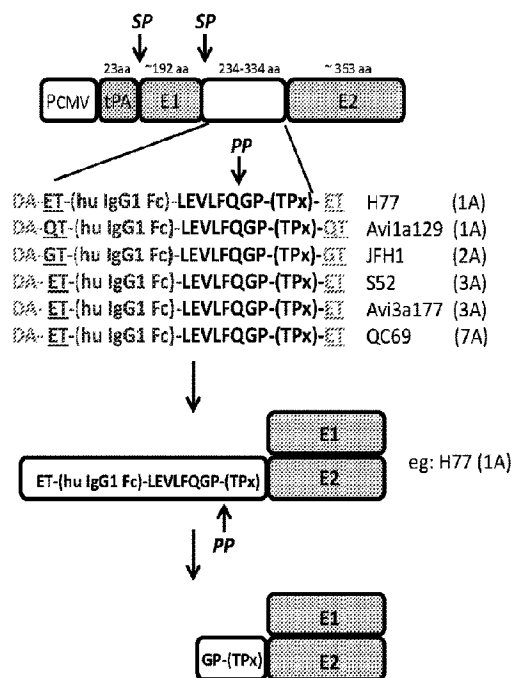




(86) Date de dépôt PCT/PCT Filing Date: 2016/07/06
(87) Date publication PCT/PCT Publication Date: 2017/01/12
(45) Date de délivrance/Issue Date: 2024/04/02
(85) Entrée phase nationale/National Entry: 2017/11/17
(86) N° demande PCT/PCT Application No.: IB 2016/001051
(87) N° publication PCT/PCT Publication No.: 2017/006182
(30) Priorité/Priority: 2015/07/07 (US62/189,657)

(51) Cl.Int./Int.Cl. *C07K 19/00* (2006.01),
A61K 39/295 (2006.01), *A61P 31/04* (2006.01),
A61P 31/14 (2006.01), *A61P 37/04* (2006.01),
C07K 1/14 (2006.01)
(72) Inventeurs/Inventors:
HOUGHTON, MICHAEL, CA;
LAW, JOHN L., CA;
LOGAN, MICHAEL, CA;
HOCKMAN, DARREN, CA;
LANDI, ABDOLAMIR, CA
(73) Propriétaire/Owner:
THE GOVERNORS OF THE UNIVERSITY OF
ALBERTA, CA
(74) Agent: GOWLING WLG (CANADA) LLP

(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 E1 polypeptide; 2) a variant HCV E1 polypeptide and an HCV E2 polypeptide; or 3) a variant HCV E1 polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide and/or the HCV E1 polypeptide comprises 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 polypeptide that includes E1 and variant E2, E2 and variant E1, or variant E1 and variant E2. 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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number
WO 2017/006182 A1

(43) International Publication Date
12 January 2017 (12.01.2017)

(51) International Patent Classification:

C07K 19/00 (2006.01) *A61P 31/14* (2006.01)
A61K 39/295 (2006.01) *A61P 37/04* (2006.01)
A61P 31/04 (2006.01) *C07K 1/14* (2006.01)

(21) International Application Number:

PCT/IB2016/001051

(22) International Filing Date:

6 July 2016 (06.07.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/189,657 7 July 2015 (07.07.2015) US

(71) Applicant: **THE GOVERNORS OF THE UNIVERSITY OF ALBERTA** [CA/CA]; 10230 Jasper Avenue, #4000, Edmonton, Alberta T5J 4P6 (CA).

(72) Inventors: **HOUGHTON, Michael**; Department of Medical Microbiology and Immunology, 6-020 Katz Group Centre, Edmonton, Alberta T6G 2E1 (CA). **LAW, John, L.**; Department of Medical Microbiology and Immunology, 6-020 Katz Group Centre, Edmonton, Alberta T6G 2E1 (CA). **LOGAN, Michael**; Department of Medical Microbiology and Immunology, 6-020 Katz Group Centre, Edmonton, Alberta T6G 2E1 (CA). **HOCKMAN, Darren**; Department of Medical Microbiology and Immunology, 6-020 Katz Group Centre, Edmonton, Alberta T6G 2E1 (CA). **LANDI, Abdolamir**; Department of Medical Microbiology and Immunology, 6-020 Katz Group Centre, Edmonton, Alberta T6G 2E1 (CA).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(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 E1 polypeptide; 2) a variant HCV E1 polypeptide and an HCV E2 polypeptide; or 3) a variant HCV E1 polypeptide and a variant HCV E2 polypeptide, where the variant HCV E2 polypeptide and/or the HCV E1 polypeptide comprises 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 polypeptide that includes E1 and variant E2, E2 and variant E1, or 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 same.



WO 2017/006182 A1

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:

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 (HCVec) 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).

[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:

AIPLEVIKGGRLIFCHSKKKCDELA AKL (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:

AIPLEVIKGGRLIFCHSKKKCDELA AKLVALGINAVAYYRGLDVSVIPTSG (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:

KGGRLIFCHSKKKCDELA AKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD 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:

VALSTTGEIPFYGKAIPLEVIKGGRLIFCHSKKKCDELA AKLVALGINAVAYYR 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:

AIPLEVIKGGRLIFCHSKKKCDELA AKL (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:

AIPLEVIKGGRLIFCHSKKKCDELA AKLV ALGINAVAYYRGLDVSVIPTSG

(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:

KGGRHLIFCHSKKKCDELA AKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD
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:

VALSTTGEIPFYGKAIPLEVIKGG RHLIFCHSKKKCDELA AKLVALGINAVAYYR
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: AIPLEVIKGGRHLIFCHSKKKCDELA AKL (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: AIPLEVIKGGRHLIFCHSKKKCDELA AKLV ALGINAVAYYRGLDVSVIPTSG (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: KGGRHLIFCHSKKKCDELA AKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATD 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: VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELA AKLV ALGINAVAYYR 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:

AIPLEVIKGGRLIFCHSKKKCDELA AKL (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:

AIPLEVIKGGRLIFCHSKKKCDELA AKLVALGINAVAYYRGLDVSVIPTSG

(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:

KGGRHLIFCHSKKKCDELA AKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD
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:

VALSTTGEIPFYGKAIPLEVIKGGRLIFCHSKKKCDELA AKLVALGINAVAYYR
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: AIPLEVIKGGRHLIFCHSKKKCDELA AKL (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:

AIPLEVIKGGRHLIFCHSKKKCDELA AKLVALGINAVAYYRGLDVSVIPTSG (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:

KGGRHLIFCHSKKKCDELA AKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD 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:

VALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKCDELA AKLVALGINAVAYYR 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 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: AIPLEVIKGGRLIFCHSKKKCDELA AKL (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:
AIPLEVIKGGRLIFCHSKKKCDELA AKLV ALGINAVAYYRGLDVSVIPTSG

(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:

KGGRHLIFCHSKKKCDELA AKLVALGINAVAYYRGLDVSVIPTSGDVVVVATD
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:

VALSTTGEIPFYGKAIPLEVIKGGRRHLIFCHSKKKCDELA AKLVALGINAVAYYR
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 among 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

HCV E2 polypeptide; and 3) 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, 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 comprising 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 epitopes 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 as 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](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, 73, 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: AIPLEVIKGGRLIFCHSKKKCELAACKL (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: AIPLEVIKGGRLIFCHSKKKCELAACKL (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: AIPLEVIKGGRLIFCHSKKKCELAACKL (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: AIPLEVIKGGRLIFCHSKKKCELAALKLVALGINAVAYYRGLDVSVIPTSG (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: AIPLEVIKGGRLIFCHSKKKCELAALKLVALGINAVAYYRGLDVSVIPTSG (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: AIPLEVIKGGRLIFCHSKKKCELAALKLVALGINAVAYYRGLDVSVIPTSG (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: KGGRHLIFCHSKKKCELAALKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCN (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:

KGGRHLIFCHSKKKCDELAACLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCN (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: VALSTTGEIPFYGKAIPLEVIKGGGRHLIFCHSKKKCDELAACLVALGINAVAYYRGLDVS 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: VALSTTGEIPFYGKAIPLEVIKGGGRHLIFCHSKKKCDELAACLVALGINAVAYYRGLDVS 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: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSESRQP RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRS

RNLGKVIDTLTCGFADLMGYIPLVGAPLGGGAARALAHGVRVLEDGVNYATGNLPGCSF 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: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSESRQP RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS RNLGKVIDTLTCGFADLMGYIPLVGAPLGGGAARALAHGVRVLEDGVNYATGNLPGCSF 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: LHAPTGSGKSTKVPAAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGRHLIFCHSKKKCDELAACKLV 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 aa, 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: LHAPTGSGKSTKVPAAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGRHLIFCHSKKKCDELAACKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCN (SEQ ID NO:10); and has a length of 228 amino acids. Such a polypeptide 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 70%, at least about 75%, at least about 80%, at least about 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: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSEERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPG (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: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSEERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPG (SEQ ID NO:63); and has a length of 171 amino acids. Such a polypeptide 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
 EILLGPADGMVSKGWRLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS
 TAAQTFLATCINGVCWTVYHGAGTRTIA SPKGPVIQMYTNVDQDLVGWPAPQG
 ARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCP
 AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA
 HLHAPTGS GKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
 TGVRTITTGSPITYSTY GKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQA
 ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGRHLIF
 CHSKKKCEDELA AKLV ALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTG
 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: QASLLKVPYFVRVQGLLRICALARKMAGGHYVQMAIIKLGALTGTYYVYNALTP LRDWAHNGLRDLAVAVEPVVFSQMETKLITWGADTAACGDIINGLPVSARRGR EILLGPADGMVSKGWRLAPITAYAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS TAAQTFLATCINGVCWTVYHGAGTRTIA SPKGPVIQMYTNVDQDLVGWPAPQG ARSLTPCTCGSSDLYLVT RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCP AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA HLHAPTGS GKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIICDECHSTDATSILGIGTVLDQA ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRRHLIF CHSKKKCDELA AKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG 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
TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGRHLIFCHSKKKCDELAACKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSVLCECYDAGCA
WYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT
KYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
YREFDEMEEC SQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
EDLVNLLPAILSPGALVVGVC AAILRRHVGPGE GAVQWMNRLIAFASRGNHVSPTHY
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
TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGRHLIFCHSKKKCDELAACKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSVLCECYDAGCA
WYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT
KYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
YREFDEMEEC SQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA

FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
 QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
 EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEVAVQWMNRLIAFASRGNHVSPTHY
 VPESDAAARVTAISSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW
 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
 TGSPITYSTYGKFLADGGCSGGAYDIICDECHSTDATSIIGIGTVLDQAETAGARLVVLA
 TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGRHLIFCHSKKKCDELAACKLV
 ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
 PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSVLCCEYDAGCA
 WYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
 YLVAYQATVCARAQAPPPSWDQMWKCLIRLKP TLHGPTPLLYRLGAVQNEVTLTHPIT
 KYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
 YREFDEMEECQHLPIYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
 FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
 QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
 EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEVAVQWMNRLIAFASRGNHVSPTHY
 VPESDAAARVTAISSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW
 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
YHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQGARS LTPCTCGSSDL YLV
RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGS GKSTKVPAA
YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYG
KFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRH LIFCHSKKKCDELA AKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
VDFSLDPTFTIETTTLPQDAVSRTQRRGR TGRGKPGIYRFVAPGERPSGMFDSSV
LCECYDAGCAWYELTPAETTVRLRAYMNT PGLPVCQDHLEFWEGVFTGLTHID
AHFLSQTKQSGENLPYLVAYQATVCARAQAPPSWDQMWKCLIRLKP TLHGPT
PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCL
STGCVVIVGRIVLSGKPAIIPDREVL YREFDEMEEC SQHLPYIEQGMMLAEQFKQ
KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
NPAIASLMAFTA AVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
VVGVVCAAILRRHVGPGE GAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL
MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
TTDNLKCPCQVPSPEFFTEL DGVRLHRFAPPCKPLLREEVSFRVGLHEYVPGSQL
PCEPEPDVAVLTSM LTPSHITAEAAAGRRLARGSPPSVASSSASQLSAPSLKATCT
ANHDS PDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPV VHGCP LPPQSPVP
RKKRTVVLTESTVSTALAE LATSFGSSSTSGITGDNTTTSSEPAPSGCPPDS
SYSSMPPLEGEPGDPDLS DGSWSTVSSEADTEDVCCSMSYSWTGALVTPCAA
EQKL PINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSHYQDVLKEV
KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
KDILLED SVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD

VVSKLPLAVMGSSYGFQYSPGQ RVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
SDIRTEEAITYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCYRRRCRASGVL
TTSCGNTLTICYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
FTEAMTRYSAPPGDPPQPEYDLELITSCSSNVSV AHDGAGKRVYYLTRDPTTPLA
RAAWETARHTPVNSWLGNII MFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
YGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVA ACLRKLGVPPLRAWRHR
ARSVRARLLSRGGRAAICGKYLFWAVRTKLKLTPIAAAGQLDL SGWFTAGYS
GGDIYHSVSHARPRWFWFCLLLAAGVGIYLLPNR (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
YHGAGTRTIA SPKGPVIQMYTNVDQDLVGWPAPQGARS LTPCTCGSSDLYLVT
RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPT GSGKSTKVPAA
YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTTGSPITYSTYG
KFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRH LIFCHSKKKCDELA AKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSV
LCECYDAGCAWYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHID
AHFLSQTKQSGENLPYLVAYQATVCARAQAPPSWDQMWKCLIRL KPTLHGPT
PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCL
STGCVVIVGRIVLSGKPAIIPDREVL YREFDEMEEC SQHLPYIEQGMMLAEQFKQ
KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
NPAIASLMAFTA AVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
VVGVVCAAILRRHVGPGE GAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVL SDFKTWLKAKL

MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
 RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
 TTDNLKCPCQVPSPEFFTELDGVRLHRFAPPCKPLLREEVSFRVGLHEYPVGSQ
 L PCEPEPDVAVLTSMMLTDP SHITAEAAAGRRLARGSPPSVASSASQLSAPSLKATCT
 ANHDSFDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
 AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVVHGCPLPPPQSPVPPP
 RKKRTVVLTSTVSTALAEATKSFSGSSSTSGITGDNTTTSSEPAPSGCPPDSAE
 SYSSMPPLEGEPGDPDLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAE
 EQKLPINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSDHYQDVLKEV
 KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
 KDLLEDSTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
 VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
 SDIRTEEAIYQCCDLPQARVAIKSLTERLYVGGPLTNSRGENCYRRCRASGVL
 TTSCGNTLTICYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
 FTEAMTRYSAAPPDPPQPEYDLELITSCSSNVSVVAHDGAGKRVYYLTRDPTPLA
 RAAWETARHTPVNSWLGNII MFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
 YGACYSIEPLDLPPIIQLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRAWRHR
 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](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 NKTPHAI AAI 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: VNSESSE (SEQ ID NO:17). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: PGINGKAIHLVNSESSE (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] 1addvvdssksfvmenfssyhgtpgyvdsiqkigkpksgtqgnydddwkefystdnky
 daagysvdenenplsgkaggvkvtypgltkvlalkvdnaetikkelglslteplmeqvgteefikrfgdgarvvslpfae
 gsssvyinnweqakalsveleinfetrgrgqdamyeymaqacagnrvrrsvgsslsclndwdvirdkttkieslkeh
 gpiknksmespnktvseekakqyleefhqtahepelselktvtgtnpvfaganyaawavnvaqidsetadnlekttaal
 silpgigsvmgiadgavhhnteeivaqsialsslmvaqaiplvgelvdigfaaynfvesiinlfqvvhnsynrpayspghkt
 qpflhdgyavswntvedsiirtgfqgesghdikitaentplpiagvllptipgkldvnkskthisvngrkirmrcraidgdvtf
 crpkspvyvngvhanlhvafhrsssekihsneissdsigvlygqktvdhtkvnsklsffeiks (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 as 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, HCV 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](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, 73, 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: AIPLEVIKGGRLIFCHSKKKCDELA AKL (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:

AIPLEVIKGGRLIFCHSKKKCELAALKL (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: AIPLEVIKGGRLIFCHSKKKCELAALKL (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: AIPLEVIKGGRLIFCHSKKKCELAALKLVALGINAVAYYRGLDVS IPTSG (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: AIPLEVIKGGRLIFCHSKKKCELAALKLVALGINAVAYYRGLDVS IPTSG (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: AIPLEVIKGGRLIFCHSKKKCELAALKLVALGINAVAYYRGLDVS IPTSG (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: KGGRHLIFCHSKKKCDELA AKLV ALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTG 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: KGGRHLIFCHSKKKCDELA AKLV ALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTG 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: VALSTTGEIPFYGKAIPLEVIKGG RHLIFCHSKKKCDELA AKLV ALGINAVAYYRGLDVS 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:

VALSTTGEIPFYGKAIPLEVIKGGRHILFCHSKKKCDELAACKLVALGINAVAYYRGLDVS
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:
MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSEERSQP
RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS
RNLGKVIDTLTCGFADLMGYIPLVGAPLGGAAARALAHGVRVLEDGVNYATGNLPGCSF
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:
MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSEERSQP
RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS
RNLGKVIDTLTCGFADLMGYIPLVGAPLGGAAARALAHGVRVLEDGVNYATGNLPGCSF
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:
LHAPTGS GKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT
TGSPITYSTY GKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA
TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHILFCHSKKKCDELAACKLV
ALGINAVAYYRGLDVS IPTSGDVVVVATDALMTGFTGDFDSVIDCN (SEQ ID NO:10);
and has a length of from 215 amino acids (aa) to 235 aa (e.g., 215 aa, 216 aa, 217 aa, 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
TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRRHLIFCHSKKKCDELAACKLV
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 70%, at least about 75%, at least about 80%, at least about 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 191 aa) 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: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSEERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPG (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: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSESRQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGAARALAHGVRVLEDGVNYATGNLPG (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
 EILLGPADGMVSKGWRLAPITAYAAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS
 TAAQTFLATCINGVCWTVYHGAGTRTIA SPKGPVIQMYTNVDQDLVGWPAPQG
 ARSLTPCTCGSSDLYL VTRHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCP
 AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA
 HLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
 TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIICDECHSTDATSILGIGTVLDQA
 ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRH LIF
 CHSKKKCDELA AKLV ALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTG
 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
 EILLGPADGMVSKGWRLAPITAYAAQQTRGLLGCIITSLTGRDKNQVEGEVQIVS
 TAAQTFLATCINGVCWTVYHGAGTRTIA SPKGPVIQMYTNVDQDLVGWPAPQG
 ARSLTPCTCGSSDLYL VTRHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCP
 AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA
 HLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
 TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIICDECHSTDATSILGIGTVLDQA
 ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRH LIF
 CHSKKKCDELA AKLV ALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTGFTG
 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:
 LHAPTGSGKSTKVPAAYAAQGYKVLVLPNSVAATLGFAYMSKAHGIDPNIRTGVRTIT
 TGSPITYSTYGKFLADGGCSGGAYDIICDECHSTDATSIIGIGTVLDQAETAGARLVVLA
 TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRLIFCHSKKKCDELAACKLV
 ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
 PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDDSSVLCECYDAGCA
 WYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHIDAHFLSQTQSGENLP
 YLVAYQATVCARAQAPPSWDQMWKCLIRLKP TLHGPTPLLYRLGAVQNEVT LTHPIT
 KYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
 YREFDEMEECQHLPIYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
 FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSP LTTSTLLFNILGGWVAA
 QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
 EDLVNLLPAILSPGALVVGVC AAILRRHVGPGE GAVQWMNR LIAFASRGNHVSP THY
 VPESDAAARVTAILSSLTVTQLLRRLHQWISSECTTPCSG SWLRDIWDWICEVLSDFKTW
 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:

LHAPTGSGKSTKVPAAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT
 TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA
 TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGRHLIFCHSKKKCDELAACKLV
 ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
 PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA
 WYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
 YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT
 KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
 YREFDEMEEC SQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
 FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
 QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
 EDLVNLLPAILSPGALVVGVCAILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHY
 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:
 LHAPTGSGKSTKVPAAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT
 TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA
 TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGRHLIFCHSKKKCDELAACKLV
 ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
 PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA
 WYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
 YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT
 KYIMTCMSADLEVVTSTWVLVGGVLAALAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
 YREFDEMEEC SQHLPYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
 FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
 QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST

EDLVNLLPAILSPGALVVGVVCAAILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHY
VPESDAAARVTAISSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTW
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
YHGAGTRTIA SPKGPVIQMYTNVDQDLVGWPAPQGARS LTPCTCGSSDLYLV
T RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPT GSGKSTKVPAA
YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTTGSPITYSTYG
KFLADGGCSGGAYDIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGRHLIFCHSKKKCDELA AKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSV
LCECYDAGCAWYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHID
AHFLSQTKQSGENLPYLVA YQATVCARAQAPPSWDQMWKCLIRLKPTLHGPT
PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCL
STGCVVIVGRIVLSGKPAIIPDREVL YREFDEMEEC SQHLPYIEQGMMLAEQFKQ
KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
NPAIASLMAFTA AVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
VVGVVCAAILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
TAISSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWL KAKL

MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
 RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
 TTDNLKCPCQVPSPEFFTEL DGVRLHRFAPPCKPLLREEVSFRVGLHEYPVGSQ L
 PCEPEPDVAVLTSMLTDPSHITAEAAAGRRLARGSPPSVASSASQLSAPSLKATCT
 ANHDSFDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
 AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVVHGCPLPPPQSPVPPP
 RKKRTTVVLTESTVSTALAEATKSFSSSTSGITGDNTTTSSEPAPSGCPPDSAE
 SYSSMPPLEGEPPDPLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAE
 EQKL PINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSHYQDVLKEV
 KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
 KDILLEDVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
 VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
 SDIRTEEAIYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCYRRCRASGVL
 TTSCGNTLTICYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
 FTEAMTRYSAAPPDPPQPEYDLELITSCSSNVSVAHDGAGKRVYYLTRDPTTPLA
 RAAWETARHTPVNSWLGNIMFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
 YGACYSIEPLDLPPIIQLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRAWRHR
 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
 YHGAGTRTIA SPKGPVIQMYTNVDQDLVGWPAPQGARS LTPCTCGSSDLYLVT
 RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
 AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGS GKSTKVPAA
 YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYG
 KFLADGGCSGGAYDIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
 GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRH LIFCHSKKKCDELA AKLV

ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
 VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSV
 LCECYDAGCAWYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHID
 AHFLSQTKQSGENLPYLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPT
 PLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCL
 STGCVVIVGRIVLSGKPAIIPDREVLVREFDEMEECSEQHLPYIEQGMMLAEQFKQ
 KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
 NPAIASLMAFTA AVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
 AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
 VVGVVCAAILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
 TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL
 MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
 RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
 TTDNLKCPCQVPSPEFFTELDGVRLHRFAPPCKPLLREEVSFRVGLHEYPVGSQ
 L PCEPEPDVAVLTSMMLTDP SHITAEAAAGRRLARGSPPSVASSASQLSAPSLKATCT
 ANHDSPDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
 AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVHGCPLPPPQSPPVPPP
 RKKRTVVLTSTVSTALAEATKSFGSSSTSGITGDNTTTSSEPAPSGCPPDSDAE
 SYSSMPPLEGEPGDPDLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAE
 EQKLPINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLD SHYQDVLKEV
 KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
 KDILLEDVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
 VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
 SDIRTEEA IYQCCDLPQARVAIKSLTERLYVGGPLTNSRGENCYRRCRASGVL
 TTSCGNTLT CYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
 FTEAMTRYSA PP GDPPQPEYDLELITSCSSNVSV AHDGAGKRVYYLTRDPTTPLA
 RAAWETARHTPVNSWLGNII MFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
 YGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVA ACLRKLGVPLRAWRHR
 ARSVRARLLSRGGRAAICGKYLFNWAVRTKLKLTPIAAAGQLDL SGWFTAGYS
 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](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 NKTPHAI AAI 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: VN NESSE (SEQ ID NO:17). In some cases, a suitable heterologous polypeptide comprising a tetanus toxin T-cell epitope comprises the amino acid sequence: PGINGKAIHLVN NESSE (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](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, 73, 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: AIPLEVIKGGRLIFCHSKKKCEDELA AKL (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: AIPLEVIKGGRLIFCHSKKKCEDELA AKL (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: AIPLEVIKGGRLIFCHSKKKCEDELA AKL (SEQ ID NO:1); and has a length of 29 amino acids. Such a polypeptide 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: AIPLEVIKGGRLIFCHSKKKCEDELA AKLVALGINAVAYYRGLDVS VIPTSG (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: AIPLEVIKGGRLIFCHSKKKCEDELA AKLVALGINAVAYYRGLDVS VIPTSG (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: AIPLEVIKGGRLIFCHSKKKCEDELA AKLVALGINAVAYYRGLDVS VIPTSG (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: KGGRHLIFCHSKKKCEDELA AKLVALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTG 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: KGGRHLIFCHSKKKCEDELA AKLVALGINAVAYYRGLDVS VIPTSGDVVVVATDALMTG 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: VALSTTGEIPFYGKAIPLEVIKGGRLIFCHSKKKCDELAACKLVALGINAVAYYRGLDVS 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: VALSTTGEIPFYGKAIPLEVIKGGRLIFCHSKKKCDELAACKLVALGINAVAYYRGLDVS 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: MSTNPKPQRKTKRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSEERSQP RGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSPRGSRPSWGPTDPRRRS RNLGKVIDTLTCGFADLMGYIPLVGAPLGGAAARALAHGVRVLEDGVNYATGNLPGCSF 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 RNLGKVIDTLTCGFADLMGYIPLVGAPLGGGAARALAHGVRVLEDGVNYATGNLPGCSF 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: LHAPTGSGKSTKVPAAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHILFCHSKKKCDELAACKLV 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 aa, 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: LHAPTGSGKSTKVPAAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRHILFCHSKKKCDELAACKLV 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 70%, at least about 75%, at least about 80%, at least about 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 191 aa) 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
 EILLGPADGMVSKGWRLAPITAYAQTRGLLGCIITSLTGRDKNQVEGEVQIVS
 TAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQG
 ARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGS~~A~~GGPLLCP
 AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA
 HLHAPTGSKGSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
 TGVRTITTGSPITYSTYGKFLADGGCSGGAYDIICDECHSTDATSILGIGTVLDQA
 ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRRHLIF
 CHSKKKCDELA AKLV ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG
 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
 EILLGPADGMVSKGWRLAPITAYAQTRGLLGCIITSLTGRDKNQVEGEVQIVS
 TAAQTFLATCINGVCWTVYHGAGTRTIASPKGPVIQMYTNVDQDLVGWPAPQG
 ARSLTPCTCGSSDLYLVTRHADVIPVRRRGDSRGSLLSPRPISYLKGS~~A~~GGPLLCP
 AGHAVGIFRAAVCTRGVAKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVA

HLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
 TGVRTITTGSPITYSTYGGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQA
 ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRLIF
 CHSKKKCDELAACKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG
 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:

LHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIR
 TGVRTITTGSPITYSTYGGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQA
 ETAGARLVVLATATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRLIF
 CHSKKKCDELAACKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTG
 DFDSVIDCNTCVTQTVDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA
 WYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
 YLVAYQATVCARAQAPPPSWDQMWKCLIRLKP TLHGPTPLLYRLGAVQNEVT LTHPIT
 KYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
 YREFDEMEEC SQHLPYIEQGMMLAEQFKQKALG LLQTASRQAEVIAPAVQTNWQKLEA
 FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
 QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
 EDLVNLLPAILSPGALVVGVC AAILRRHVGPGE GAVQWMNR LIAFASRGNHVSPTHY

VPESDAAARVTAISSLTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTLW 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:

LHAPTGSGBKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT
TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA
TATPPGSVTVPHPNIEEV ALSTTGEIPFYGKAIPLEVIKGRHLIFCHSKKKCDELAACKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFSLD
PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDSSVLCECYDAGCA
WYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
YLVAYQATVCARAQAPPPSWDQMWKCLIRLKP TLHGPTPLLYRLGAVQNEVTLTHPIT
KYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
YREFDEMEECQHLPIYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
EDLVNLLPAILSPGALVVGVC AAILRRHVGPGE GAVQWMNRLIAFASRGNHVSPHTY
VPESDAAARVTAISSLTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTLW
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:
LHAPTGSGBKSTKVPAAYAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTIT
TGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLA

TATPPGSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRLHIFCHSKKKCDELAACKLV
 ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVD FSLD
 PTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDDSSVLCECYDAGCA
 WYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHIDAHFLSQTKQSGENLP
 YLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPTPLLYRLGAVQNEVTLTHPIT
 KYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCLSTGCVVIVGRIVLSGKPAIIPDREVL
 YREFDEMEECQHLPIYIEQGMMLAEQFKQKALGLLQTASRQAEVIAPAVQTNWQKLEA
 FWAKHMWNFISGIQYLAGLSTLPGNPAIASLMAFTAAVTSPLTTSQTLLFNILGGWVAA
 QLAAPGAATAFVGAGLAGAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPST
 EDLVNLLPAILSPGALVVGVC AAILRRHVGPGE GAVQWMNRLIAFASRGNHVSPTHY
 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
 YHGAGTRTIA SPKGPVIQMYTNVDQDLVGWPAPQGARS LTPCTCGSSDLYLVT
 RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
 AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAA
 YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYG
 KFLADGGCSGGAYDIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
 GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRLHIFCHSKKKCDELAACKLV
 ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
 VDFSLDPTFTIETTTLPQDAVSRTQRRGRTGRGKPGIYRFVAPGERPSGMFDDSSV
 LCECYDAGCAWYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHID

AHFLSQTKQSGENLPYLVAYQATVCARAQAPPPSWDQMWKCLIRLKPTLHGPT
 PLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCL
 STGCVVIVGRIVLSGKPAIIPDREVLVREFDEMEECSEQHLPYIEQGMMLAEQFKQ
 KALGLLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
 NPAIASLMAFTA AVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
 AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
 VVGVVCAAILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
 TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL
 MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
 RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
 TTDNLKCPCQVPSPEFFTELDGVRLHRFAPPCKPLLREEVSFRVGLHEYVPGSQL
 PCEPEPDVAVLTSMMLTDPSHITAEAAAGRRLARGSPPSVASSASQLSAPSLKATCT
 ANHDSFDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
 AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVHGCPLPPPQSPVPPP
 RKKRTVVLTESTVSTALAEATKSFGSSSTSGITGDNTTTSSEPAPSGCPPDSAE
 SYSSMPPLEGEPGDPDLSDGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAAEE
 EQKLPINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSDHYQDVLKEV
 KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKAVNHINSVW
 KDILLEDVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
 VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
 SDIRTEEAIYQCCDLPQARVAIKSLTERLYVGGPLTNSRGENCYRRCRASGVL
 TTSCGNTLTICYIKARAACRAAGLQDCTMLVCGNNLVVICESAGVQEDAASLRA
 FTEAMTRYSAAPPGDPPQPEYDLELITCSSNVSVVAHDGAGKRVYYLTRDPTTPLA
 RAAWETARHTPVNSWLGNII MFAPTLWARMILMTHFFSVLIARDQLEQALDCEI
 YGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRAWRHR
 ARSVRARLLSRGGRAAICGKYLFNWAVRTKLKLTPIAAAGQLDLSGWFTAGYS
 GGDYHSVSHARPRWFWFCLLLLAAGVGIYLLPNR (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
YHGAGTRTIA SPKGPVIQMYTNVDQDLVGWPAPQGARS LTPCTCGSSDLYLVT
RHADVIPVRRRGDSRGSLLSPRPISYLKGSAGGPLLCPAGHAVGIFRAAVCTRGV
AKAVDFIPVENLETTMRSPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAA
YAAQGYKVLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTTGSPITYSTYG
KFLADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATATPP
GSVTVPHPNIEEVALSTTGEIPFYGKAIPLEVIKGGRH LIFCHSKKKCDELA AKLV
ALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQT
VDFS LDPTFTIETTTLPQDAVSRTQRRGR TGRGKPGIYRFVAPGERPSGMFDSSV
LCECYDAGCAWYELTPAETTVRLRAYMNTPLPVCQDHLEFWEGVFTGLTHID
AHFLSQTKQSGENLPYLVAYQATVCARAQAPPSWDQMWKCLIRLKP TLHGPT
PLLYRLGAVQNEVTLTHPITKYIMTCMSADLEVVTSTWVLVGGVLAALAAAYCL
STGCVVIVGRIVLSGKPAIIPDREVL YREFDEMEEC SQHLPYIEQGMMLAEQFKQ
KALG LLQTASRQAEVIAPAVQTNWQKLEAFWAKHMWNFISGIQYLAGLSTLPG
NPAIASLMAFTA AVTSPLTTSQTLLFNILGGWVAAQLAAPGAATAFVGAGLAGA
AIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPSTEDLVNLLPAILSPGAL
VVGVVCAAILRRHVGPGE GAVQWMNRLIAFASRGNHVSPTHYVPESDAAARV
TAILSSLTVTQLLRRLHQWISSECTTPCSGSWLRDIWDWICEVLSDFKTWLKAKL
MPQLPGIPFVSCQRGYRGVWRGDGIMHTRCHCGAEITGHVKNGTMRIVGPRTC
RNMWSGTFPINAYTTGPCTPLPAPNYTFALWRVSAEEYVEIRQVGDFHYVTGM
TTDNLCPCQVPSPEFFTEL DGVRLHRFAPPCKPLLREEVSFRVGLHEYVPVGSQ L
PCEPEPDVAVLTSM L TDPSHITAEAAAGRRLARGSPPSVASSSASQLSAPSLKATCT
ANHDS PDAELIEANLLWRQEMGGNITRVESENKVVILDSFDPLVAEEDEREISVP
AEILRKSRRFAPALPIWARPDYNPPLLETWKKPDYEPPVHGCPLPPPQSPPVPPP
RKKRTVVLTESTVSTALAE L ATKSFGSSSTSGITGDNTTTSSEPAPSGCPPDSDAE
SYSSMPPLEGEPGDPDLS DGSWSTVSSEADTEDVVCCSMSYSWTGALVTPCAA E
EQKL PINALSNSLLRHHNLVYSTTSRSACQRQKKVTFDRLQVLDSHYQDVLKEV
KAAASKVKANLLSVEEACSLTPPHSAKSKFGYGAKDV RCHARKAVNHINSVW
KDILLED SVTPIDTTIMAKNEVFCVQPEKGGRKPARLIVFPDLGVRVCEKMALYD
VVSKLPLAVMGSSYGFQYSPGQRVEFLVQAWKSKKTPMGFSYDTRCFDSTVTE
SDIRTEEAIYQCCDLDPQARVAIKSLTERLYVGGPLTNSRGENCYRRCRASGVL

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,

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.

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.

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.

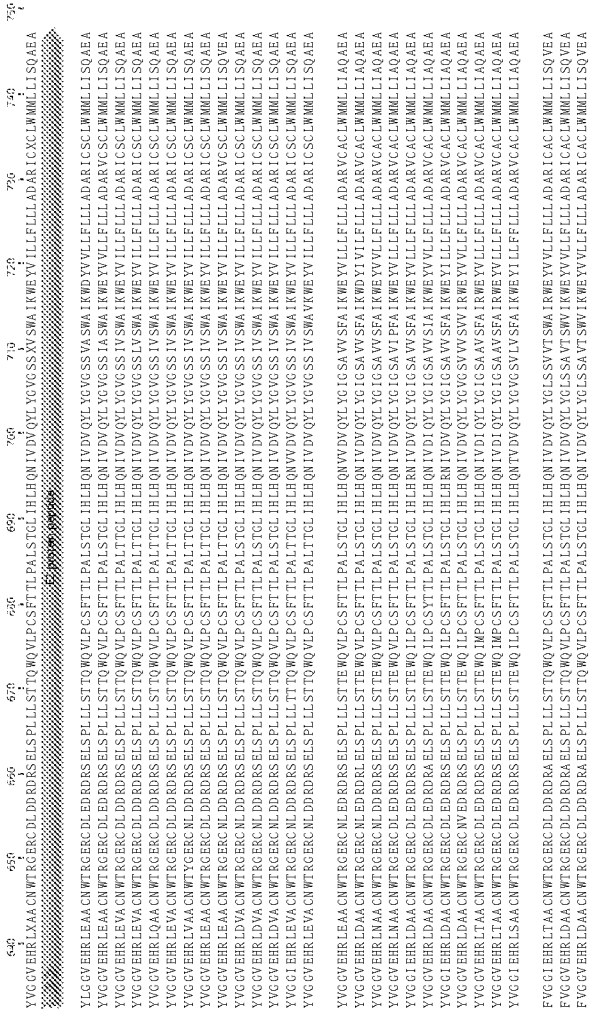


FIG. 1C

2A	Consensus	AB047639 (JFH1)	1	MS	TNPKPQRKTKRNTNRRPQDVKFFGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKDRRSTGKSWGKPGYPWPLYG	20	30	40	50	60	70	80
		AB047645			Core							
		AF238482			MS	TNPKPQRKTKRNTNRRPQDVKFFGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKDRRSTGKSWGKPGYPWPLYG						
		AF169005			MS	TNPKPQRKTKRNTNRRPQDVKFFGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKDRRSTGKSWGKPGYPWPLYG						
		AY746460			MS	TNPKPQRKTKRNTNRRPQDVKFFGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKDRRSTGKSWGKPGYPWPLYG						
		HPCPOLP			MS	TNPKPQRKTKRNTNRRPQDVKFFGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKDRRSTGKSWGKPGYPWPLYG						
		NC_009823			MS	TNPKPQRKTKRNTNRRPQDVKFFGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKDRRSTGKSWGKPGYPWPLYG						
		HPJ8G HC-J8			MS	TNPKPQRKTKRNTNRRPQDVKFFGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKDRRSTGKSWGKPGYPWPLYG						
		AY232730			MS	TNPKPQRKTKRNTNRRPQDVKFFGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKDRRSTGKSWGKPGYPWPLYG						
		AB030907			MS	TNPKPQRKTKRNTNRRPQDVKFFGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRRQPIPKDRRSTGKSWGKPGYPWPLYG						
2B	Consensus	DQ430817	90	100	110	120	130	140	150	160	170	
			NE	GL	GWA	GWLL	SPR	GS	RP	SWG	P	NE
			GL	GWA	GWLL	SPR	GS	RP	SWG	P	NE	GL
			GL	GWA	GWLL	SPR	GS	RP	SWG	P	NE	GL
			GL	GWA	GWLL	SPR	GS	RP	SWG	P	NE	GL
			GL	GWA	GWLL	SPR	GS	RP	SWG	P	NE	GL
			GL	GWA	GWLL	SPR	GS	RP	SWG	P	NE	GL
			GL	GWA	GWLL	SPR	GS	RP	SWG	P	NE	GL
			GL	GWA	GWLL	SPR	GS	RP	SWG	P	NE	GL
			GL	GWA	GWLL	SPR	GS	RP	SWG	P	NE	GL
2A	Consensus	AB047639 (JFH1)	180	190	200	210	220	230	240	250		
		AB047645										
		AF238482										
		AF169005										
		AY746460										
		HPCPOLP										
		NC_009823										
		HPJ8G HC-J8										
		AY232730										
		AB030907										
2B	Consensus	DQ430817	180	190	200	210	220	230	240	250		
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
2A	Consensus	AB047639 (JFH1)	260	270	280	290	300	310	320	330	340	
		AB047645										
		AF238482										
		AF169005										
		AY746460										
		HPCPOLP										
		NC_009823										
		HPJ8G HC-J8										
		AY232730										
		AB030907										
2B	Consensus	DQ430817	260	270	280	290	300	310	320	330	340	
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI
			SI	FL	LA	LL	SC	IT	VP	VS	AE	VI

FIG. 2A

2A	Consensus	AB047639 (JFH1)	HIDMVM	SA	T	L	C	S	A	L	Y	V	G	D	L	C	G	G	M	L	A	A	Q	X	F	I	V	P	S	P	Q	R	H	W	F	V	Q	E	C	N	C	S	I	Y	P	G	T	T	G	H	R	M	A	W	D	M	M	N	W	S	P	T	A	T	M	L	A	Y	A	M	R	V	P	E	V	I	I	D									
		AB047645	HIDMVM	SA	T	L	C	S	A	L	Y	V	G	D	L	C	G	G	M	L	A	A	Q	X	F	I	V	P	S	P	Q	R	H	W	F	V	Q	E	C	N	C	S	I	Y	P	G	T	T	G	H	R	M	A	W	D	M	M	N	W	S	P	T	A	T	M	L	A	Y	A	M	R	V	P	E	V	I	I	D									
		AF238482	HIDMVM	SA	T	L	C	S	A	L	Y	V	G	D	L	C	G	G	M	L	A	A	Q	X	F	I	V	P	S	P	Q	R	H	W	F	V	Q	E	C	N	C	S	I	Y	P	G	T	T	G	H	R	M	A	W	D	M	M	N	W	S	P	T	A	T	M	L	A	Y	A	M	R	V	P	E	V	I	I	D									
		AF169005	HIDMVM	SA	T	L	C	S	A	L	Y	V	G	D	L	C	G	G	M	L	A	A	Q	X	F	I	V	P	S	P	Q	R	H	W	F	V	Q	E	C	N	C	S	I	Y	P	G	T	T	G	H	R	M	A	W	D	M	M	N	W	S	P	T	A	T	M	L	A	Y	A	M	R	V	P	E	V	I	I	D									
		AY746460	HIDMVM	SA	T	L	C	S	A	L	Y	V	G	D	L	C	G	G	M	L	A	A	Q	X	F	I	V	P	S	P	Q	R	H	W	F	V	Q	E	C	N	C	S	I	Y	P	G	T	T	G	H	R	M	A	W	D	M	M	N	W	S	P	T	A	T	M	L	A	Y	A	M	R	V	P	E	V	I	I	D									
		HPCPOLP	HIDMVM	SA	T	L	C	S	A	L	Y	V	G	D	L	C	G	G	M	L	A	A	Q	X	F	I	V	P	S	P	Q	R	H	W	F	V	Q	E	C	N	C	S	I	Y	P	G	T	T	G	H	R	M	A	W	D	M	M	N	W	S	P	T	A	T	M	L	A	Y	A	M	R	V	P	E	V	I	I	D									
		NC_009823	HIDMVM	SA	T	L	C	S	A	L	Y	V	G	D	L	C	G	G	M	L	A	A	Q	X	F	I	V	P	S	P	Q	R	H	W	F	V	Q	E	C	N	C	S	I	Y	P	G	T	T	G	H	R	M	A	W	D	M	M	N	W	S	P	T	A	T	M	L	A	Y	A	M	R	V	P	E	V	I	I	D									
		HPJ8G HC-J8	HVDI	IV	MA	A	T	C	S	A	L	Y	V	G	D	V	C	G	A	V	M	I	S	O	A	F	M	V	S	P	Q	R	H	N	F	T	Q	E	C	N	C	S	I	Y	Q	G	H	I	T	G	H	R	M	A	W	D	M	M	L	S	W	S	P	T	L	T	M	L	A	Y	A	A	R	I	P	E	L	V	L	E	I						
		AY232730	HVDI	IV	MA	A	T	C	S	A	L	Y	V	G	D	V	C	G	A	V	M	I	S	O	A	F	M	V	S	P	Q	R	H	N	F	T	Q	E	C	N	C	S	I	Y	Q	G	H	I	T	G	H	R	M	A	W	D	M	M	L	S	W	S	P	T	L	T	M	L	A	Y	A	A	R	I	P	E	L	V	L	E	I						
		AY232747	HVDI	IV	MA	A	T	C	S	A	L	Y	V	G	D	V	C	G	A	V	M	I	S	O	A	F	M	V	S	P	Q	R	H	N	F	T	Q	E	C	N	C	S	I	Y	Q	G	H	I	T	G	H	R	M	A	W	D	M	M	L	S	W	S	P	T	L	T	M	L	A	Y	A	A	R	I	P	E	L	V	L	E	I						
		AB030907	HVDI	IV	MA	A	T	C	S	A	L	Y	V	G	D	V	C	G	A	V	M	I	S	O	A	F	M	V	S	P	Q	R	H	N	F	T	Q	E	C	N	C	S	I	Y	Q	G	H	I	T	G	H	R	M	A	W	D	M	M	L	S	W	S	P	T	L	T	M	L	A	Y	A	A	R	I	P	E	L	V	L	E	I						
DQ430817	HVDI	IV	MA	A	T	C	S	A	L	Y	V	G	D	V	C	G	A	V	M	I	S	O	A	F	M	V	S	P	Q	R	H	N	F	T	Q	E	C	N	C	S	I	Y	Q	G	H	I	T	G	H	R	M	A	W	D	M	M	L	G	W	S	P	T	L	T	M	L	A	Y	A	A	R	V	P	E	?V	L	E	V									
2B	Consensus	I	F	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	X	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q	
		359	V	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
		360	I	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
		361	I	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
		362	I	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
		363	I	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
		364	I	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
		365	I	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
		366	I	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
		367	I	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
		368	I	S	G	A	H	W	G	V	N	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	V	I	L	L	A	A	G	V	D	A	R	T	H	T	V	G	S	X	G	R	T	T	S	G	X	A	C	L	F	S	S	G	P	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q
2A	Consensus	HPJ8G HC-J8	I	F	G	H	W	G	V	V	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	A	I	L	L	V	A	G	V	D	A	T	T	S	S	G	O	E	A	G	R	T	V	A	G	F	A	G	L	F	T	G	A	K	Q	N	L	Y	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q		
		AY232730	I	F	G	H	W	G	V	V	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	A	I	L	L	V	A	G	V	D	A	R	H	T	T	G	L	O	A	G	K	T	L	A	R	V	T	S	L	F	S	I	G	A	K	Q	N	I	Q	L	I	N	T	N	G	S	W	H	I	N	R	T	A	L	N	C	N	D	S	L	Q	
		AY232747	I	F	G	H	W	G	V	V	F	G	L	A	Y	F	S	M	Q	G	A	W	A	K	V	I	A	I	L	L	V	A	G	V	D	A	T	T	S	S	G	O	E	A	G	R	T	V	A	G	F	A	G	L	F	T	G	A	K</																												

SUBSTITUTE SHEET (RULE 26)

Consensus	1 20 30 40 50 60 70 80	MSTLPKPQRKTKRNTIRRPQDVKFPGGQIVGGVYVLPRRGPRLGVRA ¹ TRKTSERSQPRGRRQPIPKARRSEGRSWAQPGYPWPPLYGN
3A	90 100 110 120 130 140 150 160 170	E ² CGGWA ³ GWLLSPRGSRPSWGNPDRRRSRNLGKVIDTLTCGFADLMGYIPLVGA ⁴ PVGGVARALAHGVRALEDGINFATGNLPGCSFSI
3B	95 100 110 120 130 140 150 160 170	E ² CGGWA ³ GWLLSPRGSRPSWGNPDRRRSRNLGKVIDTLTCGFADLMGYIPLVGA ⁴ PVGGVARALAHGVRALEDGINFATGNLPGCSFSI
3K	95 100 110 120 130 140 150 160 170	E ² CGGWA ³ GWLLSPRGSRPSWGNPDRRRSRNLGKVIDTLTCGFADLMGYIPLVGA ⁴ PVGGVARALAHGVRALEDGINFATGNLPGCSFSI
Consensus	180 190 200 210 220 230 240 250 260	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	270 280 290 300 310 320 330 340 350	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	270 280 290 300 310 320 330 340 350	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	270 280 290 300 310 320 330 340 350	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	360 370 380 390 400 410 420 430 440	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	450 460 470 480 490 500 510 520 530	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	450 460 470 480 490 500 510 520 530	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	450 460 470 480 490 500 510 520 530	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	540 550 560 570 580 590 600 610 620	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	630 640 650 660 670 680 690 700 710	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	630 640 650 660 670 680 690 700 710	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	630 640 650 660 670 680 690 700 710	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	720 730 740 750 760 770 780 790 800	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	810 820 830 840 850 860 870 880 890	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	810 820 830 840 850 860 870 880 890	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	810 820 830 840 850 860 870 880 890	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	900 910 920 930 940 950 960 970 980	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	990 1000 1010 1020 1030 1040 1050 1060 1070	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	990 1000 1010 1020 1030 1040 1050 1060 1070	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	990 1000 1010 1020 1030 1040 1050 1060 1070	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	1080 1090 1100 1110 1120 1130 1140 1150 1160	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	1170 1180 1190 1200 1210 1220 1230 1240 1250	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	1170 1180 1190 1200 1210 1220 1230 1240 1250	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	1170 1180 1190 1200 1210 1220 1230 1240 1250	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	1260 1270 1280 1290 1300 1310 1320 1330 1340	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	1350 1360 1370 1380 1390 1400 1410 1420 1430	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	1350 1360 1370 1380 1390 1400 1410 1420 1430	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	1350 1360 1370 1380 1390 1400 1410 1420 1430	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	1440 1450 1460 1470 1480 1490 1500 1510 1520	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	1530 1540 1550 1560 1570 1580 1590 1600 1610	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	1530 1540 1550 1560 1570 1580 1590 1600 1610	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	1530 1540 1550 1560 1570 1580 1590 1600 1610	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	1620 1630 1640 1650 1660 1670 1680 1690 1700	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	1710 1720 1730 1740 1750 1760 1770 1780 1790	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	1710 1720 1730 1740 1750 1760 1770 1780 1790	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	1710 1720 1730 1740 1750 1760 1770 1780 1790	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	1800 1810 1820 1830 1840 1850 1860 1870 1880	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	1890 1900 1910 1920 1930 1940 1950 1960 1970	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	1890 1900 1910 1920 1930 1940 1950 1960 1970	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	1890 1900 1910 1920 1930 1940 1950 1960 1970	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	1980 1990 2000 2010 2020 2030 2040 2050 2060	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3A	2070 2080 2090 2100 2110 2120 2130 2140 2150	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3B	2070 2080 2090 2100 2110 2120 2130 2140 2150	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
3K	2070 2080 2090 2100 2110 2120 2130 2140 2150	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD
Consensus	2160 2170 2180 2190 2200 2210 2220 2230 2240	FLALF ⁵ SCLIHPAASLEWRNTSGLYVLTNDCSNSSIVYEADDVILHTPGICPCVQ ⁶ -DGNSTCWTPTVTVAVRYVGA ⁷ TASIRSHVD

Consensus	3A	270	280	290	300	310	320	330	340	350	LLV GAA TMC SAL YVGD MCG AVFLV GQAF TFR PRRH QTVQT C NCSLYP GHLS GHRMA WDM MNWSPA VGMVVA HVLRLPQTLFDIIAGA
		E1									
		360	370	380	390	400	410	420	430	440	LLV GAA TLCSAL YVGD MCG AVFLV GQAF TFR PRRH QTVQT C NCSLYP GHLS GHRMA WDM MNWSPA VGMVVA HVLRMRPQTLFDIIAGA
		450	460	470	480	490	500	510	520	530	LLV GAA TMC SAL YVGD MCG AVFLV GQAF TFR PRRH QTVQT C NCSLYP GHLS GHRMA WDM MNWSPA VGMVVA HVLRPQTLFDIIAGA
Consensus	3A	540	550	560	570	580	590	600	610	620	LLV GAA TMC SAL YVGD MCG AVFLV GQAF TFR PRRH QTVQT C NCSLYP GHLS GHRMA WDM MNWSPA VGMVVA HVLRPQTLFDIIAGA
		630	640	650	660	670	680	690	700	710	LLV GAA TMC SAL YVGD MCG AVFLV GQAF TFR PRRH QTVQT C NCSLYP GHLS GHRMA WDM MNWSPA VGMVVA HVLRPQTLFDIIAGA
		720	730	740	750	760	770	780	790	800	LLV GAA TMC SAL YVGD MCG AVFLV GQAF TFR PRRH QTVQT C NCSLYP GHLS GHRMA WDM MNWSPA VGMVVA HVLRPQTLFDIIAGA
		810	820	830	840	850	860	870	880	890	LLV GAG TMC SAL YVGD MCG PVFLV GQAF TFR PRRH QTVQT C NCSLYP GHLS GQRMADWDM MNWSPA VGMVVA HVLRPQTLFDVVAGA
Consensus	3B	900	910	920	930	940	950	960	970	980	MLVAPPTLCSAL YVEDAF GAVSLV GQAF TFR PRRH QTVQT C NCSLYP GHVS GHRMA WDM MNWSPA IGLVISHLMRLPQTFFDLVVGA
		990	1000	1010	1020	1030	1040	1050	1060	1070	MMV GAA TLCSAL YVGD LCGALFLV GQGF SWRH RQHWT VQDC NCSLYP GHSLT GHRMA WDM MNWSPA MTLIVSQVLRPQTMFDLIVIGA
		1080	1090	1100	1110	1120	1130	1140	1150	1160	HWG ILAGL A Y YSMQGNWAKVA IIMVMFSGVDATTY TTGGSAARGAGLTSLSFSVGA KQKQLVNTNGSWHINSTALNCNXSINTGFIA
		E2									
Consensus	3A	1170	1180	1190	1200	1210	1220	1230	1240	1250	HWG ILAGL A Y YSMQGNWAKVA IIMVMFSGVDAETH TTGGTAARNAFTLTGLTQGARQKLELINTNGSWHINRTALNCNESLNTGFIA
		1260	1270	1280	1290	1300	1310	1320	1330	1340	HWG ILAGL A Y YSMQGNWAKVA IIMVMFSGVDAET YVTGGVAHSARGLTSLSFSGAKQKQLVNTNGSWHINSTALNCNESINTGFIA
		1350	1360	1370	1380	1390	1400	1410	1420	1430	HWG ILAGL A Y YSMQGNWAKVA IIMVMFSGVDAET YTTGGTASRHTQAFAGLFDIGPQKQLVNTNGSWHINSTALNCNESINTGFIA
		1440	1450	1460	1470	1480	1490	1500	1510	1520	HWG ILAGL A Y YSMQGNWAKVA IIMVMFSGVDAET YTTGGSAAGHVS TLTSLFSSGPQKQLVNTNGSWHINSTALNCNESINTGFIA
Consensus	3A	1530	1540	1550	1560	1570	1580	1590	1600	1610	HWG ILAGL A Y YSMQGNWAKVA IIMVMFSGVDAET YTTGGSAHA TRLTSLFSGAKQKQLVNTNGSWHINSTALNCNESINTGFIA
		1620	1630	1640	1650	1660	1670	1680	1690	1700	HWG ILAGL A Y YSMQGNWAKVI IIMVMFSGVDA TTHVTGGTGLTAFRLTGLTVGQKQLVNTNGSWHINRTALNCNDSINTGFIA
		1710	1720	1730	1740	1750	1760	1770	1780	1790	HWG ILAGL A Y YSMQGNWAKVI IIMVMFSGVDA TTYTSGGSAQAARGLADLFSVGA KQNLVNTNGSWHINSTALNCNDSINTGFIA
		1800	1810	1820	1830	1840	1850	1860	1870	1880	HWG ILAGL A Y YSMQGNWAKVI IIMVMFSGVDA TTYTSGGSAQAARGLADLFSVGA KQNLVNTNGSWHINSTALNCNDSINTGFIA
Consensus	3A	1890	1900	1910	1920	1930	1940	1950	1960	1970	HWG ILAGL A Y YSMQGNWAKVI IIMVMFSGVDA TTYTGGNAARGASGIVSLFTPGA KQNLVNTNGSWHINRTALNCNDSINTGFIA
		1980	1990	2000	2010	2020	2030	2040	2050	2060	HWG ILAGL A Y YSMQGNWAKVI IIMVMFSGVDA TTHVTA GQAARNAYGITSLSFSVGA KQNLVNTNGSWHINRTALNCNESINTGFIA
		2070	2080	2090	2100	2110	2120	2130	2140	2150	HWGVMAGL A Y YSMQGNWAKVVIIVLIMFSGVDA TTH TTGGSAQAQATAGTSTFFTRGPSQNLQLVNSNGSWHINSTALNCNDSINTGFIA
		2160	2170	2180	2190	2200	2210	2220	2230	2240	HWGVMAGV A Y YSMQGNWAKVFLVLCFLFSGVDA STTITGGVAASGAF TITSLFSTGAKQPLHLVNTNGSWHINRTALNCNDSINTGFIA
Consensus	3A	2250	2260	2270	2280	2290	2300	2310	2320	2330	GLFY YHKFNSTGCPQRLSSCKPITFFXQGWGPLTDANITGPSSDDKPYCWHYAPRPCDVVPASSVCGPVYCF TSPVVVGT TDAKGVPT
		E2									
		2340	2350	2360	2370	2380	2390	2400	2410	2420	GLFY LHKFNSTGCPERLSSCKPITFFRQGWGLTDANITGPSDDKPYCWHYAPRPCEVVPALNVCGPVYCF TSPVVVGT TDRQGVPT
		2430	2440	2450	2460	2470	2480	2490	2500	2510	GLFY YHKFNSTGCPQRLSSCKPIISFRQGWGPLTDANITGPSDDRPY CWHYAPRPCSVVPASSVCGPVYCF TSPVVVGT TDIKPKPT
Consensus	3A	2520	2530	2540	2550	2560	2570	2580	2590	2600	GLFY YHKFNSTGCPQRLSSCKPITFFRQGWGLTDANITGPSDDRPY CWHYAPRPCDIVPASSVCGPVYCF TSPVVVGT TDAKGVPT
		2610	2620	2630	2640	2650	2660	2670	2680	2690	GLFY YHKFNSTGCPQRLSSCKPITFFRQGWGLTDANITGPSDDRPY CWHYAPRPCDVVPALNVCGPVYCF TSPVVVGT TDRKGVPT
		2700	2710	2720	2730	2740	2750	2760	2770	2780	GLFY YHRENS TGC PQLSSCKPITFFXQGWGGLTDANISGPSDDKPYCWHYAPRPCKVVPASGCGPVYCF TSPVVVGT TDAKGVPT
		2790	2800	2810	2820	2830	2840	2850	2860	2870	GLFRHKNSTGCPERLSSCKPITFFKQGWGLTDANITGPSDDRPY CWHYAPRPCVVVPALNVCGPVYCF TSPVVVGT TDAKGVPT
Consensus	3A	2880	2890	2900	2910	2920	2930	2940	2950	2960	GLFY YHKFNSTGCPQRLSDCKPITFFKQGWGLTDANITGPSDDRPY CWHYAPRPCVVVPALNVCGPVYCF TSPVVVGT TDAKGVPT
		2970	2980	2990	3000	3010	3020	3030	3040	3050	GLFY YHKFNSTGCPQRLSDCKPITFFKQGWGLTDANITGPSDDRPY CWHYAPRPCVVVPALNVCGPVYCF TSPVVVGT TDAKGVPT
		3060	3070	3080	3090	3100	3110	3120	3130	3140	GLFY YHKFNSTGCPQRLSDCKPITFFKQGWGLTDANITGPSDDRPY CWHYAPRPCVVVPALNVCGPVYCF TSPVVVGT TDAKGVPT
		3150	3160	3170	3180	3190	3200	3210	3220	3230	GLIY YHKFNSTGCPQRLSSCKPITFFRQGWGLTDANITGPSDDRPY CWHYAPRPCDTIRASSVCGPVYCF TSPVVVGT TDAK GAPT
Consensus	3B	3240	3250	3260	3270	3280	3290	3300	3310	3320	GLFY YHKFNSTGCPQRLSSCKPITFFKQGWGLTDANITGPSDDRPY CWHYAPRPCGIVPALNVCGPVYCF TSPVVVGT TDAK GAPT
		3330	3340	3350	3360	3370	3380	3390	3400	3410	GLFY YHKFNSSGCPERMSSCKPIT YFNQGWGGLTDANINGPSEDRPY CWHYAPRPCNITKPLNVCGPVYCF TSPVVVGT TDIKGLPT
		3420	3430	3440	3450	3460	3470	3480	3490	3500	GLLY YHKFNSSGCVVERMSA CSP LDRFAQGWGLPGPANISGPSSEKPY CWHYAPRPCDTVP AQSVCGPVYCF TSPVVVGT TDKRGAPT
		3510	3520	3530	3540	3550	3560	3570	3580	3590	FIG. 3B

Consensus	3A	YTWGENETDVFLLESRLRPPSGRWFSGCIWMNSTGFVKTCGAPPCNIYGGGNPH-NESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCM	530540550560570580590600610
		E2	
		YTWGENETDVFLLESRLRPPSGQWFGCIWMNSTGFVKTCGAPPCDIYGGGNRC-NESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCL	
		YTWGENETDVFLLESRLRPPSGRWFGCWNNSTGFLKTCGAPPCNIYGGEDPE-NESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCM	
3B	3K	YTWGENEKDVFLLESRLRPPSGRWFSCWNNSTGFLKTCGAPPCNIYGGGNPH-NESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCM	
		YTWGENESDVFLLESRLRPPSGRWFGCWNNSTGFLKTCGAPPCNIYGGGNPN-NESHLFCPTDCFRKHHPDATYSRCGAGPWLTPRCM	
		YTWGANEKDVFLLESRLRPPSGRWFSCWNNSTGFLKTCGAPPCNIYGGGNPG-NESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCM	
		YTWGANETDVFLLESRLRPPSGRWFSCWNNSTGFLKTCGAPPCNIYGGGNPG-NESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCM	
3B	3K	YTWGANETDVFLLESRLRPPSGRWFSCWNNSTGFLKTCGAPPCNIYGGGNPN-NESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCL	
		YTWGANETDMFLQLSLRPPSGRWFSCWNNSTGFTKTCGAPPCNIYGGGNLN-NESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCL	
		YTWGANKTDVFLLESRLRPPSGRWFSCWNNSTGFVKTCGAPPCNIYGDGRDAQ-NESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCL	
		YRFGVNESDVFLLESRLRPPQGRWFGCVWMNSTGFVKTCGAPPCNIYGGMKDIEANQTHLKCPDTCFRKHHDATFTRCGSGPWLTPRCL	
Consensus	3A	YTWGENESDVFLLESARPPTEPWFPGCTWMNGSGYVKTCGAPPCHIYGGREGK--SNNSLVCPDTCFRKHHPDATYNRCGAGPWLTPRCL	620630640650660670680690700
		E2	
		VDYPYRLWHYPCTVNFRLFVKRMFVGGEGHFRFTAA CNWTRGERCDIEDRDRSEQHPLHSHSTTEIA ILPCSFTPMPALSTGLIHLHQNI	
		VDYPYRLWHYPCTVNFRLFVKRMFVGGEGHFRFTAA CNWTRGERCNIEDRDRSEQHPLHSHSTTEIA ILPCSFTPMPALSTGLIHLHQNI	
3B	3K	VDYPYRLWHYPCTVNFRLFVKRMFVGGEGHFRFTAA CNWTRGERCNIEDRDRSEQHPLHSHSTTEIA ILPCSFTPMPALSTGLIHLHQNI	
		VDYPYRLWHYPCTVNFRLFVKRMFVGGEGHFRFTAA CNWTRGERCDIEDRDRSEQHPLHSHSTTEIA ILPCSFTPMPALSTGLIHLHQNI	
		VDYPYRLWHYPCTVNFRLFVKRMFVGGEGHFRFTAA CNWTRGERCDIEDRDRSEQHPLHSHSTTEIA ILPCSFTPMPALSTGLIHLHQNI	
		VDYPYRLWHYPCTVNFRLFVKRMFVGGEGHFRFTAA CNWTRGERCDIEDRDRSEQHPLHSHSTTEIA ILPCSFTPMPALSTGLIHLHQNI	
Consensus	3A	VDVQYLYGVGSGMVGWALKWEFVILVFLLLADARVCVALWMLMISQAEA	710720730740750760770780790800810
		E2	
		VDVQYLYGVGSGVVGWALRWEFVILVFLLLADARVCVALWMLMISQAEA	
		VDVQYLYGVGSDMVGWALKWEFVILVFLLLADARVCVALWMLMISQAEA	
3B	3K	VDVQYLYGVGSGMVGWALKWEFVILVFLLLADARVCVALWMLMISQAEA	
		VDVQYLYGVGSGMVGWALKWEFVILVFLLLADARVCVALWMLMISQAEA	
		VDVQYLYGVGSGMVGWALKWEFVILVFLLLADARVCVALWMLMISQAEA	
		VDVQYLYGVGSGMVGWALKWEFVILVFLLLADARVCVALWMLMISQAEA	
Consensus	3A	VDVQYLYGVGSGVVGWALKWEFVILVFLLLADARVCVALWMLMISQAEA	8108208308408508608708808909009109209309409509609709809901000
		E2	
		VDVQYLYGVGSAVVGWALKWEFVILVFLLLADARVCVALWMLMISQAEA	
		VDVQYLYGIGSSGLVGWAIKWEFVILVFLLLADARVCVVLWMLMISQAEA	
3B	3K	VDVQYLYGIGSSGLVGWAIKWEFVILVFLLLADARVCVVLWMLMISQAEA	
		VDVQYLYGIGSSGLVGWAIKWEFVILVFLLLADARVCVVLWMLMISQAEA	
		VDVQYLYGIGSSGLVGWAIKWEFVILVFLLLADARVCVVLWMLMISQAEA	
		VDVQYLYGIGSSGLVGWAIKWEFVILVFLLLADARVCVVLWMLMISQAEA	

FIG. 3C

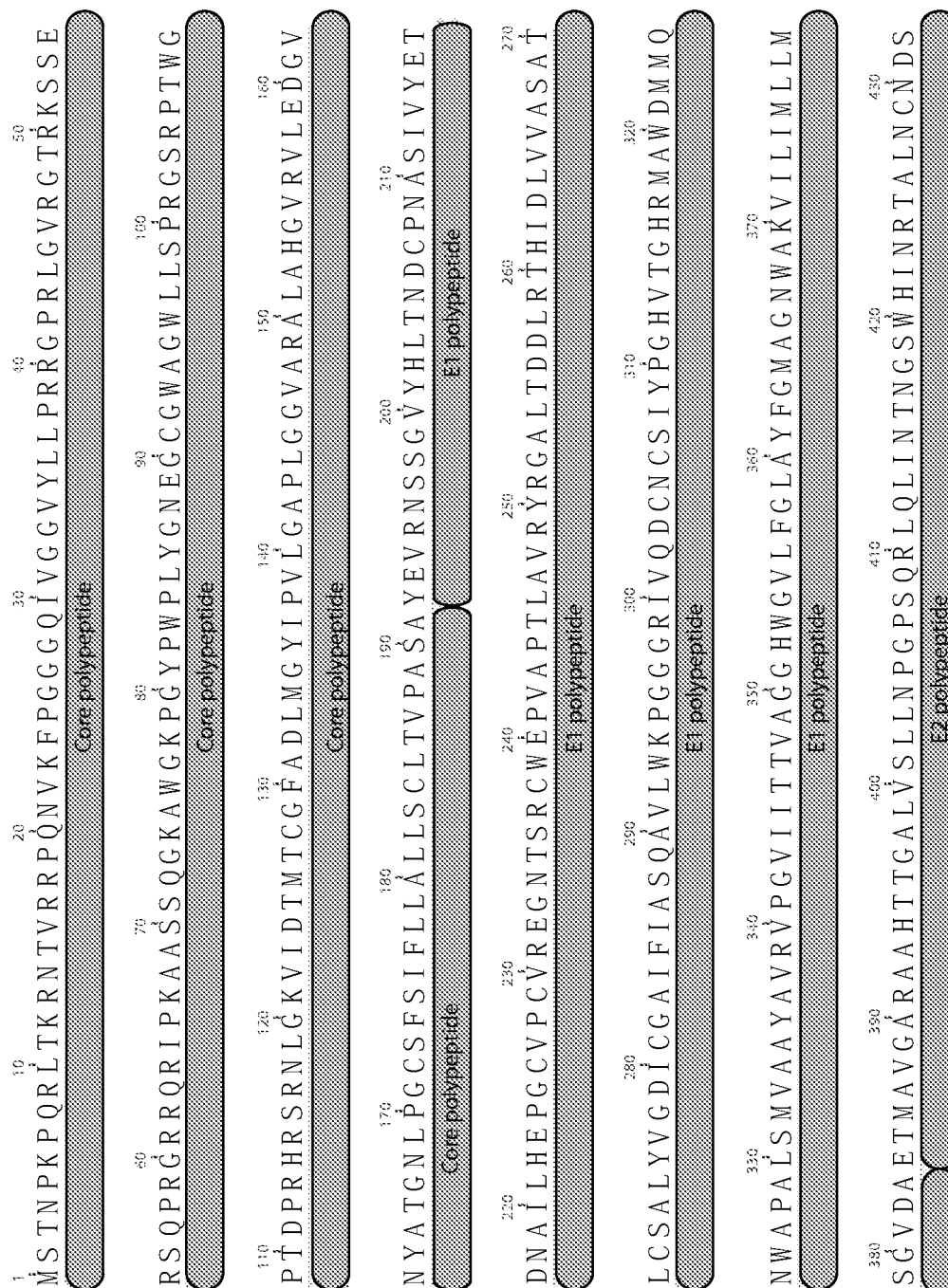


FIG. 4A

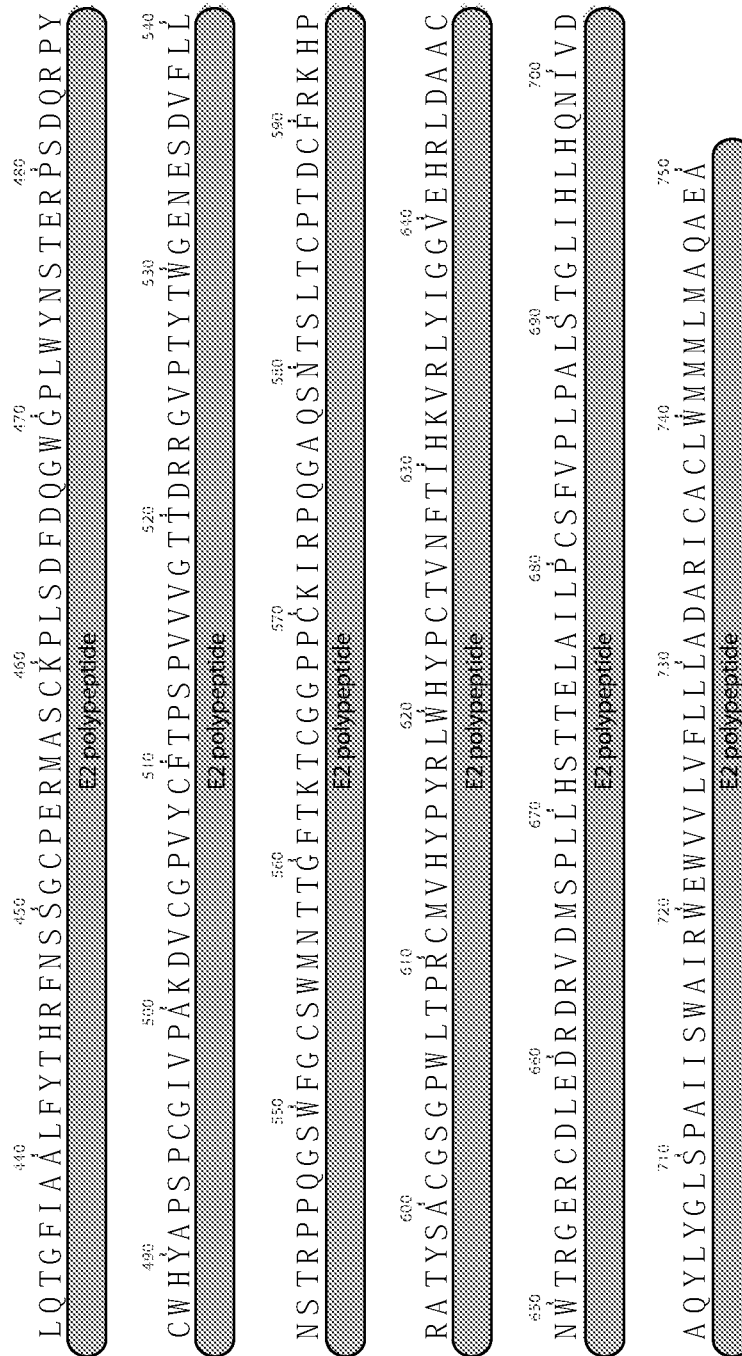


FIG. 4B

FIG. 5A

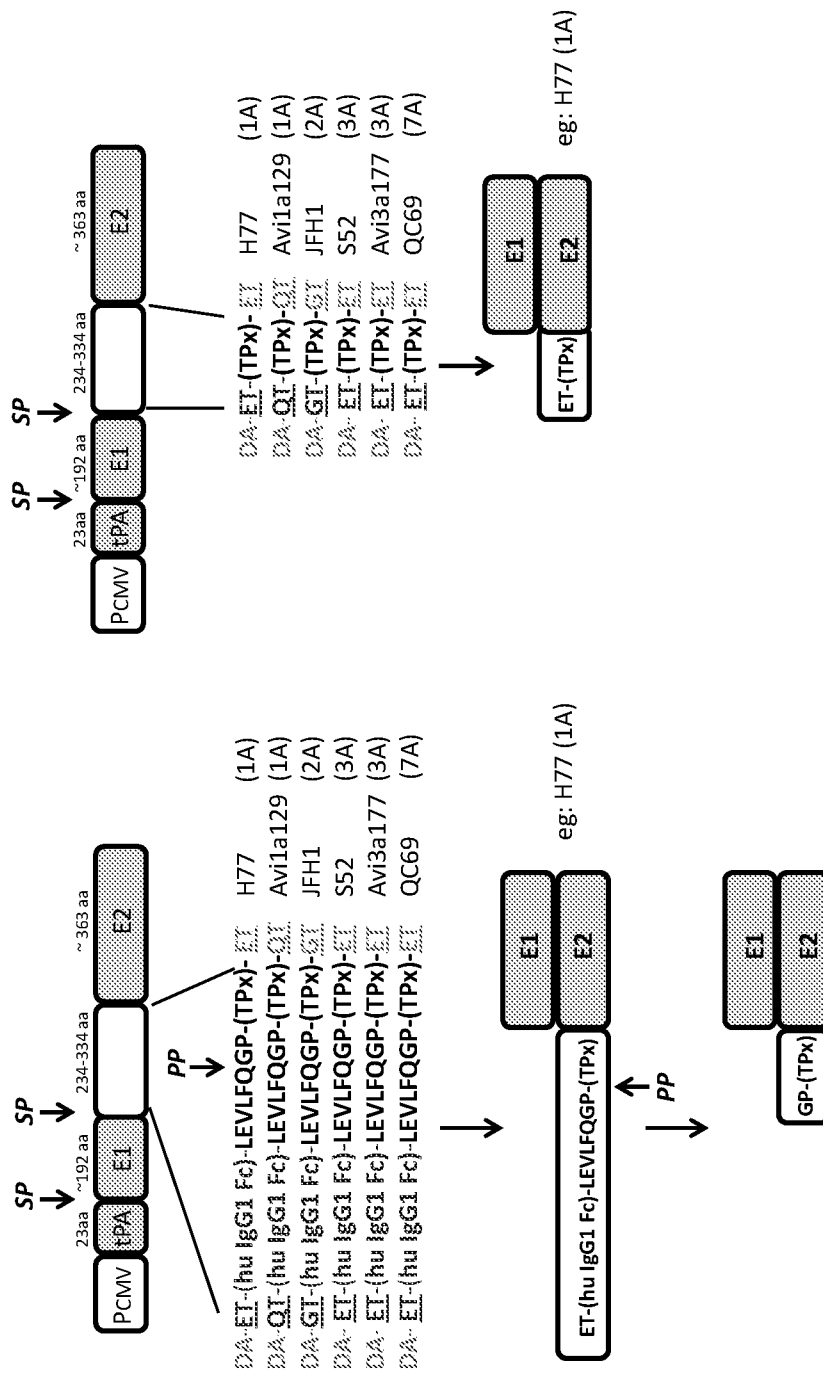
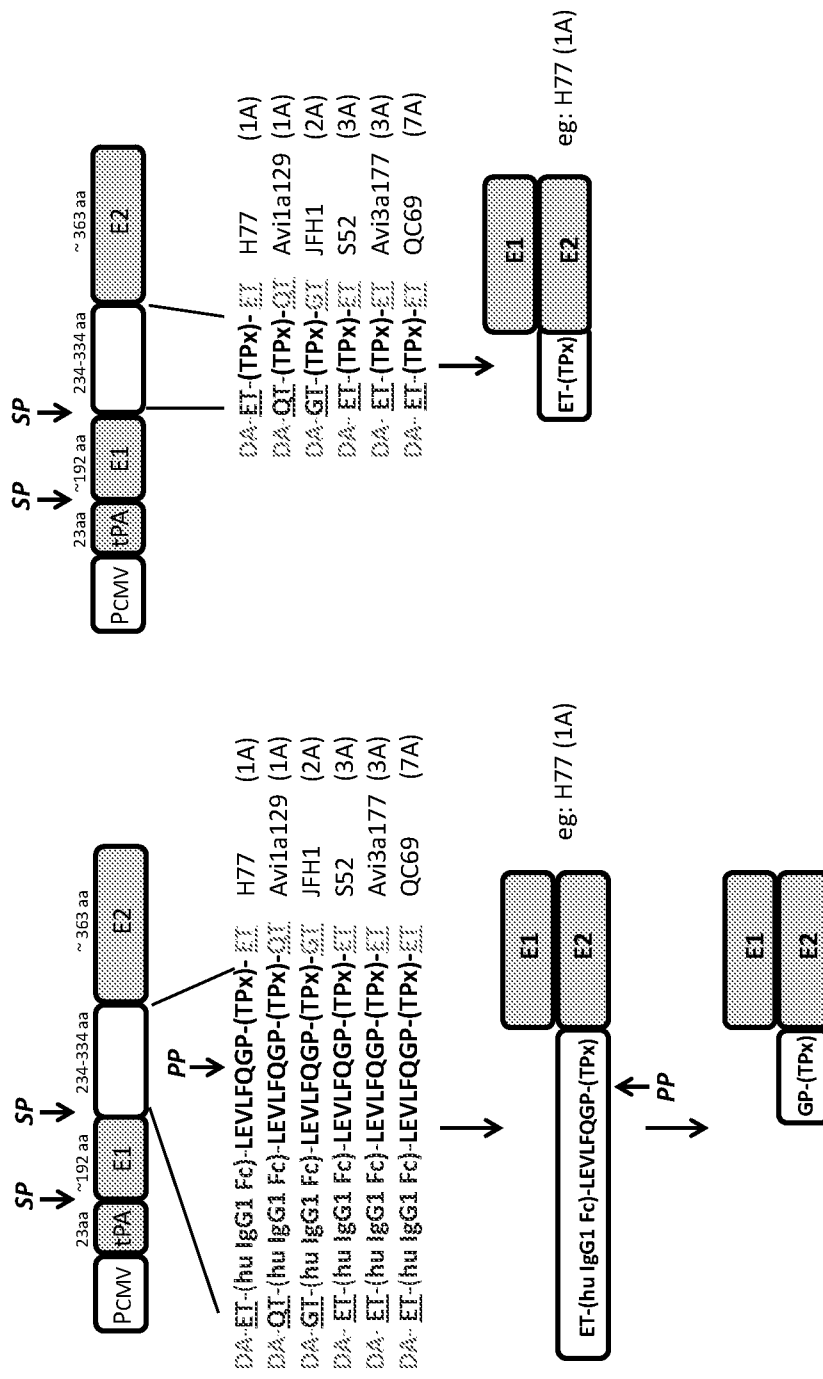


FIG. 5B



AV11a129	1 MDAMKRLCCVLLLCGAVFVSPSYQVRNSTGLYHVTNDCPNSSIVYEAADAILHTPGCVPCVREGNTSRCWVAMTPTVATRDGK
AV11a129 TP29	MDAMKRLCCVLLLCGAVFVSPSYQVRNSTGLYHVTNDCPNSSIVYEAADAILHTPGCVPCVREGNTSRCWVAMTPTVATRDGK
AV11a129 TP52	MDAMKRLCCVLLLCGAVFVSPSYQVRNSTGLYHVTNDCPNSSIVYEAADAILHTPGCVPCVREGNTSRCWVAMTPTVATRDGK
AV11a129 TP100	MDAMKRLCCVLLLCGAVFVSPSYQVRNSTGLYHVTNDCPNSSIVYEAADAILHTPGCVPCVREGNTSRCWVAMTPTVATRDGK
H77	MDAMKRLCCVLLLCGAVFVSPSYQVRNSTGLYHVTNDCPNSSIVYEAADAILHTPGCVPCVREGNTSRCWVAMTPTVATRDGK
H77 TP29	MDAMKRLCCVLLLCGAVFVSPSYQVRNSTGLYHVTNDCPNSSIVYEAADAILHTPGCVPCVREGNTSRCWVAMTPTVATRDGK
H77 TP52	MDAMKRLCCVLLLCGAVFVSPSYQVRNSTGLYHVTNDCPNSSIVYEAADAILHTPGCVPCVREGNTSRCWVAMTPTVATRDGK
H77 TP100	MDAMKRLCCVLLLCGAVFVSPSYQVRNSTGLYHVTNDCPNSSIVYEAADAILHTPGCVPCVREGNTSRCWVAMTPTVATRDGK
	IPA Signal Sequence E1
AV11a129	90 LPTTQLRRHIDLLVGSATLCSALYVGDLCGSI FLVGQMFTE SPRRHWTQDCNCSLYPGHITGHRMAWDMMNWSPTAALITAQ
AV11a129 TP29	LPTTQLRRHIDLLVGSATLCSALYVGDLCGSI FLVGQMFTE SPRRHWTQDCNCSLYPGHITGHRMAWDMMNWSPTAALITAQ
AV11a129 TP52	LPTTQLRRHIDLLVGSATLCSALYVGDLCGSI FLVGQMFTE SPRRHWTQDCNCSLYPGHITGHRMAWDMMNWSPTAALITAQ
AV11a129 TP100	LPTTQLRRHIDLLVGSATLCSALYVGDLCGSI FLVGQMFTE SPRRHWTQDCNCSLYPGHITGHRMAWDMMNWSPTAALITAQ
H77	LPTTQLRRHIDLLVGSATLCSALYVGDLCGSI FLVGQMFTE SPRRHWTQDCNCSLYPGHITGHRMAWDMMNWSPTAALITAQ
H77 TP29	LPTTQLRRHIDLLVGSATLCSALYVGDLCGSI FLVGQMFTE SPRRHWTQDCNCSLYPGHITGHRMAWDMMNWSPTAALITAQ
H77 TP52	LPTTQLRRHIDLLVGSATLCSALYVGDLCGSI FLVGQMFTE SPRRHWTQDCNCSLYPGHITGHRMAWDMMNWSPTAALITAQ
H77 TP100	LPTTQLRRHIDLLVGSATLCSALYVGDLCGSI FLVGQMFTE SPRRHWTQDCNCSLYPGHITGHRMAWDMMNWSPTAALITAQ
	E1
AV11a129	170 LLRIPQAILDMIAGAHWGVLAGIAYFSMVGNGWAKVLVLLLFAGVDAQTDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISR
AV11a129 TP29	LLRIPQAILDMIAGAHWGVLAGIAYFSMVGNGWAKVLVLLLFAGVDAQTDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISR
AV11a129 TP52	LLRIPQAILDMIAGAHWGVLAGIAYFSMVGNGWAKVLVLLLFAGVDAQTDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISR
AV11a129 TP100	LLRIPQAILDMIAGAHWGVLAGIAYFSMVGNGWAKVLVLLLFAGVDAQTDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISR
H77	LLRIPQAILDMIAGAHWGVLAGIAYFSMVGNGWAKVLVLLLFAGVDAQTDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISR
H77 TP29	LLRIPQAILDMIAGAHWGVLAGIAYFSMVGNGWAKVLVLLLFAGVDAQTDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISR
H77 TP52	LLRIPQAILDMIAGAHWGVLAGIAYFSMVGNGWAKVLVLLLFAGVDAQTDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISR
H77 TP100	LLRIPQAILDMIAGAHWGVLAGIAYFSMVGNGWAKVLVLLLFAGVDAQTDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTLMISR
	E1 FC Tag
AV11a129	260 TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISK
AV11a129 TP29	TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISK
AV11a129 TP52	TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISK
AV11a129 TP100	TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISK
H77	TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISK
H77 TP29	TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISK
H77 TP52	TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISK
H77 TP100	TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISK
	FC Tag
AV11a129	240 KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
AV11a129 TP29	KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
AV11a129 TP52	KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
AV11a129 TP100	KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
H77	KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
H77 TP29	KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
H77 TP52	KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
H77 TP100	KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
	FC Tag
AV11a129	430 SCSVMHEALHNHYTQKSLSLSPGKLEVLFGQP-----AIPL EVIKGGRHL IFCHSKKKCDELA AKL-----
AV11a129 TP29	SCSVMHEALHNHYTQKSLSLSPGKLEVLFGQP-----AIPL EVIKGGRHL IFCHSKKKCDELA AKL-----
AV11a129 TP52	SCSVMHEALHNHYTQKSLSLSPGKLEVLFGQP-----AIPL EVIKGGRHL IFCHSKKKCDELA AKL-----
AV11a129 TP100	SCSVMHEALHNHYTQKSLSLSPGKLEVLFGQP-----AIPL EVIKGGRHL IFCHSKKKCDELA AKL-----
H77	SCSVMHEALHNHYTQKSLSLSPGKLEVLFGQP-----AIPL EVIKGGRHL IFCHSKKKCDELA AKL-----
H77 TP29	SCSVMHEALHNHYTQKSLSLSPGKLEVLFGQP-----AIPL EVIKGGRHL IFCHSKKKCDELA AKL-----
H77 TP52	SCSVMHEALHNHYTQKSLSLSPGKLEVLFGQP-----AIPL EVIKGGRHL IFCHSKKKCDELA AKL-----
H77 TP100	SCSVMHEALHNHYTQKSLSLSPGKLEVLFGQP-----AIPL EVIKGGRHL IFCHSKKKCDELA AKL-----
	FC Tag PP Site TPx

FIG. 6A

AVI1a129	-----QTHVTGGRAAHITAGLTSLSFSPGPSQKLQLVNTNGS
AVI1a129 TP29	-----QTHVTGGRAAHITAGLTSLSFSPGPSQKLQLVNTNGS
AVI1a129 TP52	-----QTHVTGGRAAHITAGLTSLSFSPGPSQKLQLVNTNGS
AVI1a129 TP100	-----QTHVTGGRAAHITAGLTSLSFSPGPSQKLQLVNTNGS
H77	-----ETHVTGGSAGRITAGLVGLLTPGAKQNIQLINTNGS
H77 TP29	-----ETHVTGGSAGRITAGLVGLLTPGAKQNIQLINTNGS
H77 TP52	-----ETHVTGGSAGRITAGLVGLLTPGAKQNIQLINTNGS
H77 TP100	-----ETHVTGGSAGRITAGLVGLLTPGAKQNIQLINTNGS
	-----TPx-----E2 Protein-----
AVI1a129	WHINSTALNCNDSLKTGWIAGLLYSYKFNSGCPERLASCRRLTDFAQGWGPISHANGSGPDERPYCWHYPPRPGCI VPAKSVC
AVI1a129 TP29	WHINSTALNCNDSLKTGWIAGLLYSYKFNSGCPERLASCRRLTDFAQGWGPISHANGSGPDERPYCWHYPPRPGCI VPAKSVC
AVI1a129 TP52	WHINSTALNCNDSLKTGWIAGLLYSYKFNSGCPERLASCRRLTDFAQGWGPISHANGSGPDERPYCWHYPPRPGCI VPAKSVC
AVI1a129 TP100	WHINSTALNCNDSLKTGWIAGLLYSYKFNSGCPERLASCRRLTDFAQGWGPISHANGSGPDERPYCWHYPPRPGCI VPAKSVC
H77	WHINSTALNCNESLNTGWLAGLFYQHKFNSSGCPERLASCRRLTDFAQGWGPISYANGSGLDERPYCWHYPPRPGCI VPAKSVC
H77 TP29	WHINSTALNCNESLNTGWLAGLFYQHKFNSSGCPERLASCRRLTDFAQGWGPISYANGSGLDERPYCWHYPPRPGCI VPAKSVC
H77 TP52	WHINSTALNCNESLNTGWLAGLFYQHKFNSSGCPERLASCRRLTDFAQGWGPISYANGSGLDERPYCWHYPPRPGCI VPAKSVC
H77 TP100	WHINSTALNCNESLNTGWLAGLFYQHKFNSSGCPERLASCRRLTDFAQGWGPISYANGSGLDERPYCWHYPPRPGCI VPAKSVC
	-----E2 Protein-----
AVI1a129	GPVYCFTSPVTVVGTDDKSGAPTYNWGENDWDVFLNNTRPPLGNWFGCTWMNSTGFTKVCGAPPCVI GGAGNNTLCPTDCFR
AVI1a129 TP29	GPVYCFTSPVTVVGTDDKSGAPTYNWGENDWDVFLNNTRPPLGNWFGCTWMNSTGFTKVCGAPPCVI GGAGNNTLCPTDCFR
AVI1a129 TP52	GPVYCFTSPVTVVGTDDKSGAPTYNWGENDWDVFLNNTRPPLGNWFGCTWMNSTGFTKVCGAPPCVI GGAGNNTLCPTDCFR
AVI1a129 TP100	GPVYCFTSPVTVVGTDDKSGAPTYNWGENDWDVFLNNTRPPLGNWFGCTWMNSTGFTKVCGAPPCVI GGAGNNTLCPTDCFR
H77	GPVYCFTSPVTVVGTDDKSGAPTYSWGANDTDVFLNNTRPPLGNWFGCTWMNSTGFTKVCGAPPCVI GGVGNNTLLCPTDCFR
H77 TP29	GPVYCFTSPVTVVGTDDKSGAPTYSWGANDTDVFLNNTRPPLGNWFGCTWMNSTGFTKVCGAPPCVI GGVGNNTLLCPTDCFR
H77 TP52	GPVYCFTSPVTVVGTDDKSGAPTYSWGANDTDVFLNNTRPPLGNWFGCTWMNSTGFTKVCGAPPCVI GGVGNNTLLCPTDCFR
H77 TP100	GPVYCFTSPVTVVGTDDKSGAPTYSWGANDTDVFLNNTRPPLGNWFGCTWMNSTGFTKVCGAPPCVI GGVGNNTLLCPTDCFR
	-----E2 Protein-----
AVI1a129	KHPDATYSRCGSGPWITPRCLVDYPYRLWHYPCTVNYISIFKIRMYLGGVEHRLEAACNWTGERCDLEDRDRSELSPLLLSTTQ
AVI1a129 TP29	KHPDATYSRCGSGPWITPRCLVDYPYRLWHYPCTVNYISIFKIRMYLGGVEHRLEAACNWTGERCDLEDRDRSELSPLLLSTTQ
AVI1a129 TP52	KHPDATYSRCGSGPWITPRCLVDYPYRLWHYPCTVNYISIFKIRMYLGGVEHRLEAACNWTGERCDLEDRDRSELSPLLLSTTQ
AVI1a129 TP100	KHPDATYSRCGSGPWITPRCLVDYPYRLWHYPCTVNYISIFKIRMYLGGVEHRLEAACNWTGERCDLEDRDRSELSPLLLSTTQ
H77	KHPEATYSRCGSGPWITPRCMVDYPYRLWHYPCTINYIFKVRMYVGGVEHRLEAACNWTGERCDLEDRDRSELSPLLLSTTQ
H77 TP29	KHPEATYSRCGSGPWITPRCMVDYPYRLWHYPCTINYIFKVRMYVGGVEHRLEAACNWTGERCDLEDRDRSELSPLLLSTTQ
H77 TP52	KHPEATYSRCGSGPWITPRCMVDYPYRLWHYPCTINYIFKVRMYVGGVEHRLEAACNWTGERCDLEDRDRSELSPLLLSTTQ
H77 TP100	KHPEATYSRCGSGPWITPRCMVDYPYRLWHYPCTINYIFKVRMYVGGVEHRLEAACNWTGERCDLEDRDRSELSPLLLSTTQ
	-----E2 Protein-----
AVI1a129	WQVLPSCSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSVASWAIKWDYVVLLFLLADARICSCSCLWMMLLSQAEA
AVI1a129 TP29	WQVLPSCSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSVASWAIKWDYVVLLFLLADARICSCSCLWMMLLSQAEA
AVI1a129 TP52	WQVLPSCSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSVASWAIKWDYVVLLFLLADARICSCSCLWMMLLSQAEA
AVI1a129 TP100	WQVLPSCSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSVASWAIKWDYVVLLFLLADARICSCSCLWMMLLSQAEA
H77	WQVLPSCSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSIASWAIKWEYVVLLFLLADARVCSCLWMMLLSQAEA
H77 TP29	WQVLPSCSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSIASWAIKWEYVVLLFLLADARVCSCLWMMLLSQAEA
H77 TP52	WQVLPSCSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSIASWAIKWEYVVLLFLLADARVCSCLWMMLLSQAEA
H77 TP100	WQVLPSCSFTTLPALSTGLIHLHQNIVDVQYLYGVGSSIASWAIKWEYVVLLFLLADARVCSCLWMMLLSQAEA
	-----E2 Protein-----

FIG. 6B

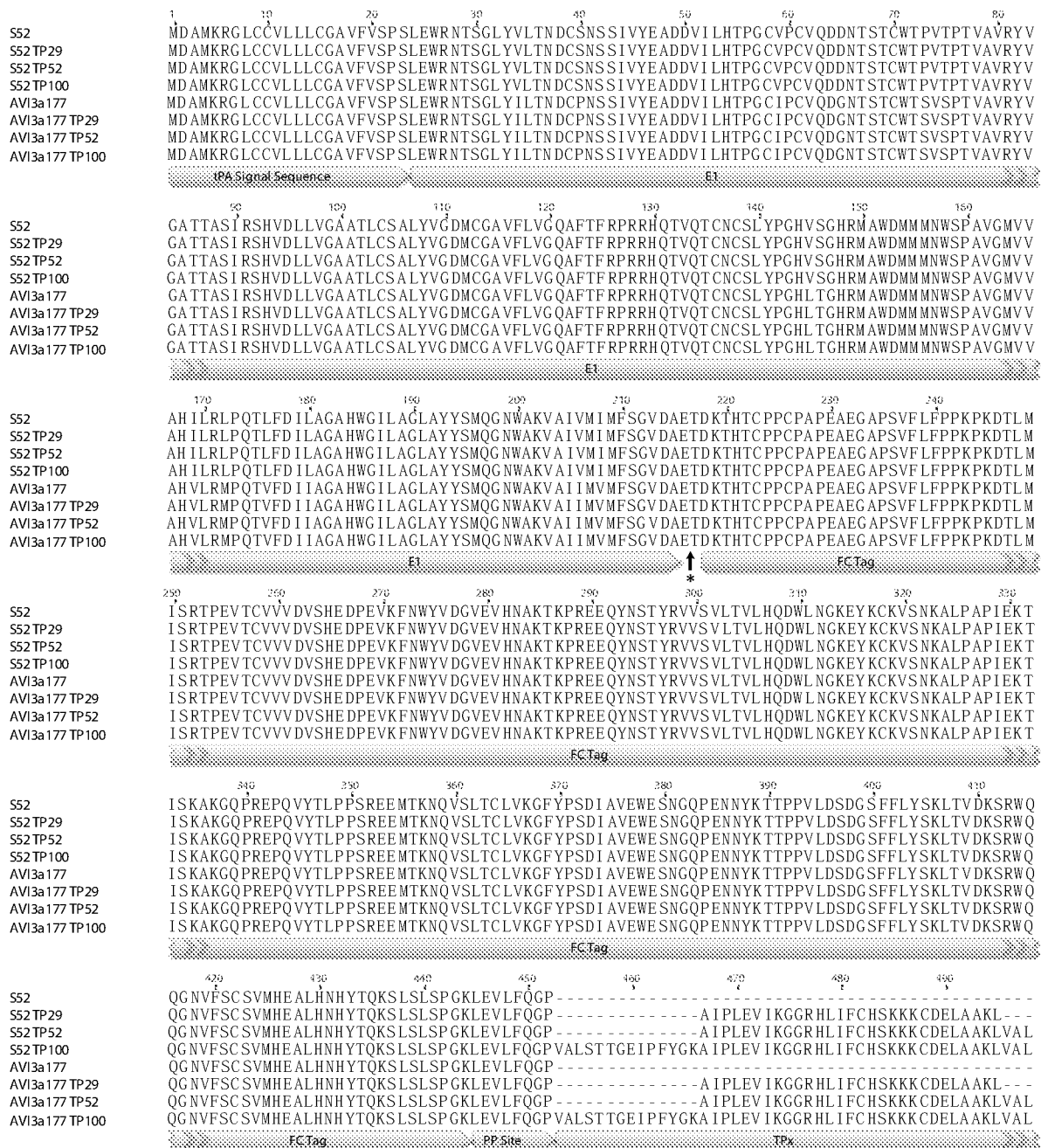


FIG. 7A

S52	590 510 520 530 540 550 560 570 580	-----ETYYVTGGSVAHSARGLTSLFSMGAQKQLQ
S52 TP29		-----ETYYVTGGSVAHSARGLTSLFSMGAQKQLQ
S52 TP52		-----ETYYVTGGSVAHSARGLTSLFSMGAQKQLQ
S52 TP100		-----ETYYVTGGSVAHSARGLTSLFSMGAQKQLQ
AVI3a177		-----ETHTTGGTAARNAFTLTGLFTQGARQKLE
AVI3a177 TP29		-----ETHTTGGTAARNAFTLTGLFTQGARQKLE
AVI3a177 TP52		-----ETHTTGGTAARNAFTLTGLFTQGARQKLE
AVI3a177 TP100		-----ETHTTGGTAARNAFTLTGLFTQGARQKLE
		GINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFETHTTGGTAARNAFTLTGLFTQGARQKLE
		TPx E2 Protein
S52	590 600 610 620 630 640 650 660	LVNTNGSWHINSTALNCNESINTGFIAGLFYYHKFNSTGCPQRLSSCKPIISFRQGWGPLTDANITGPSDDRPYCWYAPRPC
S52 TP29		LVNTNGSWHINSTALNCNESINTGFIAGLFYYHKFNSTGCPQRLSSCKPIISFRQGWGPLTDANITGPSDDRPYCWYAPRPC
S52 TP52		LVNTNGSWHINSTALNCNESINTGFIAGLFYYHKFNSTGCPQRLSSCKPIISFRQGWGPLTDANITGPSDDRPYCWYAPRPC
S52 TP100		LVNTNGSWHINSTALNCNESINTGFIAGLFYYHKFNSTGCPQRLSSCKPIISFRQGWGPLTDANITGPSDDRPYCWYAPRPC
AVI3a177		LI NTNGSWHINRTALNCNESLNTGFIAGLFYH HKFNSTGCPERLSSCKPITFFRQGWGSLTDANITGPSDDKPYCWYAPRPC
AVI3a177 TP29		LI NTNGSWHINRTALNCNESLNTGFIAGLFYH HKFNSTGCPERLSSCKPITFFRQGWGSLTDANITGPSDDKPYCWYAPRPC
AVI3a177 TP52		LI NTNGSWHINRTALNCNESLNTGFIAGLFYH HKFNSTGCPERLSSCKPITFFRQGWGSLTDANITGPSDDKPYCWYAPRPC
AVI3a177 TP100		LI NTNGSWHINRTALNCNESLNTGFIAGLFYH HKFNSTGCPERLSSCKPITFFRQGWGSLTDANITGPSDDKPYCWYAPRPC
		E2 Protein
S52	670 680 690 700 710 720 730 740	SVVPASSVCGPVYCFTPSPVVVGTTDIK GKPTYNWGENETDVFLLESRLPPSGRWFGCAWMNSTGFLKTCGAPPCNIYGGEGD
S52 TP29		SVVPASSVCGPVYCFTPSPVVVGTTDIK GKPTYNWGENETDVFLLESRLPPSGRWFGCAWMNSTGFLKTCGAPPCNIYGGEGD
S52 TP52		SVVPASSVCGPVYCFTPSPVVVGTTDIK GKPTYNWGENETDVFLLESRLPPSGRWFGCAWMNSTGFLKTCGAPPCNIYGGEGD
S52 TP100		SVVPASSVCGPVYCFTPSPVVVGTTDIK GKPTYNWGENETDVFLLESRLPPSGRWFGCAWMNSTGFLKTCGAPPCNIYGGEGD
AVI3a177		EVVPALNVCGPVYCFTPSPVVVGTTDRQGVPTYTWGENETDVFLLESRLPPSGQWFGCTWMNSTGTFVKTCCGAPPCDIYGGGGN
AVI3a177 TP29		EVVPALNVCGPVYCFTPSPVVVGTTDRQGVPTYTWGENETDVFLLESRLPPSGQWFGCTWMNSTGTFVKTCCGAPPCDIYGGGGN
AVI3a177 TP52		EVVPALNVCGPVYCFTPSPVVVGTTDRQGVPTYTWGENETDVFLLESRLPPSGQWFGCTWMNSTGTFVKTCCGAPPCDIYGGGGN
AVI3a177 TP100		EVVPALNVCGPVYCFTPSPVVVGTTDRQGVPTYTWGENETDVFLLESRLPPSGQWFGCTWMNSTGTFVKTCCGAPPCDIYGGGGN
		E2 Protein
S52	750 760 770 780 790 800 810 820 830	PENETDLFCPTDCFRKHPEATYSRCGAGPWLTPRCMVDYPYRLWHYPCTVNF TLFKVRMFVGGFEHRFTAACNWTGGERCNI E
S52 TP29		PENETDLFCPTDCFRKHPEATYSRCGAGPWLTPRCMVDYPYRLWHYPCTVNF TLFKVRMFVGGFEHRFTAACNWTGGERCNI E
S52 TP52		PENETDLFCPTDCFRKHPEATYSRCGAGPWLTPRCMVDYPYRLWHYPCTVNF TLFKVRMFVGGFEHRFTAACNWTGGERCNI E
S52 TP100		PENETDLFCPTDCFRKHPEATYSRCGAGPWLTPRCMVDYPYRLWHYPCTVNF TLFKVRMFVGGFEHRFTAACNWTGGERCNI E
AVI3a177		RCNESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCLVDYPYRLWHYPCTVNF TLFKVRMFVGGFEHRFTAACNWTGGERCNI E
AVI3a177 TP29		RCNESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCLVDYPYRLWHYPCTVNF TLFKVRMFVGGFEHRFTAACNWTGGERCNI E
AVI3a177 TP52		RCNESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCLVDYPYRLWHYPCTVNF TLFKVRMFVGGFEHRFTAACNWTGGERCNI E
AVI3a177 TP100		RCNESDLFCPTDCFRKHPEATYSRCGAGPWLTPRCLVDYPYRLWHYPCTVNF TLFKVRMFVGGFEHRFTAACNWTGGERCNI E
		E2 Protein
S52	840 850 860 870 880 890 900 910	DRDRSEQHPLLHSTTELA ILPC SFTPM PALSTGLIHLHQN IVDVQYL YGVGSDMVGWALKWEFVILVFLLLADARVCVALWLM
S52 TP29		DRDRSEQHPLLHSTTELA ILPC SFTPM PALSTGLIHLHQN IVDVQYL YGVGSDMVGWALKWEFVILVFLLLADARVCVALWLM
S52 TP52		DRDRSEQHPLLHSTTELA ILPC SFTPM PALSTGLIHLHQN IVDVQYL YGVGSDMVGWALKWEFVILVFLLLADARVCVALWLM
S52 TP100		DRDRSEQHPLLHSTTELA ILPC SFTPM PALSTGLIHLHQN IVDVQYL YGVGSDMVGWALKWEFVILVFLLLADARVCVALWLM
AVI3a177		DRDRSEQHPLLHSTTELA ILPC SFTPM PALSTGLIHLHQN IVDVQYL YGVGSGVVGWALRWEFVVLVFLLLADARVCVALWLM
AVI3a177 TP29		DRDRSEQHPLLHSTTELA ILPC SFTPM PALSTGLIHLHQN IVDVQYL YGVGSGVVGWALRWEFVVLVFLLLADARVCVALWLM
AVI3a177 TP52		DRDRSEQHPLLHSTTELA ILPC SFTPM PALSTGLIHLHQN IVDVQYL YGVGSGVVGWALRWEFVVLVFLLLADARVCVALWLM
AVI3a177 TP100		DRDRSEQHPLLHSTTELA ILPC SFTPM PALSTGLIHLHQN IVDVQYL YGVGSGVVGWALRWEFVVLVFLLLADARVCVALWLM
		E2 Protein
S52	921	LMVSQAEA
S52 TP29		LMVSQAEA
S52 TP52		LMVSQAEA
S52 TP100		LMVSQAEA
AVI3a177		LMISQAEA
AVI3a177 TP29		LMISQAEA
AVI3a177 TP52		LMISQAEA
AVI3a177 TP100		LMISQAEA
		E

FIG. 7B

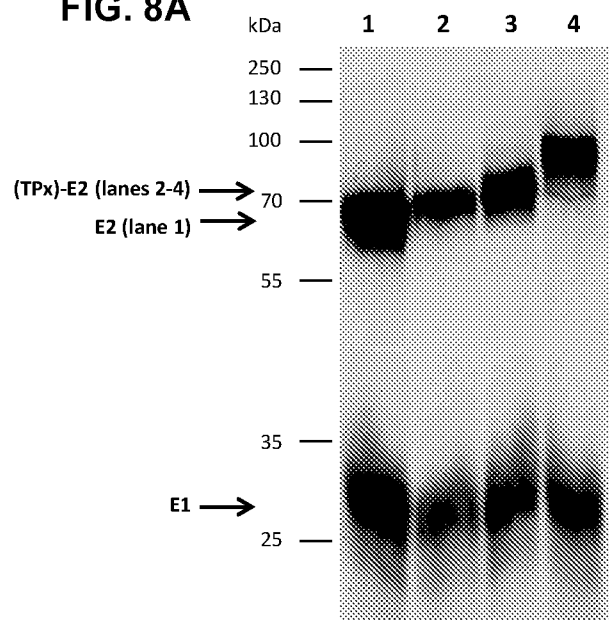
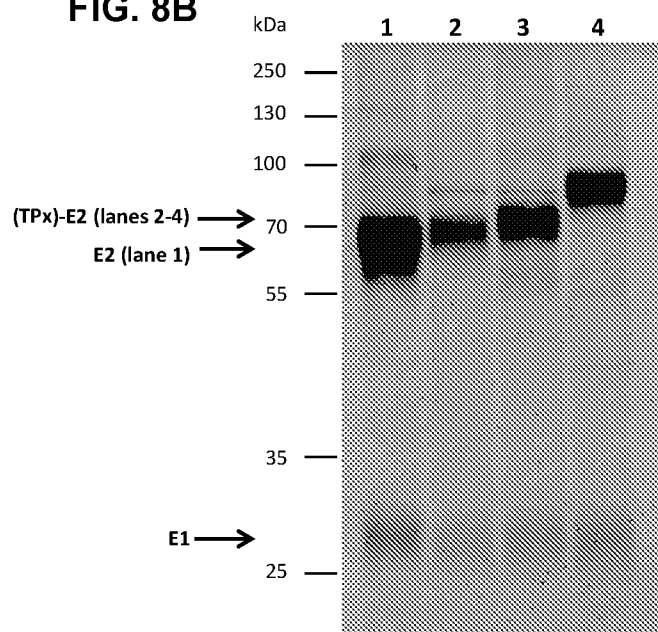
FIG. 8A**FIG. 8B**

FIG. 9A

GenBank 3S7G_A

Homo sapiens **IgG1 Fc**

227 aa

```

1 dkthtcpcp apellgppsv flfppkpkdt lmisrtpevt cvvvdvshed pevknwvyvd
61 gvevhnaktk preegynsty rvsvltvlh qdwlngkeyk ckvsnkappa piektiskak
121 gqprepqvyt lpsrdeltk nqvsitclvk gfypsdiave wesngqpenn ykttppvlids
181 dgsfflyskl tvdksrwqgg nvfscvmhe alnhytqks lsispqk

```

GenBank AAN76044

Homo sapiens **IgG2 Fc** (amino acids 99-325)

227 aa

```

1 stkgpsvfpl apcsrstses taalgcclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg
61 lyslssvvtv psnfgtqty tcnvdhkpsn tkvdktverk ccvecpcpa ppvagpsvfl
121 fppkpkdtlm isrtpevtcv vvdvshedpe vqfnwyvdgv evhnaktkpr eeqfnstfir
181 vsvltvvhqd wlngkeykck vsnkglpapi ektisktkgq prepqvytlp psreemtknq
241 vsltclvkqf ypsdiawe sngqpennyk ttpmldsdg sfflyskltv dksrwqggnv
301 fscsvmheal hnhytqksls lspqk

```

GenBank AAW65947

Homo sapiens **IgG3 Fc** (amino acids 19-246)

238 aa

```

1 hkpsntkvdk rvelktplgd tthtcpcpa pellggpsvf lfppkpkdtl misrtpevtc
61 vvvdvshedp evkfnwyvdg vevhnaktkp reegynstyr vsvltvlhq dwlngkeykc
121 kvsnkai pap iektiskakg qppepqvytl ppsrdeltkn qvsltclvkq fypsdiavew
181 esngqpenny kttppvlbsd gsfflysklt vdksrwqggv vfscsvmhea lnhytqksl
241 slspqk

```

FIG. 9B

GenBank AAA52770

Homo sapiens IgD Fc (amino acids 162-383)

222 aa

```

1  ptkapdvfpi isgcrhpkdn spvviacilit gyhptsvtvt wymgtqspq rtfpeiqrdrd
61  syymtssqls tpiqqwrqge ykcvvqhtas kskkeifrwv espkagassv ptaqpqaegs
121 lakattapat trntgrggee kkekekeeq eeretktpec pshtqplgvy lltpavqdlw
181 lrdkatftcf vvgdldkdah ltwevagkvp tggveegllie rhnsgsgsqh srlltprslw
241 nagtsvtctl nhpslppqrl malrepaada pvklslnlla ssdppeaasw llcevsqfsp
301 pnillmwled grevntsgfa parppqprrs ttfwawsvlr vpappspqpa tytctvshed
361 srtllnaars levsyvtldhg pmk

```

GenBank 0308221A

Homo sapiens IgM Fc

276 aa

```

1  vtstltikzs dwigesmftc rvdhrgltfq gnassmcvdp qdtairvfai ppsfasiflt
61  kstkltlclvt dltybsvti swtreengav kthtnishes pnatfsavge asicedbqws
121 gerftctvth tdlpsplkqt isrpkgvalh rpbvyllypa rzzlnlresa titclvtgfs
181 padvfvevmq rgeplspqky vtsapmpcpq apgryfahsi ltvseeewnt ggtytcvvah
241 ealpnrvter tvdkstgkpt lynvslvmsd tagtcy

```

FIG. 9C

GenBank P01876

Homo sapiens **IgA** Fc (amino acids 120-353)

234 aa

```

1 asptspkvfp lsicstqpdg nvviacivqg ffpqeplsvt wsegqgvta rnfppsgdas
61 gdlyttssql tlpateqlag ksvtchvkhy tnpqdvtvp cpvstptp spstptps
121 scchprish rpaledlllg seanltctlt girdasgtf twtpssgksa vggpperdlc
181 gcysvssvlp gcaepwnhkg tftctaaype sktpltatis ksgntfirpev hllpppseel
241 alnelvtltc largfspkdv lvrwlqgsqe lprekyltwa srqepsqgtt tfavtsilrv
301 aaedwkkgdt fscmvgheal plaftgktid rlagkpthvn vsvvmaevdg tcy

```

GenBank 1F6A_B

Homo sapiens **IgE** Fc (amino acids 6-222)

212 aa

```

1 adpcdsnprg vsaylsrpsp fdlfirkst itclvvdlap skgtvnltws rasgkpvnhs
61 trkeekqng tltvtstlpv gtrdwieget yqcrvthphl pralmrsttk tsgraaapev
121 yafatpewpg srckrtlac1 ignfmpedis vqwlhnevql pdarhsttqp rktkgsqffv
181 fsrlevtrae weqkdeficr avheaaspsq tvgravsvnp gk

```

GenBank P01861

Homo sapiens **IgG4** Fc (amino acids 100-327)

228 aa

```

1 astkqpsvfp lapcsrstse staaalgc1vk dyfpepvtvs wnsгалtsgv htfpavlgss
61 glylssvvt vpssslgtkt ytcnvdhkps ntkvdkrves kygppepcsp afe1lggpsv
121 flfppkpkt lmiisrtpevt cvvvdvsqged pevqfnwyvd gvevhnaktk preeqfnsty
181 rvsvitvlh qdwingkeyk ekvsnkqlps siektiskak gqprepqvvt lppsdeemtk
241 nqvs1tc1vk gfypsdiave wesngqpenn ykttppvlds dgsfflysr1 tvdksrwqeg
301 nvfscsvmhe alnhhytqks ls1slgk

```

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	ATDALMTGTGDFDSV ID	HCV1a, 1b, 3, 4, 7	2
CD4-R6	1563-1577	15	TGLTHIDAHFLSQTG	HCV1a, 1b, 2a, 2b, 3, 7	1
CD4-R7	1773-1785	13	QYLAGLSTLPNGP	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	RHVGPGEAGVQWMN 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	Others
B*40:02	2	2	Y, K, R, A, H, W, G, F, Q, L, S, C, I, T, M, V	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	TYSTY/GKFL	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	AIPLEVIKGRHLIFCHSKKKCDELAACL	1,393	1,421	NS3-3, NS3-4, NS3-11
TP50	LGALTGTYYVYNHLTPLRDWAHNGLRDLA VAVEPVVFSQMETKLITWGADT	955	1,004	NS2-1, NS2-2, NS2-3, NS2-7, NS2-8
TP52	AIPLEVIKGRHLIFCHSKKKCDELAACL ALGINAVAYYRGLDVSIVPTSG	1,393	1,444	NS3-3, NS3-4, NS3-5, NS3-11
TP70	KGGRHLIFCHSKKKCDELAACLVALGINA VAYYRGLDVSIVPTSGDVVVVATDALMTG FTGDFDSVIDCN	1,400	1,469	NS3-3, NS3-4, NS3-5, NS3-6, NS3-7, NS3-11, NS3-12, NS3-13
TP100	VALSTTGEIPFYGKAIPLEVIKGRHLIFCHS KKKCDELAACLVALGINAVAYYRGLDVS IVPTSGDVVVVATDALMTGFTGDFDSVIDC 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 WLLSPRGRPSWGPTDPRRRSRNLGKVIDTLT 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	LHAPTGSKGSTKVPAAAYAAQGYKVLVLNP SVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYKFLADGGCSGGAYDIIICDE CHSTDATSLIGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGK AIPLEVIKGRHLIFCHSKKKCDELAACL ALGINAVAYYRGLDVSIVPTSGDVVVVAT 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 HYVQMAIIKLGALTGTYYVYNALTPLRDWA HNGLRDLAVAVEPVVFSQMETKLITWGAD TAACGDIINGLPVSARRGREILLGPADGMV SKGWRLAPITAYAQQTRGLLGCIITSLTG RDKNQVEGEVQIVSTAAQTFLATCINGVC WTVYHGAGTRTIASPKGPVIQMYTNVDQD LVGWPA PQGARSLTPCTCGSSDLVLVTRH ADVIPVRRRGDSRGSLLSPRISYLKGSAGG PLLCPAGHAVGIFRAAVCTRGVAKAVDFIP VENLETTMRSPVFTDNSSPPAVPQSFQVAH LHAPTGSKGSTKVPAAAYAAQGYKVLVLNP SVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYKFLADGGCSGGAYDIIICDE CHSTDATSLIGIGTVLDQAETAGARLVVLA 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

	AIPLEVIKGGRLIFCHSKKKCDELAACKLV ALGINAVAYYRGLDVSVIPTSGDVVVVAT DALMTGFTGDFDSVIDCN			
TP778	LHAPTGS GKSTKVPAAAYAAQGYKVLVLP SVAATLGFGAYMSKAHGIDPNIRTGVRTIT TGSPITYSTYGKFLADGGCSGGAYDIIICDE CHSTDATSILGIGTVLDQAETAGARLVVLA TATPPGSVTVPHPNIEEVALSTTGEIPFYGK AIPLEVIKGGRLIFCHSKKKCDELAACKLV ALGINAVAYYRGLDVSVIPTSGDVVVVAT DALMTGFTGDFDSVIDCNTCVTQTVDFSL DPTFTIETTTLPQDAVSRTQRRGRTGRGKP GIYRFVAPGERPSGMFDSSVLCECYDAGCA WYELTPAETTVRLRAYMNTPLPVCQDHL EFWEGVFTGLTHIDAHFLSQTKQSGENLPY LVAYQATVCARAQAPPSWDQMWKCLIR LKPTLHGPTPLLYRLGAVQNEVTLTHPITK YIMTCMSADLEVVTSTWVLVGGVLAALA AYCLSTGCVVIVGRIVLSGKPAIIPDREVL REFDEMEEC SQHLPYIEQGMMLAEQFKQK ALGLLQTASRQAEVIAPAVQTNWQKLEAF WAKHMWNFISGIQYLAGLSTLPGNPAIASL MAFTA AVTSPLTTSQTLLFNILGGWVAAQ LAAPGAATAFVGAGLAGAAIGSVGLGKVL VDILAGYGAGVAGALVAFKIMSGEVPSTE DLVNLLPAILSPGALVVGVVCAAILRRHVG PGE GAVQWMNRLIAFASRGNHVSPTHYVP 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 RGDSRGSLLSPRPISYLKGSAGGPLLCAG HAVGIFRAAVCTRGVAKAVDFIPVENLETT MRSPVFTDNSSPPAVPQSFQVAHLHAPTGS GKSTKVPAAYAAQGYKVLVLNPSVAATL GFGAYMSKAHGIDPNIRTGVRTITTGSPITY STYGKFLADGGCSGGAYDIIICDECHSTDA TSILGIGTVLDQAETAGARLVVLATATPPG SVTVPHPNIEEVALSTTGEIPFYGKAIPLEVI KGGRHLIFCHSKKKCDELAACLVALGINA VAYYRGLDVSIVPTSGDVVVVATDALMTG FTGDFDSVIDCNTCTVTQTVDFSLDPTFTIET TTLPQDAVSRQTQRRGRTGRGKPGIYRFVAP GERPSGMFDSSVLCECYDAGCAWYELTPA ETTVRLRAYMNTPLPVCQDHLEFWEGVF TGLTHIDAHFLSQTKQSGENLPYLVAYQAT VCARAQAPPPSWDQMWKCLIRLKPTLHGP TPLLYRLGAVQNEVTLTHPITKYIMTCMSA DLEVVTSTWVLVGGVLAALAAYCLSTGC VVIVGRIVLSGKPAIIPDREVLYREFDEMEE CSQHLPIYIEQGMMLAEQFKQKALGLLQTA SRQAEVIAPAVQTNWQKLEAFWAKHMWN FISGIQYLAGLSTLPGNPAIASLMAFTAAVT SPLTTSQTLLFNILGGWVAAQLAAPGAATA FVGAGLAGAAIGSVGLGKVLVDILAGYGA GVAGALVAFKIMSGEVPSTEDLVNLLPAIL SPGALVVGVVCAAILRRHVGPGEAVQW MNRLIAFASRGNHVSPTHYVPESDAAARV TAILSSLTVTQLLRRRLHQWISSECTTPCSGS WLRDIWDWICEVLSDFKTWLKAKLMPQLP GIPFVSCQRGYRGVWRGDGIMHTRCHCGA EITGHVKNGTMRIVGPRTCRNMWSGTFPIN AYTTGPCTPLPAPNYTFALWRVSAEEYVEI RQVGDFHYVTGMTTDNLKCPCQVPSPEFF TELDGVRLHRFAPPCKPLLREEVSFRVGLH EYPVGSQLPCEPEPDVAVLTSMLTDP SHIT AEAAGRRLARGSPPSVASSASQLSAPSLK ATCTANHDSPPDAELIEANLLWRQEMGGNI TRVESENKVILDSFDPLVAEEDEREISVPA EILRKSRRFAPALPIWARPDYNPPLLETWK KPDYEPPVVHGCPLPPPQSPVPVPPRKKRT VVLTESTVSTALAEATKSFGSSSTSGITGD 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 SVWKDLLEDSTPIDTTIMAKNEVFCVQPE KGGRKPARLIVFPDLGVRVCEKMALYDVV SKLPLAVMGSSYGFQYSPGQRVEFLVQAW KSKKTPMGFSYDTRCFDSTVTESDIRTEEI YQCCDLPQARVAIKSLTERLYVGGPLTNS RGENCGYRRCRASGVLTTS CGNTLT CYIK ARAACRAAGLQDCTMLVCGNNLVVICESA GVQEDAASLRAFTEAMTRYSAAPPDPPQP EYDLELITSCSSNVSV AHDGAGKRVYYLTR DPTTPLARA AWETARHTPVNSWLGNIIMF APTLWARMILMTHFFSVLIARDQLEQALD CEIYGACYSIEPLDLPPIIQR LHGLSAFSLHS YSPGEINRVAACLRLKLGVPPLRAWHRAR SVRARLLSRGGRAAICGKYLFWAVRTKL KLTPIAAAGQLDLSGWFTAGYSGGDIYHS VSHARPRWFWFCLLLAAGVGIYLLPNR			
---	--	--	--

* 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.

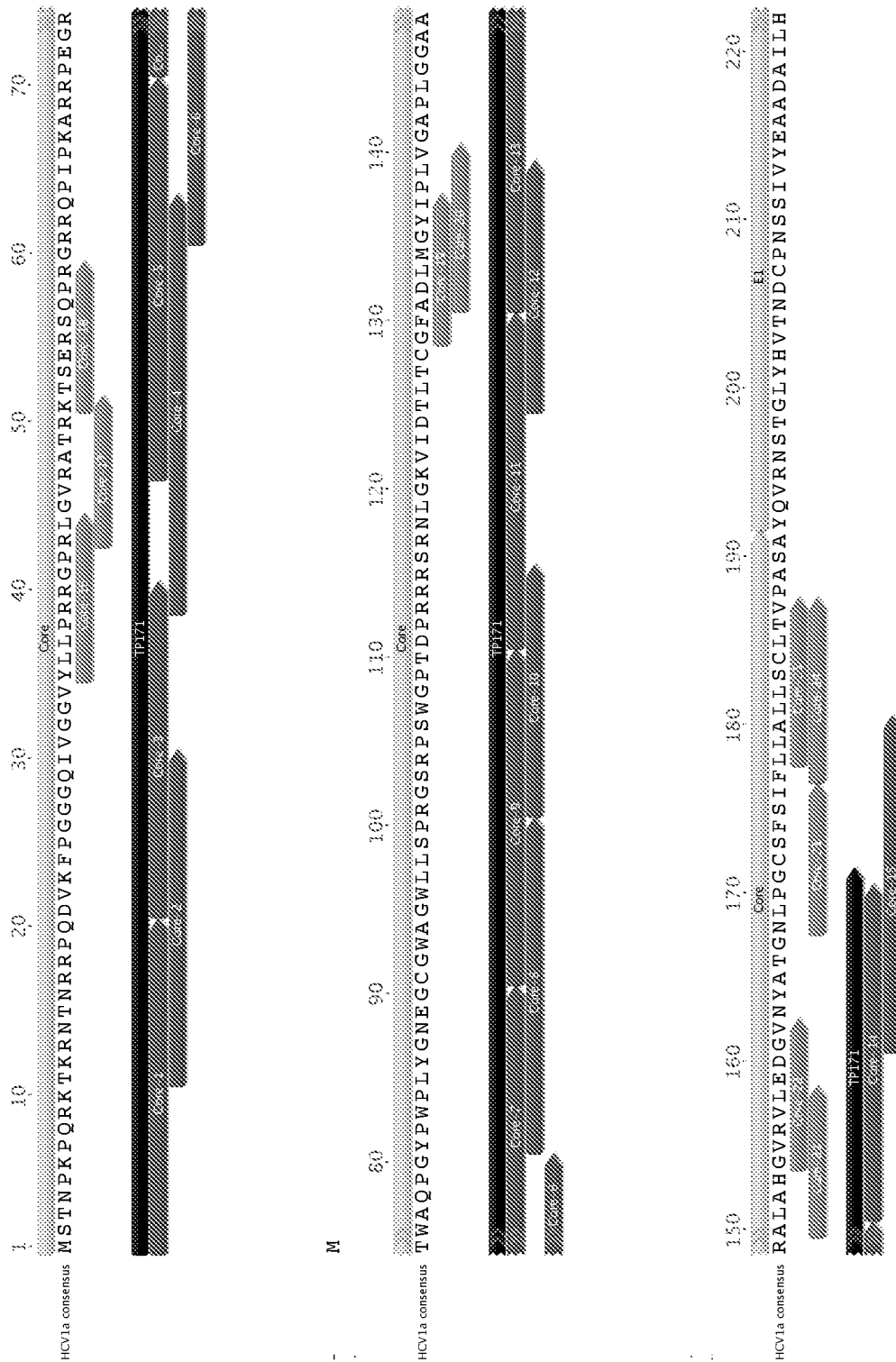


FIG. 15A

230 240 250 260 270 280 290
 HCV1a consensus TPGCVPCVR-EGNASRCWVAVTPTVATRDGKLP^{ET}TTQLRRRHIDLLVGSATLCSALYVGDLCGSVFLVGQLFTFSP

300 310 320 330 340 350 360 370
 HCV1a consensus RRHWTQDCNC^{ET}SIYPGHI^{ET}TGHRMAWDMMNWSP^{ET}TALVVAQLLRIPQAILDMIAGAHWGVLAGIAYFSMVGNWA

380 390 400 410 420 430 440
 HCV1a consensus KVLV^{ET}VLLLLFAGVDAETHVTGGSAA^{ET}RTTSGLASLFTPGAKQNIQLINTNGSWHINRTALNCNDSLNTGWLGLFY

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 VVVGTDRSGAPTYNWGENDTDVFLNNTTRPPLGNWFGCTWMNST-GFTKVCGAPPCVI-GGVGN-----NTLH

600 610 620 630 640 650 660
HCV1a consensus CPTDCFRKKHPEATYSRCGSGPWITPRCLVDYPYRLWHYPCTINYTIFKVRMYVGGVEHRLEAACNWTGRGERCDL

FIG. 15C

HCV1a consensus
670 680 690 700 710 720 730 740
EDRDRSELSPLLLSLTQWQVLPCSFSTLPAALSTGLIHLHQNIVDVQYLYGVGSSIASWAIAKWEYVVLFLLLAD

HCV1a consensus
750 760 770 780 790 800 810
ARVCSCLVMMMLLISQAEAALENLVVINAASLAGTHGLVSFLVFFCFAWYIK--GRWVPGAAYALYGMWPLLLLL

HCV1a consensus
820 830 840 850 860 870 880
LALPQRAYALDTEVAASC GGVLVGLMALTLSPYKRYISWCLWWLQYFLTRVEAQLHVVWVPPPLNVRGGRDAVI

FIG. 15D

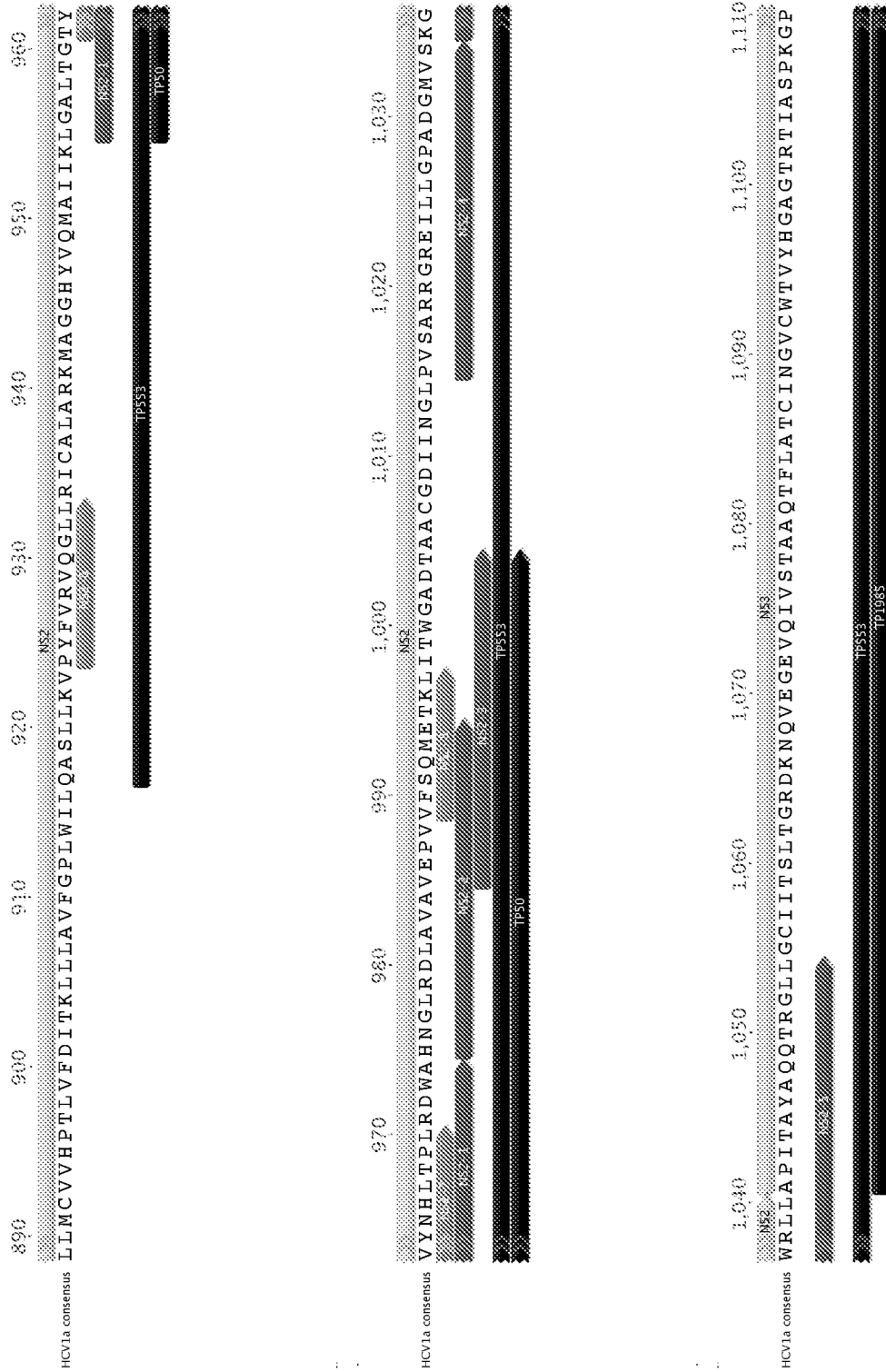


FIG. 15E

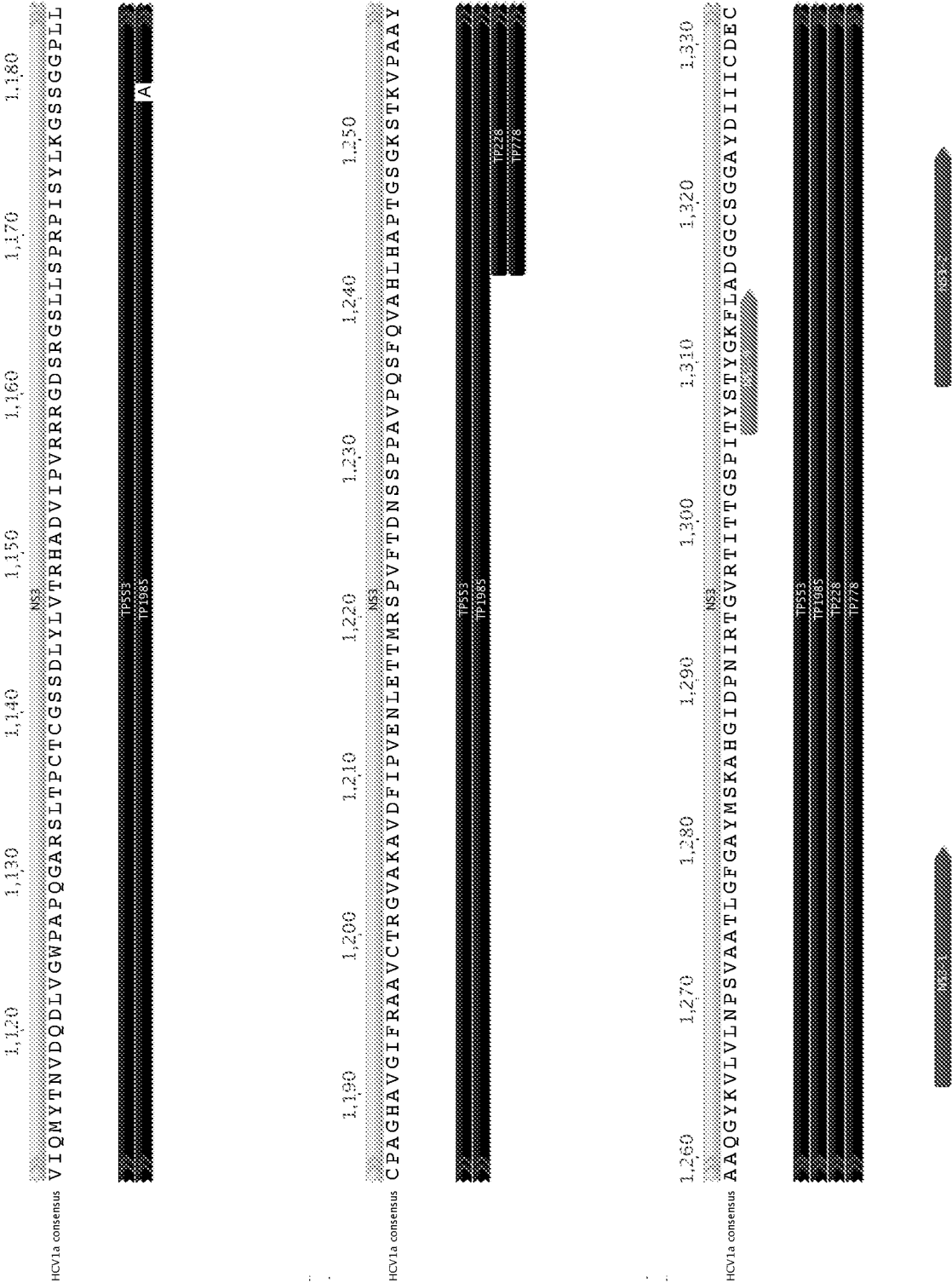


FIG. 15F

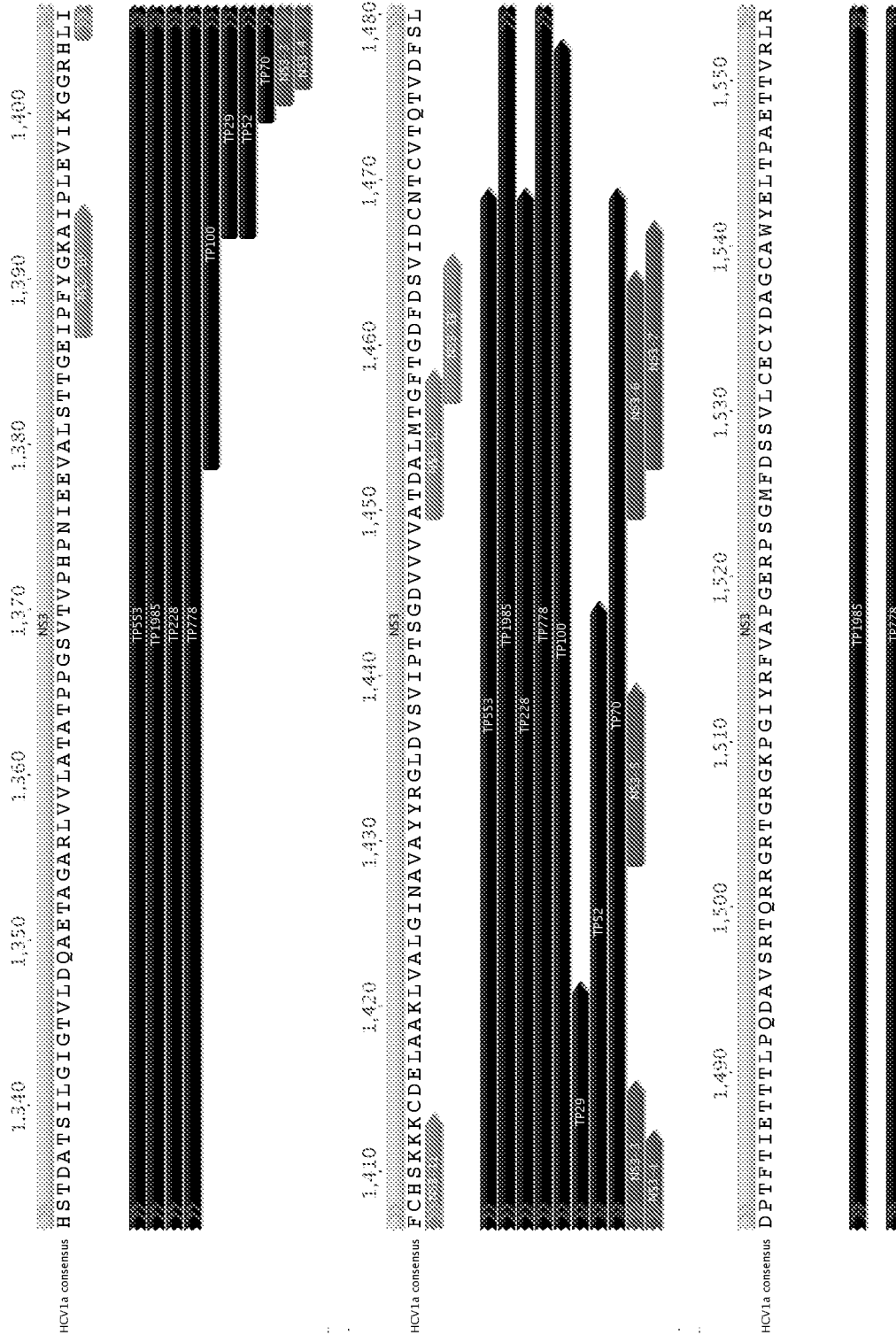


FIG. 15G



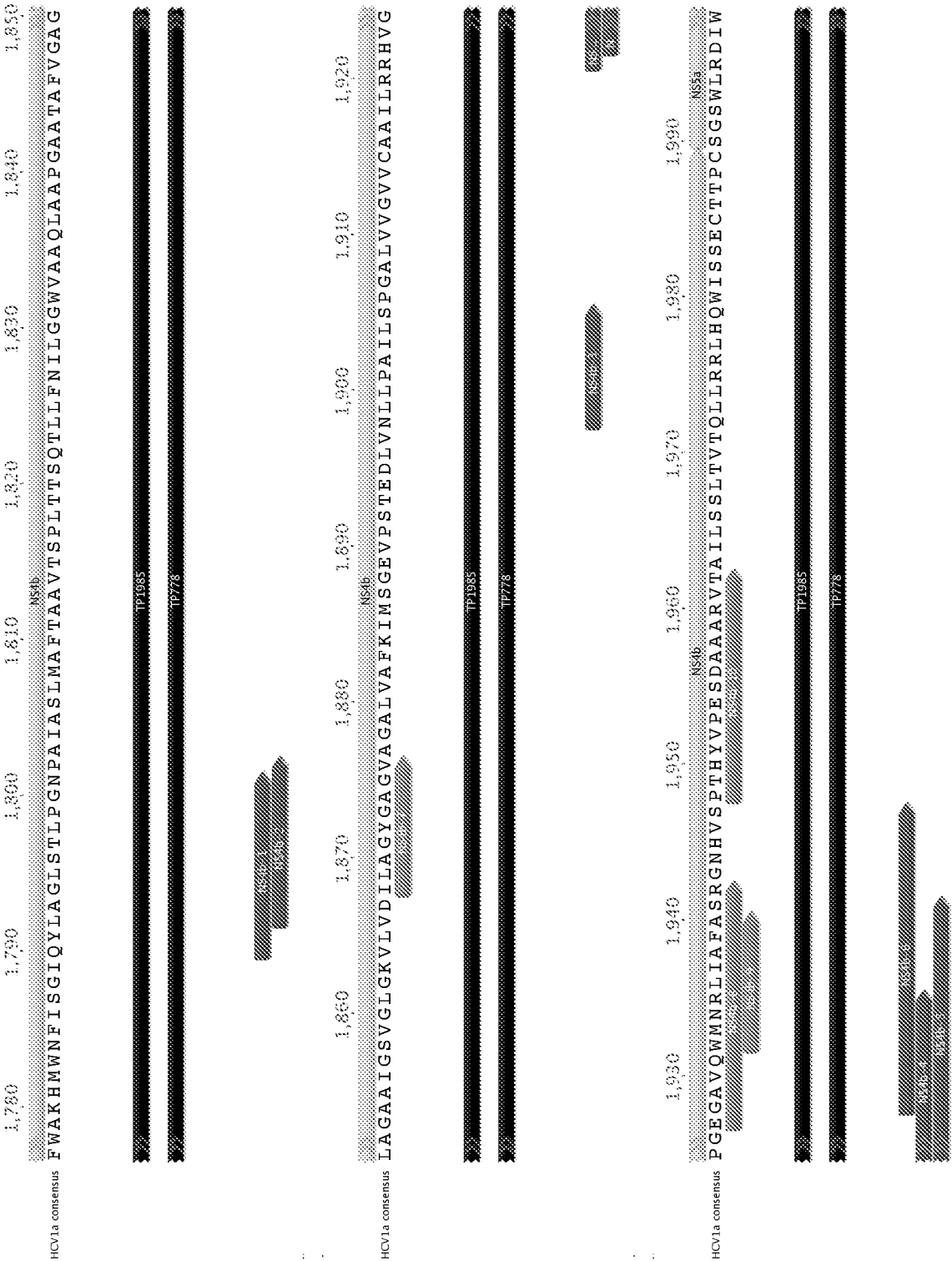


FIG. 15I

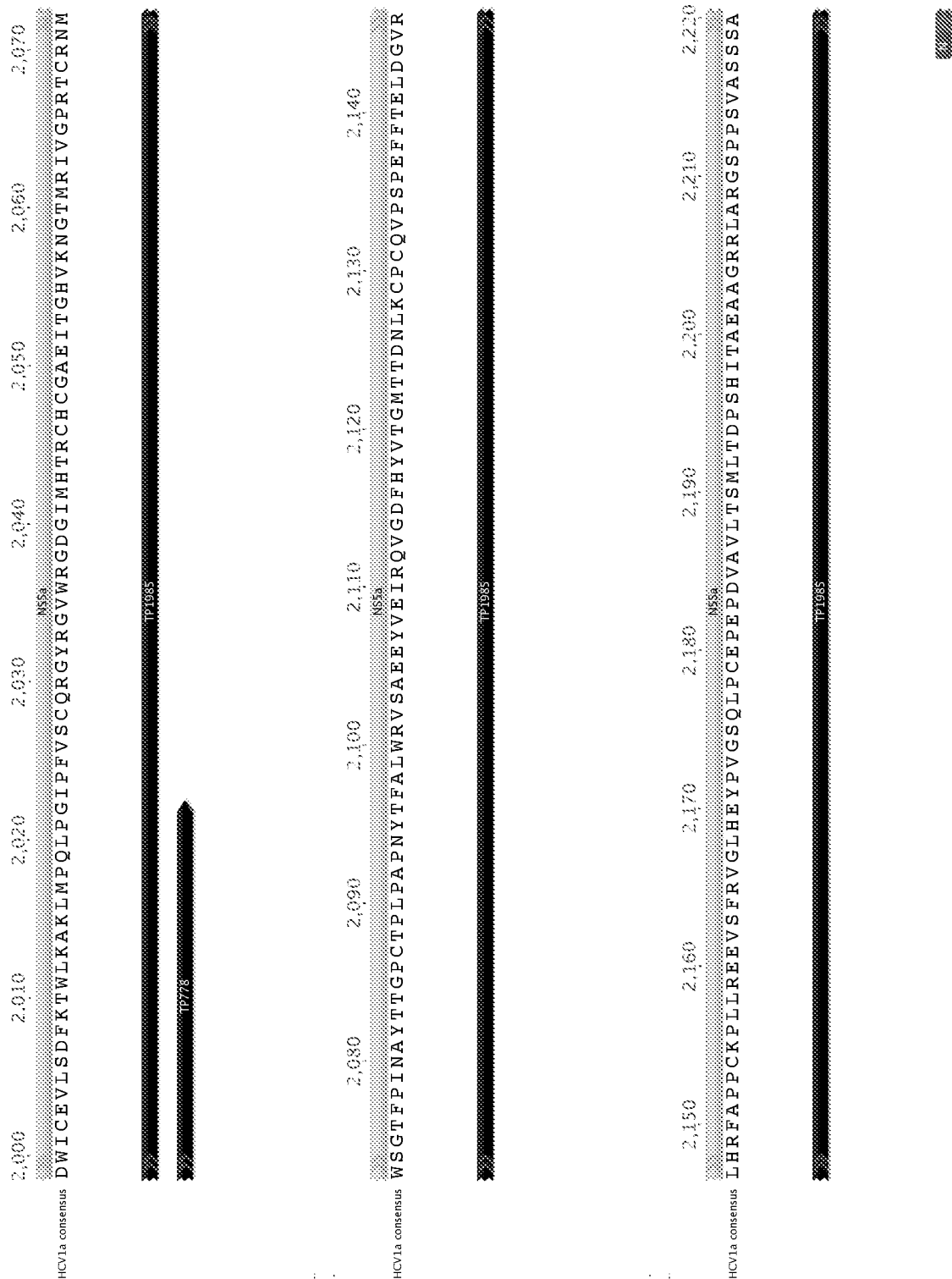


FIG. 15J

HCV1a consensus
2,230 2,240 2,250 2,260 2,270 2,280 2,290
S Q L S A P S L K A T C T A N H D S P D A E L I E A N L L W R Q E M G G N I T R V E S E N K V V I L D S F D P L V A E - E D E R E I S V P A E I L R

TP1985

NS5a

HCV1a consensus
2,300 2,310 2,320 2,330 2,340 2,350 2,360
K S R - R F A P A L P I W A R P D Y N P P L L E T W K K P D Y E P P V V H G C P L P P P Q S P P V P P P R K K - R T V V L T E S T V S T A L A E L A

TP1985

HCV1a consensus
2,370 2,380 2,390 2,400 2,410 2,420 2,430 2,440
T K S F G S S T S G I - - - - T G D N T T T S S E P A P S - G C P P D S D A E S Y S S M P P L E G E P G D P D L S D - - - - -

TP1985

FIG. 15K

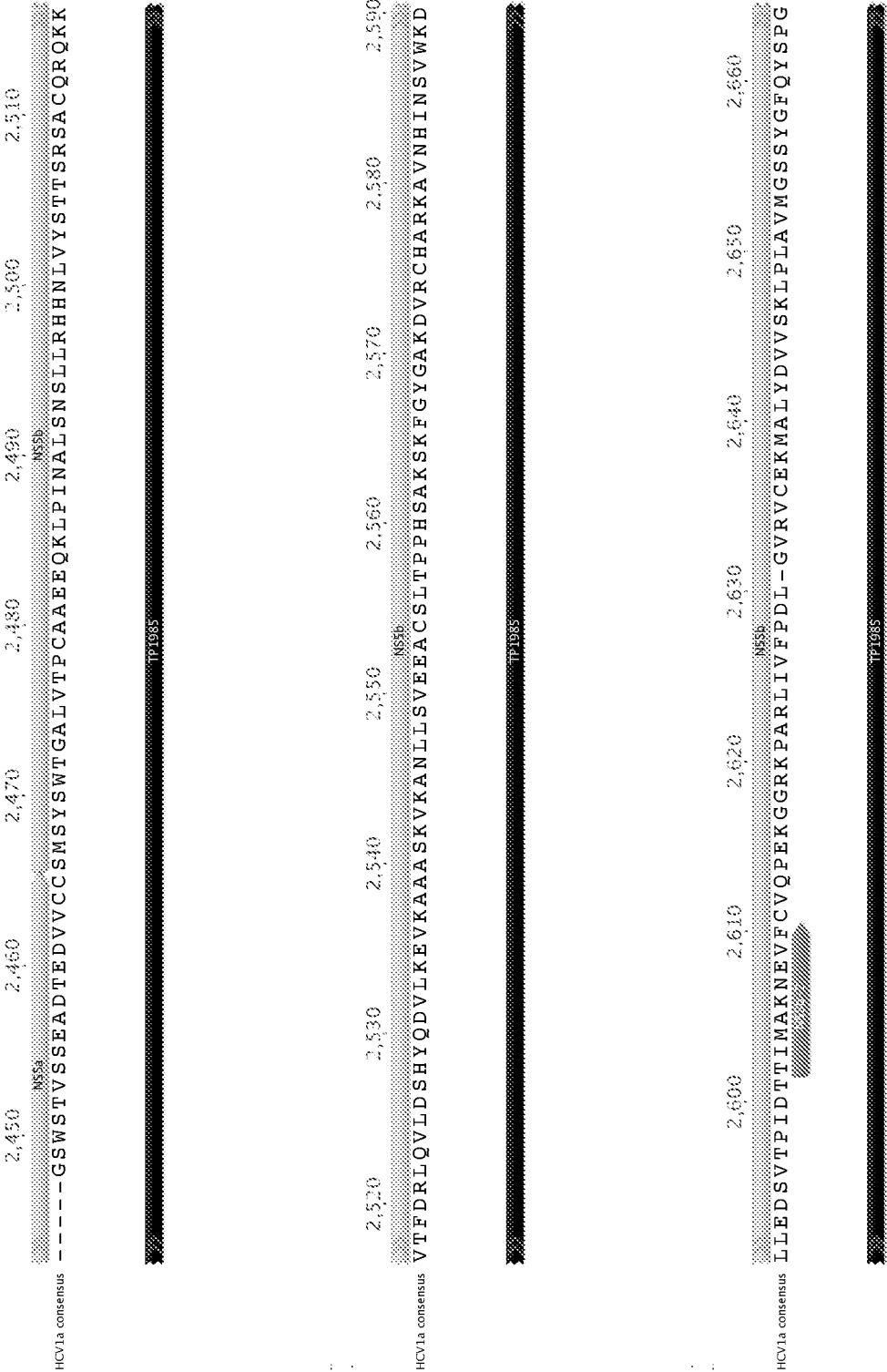


FIG. 15L

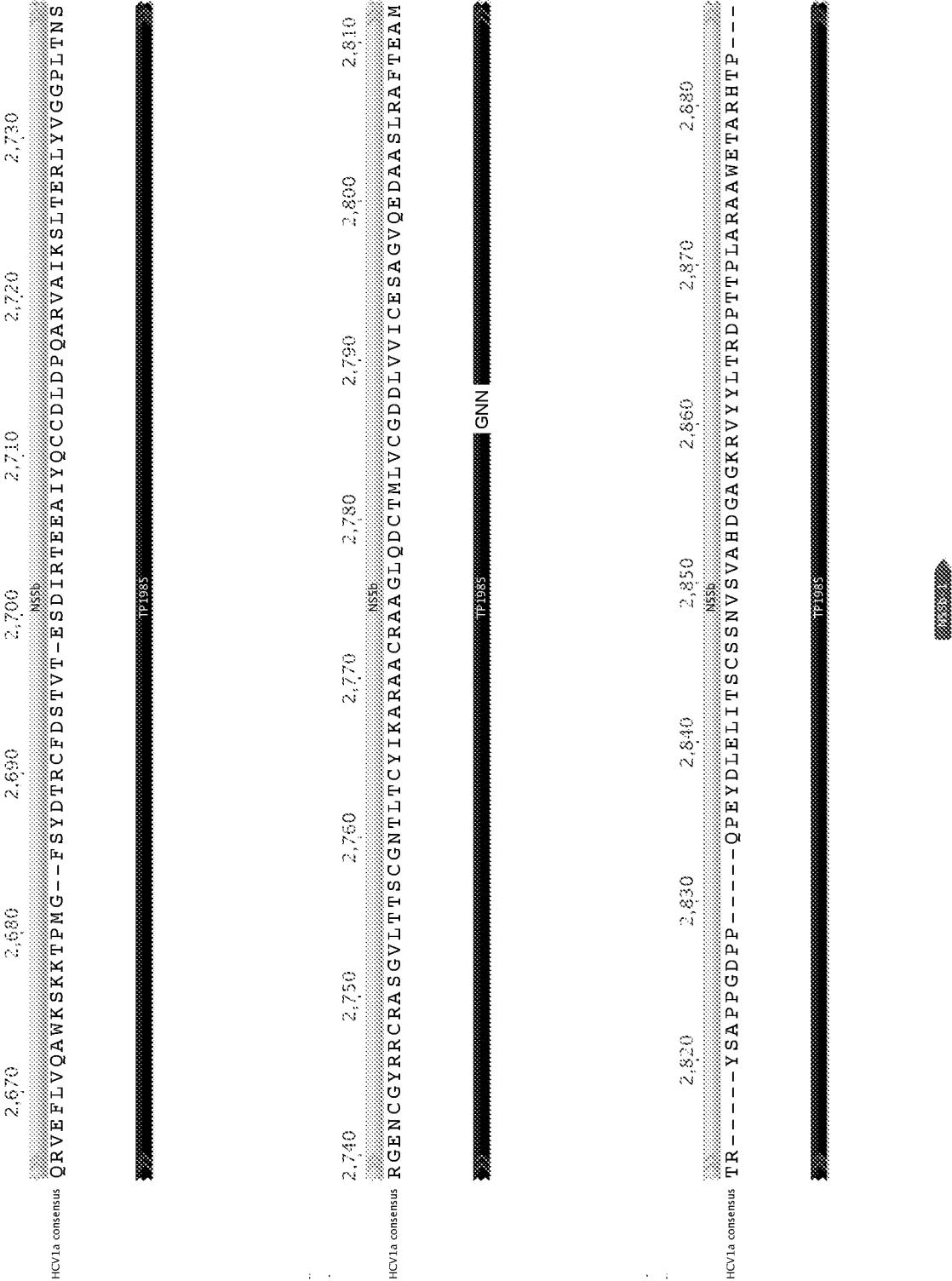


FIG. 15M

2,890 2,900 2,910 2,920 2,930 2,940 2,950 2,960
HCV1a consensus VNSWLGNIIMFAPTILWARMILMTHFFSVLIARDQLEQALDCEIYGACYSIEPLDLPPIIQRIHGLSAFSLHSYS

TP1985

2,970 2,980 2,990 3,000 3,010 3,020 3,030
HCV1a consensus PGEINRVAACLRKLGVPPLRAWRRHRSVRARLLSRGGRAAICGKYLFWAVRTKIKLTPIAAAGQLDLSGWFT

TP1985

3,040 3,050 3,060 3,070 3,074
HCV1a consensus AGYSGGDIYHSVSHARPRWFWFCLLLAAGVGIVLLPNRX

TP1985

FIG. 15N

Consensus	1	20	30	40	50	60	70	80
	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
	Core							
1. HCV1a consensus	1	20	30	40	50	60	70	80
2. HCV1b consensus	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
3. HCV2a Consensus	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
4. HCV2b Consensus	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
5. HCV 3 Consensus	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
6. HCV 4 Consensus	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
7. HCV5 consensus	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
8. HCV6 consensus	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
9. HCV7: ABN05226	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
14. AV11a-129	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
15. AV13a-177	MSTNPKPQRTKTRNTNRRPQDVKFPGGGQIVGGVYLLPRRGPRLGVRATRKTSERSQPRGRQPIPKARRSEGRSWAQPYPWPPLY							
Consensus	90	100	110	120	130	140	150	160
	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
	Core							
1. HCV1a consensus	1	20	30	40	50	60	70	80
2. HCV1b consensus	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
3. HCV2a Consensus	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
4. HCV2b Consensus	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
5. HCV 3 Consensus	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
6. HCV 4 Consensus	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
7. HCV5 consensus	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
8. HCV6 consensus	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
9. HCV7: ABN05226	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
14. AV11a-129	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
15. AV13a-177	GNEGCGWAGWLLSPRGSRPSWGPTDPRRRSRNLGKVIDTLTCGFADLMGYIPLVGAPLGGVARALAHGVRVLEGGINYATGNLPGC							
Consensus	180	190	200	210	220	230	240	250
	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
	Core							
	E1							
1. HCV1a consensus	1	20	30	40	50	60	70	80
2. HCV1b consensus	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
3. HCV2a Consensus	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
4. HCV2b Consensus	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
5. HCV 3 Consensus	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
6. HCV 4 Consensus	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
7. HCV5 consensus	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
8. HCV6 consensus	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
9. HCV7: ABN05226	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
14. AV11a-129	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							
15. AV13a-177	SFSIFLLALLSCLTPASAYEVNRNKSGLYHVTNDCPNSSIVYEADDAILHTPGCVPCVR-EGNTSRCWVXVTPVAVRYXGAPTTT							

FIG. 16A

Consensus	260	270	280	290	300	310	320	330	340	
	E1									
	LRRHVDLLVGAATLCSALYVGDLCGAVFLVGQXFTFSRRRHWTVDQNCNSIYPGHITGHRNAWDMMMNWSPTTLLVXAQLLRIPQX									
1. HCV1a consensus	LRRH IDLLVGSATLCSALYVGDLCGVSFLVQLGFTFSRRRHWTVDQNCNSIYPGHITGHRNAWDMMMNWSPTTALVVAQLLRIPQA									
2. HCV1b consensus	LRRHVDLLVGAATLCSALYVGDLCGVSFLVQLGFTFSRRRHWTVDQNCNSIYPGHVSGHRNAWDMMMNWSPTTALVVSQLLRIPQA									
3. HCV2a Consensus	LRRH IDLVVMSATLCSALYVGDLCGVMFLAQMFIIVSPQHWFVQECNCSIYPGTITGHRNAWDMMMNWSPTATMLAYAMRVPEV									
4. HCV2b Consensus	LRRHVDMLVMAATVCSALYVGDLCGAVMVSQALIVSPERHNFOTECNCSIYQGHITGHRNAWDMMLNWSPTLLMLAYAAARVPEL									
5. HCV 3 Consensus	LRRHVDLLVGAATLCSALYVGDLCGAVFLVQAFTFSRRRHWTVDQNCNSIYPGHISGHRNAWDMMMNWSPTTLLVVAQVLRIPQT									
6. HCV 4 Consensus	LRRHVDLMVGAATVCSALYVGDLCGGLFVLGQFTRRRRHWTVDQNCNSIYTGHTGHRNAWDMMMNWSPTTLLVLAQVLRIPQT									
7. HCV5 consensus	LRRHVDLAVGAAALCSALYVGDLCGAVXLVQMFYSRHHXTVDQNCNSIYSGHTGHRNAWDMMMNWSPTTALXMAQLLRIPQV									
8. HCV6 consensus	LRRHVDLLVGAATLCSALYVGDLCGGLFVLGQFTRRRRHWTVDQNCNSIYTGHTGHRNAWDMMMNWSPTTLLVLAQVLRIPQV									
9. HCV7: ABN05226	LRRH IDLVVASATLCSALYVGDLCGAVFLVQMFYSRHHXTVDQNCNSIYSGHTGHRNAWDMMMNWSPTTALVVAQVLRIPQV									
14. AV11a-129	LRRH IDLVVASATLCSALYVGDLCGVSFLVQMFYSRHHXTVDQNCNSIYPGHITGHRNAWDMMMNWSPTTALVVAQVLRIPQV									
15. AV13a-177	LRRHVDLLVGAATLCSALYVGDLCGAVFLVQMFYSRHHXTVDQNCNSIYPGHITGHRNAWDMMMNWSPTTALVVAQVLRIPQV									
Consensus	350	360	370	380	390	400	410	420	430	
	E1									
	XLDIIAGAHWGLAGLAYFSMQGNWAKVJXVILLFAGVDAETHTTGGXAARTTSGLTSLFSPGPXQNLQLintNGSWHINRTALNC									
	E2									
1. HCV1a consensus	LDDM IAGAHWGLAGLAYFSMVGNWAKVLVLLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
2. HCV1b consensus	VDDM VAGAHWGLAGLAYFSMVGNWAKVLIVMLFAGVDG-THVTGGAAARTTSGTSLFSPGPSQK IQLINTNGSWHINRTALNC									
3. HCV2a Consensus	LDDM IISGAHWGLAGLAYFSMQGAWAKVIVLLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
4. HCV2b Consensus	VLEVFVGGHWGLAGLAYFSMQGAWAKVIAILLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
5. HCV 3 Consensus	LDDM IAGAHWGLAGLAYFSMVGNWAKVIAIMVFSVGDAXTHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
6. HCV 4 Consensus	LDDM IAGAGHGWGLVGLVAYFSMQGNWAKVILVLLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
7. HCV5 consensus	LDDM IAGAHWGLVGLVGLVAYFSMVANWAKVILVLLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
8. HCV6 consensus	LDDM IAGAHWGLVGLVGLVAYFSMVANWAKVILVLLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
9. HCV7: ABN05226	LDDM IAGAHWGLVGLVGLVAYFSMVANWAKVILVLLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
14. AV11a-129	LDDM IAGAHWGLVGLVGLVAYFSMVANWAKVILVLLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
15. AV13a-177	LDDM IAGAHWGLVGLVGLVAYFSMVANWAKVILVLLFAGVDAETHVTGGSAARTTSGLASLFTPGAKQN IQLINTNGSWHINRTALNC									
Consensus	440	450	460	470	480	490	500	510		
	E2									
	NDSLXTGFIAGLPHYTHKFNSSGCPERLASCRPLTDFDQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
1. HCV1a consensus	NDSLNTGWLGLAGLPHYTHKFNSSGCPERLASCRPLTDFDQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
2. HCV1b consensus	NDSLQGTGFLAALPHYTHKFNSSGCPERLASCRPIDKFAQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
3. HCV2a Consensus	NDSLNTGFLASLPHYTHKFNSSGCPERLASCRPIEAFRIGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
4. HCV2b Consensus	NDSLQGTGFIAGLPHYTHKFNSSGCPERLASCRPIDKFAQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
5. HCV 3 Consensus	NDSLNTGFIAGLPHYTHKFNSSGCPERLASCRPIDKFAQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
6. HCV 4 Consensus	NDSLNTGFLASLPHYTHKFNSSGCPERLASCRPIDKFAQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
7. HCV5 consensus	NDSLQGTGFIAGLPHYTHKFNSSGCPERLASCRPIDKFAQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
8. HCV6 consensus	NDSLQGTGFIAGLPHYTHKFNSSGCPERLASCRPIDKFAQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
9. HCV7: ABN05226	NDSLQGTGFIAGLPHYTHKFNSSGCPERLASCRPIDKFAQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
14. AV11a-129	NDSLQGTGFIAGLPHYTHKFNSSGCPERLASCRPIDKFAQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									
15. AV13a-177	NDSLQGTGFIAGLPHYTHKFNSSGCPERLASCRPIDKFAQGWGLTVANXISGPSDDRPYCNWHPYPRPCGIVPARSVCGPVYCFTP--									

FIG. 16B

Consensus	520	530	540	550	560	570	580	590	600
	SPVVVGTTDRXGVPTYTWGENETDVFLNSTRPPQGNWFGCTWNNST-GFTKTCGAPPCNI-GGGN-----NDLLCPTDCFRKHP								
	E2								
1. HCV1a consensus	510	520	530	540	550	560	570	580	590
2. HCV1b consensus	SPVVVGTTDRSGAPTYNWGENETDVFLNSTRPPPLGNWFGCTWNNST-GFTKVCGAPPCVI-GGVGN-----NTLHCPTDCFRKHP								
3. HCV2a Consensus	SPVVVGTTDRFGVPTYSWGENETDVLLNSTRPPQGNWFGCTWNNST-GFTKTCGGPPCNI-GGVGN-----NTLTCPTDCFRKHP								
4. HCV2b Consensus	SPVVVGTTDRDLGPTYTWGENETDVFLNSTRPPQGSWFGCTWNNST-GFTKTCGAPPCNI-RADFNAS-----TDLLCPTDCFRKHP								
5. HCV 3 Consensus	SPVVVGTTDRQGVPTYSWGENETDVFLNSTRPPQGAWFGCTWNNST-GFTKTCGAPPCNI-RRDYNST---LDLLCPTDCFRKHP								
6. HCV 4 Consensus	SPVVVGTTDRQGVPTYTWGENETDVFLNSTRPPSGRWFCTWNNSTGTRGVKTCGAPPCNIYGGGNGXNNE-SDLFCPTDCFRKHP								
7. HCV5 consensus	SPVVVGTTDRGLGPTYTWGENESDFLLNSTRPPQGAWFGCVWNNST-GFTKACGAPPCVIRTNNGT---TDWPCPTDCFRKHP								
8. HCV6 consensus	SPVVVGTTDRXGXPTYXWGXNETDIFLLNSTRPPXGNWFGCTWNNST-GFVKTGAPPCNI-GPTGN-----NSLKCPTDCFRKHP								
9. HCV7: ABN05226	SPVVVGTTDRRGLPTYTWGENETDVFLNSTRPPPTGGWFGCTWNNST-GFVKTGAPPCNIXPNSSN-----NSLTCPTDCFRKHP								
14. AVI1a-129	SPVVVGTTDRRGVPTYTWGENESDFLLNSTRPPQGSWFGCTWNNST-GFTKTCGGPPCKIRPQGAQN---TSLTCPTDCFRKHP								
15. AVI3a-177	SPVVVGTTDRSGAPTYNWGENETDVFLNSTRPPPLGNWFGCTWNNST-GFTKVCGAPPCVI-GGAGN-----NTRCPTDCFRKHP								
	510	520	530	540	550	560	570	580	590
Consensus	EATYSXCGSGPWLTPRCLVDYPIYRLWHYPCIVNFTIFKVRMYVGVGVEHRLAECNWTGRGCDLEDRDRSELSPLLHSTTEWA ILP								
	E2								
1. HCV1a consensus	690	700	710	720	730	740	750	760	770
2. HCV1b consensus	EATYSRCGSGPWITPRCLVDYPIYRLWHYPCIVNFTIFKVRMYVGVGVEHRLAECNWTGRGCDLEDRDRSELSPLLHSTTQWQVLP								
3. HCV2a Consensus	EATYTKCGSGPWLTPRCLVDYPIYRLWHYPCIVNFTIFKVRMYVGVGVEHRLAECNWTGRGCDLEDRDRSELSPLLHSTTEWQ ILP								
4. HCV2b Consensus	DATYKCGAGPWLTPRCLVDYPIYRLWHYPCIVNFTIFKVRMYVGVGVEHRLAECNFTRGDCRLEDRDRGQSPLLHSTTEWAVLP								
5. HCV 3 Consensus	EATYSRCGAGPWLTPRCLVDYPIYRLWHYPCIVNFTIFKVRMYVGVGVEHRLAECNWTGRGCDIEDRDRSEQHPLHSTTELA ILP								
6. HCV 4 Consensus	ETTYAKCGSGPWITPRCLIHYPYRLWHYPCIVNFTIFKVRMYVGVGVEHRLAECNWTGRGCDLEDRDRSELSPLLHSTTQWXLPL								
7. HCV5 consensus	DATYKCGSGPWLTPRCLVHYPIYRLWHYPCIVNFTIFKVRMF IGGLEHRLAECNWTGRGCDLEDRDRSELSPLLHSTTQWAILP								
8. HCV6 consensus	EATYARCGSGPWLTPRCLVDYPIYRLWHYPCIVNFTIFKVRMFVGVGVEHRLAECNWTGRGCDLEDRDR IEMSPILFSTTELA ILP								
9. HCV7: ABN05226	RATYSACGSGPWLTPRCLVHYPIYRLWHYPCIVNFTIFKVRLY IGGVEHRLAECNWTGRGCDLEDRDRVDMSPLLHSTTELA ILP								
14. AVI1a-129	DATYSRCGSGPWITPRCLVDYPIYRLWHYPCIVNFTIFKVRMYVGVGVEHRLAECNWTGRGCDLEDRDRSELSPLLHSTTQWQVLP								
15. AVI3a-177	EATYSRCGAGPWLTPRCLVDYPIYRLWHYPCIVNFTIFKVRMFVGVGVEHRLAECNWTGRGCDLEDRDRSEQHPLHSTTELA ILP								
Consensus	690	700	710	720	730	740	750	760	770
	CSFTTLPALSTGL IHLHQ NVLDVQYLYGVGSVAVSWAKWEYVLLFLLLADARVCACILWMLLISQAEAALENVLNVAASAAGT								
	E2								
1. HCV1a consensus	690	700	710	720	730	740	750	760	770
2. HCV1b consensus	CSFTTLPALSTGL IHLHQ NVLDVQYLYGVGS IASWA IKWEYVLLFLLLADARVCSCILWMLLISQAEAALENVLNVAASAAGT								
3. HCV2a Consensus	CSFTTLPALSTGL IHLHQ NVLDVQYLYGIGSAVVSFA IKWEYVLLFLLLADARVCACILWMLL IAGAEAALENVLNVAASAAGT								
4. HCV2b Consensus	CSYSDLPALSTGL IHLHQ NVLDVQYMYGLSPALTKYVVRWEWVLLFLLLADARVCACILWML ILLGQAEAALEKLVNLHSAASA								
5. HCV 3 Consensus	CSFSDLPALSTGL IHLHQ NVLDVQYLYGLSPAITRY IVKWEWVLLFLLLADARVCACILWML ILLGQAEAALEKLI ILSASAASA								
6. HCV 4 Consensus	CSFTPMPALSTGL IHLHQ NVLDVQYLYGVSGMVGWALKWEFV ILVFLLLADARVCALWMLM ISQAEAALENVLNVAASAAGT								
7. HCV5 consensus	CSFTTLPALSTGL IHLHQ NVLDVQYLYGVGSVAVSWALKWEYVLLFLLLADARVCACILWMLFMVSVQEAALSNL IN INAAASAAGT								
8. HCV6 consensus	CSFTTLPALSTGL IHLHQ NVLDVQYLYGLSS IVSWAKWEY IVLXFLLLADAR ICTCLWLLXCCQAEAALENVLNVAASAAGT								
9. HCV7: ABN05226	CSFTTLPALSTGL IHLHQ NVLDVQYLYGVSSVAVSWALKWEYVLLFLLLADAR ICACILWML IGGAEAALENVLNVAASAAGT								
14. AVI1a-129	CSFVPLPALSTGL IHLHQ NVDAQYLYGLSPA IISWA IRWEWVLLFLLLADAR ICACILWMLM IGGAEAALENVLNVAASAAGT								
15. AVI3a-177	CSFTTLPALSTGL IHLHQ NVLDVQYLYGVGSVAVSWA IKWDVLLFLLLADAR ICACILWML IGGAEAALENVLNVAASAAGT								
	CSFTPMPALSTGL IHLHQ NVLDVQYLYGVSGVGVWALRWEFVLLFLLLADARVCALWMLM ISQAEAALENVLNVAASAAGT								
	P7								

FIG. 16C

	780	790	800	810	820	830	840	850	860
Consensus	HGIKWFLLVFFCAAWYIK--GRLVPXATYALXGLWPLLLLLLALPORAVALDREVAASLGXAVLVXLTIFTLSPHYKHLLSRXLWNL								
	NS2								
1. HCV1a consensus	HGLVSFLVFFCFAWYIK--GRWVPGAAYALYGMWPLLLLLLALPORAVALDTEVAASCGGVVLVGLMALTLSPYKRYISWCLWNL								
2. HCV1b consensus	HGLVSFLVFFCAAWYIK--GRLVPGAAYAFYGVWPLLLLLLALPORAVALDREMAASCGGAVFVGLALLTLSPHYKVFARLIWNL								
3. HCV2a Consensus	NGFLYFVIFVAAWYIK--GRAVPLAAYSLTGLWPFLLLLLALPQAYADASVHGQIGALLILITFTLTPGYKTLLSRCLWNL								
4. HCV2b Consensus	NGPLWFFIFFTAAWYIK--GRVVPVATYSVLGWSFLLLLLLALPQAYALDAEQGELGLVLVLIISIFTLTPAYKILLSRSVWNL								
5. HCV 3 Consensus	HGIWYLVAFCAAWHVRRAGKLVPLVTYSLTGLWSLALLLVLLLPORAYAWSGEDSATLGALIVLFGFTTSPWYKHWIGRLMWNL								
6. HCV 4 Consensus	HGFWYAFFICIAHWYK--GRLPAAATYACGMWPLLLLLLMLPERAYADREVAASLGAVVVALTILTLSPHYKSWLARGLWNI								
7. HCV5 consensus	HGFWGLLVXCAWHXK--GRLVPGATYCLGXWPLLLLLLALPORAALDSSDGGTVGCVLVLXILITFTLTPGYKXVVLVXWNL								
8. HCV6 consensus	QGWGGLLFLCCAWYK--GRLVPACTYALGLWPLLLLLLALPRAAYADNEQAASLGALVLLVITFTLTPAYKQLLVSVFLWNL								
9. HCV7: ABN05226	HGIWLLLLVFCASWHLR--GRVPLVTYIGCGWPFLLMLSLPRAVALDREVAASALGTGMLAIIILLTLGPHYKRLALILWNL								
14. AVI1a-129	HGIAPFLVFFCLAWYIK--GKWAPGAVYAVYGMWPLLLLLLALPORAVALDTEVAASCGGAVLVGLMVLTLSPHYKHYISWCLWNL								
15. AVI3a-177	HGIWYLVAFCAAWHLR--GKLVPLVTYSLTGLWSLAVLVLLLPORAYAWSGEDSATLGAGILVLFGFTTSPWYKHWIGRLMWNL								
	870	880	890	900	910	920	930	940	
Consensus	QYFITRAEAQLQVWVPPNLVNRGGRDXXILLTCLLHPXLVFDITKLLAVLGLPLYLLOASLRLVPYFVRAHALLRXCMLVRXLGGK								
	NS2								
1. HCV1a consensus	QYFLTRVEAQLHVWVPPNLVNRGGRDAVILLMCVVHPTLVFDITKLLAVFGPLWILQASLLKVPYFVRVQGLLRICALARKMAGGH								
2. HCV1b consensus	QYFITRAEAHLQVWIPPLNVRGGRDAIILLTCAVHPELIFDITKLLAALGPLMVLQAGITRVPYFVRAQGLIRACMLVRKVAGGH								
3. HCV2a Consensus	CYLLTLGEAMVQEWAPPMQARGGRDGIWAATIFCPGVVFDITKLLAVLGLPAYLLRDALTFRVPYFVRAHALLRNMCTMVRHLAGGR								
4. HCV2b Consensus	SYMLVLAEAQIQQWVPLEARGGRDGIWAVILHPRLVFEVTKWLLAALGPAVLLKASLRLVPYFVRAHALLRVTCLVRHLAGGR								
5. HCV 3 Consensus	QYTICRCEAALQVWVPPNLARGSRDGVILLTSLLYPSLIFDITKLLIAVLGPLYLIQAAITTPYFVRAHVLRLCMLVRSVMGGK								
6. HCV 4 Consensus	QYFIARAEALLHVVPSPDVRGGRDLSILAVLACPHLVFDITKLLAALGPLYLLOASLRLVPYFVRAHALVKICSLRGVVYGGK								
7. HCV5 consensus	QYFIARVAXIHVVVPPQLVNRGGRDAIIMLTCLFHPALGFVETKILGLGLPYLLQXSLKXVPYFVRARALLRACLLAKHLVXGK								
8. HCV6 consensus	QYFIARAEAMLHVVPSPRLVRGGRDAVILTLCLHPQLGFVETKILALLGLPLYLLQYSLKVPYFVRAHALLRACLLVRLLAGGK								
9. HCV7: ABN05226	TYFLTRCEAALQVWVPPNLPRGGRDGFILCVLLCYPLVFDITKLLVMCMCPYLLQLCLVTPYFVRAQALIRVCSLFTLAGGR								
14. AVI1a-129	QYFLTRAEAQLHVWVPPNLVNRGGRDAVILLMCVVHPTLVFDITKLLAVLGLPLYLLOASLRLVPYFVRVQGLLRICALARKIAGGH								
15. AVI3a-177	QYTICRCEAALQVWVPPNLARGSRDGAILLTSLLYPSLIFDITKLLIAVLGPLYLIQAAITTPYFVRAHVLRLCMLVRSVMGGK								
	950	960	970	980	990	1,000	1,010	1,020	1,030
Consensus	YVQMALKLGRWTGTYYDHLXPLSDWAAAGLRDLAVAVEPVIFSPMEKKVITWGADTAACGDILCGLPVSARLGREILLGPADDY								
	NS2								
1. HCV1a consensus	YVQMAIIKLGALTGTYYNHLTPLRDWAHNGRDLAVAVEPVVFSQMETKLIITWGADTAACGDIINGLPVSARRGREILLGPADGM								
2. HCV1b consensus	YVQMAFMKLAALTGTYYDHLTPLRDWAHAGLRDLAVAVEPVVFSQMETKIITWGADTAACGDIILGLPVSARRGREILLGPADSL								
3. HCV2a Consensus	YVQMALALGRWTGTYYDHLTPMSDWAASGRDLAVAVEPIIFSPMEKKVIVWGAETAAACGDIILHGLPVSARLGREILLGPADGY								
4. HCV2b Consensus	YIQMLLITIGRWTGTYYDHLSPSTWAAQGRDLAVAVEPVVFSQMETKVIWGAETAAACGDIILHGLPVSARLGREVLLGPADSY								
5. HCV 3 Consensus	YFQMILSIGRWFNTYLDHLAPMQHWAAGLRDLAVATEPVIFSPMEIKVITWGADTAACGDIILCGLPVSARLGREVLLGPADDDY								
6. HCV 4 Consensus	YQMAVLKVGALTGTYYDHLTPMSDWAAGLRDLAVALEPVVFTPMMEKKVIVWGAETAAACGDIIXGLPVSARLGREILLGPADSE								
7. HCV5 consensus	YVQAALLHGLRLTGTYYDHLAPMKDWAASGRDLAVATEPIIFSPMETKVITWGADTAACGDIILAGLPVSARRGREIFLGPADDI								
8. HCV6 consensus	YVQACLLRLGALTGTYYDHLAPLSDWAASGRDLAVATEPVIFSPMEKKVITWGADTAACGDIILAGLPVSARRGNIVLLGPADDM								
9. HCV7: ABN05226	YVQAALLTIGRWTGTYYNHLAPLETWAAAGLRDLAVATEPVIFSPMEKKIIVWGAETAAACGDIILCGLPVSARLGREVLLGPADGY								
14. AVI1a-129	YVQMAIIKLGALTGTYYDHLTPLRDWAHNGRDLAVAVEPVVFSQMETKLIITWGADTAACGDIINGLPVSARRGREILLGPADGM								
15. AVI3a-177	YFQMILSIGRWFNTYLDHLAPMQHWAAGLRDLAVATEPVIFSPMEIKVITWGADTAACGDIILCGLPVSARLGREVLLGPADDDY								

FIG. 16D

Consensus	1,040	1,050	1,060	1,070	1,080	1,090	1,100	1,110
XSKGWRLIAP	ITAYAQOTRGLLGT	IVTSLTGRDKNEVE	GEVQVLS	TATQTFLGTC	INGVMWTVYH	GAGSKTLAGPKGPV	XQMYTNV	
NS2	NS3							
1. HCV1a consensus	1,120	1,130	1,140	1,150	1,160	1,170	1,180	1,190
2. HCV1b consensus	EGQGWRLIAP	ITAYSQOTRGLLGC	IITSLTGRDKNQ	VEGEVQIVSTAA	QTFLATC	INGVWTVYH	GAGTRT	IASPKGPV
3. HCV2a Consensus	TSKGWRLIAP	ITAYAQOTRGLLGA	IVVSMTRDKTE	QAGEIQVLS	TQTSFLGTS	ISGLWTVYH	GAGNKTLAGR	KPVTQMYSSA
4. HCV2b Consensus	TSKGWRLIAP	ITAYTQOTRGLLGA	IVVSLTGRDKNE	QAGVQVLS	TQTSFLGTS	ISGLWTVYH	GAGNKTLAGR	KPVTQMYTSA
5. HCV 3 Consensus	REMGWRLIAP	ITAYAQOTRGLLGT	IVTSLTGRDKNQ	VEGEVQVLS	TATQTFLGTT	VGGVMWTVYH	GAGSKT	ISGPKGPV
6. HCV 4 Consensus	TSKGWRLIAP	ITAYAQOTRGLFST	IITSLTGRDKT	NENCGE	VQVLS	TATQTSFLGTA	INGVMWTVYH	GAGSKT
7. HCV5 consensus	XXAGWRLIAP	ITAYAQOTRGLVGA	IVVSLTGRDKNE	AGEVQVLS	TATQTF	LGTCINGVMWTV	FHGA	GAXKTL
8. HCV6 consensus	KRGWRLIAP	ITAYAQOTRGLLGT	IVTSLTGRDKNE	VEGEVQVLS	TATQTSFLGTS	INGVWTVYH	GAGSKTLAGR	KPVCQMYTNV
9. HCV7: ABN05226	RSMGWQLLAP	ISAYAQOTRGLI	ISTLVSLTGRDKNE	TAGEVQVLS	TQTSFLGTV	NGVMWGPYH	GAGTRTV	AGRG
14. AVI1a-129	VSXGWRLIAP	ITAYAQOTRGLLGC	IITSLTGRDKNQ	VEGEVQIVSTAA	QTFLATC	INGVWTVYH	GAGTRT	IASPKGPV
15. AVI3a-177	REMGWRLIAP	ITAYAQOTRGLLGT	IVTSLTGRDKNV	TGEVQVLS	TATQTF	LGTTIGVMWTVYH	GAGSRT	LAGV
Consensus	1,120	1,130	1,140	1,150	1,160	1,170	1,180	1,190
DQDLVGPAP	PPGAKSLTPCTCGSSD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISX	LKSSGGPVL	CPSGH	AVGFRAA
NS2	NS3							
1. HCV1a consensus	1,210	1,220	1,230	1,240	1,250	1,260	1,270	1,280
2. HCV1b consensus	DQDLVGPAP	PPGAKSLTPCTCGSSD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
3. HCV2a Consensus	EGDLVGPSP	PPGAKSLTPCTCGAVD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
4. HCV2b Consensus	EGDLVGPSP	PPGAKSLTPCTCGAVD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
5. HCV 3 Consensus	DQDLVGPAP	PPGAKSLTPCTCGASD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
6. HCV 4 Consensus	DQDLVGPAP	PPGAKSLTPCTCGASD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
7. HCV5 consensus	DQDLVGPAP	PPGAKSLTPCTCGASD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
8. HCV6 consensus	DQDLVGPAP	PPGAKSLTPCTCGASD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
9. HCV7: ABN05226	SDDLVPAP	PPGAKSLTPCTCGASD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
14. AVI1a-129	DQDLVGPAP	PPGAKSLTPCTCGSSD	LYLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
15. AVI3a-177	DQDLVGPAP	PPGAKSLTPCTCGST	DLVTRHADV	IPVRRRGDS	RGSLLSPRP	ISY	LKSSGGPVL	CPAGH
Consensus	1,210	1,220	1,230	1,240	1,250	1,260	1,270	1,280
KAVDFIP	VPESLETTMRSP	XFTDNSTPP	AVPQXYQVGYLH	APTGS	GKSTKVP	AAAYAAQ	QYKVLV	LNPSVA
NS2	NS3							
1. HCV1a consensus	KAVDFIP	VPENLETTMRSP	VFTDNSSPP	AVPQSFQVAH	LHAPTGS	GKSTKVP	AAAYAAQ	QYKVLV
2. HCV1b consensus	KAVDFIP	VPESMETTMRSP	VFTDNSSPP	AVPQTFQVAH	LHAPTGS	GKSTKVP	AAAYAAQ	QYKVLV
3. HCV2a Consensus	KSIDFIP	VPETLDIVTRSP	TFSNDSTPP	AVPQTYQVGYLH	APTGS	GKSTKVP	AAAYAAQ	QYKVLV
4. HCV2b Consensus	KSIDFIP	VPESLDIATRP	TFSNDSTPP	AVPQTYQVGYLH	APTGS	GKSTKVP	AAAYAAQ	QYKVLV
5. HCV 3 Consensus	KALQFIP	VPETLTQARSP	SFSDNSTPP	AVPQTYQVGYLH	APTGS	GKSTKVP	AAAYAAQ	QYKVLV
6. HCV 4 Consensus	KAVDFIP	VPESLETTMRSP	VFTDNSTPP	AVPQTYQVAH	LHAPTGS	GKSTKVP	AAAYAAQ	QYKVLV
7. HCV5 consensus	KALDFIP	VPENLETTMRSP	VFTDNSTPP	AVPHEFQVGH	LHAPTGS	GKSTKVP	AAAYAAQ	QYKVLV
8. HCV6 consensus	KSIDFIP	VPENMETTMRSP	SFSDNSTPP	AVPQTYQVGYLH	APTGS	GKSTKVP	AAAYAAQ	QYKVLV
9. HCV7: ABN05226	KAVQFVP	IEKMVAQ	RSFSDNSTPP	AVPQTYQVGYLH	APTGS	GKSTKVP	AAAYAAQ	QYKVLV
14. AVI1a-129	KAVDFIP	VPESLETTMRSP	VFTDNSSPP	AVPQSFQVAH	LHAPTGS	GKSTKVP	AAAYAAQ	QYKVLV
15. AVI3a-177	KALQFIP	VPETLSAQA	RSFSDNSTPP	IVPQSYQVGYLH	APTGS	GKSTKVP	AAAYAAQ	QYKVLV

FIG. 16E

Consensus	1.300	1.310	1.320	1.330	1.340	1.350	1.360	1.370
	NS3							
	NIRTGVRTVTTGAPITYSTYKFLADGGCGSGAYDIIICDECHSDATTTILGIGTVLDQAGTAGRVLVLTATATPPGSVTVPHNII							
1. HCV1a consensus	NIRTGVRTITTTGSPITYSTYKFLADGGCGSGAYDIIICDECHSDATSIILGIGTVLDQAGTAGRVLVLTATATPPGSVTVPHNII							
2. HCV1b consensus	NIRTGVRTITTTGAPITYSTYKFLADGGCGSGAYDIIICDECHSDSTTTILGIGTVLDQAGTAGRVLVLTATATPPGSVTVPHNII							
3. HCV2a Consensus	NIRTGVRTITTTGAPITYSTYKFLADGGCGAGAYDIIICDECHAVDATTTILGIGTVLDQAGTAGRVLVLTATATPPGSVTVPHNII							
4. HCV2b Consensus	NIRTGVRTVTTGDPITYSTYKFLADGGCGSAGAYDIIICDECHSDATTTILGIGTVLDQAGTAGRVLVLTATATPPGTVTTPHNSII							
5. HCV 3 Consensus	NIRTGVRTVTTGAKLTYSTYKFLADGGCGSGAYDIIICDECHADATSIILGIGTVLDQAGTAGRVLVLTATATPPGSIITVPHNSII							
6. HCV 4 Consensus	NIRSGVRTITTTGAPITYSTYKFLADGGCGSGAYDIIICDECHSDSTTTILGIGTVLDQAGTAGRVLVLTATATPPGSVTVPHNSII							
7. HCV5 consensus	NIRTGVRTITTTGAAITYSTYKFLADGGCGSGAYDIIICDECHSDATTTILGIGTVLDQAGTAGRVLVLTATATPPGSVTVPHNII							
8. HCV6 consensus	NIRTGVRTITTTGGAITYSTYKFLADGGCGSGAYDIIICDECHSDPTTTLGIGTVLDQAGTAGRVLVLTATATPPGSVTVPHNII							
9. HCV7: ABN05226	SVRTGARTVTTGAPITYSTYKFLADGGCGSGAYDIIICDECHADATTTVVGIGTVLDQAGTAGRVLVLTATATPPGSVTVPHNII							
14. AV11a-129	NIRTGVRTITTTGSPITYSTYKFLADGGCGSGAYDIIICDECHSDATSIILGIGTVLDQAGTAGRVLVLTATATPPGSVTVPHNII							
15. AV13a-177	NIRTGVRTVTTGAKLTYSTYKFLADGGCGSGAYDIIICDECHADATSIILGIGTVLDQAGTAGRVLVLTATATPPGSIITVPHNSII							
Consensus	1.380	1.390	1.400	1.410	1.420	1.430	1.440	1.450
	NS3							
	EVALGTXGEIPFYGKAIPLEXIKGGRHLIFCHSKKCCDELAALKLGLGLNAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDF							
1. HCV1a consensus	EVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKCCDELAALKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDF							
2. HCV1b consensus	EVALSNTGEIPFYGKAIP IETIKGGRHLIFCHSKKCCDELAALKSLGLNNAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDF							
3. HCV2a Consensus	EVALGQEGEIPFYGKAIPLSYIKGGRHLIFCHSKKCCDELAALKURGMGLNNAVAYYRGLDVSVIPTSGDVVVVATDALMTGFTGDF							
4. HCV2b Consensus	EVALGHEGEIPFYGKAIP LAFIKGGRHLIFCHSKKCCDELAALKRGMGNNAVAYYRGLDVSVIPTQGDVVVVATDALMTGYTGDF							
5. HCV 3 Consensus	EVALGSEGEIPFYGKAIP I AQLKGGRHLIFCHSKKCCDE IASKURGMGLNNAVAYYRGLDVSVIPTTGDVVVVCATDALMTGFTGDF							
6. HCV 4 Consensus	EVALPTTGEIPFYGKAIPLELIKGGHLLIFCHSKKCCDELAQKLTSLGLNNAVAYYRGLDVSVIPTSGDVVVVCATDALMTGFTGDF							
7. HCV5 consensus	EVALPSEGEIPFYGKAIP LXLIKGGHLLIFCHSKKCCDELAQKLTSLGLNNAVAYYRGLDVAVIPATSGDVVVVCATDALMTGFTGDF							
8. HCV6 consensus	TETALPTTGEIPFYGKAIPLEYIKGGHLLIFCHSKKCCDELAQKLTSLGLNNAVAFYRGLDVSVIPTSGDVVVVCATDALMTGYTGDF							
9. HCV7: ABN05226	EVALGNDGEIPFYGKAIP LQHIKGGHLLIFCHSKKCCDELAGKLTSLGLTAVAYYRGLDVSVIPTSGDVVVVCATDALMTGFTGDF							
14. AV11a-129	EVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKCCDELAALKLVALGINAVAYYRGLDVSVIPTSGDVVVVATDALMTGYTGDF							
15. AV13a-177	EVALGSEGEIPFYGKAIP L AQLKGGRHLIFCHSKKCCDEMAASKLRGMGLNNAVAYYRGLDVSVIPTAGDVVVVCATDALMTGFTGDF							
Consensus	1.470	1.480	1.490	1.500	1.510	1.520	1.530	1.540
	NS3							
	DSVIDCNVAVTQTVDPSLDPTFTIETTTPQDAVSRQRRGRTGRGLGIYRYVSPGERPSGMFDSVLCECYDAGCAWYELTPAE							
1. HCV1a consensus	DSVIDCNTCVTQTVDFSLDPTFTIETTTLPQDAVSRQTQRRGRTGRGKPGIYRFVAPGERPSGMFDSVLCECYDAGCAWYELTPAE							
2. HCV1b consensus	DSVIDCNTCVTQTVDFSLDPTFTIETTTPQDAVSRQRRGRTGRGRRGIYRFVTPGERPSGMFDSVLCECYDAGCAWYELTPAE							
3. HCV2a Consensus	DSVIDCNVAVTQVDFSLDPTFTITTTQTPQDAVSRQRRGRTGRGLGIYRYVSTGERPSGMFDSVLCECYDAGAAWYELTPAE							
4. HCV2b Consensus	DSVIDCNVAVTQIVDFSLDPTFTITTTQTPQDAVSRQRRGRTGRGLGIYRYVSSGERPSGMFDSVLCECYDAGAAWYELTPAE							
5. HCV 3 Consensus	DSVIDCNVAVEQVDFSLDPTFTSIETRTAPQDAVSRQRRGRTGRGLGIYRYVTPGERPSGMFDSVLCECYDAGCSWYDLQPAE							
6. HCV 4 Consensus	DSVIDCNTSVIQTVDFSLDPTFTSIETTTPQDAVSRQRRGRTGRGLGIYRYVTPGERPSGMFDTSVLCECYDAGCAWYELTPAE							
7. HCV5 consensus	DSVIDCNTAVTQTVDFSLDPTFTIETTTPQDAVSRQRRGRTGRGHHGIYRYVSSGERPSGIFDSVLCECYDAGCAWYDLTPAE							
8. HCV6 consensus	DSVIDCNVAVTQVDFSLDPTFTSIETTTPQDAVSRQRRGRTGRGKPGIYRYVSSQGERPSGMFDTVLLCEAYDTCAWYELTPSE							
9. HCV7: ABN05226	DSVIDCNVAVTQTVDFSLDPTFTIETTTPQDSVSRQRRGRTGRGLGIYRYVSSGERPSGMFDTSVLCECYDLGCSWYELTPSE							
14. AV11a-129	DSVIDCNTCVTQTVDFSLDPTFTIETTLPQDAVSRQTQRRGRTGRGKPGIYRFVAPGERPSGMFDSVLCECYDAGCAWYELTPAE							
15. AV13a-177	DSVIDCNVTVEQVDFSLDPTFTSIETRTAPQDAVSRQRRGRTGRGLGIYRYVAPGERPSGMFDSVLCECYDAGCSWYDLQPAE							

FIG. 16F

Consensus	1,550	1,560	1,570	1,580	1,590	1,600	1,610	1,620	1,630
	NS3								
1. HCV1a consensus	TTVRLRAYLNT	PGLPVCQDHL	FEWEGVFTGL	THIDAHFL	SQTKQSGEN	FPYLVA	YQATVCARA	QAAPPSWD	XMWKCLIRL
2. HCV1b consensus	TSVRLRAYLNT	PGLPVCQDHL	FEWESVFTGL	THIDAHFL	SQTKQAGDN	FPYLVA	YQATVCARA	QAAPPSWD	QMWKCLIRL
3. HCV2a Consensus	TTVRLRAYFNT	PGLPVCQDHL	FEWAEVFTGL	THIDAHFL	SQTKQSGEN	FAYLVA	YQATVCARA	KAAPPSWD	VMMKCLIRL
4. HCV2b Consensus	TTVRLRAYFNT	PGLPVCQDHL	FEWAEVFTGL	THIDAHFL	SQTKQSGEN	FAYLVA	YQATVCARA	KAAPPSWD	VMMKCLIRL
5. HCV 3 Consensus	TTVRLRAYFNT	PGLPVCQDHL	FEWESVFTGL	THIDAHFL	SQTKQSGEN	FAYLVA	YQATVCARA	QAAPPSWD	ETWKCLIRL
6. HCV 4 Consensus	TTVRLRAYFNT	PGLPVCQDHL	FEWESVFTGL	THIDAHFL	SQTKQSGEN	FAYLVA	YQATVCARA	QAAPPSWD	ETWKCLIRL
7. HCV5 consensus	TTVRLRAYLNT	PGLPVCQDHL	FEWEGVFTGL	THIDAHML	SQTKQSGEN	FPYLVA	YQATVCARA	KAAPPSWD	TMWKCMXRL
8. HCV6 consensus	TTVRLRAYLNT	PGLPVCQDHL	FEWEGVFTGL	THIDAHFL	SQTKQSGEN	FAYLVA	YQATVCARA	KAAPPSWD	TMWKCLIRL
9. HCV7: ABN05226	TTVRLRAYLNC	PGLPVCQDHL	FEWEGVFTGL	THIDAHFL	SQTKQSGEN	FAYLVA	YQATVCARA	KAAPPSWD	VQWKCLIRL
14. AVI1a-129	TTVRLRAYMNT	PGLPVCQDHL	FEWEGVFTGL	THIDAHFL	SQTKQSGEN	FPYLVA	YQATVCARA	QAAPPSWD	QMWKCLIRL
15. AVI3a-177	TTVRLRAYLST	PGLPVCQDHL	FEWESVFTGL	THIDAHFL	SQTKQSGEN	FAYLVA	YQATVCARA	QAAPPSWD	EMWKCLIRL
Consensus	1,640	1,650	1,660	1,670	1,680	1,690	1,700	1,710	1,720
	NS3								
	NS4a								
1. HCV1a consensus	PTPLLRYRLG	AVQNEVTL	THPITKY	IMTCSAD	LEVTT--	STWVL	GGVLAAL	AAYCLST	GCVVIVGR
2. HCV1b consensus	PTPLLRYRLG	AVQNEVTL	THPITKY	IMACMSAD	LEVTT--	STWVL	GGVLAAL	AAYCLST	TSVVIVGR
3. HCV2a Consensus	PTPLLRYRLG	AVTNEVTL	THPVTKY	IATCMQAD	LEMT--	STWVL	AGVLAAL	AAYCLAT	GCVSIGR
4. HCV2b Consensus	PTPLLRYRLG	AVTNEVTL	THPVTKY	IATCMQAD	LEMT--	STWVL	AGVLAAL	AAYCLAT	GCVSIGR
5. HCV 3 Consensus	PTPLLRYRLG	VPQNEICL	THPITKY	IMACMSAD	LEVTTST	WTVL	GGVLAAL	AAYCLSV	GCVVIVGH
6. HCV 4 Consensus	PTPLLRYRLG	SVQNEVTL	THPITKY	IMACMSAD	LEVTT--	STWVL	GGVLAAL	AAYCLSV	GCVVIVGR
7. HCV5 consensus	PTPLLRYRLG	AVQNEITL	THPITKY	IMACMSAD	LEVIT--	STWVL	GGVLAAL	AAYCLTV	GSVAIVGR
8. HCV6 consensus	PTPLLRYRLG	AVQNEITL	THPITKY	IMTCSAD	LEVIT--	STWVL	GGVLAAL	AAYCLSV	GCVVICGR
9. HCV7: ABN05226	PTPLLRYRLG	SVTNEVTL	THPITKY	IATCMAAD	LEVTT--	STWV	IVGGVLA	AAVAA	CMSTGSVVVGR
14. AVI1a-129	PTPLLRYRLG	AVQNEVTL	THPITKY	IMTCSAD	LEVTT--	STWVL	GGVLAAL	AAYCLST	GCVVIVGR
15. AVI3a-177	PTPLLRYRLG	VPQNETCL	THPVTKY	IMACMSAD	LEVTT--	STWVL	GGVLAAL	AAYCLSV	GCVVIVGH
Consensus	1,730	1,740	1,750	1,760	1,770	1,780	1,790	1,800	
	NS4b								
	NS4b								
1. HCV1a consensus	EPDEMEEC	SQHL	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
2. HCV1b consensus	EPDEMEEC	SQHL	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
3. HCV2a Consensus	AFDEMEEC	CASRL	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
4. HCV2b Consensus	AFDEMEEC	CASRL	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
5. HCV 3 Consensus	AFDEMEEC	SQAAP	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
6. HCV 4 Consensus	AFDEMEEC	SKHLP	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
7. HCV5 consensus	AFDEMEEC	SASLP	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
8. HCV6 consensus	AFDEMEEC	SRH	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
9. HCV7: ABN05226	AFDEMEEC	SKAP	PELLKHAQ	TIGMFKD	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
14. AVI1a-129	AFDEMEEC	SQHL	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL
15. AVI3a-177	AFDEMEEC	SQAAP	PIEQGQ	IAEQFKQ	KALGLL	QTATKQAEV	IAPAVQX	NWQKLEQ	FWAKHMWNFISGIQYLAGL

FIG. 16G

	1,810	1,820	1,830	1,840	1,850	1,860	1,870	1,880	1,890
Consensus	LMAFTAAVTSPLTTSQTLLFNILGGWVASQALAPPTAATAFVVSGLAAGAVGSIGLKGVLVDILAGYGAGVAGALVAFKIMSGEXPS								
	NS4b								
1. HCV1a consensus	LMAFTAAVTSPLTTSQTLLFNILGGWAAQAALPAAATAFVAGAGLAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEVPS								
2. HCV1b consensus	LMAFTASITSPLTTOHTLLFNILGGWAAQAALPAAATAFVAGAGLAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGEMPS								
3. HCV2a Consensus	MMAFSAALTSPSTSTTILNILGGWLASQIAPPAGATGFVVSGLVGAAGVSGIGLKGVLVDILAGYGAGISGALVAFKIMSGEKPS								
4. HCV2b Consensus	MMAFSAALTSPSTSTTILNIMGGWLASQIAPPAGATGFVVSGLVGAAGVSGIGLKGVLVDILAGYGAGISGALVAFKIMSGEKPS								
5. HCV 3 Consensus	LMAFTASVTSPLTTNTMFFNILGGWVATHUAGPQSSAFVVSGLAAGIIGLGRVLVDILAGYGAGVAGALVAFKIMSGELPT								
6. HCV 4 Consensus	LMSFTAAVTSPLTTOHTLLFNILGGWVASQIATPTASTAFVVSGLAAGVSGIGLGRVLVDILAGYGAGVAGALVAFKIMSGEMPS								
7. HCV5 consensus	LMSFTAAVTSPLTTOHTLLFNILGGWVASQIATPTASTAFVVSGLAAGVSGIGLGRVLVDILAGYGAGVAGALVAFKIMSGERPT								
8. HCV6 consensus	LMSFASLTSPSTSTTLLNILGGWVASQIAPPATASTAFVVSGLAAGVSGIGLGRVLVDILAGYGAGVAGALVAFKIMSGETPA								
9. HCV7: ABN05226	LMAFTASVTSPLATSTLLNILGGWFAAQIAPPAAATFVVSGLAAGVSGIGLGRVLVDILAGYGAGIAGALVAFKIMSGEVPS								
14. AV11a-129	LMAFTAAVTSPLTTSQTLLFNILGGWAAQAALPAAATAFVAGAGLAAIGSVGLGKVLVDILAGYGAGVAGALVAFKIMSGE?PS								
15. AV13a-177	LMAFTASVTSPLTTNTMFFNILGGWVATHUAGPQSSAFVVSGLAAGIIGLGRVLVDILAGYGAGVAGALVAFKIMSGE IPT								
	1,900	1,910	1,920	1,930	1,940	1,950	1,960	1,970	
Consensus	TEDLVNLLPAILSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAAARVTQILSSLTVTSLRLRH								
	NS4b								
1. HCV1a consensus	TEDLVNLLPAILSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAAARVTAILSSLTVTQLLRLRH								
2. HCV1b consensus	TEDLVNLLPAILSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAAARVTQILSSLTITQLLRLH								
3. HCV2a Consensus	MEDVNNLLPILSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAQRVTQLLGSLTITSLRLRH								
4. HCV2b Consensus	VEDVNNLLPILSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAQRVTQVLSLTITSLRLRH								
5. HCV 3 Consensus	AEDMVNNLLPILSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAAARVTALLSSLTVTSLRLRH								
6. HCV 4 Consensus	TEDLVNLLPAILSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAAARVTQILSSLTVTSLRLRH								
7. HCV5 consensus	AEDLVNLLPSILCPGALVVGVCALILRRHIGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAAARVTQILSSLTVTSLRLRH								
8. HCV6 consensus	XEDMVNNLLPALSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAARVTQILSSLTITSLRLRH								
9. HCV7: ABN05226	TEDLVNLLPAILSPGALVVGVCALILRRHIGTSEGVQWMNRLIAFASRGNHVSPTHVPESDAARVTQILSSLTITSLIKRVL								
14. AV11a-129	TEDLVNLLPAILSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAAARVTAILSSLTVTQLLRLRH								
15. AV13a-177	AEDMVNNLLPAILSPGALVVGVCALILRRHVGPGEAVQWMNRLIAFASRGNHVSPTHVPESDAAARVTALLSSLTVTSLRLRH								
	1,980	1,990	2,000	2,010	2,020	2,030	2,040	2,050	
Consensus	QWINEDCSTPCSGSWLRIWDWVCTVLSDFKTWLKAKLLPQLPGIPFLSCQRYKGVWRGDMHTRCPCGAEITGHVKNKGMRIIV								
	NS4b								
	NS5a								
1. HCV1a consensus	QWISSECTTPCSGSWLRIWDWICEVLSDFTWLKAKLMPQLPGIPFVSCQRYKGVWRGDMHTRCHCGAEITGHVKNKGMRIIV								
2. HCV1b consensus	QWINEDCSTPCSGSWLRIWDWICTVLTDFKTWLKAKLMPQLPGIPFVSCQRYKGVWRGDMHTRCHCGAEITGHVKNKGMRIIV								
3. HCV2a Consensus	NWITEDCPIPCAGSWLRIWDWVCTILTDFKNWLTSLFKMPGLPFIISCKQYKGVWAGTGMHTRCPCGANISGNVRLGSMRIT								
4. HCV2b Consensus	AWITEDCPIPCAGSWLRIWDWVCSILTDFKNWLTSLFKMPGLPFIISCKQYKGVWAGTGMHTRCPCGANISGNVRLGSMRIT								
5. HCV 3 Consensus	QWINEDCSTPCSGSWLRIWDWVCTVLSDFKTWLKAKLMPQLPGIPFVSCQRYKGVWRGDMHTRCPCGANISGNVRLGSMRIT								
6. HCV 4 Consensus	QWINEDCSTPCAGSWLRIWDWVCTVLSDFKTWLKAKLMPQLPGIPFVSCQRYKGVWRGDMHTRCPCGANISGNVRLGSMRIT								
7. HCV5 consensus	TWIGEDYSTPCDGTWLRIWDWVCTVLSDFKTWLKAKLMPQLPGIPFVSCQRYKGVWRGDMHTRCPCGANISGNVRLGSMRIT								
8. HCV6 consensus	EWINXDWSTPCATSWLRIWDWVCTVLSDFKTWLKAKLMPQLPGIPFVSCQRYKGVWRGDMHTRCPCGANISGNVRLGSMRIT								
9. HCV7: ABN05226	AWAQTDYSAPCAGSWLRIWDWVCTVLSDFKTWLKAKLMPQLPGIPFVSCQRYKGVWRGDMHTRCPCGANISGNVRLGSMRIT								
14. AV11a-129	QWISSECTTPCSGSWLRIWDWICEVLSDFTWLKAKLMPQLPGIPFVSCQRYKGVWRGDMHTRCHCGAEITGHVKNKGMRIIV								
15. AV13a-177	EWINEDYSPCSGSWLRIWDWVCTVLSDFKTWLKAKLMPQLPGIPFVSCQRYKGVWRGDMHTRCPCGANISGNVRLGSMRIT								

FIG. 16H

Consensus	2,070	2,080	2,090	2,100	2,110	2,120	2,130	2,140	2,150
	NS5a								
1. HCV1a consensus	GPKTCSTNTWHGTFPPINAYTTGPCTPLPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
2. HCV1b consensus	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
3. HCV2a Consensus	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
4. HCV2b Consensus	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
5. HCV 3 Consensus	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
6. HCV 4 Consensus	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
7. HCV5 consensus	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
8. HCV6 consensus	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
9. HCV7: ABN05226	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
14. AV11a-129	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
15. AV13a-177	GPKTCSTNTWHGTFPPINAYTTGPCTPSPAPNTYFALWRVSAEEYVEIRQVGDFFHYVTGMDTDLNLCPCQVPSPPEFFTELDGVRLLHRF								
Consensus	2,160	2,170	2,180	2,190	2,200	2,210	2,220	2,230	
	NS5a								
1. HCV1a consensus	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
2. HCV1b consensus	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
3. HCV2a Consensus	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
4. HCV2b Consensus	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
5. HCV 3 Consensus	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
6. HCV 4 Consensus	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
7. HCV5 consensus	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
8. HCV6 consensus	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
9. HCV7: ABN05226	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
14. AV11a-129	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
15. AV13a-177	APPKPPLLRDEVTFSVGLNSYVVGSQLPCEPEPDVAVLTSMLTDPSSHITAEATAARRLARGSPPSLASSASQLSAPSLKATCTTHH								
Consensus	2,240	2,250	2,260	2,270	2,280	2,290	2,300	2,310	2,320
	NS5a								
1. HCV1a consensus	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
2. HCV1b consensus	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
3. HCV2a Consensus	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
4. HCV2b Consensus	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
5. HCV 3 Consensus	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
6. HCV 4 Consensus	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
7. HCV5 consensus	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
8. HCV6 consensus	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
9. HCV7: ABN05226	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
14. AV11a-129	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								
15. AV13a-177	DHPDAELIEANLLWRQEMGNGNITRVESENKVVILDSFDPLVAE-EDDEREISVPAECLRKXK-KFPPALP IWARPDYNPPLLETWKR								

FIG. 16I

	2,330	2,340	2,350	2,360	2,370	2,380	2,390	2,400	
Consensus	PDYEPPTVHGCGALPPXPAPPVPPRRK-RTVXLTESTVSTALAEIAEKSPGSEXSXGX-SXSGXDTTSSXXSXPP-DCDAXSDAE								
	NS5a								
1. HCV1a consensus	PDYEPVVHGCPLPPQSPVPPRRK-RTVVLTESTVSTALAEIAEKSPGSSSTSGI-----TGDNTTTSEPPAPS-GCPPDSDAE								
2. HCV1b consensus	PDYVPVVHGCPLPPTKAPPVPPRRK-RTVVLTESTVSSALAEIAEKTFGSSSESA-----VDSGTATAPPDQPSDDGDAGSDVE								
3. HCV2a Consensus	PDYQPTVAGCALPPKKTPTPPRRR-RTVGLSESTIGDALQQA IKTFQPPPSGDSGLTGADAAADSGRTTP-DELALETG								
4. HCV2b Consensus	PGYEPPTVLCALPPTPQAPVPPRRR-RAKVLTDQNVGVLREMAKVLSPLOQDNDHSGHSTGADTGGDSVQQPS-DETAASEAG								
5. HCV 3 Consensus	PDYVPTVHGCGALPPRGAPPVPPRRK-RTVQLDGSNVAALAEIAEKSPGSKPQSEENSSGVDTSSTTSKVPPSPGSESDSE								
6. HCV 4 Consensus	QDYKPTVHGCGALPPSQPPVPPRRK-RTVQLDGSNVAALAEIAEKTFQSELDSDSGADLTGTETDTSGLTIVDDA-SDDG								
7. HCV5 consensus	PDYDPQVSGCPLPPAGLPVPPRRKRPVELSDSTVSQVLADADARF-KXDTPSIEGQDSAVGTSSQXDSGPEEKRDDXSDAA								
8. HCV6 consensus	PDYEPVVSGCALPPPGPPVPPRRK-KVHLDESIVSHALAEIAEKSPFESSSDSTS--SDSGLSITSSGSPETTTDDDACSEAG								
9. HCV7: ABN05226	PEYAPQVSGCALPPAQTPVPPRRKRAVQLTESAVSTALAEIAEKSPFKEEAPP-----SDSAISLDSPAANDPSPDCDQGEI-								
14. AVI1a-129	PDYEPVVHGCPLPPKSPVPPRRK-RTVVLTESTLSTALAEIAEKSPGSSSTSGI-----TGDNTTTSEPPAPP-GCSPDSDAE								
15. AVI3a-177	PDYVPTVHGCGALPPRGAPPVPPRRK-RTVQLDGSNVAALAEIAEKSPFSLFPQGENSSSGIDIQSSTASEVPPSPGSESDSE								
	2,410	2,420	2,430	2,440	2,450	2,460	2,470	2,480	2,490
Consensus	SYSSMPPLEGEGDPDLSD-----GSWSTVSDEE--DSVVCSSMSYSWTGALITPCAEEKLPINPLSNS								
	NS5b								
1. HCV1a consensus	SYSSMPPLEGEGDPDLSD-----GSWSTVSSEADTEDVVCSSMSYSWTGALVTPCAEEKLPINALSNS								
2. HCV1b consensus	SYSSMPPLEGEGDPDLSD-----GSWSTVSSEAS-EDVVCSSMSYTWGALITPCAEEKLPINALSNS								
3. HCV2a Consensus	SYSSMPPLEGEGDPDLPEQVELQPPQGEVAPGSDSGSWSTGSEED--DSVVCSSMSYSWTGALITPCAEEKLPINALSNS								
4. HCV2b Consensus	SYSSMPPLEGEGDPDLPEFAGSAPPSEGECEVIDSDKSWSTVSDQE--DSVVCSSMSYSWTGALITPCAEEKLPINALSNS								
5. HCV 3 Consensus	SYSSMPPLEGEGDPDLSDQVELQPPQGGVAPGSGSGSWSTVSDSEE-QSVVCSSMSYSWTGALITPCAEEKLPINALSNS								
6. HCV 4 Consensus	SYSSMPPLEGEGDPDLSDQVELQPPQGGVAPGSGSGSWSTVSDSEE-QSVVCSSMSYSWTGALITPCAEEKLPINALSNS								
7. HCV5 consensus	SYSSMPPLEGEGDPDLSD-----GSWSTVSDEE--DSVVCSSMSYSWTGALITPCAEEKLPINALSNS								
8. HCV6 consensus	SYSSMPPLEGEGDPDLSD-----GSWSTVSDEE--DSVVCSSMSYSWTGALITPCAEEKLPINALSNS								
9. HCV7: ABN05226	SYSSMPPLEGEGDPDLSD-----GSWSTVSDEE--SDVVCSSMSYSWTGALITPCAEEKLPINALSNS								
14. AVI1a-129	SYSSMPPLEGEGDPDLSD-----GSWSTVSSEADTEDVVCSSMSYSWTGALITPCAEEKLPINALSNS								
15. AVI3a-177	SYSSMPPLEGEGDPDLSD-----GSWSTVSDEE-QSVVCSSMSYSWTGALITPCAEEKLPINALSNS								
	2,500	2,510	2,520	2,530	2,540	2,550	2,560	2,570	2,580
Consensus	LLRHHNLVYSTTSRSASQKQKVTFRDLQVLDDHYXDLVKEVKAKSVKARLLSVEEACALTPPHSARSKFGYGAKDVRSLSRKA								
	NS5b								
1. HCV1a consensus	LLRHHNLVYSTTSRSASQKQKVTFRDLQVLDDSHYQDVLKEVKAASVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKA								
2. HCV1b consensus	LLRHHNMVYATTSRSASQKQKVTFRDLQVLDDHYRDLVKEMKAKASTVKAKLLSVEEACKLTPPHSARSKFGYGAKDVRNLSSKA								
3. HCV2a Consensus	LLRYHNKVYCTTSKSLRAKKTFRDMQVLDAHYDSVLKD IKLAASKVSARLLTLEEACQLTPPHSARSKYGFGAKEVRSLSGRA								
4. HCV2b Consensus	LMRFHNKVYSTTSRSASLRAKKTFRDVQVLDAHYDSVLQDVKRAASKVSARLLSVEEACALTPPHSAKSKYGFGAKEVRSLSGRA								
5. HCV 3 Consensus	LLRHHNLVYSTTSRSASQKQKVTFRDLQVLDDHYK TALKEVKERASRVKARMLTIEEACALTPPHSARSKFGYGAKDVRSLSRKA								
6. HCV 4 Consensus	LLRHHNMVYATTSRSVTRQKKTFRDLQVLDDHYNETLKE IKARASRVKARLLTTEEACQLTPPHSAKSKFGYGAKDVRSHSRKA								
7. HCV5 consensus	LLRHHNLVYSTTSRSAGLRQKKTFRDLQVLDDHYREVDEMRLAASKVKARLLPLEEACQLTPPHSARSKYGFGAKEVRSLSRKA								
8. HCV6 consensus	LLRHHNLVYSTTSRSASLQKKTFRDLQVLDDHYQDVLKE IKRASQVQARLLSTEEACQLTPPHSARSKYGFGAKEVRSLSRKA								
9. HCV7: ABN05226	MLRHHNMVYSTTSRSASQKQKVTFRDLQVLDDHYKRALADVKADASTVKAKLLSVEEAAALTPAHSAKSKFGYGAKEVRSLSRKA								
14. AVI1a-129	LLRHHNLVYSTTSRSASQKQKVTFRDLQVLDDHYQDVLKEVKAASVKANLLSVEEACSLTPPHSAKSKFGYGAKDVRCHARKA								
15. AVI3a-177	LLRHHNLVYSTTSRSASQKQKVTFRDLQVLDDHYKAVLKEVKERASRVKARMLTIEEACALTPPHSARSKFGYGAKDVRSLSRKA								

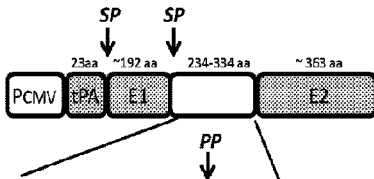
FIG. 16J

Consensus	2,590	2,600	2,610	2,620	2,630	2,640	2,650	2,660	
	NS5b								
	VNHIKSVWDXDLEDSTTP IPTT IMAKNEVFCVDPKXGGRKPARLIVFPDL-GVRVCEKRALYDVXQKLPKAVMGSSYGFQYSPAQR								
1. HCV1a consensus	VNHIKSVWDXDLEDSTTP IDTT IMAKNEVFCVQPEKGGKPARLIVFPDL-GVRVCEKRALYDVVSKLPLAVMGSSYGFQYSPGQR								
2. HCV1b consensus	VNHIKSVWDXDLEDSTTP IDTT IMAKNEVFCVQPEKGGKPARLIVFPDL-GVRVCEKRALYDVVSTLPLQAVMGSSYGFQYSPGQR								
3. HCV2a Consensus	VNHIKSVWDXDLEDSTTP IPTT IMAKNEVFCVDPKXGGRKPARLIVFPDL-GVRVCEKRALYDVVSKLPLQAVMGSSYGFQYSPAQR								
4. HCV2b Consensus	VNHIKSVWDXDLEDSTTP IDTT IMAKNEVFCVDPKXGGRKPARLIVFPDL-GVRVCEKRALYDVVSKLPLQAVMGSSYGFQYSPAQR								
5. HCV 3 Consensus	VNHIKSVWDXDLEDSTTP IPTT IMAKNEVFCVDPKXGGRKPARLIVFPDL-GVRVCEKRALYDVVSKLPLQAVMGSSYGFQYSPAQR								
6. HCV 4 Consensus	VNHIKSVWDXDLEDSTTP IPTT IMAKNEVFCVDPKXGGRKPARLIVFPDL-GVRVCEKRALYDVVSKLPLQAVMGSSYGFQYSPAQR								
7. HCV5 consensus	VNHIKSVWDXDLEDSTTP IPTT IMAKNEVFCVDPKXGGRKPARLIVFPDL-GVRVCEKRALYDVVSKLPLQAVMGSSYGFQYSPAQR								
8. HCV6 consensus	VNHIKSVWDXDLEDSTTP IPTT IMAKNEVFCVDPKXGGRKPARLIVFPDL-GVRVCEKRALYDVVSKLPLQAVMGSSYGFQYSPAQR								
9. HCV7: ABN05226	VNHIKSVWDXDLEDSTTP IPTT IMAKNEVFCVDPKXGGRKPARLIVFPDL-GVRVCEKRALYDVVSKLPLQAVMGSSYGFQYSPAQR								
14. AVI1a-129	VNHIKSVWDXDLEDSTTP IDTT IMAKNEVFCVQPEKGGKPARLIVFPDL-GVRVCEKRALYDVVSKLPLQAVMGSSYGFQYSPAQR								
15. AVI3a-177	VNHIKSVWDXDLEDSTTP IPTT IMAKNEVFCVDPKXGGRKPARLIVFPDL-GVRVCEKRALYDVVSKLPLQAVMGSSYGFQYSPAQR								
Consensus	2,670	2,680	2,690	2,700	2,710	2,720	2,730	2,740	2,750
	NS5b								
	VEFLKAWKSKKTPMG--FSYDTRCFDSTVT-EKD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPMXNSKGCXGYYRRCRASG								
1. HCV1a consensus	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
2. HCV1b consensus	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
3. HCV2a Consensus	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
4. HCV2b Consensus	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
5. HCV 3 Consensus	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
6. HCV 4 Consensus	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
7. HCV5 consensus	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
8. HCV6 consensus	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
9. HCV7: ABN05226	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
14. AVI1a-129	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-ESD IRTEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
15. AVI3a-177	VEFLVQAWKSKKTPMG--FSYDTRCFDSTVT-EQD IRVEEXIYQCCDLDPQARVA IKSLTERLYVGGPLTNSRGNCGYRRCRASG								
Consensus	2,760	2,770	2,780	2,790	2,800	2,810	2,820	2,830	
	NS5b								
	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
1. HCV1a consensus	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
2. HCV1b consensus	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
3. HCV2a Consensus	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
4. HCV2b Consensus	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
5. HCV 3 Consensus	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
6. HCV 4 Consensus	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
7. HCV5 consensus	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
8. HCV6 consensus	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
9. HCV7: ABN05226	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
14. AVI1a-129	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								
15. AVI3a-177	VLTSMGNLTTCY IKAXAACRAAGLRDCTMLVCGDDLIV ICESAGVZEDAAKXLRAPTEAMTR-----YSAPPGDPP-----QPEYD								

FIG. 16K

Consensus	2,840	2,850	2,860	2,870	2,880	2,890	2,900	2,910	2,920
	LELITSCSSNVSAHDXGKRVYLLTRDPTPLARAAWETARHTP---VNSWLGNIIMYAPT IWVRMVLMTHTFFSILQXQEQLEXA								
	NS5b								
1. HCV1a consensus	LELITSCSSNVSAHDGAGKRVYLLTRDPTPLARAAWETARHTP---VNSWLGNIIMFAPTLWARMILMTHTFFSVLIARDQLEQA								
2. HCV1b consensus	LELITSCSSNVSAHDASGKRVYLLTRDPTPLARAAWETARHTP---VNSWLGNIIMYAPTLWARMILMTHTFFSILLAQEQLKA								
3. HCV2a Consensus	LELITSCSSNVSAVGQRRRYLLTRDPTPLARAAWETVRHSP---VNSWLGNIIMYAPT IWVRMVLMTHTFFSILMAQDTLDQN								
4. HCV2b Consensus	LELITSCSSNVSAVDSRRRYLLTRDPTPLARAAWETVRHSP---VNSWLGNIIMYAPT IWVRMVIMTHTFFSILLAQDTLNQN								
5. HCV 3 Consensus	LELITSCSSNVSAVDNKGKRVYLLTRDPTPLARAAWETARHTP---VNSWLGNIIMYAPTPGWGVMMTHTFFSILQSQEILDRP								
6. HCV 4 Consensus	LELITSCSSNVSAHDATGKRVYLLTRDPTPLARAAWETVRHTP---VNSWLGNIIMYAPT IWVRMVLMTHTFFSILQSQEALEKA								
7. HCV5 consensus	LELITSCSSNVSAVDASGNRVYLLTRDPTPLARAAWETAKHSP---VNSWLGNIIMYAPTLWARMILMTHTFFSVLQSQEQLKA								
8. HCV6 consensus	LELITSCSSNVSAHDGTGQRYLLTRDPTPLARAAWETARHTP---VNSWLGNIIMYAPT IWVRMVLMTHTFFQILQSQEQLEHKA								
9. HCV7: ABN05226	LEHIDSCSSNVSAVDNSGKRVYLLTRDPTPLARAAWETARHTP---VNSWVGNIIMFAPTLWARMILMTHTFFALLNEERLNDP								
14. AVI1a-129	LELITSCSSNVSAHDGAGKRVYLLTRDPTPLARAAWETARHTP---VNSWLGNIIMFAPTLWARMILMTHTFFSVLIARDQLEQA								
15. AVI3a-177	LELITSCSSNVSAVDNKGKRVYLLTRDPTPLARAAWETARHTP---VNSWLGNIIMYAPT IWVRMVLMTHTFFSILQSQEILDRP								
Consensus	2,930	2,940	2,950	2,960	2,970	2,980	2,990	3,000	3,010
	LDFEMYGATYSVTPLDLPALIQRLHGLSAFSLHSYSPGELNRVAACLRKLGVPPLRAWHRARAVRAKLI AQGGRAAICGKYLFNW								
	NS5b								
1. HCV1a consensus	LDCEIYGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRAWHRARSVRARLLSRGGRAAICGKYLFNW								
2. HCV1b consensus	LDCEIYGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRVHRARSVRARLLSQGGRAATCGKYLFNW								
3. HCV2a Consensus	LNFEMYGSVYSPPLDLPALIERLHGLDAFSLHTYTPHELTRVAAALRKLGAAPPLRAWKSRARAVRASLI AQGGRAAICGKYLFNW								
4. HCV2b Consensus	LNFEMYGAVYSPNPLDLPALIERLHGLDAFSLHTYTPHELTRVAAALRKLGAAPPLRAWKSRARAVRASLI AQGGRAAICGKYLFNW								
5. HCV 3 Consensus	LDFEMYGATYSVTPLDLPALIERLHGLSAFSLHSYSPVELNRVAGTLRKLGCPPPLRAWHRARAVRAKLI AQGGRAAICGKYLFNW								
6. HCV 4 Consensus	LDFEMYGVYTSITPLDLPALIQRLHGLSAFSLHSYSPHELNRVAGTLRKLGCPPPLRAWHRARAVRAKLI AQGGRAAICGKYLFNW								
7. HCV5 consensus	LAFEMYGSVYSPPLDLPALIQRLHGLSAFSLHSYSPSEINRVAACLRKLGVPPLRAWHRARAVRAKLI AQGGRAAICGKYLFNW								
8. HCV6 consensus	LDFDIYGVYTSITPLDLPALIQRLHGLSAFSLHSYSPGELNRVAGTLRKLGCPPPLRAWHRARAVRAKLI AQGGRAAICGKYLFNW								
9. HCV7: ABN05226	VSFEMYGATYTCPTDLPDIQRLHGLRAFEHLHTYSPAELTRVAAALRKLGCPPPLRTWRQARKVRAGLI AQGGRAAICGKYLFNW								
14. AVI1a-129	LDCEIYGACYSIEPLDLPPIIQRLHGLSAFSLHSYSPGEINRVAACLRKLGVPPLRTWRHRARSVRARLLSRGGRAAICGKYLFNW								
15. AVI3a-177	LDFEMYGATYSVTPLDLPALIERLHGLSAFSLHSYSPVELNRVAGTLRKLGCPPPLRAWHRARAVRAKLI AQGGRAAICGKYLFNW								
Consensus	3,020	3,030	3,040	3,050	3,060	3,070	3,080	3,090	3,100
	AVRTKLLTLPAAAGQLDLSWFTVGAGGGDIYHSVSRARPRWLLCLLLXVGVGIFLLPARX								
	NS5b								
1. HCV1a consensus	AVRTKLLTLPAAAGQLDLSGWFTAGYSGGDIYHSVSHARPRWFWFCLLLLAAGVGIYLLPNRX								
2. HCV1b consensus	AVRTKLLTLPAAASQLDLSGWFTAGYSGGDIYHSLSRARPRWFWWCLLLLSVGVGIYLLPNRX								
3. HCV2a Consensus	AVTKKLLTLPPEARLDDLSWFTVGAGGGDIYHSVSRARPRLLLSLLLSXVGVGLFLDPAR								
4. HCV2b Consensus	AVTKKLLTLPPEASRLDLSGWFTVGAGGGDIYHSVSHARPRLLLSLLLSXVGVGLFLDPAR								
5. HCV 3 Consensus	AVRTKLLTLPAAAGQLDLSWFTVGAGGGDIYHSVSRARTRXLLLSLLLSXVGVGLFLDPAR								
6. HCV 4 Consensus	AVTKKLLTLPAAANLDDLSWFTVGAGGGDIYHSVSRARPRYLLLSLLLSXVGVGLFLDPAR								
7. HCV5 consensus	AVTKKLLTLPADADRLDLSWFTVGAGGGDIYHSMSSRARPRXJLLLSLLLSXVGVGLFLDPAR								
8. HCV6 consensus	AVTKKLLTPLRGASKLDDLSGWFTAGYSGGDIYHSVSRARPRMLLCLLLTSVGVGLFLDPAR								
9. HCV7: ABN05226	AVRTKIKLTPLAGARLDDLSWFWSCAGADVDHSTPRAHPRLLLSLLLSXVGVGLFLDPAR								
14. AVI1a-129	AVRTKLLTLPAAAGRLDLSGWFTAGYSGGDIYHSVSHARPRWFWFCLLLLAAGVGIYLLPNR								
15. AVI3a-177	AVRTKTNLTPLPAAGQLDLSWFTVGAGGGDIYHSVSRARTRHLLLSLLLSXVGVGLFLDPAR								

FIG. 16L



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)

