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(56) Fremdragne publikationer:
WO-A1-02/19986
WO-A1-93/03753
WO-A1-95/03777
DATABASE UniProt [Online] 1 March 2001 (2001-03-01), "SubName: Full=Precore/core protein;", XP002720153, retrieved from EBI accession no. UNIPROT:Q9DH31 Database accession no. Q9DH31
CAO T. ET AL.: "Characterization of HLA DR13-restricted CD4+T cell epitopes of hepatitis B core antigen associated with self-limited, acute hepatitis B.", J. GEN. VIROL., vol. 83, 2002, pages 3023-3033, XP002720154,
REHERMANN B ET AL: "The cytotoxic T lymphocyte response to multiple Hepatitis B virus polymerase epitopes during and after acute viral hepatitis", THE JOURNAL OF EXPERIMENTAL MEDICINE, ROCKEFELLER UNIVERSITY PRESS, US, vol. 181, no. 3, 1 March 1995 (1995-03-01) , pages 1047-1058, XP001181423, ISSN: 0022-1007, DOI: 10.1084/JEM.181.3.1047
BERTOLETTI A ET AL: "HLA Class I-restricted human cytotoxic T cells recognize endogenously synthesized Hepatitis B virus nucleocapsid antigen", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 88, no. 23, 1991, pages 10445-10449, ISSN: 0027-8424
ILAN Y ET AL: "Ablation of Persistant Hepatitis B by Bone Marrow Transplantation from a Hepatitis B-Immune Donor", GASTROENTEROLOGY, ELSEVIER, US, vol. 104, no. 6, 1 June 1993 (1993-06-01), pages 1818-1821,

Fortsættes ...

XP002978426, ISSN: 0016-5085
LAU GEORGE K K ET AL: "Clearance of hepatitis B surface antigen after bone marrow transplantation: Role of adoptive immunity transfer", HEPATOLOGY, vol. 25, no. 6, 1997, pages 1497-1501, ISSN: 0270-9139
LAU GEORGE K K ET AL: "Resolution of chronic hepatitis B and anti-HBs seroconversion in humans by adoptive transfer of immunity to hepatitis B core antigen", GASTROENTEROLOGY, vol. 122, no. 3, March 2002 (2002-03), pages 614-624, XP029479411, ISSN: 0016-5085, DOI: 10.1053/GAST.2002.31887
BONI CAROLINA ET AL: "Restored Function of HBV-Specific T Cells After Long-term Effective Therapy With Nucleos(t)ide Analogues", GASTROENTEROLOGY, vol. 143, no. 4, October 2012 (2012-10), page 963,
WURSTHORN KARSTEN ET AL: "Kinetics of Hepatitis B Surface Antigen Decline During 3 Years of Telbivudine Treatment in Hepatitis B e Antigen-Positive Patients", HEPATOLOGY, vol. 52, no. 5, November 2010 (2010-11), pages 1611-1620, ISSN: 0270-9139
DE NIET ANNIKKI ET AL: "Restoration of T cell function in chronic hepatitis B patients upon treatment with interferon based combination therapy", JOURNAL OF HEPATOLOGY, ELSEVIER, AMSTERDAM, NL, vol. 64, no. 3, 24 October 2015 (2015-10-24), pages 539-546, XP029420238, ISSN: 0168-8278, DOI: 10.1016/J.JHEP.2015.10.013
A. T. HEINY ET AL: "Evolutionarily Conserved Protein Sequences of Influenza A Viruses, Avian and Human, as Vaccine Targets", PLOS ONE, vol. 2, no. 11, 21 November 2007 (2007-11-21), page e1190, XP055002101, ISSN: 1932-6203, DOI: 10.1371/journal.pone.0001190
KHAN ASIF M ET AL: "Conservation and variability of dengue virus proteins: implications for vaccine design.", PLOS NEGLECTED TROPICAL DISEASES 13 AUG 2008, vol. 2, no. 8, 13 August 2008 (2008-08-13) , page e272, ISSN: 1935-2735
ZHANG GUANG LAN ET AL: "Hotspot Hunter: a computational system for large-scale screening and selection of candidate immunological hotspots in pathogen proteomes.", BMC BIOINFORMATICS 2008, vol. 9 Suppl 1, 2008, page S19, ISSN: 1471-2105
BIJKER MARTIJN S. ET AL: "CD8 + CTL Priming by Exact Peptide Epitopes in Incomplete Freund's Adjuvant Induces a Vanishing CTL Response, whereas Long Peptides Induce Sustained CTL Reactivity", THE JOURNAL OF IMMUNOLOGY, vol. 179, no. 8 15 October 2007 (2007-10-15), pages 5033-5040, XP055798792, US ISSN: 0022-1767, DOI: 10.4049/jimmunol.179.8.5033 Retrieved from the Internet:
URL:https://www.jimmunol.org/content/jimmu nol/179/8/5033.full.pdf

DESCRIPTION

Field of the Invention

[0001] The present invention relates to an immunogenic HBV peptide composition and to the treatment of HBV using the composition.

Background to the Invention

[0002] Hepatitis B virus (HBV) infection is a major cause of liver-related morbidity and mortality in Europe and worldwide. An estimated 650,000 individuals die each year from liver failure or hepatocellular carcinoma. Even though vaccination programs have led to declines in *de novo* HBV infections in many countries, chronic hepatitis B (CHB) is a rapidly growing problem in Europe due to immigration of HBV carriers from endemic areas.

[0003] From a conceptual standpoint, chronic HBV infection can be classified into three phases (or types of immune responses): immune tolerant, immune active and inactive chronic carrier. These distinct phases of chronic infection correspond with characteristic serologic patterns and correlate with the patient's immune response to HBV. In general, patients with persistent immune active chronic HBV infection receive HBV therapy.

[0004] Limited treatment options are available for chronic hepatitis B (CHB). Suppression of viral replication with antivirals such as interferon-alpha and nucleoside/nucleotide analogues (NUCs) is the only way to reduce morbidity and mortality from chronic HBV infection with the ultimate aim of improving survival. Nevertheless, the loss of serum HBsAg and development of anti-HBs antibodies (seroconversion) is the hallmark of a successful immunological response to HBV infection and the closest outcome to clinical cure. Only interferon-alpha has been able to induce significant HBsAg loss but in a relatively low proportion of patients (<10%). Interferons have a high cost, a poor tolerability and some HBV genotypes remain poorly responsive to treatment.

[0005] Consequently, NUCs remain the main treatment strategies with five NUCs being approved in Europe to treat CHB. The most potent and preferred drugs, tenofovir and entecavir, have a very favourable side-effect profile and are able to induce HBV DNA suppression in almost all patients. However, life-long therapy is required for the majority of patients under most national and international guidelines. Only very few HBeAg-positive patients, and no HBeAg-negative patients, are able to clear HBsAg even after several years of NUC therapy. The long-term safety of NUC therapy is currently unknown. Therefore, concepts to enable a timely cessation of NUC therapy are urgently needed.

[0006] Therapeutic vaccination is a promising intervention for hepatitis B as a way to induce immune control over the disease. T-cell responses have been shown to be critical for clearance of acute HBV infection. However, therapeutic HBV vaccines based on HBsAg have failed to show benefit due to induced immune tolerance from high levels of circulating HBsAg, even under effective antiviral treatment. Combinations of HBV peptides for use in the treatment or prevention of HBV infection are known from WO02/19986, no therapeutic efficacy has been shown.

Summary of the Invention

[0007] The present inventors have identified regions of the HBV proteome that have a high degree of conservation between different HBV genotypes and that have unexpectedly better immunogenic properties compared to other similarly conserved regions of HBV proteins. In particular, the inventors have unexpectedly shown using an *in vitro* assay that peptide sequences within particular domains of HBV polymerase and HBV core protein are able to elicit a response in PBMC from chronically infected HBV patients infected with different HBV genotypes and/or from chronically infected HBV patients of different ethnicities. In particular, the inventors have surprisingly identified an

immunodominant region in the terminal domain of HBV polymerase.

[0008] The invention provides a pharmaceutical composition for use in the treatment or prevention of HBV infection, the composition comprising:

a first peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 24,

a second peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 25,

a third peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 28,

a fourth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 33,

a fifth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 34,

a sixth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 36,

a seventh peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 37,

an eighth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 38, and

a ninth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 222,

wherein each peptide is up to 60 amino acids in length.

[0009] The peptides may each be linked to a fluorocarbon vector.

[0010] The composition may further comprise an adjuvant.

[0011] The composition is capable of eliciting an immune response in PBMC from at least two individuals of different ethnicities and from two individuals infected with different HBV genotypes.

[0012] The composition is capable of eliciting an immune response: (a) in PBMC from two, three or all of: an individual infected with HBV genotype A, an individual infected with HBV genotype B, an individual infected with HBV genotype C and an individual infected with HBV genotype D; and/or in PBMC from two, three or all of: an Oriental or Indian individual infected with HBV, a Caucasian individual infected with HBV and an African or Arabic individual infected with HBV.

[0013] The invention provides the composition of the invention for use in the treatment or prevention of HBV infection, particularly for the treatment of HBeAg-negative patients or HBeAg-positive patients. The composition of the invention may be used in combination with: (i) interferon-alpha and/or nucleoside/nucleotide analogues (NUCs); and/or (ii) anti-PD1 blocking antibodies, anti-CTLA4 blocking antibodies, anti-PDIL blocking antibodies, anti-LAG3 blocking antibodies, anti-TIM3 blocking antibodies and/or cyclophosphamide. Treatment with the composition may result in HBsAg loss or HBsAg seroconversion.

[0014] The invention also provides the composition of the invention for use in the treatment or prevention of end-stage liver disease or hepatocellular carcinoma or for use in the treatment or prevention of hepatitis D virus (HDV) infection.

Brief Description of the Figures

[0015]

Figure 1 is a comparison of IFNγ responses in chronic HBV-infected subjects in immune control phase or

undergoing active treatment. Following a 10 day culture with an HBV-derived overlapping short peptide pool library (0.1 µg/peptide/mL), PBMC were restimulated (5µg/peptide/mL) in an 18h IFNγ ELISpot assay with one of pools 1 to 23 of the overlapping peptides representing specific regions of the HBV proteome.

Figure 2 shows the specificity of IFNγ responses to HBV-derived short peptide pools in HBV-infected subjects grouped by infecting HBV genotypes. Following a 10 day culture with an HBV-derived overlapping short peptide pool library (0.1µg/peptide/mL), PBMC were restimulated (5 µg/peptide/mL) in an 18h IFNγ ELISpot assay with one of pools 1 to 23 of the overlapping peptides representing specific regions of the HBV proteome.

Figure 3 shows IFNγ responses to HBV-derived short peptide pools in chronic HBV-infected subjects grouped by ethnic background. Following a 10 day culture with an HBV-derived overlapping short peptide pool library (0.1 µg/peptide/mL), PBMC were restimulated (5µg/peptide/mL) in an 18h IFNγ ELISpot assay with one of pools 1 to 23 of the overlapping peptides representing specific regions of the HBV proteome.

Figure 4 shows representative dot plots of CD4 and CD8 T-cell IFNγ production in PBMC from chronic HBV and healthy control subjects following stimulation with HBV polymerase- and core-derived short peptide pools. PBMC from subjects were stimulated for 10 days with a short peptide pool library (0.1µg/peptide/mL), followed by overnight stimulation (5µg/peptide/mL) with HBV derived short peptide pool 2 or 14, representing regions of the HBV polymerase and core respectively. Results are expressed as IFNγ-producing cells, as a percentage of parent CD3/CD4 or CD3/CD8 T-cell populations. Stimulation in culture medium or PMA/ionomycin were used as negative and positive controls respectively and the gating strategy was based on negative control IFNγ production.

Figure 5 is a comparison of IFNγ responses to HBV-derived short peptide pools representing 35-40mer peptides in PBMC from healthy subjects and chronic HBV-infected HBeAg-negative subjects in immune control phase or undergoing active treatment. Following a 10 day culture with an HBV-derived overlapping short peptide pool library (0.1µg/peptide/mL), PBMC were restimulated (5µg/peptide/mL) in an 18h IFNγ ELISpot assay with one of pools 24 to 46 of the overlapping peptides, each representing 35-40mer regions of the HBV proteome.

Figure 6 shows the specificity of IFNγ responses to HBV-derived short peptide pools representing 35-40mer peptides in HBV-infected subjects grouped by infecting HBV genotype. Following a 10 day culture with an HBV-derived overlapping short peptide pool library (0.1µg/peptide/mL), PBMC were restimulated in an 18h IFNγ ELISpot assay with one of pools 24 to 46 of the overlapping peptides, each representing specific regions of the HBV proteome.

Figure 7 shows IFNγ responses to HBV-derived short peptide pools representing 35-40mer peptides in chronic HBeAg-negative HBV-infected subjects grouped by ethnic background. Following a 10 day culture with an HBV-derived overlapping short peptide pool library (0.1µg/peptide/mL), PBMC were restimulated (5µg/peptide/mL) in an 18h IFNγ ELISpot assay with one of pools 24 to 46 of the overlapping peptides, each representing 35-40mer regions of the HBV proteome.

Figure 8 is a summary of cytokine responses by PBMC from HBV-infected subjects to individual short peptide pools representing 35-40mer peptides. Following a 10 day short-term culture with an HBV-derived short peptide pool library, PBMC from chronic eAg-negative HBV-infected subjects (n=7-14) were cultured overnight with one of HBV peptide pools 25, 38, 26, 39, 42, 43, 28 and 31 (representing peptides P113, P753, P151, P797, P856, P877, P277 and P376) at a final concentration of 5µg/peptide/mL. Cells were stained for extracellular expression of CD3, CD4 and CD8, followed by intracellular expression of IFNγ, IL-2 and TNFα. Cells were assessed by flow cytometry. Cytokine expression was normalised to media negative controls for each subject. Data represents mean expression for each cytokine assessed. Breadth of responses are shown above each stacked bar.

Figure 9 shows the number of IFNγ spot forming cells (mean values) measured in PBMCs from chronic HBV-infected (either HBeAg-negative inactive carriers or HBeAg-negative treated subjects). Following a 10 day culture with the nine unconjugated HBV peptides (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) (0.1µg/peptide/mL), PBMC were restimulated in an 18h IFNγ ELISpot assay with individual peptides at a concentration of 5µg/ml.

Figure 10 shows the frequency of responders to the IFNγ ELISpot assay in response to HBV peptides measured in

PBMCs from chronic HBV-infected (either HBeAg-negative inactive carriers or HBeAg-negative treated subjects). Following a 10 day culture with the nine unconjugated HBV peptides (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) (0.1µg/peptide/mL), PBMC were restimulated in an 18h IFNγ ELISpot assay with individual peptides at a concentration of 5µg/ml.

Figure 11 shows the number of IFNγ spot forming cells (mean values) measured in PBMCs from chronic HBV-infected subjects grouped by infecting HBV genotypes. Following a 10 day culture with the nine unconjugated HBV peptides (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) (0.1µg/peptide/mL), PBMC were restimulated in an 18h IFNγ ELISpot assay with individual peptides at a concentration of 5µg/ml.

Figure 12 shows the number of IFNγ spot forming cells measured (mean values) in PBMCs from chronic HBV-infected subjects grouped by ethnic background. Following a 10 day culture with the nine unconjugated HBV peptides (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) (0.1µg/peptide/mL), PBMC were restimulated in an 18h IFNγ ELISpot assay with individual peptides at a concentration of 5µg/ml.

Figure 13 shows the frequency of cytokine-producing CD4+ and CD8+ T cell in PBMC from chronic HBV following stimulation with HBV derived peptides. Figures 13A, 13B, 13C, 13D and 13E correspond to results obtained for groups of individuals infected by HBV genotypes A, B, C, D and non-A/B/C/D respectively. Following a 10 day culture with the nine unconjugated HBV peptides (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) (0.1µg/peptide/mL), PBMC were restimulated in an 18h IFNγ ELISpot assay with individual peptides at a concentration of 5µg/ml.Results are expressed as cytokine-producing cells, as a percentage of parent CD3/CD4 or CD3/CD8 T cell populations. Stimulation in culture medium or PMA/ionomycin were used as negative and positive controls respectively and the gating strategy was based on negative control IFNγ production.

Figure 14 shows IFNγ production by splenocytes from BALB/c mice (n=7) immunised with FP-02.1 or NP02.1. The graphic represents the number of IFNγ spotforming cells per 10^6 splenocytes measured in response to the 9 peptide components of the vaccines. Statistical analyses were performed using paired t tests, ns = not significant.

Figure 15 shows IFNγ production by splenocytes from BALB/c mice (n=7) immunised with FP-02.1 or NP02.1. The graphic represents the number of IFNγ spotforming cells per 10^6 splenocytes measured in response each of the 9 peptide components of the vaccines. Bars represent cumulative median responses to each individual peptide.

Figure 16 shows that FP02.1 promotes T cell responses against CTL epitopes restricted by MHC class I molecules after a single immunisation.

Figure 17 shows IFNγ production by BALB/c mice immunised with FP-02.1 or NP02.1. Number of IFNγ SFC/10^6 splenocytes produced in response to a mixture of the nine peptides for each splenocyte population.

Brief Description of the Sequence Listing

[0016] SEQ ID NOs: 1 to 38 and 40 to 72 are the amino acid sequences of regions of the reference HBV sequence shown in SEQ ID NO: 39 of HBV polymerase as shown in Table 1 below.

SEQ ID NO:	Reference in Examples	Region of virtual HBV proteome sequence	HBV protein
1	Pools 2/3	93-186	polymerase
2	Pools 4 to 7	211-426	polymerase
3	Pools 12 and 13	592-700	polymerase
4	Pools 14 to 17	703-912	core

SEQ ID NO:	Reference in Examples	Region of virtual HBV proteome sequence	HBV protein
5	Pool 2	93-145	polymerase
6	Pool 3	133-186	polymerase
7	Pool 5 +	260-326	polymerase
	additional N-terminal residues		
8	Pool 6	332-384	polymerase
9	Pools 6/7	332-426	polymerase
10	Pools 14/15	703-812	core
11	Pools 15/16	749-871	core
12	Pools 16/17	811-912	core
13	Pool 17	859-912	core
14	Pool 25	93-132	polymerase
15	Pool 26	133-171	polymerase
16	Pool 28 + additional N-terminal residues	260-301	polymerase
17	Pool 30	332-378	polymerase
18	Pool 31	359-398	polymerase
19	Pool 35	626-663	polymerase
20	Pool 38	738-775	core
21	Pool 39/40	778-837	core
22	Pool 42	838-878	core
23	Pool 43	859-891	core
24	P113	96-130	polymerase
25	P151	134-168	polymerase
26	P277	260-295	polymerase
27	P360	342-378	polymerase
28	P376	359-398 (C to S substitution at 393)	polymerase
29	P645	627-662	polymerase
30	P753	738-770 (S to T substitution at 743)	core
31	P797	780-814 (C to S substitution at 793)	core
32	P856	839-873	core
33	P877	860-890	core
34	P277(K)	260-293 + KKK	polymerase
35	P645(K)	KKK + 627-662	polymerase
36	P753(K)	KK + 738-770 (S to T at 743) + KKK	core
37	P797(K)	780-814 (C to S at 792) +KKK	core
38	P856(K)	839-873 +KKK	core
40	Pool 1	25-79	polymerase
41	Pool 4	211-261	polymerase
42	Pool 7	372-426	polymerase
43	Pool 8	414-465	polymerase
44	Pool 9	473-531	polymerase
45	Pool 10	520-569	polymerase

SEQ ID NO:	Reference in Examples	Region of virtual HBV proteome sequence	HBV protein
46	Pool 11	557-604	polymerase
47	Pool 12	592-650	polymerase
48	Pool 13	638-700	polymerase
49	Pool 14	703-762	core
50	Pool 15	749-812	core
51	Pool 16	811-871	core
52	Pool 18	966-1017	X
53	Pool 19	1005-1062	X
54	Pool 20	1171-1224	surface
55	Pool 21	1241-1296	surface
56	Pool 22	1312-1346	surface
57	Pool 23	1392-1447	surface
58	Pool 24	31-79	polymerase
59	Pool 27	223-261	polymerase
60	Pool 28	265-301	polymerase
61	Pool 29	289-326	polymerase
62	Pool 32	404-440	polymerase
63	Pool 33	428-465	polymerase
64	Pool 34	557-597	polymerase
65	Pool 36	645-685	polymerase
66	Pool 37	659-700	polymerase
67	Pool 39	778-812	core
68	Pool 40	811-837	core
69	Pool 41	811-850	core
70	Pool 44	979-1024	X
71	Pool 45	1247-1289	surface
72	Pool 46	1399-1439	surface
220	Pool 5	265-326	polymerase
221	P1266	1252-1284 (K to R at 1266)	surface
222	P1266(K)	KKK+1252-1284 (K to R at 1266)+KKK	surface

[0017] SEQ ID NO: 39 is a virtual HBV protein sequence built by linear coassembly of the terminal domain of polymerase (positions 1 to 181), the reverse transcriptase domain of polymerase (position 182 to 549) the RNase domain H of polymerase (position 550 to 702), the core protein (position 703 to 914), the X protein (position 915 to 1068) and the surface protein (positions 1069 to 1468). The proteome sequence was obtained from consensus of consensus sequences generated from genotype A, B, C and D consensus sequences.

[0018] SEQ ID NOs: 73 to 219 are the amino acid sequences of short peptides within each of pools 1 to 46. SEQ ID NO: 220 is the amino acid sequence of pool 5.

Detailed Description of the Invention

Peptide Composition

[0019] The invention provides a pharmaceutical composition for use in the treatment or prevention of HBV infection, the composition comprising:

a first peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 24,

a second peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 25,

a third peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 28,

a fourth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 33,

a fifth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 34,

a sixth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 36,

a seventh peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 37,

an eighth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 38, and

a ninth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 222,

wherein each peptide is up to 60 amino acids in length.

Peptide sequences

[0020] The composition of the invention comprises peptides comprising or consisting of the following sequences:

VGPLTVNEKRRLKLIMPARFYPNVTKYLPLDKGIK (SEQ ID NO: 24);

PEHVVNHYFQTRHYLHTLWKAGILYKRETTRSASF (SEQ ID NO: 25);

KLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAISSVVRR (SEQ ID NO: 28);

PPAYRPPNAPILSTLPETTVVRRRGRSPRRR (SEQ ID NO: 33);

RVSWPKFAVPNLQSLTNLLSSNLSWLSLDVSAAFYHKKK (SEQ ID NO: 34),

KKKEFGATVELLSFLPSDFFPSVRDLLDTASALYRKKK (SEQ ID NO: 36);

SPHHTALRQAILSWGELMTLATWVGSNLEDPASRDKKK (SEQ ID NO: 37);

LTFGRETVLEYLVSFGVWIRTPPAYRPPNAPILSTKKK (SEQ ID NO: 38);

KKKGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLKKK (SEQ ID NO: 222).

[0021] Each peptide thas a length of up to 60 amino acids, such as up to 40 amino acids.

[0022] The peptide may include additional sequences. The additional sequences may facilitate manufacture or formulation of the peptide or enhance stability of the peptide. For example, the peptide may comprise one or more additional amino acids, typically at the N-terminus and/or the C-terminus to enhance the net positive charge of the peptide and/or to reduce the hydrophobicity of the peptide. The net positive charge may be increased so that the

peptide has an isoelectric point greater than or equal to 7. For example, in some of the peptides, two or three positively charged amino acids (arginine and/or lysine) are added to the N- and/or C-terminus of one or more of the peptides in the composition. For example, three lysine residues may be added to the N- and/or C-terminus of one or more of the peptides. Positive amino acids are typically added at the end(s) of peptides that have an overall hydrophobicity of more than 65%, a net charge of less than zero and/or include cluster of hydrophobic amino acids. Particular examples of peptides that include N- and/or C-terminal lysine residues are shown in SEQ ID NOs: 34 to 38 and 222.

[0023] Where the peptide is linked to a fluorocarbon, the terminus of the peptide, such as the terminus that is not conjugated to the fluorocarbon, or other attachment, can be altered, for example to promote solubility of the fluorocarbon-peptide construct via the formation of micelles. To facilitate large-scale synthesis of the construct, the N- or C-terminal amino acid residues of the peptide can be modified. When the desired peptide is particularly sensitive to cleavage by peptidases, the normal peptide bond can be replaced by a non-cleavable peptide mimetic. Such bonds and methods of synthesis are well known in the art.

[0024] The peptide may be a native peptide. The peptide may be modified to increase longevity, such as half-life or persistence at the site of administration, of the peptide *in vivo* or to direct the peptide to antigen-presenting cells. For example, the immunogenic peptide can contain one or more non-naturally occurring amino acids and/or non-naturally occurring covalent bonds for covalently connecting adjacent amino acids. In certain embodiments, the non-standard, non-naturally occurring amino acids can also be incorporated into the immunogenic peptides provided that they do not interfere with the ability of the peptide to interact with MHC molecules and remain cross-reactive with T-cells recognising the natural sequences. Non-natural amino acids can be used to improve peptide resistance to protease or chemical stability. Examples of non-natural amino acids include D-amino acids and cysteine modifications.

[0025] The peptide may be coupled to a carrier, such as a protein carrier or a delivery vector. Suitable delivery vectors include lipopeptides, for example fatty acyl chains such as a monopalmitoyl chain, virosomes, liposomes and cell penetrating peptides, such as penetratin and transactivator of transcription (TAT).

[0026] One or more, and preferably all, of the HBV peptides in the composition for use according to the invention are preferably covalently linked to a fluorocarbon vector.

Combinations of peptides

[0027] The composition for use according to the invention comprises multiple peptides. The composition comprises eight peptides, each comprising a sequence of at least 15 contiguous amino acids of one of SEQ ID NOs: 1 to 4 as defined in the claims and additionally a peptide comprising a sequence of at least 15 contiguous amino acids of SEQ ID NO: 55 as defined in the claims. Specifically, the composition comprises:

a first peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 24,

a second peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 25,

a third peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 28,

a fourth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 33,

a fifth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 34,

a sixth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 36,

a seventh peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 37,

an eighth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 38, and

a ninth peptide comprising or consisting of the amino acid sequence shown in SEQ ID NO: 222,

wherein each peptide is up to 60 amino acids in length.

HBV Genotypes

[0028] The combination of peptide sequences in the composition provides epitopes, preferably both CD8+ and CD4+ epitopes, present in multiple HBV genotypes. HBV genotypes include genotypes A, B, C, D, E and F. For example, the long peptides may comprise epitopes from at least two HBV genotypes, such as A and D (the most highly prevalent genotypes in Europe) or B and C (the most highly prevalent genotypes in Asia). More preferably, the composition comprises epitopes from at least three HBV genotypes, such as for example, A, B and C, A, B and D, A, C and D or B, C and D. Most preferably, the composition comprises epitopes from at least HBV genotypes A, B, C and D. In addition to including any combination of epitopes from any combination of one or more of genotypes A, B, C and D, the composition may comprise epitopes to genotypes E, F and/or G. This may be determined by any suitable means, for example by using an *in vitro* PBMC assay as described herein.

[0029] Thus, the present invention provides a composition capable of eliciting an immune response in PBMC from two, three, four or all of: an individual infected with HBV genotype A, an individual infected with HBV genotype B, an individual infected with HBV genotype C, an individual infected with HBV genotype D and an individual infected with another HBV genotype.

[0030] In one aspect, the composition for use according to the invention may also elicit an *in vitro* response in peripheral blood mononuclear cells (PBMC) from at least one individual chronically infected with HBV genotype A, one individual chronically infected with HBV genotype B, one individual chronically infected with HBV genotype C and one individual chronically infected with HBV genotype D. This may be determined by any suitable method, such as a method described in the Examples herein. The individuals may be of the same or different ethnicities, preferably from at least two different ethnicities. The individuals may be of the same or different HLA subtypes, preferably at least two different HLA subtypes.

Ethnicities

[0031] The invention provides a composition for use in the treatment or prevention of HBV infection, capable of eliciting an immune response in individuals of at least two, such as three or more different ethnicities. This can be assessed using an *in vitro* PBMC assay as described in the Examples. The composition for use according to the invention may be capable of eliciting an immune response in PBMC from two, three or all of: an Oriental or Indian individual infected with HBV, a Caucasian individual infected with HBV and an African or Arabic individual infected with HBV.

Epitopes

[0032] HLA class I and class II molecules are polymorphic and their frequency varies between ethnic groups. Most of the polymorphism is located in the peptide-binding region, and as a result each variant is believed to bind a unique repertoire of peptide ligands. HLA polymorphism represents a major challenge for vaccine designers since HLA polymorphism is the basis for differential peptide binding. Moreover, specific HLA alleles are expressed at dramatically different frequencies in different ethnicities.

[0033] Despite such polymorphisms, HLA molecules bind overlapping set of peptides, and therefore, may be grouped accordingly into supertypes (Lund et al (2004) Immunogenetics 55(12):797-810, Sette et al (1999)

Immunogenetics 50(3-4):201-212). A supertype is defined as a family of different HLA molecules having similar peptide binding repertoire and consequently sharing overlapping sets of peptides. In other words, a peptide that binds to an HLA allele belonging to a given supertype is likely to present a binding activity to the other supertype members.

[0034] Binding capacity of the peptides for different HLA class II alleles can be determined using a heterologous competitive assay using a specific biotinylated tracer peptide for each HLA class II allele as described in Texier et al (2000) J Immunol 164:3177-3184, Texier et al (2001) Eur J Immunol 31:1837-1846 and Castelli et al (2002) J Immunol 169:6928-6934.

[0035] The following nine HLA class II alleles represent major supertypes or HLA clusters based on sequences analysis and binding-motif specificities as described in Lund et al (2004) Immunogenetics 55(12):797-810 and Greenbaum et al (2011) Immunogenetics 63(6):325-35: HLA-DR1 (al*01:01;01*01:01), HLA-DR3 (α1*01:01;β1*01:01), HLA-DR4 (α1*01:01;β1*04:01), HLA-DR7 (α1*01:01;β1*07:01), HLA-DR11 (α1*01:01;β1*11:01), HLA-DR13 (α1*01:01;β1*13:01), HLA-DR15 (α1*01:01;β1*15:01), HLA-DR51 (α1*01:01;β5*01:01) and HLA-DP4 (α1*01:03;β1*04:01). These alleles have a high prevalence across different ethnicities (see Wilson et al (2001) J Virol. 75(9):4195-4207).

[0036] A peptide present in a composition for use according to the invention typically binds to at least two, preferably at least three, of the nine major HLA class II alleles, such as to at least two, preferably at least three, of the seven HLA class II alleles described in Example 10. One or more of the peptides present in the composition may bind to at least four, five, six, seven, eight or all of the nine major HLA class II alleles or to at least four, five, six or all of the seven HLA class II alleles described in Example 10. The composition for use according to the invention comprises peptides that can bind to at least seven, at least eight or all nine of the major HLA class II alleles described above, such as to all of the seven HLA class II alleles described in Example 10.

[0037] The number of HLA class I binding registers contained in each peptide may be determined by determining the ability of the peptide to bind to a range of frequently occurring HLA class I molecules. HLA class I binding may be measured using the ProImmune REVEAL® MHC-peptide Binding Assay (ProImmune Ltd, Oxford, UK). The REVEAL™ MHC peptide-binding assay measures the ability of each peptide to stabilize the ternary MHC-peptide complex for HLA-A*0101, HLA-A*0201, HLA-A*0301, HLA-A*2402, HLA-B*0702, HLA-B*0801, HLA-B*3501 representative of main HLA class I supertypes. Each tested peptide is given a score relative to a pass/fail control peptide and also compared to a positive control peptide.

[0038] HLA class I molecules bind short peptides having length varying from 8 to 11 amino acids. In theory, 102 short peptides (27 × 8-mers, 26 × 9-mers, 25 × 10-mers & 24 × 11-mers) could be derived from a 35-mer peptide sequences. In order to limit the number of peptides to be tested, binding assays can be conducted using only nonamer peptides (the most frequent length for HLA class I binding peptides) with a good prediction score based on publically available algorithms.

[0039] The following HLA class I alleles are highly represented in human populations and (2) they belong to well-defined HLA supertypes (http://bioinformatics.nmdp.org/): HLA-A*0101, HLA-A*0201, HLA-A*0301, HLA-A*2402, HLA-B*0702, HLA-B*0801, HLA-B*3501 and HLA-A*1101.

[0040] A peptide present in the composition for use according to the invention typically comprises shorter peptides that bind to at least one, preferably at least two or at least three of these HLA class I alleles, such as to the first seven class I alleles listed above and preferably to the seven HLA class I alleles mentioned in Example 9. One or more of the peptides present in the composition may comprise shorter peptides that bind to at least four, five, six or all of the seven HLA class I alleles. The composition for use according to the invention preferably comprises peptides that comprise shorter peptides that can bind to at least five, at least six or all seven of the HLA class I alleles described above.

[0041] A pharmaceutical composition for use according to the invention comprises the peptides as defined in the claims comprising one or more T-cell epitopes that bind to different MHC alleles to give broad population coverage. The composition comprises peptides known or predicted to contain one or more MHC binding motif related to highly frequent MHC alleles in a specific ethnic group or across multiple ethnic groups. The composition comprises one or more promiscuous CD4+ and CD8+ T-cell epitopes that bind to more than one allelic variant. The combination of peptide sequences in the composition provides T-cell epitopes that bind to different HLA subtypes.

[0042] In one aspect, the composition for use according to the invention also elicits a response *in vitro* in peripheral blood mononuclear cells (PBMC) from at least two individuals with different HLA subtypes. The composition may elicit an immune response in at least three, four, five, six or seven individuals each having a different HLA genotype, who may be Individuals of different ethnicities.

Fluorocarbon

[0043] The fluorocarbon can comprise one or more chains derived from perfluorocarbon or mixed fluorocarbon/hydrocarbon radicals, and may be saturated or unsaturated, each chain having from 3 to 30 carbon atoms. Thus, the chains in the fluorocarbon attachment are typically saturated or unsaturated, preferably saturated. The chains in the fluorocarbon attachment may be linear or branched, but preferably are linear. Each chain typically has from 3 to 30 carbon atoms, from 5 to 25 carbon atoms, or from 8 to 20 carbon atoms. In order to covalently link the fluorocarbon vector to the peptide, a reactive group, or ligand, for example -CO-, -NH-, S, O or any other suitable group is included in the vector. The use of such ligands for achieving covalent linkages is well known in the art. The reactive group may be located at any position on the fluorocarbon vector.

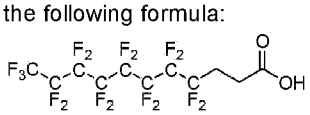
[0044] Coupling of the fluorocarbon vector to the peptide may be achieved through functional groups such as -OH, -SH, -COOH and $-NH_2$, naturally present or introduced onto any site of the peptide. Examples of such linkages include amide, hydrazone, disulphide, thioether and oxime bonds.

[0045] Optionally, a spacer element (peptidic or non-peptidic) can be incorporated to permit cleavage of the peptide from the fluorocarbon element for processing within an antigen-presenting cell and to optimize steric presentation of the peptide. The spacer can also be incorporated to assist in the synthesis of the molecule and to improve its stability and/or solubility. Examples of spacers include polyethylene glycol (PEG) or amino acids such as lysine or arginine that may be cleaved by proteolytic enzymes.

[0046] In one embodiment, the fluorocarbon-linked peptide can have the chemical structure C_mF_n-C_yH_x-(Sp)-R or derivatives thereof, where m = 3 to 30, $n \leq 2m + 1$, y = 0 to 15, $x \leq 2y$, (m + y) = 3 to 30 and Sp is an optional chemical spacer moiety and R is an immunogenic peptide. Typically m and n satisfy the relationship $2m-1 \leq n \leq 2m + 1$, and preferably $n = 2m + 1$. Typically x and y satisfy the relationship $2y-2 \leq x \leq 2y$, and preferably $x = 2y$. Preferably the C_mF_n-C_yH_x moiety is linear.

[0047] It is preferred that m is from 5 to 15, more preferably from 8 to 12. It is also preferred that y is from 0 to 8, more preferably from 0 to 6 or 0 to 4. It is preferred that the C_mF_n-C_yH_x moiety is saturated (i.e., $n = 2m + 1$ and $x = 2y$) and linear, and that m = 8 to 12 and y = 0 to 6 or 0 to 4.

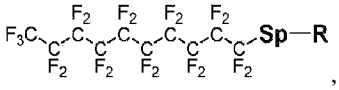
[0048] In a particular example, the fluorocarbon vector is derived from 2H, 2H, 3H, 3H-perfluoroundecanoic acid of the following formula:



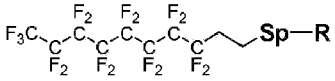
[0049] Thus, a preferred fluorocarbon attachment is the linear saturated moiety $C_8F_{17}(CH_2)_2$- which is derived from $C_8F_{17}(CH_2)_2COOH$.

[0050] Further examples of fluorocarbon attachments have the following formulae: $C_6F_{13}(CH_2)_2$-, $C_7F_{15}(CH_2)_2$-, $C_9F_{19}(CH_2)_2$-, $C_{10}F_{21}(CH_2)_2$-, $C_5F_{11}(CH_2)_3$-, $C_6F_{13}(CH_2)_3$-, $C_7F_{15}(CH_2)_3$-, $C_8F_{17}(CH_2)_3$- and $C_9F_{19}(CH_2)_3$- which are derived from $C_6F_{13}(CH_2)_2COOH$, $C_7F_{15}(CH_2)_2COOH$, $C_9F_{19}(CH_2)_2COOH$, $C_{10}F_{21}(CH_2)_2COOH$, $C_5F_{11}(CH_2)_3COOH$, $C_6F_{13}(CH_2)_3COOH$, $C_7F_{15}(CH_2)_3COOH$, $C_8F_{17}(CH_2)_3COOH$ and $C_9F_{19}(CH_2)_3COOH$ respectively.

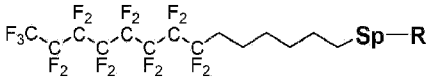
[0051] Preferred examples of suitable structures for the fluorocarbon vector-antigen constructs have the formula:



,



or



in which Sp and R are as defined above. In certain embodiments Sp is derived from a lysine residue and has the formula -CONH-$(CH_2)_4$-CH(NH_2)-CO-. Preferably R is any one of SEQ ID NOs: 1 to 14, preferably R is any one of SEQ ID NOs: 1 to 6. The amino group of the N-terminal amino acid of each peptide, for example, SEQ ID NO: 1, 2, 3, 4, 5 or 6, forms an amide linkage with the C-terminal carboxy group of the spacer of formula -CONH-$(CH_2)_4$-CH(NH_2)-CO-.

[0052] In the context of the current invention, the fluorocarbon attachment may be modified such that the resulting compound is still capable of delivering the peptide to antigen presenting cells. Thus, for example, a number of the fluorine atoms may be replaced with other halogen atoms such as chlorine, bromine or iodine. In addition, it is possible to replace a number of the fluorine atoms with methyl groups and still retain the properties of the molecule described herein.

[0053] The peptides may be linked to the fluorocarbon vector via a spacer moiety. The spacer moiety is preferably a lysine residue. This spacer residue may be present in addition to any terminal lysine residues as described above, so that the peptide may, for example, have a total of four N-terminal lysine residues. Accordingly, the preferred formulation for use according to the invention may comprise fluorocarbon-linked peptides in which the peptides have a C-terminal or N-terminal lysine residue, preferably an N-terminal lysine residue. The terminal lysine in the peptides is preferably linked to a fluorocarbon having the formula C_8F_{17} $(CH_2)_2COOH$. The fluorocarbon is preferably coupled to the epsilon chain of the N-terminal lysine residue.

[0054] It is contemplated that the pharmaceutical compositions described herein comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 or more immunogenic peptides optionally each covalently linked to its own fluorocarbon vector.

Other Components

[0055] The composition of the invention may comprise an additional immunogen. The immunogen may be a B-cell antigen. The B-cell antigen can serve to stimulate an antibody response to HBV. A pharmaceutical composition of the invention can, for example, comprise one or more fluorocarbon-linked peptides, which can stimulate a T-cell response, and a B-cell antigen.

[0056] Suitable immunogens that act as B-cell antigens include protein antigens such as hepatitis B surface antigen (HBsAg) or hepatitis B core antigen (HBcAg or HBeAg)

[0057] In one aspect, the present invention provides a composition comprising two or more peptides, such as

fluorocarbon-linked peptides, further comprising an adjuvant and/or optionally a pharmaceutically acceptable carrier or excipient. The excipient may be a stabilizer or bulking agent necessary for efficient lyophilisation. Examples include sorbitol, mannitol, polyvinylpyrrolidone and mixtures thereof, preferably mannitol. Other excipients that may be present include preservatives such as antioxidants, lubricants, cryopreservatives and binders well known in the art.

[0058] An adjuvant is an agent that is able to modulate the immune response directed to a co-administered antigen while having few if any direct effects when given on its own. Such adjuvants may be capable of potentiating the immune response in terms of magnitude and/or cytokine profile. Examples of adjuvants include: natural or synthetically derived refinements of natural components of bacteria such as Freund's adjuvant & its derivatives, muramyldipeptide (MDP) derivatives, CpG, monophosphoryl lipid A; other known adjuvant or potentiating agents such as saponins, aluminium salts and cytokines; oil in water adjuvants, water-in-oil adjuvants, immunostimulating complex (ISCOMs), liposomes, formulated nano and microparticles; bacterial toxins and toxoids; inulin, particularly gamma inulin; and TLR agonists.

[0059] Preferably, the adjuvant may be selected from the group consisting of: Peptidoglycan (such as TDM, MDP, muramyl dipeptide, Murabutide); alum solution (such as aluminium hydroxide, ADJUMER™ (polyphosphazene) or aluminium phosphate gel); glucans; algammulin; surfactants (such as squalane, Tween 80, Pluronic or squalene); calcium phosphate gel; bacterial toxins or toxoids (such as cholera holotoxin, cholera-toxin-Al-protein-A-D-fragment fusion protein, sub-unit B of the cholera toxin, or block copolymers); cytokine-containing liposomes; water-in-oil adjuvants (such as Freund's complete adjuvant, Freund's incomplete adjuvant or Montanide such as ISA 51 or ISA 720); oil-in-water adjuvants (such as MF-59); inulin-based adjuvants; cytokines (such as interferon-gamma; interleukin-lbeta; interleukin-2; interleukin-7 or interleukin-12); ISCOMs (such as iscomatrix); microspheres and microparticles of any composition; and Toll-like receptor agonists (such as CpG, ligands of human TLR 1-10, ligands of murine TLR 1-13, ISS-1018, IC31, Imidazoquinolines, Poly(I:C), Monophosphoryl lipid A, Ribi529, cholera toxin, heatlabile toxin, Pam3Cys or Flagellin).

Preparation of Pharmaceutical Compositions

[0060] The pharmaceutical compositions for use according to the invention can be prepared by solubilising at least one peptide, such as a fluorocarbon-linked peptide, in acetic acid or in other solvents as a first step in formulating a pharmaceutical product. Examples of other solvents that may be used to disperse one or more of the fluorocarbon-linked peptides in the blend include phosphate buffered saline (PBS), propan-2-ol, tert-butanol, acetone and other organic solvents. Approaches for solubilising fluorocarbon vector-peptide conjugates are described in WO2012/090002.

[0061] The peptide or fluorocarbon-linked peptide used as a starting material is typically desiccated. Peptides and fluorocarbon-linked peptides that comprise peptides shorter than 20 amino acids and/or that have fewer than 50% hydrophobic residues can be solubilised in a solvent other than acetic acid. Acetic acid is typically used where the peptide has more than 20 amino acids and/or has more than 50% hydrophobic residues.

[0062] The concentration of fluorocarbon-linked peptide in the solution typically is from about 0.1 mM to about 10 mM, such as about 0.5 mM, 1 mM, 2 mM, 2.5 mM or 5 mM. An example of a suitable concentration is about 10 mg/mL.

[0063] The input components may be blended homogenously together to the desired ratios with any aggregates dispersed, rendered sterile and presented in a suitable format for administration. Such examples could include the introduction of a vortexing and/or sonication post-blending or post-dilution stage to facilitate solubilisation. Other permutations of the manufacturing process flow could include sterile filtration being performed at an earlier stage of the process or the omission of lyophilisation to permit a liquid final presentation.

[0064] Where the different peptides or fluorocarbon-linked peptides are solubilised separately, for example in

different solvents or in different concentrations of acetic acid, the solubilised peptides or fluorocarbon-linked peptides are blended to create a mixture of peptides or fluorocarbon-linked peptides.

[0065] The optional adjuvant and/or one or more pharmaceutically acceptable excipients can also be added to the solubilised peptide/fluorocarbon-linked peptide or mixture of peptides/fluorocarbon-linked peptides. Typically, the solubilised fluorocarbon-linked peptides are mixed with the excipient and/or adjuvant.

[0066] After solubilisation and blending the solution of fluorocarbon-linked peptide(s) may be diluted. For example, the blend may be diluted in water.

[0067] The solution containing the peptides or fluorocarbon-linked peptides is preferably sterilised. Sterilisation is particularly preferred where the formulation is intended for systemic use. Any suitable means of sterilisation may be used, such as UV sterilisation or filter sterilisation. Preferably, filter sterilisation is used. Sterile filtration may include a 0.45 μm filter followed by a 0.22 μm sterilizing grade filter train.

[0068] Sterilisation may be carried out before or after addition of any excipients and/or adjuvants.

[0069] The composition for use according to the invention may be in dried, such as lyophilized, form.

[0070] The composition for use according to the invention may be an aqueous solution, for example an aqueous solution formed by dissolving a lyophilisate or other dried formulation in an aqueous medium. The aqueous solution is typically pH neutral.

[0071] Drying the formulation facilitates long-term storage. Any suitable drying method may be used. Lyophilisation is preferred but other suitable drying methods may be used, such as vacuum drying, spray-drying, spray freeze-drying or fluid bed drying. The drying procedure can result in the formation of an amorphous cake within which the peptides or fluorocarbon-linked peptides are incorporated.

[0072] For long-term storage, the sterile composition may be lyophilized. Lyophilisation can be achieved by freeze-drying. Freeze-drying typically includes freezing and then drying. For example, the fluorocarbon-linked peptide mixture may be frozen for 2 hours at -80°C and freeze-dried in a freeze drying machine for 24 hours.

[0073] Pharmaceutically acceptable compositions for use according to the invention may be solid compositions. The fluorocarbon-linked peptide composition may be obtained in a dry powder form. A cake resulting from lyophilisation can be milled into powder form. A solid composition for use according to the invention thus may take the form of free-flowing particles. The solid composition typically is provided as a powder in a sealed vial, ampoule or syringe. If for inhalation, the powder can be provided in a dry powder inhaler. The solid matrix can alternatively be provided as a patch. A powder may be compressed into tablet form.

[0074] The dried, for example, lyophilized, peptide or fluorocarbon-linked peptide composition may be reconstituted prior to administration. As used herein, the term *"reconstitution"* is understood to mean dissolution of the dried vaccine product prior to use. Following drying, such as lyophilisation, the immunogenic peptide, for example, the fluorocarbon-linked peptide product, preferably is reconstituted to form an isotonic, pH neutral, homogeneous suspension. The formulation is typically reconstituted in the aqueous phase, for example by adding Water for Injection, histidine buffer solution (such as 28mM L-histidine buffer), sodium bicarbonate, Tris-HCl or phosphate buffered saline (PBS). The reconstituted formulation is typically dispensed into sterile containers, such as vials, syringes or any other suitable format for storage or administration.

[0075] The composition may be stored in a container, such as a sterile vial or syringe, prior to use.

Medical Uses

[0076] The invention provides the composition of the invention for use in the treatment of the human or animal body by therapy. In particular, the composition of the invention is provided for use in a method of treating or preventing HBV infection. The composition of the invention elicits an immune response that may also be useful in HBV prophylaxis. The composition of the invention is preferably for use as a therapeutic vaccine to treat individuals infected with HBV. The composition of the invention is particularly useful in the treatment of patients with persistent chronic HBV infection, but may also be used to treat immune tolerant patients or inactive chronic carriers.

[0077] The present invention provides a therapeutic vaccine as a disruptive technology for the treatment of chronic HBV (CHB). The compositions of the invention enhance antiviral T-cell responses leading to spontaneous immune control of HBV infection. This allows cessation of antiviral NUC therapy and could potentially also lead to serological cure of HBV infection. HBsAg decline is used as a predictor of long term improved clinical outcome. HBsAg levels can be linked to the number of HBV-infected hepatocytes and are determined by transcriptional activity of intrahepatic cccDNA controlled by various cytokines. Treatment using a composition of the invention may lead to HBsAg loss or HBsAg seroconversion.

[0078] The compositions of the invention are particularly useful in treating NUC-treated CHB patients. The peptides also represent an affordable treatment for HBeAg-positive patients in developing countries who may not be able to afford long-term NUC treatment. Vaccination of NUC-treated, HBV-DNA suppressed, HBeAg-negative patients in particular with the peptide compositions of the invention facilitates and accelerates HBsAg clearance. HBeAg-positive patients may also be treated. The compositions of the invention may also be used to treat inactive carriers of HBV.

[0079] Hepatitis B virus (HBV) infection is a major cause of liver-related morbidity and mortality. The compositions of the invention are provided for use in the treatment of liver failure, end-stage liver disease and hepatocellular carcinoma.

[0080] The compositions of the invention are useful in the vaccination of patients with hepatitis delta (HDV), the most severe form of viral hepatitis, for whom no approved therapy is available and which only occurs as a co-infection in HBsAg-positive individuals.

[0081] Also described is the use of the pharmaceutical composition of the disclosure in the manufacture of a medicament for treating or preventing HBV infection, particularly CHB, for treating or preventing liver failure, end-stage liver disease or hepatocellular carcinoma, or for treating or preventing HDV.

[0082] Similarly, described is a method of treating or preventing HBV infection in a subject in need thereof, said method comprising administering to said subject a prophylactic or therapeutic amount of a composition of the present disclosure.

[0083] The composition for use according to the invention may be administered in combination with a second therapeutic or prophylactic agent. For example, the second agent may comprise a further immunogen (such as a globular antigen or a recombinant or naturally occurring antigen), to further stimulate an immune response, for example to stimulate a humoral immune response where the fluorocarbon-linked peptide stimulates a cellular immune response, to HBV. It is understood that the second agent can be a B-cell antigen. Suitable B-cell antigens include HBsAg, HBcAg and HBeAg.

[0084] In a preferred embodiment, the second agent is an agent known for use in an existing HBV therapeutic treatment. The existing HBV therapeutic agent may be an interferon, such as interferon-alpha, or NUC, such as entecavir and tenofovir. The HBV therapeutic treatment may be a treatment that blocks suppressive cell types. Agents useful in such blocking treatments include anti-PDl blocking antibodies, anti-PDIL blocking antibodies, anti-LAG3 blocking antibodies, anti-TIM3 blocking antibodies, anti-CTLA4 blocking antibodies and cyclophosphamide.

[0085] Where a second therapeutic agent or prophylactic agent is used in conjunction with a composition of the invention, administration may be contemporaneous or separated by time. The composition for use according to the

invention may be administered before, together with or after the second therapeutic agent.

[0086] Compositions for use according to the invention can be administered to a human or animal subject *in vivo* using a variety of known routes and techniques. For example, the composition may be provided as an injectable solution, suspension or emulsion and administered via parenteral, subcutaneous, oral, epidermal, intradermal, intramuscular, interarterial, intraperitoneal, intravenous injection using a conventional needle and syringe, or using a liquid jet injection system. The composition may be administered topically to skin or mucosal tissue, such as nasally, intratrachealy, intestinally, sublingually, rectally or vaginally, or provided as a finely divided spray suitable for respiratory or pulmonary administration. In a preferred embodiment, the compositions are administered intramuscularly.

[0087] The composition can be administered to a subject in an amount that is compatible with the dosage composition and that will be prophylactically and/or therapeutically effective. The administration of the composition of the invention may be for either "prophylactic" or "therapeutic" purpose. As used herein, the term "therapeutic" or "treatment" includes any one or more of the following: the prevention of infection or reinfection; the reduction or elimination of symptoms; and the reduction or complete elimination of a pathogen. Treatment may be effected prophylactically (prior to infection) or therapeutically (following infection).

[0088] The choice of carrier, if required, is frequently a function of the route of delivery of the composition. Within this invention, compositions may be formulated for any suitable route and means of administration. Pharmaceutically acceptable carriers or diluents include those used in compositions suitable for oral, ocular, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, transdermal) administration.

[0089] The composition may be administered in any suitable form, for example as a liquid, solid or aerosol. For example, oral formulations may take the form of emulsions, syrups or solutions or tablets or capsules, which may be enterically coated to protect the active component from degradation in the stomach. Nasal formulations may be sprays or solutions. Transdermal formulations can be adapted for their particular delivery system and may comprise patches. Formulations for injection may be solutions or suspensions in distilled water or another pharmaceutically acceptable solvent or suspending agent.

[0090] The appropriate dosage of the prophylactic or therapeutic vaccine to be administered to a patient will be determined in the clinic. However, as a guide, a suitable human dose, which may be dependent upon the preferred route of administration, may be from 1 to 1000 µg, such as about 100 µg, 200 µg or 500 µg. Multiple doses may be required to achieve an immunological or clinical effect, which, if required, will be typically administered between 2 to 12 weeks apart. Where boosting of the immune response over longer periods is required, repeat doses 1 month to 5 years apart may be applied.

[0091] The following Examples illustrate the invention.

Example 1: Assessment *of ex vivo* immunogenicity of HBV-derived short peptide pools in human PBMC (for illustration only)

Methods and Materials

Populations

HBV-infected subjects

[0092] Ninety-nine subjects, clinically defined as chronically HBV-infected, were enrolled into a REC-approved protocol in the Imperial Healthcare NHS Trust, the Chelsea and Westminster Hospital NHS Foundation Trust, and Barts and the London NHS Trust in London. Following written informed consent from all subjects, fresh venous blood was collected and PBMC and plasma were isolated and cryopreserved within 18 hours of blood collection. These subjects conformed to the following criteria: Good general health, HBV specific treatment: antiviral nucleos(t)ide analogue inhibitors and/or interferon therapy where clinically indicated, Clinical status (Chronic HBV infection, HBeAg-negative, and ALT normal, persistent or intermittent elevation), HIV-negative, HCV-negative and HDV-negative.

Healthy control subjects

[0093] Cryopreserved PBMC from 17 subjects were obtained from CTL Technologies. These subjects conformed to the following criteria: Good general health, Unvaccinated to HBV, HBV surface antigen-negative, HBV core antibody-negative, HIV-negative and HCV-negative

Short-term culture of PBMC

[0094] One vial of PBMC from each subject (containing 1×10^7 cells) was thawed and lymphocyte numbers were determined using a Scepter™ automated handheld cell counter. PBMC were cultured in 2mL culture medium (CM: RPMI-1640 Glutamax supplemented with 5% human AB serum) in 24 well cell culture plates at a concentration of 1×10^6 cells/mL for a total of 11 days. Cells were stimulated with a peptide pool containing 144 overlapping HBV-derived short peptides (SEQ ID NOs: 73 to 210 and SEQ ID NOs: 214 to 219), ranging in length from 15-20 amino acids and in overlap from 10 to 13 amino acids, at a final concentration of 0.1µg/peptide/mL. On Day 4, IL-2 and IL-15 were added to the cultures to final concentrations of 10 IU/mL and 10ng/mL respectively. On Day 10, cells were washed twice in CM and cultured with 10 IU/mL IL-2 for 1 additional day. On Day 11, cells were washed twice in CM, counted and incorporated in a human IFNγ ELISpot assay or intracellular cytokine staining.

Human IFNγ ELISpot assay

[0095] Ninety-six well multiscreen PVDF filter plates (Millipore) were coated overnight at 4°C with 100µl (1:80) of anti-human IFNγ capture mAb (R&D Systems). Plates were then blocked with PBS supplemented with 1% BSA and 5% sucrose for 2h at 4°C. Cells were plated in triplicate wells at 5×10^4 PBMC/well. Final antigen concentrations used were: 22 HBV-derived short peptide pools (see below; note pool 22 could not be prepared as peptides with SEQ ID NOs: 212 and 213 could not be dispersed due to insolubility) and HIV-3 35-mer negative peptide control: 5µg/peptide/mL; PHA positive control: 1µg/mL. ELISpot plates were incubated for 18h at 37°C, 5% CO_2 in a humidified environment. Plates were then washed and incubated with 100µl (1:80) of biotinylated anti-human IFNγ detection mAb (R&D Systems) for 2h at room temperature. Following washing, plates were incubated with a streptavidin-conjugated alkaline phosphatase (1:80) for 1h followed by a substrate (30min) according to the manufacturer's instructions (R&D Systems). The developed spots were counted using an automated plate counting system (CTL Europe).

Table 2: Identification of peptides in pools 1 to 23

Pool	SEQ ID NOs. of short peptides in pool
1	73, 74, 75, 76, 77, 78, 79
2	80, 81, 82, 83, 84, 85
3	86, 87, 88, 89, 90, 91
4	92, 93, 94, 95, 96, 97
5	98, 99, 100, 101, 102, 103, 104

Pool	SEQ ID NOs. of short peptides in pool
6	105, 106, 107, 108, 109, 110
7	111, 112, 113, 114, 115, 116, 117
8	118, 119, 120, 121, 122, 123
9	124, 125, 126, 127, 128, 129, 130
10	131, 132, 133, 134, 135, 136
11	137, 138, 139, 140, 141
12	142, 143, 144, 145, 146, 147, 148
13	149, 150, 151, 152, 153, 154, 155, 156
14	157, 158, 159, 160, 161, 162, 163, 164
15	165, 166, 167, 168, 169, 170, 171
16	172, 173, 174, 175, 176, 177, 178
17	179, 180, 181, 182, 183, 184
18	185, 186, 187, 188, 189, 190
19	191, 192, 193, 194, 195, 196, 197
20	198, 199, 200, 201, 202, 203
21	204, 205, 206, 207, 208, 209, 210
22	211, 212, 213
23	214,215,216,217,218,219

Intracellular cytokine staining assay

[0096] Cells were plated in a 96 well round bottom plate at 5×10^5 PBMC/well with stimulation from HBV-derived peptide pools at final concentrations of 5µg/peptide/mL. The plate was incubated at 37°C in a 5% CO_2 incubator for 20h. For the final 3h of the assay, PMA/Ionomycin was added to respective wells and Golgi plug was added to all wells. The cells were harvested and washed with PBS + 0.1% BSA (wash buffer) and stained with anti-CD3, anti-CD4 and anti-CD8 (BD Biosciences) for 30 minutes at 4°C. After another wash, the cells were fixed and permeabilised with 100µL of BD Cytofix/Cytoperm solution for 20 minutes at 4°C, followed by two washes with 1x BD Perm/Wash solution. Finally, cells were stained with ant-IL-2-FITC, anti-IFNy-PE and anti-TNFa PerCP-Cy5.5 (BD Biosciences) for 30 minutes at 4°C. Samples were acquired on a FACSCanto II flow cytometer (BD Biosciences). Gating was based on media stimulated samples for each subject.

Infecting HBV genotype determination

[0097] A nested PCR method followed by direct nucleotide sequencing was initially employed for HBV genotyping. However, due to the low viral load in plasma from the majority of samples, HBV genotype could not be determined using this method. The IMMUNIS® HBV genotype enzyme immunoassay (EIA) kit was subsequently employed. This assay used four genotype-dependent epitopes in the PreS2 region of the HBsAg, with genotypes being determined serologically by positive/negative combinations of four EIA that were specific for each of the epitopes.

Results

[0098] The initial step in identifying regions of interest in the HBV proteome was the comparison of IFNγ ELISpot

responses of PBMC from HBV-uninfected, unvaccinated healthy subjects with those from chronic HBV-infected HBeAg negative - inactive carrier subjects in sustained control phase of the disease and chronic HBV-infected HBeAg negative subjects under treatment. Following short-term culture with a library of overlapping short peptides (15-20mers overlapping by 10-13 amino acids), representing approximately 70% of the HBV proteome, PBMC were restimulated overnight with pools of these short peptides representing specific regions of interest within the HBV polymerase, core, X and surface antigens respectively. IFNγ responses to these peptide pools were then assessed using a human IFNγ ELISpot assay.

[0099] Pools representing a number of antigenic regions were found to stimulate IFNγ responses which were specific to the chronic HBV subjects. Specifically, stimulation with pools representing terminal regions of the HBV polymerase (pool 2 & pool 3) and regions of the HBV core (pools 14-17) resulted in the greatest magnitude and population coverage of IFNγ responses in the HBV-infected subjects (Figure 1). To a lesser extent, pools 4 to 9 and pools 11 to 13 also tend to promote HBV-specific T-cell responses.

[0100] In order to establish the role of the infecting HBV genotype on the nature of HBV-specific responses to short peptide pools, infecting HBV genotype was determined for each subject. This was determined by means of HBV surface antigen epitope assessment in plasma samples. IFNγ responses of PBMC from both immune control and treated HBV-infected subjects were subsequently grouped according to HBV genotypes A, B, C and D. Some subjects were not classified into these genotypes due to the sensitivity limitations of the assay and possible rare sera being assessed. These subjects were therefore not included in this assessment. Response profiles between the four genotypes showed similarities in that the regions showing the greatest magnitude of IFNγ responses were generally in the terminal polymerase and core regions of the HBV proteome (Figure 2). Pools 2, 3, 10, 12, 14, 15, 16 and 17 appear to provide responses against multiple genotypes.

[0101] In order to establish the role of the genetic background of the host subject on the nature of HBV-specific responses to short peptide pools, subjects in the study were grouped according their ethnicity. IFNγ responses of PBMC from both immune control and treated HBV-infected subjects were subsequently compared in three broad ethnic groups, namely African/Arabic, Caucasian and Oriental/Indian. Responses profiles between the ethnic groups showed similarities again through the greatest magnitude of IFNγ response, with associated high population coverage, being found against pools from the terminal polymerase and core regions of the HBV proteome (Figure 3). The Caucasian group appeared to differ slightly from the other two ethnic groups in that the average magnitude of responses to a number of pools were found to be highest in the treated group of subjects, when compared to those under immune control. Pools 2, 3, 10, 14, 15, 16 17 and 21 tend to promote responses in multiple ethnic groups.

[0102] Finally, in order to further describe the type of IFNγ responses by PBMC to the short peptide pools, short-term cultured cells were restimulated overnight for intracellular cytokine staining. Cells were then assessed for CD3, CD4, CD8 and IFNγ expression by flow cytometry. A comparison was made of IFNγ responses to the short peptide pools 2 and 14 in PBMC from healthy and chronic HBV-infected subjects (Figure 4). These were two of the peptide pools which elicited the strongest HBV-specific responses in the IFNγ ELISpot assay. Consistent with the IFNγ ELISpot assay, increased IFNγ expression was found specifically in PBMC from chronic HBV-infected subjects. Moreover, this was found to be a dual CD4 and CD8 T-cell response.

Example 2: Assessment of *ex vivo* immunogenicity of HBV-derived Densigen-associated short peptide pools in human PBMC (for illustration only)

Methods and Materials

Populations

HBV-infected subjects

[0103] 104 subjects, clinically defined as chronically HBV-infected, were enrolled into a REC-approved protocol in the Imperial Healthcare NHS Trust, the Chelsea and Westminster Hospital NHS Foundation Trust, and Barts and the London NHS Trust in London. Following written informed consent from all subjects, fresh venous blood was collected and PBMC and plasma were isolated and cryopreserved within 18 hours of blood collection. These subjects conformed to the following criteria: Good general health, HBV specific treatment: antiviral nucleos(t)ide analogue inhibitors and/or interferon therapy where clinically indicated, Clinical status (Chronic HBV infection, HBeAg-negative, and ALT normal, persistent or intermittent elevation), HIV-negative, HCV-negative and HDV-negative.

Healthy control subjects

[0104] Cryopreserved PBMC from 17 subjects were obtained from CTL Technologies. These subjects conformed to the following criteria: Good general health, Unvaccinated to HBV, HBV surface antigen-negative, HBV core antibody-negative, HIV-negative and HCV-negative

Short-term culture of PBMC

[0105] One vial of PBMC from each subject (containing 1×10^7 cells) was thawed and lymphocyte numbers were determined using a Scepter™ automated handheld cell counter. PBMC were cultured in 2mL culture medium (CM: RPMI-1640 Glutamax supplemented with 5% human AB serum) in 24 well cell culture plates at a concentration of 1×10^6 cells/mL for a total of 11 days. Cells were stimulated with a peptide pool containing 144 overlapping HBV-derived short peptides (SEQ ID NO: 73 to 210 and SEQ ID NO: 142 to 147), ranging in length from 15-20 amino acids and in overlap from 10 to 13 amino acids, at a final concentration of 0.1µg/peptide/mL. On Day 4, IL-2 and IL-15 were added to the cultures to final concentrations of 10 IU/mL and 10ng/mL respectively. On Day 10, cells were washed twice in CM and cultured with 10 IU/mL IL-2 for 1 additional day. On Day 11, cells were washed twice in CM, counted and incorporated in a human IFNγ ELISpot assay or intracellular cytokine staining.

Human IFNγ ELISpot assay

[0106] 96 well multiscreen PVDF filter plates (Millipore) were coated overnight at 4°C with 100µl (1:80) of anti-human IFNγ capture mAb (R&D Systems). Plates were then blocked with PBS supplemented with 1% BSA and 5% sucrose for 2h at 4°C. Cells were plated in triplicate wells at 5×10^4 PBMC/well. Final antigen concentrations used were: 23 HBV-derived Densigen-associated short peptide pools (see below): 5µg/peptide/mL; CEF peptide pool positive control: 1µg/peptide/mL; PHA positive control: 1µg/mL. ELISpot plates were incubated for 18h at 37°C, 5% CO_2 in a humidified environment. Plates were then washed and incubated with 100µl (1:80) of biotinylated anti-human IFNγ detection mAb (R&D Systems) for 2h at room temperature. Following washing, plates were incubated with a streptavidin-conjugated alkaline phosphatase (1:80) for 1h followed by a substrate (30min) according to the manufacturer's instructions (R&D Systems). The developed spots were counted using an automated plate counting system (CTL Europe).

Table 3: Identification of peptides in pools 24 to 46

Pool	SEQ ID NOs. of short peptides in pool
24	74, 75, 76, 77, 78, 79
25	80, 81, 82, 83
26	86, 87, 88, 89

Pool	SEQ ID NOs. of short peptides in pool
27	94, 95, 96, 97
28	98, 99, 100, 101
29	102, 103, 104
30	105, 106, 107, 108, 109
31	109, 110, 111, 112
32	116, 117, 118, 119
33	120, 121, 122, 123
34	137, 138, 139, 140
35	146, 147, 148, 149, 150
36	150, 151, 152, 153, 154
37	152, 153, 154, 155, 156
38	163, 164, 165, 166
39	169, 170, 171
40	172, 173
41	172, 173, 174, 175
42	176, 177, 178, 179
43	179, 180, 181
44	187, 188, 189, 190, 191
45	204, 205, 206, 207, 208, 209
46	215,216,217,218

Intracellular cytokine staining (ICS) assay

[0107] Cells were plated in a 96 well round bottom plate at 5×10^5 PBMC/well with stimulation from HBV-derived peptide pools at final concentrations of 5µg/peptide/mL. The plate was incubated at 37°C in a 5% CO_2 incubator for 20h. For the final 3h of the assay, PMA/Ionomycin was added to respective wells and Golgi plug was added to all wells. The cells were harvested and washed with PBS + 0.1% BSA (wash buffer) and stained with anti-CD3, anti-CD4 and anti-CD8 (BD Biosciences) for 30 minutes at 4°C. After another wash, the cells were fixed and permeabilised with 100µL of BD Cytofix/Cytoperm solution for 20 minutes at 4°C, followed by two washes with 1x BD Perm/Wash solution. Finally, cells were stained with ant-IL-2-FITC, anti-IFNy-PE and anti-TNFa PerCP-Cy5.5 (BD Biosciences) for 30 minutes at 4°C. Samples were acquired on a FACSCanto II flow cytometer (BD Biosciences). Gating was based on media stimulated samples for each subject.

Infecting HBV genotype determination

[0108] A nested PCR method followed by direct nucleotide sequencing was initially employed for HBV genotyping. However, due to the low viral load in plasma from the majority of samples, HBV genotype could not be determined using this method. The IMMUNIS® HBV genotype enzyme immunoassay (EIA) kit was subsequently employed. This assay used four genotype-dependent epitopes in the PreS2 region of the HBsAg, with genotypes being determined serologically by positive/negative combinations of four EIA that were specific for each of the epitopes.

Results

[0109] Subsequent to screening of responses to HBV-derived short peptide pools, 35-40mer regions of interest were identified. These regions were further assessed with a view to using 35-40mer peptides in a vaccine. Further assessment involved redesign of short peptide pools previously used for restimulation following short-term culture. Terminal short peptides extending beyond the 35-40mer regions of interest were removed from pools in order to more accurately reflect the peptides that would be used in a vaccine. Following short-term culture with the peptide library, as before, these short peptide pools were then used for restimulation in human IFNγ ELISpot and ICS assays.

[0110] Restimulation with pools 24 to 46 indicated dominant HBV-specific T-cell responses to regions from terminal polymerase (pool 25 and pool 26) and core (pools 38 and 39 and pool 41 to 43) regions of the HBV proteome (Figure 5). An HBV-specific response was also found following stimulation with the surface region pool 45. Regions of polymerase corresponding to pool 28, pool 32, pool 33, pool 36 and pool 37 also gave a significant T-cell response.

[0111] IFNγ ELISpot responses to pools 24 to 46 were grouped according to infecting HBV genotype (Figure 6). Pool 27, 28, 29, 32, 35, 36 each give a predominant responses against genotype C. Pools 25 and 26 give a predominant response against genotype D. Pools 30 and 31 give a predominant response against genotype B. Pools 38, 42, 43 and 44 give a predominant response against genotype A. Some pools tend to promote responses against more than one genotype: two genotypes for pools 26, 32, 33, 36 and 43, three genotypes for pools 37, 38, 41 and 42 or even four genotypes for pool 25.

[0112] IFNγ ELISpot responses to pools 24 to 46 were grouped according to infecting HBV genotype (Figure 7). Pools 28, 29 and 30 give a predominant response in Oriental/Indian ethnicities. Pools 25, 33, 34, 35 and 37 give a predominant responses in Caucasian. Pools 38, 39, 41, 42 and 43 give a predominant response in African/Arabic ethnicities. Some pools tend to promote responses in more than one ethnic group: two ethnic groups for each of pools 26, 39 and 43 or three ethnic groups for each of pools 25, 38 and 42.

[0113] The results are summarised in Table 4 below.

Table 4 : Summary of predominant responses of peptides from selected regions of the HBV proteome against different HBV genotypes (A, B, C and D) and in patients of different ethnicities (OI = Oriental/Indian, C = Caucasian, AA = African/Arabic). Where a region elicits an immune response against multiple HBV genotypes or multiple ethnicities, the predominant response is indicated in bold.

HBV proteome region	**Terminal domain of polymerase**		**Reverse transcriptase domain of polymerase**			**RNase H domain of polymerase**	**Core protein**			
Pool No.	25	26	28	30	31	35	38	39	42	43
Peptide	P113	P151	P277	P360	P376	P645	P753	P797	P856	P877
SEQ ID NOs:	14	15	16	17	18	19	20	21	22	23
	24	25	60	27	28	29	30	67	32	33
			26			35	36	31	38	
			34					37		
Genotype	AB	A**D**	C	B	B	C	**A**C	**A**B	**A**C	**A**D
	C**D**						D	D	D	
Ethnicity	OI	C	OI	OI	OI	C	OI	OI	OI C	C
	C	AA					C	**AA**	**AA**	**AA**
	AA						**AA**			

[0114] Eight pools were selected for further analysis of T-cell responses by intracellular cytokine staining. PBMC from between 7 and 14 subjects (depending on the number of cells available following the IFNγ ELISpot assay)

were stimulated overnight with the one of the eight pools and cells were stained for surface CD3, CD4 and CD8 expression, together with intracellular IFNγ, TNFα and IL-2 expression (Figure 8). IFNγ expression was found in both CD8 and CD4 T-cell populations, with a respective breadth of response to 5/8 and 8/8 of the peptide pools assessed. Similarly, TNFα expression was found in both CD8 and CD4 T-cells populations with a breadth of peptide pool response of 3/8 and 6/8 respectively. CD8 T-cells were found to express no IL-2 following peptide pool stimulation, yet CD4 T-cells expressed IL-2 following stimulation with 7 of the 8 pools.

Example 3: Construction of fluorocarbon-linked HBV peptides

[0115] Peptides having the amino acid sequences shown in SEQ ID NOs: 24, 25, 28, 33, 34, 36, 37 and 38 and 222 were synthesised by FMOC (fluorenylmethyloxycarbonyl chloride) solid-phase synthesis. The fluorocarbon chain ($C_8F_{17}(CH_2)_2COOH$) was then incorporated on the epsilon-chain of an additional N-terminal lysine of each peptide to derive the fluorocarbon-linked peptide. Purified fluorocarbon-linked peptides or unmodified peptides were obtained through cleavage in the presence of trifluoroacetic acid (TFA) and a final purification by reverse phase-high performance liquid chromatography (RP-HPLC). All preparations had a purity of 90% or greater.

FA-P113: K(FA)-VGPLTVNEKRRLKLIMPARFYPNVTKYLPLDKGIK-NH_2 (SEQ ID NO: 24);

FA-P151: K(FA)-PEHVVNHYFQTRHYLHTLWKAGILYKRETTRSASF-NH_2 (SEQ ID NO: 25);

FA-P376: K(FA)-KLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAISSVVRR-NH_2 (SEQ ID NO: 28);

FA-753(K): K(FA)-KKKEFGATVELLSFLPSDFFPSVRDLLDTASALYRKKK-NH_2 (SEQ ID NO: 36);

FA-P856(K): K(FA)-LTFGRETVLEYLVSFGVWIRTPPAYRPPNAPILSTKKK-NH_2 (SEQ ID NO: 38);

FA-P877: K(FA)-PPAYRPPNAPILSTLPETTVVRRRGRSPRRR-NH_2 (SEQ ID NO: 33);

FA-P277(K): K(FA)-RVSWPKFAVPNLQSLTNLLSSNLSWLSLDVSAAFYHKKK-NH_2 (SEQ ID NO: 34),

FA-P797(K): K(FA)-SPHHTALRQAILSWGELMTLATWVGSNLEDPASRDKKK-NH_2 (SEQ ID NO: 37);

FA-P1266(K): K(FA)-KKKGPLLVLQAGFFLLTRILTIPQSLDSW WTSLNFLKKK-NH_2 (SEQ ID NO: 222)

NP113: VGPLTVNEKRRLKLIMPARFYPNVTKYLPLDKGIK (SEQ ID NO: 24);

NP151: PEHVVNHYFQTRHYLHTLWKAGILYKRETTRSASF (SEQ ID NO: 25);

NP376: KLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAISSVVRR (SEQ ID NO: 28);

NP753(K): KKKEFGATVELLSFLPSDFFPSVRDLLDTASALYRKKK (SEQ ID NO: 36);

NP856(K): LTFGRETVLEYLVSFGVWIRTPPAYRPPNAPILSTKKK (SEQ ID NO: 38);

NP877: PPAYRPPNAPILSTLPETTVVRRRGRSPRRR (SEQ ID NO: 33);

NP277(K): RVSWPKFAVPNLQSLTNLLSSNLSWLSLDVSAAFYHKKK (SEQ ID NO: 34),

NP797(K): SPHHTALRQAILSWGELMTLATWVGSNLEDPASRDKKK (SEQ ID NO: 37);

NP1266(K): KKKGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLKKK (SEQ ID NO: 222).

Example 4: Long HBV peptide formulation

[0116] A vaccine candidate, FP02.1, composed of the nine fluorocarbon-conjugated HBV-derived peptides prepared as described in Example 3 were formulated as described below. Conditions for peptide solubilization are described in Table 5. Briefly, each of the nine fluorocarbon-conjugated peptides was weighed in a 5ml glass vial. Each peptide was then solubilised with 2 to 12% acetic acid in water solutions to achieve a peptide concentration of 10mg. Peptide solutions (3.9ml for each peptide) were blended in a 150ml sterile container before 3.9ml of 10% acetic acid solution in water was added. After stirring with a magnetic stirrer for 2 minutes, 39mL of 9.0% mannitol in water solution was added. After stirring with a magnetic stirrer for a further 2 minutes, the solution was filtered using a 0.22µm 33mm Millex filter. 1.2mL of the filtered solution was dispatched into autoclaved 2ml glass vials. Filtration recovery measured by RP-HPLC was > 95%. The vials were frozen at -80°C for one hour. The samples were then freeze-dried for 36 hours. Freeze drying ventilation was performed under nitrogen and vial stoppering was carried out at a pressure between 400 and 600 mbar. The amount of peptide was 600µg per peptide per vial; upon reconstitution with 1.2mL, the final concentration was 500µg/peptide/ml.

Table 5: Solubilisation conditions for preparation of FP02.1

Peptide	Gross mass (mg)	Peptide content (%)	Net Mass (mg)	Targeted concentration (mg/ml)	Acetic acid (%)	Volume added
FA-P113	46.54	86.8	40.40	20	2	4.040
FA-P151	45.87	88.0	40.37	20	12	4.036
FA-P277(K)	49.76	81.8	40.70	20	4	4.170
FA-P376	47.62	85.3	40.62	20	2	4.062
FA-P797(K)	44.69	92.0	41.11	20	2	4.112
FA-P877	49.25	81.9	40.34	20	2	4.034
FA-P753(K)	47.47	85.1	40.40	20	2	4.040
FA-P1266(K)	45.82	86.4	40.45	20	2	4.046
FA-P856(K)	47.02	86.8	40.81	20	2	4.082

Example 5: Preferred HBV peptides and mixtures are immunogenic in chronic HBV carriers irrespective of the disease stage, the genotype of the HBV virus and the ethnicity of the subjects.

Methods and Materials

Populations

[0117] 40 subjects, clinically defined as chronically HBV-infected, were enrolled into a REC-approved protocol in the Imperial Healthcare NHS Trust, the Chelsea and Westminster Hospital NHS Foundation Trust, and Barts and the London NHS Trust in London. Following written informed consent from all subjects, fresh venous blood was collected and PBMC and plasma were isolated and cryopreserved within 18 hours of blood collection. These subjects conformed to the following criteria: Good general health, HBV specific treatment: antiviral nucleos(t)ide analogue inhibitors and/or interferon therapy where clinically indicated, Clinical status (Chronic HBV infection, HBeAg-negative, and ALT normal, persistent or intermittent elevation), HIV-negative, HCV-negative and HDV-

negative.

Short-term culture of PBMC

[0118] One vial of PBMC from each subject (containing 1×10^7 cells) was thawed and lymphocyte numbers were determined using a Scepter™ automated handheld cell counter. PBMC were cultured in 2mL culture medium (CM: RPMI-1640 Glutamax supplemented with 5% human AB serum) in 24 well cell culture plates at a concentration of 1×10^6 cells/mL for a total of 11 days. Cells were stimulated with a mixture of the nine HBV-derived long peptides described in Example 3.

[0119] Each peptide was used at a final concentration of 0.1 µg/peptide/mL. On Day 4, IL-2 and IL-15 were added to the cultures to final concentrations of 10 IU/mL and 10ng/mL respectively. On Day 10, cells were washed twice in CM and cultured with 10 IU/mL IL-2 for 1 additional day. On Day 11, cells were washed twice in CM, counted and incorporated in a human IFNγ (interferon-gamma) ELISpot assay or intracellular cytokine staining.

Human IFNγ ELISpot assay

[0120] 96 well multiscreen PVDF filter plates (Millipore) were coated overnight at 4°C with 100µl (1:80) of anti-human IFNγ capture mAb (R&D Systems). Plates were then blocked with PBS supplemented with 1% BSA and 5% sucrose for 2h at 4°C. Cells from short term cultures were plated in triplicate wells at 5×10^4 PBMC/well. Final antigen concentrations used were: 5µg/mL for each individual peptides; PHA positive control: 1µg/mL. ELISpot plates were incubated for 18h at 37°C, 5% CO_2 in a humidified environment. Plates were then washed and incubated with 100µl (1:80) of biotinylated anti-human IFNγ detection mAb (R&D Systems) for 2h at room temperature. Following washing, plates were incubated with a streptavidin-conjugated alkaline phosphatase (1:80) for 1h followed by a substrate (30min) according to the manufacturer's instructions (R&D Systems). The developed spots were counted using an automated plate counting system (CTL Europe).

Intracellular cytokine staining assay

[0121] Cells from short-term culture were plated in a 96 well round bottom plate at 5×10^5 PBMC/well with stimulation from 9 HBV-derived long peptides (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) at final concentrations of 5µg/mL. The plate was incubated at 37°C in a 5% CO2 incubator for 20h. For the final 3h of the assay, PMA/Ionomycin was added to respective wells and Golgi plug was added to all wells. The cells were harvested and washed with PBS + 0.1% BSA (wash buffer) and stained with anti-CD3, anti-CD4 and anti-CD8 (BD Biosciences) for 30 minutes at 4°C. After another wash, the cells were fixed and permeabilised with 100µL of BD Cytofix/Cytoperm solution for 20 minutes at 4°C, followed by two washes with 1x BD Perm/Wash solution. Finally, cells were stained with ant-IL-2-FITC, anti-IFNy-PE and anti-TNFa PerCP-Cy5.5 (BD Biosciences for 30 minutes at 4°C. Samples were acquired on a FACSCanto II flow cytometer (BD Biosciences). Gating was based on media stimulated samples for each subject.

Infecting HBV genotype determination

[0122] A nested PCR method followed by direct nucleotide sequencing was initially employed for HBV genotyping. However, due to the low viral load in plasma from the majority of samples, HBV genotype could not be determined using this method. The IMMUNIS® HBV genotype enzyme immunoassay (EIA) kit was subsequently employed. This assay used four genotype-dependent epitopes in the PreS2 region of the HBsAg, with genotypes being determined serologically by positive/negative combinations of four EIA that were specific for each of the epitopes.

Results

[0123] All peptide promoted detectable T cell responses in HBV carriers either HBeAg-negative inactive carriers and HBeAg-negative treated subjects (see Figures 9 and 10). Among the different peptides tested, NP113, NP151, NP376, NP753(K), NP797(K), NP856(K) and NP877 promote the highest level of responses in both patient populations and in the highest proportion of subjects. Surprisingly, the cumulative response to NP113 and NP151 is higher in both populations compared than any other combination of two peptides tested. Moreover, the cumulative response to NP113, NP151 and NP376 induces the highest level of response in both populations compared to any other combinations of three peptides tested. As shown in Figure 11, all tested peptides promote cross-reactive T cell responses across all four HBV genotypes. Peptides NP113, NP151, NP376, NP753(K), NP797(K), NP856(K) and NP877 promote the highest responses across all four genotypes A, B, C & D compared to peptides NP2777(K) and NP1226(K). Surprisingly, P113 promotes the highest T cell response across all four genotypes compared to all other peptides.

[0124] Figure 12 shows that all peptides promote T cell responses across all ethnic groups tested. Peptides NP113, NP151, NP376, NP753(K), NP797(K), NP856(K) and NP877 promote the highest responses across all three ethnic groups compared to NP277(K) and NP1266(K).

[0125] In addition, all nine peptides show the ability to promote Th1 cytokine-producing CD4 and/or CD8 T cell responses as measured by intracellular cytokine staining across all HBV genotypes (Figure 13).

Example 6: Superiority of the Fluorocarbon-coniugated peptides compared to unconjugated peptides in their ability to promote T cell responses in vivo

Methods and materials

[0126] The immunogenicity in mice of FP02.1 (containing nine fluorocarbon-conjugated peptides) was compared to NP02.1 (containing nine equivalent unconjugated peptides). Female BALB/c mice (n = 7/group) were immunised intramuscularly with FP02.1 at a dose of 50 µg per peptide in a volume of 50 µL or with NP02.1 (containing the unconjugated HBV peptides (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) at a equimolar dose (compared to FP02.1) of 43.8 µg per peptide in a volume of 50 µL. Mice were immunised on day 0 and sacrificed on day 14. Splenocytes were stimulated *in vitro* with 5µg/mL/peptide of a mixture of each of the nine HBV peptides described in Example 3 for 18 hours in an ELISpot assay.

[0127] Alternatively, splenocytes were stimulated *in vitro* with 5µg/mL/peptide of nine individual peptides for 18 hours in an ELISpot assay. The number of $IFN\gamma^+$ spot forming cells (SFC) was counted. Plates then were washed with PBS, incubated with an IFNγ detection peroxidase-labelled antibody, followed by a substrate, according to the manufacturer's instructions. The developed spots were counted using an automated plate counting system (CTL Europe) to quantify the number of $IFN\gamma^+$ SFCs.

Results

[0128] Significantly higher magnitude T cell responses were observed in mice immunised with the mixture of fluorocarbon-conjugated peptides (FP02.1) compared to the equivalent mixture of unconjugated peptides (NP02.1) (see Figure 14). Due to the MHC restriction in the syngeneic BALC/C model, immune responses were dominated by four out of the 9 peptides contained in the vaccine (peptides NP113, NP151, NP376 andNP1266(K); see Figure 15).

[0129] Responses induced by FP02.1 were dominated by peptides NP113, NP151, NP376 and NP1266(K). Surprisingly, immune responses against peptide P113 and P376 were only observed with the formulation containing the fluorocarbon-conjugated peptides (see Figure 15).

[0130] In conclusion, the conjugation of a fluorocarbon vector to the HBV derived peptide sequences promote higher and broader T cell responses compared to the equivalent unconjugated peptides.

Example 7: Fluorocarbon-conjugated peptides promote a CTL/CD8+ T cell response

Methods and materials

[0131] The quality of the immune response induced by FP02.1 (containing nine fluorocarbon-conjugated peptides) was evaluated in mice. Female BALB/c mice (n = 7/group) were immunized intramuscularly with FP02.1 at a dose of 25 µg per peptide in a volume of 50 µL. Mice were immunised on day 0 and sacrificed on day 14.

[0132] Splenocytes were stimulated *in vitro* with either a CTL epitope derived from peptide NP113 (CTL1 KYLPLDKGI) or a CTL epitope derived from NP151 (CTL 2 HYFQTRHYL) at concentrations ranging from 10^{1} to 10^{-9} µg/ml for 18 hours in an ELISpot assay. The number of IFNγ^{+} SFC was counted. Plates then were washed with PBS, incubated with an IFNγ detection peroxidase-labelled antibody, followed by a substrate, according to the manufacturer's instructions. The developed spots were counted using an automated plate counting system (CTL Europe) to quantify the number of IFNγ^{+} SFCs.

Results

[0133] As shown in Figure 16, FP02.1 promotes T cell responses against CTL epitopes restricted by MHC class I molecules after a single immunisation.

Example 8: Synergy between fluorocarbon-peptides contained in the same formulation

Methods and materials

[0134] The immunogenicity of FA-P113 administered in mice alone or as part of a co-formulation with other fluorocarbon-conjugated peptides (FP02.1) was evaluated in mice. Female BALB/c mice (n = 7/group) were immunised intramuscularly with FA-P113 at a dose of 25 µg or FP02.1 at a dose of 25 µg per peptide in a volume of 50 µL. Mice were immunised on day 0 and sacrificed on day 14. Splenocytes were stimulated *in vitro* with 5µg/mL of NP113 (not conjugated to a fluorocarbon vector) for 18 hours in an ELISpot assay. The number of IFNγ^{+} SFC was counted. Plates then were washed with PBS, incubated with an IFNγ detection peroxidase-labeled antibody, followed by a substrate, according to the manufacturer's instructions. The developed spots were counted using an automated plate counting system (CTL Europe) to quantify the number of IFNγ^{+} SFCs.

Results

[0135] A higher magnitude of NP-113-specific T cell responses was observed in mice immunised with the mixture

of fluorocarbon-conjugated peptides (FP02.1) than FA-P113 alone (see Figure 17).

Example 9: Preferred HBV peptides and combinations contain epitopes having the ability to bind to a broad range of HLA class I molecules

Methods and materials

[0136] The ProImmune REVEAL binding assay was used to determine the ability of short peptides of nine amino-acids (derived from the HBV long peptides NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) to bind to one or more MHC class I alleles and stabilize the MHC-peptide complex. Detection is based on the presence or absence of the native conformation of the MHC-peptide complex. The highly frequent HLA class I alleles (HLA-A*0201, A*0301, A*1101, A*2402, B*0702, B*0801, and B*3501) were selected. Binding to MHC molecules was compared to that of a known T-cell epitope, a positive control peptide, with very strong binding properties. All potential nonamers for each HBV peptides (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) except those containing extra-lysines not present in the consensus HBV sequences were synthesised at a purity >90%. The score of the test peptide is reported quantitatively as a percentage of the signal generated by the positive control peptide, and the peptide is indicated as having a putative pass or fail result. Good binders are considered to be those peptides with scores 45% of the positive control as defined by ProImmune.

Results

[0137] The results shown in Table 6 represent the number of nonamers derived from each HBV long peptide (NP113, NP151, NP277, NP376, NP753, NP797, NP856, NP877 and NP1266) having a binding score >= 45% for each HLA allele. All long HBV peptides contain at least six epitopes having the ability to bind to at least 4 alleles. Any combination of six long peptides contains nonamer epitopes having the ability to bind to all alleles tested.

Table 6: Number of nonamers derived from each HBV long peptide (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) having a binding score >= 45% for each HLA class I alleles. (a) represents the total number binding epitopes detected for each long peptide (b) represents the number of alleles for which positive binding was detected for each long peptide

Long peptide	HLA-A*0201	HLA-A*0301	HLA-A*1101	HLA-A*2402	HLA-B*0702	HLA-B*0801	HLA-B*3501	Number of HLA binders (a)	Number of alleles (b)
NP113	2	3	5	3	2	3	2	20	7
NP797(K)	6	1	1	5	4	3	2	22	7
NP151	3	4	3	4	3	4	0	21	6
NP376	8	0	1	10	4	6	6	35	6
NP753(K)	3	0	1	3	1	1	1	10	6
NP1266(K)	6	3	3	9	0	1	2	24	6
NP277(K)	6	0	0	5	3	1	3	18	5
NP856(K)	4	0	0	4	2	1	0	11	4
NP877	2	0	0	2	1	1	0	6	4

Example 10: Preferred HBV peptides and combinations contain epitopes having the ability to bind to a broad range of HLA class II molecules

Methods

[0138] The ProImmune REVEAL® MHC-peptide binding assay was used to determine the ability of each HBV long peptide (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) to bind one or more MHC class II allele and stabilise the MHC-peptide complex. The highly frequent HLA class II alleles HLA-DR1 (α1*01:01; β1*01:01), HLA-DR15 (α1*01:01; β1*15:01), HLA-DR3 (α1*01:01; β1*01:01), HLA-DR4 (α1*01:01; β1*04:01), HLA-DR11 (α1*01:01; β1*11:01), HLA-DR13 (α1*01:01; β1*13:01) and HLA-DR7 (α1*01:01; β1*07:01) were selected. Each peptide was given a score relative to the positive control peptide, which is a known T-cell epitope. The score of the test peptide is reported quantitatively as a percentage of the signal generated by the positive control peptide, and the peptide is indicated as having a putative pass or fail result. Good binders are considered to be those peptides with scores >= 15% of the positive control as defined by Proimmune.

Results

[0139] The results in Table 7 represent the binding score of each HBV long peptide (NP113, NP151, NP277(K), NP376, NP753(K), NP797(K), NP856(K), NP877 and NP1266(K)) across the range of HLA class II alleles. Six out of the nine HBV peptides bind to at least one HLA allele with a score >= 15%. NP113, NP151 and NP376 bind to more than 3 different HLA class II alleles. Surprisingly, P113 binds to a total 6 alleles. The combination of peptides NP113 and NP877 binds to all HLA class II alleles tested.

Table 7: Binding of HBV peptides to a range of HLA class II molecules. Positive binding was defined as score >=15% (a) represents the number of alleles for which positive binding was detected for each long peptide.

Long peptide	HLA-DR1 (α1*01:01; β1*01:01)	HLA-DR15 (α1*01:01; β1*15:01)	HLA-DR3 (α1*01:01; β1*01:01)	HLA-DR4 (α1*01:01; β1*04:01)	HLA-DR11 (α1*01:01; β1*11:01)	HLA-DR13 (α1*01:01; β1*13:01)	HLA-DR7 (α1*01:01; β1*07:01)	Number of alleles (a)
NP113	54.44	28.04	49.98	33.51	52.86	0.00	99.17	6
NP151	14.59	38.96	0.00	74.36	49.16	0.00	19.41	4
NP277(K)	0.49	0.18	0.10	36.19	1.25	0.00	0.01	1
NP376	27.71	6.29	0.00	53.66	31.38	0.00	8.83	3
NP753(K)	0.11	0.00	0.00	0.65	1.51	0.00	0.00	0
NP797(K)	0.20	1.14	0.00	6.65	2.86	0.00	0.01	0
NP856(K)	2.33	5.71	0.13	10.72	0.33	0.00	0.40	0
NP877	0.24	0.09	5.58	0.04	4.98	16.34	2.78	1
NP1266(K)	1.48	0.64	0.00	11.22	21.64	0.00	0.62	1

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            20                  25                  30

Leu Asp Lys Gly Ile Lys Pro Tyr Tyr Pro Glu His Val Val Asn His
        35                  40                  45

Tyr Phe Gln Thr Arg His Tyr Leu His Thr Leu Trp Lys Ala Gly Ile
    50                  55                  60

Leu Tyr Lys Arg Glu Thr Thr Arg Ser Ala Ser Phe Cys Gly Ser Pro
65                  70                  75                  80

Tyr Ser Trp Glu Gln Glu Leu Gln Ser Cys Trp Trp Leu Gln
                85                  90
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            20                  25                  30

Thr Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Asn
        35                  40                  45

Thr Arg Val Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu
    50                  55                  60
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Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser
65                  70                  75                  80

Ala Ala Phe Tyr His Ile Pro Leu His Pro Ala Ala Met Pro His Leu
                85                  90                  95

Leu Val Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser
            100                 105                 110

Asn Ser Arg Ile Ile Asn Asn Gln His Gly Thr Met Gln Asn Leu His
        115                 120                 125

Asp Ser Cys Ser Arg Asn Leu Tyr Val Ser Leu Met Leu Leu Tyr Lys
    130                 135                 140

Thr Tyr Gly Arg Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly
145                 150                 155                 160

Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala
                165                 170                 175

Gln Phe Thr Ser Ala Ile Xaa Ser Val Val Arg Arg Ala Phe Pro His
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            20                  25                  30

Gly Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe Val Tyr Val
        35                  40                  45

Pro Ser Ala Leu Asn Pro Ala Asp Asp Pro Ser Arg Gly Arg Leu Gly
    50                  55                  60

Leu Tyr Arg Pro Leu Leu Arg Leu Pro Phe Arg Pro Thr Thr Gly Arg
65                  70                  75                  80

Thr Ser Leu Tyr Ala Val Ser Pro Ser Val Pro Ser His Leu Pro Asp
                85                  90                  95

Arg Val His Phe Ala Ser Pro Leu His Val Ala Trp Arg
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            20                  25                  30

Asp Pro Tyr Lys Glu Phe Gly Ala Xaa Val Glu Leu Leu Ser Phe Leu
        35                  40                  45

Pro Ser Asp Phe Phe Pro Ser Val Arg Asp Leu Leu Asp Thr Ala Ser
    50                  55                  60

Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys Ser Pro His
65                  70                  75                  80

His Thr Ala Leu Arg Gln Ala Ile Leu Xaa Trp Gly Glu Leu Met Thr
                85                  90                  95

Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala Ser Arg Asp
            100                 105                 110

Leu Val Val Ser Tyr Val Asn Thr Asn Met Gly Leu Lys Ile Arg Gln
        115                 120                 125

Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly Arg Glu Thr Val
    130                 135                 140

Leu Glu Tyr Leu Val Ser Phe Gly Val Trp Ile Arg Thr Pro Pro Ala
145                 150                 155                 160

Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro Glu Thr Thr
                165                 170                 175

Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg Thr Pro Ser Pro
            180                 185                 190

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            20                  25                  30

Leu Asp Lys Gly Ile Lys Pro Tyr Tyr Pro Glu His Val Val Asn His
        35                  40                  45

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            20                  25                  30

Ser Ala Ser Phe Cys Gly Ser Pro Tyr Ser Trp Glu Gln Glu Leu Gln
        35                  40                  45

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            20                  25                  30

Ala Phe Tyr His Ile Pro Leu His Pro Ala Ala Met Pro His Leu Leu
        35                  40                  45

Val Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Asn
    50                  55                  60

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            20                  25                  30

Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly
        35                  40                  45

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            20                  25                  30

Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly
        35                  40                  45

Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Xaa Ser Val
    50                  55                  60

Val Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp
65                  70                  75                  80

Val Val Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Tyr
                85                  90                  95
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            20                  25                  30

Asp Pro Tyr Lys Glu Phe Gly Ala Xaa Val Glu Leu Leu Ser Phe Leu
        35                  40                  45

Pro Ser Asp Phe Phe Pro Ser Val Arg Asp Leu Leu Asp Thr Ala Ser
    50                  55                  60

Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys Ser Pro His
65                  70                  75                  80

His Thr Ala Leu Arg Gln Ala Ile Leu Xaa Trp Gly Glu Leu Met Thr
                85                  90                  95

Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala Ser
            100                 105                 110
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Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Xaa Trp Gly Glu Leu
        35                  40                  45

Met Thr Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala Ser
    50                  55                  60

Arg Asp Leu Val Val Ser Tyr Val Asn Thr Asn Met Gly Leu Lys Ile
65                  70                  75                  80

Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly Arg Glu
                85                  90                  95

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            100                 105                 110

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            20                  25                  30

Arg Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly Val Trp Ile Arg
        35                  40                  45

Thr Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu
    50                  55                  60

Pro Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg
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Thr Pro Ser Pro Arg Arg Arg Arg Ser Gln Ser Pro Arg Arg Arg Arg
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Leu Asp Lys Gly Ile Lys Pro Tyr

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Ala Phe Tyr His Ile Pro Leu His Pro Ala
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            20                  25                  30

Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val
        35                  40                  45
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Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser
            20                  25                  30

Ala Ile Xaa Ser Val Val Arg Arg
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Ala Leu Asn Pro Ala Asp Asp Pro Ser Arg Gly Arg Leu Gly Leu Tyr
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Arg Pro Leu Leu Arg Leu
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Phe Phe Pro Ser Val Arg Asp Leu Leu Asp Thr Ala Ser Ala Leu Tyr
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            20                  25                  30

Pro Ala Ser Arg Asp Leu Val Val Ser Tyr Val Asn Thr Asn Met Gly
        35                  40                  45

Leu Lys Ile Arg Gln Leu Leu Trp Phe His Ile Ser
    50                  55                  60
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<400> 23
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Thr Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu
1               5                   10                  15

Pro Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg
            20                  25                  30

Thr
```

<210> 24
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 24
```
Val Gly Pro Leu Thr Val Asn Glu Lys Arg Arg Leu Lys Leu Ile Met
1               5                   10                  15
```

```
Pro Ala Arg Phe Tyr Pro Asn Val Thr Lys Tyr Leu Pro Leu Asp Lys
            20                  25                  30

Gly Ile Lys
        35
```

<210> 25

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 25

```
Pro Glu His Val Val Asn His Tyr Phe Gln Thr Arg His Tyr Leu His
1               5                   10                  15

Thr Leu Trp Lys Ala Gly Ile Leu Tyr Lys Arg Glu Thr Thr Arg Ser
            20                  25                  30

Ala Ser Phe
        35
```

<210> 26

<211> 36

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 26

```
Arg Val Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr
1               5                   10                  15

Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala
            20                  25                  30

Ala Phe Tyr His
        35
```

<210> 27

<211> 37

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 27

```
Ser Arg Asn Leu Tyr Val Ser Leu Met Leu Leu Tyr Lys Thr Tyr Gly
1               5                   10                  15

Arg Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys
            20                  25                  30

Ile Pro Met Gly Val
        35
```

<210> 28

<211> 40

<212> PRT

<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 28
```
Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile
1               5                   10                  15

Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser
            20                  25                  30

Ala Ile Ser Ser Val Val Arg Arg
        35                  40
```

<210> 29
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 29
```
Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe Val Tyr Val Pro Ser Ala
1               5                   10                  15

Leu Asn Pro Ala Asp Asp Pro Ser Arg Gly Arg Leu Gly Leu Tyr Arg
            20                  25                  30

Pro Leu Leu Arg
        35
```

<210> 30
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 30
```
Lys Glu Phe Gly Ala Thr Val Glu Leu Leu Ser Phe Leu Pro Ser Asp
1               5                   10                  15

Phe Phe Pro Ser Val Arg Asp Leu Leu Asp Thr Ala Ser Ala Leu Tyr
            20                  25                  30

Arg
```

<210> 31
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 31
```
Ser Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Ser Trp Gly Glu
1               5                   10                  15

Leu Met Thr Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala
            20                  25                  30
```

```
Ser Arg Asp
        35
```

<210> 32
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 32
```
Leu Thr Phe Gly Arg Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly
1               5                   10                  15

Val Trp Ile Arg Thr Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile
            20                  25                  30

Leu Ser Thr
        35
```

<210> 33
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 33
```
Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro
1               5                   10                  15

Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg
            20                  25                  30
```

<210> 34
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 34
```
Arg Val Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr
1               5                   10                  15

Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala
            20                  25                  30

Ala Phe Tyr His Lys Lys Lys
        35
```

<210> 35
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 35

```
Lys Lys Lys Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe Val Tyr Val
1               5                   10                  15

Pro Ser Ala Leu Asn Pro Ala Asp Asp Pro Ser Arg Gly Arg Leu Gly
            20                  25                  30

Leu Tyr Arg Pro Leu Leu Arg
        35
```

<210> 36

<211> 38

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 36

```
Lys Lys Lys Glu Phe Gly Ala Thr Val Glu Leu Leu Ser Phe Leu Pro
1               5                   10                  15

Ser Asp Phe Phe Pro Ser Val Arg Asp Leu Leu Asp Thr Ala Ser Ala
            20                  25                  30

Leu Tyr Arg Lys Lys Lys
        35
```

<210> 37

<211> 38

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 37

```
Ser Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Ser Trp Gly Glu
1               5                   10                  15

Leu Met Thr Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala
            20                  25                  30

Ser Arg Asp Lys Lys Lys
        35
```

<210> 38

<211> 38

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 38

```
Leu Thr Phe Gly Arg Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly
1               5                   10                  15

Val Trp Ile Arg Thr Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile
            20                  25                  30

Leu Ser Thr Lys Lys Lys
        35
```

<210> 39

<211> 1468

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 39

```
Met Pro Leu Ser Tyr Gln His Phe Arg Lys Leu Leu Leu Leu Asp Asp
1               5                  10                  15

Glu Ala Gly Pro Leu Glu Glu Glu Leu Pro Arg Leu Ala Asp Glu Gly
            20                  25                  30

Leu Asn Arg Arg Val Ala Glu Asp Leu Asn Leu Gly Asn Leu Asn Val
        35                  40                  45

Ser Ile Pro Trp Thr His Lys Val Gly Asn Phe Thr Gly Leu Tyr Ser
    50                  55                  60

Ser Thr Val Pro Val Phe Asn Pro Glu Trp Gln Thr Pro Ser Phe Pro
65                  70                  75                  80

His Ile His Leu Gln Glu Asp Ile Ile Asn Arg Cys Gln Gln Phe Val
                85                  90                  95

Gly Pro Leu Thr Val Asn Glu Lys Arg Arg Leu Lys Leu Ile Met Pro
            100                 105                 110

Ala Arg Phe Tyr Pro Asn Val Thr Lys Tyr Leu Pro Leu Asp Lys Gly
        115                 120                 125

Ile Lys Pro Tyr Tyr Pro Glu His Val Val Asn His Tyr Phe Gln Thr
    130                 135                 140

Arg His Tyr Leu His Thr Leu Trp Lys Ala Gly Ile Leu Tyr Lys Arg
145                 150                 155                 160

Glu Thr Thr Arg Ser Ala Ser Phe Cys Gly Ser Pro Tyr Ser Trp Glu
                165                 170                 175

Gln Glu Leu Gln Ser Cys Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro
            180                 185                 190

Cys Ser Glu Tyr Cys Leu Ser His Ile Val Asn Leu Leu Glu Asp Trp
        195                 200                 205

Gly Pro Cys Thr Glu His Gly Glu His His Ile Arg Ile Pro Arg Thr
    210                 215                 220

Pro Ala Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn Pro His
225                 230                 235                 240

Asn Thr Thr Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg
                245                 250                 255

Gly Asn Thr Arg Val Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln
            260                 265                 270

Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu Ser Leu Asp
        275                 280                 285

Val Ser Ala Ala Phe Tyr His Ile Pro Leu His Pro Ala Ala Met Pro
    290                 295                 300

His Leu Leu Val Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu
305                 310                 315                 320
```

```
Ser Ser Asn Ser Arg Ile Ile Asn Asn Gln His Gly Thr Met Gln Asn
                325                 330                 335

Leu His Asp Ser Cys Ser Arg Asn Leu Tyr Val Ser Leu Met Leu Leu
            340                 345                 350

Tyr Lys Thr Tyr Gly Arg Lys Leu His Leu Tyr Ser His Pro Ile Ile
        355                 360                 365

Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser Pro Phe Leu
    370                 375                 380

Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Val Arg Arg Ala Phe
385                 390                 395                 400

Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val Val Leu Gly Ala
                405                 410                 415

Lys Ser Val Gln His Leu Glu Ser Leu Tyr Thr Ala Val Thr Asn Phe
            420                 425                 430

Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn Lys Thr Lys Arg Trp
        435                 440                 445

Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val Ile Gly Ser Trp Gly Thr
    450                 455                 460

Leu Pro Gln Glu His Ile Val Gln Lys Ile Lys Gln Cys Phe Arg Lys
465                 470                 475                 480

Leu Pro Val Asn Arg Pro Ile Asp Trp Lys Val Cys Gln Arg Ile Val
                485                 490                 495

Gly Leu Leu Gly Phe Ala Ala Pro Phe Thr Gln Cys Gly Tyr Pro Ala
            500                 505                 510

Leu Met Pro Leu Tyr Ala Cys Ile Gln Ala Lys Gln Ala Phe Thr Phe
        515                 520                 525

Ser Pro Thr Tyr Lys Ala Phe Leu Cys Lys Gln Tyr Leu Asn Leu Tyr
    530                 535                 540

Pro Val Ala Arg Gln Arg Pro Gly Leu Cys Gln Val Phe Ala Asp Ala
545                 550                 555                 560

Thr Pro Thr Gly Trp Gly Leu Ala Ile Gly His Gln Arg Met Arg Gly
                565                 570                 575

Thr Phe Val Ala Pro Leu Pro Ile His Thr Ala Glu Leu Leu Ala Ala
            580                 585                 590

Cys Phe Ala Arg Ser Arg Ser Gly Ala Lys Leu Ile Gly Thr Asp Asn
        595                 600                 605

Ser Val Val Leu Ser Arg Lys Tyr Thr Ser Phe Pro Trp Leu Leu Gly
    610                 615                 620

Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe Val Tyr Val Pro
625                 630                 635                 640

Ser Ala Leu Asn Pro Ala Asp Asp Pro Ser Arg Gly Arg Leu Gly Leu
                645                 650                 655

Tyr Arg Pro Leu Leu Arg Leu Pro Phe Arg Pro Thr Thr Gly Arg Thr
            660                 665                 670

Ser Leu Tyr Ala Val Ser Pro Ser Val Pro Ser His Leu Pro Asp Arg
        675                 680                 685

Val His Phe Ala Ser Pro Leu His Val Ala Trp Arg Pro Pro Met Gln
```

```
Val His Phe Ala Ser Pro Leu His Val Ala Trp Arg Pro Pro Met Gln
    690                 695                 700

Leu Phe His Leu Cys Leu Ile Ile Ser Cys Ser Cys Pro Thr Val Gln
705                 710                 715                 720

Ala Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly Met Asp Ile Asp Pro
                725                 730                 735

Tyr Lys Glu Phe Gly Ala Ser Val Glu Leu Leu Ser Phe Leu Pro Ser
            740                 745                 750

Asp Phe Phe Pro Ser Val Arg Asp Leu Leu Asp Thr Ala Ser Ala Leu
        755                 760                 765

Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys Ser Pro His His Thr
    770                 775                 780

Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu Leu Met Thr Leu Ala

785                 790                 795                 800

Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala Ser Arg Asp Leu Val
                805                 810                 815

Val Ser Tyr Val Asn Thr Asn Met Gly Leu Lys Ile Arg Gln Leu Leu
            820                 825                 830

Trp Phe His Ile Ser Cys Leu Thr Phe Gly Arg Glu Thr Val Leu Glu
        835                 840                 845

Tyr Leu Val Ser Phe Gly Val Trp Ile Arg Thr Pro Pro Ala Tyr Arg
    850                 855                 860

Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro Glu Thr Thr Val Val
865                 870                 875                 880

Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg Thr Pro Ser Pro Arg Arg
                885                 890                 895

Arg Arg Ser Gln Ser Pro Arg Arg Arg Arg Ser Gln Ser Arg Glu Ser
            900                 905                 910

Gln Cys Met Ala Ala Arg Leu Cys Cys Gln Leu Asp Pro Ala Arg Asp
        915                 920                 925

Val Leu Cys Leu Arg Pro Val Gly Ala Glu Ser Arg Gly Arg Pro Leu
    930                 935                 940

Ser Gly Pro Leu Gly Thr Leu Pro Ser Pro Ser Pro Ser Ala Val Pro
945                 950                 955                 960

Ala Asp His Gly Ala His Leu Ser Leu Arg Gly Leu Pro Val Cys Ala
                965                 970                 975

Phe Ser Ser Ala Gly Pro Cys Ala Leu Arg Phe Thr Ser Ala Arg Arg
            980                 985                 990

Met Glu Thr Thr Val Asn Ala His  Gln Ile Leu Pro Lys  Val Leu His
        995                 1000                1005

Lys Arg  Thr Leu Gly Leu Ser  Ala Met Ser Thr Thr  Asp Leu Glu
    1010                1015                1020

Ala Tyr  Phe Lys Asp Cys Val  Phe Lys Asp Trp Glu  Glu Leu Gly
    1025                1030                1035

Glu Glu  Ile Arg Leu Lys Val  Phe Val Leu Gly Gly  Cys Arg His
    1040                1045                1050
```

```
Lys Leu  Val Cys Ser Pro Ala  Pro Cys Asn Phe Phe  Thr Ser Ala
    1055                 1060                 1065

Met Gly  Gly Trp Ser Ser Lys  Pro Arg Lys Gly Met  Gly Thr Asn
    1070                 1075                 1080

Leu Ser  Val Pro Asn Pro Leu  Gly Phe Phe Pro Asp  His Gln Leu
    1085                 1090                 1095

Asp Pro  Ala Phe Arg Ala Asn  Ser Asn Asn Pro Asp  Trp Asp Phe
    1100                 1105                 1110

Asn Pro  Asn Lys Asp Gln Trp  Pro Ala Ala Asn Gln  Val Gly Val
    1115                 1120                 1125

Gly Ala  Phe Gly Pro Gly Phe  Thr Pro Pro His Gly  Gly Leu Leu
    1130                 1135                 1140

Gly Trp  Ser Pro Gln Ala Gln  Gly Ile Leu Thr Thr  Val Pro Ala
    1145                 1150                 1155

Asp Pro  Pro Pro Ala Ser Thr  Asn Arg Gln Ser Gly  Arg Gln Pro
    1160                 1165                 1170

Thr Pro  Ile Ser Pro Pro Leu  Arg Asp Ser His Pro  Gln Ala Met
    1175                 1180                 1185

Gln Trp  Asn Ser Thr Thr Phe  His Gln Ala Leu Gln  Asp Pro Arg
    1190                 1195                 1200

Val Arg  Gly Leu Tyr Phe Pro  Ala Gly Gly Ser Ser  Ser Gly Thr
    1205                 1210                 1215

Val Asn  Pro Ala Pro Thr Thr  Ala Ser Leu Ile Ser  Ser Ile Phe
    1220                 1225                 1230

Ser Arg  Thr Gly Asp Pro Ala  Pro Asn Met Glu Asn  Ile Thr Ser
    1235                 1240                 1245

Gly Phe  Leu Gly Pro Leu Leu  Val Leu Gln Ala Gly  Phe Phe Leu
    1250                 1255                 1260

Leu Thr  Lys Ile Leu Thr Ile  Pro Gln Ser Leu Asp  Ser Trp Trp
    1265                 1270                 1275

Thr Ser  Leu Asn Phe Leu Gly  Gly Thr Pro Val Cys  Leu Gly Gln
    1280                 1285                 1290

Asn Ser  Gln Ser Pro Thr Ser  Asn His Ser Pro Thr  Ser Cys Pro
    1295                 1300                 1305

Pro Ile  Cys Pro Gly Tyr Arg  Trp Met Cys Leu Arg  Arg Phe Ile
    1310                 1315                 1320

Ile Phe  Leu Phe Ile Leu Leu  Leu Cys Leu Ile Phe  Leu Leu Val
    1325                 1330                 1335

Leu Leu  Asp Tyr Gln Gly Met  Leu Pro Val Cys Pro  Leu Ile Pro
    1340                 1345                 1350

Gly Ser  Ser Thr Thr Ser Thr  Gly Pro Cys Lys Thr  Cys Thr Thr
    1355                 1360                 1365

Pro Ala  Gln Gly Thr Ser Met  Phe Pro Ser Cys Cys  Cys Thr Lys
    1370                 1375                 1380

Pro Ser  Asp Gly Asn Cys Thr  Cys Ile Pro Ile Pro  Ser Ser Trp
    1385                 1390                 1395
```

```
1385                1390                1395

Ala Phe  Gly Lys Tyr Leu Trp  Glu Trp Ala Ser Ala  Arg Phe Ser
    1400                1405                1410

Trp Leu  Ser Leu Leu Val Pro  Phe Val Gln Trp Phe  Val Gly Leu
    1415                1420                1425

Ser Pro  Thr Val Trp Leu Ser  Val Ile Trp Met Met  Trp Tyr Trp
    1430                1435                1440

Gly Pro  Ser Leu Tyr Asn Ile  Leu Ser Pro Phe Ile  Pro Leu Leu
    1445                1450                1455

Pro Ile  Phe Phe Cys Leu Trp  Val Tyr Ile
    1460                1465
```

<210> 40

<211> 55

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 40

```
Leu Pro Arg Leu Ala Asp Glu Gly Leu Asn Arg Arg Val Ala Glu Asp
1               5                   10                  15

Leu Asn Leu Gly Asn Leu Asn Val Ser Ile Pro Trp Thr His Lys Val
            20                  25                  30

Gly Asn Phe Thr Gly Leu Tyr Ser Ser Thr Val Pro Val Phe Asn Pro
        35                  40                  45

Glu Trp Gln Thr Pro Ser Phe
    50                  55
```

<210> 41

<211> 51

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 41

```
Cys Thr Glu His Gly Glu His His Ile Arg Ile Pro Arg Thr Pro Ala
1               5                   10                  15

Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn Pro His Asn Thr
            20                  25                  30

Thr Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Asn
        35                  40                  45

Thr Arg Val
    50
```

<210> 42

<211> 55

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> C OR S

<400> 42

```
Arg Lys Ile Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln
1               5                   10                  15

Phe Thr Ser Ala Ile Xaa Ser Val Val Arg Arg Ala Phe Pro His Cys
            20                  25                  30

Leu Ala Phe Ser Tyr Met Asp Asp Val Val Leu Gly Ala Lys Ser Val
        35                  40                  45

Gln His Leu Glu Ser Leu Tyr
    50                  55
```

<210> 43
<211> 52
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 43

```
Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Tyr Thr Ala Val
1               5                   10                  15

Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn Lys Thr
            20                  25                  30

Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val Ile Gly Ser
        35                  40                  45

Trp Gly Thr Leu
    50
```

<210> 44
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 44

```
Lys Ile Lys Gln Cys Phe Arg Lys Leu Pro Val Asn Arg Pro Ile Asp
1               5                   10                  15

Trp Lys Val Cys Gln Arg Ile Val Gly Leu Leu Gly Phe Ala Ala Pro
            20                  25                  30

Phe Thr Gln Cys Gly Tyr Pro Ala Leu Met Pro Leu Tyr Ala Cys Ile
        35                  40                  45

Gln Ala Lys Gln Ala Phe Thr Phe Ser Pro Thr
    50                  55
```

<210> 45

<211> 50
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 45
```
Ile Gln Ala Lys Gln Ala Phe Thr Phe Ser Pro Thr Tyr Lys Ala Phe
1               5                   10                  15

Leu Cys Lys Gln Tyr Leu Asn Leu Tyr Pro Val Ala Arg Gln Arg Pro
            20                  25                  30

Gly Leu Cys Gln Val Phe Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu
        35                  40                  45

Ala Ile
    50
```

<210> 46
<211> 48
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 46
```
Phe Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu Ala Ile Gly His Gln
1               5                   10                  15

Arg Met Arg Gly Thr Phe Val Ala Pro Leu Pro Ile His Thr Ala Glu
            20                  25                  30

Leu Leu Ala Ala Cys Phe Ala Arg Ser Arg Ser Gly Ala Lys Leu Ile
        35                  40                  45
```

<210> 47
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 47
```
Ala Cys Phe Ala Arg Ser Arg Ser Gly Ala Lys Leu Ile Gly Thr Asp
1               5                   10                  15

Asn Ser Val Val Leu Ser Arg Lys Tyr Thr Ser Phe Pro Trp Leu Leu

            20                  25                  30

Gly Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe Val Tyr Val
        35                  40                  45

Pro Ser Ala Leu Asn Pro Ala Asp Asp Pro Ser
    50                  55
```

<210> 48
<211> 63
<212> PRT
<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 48

```
Tyr Val Pro Ser Ala Leu Asn Pro Ala Asp Asp Pro Ser Arg Gly Arg
1               5                  10                  15

Leu Gly Leu Tyr Arg Pro Leu Leu Arg Leu Pro Phe Arg Pro Thr Thr
            20                  25                  30

Gly Arg Thr Ser Leu Tyr Ala Val Ser Pro Ser Val Pro Ser His Leu
        35                  40                  45

Pro Asp Arg Val His Phe Ala Ser Pro Leu His Val Ala Trp Arg
    50                  55                  60
```

<210> 49

<211> 60

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<220>

<221> MISC_FEATURE

<222> (41)..(41)

<223> S OR T

<400> 49

```
Met Gln Leu Phe His Leu Cys Leu Ile Ile Ser Cys Ser Cys Pro Thr
1               5                  10                  15

Val Gln Ala Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly Met Asp Ile
            20                  25                  30

Asp Pro Tyr Lys Glu Phe Gly Ala Xaa Val Glu Leu Leu Ser Phe Leu
        35                  40                  45

Pro Ser Asp Phe Phe Pro Ser Val Arg Asp Leu Leu
    50                  55                  60
```

<210> 50

<211> 64

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<220>

<221> MISC_FEATURE

<222> (44)..(44)

<223> C OR S

<400> 50

```
Phe Leu Pro Ser Asp Phe Phe Pro Ser Val Arg Asp Leu Leu Asp Thr
1               5                  10                  15

Ala Ser Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys Ser
            20                  25                  30

Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Xaa Trp Gly Glu Leu
```

```
                35                  40                  45

Met Thr Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala Ser
    50                  55                  60
```

<210> 51

<211> 61

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 51

```
Ala Ser Arg Asp Leu Val Val Ser Tyr Val Asn Thr Asn Met Gly Leu
1               5                   10                  15

Lys Ile Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly
            20                  25                  30

Arg Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly Val Trp Ile Arg
        35                  40                  45

Thr Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu
    50                  55                  60
```

<210> 52

<211> 52

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 52

```
His Leu Ser Leu Arg Gly Leu Pro Val Cys Ala Phe Ser Ser Ala Gly
1               5                   10                  15

Pro Cys Ala Leu Arg Phe Thr Ser Ala Arg Arg Met Glu Thr Thr Val
            20                  25                  30

Asn Ala His Gln Ile Leu Pro Lys Val Leu His Lys Arg Thr Leu Gly
        35                  40                  45

Leu Ser Ala Met
    50
```

<210> 53

<211> 58

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 53

```
Lys Val Leu His Lys Arg Thr Leu Gly Leu Ser Ala Met Ser Thr Thr
1               5                   10                  15

Asp Leu Glu Ala Tyr Phe Lys Asp Cys Val Phe Lys Asp Trp Glu Glu
            20                  25                  30

Leu Gly Glu Glu Ile Arg Leu Lys Val Phe Val Leu Gly Gly Cys Arg
        35                  40                  45
```

```
His Lys Leu Val Cys Ser Pro Ala Pro Cys
    50                  55
```

<210> 54

<211> 54

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 54

```
Arg Gln Pro Thr Pro Ile Ser Pro Pro Leu Arg Asp Ser His Pro Gln
1               5                   10                  15

Ala Met Gln Trp Asn Ser Thr Thr Phe His Gln Ala Leu Gln Asp Pro
            20                  25                  30

Arg Val Arg Gly Leu Tyr Phe Pro Ala Gly Gly Ser Ser Ser Gly Thr
        35                  40                  45

Val Asn Pro Ala Pro Thr
    50
```

<210> 55

<211> 56

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 55

```
Pro Asn Met Glu Asn Ile Thr Ser Gly Phe Leu Gly Pro Leu Leu Val
1               5                   10                  15

Leu Gln Ala Gly Phe Phe Leu Leu Thr Lys Ile Leu Thr Ile Pro Gln
            20                  25                  30

Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Thr Pro
        35                  40                  45

Val Cys Leu Gly Gln Asn Ser Gln
    50                  55
```

<210> 56

<211> 35

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 56

```
Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile Ile Phe Leu Phe
1               5                   10                  15

Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val Leu Leu Asp Tyr Gln
            20                  25                  30

Gly Met Leu
        35
```

<210> 57

<211> 56
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 57
```
Ile Pro Ile Pro Ser Ser Trp Ala Phe Gly Lys Tyr Leu Trp Glu Trp
1               5                   10                  15

Ala Ser Ala Arg Phe Ser Trp Leu Ser Leu Leu Val Pro Phe Val Gln
            20                  25                  30

Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu Ser Val Ile Trp Met
        35                  40                  45

Met Trp Tyr Trp Gly Pro Ser Leu
    50                  55
```

<210> 58
<211> 49
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 58
```
Glu Gly Leu Asn Arg Arg Val Ala Glu Asp Leu Asn Leu Gly Asn Leu
1               5                   10                  15

Asn Val Ser Ile Pro Trp Thr His Lys Val Gly Asn Phe Thr Gly Leu
            20                  25                  30

Tyr Ser Ser Thr Val Pro Val Phe Asn Pro Glu Trp Gln Thr Pro Ser
        35                  40                  45

Phe
```

<210> 59
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 59
```
Arg Thr Pro Ala Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn
1               5                   10                  15

Pro His Asn Thr Thr Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe
            20                  25                  30

Ser Arg Gly Asn Thr Arg Val
        35
```

<210> 60
<211> 37
<212> PRT
<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 60

```
Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser
1               5                   10                  15

Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Ile
            20                  25                  30

Pro Leu His Pro Ala
        35
```

<210> 61

<211> 38

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 61

```
Val Ser Ala Ala Phe Tyr His Ile Pro Leu His Pro Ala Ala Met Pro
1               5                   10                  15

His Leu Leu Val Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu
            20                  25                  30

Ser Ser Asn Ser Arg Ile
        35
```

<210> 62

<211> 37

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 62

```
Leu Ala Phe Ser Tyr Met Asp Asp Val Val Leu Gly Ala Lys Ser Val
1               5                   10                  15

Gln His Leu Glu Ser Leu Tyr Thr Ala Val Thr Asn Phe Leu Leu Ser
            20                  25                  30

Leu Gly Ile His Leu
        35
```

<210> 63

<211> 38

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 63

```
Ala Val Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn
1               5                   10                  15

Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val Ile
            20                  25                  30

Gly Ser Trp Gly Thr Leu
        35
```

<210> 64
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 64
```
Phe Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu Ala Ile Gly His Gln
1               5                   10                  15

Arg Met Arg Gly Thr Phe Val Ala Pro Leu Pro Ile His Thr Ala Glu
            20                  25                  30

Leu Leu Ala Ala Cys Phe Ala Arg Ser
        35                  40
```

<210> 65
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 65
```
Pro Ala Asp Asp Pro Ser Arg Gly Arg Leu Gly Leu Tyr Arg Pro Leu
1               5                   10                  15

Leu Arg Leu Pro Phe Arg Pro Thr Thr Gly Arg Thr Ser Leu Tyr Ala
            20                  25                  30

Val Ser Pro Ser Val Pro Ser His Leu
        35                  40
```

<210> 66
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 66
```
Pro Leu Leu Arg Leu Pro Phe Arg Pro Thr Thr Gly Arg Thr Ser Leu
1               5                   10                  15

Tyr Ala Val Ser Pro Ser Val Pro Ser His Leu Pro Asp Arg Val His
            20                  25                  30

Phe Ala Ser Pro Leu His Val Ala Trp Arg
        35                  40
```

<210> 67
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<220>

<221> MISC_FEATURE
<222> (15)..(15)
<223> C OR S

<400> 67
```
His Cys Ser Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Xaa Trp
1               5                   10                  15

Gly Glu Leu Met Thr Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp
            20                  25                  30

Pro Ala Ser
        35
```

<210> 68
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 68
```
Ala Ser Arg Asp Leu Val Val Ser Tyr Val Asn Thr Asn Met Gly Leu
1               5                   10                  15

Lys Ile Arg Gln Leu Leu Trp Phe His Ile Ser
            20                  25
```

<210> 69
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 69
```
Ala Ser Arg Asp Leu Val Val Ser Tyr Val Asn Thr Asn Met Gly Leu
1               5                   10                  15

Lys Ile Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly
            20                  25                  30

Arg Glu Thr Val Leu Glu Tyr Leu
        35                  40
```

<210> 70
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 70
```
Ser Ala Gly Pro Cys Ala Leu Arg Phe Thr Ser Ala Arg Arg Met Glu
1               5                   10                  15

Thr Thr Val Asn Ala His Gln Ile Leu Pro Lys Val Leu His Lys Arg
            20                  25                  30

Thr Leu Gly Leu Ser Ala Met Ser Thr Thr Asp Leu Glu Ala
        35                  40                  45
```

<210> 71
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 71
```
Thr Ser Gly Phe Leu Gly Pro Leu Leu Val Leu Gln Ala Gly Phe Phe
1               5                   10                  15

Leu Leu Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu Asp Ser Trp Trp
            20                  25                  30

Thr Ser Leu Asn Phe Leu Gly Gly Thr Pro Val
        35                  40
```

<210> 72
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 72
```
Ala Phe Gly Lys Tyr Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp
1               5                   10                  15

Leu Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro
            20                  25                  30

Thr Val Trp Leu Ser Val Ile Trp Met
        35                  40
```

<210> 73
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 73
```
Leu Pro Arg Leu Ala Asp Glu Gly Leu Asn Arg Arg Val Ala Glu Asp
1               5                   10                  15

Leu Asn Leu
```

<210> 74
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 74
```
Glu Gly Leu Asn Arg Arg Val Ala Glu Asp Leu Asn Leu Gly Asn Leu
1               5                   10                  15

Asn Val Ser Ile
            20
```

<210> 75
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 75
Ala Glu Asp Leu Asn Leu Gly Asn Leu Asn Val Ser Ile Pro Trp Thr
1 5 10 15

His Lys Val

<210> 76
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 76
Asn Leu Gly Asn Leu Asn Val Ser Ile Pro Trp Thr His Lys Val Gly
1 5 10 15

Asn Phe

<210> 77
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 77
Leu Asn Val Ser Ile Pro Trp Thr His Lys Val Gly Asn Phe Thr Gly
1 5 10 15

Leu Tyr Ser Ser
20

<210> 78
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 78
Thr His Lys Val Gly Asn Phe Thr Gly Leu Tyr Ser Ser Thr Val Pro
1 5 10 15

Val Phe Asn Pro
20

<210> 79
<211> 19
<212> PRT

<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 79
Gly Leu Tyr Ser Ser Thr Val Pro Val Phe Asn Pro Glu Trp Gln Thr
1 5 10 15

Pro Ser Phe

<210> 80
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 80
Lys Gln Gln Phe Val Gly Pro Leu Thr Val Asn Glu Lys Arg Arg Leu
1 5 10 15

Lys Leu Ile Met

20

<210> 81
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 81
Leu Thr Val Asn Glu Lys Arg Arg Leu Lys Leu Ile Met Pro Ala Arg
1 5 10 15

Phe Tyr Pro Asn
20

<210> 82
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 82
Arg Leu Lys Leu Ile Met Pro Ala Arg Phe Tyr Pro Asn Val Thr Lys
1 5 10 15

Tyr Leu Pro Leu
20

<210> 83
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 83
Ala Arg Phe Tyr Pro Asn Val Thr Lys Tyr Leu Pro Leu Asp Lys Gly
1 5 10 15

Ile Lys Pro Tyr
20

<210> 84
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 84
Thr Lys Tyr Leu Pro Leu Asp Lys Gly Ile Lys Pro Tyr Tyr Pro Glu
1 5 10 15

His Val Val

<210> 85
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 85
Asp Lys Gly Ile Lys Pro Tyr Tyr Pro Glu His Val Val Asn His Tyr
1 5 10 15

Phe Gln Thr Arg
20

<210> 86
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 86
Tyr Pro Glu His Val Val Asn His Tyr Phe Gln Thr Arg His Tyr Leu
1 5 10 15

His Thr Leu

<210> 87
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 87
Asn His Tyr Phe Gln Thr Arg His Tyr Leu His Thr Leu Trp Lys Ala
1 5 10 15

Gly Ile Leu Tyr

20

<210> 88
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 88
Arg His Tyr Leu His Thr Leu Trp Lys Ala Gly Ile Leu Tyr Lys Arg
1 5 10 15

Glu Thr Thr Arg
20

<210> 89
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 89
Trp Lys Ala Gly Ile Leu Tyr Lys Arg Glu Thr Thr Arg Ser Ala Ser
1 5 10 15

Phe Cys Gly Ser
20

<210> 90
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 90
Arg Glu Thr Thr Arg Ser Ala Ser Phe Cys Gly Ser Pro Tyr Ser Trp
1 5 10 15

Glu Gln Glu Leu
20

<210> 91
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 91
Ser Phe Cys Gly Ser Pro Tyr Ser Trp Glu Gln Glu Leu Gln Ser Cys
1 5 10 15

```
Trp Trp Leu Gln
            20
```

<210> 92
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 92

```
Cys Thr Glu His Gly Glu His His Ile Arg Ile Pro Arg Thr Pro Ala
1               5                   10                  15

Arg Val
```

<210> 93
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 93

```
His His Ile Arg Ile Pro Arg Thr Pro Ala Arg Val Thr Gly Gly Val
1               5                   10                  15

Phe Leu Val
```

<210> 94
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 94

```
Arg Thr Pro Ala Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn
1               5                   10                  15

Pro His Asn
```

<210> 95
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 95

```
Thr Gly Gly Val Phe Leu Val Asp Lys Asn Pro His Asn Thr Thr Glu
1               5                   10                  15

Ser Arg Leu Val
            20
```

<210> 96
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 96
```
Asp Lys Asn Pro His Asn Thr Thr Glu Ser Arg Leu Val Val Asp Phe
1               5                   10                  15

Ser Gln Phe Ser
            20
```

<210> 97
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 97
```
Thr Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Asn
1               5                   10                  15

Thr Arg Val
```

<210> 98
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 98
```
Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser
1               5                   10                  15

Asn Leu Ser Trp
            20
```

<210> 99
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 99
```
Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu Ser
1               5                   10                  15

Leu Asp Val
```

<210> 100
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 100
Leu Leu Ser Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala
1 5 10 15

Phe Tyr

<210> 101
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 101
Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Ile Pro
1 5 10 15

Leu His Pro Ala

20

<210> 102
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 102
Val Ser Ala Ala Phe Tyr His Ile Pro Leu His Pro Ala Ala Met Pro
1 5 10 15

His Leu Leu Val
20

<210> 103
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 103
Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly Ser Ser Gly Leu
1 5 10 15

Ser Arg Tyr

<210> 104
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 104
His Leu Leu Val Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu
1 5 10 15

Ser Ser Asn Ser Arg Ile
20

<210> 105
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 105
Gly Thr Met Gln Asn Leu His Asp Ser Cys Ser Arg Asn Leu Tyr Val
1 5 10 15

Ser Leu Met Leu
20

<210> 106
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 106
Asp Ser Cys Ser Arg Asn Leu Tyr Val Ser Leu Met Leu Leu Tyr Lys
1 5 10 15

Thr Tyr Gly Arg
20

<210> 107
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 107
Tyr Val Ser Leu Met Leu Leu Tyr Lys Thr Tyr Gly Arg Lys Leu His
1 5 10 15

Leu Tyr Ser His
20

<210> 108
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 108
Tyr Lys Thr Tyr Gly Arg Lys Leu His Leu Tyr Ser His Pro Ile Ile
1 5 10 15

Leu Gly Phe Arg

<210> 109
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 109
```
Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile
1               5                   10                  15

Pro Met Gly Val
            20
```

<210> 110
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 110
```
Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser
1               5                   10                  15

Pro Phe Leu
```

<210> 111
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 111
```
Arg Lys Ile Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln
1               5                   10                  15

Phe Thr Ser Ala
            20
```

<210> 112
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> C OR S

<400> 112
```
Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Xaa Ser
1               5                   10                  15
```

Val Val Arg Arg
20

<210> 113
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 113
Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Val Arg Arg Ala
1 5 10 15

Phe Pro His

<210> 114
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 114
Ser Ala Ile Cys Ser Val Val Arg Arg Ala Phe Pro His Cys Leu Ala
1 5 10 15

Phe Ser Tyr Met
20

<210> 115
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 115
Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val Val
1 5 10 15

Leu Gly Ala

<210> 116
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 116
Leu Ala Phe Ser Tyr Met Asp Asp Val Val Leu Gly Ala Lys Ser Val
1 5 10 15

Gln His Leu

<210> 117
<211> 19
<212> PRT

<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 117
```
Tyr Met Asp Asp Val Val Leu Gly Ala Lys Ser Val Gln His Leu Glu
1               5                   10                  15

Ser Leu Tyr
```

<210> 118
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 118
```
Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Tyr Thr Ala Val
1               5                   10                  15

Thr Asn Phe Leu
            20
```

<210> 119
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 119
```
His Leu Glu Ser Leu Tyr Thr Ala Val Thr Asn Phe Leu Leu Ser Leu
1               5                   10                  15

Gly Ile His Leu
            20
```

<210> 120
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 120
```
Ala Val Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn
1               5                   10                  15

Lys Thr Lys Arg
            20
```

<210> 121
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 121
Ser Leu Gly Ile His Leu Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr
1 5 10 15

Ser Leu Asn Phe
20

<210> 122
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 122
His Leu Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe
1 5 10 15

Met Gly Tyr Val
20

<210> 123
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 123
Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val Ile Gly Ser
1 5 10 15

Trp Gly Thr Leu
20

<210> 124
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 124
Lys Ile Lys Gln Cys Phe Arg Lys Leu Pro Val Asn Arg Pro Ile Asp
1 5 10 15

Trp Lys

<210> 125
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 125
Phe Arg Lys Leu Pro Val Asn Arg Pro Ile Asp Trp Lys Val Cys Gln
1 5 10 15

```
Arg Ile Val Gly
            20
```

<210> 126

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 126

```
Arg Pro Ile Asp Trp Lys Val Cys Gln Arg Ile Val Gly Leu Leu Gly
1               5                   10                  15

Phe Ala Ala
```

<210> 127

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 127

```
Val Cys Gln Arg Ile Val Gly Leu Leu Gly Phe Ala Ala Pro Phe Thr
1               5                   10                  15

Gln Cys Gly Tyr
            20
```

<210> 128

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 128

```
Gly Leu Leu Gly Phe Ala Ala Pro Phe Thr Gln Cys Gly Tyr Pro Ala
1               5                   10                  15

Leu Met Pro Leu
            20
```

<210> 129

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> HBV CONSENSUS SEQUENCE

<400> 129

```
Phe Thr Gln Cys Gly Tyr Pro Ala Leu Met Pro Leu Tyr Ala Cys Ile
1               5                   10                  15

Gln Ala Lys
```

<210> 130

<211> 20

<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 130
Ala Leu Met Pro Leu Tyr Ala Cys Ile Gln Ala Lys Gln Ala Phe Thr
1 5 10 15

Phe Ser Pro Thr
20

<210> 131
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 131
Ile Gln Ala Lys Gln Ala Phe Thr Phe Ser Pro Thr Tyr Lys Ala Phe
1 5 10 15

Leu Cys Lys

<210> 132
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 132
Phe Thr Phe Ser Pro Thr Tyr Lys Ala Phe Leu Cys Lys Gln Tyr Leu
1 5 10 15

Asn Leu Tyr

<210> 133
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 133
Tyr Lys Ala Phe Leu Cys Lys Gln Tyr Leu Asn Leu Tyr Pro Val Ala
1 5 10 15

Arg Gln Arg

<210> 134
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 134
Lys Gln Tyr Leu Asn Leu Tyr Pro Val Ala Arg Gln Arg Pro Gly Leu
1 5 10 15

Cys Gln Val

<210> 135
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 135
Tyr Pro Val Ala Arg Gln Arg Pro Gly Leu Cys Gln Val Phe Ala Asp
1 5 10 15

Ala Thr Pro Thr
20

<210> 136
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 136
Gly Leu Cys Gln Val Phe Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu
1 5 10 15

Ala Ile

<210> 137
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 137
Phe Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu Ala Ile Gly His Gln
1 5 10 15

Arg Met Arg

<210> 138
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 138
Gly Trp Gly Leu Ala Ile Gly His Gln Arg Met Arg Gly Thr Phe Val
1 5 10 15

Ala Pro Leu

<210> 139
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 139
```
Gly His Gln Arg Met Arg Gly Thr Phe Val Ala Pro Leu Pro Ile His
1               5                   10                  15

Thr Ala Glu Leu
            20
```

<210> 140
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 140
```
Phe Val Ala Pro Leu Pro Ile His Thr Ala Glu Leu Leu Ala Ala Cys
1               5                   10                  15

Phe Ala Arg Ser
            20
```

<210> 141
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 141
```
His Thr Ala Glu Leu Leu Ala Ala Cys Phe Ala Arg Ser Arg Ser Gly
1               5                   10                  15

Ala Lys Leu Ile
            20
```

<210> 142
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 142
```
Ala Cys Phe Ala Arg Ser Arg Ser Gly Ala Lys Leu Ile Gly Thr Asp
1               5                   10                  15

Asn Ser Val Val
            20
```

<210> 143
<211> 20
<212> PRT

<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 143
```
Gly Ala Lys Leu Ile Gly Thr Asp Asn Ser Val Val Leu Ser Arg Lys
1               5                   10                  15

Tyr Thr Ser Phe
            20
```

<210> 144
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 144
```
Asp Asn Ser Val Val Leu Ser Arg Lys Tyr Thr Ser Phe Pro Trp Leu
1               5                   10                  15

Leu Gly Cys Ala
            20
```

<210> 145
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 145
```
Arg Lys Tyr Thr Ser Phe Pro Trp Leu Leu Gly Cys Ala Ala Asn Trp
1               5                   10                  15

Ile Leu
```

<210> 146
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 146
```
Phe Pro Trp Leu Leu Gly Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr
1               5                   10                  15

Ser Phe Val
```

<210> 147
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 147
Ala Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe Val Tyr Val Pro Ser
1 5 10 15

Ala Leu Asn

<210> 148
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 148
Ile Leu Arg Gly Thr Ser Phe Val Tyr Val Pro Ser Ala Leu Asn Pro
1 5 10 15

Ala Asp Asp Pro Ser
20

<210> 149
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 149
Tyr Val Pro Ser Ala Leu Asn Pro Ala Asp Asp Pro Ser Arg Gly Arg
1 5 10 15

Leu Gly Leu Tyr
20

<210> 150
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 150
Pro Ala Asp Asp Pro Ser Arg Gly Arg Leu Gly Leu Tyr Arg Pro Leu
1 5 10 15

Leu Arg Leu

<210> 151
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 151
Arg Leu Gly Leu Tyr Arg Pro Leu Leu Arg Leu Pro Phe Arg Pro Thr
1 5 10 15

Thr Gly Arg

<210> 152
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 152
```
Pro Leu Leu Arg Leu Pro Phe Arg Pro Thr Thr Gly Arg Thr Ser Leu
1               5                   10                  15

Tyr Ala Val
```

<210> 153
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 153
```
Phe Arg Pro Thr Thr Gly Arg Thr Ser Leu Tyr Ala Val Ser Pro Ser
1               5                   10                  15

Val
```

<210> 154
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 154
```
Thr Thr Gly Arg Thr Ser Leu Tyr Ala Val Ser Pro Ser Val Pro Ser
1               5                   10                  15

His Leu
```

<210> 155
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 155
```
Ser Leu Tyr Ala Val Ser Pro Ser Val Pro Ser His Leu Pro Asp Arg
1               5                   10                  15

Val His Phe Ala
            20
```

<210> 156
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 156
Ser Val Pro Ser His Leu Pro Asp Arg Val His Phe Ala Ser Pro Leu
1 5 10 15

His Val Ala Trp Arg
20

<210> 157
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 157
Met Gln Leu Phe His Leu Cys Leu Ile Ile Ser Cys Ser Cys Pro Thr
1 5 10 15

Val Gln Ala

<210> 158
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 158
Leu Ile Ile Ser Cys Ser Cys Pro Thr Val Gln Ala Ser Lys Leu Cys
1 5 10 15

Leu Gly Trp

<210> 159
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 159
Cys Pro Thr Val Gln Ala Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly
1 5 10 15

Met Asp Ile

<210> 160
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 160
Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly Met Asp Ile Asp Pro Tyr
1 5 10 15

Lys Glu Phe

<210> 161
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 161
Trp Leu Trp Gly Met Asp Ile Asp Pro Tyr Lys Glu Phe Gly Ala Ser
1 5 10 15

Val Glu Leu Leu
20

<210> 162
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 162
Ile Asp Pro Tyr Lys Glu Phe Gly Ala Ser Val Glu Leu Leu Ser Phe
1 5 10 15

Leu Pro Ser Asp
20

<210> 163
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 163
Lys Glu Phe Gly Ala Ser Val Glu Leu Leu Ser Phe Leu Pro Ser Asp
1 5 10 15

Phe Phe Pro Ser Val
20

<210> 164
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 164
Glu Leu Leu Ser Phe Leu Pro Ser Asp Phe Phe Pro Ser Val Arg Asp
1 5 10 15

Leu Leu

<210> 165

<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 165
```
Phe Leu Pro Ser Asp Phe Phe Pro Ser Val Arg Asp Leu Leu Asp Thr
1               5                   10                  15

Ala Ser Ala Leu Tyr
            20
```

<210> 166
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 166
```
Ser Val Arg Asp Leu Leu Asp Thr Ala Ser Ala Leu Tyr Arg Glu Ala
1               5                   10                  15

Leu Glu Ser
```

<210> 167
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 167
```
Asp Thr Ala Ser Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His
1               5                   10                  15

Cys Ser Pro His
            20
```

<210> 168
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 168
```
Arg Glu Ala Leu Glu Ser Pro Glu His Cys Ser Pro His His Thr Ala
1               5                   10                  15

Leu Arg Gln Ala
            20
```

<210> 169
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 169
His Cys Ser Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Cys Trp
1 5 10 15

Gly Glu Leu Met
20

<210> 170
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 170
Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu Leu Met Thr Leu Ala
1 5 10 15

Thr Trp Val

<210> 171
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 171
Trp Gly Glu Leu Met Thr Leu Ala Thr Trp Val Gly Ser Asn Leu Glu
1 5 10 15

Asp Pro Ala Ser
20

<210> 172
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 172
Ala Ser Arg Asp Leu Val Val Ser Tyr Val Asn Thr Asn Met Gly Leu
1 5 10 15

Lys Ile Arg

<210> 173
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 173
Ser Tyr Val Asn Thr Asn Met Gly Leu Lys Ile Arg Gln Leu Leu Trp
1 5 10 15

```
1               5                   10                  15

Phe His Ile Ser
            20
```

<210> 174
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 174

```
Gly Leu Lys Ile Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr
1               5                   10                  15

Phe Gly Arg
```

<210> 175
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 175

```
Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly Arg Glu Thr Val
1               5                   10                  15

Leu Glu Tyr Leu
            20
```

<210> 176
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 176

```
Cys Leu Thr Phe Gly Arg Glu Thr Val Leu Glu Tyr Leu Val Ser Phe
1               5                   10                  15

Gly Val Trp Ile
            20
```

<210> 177
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 177

```
Thr Val Leu Glu Tyr Leu Val Ser Phe Gly Val Trp Ile Arg Thr Pro
1               5                   10                  15

Pro Ala Tyr Arg
            20
```

<210> 178
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 178
```
Ser Phe Gly Val Trp Ile Arg Thr Pro Pro Ala Tyr Arg Pro Pro Asn
1               5                   10                  15

Ala Pro Ile Leu
            20
```

<210> 179
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 179
```
Thr Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu
1               5                   10                  15

Pro Glu Thr Thr
            20
```

<210> 180
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 180
```
Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro Glu Thr Thr Val Val Arg
1               5                   10                  15

Arg Arg Gly Arg
            20
```

<210> 181
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 181
```
Thr Leu Pro Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser Pro Arg
1               5                   10                  15

Arg Arg Thr
```

<210> 182
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 182
```
Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg Thr Pro Ser Pro
1               5                   10                  15

Arg Arg Arg Arg
            20
```

<210> 183
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 183
```
Ser Pro Arg Arg Arg Thr Pro Ser Pro Arg Arg Arg Arg Ser Gln Ser
1               5                   10                  15

Pro Arg Arg Arg
            20
```

<210> 184
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 184
```
Ser Pro Arg Arg Arg Arg Ser Gln Ser Pro Arg Arg Arg Arg Ser Gln
1               5                   10                  15

Ser Arg Glu Ser
            20
```

<210> 185
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 185
```
His Leu Ser Leu Arg Gly Leu Pro Val Cys Ala Phe Ser Ser Ala Gly
1               5                   10                  15

Pro Cys Ala Leu
            20
```

<210> 186
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 186
Leu Pro Val Cys Ala Phe Ser Ser Ala Gly Pro Cys Ala Leu Arg Phe
1 5 10 15

Thr Ser Ala Arg
20

<210> 187
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 187
Ser Ala Gly Pro Cys Ala Leu Arg Phe Thr Ser Ala Arg Arg Met Glu
1 5 10 15

Thr Thr Val

<210> 188
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 188
Leu Arg Phe Thr Ser Ala Arg Arg Met Glu Thr Thr Val Asn Ala His
1 5 10 15

Gln Ile Leu

<210> 189
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 189
Arg Arg Met Glu Thr Thr Val Asn Ala His Gln Ile Leu Pro Lys Val
1 5 10 15

Leu His Lys Arg
20

<210> 190
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 190
Asn Ala His Gln Ile Leu Pro Lys Val Leu His Lys Arg Thr Leu Gly
1 5 10 15

Leu Ser Ala Met
20

<210> 191
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 191
Lys Val Leu His Lys Arg Thr Leu Gly Leu Ser Ala Met Ser Thr Thr
1 5 10 15

Asp Leu Glu Ala
20

<210> 192
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 192
Leu Gly Leu Ser Ala Met Ser Thr Thr Asp Leu Glu Ala Tyr Phe Lys
1 5 10 15

Asp Cys Val Phe
20

<210> 193
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 193
Thr Thr Asp Leu Glu Ala Tyr Phe Lys Asp Cys Val Phe Lys Asp Trp
1 5 10 15

Glu Glu Leu

<210> 194
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 194
Tyr Phe Lys Asp Cys Val Phe Lys Asp Trp Glu Glu Leu Gly Glu Glu
1 5 10 15

Ile Arg Leu

<210> 195
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 195
```
Phe Lys Asp Trp Glu Glu Leu Gly Glu Glu Ile Arg Leu Lys Val Phe
1               5                   10                  15

Val Leu
```

<210> 196
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 196
```
Glu Leu Gly Glu Glu Ile Arg Leu Lys Val Phe Val Leu Gly Gly Cys
1               5                   10                  15

Arg His Lys Leu
            20
```

<210> 197
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 197
```
Leu Lys Val Phe Val Leu Gly Gly Cys Arg His Lys Leu Val Cys Ser
1               5                   10                  15

Pro Ala Pro Cys
            20
```

<210> 198
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 198
```
Arg Gln Pro Thr Pro Ile Ser Pro Pro Leu Arg Asp Ser His Pro Gln
1               5                   10                  15

Ala Met Gln Trp
            20
```

<210> 199
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 199
Pro Pro Leu Arg Asp Ser His Pro Gln Ala Met Gln Trp Asn Ser Thr
1 5 10 15

Thr Phe His

<210> 200
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 200
His Pro Gln Ala Met Gln Trp Asn Ser Thr Thr Phe His Gln Ala Leu
1 5 10 15

Gln Asp Pro Arg
20

<210> 201
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 201
Ser Thr Thr Phe His Gln Ala Leu Gln Asp Pro Arg Val Arg Gly Leu
1 5 10 15

Tyr Phe Pro Ala
20

<210> 202
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 202
Leu Gln Asp Pro Arg Val Arg Gly Leu Tyr Phe Pro Ala Gly Gly Ser
1 5 10 15

Ser Ser Gly

<210> 203
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 203
Arg Gly Leu Tyr Phe Pro Ala Gly Gly Ser Ser Ser Gly Thr Val Asn
1 5 10 15

Pro Ala Pro Thr
20

<210> 204
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 204
Pro Asn Met Glu Asn Ile Thr Ser Gly Phe Leu Gly Pro Leu Leu Val
1 5 10 15

Leu Gln Ala

<210> 205
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 205
Thr Ser Gly Phe Leu Gly Pro Leu Leu Val Leu Gln Ala Gly Phe Phe
1 5 10 15

Leu Leu Thr Lys
20

<210> 206
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 206
Leu Leu Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Lys Ile Leu Thr
1 5 10 15

Ile

<210> 207
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 207
Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Lys Ile Leu Thr Ile Pro
1 5 10 15

Gln Ser Leu

<210> 208
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 208
Phe Leu Leu Thr Lys Ile Leu Thr Ile Pro Gln Ser Leu Asp Ser Trp
1 5 10 15

Trp Thr Ser Leu
20

<210> 209
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 209
Thr Ile Pro Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu
1 5 10 15

Gly Gly Thr Pro Val
20

<210> 210
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 210
Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Thr Pro Val Cys Leu Gly
1 5 10 15

Gln Asn Ser Gln
20

<210> 211
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 211
Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile Ile Phe Leu Phe
1 5 10 15

Ile Leu Leu Leu
20

<210> 212
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 212
Leu Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile
1 5 10 15

Phe Leu Leu Val
20

<210> 213
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 213
Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val Leu Leu Asp Tyr
1 5 10 15

Gln Gly Met Leu
20

<210> 214
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 214
Ile Pro Ile Pro Ser Ser Trp Ala Phe Gly Lys Tyr Leu Trp Glu Trp
1 5 10 15

Ala Ser Ala Arg
20

<210> 215
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 215
Ala Phe Gly Lys Tyr Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp
1 5 10 15

Leu Ser Leu Leu
20

<210> 216
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 216
Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu Ser Leu Leu Val Pro Phe
1 5 10 15

```
Val Gln Trp Phe
            20
```

<210> 217
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 217
```
Ser Trp Leu Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu
1               5                   10                  15

Ser Pro Thr Val
            20
```

<210> 218
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 218
```
Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu Ser
1               5                   10                  15

Val Ile Trp Met
            20
```

<210> 219
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 219
```
Gly Leu Ser Pro Thr Val Trp Leu Ser Val Ile Trp Met Met Trp Tyr
1               5                   10                  15

Trp Gly Pro Ser Leu
            20
```

<210> 220
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 220
```
Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser
1               5                   10                  15

Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Ile
            20                  25                  30

Pro Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly Ser Ser Gly
        35                  40                  45
```

```
Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Asn Ser Arg Ile
    50                  55                  60
```

<210> 221
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 221

```
Gly Pro Leu Leu Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Arg Ile
1               5                   10                  15

Leu Thr Ile Pro Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe
            20                  25                  30

Leu
```

<210> 222
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> HBV CONSENSUS SEQUENCE

<400> 222

```
Lys Lys Lys Gly Pro Leu Leu Val Leu Gln Ala Gly Phe Phe Leu Leu
1               5                   10                  15

Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu Asp Ser Trp Trp Thr Ser
            20                  25                  30

Leu Asn Phe Leu Lys Lys Lys
        35
```

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO0219986A [0006]
- WO2012090002A [0060]
- GB1223386A [0140]

Non-patent literature cited in the description

- **LUND et al.**Immunogenetics, 2004, vol. 55, 12797-810 [0033] [0035]
- **SETTE et al.**Immunogenetics, 1999, vol. 50, 3-4201-212 [0033]
- **TEXIER et al.**J Immunol, 2000, vol. 164, 3177-3184 [0034]
- **TEXIER et al.**Eur J Immunol, 2001, vol. 31, 1837-1846 [0034]
- **CASTELLI et al.**J Immunol, 2002, vol. 169, 6928-6934 [0034]
- **GREENBAUM et al.**Immunogenetics, 2011, vol. 63, 6325-35 [0035]
- **WILSON et al.**J Virol, 2001, vol. 75, 94195-4207 [0035]

PATENTKRAV

1. Farmaceutisk sammensætning til anvendelse i behandling eller forebyggelse af HBV-infektion, hvilken sammensætning omfatter:

et første peptid, der omfatter eller består af aminosyresekvens vist i SEQ ID NO: 24,

et andet peptid, der omfatter eller består af aminosyresekvens vist i SEQ ID NO: 25,

et tredje peptid, der omfatter eller består af aminosyresekvens vist i SEQ ID NO: 28,

et fjerde peptid, der omfatter eller består af aminosyresekvens vist i SEQ ID NO: 33,

et femte peptid, der omfatter eller består af aminosyresekvens vist i SEQ ID NO: 34,

et sjette peptid, der omfatter eller består af aminosyresekvens vist i SEQ ID NO: 36,

et syvende peptid, der omfatter eller består af aminosyresekvens vist i SEQ ID NO: 37,

et ottende peptid, der omfatter eller består af aminosyresekvens vist i SEQ ID NO: 38, og

et niende peptid, der omfatter eller består af aminosyresekvens vist i SEQ ID NO: 222,

hvor hvert peptid er op til 60 aminosyrer i længden.

2. Sammensætning ifølge krav 1, hvor hver af det første, andet, tredje, fjerde, femte, sjette, syvende, ottende og niende peptid er bundet til en fluorcarbonvektor.

3. Sammensætning ifølge et hvilket som helst af de foregående krav, der endvidere omfatter et adjuvans.

4. Sammensætning ifølge et hvilket som helst af de foregående krav, hvor hver af det første, andet, tredje, fjerde, femte, sjette, syvende, ottende og niende peptid består af aminosyresekvenserne vist i henholdsvis SEQ ID NO: 24, 25, 28, 33, 34, 36, 37, 38 og 222.

DRAWINGS

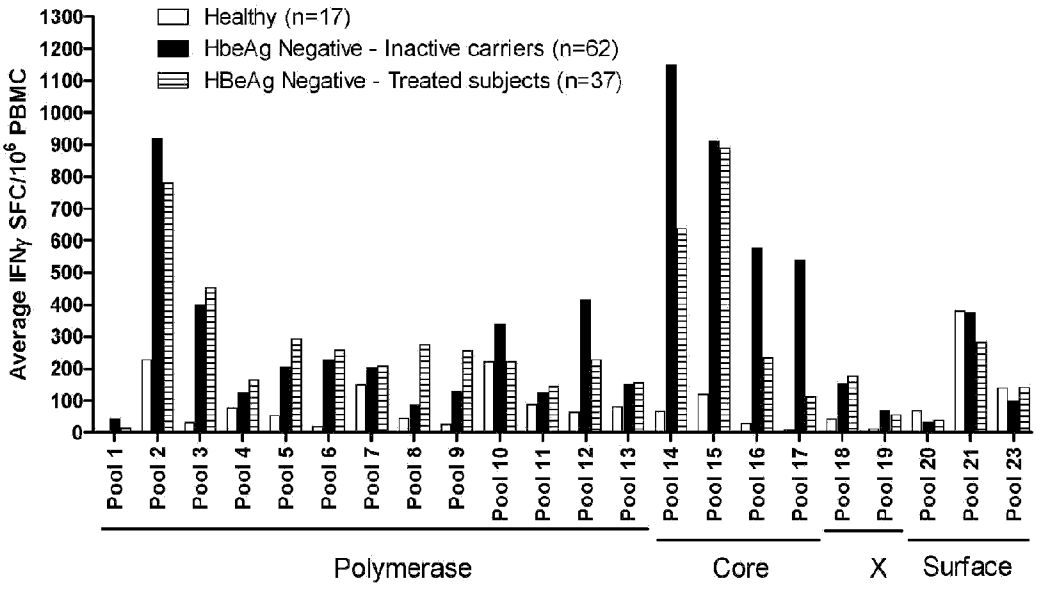

Figure 1

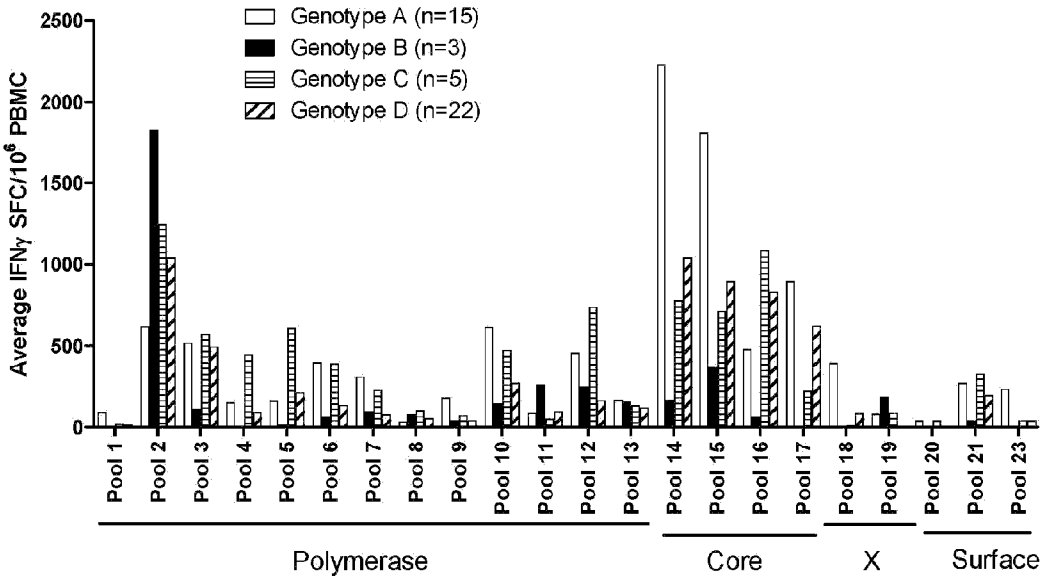
Genotype A (n=15)
Genotype B (n=3)
Genotype C (n=5)
Genotype D (n=22)
Average IFNγ SFC/10^6 PBMC
2500
2000
1500
1000
500
0
Pool 1
Pool 2
Pool 3
Pool 4
Pool 5
Pool 6
Pool 7
Pool 8
Pool 9
Pool 10
Pool 11
Pool 12
Pool 13
Pool 14
Pool 15
Pool 16
Pool 17
Pool 18
Pool 19
Pool 20
Pool 21
Pool 23
Polymerase
Core
X
Surface

Figure 2

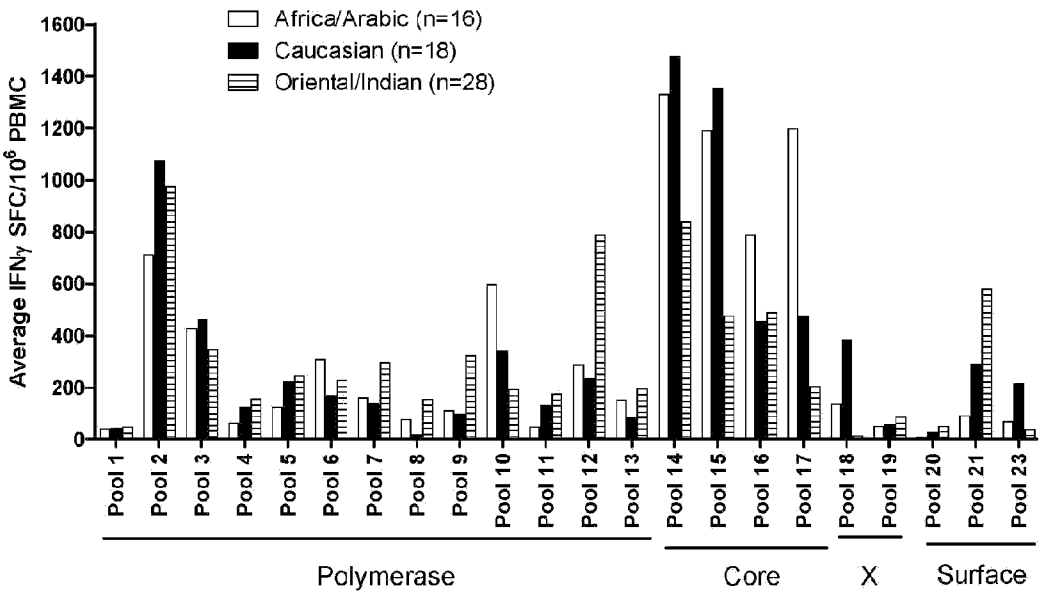
Africa/Arabic (n=16)
Caucasian (n=18)
Oriental/Indian (n=28)
Average IFNγ SFC/10^6 PBMC
1600
1400
1200
1000
800
600
400
200
0
Pool 1
Pool 2
Pool 3
Pool 4
Pool 5
Pool 6
Pool 7
Pool 8
Pool 9
Pool 10
Pool 11
Pool 12
Pool 13
Pool 14
Pool 15
Pool 16
Pool 17
Pool 18
Pool 19
Pool 20
Pool 21
Pool 23
Polymerase
Core
X
Surface

Figure 3

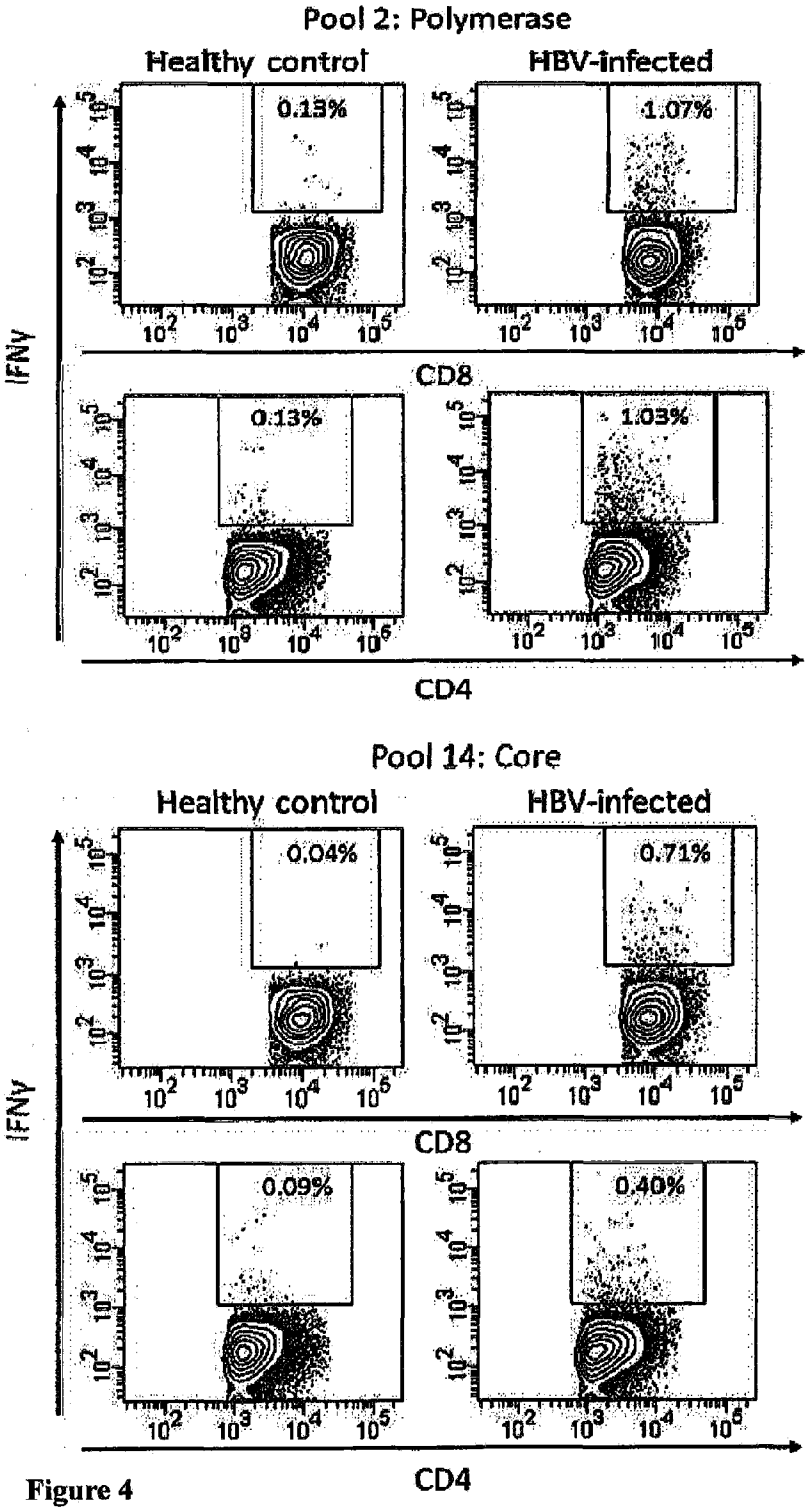
Pool 2: Polymerase
Healthy control
HBV-infected
0.13%
1.07%
IFNγ
CD8
0.13%
1.03%
CD4
Pool 14: Core
Healthy control
HBV-infected
0.04%
0.71%
IFNγ
CD8
0.09%
0.40%
CD4

Figure 4

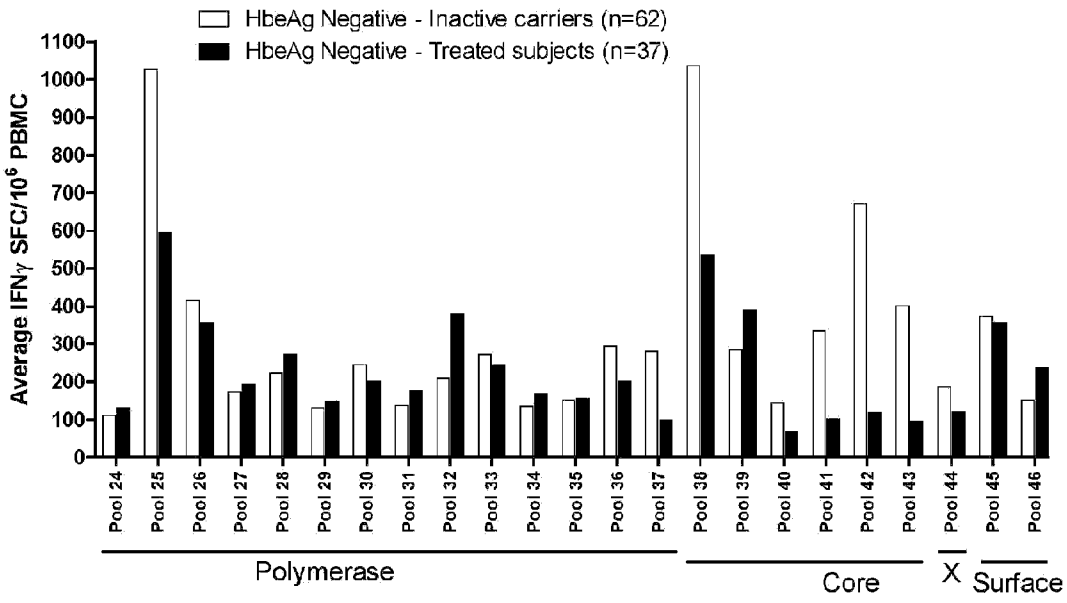
HbeAg Negative - Inactive carriers (n=62)
HbeAg Negative - Treated subjects (n=37)
Average IFNγ SFC/10^6 PBMC
1100
1000
900
800
700
600
500
400
300
200
100
0
Pool 24
Pool 25
Pool 26
Pool 27
Pool 28
Pool 29
Pool 30
Pool 31
Pool 32
Pool 33
Pool 34
Pool 35
Pool 36
Pool 37
Pool 38
Pool 39
Pool 40
Pool 41
Pool 42
Pool 43
Pool 44
Pool 45
Pool 46
Polymerase
Core
X
Surface

Figure 5

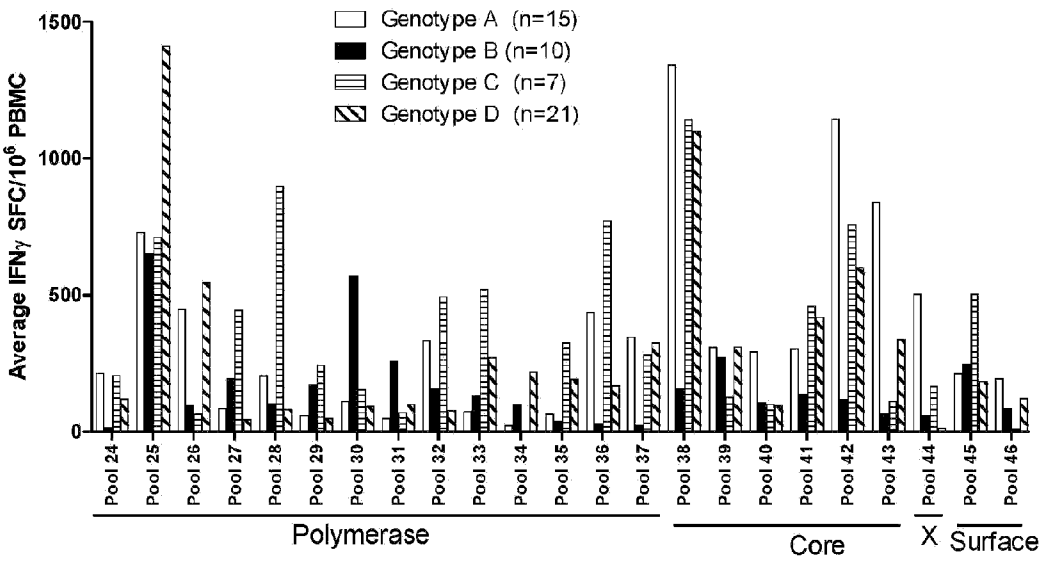
Genotype A (n=15)
Genotype B (n=10)
Genotype C (n=7)
Genotype D (n=21)
Average IFNγ SFC/10^6 PBMC
1500
1000
500
0
Pool 24
Pool 25
Pool 26
Pool 27
Pool 28
Pool 29
Pool 30
Pool 31
Pool 32
Pool 33
Pool 34
Pool 35
Pool 36
Pool 37
Pool 38
Pool 39
Pool 40
Pool 41
Pool 42
Pool 43
Pool 44
Pool 45
Pool 46
Polymerase
Core
X
Surface

Figure 6

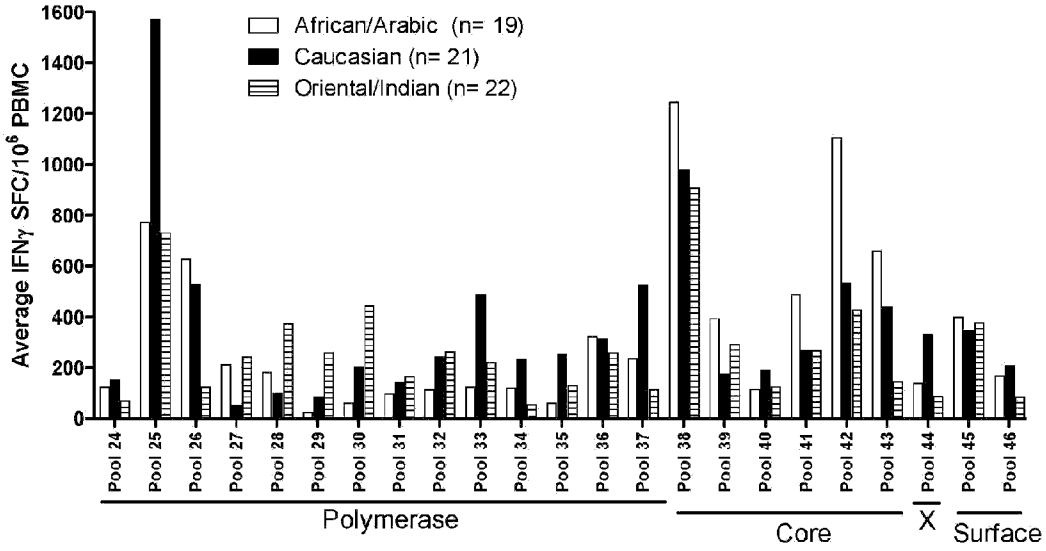
African/Arabic (n= 19)
Caucasian (n= 21)
Oriental/Indian (n= 22)
Average IFNγ SFC/10^6 PBMC
1600
1400
1200
1000
800
600
400
200
0
Pool 24
Pool 25
Pool 26
Pool 27
Pool 28
Pool 29
Pool 30
Pool 31
Pool 32
Pool 33
Pool 34
Pool 35
Pool 36
Pool 37
Pool 38
Pool 39
Pool 40
Pool 41
Pool 42
Pool 43
Pool 44
Pool 45
Pool 46
Polymerase
Core
X
Surface

Figure 7

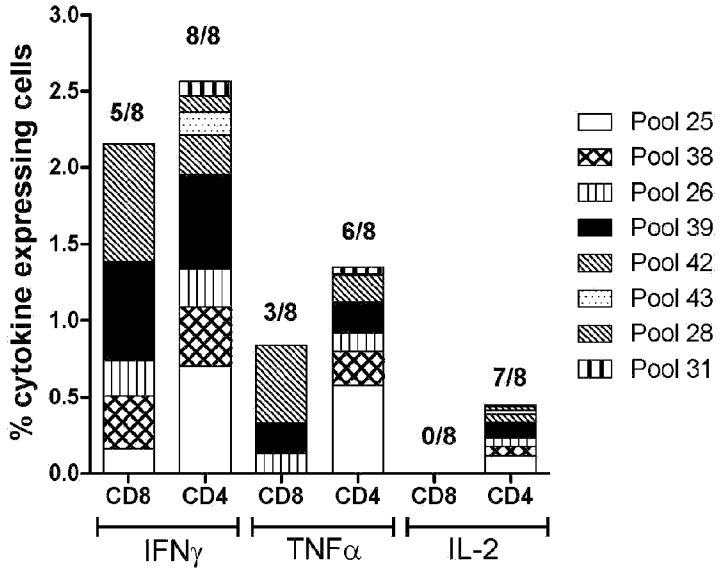
% cytokine expressing cells
3.0
2.5
2.0
1.5
1.0
0.5
0.0
5/8
8/8
3/8
6/8
0/8
7/8
CD8
CD4
CD8
CD4
CD8
CD4
IFNγ
TNFα
IL-2
Pool 25
Pool 38
Pool 26
Pool 39
Pool 42
Pool 43
Pool 28
Pool 31

Figure 8

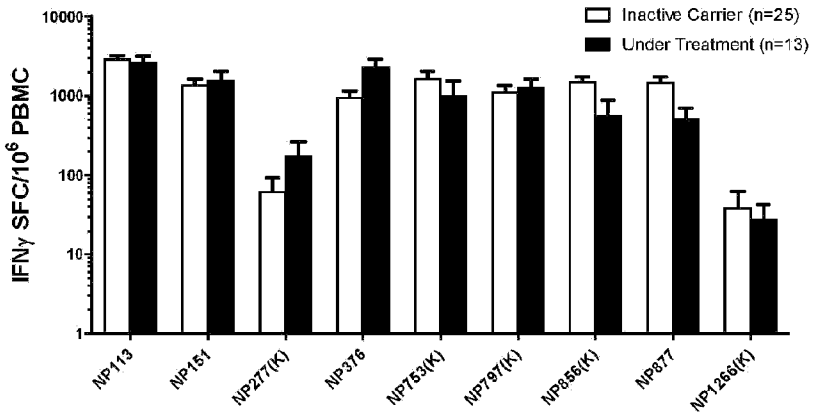

Figure 9

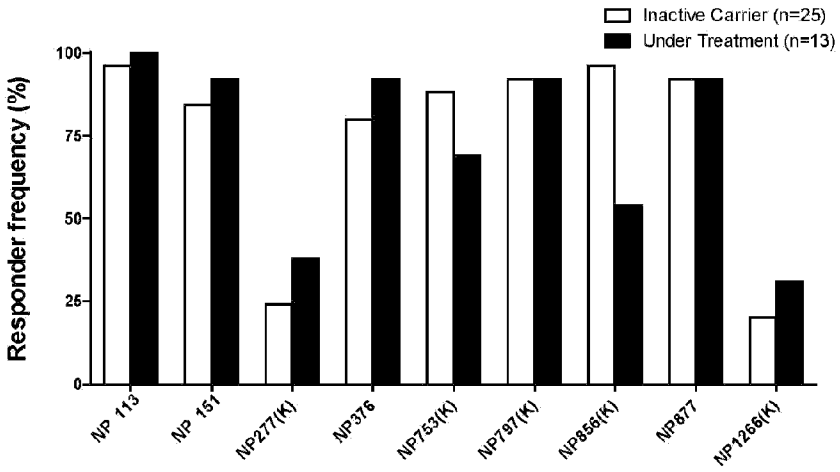

Figure 10

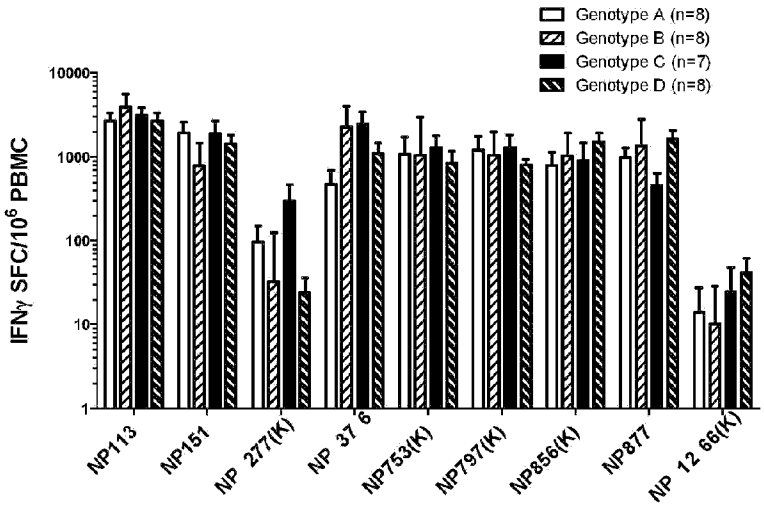

Figure 11

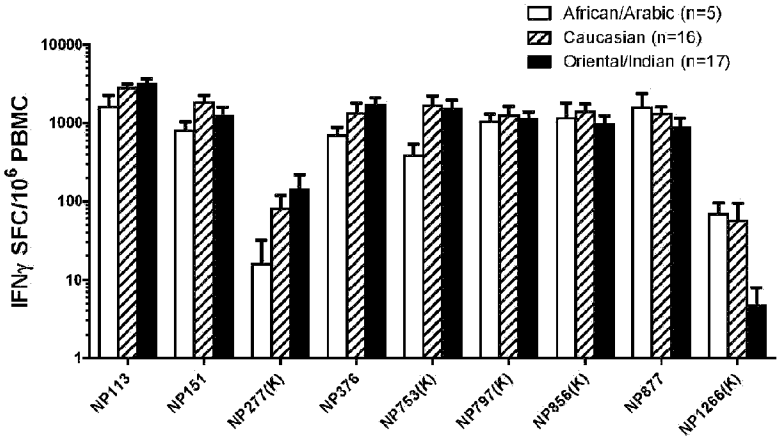

Figure 12

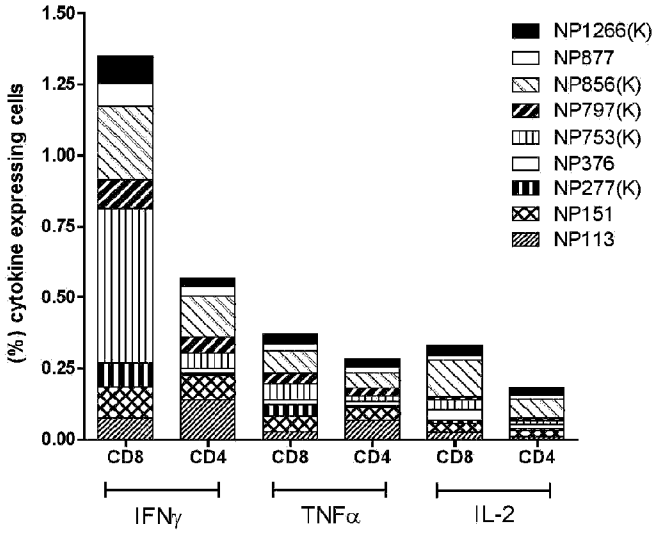

Figure 13A

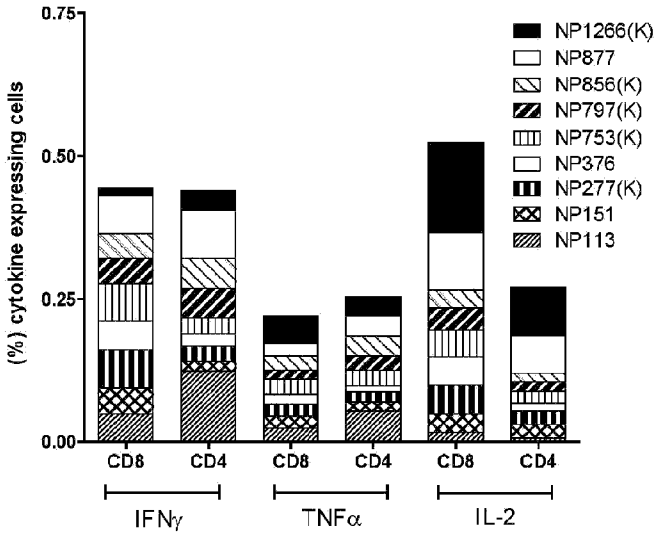

Figure 13B

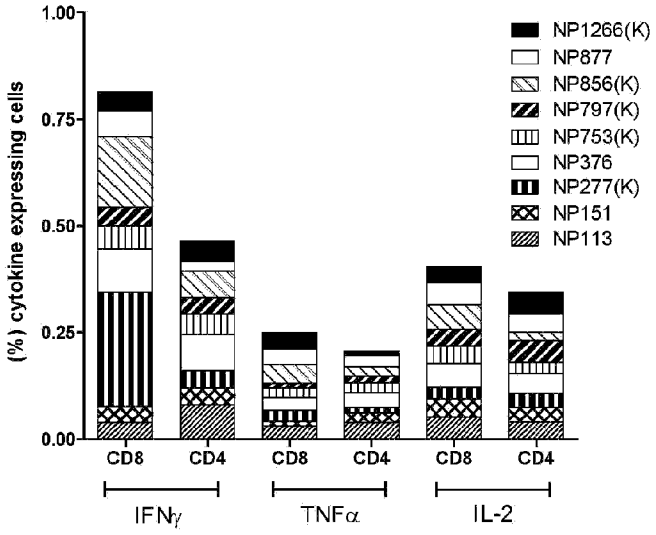

Figure 13C

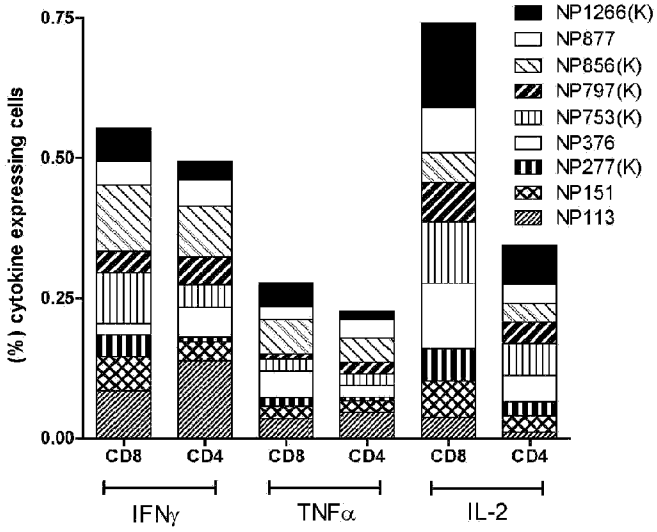

Figure 13D

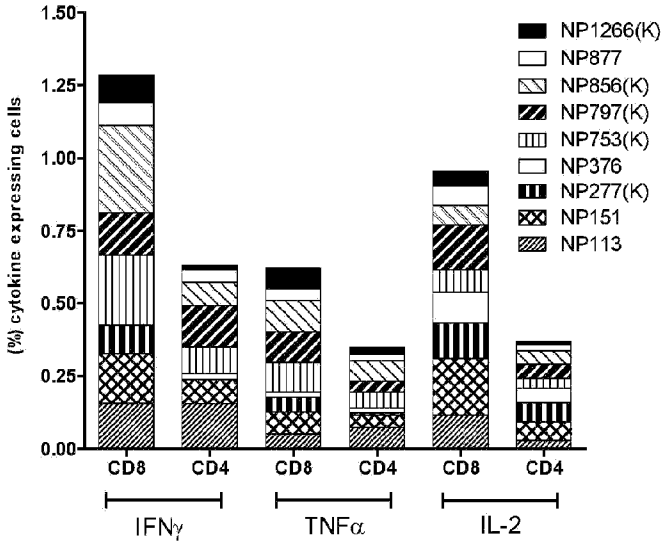

Figure 13E

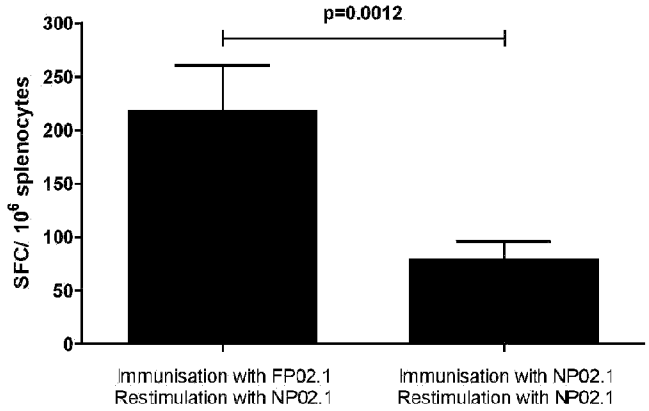

Figure 14

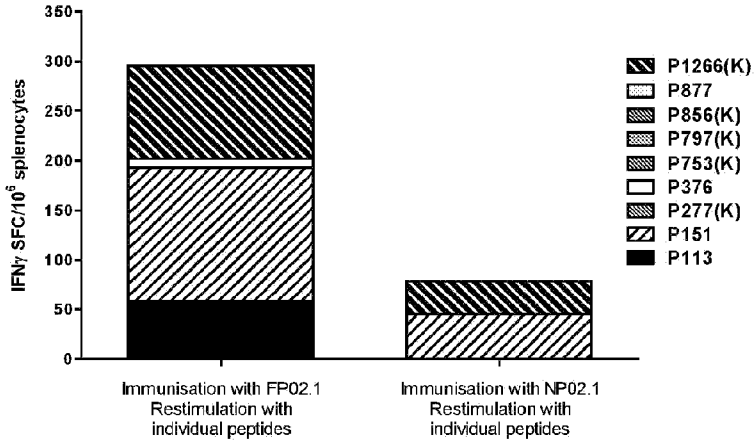

Figure 15

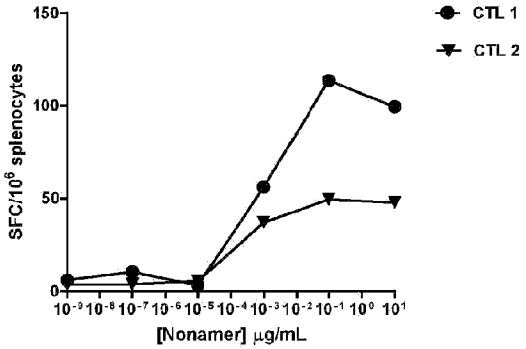

Figure 16

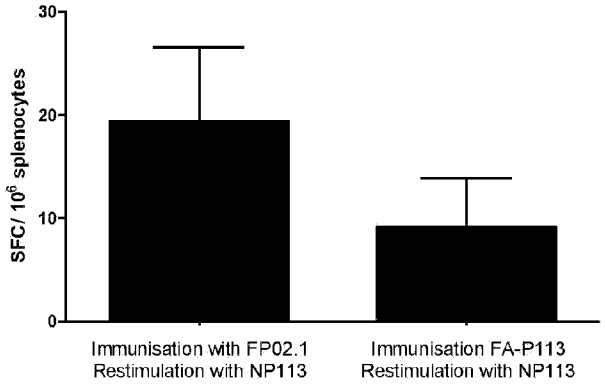
30
20
10
0
SFC/ 10^6 splenocytes
Immunisation with FP02.1
Restimulation with NP113
Immunisation FA-P113
Restimulation with NP113

Figure 17