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(54) Title: ANTI-HLA-HBV PEPTIDE ANTIBODIES

(57) Abstract: The present invention relates to anti-HLA-HBV antibodies, antigen binding fragments thereof, and their uses for the prevention and treatment of hepatitis B virus infection and associated diseases.

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ANTI-HLA-HBV PEPTIDE ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Serial No. 62/729292, filed 10 September 2018, the contents of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present disclosure is directed to anti-Hepatitis B antibodies, antigen binding fragments thereof, and their uses for the reducing the likelihood or treatment of Hepatitis B viral infection.

BACKGROUND OF THE INVENTION

[0003] Hepatitis B virus (HBV) is an enveloped, hepatotropic virus that infects the liver and may result in chronic hepatitis B (CHB), liver cirrhosis and hepatocellular carcinoma (HCC). While there is a safe vaccine against HBV, at least 600,000 people worldwide die annually of HBV related disorders. Disease progression is affected by viral load, genotype and specific viral mutations (Biswas et al., Med. Virol. 2013; 85:1340-1347). HBV is classified into ten genotypes or classified into four serotypes (asw, adr, ayw and ayr) based on the antigenic determinants found in HBV surface antigen (HBsAg).

[0004] HBV is a member of the Hepadnaviridae family and can only infect humans and primates. The virion is constituted by a small 3.2 kb partially double-stranded circular DNA, surrounded by the envelope that interact with hepatocytes. HBV first binds with low-affinity to heparin sulfate proteoglycans on hepatocytes. Subsequently, the pre-S1 lipopeptide of the large envelope protein binds to its higher affinity receptor on the hepatocyte, the bile acid transporter NCTP (sodium taurocholate cotransporting polypeptide). Then, the virus enters the cytoplasm by endocytosis.

[0005] HBV clearance and pathogenesis are largely mediated by the adaptive immune response in HBV infection (Guidotti et al., Annu Rev Pathol. 2006; 1:23-61). For HBV to persist it must either not induce a response or it must evade or overwhelm it. Interestingly, HBV "evades" the innate immune response by simply not inducing it (Wieland et al., Proc Natl Acad Sci U S A. 2004; 101(17):6669-74). On the other hand, viral persistence is characterized by a state of relative hyporesponsiveness of HBV-specific T cells (Chisari Annu Rev Immunol. 1995; 13:29-60). Several viral proteins have been shown to regulate the adaptive immune response to HBV, suggesting that HBV may employ active evasion strategies that target the adaptive immune response (Thimme et al., J Virol. 2003; 77(1):68-76). It has previously reported that antiviral treatment can overcome CD8+ T cell hyporesponsiveness in chronic HBV infection, suggesting that the T cells are present in these subjects but exhausted (Boni et al., Hepatology. 2001; 33(4):963-71). Induction of an effective HBV specific CD8+ T cell response may be

dependent on early CD4+ T cell priming which is regulated by the size of the viral inoculum (Asabe J Virol. 2009; 83(19):9652-62).

[0006] The current standard of care for HBV infection are two formulations of alpha-interferon (IFN-α) and five nucleoside analogues. While the nucleosides inhibit HBV DNA polymerase activity with varying potencies and barriers to resistance, the therapy does not eliminate the virus and the patient is on this therapy for life. Therefore, superior therapeutics to reduce Hepatitis B viral infection are needed.

SUMMARY OF THE INVENTION

[0007] The present disclosure is directed to antibodies and or fragments thereof, which bind to a complex of human leukocyte antigens (HLA) and HBV peptide and do not bind to either HLA or HBV peptide when the HBV peptide is not complexed with HLA.

[0008] An antibody, wherein the antibody or antigen binding fragment thereof specifically binds Hepatitis B virus (HBV) peptides and HLA.

[0009] The antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof specifically binds HBV and HLA-A.

[0010] The antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof specifically binds HBV and HLA-A2.

[0011] The antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof specifically binds HBV and HLA-A2:01.

[0012] The antibody or antigen binding fragment, wherein the antibody or antigen binding fragment thereof specifically binds HBV and HLA-A24:01.

[0013] The antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof specifically binds HBx92-100 peptide (SEQ ID NO:1) and HLA.

[0014] The antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof specifically binds HBx52-60 peptide (SEQ ID NO:2) and HLA.

[0015] The antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof specifically binds HBs172-180 peptide (SEQ ID NO:3) and HLA.

[0016] An antibody, wherein the antibody or antigen binding fragment thereof comprises:

(i) a heavy chain variable region that comprises (a) a HCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:7, (b) a HCDR2 of SEQ ID NO:8, (c) a HCDR3 of SEQ ID NO:9 and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:23, (e) a LCDR2 of SEQ ID NO:24, and (f) a LCDR3 of SEQ ID NO:25;

(ii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:39, (b) a HCDR2 of SEQ ID NO:40, (c) a HCDR3 of SEQ ID NO:41; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:55, (e) a LCDR2 of SEQ ID NO:56, and (f) a LCDR3 of SEQ ID NO:57;

(iii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:71, (b) a HCDR2 of SEQ ID NO:72, (c) a HCDR3 of SEQ ID NO:73; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO: 87, (e) a LCDR2 of SEQ ID NO:88, and (f) a LCDR3 of SEQ ID NO:89;

(iv) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:103, (b) a HCDR2 of SEQ ID NO:104, (c) a HCDR3 of SEQ ID NO:105; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:119, (e) a LCDR2 of SEQ ID NO:120, and (f) a LCDR3 of SEQ ID NO:121;

(v) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:135, (b) a HCDR2 of SEQ ID NO:136, (c) a HCDR3 of SEQ ID NO:137; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO: 151, (e) a LCDR2 of SEQ ID NO:152, and (f) a LCDR3 of SEQ ID NO:153;

(vi) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:167, (b) a HCDR2 of SEQ ID NO:168, (c) a HCDR3 of SEQ ID NO:169; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:183, (e) a LCDR2 of SEQ ID NO:184, and (f) a LCDR3 of SEQ ID NO:185;

(vii) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO: 199, (b) a HCDR2 of SEQ ID NO: 200, (c) a HCDR3 of SEQ ID NO: 201; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO: 215, (e) a LCDR2 of SEQ ID NO: 216, and (f) a LCDR3 of SEQ ID NO: 217;

(viii) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:231, (b) a HCDR2 of SEQ ID NO:232, (c) a HCDR3 of SEQ ID NO:233; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:247, (e) a LCDR2 of SEQ ID NO:248, and (f) a LCDR3 of SEQ ID NO:249;

(ix) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:263, (b) a HCDR2 of SEQ ID NO:264, (c) a HCDR3 of SEQ ID NO:265; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:279, (e) a LCDR2 of SEQ ID NO:280, and (f) a LCDR3 of SEQ ID NO:281;

(x) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:295, (b) a HCDR2 of SEQ ID NO:296, (c) a HCDR3 of SEQ ID NO:297; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:311, (e) a LCDR2 of SEQ ID NO:312, and (f) a LCDR3 of SEQ ID NO:313;

(xi) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:327, (b) a HCDR2 of SEQ ID NO:328, (c) a HCDR3 of SEQ ID NO:329; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:343, (e) a LCDR2 of SEQ ID NO:344, and (f) a LCDR3 of SEQ ID NO:345;

(xii) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO: 359, (b) a HCDR2 of SEQ ID NO:360, (c) a HCDR3 of SEQ ID NO:361; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:375, (e) a LCDR2 of SEQ ID NO:376, and (f) a LCDR3 of SEQ ID NO:377; or

(xiii) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:391, (b) a HCDR2 of SEQ ID NO:392, (c) a HCDR3 of SEQ ID NO:393; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO: 407, (e) a LCDR2 of SEQ ID NO: 408, and (f) a LCDR3 of SEQ ID NO:409.

[0017] The antibody or antigen binding fragment thereof, wherein one or two amino acids within a CDR have been modified, deleted or substituted.

[0018] The antibody or antigen binding fragment thereof, that retains at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identity over either the variable heavy chain region or the variable light chain region.

[0019] The antibody or antigen binding fragment thereof, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a human antibody, a single chain antibody(scFv) or an antibody fragment.

[0020] The antibody or antigen binding fragment thereof, wherein the antibody has reduced carbohydrate modification.

[0021] The antibody or antigen binding fragment thereof, wherein the antibody is low in glycosylation or fucosylation.

[0022] The antibody or antigen binding fragment thereof, wherein the antibody is hypofucosylated.

[0023] The antibody or antigen binding fragment thereof, wherein the antibody FC region is modified, allowing for a reduction in glycosylation.

[0024] An antibody or antigen binding fragment thereof, wherein said antibody or antigen binding fragment thereof comprises:

(i) a heavy chain variable region (vH) that comprises SEQ ID NO: 16, and a light chain variable region (vL) that comprises SEQ ID NO: 32;

(ii) a heavy chain variable region (vH) that comprises SEQ ID NO:48, and a light chain variable region (vL) that comprises SEQ ID NO: 64;

(iii) a heavy chain variable region (vH) that comprises SEQ ID NO:80, and a light chain variable region (vL) that comprises SEQ ID NO:96;

(iv) a heavy chain variable region (vH) that comprises SEQ ID NO: 112, and a light chain variable region (vL) that comprises SEQ ID NO:128;

(v) a heavy chain variable region (vH) that comprises SEQ ID NO:144, and a light chain variable region (vL) that comprises SEQ ID NO:160;

(vi) a heavy chain variable region (vH) that comprises SEQ ID NO: 176, and a light chain variable region (vL) that comprises SEQ ID NO:192;

(vii) a heavy chain variable region (vH) that comprises SEQ ID NO:208, and a light chain variable region (vL) that comprises SEQ ID NO:224;

(viii) a heavy chain variable region (vH) that comprises SEQ ID NO:240, and a light chain variable region (vL) that comprises SEQ ID NO:256;

(ix) a heavy chain variable region (vH) that comprises SEQ ID NO:272, and a light chain variable region (vL) that comprises SEQ ID NO:288;

(x) a heavy chain variable region (vH) that comprises SEQ ID NO:304, and a light chain variable region (vL) that comprises SEQ ID NO:320;

(xi) a heavy chain variable region (vH) that comprises SEQ ID NO:336, and a light chain variable region (vL) that comprises SEQ ID NO:352;

(xii) a heavy chain variable region (vH) that comprises SEQ ID NO: 368, and a light chain variable region (vL) that comprises SEQ ID NO: 384; or

(xiii) a heavy chain variable region (vH) that comprises SEQ ID NO: 400, and a light chain variable region (vL) that comprises SEQ ID NO: 416.

[0025] The antibody or antigen binding fragment thereof, that retains at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identity over either the variable light or variable heavy region.

[0026] The antibody or antigen binding fragment thereof, wherein one, two, three, four or five, but less than 10 amino acids within the variable light or variable heavy region have been modified, deleted or substituted.

[0027] The antibody or antigen binding fragment thereof, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a human antibody, a single chain antibody(scFv) or an antibody fragment.

[0028] The antibody or antigen binding fragment thereof, wherein the antibody has reduced carbohydrate modification.

[0029] The antibody or antigen binding fragment thereof, wherein the antibody is low in glycosylation or fucosylation.

[0030] The antibody or antigen binding fragment thereof, wherein the antibody is hypofucosylated.

[0031] The antibody or antigen binding fragment thereof, wherein the antibody FC region is modified, allowing for a reduction in glycosylation.

[0032] A pharmaceutical composition comprising the antibody or antigen binding fragment thereof, further comprising a pharmaceutically acceptable carrier.

[0033] The pharmaceutical composition, wherein the pharmaceutically acceptable carrier contains histadine or a sugar.

[0034] The pharmaceutical composition, wherein the sugar is sucrose.

[0035] A pharmaceutical composition comprising a plurality of an antibody or antigen binding fragment thereof, wherein at least 0.05%, 0.1%, 0.5%, 1%, 2%, 3%, 5% or more or more of the antibodies in the composition have an α2,3–linked sialic acid residue.

[0036] A pharmaceutical composition comprising a plurality of an antibody or antigen binding fragment thereof, wherein the antibodies comprise increased bisecting GlcNAc.

[0037] The pharmaceutical composition comprising the antibody or antigen binding fragment thereof, wherein the composition is prepared as a lyophilisate.

[0038] A method of reducing a hepatitis B virus infection comprising administering via injection or infusion to a patient in need thereof an effective amount of the antibody or antigen binding fragment thereof.

[0039] The method, wherein the patient in need is diagnosed with hepatitis B viruria or hepatitis B viremia.

[0040] The method, wherein the patient is diagnosed with hepatitis B viremia in the blood or serum.

[0041] A method of treating or reducing the likelihood of a hepatitis B virus associated disorder, comprising administering via injection or infusion to a patient in need thereof an effective amount of the antibody or antigen binding fragment thereof, and wherein the disorder is: liver failure, liver cirrhosis, or hepatocellular carcinoma.

[0042] The method, wherein the antibody or antigen binding fragment thereof, or pharmaceutical composition is reconstituted prior to injection or infusion.

[0043] The method, wherein the antibody or antigen binding fragment thereof, or the pharmaceutical composition is administered in combination with another therapeutic agent.

[0044] The method, wherein the therapeutic agent is another anti-viral agent.

[0045] The method, wherein the anti-viral agent is: lamivudine, entecavir and tenofovir or alpha-interferon.

[0046] The method, wherein the therapeutic agent is an immune checkpoint inhibitor.

[0047] The method, wherein the immune checkpoint is selected from the group consisting of: PD-1, PD-L1, PD-L2, TIM3, CTLA-4, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR.

[0048] The method, wherein the immune checkpoint inhibitor is an anti-PD-L1 antibody.

[0049] The method, wherein the therapeutic agent is an additional anti-HBV antibody.

[0050] The method, wherein the additional anti-HBV antibody is an anti-Hepatitis B surface antigen (HBVsAg) antibody.

[0051] The method, wherein the therapeutic agent is a TLR agonist.

[0052] The method, wherein the TRL agonist is a TLR7 or TLR8 agonist.

[0053] The method, wherein the therapeutic agent is viral replication inhibitor.

[0054] The method, wherein the viral replication inhibitor is a capsid inhibitor.

[0055] Use of the antibody or antigen binding fragment thereof, for reducing hepatitis B virus infection.

[0056] Use of the antibody or antigen binding fragment thereof, in the treatment or reducing the likelihood of: liver failure, liver cirrhosis, and/or hepatocellular carcinoma.

[0057] The use, wherein the antibody is administered in combination with another therapeutic agent.

[0058] The use, wherein the therapeutic agent is an anti-viral agent.

[0059] The use, wherein the anti-viral agent is: lamivudine, entecavir and tenofovir or alpha-interferon.

[0060] The use, wherein the therapeutic agent is an immune checkpoint modulator.

[0061] The use, wherein the immune checkpoint modulator is selected from the group consisting of: PD-1, PD-L1, PD-L2, TIM3, CTLA-4, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR.

[0062] The use, wherein the immune checkpoint modulator is an anti-PD-L1 antibody.

[0063] The use, wherein the therapeutic agent is an additional anti-HBV antibody.

[0064] A nucleic acid that encodes the antibody or antigen binding fragment any one of the above.

[0065] A vector comprising the nucleic acid above.

[0066] A host cell comprising the vector above.

[0067] A diagnostic reagent comprising the antibody or antigen binding fragment thereof any of the above which is labeled.

[0068] The diagnostic reagent, wherein the label is selected from the group consisting of a radiolabel, a fluorophore, a chromophore, an imaging agent, and a metal ion.

Definitions

[0069] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0070] The term “antibody” as used herein refers to a polypeptide of the immunoglobulin family that is capable of binding a corresponding antigen non-covalently, reversibly, and in a specific manner. For example, a naturally occurring IgG antibody is a tetramer comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each

light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (Clq) of the classical complement system.

[0071] The term "antibody" includes, but is not limited to, monoclonal antibodies, human antibodies, humanized antibodies, camelid antibodies, chimeric antibodies, and anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the present disclosure). The antibodies can be of any isotype/class (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), or subclass (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2).

[0072] "Complementarity-determining domains" or "complementarity-determining regions" ("CDRs") interchangeably refer to the hypervariable regions of VL and VH. The CDRs are the target protein-binding site of the antibody chains that harbors specificity for such target protein. There are three CDRs (CDR1-3, numbered sequentially from the N-terminus) in each human VL or VH, constituting in total about 15-20% of the variable domains. CDRs can be referred to by their region and order. For example, "VHCDR1" or "HCDR1" both refer to the first CDR of the heavy chain variable region. The CDRs are structurally complementary to the epitope of the target protein and are thus directly responsible for the binding specificity. The remaining stretches of the VL or VH, the so-called framework regions, exhibit less variation in amino acid sequence (Kuby, Immunology, 4th ed., Chapter 4. W.H. Freeman & Co., New York, 2000).

[0073] The positions of the CDRs and framework regions can be determined using various well known definitions in the art, *e.g.*, Kabat, Chothia, IMGT, and AbM (see, *e.g.*, Johnson *et al.*, Nucleic Acids Res., 29:205-206 (2001); Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987); Chothia *et al.*, Nature, 342:877-883 (1989); Chothia *et al.*, J. Mol. Biol., 227:799-817 (1992); Lefranc, M.P., Nucleic Acids Res., 29:207-209 (2001); Al-Lazikani *et al.*, J.Mol.Biol., 273:927-748 (1997)). Definitions of antigen combining sites are also described in the following: Ruiz *et al.*, Nucleic Acids Res., 28:219–221 (2000); MacCallum *et al.*, J. Mol. Biol., 262:732-745 (1996); and Martin *et al.*, Proc. Natl. Acad. Sci. USA, 86:9268–9272 (1989); Martin *et al.*, Methods Enzymol., 203:121–153 (1991); and Rees *et al.*, In Sternberg M.J.E. (ed.), Protein Structure Prediction, Oxford University Press, Oxford, 141–172 (1996). In a combined Kabat and Chothia numbering scheme, in some embodiments, the CDRs correspond to the amino acid residues that are part of a Kabat CDR, a

Chothia CDR, or both. For instance, in some embodiments, the CDRs correspond to amino acid residues 26-35 (HC CDR1), 50-65 (HC CDR2), and 95-102 (HC CDR3) in a VH, e.g., a mammalian VH, e.g., a human VH; and amino acid residues 24-34 (LC CDR1), 50-56 (LC CDR2), and 89-97 (LC CDR3) in a VL, e.g., a mammalian VL, e.g., a human VL. Under IMGT the CDR amino acid residues in the VH are numbered approximately 26-35 (CDR1), 51-57 (CDR2) and 93-102 (CDR3), and the CDR amino acid residues in the VL are numbered approximately 27-32 (CDR1), 50-52 (CDR2), and 89-97 (CDR3) (numbering according to "Kabat"). Under IMGT, the CDR regions of an antibody can be determined using the program IMGT/DomainGap Align.

[0074] Both the light and heavy chains are divided into regions of structural and functional homology. The terms "constant" and "variable" are used functionally. In this regard, it will be appreciated that the variable domains of both the light (VL) and heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2, or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. By convention, the numbering of the constant region domains increases as they become more distal from the antigen binding site or amino-terminus of the antibody. The N-terminus is a variable region and at the C-terminus is a constant region; the CH3 and CL domains actually comprise the carboxy-terminal domains of the heavy and light chain, respectively.

[0075] The term "antigen binding fragment," as used herein, refers to one or more portions of an antibody that retain the ability to specifically interact with (*e.g.*, by binding, steric hindrance, stabilizing/destabilizing, spatial distribution) an epitope of an antigen. Examples of binding fragments include, but are not limited to, single-chain Fvs (scFv), disulfide-linked Fvs (sdFv), Fab fragments, F(ab') fragments, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward *et al.*, Nature 341:544-546, 1989), which consists of a VH domain; and an isolated complementarity determining region (CDR), or other epitope-binding fragments of an antibody.

[0076] Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv ("scFv"); see, *e.g.*, Bird *et al.*, Science 242:423-426, 1988; and Huston *et al.*, Proc. Natl. Acad. Sci. 85:5879-5883, 1988). Such single chain antibodies are also intended to be encompassed within the term "antigen binding fragment." These antigen binding fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0077] Antigen binding fragments can also be incorporated into single domain antibodies, maxibodies, minibodies, nanobodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR, and bis-scFv (see, *e.g.*, Hollinger and Hudson, Nature Biotechnology 23:1126-1136, 2005). Antigen binding fragments can be grafted into scaffolds based on polypeptides such as fibronectin type III (Fn3) (see U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide monobodies).

[0078] Antigen binding fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions (Zapata *et al.*, Protein Eng. 8:1057-1062, 1995; and U.S. Pat. No. 5,641,870).

[0079] The term "monoclonal antibody" or "monoclonal antibody composition" as used herein refers to polypeptides, including antibodies and antigen binding fragments that have substantially identical amino acid sequence or are derived from the same genetic source. This term also includes preparations of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

[0080] The term "human antibody," as used herein, includes antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, *e.g.*, human germline sequences, or mutated versions of human germline sequences or antibody containing consensus framework sequences derived from human framework sequences analysis, for example, as described in Knappik *et al.*, J. Mol. Biol. 296:57-86, 2000).

[0081] The human antibodies of the present disclosure can include amino acid residues not encoded by human sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo, or a conservative substitution to promote stability or manufacturing).

[0082] The term "recognize" as used herein refers to an antibody or antigen binding fragment thereof that finds and interacts (*e.g.*, binds) with its epitope, whether that epitope is linear or conformational. The term "epitope" refers to a site on an antigen to which an antibody or antigen binding fragment of the disclosure specifically binds. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include techniques in the art, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance (see, *e.g.*, Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66, G. E. Morris, Ed. (1996)), or

electron microscopy. A "paratope" is the part of the antibody which recognizes the epitope of the antigen.

[0083] The phrase "specifically binds" or "selectively binds," when used in the context of describing the interaction between an antigen (*e.g.*, a protein) and an antibody, antibody fragment, or antibody-derived binding agent, refers to a binding reaction that is determinative of the presence of the antigen in a heterogeneous population of proteins and other biologics, *e.g.*, in a biological sample, *e.g.*, a blood, serum, plasma or tissue sample. Thus, under certain designated immunoassay conditions, the antibodies or binding agents with a particular binding specificity bind to a particular antigen at least two times the background and do not substantially bind in a significant amount to other antigens present in the sample. In one aspect, under designated immunoassay conditions, the antibody or binding agent with a particular binding specificity binds to a particular antigen at least ten (10) times the background and does not substantially bind in a significant amount to other antigens present in the sample. Specific binding to an antibody or binding agent under such conditions may require the antibody or agent to have been selected for its specificity for a particular protein. As desired or appropriate, this selection may be achieved by subtracting out antibodies that cross-react with molecules from other species (*e.g.*, mouse or rat) or other subtypes. Alternatively, in some aspects, antibodies or antibody fragments are selected that cross-react with certain desired molecules.

[0084] The term "affinity" as used herein refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity.

[0085] The term "isolated antibody" refers to an antibody that is substantially free of other antibodies having different antigenic specificities. An isolated antibody that specifically binds to one antigen may, however, have cross-reactivity to other antigens. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0086] The term "corresponding human germline sequence" refers to the nucleic acid sequence encoding a human variable region amino acid sequence or subsequence that shares the highest determined amino acid sequence identity with a reference variable region amino acid sequence or subsequence in comparison to all other all other known or inferred variable region amino acid sequences encoded by human germline immunoglobulin variable region sequences. The corresponding human germline sequence can also refer to the human variable region amino acid sequence or subsequence with the highest amino acid sequence identity with a reference variable region amino acid sequence or subsequence in comparison to all other evaluated variable region amino acid sequences. The corresponding human germline sequence can be framework regions only, complementarity determining regions only, framework and complementary determining regions, a variable segment (as defined above), or other combinations of sequences or subsequences that

comprise a variable region. Sequence identity can be determined using the methods described herein, for example, aligning two sequences using BLAST, ALIGN, or another alignment algorithm known in the art. The corresponding human germline nucleic acid or amino acid sequence can have at least about 90%, 91% 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the reference variable region nucleic acid or amino acid sequence.

[0087] A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (see, *e.g.*, Harlow & Lane, Using Antibodies, A Laboratory Manual (1998), for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity). Typically, a specific or selective binding reaction will produce a signal at least twice over the background signal and, more typically, at least 10 to 100 times over the background.

[0088] The term "equilibrium dissociation constant (KD, M)" refers to the dissociation rate constant (kd, time-1) divided by the association rate constant (ka, time-1, M-1). Equilibrium dissociation constants can be measured using any known method in the art. The antibodies of the present disclosure generally will have an equilibrium dissociation constant of less than about 10^{-7} or 10^{-8} M, for example, less than about 10^{-9} M or 10^{-10} M, in some aspects, less than about 10^{-11} M, 10^{-12} M or 10^{-13} M.

[0089] The term "bioavailability" refers to the systemic availability (i.e., blood/plasma levels) of a given amount of drug administered to a patient. Bioavailability is an absolute term that indicates measurement of both the time (rate) and total amount (extent) of drug that reaches the general circulation from an administered dosage form.

[0090] As used herein, the phrase "consisting essentially of" refers to the genera or species of active pharmaceutical agents included in a method or composition, as well as any excipients inactive for the intended purpose of the methods or compositions. In some aspects, the phrase "consisting essentially of" expressly excludes the inclusion of one or more additional active agents other than an anti-HLA-HBV peptide antibody of the present disclosure. In some aspects, the phrase "consisting essentially of" expressly excludes the inclusion of one or more additional active agents other than an anti-HLA-HBV peptide antibody of the present disclosure and a second co-administered agent.

[0091] The term "amino acid" refers to naturally occurring, synthetic, and unnatural amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α-carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide,

methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0092] The term "conservatively modified variant" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For example, the codons GCA, GCC, GCG, and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid that encodes a polypeptide is implicit in each described sequence.

[0093] For polypeptide sequences, "conservatively modified variants" include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles. The following eight groups contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (see, *e.g.*, Creighton, Proteins (1984)). In some aspects, the term "conservative sequence modifications" are used to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence.

[0094] The term "optimized" as used herein refers to a nucleotide sequence that has been altered to encode an amino acid sequence using codons that are preferred in the production cell or organism, generally a eukaryotic cell, for example, a yeast cell, a Pichia cell, a fungal cell, a Trichoderma cell, a Chinese Hamster Ovary cell (CHO) or a human cell. The optimized nucleotide

sequence is engineered to retain completely or as much as possible the amino acid sequence originally encoded by the starting nucleotide sequence, which is also known as the "parental" sequence.

[0095] The terms "percent identical" or "percent identity," in the context of two or more nucleic acids or polypeptide sequences, refers to the extent to which two or more sequences or subsequences that are the same. Two sequences are "identical" if they have the same sequence of amino acids or nucleotides over the region being compared. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (i.e., 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 30 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length.

[0096] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0097] A "comparison window," as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman, Adv. Appl. Math. 2:482c (1970), by the homology alignment algorithm of Needleman and Wunsch, J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson and Lipman, Proc. Natl. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, *e.g.*, Brent *et al.*, Current Protocols in Molecular Biology, 2003).

[0098] Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, Nuc. Acids Res. 25:3389-3402, 1977; and Altschul *et al.*, J. Mol. Biol. 215:403-410,

1990, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, supra). These initial neighborhood word hits act as a basis for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a word length (W) of 11, an expectation (E) or 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a word length of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff, (1989) Proc. Natl. Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0099] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, *e.g.*, Karlin and Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5787, 1993). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[00100] The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller, (Comput. Appl. Biosci. 4:11-17, 1988) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch, (J. Mol. Biol. 48:444-453, 1970), algorithm which has been incorporated into the GAP program in the GCG software package (available from University of South Florida), using either a BLOSUM 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[00101] Other than percentage of sequence identity noted above, another indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[00102] The term "nucleic acid" is used herein interchangeably with the term "polynucleotide" and refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

[00103] Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, as detailed below, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer *et al.*, (1991) Nucleic Acid Res. 19:5081; Ohtsuka *et al.*, (1985) J. Biol. Chem. 260:2605-2608; and Rossolini *et al.*, (1994) Mol. Cell. Probes 8:91-98).

[00104] The term "operably linked" in the context of nucleic acids refers to a functional relationship between two or more polynucleotide (*e.g.*, DNA) segments. Typically, it refers to the functional relationship of a transcriptional regulatory sequence to a transcribed sequence. For example, a promoter or enhancer sequence is operably linked to a coding sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system. Generally, promoter transcriptional regulatory sequences that are operably linked to a transcribed sequence are physically contiguous to the transcribed sequence, i.e., they are cis-acting. However, some transcriptional regulatory sequences, such as enhancers, need not be physically contiguous or located in close proximity to the coding sequences whose transcription they enhance.

[00105] The terms "polypeptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as

well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Unless otherwise indicated, a particular polypeptide sequence also implicitly encompasses conservatively modified variants thereof.

[00106] The term "subject" includes human and non-human animals. Non-human animals include all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms "patient" or "subject" are used herein interchangeably.

[00107] The terms "hepatitis B," "hepatitis B virus" or "HBV" refer to a member of the family *Hepadnaviridae,* genus *Orthohepadnavirus.* HBV is a double stranded DNA virus. The virus is divided into four major serotypes (adr, adw, ayr, ayw).

[00108] Hepatitis B peptides used to generate anti-HLA-HBV peptide antibodies are show in Table 1.

Table 1

SEQ ID NO:	Name	SEQUENCE
SEQ ID NO:1	HBV peptide HBx92-100	VLHKRTLGL
SEQ ID NO:2	HBV peptide HBx52-60	HLSLRGLPV
SEQ ID NO:3	HBV peptide HBs172-180	WLSLLVPFV

[00109] "IC50" (half-maximal inhibitory concentration) refers to the concentration of a particular antibody or fragment thereof which inhibits a signal halfway (50%) between the baseline control and the maximum possible signal.

[00110] "EC50" (half-maximal effective concentration) refers to the concentration of a particular antibody or fragment thereof which induces a response halfway (50%) between the baseline control and the maximum possible effect after a specific exposure or treatment time. For example, the EC50 is the concentration of antibody at which virus infection is reduced by 50%.

[00111] "EC90" refers to the concentration of a particular antibody or fragment thereof which induces a response corresponding to 90% of the maximum possible effect after a specific exposure or treatment time. For example, the EC90 is the concentration of an antibody or fragment thereof at which virus infection is reduced by 90%.

[00112] "Human Leukocyte Antigen" or "HLA" encodes the major histocompatibility complex (MHC) proteins. HLAs of MHC class 1 (A, B and C), present short peptides from inside the cell to the cell surface. For example, when a cell is infected by a virus, the cell will process the viral

peptides, and the complex of HLA-class I protein and their bound viral peptides is transported to the surface of the infected cells where it can be recognized by the T cell receptor present on cytotoxic CD8 T lymphocytes. Approximately, 50% of the population expresses the HLA-class I molecule HLA-A2, which represent a family of HLA-class I molecules produced by gene products of many HLA-A2 alleles (for example, HLA-A2:01 and HLA-A24:01)

[00113] As used herein, the terms "treat," "treating," or "treatment" of any disease or disorder refer in one aspect, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another aspect, "treat," "treating," or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another aspect, "treat," "treating," or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both.

[00114] The phrase "reducing the likelihood" refers to delaying the onset or development or progression of a disease, infection or disorder.

[00115] The term "therapeutically acceptable amount" or "therapeutically effective dose" interchangeably refers to an amount sufficient to effect the desired result (i.e., a reduction in tumor size, inhibition of tumor growth, prevention of metastasis, inhibition or prevention of viral, bacterial, fungal or parasitic infection). In some aspects, a therapeutically acceptable amount does not induce or cause undesirable side effects. A therapeutically acceptable amount can be determined by first administering a low dose, and then incrementally increasing that dose until the desired effect is achieved. A "prophylactically effective dosage," and a "therapeutically effective dosage," of the molecules of the present disclosure can prevent the onset of, or result in a decrease in severity of, respectively, disease symptoms, including symptoms associated with HBV viral infection.

[00116] The term "co-administer" refers to the simultaneous presence of two active agents in the blood of an individual. Active agents that are co-administered can be concurrently or sequentially delivered.

BRIEF DESCRIPTION OF THE DRAWINGS

[00117] Figures 1A-D show the SPR binding of antibodies directed to HLA-HBx92-100 complexes.

[00118] Figures 2A-C show the SPR binding of antibodies directed to HLA-HBx92-100 complexes.

[00119] Figures 3A-D show the SPR binding of antibodies directed to HBx52-60/HLA or HBs172-180 complexes.

[00120] Figure 4 graphically depicts a T2 pulse assay for antibodies specific for HLA presented HBV peptides.

[00121] Figure 5 shows T2 pulse data of the NOV2353 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00122] Figure 6 shows T2 pulse data of the NOV2361 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00123] Figure 7 shows T2 pulse data of the NOV2734 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00124] Figure 8 shows T2 pulse data of the NOV2800 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00125] Figure 9 shows T2 pulse data of the NOV2772 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00126] Figure 10 shows T2 pulse data of the NOV3040 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00127] Figure 11 shows T2 pulse data of the NOV3499 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00128] Figure 12 shows T2 pulse data of the NOV3771 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00129] Figure 13 shows T2 pulse data of the NOV3638 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00130] Figure 14 shows T2 pulse data of the NOV3635 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00131] Figure 15 shows T2 pulse data of the NOV2505 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00132] Figure 16 shows T2 pulse data of the NOV3522 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00133] Figure 17 shows T2 pulse data of the ATG.B.E211 antibody binding profile against an alanine substituted HLA-HBV peptide.

[00134] Figure 18 is a table of NOV3040 binding affinity to an HLA-HBx92-100 toggled peptide.

[00135] Figure 19 is a table of NOV3499 binding affinity to an HLA-HBx92-100 toggled peptide.

[00136] Figure 20 depicts the experimental design for testing anti-HLA-HBV peptide antibodies in a mouse model.

[00137] Figures 21A-C shows IHC staining for human HLA presentation in a murine cell line expressing human HLA-HBx92-100.

[00138] Figures 22D-F show tumors taken from the mouse model expressing human HLA.

[00139] Figure 23 graphically depicts the reduction in tumor cells in the mouse model when treated with either an anti-human HLA-A2 antibody or NOV2353.

[00140] Figure 24 shows FACs analysis of anti-HLA-HBV antibodies in infected FRGN mouse livers.

[00141] Figure 25 shows the binding of anti-HLA-HBV antibodies on uninfected immune cells.

[00142] Figure 26 shows the binding of anti-HLA-HBV antibodies on uninfected immune cells.

[00143] Figure 27 shows the binding of anti-HLA-HBV antibodies on uninfected PBMCs.

[00144] Figure 28 shows the binding of anti-HLA-HBV antibodies on uninfected PBMCs.

[00145] Figure 29 shows the binding of anti-HLA-HBV antibodies on uninfected hepatocytes.

[00146] Figure 30 is a table of peptides used in off-target binding assays.

[00147] Figure 31 is ELISA binding data for the NOV3040 antibody on other HLA presented peptides.

[00148] Figure 32 is ELISA binding data for the NOV3499 antibody on other HLA presented peptides.

[00149] Figure 33 is ELISA binding data for the NOV3771 antibody on other HLA presented peptides.

[00150] Figure 34 is ELISA binding data for the NOV3638 antibody on other HLA presented peptides.

[00151] Figure 35 is ELISA binding data for the NOV2505 antibody on other HLA presented peptides.

[00152] Figure 36 is ELISA binding data for the NOV3522 antibody on other HLA presented peptides.

[00153] Figure 37 shows that NOV2353 can induce ADCC.

[00154] Figure 38 shows that NOV2772 can induce ADCC.

[00155] Figure 39 shows that NOV3040 can induce ADCC.

[00156] Figure 40 shows that NOV3499 can induce ADCC.

[00157] Figure 41 shows that NOV2505 can induce ADCC.

[00158] Figure 42 shows that ATG.B.E211 can induce ADCC.

[00159] Figure 43 is a crystal structure derived map of interactions between NOV2353 and the HLA-A2/HBx92-100 complex.

[00160] Figure 44 graphically depicts the crystal structure of NOV2353 and the HLA-A2/HBx92-100 complex.

[00161] Figure 45 is a crystal structure derived map of interactions between NOV2772 and the HLA-A2/HBx92-100 complex.

[00162] Figure 46 graphically shows the crystal structure of NOV2722 and the HLA-A2/HBx92-100 complex.

[00163] Figure 47 is a crystal structure derived map of interactions between NOV2505 and the HLA-A2/HBx52-60 complex.

[00164] Figure 48 graphically shows the crystal structure of NOV2505 and the HLA-A2/ HBx52-60 complex.

DETAILED DESCRIPTION

[00165] The present disclosure provides for antibodies, antibody fragments (*e.g.*, antigen binding fragments), that bind to HLA-HBV peptides and reduce HBV infection. Furthermore, the present disclosure provides antibodies that have desirable pharmacokinetic characteristics and other desirable attributes, and thus can be used for reducing the likelihood of or treating HBV associated liver failure, liver cirrhosis or hepatocellular cancer. The present disclosure further provides pharmaceutical compositions comprising the antibodies and/or fragments thereof and methods of making and using such pharmaceutical compositions for the prevention and treatment of HBV infection and associated disorders.

Anti-HLA-HBV peptide antibodies

[00166] The present disclosure provides for antibodies or antigen binding fragments thereof that specifically bind to a complex of HLA-HBV peptides. Antibodies or antigen binding fragments thereof of the present disclosure include, but are not limited to, the human monoclonal antibodies or antigen binding fragments thereof, isolated as described in the Examples below.

[00167] The present disclosure in certain aspects provides antibodies or antigen binding fragments thereof that specifically bind to a complex of HLA-HBV peptides, said antibodies or antigen binding fragments thereof comprise a VH domain comprising an amino acid sequence of SEQ ID NO: 16, 48, 80, 112, 144, 176, 208, 240, 272, 304, 336, 368, and 400 (Table 2). The present disclosure also provides antibodies or antigen binding fragments thereof that specifically bind to a complex of HLA-HBV peptides, said antibodies or antigen binding fragments thereof comprise a VH CDR having an amino acid sequence of any one of the VH CDRs listed in Table 2. In particular aspects, the present disclosure provides antibodies or antigen binding fragments thereof that specifically bind to a complex of HLA-HBV peptides, said antibodies comprising (or alternatively, consist of) one, two, three, or more VH CDRs having an amino acid sequence of any of the VH CDRs listed in Table 2.

[00168] The present disclosure provides antibodies or antigen binding fragments thereof that specifically bind to a complex of HLA-HBV peptides, said antibodies or antigen binding fragments thereof comprise a VL domain having an amino acid sequence of SEQ ID NO: 32, 64, 96, 128, 160,

192, 224, 256, 288, 320, 352, 384 and 416 (Table 2). The present disclosure also provides antibodies or antigen binding fragments thereof that specifically bind to a complex of HLA-HBV peptides, said antibodies or antigen binding fragments thereof comprise a VL CDR having an amino acid sequence of any one of the VL CDRs listed in Table 2. In particular, the disclosure provides antibodies or antibody fragments (*e.g.*, antigen binding fragments) that specifically bind to a complex of HLA-HBV peptides, said antibodies or antigen binding fragments thereof comprise (or alternatively, consist of) one, two, three or more VL CDRs having an amino acid sequence of any of the VL CDRs listed in Table 2.

[00169] Other antibodies or antigen binding fragments thereof of the present disclosure include amino acids that have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity in the CDR regions with the CDR regions depicted in the sequences described in Table 2. In some aspects, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the CDR regions when compared with the CDR regions depicted in the sequence described in Table 2.

[00170] The present disclosure also provides nucleic acid sequences that encode VH, VL, the full length heavy chain, and the full length light chain of the antibodies that specifically bind to a complex of HLA-HBV peptides. Such nucleic acid sequences can be optimized for expression in mammalian cells.

Table 2: anti-HBV peptide Antibodies

NOV3499 HC		
SEQ ID NO:4 (Combined)	HCDR1	GYSFTSYWIG
SEQ ID NO:5 (Combined)	HCDR2	IIYPGDSDTRYSPSFQG
SEQ ID NO:6 (Combined)	HCDR3	GGSSFYPGGFDY
SEQ ID NO:7 (Kabat)	HCDR1	SYWIG
SEQ ID NO:8 (Kabat)	HCDR2	IIYPGDSDTRYSPSFQG
SEQ ID NO:9 (Kabat)	HCDR3	GGSSFYPGGFDY
SEQ ID NO:10 (Chothia)	HCDR1	GYSFTSY
SEQ ID NO:11 (Chothia)	HCDR2	YPGDSD
SEQ ID NO:12 (Chothia)	HCDR3	GGSSFYPGGFDY
SEQ ID NO:13 (IMGT)	HCDR1	GYSFTSYW
SEQ ID NO:14 (IMGT)	HCDR2	IYPGDSDT
SEQ ID NO:15 (IMGT)	HCDR3	ARGGSSFYPGGFDY
SEQ ID NO:16	VH	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQM PGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQ WSSLKASDTAMYYCARGGSSFYPGGFDYWGQGTLVTVSS

SEQ ID NO:17	DNA VH	GAGGTCCAATTGGTGCAGTCTGGCGCCGAAGTGAAGAA GCCTGGCGAGAGCCTGAAGATCAGCTGCAAAGGCAGCG GCTACAGCTTCACCAGCTATTGGATCGGCTGGGTCCGAC AGATGCCTGGAAAAGGACTCGAGTGGATGGGCATCATC TACCCCGGCGACAGCGATACCAGATACAGCCCTAGCTTT CAGGGCCAAGTGACCATCAGCGCCGACAAGAGCATCAG CACAGCCTACCTGCAGTGGTCTAGCCTGAAGGCCAGCGA CACAGCCATGTATTATTGCGCGCGTGGCGGCAGCTCTTT CTACCCTGGCGGATTTGATTACTGGGGCCAGGGCACACT GGTCACCGTTAGCTCA
SEQ ID NO:18	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQM PGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQ WSSLKASDTAMYYCARGGSSFYPGGFDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
SEQ ID NO:19	DNA Heavy Chain	GAGGTCCAATTGGTGCAGTCTGGCGCCGAAGTGAAGAA GCCTGGCGAGAGCCTGAAGATCAGCTGCAAAGGCAGCG GCTACAGCTTCACCAGCTATTGGATCGGCTGGGTCCGAC AGATGCCTGGAAAAGGACTCGAGTGGATGGGCATCATC TACCCCGGCGACAGCGATACCAGATACAGCCCTAGCTTT CAGGGCCAAGTGACCATCAGCGCCGACAAGAGCATCAG CACAGCCTACCTGCAGTGGTCTAGCCTGAAGGCCAGCGA CACAGCCATGTATTATTGCGCGCGTGGCGGCAGCTCTTT CTACCCTGGCGGATTTGATTACTGGGGCCAGGGCACACT GGTCACCGTTAGCTCAGCTAGCACCAAGGGCCCCAGCGT GTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCG GCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCC CCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGA CCTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCA GCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCA GCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGA ACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTG GAGCCCAAGAGCTGCGACAAGACCCACACATGCCCCCC CTGCCCGGCGCCAGAGCTGCTGGGCGGACCCTCCGTGTT CCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAG CAGGACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGA GCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCAG AGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCG TGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAG GAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCAGC CCCCATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGC CACGGGAGCCCCAGGTGTACACCCTGCCCCCCTCCCGGG AGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCTGG TGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG AGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACC CCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTAC

		AGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGG CAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGAGCCTGAGCTTAAGCCCCG GCAAG
NOV3499 LC		
SEQ ID NO:20 (Combined)	LCDR1	QASQDISNYLN
SEQ ID NO:21 (Combined)	LCDR2	DASNLET
SEQ ID NO:22 (Combined)	LCDR3	QQYDNLPLT
SEQ ID NO:23 (Kabat)	LCDR1	QASQDISNYLN
SEQ ID NO:24 (Kabat)	LCDR2	DASNLET
SEQ ID NO:25 (Kabat)	LCDR3	QQYDNLPLT
SEQ ID NO:26 (Chothia)	LCDR1	SQDISNY
SEQ ID NO:27 (Chothia)	LCDR2	DAS
SEQ ID NO:28 (Chothia)	LCDR3	YDNLPL
SEQ ID NO:29 (IMGT)	LCDR1	QDISNY
SEQ ID NO:30 (IMGT)	LCDR2	DAS
SEQ ID NO:31 (IMGT)	LCDR3	QQYDNLPLT
SEQ ID NO:32	VL	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQQYDNLPLTFGQGTKVEIK
SEQ ID NO:33	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGTCAGGCCAGC CAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAA ACCTGGCAAAGCCCCCAAATTATTAATCTACGACGCCAG CAACCTGGAAACCGGCGTGCCAAGCCGCTTCAGCGGATC CGGCAGCGGCACCGACTTCACCTTCACCATCAGCAGCCT TCAGCCTGAAGACATTGCCACCTACTACTGCCAGCAGTA CGACAACCTGCCTCTGACCTTTGGCCAGGGCACCAAAGT GGAAATCAAA
SEQ ID NO:34	Light Chain	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQQYDNLPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
SEQ ID NO:35	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGTCAGGCCAGC CAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAA ACCTGGCAAAGCCCCCAAATTATTAATCTACGACGCCAG CAACCTGGAAACCGGCGTGCCAAGCCGCTTCAGCGGATC CGGCAGCGGCACCGACTTCACCTTCACCATCAGCAGCCT TCAGCCTGAAGACATTGCCACCTACTACTGCCAGCAGTA CGACAACCTGCCTCTGACCTTTGGCCAGGGCACCAAAGT GGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCAT CTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG

		AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV3040 HC		
SEQ ID NO:36 (Combined)	HCDR1	GYSFTSYWIG
SEQ ID NO:37 (Combined)	HCDR2	IIYPGDSDTRYSPSFQG
SEQ ID NO:38 (Combined)	HCDR3	GGSSYYPGGFDY
SEQ ID NO:39 (Kabat)	HCDR1	SYWIG
SEQ ID NO:40 (Kabat)	HCDR2	IIYPGDSDTRYSPSFQG
SEQ ID NO:41 (Kabat)	HCDR3	GGSSYYPGGFDY
SEQ ID NO:42 (Chothia)	HCDR1	GYSFTSY
SEQ ID NO:43 (Chothia)	HCDR2	YPGDSD
SEQ ID NO:44 (Chothia)	HCDR3	GGSSYYPGGFDY
SEQ ID NO:45 (IMGT)	HCDR1	GYSFTSYW
SEQ ID NO:46 (IMGT)	HCDR2	IYPGDSDT
SEQ ID NO:47 (IMGT)	HCDR3	ARGGSSYYPGGFDY
SEQ ID NO:48	VH	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQM PGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQ WSSLKASDTAMYYCARGGSSYYPGGFDYWGQGTLVTVSS
SEQ ID NO:49	DNA VH	GAAGTGCAATTGGTGCAGTCTGGCGCCGAAGTGAAGAA GCCTGGCGAGAGCCTGAAGATCAGCTGCAAAGGCAGCG GCTACAGCTTCACCAGCTATTGGATCGGCTGGGTCCGAC AGATGCCTGGAAAAGGACTCGAGTGGATGGGCATCATC TACCCCGGCGACAGCGATACCAGATACAGCCCTAGCTTT CAGGGCCAAGTGACCATCAGCGCCGACAAGAGCATCAG CACAGCCTACCTGCAGTGGTCTAGCCTGAAGGCCAGCGA CACAGCCATGTATTATTGCGCGCGTGGCGGCAGCTCTTA CTACCCTGGCGGATTTGATTACTGGGGCCAGGGCACACT GGTCACCGTTAGCTCA
SEQ ID NO:50	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQM PGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQ WSSLKASDTAMYYCARGGSSYYPGGFDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
SEQ ID NO:51	DNA Heavy Chain	GAAGTGCAATTGGTGCAGTCTGGCGCCGAAGTGAAGAA GCCTGGCGAGAGCCTGAAGATCAGCTGCAAAGGCAGCG GCTACAGCTTCACCAGCTATTGGATCGGCTGGGTCCGAC AGATGCCTGGAAAAGGACTCGAGTGGATGGGCATCATC

		TACCCCGGCGACAGCGATACCAGATACAGCCCTAGCTTT CAGGGCCAAGTGACCATCAGCGCCGACAAGAGCATCAG CACAGCCTACCTGCAGTGGTCTAGCCTGAAGGCCAGCGA CACAGCCATGTATTATTGCGCGCGTGGCGGCAGCTCTTA CTACCCTGGCGGATTTGATTACTGGGGCCAGGGCACACT GGTCACCGTTAGCTCAGCTAGCACCAAGGGCCCCAGCGT GTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCG GCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCC CCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGA CCTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCA GCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCA GCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGA ACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTG GAGCCCAAGAGCTGCGACAAGACCCACACATGCCCCCC CTGCCCAGCCCCAGAGCTGCTGGGCGGACCCTCCGTGTT CCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAG CAGGACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGA GCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCAG AGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCG TGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAG GAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCAGC CCCCATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGC CACGGGAGCCCCAGGTGTACACCCTGCCCCCCTCCCGGG AGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCTGG TGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG AGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACC CCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTAC AGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGG CAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGG CAAG
NOV3040 LC		
SEQ ID NO:52 (Combined)	LCDR1	QASQDISNYLN
SEQ ID NO:53 (Combined)	LCDR2	DASNLET
SEQ ID NO:54 (Combined)	LCDR3	QQYDNLPLT
SEQ ID NO:55 (Kabat)	LCDR1	QASQDISNYLN
SEQ ID NO:56 (Kabat)	LCDR2	DASNLET
SEQ ID NO:57 (Kabat)	LCDR3	QQYDNLPLT
SEQ ID NO:58(Chothia)	LCDR1	SQDISNY
SEQ ID NO:59 (Chothia)	LCDR2	DAS
SEQ ID NO:60 (Chothia)	LCDR3	YDNLPL
SEQ ID NO:61 (IMGT)	LCDR1	QDISNY
SEQ ID NO:62 (IMGT)	LCDR2	DAS
SEQ ID NO:63 (IMGT)	LCDR3	QQYDNLPLT

SEQ ID NO:64	VL	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQQYDNLPLTFGQGTKVEIK
SEQ ID NO:65	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGTCAGGCCAGC CAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAA ACCTGGCAAAGCCCCCAAATTATTAATCTACGACGCCAG CAACCTGGAAACCGGCGTGCCAAGCCGCTTCAGCGGATC CGGCAGCGGCACCGACTTCACCTTCACCATCAGCAGCCT TCAGCCTGAAGACATTGCCACCTACTACTGCCAGCAGTA CGACAACCTGCCTCTGACCTTTGGCCAGGGCACCAAAGT GGAAATCAAA
SEQ ID NO:66	Light Chain	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQQYDNLPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
SEQ ID NO:67	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGTCAGGCCAGC CAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAA ACCTGGCAAAGCCCCCAAATTATTAATCTACGACGCCAG CAACCTGGAAACCGGCGTGCCAAGCCGCTTCAGCGGATC CGGCAGCGGCACCGACTTCACCTTCACCATCAGCAGCCT TCAGCCTGAAGACATTGCCACCTACTACTGCCAGCAGTA CGACAACCTGCCTCTGACCTTTGGCCAGGGCACCAAAGT GGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCAT CTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV3771 HC		
SEQ ID NO:68 (Combined)	HCDR1	GYWFTSYWIG
SEQ ID NO:69 (Combined)	HCDR2	IIYPGDSDTRYSPSFQG
SEQ ID NO:70 (Combined)	HCDR3	GGSSFYPGGFDY
SEQ ID NO:71 (Kabat)	HCDR1	SYWIG
SEQ ID NO:72 (Kabat)	HCDR2	IIYPGDSDTRYSPSFQG
SEQ ID NO:73 (Kabat)	HCDR3	GGSSFYPGGFDY
SEQ ID NO:74 (Chothia)	HCDR1	GYWFTSY
SEQ ID NO:75 (Chothia)	HCDR2	YPGDSD
SEQ ID NO:76 (Chothia)	HCDR3	GGSSFYPGGFDY
SEQ ID NO:77 (IMGT)	HCDR1	GYWFTSYW
SEQ ID NO:78 (IMGT)	HCDR2	IYPGDSDT

SEQ ID NO:79 (IMGT)	HCDR3	ARGGSSFYPGGFDY
SEQ ID NO:80	VH	EVQLVQSGAEVKKPGESLKISCKGSGYWFTSYWIGWVRQ MPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAY LQWSSLKASDTAMYYCARGGSSFYPGGFDYWGQGTLVTV SS
SEQ ID NO:81	DNA VH	GAGGTCCAATTGGTGCAGTCTGGCGCCGAAGTGAAGAA GCCTGGCGAGAGCCTGAAGATCAGCTGCAAAGGCAGCG GCTACTGGTTCACCAGCTATTGGATCGGCTGGGTCCGAC AGATGCCTGGAAAAGGACTCGAGTGGATGGGCATCATC TACCCCGGCGACAGCGATACCAGATACAGCCCTAGCTTT CAGGGCCAAGTGACCATCAGCGCCGACAAGAGCATCAG CACAGCCTACCTGCAGTGGTCTAGCCTGAAGGCCAGCGA CACAGCCATGTATTATTGCGCGCGTGGCGGCAGCTCTTT CTACCCTGGCGGATTTGATTACTGGGGCCAGGGCACACT GGTCACCGTTAGCTCA
SEQ ID NO:82	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYWFTSYWIGWVRQ MPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAY LQWSSLKASDTAMYYCARGGSSFYPGGFDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK
SEQ ID NO:83	DNA Heavy Chain	GAGGTCCAATTGGTGCAGTCTGGCGCCGAAGTGAAGAA GCCTGGCGAGAGCCTGAAGATCAGCTGCAAAGGCAGCG GCTACTGGTTCACCAGCTATTGGATCGGCTGGGTCCGAC AGATGCCTGGAAAAGGACTCGAGTGGATGGGCATCATC TACCCCGGCGACAGCGATACCAGATACAGCCCTAGCTTT CAGGGCCAAGTGACCATCAGCGCCGACAAGAGCATCAG CACAGCCTACCTGCAGTGGTCTAGCCTGAAGGCCAGCGA CACAGCCATGTATTATTGCGCGCGTGGCGGCAGCTCTTT CTACCCTGGCGGATTTGATTACTGGGGCCAGGGCACACT GGTCACCGTTAGCTCAGCTAGCACCAAGGGCCCCAGCGT GTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCG GCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCC CCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGA CCTCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCA GCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCA GCAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGA ACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTG GAGCCCAAGAGCTGCGACAAGACCCACACATGCCCCCC CTGCCCGGCGCCAGAGCTGCTGGGCGGACCCTCCGTGTT CCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAG CAGGACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGA GCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCAG AGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCG TGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAG GAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCAGC CCCCATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGC

		CACGGGAGCCCCAGGTGTACACCCTGCCCCCCTCCCGGG AGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCTGG TGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG AGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACC CCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTAC AGCAAGCTGACCGTGGACAAGTCCAGGTGGCAGCAGGG CAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGAGCCTGAGCTTAAGCCCCG GCAAG
NOV3771 LC		
SEQ ID NO:84 (Combined)	LCDR1	QASQDISNYLN
SEQ ID NO:85 (Combined)	LCDR2	DASNLET
SEQ ID NO:86 (Combined)	LCDR3	QQYDNLPLT
SEQ ID NO:87 (Kabat)	LCDR1	QASQDISNYLN
SEQ ID NO:88 (Kabat)	LCDR2	DASNLET
SEQ ID NO:89 (Kabat)	LCDR3	QQYDNLPLT
SEQ ID NO:90 (Chothia)	LCDR1	SQDISNY
SEQ ID NO:91 (Chothia)	LCDR2	DAS
SEQ ID NO:92 (Chothia)	LCDR3	YDNLPL
SEQ ID NO:93 (IMGT)	LCDR1	QDISNY
SEQ ID NO:94 (IMGT)	LCDR2	DAS
SEQ ID NO:95 (IMGT)	LCDR3	QQYDNLPLT
SEQ ID NO:96	VL	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQQYDNLPLTFGQGTKVEIK
SEQ ID NO:97	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGTCAGGCCAGC CAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAA ACCTGGCAAAGCCCCCAAATTATTAATCTACGACGCCAG CAACCTGGAAACCGGCGTGCCAAGCCGCTTCAGCGGATC CGGCAGCGGCACCGACTTCACCTTCACCATCAGCAGCCT TCAGCCTGAAGACATTGCCACCTACTACTGCCAGCAGTA CGACAACCTGCCTCTGACCTTTGGCCAGGGCACCAAAGT GGAAATCAAA
SEQ ID NO:98	Light Chain	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQQYDNLPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
SEQ ID NO:99	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGTCAGGCCAGC CAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAA ACCTGGCAAAGCCCCCAAATTATTAATCTACGACGCCAG CAACCTGGAAACCGGCGTGCCAAGCCGCTTCAGCGGATC CGGCAGCGGCACCGACTTCACCTTCACCATCAGCAGCCT TCAGCCTGAAGACATTGCCACCTACTACTGCCAGCAGTA

		CGACAACCTGCCTCTGACCTTTGGCCAGGGCACCAAAGT GGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCAT CTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV3638 HC		
SEQ ID NO:100 (Combined)	HCDR1	GFTFSSYAMS
SEQ ID NO:101 (Combined)	HCDR2	AISGSGGSTYYADSVKG
SEQ ID NO:102 (Combined)	HCDR3	DWGAWDVYEFDY
SEQ ID NO:103 (Kabat)	HCDR1	SYAMS
SEQ ID NO:104 (Kabat)	HCDR2	AISGSGGSTYYADSVKG
SEQ ID NO:105 (Kabat)	HCDR3	DWGAWDVYEFDY
SEQ ID NO:106 (Chothia)	HCDR1	GFTFSSY
SEQ ID NO:107 (Chothia)	HCDR2	SGSGGS
SEQ ID NO:108 (Chothia)	HCDR3	DWGAWDVYEFDY
SEQ ID NO:109 (IMGT)	HCDR1	GFTFSSYA
SEQ ID NO:110 (IMGT)	HCDR2	ISGSGGST
SEQ ID NO:111 (IMGT)	HCDR3	ARDWGAWDVYEFDY
SEQ ID NO:112	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARDWGAWDVYEFDYWGQGTLVT VSS
SEQ ID NO:113	DNA VH	GAGGTCCAATTGCTGGAATCTGGCGGAGGACTGGTTCAG CCTGGTGGCTCTCTGAGACTGTCTTGTGCCGCCAGCGGC TTCACCTTTAGCAGCTATGCCATGTCCTGGGTCCGACAG GCTCCTGGAAAAGGACTCGAGTGGGTGTCCGCCATTTCT GGCTCTGGCGGCAGCACATATTACGCCGATAGCGTGAAG GGCAGATTCACCATCAGCCGGGACAACAGCAAGAACAC CCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACA CAGCCGTGTACTACTGCGCGCGTGATTGGGGCGCTTGGG ACGTGTACGAGTTCGATTACTGGGGCCAGGGCACCCTGG TCACAGTTAGCTCA
SEQ ID NO:114	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARDWGAWDVYEFDYWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK

		EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
SEQ ID NO:115	DNA Heavy Chain	GAGGTCCAATTGCTGGAATCTGGCGGAGGACTGGTTCAG CCTGGTGGCTCTCTGAGACTGTCTTGTGCCGCCAGCGGC TTCACCTTTAGCAGCTATGCCATGTCCTGGGTCCGACAG GCTCCTGGAAAAGGACTCGAGTGGGTGTCCGCCATTTCT GGCTCTGGCGGCAGCACATATTACGCCGATAGCGTGAAG GGCAGATTCACCATCAGCCGGGACAACAGCAAGAACAC CCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACA CAGCCGTGTACTACTGCGCGCGTGATTGGGGCGCTTGGG ACGTGTACGAGTTCGATTACTGGGGCCAGGGCACCCTGG TCACAGTTAGCTCAGCTAGCACCAAGGGCCCCAGCGTGT TCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGC ACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC GAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACC TCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGC GGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGC AGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAAC CACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGA GCCCAAGAGCTGCGACAAGACCCACACATGCCCCCCCTG CCCGGCGCCAGAGCTGCTGGGCGGACCCTCCGTGTTCCT GTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAG GACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGCC ACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCACAACGCCAAGACCAAGCCCAGAGA GGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCT GACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAAT ACAAGTGCAAGGTCTCCAACAAGGCCCTGCCAGCCCCCA TCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGG GAGCCCCAGGTGTACACCCTGCCCCCCTCCCGGGAGGAG ATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAG GGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGC AACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCC AGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACG TGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACC ACTACACCCAGAAGAGCCTGAGCTTAAGCCCCGGCAAG
NOV3638 LC		
SEQ ID NO:116 (Combined)	LCDR1	RASQSISSYLN
SEQ ID NO:117 (Combined)	LCDR2	AASSLQS
SEQ ID NO:118 (Combined)	LCDR3	QQSYSTPLT
SEQ ID NO:119 (Kabat)	LCDR1	RASQSISSYLN
SEQ ID NO:120 (Kabat)	LCDR2	AASSLQS
SEQ ID NO:121 (Kabat)	LCDR3	QQSYSTPLT
SEQ ID NO:122 (Chothia)	LCDR1	SQSISSY

SEQ ID NO:123 (Chothia)	LCDR2	AAS
SEQ ID NO:124 (Chothia)	LCDR3	SYSTPL
SEQ ID NO:125 (IMGT)	LCDR1	QSISSY
SEQ ID NO:126 (IMGT)	LCDR2	AAS
SEQ ID NO:127 (IMGT)	LCDR3	QQSYSTPLT
SEQ ID NO:128	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIK
SEQ ID NO:129	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAA
SEQ ID NO:130	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
SEQ ID NO:131	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCA TCTTCCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV3635 HC		
SEQ ID NO:132 (Combined)	HCDR1	GFTFSSYAMS
SEQ ID NO:133 (Combined)	HCDR2	AISGSGGSTYYADSVKG
SEQ ID NO:134 (Combined)	HCDR3	DWGAWDVYDFDY
SEQ ID NO:135 (Kabat)	HCDR1	SYAMS
SEQ ID NO:136 (Kabat)	HCDR2	AISGSGGSTYYADSVKG

SEQ ID NO:137 (Kabat)	HCDR3	DWGAWDVYDFDY
SEQ ID NO:138 (Chothia)	HCDR1	GFTFSSY
SEQ ID NO:139 (Chothia)	HCDR2	SGSGGS
SEQ ID NO:140 (Chothia)	HCDR3	DWGAWDVYDFDY
SEQ ID NO:141 (IMGT)	HCDR1	GFTFSSYA
SEQ ID NO:142 (IMGT)	HCDR2	ISGSGGST
SEQ ID NO:143 (IMGT)	HCDR3	ARDWGAWDVYDFDY
SEQ ID NO:144	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARDWGAWDVYDFDYWGQGTLVT VSS
SEQ ID NO:145	DNA VH	GAGGTCCAATTGCTGGAATCTGGCGGAGGACTGGTTCAG CCTGGTGGCTCTCTGAGACTGTCTTGTGCCGCCAGCGGC TTCACCTTTAGCAGCTATGCCATGTCCTGGGTCCGACAG GCTCCTGGAAAAGGACTCGAGTGGGTGTCCGCCATTTCT GGCTCTGGCGGCAGCACATATTACGCCGATAGCGTGAAG GGCAGATTCACCATCAGCCGGGACAACAGCAAGAACAC CCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACA CAGCCGTGTACTACTGCGCGCGTGATTGGGGCGCTTGGG ACGTGTACGATTTCGATTACTGGGGCCAGGGCACCCTGG TCACAGTTAGCTCA
SEQ ID NO:146	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARDWGAWDVYDFDYWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
SEQ ID NO:147	DNA Heavy Chain	GAGGTCCAATTGCTGGAATCTGGCGGAGGACTGGTTCAG CCTGGTGGCTCTCTGAGACTGTCTTGTGCCGCCAGCGGC TTCACCTTTAGCAGCTATGCCATGTCCTGGGTCCGACAG GCTCCTGGAAAAGGACTCGAGTGGGTGTCCGCCATTTCT GGCTCTGGCGGCAGCACATATTACGCCGATAGCGTGAAG GGCAGATTCACCATCAGCCGGGACAACAGCAAGAACAC CCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACA CAGCCGTGTACTACTGCGCGCGTGATTGGGGCGCTTGGG ACGTGTACGATTTCGATTACTGGGGCCAGGGCACCCTGG TCACAGTTAGCTCAGCTAGCACCAAGGGCCCCAGCGTGT TCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGC ACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC GAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACC TCCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGC GGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGC AGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAAC CACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGA

		GCCCAAGAGCTGCGACAAGACCCACACATGCCCCCCCTG CCCGGCGCCAGAGCTGCTGGGCGGACCCTCCGTGTTCCT GTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAG GACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGCC ACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCACAACGCCAAGACCAAGCCCAGAGA GGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCT GACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAAT ACAAGTGCAAGGTCTCCAACAAGGCCCTGCCAGCCCCCA TCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGG GAGCCCCAGGTGTACACCCTGCCCCCCTCCCGGGAGGAG ATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAG GGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGC AACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCC AGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACG TGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACC ACTACACCCAGAAGAGCCTGAGCTTAAGCCCCGGCAAG
NOV3635 LC		
SEQ ID NO:148 (Combined)	LCDR1	RASQSISSYLN
SEQ ID NO:149 (Combined)	LCDR2	AASSLQS
SEQ ID NO:150 (Combined)	LCDR3	QQSYSTPLT
SEQ ID NO:151 (Kabat)	LCDR1	RASQSISSYLN
SEQ ID NO:152 (Kabat)	LCDR2	AASSLQS
SEQ ID NO:153 (Kabat)	LCDR3	QQSYSTPLT
SEQ ID NO:154 (Chothia)	LCDR1	SQSISSY
SEQ ID NO:155 (Chothia)	LCDR2	AAS
SEQ ID NO:156 (Chothia)	LCDR3	SYSTPL
SEQ ID NO:157 (IMGT)	LCDR1	QSISSY
SEQ ID NO:158 (IMGT)	LCDR2	AAS
SEQ ID NO:159 (IMGT)	LCDR3	QQSYSTPLT
SEQ ID NO:160	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIK
SEQ ID NO:161	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAA
SEQ ID NO:162	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA

		TYYCQQSYSTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
SEQ ID NO:163	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCA TCTTCCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV2361 HC		
SEQ ID NO:164 (Combined)	HCDR1	GYTFTSYYMH
SEQ ID NO:165 (Combined)	HCDR2	IISPSGGSTSYAQKFQG
SEQ ID NO:166 (Combined)	HCDR3	DGWGEVWSYDYFDY
SEQ ID NO:167 (Kabat)	HCDR1	SYYMH
SEQ ID NO:168 (Kabat)	HCDR2	IISPSGGSTSYAQKFQG
SEQ ID NO:169 (Kabat)	HCDR3	DGWGEVWSYDYFDY
SEQ ID NO:170 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO:171 (Chothia)	HCDR2	SPSGGS
SEQ ID NO:172 (Chothia)	HCDR3	DGWGEVWSYDYFDY
SEQ ID NO:173 (IMGT)	HCDR1	GYTFTSYY
SEQ ID NO:174 (IMGT)	HCDR2	ISPSGGST
SEQ ID NO:175 (IMGT)	HCDR3	ARDGWGEVWSYDYFDY
SEQ ID NO:176	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQ APGQGLEWMGIISPSGGSTSYAQKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYCARDGWGEVWSYDYFDYWGQGT LVTVSS
SEQ ID NO:177	DNA VH	CAGGTGCAATTGGTGCAGAGCGGAGCCGAAGTGAAAAA ACCTGGGGCCAGCGTGAAAGTGTCCTGCAAAGCCTCCGG ATACACCTTCACCAGCTACTACATGCACTGGGTCCGCCA GGCCCCAGGCCAGGGACTCGAGTGGATGGGCATCATCA GCCCTAGCGGCGGCAGCACCAGCTACGCCCAGAAATTCC AGGGCCGGGTGACCATGACCCGCGACACCAGCACCAGC ACCGTGTACATGGAACTGAGCAGCCTGCGCAGCGAGGA

		CACCGCCGTGTATTATTGCGCGCGTGACGGTTGGGGTGA AGTTTGGTCTTACGACTACTTCGACTACTGGGGTCAAGG CACCCTGGTTACAGTCAGCTCA
SEQ ID NO:178	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQ APGQGLEWMGIISPSGGSTSYAQKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYCARDGWGEVWSYDYFDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
SEQ ID NO:179	DNA Heavy Chain	CAGGTGCAATTGGTGCAGAGCGGAGCCGAAGTGAAAAA ACCTGGGGCCAGCGTGAAAGTGTCCTGCAAAGCCTCCGG ATACACCTTCACCAGCTACTACATGCACTGGGTCCGCCA GGCCCCAGGCCAGGGACTCGAGTGGATGGGCATCATCA GCCCTAGCGGCGGCAGCACCAGCTACGCCCAGAAATTCC AGGGCCGGGTGACCATGACCCGCGACACCAGCACCAGC ACCGTGTACATGGAACTGAGCAGCCTGCGCAGCGAGGA CACCGCCGTGTATTATTGCGCGCGTGACGGTTGGGGTGA AGTTTGGTCTTACGACTACTTCGACTACTGGGGTCAAGG CACCCTGGTTACAGTCAGCTCAGCTAGCACCAAGGGCCC CAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAG CGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACT ACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAG CCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCTGC AGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACA GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGC AACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAA GAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACCT GCCCCCCCTGCCCAGCCCCAGAGCTGCTGGGCGGACCCT CCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGA TGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTGG ACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGG TACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAA GCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGG TGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACG GCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTG CCAGCCCCCATCGAAAAGACCATCAGCAAGGCCAAGGG CCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCCTC CCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCT GTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGG AGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAG ACCACCCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTC CTGTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCA GCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGG CCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGT CCCCCGGCAAG
NOV2361 LC		

SEQ ID NO:180 (Combined)	LCDR1	RASQSISSYLN
SEQ ID NO:181 (Combined)	LCDR2	AASSLQS
SEQ ID NO:182 (Combined)	LCDR3	QQSYSTPLT
SEQ ID NO:183 (Kabat)	LCDR1	RASQSISSYLN
SEQ ID NO:184 (Kabat)	LCDR2	AASSLQS
SEQ ID NO:185 (Kabat)	LCDR3	QQSYSTPLT
SEQ ID NO:186 (Chothia)	LCDR1	SQSISSY
SEQ ID NO:187 (Chothia)	LCDR2	AAS
SEQ ID NO:188 (Chothia)	LCDR3	SYSTPL
SEQ ID NO:189 (IMGT)	LCDR1	QSISSY
SEQ ID NO:190 (IMGT)	LCDR2	AAS
SEQ ID NO:191 (IMGT)	LCDR3	QQSYSTPLT
SEQ ID NO:192	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIK
SEQ ID NO:193	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAA
SEQ ID NO:194	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
SEQ ID NO:195	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCA TCTTCCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT

		GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV2734 HC		
SEQ ID NO:196 (Combined)	HCDR1	GYTFTSYYKH
SEQ ID NO:197 (Combined)	HCDR2	IISPSGGSTSYAQKFQG
SEQ ID NO:198 (Combined)	HCDR3	DGWGEVWSYDYFDY
SEQ ID NO:199 (Kabat)	HCDR1	SYYKH
SEQ ID NO:200 (Kabat)	HCDR2	IISPSGGSTSYAQKFQG
SEQ ID NO:201 (Kabat)	HCDR3	DGWGEVWSYDYFDY
SEQ ID NO:202 (Chothia)	HCDR1	GYTFTSY
SEQ ID NO:203 (Chothia)	HCDR2	SPSGGS
SEQ ID NO:204 (Chothia)	HCDR3	DGWGEVWSYDYFDY
SEQ ID NO:205 (IMGT)	HCDR1	GYTFTSYY
SEQ ID NO:206 (IMGT)	HCDR2	ISPSGGST
SEQ ID NO:207 (IMGT)	HCDR3	ARDGWGEVWSYDYFDY
SEQ ID NO:208	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYKHWVRQ APGQGLEWMGIISPSGGSTSYAQKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYCARDGWGEVWSYDYFDYWGQGT LVTVSS
SEQ ID NO:209	DNA VH	CAGGTGCAATTGGTGCAGTCTGGCGCCGAAGTGAAGAA ACCAGGCGCCAGCGTGAAGGTGTCCTGCAAGGCCAGCG GCTACACCTTTACCAGCTACTACAAGCACTGGGTGCGCC AGGCCCCTGGACAGGGACTCGAGTGGATGGGCATCATC AGCCCTAGCGGCGGCAGCACAAGCTACGCCCAGAAATT CCAGGGCCGGGTGACCATGACCCGGGACACAAGCACCA GCACCGTGTACATGGAACTGAGCAGCCTGCGGAGCGAG GACACCGCCGTGTATTACTGCGCGCGTGATGGCTGGGGC GAAGTGTGGTCCTACGACTACTTCGACTACTGGGGCCAG GGCACCCTCGTGACCGTCAGCTCA
SEQ ID NO:210	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYKHWVRQ APGQGLEWMGIISPSGGSTSYAQKFQGRVTMTRDTSTSTV YMELSSLRSEDTAVYYCARDGWGEVWSYDYFDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
SEQ ID NO:211	DNA Heavy Chain	CAGGTGCAATTGGTGCAGTCTGGCGCCGAAGTGAAGAA ACCAGGCGCCAGCGTGAAGGTGTCCTGCAAGGCCAGCG GCTACACCTTTACCAGCTACTACAAGCACTGGGTGCGCC AGGCCCCTGGACAGGGACTCGAGTGGATGGGCATCATC

		AGCCCTAGCGGCGGCAGCACAAGCTACGCCCAGAAATT CCAGGGCCGGGTGACCATGACCCGGGACACAAGCACCA GCACCGTGTACATGGAACTGAGCAGCCTGCGGAGCGAG GACACCGCCGTGTATTACTGCGCGCGTGATGGCTGGGGC GAAGTGTGGTCCTACGACTACTTCGACTACTGGGGCCAG GGCACCCTCGTGACCGTCAGCTCAGCTAGCACCAAGGGC CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACC AGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGA CTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGG AGCCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCT GCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGAC AGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTG CAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACA AGAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACC TGCCCCCCCTGCCCAGCCCCAGAGCTGCTGGGCGGACCC TCCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTG ATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTG GACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTG GTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCA AGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAAC GGCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCT GCCAGCCCCCATCGAAAAGACCATCAGCAAGGCCAAGG GCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCCT CCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACC TGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTG GAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAA GACCACCCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTT CCTGTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGC AGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAG GCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTG TCCCCCGGCAAG
NOV2734 LC		
SEQ ID NO:212 (Combined)	LCDR1	RASQSISSYLN
SEQ ID NO:213 (Combined)	LCDR2	AASSLQS
SEQ ID NO:214 (Combined)	LCDR3	QQSYSTPLT
SEQ ID NO:215 (Kabat)	LCDR1	RASQSISSYLN
SEQ ID NO:216 (Kabat)	LCDR2	AASSLQS
SEQ ID NO:217 (Kabat)	LCDR3	QQSYSTPLT
SEQ ID NO:218 (Chothia)	LCDR1	SQSISSY
SEQ ID NO:219 (Chothia)	LCDR2	AAS
SEQ ID NO:220 (Chothia)	LCDR3	SYSTPL
SEQ ID NO:221 (IMGT)	LCDR1	QSISSY
SEQ ID NO:222 (IMGT)	LCDR2	AAS
SEQ ID NO:223 (IMGT)	LCDR3	QQSYSTPLT

SEQ ID NO:224	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIK
SEQ ID NO:225	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAA
SEQ ID NO:226	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
SEQ ID NO:227	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCA TCTTCCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV2505 HC		
SEQ ID NO:228 (Combined)	HCDR1	GYSFTSYWIG
SEQ ID NO:229 (Combined)	HCDR2	IIYPGDSDTRYSPSFQG
SEQ ID NO:230 (Combined)	HCDR3	GWYYSPYWYPYSYSGFDV
SEQ ID NO:231 (Kabat)	HCDR1	SYWIG
SEQ ID NO:232 (Kabat)	HCDR2	IIYPGDSDTRYSPSFQG
SEQ ID NO:233 (Kabat)	HCDR3	GWYYSPYWYPYSYSGFDV
SEQ ID NO:234 (Chothia)	HCDR1	GYSFTSY
SEQ ID NO:235 (Chothia)	HCDR2	YPGDSD
SEQ ID NO:236 (Chothia)	HCDR3	GWYYSPYWYPYSYSGFDV

SEQ ID NO:237 (IMGT)	HCDR1	GYSFTSYW
SEQ ID NO:238 (IMGT)	HCDR2	IYPGDSDT
SEQ ID NO:239 (IMGT)	HCDR3	ARGWYYSPYWYPYSYSGFDV
SEQ ID NO:240	VH	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQM PGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQ WSSLKASDTAMYYCARGWYYSPYWYPYSYSGFDVWGQG TLVTVSS
SEQ ID NO:241	DNA VH	GAGGTGCAATTGGTGCAGAGCGGAGCCGAAGTGAAAAA ACCTGGCGAGAGCCTGAAAATCAGCTGCAAAGGCTCCG GATACAGCTTCACCAGCTACTGGATCGGCTGGGTCCGCC AGATGCCTGGCAAAGGCCTCGAGTGGATGGGCATCATCT ACCCTGGCGACAGCGACACCCGCTACAGCCCTAGCTTCC AGGGCCAGGTGACCATCAGCGCCGACAAATCCATCAGC ACCGCCTACCTTCAGTGGTCCAGCCTGAAAGCCAGCGAC ACCGCCATGTATTATTGCGCGCGTGGTTGGTACTACTCTC CGTACTGGTACCCGTACTCTTACTCTGGTTTCGACGTCTG GGGTCAAGGCACCCTGGTTACAGTCAGCTCA
SEQ ID NO:242	Heavy Chain	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQM PGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQ WSSLKASDTAMYYCARGWYYSPYWYPYSYSGFDVWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK
SEQ ID NO:243	DNA Heavy Chain	GAGGTGCAATTGGTGCAGAGCGGAGCCGAAGTGAAAAA ACCTGGCGAGAGCCTGAAAATCAGCTGCAAAGGCTCCG GATACAGCTTCACCAGCTACTGGATCGGCTGGGTCCGCC AGATGCCTGGCAAAGGCCTCGAGTGGATGGGCATCATCT ACCCTGGCGACAGCGACACCCGCTACAGCCCTAGCTTCC AGGGCCAGGTGACCATCAGCGCCGACAAATCCATCAGC ACCGCCTACCTTCAGTGGTCCAGCCTGAAAGCCAGCGAC ACCGCCATGTATTATTGCGCGCGTGGTTGGTACTACTCTC CGTACTGGTACCCGTACTCTTACTCTGGTTTCGACGTCTG GGGTCAAGGCACCCTGGTTACAGTCAGCTCAGCTAGCAC CAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAA GAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGG TGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGA ACAGCGGAGCCCTGACCTCCGGCGTGCACACCTTCCCCG CCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCG TGGTGACAGTGCCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAG GTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACAAGAC CCACACCTGCCCCCCCCTGCCCAGCCCCAGAGCTGCTGGG CGGACCCTCCGTGTTCCTGTTCCCCCCCAAGCCCAAGGA CACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGT GGTGGTGGACGTGAGCCACGAGGACCCAGAGGTGAAGT TCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCC AAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTA

		CAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTG GCTGAACGGCAAGGAATACAAGTGCAAGGTCTCCAACA AGGCCCTGCCAGCCCCCATCGAAAAGACCATCAGCAAG GCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCT GCCCCCCTCCCGGGAGGAGATGACCAAGAACCAGGTGT CCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACA TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAAC AACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGG CAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTC CAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGA TGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGC CTGAGCCTGTCCCCCGGCAAG
NOV2505 LC		
SEQ ID NO:244 (Combined)	LCDR1	QASQDISNYLN
SEQ ID NO:245 (Combined)	LCDR2	DASNLET
SEQ ID NO:246 (Combined)	LCDR3	QQYDNLPLT
SEQ ID NO:247 (Kabat)	LCDR1	QASQDISNYLN
SEQ ID NO:248 (Kabat)	LCDR2	DASNLET
SEQ ID NO:249 (Kabat)	LCDR3	QQYDNLPLT
SEQ ID NO:250 (Chothia)	LCDR1	SQDISNY
SEQ ID NO:251 (Chothia)	LCDR2	DAS
SEQ ID NO:252 (Chothia)	LCDR3	YDNLPL
SEQ ID NO:253 (IMGT)	LCDR1	QDISNY
SEQ ID NO:254 (IMGT)	LCDR2	DAS
SEQ ID NO:255 (IMGT)	LCDR3	QQYDNLPLT
SEQ ID NO:256	VL	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQQYDNLPLTFGQGTKVEIK
SEQ ID NO:257	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGTCAGGCCAGC CAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAA ACCTGGCAAAGCCCCCAAATTATTAATCTACGACGCCAG CAACCTGGAAACCGGCGTGCCAAGCCGCTTCAGCGGATC CGGCAGCGGCACCGACTTCACCTTCACCATCAGCAGCCT TCAGCCTGAAGACATTGCCACCTACTACTGCCAGCAGTA CGACAACCTGCCTCTGACCTTTGGCCAGGGCACCAAAGT GGAAATCAAA
SEQ ID NO:258	Light Chain	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPG KAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIA TYYCQQYDNLPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
SEQ ID NO:259	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGTCAGGCCAGC

		CAGGACATCAGCAACTACCTGAACTGGTACCAGCAGAA ACCTGGCAAAGCCCCCAAATTATTAATCTACGACGCCAG CAACCTGGAAACCGGCGTGCCAAGCCGCTTCAGCGGATC CGGCAGCGGCACCGACTTCACCTTCACCATCAGCAGCCT TCAGCCTGAAGACATTGCCACCTACTACTGCCAGCAGTA CGACAACCTGCCTCTGACCTTTGGCCAGGGCACCAAAGT GGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCAT CTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV3522 HC		
SEQ ID NO:260 (Combined)	HCDR1	GFTFSSYAMS
SEQ ID NO:261 (Combined)	HCDR2	AISGSGGSTYYADSVKG
SEQ ID NO:262 (Combined)	HCDR3	GDYYLLGVDSQYFDY
SEQ ID NO:263 (Kabat)	HCDR1	SYAMS
SEQ ID NO:264 (Kabat)	HCDR2	AISGSGGSTYYADSVKG
SEQ ID NO:265 (Kabat)	HCDR3	GDYYLLGVDSQYFDY
SEQ ID NO:266 (Chothia)	HCDR1	GFTFSSY
SEQ ID NO:267 (Chothia)	HCDR2	SGSGGS
SEQ ID NO:268 (Chothia)	HCDR3	GDYYLLGVDSQYFDY
SEQ ID NO:269 (IMGT)	HCDR1	GFTFSSYA
SEQ ID NO:270 (IMGT)	HCDR2	ISGSGGST
SEQ ID NO:271 (IMGT)	HCDR3	ARGDYYLLGVDSQYFDY
SEQ ID NO:272	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARGDYYLLGVDSQYFDYWGQGTL VTVSS
SEQ ID NO:273	DNA VH	GAGGTCCAATTGCTGGAATCTGGCGGAGGACTGGTTCAG CCTGGTGGCTCTCTGAGACTGTCTTGTGCCGCCAGCGGC TTCACCTTTAGCAGCTATGCCATGTCCTGGGTCCGACAG GCTCCTGGAAAAGGACTCGAGTGGGTGTCCGCCATTTCT GGCTCTGGCGGCAGCACATATTACGCCGATAGCGTGAAG GGCAGATTCACCATCAGCCGGGACAACAGCAAGAACAC CCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACA CAGCCGTGTACTATTGCGCGCGTGGCGATTACTACCTGC TGGGCGTCGACAGCCAGTACTTTGATTATTGGGGCCAGG GCACCCTGGTCACCGTTAGCTCA
SEQ ID NO:274	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARGDYYLLGVDSQYFDYWGQGTL

		VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK
SEQ ID NO:275	DNA Heavy Chain	GAGGTCCAATTGCTGGAATCTGGCGGAGGACTGGTTCAG CCTGGTGGCTCTCTGAGACTGTCTTGTGCCGCCAGCGGC TTCACCTTTAGCAGCTATGCCATGTCCTGGGTCCGACAG GCTCCTGGAAAAGGACTCGAGTGGGTGTCCGCCATTTCT GGCTCTGGCGGCAGCACATATTACGCCGATAGCGTGAAG GGCAGATTCACCATCAGCCGGGACAACAGCAAGAACAC CCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACA CAGCCGTGTACTATTGCGCGCGTGGCGATTACTACCTGC TGGGCGTCGACAGCCAGTACTTTGATTATTGGGGCCAGG GCACCCTGGTCACCGTTAGCTCAGCTAGCACCAAGGGCC CCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCA GCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGAC TACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGA GCCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCTG CAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACA GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGC AACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAA GAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACAT GCCCCCCCTGCCCGGCGCCAGAGCTGCTGGGCGGACCCT CCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGA TGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTGG ACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGG TACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAA GCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGG TGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACG GCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTG CCAGCCCCCATCGAAAAGACCATCAGCAAGGCCAAGGG CCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCCTC CCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCT GTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGG AGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAG ACCACCCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTC CTGTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCA GCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGG CCCTGCACAACCACTACACCCAGAAGAGCCTGAGCTTAA GCCCCGGCAAG
NOV3522 LC		
SEQ ID NO:276 (Combined)	LCDR1	RASQSISSYLN
SEQ ID NO:277 (Combined)	LCDR2	AASSLQS
SEQ ID NO:278 (Combined)	LCDR3	QQSYSTPLT

SEQ ID NO:279 (Kabat)	LCDR1	RASQSISSYLN
SEQ ID NO:280 (Kabat)	LCDR2	AASSLQS
SEQ ID NO:281 (Kabat)	LCDR3	QQSYSTPLT
SEQ ID NO:282 (Chothia)	LCDR1	SQSISSY
SEQ ID NO:283 (Chothia)	LCDR2	AAS
SEQ ID NO:284 (Chothia)	LCDR3	SYSTPL
SEQ ID NO:285 (IMGT)	LCDR1	QSISSY
SEQ ID NO:286 (IMGT)	LCDR2	AAS
SEQ ID NO:287 (IMGT)	LCDR3	QQSYSTPLT
SEQ ID NO:288	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIK
SEQ ID NO:289	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAA
SEQ ID NO:290	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
SEQ ID NO:291	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCA TCTTCCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV2353 HC		
SEQ ID NO:292 (Combined)	HCDR1	GFTFSSYAMS

SEQ ID NO:293 (Combined)	HCDR2	AISGSGGSTYYADSVKG
SEQ ID NO:294 (Combined)	HCDR3	EAWAEEAFDY
SEQ ID NO:295 (Kabat)	HCDR1	SYAMS
SEQ ID NO:296 (Kabat)	HCDR2	AISGSGGSTYYADSVKG
SEQ ID NO:297 (Kabat)	HCDR3	EAWAEEAFDY
SEQ ID NO:298 (Chothia)	HCDR1	GFTFSSY
SEQ ID NO:299 (Chothia)	HCDR2	SGSGGS
SEQ ID NO:300(Chothia)	HCDR3	EAWAEEAFDY
SEQ ID NO:301 (IMGT)	HCDR1	GFTFSSYA
SEQ ID NO:302 (IMGT)	HCDR2	ISGSGGST
SEQ ID NO:303 (IMGT)	HCDR3	AREAWAEEAFDY
SEQ ID NO:304	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAREAWAEEAFDYWGQGTLVTVSS
SEQ ID NO:305	DNA VH	GAGGTGCAATTGCTGGAAAGCGGCGGAGGCCTGGTGCA GCCTGGCGGATCTCTGCGCCTGTCTTGTGCCGCCTCCGG ATTCACCTTCAGCTCCTACGCCATGAGCTGGGTCCGCCA GGCCCCTGGCAAAGGCCTCGAGTGGGTGTCCGCCATCTC TGGCTCTGGCGGCAGCACCTACTACGCCGACAGCGTGAA AGGCCGCTTCACCATCAGCCGCGACAATTCGAAGAACAC CCTGTACCTTCAGATGAACAGCCTGCGGGCCGAGGACAC CGCCGTGTATTATTGCGCGCGTGAAGCTTGGGCTGAAGA AGCTTTCGACTACTGGGGTCAAGGCACCCTGGTTACAGT CAGCTCA
SEQ ID NO:306	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAREAWAEEAFDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
SEQ ID NO:307	DNA Heavy Chain	GAGGTGCAATTGCTGGAAAGCGGCGGAGGCCTGGTGCA GCCTGGCGGATCTCTGCGCCTGTCTTGTGCCGCCTCCGG ATTCACCTTCAGCTCCTACGCCATGAGCTGGGTCCGCCA GGCCCCTGGCAAAGGCCTCGAGTGGGTGTCCGCCATCTC TGGCTCTGGCGGCAGCACCTACTACGCCGACAGCGTGAA AGGCCGCTTCACCATCAGCCGCGACAATTCGAAGAACAC CCTGTACCTTCAGATGAACAGCCTGCGGGCCGAGGACAC CGCCGTGTATTATTGCGCGCGTGAAGCTTGGGCTGAAGA AGCTTTCGACTACTGGGGTCAAGGCACCCTGGTTACAGT CAGCTCAGCTAGCACCAAGGGCCCCAGCGTGTTCCCCCT GGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCG

		CCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCG TGACCGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGCG TGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGT ACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCAGCC TGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGC CCAGCAACACCAAGGTGGACAAGAGAGTGGAGCCCAAG AGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCC CCAGAGCTGCTGGGCGGACCCTCCGTGTTCCTGTTCCCC CCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCC CGAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGG ACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTG GAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCA GTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGT GCTGCACCAGGACTGGCTGAACGGCAAGGAATACAAGT GCAAGGTCTCCAACAAGGCCCTGCCAGCCCCCATCGAAA AGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCC CAGGTGTACACCCTGCCCCCCTCCCGGGAGGAGATGACC AAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTC TACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGG CCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCT GGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCTGAC CGTGGACAAGTCCAGGTGGCAGCAGGGCAACGTGTTCA GCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACA CCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
NOV2353 LC		
SEQ ID NO:308 (Combined)	LCDR1	RASQSISSYLN
SEQ ID NO:309 (Combined)	LCDR2	AASSLQS
SEQ ID NO:310 (Combined)	LCDR3	QQSYSTPLT
SEQ ID NO:311 (Kabat)	LCDR1	RASQSISSYLN
SEQ ID NO:312 (Kabat)	LCDR2	AASSLQS
SEQ ID NO:313 (Kabat)	LCDR3	QQSYSTPLT
SEQ ID NO:314 (Chothia)	LCDR1	SQSISSY
SEQ ID NO:315 (Chothia)	LCDR2	AAS
SEQ ID NO:316 (Chothia)	LCDR3	SYSTPL
SEQ ID NO:317 (IMGT)	LCDR1	QSISSY
SEQ ID NO:318 (IMGT)	LCDR2	AAS
SEQ ID NO:319 (IMGT)	LCDR3	QQSYSTPLT
SEQ ID NO:320	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIK
SEQ ID NO:321	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT

		CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAA
SEQ ID NO:322	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
SEQ ID NO:323	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCA TCTTCCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV2772 HC		
SEQ ID NO:324 (Combined)	HCDR1	GFTFSSYAMS
SEQ ID NO:325 (Combined)	HCDR2	AISGSGGSTYYADSVKG
SEQ ID NO:326 (Combined)	HCDR3	EGDWEYYFDY
SEQ ID NO:327 (Kabat)	HCDR1	SYAMS
SEQ ID NO:328 (Kabat)	HCDR2	AISGSGGSTYYADSVKG
SEQ ID NO:329 (Kabat)	HCDR3	EGDWEYYFDY
SEQ ID NO:330 (Chothia)	HCDR1	GFTFSSY
SEQ ID NO:331 (Chothia)	HCDR2	SGSGGS
SEQ ID NO:332 (Chothia)	HCDR3	EGDWEYYFDY
SEQ ID NO:333 (IMGT)	HCDR1	GFTFSSYA
SEQ ID NO:334 (IMGT)	HCDR2	ISGSGGST
SEQ ID NO:335 (IMGT)	HCDR3	AREGDWEYYFDY
SEQ ID NO:336	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAREGDWEYYFDYWGQGTLVTVSS
SEQ ID NO:337	DNA VH	GAGGTGCAATTGCTGGAAAGCGGCGGAGGCCTGGTGCA GCCTGGCGGATCTCTGAGACTGAGCTGTGCCGCCAGCGG

		CTTCACCTTCAGCAGCTACGCCATGAGCTGGGTGCGCCA GGCCCCTGGAAAAGGACTCGAGTGGGTGTCCGCCATCTC TGGCAGCGGCGGCAGCACCTACTACGCCGATTCTGTGAA GGGCCGGTTCACCATCAGCCGGGACAACAGCAAGAACA CCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGAC ACCGCCGTGTATTATTGCGCGCGTGAAGGCGACTGGGAG TACTACTTCGACTACTGGGGCCAGGGCACCCTCGTGACC GTCAGCTCA
SEQ ID NO:338	Heavy Chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQA PGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCAREGDWEYYFDYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
SEQ ID NO:339	DNA Heavy Chain	GAGGTGCAATTGCTGGAAAGCGGCGGAGGCCTGGTGCA GCCTGGCGGATCTCTGAGACTGAGCTGTGCCGCCAGCGG CTTCACCTTCAGCAGCTACGCCATGAGCTGGGTGCGCCA GGCCCCTGGAAAAGGACTCGAGTGGGTGTCCGCCATCTC TGGCAGCGGCGGCAGCACCTACTACGCCGATTCTGTGAA GGGCCGGTTCACCATCAGCCGGGACAACAGCAAGAACA CCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGAC ACCGCCGTGTATTATTGCGCGCGTGAAGGCGACTGGGAG TACTACTTCGACTACTGGGGCCAGGGCACCCTCGTGACC GTCAGCTCAGCTAGCACCAAGGGCCCCAGCGTGTTCCCC CTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGC CGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCC CGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCTCCGG CGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCT GTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAA GCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGCCCA AGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAG CCCCAGAGCTGCTGGGCGGACCCTCCGTGTTCCTGTTCC CCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACC CCCGAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGA GGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCG TGGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGAG CAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACC GTGCTGCACCAGGACTGGCTGAACGGCAAGGAATACAA GTGCAAGGTCTCCAACAAGGCCCTGCCAGCCCCCATCGA AAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGC CCCAGGTGTACACCCTGCCCCCCTCCCGGGAGGAGATGA CCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCT TCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAC GGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGT GCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCT GACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGTGT

		TCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACT ACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
NOV2772 LC		
SEQ ID NO:340 (Combined)	LCDR1	RASQSISSYLN
SEQ ID NO:341 (Combined)	LCDR2	AASSLQS
SEQ ID NO:342 (Combined)	LCDR3	QQSYSTPLT
SEQ ID NO:343 (Kabat)	LCDR1	RASQSISSYLN
SEQ ID NO:344 (Kabat)	LCDR2	AASSLQS
SEQ ID NO:345 (Kabat)	LCDR3	QQSYSTPLT
SEQ ID NO:346 (Chothia)	LCDR1	SQSISSY
SEQ ID NO:347 (Chothia)	LCDR2	AAS
SEQ ID NO:348 (Chothia)	LCDR3	SYSTPL
SEQ ID NO:349 (IMGT)	LCDR1	QSISSY
SEQ ID NO:350 (IMGT)	LCDR2	AAS
SEQ ID NO:351 (IMGT)	LCDR3	QQSYSTPLT
SEQ ID NO:352	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIK
SEQ ID NO:353	DNA VL	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAA
SEQ ID NO:354	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
SEQ ID NO:355	DNA Light Chain	GATATCCAGATGACCCAGAGCCCTAGCAGCCTGAGCGCC AGCGTGGGCGACCGCGTGACCATTACCTGCAGAGCCAG CCAGAGCATCAGCAGCTACCTGAACTGGTACCAGCAGA AACCTGGCAAGGCGCCCAAACTATTAATCTACGCCGCCA GCAGCCTTCAGAGCGGCGTGCCAAGCCGCTTTAGCGGAT CCGGCAGCGGCACCGACTTCACCCTGACCATCAGCTCCC TTCAGCCTGAAGACTTCGCCACCTACTACTGCCAGCAGA GCTACAGCACCCCTCTGACCTTTGGCCAGGGCACCAAAG TGGAAATCAAACGTACGGTGGCCGCTCCCAGCGTGTTCA TCTTCCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG

		AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
NOV2800 HC		
SEQ ID NO:356 (Combined)	HCDR1	GQTQTSYYMH
SEQ ID NO:357 (Combined)	HCDR2	IISPSGYSTSYAQKFQG
SEQ ID NO:358 (Combined)	HCDR3	DGWGHEWSYDYFDY
SEQ ID NO:359 (Kabat)	HCDR1	SYYMH
SEQ ID NO:360 (Kabat)	HCDR2	IISPSGYSTSYAQKFQG
SEQ ID NO:361 (Kabat)	HCDR3	DGWGHEWSYDYFDY
SEQ ID NO:362 (Chothia)	HCDR1	GQTQTSY
SEQ ID NO:363 (Chothia)	HCDR2	SPSGYS
SEQ ID NO:364 (Chothia)	HCDR3	DGWGHEWSYDYFDY
SEQ ID NO:365 (IMGT)	HCDR1	GQTQTSYY
SEQ ID NO:366 (IMGT)	HCDR2	ISPSGYST
SEQ ID NO:367 (IMGT)	HCDR3	ARDGWGHEWSYDYFDY
SEQ ID NO:368	VH	QVQLVQSGAEVKKPGASVKVSCKASGQTQTSYYMHWVR QAPGQGLEWMGIISPSGYSTSYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARDGWGHEWSYDYFDYWGQG TLVTVSS
SEQ ID NO:369	DNA VH	CAGGTGCAATTGGTTCAGTCTGGCGCCGAAGTGAAGAA ACCAGGCGCCAGCGTGAAGGTGTCCTGTAAAGCCTCTGG ACAGACCCAGACCAGCTACTACATGCACTGGGTTCGACA GGCTCCAGGACAGGGACTCGAGTGGATGGGAATCATCA GCCCTAGCGGCTACAGCACCAGCTACGCCCAGAAATTCC AGGGCAGAGTGACCATGACCAGAGACACCAGCACCTCC ACCGTGTACATGGAACTGAGCAGCCTGAGAAGCGAGGA CACCGCCGTGTATTATTGCGCGCGAGATGGCTGGGGCCA CGAGTGGTCCTACGACTACTTCGATTACTGGGGCCAGGG CACCCTGGTCACAGTTAGCTCA
SEQ ID NO:370	Heavy Chain	QVQLVQSGAEVKKPGASVKVSCKASGQTQTSYYMHWVR QAPGQGLEWMGIISPSGYSTSYAQKFQGRVTMTRDTSTST VYMELSSLRSEDTAVYYCARDGWGHEWSYDYFDYWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK

SEQ ID NO:371	DNA Heavy Chain	CAGGTGCAATTGGTTCAGTCTGGCGCCGAAGTGAAGAA ACCAGGCGCCAGCGTGAAGGTGTCCTGTAAAGCCTCTGG ACAGACCCAGACCAGCTACTACATGCACTGGGTTCGACA GGCTCCAGGACAGGGACTCGAGTGGATGGGAATCATCA GCCCTAGCGGCTACAGCACCAGCTACGCCCAGAAATTCC AGGGCAGAGTGACCATGACCAGAGACACCAGCACCTCC ACCGTGTACATGGAACTGAGCAGCCTGAGAAGCGAGGA CACCGCCGTGTATTATTGCGCGCGAGATGGCTGGGGCCA CGAGTGGTCCTACGACTACTTCGATTACTGGGGCCAGGG CACCCTGGTCACAGTTAGCTCAGCTAGCACCAAGGGCCC CAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAG CGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACT ACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAG CCCTGACCTCCGGCGTGCACACCTTCCCCGCCGTGCTGC AGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACA GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGC AACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAA GAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACAT GCCCCCCCTGCCCAGCCCCAGAGCTGCTGGGCGGACCCT CCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGA TGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTGG ACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGG TACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAA GCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGG TGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACG GCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTG CCAGCCCCCATCGAAAAGACCATCAGCAAGGCCAAGGG CCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCCTC CCGGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCT GTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGG AGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAG ACCACCCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTC CTGTACAGCAAGCTGACCGTGGACAAGTCCAGGTGGCA GCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGG CCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGT CCCCCGGCAAG
NOV2800 LC		
SEQ ID NO:372 (Combined)	LCDR1	RASQYISGYLN
SEQ ID NO:373 (Combined)	LCDR2	AASSLQS
SEQ ID NO:374 (Combined)	LCDR3	QQSYSTPLT
SEQ ID NO:375 (Kabat)	LCDR1	RASQYISGYLN
SEQ ID NO:376 (Kabat)	LCDR2	AASSLQS
SEQ ID NO:377 (Kabat)	LCDR3	QQSYSTPLT
SEQ ID NO:378 (Chothia)	LCDR1	SQYISGY
SEQ ID NO:379 (Chothia)	LCDR2	AAS
SEQ ID NO:380 (Chothia)	LCDR3	SYSTPL
SEQ ID NO:381 (IMGT)	LCDR1	QYISGY

SEQ ID NO:382 (IMGT)	LCDR2	AAS
SEQ ID NO:383 (IMGT)	LCDR3	QQSYSTPLT
SEQ ID NO:384	VL	DIQMTQSPSSLSASVGDRVTITCRASQYISGYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIK
SEQ ID NO:385	DNA VL	GATATCCAGATGACCCAGAGCCCCAGCAGCCTGTCTGCC AGCGTGGGCGACAGAGTGACCATTACCTGCAGAGCCAG CCAGTACATCAGCGGCTACCTGAATTGGTACCAGCAGAA GCCCGGCAAGGCCCCCAAGCTGCTGATCTATGCCGCCAG CTCTCTCCAGAGCGGCGTGCCCAGCAGATTCAGCGGATC CGGCAGCGGCACCGACTTCACCCTGACCATCTCTAGCCT CCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGAG CTACAGCACCCCCCTGACCTTTGGCCAGGGCACCAAGGT GGAAATCAAG
SEQ ID NO:386	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQYISGYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
SEQ ID NO:387	DNA Light Chain	GATATCCAGATGACCCAGAGCCCCAGCAGCCTGTCTGCC AGCGTGGGCGACAGAGTGACCATTACCTGCAGAGCCAG CCAGTACATCAGCGGCTACCTGAATTGGTACCAGCAGAA GCCCGGCAAGGCCCCCAAGCTGCTGATCTATGCCGCCAG CTCTCTCCAGAGCGGCGTGCCCAGCAGATTCAGCGGATC CGGCAGCGGCACCGACTTCACCCTGACCATCTCTAGCCT CCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGAG CTACAGCACCCCCCTGACCTTTGGCCAGGGCACCAAGGT GGAAATCAAGCGTACGGTGGCCGCTCCCAGCGTGTTCAT CTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCG CCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG AGCGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAG CAAGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCT GAGCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACAGGGGCGAGTGC
ATG.B.E211 HC		
SEQ ID NO:388 (Combined)	HCDR1	GYTFTTYGMS
SEQ ID NO:389 (Combined)	HCDR2	WINTFSGVPTYADDFKG
SEQ ID NO:390 (Combined)	HCDR3	IYDYDETDAMDY
SEQ ID NO:391 (Kabat)	HCDR1	TYGMS
SEQ ID NO:392 (Kabat)	HCDR2	WINTFSGVPTYADDFKG
SEQ ID NO:393 (Kabat)	HCDR3	IYDYDETDAMDY
SEQ ID NO:394 (Chothia)	HCDR1	GYTFTTY
SEQ ID NO:395 (Chothia)	HCDR2	NTFSGV

SEQ ID NO:396 (Chothia)	HCDR3	IYDYDETDAMDY
SEQ ID NO:397 (IMGT)	HCDR1	GYTFTTYG
SEQ ID NO:398 (IMGT)	HCDR2	INTFSGVP
SEQ ID NO:399 (IMGT)	HCDR3	ARIYDYDETDAMDY
SEQ ID NO:400	VH	EIQLVQSGAEVKKPGASVKVSCKASGYTFTTYGMSWVRQ APGQGLEWMGWINTFSGVPTYADDFKGRFTFTLDTSTSTA YLELSSLRSEDTAVYFCARIYDYDETDAMDYWGQGTLVTV SS
SEQ ID NO:401	DNA VH	GAGATCCAGCTCGTACAATCCGGTGCAGAGGTTAAGAA ACCAGGTGCGTCTGTGAAAGTCTCTTGTAAGGCATCTGG CTACACGTTCACAACCTACGGCATGAGCTGGGTTAGACA AGCACCGGGACAAGGGCTGGAATGGATGGGCTGGATTA ATACATTTAGCGGGGTACCAACCTATGCTGATGACTTCA AGGGAAGATTTACATTTACCCTCGACACCTCCACCAGTA CGGCTTATCTTGAATTGTCCTCACTCCGATCTGAGGATAC AGCCGTGTACTTCTGCGCCCGGATTTATGACTACGACGA GACCGACGCGATGGACTACTGGGGTCAGGGCACCTTGGT AACCGTTAGCTCA
SEQ ID NO:402	Heavy Chain	EIQLVQSGAEVKKPGASVKVSCKASGYTFTTYGMSWVRQ APGQGLEWMGWINTFSGVPTYADDFKGRFTFTLDTSTSTA YLELSSLRSEDTAVYFCARIYDYDETDAMDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY ICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK
SEQ ID NO:403	DNA Heavy Chain	GAGATCCAGCTCGTACAATCCGGTGCAGAGGTTAAGAA ACCAGGTGCGTCTGTGAAAGTCTCTTGTAAGGCATCTGG CTACACGTTCACAACCTACGGCATGAGCTGGGTTAGACA AGCACCGGGACAAGGGCTGGAATGGATGGGCTGGATTA ATACATTTAGCGGGGTACCAACCTATGCTGATGACTTCA AGGGAAGATTTACATTTACCCTCGACACCTCCACCAGTA CGGCTTATCTTGAATTGTCCTCACTCCGATCTGAGGATAC AGCCGTGTACTTCTGCGCCCGGATTTATGACTACGACGA GACCGACGCGATGGACTACTGGGGTCAGGGCACCTTGGT AACCGTTAGCTCAGCTAGCACCAAGGGCCCCAGCGTGTT CCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCA CAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCG AGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCT CCGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCG GCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCA GCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACC ACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAG CCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGC CCAGCCCCAGAGCTGCTGGGCGGACCCTCCGTGTTCCTG TTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGG ACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGCCAC GAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGG

		CGTGGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGG AGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGA CCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAATAC AAGTGCAAGGTCTCCAACAAGGCCCTGCCAGCCCCCATC GAAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGA GCCCCAGGTGTACACCCTGCCCCCCTCCCGGGAGGAGAT GACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGG CTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA CGGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAG TGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGC TGACCGTGGACAAGTCCAGGTGGCAGCAGGGCAACGTG TTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCAC TACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
ATG.B.E211 LC		
SEQ ID NO:404 (Combined)	LCDR1	RASGNIHNFLA
SEQ ID NO:405 (Combined)	LCDR2	NAKTLAD
SEQ ID NO:406 (Combined)	LCDR3	QLFWSTPWT
SEQ ID NO:407 (Kabat)	LCDR1	RASGNIHNFLA
SEQ ID NO:408 (Kabat)	LCDR2	NAKTLAD
SEQ ID NO:409 (Kabat)	LCDR3	QLFWSTPWT
SEQ ID NO:410(Chothia)	LCDR1	SGNIHNF
SEQ ID NO:411 (Chothia)	LCDR2	NAK
SEQ ID NO:412 (Chothia)	LCDR3	FWSTPW
SEQ ID NO:413 (IMGT)	LCDR1	GNIHNF
SEQ ID NO:414 (IMGT)	LCDR2	NAK
SEQ ID NO:415 (IMGT)	LCDR3	QLFWSTPWT
SEQ ID NO:416	VL	DIQMTQSPSSLSASVGDRVTITCRASGNIHNFLAWYQQKPG KSPKLLVYNAKTLADGVPSRFSGSGSGTDYTLTISSLQPEDF ATYYCQLFWSTPWTFGQGTKVEIK
SEQ ID NO:417	DNA VL	GACATCCAAATGACACAGAGCCCAAGTTCATTGTCAGCA TCTGTTGGCGACAGAGTGACTATAACTTGTCGCGCCAGC GGTAATATCCACAATTTTCTTGCTTGGTATCAGCAAAAA CCGGGAAAGTCACCAAAGCTGCTGGTTTACAATGCTAAA ACACTCGCAGACGGAGTGCCCTCCCGCTTCTCTGGTTCA GGTAGTGGCACCGATTATACATTGACAATCTCTAGTCTG CAGCCCGAGGACTTCGCTACTTACTATTGTCAACTCTTCT GGTCTACACCCTGGACGTTTGGTCAGGGAACGAAGGTTG AAATAAAG
SEQ ID NO:418	Light Chain	DIQMTQSPSSLSASVGDRVTITCRASGNIHNFLAWYQQKPG KSPKLLVYNAKTLADGVPSRFSGSGSGTDYTLTISSLQPEDF ATYYCQLFWSTPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

SEQ ID NO:419	DNA Light Chain	GACATCCAAATGACACAGAGCCCAAGTTCATTGTCAGCA TCTGTTGGCGACAGAGTGACTATAACTTGTCGCGCCAGC GGTAATATCCACAATTTTCTTGCTTGGTATCAGCAAAAA CCGGGAAAGTCACCAAAGCTGCTGGTTTACAATGCTAAA ACACTCGCAGACGGAGTGCCCTCCCGCTTCTCTGGTTCA GGTAGTGGCACCGATTATACATTGACAATCTCTAGTCTG CAGCCCGAGGACTTCGCTACTTACTATTGTCAACTCTTCT GGTCTACACCCTGGACGTTTGGTCAGGGAACGAAGGTTG AAATAAAGCGTACGGTGGCCGCTCCCAGCGTGTTCATCT TCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCC AGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGGAG GCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAG CGGCAACAGCCAGGAGAGCGTCACCGAGCAGGACAGCA AGGACTCCACCTACAGCCTGAGCAGCACCCTGACCCTGA GCAAGGCCGACTACGAGAAGCATAAGGTGTACGCCTGC GAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAA GAGCTTCAACAGGGGCGAGTGC

[00171] Other antibodies of the present disclosure include those where the amino acids or nucleic acids encoding the amino acids have been mutated; yet have at least 60, 70, 80, 90 or 95 percent identity to the sequences described in Table 2. In some aspects, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the variable regions when compared with the variable regions depicted in the sequence described in Table 2, while retaining substantially the same therapeutic activity;

[00172] Since these antibodies can bind to a complex of HLA-HBV peptides, the VH, VL, full length light chain, and full length heavy chain sequences (amino acid sequences and the nucleotide sequences encoding the amino acid sequences) can be "mixed and matched" to create other HLA-HBV peptide-binding antibodies. Such "mixed and matched" anti-HLA-HBV peptide antibodies can be tested using the binding assays known in the art (*e.g.*, ELISAs, and other assays described in the Example section). When these chains are mixed and matched, a VH sequence from a particular VH/VL pairing should be replaced with a structurally similar VH sequence. Likewise a full length heavy chain sequence from a particular full length heavy chain/full length light chain pairing should be replaced with a structurally similar full length heavy chain sequence. Likewise, a VL sequence from a particular VH/VL pairing should be replaced with a structurally similar VL sequence. Likewise, a full length light chain sequence from a particular full length heavy chain/full length light chain pairing should be replaced with a structurally similar full length light chain sequence. Accordingly, in one aspect, the disclosure provides for an isolated monoclonal antibody or antigen binding region thereof having: a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:16, 48, 80, 112, 144, 176, 208, 240, 272, 304, 336, 368, and 400 (Table 2); and a light chain variable region comprising an amino acid sequence selected from the group

consisting of SEQ ID NO:32, 64, 96, 128, 160, 192, 224, 256, 288, 320, 352, 384 and 416 (Table 2); wherein the antibody specifically binds to HLA-HBV peptides.

[00173] In another aspect, the disclosure provides (i) an isolated monoclonal antibody having: a full length heavy chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NOs: 18, 50, 82, 114, 146, 178, 210, 242, 274, 306, 338, 370 and 402 (Table 2) and a full length light chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NOs:34, 66, 98, 130, 162, 194, 226, 258, 290, 322, 354, 386 and 418 (Table 2) or (ii) a functional protein comprising an antigen binding portion thereof.

[00174] In another aspect, the present disclosure provides anti-HLA-HBV peptide antibodies or antigen binding fragments thereof that comprise the heavy chain and light chain CDR1s, CDR2s and CDR3s as described in Table 2, or combinations thereof. The amino acid sequences of the VH CDR1s of the antibodies are shown in SEQ ID NOs 7, 39, 71, 103, 135, 167, 199, 231, 263, 295, 327, 359 and 391. The amino acid sequences of the VH CDR2s of the antibodies and are shown in SEQ ID NOs: 8, 40, 72, 104, 136, 168, 200, 232, 264, 296, 328, 360 and 392. The amino acid sequences of the VH CDR3s of the antibodies are shown in SEQ ID NOs: 9, 41, 73, 105, 137, 169, 201, 233, 265, 297, 329, 361 and 393 . The amino acid sequences of the VL CDR1s of the antibodies are shown in SEQ ID NOs: 23, 55, 87, 119, 151, 183, 215, 247, 279, 311, 343, 375 and 407. The amino acid sequences of the VL CDR2s of the antibodies are shown in SEQ ID NOs 24, 56, 88, 120, 152, 184, 216, 248, 280, 312, 344, 376 and 408. The amino acid sequences of the VL CDR3s of the antibodies are shown in SEQ ID NOs: 25, 57, 89, 121, 153, 185, 217, 249, 281, 313, 345, 377 and 409.

[00175] Given that each of these antibodies can bind to a complex of HLA-HBV peptides and that antigen-binding specificity is provided primarily by the CDR1, 2 and 3 regions, the VH CDR1, 2 and 3 sequences and VL CDR1, 2 and 3 sequences can be "mixed and matched" (i.e., CDRs from different antibodies can be mixed and matched, although each antibody must contain a VH CDR1, 2 and 3 and a VL CDR1, 2 and 3) to create other anti-HLA-HBV peptide antibodies. Such "mixed and matched" anti-HLA-HBV peptide-binding antibodies can be tested using the binding assays known in the art and those described in the Examples (*e.g.*, ELISAs). When VH CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VH sequence should be replaced with a structurally similar CDR sequence(s). Likewise, when VL CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VL sequence should be replaced with a structurally similar CDR sequence(s). It will be readily apparent to the ordinarily skilled artisan that novel VH and VL sequences can be created by substituting one or more VH and/or VL CDR sequences with structurally similar sequences from the CDR sequences shown herein for antibodies of the present disclosure.

[00176] Accordingly, the present disclosure provides an isolated monoclonal antibody or antigen binding fragment thereof comprising a heavy chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 39, 71, 103, 135, 167, 199, 231, 263, 295, 327, 359 and 391; a heavy chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 40, 72, 104, 136, 168, 200, 232, 264, 296, 328, 360 and 392; a heavy chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 9, 41, 73, 105, 137, 169, 201, 233, 265, 297, 329, 361 and 393; a light chain CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 23, 55, 87, 119, 151, 183, 215, 247, 279, 311, 343, 375 and 407; a light chain CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 56, 88, 120, 152, 184, 216, 248, 280, 312, 344, 376 and 408; and a light chain CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 25, 57, 89, 121, 153, 185, 217, 249, 281, 313, 345, 377 and 409; wherein the antibody specifically binds to a complex of HLA-HBV peptides.

[00177] In certain aspects, an antibody that specifically binds to a complex of HLA-HBV peptides is an antibody or antigen binding fragment thereof that is described in Table 2.

1. Identification of Antibodies

[00178] The present disclosure provides antibodies and antibody fragments (*e.g.*, antigen binding fragments) that bind to a complex of HLA-HBV peptides. In certain aspects the antibodies and antigen binding fragments thereof can bind to the same HBV epitope within all four HBV serotypes.

[00179] The present disclosure also provides antibodies and antigen binding fragments thereof that bind to the same epitope as do the anti-HLA-HBV peptide antibodies described in Table 2. Additional antibodies and antigen binding fragments thereof can therefore be identified based on their ability to cross-compete (*e.g.*, to competitively inhibit the binding of, in a statistically significant manner) with other antibodies in binding assays. The ability of a test antibody to inhibit the binding of antibodies and antigen binding fragments thereof of the present disclosure to a complex of HLA-HBV peptides demonstrates that the test antibody can compete with that antibody or antigen binding fragments thereof, for binding to a complex of HLA-HBV peptides; such an antibody may, according to non-limiting theory, bind to the same or a related (*e.g.*, a structurally similar or spatially proximal) epitope as the antibody or antibody fragment (*e.g.*, antigen binding fragments) with which it competes. In a certain aspect, the antibody that binds to the same epitope as the antibodies or antigen binding fragments thereof of the present disclosure is a human or humanized monoclonal antibody. Such human or humanized monoclonal antibodies can be prepared and isolated as described herein.

2. Further Alteration of the Framework of Fc Region

[00180] The present disclosure disclosed specific anti-HLA-HBV peptide antibodies. These antibodies comprise modified antibodies or antigen binding fragments thereof that further comprise modifications to framework residues within VH and/or VL, *e.g.* to improve the properties of the antibody. Typically, such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "back-mutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived. To return the framework region sequences to their germline configuration, the somatic mutations can be "back-mutated" to the germline sequence by, for example, site-directed mutagenesis. Such "back-mutated" antibodies are also intended to be encompassed.

[00181] Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T-cell epitopes to thereby reduce the potential immunogenicity of the antibody. This approach is also referred to as "deimmunization" and is described in further detail in U.S. Patent Publication No. 2003/0153043 by Carr et al.

[00182] In addition, or alternative to modifications made within the framework or CDR regions, antibodies can be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody can be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Each of these aspects is described in further detail below.

[00183] In one aspect, the hinge region of CH1 is modified such that the number of cysteine residues in the hinge region is altered, *e.g.*, increased or decreased. This approach is described further in U.S. Patent No. 5,677,425 by Bodmer *et al.* The number of cysteine residues in the hinge region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

[00184] In another aspect, the Fc hinge region of an antibody is mutated to decrease the biological half-life of the antibody. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired Staphylococcyl protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Patent No. 6,165,745 by Ward *et al.*

[00185] In yet other aspects, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For

example, one or more amino acids can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in, *e.g.*, U.S. Patent Nos. 5,624,821 and 5,648,260, both by Winter *et al.*

[00186] In another aspect, one or more amino acids selected from amino acid residues can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in, *e.g.*, U.S. Patent Nos. 6,194,551 by Idusogie *et al.*

[00187] In another aspect, one or more amino acid residues are altered to thereby alter the ability of the antibody to fix complement. This approach is described in, *e.g.*, the PCT Publication WO 94/29351 by Bodmer *et al.* In a specific aspect, one or more amino acids of an antibody or antigen binding fragment thereof of the present disclosure are replaced by one or more allotypic amino acid residues, for the IgG1 subclass and the kappa isotype. Allotypic amino acid residues also include, but are not limited to, the constant region of the heavy chain of the IgG1, IgG2, and IgG3 subclasses as well as the constant region of the light chain of the kappa isotype as described by Jefferis *et al.*, MAbs. 1:332-338 (2009).

[00188] In yet another aspect, the Fc region is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fcγ receptor by modifying one or more amino acids. This approach is described in, *e.g.*, the PCT Publication WO 00/42072 by Presta. Moreover, the binding sites on human IgG1 for FcγRl, FcγRII, FcγRIII and FcRn have been mapped and variants with improved binding have been described (see Shields *et al.*, J. Biol. Chem. 276:6591-6604, 2001).

[00189] In still another aspect, the glycosylation of an antibody is modified. For example, an aglycosylated antibody can be made (i.e., the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for "antigen." Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in, *e.g.*, U.S. Patent Nos. 5,714,350 and 6,350,861 by Co *et al.*

[00190] Additionally, or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation

machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies to thereby produce an antibody with altered glycosylation. For example, EP 1,176,195 by Hang *et al.* describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation. PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lecl3 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields et al., (2002) J. Biol. Chem. 277:26733-26740). PCT Publication WO 99/54342 by Umana et al. describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (*e.g.*, beta (1,4)-N acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana et al., Nat. Biotech. 17:176-180, 1999).

[00191] In another aspect, the antibody is modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Patent No. 6,277,375 to Ward. Alternatively, to increase the biological half-life, the antibody can be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121,022 by Presta et al.

[00192] In order to minimize the ADCC activity of an antibody, specific mutations in the Fc region result in “Fc silent” antibodies that have minimal interaction with effector cells. In general, the "IgG Fc region" is used to define the C-terminal region of an immunoglobulin heavy chain, including native sequence Fc region and variant Fc regions. The human IgG heavy chain Fc region is generally defined as comprising the amino acid residue from position C226 or from P230 to the carboxyl-terminus of the IgG antibody. The numbering of residues in the Fc region is that of the EU index of Kabat. The C- terminal lysine (residue K447) of the Fc region may be removed, for example, during production or purification of the antibody.

[00193] Silenced effector functions can be obtained by mutation in the Fc region of the antibodies and have been described in the art: LALA and N297A (Strohl, W., 2009, Curr. Opin. Biotechnol. vol. 20(6):685-691); and D265A (Baudino et al., 2008, J. Immunol. 181: 6664- 69) see also Heusser et al., WO2012065950. Examples of silent Fc lgG1 antibodies are the LALA mutant comprising L234A and L235A mutation in the lgG1 Fc amino acid sequence. Another example of a silent lgG1 antibody is the DAPA (D265A, P329A) mutation (US 6,737,056). Another silent lgG1 antibody comprises the N297A mutation, which results in aglycosylated/non-glycosylated antibodies.

[00194] Fc silent antibodies result in no or low ADCC activity, meaning that an Fc silent antibody exhibits an ADCC activity that is below 50% specific cell lysis (low ADCC activity), or that is below 1% specific cell lysis (no ADCC activity).

3. Production of the Antibodies

[00195] Anti-HLA-HBV peptide antibodies and antigen binding fragments thereof can be produced by any means known in the art, including but not limited to, recombinant expression, chemical synthesis, and enzymatic digestion of antibody tetramers, whereas full-length monoclonal antibodies can be obtained by, *e.g.*, hybridoma or recombinant production. Recombinant expression can be from any appropriate host cells known in the art, for example, mammalian host cells, bacterial host cells, yeast host cells, insect host cells, etc.

[00196] The disclosure further provides polynucleotides encoding the antibodies described herein, *e.g.*, polynucleotides encoding heavy or light chain variable regions or segments comprising the complementarity determining regions as described herein. In some aspects, the polynucleotide encoding the heavy chain variable regions has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide selected from the group consisting of SEQ ID NOs: 17, 49, 81, 113, 145, 177, 209, 241, 273, 305, 337, 369, and 401 (Table 2). In some aspects, the polynucleotide encoding the light chain variable regions has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide selected from the group consisting of SEQ ID NOs: 33, 65, 97, 129, 161, 193, 225, 257, 289, 321, 353, 385 and 417 (Table 2).

[00197] In some aspects, the polynucleotide encoding the heavy chain has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide of SEQ ID NO: 19, 51, 83, 115, 147, 179, 211, 243, 275, 307, 339, 371 or 403 (Table 2). In some aspects, the polynucleotide encoding the light chain has at least 85%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% nucleic acid sequence identity with a polynucleotide of SEQ ID NO: 35, 67, 99, 131, 163, 195, 227, 259, 291, 323, 355, 387 or 419,

[00198] The polynucleotides of the present disclosure can encode only the variable region sequence of an anti-HLA-HBV peptide antibody. They can also encode both a variable region and a constant region of the antibody. Some of the polynucleotide sequences encode a polypeptide that comprises variable regions of both the heavy chain and the light chain of an exemplified anti-HLA-HBV peptide antibody. Some other polynucleotides encode two polypeptide segments that respectively are substantially identical to the variable regions of the heavy chain and the light chain of one of the antibodies.

[00199] The polynucleotide sequences can be produced by de novo solid-phase DNA synthesis or by PCR mutagenesis of an existing sequence encoding an anti-HLA-HBV peptide antibody or antigen binding fragments thereof. Direct chemical synthesis of nucleic acids can be accomplished by methods known in the art, such as the phosphotriester method of Narang *et al.*, Meth. Enzymol. 68:90, 1979; the phosphodiester method of Brown *et al.*, Meth. Enzymol. 68:109, 1979; the diethylphosphoramidite method of Beaucage *et al.*, Tetra. Lett., 22:1859, 1981; and the solid support

method of U.S. Patent No. 4,458,066. Introducing mutations to a polynucleotide sequence by PCR can be performed as described in, *e.g.*, PCR Technology: Principles and Applications for DNA Amplification, H.A. Erlich (Ed.), Freeman Press, NY, NY, 1992; PCR Protocols: A Guide to Methods and Applications, Innis *et al.* (Ed.), Academic Press, San Diego, CA, 1990; Mattila *et al.*, Nucleic Acids Res. 19:967, 1991; and Eckert *et al.*, PCR Methods and Applications 1:17, 1991.

[00200] Also provided in the present disclosure are expression vectors and host cells for producing the anti-HLA-HBV peptide antibodies described above. Various expression vectors can be employed to express the polynucleotides encoding the anti-HLA-HBV peptide antibody chains or antigen binding fragments thereof. Both viral-based and nonviral expression vectors can be used to produce the antibodies in a mammalian host cell. Nonviral vectors and systems include plasmids, episomal vectors, typically with an expression cassette for expressing a protein or RNA, and human artificial chromosomes (see, *e.g.*, Harrington *et al.*, Nat Gen. 15:345, 1997). For example, nonviral vectors useful for expression of the anti-HLA-HBV peptide antibody polynucleotides and polypeptides in mammalian (*e.g.*, human) cells include pThioHis A, B & C, pcDNA3.1/His, pEBVHis A, B & C (Invitrogen, San Diego, CA), MPSV vectors, and numerous other vectors known in the art for expressing other proteins. Useful viral vectors include vectors based on retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, vectors based on SV40, papilloma virus, HBP Epstein Barr virus, vaccinia virus vectors and Semliki Forest virus (SFV). See, Brent *et al.*, supra; Smith, Annu. Rev. Microbiol. 49:807, 1995; and Rosenfeld *et al.*, Cell 68:143, 1992.

[00201] The choice of expression vector depends on the intended host cells in which the vector is to be expressed. Typically, the expression vectors contain a promoter and other regulatory sequences (*e.g.*, enhancers) that are operably linked to the polynucleotides encoding an anti-HLA-HBV peptide antibody chain or antigen binding fragment thereof. In some aspects, an inducible promoter is employed to prevent expression of inserted sequences except under inducing conditions. Inducible promoters include, *e.g.*, arabinose, lacZ, metallothionein promoter or a heat shock promoter. Cultures of transformed organisms can be expanded under non-inducing conditions without biasing the population for coding sequences whose expression products are better tolerated by the host cells. In addition to promoters, other regulatory elements may also be required or desired for efficient expression of an anti-HLA-HBV peptide antibody chain or antigen binding fragments thereof. These elements typically include an ATG initiation codon and adjacent ribosome binding site or other sequences. In addition, the efficiency of expression may be enhanced by the inclusion of enhancers appropriate to the cell system in use (see, *e.g.*, Scharf *et al.*, Results Probl. Cell Differ. 20:125, 1994; and Bittner *et al.*, Meth. Enzymol., 153:516, 1987). For example, the SV40 enhancer or CMV enhancer may be used to increase expression in mammalian host cells.

[00202] The expression vectors may also provide a secretion signal sequence position to form a fusion protein with polypeptides encoded by inserted anti-HLA-HBV peptide antibody sequences.

More often, the inserted anti-HLA-HBV peptide antibody sequences are linked to a signal sequences before inclusion in the vector. Vectors to be used to receive sequences encoding anti-HLA-HBV peptide antibody light and heavy chain variable domains sometimes also encode constant regions or parts thereof. Such vectors allow expression of the variable regions as fusion proteins with the constant regions thereby leading to production of intact antibodies or fragments thereof. Typically, such constant regions are human.

[00203] The host cells for harboring and expressing the anti-HLA-HBV peptide antibody chains can be either prokaryotic or eukaryotic. E. coli is one prokaryotic host useful for cloning and expressing the polynucleotides of the present disclosure. Other microbial hosts suitable for use include bacilli, such as Bacillus subtilis, and other enterobacteriaceae, such as Salmonella, Serratia, and various Pseudomonas species. In these prokaryotic hosts, one can also make expression vectors, which typically contain expression control sequences compatible with the host cell (*e.g.*, an origin of replication). In addition, any number of a variety of well-known promoters will be present, such as the lactose promoter system, a tryptophan (trp) promoter system, a beta-lactamase promoter system, or a promoter system from phage lambda. The promoters typically control expression, optionally with an operator sequence, and have ribosome binding site sequences and the like, for initiating and completing transcription and translation. Other microbes, such as yeast, can also be employed to express anti-HLA-HBV peptide antibodies. Insect cells in combination with baculovirus vectors can also be used.

[00204] In other aspects, mammalian host cells are used to express and produce the anti-HLA-HBV peptide antibodies of the present disclosure. For example, they can be either a hybridoma cell line expressing endogenous immunoglobulin genes (*e.g.*, the myeloma hybridoma clones) or a mammalian cell line harboring an exogenous expression vector. These include any normal mortal or normal or abnormal immortal animal or human cell. For example, a number of suitable host cell lines capable of secreting intact immunoglobulins have been developed, including the CHO cell lines, various COS cell lines, HeLa cells, myeloma cell lines, transformed B-cells and hybridomas. The use of mammalian tissue cell culture to express polypeptides is discussed generally in, *e.g.*, Winnacker, From Genes to Clones, VCH Publishers, N.Y., N.Y., 1987. Expression vectors for mammalian host cells can include expression control sequences, such as an origin of replication, a promoter, and an enhancer (see, *e.g.*, Queen *et al.*, Immunol. Rev. 89:49-68, 1986), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. These expression vectors usually contain promoters derived from mammalian genes or from mammalian viruses. Suitable promoters may be constitutive, cell type-specific, stage-specific, and/or modulatable or regulatable. Useful promoters include, but are not limited to, the metallothionein promoter, the constitutive adenovirus major late promoter, the dexamethasone-inducible MMTV promoter, the SV40 promoter, the MRP polIII promoter, the

constitutive MPSV promoter, the tetracycline-inducible CMV promoter (such as the human immediate-early CMV promoter), the constitutive CMV promoter, and promoter-enhancer combinations known in the art.

[00205] Methods for introducing expression vectors containing the polynucleotide sequences of interest vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment or electroporation may be used for other cellular hosts (see generally Sambrook *et al.*, supra). Other methods include, *e.g.*, electroporation, calcium phosphate treatment, liposome-mediated transformation, injection and microinjection, ballistic methods, virosomes, immunoliposomes, polycation:nucleic acid conjugates, naked DNA, artificial virions, fusion to the herpes virus structural protein VP22 (Elliot and O'Hare, Cell 88:223, 1997), agent-enhanced uptake of DNA, and ex vivo transduction. For long-term, high-yield production of recombinant proteins, stable expression will often be desired. For example, cell lines which stably express anti-HLA-HBV peptide antibody chains or antigen binding fragments thereof, can be prepared using expression vectors which contain viral origins of replication or endogenous expression elements and a selectable marker gene. Following introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth of cells which successfully express the introduced sequences in selective media. Resistant, stably transfected cells can be proliferated using tissue culture techniques appropriate to the cell type.

Therapeutic and Diagnostic Uses

[00206] The antibodies, antibody fragments (*e.g.*, antigen binding fragments) of the present disclosure are useful in a variety of applications including, but not limited to, treating or preventing a hepatitis B viral infection or disease. In certain aspects, the antibodies, antibody fragments (*e.g.*, antigen binding fragments) are useful for reducing hepatitis B infection and/or the prevention or treatment of liver cirrhosis or liver cancer. The methods of use can be in vitro, ex vivo, or in vivo methods.

[00207] In one aspect, the antibodies or antigen binding fragments thereof, are useful for detecting the presence of HBV in a biological sample. The term "detecting" as used herein encompasses quantitative or qualitative detection. In certain aspects, a biological sample comprises a cell or tissue. In certain aspects, such tissues include normal and/or cancerous tissues that express HBV at higher levels relative to other tissues.

[00208] In one aspect, the present disclosure provides a method of detecting the presence of HBV in a biological sample. In certain aspects, the method comprises contacting the biological sample with an anti-HLA-HBV peptide antibody under conditions permissive for binding of the

antibody to the antigen, and detecting whether a complex is formed between the antibody and the antigen. The biological sample can include, without limitation, urine or blood samples.

[00209] Also included is a method of diagnosing a disorder associated with expression of HBV. In certain aspects, the method comprises contacting a test cell with an anti-HLA-HBV peptide antibody; determining the level of expression (either quantitatively or qualitatively) of HBV peptide in the test cell by detecting binding of the antibody to a complex of HLA-HBV peptides; and comparing the level of expression of HBV peptide in the test cell with the level of expression of HBV peptide in a control cell (*e.g.*, a normal cell of the same tissue origin as the test cell or a non-virus infected cell), wherein a higher level of presence of HBV peptide in the test cell as compared to the control cell indicates the presence of a disorder associated with HBV infection. In certain aspects, the test cell is obtained from an individual suspected of having a HBV infection.

[00210] In certain aspects, a method of diagnosis or detection, such as those described above, comprises detecting binding of an anti-HLA-HBV peptide antibody to a hepatitis B virus infected cell. An exemplary assay for detecting binding of an anti-HLA-HBV peptide antibody to a hepatitis B infected cell is a "FACS" assay.

[00211] Certain other methods can be used to detect binding of anti-HLA-HBV peptide antibodies. Such methods include, but are not limited to, antigen-binding assays that are well known in the art, such as Western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, fluorescent immunoassays, protein A immunoassays, and immunohistochemistry (IHC).

[00212] In certain aspects, the anti-HLA-HBV peptide antibodies are labeled. Labels include, but are not limited to, labels or moieties that are detected directly (such as fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels), as well as moieties, such as enzymes or ligands, that are detected indirectly, *e.g.*, through an enzymatic reaction or molecular interaction.

[00213] In certain aspects, the anti-HLA-HBV peptide antibodies are immobilized on an insoluble matrix. Immobilization entails separating the anti-HLA-HBV peptide antibody from any proteins that remain free in solution. This conventionally is accomplished by either insolubilizing the anti-HLA-HBV peptide antibody before the assay procedure, as by adsorption to a water-insoluble matrix or surface (Bennich et al, U.S. Patent No. 3,720,760), or by covalent coupling (for example, using glutaraldehyde cross-linking), or by insolubilizing the anti-HLA-HBV peptide antibody after formation of a complex between the anti-HLA-HBV peptide antibody and a complex HLA-HBV peptide, *e.g.*, by immunoprecipitation.

[00214] Any of the above aspects of diagnosis or detection can be carried out using an anti-HLA-HBV peptide antibody of the present disclosure in place of or in addition to another anti-HBV antibody.

[00215] In one aspect, the disclosure provides for a method of treating, reducing the likelihood of or ameliorating a disease comprising administering the antibodies, antibody fragments (*e.g.*, antigen binding fragments) disclosed herein, to a patient, thereby treating, reducing the likelihood of or ameliorating the disease. In certain aspects, the disease treated with the antibodies or antigen binding fragments thereof disclosed herein, is a hepatitis B viral infection. Examples of HBV associated diseases which can be treated and/or prevented include, but are not limited to: liver failure, liver cirrhosis, and hepatocellular carcinoma. In certain aspects, the infection or HBV associated disease is characterized by HBV infected cells to which the anti-HLA-HBV peptide antibody or antigen binding fragments thereof, can specifically bind.

[00216] The present disclosure provides for methods of treating, reducing the likelihood of or ameliorating hepatitis B viral infection and liver failure, liver cirrhosis, and/or hepatocellular carcinoma associated with HBV infection comprising administering to a subject in need thereof a therapeutically effective amount of the antibodies or antigen binding fragments thereof. In certain aspects, the subject is a human.

[00217] In certain aspects, the method of reducing hepatitis B viral infection comprises administering to a subject a therapeutically effective amount of antibodies or antibody fragments (*e.g.*, antigen binding fragments). In certain aspects, the subject is a human. In certain aspects, the subject is immunosuppressed, immunocompromised or has reduced immune function. For immunosuppresed subjects, the amount of immunosuppression can be increased or decreased due to the therapeutic effects of the anti-HLA-HBV peptide antibodies.

[00218] For the treatment of hepatitis B viral infection, the appropriate dosage of the anti-HLA-HBV peptide antibody, or antigen binding fragments thereof, depend on various factors, such as the type of infection to be treated, the severity and course of the infection, the responsiveness of the infection, the generation of viral resistance to therapy, previous therapy, patient's clinical history, and so on. The antibody can be administered one time or over a series of treatments lasting from several days to several months, or until a cure is effected or a diminution of the infection is achieved (*e.g.*, reduction in viruria or viral damage to the liver). Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient and will vary depending on the relative potency of an individual antibody or antibody fragment (*e.g.*, antigen binding fragment). In certain aspects, dosage is from 0.01mg to 100 mg (*e.g.*, 0.01 mg, 0.05mg, 0.1mg, 0.5mg, 1mg, 2mg, 3mg, 4mg, 5mg, 7mg, 8mg, 9mg, 10mg, 20mg, 30mg, 40mg, 50mg, 60mg, 70mg, 80mg. 90mg or 100mg) per kg of body weight, and can be given once or more daily, weekly, monthly or yearly. In certain aspects, the antibody or antibody fragment (*e.g.*, antigen binding fragment), of the present disclosure is given once every two weeks or once every three weeks. The treating physician can estimate repetition rates for dosing based on measured half-life and concentrations of the antibody in bodily fluids or tissues.

Combination Therapy

[00219] In certain instances, the antibody or antibody fragment (*e.g.*, antigen binding fragment), of the present disclosure is combined with other therapeutic agents, such as other anti-viral agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, immunosuppressants and combinations thereof.

[00220] The term "pharmaceutical combination" as used herein refers to either a fixed combination in one dosage unit form, or non-fixed combination or a kit of parts for the combined administration where two or more therapeutic agents may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, *e.g.* synergistic effect.

[00221] The term "combination therapy" refers to the administration of two or more therapeutic agents to treat a therapeutic condition or infection described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration encompasses co-administration in multiple, or in separate containers (*e.g.*, capsules, powders, and liquids) for each active ingredient. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[00222] The combination therapy can provide "synergy" and prove "synergistic", *i.e.*, the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the individual components separately. A synergistic effect can be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect can be attained when the individual components are administered or delivered sequentially, *e.g.*, by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.*, serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

[00223] In one aspect, the present disclosure provides a method of treating hepatitis B infection by administering to a subject in need thereof an anti-HLA-HBV peptide antibody in combination with immunosuppressant therapies. Immunosuppressant therapies are most often administered in organ or bone marrow transplantation, in order to reduce the chances of graft rejection. However, immunosuppression renders the patient more susceptible to infection by bacteria or virus, such as HBV. The anti-HLA-HBV peptide antibody can reduce the chance of HBV infection and the

consequences of HBV infection resulting from the immunosuppressant therapy prior to or post administration. Examples of immunosuppressant therapy include, but are not limited to; a monophosphate dehydrogenase inhibitor, a purine synthesis inhibitor, a calcineurin inhibitor or an mTOR inhibitor. Specific examples of immunosuppressive therapeutics include but are not limited to; mycophenolate mofetil (MMF), mycophenolate sodium, azathioprine, tacrolimus, sirolimus and cyclosporine.

[00224] In another embodiment, anti-HLA-HBV peptide antibody is used in combination with a PD-1 inhibitor, e.g., as described in WO2015/026684 or WO2016/057846. In some embodiments, the PD-1 inhibitor is an anti-PD-1 antibody chosen from Nivolumab, Pembrolizumab or Pidilizumab.

[00225] In some embodiments, the anti-PD-1 antibody is Nivolumab. Alternative names for Nivolumab include MDX-1106, MDX-1106-04, ONO-4538, or BMS-936558. In some embodiments, the anti-PD-1 antibody is Nivolumab (CAS Registry Number: 946414-94-4). Nivolumab is a fully human IgG4 monoclonal antibody which specifically blocks PD1. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD1 are disclosed in US 8,008,449 and WO2006/121168. In one embodiment, the inhibitor of PD-1 is Nivolumab, and having a sequence disclosed therein (or a sequence substantially identical or similar thereto, e.g., a sequence at least 85%, 90%, 95% identical or higher to the sequence specified).

[00226] In some embodiments, the anti-PD-1 antibody is Pembrolizumab. Pembrolizumab (also referred to as Lambrolizumab, MK-3475, MK03475, SCH-900475 or KEYTRUDA™; Merck) is a humanized IgG4 monoclonal antibody that binds to PD-1. Pembrolizumab and other humanized anti-PD-1 antibodies are disclosed in Hamid, O. et al. (2013) New England Journal of Medicine 369 (2): 134–44, US 8,354,509 and WO2009/114335.

[00227] In one embodiment, the inhibitor of PD-1 is Pembrolizumab, disclosed in, e.g., US 8,354,509 and WO 2009/114335, and having a sequence disclosed therein (or a sequence substantially identical or similar thereto, e.g., a sequence at least 85%, 90%, 95% identical or higher to the sequence specified).

[00228] In some embodiments, the anti-PD-1 antibody is Pidilizumab. Pidilizumab (CT-011; Cure Tech) is a humanized IgG1k monoclonal antibody that binds to PD1. Pidilizumab and other humanized anti-PD-1 monoclonal antibodies are disclosed in WO2009/101611. Other anti-PD1 antibodies include AMP 514 (Amplimmune), among others, e.g., anti-PD1 antibodies disclosed in US 8,609,089, US 2010028330, and/or US 20120114649.

[00229] In some embodiments, the PD-1 inhibitor is an immunoadhesin (e.g., an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-Ll or PD-L2 fused to a constant region (e.g., an Fc region of an immunoglobulin sequence). In some embodiments, the PD-1 inhibitor is AMP-224 (B7-DCIg; Amplimmune; e.g., disclosed in WO2010/027827 and

WO2011/066342), is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD-1 and B7-H1.

[00230] In one embodiment, an anti-HLA-HBV peptide antibody is used in combination with an anti-PD-L1 antibody, e.g., as described in WO2016/061142. In some embodiments, the anti-PD-L1 antibody is Atezolizumab, Avelumab or Durvalumab. In some embodiments, the anti-PD-L1 antibody is Atezolizumab, disclosed in WO2010/077634. In some embodiments, the anti-PD-L1 antibody is Durvalumab, disclosed in WO2011/066389. Other anti-PD-L1 antibodies include BMS-936559 also known as MDX-1105, as disclosed in WO2007/005874 and AMP-224 also known as GSK2661380 disclosed in WO2010/027423.

[00231] In one embodiment, an anti-HLA-HBV peptide antibody is used in combination with a nucleoside viral inhibitor. Nucleosides act as chain terminators, resulting in the reduction of HBV nucleic acid replication. Nucleosides are often part of the standard of care for patients with viral infection. The anti-HLA-HBV peptide antibody in combination with nucleosides, for example, lamivudine (e.g. Epivir™), entecavir (e.g. Baraclude™) and tenofovir (e.g.Viread™) administered to patients can be beneficial in the reduction of HBV infection.

[00232] An anti-HLA-HBV peptide antibody can be used in combination with a TLR7 or TLR8 agonist to reduce HBV viral infection. Toll-like receptor (TLR) agonists act to activate immune cells, including dendritic cells, macrophages and natural killer cells. As such, anti-HLA-HBV peptide antibodies can be combined with TLR7 agonists, for example, vesatolimod (GS-9620), AL-034 and RG-7854 and administered to patients for the reduction of HBV infection. Alternatively, anti-HLA-HBV peptide antibodies can be combined with TLR8 agonists, for example, GS-9688 and administered to patients for the reduction of HBV.

[00233] In another aspect, the anti-HLA-HBV peptide antibody can be used in combination with nucleic acid polymers (NAPs). NAPs interfere with assembly and release of HBV subviral particles from infected liver cells. For example, NAPs REP2139 and REP2165 in combination therapy with anti-HLA-HBV peptide antibodies, can be beneficial in the reduction of HBV infection.

[00234] HBV replication is dependent upon viral capsid assembly and molecules that interfere with capsid assembly results in antiviral activity. In another embodiment, anti-HLA-HBV peptide antibodies can be administered in combination with capsid inhibitors, for example, AB-506, ABI-H0731, ABI-H2158, JNJ-379, BAY41-4109 and RG-7907 in the treatment of HBV infection.

[00235] In one embodiment, an anti-HLA-HBV peptide antibody is used in combination with molecules directed to retinoic acid-inducible gene 1 (RIG-I). RIG-I acts as a sensor of viral replication in the cytoplasm of mammalian cells, and is active in the innate immune response. In another embodiment, anti-HLA-HBV peptide antibodies can be administered in combination with RIG-I molecules, for example, GS9992 and SB9200.

[00236] Vaccination has reduced the infection rate of HBV in children in the US. However, in developing countries, mother to child transmission remains high. As vaccines help to stimulate the immune system, anti-HLA-HBV peptide antibodies can be administered in combination with vaccines, for example, GS-4774, JNJ-0535, ABX-203, INO-1800 and TG-1050.

Pharmaceutical Compositions

[00237] To prepare pharmaceutical or sterile compositions including anti-HLA-HBV peptide antibodies, the antibodies of the present disclosure are mixed with a pharmaceutically acceptable carrier or excipient. The compositions can additionally contain one or more other therapeutic agents that are suitable for reducing Hepatitis B infection.

[00238] Formulations of therapeutic and diagnostic agents can be prepared by mixing with physiologically acceptable carriers, excipients, or stabilizers in the form of, *e.g.*, lyophilized powders, slurries, aqueous solutions, lotions, or suspensions (see, *e.g.*, Hardman *et al.*, Goodman and Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, N.Y., 2001; Gennaro, Remington: The Science and Practice of Pharmacy, Lippincott, Williams, and Wilkins, New York, N.Y., 2000; Avis, *et al.* (eds.), Pharmaceutical Dosage Forms: Parenteral Medications, Marcel Dekker, NY, 1993; Lieberman, *et al.* (eds.), Pharmaceutical Dosage Forms: Tablets, Marcel Dekker, NY, 1990; Lieberman, *et al.* (eds.) Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, NY, 1990; Weiner and Kotkoskie, Excipient Toxicity and Safety, Marcel Dekker, Inc., New York, N.Y., 2000).

[00239] In a specific aspect, the anti-HLA-HBV peptide antibody is a lyophilisate in a vial containing the antibody. The lyophilisate can be reconstituted with water or a pharmaceutical carrier suitable for injection. For subsequent intravenous administration, the obtained solution will usually be further diluted into a carrier solution.

[00240] The antibodies disclosed herein are useful in the reduction of HBV in patients suffering from liver failure, cirrhosis, and/or hepatocellular carcinoma, so a pharmaceutical carrier of sucrose and human albumin as used previously in bone marrow transplant patients receiving CytoGam™ can be used (DeRienzo et al. Pharmacotherapy 2000; 20:1175-8). Alternatively, the anti-HLA-HBV peptide antibody can be introduced into transplant patients via a pharmaceutical carrier as described for another anti-viral antibody, Synagis™, as described in WO2003/105894. In this publication, the pharmaceutical carrier was comprised of histidine and/or glycine, a saccharide (e.g. sucrose) and a polyol (e.g. polysorbate).

[00241] Selecting an administration regimen for a therapeutic depends on several factors, including the severity of the infection, the level of symptoms, and the accessibility of the target cells in the biological matrix. In certain aspects, an administration regimen maximizes the amount of

therapeutic delivered to the patient consistent with an acceptable level of side effects. Accordingly, the amount of biologic delivered depends in part on the particular entity and the severity of the condition being treated. Guidance in selecting appropriate doses of antibodies, cytokines, and small molecules are available (see, *e.g.*, Wawrzynczak, Antibody Therapy, Bios Scientific Pub. Ltd, Oxfordshire, UK, 1996; Kresina (ed.), Monoclonal Antibodies, Cytokines and Arthritis, Marcel Dekker, New York, N.Y., 1991; Bach (ed.), Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases, Marcel Dekker, New York, N.Y., 1993; Baert *et al.*, New Engl. J. Med. 348:601-608, 2003; Milgrom *et al.*, New Engl. J. Med. 341:1966-1973, 1999; Slamon *et al.*, New Engl. J. Med. 344:783-792, 2001; Beniaminovitz *et al.*, New Engl. J. Med. 342:613-619, 2000; Ghosh *et al.*, New Engl. J. Med. 348:24-32, 2003; Lipsky *et al.*, New Engl. J. Med. 343:1594-1602, 2000).

[00242] Determination of the appropriate dose is made by the clinician, *e.g.*, using parameters or factors known or suspected in the art to affect treatment or predicted to affect treatment. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved relative to any negative side effects. Important diagnostic measures include those of symptoms of, *e.g.*, infusion reactions.

[00243] Actual dosage levels of the active ingredients in the pharmaceutical compositions with the anti-HLA-HBV peptide antibodies can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the antibodies, the route of administration, the time of administration, the half-life of the antibody in the patient, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors known in the medical arts.

[00244] Compositions comprising antibodies or fragments thereof can be provided by continuous infusion, or by doses at intervals of, *e.g.*, one day, one week, or 1-7 times per week. Doses can be provided intravenously, subcutaneously, topically, orally, nasally, rectally, intramuscular, intracerebrally, or by inhalation. A specific dose protocol is one involving the maximal dose or dose frequency that avoids significant undesirable side effects.

[00245] For the antibodies described herein, the dosage administered to a patient may be 0.0001 mg/kg to 100 mg/kg of the patient's body weight. The dosage may be between 0.0001 mg/kg and 20 mg/kg, 0.0001 mg/kg and 10 mg/kg, 0.0001 mg/kg and 5 mg/kg, 0.0001 and 2 mg/kg, 0.0001 and 1 mg/kg, 0.0001 mg/kg and 0.75 mg/kg, 0.0001 mg/kg and 0.5 mg/kg, 0.0001 mg/kg to 0.25 mg/kg, 0.0001 to 0.15 mg/kg, 0.0001 to 0.10 mg/kg, 0.001 to 0.5 mg/kg, 0.01 to 0.25 mg/kg or 0.01 to 0.10 mg/kg of the patient's body weight. The dosage of the antibodies or fragments thereof can be

calculated using the patient's weight in kilograms (kg) multiplied by the dose to be administered in mg/kg.

[00246] Doses of the antibodies then can be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or at least 6 months.

[00247] An effective amount for a particular patient may vary depending on factors such as the condition being treated, the overall health of the patient, the method, route and dose of administration and the severity of side effects (see, *e.g.*, Maynard *et al.*, A Handbook of SOPs for Good Clinical Practice, Interpharm Press, Boca Raton, Fla., 1996; Dent, Good Laboratory and Good Clinical Practice, Urch Publ., London, UK, 2001).

[00248] The route of administration may be by, *e.g.*, topical or cutaneous application, injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial, intracerebrospinal, intralesional, or by sustained release systems or an implant (see, *e.g.*, Sidman *et al.*, Biopolymers 22:547-556, 1983; Langer *et al.*, J. Biomed. Mater. Res. 15:167-277, 1981; Langer, Chem. Tech. 12:98-105, 1982; Epstein *et al.*, Proc. Natl. Acad. Sci. USA 82:3688-3692, 1985; Hwang *et al.*, Proc. Natl. Acad. Sci. USA 77:4030-4034, 1980; U.S. Pat. Nos. 6,350,466 and 6,316,024). Where necessary, the composition may also include a solubilizing agent or a local anesthetic such as lidocaine to ease pain at the site of the injection, or both. In addition, pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, *e.g.*, U.S. Pat. Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entirety.

[00249] A composition of the present disclosure can also be administered via one or more routes of administration using one or more of a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. Selected routes of administration for the antibodies include intravenous, intramuscular, intradermal, intraperitoneal, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. Parenteral administration can represent modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion. Alternatively, a composition of the present disclosure can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally,

sublingually or topically. In one aspect, the antibodies of the present disclosure are administered by infusion. In another aspect, the antibodies are administered subcutaneously.

[00250] If the antibodies of the present disclosure are administered in a controlled release or sustained release system, a pump may be used to achieve controlled or sustained release (see Langer, supra; Sefton, CRC Crit. Ref Biomed. Eng. 14:20, 1987; Buchwald *et al.*, Surgery 88:507, 1980; Saudek *et al.*, N. Engl. J. Med. 321:574, 1989). Polymeric materials can be used to achieve controlled or sustained release of the therapies of the antibodies (see *e.g.*, Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla., 1974; Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York, 1984; Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61, 1983; see also Levy *et al.*, Science 228:190, 1985; During *et al.*, Ann. Neurol. 25:351, 1989; Howard *et al.*, J. Neurosurg. 7 1:105, 1989; U.S. Pat. No. 5,679,377; U.S. Pat. No. 5,916,597; U.S. Pat. No. 5,912,015; U.S. Pat. No. 5,989,463; U.S. Pat. No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In one aspect, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. A controlled or sustained release system can be placed in proximity of the prophylactic or therapeutic target, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138, 1984).

[00251] Controlled release systems are discussed in the review by Langer, Science 249:1527-1533, 1990). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more antibodies of the present disclosure. See, *e.g.*, U.S. Pat. No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning *et al.*, Radiotherapy & Oncology 39:179-189, 1996; Song *et al.*, PDA Journal of Pharmaceutical Science & Technology 50:372-397, 1995; Cleek *et al.*, Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, 1997; and Lam *et al.*, Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, 1997, each of which is incorporated herein by reference in their entirety.

[00252] If the antibodies of the disclosure are administered topically, they can be formulated in the form of an ointment, cream, transdermal patch, lotion, gel, spray, aerosol, solution, emulsion, or other form well-known to one of skill in the art. See, *e.g.*, Remington's Pharmaceutical Sciences and Introduction to Pharmaceutical Dosage Forms, 19th ed., Mack Pub. Co., Easton, Pa. (1995). For non-sprayable topical dosage forms, viscous to semi-solid or solid forms comprising a carrier or one or more excipients compatible with topical application and having a dynamic viscosity, in some

instances, greater than water are typically employed. Suitable formulations include, without limitation, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, and the like, which are, if desired, sterilized or mixed with auxiliary agents (*e.g.*, preservatives, stabilizers, wetting agents, buffers, or salts) for influencing various properties, such as, for example, osmotic pressure. Other suitable topical dosage forms include sprayable aerosol preparations wherein the active ingredient, in some instances, in combination with a solid or liquid inert carrier, is packaged in a mixture with a pressurized volatile (*e.g.*, a gaseous propellant, such as freon) or in a squeeze bottle. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well-known in the art.

[00253] If the compositions comprising the antibodies are administered intranasally, it can be formulated in an aerosol form, spray, mist or in the form of drops. In particular, prophylactic or therapeutic agents for use according to the present disclosure can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges (composed of, *e.g.*, gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00254] Methods for co-administration or treatment with a second therapeutic agent, *e.g.*, an immunosuppressant, a cytokine, steroid, chemotherapeutic agent, antibiotic, or radiation, are known in the art (see, *e.g.*, Hardman *et al.*, (eds.) (2001) Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed., McGraw-Hill, New York, N.Y.; Poole and Peterson (eds.) (2001) Pharmacotherapeutics for Advanced Practice: A Practical Approach, Lippincott, Williams & Wilkins, Phila., Pa.; Chabner and Longo (eds.) (2001) Cancer Chemotherapy and Biotherapy, Lippincott, Williams & Wilkins, Phila., Pa.). An effective amount of therapeutic may decrease the symptoms by at least 10%; by at least 20%; at least about 30%; at least 40%, or at least 50%.

[00255] Additional therapies (*e.g.*, prophylactic or therapeutic agents), which can be administered in combination with the anti-HLA-HBV peptide antibodies may be administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours

apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours apart from the anti-HLA-HBV peptide antibodies of the present disclosure. The two or more therapies may be administered within one same patient visit.

[00256] In certain aspects, anti-HLA-HBV peptide antibodies can be formulated to ensure proper distribution in vivo. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the anti-HLA-HBV peptide antibodies cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, *e.g.*, U.S. Pat. Nos. 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties, which are selectively transported into specific cells or organs, thus enhance targeted drug delivery (see, *e.g.*, Ranade, (1989) J. Clin. Pharmacol. 29:685). Exemplary targeting moieties include folate or biotin (see, *e.g.*, U.S. Pat. No. 5,416,016 to Low *et al.*); mannosides (Umezawa *et al.*, (1988) Biochem. Biophys. Res. Commun. 153:1038); antibodies (Bloeman *et al.*, (1995) FEBS Lett. 357:140; Owais *et al.*, (1995) Antimicrob. Agents Chemother. 39:180); surfactant protein A receptor (Briscoe *et al.*, (1995) Am. J. Physiol. 1233:134); p 120 (Schreier et al, (1994) J. Biol. Chem. 269:9090); see also K. Keinanen; M. L. Laukkanen (1994) FEBS Lett. 346:123; J. J. Killion; I. J. Fidler (1994) Immunomethods 4:273.

[00257] The present disclosure provides protocols for the administration of pharmaceutical composition comprising anti-HLA-HBV antibodies alone or in combination with other therapies to a subject in need thereof. The combination therapies (*e.g.*, prophylactic or therapeutic agents) can be administered concomitantly or sequentially to a subject. The therapy (*e.g.*, prophylactic or therapeutic agents) of the combination therapies can also be cyclically administered. Cycling therapy involves the administration of a first therapy (*e.g.*, a first prophylactic or therapeutic agent) for a period of time, followed by the administration of a second therapy (*e.g.*, a second prophylactic or therapeutic agent) for a period of time and repeating this sequential administration, i.e., the cycle, in order to reduce the development of resistance to one of the therapies (*e.g.*, agents) to avoid or reduce the side effects of one of the therapies (*e.g.*, agents), and/or to improve, the efficacy of the therapies.

[00258] The therapies (*e.g.*, prophylactic or therapeutic agents) of the combination therapies of the disclosure can be administered to a subject concurrently. The term "concurrently" is not limited to the administration of therapies (*e.g.*, prophylactic or therapeutic agents) at exactly the same time, but rather it is meant that a pharmaceutical composition comprising antibodies or fragments thereof are administered to a subject in a sequence and within a time interval such that the antibodies can act together with the other therapy(ies) to provide an increased benefit than if they were administered otherwise. For example, each therapy may be administered to a subject at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or

prophylactic effect. Each therapy can be administered to a subject separately, in any appropriate form and by any suitable route. In various aspects, the therapies (*e.g.*, prophylactic or therapeutic agents) are administered to a subject less than 15 minutes, less than 30 minutes, less than 1 hour apart, at about 1 hour apart, at about 1 hour to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, 24 hours apart, 48 hours apart, 72 hours apart, or 1 week apart. In other aspects, two or more therapies (*e.g.*, prophylactic or therapeutic agents) are administered to a within the same patient visit.

[00259] The prophylactic or therapeutic agents of the combination therapies can be administered to a subject in the same pharmaceutical composition. Alternatively, the prophylactic or therapeutic agents of the combination therapies can be administered concurrently to a subject in separate pharmaceutical compositions. The prophylactic or therapeutic agents may be administered to a subject by the same or different routes of administration.

EXAMPLES

Example 1: Generation of anti-HLA-HBV antibodies

[00260] Methods for generation of monoclonal antibodies using phage display technology are known in the art (Proetzel, G., Ebersbach, H. (Eds.) Antibody Methods and Protocols. Humana Press ISBN 978-1-61779-930-3; 2012). In brief, a synthetic library expressing human Fab fused to the pIII coat protein of the filamentous bacteriophage lambda was used as the source for the antibodies. The synthetic library consisted of 3 fixed human germline VH – VL framework combinations (VH3-23 – Vk1-39, VH1-46 – Vk1-39 and VH5-51 – Vk1-33) randomized in HCDR3 using the TRIM (trinucleotide-directed mutagenesis) technology. The HCDR3 varied in length between 10 and 20 amino acids and amino acid composition using natural amino acids beside Asn, Met and Cys. Panning of the synthetic library against HLA-peptide complexes (target) was either done in solid phase mode in which phages were added to 96-well Maxisorp plates (ThermoFisher Cat #44-24) directly coated with the target or in liquid phase mode in which phages were incubated with the biotinylated target for 1 hour, before phage-target complexes were captured on NeutrAvidin™ coated wells. The washing regimen stringency intensified during the selection rounds as follows: 1) 5 cycles (3x quick, 2x 5 min) with PBS plus 0.05% Tween 20, followed by 5 cycles (3x quick, 2x 5 min) using PBS in the first round, 2) 5 cycles (1x quick, 4x 5 min) with PBS plus 0.05% Tween 20 followed by 5 cycles (1x quick, 4x 5 min) using PBS in the first round, and 3) 15 cycles (10x quick, 5x5 min) with PBS plus 0.05% Tween 20 followed by 15 cycles (10x quick, 5x5 min) with the first 2 cycles containing PBS plus 0.05% Tween and the remaining cycles containing PBS. Phage was eluted with 10mM

Glycine/HCl pH 2.0 and the reaction neutralized with 1M Tris/HCL pH8.0. Eluted phage were used to infect E.coli TG1F+ and further propogated using VCSM13 helper phage (Agilent were infected with eluted phages which were neutralized beforehand using 1M Tris/HCl, pH8.0. Propagation of phage between rounds was performed using VCSM13 helper phage (Agilent Cat# 200251).

[00261] Using ELISA screening, single Fab clones were identified specifically binding to HLA-peptide complex as follows: 384-well Maxisorp plates were coated with 10µg/mL NeutrAvidin™ before adding the biotinylated targets. After blocking of plates with Superblock™ (Thermo Scientific Cat# 37515), Fab-containing E. coli lysates were added. The binding of Fabs was detected by goat anti-human Fab specific antibody (Fab format), AP-conjugated (Jackson Immuno Research cat# 109-056-006) using AttoPhos™ substrate (Roche 11681982001) as per the manufacturer's protocol.

[00262] Alternatively, Fab clones specifically binding to HLA-peptide complexes were identified using deep sequencing. The DNA of a panning round was extracted and the HCDR3 regions amplified in two consecutive PCR reactions followed by adapter ligation and multiplexing using Illumina™ technology. The raw data in FastQ format were used to extract the amino acid sequences, align the sequences and count the occurrence of individual sequences. By comparing occurrences of individual clones derived from different panning strategies, clones with desired binding profile (enriched on wanted HLA-peptide complex and depleted on irrelevant HLA-peptide complex) were identified. The genes of clones of interest were synthesized.

[00263] Anti-HLA-HBV peptide antibodies were affinity matured by CDR-directed mutagenesis. Beneficial mutations were identified by comparing enrichment after two rounds of phage display in relation to the initial mutagenesis library by deep sequencing. Selected beneficial mutations alone and in combination were then cloned and expressed as human IgG1 as previously described in Fischer, S. et. al., Biotechnol. Bioeng. 109: 2250–2261 (2012). In brief, genes of light and heavy chains were synthesized, separately cloned into pRS5a plasmids and co-transfected using PEI MAX (Polysciences cat # 24765-1) into CAP-T cell line (CEVEC Pharmaceuticals, Koln, Germany). Supernatants were purified using protein A affinity chromatography. Purified samples were checked on SDS-PAGE and analytical size exclusion chromatography.

NOV2353 was identified from the primary VH3-23 – Vk1-39 library by using liquid phase panning on biotinylated HLA(A2)-HBVx92-100 refolded complex and screening in ELISA.

NOV2772 was identified from the primary VH3-23 – Vk1-39 library by using liquid phase panning on biotinylated HLA(A2)-HBVx92-100 refolded complex and deep sequencing screening.

NOV3040 was identified from the primary VH5-51 – Vk1-33 library by using liquid phase panning on biotinylated HLA(A2)-HBVx92-100 refolded complex and deep sequencing screening.

NOV3499 is an affinity matured version of NOV3040 with an altered HCDR3.

NOV3771 is an affinity matured version of NOV3040 with altered HCDR1 and HCDR3.

NOV3635 was identified from the primary VH3-23 – Vk1-39 library by using solid phase panning on HLA(A2)-HBVx92-100 [V92F, H94M] single-chain complex and deep sequencing screening.

NOV3638 was identified from the primary VH3-23 – Vk1-39 library by using solid phase panning on HLA(A2)-HBVx92-100 [V92F, H94M] single-chain complex and deep sequencing screening.

NOV2361 was identified from the primary VH1-46 – Vk1-39 library by using liquid phase panning on biotinylated HLA(A2)-HBVs172-180 refolded complex and screening in ELISA.

NOV2734 is an affinity matured version of NOV2361 with altered HCDR1.

NOV2800 is an affinity matured version of NOV2361 with altered LCDR1, HCDR1, HCDR2 and HCDR3.

NOV2505 was identified from the primary VH5-51 – Vk1-33 library by using liquid phase panning on biotinylated HLA(A2)-HBVx52-60 refolded complex and screening in ELISA.

NOV3522 was identified from the primary VH3-23 – Vk1-39 library by using liquid phase panning on biotinylated HLA(A2)-HBVx52-60 [H52F, S54M] refolded complex and deep sequencing screening.

[00264] Monoclonal antibodies binding HLA-A2:01-HBx92-100 were also isolated from mouse B-cells. Female BALB/c mice were immunized with cDNA encoding full length HLA-A2:01-HBx92-100 by introducing two separate constructs. A fusion construct encoding the HBx92-100 peptide/β2m and a second separate plasmid encoding HLA. The plasmids were introduced in combination with immune modulators via hydrodynamic tail vein injection, as described previously (Hazen M, et al., mAbs 2014;6:1, 95-107). B-cells expressing anti-HLA-HBx92-100 antibodies were lysed, and the VH (heavy) and VL (light) chains were amplified using RT-PCR. Synthesized gene fragments were subcloned into expression plasmids containing human IgG1 or human kappa constant and Fc regions. Plasmids of the paired VH and VL chains were then co-transfected in a CHO mammalian cell line for expression of the full-length, chimeric IgG1 antibodies. Furthermore, CDRs from select murine IgGs were humanized by grafting onto human framework acceptor templates, cloned into mammalian IgG1 backbone expression vectors and transfected in a CHO mammalian cell line for expression of the full IgG1 antibodies.

Example 2: Generation and purification of HLA-HBV-peptide complexes

[00265] The HLA-A2 and β2M sequences were cloned into separate *E.coli* expression vector pET22b as an NdeI-EcoRI fragment. The plasmids were transformed independently into BL21 (DE3) chemically competent *E. coli* cells and plated on LB+100 ug/mL carbenicillin agar plates. A single colony was used to inoculate a 50mL overnight starter culture (37°C, 250rpm) in LB+100 µg/mL

carbenicillin. The starter culture was used to inoculate 1L of LB+100 µg/mL carbenicillin in a 3L Fernbach flask to a starting OD600 of 0.05 OD/mL. The flasks were incubated at 37°C, 225rpm for approximately 3.5 hours (to OD600=0.6). The cultures were induced with 1mL of 1M IPTG. The cultures were returned to 37°C, 225rpm shaking incubation for approximately 5 hours. The final OD600 was measured and the cells pelleted in 2 x 500mL aliquots. The liquid was removed from the cell pellets and the pellets were stored at -80°C.

Table 3

Construct	Amino acid sequence in one letter code	SEQ ID NO
Human HLA-A2-AviTag	MGSHSMRYFFTSVSRPGRGEPRFIAVGYVDDTQFVRFDSDAAS QRMEPRAPWIEQEGPEYWDGETRKVKAHSQTHRVDLGTLRGY YNQSEAGSHTVQRMYGCDVGSDWRFLRGYHQYAYDGKDYIA LKEDLRSWTAADMAAQTTKHKWEAAHVAEQLRAYLEGTCVE WLRRYLENGKETLQRTDAPKTHMTHHAVSDHEATLRCWALSF YPAEITLTWQRDGEDQTQDTELVETRPAGDGTFQKWAAVVVPS GQEQRYTCHVQHEGLPKPLTLRWEPSSQPGSGLNDIFEAQKIEW HE	SEQ ID NO:420
Human Beta-2 Microglobulin	MIQRTPKIQVYSRHPAENGKSNFLNCYVSGFHPSDIEVDLLKNG ERIEKVEHSDLSFSKDWSFYLLYYTEFTPTEKDEYACRVNHVTL SQPKIVKWDRDM	SEQ ID NO:421

AviTag sequence is bolded, underlined
Human HLA-A2, residues 25-304-(accession numbers NM_001242758.1, NP_001229687)
Human Beta-2-microglobulin, residues 21-119 (accession numbers NM_004048.3, NP_004039)

[00266] *In vitro* refolding was based on the method published by Garboczi et al (Garboczi et al., 1992). MHC class I alpha (α) and beta 2 microglobulin (β2m) subunits were expressed as separate inclusion bodies in *E.Coli*. The inclusion bodies were extracted from 5g of cell pellet which was resuspended in 25ml of Tris, pH 7.5, 200mM NaCl, 1mM EDTA, 5mM DTT, 25% (w/v) sucrose, and Benzonase™ (Sigma-Aldrich, cat#E1014-25KU). Cells were lysed by sonication on ice for 1 min and rested on ice for 1 min. This process was repeated two more times. Lysate was centrifuged for 20 minutes at 18,000 rpm at 4°C. The supernatant was discarded and the inclusion bodies were washed two more times with buffer A (25ml of Tris, pH 7.5, 200mM NaCl, 1mM EDTA, 5mM DTT, 1% (w/v) sodium deoxycholate monohydrate, and 1% Nonidet P40) and buffer B (25ml of Tris, pH 7.5, 200mM NaCl, 1mM EDTA, 5mM DTT, 0.5% (v/v) Triton X-100). With each wash, the pellet was sonicated and centrifuged under the same conditions as stated above. The final pellet was solubilized into 25ml of Tris, pH 7.5, 200mM NaCl, 1mM EDTA, and 5mM DTT and made 1ml aliquots. Supernatant was discarded after the aliquots were centrifuged at 16,000 x g for 20min. *In vitro*

refolding was conducted at 4°C. The refolding buffer was 100mM Tris, pH 8, 400mM L-arginine-HCl, 5mM reduced glutathione, 0.5mM oxidized glutathione, 2mM EDTA, Roche protease inhibitor tablets and 60 μM peptide. One aliquot of α and β2m were dissolved in 1ml of 8M urea, 0.1M Tris, pH8 and centrifuged at 16,000xg for 2 minutes. Protein concentration was determined by absorbance at 280nm. For a 50ml refolding reaction, 3 μM of α and 6 μM of β2m was added dropwise into refolding buffer over three consecutive days. The mixture stirred overnight. After the last addition of α and β2m, the reaction continued to stir for additional 48 hours. Before purification, the solution was filtered through a 0.22 μM filter and concentrated to 15ml. The refolded MHC was purified over a Superdex™ 75 26/60 column (GE Healthcare) which was pre-equilibrated with PBS. Relevant fractions were analyzed by SDS-PAGE gel and pooled accordingly. The complex was biotinylated with in house produced GST-BirA enzyme at the carboxyl terminal end of the MHC alpha chain at room temperature for 3 hours. A ratio of 20μg refolded MHC to 1μg of enzyme was used. The *in vitro* reaction also included 10mM ATP, 5mM MgCl2, and 100μM d-biotin. Biotinylated material was put over 1ml GSTrap Glutathione (GE Healthcare) drip column and flowthrough was collected. GSTrap Glutathione flowthrough was purified over Superdex 75 26/60 pre-equilibrated in PBS. Pertinent fractions were analyzed by SDS-PAGE gel and pooled accordingly.

[00267] Production of Fc-fusion proteins p(HBx 92-100[V92F,H94M])-b2m-HLA A2-hFc1P and p(HBx 52-60[H52F,S54M])-b2m-HLA A2-hFc1P. The human Fc-fusion proteins were produced by transient transfection and purified via chromatographic methods. In short, HKB11 (Bayer HealthCare, Berkeley, CA, USA) cells were transiently transfected with expression plasmids encoding the HBx peptide variants with increase affinity to MHC I, GS linker, β2m, GS linker, HLA A2 fused to a human Fc1 domain. Cell culture supernatants were harvested by centrifugation and the protein was purified by standard chromatographic methods using Protein A and preparative size exclusion for polishing (MabSelect SURE™, GE Healthcare and HiLoad Superdex™ 200 prep grade, GE Healthcare). Purity of the protein was analyzed under denaturing, reducing and non-reducing conditions in SDS-PAGE and in native state by HP-SEC. The proteins were analyzed by reduced and de-glycosylated LC-MS.

Example 3: Binding of anti-HLA-HBV-peptide antibodies to HLA-HBV-peptide complexes

[00268] Binding affinity interaction (K_D) of the anti-HLA-HBV peptide antibodies to (1) HLA(A2)-HBVs172-180, (2)HLA(A2)-HBVx92-100, or (3)HLA(A2)-HBVx52-60 refolded complexes was determined by surface plasma resonance (SPR) technology on Biacore T200™ instrument (GE Healthcare). Association and dissociation curves were obtained to determine affinity and kinetic values. The experimental buffer was HBS-P (0.01 M HEPES, pH 7.4, 0.15 M NaCl, 0.05% Surfactant P20). Anti-human antibody was covalently coupled by amine coupling onto all four flow cells on a CM5 sensor chip following manufacture's specifications. For affinity and kinetic determination, individual antibodies were injected at 10 μl/min for 1 minute over the three test flow

cells at 0.01-0.25 µg/ml. The flow cell without any captured pMHC antibody was used as reference. Captured levels of the antibodies were generally kept below 400 RUs. Subsequently, various concentrations of pMHC complex were diluted in a 3-fold dilution series and injected at a flow rate of 40 µl/min for 2-4 min over both reference and test flow cells. Dissociation of the binding was followed for 5 min. After each injection cycle, the chip surface was regenerated with 3M MgCl2 at 10 µl/min for 30 seconds. All experiments were performed at 25°C and the response data were globally fitted using Biacore T200™ Evaluation Software version 2 (GE Healthcare) to obtain on rate (k_a), off-rate (k_d) and affinity (K_D).

[00269] Antibodies NOV2361, NOV2505, NOV2734, NOV3040, NOV3499, NOV3522, NOV3638, NOV3771, and ATG.B.E211 were fitted using a 1:1 binding model; Steady state affinity was used to estimate binding affinities for NOV2353 and NOV2772 due to poor fitting with the 1:1 model (O'Shannessy et al. Anal. Biochem 1993;212:457-468; Karlsson, Fält J. Immunol. Methods. 1997; 200: 121-133).

[00270] Biacore measured K_D values for NOV2361 and NOV2734, antibodies specific for HLA(2)-HBVs172-180 complex, ranged from 18.3nM to 54.9nM. Biacore measured K_D values for NOV2353, NOV2772, NOV3040, NOV3499, NOV3638, NOV3771, and ATG.B.E211, antibodies specific for HLA(A2)-HBVx92-100 complex, ranged from 1.94 µM to 18.1nM. Biacore measured K_D values for NOV2505 and NOV3522, antibodies specific for HLA(A2)-HBVx52-60 complex, ranged from 32.0nM to 28.5nM. A summary of Biacore affinity data for the anti-HLA-HBV antibodies is found in Table 4 below, and SPR results are found in Figures 1A-D to Figure-3A-D.

Table 4

Antigen	Antibody	ka (1/Ms)	kd (1/s)	KD (M)
HBx92-100	NOV2353			4.71E-07
HBs172-180	NOV2361	1.30E+05	0.00711	5.49E-08
HBx52-60	NOV2505	3.54E+04	0.001133	3.20E-08
HBs172-180	NOV2734	4.09E+05	0.00746	1.83E-08
HBx92-100	NOV2772			2.87E-07
HBx92-100	NOV3040	2.92E+04	0.05664	1.94E-06
HBx92-100	NOV3499	6.30E+04	0.03321	5.28E-07
HBx52-60	NOV3522	5.47E+04	0.001556	2.85E-08
HBx92-100	NOV3638	6.54E+05	0.467	7.14E-07
HBx92-100	NOV3771	8.37E+04	0.001752	2.09E-08
HBx92-100	ATG.B.E211	5.15E+06	0.09315	1.81E-08

Example 4: T2 pulse data

[00271] To monitor HLA antibody specific binding to a complex of HLA-HBV peptide on cellular surface, TAP deficient T2 cells (ATCC CRL-1922) were pulsed with 9-mer HLA-A2 presented peptides HBs172-180:WLSLLVPFV(SEQ ID NO:3), HBx92-100:VLHKRTLGL(SEQ ID NO:1), and HBx52-60:HLSLRGLPV(SEQ ID NO:2) and binding monitored by FACS analysis as previously described (Kessler et al. Current Protocols in Immunology; 2004;18.12.1-18.12.15). Briefly, in order to remove endogenous HLA peptides on the cellular surface, T2 cells (500,000 cells/well) were rinsed in PBS and resuspended for 1 min in 2ml ice cold 1:1 mixture of 0.263 M Citric Acid and 0.123 M NaHPO4, pH 3.1. Cells were diluted in 12ml of ice cold Iscove's MDM (Mediatech MT10-016-CV) with 1% FBS and centrifuged at 1200rpm for 5 min at room temperature. Supernatant was aspirated out and cells resuspended in 12ml ice cold Iscove's MDM with 1% FBS followed by centrifugation at 1200rpm for 5 min at room temperature. Supernatant again aspirated and cells resuspended at a density of $1x10^6$ cells/ml of ice cold Iscove's MDM with 1% FBS and 2µg/ml β2-Microglobulin (Sigma cat#M4890). Peptides were then added to a final concentration of 25 µg/ml and 200µl of the final cell suspension (at 10^5 to $2x10^5$ cells/well) aliquoted into a 96-well v-bottom plate. Cells were incubated overnight at 4°C and protected from light. The following day cells were pelleted, supernatant removed, and washed two times with stain buffer (eBioscience cat#00-4222) and resuspended in 100µl Viability Dye (eFluor780™ Affymetrix eBioscience #65-0865) diluted 1:1000 for 30 min on ice. Cells were washed two times with PBS and resuspended in 10 µg/ml anti-HBV-HLA antibodies or suitable controls (anti-human HLA-A2 BB7.2 Biolegend #343304) on ice for 1 hour. Samples were washed three times with stain buffer and resuspended in goat anti-human IgG (Jackson ImmunoResearch cat#109-116-088) diluted 1:10000 for 1 hour on ice. Samples again washed three times in stain buffer and cells resuspended in IC Fixation Buffer (eBioscience cat#00-8222) and analyzed by FACS for mean fluorescence intensity (MFI).

[00272] Data for the anti-HLA-HBV antibodies against the HLA displayed HBV peptides HBx52-60, HBx92-100 and HBs172-180 is provided in Figure 4 and is graphically represented as signal fold change over isotype control. Antibodies specific for targeting HBx52-60 peptide (NOV2505 and NOV3522) showed specific fold shifts over isotype control ranging from 4.2 to 5.9 for the HBx52-60 peptide with other peptides tested (no peptide, HBx92-100 and HBs172-180) remaining at or below the level of isotype control. Similarly, antibodies NOV2353, NOV3040, NOV3499, NOV3635, NOV3638, and ATG.B.E211 showed specific fold shifts over isotype control (2.2 to 7.4) for the HBx92-100 peptide with other peptides tested remaining at or below the level of isotype control. NOV2772, another antibody targeting HBx92-100 showed a 2.1 fold shift over isotype control for the target peptide. Lastly, antibodies specifically targeting the HBs172-180 peptide (NOV2361, NOV2734, and NOV2800) show specific fold shifts over isotype control ranging from 6.6 to 8.8 for the HBs172-180 peptide with other peptides tested remaining at or near the level of isotype control.

Example 5: Alanine scanning.

[00273] To identify specific residues important for anti-HLA-HBV peptide antibody binding within the target HLA presented peptide, peptides in which an alanine replaced individual residues were assayed in a T2 pulse experiment as described above in Example 4. Data for the individual anti-HLA-HBV peptide antibodies binding profile against the alanine substituted HLA-HBV peptides is presented in Figures 5-17 and data is represented as signal fold change over isotype control. An antibody targeting pan-HLA-A2 (anti-human HLA-A2 BB7.2 Biolegend cat#343304) was used as a control to validate refolding of peptide complex with the alanine substituted peptides.

[00274] The HBx52-60 peptide has two anchor positions within the HLA-A2 pocket complex (position 2 and position 9) leaving seven additional points of contact available for our individual antibodies. Utilizing alanine scanning in the T2 pulse system, NOV2505 no longer showed binding to the HBx52-60 peptide when residues 4(Leu) and 5(Arg) were substituted with an alanine suggesting that these two residues are critical for antibody binding. In addition, residue 6(Gly) shows some partial loss of binding when mutated to an alanine indicating an indirect interaction (Figure 15). The resolution of the crystal structure of NOV2505:HLA-A2-HBx52-60 (see Example 13 below) confirmed this finding. Another antibody targeting HBx52-60 displayed a different binding pattern; NOV3522 showed three critical (3Ser, 4Leu, and 5Arg) and two partial (7Leu and 8Pro) binding sites (Figure 16).

[00275] The HBx92-100 peptide has one anchor residue at position 2 within the HLA-A2 pocket leaving eight additional points of antibody contact available. NOV2353 showed loss of binding when positions 4(Lys) and 5(Arg) were mutated to alanine (Figure 5). Affinity maturation of NOV2353 resulted in NOV2772 (Figure 9) which showed loss of binding to residues 1 (Val), residue 3 (His), and residue 7 (Leu) in addition to positions 4 and 5. Both NOV2353 and NOV2772 contacts were confirmed through crystallography (see Example 13 below). Another antibody family targeting HBx92-100, NOV3040 showed a very different profile. NOV3040 showed loss of binding when seven out of the nine peptides residues are mutated to an alanine in addition to the anchor residue (4Lys, 5Arg, 6Thr, 7Leu, 8Gly, and 9Leu) (Figure 10). Affinity maturation of NOV3040 resulted in NOV3499 that demonstrated increased affinity to the HBx92-100/HLA complex with no major changes in antibody contact residues (Figure 11). Further maturation of NOV3499 resulted in NOV3771, which demonstrated increased affinity, but did not contact residues at position 8Gly and position 9Leu (Figure 12). Additional antibodies targeting HBx92-100 include NOV3635, NOV3638, and ATG.B.E211. NOV3635 showed loss of binding when residues 4Lys, 5Arg, and 9Leu were mutated and a partial loss of binding when residues 3His, 6Thr, 7Leu, and 8Gly were mutated (Figure 14). NOV3638 showed loss of binding with residues 4Lys, 5Arg, 7Leu, and 9Leu and a partial loss of binding to residues 3His, 6Thr, and 8Gly when these residues were mutated to alanine (Figure 13). Finally, ATG.B.E211, an antibody identified from immunized mouse B cells, showed loss of binding

to residues 4Lys, and 5Arg with partial loss at residues 1Val and 9Leu when these residues were mutated to an alanine (Figure 17).

[00276] The HBs172-180 peptide has two anchor residues at position 2 and 9 within the HLA-A2 pocket. NOV2361 demonstrated loss of binding at residues 5Leu, 6Val, and 8Phe with a partial loss of binding at residue 7Pro (Figure 6). NOV2734 showed a very similar profile at mutated residues (5Leu, 6Val, and 8Phe) but did not show a partial loss of binding at position 7 (Figure 7). NOV2800 demonstrated loss of binding at residue 4Leu in addition to residues 5, 6, and 8 which were seen with NOV2734 (Figure 8).

Example 6: antibody binding affinity to HBx toggled peptide

[00277] In addition to the alanine scan which was used to identify important residues, a toggle experiment was performed for the HBx92-100 peptides in which all 9 positions of the peptide were modified to all 20 amino acid possibilities and assayed for binding by the anti-HLA-HBV peptide antibodies through SPR as described in Example 3 above. Assay of the toggle peptides in MHC complexes was done through UV mediated peptide exchange on a 96 well plate in a 100µl reaction. For each well, 5µg of biotinylated MHC was refolded with conditional peptide (KILGFVFJV (SEQ ID NO:422); J = α-amino acid with (2-nitro)phenyl side chain; GenScript), 50µM of peptide of interest, and phosphate buffered saline buffer were added. The plate was exposed to 366nm UV light (CAMAG Scientific, Wilmington NC) for 1 hour on ice to complete the reaction. Binding affinity interaction (K_D) of the anti-HLA-HBV-peptide antibodies to HLA(A2)-HBVx92-100 toggle peptides was then determined by surface plasma resonance (SPR) technology on Biacore T200™ instrument (GE Healthcare). Association and dissociation curves were obtained to determine affinity and kinetic values. The experimental buffer was HBS-P (0.01 M HEPES, pH 7.4, 0.15 M NaCl, 0.05% Surfactant P20). Biotinylated MHC loaded with peptide of interest was captured onto CAP sensor chip (GE Healthcare) using Biotin CAPture Kit™ (GE Healthcare) following the manufacture's instructions. For affinity and kinetic determination, single-cycle kinetics were performed. The exchanged MHC was diluted ten fold and captured on three test flow cells at 5µl/min for 2 minutes. The flow cell without any captured MHC complex was used as a reference flow cell. A three fold, 5 step dilution series of antibody concentrations were injected sequentially for 10 minutes in a single cycle with no regeneration between injections at 40µl/min across all flow cells with 5 minutes of dissociation data collected per cycle. After each cycle, the chip surface was regenerated per manufacture's specifications. All experiments were performed at 25°C and the response data were globally fitted using Biacore T200™ Evaluation Software version 2 (GE Healthcare) to obtain on rate (k_a), off-rate (k_d) and affinity (K_D). Data was either fitted using a 1:1 binding model or the steady state affinity model (O'Shannessy et al. Anal. Biochem 1993;212:457-468; Karlsson, Fält J. Immunol. Methods. 1997; 200: 121-133).

[00278] Resulting kinetic binding data (K_D) for NOV3040 and NOV3499 is shown in Figures 18 and 19, respectively. Columns represent the individual peptide position across HBx92-100 and the rows represent each individual amino acid that was substituted in place of the wild-type amino acid. K_D values for each toggled peptide is displayed in μM. The critical residues identified in the alanine scan for NOV3040 and NOV3499 were positions 4, 5, 6, 7, 8, and 9. As expected for both NOV3040 and NOV3499, positions 1 and 3 can tolerate a wide degree of amino acid substitutions and still allow binding of the antibody. For NOV3040, positions 4, 5, 6, and 7 showed very little tolerability for binding of amino acid substitutions while positions 8 and 9 displayed more flexibility. NOV3499 displayed a different pattern to that of its parent antibody NOV3040. Similar to NOV3040, NOV3499 had little tolerability to amino acid substitutions in positions 5, 6 and 7 with positions 8 and 9 displaying more flexibility, however, in contrast, NOV3499 showed a wide degree of tolerability to amino acid substitutions in position 4.

Example 7: anti-HLA-HBV antibodies show efficacy in a tumor syngeneic mouse model

[00279] A tumor syngeneic mouse model was established for the purposes of assessing NK mediated targeting of the anti-HLA-HBV peptide antibodies. A stable pool was generated in mouse Hepa1-6 (ATCC CRL-1830) hepatocytes expressing the fusion p(HBx92-100)-β2m-HLA A2-DHFR with firefly luciferase co-expression to use for tumor development. Female Balb/C nude mice were implanted in the hind flank with $5x10^6$ cells/200 μl in Hank's Balanced Salt Solution (Sigma-Aldrich H6648). Day 12 after implantation the mice were treated with either the isotype control (5mg/kg), the pan anti-human-HLA-A2 antibody modified for enhanced NK cell recognition by specific mutations of the Fc region (eADCC BB7.2 5mg/kg), or the specific anti-HLA-HBx92-100 antibody NOV2353 modified for enhanced NK cell recognition identical to eADCC (eADCC NOV2353 30mg/kg). These mutations [S239D, A330L, I332E] are well characterized to greatly increase the affinity for FcγRIIIa (CD16) on NK cells (Lazar et al. Proceeding of the National Academy of Sciences of the United States of America 2006; 103(11):4005–4010). Mice were treated every three days for a total of four treatments according to the study plan (Figure 20) monitoring tumor size and human HLA presentation.

[00280] The clonal pool cell line used for tumor establishment showed varying degrees of human HLA presentation shown by black arrows (Figure 21A) detected by immunohistochemistry using anti-HLA antibody (Abcam cat#EP1395Y) (Figure 21A-C). Tumors taken from mice treated with the isotype control further displayed heterogenetic outgrowth of HLA expression as seen by immunohistochemistry and depicted by black arrows (Figure 22D and Figure 22F). In focusing on the HLA-A2 positive tissue area as determined by IHC, there is a clear decline in the cells expressing the target in animals treated with the pan anti-human HLA-A2 antibody as expected as well as an observable reduction in the target cells when treated with eADCC NOV2353 (Figure 23).

Example 8: Binding analysis of antibodies in an FRGN mouse model

[00281] To assess binding of the anti-HLA-HBV antibodies in a chronic HBV mouse model, livers were harvested from human liver chimeric FRGN mice chronically infected with HBV. Human hepatocyte repopulated (>70%) female FRG KO on NOD (FRGN) mice (Yecuris, Tualatin OR) were infected with HBV Genotype C positive serum (1.5-1.8x10^8 IU/mouse) and viral DNA titers monitored weekly until plateau reached (~2 months). six months post infection, three mice were sacrificed and livers harvested for analysis. Fresh livers dissected into small pieces and placed into a 50ml conical vial containing HBSS (Sigma-Aldrich cat#H6648) + 0.5mM EDTA for 8 min in 37°C followed by centrifugation at 100g. The supernatant was then decanted and the sample placed into 12ml DMEM (ATCC 30-2002) containing 0.8mg/ml Collagenase (Sigma cat#SCR103) and 0.5mg/ml DNaseI (Sigma cat#AMPD1). This mixture was incubated in a shaker at 37°C for 30 minutes and then the sample was strained through a cell strainer into a 50ml conical vial followed by lysis of red blood cells with ACK buffer (Gibco cat#A1049201) for 5 min at room temperature. Cells were washed and resuspended in Live/Dead cell fixable (ThermoFisher cat#L3974) in PBS at 4°C for 20 min. Cells were washed two times with PBS and resuspended in either 500nM or 50nM anti-HLA-HBV peptide antibodies, pan anti-HLA-A2 (BB7.2), or isotype control on ice for 1 hour. Samples were washed three times with stain buffer and resuspended in goat anti-human IgG (Jackson ImmunoResearch cat#109-116-088) diluted 1:10000 for 1 hour on ice. Samples again washed three times in stain buffer and cells resuspended in IC Fixation Buffer (eBioscience cat#00-8222) and analyzed by FACS for mean fluorescence intensity (MFI).

[00282] The data is shown in Figure 24 and represented as signal fold change over isotype control. In this mouse model, NOV3040, NOV3499, and NOV3771 all display evidence of binding to chronic HBV infected livers. At a concentration of 50nM, NOV3040 shows a range of binding from 1.41 to 4.62 fold over isotype control while at 500nM ranges from 2.70 to 18.0 fold over control. NOV3499 displayed the highest level of binding ranging from 1.53 to 6.00 fold over isotype control when tested at 50nM and 23.7 to 35.5 fold when tested at 500nM. NOV3771 displayed signal fold binding ranging from 1.03 to 7.54 at 50nM and 1.74 to 3.26 at 500nM.

Example 9: Binding analysis on human T cell and B cell lines

[00283] In order to measure potential off-target binding, the binding of anti-HLA-HBV antibodies was assessed on immortalized B cell and T cell lines from HLA-A2:01 and HLA-A24:01 donors. Frozen peripheral blood mononuclear cells (PBMC) from donors of the desired HLA haplotype (HLA-A2:01, n=5 and HLA-A24:01 n=5) were acquired from commercial vendors (HemaCare Van Nuys, CA) and $CD22^+$ B lymphocytes isolated through positive selection using CD22 microbeads (Miltenyi Biotech, Cambridge MA) after thawing PBMCs at 37°C. Isolated human B lymphocytes were then immortalized with Epstein-Barr virus. The supernatant used for EBV infection of isolated human

memory B cells was produced from the recombinant marmoset cell line B95-8, which constitutively sheds infectious Epstein-Barr virions into the supernatant (ATCC cat#VR-1492). Briefly, 2.5 x 10^5 $CD22^+$ B lymphocytes were resuspended in 1 ml of EBV-containing supernatant. The mixture of cells and virus was transferred into a sterile 1.5 mL Eppendorf tube and centrifuged for 3 hr at 2000 rpm at 30°C. Following the spin-infection, the supernatant was removed and the cell pellet resuspended in 1 mL complete B cell medium (RPMI medium supplemented with 1× L-glutamine, 10% FCS, 1% Kanamycin, 1% Penicillin-Streptomycin, 1% non-essential amino acids, 1% sodium pyruvate and 50 μM β-Mercaptoethanol) containing the following growth factors: 2.5×10^5 irradiated allogenic PBMCs per mL, 30 μg/ml human holo transferrin (Merck Millipore #616424), and 2.5 μg/ml ODN 2006 (5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO:423) with a nuclease-resistant phosphorothioate backbone, (Microsynth AG, Balgach, Switzerland), 4% v/v EBV-containing supernatant. The EBV-infected B cells were then diluted and plated in 96-well round bottom plates at 100 cells/well.

[00284] For T cell lines, the negative fraction of $CD22^+$isolation were collected and $CD3^+$ T cells isolated using CD3 microbeads (Miltenyi Biotech, Cambridge MA). Isolated CD3+ T cells were then cultured with 1μg/ml of Phytohemagglutinin (PHA, Sigma), IL2 at 4μg/ml (Proleukin, Boheringer) and 2.5×10^5 irradiated allogenic PBMCs per mL. T cells were diluted to 10^5 cells/ml in 96 well round bottom plates. T cell lines were expanded in vitro, stimulating every 2 weeks with PHA (1 μg/ml) and IL2 (4μg/ml).

[00285] Binding analysis profiles of anti-HLA-HBV antibodies at both 500nM and 100nM are shown in Figure 25 and Figure 26, respectively. Of the anti-HLA-HBV antibodies targeting HBx52-60, NOV2505 displayed binding to both B and T cells derived from HLA-A2:01 donors as well as T cells derived from HLA-A24:01 donors at both 500nM and 100nM concentrations. Minimal binding was identified to HLA-A24:01 B cells at either concentration. In contrast, NOV3522 showed no binding to any of the cell populations at either concentration of antibody. Of the anti-HLA-HBV antibodies targeting HBx92-100, NOV3040 and NOV3499 showed no binding to any of the cell populations while NOV2772 and NOV2353 displayed only minimal binding to HLA-A2:01 B cells.

Example 10: Binding analysis on primary human peripheral blood mononuclear cells

[00286] Frozen PBMC from donors of the desired HLA haplotype (HLA-A2:01, n=2) were acquired from commercial vendors (HemaCare Van Nuys, CA) as described in Example 8 above. Frozen PBMC were thawed in a 37°C water bath, and washed in FACS buffer (PBS w/o Ca and Mg, 2% FCS, 1 mM EDTA) before transferring them to 96 well v-bottom plates and treating with Fc block (1:50 dilution 20 μl/ well Becton-Dickinson cat#564220) for 15 minutes at +4°C. Cells were washed again in FACS buffer and anti-HLA-HBV peptide antibodies (NOV3040, NOV3638, NOV3499, NOV3771, NOV2505, NOV3522) and an isotype control were added in FACS buffer at 500 and 100 nM and incubated for 30 minutes at +4°C. Cells washed in FACS buffer and 20 μl of a 1:700 diluted secondary anti human IgG PE labelled (eBioscience, cat#12-4998-82) was added and cells allowed to

incubate for 20 minutes at +4°C. Cells were again washed in FACS buffer and the following antibodies, diluted at 1:100 in FACS buffer, added for the identification of the different lymph mononuclear subsets: CD3 (PerCp Cy5.5 eBioscience cat#45-0037-41), CD4 (PE-Cy7 Biolegend cat#317414), CD8 (Pacific Blue ABD Serotec cat#MCA1226PB), CD11b (APC Biolegend cat#301310ICRF44), CD14 (BV650 BD 563419), CD19 (BV785 Biolegend cat#302240 HIB19) and CD56 (APC Cy7 Biolegend cat#318332HCD56). These surface markers allow for the identification of the following lymph mononuclear cell subsets: $CD19^{+}lin^{-}$ B lymphocytes, $CD3^{+}CD4^{+}lin^{-}$ T helper lymphocytes, $CD3^{+}CD8^{+}lin^{-}$ Cytotoxic T lymphocytes, $CD11b^{+}lin^{-}$ dendritic cells, $CD56^{+}lin^{-}$ natural killer NK cells and $CD14^{+}lin^{-}$ monocytes. The binding of the anti-HLA-HBV peptide antibody candidates on the different cell subsets have been calculated as ratio of the PE mean fluorescence intensity over the isotype control.

[00287] As shown in Figure 27 and 28 of the anti-HLA-HBV peptide antibodies targeting HBx52-60, NOV3522 showed no binding to any of the cell populations at either concentration of antibody. Of the anti-HLA-HBV peptide antibodies targeting HBx92-100, NOV3040 showed no binding to any of the cell populations at either concentration of antibody. NOV3499 showed only minimal binding to the CD8 T lymphocyte population at 100nM and no binding at the higher 500nM concentration.

Example 10: Antibody binding to uninfected hepatocytes

[00288] Uninfected HLA-A2:01 hepatocytes (Yecuris #20-0003, Donor HHM19027) were assessed for potential off-target binding by the anti-HLA-HBV antibodies. Fresh hepatocytes were incubated with Viability Dye (eFluor780™ Affymetrix eBioscience cat#65-0865) diluted 1:1000 for 30 min on ice. Cells were washed two times with PBS and resuspended in either 100 µg/ml or 10 µg/ml anti-HLA-HBV peptide antibodies or isotype control on ice for 1 hour. Samples were washed three times with stain buffer and resuspended in goat anti-human IgG (Jackson ImmunoResearch cat#109-116-088) diluted 1:10000 for 1 hour on ice. Samples were again washed three times in stain buffer and cells resuspended in IC Fixation Buffer (eBioscience cat#00-8222) and analyzed by FACS for mean fluorescence intensity (MFI).

[00289] Data for the anti-HLA-HBV peptide antibodies binding to uninfected hepatocytes is shown in Figure 29 and represented as signal fold change over isotype control. Antibodies targeting HLA-A2-HBx92-100 (NOV3040, NOV3499, and NOV3771) showed no binding over background to uninfected haplotype specific hepatocytes at either concentration tested. The same result was found for NOV2505 and NOV3522, which are antibodies specific for HLA-A2-HBx52-60.

Example 11: UV peptide exchange

[00290] To further characterize potential off-target binding of the anti-HLA-HBV peptide antibodies, a panel of known HLA-A2:01 presented peptides was chosen (Figure 30) with at least 1 or

more identical residues to either the HBx92-100 or HBx52-60 peptide. Mixes of 5 µM UV-sensitive biotinylated HLA complex with 500 µM of each peptide were prepared in a 96-well plate which was then placed under a 365nm UV lamp, at 2cm distance for 1 hour on ice. Following the reaction, the plate was centrifuged and supernatants transferred to a new 96-well plate. A black 384-well Maxisorp plate (ThermoFisher cat#460518) was coated with 10 µg/ml of neutravidin and incubated overnight at 4°C. Plates were washed twice with TBST and blocked with Superblock™ (ThermoFisher cat#37537) for 2 hours. UV-exchanged peptides along with HBx92-100 and HBx52-60 as controls were diluted to 90nM in PBS, added to the blocked neutravidin coated plates, and incubated for 30 minutes. Candidates in IgG format were diluted 10 fold, 4 steps starting at 200nM until 0.2nM in PBS with 0.5% BSA, 0.05% Tween and added to the wells for 1 hour incubation. Anti-human Fab-AP (Jackson Immunoresearch cat#109-056-006), diluted 1:5000 in 0.5% BSA in PBST was used as secondary antibodies for 1 hour. Plates were washed six times with TBST and reaction measured with AttoPhos™ substrate (Roche cat#11681982001) per manufacturer's protocol.

[00291] Binding ELISA data for the anti-HLA-HBV peptide antibodies across the selected panel of peptides is shown in Figures 31-36 and represented as signal fold change relative to the isotype control. Antibodies NOV3040, NOV3499, and NOV3771, which target the HLA-HBV presented HBx92-100 peptide, show a high degree of specificity only binding to the HBx92-100 target at all concentrations tested (see Figures 31, 32 and 33 respectively). Similarly, antibodies NOV2505 (Figure 35) and NOV3522 (Figure 36) also show binding only to their intended target HLA-HBx52-60.

Example 12: Jurkat ADCC assay

[00292] The functionality of the anti-HLA-HBV peptide antibodies to induce an antibody-dependent cellular cytotoxicity (ADCC) was measured utilizing an FcγRIIa-expressing reporter cell line in which the reporter luciferase gene expresses upon activation via crosslinking by antigen bound antibodies described previously (Tada et al. PLoS One 2014; 9(4): e95787). Reporter cells were co-cultured with CHO stable cells over-expressing the fusion p(HBV-peptide)-β2m-HLA A2-DHFR target cells in a 12 point, 5 fold dose response starting at 10 µg/ml of the anti-HLA-HBV peptide antibodies. In addition to the native IgG1 backbone, antibodies tested were modified for enhanced NK cell recognition by specific mutations (S239D, A330L, I332E) of the Fc region (eADCC) (Lazar et al. Proceeding of the National Academy of Sciences of the United States of America 2006; 103(11):4005–4010) (hypofucosylation). Data is shown for individual antibodies in Figures 37-42 and AC50 values are represented as antibody concentration in which 50 percent of max luminescence is achieved.

[00293] All antibodies tested show clear induction of the NFAT pathway on their intended target as depicted by dose dependent luminescence signal. Upon modification of the anti-HLA-HBV

peptide antibodies to enhance NK cell recognition by eADCC, there is an expected and clear shift towards greater potency of the response. Antibodies targeting the HBx92-100 peptide, NOV2353 (Figure 37), NOV2772 (Figure 38), NOV3040 (Figure 39), NOV3499 (Figure 40), and ATG.B.E211 (Figure 42), show efficacy with AC50s for the IgG antibody ranging from 0.018nM to 14.8nM that further shift to an AC50 range of $3.4E^{-06}$nM to 0.052nM when modified to eADCC. ATG.B.E211 modified as eADCC shows a slight induction (AC50 3.77nM) on the HBx52-60 off-target CHO cell line (Figure 42). NOV2505, an antibody targeting HBx52-60, also demonstrates NFAT induction on the cell lines expressing their target with AC50s for the IgG antibody at 3.78nM that is further enhanced to 0.1nM upon eADCC modification (Figure 41).

Example 13: Crystal structures of NOV2505, NOV2353, and NOV2772

[00294] Crystal structures of the Fab portion of the anti-HLA-HBV peptide antibody complexed with HLA-A2 and peptide were solved for antibodies NOV2505, NOV2353, and NOV2772. The complex was prepared by pre-forming Fab:HLA-A2:Peptide complex and running this preparation over a size-exclusion column to remove unbound protein and peptide. The resulting complex was used for crystal screening at a concentration of 20 mg/mL. Crystallization trials were set up using a Mosquito crystallization robot in Intelli 3-drop trays (ART Robins Instruments Cat# 102-0001-03) using either Hampton Research Natrix, -Index, PEG-Ion, Qiagen-ComPAS, JCSG, or ProComplex screens. The protein was combined with precipitant at a ratio of 3:1 protein:crystallant in a sitting drop configuration. Trays were screened for crystallization events at regular intervals. Before data collection, resulting crystals were cryoprotected using cryoprotectant comprised of 75% of reservoir solutions (v:v) and 25% (v:v) glycerol and flash cooled in liquid nitrogen. Diffraction data was collected on the ALS 5.0.1 beamline using the ADSC Quantum R-315 detector.

[00295] NOV2353 Fab complexed with HLA-A2:HBx92-100 crystallized in 0.2M potassium/sodium tartrate with 20% PEG3350 (v:v,pH 7.4) diffracting to 2.85 Angstroms (hereafter, Ang) in space group P21221 with cell dimensions a=49.58 Ang, b=130.63 Ang, c=158.7 Ang, alpha=90°, beta=90°, gamma=90°. The final model was built using COOT (Emsley & Cowtan (2004) Acta Cryst. D60:2126-2132) and refined with Buster (Global phasing, LTD, Cambridge, UK) with PDB accession 3hla for HLA-A2 and a proprietary FAB structure for the Fab molecule. The Rwork and Rfree values are 22.8% and 28.6%, respectively. There is good electron density for HLA-A2, beta2-microglobulin, peptide and the variable domains of Fab NOV2353 (heavy and light chains). The main interactions of the HBx92-100 peptide to NOV2353 Fab are Lys4 (heavy chain CDR3-Glu99 (side-chain), Glu103 (backbone) and an additional contact from Ala100) and Arg5 (heavy chain CDR3-Glu104(side-chain)); position Leu2 is the peptide:HLA anchor position (see Figures 43 and 44).

[00296] NOV2772 Fab complexed with HLA-A2:HBx92-100 crystallized in 100mM Sodium citrate tribasic trihydrate (pH 5.5), 16% PEG 8000. The structure diffracted to 2.8 Ang in space group P1211 with cell dimensions a=49.46 Ang, b=168.67 Ang, c=129.85 Ang, alpha=90°, beta=96.94°, gamma=90°. The final model was built in COOT (Emsley & Cowtan (2004) Acta Cryst. D60:2126-2132) and refined with Buster (Global phasing, LTD, Cambridge, UK) with starting models 3hla for HLA-A2 and NOV2353 for Fab. The Rwork and Rfree values are 19.3% and 24.0% respectively. There is good electron density for HLA-A2, beta2-microglobulin, peptide and the variable domains of Fab NOV2772 (heavy and light chains). The peptide binding surface to both HLA-A2 and NOV2772 is well-resolved and a full description of the epitope can be made. Despite the consistent framework and only a few amino acid changes from NOV2353, there is considerable twist in binding of NOV2772 compared to NOV2353. The main interactions of the HBx92-100 peptide to NOV2772 Fab are His3 (HCDR3 Tyr104 (side-chain)), Lys4 (HCDR3-Glu99 (side-chain)), HCDR3 Gly100 (backbone), and additional hydrophobic packing of Lys4 sidechain to HCDR3 Tyr104(sidechain), Arg5 (HCDR3 Glu103 (sidechain)) bi-furcated salt bridge, LCDR3 Ser91 (backbone and sidechain) and an additional hydrophobic packing of Arg5 to HCDR1 Tyr32 (sidechain), and Leu7 via (LCDR3 Tyr92 shifted close to HLA and forms hydrogen bond to Lys146, and a water bridge between LCDR1 Ser30 and Gly8 (backbone) (see Figure 45 and 46). The increase in number of contacts to HBx92-100 by NOV2772 increases the specificity but does not have a dramatic increase in affinity.

[00297] NOV2505 Fab complexed with HLA-A2:HBx52-60 crystallized in 0.2M Lithium citrate tribasic tetrahydrate, 20% (w/v) PEG 3350 (pH 8.4). The structure diffracted to 2.4 Ang in space group P43212 with cell dimensions a=122.176 Ang, b=122.176 Ang, c=145.714 Ang, alpha=90°, beta=90°, gamma=90°. The final model was built in COOT (Emsley & Cowtan (2004) Acta Cryst. D60:2126-2132) and refined with Buster (Global phasing, LTD, Cambridge, UK) with starting models 3hla for HLA-A2 and NOV2353 for Fab. The Rwork and Rfree values are 20.1% and 24.1% respectively. There is good electron density for HLA-A2, beta2-microglobulin, peptide and the variable domains of Fab NOV2505 (heavy and light chains). There is poor density for the distal regions of the Fab (exposed to solvent). Side-chains are built in most regions except for the distal ends where they are cut back and the fit to density is poor. The peptide binding surface to both HLA-A2 and NOV2505 is well-resolved and a full description of the epitope can be made. The main interactions of the HBx52-60 peptide to NOV2505 Fab are Leu4 (heavy chain CDR3-Trp100 (sidechain)), Tyr101 (sidechain), Tyr107 (sidechain), Tyr111 (backbone), and Ser122 (backbone), Arg5 (Lys NH1 and NH2 (sidechain)) to light chain CDR1 Tyr91-carbonyl (backbone) and Asp92-carbonyl (backbone), heavy chain CDR3-Ser110 (backbone), Tyr111 (backbone/sidechain), light chain CDR1 Tyr32 (sidechain) and this is shown in Figures 47 and 48.

Example 14: Formulation

[00298] The anti-HLA-HBV peptide antibodies described herein are monoclonal antibodies, IgG1 isotype with kappa or lambda light chains, and can be lyophilized. For subsequent intravenous administration, the obtained solution will usually be further diluted into a carrier solution to the ready-to-use antibody solution for infusion. Important stability-indicating analytical methods to select the most stable formulation encompassed, amongst others, size-exclusion chromatography to determine aggregation levels, subvisible particulate matter testing, and potency testing.

[00299] It is understood that the examples and aspects described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

What is claimed is:

1. An antibody, wherein the antibody or antigen binding fragment thereof specifically binds a complex of human leukocyte antigens (HLA) and Hepatitis B virus (HBV) peptides and do not specifically bind either HLA or HBV peptides when the HBV peptide is not complexed with HLA.
2. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof specifically binds HBV and HLA-A.
3. The antibody or antigen binding fragment thereof of claim 2, wherein the antibody or antigen binding fragment thereof specifically binds HBV and HLA-A2.
4. The antibody or antigen binding fragment thereof of claim 3, wherein the antibody or antigen binding fragment thereof specifically binds HBV and HLA-A2:01.
5. The antibody or antigen binding fragment thereof of claim 3, wherein the antibody or antigen binding fragment thereof specifically binds HBV and HLA-A24:01.
6. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof specifically binds HBx92-100 peptide (SEQ ID NO:1) and HLA.
7. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof specifically binds HBx52-60 peptide (SEQ ID NO:2) and HLA.
8. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof specifically binds HBs172-180 peptide (SEQ ID NO:3) and HLA.
9. An antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof comprises:

   (i) a heavy chain variable region that comprises (a) a HCDR1 (CDR-Complementarity Determining Region) of SEQ ID NO:7, (b) a HCDR2 of SEQ ID NO:8, (c) a HCDR3 of SEQ ID NO:9 and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:23, (e) a LCDR2 of SEQ ID NO:24, and (f) a LCDR3 of SEQ ID NO:25;

   (ii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:39, (b) a HCDR2 of SEQ ID NO:40, (c) a HCDR3 of SEQ ID NO:41; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:55, (e) a LCDR2 of SEQ ID NO:56, and (f) a LCDR3 of SEQ ID NO:57;

   (iii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:71, (b) a HCDR2 of SEQ ID NO:72, (c) a HCDR3 of SEQ ID NO:73; and a light chain variable region

that comprises: (d) a LCDR1 of SEQ ID NO: 87, (e) a LCDR2 of SEQ ID NO:88, and (f) a LCDR3 of SEQ ID NO:89;

(iv) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:103, (b) a HCDR2 of SEQ ID NO:104, (c) a HCDR3 of SEQ ID NO:105; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:119, (e) a LCDR2 of SEQ ID NO:120, and (f) a LCDR3 of SEQ ID NO:121;

(v) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:135, (b) a HCDR2 of SEQ ID NO:136, (c) a HCDR3 of SEQ ID NO:137; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO: 151, (e) a LCDR2 of SEQ ID NO:152, and (f) a LCDR3 of SEQ ID NO:153;

(vi) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:167, (b) a HCDR2 of SEQ ID NO:168, (c) a HCDR3 of SEQ ID NO:169; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:183, (e) a LCDR2 of SEQ ID NO:184, and (f) a LCDR3 of SEQ ID NO:185;

(vii) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO: 199, (b) a HCDR2 of SEQ ID NO: 200, (c) a HCDR3 of SEQ ID NO: 201; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO: 215, (e) a LCDR2 of SEQ ID NO: 216, and (f) a LCDR3 of SEQ ID NO: 217;

(viii) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:231, (b) a HCDR2 of SEQ ID NO:232, (c) a HCDR3 of SEQ ID NO:233; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:247, (e) a LCDR2 of SEQ ID NO:248, and (f) a LCDR3 of SEQ ID NO:249;

(ix) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:263, (b) a HCDR2 of SEQ ID NO:264, (c) a HCDR3 of SEQ ID NO:265; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:279, (e) a LCDR2 of SEQ ID NO:280, and (f) a LCDR3 of SEQ ID NO:281;

(x) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:295, (b) a HCDR2 of SEQ ID NO:296, (c) a HCDR3 of SEQ ID NO:297; and a light chain variable

region that comprises: (d) a LCDR1 of SEQ ID NO:311, (e) a LCDR2 of SEQ ID NO:312, and (f) a LCDR3 of SEQ ID NO:313;

(xi) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:327, (b) a HCDR2 of SEQ ID NO:328, (c) a HCDR3 of SEQ ID NO:329; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:343, (e) a LCDR2 of SEQ ID NO:344, and (f) a LCDR3 of SEQ ID NO:345;

(xii) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO: 359, (b) a HCDR2 of SEQ ID NO:360, (c) a HCDR3 of SEQ ID NO:361; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:375, (e) a LCDR2 of SEQ ID NO:376, and (f) a LCDR3 of SEQ ID NO:377; or

(xiii) a heavy chain variable region that comprises: (a) a HCDR1 of SEQ ID NO:391, (b) a HCDR2 of SEQ ID NO:392, (c) a HCDR3 of SEQ ID NO:393; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO: 407, (e) a LCDR2 of SEQ ID NO: 408, and (f) a LCDR3 of SEQ ID NO:409.

10. The antibody or antigen binding fragment thereof of claim 9, wherein one or two amino acids within a CDR have been modified, deleted or substituted.

11. The antibody or antigen binding fragment thereof of claim 9, that retains at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identity over either the variable heavy chain region or the variable light chain region.

12. The antibody or antigen binding fragment thereof of claim 9, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a human antibody, a single chain antibody(scFv) or an antibody fragment.

13. The antibody or antigen binding fragment thereof of claim 9, wherein the antibody has reduced carbohydrate modification.

14. The antibody or antigen binding fragment thereof of claim 9, wherein the antibody is low in glycosylation or fucosylation.

15. The antibody or antigen binding fragment thereof of claim 9, wherein the antibody is hypofucosylated.

16. The antibody or antigen binding fragment thereof of claim 9, wherein the antibody FC region is modified, allowing for a reduction in glycosylation.

17. An antibody or antigen binding fragment thereof, wherein said antibody or antigen binding fragment thereof comprises:
(i) a heavy chain variable region (vH) that comprises SEQ ID NO: 16, and a light chain variable region (vL) that comprises SEQ ID NO: 32;

(ii) a heavy chain variable region (vH) that comprises SEQ ID NO:48, and a light chain variable region (vL) that comprises SEQ ID NO: 64;

(iii) a heavy chain variable region (vH) that comprises SEQ ID NO:80, and a light chain variable region (vL) that comprises SEQ ID NO:96;

(iv) a heavy chain variable region (vH) that comprises SEQ ID NO: 112, and a light chain variable region (vL) that comprises SEQ ID NO:128;

(v) a heavy chain variable region (vH) that comprises SEQ ID NO:144, and a light chain variable region (vL) that comprises SEQ ID NO:160;

(vi) a heavy chain variable region (vH) that comprises SEQ ID NO: 176, and a light chain variable region (vL) that comprises SEQ ID NO:192;

(vii) a heavy chain variable region (vH) that comprises SEQ ID NO:208, and a light chain variable region (vL) that comprises SEQ ID NO:224;

(viii) a heavy chain variable region (vH) that comprises SEQ ID NO:240, and a light chain variable region (vL) that comprises SEQ ID NO:256;

(ix) a heavy chain variable region (vH) that comprises SEQ ID NO:272, and a light chain variable region (vL) that comprises SEQ ID NO:288;

(x) a heavy chain variable region (vH) that comprises SEQ ID NO:304, and a light chain variable region (vL) that comprises SEQ ID NO:320;

(xi) a heavy chain variable region (vH) that comprises SEQ ID NO:336, and a light chain variable region (vL) that comprises SEQ ID NO:352;

(xii) a heavy chain variable region (vH) that comprises SEQ ID NO: 368, and a light chain variable region (vL) that comprises SEQ ID NO: 384; or

(xiii) a heavy chain variable region (vH) that comprises SEQ ID NO: 400, and a light chain variable region (vL) that comprises SEQ ID NO: 416.

18. The antibody or antigen binding fragment thereof of claim 17, that retains at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identity over either the variable light or variable heavy region.

19. The antibody or antigen binding fragment thereof of claim 17, wherein one, two, three, four or five, but less than 10 amino acids within the variable light or variable heavy region have been modified, deleted or substituted.

20. The antibody or antigen binding fragment thereof of claim 17, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a human antibody, a single chain antibody(scFv) or an antibody fragment.

21. The antibody or antigen binding fragment thereof of claim 17, wherein the antibody has reduced carbohydrate modification.

22. The antibody or antigen binding fragment thereof of claim 17, wherein the antibody is low in glycosylation or fucosylation.

23. The antibody or antigen binding fragment thereof of claim 17, wherein the antibody is hypofucosylated.

24. The antibody or antigen binding fragment thereof of claim 17, wherein the antibody FC region is modified, allowing for a reduction in glycosylation.

25. A pharmaceutical composition comprising the antibody or antigen binding fragment thereof, of claim 9 or 17, further comprising a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, wherein the pharmaceutically acceptable carrier contains histadine or a sugar.

27. The pharmaceutical composition of claim 26, wherein the sugar is sucrose.

28. A pharmaceutical composition comprising a plurality of an antibody or antigen binding fragment thereof of claim 9 or 17, wherein at least 0.05%, 0.1%, 0.5%, 1%, 2%, 3%, 5% or more or more of the antibodies in the composition have an α2,3–linked sialic acid residue.

29. A pharmaceutical composition comprising a plurality of an antibody or antigen binding fragment thereof of claim 9 or 17, wherein the antibodies comprise increased bisecting GlcNAc.

30. A method of reducing a hepatitis B virus infection comprising administering via injection or infusion to a patient in need thereof an effective amount of the antibody or antigen binding fragment thereof of claim 9 or 17.

31. The method of claim 30, wherein the patient in need is diagnosed with hepatitis B viruria or hepatitis B viremia.

32. The method of claim 31, wherein the patient is diagnosed with hepatitis B viremia in the blood or serum.

33. A method of treating or reducing the likelihood of a hepatitis B virus associated disorder, comprising administering via injection or infusion to a patient in need thereof an effective amount of the antibody or antigen binding fragment thereof, of any one of claims 1-29, and wherein the disorder is: liver failure, liver cirrhosis, or hepatocellular carcinoma.

34. The method of claim 33, wherein the antibody or antigen binding fragment thereof, or the pharmaceutical composition is administered in combination with another therapeutic agent.

35. The method of claim 34, wherein the therapeutic agent is another anti-viral agent.

36. The method of claim 35, wherein the anti-viral agent is: lamivudine, entecavir and tenofovir or alpha-interferon.

37. The method of claim 34, wherein the therapeutic agent is an immune checkpoint inhibitor.

38. The method of claim 37, wherein the immune checkpoint is selected from the group consisting of: PD-1, PD-L1, PD-L2, TIM3, CTLA-4, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR.

39. The method of claim 38, wherein the immune checkpoint inhibitor is an anti-PD-L1 antibody.

40. The method of claim 34, wherein the therapeutic agent is an additional anti-HBV antibody.

41. The method of claim 40, wherein the additional anti-HBV antibody is an anti-Hepatitis B surface antigen (HBVsAg) antibody.

42. The method of claim 34, wherein the therapeutic agent is a TLR agonist.

43. The method of claim 42, wherein the TRL agonist is a TLR7 or TLR8 agonist.

44. The method of claim 34, wherein the therapeutic agent is viral replication inhibitor.

45. The method of claim 44, wherein the viral replication inhibitor is a capsid inhibitor.

46. Use of the antibody or antigen binding fragment thereof, of any one of claims 1-29 for reducing hepatitis B virus infection.

47. Use of the antibody or antigen binding fragment thereof, of any one of claims 1-29 in the treatment or reducing the likelihood of: liver failure, liver cirrhosis, and/or hepatocellular carcinoma.

48. The use according to claim 47, wherein the antibody or antigen binding fragment thereof, is administered in combination with another therapeutic agent.

49. The use according to claim 48, wherein the therapeutic agent is an anti-viral agent.

50. The use according to claim 49, wherein the anti-viral agent is: lamivudine, entecavir and tenofovir or alpha-interferon.

51. The use according to claim 48, wherein the therapeutic agent is an immune checkpoint modulator.

52. The use according to claim 51, wherein the immune checkpoint modulator is selected from the group consisting of: PD-1, PD-L1, PD-L2, TIM3, CTLA-4, LAG-3, CEACAM-1, CEACAM-5, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR.

53. The use according to claim 52, wherein the immune checkpoint modulator is an anti-PD-L1 antibody.

54. The use according to claim 48, wherein the therapeutic agent is an additional anti-HBV antibody.

55. A nucleic acid that encodes the antibody or antigen binding fragment any one of claims 1-29.

56. A vector comprising the nucleic acid of claim 55.

57. A host cell comprising the vector of claim 56.

58. A diagnostic reagent comprising the antibody or antigen binding fragment thereof any one of claims 1-29 which is labeled.

59. The diagnostic reagent of claim 58, wherein the label is selected from the group consisting of a radiolabel, a fluorophore, a chromophore, an imaging agent, and a metal ion.

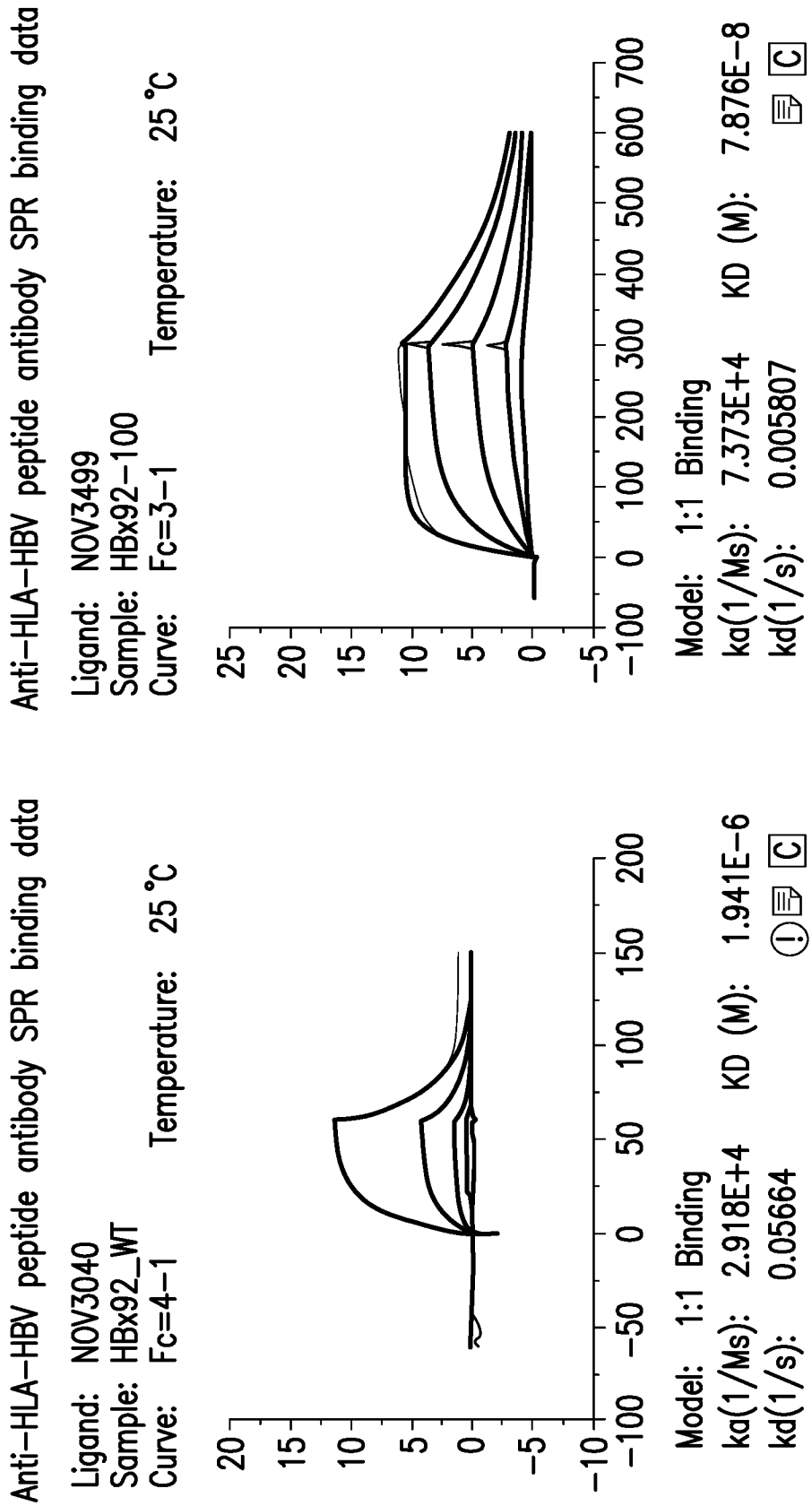

Anti-HLA-HBV peptide antibody SPR binding data
Ligand: NOV3040
Sample: HBx92_WT
Curve: Fc=4-1
Temperature: 25 °C
20
15
10
5
0
-5
-10
-100 -50 0 50 100 150 200
Model: 1:1 Binding
ka(1/Ms): 2.918E+4
KD (M): 1.941E-6
kd(1/s): 0.05664
Anti-HLA-HBV peptide antibody SPR binding data
Ligand: NOV3499
Sample: HBx92-100
Curve: Fc=3-1
Temperature: 25 °C
25
20
15
10
5
0
-5
-100 0 100 200 300 400 500 600 700
Model: 1:1 Binding
ka(1/Ms): 7.373E+4
KD (M): 7.876E-8
kd(1/s): 0.005807

FIG.1A

FIG.1B

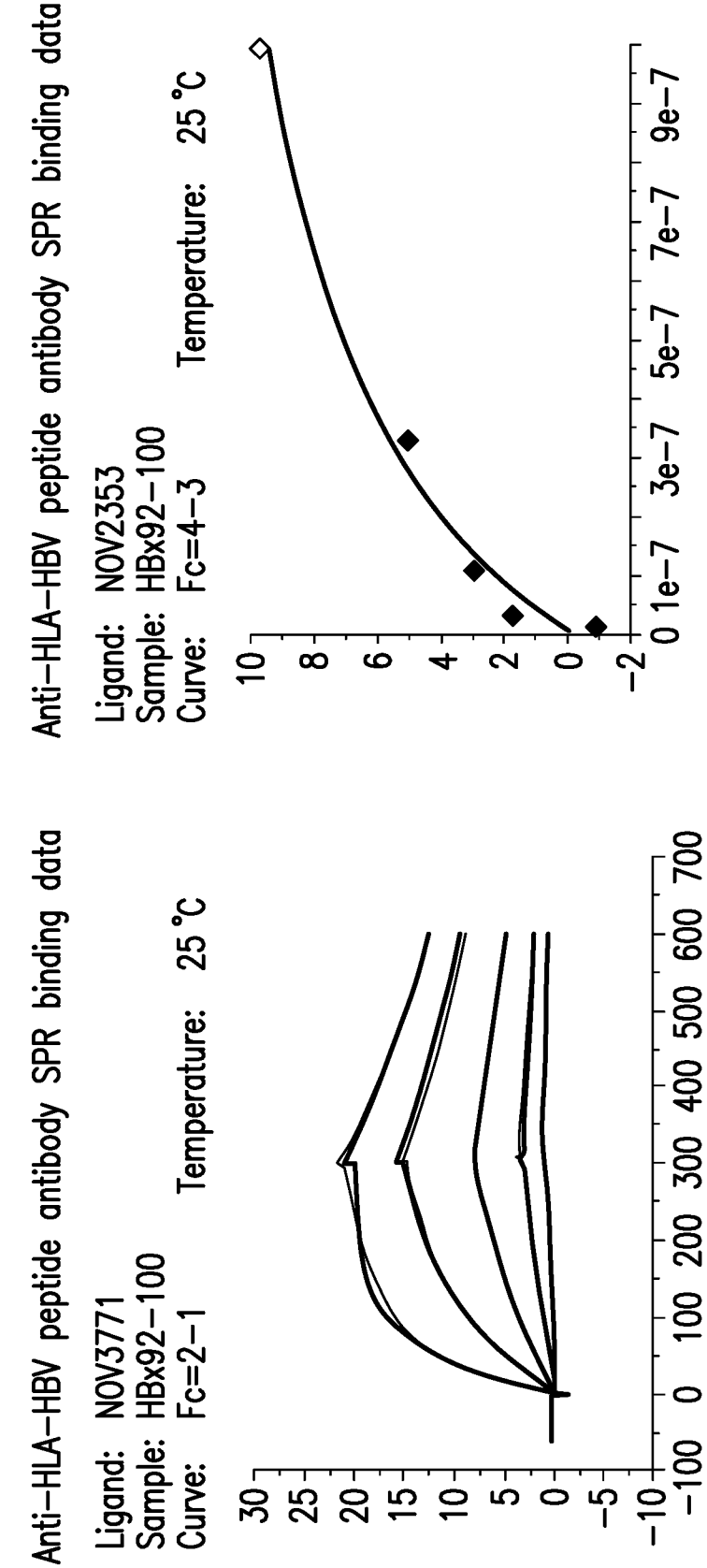
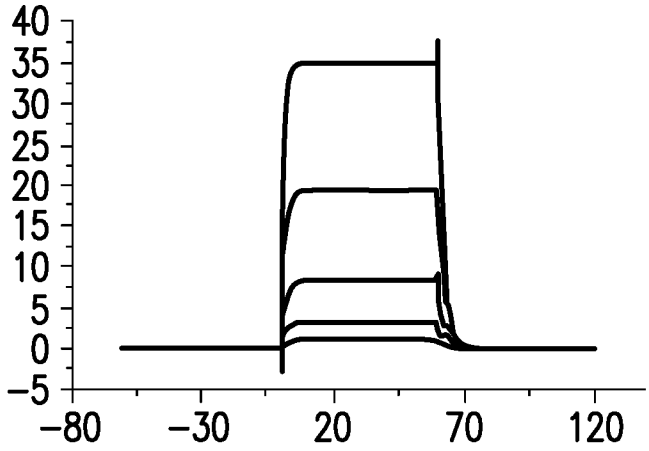

Anti-HLA-HBV peptide antibody SPR binding data
Ligand: NOV3771
Sample: HBx92-100
Curve: Fc=2-1
Temperature: 25 °C
30
25
20
15
10
5
0
-5
-10
-100 0 100 200 300 400 500 600 700
Model: 1:1 Binding
ka(1/Ms): 8.366E+4
KD (M): 2.094E-8
kd(1/s): 0.001752
C
Anti-HLA-HBV peptide antibody SPR binding data
Ligand: NOV2353
Sample: HBx92-100
Curve: Fc=4-3
Temperature: 25 °C
10
8
6
4
2
0
-2
0 1e-7 3e-7 5e-7 7e-7 9e-7
Model: Steady State Affinity
KD (M): 4.706E-7
C

FIG.1C

FIG.1D

Anti-HLA-HBV peptide antibody SPR binding data

Ligand: NOV3638
Sample: HBx92-100
Curve: Fc=3-1 Temperature: 25 °C

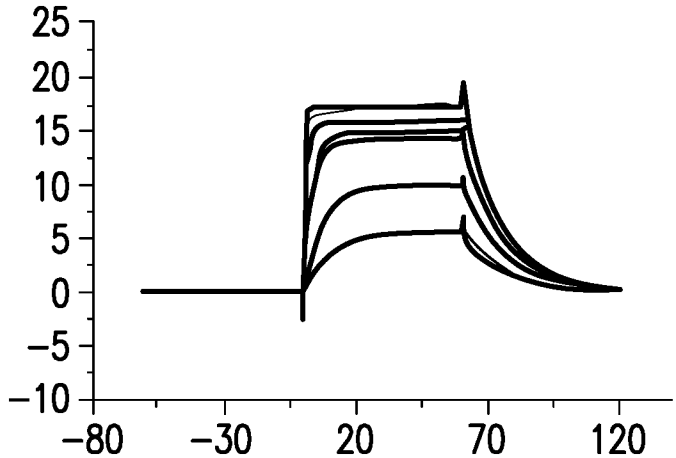


Model: 1:1 Binding
ka(1/Ms): 6.544E+5 KD (M): 7.136E-7
kd(1/s): 0.4670

FIG.2A

Anti-HLA-HBV peptide antibody SPR binding data

Ligand: ATG.E211
Sample: HBx92-100
Curve: Fc=2-1 Temperature: 25 °C



Model: 1:1 Binding
ka(1/Ms): 5.154E+6 KD (M): 1.807E-8
kd(1/s): 0.09315

FIG.2B

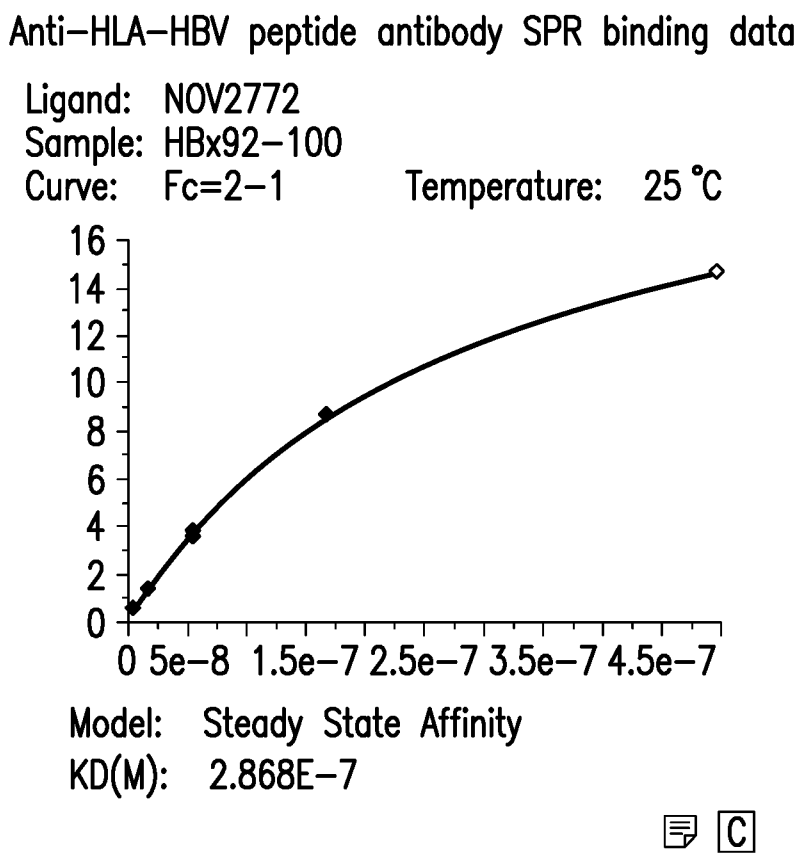

Anti-HLA-HBV peptide antibody SPR binding data
Ligand: NOV2772
Sample: HBx92-100
Curve: Fc=2-1
Temperature: 25 °C
16
14
12
10
8
6
4
2
0
0 5e-8 1.5e-7 2.5e-7 3.5e-7 4.5e-7
Model: Steady State Affinity
KD(M): 2.868E-7
C

FIG.2C

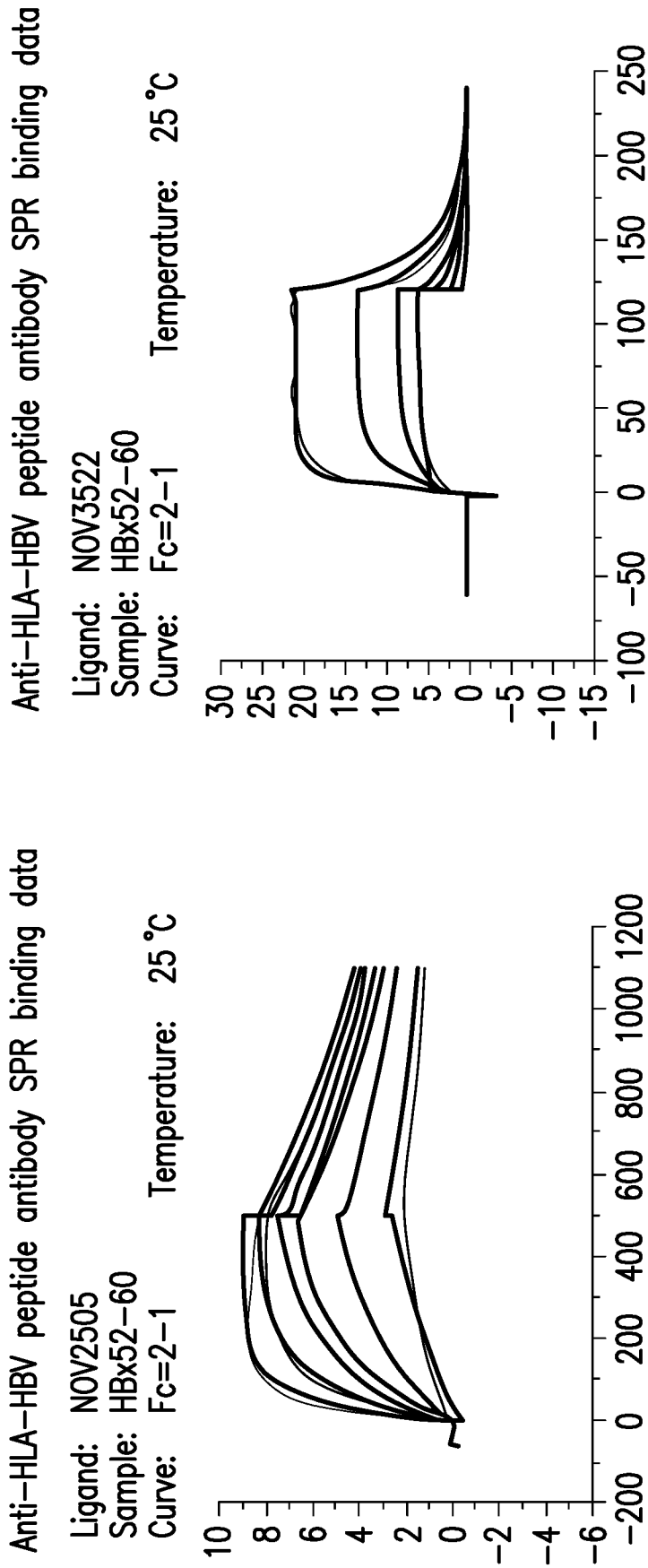

Anti-HLA-HBV peptide antibody SPR binding data
Ligand: NOV2505
Sample: HBx52-60
Curve: Fc=2-1
Temperature: 25 °C
10
8
6
4
2
0
-2
-4
-6
-200 0 200 400 600 800 1000 1200
Model: 1:1 Binding
ka(1/Ms): 3.539E+4
KD (M): 3.201E-8
kd(1/s): 0.001133
Anti-HLA-HBV peptide antibody SPR binding data
Ligand: NOV3522
Sample: HBx52-60
Curve: Fc=2-1
Temperature: 25 °C
30
25
20
15
10
5
0
-5
-10
-15
-100 -50 0 50 100 150 200 250
Model: 1:1 Binding
ka(1/Ms): 3.419E+5
KD (M): 2.289E-7
kd(1/s): 0.07828

FIG.3A

FIG.3B

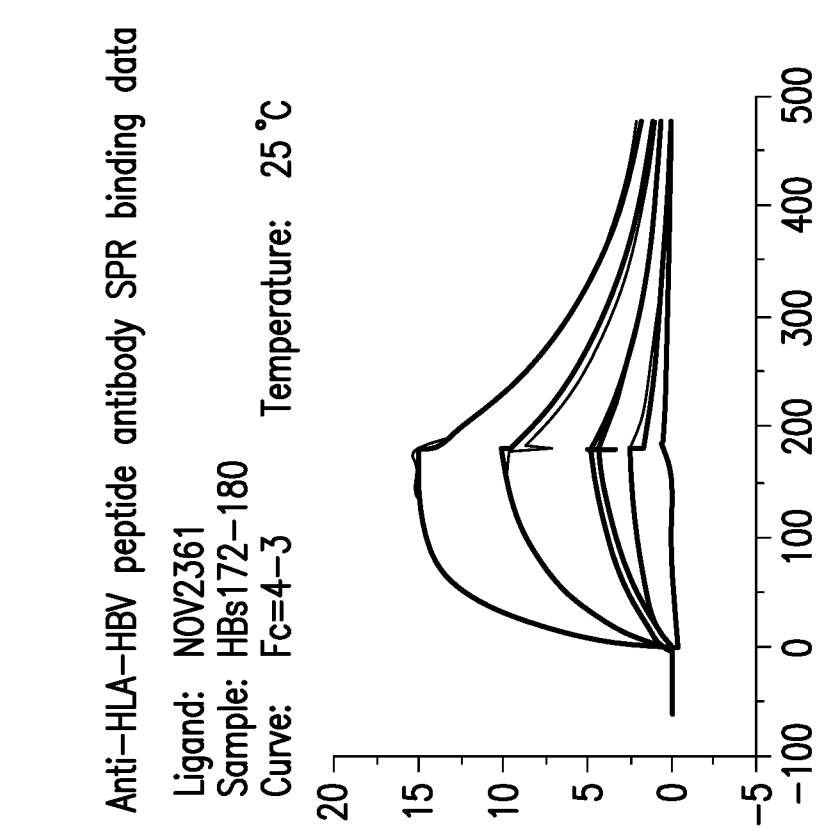

Anti-HLA-HBV peptide antibody SPR binding data
Ligand: NOV2361
Sample: HBs172-180
Curve: Fc=4-3
Temperature: 25 °C
20
15
10
5
0
-5
-100 0 100 200 300 400 500
Model: 1:1 Binding
ka(1/Ms): 1.295E+5
KD (M): 5.489E-8
kd(1/s): 0.007110
C

FIG.3C

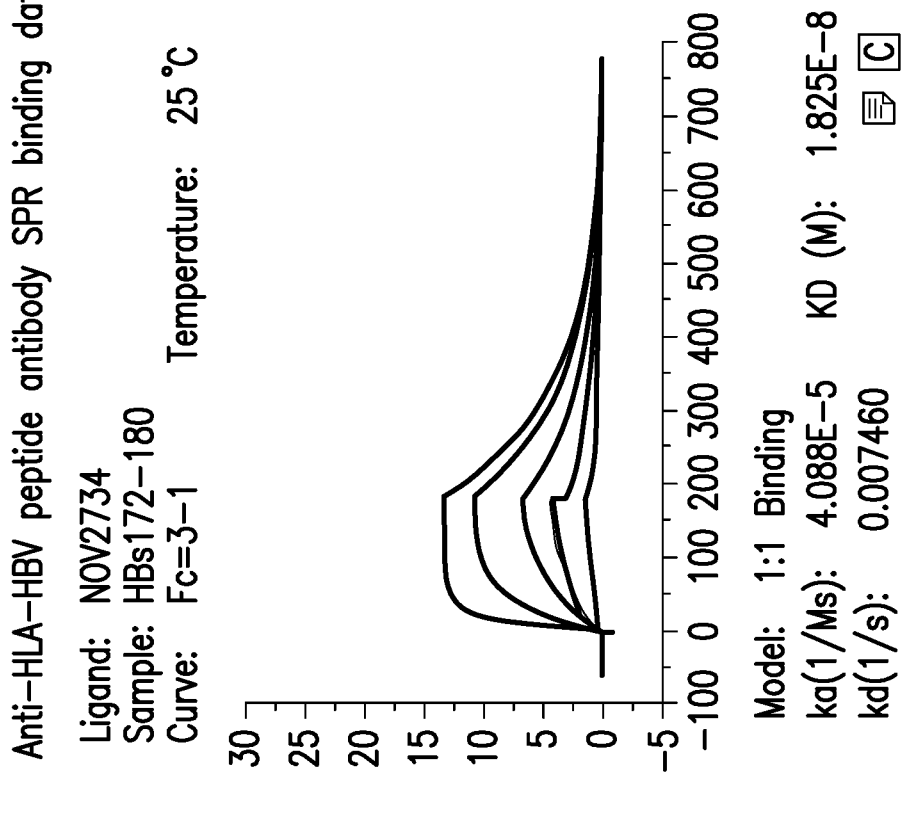

Anti-HLA-HBV peptide antibody SPR binding data
Ligand: NOV2734
Sample: HBs172-180
Curve: Fc=3-1
Temperature: 25 °C
30
25
20
15
10
5
0
-5
-100 0 100 200 300 400 500 600 700 800
Model: 1:1 Binding
ka(1/Ms): 4.088E-5
KD (M): 1.825E-8
kd(1/s): 0.007460
C

FIG.3D

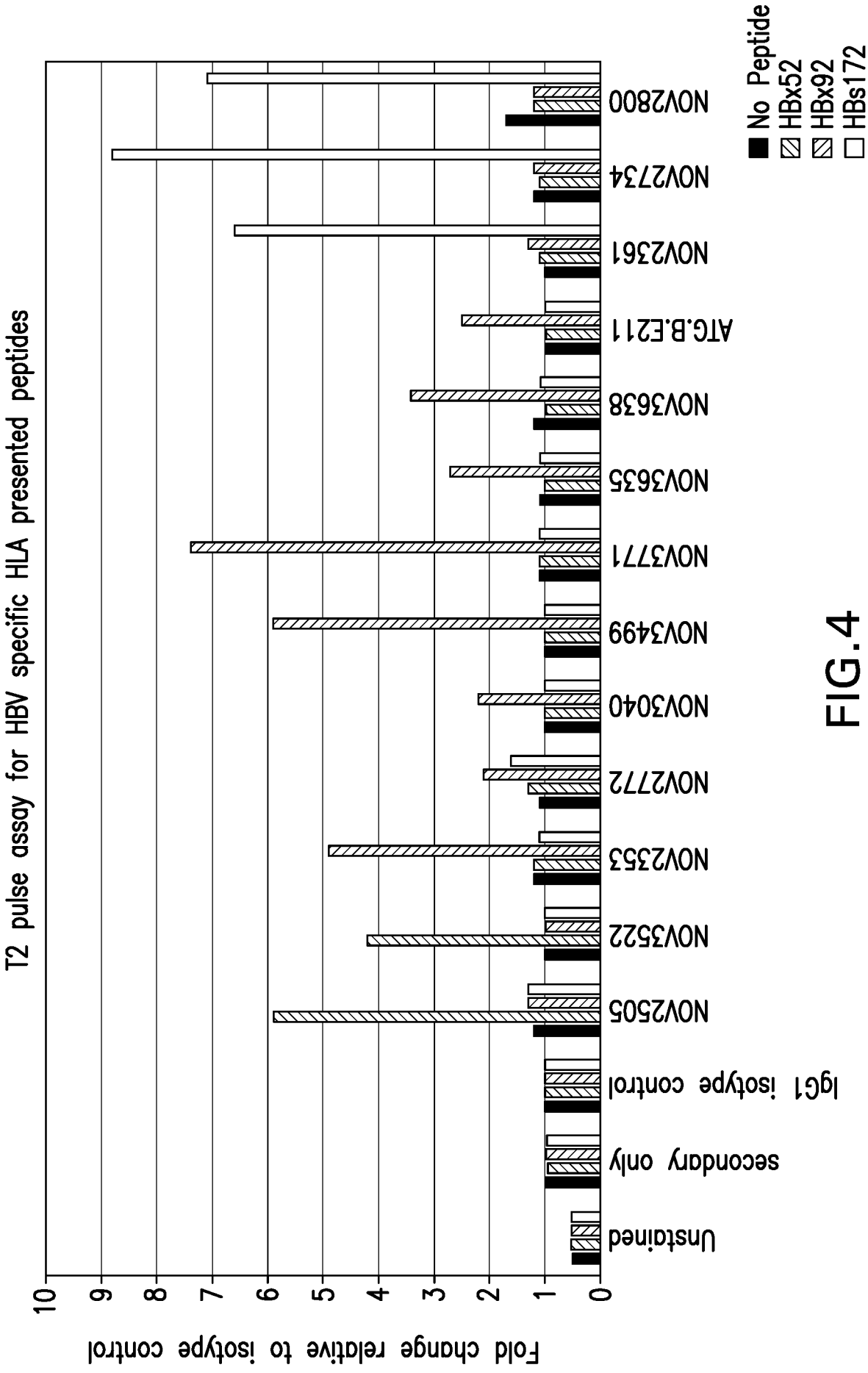

T2 pulse assay for HBV specific HLA presented peptides
Fold change relative to isotype control
0
1
2
3
4
5
6
7
8
9
10
Unstained
secondary only
Igg1 isotype control
NOV2505
NOV3522
NOV2353
NOV2772
NOV3040
NOV3499
NOV3771
NOV3635
NOV3638
ATG.B.E211
NOV2361
NOV2734
NOV2800
No Peptide
HBx52
HBx92
HBs172

FIG.4

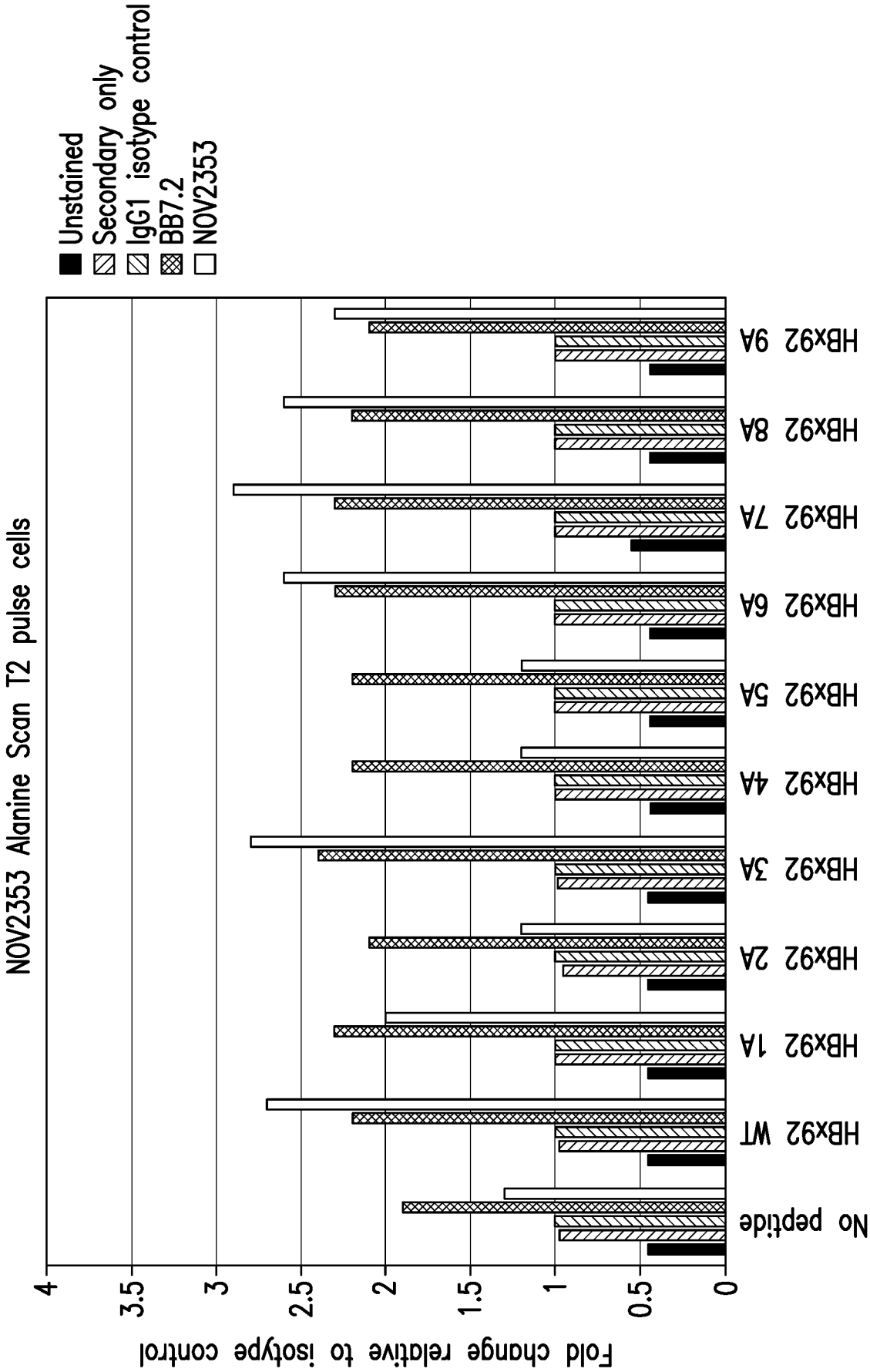

NOV2353 Alanine Scan T2 pulse cells
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV2353
Fold change relative to isotype control
4
3.5
3
2.5
2
1.5
1
0.5
0
No peptide
HBx92 WT
HBx92 1A
HBx92 2A
HBx92 3A
HBx92 4A
HBx92 5A
HBx92 6A
HBx92 7A
HBx92 8A
HBx92 9A

FIG.5

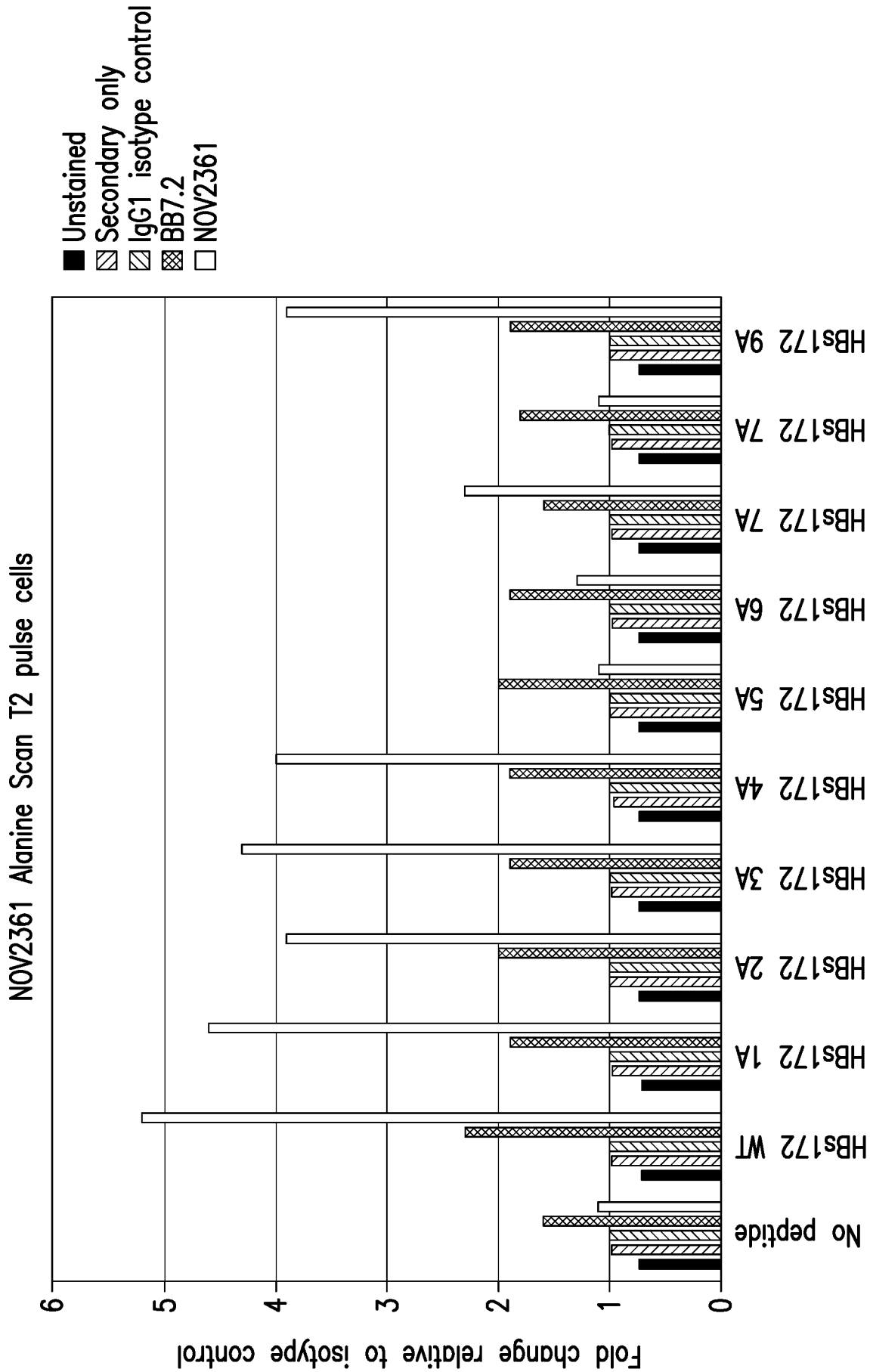

Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV2361
NOV2361 Alanine Scan T2 pulse cells
Fold change relative to isotype control
0
1
2
3
4
5
6
No peptide
HBs172 WT
HBs172 1A
HBs172 2A
HBs172 3A
HBs172 4A
HBs172 5A
HBs172 6A
HBs172 7A
HBs172 7A
HBs172 9A

FIG.6

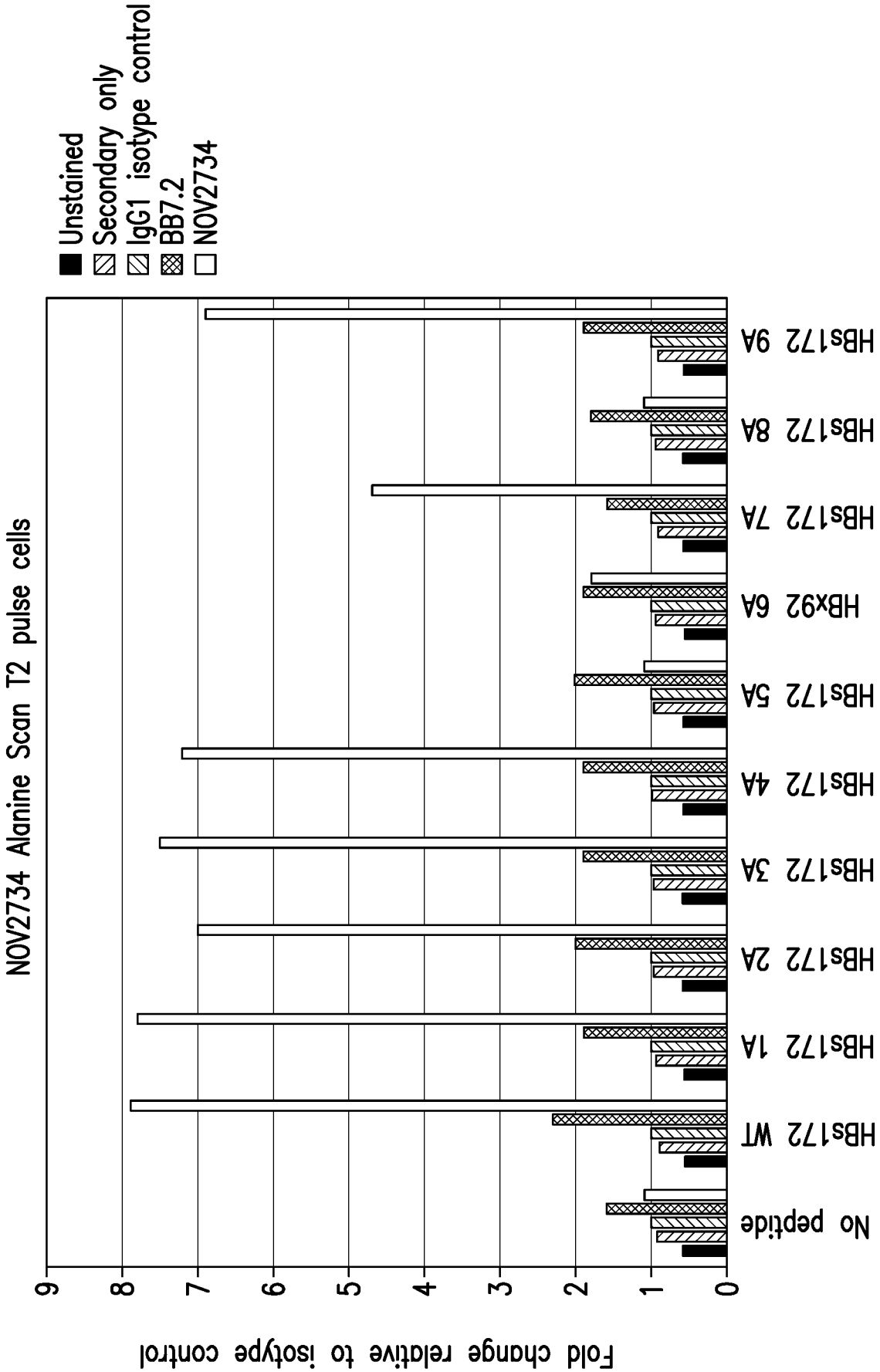

NOV2734 Alanine Scan T2 pulse cells
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV2734
Fold change relative to isotype control
0
1
2
3
4
5
6
7
8
9
No peptide
HBs172 WT
HBs172 1A
HBs172 2A
HBs172 3A
HBs172 4A
HBs172 5A
HBx92 6A
HBs172 7A
HBs172 8A
HBs172 9A

FIG. 7

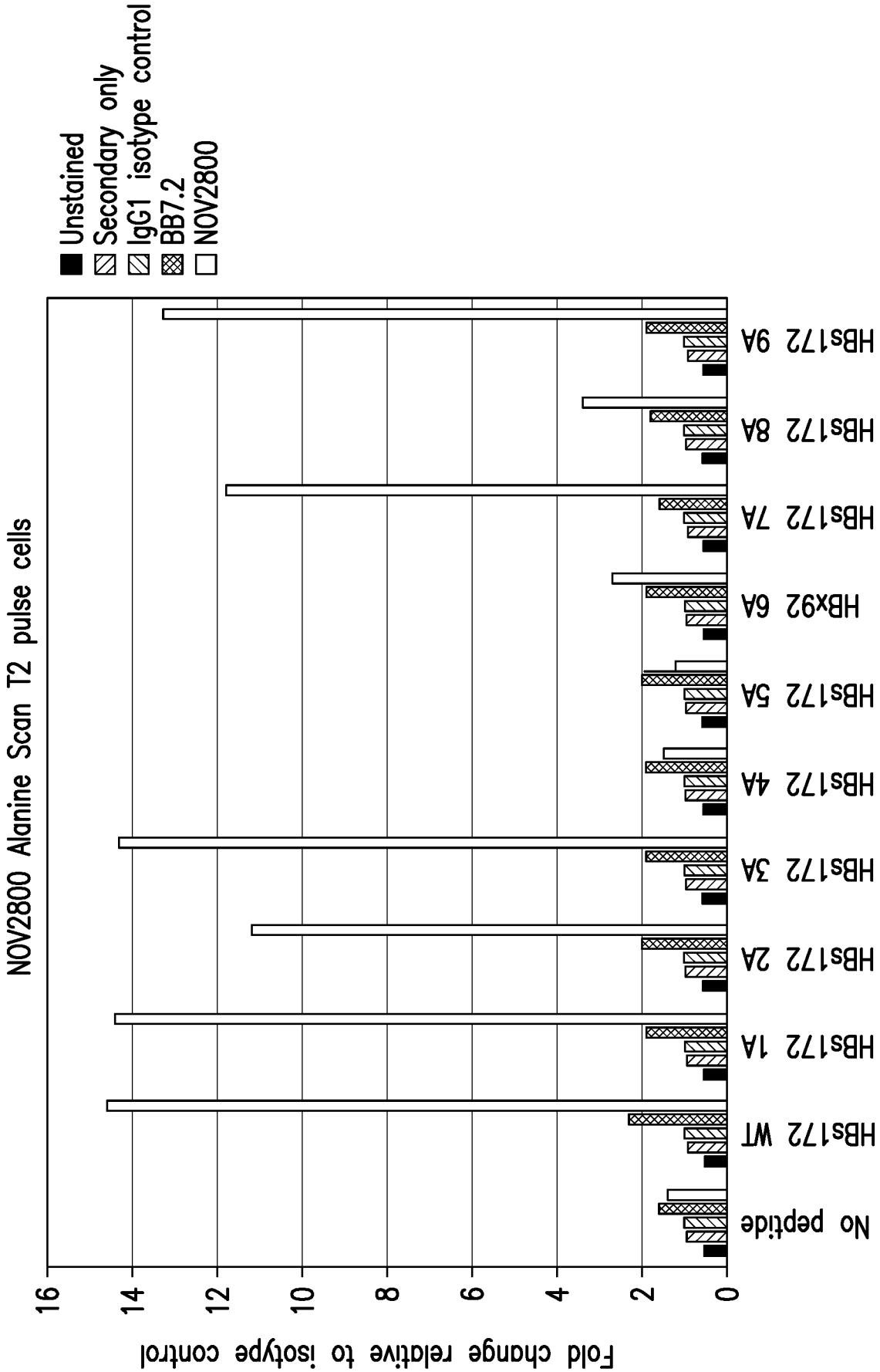

NOV2800 Alanine Scan T2 pulse cells
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV2800
Fold change relative to isotype control
0
2
4
6
8
10
12
14
16
No peptide
HBs172 WT
HBs172 1A
HBs172 2A
HBs172 3A
HBs172 4A
HBs172 5A
HBx92 6A
HBs172 7A
HBs172 8A
HBs172 9A

FIG.8

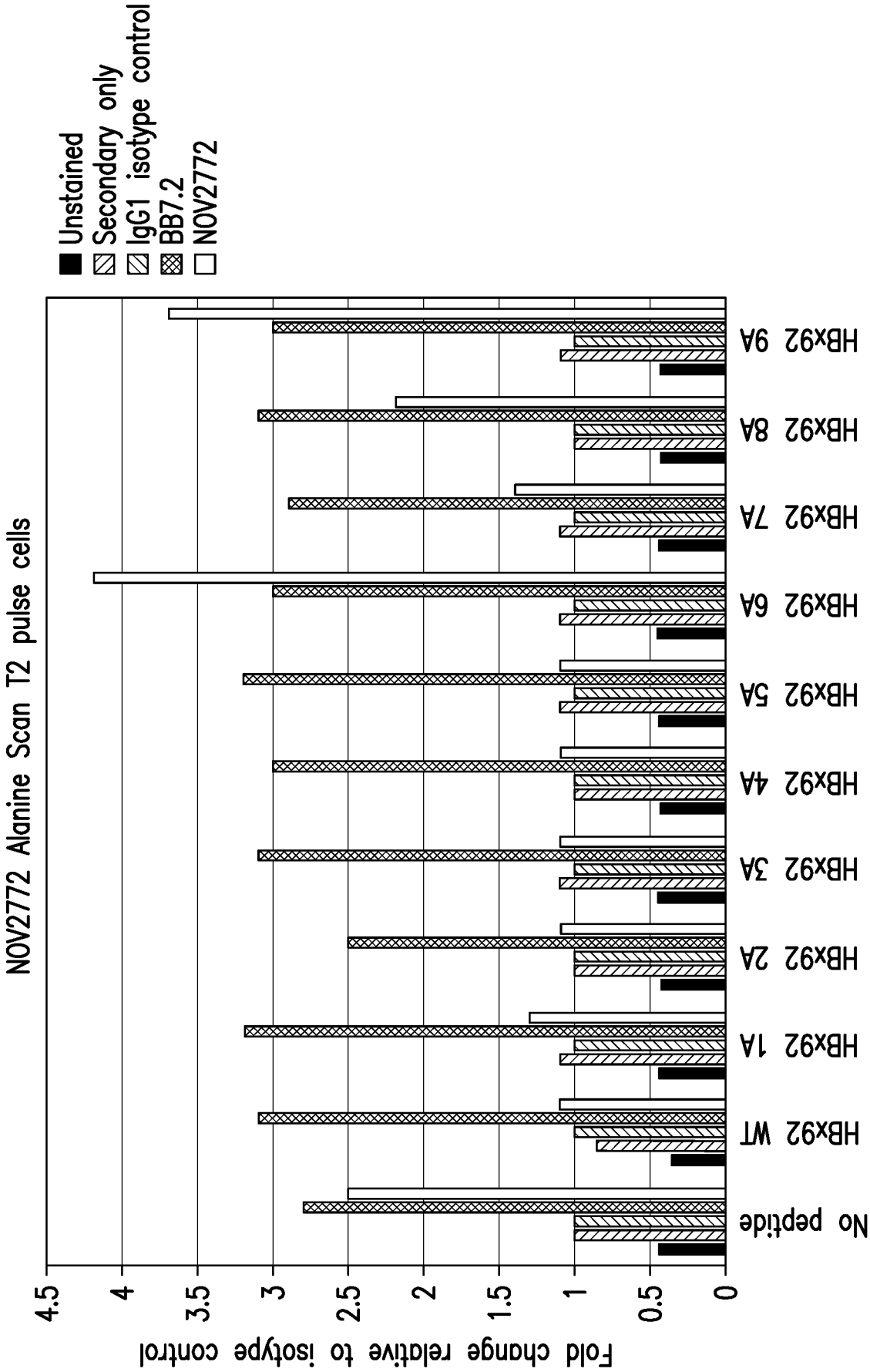

NOV2772 Alanine Scan T2 pulse cells
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV2772
Fold change relative to isotype control
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
No peptide
HBx92 WT
HBx92 1A
HBx92 2A
HBx92 3A
HBx92 4A
HBx92 5A
HBx92 6A
HBx92 7A
HBx92 8A
HBx92 9A

FIG.9

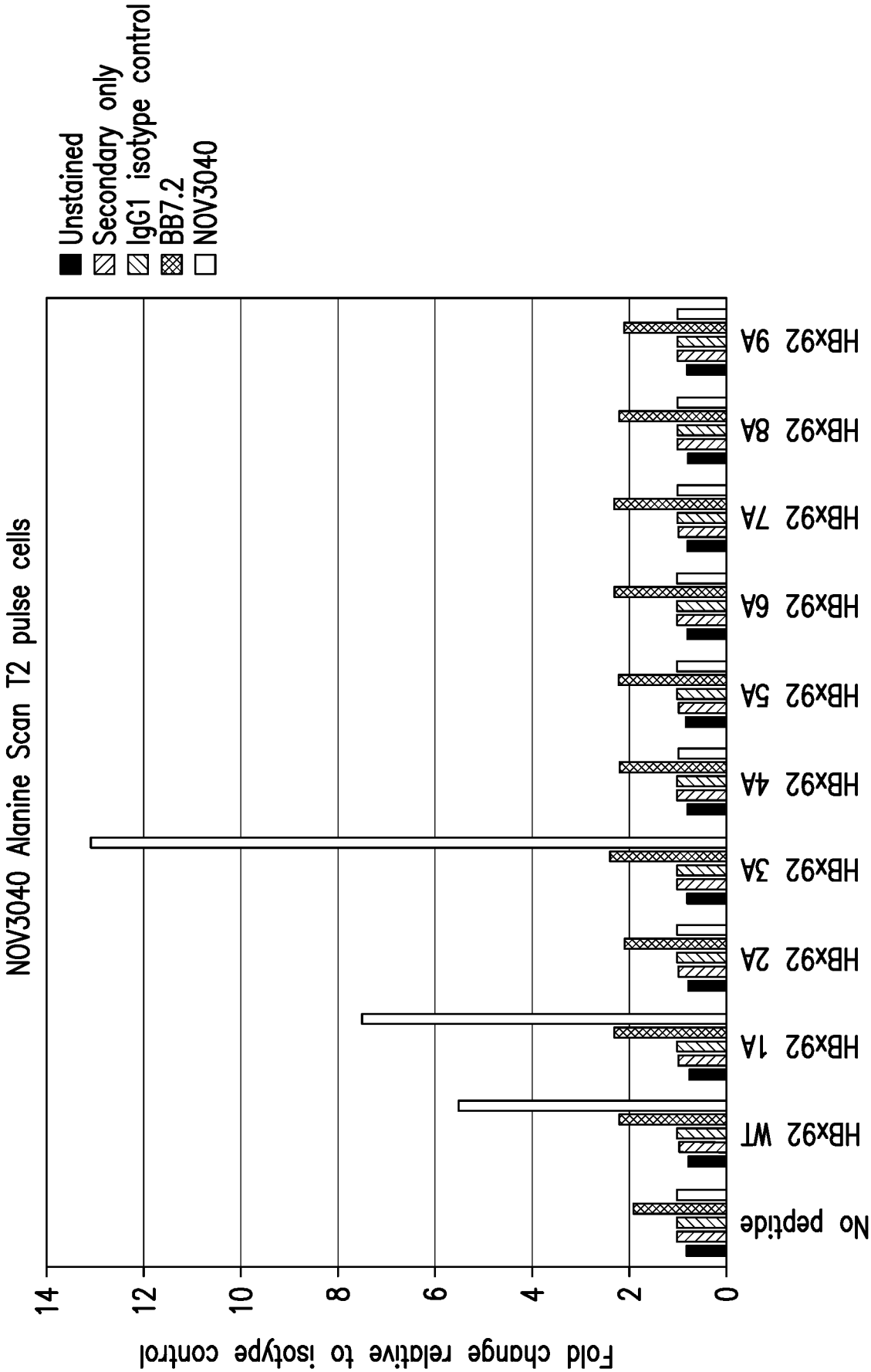

NOV3040 Alanine Scan T2 pulse cells
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV3040
Fold change relative to isotype control
0
2
4
6
8
10
12
14
No peptide
HBx92 WT
HBx92 1A
HBx92 2A
HBx92 3A
HBx92 4A
HBx92 5A
HBx92 6A
HBx92 7A
HBx92 8A
HBx92 9A

FIG.1O

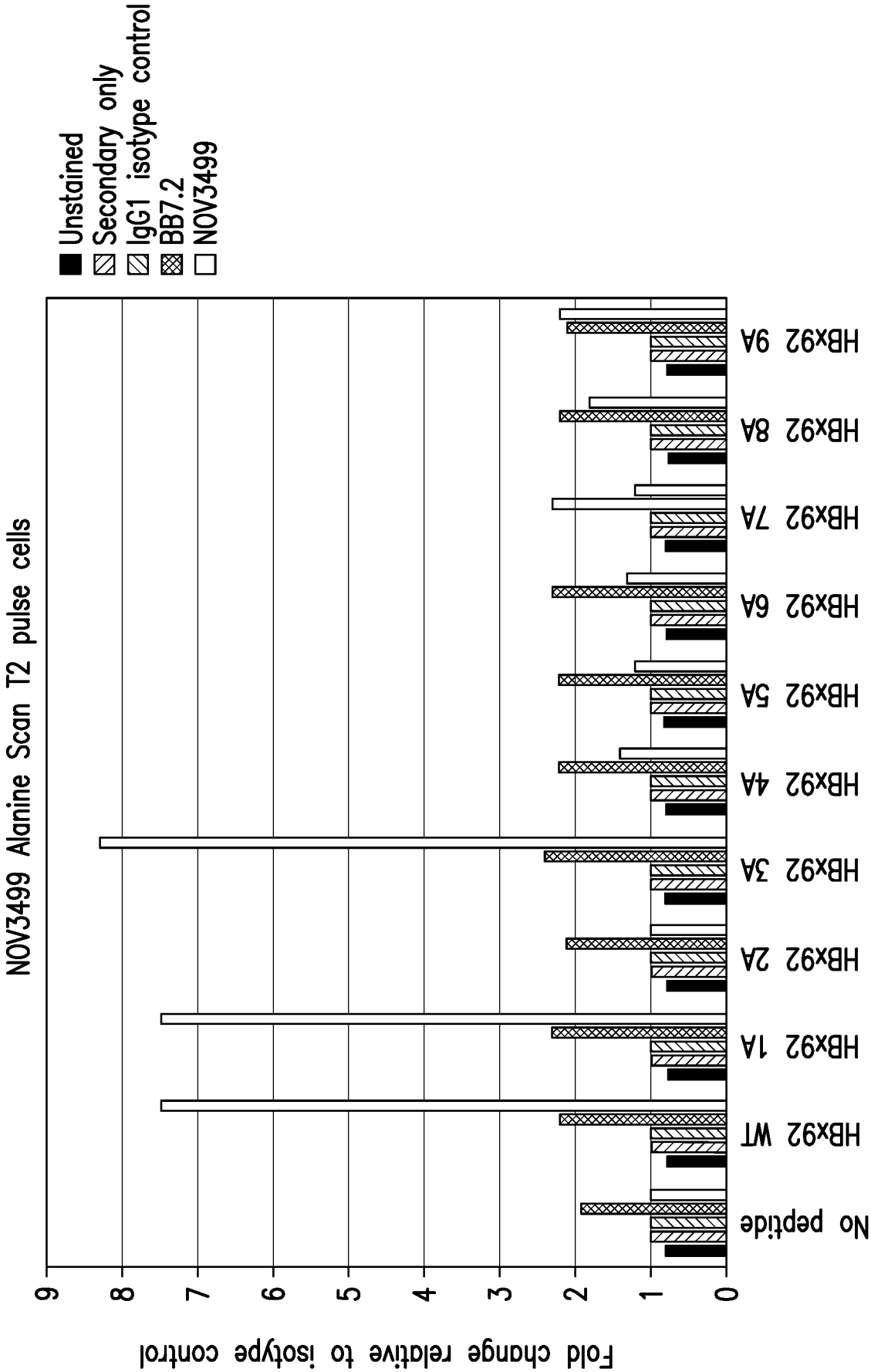

NOV3499 Alanine Scan T2 pulse cells
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV3499
Fold change relative to isotype control
0
1
2
3
4
5
6
7
8
9
No peptide
HBx92 WT
HBx92 1A
HBx92 2A
HBx92 3A
HBx92 4A
HBx92 5A
HBx92 6A
HBx92 7A
HBx92 8A
HBx92 9A

FIG.11

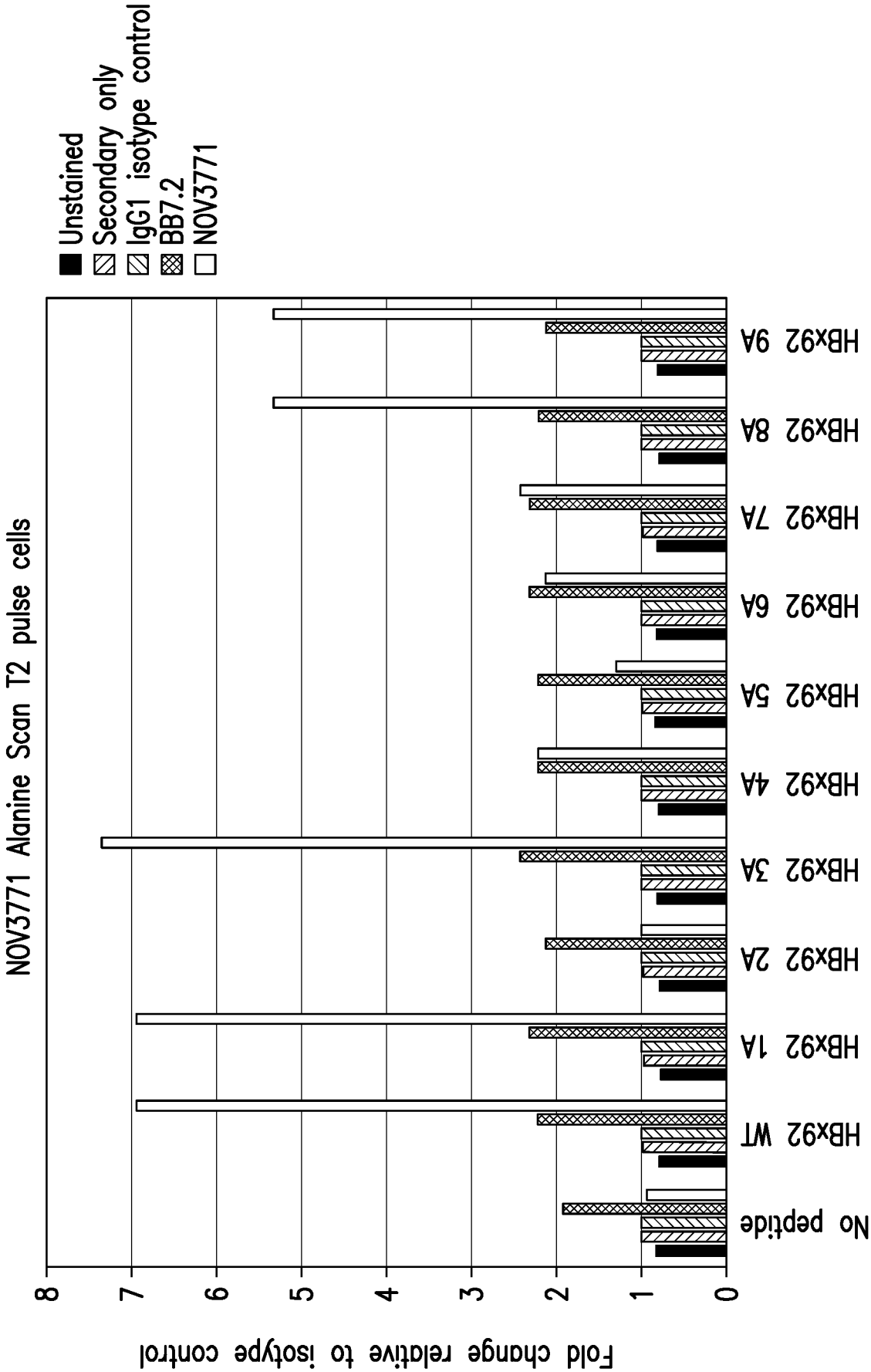

NOV3771 Alanine Scan T2 pulse cells
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV3771
Fold change relative to isotype control
0
1
2
3
4
5
6
7
8
No peptide
HBx92 WT
HBx92 1A
HBx92 2A
HBx92 3A
HBx92 4A
HBx92 5A
HBx92 6A
HBx92 7A
HBx92 8A
HBx92 9A

FIG.12

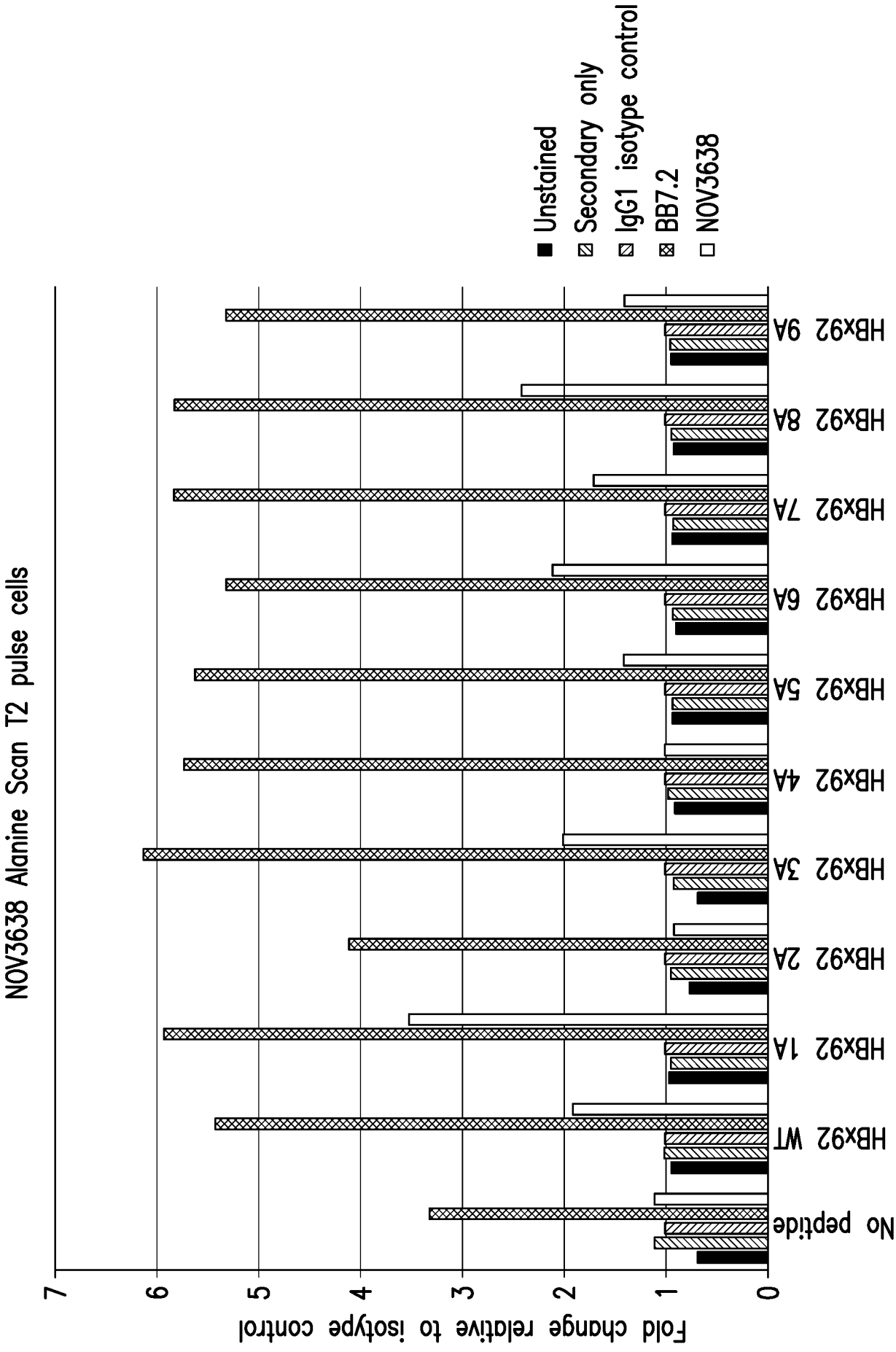

NOV3638 Alanine Scan T2 pulse cells
Fold change relative to isotype control
0
1
2
3
4
5
6
7
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV3638
No peptide
HBx92 WT
HBx92 1A
HBx92 2A
HBx92 3A
HBx92 4A
HBx92 5A
HBx92 6A
HBx92 7A
HBx92 8A
HBx92 9A

FIG.13

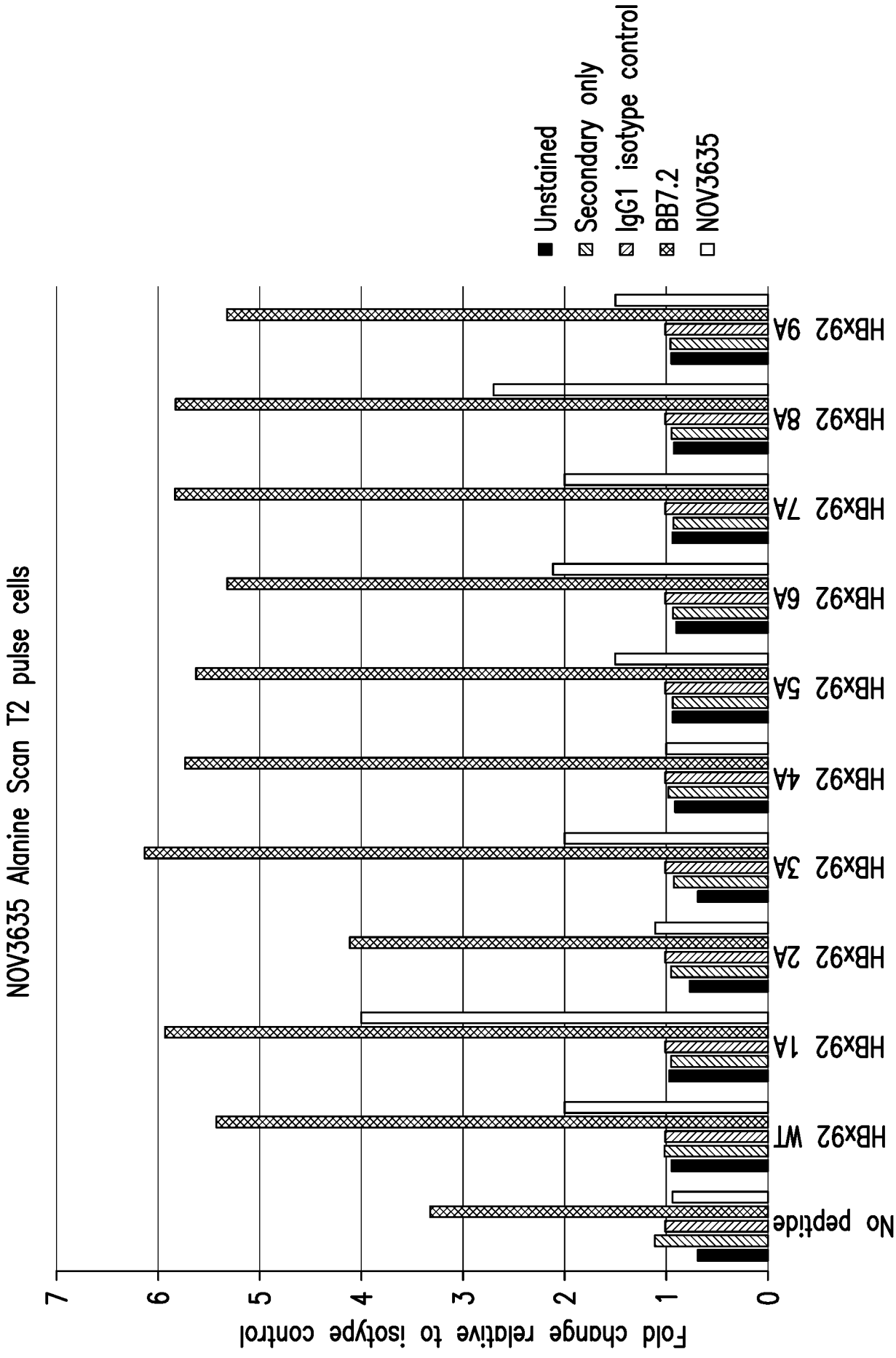

NOV3635 Alanine Scan T2 pulse cells
Fold change relative to isotype control
0
1
2
3
4
5
6
7
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV3635
No peptide
HBx92 WT
HBx92 1A
HBx92 2A
HBx92 3A
HBx92 4A
HBx92 5A
HBx92 6A
HBx92 7A
HBx92 8A
HBx92 9A

FIG.14

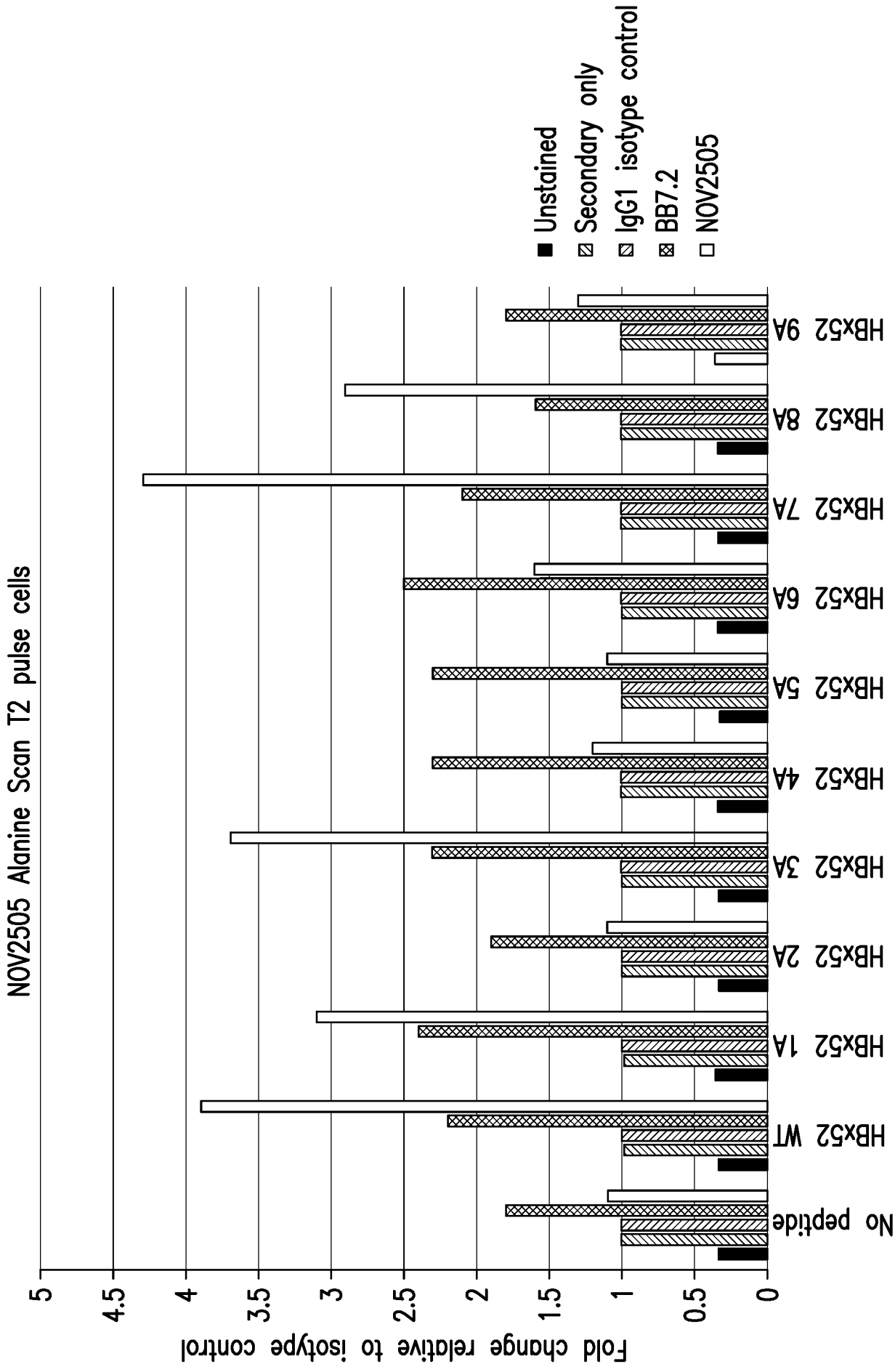

NOV2505 Alanine Scan T2 pulse cells
Fold change relative to isotype control
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
No peptide
HBx52 WT
HBx52 1A
HBx52 2A
HBx52 3A
HBx52 4A
HBx52 5A
HBx52 6A
HBx52 7A
HBx52 8A
HBx52 9A
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV2505

FIG.15

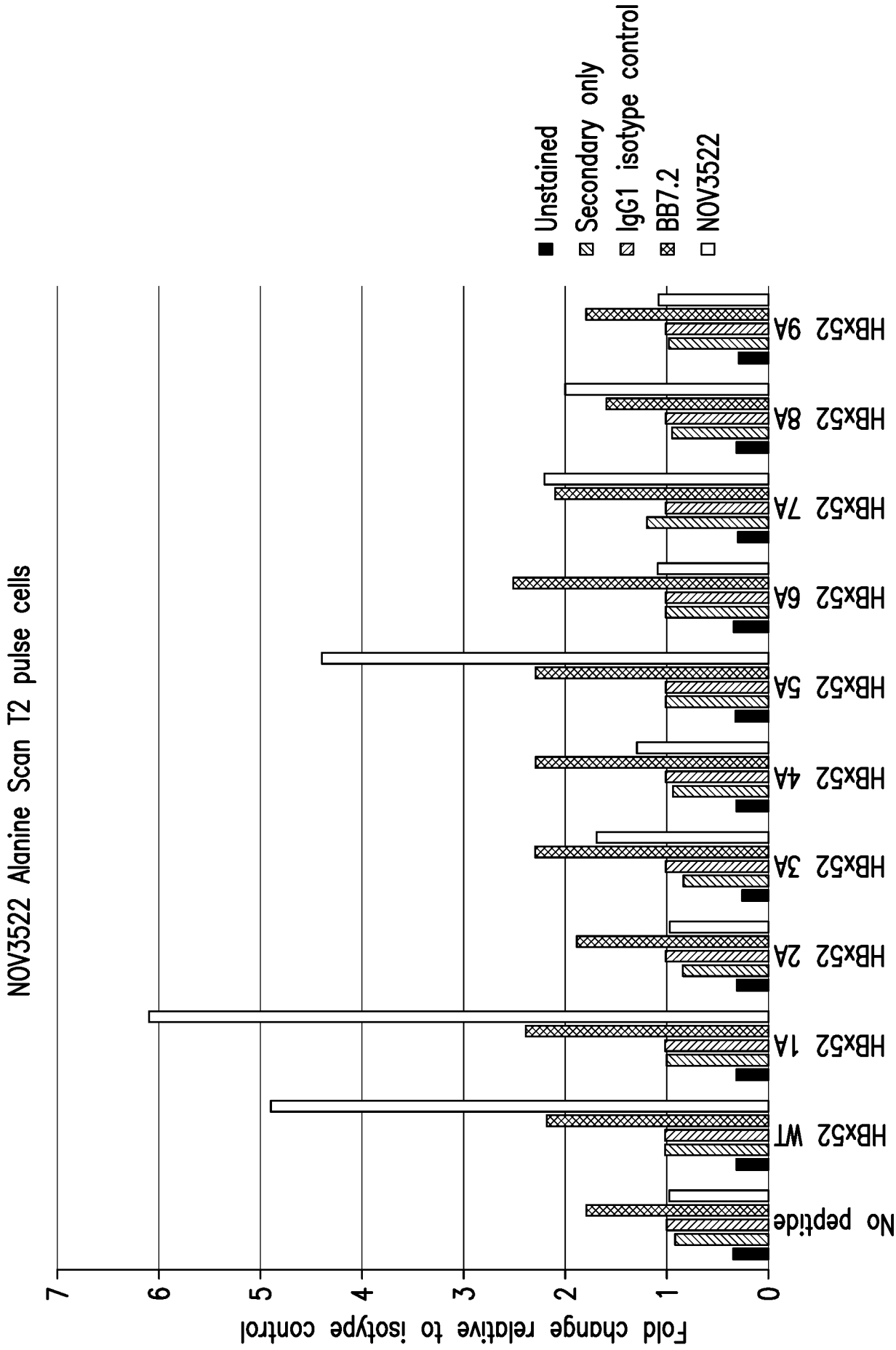

NOV3522 Alanine Scan T2 pulse cells
Fold change relative to isotype control
0
1
2
3
4
5
6
7
Unstained
Secondary only
IgG1 isotype control
BB7.2
NOV3522
No peptide
HBx52 WT
HBx52 1A
HBx52 2A
HBx52 3A
HBx52 4A
HBx52 5A
HBx52 6A
HBx52 7A
HBx52 8A
HBx52 9A

FIG.16

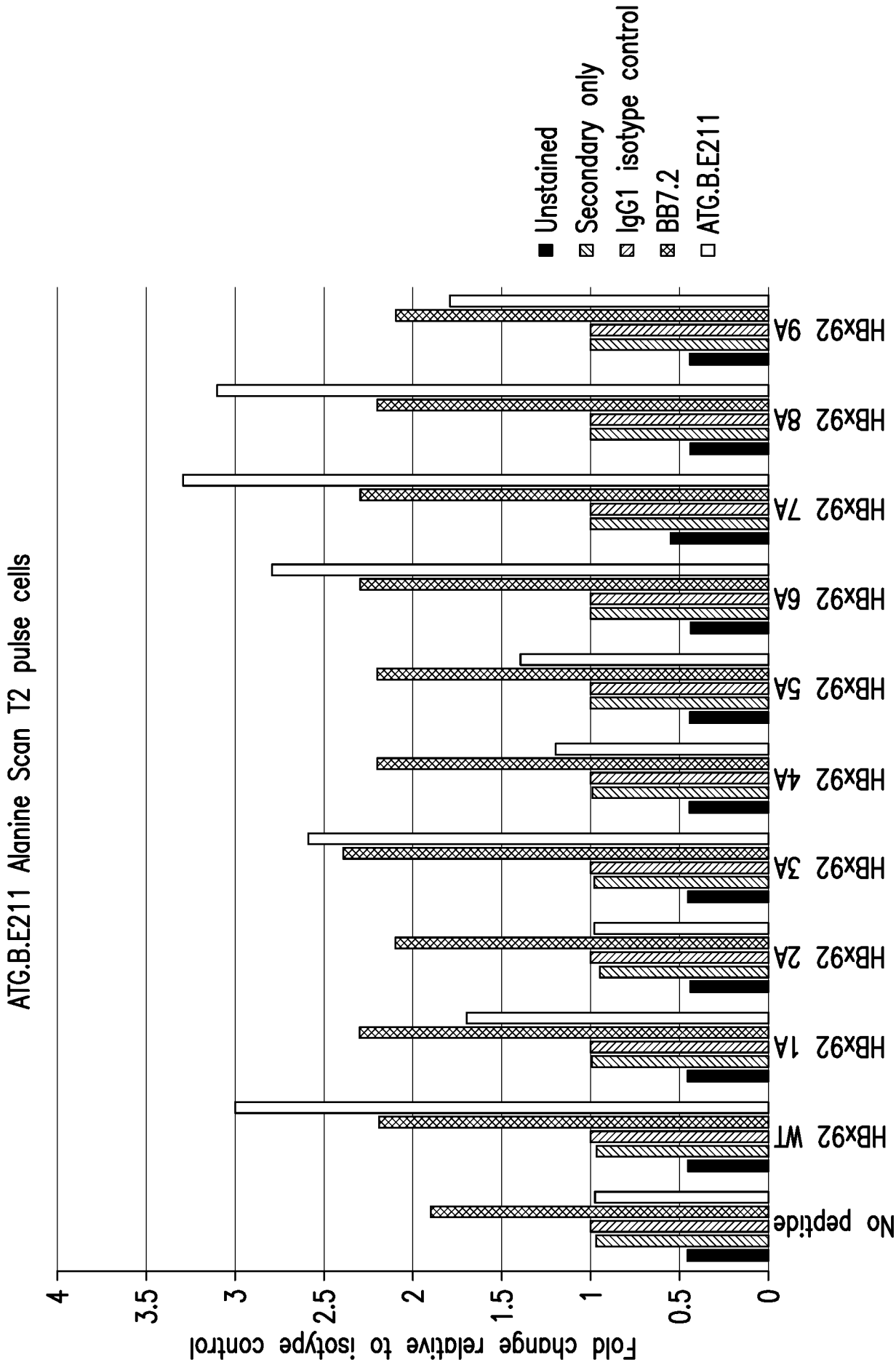

ATG.B.E211 Alanine Scan T2 pulse cells
Fold change relative to isotype control
0
0.5
1
1.5
2
2.5
3
3.5
4
No peptide
HBx92 WT
HBx92 1A
HBx92 2A
HBx92 3A
HBx92 4A
HBx92 5A
HBx92 6A
HBx92 7A
HBx92 8A
HBx92 9A
Unstained
Secondary only
IgG1 isotype control
BB7.2
ATG.B.E211

FIG.17

NOV3040 binding affinity to HLA-HBx92-100 toggled peptide

	1	2	3	4	5	6	7	8	9	
Residue	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	Residue
A	7.56E-07	--	6.05E-08	--	2.20E-06	--	--	4.43E-06	6.18E-02	A
C	1.26E-06	--	2.24E-07	--	--	--	--	--	4.39E-06	C
D	--	--	3.93E-09	--	--	--	--	--	--	D
E	4.66E-07	--	6.73E-09	--	--	--	--	--	--	E
F	7.22E-07	--	4.03E-07	--	--	--	--	6.92E-03	4.98E-08	F
G	6.97E-07	--	1.00E-07	--	--	--	1.07E-06		--	G
H	6.76E-07	--		--	--	--	--	1.56E-06	--	H
I	1.08E-06	2.73E-07	2.51E-08	--	--	--	--	--	1.41E-06	I
K	1.85E-06	--	6.02E-08		4.59E-07	--	--	7.27E-06	--	K
L	1.09E-06		7.30E-08	--	--	--		--		L
M	1.08E-06	6.41E-07	2.02E-08	--	--	--	--	--	2.72E-07	M
N	9.98E-07	--	2.04E-07	--	--	--	--	8.20E-03	--	N
P	--	--	1.53E-07	--	6.04E-07	--	--	1.16E-05	--	P
Q	9.56E-07	--	4.30E-08	--	4.46E-06	--	--	6.57E-02	--	Q
R	1.63E-06	--	--	9.57E-07		--	--	5.14E-02	--	R
S	6.38E-07	--	9.94E-08	--	--	7.38E-02	--	8.59E-06	5.59E-02	S
T	1.07E-06	--	9.33E-08	--	--		--	1.86E-06	3.26E-06	T
V		--	5.53E-08	--	--	--	--	--	1.65E-06	V
W	4.80E-07	--	--	--	--	--	--	1.99E-06	--	W
Y	7.18E-07	--	1.14E-06	--	--	--	--	2.08E-06	--	Y

FIG.18

NOV3499 binding affinity to HLA-HBx92-100 toggled peptide

	1	2	3	4	5	6	7	8	9	
Residue	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	VLHKRTLGL	Residue
A	4.42E-08		1.40E-08	1.26E-06	2.34E-06		1.81E-06	9.20E-07	7.57E-07	A
C	1.04E-07		2.66E-08	1.59E-06				1.21E-06	3.99E-07	C
D			1.82E-07	3.45E-06				2.13E-06		D
E	1.59E-08		3.13E-10	1.37E-06						E
F	4.40E-08		1.91E-07	1.89E-06				5.32E-07	3.22E-09	F
G	4.20E-08		4.21E-08	5.14E-06		1.52E-06	6.15E-08		6.19E-07	G
H	3.34E-08			1.69E-06				1.35E-07		H
I	8.78E-08	2.66E-08	9.54E-10	2.70E-06			1.21E-06	5.18E-06	1.10E-07	I
K	1.27E-07		1.72E-08		5.70E-08			4.62E-07		K
L	7.41E-08		1.70E-09	1.98E-06				1.23E-06		L
M	7.91E-08	8.32E-08	5.84E-09	1.47E-06			5.44E-06	1.47E-06	1.37E-08	M
N	4.97E-08		6.61E-08	3.24E-06				4.95E-07		N
P		1.35E-07	1.01E-07	2.50E-06	4.22E-07			5.51E-07	2.81E-07	P
Q	5.54E-08	3.20E-08	1.95E-08	8.61E-07	4.19E-07	1.97E-06		7.38E-07		Q
R	1.16E-07		2.62E-07	7.58E-08				4.73E-07		R
S	3.27E-08		3.14E-08	1.27E-06	1.63E-06	1.66E-06		4.09E-07		S
T	7.31E-08	1.13E-08	1.95E-08	1.50E-06				1.62E-07	3.34E-07	T
V		1.83E-08	2.55E-09	3.12E-06		9.11E-06	1.78E-06	1.10E-05	6.01E-07	V
W	2.18E-08			2.30E-06				5.44E-07		W
Y	4.06E-08		5.83E-07					1.57E-07		Y

FIG.19

Experimental design for HLA-HBV efficacy study

- Nude balb/c mice
- Cell line: Hepa 1-6 luc pool-HLA(A2)HBx92-100 (luciferase expressing mouse hepatoma line with stable expression of HLA-A2-HBx92-100)

Group	N	Animal #	Cell concentration (route)	Treatment	Dose (i.p)	Termination date
1	8	1-8	$5x10^6$ cells, s.c.	eADCC BB7.2	5 mg/kg	24 d.p.i.
2	8	9-16	$5x10^6$ cells, s.c.	Isotype control (MOR3207)	5 mg/kg	24 d.p.i.
3	8	7-24	$5x10^6$ cells, s.c.	eADCC NOV2353	30 mg/kg	24 d.p.i.

Day 0	BW/CO and implant all mice.
Day 3-4	Initial tumor measurement and imaging
Day 7-24	Weekly tumor measurement and imaging
Day 12, 15, 18, 21	IP dose antibody treatments according to study plan.
Day 24	Final tumor measurement and tumor harvest.

FIG.20

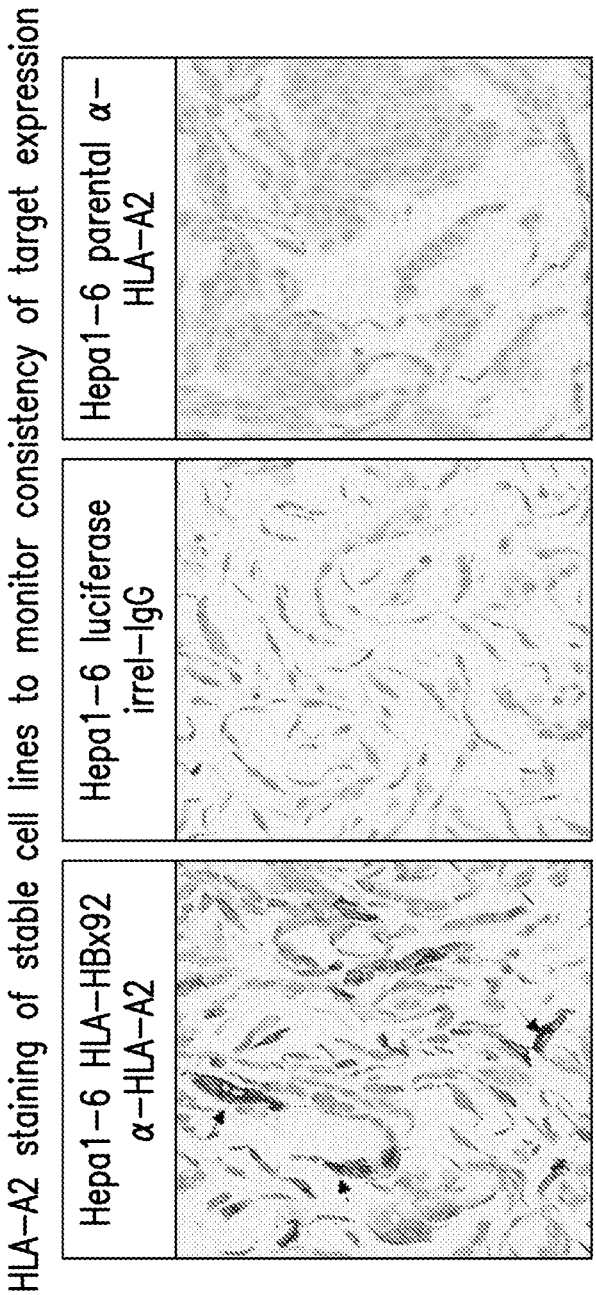


FIG.21A FIG.21B FIG.21C

HLA-A2 staining of tumor arising from mouse treated with non-targeting antibody

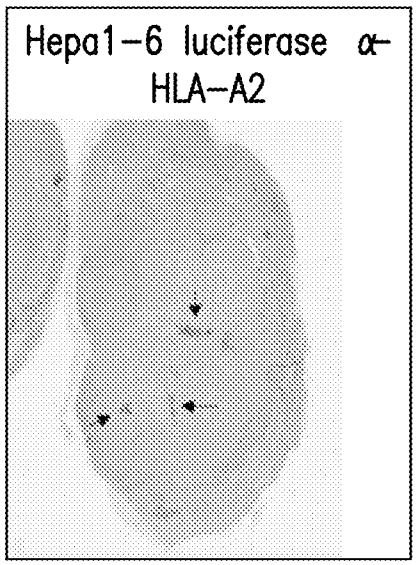


FIG.22A

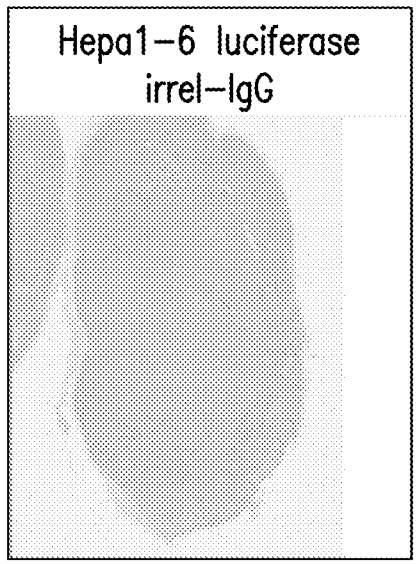


FIG.22B

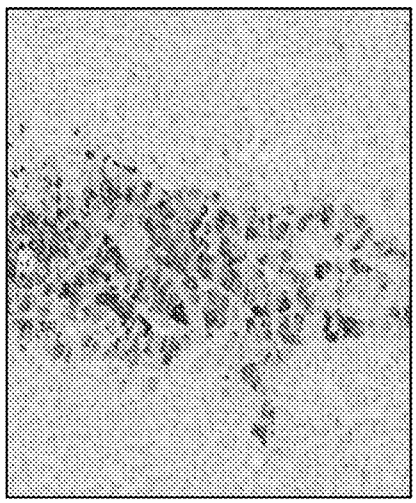


FIG.22C

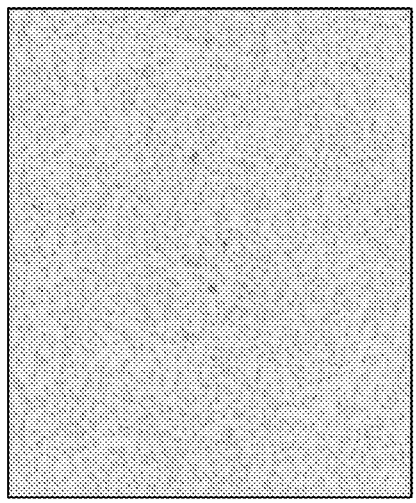


FIG.22D

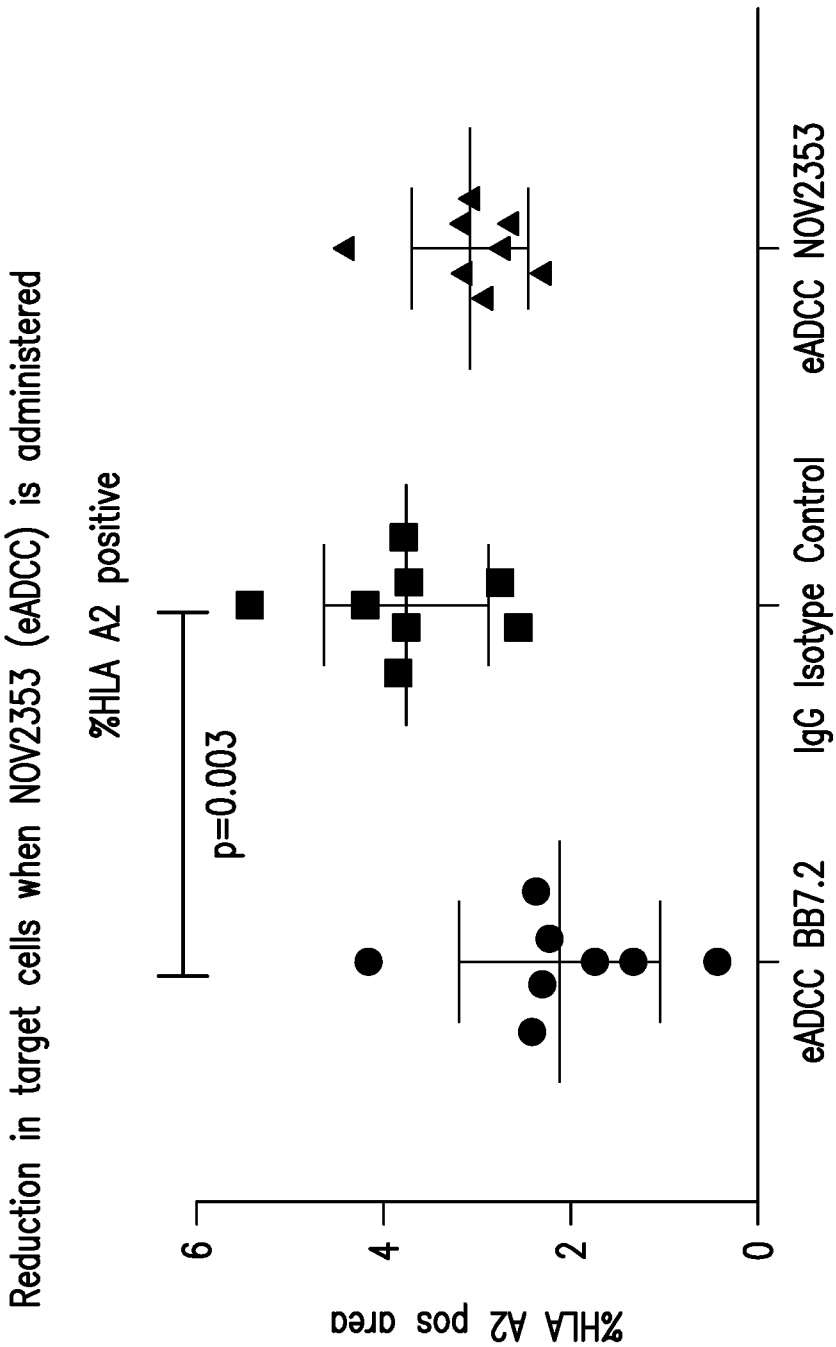

Reduction in target cells when NOV2353 (eADCC) is administered
%HLA A2 positive
p=0.003
%HLA A2 pos area
0
2
4
6
eADCC BB7.2
IgG Isotype Control
eADCC NOV2353

FIG.23

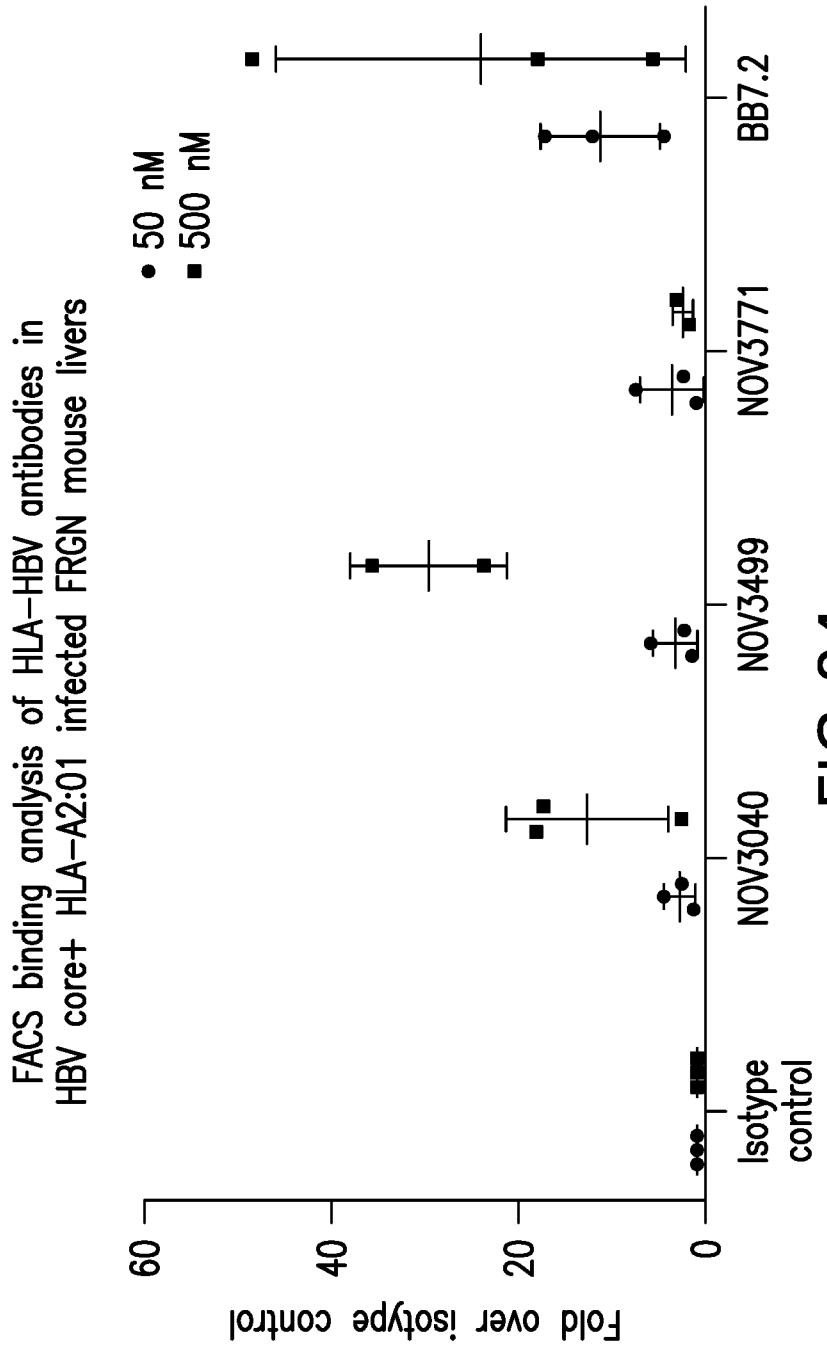

FACS binding analysis of HLA-HBV antibodies in
HBV core+ HLA-A2:01 infected FRGN mouse livers
50 nM
500 nM
Fold over isotype control
0
20
40
60
Isotype control
NOV3040
NOV3499
NOV3771
BB7.2

FIG.24

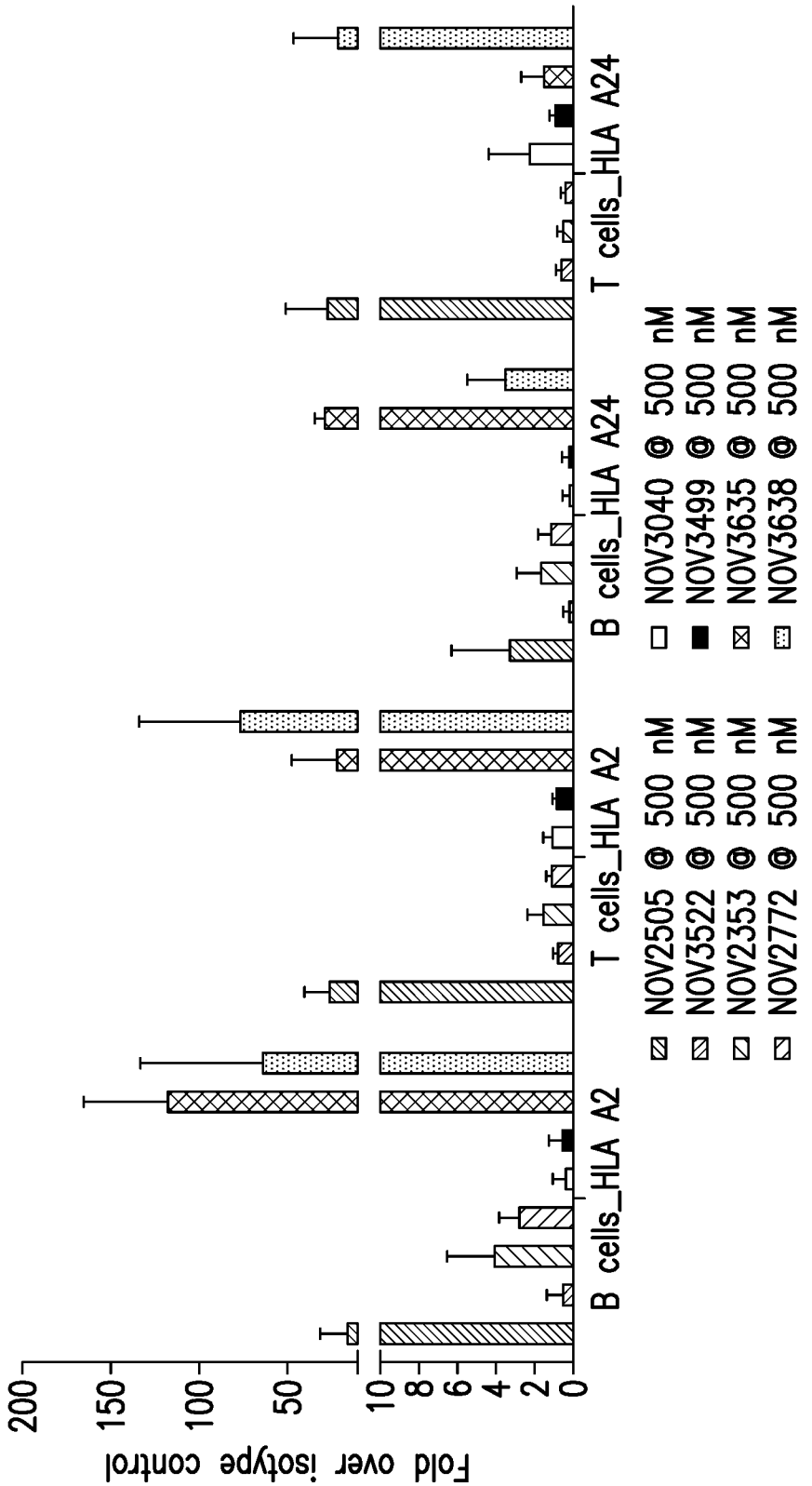

Binding Analysis of HLA antibodies on uninfected immune cells @ 500 nM
Fold over isotype control
200
150
100
50
10
8
6
4
2
0
B cells_HLA A2
T cells_HLA A2
B cells_HLA A24
T cells_HLA A24
NOV2505 @ 500 nM
NOV3522 @ 500 nM
NOV2353 @ 500 nM
NOV2772 @ 500 nM
NOV3040 @ 500 nM
NOV3499 @ 500 nM
NOV3635 @ 500 nM
NOV3638 @ 500 nM

FIG.25

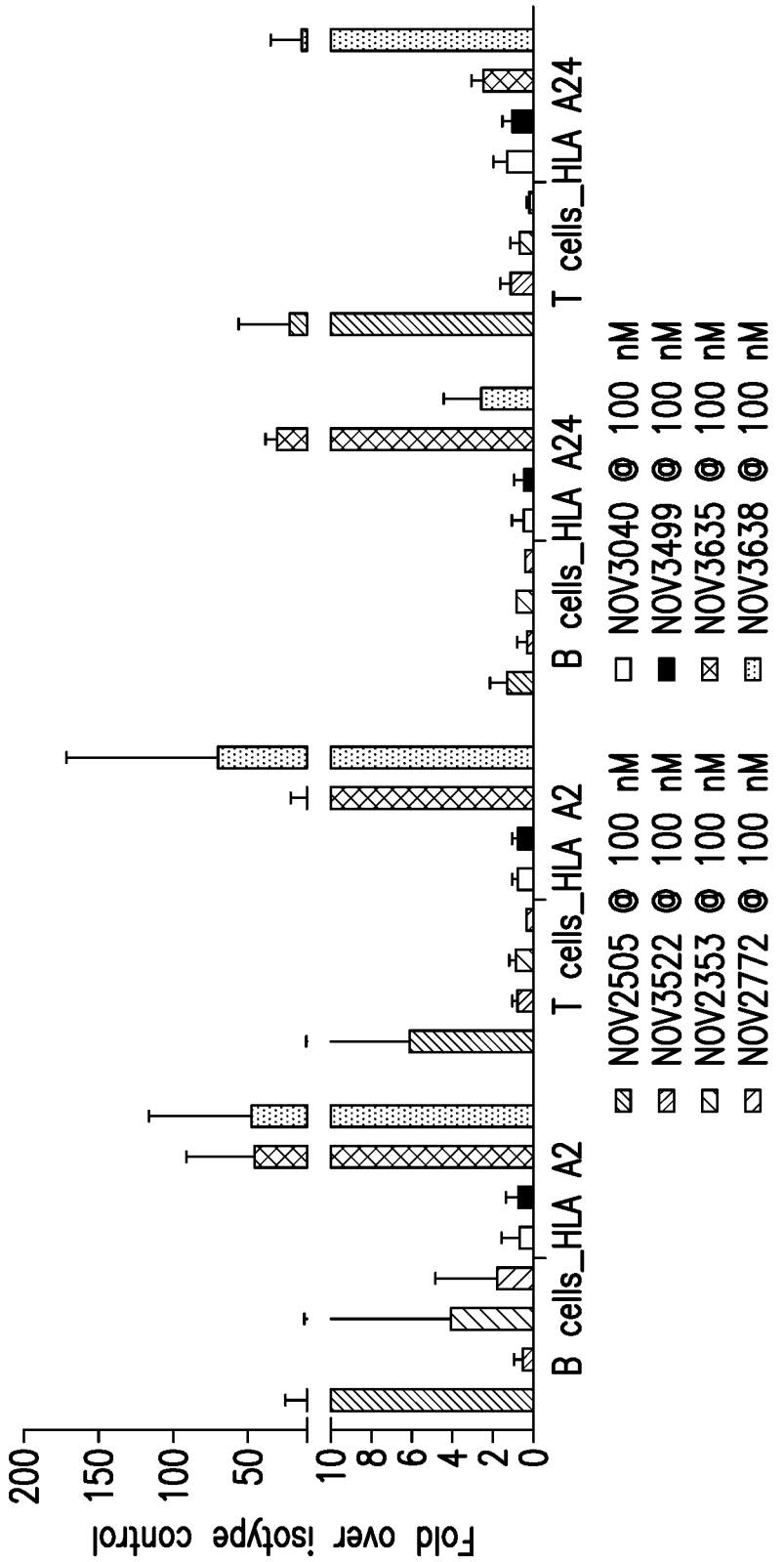

Binding Analysis of HLA antibodies on uninfected immune cells @ 100 nM
Fold over isotype control
200
150
100
50
10
8
6
4
2
0
B cells_HLA A2
T cells_HLA A2
B cells_HLA A24
T cells_HLA A24
NOV2505 @ 100 nM
NOV3522 @ 100 nM
NOV2353 @ 100 nM
NOV2772 @ 100 nM
NOV3040 @ 100 nM
NOV3499 @ 100 nM
NOV3635 @ 100 nM
NOV3638 @ 100 nM

FIG.26

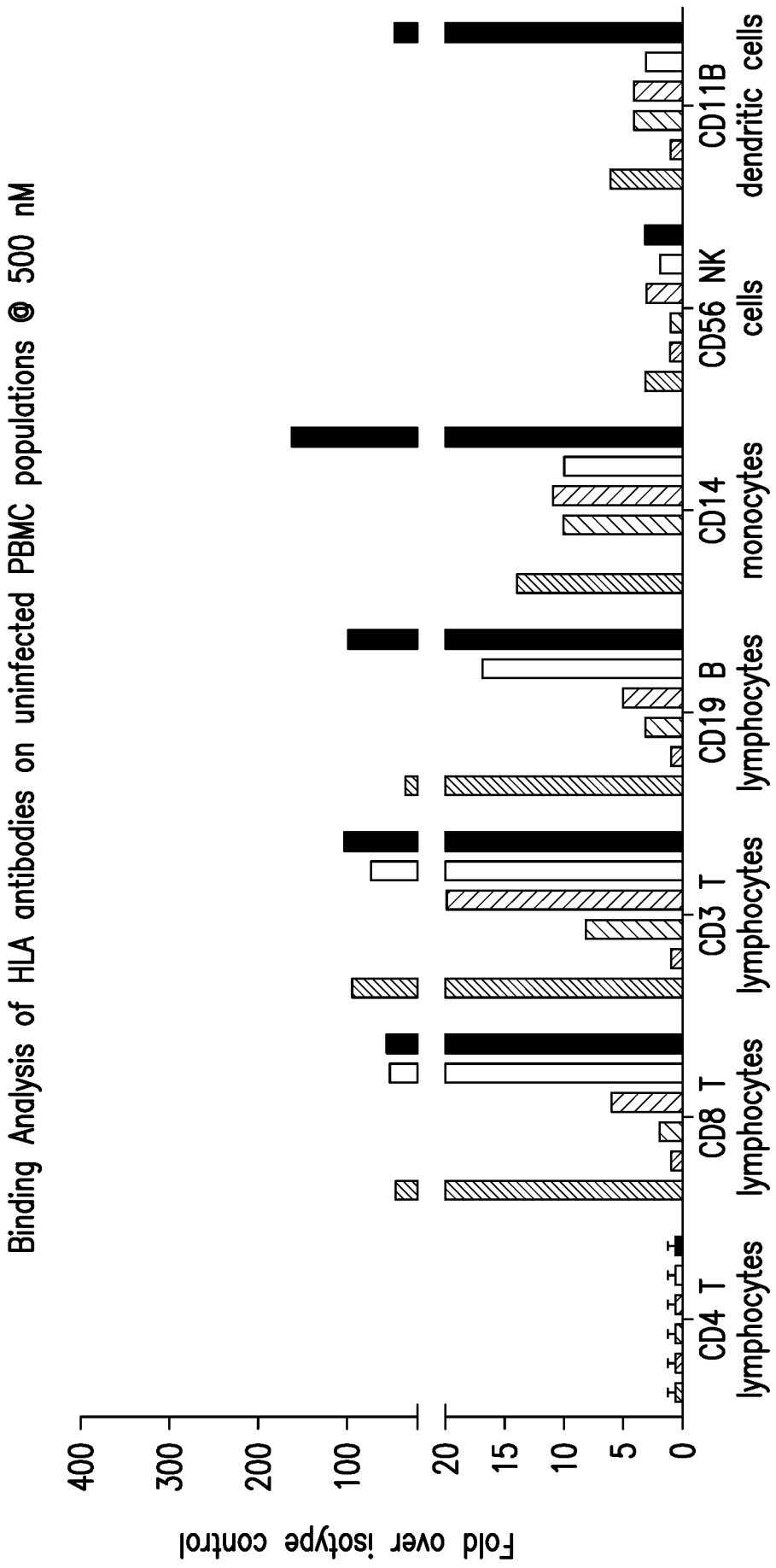

Binding Analysis of HLA antibodies on uninfected PBMC populations @ 500 nM
Fold over isotype control
400
300
200
100
20
15
10
5
0
CD4 T lymphocytes
CD8 T lymphocytes
CD3 T lymphocytes
CD19 B lymphocytes
CD14 monocytes
CD56 NK cells
CD11B dendritic cells
NOV2505
NOV3522
NOV3040
NOV3499
NOV3771
NOV3638

FIG.27

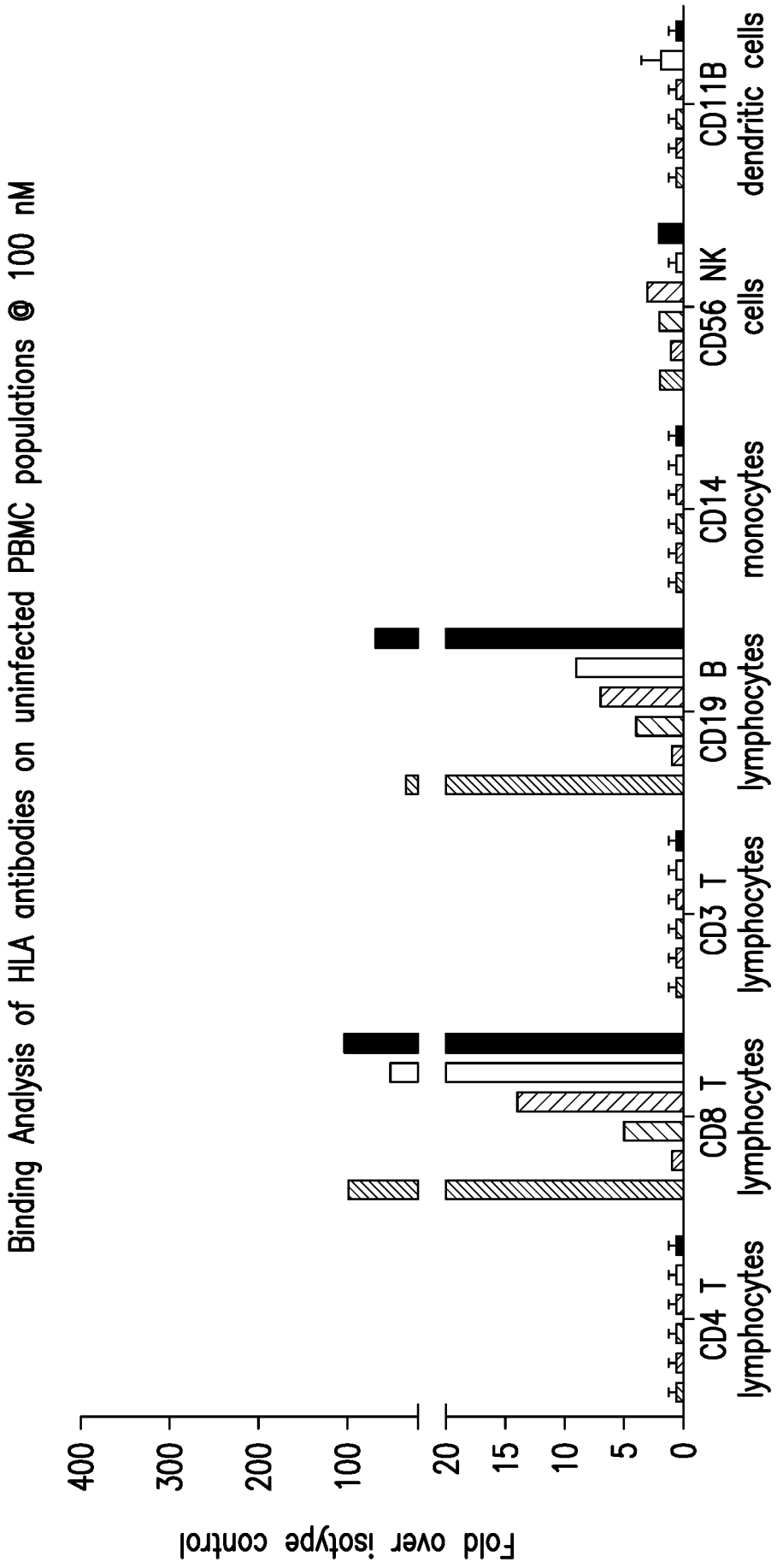

Binding Analysis of HLA antibodies on uninfected PBMC populations @ 100 nM
Fold over isotype control
400
300
200
100
20
15
10
5
0
CD4 T lymphocytes
CD8 T lymphocytes
CD3 T lymphocytes
CD19 B lymphocytes
CD14 monocytes
CD56 NK cells
CD11B dendritic cells
NOV2505
NOV3522
NOV3040
NOV3499
NOV3771
NOV3638

FIG.28

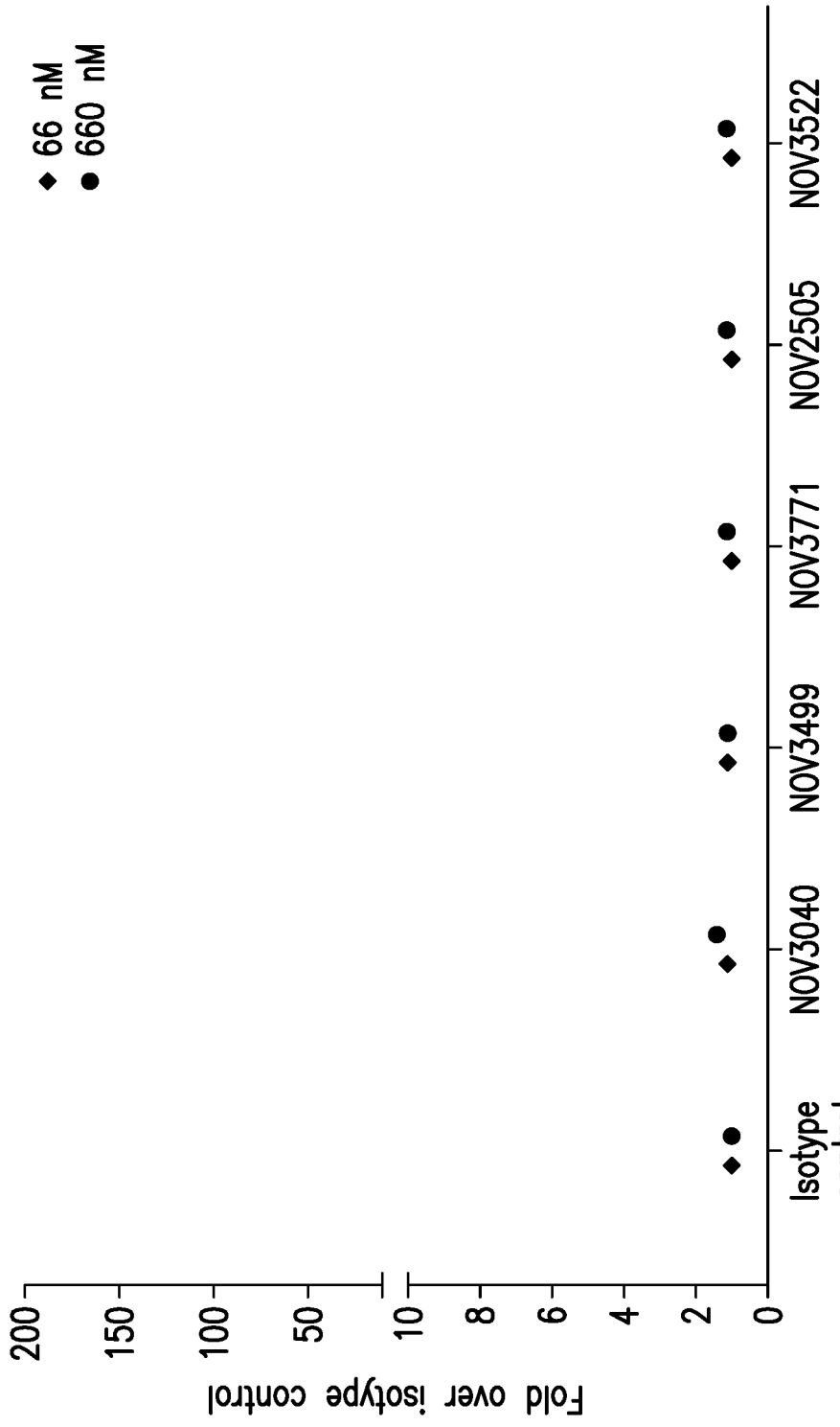

FACS binding analysis of HLA-HBV antibodies on uninfected hepatocytes
HLA_A2:01 (yecuris)
66 nM
660 nM
Fold over isotype control
200
150
100
50
10
8
6
4
2
0
Isotype control
NOV3040
NOV3499
NOV3771
NOV2505
NOV3522

FIG.29

Pep#39	SEQ ID NO:424	TMVSLQLGI
Pep#41	SEQ ID NO:425	FASLATHFI
Pep#49	SEQ ID NO:426	CLHLLLLTLV
Pep#57	SEQ ID NO:427	ALGQLLGGV
Pep#60	SEQ ID NO:428	CLGGRLVHV
Pep#62	SEQ ID NO:429	VLGWLGTLV
HIV Pol	SEQ ID NO:430	ILKEPVHGV
Proteinase 3	SEQ ID NO:431	VLQELNVTV
P53	SEQ ID NO:432	LLGRNSFEV
UV peptide (control)	SEQ ID NO:433	KILGFVFJV

FIG.30

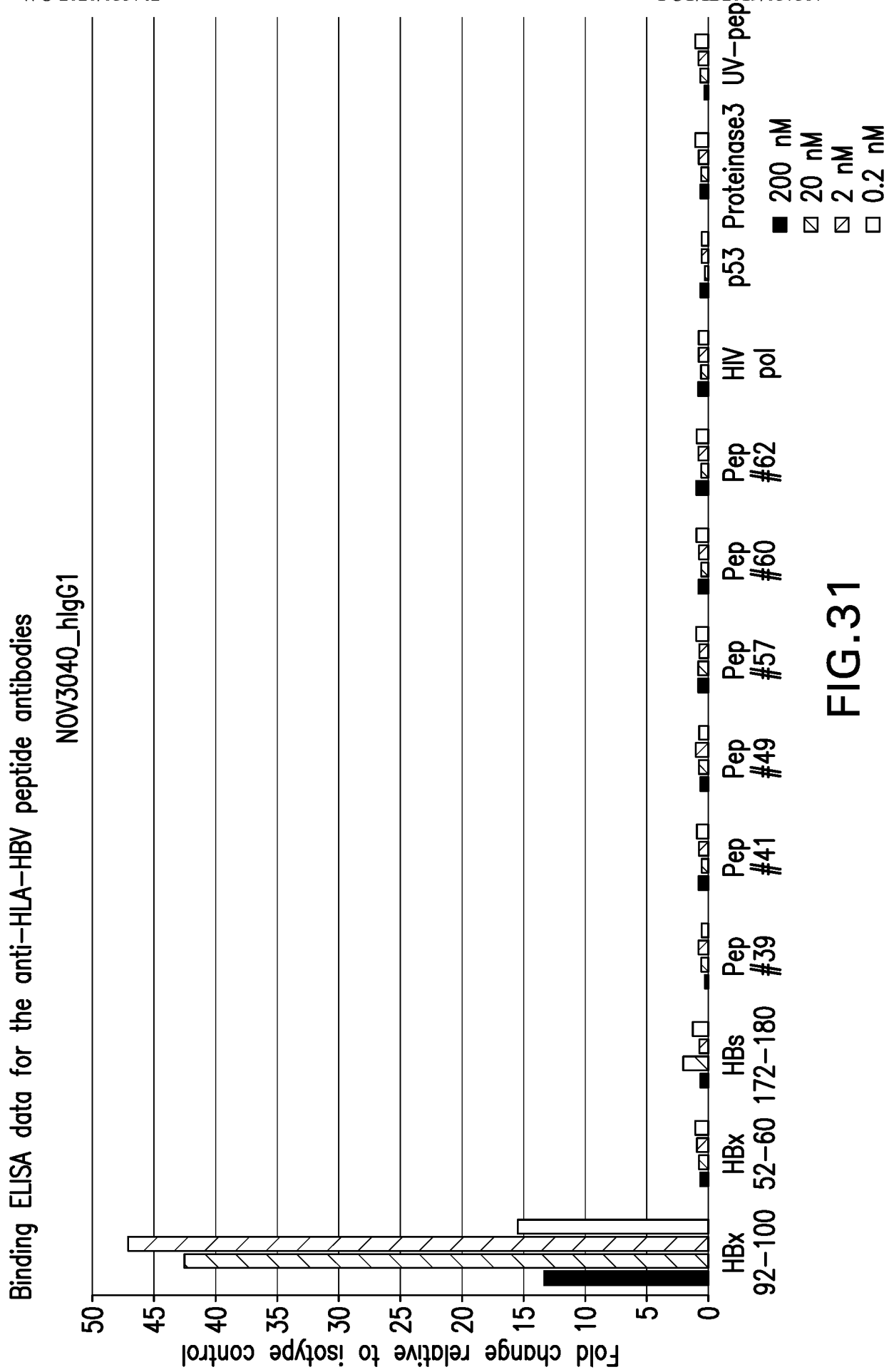

Binding ELISA data for the anti-HLA-HBV peptide antibodies
NOV3040_hIgG1
Fold change relative to isotype control
0
5
10
15
20
25
30
35
40
45
50
HBx 92-100
HBx 52-60
HBs 172-180
Pep #39
Pep #41
Pep #49
Pep #57
Pep #60
Pep #62
HIV pol
p53
Proteinase3
UV-pep
200 nM
20 nM
2 nM
0.2 nM

FIG.31

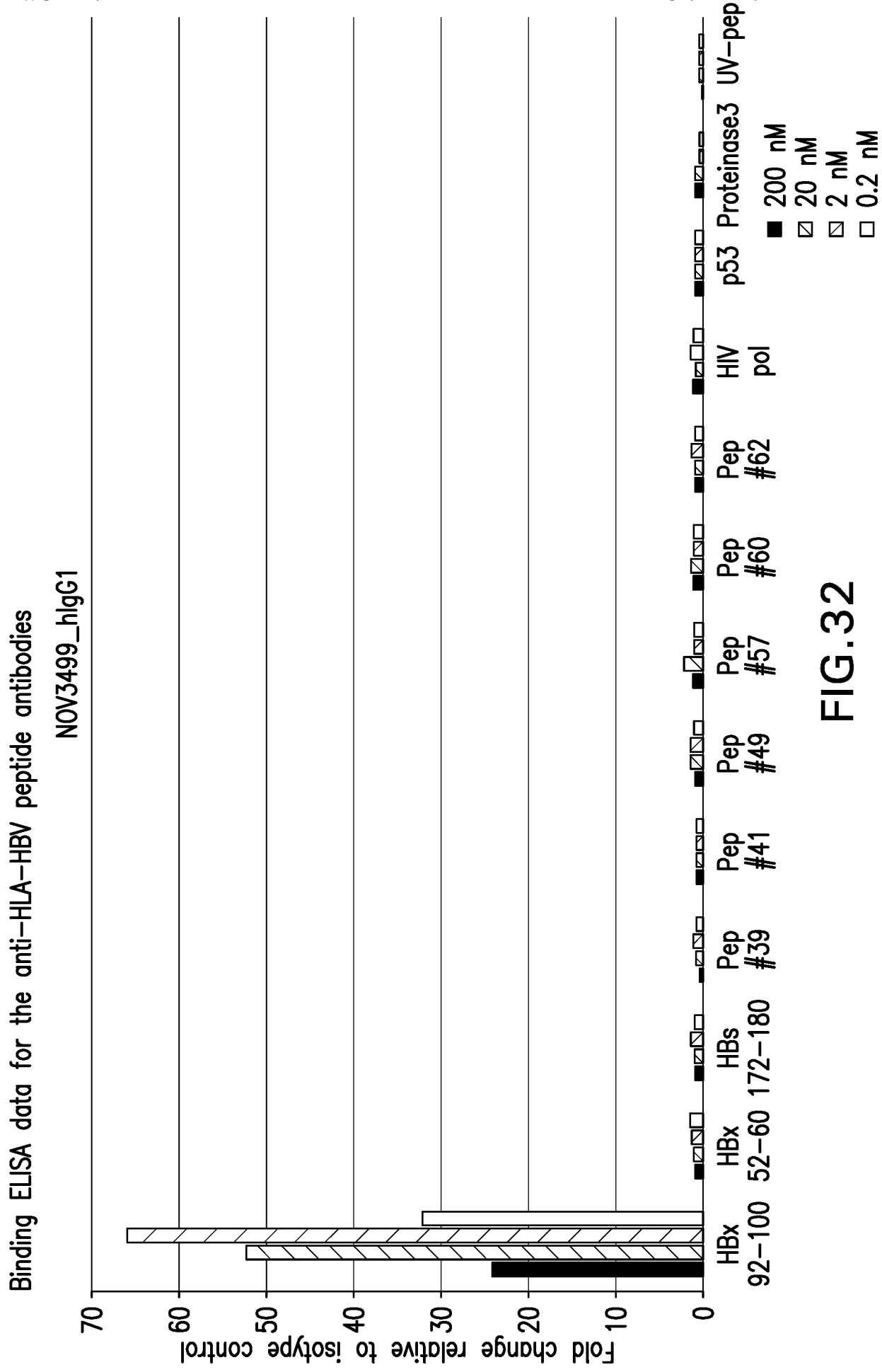

Binding ELISA data for the anti-HLA-HBV peptide antibodies
NOV3499_hIgG1
Fold change relative to isotype control
0
10
20
30
40
50
60
70
HBx 92-100
HBx 52-60
HBs 172-180
Pep #39
Pep #41
Pep #49
Pep #57
Pep #60
Pep #62
HIV pol
p53
Proteinase3
UV-pep
200 nM
20 nM
2 nM
0.2 nM

FIG.32

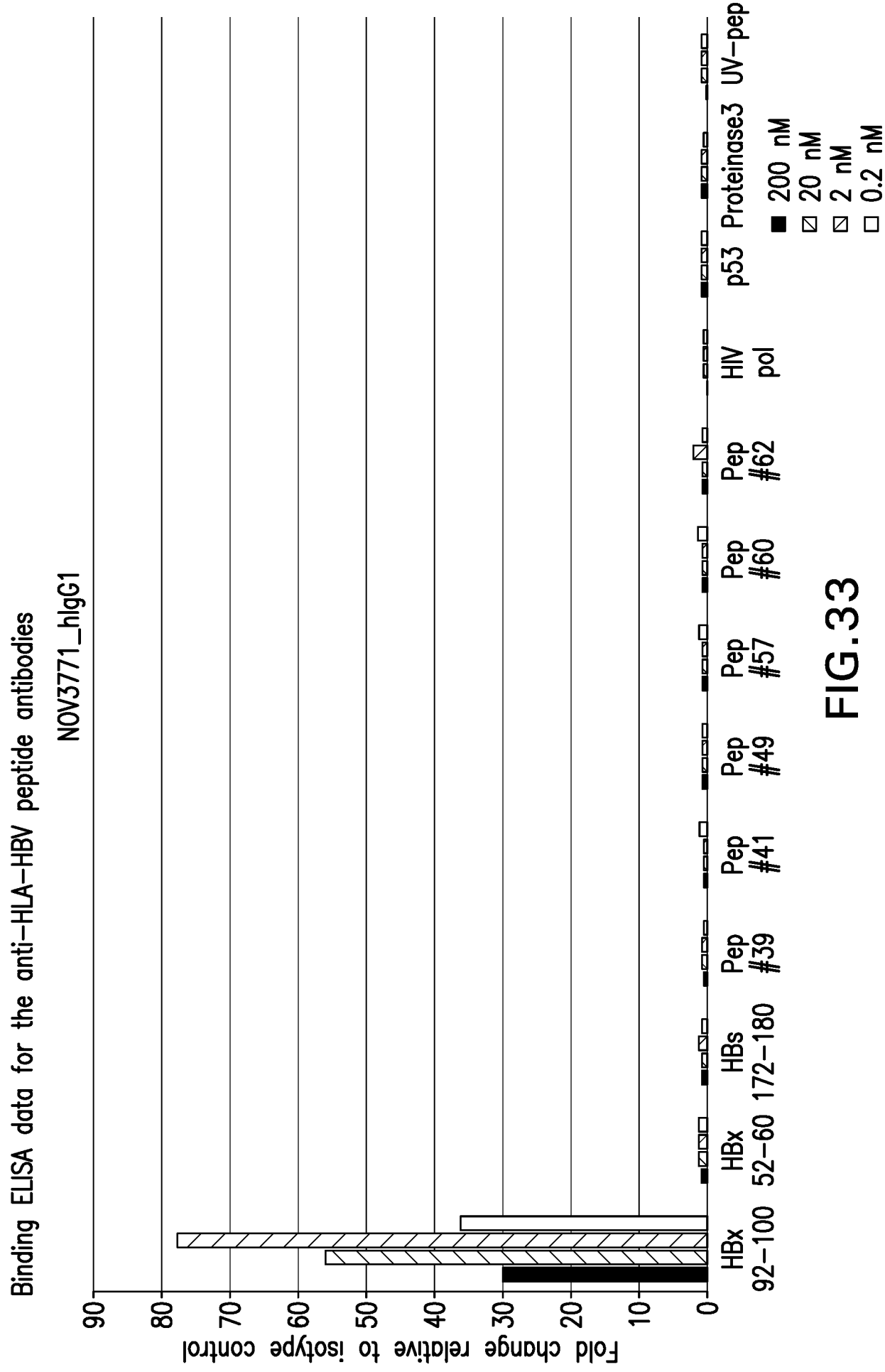

Binding ELISA data for the anti-HLA-HBV peptide antibodies
NOV3771_hIgG1
Fold change relative to isotype control
0
10
20
30
40
50
60
70
80
90
HBx 92-100
HBx 52-60
HBs 172-180
Pep #39
Pep #41
Pep #49
Pep #57
Pep #60
Pep #62
HIV pol
p53 Proteinase3 UV-pep
200 nM
20 nM
2 nM
0.2 nM

FIG.33

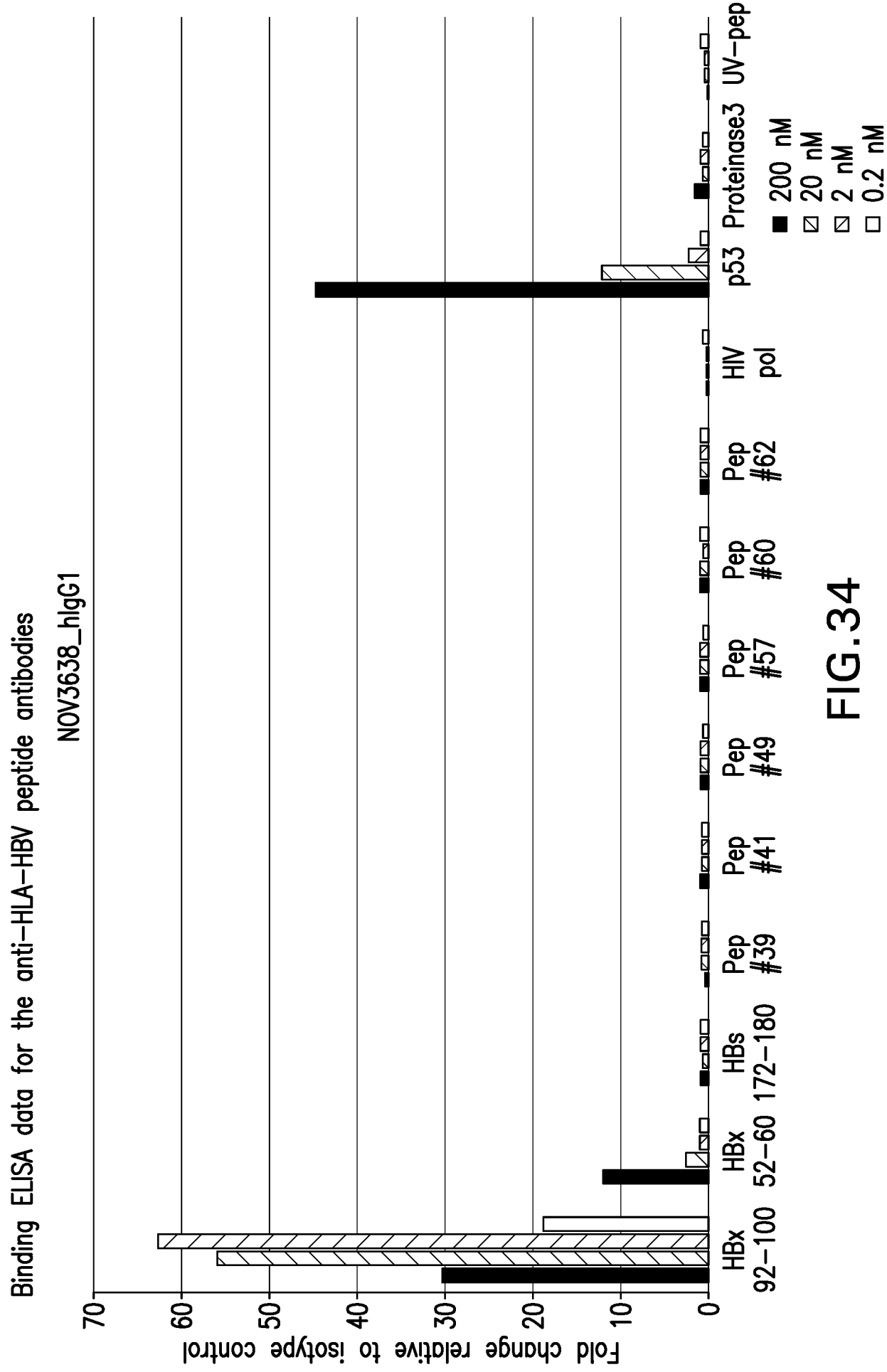

Binding ELISA data for the anti-HLA-HBV peptide antibodies
NOV3638_hIgG1
Fold change relative to isotype control
0
10
20
30
40
50
60
70
HBx 92-100
HBx 52-60
HBs 172-180
Pep #39
Pep #41
Pep #49
Pep #57
Pep #60
Pep #62
HIV pol
p53
Proteinase3
UV-pep
200 nM
20 nM
2 nM
0.2 nM

FIG.34

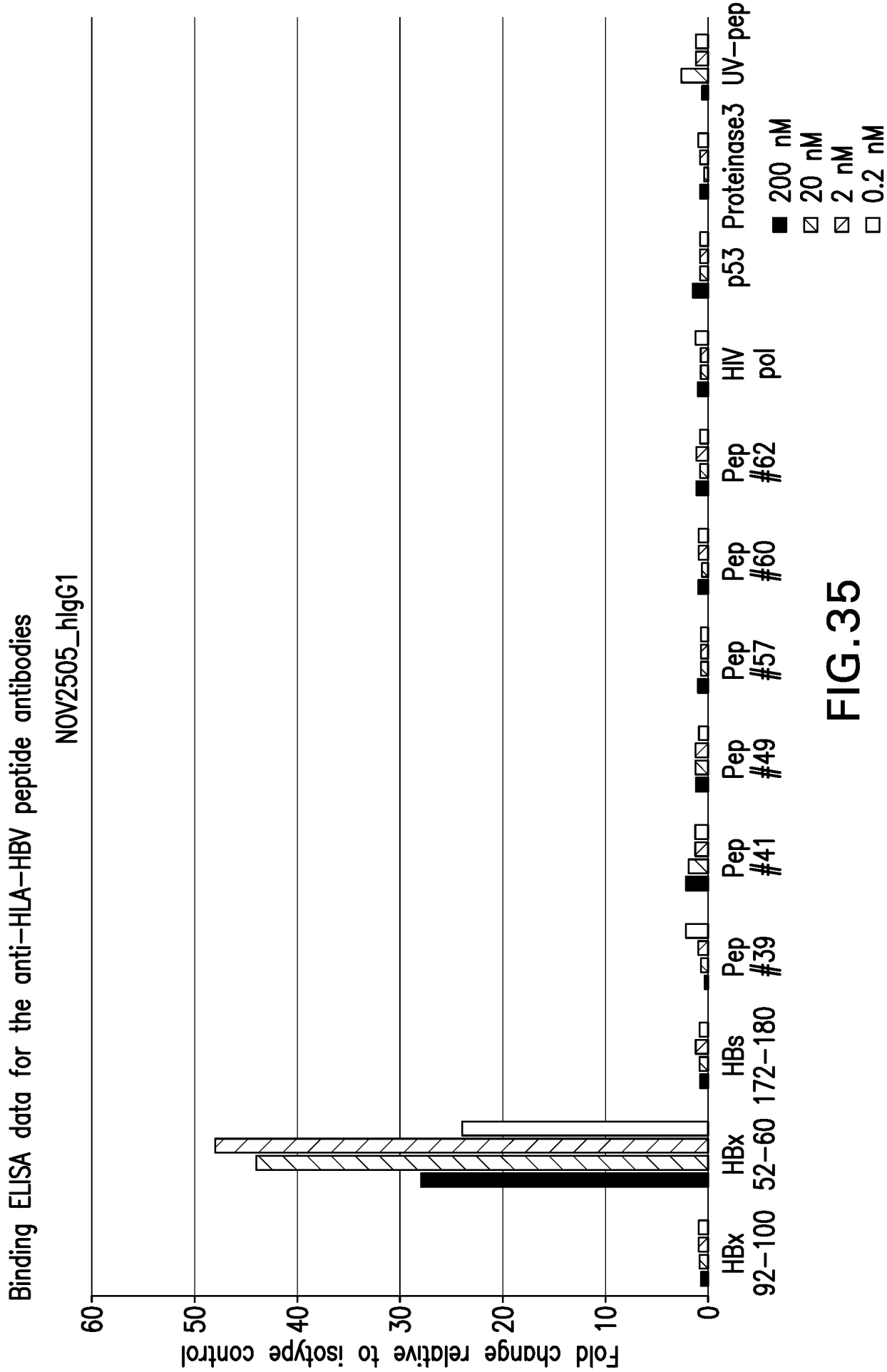

Binding ELISA data for the anti-HLA-HBV peptide antibodies
NOV2505_hIgG1
Fold change relative to isotype control
0
10
20
30
40
50
60
HBx 92-100
HBx 52-60
HBs 172-180
Pep #39
Pep #41
Pep #49
Pep #57
Pep #60
Pep #62
HIV pol
p53
Proteinase3
UV-pep
200 nM
20 nM
2 nM
0.2 nM

FIG.35

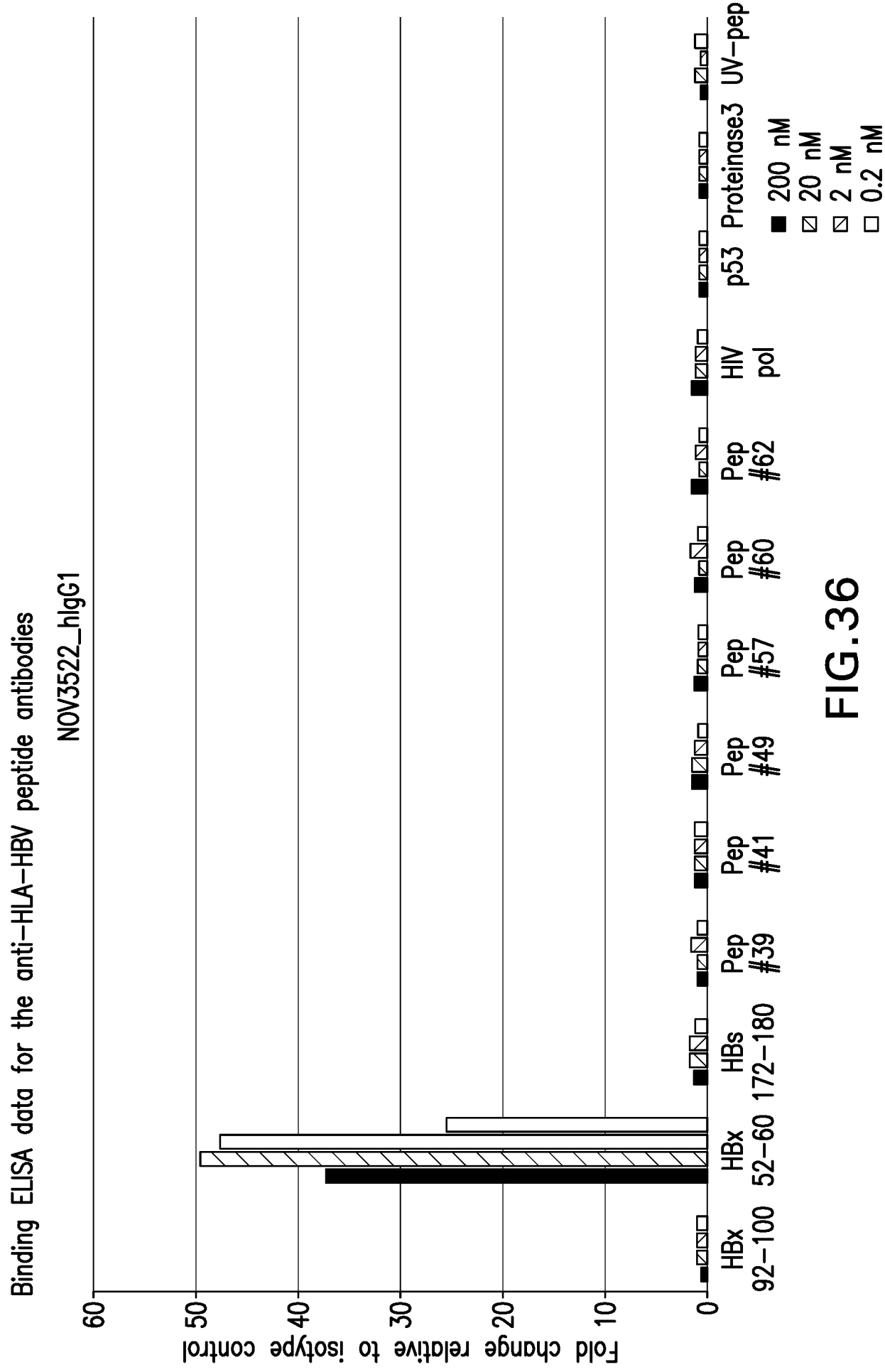
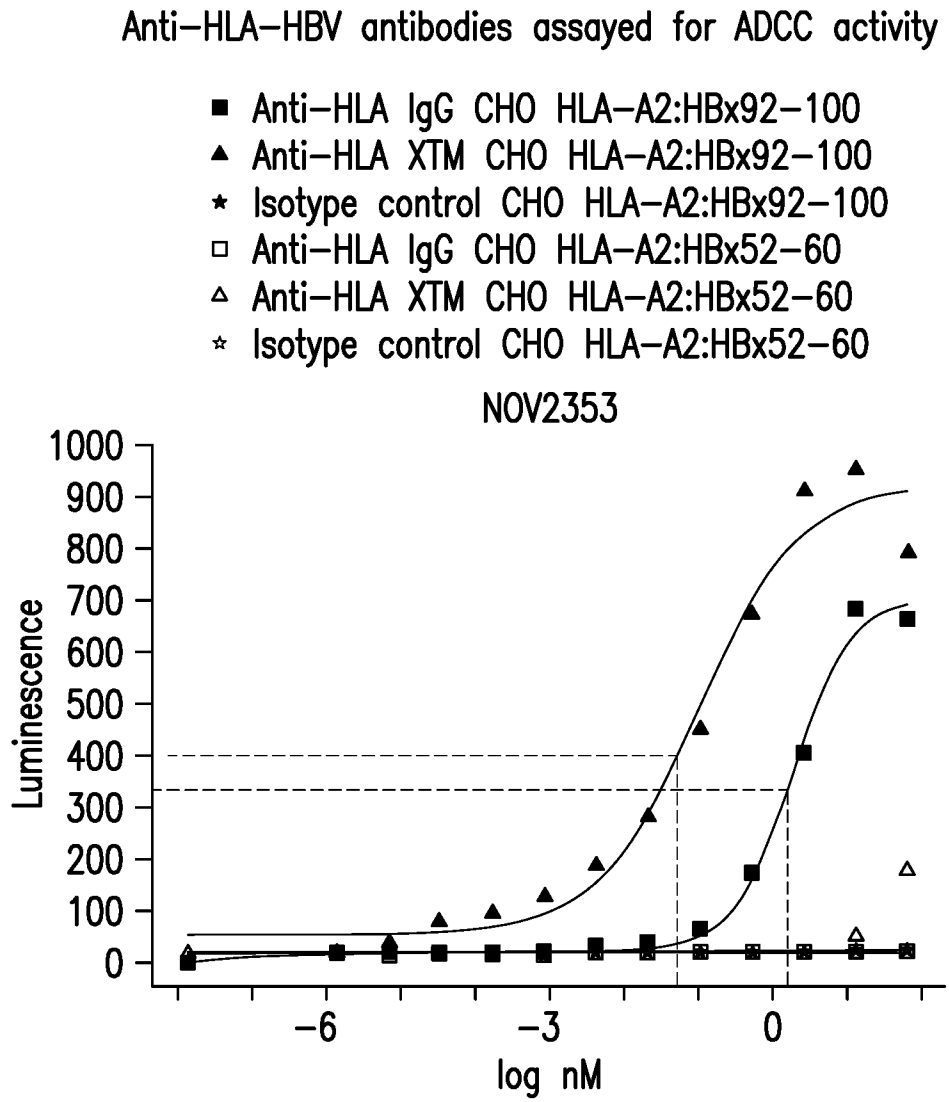
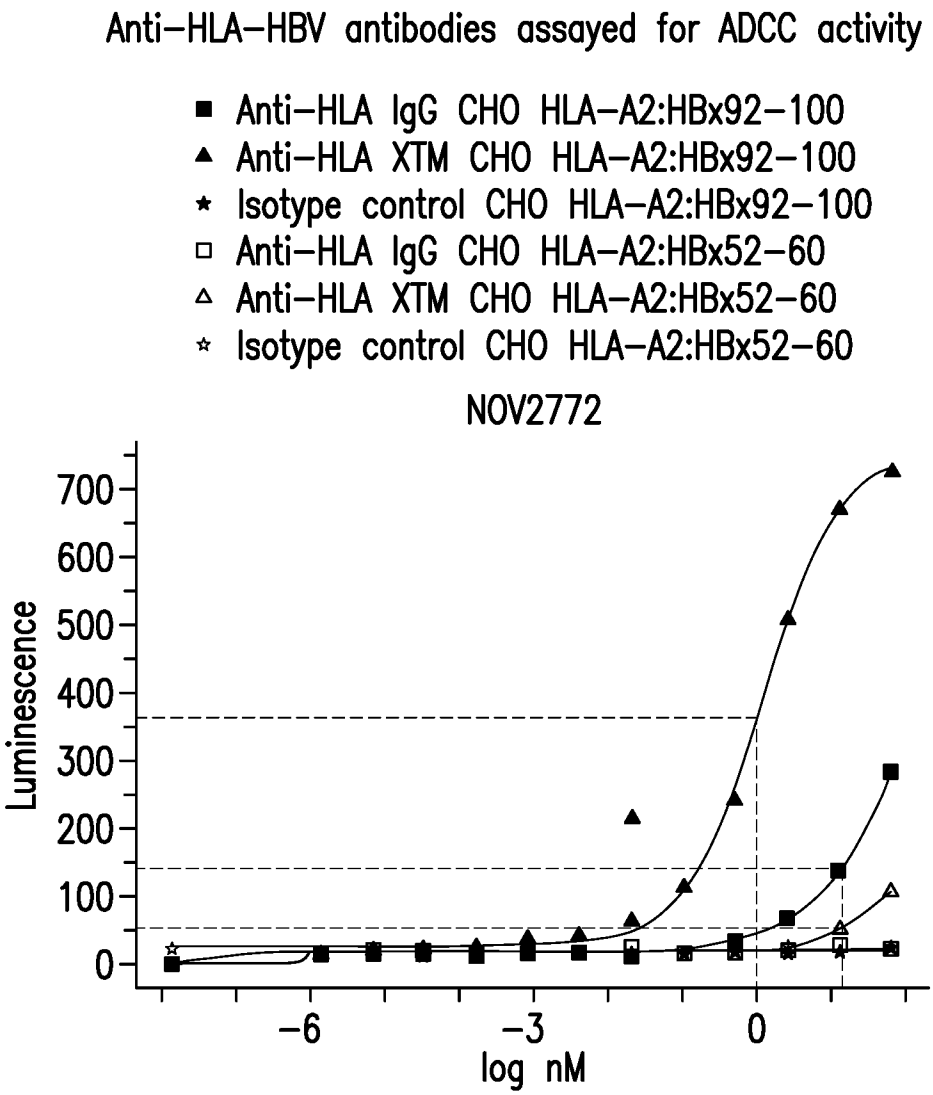

Binding ELISA data for the anti-HLA-HBV peptide antibodies
NOV3522_hIgG1
Fold change relative to isotype control
0
10
20
30
40
50
60
HBx 92-100
HBx 52-60
HBs 172-180
Pep #39
Pep #41
Pep #49
Pep #57
Pep #60
Pep #62
HIV pol
p53
Proteinase3
UV-pep
200 nM
20 nM
2 nM
0.2 nM

FIG.36



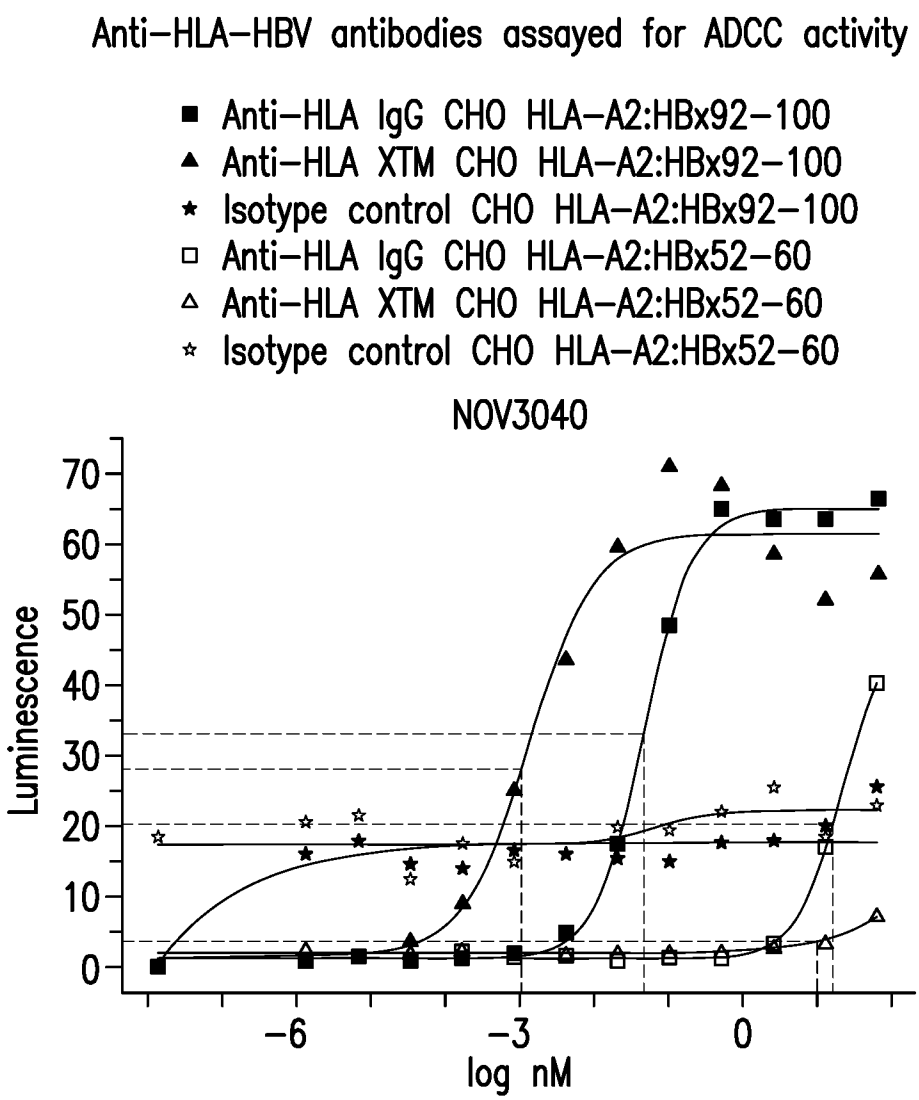
	AC50 (nM)	
	HBx92-100	HBx52-60
NOV2353-IgG1	1.57	--
NOV2353-XTM	0.0524	--
Isotype control	--	--

FIG.37



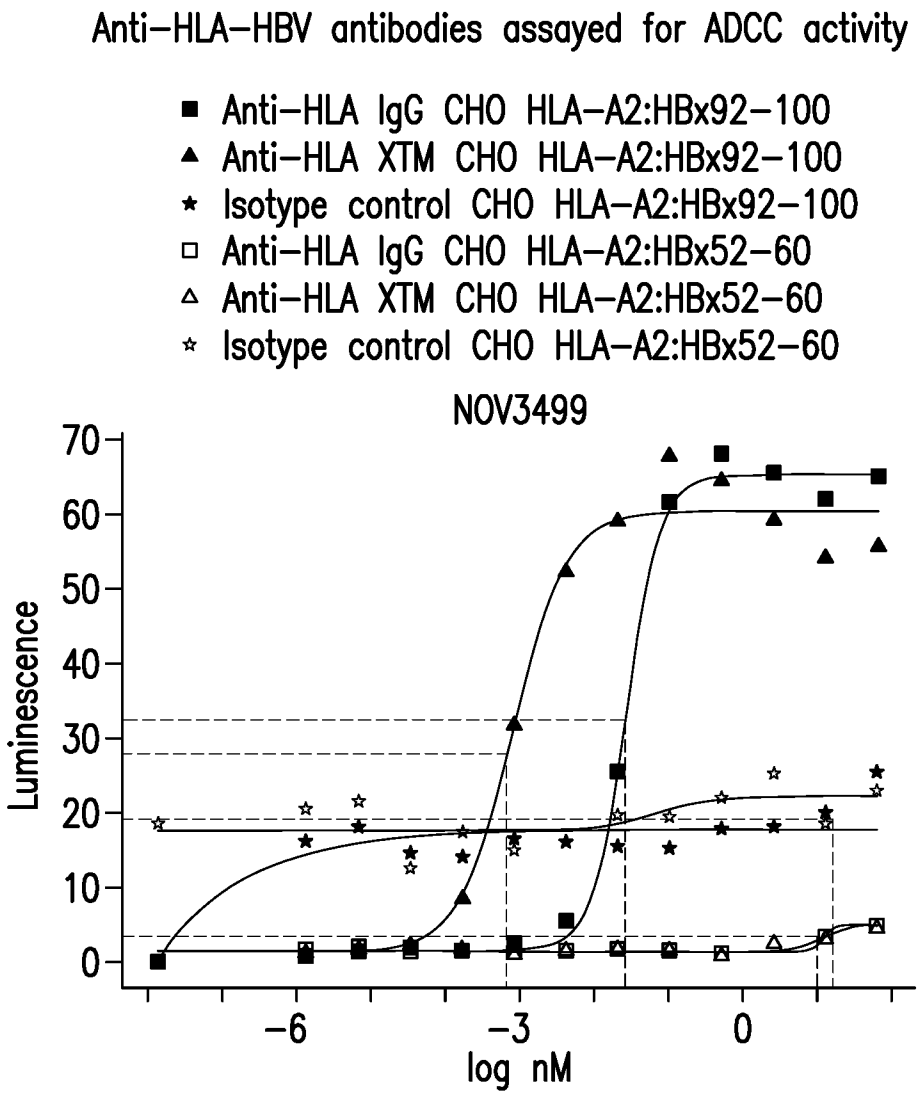
	AC50 (nM)	
	HBx92-100	HBx52-60
NOV2772-IgG1	14.8	--
NOV2772-XTM	1	14.5
Isotype control	--	--

FIG.38



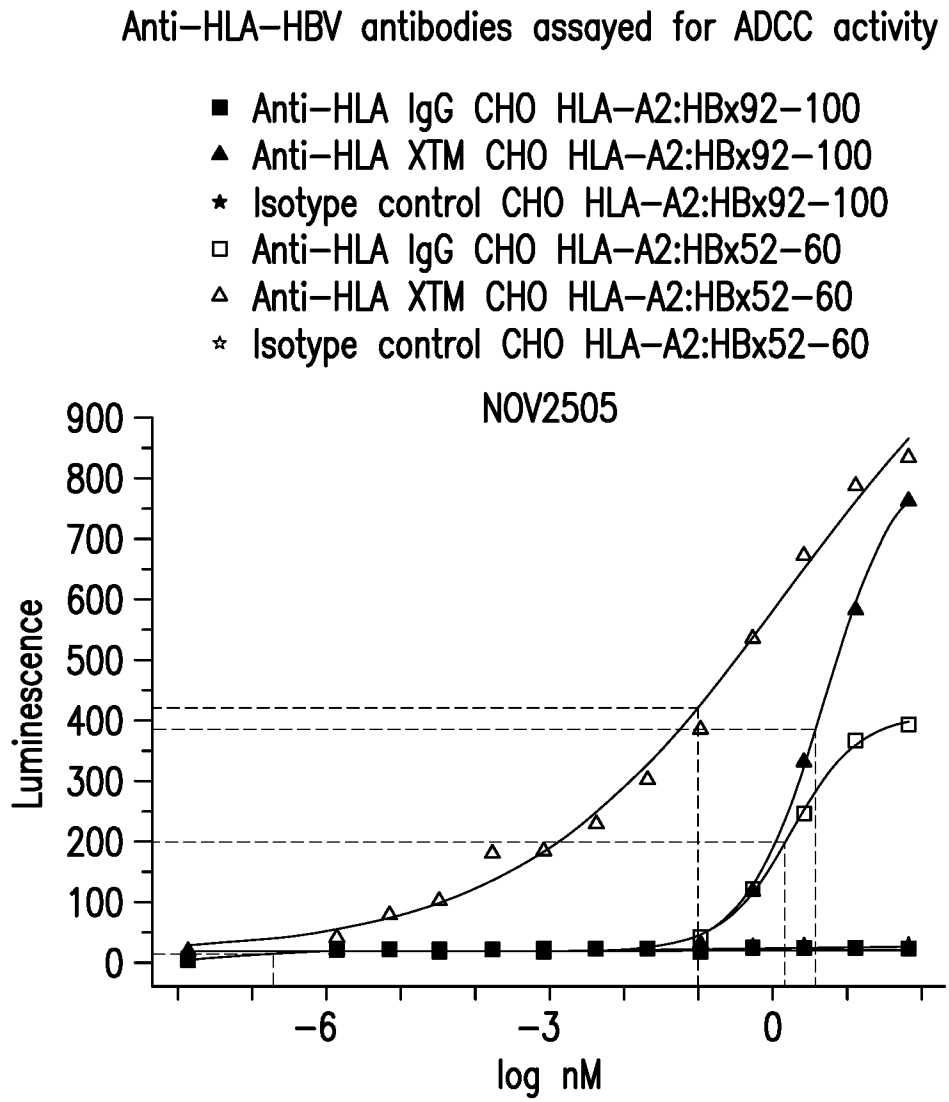
	AC50 (nM)	
	HBx92-100	HBx52-60
NOV3040-IgG1	0.0479	16.2
NOV3040-XTM	0.00107	10
Isotype control	--	--

FIG.39



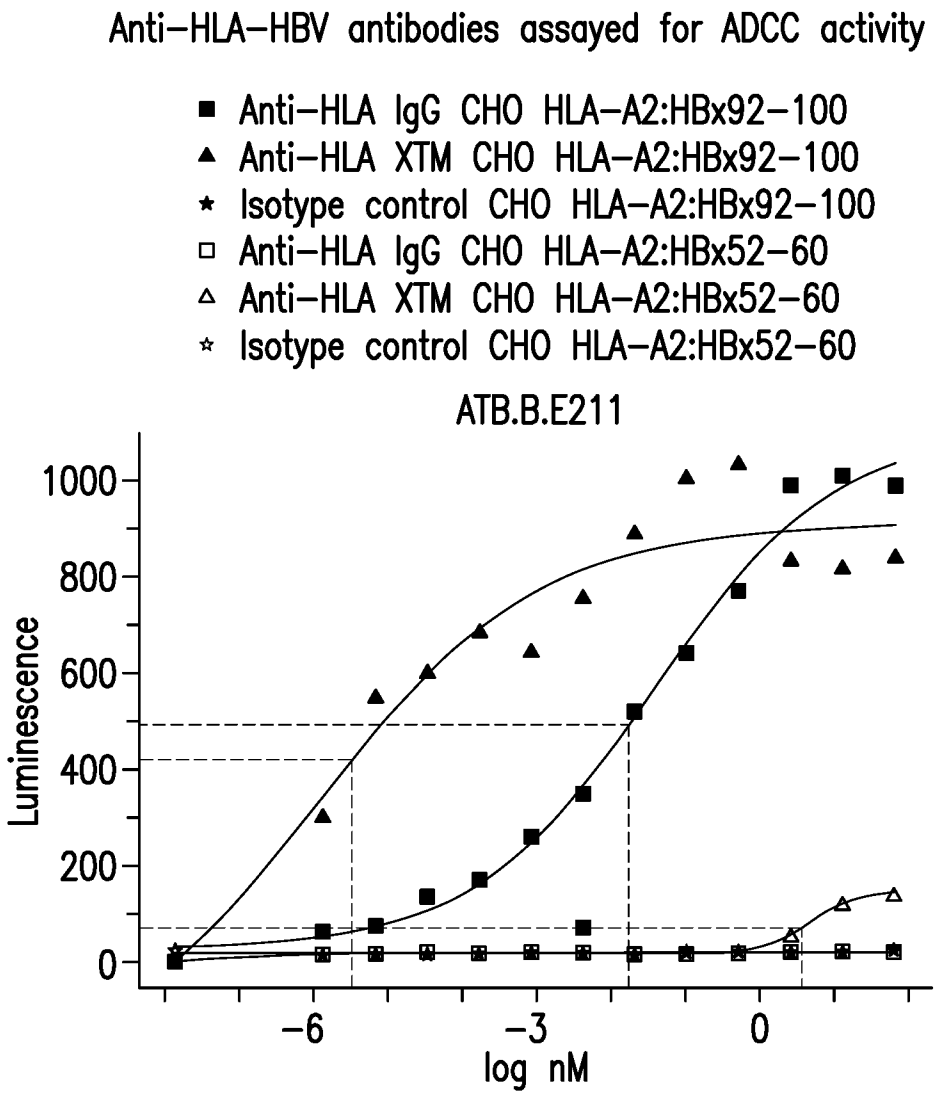
	AC50 (nM)	
	HBx92-100	HBx52-60
NOV3499-IgG1	0.0263	--
NOV3499-XTM	0.000692	--
Isotype control	--	--

FIG.40



	AC50 (nM)	
	HBx92-100	HBx52-60
NOV2505-IgG1	--	3.78
NOV2505-XTM	1.48	0.1
Isotype control	--	--

FIG.41



	AC50 (nM)	
	HBx92-100	HBx52-60
ATG.B.E211-IgG1	0.018	--
ATG.B.E211-XTM	3.40E-06	3.77
Isotype control	--	--

FIG.42

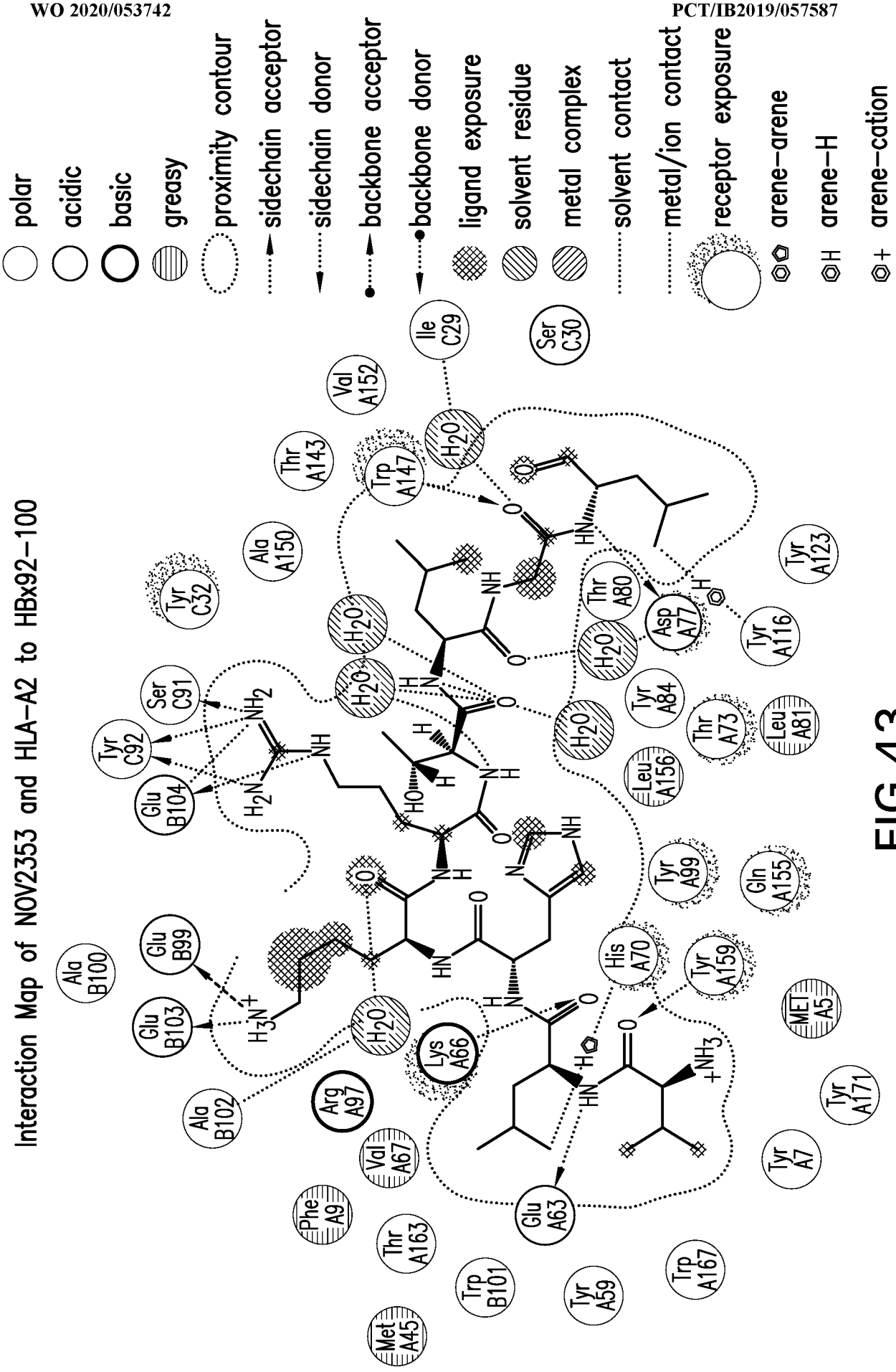

Interaction Map of NOV2353 and HLA-A2 to HBx92-100
polar
acidic
basic
greasy
proximity contour
sidechain acceptor
sidechain donor
backbone acceptor
backbone donor
ligand exposure
solvent residue
metal complex
solvent contact
metal/ion contact
receptor exposure
arene-arene
arene-H
arene-cation
Ala B100
Glu B99
Glu B103
Ala B102
Arg A97
Val A67
Phe A9
Thr A163
Trp B101
Met A45
Tyr A59
Glu A63
Lys A66
Tyr C32
Ala A150
Thr A143
Val A152
Trp A147
Ile C29
Ser C30
Ser C91
Tyr C92
Glu B104
Tyr A99
His A70
Tyr A159
Gln A155
Leu A156
Tyr A84
Thr A73
Leu A81
Thr A80
Asp A77
Tyr A116
Tyr A123
MET A5
Tyr A7
Tyr A171
Trp A167

FIG.43

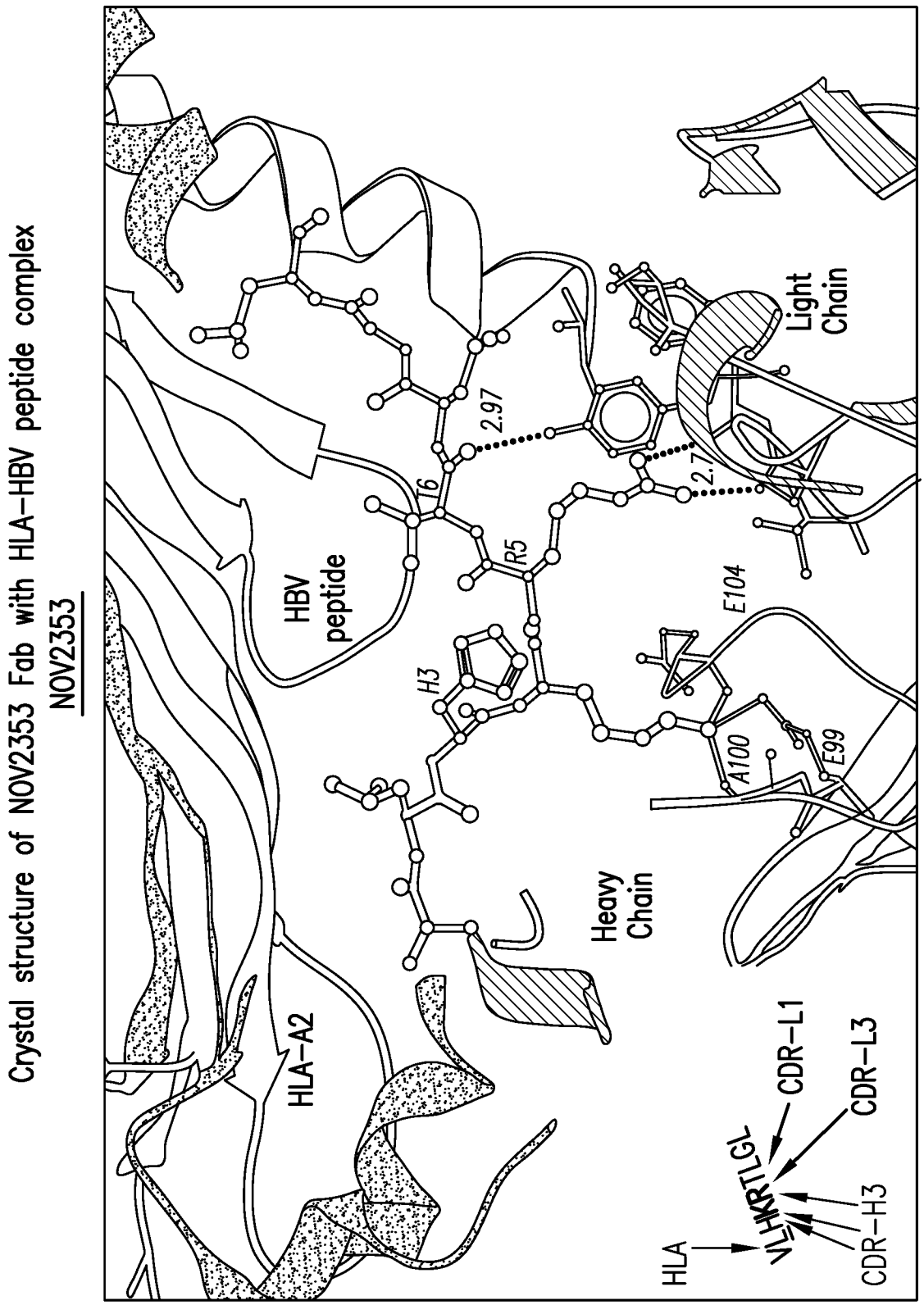

Crystal structure of NOV2353 Fab with HLA-HBV peptide complex
NOV2353
HLA-A2
HBV peptide
Heavy Chain
Light Chain
T6
R5
H3
2.97
2.7
E104
A100
E99
HLA
VLHKRTLGL
CDR-L1
CDR-L3
CDR-H3

FIG.44

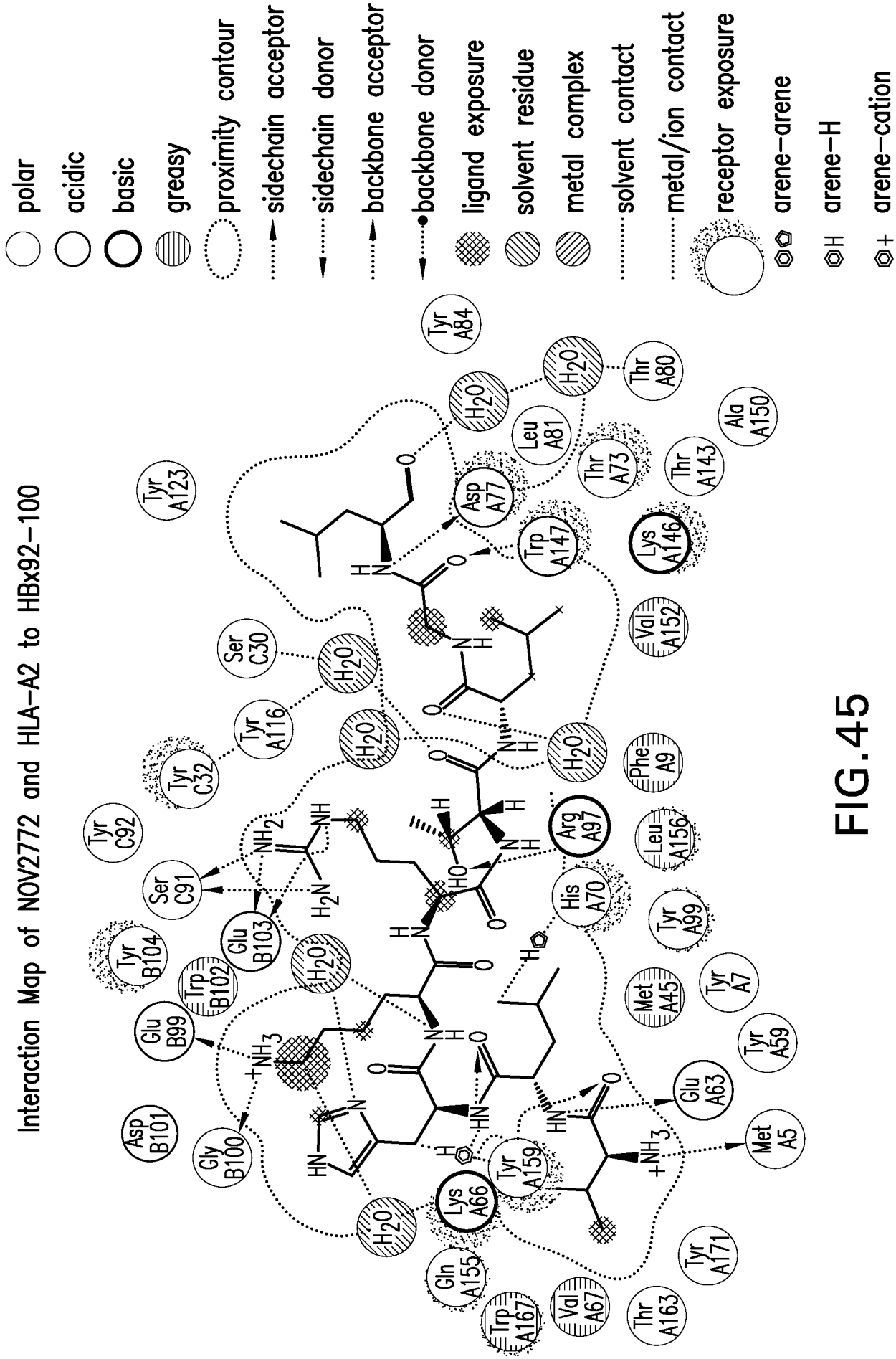

Interaction Map of NOV2772 and HLA-A2 to HBx92-100
polar
acidic
basic
greasy
proximity contour
sidechain acceptor
sidechain donor
backbone acceptor
backbone donor
ligand exposure
solvent residue
metal complex
solvent contact
metal/ion contact
receptor exposure
arene-arene
arene-H
arene-cation
Tyr A84
Thr A80
Leu A81
Ala A150
Thr A143
Thr A73
Asp A77
Trp A147
Lys A146
Val A152
Tyr A123
Ser C30
Tyr A116
Tyr C32
Tyr C92
Ser C91
Glu B103
Tyr B104
Trp B102
Glu B99
Asp B101
Gly B100
Phe A9
Leu A156
Arg A97
His A70
Tyr A99
Met A45
Tyr A7
Tyr A59
Glu A63
Met A5
Tyr A159
Lys A66
Gln A155
Trp A167
Val A67
Thr A163
Tyr A171

FIG.45

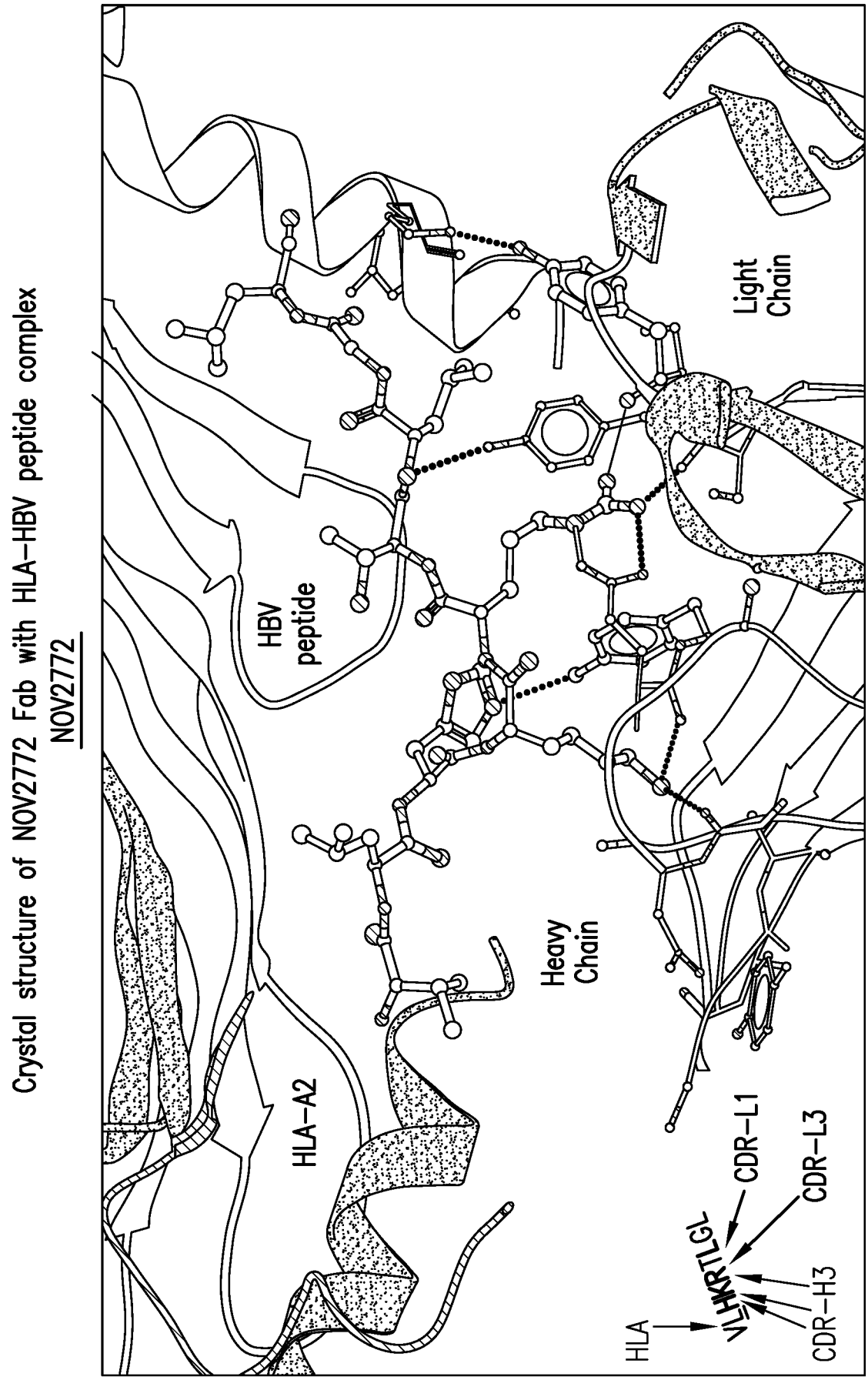

Crystal structure of NOV2772 Fab with HLA-HBV peptide complex
NOV2772
HBV peptide
Light Chain
Heavy Chain
HLA-A2
HLA
VLHKRTLGL
CDR-L1
CDR-L3
CDR-H3

FIG.46

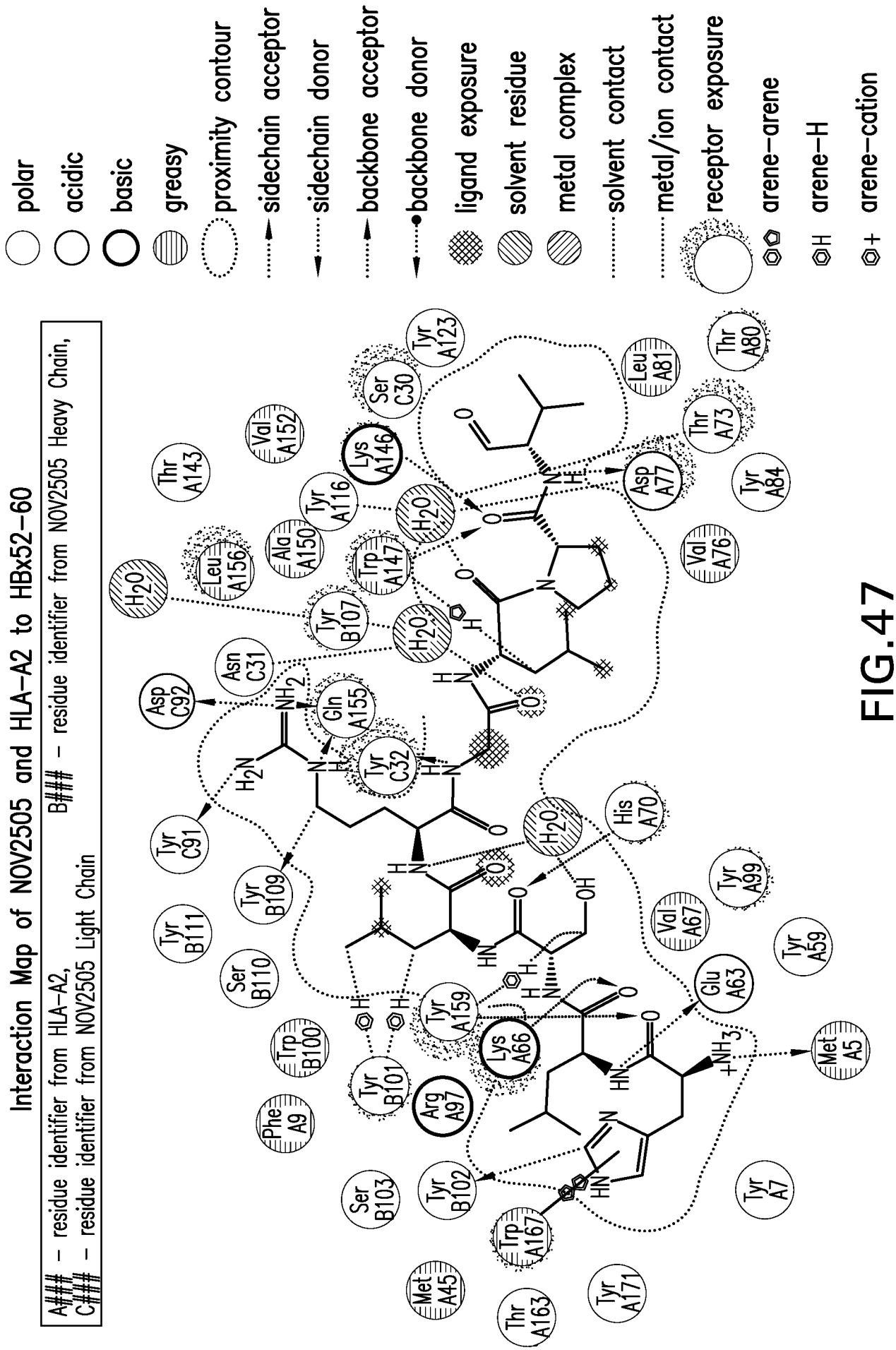

Interaction Map of NOV2505 and HLA-A2 to HBx52-60
A### – residue identifier from HLA-A2, B### – residue identifier from NOV2505 Heavy Chain,
C### – residue identifier from NOV2505 Light Chain
polar
acidic
basic
greasy
proximity contour
sidechain acceptor
sidechain donor
backbone acceptor
backbone donor
ligand exposure
solvent residue
metal complex
solvent contact
metal/ion contact
receptor exposure
arene–arene
arene–H
arene–cation

FIG.47

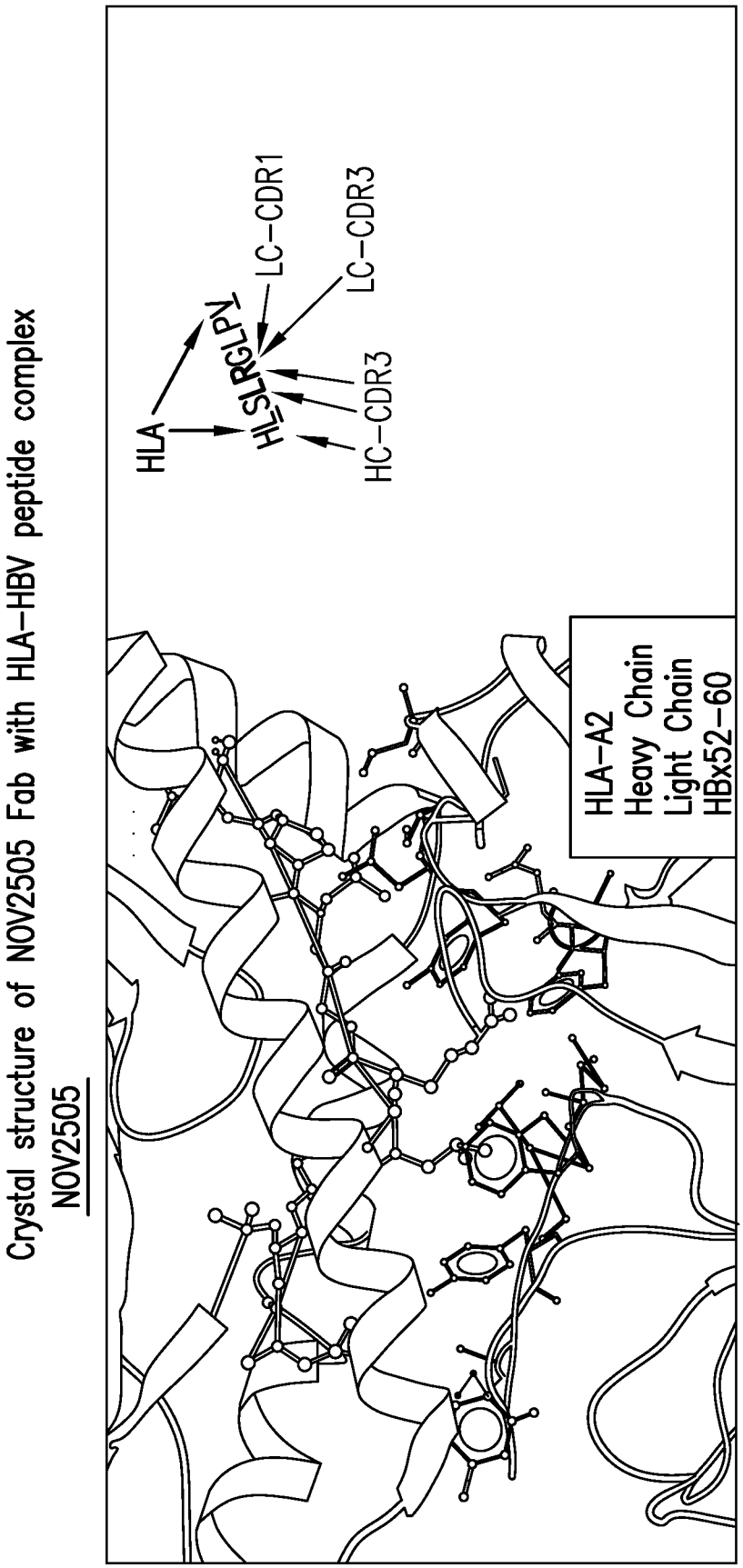

Crystal structure of NOV2505 Fab with HLA-HBV peptide complex
NOV2505
HLA
HLSLRGLPV
LC-CDR1
LC-CDR3
HC-CDR3
HLA-A2
Heavy Chain
Light Chain
HBx52-60

FIG.48