



(19) 대한민국특허청(KR)
(12) 등록특허공보(B1)

(45) 공고일자 2024년08월30일
(11) 등록번호 10-2700586
(24) 등록일자 2024년08월26일

(51) 국제특허분류(Int. Cl.)
A61K 39/29 (2006.01) A61K 39/00 (2006.01)
A61P 31/20 (2006.01)
(52) CPC특허분류
A61K 39/292 (2013.01)
A61P 31/20 (2018.01)
(21) 출원번호 10-2019-7031896
(22) 출원일자(국제) 2018년04월10일
심사청구일자 2021년04월09일
(85) 번역문제출일자 2019년10월28일
(65) 공개번호 10-2020-0024130
(43) 공개일자 2020년03월06일
(86) 국제출원번호 PCT/GB2018/050948
(87) 국제공개번호 WO 2018/189522
국제공개일자 2018년10월18일
(30) 우선권주장
1705765.4 2017년04월10일 영국(GB)
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WO2005017149 A1*
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전체 청구항 수 : 총 24 항

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(54) 발명의 명칭 HBV 백신

(57) 요약

본 발명은, 면역원 발현 카세트를 포함하는 바이러스 벡터를 포함하는 멀티-HBV 면역원 바이러스 벡터 백신으로서, 상기 발현 카세트에 의해 코딩된 단백질의 발현은 프로모터에 의해 유도되도록 정렬되어 있고, 상기 면역원 발현 카세트는 a) HBV 코어; b) 변형된 HBV 폴리머라제(P_{mut})로서, 상기 변형이 폴리머라제 기능을 실질적으로 제거하기 위한 야생형 HBV 폴리머라제에 대한 돌연변이인, 변형된 HBV 폴리머라제(P_{mut}); c) HBV 표면 항원(HbsAg); 및 d) HBV 코어 및 변형된 HBV 폴리머라제(P_{mut})와는 별개의 단백질로서 적어도 HBV 표면 항원(HbsAg)의 발현을 유발하도록 정렬되는 유전자간 서열을 코딩하고, 상기 유전자간 서열은 HBV 코어 및 변형된 HBV 폴리머라제(P_{mut})를 코딩하는 서열의 하류(3'), 및 HBV 표면 항원(HbsAg)을 코딩하는 서열의 상류(5')에 존재하는, 멀티-HBV 면역원 바이러스 벡터 백신; 관련 조성물, 백신접종 방법 및 HBV 감염의 치료 또는 예방 방법에 관한 것이다.

대표도 - 도4a



(52) CPC특허분류

A61K 2039/5256 (2013.01)
C12N 2710/10041 (2013.01)
C12N 2710/24041 (2013.01)
C12N 2730/10134 (2013.01)

(56) 선행기술조사문헌

W02013007772 A1*
US20130243805 A1
W02011015656 A2
W02012109404 A1

*는 심사관에 의하여 인용된 문헌

명세서

청구범위

청구항 1

면역원 발현 카세트(immunogen expression cassette)를 포함하는 바이러스 벡터를 포함하는 멀티-HBV 면역원 바이러스 벡터 백신으로서,

상기 발현 카세트에 의해 코딩된(encoded) 단백질의 발현은 프로모터에 의해 유도되도록 정렬되어 있고,

상기 면역원 발현 카세트는

- a) HBV 코어;
- b) 변형된 HBV 폴리머라제(P_{mut})로서, 상기 변형이 폴리머라제 기능을 실질적으로 제거하기 위한 야생형 HBV 폴리머라제에 대한 돌연변이인, 변형된 HBV 폴리머라제(P_{mut});
- c) HBV 표면 항원(HbsAg); 및
- d) HBV 코어 및 변형된 HBV 폴리머라제(P_{mut})와는 별개의 단백질로서 적어도 HBV 표면 항원(HbsAg)의 발현을 유발하도록 정렬되는 유전자간 서열

을 코딩하고,

상기 유전자간 서열은 HBV 코어 및 변형된 HBV 폴리머라제(P_{mut})를 코딩하는 서열의 하류(3'), 및 HBV 표면 항원(HbsAg)을 코딩하는 서열의 상류(5')에 존재하는, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 2

제1항에 있어서, 유전자간 서열이 절단 도메인, IRES(내부 리보솜 도입 부위), 스플라이싱 시그널(splicing signal), 또는 이차 프로모터를 포함하거나; 유전자간 서열이 절단 도메인을 포함하는, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 3

제1항 또는 제2항에 있어서, 상기 면역원 발현 카세트가 HBV 프레-코어(PreC)를 추가로 코딩하는 것이고/이거나;

상기 면역원 발현 카세트가 HBV PreS1 및/또는 이의 절단된 형태(truncated form)를 추가로 코딩하는 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 4

제1항 또는 제2항에 있어서, 상기 면역원 발현 카세트가 HBV PreS2를 추가로 코딩하는 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 5

제1항 또는 제2항에 있어서, 상기 면역원 발현 카세트가 HBV 프레-코어(PreC) 및 HBV PreS1, 및 PreS1의 절단된 형태를 코딩하는 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 6

제1항 또는 제2항에 있어서, 상기 면역원 발현 카세트가 HBV e-항원을 발현시킬 수 있는 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 7

제1항 또는 제2항에 있어서, 상기 HBV 코어 및 변형된 폴리머라제(Pmut)가 융합 단백질로서 발현되도록 정렬되어 있는, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 8

제1항 또는 제2항에 있어서, HBV 프레-코어, HBV 코어 및 변형된 폴리머라제(Pmut)가 융합 단백질로서 발현되도록 정렬되어 있는, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 9

제1항 또는 제2항에 있어서, 상기 면역원 발현 카세트가 HBV X 단백질을 코딩하지 않는 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 10

제1항 또는 제2항에 있어서,

상기 면역원 발현 카세트가

서열번호 46(SIi-HBV-CPmutS), 또는 서열번호 46과 적어도 95%의 서열 상동성을 갖는 이의 변이체;

서열번호 48(SIi-HBV-CPmutPreS-S(sh)), 또는 서열번호 48과 적어도 95%의 서열 상동성을 갖는 이의 변이체;

서열번호 49(SIi-HBV-CPmutPreS-TPA-S(sh)), 또는 서열번호 49와 적어도 95%의 서열 상동성을 갖는 이의 변이체;

서열번호 24(MVA-SIi-HBV-PreS-Pmut-C-S(sh)), 또는 서열번호 24와 적어도 95%의 서열 상동성을 갖는 이의 변이체; 또는

서열번호 27 또는 서열번호 58(MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh)), 또는 서열번호 27 또는 서열번호 58과 적어도 95%의 서열 상동성을 갖는 이의 변이체

의 서열로 이루어진 핵산을 포함하는 것이고/이거나;

상기 바이러스 벡터가

서열번호 3(SIi-HBV-CPmutS), 또는 서열번호 3과 적어도 95%의 서열 상동성을 갖는 이의 변이체;

서열번호 13(SIi-HBV-CPmutPreS-S(sh)), 또는 서열번호 13과 적어도 95%의 서열 상동성을 갖는 이의 변이체;

서열번호 25(SIi-HBV-CPmutPreS-TPA-S(sh)), 또는 서열번호 25와 적어도 95%의 서열 상동성을 갖는 이의 변이체;

서열번호 23(MVA-SIi-HBV-PreS-Pmut-C-S(sh)), 또는 서열번호 23과 적어도 95%의 서열 상동성을 갖는 이의 변이체; 또는

서열번호 26(MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh)), 또는 서열번호 26과 적어도 95%의 서열 상동성을 갖는 이의 변이체

의 아미노산 서열을 코딩하는 것인,

멀티-HBV 면역원 바이러스 벡터 백신.

청구항 11

제1항 또는 제2항에 있어서, 상기 바이러스 벡터가 아테노바이러스 벡터 또는 변형된 백신시아 안카라(Modified Vaccinia Ankara)(MVA) 벡터를 포함하거나;

상기 바이러스 벡터가 그룹 E 시미안(simian) 아테노바이러스 벡터를 포함하는 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 12

제1항 또는 제2항에 있어서, 상기 프로모터가 면역원 발현 카세트 내에 코딩되어 있거나; 또는

상기 프로모터가 면역원 발현 카세트의 외측의 바이러스 벡터 핵산의 일부로서 코딩될 수 있고/있거나; 상기 프로모터가 CMV 프로모터 또는 폭스 바이러스 프로모터를 포함하는 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 13

제1항 또는 제2항에 있어서, 상기 프로모터가 면역원 발현 카세트의 모든 코딩된 단백질의 발현을 촉진하는, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 14

제1항 또는 제2항에 있어서, 상기 면역원 발현 카세트가 이차 프로모터를 포함하고,

상기 프로모터가, 적어도 HBV 코어 및 변형된 폴리머라제(P_{mut})의 발현을 촉진하되, 상기 이차 프로모터에 의해 별도로 촉진되도록 정렬되어 있는 HBV 표면 항원(HbsAg)은 촉진하지 않도록 정렬되어 있는 일차 프로모터이고/있거나;

상기 프로모터가 CMV 프로모터 또는 폭스 바이러스 프로모터를 포함하는 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 15

제1항 또는 제2항에 있어서, 상기 HBV 코어가 전장 야생형(full length wild-type) HBV 코어 서열을 포함하거나 이로 이루어진 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 16

제1항 또는 제2항에 있어서, 상기 변형된 HBV 폴리머라제(P_{mut})가 절단된 형태의 HBV 폴리머라제가 아니고/아니거나;

상기 변형된 HBV 폴리머라제(P_{mut})가 서열번호 8의 서열 또는 서열번호 8과 적어도 95%의 서열 상동성을 갖는 이의 변이체로 이루어지는 것이고/있거나;

상기 HbsAg가 전장 야생형 HbsAg 서열, 또는 서열번호 10과 적어도 95%의 서열 상동성을 갖는 이의 변이체로 이루어지는 것인, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 17

제1항 또는 제2항에 있어서, 상기 면역원 발현 카세트가 절단된 형태의 HBV PreS1을 코딩하고, 상기 절단된 PreS1이 HBV 표면 항원(S/HbsAg)과의 융합 단백질을 발현하도록 정렬된, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 18

제1항 또는 제2항에 있어서, 상기 발현 카세트가 NΔPreS1 및 PreS2 융합 서열을 코딩하는, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 19

제1항 또는 제2항에 있어서, 상기 면역원 발현 카세트가 펩티드 애주반트(adjuvant)를 추가로 코딩하는, 멀티-HBV 면역원 바이러스 벡터 백신.

청구항 20

HBV 면역원 발현 카세트를 포함하거나 이로 이루어지는 핵산으로서,

상기 면역원 발현 카세트는

- a) HBV 코어;
- b) 변형된 HBV 폴리머라제(P_{mut})로서, 상기 변형이 폴리머라제 기능을 실질적으로 제거하기 위한 야생형 HBV 폴리머라제에 대한 돌연변이인, 변형된 HBV 폴리머라제(P_{mut});

c) HBV 표면 항원(HbsAg); 및

d) HBV 코어 및 변형된 HBV 폴리머라제(P_{mut})와는 별개의 단백질로서 적어도 HBV 표면 항원(HbsAg)의 발현을 유발하도록 정렬되는 유전자간 서열

을 코딩하고,

상기 유전자간 서열은 HBV 코어 및 변형된 HBV 폴리머라제(P_{mut})를 코딩하는 서열의 하류(3'), 및 HBV 표면 항원(HbsAg)을 코딩하는 서열의 상류(5')에 존재하는, 핵산.

청구항 21

제20항에 있어서, 상기 면역원 발현 카세트가 프로모터를 추가로 코딩하는 것이고/이거나;

상기 면역원 발현 카세트가 단리된 것 또는 비-바이러스 벡터 내에 제공되어있는 것인, 핵산.

청구항 22

제1항 또는 제2항에 따른 바이러스 벡터, 또는 제20항 또는 제21항에 따른 핵산을 포함하는 조성물로서, 상기 조성물은 HBV 감염을 예방 또는 치료하는 데 사용하기 위해 약제학적으로 허용되는 조성물인, 조성물.

청구항 23

제22항에 있어서, 대상체에서 HBV 감염을 예방 또는 치료하는 데 사용하기 위한 것으로서, 백신으로 사용하기 위한, 조성물.

청구항 24

프라임 부스트 백신접종 키트(prime boost vaccination kit)로서,

- 제1항 또는 제2항에 따른 바이러스 벡터, 제20항 또는 제21항에 따른 핵산, 또는 상기 바이러스 벡터 또는 상기 핵산을 포함하는 조성물을 포함하는 프라임 백신접종; 및

- 제1항 또는 제2항에 따른 바이러스 벡터, 제20항 또는 제21항에 따른 핵산, 또는 상기 바이러스 벡터 또는 상기 핵산을 포함하는 조성물을 포함하는 부스트 백신접종

을 포함하는, 프라임 부스트 백신접종 키트.

청구항 25

삭제

청구항 26

삭제

청구항 27

삭제

청구항 28

삭제

청구항 29

삭제

청구항 30

삭제

청구항 31

삭제

청구항 32

삭제

청구항 33

삭제

청구항 34

삭제

청구항 35

삭제

청구항 36

삭제

청구항 37

삭제

청구항 38

삭제

청구항 39

삭제

청구항 40

삭제

청구항 41

삭제

청구항 42

삭제

청구항 43

삭제

청구항 44

삭제

청구항 45

삭제

발명의 설명

기술 분야

[0001] 본 발명은, 만성 B형 간염의 치료적 백신접종을 위한 바이러스 벡터화 백신을 위한 멀티-항원 HBV 면역원에 관한 것이다.

배경 기술

- [0002] B형 간염은, 간장을 공격하는 바이러스 감염이고, 급성 및 만성 질환 둘 다를 유발할 수 있다. B형 간염 바이러스(HBV)는 감염된 개인의 혈액 또는 기타 체액과의 접촉을 통해 감염된다. 급성 B형 간염에 대한 특별한 치료법은 없다. 따라서, 관리는, 구토 및 설사로부터 상실된 체액의 보충을 포함하는, 쾌적한 및 적절한 영양 밸런스를 유지하는 것을 목적으로 한다. 그러나, 급성 B형 간염 치료의 주력은 백신접종을 사용하는 예방이다. 확립되면, 만성 B형 간염 감염은 경구 항바이러스제를 포함하는 약물로 치료될 수 있다. 치료는 간경변의 진행을 지연시키고 간암의 발생율을 저하시키고 장기간 생존을 개선시킬 수 있다. 그러나, 만성 감염이 확립되면, 자발적 바이러스 제어는 희박하다. 따라서, 주요 목표는 바이러스의 제어 또는 치유를 유도하는 면역요법 HBV 백신을 개발하는 것이다.
- [0003] 현재, 제1 상 및 제2 상 임상 시험에서 상이한 T 세포 유도 백신은 거의 없고, 이들 모두는 1 또는 2개의 전장 HBV-항원에 기초하거나, 또는 복수 절단된 또는 전장 키메라 HBV-항원 또는 HBV-프로테오솜에 기반한 합성 펩티드에 기초한다. 글로브이문(GlobeImmune)에 의한 GS-4774는 현재 제2 상 임상 시험 중에 있다(GS-4774는 HBx HBsAg 및 HbcAg의 키메라를 발현하는 열-불활성화된 효모 세포를 갖는다). 트랜스진(Transgene)에 의한 TG1050은 현재 제1 상 임상 시험 중에 있다(TG1050은 3개 HBV 항원, 코어-폴리머라제-엔벨로프의 절단된 버전의 키메라를 코딩하는 인간 아데노바이러스 혈청형 5 기반 백신이다). 알티문(Altimmune)에 의한 HepTcellTM은 현재 제1 상 임상 시험 중에 있다(HepTcell은 HBV 단백질의 보존된 영역으로부터 유래하는 9 합성 32-머 펩티드에 기초하는 완전 합성 펩티드 생성물이다). 이노비오(Inovio)에 의한 INO-1800은 현재 제1 상 임상 시험중에 있다(INO-1800은 B형 간염 바이러스 클레이드 A 및 C 표면 항원 및 HBV 코어 항원을 표적화하는 멀티-항원 SynCon® DNA 면역요법이다). 현재 이용가능한 예방적 HBV 백신(일반적으로 HBV 단백질 백신에 기초)은 만성 감염된 HBV 개체에 대한 치료 효과를 갖지 않고, 따라서 이들은 만성 HBV 감염을 제어할 수 없다.
- [0004] 따라서, 본 발명의 목적은 HBV 감염을 위한 개선된 백신을 제공하는 것이다.

발명의 내용

- [0005] 본 발명의 제1 양태에 따르면, 면역원 발현 카세트(immunogen expression cassette)를 포함하는 바이러스 벡터를 포함하는 멀티-HBV 면역원 바이러스 벡터 백신으로서,
- [0006] 상기 발현 카세트에 의해 코딩된(encoded) 단백질의 발현은 프로모터에 의해 유도되도록 정렬되어 있고,
- [0007] 상기 면역원 발현 카세트는
- [0008] a) HBV 코어;
- [0009] b) 변형된 HBV 폴리머라제(P_{mut})로서, 상기 변형이 폴리머라제 기능을 실질적으로 제거하기 위한 야생형 HBV 폴리머라제에 대한 돌연변이인, 변형된 HBV 폴리머라제(P_{mut});
- [0010] c) HBV 표면 항원(HbsAg); 및
- [0011] d) HBV 코어 및 변형된 HBV 폴리머라제(P_{mut})와는 별개의 단백질로서 적어도 HBV 표면 항원(HbsAg)의 발현을 유발하도록 정렬되는 유전자간 서열을 코딩하고,
- [0012] 상기 유전자간 서열은 HBV 코어 및 변형된 HBV 폴리머라제(P_{mut})를 코딩하는 서열의 하류(3'), 및 HBV 표면 항원(HbsAg)을 코딩하는 서열의 상류(5')에 존재하는, 멀티-HBV 면역원 바이러스 벡터 백신을 제공한다.
- [0013] 상기 유전자간 서열은 절단 도메인, IRES(내부 리보솜 도입 부위), 스플라이싱 시그널(splicing signal) 또는 이차 프로모터를 포함할 수 있다. 한 가지 실시형태에서, 유전자간 서열은 리보솜 스킵을 유발하도록 정렬된 서열을 포함하는 절단 도메인을 포함한다. 또 다른 실시형태에서, 유전자간 서열은 적어도 표면 항원(HbsAg)의 발현을 촉진시키는 이차 프로모터를 포함한다.
- [0014] 상이한 HBV 단백질에 대한 강력한 멀티-항원 특이적 T 세포 반응의 도입은 분석하는 만성 HBV 감염의 바이러스 정화에 중요한 역할을 담당하는 것으로 생각된다. 멀티-항원 T-세포 반응의 도입을 위해, T-세포 유도 HBV 백신 내에서 전장 HBV 단백질을 코딩할 필요가 있는 최대수의 T-세포 에피토프를 갖는 것이 중요하다. 개발중의 현재의 HBV 백신의 일부는 전장 HBV 항원을 코딩하지 않는다. 본 발명의 백신은 HBV의 3개 전장 단백질을 코딩할 수 있다(즉, 임의로 프레-코어 영역, 폴리머라제 및 표면 단백질을 수반하는 코어). 또한, 백신 설계는, 예

를 들면, 별도의 표면 단백질을 코딩하기 위해 F2A 캡티드 절단 전략을 사용하여 적어도 2개-단백질 발현을 이용하고, 이는 T-세포 반응의 유도에 추가하여, T-세포 백신의 치료 효과를 증강하는 역할을 할 수 있는 항체 반응을 또한 유도할 수 있고, 만성적으로 감염된 개체에서 바이러스의 정화에 도움을 줄 수 있다. 포유동물 시스템(다른 시스템, 예를 들면, 효모와 비교하여)에 기초한 항체의 유도는 천연 숙주에 적절한 항체를 유도할 수 있는 포유동물형 글리코실화를 제공하는 선택적 잇점을 갖는다.

[0015] 본 발명은, 유리하게는, 광범위한 T-세포 반응을 유도하고 추가로 표면 단백질에 대한 항체를 또한 유도할 수 있는 전장 멀티-HBV 항원을 코딩하는 단일 백신을 제공한다. 새로운 HBV 면역원은 적어도 3개 전장 HBV-항원(즉, 코어, 폴리머라제 및 표면)을 포함하고, 이들을 칩앤지 아데노 및 MVA 바이러스 벡터 등의 바이러스 벡터에 코딩했다. 또한, 면역원 중의 HBV-폴리머라제 단백질에는 이의 기능을 무력화하는 돌연변이가 제공되고, 이는 HBV 게놈 복제에 대한 관여를 회피하고 백신의 안전성을 개선시킨다.

[0016] 캡티드 절단 전략을 사용함으로써, 예를 들면, 퓨린-2A 절단 서열 또는 이차 프로모터를 사용함으로써, 도입유전자 카세트는 적어도 2개 단백질, 융합 코어 및 폴리머라제 단백질 및 별도의 표면 단백질을 생성할 수 있고, 이들 둘 다는 T-세포 면역 반응을 생성한다. 코딩된 표면 단백질은, T-세포 면역 반응의 생성에 추가하여, 항체 반응을 또한 생성할 수 있다.

[0017] **면역원 발현 카세트**

[0018] 당업자는, 절단 도메인이 모든 경우에 대해 절단을 유도하지 않을 수 있고, 예를 들면, F2A 기반 리보솜 스킵 사상이 작은 비율의 발현에서 발생할 수 있음을 인식하고, 그 결과, 제조된 작은 비율의 단백질은 절단에 의해 분리될 수 있는 HBV 단백질/항원 모두의 융합체일 수 있다. 따라서, 한 가지 실시형태에서, 면역원 발현 카세트는 적어도 HBV 코어, 변형된 HBV 폴리머라제(Pmut) 및 HBV 표면 항원을 포함하는 융합 단백질을 추가로 코딩할 수 있다.

[0019] 한 가지 실시형태에서, 면역원 발현 카세트는 HBV 프레-코어(PreC)를 추가로 코딩한다. 또 다른 실시형태에서, 면역원 발현 카세트는 HBV PreS1 및/또는 이의 절단된 형태(truncated form)를 추가로 코딩한다. 또 다른 실시형태에서, 면역원 발현 카세트는 HBV PreS2를 추가로 코딩한다.

[0020] 한 가지 실시형태에서, 면역원 발현 카세트는 HBV 프레-코어(PreC) 및 HBV PreS1, 또는 절단된 형태의 HBV PreS1을 추가로 코딩한다. 또 다른 실시형태에서, 면역원 발현 카세트는 HBV 프레-코어(PreC) 및 HBV PreS2를 추가로 코딩한다. 한 가지 실시형태에서, 면역원 발현 카세트는 HBV 프레-코어(PreC) 및 HBV PreS1, 및 절단된 형태의 PreS1을 추가로 코딩한다. 한 가지 실시형태에서, 면역원 발현 카세트는 HBV 프레-코어(PreC), HBV PreS1, 및/또는 이의 절단된 형태 및 HBV PreS2를 추가로 코딩한다.

[0021] HBV 프레-코어 및 코어가 코딩되는 실시형태에서, 면역원 발현 카세트는 HBV e-항원을 발현할 수 있다. 당업자는, HBV e-항원이 프레-코어의 10 C-말단 아미노산 및 코어의 149 N-말단 아미노산을 포함하거나 이들로 이루어지는 것을 인식한다. HBV e-항원의 발현을 위해, 프레-코어 및 코어는 함께 발현되고, 이러한 전체 발현된 단백질은 N-말단 및 C-말단 절단을 받는다.

[0022] 한 가지 실시형태에서, HBV 코어 및 변형된 폴리머라제(Pmut)는 융합 단백질로서 발현되도록 정렬된다. 면역원 발현 카세트가 HBV 프레-코어를 코딩하는 실시형태에서, HBV 프레-코어, HBV 코어 및 변형된 폴리머라제(Pmut)는 융합 단백질로서 발현되도록 정렬된다.

[0023] 한 가지 실시형태에서, 면역원 발현 카세트는, 적어도 HBV 코어 및 변형된 HBV 폴리머라제(Pmut)를 포함하는 제1 융합 단백질, 및 적어도 HBV 표면 항원(HbsAg)을 포함하는 제2 단백질을 포함하는, 적어도 2개 단백질을 코딩한다. 또 다른 실시형태에서, 면역원 발현 카세트는, 적어도 HBV 코어 및 변형된 HBV 폴리머라제(Pmut)를 포함하는 제1 융합 단백질, 및 적어도 HBV 표면 항원(HbsAg)을 포함하는 제2 단백질을 포함하는, 2개 단백질만을 코딩한다.

[0024] 한 가지 실시형태에서, 면역원 발현 카세트는 HBV X 단백질을 코딩하지 않는다.

[0025] 한 가지 실시형태에서, 면역원 발현 카세트는, 본원에 기재된 바와 같이,

[0026] SIi-HBV-CPmutS;

[0027] SIi-HBV-SCPmut;

[0028] HBV-CPmutS;

- [0029] SIi-HBV-CPmutPreS-S(sh);
- [0030] SIi-HBV-CPmutPreS-TPA-S(sh);
- [0031] SIi-HBV-PreS-Pmut-C;
- [0032] MVA-SIi-HBV-PreS-Pmut-C-S(sh); 또는
- [0033] MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh) 중의 어느 하나를 코딩하는 핵산 서열을 포함할 수 있다.
- [0034] 한 가지 실시형태에서, 면역원 발현 카세트는 서열번호 46(SIi-HBV-CPmutS) 또는 이의 변이체를 포함한다. 서열번호 46의 변이체는 서열번호 46과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 46의 변이체는, 서열번호 46에 의해 코딩된 동등한 단백질의 면역원성을 실질적으로 보유하는 단백질을 코딩할 수 있다.
- [0035] 한 가지 실시형태에서, 면역원 발현 카세트는 서열번호 47(SIi-HBV-SCPmut) 또는 이의 변이체를 포함한다. 서열번호 47의 변이체는 서열번호 47과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 47의 변이체는, 서열번호 47에 의해 코딩된 동등한 단백질의 면역원성을 실질적으로 보유하는 단백질을 코딩할 수 있다.
- [0036] 또 다른 실시형태에서, 면역원 발현 카세트는 서열번호 48(SIi-HBV-CPmutPreS-S(sh)) 또는 이의 변이체를 포함한다. 서열번호 48의 변이체는 서열번호 48과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 48의 변이체는, 서열번호 48에 의해 코딩된 동등한 단백질의 면역원성을 실질적으로 보유하는 단백질을 코딩할 수 있다.
- [0037] 또 다른 실시형태에서, 면역원 발현 카세트는 서열번호 49(SIi-HBV-CPmutPreS-TPA-S(sh)) 또는 이의 변이체를 포함한다. 서열번호 49의 변이체는 서열번호 49와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 49의 변이체는, 서열번호 49에 의해 코딩된 동등한 단백질의 면역원성을 실질적으로 보유하는 단백질을 코딩할 수 있다.
- [0038] 한 가지 실시형태에서, 면역원 발현 카세트는 서열번호 59(SIi-HBV-PreS-Pmut-C) 또는 이의 변이체를 포함한다. 서열번호 59의 변이체는 서열번호 59와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 59의 변이체는, 서열번호 59에 의해 코딩된 동등한 단백질의 면역원성을 실질적으로 보유하는 단백질을 코딩할 수 있다.
- [0039] 한 가지 실시형태에서, 면역원 발현 카세트는 서열번호 24(MVA-SIi-HBV-PreS-Pmut-C-S(sh)) 또는 이의 변이체를 포함한다. 서열번호 24의 변이체는 서열번호 24와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 24의 변이체는, 서열번호 24에 의해 코딩된 동등한 단백질의 면역원성을 실질적으로 보유하는 단백질을 코딩할 수 있다.
- [0040] 한 가지 실시형태에서, 면역원 발현 카세트는 서열번호 27(MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh)) 또는 이의 변이체를 포함한다. 서열번호 27의 변이체는 서열번호 27과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 27의 변이체는, 서열번호 27에 의해 코딩된 동등한 단백질의 면역원성을 실질적으로 보유하는 단백질을 코딩할 수 있다. 한 가지 실시형태에서, 면역원 발현 카세트는 서열번호 58(MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh)) 또는 이의 변이체를 포함한다. 서열번호 58의 변이체는 서열번호 58과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 58의 변이체는, 서열번호 58에 의해 코딩된 동등한 단백질의 면역원성을 실질적으로 보유하는 단백질을 코딩할 수 있다.
- [0041] **바이러스 벡터**
- [0042] 바이러스 벡터는 바이러스를 포함할 수 있다. 본 발명의 면역원 발현 카세트는, 양호한 면역 반응을 유발하는 것으로 공지되어 있는 임의의 적합한 바이러스 벡터에 클로닝시킬 수 있다. 적합한 바이러스 벡터는 문헌[참조: Dicks et al (Vaccine. 2015 Feb 25;33(9):1121-8. doi: 10.1016/j.vaccine.2015.01.042. Epub 2015 Jan 25), Antrobus et al (Mol Ther. 2014 Mar;22(3):668-74. doi: 10.1038/mt.2013.284. Epub 2013 Dec 30.), 및 Warimwe et al. (Virol J. 2013 Dec 5;10:349. doi: 10.1186/1743-422X-10-349)]에 기재되어 있고, 이들은 참조에 의해 본원에 도입된다.
- [0043] 바이러스 벡터는 약독화 바이러스 벡터일 수 있다. 바이러스 벡터는 아데노바이러스, 예를 들면, 인간 또는 시

미안(simian) 아데노바이러스를 포함할 수 있다. 한 가지 실시형태에서, 바이러스 벡터는 아데노바이러스, 예를 들면, 프라임 부스트 접생의 프라임 백신에 사용되는 경우, 그룹 E 시미안 아데노바이러스를 포함한다. 바이러스 벡터는 그룹 E 시미안 아데노바이러스를 포함할 수 있다. 바이러스 벡터는 ChAdOx1(그룹 E 시미안 아데노바이러스, 예를 들면, 말라리아 시험에서 안전하게 사용되는 AdCh63 벡터) 또는 ChAdOx2를 포함할 수 있다. 당업자는, 예를 들면, 본원에서 참조로서 도입되는 특허 공보 W02012172277로부터, ChAdOx1 기반 바이러스 벡터에 친숙할 것이다. 바이러스 벡터는 AdCh63을 포함할 수 있다. 바이러스 벡터는 AdC3 또는 AdH6을 포함할 수 있다. 한 가지 실시형태에서, 바이러스 벡터는 인간 혈청형이다. 또 다른 실시형태에서, 바이러스 벡터는 변형된 백신시아 안카라(Modified Vaccinia Ankara)(MVA)를 포함한다. 바이러스 벡터는, 프라임 부스트 접생에서 백신 부스트로서 사용되는 경우, MVA를 포함할 수 있다. 한 가지 실시형태에서, 바이러스 벡터는 아데노바이러스, 예를 들면, 프라임 부스트 접생의 프라임 백신에 사용되는 경우, 그룹 E 시미안 아데노바이러스를 포함하고, 프라임 부스트 접생에서 백신 부스트로서 사용되는 경우, MVA를 포함할 수 있다. 당업자는, 예를 들면, 본원에서 참조로서 도입되는 미국 특허 공보 US9273327호로부터 MVA 기반 바이러스 벡터에 친숙할 것이다.

[0044] MVA는 유리하게는 상이한 폭스 바이러스 프로모터를 사용하여 하나 이상의 단백질의 발현을 가능하게 한다.

[0045] 대체 실시형태에서, 바이러스 벡터는 아데노-연관 바이러스(AAV) 또는 렌티바이러스(*Lentivirus*)를 포함할 수 있다. 또 다른 실시형태에서, 바이러스 벡터는 임의의 백신시아 바이러스, 계두 바이러스 또는 카나리폭스 바이러스(예를 들면, 폭스비리다에(*Poxviridae*) 및 아비폭스바이러스(*Avipoxvirus*)속의 구성원) 또는 뉴욕 약독화 백신시아 바이러스[참조: Tartaglia *et al.* Virology. 1992 May;188(1):217-32, 이는 본원에서 참조로서 도입된다]를 포함할 수 있다. 또 다른 실시형태에서, 바이러스 벡터는 임의의 헤르페스 심플렉스 바이러스, 인간 사이토메갈로 바이러스, 메아슬레스 바이러스(MeV), 센다이 바이러스(SeV), 플라비바이러스(*Flavivirus*)(예: 황열병 바이러스-17D), 또는 알파바이러스(*alphavirus*) 벡터, 예를 들면, 신디비스 바이러스(SINV), 벤-에주엘란 말 뇌염 바이러스, 또는 쉼리키 산립 바이러스를 포함할 수 있다.

[0046] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 39 및 40(ChAdOx1)의 서열 또는 이의 변이체를 포함하는 핵산을 포함할 수 있다. 서열번호 39 및 40의 변이체는 서열번호 39 및 40과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 39 및 40의 변이체는, 서열번호 39 및 40(ChAdOx1)의 바이러스 벡터의 기능을 실질적으로 보유하는 바이러스 벡터를 코딩할 수 있다.

[0047] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 41 및 42(ChAdOx2)의 서열 또는 이의 변이체를 포함하는 핵산을 포함할 수 있다. 서열번호 41 및 42의 변이체는 서열번호 41 및 42와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 41 및 42의 변이체는, 서열번호 41 및 42(ChAdOx2)의 바이러스 벡터의 기능을 실질적으로 보유하는 바이러스 벡터를 코딩할 수 있다.

[0048] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 44 및 45(MVA)의 서열 또는 이의 변이체를 포함하는 핵산을 포함할 수 있다. 서열번호 44 및 45의 변이체는 서열번호 44 및 45와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 44 및 45의 변이체는, 서열번호 44 및 45(MVA)의 바이러스 벡터의 기능을 실질적으로 보유하는 바이러스 벡터를 코딩할 수 있다.

[0049] 한 가지 실시형태에서, 바이러스 벡터는, 본원에 기재된 바와 같이,

[0050] SIi-HBV-CPmutS;

[0051] SIi-HBV-SCPmut;

[0052] SIi-HBV-CPmutPreS-S(sh);

[0053] SIi-HBV-CPmutPreS-TPA-S(sh);

[0054] MVA-SIi-HBV-PreS-Pmut-C-S(sh); 또는

[0055] MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh) 중의 어느 하나를 코딩한다.

[0056] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 3(SIi-HBV-CPmutS) 또는 이의 변이체를 코딩한다. 서열번호 3의 변이체는 서열번호 3과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 3의 변이체는 실질적으로 서열번호 3의 면역원성을 보유할 수 있다.

[0057] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 11(SIi-HBV-SCPmut) 또는 이의 변이체를 코딩한다. 서열번호 11의 변이체는 서열번호 11과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열

을 포함할 수 있다. 서열번호 11의 변이체는 실질적으로 서열번호 11의 번역원성을 보유할 수 있다.

- [0058] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 13(SIi-HBV-CPmutPreS-S(sh)) 또는 이의 변이체를 코딩한다. 서열번호 13의 변이체는 서열번호 13과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 13의 변이체는 실질적으로 서열번호 13의 번역원성을 보유할 수 있다.
- [0059] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 25(SIi-HBV-CPmutPreS-TPA-S(sh)) 또는 이의 변이체를 코딩한다. 서열번호 25의 변이체는 서열번호 25와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 25의 변이체는 실질적으로 서열번호 25의 번역원성을 보유할 수 있다.
- [0060] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 23(MVA-SIi-HBV-PreS-Pmut-C-S(sh)) 또는 이의 변이체를 코딩한다. 서열번호 23의 변이체는 서열번호 23과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 23의 변이체는 실질적으로 서열번호 23의 번역원성을 보유할 수 있다.
- [0061] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 26(MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh)) 또는 이의 변이체를 코딩한다. 서열번호 26의 변이체는 서열번호 26과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 26의 변이체는 실질적으로 서열번호 26의 번역원성을 보유할 수 있다.
- [0062] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 46(SIi-HBV-CPmutS)의 핵산 서열 또는 이의 변이체를 포함한다. 서열번호 46의 변이체는 서열번호 46과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다.
- [0063] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 47(SIi-HBV-SCPmut)의 핵산 서열 또는 이의 변이체를 포함한다. 서열번호 47의 변이체는 서열번호 47과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다.
- [0064] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 48(SIi-HBV-CPmutPreS-S(sh))의 핵산 서열 또는 이의 변이체를 포함한다. 서열번호 48의 변이체는 서열번호 48과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다.
- [0065] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 49(SIi-HBV-CPmutPreS-TPA-S(sh))의 핵산 서열 또는 이의 변이체를 포함한다. 서열번호 49의 변이체는 서열번호 49와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다.
- [0066] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 24(MVA-SIi-HBV-PreS-Pmut-C-S(sh))의 핵산 서열 또는 이의 변이체를 포함한다. 서열번호 24의 변이체는 서열번호 24와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다.
- [0067] 한 가지 실시형태에서, 바이러스 벡터는 서열번호 27(MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh))의 핵산 서열 또는 이의 변이체를 포함한다. 서열번호 27의 변이체는 서열번호 27과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 한 가지 실시형태에서, 바이러스 벡터는 서열번호 58(MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh))의 핵산 서열 또는 이의 변이체를 포함한다. 서열번호 58의 변이체는 서열번호 58과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다.
- [0068] **프로모터**
- [0069] 한 가지 실시형태에서, 프로모터는 번역원 발현 카세트에서 코딩되고, 예를 들면, 프로모터는 번역원 발현 카세트의 5' 말단에 또는 이에 인접하여 코딩될 수 있다. 또는, 프로모터는 번역원 발현 카세트의 외측의 바이러스 벡터 핵산의 일부로서 코딩될 수 있다. 예를 들면, 프로모터는 번역원 발현 카세트의 상류(5')에 코딩될 수 있다.
- [0070] 프로모터는 번역원 발현 카세트의 모든 코딩된 단백질의 발현을 촉진할 수 있다. 번역원 발현 카세트가 이차 프로모터를 포함하는 대체 실시형태에서, 프로모터는 적어도 HBV 코어 및 변형된 폴리머라제(Pmut)의 발현을 촉진하도록 정렬되는 일차 프로모터일 수 있고, 임의로 이차 프로모터에 의해 별개로 촉진되도록 정렬될 수 있는

HBV 표면 항원(HbsAg)은 아닐 수 있다.

- [0071] 당업자는, 발현을 위한 숙주 세포에 적절하도록, 임의의 적합한 프로모터를 일차 및/또는 이차 프로모터로서 사용할 수 있음을 인식할 것이다. 한 가지 실시형태에서, 프로모터는 CMV 프로모터를 포함한다. CMV 프로모터는 긴 또는 짧은 CMV 프로모터를 포함할 수 있다. 바이러스 벡터가 아데노바이러스 벡터, 예를 들면, ChAdOx1 또는 2를 포함하는 실시형태에서, 프로모터는 CMV 프로모터, SV40 프로모터 또는 EF1a 프로모터를 포함할 수 있다. 바이러스 벡터가 아데노바이러스 벡터, 예를 들면, ChAdOx1 또는 2를 포함하는 실시형태에서, 프로모터는 CMV 프로모터를 포함할 수 있다.
- [0072] 벡터, 예를 들면, 아데노바이러스 벡터(예: ChAdOx1 또는 2)에 사용된 프로모터 요소(들)는 테트라사이클린 오퍼레이터(*tetO*) 서열을 포함할 수 있다. 테트라사이클린 오퍼레이터(*tetO*) 서열은, 이들이 생성되는 세포에 독성인 외래 단백질을 발현할 수 있는 바이러스 벡터의 생성에 유용하다.
- [0073] 또 다른 실시형태에서, 프로모터는 폭스 바이러스 프로모터를 포함한다. 바이러스 벡터가 MVA를 포함하는 실시형태에서, 프로모터는 폭스 바이러스 프로모터, 예를 들면, F11을 포함할 수 있다. 한 가지 실시형태에서, 프로모터는 초기 F11 프로모터를 포함한다. 또는, 폭스 바이러스 프로모터는, 예를 들면, B8R, K6L, A44L, C11R 및 B2R의 어느 하나로부터 선택된 초기 프로모터, 초기 및 후기 활성을 갖는 프로모터, 예를 들면, mH5, p7.5 및 SSP로부터 선택된 프로모터, 또는 후기 프로모터, 예를 들면, FP4b를 포함할 수 있다.
- [0074] 초기 프로모터 기반 도입유전자 발현은 주로 T-세포 반응을 목적으로 하는 면역원에 유용할 수 있다(이들 초기 프로모터를 사용하면, T-세포 유도가 보다 커진다). 그러나, 초기 및 후기 활성 둘 다를 갖는 프로모터는 항원 반응의 유도를 목적으로 한 면역원에 사용할 수 있다. 그러나, 이들 초기 및 후기 활성 프로모터는 T-세포 유도를 목적으로 한 면역원에도 사용할 수 있다.
- [0075] 한 가지 실시형태에서, 프로모터는 서열번호 50 또는 52(CMV 긴 또는 짧은 프로모터)의 핵산 서열 또는 이의 변이체를 포함하거나 이로 이루어진다. 서열번호 50 또는 52의 변이체는 각각 서열번호 50 또는 52와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 변이체는 서열번호 50 또는 52의 프로모터 기능을 실질적으로 보유할 수 있다.
- [0076] 한 가지 실시형태에서, 프로모터는 F11 좌측 인접 서열(서열번호 35)에 위치하는 서열 또는 이의 변이체를 포함하거나 이로 이루어진다. 변이체는 F11 좌측 인접 서열(서열번호 35)에 위치한 프로모터 서열과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 변이체는 F11 좌측 인접 서열(서열번호 35)에 위치한 프로모터의 프로모터 기능을 실질적으로 보유할 수 있다.
- [0077] **이차 프로모터**
- [0078] 한 가지 실시형태에서, 면역원 발현 카세트는 이차 프로모터를 코딩한다. 이차 프로모터가 제1/일차 프로모터에 추가하여 제공되는 실시형태에서, 이차 프로모터는 면역원 발현 카세트에 의해/내에 코딩될 수 있다. 이차 프로모터는 제1/일차 프로모터의 3'에 코딩될 수 있다. 이차 프로모터는 발현되는 제1 단백질/항원의 3', 예를 들면, HBV 코어 및 HBV 변형된 폴리머라제의 하류 및 HBV 표면 항원의 상류에 코딩될 수 있다. 이차 프로모터는 적어도 HBV 표면 항원의 발현을 촉진시킬 수 있다.
- [0079] 이차 프로모터는 폭스 바이러스 프로모터를 포함할 수 있다. 이차 프로모터는 폭스 바이러스 초기 프로모터, 예를 들면, 임의의 B8R, K6L, A44L, C11R 및 B2R, 또는 초기 및 후기 활성을 갖는 폭스 바이러스 프로모터, 예를 들면, mH5, p7.5 또는 SSP, 또는 후기 프로모터, 예를 들면, FP4b를 포함할 수 있다.
- [0080] 한 가지 실시형태에서, 이차 프로모터는 초기/후기 프로모터 mH5를 포함한다. 한 가지 실시형태에서, 이차 프로모터는 서열번호 28(mH5 프로모터)의 핵산 서열 또는 이의 변이체를 포함하거나 이로 이루어진다. 서열번호 28의 변이체는 서열번호 28과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 변이체는 서열번호 28의 이차 프로모터 기능을 실질적으로 보유할 수 있다.
- [0081] 또 다른 실시형태에서, 이차 프로모터는 SV40 프로모터 또는 EF1a 프로모터를 포함할 수 있다.
- [0082] **절단 도메인**
- [0083] 한 가지 실시형태에서, 면역원 발현 카세트는 절단 도메인을 코딩한다. 한 가지 실시형태에서, 절단 도메인은 번역후 단백질분해 절단 도메인이고, 이는, 예를 들면, 단백질분해 절단 효소에 의해 번역된 단백질의 절단을 가능하게 한다. 절단 효소는 숙주, 예를 들면, 백신접종되는 숙주, 예를 들면, 인간에 의해 제공될 수 있다.

또 다른 실시형태에서, 절단 효소는 면역원 발현 카세트 또는 바이러스 벡터에 코딩될 수 있다. 한 가지 실시 형태에서, 절단 도메인은 비-HBV 서열, 예를 들면, 포유동물 서열을 포함한다. 한 가지 실시형태에서, 절단 도메인은 인간 유래 서열을 포함한다.

[0084] 한 가지 실시형태에서, 절단 도메인은 리보솜 스킵 절단 도메인(ribosome skipping cleavage domain)을 포함한다. 한 가지 실시형태에서, 절단 도메인은, 서열 RXRR(여기서 X는 임의의 아미노산일 수 있다)을 포함하거나 이들로 이루어지는 퓨린 인식 부위를 포함한다. 한 가지 실시형태에서, 절단 도메인은 퓨린 인식 부위 및 2A 펩티드 서열을 포함한다. 2A 펩티드 서열은 FMDV(구제역 질환 바이러스) 2A 펩티드 서열(APVKQTLNFDLLKLAGDVESNPGP-서열번호 43)을 포함할 수 있다. 또는, 2A 펩티드는 P2A(돼지 테스코바이러스-1 2A), T2A(토세아시그나 바이러스 2A) 및 E2A(말 비염 A 바이러스 [ERAV] 2A)로부터 선택될 수 있다. 임의의 피코르나 바이러스 2A 펩티드 서열은 펩티드 절단 부위를 위해 제공될 수 있고 펩티드 절단 부위로서 기능할 수 있다. 따라서, 절단 도메인은 피코르나 바이러스 2A 펩티드 서열을 코딩하는 서열을 포함할 수 있다.

[0085] 한 가지 실시형태에서, 절단 도메인은 퓨린-2A(F2A) 펩티드 서열 또는 이의 기능적 변이체를 포함하거나 이로 이루어진다. 절단 도메인은 서열번호 9의 서열 또는 이의 변이체를 포함하거나 이로 이루어진다. 서열번호 9의 변이체는 서열번호 9와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 9의 변이체는 서열번호 9의 절단 기능을 실질적으로 보유할 수 있다.

[0086] F2A는 유리하게는 짧고(단지 28 아미노산), 이는 적절한 삽입체를 제공하고, ChAdOx1/2을 포함하는 아데노바이러스 기반 벡터 등의 크기 제한을 가질 수 있는 벡터로부터 하나 이상의 단백질을 발현하는 역할을 한다.

[0087] 바이러스 벡터가 MVA이거나, 달리는 바이러스 벡터가 프라임 백신접종후 부스트 백신접종으로 사용되는 한 가지 실시형태에서, 프라임 백신접종의 절단 도메인에 대한 T-세포 반응의 임의의 잠재적 부스팅을 회피하기 위해 상이한 절단 도메인이 제공될 수 있다. 또는, 이차 프로모터는 프라임 백신접종의 절단 도메인에 대한 T-세포 반응의 임의의 잠재적 부스팅을 회피하기 위해 절단 도메인 대신에 사용될 수 있다.

[0088] IRES(내부 리보솜 도입 부위)

[0089] 한 가지 실시형태에서, 면역원 발현 카세트는 내부 리보솜 도입 부위(IRES)를 코딩한다. 당업자는 IRES가 번역의 캡 독립적 개시를 가능하게 하고 메신저 RNA의 도중에서 번역을 개시할 수 있는 RNA 구조인 것을 인식할 것이다.

[0090] 스플라이싱 시그널

[0091] 한 가지 실시형태에서, 면역원 발현 카세트는 mRNA 스플라이싱 시그널을 코딩한다. 당업자는, 이러한 사용에 적절한 일반적으로 사용되는 스플라이싱 시그널에 친숙할 것이다. 사용될 수 있는 mRNA 스플라이싱 시그널의 이러한 일례는, 인간 β -글로빈 유전자 및 분지의 제1 인트론의 5' 공여체 부위, 및 발현 벡터 pCI-네오 포유동물 발현 벡터(Promega) 중의 면역글로불린 유전자 중쇄 가변 영역의 인트론으로부터의 3' 어셉터 부위로 구성된 키메라 인트론이다.

[0092] HBV 프레-코어(PreC)

[0093] HBV PreC는 전장 야생형(full length wild-type) HBV PreC 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. HBV PreC 변이체는 절단된 HBV PreC 서열을 포함하거나 이들로 이루어질 수 있다.

[0094] HBV PreC는 서열번호 16의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 16의 변이체는 서열번호 16과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 16의 변이체는 서열번호 16의 면역원성을 실질적으로 보유할 수 있다. 서열번호 16의 변이체는 서열번호 16의 삼차 구조를 실질적으로 보유할 수 있다.

[0095] HBV 코어

[0096] HBV 코어는 전장 야생형 HBV 코어 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. HBV 코어 변이체는 절단된 HBV 코어 서열을 포함하거나 이들로 이루어질 수 있다. HBV 코어는 HBV 프레-코어를 포함하지 않을 수 있다.

[0097] HBV 코어는 서열번호 6의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 6의 변이체는 서열번호 6과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 6의 변이체는 서열번호 6의 면역원성을 실질적으로 보유할 수 있다. 서열번호 6의 변이체는 서

열번호 6의 삼차 구조를 실질적으로 보유할 수 있다.

[0098] **HBV e-항원(HBeAg)**

[0099] HBV e-항원(HBeAg)는 전장 야생형 HBV e-항원 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. HBV e-항원 변이체는 절단된 HBV e-항원 서열을 포함하거나 이들로 이루어질 수 있다.

[0100] HBV e-항원(HBeAg)는 서열 :
SKLCLGWLWGMDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALSPEHCSPHHTALRQAILCWGELMNLATWVGSNLEDPASREL VVS YVNVN
MGLKIRQLLWFHISCLTFGRETVLEYLVSFVWIRTPPAYRPPNAPILSTLPETTVV(서열번호 17)을 포함하거나 이들로 이루어질 수 있다.

[0101] HBV e-항원(HBeAg)는 서열번호 17의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 17의 변이체는 서열번호 17과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 17의 변이체는 서열번호 17의 번역원성을 실질적으로 보유할 수 있다. 서열번호 17의 변이체는 서열번호 17의 삼차 구조를 실질적으로 보유할 수 있다.

[0102] **변형된 HBV 폴리머라제**

[0103] 변형된 HBV 폴리머라제(P_{mut})는 절단된 HBV 폴리머라제를 포함하거나 이들로 이루어질 수 있다. 특히, 폴리머라제 기능을 실질적으로 제거하기 위한 야생형 HBV 폴리머라제에 대한 돌연변이는 절단된 HBV 폴리머라제를 코딩하는 서열을 포함할 수 있다. 대체적 또는 추가로, 돌연변이는 코딩된 HBV 폴리머라제 서열에 대한 하나 이상의 점 돌연변이를 포함한다. 변형은 코딩된 HBV 폴리머라제 서열에서 하나 이상의 아미노산 치환, 결실 또는 부가를 포함할 수 있다. 한 가지 실시형태에서, 변형된 HBV 폴리머라제(P_{mut})는 절단된 형태의 HBV 폴리머라제가 아니다(즉, 이는 야생형 HBV 폴리머라제에 대해 전장이다).

[0104] 변형된 HBV 폴리머라제(P_{mut})는 서열번호 8의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 8의 변이체는 서열번호 8과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 8의 변이체는 서열번호 8의 번역원성을 실질적으로 보유할 수 있다. 서열번호 8의 변이체는 서열번호 8의 삼차 구조를 실질적으로 보유할 수 있다.

[0105] 변형은, 단백질 프라이밍을 방지하는 돌연변이일 수 있다. 추가로 또는 대안적으로, 돌연변이는 이들의 기능을 방지하기 위해 역전사효소 및/또는 RNAase 도메인에 제공될 수 있다. 추가로 또는 대안적으로, 돌연변이는 폴리머라제의 정확한 단백질 폴딩을 파괴하도록 하는 구조일 수 있다. 변형은, 본원에서 야생형 HBV 폴리머라제 컨센서스 서열(즉, 서열번호 19)을 참조하여 Y63, C323, C334, C338, C352, R714, D788, R792 또는 이의 동등한 잔기 중의 하나 이상 또는 전부를 포함할 수 있다. 한 가지 실시형태에서, 변형은, 본원에서 야생형 HBV 폴리머라제 컨센서스 서열(즉, 서열번호 19)을 참조하여 Y63A, C323A, C334A, C338A, C352A, R714A, D788A, R792A 또는 이의 동등한 잔기 중의 하나 이상 또는 전부를 포함할 수 있다. 또 다른 실시형태에서, 변형은, 본원에서 야생형 HBV 폴리머라제 컨센서스 서열(즉, 서열번호 19)을 참조하여 R714, D788 및 R792 중의 하나 이상 또는 전부, 또는 이의 동등한 잔기를 포함할 수 있다. 한 가지 실시형태에서, 변형은, 본원에서 야생형 HBV 폴리머라제 컨센서스 서열(즉, 서열번호 19)을 참조하여 R714A, D788A 및 R792A 중의 하나 이상 또는 전부, 또는 이의 동등한 잔기를 포함할 수 있다. 동등한 잔기에 대한 언급은 HBV 폴리머라제가 본원에 제공된 HBV 폴리머라제 서열 이외의 대체 서열에 기초할 수 있고 아미노산 잔기의 넘버링 또는 동정이 서열 사이에서 상이할 수 있음을 의미하는 것으로 이해된다. 이러한 상위 또는 동등성은 HBV 폴리머라제 서열과 본원에서 야생형 HBV 폴리머라제 컨센서스 서열(즉, 서열번호 19)과의 정렬에 의해 용이하게 결정될 수 있다.

[0106] 돌연변이 R714A, D788A, R792A는 유리하게는 폴리머라제 기능을 정지한다. 그러나, Y63의 하나 이상 또는 전부의 추가 돌연변이 또는 C323, C334, C338 및 C352의 기타 시스테인 돌연변이는 이들 기능적 돌연변이 내에서 복귀한 경우에 특별한 수단으로서 추가될 수 있다. 추가의 돌연변이는 Y63A, C323A, C334A, C338A 및/또는 C352A를 포함할 수 있다.

[0107] 돌연변이는 유리하게는, HBV 폴리머라제 기능이 (a) 이의 효소 활성을 정지시키기 위해 RNAase H 기능적 돌연변이 및/또는 (b) 복제의 제1 단계(DNA 합성의 프라이밍)를 정지시키기 위해 Y63A 돌연변이, 및/또는 (c) 이의 천연 형태를 파괴하고 HBV 폴리머라제가 바이러스 복제의 초기 단계(단백질 프라이밍, RNA 결합 및 RNA 팩키징)에 관여하는 것을 정지하기 위해 시스테인 돌연변이에 의해 파괴되는 것을 제공한다.

[0108] 당업자는, 기능을 유의적으로 저하시키거나 제거하는, 제공할 수 있는, 본 발명에 따라 변형된 폴리머라제에서

제공될 수 있는 다양한 HBV 폴리머라제 변형에 친숙할 것이다. 이러한 변형은, 예를 들면, 본원에서 참조로서 도입되는, WO2016020538, WO2013007772 및 WO2011015656에 기재되어 있다.

[0109] 한 가지 실시형태에서, 변형된 폴리머라제는 야생형 HBV 폴리머라제에 대하여 저하된 역전사효소(RTase) 효소 활성을 나타내도록 변형된다. RTase 활성의 저하는 RTase 효소 활성에 관여하는 도메인 내의 하나 이상의 돌연변이(들)에 의해 제공될 수 있다. 4개 잔기가 RTase 활성에 관여하여 야생형 HBV 폴리머라제의 대략 위치 538로부터 대략 위치 541까지 모티프 "YMDD"(Tyr, Met, Asp 및 Asp 잔기)를 형성하는 것으로 밝혀졌다. 본 발명은 이러한 모티프 또는 그 밖의 RTase 도메인 중의 임의의 돌연변이(들)를 포함하고, 이는 RTase 활성의 현저한 저하(예: 적어도 10배 저하) 또는 무력화를 제공한다. 적합한 RTase-결합 폴리머라제 돌연변이체의 대표적 예는 문헌[참조: Radziwill et al. (1990, J. Virol. 64:613), Bartenschlager et al. (1990, J. Virol. 64:5324) 및 Jeong et al. (1996, Biochem Bioph Res Commun. 223(2):264)]에 기재되어 있고, 이는 본원에서 참조로서 도입된다. 한 가지 실시형태에서, 변형된 폴리머라제는, His 잔기에 대한 임의의 치환(D540H 돌연변이)과 함께, Asp 이외의 임의의 아미노산으로 YMDD 모티프 또는 천연 HBV 폴리머라제 내의 동등한 위치에 위치한 아미노산 잔기의 제1 Asp 잔기의 치환을 포함할 수 있다.

[0110] 추가적 또는 대안적으로, 변형된 폴리머라제는 야생형 HBV 폴리머라제에 대하여 저하된 RNase H 효소 활성을 제공하도록 변형될 수 있다. RNase H 활성의 저하는 RNase H 효소 활성에 관여하는 도메인 내의 하나 이상의 돌연변이에 의해 제공될 수 있다. RNase H 활성에 관여하는 기능적 도메인은 HBV 폴리머라제의 C-말단 부분, 대략적으로 야생형 폴리머라제의 위치 680 내지 C-말단 위치 832에 존재하고, 본 발명의 변형된 폴리머라제는, RNase H 활성의 현저한 저하(예: 적어도 10배 저하) 또는 무력화를 제공하는 이러한 도메인 내의 임의의 돌연변이(들)를 포함할 수 있다. 적합한 RNase H-결합 폴리머라제 돌연변이체의 대표적 예는 문헌[참조: Radziwill et al. (1990, J. Virol. 64:613), in Bartenschlager et al. (1990, J. Virol. 64:5324)]에 기재되어 있다.

[0111] **HBV 표면 항원(HbsAg)**

[0112] 당업자는, PreS1 및 PreS2가 거대(L) 형태의 HBV 표면 단백질(예: L 형태 = PreS1+PreS2+S)의 성분인 것을 이해할 것이다. 중간(M) 형태의 HBV 표면 단백질은 PreS2+S를 갖는다. 이러한 서열을 함께 갖는다는 것은 T-세포 에피토프가 이들 연속 순서에 포함되는 것을 의미한다.

[0113] HbsAg는 전장 야생형 HbsAg 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. HbsAg 변이체는 절단된 HbsAg 서열을 포함하거나 이들로 이루어질 수 있다.

[0114] PreS1 및 PreS2 서열을 포함하는 HbsAg는 서열번호 10의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 10의 변이체는 서열번호 10과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 10의 변이체는 서열번호 10의 면역원성을 실질적으로 보유할 수 있다. 서열번호 10의 변이체는 서열번호 10의 삼차 구조를 실질적으로 보유할 수 있다.

[0115] 또 다른 실시형태에서, HbsAg는 PreS1 및/또는 PreS2의 부재하에 표면 항원을 포함할 수 있다. HbsAg는 서열번호 18의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 18의 변이체는 서열번호 18과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 18의 변이체는 서열번호 18의 면역원성을 실질적으로 보유할 수 있다. 서열번호 18의 변이체는 서열번호 18의 삼차 구조를 실질적으로 보유할 수 있다.

[0116] 한 가지 실시형태에서, HbsAg는 HbsAg(아미노산 1-226) 내에 4개 공지된 막관통 영역의 어느 하나 또는 전부를 포함하거나 이들로 이루어질 수 있고, 이는 각각 아미노산(8-32) FLGPLLVLQAGFFLLTRILTIPQSL(서열번호 54), 아미노산(80-98) FIIFLFILLCLIFLLVLL(서열번호 55), 아미노산(160-184) RFLWEWASVRFWSLLVPFVQWFV(서열번호 56) 및 아미노산(189-210) TVWLSVIWMMWYWGPSLYNLS(서열번호 57)이다. 한 가지 실시형태에서, HbsAg는 아미노산(8-32) FLGPLLVLQAGFFLLTRILTIPQSL(서열번호 54)의 HbsAg 막관통 영역을 적어도 포함하거나 이들로 이루어질 수 있다.

[0117] **HBV PreS1**

[0118] HBV PreS1은 전장 야생형 HBV PreS1 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. HBV PreS1은 서열번호 52의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 52의 변이체는 서열번호 52와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 52의 변이체는 서열번호 52의 면역원성을 실질적으로 보유할 수 있다. 서열번호 52의 변이체는 서열번호

호 52의 삼차 구조를 실질적으로 보유할 수 있다.

[0119] HBV PreS1 변이체는 절단된 HBV PreS1 서열, 예를 들면, 본원에 기재된 CΔPreS1 또는 NΔPreS1을 포함하거나 이들로 이루어질 수 있다(CΔPreS1은 C-말단 절단된 PreS1을 지칭하고, NΔPreS1은 N-말단 절단된 PreS1을 지칭한다). 한 가지 실시형태에서, 면역원 발현 카세트는 NΔPreS1 및 CΔPreS1 둘 다를 코딩할 수 있다. 면역원 발현 카세트가 NΔPreS1 및 CΔPreS1 둘 다를 코딩하는 실시형태에서, NΔPreS1은 유전자간 서열의 상류(5')에서 코딩될 수 있고, CΔPreS1은 유전자간 서열의 하류(3')에서 코딩될 수 있다. 면역원 발현 카세트가 유전자간 서열의 상류(5')에서 NΔPreS1을 코딩하는 실시형태에서, 이는 PreS2 및/또는 변형된 폴리머라제(Pmut)와 융합시킬 수 있다. 면역원 발현 카세트가 유전자간 서열의 상류(5')에서 NΔPreS1을 코딩하는 실시형태에서, 이는 PreS2 및/또는 변형된 폴리머라제(Pmut)와 융합시킬 수 있고, 유전자간 서열의 하류(3')에서 코딩된 CΔPreS1은 표면 항원(HbsAg)과 융합시킬 수 있다.

[0120] CΔPreS1

[0121] 한 가지 실시형태에서, 면역원 발현 카세트는 절단된 형태의 HBV PreS1을 코딩한다. 절단은 C-말단 절단을 포함할 수 있다. 한 가지 실시형태에서, 절단된 HBV PreS1은 본원에 기재된 CΔPreS1(서열번호 21)을 포함한다. 한 가지 실시형태에서, 절단된 PreS1, 예를 들면, 본원에 기재된 CΔPreS1은 HBV 표면 항원(S/HbsAg)과의 융합 단백질을 발현하도록 정렬된다. 링커 서열, 예를 들면, 본원에 기재된 링커는 절단된 PreS1과 표면 항원(S/HbsAg) 사이에 제공될 수 있다. 예를 들면, CΔPreS1 + 링커 + S(S(sh)로서 본원에 기재됨). S(sh)를 코딩하는 뉴클레오티드 서열은 서열번호 61을 포함하거나 이들로 이루어질 수 있다.

[0122] CΔPreS1은 서열번호 21의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 21의 변이체는 서열번호 21과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 21의 변이체는 서열번호 21의 면역원성을 실질적으로 보유할 수 있다. 서열번호 21의 변이체는 서열번호 21의 삼차 구조를 실질적으로 보유할 수 있다.

[0123] 한 가지 실시형태에서, 절단된 PreS1, 예를 들면, 본원에 기재된 CΔPreS1은, 임의로 융합된 표면 항원과 함께, 유전자간 서열의 하류(3')에서 코딩된다.

[0124] PreS1 절단은 유리하게는 면역원 발현 카세트에 제공된 HBV 항원에 대한 T-세포 및 항체 반응 둘 다에 대한 항체 생성을 조장한다. 이론에 국한시키고자 하는 것은 아니지만, 항체 생성은 PreS1 및 표면 항원의 적절한 폴딩에 기인할 수 있다.

[0125] NΔPreS1

[0126] 한 가지 실시형태에서, 절단된 PreS1은 본원에 기재된 NΔPreS1을 포함한다. NΔPreS1 및 PreS2 융합체는 서열번호 15/38 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 15/38의 변이체는 서열번호 15/38과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 15/38의 변이체는 서열번호 15/38의 면역원성을 실질적으로 보유할 수 있다.

[0127] NΔPreS1 및 PreS2 융합 서열은 유리하게는 양호한 T-세포 반응을 제공한다. NΔPreS1은, T-세포 에피토프(CD8 T-세포 에피토프의 경우에 8-11 아미노산 및 CD4 T-세포 에피토프의 경우에 약간 더 긴(12-16))를 여전히 보존하는 서열에 아미노산을 포함한다.

[0128] 면역원 발현 카세트가 유전자간 서열의 상류(5')에서 PreS2와 융합된 NΔPreS1을 코딩하는 실시형태에서, 이는 변형된 폴리머라제(Pmut)와 추가로 융합시킬 수 있다. 링커 서열, 예를 들면, 본원에 기재된 링커는 PreS2 과 변형된 폴리머라제(Pmut) 사이에 제공될 수 있다. 예를 들면, NΔPreS1 + PreS2 + 링커 + Pmut.

[0129] HBV PreS2

[0130] HBV PreS2는 전장 야생형 PreS2 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. HBV PreS2 변이체는 절단된 HBV PreS2 서열을 포함하거나 이들로 이루어질 수 있다.

[0131] HBV PreS2는 서열번호 53의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 53의 변이체는 서열번호 53과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 53의 변이체는 서열번호 53의 면역원성을 실질적으로 보유할 수 있다. 서열번호 53의 변이체는 서열번호 53의 삼차 구조를 실질적으로 보유할 수 있다.

[0132] 펩티드 애드juvant(adjuvant)

- [0133] 면역원 발현 카세트는 펩티드 애주번트를 추가로 코딩할 수 있다. 펩티드 애주번트는 TPA(조직 플라스미노겐 활성화인자)를 포함할 수 있다. 한 가지 실시형태에서, 펩티드 애주번트는 인간 또는 비-인간 불변 쇠(Ii) 또는 이의 변이체를 포함할 수 있다. 긴 이소형(이소형 (b))의 인간 CD74 분자의 단편은 불변 쇠로서 또한 공지되어 있다[참조: Nucleic Acids Res. 1985 December 20; 13(24): 8827-8841]. 적어도 이의 막관통 도메인을 포함하는 불변 쇠(Ii)의 N-말단 단편은, 목적하는 항원과의 융합 단백질로서 발현되는 경우, 놀랍게도 효과적인 애주번트 기능을 제공하는 것으로 공지되어 있다. 막관통 도메인 및 세포질 도메인을 포함하고 바람직하게는 긴 이소형의 단백질의 N-말단 16 아미노산을 포함하는 단편이 특히 유효하다.
- [0134] 불변 쇠는 상어 불변 쇠(SIi) 또는 이의 단편 또는 기능적 변이체를 포함하거나 이로 이루어질 수 있다. 변이체 상어 불변 쇠(SIi)는 절단된 불변 상어 불변 쇠를 포함할 수 있다. 불변 쇠 또는 이의 단편의 기타 비-인간 동물 공급원은 닭, 메추라기, 송어, 제브라피쉬, 잉어, 개구리, 그루퍼, 상어, 만다린 물고기 또는 청동오리를 포함한다. 당업자는 발현 카세트/백터에서 코딩된 펩티드 애주번트로서 사용하기 위한 적절한 불변 쇠 또는 이의 단편에 친숙할 것이고, 예를 들면, 불변 쇠는, 본원에서 참조로서 도입되는 W02015082922에 제공된 바와 같은 임의의 불변 쇠일 수 있다.
- [0135] 펩티드 애주번트는 서열번호 4(SIi)의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 4의 변이체는 서열번호 4와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 4의 변이체는 서열번호 4의 애주번트 기능을 실질적으로 보유할 수 있다.
- [0136] 펩티드 애주번트는 서열번호 29(TPA 핵산 서열)의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 29의 변이체는 서열번호 29와 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 29의 변이체는 서열번호 29에 의해 코딩된 TPA의 애주번트 기능을 실질적으로 보유하는 펩티드 애주번트를 코딩할 수 있다. 펩티드 애주번트는 서열번호 60(TPA 핵산 서열)의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 60의 변이체는 서열번호 60과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 60의 변이체는 서열번호 60에 의해 코딩된 TPA의 애주번트 기능을 실질적으로 보유하는 펩타이드 애주번트를 코딩할 수 있다.
- [0137] 펩티드 애주번트는 서열번호 30(TPA)의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 30의 변이체는 서열번호 30과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 30의 변이체는 서열번호 30의 애주번트 기능을 실질적으로 보유할 수 있다.
- [0138] 펩티드 애주번트는 면역원 발현 카세트로부터 발현되는 단백질/항원의 N-말단 위치에서 코딩될 수 있다. 제1 펩티드 애주번트는 면역원 발현 카세트로부터 발현되는 제1 단백질/항원(예를 들면, 코어 및 폴리머라제 융합체)의 N-말단 위치에서 코딩될 수 있고, 제2 펩티드 애주번트는 면역원 발현 카세트로부터 발현되는 제2 단백질/항원(예를 들면, 표면 항원)의 N-말단 위치에서 코딩될 수 있다.
- [0139] **HBV 유전자형**
- [0140] HBV는 HBV 유전자형 C일 수 있다. 또 다른 실시형태에서, HBV는 10 유전자형(A-J)의 어느 하나일 수 있다. 모든 코딩된 HBV 단백질/항원은 하나의 유전자형, 예를 들면, HBV 유전자형 C로부터 유래할 수 있다.
- [0141] **링커**
- [0142] 한 가지 실시형태에서, 링커 잔기는, 융합 단백질에서 제공되는 단백질/항원 서열 중의 하나 이상 또는 전부의 사이에서 코딩될 수 있다(예를 들면, 단백질 중의 서열 사이의 접합부를 제공한다). 펩티드 애주번트를 포함하는 실시형태에서, 링커는 펩티드 애주번트와 하류 코딩된 단백질/항원 사이에 코딩될 수 있다. 한 가지 실시형태에서, 링커는 HBV 코어의 서열과 변형된 HBV 폴리머라제 사이에 코딩된다.
- [0143] 링커 잔기는 랜덤 아미노산 서열을 포함할 수 있거나, 동물 모델에서 에피토프 예측 컴퓨터 프로그램 또는 실험에 기초하여 비-면역원성으로 되도록 선택된 아미노산을 포함할 수 있다. 예를 들면, 링커는 에피토프인 것으로 예측되거나 공지되어 있는 경우에 고려하지 않을 수 있다(즉, 에피토프, 예를 들면, HBV에서 발견되지 않는 인공 에피토프에 대한 면역 반응을 회피하기 위해). 링커는 유연성일 수 있다. 링커는 K, G, P 또는 S 아미노산 또는 이들의 조합을 포함하거나 이들로 이루어질 수 있다. 한 가지 실시형태에서, 링커는 G 및/또는 P 아미노산 잔기를 포함하거나 이들로 이루어질 수 있다. 링커 잔기의 길이는 1 내지 10 아미노산일 수 있다. 또 다른 실시형태에서, 링커 잔기의 길이는 2 내지 8 잔기일 수 있다. 또 다른 실시형태에서, 링커 잔기의 길이는 1

내지 6 잔기일 수 있다.

- [0144] 링커는 임의의 서열 KGGGPGGG(서열번호 5), GGGSGGG(서열번호 7), KGGS(서열번호 14), KSP, GSKGK(서열번호 20), LEGGSGG(서열번호 22), SKSGPPSGKS(서열번호 31), GSKSGSK(서열번호 32), SKSPGSGPP(서열번호 33) 또는 ASKGGKSG(서열번호 34)를 포함하거나 이들로 이루어질 수 있다.
- [0145] 한 가지 실시형태에서, 링커는 서열 KGGGPGGG(서열번호 5)를 포함할 수 있다. 또 다른 실시형태에서, 링커는 서열 GGGSGGG(서열번호 7)를 포함할 수 있다. 또 다른 실시형태에서, 링커는 서열 KGGS(서열번호 14)를 포함할 수 있다. 또 다른 실시형태에서, 링커는 서열 KSP를 포함할 수 있다. 또 다른 실시형태에서, 링커는 서열 GSKGK(서열번호 20)를 포함할 수 있다. 또 다른 실시형태에서, 링커는 서열 LEGGSGG(서열번호 22)를 포함할 수 있다. 또 다른 실시형태에서, 링커는 서열 SKSGPPSGKS(서열번호 31)를 포함할 수 있다. 또 다른 실시형태에서, 링커는 서열 GSKSGSK(서열번호 32)를 포함할 수 있다. 또 다른 실시형태에서, 링커는 서열 SKSPGSGPP(서열번호 33)를 포함할 수 있다. 또 다른 실시형태에서, 링커는 서열 ASKGGKSG(서열번호 34)를 포함할 수 있다.
- [0146] 유리하게는, 링커의 사용은 인간 프로테옴(이는 잠재적으로 자가-항원에 대한 면역 반응을 생성할 수 있다)에 대해 상동성을 갖는 펩티드의 생성을 회피할 수 있고, 이들은 면역-우성 인공 에피토프를 회피한다. 추가로, 링커는 단백질의 세그먼트 사이에 유연한 힌지를 제공하고, 따라서 이들은 이들의 천연 형태로 폴딩할 수 있다. 예를 들면, CΔPreS1 및 S 사이의 링커는 CΔPreS1 및 S의 독립적 폴딩을 가능하게 하고, 따라서 이들은 각 단백질의 입체구조 에피토프에 대한 항체를 생성할 수 있다.
- [0147] 링커는 상이한 면역원 발현 카세트 사이에서 상이할 수 있다. 상이한 링커의 사용은 임의의 잠재적 인공 에피토프에 대해 생성된 임의의 T-세포 반응의 부스팅을 회피한다(즉, 링커의 변경 또는 접합부의 변경에 의해). 예를 들면, 백신이 프라임 부스트 백신접종 전략에 사용되는 경우, 링커 또는 면역원 레이아웃 내의 단백질 순서의 변경은 인공 에피토프 반응의 부스팅을 극복하는 역할을 한다.
- [0148] **기타 면역원 발현 카세트(들)의 요소**
- [0149] 면역원 발현 카세트가 MVA 벡터에서 사용하기 위한 것인 실시형태에서, 면역원 발현 카세트는 상동성 재조합에 의해 MVA F11 유전자와 내로의 삽입을 가능하게 하기 위해 F11 좌우 인접 서열을 추가로 포함할 수 있다.
- [0150] F11-좌측 인접 서열은 서열번호 35의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. F11-우측 인접 서열은 서열번호 36의 서열 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 서열번호 35 또는 36의 변이체는 각각 서열번호 35 또는 36과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99% 또는 99.5% 동일성을 갖는 서열을 포함할 수 있다. 서열번호 35 또는 36의 변이체는 각각 서열번호 35 또는 36의 상동성 재조합 기능을 실질적으로 보유할 수 있다. 당업자는 기능에 영향을 미치지 않고서 1, 2, 3, 4, 5 또는 그 이상의 아미노산 잔기가 치환, 부가 또는 제거될 수 있음을 인지할 것이다. 예를 들면, 보존적 치환이 고려될 수 있다.
- [0151] 면역원 발현 카세트는 전사 터미네이터 서열을 추가로 포함할 수 있다. 전사 터미네이터 서열은 이차 프로모터를 포함하는 면역원 발현 카세트의 실시형태에서 제공될 수 있다. 예를 들면, 전사 터미네이터 서열은 일차 프로모터에 의해 발현된 단백질의 하류에, 그러나 이차 프로모터 전(상류)에 제공될 수 있다. 전사 터미네이터 서열은 서열 TTTTGT 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다.
- [0152] 한 가지 실시형태에서, 본원에 기재된 면역원 발현 카세트는 단리되거나 비-바이러스 벡터에 제공될 수 있다.
- [0153] 따라서, 본 발명의 또 다른 양태에 따르면, 본원에 기재된 면역원 발현 카세트를 포함하는 핵산이 제공되고, 임의로 상기 핵산은 단리된 핵산이다.
- [0154] 본 발명의 또 다른 양태에 따르면, 본 발명에 따르는 바이러스 벡터를 포함하는 조성물이 제공되고, 임의로 상기 조성물은 약제학적으로 허용되는 조성물이다.
- [0155] 조성물은, 예를 들면, 인간 등의 포유동물에서 면역원성일 수 있다. 조성물은 약제학적으로 허용되는 담체를 포함할 수 있다. 조성물은 약제학적으로 허용되는 담체를 포함하는 약제학적 조성물일 수 있다. 조성물은 HBV 감염의 예방 또는 치료에 사용하기 위한 것일 수 있다.
- [0156] 본 발명의 또 다른 양태에 따르면, 본 발명에 따르는 바이러스 벡터, 핵산 또는 조성물의 투여를 포함하는 HBV 감염의 치료 또는 예방 방법이 제공된다.
- [0157] HBV 감염의 치료 또는 예방 방법은 백신접종 방법일 수 있다.

- [0158] 본 발명의 또 다른 양태에 따르면, HBV 감염의 치료 또는 예방에 사용하기 위한 본 발명에 따르는 바이러스 벡터, 핵산 또는 조성물이 제공되고, 임의로 상기 사용은 백신에서의 사용이다.
- [0159] 본 발명의 또 다른 양태에 따르면, 본 발명에 따르는 바이러스 벡터, 핵산 또는 조성물을 포함하는 백신에 제공된다.
- [0160] 백신은 프라임 백신일 수 있다. 백신은 부스트 백신일 수 있다. 부스트 백신이 프라임 백신 후에 제공되는 경우, 바이러스 벡터는 본 발명에 따르는 상이한 바이러스 벡터일 수 있다.
- [0161] 유리하게는, 프라임 및 부스트 백신 사이에 상이한 바이러스 벡터의 제공은 어느 단백질/항원 서열과 또 다른 단백질/항원 서열의 접합부에 걸쳐 형성된 "필스(false)" 에피토프의 제공을 회피할 수 있고, 즉 동일한 접합부는 재-배열된 단백질에서 발생하지 않을 수 있다.
- [0162] 본 발명의 또 다른 양태에 따르면,
- [0163] - 본 발명에 따르는 프라임 백신접종;
- [0164] - 본 발명에 따르는 부스트 백신접종을 포함하는, 프라임 부스트 백신접종 키트(prime boost vaccination kit)가 제공된다.
- [0165] 프라임 및 부스트 백신접종은 상이한 바이러스 벡터를 포함할 수 있다.
- [0166] 바이러스 벡터는 또 다른 치료학적 또는 예방학적 활성 성분과 조합하여 백신에서 사용될 수 있다. 바이러스 벡터는 애주버트와 조합하여 백신에서 사용될 수 있다.
- [0167] 바이러스 벡터, 바이러스 벡터를 코딩하는 핵산은 약제학적으로 허용되는 담체에 제공될 수 있다.
- [0168] 본 발명에 따르는 바이러스 벡터 또는 조성물은 야생형 HBV를 포함하지 않거나, 본 발명에 따르는 핵산은 야생형 HBV를 코딩하지 않을 수 있다.
- [0169] 본원에 사용되는 서열 "동일성"에 대한 언급은 표준 NCBI BLASTp 파라미터(<http://blast.ncbi.nlm.nih.gov>)를 사용하여 2개 정렬된 서열 사이의 퍼센트 동일성을 지칭할 수 있다.
- [0170] 용어 "면역원성"은, 본 발명의 바이러스 벡터, 핵산 또는 조성물에 적용되는 경우, 인간 또는 동물 체내에서 면역 반응을 유발할 수 있는 것을 의미한다. 면역 반응은 HBV의 보호일 수 있다. 용어 "보호"는 B형 간염 질환의 예방, B형 간염 질환의 위험 감소, HBV 감염, 전파 및/또는 진행 위험의 감소, B형 간염 질환의 중증도 감소, B형 간염의 치유, B형 간염의 중증도 완화, 또는 B형 간염 질환 증상의 중증도 감소를 의미한다.
- [0171] 용어 "예방"은 B형 간염의 예방 또는 보호 치료를 의미한다. 예방은 HBV 감염, 전파 및/또는 B형 간염 질환 진행 위험의 감소, 또는 B형 간염 질환의 중증도 감소를 포함할 수 있다.
- [0172] 용어 "치료"는 B형 간염의 치유, 증상 완화, 또는 B형 간염 질환 또는 B형 간염 질환 증상의 중증도 감소를 의미한다.
- [0173] "변이체" 핵산 서열과 관련하여, 당업자는 1, 2, 3, 4, 5 또는 그 이상의 코돈이, 기능에 영향을 미치지 않고서, 치환, 부가 또는 제거될 수 있음을 이해할 것이다. 예를 들면, 보존적 치환이 고려될 수 있다.
- [0174] "변이체" 아미노산 서열과 관련하여, 당업자는 1, 2, 3, 4, 5 또는 그 이상의 아미노산이, 기능에 영향을 미치지 않고서, 치환, 부가 또는 제거될 수 있음을 이해할 것이다. 예를 들면, 보존적 치환이 고려될 수 있다.
- [0175] 당업자는 본 발명의 한 가지 실시형태 또는 양태의 임의의 특징이, 적절한 경우, 본 발명의 다른 실시형태 또는 양태에 적용가능하다는 것을 이해할 것이다.
- [0176] 이제, 본 발명의 실시형태는, 첨부 도면을 참조하여, 단순한 예로서 보다 상세하게 기재된다.

도면의 간단한 설명

- [0177] 도 1: (a) 컨센서스 서열을 생성하기 위해 사용된 1447 HBV 유전자형 C 서열의 계통발생적 관계; (b) HBV 유전자형 C 컨센서스(서열번호 1) 및 KP017269.1 HBV 단리주 JP-02(서열번호 2)의 비교. HBV 데이터 베이스, HBVdb: <https://hbvdb.ibcp.fr/HBVdb/HBVdbIndex>로부터 다운로드한 1447 HBV 유전자형 C 뉴클레오타이드 서열은 MAFFT(다중 서열 정렬 프로그램)을 사용하여 정렬시켜 HBV 유전자형 C 컨센서스 서열 및 계통발생적 트리를 생성했다. 컨센서스 및 선택된 환자의 서열(KP017269.1 HBV 단리주 JP-02)의 3215 뉴클레오타이드 서열의 정렬은 3

개 뉴클레오티드 차이(위치 52, 1053 및 2699에서)를 나타냈고, 이는 회색으로 강조되어 있다. 1447 유전자형 C 단리주 JP-02로부터 생성된 HBV 유전자형 C 센서서열의 서열은 하기에 제공되어 있다.

도 2: (a) HBV 바이러스 게놈 및 코돈 레이아웃. HBV 바이러스는 부분 이분체 DNA를 갖는다(폴리머라제 단백질에 부착된 전장 음성 체 DNA 및 부분 합성된 양성 체 DNA를 가짐). 게놈은 대략 3.2Kb 길이이고, 4개 주요 코돈을 갖는다: 코어(프레코어 영역 포함), 폴리머라제, 표면(preS1 및 preS2 영역을 포함) 및 X. **(b) HBV 면역원 레이아웃.** 2개 면역원 SIi-HBV-CPmutS 및 SIi-HBV-SCPmut를 설계했다. 면역원 둘 다는 HBV 코돈(프레코어, 코어, 폴리머라제[Pmut], preS1, preS2 및 표면 단백질을 포함) 및 비-HBV 코돈(절단된 상어 불변 체 [SIi], 2개 링커[청록색으로 표시됨] 및 퓨린 2A[F2A] 펩티드 서열을 포함함)를 코딩한다. 포유동물 발현 카세트 내에서, 면역원 코돈 서열은 CMV 프로모터에 인접하여 배치된다. **(c) 시험관내 발현 분석.** SIi-HBV-CPmutS 및 SIi-HBV-SCPmut를 코딩하는 플라스미드를 HEK293A 세포에 형질감염시켰다. 형질감염 24시간 후, 세포를 용해시키고, 용해물은 마우스 항-HBV-PreS1 및 마우스 항-HBV-폴리머라제 항체를 사용하는 웨스턴 블롯 실험으로 분석했다. 마우스 항-GAPDH로 프로빙된 블롯은 로딩 대조군으로 사용했다. **(d) ChAdOx2-SIi-HBV-CPmutS.** SIi-HBV-CPmutS 면역원 코돈을 갖는 포유동물 발현 카세트를 복제 결합 ChAdOx2 벡터에 삽입했다. 재조합 ChAdOx2-SIi-HBV-CPmutS 바이러스는, 상기 기재된 바와 같은 표준 방법을 사용하여, ChAdOx2-SIi-HBV-CPmutS 벡터를 T-REx™-293 세포(Thermo Fisher Scientific)에 형질감염시켜 생성했다.

도 3: 천연 마우스 모델에서 ChAdOx2-SIi-HBV-CPmutS 백신의 시험. **(a) BALB/c 마우스에서 비장세포 반응;** **(b) BALB/c 마우스에서 간장내 림프구 반응;** **(c) CD1 마우스에서 비장세포 반응;** **(d) CD1 마우스에서 간장내 림프구 반응.** BALB/c 마우스(7주령의 4마리 마우스) 및 CD1(18주령의 2마리 마우스 및 13주령의 5마리 마우스)은 각각 4×10^7 IU 및 5×10^7 IU/마우스의 ChAdOx2-SIi-HBV-CPmutS 백신을 사용한 근육내 주사에 의해 백신접종했다. 백신접종 14일 후, 마우스를 희생시키고, 비장세포 및 간장내 림프구(IHL)를 표준 프로토콜에 따라 비장 및 간장으로부터 단리했다. 2×10^5 비장세포 및 1×10^5 IHL을, DMSO(1%) 또는 비-HBV 펩티드 풀($3 \mu\text{g/ml}$ 의 농도에서 A.I.L) 또는 HBV 펩티드 풀($3 \mu\text{g/ml}$ 의 농도에서 코어, Pol-1, Pol-2, Pol-3, Pol-4, PreS1/S2 및 표면) 또는 양성 대조군 미토젠(각각 $10 \mu\text{g/ml}$ 및 $12.5 \mu\text{g/ml}$ 의 농도에서 PHA 또는 콘카나발린 A)와 함께, ELISPOT 플레이트(항-마우스 INF γ 모노클로날 항체로 예비-코팅, 밤새 인큐베이션에 의해)에 플레이팅했다. 37°C에서 밤새 15시간 인큐베이션 후, 플레이트를 PBS로 7회 세척하고, 실온에서 2시간 동안 비오틴 접합된 마우스 항-INF γ 로 인큐베이션한 다음, PBS에 의한 4회 세척 및 실온에서 2시간 동안 AP 접합된 항-비오틴 인큐베이션을 수행했다. 이어서, 플레이트를 PBS로 4회 세척하고, 스팟이 웰 상에 나타날 때까지 BCIP/NBT 기질로 발색시켰다. 물에 의한 최종 세척 및 건조 후, 개개 웰로부터 스팟 형성 단위(SFU)/세포 100만개를 자동화 ELISPOT 플레이트 판독기로 계수했다. BALB/c 및 CD1 마우스로부터 비장세포 및 IHL에 의한 각 펩티드 풀 자극에 대한 ELISPOT 반응을 별도의 차트로 나타낸다. HBV 펩티드 자극으로부터의 전체 반응은 모든 HBV 펩티드 풀(코어, Pol-1, Pol-2, Pol-3, Pol-4, PreS1/S2 및 표면)에 대한 ELISPOT 반응을 조합하여 또한 계산한다.

도 4: 상어 불변 체(SIi)의 존재 및 부재하의 HBV 면역원 SIi-HBV-CPmutS의 면역원성의 비교. **(a) HBV-CPmutS 면역원 레이아웃.** 면역원 HBV-CPmutS는 SIi를 결실시켜 생성했고, 제1 링커는 SIi-HBV-CPmutS에 존재한다. HBV-CPmutS는, SIi-HBV-CPmutS 면역원에 존재하는 SIi 및 제1 링커 서열을 결여하는 것을 제외하고는, 정확하게 동일한 아미노산을 갖는다. **(b) CD1 마우스에서 비장세포 반응.** **(c) CD1 마우스에서 간장내 림프구 반응.** ChAdOx2-HBV-CPmutS는 전술한 바와 같이 생성했고, CD1 마우스(7주령의 10마리 마우스)는 마우스당 5×10^7 IU의 ChAdOx2-HBV-CPmutS 백신을 사용한 근육내 주사에 의해 백신접종하고, 백신접종 14일 후에 마우스를 희생시키고, 비장세포 및 간장내 림프구 반응 데이터를 전술한 바와 같이 생성했다. 각각 ChAdOx2-SIi-HBV-CPmutS 및 ChAdOx2-HBV-CPmutS로 백신접종한 5 및 10마리 CD1 마우스로부터의 데이터를 비교하고, 비교를 용이하게 하기 위해 차트로 나타냈다.

도 5a: SIi-HBV-CPmutPreS-S(sh)의 개략적 레이아웃.

도 5b: SIi-HBV-CPmutPreS-TPA-S(sh)의 개략적 레이아웃.

도 6a: MVA-SIi-HBV-PreS-Pmut-C-S(sh)의 개략적 레이아웃.

도 6b: MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh)의 개략적 레이아웃.

도 7: BALB/c 마우스에서 ChAdOx1-SIi-HBV-CPmutS 백신의 시험, 비장세포 반응: BALB/c 마우스(8주령의 8마리

마우스)는 마우스당 5×10^7 IU의 ChAdOx1-SII-HBV-CPmutS 백신을 사용한 근육내 주사에 의해 백신접종했다. 백신접종 14일 후, 마우스를 희생시키고; 비장세포 반응 데이터를 전술한 바와 같이 생성했다. 각 펩티드 풀 자극에 대한 비장세포 T-세포 반응 및 모든 HBV-펩티드 풀로부터의 풀링된 전체 반응을 막대 차트에 나타낸다.

도 8: ChAdOx1 및 ChAdOx2를 통해 코딩된 HBV 면역원 SII-HBV-CPmutS의 면역원성의 비교. ChAdOx1 및 ChAdOx2 바이러스 벡터화 백신을 코딩하는 HBV-CPmutS 면역원을 전술한 바와 같이 생성했다(도 2d). 7주령의 10마리 CD1 마우스 및 8주령의 8마리 CD1 마우스는 각각 마우스당 5×10^7 IU의 ChAdOx2-HBV-CPmutS 및 ChAdOx1-HBV-CPmutS 백신을 사용한 근육내 주사에 의해 백신접종하고, 백신접종 14일 후에 마우스를 희생시키고, 비장세포 반응 데이터를 전술한 바와 같이 생성했다. ChAdOx2-SII-HBV-CPmutS 및 ChAdOx1-HBV-CPmutS로 백신접종한 10마리 및 8마리 CD1 마우스로부터의 데이터를 비교하고, 비교를 용이하게 하기 위해 차트로 나타냈다. 통계학적으로 유의하게 높은 전체 비장세포 T-세포 반응은, ChAdOx1-HBV-CPmutS 백신과 비교하여, ChAdOx2-HBV-CPmutS 백신으로 백신접종한 마우스에서 관찰되었다.

도 9: 짧은 CMV 프로모터 또는 긴 CMV 프로모터를 사용하여 ChAdOx1 및 ChAdOx2 바이러스 벡터에 의해 코딩된 HBV 면역원 SII-HBV-CPmutPreS-S(sh)(HBV-v2로서 명명)의 면역원성의 비교. ChAdOx1(ChAdOx1-LP-HBV-v2 및 ChAdOx1-SP-HBV-v2) 및 ChAdOx2(ChAdOx2-SP-HBV-v2) 백신을 코딩하는 2개 짧은 CMV 프로모터 및 1개 긴 CMV 프로모터 기반 SII-HBV-CPmutPreS-S(sh) 면역원(HBV-v2로 명명)을 전술한 바와 같이 생성했다. 8주령의 15마리 Balbc 마우스를 3개 그룹(그룹당 5마리)으로 분할하고, 5×10^7 IU의 ChAdOx1-SP-HBV-v2 또는 ChAdOx2-SP-HBV-v2 또는 ChAdOx1-LP-HBV-v2 백신을 사용한 근육내 주사에 의해 백신접종했다. 백신접종 14일 후, 마우스를 희생시키고, 비장세포 반응 데이터를 전술한 바와 같이 생성했다. 모든 3개 HBV-v2 백신으로부터의 비교 데이터는 비교를 용이하게 하기 위해 동일한 차트에 나타낸다. 통계학적으로 유의하게 높은 전체 비장세포 T-세포 반응은, 다른 2개 HBV-v2 백신과 비교하여, ChAdOx1-SP-HBV-v2 백신으로 백신접종한 마우스에서 관찰되었다. 또한, ChAdOx2-SP-HBV-v2 백신은, ChAdOx1-LP-HBV-v2 백신과 비교하여, 통계학적으로 유의하게 높은 전체 비장세포 T-세포 반응을 나타냈다.

도 10a-g: (a) SII-HBV-CPmutS; (b) SII-HBV-SCPmut; (c) HBV-CPmutS; (d) SII-HBV-CPmutPreS-S(sh); (e) MVA-SII-HBV-PreS-Pmut-C-S(sh); (f) SII-HBV-CPmutPreS-TPA-S(sh); 및 (g) MVA-SII-HBV-PreS-Pmut-C-TPA-S(sh)의 면역원 레이아웃을 나타낸다.

발명을 실시하기 위한 구체적인 내용

[0178] HBV 백신은, 만성 HBV 감염과 보다 빈번하게 관련을 갖는 남동아시아에서 가장 일반적인 HBV 유전자형 중의 하나인 HBV 유전자형 C에 기초하여 생성했다. HBV 면역원을 설계하기 위해, 컨센서스에 가장 근접하는 환자의 HBV 유전자형 C 서열(GeneBank: KP017269.1)을 선택하고, 이는 HBVdb, 간염 바이러스 B 데이터베이스(도 1a 및 1b)로부터 1447 HBV-유전자형-C 서열을 정렬함으로써 생성했다. 선택된 HBV 유전자형 C 서열은 컨센서스와 비교하여 3개의 뉴클레오타이드 변화만을 갖고, 이중 2개는 침묵 돌연변이이고, 하나는 폴리머라제 단백질 중의 돌연변이를 갖는다(도 1c).

[0179] 상이한 HBV 단백질에 대한 강력한 및 멀티-항원 특이적 T 세포 반응은 분석 HBV 감염의 바이러스 정화에 주요한 역할을 담당하는 것으로 생각된다. 이에 기초하여, 바이러스의 모든 주요 단백질, 즉 코어(프레-코어 영역을 포함), 비-기능적 폴리머라제 Pmut(Pmut: HBV 바이러스 복제에 관여하는 백신 코딩된 폴리머라제 능력을 저지하는 것을 목적으로 하는, 기능적 돌연변이를 갖는 HBV 폴리머라제), 및 표면 단백질(이의 PreS1 및 PreS2 영역을 포함함)을 코딩하는 HBV 면역원을 설계했다. 도 2a 및 2b는 HBV 게놈의 코돈 레이아웃, 및 최초 2개 HBV 백신 면역원 설계의 개략도를 각각 나타낸다. 레이아웃은, 퓨린 2A(F2A) 펩티드 절단 메카니즘을 사용하여, 프레-코어, 코어 및 Pmut를 융합 단백질 및 개별 표면 단백질로서 코딩하도록 설계하고, 리보솜 스킵 사상을 유발함으로써 단일 개방 관독 프레임으로부터 2개 단백질을 코딩하도록 한다.

[0180] 단일 도입유전자 카세트 내에서 멀티 단백질의 코딩은, CMV 프로모터에 대한 코돈 서열의 접근이 코딩된 단백질의 발현 수준에 중요한 역할을 담당하는 신중한 설계를 필요로 한다. 이러한 2개 면역원(도 2b), SII-HBV-CPmutS 및 SII-HBV-SCPmut를 분석하기 위해, 본 발명자들은 각각 면역원 카세트의 종료 또는 개시에서 표면 단백질을 코딩하는 것을 생성했고, 이들을 웨스턴 블롯 발현 연구로 시험했다. 웨스턴 블롯 발현 분석은 레이아웃 SII-HBV-CPmutS가 최상의 F2A 절단 가능성을 갖는 것을 나타냈고, 이는, SII-HBV-SCPmut와 비교하는 경우, 대량의 예상된 CPmut 및 S 단백질을 생성한다(도 2c).

- [0181] 이러한 관찰에 기초하여, 본 발명자들은, 침팬지 아데노바이러스(ChAdOx2) 기반 T-세포 유도 HBV 백신의 생성을 위한 전방 SIi-HBV-CPmutS 면역원 레이아웃을 수행하기로 결정했다(도 2d). ChAdOx2-SIi-HBV-CPmutS의 소규모 배치는, 옥스포드 대학의 제너 인스티튜트(Jenner Institute)의 바이러스 벡터 코어 시설에서 적절한 제조 관행에 따라 제조하고, 마우스 면역원성 연구에 사용했다.
- [0182] T-세포 면역 반응을 생성하는 ChAdOx2-SIi-HBV-CPmutS 백신의 능력은 천연 마우스 모델을 사용하여 시험했다. 천연 BALB/c 및 CD1 마우스를 각각 4×10^7 IU 및 5×10^7 IU/마우스의 ChAdOx2-SIi-HBV-CPmutS 백신으로 근육내 주사에 의해 면역화시켰다. 백신접종 14일 후, 마우스를 희생시키고, 비장 및 간장으로부터 단리된 비장세포 및 간장내 림프구(IHL)로 IFN- γ ELISPOT 검정을 실시했다. 전체 SIi-HBV-CPmutS 면역원에 걸쳐 생성된, 11 아미노산이 중첩하는, 15개의 합성 펩티드를 특정 풀(SIi-HBV-CPmutS 면역원의 상이한 영역을 나타냄)과 조합하고, IFN- γ ELISPOT 검정에서 자극제로서 사용했다. 결과는 ChAdOx2-SIi-HBV-CPmutS 백신이 SIi-HBV-CPmutS 면역원에 대해 양호한 IFN- γ ELISPOT 반응을 생성했음을 나타냈다(도 3). BALB/c 및 CD1 마우스 둘 다는 면역원에서 폴리머라제 및 표면 단백질에 대한 보다 강력한 반응, 코어 단백질에 대한 약한 반응 및 비-HBV 단백질(상어 불변 쇄[SIi], F2A 및 링커)에 대한 무시가능한 반응 또는 무반응을 나타냈다.
- [0183] 이전 연구는 상어 불변 쇄(SIi)이, 면역원의 N-말단에 위치하는 경우, 분자 애주버트로서 기능하고 면역원에 대한 전체 T-세포 면역 반응을 증가시키는 것을 나타냈다. 이를 시험하기 위해, 본 발명자들은 SIi(HBV-CPmutS 백신)의 부재하에 HBV 면역원을 생성했고(도 4a), 이어서 ChAdOx2-HBV-CPmutS 백신을 생성하고, 이들을 유사한 CD1 마우스 면역원성 실험에서 시험했다. 결과는 SIi 백신(ChAdOx2-SIi-HBV-CPmutS)이, 비-SIi 백신(ChAdOx2-HBV-CPmutS)과 비교하여, 보다 높은 정도의 IFN- γ ELISPOT 반응(비장세포 및 간장내 림프구 둘 다의 IFN- γ ELISPOT 반응, 도 4b, 4c에 나타냄)을 생성하는 것을 나타냈다.
- [0184] 바이러스 벡터화 HBV 백신 설계의 주요 목적은 HBV 면역원에 대한 T-세포 및 항체 반응 둘 다를 생성하는 것이다. 성공적 항체 반응을 생성하기 위해, 면역원 코딩된 단백질을 이의 천연 입체구조로 폴딩해야 한다. 이를 제공하기 위해, HBV 면역원, SIi-HBV-CPmutPreS-S(sh) 및 SIi-HBV-CPmutPreS-TPA-S(sh)(도 5a 및 5b)를 설계했고, 이는 항체 유도 면역원 성분으로서 표면 단백질의 S 도메인에 링커와 융합된 PreS1 도메인의 N-말단 절반을 코딩하고, 표면 단백질의 나머지 펩티드 서열(PreS1 도메인의 C-말단 절반 및 전체 PreS2 도메인)을 프레코어/코어/Pmut에 융합시켜, T-세포 면역 반응의 생성에 요구될 수 있는 T-세포 에피토프를 보존했다. 도 5a 및 5b는 SIi-HBV-CPmutPreS-S(sh)의 개략적 레이아웃을 나타낸다.
- [0185] 또한, SIi-HBV-CPmutPreS-S(sh) 및 SIi-HBV-CPmutPreS-TPA-S(sh)와 유사하게 설계한 다음과 같은 MVA-HBV 면역원을 설계했다. 그러나, HBV 면역원 SIi-HBV-CPmutPreS의 T-세포 성분은 초기 프로모터 F11에 의해 코딩되고, 항체 유도 성분 S(sh) 또는 TPA-S(sh)는 초기/후기 프로모터 mH5에 의해 코딩된다. 클로닝 카세트는 또한 F11-좌측 인접 및 F11-우측 인접 서열을 가져, 상동성 재조합에 의해 F11 유전자좌 내로의 삽입을 가능하게 한다. 도 6a 및 6b는 각각 MVA-SIi-HBV-PreS-Pmut-C-S(sh) 및 MVA-SIi-HBV-CPmutPreS-TPA-S(sh)의 개략적 레이아웃을 나타낸다.
- [0186] **결론:** 신규한 멀티-항원 HBV 면역원 기반 ChAdOx2-SIi-HBV-CPmutS는 천연 마우스 모델에서 고도의 면역원성이다. 이들 연구는 만성 HBV 마우스 모델에서 장래 연구의 길을 열어, 면역요법 접근법을 통한 만성 HBV 감염을 극복하는 이들의 능력을 평가한다.
- [0187] **서열:**
- [0188] 1447 유전자형 C 서열(3215 염기 쌍)으로부터 생성된 HBV 유전자형 C 컨센서스 서열은 서열번호 1로서 제공된다. KP017269.1 HBV 단리주 JP-02의 서열은 서열번호 2로서 제공된다.
- [0189] **카세트의 예**
- [0190] 1. SIi-HBV-CP_{mut}S
- [0191] 1.1. SIi-HBV-CP_{mut}S: 면역원 레이아웃은 도 10a에 제시되어 있다.
- [0192] 1.2. SIi-HBV-CP_{mut}S: 아미노산 서열(서열번호 3)
- [0193] MSLWGVTVLAAMLIAGQVASVVLV**KGGGPGGG**MQLFHLCLII SCSCPTVQASKLCLGWLGMDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALY
REALESPEHCSPHHTALRQAILCWGELMNLATWVGSNLEDPASRELVSYSVNVNMGKIRQLLWFHISCLTFGRETVEYLVSVFGVWIRTPPAYRPPNAPIL

STLPETTVVRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQCGGGSGGGMPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNVSI PW
THKVGNTGLASSTVPVFNPWEQTPSFPHIHLQEDI INRCQQYVGPLTVNEKRRLKL IMPARFYPNLTKYLPLDKGIKPYYPEHAVNHYFKTRHYLHTLWKA
GILYKRETTASFCGSPYSWEQELQHGRLVFQTSTRHGDESFCSSGILSRSPVGPCVRSQKQSRGLQPQQGSLARGKSGRSGSIRARVHPTTRRSFG
VEPSGSGHIDNSASSTSSCLHQSAVRKTAYSHLSTSKRQSSSGHVELHNIPPSSARSQSEGFIFSAWWLQFRNSKPAASDYALTHIVNLEDWGPATEHGEH
NIRIPRTPARVTGGVFLVDKNPHNTTESRLVDFSQFSRGSTHVSWPKFAPVNLQSLTNLSSNLSWLSLDVSAAFYHIIPLHPAAMPHELLVGSSGLPRYVAR
LSSTSRNINYQHGTMQDLHDSCSRNLYVSLLLLYKTFRKHLHYSHPI ILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAPPHCLAFSYMDDVVLGAKSVQH
LESFTSITNFLSLGIHLNPNKTKRWGYSNFMGYVIGSWGTLQEHIVLKI KQCFRKL PVNRPIDWVCQRIVGLLGFAAPFTQCGYPALMPLYACIQSK
QAFTFSPTYKAFLCKQYLNLYPVARQRSGLCQVFADATPTGWGLAIGHRA MRGTFVAPLP IHTAELLAACFARSRSAGAKLIGTDNSVLSRKYTSFPWLLGC
AANWILRGTSFVYVPSALNPAADPSAAGRLGLYRPLLHLPFRPTTGRTSLYAVSPSVPSHL PDRVHFASPLHVAWRPP RKRRAPVKQTLNFDLLKLAGDVESN
PGPMGWSSKPRQGMGTNLVSNPLGFFPDHQLDPAFGANSNPDWDFNPNKDHWEANQVAGAGFGPGFTPPHGGLLGWSPQAQGILTTVPAAPPASTNR
QSGRQPTPI SPPLRDSHPQAMQWNSTTFHQALLDPRVRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPNMENTTSGFLGPLLVLAGFLLTRILT
IPQSLDSWWTSLNFLGGAPTCPGQNSQSPTSNSHPTSCPPICPGYRWMLRRFI IFLFILLCLIFLLVLLDYQGMLPVCPLLPGTSTTSTGPKCTCTIPAQ
GTSMPFSCCCTKPSDGNCTCIPIPSSWAFARFLWEWASVRFWSLSLLVPFVQWVGLSPTVWLSVIWMMWYWGPSLYNILSPFLPLPIFFCLWVYI

[0194] 1.3. Sii-HBV-CP_{mut}S: HBV 면역원의 아미노산 서열의 기재

[0195] 1.3.1. 폴리펩티드의 최초 아미노산 = M

[0196] 1.3.2. 상어 불변 쇠(Sii) = SLLWGGVTVLAAML IAGQVASVVFLV (서열번호 4)

[0197] 1.3.3. 링커 = KGGGPGGG (서열번호 5)

[0198] 1.3.4. C =

[0199] 1.3.4.1. PreC =

[0200] MQLFHLCLIISCSCTVQASKLCLGWLWG (서열번호 16)

[0201] 1.3.4.2. 코어
MDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALSEPHCSPHHTALRQAILCWGELMNLATWVGSNLEDPASREL VVSYYVNVNMGKIRQLLW
FHISCLTFGRETVLEYLVSFVWIRTPPAYRPPNAPILSTLPETTVVRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQC (서열번호 6)

[0202] 1.3.5. 링커 = GGGSGGG (서열번호 7)

[0203] 1.3.6. Pmut = (돌연변이: Y63A, C323A, C334A, C338A, C352A, R714A, D788A, R792A)

[0204] MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNVSI PWTHKVGNTGLASSTVPVFNPWEQTPSFPHIHLQEDI INRCQQYVGPLTVN
EKRRRLKL IMPARFYPNLTKYLPLDKGIKPYYPEHAVNHYFKTRHYLHTLWKA GILYKRETTASFCGSPYSWEQELQHGRLVFQTSTRHGDESFCSSGI
LSRSPVGPCVRSQKQSRGLQPQQGSLARGKSGRSGSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQSAVRKTAYSHLSTSKRQSSSGHVELHN
IPPSSARSQSEGFIFSAWWLQFRNSKPAASDYALTHIVNLEDWGPATEHGEHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVDFSQFSRGSTHVSWPKFA
VNLQSLTNLSSNLSFGRKHLHYSHPI ILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAPPHCLAFSYMDDVVLGAKSVQHLESFTSITNFLSLGIHL
NPNKTKRWGYSNFMGYVIGSWGTLQEHIVLKI KQCFRKL PVNRPIDWVCQRIVGLLGFAAPFTQCGYPALMPLYACIQSKQAFTFSPTYKAFLCKQYLN
LYPVARQRSGLCQVFADATPTGWGLAIGHRA MRGTFVAPLP IHTAELLAACFARSRSAGAKLIGTDNSVLSRKYTSFPWLLGCAANWILRGTSFVYVPSALN
PAADPSAAGRLGLYRPLLHLPFRPTTGRTSLYAVSPSVPSHL PDRVHFASPLHVAWRPP (서열번호 8)

[0205] 1.3.7. 퓨린 2A (F2A) = RKRRAPVKQTLNFDLLKLAGDVESNPGP (서열번호 9)

[0206] 1.3.8. 표면 단백질(S) =

[0207] 1.3.8.1. PreS1 =

[0208] MGGWSSKPRQGMGTNLVSNPLGFFPDHQLDPAFGANSNPDWDFNPNKDHWEANQVAGAGFGPGFTPPHGGLLGWSPQAQGILTTVPAAPPASTNRQSG
RQPTPI SPPLRDSHPQA (서열번호 52)

[0209] 1.3.8.2. PreS2 =

[0210] MQWNSTTFHQALLDPRVRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPN (서열번호 53)

[0211] 1.3.8.3. 표면 (S) =

[0212] MENTTSGFLGPLLVLAGFLLTRILTIPQSLDSWWTSLNFLGGAPTCPGQNSQSPTSNSHPTSCPPICPGYRWMLRRFI IFLFILLCLIFLLVLLDYQG
MLPVCPLLPGTSTTSTGPKCTCTIPAQGTSMFPSCCCTKPSDGNCTCIPIPSSWAFARFLWEWASVRFWSLSLLVPFVQWVGLSPTVWLSVIWMMWYWGPS

LYNILSPFLPLLP₁IFFCLWVYI (서열번호 10)

[0213] SII-HBV-CP_{mut}S 뉴클레오티드 서열은 서열번호 46으로서 제공된다.

[0214] 2. SII-HBV-SCP_{mut}

[0215] 2.1. SII-HBV-SCP_{mut}: 번역원 레이아웃은 도 10b에 제시된다

[0216] 2.2. SII-HBV-SCP_{mut}: 아미노산 서열 (서열번호 11)

[0217] MSLWGGVTVLAAML₁IAGQVASVFLV₁KGGSMGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNPNKDHWPEANQVGAGAFGPGFTPPH
GGLLWSPQAQGI₁LTTPVAAPPPASTNRQSGRQPTP₁ISPLRDSHPQAMQWNSTTFHQALLDPRVRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAP
NMENTTSGFLGPLLV₁LQAGFFLLTRIL₁TIPQSLDSWWTSLN₁FLGGAPTCPGQNSQSPTS₁NHSPTSCPP₁ICPGYRWMCLRRFI₁IFLFI₁LLLCLIFLLVLLDYQ
GMLPVCPLLP₁GTSTTSTGPKCTCTIP₁AGQTSMFPSCCCTKPSDGNCTCIP₁IPSSWAFARFLWEWASVRF₁SWLSLLVPFVQWFVGLSPTVWLSV₁IWMWYWG
SLYNILSPFLPLLP₁IFFCLWVYI₁RKRRAPVKQTLNFDLLKLAGDVESNPGPMLFHLCLI₁ISCSCPTVQASKLCLGWLWGMDIDPYKEFGASVELLSFLPSD
FFPSIRDLLDTASALYREALSPEHCSPHHTALRQA₁ILCWGELMNLATWVGSNLEDPASREL₁VVS₁VNVNMG₁LKIRQLLWFH₁ISCLTFGRETVLEYLV₁SFGV
WIRTPPAYRPPNAPILSTLPETTVVRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQCGGGSGGGMPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRR
VAEDNLGNLNV₁IPWTHKVGNTGL₁ASSTVPVFNPEWQTPSFPHIHLQEDI₁INRCQYVGPLTVNEKRLKLIMPARFYPNLT₁KYLPLDKGIKPYYPEHAV
NHYFKTRHYLHTLWKAGILYKRETT₁SASFCGSPYSWEQELQHGR₁LVFQTSTRHGDESFCSSQSSGILSRSPVGPCVRSQ₁LKQSR₁GLQPQ₁QGLARGKSGRS
GSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQSAVRKTAYSHLSTSKRQSSSGHAVELHNIPPSARSQSEGPIFSAWWLQFRNSKPASDYALTHI
VNLEDWGPATEHEGHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVVD₁FSQFSRGSTHVS₁WPKFAV₁PNLQSLTNLLSSNL₁SWLSDVSAAFYHIPLHPAAM
PHLLVGSSGLPRYVARLSSTSRNIN₁YQHTMQDLHDSCSRNLYSLLLLYKTFGRKLHLYSHPI₁ILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAFPHCLA
FSYMDDVVLGA₁KSQVHLESLFTSITN₁FLLSLGIHLNPNKTKRWGYS₁NFMGYVIGSWGTL₁PQEHIVLKIKQCFRKL₁PVNRPIDW₁KVCQRI₁VGLLGFAAPFTQ
CGYPALMPLYACIQSKAQFTFSPTYKAFLCKQYLNLYPVARQ₁RSGLCQVFADATPTGWGLAIGHRAMRGTFVAPLP₁IHTAELLAACFARSRS₁GAKLIGTDNS
VVL₁SRKYS₁TFPWL₁LGCAANWILRGTSFVYVPSALNPAADPSAGRLGLYRPLHL₁PF₁RPTTGR₁TS₁LYAVSPSVPSHL₁PDRVHFASPLHVAWRPP

[0218] 2.3. SII-HBV-SCP_{mut}: HBV 번역원의 아미노산 서열의 기재

[0219] 2.3.1. 폴리펩티드의 최초 아미노산 = M

[0220] 2.3.2. 상어 불변 쇠 (SII) = SLLWGGVTVLAAML₁IAGQVASVFLV (서열번호 4)

[0221] 2.3.3. 링커 = KGGS (서열번호 14)

[0222] 2.3.4. 표면 단백질(S) =

[0223] 2.3.4.1. PreS1 =

[0224] MGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNPNKDHWPEANQVGAGAFGPGFTPPHGGLLWSPQAQGI₁LTTPVAAPPPASTNRQSG
RQPTPISPLRDSHPQA (서열번호 52)

[0225] 2.3.4.2. PreS2 =

[0226] MQWNSTTFHQALLDPRVRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPN (서열번호 53)

[0227] 2.3.4.3. 표면 (S) =

[0228] MENTTSGFLGPLLV₁LQAGFFLLTRIL₁TIPQSLDSWWTSLN₁FLGGAPTCPGQNSQSPTS₁NHSPTSCPP₁ICPGYRWMCLRRFI₁IFLFI₁LLLCLIFLLVLLDYQ
MLPVCPLLP₁GTSTTSTGPKCTCTIP₁AGQTSMFPSCCCTKPSDGNCTCIP₁IPSSWAFARFLWEWASVRF₁SWLSLLVPFVQWFVGLSPTVWLSV₁IWMWYWG
LYNILSPFLPLLP₁IFFCLWVYI (서열번호 10)

[0229] 2.3.5. 퓨린 2A (F2A) = RKRRAPVKQTLNFDLLKLAGDVESNPGP (서열번호 9)

[0230] 2.3.6. C =

[0231] 2.3.6.1. 프레코어 =

[0232] MQLFHLCLI₁ISCSCPTVQASKLCLGWLWG (서열번호 16)

[0233] 2.3.6.2. 코어 =
MDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALSPEHCSPHHTALRQA₁ILCWGELMNLATWVGSNLEDPASREL₁VVS₁VNVNMG₁LKIRQLLWFH
FHI₁SCLTFGRETVLEYLV₁SFGVWIRTPPAYRPPNAPILSTLPETTVVRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQC (서열번호 6)

- [0234] 2.3.7. 링커 = GGGSGGG (서열번호 7)
- [0235] 2.3.8. Pmut = (돌연변이: Y63A, C323A, C334A, C338A, C352A, R714A, D788A, R792A)
- [0236] MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNVSIPTWTHKVGNTGLASSTVPVFNPEWQTPSFPHIHLQEDIINRCQQYVGPLTVN
EKRRLLKLIMPARFYFNLTKYLPLDKGIKPYYPEHAVNHYFKTRHYLHTLWKAGILYKRETTTSASFCGSPYSWEQELQHGRVLFQTS
TRHGDESFCSSQSSGILSRSPVGPCVRSQKQSLGLQPPQGSGLARGKSGRSGSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQS
AVRKTAYSHLSTSKRQSSSGHAVELHNIPPSSARSQSEGPIFSAWWLQFRNSKPASDYALTHIVNLEDWGPATEHGEHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVVD
FSQFSRGSTHVSWPKFAPVNLQSLTNLLSSNLSTFGRKLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAPPHCLAFSYMDDVVLGAKSVQH
LESFTSITNFFLLSLGIHLNPNKTKRWGYSNFMGYVIGSWGTLPEHIVLKIKQCFRKLVPVNRPIDWKCQRIVGLLGAAPFTQCGYPALMPLYACIQSKQAFT
FSPTYKAFLCKQYLNLYPVARQSRGLCQVFADATPTGWGLAIGHRAMRGTFVAPLPIHTAELLAACFARSRSAGKIGTDNSVLSRKYTSFPWLLGCAANWILRGTSFVYVPSALN
PAADPSAGRLGLYRPLHLPFRPTTGRTSLYAVSPSPVSHLPDRVHFASPLHVAVRPP (서열번호 8)
- [0237] Si-HBV-SCPmut 뉴클레오타이드 서열은 서열번호 47로서 제공된다:
- [0238] **3. HBV-CP_{mut}S**
- [0239] 3.1. HBV-CP_{mut}S: 번역원 레이아웃은 도 10c에 제시된다
- [0240] 3.2. HBV-CP_{mut}S: 아미노산 서열 (서열번호 12)
- [0241] MQLFHLCLIISCSCTPTVQASKLCLGWLWGMDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALSPEHCSPHHTALRQAILCWGELMNLATWVG
SNLEDPASRELVSYSVNVNMGKIRQLLWFHISCLTFGRETVLEYLVSGVWIRTTPAYRPPNAPILSTLPETTIVRRRGRSPRRRTSPRRRRSQSPRRRR
SQSRESQCGGGSGGGMPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNVSIPTWTHKVGNTGLASSTVPVFNPEWQTPSFPHIHLQED
IINRCQQYVGPLTVNEKRRLLKLIMPARFYFNLTKYLPLDKGIKPYYPEHAVNHYFKTRHYLHTLWKAGILYKRETTTSASFCGSPYSWEQELQHGRVLFQTS
TRHGDESFCSSQSSGILSRSPVGPCVRSQKQSLGLQPPQGSGLARGKSGRSGSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQS
AVRKTAYSHLSTSKRQSSSGHAVELHNIPPSSARSQSEGPIFSAWWLQFRNSKPASDYALTHIVNLEDWGPATEHGEHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVVD
FSQFSRGSTHVSWPKFAPVNLQSLTNLLSSNLVSLDVSAAFYHIPLHPAAMPHELLVGSSGLPRYVARLSSTSRNINYQHGTMDLHDCSRNLYVSLLLLYK
TFGRKLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAPPHCLAFSYMDDVVLGAKSVQHLESFTSITNFFLLSLGIHLNPNKTKRWGYSNFMG
YVIGSWGTLPEHIVLKIKQCFRKLVPVNRPIDWKCQRIVGLLGAAPFTQCGYPALMPLYACIQSKQAFTFSPTYKAFLCKQYLNLYPVARQSRGLCQVFA
DATPTGWGLAIGHRAMRGTFVAPLPIHTAELLAACFARSRSAGKIGTDNSVLSRKYTSFPWLLGCAANWILRGTSFVYVPSALNPAADPSAGRLGLYRPL
LHLPFRPTTGRTSLYAVSPSPVSHLPDRVHFASPLHVAVRPPRKRRAPVKQTLNFDLLKLAGDVESNPGPMGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDP
AFGANSNPDWDFNPNKDHWEANQVGAGAFGPGFTPPHGGLLWSPQAQGITTPAAPPASTNRQSGRQPTIPSPPLRDSHPQAMQWNSTTFHQALLDP
RVRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPNMENTTSGFLGPLLVLAGGFLLTRILTIPQLSDSWWTSNLFLLGGATCPGQNSQSPTS
NHSP TSCPPICPGYRWMLRRFIIFLFIILLCLIFLLVLLDYQGMPLVCPLLPGTSTTSTGPKCTCTIPAQGTSMFPSCCCTKPSDGNCTCIPIPSSWAFARFLWE
WASVRFSWLSLLVPFVQWVGLSPTVWLSVIWMMWYWGPSLYNILSPFLPLLPFFCLWVYI
- [0242] **3.3. HBV-CP_{mut}S: HBV 번역원의 아미노산 서열의 기재**
- [0243] 3.3.1. C =
- [0244] 3.3.1.1. 프레코어 =
- [0245] MQLFHLCLIISCSCTPTVQASKLCLGWLWG (서열번호 16)
- [0246] 3.3.1.2. 코어 =
MDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALSPEHCSPHHTALRQAILCWGELMNLATWVGSNLEDPASRELVSYSVNVNMGKIRQLLW
FHISCLTFGRETVLEYLVSGVWIRTTPAYRPPNAPILSTLPETTIVRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQC (서열번호 6)
- [0247] 3.3.2. 링커 = GGGSGGG (서열번호 7)
- [0248] 3.3.3. Pmut = (돌연변이: Y63A, C323A, C334A, C338A, C352A, R714A, D788A, R792A)
- [0249] MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNVSIPTWTHKVGNTGLASSTVPVFNPEWQTPSFPHIHLQEDIINRCQQYVGPLTVN
EKRRLLKLIMPARFYFNLTKYLPLDKGIKPYYPEHAVNHYFKTRHYLHTLWKAGILYKRETTTSASFCGSPYSWEQELQHGRVLFQTS
TRHGDESFCSSQSSGILSRSPVGPCVRSQKQSLGLQPPQGSGLARGKSGRSGSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQS
AVRKTAYSHLSTSKRQSSSGHAVELHNIPPSSARSQSEGPIFSAWWLQFRNSKPASDYALTHIVNLEDWGPATEHGEHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVVD
FSQFSRGSTHVSWPKFAPVNLQSLTNLLSSNLSTFGRKLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAPPHCLAFSYMDDVVLGAKSVQH
LESFTSITNFFLLSLGIHLNPNKTKRWGYSNFMGYVIGSWGTLPEHIVLKIKQCFRKLVPVNRPIDWKCQRIVGLLGAAPFTQCGYPALMPLYACIQSKQAFT
FSPTYKAFLCKQYLNLYPVARQSRGLCQVFADATPTGWGLAIGHRAMRGTFVAPLPIHTAELLAACFARSRSAGKIGTDNSVLSRKYTSFPWLLGCAANWILRGTSFVYVPSALN
PAADPSAGRLGLYRPLHLPFRPTTGRTSLYAVSPSPVSHLPDRVHFASPLHVAVRPP

NPNKTKRWGYSLNFMGYVIGSWGTLPQEHIVLKIKQCFRKLVPNRPIDWKVCQRIVGLLGFAAPFTQCGYPALMPLYACIQSKQAFTFSPTYKAFLCKQYLN
LYPVARQRSGLCQVFADATPTGWGLAIGHRA~~MR~~GTFFVAPLP~~IHTAELLAACFARSRS~~GAKLIGTDNSVLSRKYTSFPWLLGCAANWILRGTSFVYVPSALN
PAADPS~~AGRLGLYRPLLHLPFRPTTGR~~TSLYAVSPSVPSHLPDRVHFASPLHVAWRPP (서열번호 8)

[0250] 3.3.4. 퓨린 2A (F2A) = KKRRAPVKQTLNFDLLKLAGDVESNPGP (서열번호 9)

[0251] 3.3.5. 표면 단백질(S) =

[0252] 3.3.5.1. PreS1 =

[0253] MGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNPNKDHWEANQVGAGAFGPGFTPPHGGLLGWSPQAQGI~~LT~~TPAAPP~~PASTNR~~QSG
RQPTPI~~SPPLRDSHP~~QA (서열번호 52)

[0254] 3.3.5.2. PreS2 =

[0255] MQWNSTTFHQALLDPRVRGLYFPAGSSSGTVNPVPTTASPISSIFSR~~TGDP~~APN (서열번호 53)

[0256] 3.3.5.3. 표면(S)

[0257] MENTTSGFLGPLLVLQAGFFLLTRILTI~~PQSLDSWW~~TSN~~FLGGAPT~~CPGQNSQSPTS~~NHSPTSCPP~~ICPGYRWMCLRRFIIFLFI~~LLCLIFLLVLLDYQ~~
MLPVCPLLP~~GTSTTSTG~~PCKTCTIPAQGTSMF~~PPSCCCTKPSDGNCTC~~IP~~IPSSWAFARFLWEWASVRFSWL~~SLLVPFVQW~~FVGLSPTVWLSVIWMMWYWG~~PS
LYNILSPFLPLLP~~IFFCLWVYI~~ (서열번호 10)

[0258] 4. SIi-HBV-CP_{mut}PreS-S(sh)

[0259] 4.1. SIi-HBV-CP_{mut}PreS-S(sh): 면역원 레이아웃은 도 10d에 제시된다

[0260] 4.2. SIi-HBV-CP_{mut}PreS-S(sh): 아미노산 서열 (서열번호 13)

[0261] MSL~~WGGVT~~VLAAML~~IAGQVASV~~FLV~~KGGGPGGG~~MQLFHLCLII~~SCSCPTVQASKLCLGWLWGMDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALY~~
REALE~~SPEHCSPHHTALRQAILCWGELMNLATWVGSNLEDPASREL~~VVS~~VNVNMG~~LKIRQLLWFHISCLTFGRET~~VLEYLVSFGVWIRTPPAYRPPNAPIL~~
STLPETTV~~VRRRGRSPRRRTPSPRRRRSQSPRRRRSQSRESQC~~~~GGS~~GGG~~MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNV~~IPW
THK~~VGNFTGLASSTVPVFNPEWQTPS~~PHIHLQEDIINRCQYV~~GPLTVNEKRRLKLIMPARFY~~PNLTKYLPLDKGIKPY~~PEHAVNHYFKTRHYLHTLWKA~~
GILYKRETT~~RSASFCGPYSWEQELQHGR~~LVFQTSTRHGDESFCSSGILSRSPVGPCVRSQ~~LKQSRGLQPQGS~~LARGKSGRSGSIRARVHPT~~TRRSFG~~
VEPSGSGHIDNSASSTSSCLHQSAVRKTAYSHLSTSKRQSSSGH~~AVELHNIPSSARSQSEGI~~IFS~~AWWLQFRNSKPA~~SDY~~AL~~THIVN~~LEDWGP~~A~~TEHGEH~~
NIRIPRT~~PARVTGGVFLVDKNPHNTTESRLVDFSQFSRGSTHVS~~WPKFAV~~PNLQSLTNLSSNLSTFGRKLHLYSHPIILGFRKIPMGVGLSPFL~~LAQFTS
AICSV~~VRAFP~~HCLAFS~~YMDVVLAGAKSVQHLES~~LFTSITN~~FLSLGIHLNPNKTKRWGYSLNFMGYVIGSWGTLPQEHIVLKIKQCFRKLVPNRPIDWKVC~~
QRIVGLLGFAAPFTQCGYPALMPLYACIQSKQAFTFSPTYKAFLCKQYLNLYPVARQRSGLCQVFADATPTGWGLAIGHRA~~MR~~GTFFVAPLP~~IHTAELLAACF~~
ARSRS~~GAKLIGTDNSVLSRKYTSFPWLLGCAANWILRGTSFVYVPSALNPAADPS~~AGRLGLYRPLLHLPFRPTTGR~~TSLYAVSPSVPSHLPDRVHFASPLH~~
VAWRPP~~KSP~~SN~~NPDWDFNPNKDHWEANQVGAGAFGPGFTPPHGGLLGWSPQAQGI~~LTTPAAPP~~PASTNRQSGRQPTPI~~SPPLRDSHPQAMQWNSTTFHQ
ALLDPRVRGLYFPAGSSSGTVNPVPTTASPISSIFSR~~TGDP~~APN~~GSKGKRKR~~APVKQTLNFDLLKL~~AGDVESNPGP~~MGGWSSKPRQGMGTNLSVPNPLGF
FPDHQLDPAFGANSNNPDWDFNPNKDHWEANQV~~GLEGSGG~~MENTTSGFLGPLLVLQAGFFLLTRILTI~~PQSLDSWW~~TSN~~FLGGAPT~~CPGQNSQSPTS~~NH~~
SPTSCPPICPGYRWMCLRRFIIFLFI~~LLCLIFLLVLLDYQ~~MLPVCPLLP~~GTSTTSTG~~PCKTCTIPAQGTSMF~~PPSCCCTKPSDGNCTC~~IP~~IPSSWAFARFL~~
WEWASVRFSWL~~SLLVPFVQW~~FVGLSPTVWLSVIWMMWYWG~~PSLYNILSPFLPLLP~~IFFCLWVYI

[0262] 4.3. SIi-HBV-CP_{mut}PreS-S(sh): HBV 면역원의 아미노산 서열의 기재

[0263] 4.3.1. 폴리펩티드의 최초 아미노산 = M

[0264] 4.3.2. 상어 불변 쇠(SIi) = SLLWGGVTVLAAML~~IAGQVASV~~FLV (서열번호 4)

[0265] 4.3.3. 링커 = KGGGPGGG (서열번호 5)

[0266] 4.3.4. C =

[0267] 4.3.4.1. 프레코어 =

[0268] MQLFHLCLII~~SCSCPTVQASKLCLGWLWG~~ (서열번호 16)

[0269] 4.3.4.2. 코어 =
MDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALE~~SPEHCSPHHTALRQAILCWGELMNLATWVGSNLEDPASREL~~VVS~~VNVNMG~~LKIRQLLW

FHISCLTFGRETVEYLVSFGVWIRTPPAYRPPNAPILSTLPETTVVRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQC (서열번호 6)

[0270]

4.3.5. 링커 = GGGSGGG (서열번호 7)

[0271]

4.3.6. Pmut = (돌연변이: Y63A, C323A, C334A, C338A, C352A, R714A, D788A, R792A)

[0272]

MPLSYQHFRKLLLDDEAGPLEELPRLADEGLNRRVAEDLNLGNLNVSIPTWTHKVGNTGLASSTVPVFNPEWQTPSFPHIHLQEDIINRCQQYVGPLTVN
EKRRLKLIMPARFYPNLTkYLPDLKGIKPYYPEHAVNHYFKTRHYLHTLWKAGILYKRETTTSASFSGSPYSWEQELQHGRLVFQTSTRHGDESFCSSSGI
LSRSPVGPCVRSQKQSLGLQPPQGSARGKSGRSGSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQSARVKTAYSHLSTSKRQSSSGHVELHN
IPPSSARSQSEGIFFSAWWLQFRNSKPASDYALTHIVNLEDWGPATEHGEHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVVDQSFSRGSTHVSWPKFA
VPLNQLSTNLSSNLSTFGRKLHLYSHPILGFRKIPMGVGLSPFLLAQFTSAICSVVRAFPCHLAFSYMDDVVLGAKSVQHLESFTSITNLLSLGHL
NPNKTKRWGYSNFMGYVIGSWGTLPOEHVLKIKQCFRKLVPNRPIDWKVCQIRIVGLLGFAAPFTQCGYPALMPLYACIQSKQAFTFSPTYKAFLCKQYLN
LYPVARQRSGLCQVFADATPTGWGLAIGHRAMRGTFVAPLPIHTAELLAACFARSRSAGAKLIGTDNSVLSRKYSFSPWLLGCAANWILRGTSFVYVPSALN
PAADPSAGRLGLYRPLLHLPFRPTTGRTSLYAVSPSPVSHLPDRVHFASPLHVAWRPP (서열번호 8)

[0273]

4.3.7. 링커 = KSP

[0274]

4.3.8. NΔPreS1 및 PreS2 =

[0275]

NSNPDWDFNPNKDHWEANQVAGAGFGPGFTPPHGGLLGWSPQAQGITTVPAAPPPASTNRQSGRQPTIPSPPLRDSHPQAMQWNSTTFHQALLDPRVRG
LYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPN (서열번호 15)

[0276]

4.3.9. 링커 = GSKGK (서열번호 20)

[0277]

4.3.10. 퓨린 2A (F2A) = RKRRAPVKQTLNFDLLKLAGDVESNPGP (서열번호 9)

[0278]

4.3.11. S(sh) =

[0279]

4.3.11.1. CΔPreS1 = MGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNPDWDFNPNKDHWEANQV (서열번호 21)

[0280]

4.3.11.2. 링커 = LEGGSGG (서열번호 22)

[0281]

4.3.11.3. 표면 (S) =

[0282]

MENTTSGFLGPLLVLAGFFLLTRILTIPTQSLDSWWTSLNFLGGAPTCPGQNSQSPTSNSHPTSCPPICPGYRWMCLRRFIIFLFIILLCLIFLLVLLDYQG
MLPVCPLPGTSTTSTGPCKTCTIPAQGTSMFPSCCTKPSDGNCTCIPIPSSWAFARFLWEWASVRFSWLSLLVPFVQWVGLSPTVWLSVIWMWYWG
LYNLSPLPLPIFFCLWVYI (서열번호 18)

[0283]

SIi-HBV-CPmutPreS-S(sh) 뉴클레오티드 서열은 서열번호 48로서 제공된다.

[0284]

5. MVA-SIi-HBV-PreS-P_{mut}-C-S(sh)

[0285]

5.1. MVA-SIi-HBV-PreS-P_{mut}-C-S(sh): 번역원 레이아웃은 도 10e에 제시된다

[0286]

5.2. MVA-SIi-HBV-PreS-P_{mut}-C-S(sh): 아미노산 서열 (서열번호 23)

[0287]

MSLLWGGVTVLAAML IAGQVASVVFLVSKSGPPSGKSNSNPDWDFNPNKDHWEANQVAGAGFGPGFTPPHGGLLGWSPQAQGITTVPAAPPPASTNRQS
GRQPTIPSPPLRDSHPQAMQWNSTTFHQALLDPRVRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPNGSKSGSKMPLSYQHFRKLLLDDEAGPLE
EELPRLADEGLNRRVAEDLNLGNLNVSIPTWTHKVGNTGLASSTVPVFNPEWQTPSFPHIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPNLTkYLP
LDKGIKPYYPEHAVNHYFKTRHYLHTLWKAGILYKRETTTSASFSGSPYSWEQELQHGRLVFQTSTRHGDESFCSSSGILSRSPVGPCVRSQKQSLGLQ
PQQGSARGKSGRSGSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQSARVKTAYSHLSTSKRQSSSGHVELHNIPPSSARSQSEGIFFSAWWLQF
RNSKPASDYALTHIVNLEDWGPATEHGEHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVVDQSFSRGSTHVSWPKFAVPLNQLSTNLSSNLVSLDV
SAAFYHIPLHPAAMPPLLVGSSGLPRYVARLSSTSRNINQHGTMQDLHDCSRNLYVSLLLLYKTFGRKLHLYSHPILGFRKIPMGVGLSPFLLAQFTSA
ICSVVRAFPCHLAFSYMDDVVLGAKSVQHLESFTSITNLLSLGHLNPNKTKRWGYSNFMGYVIGSWGTLPOEHVLKIKQCFRKLVPNRPIDWKVCQ
RIVGLLGFAAPFTQCGYPALMPLYACIQSKQAFTFSPTYKAFLCKQYLNLYPVARQRSGLCQVFADATPTGWGLAIGHRAMRGTFVAPLPIHTAELLAACFA
RSRSGAKLIGTDNSVLSRKYSFSPWLLGCAANWILRGTSFVYVPSALNPAADPSAGRLGLYRPLLHLPFRPTTGRTSLYAVSPSPVSHLPDRVHFASPLHV
AWRPPSKSPGSGPPQLFHLCLIISCSCTVQASKLCLGWLWGMIDIPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALESPEHCSPHHTALRQAI
LCWGELMNLATWVGSNLEDPASRELVSYNVNMGLKIRQLWFHISCLTFGRETVEYLVSFGVWIRTPPAYRPPNAPILSTLPETTVVRRRGRSPRRRT
SPRRRRSQSPRRRRSQSRESQC

[0288]

MGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNPDWDFNPNKDHWEANQVASKGKSGKMENTTSGFLGPLLVLAGFFLLTRILTIPTQSLDSW

WTSNLFLLGGAPTCPGQNSQSPTSNNHSTSCPPICPGYRWMCLRRFIIFLFILLCLIFLLVLLDYQGMLPVCPLLPSTSTGPKCTCTIPAQGTSMFPSC
CCTKPSDGNCTCIPISSWAFARFLWEWASVRFWSLLVPFVQWVGLSPTVWLSVIWMMWYWGPSLYNLSPLPLLPFFCLWVYI

[0289] 5.3. MVA-SIi-HBV-PreS-P_{mut}-C-S(sh): HBV 면역원의 아미노산 서열의 기재

[0290] 5.3.1.1. 폴리펩티드의 최초 아미노산 = M

[0291] 5.3.1.2. 상어 불변 쇠 (SIi) = SLLWGGVTVLAAMLIAGQVASVFLV (서열번호 4)

[0292] 5.3.1.3. 링커 = SKSGPPSGKS(서열번호 31)

[0293] 5.3.1.4. NΔPreS1 및 PreS2 =
NSNNPDWDFNPNKDHWEANQVGAGAFPGFTPPHGGLLGWSPQAQGITTPVAAPPPASTNRQSGRQPTIPSPPLRDSHPQAMQWNSTTFHQALLDPRVRG
LYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPN (서열번호 15)

[0294] 5.3.1.5. 링커 = GSKSGSK (서열번호 32)

[0295] 5.3.1.6. Pmut = (돌연변이: Y63A, C323A, C334A, C338A, C352A, R714A, D788A, R792A)

[0296] MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNVSIPTWTHKVGNTGLASSTVPVFNPWEQTPSEPHIHLQEDIINRCQQYVGPLTVN
EKRRRLKLIMPARFYFNLTKYLPLDKGIKPYYPEHAVNHYFKTRHYLHTLWKAGILYKRETTTRSASFSGSPYSWEQELQHGRVLFQTSTRHGDESFCSSSGI
LSRSPVGPVCVRSQKQSLGLQPPQGSGLARGKSGRSGSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQSASVRKTAYSHLSTSKRQSSSGHAVELHN
IPPSSARSQSEGFIFS~~A~~WWLQFRNSKP~~A~~SDY~~A~~LTHIVNLEDWGP~~A~~TEHGEHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVVDFSQFSRGSTHVSWPKFA
VPLNQLSTNLSSNLSTFGRKLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAPPHCLAFSYMDDVVLGAKSVQHLESFTSITNLLSLGIHL
NPNKTKRWGYSLNFMGYVIGSWGTLPEHIVLKI~~K~~QCFRKL~~P~~VNRPIDW~~K~~VQRI~~V~~GLLGFAAPFTQCGYPALMPLYACIQSKQAFTFSPTYKAFLCKQYLN
LYPVARQRSGLCQVFADATPTGWGLAIGHRA~~M~~RGTFVAPLPIHTAELLAACFARSRS~~G~~AKLIGTDNSVVL~~S~~RKYTSFPWLLGCAANWILRGTSFVYVPSALN
PAADPSA~~A~~GRLLGLYRPLHLPFRPTTGR~~T~~SLYAVSPSVPSHL~~P~~DRVHFASPLHVAWRPP (서열번호 8)

[0297] 5.3.1.7. 링커 = SKSPGSGPP (서열번호 33)

[0298] 5.3.1.8. C =

[0299] 5.3.1.8.1. 프레코어

[0300] MQLFHLCLIIISCSCPTVQASKLCLGWLWG (서열번호 16)

[0301] 5.3.1.8.2. 코어 =

[0302] MDIDPYKEFGASVELLSFLPSDFFPISIRDLLDTASALYREALSEPHCSPHHTALRQAILCWGELMNLATWVGSNLEDPASRELVS~~Y~~VNVNMG~~L~~KIRQLLW
FHISCLTFGRET~~V~~LEYLSVSGVWIRTPPAYRPPNAPILSTLPETTVVRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQC (서열번호 6)

[0303] 5.3.1.9. S(sh)

[0304] 5.3.1.9.1. CΔPreS1 =

[0305] MGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNPDWDFNPNKDHWEANQVG

[0306] 5.3.1.9.2. 링커 =

[0307] ASKGGKSG (서열번호 34)

[0308] 5.3.1.9.3. 표면 =

[0309] MENTTSGFLGPLLVLAGFFLLTRILTIPQSLDSWWTSNLFLLGGAPTCPGQNSQSPTSNNHSTSCPPICPGYRWMCLRRFIIFLFILLCLIFLLVLLDYQG
MLPVCPLLPSTSTSTGPKCTCTIPAQGTSMFPSCCCTKPSDGNCTCIPISSWAFARFLWEWASVRFWSLLVPFVQWVGLSPTVWLSVIWMMWYWGPS
LYNLSPLPLLPFFCLWVYI (서열번호 18)

[0310] 5.4. MVA-SIi-HBV-PreS-P_{mut}-C-S(sh)의 뉴클레오티드 서열은 서열번호 24로서 제공된다.

[0311] 5.5. MVA-SIi-HBV-PreS-P_{mut}-C-S(sh)의 뉴클레오티드 서열의 기재:

[0312] 5.5.1. F11-L-인접 = 염기 1 - 1097 (서열번호 35)

[0313] 5.5.2. SIi-HBV-PreS-P_{mut}-C = 염기 1098 - 4838 (서열번호 37)

- [0314] 5.5.3. 전사 터미네이터 서열 = 염기 4839 - 4845
- [0315] TTTTGT
- [0316] 5.5.4. mH5 프로모터 = 염기 4846 - 4942 (서열번호 28)
- [0317] 5.5.5. S(sh) = 염기 4943 - 5824 (서열번호 38)
- [0318] 5.5.6. F11-R-인접 = 염기 5825 - 7143 (서열번호 36)
- [0319] **6. SIi-HBV-CP_{mut}PreS-TPA-S(sh)**
- [0320] 6.1. SIi-HBV-CP_{mut}PreS-TPA-S(sh): 번역원 레이아웃은 도 10f에 제시된다
- [0321] 6.2. SIi-HBV-CP_{mut}PreS-TPA-S(sh): 아미노산 서열 (서열번호 25)
- [0322] MSLWGGVTVLAAMLIAGQVASVVFLVKGGGPGGGMQLFHLCLIISCSCTVQASKLCLGWLGMDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALY
 REALESPEHCSPHHTALRQAAILCWGELMNLATWVGSNLEDPASRELVVSYYVNVNMGKIRQLLWFHISCLTFGRETVLEYLVSFVWIRTTPAYRPPNAPIL
 STLPETTVVRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQCGGGSGGGMPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNVSI
 PWTHKVGNTGLASSTVPVFNPFWQTPSFPHIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPNLTLYPLDKGIKPYYPEHAVNHYFKTRHYLHTLWKA
 GILYKRETTASFCGSPYSWEQELQHGRVLFQTSRHHGDESFCSSGILSRSPVGPVRSQSLKQSLGLQPQQSLARGKSGRSGSIRARVHPTTTRRSFG
 VEPGSGHIDNSASSTSSCLHQSARVKTAYSHLSTSKRQSSSGHVELHNIPPSSARSQSEGFIFSAWWLQFRNSKPASDYALTHIVNLEDWGPATEHGEH
 NIRIPRTPARVTGGVFLVDKNPHNTTESRLVDFSQFSRGSTHVSWPKFAPVNLQSLTNLSSNLSTFGRKLHLYSHPILGFRKIPMGVGLSPFLLAQFTS
 AICSVVRRAPPHCLAFSYMDDVVLGAKSVQHLESLSITSITNLLSLGILHNPNTKRWGYSNFMGYVIGSWGTLPEHIVLKIKQCFRKLVPVNRPIDWKVC
 QRIVGLLGFAAPFTQCGYPALMPLYACIQSKQAFSTPTKYKAFCKQYLNLYPVARQSRGLCQVFADATPTGWGLAIGHRAMRGTFVAPLPIHTAELLAACF
 ARSRSGAKLIGTDNSVLSRKYTSFPWLLGCAANWILRGTSFVYVPSALNPAADPSAGRLGLYRPLHLPRPTTGRSLYAVSPSPVSHLPDRVHFASPLH
 VAWRPPKSPNSNNPDWDFNPNKDHWEANQVAGAFGPGFTPPHGGLLGWSPQAQGITTVPAAPPPASTNRQSGRQPTIPSPPLRDSHPQAMQWNSTTFHQ
 ALLDPRVRGLYFPAGGSSSGTVNPVPTASPISSIFSRGTDPAPNGSKGKRKRAPVKQTLNFDLLKLAGDVESNPGPMDAMKRGLCCVLLLCGAVFVSPSQ
 EIHARFRRMGGWSSKPRQGMGTNLSPVNPGLGFFPDHQLDPAFGANSNPDWDFNPNKDHWEANQVLEGGSGGMENTTSGLGPLLVLQAGFLLTRILTI
 PQSLDSWWTSLNFLGGAPTCPGQNSQSPSTSNHSPSCCPICPGYRWMCLRRFIFLFIILLCLIFLLVLLDYQGMLPVCPLLPGTSTSTGPKCTCTIPAQG
 TSMFPSCCCTKPSDGNCTCIPIPSSWAFARFLWEWASVRFSWLSLLVPFVQWVGLSPTVWLSVIWMWYWGPSLYNILSPFLPLLPFFCLWVYI
- [0323] **6.3. SIi-HBV-CP_{mut}PreS-TPA-S(sh): HBV 번역원의 아미노산 서열의 기재**
- [0324] 6.3.1. 폴리펩티드의 최초 아미노산 = M
- [0325] 6.3.2. 상어 불변 쇄 (SIi) = SLLWGGVTVLAAMLIAGQVASVVFLV (서열번호 4)
- [0326] 6.3.3. 링커 = KGGGPGGG (서열번호 5)
- [0327] 6.3.4. C =
- [0328] 6.3.4.1. 프레코어
- [0329] MQLFHLCLIISCSCTVQASKLCLGWLG (서열번호 16)
- [0330] 6.3.4.2. 코어 =
 MDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALESPEHCSPHHTALRQAAILCWGELMNLATWVGSNLEDPASRELVVSYYVNVNMGKIRQLLW
 FHISCLTFGRETVLEYLVSFVWIRTTPAYRPPNAPILSTLPETTVVRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQC (서열번호 6)
- [0331] 6.3.5. 링커 = GGGSGGG (서열번호 7)
- [0332] 6.3.6. Pmut = (돌연변이: Y63A, C323A, C334A, C338A, C352A, R714A, D788A, R792A)
- [0333] MPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNVSI PWTHKVGNTGLASSTVPVFNPFWQTPSFPHIHLQEDIINRCQQYVGPLTVN
 EKRRRLKLIMPARFYPNLTLYPLDKGIKPYYPEHAVNHYFKTRHYLHTLWKA
 GILYKRETTASFCGSPYSWEQELQHGRVLFQTSRHHGDESFCSSGILSRSPVGPVRSQSLKQSLGLQPQQSLARGKSGRSGSIRARVHPTTTRRSFGVEPGSGHIDNSASSTSSCLHQSARVKTAYSHLSTSKRQSSSGHVELHN
 IPPSSARSQSEGFIFSAWWLQFRNSKPASDYALTHIVNLEDWGPATEHGEHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVDFSQFSRGSTHVSWPKFAPVNLQSLTNLSSNLSTFGRKLHLYSHPILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAPPHCLAFSYMDDVVLGAKSVQHLESLSITSITNLLSLGILH
 NPNNTKRWGYSNFMGYVIGSWGTLPEHIVLKIKQCFRKLVPVNRPIDWKVCQRIVGLLGFAAPFTQCGYPALMPLYACIQSKQAFSTPTKYKAFCKQYLNLYPVARQSRGLCQVFADATPTGWGLAIGHRAMRGTFVAPLPIHTAELLAACFARSRSGAKLIGTDNSVLSRKYTSFPWLLGCAANWILRGTSFVYVPSALN

PAADPSAGRLGLYRPLLHLPRPTTGRSTLYAVSPSPVSHLPDRVHFASPLHVAWRPP (서열번호 8)

- [0334] 6.3.7. 링커 = KSP
- [0335] 6.3.8. NΔPreS1 및 PreS2 =
- [0336] NSNNPDWDFNPNKDHWEANQVGAGAFGPGFTPPHGGLLGWSPQAQGITTVPAAPPPASTNRQSGRQPTPISPLRDSHPQAMQWNSTTFHQALLDPRVRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPN (서열번호 15)
- [0337] 6.3.9. 링커 = GSKGK (서열번호 20)
- [0338] 6.3.10. 퓨린 2A (F2A) = RKRRAPVKQTLNFDLLKLAGDVESNPGP (서열번호 9)
- [0339] 6.3.11. TPA = MDAMKRLCCVLLLCGAVFVSPSQEIHFARFR (서열번호 30)
- [0340] 6.3.12. S(sh) =
- [0341] 6.3.12.1. CΔPreS1 = MGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNPNKDHWEANQVG (서열번호 21)
- [0342] 6.3.12.2. 링커 = LEGGSGG (서열번호 22)
- [0343] 6.3.12.3. 표면 (S) =
- [0344] MENTTSGFLGPLLVLAGFFLLTRILTIPQSLDSWWTSLNFLGGAPTCPGQNSQSPTSNSHSPTSCPPICPGYRWMCLRRFIIFLFIILLCLIFLLVLLDYQGMLPVCPLLPGTSTTSTGPKCTCTIPAQGTSMFPPSCCTKPSDGNCTCIPIPSSWAFARFLWEWASVRFWSLSLLVPFVQWVFGLSPTVWLSVIWMMWYWGPSLYNILSPFLPLLPFFCLWVYI (서열번호 18)
- [0345] SII-HBV-CPmutPreS-TPA-S(sh) 뉴클레오티드 서열은 서열번호 49로서 제공된다.
- [0346] 7. MVA-SII-HBV-PreS-P_{mut}-C-TPA-S(sh)
- [0347] 7.1. MVA-SII-HBV-PreS-P_{mut}-C-TPA-S(sh): 번역원 레이아웃은 도 10g에 제시된다
- [0348] 7.2. MVA-SII-HBV-PreS-P_{mut}-C-TPA-S(sh): 아미노산 서열 (서열번호 26)
- [0349] MSLWGGVTVLAAMLIAGQVASVFLVSKSGPPSGKSNSNNPDWDFNPNKDHWEANQVGAGAFGPGFTPPHGGLLGWSPQAQGITTVPAAPPPASTNRQSGRQPTPISPLRDSHPQAMQWNSTTFHQALLDPRVRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPNGSKSGSKMPLSYQHFRKLLLLDDEAGPLEEELPRLADEGLNRRVAEDNLGNLNVIPWTHKVGNTGLASSTVPVFNPFWQTPSPFPHIHLQEDIINRCQQYVGPLTVNEKRRLKLIMPARFYPNLTKYLP LDKGIKPYYPEHAVNHYFKTRHYLHTLWKAGILYKRETTASFCGSPYSWEQELQHGRLVFQTSTRHGDESFCSSQSSGILSRSPVGCVRSQLKQSRGLQPQQGSLARGKSGRSGSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQSAVRKTAYSHLSTSKRQSSSGHVELHNIPSSARSQSEGFIFSAWWLQFRNSKPASDYALTHIVNLLEDWGPATEHEGHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVVDFSQFSRGSTHVSWPKFAVPNLQSLTNLLSSNLSWLSLDVSAAFYHILPHPAAMPHELLVGSSGLPRYVARLSSTSRNINYQHGTMQDLHDSCSRNLVSLLLLYKTFGRKLHLYSHPIILGFRKIPMGVGLSPFLLAQFTSAICSVRRAPFHCLAFSYMDDVVLGAKSVQHLESFTSITNFLSLGILHLPNKTKRWGYSNFMGYVIGSWGTLPEHIVLKIQCFRKLPVNRPIDWKVCQRIVGLLGFAAPFTQCGYPALMPYACIQSKQAFTFSPTYKAFLCKQYLNLYPVARQRSGLCQVFADATPTGWGLAIGHRAMRGTFTVAPLPITHAELLAACFARSRSAGKLIGTDNSVLSRKYTSFPWLLGCAANWILRGTSFVYVPSALNPAADPSAGRLGLYRPLLHLPRPTTGRSTLYAVSPSPVSHLPDRVHFASPLHVAWRPPSKSPGSGPPMQFLHCLII SCSCPTVQASKLCLGWLWGMDIDPYKEFGASVELLSFLPSDFFPSIRDLLDTASALYREALESPHCSPHHTALRQAILCWGELMNLATWVGSNLEDPASRELVSYSVNNMGLKIRQLLWFHISCLTFGRETVEYLVSGVWIRTTPPAYRPPNAPILSTLPETTIVRRRGRSPRRRTPSPRRRSQSPPRRRSQSRESQCMMDAMKRLCCVLLLCGAVFVSPSQEIHFARFRRMGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNPNKDHWEANQVGASKGKSGMMENTTSGFLGPLLVLAGFFLLTRILTIPQSLDSWWTSLNFLGGAPTCPGQNSQSPTSNSHSPTSCPPICPGYRWMCLRRFIIFLFIILLCLIFLLVLLDYQGMLPVCPLLPGTSTTSTGPKCTCTIPAQGTSMFPPSCCTKPSDGNCTCIPIPSSWAFARFLWEWASVRFWSLSLLVPFVQWVFGLSPTVWLSVIWMMWYWGPSLYNILSPFLPLLPFFCLWVYI
- [0350] 7.3. MVA-SII-HBV-PreS-P_{mut}-C-TPA-S(sh): HBV 번역원의 아미노산 서열의 기재
- [0351] 7.3.1.1. 폴리펩티드의 최초 아미노산 = M
- [0352] 7.3.1.2. 상어 불변 쇄 (SII) = SLLWGGVTVLAAMLIAGQVASVFLV (서열번호 4)
- [0353] 7.3.1.3. 링커 = SKSGPPSGKS (서열번호 31)
- [0354] 7.3.1.4. NΔPreS1 및 PreS2 = NSNNPDWDFNPNKDHWEANQVGAGAFGPGFTPPHGGLLGWSPQAQGITTVPAAPPPASTNRQSGRQPTPISPLRDSHPQAMQWNSTTFHQALLDPRVRG

LYFPAGSSSGTVNPVPTTASPISSIFSRTGDPAPN (서열번호 15)

- [0355] 7.3.1.5. 링커 = GSKSGSK (서열번호 32)
- [0356] 7.3.1.6. Pmut = (돌연변이: Y63A, C323A, C334A, C338A, C352A, R714A, D788A, R792A)
- [0357] MPLSYQHFRKLLLDDEAGPLEELPRLADEGLNRRVAEDLNLGNLNVSIPTWTHKVGNTGLASSTVPVFNPFWQTPSFPHIHLQEDIINRCQQYVGPLTVN
EKRRLLKLIMPARFYPNLTKYLPDLKGIKPYYPEHAVNHFKTRHYLHTLWKAGILYKRETTTSASFSGSPYSWEQELQHGRVLFQTSTRHGDESFCSSSGI
LSRSPVGPVRSQSLKQSRGLQPPQGLARGKSGRSGSIRARVHPTTRRSFGVEPSGSGHIDNSASSTSSCLHQSAVRKTAYSHLSTSKRQSSSGHVELHN
IPPSSARSQSEGPIFS~~A~~WWLQFRNSKP~~A~~SDY~~A~~LTHIVNLEDWGP~~A~~TEHGEHNIRIPRTPARVTGGVFLVDKNPHNTTESRLVVD~~F~~SQFSRGSTHVS~~W~~PKFA
V~~P~~NLQSLTNLLSSNLSTFGRKLHLYSHPILGFRKIPMGVGLSPFLLAQFTSAICSVVRRAPPHCLAFSYMDDVVLGA~~K~~SVQHLES~~L~~FTSITN~~F~~LLSLGIHL
NPNKTKRWGYS~~L~~NFMGYVIGSWGTL~~P~~QEHIVLKIKQCFRKL~~P~~VNRPIDW~~K~~VQRI~~V~~GLLGFAAPFTQCGYPALMPLYACIQSKQAFTFSPTYKAFLCKQYL~~N~~
LYPVARQ~~R~~SGLCQVFADATPTGWGLAIGHRA~~M~~RGTFVAPLPIHTAELLAACFARS~~R~~SGAKLIGTDNSV~~L~~SRKYTSFPWLLGCAANWILRGTSFVYVPSALN
PA~~A~~D~~P~~S~~A~~GRGLGYRLLHLPFRPTTGRTSLYAVSPSVPSHLPDRVHFASPLHVAWRPP (서열번호 8)
- [0358] 7.3.1.7. 링커 = SKSPGSGPP (서열번호 33)
- [0359] 7.3.1.8. C =
- [0360] 7.3.1.8.1. 프레코어 =
- [0361] MQLFHLCLIIISCSCPTVQASKLCLGWLWG (서열번호 16)
- [0362] 7.3.1.8.2. 코어 =
- [0363] MDIDPYKEFGASVELLSFLPSDFFPISIRDLDTASALYREALESPEHCSPHHTALRQAILCWGELMNLATWVGSNLEDPASRELVS~~Y~~VNVNMG~~L~~KIRQLLW
FHI~~S~~CLTFGRET~~V~~LEYLV~~S~~FGVWIRTPPAYRPPNAPILSTLPETTVRRRRGRSPRRRTSPRRRRSQSPRRRRSQSRESQC (서열번호 6)
- [0364] 7.3.1.9. TPA = MDAMKRG~~L~~CCVLLLCGAVFVSPSQEI~~H~~ARFR (서열번호 30)
- [0365] 7.3.1.10. S(sh)_ =
- [0366] 7.3.1.10.1. CΔPreS1 =
- [0367] MGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNPNK~~D~~HWPEANQVG (서열번호 21)
- [0368] 7.3.1.10.2. 링커 = ASKGGKSG (서열번호 34)
- [0369] 7.3.1.10.3. 표면 (S) =
MENTTSGFLP~~L~~VLQAGFFLLTRILTIPQSLDSWWTSLN~~F~~LGGAPTCPGQNSQSPTS~~N~~HSPTSCPPICPGYRWMCLRRFIIFLFILLCLIFLLVLLDYQG
MLPVCPLLPGTSTTSTGPKCTCTIPAQGTSMFPSCCCTKPSDGNCTCIP~~I~~PSSWAFARFLWEWASVRFWSL~~L~~LVPFVQW~~F~~VGLSPTVWLSVIWMMWYWG~~P~~S
LYN~~I~~LSPFLPLLP~~I~~FFCLWVYI (서열번호 18)
- [0370] 7.4. MVA-SIi-HBV-PreS-P_{mut}-C-TPA-S(sh)의 뉴클레오타이드 서열은 서열번호 27로서 제공된다
- [0371] 7.5. MVA-SIi-HBV-PreS-P_{mut}-C-TPA-S(sh)의 뉴클레오타이드 서열의 기재:
- [0372] 7.5.1. F11-L-인접 = 염기 1 - 1097 (서열번호 35)
- [0373] 7.5.2. SIi-HBV-PreS-P_{mut}-C = 염기 1098 - 4838 (서열번호 37)
- [0374] 7.5.3. 전사 터미네이터 서열 = 염기 4839 - 4845
- [0375] TTTTGT
- [0376] 7.5.4. mH5 프로모터 = 염기 4846 - 4942 (서열번호 28)
- [0377] 7.5.5. TPA = 염기 4943 - 5038 (서열번호 29)
- [0378] 7.5.6. S(sh) = 염기 5039 - 5920 (서열번호 38)
- [0379] 7.5.7. F11-R-인접 = 염기 5921 - 7239 (서열번호 36)
- [0380] 8. 낮은 GC 함량 버전 MVA-SIi-HBV-PreS-Pmut-C-TPA-S(sh)(서열번호 58)의 뉴클레오타이드 서열:
- [0381] gtaatctattcgatataccgttgctaacagtatactggcccaataactgtggatggaaaatctataataatacatattaatcatccgatgggtgctagggtta

tttggatggatgcgtataaatttcttgcggtttatctttacaagactattgttatcattggggtagcaaaccagagagccgaccattcgatttaataaaaa
aatcagatgctaaacgcaattctaaatcggttggtcaaagaatctatggcatccttgaatccttgcagaggcatcgagacacaatcaggagcgtagaag
ttttaatgagtcctatgtaggatgttttcgttttctagaatagaagacatgttcttaactagtgtcattaatagagtatccgagaatactggaatggggatgt
attatcctaccaacgataaccttctctatttctgaatcatctatctgtctagattatattatagtaaaataatcaggaatccaacaatatcgatacaaat
ctgttctcgatatcatttcttcaaaacaataaccctgcaggacgtcccaactacgttaaaaaatggtagaaaaggaaagtatatatcgcggttgtgtaaagtt
ccgtacctactaacgaccatattccagtagtttatcacgatgatgacaatactaccacctttattacagatttgacgtccgtcgatatgaaactgctatca
gagcaggatatcgatagtcgaattaggggctttacaatgggataataatatccagaacttaaaaacgggttactggatagatcaagatgatttatgact
tgaacgcagttacaacaataatttattggaacagctcatagaaaatatctaactttaacaactctagataaatttcgttgttttatacatttgccattagtt
attgcccagcattcatttactcaattatggaaccatagatccgggtgtatataatctcagttcagttataaagaattatcagtttagtagctcttataaagata
ttaatgaatccatgagtcagatggtaaaattataaaaagtgaaaacaatatatttttatcgttggttgttacactATGTCACCTCTTTGGGCGGAGTTA
CAGTTCCTGCTGCTATGCTTATTGCTGGACAAGTTGCTTCTGTTGTGTTCTTGTGTTTCTAAATCTGGACCTCCTTCTGGAATCTAATCTAACAACTCTG
ATTGGGATTTCATCTCAACAAAGATCATTGGCCTGAAGCTAATCAAGTTGGAGCTGGTGTCTTTGGACCTGGTTTACACCTCCTCATGTTGGATTGCTTG
GATGGTCACCTCAAGCTCAGGAATTCTTACAACAGTTCCAGCTGTCTCTCTGCTTCTACAAATAGACAATCTGGTAGACAACCTACACCTATTTCTC
CACCTCTTAGAGATTCTCATCTCAAGCTATGCAATGGAATTCTACTACATTCATCAAGCTTTGCTTGATCCTAGAGTTAGAGGACTTTATTTCTGCTG
GTGGAAGTTCTTCTGGAACAGTTAATCTGTTCTACAACAGCTTCTCAATTTCTTCTATATTTCTAGAACAGGCGATCCTGCTCCTAATGGATCAAAAT
CTGGATCAAAAATGCCTCTGTCTTATCAACACTTTAGAAAATTGCTGCTTCTTGATGATGAAGCTGGACCTCTTGAAGAAGAAATGGCTAGACTTGCTGATG
AAGGACTTAATAGAAAGATTGCTGAAGATCTTAATCTGGGAAATCTTAATGTTTCTATTCTTGGACACACAAAGTTGGAATTTACAGGACTTGCTCTT
CTACAGTGCCTGTTTTAATCTGAATGGCAAACACCTTCTTTCCACATATTCATCTGCAAGAGGATATCATCAATAGATGTCAACAATATGTTGGACCAC
TGACAGTTAATGAGAAGAGAAGGCTTAAACTTATTATGCCTGCTAGATTCTATCCTAATCTTACAAAGTATTTGCCTCTGGATAAGGGAATCAACCTTATT
ATCCTGAACATGCTGTGAATCACTACTTTAAAACAAGACATTATCTGCATACACTGTGGAAGCTGGTATTCTTTACAAAAGAGAAAACAAGATCTGCTT
CATTTTGTGGATCTCCATATTCTTGGGAACAAGAACTTCAACATGGTAGACTTGTTTTTCAACATCTACAAGACATGGGGATGAATCATTTTGTCTCTCAA
GTTTCTGGAATTCTTTCTAGATCTCCTGTTGGACCTTGTTGTAGATCTCAACTTAAACAATCTAGACTTGACTTCAACCTCAACAAGGATCTCTTGCTAGAG
GAAAAAGTGAAGATCTGGATCTATTAGAGCTAGAGTTATCCTACAAGATAGATCTTTTGGAGTTGAACCTTCTGGATCTGGACATATTGATAATTCTG
CCTCTTCTACATCTTCTGTCTGCATCAATCTGCTGTTAGAAAGACAGCTTATTCTCATTGTGCTACTTCTAAGAGACAATCATCTCTGGACATGCTGTTG
AACTTCATAATATCCTCCAAGTAGTGCTAGAAGTCAATCTGAAGGACCAATATTTTCAGCTTGGTGGCTTCAATTCAGAAATTTCTAAACCTGCTTCTGATT
ATGCTCTGACACATATAGTTAATTTGCTTGAAGATTGGGGACCTGCTACAGAACATGGCGAACACAATATTAGAATACCTAGAACTCCTGCTAGAGTTACAG
GCGGAGTCTTTTTGGTTGATAAGAATCCTCATAATACCAGAAATCAAGACTTGTTGTTGATTTTTACAGTTTTCTAGAGGATCTACACATGTTTCTTGGC
CTAAATTTGCTGTTCCAAATCTTCAATCTCTTACAAATTTGCTTTCATCTAATCTTTCTTGCTGTCTCTTGATGTTTCTGCTGCCTTTTATCATATTCCTC
TTCATCTGCTGCAATGCCTCATTGCTTGTGGATCATCTGGACTTCCAAGATATGTTGCTAGACTTAGCTCTACATCTAGAAATATCAATTATCAGCATG
GAACAATGCAGGATCTTCAGATTCTTGTAGTAGGAATCTGTATGTTTCTTTGCTTCTGCTGTATAAGACATTGGAAGAAAACCTTCATCTGTATTCTCACC
CTATTATTCTGGGTTTTAGAAAGATTCCATGGGAGTTGGACTTCTCCTTTTTTGTGCTGCTCAATTCACATCTGCTATTGTTCTGTTGTTAGAAAGGCTT
TTCCTCATTGCTTGCAATTTCTTATATGGATGATGTTGTTCTTGGAGCTAAATCTGTTCAACATCTTGAAGTCTGTTTACCTCTATTACTAATTTCTGCTG
TTTCTCTGGGAATTCATCTGAATCCAAACAAAACAAAGAGATGGGGATATTCTCTTAATTTTCATGGGATATGTTATTGGATCTTGGGGAACACTTCCTCAAG
AACATATCGTTTTGAAAATCAAGCAATGTTTCAGAAAATGCCTGTGAATAGACCTATTGATTGGAAGTTTGTCAAAAGAATTGTGGGACTTCTTGGATTG
CTGCTCCTTTTACACAATGTGGATATCTGCTCTTATGCCACTTTATGCTTGTATTCAATCTAAACAGGCTTTTACATTTCTCCAACATACAAAGCTTTTC
TGTGTAACAGTATCTGAATCTTTATCTGTGGCTAGACAAAGATCTGGTCTTTGTCAAGTTTTTGTGATGCTACACCAACAGGATGGGGACTTGCTATTG
GACATAGAGCTATGAGAGGAACATTTGTTGCTCCATTGCCTATTATACAGCTGAATTGCTTGTGCTGCTGTTTTGCTAGATCTAGAAGCGGAGCAAACTTA
TTGGTACAGATAATAGTGTGCTGCTGAGTAGAAAGTACACATCTTTCCATGGTGTGTTGGGATGTGCTGCTAATTGGATTCTTAGAGGAATCTTTTGTGTT
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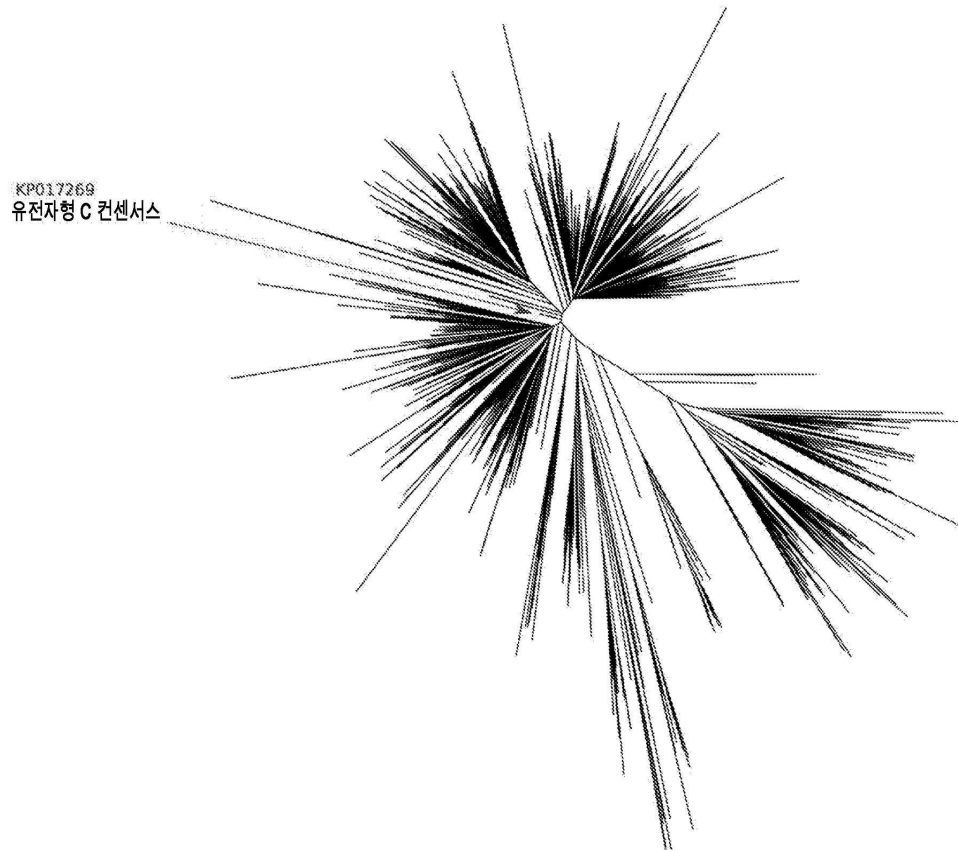
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- [0382] 8.1 낮은 GC 함량 버전의 MVA-SIi-HBV-PreS-Pmut-C-S(sh)의 뉴클레오타이드 서열의 기재:
- [0383] 8.1.1 F11-L-인접 = 염기 1 - 1097 (서열번호 35)
- [0384] 8.1.2 SIi-HBV-PreS-Pmut-C = 염기 1098 - 4838 (서열번호 59)
- [0385] 8.1.3 전사 터미네이터 서열 = 염기 4839 - 4845
- [0386] TTTTGT
- [0387] 8.1.4 mH5 프로모터 = 염기 4846 - 4942 (서열번호 28)
- [0388] 8.1.5 TPA = 염기 4943 - 5038 (서열번호 60)
- [0389] 8.1.6 S(sh) = 염기 5039 - 5920 (서열번호 61)
- [0390] 8.1.7 F11-R-인접 = 염기 5921 - 7239 (서열번호 36)
- [0391] 야생형 HBV 폴리머라제의 서열은 서열번호 19로서 제공된다.
- [0392] **ChAdOx1 서열**
- [0393] 번역원 카세트의 5' 측의 ChAdOx1 서열은 서열번호 39로서 제공된다. 번역원 카세트의 3' 측의 ChAdOx1 서열은 서열번호 40으로서 제공된다.
- [0394] **ChAdOx2 서열**
- [0395] 번역원 카세트의 5' 측의 ChAdOx2 서열은 서열번호 41로서 제공된다. 번역원 카세트의 3' 측의 ChAdOx2 서열은 서열번호 42로서 제공된다.
- [0396] **MVA 서열**
- [0397] 번역원 카세트의 5' 측의 MVA 서열은 서열번호 44로서 제공된다. 번역원 카세트의 3' 측의 MVA 서열은 서열번호 45로서 제공된다.
- [0398] 테트론 오퍼레이터 서열을 갖는 CMV 긴 프로모터는 서열번호 50로서 제공된다. 테트론 오퍼레이터 서열을 갖는 CMV 짧은 프로모터는 서열번호 51로서 제공된다.
- [0399] PreS1 서열 (서열번호 52):
- [0400] MGGWSSKPRQGMGTNLSVPNPLGFFPDHQLDPAFGANSNNPDWDFNPNDKHWPANQVGAGAFGPGFTTPHGGLLGWSPQAQGILTTVPAAPPPASTNRQSG
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[0401] PreS2 서열 (서열번호 53):
 [0402] MQWNSTTFHQALLDPRVRGLYFPAGGSSSGTVNPVPTTASPISSIFSRTGDPAPN

도면

도면1a



도면 1ba

유전자형 C 컨센서스:
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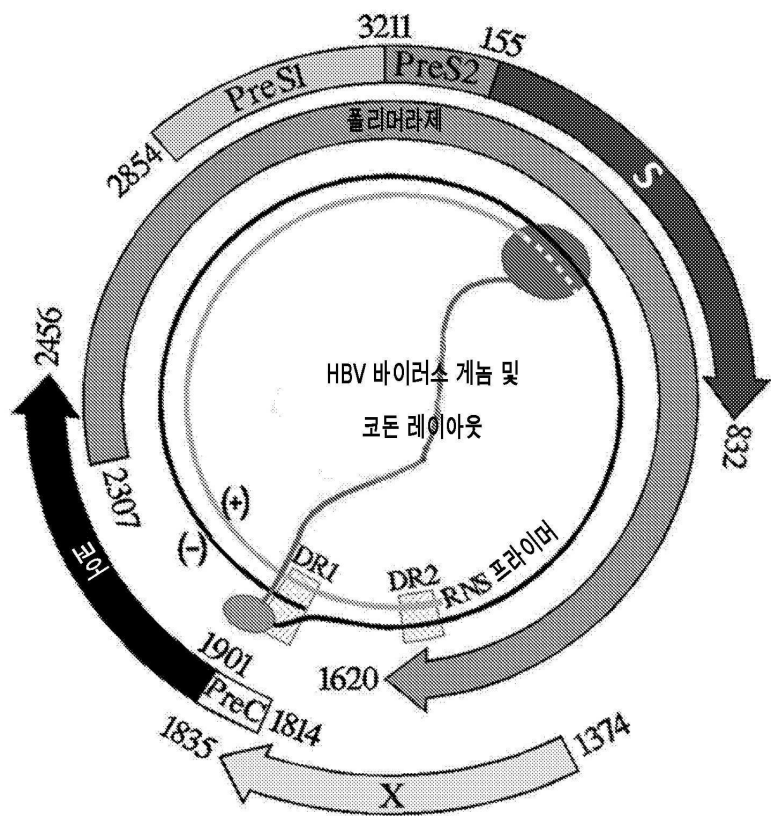
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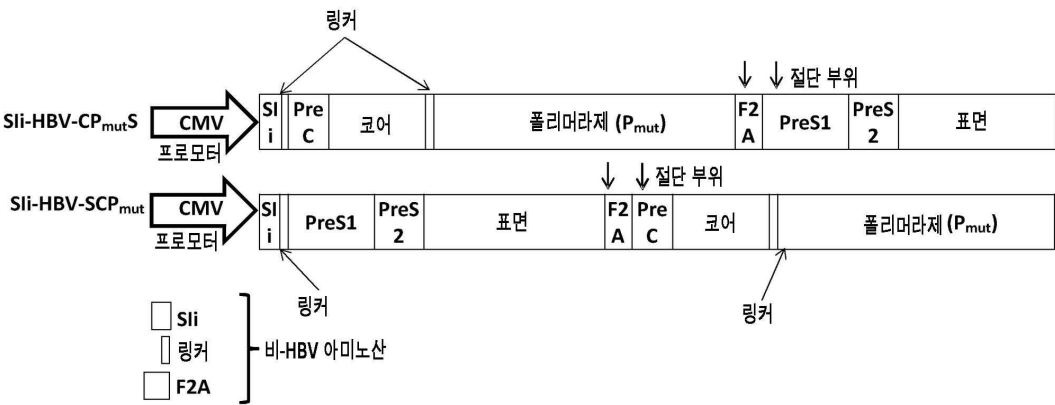
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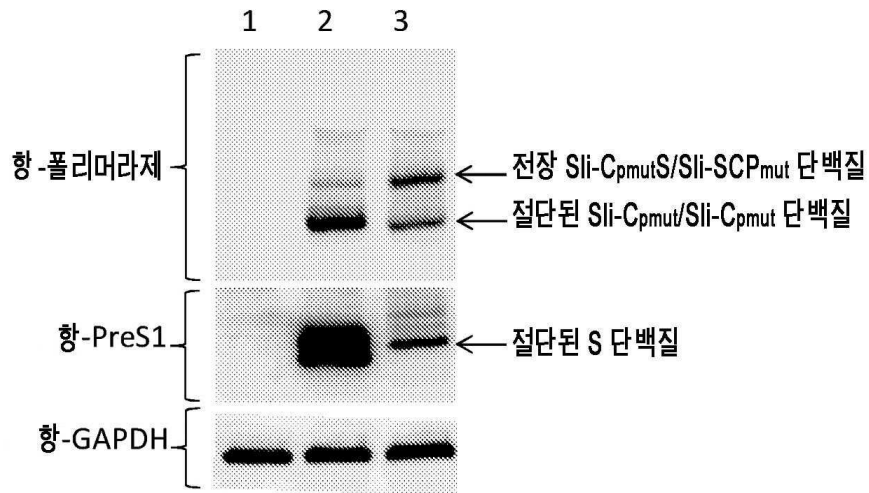
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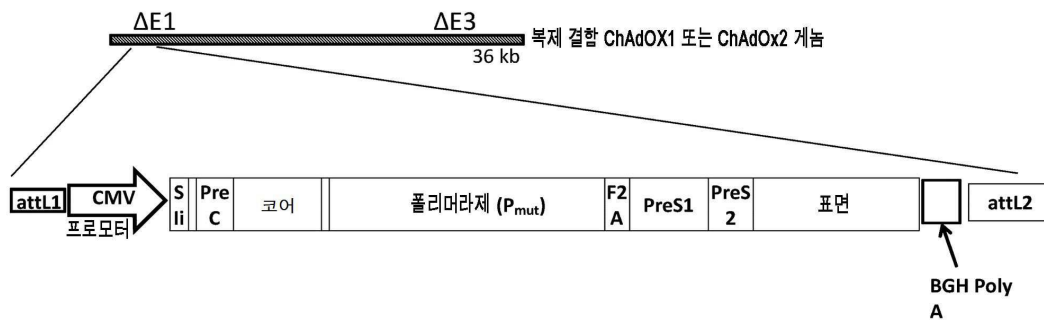
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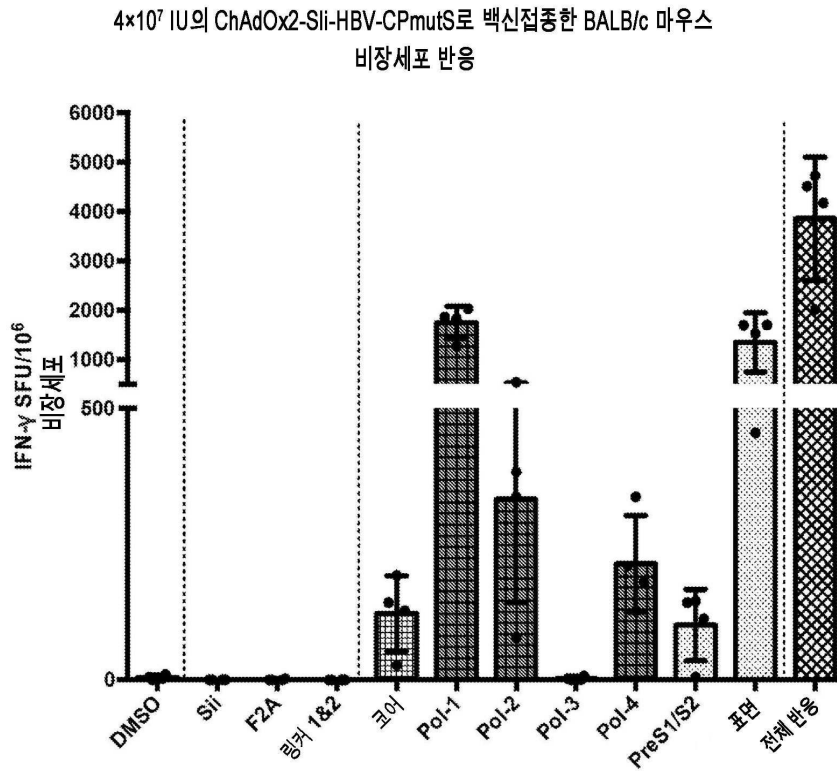
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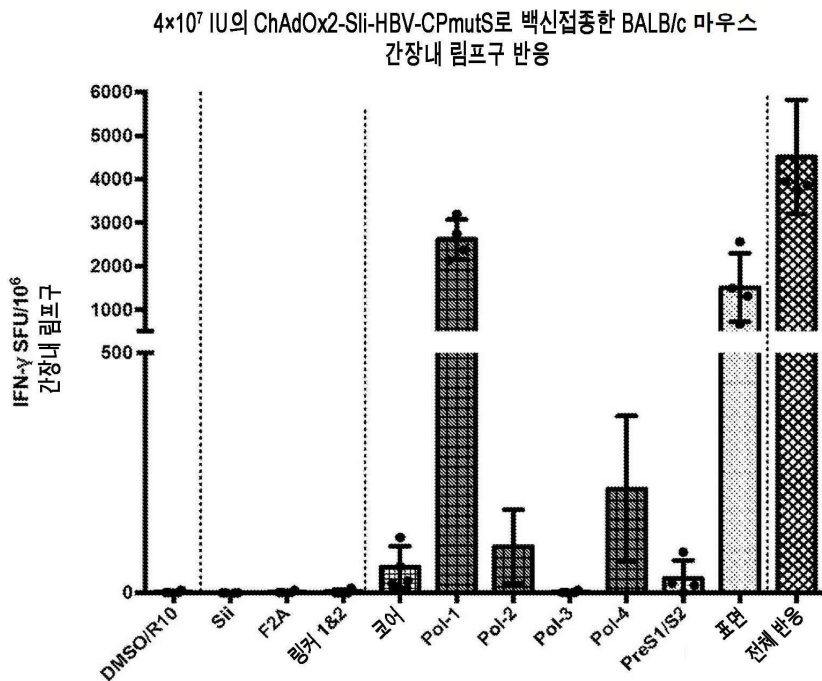
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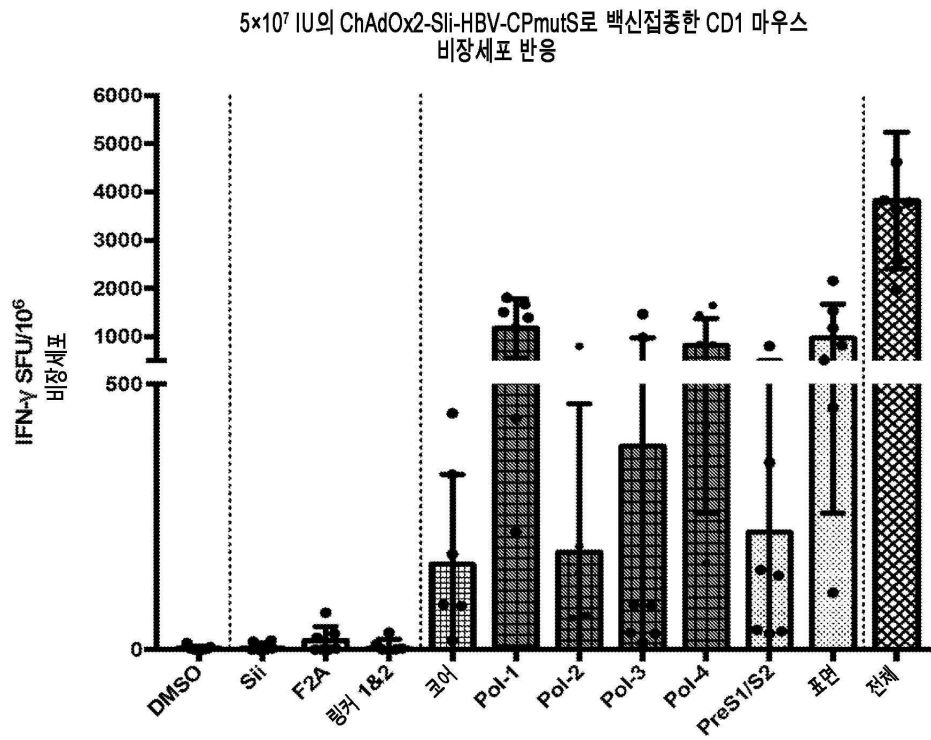
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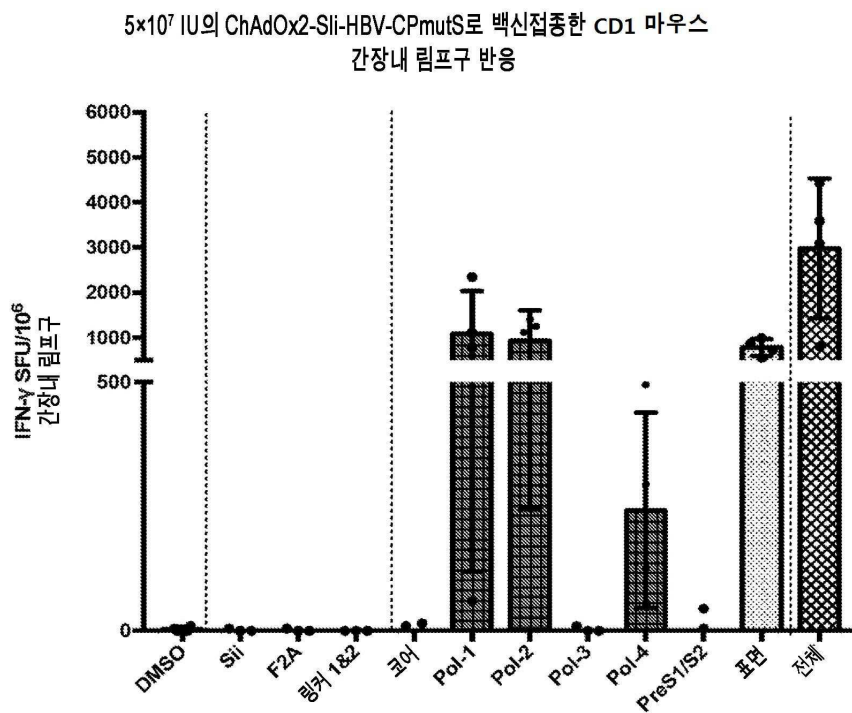
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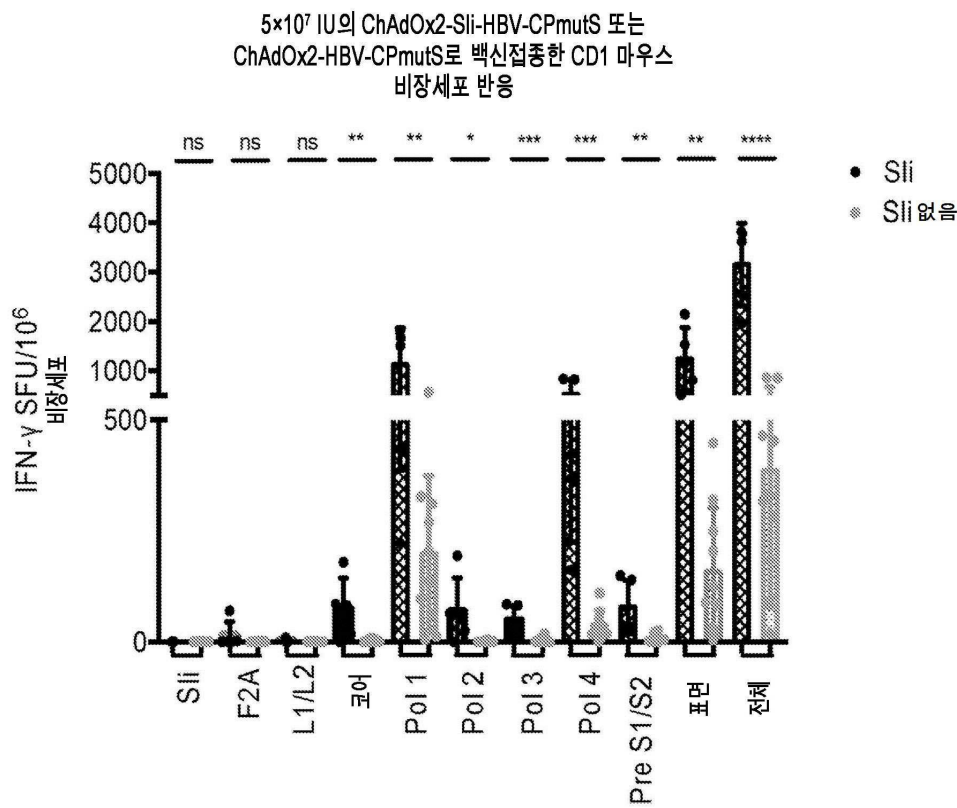
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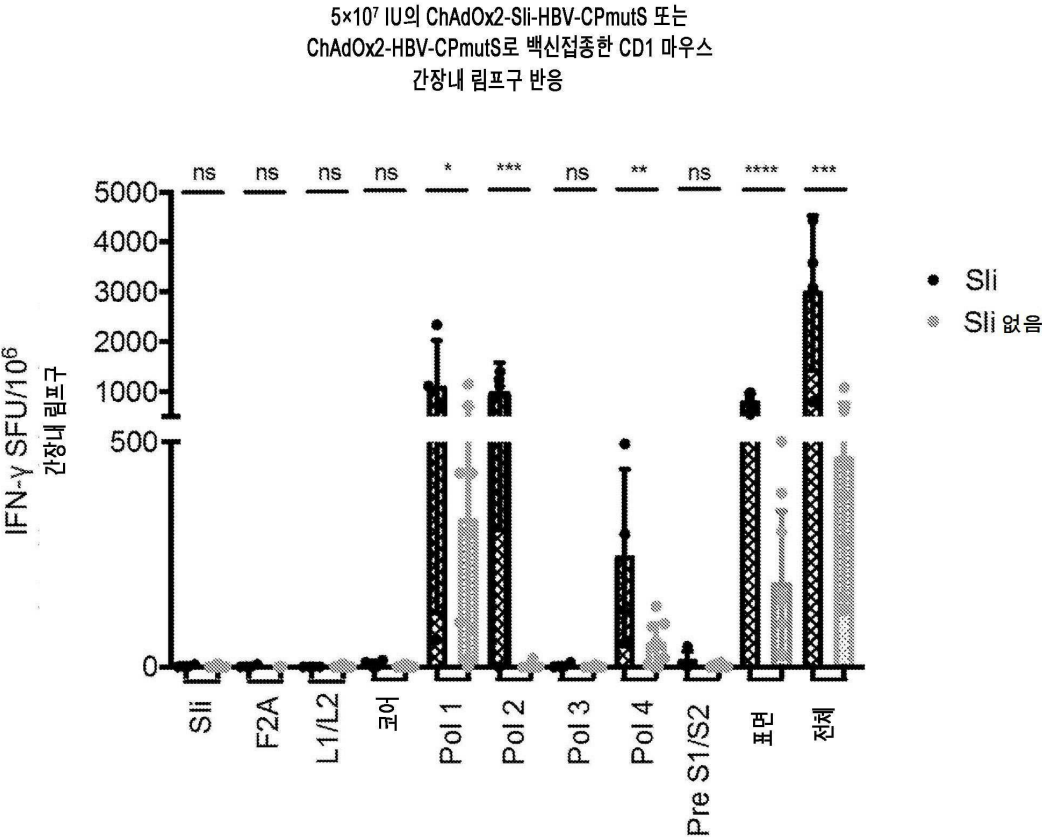
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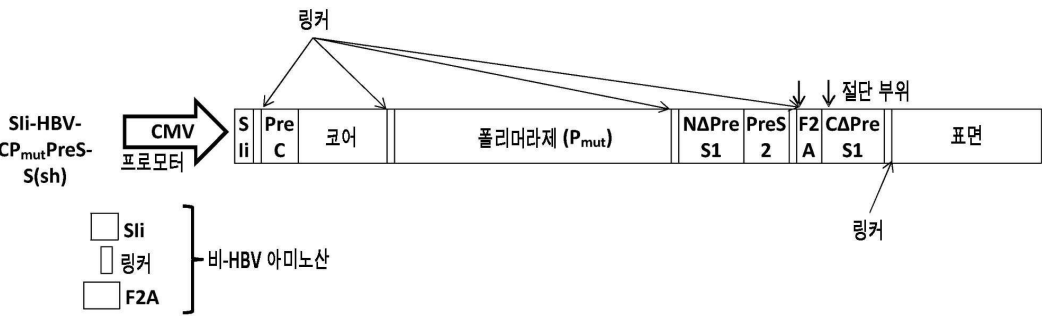
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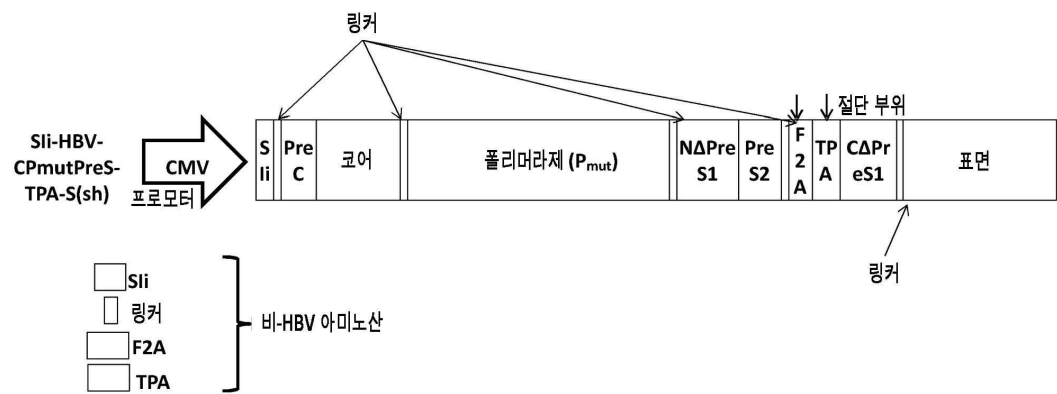
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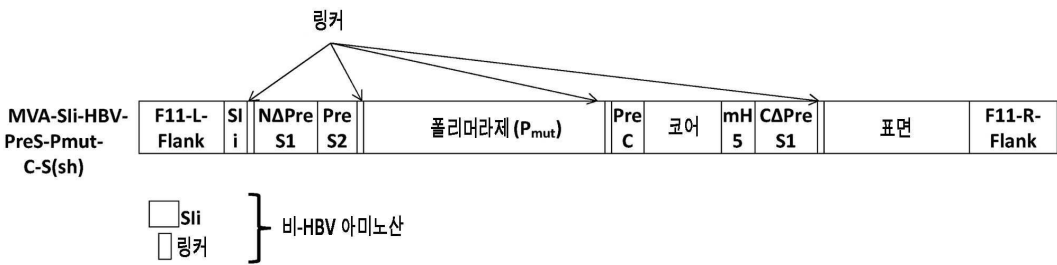
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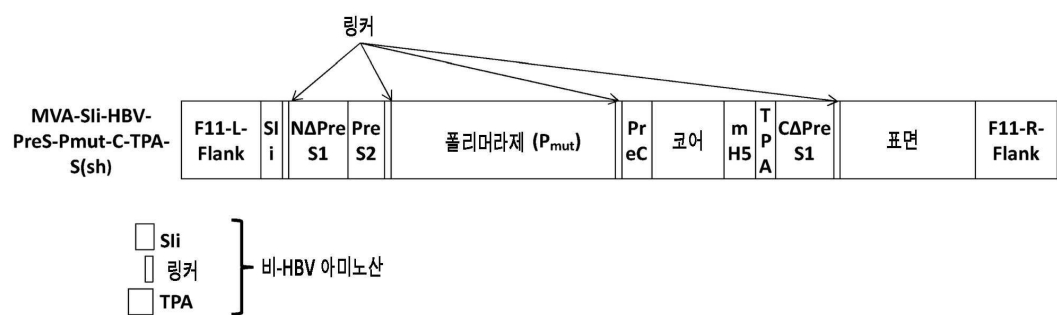
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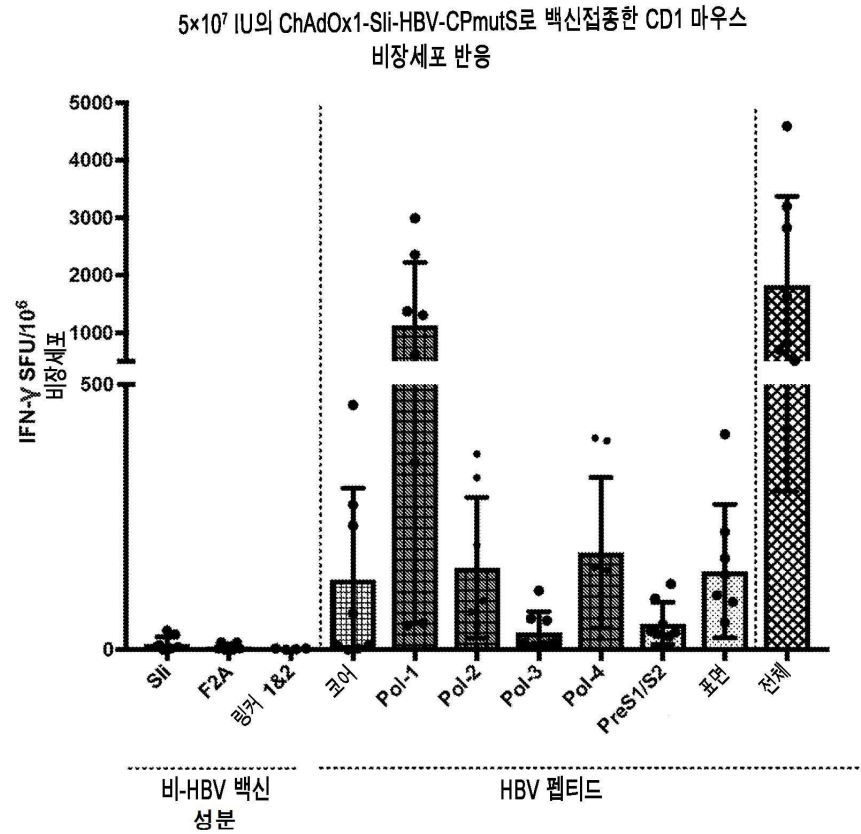
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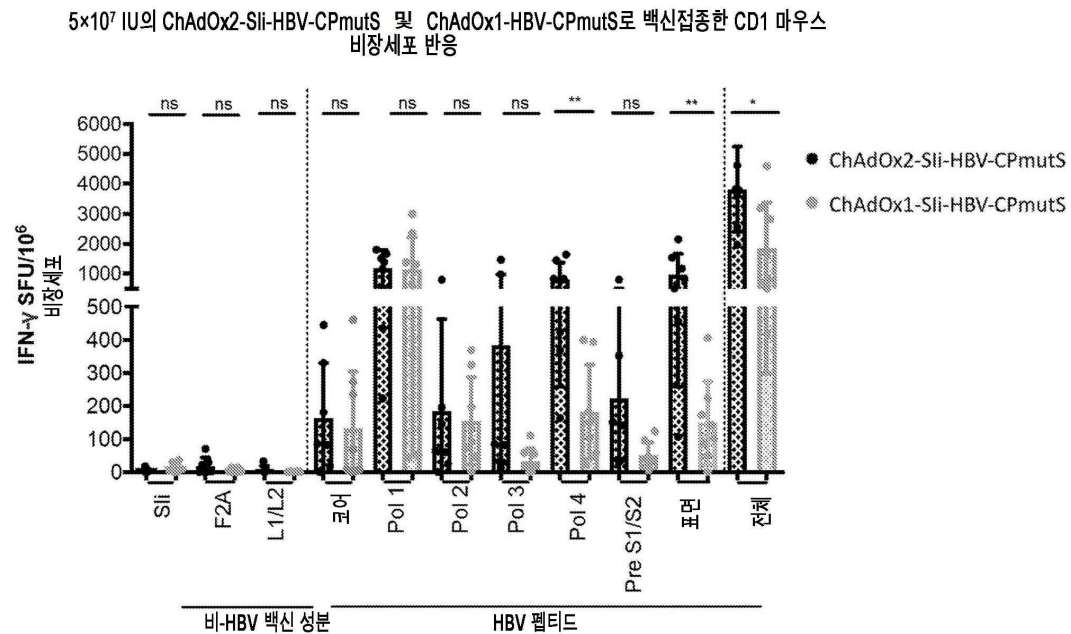
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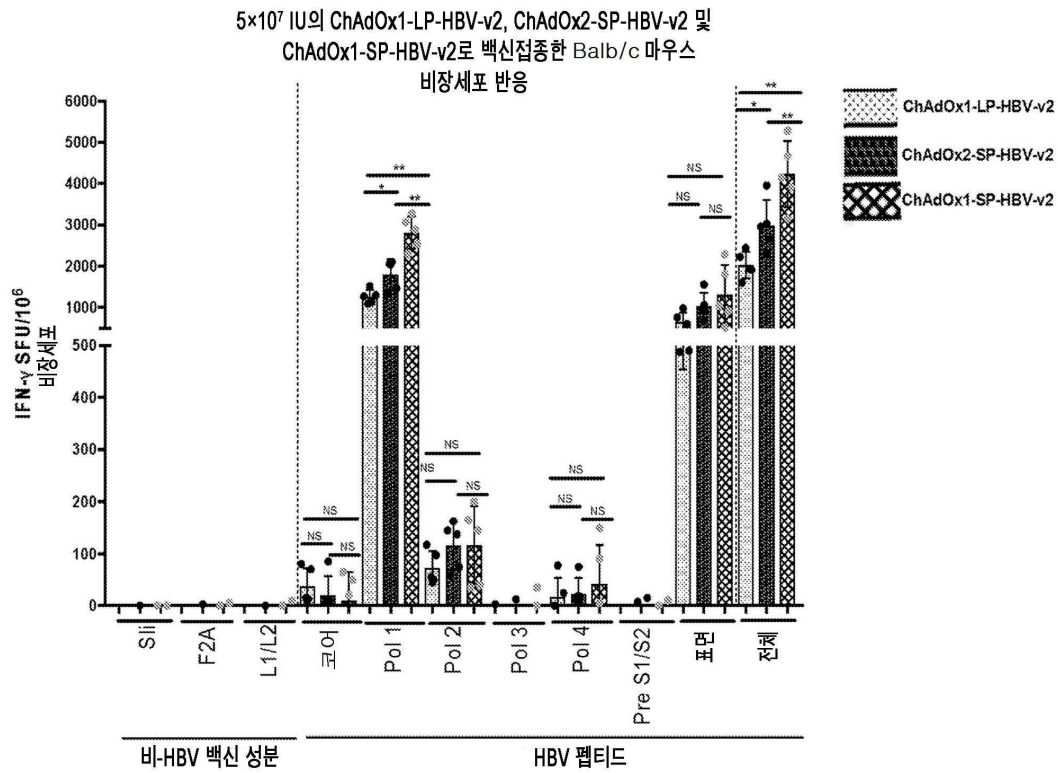
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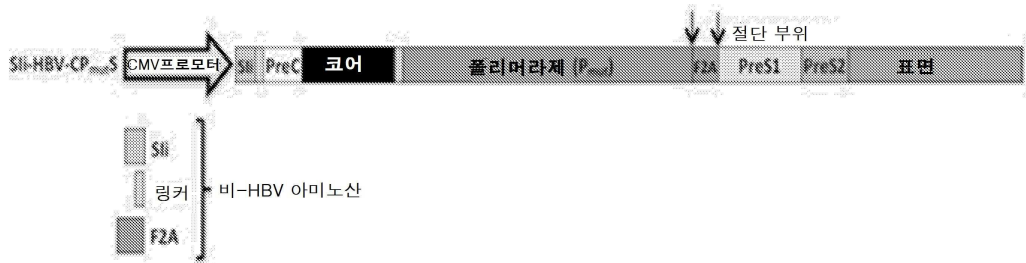
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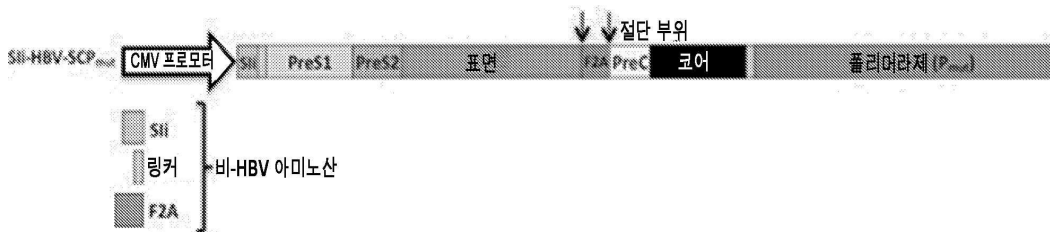
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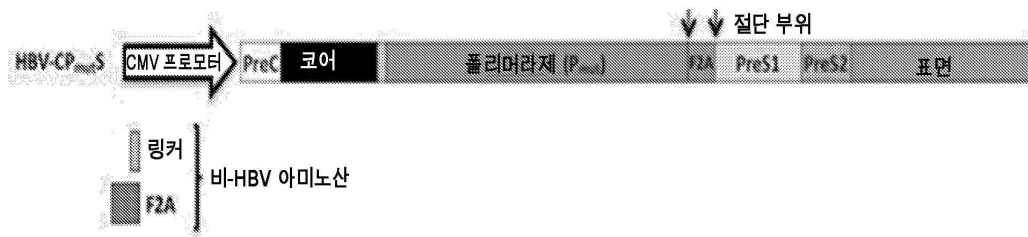
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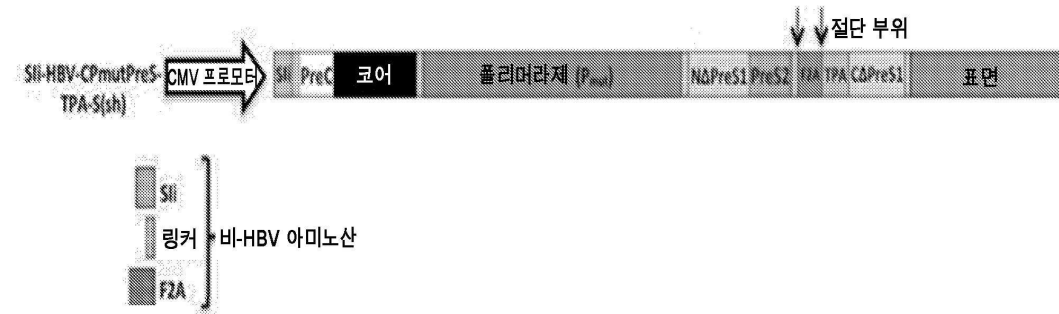
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ctaagagaca gtcatcctca ggccatgcag tggaa 3215

<210> 2

<211> 3215

<212> DNA

<213> Artificial Sequence

<220><223> HBV consensus sequence

<400> 2

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aatcttctcg aggactgggg accctgcacc gaacatggag aacacaacat caggattcct 180

aggaccctcg ctctgttac aggcgggggt tttcttgttg acaagaatcc tcacaatacc 240

acagagtcta gactcgtggt ggacttctct caattttcta gggggagcac ccacgtgtcc 300

tggccaaaat tcgcagtccc caacctccaa tctctacca acctcttgtc ctccaatttg 360

tcctggctat cgctggatgt gtctcggcg tttatcata ttctcttca tcctgtctgt 420

atgcctcatc ttctgttgg ttctctgga ctaccaaggt atgttgccc tttgtctct 480

acttcagga acatcaacta ccagcacggg accatgcaag acctgcacga ttctgtctca 540

aggaacctct atgtttccct ctgtgtctg taaaaacct tcggacggaa actgcacttg 600

tattcccatc ccatcatcct gggctttcgc aagattccta tgggagtggg cctcagtcgg 660

tttctcctgg ctcatgttac tagtgccatt tgttcagtgg ttcgtagggc ttccccccac 720

tgtttggctt tcagttatat ggatgatgtg gtattggggg ccaagtctgt acaacatctt 780

gagtcctctt ttacctctat taccaatttt cttttgtctt tgggtataca ttggaaccct 840

aataaaacca aacgttgggg ctactccctt aacttcatgg gatatgtaat tgggaagtgg 900

ggtactttac cacaggaaca tattgtacta aaaatcaagc aatgttttcg aaaactgcct 960

gtaaatagac ctattgattg gaaagtatgt caaagaattg tgggtctttt gggtttgtct 1020

gcccccttta cacaatgtgg ctatcctgcc ttgatgcctt tatatgcatg tataaatct 1080

aagcaggctt tcactttctc gccaaacttac aaggcctttc tgtgtaaaca atatctgaac 1140

ctttaccccg ttgcccgga acggtcaggt ctctgccaag tgtttgtga cgcaaccccc 1200

actggatggg gcttggccat aggcctcgg cgcatgcgtg gaacctttgt ggctcctctg 1260

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cctcctcctg cctccaccaa tcggcagtca ggaagacagc ctactcccat ctctccacct 3180
ctaagagaca gtcacccca ggccatgcag tggaa 3215

<210> 3

<211> 1525

<212> PRT

<213> Artificial Sequence

<220><223> Vaccine construct

<400> 3

Met Ser Leu Leu Trp Gly Gly Val Thr Val Leu Ala Ala Met Leu Ile

1 5 10 15

Ala Gly Gln Val Ala Ser Val Val Phe Leu Val Lys Gly Gly Gly Pro

20 25 30

Gly Gly Gly Met Gln Leu Phe His Leu Cys Leu Ile Ile Ser Cys Ser

35 40 45

Cys Pro Thr Val Gln Ala Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly

50 55 60

Met Asp Ile Asp Pro Tyr Lys Glu Phe Gly Ala Ser Val Glu Leu Leu

65 70 75 80

Ser Phe Leu Pro Ser Asp Phe Phe Pro Ser Ile Arg Asp Leu Leu Asp

85 90 95

Thr Ala Ser Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys

100 105 110

Ser Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu

115 120 125

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

130 135 140

Ser Arg Glu Leu Val Val Ser Tyr Val Asn Val Asn Met Gly Leu Lys

145 150 155 160

Ile Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly Arg

165 170 175

Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly Val Trp Ile Arg Thr

180 185 190
 Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro
 195 200 205
 Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg Thr
 210 215 220
 Pro Ser Pro Arg Arg Arg Arg Ser Gln Ser Pro Arg Arg Arg Arg Ser
 225 230 235 240
 Gln Ser Arg Glu Ser Gln Cys Gly Gly Gly Ser Gly Gly Gly Met Pro

 245 250 255
 Leu Ser Tyr Gln His Phe Arg Lys Leu Leu Leu Leu Asp Asp Glu Ala
 260 265 270
 Gly Pro Leu Glu Glu Glu Leu Pro Arg Leu Ala Asp Glu Gly Leu Asn
 275 280 285
 Arg Arg Val Ala Glu Asp Leu Asn Leu Gly Asn Leu Asn Val Ser Ile
 290 295 300
 Pro Trp Thr His Lys Val Gly Asn Phe Thr Gly Leu Ala Ser Ser Thr

 305 310 315 320
 Val Pro Val Phe Asn Pro Glu Trp Gln Thr Pro Ser Phe Pro His Ile
 325 330 335
 His Leu Gln Glu Asp Ile Ile Asn Arg Cys Gln Gln Tyr Val Gly Pro
 340 345 350
 Leu Thr Val Asn Glu Lys Arg Arg Leu Lys Leu Ile Met Pro Ala Arg
 355 360 365
 Phe Tyr Pro Asn Leu Thr Lys Tyr Leu Pro Leu Asp Lys Gly Ile Lys

 370 375 380
 Pro Tyr Tyr Pro Glu His Ala Val Asn His Tyr Phe Lys Thr Arg His
 385 390 395 400
 Tyr Leu His Thr Leu Trp Lys Ala Gly Ile Leu Tyr Lys Arg Glu Thr
 405 410 415
 Thr Arg Ser Ala Ser Phe Cys Gly Ser Pro Tyr Ser Trp Glu Gln Glu
 420 425 430

Leu Gln His Gly Arg Leu Val Phe Gln Thr Ser Thr Arg His Gly Asp

435 440 445
 Glu Ser Phe Cys Ser Gln Ser Ser Gly Ile Leu Ser Arg Ser Pro Val
 450 455 460
 Gly Pro Cys Val Arg Ser Gln Leu Lys Gln Ser Arg Leu Gly Leu Gln
 465 470 475 480
 Pro Gln Gln Gly Ser Leu Ala Arg Gly Lys Ser Gly Arg Ser Gly Ser
 485 490 495
 Ile Arg Ala Arg Val His Pro Thr Thr Arg Arg Ser Phe Gly Val Glu

500 505 510
 Pro Ser Gly Ser Gly His Ile Asp Asn Ser Ala Ser Ser Thr Ser Ser
 515 520 525
 Cys Leu His Gln Ser Ala Val Arg Lys Thr Ala Tyr Ser His Leu Ser
 530 535 540
 Thr Ser Lys Arg Gln Ser Ser Ser Gly His Ala Val Glu Leu His Asn
 545 550 555 560
 Ile Pro Pro Ser Ser Ala Arg Ser Gln Ser Glu Gly Pro Ile Phe Ser

565 570 575
 Ala Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Ala Ser Asp Tyr Ala
 580 585 590
 Leu Thr His Ile Val Asn Leu Leu Glu Asp Trp Gly Pro Ala Thr Glu
 595 600 605
 His Gly Glu His Asn Ile Arg Ile Pro Arg Thr Pro Ala Arg Val Thr
 610 615 620
 Gly Gly Val Phe Leu Val Asp Lys Asn Pro His Asn Thr Thr Glu Ser

625 630 635 640
 Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Ser Thr His Val
 645 650 655
 Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu
 660 665 670
 Leu Ser Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe

675 680 685
Tyr His Ile Pro Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly

690 695 700
Ser Ser Gly Leu Pro Arg Tyr Val Ala Arg Leu Ser Ser Thr Ser Arg
705 710 715 720

Asn Ile Asn Tyr Gln His Gly Thr Met Gln Asp Leu His Asp Ser Cys
725 730 735

Ser Arg Asn Leu Tyr Val Ser Leu Leu Leu Leu Tyr Lys Thr Phe Gly
740 745 750

Arg Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys

755 760 765
Ile Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr
770 775 780

Ser Ala Ile Cys Ser Val Val Arg Arg Ala Phe Pro His Cys Leu Ala
785 790 795 800

Phe Ser Tyr Met Asp Asp Val Val Leu Gly Ala Lys Ser Val Gln His
805 810 815

Leu Glu Ser Leu Phe Thr Ser Ile Thr Asn Phe Leu Leu Ser Leu Gly

820 825 830
Ile His Leu Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn
835 840 845

Phe Met Gly Tyr Val Ile Gly Ser Trp Gly Thr Leu Pro Gln Glu His
850 855 860

Ile Val Leu Lys Ile Lys Gln Cys Phe Arg Lys Leu Pro Val Asn Arg
865 870 875 880

Pro Ile Asp Trp Lys Val Cys Gln Arg Ile Val Gly Leu Leu Gly Phe

885 890 895
Ala Ala Pro Phe Thr Gln Cys Gly Tyr Pro Ala Leu Met Pro Leu Tyr
900 905 910

Ala Cys Ile Gln Ser Lys Gln Ala Phe Thr Phe Ser Pro Thr Tyr Lys
915 920 925

Ala Phe Leu Cys Lys Gln Tyr Leu Asn Leu Tyr Pro Val Ala Arg Gln
930 935 940
Arg Ser Gly Leu Cys Gln Val Phe Ala Asp Ala Thr Pro Thr Gly Trp
945 950 955 960
Gly Leu Ala Ile Gly His Arg Ala Met Arg Gly Thr Phe Val Ala Pro
965 970 975
Leu Pro Ile His Thr Ala Glu Leu Leu Ala Ala Cys Phe Ala Arg Ser
980 985 990
Arg Ser Gly Ala Lys Leu Ile Gly Thr Asp Asn Ser Val Val Leu Ser
995 1000 1005
Arg Lys Tyr Thr Ser Phe Pro Trp Leu Leu Gly Cys Ala Ala Asn
1010 1015 1020
Trp Ile Leu Arg Gly Thr Ser Phe Val Tyr Val Pro Ser Ala Leu
1025 1030 1035
Asn Pro Ala Ala Asp Pro Ser Ala Gly Arg Leu Gly Leu Tyr Arg
1040 1045 1050
Pro Leu Leu His Leu Pro Phe Arg Pro Thr Thr Gly Arg Thr Ser
1055 1060 1065
Leu Tyr Ala Val Ser Pro Ser Val Pro Ser His Leu Pro Asp Arg
1070 1075 1080
Val His Phe Ala Ser Pro Leu His Val Ala Trp Arg Pro Pro Arg
1085 1090 1095
Lys Arg Arg Ala Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu
1100 1105 1110
Lys Leu Ala Gly Asp Val Glu Ser Asn Pro Gly Pro Met Gly Gly
1115 1120 1125
Trp Ser Ser Lys Pro Arg Gln Gly Met Gly Thr Asn Leu Ser Val
1130 1135 1140
Pro Asn Pro Leu Gly Phe Phe Pro Asp His Gln Leu Asp Pro Ala
1145 1150 1155
Phe Gly Ala Asn Ser Asn Asn Pro Asp Trp Asp Phe Asn Pro Asn

1160	1165	1170
Lys Asp His Trp Pro Glu Ala	Asn Gln Val Gly Ala	Gly Ala Phe
1175	1180	1185
Gly Pro Gly Phe Thr Pro Pro	His Gly Gly Leu Leu	Gly Trp Ser

1190	1195	1200
Pro Gln Ala Gln Gly Ile Leu	Thr Thr Val Pro Ala	Ala Pro Pro
1205	1210	1215
Pro Ala Ser Thr Asn Arg Gln	Ser Gly Arg Gln Pro	Thr Pro Ile
1220	1225	1230
Ser Pro Pro Leu Arg Asp Ser	His Pro Gln Ala Met	Gln Trp Asn
1235	1240	1245
Ser Thr Thr Phe His Gln Ala	Leu Leu Asp Pro Arg	Val Arg Gly

1250	1255	1260
Leu Tyr Phe Pro Ala Gly Gly	Ser Ser Ser Gly Thr	Val Asn Pro
1265	1270	1275
Val Pro Thr Thr Ala Ser Pro	Ile Ser Ser Ile Phe	Ser Arg Thr
1280	1285	1290
Gly Asp Pro Ala Pro Asn Met	Glu Asn Thr Thr Ser	Gly Phe Leu
1295	1300	1305
Gly Pro Leu Leu Val Leu Gln	Ala Gly Phe Phe Leu	Leu Thr Arg

1310	1315	1320
Ile Leu Thr Ile Pro Gln Ser	Leu Asp Ser Trp Trp	Thr Ser Leu
1325	1330	1335
Asn Phe Leu Gly Gly Ala Pro	Thr Cys Pro Gly Gln	Asn Ser Gln
1340	1345	1350
Ser Pro Thr Ser Asn His Ser	Pro Thr Ser Cys Pro	Pro Ile Cys
1355	1360	1365
Pro Gly Tyr Arg Trp Met Cys	Leu Arg Arg Phe Ile	Ile Phe Leu

1370	1375	1380
Phe Ile Leu Leu Leu Cys Leu	Ile Phe Leu Leu Val	Leu Leu Asp
1385	1390	1395

Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Leu Pro Gly Thr Ser
1400 1405 1410

Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Ile Pro Ala Gln
1415 1420 1425

Gly Thr Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp

1430 1435 1440

Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala
1445 1450 1455

Arg Phe Leu Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Leu Ser
1460 1465 1470

Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr
1475 1480 1485

Val Trp Leu Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser

1490 1495 1500

Leu Tyr Asn Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe
1505 1510 1515

Phe Cys Leu Trp Val Tyr Ile
1520 1525

<210> 4

<211> 26

<212> PRT

<213> Unknown

<220><223> Shark Invariant Chain

<400> 4

Ser Leu Leu Trp Gly Gly Val Thr Val Leu Ala Ala Met Leu Ile Ala
1 5 10 15

Gly Gln Val Ala Ser Val Val Phe Leu Val

20 25

<210> 5

<211> 8

<212> PRT

<213> Artificial Sequence

<220><223> Linker peptide

<400> 5

Lys Gly Gly Gly Pro Gly Gly Gly

1 5

<210> 6

<211> 183

<212> PRT

<213> Hepatitis B virus

<400> 6

Met Asp Ile Asp Pro Tyr Lys Glu Phe Gly Ala Ser Val Glu Leu Leu

1 5 10 15

Ser Phe Leu Pro Ser Asp Phe Phe Pro Ser Ile Arg Asp Leu Leu Asp

20 25 30

Thr Ala Ser Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys

35 40 45

Ser Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu

50 55 60

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

65 70 75 80

Ser Arg Glu Leu Val Val Ser Tyr Val Asn Val Asn Met Gly Leu Lys

85 90 95

Ile Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly Arg

100 105 110

Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly Val Trp Ile Arg Thr

115 120 125

Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro

130 135 140

Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg Thr

145 150 155 160

Pro Ser Pro Arg Arg Arg Arg Ser Gln Ser Pro Arg Arg Arg Arg Ser

165 170 175

Gln Ser Arg Glu Ser Gln Cys

180

<210> 7

<211> 7

<212> PRT

<213> Artificial Sequence

<220><223> Linker peptide

<400> 7

Gly Gly Gly Ser Gly Gly Gly

1 5

<210> 8

<211> 772

<212> PRT

<213> Hepatitis B virus

<400> 8

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 Ala 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 Tyr 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 Leu Thr Lys Tyr Leu Pro Leu Asp Lys Gly

115 120 125

Ile Lys Pro Tyr Tyr Pro Glu His Ala Val Asn His Tyr Phe Lys 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 His Gly Arg Leu Val Phe Gln Thr Ser Thr Arg His
 180 185 190
 Gly Asp Glu Ser Phe Cys Ser Gln Ser Ser Gly Ile Leu Ser Arg Ser
 195 200 205

 Pro Val Gly Pro Cys Val Arg Ser Gln Leu Lys Gln Ser Arg Leu Gly
 210 215 220
 Leu Gln Pro Gln Gln Gly Ser Leu Ala Arg Gly Lys Ser Gly Arg Ser
 225 230 235 240
 Gly Ser Ile Arg Ala Arg Val His Pro Thr Thr Arg Arg Ser Phe Gly
 245 250 255
 Val Glu Pro Ser Gly Ser Gly His Ile Asp Asn Ser Ala Ser Ser Thr
 260 265 270

 Ser Ser Cys Leu His Gln Ser Ala Val Arg Lys Thr Ala Tyr Ser His
 275 280 285
 Leu Ser Thr Ser Lys Arg Gln Ser Ser Ser Gly His Ala Val Glu Leu
 290 295 300
 His Asn Ile Pro Pro Ser Ser Ala Arg Ser Gln Ser Glu Gly Pro Ile
 305 310 315 320
 Phe Ser Ala Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Ala Ser Asp
 325 330 335

 Tyr Ala Leu Thr His Ile Val Asn Leu Leu Glu Asp Trp Gly Pro Ala
 340 345 350
 Thr Glu His Gly Glu His Asn Ile Arg Ile Pro Arg Thr Pro Ala Arg
 355 360 365
 Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn Pro His Asn Thr Thr
 370 375 380
 Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Ser Thr

385 390 395 400
 His Val Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr
 405 410 415
 Asn Leu Leu Ser Ser Asn Leu Ser Thr Phe Gly Arg Lys Leu His Leu
 420 425 430
 Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val
 435 440 445
 Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser
 450 455 460

 Val Val Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp
 465 470 475 480
 Asp Val Val Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Phe
 485 490 495
 Thr Ser Ile Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro
 500 505 510
 Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val
 515 520 525

 Ile Gly Ser Trp Gly Thr Leu Pro Gln Glu His Ile Val Leu Lys Ile
 530 535 540
 Lys Gln Cys Phe Arg Lys Leu Pro Val Asn Arg Pro Ile Asp Trp Lys
 545 550 555 560
 Val Cys Gln Arg Ile Val Gly Leu Leu Gly Phe Ala Ala Pro Phe Thr
 565 570 575
 Gln Cys Gly Tyr Pro Ala Leu Met Pro Leu Tyr Ala Cys Ile Gln Ser
 580 585 590

 Lys Gln Ala Phe Thr Phe Ser Pro Thr Tyr Lys Ala Phe Leu Cys Lys
 595 600 605
 Gln Tyr Leu Asn Leu Tyr Pro Val Ala Arg Gln Arg Ser Gly Leu Cys
 610 615 620
 Gln Val Phe Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu Ala Ile Gly
 625 630 635 640

His Arg Ala Met Arg Gly Thr Phe Val Ala Pro Leu Pro Ile His Thr
645 650 655

Ala Glu Leu Leu Ala Ala Cys Phe Ala Arg Ser Arg Ser Gly Ala Lys
660 665 670

Leu Ile Gly Thr Asp Asn Ser Val Val Leu Ser Arg Lys Tyr Thr Ser
675 680 685

Phe Pro Trp Leu Leu Gly Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr
690 695 700

Ser Phe Val Tyr Val Pro Ser Ala Leu Asn Pro Ala Ala Asp Pro Ser
705 710 715 720

Ala Gly Arg Leu Gly Leu Tyr Arg Pro Leu Leu His Leu Pro Phe Arg
725 730 735

Pro Thr Thr Gly Arg Thr Ser Leu Tyr Ala Val Ser Pro Ser Val Pro
740 745 750

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

Trp Arg Pro Pro
770

<210> 9

<211> 28

<212> PRT

<213> Unknown

<220><223> Furin 2A

<

400> 9

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

Lys Leu Ala Gly Asp Val Glu Ser Asn Pro Gly Pro
20 25

<210> 10

<211> 226

<212> PRT

<213> Hepatitis B virus

<400> 10

Met Glu Asn Thr Thr Ser Gly Phe Leu Gly Pro Leu Leu Val Leu Gln

1 5 10 15

Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu

20 25 30

Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Ala Pro Thr Cys

35 40 45

Pro Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser Pro Thr Ser

50 55 60

Cys Pro Pro Ile Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe

65 70 75 80

Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val

85 90 95

Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Leu Pro Gly

100 105 110

Thr Ser Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Ile Pro Ala

115 120 125

Gln Gly Thr Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp

130 135 140

Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala Arg

145 150 155 160

Phe Leu Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Leu Ser Leu Leu

165 170 175

Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu

180 185 190

Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Asn Ile

195 200 205

Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val

210 215 220

Tyr Ile

225

<210> 11

<211> 1521

<212> PRT

<213> Artificial Sequence

<220><223> Vaccine construct

<400> 11

Met Ser Leu Leu Trp Gly Gly Val Thr Val Leu Ala Ala Met Leu Ile

1 5 10 15

Ala Gly Gln Val Ala Ser Val Val Phe Leu Val Lys Gly Gly Ser Met

20 25 30

Gly Gly Trp Ser Ser Lys Pro Arg Gln Gly Met Gly Thr Asn Leu Ser

35 40 45

Val Pro Asn Pro Leu Gly Phe Phe Pro Asp His Gln Leu Asp Pro Ala

50 55 60

Phe Gly Ala Asn Ser Asn Asn Pro Asp Trp Asp Phe Asn Pro Asn Lys

65 70 75 80

Asp His Trp Pro Glu Ala Asn Gln Val Gly Ala Gly Ala Phe Gly Pro

85 90 95

Gly Phe Thr Pro Pro His Gly Gly Leu Leu Gly Trp Ser Pro Gln Ala

100 105 110

Gln Gly Ile Leu Thr Thr Val Pro Ala Ala Pro Pro Pro Ala Ser Thr

115 120 125

Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro Ile Ser Pro Pro Leu Arg

130 135 140

Asp Ser His Pro Gln Ala Met Gln Trp Asn Ser Thr Thr Phe His Gln

145 150 155 160

Ala Leu Leu Asp Pro Arg Val Arg Gly Leu Tyr Phe Pro Ala Gly Gly

165 170 175

Ser Ser Ser Gly Thr Val Asn Pro Val Pro Thr Thr Ala Ser Pro Ile

180 185 190

Ser Ser Ile Phe Ser Arg Thr Gly Asp Pro Ala Pro Asn Met Glu Asn

195 200 205

Thr Thr Ser Gly Phe Leu Gly Pro Leu Leu Val Leu Gln Ala Gly Phe
210 215 220

Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu Asp Ser Trp

225 230 235 240

Trp Thr Ser Leu Asn Phe Leu Gly Gly Ala Pro Thr Cys Pro Gly Gln
245 250 255

Asn Ser Gln Ser Pro Thr Ser Asn His Ser Pro Thr Ser Cys Pro Pro
260 265 270

Ile Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile Ile Phe
275 280 285

Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val Leu Leu Asp

290 295 300

Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Leu Pro Gly Thr Ser Thr
305 310 315 320

Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Ile Pro Ala Gln Gly Thr
325 330 335

Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp Gly Asn Cys
340 345 350

Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala Arg Phe Leu Trp

355 360 365

Glu Trp Ala Ser Val Arg Phe Ser Trp Leu Ser Leu Leu Val Pro Phe
370 375 380

Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu Ser Val Ile
385 390 395 400

Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Asn Ile Leu Ser Pro
405 410 415

Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val Tyr Ile Arg

420 425 430

Lys Arg Arg Ala Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys
435 440 445

Leu Ala Gly Asp Val Glu Ser Asn Pro Gly Pro Met Gln Leu Phe His

450 455 460
 Leu Cys Leu Ile Ile Ser Cys Ser Cys Pro Thr Val Gln Ala Ser Lys
 465 470 475 480
 Leu Cys Leu Gly Trp Leu Trp Gly Met Asp Ile Asp Pro Tyr Lys Glu

 485 490 495
 Phe Gly Ala Ser Val Glu Leu Leu Ser Phe Leu Pro Ser Asp Phe Phe
 500 505 510
 Pro Ser Ile Arg Asp Leu Leu Asp Thr Ala Ser Ala Leu Tyr Arg Glu
 515 520 525
 Ala Leu Glu Ser Pro Glu His Cys Ser Pro His His Thr Ala Leu Arg
 530 535 540
 Gln Ala Ile Leu Cys Trp Gly Glu Leu Met Asn Leu Ala Thr Trp Val

 545 550 555 560
 Gly Ser Asn Leu Glu Asp Pro Ala Ser Arg Glu Leu Val Val Ser Tyr
 565 570 575
 Val Asn Val Asn Met Gly Leu Lys Ile Arg Gln Leu Leu Trp Phe His
 580 585 590
 Ile Ser Cys Leu Thr Phe Gly Arg Glu Thr Val Leu Glu Tyr Leu Val
 595 600 605
 Ser Phe Gly Val Trp Ile Arg Thr Pro Pro Ala Tyr Arg Pro Pro Asn

 610 615 620
 Ala Pro Ile Leu Ser Thr Leu Pro Glu Thr Thr Val Val Arg Arg Arg
 625 630 635 640
 Gly Arg Ser Pro Arg Arg Arg Thr Pro Ser Pro Arg Arg Arg Arg Ser
 645 650 655
 Gln Ser Pro Arg Arg Arg Arg Ser Gln Ser Arg Glu Ser Gln Cys Gly
 660 665 670
 Gly Gly Ser Gly Gly Gly Met Pro Leu Ser Tyr Gln His Phe Arg Lys

 675 680 685
 Leu Leu Leu Leu Asp Asp Glu Ala Gly Pro Leu Glu Glu Glu Leu Pro
 690 695 700

Arg Leu Ala Asp Glu Gly Leu Asn Arg Arg Val Ala Glu Asp Leu Asn
 705 710 715 720
 Leu Gly Asn Leu Asn Val Ser Ile Pro Trp Thr His Lys Val Gly Asn
 725 730 735
 Phe Thr Gly Leu Ala Ser Ser Thr Val Pro Val Phe Asn Pro Glu Trp

 740 745 750
 Gln Thr Pro Ser Phe Pro His Ile His Leu Gln Glu Asp Ile Ile Asn
 755 760 765
 Arg Cys Gln Gln Tyr Val Gly Pro Leu Thr Val Asn Glu Lys Arg Arg
 770 775 780
 Leu Lys Leu Ile Met Pro Ala Arg Phe Tyr Pro Asn Leu Thr Lys Tyr
 785 790 795 800
 Leu Pro Leu Asp Lys Gly Ile Lys Pro Tyr Tyr Pro Glu His Ala Val

 805 810 815
 Asn His Tyr Phe Lys Thr Arg His Tyr Leu His Thr Leu Trp Lys Ala
 820 825 830
 Gly Ile Leu Tyr Lys Arg Glu Thr Thr Arg Ser Ala Ser Phe Cys Gly
 835 840 845
 Ser Pro Tyr Ser Trp Glu Gln Glu Leu Gln His Gly Arg Leu Val Phe
 850 855 860
 Gln Thr Ser Thr Arg His Gly Asp Glu Ser Phe Cys Ser Gln Ser Ser

 865 870 875 880
 Gly Ile Leu Ser Arg Ser Pro Val Gly Pro Cys Val Arg Ser Gln Leu
 885 890 895
 Lys Gln Ser Arg Leu Gly Leu Gln Pro Gln Gln Gly Ser Leu Ala Arg
 900 905 910
 Gly Lys Ser Gly Arg Ser Gly Ser Ile Arg Ala Arg Val His Pro Thr
 915 920 925
 Thr Arg Arg Ser Phe Gly Val Glu Pro Ser Gly Ser Gly His Ile Asp

 930 935 940
 Asn Ser Ala Ser Ser Thr Ser Ser Cys Leu His Gln Ser Ala Val Arg

945 950 955 960
 Lys Thr Ala Tyr Ser His Leu Ser Thr Ser Lys Arg Gln Ser Ser Ser
 965 970 975
 Gly His Ala Val Glu Leu His Asn Ile Pro Pro Ser Ser Ala Arg Ser
 980 985 990
 Gln Ser Glu Gly Pro Ile Phe Ser Ala Trp Trp Leu Gln Phe Arg Asn

 995 1000 1005
 Ser Lys Pro Ala Ser Asp Tyr Ala Leu Thr His Ile Val Asn Leu
 1010 1015 1020
 Leu Glu Asp Trp Gly Pro Ala Thr Glu His Gly Glu His Asn Ile
 1025 1030 1035
 Arg Ile Pro Arg Thr Pro Ala Arg Val Thr Gly Gly Val Phe Leu
 1040 1045 1050
 Val Asp Lys Asn Pro His Asn Thr Thr Glu Ser Arg Leu Val Val

 1055 1060 1065
 Asp Phe Ser Gln Phe Ser Arg Gly Ser Thr His Val Ser Trp Pro
 1070 1075 1080
 Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser
 1085 1090 1095
 Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr
 1100 1105 1110
 His Ile Pro Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly

 1115 1120 1125
 Ser Ser Gly Leu Pro Arg Tyr Val Ala Arg Leu Ser Ser Thr Ser
 1130 1135 1140
 Arg Asn Ile Asn Tyr Gln His Gly Thr Met Gln Asp Leu His Asp
 1145 1150 1155
 Ser Cys Ser Arg Asn Leu Tyr Val Ser Leu Leu Leu Leu Tyr Lys
 1160 1165 1170
 Thr Phe Gly Arg Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu

1175 1180 1185

Gly Phe	Arg Lys Ile Pro Met	Gly Val Gly Leu Ser	Pro Phe Leu
1190	1195	1200	
Leu Ala	Gln Phe Thr Ser Ala	Ile Cys Ser Val Val	Arg Arg Ala
1205	1210	1215	
Phe Pro	His Cys Leu Ala Phe	Ser Tyr Met Asp Asp	Val Val Leu
1220	1225	1230	
Gly Ala	Lys Ser Val Gln His	Leu Glu Ser Leu Phe	Thr Ser Ile
1235	1240	1245	
Thr Asn	Phe Leu Leu Ser Leu	Gly Ile His Leu Asn	Pro Asn Lys
1250	1255	1260	
Thr Lys	Arg Trp Gly Tyr Ser	Leu Asn Phe Met Gly	Tyr Val Ile
1265	1270	1275	
Gly Ser	Trp Gly Thr Leu Pro	Gln Glu His Ile Val	Leu Lys Ile
1280	1285	1290	
Lys Gln	Cys Phe Arg Lys Leu	Pro Val Asn Arg Pro	Ile Asp Trp
1295	1300	1305	
Lys Val	Cys Gln Arg Ile Val	Gly Leu Leu Gly Phe	Ala Ala Pro
1310	1315	1320	
Phe Thr	Gln Cys Gly Tyr Pro	Ala Leu Met Pro Leu	Tyr Ala Cys
1325	1330	1335	
Ile Gln	Ser Lys Gln Ala Phe	Thr Phe Ser Pro Thr	Tyr Lys Ala
1340	1345	1350	
Phe Leu	Cys Lys Gln Tyr Leu	Asn Leu Tyr Pro Val	Ala Arg Gln
1355	1360	1365	
Arg Ser	Gly Leu Cys Gln Val	Phe Ala Asp Ala Thr	Pro Thr Gly
1370	1375	1380	
Trp Gly	Leu Ala Ile Gly His	Arg Ala Met Arg Gly	Thr Phe Val
1385	1390	1395	
Ala Pro	Leu Pro Ile His Thr	Ala Glu Leu Leu Ala	Ala Cys Phe
1400	1405	1410	
Ala Arg	Ser Arg Ser Gly Ala	Lys Leu Ile Gly Thr	Asp Asn Ser

1415 1420 1425
Val Val Leu Ser Arg Lys Tyr Thr Ser Phe Pro Trp Leu Leu Gly
1430 1435 1440
Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe Val Tyr Val
1445 1450 1455
Pro Ser Ala Leu Asn Pro Ala Ala Asp Pro Ser Ala Gly Arg Leu
1460 1465 1470
Gly Leu Tyr Arg Pro Leu Leu His Leu Pro Phe Arg Pro Thr Thr

1475 1480 1485
Gly Arg Thr Ser Leu Tyr Ala Val Ser Pro Ser Val Pro Ser His
1490 1495 1500
Leu Pro Asp Arg Val His Phe Ala Ser Pro Leu His Val Ala Trp
1505 1510 1515
Arg Pro Pro

1520

<210> 12

<211> 1490

<212> PRT

<213> Artificial Sequence

<220><223> Vaccine construct

<400> 12

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 Ser Val Glu Leu Leu Ser Phe Leu
35 40 45
Pro Ser Asp Phe Phe Pro Ser Ile 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 Cys Trp Gly Glu Leu Met Asn

85	90	95	
Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala Ser Arg Glu			
100	105	110	
Leu Val Val Ser Tyr Val Asn Val 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	
Arg Arg Arg Arg Ser Gln Ser Pro Arg Arg Arg Arg Ser Gln Ser Arg			
195	200	205	
Glu Ser Gln Cys Gly Gly Gly Ser Gly Gly Gly Met Pro Leu Ser Tyr			
210	215	220	
Gln His Phe Arg Lys Leu Leu Leu Leu Asp Asp Glu Ala Gly Pro Leu			
225	230	235	240
Glu Glu Glu Leu Pro Arg Leu Ala Asp Glu Gly Leu Asn Arg Arg Val			
245	250	255	
Ala Glu Asp Leu Asn Leu Gly Asn Leu Asn Val Ser Ile Pro Trp Thr			
260	265	270	
His Lys Val Gly Asn Phe Thr Gly Leu Ala Ser Ser Thr Val Pro Val			
275	280	285	
Phe Asn Pro Glu Trp Gln Thr Pro Ser Phe Pro His Ile His Leu Gln			
290	295	300	
Glu Asp Ile Ile Asn Arg Cys Gln Gln Tyr Val Gly Pro Leu Thr Val			
305	310	315	320
Asn Glu Lys Arg Arg Leu Lys Leu Ile Met Pro Ala Arg Phe Tyr Pro			
325	330	335	

Asn Leu Thr Lys Tyr Leu Pro Leu Asp Lys Gly Ile Lys Pro Tyr Tyr
 340 345 350
 Pro Glu His Ala Val Asn His Tyr Phe Lys Thr Arg His Tyr Leu His
 355 360 365
 Thr Leu Trp Lys Ala Gly Ile Leu Tyr Lys Arg Glu Thr Thr Arg Ser
 370 375 380
 Ala Ser Phe Cys Gly Ser Pro Tyr Ser Trp Glu Gln Glu Leu Gln His

 385 390 395 400
 Gly Arg Leu Val Phe Gln Thr Ser Thr Arg His Gly Asp Glu Ser Phe
 405 410 415
 Cys Ser Gln Ser Ser Gly Ile Leu Ser Arg Ser Pro Val Gly Pro Cys
 420 425 430
 Val Arg Ser Gln Leu Lys Gln Ser Arg Leu Gly Leu Gln Pro Gln Gln
 435 440 445
 Gly Ser Leu Ala Arg Gly Lys Ser Gly Arg Ser Gly Ser Ile Arg Ala

 450 455 460
 Arg Val His Pro Thr Thr Arg Arg Ser Phe Gly Val Glu Pro Ser Gly
 465 470 475 480
 Ser Gly His Ile Asp Asn Ser Ala Ser Ser Thr Ser Ser Cys Leu His
 485 490 495
 Gln Ser Ala Val Arg Lys Thr Ala Tyr Ser His Leu Ser Thr Ser Lys
 500 505 510
 Arg Gln Ser Ser Ser Gly His Ala Val Glu Leu His Asn Ile Pro Pro

 515 520 525
 Ser Ser Ala Arg Ser Gln Ser Glu Gly Pro Ile Phe Ser Ala Trp Trp
 530 535 540
 Leu Gln Phe Arg Asn Ser Lys Pro Ala Ser Asp Tyr Ala Leu Thr His
 545 550 555 560
 Ile Val Asn Leu Leu Glu Asp Trp Gly Pro Ala Thr Glu His Gly Glu
 565 570 575
 His Asn Ile Arg Ile Pro Arg Thr Pro Ala Arg Val Thr Gly Gly Val

580 585 590
 Phe Leu Val Asp Lys Asn Pro His Asn Thr Thr Glu Ser Arg Leu Val
 595 600 605
 Val Asp Phe Ser Gln Phe Ser Arg Gly Ser Thr His Val Ser Trp Pro
 610 615 620
 Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser
 625 630 635 640
 Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Ile

 645 650 655
 Pro Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly Ser Ser Gly
 660 665 670
 Leu Pro Arg Tyr Val Ala Arg Leu Ser Ser Thr Ser Arg Asn Ile Asn
 675 680 685
 Tyr Gln His Gly Thr Met Gln Asp Leu His Asp Ser Cys Ser Arg Asn
 690 695 700
 Leu Tyr Val Ser Leu Leu Leu Leu Tyr Lys Thr Phe Gly Arg Lys Leu

 705 710 715 720
 His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met
 725 730 735
 Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile
 740 745 750
 Cys Ser Val Val Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr
 755 760 765
 Met Asp Asp Val Val Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser

 770 775 780
 Leu Phe Thr Ser Ile Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu
 785 790 795 800
 Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly
 805 810 815
 Tyr Val Ile Gly Ser Trp Gly Thr Leu Pro Gln Glu His Ile Val Leu
 820 825 830

Lys Ile Lys Gln Cys Phe Arg Lys Leu Pro Val Asn Arg Pro Ile Asp

835 840 845

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

850 855 860

Phe Thr Gln Cys Gly Tyr Pro Ala Leu Met Pro Leu Tyr Ala Cys Ile

865 870 875 880

Gln Ser Lys Gln Ala Phe Thr Phe Ser Pro Thr Tyr Lys Ala Phe Leu

885 890 895

Cys Lys Gln Tyr Leu Asn Leu Tyr Pro Val Ala Arg Gln Arg Ser Gly

900 905 910

Leu Cys Gln Val Phe Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu Ala

915 920 925

Ile Gly His Arg Ala Met Arg Gly Thr Phe Val Ala Pro Leu Pro Ile

930 935 940

His Thr Ala Glu Leu Leu Ala Ala Cys Phe Ala Arg Ser Arg Ser Gly

945 950 955 960

Ala Lys Leu Ile Gly Thr Asp Asn Ser Val Val Leu Ser Arg Lys Tyr

965 970 975

Thr Ser Phe Pro Trp Leu Leu Gly Cys Ala Ala Asn Trp Ile Leu Arg

980 985 990

Gly Thr Ser Phe Val Tyr Val Pro Ser Ala Leu Asn Pro Ala Ala Asp

995 1000 1005

Pro Ser Ala Gly Arg Leu Gly Leu Tyr Arg Pro Leu Leu His Leu

1010 1015 1020

Pro Phe Arg Pro Thr Thr Gly Arg Thr Ser Leu Tyr Ala Val Ser

1025 1030 1035

Pro Ser Val Pro Ser His Leu Pro Asp Arg Val His Phe Ala Ser

1040 1045 1050

Pro Leu His Val Ala Trp Arg Pro Pro Arg Lys Arg Arg Ala Pro

1055 1060 1065

Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala Gly Asp

1070	1075	1080
Val Glu Ser Asn Pro Gly Pro	Met Gly Gly Trp Ser	Ser Lys Pro
1085	1090	1095
Arg Gln Gly Met Gly Thr Asn	Leu Ser Val Pro Asn	Pro Leu Gly
1100	1105	1110
Phe Phe Pro Asp His Gln Leu	Asp Pro Ala Phe Gly	Ala Asn Ser
1115	1120	1125
Asn Asn Pro Asp Trp Asp Phe	Asn Pro Asn Lys Asp	His Trp Pro
1130	1135	1140
Glu Ala Asn Gln Val Gly Ala	Gly Ala Phe Gly Pro	Gly Phe Thr
1145	1150	1155
Pro Pro His Gly Gly Leu Leu	Gly Trp Ser Pro Gln	Ala Gln Gly
1160	1165	1170
Ile Leu Thr Thr Val Pro Ala	Ala Pro Pro Pro Ala	Ser Thr Asn
1175	1180	1185
Arg Gln Ser Gly Arg Gln Pro	Thr Pro Ile Ser Pro	Pro Leu Arg
1190	1195	1200
Asp Ser His Pro Gln Ala Met	Gln Trp Asn Ser Thr	Thr Phe His
1205	1210	1215
Gln Ala Leu Leu Asp Pro Arg	Val Arg Gly Leu Tyr	Phe Pro Ala
1220	1225	1230
Gly Gly Ser Ser Ser Gly Thr	Val Asn Pro Val Pro	Thr Thr Ala
1235	1240	1245
Ser Pro Ile Ser Ser Ile Phe	Ser Arg Thr Gly Asp	Pro Ala Pro
1250	1255	1260
Asn Met Glu Asn Thr Thr Ser	Gly Phe Leu Gly Pro	Leu Leu Val
1265	1270	1275
Leu Gln Ala Gly Phe Phe Leu	Leu Thr Arg Ile Leu	Thr Ile Pro
1280	1285	1290
Gln Ser Leu Asp Ser Trp Trp	Thr Ser Leu Asn Phe	Leu Gly Gly
1295	1300	1305

Ala Pro Thr Cys Pro Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn
1310 1315 1320

His Ser Pro Thr Ser Cys Pro Pro Ile Cys Pro Gly Tyr Arg Trp
1325 1330 1335

Met Cys Leu Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu
1340 1345 1350

Cys Leu Ile Phe Leu Leu Val Leu Leu Asp Tyr Gln Gly Met Leu
1355 1360 1365

Pro Val Cys Pro Leu Leu Pro Gly Thr Ser Thr Thr Ser Thr Gly
1370 1375 1380

Pro Cys Lys Thr Cys Thr Ile Pro Ala Gln Gly Thr Ser Met Phe
1385 1390 1395

Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp Gly Asn Cys Thr Cys
1400 1405 1410

Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala Arg Phe Leu Trp Glu
1415 1420 1425

Trp Ala Ser Val Arg Phe Ser Trp Leu Ser Leu Leu Val Pro Phe
1430 1435 1440

Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu Ser Val
1445 1450 1455

Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Asn Ile Leu
1460 1465 1470

Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val
1475 1480 1485

Tyr Ile
1490

<210> 13

<211> 1492

<212> PRT

<213> Artificial Sequence

<220><223> Vaccine construct

<400> 13

Met Ser Leu Leu Trp Gly Gly Val Thr Val Leu Ala Ala Met Leu Ile

1 5 10 15
Ala Gly Gln Val Ala Ser Val Val Phe Leu Val Lys Gly Gly Gly Pro
20 25 30
Gly Gly Gly Met Gln Leu Phe His Leu Cys Leu Ile Ile Ser Cys Ser
35 40 45
Cys Pro Thr Val Gln Ala Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly
50 55 60
Met Asp Ile Asp Pro Tyr Lys Glu Phe Gly Ala Ser Val Glu Leu Leu

65 70 75 80
Ser Phe Leu Pro Ser Asp Phe Phe Pro Ser Ile Arg Asp Leu Leu Asp
85 90 95
Thr Ala Ser Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys
100 105 110
Ser Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu
115 120 125
Leu Met Asn Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala

130 135 140
Ser Arg Glu Leu Val Val Ser Tyr Val Asn Val Asn Met Gly Leu Lys
145 150 155 160
Ile Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly Arg
165 170 175
Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly Val Trp Ile Arg Thr
180 185 190
Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro

195 200 205
Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg Thr
210 215 220
Pro Ser Pro Arg Arg Arg Arg Ser Gln Ser Pro Arg Arg Arg Arg Ser
225 230 235 240
Gln Ser Arg Glu Ser Gln Cys Gly Gly Gly Ser Gly Gly Gly Met Pro

245 250 255
Leu Ser Tyr Gln His Phe Arg Lys Leu Leu Leu Leu Asp Asp Glu Ala

260 265 270
Gly Pro Leu Glu Glu Glu Leu Pro Arg Leu Ala Asp Glu Gly Leu Asn

275 280 285
Arg Arg Val Ala Glu Asp Leu Asn Leu Gly Asn Leu Asn Val Ser Ile

290 295 300
Pro Trp Thr His Lys Val Gly Asn Phe Thr Gly Leu Ala Ser Ser Thr

305 310 315 320
Val Pro Val Phe Asn Pro Glu Trp Gln Thr Pro Ser Phe Pro His Ile

325 330 335
His Leu Gln Glu Asp Ile Ile Asn Arg Cys Gln Gln Tyr Val Gly Pro

340 345 350
Leu Thr Val Asn Glu Lys Arg Arg Leu Lys Leu Ile Met Pro Ala Arg

355 360 365
Phe Tyr Pro Asn Leu Thr Lys Tyr Leu Pro Leu Asp Lys Gly Ile Lys

370 375 380
Pro Tyr Tyr Pro Glu His Ala Val Asn His Tyr Phe Lys Thr Arg His

385 390 395 400
Tyr Leu His Thr Leu Trp Lys Ala Gly Ile Leu Tyr Lys Arg Glu Thr

405 410 415
Thr Arg Ser Ala Ser Phe Cys Gly Ser Pro Tyr Ser Trp Glu Gln Glu

420 425 430
Leu Gln His Gly Arg Leu Val Phe Gln Thr Ser Thr Arg His Gly Asp

435 440 445
Glu Ser Phe Cys Ser Gln Ser Ser Gly Ile Leu Ser Arg Ser Pro Val

450 455 460
Gly Pro Cys Val Arg Ser Gln Leu Lys Gln Ser Arg Leu Gly Leu Gln

465 470 475 480
Pro Gln Gln Gly Ser Leu Ala Arg Gly Lys Ser Gly Arg Ser Gly Ser

485 490 495

Ile Arg Ala Arg Val His Pro Thr Thr Arg Arg Ser Phe Gly Val Glu
500 505 510
Pro Ser Gly Ser Gly His Ile Asp Asn Ser Ala Ser Ser Thr Ser Ser
515 520 525
Cys Leu His Gln Ser Ala Val Arg Lys Thr Ala Tyr Ser His Leu Ser
530 535 540
Thr Ser Lys Arg Gln Ser Ser Ser Gly His Ala Val Glu Leu His Asn
545 550 555 560
Ile Pro Pro Ser Ser Ala Arg Ser Gln Ser Glu Gly Pro Ile Phe Ser
565 570 575
Ala Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Ala Ser Asp Tyr Ala
580 585 590
Leu Thr His Ile Val Asn Leu Leu Glu Asp Trp Gly Pro Ala Thr Glu
595 600 605
His Gly Glu His Asn Ile Arg Ile Pro Arg Thr Pro Ala Arg Val Thr
610 615 620
Gly Gly Val Phe Leu Val Asp Lys Asn Pro His Asn Thr Thr Glu Ser
625 630 635 640
Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Ser Thr His Val
645 650 655
Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu
660 665 670
Leu Ser Ser Asn Leu Ser Thr Phe Gly Arg Lys Leu His Leu Tyr Ser
675 680 685
His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu
690 695 700
Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Val
705 710 715 720
Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val
725 730 735
Val Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Phe Thr Ser

740	745	750	
Ile Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn Lys			
755	760	765	
Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val Ile Gly			
770	775	780	
Ser Trp Gly Thr Leu Pro Gln Glu His Ile Val Leu Lys Ile Lys Gln			
785	790	795	800
Cys Phe Arg Lys Leu Pro Val Asn Arg Pro Ile Asp Trp Lys Val Cys			
805	810	815	
Gln Arg Ile Val Gly Leu Leu Gly Phe Ala Ala Pro Phe Thr Gln Cys			
820	825	830	
Gly Tyr Pro Ala Leu Met Pro Leu Tyr Ala Cys Ile Gln Ser Lys Gln			
835	840	845	
Ala Phe Thr Phe Ser Pro Thr Tyr Lys Ala Phe Leu Cys Lys Gln Tyr			
850	855	860	
Leu Asn Leu Tyr Pro Val Ala Arg Gln Arg Ser Gly Leu Cys Gln Val			
865	870	875	880
Phe Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu Ala Ile Gly His Arg			
885	890	895	
Ala Met Arg Gly Thr Phe Val Ala Pro Leu Pro Ile His Thr Ala Glu			
900	905	910	
Leu Leu Ala Ala Cys Phe Ala Arg Ser Arg Ser Gly Ala Lys Leu Ile			
915	920	925	
Gly Thr Asp Asn Ser Val Val Leu Ser Arg Lys Tyr Thr Ser Phe Pro			
930	935	940	
Trp Leu Leu Gly Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe			
945	950	955	960
Val Tyr Val Pro Ser Ala Leu Asn Pro Ala Ala Asp Pro Ser Ala Gly			
965	970	975	
Arg Leu Gly Leu Tyr Arg Pro Leu Leu His Leu Pro Phe Arg Pro Thr			
980	985	990	

Thr Gly Arg Thr Ser Leu Tyr Ala	Val Ser Pro Ser Val	Pro Ser His
995	1000	1005
Leu Pro Asp Arg Val His Phe	Ala Ser Pro Leu His	Val Ala Trp
1010	1015	1020
Arg Pro Pro Lys Ser Pro Asn	Ser Asn Asn Pro Asp	Trp Asp Phe
1025	1030	1035
Asn Pro Asn Lys Asp His Trp	Pro Glu Ala Asn Gln	Val Gly Ala
1040	1045	1050
Gly Ala Phe Gly Pro Gly Phe	Thr Pro Pro His Gly	Gly Leu Leu
1055	1060	1065
Gly Trp Ser Pro Gln Ala Gln	Gly Ile Leu Thr Thr	Val Pro Ala
1070	1075	1080
Ala Pro Pro Pro Ala Ser Thr	Asn Arg Gln Ser Gly	Arg Gln Pro
1085	1090	1095
Thr Pro Ile Ser Pro Pro Leu	Arg Asp Ser His Pro	Gln Ala Met
1100	1105	1110
Gln Trp Asn Ser Thr Thr Phe	His Gln Ala Leu Leu	Asp Pro Arg
1115	1120	1125
Val Arg Gly Leu Tyr Phe Pro	Ala Gly Gly Ser Ser	Ser Gly Thr
1130	1135	1140
Val Asn Pro Val Pro Thr Thr	Ala Ser Pro Ile Ser	Ser Ile Phe
1145	1150	1155
Ser Arg Thr Gly Asp Pro Ala	Pro Asn Gly Ser Lys	Gly Lys Arg
1160	1165	1170
Lys Arg Arg Ala Pro Val Lys	Gln Thr Leu Asn Phe	Asp Leu Leu
1175	1180	1185
Lys Leu Ala Gly Asp Val Glu	Ser Asn Pro Gly Pro	Met Gly Gly
1190	1195	1200
Trp Ser Ser Lys Pro Arg Gln	Gly Met Gly Thr Asn	Leu Ser Val
1205	1210	1215
Pro Asn Pro Leu Gly Phe Phe	Pro Asp His Gln Leu	Asp Pro Ala

1220	1225	1230
Phe Gly Ala Asn Ser Asn Asn	Pro Asp Trp Asp Phe	Asn Pro Asn
1235	1240	1245
Lys Asp His Trp Pro Glu Ala	Asn Gln Val Gly Leu	Glu Gly Gly
1250	1255	1260
Ser Gly Gly Met Glu Asn Thr	Thr Ser Gly Phe Leu	Gly Pro Leu
1265	1270	1275
Leu Val Leu Gln Ala Gly Phe	Phe Leu Leu Thr Arg	Ile Leu Thr
1280	1285	1290
Ile Pro Gln Ser Leu Asp Ser	Trp Trp Thr Ser Leu	Asn Phe Leu
1295	1300	1305
Gly Gly Ala Pro Thr Cys Pro	Gly Gln Asn Ser Gln	Ser Pro Thr
1310	1315	1320
Ser Asn His Ser Pro Thr Ser	Cys Pro Pro Ile Cys	Pro Gly Tyr
1325	1330	1335
Arg Trp Met Cys Leu Arg Arg	Phe Ile Ile Phe Leu	Phe Ile Leu
1340	1345	1350
Leu Leu Cys Leu Ile Phe Leu	Leu Val Leu Leu Asp	Tyr Gln Gly
1355	1360	1365
Met Leu Pro Val Cys Pro Leu	Leu Pro Gly Thr Ser	Thr Thr Ser
1370	1375	1380
Thr Gly Pro Cys Lys Thr Cys	Thr Ile Pro Ala Gln	Gly Thr Ser
1385	1390	1395
Met Phe Pro Ser Cys Cys Cys	Thr Lys Pro Ser Asp	Gly Asn Cys
1400	1405	1410
Thr Cys Ile Pro Ile Pro Ser	Ser Trp Ala Phe Ala	Arg Phe Leu
1415	1420	1425
Trp Glu Trp Ala Ser Val Arg	Phe Ser Trp Leu Ser	Leu Leu Val
1430	1435	1440
Pro Phe Val Gln Trp Phe Val	Gly Leu Ser Pro Thr	Val Trp Leu
1445	1450	1455

Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Asn
1460 1465 1470

Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu
1475 1480 1485

Trp Val Tyr Ile
1490

<210> 14

<211> 4

<212> PRT

<213> Artificial Sequence

<220><223> Linker peptide

<400> 14

Lys Gly Gly Ser

1

<210

> 15

<211> 138

<212> PRT

<213> Hepatitis B virus

<400> 15

Asn Ser Asn Asn Pro Asp Trp Asp Phe Asn Pro Asn Lys Asp His Trp

1 5 10 15

Pro Glu Ala Asn Gln Val Gly Ala Gly Ala Phe Gly Pro Gly Phe Thr

20 25 30

Pro Pro His Gly Gly Leu Leu Gly Trp Ser Pro Gln Ala Gln Gly Ile

35 40 45

Leu Thr Thr Val Pro Ala Ala Pro Pro Pro Ala Ser Thr Asn Arg Gln

50 55 60

Ser Gly Arg Gln Pro Thr Pro Ile Ser Pro Pro Leu Arg Asp Ser His

65 70 75 80

Pro Gln Ala Met Gln Trp Asn Ser Thr Thr Phe His Gln Ala Leu Leu

85 90 95

Asp Pro Arg Val Arg Gly Leu Tyr Phe Pro Ala Gly Gly Ser Ser Ser

100 105 110

Gly Thr Val Asn Pro Val Pro Thr Thr Ala Ser Pro Ile Ser Ser Ile

115 120 125

Phe Ser Arg Thr Gly Asp Pro Ala Pro Asn

130 135

<210> 16

<211> 29

<212> PRT

<213> Hepatitis B virus

<400> 16

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

20 25

<210> 17

<211> 159

<212> PRT

<213>

Hepatitis B virus

<400> 17

Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly Met Asp Ile Asp Pro Tyr

1 5 10 15

Lys Glu Phe Gly Ala Ser Val Glu Leu Leu Ser Phe Leu Pro Ser Asp

20 25 30

Phe Phe Pro Ser Ile Arg Asp Leu Leu Asp Thr Ala Ser Ala Leu Tyr

35 40 45

Arg Glu Ala Leu Glu Ser Pro Glu His Cys Ser Pro His His Thr Ala

50 55 60

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

65 70 75 80

Trp Val Gly Ser Asn Leu Glu Asp Pro Ala Ser Arg Glu Leu Val Val

85 90 95

Ser Tyr Val Asn Val Asn Met Gly Leu Lys Ile Arg Gln Leu Leu Trp

100 105 110

Phe His Ile Ser Cys Leu Thr Phe Gly Arg Glu Thr Val Leu Glu Tyr

115 120 125

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

130 135 140

Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro Glu Thr Thr Val Val

145 150 155

<210> 18

<211> 226

<212> PRT

<213> Hepatitis B virus

<400> 18

Met Glu Asn Thr Thr Ser Gly Phe Leu Gly Pro Leu Leu Val Leu Gln

1 5 10 15

Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu

20 25 30

Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Ala Pro Thr Cys

35 40 45

Pro Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser Pro Thr Ser

50 55 60

Cys Pro Pro Ile Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe

65 70 75 80

Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val

85 90 95

Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Leu Pro Gly

100 105 110

Thr Ser Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Ile Pro Ala

115 120 125

Gln Gly Thr Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp

130 135 140

Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala Arg

145 150 155 160

Phe Leu Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Leu Ser Leu Leu
 165 170 175
 Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu
 180 185 190
 Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Asn Ile
 195 200 205
 Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val
 210 215 220
 Tyr Ile
 225
 <210> 19
 <211> 843
 <212> PRT
 <213> Hepatitis B virus
 <400> 19
 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 Tyr 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 Leu Thr Lys Tyr Leu Pro Leu Asp Lys Gly
 115 120 125
 Ile Lys Pro Tyr Tyr Pro Glu His Ala Val Asn His Tyr Phe Lys 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 His Gly Arg Leu Val Phe Gln Thr Ser Thr Arg His			
	180	185	190
Gly Asp Glu Ser Phe Cys Ser Gln Ser Ser Gly Ile Leu Ser Arg Ser			
	195	200	205
Pro Val Gly Pro Cys Val Arg Ser Gln Leu Lys Gln Ser Arg Leu Gly			
	210	215	220
Leu Gln Pro Gln Gln Gly Ser Leu Ala Arg Gly Lys Ser Gly Arg Ser			
225	230	235	240
Gly Ser Ile Arg Ala Arg Val His Pro Thr Thr Arg Arg Ser Phe Gly			
	245	250	255
Val Glu Pro Ser Gly Ser Gly His Ile Asp Asn Ser Ala Ser Ser Thr			
	260	265	270
Ser Ser Cys Leu His Gln Ser Ala Val Arg Lys Thr Ala Tyr Ser His			
	275	280	285
Leu Ser Thr Ser Lys Arg Gln Ser Ser Ser Gly His Ala Val Glu Leu			
	290	295	300
His Asn Ile Pro Pro Ser Ser Ala Arg Ser Gln Ser Glu Gly Pro Ile			
305	310	315	320
Phe Ser Cys Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Cys Ser Asp			
	325	330	335
Tyr Cys Leu Thr His Ile Val Asn Leu Leu Glu Asp Trp Gly Pro Cys			
	340	345	350
Thr Glu His Gly Glu His Asn Ile Arg Ile Pro Arg Thr Pro Ala Arg			
	355	360	365
Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn Pro His Asn Thr Thr			
	370	375	380

Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Ser Thr
 385 390 395 400
 His Val Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr
 405 410 415
 Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala
 420 425 430

 Ala Phe Tyr His Ile Pro Leu His Pro Ala Ala Met Pro His Leu Leu
 435 440 445
 Val Gly Ser Ser Gly Leu Pro Arg Tyr Val Ala Arg Leu Ser Ser Thr
 450 455 460
 Ser Arg Asn Ile Asn Tyr Gln His Gly Thr Met Gln Asp Leu His Asp
 465 470 475 480
 Ser Cys Ser Arg Asn Leu Tyr Val Ser Leu Leu Leu Leu Tyr Lys Thr
 485 490 495

 Phe Gly Arg Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe
 500 505 510
 Arg Lys Ile Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln
 515 520 525
 Phe Thr Ser Ala Ile Cys Ser Val Val Arg Arg Ala Phe Pro His Cys
 530 535 540
 Leu Ala Phe Ser Tyr Met Asp Asp Val Val Leu Gly Ala Lys Ser Val
 545 550 555 560

 Gln His Leu Glu Ser Leu Phe Thr Ser Ile Thr Asn Phe Leu Leu Ser
 565 570 575
 Leu Gly Ile His Leu Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser
 580 585 590
 Leu Asn Phe Met Gly Tyr Val Ile Gly Ser Trp Gly Thr Leu Pro Gln
 595 600 605
 Glu His Ile Val Leu Lys Ile Lys Gln Cys Phe Arg Lys Leu Pro Val
 610 615 620

 Asn Arg Pro Ile Asp Trp Lys Val Cys Gln Arg Ile Val Gly Leu Leu

625 630 635 640
 Gly Phe Ala Ala Pro Phe Thr Gln Cys Gly Tyr Pro Ala Leu Met Pro
 645 650 655
 Leu Tyr Ala Cys Ile Gln Ser Lys Gln Ala Phe Thr Phe Ser Pro Thr
 660 665 670
 Tyr Lys Ala Phe Leu Cys Lys Gln Tyr Leu Asn Leu Tyr Pro Val Ala
 675 680 685

Arg Gln Arg Ser Gly Leu Cys Gln Val Phe Ala Asp Ala Thr Pro Thr
 690 695 700
 Gly Trp Gly Leu Ala Ile Gly His Arg Arg Met Arg Gly Thr Phe Val
 705 710 715 720
 Ala Pro Leu Pro Ile His Thr Ala Glu Leu Leu Ala Ala Cys Phe Ala
 725 730 735
 Arg Ser Arg Ser Gly Ala Lys Leu Ile Gly Thr Asp Asn Ser Val Val
 740 745 750

Leu Ser Arg Lys Tyr Thr Ser Phe Pro Trp Leu Leu Gly Cys Ala Ala
 755 760 765
 Asn Trp Ile Leu Arg Gly Thr Ser Phe Val Tyr Val Pro Ser Ala Leu
 770 775 780
 Asn Pro Ala Asp Asp Pro Ser Arg Gly Arg Leu Gly Leu Tyr Arg Pro
 785 790 795 800
 Leu Leu His Leu Pro Phe Arg Pro Thr Thr Gly Arg Thr Ser Leu Tyr
 805 810 815

Ala Val Ser Pro Ser Val Pro Ser His Leu Pro Asp Arg Val His Phe
 820 825 830
 Ala Ser Pro Leu His Val Ala Trp Arg Pro Pro
 835 840

<210> 20

<211> 5

<212> PRT

<213> Artificial Sequence

<220><223> Linker peptide

<400> 20

Gly Ser Lys Gly Lys

1 5

<210> 21

<211> 59

<212> PRT

<213> Hepatitis B virus

<400> 21

Met Gly Gly Trp Ser Ser Lys Pro Arg Gln Gly Met Gly Thr Asn Leu

1 5 10 15

Ser Val Pro Asn Pro Leu Gly Phe Phe Pro Asp His Gln Leu Asp Pro

20 25 30

Ala Phe Gly Ala Asn Ser Asn Asn Pro Asp Trp Asp Phe Asn Pro Asn

35 40 45

Lys Asp His Trp Pro Glu Ala Asn Gln Val Gly

50 55

<210> 22

<211> 7

<212> PRT

<213> Artificial Sequence

<220><223> Linker peptide

<400> 22

Leu Glu Gly Gly Ser Gly Gly

1 5

<210> 23

<211> 1539

<212> PRT

<213> Hepatitis B virus

<400> 23

Met Ser Leu Leu Trp Gly Gly Val Thr Val Leu Ala Ala Met Leu Ile

1 5 10 15

Ala Gly Gln Val Ala Ser Val Val Phe Leu Val Ser Lys Ser Gly Pro

20 25 30

Pro Ser Gly Lys Ser Asn Ser Asn Asn Pro Asp Trp Asp Phe Asn Pro
35 40 45

Asn Lys Asp His Trp Pro Glu Ala Asn Gln Val Gly Ala Gly Ala Phe
50 55 60

Gly Pro Gly Phe Thr Pro Pro His Gly Gly Leu Leu Gly Trp Ser Pro
65 70 75 80

Gln Ala Gln Gly Ile Leu Thr Thr Val Pro Ala Ala Pro Pro Pro Ala
85 90 95

Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro Ile Ser Pro Pro
100 105 110

Leu Arg Asp Ser His Pro Gln Ala Met Gln Trp Asn Ser Thr Thr Phe
115 120 125

His Gln Ala Leu Leu Asp Pro Arg Val Arg Gly Leu Tyr Phe Pro Ala
130 135 140

Gly Gly Ser Ser Ser Gly Thr Val Asn Pro Val Pro Thr Thr Ala Ser
145 150 155 160

Pro Ile Ser Ser Ile Phe Ser Arg Thr Gly Asp Pro Ala Pro Asn Gly
165 170 175

Ser Lys Ser Gly Ser Lys Met Pro Leu Ser Tyr Gln His Phe Arg Lys
180 185 190

Leu Leu Leu Leu Asp Asp Glu Ala Gly Pro Leu Glu Glu Glu Leu Pro
195 200 205

Arg Leu Ala Asp Glu Gly Leu Asn Arg Arg Val Ala Glu Asp Leu Asn
210 215 220

Leu Gly Asn Leu Asn Val Ser Ile Pro Trp Thr His Lys Val Gly Asn
225 230 235 240

Phe Thr Gly Leu Ala Ser Ser Thr Val Pro Val Phe Asn Pro Glu Trp
245 250 255

Gln Thr Pro Ser Phe Pro His Ile His Leu Gln Glu Asp Ile Ile Asn
260 265 270

Arg Cys Gln Gln Tyr Val Gly Pro Leu Thr Val Asn Glu Lys Arg Arg

275 280 285
 Leu Lys Leu Ile Met Pro Ala Arg Phe Tyr Pro Asn Leu Thr Lys Tyr
 290 295 300

 Leu Pro Leu Asp Lys Gly Ile Lys Pro Tyr Tyr Pro Glu His Ala Val
 305 310 315 320
 Asn His Tyr Phe Lys Thr Arg His Tyr Leu His Thr Leu Trp Lys Ala
 325 330 335
 Gly Ile Leu Tyr Lys Arg Glu Thr Thr Arg Ser Ala Ser Phe Cys Gly
 340 345 350
 Ser Pro Tyr Ser Trp Glu Gln Glu Leu Gln His Gly Arg Leu Val Phe
 355 360 365

 Gln Thr Ser Thr Arg His Gly Asp Glu Ser Phe Cys Ser Gln Ser Ser
 370 375 380
 Gly Ile Leu Ser Arg Ser Pro Val Gly Pro Cys Val Arg Ser Gln Leu
 385 390 395 400
 Lys Gln Ser Arg Leu Gly Leu Gln Pro Gln Gln Gly Ser Leu Ala Arg
 405 410 415
 Gly Lys Ser Gly Arg Ser Gly Ser Ile Arg Ala Arg Val His Pro Thr
 420 425 430

 Thr Arg Arg Ser Phe Gly Val Glu Pro Ser Gly Ser Gly His Ile Asp
 435 440 445
 Asn Ser Ala Ser Ser Thr Ser Ser Cys Leu His Gln Ser Ala Val Arg
 450 455 460
 Lys Thr Ala Tyr Ser His Leu Ser Thr Ser Lys Arg Gln Ser Ser Ser
 465 470 475 480
 Gly His Ala Val Glu Leu His Asn Ile Pro Pro Ser Ser Ala Arg Ser
 485 490 495

 Gln Ser Glu Gly Pro Ile Phe Ser Ala Trp Trp Leu Gln Phe Arg Asn
 500 505 510
 Ser Lys Pro Ala Ser Asp Tyr Ala Leu Thr His Ile Val Asn Leu Leu
 515 520 525

Glu Asp Trp Gly Pro Ala Thr Glu His Gly Glu His Asn Ile Arg Ile
 530 535 540
 Pro Arg Thr Pro Ala Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys
 545 550 555 560

 Asn Pro His Asn Thr Thr Glu Ser Arg Leu Val Val Asp Phe Ser Gln
 565 570 575
 Phe Ser Arg Gly Ser Thr His Val Ser Trp Pro Lys Phe Ala Val Pro
 580 585 590
 Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu
 595 600 605
 Ser Leu Asp Val Ser Ala Ala Phe Tyr His Ile Pro Leu His Pro Ala
 610 615 620

 Ala Met Pro His Leu Leu Val Gly Ser Ser Gly Leu Pro Arg Tyr Val
 625 630 635 640
 Ala Arg Leu Ser Ser Thr Ser Arg Asn Ile Asn Tyr Gln His Gly Thr
 645 650 655
 Met Gln Asp Leu His Asp Ser Cys Ser Arg Asn Leu Tyr Val Ser Leu
 660 665 670
 Leu Leu Leu Tyr Lys Thr Phe Gly Arg Lys Leu His Leu Tyr Ser His
 675 680 685

 Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser
 690 695 700
 Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Val Arg
 705 710 715 720
 Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val Val
 725 730 735
 Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Phe Thr Ser Ile
 740 745 750

 Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn Lys Thr
 755 760 765
 Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val Ile Gly Ser

770	775	780	
Trp Gly Thr Leu Pro Gln Glu His Ile Val Leu Lys Ile Lys Gln Cys			
785	790	795	800
Phe Arg Lys Leu Pro Val Asn Arg Pro Ile Asp Trp Lys Val Cys Gln			
805	810	815	
Arg Ile Val Gly Leu Leu Gly Phe Ala Ala Pro Phe Thr Gln Cys Gly			
820	825	830	
Tyr Pro Ala Leu Met Pro Leu Tyr Ala Cys Ile Gln Ser Lys Gln Ala			
835	840	845	
Phe Thr Phe Ser Pro Thr Tyr Lys Ala Phe Leu Cys Lys Gln Tyr Leu			
850	855	860	
Asn Leu Tyr Pro Val Ala Arg Gln Arg Ser Gly Leu Cys Gln Val Phe			
865	870	875	880
Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu Ala Ile Gly His Arg Ala			
885	890	895	
Met Arg Gly Thr Phe Val Ala Pro Leu Pro Ile His Thr Ala Glu Leu			
900	905	910	
Leu Ala Ala Cys Phe Ala Arg Ser Arg Ser Gly Ala Lys Leu Ile Gly			
915	920	925	
Thr Asp Asn Ser Val Val Leu Ser Arg Lys Tyr Thr Ser Phe Pro Trp			
930	935	940	
Leu Leu Gly Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe Val			
945	950	955	960
Tyr Val Pro Ser Ala Leu Asn Pro Ala Ala Asp Pro Ser Ala Gly Arg			
965	970	975	
Leu Gly Leu Tyr Arg Pro Leu Leu His Leu Pro Phe Arg Pro Thr Thr			
980	985	990	
Gly Arg Thr Ser Leu Tyr Ala Val Ser Pro Ser Val Pro Ser His Leu			
995	1000	1005	
Pro Asp Arg Val His Phe Ala Ser Pro Leu His Val Ala Trp Arg			
1010	1015	1020	

Pro Pro Ser Lys Ser Pro Gly Ser Gly Pro Pro Met Gln Leu Phe		
1025	1030	1035
His Leu Cys Leu Ile Ile Ser Cys Ser Cys Pro Thr Val Gln Ala		
1040	1045	1050
Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly Met Asp Ile Asp Pro		
1055	1060	1065
Tyr Lys Glu Phe Gly Ala Ser Val Glu Leu Leu Ser Phe Leu Pro		
1070	1075	1080
Ser Asp Phe Phe Pro Ser Ile Arg Asp Leu Leu Asp Thr Ala Ser		
1085	1090	1095
Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys Ser Pro		
1100	1105	1110
His His Thr Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu Leu		
1115	1120	1125
Met Asn Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala		
1130	1135	1140
Ser Arg Glu Leu Val Val Ser Tyr Val Asn Val Asn Met Gly Leu		
1145	1150	1155
Lys Ile Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe		
1160	1165	1170
Gly Arg Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly Val Trp		
1175	1180	1185
Ile Arg Thr Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu		
1190	1195	1200
Ser Thr Leu Pro Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser		
1205	1210	1215
Pro Arg Arg Arg Thr Pro Ser Pro Arg Arg Arg Arg Ser Gln Ser		
1220	1225	1230
Pro Arg Arg Arg Arg Ser Gln Ser Arg Glu Ser Gln Cys Met Gly		
1235	1240	1245
Gly Trp Ser Ser Lys Pro Arg Gln Gly Met Gly Thr Asn Leu Ser		

1250	1255	1260
Val Pro Asn Pro Leu Gly Phe	Phe Pro Asp His Gln	Leu Asp Pro
1265	1270	1275
Ala Phe Gly Ala Asn Ser Asn	Asn Pro Asp Trp Asp	Phe Asn Pro
1280	1285	1290
Asn Lys Asp His Trp Pro Glu	Ala Asn Gln Val Gly	Ala Ser Lys
1295	1300	1305
Gly Gly Lys Ser Gly Met Glu	Asn Thr Thr Ser Gly	Phe Leu Gly
1310	1315	1320
Pro Leu Leu Val Leu Gln Ala	Gly Phe Phe Leu Leu	Thr Arg Ile
1325	1330	1335
Leu Thr Ile Pro Gln Ser Leu	Asp Ser Trp Trp Thr	Ser Leu Asn
1340	1345	1350
Phe Leu Gly Gly Ala Pro Thr	Cys Pro Gly Gln Asn	Ser Gln Ser
1355	1360	1365
Pro Thr Ser Asn His Ser Pro	Thr Ser Cys Pro Pro	Ile Cys Pro
1370	1375	1380
Gly Tyr Arg Trp Met Cys Leu	Arg Arg Phe Ile Ile	Phe Leu Phe
1385	1390	1395
Ile Leu Leu Leu Cys Leu Ile	Phe Leu Leu Val Leu	Leu Asp Tyr
1400	1405	1410
Gln Gly Met Leu Pro Val Cys	Pro Leu Leu Pro Gly	Thr Ser Thr
1415	1420	1425
Thr Ser Thr Gly Pro Cys Lys	Thr Cys Thr Ile Pro	Ala Gln Gly
1430	1435	1440
Thr Ser Met Phe Pro Ser Cys	Cys Cys Thr Lys Pro	Ser Asp Gly
1445	1450	1455
Asn Cys Thr Cys Ile Pro Ile	Pro Ser Ser Trp Ala	Phe Ala Arg
1460	1465	1470
Phe Leu Trp Glu Trp Ala Ser	Val Arg Phe Ser Trp	Leu Ser Leu
1475	1480	1485

Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val
 1490 1495 1500
 Trp Leu Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu
 1505 1510 1515
 Tyr Asn Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe
 1520 1525 1530
 Cys Leu Trp Val Tyr Ile
 1535

<210> 24

<211> 7143

<212> DNA

<213> Artificial Sequence

<220><223> Vaccine construct

<400> 24

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tctataataa tacattaata tcatccgatg gtgctagggt tatttggatg gatgcgtata	120
aattttcttg cggtttatct ttacaagact attgttatca ttggggtagc aaaccagaga	180
gccgaccatt cgatttaata aaaaaatcag atgctaaacg caattctaaa tcgttgggtca	240
aagaatctat ggcacacctg aaatccttgi acgaggcatt cgagacacaa tcaggagcgt	300
tagaagtttt aatgagtcca tgtaggatgt ttctgttttc tagaatagaa gacatgttct	360
taactagtgt cattaataga gtatccgaga atactggaat ggggatgtat taccctacca	420
acgatatacc ttctctatct atcgaatcat ctatctgtct agattatatt atagtaaata	480
atcaggaatc caacaaatat cgtatcaaat ctgttctcga tatcatttct tcaaaacaat	540
accctgcagg acgtcccaac tacgttaaaa atggtacaaa aggaaagttat tatatcgcgt	600
tgtgtaaagt taccgtacct actaacgacc atattccagt agtttatcac gatgatgaca	660
atactaccac ctttattaca gtattgacgt ccgtcgatat tgaaactgct atcagagcag	720
gatattcgat agtcgaatta ggggctttac aatgggataa taatattcca gaacttaaaa	780
acggtttact ggatagtatc aagatgattt atgacttgaa cgcagttaca acaataaatt	840
tattggaaca gctcatagaa aatattaact ttaacaactc tagtataatt tcgttgtttt	900
atacatttgc cattagttat tgccgagcat tcatttactc aattatggaa accatagatc	960
cgggtgtatat atctcagttc agttataaag aattatacgt tagtagctct tataaagata	1020
ttaatgaatc catgagtcag atggtaaaat tataaaaagt gaaaaacaat attattttta	1080

tcgttggttg ttacactatg tctctgctgt ggggcggagt gacagtgtg gccgctatgc	1140
tgattgctgg acaggtggcc agcgtggtgt tcttggtgtc taagtctgga cctcctagcg	1200
gcaagagcaa cagcaacaac cccgactggg acttcaaccc caacaaggac cattggccag	1260
aggccaatca agtcggagcc ggcgcttttg gccctggctt tacacctcct catggcggac	1320
tgcttggatg gtcacctcag gctcagggca tcttgacaac agtgccctgct gctccacctc	1380
ctgccagcac caatagacag tctggcagac agcccacacc tatcagccct cactgagag	1440
acagccatcc tcaggccatg cagtggaaaca gcaccacctt tcatcaggcc ctgctggacc	1500
ctagagtgcg gggcctttat ttctctgccg gcggatctag cagcggcacc gtgaatcctg	1560
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acggcagcaa gtctggctcc aagatgcccc tgagctacca gcacttcaga aaactgctgc	1680
tgctggacga cgaggccgga cctctggaag aagaactgcc tagactggcc gacgagggcc	1740
tgaatagaag agtggccgag gacctgaacc tgggcaacct gaatgtgtct atcccctgga	1800
cacacaaagt gggcaacttc acaggcctgg ccagctctac cgtgcctgtg ttcaatcccg	1860
agtggcagac cctagcttc cctcacatcc atctgcaaga ggacatcacc aaccggtgcc	1920
agcagtlactg gggccctctg accgtgaacg agaagcggag actgaagctg atcatgcccc	1980
ccagattcta cccaacctg accaagtacc tgcctctgga caagggcacc aagccttact	2040
accctgagca cgccgtgaac cactacttca agaccggca ctacctgcac accctgtgga	2100
aggccggcat cctgtataag agagagacaa ccagaagcgc cagcttctgc ggcagccctt	2160
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gcgacgagtc ttctgcagc cagagcagcg gaatcctgag cagatctcct gtgggacctt	2280
gtgtgcggag ccagctgaaa cagagtagac tgggcctgca gcctcagcag ggatctctgg	2340
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gaagctttgg cgtcagacct agcggctccg gccacatcga taatagcgc agcagcacca	2460
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 ttaaaccgca taatatctta ctttttgatt ccaatgaacc aataataatt catctaaagg 7080
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aag 7143

<210> 25

<211> 1524

<212> PRT

<213> Artificial Sequence

<220><223> Vaccine construct

<400> 25

Met Ser Leu Leu Trp Gly Gly Val Thr Val Leu Ala Ala Met Leu Ile

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Ala Gly Gln Val Ala Ser Val Val Phe Leu Val Lys Gly Gly Gly Pro

20 25 30

Gly Gly Gly Met Gln Leu Phe His Leu Cys Leu Ile Ile Ser Cys Ser

35 40 45

Cys Pro Thr Val Gln Ala Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly

50 55 60

Met Asp Ile Asp Pro Tyr Lys Glu Phe Gly Ala Ser Val Glu Leu Leu

65 70 75 80

Ser Phe Leu Pro Ser Asp Phe Phe Pro Ser Ile Arg Asp Leu Leu Asp

85 90 95

Thr Ala Ser Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys

100	105	110	
Ser Pro His His Thr Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu			
115	120	125	
Leu Met Asn Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala			
130	135	140	
Ser Arg Glu Leu Val Val Ser Tyr Val Asn Val Asn Met Gly Leu Lys			
145	150	155	160
Ile Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly Arg			
165	170	175	
Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly Val Trp Ile Arg Thr			
180	185	190	
Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro			
195	200	205	
Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg Thr			
210	215	220	
Pro Ser Pro Arg Arg Arg Arg Ser Gln Ser Pro Arg Arg Arg Arg Ser			
225	230	235	240
Gln Ser Arg Glu Ser Gln Cys Gly Gly Gly Ser Gly Gly Gly Met Pro			
245	250	255	
Leu Ser Tyr Gln His Phe Arg Lys Leu Leu Leu Leu Asp Asp Glu Ala			
260	265	270	
Gly Pro Leu Glu Glu Glu Leu Pro Arg Leu Ala Asp Glu Gly Leu Asn			
275	280	285	
Arg Arg Val Ala Glu Asp Leu Asn Leu Gly Asn Leu Asn Val Ser Ile			
290	295	300	
Pro Trp Thr His Lys Val Gly Asn Phe Thr Gly Leu Ala Ser Ser Thr			
305	310	315	320
Val Pro Val Phe Asn Pro Glu Trp Gln Thr Pro Ser Phe Pro His Ile			
325	330	335	
His Leu Gln Glu Asp Ile Ile Asn Arg Cys Gln Gln Tyr Val Gly Pro			
340	345	350	

Leu Thr Val Asn Glu Lys Arg Arg Leu Lys Leu Ile Met Pro Ala Arg

355 360 365

Phe Tyr Pro Asn Leu Thr Lys Tyr Leu Pro Leu Asp Lys Gly Ile Lys

370 375 380

Pro Tyr Tyr Pro Glu His Ala Val Asn His Tyr Phe Lys Thr Arg His

385 390 395 400

Tyr Leu His Thr Leu Trp Lys Ala Gly Ile Leu Tyr Lys Arg Glu Thr

405 410 415

Thr Arg Ser Ala Ser Phe Cys Gly Ser Pro Tyr Ser Trp Glu Gln Glu

420 425 430

Leu Gln His Gly Arg Leu Val Phe Gln Thr Ser Thr Arg His Gly Asp

435 440 445

Glu Ser Phe Cys Ser Gln Ser Ser Gly Ile Leu Ser Arg Ser Pro Val

450 455 460

Gly Pro Cys Val Arg Ser Gln Leu Lys Gln Ser Arg Leu Gly Leu Gln

465 470 475 480

Pro Gln Gln Gly Ser Leu Ala Arg Gly Lys Ser Gly Arg Ser Gly Ser

485 490 495

Ile Arg Ala Arg Val His Pro Thr Thr Arg Arg Ser Phe Gly Val Glu

500 505 510

Pro Ser Gly Ser Gly His Ile Asp Asn Ser Ala Ser Ser Thr Ser Ser

515 520 525

Cys Leu His Gln Ser Ala Val Arg Lys Thr Ala Tyr Ser His Leu Ser

530 535 540

Thr Ser Lys Arg Gln Ser Ser Ser Gly His Ala Val Glu Leu His Asn

545 550 555 560

Ile Pro Pro Ser Ser Ala Arg Ser Gln Ser Glu Gly Pro Ile Phe Ser

565 570 575

Ala Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Ala Ser Asp Tyr Ala

580 585 590

Leu Thr His Ile Val Asn Leu Leu Glu Asp Trp Gly Pro Ala Thr Glu

595 600 605
 His Gly Glu His Asn Ile Arg Ile Pro Arg Thr Pro Ala Arg Val Thr

 610 615 620
 Gly Gly Val Phe Leu Val Asp Lys Asn Pro His Asn Thr Thr Glu Ser
 625 630 635 640
 Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Ser Thr His Val
 645 650 655
 Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu
 660 665 670
 Leu Ser Ser Asn Leu Ser Thr Phe Gly Arg Lys Leu His Leu Tyr Ser

 675 680 685
 His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu
 690 695 700
 Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Val
 705 710 715 720
 Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val
 725 730 735
 Val Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Phe Thr Ser

 740 745 750
 Ile Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn Lys
 755 760 765
 Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val Ile Gly
 770 775 780
 Ser Trp Gly Thr Leu Pro Gln Glu His Ile Val Leu Lys Ile Lys Gln
 785 790 795 800
 Cys Phe Arg Lys Leu Pro Val Asn Arg Pro Ile Asp Trp Lys Val Cys

 805 810 815
 Gln Arg Ile Val Gly Leu Leu Gly Phe Ala Ala Pro Phe Thr Gln Cys
 820 825 830
 Gly Tyr Pro Ala Leu Met Pro Leu Tyr Ala Cys Ile Gln Ser Lys Gln
 835 840 845

Ala Phe Thr Phe Ser Pro Thr Tyr Lys Ala Phe Leu Cys Lys Gln Tyr
850 855 860
Leu Asn Leu Tyr Pro Val Ala Arg Gln Arg Ser Gly Leu Cys Gln Val
865 870 875 880
Phe Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu Ala Ile Gly His Arg
885 890 895
Ala Met Arg Gly Thr Phe Val Ala Pro Leu Pro Ile His Thr Ala Glu
900 905 910
Leu Leu Ala Ala Cys Phe Ala Arg Ser Arg Ser Gly Ala Lys Leu Ile
915 920 925
Gly Thr Asp Asn Ser Val Val Leu Ser Arg Lys Tyr Thr Ser Phe Pro
930 935 940
Trp Leu Leu Gly Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe
945 950 955 960
Val Tyr Val Pro Ser Ala Leu Asn Pro Ala Ala Asp Pro Ser Ala Gly
965 970 975
Arg Leu Gly Leu Tyr Arg Pro Leu Leu His Leu Pro Phe Arg Pro Thr
980 985 990
Thr Gly Arg Thr Ser Leu Tyr Ala Val Ser Pro Ser Val Pro Ser His
995 1000 1005
Leu Pro Asp Arg Val His Phe Ala Ser Pro Leu His Val Ala Trp
1010 1015 1020
Arg Pro Pro Lys Ser Pro Asn Ser Asn Asn Pro Asp Trp Asp Phe
1025 1030 1035
Asn Pro Asn Lys Asp His Trp Pro Glu Ala Asn Gln Val Gly Ala
1040 1045 1050
Gly Ala Phe Gly Pro Gly Phe Thr Pro Pro His Gly Gly Leu Leu
1055 1060 1065
Gly Trp Ser Pro Gln Ala Gln Gly Ile Leu Thr Thr Val Pro Ala
1070 1075 1080
Ala Pro Pro Pro Ala Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro

1085	1090	1095
Thr Pro Ile Ser Pro Pro Leu	Arg Asp Ser His Pro	Gln Ala Met
1100	1105	1110
Gln Trp Asn Ser Thr Thr Phe	His Gln Ala Leu Leu	Asp Pro Arg
1115	1120	1125
Val Arg Gly Leu Tyr Phe Pro	Ala Gly Gly Ser Ser	Ser Gly Thr
1130	1135	1140
Val Asn Pro Val Pro Thr Thr	Ala Ser Pro Ile Ser	Ser Ile Phe
1145	1150	1155
Ser Arg Thr Gly Asp Pro Ala	Pro Asn Gly Ser Lys	Gly Lys Arg
1160	1165	1170
Lys Arg Arg Ala Pro Val Lys	Gln Thr Leu Asn Phe	Asp Leu Leu
1175	1180	1185
Lys Leu Ala Gly Asp Val Glu	Ser Asn Pro Gly Pro	Met Asp Ala
1190	1195	1200
Met Lys Arg Gly Leu Cys Cys	Val Leu Leu Leu Cys	Gly Ala Val
1205	1210	1215
Phe Val Ser Pro Ser Gln Glu	Ile His Ala Arg Phe	Arg Arg Met
1220	1225	1230
Gly Gly Trp Ser Ser Lys Pro	Arg Gln Gly Met Gly	Thr Asn Leu
1235	1240	1245
Ser Val Pro Asn Pro Leu Gly	Phe Phe Pro Asp His	Gln Leu Asp
1250	1255	1260
Pro Ala Phe Gly Ala Asn Ser	Asn Asn Pro Asp Trp	Asp Phe Asn
1265	1270	1275
Pro Asn Lys Asp His Trp Pro	Glu Ala Asn Gln Val	Gly Leu Glu
1280	1285	1290
Gly Gly Ser Gly Gly Met Glu	Asn Thr Thr Ser Gly	Phe Leu Gly
1295	1300	1305
Pro Leu Leu Val Leu Gln Ala	Gly Phe Phe Leu Leu	Thr Arg Ile
1310	1315	1320

Leu Thr Ile Pro Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn
 1325 1330 1335
 Phe Leu Gly Gly Ala Pro Thr Cys Pro Gly Gln Asn Ser Gln Ser
 1340 1345 1350
 Pro Thr Ser Asn His Ser Pro Thr Ser Cys Pro Pro Ile Cys Pro
 1355 1360 1365
 Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile Ile Phe Leu Phe
 1370 1375 1380
 Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val Leu Leu Asp Tyr
 1385 1390 1395
 Gln Gly Met Leu Pro Val Cys Pro Leu Leu Pro Gly Thr Ser Thr
 1400 1405 1410
 Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Ile Pro Ala Gln Gly
 1415 1420 1425
 Thr Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp Gly
 1430 1435 1440
 Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala Arg
 1445 1450 1455
 Phe Leu Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Leu Ser Leu
 1460 1465 1470
 Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val
 1475 1480 1485
 Trp Leu Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu
 1490 1495 1500
 Tyr Asn Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe
 1505 1510 1515
 Cys Leu Trp Val Tyr Ile
 1520
 <210> 26
 <211> 1571
 <212> PRT
 <213> Artificial Sequence

<220><223> Vaccine construct

<400> 26

Met Ser Leu Leu Trp Gly Gly Val Thr Val Leu Ala Ala Met Leu Ile

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Ala Gly Gln Val Ala Ser Val Val Phe Leu Val Ser Lys Ser Gly Pro

20 25 30
Pro Ser Gly Lys Ser Asn Ser Asn Asn Pro Asp Trp Asp Phe Asn Pro

35 40 45
Asn Lys Asp His Trp Pro Glu Ala Asn Gln Val Gly Ala Gly Ala Phe

50 55 60
Gly Pro Gly Phe Thr Pro Pro His Gly Gly Leu Leu Gly Trp Ser Pro

65 70 75 80
Gln Ala Gln Gly Ile Leu Thr Thr Val Pro Ala Ala Pro Pro Pro Ala

85 90 95
Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro Ile Ser Pro Pro

100 105 110
Leu Arg Asp Ser His Pro Gln Ala Met Gln Trp Asn Ser Thr Thr Phe

115 120 125
His Gln Ala Leu Leu Asp Pro Arg Val Arg Gly Leu Tyr Phe Pro Ala

130 135 140
Gly Gly Ser Ser Ser Gly Thr Val Asn Pro Val Pro Thr Thr Ala Ser

145 150 155 160
Pro Ile Ser Ser Ile Phe Ser Arg Thr Gly Asp Pro Ala Pro Asn Gly

165 170 175
Ser Lys Ser Gly Ser Lys Met Pro Leu Ser Tyr Gln His Phe Arg Lys

180 185 190
Leu Leu Leu Leu Asp Asp Glu Ala Gly Pro Leu Glu Glu Glu Leu Pro

195 200 205
Arg Leu Ala Asp Glu Gly Leu Asn Arg Arg Val Ala Glu Asp Leu Asn

210 215 220
Leu Gly Asn Leu Asn Val Ser Ile Pro Trp Thr His Lys Val Gly Asn

225 230 235 240
 Phe Thr Gly Leu Ala Ser Ser Thr Val Pro Val Phe Asn Pro Glu Trp
 245 250 255
 Gln Thr Pro Ser Phe Pro His Ile His Leu Gln Glu Asp Ile Ile Asn

 260 265 270
 Arg Cys Gln Gln Tyr Val Gly Pro Leu Thr Val Asn Glu Lys Arg Arg
 275 280 285
 Leu Lys Leu Ile Met Pro Ala Arg Phe Tyr Pro Asn Leu Thr Lys Tyr
 290 295 300
 Leu Pro Leu Asp Lys Gly Ile Lys Pro Tyr Tyr Pro Glu His Ala Val
 305 310 315 320
 Asn His Tyr Phe Lys Thr Arg His Tyr Leu His Thr Leu Trp Lys Ala

 325 330 335
 Gly Ile Leu Tyr Lys Arg Glu Thr Thr Arg Ser Ala Ser Phe Cys Gly
 340 345 350
 Ser Pro Tyr Ser Trp Glu Gln Glu Leu Gln His Gly Arg Leu Val Phe
 355 360 365
 Gln Thr Ser Thr Arg His Gly Asp Glu Ser Phe Cys Ser Gln Ser Ser
 370 375 380
 Gly Ile Leu Ser Arg Ser Pro Val Gly Pro Cys Val Arg Ser Gln Leu

 385 390 395 400
 Lys Gln Ser Arg Leu Gly Leu Gln Pro Gln Gln Gly Ser Leu Ala Arg
 405 410 415
 Gly Lys Ser Gly Arg Ser Gly Ser Ile Arg Ala Arg Val His Pro Thr
 420 425 430
 Thr Arg Arg Ser Phe Gly Val Glu Pro Ser Gly Ser Gly His Ile Asp
 435 440 445
 Asn Ser Ala Ser Ser Thr Ser Ser Cys Leu His Gln Ser Ala Val Arg

 450 455 460
 Lys Thr Ala Tyr Ser His Leu Ser Thr Ser Lys Arg Gln Ser Ser Ser
 465 470 475 480

Gly His Ala Val Glu Leu His Asn Ile Pro Pro Ser Ser Ala Arg Ser
485 490 495

Gln Ser Glu Gly Pro Ile Phe Ser Ala Trp Trp Leu Gln Phe Arg Asn
500 505 510

Ser Lys Pro Ala Ser Asp Tyr Ala Leu Thr His Ile Val Asn Leu Leu
515 520 525

Glu Asp Trp Gly Pro Ala Thr Glu His Gly Glu His Asn Ile Arg Ile
530 535 540

Pro Arg Thr Pro Ala Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys
545 550 555 560

Asn Pro His Asn Thr Thr Glu Ser Arg Leu Val Val Asp Phe Ser Gln
565 570 575

Phe Ser Arg Gly Ser Thr His Val Ser Trp Pro Lys Phe Ala Val Pro
580 585 590

Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu
595 600 605

Ser Leu Asp Val Ser Ala Ala Phe Tyr His Ile Pro Leu His Pro Ala
610 615 620

Ala Met Pro His Leu Leu Val Gly Ser Ser Gly Leu Pro Arg Tyr Val
625 630 635 640

Ala Arg Leu Ser Ser Thr Ser Arg Asn Ile Asn Tyr Gln His Gly Thr
645 650 655

Met Gln Asp Leu His Asp Ser Cys Ser Arg Asn Leu Tyr Val Ser Leu
660 665 670

Leu Leu Leu Tyr Lys Thr Phe Gly Arg Lys Leu His Leu Tyr Ser His
675 680 685

Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser
690 695 700

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

Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val Val

725 730 735
 Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Phe Thr Ser Ile
 740 745 750
 Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn Lys Thr
 755 760 765
 Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val Ile Gly Ser

 770 775 780
 Trp Gly Thr Leu Pro Gln Glu His Ile Val Leu Lys Ile Lys Gln Cys
 785 790 795 800
 Phe Arg Lys Leu Pro Val Asn Arg Pro Ile Asp Trp Lys Val Cys Gln
 805 810 815
 Arg Ile Val Gly Leu Leu Gly Phe Ala Ala Pro Phe Thr Gln Cys Gly
 820 825 830
 Tyr Pro Ala Leu Met Pro Leu Tyr Ala Cys Ile Gln Ser Lys Gln Ala

 835 840 845
 Phe Thr Phe Ser Pro Thr Tyr Lys Ala Phe Leu Cys Lys Gln Tyr Leu
 850 855 860
 Asn Leu Tyr Pro Val Ala Arg Gln Arg Ser Gly Leu Cys Gln Val Phe
 865 870 875 880
 Ala Asp Ala Thr Pro Thr Gly Trp Gly Leu Ala Ile Gly His Arg Ala
 885 890 895
 Met Arg Gly Thr Phe Val Ala Pro Leu Pro Ile His Thr Ala Glu Leu

 900 905 910
 Leu Ala Ala Cys Phe Ala Arg Ser Arg Ser Gly Ala Lys Leu Ile Gly
 915 920 925
 Thr Asp Asn Ser Val Val Leu Ser Arg Lys Tyr Thr Ser Phe Pro Trp
 930 935 940
 Leu Leu Gly Cys Ala Ala Asn Trp Ile Leu Arg Gly Thr Ser Phe Val
 945 950 955 960
 Tyr Val Pro Ser Ala Leu Asn Pro Ala Ala Asp Pro Ser Ala Gly Arg

 965 970 975

Leu Gly Leu Tyr Arg Pro Leu Leu His Leu Pro Phe Arg Pro Thr Thr
 980 985 990
 Gly Arg Thr Ser Leu Tyr Ala Val Ser Pro Ser Val Pro Ser His Leu
 995 1000 1005
 Pro Asp Arg Val His Phe Ala Ser Pro Leu His Val Ala Trp Arg
 1010 1015 1020
 Pro Pro Ser Lys Ser Pro Gly Ser Gly Pro Pro Met Gln Leu Phe
 1025 1030 1035
 His Leu Cys Leu Ile Ile Ser Cys Ser Cys Pro Thr Val Gln Ala
 1040 1045 1050
 Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly Met Asp Ile Asp Pro
 1055 1060 1065
 Tyr Lys Glu Phe Gly Ala Ser Val Glu Leu Leu Ser Phe Leu Pro
 1070 1075 1080
 Ser Asp Phe Phe Pro Ser Ile Arg Asp Leu Leu Asp Thr Ala Ser
 1085 1090 1095
 Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys Ser Pro
 1100 1105 1110
 His His Thr Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu Leu
 1115 1120 1125
 Met Asn Leu Ala Thr Trp Val Gly Ser Asn Leu Glu Asp Pro Ala
 1130 1135 1140
 Ser Arg Glu Leu Val Val Ser Tyr Val Asn Val Asn Met Gly Leu
 1145 1150 1155
 Lys Ile Arg Gln Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe
 1160 1165 1170
 Gly Arg Glu Thr Val Leu Glu Tyr Leu Val Ser Phe Gly Val Trp
 1175 1180 1185
 Ile Arg Thr Pro Pro Ala Tyr Arg Pro Pro Asn Ala Pro Ile Leu
 1190 1195 1200
 Ser Thr Leu Pro Glu Thr Thr Val Val Arg Arg Arg Gly Arg Ser

1205	1210	1215
Pro Arg Arg Arg Thr Pro Ser	Pro Arg Arg Arg Arg	Ser Gln Ser
1220	1225	1230
Pro Arg Arg Arg Arg Ser Gln	Ser Arg Glu Ser Gln	Cys Met Asp
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1250	1255	1260
Val Phe Val Ser Pro Ser Gln	Glu Ile His Ala Arg	Phe Arg Arg

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1280	1285	1290
Leu Ser Val Pro Asn Pro Leu	Gly Phe Phe Pro Asp	His Gln Leu
1295	1300	1305
Asp Pro Ala Phe Gly Ala Asn	Ser Asn Asn Pro Asp	Trp Asp Phe
1310	1315	1320
Asn Pro Asn Lys Asp His Trp	Pro Glu Ala Asn Gln	Val Gly Ala

1325	1330	1335
Ser Lys Gly Gly Lys Ser Gly	Met Glu Asn Thr Thr	Ser Gly Phe
1340	1345	1350
Leu Gly Pro Leu Leu Val Leu	Gln Ala Gly Phe Phe	Leu Leu Thr
1355	1360	1365
Arg Ile Leu Thr Ile Pro Gln	Ser Leu Asp Ser Trp	Trp Thr Ser
1370	1375	1380
Leu Asn Phe Leu Gly Gly Ala	Pro Thr Cys Pro Gly	Gln Asn Ser

1385	1390	1395
Gln Ser Pro Thr Ser Asn His	Ser Pro Thr Ser Cys	Pro Pro Ile
1400	1405	1410
Cys Pro Gly Tyr Arg Trp Met	Cys Leu Arg Arg Phe	Ile Ile Phe
1415	1420	1425
Leu Phe Ile Leu Leu Leu Cys	Leu Ile Phe Leu Leu	Val Leu Leu
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Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Leu Pro Gly Thr

1445 1450 1455

Ser Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Ile Pro Ala

1460 1465 1470

Gln Gly Thr Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser

1475 1480 1485

Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe

1490 1495 1500

Ala Arg Phe Leu Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Leu

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<400> 28

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<400> 31

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1 5

<210> 33

<211> 9

<212> PRT

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<400> 33

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<210> 34

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<400> 34

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1 5

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<211> 1097

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【심사관 직권보정사항】

【직권보정 1】

【보정항목】 청구범위

【보정세부항목】 청구항 8

【변경전】

제1항 또는 제2항에 있어서, 상기 HBV 프레-코어, HBV 코어 및 변형된 폴리머라제(Pmut)가 융합 단백질로

서 발현되도록 정렬되어 있는, 멀티-HBV 면역원 바이러스 벡터 백신.

【변경후】

제1항 또는 제2항에 있어서, HBV 프레-코어, HBV 코어 및 변형된 폴리머라제(Pmut)가 융합 단백질로서 발현되도록 정렬되어 있는, 멀티-HBV 면역원 바이러스 벡터 백신.