This technical problem is solved by the provision of the embodiments as defined in the claims.

Other and further aspects, features and advantages of the present invention will be apparent from the following description of the presently preferred embodiments of the invention. These embodiments are given for the purpose of disclosure.

SUMMARY OF THE INVENTION

In one embodiment~~aspect~~, the present disclosure~~invention~~ concerns a mutant polymerase polypeptide which comprises at least 500 amino acid residues of a native HBV polymerase wherein said mutant polymerase polypeptide comprises a polymerase domain with an internal deletion that functionally disrupts the polymerase activity and wherein said internal deletion includes at least the YMDD motif naturally present in the polymerase domain of a native polymerase.

The present disclosure~~invention~~ also concerns a nucleic acid molecule encoding said mutant polymerase polypeptide, a vector comprising said nucleic acid molecule, or a composition comprising or encoding said mutant polymerase polypeptide.

The present disclosure~~invention~~ also relates to the use of this mutant polymerase polypeptide, nucleic acid molecule, vector or composition, preferably in combination with additional polypeptides (e.g. with one or more HBV polypeptide(s)) for the purpose of treating, preventing or inhibiting an HBV infection or ameliorating a condition associated with an HBV infection.

Still a further embodiment~~aspect~~ of the present disclosure~~invention~~ includes a method of treating, preventing or inhibiting HBV infection or ameliorating a condition associated with HBV infection in a subject in need thereof, comprising providing or administering this mutant polymerase polypeptide, nucleic acid molecule, vector or composition, eventually in combination with additional polypeptides (e.g. with one or more HBV polypeptide(s)) and/or with the standard of care.

Still yet a further embodiment~~aspect~~ of the present disclosure~~invention~~ concerns a method of eliciting an immune response in a subject in need thereof, comprising providing or administering this mutant polymerase polypeptide, nucleic acid molecule, vector or composition, eventually in combination with additional polypeptides (e.g. with one or more HBV

polypeptide(s)) and/or with the standard of care, for the purpose of inducing or stimulating an immune response in this subject or for treating an HBV infection or ameliorating a condition or symptom associated with HBV infection.

Still more embodiment~~aspect~~ of the present disclosure~~invention~~ provides a kit of parts comprising a plurality of containers and instructions for providing or administering to a subject this mutant polymerase polypeptide, nucleic acid molecule, vector or composition, eventually in combination with additional polypeptides (e.g. with one or more HBV polypeptide(s)), in accordance with the compositions and methods described herein.

In one aspect, there is provided 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 7 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.

In another aspect, there is provided a fusion protein comprising the mutant polymerase polypeptide as defined herein and a HBV core polypeptide.

In another aspect, there is provided a fusion protein comprising the mutant polypeptide as defined herein and one or more HBsAg immunogenic domain(s) or the fusion protein as defined herein further comprising one or more HBsAg immunogenic domain(s).

In another aspect, there is provided a nucleic acid molecule coding for the mutant polypeptide as defined herein or the fusion protein as defined herein.

In another aspect, there is provided a vector comprising a nucleic acid molecule as defined herein.

In another aspect, there is provided a process of producing the vector as defined herein 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.

In another aspect, there is provided a host cell comprising the nucleic acid molecule as defined herein or the vector as defined herein.

In another aspect, there is provided a method for recombinant production of the mutant polypeptide as defined herein or the fusion protein as defined herein, comprising the steps of introducing the vector as defined herein 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.

In another aspect, there is provided a composition comprising at least the mutant polypeptide as defined herein, the fusion protein as defined herein, the nucleic acid molecule as defined herein, the vector as defined herein, the host cell as defined herein or any combination thereof.

In another aspect, there is provided the use of the mutant polypeptide as defined herein, the fusion protein as defined herein, the nucleic acid molecule as defined herein, the vector as defined herein, the host cell as defined herein or the composition as defined herein in the manufacture of a medicament for treating or preventing an HBV infection or HBV-associated diseases and pathological conditions.

In another aspect, there is provided 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 as defined herein, the fusion protein as defined herein, the nucleic acid molecule as defined herein, the vector as defined herein, the host cell as defined herein or the composition as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a mutant polymerase polypeptide which comprises a mutated polymerase domain with an internal deletion that functionally disrupts the polymerase activity, wherein said internal deletion comprises at least the YMDD motif naturally present in the polymerase domain of a native HBV polymerase. Such a mutant polymerase polypeptide or vector encoding it can be used in compositions and methods for the treatment or prevention of an HBV infection or a condition associated with an HBV infection, eventually in combination with other HBV polypeptides and/or standard of care. This invention permits to envisage expression and production of the mutant polymerase polypeptide in various vector systems due to the disruption of the associated enzymatic activities. The invention is also particularly adapted for human use and may be used to reinforce standard therapies (e.g. SOC). Immunization of animal models with a vector encoding this mutant polymerase polypeptide in fusion with HBc and Hbs immunogenic domains, elicited HBV specific T cell responses, and surprisingly a strong immunity against both HBc and Polymerase was observed

The following section provides a greater explanation of the meaning of some of the terms used herein.

Definitions

As used herein throughout the entire application, the terms "a" and "an" are used in the sense that they mean "at least one", "at least a first", "one or more" or "a plurality" of the referenced compounds or steps, unless the context dictates otherwise.

57. The use according to any one of claims 48 to 56, wherein said use is carried out according to prime boost modality.

58. The use according to claim 57, wherein the priming is carried out with a MVA vector and the boosting with an Ad vector.

59. The use according to claim 58, and wherein the MVA and/or the Ad vector encodes the fusion protein shown in SEQ ID NO: 8.

60. The use according to claim 58 or 59 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.

61. The use according to claim 57, wherein the priming is carried out with a plasmid DNA vector and the boosting with a MVA vector.

62. The use according to claim 61, wherein the plasmid and/or the Ad vector encodes the fusion protein shown in SEQ ID NO: 8.

63. The use according to claim 61 or 62, comprising at least 3 intramuscular administrations of the DNA vector separated