WO2014102540, WO15187009). However, many of these proposed antigens have one or more of the following drawbacks:

- Poor sequence conservation across HBV genotypes, resulting in efficacy against a (small) subset of HBV genotypes only,
- No functional link of the antigenic region they derive from to viral replication, reducing the probability that an immune response against this region will interfere with viral replication,
- Ineffective immune response because of immune exhaustion due to antigen overexposure,
- Collectively covering one or a few HLA types only, resulting in lack of efficacy in certain populations lacking these HLA types,
- Difficult to manufacture (in particular for longer peptides),
- No confirmed potential to induce a T cell response,
- No indication as to whether an immune response against the peptide antigen has the potential to resolve an infection.

SUMMARY

The present disclosure provides novel long peptide antigens derived from the HBV-X and HBV polymerase proteins which resolve all or most of the disadvantages associated with previously-described peptide antigens.

The HBV long peptide antigens described herein contain novel HLA-binding peptide sequences that are well-conserved across multiple HBV genotypes, are derived from conserved regions of the proteins that are essential for viral replication and are therefore less likely to escape from HBV-specific immune responses. Moreover, the novel HBV-derived long peptide antigens harbor multiple HLA-binding peptide sequences which have the capacity to be presented by a diversity of HLA types. Furthermore, synthetic long peptides (SLPs) containing these HLA-binding peptide sequences that can be manufactured with sufficient yield and of sufficient purity are described. Moreover, SLPs that contain the newly identified HLA-binding peptide sequences have been found to elicit IFNγ responses in PBMCs from persons that have resolved HBV infection (HBV resolvers).

In a first main example, the disclosure relates to an immunogenic peptide comprising a fragment of an HBV protein, wherein said fragment is 20-34 amino acids in length and wherein said fragment comprises:

a) at least 10 consecutive amino acids of the region from position 57 to position 78 of HBV-X, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:1(x70-78), and/or
- the amino acid sequence set forth in SEQ ID NO:2(x67-75), and/or

- the amino acid sequence set forth in SEQ ID NO:22(p697-706),

or

k) the amino acid sequence set forth in SEQ ID NO:23(p723-731),

or

l) at least 10 consecutive amino acids of the region from position 755 to position 765 of HBV polymerase, comprising:

- the amino acid sequence set forth in SEQ ID NO:24(p755-764), and/or
- the amino acid sequence set forth in SEQ ID NO:25(p756-765),

or

m) the amino acid sequence set forth in SEQ ID NO:26(p829-837).

In further examples, the disclosure relates to polynucleotides comprising a nucleotide sequence encoding a peptide according to the disclosure, to immunogenic compositions comprising immunogenic peptides or polynucleotides of the disclosure and to uses of peptides, polynucleotides, recombinant viruses or immunogenic compositions of the disclosure in the treatment of HBV related diseases.

In one aspect, the disclosure relates to an immunogenic peptide comprising a fragment of an HBV protein, wherein said fragment is 20-34 amino acids in length and wherein said fragment comprises:

a) at least 10 consecutive amino acids of the region from position 57 to position 78 of HBV-X, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:1(x70-78), and/or
- the amino acid sequence set forth in SEQ ID NO:2(x67-75), and/or
- the amino acid sequence set forth in SEQ ID NO:3(x62-73), and/or
- the amino acid sequence set forth in SEQ ID NO:4(x58-66), and/or
- the amino acid sequence set forth in SEQ ID NO:5(x57-66),

or

b) at least 11 consecutive amino acids of the region from position 103 to position 120 of HBV-X, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:6(x103-111), and/or
- the amino acid sequence set forth in SEQ ID NO:7(x104-113), and/or
- the amino acid sequence set forth in SEQ ID NO:8(x105-113), and/or
- the amino acid sequence set forth in SEQ ID NO:9(x110-120),

or

c) the amino acid sequence set forth in SEQ ID NO:10(x132-140),

or

d) the amino acid sequence set forth in SEQ ID NO:11(p124-133),

or

e) the amino acid sequence set forth in SEQ ID NO:12(p164-173),

or

f) the amino acid sequence set forth in SEQ ID NO:13(p275-283),

or

g) at least 10 consecutive amino acids of the region from position 403 to position 415 of HBV polymerase, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:14(p403-412), and/or
- the amino acid sequence set forth in SEQ ID NO:15(p404-412), and/or
- the amino acid sequence set forth in SEQ ID NO:16(p407-415),

or

h) at least 9 consecutive amino acids of the region from position 509 to position 523 of HBV polymerase, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:17(p509-517), and/or
- the amino acid sequence set forth in SEQ ID NO:18(p515-523),

or

i) at least 10 consecutive amino acids of the region from position 649 to position 658 of HBV polymerase, comprising:

- the amino acid sequence set forth in SEQ ID NO:19(p649-658), and/or
- the amino acid sequence set forth in SEQ ID NO:20(p650-658),

or

j) at least 10 consecutive amino acids of the region from position 693 to position 706 of HBV polymerase, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:21(p693-701), and/or
- the amino acid sequence set forth in SEQ ID NO:22(p697-706),

or

k) the amino acid sequence set forth in SEQ ID NO:23(p723-731),

or

l) at least 10 consecutive amino acids of the region from position 755 to position 765 of HBV polymerase, comprising:

- the amino acid sequence set forth in SEQ ID NO:24(p755-764), and/or
- the amino acid sequence set forth in SEQ ID NO:25(p756-765),

or

m) the amino acid sequence set forth in SEQ ID NO:26(p829-837),

wherein the numbering of amino acid positions within HBV polymerase and HBV-X corresponds to the numbering in the consensus sequences set forth in SEQ ID NO:28 and SEQ ID NO:30, respectively.

In another aspect, the disclosure relates to an immunogenic peptide comprising a fragment of an HBV protein, wherein said peptide is 20-34 amino acids in length and wherein said fragment comprises a sequence selected from the group consisting of: SEQ ID NO:1 to SEQ ID NO:26.

In another aspect, the disclosure relates to a polynucleotide comprising a nucleotide sequence encoding a peptide according to the disclosure.

In another aspect, the disclosure relates to a recombinant virus comprising a polynucleotide according to the disclosure.

In another aspect, the disclosure relates to an immunogenic composition comprising:
- a peptide according to the disclosure, a polynucleotide according to claim 8 or a recombinant virus according to the disclosure, and
- a pharmaceutically-acceptable carrier,

optionally further comprising an adjuvant.

In another aspect, the disclosure relates to a use of:

- a peptide as described in 1a) and a peptide as described in 1b), or
- a peptide as described in 1a) and a peptide as described in 1c), or
- a peptide as described in 1a) and a peptide as described in 1d), or
- a peptide as described in 1a) and a peptide as described in 1e), or
- a peptide as described in 1a) and a peptide as described in 1f), or
- a peptide as described in 1a) and a peptide as described in 1g), or
- a peptide as described in 1a) and a peptide as described in 1h), or
- a peptide as described in 1a) and a peptide as described in 1i), or
- a peptide as described in 1a) and a peptide as described in 1j), or
- a peptide as described in 1a) and a peptide as described in 1k), or
- a peptide as described in 1a) and a peptide as described in 1l), or
- a peptide as described in 1a) and a peptide as described in 1m), or
- a peptide as described in 1b) and a peptide as described in 1c), or
- a peptide as described in 1b) and a peptide as described in 1d), or
- a peptide as described in 1b) and a peptide as described in 1e), or
- a peptide as described in 1b) and a peptide as described in 1f), or

- a peptide as described in 1b) and a peptide as described in 1g), or
- a peptide as described in 1b) and a peptide as described in 1h), or
- a peptide as described in 1b) and a peptide as described in 1i), or
- a peptide as described in 1b) and a peptide as described in 1j), or
- a peptide as described in 1b) and a peptide as described in 1k), or
- a peptide as described in 1b) and a peptide as described in 1l), or
- a peptide as described in 1b) and a peptide as described in 1m), or
- a peptide as described in 1c) and a peptide as described in 1d), or
- a peptide as described in 1c) and a peptide as described in 1e), or
- a peptide as described in 1c) and a peptide as described in 1f), or
- a peptide as described in 1c) and a peptide as described in 1g), or
- a peptide as described in 1c) and a peptide as described in 1h), or
- a peptide as described in 1c) and a peptide as described in 1i), or
- a peptide as described in 1c) and a peptide as described in 1j), or
- a peptide as described in 1c) and a peptide as described in 1k), or
- a peptide as described in 1c) and a peptide as described in 1l), or
- a peptide as described in 1c) and a peptide as described in 1m), or
- a peptide as described in 1d) and a peptide as described in 1e), or
- a peptide as described in 1d) and a peptide as described in 1f), or
- a peptide as described in 1d) and a peptide as described in 1g), or
- a peptide as described in 1d) and a peptide as described in 1h), or
- a peptide as described in 1d) and a peptide as described in 1i), or
- a peptide as described in 1d) and a peptide as described in 1j), or
- a peptide as described in 1d) and a peptide as described in 1k), or
- a peptide as described in 1d) and a peptide as described in 1l), or
- a peptide as described in 1d) and a peptide as described in 1m), or
- a peptide as described in 1e) and a peptide as described in 1f), or
- a peptide as described in 1e) and a peptide as described in 1g), or
- a peptide as described in 1e) and a peptide as described in 1h), or
- a peptide as described in 1e) and a peptide as described in 1i), or
- a peptide as described in 1e) and a peptide as described in 1j), or
- a peptide as described in 1e) and a peptide as described in 1k), or
- a peptide as described in 1e) and a peptide as described in 1l), or
- a peptide as described in 1e) and a peptide as described in 1m), or
- a peptide as described in 1f) and a peptide as described in 1g), or
- a peptide as described in 1f) and a peptide as described in 1h), or
- a peptide as described in 1f) and a peptide as described in 1i), or
- a peptide as described in 1f) and a peptide as described in 1j), or

- a peptide as described in 1f) and a peptide as described in 1k), or
- a peptide as described in 1f) and a peptide as described in 1l), or
- a peptide as described in 1f) and a peptide as described in 1m), or
- a peptide as described in 1g) and a peptide as described in 1h), or
- a peptide as described in 1g) and a peptide as described in 1i), or
- a peptide as described in 1g) and a peptide as described in 1j), or
- a peptide as described in 1g) and a peptide as described in 1k), or
- a peptide as described in 1g) and a peptide as described in 1l), or
- a peptide as described in 1g) and a peptide as described in 1m), or
- a peptide as described in 1h) and a peptide as described in 1i), or
- a peptide as described in 1h) and a peptide as described in 1j), or
- a peptide as described in 1h) and a peptide as described in 1k), or
- a peptide as described in 1h) and a peptide as described in 1l), or
- a peptide as described in 1h) and a peptide as described in 1m), or
- a peptide as described in 1i) and a peptide as described in 1j), or
- a peptide as described in 1i) and a peptide as described in 1k), or
- a peptide as described in 1i) and a peptide as described in 1l), or
- a peptide as described in 1i) and a peptide as described in 1m), or
- a peptide as described in 1j) and a peptide as described in 1k), or
- a peptide as described in 1j) and a peptide as described in 1l), or
- a peptide as described in 1j) and a peptide as described in 1m), or
- a peptide as described in 1k) and a peptide as described in 1l), or
- a peptide as described in 1k) and a peptide as described in 1m), or
- a peptide as described in 1l) and a peptide as described in 1m) or
- one or two polynucleotides comprising sequences encoding any one of the afore-mentioned combinations of peptides of the disclosure

in the manufacture of a medicament for treating or preventing an HBV-related disease.

In another aspect, the disclosure relates to a use of the peptide according to the disclosure, a polynucleotide according to the disclosure, a recombinant virus according to the disclosure or an immunogenic composition according to the disclosure in the manufacture of a medicament for treating or preventing an HBV-related disease.

In another aspect, the disclosure relates to a method of ex vivo stimulation of antigen-loaded activated antigen-presenting cells or expanded antigen-specific T cells, wherein the method comprises that the peptide according to the disclosure or

a peptide comprising a sequence selected from the group consisting of: SEQ ID NO:1 to SEQ ID NO:26 is contacted with the antigen-loaded activated antigen-presenting cells or expanded antigen-specific T cells.

In another aspect, the disclosure relates to a use of the peptide according to the disclosure, a polynucleotide according to the disclosure, a recombinant virus according to the disclosure or an immunogenic composition according to the disclosure in the manufacture of a medicament for treating an HBV-related disease, wherein:

(i) antiviral treatment is to be given to an HBV infected patient to reduce viral load,

(ii) when the viral load is significantly reduced, the immunogenic peptide(s), polynucleotide, recombinant virus or immunogenic composition is to be administered, and

(iii) when sufficient time has passed for an initial T cell response in the patient to have occurred, antiviral treatment is to be interrupted or discontinued.

BRIEF DESCRIPTION OF FIGURES

Figure 1. Alignment of validated HLA-I epitopes and predicted HLA-binding peptide sequences to protein conservation and function for HBx. A centered bar diagram depicts the length of the consensus sequence of the HBx protein (methods) in which the conservation score across viral genotypes is indicated by a grey scale code (legend) for each amino acid. Reported validated epitope sequences obtained from the Hepitopes database are aligned to this consensus protein sequence and shown on top. Below this, potential novel binders predicted by NetMHCpan (9-11 amino acids), are depicted for each HLA-supertype representative. Below the aligned binders we plotted the frequency distribution of each amino acid within all predicted binders (8-14 amino acids in length) over the protein sequence. The conservation score (legend) of each amino acid is shown as a horizontal grey scale-coded bar diagram. Essential amino acids of which mutation leads to loss of viral persistence are indicated by arrows matching the color of the conservation score. Functional domains are depicted at the bottom according to the nomenclature of HBVdb.

Figure 2. Alignment of validated HLA-I epitopes and predicted HLA-binding peptide sequences to protein conservation and function for Polymerase. Depicted are the first 200 amino acids (A, E), amino acids 201-474 (B, F), 475-631 (C, G) and amino acids 632-843 (D, H). Reported validated epitope sequences obtained from the Hepitopes database are shown on top. Below this, potential novel

Claims

1. An immunogenic peptide comprising a fragment of an HBV protein, wherein said fragment is 20-34 amino acids in length and wherein said fragment comprises:

a) at least 10 consecutive amino acids of the region from position 57 to position 78 of HBV-X, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:1(x70-78), and/or
- the amino acid sequence set forth in SEQ ID NO:2(x67-75), and/or
- the amino acid sequence set forth in SEQ ID NO:3(x62-73), and/or
- the amino acid sequence set forth in SEQ ID NO:4(x58-66), and/or
- the amino acid sequence set forth in SEQ ID NO:5(x57-66),

or

b) at least 11 consecutive amino acids of the region from position 103 to position 120 of HBV-X, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:6(x103-111), and/or
- the amino acid sequence set forth in SEQ ID NO:7(x104-113), and/or
- the amino acid sequence set forth in SEQ ID NO:8(x105-113), and/or
- the amino acid sequence set forth in SEQ ID NO:9(x110-120),

or

c) the amino acid sequence set forth in SEQ ID NO:10(x132-140),

or

d) the amino acid sequence set forth in SEQ ID NO:11(p124-133),

or

e) the amino acid sequence set forth in SEQ ID NO:12(p164-173),

or

f) the amino acid sequence set forth in SEQ ID NO:13(p275-283),

or

g) at least 10 consecutive amino acids of the region from position 403 to position 415 of HBV polymerase, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:14(p403-412), and/or
- the amino acid sequence set forth in SEQ ID NO:15(p404-412), and/or
- the amino acid sequence set forth in SEQ ID NO:16(p407-415),

or

h) at least 9 consecutive amino acids of the region from position 509 to position 523 of HBV polymerase, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:17(p509-517), and/or
- the amino acid sequence set forth in SEQ ID NO:18(p515-523),

or

i) at least 10 consecutive amino acids of the region from position 649 to position 658 of HBV polymerase, comprising:

- the amino acid sequence set forth in SEQ ID NO:19(p649-658), and/or
- the amino acid sequence set forth in SEQ ID NO:20(p650-658),

or

j) at least 10 consecutive amino acids of the region from position 693 to position 706 of HBV polymerase, preferably comprising:

- the amino acid sequence set forth in SEQ ID NO:21(p693-701), and/or
- the amino acid sequence set forth in SEQ ID NO:22(p697-706),

or

k) the amino acid sequence set forth in SEQ ID NO:23(p723-731),

or

l) at least 10 consecutive amino acids of the region from position 755 to position 765 of HBV polymerase, comprising:

- the amino acid sequence set forth in SEQ ID NO:24(p755-764), and/or
- the amino acid sequence set forth in SEQ ID NO:25(p756-765),

or

m) the amino acid sequence set forth in SEQ ID NO:26(p829-837),

wherein the numbering of amino acid positions within HBV polymerase and HBV-X corresponds to the numbering in the consensus sequences set forth in SEQ ID NO:28 and SEQ ID NO:30, respectively.

2. The peptide according to claim 1, wherein the peptide consists of said fragment of an HBV protein.

3. The peptide according to claim 1 or 2, wherein said peptide is 20-34 amino acids in length, such as 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33 or 34 amino acids length, such as 20-33 amino acids in length, e.g. 20-32 amino acids in length, such as 20-31 amino acids in length, e.g. 20-30 amino acids in length, such as 20-29 amino acids in length, e.g. 20-28 amino acids in length, such as 20-27 amino acids in length, e.g. 20-26 or 20-25 amino acids in length.

4. The peptide according to any one of the preceding claims, wherein said fragment is 20-33 amino acids in length, such as 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 or, 33 amino acids length, such as 20-32 amino acids in length, such as 20-31 amino acids in length, e.g. 20-30 amino acids in length, such as 20-29 amino

acids in length, e.g. 20-28 amino acids in length, such as 20-27 amino acids in length, e.g. 20-26 or 20-25 amino acids in length.

5. The peptide according to any one of the preceding claims, wherein

a) the fragment comprises at least 10 consecutive amino acids of the region from position 57 to position 78 of HBV-X, and the fragment comprises:

- the amino acid sequence set forth in SEQ ID NO:1(x70-78) and the amino acid sequence set forth in SEQ ID NO:2(x67-75), or
- the amino acid sequence set forth in SEQ ID NO:1(x70-78) and the amino acid sequence set forth in SEQ ID NO:3(x62-73), or
- the amino acid sequence set forth in SEQ ID NO:1(x70-78) and the amino acid sequence set forth in SEQ ID NO:4(x58-66), or
- the amino acid sequence set forth in SEQ ID NO:1(x70-78) and the amino acid sequence set forth in SEQ ID NO:5(x57-66), or
- the amino acid sequence set forth in SEQ ID NO:2(x67-75) and the amino acid sequence set forth in SEQ ID NO:3(x62-73), or
- the amino acid sequence set forth in SEQ ID NO:2(x67-75) and the amino acid sequence set forth in SEQ ID NO:4(x58-66), or
- the amino acid sequence set forth in SEQ ID NO:2(x67-75) and the amino acid sequence set forth in SEQ ID NO:5(x57-66), or
- the amino acid sequence set forth in SEQ ID NO:3(x62-73) and the amino acid sequence set forth in SEQ ID NO:4(x58-66), or
- the amino acid sequence set forth in SEQ ID NO:3(x62-73) and the amino acid sequence set forth in SEQ ID NO:5(x57-66).

or

b) the fragment comprises at least 11 consecutive amino acids of the region from position 103 to position 120 of HBV-X, and the fragment comprises:

- the amino acid sequence set forth in SEQ ID NO:6(x103-111) and the amino acid sequence set forth in SEQ ID NO:7(x104-113), or
- the amino acid sequence set forth in SEQ ID NO:6(x103-111) and the amino acid sequence set forth in SEQ ID NO:8(x105-113), or
- the amino acid sequence set forth in SEQ ID NO:6(x103-111) and the amino acid sequence set forth in SEQ ID NO:9(x110-120), or
- the amino acid sequence set forth in SEQ ID NO:7(x104-113) and the amino acid sequence set forth in SEQ ID NO:9(x110-120), or
- the amino acid sequence set forth in SEQ ID NO:8(x105-113) and the amino acid sequence set forth in SEQ ID NO:9(x110-120),

or

c) the fragment comprises at least 10 consecutive amino acids of the region from position 403 to position 415 of HBV polymerase, and the fragment comprises:

- the amino acid sequence set forth in SEQ ID NO:14(p403-412) and the amino acid sequence set forth in SEQ ID NO:16(p407-415), or
- the amino acid sequence set forth in SEQ ID NO:15(p404-412) and the amino acid sequence set forth in SEQ ID NO:16(p407-415).

6. The peptide according to any one of the preceding claims, wherein the peptide comprises or consists of a sequence selected from the group consisting of:
SEQ ID NO:31(SLP1), SEQ ID NO:32(SLP2), SEQ ID NO:33(SLP3), SEQ ID NO:34(SLP4), SEQ ID NO:35(SLP5), SEQ ID NO:36(SLP6) and SEQ ID NO:37(SLP7).

7. An immunogenic peptide comprising a fragment of an HBV protein, wherein said peptide is 20-34 amino acids in length and wherein said fragment comprises a sequence selected from the group consisting of: SEQ ID NO:1 to SEQ ID NO:26.

8. A polynucleotide comprising a nucleotide sequence encoding a peptide according to any one of the preceding claims.

9. A recombinant virus comprising a polynucleotide according to claim 8.

10. An immunogenic composition comprising:
- a peptide according to any one of the claims 1 to 7, a polynucleotide according to claim 8 or a recombinant virus according to claim 9, and
- a pharmaceutically-acceptable carrier,
optionally further comprising an adjuvant.

11. Use of:

- a peptide as described in claim 1a) and a peptide as described in claim 1b), or
- a peptide as described in claim 1a) and a peptide as described in claim 1c), or
- a peptide as described in claim 1a) and a peptide as described in claim 1d), or
- a peptide as described in claim 1a) and a peptide as described in claim 1e), or
- a peptide as described in claim 1a) and a peptide as described in claim 1f), or
- a peptide as described in claim 1a) and a peptide as described in claim 1g), or
- a peptide as described in claim 1a) and a peptide as described in claim 1h), or
- a peptide as described in claim 1a) and a peptide as described in claim 1i), or
- a peptide as described in claim 1a) and a peptide as described in claim 1j), or
- a peptide as described in claim 1a) and a peptide as described in claim 1k), or

- a peptide as described in claim 1a) and a peptide as described in claim 1l), or
- a peptide as described in claim 1a) and a peptide as described in claim 1m), or
- a peptide as described in claim 1b) and a peptide as described in claim 1c), or
- a peptide as described in claim 1b) and a peptide as described in claim 1d), or
- a peptide as described in claim 1b) and a peptide as described in claim 1e), or
- a peptide as described in claim 1b) and a peptide as described in claim 1f), or
- a peptide as described in claim 1b) and a peptide as described in claim 1g), or
- a peptide as described in claim 1b) and a peptide as described in claim 1h), or
- a peptide as described in claim 1b) and a peptide as described in claim 1i), or
- a peptide as described in claim 1b) and a peptide as described in claim 1j), or
- a peptide as described in claim 1b) and a peptide as described in claim 1k), or
- a peptide as described in claim 1b) and a peptide as described in claim 1l), or
- a peptide as described in claim 1b) and a peptide as described in claim 1m), or
- a peptide as described in claim 1c) and a peptide as described in claim 1d), or
- a peptide as described in claim 1c) and a peptide as described in claim 1e), or
- a peptide as described in claim 1c) and a peptide as described in claim 1f), or
- a peptide as described in claim 1c) and a peptide as described in claim 1g), or
- a peptide as described in claim 1c) and a peptide as described in claim 1h), or
- a peptide as described in claim 1c) and a peptide as described in claim 1i), or
- a peptide as described in claim 1c) and a peptide as described in claim 1j), or
- a peptide as described in claim 1c) and a peptide as described in claim 1k), or
- a peptide as described in claim 1c) and a peptide as described in claim 1l), or
- a peptide as described in claim 1c) and a peptide as described in claim 1m), or
- a peptide as described in claim 1d) and a peptide as described in claim 1e), or
- a peptide as described in claim 1d) and a peptide as described in claim 1f), or
- a peptide as described in claim 1d) and a peptide as described in claim 1g), or
- a peptide as described in claim 1d) and a peptide as described in claim 1h), or
- a peptide as described in claim 1d) and a peptide as described in claim 1i), or
- a peptide as described in claim 1d) and a peptide as described in claim 1j), or
- a peptide as described in claim 1d) and a peptide as described in claim 1k), or
- a peptide as described in claim 1d) and a peptide as described in claim 1l), or
- a peptide as described in claim 1d) and a peptide as described in claim 1m), or
- a peptide as described in claim 1e) and a peptide as described in claim 1f), or
- a peptide as described in claim 1e) and a peptide as described in claim 1g), or
- a peptide as described in claim 1e) and a peptide as described in claim 1h), or
- a peptide as described in claim 1e) and a peptide as described in claim 1i), or
- a peptide as described in claim 1e) and a peptide as described in claim 1j), or
- a peptide as described in claim 1e) and a peptide as described in claim 1k), or

- a peptide as described in claim 1e) and a peptide as described in claim 1l), or
- a peptide as described in claim 1e) and a peptide as described in claim 1m), or
- a peptide as described in claim 1f) and a peptide as described in claim 1g), or
- a peptide as described in claim 1f) and a peptide as described in claim 1h), or
- a peptide as described in claim 1f) and a peptide as described in claim 1i), or
- a peptide as described in claim 1f) and a peptide as described in claim 1j), or
- a peptide as described in claim 1f) and a peptide as described in claim 1k), or
- a peptide as described in claim 1f) and a peptide as described in claim 1l), or
- a peptide as described in claim 1f) and a peptide as described in claim 1m), or
- a peptide as described in claim 1g) and a peptide as described in claim 1h), or
- a peptide as described in claim 1g) and a peptide as described in claim 1i), or
- a peptide as described in claim 1g) and a peptide as described in claim 1j), or
- a peptide as described in claim 1g) and a peptide as described in claim 1k), or
- a peptide as described in claim 1g) and a peptide as described in claim 1l), or
- a peptide as described in claim 1g) and a peptide as described in claim 1m), or
- a peptide as described in claim 1h) and a peptide as described in claim 1i), or
- a peptide as described in claim 1h) and a peptide as described in claim 1j), or
- a peptide as described in claim 1h) and a peptide as described in claim 1k), or
- a peptide as described in claim 1h) and a peptide as described in claim 1l), or
- a peptide as described in claim 1h) and a peptide as described in claim 1m), or
- a peptide as described in claim 1i) and a peptide as described in claim 1j), or
- a peptide as described in claim 1i) and a peptide as described in claim 1k), or
- a peptide as described in claim 1i) and a peptide as described in claim 1l), or
- a peptide as described in claim 1i) and a peptide as described in claim 1m), or
- a peptide as described in claim 1j) and a peptide as described in claim 1k), or
- a peptide as described in claim 1j) and a peptide as described in claim 1l), or
- a peptide as described in claim 1j) and a peptide as described in claim 1m), or
- a peptide as described in claim 1k) and a peptide as described in claim 1l), or
- a peptide as described in claim 1k) and a peptide as described in claim 1m), or
- a peptide as described in claim 1l) and a peptide as described in claim 1m) or
- one or two polynucleotides comprising sequences encoding any one of the aforementioned combinations of peptides

in the manufacture of a medicament for treating or preventing an HBV-related disease.

12. The peptide according to any one of the claims 1 to 7, a polynucleotide according to claim 8, a recombinant virus according to claim 9 or an immunogenic composition according to claim 10 for use in therapy.

13. Use of the peptide according to any one of the claims 1 to 7, a polynucleotide according to claim 8, a recombinant virus according to claim 9 or an immunogenic composition according to claim 10 in the manufacture of a medicament for treating or preventing an HBV-related disease.

14. A method of ex vivo stimulation of antigen-loaded activated antigen-presenting cells or expanded antigen-specific T cells, wherein the method comprises that the peptide according to any one of the claims 1 to 7 or a peptide comprising a sequence selected from the group consisting of: SEQ ID NO:1 to SEQ ID NO:26 is contacted with the antigen-loaded activated antigen-presenting cells or expanded antigen-specific T cells.

15. Use of the peptide according to any one of the claims 1 to 7, a polynucleotide according to claim 8, a recombinant virus according to claim 9 or an immunogenic composition according to claim 10 in the manufacture of a medicament for treating an HBV-related disease, wherein:

(i) antiviral treatment is to be given to an HBV infected patient to reduce viral load,

(ii) when the viral load is significantly reduced, the immunogenic peptide(s), polynucleotide, recombinant virus or immunogenic composition is to be administered, and

(iii) when sufficient time has passed for an initial T cell response in the patient to have occurred, antiviral treatment is to be interrupted or discontinued.