CLAIMS

1. A mutant polypeptide which comprises a mutated HBV polymerase domain with an internal deletion that functionally disrupts the polymerase activity, wherein said internal deletion is of at least 47 amino acid residues and at most 30 amino acid residues and comprises at least the YMDD motif naturally present in the polymerase domain of a native HBV polymerase, and wherein said mutated polymerase domain comprises the amino acid sequence shown in SEQ ID NO: 1 but lacks at least the Tyr residue in position 203, the Met residue in position 204, the Asp residue in position 205, the Asp residue in position 206, the Val residue in position 207, the Val residue in position 208 and the Leu residue in position 209.

2. The mutant polypeptide according to claim 1, wherein said mutated polymerase domain comprises the amino acid sequence shown in SEQ ID NO: 1 but lacks at least the Tyr residue in position 203, the Met residue in position 204, the Asp residue in position 205 and the Asp residue in position 206.

~~3. The mutant polypeptide according to claim 2, wherein said mutated polymerase domain comprises the amino acid sequence shown in SEQ ID NO: 1 but lacks at least the Tyr residue in position 203, the Met residue in position 204, the Asp residue in position 205, the Asp residue in position 206, the Val residue in position 207, the Val residue in position 208 and the Leu residue in position 209.~~

34. The mutant polypeptide according to claim ~~3~~1, wherein said mutated polymerase domain comprises an amino acid sequence which exhibits at least 80% identity with the amino acid sequence shown in SEQ ID NO: 2.

~~5~~4. The mutant polypeptide according to claim 43, wherein said mutated polymerase domain comprises the amino acid sequence shown in SEQ ID NO: 2.

~~6~~5. The mutant polypeptide according to any one of claims 1 to 43, which further comprises a mutated RNaseH domain comprising mutation(s) of one or more amino acid residue(s) that functionally disrupt(s) the RNaseH activity normally exhibited by a native HBV polymerase.

~~7~~6. The mutant polypeptide according to claim ~~6~~5, wherein said one or more mutation(s) comprised in the mutated RNaseH domain are selected from the group consisting of:

- a deletion of at least 8 amino acids and at most 60 amino acids including at least the portion of SEQ ID NO: 3 extending from approximately the Glu residue (E) in position 39 to approximately the Ala (A) residue in position 46;
- the substitution of the Asp (D) residue in position 10 of SEQ ID NO: 3 with an amino acid residue other than Asp (D);
- the substitution of the Val (V) residue in position 90 of SEQ ID NO: 3 with an amino acid residue other than Val (V);
- the substitution of the Thr (T) or Ala (A) residue in position 97 of SEQ ID NO: 3 with an amino acid residue other than Thr (T) or Ala (A);
- the substitution of the Asp (D) residue in position 98 of SEQ ID NO: 3 with an amino acid residue other than Asp (D); and
- any combination thereof.

~~8~~7. The mutant polypeptide according to claim ~~7~~6, wherein aid substituted residue(s) in position 10, 90, 97 or 98 of SEQ ID NO: 3 are replaced with a His (H) residue or with a Tyr (Y) residue.

~~9~~8. The mutant polypeptide according to claim ~~8~~7, wherein said residue in position 10 of SEQ ID NO: 3 is substituted with a His (H) residue, said residue in position 90 of SEQ ID NO: 3 is substituted with a Tyr (Y) residue, said residue in position 97 of SEQ ID NO: 3 is substituted with a Tyr (Y) residue and/or said residue in position 98 of SEQ ID NO: 3 is substituted with a His (H) residue.

~~10~~9. The mutant polypeptide according to any one of claims ~~7~~6 to ~~9~~8, wherein said deletion comprised in the mutated RNaseH domain comprises a portion of at least 25 amino acids extending from approximately the Glu residue (E) in

position 39 to approximately the Leu (L) residue in position 63 of SEQ ID NO: 3, and more preferably a portion of at least 33 amino acids extending from approximately the Xaa residue in position 31 to approximately the Leu (L) residue in position 63 of SEQ ID NO: 3.

~~11~~10. The mutant polypeptide according to claim ~~10~~9, wherein the mutated RNaseH domain comprises the amino acid sequence shown in SEQ ID NO: 3 but (a) lacking the portion of 33 amino acid residues extending from the residue Xaa in position 31 to approximately the Leu (L) residue in position 63 and comprises (b) the substitution of the Asp (D) residue in position 10 with a His (H) residue (D689H); (c) the substitution of the Val (V) residue in position 90 with a Tyr (Y) residue (V769Y); (d) the substitution of the residue in position 97 with a Tyr (Y) residue (T/A776Y) and (e) the substitution of the Asp (D) residue in position 98 with a His (H) residue (D777H).

~~12~~11. The mutant polypeptide according to claim ~~11~~10, which comprises a mutated RNaseH domain comprising an amino acid sequence exhibiting at least 80% identity with the amino acid sequence shown in SEQ ID NO: 4.

~~13~~12. The mutant polypeptide according to any one of claims ~~3~~1 to ~~11~~10, which comprises an amino acid sequence exhibiting at least 80% identity with the amino acid sequence shown in SEQ ID NO: 5.

~~14~~13. The mutant polypeptide according to claim ~~13~~12, which comprises the amino acid sequence shown in SEQ ID NO: 5.

~~15~~14. The mutant polypeptide according to any one of claims 1 to ~~14~~13, used in combination with one or more additional polypeptide(s) or peptide(s).

~~16~~15. The mutant polypeptide according to claim ~~15~~14, wherein said one or more additional polypeptide(s) or peptide(s) is an HBV polypeptide or peptide selected

from the group consisting of HBc, HBs, X protein and immunogenic fragments thereof.

~~17~~16. The mutant polymerase polypeptide according to claim ~~16~~15, wherein said additional HBV polypeptide(s) or peptide(s) originate from a genotype D HBV such as the Y07587 isolate.

~~18~~17. A fusion protein comprising the mutant polymerase polypeptide according to any one of claims 1 to ~~17~~ 16 and a HBV core polypeptide.

~~19~~18. The fusion protein according to claim ~~18~~17, wherein said HBV core polypeptide is C-terminally truncated and especially truncated at residue 148 or 149.

~~20~~19. The fusion protein according to claim 17 or 18 ~~or 19~~, wherein said HBV core polypeptide is fused in frame to the N-terminus of the mutant ~~polymerase~~ polypeptide.

~~21~~20. The fusion protein according to claim ~~20~~19, wherein said fusion protein comprises an amino acid sequence exhibiting at least 80% identity with the amino acid sequence shown in SEQ ID NO: 6.

~~22~~21. The fusion protein according to claim ~~21~~20, wherein said fusion protein comprises the amino acid sequence shown in SEQ ID NO: 6.

~~23~~22. A fusion protein comprising the mutant polypeptide according to any one of claims 1 to ~~17~~ 16 and one or more HBsAg immunogenic domain(s) or the fusion protein according to any one of claims ~~19~~ 18 to ~~23~~ 22 further comprising one or more HBsAg immunogenic domain(s).

234. The fusion protein according to any one of claims ~~18~~ 17 to ~~23~~22, comprising at its N- terminus a core polypeptide fused to the mutant polypeptide and one or two HbsAg immunogenic domains fused in place of the internal deletion in the

mutated polymerase domain and/or in place of the deletion in the mutated RNaseH domain.

2524. The fusion protein according to claim 2423, comprising an amino acid sequence exhibiting at least 80% identity with the amino acid sequence shown in any of SEQ ID NO: 7 to 9.

2625. The fusion protein according to claim 2524, comprising the amino acid sequence shown in SEQ ID NO: 8.

2726. The mutant polypeptide according to any one of claims 1 to 17 16 and the fusion protein according any one of claims 18 17 to 2625, which is fused in frame to a signal peptide and to a trans-membrane peptide.

278. The mutant polypeptide and the fusion protein according to claim 267, comprising an amino acid sequence exhibiting at least 80% identity with the amino acid sequence shown in any of SEQ ID NO: 10 to 12.

289. A nucleic acid molecule coding for the mutant polypeptide according to any one of claims 1 to 17 16 and 26 to 27 to 28 or the fusion protein according to any one of claims 178 to 2827.

3029. The nucleic acid molecule according to claim 29 28 which is selected from the group consisting of:

- A nucleic acid molecule which encodes a mutant polypeptide comprising a polymerase domain having the amino acid sequence shown in SEQ ID NO: 1 or 2;

- A nucleic acid molecule which encodes a mutant polypeptide comprising a RNaseH domain having the amino acid sequence shown in SEQ ID NO: 3 or 4;

- A nucleic acid molecule which encodes a mutant polypeptide comprising an amino acid sequence which exhibits at least 80% of identity with the amino acid sequence shown in SEQ ID NO: 5; or

- A nucleic acid molecule which encodes a fusion protein comprising an amino acid sequence which exhibits at least 80% of identity with the amino acid sequence shown in any of SEQ ID NO: 6-12.

~~31~~30. The nucleic acid molecule according to claim ~~29~~ 28 which comprises a nucleotide sequence exhibiting at least 80%> of identity with the nucleotide sequence shown in any of SEQ ID NO: 13-17.

~~32~~31. A vector comprising a nucleic acid molecule according to any one of claims ~~29~~ 28 to ~~31~~30.

~~33~~32. The vector according to claim ~~32~~31, wherein said vector is a plasmid or a viral vector for expression in higher eukaryotic cells or organisms.

~~34~~33. The vector according to claim ~~33~~32, wherein said vector is a viral vector originating from a retrovirus, adenovirus, adenovirus-associated virus (AAV), poxvirus, herpes virus, measle virus, foamy virus, alphavirus, or vesicular stomatis virus.

~~35~~34. The vector according to claim ~~34~~33, wherein said vector is a replication-defective adenoviral vector originating from a human or from a chimpanzee adenovirus.

~~36~~35. The vector according to claim ~~35~~34, wherein the nucleic acid molecule is inserted in the adenoviral E1 region and placed under the control of a CMV promoter.

~~37~~36. The vector according to claim ~~34~~33, wherein said vector is a poxviral vector originating from a canarypox, a fowlpox or a vaccinia virus.

~~38~~37. The vector according to claim ~~37~~36, wherein said vaccinia virus is the Copenhagen strain, the Wyeth strain and the modified Ankara (MVA) strain.

~~39~~38. The vector according to claim ~~38~~37, wherein the nucleic acid molecule is inserted in deletion III of the MVA vector and placed under the control the vaccinia 7.5K or pH5R promoter.

~~40~~39. The vector according to any one of claims ~~34~~33 to ~~39~~38, wherein said vector is selected from the group consisting of:

- A defective Ad vector comprising inserted in place of the E1 region a nucleic acid molecule placed under the control of a promoter such as the CMV promoter, and encoding a mutant polypeptide comprising an amino acid sequence as shown in SEQ ID NO: 5 or a fusion protein comprising an amino acid sequence as shown in SEQ ID NO: 6 or SEQ ID NO: 8;

- A replication-defective Ad vector comprising inserted in place of the E1 region a nucleic acid molecule placed under the control of a promoter such as the CMV promoter, and comprising the nucleotide sequence shown in SEQ ID NO: 13, SEQ ID NO: 14 or SEQ ID NO: 15;

- A replication-defective Ad vector, especially a defective AdCh3 comprising inserted in place of the E1 region a nucleic acid molecule placed under the control of a promoter such as the CMV promoter and comprising the nucleotide sequence shown in SEQ ID NO: 16 or SEQ ID NO: 17;

- A MVA vector comprising a nucleic acid molecule placed under the control of a vaccinia promoter such as the 7.5K or pH5R promoter, and encoding a mutant polypeptide comprising an amino acid sequence as shown in SEQ ID NO: 5 or SEQ ID NO: 10 or a fusion protein comprising an amino acid sequence as shown in SEQ ID NO: 6, SEQ ID NO: 8 or SEQ ID NO: 12; and

- A MVA vector comprising a nucleic acid molecule placed under the control of a vaccinia promoter such as the 7.5K or pH5R promoter, and

comprising the nucleotide sequence shown in SEQ ID NO: 13, SEQ ID NO: 14 or SEQ ID NO: 15.

4140. The vector according to any one of claims 34-33 to 4039, wherein said vector is in the form of infectious viral particles.

4241. A process of producing the vector of claim 41-40 comprising the steps of introducing the viral vector into a suitable cell line, culturing said cell line under suitable conditions so as to allow the production of said infectious viral particle, recovering the produced infectious viral particle from the culture of said cell line and optionally purifying said viral particle.

4342. A host cell comprising the nucleic acid molecule according to any one of claims 29-28 to 31-30 or the vector according to any one of claims 32-31 to 4140.

4443. A method for recombinant production of the mutant polypeptide according to any one of claims 1 to 17-16 and 26 to 27-to-28 or the fusion protein according to any one of claims 178 to 278, comprising the steps of introducing the vector according to any one of claims 312 to 401 into a suitable host cell to produce a transfected or infected host cell, culturing *in vitro* said transfected or infected host cell under conditions suitable for growth of the host cell, recovering the cell culture and optionally purifying the produced mutant polypeptide or fusion protein.

4544. A composition comprising at least the mutant polypeptide according to any one of claims 1 to 167 and 26 to 27-to-28, the fusion protein according to any one of claims 178 to 278, the nucleic acid molecule according to any one of claims 289 to 301, the vector according to any one of claims 312 to 401, the host cell according to claim 423 or any combination thereof.

4645. The composition according to claim 445, further comprising a pharmaceutically acceptable vehicle.

4746. The composition according to claim 445 or 456, wherein said composition is formulated for intramuscular, subcutaneous, intradermal administration scarification.

4847. The composition according to any one of claims 445 to 467, wherein said composition comprises doses of about 5 x 10^8, about 10^9, about 5x 10^9, about 10^{10}, about 5x 10^{10} vp or about 10^{11} vp of an adenoviral vector.

4948. The composition according to any one of claims 445 to 467, wherein said composition comprises doses of about 5x 10^6, about 10^7, about 5x 10^7, about 10^8, or about 5x 10^8 pfu of a MVA vector.

5049. Use of Tthe mutant polypeptide according to any one of claims 1 to 167 and 267 to 278, the fusion protein according to any one of claims 178 to 278, the nucleic acid molecule according to any one of claims 289 to 301, the vector according to any one of claims 312 to 401, the host cell according to claim 423 or the composition according to any one of claims 445 to 489 in the manufacture of a medicament for use in treating or preventing an HBV infection or HBV-associated diseases and pathological conditions.

5150. The use of mutant polypeptide according to any one of claims 1 to 17 and 27 to 28, the fusion protein according to any one of claims 18 to 28, the nucleic acid molecule according to any one of claims 29 to 31, the vector according to any one of claims 32 to 41, the host cell according to claim 43 or the composition according to any one of claim s 45 to 49 for use in treating a chronic HBV infection.

5251. The mutant polypeptide according to any one of claims 1 to 17 and 27 to 28, the fusion protein according to any one of claims 18 to 28, the nucleic acid molecule according to any one of claims 29 to 31, the vector according to any one of claims 32 to 41, the host cell according to claim 43 or the composition according to any one of claims 45 touse of claim 49 for use for eliciting or stimulating an immune response in the treated organism.

~~5352~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition for~~ use according to claim ~~5251~~, wherein said elicited or stimulated immune response is specific and/or non-specific, humoral and/or cellular.

~~5453~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to claim ~~5352~~, wherein said immune response is a T cell response CD4+ or CD8+-mediated or both, directed to an HBV polypeptide/epitope.

~~5554~~. The use ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~ according to any one of claims ~~50~~-49 to ~~5453~~, wherein said use comprises one or more administration(s) of a therapeutically effective amount of said mutant ~~polymerase~~ polypeptide, fusion protein, nucleic acid molecule, vector or composition.

~~5655~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to any one of claims ~~50~~-49 to ~~5453~~, wherein said vector is a MVA vector and said use comprises three subcutaneous administrations separated from each other by approximately one week.

~~5756~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to any one of claims ~~50~~-49 to ~~5453~~, wherein said vector is an adenoviral vector and said use comprises one or two intramuscular or subcutaneous administrations.

5~~78~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to any one of claims ~~50~~-49 to ~~5756~~, wherein said use is carried out in combination with the standard of care, and said standard care comprises treatment with nucleoside or nucleoside analogs.

~~5958~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to any one of claims ~~50~~ 49 to ~~58~~57, wherein said use is carried out according to prime boost modality.

~~6059~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to claim ~~59~~58, wherein the priming is carried out with a MVA vector and the boosting with an Ad vector.

~~6160~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to claim ~~60~~59, and wherein the MVA and/or the Ad vector encodes the fusion protein shown in SEQ ID NO: 8.

~~6261~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~ according to claim 59 or 60 ~~or 61~~ comprising at least 3 subcutaneous administrations of the MVA vector separated by a period of time varying from 3 days to 3 months followed by a intramuscular or subcutaneous boost of the adenovirus vector.

~~6362~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to claim ~~59~~58, wherein the priming is carried out with a plasmid DNA vector and the boosting with a MVA vector.

~~6463~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to claim ~~63~~62, wherein the plasmid and/or the Ad vector encodes the fusion protein shown in SEQ ID NO: 8.

~~6564~~. The ~~mutant polypeptide, the fusion protein, the nucleic acid molecule, the vector, the host cell or the composition~~use according to claim 62 or 63 ~~or 64~~, comprising at least 3 intramuscular administrations of the DNA vector separated

by a period of time varying from 2 weeks to 3 months and at least one subcutaneous boost of the MVA vector.

6665. A kit of parts for use in the treatment of an HBV infection or for eliciting an immune response in a subject, wherein said kit comprises a plurality of active agents selected from the group consisting of the mutant polypeptide according to any one of claims 1 to 167 and 267 to 278, the fusion protein according to any one of claims 178 to 278, the nucleic acid molecule according to any one of claims 289 to 301, the vector according to any one of claims 312 to 401, the host cell according to claim 423 or the composition according to any one of claims 445 to 489.