alanine aminotransferase (ALT) levels and loss of HBsAg – ideally followed by anti-HBs seroconversion. Hence, a sustained therapeutic effect requires both antiviral suppression but in particular restoration of effector immune cell responses. Thus, a cure of an HBV infection should ideally be associated with virus-specific CD4+ and CD8+ T-cell responses. For example, chimpanzees were only able to cure an acute HBV infection, when functional CD4+ and CD8+ T-cell responses were restored after antibody-mediated depletion (cf., e.g., Thimme et al., CD8(+) T cells mediate viral clearance and disease pathogenesis during acute hepatitis B virus infection, J Virol, 2003. 77(1): p. 68-76). The essentials of T-cell responses to achieve an HBV cure is assumed to be based on their ability to eliminate HBV infected cells by their cytotoxic activity but also control HBV persistence, gene expression and replication in a non-cytolytic fashion (Guidotti., The role of cytotoxic T cells and cytokines in the control of hepatitis B virus infection, Vaccine, 2002. 20 Suppl 4: p. A80-2). Thus, a functional immune system and in particular HBV-specific T-cell responses are required to treat and, ideally, cure an HBV infection.

[0005] Currently available treatment strategies can be basically divided into i) concepts focusing on directly acting antivirals affecting different parts of the viral life cycle and ii) immune therapeutic approaches intending to stimulate the host immune response. Approved therapies for an HBV infection comprise nucleoside and/or nucleotide analogues and interferon alpha. Nucleoside and/or nucleotide analogues are costly and have cure rates comparable to cure rates of spontaneous HBV elimination by the immune system, and the use of interferon alpha is declining due to severe side effects when used for treatment. Alternative approaches are in clinical development, which comprise, e.g., attempting to specifically suppress the replication of HBV and/or viral protein expression. Attempts are also being made to stimulate the innate immune system or to induce specific adaptive immune responses against HBV components through the administration of HBV antigens. However, current treatment options are of limited efficacy so far, thus failing to cure an HBV infection.

[0006] Hence, there is still a need to have at hand alternative solutions for being able to treat an HBV infection, in particular a chronic HBV infection, that are preferably capable of providing an efficient immune stimulation.

III. SUMMARY

[0007] The disclosure aims at providing a, preferably curative, therapeutic vaccination of a Hepatitis B Virus (HBV) infection.

[0007a] In one aspect, the present disclosure refers to use of an HBcAg particle, an HBsAg, and a vaccine vector in the manufacture of a medicament for combination therapy for vaccination against hepatitis B, wherein the medicament is to be administered in (i) a first

dose of the HBcAg particle, wherein the HBcAg particle comprises Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, and of the HBsAg, (ii) a second dose of the HBcAg particle and of the HBsAg, and (iii) a dose of the vaccine vector; wherein the vaccine vector expresses a. an HBsAg from HBV genotype A; b. an HBcAg from HBV genotype D; c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7; d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

[0007b] In another aspect, the present disclosure refers to use of an HBcAg particle in the manufacture of a first medicament, use of an HBsAg in the manufacture of a second medicament, and use of a vaccine vector in the manufacture of a third medicament, wherein the first, second and third medicaments are to be used in combination therapy for vaccination against hepatitis B, wherein the first, second and third medicaments are to be administered in (i) a first dose of the HBcAg particle, wherein the HBcAg particle comprises Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, and of the HBsAg, (ii) a second dose of the HBcAg particle and of the HBsAg, and (iii) a dose of the vaccine vector; wherein the vaccine vector expresses a. an HBsAg from HBV genotype A; b. an HBcAg from HBV genotype D; c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7; d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

[0007c] In another aspect, the present disclosure refers to use of an HBcAg particle in the manufacture of a medicament for use in combinatorial therapy for vaccination against hepatitis B, wherein said medicament is to be administered in combination with an HBsAg and a vaccine vector in (i) a first dose of the HBcAg particle, wherein the HBcAg particle comprises Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, and of the HBsAg, (ii) a second dose of the HBcAg particle and of the HBsAg, and (iii) a dose of the vaccine vector; wherein the vaccine vector expresses a. an HBsAg from HBV genotype A; b. an HBcAg from HBV genotype D; c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7; d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

[0007d] In another aspect, the present disclosure refers to use of a vaccine vector in the manufacture of a medicament for use in combinatorial therapy for vaccination against hepatitis B, wherein said medicament is to be administered in combination with an HBcAg particle and an HBsAg in (i) a first dose of the HBcAg particle, wherein the HBcAg particle comprises Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, and of the HBsAg, (ii) a second dose of the HBcAg particle and of the HBsAg, and (iii) a dose of the vaccine vector; wherein the vaccine vector expresses a. an HBsAg from HBV genotype A; b. an HBcAg from HBV genotype D; c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7; d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

[0007e] In another aspect, the present disclosure refers to a Hepatitis B Virus core antigen (HBcAg) particle, comprising Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, wherein the HBcAg particle is preferably an isolated HBcAg particle.

[0007f]In another aspect, the present disclosure refers to a pharmaceutical composition comprising the HBcAg particle disclosed herein and optionally a pharmaceutically acceptable carrier or excipient.

[0007g] In another aspect, the present disclosure refers to a container comprising one or more doses of the pharmaceutical composition disclosed herein.

[0007h] In another aspect, the present disclosure refers to a kit comprising the pharmaceutical composition disclosed herein and a second pharmaceutical composition comprising an HBsAg, wherein the HBsAg is preferably a particulate HBsAg.

[0007i] In another aspect, the present disclosure refers to an expression cassette, an mRNA, or a cDNA, wherein the expression cassette, mRNA, or cDNA, encodes an HBV core protein from HBV genotype C and an HBV core protein from HBV genotype D, wherein the expression cassette, mRNA, or cDNA, only comprises coding sequences for two or more HBV core proteins.

[0007j] In another aspect, the present disclosure refers to a nucleic acid molecule comprising the expression cassette, the mRNA, or the cDNA disclosed herein.

[0007k] In another aspect, the present disclosure refers to an expression vector comprising the expression cassette or the cDNA disclosed herein or the nucleic acid molecule disclosed herein.

[0007l] In another aspect, the present disclosure refers to a vaccine vector, wherein the vaccine vector is preferably an MVA viral vector, and wherein the vaccine vector comprises a nucleic acid molecule comprising a nucleotide sequence having at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO: 5.

[0007m] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the vaccine vector disclosed herein and optionally a pharmaceutically acceptable carrier or excipient.

[0007n] In another aspect, the present disclosure refers to a container comprising one or more doses of the pharmaceutical composition disclosed herein, wherein a dose of the pharmaceutical composition comprises the vaccine vector in an amount from about 1x 10^7 ifu to about 1x 10^9 ifu.

[0007o] In another aspect, the present disclosure refers to use of an HBcAg particle disclosed herein in the manufacture of a medicament for the vaccination against hepatitis B.

[0008] The present disclosure relates to a Hepatitis B Virus core antigen (HBcAg) particle, comprising Hepatitis B Virus (HBV) core proteins from at least two different HBV

genotypes, wherein the HBcAg particle is preferably an isolated HBcAg particle. The HBcAg particle is preferably a mosaic HBcAg particle.

[0009] The present disclosure relates also to a pharmaceutical composition comprising the HBcAg particle disclosed herein and optionally a pharmaceutically acceptable carrier or excipient.

[0010] The present disclosure relates also to a container comprising one or more doses of the pharmaceutical composition comprising the HBcAg particle disclosed herein.

[0011] The present disclosure relates also to a kit comprising the pharmaceutical composition comprising the HBcAg particle disclosed herein and a second pharmaceutical composition comprising a HBsAg.

[0012] The present disclosure relates also to the HBcAg particle disclosed herein, optionally comprised in the pharmaceutical composition disclosed herein, optionally comprised in the container disclosed herein or in the kit disclosed herein, for use in therapy.

[0013] The present disclosure relates also to the HBcAg particle disclosed herein, optionally comprised in the pharmaceutical composition disclosed herein, optionally comprised in the container disclosed herein or in the kit disclosed herein, for use in treating an HBV infection.

[0014] The present disclosure relates also to an expression cassette, mRNA, or cDNA encoding an HBV core protein from HBV genotype C and an HBV core protein from HBV genotype D, wherein the expression cassette only comprises coding sequences for two or more HBV core proteins.

[0015] The present disclosure relates also to a nucleic acid molecule comprising the expression cassette, mRNA, or cDNA disclosed herein.

[0016] The present disclosure relates also to an expression vector comprising the expression cassette or cDNA disclosed herein or the nucleic acid molecule disclosed herein.

[0017] The present disclosure relates also to an expression vector or an mRNA encoding full-length or trincated HBV core proteins from two different HBV genotypes.

[0018] The present disclosure relates also to an expression vector or an mRNA encoding an HBV core protein from HBV genotype C and ananan HBV core protein from HBV genotype D, wherein the expression vector has at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO: 10.

[0019] The present disclosure relates also to a vaccine vector, wherein the vaccine vector is preferably an MVA viral vector, and wherein the vaccine vector comprises a nucleic acid molecule comprising a nucleotide sequence having at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO: 5.

[0020] The present disclosure relates also to the vaccine vector disclosed herein, optionally comprised in the pharmaceutical composition disclosed herein, optionally comprised in the container disclosed herein, for use in therapy.

[0021] The present disclosure relates also to the vaccine vector disclosed herein, optionally comprised in the pharmaceutical composition disclosed herein, optionally comprised in the container disclosed herein, for use in treating an HBV infection.

[0022] The present disclosure relates also to a pharmaceutical composition comprising the vaccine vector or mRNA disclosed herein and optionally a pharmaceutically acceptable carrier or excipient.

[0023] The present disclosure relates also to a container comprising one or more doses of the pharmaceutical composition comprising the vaccine vector disclosed herein, wherein a dose of the pharmaceutical composition comprises the vaccine vector in an amount from about 1x 10^7 ifu to about 1x 10^9 ifu.

[0024] The present disclosure relates also to a method of vaccination, comprising administering to a human subject

(i) a first dose of an HBcAg particle and of an HBsAg,

(ii) a second dose of the HBcAg particle and of the HBsAg,

(iii) a dose of a vaccine vector

wherein the vaccine vector expresses

a. an HBsAg from HBV genotype A;

b. an HBcAg from HBV genotype D;

c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7;

d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and

e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

[0025] The present disclosure relates also to an HBcAg particle, and optionally an HBsAg, for use in a method of vaccination.

[0026] The present disclosure relates also to a vaccine vector expressing

a. an HBsAg from HBV genotype A;
b. an HBcAg from HBV genotype D;
c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7;
d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and
e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

for use in a method of vaccination.

[0027] The present disclosure relates also to the use of an HBcAg particle, and optionally an HBsAg, for the manufacture of a medicament.

[0028] The present disclosure relates also to the use of a vaccine vector expressing

a. an HBsAg from HBV genotype A;
b. an HBcAg from HBV genotype D;
c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7;
d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8; and
e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9,

for the manufacture of a medicament.

[0029] The present disclosure relates also to the use of the expression cassette, mRNA, or cDNA disclosed herein, the nucleic acid molecule disclosed herein, the expression vector comprising the expression cassette or cDNA disclosed herein, and/or the expression vector encoding an HBV core protein from HBV genotype C and an HBV core protein from HBV genotype D disclosed herein, for the manufacture of a medicament.

IV. DETAILED DESCRIPTION

A. General structure of a Hepatitis B Virus (HBV) particle and HBV types

[0030] HBV particles comprise an outer envelope and an inner core that encloses both viral DNA and a DNA polymerase with reverse transcriptase activity. The outer envelope comprises lipids and embedded proteins, which are involved in viral binding of, and entry into, susceptible cells like human cells. A protein embedded in the outer envelope of an HBV particle is also herein referred to as both an HBV surface protein (HBs). The inner core of an HBV particle is a particulate capsid, more specifically an icosahedral nucleocapsid. A structural

Claims

1. Use of an HBcAg particle, an HBsAg, and a vaccine vector in the manufacture of a medicament for combination therapy for vaccination against hepatitis B, wherein the medicament is to be administered in
   (i) a first dose of the HBcAg particle, wherein the HBcAg particle comprises Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, and of the HBsAg,
   (ii) a second dose of the HBcAg particle and of the HBsAg, and
   (iii) a dose of the vaccine vector;
   wherein the vaccine vector expresses
      a. an HBsAg from HBV genotype A;
      b. an HBcAg from HBV genotype D;
      c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7;
      d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and
      e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

2. Use of an HBcAg particle in the manufacture of a first medicament, use of an HBsAg in the manufacture of a second medicament, and use of a vaccine vector in the manufacture of a third medicament, wherein the first, second and third medicaments are to be used in combination therapy for vaccination against hepatitis B, wherein the first, second and third medicaments are to be administered in

   (i) a first dose of the HBcAg particle, wherein the HBcAg particle comprises Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, and of the HBsAg,
   (ii) a second dose of the HBcAg particle and of the HBsAg, and
   (iii) a dose of the vaccine vector;
   wherein the vaccine vector expresses
      a. an HBsAg from HBV genotype A;
      b. an HBcAg from HBV genotype D;
      c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7;

d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and

e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

3. Use of an HBcAg particle in the manufacture of a medicament for use in combinatorial therapy for vaccination against hepatitis B, wherein said medicament is to be administered in combination with an HBsAg and a vaccine vector in

(i) a first dose of the HBcAg particle, wherein the HBcAg particle comprises Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, and of the HBsAg,

(ii) a second dose of the HBcAg particle and of the HBsAg, and

(iii) a dose of the vaccine vector;

wherein the vaccine vector expresses

a. an HBsAg from HBV genotype A;
b. an HBcAg from HBV genotype D;
c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7;
d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and
e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

4. Use of a vaccine vector in the manufacture of a medicament for use in combinatorial therapy for vaccination against hepatitis B, wherein said medicament is to be administered in combination with an HBcAg particle and an HBsAg in

(i) a first dose of the HBcAg particle, wherein the HBcAg particle comprises Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, and of the HBsAg,

(ii) a second dose of the HBcAg particle and of the HBsAg, and

(iii) a dose of the vaccine vector;

wherein the vaccine vector expresses

a. an HBsAg from HBV genotype A;
b. an HBcAg from HBV genotype D;

c. an HBsAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 7;
d. an HBcAg comprising a sequence having at least 90% sequence identity to the amino acid sequence set forth in SEQ ID NO: 8 or 17; and
e. an RT domain of a polymerase from HBV comprising a sequence having at least 90 % sequence identity to the amino acid sequence set forth in SEQ ID NO: 9.

5. The use of any one of claims 1-4, wherein the first dose and the second dose each comprise the HBcAg particle in an amount from about 10µg to about 100µg and the HBsAg in an amount from about 5µg to about 100µg, and/or wherein the dose of the vaccine vector comprises the vaccine vector in an amount from about 1x 10^7 ifu to about 1x 10^9 ifu.

6. The use of any one of claims 1-5, wherein the vaccination is therapeutic vaccination.

7. The use of any one of claims 1 to 6, wherein the HBcAg particle comprises HBV core proteins from HBV genotypes C and D.

8. A Hepatitis B Virus core antigen (HBcAg) particle, comprising Hepatitis B Virus (HBV) core proteins from at least two different HBV genotypes, wherein the HBcAg particle is preferably an isolated HBcAg particle.

9. A pharmaceutical composition comprising the HBcAg particle of claim 8 and optionally a pharmaceutically acceptable carrier or excipient.

10. A container comprising one or more doses of the pharmaceutical composition of claim 9.

11. A kit comprising the pharmaceutical composition of claim 9 and a second pharmaceutical composition comprising an HBsAg, wherein the HBsAg is preferably a particulate HBsAg.

12. An expression cassette, an mRNA, or a cDNA, wherein the expression cassette, mRNA, or cDNA, encodes an HBV core protein from HBV genotype C and an HBV core protein from HBV genotype D, wherein the expression cassette, mRNA, or cDNA, only comprises coding sequences for two or more HBV core proteins.

13. A nucleic acid molecule comprising the expression cassette, the mRNA, or the cDNA, of claim 12.

14. An expression vector comprising the expression cassette or the cDNA of claim 19 or the nucleic acid molecule of claim 13.

15. A vaccine vector, wherein the vaccine vector is preferably an MVA viral vector, and wherein the vaccine vector comprises a nucleic acid molecule comprising a nucleotide sequence having at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO: 5.

16. A pharmaceutical composition comprising the vaccine vector of claim 15 and optionally a pharmaceutically acceptable carrier or excipient.

17. A container comprising one or more doses of the pharmaceutical composition of claim 16, wherein a dose of the pharmaceutical composition comprises the vaccine vector in an amount from about 1x 10^7 ifu to about 1x 10^9 ifu.

18. Use of an HBcAg particle of claim 8 in the manufacture of a medicament for the vaccination against hepatitis B.