. The heterologous polypeptide can have a length of from 40 aa to 50 aa. The heterologous polypeptide can have a length of from 50 aa to 60 aa (e.g., 50 aa, 51 aa, 52, aa, 53 aa, 54 aa, 55 aa, 56 aa, 57 aa, 58 aa, 59 aa, or 60 aa). The heterologous polypeptide can have a length of from

60 aa to 70 aa. The heterologous polypeptide can have a length of from 65 aa to 75 aa (e.g., 65, 66, 67, 68, 69, 70, 71, 72, 7, 74, or 75 aa). The heterologous polypeptide can have a length of 70 aa. The heterologous polypeptide can have a length of from 70 aa to 80 aa. The heterologous polypeptide can have a length of from 80 aa to 90 aa. The heterologous polypeptide can have a length of from 90 aa to 100 aa. The heterologous polypeptide can have a length of from 100 aa to 105 aa (e.g., 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, or 110 aa). The heterologous polypeptide can have a length of 100 aa. The heterologous polypeptide can have a length of from 10 amino acids (aa) to 50 aa; e.g., from 10 aa to 15 aa, from 15 aa to 20 aa, from 20 aa to 25 aa, from 25 aa to 30 aa, from 30 aa to 35 aa, from 35 aa to 40 aa, from 40 aa to 45 aa, or from 45 aa to 50 aa. The heterologous polypeptide can have a length of from 10 amino acids (aa) to 20 aa, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 aa.

HCV NS3 T-cell epitopes

[00102] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS3 polypeptide. Examples of T-cell epitopes present in NS3 polypeptides are depicted in **FIG. 15A-15N, FIG. 13B, and FIG. 14A-14B**.

[00103] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1); and has a length of from 25 aa to 35 aa (e.g., 25 aa, 26 aa, 27 aa, 28 aa, 29 aa, 30 aa, 31 aa, 32 aa, 33 aa, 34 aa, or 35 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1); and has a length of 29 amino

acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, and NS3-11 in FIG. 13B and FIG. 15A-15N.

[00104] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2); and has a length of from 45 amino acids to 60 amino acids (e.g., 45 aa, 46 aa, 47 aa, 48 aa, 49 aa, 50 aa, 51 aa, 52 aa, 53 aa, 54 aa, 55 aa, 56 aa, 57 aa, 58 aa, 59 aa, or 60 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2); and has a length of 52 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, NS3-5, and NS3-11 in FIG. 13B and FIG. 15A-15N.

[00105] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTG FTGDFDSVIDCN (SEQ ID NO:3); and has a length of from 65 amino acids to 80 amino acids (e.g., 65 aa, 66 aa, 67 aa, 68 aa, 69 aa, 70 aa, 71 aa, 72 aa, 73 aa, 74 aa, 75 aa, 76 aa, 77 aa, 78 aa, 79 aa, or 80 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at

least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:
KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTG FTGDFDSVIDCN (SEQ ID NO:3); and has a length of 70 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-11, NS3-12, and NS3-13 in FIG. 13B and FIG. 15A-15N.

[00106] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:
VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4); and has a length of from 95 amino acids (aa) to 105 aa (e.g., 95 aa, 96 aa, 97 aa, 98 aa, 99 aa, 100 aa, 101 aa, 102 aa, 103 aa, 104 aa, or 105 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:
VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4); and has a length of 100 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-10, NS3-11, NS3-12, and NS3-13 in FIG. 13B and FIG. 15A-15N.

[00107] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:
MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQP RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS

RNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPGCSF SIFLLALLSCLTVPASA (SEQ ID NO:9); and has a length of from 190 amino acids (aa) to 200 aa (e.g., 190 aa, 191 aa, 192 aa, 193 aa, 194 aa, 195 aa, 196 aa, 197 aa, 198 aa, 199 aa, or 200 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQP RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS RNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPGCSF SIFLLALLSCLTVPASA (SEQ ID NO:9); and has a length of 191 amino acids.

[00108] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCN (SEQ ID NO:10); and has a length of from 215 amino acids (aa) to 235 aa (e.g., 215 aa, 216 aa, 217 11, 218 aa, 219 aa, 220 aa, 221 aa, 222 aa, 223 aa, 224 aa, 225 aa, 226 aa, 227 aa, 228 aa, 229 aa, 230 aa, 231 aa, 232 aa, 233 aa, 234 aa, or 235 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCN (SEQ ID NO:10); and has a length of 228 amino acids. Such a polytope can include NS3 T-cell epitopes designated

NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in FIG. 13B and FIG. 15A-15N.

[00109] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1265-1279 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00110] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1309-1323 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00111] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1401-1415 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00112] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino

acid sequence identity to amino acids 1402-1412 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 11 amino acids (aa) to 16 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, or 16 aa).

[00113] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1429-1439 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 11 amino acids (aa) to 16 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, or 16 aa).

[00114] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1450-1464 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00115] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1453-1467 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00116] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%,

at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1577-1591 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00117] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1306-1314 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00118] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1387-1394 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 1 amino acids (aa) to 15 amino acids (e.g., 8 aa, 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00119] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1405-1413 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00120] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at

least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1450-1458 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00121] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1457-1465 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00122] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1610-1618 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV NS2 T-cell epitopes

[00123] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS2 polypeptide. Examples of T-cell epitopes present in NS2 polypeptides are depicted in **FIG. 15A-15N**, and **FIG. 13A**.

[00124] For example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 955-974 of the amino acid sequence designated "Consensus" in

FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00125] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 975-994 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00126] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 985-1004 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00127] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1015-1034 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00128] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid

sequence identity to amino acids 1035-1054 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00129] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 924-933 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00130] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 961-970 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00131] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 989-997 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00132] In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least

about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 10 amino acids (aa) to 50 aa (e.g., from 10 aa to 25 aa, or from 25 aa to 50 aa) of amino acids 955-1004 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and has a length of from 10 amino acids (aa) to 25 aa, or from 25 aa to 50 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 955-1004 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and has a length of about 50 amino acids.

[00133] In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 10 amino acids (aa) to 553 aa (e.g., from 10 aa to 25 aa, from 25 aa to 50 aa, from 50 aa to 100 aa, from 100 aa to 200 aa, from 200 aa to 300 aa, from 300 aa to 400 aa, from 400 aa to 500 aa, or from 500 aa to 553 aa) of amino acids 917-1469 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 and NS3 amino acid sequence of any HCV genotype; and has a length of from 10 amino acids (aa) to 25 aa, from 25 aa to 50 aa, from 50 aa to 100 aa, from 100 aa to 200 aa, from 200 aa to 300 aa, from 300 aa to 400 aa, from 400 aa to 500 aa, or from 500 aa to 553 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 917-1469 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 and NS3 amino acid sequence of any HCV genotype; and has a length of about 553 amino acids.

[00134] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 0%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at

least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LGALTGTYVYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADT (SEQ ID NO:11). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LGALTGTYVYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADT (SEQ ID NO:11); and has a length of from 50 amino acids to 60 amino acids (e.g., 50 aa, 51 aa, 52 aa, 53 aa, 54 aa, 55 aa, 56 aa, 57 aa, 58 aa, 59 aa, or 60 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LGALTGTYVYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADT (SEQ ID NO:11); and has a length of 50 amino acids. Such a polytope can include NS2 T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-7, and NS2-8 in FIG. 13A and FIG. 15A-15N.

HCV NS4A T-cell epitopes

[00135] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS4A polypeptide. Examples of T-cell epitopes present in NS4A polypeptides are depicted in **FIG. 15A-15N** and **FIG. 13B**.

[00136] The heterologous polypeptide can comprise an NS4A T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1683-1692 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4A amino acid sequence of any HCV genotype; and the NS4A T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV NS4B T-cell epitopes

[00137] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS4B polypeptide. Examples of T-cell epitopes present in NS4B polypeptides are depicted in **FIG. 15A-15N** and **FIG. 13B**.

[00138] As one example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1790-1801 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 12 amino acids (aa) to 20 amino acids (e.g., 12 aa, 13 aa, 14 aa, 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00139] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1792-1802 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 11 amino acids (aa) to 20 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00140] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1898-1905 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 8 amino acids (aa) to 15 amino acids (e.g., 8 aa, 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00141] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about

30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1921-1935 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00142] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1922-1941 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00143] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1928-1947 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00144] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1868-1876 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00145] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1927-1942 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 16 amino acids (aa) to 20 amino acids (e.g., 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00146] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1932-1940 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00147] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1948-1962 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

HCV NS5A T-cell epitopes

[00148] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS5A polypeptide. Examples of T-cell epitopes present in NS5A polypeptides are depicted in **FIG. 15A-15N** and **FIG. 13B**.

[00149] As one example, the heterologous polypeptide can comprise an NS5A T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about

30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2218-2232 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5A amino acid sequence of any HCV genotype; and the NS5A T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00150] As another example, the heterologous polypeptide can comprise an NS5A T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2309-2317 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5A amino acid sequence of any HCV genotype; and the NS5A T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV NS5B T-cell epitopes

[00151] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS5B polypeptide. Examples of T-cell epitopes present in NS5B polypeptides are depicted in **FIG. 15A-15N** and **FIG. 13B**.

[00152] As one example, the heterologous polypeptide can comprise an NS5B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2847-2851 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5B amino acid sequence of any HCV genotype; and the NS5B T-cell epitope can have a length of from 5 amino acids (aa) to 10 amino acids (e.g., 5 aa, 6 aa, 7 aa, 8 aa, 9 aa, or 10 aa).

[00153] As another example, the heterologous polypeptide can comprise an NS5B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid

sequence identity to amino acids 2602-2610 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5B amino acid sequence of any HCV genotype; and the NS5B T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV core T-cell epitopes

[00154] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV core polypeptide. Examples of T-cell epitopes present in HCV Core polypeptides are depicted in **FIG. 15A-15N** and **FIG.13A**.

[00155] As one example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1-20 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00156] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 11-30 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00157] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 21-40 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and

the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00158] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 39-63 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 23 amino acids (aa) to 28 amino acids (e.g., 23 aa, 24 aa, 25 aa, 26 aa, 27 aa, or 28 aa).

[00159] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 47-70 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 24 amino acids (aa) to 29 amino acids (e.g., 24 aa, 25 aa, 26 aa, 27 aa, 28 aa, or 29 aa).

[00160] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 61-80 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00161] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 71-90 of the amino acid sequence designated "Consensus"

in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00162] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 81-100 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00163] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 91-110 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00164] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 101-115 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00165] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino

acid sequence identity to amino acids 111-130 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00166] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 125-139 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00167] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 131-150 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00168] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 151-170 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00169] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%,

at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 161-180 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00170] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 35-44 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00171] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 43-51 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00172] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 51-59 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00173] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at

least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 129-137 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00174] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 131-140 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00175] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 150-158 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00176] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 154-162 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00177] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at

least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 168-176 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00178] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 177-187 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 11 amino acids (aa) to 16 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, or 16 aa).

[00179] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 178-187 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00180] In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 10 amino acids (aa) to 191 aa (e.g., from 10 aa to 25 aa, from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, or from 150 aa to 191aa) of amino acids 1-191 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and has a length of from 10 amino acids (aa) to 25 aa, from 25 aa to 50 aa, from 50 aa to 100 aa, or from 100 aa to 150 aa, or from 150 aa

to 191 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1-191 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and has a length of about 191 amino acids.

[00181] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTS ERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPS WGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLE DGVNYATGNLPG (SEQ ID NO:63); and has a length of from 171 amino acids (aa) to 180 aa (e.g., 171 aa, 172 aa, 173 aa, 174 aa, 175 aa, 176 aa, 177 aa, 178 aa, 179 aa, or 180 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTS ERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPS WGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLE DGVNYATGNLPG (SEQ ID NO:63); and has a length of 171 amino acids. Such a polytope can include core T-cell epitopes designated Core-1, Core-2, Core-3, Core-4, Core-5, Core-6, Core-7, Core-8, Core-9, Core-10, Core-11, Core-12, Core-13, Core-14, Core-16, Core-17, Core-18, Core-19, Core-20, Core-21, Core-22 in FIG. 13A and FIG. 15A-15N.

HCV p7 T-cell epitopes

[00182] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV p7 polypeptide. Examples of T-cell epitopes present in HCV p7 polypeptides are depicted in **FIG. 15A-15N** or **FIG. 13A**.

[00183] As another example, the heterologous polypeptide can comprise an HCV p7 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 803-811 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV p7 amino acid sequence of any HCV genotype; and the HCV p7 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

Polytopes including HCV T-cell epitopes from more than one HCV polypeptide other than E1 and E2

[00184] As noted above, a heterologous polypeptide can include T-cell epitopes from more than one HCV polypeptide other than E1 and E2.

[00185] As one example, a heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

QASLLKVPYFVRVQGLLRICALARKMAGGHYVQMAIIKLGALTGTYVYNALTP
LRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADTAACGDIINGLPVSARRGR
EILLGPADGMVSKGWRLLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS
TAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQG
ARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCP
AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA
HLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQA
ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIF
CHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG
DFDSVIDCN (SEQ ID NO:12); and has a length of from 550 amino acids (aa) to 560 aa (e.g., 550 aa, 551 aa, 552 aa, 553 aa, 554 aa, 555 aa, 556 aa, 557 aa, 558 aa, 559 aa, or 560 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at

least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: QASLLKVPYFVRVQGLLRICALARKMAGGHYVQMAIIKLGALTGTYVYNALTP LRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADTAACGDIINGLPVSARRGR EILLGPADGMVSKGWRLLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS TAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQG ARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCP AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA HLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQA ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIF CHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG DFDSVIDCN (SEQ ID NO:12); and has a length of 553 amino acids. Such a polytope can include T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-4, NS2-5, NS2-6, NS2-7, NS2-8, NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. This polytope is also referred to as "TP553" (FIG. 14A-14D). In order to prevent self cleavage of the TP553 polytope (amino acids 917-1469) (FIG. 15E-G) at the NS2-NS3 junction that is mediated by the catalytic domain of the NS2 protease (amino acids 917-1040), the histidine at position 966 (H966), a critical residue for NS2 protease activity, is mutated to alanine (H966A) (FIG. 15E). See, e.g., Grakoui, A. et al. A second hepatitis C virus-encoded proteinase. Proc. Natl Acad. Sci. USA 90, 10583—10587 (1993); Hijikata, M. et al. Two distinct proteinase activities required for the processing of a putative nonstructural precursor protein of hepatitis C virus. J. Virol. 67, 4665—4675 (1993); and Lorenz. IC. Structure of the catalytic domain of the hepatitis C virus NS2-3 protease. Nature. Aug 17;442(7104):831-5 (2006).

[00186] As another example, the heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 25 amino acids (aa) to 778 aa (e.g., from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 450 aa, from 450 aa to

500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 778 aa) the following amino acid sequence: LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA WYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL YREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHY VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW LKAKLMPQLPG (SEQ ID NO:64). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 25 amino acids (aa) to 778 aa (e.g., from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 450 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 778 aa) of the following amino acid sequence:
LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA WYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL YREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA

FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHY
VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW
LKAKLMPQLPG (SEQ ID NO:64); and has a length of from 25 amino acids (aa) to 50 aa, from 50 aa to 100 aa, from 100 aa to 200 aa, from 200 aa to 300 aa, from 300 aa to 400 aa, from 400 aa to 500 aa, from 500 aa to 600 aa, from 600 aa to 700 aa, or from 700 aa to 778 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:
LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT
TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA
TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA
WYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT
KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
YREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHY
VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW
LKAKLMPQLPG (SEQ ID NO:64); and has a length of 778 amino acids. Such a polytope can include T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS2-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, and NS4b-10 in Fig. 13B and Fig. 15A-15N.

[00187] As another example, the heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 25 amino acids (aa) to 1985 aa (e.g., from 25 aa to 50 aa, from 50 aa

to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 500 aa, from 500 aa to 750 aa, from 750 aa to 1000 aa, from 1000 aa to 1500 aa, or from 1500 aa to 1985 aa) of the following amino acid sequence:

APITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVSTAAQTFLATCINGVCWTV
YHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQGARSLTPCTCGSSDLYLVT
RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAA
YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYG
KFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSV
LCECYDAGCAWYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHID
AHFLSQTKQSGENLPYLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPT
PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAYCL
STGCVVIVGRIVLSGKPAIIPDREVLYREFDEMEECSQHLPYIEQGMMLAEQFKQ
KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
NPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
VVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL
MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
TTDNLKCPCQVPSPEFFTELDGVRLHRFAPPCKPLLREEVSFRVGLHEYPVGSQL
PCEPEPDVAVLTSMLTDPSHITAEAAGRRLARGSPPSVASSSASQLSAPSLKATCT
ANHDSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVVHGCPLPPPQSPPVPPP
RKKRTVVLTESTVSTALAELATKSFGSSSTSGITGDNTTTSSEPAPSGCPPDSDAE
SYSSMPPLEGEPGDPDLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAE
EQKLPINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSHYQDVLKEV
KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
KDLLEDSVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD

VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
SDIRTEEAIYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCGYRRCRASGVL
TTSCGNTLTCYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
FTEAMTRYSAPPGDPPQPEYDLELITSCSSNVSVAHDGAGKRVYYLTRDPTTPLA
RAAWETARHTPVNSWLGNIIMFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
YGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRAWRHR
ARSVRARLLSRGGRAAICGKYLFNWAVRTKLKLTPIAAAGQLDLSGWFTAGYS
GGDIYHSVSHARPRWFWFCLLLLAAGVGIYLLPNR (SEQ ID NO:13).

[00188] In some cases, the heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

APITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVSTAAQTFLATCINGVCWTV
YHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQGARSLTPCTCGSSDLYLVT
RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAA
YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYG
KFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSV
LCECYDAGCAWYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHID
AHFLSQTKQSGENLPYLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPT
PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAYCL
STGCVVIVGRIVLSGKPAIIPDREVLYREFDEMEECSQHLPYIEQGMMLAEQFKQ
KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
NPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
VVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL

MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
TTDNLKCPCQVPSPEFFTELDGVRLHRFAPPCKPLLREEVSFRVGLHEYPVGSQL
PCEPEPDVAVLTSMLTDPSHITAEAAGRRLARGSPPSVASSSASQLSAPSLKATCT
ANHDSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVVHGCPLPPPQSPPVPPP
RKKRTVVLTESTVSTALAELATKSFGSSSTSGITGDNTTTSSEPAPSGCPPDSDAE
SYSSMPPLEGEPGDPDLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAE
EQKLPINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSHYQDVLKEV
KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
KDLLEDSVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
SDIRTEEAIYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCGYRRCRASGVL
TTSCGNTLTCYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
FTEAMTRYSAPPGDPPQPEYDLELITSCSSNVSVAHDGAGKRVYYLTRDPTTPLA
RAAWETARHTPVNSWLGNIIMFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
YGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRAWRHR
ARSVRARLLSRGGRAAICGKYLFNWAVRTKLKLTPIAAAGQLDLSGWFTAGYS
GGDIYHSVSHARPRWFWFCLLLLAAGVGIYLLPNR (SEQ ID NO:13); and has a length of 1985 amino acids. Such a polytope can include T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, NS4b-10, NS5a-1, NS5a-2, NS5b-1, NS5b-2 in Fig. 13A-13B and Fig. 15A-15N.

Additional T-cell epitopes

[00189] As discussed above, an E1/E2 a heterodimeric polypeptide of the present disclosure includes: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide). The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some

cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein.

[00190] Thus, in some cases, a variant HCV E2 polypeptide of an E1/E2 heterodimer of the present disclosure includes: a) an HCV E2 polypeptide; and b) a heterologous polypeptide that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein.

[00191] A T helper tetanus toxin epitope or other bacterial T-cell epitope could be fused (e.g., by recombinant expression) or chemically conjugated to the HCV polytope/E2 fusion protein and/or to the HCV polytope E1 fusion protein of an E1/E2 heterodimer of the present disclosure to further enhance both T and B cell responses to both the HCV polytope and E1/E2 moieties. Alternatively, the whole or part of the detoxified toxin ("toxoid") could be fused (e.g., by recombinant expression) or chemically conjugated to the HCV polytope/E1E2 protein, wherein specific amino acids of the toxins are mutated to render the toxins inactive, thereby generating toxoids. Methods of generating toxoids are well known in the art. Examples of bacterial epitopes include the use of diphtheria toxoid, meningococcal outer membrane protein, or mutant diphtheria protein CRM197 (see, e.g.: http://www(dot)medscape(dot)com/viewarticle/431127)

[00192] In some cases, a suitable tetanus toxoid polypeptide comprises the amino acid sequence QYIKANSKFIGIFE (SEQ ID NO:14). In some cases, a suitable tetanus toxoid polypeptide comprises the amino acid sequence QYIKANSKFIGITE (SEQ ID NO:65).

[00193] In some cases, a heterologous polypeptide can comprise cholera toxin (or toxoid) epitope. In some cases, a suitable heterologous polypeptide comprising a cholera toxoid epitope comprises a fragment of cholera toxin-B subunit (CT-B), e.g., a fragment of from 5 amino acids to 25 amino acids, or from 25 amino acids to 50 amino acids, of the following amino acid sequence: MIKLKFGVFF TVLLSSAYAH GTPQNITDLC AEYHNTQIHT LNDKIFSYTE SLAGKREMAI ITFKNGATFQ VEVPGSQHID SQKKAIERMK DTLRIAYLTE AKVEKLCVWN NKTPHAIAAI SMAN (SEQ ID NO:15).

[00194] In some cases, a heterologous polypeptide can comprise a tetanus toxin (or toxoid) T-cell epitope. In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: ILMQYIKANSKFIGI (SEQ ID NO:16); and has a length of from 15 amino acids to 20 amino acids. In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: VNNESSE (SEQ ID NO:17). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: PGINGKAIHLVNNESSE (SEQ ID NO:18). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: PNRDIL (SEQ ID NO:19). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: FIGITEL (SEQ ID NO:20). In some cases, a suitable tetanus toxin T-cell epitope comprises the amino acid sequence: SYFPSV (SEQ ID NO:21). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: NSVDDALINSTKIYSYFPSV (SEQ ID NO:22). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: IDKISDVSTIVPYIGPALNI (SEQ ID NO:23).

[00195] In some cases, a heterologous polypeptide can comprise a diphtheria toxin T-cell epitope In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: QSIALSSLMVAQAIP (SEQ ID NO:24); and has a length of from 15 amino acids to 20 amino acids. In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: PVFAGANYAAWAVNVAQVI (SEQ ID NO:25). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: VHHNTEEIVAQSIALSSLMV (SEQ ID NO:26). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: QSIALSSLMVAQAIPLVGEL (SEQ ID NO:66). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: VDIGFAAYNFVESIINLFQV (SEQ ID NO:67). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: QGESGHDIKITAENTPLPIA (SEQ ID NO:68). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: GVLLPTIPGKLDVNKSKTHI (SEQ ID NO:69). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence of CRM197 (see, e.g., Giannini et al. (1984) *Nucl. Acids. Res.* 12:4063).

[00196] The amino acid sequence of CRM197 is as follows:

[00197] 1addvvdssksfvmenfssyhgtkpgyvdsiqkgiqkpksgtqgnydddwkefystdnky daagysvdnenplsgkaggvvkvtypgltkvlalkvdnaetikkelglslteplmeqvgteefikrfgdgasrvvlslpfae gsssveyinnweqakalsveleinfetrgkrgqdamyeymaqacagnrvrrsvgsslscinldwdvirdktktkieslkeh gpiknkmsespnktvseekakqyleefhqtalehpelselktvtgtnpvfaganyaawavnvaqvidsetadnlekttaal silpgigsvmgiadgavhhnteeivaqsialsslmvaqaiplvgelvdigfaaynfvesiinlfqvvhnsynrpayspghkt qpflhdgyavswntvedsiirtgfqgesghdikitaentplpiagvllptipgkldvnkskthisvngrkirmrcraidgdvtf crpkspvyvgngvhanlhvafhrsssekihsneissdsigvlgyqktvdhtkvnsklslffeiks (SEQ ID NO:27).

[00198] In some cases, a heterologous polypeptide can comprise a tetanus toxin T-cell epitope and a diphtheria toxin T-cell epitope. In some of these cases, the heterologous polypeptide can comprise the amino acid sequence: IMQYIKANSKFIGIQSIALSSLMVAQ (SEQ ID NO:28); and can have a length of from 26 amino acids to 30 amino acids.

E1

[00199] An HCV E1 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure can have a length of from about 150 amino acids (aa) to about 175 aa, from about 175 aa to about 195 aa, from about 131 aa to about 175 aa, or from about 175 aa to about 193 aa. In some cases, an HCV E1 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure is an HCV E1 ectodomain polypeptide. In some cases, an HCV E1 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure is a full-length HCV E1 polypeptide.

[00200] In FIG. 1A-1C, the amino acid sequence of E1 is amino acid 192 to amino acid 383. In FIG. 2A-2C, the amino acid sequence of E1 is amino acid 192 to amino acid 383. In FIG. 3A-3C, the amino acid sequence of E1 is amino acid 192 to amino acid 384. In FIG. 4A-4B, the amino acid sequence of E1 is amino acid 192 to amino acid 383. Amino acids at around 170 through approximately 191 serve as a signal sequence for E1. As used herein, "E1 polypeptide" includes a precursor E1 protein, including the signal sequence; includes a mature E1 polypeptide which lacks this sequence; and includes an E1 polypeptide with a heterologous signal sequence. An E1 polypeptide can include a C-terminal membrane anchor sequence which occurs at approximately amino acid positions 360-383 (see, e.g., WO 96/04301). In some cases, a suitable E1 polypeptide lacks a C-terminal portion that includes a transmembrane region. For example, in some cases, a suitable E1 polypeptide lacks the C-terminal portion from amino acid 330 to amino acid 384, or from amino acid 360 to amino acid 384. E1 polypeptides can be an E1 polypeptide of any genotype, subtype or isolate of HCV. E1 polypeptides of genotype 1 and E1 polypeptides of genotype 3 are included in an E1/E2 heterodimer of the present disclosure.

[00201] An E1 polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, or FIG. 4A-4B.

[00202] An E1 polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 1A-1C. For example, an E1 polypeptide of genotype 1A can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 1A and depicted in FIG. 1A-1C. For example, an E1 polypeptide of genotype 1B can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 1B and depicted in FIG. 1A-1C. For example, an E1 polypeptide of genotype 1C can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 1C and depicted in FIG. 1A-1C.

[00203] An E1 polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 2A-2C. For example, an E1 polypeptide of genotype 2A can comprise an

amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 2A and depicted in FIG. 2A-2C. For example, an E1 polypeptide of genotype 2B can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 2B and depicted in FIG. 2A-2C.

[00204] An E1 polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the consensus E1 polypeptide amino acid sequence depicted in FIG. 3A-3C.

[00205] An E1 polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 4A-4B. For example, an E1 polypeptide of genotype 7A can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of the amino acid sequence depicted in FIG. 4A-4B.

Additional polypeptides

[00206] In any of the above-described embodiments, one or both of the polypeptide chains of the E1/E2 heterodimer can include one or more additional polypeptides. For example, in some cases, the E1 polypeptide or the variant E2 polypeptide can include an Ig Fc polypeptide at the C-terminus of the E1 polypeptide or the variant E2 polypeptide. As another example, in some cases, the E1 polypeptide or the variant E2 polypeptide can include an Ig Fc polypeptide at the

N-terminus of the E1 polypeptide or the variant E2 polypeptide. Ig Fc polypeptides are known in the art, and are described elsewhere herein.

IB. E1E2 heterodimers comprising a variant HCV E1 and HCV E2

[00207] The present disclosure provides an E1/E2 heterodimer, where the E1/E2 heterodimer comprises: a) a variant HCV E1 polypeptide, where the variant HCV E1 polypeptide comprises: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T-cell epitopes not present in an HCV E1 or an HCV E2 polypeptide; e.g., one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 or an HCV E2 polypeptide); and b) an HCV E2 polypeptide. Thus, in some cases, a heterodimeric polypeptide of the present disclosure includes: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide). The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein. The heterologous polypeptide is also referred to as a "polytope."

[00208] An E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes), when administered to an individual in need thereof, induces an immune response in the individual to one or more HCV genotypes. An E1/E2 heterodimer of the present disclosure, when administered to an individual in need thereof, induces an immune response in the individual to one or more HCV genotypes, where the immune response is greater than the immune response induced by administration of an HCV E1/E2 heterodimer comprising a wild-type E2 and a wild-type E1 polypeptide or an E1 polypeptide lacking the polytope.

[00209] For example, in some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes), when administered to an individual in need thereof, induces CTLs specific for HCV, where the number of HCV-specific CTLs induced is at least

10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 7.5-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold, or more than 100-fold, higher than the number of HCV-specific CTLs induced by administration of an HCV E1/E2 heterodimer comprising a wild-type E2 and a wild-type E1 polypeptide or an E1 polypeptide lacking the polytope.

[00210] In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces production of HCV-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual, where the number of HCV-specific $CD4^+$ T cells and $CD8^+$ T cells is increased, such that the percent of the total peripheral blood T cells (i.e., the total number of $CD4^+$ T cells + $CD8^+$ T cells in the peripheral blood) that are HCV-specific $CD4^+$ T cells and $CD8^+$ T cells is from 0.5% to 10% (e.g., from 0.5% to 1%, from 1% to 2%, from 2% to 5%, or from 5% to 10%). The number of HCV-specific $CD4^+$ T cells and $CD8^+$ T cells in a control individual (e.g., an individual not infected with HCV) not treated with the E1/E2 heterodimer would be undetectable.

[00211] For example, in some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more HCV NS3 T-cell epitopes), when administered to an individual in need thereof, induces production of HCV NS3-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual, where the number of HCV NS3-specific $CD4^+$ T cells and $CD8^+$ T cells is increased, such that the percent of the total peripheral blood T cells (i.e., the total number of $CD4^+$ T cells + $CD8^+$ T cells in the peripheral blood) that are HCV NS3-specific $CD4^+$ T cells and $CD8^+$ T cells is from 0.1% to 10% (e.g., from 0.1% to 0.5%, from 0.5% to 1%, from 1% to 2%, from 2% to 5%, or from 5% to 10%). The number of HCV NS3-specific $CD4^+$ T cells and $CD8^+$ T cells in a control individual (e.g., an individual not infected with HCV) not treated with the E1/E2 heterodimer would be undetectable.

[00212] In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, increases the number

of HCV E1/E2-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 7.5-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold, or more than 100-fold, compared to the number of HCV E1/E2-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual induced by administration of an E1/E2 heterodimer comprising a wild-type E2 polypeptide and a wild-type E1 polypeptide, or an E1 polypeptide lacking the polytope, or compared to the number of HCV E1/E2-specific $CD4^+$ T cells and $CD8^+$ T cells in the individual before administration of the E1/E2 heterodimer of the present disclosure.

[00213] As another example, in some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces helper T lymphocytes (e.g., $CD4^+$ T cells) specific for HCV, where the number of HCV-specific helper T lymphocytes induced is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 7.5-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold, or more than 100-fold, higher than the number of HCV-specific helper T cells induced by administration of an E1/E2 heterodimer comprising a wild-type E2 polypeptide and a wild-type E1 polypeptide, or an E1 polypeptide lacking the polytope, or compared to the number of HCV-specific helper T cells in the individual before administration of the E1/E2 heterodimer of the present disclosure.

[00214] In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces antibody specific for HCV, where the level of HCV-specific antibody induced is at least at high as the level of HCV-specific antibody induced by administration of an E1/E2 heterodimer comprising a wild-type E2 polypeptide and a wild-type E1 polypeptide, or an E1 polypeptide lacking the polytope.

[00215] In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or

more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces antibody specific for HCV, where the level of HCV-specific antibody induced is at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 75%, at least 100% (or 2-fold), at least 2.5-fold, at least 5-fold, at least 7.5-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold, or more than 100-fold, higher than the level of HCV-specific antibody induced by administration of an E1/E2 heterodimer comprising a wild-type E2 polypeptide and a wild-type E1 polypeptide, or an E1 polypeptide lacking the polytope.

[00216] An E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response (e.g., a cellular immune response) in the individual to one or more HCV genotypes. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 1. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 2. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 3. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype

1 and HCV genotype 3. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 1, HCV genotype 2, and HCV genotype 3. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 1, HCV genotype 2, HCV genotype 3, and HCV genotype 7. In some cases, an E1/E2 heterodimer of the present disclosure (e.g., an E1/E2 heterodimer comprising: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide), when administered to an individual in need thereof, induces an immune response in the individual to HCV genotype 1, HCV genotype 2, HCV genotype 3, HCB genotype 4, HCV genotype 5, HCV genotype 6, and HCV genotype 7.

Variant E1

[00217] As noted above, a variant E1 polypeptide of an HCV E1/E2 heterodimer of the present disclosure comprises: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes (e.g., one or more T-cell epitopes not present in an HCV E1 or an HCV E2 polypeptide; e.g., one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 or an HCV E2 polypeptide). In some cases, the variant HCV E1 polypeptide comprises, in order from amino terminus (N-terminus) to carboxyl terminus (C-terminus): i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes. In some cases, the variant HCV E1 polypeptide comprises, in order from N-terminus to C-terminus: i) a heterologous polypeptide comprising one or more T cell epitopes; and ii) an HCV E1 polypeptide.

E1

[00218] An HCV E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can have a length of from about 150 amino acids (aa) to about 175 aa, from about 175 aa to about 195 aa, from about 131 aa to about 175 aa, or from about 175 aa to about 193 aa. In some cases, an HCV E1 polypeptide suitable for inclusion in a

variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure is an HCV E1 ectodomain polypeptide. In some cases, an HCV E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure is a full-length HCV E1 polypeptide.

[00219] In FIG. 1A-1C, the amino acid sequence of E1 is amino acid 192 to amino acid 383. In FIG. 2A-2C, the amino acid sequence of E1 is amino acid 192 to amino acid 383. In FIG. 3A-3C, the amino acid sequence of E1 is amino acid 192 to amino acid 384. In FIG. 4A-4B, the amino acid sequence of E1 is amino acid 192 to amino acid 383. Amino acids at around 170 through approximately 191 serve as a signal sequence for E1. As used herein, "E1 polypeptide" includes a precursor E1 protein, including the signal sequence; includes a mature E1 polypeptide which lacks this sequence; and includes an E1 polypeptide with a heterologous signal sequence. An E1 polypeptide can include a C-terminal membrane anchor sequence which occurs at approximately amino acid positions 360-383 (see, e.g., WO 96/04301). In some cases, a suitable E1 polypeptide lacks a C-terminal portion that includes a transmembrane region. For example, in some cases, a suitable E1 polypeptide lacks the C-terminal portion from amino acid 330 to amino acid 384, or from amino acid 360 to amino acid 384. E1 polypeptides can be an E1 polypeptide of any genotype, subtype or isolate of HCV. E1 polypeptides of genotype 1 and E1 polypeptides of genotype 3 are included in an E1/E2 heterodimer of the present disclosure.

[00220] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, or FIG. 4A-4B.

[00221] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 1A-1C. For example, an E1 polypeptide of genotype 1A can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about

60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 1A and depicted in FIG. 1A-1C. For example, an E1 polypeptide of genotype 1B can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 1B and depicted in FIG. 1A-1C. For example, an E1 polypeptide of genotype 1C can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 1C and depicted in FIG. 1A-1C.

[00222] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 2A-2C. For example, an E1 polypeptide of genotype 2A can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 2A and depicted in FIG. 2A-2C. For example, an E1 polypeptide of genotype 2B can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 2B and depicted in FIG. 2A-2C.

[00223] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the consensus E1 polypeptide amino acid sequence depicted in FIG. 3A-3C.

[00224] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 4A-4B. For example, an E1 polypeptide of genotype 7A can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of the amino acid sequence depicted in FIG. 4A-4B.

Heterologous polypeptide

[00225] In some cases, the heterologous polypeptide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10 (e.g., from 10 to 15, from 15 to 20, from 20 to 25, or from 25 to 30, or more than 30), T cell epitopes. T-cell epitopes are epitopes that, when presented with a major histocompatibility complex (MHC) (e.g., a human leukocyte antigen (HLA)) Class I or MHC Class II molecule, are recognized and bound by a T-cell receptor (TCR) present on a T cell surface. T-cell epitopes include epitopes recognized by cytotoxic T cells (e.g., $CD8^+$ T cells), and epitopes recognized by helper T cells (e.g., $CD4^+$ T cells).

[00226] The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal

outer membrane protein. Other examples of strong T helper epitopes are diphtheria toxoid, tetanus toxoid, meningococcal outer membrane protein, or mutant diphtheria protein CRM197 (see, e.g.: http://www(dot)medscape(dot)com/viewarticle/431127).

[00227] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS3 T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS3 T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS3 T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS3 T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS3 $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS3 $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS3 $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS3 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS3 $CD4^+$ T cell epitope and at least one HCV-NS3 $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS3 $CD4^+$ T-cell epitopes and 2 or more HCV-NS3 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS3 $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS3 $CD8^+$ T-cell epitopes.

[00228] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS2 T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS2 T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS2 T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS2 T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS2 $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS2 $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS2 $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS2 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS2 $CD4^+$ T cell epitope and at least one HCV-NS2 $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS2 $CD4^+$ T-cell epitopes and 2 or

more HCV-NS2 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS2 $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS2 $CD8^+$ T-cell epitopes.

[00229] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS4A T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS4A T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS4A T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS4A T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS4A $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS4A $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS4A $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS4A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS4A $CD4^+$ T cell epitope and at least one HCV-NS4A $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS4A $CD4^+$ T-cell epitopes and 2 or more HCV-NS4A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS4A $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS4A $CD8^+$ T-cell epitopes.

[00230] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS5A T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5A T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS5A T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS5A T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5A $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5A $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5A $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS5A $CD4^+$ T cell epitope and at least one HCV-NS5A $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS5A $CD4^+$ T-cell

epitopes and 2 or more HCV-NS5A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS5A $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS5A $CD8^+$ T-cell epitopes.

[00231] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS5B T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5B T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS5B T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS5B T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5B $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5B $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5B $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5B $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS5B $CD4^+$ T cell epitope and at least one HCV-NS5B $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS5B $CD4^+$ T-cell epitopes and 2 or more HCV-NS5B $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS5B $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS5B $CD8^+$ T-cell epitopes.

[00232] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-core T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-core T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-core T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-core T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-core $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-core $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-core $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-core $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-core $CD4^+$ T cell epitope and at least one HCV-core $CD8^+$ T cell epitope. In some

cases, heterologous polypeptide comprises 2 or more HCV-core $CD4^+$ T-cell epitopes and 2 or more HCV-core $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-core $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-core $CD8^+$ T-cell epitopes.

[00233] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-p7 T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-p7 T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-p7 T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-p7 T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-p7 $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-core $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-p7 $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-p7 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-p7 $CD4^+$ T cell epitope and at least one HCV-p7 $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-p7 $CD4^+$ T-cell epitopes and 2 or more HCV-p7 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-p7 $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-p7 $CD8^+$ T-cell epitopes.

[00234] In some cases, the heterologous polypeptide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, or 63, of the T-cell epitopes set out in Fig. 13A-13B. In some cases, the heterologous polypeptide comprises from 1 to 3, from 3 to 5, from 5 to 10, from 10 to 15, from 15 to 20, from 20 to 25, or from 25 to 30 of the T-cell epitopes set out in Fig. 13A-13B. For example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, and NS3-11 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-7, and NS2-8 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, NS3-5, and NS3-11 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As

another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated Core-1, Core-2, Core-3, Core-4, Core-5, Core-6, Core-7, Core-8, Core-9, Core-10, Core-11, Core-12, Core-13, Core-14, Core-16, Core-17, Core-18, Core-19, Core-20, Core-21, and Core-22 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-4, NS2-5, NS2-6, NS2-7, NS2-8, NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, and NS4b-10 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, NS4b-10, NS5a-1, NS5a-2, NS5b-1, and NS5b-2 in Fig. 13A-13B and Fig. 15A-15N. In some cases, the T-cell epitopes are contiguous. In some cases, any two T-cell epitopes are separated by linkers (e.g., a linker having a length of from 1 amino acid to about 50 amino acids, e.g., from 1 amino acid to 5 amino acids (aa), from 5 aa to 10 aa, from 10 aa to 15 aa, from 15 aa to 20 aa, from 20 aa to 25 aa, from 25 aa to 30 aa, from 30 aa to 40 aa, or from 40 aa to 50 aa).

[00235] In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1 and 2. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1 and 3. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are

conserved among HCV genotypes 1, 2, and 3. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1, 2, 3, and 7. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1-7.

[00236] The heterologous polypeptide can have a length of from about 10 amino acids to about 2000 amino acids; e.g., the heterologous polypeptide can have a length of from 10 amino acids (aa) to 15 aa, from 15 aa to 20 aa, from 20 aa to 25 aa, from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 800 aa. The heterologous polypeptide can have a length of from about 25 amino acids to about 2000 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 500 aa, from 500 aa to 600 aa, from 600 aa to 700 aa, from 700 aa to 800 aa, from 800 aa to 900 aa, from 900 aa to 1000 aa, from 1000 aa to 1100 aa, from 1100 aa to 1200 aa, from 1200 aa to 1300 aa, from 1300 aa to 1400 aa, from 1400 aa to 1500 aa, from 1500 aa to 1600 aa, from 1600 aa to 1700 aa, from 1700 aa to 1800 aa, from 1800 aa to 1900 aa, or from 1900 aa to 2000 aa. The heterologous polypeptide can have a length of from about 25 amino acids to about 3000 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 500 aa, from 500 aa to 600 aa, from 600 aa to 700 aa, from 700 aa to 800 aa, from 800 aa to 900 aa, from 900 aa to 1000 aa, from 1000 aa to 1100 aa, from 1100 aa to 1200 aa, from 1200 aa to 1300 aa, from 1300 aa to 1400 aa, from 1400 aa to 1500 aa, from 1500 aa to 1600 aa, from 1600 aa to 1700 aa, from 1700 aa to 1800 aa, from 1800 aa to 1900 aa, from 1900 aa to 2000 aa, from 2000 aa to 2250 aa, from 2250 aa to 2500 aa, from 2500 aa to 2750 aa, or from 2750 aa to 3000 aa.

[00237] The heterologous polypeptide can have a length of from about 25 amino acids to about 800 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 800 aa. The heterologous polypeptide can have a length of from about 25 amino acids to about 400 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa

to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, or from 350 aa to 400 aa. The heterologous polypeptide can have a length of 25 amino acids (aa), 26 aa, 27 aa, 28 aa, 29 aa, 30 aa, 31 aa, 32 aa, 33 aa, 34 aa, 35 aa, 36 aa, 37 aa, 38 aa, 39 aa, 40 aa, 41 aa, 42 aa, 43 aa, 44 aa, 45 aa, 46 aa, 47 aa, 48 aa, 49 aa, or 50 aa. The heterologous polypeptide can have a length of from about 100 amino acids (aa) to 800 aa, e.g., from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 800 aa. The heterologous polypeptide can have a length of from 25 aa to 30 aa. The heterologous polypeptide can have a length of from 30 aa to 40 aa. The heterologous polypeptide can have a length of from 40 aa to 50 aa. The heterologous polypeptide can have a length of from 50 aa to 60 aa (e.g., 50 aa, 51 aa, 52, aa, 53 aa, 54 aa, 55 aa, 56 aa, 57 aa, 58 aa, 59 aa, or 60 aa). The heterologous polypeptide can have a length of from 60 aa to 70 aa. The heterologous polypeptide can have a length of from 65 aa to 75 aa (e.g., 65, 66, 67, 68, 69, 70, 71, 72, 7, 74, or 75 aa). The heterologous polypeptide can have a length of 70 aa. The heterologous polypeptide can have a length of from 70 aa to 80 aa. The heterologous polypeptide can have a length of from 80 aa to 90 aa. The heterologous polypeptide can have a length of from 90 aa to 100 aa. The heterologous polypeptide can have a length of from 100 aa to 105 aa (e.g., 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, or 110 aa). The heterologous polypeptide can have a length of 100 aa. The heterologous polypeptide can have a length of from 10 amino acids (aa) to 50 aa; e.g., from 10 aa to 15 aa, from 15 aa to 20 aa, from 20 aa to 25 aa, from 25 aa to 30 aa, from 30 aa to 35 aa, from 35 aa to 40 aa, from 40 aa to 45 aa, or from 45 aa to 50 aa. The heterologous polypeptide can have a length of from 10 amino acids (aa) to 20 aa, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 aa.

HCV NS3 T-cell epitopes

[00238] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS3 polypeptide. Examples of T-cell epitopes present in NS3 polypeptides are depicted in **FIG. 15A-15N, FIG. 13B, and FIG. 14A-14B**.

[00239] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1). In some cases, the heterologous

polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1); and has a length of from 25 aa to 35 aa (e.g., 25 aa, 26 aa, 27 aa, 28 aa, 29 aa, 30 aa, 31 aa, 32 aa, 33 aa, 34 aa, or 35 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1); and has a length of 29 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, and NS3-11 in FIG. 13B and FIG. 15A-15N.

[00240] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2); and has a length of from 45 amino acids to 60 amino acids (e.g., 45 aa, 46 aa, 47 aa, 48 aa, 49 aa, 50 aa, 51 aa, 52 aa, 53 aa, 54 aa, 55 aa, 56 aa, 57 aa, 58 aa, 59 aa, or 60 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID

NO:2); and has a length of 52 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, NS3-5, and NS3-11 in FIG. 13B and FIG. 15A-15N.

[00241] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTG FTGDFDSVIDCN (SEQ ID NO:3); and has a length of from 65 amino acids to 80 amino acids (e.g., 65 aa, 66 aa, 67 aa, 68 aa, 69 aa, 70 aa, 71 aa, 72 aa, 73 aa, 74 aa, 75 aa, 76 aa, 77 aa, 78 aa, 79 aa, or 80 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTG FTGDFDSVIDCN (SEQ ID NO:3); and has a length of 70 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-11, NS3-12, and NS3-13 in FIG. 13B and FIG. 15A-15N.

[00242] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4); and has a length of from 95 amino acids (aa) to 105 aa (e.g., 95 aa, 96 aa, 97 aa, 98 aa, 99 aa, 100 aa, 101 aa, 102 aa, 103 aa, 104 aa, or 105 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4); and has a length of 100 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-10, NS3-11, NS3-12, and NS3-13 in FIG. 13B and FIG. 15A-15N.

[00243] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQP RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS RNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPGCSF SIFLLALLSCLTVPASA (SEQ ID NO:9); and has a length of from 190 amino acids (aa) to 200 aa (e.g., 190 aa, 191 aa, 192 aa, 193 aa, 194 aa, 195 aa, 196 aa, 197 aa, 198 aa, 199 aa, or 200 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQP RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS RNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPGCSF SIFLLALLSCLTVPASA (SEQ ID NO:9); and has a length of 191 amino acids.

[00244] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCN (SEQ ID NO:10); and has a length of from 215 amino acids (aa) to 235 aa (e.g., 215 aa, 216 aa, 217 11, 218 aa,

219 aa, 220 aa, 221 aa, 222 aa, 223 aa, 224 aa, 225 aa, 226 aa, 227 aa, 228 aa, 229 aa, 230 aa, 231 aa, 232 aa, 233 aa, 234 aa, or 235 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCN (SEQ ID NO:10); and has a length of 228 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in FIG. 13B and FIG. 15A-15N.

[00245] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1265-1279 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00246] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1309-1323 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00247] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at

least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1401-1415 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00248] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1402-1412 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 11 amino acids (aa) to 16 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, or 16 aa).

[00249] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1429-1439 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 11 amino acids (aa) to 16 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, or 16 aa).

[00250] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1450-1464 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00251] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at

least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1453-1467 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00252] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1577-1591 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00253] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1306-1314 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00254] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1387-1394 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 1 amino acids (aa) to 15 amino acids (e.g., 8 aa, 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00255] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1405-1413 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00256] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1450-1458 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00257] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1457-1465 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00258] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1610-1618 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV

genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV NS2 T-cell epitopes

[00259] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS2 polypeptide. Examples of T-cell epitopes present in NS2 polypeptides are depicted in **FIG. 15A-15N**, and **FIG. 13A**.

[00260] For example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 955-974 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00261] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 975-994 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00262] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 985-1004 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00263] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1015-1034 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00264] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1035-1054 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00265] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 924-933 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00266] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 961-970 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and

the NS2 T cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00267] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 989-997 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00268] In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 10 amino acids (aa) to 50 aa (e.g., from 10 aa to 25 aa, or from 25 aa to 50 aa) of amino acids 955-1004 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and has a length of from 10 amino acids (aa) to 25 aa, or from 25 aa to 50 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 955-1004 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and has a length of about 50 amino acids.

[00269] In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 10 amino acids (aa) to 553 aa (e.g., from 10 aa to 25 aa, from 25 aa to 50 aa, from 50 aa to 100 aa, from 100 aa to 200 aa, from 200 aa to 300 aa, from 300 aa to 400 aa, from 400 aa to 500 aa, or from 500 aa to 553 aa) of amino acids 917-1469 of the amino acid sequence designated

"Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 and NS3 amino acid sequence of any HCV genotype; and has a length of from 10 amino acids (aa) to 25 aa, from 25 aa to 50 aa, from 50 aa to 100 aa, from 100 aa to 200 aa, from 200 aa to 300 aa, from 300 aa to 400 aa, from 400 aa to 500 aa, or from 500 aa to 553 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 917-1469 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 and NS3 amino acid sequence of any HCV genotype; and has a length of about 553 amino acids.

[00270] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 0%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LGALTGTYVYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADT (SEQ ID NO:11). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LGALTGTYVYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADT (SEQ ID NO:11); and has a length of from 50 amino acids to 60 amino acids (e.g., 50 aa, 51 aa, 52 aa, 53 aa, 54 aa, 55 aa, 56 aa, 57 aa, 58 aa, 59 aa, or 60 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LGALTGTYVYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADT (SEQ ID NO:11); and has a length of 50 amino acids. Such a polytope can include NS2 T-cell

epitopes designated NS2-1, NS2-2, NS2-3, NS2-7, and NS2-8 in FIG. 13A and FIG. 15A-15N.

HCV NS4A T-cell epitopes

[00271] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS4A polypeptide. Examples of T-cell epitopes present in NS4A polypeptides are depicted in FIG. 15A-15N and FIG. 13B.

[00272] The heterologous polypeptide can comprise an NS4A T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1683-1692 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4A amino acid sequence of any HCV genotype; and the NS4A T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV NS4B T-cell epitopes

[00273] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS4B polypeptide. Examples of T-cell epitopes present in NS4B polypeptides are depicted in FIG. 15A-15N and FIG. 13B.

[00274] As one example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1790-1801 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 12 amino acids (aa) to 20 amino acids (e.g., 12 aa, 13 aa, 14 aa, 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00275] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least

about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1792-1802 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 11 amino acids (aa) to 20 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00276] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1898-1905 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 8 amino acids (aa) to 15 amino acids (e.g., 8 aa, 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00277] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1921-1935 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00278] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1922-1941 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00279] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about

60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1928-1947 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00280] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1868-1876 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00281] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1927-1942 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 16 amino acids (aa) to 20 amino acids (e.g., 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00282] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1932-1940 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00283] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about

30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1948-1962 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

HCV NS5A T-cell epitopes

[00284] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS5A polypeptide. Examples of T-cell epitopes present in NS5A polypeptides are depicted in **FIG. 15A-15N** and **FIG. 13B**.

[00285] As one example, the heterologous polypeptide can comprise an NS5A T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2218-2232 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5A amino acid sequence of any HCV genotype; and the NS5A T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00286] As another example, the heterologous polypeptide can comprise an NS5A T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2309-2317 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5A amino acid sequence of any HCV genotype; and the NS5A T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV NS5B T-cell epitopes

[00287] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS5B polypeptide. Examples of T-cell epitopes present in NS5B polypeptides are depicted in **FIG. 15A-15N** and **FIG. 13B**.

[00288] As one example, the heterologous polypeptide can comprise an NS5B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2847-2851 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5B amino acid sequence of any HCV genotype; and the NS5B T-cell epitope can have a length of from 5 amino acids (aa) to 10 amino acids (e.g., 5 aa, 6 aa, 7 aa, 8 aa, 9 aa, or 10 aa).

[00289] As another example, the heterologous polypeptide can comprise an NS5B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2602-2610 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5B amino acid sequence of any HCV genotype; and the NS5B T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV core T-cell epitopes

[00290] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV core polypeptide. Examples of T-cell epitopes present in HCV Core polypeptides are depicted in **FIG. 15A-15N** and **FIG.13A**.

[00291] As one example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1-20 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00292] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at

least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 11-30 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00293] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 21-40 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00294] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 39-63 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 23 amino acids (aa) to 28 amino acids (e.g., 23 aa, 24 aa, 25 aa, 26 aa, 27 aa, or 28 aa).

[00295] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 47-70 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 24 amino acids (aa) to 29 amino acids (e.g., 24 aa, 25 aa, 26 aa, 27 aa, 28 aa, or 29 aa).

[00296] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 61-80 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00297] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 71-90 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00298] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 81-100 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00299] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 91-110 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV

genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00300] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 101-115 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00301] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 111-130 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00302] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 125-139 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00303] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 131-150 of the amino acid sequence designated

"Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00304] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 151-170 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00305] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 161-180 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00306] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 35-44 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00307] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino

acid sequence identity to amino acids 43-51 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00308] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 51-59 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00309] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 129-137 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00310] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 131-140 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00311] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%,

at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 150-158 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00312] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 154-162 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00313] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 168-176 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00314] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 177-187 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 11 amino acids (aa) to 16 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, or 16 aa).

[00315] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at

least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 178-187 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00316] In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 10 amino acids (aa) to 191 aa (e.g., from 10 aa to 25 aa, from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, or from 150 aa to 191aa) of amino acids 1-191 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and has a length of from 10 amino acids (aa) to 25 aa, from 25 aa to 50 aa, from 50 aa to 100 aa, or from 100 aa to 150 aa, or from 150 aa to 191 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1-191 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and has a length of about 191 amino acids.

[00317] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTS ERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPS WGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLE DGVNYATGNLPG (SEQ ID NO:63); and has a length of from 171 amino acids (aa) to 180 aa (e.g., 171 aa, 172 aa, 173 aa, 174 aa, 175 aa, 176 aa, 177 aa, 178 aa, 179 aa, or 180 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about

20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTS ERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPS WGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLE DGVNYATGNLPG (SEQ ID NO:63); and has a length of 171 amino acids. Such a polytope can include core T-cell epitopes designated Core-1, Core-2, Core-3, Core-4, Core-5, Core-6, Core-7, Core-8, Core-9, Core-10, Core-11, Core-12, Core-13, Core-14, Core-16, Core-17, Core-18, Core-19, Core-20, Core-21, Core-22 in FIG. 13A and FIG. 15A-15N.

HCV p7 T-cell epitopes

[00318] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV p7 polypeptide. Examples of T-cell epitopes present in HCV p7 polypeptides are depicted in FIG. 15A-15N or FIG. 13A.

[00319] As another example, the heterologous polypeptide can comprise an HCV p7 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 803-811 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV p7 amino acid sequence of any HCV genotype; and the HCV p7 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

Polytopes including HCV T-cell epitopes from more than one HCV polypeptide other than E1 and E2

[00320] As noted above, a heterologous polypeptide can include T-cell epitopes from more than one HCV polypeptide other than E1 and E2.

[00321] As one example, a heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following

amino acid sequence:
QASLLKVPYFVRVQGLLRICALARKMAGGHYVQMAIIKLGALTGTYVYNALTP
LRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADTAACGDIINGLPVSARRGR
EILLGPADGMVSKGWRLLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS
TAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQG
ARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCP
AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA
HLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQA
ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIF
CHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG
DFDSVIDCN (SEQ ID NO:12); and has a length of from 550 amino acids (aa) to 560 aa (e.g., 550 aa, 551 aa, 552 aa, 553 aa, 554 aa, 555 aa, 556 aa, 557 aa, 558 aa, 559 aa, or 560 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:
QASLLKVPYFVRVQGLLRICALARKMAGGHYVQMAIIKLGALTGTYVYNALTP
LRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADTAACGDIINGLPVSARRGR
EILLGPADGMVSKGWRLLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS
TAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQG
ARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCP
AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA
HLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQA
ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIF
CHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG
DFDSVIDCN (SEQ ID NO:12); and has a length of 553 amino acids. Such a polytope can include T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-4, NS2-5, NS2-6, NS2-7, NS2-8, NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. This polytope is also referred to as "TP553" (FIG. 14A-14D). In order to prevent self cleavage of the TP553 polytope (amino acids 917-

1469) (FIG. 15E-G) at the NS2-NS3 junction that is mediated by the catalytic domain of the NS2 protease (amino acids 917-1040), the histidine at position 966 (H966), a critical residue for NS2 protease activity, is mutated to alanine (H966A) (FIG. 15E).

[00322] As another example, the heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 25 amino acids (aa) to 778 aa (e.g., from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 450 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 778 aa) the following amino acid sequence: LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA WYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL YREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHY VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW LKAKLMPQLPG (SEQ ID NO:64). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 25 amino acids (aa) to 778 aa (e.g., from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400

aa to 450 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 778 aa) of the following amino acid sequence:

LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT
TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA
TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA
WYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT
KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
YREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHY
VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW
LKAKLMPQLPG (SEQ ID NO:64); and has a length of from 25 amino acids (aa) to 50 aa, from 50 aa to 100 aa, from 100 aa to 200 aa, from 200 aa to 300 aa, from 300 aa to 400 aa, from 400 aa to 500 aa, from 500 aa to 600 aa, from 600 aa to 700 aa, or from 700 aa to 778 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT
TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA
TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA
WYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT
KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
YREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST

EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHY VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW LKAKLMPQLPG (SEQ ID NO:64); and has a length of 778 amino acids. Such a polytope can include T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS2-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, and NS4b-10 in Fig. 13B and Fig. 15A-15N.

[00323] As another example, the heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 25 amino acids (aa) to 1985 aa (e.g., from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 500 aa, from 500 aa to 750 aa, from 750 aa to 1000 aa, from 1000 aa to 1500 aa, or from 1500 aa to 1985 aa) of the following amino acid sequence:

APITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVSTAAQTFLATCINGVCWTV YHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQGARSLTPCTCGSSDLYLVT RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAA YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYG KFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSV LCECYDAGCAWYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHID AHFLSQTKQSGENLPYLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPT PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAYCL STGCVVIVGRIVLSGKPAIIPDREVLYREFDEMEECSQHLPYIEQGMMLAEQFKQ KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG NPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL VVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL

MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
TTDNLKCPCQVPSPEFFTELDGVRLHRFAPPCKPLLREEVSFRVGLHEYPVGSQL
PCEPEPDVAVLTSMLTDPSHITAEAAGRRLARGSPPSVASSSASQLSAPSLKATCT
ANHDSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVVHGCPLPPPQSPPVPPP
RKKRTVVLTESTVSTALAELATKSFGSSSTSGITGDNTTTSSEPAPSGCPPDSDAE
SYSSMPPLEGEPGDPDLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAE
EQKLPINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSHYQDVLKEV
KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
KDLLEDSVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
SDIRTEEAIYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCGYRRCRASGVL
TTSCGNTLTCYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
FTEAMTRYSAPPGDPPQPEYDLELITSCSSNVSVAHDGAGKRVYYLTRDPTTPLA
RAAWETARHTPVNSWLGNIIMFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
YGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRAWRHR
ARSVRARLLSRGGRAAICGKYLFNWAVRTKLKLTPIAAAGQLDLSGWFTAGYS
GGDIYHSVSHARPRWFWFCLLLLAAGVGIYLLPNR (SEQ ID NO:13).

[00324] In some cases, the heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

APITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVSTAAQTFLATCINGVCWTV
YHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQGARSLTPCTCGSSDLYLVT
RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAA
YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYG
KFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV

ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSV
LCECYDAGCAWYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHID
AHFLSQTKQSGENLPYLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPT
PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAYCL
STGCVVIVGRIVLSGKPAIIPDREVLYREFDEMEECSQHLPYIEQGMMLAEQFKQ
KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
NPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
VVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL
MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
TTDNLKCPCQVPSPEFFTELDGVRLHRFAPPCKPLLREEVSFRVGLHEYPVGSQL
PCEPEPDVAVLTSMLTDPSHITAEAAGRRLARGSPPSVASSSASQLSAPSLKATCT
ANHDSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVVHGCPLPPPQSPPVPPP
RKKRTVVLTESTVSTALAELATKSFGSSSTSGITGDNTTTSSEPAPSGCPPDSDAE
SYSSMPPLEGEPGDPDLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAE
EQKLPINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSHYQDVLKEV
KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
KDLLEDSVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
SDIRTEEAIYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCGYRRCRASGVL
TTSCGNTLTCYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
FTEAMTRYSAPPGDPPQPEYDLELITSCSSNVSVAHDGAGKRVYYLTRDPTTPLA
RAAWETARHTPVNSWLGNIIMFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
YGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRAWRHR
ARSVRARLLSRGGRAAICGKYLFNWAVRTKLKLTPIAAAGQLDLSGWFTAGYS
GGDIYHSVSHARPRWFWFCLLLLAAGVGIYLLPNR (SEQ ID NO:13); and has a length of 1985 amino acids. Such a polytope can include T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12,

NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, NS4b-10, NS5a-1, NS5a-2, NS5b-1, NS5b-2 in Fig. 13A-13B and Fig. 15A-15N.

Additional T-cell epitopes

[00325] As discussed above, an E1/E2 a heterodimeric polypeptide of the present disclosure includes: a) an HCV E2 polypeptide; and b) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide). The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein.

[00326] Thus, in some cases, a variant HCV E1 polypeptide of an E1/E2 heterodimer of the present disclosure includes: a) an HCV E1 polypeptide; and b) a heterologous polypeptide that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein.

Additional T-cell epitopes

[00327] As discussed above, an E1/E2 a heterodimeric polypeptide of the present disclosure includes: a) an HCV E1 polypeptide; and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide). The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In

some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein.

[00328] Thus, in some cases, a variant HCV polypeptide of an E1/E2 heterodimer of the present disclosure includes: a) an HCV E2 polypeptide; and b) a heterologous polypeptide that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein.

[00329] A T helper tetanus toxin epitope or other bacterial T-cell epitope could be fused (e.g., by recombinant expression) or chemically conjugated to the HCV polytope/E2 fusion protein and/or to the HCV polytope E1 fusion protein of an E1/E2 heterodimer of the present disclosure to further enhance both T and B cell responses to both the HCV polytope and E1/E2 moieties. Alternatively, the whole or part of the detoxified toxin ("toxoid") could be fused (e.g., by recombinant expression) or chemically conjugated to the HCV polytope/E1E2 protein, wherein specific amino acids of the toxins are mutated to render the toxins inactive, thereby generating toxoids. Methods of generating toxoids are well known in the art. Examples of bacterial epitopes include the use of diphtheria toxoid, meningococcal outer membrane protein, or mutant diphtheria protein CRM197 (see, e.g.: http://www(dot)medscape(dot)com/viewarticle/431127)

[00330] In some cases, a suitable tetanus toxoid polypeptide comprises the amino acid sequence QYIKANSKFIGIFE (SEQ ID NO:14). In some cases, a suitable tetanus toxoid polypeptide comprises the amino acid sequence QYIKANSKFIGITE (SEQ ID NO:65).

[00331] In some cases, a heterologous polypeptide can comprise cholera toxin (or toxoid) epitope. In some cases, a suitable heterologous polypeptide comprising a cholera toxoid epitope comprises a fragment of cholera toxin-B subunit (CT-B), e.g., a fragment of from 5 amino acids to 25 amino acids, or from 25 amino acids to 50 amino acids, of the following amino acid sequence: MIKLKFGVFF TVLLSSAYAH GTPQNITDLC AEYHNTQIHT LNDKIFSYTE SLAGKREMAI ITFKNGATFQ VEVPGSQHID SQKKAIERMK DTLRIAYLTE AKVEKLCVWN NKTPHAIAAI SMAN (SEQ ID NO:15).

[00332] In some cases, a heterologous polypeptide can comprise a tetanus toxin (or toxoid) T-cell epitope. In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell

epitope comprises the amino acid sequence: ILMQYIKANSKFIGI (SEQ ID NO:16); and has a length of from 15 amino acids to 20 amino acids. In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: VNNESSE (SEQ ID NO:17). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: PGINGKAIHLVNNESSE (SEQ ID NO:18). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: PNRDIL (SEQ ID NO:19). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: FIGITEL (SEQ ID NO:20). In some cases, a suitable tetanus toxin T-cell epitope comprises the amino acid sequence: SYFPSV (SEQ ID NO:21). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: NSVDDALINSTKIYSYFPSV (SEQ ID NO:22). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: IDKISDVSTIVPYIGPALNI (SEQ ID NO:23).

[00333] In some cases, a heterologous polypeptide can comprise a diphtheria toxin T-cell epitope In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: QSIALSSLMVAQAIP (SEQ ID NO:24); and has a length of from 15 amino acids to 20 amino acids. In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: PVFAGANYAAWAVNVAQVI (SEQ ID NO:25). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: VHHNTEEIVAQSIALSSLMV (SEQ ID NO:26). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: QSIALSSLMVAQAIPLVGEL (SEQ ID NO:66). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: VDIGFAAYNFVESIINLFQV (SEQ ID NO:67). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: QGESGHDIKITAENTPLPIA (SEQ ID NO:68). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence: GVLLPTIPGKLDVNKSKTHI (SEQ ID NO:69). In some cases, a suitable heterologous polypeptide comprising a diphtheria toxin T-cell epitope comprises the amino acid sequence of CRM197 (see, e.g., Giannini et al. (1984) *Nucl. Acids. Res.* 12:4063). The amino acid sequence of CRM197 is provided above.

[00334] In some cases, a heterologous polypeptide can comprise a tetanus toxin T-cell epitope and a diphtheria toxin T-cell epitope. In some of these cases, the heterologous polypeptide can

comprise the amino acid sequence: IMQYIKANSKFIGIQSIALSSLMVAQ (SEQ ID NO:28); and can have a length of from 26 amino acids to 30 amino acids.

E2

[00335] An E2 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure can have a length of from about 200 amino acids (aa) to about 250 aa, from about 250 aa to about 275 aa, from about 275 aa to about 300 aa, from about 300 aa to about 325 aa, from about 325 aa to about 350 aa, or from about 350 aa to about 365 aa. In some cases, an E2 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure is a full-length HCV E2 polypeptide. In some cases, an E2 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure is an HCV E2 ectodomain polypeptide.

[00336] In FIG. 1A-AC, the amino acid sequence of E2 is amino acid 384 to amino acid 746. In FIG. 2A-2B, the amino acid sequence of E2 is amino acid 384 to amino acid 751. In FIG. 3A-3C, the amino acid sequence of E2 is amino acid 385 to amino acid 754. In FIG. 4A-4B, the amino acid sequence of E2 is amino acid 384 to amino acid 750. As used herein, an "E2 polypeptide" includes a precursor E2 protein, including the signal sequence; includes a mature E2 polypeptide which lacks this sequence; and includes an E2 polypeptide with a heterologous signal sequence. An E2 polypeptide can include a C-terminal membrane anchor sequence which occurs at approximately amino acid positions 715-730 and may extend as far as approximately amino acid residue 746 (see, Lin et al., J. Virol. (1994) 68:5063-5073).

[00337] In some cases, a E2 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure lacks a portion of its C-terminal region, e.g., from about amino acid 715 to the C-terminus; from about amino acid 625 to the C-terminus; from about amino acid 661 to the C-terminus; from about amino acid 655 to the C-terminus; from about amino acid 500 to the C-terminus, where the amino acid numbering is with reference to the numbering in FIG. 1A-1C. See, e.g., U.S. Patent No. 6,521,423.

[00338] An E2 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%,at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, or FIG. 4A-4B.

[00339] An E2 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about

25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1 can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence identified as 1A and depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1B can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence identified as 1B and depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1C can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence identified as 1C and depicted in FIG. 1A-1C.

[00340] An E2 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in

FIG. 2A-2C. For example, an E2 polypeptide can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence depicted in FIG. 2A-2C. For example, an E2 polypeptide of genotype 2A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-751 of the "consensus" amino acid sequence depicted in FIG. 2A-2C. For example, an E2 polypeptide of genotype 2B can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-751 of the "consensus" amino acid sequence depicted in FIG. 2A-2C.

[00341] An E2 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3 can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of an amino acid sequence depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at

least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of an amino acid sequence identified as 3A and depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3B can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of the amino acid sequence identified as 3B and depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3K can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of the amino acid sequence identified as 3K and depicted in FIG. 3A-3C.

[00342] An E2 polypeptide suitable for inclusion in an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence of the E2 polypeptide depicted in FIG. 4A-4B. For example, an E2 polypeptide of genotype 7A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-750 of the amino acid sequence depicted in FIG. 4A-4B.

Additional polypeptides

[00343] In any of the above-described embodiments, one or both of the polypeptide chains of the E1/E2 heterodimer can include one or more additional polypeptides. For example, in some cases, the variant E1 polypeptide or the E2 polypeptide can include an Ig Fc polypeptide at the C-terminus of the variant E1 polypeptide or the E2 polypeptide. As another example, in some cases, the variant E1 polypeptide or the E2 polypeptide can include an Ig Fc polypeptide at the N-terminus of the variant E1 polypeptide or the E2 polypeptide. Ig Fc polypeptides are known in the art, and are described elsewhere herein.

IC. E1E2 heterodimers comprising a variant HCV E1 and a variant HCV E2

[00344] The present disclosure provides an E1/E2 heterodimer, where the E1/E2 heterodimer includes both a variant E1 polypeptide and a variant E2 polypeptide.

[00345] Thus, in some cases, a heterodimeric polypeptide of the present disclosure includes: a) a variant HCV E1 polypeptide comprising: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide); and b) a variant HCV E2 polypeptide comprising: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide that comprises one or more T-cell epitopes (e.g., one or more T cell epitopes present in an HCV polypeptide other than an HCV E1 polypeptide or an HCV E2 polypeptide). The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein. In some cases, a variant HCV E2 and a variant HCV E1 polypeptide of an E1/E2 heterodimer of the present disclosure includes: 1) a) an HCV E2 polypeptide; and b) a heterologous polypeptide that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein; and 2) a) an HCV E1 polypeptide; and b) a heterologous polypeptide that comprises one or more T-cell epitopes, where the one or more T-cell epitopes are T-cell epitopes present in: i) one or more of an HCV NS3 polypeptide, an HCV NS2 polypeptide, an HCV NS4A polypeptide, an HCV NS4B polypeptide, an HCV NS5A polypeptide, an HCV NS5B polypeptide, an HCV core polypeptide, and an HCV p7 polypeptide; and ii) one or more of cholera toxin or toxoid, tetanus toxin or toxoid, diphtheria toxin or toxoid, and a meningococcal outer membrane protein.

[00346] In some cases, a variant E2 polypeptide present in an E1/E2 heterodimer of the present disclosure comprises, in order from N-terminus to C-terminus: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes. In some cases, a variant HCV E2 polypeptide present in an E1/E2 heterodimer of the present disclosure comprises, in

order from N-terminus to C-terminus: i) a heterologous polypeptide comprising one or more T cell epitopes; and ii) an HCV E2 polypeptide. In some cases, a variant E1 polypeptide present in an E1/E2 heterodimer of the present disclosure comprises, in order from N-terminus to C-terminus: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes. In some cases, a variant HCV E1 polypeptide present in an E1/E2 heterodimer of the present disclosure comprises, in order from N-terminus to C-terminus: i) a heterologous polypeptide comprising one or more T cell epitopes; and ii) an HCV E1 polypeptide. In some cases, both the variant E1 and the variant E2 polypeptide include the heterologous polypeptide at the N-terminus of the E1 and E2 polypeptides. In some cases, both the variant E1 and the variant E2 polypeptide include the heterologous polypeptide at the C-terminus of the E1 and E2 polypeptides. In some cases, the variant E1 polypeptide comprises the heterologous polypeptide at the N-terminus of the E1 polypeptide; and the variant E2 polypeptide comprises the heterologous polypeptide at the C-terminus of the E2 polypeptide. In some cases, the variant E1 polypeptide comprises the heterologous polypeptide at the C-terminus of the E1 polypeptide; and the variant E2 polypeptide comprises the heterologous polypeptide at the N-terminus of the E2 polypeptide.

Variant E1

[00347] As noted above, a variant E1 polypeptide of an HCV E1/E2 heterodimer of the present disclosure comprises: i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes (e.g., one or more T-cell epitopes not present in an HCV E1 or an HCV E2 polypeptide; e.g., one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 or an HCV E2 polypeptide). In some cases, the variant HCV E1 polypeptide comprises, in order from amino terminus (N-terminus) to carboxyl terminus (C-terminus): i) an HCV E1 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes. In some cases, the variant HCV E1 polypeptide comprises, in order from N-terminus to C-terminus: i) a heterologous polypeptide comprising one or more T cell epitopes; and ii) an HCV E1 polypeptide.

E1

[00348] An HCV E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can have a length of from about 150 amino acids (aa) to about 175 aa, from about 175 aa to about 195 aa, from about 131 aa to about 175 aa, or from about 175 aa to about 193 aa. In some cases, an E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an HCV E1/E2 heterodimer of the present disclosure is a full-length HCV E1 polypeptide. In some cases, an E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an HCV E1/E2 heterodimer of the present disclosure is an HCV E1 ectodomain polypeptide.

[00349] In FIG. 1A-1C, the amino acid sequence of E1 is amino acid 192 to amino acid 383. In FIG. 2A-2C, the amino acid sequence of E1 is amino acid 192 to amino acid 383. In FIG. 3A-3C, the amino acid sequence of E1 is amino acid 192 to amino acid 384. In FIG. 4A-4B, the amino acid sequence of E1 is amino acid 192 to amino acid 383. Amino acids at around 170 through approximately 191 serve as a signal sequence for E1. As used herein, "E1 polypeptide" includes a precursor E1 protein, including the signal sequence; includes a mature E1 polypeptide which lacks this sequence; and includes an E1 polypeptide with a heterologous signal sequence. An E1 polypeptide can include a C-terminal membrane anchor sequence which occurs at approximately amino acid positions 360-383 (see, e.g., WO 96/04301). In some cases, a suitable E1 polypeptide lacks a C-terminal portion that includes a transmembrane region. For example, in some cases, a suitable E1 polypeptide lacks the C-terminal portion from amino acid 330 to amino acid 384, or from amino acid 360 to amino acid 384. E1 polypeptides can be an E1 polypeptide of any genotype, subtype or isolate of HCV. E1 polypeptides of genotype 1 and E1 polypeptides of genotype 3 are included in an E1/E2 heterodimer of the present disclosure.

[00350] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, or FIG. 4A-4B.

[00351] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 1A-1C. For example, an E1 polypeptide of genotype 1A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 1A and depicted in FIG. 1A-1C. For example, an E1 polypeptide of genotype 1B can comprise an amino

acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 1B and depicted in FIG. 1A-1C. For example, an E1 polypeptide of genotype 1C can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 1C and depicted in FIG. 1A-1C.

[00352] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 2A-2C. For example, an E1 polypeptide of genotype 2A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 2A and depicted in FIG. 2A-2C. For example, an E1 polypeptide of genotype 2B can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of an amino acid sequence identified as 2B and depicted in FIG. 2A-2C.

[00353] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%,

at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the consensus E1 polypeptide amino acid sequence depicted in FIG. 3A-3C.

[00354] An E1 polypeptide suitable for inclusion in a variant E1 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E1 polypeptide depicted in FIG. 4A-4B. For example, an E1 polypeptide of genotype 7A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 192-383 of the amino acid sequence depicted in FIG. 4A-4B.

Variant E2

[00355] As noted above, a variant E2 polypeptide of an HCV E1/E2 heterodimer of the present disclosure comprises: i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes (e.g., one or more T-cell epitopes not present in an HCV E1 or an HCV E2 polypeptide; e.g., one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 or an HCV E2 polypeptide). In some cases, the variant HCV E2 polypeptide comprises, in order from amino terminus (N-terminus) to carboxyl terminus (C-terminus): i) an HCV E2 polypeptide; and ii) a heterologous polypeptide comprising one or more T cell epitopes. In some cases, the variant HCV E2 polypeptide comprises, in order from N-terminus to C-terminus: i) a heterologous polypeptide comprising one or more T cell epitopes; and ii) an HCV E2 polypeptide.

[00356] In some cases, a variant E2 polypeptide of an HCV E1/E2 heterodimer of the present disclosure comprises from 1 to 10 amino acids at the N-terminus of the variant E2 polypeptide, which 1 to 10 amino acids are part of a cleavable linker that remains following cleavage of a polyprotein precursor, as described below. For example, where the cleavable linker comprises the amino acid sequence LEVLFQGP (SEQ ID NO:5), the variant E2 polypeptide can comprise Gly-Pro residues at the N-terminus of the polypeptide, e.g., as depicted in FIG. 5A.

E2

[00357] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can have a length of from about 200 amino acids (aa) to about 250 aa, from about 250 aa to about 275 aa, from about 275 aa to about 300 aa, from about 300 aa to about 325 aa, from about 325 aa to about 350 aa, or from about 350 aa to about 365 aa. In some cases, an E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an HCV E1/E2 heterodimer of the present disclosure is a full-length HCV E1 polypeptide. In some cases, an E2 polypeptide suitable for inclusion in a variant E1 polypeptide of an HCV E1/E2 heterodimer of the present disclosure is an HCV E2 ectodomain polypeptide.

[00358] In FIG. 1A-AC, the amino acid sequence of E2 is amino acid 384 to amino acid 746. In FIG. 2A-2B, the amino acid sequence of E2 is amino acid 384 to amino acid 751. In FIG. 3A-3C, the amino acid sequence of E2 is amino acid 385 to amino acid 754. In FIG. 4A-4B, the amino acid sequence of E2 is amino acid 384 to amino acid 750. As used herein, an "E2 polypeptide" includes a precursor E2 protein, including the signal sequence; includes a mature E2 polypeptide which lacks this sequence; and includes an E2 polypeptide with a heterologous signal sequence. An E2 polypeptide can include a C-terminal membrane anchor sequence which occurs at approximately amino acid positions 715-730 and may extend as far as approximately amino acid residue 746 (see, Lin et al., J. Virol. (1994) 68:5063-5073).

[00359] In some cases, a E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure lacks a portion of its C-terminal region, e.g., from about amino acid 715 to the C-terminus; from about amino acid 625 to the C-terminus; from about amino acid 661 to the C-terminus; from about amino acid 655 to the C-terminus; from about amino acid 500 to the C-terminus, where the amino acid numbering is with reference to the numbering in FIG. 1A-1C. See, e.g., U.S. Patent No. 6,521,423.

[00360] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%,at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, or FIG. 4A-4B.

[00361] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at

least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1 can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence identified as 1A and depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1B can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence identified as 1B and depicted in FIG. 1A-1C. For example, an E2 polypeptide of genotype 1C can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence identified as 1C and depicted in FIG. 1A-1C.

[00362] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 2A-2C. For example, an E2 polypeptide can comprise an amino

acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-746 of an amino acid sequence depicted in FIG. 2A-2C. For example, an E2 polypeptide of genotype 2A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-751 of the "consensus" amino acid sequence depicted in FIG. 2A-2C. For example, an E2 polypeptide of genotype 2B can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-751 of the "consensus" amino acid sequence depicted in FIG. 2A-2C.

[00363] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an E2 polypeptide depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3 can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of an amino acid sequence depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids

385-754 of an amino acid sequence identified as 3A and depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3B can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of the amino acid sequence identified as 3B and depicted in FIG. 3A-3C. For example, an E2 polypeptide of genotype 3K can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 385-754 of the amino acid sequence identified as 3K and depicted in FIG. 3A-3C.

[00364] An E2 polypeptide suitable for inclusion in a variant E2 polypeptide of an E1/E2 heterodimer of the present disclosure can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the amino acid sequence of the E2 polypeptide depicted in FIG. 4A-4B. For example, an E2 polypeptide of genotype 7A can comprise an amino acid sequence having having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 384-750 of the amino acid sequence depicted in FIG. 4A-4B.

Heterologous polypeptide

[00365] As noted above, in some embodiments, an E1/E2 heterodimer of the present disclosure comprises: a) a variant E1 polypeptide comprising: i) an HCV E1 polypeptide; and 2) a heterologous polypeptide comprising one or more T cell epitopes (e.g., one or more T-cell epitopes not present in an HCV E1 or an HCV E2 polypeptide; e.g., one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 or an HCV E2 polypeptide); and b) a variant E2 polypeptide comprising: i) an HCV E2 polypeptide; and 2) a heterologous polypeptide comprising one or more T cell epitopes (e.g., one or more T-cell epitopes not present

in an HCV E1 or an HCV E2 polypeptide; e.g., one or more T-cell epitopes present in an HCV polypeptide other than an HCV E1 or an HCV E2 polypeptide).

[00366] In some cases, the heterologous polypeptide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or more than 10 (e.g., from 10 to 15, from 15 to 20, from 20 to 25, or from 25 to 30, or more than 30), T cell epitopes. T-cell epitopes are epitopes that, when presented with a major histocompatibility complex (MHC) (e.g., a human leukocyte antigen (HLA)) Class I or MHC Class II molecule, are recognized and bound by a T-cell receptor (TCR) present on a T cell surface. T-cell epitopes include epitopes recognized by cytotoxic T cells (e.g., $CD8^+$ T cells), and epitopes recognized by helper T cells (e.g., $CD4^+$ T cells).

[00367] The one or more T-cell epitopes can include one or more T-cell epitopes present in: a) an HCV NS3 polypeptide; b) an HCV NS2 polypeptide; c) an HCV NS4A polypeptide; d) an HCV NS4B polypeptide; e) an HCV NS5A polypeptide; f) an HCV NS5B polypeptide; g) an HCV core polypeptide; or h) an HCV p7 polypeptide. In some cases, the one or more T-cell epitopes are T-cell epitopes present in an HCV NS3 polypeptide. In some cases, the heterologous polypeptide further comprises one or more T cell epitopes present in: a) cholera toxin or toxoid; and/or b) tetanus toxin or toxoid; and/or c) diphtheria toxin or toxoid; and/or d) a meningococcal outer membrane protein. Other examples of strong T helper epitopes are diphtheria toxoid, tetanus toxoid, meningococcal outer membrane protein, or mutant diphtheria protein CRM197 (see, e.g.: http://www(dot)medscape(dot)com/viewarticle/431127).

[00368] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS3 T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS3 T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS3 T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS3 T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS3 $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS3 $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS3 $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS3 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS3 $CD4^+$ T cell epitope and at least one HCV-NS3 $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS3 $CD4^+$ T-cell epitopes and 2 or

more HCV-NS3 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS3 $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS3 $CD8^+$ T-cell epitopes.

[00369] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS2 T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS2 T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS2 T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS2 T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS2 $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS2 $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS2 $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS2 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS2 $CD4^+$ T cell epitope and at least one HCV-NS2 $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS2 $CD4^+$ T-cell epitopes and 2 or more HCV-NS2 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS2 $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS2 $CD8^+$ T-cell epitopes.

[00370] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS4A T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS4A T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS4A T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS4A T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS4A $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS4A $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS4A $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS4A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS4A $CD4^+$ T cell epitope and at least one HCV-NS4A $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS4A $CD4^+$ T-cell epitopes and 2 or more HCV-NS4A $CD8^+$ T-cell epitopes. In some cases, the heterologous

polypeptide comprises 2, 3, 4, or 5 HCV-NS4A $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS4A $CD8^+$ T-cell epitopes.

[00371] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS5A T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5A T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS5A T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS5A T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5A $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5A $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5A $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS5A $CD4^+$ T cell epitope and at least one HCV-NS5A $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS5A $CD4^+$ T-cell epitopes and 2 or more HCV-NS5A $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS5A $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS5A $CD8^+$ T-cell epitopes.

[00372] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-NS5B T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5B T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-NS5B T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-NS5B T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5B $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5B $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-NS5B $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-NS5B $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-NS5B $CD4^+$ T cell epitope and at least one HCV-NS5B $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-NS5B $CD4^+$ T-cell

epitopes and 2 or more HCV-NS5B $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-NS5B $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-NS5B $CD8^+$ T-cell epitopes.

[00373] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-core T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-core T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-core T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-core T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-core $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-core $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-core $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-core $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-core $CD4^+$ T cell epitope and at least one HCV-core $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-core $CD4^+$ T-cell epitopes and 2 or more HCV-core $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-core $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-core $CD8^+$ T-cell epitopes.

[00374] In some cases, the heterologous polypeptide comprises a single T-cell epitope. In some cases, the heterologous polypeptide comprises a single HCV-p7 T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more T-cell epitopes. In some cases, the heterologous polypeptide comprises 2 or more HCV-p7 T-cell epitopes. In some cases, the heterologous polypeptide comprises 3 or more HCV-p7 T-cell epitopes. In some cases, the heterologous polypeptide comprises 4 or more HCV-p7 T-cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-p7 $CD4^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-core $CD4^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises one or more HCV $CD8^+$ T cell epitopes. In some cases, the heterologous polypeptide comprises a single HCV-p7 $CD8^+$ T-cell epitope. In some cases, the heterologous polypeptide comprises 2 or more HCV-p7 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope. In some cases, the heterologous polypeptide comprises at least one HCV-p7 $CD4^+$ T cell epitope and at least one HCV-p7 $CD8^+$ T cell epitope. In some cases, heterologous polypeptide comprises 2 or more HCV-p7 $CD4^+$ T-cell epitopes and 2 or more

HCV-p7 $CD8^+$ T-cell epitopes. In some cases, the heterologous polypeptide comprises 2, 3, 4, or 5 HCV-p7 $CD4^+$ T-cell epitopes and 2, 3, 4, or 5 HCV-p7 $CD8^+$ T-cell epitopes.

[00375] In some cases, the heterologous polypeptide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, or 63, of the T-cell epitopes set out in Fig. 13A-13B. In some cases, the heterologous polypeptide comprises from 1 to 3, from 3 to 5, from 5 to 10, from 10 to 15, from 15 to 20, from 20 to 25, or from 25 to 30 of the T-cell epitopes set out in Fig. 13A-13B. For example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, and NS3-11 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-7, and NS2-8 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, NS3-5, and NS3-11 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated Core-1, Core-2, Core-3, Core-4, Core-5, Core-6, Core-7, Core-8, Core-9, Core-10, Core-11, Core-12, Core-13, Core-14, Core-16, Core-17, Core-18, Core-19, Core-20, Core-21, and Core-22 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-4, NS2-5, NS2-6, NS2-7, NS2-8, NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, and

NS4b-10 in Fig. 13A-13B and Fig. 15A-15N. As another example, in some cases, the heterologous polypeptide comprises the T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, NS4b-10, NS5a-1, NS5a-2, NS5b-1, and NS5b-2 in Fig. 13A-13B and Fig. 15A-15N. In some cases, the T-cell epitopes are contiguous. In some cases, any two T-cell epitopes are separated by linkers (e.g., a linker having a length of from 1 amino acid to about 50 amino acids, e.g., from 1 amino acid to 5 amino acids (aa), from 5 aa to 10 aa, from 10 aa to 15 aa, from 15 aa to 20 aa, from 20 aa to 25 aa, from 25 aa to 30 aa, from 30 aa to 40 aa, or from 40 aa to 50 aa).

[00376] In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1 and 2. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1 and 3. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1, 2, and 3. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1, 2, 3, and 7. In some cases, the heterologous polypeptide comprises at least one HCV $CD4^+$ T cell epitope and at least one HCV $CD8^+$ T cell epitope, where epitopes are conserved among HCV genotypes 1-7.

[00377] The heterologous polypeptide can have a length of from about 10 amino acids to about 2000 amino acids; e.g., the heterologous polypeptide can have a length of from 10 amino acids (aa) to 15 aa, from 15 aa to 20 aa, from 20 aa to 25 aa, from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 800 aa. The heterologous polypeptide can have a length of from about 25 amino acids to about 2000 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 500 aa, from 500 aa to 600 aa, from 600 aa to 700 aa, from 700 aa to 800 aa, from 800 aa to 900 aa, from 900 aa to 1000 aa, from 1000 aa to 1100 aa, from 1100 aa to 1200 aa, from 1200 aa to 1300 aa, from 1300 aa to 1400 aa, from 1400 aa to 1500 aa, from 1500 aa to 1600 aa, from 1600 aa to

1700 aa, from 1700 aa to 1800 aa, from 1800 aa to 1900 aa, or from 1900 aa to 2000 aa. The heterologous polypeptide can have a length of from about 25 amino acids to about 3000 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 500 aa, from 500 aa to 600 aa, from 600 aa to 700 aa, from 700 aa to 800 aa, from 800 aa to 900 aa, from 900 aa to 1000 aa, from 1000 aa to 1100 aa, from 1100 aa to 1200 aa, from 1200 aa to 1300 aa, from 1300 aa to 1400 aa, from 1400 aa to 1500 aa, from 1500 aa to 1600 aa, from 1600 aa to 1700 aa, from 1700 aa to 1800 aa, from 1800 aa to 1900 aa, from 1900 aa to 2000 aa, from 2000 aa to 2250 aa, from 2250 aa to 2500 aa, from 2500 aa to 2750 aa, or from 2750 aa to 3000 aa.

[00378] The heterologous polypeptide can have a length of from about 25 amino acids to about 800 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 800 aa. The heterologous polypeptide can have a length of from about 25 amino acids to about 400 amino acids, e.g., from about 25 amino acids (aa) to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, or from 350 aa to 400 aa. The heterologous polypeptide can have a length of 25 amino acids (aa), 26 aa, 27 aa, 28 aa, 29 aa, 30 aa, 31 aa, 32 aa, 33 aa, 34 aa, 35 aa, 36 aa, 37 aa, 38 aa, 39 aa, 40 aa, 41 aa, 42 aa, 43 aa, 44 aa, 45 aa, 46 aa, 47 aa, 48 aa, 49 aa, or 50 aa. The heterologous polypeptide can have a length of from about 100 amino acids (aa) to 800 aa, e.g., from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 800 aa. The heterologous polypeptide can have a length of from 25 aa to 30 aa. The heterologous polypeptide can have a length of from 30 aa to 40 aa. The heterologous polypeptide can have a length of from 40 aa to 50 aa. The heterologous polypeptide can have a length of from 50 aa to 60 aa (e.g., 50 aa, 51 aa, 52, aa, 53 aa, 54 aa, 55 aa, 56 aa, 57 aa, 58 aa, 59 aa, or 60 aa). The heterologous polypeptide can have a length of from 60 aa to 70 aa. The heterologous polypeptide can have a length of from 65 aa to 75 aa (e.g., 65, 66, 67, 68, 69, 70, 71, 72, 7, 74, or 75 aa). The heterologous polypeptide can have a length of 70 aa. The heterologous polypeptide can have a length of from 70 aa to 80 aa. The heterologous polypeptide can have a length of from 80 aa to 90 aa. The heterologous polypeptide can have a length of from 90 aa to 100 aa. The heterologous polypeptide can have a length of from 100 aa to

105 aa (e.g., 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, or 110 aa). The heterologous polypeptide can have a length of 100 aa. The heterologous polypeptide can have a length of from 10 amino acids (aa) to 50 aa; e.g., from 10 aa to 15 aa, from 15 aa to 20 aa, from 20 aa to 25 aa, from 25 aa to 30 aa, from 30 aa to 35 aa, from 35 aa to 40 aa, from 40 aa to 45 aa, or from 45 aa to 50 aa. The heterologous polypeptide can have a length of from 10 amino acids (aa) to 20 aa, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 aa.

HCV NS3 T-cell epitopes

[00379] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS3 polypeptide. Examples of T-cell epitopes present in NS3 polypeptides are depicted in **FIG. 15A-15N, FIG. 13B, and FIG. 14A-14B**.

[00380] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1); and has a length of from 25 aa to 35 aa (e.g., 25 aa, 26 aa, 27 aa, 28 aa, 29 aa, 30 aa, 31 aa, 32 aa, 33 aa, 34 aa, or 35 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKL (SEQ ID NO:1); and has a length of 29 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, and NS3-11 in FIG. 13B and FIG. 15A-15N.

[00381] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at

least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2); and has a length of from 45 amino acids to 60 amino acids (e.g., 45 aa, 46 aa, 47 aa, 48 aa, 49 aa, 50 aa, 51 aa, 52 aa, 53 aa, 54 aa, 55 aa, 56 aa, 57 aa, 58 aa, 59 aa, or 60 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: AIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSG (SEQ ID NO:2); and has a length of 52 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, NS3-5, and NS3-11 in FIG. 13B and FIG. 15A-15N.

[00382] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTG FTGDFDSVIDCN (SEQ ID NO:3); and has a length of from 65 amino acids to 80 amino acids (e.g., 65 aa, 66 aa, 67 aa, 68 aa, 69 aa, 70 aa, 71 aa, 72 aa, 73 aa, 74 aa, 75 aa, 76 aa, 77 aa, 78 aa, 79 aa, or 80 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: KGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTG FTGDFDSVIDCN (SEQ ID NO:3); and has a length of 70 amino acids. Such a polytope can

include NS3 T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-11, NS3-12, and NS3-13 in FIG. 13B and FIG. 15A-15N.

[00383] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4); and has a length of from 95 amino acids (aa) to 105 aa (e.g., 95 aa, 96 aa, 97 aa, 98 aa, 99 aa, 100 aa, 101 aa, 102 aa, 103 aa, 104 aa, or 105 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLVALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDF (SEQ ID NO:4); and has a length of 100 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-10, NS3-11, NS3-12, and NS3-13 in FIG. 13B and FIG. 15A-15N.

[00384] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQP RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS RNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPGCSF SIFLLALLSCLTVPASA (SEQ ID NO:9); and has a length of from 190 amino acids (aa) to 200 aa (e.g., 190 aa, 191 aa, 192 aa, 193 aa, 194 aa, 195 aa, 196 aa, 197 aa, 198 aa, 199 aa, or 200 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at

least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQP RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS RNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPGCSF SIFLLALLSCLTVPASA (SEQ ID NO:9); and has a length of 191 amino acids.

[00385] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCN (SEQ ID NO:10); and has a length of from 215 amino acids (aa) to 235 aa (e.g., 215 aa, 216 aa, 217 11, 218 aa, 219 aa, 220 aa, 221 aa, 222 aa, 223 aa, 224 aa, 225 aa, 226 aa, 227 aa, 228 aa, 229 aa, 230 aa, 231 aa, 232 aa, 233 aa, 234 aa, or 235 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCN (SEQ ID NO:10); and has a length of 228 amino acids. Such a polytope can include NS3 T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in FIG. 13B and FIG. 15A-15N.

[00386] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino

acid sequence identity to amino acids 1265-1279 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00387] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1309-1323 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00388] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1401-1415 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00389] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1402-1412 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 11 amino acids (aa) to 16 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, or 16 aa).

[00390] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%,

at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1429-1439 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 11 amino acids (aa) to 16 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, or 16 aa).

[00391] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1450-1464 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00392] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1453-1467 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00393] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1577-1591 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00394] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at

least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1306-1314 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00395] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1387-1394 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 1 amino acids (aa) to 15 amino acids (e.g., 8 aa, 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00396] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1405-1413 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00397] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1450-1458 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00398] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at

least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1457-1465 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00399] As another example, the heterologous polypeptide can comprise an HCV NS3 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1610-1618 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS3 amino acid sequence of any HCV genotype; and the HCV NS3 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV NS2 T-cell epitopes

[00400] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS2 polypeptide. Examples of T-cell epitopes present in NS2 polypeptides are depicted in **FIG. 15A-15N**, and **FIG. 13A**.

[00401] For example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 955-974 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00402] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid

sequence identity to amino acids 975-994 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00403] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 985-1004 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00404] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1015-1034 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00405] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1035-1054 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00406] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least

about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 924-933 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00407] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 961-970 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00408] As another example, the heterologous polypeptide can comprise an NS2 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 989-997 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and the NS2 T cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00409] In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 10 amino acids (aa) to 50 aa (e.g., from 10 aa to 25 aa, or from 25 aa to 50 aa) of amino acids 955-1004 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and has a length of from 10 amino acids (aa) to 25 aa, or from 25 aa to 50 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least

about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 955-1004 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 amino acid sequence of any HCV genotype; and has a length of about 50 amino acids.

[00410] In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 10 amino acids (aa) to 553 aa (e.g., from 10 aa to 25 aa, from 25 aa to 50 aa, from 50 aa to 100 aa, from 100 aa to 200 aa, from 200 aa to 300 aa, from 300 aa to 400 aa, from 400 aa to 500 aa, or from 500 aa to 553 aa) of amino acids 917-1469 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 and NS3 amino acid sequence of any HCV genotype; and has a length of from 10 amino acids (aa) to 25 aa, from 25 aa to 50 aa, from 50 aa to 100 aa, from 100 aa to 200 aa, from 200 aa to 300 aa, from 300 aa to 400 aa, from 400 aa to 500 aa, or from 500 aa to 553 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 917-1469 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS2 and NS3 amino acid sequence of any HCV genotype; and has a length of about 553 amino acids.

[00411] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 0%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LGALTGTYVYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADT (SEQ ID NO:11). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

LGALTGTYVYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADT (SEQ ID NO:11); and has a length of from 50 amino acids to 60 amino acids (e.g., 50 aa, 51 aa, 52 aa, 53 aa, 54 aa, 55 aa, 56 aa, 57 aa, 58 aa, 59 aa, or 60 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: LGALTGTYVYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADT (SEQ ID NO:11); and has a length of 50 amino acids. Such a polytope can include NS2 T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-7, and NS2-8 in FIG. 13A and FIG. 15A-15N.

HCV NS4A T-cell epitopes

[00412] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS4A polypeptide. Examples of T-cell epitopes present in NS4A polypeptides are depicted in FIG. 15A-15N and FIG. 13B.

[00413] The heterologous polypeptide can comprise an NS4A T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1683-1692 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4A amino acid sequence of any HCV genotype; and the NS4A T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV NS4B T-cell epitopes

[00414] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS4B polypeptide. Examples of T-cell epitopes present in NS4B polypeptides are depicted in FIG. 15A-15N and FIG. 13B.

[00415] As one example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about

60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1790-1801 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 12 amino acids (aa) to 20 amino acids (e.g., 12 aa, 13 aa, 14 aa, 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00416] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1792-1802 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 11 amino acids (aa) to 20 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00417] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1898-1905 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 8 amino acids (aa) to 15 amino acids (e.g., 8 aa, 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00418] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1921-1935 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00419] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about

30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1922-1941 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00420] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1928-1947 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00421] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1868-1876 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00422] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1927-1942 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 16 amino acids (aa) to 20 amino acids (e.g., 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00423] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1932-1940 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00424] As another example, the heterologous polypeptide can comprise an NS4B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1948-1962 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS4B amino acid sequence of any HCV genotype; and the NS4B T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

HCV NS5A T-cell epitopes

[00425] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS5A polypeptide. Examples of T-cell epitopes present in NS5A polypeptides are depicted in **FIG. 15A-15N** and **FIG. 13B**.

[00426] As one example, the heterologous polypeptide can comprise an NS5A T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2218-2232 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5A amino acid sequence of any HCV genotype; and the NS5A T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00427] As another example, the heterologous polypeptide can comprise an NS5A T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about

30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2309-2317 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5A amino acid sequence of any HCV genotype; and the NS5A T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV NS5B T-cell epitopes

[00428] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV NS5B polypeptide. Examples of T-cell epitopes present in NS5B polypeptides are depicted in **FIG. 15A-15N** and **FIG. 13B**.

[00429] As one example, the heterologous polypeptide can comprise an NS5B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2847-2851 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5B amino acid sequence of any HCV genotype; and the NS5B T-cell epitope can have a length of from 5 amino acids (aa) to 10 amino acids (e.g., 5 aa, 6 aa, 7 aa, 8 aa, 9 aa, or 10 aa).

[00430] As another example, the heterologous polypeptide can comprise an NS5B T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 2602-2610 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV NS5B amino acid sequence of any HCV genotype; and the NS5B T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

HCV core T-cell epitopes

[00431] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV core polypeptide. Examples of T-cell epitopes present in HCV Core polypeptides are depicted in **FIG. 15A-15N** and **FIG.13A**.

[00432] As one example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1-20 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00433] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 11-30 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00434] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 21-40 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00435] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 39-63 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and

the HCV core T-cell epitope can have a length of from 23 amino acids (aa) to 28 amino acids (e.g., 23 aa, 24 aa, 25 aa, 26 aa, 27 aa, or 28 aa).

[00436] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 47-70 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 24 amino acids (aa) to 29 amino acids (e.g., 24 aa, 25 aa, 26 aa, 27 aa, 28 aa, or 29 aa).

[00437] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 61-80 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00438] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 71-90 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00439] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 81-100 of the amino acid sequence designated

"Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00440] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 91-110 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00441] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 101-115 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00442] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 111-130 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00443] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino

acid sequence identity to amino acids 125-139 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 15 amino acids (aa) to 20 amino acids (e.g., 15 aa, 16 aa, 17 aa, 18 aa, 19 aa, or 20 aa).

[00444] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 131-150 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00445] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 151-170 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00446] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 161-180 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 20 amino acids (aa) to 25 amino acids (e.g., 20 aa, 21 aa, 22 aa, 23 aa, 24 aa, or 25 aa).

[00447] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%,

at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 35-44 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00448] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 43-51 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00449] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 51-59 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00450] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 129-137 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00451] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at

least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 131-140 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00452] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 150-158 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00453] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 154-162 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00454] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 168-176 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00455] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at

least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 177-187 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 11 amino acids (aa) to 16 amino acids (e.g., 11 aa, 12 aa, 13 aa, 14 aa, 15 aa, or 16 aa).

[00456] As another example, the heterologous polypeptide can comprise an HCV core T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 178-187 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and the HCV core T-cell epitope can have a length of from 10 amino acids (aa) to 15 amino acids (e.g., 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

[00457] In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 10 amino acids (aa) to 191 aa (e.g., from 10 aa to 25 aa, from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, or from 150 aa to 191aa) of amino acids 1-191 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and has a length of from 10 amino acids (aa) to 25 aa, from 25 aa to 50 aa, from 50 aa to 100 aa, or from 100 aa to 150 aa, or from 150 aa to 191 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 1-191 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV core amino acid sequence of any HCV genotype; and has a length of about 191 amino acids.

[00458] The heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least

about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTS ERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPS WGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLE DGVNYATGNLPG (SEQ ID NO:63); and has a length of from 171 amino acids (aa) to 180 aa (e.g., 171 aa, 172 aa, 173 aa, 174 aa, 175 aa, 176 aa, 177 aa, 178 aa, 179 aa, or 180 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTS ERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPS WGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLE DGVNYATGNLPG (SEQ ID NO:63); and has a length of 171 amino acids. Such a polytope can include core T-cell epitopes designated Core-1, Core-2, Core-3, Core-4, Core-5, Core-6, Core-7, Core-8, Core-9, Core-10, Core-11, Core-12, Core-13, Core-14, Core-16, Core-17, Core-18, Core-19, Core-20, Core-21, Core-22 in FIG. 13A and FIG. 15A-15N.

HCV p7 T-cell epitopes

[00459] In some cases, the heterologous polypeptide present in an E2 variant polypeptide of an E1/E2 heterodimer of the present disclosure includes one or more T-cell epitopes present in an HCV p7 polypeptide. Examples of T-cell epitopes present in HCV p7 polypeptides are depicted in **FIG. 15A-15N** or **FIG. 13A**.

[00460] As another example, the heterologous polypeptide can comprise an HCV p7 T cell epitope comprising an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to amino acids 803-811 of the amino acid sequence designated "Consensus" in FIG. 16A-16L, or a corresponding HCV p7 amino acid sequence of any HCV genotype; and the HCV p7 T-cell epitope can have a length of from 9 amino acids (aa) to 15 amino acids (e.g., 9 aa, 10 aa, 11 aa, 12 aa, 13 aa, 14 aa, or 15 aa).

Polytopes including HCV T-cell epitopes from more than one HCV polypeptide other than E1 and E2

[00461] As noted above, a heterologous polypeptide can include T-cell epitopes from more than one HCV polypeptide other than E1 and E2.

[00462] As one example, a heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

QASLLKVPYFVRVQGLLRICALARKMAGGHYVQMAIIKLGALTGTYVYN**A**LTP
LRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADTAACGDIINGLPVSARRGR
EILLGPADGMVSKGWRLLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS
TAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQG
ARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGS**A**GGPLLCP
AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA
HLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQA
ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIF
CHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG
DFDSVIDCN (SEQ ID NO:12); and has a length of from 550 amino acids (aa) to 560 aa (e.g., 550 aa, 551 aa, 552 aa, 553 aa, 554 aa, 555 aa, 556 aa, 557 aa, 558 aa, 559 aa, or 560 aa). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

QASLLKVPYFVRVQGLLRICALARKMAGGHYVQMAIIKLGALTGTYVYN**A**LTP
LRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADTAACGDIINGLPVSARRGR
EILLGPADGMVSKGWRLLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS
TAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQG
ARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGS**A**GGPLLCP
AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA

HLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQA ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIF CHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG DFDSVIDCN (SEQ ID NO:12); and has a length of 553 amino acids. Such a polytope can include T-cell epitopes designated NS2-1, NS2-2, NS2-3, NS2-4, NS2-5, NS2-6, NS2-7, NS2-8, NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, and NS3-13 in Fig. 13A-13B and Fig. 15A-15N. This polytope is also referred to as "TP553" (FIG. 14A-14D). In order to prevent self cleavage of the TP553 polytope (amino acids 917-1469) (FIG. 15E-G) at the NS2-NS3 junction that is mediated by the catalytic domain of the NS2 protease (amino acids 917-1040), the histidine at position 966 (H966), a critical residue for NS2 protease activity, is mutated to alanine (H966A) (FIG. 15E).

[00463] As another example, the heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 25 amino acids (aa) to 778 aa (e.g., from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 450 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 778 aa) the following amino acid sequence: LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA WYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL YREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHY

VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW LKAKLMPQLPG (SEQ ID NO:64). In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 25 amino acids (aa) to 778 aa (e.g., from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 300 aa, from 300 aa to 350 aa, from 350 aa to 400 aa, from 400 aa to 450 aa, from 450 aa to 500 aa, from 500 aa to 550 aa, from 550 aa to 600 aa, from 600 aa to 650 aa, from 650 aa to 700 aa, from 700 aa to 750 aa, or from 750 aa to 778 aa) of the following amino acid sequence:

LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA WYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL YREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHY VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW LKAKLMPQLPG (SEQ ID NO:64); and has a length of from 25 amino acids (aa) to 50 aa, from 50 aa to 100 aa, from 100 aa to 200 aa, from 200 aa to 300 aa, from 300 aa to 400 aa, from 400 aa to 500 aa, from 500 aa to 600 aa, from 600 aa to 700 aa, or from 700 aa to 778 aa. In some cases, the heterologous polypeptide comprises an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following amino acid sequence:

LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA

TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA
WYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT
KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
YREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHY
VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW
LKAKLMPQLPG (SEQ ID NO:64); and has a length of 778 amino acids. Such a polytope can include T-cell epitopes designated NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS2-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, and NS4b-10 in Fig. 13B and Fig. 15A-15N.

[00464] As another example, the heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from 25 amino acids (aa) to 1985 aa (e.g., from 25 aa to 50 aa, from 50 aa to 75 aa, from 75 aa to 100 aa, from 100 aa to 150 aa, from 150 aa to 200 aa, from 200 aa to 250 aa, from 250 aa to 500 aa, from 500 aa to 750 aa, from 750 aa to 1000 aa, from 1000 aa to 1500 aa, or from 1500 aa to 1985 aa) of the following amino acid sequence:

APITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVSTAAQTFLATCINGVCWTV
YHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQGARSLTPCTCGSSDLYLVT
RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAA
YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYG
KFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSV
LCECYDAGCAWYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHID

AHFLSQTKQSGENLPYLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPT
PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAYCL
STGCVVIVGRIVLSGKPAIIPDREVLYREFDEMEECSQHLPYIEQGMMLAEQFKQ
KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
NPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
VVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL
MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
TTDNLKCPCQVPSPEFFTELDGVRLHRFAPPCKPLLREEVSFRVGLHEYPVGSQL
PCEPEPDVAVLTSMLTDPSHITAEAAGRRLARGSPPSVASSSASQLSAPSLKATCT
ANHDSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVVHGCPLPPPQSPPVPPP
RKKRTVVLTESTVSTALAELATKSFGSSSTSGITGDNTTTSSEPAPSGCPPDSDAE
SYSSMPPLEGEPGDPDLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAE
EQKLPINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSHYQDVLKEV
KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
KDLLEDSVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
SDIRTEEAIYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCGYRRCRASGVL
TTSCGNTLTCYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
FTEAMTRYSAPPGDPPQPEYDLELITSCSSNVSVAHDGAGKRVYYLTRDPTTPLA
RAAWETARHTPVNSWLGNIIMFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
YGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRAWRHR
ARSVRARLLSRGGRAAICGKYLFNWAVRTKLKLTPIAAAGQLDLSGWFTAGYS
GGDIYHSVSHARPRWFWFCLLLLAAGVGIYLLPNR (SEQ ID NO:13).

[00465] In some cases, the heterologous polypeptide can comprise an amino acid sequence having at least about 20%, at least about 25%, at least about 30%,at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to the following

amino acid sequence:

APITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVSTAAQTFLATCINGVCWTV
YHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQGARSLTPCTCGSSDLYLVT
RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAA
YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYG
KFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELAAKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSV
LCECYDAGCAWYELTPAETTVRLRAYMNTPGLPVCQDHLEFWEGVFTGLTHID
AHFLSQTKQSGENLPYLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPT
PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAYCL
STGCVVIVGRIVLSGKPAIIPDREVLYREFDEMEECSQHLPYIEQGMMLAEQFKQ
KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
NPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
VVGVVCAAILRRHVGPGEGAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL
MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
TTDNLKCPCQVPSPEFFTELDGVRLHRFAPPCKPLLREEVSFRVGLHEYPVGSQL
PCEPEPDVAVLTSMLTDPSHITAEAAGRRLARGSPPSVASSSASQLSAPSLKATCT
ANHDSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVVHGCPLPPPQSPPVPPP
RKKRTVVLTESTVSTALAELATKSFGSSSTSGITGDNTTTSSEPAPSGCPPDSDAE
SYSSMPPLEGEPGDPDLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAE
EQKLPINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSHYQDVLKEV
KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
KDLLEDSVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
SDIRTEEAIYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCGYRRCRASGVL

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 176

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 176

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

What is Claimed is:

1. A heterodimeric polypeptide comprising:

a) a variant hepatitis C virus (HCV) E2 polypeptide comprising:

i) an HCV E2 polypeptide; and

ii) a heterologous polypeptide comprising a T-cell epitope present in an HCV protein other than E1 and E2,

wherein the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the amino acid sequence selected from: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:10, SEQ ID NO: 11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:63, and SEQ ID NO:64; and

b) an HCV E1 polypeptide.

2. A heterodimeric polypeptide comprising:

a) a variant hepatitis C virus (HCV) E1 polypeptide comprising:

i) an HCV E1 polypeptide; and

ii) a heterologous polypeptide comprising a T-cell epitope present in an HCV protein other than E1 and E2,

wherein the heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the amino acid sequence selected from: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:10, SEQ ID NO: 11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:63, and SEQ ID NO:64; and

b) an HCV E2 polypeptide.

3. A heterodimeric polypeptide comprising:

a) a variant hepatitis C virus (HCV) E1 polypeptide comprising:

i) an HCV E1 polypeptide; and

ii) a first heterologous polypeptide comprising a T-cell epitope present in an HCV protein other than E1 and E2; and

b) a variant hepatitis C virus (HCV) E2 polypeptide comprising:

i) an HCV E2 polypeptide; and

ii) a second heterologous polypeptide comprising a T-cell epitope present in an HCV protein other than E1 and E2,

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wherein the first and/or the second heterologous polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to the amino acid sequence selected from: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:10, SEQ ID NO: 11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:63, and SEQ ID NO:64.

4. The heterodimeric polypeptide of any one of claims 1-3, wherein:
a) the HCV E2 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7; and
b) the HCV E1 polypeptide is derived from an HCV of genotype 1, 2, 3, or 7.

5. The heterodimeric polypeptide of any one of claims 1-4, wherein the HCV E2 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E2 polypeptide depicted in one of FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B.

6. The heterodimeric polypeptide of any one of claims 1-5, wherein the heterologous polypeptide has a length of from about 29 amino acids to about 2000 amino acids.

7. The heterodimeric polypeptide of any one of claims 1-5, wherein the E2 polypeptide lacks a C-terminal transmembrane domain.

8. The heterodimeric polypeptide of any one of claims 1-7, wherein the E1 polypeptide lacks a C-terminal transmembrane domain.

9. The heterodimeric polypeptide of any one of claims 1-8, wherein the HCV E2 polypeptide and the HCV E1 polypeptide are derived from an HCV of the same genotype.

10. The heterodimeric polypeptide of any one of claims 1-8, wherein the modified HCV E2 polypeptide and the HCV E1 polypeptide are derived from an HCV of different genotypes.

11. The heterodimeric polypeptide of any one of claims 1-10, wherein the HCV E1 polypeptide comprises an amino acid sequence having at least 20% amino acid sequence identity to an E1 polypeptide depicted in FIG. 1A-1C, FIG. 2A-2C, FIG. 3A-3C, and FIG. 4A-4B.

12. One or more nucleic acids comprising nucleotide sequences encoding the heterodimeric polypeptide of any one of claims 1-11.

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13. The one or more nucleic acids of claim 12, wherein the nucleotide sequences are operably linked to a promoter.

14. The one or more nucleic acids of claim 12, wherein the one or more nucleic acids are one or more RNA molecules.

15. The one or more nucleic acids of claim 14, wherein the one or more RNA molecules are formulated with a liposome.

16. One or more recombinant expression vectors comprising the one or more nucleic acids of claim 12 or claim 13.

17. A genetically modified *in vitro* host cell comprising the one or more nucleic acids of claim 12 or claim 13, or the one or more recombinant vectors of claim 16.

18. The genetically modified host cell of claim 17, wherein the host cell is a eukaryotic cell.

19. The genetically modified host cell of claim 18, wherein the host cell is a mammalian cell.

20. A composition comprising the heterodimeric polypeptide of any one of claims 1-11.

21. A composition comprising the one or more nucleic acids of any one of claims 12-15 or the one or more recombinant expression vectors of claim 16.

22. Use of the heterodimeric polypeptide of any one of claims 1-11 for inducing an immune response in an individual.

23. Use of the heterodimeric polypeptide of any one of claims 1-11 to formulate a medicament for inducing an immune response in an individual.

24. Use of the one or more nucleic acids of any one of claims 12-15 or the one or more recombinant expression vectors of claim 16 for inducing an immune response in an individual.

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25. Use of the one or more nucleic acids of any one of claims 12-15 or the one or more recombinant expression vectors of claim 16 to formulate a medicament for inducing an immune response in an individual.

26. The use of any one of claims 22 to 25, wherein the use is intramuscular.

27. The use of any one of claims 22 to 25, wherein the use is subcutaneous.

28. The heterodimeric polypeptide of any one of claims 1-11 for use in inducing an immune response in an individual.

29. The heterodimeric polypeptide of any one of claims 1-11, for use to formulate a medicament for inducing an immune response in an individual.

30. The one or more nucleic acids of any one of claims 12-15 or the one or more recombinant expression vectors of claim 16, for use in inducing an immune response in an individual.

31. The one or more nucleic acids of any one of claims 12-15 or the one or more recombinant expression vectors of claim 16, for use to formulate a medicament for inducing an immune response in an individual.

32. The heterodimeric polypeptide of claim 28 or 29, wherein the use is intramuscular.

33. The one or more nucleic acids or the one or more recombinant expression vectors of claim 30 or 31, wherein the use is intramuscular.

34. The heterodimeric polypeptide of claim 28 or 29, wherein the use is subcutaneous.

35. The one or more nucleic acids or the one or more recombinant expression vectors of claim 30 or 31, wherein the use is subcutaneous.

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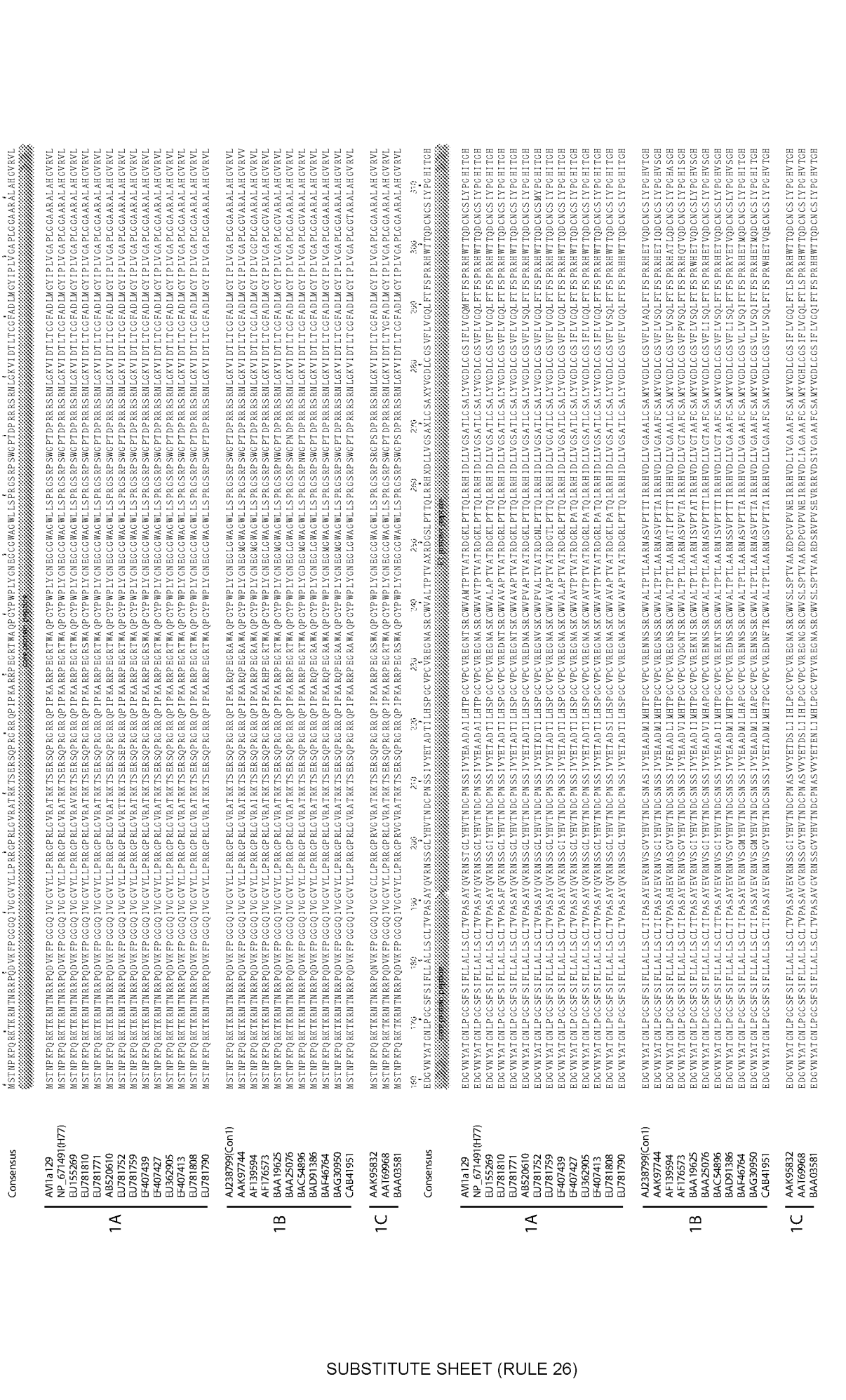

FIG. 1A

1A
1B
1C
Consensus
AVI1a129
NP_671491(H77)
EU155269
EU781810
EU781771
AB520610
EU781752
EU781759
EF407439
EF407427
EU362905
EF407413
EU781808
EU781790
AJ238799(Con1)
AAK97444
AF139594
AF176573
BAA19625
BAA25076
BAC54896
BAD91386
BAF46764
BAG30950
CAB41951
AAK95832
AAT69968
BAA03581

FIG. 1B

Consensus
1A
AVI1a129
NP_671491(H77)
EU155269
EU781810
EU781771
AB520610
EU781752
EU781759
EF407439
EF407427
EU362905
EF407413
EU781808
EU781790
1B
AJ238799(Con1)
AAK97744
AF139594
AF176573
BAA19625
BAA25076
BAC54896
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BAF46764
BAG30950
CAB41951
1C
AAK95832
AAT69968
BAA03581

FIG. 1C

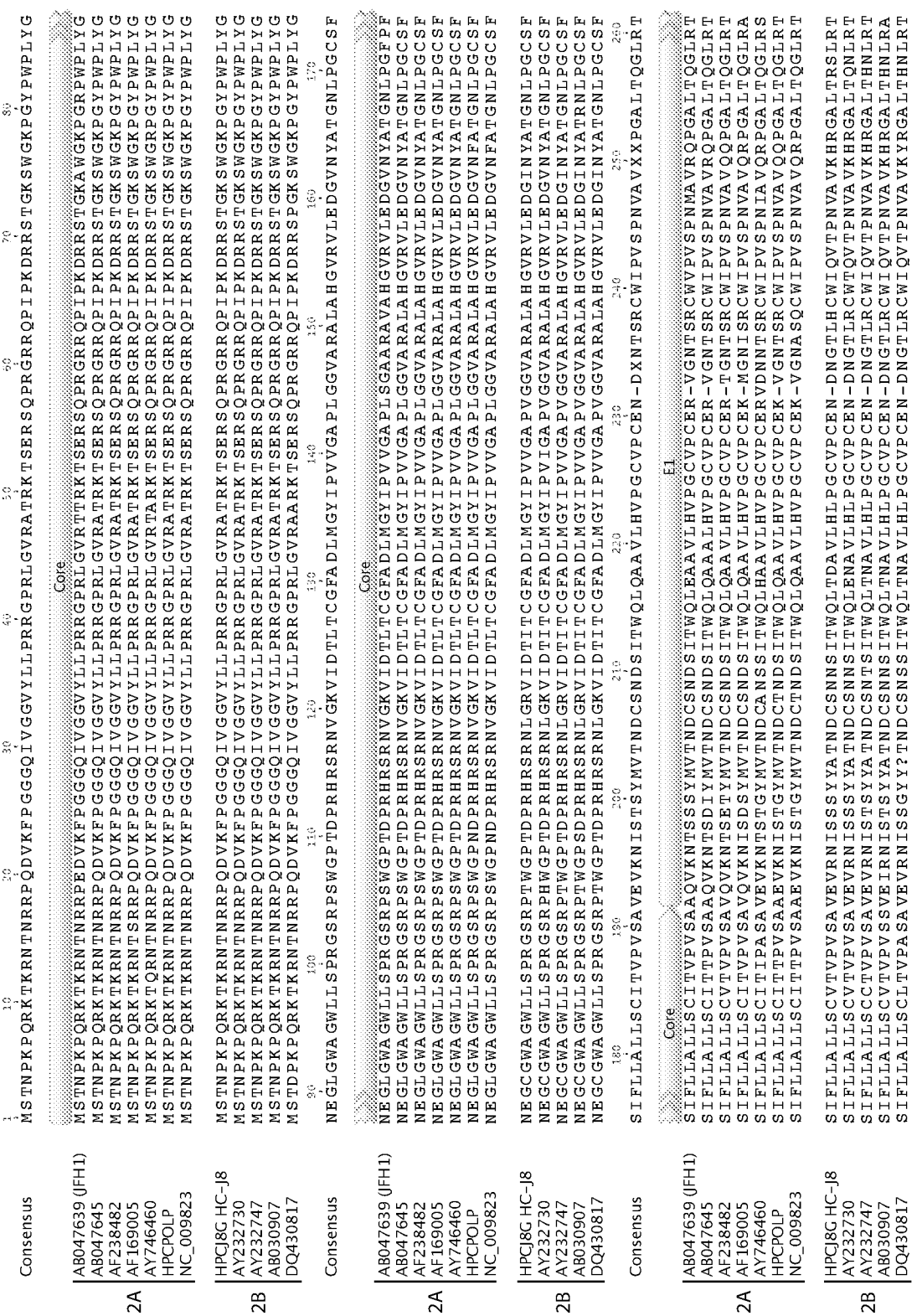


FIG. 2A

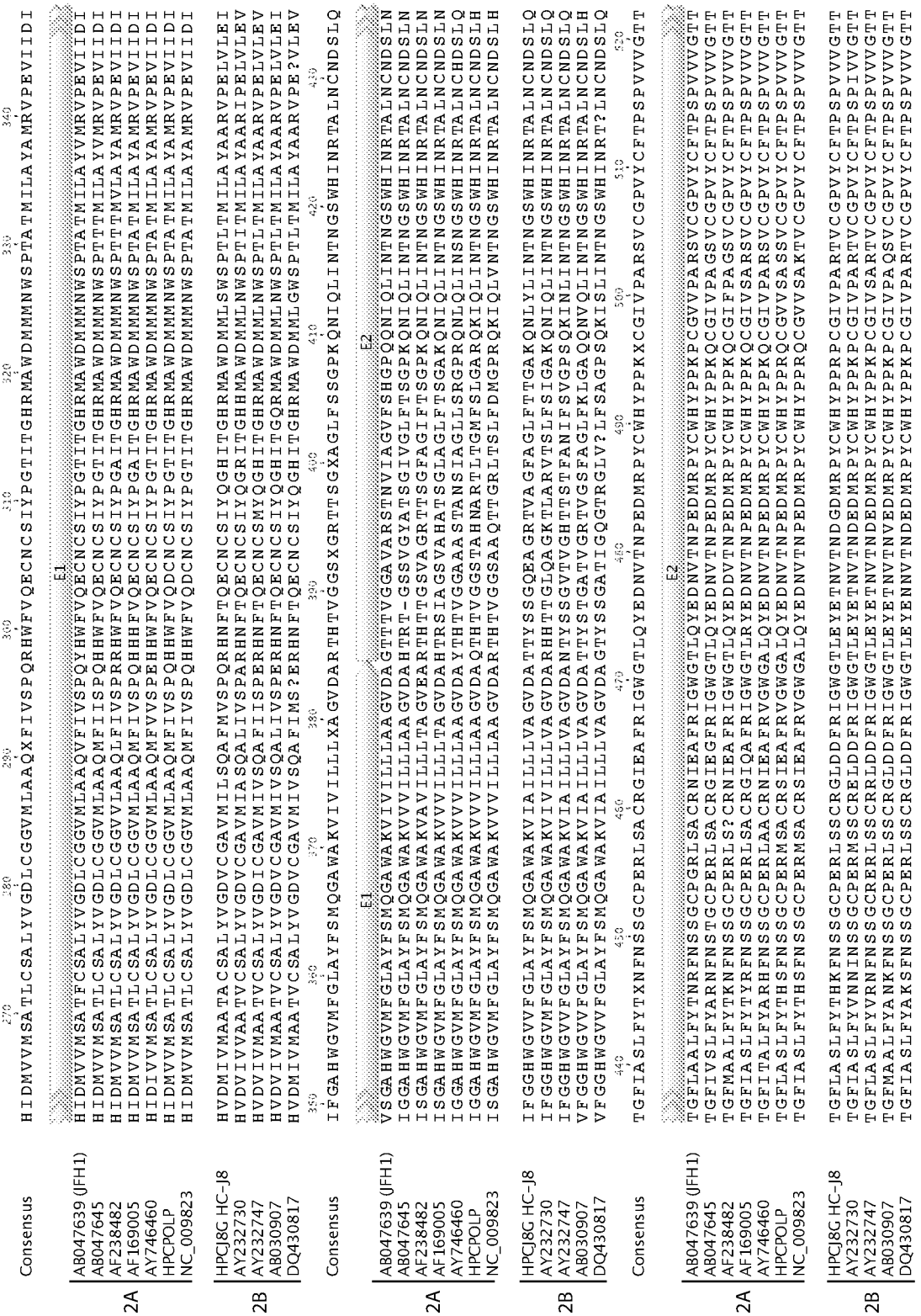


FIG. 2B

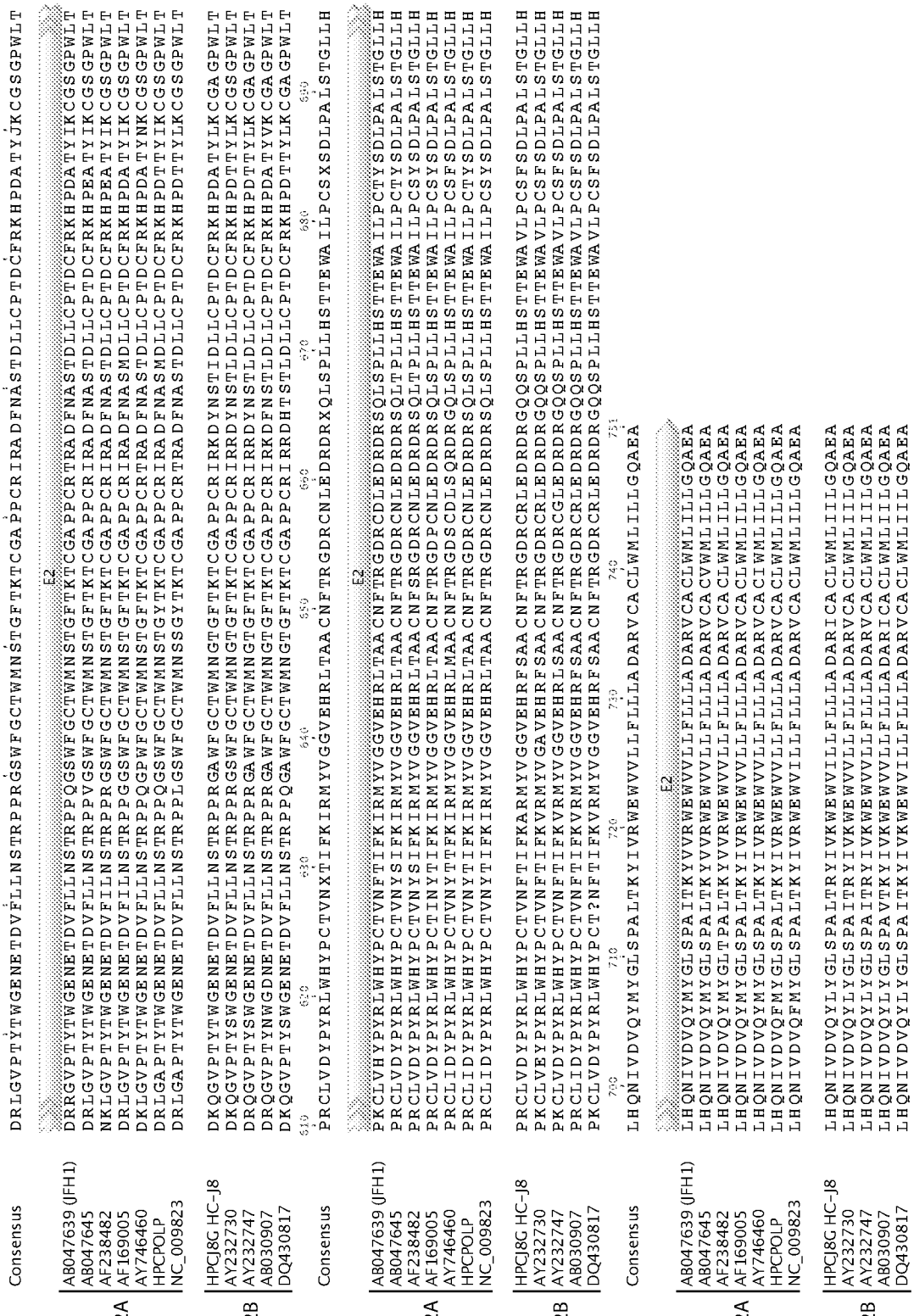

Consensus
2A
AB047639 (JFH1)
AB047645
Af238482
AF169005
AY746460
HPCPOLP
NC_009823
2B
HPCJ8G HC-J8
AY232730
AY232747
AB030907
DQ430817
E2

FIG. 2C

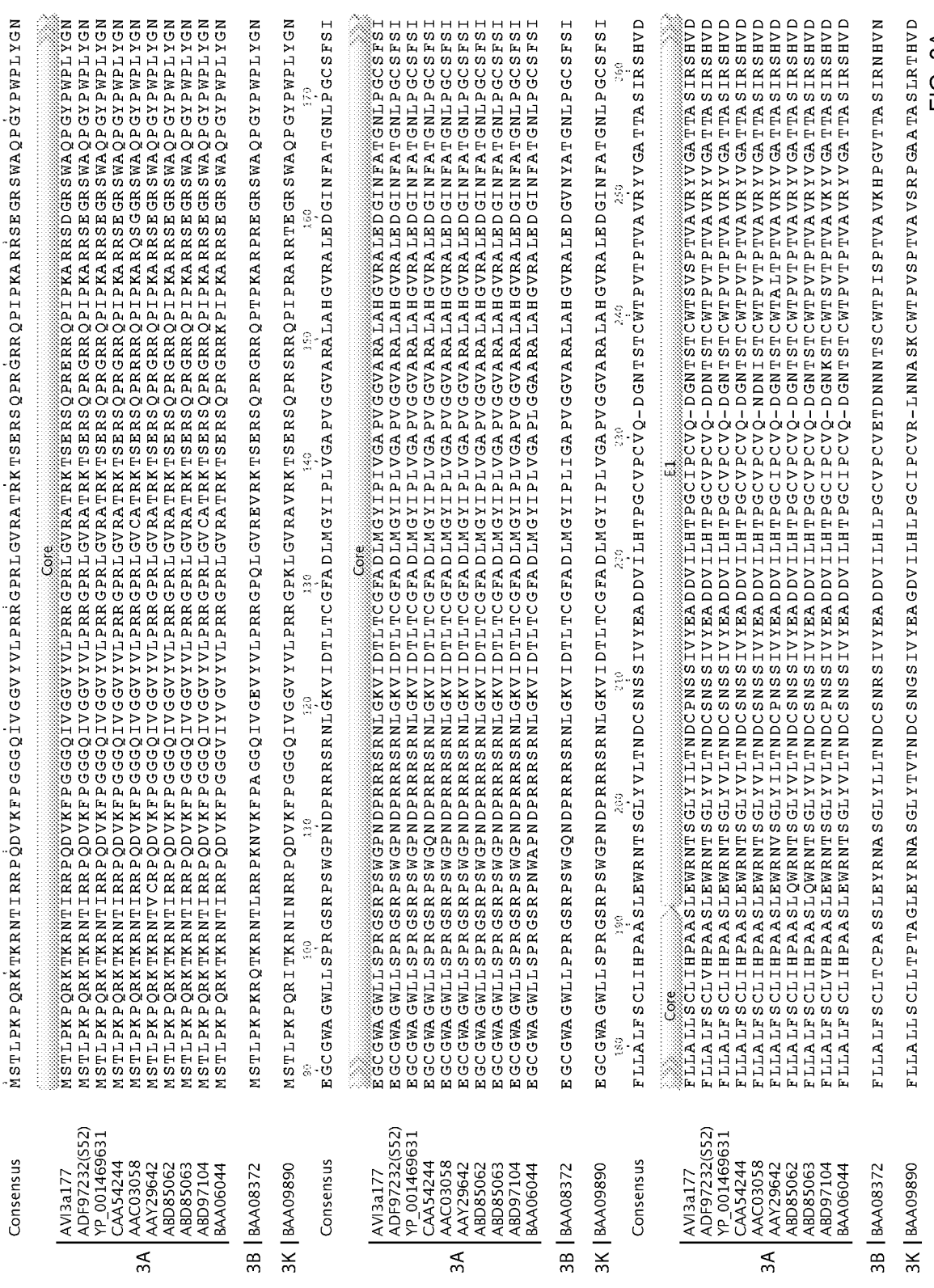


FIG. 3A

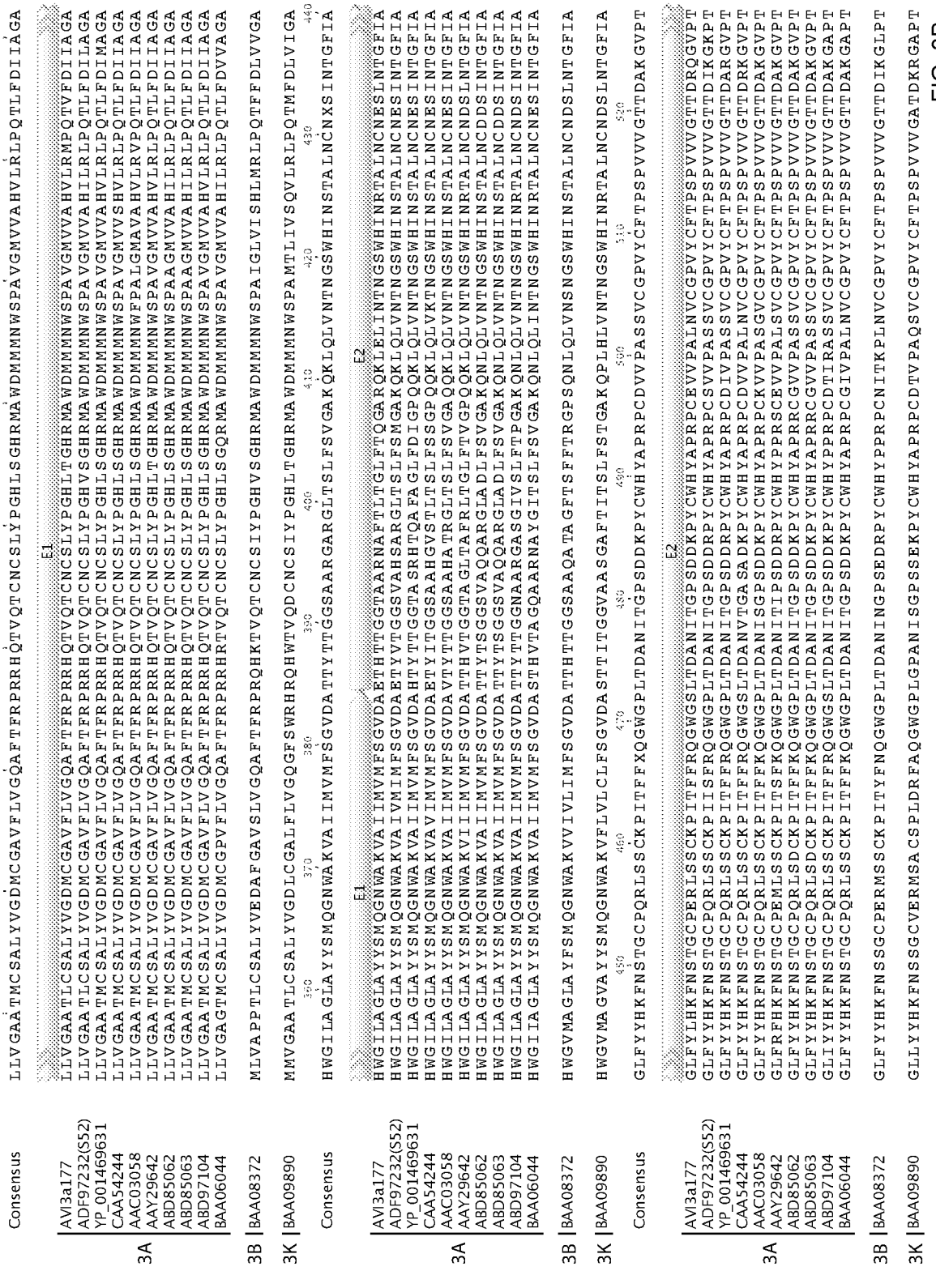


FIG. 3B

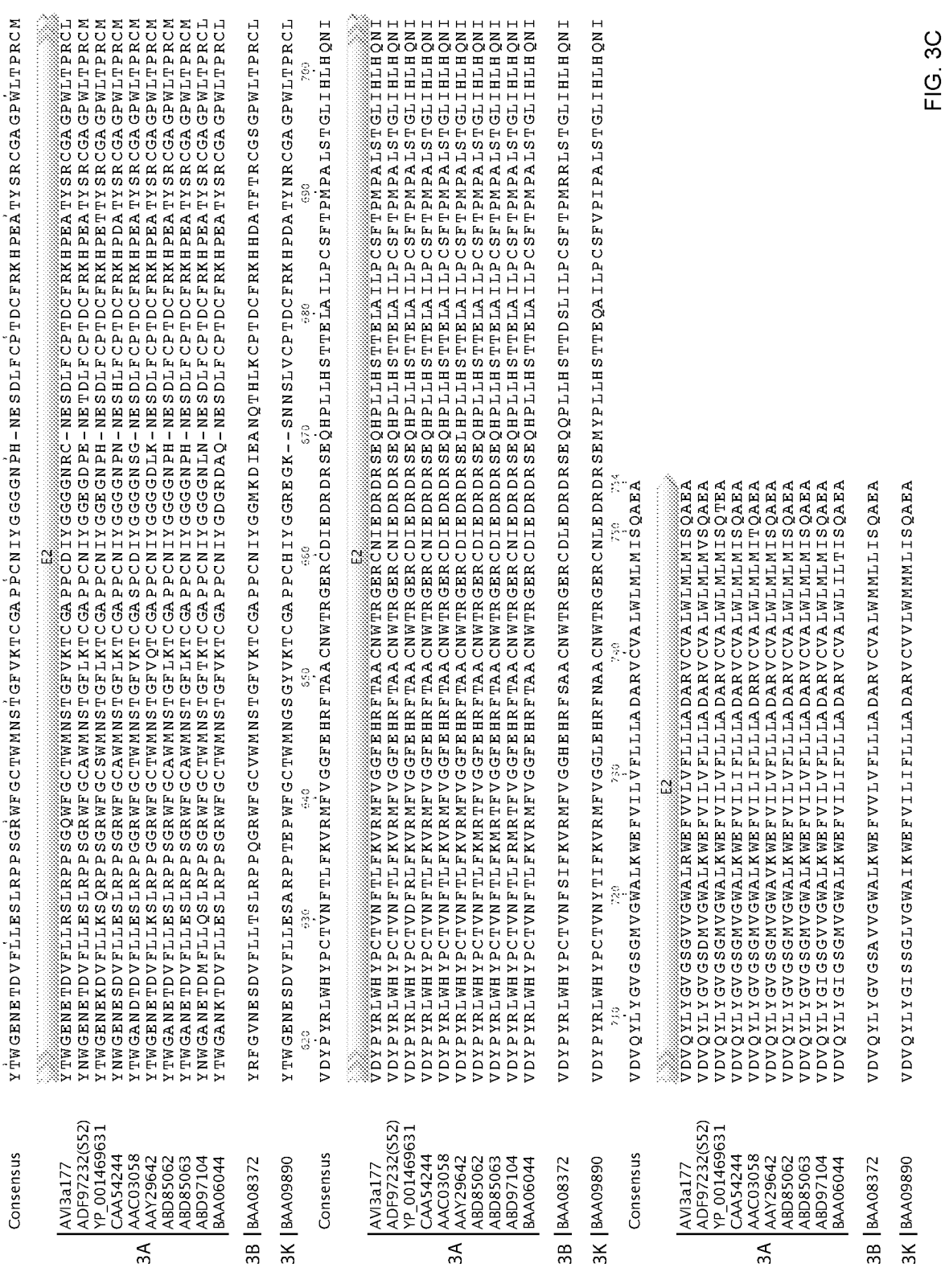


FIG. 3C

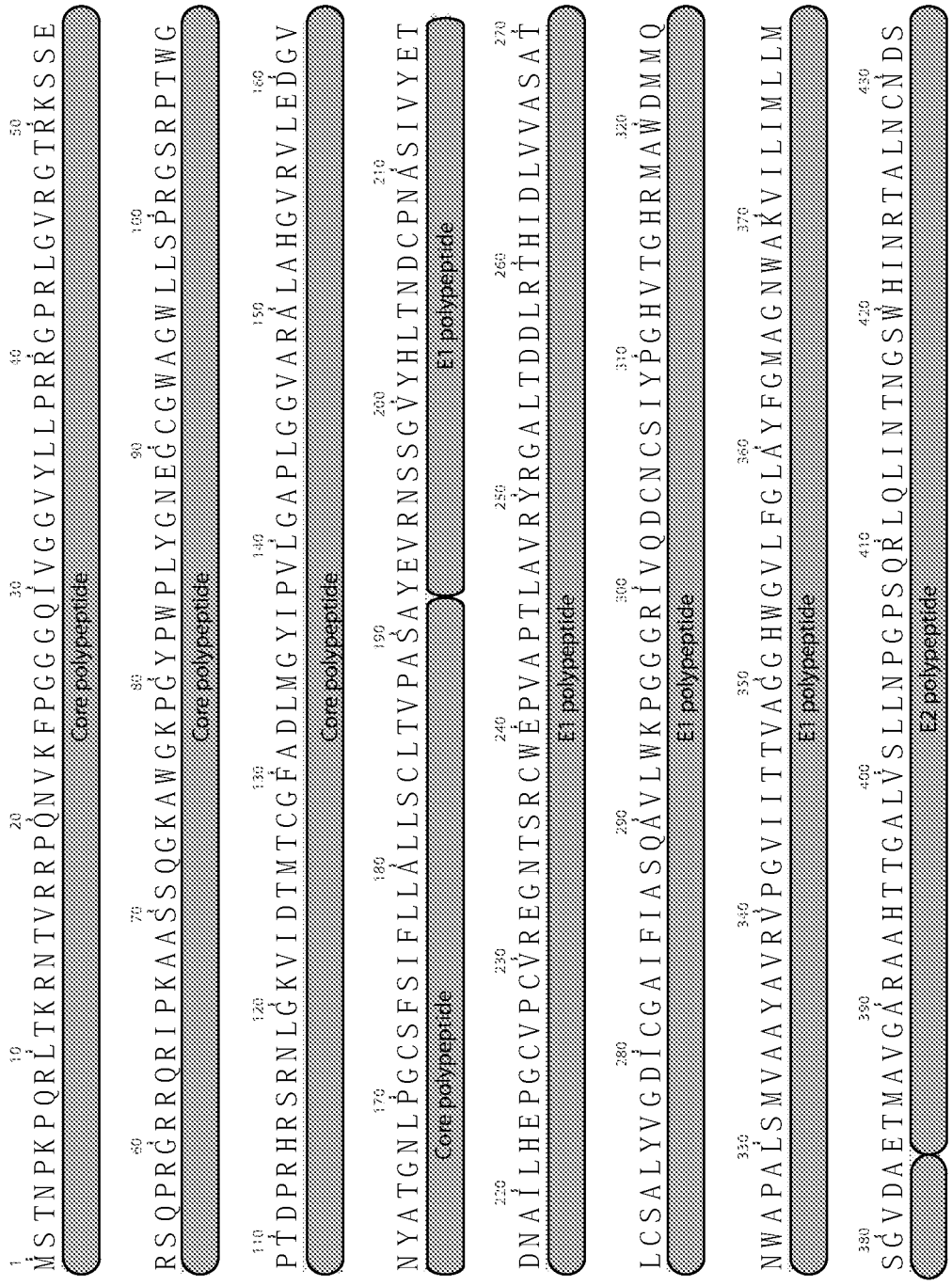

Core polypeptide
Core polypeptide
Core polypeptide
Core polypeptide
E1 polypeptide
E1 polypeptide
E1 polypeptide
E1 polypeptide
E2 polypeptide

FIG. 4A

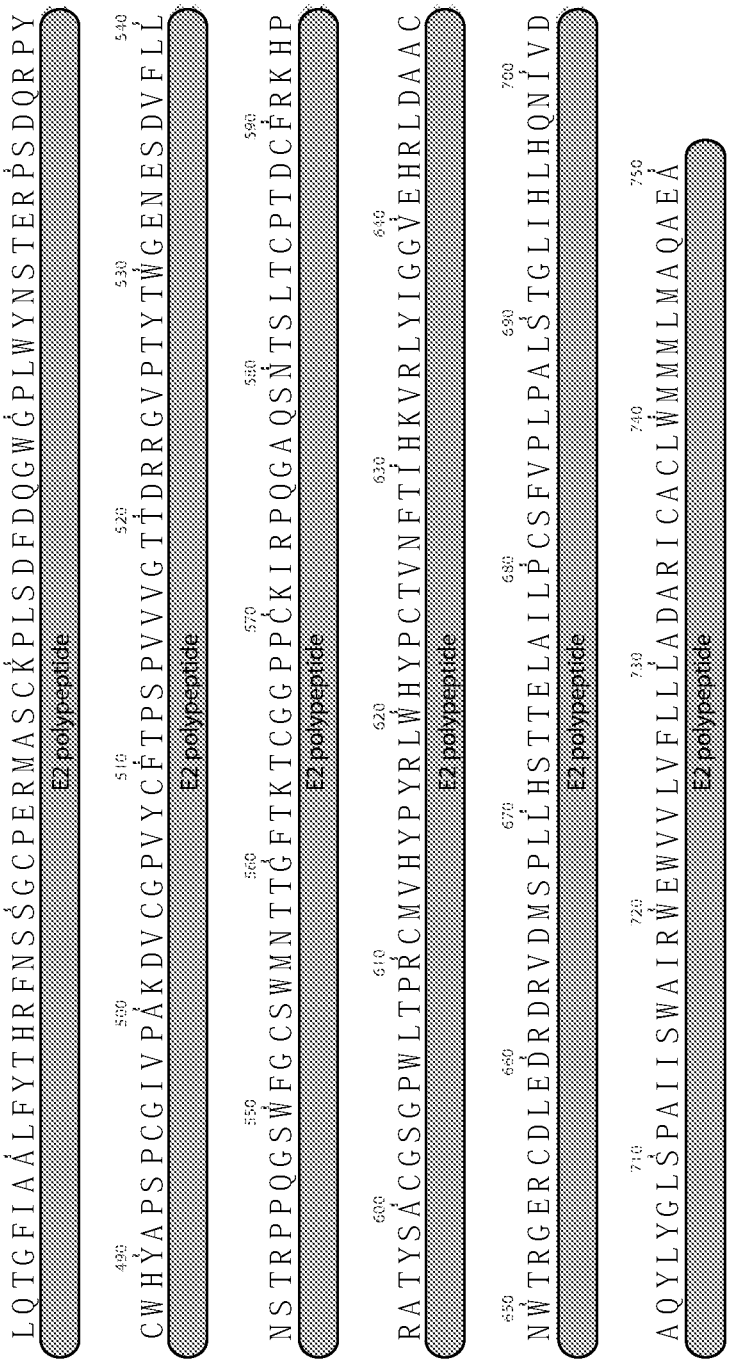

E2 polypeptide
E2 polypeptide
E2 polypeptide
E2 polypeptide
E2 polypeptide
E2 polypeptide

FIG. 4B

FIG. 5A

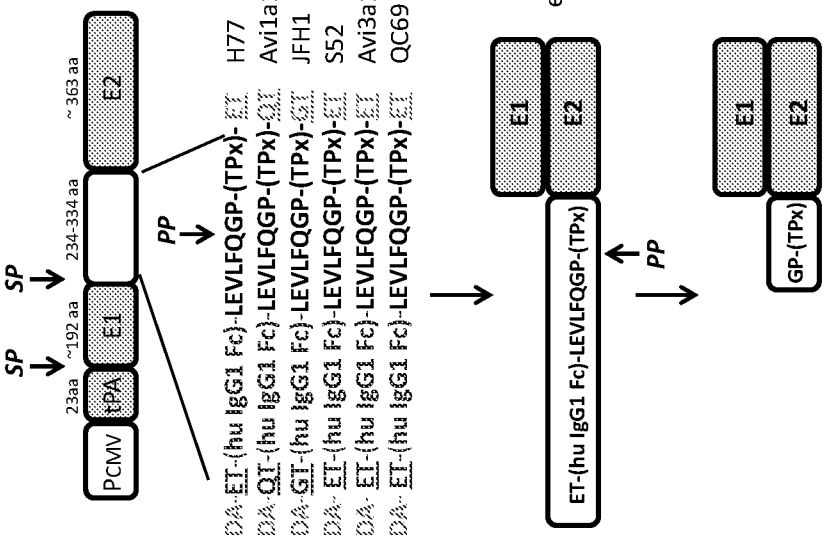
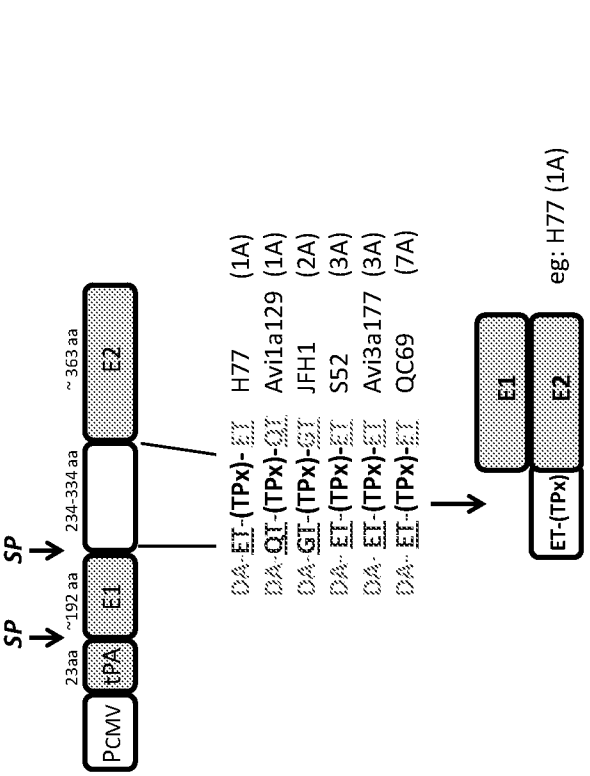

SP
SP
SP
PP
PCMV
tPA
23aa
E1
~192 aa
234-334 aa
E2
~ 363 aa
DA-ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)- ET H77 (1A)
DA-QT-(hu IgG1 Fc)-LEVLFQGP-(TPx)-QT Avi1a129 (1A)
DA-GT-(hu IgG1 Fc)-LEVLFQGP-(TPx)-GT JFH1 (2A)
DA-ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)-ET S52 (3A)
DA-ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)-ET Avi3a177 (3A)
DA-ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)-ET QC69 (7A)
E1
E2
eg: H77 (1A)
ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)
PP
GP-(TPx)

FIG. 5B


SP
SP
SP
PCMV
tPA
23aa
E1
~192 aa
234-334 aa
E2
~ 363 aa
DA-ET-(TPx)- ET H77 (1A)
DA-QT-(TPx)-QT Avi1a129 (1A)
DA-GT-(TPx)-GT JFH1 (2A)
DA-ET-(TPx)-ET S52 (3A)
DA-ET-(TPx)-ET Avi3a177 (3A)
DA-ET-(TPx)-ET QC69 (7A)
E1
E2
eg: H77 (1A)
ET-(TPx)

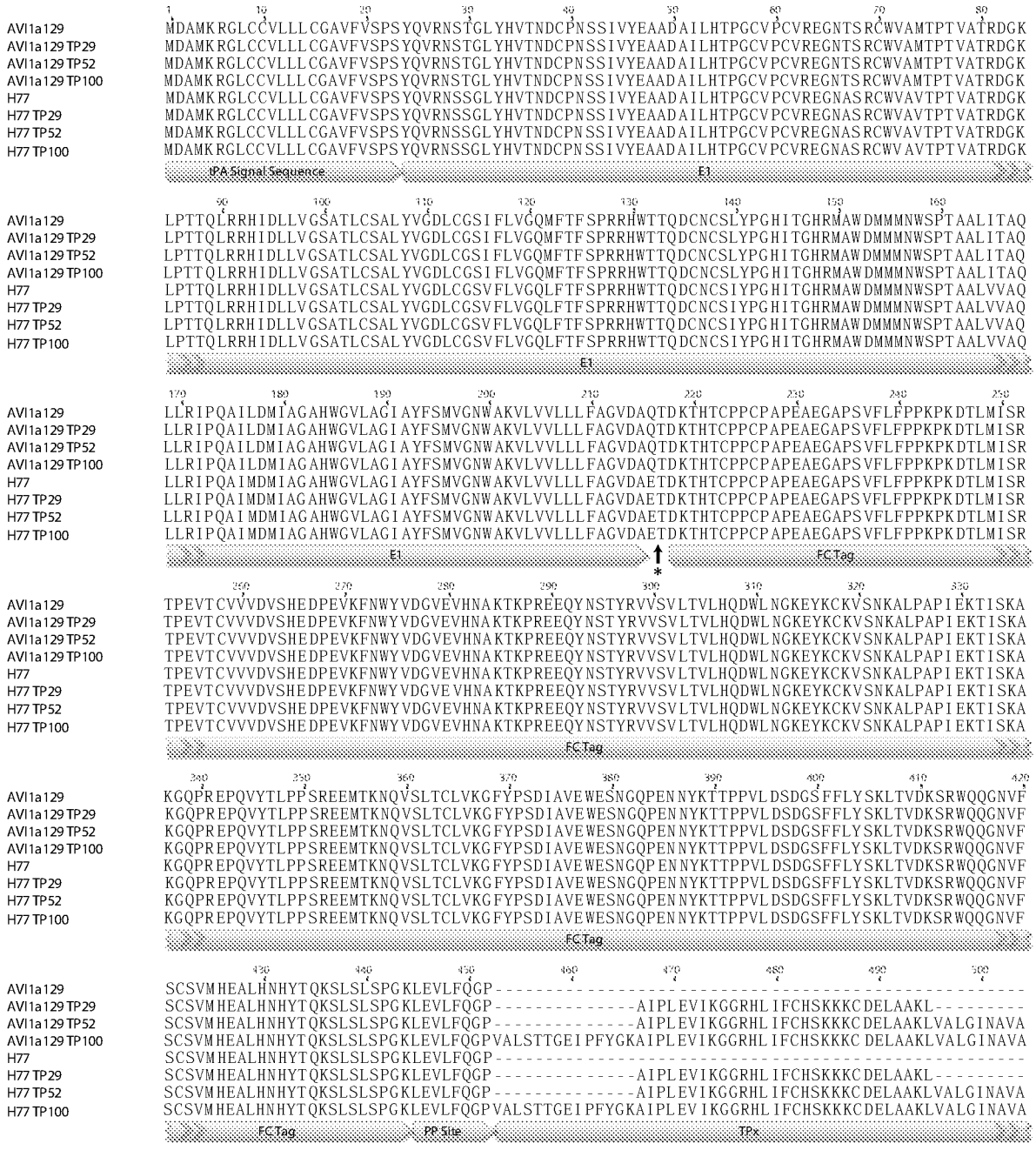

AVI1a129
AVI1a129 TP29
AVI1a129 TP52
AVI1a129 TP100
H77
H77 TP29
H77 TP52
H77 TP100
IPA Signal Sequence
E1
FC Tag
PP Site
TPx

FIG. 6A

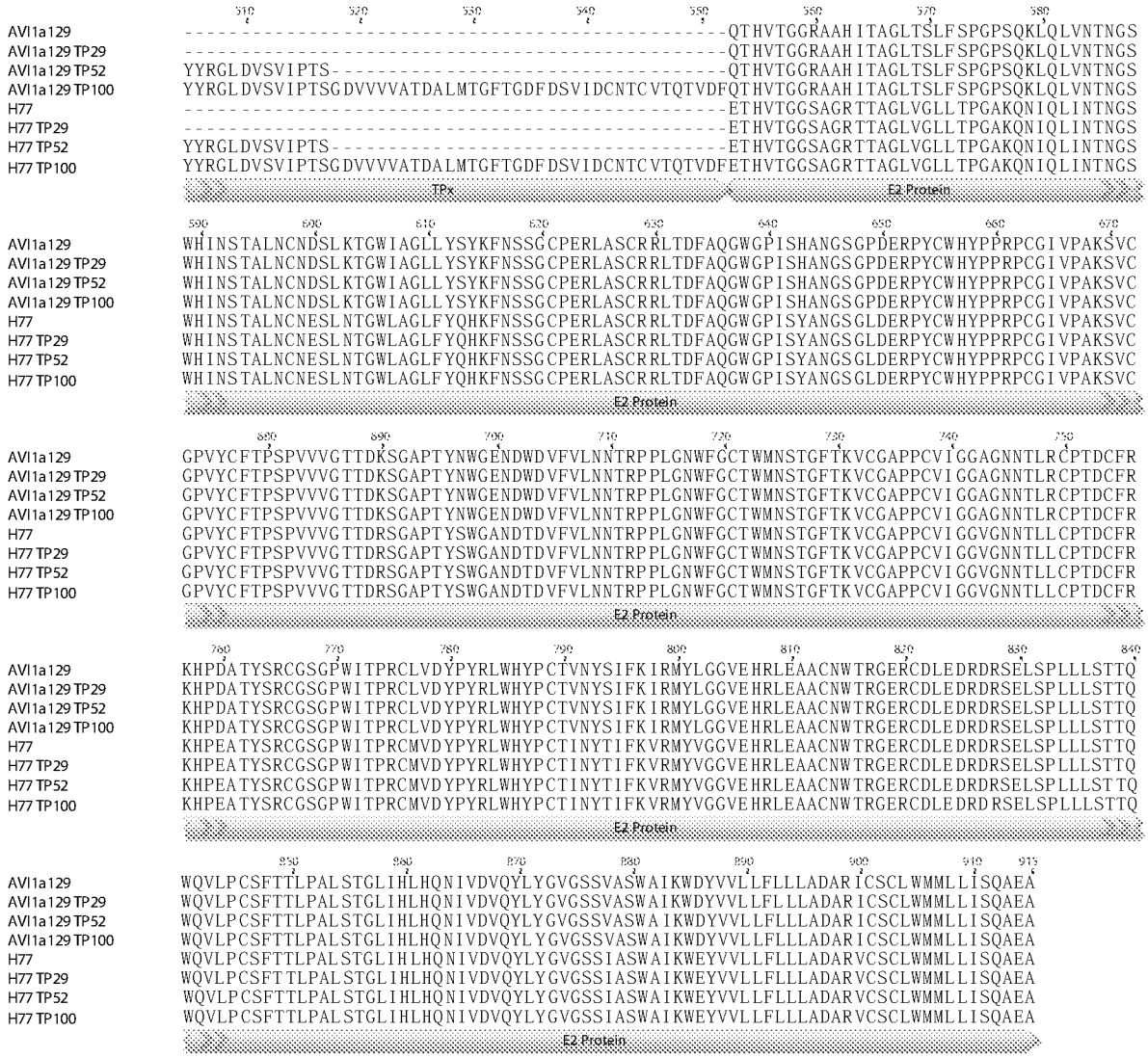

AVI1a129
AVI1a129 TP29
AVI1a129 TP52
AVI1a129 TP100
H77
H77 TP29
H77 TP52
H77 TP100
TPx
E2 Protein

FIG. 6B

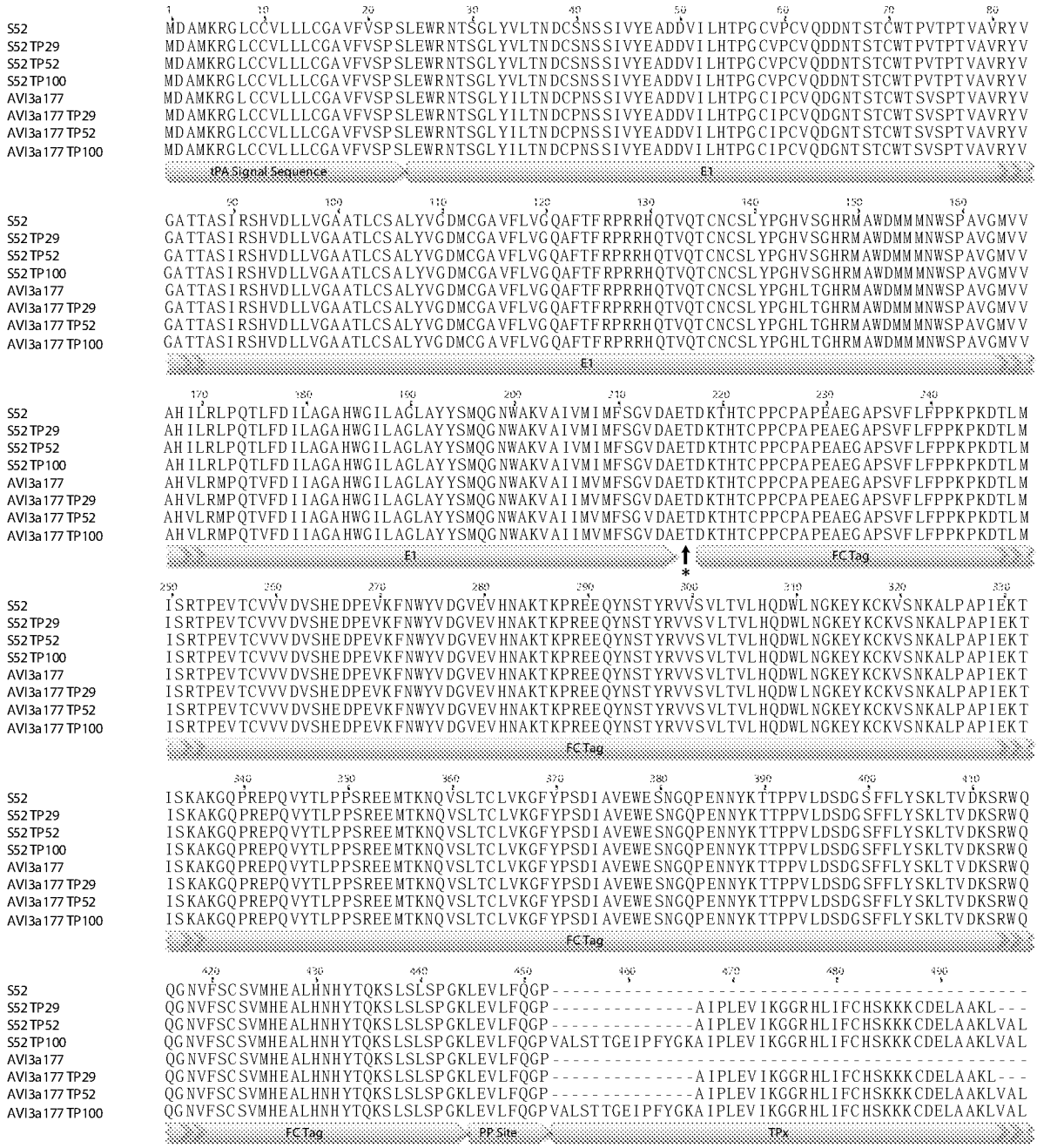

S52
S52TP29
S52TP52
S52TP100
AVI3a177
AVI3a177TP29
AVI3a177TP52
AVI3a177TP100
tPA Signal Sequence
E1
FC Tag
PP Site
TPx

FIG. 7A

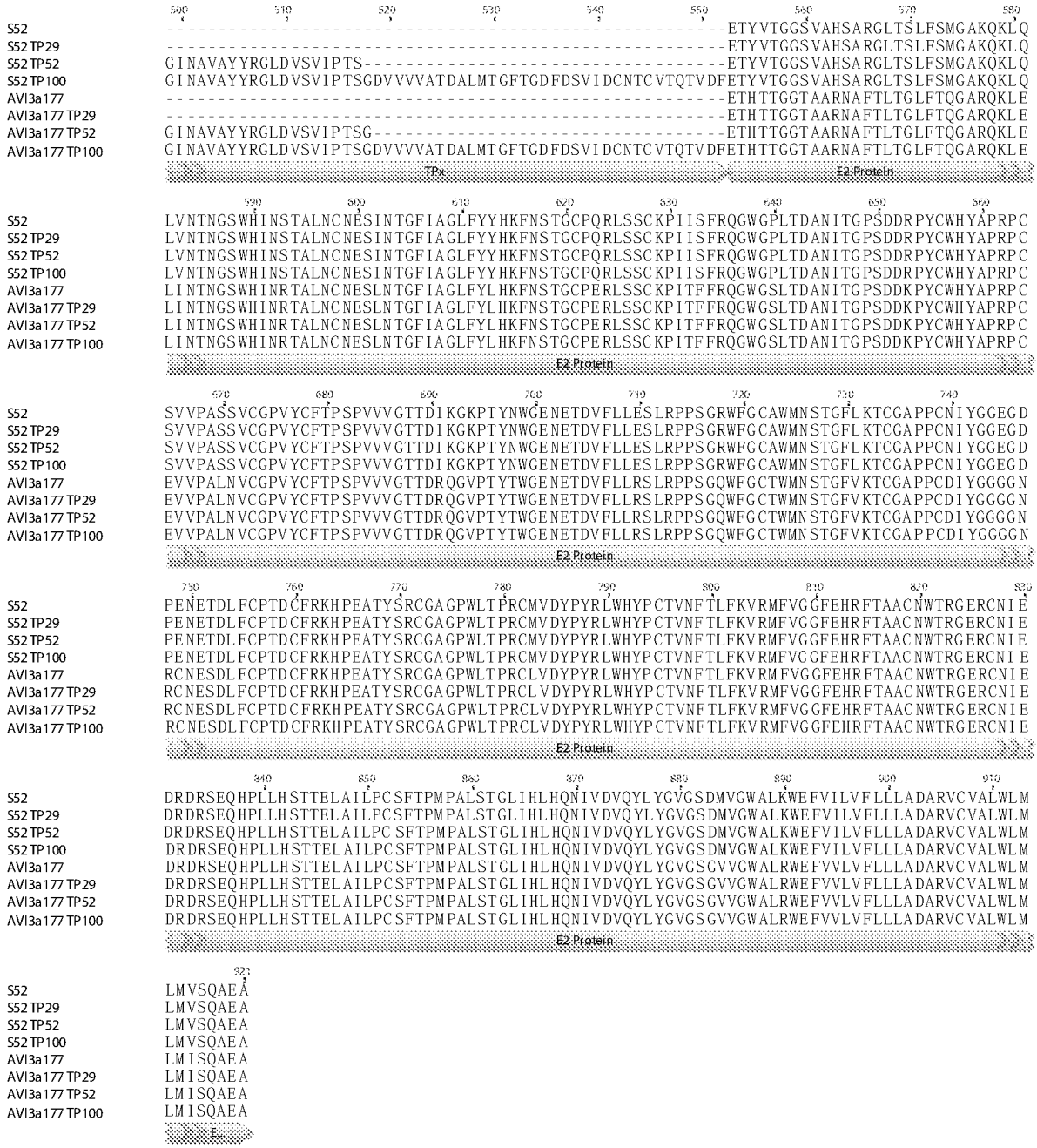

S52
S52TP29
S52TP52
S52TP100
AVI3a177
AVI3a177TP29
AVI3a177TP52
AVI3a177TP100
TPx
E2 Protein

FIG. 7B

FIG. 8A

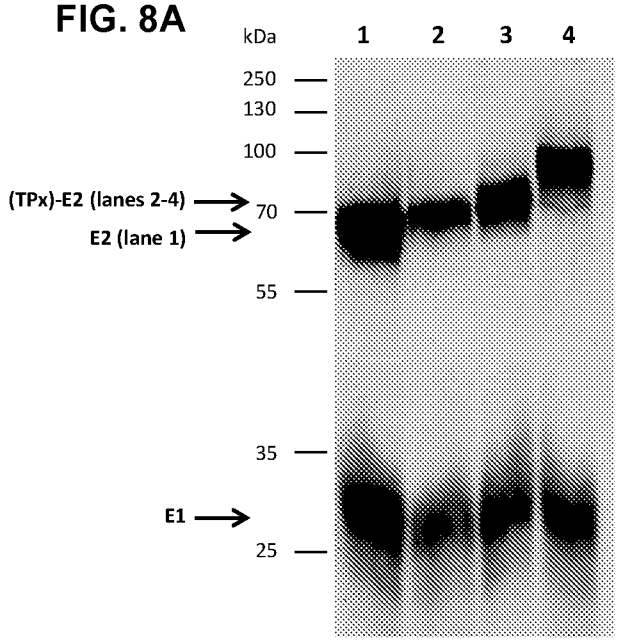

kDa
1
2
3
4
250
130
100
(TPx)-E2 (lanes 2-4)
70
E2 (lane 1)
55
35
E1
25

FIG. 8B

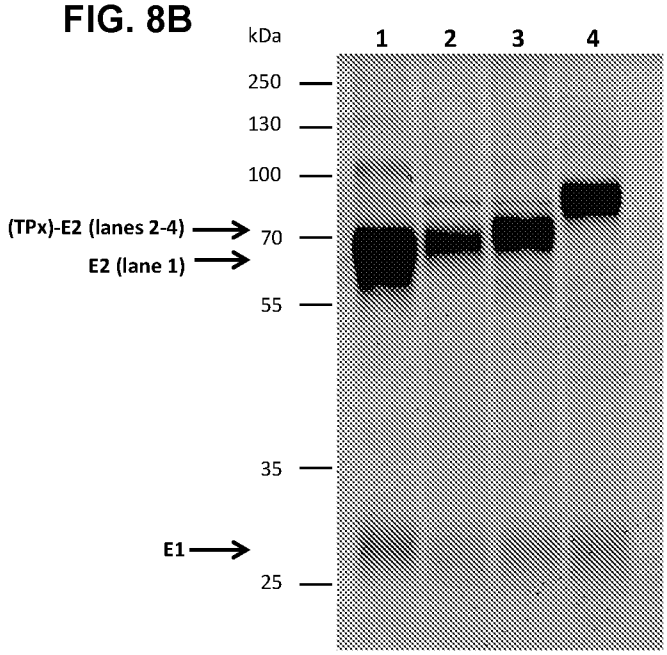

kDa
1
2
3
4
250
130
100
(TPx)-E2 (lanes 2-4)
70
E2 (lane 1)
55
35
E1
25

FIG. 9A
GenBank 3S7G_A
Homo sapiens **IgG1** Fc
227 aa

```
  1 dkthtcppcp apellggpsv flfppkpkdt lmisrtpevt cvvvdvshed pevkfnwyvd
 61 gvevhnaktk preeqynsty rvvsvltvlh qdwlngkeyk ckvsnkalpa piektiskak
121 gqprepqvyt lppsrdeltk nqvsltclvk gfypsdiave wesngqpenn yklppvlds
181 dgsfflyskl tvdksrwqqg nvfscsvmhe alhnhytqks lslspgk
```

GenBank AAN76044
Homo sapiens **IgG2** Fc (amino acids 99-325)
227 aa

```
  1 stkgpsvfpl apcsrstses taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg
 61 lyslssvvtv pssnfgtqty tcnvdhkpsn tkvdktverk ccvecppcpa ppvagpsvfl
121 fppkpkdtlm isrtpevtcv vvdvshedpe vqfnwyvdgv evhnaktkpr eeqfnstfrv
181 vsvltvvhqd wlngkeykck vsnkglpapi ektisktkgq prepqvytlp psreemtknq
241 vsltclvkgf ypsdiavewe sngqpennyk ttppmldsdg sfflysklтv dksrwqqgnv
301 fscsvmheal hnhytqksls lspgk
```

GenBank AAW65947
Homo sapiens **IgG3** Fc (amino acids 19-246)
238 aa

```
  1 hkpsntkvdk rvelktplgd tthtcppcpa pellggpsvf lfppkpkdtl misrtpevtc
 61 vvvdvshedp evkfnwyvdg vevhnaktkp reeqynstyr vvsvltvlhq dwlngkeykc
121 kvsnkalpap iektiskakg qprepqvytl ppsrdeltkn qvsltclvkg fypsdiavew
181 esngqpenny kttppvldsd gsfflysklt vdksrwqqgn vfscsvmhea lhnhytqksl
241 slspgk
```

FIG. 9B

GenBank AAA52770
Homo sapiens **IgD** Fc (amino acids 162-383)
222 aa

```
   1 ptkapdvfpi isgcrhpkdn spvvlaclit gyhptsvtvt wymgtqsqpq rtfpeiqrrd
  61 syymtssqls tplqqwrqge ykcvvqhtas kskkeifrwp espkaqassv ptaqpqaegs
 121 lakattapat trntgrggee kkkekekeeq eeretktpec psht**qp**lgvy lltpavqdlw
 181 lrdkatftcf vvgsdlkdah ltwevagkvp tggveeglle rhsngsqsqh srltlprslw
 241 nagtsvtctl nhpslppqrl malrepaaqa pvklslnlla sscppeaasw llcevsgfsp
 301 pnillmwled qrevntsgfa parpppqprs ttfwawsvlr vpappspqpa tytcvvshed
 361 srtllnasrs levsyvtdhg pmk
```

GenBank 0308221A
Homo sapiens **IgM** Fc
276 aa

```
   1 vtstltikzs dwlgesmftc rvdhrgltfq qnassmcvpd qdtairvfai ppsfasiflt
  61 kstkltclvt dlttybsvti swtreengav kthtnisesh pnatfsavge asicedbdws
 121 gerftctvth tdlpsplkqt isrpkgvalh rpbvyllppa rzzlnlresa titclvtgfs
 181 padvfvewmq rgeplspqky vtsapmpepq apgryfahsi ltvseeewnt ggtytcvvah
 241 ealpnrvter tvdkstgkpt lynvslvmsd tagtcy
```

FIG. 9C

GenBank P01876
Homo sapiens **IgA** Fc (amino acids 120-353)
234 aa

```
  1 asptspkvfp lslcstqpdg nvviaclvqg ffpqeplsvt wsesgqgvta rnfppsqdas
 61 gdlyttssql tlpatqclag ksvtchvkhy tnpsqdvtvp cpvpstpptp spstpptpsp
121 scchprlslh rpaledlllg seanltctlt glrdasgvtf twtpssgksa vqgpperdlc
181 gcysvssvlp gcaepwnhgk tftctaaype sktpltatls ksgntfrpev hllpppseel
241 alnelvtltc largfspkdv lvrwlqgsqe lprekyltwa srqepsqgtt tfavtsilrv
301 aaedwkkgdt fscmvgheal plaftqktid rlagkpthvn vsvvmaevdg tcy
```

GenBank 1F6A_B
Homo sapiens **IgE** Fc (amino acids 6-222)
212 aa

```
  1 acpcdsnprg vsaylsrpsp fdlfirkspt itclvvdlap skgtvnltws rasgkpvnhs
 61 trkeekqrng tltvtstlpv gtrdwieget yqcrvthphl pralmrsttk tsgpraapev
121 yafatpewpg srdkrtlacl iqnfmpedis vqwlhnevql pdarhsttqp rktkgsgffv
181 fsrlevtrae weqkdeficr avheaaspsq tvqravsvnp gk
```

GenBank P01861
Homo sapiens **IgG4** Fc (amino acids 100-327)
228 aa

```
  1 astkgpsvfp lapcsrstse staalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
 61 glyslssvvt vpssslgtkt ytcnvdhkps ntkvdkrves kygppcpscp apeflggpsv
121 flfppkpkdt lmisrtpevt cvvvdvsqed pevqfnwyvd gvevhnaktk preeqfnsty
181 rvvsvltvlh qdwlngkeyk ckvsnkglps siektiskak gqprepqvyt lppsqeemtk
241 ngvsltclvk gfypsdiave wesngqpenn ykttppvlds dgsfflysrl tvdksrwqeg
301 nvfscsvmhe alhnhytqks lslslgk
```

FIG. 10

Table 1. Conserved Regions based on the conserved CD4 epitopes

No.	Residues*	Length	Sequence	Genotype Conservancy	# of included Epitopes
CD4-R1	1251-1265	15	VLVLNPSVAATLGFG	HCV1a, 1b, 2a, 2b, 3, 4, 5, 6, 7	2
CD4-R2	1295-1309	15	TYGKFLADGGCSGGA	HCV1a, 1b, 3, 4, 5, 6, 7	2
CD4-R3	1387-1401	15	GGRHLIFCHSKKKCD	HCV1a, 1b, 2a, 2b, 3, 4, 5, 6, 7	4
CD4-R4	1415-1425	11	VAYYRGLDVSV	HCV1a, 1b, 2b, 3, 4, 7	4
CD4-R5	1436-1453	18	ATDALMTGFTGDFDSV ID	HCV1a, 1b, 3, 4, 7	2
CD4-R6	1563-1577	15	TGLTHIDAHFLSQTK	HCV1a, 1b, 2a, 2b, 3, 7	1
CD4-R7	1773-1785	13	QYLAGLSTLPGNP	HCV1a, 1b, 2a, 2b, 3, 4, 5, 6, 7	4
CD4-R8	1881-1888	8	NLLPAILS	HCV1a, 1b, 2b, 3, 4, 7	1
CD4-R9	1904-1930	27	RHVGPGEGAVQWMN RLIAFASRGNHVS	HCV1a, 1b, 3, 4	3
CD4-R10	2201-2215	15	SSASQLSAPSLKATC	HCV1a, 1b, 2b, 3, 4, 5, 6	1
CD4-R11	2788-2792	5	SNVSV	HCV1a, 1b, 2a, 2b, 3, 4, 5, 6, 7	1

*** Numbers are based on HCV1a genotype sequence. R = region**

FIG. 11

Table 2. Number of located HCV CD8 T cell epitopes and anchor positions for common each MHC-I Alleles in USA

MHC-I Allele	Total Epitopes (#)	Located Epitopes (#)	Allele-specific Anchor Positions			
			2	9	Others
A*02:01	48	29	**M#, L**, Q, V, I	**V, L, I**, A, M	F (1, 3, 7)
A*24:02	33	20	**Y, W**, F	**F, I, W**, L, M	F, W (7)
A*03:01	10	6	**M,L, I, V, T**, S, Q, A	**K**, Y, R	F & Y (3), K & R (1)
A*01:01	4	3	**T, S**, A, V, M, I, L	**Y**, F	**D** (3)
B*35:01	1	1	**P**, G, A	**Y, M, F**, H	M (1), A (8), W (1), F (1), Y (1), P (8)
			5	**9**	**Others**
B*08:01	2	1	**R, K, H**, F	**L, M, I, F, V**, A, W	K (3), R (3), L (2), F (6), M (1, 2, 3), P (2), S (8)
			1	**2**	**9**	**Others**
B*40:02	2	2	**Y, K, R, A, H, W, G, F**, Q, L, S, C, I, T, M, V	E, D	**I, L, A, V, F, M, T**, W, S, C	F (3), P (8), A (8)
C*03:03	2	2	NA##		NA	NA
A*33:03	1	0	-		-	-
A*02:06	1	0	-		-	-
A*26:01	1	0	-		-	-
A*31:01	1	0	-		-	-
Total	106	64				

 # Bold Anchor positions describe the optimal amino acid for that location. ## Not Available

FIG. 12

Table 3. Conserved Regions based on the conserved CD8 Epitopes

No.	Residues*	Length	Sequence	Conserved HCV1a, 1b, & 3	Conserved 9** Genotypes	# of epitopes
CD8-R1	1292-1300	9	TYSTYGKFL	Yes	Yes	2
CD8-R2	1391-1399	9	LIFCHSKKK	Yes	Yes	2
CD8-R3	1436-1451	16	ATDALMTGFTGDFDSV	Yes	No	2
CD8-R4	1666-1675	10	VLAALAAYCL	Yes	No	1
CD8-R5	1851-1859	9	ILAGYGAGV	Yes	No	1
CD8-R6	1373-1380	8	IPFYGKAI	Yes	No	1
CD8-R7	1596-1604	9	RAQAPPPSW	Yes	No	1
CD8-R8	1910-1945	36	EGAVQWMNRLIAFASRGN HVSPTHYVPESDAAARVT	Yes	No	3
CD8-R9	2290-2298	9	RPDYNPPLL	Yes	No	1
CD8-R10	2557-2565	9	TIMAKNEVF	Yes	Yes	1

* Numbers are based on HCV1a genotype sequence.
** Nine genotypes include HCV1a, 1b, 2a, 2b, 3, 4, 5, 6, and 7

FIG. 13A. CD4 and CD8 epitopes for Core, P7, and NS2 regions

Name	Type of epitope	Start*	End*
Core-1	CD4	1	20
Core-2	CD4	11	30
Core-3	CD4	21	40
Core-4	CD4	39	63
Core-5	CD4	47	70
Core-6	CD4	61	80
Core-7	CD4	71	90
Core-8	CD4	81	100
Core-9	CD4	91	110
Core-10	CD4	101	115
Core-11	CD4	111	130
Core-12	CD4	125	139
Core-13	CD4	131	150
Core-14	CD4	151	170
Core-15	CD4	161	180
Core-16	CD8	35	44
Core-17	CD8	43	51
Core-18	CD8	51	59
Core-19	CD8	129	137
Core-20	CD8	131	140
Core-21	CD8	150	158
Core-22	CD8	154	162
Core-23	CD8	168	176
Core-24	CD8	177	187
Core-25	CD8	178	187
P7-1	CD8	803	811
NS2-1	CD4	955	974
NS2-2	CD4	975	994
NS2-3	CD4	985	1,004
NS2-4	CD4	1,015	1,034
NS2-5	CD4	1,035	1,054
NS2-6	CD8	924	933
NS2-7	CD8	961	970
NS2-8	CD8	989	997

* Start and End numbers are based on sequence designated "Consensus" in Fig. 16A-16L.

FIG. 13B. CD4 and CD8 epitopes that are conserved among genotypes 1a, 1b, 2a, 2b, and 3

Name	Type of epitope	Start*	End*
NS3-1	CD4	1,265	1,279
NS3-2	CD4	1,309	1,323
NS3-3	CD4	1,401	1,415
NS3-4	CD4	1,402	1,412
NS3-5	CD4	1,429	1,439
NS3-6	CD4	1,450	1,464
NS3-7	CD4	1,453	1,467
NS3-8	CD4	1,577	1,591
NS3-9	CD8	1,306	1,314
NS3-10	CD8	1,387	1,394
NS3-11	CD8	1,405	1,413
NS3-12	CD8	1,450	1,458
NS3-13	CD8	1,457	1,465
NS3-14	CD8	1,610	1,618
NS4a-1	CD8	1,683	1,692
NS4b-1	CD4	1,790	1,801
NS4b-2	CD4	1,792	1,802
NS4b-3	CD4	1,898	1,905
NS4b-4	CD4	1,921	1,935
NS4b-5	CD4	1,922	1,941
NS4b-6	CD4	1,928	1,947
NS4b-7	CD8	1,868	1,876
NS4b-8	CD8	1,927	1,942
NS4b-9	CD8	1,932	1,940
NS4b-10	CD8	1,948	1,962
NS5a-1	CD4	2,218	2,232
NS5a-2	CD8	2,309	2,317
NS5b-1	CD4	2,847	2,851
NS5b-2	CD8	2,602	2,610

* Start and End numbers are based on sequence designated "Consensus" in Fig. 16A-16L.

FIG. 14A

Name	Sequence*	Start**	End**	Contained Epitopes
TP29	AIPLEVIKGGRHLIFCHSKKKCDELAAKL	1,393	1,421	NS3-3, NS3-4, NS3-11
TP50	LGALTGTYVYNHLTPLRDWAHNGLRDLA VAVEPVVFSQMETKLITWGADT	955	1,004	NS2-1, NS2-2, NS2-3, NS2-7, NS2-8
TP52	AIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSG	1,393	1,444	NS3-3, NS3-4, NS3-5, NS3-11
TP70	KGGRHLIFCHSKKKCDELAAKLVALGINA VAYYRGLDVSVIPTSGDVVVVATDALMTG FTGDFDSVIDCN	1,400	1,469	NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-11, NS3-12, NS3-13
TP100	VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHS KKKCDELAAKLVALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTGDFDSVIDC NTCVTQTVDF	1,379	1,478	NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-10, NS3-11, NS3-12, NS3-13
TP171	MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVG GVYLLPRRGPRLGVRATRKTSERSQPRGRRQPI PKARRPEGRTWAQPGYPWPLYGNEGCGWAG WLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLT CGFADLMGYIPLVGAPLGGAARALAHGVRVLED GVNYATGNLPG	1	171	Core-1, Core-2, Core-3, Core-4, Core-5, Core-6, Core-7, Core-8, Core-9, Core-10, Core-11, Core-12, Core-13, Core-14, Core-16, Core-17, Core-18, Core-19, Core-20, Core-21, Core-22
TP228	LHAPTGSGKSTKVPAAYAAQGYKVLVLNP SVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDE CHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGK AIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVAT DALMTGFTGDFDSVIDCN	1,242	1,469	NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13
TP553	QASLLKVPYFVRVQGLLRICALARKMAGG HYVQMAIIKLGALTGTYVYN**A**LTPLRDWA HNGLRDLAVAVEPVVFSQMETKLITWGAD TAACGDIINGLPVSARRGREILLGPADGMV SKGWRLLAPITAYAQQTRGLLGCIITSLTG RDKNQVEGEVQIVSTAAQTFLATCINGVC WTVYHGAGTRTIASPKGPVIQMYTNVDQD LVGWPAPQGARSLTPCTCGSSDLYLVTRH ADVIPVRRRGDSRGSLLSPRPISYLKGS**A**GG PLLCPAGHAVGIFRAAVCTRGVAKAVDFIP VENLETTMRSPVFTDNSSPPAVPQSFQVAH LHAPTGSGKSTKVPAAYAAQGYKVLVLNP SVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDE CHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGK	917	1,469	NS2-1, NS2-2, NS2-3, NS2-4, NS2-5, NS2-6, NS2-7, NS2-8, NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13

FIG. 14B

	AIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVAT DALMTGFTGDFDSVIDCN			
TP778	LHAPTGSGKSTKVPAAYAAQGYKVLVLNP SVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDE CHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGK AIPLEVIKGGRHLIFCHSKKKCDELAAKLV ALGINAVAYYRGLDVSVIPTSGDVVVVAT DALMTGFTGDFDSVIDCNTCVTQTVDFSL DPTFTIETTTLPQDAVSRTQRRGRTGRGKP GIYRFVAPGERPSGMFDSSVLCECYDAGCA WYELTPAETTVRLRAYMNTPGLPVCQDHL EFWEGVFTGLTHIDAHFLSQTKQSGENLPY LVAYQATVCARAQAPPPSWDQMWKCLIR LKPTLHGPTPLLYRLGAVQNEVTLTHPITK YIMTCMSADLEVVTSTWVLVGGVLAALA AYCLSTGCVVIVGRIVLSGKPAIIPDREVLY REFDEMEECSQHLPYIEQGMMLAEQFKQK ALGLLQTASRQAEVIAPAVQTNWQKLEAF WAKHMWNFISGIQYLAGLSTLPGNPAIASL MAFTAAVTSPLTTSQTLLFNILGGWVAAQ LAAPGAATAFVGAGLAGAAIGSVGLGKVL VDILAGYGAGVAGALVAFKIMSGEVPSTE DLVNLLPAILSPGALVVGVVCAAILRRHVG PGEGAVQWMNRLIAFASRGNHVSPTHYVP ESDAAARVTAILSSLTVTQLLRRLHQWISS ECTTPCSGSWLRDIWDWICEVLSDFKTWL KAKLMPQLPG	1,242	2,022	NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, NS4b-10

FIG. 14C

TP1985	APITAYAQQTRGLLGCIITSLTGRDKNQVE GEVQIVSTAAQTFLATCINGVCWTVYHGA GTRTIASPKGPVIQMYTNVDQDLVGWPAP QGARSLTPCTCGSSDLYLVTRHADVIPVRR RGDSRGSLLSPRPISYLKGS**A**GGPLLCPAG HAVGIFRAAVCTRGVAKAVDFIPVENLETT MRSPVFTDNSSPPAVPQSFQVAHLHAPTGS GKSTKVPAAYAAQGYKVLVLNPSVAATL GFGAYMSKAHGIDPNIRTGVRTITTGSPITY STYGKFLADGGCSGGAYDIIICDECHSTDA TSILGIGTVLDQAETAGARLVVLATATPPG SVTVPHPNIEEVALSTTGEIPFYGKAIPLEVI KGGRHLIFCHSKKKCDELAAKLVALGINA VAYYRGLDVSVIPTSGDVVVVATDALMTG FTGDFDSVIDCNTCVTQTVDFSLDPTFTIET TTLPQDAVSRTQRRGRTGRGKPGIYRFVAP GERPSGMFDSSVLCECYDAGCAWYELTPA ETTVRLRAYMNTPGLPVCQDHLEFWEGVF TGLTHIDAHFLSQTKQSGENLPYLVAYQAT VCARAQAPPPSWDQMWKCLIRLKPTLHGP TPLLYRLGAVQNEVTLTHPITKYIMTCMSA DLEVVTSTWVLVGGVLAALAAYCLSTGC VVIVGRIVLSGKPAIIPDREVLYREFDEMEE CSQHLPYIEQGMMLAEQFKQKALGLLQTA SRQAEVIAPAVQTNWQKLEAFWAKHMWN FISGIQYLAGLSTLPGNPAIASLMAFTAAVT SPLTTSQTLLFNILGGWVAAQLAAPGAATA FVGAGLAGAAIGSVGLGKVLVDILAGYGA GVAGALVAFKIMSGEVPSTEDLVNLLPAIL SPGALVVGVVCAAILRRHVGPGEGAVQW MNRLIAFASRGNHVSPTHYVPESDAAARV TAILSSLTVTQLLRRLHQWISSECTTPCSGS WLRDIWDWICEVLSDFKTWLKAKLMPQLP GIPFVSCQRGYRGVWRGDGIMHTRCHCGA EITGHVKNGTMRIVGPRTCRNMWSGTFPIN AYTTGPCTPLPAPNYTFALWRVSAEEYVEI RQVGDFHYVTGMTTDNLKCPCQVPSPEFF TELDGVRLHRFAPPCKPLLREEVSFRVGLH EYPVGSQLPCEPEPDVAVLTSMLTDPSHIT AEAAGRRLARGSPPSVASSSASQLSAPSLK ATCTANHDSPDAELIEANLLWRQEMGGNI TRVESENKVVILDSFDPLVAEEDEREISVPA EILRKSRRFAPALPIWARPDYNPPLLETWK KPDYEPPVVHGCPLPPPQSPPVPPPRKKRT VVLTESTVSTALAELATKSFGSSSTSGITGD NTTTSSEPAPSGCPPDSDAESYSSMPPLEGE	1041	3073	NS3-1, NS3-2, NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-8, NS3-9, NS3-10, NS3-11, NS3-12, NS3-13, NS3-14, NS4a-1, NS4b-1, NS4b-2, NS4b-3, NS4b-4, NS4b-5, NS4b-6, NS4b-7, NS4b-8, NS4b-9, NS4b-10, NS5a-1, NS5a-2, NS5b-1, NS5b-2

FIG. 14D

	PGDPDLSDGSWSTVSSEADTEDVVCCSMS YSWTGALVTPCAAEEQKLPINALSNSLLRH HNLVYSTTSRSACQRQKKVTFDRLQVLDS HYQDVLKEVKAAASKVKANLLSVEEACSL TPPHSAKSKFGYGAKDVRCHARKAVNHIN SVWKDLLEDSVTPIDTTIMAKNEVFCVQPE KGGRKPARLIVFPDLGVRVCEKMALYDVV SKLPLAVMGSSYGFQYSPGQRVEFLVQAW KSKKTPMGFSYDTRCFDSTVTESDIRTEEAI YQCCDLDPQARVAIKSLTERLYVGGPLTNS RGENCGYRRCRASGVLTTSCGNTLTCYIK ARAACRAAGLQDCTMLVCGNNLVVICESA GVQEDAASLRAFTEAMTRYSAPPGDPPQP EYDLELITSCSSNVSVAHDGAGKRVYYLTR DPTTPLARAAWETARHTPVNSWLGNIIMF APTLWARMILMTHFFSVLIARDQLEQALD CEIYGACYSIEPLDLPPIIQRLHGLSAFSLHS YSPGEINRVAACLRKLGVPPLRAWRHRAR SVRARLLSRGGRAAICGKYLFNWAVRTKL KLTPIAAAGQLDLSGWFTAGYSGGDIYHS VSHARPRWFWFCLLLLAAGVGIYLLPNR			

* TP sequences are based on HCV1a consensus sequence and gaps were removed
** Start and End numbers are based on sequence designated "Consensus" in Fig. 16A-16L.

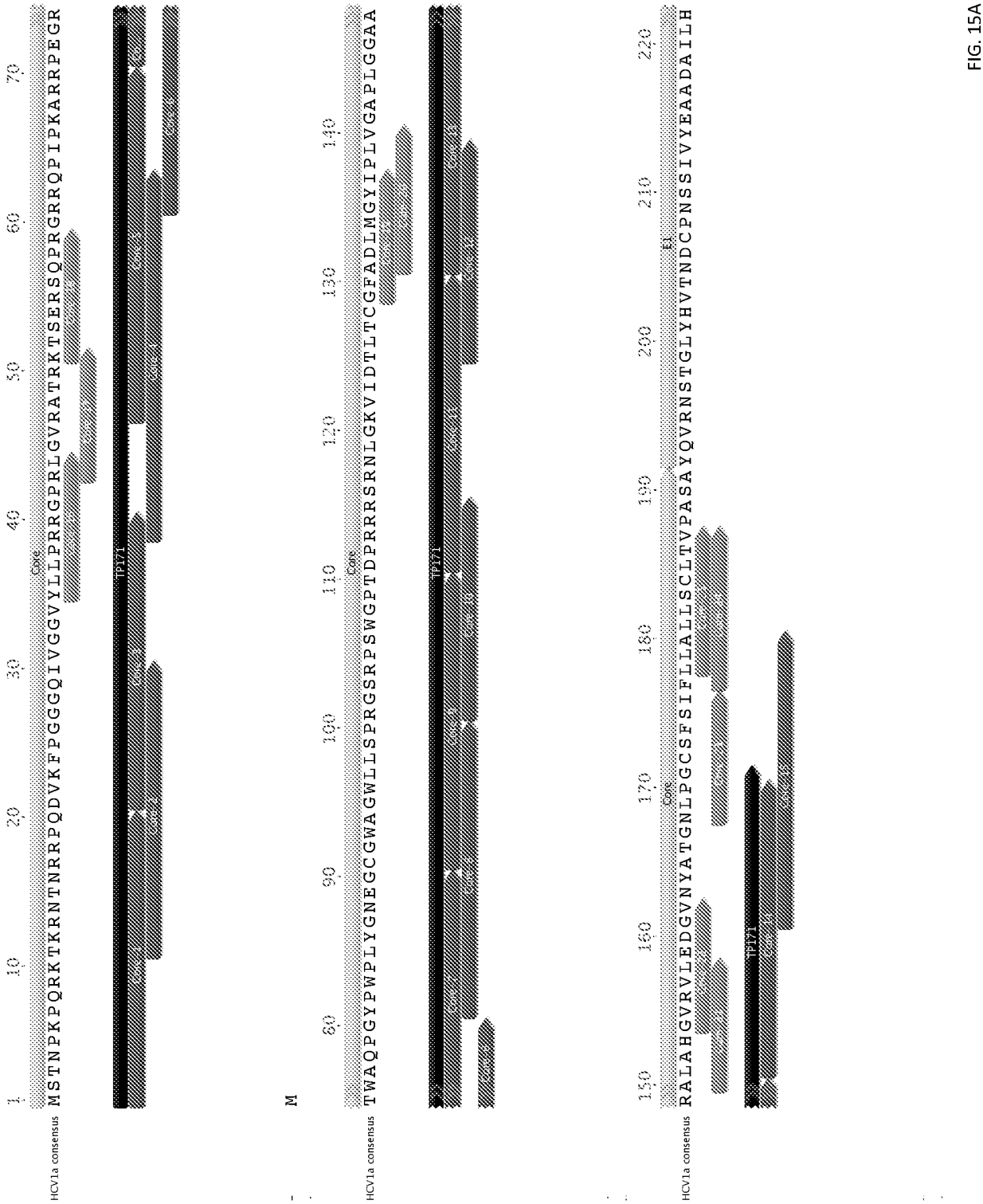

HCV1a consensus
MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKARRPEGR
Core
TP171
HCV1a consensus
TWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAA
Core
TP171
HCV1a consensus
RALAHGVRVLEDGVNYATGNLPGCSFSIFLLALLSCLTVPASAYQVRNSTGLYHVTNDCPNSSIVYEAADAILH
Core
E1
TP171

FIG. 15A

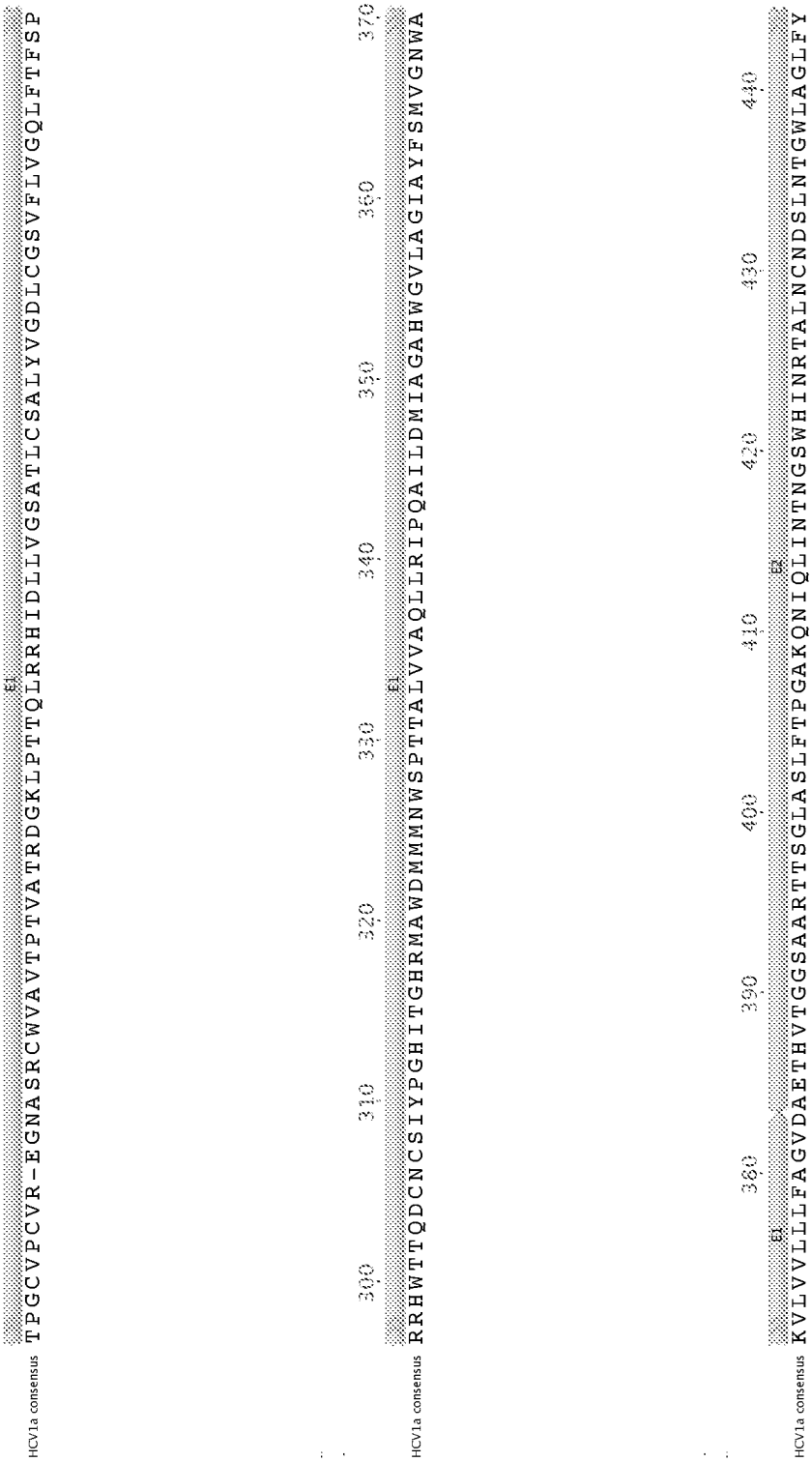

230 240 250 260 270 280 290
HCV1a consensus TPGCVPCVR-EGNASRCWVAVTPTVATRDGKLPTTQLRRHIDLLVGSATLCSALYVGDLCGSVFLVGQLFTFSP
E1
300 310 320 330 340 350 360 370
HCV1a consensus RRHWTTQDCNCSIYPGHITGHRMAWDMMMNWSPTTALVVAQLLRIPQAILDMIAGAHWGVLAGIAYFSMVGNWA
E1
380 390 400 410 420 430 440
HCV1a consensus KVLVVLLLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQNIQLINTNGSWHINRTALNCNDSLNTGWLAGLFY
E1 E2

FIG. 15B

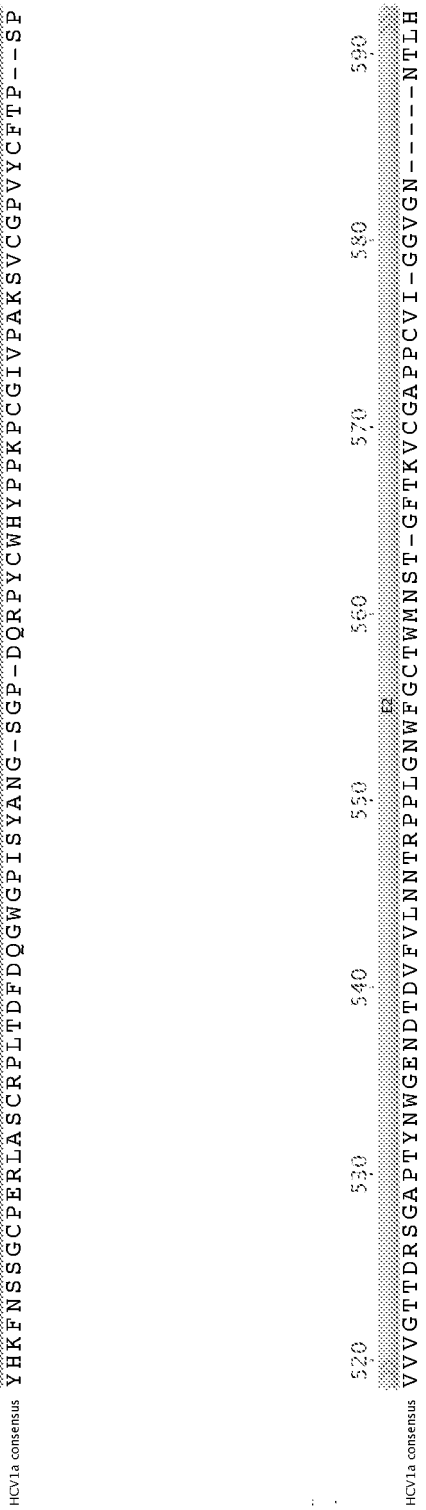

450
460
470
480
490
500
510
HCV1a consensus
YHKFNSSGCPERLASCRPLTDFDQGWGPISYANG-SGP-DQRPYCWHYPPKPCGIVPAKSVCGPVYCFTP--SP
520
530
540
550
560
570
580
590
HCV1a consensus
VVVGTTDRSGAPTYNWGENDTDVFVLNNTRPPLGNWFGCTWMNST-GFTKVCGAPPCVI-GGVGN-----NTLH
600
610
620
630
640
650
660
HCV1a consensus
CPTDCFRKHPEATYSRCGSGPWITPRCLVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCDL

FIG. 15C

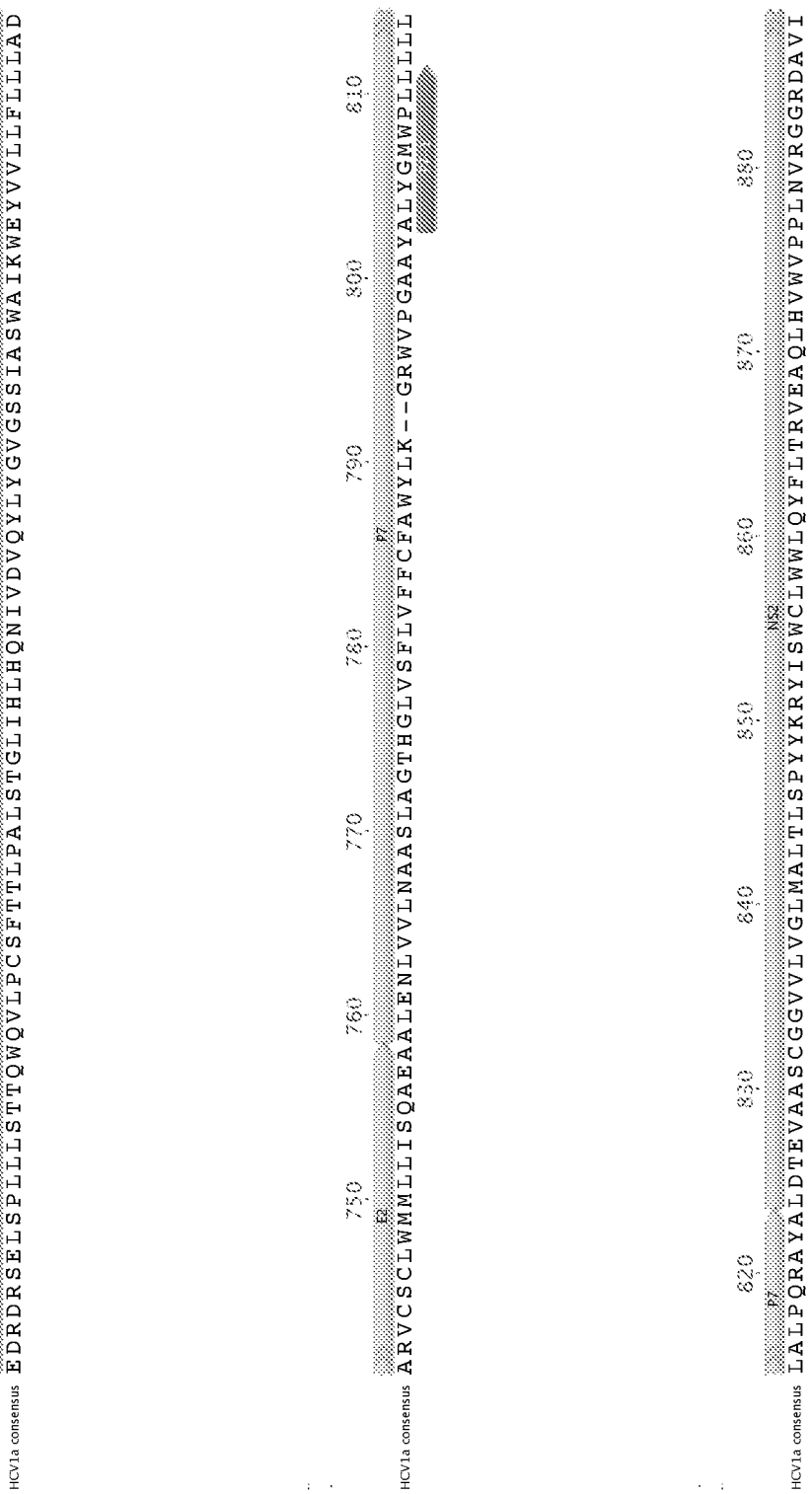

670
680
690
700
710
720
730
740
E2
HCV1a consensus EDRDRSELSPLLLSTTQWQVLPCSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSIASWAIKWEYVVLLFLLLAD
750
760
770
780
790
800
810
E2
p7
HCV1a consensus ARVCSCLWMMLLISQAEAALENLVVLNAASLAGTHGLVSFLVFFCFAWYLK--GRWVPGAAYALYGMWPLLLL
820
830
840
850
860
870
880
p7
NS2
HCV1a consensus LALPQRAYALDTEVAASCGGVVLVGLMALTLSPYYKRYISWCLWWLQYFLTRVEAQLHVWVPPLNVRGGRDAVI

FIG. 15D


HCV1a consensus
890
900
910
920
930
940
950
960
LLMCVVHPTLVFDITKLLLAVFGPLWILQASLLKVPYFVRVQGLLRICALARKMAGGHYVQMAIIKLGALTGTY
NS2
TPS53
TP50
970
980
990
1,000
1,010
1,020
1,030
VYNHLTPLRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADTAACGDIINGLPVSARRGREILLGPADGMVSKG
NS3
TP1083
1,040
1,050
1,060
1,070
1,080
1,090
1,100
1,110
WRLLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVSTAAQTFLATCINGVCWTVYHGAGTRTIASPKGP

FIG. 15E

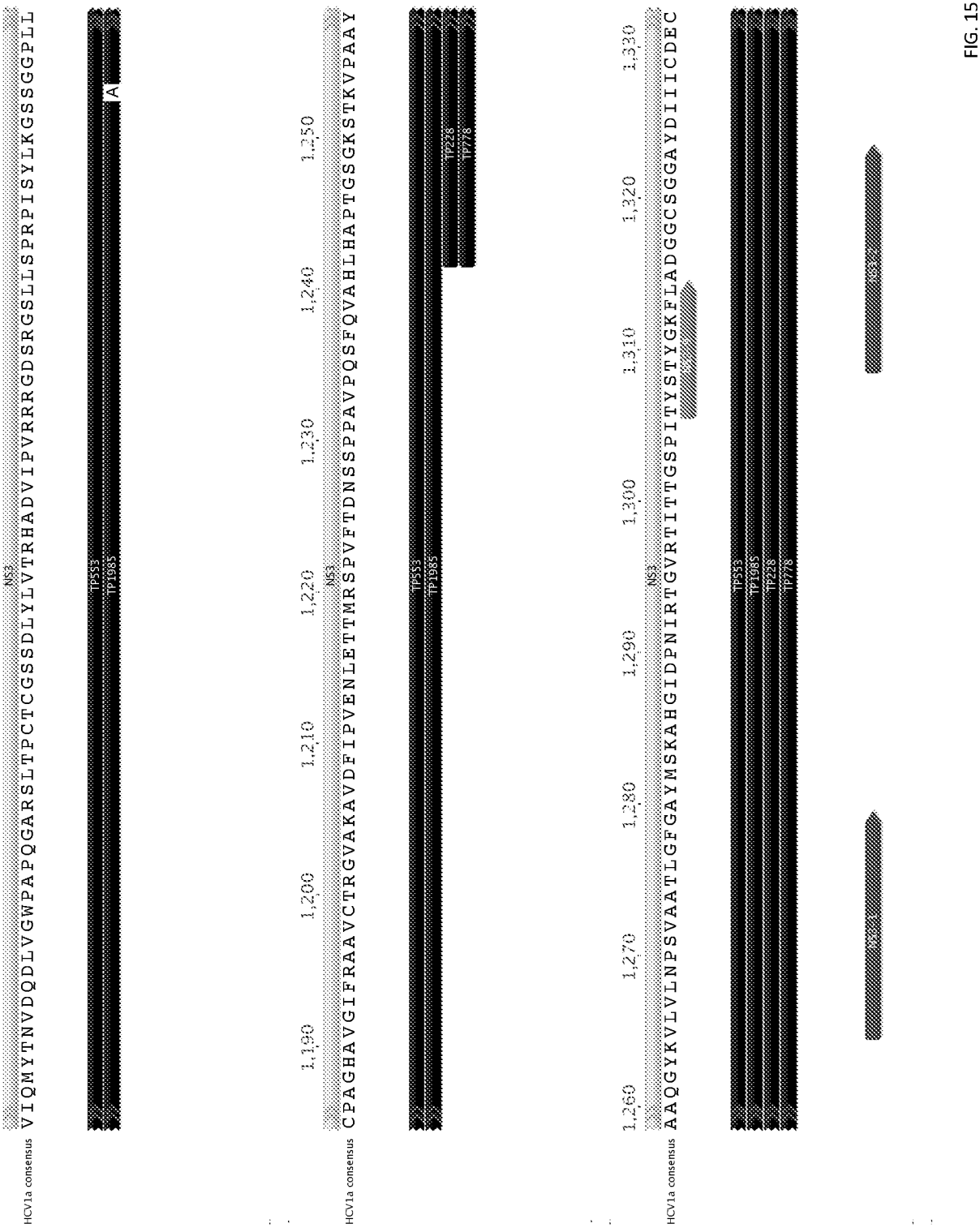

HCV1a consensus
1,120
1,130
1,140
1,150
1,160
1,170
1,180
VIQMYTNVDQDLVGWPAPQGARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGSSGGPLL
NS3
TPSS3
TP1085
A
HCV1a consensus
1,190
1,200
1,210
1,220
1,230
1,240
1,250
CPAGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAAY
NS3
TPSS3
TP1085
TP228
TP778
HCV1a consensus
1,260
1,270
1,280
1,290
1,300
1,310
1,320
1,330
AAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYGKFLADGGCSGGAYDIIICDEC
NS3
TPSS3
TP1085
TP228
TP778

FIG. 15F

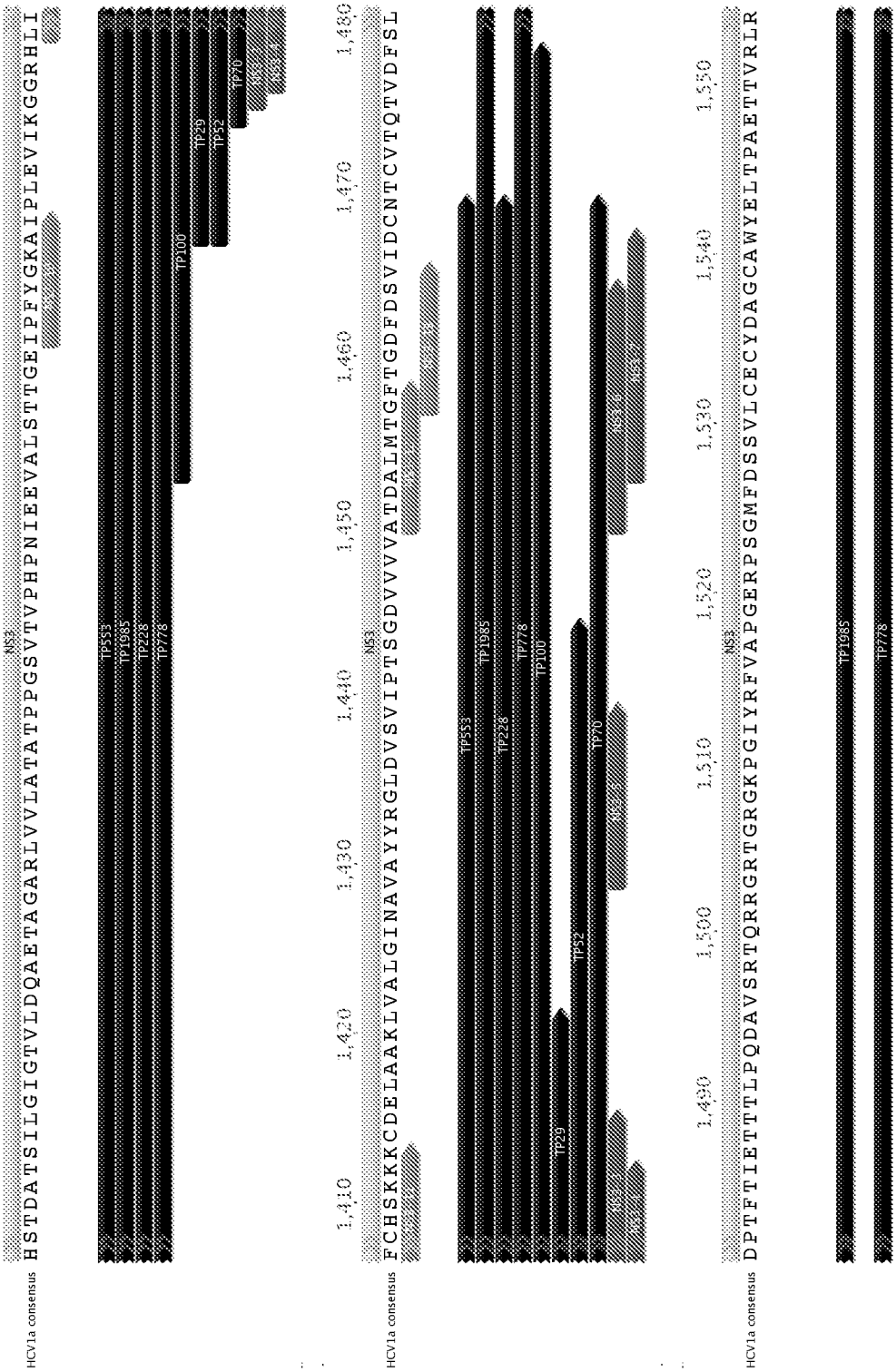

1,340
1,350
1,360
1,370
1,380
1,390
1,400
HCV1a consensus
HSTDATSILGIGTVLDQAETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHLI
NS3
TPSS3
TP1085
TP228
TP778
TP100
TP29
TP52
TP70
1,410
1,420
1,430
1,440
1,450
1,460
1,470
1,480
HCV1a consensus
FCHSKKKCDELAAKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSL
NS3
TPSS3
TP1085
TP228
TP778
TP100
TP29
TP52
TP70
1,490
1,500
1,510
1,520
1,530
1,540
1,550
HCV1a consensus
DPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCAWYELTPAETTVRLR
NS3
TP1085
TP778

FIG. 15G

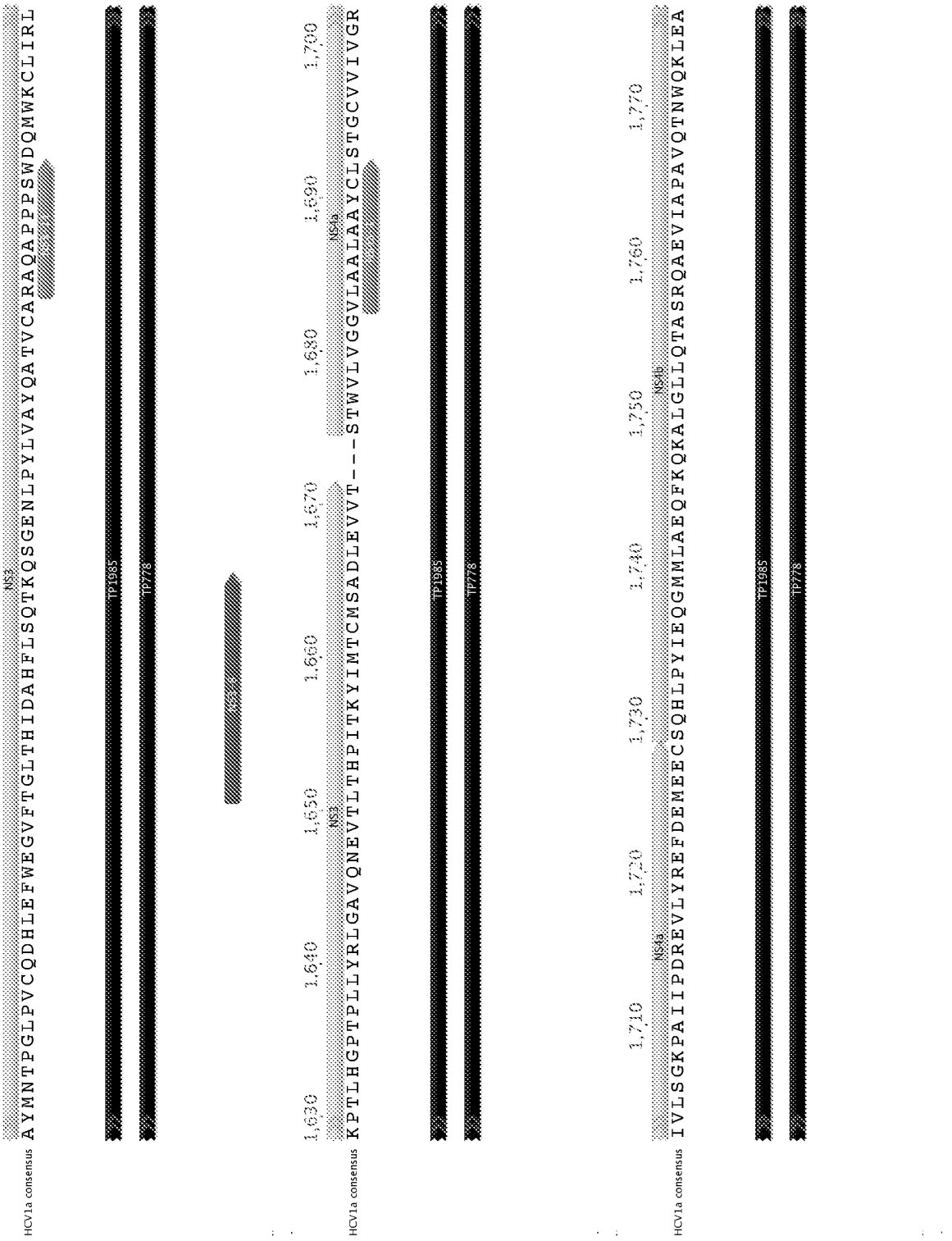

1,560
1,570
1,580
1,590
1,600
1,610
1,620
HCV1a consensus AYMNTPGLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLPYLVAYQATVCARAQAPPPSWDQMWKCLIRL
NS3
TP1985
TP778
NS3
1,630
1,640
1,650
1,660
1,670
1,680
1,690
1,700
HCV1a consensus KPTLHGPTPLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVT---STWVLVGGVLAALAAYCLSTGCVVIVGR
NS3
NS4a
TP1985
TP778
1,710
1,720
1,730
1,740
1,750
1,760
1,770
HCV1a consensus IVLSGKPAIIPDREVLYREFDEMEECSQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
NS4a
NS4b
TP1985
TP778

FIG. 15H

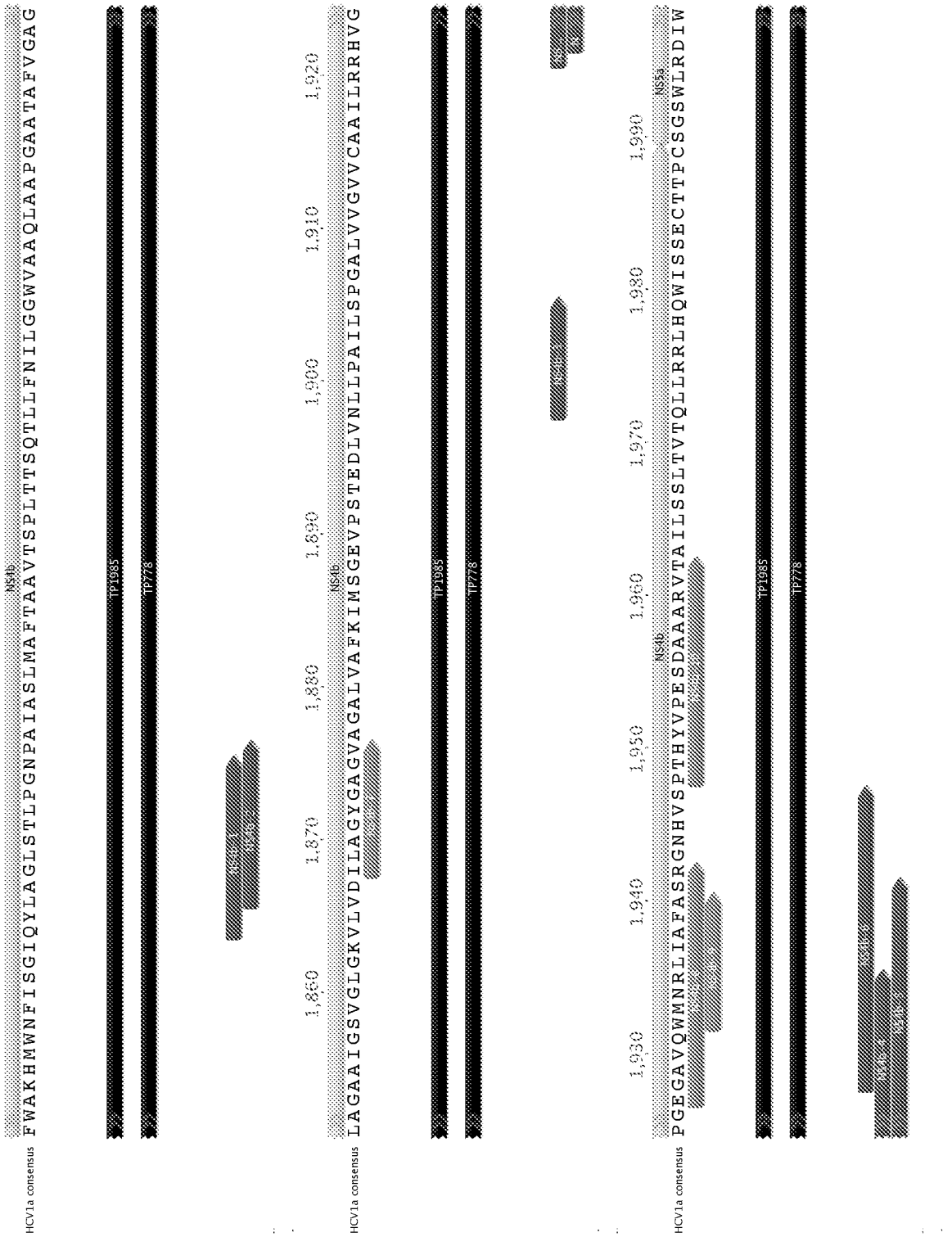

1,760
1,790
1,810
1,820
1,830
1,840
1,850
HCV1a consensus
FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAG
NS4b
TP1985
TP778
1,860
1,870
1,880
1,890
1,900
1,910
1,920
HCV1a consensus
LAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGALVVGVVCAAILRRHVG
NS4b
TP1985
TP778
1,930
1,940
1,950
1,960
1,970
1,980
1,990
HCV1a consensus
PGEGAVQWMNRLIAFASRGNHVSPTHYVPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIW
NS4b
NS5a
TP1985
TP778

FIG. 15I

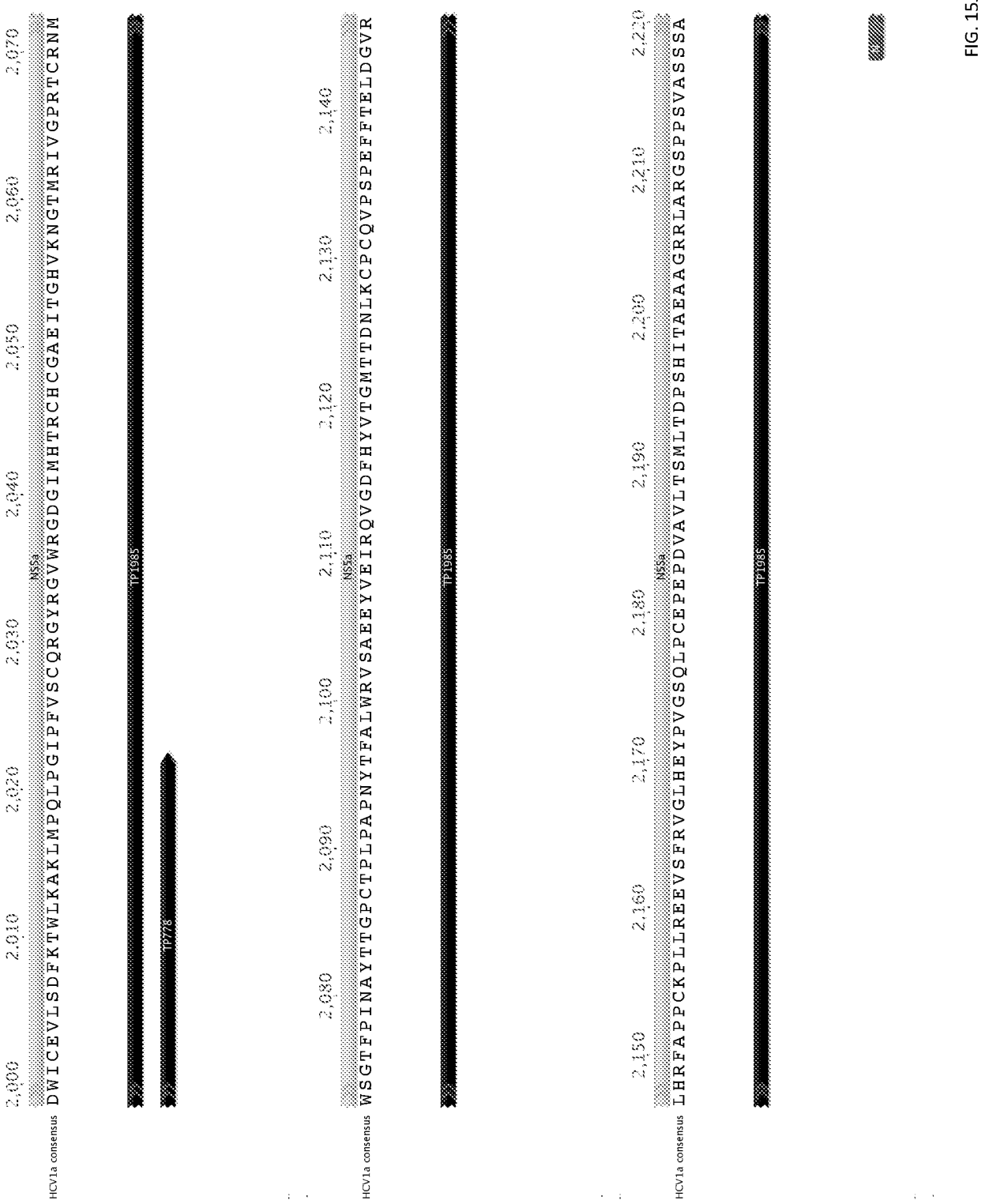

2,000
2,010
2,020
2,030
2,040
2,050
2,060
2,070
HCV1a consensus
DWICEVLSDFKTWLKAKLMPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTCRNM
NS5a
TP1985
TP778
2,080
2,090
2,100
2,110
2,120
2,130
2,140
HCV1a consensus
WSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGMTTDNLKCPCQVPSPEFFTELDGVR
NS5a
TP1985
2,150
2,160
2,170
2,180
2,190
2,200
2,210
2,220
HCV1a consensus
LHRFAPPCKPLLREEVSFRVGLHEYPVGSQLPCEPEPDVAVLTSMLTDPSHITAEAAGRRLARGSPPSVASSSA
NS5a
TP1985

FIG. 15J

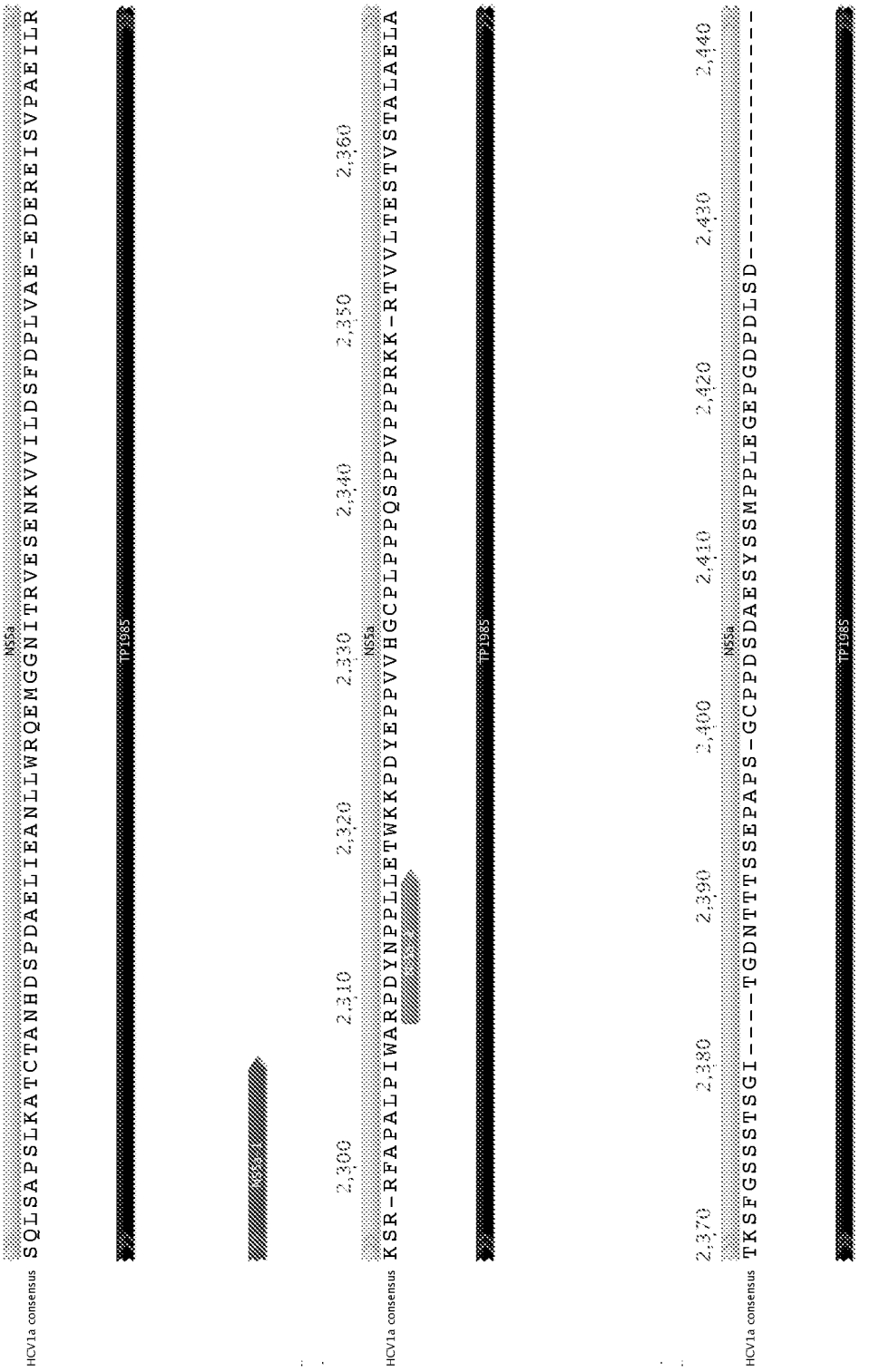

HCV1a consensus
SQLSAPSLKATCTANHDSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAE-EDEREISVPAEILR
2,230
2,240
2,250
2,260
2,270
2,280
2,290
NS5a
TP1085
HCV1a consensus
KSR-RFAPALPIWARPDYNPPLLETWKKPDYEPPVVHGCPLPPPQSPPVPPPRKK-RTVVLTESTVSTALAELA
2,300
2,310
2,320
2,330
2,340
2,350
2,360
NS5a
TP1085
HCV1a consensus
TKSFGSSSTSGI----TGDNTTSSEPAPS-GCPPDSDAESYSSMPPLEGEPGDPDLSD----------
2,370
2,380
2,390
2,400
2,410
2,420
2,430
2,440
NS5a
TP1085

FIG. 15K

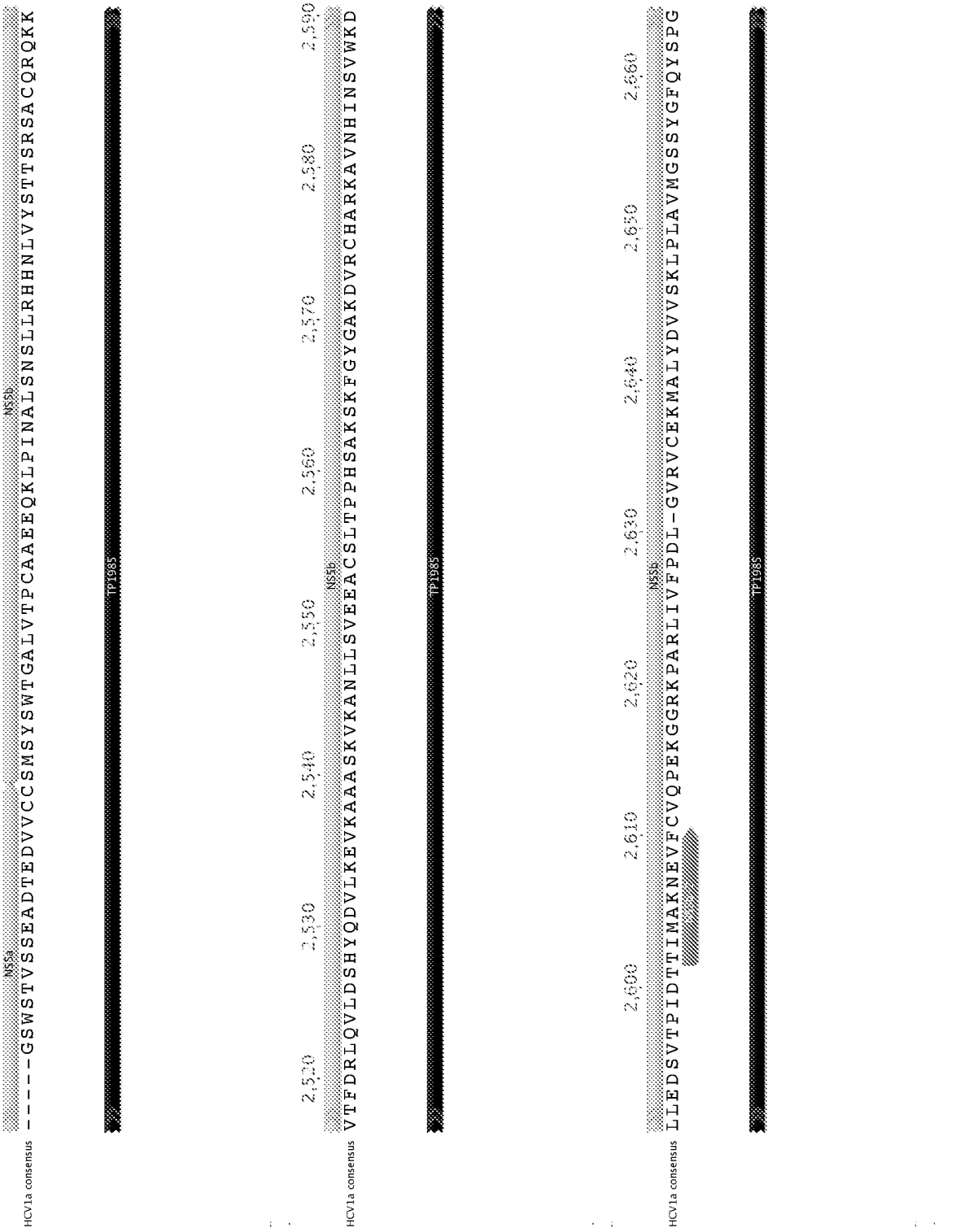

2,450
2,460
2,470
2,480
2,490
2,500
2,510
NS5a
HCV1a consensus
----GSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAEEQKLPINALSNSLLRHHNLVYSTTSRSACQRQKK
TP1985
2,520
2,530
2,540
2,550
2,560
2,570
2,580
2,590
NS5b
HCV1a consensus
VTFDRLQVLDSHYQDVLKEVKAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVWKD
TP1985
2,600
2,610
2,620
2,630
2,640
2,650
2,660
NS5b
HCV1a consensus
LLEDSVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDL-GVRVCEKMALYDVVSKLPLAVMGSSYGFQYSPG
TP1985

FIG. 15L

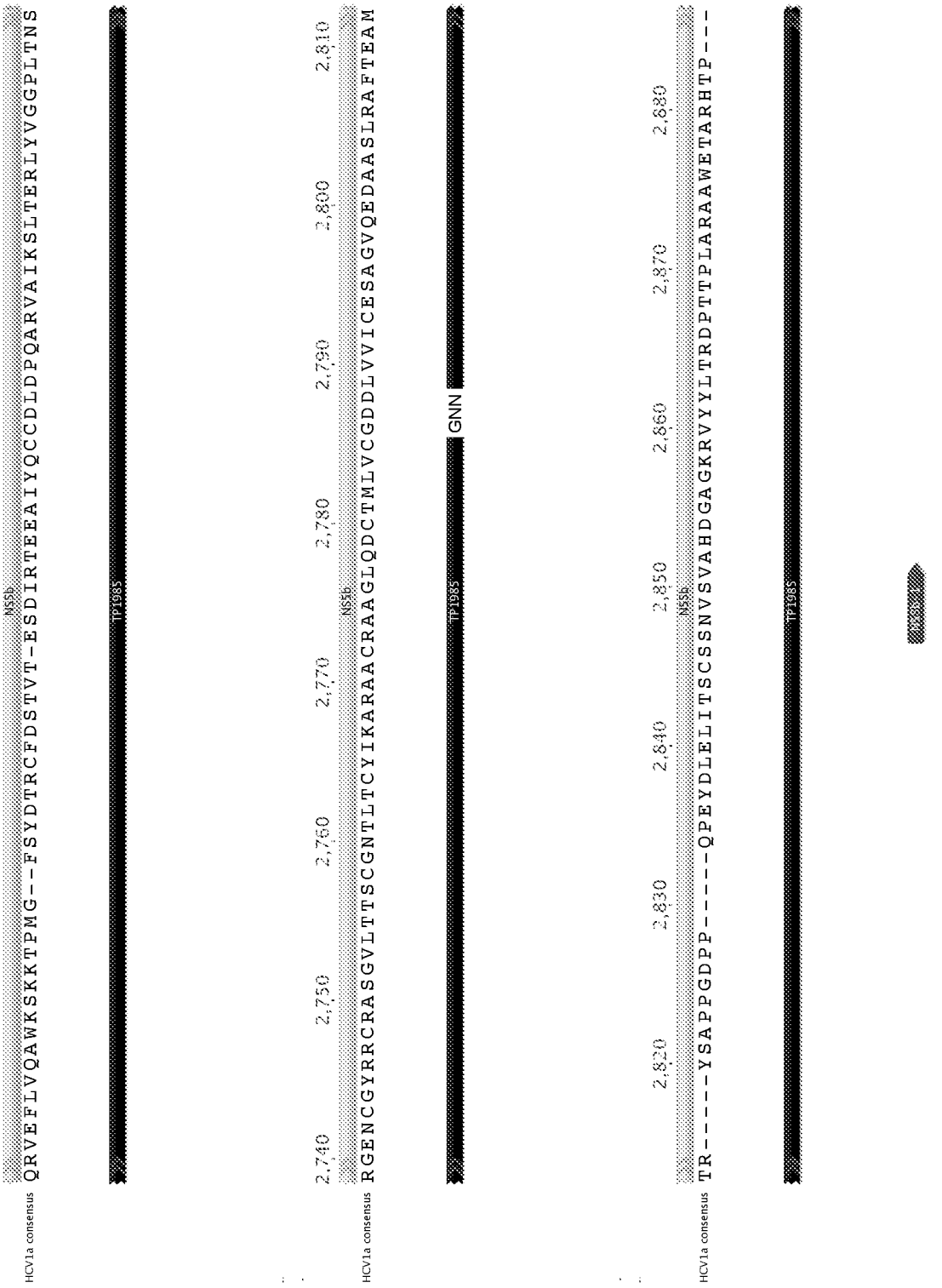

2,670
2,680
2,690
2,700
2,710
2,720
2,730
HCV1a consensus
QRVEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESDIRTEEAIYQCCDLDPQARVAIKSLTERLYVGGPLTNS
NS5b
TP1085
2,740
2,750
2,760
2,770
2,780
2,790
2,800
2,810
HCV1a consensus
RGENCGYRRCRASGVLTTSCGNTLTCYIKARAACRAAGLQDCTMLVCGDDLVVICESAGVQEDAASLRAFTEAM
NS5b
TP1085
GNN
2,820
2,830
2,840
2,850
2,860
2,870
2,880
HCV1a consensus
TR-----YSAPPGDPP-----QPEYDLELITSCSSNVSVAHDGAGKRVYYLTRDPTTPLARAAWETARHTP---
NS5b
TP1085

FIG. 15M

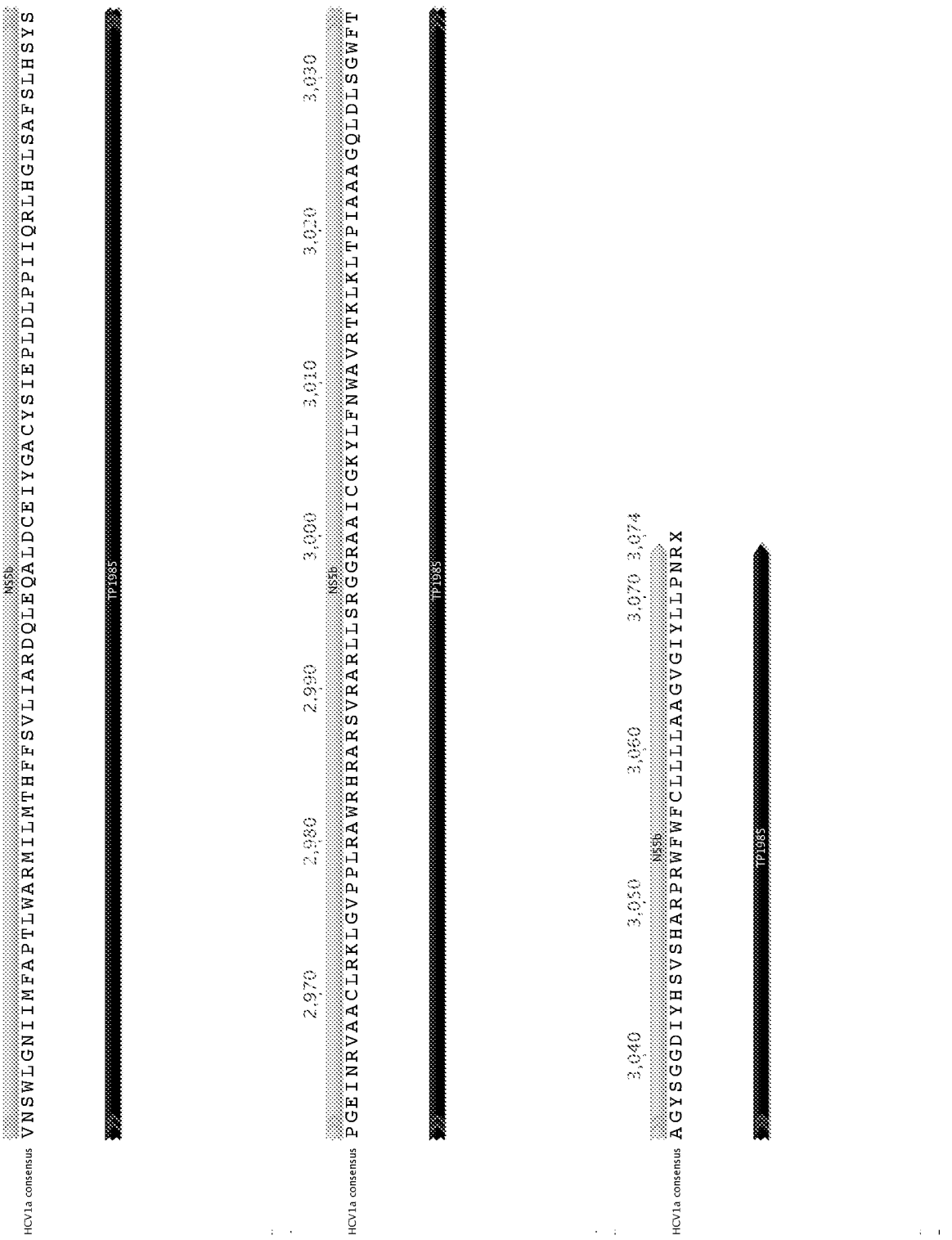

2,890
2,900
2,910
2,920
2,930
2,940
2,950
2,960
HCV1a consensus
VNSWLGNIIMFAPTLWARMILMTHFFSVLIARDQLEQALDCEIYGACYSIEPLDLPPIIQRLHGLSAFSLHSYS
TP1085
NS5b
2,970
2,980
2,990
3,000
3,010
3,020
3,030
HCV1a consensus
PGEINRVAACLRKLGVPPLRAWRHRARSVRARLLSRGGRAAICGKYLFNWAVRTKLKLTPIAAAGQLDLSGWFT
TP1085
NS5b
3,040
3,050
3,060
3,070
3,074
HCV1a consensus
AGYSGGDIYHSVSHARPRWFWFCLLLLAAGVGIYLLPNRX
TP1085
NS5b

FIG. 15N

Consensus
Core
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
Consensus
Core
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
Consensus
Core
E1
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177

FIG. 16A

260 270 280 290 300 310 320 330 340
Consensus
E1
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
330 360 370 380 390 400 410 420 430
Consensus
E1
E2
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
440 450 460 470 480 490 500 510
Consensus
E2
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177

FIG. 16B

```
                520       530       540       550       560       570       580       590       600
Consensus       SPVVVGTTDRXGVPTYTWGENETDVFLLNSTRPPQGNWFGCTWMNST-GFTKTCGAPPCNI-GGGGN-----NDLLCPTDCFRKHP
                                                                  E2                                  

1. HCV1a consensus SPVVVGTTDRSGAPTYNWGENDTDVFVLNNTRPPLGNWFGCTWMNST-GFTKVCGAPPCVI-GGVGN-----NTLHCPTDCFRKHP
2. HCV1b consensus SPVVVGTTDRFGVPTYSWGENETDVLLLNNTRPPQGNWFGCTWMNST-GFTKTCGGPPCNI-GGVGN-----NTLTCPTDCFRKHP
3. HCV2a Consensus SPVVVGTTDRLGVPTYTWGENETDVFLLNSTRPPQGSWFGCTWMNST-GFTKTCGAPPCRI-RADFNAS---TDLLCPTDCFRKHP
4. HCV2b Consensus SPVVVGTTDRQGVPTYSWGENETDVFLLNSTRPPQGAWFGCTWMNGT-GFTKTCGAPPCRI-RRDYNST---LDLLCPTDCFRKHP
5. HCV 3 Consensus SPVVVGTTDAKGVPTYTWGENETDVFLLESLRPPSGRWFGCTWMNSTRGFVKTCGAPPCNIYGGGGNPXNNESDLFCPTDCFRKHP
6. HCV 4 Consensus SPVVVGTTDRLGVPTYTWGENESDVFLLNSTRPPQGAWFGCVWMNST-GFTKACGAPPCEVRTNNGTS----TDWPCPTDCFRKHP
7. HCV5 consensus SPVVVGTTDRXGXPTYXWGXNETDIFLLNNTRPPXGNWFGCTWMNST-GFVKTCGAPPCNL-GPTGN-----NSLKCPTDCFRKHP
8. HCV6 consensus SPVVVGTTDRRGLPTYTWGENETDVFLLESLRPPTGGWFGCTWMNST-GFVKTCGAPPCNIXPNSSN-----NSLLCPTDCFRKHP
9. HCV7: ABN05226 SPVVVGTTDRRGVPTYTWGENESDVFLLNSTRPPQGSWFGCSWMNTT-GFTKTCGGPPCKIRPQGAQSN---TSLTCPTDCFRKHP
14. AVI1a-129 SPVVVGTTDKSGAPTYNWGENDWDVFVLNNTRPPLGNWFGCTWMNST-GFTKVCGAPPCVI-GGAGN-----NTLRCPTDCFRKHP
15. AVI3a-177 SPVVVGTTDRQGVPTYTWGENETDVFLLRSLRPPSGQWFGCTWMNST-GFVKTCGAPPCDIYGGGGNRCN-ESDLFCPTDCFRKHP
                610       620       630       640       650       660       670       680       
Consensus       EATYSXCGSGPWLTPRCLVDYPYRLWHYPCTVNFTIFKVRMYVGGVEHRLEAACNWTRGERCDLEDRDRSELSPLLHSTTEWAILP
                                                                  E2                                  

1. HCV1a consensus EATYSRCGSGPWITPRCLVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTRGERCDLEDRDRSELSPLLLSTTQWQVLP
2. HCV1b consensus EATYTKCGSGPWLTPRCLVDYPYRLWHYPCTVNFTIFKVRMYVGGVEHRLNAACNWTRGERCDLEDRDRSELSPLLLSTTEWQILP
3. HCV2a Consensus EATYIKCGSGPWLTPRCLVDYPYRLWHYPCTVNYTIFKIRMYVGGVEHRLTAACNFTRGDRCNLEDRDRSQLSPLLHSTTEWAILP
4. HCV2b Consensus DATYLKCGAGPWLTPRCLVDYPYRLWHYPCTVNFTIFKVRMYVGGVEHRLSAACNFTRGDRCRLEDRDRGQQSPLLHSTTEWAVLP
5. HCV 3 Consensus EATYSRCGAGPWLTPRCMVDYPYRLWHYPCTVNFTLFKVRMFVGGFEHRFTAACNWTRGERCDIEDRDRSEQHPLLHSTTELAILP
6. HCV 4 Consensus ETTYAKCGSGPWITPRCLIHYPYRLWHYPCTVNFTVFKIRTFIGGIEHRMEAACNWTRGEVCGLEHRDRAELSPLLLSTTTWQXLP
7. HCV5 consensus DATYTKCGSGPWLTPRCLVHYPYRLWHYPCTVNYTIFKVRMFIGGLEHRLEAACNWTRGERCDLEDRDRAELSPLLHTTTQWAILP
8. HCV6 consensus EATYARCGSGPWLTPRCLVDYPYRLWHYPCTVNFTIHKVRMFVGGVEHRFDAACNWTRGERCELDDRDRIEMSPLLFSTTELAILP
9. HCV7: ABN05226 RATYSACGSGPWLTPRCMVHYPYRLWHYPCTVNFTIHKVRLYIGGVEHRLDAACNWTRGERCDLEDRDRVDMSPLLHSTTELAILP
14. AVI1a-129 DATYSRCGSGPWITPRCLVDYPYRLWHYPCTVNYSIFKIRMYLGGVEHRLEAACNWTRGERCDLEDRDRSELSPLLLSTTQWQVLP
15. AVI3a-177 EATYSRCGAGPWLTPRCLVDYPYRLWHYPCTVNFTLFKVRMFVGGFEHRFTAACNWTRGERCNIEDRDRSEQHPLLHSTTELAILP
                690       700       710       720       730       740       750       760       770
Consensus       CSFTTLPALSTGLIHLHQNIVDVQYLYGVGSAVVSWAXKWEYVVLLFLLLADARVCACLWMMLLISQAEAALENLVVLNAASAAGT
                                                                  E2                  P7              

1. HCV1a consensus CSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSIASWAIKWEYVVLLFLLLADARVCSCLWMMLLISQAEAALENLVVLNAASLAGT
2. HCV1b consensus CSFTTLPALSTGLIHLHQNIVDVQYLYGIGSAVVSFAIKWEYVLLFLLLADARVCACLWMMLLIAQAEAALENLVVLNAASVAGA
3. HCV2a Consensus CSYSDLPALSTGLLHLHQNIVDVQYMYGLGSPALTKYVVRWEWVVLLFLLLADARVCACLWMLILLGQAEAALEKLVVLHAASAASC
4. HCV2b Consensus CSFSDLPALSTGLLHLHQNIVDVQYLYGLGSPAITRYIVKWEWVVLLFLLLADARVCACLWMLIILGQAEAALEKLIILHSASAASA
5. HCV 3 Consensus CSFTTPMPALSTGLIHLHQNIVDVQYLYGVGSGMVGWALKWEFVIVFLLLADARVCVALWLMLMISQAEAALENLVTLNAVAAAGT
6. HCV 4 Consensus CSFTTLPALSTGLIHLHQNIVDVQYLYGVGSAVVSWALKWEYVVLAFLLLADARVSACLWMMFMVSQVEAALSNLININAASAAGT
7. HCV5 consensus CSFTPTPALSTGLIHLHQNIVDTQYLYGLGSSIVSWAVKWEYIVLXFLLLADARICTCLWILLLXCQAEAALENVIVLNAAAAAGX
8. HCV6 consensus CSFTTMPALSTGLIHLHQNIVDVQYLYGVGSSVVSWAVKWEYVVLAFLVLADARICACLWLMLLIGQAEAALENLIVLNAASAAST
9. HCV7: ABN05226 CSFVPLPALSTGLIHLHQNIVDAQYLYGLGSPAIISWAIRWEWVVLVFLLLADARICACLWMMMLMAQAEAALENLIHLNAASLAGT
14. AVI1a-129 CSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSVASWAIKWDYVVLLFLLLADARICSCLWMMLLISQAEAALENLVVLNAASLAGT
15. AVI3a-177 CSFTPMPALSTGLIHLHQNIVDVQYLYGVGSGVVGWALRWEFVVLVFLLLADARVCVALWLMLMISQAEAALENLVTLNAVAAAGT
```

FIG. 16C

Consensus
P7
NS2
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
Consensus
NS2
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
Consensus
NS2
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177

FIG. 16D

```
                    1,040     1,050     1,060     1,070     1,080     1,090     1,100     1,110
Consensus           XSKGWRLLAPITAYAQQTRGLLGTIVTSLTGRDKNEVEGEVQVLSTATQTFLGTCINGVCWTVYHGAGSKTLAGPKGPVXQMYTNV
                          NS2                                       NS3

1. HCV1a consensus  VSKGWRLLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQVVSTAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNV
2. HCV1b consensus  EGQGWRLLAPITAYSQQTRGLLGCIITSLTGRDKNQVEGEVQVVSTATQSFLATCVNGVCWTVYHGAGSKTLAGPKGPITQMYTNV
3. HCV2a Consensus  TSKGWRLLAPITAYAQQTRGLLGAIVVSMTGRDKTEQAGEIQVLSTVTQSFLGTSISGVLWTVYHGAGNKTLAGSRGPVTQMYSSA
4. HCV2b Consensus  TSKGWKLLAPITAYTQQTRGLLGAIVVSLTGRDKNEQAGQVQVLSSVTQSFLGTSISGVLWTVYHGAGNKTLAGPKGPVTQMYTSA
5. HCV 3 Consensus  REMGWRLLAPITAYAQQTRGLLGTIVTSLTGRDKNVVTGEVQVLSTATQTFLGTTVGGVMWTVYHGAGSRTLAGAKHPALQMYTNV
6. HCV 4 Consensus  TSKGWRLLAPITAYAQQTRGLFSTIITSLTGRDTNENCGEVQVLSTATQSFLGTAVNGVMWTVYHGAGSKTISGPKGPVNQMYTNV
7. HCV5 consensus   XXAGWRLLAPITAYAQQTRGVLGAIVVSLTGRDKNEAEGEVQVLSTATQTFLGTCINGVMWTVFHGAGXKTLAGPKGPVVQMYTNV
8. HCV6 consensus   KRGGWRLLAPITAYAQQTRGLLGTIVTSLTGRDKNEVEGEVQVVSTATQSFLATSINGVLWTVYHGAGSKTLAGPKGPVCQMYTNV
9. HCV7: ABN05226   RSMGWQLLAPISAYAQQTRGLISTLVVSLTGRDKNETAGEVQVLSTSTQTFLGTNVGGVMWGPYHGAGTRTVAGRGGPVLQMYTSV
14. AVI1a-129        VSKGWRLLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVSTAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNV
15. AVI3a-177        REMGWRLLAPITAYAQQTRGLLGTIVTSLTGRDKNVVTGEVQVLSTATQTFLGTTIGGVMWTVYHGAGSRTLAGVKHPALQMYTNV
                    1,120     1,130     1,140     1,150     1,160     1,170     1,180     1,190     1,200
Consensus           DQDLVGWPAPPGAKSLTPCTCGSSDLYLVTRHADVIPXRRRGDSRGSLLSPRPISXLKGSSGGPVLCPSGHAVGIFRAAVCTRGVA
                                                      NS3

1. HCV1a consensus  DQDLVGWPAPQGARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGSSGGPLLCPAGHAVGIFRAAVCTRGVA
2. HCV1b consensus  DQDLVGWQAPPGARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPVSYLKGSSGGPLLCPSGHAVGIFRAAVCTRGVA
3. HCV2a Consensus  EGDLVGWPSPPGTKSLEPCTCGAVDLYLVTRNADVIPARRRGDKRGALLSPRPLSTLKGSSGGPVLCPRGHAVGIFRAAVCSRGVA
4. HCV2b Consensus  EGDLVGWPSPPGTKSLDPCTCGAVDLYLVTRNADVIPVRRKDDRRGALLSPRPLSTLKGSSGGPVLCPRGHAVGLFRAAVCARGVA
5. HCV 3 Consensus  DQDLVGWPAPPGAKSLEPCACGSADLYLVTRDADVIPARRRGDSTASLLSPRPLACLKGSSGGPVMCPSGHVAGIFRAAVCTRGVA
6. HCV 4 Consensus  DQDLVGWPAPPGVKSLAPCTCGASDLYLVTRHADVVPVRRRGDTRGALLSPRPISTLKGSSGGPLLCPMGHAAGIFRAAVCTRGVA
7. HCV5 consensus   DKDLVGWPXPPGXRSLTPCTCGSADLYLVTRHADVIPARRRGDTRASLLSPRPISYLKGSSGGPIMCPSGHVVGVFRAAVCTRGVA
8. HCV6 consensus   DQDLVGWPAPPGARSLTPCTCGSSDLYLVTRNADVIPARRRGDTRAALLSPRPISTLKGSSGGPILCPSGHVVGLFRAAVCTRGVA
9. HCV7: ABN05226   SDDLVGWPAPPGSKSLEPCSCGSADLYLVTRNADVLPLRRKGDGTASLLSPRPVSSLKGSSGGPVLCPQSHCVGIFRAAVCTRGVA
14. AVI1a-129        DKDLVGWPAPPGSRSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGSSGGPLLCPAGHAVGIFRAAVCTRGVA
15. AVI3a-177        DQDLVGWPAPPGAKSLEPCSCGSTDLYLVTREADVIPARRRGDSTASLLSPRPLACLKGSSGGPVMCPSGHVAGIFRAAVCTRGVA
                    1,210     1,220     1,230     1,240     1,250     1,260     1,270     1,280     1,290
Consensus           KAVDFIPVESLETTMRSPXFTDNSTPPAVPQXYQVGYLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDP
                                                      NS3

1. HCV1a consensus  KAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDP
2. HCV1b consensus  KAVDFVPVESMETTMRSPVFTDNSSPPAVPQTFQVAHLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGVDP
3. HCV2a Consensus  KSIDFIPVETLDIVTRSPTFSDNSTPPAVPQTYQVGYLHAPTGSGKSTKVPVAYAAQGYKVLVLNPSVAATLGFGAYLSKAHGINP
4. HCV2b Consensus  KSIDFIPVESLDIATRTPSFSDNSTPPAVPQSYQVGYLHAPTGSGKSTKVPAAYASQGYKVLVLNPSVAATLGFGAYMSKAHGINP
5. HCV 3 Consensus  KALQFIPVETLSTQARSPSFSDNSTPPAVPQSYQVGYLHAPTGSGKSTKVPAAYVAQGYNVLVLNPSVAATLGFGSFMSRAYGIDP
6. HCV 4 Consensus  KAVDFVPVESLETTMRSPVFTDNSTPPAVPQTYQVAHLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAYGIDP
7. HCV5 consensus   KALDFIPVENLETTMRSPVFTDNSTPPAVPHEFQVGHLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSRAYGVDP
8. HCV6 consensus   KSLDFVPVENMETTMRSPSFTDNSTPPAVPQTYQVGYLHAPTGSGKSTKVPAAYASQGYKVLVLNPSVAATLGFGSYMSKAHGIDP
9. HCV7: ABN05226   KAVQFVPIEKMQVAQRSPSFSDNSTPPAVPSTYQVGYLHAPTGSGKSTKVPAAYASQGYKVLVLNPSVAATLGFGAYMSKAYGIDP
14. AVI1a-129        KAVDFIPVESLETTMRSPVFTDNSSPPVVPQSFQVAHLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATL?FGAYMSKAHGVDP
15. AVI3a-177        KALQFIPVETLSAQARSPSFSDNSTPPIVPQSYQVGYLHAPTGSGKSTKVPAAYVAQGYNVLVLNPSVAATLGFGSFMSRAYGIDP
```

FIG. 16E

1,300 1,310 1,320 1,330 1,340 1,350 1,360 1,370
Consensus
NS3
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
1,380 1,390 1,400 1,410 1,420 1,430 1,440 1,450 1,460
Consensus
NS3
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
1,470 1,480 1,490 1,500 1,510 1,520 1,530 1,540
Consensus
NS3
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177

FIG. 16F

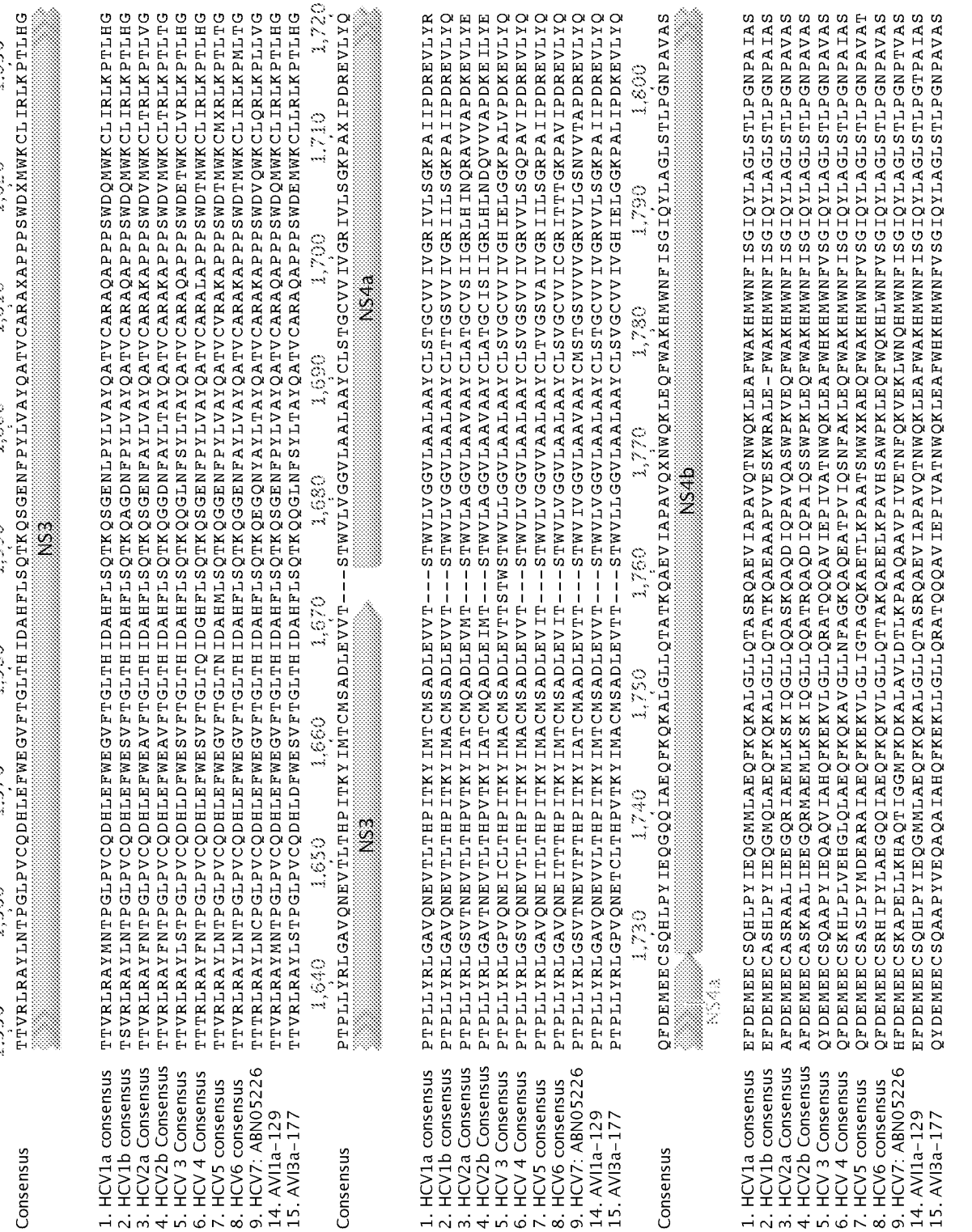

1,550 1,560 1,570 1,580 1,590 1,600 1,610 1,620 1,630
Consensus
NS3
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
1,640 1,650 1,660 1,670 1,680 1,690 1,700 1,710 1,720
Consensus
NS3
NS4a
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
1,730 1,740 1,750 1,760 1,770 1,780 1,790 1,800
Consensus
NS4a
NS4b
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177

FIG. 16G

1,810 1,820 1,830 1,840 1,850 1,860 1,870 1,880 1,890
Consensus
NS4b
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
1,900 1,910 1,920 1,930 1,940 1,950 1,960 1,970
Consensus
NS4b
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
1,980 1,990 2,000 2,010 2,020 2,030 2,040 2,050 2,060
Consensus
NS4b
NS5a
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177

FIG. 16H

2,070 2,080 2,090 2,100 2,110 2,120 2,130 2,140 2,150
Consensus GPKTCSNTWHGTFPINAYTTGPXXPXPAPNYKRALWRVXAEEYVEVRRVGDFHYVTGXTTDNLKCPCQVPAPEFFTEVDGVRLHRX
NS5a
1. HCV1a consensus GPRTCRNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGMTTDNLKCPCQVPSPEFFTELDGVRLHRF
2. HCV1b consensus GPKTCSNTWHGTFPINAYTTGPCTPSPAPNYSRALWRVAAEEYVEVTRVGDFHYVTGMTTDNVKCPCQVPAPEFFTEVDGVRLHRY
3. HCV2a Consensus GPKTCMNTWQGTFPINCYTEGQCVPKPAPNFKTAIWRVAASEYAEVTQHGSYSYITGLTTDNLKVPCQLPSPEFFSWVDGVQIHRF
4. HCV2b Consensus GPKTCLNLWQGTFPINCYTEGPCVPKPPPNYKTAIWRVAASEYVEVTQHGSFSYVTGLTSDNLKVPCQVPAPEFFSWVDGVQIHRF
5. HCV 3 Consensus GPRTCANMWHGTFPINEYTTGPSTPCPSPNYTRALWRVAANSYVEVRRVGDFHYITGATEDELKCPCQVPAAEFFTEVDGVRLHRY
6. HCV 4 Consensus GPKTCSNTWHGTFPINAYTTGPGVPIPAPNYKFALWRVSAEEYVEVRRVGDFHYVTGVTQDNIKCPCQVPSPEFFTELDGIRLHRH
7. HCV5 consensus GPKLCSNTWHGTFPINATTTGPSVPAPAPNYKFALWRVGAADYAEVRRVGDYHYITGVTQDNLKCPCQVPSPEFFTELDGVRIHRY
8. HCV6 consensus GPRTCSNTWHGTFPINATTTGPSVPIPEPNYKRALWRVSAEDYVEVVRVGDCHYVVGATADNLKCPCQVPAPEFFTEVDGVRLHRY
9. HCV7: ABN05226 GPKTCRNTWWGTFPINSHTTGPSSPVPSHCYQRALWRVSATEYVEILRHNDQHYVVGVTAEDLKCPCQVPSPEFFSFVDGVRIHRF
14. AVI1a-129 GPRTCRNMWSGTFPINAYTTGPCTPLPAPNYKFALWRVSAEEYVEIRQVGDFHYVTGMTTDDLKCPCQVPSPEFFTELDGVRLHRF
15. AVI3a-177 GPRTCANMWHGTFPINEYTTGPSTPCPSPNYTRALWRVAANSYVEVRQVGDFHYITGATEDGLKCPCQVPAAEFFTEVDGVRLHRY
2,160 2,170 2,180 2,190 2,200 2,210 2,220 2,230
Consensus APPCKPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSHITAETAARRLARGSPPSLASSSASQLSAPSLKATCTHH
NS5a
1. HCV1a consensus APPCKPLLREEVSFRVGLHEYPVGSQLPCEPEPDVAVLTSMLTDPSHITAEAGRRLARGSPPSVASSSASQLSAPSLKATCTANH
2. HCV1b consensus APACKPLLREEVTFQVGLNQYLVGSQLPCEPEPDVAVLTSMLTDPSHITAETAKRRLARGSPPSLASSSASQLSAPSLKATCTTRH
3. HCV2a Consensus APTPKPFFRDEVSFCVGLNSFVVGSQLPCDPEPDTDVLMSMLTDPSHITAEAAARRLARGSPPSEASSSASQLSAPSLRATCTTHG
4. HCV2b Consensus APTPGPFFRDEVTFTVGLNSFVVGSQLPCDPEPDTEVLASMLTDPSHITAEAAARRLARGSPPSQASSSASQLSAPSLKATCTTHK
5. HCV 3 Consensus APPCKPLLRDEITFMVGLNSYAIGSQLPCEPEPDVSVLTSMLRDPSHITAETAARRLARGSPPSEASSSASQLSAPSLKATCQTHR
6. HCV 4 Consensus APKCKPLLRDEVSFSVGLNSFVVGSQLPCEPEPDVAVLTSMLTDPSHITAETASRRLARGSPPSLASSSASQLSAPSLKATCTARH
7. HCV5 consensus APPCNPLLREEVCFSVGLHSYVVGSQLPCEPEPDVTVLTSMLSDPAHITAETAKRRLDRGSPPSLASSSASQLSAPSLKATCTTQG
8. HCV6 consensus APPCKPLLRDEVTFSVGLSSYAIGSQLPCEPEPDVTVVTSMLTDPSHITAETAARRLARGSPPSLASSSASQLSAPSLKATCTTHG
9. HCV7: ABN05226 APEPKPMIREEAAFVVGLHSYVVGSQLPCEPEPDVQTVSQLLTDPSHITAETAARRLRRGSPPSNASSSASQLSAPSLKATHTTLP
14. AVI1a-129 APPCKPLLREEVSFRVGLHAYPVGSQLPCEPEPDVAVLTSMLTDPSHITAETA?RRLARGSPPSVASSSASQLSAPSLKATCTANH
15. AVI3a-177 APPCKPLLRDEITFMVGLNSYAIGSQLPCEPEPDVSVLTSMLRDPSHITAETAARRLARGSPPSEASSSASQLSAPSLKATCQTHR
2,240 2,250 2,260 2,270 2,280 2,290 2,300 2,310 2,320
Consensus DHPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAE-EDDREISVPAECLRKXR-KFPPALPIWARPDYNPPLLETWKR
NS5a
1. HCV1a consensus DSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAE-EDERE ISVPAE ILRKSR-RFAPALPIWARPDYNPPLLETWKK
2. HCV1b consensus DSPDADLIEANLLWRQEMGGNITRVESENKVVILDSFDPLRAE-EDEREVSVPAE ILRKSR-KFPPAMPIWARPDYNPPLLESWKD
3. HCV2a Consensus KTYDVDMVDANLF----MGGDVTRIESESKVVVLDSLDPM-AEERSDLEPSIPSEYMLPRN-RFPPALPAWARPDYNPPLVESWKR
4. HCV2b Consensus MAYDCDMVDANLF----MGGDVTRIESDSKVIVLDSLDSM-TEVEDDREPSVPSEYLTRRR-KFPPALPPWARPDYNPPVIETWKR
5. HCV 3 Consensus PHPDAELVDANLLWRQEMGSNITRVESETKVVILDSFEPLRAE-TDDAELSVAAECFKKPP-KYPPALPIWARPDYNPPLLDRWKA
6. HCV 4 Consensus DSPGTDLLEANLLW----GSTATRVETDEKVIILDSFEPCVAEPDDDREVSVAAE ILRPTK-KFPPALPIWARPDYNPPLTETWKQ
7. HCV5 consensus HHPDADLIEANLLWRQCMGGNITRVEAENKVVILDSFEPLKXE-EDDREISVSADCFRRGP-AFPPALPIWARPGYDPPLLETWKR
8. HCV6 consensus DHPDAELIEANLLWRQEMGGNITRVESENKVIVLDSFDPLVAE-YDDREISVSAECHRPPRPKFPPALPIWARPDYNPPLLETWKA
9. HCV7: ABN05226 QHPDAELIEANLMWEHKVGA-IRRMETDTKVIILDSFDSA-SSVEDDMEPSTAAECLRTRK-VFPPAMPIWARPDYNPPVVENWKD
14. AVI1a-129 DSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAE-EDERE ISVPAE ILRKSR-RFTQALPVWARPDYNPPLVEAWKK
15. AVI3a-177 PHPDAELVDANLLWRQEMGSNITRVESETKVVILDSFEPLRAE-ADDAELSVAAECFKKPP-KYPPALPIWARPDYNPPLLDRWKT

FIG. 16I

2,330 2,340 2,350 2,360 2,370 2,380 2,390 2,400
Consensus
NS5a
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
2,410 2,420 2,430 2,440 2,450 2,460 2,470 2,480 2,490
Consensus
NS5a
NS5b
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
2,500 2,510 2,520 2,530 2,540 2,550 2,560 2,570 2,580
Consensus
NS5b
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177

FIG. 16J

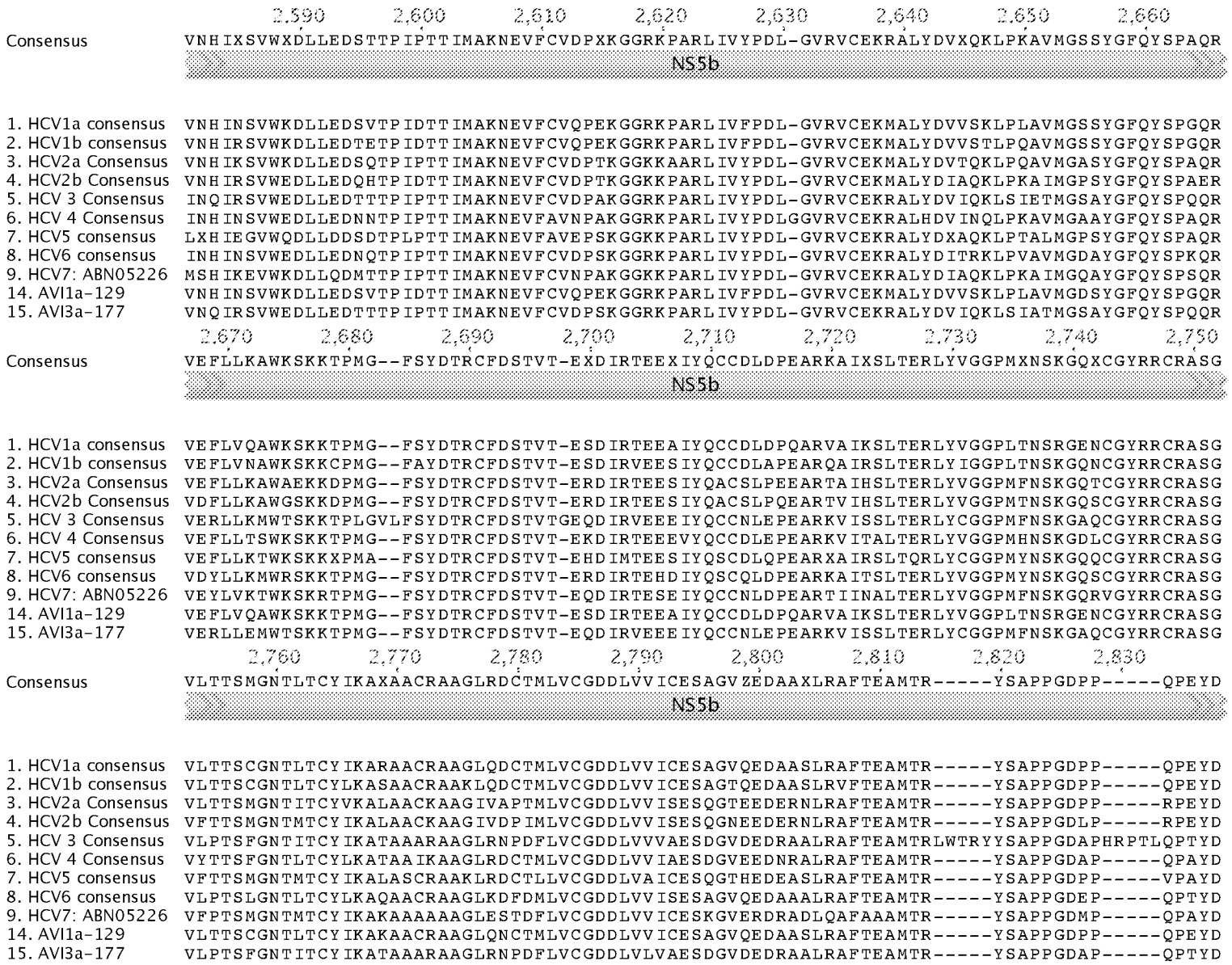
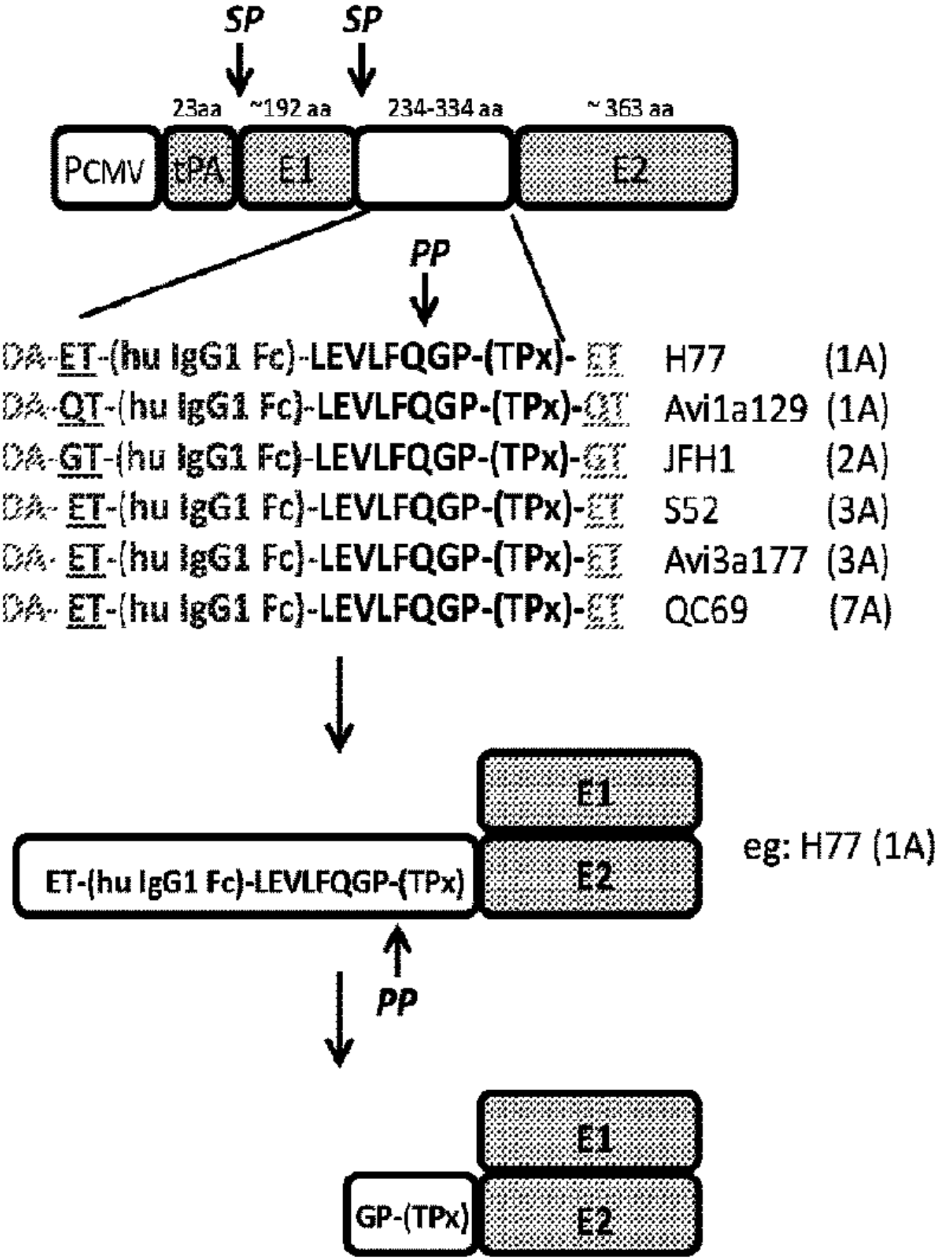


FIG. 16K

2,840 2,850 2,860 2,870 2,880 2,890 2,900 2,910 2,920
Consensus
NS5b
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
2,930 2,940 2,950 2,960 2,970 2,980 2,990 3,000 3,010
Consensus
NS5b
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177
3,020 3,030 3,040 3,050 3,060 3,074
Consensus
NS5b
1. HCV1a consensus
2. HCV1b consensus
3. HCV2a Consensus
4. HCV2b Consensus
5. HCV 3 Consensus
6. HCV 4 Consensus
7. HCV5 consensus
8. HCV6 consensus
9. HCV7: ABN05226
14. AVI1a-129
15. AVI3a-177

FIG. 16L


SP
SP
23aa
~192 aa
234-334 aa
~ 363 aa
PCMV
tPA
E1
E2
PP
DA-ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)-GT H77 (1A)
DA-QT-(hu IgG1 Fc)-LEVLFQGP-(TPx)-GT Avi1a129 (1A)
DA-GT-(hu IgG1 Fc)-LEVLFQGP-(TPx)-GT JFH1 (2A)
DA-ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)-GT S52 (3A)
DA-ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)-GT Avi3a177 (3A)
DA-ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)-GT QC69 (7A)
E1
E2
ET-(hu IgG1 Fc)-LEVLFQGP-(TPx)
eg: H77 (1A)
PP
E1
E2
GP-(TPx)