



등록특허 10-2535670



(19) 대한민국특허청(KR)

(12) 등록특허공보(B1)

(45) 공고일자 2023년05월22일

(11) 등록번호 10-2535670

(24) 등록일자 2023년05월18일

(51) 국제특허분류(Int. Cl.)
C07K 14/075 (2006.01) A61K 39/00 (2006.01)
A61K 39/12 (2006.01) C12N 15/86 (2006.01)
(52) CPC특허분류
C07K 14/075 (2013.01)
A61K 39/12 (2013.01)
(21) 출원번호 10-2017-7037436
(22) 출원일자(국제) 2016년06월10일
심사청구일자 2021년03월23일
(85) 번역문제출일자 2017년12월27일
(65) 공개번호 10-2018-0011265
(43) 공개일자 2018년01월31일
(86) 국제출원번호 PCT/EP2016/063329
(87) 국제공개번호 WO 2016/198621
국제공개일자 2016년12월15일
(30) 우선권주장
PCT/EP2015/063248 2015년06월12일
유럽특허청(EPO)(EP)
(뒷면에 계속)
(56) 선행기술조사문헌
KR1020100105630 A
KR1020110116144 A

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전체 청구항 수 : 총 12 항

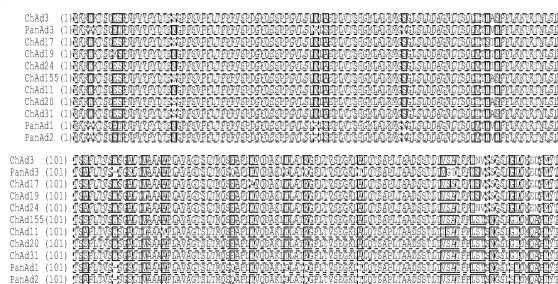
심사관 : 문명순

(54) 발명의 명칭 아데노바이러스 폴리뉴클레오타이드 및 폴리펩티드

(57) 요약

단리된 폴리뉴클레오타이드가 특히 제공되며, 상기 폴리뉴클레오타이드는 (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드, (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 기능성 유도체, 및 (c) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드로 구성된 군으로부터 선택되는 폴리펩티드를 인코딩한다.

대표도



(52) CPC특허분류

C12N 15/86 (2013.01)

A61K 2039/5256 (2013.01)

C12N 2710/10321 (2013.01)

C12N 2710/10343 (2013.01)

C12N 2740/16234 (2013.01)

C12N 2760/18534 (2013.01)

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1510357.5 2015년06월12일 영국(GB)

1514772.1 2015년08월19일 영국(GB)

명세서

청구범위

청구항 1

- (a) SEQ ID NO: 3에 따른 아미노산 서열로 이루어진 아데노바이러스 펜톤 폴리펩티드;
- (b) SEQ ID NO: 5에 따른 아미노산 서열로 이루어진 아데노바이러스 핵소 폴리펩티드;
- (c) SEQ ID NO: 1에 따른 아미노산 서열로 이루어진 아데노바이러스 섬유 폴리펩티드; 및
- (d) 자연 발생 아데노바이러스에 존재하거나 이로부터 단리한 것이 아닌 항원 단백질을 인코딩하는 단리된 재조합 아데노바이러스 폴리뉴클레오티드로서,

상기 단리된 재조합 아데노바이러스 폴리뉴클레오티드는 E1A, E1B, E2A, E2B, E3 및 E4로 구성된 군으로부터 선택된 아데노바이러스 유전체 영역의 적어도 하나의 유전자의 결실을 포함하고, 상기 결실은 아데노바이러스 폴리뉴클레오티드의 백본 내로 재조합적으로 도입됨으로써 상기 유전자를 비-기능성이 되도록 하는 것인, 단리된 재조합 아데노바이러스 폴리뉴클레오티드.

청구항 2

제1항의 단리된 재조합 아데노바이러스 폴리뉴클레오티드 및 약학적으로 허용되는 부형제를 포함하는 면역원성 조성물.

청구항 3

제1항의 단리된 재조합 아데노바이러스 폴리뉴클레오티드를 포함하는, 단리된 숙주 세포.

청구항 4

제3항에 있어서, 상기 단리된 숙주 세포는 현탁액에서 성장될 수 있는 것인, 단리된 숙주 세포.

청구항 5

제1항에 있어서, 상기 폴리뉴클레오티드는 하기로 구성된 군으로부터 선택된 하나 이상을 포함하는, 단리된 재조합 아데노바이러스 폴리뉴클레오티드:

- (a) 아데노바이러스 5'-역 말단 반복(ITR);
- (b) E1A_{280R} 및 E1A_{243R} 영역으로부터 선택되는 아데노바이러스 E1A 영역;
- (c) E1B_{19K} 및 E1B_{55K}로 구성된 군으로부터 선택되는 아데노바이러스 E1B, 또는 IX 영역;
- (d) E2B_{pTP}, E2B_{중합효소} 및 E2B_{IVa2} 영역으로 구성된 군으로부터 선택되는 아데노바이러스 E2B 영역;
- (e) L1_{13.6K} 단백질, L1_{52K} 및 L1_{pIIIa} 단백질로 구성된 군으로부터 선택되는 아데노바이러스 L1 영역;
- (f) L2_{펜톤} 단백질, L2_{pVII} 단백질, L2_V 단백질 및 L2_{pX} 단백질로 구성된 군으로부터 선택되는 아데노바이러스 L2 영역;
- (g) L3_{pVI} 단백질, L3_{핵소} 단백질 및 L3_{프로테아제}로 구성된 군으로부터 선택되는 아데노바이러스 L3 영역;
- (h) 아데노바이러스 E2A 영역;
- (i) L4_{100k} 단백질, L4_{33K} 단백질 및 단백질 L4_{VIII}로 구성된 군으로부터 선택되는 아데노바이러스 L4 영역;
- (j) E3 ORF1, E3 ORF2, E3 ORF3, E3 ORF4, E3 ORF5, E3 ORF6, E3 ORF7, E3 ORF8, 및 E3 ORF9로 구성된 군으로부터 선택되는 아데노바이러스 E3 영역;
- (k) 아데노바이러스 L5 영역;
- (l) E4 ORF7, E4 ORF6, E4 ORF4, E4 ORF3, E4 ORF2 및 E4 ORF1으로 구성된 군으로부터 선택되는 아데노바이러스

스 E4 영역; 및

(m) 아데노바이러스 3'-ITR.

청구항 6

제5항에 있어서, VAI 또는 VAII RNA 영역을 추가로 포함하는, 폴리뉴클레오티드.

청구항 7

제6항에 있어서, VAI 또는 VAII RNA 영역이 Ad5로부터 유래되는, 폴리뉴클레오티드.

청구항 8

제1항에 있어서, 유전체 영역은 E1A, E1B, 또는 이의 조합인, 폴리뉴클레오티드.

청구항 9

제1항에 있어서, 재조합 아데노바이러스 폴리뉴클레오티드는 숙주 세포로 감염시 복제 결함(replication-incompetent)인 폴리뉴클레오티드.

청구항 10

제2항에 있어서, 상기 조성물은 투여시 포유동물 대상체에서 면역 반응을 유도하는 것인, 면역원성 조성물.

청구항 11

제1항에 있어서, 상기 폴리뉴클레오티드는 동일한 항원 단백질을 인코딩하는 PanAd3 아데노바이러스 벡터에 비해 숙주 세포로 감염시 인코딩된 항원 단백질의 더 높은 발현을 생성하는, 단리된 재조합 아데노바이러스 폴리뉴클레오티드.

청구항 12

제1항에 있어서, 상기 폴리뉴클레오티드는 동일한 항원 단백질을 인코딩하는 PanAd3 아데노바이러스 벡터에 비해 숙주 세포로 감염시 세포 당 더 많은 바이러스 입자를 생성시키는 것인, 단리된 재조합 아데노바이러스 폴리뉴클레오티드.

청구항 13

삭제

청구항 14

삭제

청구항 15

삭제

청구항 16

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청구항 68

삭제

발명의 설명

기술 분야

[0001] 본 발명은 신규한 침팬지 아데노바이러스 ChAd155로부터 유래된 단리된 폴리뉴클레오티드 및 폴리펩티드 서열, 및 상기 폴리뉴클레오티드 및 폴리펩티드 서열을 포함하는 재조합 폴리뉴클레오티드, 벡터, 아데노바이러스, 세포 및 조성물에 관한 것이다.

배경 기술

[0002] 아데노바이러스는 다양한 표적 조직에서 매우 효과적인 유전자 전달 및 큰 트랜스진(transgene) 용량을 달성하는 이의 능력으로 인해 유전자 전달 용도로 널리 사용되어 왔다. 통상적으로, 아데노바이러스의 E1 유전자는 결실되고, 선택 프로모터, 관심 유전자의 cDNA 서열 및 poly A 신호로 구성된 트랜스진 카세트에 대체되어, 복제 결합 재조합 바이러스를 발생시킨다.

[0003] 재조합 아데노바이러스는 유전자 요법 및 백신으로 유용하다. 침팬지 아데노바이러스를 기초로 한 바이러스 벡터는 유전학적 백신의 개발을 위한 인간 유래 Ad 벡터의 사용에 대한 대안이다. 침팬지로부터 단리된 아데노바이러스는 인간 기원의 세포에서의 이들의 효율적인 증식에 의해 입증된 바와 같이 인간으로부터 단리된 아데노바이러스와 밀접한 관련이 있다. 그러나, 인간 및 침팬지 아데노바이러스는 밀접하게 관련이 있어, 2개의 바이러스 종 사이의 혈청학적 교차 반응성이 가능하다.

[0004] 분자를 표적에 효과적으로 전달하고, 집단 내 선택된 아데노바이러스 혈청형에 대한 기존 면역의 효과를 최소화하는 벡터에 대한 요구가 있다. 인간에서 관찰되는 기존 면역의 한 양태는 체액성 면역이며, 이는 아데노바이러스 단백질에 특이적인 항체의 생성 및 지속을 발생시킬 수 있다. 아데노바이러스에 의해 유도된 체액성 반응은 주로 섬유, 펜톤 및 핵소의 3개의 주요 구조 캡시드 단백질에 대해 유도된다.

[0005] 본 발명의 벡터, 조성물 및 방법은 선행 기술에 비해 높은 생산성, 개선된 면역원성 및 증가된 트랜스진 발현을 포함하나 이에 제한되지는 않는 하나 이상의 개선된 특징을 가질 수 있다.

발명의 내용

[0006] 단리된 폴리뉴클레오티드가 제공되며, 상기 폴리뉴클레오티드는 하기로 구성된 군으로부터 선택되는 폴리펩티드를 인코딩한다:

[0007] (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드,

[0008] (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 기능성 유도체, 및

[0009] (c) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드.

[0010] 또한, 하기로 구성된 군으로부터 선택되는 폴리뉴클레오티드를 포함하는 재조합 폴리뉴클레오티드가 제공된다:

[0011] (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드,

[0012] (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체를 인코딩하는 폴리뉴클레오티드로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 폴리뉴클레오티드, 및

[0013] (c) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드.

[0014] 또한, 하기로 구성된 군으로부터 선택되는 폴리뉴클레오티드를 포함하는 재조합 벡터가 제공된다:

- [0015] (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드,
- [0016] (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체를 인코딩하는 폴리뉴클레오티드로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 폴리뉴클레오티드, 및
- [0017] (c) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드,
- [0018] 또한, 하기로 구성된 군으로부터 선택되는 적어도 하나의 폴리뉴클레오티드 또는 폴리펩티드를 포함하는 재조합 아데노바이러스가 제공된다:
- [0019] (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드,
- [0020] (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체를 인코딩하는 폴리뉴클레오티드로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 폴리뉴클레오티드,
- [0021] (c) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드,
- [0022] (d) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드,
- [0023] (e) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 기능성 유도체, 및
- [0024] (f) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드,
- [0025] 또한, 하기 중 적어도 하나 및 약학적으로 허용되는 부형제를 포함하는 조성물이 제공된다:
- [0026] (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드,
- [0027] (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체를 인코딩하는 폴리뉴클레오티드로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 폴리뉴클레오티드,
- [0028] (c) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드,
- [0029] (d) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드,
- [0030] (e) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 기능성 유도체,
- [0031] (f) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드,
- [0032] (g) 상기 (a), (b) 또는 (c)에 기재된 바와 같은 폴리뉴클레오티드를 포함하는 벡터, 및
- [0033] (h) 상기 (a), (b) 또는 (c)에 기재된 바와 같은 폴리뉴클레오티드를 포함하는 재조합 아데노바이러스.
- [0034] 또한, 하기 중 적어도 하나 및 약학적으로 허용되는 부형제를 포함하는 세포가 제공된다:
- [0035] (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드,
- [0036] (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체를 인코딩하는 폴리뉴클레오티드로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 폴리뉴클레오티드,
- [0037] (c) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드,
- [0038] (d) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드,
- [0039] (e) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 기능성 유도체,
- [0040] (f) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드,
- [0041] (g) 상기 (a), (b) 또는 (c)에 기재된 바와 같은 폴리뉴클레오티드를 포함하는 벡터, 및

- [0042] (h) 상기 (a), (b) 또는 (c)에 기재된 바와 같은 폴리뉴클레오티드를 포함하는 재조합 아데노바이러스.
- [0043] 또한, 하기로 구성된 군으로부터 선택되는 단리된 아데노바이러스 폴리펩티드가 제공된다:
- [0044] (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드,
- [0045] (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 기능성 유도체, 및
- [0046] (c) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드.
- [0047] 또한, SEQ ID NO: 6에 따른 서열을 포함하거나 이로 구성되는 단리된 폴리뉴클레오티드, 벡터, 재조합 아데노바이러스, 조성물 또는 세포가 제공된다.

도면의 간단한 설명

- [0048] 도 1a-c - 표시된 유인원 아데노바이러스로부터의 섬유 단백질 서열의 정렬.

ChAd3 (SEQ ID NO:27)

PanAd3 (SEQ ID NO:28)

ChAd17 (SEQ ID NO:29)

ChAd19 (SEQ ID NO:30)

ChAd24 (SEQ ID NO:31)

ChAd155 (SEQ ID NO:1)

ChAd11 (SEQ ID NO:32)

ChAd20 (SEQ ID NO:33)

ChAd31 (SEQ ID NO:34)

PanAd1 (SEQ ID NO:35)

PanAd2 (SEQ ID NO:36)

도 2 - 특정 ChAd155 BAC 및 플라스미드 벡터의 생성을 위한 흐름도

도 3 - 종 C BAC 셔틀(Shuttle) #1365 개략도

도 4 - pArsChAd155 Ad5E4orf6-2 (#1490) 개략도

도 5 - pChAd155/RSV 개략도

도 6 - BAC ChAd155/RSV 개략도

도 7 - HIV Gag 트랜스진을 발현하는 ChAd3 및 ChAd155 벡터의 생산성(실험 1)

도 8 - HIV Gag 트랜스진을 발현하는 ChAd3 및 ChAd255 벡터의 생산성(실험 2)

도 9 - RSV 트랜스진을 발현하는 PanAd3 및 ChAd155 벡터의 생산성

도 10 - HIV Gag 트랜스진을 발현하는 ChAd3 및 ChAd155 벡터의 발현 수준

도 11 - HIV Gag 트랜스진을 발현하는 PanAd3 및 ChAd155 벡터의 발현 수준 - 웨스턴 블롯

도 12 - HIV Gag 트랜스진을 발현하는 ChAd3 및 ChAd155 벡터의 면역원성 - IFN-감마 ELISpot

도 13 - HIV Gag 트랜스진을 발현하는 PanAd3 및 ChAd155 벡터의 면역원성 - IFN-감마 ELISpot

발명을 실시하기 위한 구체적인 내용

- [0049] 서열의 설명

- [0050] SEQ ID NO: 1 - ChAd155 섬유의 폴리펩티드 서열

[0051]	SEQ ID NO: 2 - ChAd155 섬유를 인코딩하는 폴리뉴클레오티드 서열
[0052]	SEQ ID NO: 3 - ChAd155 펜톤의 폴리펩티드 서열
[0053]	SEQ ID NO: 4 - ChAd155 펜톤을 인코딩하는 폴리뉴클레오티드 서열
[0054]	SEQ ID NO: 5 - ChAd155 핵손의 폴리펩티드 서열
[0055]	SEQ ID NO: 6 - ChAd155 핵손을 인코딩하는 폴리뉴클레오티드 서열
[0056]	SEQ ID NO: 7 - ChAd155#1434를 인코딩하는 폴리뉴클레오티드 서열
[0057]	SEQ ID NO: 8 - ChAd155#1390을 인코딩하는 폴리뉴클레오티드 서열
[0058]	SEQ ID NO: 9 - ChAd155#1375를 인코딩하는 폴리뉴클레오티드 서열
[0059]	SEQ ID NO: 10 - 야생형 ChAd155를 인코딩하는 폴리뉴클레오티드 서열
[0060]	SEQ ID NO: 11 - ChAd155/RSV를 인코딩하는 폴리뉴클레오티드 서열
[0061]	SEQ ID NO: 12 - CASI 프로모터를 인코딩하는 폴리뉴클레오티드 서열
[0062]	SEQ ID NO: 13 - Ad5orf6 프라이머 1 폴리뉴클레오티드 서열
[0063]	SEQ ID NO: 14 - Ad5orf6 프라이머 2 폴리뉴클레오티드 서열
[0064]	SEQ ID NO: 15 - BAC/CHAd155 ΔE1_TetO hCMV RpsL-Kana 프라이머 1 폴리뉴클레오티드 서열
[0065]	SEQ ID NO: 16 - BAC/CHAd155 ΔE1_TetO hCMV RpsL-Kana (#1375) 프라이머 2 폴리뉴클레오티드 서열
[0066]	SEQ ID NO: 17 - 1021-FW E4 Del Step1 프라이머 폴리뉴클레오티드 서열
[0067]	SEQ ID NO: 18 - 1022-RW E4 Del Step1 프라이머 폴리뉴클레오티드 서열
[0068]	SEQ ID NO: 19 - 1025-FW E4 Del Step2 프라이머 폴리뉴클레오티드 서열
[0069]	SEQ ID NO: 20 - 1026-RW E4 Del Step2 프라이머 폴리뉴클레오티드 서열
[0070]	SEQ ID NO: 21 - 91-SubMonte FW 프라이머 폴리뉴클레오티드 서열
[0071]	SEQ ID NO: 22 - 890-BghPolyA RW 프라이머 폴리뉴클레오티드 서열
[0072]	SEQ ID NO: 23 - CMVfor 프라이머 폴리뉴클레오티드 서열
[0073]	SEQ ID NO: 24 - CMVrev 프라이머 폴리뉴클레오티드 서열
[0074]	SEQ ID NO: 25 - CMVFAM-TAMRA qPCR 프로브 폴리뉴클레오티드 서열
[0075]	SEQ ID NO: 26 - 우드척(Woodchuck) 간염 바이러스 전사후 조절 요소(WPRE) 폴리뉴클레오티드 서열
[0076]	SEQ ID NO: 27 - ChAd3의 섬유 단백질에 대한 아미노산 서열
[0077]	SEQ ID NO: 28 - PanAd3의 섬유 단백질에 대한 아미노산 서열
[0078]	SEQ ID NO: 29 - ChAd17의 섬유 단백질에 대한 아미노산 서열
[0079]	SEQ ID NO: 30 - ChAd19의 섬유 단백질에 대한 아미노산 서열
[0080]	SEQ ID NO: 31 - ChAd24의 섬유 단백질에 대한 아미노산 서열
[0081]	SEQ ID NO: 32 - ChAd11의 섬유 단백질에 대한 아미노산 서열
[0082]	SEQ ID NO: 33 - ChAd20의 섬유 단백질에 대한 아미노산 서열
[0083]	SEQ ID NO: 34 - ChAd31의 섬유 단백질에 대한 아미노산 서열
[0084]	SEQ ID NO: 35 - PanAd1의 섬유 단백질에 대한 아미노산 서열
[0085]	SEQ ID NO: 36 - PanAd2의 섬유 단백질에 대한 아미노산 서열
[0086]	SEQ ID NO: 37 - RSV F ΔTM 아미노산 서열

- [0087] SEQ ID NO: 38 - HIV Gag 폴리뉴클레오티드 서열
- [0088] **발명의 상세한 설명**
- [0089] **아데노바이러스**
- [0090] 아데노바이러스는 3개의 주요 단백질인 핵손(II), 펜톤 베이스(III) 및 노브형 섬유(knobbed fiber)(IV)와 함께 다수의 다른 작은 단백질들인 VI, VIII, IX, IIIa 및 IVa2를 포함하는 정이십면체 캡시드를 갖는 특징적인 형태를 갖는다. 바이러스 유전체는 선형의 이중 가닥 DNA이다. 바이러스 DNA는 고도의 베이스 단백질 VII 및 작은 캡시드 pX(이전에는, 뮤로 언급됨)와 밀접하게 회합되어 있다. 또 다른 단백질인 V가 상기 DNA-단백질 복합체와 함께 패키징되고, 단백질 VI를 통해 캡시드에 대한 구조적 연결을 제공한다. 상기 바이러스는 또한 성숙한 감염성 바이러스를 생성하기 위해 일부 구조 단백질의 가공에 필요한 바이러스-인코딩된 프로테아제를 함유한다.
- [0091] 아데노바이러스 유전체는 잘 특성규명되어 있다. 유사하게 위치되는 특정 오픈 리딩 프레임과 관련하여 아데노바이러스 유전체의 전체적인 구성, 예를 들어, 각각의 바이러스의 E1A, E1B, E2A, E2B, E3, E4, L1, L2, L3, L4 및 L5 유전자의 위치에서의 전반적인 보존이 존재한다. 아데노바이러스 유전체의 각각의 말단은 바이러스 복제에 필요한 역 말단 반복(ITR)으로 공지된 서열을 포함한다. 상기 바이러스는 또한 감염성 비리온을 생성하는데 필요한 일부 구조 단백질을 가공하는데 필요한 바이러스-인코딩된 프로테아제를 포함한다. 아데노바이러스 유전체의 구조는 바이러스 유전자가 숙주 세포 형질도입 후에 발현되는 순서에 기초하여 기재된다. 더욱 특히, 바이러스 유전자는 전사가 DNA 복제의 개시 전 또는 후에 발생하는지에 따라 초기(E) 또는 후기(L) 유전자로 언급된다. 형질도입의 초기 단계에서, 아데노바이러스의 E1A, E1B, E2A, E2B, E3 및 E4 유전자가 발현되어 숙주 세포가 바이러스를 복제하도록 준비시킨다. 감염의 후기 단계 동안, 바이러스 입자의 구조 성분을 인코딩하는 후기 유전자 L1-L5의 발현이 활성화된다.
- [0092] 아데노바이러스는 종 특이적이며, 다양한 혈청형, 즉, 항체에 의해 교차-중화되지 않는 바이러스의 유형이 다양한 포유동물 종으로부터 분리되었다. 예를 들어, 서열 상동성 및 적혈구 세포를 응집시키는 능력을 기초로 하여 6개의 하위그룹(A-F; B는 B1 및 B2로 세분됨)으로 나뉘는 50개 초과 혈청형이 인간으로부터 분리되었다(Tatsis and Ertl *Molecular Therapy* (2004) 10:616-629). 다수의 아데노바이러스가 비인간 유인원, 예를 들어, 침팬지, 보노보, 히말라야 원숭이(rhesus macaque) 및 고릴라로부터 분리되었고, 이들은 핵손 또는 섬유 서열에 기초한 계통발생학적 관계를 기초로 하여 동일한 인간 그룹으로 분류된다(Colloca *et al.* (2012) *ScienceTranslational Medicine* 4:1-9; Roy *et al.* (2004) *Virology* 324: 361-372; Roy *et al.* (2010) *Journal of Gene Medicine* 13:17-25).
- [0093] **섬유 단백질을 포함하는 아데노바이러스 캡시드 단백질 및 이들 단백질을 인코딩하는 폴리뉴클레오티드**
- [0094] 상기 개시된 바와 같이, 아데노바이러스 캡시드는 3개의 주요 단백질인 핵손, 펜톤 및 섬유를 포함한다. 핵손은 캡시드의 구조 성분의 대부분을 차지하며, 이는 240개의 삼량체 핵손 캡소미어 및 12개의 펜톤 베이스로 구성된다. 핵손은 3개의 보존된 이중 배럴을 가지며, 상단은 3개의 타워(tower)를 갖고, 각각의 타워는 캡시드 대부분을 형성하는 각각의 서브유닛으로부터의 루프를 함유한다. 핵손의 베이스는 아데노바이러스 혈청형 사이에 고도로 보존되어 있는 반면, 표면 루프는 가변적이다(Tatsis and Ertl *Molecular Therapy* (2004) 10:616-629).
- [0095] 펜톤은 섬유가 부착하는 오랑체 베이스를 형성하는 또 다른 아데노바이러스 캡시드 단백질이다. 삼량체 섬유 단백질은 캡시드의 12개의 꼭지점 각각에서 펜톤 베이스로부터 돌출되어 있으며, 노브형 막대-유사 구조이다. 대부분의 다른 정이십면체 바이러스의 것과 비교하여 아데노바이러스 캡시드의 표면에서의 현저한 차이는 길고 얇은 섬유 단백질의 존재이다. 섬유 단백질의 주요 역할은 세포 수용체와의 상호작용을 통해 세포 표면에 바이러스 캡시드를 테더링(tethering)시키는 것이다.
- [0096] 많은 아데노바이러스 혈청형의 섬유 단백질은 N-말단 꼬리, 반복 서열로 이루어진 중심 축, 및 C-말단 구형 노브 도메인(또는 "헤드")의 공통 구조를 공유한다. 중심축 도메인은 다양한 수의 베타-반복으로 구성된다. 베타-반복은 연결되어 매우 견고하고 안정적인 3개의 얇은 나선형 가닥의 연장된 구조를 형성한다. 상기 축은 N-말단 꼬리와 구형 노브 구조를 연결하며, 이는 표적 세포 수용체와의 상호작용을 담당한다. 아데노바이러스 노브 도메인의 구형 특성은 수용체를 측면 및 정점으로 결합시키기 위한 큰 표면을 제공한다. 이러한 구조의 효과는 수용체-결합 부위를 바이러스 캡시드로부터 멀리 떨어져서 돌출시킴으로써 바이러스가 비교적 편평한 캡시드 표면에 의해 제공되는 입체적 구속으로부터 자유롭게 하는 것이다.
- [0097] 많은 아데노바이러스 혈청형의 섬유는 동일한 전반적인 구조를 갖지만, 이들은 이들의 기능뿐만 아니라 구조에

영향을 미치는 다양한 아미노산 서열을 갖는다. 예를 들어, 섬유 노브의 표면 상의 다수의 노출된 영역은 용이하게 적응 가능한 수용체 결합 부위를 제공한다. 섬유 노브의 구형 형태는 수용체가 노브의 측면 또는 섬유 노브의 상단에 결합되도록 한다. 이들 결합 부위는 통상적으로 인간 아데노바이러스 사이에서 불량하게 보존되는 베타-가닥을 연결하는 표면-노출 루프 상에 놓여 있다. 이들 루프 상의 노출된 측쇄는 3차 및 4차 구조를 유지하면서 노브에 다양한 표면 특징을 제공한다. 예를 들어, 노브 표면에서의 정전기 전위 및 전하 분포는 Ad 8, Ad 19 및 Ad 37에 대한 약 9의 pI로부터 하위그룹 B 아데노바이러스에 대한 약 5까지의 섬유 노브 서열에서의 광범위한 등전점으로 인해 다양할 수 있다. 구조적으로 복잡한 바이러스 리간드로서, 섬유 단백질은 바이러스 캡시드로부터 다수의 배향 및 거리(축)의 다양한 결합 표면(노브)의 제시를 가능하게 한다.

[0098] 일부 혈청형 사이의 가장 명백한 변화 중 하나는 섬유 길이이다. 섬유 축의 길이가 노브 및 바이러스와 이의 표적 수용체의 상호작용에 강하게 영향을 미치는 것이 연구에서 제시되었다. 또한, 혈청형 사이의 섬유 단백질은 또한 이들의 회는 능력이 다양할 수 있다. 축의 베타-반복은 매우 안정적이고 규칙적인 구조를 형성하나, 전자현미경(EM) 연구는 섬유 내에 별개의 힌지를 나타내었다. 여러 아데노바이러스 혈청형 섬유로부터의 단백질 서열의 분석은 EM에 의해 관찰되는 바와 같이 축 내의 힌지 중 하나와 강하게 연관된 N-말단 꼬리로부터의 세번째 베타-반복에서의 축의 반복 서열에서의 파괴를 정확하게 지적한다. 섬유 내의 힌지는 노브가 바이러스 캡시드와 관련된 다양한 배향을 채택하는 것을 가능하게 하며, 이는 노브 상의 수용체 결합 부위의 정확한 제시를 요구하는 수용체 연동에 대한 입체적 방해로 회피할 수 있다. 따라서, 예를 들어, 하위그룹 D Ad의 단단한 섬유는 이들이 스스로 뒤틀 수 없으므로 바이러스 부착을 위해 가요성 수용체 또는 사전배치된 수용체를 필요로 한다. (Nicklin et al *Molecular Therapy* 2005 12:384-393)

[0099] 다양한 Ad 혈청형에 대한 특정 세포 수용체의 확인 및 이들이 조직 향성에 기여하는 방법의 지식은 섬유 슈도타이핑(pseudotyping) 기술의 사용을 통해 달성되었다. 일부 하위그룹의 Ad가 일차 수용체로 CAR을 이용하나, 많은 Ad가 대안적 일차 수용체를 이용하여 시험관 내 및 생체 내에서 광범위하게 다양한 향성을 발생시키는 것이 명백해지고 있다. 이들 혈청형의 섬유는 이들의 일차 및 삼차 구조에서 섬유 축 강성, 섬유 축 길이, 및 CAR 결합 부위 및/또는 추정 HSPG 결합 모티프의 결핍과 같은 명백한 차이와 함께 섬유 노브 내에서의 순 전하의 차이를 나타낸다. 따라서, 대안적 섬유 축 및 노브로 Ad 5 입자를 슈도타이핑하는 것은 중요한 세포 결합 도메인을 제거할 기회를 제공하며, 또한 Ad 5로 달성된 것에 비해 규정된 세포 유형으로의 더욱 효과적인(및 잠재적으로 더 높은 세포-선택적인) 트랜스진 전달을 가능하게 할 수 있다. 섬유-슈도타이핑된 Ad 입자의 중화는 또한 백터의 성공적인 투여를 촉진하는 상황인 사용되는 섬유가 인간 또는 실험 모델에서 더 낮은 혈청유병률(seroprevalence)을 갖는 Ad로부터 유래되는 경우에 감소될 수 있다(Nicklin et al *Molecular Therapy* (2005) 12:384-393). 또한, 핵소 또는 펜톤 단독은 아니지만 전장 섬유뿐만 아니라 단리된 섬유 노브 영역은 수지상 세포 성숙을 유도할 수 있고, 효능 있는 CD8+ T 세포 반응의 유도과 관련이 있다(Molinier-Frenkel et al. *J. Biol. Chem.* (2003) 278:37175-37182). 종합하면, 아데노바이러스 섬유는 아데노바이러스 백터의 적어도 수용체-결합 및 면역원성에서 중요한 역할을 한다.

[0100] 그룹 C 유인원 아데노바이러스의 섬유 단백질 사이의 차이를 예시하는 것이 도 1에 제공된 정렬이다. 이들 아데노바이러스의 섬유 서열이 ChAd155와 같이 긴 섬유를 갖는 것, 또는 ChAd3와 같이 짧은 섬유를 갖는 것으로 광범위하게 그룹화될 수 있다는 것이 두드러진 특징이다. 이러한 길이 차이는 긴 섬유에 비해 짧은 섬유에서 대략 위치 321에서의 36개의 아미노산 결실로 인한 것이다. 또한, 짧은 섬유 하위그룹과 긴 섬유 하위그룹 사이에서는 상이하나 각각의 하위그룹 내에서는 일치하는 다수의 아미노산 치환이 존재한다. 이들 차이의 정확한 기능은 아직 밝혀지지 않았으나, 섬유의 기능 및 면역원성을 고려할 때, 이들은 유의한 것으로 보인다. 바이러스 향성의 결정인자 중 하나가 섬유 축의 길이인 것이 밝혀졌다. 더 짧은 축을 갖는 Ad5 백터가 CAR 수용체에 대한 결합의 더 낮은 효율 및 더 낮은 감염성을 갖는 것이 입증되었다(Ambriovic-Ristov A. et al.: *Virology*. (2003) 312(2):425-33). 이러한 손상은 세포 수용체에 대한 덜 효율적인 부착을 발생시키는 더 짧은 섬유의 증가된 강성의 결과인 것으로 추측되었다(Wu, E et al.: *J Virology*. (2003) 77(13): 7225-7235). 이들 연구는 더 짧은 축을 갖는 섬유를 갖는 이전에 기재된 ChAd3 및 PanAd3과 비교하여 더 길고 더욱 가요성인 섬유를 갖는 ChAd155의 개선된 특성을 설명할 수 있다.

[0101] 본 발명의 일 양태에서, 침팬지 아데노바이러스 ChAd155의 단리된 섬유, 펜톤 및 핵소 캡시드 폴리펩티드 및 침팬지 아데노바이러스 ChAd155의 섬유, 펜톤 및 핵소 캡시드 폴리펩티드를 인코딩하는 단리된 폴리뉴클레오티드가 제공된다.

[0102] 3개 모두의 캡시드 단백질은 낮은 혈청유병률에 기여할 것으로 예상되며, 따라서 미리 존재하는 중화 항체에 대한 아데노바이러스의 친화성을 억제하기 위해, 예를 들어, 감소된 혈청유병률을 갖는 재조합 아데노바이러스를

제조하기 위해 서로 독립적으로 또는 조합하여 사용될 수 있다. 상기 재조합 아데노바이러스는 ChAd155로부터의 적어도 하나의 섬유 단백질과 함께 상이한 혈청형으로부터의 캡시드 단백질을 갖는 키메라 아데노바이러스일 수 있다.

- [0103] ChAd155 섬유 폴리펩티드 서열은 SEQ ID NO: 1에 제공된다.
- [0104] ChAd155 펜톤 폴리펩티드 서열은 SEQ ID NO: 3에 제공된다.
- [0105] ChAd155 핵소 폴리펩티드 서열은 SEQ ID NO: 5에 제공된다.
- [0106] ChAd155 섬유의 폴리펩티드 서열 또는 이의 기능성 유도체를 포함하는 폴리펩티드, 재조합 아데노바이러스, 조성물 또는 세포
- [0107] 적합하게는, 본 발명의 단리된 폴리펩티드, 재조합 아데노바이러스, 조성물 또는 세포는 SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드를 포함한다.
- [0108] 적합하게는, 본 발명의 폴리펩티드, 재조합 아데노바이러스, 조성물 또는 세포는 SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체인 폴리펩티드를 포함하며, 상기 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는다. 적합하게는, SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80%, 예를 들어, 적어도 85.0%, 예를 들어, 적어도 90%, 예를 들어, 적어도 91.0%, 예를 들어, 적어도 93.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 98.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99.2%, 예를 들어, 적어도 99.4%, 예를 들어, 99.5%, 예를 들어, 적어도 99.6%, 예를 들어, 적어도 99.8%, 예를 들어, 99.9% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 1에 비해 130개 이하, 더욱 적합하게는 120개 이하, 더욱 적합하게는 110개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.
- [0109] 적합하게는, 본 발명에 따른 폴리펩티드, 재조합 아데노바이러스, 조성물 또는 세포는 하기를 추가로 포함한다:
- [0110] (a) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드; 또는
- [0111] (b) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 3의 아미노산 서열과 적어도 50.0% 동일한 아미노산 서열을 갖는, 기능성 유도체,
- [0112] 및/또는
- [0113] (a) SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드; 또는
- [0114] (b) SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 5의 아미노산 서열과 적어도 50% 동일한 아미노산 서열을 갖는, 기능성 유도체.
- [0115] 적합하게는, SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 3의 아미노산 서열과 적어도 60.0%, 예를 들어, 적어도 70.0%, 예를 들어, 적어도 80.0%, 예를 들어, 적어도 85.0%, 예를 들어, 적어도 90.0%, 예를 들어, 적어도 91.0%, 예를 들어, 적어도 93.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 98.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99.2%, 예를 들어, 적어도 99.4%, 예를 들어, 99.5%, 예를 들어, 적어도 99.6%, 예를 들어, 99.7%, 예를 들어, 적어도 99.8%, 예를 들어, 99.9% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 3에 비해 300개 이하, 더욱 적합하게는 250개 이하, 더욱 적합하게는 200개 이하, 더욱 적합하게는 150개 이하, 더욱 적합하게는 125개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.
- [0116] 적합하게는, SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 5의 아미노산 서열과 적어도 60.0%, 예를 들어, 적어도 70.0%, 예를 들어, 적어도 80.0%, 예를 들어, 적

어도 85.0%, 예를 들어, 적어도 90.0%, 예를 들어, 적어도 91.0%, 예를 들어, 적어도 93.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 98.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99.2%, 예를 들어, 적어도 99.4%, 예를 들어, 99.5%, 예를 들어, 적어도 99.6%, 예를 들어, 99.7%, 예를 들어, 적어도 99.8%, 예를 들어, 99.9% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 5에 비해 500개 이하, 더욱 적합하게는 400개 이하, 더욱 적합하게는 450개 이하, 더욱 적합하게는 300개 이하, 더욱 적합하게는 250개 이하, 더욱 적합하게는 200개 이하, 더욱 적합하게는 150개 이하, 더욱 적합하게는 125개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.

- [0117] ChAd155 펜톤의 폴리펩티드 서열을 포함하는 폴리펩티드, 재조합 아데노바이러스, 조성물 또는 세포
- [0118] 적합하게는, 본 발명의 폴리펩티드, 재조합 아데노바이러스, 조성물 또는 세포는 SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드를 포함한다.
- [0119] 적합하게는, 본 발명의 폴리펩티드, 재조합 아데노바이러스, 조성물 또는 세포는 하기를 추가로 포함한다:
- [0120] (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드; 또는
- [0121] (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는, 기능성 유도체
- [0122] 및/또는
- [0123] (a) SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드; 또는
- [0124] (b) SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 5의 아미노산 서열과 적어도 60% 동일한 아미노산 서열을 갖는, 기능성 유도체.
- [0125] 적합하게는, SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 60.0%, 예를 들어, 적어도 70.0%, 예를 들어, 적어도 80.0%, 예를 들어, 적어도 85.0%, 예를 들어, 적어도 87.0%, 예를 들어, 적어도 89.0%, 예를 들어, 적어도 91.0%, 예를 들어, 적어도 93.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 98.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99.2%, 예를 들어, 적어도 99.4%, 예를 들어, 99.5%, 예를 들어, 적어도 99.6%, 예를 들어, 적어도 99.8%, 예를 들어, 99.9% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 1에 비해 130개 이하, 더욱 적합하게는 120개 이하, 더욱 적합하게는 110개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.
- [0126] 적합하게는, SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 5의 아미노산 서열과 적어도 60.0%, 예를 들어, 적어도 70.0%, 예를 들어, 적어도 80.0%, 예를 들어, 적어도 85.0%, 예를 들어, 적어도 90.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99.2%, 예를 들어, 적어도 99.4%, 예를 들어, 99.5%, 예를 들어, 적어도 99.6%, 예를 들어, 적어도 99.8%, 예를 들어, 99.9% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 5에 비해 500개 이하, 더욱 적합하게는 400개 이하, 더욱 적합하게는 450개 이하, 더욱 적합하게는 300개 이하, 더욱 적합하게는 250개 이하, 더욱 적합하게는 200개 이하, 더욱 적합하게는 150개 이하, 더욱 적합하게는 125개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.

- [0127] ChAd155 섬유 또는 이의 기능성 유도체를 인코딩하는 폴리뉴클레오티드를 포함하는 단리된 폴리뉴클레오티드, 벡터, 재조합 아데노바이러스, 조성물 또는 세포
- [0128] 적합하게는, 본 발명의 단리된 폴리뉴클레오티드, 벡터, 재조합 아데노바이러스, 조성물 또는 세포는 SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드를 포함한다. 적합하게는, 폴리뉴클레오티드는 SEQ ID NO: 2에 따른 서열을 갖는다.
- [0129] 대안적으로, 본 발명의 폴리뉴클레오티드, 벡터, 재조합 아데노바이러스, 조성물 또는 세포는 SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체를 인코딩하는 폴리뉴클레오티드를 포함하며, 상기 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80% 동일한 아미노산 서열을 갖는다. 적합하게는, SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 80%, 예를 들어, 적어도 85.0%, 예를 들어, 적어도 90%, 예를 들어, 적어도 91.0%, 예를 들어, 적어도 93.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 98.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99%, 예를 들어, 적어도 99.4%, 예를 들어, 적어도 99.6%, 예를 들어, 적어도 99.8% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 1에 비해 130개 이하, 더욱 적합하게는 120개 이하, 더욱 적합하게는 110개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.
- [0130] 적합하게는, 본 발명의 폴리뉴클레오티드, 벡터, 재조합 아데노바이러스, 조성물 또는 세포는 하기를 인코딩하는 폴리뉴클레오티드를 추가로 포함한다:
- [0131] (a) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드; 또는
- [0132] (b) SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 3의 아미노산 서열과 적어도 50.0% 동일한 아미노산 서열을 갖는, 기능성 유도체,
- [0133] 및/또는
- [0134] (a) SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드; 또는
- [0135] (b) SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 5의 아미노산 서열과 적어도 50% 동일한 아미노산 서열을 갖는, 기능성 유도체.
- [0136] 적합하게는, SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 3의 아미노산 서열과 적어도 60.0%, 예를 들어, 적어도 70.0%, 예를 들어, 적어도 80.0%, 예를 들어, 적어도 85.0%, 예를 들어, 적어도 90.0%, 예를 들어, 적어도 91.0%, 예를 들어, 적어도 93.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 98.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99%, 예를 들어, 적어도 99.4%, 예를 들어, 적어도 99.6%, 예를 들어, 적어도 99.8% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 3에 비해 300개 이하, 더욱 적합하게는 250개 이하, 더욱 적합하게는 200개 이하, 더욱 적합하게는 150개 이하, 더욱 적합하게는 125개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.
- [0137] 적합하게는, SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 5의 아미노산 서열과 적어도 60.0%, 예를 들어, 적어도 70.0%, 예를 들어, 적어도 80.0%, 예를 들어, 적어도 85.0%, 예를 들어, 적어도 90.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 98.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99.2%, 예를 들어, 적어도 99.4%, 예를 들어, 99.5%, 예를 들어, 적어도 99.6%, 예를 들어, 99.7%, 예를 들어, 적어도 99.8%, 예를 들어, 99.9% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 5에 비해 500개 이하, 더욱 적합하게는 400개 이하, 더욱

적합하게는 450개 이하, 더욱 적합하게는 300개 이하, 더욱 적합하게는 250개 이하, 더욱 적합하게는 200개 이하, 더욱 적합하게는 150개 이하, 더욱 적합하게는 125개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.

[0138] ChAd155 펜톤을 인코딩하는 폴리뉴클레오티드를 포함하는 단리된 폴리뉴클레오티드, 벡터, 재조합 아데노바이러스, 조성물 또는 세포

[0139] 적합하게는, 본 발명의 단리된 폴리뉴클레오티드, 벡터, 재조합 아데노바이러스, 조성물 또는 세포는 SEQ ID NO: 3에 따른 아미노산 서열을 갖는 폴리펩티드를 인코딩하는 폴리뉴클레오티드를 포함한다. 적합하게는, 폴리뉴클레오티드는 SEQ ID NO: 4에 따른 서열을 갖는다.

[0140] 적합하게는, 본 발명의 폴리뉴클레오티드, 벡터, 재조합 아데노바이러스, 조성물 또는 세포는 하기를 인코딩하는 폴리뉴클레오티드를 추가로 포함한다:

[0141] (a) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드; 또는

[0142] (b) SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 50% 동일한 아미노산 서열을 갖는, 기능성 유도체

[0143] 및/또는

[0144] (a) SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드; 또는

[0145] (b) SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체로서, 상기 기능성 유도체가 이의 전장에 걸쳐 SEQ ID NO: 5의 아미노산 서열과 적어도 50% 동일한 아미노산 서열을 갖는, 기능성 유도체.

[0146] 적합하게는, SEQ ID NO: 1에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 1의 아미노산 서열과 적어도 60.0%, 예를 들어, 적어도 70.0%, 예를 들어, 적어도 80.0%, 예를 들어, 적어도 85.0%, 예를 들어, 적어도 87.0%, 예를 들어, 적어도 89.0%, 예를 들어, 적어도 91.0%, 예를 들어, 적어도 93.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 98.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99.2%, 예를 들어, 적어도 99.4%, 예를 들어, 99.5%, 예를 들어, 적어도 99.6%, 예를 들어, 99.7%, 예를 들어, 적어도 99.8%, 예를 들어, 99.9% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 1에 비해 130개 이하, 더욱 적합하게는 120개 이하, 더욱 적합하게는 110개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.

[0147] 적합하게는, SEQ ID NO: 5에 따른 아미노산 서열을 갖는 폴리펩티드의 기능성 유도체는 이의 전장에 걸쳐 SEQ ID NO: 5의 아미노산 서열과 적어도 60.0%, 예를 들어, 적어도 70.0%, 예를 들어, 적어도 80.0%, 예를 들어, 적어도 85.0%, 예를 들어, 적어도 90.0%, 예를 들어, 적어도 95.0%, 예를 들어, 적어도 97.0%, 예를 들어, 적어도 98.0%, 예를 들어, 적어도 99.0%, 예를 들어, 적어도 99.2%, 예를 들어, 적어도 99.4%, 예를 들어, 99.5%, 예를 들어, 적어도 99.6%, 예를 들어, 99.7%, 예를 들어, 적어도 99.8%, 예를 들어, 99.9% 동일한 아미노산 서열을 갖는다. 대안적으로, 기능성 유도체는 SEQ ID NO: 5에 비해 500개 이하, 더욱 적합하게는 400개 이하, 더욱 적합하게는 450개 이하, 더욱 적합하게는 300개 이하, 더욱 적합하게는 250개 이하, 더욱 적합하게는 200개 이하, 더욱 적합하게는 150개 이하, 더욱 적합하게는 125개 이하, 더욱 적합하게는 100개 이하, 더욱 적합하게는 90개 이하, 더욱 적합하게는 80개 이하, 더욱 적합하게는 70개 이하, 더욱 적합하게는 60개 이하, 더욱 적합하게는 50개 이하, 더욱 적합하게는 40개 이하, 더욱 적합하게는 30개 이하, 더욱 적합하게는 20개 이하, 더욱 적합하게는 10개 이하, 더욱 적합하게는 5개 이하, 더욱 적합하게는 4개 이하, 더욱 적합하게는 3개 이하, 더욱 적합하게는 2개 이하, 더욱 적합하게는 1개 이하의 첨가(들), 결실(들) 또는 치환(들)을 갖는다.

[0148] **ChAd155 백본**

[0149] 본 발명은 침팬지 아데노바이러스 ChAd155의 단리된 폴리뉴클레오티드 서열, 예를 들어, 야생형의 변형되지 않

은 ChAd155(SEQ ID NO: 10)의 단리된 폴리뉴클레오타이드 서열 및 ChAd155의 변형된 백본 작제물을 제공한다. 이들 변형된 백본 작제물은 ChAd155#1434(SEQ ID NO: 7), ChAd155#1390(SEQ ID NO: 8) 및 ChAd155#1375(SEQ ID NO: 9)를 포함한다. ChAd155 백본은, 예를 들어, 트랜스진의 전달을 위한 재조합 복제-적격 또는 복제-부적격 아데노바이러스의 작제에서 사용될 수 있다.

[0150] ChAd155 야생형 서열(SEQ ID NO: 10) 서열의 주석이 하기에 제공된다.

```

LOCUS       ChAd155               37830 bp    DNA         linear         10-JUN-2015
DEFINITION   Chimp adenovirus 155, complete genome.
COMMENT      Annotation according to alignment of ChAd155 against the human
              Adenovirus 2 reference strain NC_001405
              Two putative ORFs in the E3 region added manually
FEATURES             Location/Qualifiers
     source          1..37830
                     /organism="Chimpanzee adenovirus 155"
                     /mol_type="genomic DNA"
                     /acronym="ChAd155"
     repeat_region   1..101
                     /standard_name="ITR"
                     /rpt_type=inverted
     gene            466..1622
                     /gene="E1A"
     TATA_signal     466..471
                     /gene="E1A"
     prim_transcript 497..1622
                     /gene="E1A"
     CDS             join(577..1117,1231..1532)
                     /gene="E1A"
                     /product="E1A_280R"

```

[0151]

```

CDS             join(577..979,1231..1532)
                 /gene="E1A"
                 /product="E1A_243R"
     polyA_signal    1600..1605
                 /gene="E1A"
     gene            1662..4131
                 /gene="E1B"
     TATA_signal     1662..1667
                 /gene="E1B"
     prim_transcript 1692..4131
                 /gene="E1B"
     CDS             1704..2267
                 /gene="E1B"
                 /product="E1B_19K"
     CDS             2009..3532
                 /gene="E1B"
                 /product="E1B_55K"
     gene            3571..4131
                 /gene="IX"
     TATA_signal     3571..3576
                 /gene="IX"
     prim_transcript 3601..4131
                 /gene="IX"
     CDS             3628..4092
                 /gene="IX"
                 /product="IX"
     polyA_signal    4097..4102
                 /note="E1B, IX"
     gene            complement(4117..27523)
                 /gene="E2B"
     prim_transcript complement(4117..27494)
                 /gene="E2B"
     gene            complement(4117..5896)
                 /gene="IVa2"
     prim_transcript complement(4117..5896)
                 /gene="IVa2"
     CDS             complement(join(4151..5487,5766..5778))
                 /gene="IVa2"
                 /product="E2B_IVa2"
     polyA_signal    complement(4150..4155)
                 /note="IVa2, E2B"
     CDS             complement(join(5257..8838,14209..14217))
                 /gene="E2B"
                 /product="E2B_polymerase"
     gene            6078..34605
                 /gene="L5"
     gene            6078..28612
                 /gene="L4"
     gene            6078..22658
                 /gene="L3"
     gene            6078..18164
                 /gene="L2"
     gene            6078..14216
                 /gene="L1"
     TATA_signal     6078..6083
                 /note="L"
     prim_transcript 6109..34605
                 /gene="L5"
     prim_transcript 6109..28612
                 /gene="L4"
     prim_transcript 6109..22658
                 /gene="L3"
     prim_transcript 6109..18164
                 /gene="L2"
     prim_transcript 6109..14216

```

[0152]

```

CDS      /gene="L1"
         join(8038..8457,9722..9742)
         /gene="L1"
CDS      /product="L1_13.6K"
         complement(join(8637..10640,14209..14217))
         /gene="E2B"
         /product="E2B_pTP"
gene      10671..10832
         /gene="VAI"
misc_RNA  10671..10832
         /gene="VAI"
         /product="VAI"
gene      10902..11072
         /gene="VAII"
misc_RNA  10902..11072
         /gene="VAII"
         /product="VAII"
CDS      11093..12352
         /gene="L1"
         /product="L1_52K"
CDS      12376..14157
         /gene="L1"
         /product="L1_pIIa"
polyA_signal 14197..14202
         /gene="L1"
CDS      14254..16035
         /gene="L2"
         /product="L2_penton"
CDS      16050..16646
         /gene="L2"
         /product="L2_pVII"
CDS      16719..17834
         /gene="L2"
         /product="L2_v"
CDS      17859..18104
         /gene="L2"
         /product="L2_px"
polyA_signal 18143..18148
         /gene="L2"
CDS      18196..18951
         /gene="L3"
         /product="L3_pVI"
CDS      19063..21945
         /gene="L3"
         /product="L3_hexon"
CDS      21975..22604
         /gene="L3"
         /product="L3_protease"
polyA_signal 22630..22635
         /gene="L3"
gene      complement(22632..27523)
         /gene="E2A"
prim_transcript complement(22632..27494)
         /gene="E2A"
gene      complement(22632..26357)
         /gene="E2A-L"
prim_transcript complement(22632..26328)
         /gene="E2A-L"
polyA_signal complement(22649..22654)
         /note="E2A, E2A-L"
CDS      complement(22715..24367)
         /gene="E2A"
         /note="DBP; genus-common; DBP family"
         /codon_start=1
         /product="E2A"

```

[0153]

```

CDS                24405..26915
                  /gene="L4"
                  /product="L4_100k"
TATA_signal        complement(26352..26357)
                  /gene="E2A-L"
CDS                join(26602..26941,27147..27529)
                  /gene="L4"
                  /product="L4_33K"
CDS                26602..27207
                  /gene="L4"
                  /product="L4_22K"
TATA_signal        complement(27518..27523)
                  /note="E2A, E2B; nominal"
CDS                27604..28287
                  /gene="L4"
                  /product="L4_pVIII"
gene               27969..32686
                  /gene="E3B"
gene               27969..31611
                  /gene="E3A"
TATA_signal        27969..27974
                  /note="E3A, E3B"
prim_transcript    27998..32686
                  /gene="E3B"
prim_transcript    27998..31611
                  /gene="E3A"
CDS                28288..28605
                  /gene="E3A"
                  /product="E3 ORF1"
polyA_signal       28594..28599
                  /gene="L4"
CDS                29103..29303
                  /gene="E3A"
                  /product="E3 ORF2"
CDS                29300..29797
                  /gene="E3A"
                  /product="E3 ORF3"
CDS                29826..30731
                  /gene="E3A"
                  /product="E3 ORF4"
CDS                30728..31579
                  /gene="E3A"
                  /product="E3 ORF5"
CDS                31283..31579
                  /gene="E3A"
                  /product="E3 ORF6"
polyA_signal       31578..31584
                  /gene="E3A"
CDS                31591..31863
                  /gene="E3B"
                  /product="E3 ORF7"
CDS                31866..32264
                  /gene="E3B"
                  /product="E3 ORF8"
CDS                32257..32643
                  /gene="E3B"
                  /product="E3 ORF9"
polyA_signal       32659..32664
                  /gene="E3B"
gene               complement(<32678..32838)
                  /gene="U"
CDS                complement(<32678..32838)
                  /gene="U"
                  /note="exon encoding C terminus unidentified;
                  genus-common"

```

[0154]

```

CDS                /product="protein U"
                  32849..34585
                  /gene="L5"
                  /product="L5_fiber"
polyA_signal       34581..34586
                  /gene="L5"
gene               complement(34611..37520)
                  /gene="E4"
prim_transcript    complement(34611..37490)
                  /gene="E4"
polyA_signal       complement(34625..34630)
                  /gene="E4"
CDS                complement(join(34794..35069,35781..35954))
                  /gene="E4"
                  /product="E4 ORF7"
CDS                complement(35070..35954)
                  /gene="E4"
                  /product="E4 ORF6"
CDS                complement(35875..36219)
                  /gene="E4"
                  /product="E4 ORF4"
CDS                complement(36235..36582)
                  /gene="E4"
                  /product="E4 ORF3"
CDS                complement(36579..36971)
                  /gene="E4"
                  /product="E4 ORF2"
CDS                complement(37029..37415)
                  /gene="E4"
                  /product="E4 ORF1"
TATA_signal        complement(37515..37520)
                  /gene="E4"
repeat_region      37740..37830
                  /standard_name="ITR"
                  /rpt_type=inverted

```

[0155]

[0156]

일 구현예에서, SEQ ID NO: 7, 8, 9, 10의 서열의 단편 및 이의 상보적 가닥, cDNA 및 이에 상보적인 RNA가 제 공된다. 적합하게는, 단편은 적어도 15개의 뉴클레오티드 길이, 더욱 적합하게는 30개의 뉴클레오티드 길이, 더

욱 적합하게는 60개의 뉴클레오타이드 길이, 더욱 적합하게는 120개의 뉴클레오타이드 길이, 더욱 적합하게는 240개, 더욱 적합하게는 480개의 뉴클레오타이드 길이이며, 기능성 단편, 즉, 생물학적 관심 단편을 포함한다. 예를 들어, 기능성 단편은 원하는 아데노바이러스 생성물을 발현시킬 수 있거나, 재조합 바이러스 벡터의 생성에 유용할 수 있다. 상기 단편은 상기 나열된 유전자 서열을 포함한다.

[0157] 본원에 기재된 아데노바이러스 핵산에 의해 인코딩되는 ChAd155 아데노바이러스의 유전자 생성물, 예를 들어, 단백질, 효소 및 이들의 단편이 제공된다. 상기 단백질은 상기 확인된 오픈 리딩 프레임에 의해 인코딩되는 단백질 및 서열 목록에 제공된 폴리뉴클레오타이드에 의해 인코딩되는 단백질을 포함한다.

[0158] **추가 ChAd155 폴리뉴클레오타이드 및 폴리펩티드**

[0159] 일부 구현예에서, 본 발명의 폴리뉴클레오타이드는 본 발명의 섬유 폴리펩티드; 펜톤 폴리펩티드; 핵손 폴리펩티드 및 펜톤 폴리펩티드; 핵손 폴리펩티드 및 섬유 폴리펩티드; 펜톤 폴리펩티드 및 섬유 폴리펩티드; 또는 핵손 폴리펩티드, 펜톤 폴리펩티드 및 섬유 폴리펩티드를 인코딩하는 폴리뉴클레오타이드를 포함하며; 추가의 아데노바이러스 폴리뉴클레오타이드, 적합하게는 ChAd155 폴리뉴클레오타이드를 추가로 포함할 수 있다. 따라서, 적합하게는, 본 발명에 따른 폴리뉴클레오타이드는 하기 중 하나 이상을 포함하며, SEQ ID NO:10에 비한 서열 좌표가 상기 주석에 제공된다:

- [0160] (a) 아데노바이러스 5'-역 말단 반복(ITR);
- [0161] (b) 아데노바이러스 E1A 영역, 또는 E1A_280R 및 E1A_243R 영역으로부터 선택되는 이의 단편;
- [0162] (c) 아데노바이러스 E1B 또는 IX 영역, 또는 E1B_19K, E1B_55K 및 IX 영역으로 구성된 군으로부터 선택되는 이들의 단편;
- [0163] (d) 아데노바이러스 E2B 영역; 또는 E2B_pTP, E2B_중합효소 및 E2B_IVa2 영역으로 구성된 군으로부터 선택되는 이의 단편;
- [0164] (e) 아데노바이러스 L1 영역, 또는 이의 단편으로서, 상기 단편이 L1_13.6K, L1_52K 및 L1_pIIIa 단백질로 구성된 군으로부터 선택되는 아데노바이러스 단백질을 인코딩하는, 아데노바이러스 L1 영역, 또는 이의 단편;
- [0165] (f) 아데노바이러스 L2 영역 또는 본 발명의 펜톤 단백질을 인코딩하는 폴리뉴클레오타이드를 포함하는 L2 영역, 또는 이들의 단편으로서, 상기 단편이 L2_펜톤 단백질, L2_pVII 단백질, L2_V 단백질 및 L2_pX 단백질로 구성된 군으로부터 선택되는 아데노바이러스 단백질을 인코딩하는, 아데노바이러스 L2 영역 또는 본 발명의 펜톤 단백질을 인코딩하는 폴리뉴클레오타이드를 포함하는 L2 영역, 또는 이들의 단편;
- [0166] (g) 아데노바이러스 L3 영역 또는 본 발명의 핵손 단백질을 인코딩하는 폴리뉴클레오타이드를 포함하는 L3 영역, 또는 이들의 단편으로서, 상기 단편이 L3_pVI 단백질, L3_핵손 단백질 및 L3_프로테아제 단백질로 구성된 군으로부터 선택되는 아데노바이러스 단백질을 인코딩하는, 아데노바이러스 L3 영역 또는 본 발명의 핵손 단백질을 인코딩하는 폴리뉴클레오타이드를 포함하는 L3 영역, 또는 이들의 단편;
- [0167] (h) 아데노바이러스 E2A 영역;
- [0168] (i) 아데노바이러스 L4 영역, 또는 이의 단편으로서, 상기 단편이 L4_100k 단백질, L4_33K 단백질, L4_22K 단백질 및 단백질 L4_VIII로 구성된 군으로부터 선택되는 아데노바이러스 단백질을 인코딩하는, 아데노바이러스 L4 영역, 또는 이의 단편;
- [0169] (j) 아데노바이러스 E3 영역, 또는 E3 ORF1, E3 ORF2, E3 ORF3, E3 ORF4, E3 ORF5, E3 ORF6, E3 ORF7, E3 ORF8, 및 E3 ORF9로 구성된 군으로부터 선택되는 이의 단편;
- [0170] (k) 아데노바이러스 L5 영역 또는 본 발명의 L5_섬유 섬유 폴리펩티드를 인코딩하는 폴리뉴클레오타이드를 포함하는 L5 영역;
- [0171] (l) 아데노바이러스(예를 들어, Ad5) E4 영역, 또는 E4 ORF7, E4 ORF6, E4 ORF4, E4 ORF3, E4 ORF2 및 E4 ORF1으로 구성된 군으로부터 선택되는 이의 단편; 특히 상기 E4 영역의 ORF6;
- [0172] (m) 아데노바이러스 3'-ITR; 및/또는
- [0173] (n) 아데노바이러스 VAI 또는 VAII RNA 영역, 바람직하게는 ChAd155가 아닌 아데노바이러스로부터의 아데노바이러스 VAI 또는 VAII RNA 영역, 더욱 바람직하게는 Ad5로부터의 아데노바이러스 VAI 또는 VAII RNA 영역.

- [0174] 정의
- [0175] 적합하게는, 본 발명의 폴리뉴클레오티드 또는 폴리펩티드는 단리된다. "단리된" 폴리뉴클레오티드는 이의 본래의 환경으로부터 분리된 것이다. 예를 들어, 자연 발생 폴리뉴클레오티드는 자연계의 공존하는 물질 중 일부 또는 전부로부터 분리되는 경우에 단리된다. 폴리뉴클레오티드는, 예를 들어, 이의 자연 환경의 일부가 아닌 벡터로 클로닝되거나, cDNA 내에 포함되는 경우에 단리된 것으로 간주된다.
- [0176] 적합하게는, 본 발명의 폴리뉴클레오티드는 재조합 폴리뉴클레오티드이다. 재조합은 폴리뉴클레오티드가 자연에서 발견되는 폴리뉴클레오티드와 다른 폴리뉴클레오티드를 발생시키는 클로닝, 제한 또는 라이게이션 단계, 또는 다른 절차 중 적어도 하나의 생성물인 것을 의미한다. 재조합 아데노바이러스는 재조합 폴리뉴클레오티드를 포함하는 아데노바이러스이다. 재조합 벡터는 재조합 폴리뉴클레오티드를 포함하는 벡터이다. '재조합 바이러스'는 본래의 재조합 바이러스의 프로제니(progeny)를 포함한다. '재조합 벡터'는 본래의 재조합 벡터의 복제물을 포함한다. '재조합 폴리뉴클레오티드'는 본래의 재조합 폴리뉴클레오티드의 복제물을 포함한다.
- [0177] 적합하게는, 본 발명의 폴리펩티드 서열은 자연 서열과 관련하여 적어도 하나의 변형을 함유한다. 적합하게는, 본 발명의 폴리뉴클레오티드 서열은 자연 서열과 관련하여 적어도 하나의 변형을 함유한다. 예를 들어, 유전 공학 기술에 의해 상이한 종(종종, 상이한 속, 아과 또는 과)으로부터 유래된 플라스미드 또는 벡터로 도입된 폴리뉴클레오티드는 이중성 폴리뉴클레오티드이다. 이의 자연 코딩 서열로부터 분리되고, 자연적으로 연결된 채로 발견되지 않는 코딩 서열에 작동 가능하게 연결된 프로모터는 이중성 프로모터이다. 바이러스 또는 바이러스 벡터의 유전체로 클로닝된 특정 재조합 부위(바이러스의 유전체는 이를 자연적으로 함유하지 않음)는 이중성 재조합 부위이다. 이중성 핵산 서열은 또한 아데노바이러스 유전체에서 자연적으로 발견되나, 아데노바이러스 벡터 내의 비-자연 위치에 위치되는 서열을 포함한다.
- [0178] 통상적으로, "이중성"은 비교되는 존재물의 나머지 것과 유전자형적으로 다른 존재물로부터 유래된 것을 의미한다. 이중성 핵산 서열은 아데노바이러스 벡터의 자연 발생 핵산 서열로부터 단리되거나, 이로부터 유래되거나, 이를 기초로 하지 않는 임의의 핵산 서열을 나타낸다. "자연 발생"은 자연에서 발견되고, 합성적으로 제조되거나 변형되지 않은 서열을 의미한다. 서열은 공급원으로부터 분리되거나 변형(예를 들어, 결실, 치환(돌연변이), 삽입, 또는 다른 변형)되지 않아, 적합하게는 공급원 유전자의 정상 기능을 붕괴시키지 않는 경우에 공급원으로부터 "유래"된다.
- [0179] 폴리펩티드의 "기능성 유도체"는 적합하게는 폴리펩티드의 변형된 형태, 예를 들어, 폴리펩티드의 하나 이상의 아미노산이 결실되고/되거나, 삽입되고/되거나, 변형되고/되거나, 치환될 수 있는 폴리펩티드의 변형된 형태를 나타낸다. 변형되지 않은 아데노바이러스 캡시드 단백질의 유도체는, 예를 들어, 하기와 같은 경우 기능성인 것으로 간주된다:
- [0180] (a) 캡시드 내에 유도체 캡시드 단백질을 포함하는 아데노바이러스가 변형되지 않은 캡시드 단백질을 포함하는 아데노바이러스에 비해 실질적으로 동일하거나 더 낮은 혈청유병률을 보유하고/하거나;
- [0181] (b) 캡시드 내에 유도체 캡시드 단백질을 포함하는 아데노바이러스가 변형되지 않은 캡시드 단백질을 포함하는 아데노바이러스에 비해 실질적으로 동일하거나 더 높은 숙주 세포 감염성을 보유하고/하거나;
- [0182] (c) 캡시드 내에 유도체 캡시드 단백질을 포함하는 아데노바이러스가 변형되지 않은 캡시드 단백질을 포함하는 아데노바이러스에 비해 실질적으로 동일하거나 더 높은 면역원성을 보유하고/하거나;
- [0183] (d) 캡시드 내에 유도체 캡시드 단백질을 포함하는 아데노바이러스가 변형되지 않은 캡시드 단백질을 포함하는 아데노바이러스에 비해 실질적으로 동일하거나 더 높은 수준의 트랜스진 생산성을 보유하는 경우.
- [0184] 상기 특성 (a)-(d)는 적합하게는 하기 실시예 섹션에 기재된 방법을 이용하여 측정될 수 있다.
- [0185] 적합하게는, 폴리펩티드, 벡터 또는 재조합 아데노바이러스는 인간 집단에서 낮은 혈청유병률을 갖는다. "낮은 혈청유병률"은 인간 아데노바이러스 5(Ad5)에 비해 감소된 기존 중화 항체 수준을 갖는 것을 의미할 수 있다. 유사하거나 대안적으로, "낮은 혈청유병률"은 약 20% 미만의 혈청유병률, 약 15% 미만의 혈청유병률, 약 10% 미만의 혈청유병률, 약 5% 미만의 혈청유병률, 약 4% 미만의 혈청유병률, 약 3% 미만의 혈청유병률, 약 2% 미만의 혈청유병률, 약 1% 미만의 혈청유병률 또는 검출 가능하지 않은 혈청유병률을 의미할 수 있다. 혈청유병률은 문헌[Aste-Amezaga *et al.*, Hum. Gene Ther. (2004) 15(3):293-304]에 기재된 방법을 이용하여 임상적으로 관련된 중화 역가(200 초과 50% 중화 역가로 정의됨)를 갖는 개체의 백분율로 측정될 수 있다.

- [0186] 용어 폴리펩티드, 펩티드 및 단백질은 본원에서 상호 교환적으로 사용된다.
- [0187] 용어 "유인원"은 통상적으로 비인간 영장류, 예를 들어, 구세계 원숭이, 신세계 원숭이, 원숭이 및 긴팔원숭이를 포함하는 것을 의미한다. 특히, 유인원은 비인간 원숭이, 예를 들어, 침팬지(판 트로글로디테(*Pan troglodyte*)), 보노보(판 파니스쿠스(*Pan paniscus*)) 및 고릴라(고릴라 속)를 나타낼 수 있다. 비-원숭이 유인원은 히말라야 원숭이(마카카 몰라타(*Macaca mulatta*))를 포함할 수 있다.
- [0188] **서열 비교**
- [0189] 2개의 밀접하게 관련된 폴리뉴클레오티드 또는 폴리펩티드 서열을 비교하기 위해, 제1 서열과 제2 서열 사이의 "동일성 %"는 표준 설정을 이용한 정렬 프로그램, 예를 들어, BLAST®(blast.ncbi.nlm.nih.gov에서 이용 가능함, 2015년 3월 9일에 최종 액세스)을 이용하여 계산될 수 있다. 동일성 %는 동일한 잔기의 수를 참조 서열 내의 잔기의 수로 나누고, 100을 곱한 것이다. 상기 및 청구항에서 언급된 동일성 % 숫자는 이러한 방법에 의해 계산된 백분율이다. 동일성 %의 대안적 정의는 동일한 잔기의 수를 정렬된 잔기의 수로 나누고, 100을 곱한 것이다. 대안적 방법은 정렬 내의 갭, 예를 들어, 다른 서열에 비한 한 서열에서의 결실이 스코어링 파라미터에서 갭 스코어 또는 갭 비용으로 설명되는 갭 방법(gapped method)을 이용하는 것을 포함한다. 더 많은 정보를 위해, 2015년 3월 9일에 마지막으로 액세스된 ftp.ncbi.nlm.nih.gov/pub/factsheets/HowTo_BLASTGuide.pdf에서 이용 가능한 BLAST® 팩트 시트(fact sheet)를 참조한다.
- [0190] 폴리뉴클레오티드 또는 이에 의해 인코딩된 폴리펩티드의 기능성을 보존하는 서열은 더욱 밀접하게 동일할 수 있다. 폴리펩티드 또는 폴리뉴클레오티드 서열은 이들이 이들의 전장에 걸쳐 100% 서열 동일성을 공유하는 경우에 다른 폴리펩티드 또는 폴리뉴클레오티드 서열과 동일하거나 일치하는 것으로 언급된다.
- [0191] 서열 사이의 "차이"는 제1 서열에 비해 제2 서열의 한 위치에서의 단일 아미노산 잔기의 삽입, 결실 또는 치환을 나타낸다. 2개의 폴리펩티드 서열은 1개, 2개 또는 그 초과와 상기 아미노산 차이를 함유할 수 있다. 제1 서열과 달리 동일한(100% 서열 동일성) 제2 서열에서의 삽입, 결실 또는 치환은 서열 동일성 퍼센트를 감소시킨다. 예를 들어, 동일한 서열이 9개의 아미노산 잔기 길이인 경우, 제2 서열에서의 하나의 치환은 88.9%의 서열 동일성을 발생시킨다. 동일한 서열이 17개의 아미노산 잔기 길이인 경우, 제2 서열에서의 2개의 치환은 88.2%의 서열 동일성을 발생시킨다. 동일한 서열이 7개의 아미노산 잔기 길이인 경우, 제2 서열에서의 3개의 치환은 57.1%의 서열 동일성을 발생시킨다. 제1 및 제2 폴리펩티드 서열이 9개의 아미노산 잔기 길이이고, 6개의 동일한 잔기를 공유하는 경우, 제1 및 제2 폴리펩티드 서열은 66% 초과와 동일성을 공유한다(제1 및 제2 폴리펩티드 서열은 66.7%의 동일성을 공유한다). 제1 및 제2 폴리펩티드 서열이 17개의 아미노산 잔기 길이이고, 16개의 동일한 잔기를 공유하는 경우, 제1 및 제2 폴리펩티드 서열은 94% 초과와 동일성을 공유한다(제1 및 제2 폴리펩티드 서열은 94.1%의 동일성을 공유한다). 제1 및 제2 폴리펩티드 서열이 7개의 아미노산 잔기 길이이고, 3개의 동일한 잔기를 공유하는 경우, 제1 및 제2 폴리펩티드 서열은 42% 초과와 동일성을 공유한다(제1 및 제2 폴리펩티드 서열은 42.9%의 동일성을 공유한다).
- [0192] 대안적으로, 제1의 참조 폴리펩티드 서열을 제2의 비교 폴리펩티드 서열과 비교하기 위해, 제2 서열을 생성시키기 위해 제1 서열에서 이루어진 첨가, 치환 및/또는 결실의 수가 확인될 수 있다. 첨가는 제1 폴리펩티드의 서열로의 하나의 아미노산 잔기의 첨가(제1 폴리펩티드의 어느 한 말단에서의 첨가를 포함)이다. 치환은 제1 폴리펩티드의 서열 내의 하나의 아미노산 잔기의 하나의 상이한 아미노산 잔기에 의한 치환이다. 결실은 제1 폴리펩티드의 서열로부터의 하나의 아미노산 잔기의 결실(제1 폴리펩티드의 어느 한 말단에서의 결실을 포함)이다.
- [0193] 제1의 참조 폴리뉴클레오티드 서열을 제2의 비교 폴리뉴클레오티드 서열과 비교하기 위해, 제2 서열을 생성시키기 위해 제1 서열에서 이루어진 첨가, 치환 및/또는 결실의 수가 확인될 수 있다. 첨가는 제1 폴리뉴클레오티드의 서열로의 하나의 뉴클레오티드 잔기의 첨가(제1 폴리뉴클레오티드의 어느 한 말단에서의 첨가를 포함)이다. 치환은 제1 폴리뉴클레오티드의 서열 내의 하나의 뉴클레오티드 잔기의 하나의 상이한 뉴클레오티드 잔기에 의한 치환이다. 결실은 제1 폴리뉴클레오티드의 서열로부터의 하나의 뉴클레오티드 잔기의 결실(제1 폴리뉴클레오티드의 어느 한 말단에서의 결실을 포함)이다.
- [0194] 적합하게는, 본 발명의 서열 내에서의 치환은 보존성 치환일 수 있다. 보존성 치환은 한 아미노산의 치환되는 아미노산과 유사한 화학적 특성을 갖는 또 다른 아미노산에 의한 치환을 포함한다(예를 들어, 문헌[Stryer et al, *Biochemistry*, 5th Edition 2002, pages 44-49] 참조). 바람직하게는, 보존성 치환은 (i) 염기성 아미노산의 또 다른 상이한 염기성 아미노산에 의한 치환; (ii) 산성 아미노산의 또 다른 상이한 산성 아미노산에 의한 치환; (iii) 방향족 아미노산의 또 다른 상이한 방향족 아미노산에 의한 치환; (iv) 비-극성 지방족 아미노산의

또 다른 상이한 비-극성 지방족 아미노산에 의한 치환; 및 (v) 극성의 하전되지 않은 아미노산의 또 다른 상이한 극성의 하전되지 않은 아미노산에 의한 치환으로 구성된 군으로부터 선택된 치환이다. 염기성 아미노산은 바람직하게는 아르기닌, 히스티딘, 및 리신으로 구성된 군으로부터 선택된다. 산성 아미노산은 바람직하게는 아스파테이트 또는 글루타메이트이다. 방향족 아미노산은 바람직하게는 페닐알라닌, 티로신 및 트립토판으로 구성된 군으로부터 선택된다. 비-극성의 지방족 아미노산은 바람직하게는 글리신, 알라닌, 발린, 류신, 메티오닌 및 이소류신으로 구성된 군으로부터 선택된다. 극성의 하전되지 않은 아미노산은 바람직하게는 세린, 트레오닌, 시스테인, 프롤린, 아스파라긴 및 글루타민으로 구성된 군으로부터 선택된다. 보존성 아미노산 치환과 대조적으로, 비-보존성 아미노산 치환은 한 아미노산의 상기 개설된 보존성 치환 (i) 내지 (v)에 속하지 않는 임의의 아미노산에 의한 교환이다.

[0195] **백터 및 재조합 아데노바이러스**

[0196] 본 발명의 ChAd155 서열은 치료제로서, 그리고 다양한 백터 시스템, 재조합 아데노바이러스 및 숙주 세포의 작제에서 유용하다. 적합하게는, 용어 "백터"는 야생형 서열에 비해 실질적으로 변경(예를 들어, 결실되고/되거나 비활성화된 유전자 또는 기능성 영역)되고/되었거나 이중성 서열, 즉, 상이한 공급원으로부터 획득된 핵산("삽입물"로도 언급됨)이 혼입되고, 세포(예를 들어, 숙주 세포)로 도입되는 경우 삽입된 폴리뉴클레오타이드 서열을 복제하고/하거나 발현시킬 수 있는 핵산을 나타낸다. 예를 들어, 삽입물은 본원에 기재된 ChAd155 서열 중 일부 또는 전부일 수 있다. 또한 또는 대안적으로, ChAd155 백터는 바이러스 유전자, 예를 들어, E1 또는 본원에 기재된 다른 바이러스 유전자 또는 기능성 영역의 하나 이상의 결실 또는 비활성화를 포함하는 ChAd155 아데노바이러스일 수 있다. 이중성 서열을 포함하거나 포함하지 않을 수 있는 상기 ChAd155는 종종 "백본"으로 언급되며, 그대로 사용되거나, 백터에 대한 추가 변형을 위한 시작점으로 사용될 수 있다.

[0197] 백터는 네이키드 DNA, 플라스미드, 바이러스, 코스미드, 파지 백터, 예를 들어, 람다 백터, 인공 염색체, 예를 들어, BAC(박테리아 인공 염색체), 또는 에피솜을 포함하는 임의의 적합한 핵산 분자일 수 있다. 대안적으로, 백터는 세포 비침투 시험관내 전사 또는 발현을 위한 전사 및/또는 발현 유닛, 예를 들어, T7-상용성 시스템일 수 있다. 백터는 단독으로 또는 다른 아데노바이러스 서열 또는 단편과 함께, 또는 비-아데노바이러스 서열로부터의 요소와 함께 사용될 수 있다. ChAd155 서열은 또한 안티센스 전달 백터, 유전자 요법 백터, 또는 백신 백터에서 유용할 수 있다. 따라서, 유전자 전달 백터, 및 ChAd155 서열을 함유하는 숙주 세포가 추가로 제공된다.

[0198] 용어 "복제-적격" 아데노바이러스는 세포 내에 포함된 임의의 재조합 헬퍼 단백질의 부재하에서 숙주 세포에서 복제할 수 있는 아데노바이러스를 나타낸다. 적합하게는, "복제-적격" 아데노바이러스는 다음과 같은 온전하거나 기능성 필수 초기 유전자를 포함한다: E1A, E1B, E2A, E2B, E3 및 E4. 특정 동물로부터 단리된 야생형 아데노바이러스는 상기 동물에서 복제 적격일 것이다.

[0199] 용어 "복제-부적격" 또는 "복제-결함" 아데노바이러스는 적어도 기능적 결실(또는 "기능 손실" 돌연변이), 즉, 완전히 제거되지 않고 유전자의 기능을 손상시키는 결실 또는 돌연변이, 예를 들어, 인공 정지 코돈의 도입, 활성 부위 또는 상호작용 도메인의 결실 또는 돌연변이, 유전자의 조절 서열의 돌연변이 또는 결실 등, 또는 바이러스 복제에 필수적인 유전자 생성물을 인코딩하는 유전자, 예를 들어, E1A, E1B, E2A, E2B, E3 및 E4(예를 들어, E3 ORF1, E3 ORF2, E3 ORF3, E3 ORF4, E3 ORF5, E3 ORF6, E3 ORF7, E3 ORF8, E3 ORF9, E4 ORF7, E4 ORF6, E4 ORF4, E4 ORF3, E4 ORF2 및/또는 E4 ORF1)로부터 선택되는 아데노바이러스 유전자 중 하나 이상의 완전한 제거를 포함하도록 공학 처리됨으로 인해 복제 불가능한 아데노바이러스를 나타낸다. 특히, 적합하게는 E1 및 선택적으로 E3 및/또는 E4가 결실된다. 결실되는 경우, 상기 언급된 결실된 유전자 영역은 적합하게는 또 다른 서열과 관련하여 동일성 %를 결정하는 경우에 정렬에서 고려되지 않을 것이다.

[0200] 본 발명은 치료 또는 백신 목적으로 단백질, 적합하게는 이중성 단백질을 세포로 전달하는 백터, 예를 들어, 재조합 아데노바이러스를 제공한다. 백터는 네이키드 DNA, 파지, 트랜스포존(transposon), 코스미드, 에피솜, 플라스미드, 또는 바이러스를 포함하는 임의의 유전적 요소를 포함할 수 있다. 상기 백터는 본원에 개시된 바와 같은 ChAd155의 DNA 및 미니유전자(minigene)를 함유한다. "미니유전자"(또는 "발현 카세트")는 선택된 이중성 유전자(트랜스진) 및 숙주 세포에서 유전자 생성물의 번역, 전사 및/또는 발현을 유도하는데 필요한 다른 조절 요소의 조합물을 의미한다.

[0201] 통상적으로, ChAd155-유래 아데노바이러스 백터는 미니유전자가 선택된 아데노바이러스 유전자에 고유한 영역에서 다른 아데노바이러스 서열을 함유하는 핵산 분자 내에 위치되도록 설계된다. 미니유전자는 원하는 경우 기존 유전자 영역에 삽입되어 상기 유전자의 기능을 붕괴시킬 수 있다. 대안적으로, 미니유전자는 부분적 또는 완전히 결실된 아데노바이러스 유전자의 부위에 삽입될 수 있다. 예를 들어, 미니유전자는 E1A, E1B, E2A, E2B, E3

및 E4로 구성된 군으로부터 선택되는 유전체 영역의 적어도 하나의 유전자를 비-기능성이 되도록 돌연변이, 삽입 또는 결실의 부위에 위치될 수 있다. 용어 "비-기능성이 되도록 한다"는 유전자 영역의 충분한 양이 제거되거나 달리 붕괴되어, 유전자 영역이 더 이상 유전자 발현의 기능성 생성물을 생성할 수 없는 것을 의미한다. 원하는 경우, 전체 유전자 영역이 제거될 수 있다(그리고 적합하게는 미니유전자로 대체될 수 있다).

[0202] 예를 들어, 재조합 바이러스의 생성에 유용한 생산 벡터의 경우, 벡터는 미니유전자 및 아데노바이러스 유전체의 5' 말단 또는 아데노바이러스 유전체의 3' 말단, 또는 아데노바이러스 유전체의 5' 및 3' 말단 둘 모두를 함유할 수 있다. 아데노바이러스 유전체의 5' 말단은 패키징 및 복제에 필요한 5' 시스-요소, 즉, 5' ITR 서열(복제 기점으로 기능함) 및 자연 5' 패키징 인핸서 도메인(선형 Ad 유전체 및 E1 프로모터에 대한 인핸서 요소를 패키징하는데 필요한 서열을 함유함)을 함유한다. 아데노바이러스 유전체의 3' 말단은 패키징 및 캡시드화에 필요한 3' 시스-요소(ITR을 포함함)를 포함한다. 적합하게는, 재조합 아데노바이러스는 5' 및 3' 아데노바이러스 시스-요소 둘 모두를 함유하며, 미니유전자(적합하게는 트랜스진을 함유함)는 5' 및 3' 아데노바이러스 서열 사이에 위치된다. ChAd155-기반 아데노바이러스 벡터는 또한 추가 아데노바이러스 서열을 함유할 수 있다.

[0203] 적합하게는, ChAd155-기반 벡터는 본 발명의 아데노바이러스 ChAd155 유전체로부터 유래된 하나 이상의 아데노바이러스 요소를 함유한다. 일 구현예에서, 벡터는 ChAd155로부터의 아데노바이러스 ITR 및 동일 아데노바이러스 혈청형으로부터의 추가 아데노바이러스 서열을 함유한다. 또 다른 구현예에서, 벡터는 ITR을 제공하는 것과 상이한 아데노바이러스 혈청형으로부터 유래되는 아데노바이러스 서열을 함유한다.

[0204] 본원에 정의된 바와 같이, 슈도타이핑된 아데노바이러스는 아데노바이러스의 캡시드 단백질이 ITR을 제공하는 아데노바이러스와 상이한 아데노바이러스로부터 유래되는 아데노바이러스를 나타낸다.

[0205] 추가로, 키메라 또는 하이브리드 아데노바이러스는 당업자에게 공지된 기술(예를 들어, US 7,291,498호)을 이용하여 본원에 기재된 아데노바이러스를 이용하여 작제될 수 있다.

[0206] 본 발명의 벡터에 존재하는 ITR 및 임의의 다른 아데노바이러스 서열은 많은 공급원으로부터 획득될 수 있다. 다양한 아데노바이러스 군주가 미국 미생물보존센터(American Type Culture Collection, Manassas, Virginia)로부터 이용 가능하거나, 다양한 상업 및 기관 공급처로부터 요청에 의해 이용 가능하다. 추가로, 많은 상기 군주의 서열은, 예를 들어, PubMed 및 GenBank를 포함하는 다양한 데이터베이스로부터 이용 가능하다. 다른 침팬지 또는 인간 아데노바이러스로부터 제조된 상동성 아데노바이러스 벡터는 공개된 문헌(예를 들어, US 5,240,846호)에 기재되어 있다. 유형 Ad5(GenBank 등록 번호 M73370)를 포함하는 다수의 아데노바이러스 유형의 DNA 서열이 GenBank로부터 이용 가능하다. 아데노바이러스 서열은 현재 확인된 인간 유형 중 임의의 유형을 추가로 포함하여 임의의 공지된 아데노바이러스 혈청형, 예를 들어, 혈청형 2, 3, 4, 7, 12 및 40으로부터 획득될 수 있다. 유사하게, 비인간 동물(예를 들어, 유인원)을 감염시키는 것으로 공지된 아데노바이러스가 또한 본 발명의 벡터 작제물에서 사용될 수 있다(예를 들어, US 6,083,716호). 본원에 기재된 벡터의 작제에서 사용되는 바이러스 서열, 헬퍼 바이러스(필요한 경우), 및 재조합 바이러스 입자, 및 다른 벡터 성분 및 서열은 하기 기재되는 바와 같이 획득될 수 있다.

[0207] **서열, 벡터 및 아데노바이러스 생성**

[0208] 본 발명의 서열은 재조합 생성, 화학 합성, 또는 다른 합성 수단을 포함하는 임의의 적합한 수단에 의해 생성될 수 있다. 적합한 생성 기술은 당업자에게 널리 공지되어 있다. 대안적으로, 캡티드는 또한 널리 공지된 고체상 캡티드 합성 방법에 의해 합성될 수 있다.

[0209] 아데노바이러스 플라스미드(또는 다른 벡터)가 아데노바이러스 벡터를 생성시키기 위해 사용될 수 있다. 일 구현예에서, 아데노바이러스 벡터는 복제-부적격인 아데노바이러스 입자이다. 일 구현예에서, 아데노바이러스 입자는 E1A 및/또는 E1B 유전자에서의 결실에 의해 복제-부적격이 된다. 대안적으로, 아데노바이러스는 선택적으로 E1A 및/또는 E1B 유전자를 보존하면서 또 다른 수단에 의해 복제-부적격이 된다. 유사하게는, 일부 구현예에서, 벡터에 대한 면역 반응의 감소는 E2B 및/또는 DNA 중합효소 유전자에서의 결실에 의해 달성될 수 있다. 아데노바이러스 벡터는 또한 아데노바이러스 유전체에 대한 다른 돌연변이, 예를 들어, 온도-민감성 돌연변이 또는 다른 유전자에서의 결실을 함유할 수 있다. 다른 구현예에서, 아데노바이러스 벡터에서 온전한 E1A 및/또는 E1B 영역을 보유하는 것이 바람직하다. 상기 온전한 E1 영역은 아데노바이러스 유전체 내의 이의 자연 위치에 위치될 수 있거나, 자연 아데노바이러스 유전체 내의 결실 부위(예를 들어, E3 영역 내)에 배치될 수 있다.

[0210] 포유동물(예를 들어, 인간) 세포로의 유전자의 전달을 위한 아데노바이러스 벡터의 작제에서, 광범위한 변형된 아데노바이러스 핵산 서열이 벡터에서 사용될 수 있다. 예를 들어, 아데노바이러스 지연 초기 유전자 E3의 일부

또는 전부가 재조합 바이러스의 일부를 형성하는 아데노바이러스 서열로부터 제거될 수 있다. E3의 기능은 재조합 바이러스 입자의 기능 및 생성과 관련이 없는 것으로 생각된다. 아데노바이러스 벡터는 또한 E4 유전자의 적어도 ORF6 영역, 더욱 바람직하게는 이러한 유전자의 기능에서의 중복성으로 인해 전체 E4 영역의 결실을 갖도록 작제될 수 있다. 본 발명의 또 다른 벡터는 지연 초기 유전자 E2A에서 결실을 함유한다. 결실은 또한 아데노바이러스 유전체의 후기 유전자 L1 내지 L5 중 임의의 것에서 이루어질 수 있다. 유사하게는, 중간체 유전자 IX 및 IVa2에서의 결실이 일부 목적에 유용할 수 있다. 다른 결실이 다른 구조 또는 비-구조 아데노바이러스 유전자에서 이루어질 수 있다. 상기 논의된 결실은 개별적으로 이용될 수 있으며, 즉, 본원에 기재된 바와 같은 사용을 위한 아데노바이러스 서열은 단지 하나의 영역에서 결실을 함유할 수 있다. 대안적으로, 전체 유전자 또는 이들의 생물학적 활성을 파괴하기에 효과적인 상기 유전자의 일부의 결실은 임의의 조합으로 사용될 수 있다. 예를 들어, 일 예시적 벡터에서, 아데노바이러스 서열은 E1 유전자 및 E4 유전자의 결실, 또는 E1, E2A 및 E3 유전자의 결실, 또는 E1 및 E3 유전자의 결실, 또는 E3의 결실과 함께 또는 이의 결실 없이 E1, E2A 및 E4 유전자의 결실 등을 가질 수 있다. E 유전자 중 어느 하나 이상은 적합하게는 아데노바이러스의 상이한 균주로부터 유래된 E 유전자(또는 하나 이상의 E 유전자 오픈 리딩 프레임)로 대체될 수 있다. 특히 적합하게는, ChAd155 E1 및 E3 유전자는 결실되고, ChAd155 E4 유전자는 E4Ad5orf6으로 대체된다. 상기 논의된 바와 같이, 상기 결실 및/또는 치환은 원하는 결과를 달성하기 위해 다른 돌연변이, 예를 들어, 온도-민감성 돌연변이와 함께 사용될 수 있다.

[0211] 하나 이상의 필수 아데노바이러스 서열(예를 들어, E1A, E1B, E2A, E2B, E4 ORF6, L1, L2, L3, L4 및 L5)가 결여된 아데노바이러스 벡터는 아데노바이러스 입자의 바이러스 감염성 및 증식에 필요한 손실된 아데노바이러스 유전자 생성물의 존재하에서 배양될 수 있다. 이들 헬퍼 기능은 하나 이상의 헬퍼 작제물(예를 들어, 플라스미드 또는 바이러스) 또는 패키징 숙주 세포의 존재하에서 아데노바이러스 벡터를 배양함으로써 제공될 수 있다.

[0212] 복제-부적격 벡터의 상보성

[0213] 상기 기재된 유전자 중 임의의 유전자에서 결실된 재조합 아데노바이러스를 생성시키기 위해, 바이러스의 복제 및 감염성에 필수적인 경우 결실된 유전자 영역의 기능은 헬퍼 바이러스 또는 세포주, 즉, 상보성 또는 패키징 세포주에 의해 재조합 바이러스에 제공되어야 한다.

[0214] 헬퍼 바이러스

[0215] 미니유전자를 운반하는데 사용되는 바이러스 벡터의 아데노바이러스 유전자 내용물에 따라, 미니유전자를 함유하는 감염성 재조합 바이러스 입자를 생성시키는데 필요한 충분한 아데노바이러스 유전자 서열을 제공하기 위해 헬퍼 아데노바이러스 또는 비-복제 바이러스 단편이 사용될 수 있다. 유용한 헬퍼 바이러스는 아데노바이러스 벡터 작제물에 존재하지 않고/않거나 벡터가 형질감염되는 패키징 세포주에 의해 발현되지 않는 선택된 아데노바이러스 유전자 서열을 함유한다. 일 구현예에서, 헬퍼 바이러스는 복제-결여성이며, 적합하게는 본원에 기재된 하나 이상의 서열에 더하여 아데노바이러스 유전자를 함유한다. 상기 헬퍼 바이러스는 적합하게는 E1 발현(선택적으로, 추가로 E3 발현) 세포주와 함께 사용된다.

[0216] 헬퍼 바이러스는 선택적으로 리포터 유전자를 함유할 수 있다. 다수의 상기 리포터 유전자가 당 분야에 공지되어 있을뿐만 아니라 본원에 기재되어 있다. 아데노바이러스 벡터 상의 트랜스진과 상이한 헬퍼 바이러스 상의 리포터 유전자의 존재는 아데노바이러스 벡터 및 헬퍼 바이러스 둘 모두가 독립적으로 모니터링되는 것을 가능하게 한다. 이러한 리포터는 정제시 생성된 재조합 바이러스와 헬퍼 바이러스 사이의 분리를 가능하게 하기 위해 사용된다.

[0217] 상보성 세포주

[0218] 많은 상황에서, 바이러스의 복제 및 감염성에 필수적인 하나 이상의 손실된 유전자, 예를 들어, 인간 E1을 발현하는 세포주가 침팬지 아데노바이러스 벡터를 교차보충(transcomplement)하는데 사용될 수 있다. 이는 본 발명의 침팬지 아데노바이러스 서열과 현재 이용 가능한 패키징 세포주에서 발견되는 인간 아데노바이러스 서열 사이의 다양성으로 인해 현재 인간 E1-함유 세포의 사용이 복제 및 생산 과정 동안 복제-적격 아데노바이러스의 발생을 방지함에 따라 특히 유리하다.

[0219] 대안적으로, 원하는 경우, 선택된 모 세포주에서의 발현을 위한 프로모터의 전사 조절하에서 최소한 ChAd155로부터 E1 유전자를 발현하는 패키징 세포 또는 세포주를 발생시키기 위해 본원에 제공된 서열을 이용할 수 있다. 이러한 목적을 위해 유도성 또는 항시성 프로모터가 사용될 수 있다. 상기 프로모터의 예는 본 문서의 다른 곳에 상세히 기재되어 있다. 임의의 원하는 ChAd155 유전자를 발현하는 신규한 세포주의 생성을 위해 모 세포가

선택된다. 비제한적으로, 상기 모 세포주는 다른 것 중에서도 HeLa[ATCC 등록 번호 CCL 2], A549[ATCC 등록 번호 CCL 185], HEK 293, KB[CCL 17], Detroit[예를 들어, Detroit 510, CCL 72] 및 WI-38[CCL 75] 세포일 수 있다. 이들 세포주는 미국 미생물보존센터(American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209)로부터 모두 이용 가능하다.

[0220] 상기 E1-발현 세포주는 재조합 아데노바이러스 E1 결실 벡터의 생성에서 유용하다. 추가로, 또는 대안적으로, 하나 이상의 아데노바이러스 유전자 생성물, 예를 들어, E1A, E1B, E2A, E3 및/또는 E4를 발현하는 세포주가 재조합 바이러스 벡터의 생성에서 사용되는 것과 본질적으로 동일한 절차를 이용하여 작제될 수 있다. 상기 세포주는 상기 생성물을 인코딩하는 필수 유전자가 결실된 아데노바이러스 벡터를 교차보충하거나, 헬퍼-의존성 바이러스(예를 들어, 아데노-관련 바이러스)의 패키징에 필요한 헬퍼 기능을 제공하기 위해 사용될 수 있다. 숙주 세포의 제조는 선택된 DNA 서열의 어셈블리와 같은 기술을 포함한다.

[0221] 또 다른 대안에서, 필수 아데노바이러스 유전자 생성물은 아데노바이러스 벡터 및/또는 헬퍼 바이러스에 의해 교차하여(in trans) 제공된다. 상기 예에서, 적합한 숙주 세포는 임의의 생물학적 유기체, 예를 들어, 원핵생물(예를 들어, 박테리아) 세포, 및 진핵생물 세포, 예를 들어, 곤충 세포, 효모 세포 및 포유동물 세포로부터 선택될 수 있다.

[0222] 숙주 세포는 인간, 원숭이, 마우스, 래트, 토끼, 및 햄스터를 포함하는 포유동물로부터 유래된 세포, 예를 들어, A549, WEHI, 3T3, 10'I'I/2, HEK 293 세포 또는 Per.C6(둘 모두는 기능성 아데노바이러스 E1을 발현함)[Fallaux, FJ et al, (1998), Hum Gene Ther, 9:1909-1917], Saos, C2C12, L 세포, HT1080, HepG2 및 일차 섬유모세포, 간세포 및 근육모세포를 포함하나 이에 제한되지는 않는 임의의 포유동물 종으로부터 선택될 수 있다.

[0223] 특히 적합한 상보성 세포주는 Procell192 세포주이다. Procell192 세포주는 인간 포스포글리세레이트 키나제-1(PGK) 프로모터의 조절하에서 Tet 억제인자로 형질감염된 아데노바이러스 E1 유전자, 및 G418-내성 유전자를 발현하는 HEK 293 세포를 기초로 한다(Vitelli et al. *PLoS One* (2013) 8(e55435):1-9). Procell192.S는 현탁 조건에서의 성장에 적합하며, 독성 단백질을 발현하는 아데노바이러스 벡터를 생성하는데 유용하다(www.okairos.com/e/inner.php?m=00084, 2015년 4월 13일에 마지막으로 액세스됨).

[0224] 바이러스 입자의 어셈블리 및 세포주의 형질감염

[0225] 일반적으로, 형질감염에 의해 미니유전자를 포함하는 벡터를 전달하는 경우, 벡터는 약 1×10^4 개의 세포 내지 약 1×10^{13} 개의 세포, 바람직하게는 약 10^5 개의 세포에 약 5 μ g 내지 약 100 μ g의 DNA, 바람직하게는 약 10 내지 약 50 μ g의 DNA의 양으로 전달된다. 그러나, 벡터 DNA 대 숙주 세포의 상대량은 선택된 벡터, 전달 방법 및 선택된 숙주 세포와 같은 요인을 고려하여 조정될 수 있다.

[0226] 벡터의 숙주 세포로의 도입은 형질감염 및 감염을 포함하는 당 분야에 공지된 임의의 수단에 의해 달성될 수 있다. 아데노바이러스 유전자 중 하나 이상은 숙주 세포의 유전체로 안정적으로 통합되거나, 에피솜으로서 안정적으로 발현되거나, 일시적으로 발현될 수 있다. 유전자 생성물은 모두 에피솜 상태로 또는 안정적으로 통합된 상태로 일시적으로 발현될 수 있거나, 유전자 생성물 중 일부는 안정적으로 발현될 수 있는 반면 다른 일부는 일시적으로 발현된다.

[0227] 숙주 세포로의 벡터의 도입은 또한 당업자에게 공지된 기술을 이용하여 달성될 수 있다. 적합하게는, 표준 형질감염 기술, 예를 들어, CaPC 형질감염 또는 전기천공이 사용된다.

[0228] 다양한 중간체 플라스미드로의 아데노바이러스의 선택된 DNA 서열(및 트랜스진 및 다른 벡터 요소)의 어셈블리, 및 재조합 바이러스 입자를 생성시키기 위한 플라스미드 및 벡터의 사용은 모두 통상적인 기술을 이용하여 달성된다. 상기 기술은 cDNA의 통상적인 클로닝 기술, 아데노바이러스 유전체의 중첩 올리고뉴클레오타이드 서열의 이용, 중합효소 연쇄 반응, 및 원하는 뉴클레오타이드 서열을 제공하는 임의의 적합한 방법을 포함한다. 표준 형질감염 및 공동-형질감염 기술, 예를 들어, CaPC 침전 기술이 사용된다. 사용되는 다른 통상적인 방법은 바이러스 유전체의 상동성 재조합, 아가 오버레이(agar overlay)에서의 바이러스 플라크 형성(plaquing), 신호 생성을 측정하는 방법 등을 포함한다.

[0229] 예를 들어, 원하는 미니유전자-함유 바이러스 벡터의 작제 및 어셈블리 후, 벡터는 헬퍼 바이러스의 존재하에 패키징 세포주로 시험관 내에서 형질감염된다. 상동성 재조합이 헬퍼 서열과 벡터 서열 사이에서 발생하며, 이는 벡터 내의 아데노바이러스-트랜스진 서열이 복제되고 비리온 캡시드로 패키징되는 것을 가능하게 하여, 제조

합 바이러스 벡터 입자를 생성시킨다. 생성된 재조합 아데노바이러스는 선택된 트랜스진을 선택된 세포로 전달하는데 유용하다. 패키징 세포주에서 성장된 재조합 바이러스를 이용한 생체 내 실험에서, 본 발명의 E1-결실된 재조합 아데노바이러스 벡터는 트랜스진을 비-유인원 포유동물, 바람직하게는 인간 세포로 전달하는데 있어서의 유용성을 입증한다.

[0230] 트랜스진

[0231] 트랜스진은 이러한 트랜스진에 측접한 벡터 서열과 이중성인 핵산 서열이며, 관심 단백질을 인코딩한다. 핵산 코딩 서열은 숙주 세포에서 트랜스진 전사, 번역, 및/또는 발현을 가능하게 하는 방식으로 조절 성분에 작동 가능하게 연결된다.

[0232] 트랜스진 서열의 조성은 생성되는 벡터가 사용될 용도에 좌우될 것이다. 예를 들어, 트랜스진은 치료용 트랜스진 또는 면역원성 트랜스진일 수 있다. 대안적으로, 트랜스진 서열은 발현시 검출 가능한 신호를 생성하는 리포터 서열을 포함할 수 있다. 상기 리포터 서열은, 비제한적인 예로, β -락타마제, β -갈락토시다제(LacZ), 알칼리성 포스파타제, 티미딘 키나제, 녹색 형광 단백질(GFP), 클로람페니콜 아세틸트랜스페라제(CAT), 루시페라제, 막 결합된 단백질, 예를 들어, CD2, CD4, CD8, 인플루엔자 헤마글루티닌 단백질, 및 특이적인 고 친화성 항체가 존재하거나 통상적인 수단에 의해 생성될 수 있는 당 분야에 널리 공지된 것들, 및 다른 것들 중에서 헤마글루티닌 또는 Myc로부터의 항원 태그 도메인에 적절하게 융합된 막 결합된 단백질을 포함하는 융합 단백질을 인코딩하는 DNA 서열을 포함한다. 이들 코딩 서열은 이의 발현을 유도하는 조절 요소와 회합되는 경우 효소, 방사선, 비색, 형광 또는 다른 분광 검정, 형광 활성화 세포 분류 검정 및 면역학적 검정, 예를 들어, 효소 결합 면역흡착 측정(ELISA), 방사면역측정법(RIA) 및 면역조직화학을 포함하는 통상적인 수단에 의해 검출 가능한 신호를 제공한다.

[0233] 일 구현예에서, 트랜스진은 생물학 및 의학에 유용한 생성물을 인코딩하는 비-마커 서열, 예를 들어, 치료용 트랜스진 또는 면역원성 트랜스진, 예를 들어, 단백질, RNA, 효소, 또는 촉매성 RNA이다. 바람직한 RNA 분자는 tRNA, dsRNA, 리보솜 RNA, 촉매성 RNA, 및 안티센스 RNA를 포함한다. 유용한 RNA 서열의 한 예는 치료되는 동물에서 표적화된 핵산 서열의 발현을 소멸시키는 서열이다.

[0234] 트랜스진은 암 치료제 또는 백신으로서, 예를 들어, 유전적 결함의 치료를 위해, 면역 반응의 유도를 위해, 및/또는 예방 백신 목적을 위해 사용될 수 있다. 본원에서 사용되는 바와 같은 면역 반응의 유도는 단백질에 대한 T 세포 및/또는 체액성 면역 반응을 유도하는 단백질의 능력을 나타낸다.

[0235] 조절 요소

[0236] 트랜스진에 더하여, 벡터는 또한 플라스미드 벡터로 형질감염되거나, 본 발명에 의해 생성된 바이러스로 감염된 세포에서 트랜스진의 전사, 번역 및/또는 발현을 가능하게 하는 방식으로 트랜스진에 작동 가능하게 연결되는 통상적인 조절 요소를 포함한다. 본원에서 사용되는 "작동 가능하게 연결된" 서열은 관심 유전자와 인접한 발현 조절 서열 및 관심 유전자를 조절하기 위해 교차하여(in trans) 작용하거나 멀리서 작용하는 발현 조절 서열 둘 모두를 포함한다.

[0237] 발현 조절 서열은 적절한 전사 개시, 종료, 프로모터 및 인핸서 서열; 효과적인 RNA 가공 신호, 예를 들어, 토끼 베타-글로빈 polyA를 포함하는 스플라이싱 및 아데닐중합체형성(poly A) 신호; 세포질 mRNA를 안정화시키는 서열; 번역 효율을 향상시키는 서열(예를 들어, 코작(Kozak) 컨센서스 서열); 단백질 안정성을 향상시키는 서열; 및 원하는 경우 인코딩된 생성물의 분비를 향상시키는 서열을 포함한다. 다른 서열 중에서도, 키메라 인트론이 사용될 수 있다.

[0238] 일부 구현예에서, 우드척 간염 바이러스 전사후 조절 요소(WPRE)(Zuffrey et al. (1999) J Virol; 73(4):2886-9)가 트랜스진에 작동 가능하게 연결될 수 있다. 예시적 WPRE는 SEQ ID NO: 26에 제공된다.

[0239] "프로모터"는 RNA 중합효소의 결합을 가능하게 하고, 유전자의 전사를 유도하는 뉴클레오티드 서열이다. 통상적으로, 프로모터는 유전자의 전사 시작 부위에 근접한 유전자의 5' 비-코딩 영역에 위치된다. 전사 개시에서 기능하는 프로모터 내의 서열 요소는 종종 컨센서스 뉴클레오티드 서열을 특징으로 한다. 프로모터의 예는 박테리아, 효모, 식물, 바이러스, 및 포유동물(인간을 포함함)로부터의 프로모터를 포함하나, 이에 제한되지는 않는다. 내부, 천연, 항시성, 유도성 및/또는 조직-특이성인 프로모터를 포함하는 매우 많은 수의 발현 조절 서열이 당 분야에 공지되어 있으며, 사용될 수 있다.

[0240] 항시성 프로모터의 예는 TBG 프로모터, 레트로바이러스 라우스 육종 바이러스 LTR 프로모터(선택적으로, 인핸서

를 가짐), 사이토메갈로바이러스(CMV) 프로모터(선택적으로, CMV 인핸서를 가짐, 예를 들어, 문헌[Boshart et al, Cell, 41:521-530 (1985)] 참조), CASI 프로모터, SV40 프로모터, 디하이드로폴레이트 환원효소 프로모터, β -액틴 프로모터, 포스포글리세롤 키나제(PGK) 프로모터, 및 EF1a 프로모터(Invitrogen)를 포함하나, 이에 제한되지는 않는다.

[0241] 일부 구현예에서, 프로모터는 CASI 프로모터(예를 들어, W02012/115980호 참조)이다. CASI 프로모터는 CMV 인핸서의 일부, 닭 베타-액틴 프로모터의 일부, 및 UBC 인핸서의 일부를 함유하는 합성 프로모터이다. 일부 구현예에서, CASI 프로모터는 SEQ ID NO: 12와 적어도 약 90%, 적어도 약 95%, 적어도 약 96%, 적어도 약 97%, 적어도 약 98%, 적어도 약 99% 또는 그 초과 of 서열 동일성을 갖는 핵산 서열을 포함할 수 있다. 일부 구현예에서, 프로모터는 SEQ ID NO: 12의 핵산 서열을 포함하거나, 이로 구성된다.

[0242] 유도성 프로모터는 유전자 발현의 조절을 가능하게 하며, 외인적으로 공급된 화합물, 환경 요인, 예를 들어, 온도, 또는 특정 생리학적 상태의 존재, 예를 들어, 급성기, 세포의 특정 분화 상태에 의해, 또는 복제하는 세포에서만 조절될 수 있다. 유도성 프로모터 및 유도성 시스템은 Invitrogen, Clontech 및 Ariad를 포함하나, 이에 제한되지는 않는 다양한 상업적 공급처로부터 이용 가능하다. 많은 다른 시스템이 기재되어 있으며, 당업자에 의해 용이하게 선택될 수 있다. 예를 들어, 유도성 프로모터는 아연-유도성 양 메탈로티오닌(MT) 프로모터 및 텍사메타손(Dex)-유도성 마우스 유암 바이러스(MMTV) 프로모터를 포함한다. 다른 유도성 시스템은 T7 중합효소 프로모터 시스템(WO 98/10088호); 엑디손 곤충 프로모터(No et al, Proc. Natl. Acad. Sci. USA, 93:3346-3351 (1996)), 테트라사이클린-억제성 시스템(Gossen et al, Proc. Natl. Acad. Sci. USA, 89:5547-5551 (1992)), 테트라사이클린-유도성 시스템(Gossen et al, Science, 378:1766-1769 (1995), 또한 Harvey et al, Curr. Opin. Chem. Biol, 2:512-518 (1998) 참조)을 포함한다. 다른 시스템은 FK506 이합체, 카스트라디올(castradiol), 디페놀 무리슬레론(diphenol murislerone)을 이용하는 VP16 또는 p65, RU486-유도성 시스템(Wang et al, Nat. Biotech., 15:239-243 (1997) 및 Wang et al, Gene Ther., 4:432-441 (1997)) 및 라파마이신-유도성 시스템(Magari et al, J. Clin. Invest., 100:2865-2872 (1997))을 포함한다. 일부 유도성 프로모터의 효과는 시간이 지남에 따라 증가한다. 이러한 경우에, 다수의 억제인자, 예를 들어, IRES에 의해 TetR에 연결된 TetR을 일렬로 삽입함으로써 상기 시스템의 효과를 향상시킬 수 있다.

[0243] 또 다른 구현예에서, 트랜스진에 대한 자연 프로모터가 사용될 것이다. 자연 프로모터는 트랜스진의 발현이 자연 발현을 모방해야 하는 것이 요망되는 경우에 바람직할 수 있다. 자연 프로모터는 트랜스진의 발현이 시간적 또는 발달적으로, 또는 조직-특이적 방식으로, 또는 특정 전사 자극에 반응하여 조절되어야 하는 경우에 사용될 수 있다. 추가의 구현예에서, 다른 자연 발현 조절 요소, 예를 들어, 인핸서 요소, 아데닐중합체형성 부위 또는 코작 컨센서스 서열이 또한 자연 발현을 모방하기 위해 이용될 수 있다.

[0244] 트랜스진은 조직-특이적 프로모터에 작동 가능하게 연결될 수 있다. 예를 들어, 골격근에서의 발현이 요망되는 경우, 근육에서 활성인 프로모터가 사용되어야 한다. 이들은 골격 β -액틴, 미오신 경쇄 2A, 디스트로핀, 근육 크레아틴 키나제를 인코딩하는 유전자로부터의 프로모터뿐만 아니라 자연 발생 프로모터보다 높은 활성을 갖는 합성 근육 프로모터를 포함한다(Li et al, Nat. Biotech., 17:241-245 (1999) 참조). 조직 특이적인 프로모터의 예는 다른 것들 중에서 간(알부민, Miyatake et al, J. Virol, 71:5124-32 (1997); B형 간염 바이러스 코어 프로모터, Sandig et al, Gene Ther., 3:1002-9 (1996); 알파-태아단백질(AFP), Arbutnot et al., Hum. Gene Ther., 7: 1503-14 (1996)), 뼈 오스테오칼신(Stein et al, Mol. Biol. Rep., 24:185-96 (1997)); 뼈 시알로단백질(Chen et al., J. Bone Miner. Res., 11:654-64 (1996)), 림프구(CD2, Hansal et al, J. Immunol, 161:1063-8 (1998); 면역글로불린 중쇄; T 세포 수용체 사슬), 신경세포, 예를 들어, 뉴런-특이적 에놀라제(NSE) 프로모터(Andersen et al, Cell. Mol. Neurobiol, 13:503-15 (1993)), 신경미세섬유 경쇄 유전자(Piccioli et al, Proc. Natl. Acad. Sci. USA, 88:5611-5 (1991)), 및 뉴런-특이적 vgf 유전자(Piccioli et al, Neuron, 15:373-84 (1995))에 대해 공지되어 있다.

[0245] 선택적으로, 치료적으로 유용한 생성물 또는 면역원성 생성물을 인코딩하는 트랜스진을 운반하는 벡터는 다른 것들 중에서 제네티신, 하이그로마이신 또는 퓨리마이신 내성을 인코딩하는 서열을 포함할 수 있는 선택 가능한 마커 또는 리포터 유전자를 또한 포함할 수 있다. 앰피실린 내성과 같은 상기 선택 가능한 리포터 또는 마커 유전자(바람직하게는, 바이러스 입자로 패키징되는 바이러스 유전체 외부에 위치됨)는 박테리아 세포에서 플라스미드의 존재를 알리기 위해 사용될 수 있다. 벡터의 다른 성분은 복제 기점을 포함할 수 있다.

[0246] 이들 벡터는 당업자에게 공지된 기술과 함께 본원에 제공된 기술 및 서열을 이용하여 생성된다. 상기 기술은 본문에 기재된 것과 같은 cDNA의 통상적인 클로닝 기술, 아데노바이러스 유전체의 중첩 올리고뉴클레오타이드 서열

의 이용, 중합효소 연쇄 반응, 및 원하는 뉴클레오티드 서열을 제공하는 임의의 적합한 방법을 포함한다.

[0247] **치료 및 예방**

[0248] 제조합 ChAd155-기반 벡터는 시험관 내, 생체 외, 및 생체 내에서 인간 또는 비-유인원 포유동물로의 유전자 전달에 유용하다.

[0249] 본원에 기재된 제조합 아데노바이러스 벡터는 시험관 내에서 이중성 트랜스진에 의해 인코딩된 생성물의 생성을 위한 발현 벡터로 사용될 수 있다. 예를 들어, 트랜스진을 함유하는 제조합 복제-부적격 아데노바이러스는 상기 기재된 바와 같은 상보성 세포주로 형질감염될 수 있다.

[0250] ChAd155-유래 제조합 아데노바이러스 벡터는 유기체가 하나 이상의 아데노바이러스 혈청형에 대한 중화 항체를 갖는 경우에도 생체 내 또는 생체 외에서 선택된 숙주 세포로 선택된 트랜스진을 전달할 수 있는 효과적인 유전자 전달 비히클을 제공한다. 일 구현예에서, 벡터 및 세포는 생체 외에서 혼합되고; 감염된 세포는 통상적인 방법을 이용하여 배양되고; 형질도입된 세포는 환자로 재주입된다. 이들 기술은 치료 목적 및 보호 면역 유도를 포함하는 면역화를 위한 유전자 전달에 특히 매우 적합하다.

[0251] 면역원성 트랜스진

[0252] 제조합 ChAd155 벡터는 또한 면역원성 조성물로 투여될 수 있다. 본원에 기재된 바와 같은 면역원성 조성물은 포유동물, 적합하게는 인간으로의 전달 후 벡터에 의해 전달된 트랜스진 생성물에 대해 면역 반응, 예를 들어, 체액성(예를 들어, 항체) 및/또는 세포-매개(예를 들어, 세포독성 T 세포) 반응을 유도할 수 있는 하나 이상의 제조합 ChAd155 벡터를 포함하는 조성물이다. 제조합 아데노바이러스는 원하는 면역원을 인코딩하는 유전자를 포함(적합하게는, 이의 유전자 결실 중 임의의 결실 내에 포함)할 수 있으며, 따라서 백신에서 사용될 수 있다. 제조합 아데노바이러스는 면역 반응의 유도에 중요하고, 병원체의 확산을 제한할 수 있는 항원(들)이 확인되었고, cDNA가 이용 가능한 임의의 병원체에 대한 예방 또는 치료 백신으로 사용될 수 있다.

[0253] 상기 백신 또는 다른 면역원성 조성물은 적합한 전달 비히클로 제형화될 수 있다. 일반적으로, 면역원성 조성물에 대한 용량은 하기 '전달 방법 및 투여량'에 정의된 범위 내이다. 선택된 유전자의 면역성의 수준은, 존재시, 부스터에 대한 필요성을 결정하기 위해 모니터링될 수 있다. 혈청에서의 항체 역가의 평가 후, 선택적 부스터 면역화가 요망될 수 있다.

[0254] 선택적으로, 본 발명의 백신 또는 면역원성 조성물은, 예를 들어, 애주번트, 안정화제, pH 조절제, 보존제 등을 포함하는 다른 성분을 함유하도록 제형화될 수 있다. 적합한 애주번트의 예는 하기 '애주번트'에 제공된다. 상기 애주번트는 항원만 인코딩하는 DNA 백신으로 프라이밍시 생성된 면역 반응에 비해 항원-특이적 면역 반응을 향상시키기 위해 항원을 인코딩하는 프라이밍 DNA 백신과 함께 투여될 수 있다. 대안적으로, 상기 애주번트는 본 발명의 ChAd155 벡터를 포함하는 투여 요법에서 투여되는 폴리펩티드 항원과 함께 투여될 수 있다(하기 '투여 요법'에 기재됨).

[0255] 제조합 아데노바이러스는 면역원성 양, 즉, 원하는 표적 세포를 형질감염시키기 위해 투여 경로에서 효과적이고, 면역 반응을 유도하기 위해 선택된 유전자의 충분한 수준의 발현을 제공하는 제조합 아데노바이러스의 양으로 투여된다. 보호 면역이 제공되는 경우, 제조합 아데노바이러스는 감염 및/또는 재발성 질병을 예방하는데 유용한 백신 조성물인 것으로 간주된다.

[0256] 본원에 기재된 제조합 벡터는 세포용해성 T 세포 및 벡터에 의해 발현된 삽입된 이중성 항원 단백질에 특이적인 항체를 유도하는데 매우 효과적일 것으로 예상된다.

[0257] 다른 병원체에 대해 인간 또는 비-인간 동물을 면역화시키는데 유용한 본 발명의 벡터에 의해 발현된 면역원은, 예를 들어, 인간 및 비-인간 척추동물을 감염시키는 박테리아, 진균, 기생 미생물 또는 다세포 기생충을 포함하거나, 암세포 또는 종양 세포로부터 유래된다. 예를 들어, 면역원은 다양한 바이러스 과로부터 선택될 수 있다. 면역 반응이 요망되는 바이러스 과의 예는 호흡기 바이러스, 예를 들어, 호흡기 세포 융합 바이러스(RSV) 및 다른 파라믹소바이러스, 예를 들어, 인간 메타뉴모바이러스, hMPV 및 파라인플루엔자 바이러스(PIV)를 포함한다.

[0258] 인간 또는 비-인간 동물을 면역화시키기 위한 면역원으로 유용한 RSV의 적합한 항원은 융합 단백질(F), 부착 단백질(G), 기질 단백질(M2) 및 핵단백질(N)로부터 선택될 수 있다. 용어 "F 단백질" 또는 "융합 단백질" 또는 "F 단백질 폴리펩티드" 또는 "융합 단백질 폴리펩티드"는 RSV 융합 단백질 폴리펩티드의 아미노산 서열의 일부 또는 전부를 갖는 폴리펩티드 또는 단백질을 나타낸다. 유사하게, 용어 "G 단백질" 또는 "G 단백질 폴리펩티드"는 RSV 부착 단백질 폴리펩티드의 아미노산 서열의 일부 또는 전부를 갖는 폴리펩티드 또는 단백질을 나타낸다. 용

어 "M 단백질" 또는 "기질 단백질" 또는 "M 단백질 폴리펩티드"는 RSV 기질 단백질의 아미노산 서열의 일부 또는 전부를 갖는 폴리펩티드 또는 단백질을 나타내며, M2-1(본원에서 M2.1로 기재될 수 있음) 및 M2-2 유전자 생성물 중 어느 하나 또는 둘 모두를 포함할 수 있다. 마찬가지로, 용어 "N 단백질" 또는 "뉴클레오캡시드 단백질" 또는 "N 단백질 폴리펩티드"는 RSV 핵단백질의 아미노산 서열의 일부 또는 전부를 갖는 폴리펩티드 또는 단백질을 나타낸다.

[0259] G 당단백질의 항원성에서의 차이를 주로 기초로 하여 A 및 B 그룹의 2개 그룹의 인간 RSV 균주가 기재되었다. RSV의 다수의 균주가 현재까지 단리되었고, 이 중 임의의 것이 본원에 개시된 면역원성 조합물의 항원의 상황에서 적합하다. GenBank 및/또는 EMBL 등록 번호에 의해 표시된 예시적 균주는 US 공개 출원 번호 2010/0203071호 (W02008114149호)에서 발견될 수 있으며, 이는 본 발명에서 사용하기에 적합한 RSV F 및 G 단백질의 핵산 및 폴리펩티드 서열을 개시하는 목적으로 참조로서 본원에 포함된다. 일 구현예에서, RSV F 단백질은 RSV F 단백질의 엑토도메인(F Δ TM)일 수 있다.

[0260] 예시적 M 및 N 단백질 핵산 및 단백질 서열은, 예를 들어, US 공개 출원 번호 2014/0141042호(W02012/089833호)에서 발견될 수 있으며, 이는 본 발명에서 사용하기에 적합한 RSV M 및 N 단백질의 핵산 및 폴리펩티드 서열을 개시하기 위한 목적으로 본원에 포함된다.

[0261] 적합하게는, 본 발명에서 사용하기 위해, 핵산은 RSV F 항원 및 RSV, M 및 N 항원을 인코딩한다. 더욱 특히, 핵산은 RSV F Δ TM 항원 및 RSV M2-1 및 N 항원을 인코딩하며, 여기서 자가 절단 부위가 RSV F Δ TM 항원과 RSV M2-1 사이에 포함되고, 가요성 링커가 RSV M2-1과 N 항원 사이에 포함된다. 일 구현예에서, 적합한 핵산은 SEQ ID NO:37에 의해 표시되는 폴리펩티드를 인코딩한다.

[0262] 일 구현예에서, 면역원은 레트로바이러스, 예를 들어, 렌티바이러스, 예를 들어, 인간 면역결핍 바이러스(HIV)로부터 유래될 수 있다. 상기 구현예에서, 면역원은 HIV-1 또는 HIV-2로부터 유래될 수 있다.

[0263] HIV 유전체는 다수의 상이한 단백질을 인코딩하며, 이들 각각은 본 발명의 벡터에 의해 발현되는 경우 전체적으로 또는 단편으로서 면역원성일 수 있다. 외피 단백질은, 예를 들어, gp120, gp41 및 Env 전구체 gp160을 포함한다. HIV의 비-외피 단백질은, 예를 들어, 내부 구조 단백질, 예를 들어, gag 및 pol 유전자의 생성물 및 다른 비-구조 단백질, 예를 들어, Rev, Nef, Vif 및 Tat을 포함한다. 일 구현예에서, 본 발명의 벡터는 HIV Gag를 포함하는 하나 이상의 폴리펩티드를 인코딩한다.

[0264] Gag 유전자는 전구체 다기능단백질로 번역되며, 이는 프로테아제에 의해 절단되어 기질 단백질(p17), 캡시드(p24), 뉴클레오캡시드(p9), p6 및 2개의 공간 펩티드, p2 및 p1을 포함하는 생성물을 생성시키며, 이들 모두는 Gag 단편의 예이다.

[0265] Gag 유전자는 p55로도 언급되는 55-킬로달톤(kD) Gag 전구체 단백질을 발생시키며, 이는 스플라이싱되지 않은 바이러스 mRNA로부터 발현된다. 번역 동안, p55의 N 말단은 미리스토일화되어, 세포막의 세포질 측면과 이의 회합을 촉발시킨다. 막-회합된 Gag 다기능단백질은 감염된 세포의 표면으로부터 바이러스 입자의 발아를 촉발시키는 다른 바이러스 및 세포 단백질과 함께 바이러스 유전체 RNA의 2개 카피를 모집한다. 발아 후, p55는 바이러스 성숙 과정 동안 바이러스 인코딩된 프로테아제(pol 유전자의 생성물)에 의해 MA(기질 [p17]), CA(캡시드 [p24]), NC(뉴클레오캡시드 [p9]), 및 p6으로 명명된 4개의 더 작은 단백질로 절단되며, 이들 모두는 Gag 단편의 예이다. 일 구현예에서, 본 발명의 벡터는 SEQ ID NO: 38의 Gag 폴리펩티드를 포함한다.

[0266] 애쥬번트

[0267] 본원에서 사용되는 "애쥬번트"는 면역원에 대한 면역 반응을 향상시키는 조성물을 나타낸다. 이러한 애쥬번트의 예는 무기 애쥬번트(예를 들어, 무기 금속 염, 예를 들어, 알루미늄 포스페이트 또는 알루미늄 하이드록사이드), 유기 애쥬번트(예를 들어, 사포닌, 예를 들어, QS21, 또는 스쿠알렌), 오일-기반 애쥬번트(예를 들어, 프로인트 완전 애쥬번트 및 프로인트 불완전 애쥬번트), 사이토카인(예를 들어, IL-1 β , IL-2, IL-7, IL-12, IL-18, GM-CSF, 및 INF- γ) 미립자 애쥬번트(예를 들어, 면역-자극성 복합체(ISCOMS), 리포솜, 또는 생물분해성 미세구), 바이로솜, 박테리아 애쥬번트(예를 들어, 모노포스포릴 지질 A, 예를 들어, 3-데-O-아실화 모노포스포릴 지질 A(3D-MPL), 또는 류라밀 펩티드), 합성 애쥬번트(예를 들어, 비-이온성 블록 공중합체, 류라밀 펩티드 유사체, 또는 합성 지질 A), 합성 폴리뉴클레오타이드 애쥬번트(예를 들어, 폴리아르기닌 또는 폴리리신) 및 메틸화되지 않은 CpG 디뉴클레오타이드("CpG")를 함유하는 면역자극성 올리고뉴클레오타이드를 포함하나, 이에 제한되지는 않는다.

[0268] 한 적합한 애쥬번트는 모노포스포릴 지질 A(MPL), 특히 3-데-O-아실화 모노포스포릴 지질 A(3D-MPL)이다. 화학

적으로, 이는 종종 3-데-O-아실화 포노포스포릴 지질 A와 4, 5 또는 6개의 아실화된 사슬의 혼합물로 제공된다. 이는 GB 2122204B호에 교시된 방법에 의해 정제되고 제조될 수 있으며, 상기 참조는 또한 디포스포릴 지질 A, 및 이의 3-O-데아실화된 변이체의 제조를 개시한다. 다른 정제된 지질다당류 및 합성 지질다당류가 기재되었다(U.S. 특허 번호 6,005,099호 및 EP 0 729 473 B1호; Hilgers et al., 1986, Int.Arch.Allergy.Immunol., 79(4):392-6; Hilgers et al., 1987, Immunology, 60(1):141-6; 및 EP 0 549 074 B1).

[0269] 사포닌이 또한 적합한 애주번트이다(Lacaille-Dubois, M and Wagner H, A review of the biological and pharmacological activities of saponins. Phytomedicine vol 2 pp 363-386 (1996) 참조). 예를 들어, 사포닌 Quil A(남아메리카 나무 퀴라자 사포나리아 몰리나(Quillaja Saponaria Molina)의 껍질로부터 유래됨), 및 이의 분획이 U.S. 특허 번호 5,057,540호 및 문헌[Kensil, Crit. Rev. Ther. Drug Carrier Syst., 1996, 12:1-55]; 및 EP 0 362 279 B1호에 기재되어 있다. Quil A의 정제된 분획, 예를 들어, QS21 및 QS17이 또한 면역자극제로 공지되어 있으며; 이의 생성 방법은 U.S. 특허 번호 5,057,540호 및 EP 0 362 279 B1호에 개시되어 있다. QS7(Quil-A의 비-용혈 분획)이 또한 상기 참조에 기재되어 있다. QS21의 사용은 문헌[Kensil et al. (1991, J. Immunology, 146: 431-437)]에 추가로 기재되어 있다. QS21 및 폴리소르베이트 또는 사이클로덱스트린의 조합물이 또한 공지되어 있다(WO 99/10008호). QuilA의 분획, 예를 들어, QS21 및 QS7을 포함하는 미립자 애주번트 시스템이 WO 96/33739호 및 WO 96/11711호에 기재되어 있다.

[0270] 또 다른 애주번트는 메틸화되지 않은 CpG 디뉴클레오티드("CpG")를 함유하는 면역자극성 올리고뉴클레오티드이다(Krieg, Nature 374:546 (1995)). CpG는 DNA에 존재하는 시토신-구아노신 디뉴클레오티드 모티프에 대한 약어이다. CpG는 전신 및 점막 경로 둘 모두로 투여되는 경우에 애주번트로 공지되어 있다(WO 96/02555호, EP 468520호, Davis et al, J.Immunol, 1998, 160:870-876; McCluskie and Davis, J.Immunol., 1998, 161:4463-6). 백신으로 제형화되는 경우 CpG는 자유 항원과 함께 자유 용액으로 투여될 수 있거나(WO 96/02555호), 항원에 공유적으로 컨쥬게이션될 수 있거나(WO 98/16247호), 담체, 예를 들어, 알루미늄 하이드록시드와 함께 제형화될 수 있다(Brazolot-Millan et al., Proc. Natl. Acad. Sci., USA, 1998, 95:15553-8).

[0271] 상기 기재된 것과 같은 애주번트는 담체, 예를 들어, 리포솜, 수중유 에멀전, 및/또는 금속 염(알루미늄 하이드록시드와 같은 알루미늄 염을 포함함)과 함께 제형화될 수 있다. 예를 들어, 3D-MPL은 알루미늄 하이드록시드(EP 0 689 454호) 또는 수중유 에멀전(WO 95/17210호)과 함께 제형화될 수 있고; QS21은 콜레스테롤 함유 리포솜(WO 96/33739호), 수중유 에멀전(WO 95/17210호) 또는 백반(WO 98/15287호)과 함께 제형화될 수 있고; CpG는 백반(Brazolot-Millan, 상기) 또는 다른 양이온성 담체와 함께 제형화될 수 있다.

[0272] 애주번트의 조합물, 특히 모노포스포릴 지질 A 및 사포닌 유도체의 조합물(예를 들어, WO 94/00153호; WO 95/17210호; WO 96/33739호; WO 98/56414호; WO 99/12565호; WO 99/11241호 참조), 더욱 특히 WO 94/00153호에 개시된 바와 같은 QS21 및 3D-MPL의 조합물, 또는 WO 96/33739호에 개시된 바와 같은 QS21이 콜레스테롤-함유 리포솜(DQ)에서 쉼팅되는 조성물이 본 발명에서 사용될 수 있다. 대안적으로, CpG 및 사포닌, 예를 들어, QS21의 조합물이 본 발명에서 사용하기에 적합한 애주번트이다. 수중유 에멀전 중 QS21, 3D-MPL & 토크페롤을 포함하는 효능 있는 애주번트 제형이 WO 95/17210호에 기재되어 있으며, 본 발명에서 사용하기 위한 또 다른 제형이다. 사포닌 애주번트는 리포솜 내에서 제형화될 수 있고, 면역자극성 올리고뉴클레오티드와 조합될 수 있다. 따라서, 적합한 애주번트 시스템은, 예를 들어, 모노포스포릴 지질 A, 바람직하게는 3D-MPL과 함께 알루미늄 염의 조합물을 포함한다(예를 들어, WO00/23105호에 기재됨). 추가의 예시적 애주번트는 QS21 및/또는 MPL 및/또는 CpG를 포함한다. QS21은 WO 96/33739호에 개시된 바와 같이 콜레스테롤-함유 리포솜 내에서 쉼팅될 수 있다.

[0273] 다른 적합한 애주번트는 알킬 글루코사미나이드 포스페이트(AGP), 예를 들어, WO9850399호 또는 U.S. 특허 번호 6,303,347호에 개시된 것(AGP의 제조를 위한 공정이 또한 개시됨), 또는 U.S. 특허 번호 6,764,840호에 개시된 바와 같은 AGP의 약학적으로 허용되는 염을 포함한다. 일부 AGP는 TLR4 효능제이고, 일부는 TLR4 길항제이다. 둘 모두가 애주번트로서 유용한 것으로 생각된다.

[0274] 예방접종에서 사용되는 발현 시스템에 의해 포함되는 항원에 대한 불변 사슬의 융합이 아데노바이러스와 함께 투여되는 경우 상기 항원에 대한 면역 반응을 증가시키는 것으로 밝혀졌다(US 2011/0293704호로 공개되고, 불변 사슬 서열을 개시하기 위한 참조로서 포함되는 WO 2007/062656호). 따라서, 본 발명의 일 구현예에서, 면역원성 트랜스진은 재조합 ChAd155 바이러스 벡터에서 불변 사슬과 공동-발현될 수 있다.

[0275] 또 다른 구현예에서, 본 발명은 면역조절 효과 반응을 유도하거나, 대상체에 ChAd155 캡시드를 전달함으로써 또 다른 활성제에 대한 세포독성 T 세포 반응을 향상시키거나 애주번트화시키기 위한 ChAd155의 캡시드(선택적으로, 온전한 또는 재조합 바이러스 입자 또는 빈 캡시드가 사용됨)의 용도를 제공한다. ChAd155

캡시드는 단독으로 또는 이에 대한 면역 반응을 향상시키기 위한 활성제와 함께 조합 요법으로 전달될 수 있다. 유리하게는, 원하는 효과가 숙주를 아데노바이러스로 감염시키지 않고 달성될 수 있다.

[0276] 투여 요법

[0277] 일반적으로, ChAd155 재조합 아데노바이러스 벡터는 치료용 또는 면역원성 분자(예를 들어, 단백질)의 전달에 사용될 것이다. 본 발명의 재조합 아데노바이러스 벡터가 재조합 아데노바이러스 벡터의 반복 전달을 포함하는 요법에서 사용하기에 특히 매우 적합하다는 것이 둘 모두의 적용에서 용이하게 이해될 것이다. 상기 요법은 통상적으로 바이러스 캡시드가 교대로 반복되는 일련의 바이러스 벡터의 전달을 포함한다. 바이러스 캡시드는 각각의 후속 투여에 대해, 또는 특정 혈청형 캡시드의 미리 선택된 투여 횟수(예를 들어, 1회, 2회, 3회, 4회 또는 그 초과) 후에 변경될 수 있다. 따라서, 요법은 제1 캡시드를 갖는 재조합 아데노바이러스의 전달, 제2 캡시드를 갖는 재조합 아데노바이러스의 전달, 및 제3 캡시드를 갖는 재조합 아데노바이러스의 전달을 포함할 수 있다. 본 발명의 아데노바이러스 캡시드를 단독으로, 서로 조합하여, 또는 다른 아데노바이러스(바람직하게는, 면역학적으로 비-교차반응성인 아데노바이러스)와 조합하여 사용하는 다양한 다른 요법이 당업자에게 명백할 것이다. 선택적으로, 상기 요법은 다른 비-인간 영장류 아데노바이러스, 인간 아데노바이러스, 또는 본원에 기재된 것과 같은 인공 서열의 캡시드를 갖는 재조합 아데노바이러스의 투여를 포함할 수 있다.

[0278] 본 발명의 아데노바이러스 벡터는 트랜스진의 다수의 아데노바이러스-매개 전달이 요망되는 치료 요법, 예를 들어, 동일한 트랜스진의 재전달을 포함하는 요법 또는 다른 트랜스진의 전달을 포함하는 조합 요법에 특히 매우 적합하다. 상기 요법은 ChAd155 아데노바이러스 벡터의 투여 후, 동일 혈청형 아데노바이러스로부터의 벡터를 이용한 재투여를 포함할 수 있다. 특히 바람직한 요법은 ChAd155 아데노바이러스 벡터의 투여를 포함하며, 여기서 제1 투여에서 전달되는 벡터의 아데노바이러스 캡시드 서열의 공급원은 1회 이상의 후속 투여에서 사용되는 바이러스 벡터의 아데노바이러스 캡시드 서열의 공급원과 상이하다. 예를 들어, 치료 요법은 ChAd155 벡터의 투여 및 동일하거나 상이한 혈청형의 하나 이상의 아데노바이러스 벡터를 이용한 반복 투여를 포함한다.

[0279] 또 다른 예에서, 치료 요법은 아데노바이러스 벡터의 투여 후, 첫번째 전달된 아데노바이러스 벡터 내의 캡시드의 공급원과 상이한 캡시드를 갖는 ChAd155 벡터를 이용한 반복 투여, 및 선택적으로 이전 투여 단계에서 벡터의 아데노바이러스 캡시드의 공급원과 동일하거나 바람직하게는 상이한 또 다른 벡터를 이용한 추가 투여를 포함한다. 이들 요법은 ChAd155 서열을 이용하여 작제된 아데노바이러스 벡터의 전달로 제한되지 않는다. 오히려, 이들 요법은 ChAd155 벡터와 조합된 다른 비-인간 영장류 아데노바이러스 서열, 또는 인간 아데노바이러스 서열을 포함하는 다른 아데노바이러스 서열을 포함하나 이에 제한되지는 않는 다른 아데노바이러스 서열을 용이하게 이용할 수 있다.

[0280] 추가 예에서, 치료 요법은 (i) 하나 이상의 ChAd155 아데노바이러스 벡터 및 (ii) 추가 성분, 예를 들어, 비-아데노바이러스 벡터, 비-바이러스 벡터, 및/또는 애쥬반트와 선택적으로 동시에 투여되는 다양한 다른 치료적으로 유용한 화합물 또는 분자, 예를 들어, 항원성 단백질의 동시(예를 들어, 공동-투여) 또는 순차적(예를 들어, 프라임-부스트) 전달을 포함할 수 있다. 공동-투여의 예는 동측성 공동-투여 및 대측성 공동-투여(하기 '전달 방법 및 투여량'에 추가로 기재됨)를 포함한다.

[0281] 하나 이상의 ChAd155 아데노바이러스 벡터와 동시 전달 또는 특히 순차적 전달(예를 들어, 프라임-부스트)에서 사용하기에 적합한 비-아데노바이러스 벡터는 하나 이상의 포스바이러스 벡터를 포함한다. 적합하게는, 포스바이러스 벡터는 아파 코르도포스바이러스아파, 더욱 적합하게는 오르토폭스(orthopox), 파라포스(parapox), 야타포스(yatapox), 아비포스(avipox)(적합하게는, 카나리포스(canarypox)(ALVAC) 또는 조류포스(FPV)) 및 몰루시포스(molluscipox)로 구성된 군으로부터 선택되는 상기 아파 내의 속에 속한다. 더욱 더 적합하게는, 포스바이러스 벡터는 오르토폭스에 속하며, 백시니아 바이러스, NYVAC(백시니아의 코펜하겐(Copenhagen) 균주로부터 유래됨), 변형된 백시니아 앙카라(MVA), 우두바이러스 및 원숭이포스 바이러스로 구성된 군으로부터 선택된다. 가장 적합하게는, 포스바이러스 벡터는 MVA이다.

[0282] "동시" 투여는 적합하게는 동일 진행 면역 반응을 나타낸다. 바람직하게는, 둘 모두의 성분은 동시에(예를 들어, DNA 및 단백질 둘 모두의 동시 투여) 투여되나, 한 성분은 수분 내에(예를 들어, 동일한 의학적 약속 또는 의사 방문시), 수시간 내에 투여될 수 있다. 상기 투여가 또한 공동-투여로 언급된다. 일부 구현예에서, 공동-투여는 아데노바이러스 벡터, 애쥬반트 및 단백질 성분의 투여를 나타낼 수 있다. 다른 구현예에서, 공동-투여는 아데노바이러스 벡터 및 또 다른 바이러스 벡터, 예를 들어, 제2의 아데노바이러스 벡터 또는 포스바이러스, 예를 들어, MVA의 투여를 나타낸다. 다른 구현예에서, 공동-투여는 아데노바이러스 벡터 및 선택적으로 애쥬반트화되는 단백질 성분의 투여를 나타낸다.

- [0283] 프라임-부스트 요법이 이용될 수 있다. 프라임-부스트는 (i) 면역계의 최초 프라임 후, (ii) 일차 면역 반응이 확립된 후 수주 또는 수개월 후의 면역계의 이차 또는 부스팅의 2개의 별개의 면역 반응을 나타낸다.
- [0284] 상기 요법은 면역계를 프라임하기 위한 재조합 ChAd155 벡터의 투여와 전통적인 항원, 예를 들어, 단백질(선택적으로, 애뉴먼트와 공동-투여됨), 또는 상기 항원을 인코딩하는 서열을 갖는 재조합 바이러스를 이용한 제2의 부스터 투여를 포함할 수 있다(예를 들어, WO 00/11140호). 대안적으로, 면역화 요법은 항원을 인코딩하는 벡터(바이러스 또는 DNA-기반)에 대한 면역 반응을 부스팅하기 위해 재조합 ChAd155 벡터의 투여를 포함할 수 있다. 또 다른 대안에서, 면역화 요법은 단백질의 투여 후, 항원을 인코딩하는 재조합 ChAd155 벡터를 이용한 부스터를 포함한다. 한 예에서, 프라임-부스트 요법은 항원이 유래되는 바이러스, 박테리아 또는 다른 유기체에 대한 보호 면역 반응을 제공할 수 있다. 또 다른 구현예에서, 프라임-부스트 요법은 치료가 제공되는 질환의 존재의 검출을 위한 통상적인 검정을 이용하여 측정될 수 있는 치료 효과를 제공한다.
- [0285] 바람직하게는, 부스팅 조성물은 대상체에 프라임 조성물을 투여한 후 약 2 내지 약 27주 후에 투여된다. 부스팅 조성물의 투여는 프라임 백신에 의해 투여되는 것과 동일한 항원 또는 상이한 항원을 전달할 수 있거나 이를 함유하는 유효량의 부스팅 조성물을 이용하여 달성된다. 부스팅 조성물은 동일한 바이러스 공급원 또는 또 다른 공급원으로부터 유래되는 재조합 바이러스 벡터로 구성될 수 있다. 대안적으로, 부스팅 조성물은 프라임 백신에서 인코딩된 것과 동일한 항원을 함유하나, 단백질 형태인 조성물일 수 있으며, 이러한 조성물은 숙주에서 면역 반응을 유도한다. 부스팅 조성물의 주요 필요조건은 조성물의 항원이 프라임 조성물에 의해 인코딩되는 것과 동일한 항원이거나 교차-반응성 항원이라는 것이다.
- [0286] 전달 방법 및 투여량
- [0287] 벡터는 약학적으로 또는 생리학적으로 허용되는 담체, 예를 들어, 등장성 염수; 당업자에게 명백할 등장성 염 용액 또는 다른 제형에 현탁되거나 용해됨으로써 투여를 위해 제조될 수 있다. 적절한 담체는 당업자에게 명백할 것이며, 투여 경로에 대부분 좌우될 것이다. 본원에 기재된 조성물은 생물분해성 생체적합성 중합체를 이용하는 서방형 제형으로 포유동물에 투여될 수 있거나, 마이셀, 젤 및 리포솜을 이용하여 현장 전달될 수 있다.
- [0288] 일부 구현예에서, 본 발명의 재조합 아데노바이러스는 근내 주사, 질내 주사, 정맥내 주사, 복강내 주사, 피하 주사, 경피 투여, 피내 투여, 코 투여 또는 경구 투여에 의해 대상체에 투여된다.
- [0289] 치료 요법이 각각 상이한 조성물에 제형화된 하나 이상의 ChAd155 아데노바이러스 벡터 및 추가 성분의 공동-투여를 포함하는 경우, 이들은 바람직하게는 동일 부위 또는 그 부근에서 공동-국소적으로 투여된다. 예를 들어, 성분은 동일 측면 또는 말단("공동-측면" 투여) 또는 반대 측면 또는 말단("대측성" 투여)으로 투여(예를 들어, 근내, 경피, 피내, 피하로부터 선택된 투여 경로를 포함)될 수 있다.
- [0290] 바이러스 벡터의 투여량은 주로 치료되는 질환, 환자의 연령, 체중 및 건강과 같은 요인에 좌우될 것이며, 따라서 환자마다 다를 수 있다. 예를 들어, 바이러스 벡터의 치료적으로 효과적인 성인 인간 또는 수의학적 투여량은 일반적으로 1×10^5 내지 1×10^{15} 개의 바이러스 입자, 예를 들어, 1×10^8 내지 1×10^{12} 개(예를 들어, 1×10^8 개, 2.5×10^8 개, 5×10^8 개, 1×10^9 개, 1.5×10^9 개, 2.5×10^9 개, 5×10^9 개, 1×10^{10} 개, 1.5×10^{10} 개, 2.5×10^{10} 개, 5×10^{10} 개, 1×10^{11} 개, 1.5×10^{11} 개, 2.5×10^{11} 개, 5×10^{11} 개, 1×10^{12} 개의 입자)를 함유한다. 대안적으로, 바이러스 벡터는 통상적으로 1×10^5 내지 1×10^{10} 플라크 단위(PFU), 예를 들어, 1×10^5 PFU, 2.5×10^5 PFU, 5×10^5 PFU, 1×10^6 PFU, 2.5×10^6 PFU, 5×10^6 PFU, 1×10^7 PFU, 2.5×10^7 PFU, 5×10^7 PFU, 1×10^8 PFU, 2.5×10^8 PFU, 5×10^8 PFU, 1×10^9 PFU, 2.5×10^9 PFU, 5×10^9 PFU, 또는 1×10^{10} PFU의 용량으로 투여될 수 있다. 투여량은 동물의 크기 및 투여 경로에 따라 달라질 것이다. 예를 들어, 근내 주사를 위한 적합한 인간 또는 수의학적 투여량(약 80 kg 동물에 대해)은 단일 부위에 대해 1 mL 당 약 1×10^9 내지 약 5×10^{12} 개의 입자 범위 내이다. 선택적으로, 다수의 투여 부위가 이용될 수 있다. 또 다른 예에서, 적합한 인간 또는 수의학적 투여량은 경구 제형에 대해 약 1×10^{11} 내지 약 1×10^{15} 개의 입자 범위 내일 수 있다.
- [0291] 바이러스 벡터는, 예를 들어, HCMV 프로모터를 포함하는 발현 카세트와 함께 벡터 유전체를 함유하는 플라스미드 DNA의 연속 희석액을 표준 곡선으로서 이용하여 CMV 프로모터 영역에 대해 설계된 프라이머 및 프로브를 이용한 정량적 PCR 분석(Q-PCR)에 의해 정량될 수 있다. 시험 샘플 내의 카피수는 평행선 분석 방법에 의해 결정

된다. 벡터 입자 정량을 위한 대안적 방법은 분석 HPLC 또는 A_{260} nm에 기반한 분광광도 방법일 수 있다.

- [0292] 핵산의 면역학적 유효량은 적합하게는 1 ng 내지 100 mg일 수 있다. 예를 들어, 적합한 양은 1 μ g 내지 100 mg일 수 있다. 특정 핵산(예를 들어, 벡터)의 적절한 양은 당업자에 의해 용이하게 결정될 수 있다. 핵산 성분의 예시적 유효량은 1 ng 내지 100 μ g, 예를 들어, 1 ng 내지 1 μ g(예를 들어, 100 ng-1 μ g), 또는 1 μ g 내지 100 μ g, 예를 들어, 10 ng, 50 ng, 100 ng, 150 ng, 200 ng, 250 ng, 500 ng, 750 ng, 또는 1 μ g일 수 있다. 핵산의 유효량은 또한 1 μ g 내지 500 μ g, 예를 들어, 1 μ g 내지 200 μ g, 예를 들어, 10 내지 100 μ g, 예를 들어, 1 μ g, 2 μ g, 5 μ g, 10 μ g, 20 μ g, 50 μ g, 75 μ g, 100 μ g, 150 μ g, 또는 200 μ g을 포함할 수 있다. 대안적으로, 핵산의 예시적 유효량은 100 μ g 내지 1 mg, 예를 들어, 100 μ g 내지 500 μ g, 예를 들어, 100 μ g, 150 μ g, 200 μ g, 250 μ g, 300 μ g, 400 μ g, 500 μ g, 600 μ g, 700 μ g, 800 μ g, 900 μ g 또는 1 mg일 수 있다.
- [0293] 일반적으로, 인간 용량은 0.1 ml 내지 2 ml의 부피 내일 것이다. 따라서, 본원에 기재된 조성물은, 예를 들어, 개별적 또는 조합된 면역원성 성분 당 0.1, 0.15, 0.2, 0.5, 1.0, 1.5 또는 2.0 ml 인간 용량의 부피로 제형화될 수 있다.
- [0294] 당업자는 투여 경로 및 재조합 벡터가 사용되는 치료 또는 백신 적용에 따라 상기 용량을 조정할 수 있다. 트랜스진의 발현 수준, 또는 애뉴번트에 대해, 순환 항체의 수준은 투여량의 투여 빈도를 결정하기 위해 모니터링될 수 있다.
- [0295] 하나 이상의 프라이밍 및/또는 부스팅 단계가 이용되는 경우, 이러한 단계는 매시간, 매일, 매주 또는 매달, 또는 매년 투여되는 단일 용량을 포함할 수 있다. 예로서, 포유동물은 담체 중 약 10 μ g 내지 약 50 μ g의 플라스미드를 함유하는 1회 또는 2회 용량을 투여받을 수 있다. 전달 양 또는 부위는 바람직하게는 포유동물의 정체 및 상태를 기초로 하여 선택된다.
- [0296] 선택된 트랜스진에 의해 인코딩되는 단백질의 치료 수준 또는 이에 대한 면역 반응의 수준은, 존재시, 부스터에 대한 필요성을 결정하기 위해 모니터링될 수 있다. 혈청에서의 CD8+ T 세포 반응, 또는 선택적으로, 항체 역가의 평가 후, 선택적 부스터 면역화가 요망될 수 있다. 선택적으로, 재조합 ChAd155 벡터는 단일 투여 또는 다양한 조합 요법, 예를 들어, 다른 활성 성분을 포함하는 요법 또는 치료 과정과 조합하여 또는 프라임-부스트 요법으로 전달될 수 있다.
- [0297] 본 발명은 이제 하기의 비제한적인 실시예에 의해 추가로 기재될 것이다.
- [0298] **실시예**
- [0299] **실시예 1: ChAd155의 단리**
- [0300] 야생형 침팬지 아데노바이러스 타입 155(ChAd155)를 아데노바이러스 단리 및 특성규명 기술을 기재하는 목적으로 참조로서 본원에 포함되는 문헌[Colloca *et al.* (2012)] 및 WO 2010086189호에 기재된 바와 같은 표준 절차를 이용하여 뉴 이베리아 리서치 센터 시설(New Iberia Research Center; The University of Louisiana at Lafayette)에서 사육된 건강한 어린 침팬지로부터 단리시켰다.
- [0301] **실시예 2: ChAd155 벡터 작제**
- [0302] 이후, ChAd155 바이러스 유전체를 플라스미드 또는 BAC 벡터에 클로닝한 후, ChAd155 바이러스 유전체의 다양한 영역에서 하기 변형을 갖도록 변형시켰다(도 2):
- [0303] a) 바이러스 유전체의 E1 영역(bp 449 내지 bp 3529)의 결실;
- [0304] b) 바이러스 유전체의 E4 영역(bp 34731 내지 bp 37449)의 결실;
- [0305] c) 인간 Ad5로부터 유래된 E4orf6의 삽입.
- [0306] 2.1: E1 영역의 결실: BAC/ChAd155 Δ E1 TetO hCMV RpsL-Kana#1375의 작제
- [0307] ChAd155 바이러스 유전체를 ChAd155 바이러스 DNA 및 서브그룹 C BAC 서틀(#1365)과 공동-형질전환된 E. 콜리(*E. coli*) 균주 BJ5183 전기천공 적격 세포(Stratagene 카탈로그 번호 2000154)에서의 상동성 재조합에 의해 BAC 벡터로 클로닝하였다. 도 3의 개략도에 제시된 바와 같이, 서브그룹 C 서틀은 pBeloBAC11(GenBank U51113, NEB)로부터 유래된 BAC 벡터로, 이는 종 C에 속하는 ChAd의 클로닝에 전용이며, 따라서 종 C ChAd 바이러스의 우측 및 좌측 말단(우측 및 좌측 ITR을 포함함)으로부터 유래된 DNA 단편 및 pIX 유전자를 함유한다.

- [0308] 중 C BAC 서들은 또한 좌측 말단과 pIX 유전자 사이에 삽입된 RpsL-Kana 카세트를 함유한다. 또한, ISceI 제한 부위가 축적된 Amp-LacZ-SacB 선택 카세트가 바이러스 유전체의 pIX 유전자와 우측 말단 사이에 존재한다. 특히, BAC 서들은 다음과 같은 특징부를 포함하였다: 좌측 ITR: bp 27 내지 139, hCMV(tetO) RpsL-Kana 카세트: bp 493 내지 3396, pIX 유전자: bp 3508 내지 3972, ISceI 제한 부위: bp 3990 내지 7481, Amp-LacZ-SacB 선택 카세트: bp 4000 내지 7471, 우측 ITR: bp 7805 내지 7917.
- [0309] BJ5183 세포를 ISceI 제한 효소로 절단된 후, 젤로부터 정제된 ChAd155 정제된 바이러스 DNA 및 서브그룹 C BAC 서들 벡터와의 전기천공에 의해 공동-형질전환시켰다. pIX 유전자 및 우측 ITR 서열(중 C BAC 서들 선형화 DNA 의 말단에 존재함)과 ChAd155 바이러스 DNA에 존재하는 상동성 서열 사이에서 발생하는 상동성 재조합은 BAC 서들 벡터 내에서의 ChAd155 바이러스 유전체 DNA의 삽입을 발생시켰다. 동시에, 바이러스 E1 영역을 결실시키고, RpsL-Kana 카세트로 치환시켜, BAC/ChAd155 ΔE1/TetO hCMV RpsL-Kana#1375를 생성시켰다.
- [0310] 2.2: E. 콜리 BJ5183에서의 상동성 재조합에 의한 플라스미드 작제
- [0311] 2.2.1: E4 영역의 결실 - pChAd155 ΔE1, E4_Ad5E4orf6/TetO hCMV RpsL-Kana(#1434)의 작제
- [0312] 벡터의 증식을 개선시키기 위해, E. 콜리에서 여러 단계의 클로닝 및 상동성 재조합을 포함하는 전략을 이용하여 자연 E4 영역을 Ad5 E4orf6 코딩 서열로 대체함으로써 뉴클레오타이드 34731-37449(ChAd155 야생형 서열)에 걸쳐 있는 E4 영역의 결실을 벡터 백본에 도입시켰다. E4 코딩 영역을 완전히 결실시킨 반면, E4 자연 프로모터 및 아데닐중합체형성 신호를 보존시켰다. 이를 위해, 하기 상술되는 바와 같이 E. 콜리 BJ5183에서의 상동성 재조합에 의해 ChAd155 자연 E4 영역을 대체함으로써 Ad5orf6의 삽입을 가능하게 하도록 서들 벡터를 작제하였다.
- [0313] pARS 중C Ad5E4orf6-1의 작제
- [0314] 올리고뉴클레오타이드 5'-ATACGGACTAGTGGAGAAGTACTCGCCTACATG-3'(SEQ ID NO: 13) 및 5'-ATACGGAAGATCTAAGACTTCAGGAAATATGACTAC-3'(SEQ ID NO: 14)와 함께 주형으로서 Ad5 DNA를 이용한 PCR에 의해 Ad5orf6을 함유하는 DNA 단편을 획득하였다. PCR 단편을 BglII 및 SpeI으로 절단하고, BglII 및 SpeI으로 절단된 중 C RLD-EGFP 서들에 클로닝하여, 플라스미드 pARS 중 C Ad5orf6-1을 생성시켰다. 서들에 관한 세부사항은 문헌[Colloca *et al*, Sci. Transl. Med. (2012) 4:115ra]에서 발견될 수 있다.
- [0315] pARS 중C Ad5E4orf6-2의 작제
- [0316] E4 영역을 결실시키기 위해, ChAd155 wt 서열(SEQ ID NO: 10)의 bp 34586 내지 bp 34730에 걸쳐 있는 177 bp DNA 단편을 올리고뉴클레오타이드 5'-ATTCAGTGTACAGCGCGCCAAAGCATGACGCTGTTGATTGATTTC-3'(SEQ ID NO: 15) 및 5'-ACTAGGACTAGTTATAAGCTAGAATGGGGCTTGC-3'(SEQ ID NO: 16)과 함께 주형으로서 플라스미드 BAC/ChAd155 ΔE1_TetO hCMV RpsL-Kana(#1375)를 이용한 PCR에 의해 증폭시켰다. PCR 단편을 BsrGI 및 SpeI으로 절단하고, BsrGI 및 SpeI으로 절단된 pARS 서브그룹C Ad5orf6-1으로 클로닝하여, 플라스미드 pARS 중C Ad5orf6-2(#1490)를 생성시켰다. 이러한 서들 플라스미드의 개략도가 도 4에 제공된다. 특히, 서들 플라스미드는 다음과 같은 특징부를 포함하였다: 좌측 ITR: bp 1 내지 113, 중 C 첫번째 460bp: bp 1 내지 460, ChAd155 wt(SEQ ID NO:10의 bp 34587 내지 bp 34724): bp 516 내지 650, Ad5 orf6: bp 680 내지 1561, 중 C 마지막 393 bp: bp 1567 내지 1969, 우측 ITR: bp 1857 내지 1969.
- [0317] pChAd155 ΔE1, E4_Ad5E4orf6/TetO hCMV RpsL-Kana(#1434)의 작제
- [0318] 이후, 생성된 플라스미드 pARS 서브그룹C Ad5orf6-2를 ChAd155 백본 내의 E4 영역을 Ad5orf6로 대체하기 위해 사용하였다. 이를 위해, 플라스미드 BAC/ChAd155 ΔE1_TetO hCMV RpsL-Kana(#1375)를 PacI/PmeI으로 절단하고, 절단된 플라스미드 pARS 서브그룹C Ad5orf6-2 BsrGI/AscI과 함께 BJ5183 세포로 공동-형질전환시켜, pChAd155 ΔE1, E4_Ad5E4orf6/TetO hCMV RpsL-Kana(#1434) 프리-아데노(pre-adeno) 플라스미드를 획득하였다.
- [0319] 2.2.2: RSV 발현 카세트의 삽입 - pChAd155 ΔE1, E4_Ad5E4orf6/TetO hCMV RSV의 작제
- [0320] RSV 카세트를 HCMV 프로모터와 BGH polyA 서열 사이에 존재하는 상동성을 이용하여 E. 콜리에서의 상동성 재조합을 통해 선형화된 프리-아데노 수용체 벡터에 클로닝하였다. 플라스미드 pvjTetOhCMV-bghpolyA_RSV를 SfiI 및 SpeI으로 절단하여 tetO, RSV 및 BGHpolyA 서열과 함께 HCMV 프로모터를 함유하는 4,65 Kb 단편을 절제하였다. 생성된 RSV 4,65 Kb 단편을 상동성 재조합에 의해 HCMV 및 BGHPA의 조절하에서 RpsL-Kana 선택 카세트를 갖는 pChAd155 ΔE1, E4_Ad5E4orf6/TetO hCMV RpsL-Kana(#1434) 수용체 벡터로 클로닝하였다. 수용체 프리-아데노 플라스미드를 제한 엔도뉴클레아제 SnaBI으로 선형화시켰다. 생성된 작제물은 pChAd155 ΔE1,

E4_Ad5E4orf6/TetO hCMV RSV 벡터(도 5)였다.

[0321] 2.3: 리조합니어링(recombineering)에 의한 BAC 벡터 작제

[0322] 2.3.1: E4 영역의 결실 - BAC/ChAd155 ΔE1, E4_Ad5E4orf6/TetO hCMV RpsL-Kana#1390의 작제

[0323] ChAd155 wt 서열의 뉴클레오타이드 34731-37449에 걸쳐 있는 E4 영역의 결실을 E. 콜리 SW102 적격 세포에서의 2개의 상이한 리조합니어링 단계를 포함하는 전략을 이용하여 자연 E4 영역을 Ad5 E4orf6 코딩 서열로 대체함으로써 벡터 백본에 도입시켰다.

[0324] 첫번째 단계는 재조합체의 양성/음성 선택의 목적을 위해 ChAd155의 E4 영역 내에 자살 유전자 SacB, 암피실린-R 유전자 및 lacZ(Amp-LacZ-SacB 선택 카세트)를 포함하는 선택 카세트의 삽입을 발생시켰다.

[0325] 첫번째 단계 - ChAd155 자연 E4 영역의 Amp-LacZ-SacB 선택 카세트에 의한 치환

[0326] Amp-LacZ-SacB 선택 카세트를 상동성 재조합을 가능하게 하기 위해 E4 측접 서열을 함유하는 하기 제공되는 올리고뉴클레오타이드를 이용한 PCR에 의해 증폭시켰다: 1021-FW E4 Del Step1 (5'-TTAATAGACACAGTAGCTTAATAGACCCAGTAGTGCAAAGCCCCATTCTAGCTTATAA CCCCTATTGTTATTTTCT-3')(SEQ ID NO: 17) 및 1022-RW E4 Del Step1 (5'-ATATATACTCTCTCGGCACTTGGCCTTTTACACTGCGAAGTGTGGTGTGCTGCGTTGAGAGATCTTATTGTGAAGTGAATTGTC-3')(SEQ ID NO: 18).

[0327] pAdeno 플라스미드 BAC/ChAd155 (DE1) tetO hCMV - RpsLKana#1375를 함유하는 E. 콜리 SW102 적격 세포를 형질 전환시키기 위해 PCR 생성물을 사용하였다. SW102 세포의 형질전환은 람다(λ) Red-매개 상동성 재조합을 통해 ChAd155의 E4 영역 내에 선택 카세트의 삽입을 가능하게 하여, 이에 따라 BAC/ChAd155 (DE1) TetOhCMV - RpsL Kana #1379(ChAd155 자연 E4 영역을 치환함으로써 Amp-LacZ-SacB 카세트를 포함함)를 획득하였다.

[0328] 두번째 단계 - Amp-lacZ-SacB 선택 카세트의 Ad5E4orf6 영역에 의한 치환

[0329] 이후, 생성된 플라스미드 BAC/ChAd155 (DE1) TetOhCMV - RpsL Kana #1379(ChAd155 E4 영역 대신 Amp-LacZ-SacB 카세트를 가짐)를 조작하여 ChAd155 백본 내에서 Amp-lacZ-SacB 선택 카세트를 Ad5orf6로 대체하였다. 이를 위해, 올리고뉴클레오타이드 1025-FW E4 Del Step2 (5'-TTAATAGACACAGTAGCTTAATA-3')(SEQ ID NO: 19) 및 1026-RW E4 Del Step2 (5'-GGAAGGGAGTGTCTAGTGTT-3')(SEQ ID NO: 20)를 이용한 PCR에 의해 Ad5orf6 영역을 함유하는 DNA 단편을 획득하였다. 생성된 DNA 단편을 pAdeno 플라스미드 BAC/ChAd155 (DE1) TetOhCMV - RpsL Kana#1379를 함유하는 E. 콜리 SW102 적격 세포에 도입시켜, 자연 ChAd155 E4 영역을 치환시키는 Ad5orf6를 함유하는 최종 플라스미드 BAC/ChAd155(ΔE1, E4 Ad5E4orf6) TetOhCMV - RpsL Kana#1390을 생성시켰다.

[0330] 2.3.2: RSV 발현 카세트의 삽입: BAC/ChAd155 ΔE1, E4_Ad5E4orf6/TetOhCMV RSV#1393의 작제

[0331] RpsL-Kana 선택 카세트를 치환시킴으로써 RSV 트랜스진을 BAC/ChAd155 ΔE1, E4_Ad5E4orf6/TetOhCMV RSV#1393 벡터에 클로닝하였다. 작제 전략은 E. 콜리 SW102 적격 세포에서의 2개의 상이한 리조합니어링 단계를 기초로 하였다.

[0332] 첫번째 단계 - RpsL-Kana 카세트의 Amp-LacZ-SacB 선택 카세트에 의한 치환

[0333] 올리고뉴클레오타이드 91-SubMonte FW (5'-CAATGGGCGTGGATAGCGGTTTGAC-3')(SEQ ID NO: 21) 및 890-BghPolyA RW (5'-CAGCATGCCTGCTATTGTC-3')(SEQ ID NO: 22)를 이용한 PCR에 의해 플라스미드 BAC/ChAd155 (DE1) TetO hCMV Amp-LacZ-SacB#1342로부터 Amp-LacZ-SacB 선택 카세트를 획득하였다. 생성물을 pAdeno 플라스미드 BAC/ChAd155(DE1, E4 Ad5E4orf6) TetOhCMV - RpsL Kana#1390을 함유하는 E. 콜리 SW102 적격 세포로 형질전환시켜, BAC/ChAd155(DE1, E4 Ad5E4orf6) TetOhCMV - Amp-LacZ-SacB#1386을 생성시켰다.

[0334] 두번째 단계 - Amp-lacZ-SacB 선택 카세트의 RSV 트랜스진에 의한 치환

[0335] Amp-lacZ-SacB 선택 카세트를 상동성 재조합에 의해 치환시킴으로써 RSV 트랜스진을 플라스미드 BAC/ChAd155(DE1, E4 Ad5E4orf6) TetOhCMV - Amp-LacZ-SacB#1386에 삽입하였다. 이를 위해, 플라스미드 pvjTetOhCMV-bghpolyA_RSV#1080(RSV 발현 카세트를 함유함)을 SpeI 및 SfiI로 절단하여, HCMV 프로모터, RSV 및 BGHPolyA를 포함하는 4.4 Kb 단편을 절제하였다. 생성된 RSV 4.4 Kb 단편을 pAdeno 플라스미드 BAC/ChAd155(DE1, E4 Ad5E4orf6) TetOhCMV - Amp-LacZ-SacB#1386을 함유하는 E. 콜리 SW102 적격 세포로 형질전환시켜, 최종 플라스미드 BAC/ChAd155 ΔE1, E4_Ad5E4orf6/TetO hCMV Kana#1390을 생성시켰다.

ChAd155/RSV(SEQ ID NO: 11)를 갖는 BAC의 구조가 도 6에 예시되어 있다. 특히, ChAd155/RSV는 다음과 같은 특징부를 포함하였다: 종 C 좌측 ITR: bp 1 내지 113, hCMV(tetO) bp 467 내지 1311, RSV 유전자: bp 1348 내지 4785, bghpolyA: bp 4815 내지 5032, Ad5E4orf6: bp 36270 내지 37151, 종 C 우측 ITR: bp 37447 내지 37559.

실시예 3: 벡터 생성

ChAd155의 생산성을 Procell 92 세포주에서 ChAd3 및 PanAd3와의 비교로 평가하였다.

3.1: HIV Gag 트랜스진을 포함하는 벡터의 생성

HIV Gag 단백질을 발현하는 벡터를 상기(ChAd155/GAG) 또는 이전에(ChAd3/GAG Colloca *et al*, Sci. Transl. Med. (2012) 4:115ra) 기재된 바와 같이 제조하였다. ChAd3/GAG 및 ChAd155/GAG를 회수하고, 계대배양 3(P3)까지 Procell 92에서 증폭시켰고; P3 용해질을 사용하여 각각의 벡터와 함께 단층으로 배양된 Procell 92의 2개의 T75 플라스크를 감염시켰다. 100 vp/세포의 감염다중도(MOI)를 둘 모두의 감염 실험에 이용하였다. 완전한 CPE가 명백해지는 경우(감염 후 72시간) 감염된 세포를 수거하고, 풀링(pooling)시켰고; 바이러스를 3주기의 동결/해동(-70℃/37℃)에 의해 감염된 세포로부터 방출시킨 후, 용해질을 원심분리에 의해 정화시켰다. 정화된 용해질을 CMV 프로모터 영역에 상보적인 프라이머 및 프로브를 이용한 정량적 PCR 분석에 의해 정량하였다. 올리고 뉴클레오타이드 서열은 다음과 같다: CMVfor 5'-CATCTACGTATTAGTCATCGCTATTACCA-3'(SEQ ID NO: 23), CMVrev 5'-GACTTGGAATCCCCGTGAGT-3'(SEQ ID NO: 24), CMVFAM-TAMRA 프로브 5'-ACATCAATGGGCGTGGATAGCGGTT-3'(SEQ ID NO: 25)(QPCR을 ABI Prism 7900 Sequence 검출기에서 수행하였다 - Applied Biosystem). 정화된 용해질에서 측정된 결과적 체적 역가(volumetric titer)(vp/ml) 및 세포 당 바이러스 입자에서 발현된 특정 생산성(vp/세포)이 하기 표 1에 제공되고, 도 7에 예시된다.

표 1. P3 용해질로부터의 벡터 생산성.

벡터	vp/ml	전체 vp (20 ml 농도)	vp/세포
ChAd3/GAG	9,82E+09	1,96E+11	6,61E+03
ChAd155/GAG	1,11E+10	2,22E+11	7,46E+03

HIV Gag 트랜스진을 발현하는 ChAd155 벡터의 더 높은 생산성을 확인하기 위해, 접종물로서 정제된 바이러스를 이용하여 두번째 실험을 수행하였다. 이를 위해, Procell 92 세포를 T25 플라스크에 시딩하고, 세포의 컨플루언스(confluence)가 약 80% 되었을 때 MOI=100 vp/세포의 감염을 이용하여 ChAd3/GAG 및 ChAd155/GAG로 감염시켰다. 완전한 CPE가 명백한 경우 감염된 세포를 수거하였고; 동결/해동에 의해 감염된 세포로부터 바이러스를 방출시키고, 원심분리에 의해 정화시켰다. 정화된 용해질을 다음과 같은 프라이머 및 프로브를 이용한 정량적 PCR 분석으로 정량하였다: CMVfor 5'-CATCTACGTATTAGTCATCGCTATTACCA-3'(SEQ ID NO: 23), CMV rev GACTTGGAATCCCCGTGAGT(SEQ ID NO: 24), CMV 프로모터 영역에 상보적인 CMV FAM-TAMRA 프로브 5'-ACATCAATGGGCGTGGATAGCGGTT-3'(SEQ ID NO: 25)(샘플을 ABI Prism 7900 Sequence 검출기에서 분석하였다 - Applied Biosystems). 정화된 용해질에서 측정된 결과적 체적 역가(volumetric titer)(vp/ml) 및 세포 당 바이러스 입자에서 발현된 특정 생산성(vp/세포)이 하기 표 2에 제공되고, 도 8에 예시된다.

표 2. 정제된 바이러스로부터의 벡터 생산성.

벡터	vp/ml	전체 vp/T25 플라스크 (5ml 의 용해질)	vp/세포
ChAd3/GAG	1,00E+10	5,00E+10	1,67E+04
ChAd155/GAG	1,21E+10	6,05E+10	2,02E+04

3.2: RSV 트랜스진을 포함하는 벡터의 생성

현탁액에서 배양된 Procell 92.S에서의 RSV 백신 벡터의 생산성을 평가하기 위해 다양한 세트의 실험을 수행하였다. 실험은 5×10^5 세포/ml의 세포 밀도에서 Procell 92.S를 감염시킴으로써 PanAd3/RSV(WO2012/089833호에 기

재됨) 및 Chad155/RSV를 병행하여 비교하였다. 감염된 세포를 감염 3일 후에 수거하였고; 3주기의 동결/해동에 의해 감염된 세포로부터 바이러스를 방출시키고, 용해질을 원심분리에 의해 정화시켰다. 이후, 정화된 용해질을 상기 보고된 바와 같이 정량적 PCR 분석으로 정량하였다. 체적 생산성 및 세포 특이적 생산성이 하기 표 3에 제공되고, 도 9에 예시된다.

표 3

바이러스	체적 생산성 (Vp/ml)	전체 vp	세포 특이적 생산성 (vp/세포)
PanAd3/RSV	5,82E+09	2,91E+11	1,16E+4
ChAd155/RSV	3,16E+10	1,58E+12	6,31E+04

실시예 4: 트랜스진 발현 수준

4.1: HIV Gag 트랜스진의 발현 수준

HeLa 세포를 HIV Gag 트랜스진을 포함하는 ChAd3 및 ChAd155 벡터로 감염시킴으로써 발현 수준을 병행 실험에서 비교하였다. HeLa 세포를 24 웰 플레이트에 시딩하고, MOI=250 vp/세포를 이용하여 ChAd3/GAG 및 ChAd155/GAG 정제된 바이러스로 이중으로 감염시켰다. HeLa 감염된 세포의 상층액을 감염 48시간 후에 수거하고, 상업적 ELISA 키트(HIV-1 p24 ELISA Kit, PerkinElmer Life Science)를 이용하여 분비된 HIV GAG 단백질의 생성을 정량하였다. HIV-1 p24 항원 표준 곡선을 이용하여 제조업체의 설명서에 따라 정량을 수행하였다. pg/GAG 단백질 ml로 표현되는 결과가 도 10에 예시된다.

4.1: RSV F 트랜스진의 발현 수준

HeLa 세포를 RSV F 트랜스진을 포함하는 상기 기재된 PanAd3 및 ChAd155 벡터로 감염시킴으로써 발현 수준을 병행 실험에서 비교하였다. 이를 위해, HeLa 세포를 6 웰 플레이트에 시딩하고, MOI=500 vp/세포를 이용하여 PanAd3/RSV 및 ChAd155/RSV 정제된 바이러스로 이중으로 감염시켰다. 상층액을 감염 48시간 후에 수거하고, 분비된 RSV F 단백질의 생성을 ELISA로 정량하였다. 상층액의 5개의 상이한 희석액을 상업적 마우스 항-RSV F 모노클로날 항체로 코팅된 마이크로플레이트 웰로 옮겼다. 이차 항-RSV F 토끼 항혈청 및 이후 비오틴-컨쥬게이션된 항-토끼 IgG를 이용한 후, 스트렙타비딘-AP 컨쥬게이트(BD Pharmingen cat. 554065)를 첨가하여 포획된 항원을 나타냈다. RSV F 단백질(Sino Biological cat. 11049-V08B) 표준 곡선을 이용하여 정량을 수행하였다. ug/RSV F 단백질의 ml로 표현되는 획득된 결과가 하기 표 4에 제공된다.

표 4

샘플	µg/ml RSV F 단백질
ChAd155/RSV	5,9
PanAd3/RSV	4

PanAd3 RSV 벡터에 비해 ChAd155 RSV 벡터에 의해 제공된 더 높은 수준의 트랜스진 발현을 확인하기 위해 웨스턴 블롯 분석을 또한 수행하였다. 6 웰 플레이트에 플레이트된 HeLa 세포를 MOI=250 및 500 vp/세포를 이용하여 PanAd3/RSV 및 ChAd155/RSV 정제된 바이러스로 감염시켰다. HeLa 감염된 세포의 상층액을 수거하고, 분비된 RSV F 단백질의 생성을 비-환원 SDS 젤 및 이후 웨스턴 블롯 분석에 의해 분석하였다. 동등한 양의 상층액을 비-환원 SDS 젤에 로딩하고; 전기영동 분리 후, 단백질을 니트로셀룰로스 막으로 옮겨, 항-RSV F 마우스 모노클로날 항체(클론 RSV-F-3 카탈로그 번호: ABIN308230, antibodies-online.com에서 이용 가능함(2015년 4월 13일에 마지막으로 액세스됨))로 프로빙하였다. 일차 항체와의 인큐베이션 후, 막을 세척한 후, 항-마우스 HRP 컨쥬게이트 이차 항체와 인큐베이션하였다. 최종적으로, 검정을 표준 기술(ECL 검출 시약 Pierce 카탈로그 번호 W3252282)를 이용한 전기화학발광에 의해 발달시켰다. 웨스턴 블롯 결과가 도 11에 제시된다. 화살표로 표시된 약 170 kD의 밴드가 F 단백질에 대해 발생된 모노클로날 항체 mAb 13에 의해 나타났고, 이는 삼량체 F 단백질의 예상 중량에 해당한다. ChAd155 RSV 벡터가 MOI=250 및 500vp/세포 둘 모두에서 더 어두운 밴드를 발생시킨 것이 관찰될 수 있다.

[0357] 실시예 5: 마우스 면역화 실험에 의한 면역학적 효능의 평가

[0358] 5.1: HIV Gag 트랜스진을 포함하는 벡터의 면역원성

[0359] ChAd155/GAG 벡터의 면역원성을 BALB/c 마우스(그룹 당 5마리)에서 ChAd3/GAG 벡터와 병행하여 평가하였다. 10^6 개의 바이러스 입자를 근내 주사하여 실험을 수행하였다. T-세포 반응을 BALB/c 마우스에서 맵핑된 GAG CD8+ T 세포 에피토프를 이용한 생체 외 IFN-감마 효소-결합 면역스팟(ELISpot)에 의한 면역화 3주 후에 측정하였다. 100만 개의 비장세포 당 IFN-감마 스팟 형성 세포(SFC)로 표현되는 결과가 도 12에 제시된다. 각각의 도트는 단일 마우스에서의 반응을 나타내고, 선은 각각의 용량 그룹에 대한 평균에 해당한다. 바이러스 입자의 수에서의 주사된 용량 및 CD8 면역우세 펩티드에 대한 양성 마우스의 빈도가 x 축 상에 제시된다.

[0360] 5.2: RSV 트랜스진을 포함하는 벡터의 면역원성

[0361] PanAd3/RSV 및 ChAd155/RSV 벡터의 면역학적 효능을 BALB/c 마우스에서 평가하였다. 둘 모두의 벡터를 10^8 , 10^7 및 3×10^6 vp의 용량으로 근내 주사하였다. 예방접종 3주 후, 면역화된 마우스의 비장세포를 분리시키고, BALB/c 마우스에서 맵핑된 면역우세 펩티드 F 및 M 에피토프를 항원으로 이용하여 IFN-감마-ELISpot에 의해 분석하였다. 면역-반응의 수준은 투여량 감소에 따라 감소되었으나(예상된 바와 같음), 면역 반응은 PanAd3/RSV 백신으로 면역화된 마우스의 동등한 그룹에 비해 ChAd155/RSV 벡터로 면역화된 마우스의 그룹에서 명백히 더 높았다(도 13). 도 13에서, 기호는 3개의 면역우세 에피토프(F_{51-66} , F_{85-93} 및 $M2_{1282-290}$)에 대한 반응의 합계로서 계산되고, 백그라운드에 대해 보정된 IFN-감마 스팟 형성 세포(SFC)/100만 개의 비장세포로 표현되는 개별적 마우스 데이터를 제시한다. 수평선은 각각의 용량 그룹에 대한 IFN-감마 SFC의 평균 수/100만 개의 비장세포를 나타낸다.

[0362] 결론

[0363] 종합하면, 상기 보고된 결과는 ChAd155가 ChAd3 및 PanAd3 벡터와 비교하여 개선된 아데노바이러스 벡터임을 입증하였다. ChAd155는 더 생산적이고, 따라서 제조 공정을 용이하게 하고, 시험관 내 및 또한 생체 내에서 트랜스진의 더 높은 수준을 발현시킬 수 있어, 동물 모델에서 발현된 항원에 대한 더 강한 T-세포 반응을 제공하는 것으로 나타났다.

[0364] 서열의 설명

[0365] SEQ ID NO: 1 - ChAd155 섬유의 폴리펩티드 서열

MKRTKTSDESFNPVYPYDTESGPPSPFLTPPFVSPDGFQESPPGVLSLNLAEPLVTSHGMLALKMGS
GLSLDDAGNLTSDITTASPLPKTKTNLSLETSSPLTVSTSGALTVAAAAPLAVAGTSLTMQSEAPL
TVQDAKLTATKGPLTVSEGKLALQTSAPLTAADSSLTITVSAIPPLSTNSGSLGIDMQAPIYTTNGKL
GLNFGAPLHVVDLSNALTVVTGQGLTINGTALQTRVSGALNYDTSGNLELRAAGGMRVDANGQLIL
DVAYPFDAQNNLSRLGQGPLFVNSAHNLDVNYNRGLYLFTSGNTKKLEVNIKTAKGLIYDDTAIAI
NAGDGLQFDSGSDTNPLKTKLGLLDYDSSRAIIAKLGTGLSFDNTGAI TVGNKNDDKLTWTTDPDP
SPNCRIYSEKDAKFTLVLTCKGSQVLA SVSVKGLAPISGTVTSAQIVLRFDENGVLSSNSLDPQ
YWNRYRKGDLTETGAYTNAVGFMPNLTA YPKTQSQTAKSNIVSQVYLNKDKSKPMTLTITLNGTNET
GDATVSTYSMSFSWNWNGSNYINETFQTNSFTFSYIAQE

[0366]

[0367] SEQ ID NO: 2 - PChAd155 섬유를 인코딩하는 폴리뉴클레오티드 서열

ATGAAGCGCACAAAACGTCTGACGAGAGCTTCAACCCCGTGTAACCCCTATGACACGGAAAGCG
 GCCCTCCCCTCCGTCCTCTTCCTCACCCCTCCCTTCGTGTCTCCCGATGGATTCCAAGAAAGTCCCC
 CCGGGGTCTGTCTCTGAACCTGGCCGAGCCCTGGTCACTTCCACGGCATGCTCGCCCTGAAA
 ATGGGAAGTGGCTCTCCCTGGACGACGCTGGCAACCTCACCTCTCAAGATATCACACCGCTA
 GCCCTCCCCTCAAAAAACCAAGACCAACCTCAGCCTAGAAACCTCATCCCCCTAACTGTGAG
 CACCTCAGGCGCCCTCACCGTAGCAGCCGCGCTCCCTGGCGGTGGCCGGCACCTCCCTCACC
 ATGCAATCAGAGGCCCCCTGACAGTACAGGATGCAAACTCACCTGGCCACCAAGGCCCCC
 TGACCGTGTCTGAAGGCAAACTGGCCTTGCAAAACATCGGCCCGCTGACGGCCGCTGACAGCAG
 CACCCTCAGAGTCAGTGCCACACCACCCCTTAGCACAAGCAATGGCAGCTTGGGTATTGACATG
 CAAGCCCCCATTTACACCACCAATGGAAAACTAGGACTTAACCTTTGGCGCTCCCTGCATGTGGT
 AGACAGCCTAAATGCACTGACTGTAGTTACTGGCCAAGGTCTTACGATAAACGGAACAGCCCTA
 CAACTAGAGTCTCAGGTGCCCTCACTATGACACATCAGGAAACCTAGAATTGAGAGCTGCAG
 GGGGTATGCGAGTTGATGCAATGGTCAACTTATCCTTGATGTAGCTTACCATTTGATGCACAA
 AACAATCTCAGCCTTAGGCTTGACAGGGACCCCTGTTTGTTAACTCTGCCCACAACTTGGATGT
 TAACTACAACAGAGGCTCTACCTGTTTACATCTGGAAATACAAAAAGCTAGAAGTTAATATC
 AAAACAGCCAAGGGTCTCATTTATGATGACACTGCTATAGCAATCAATGCGGGTGTGGGCTAC
 AGTTTGACTCAGGCTCAGATACAAATCCATTAATAAACTAACTTGGATTAGGACTGGATTATGA
 CTCCAGCAGAGCCATAATTGCTAACTGGGAACTGGCCTAAGCTTTGACAACACAGGTGCCATC
 ACAGTAGGCAACAAAAATGATGACAAGCTTACCTTGTGGACCACACCAGACCCATCCCCCTAACT
 GTAGAATCTATTGAGAGAAAGATGCTAAATTCACACTTGTTTGACTAAATGCGGCAGTCAGGT
 GTTGCCAGCGTTTCTGTTTATCTGTAAAAGGTAGCCTTGCGCCCATCAGTGGCACAGTAACTA
 GTGCTCAGATTGTCCTCAGATTGATGAAAAATGGAGTTCTACTAAGCAATTCTTCCCTTGACCT
 CAATACTGGAACACAGAAAAAGGTGACCTTACAGAGGGCACTGCATATACCAACGCAGTGGGA
 TTTATGCCCAACCTCAGAGCATACCCAAAAACACAGAGCCAACTGCTAAAAGCAACATTGTAA
 GTCAGGTTTACTTGAATGGGGACAAATCCAAACCCATGACCTCACCATTACCTCAATGGAAC
 TAATGAAACAGGAGATGCCACAGTAAGCACTTACTCCATGTCATTCTCATGGAACGGAATGGA
 AGTAATTACATTAATGAAACGTTCCAAACCAACTCCTTCACCTTCTCCTACATCGCCCAAGAA

[0368]

[0369] SEQ ID NO: 3 - ChAd155 펜톤의 폴리펩티드 서열

MRRAAMYQEGPPPSYESVVGAAAAAPSSPFASQLLEPPYVPPRYLRPTGGRNSIRYSELAPLFDTRV
 YLVDNKSADVASLNYQNDHSNFLTIVIQNDYSPSEASTQTINLDDRSHWGGDLKTLHTNMPNVN
 EFMFTNKFARVMVRSRSHTKEDRVELKYEWVEFELPEGNYSETMTIDL MNNAIVEHYLKVGRQNG
 VLES DIGVKFDTRNFRGLDPVTGLVMPGVYTNEAFHPDIILLPGCGVDFYTSRLSNLLGIRKRQPFQE
 GFRITYEDLEGGNIPALLDVEAYQDSLKENEAGQEDTAPAASAAAEQGEDAADTAAADGAEADPA
 MVVEAPEQEEDMNDASVRGDTFVTRGEEKQAEAEAAAEKQLAAAAAALAAAEAESEGTKPA
 KEPVIKPLTEDSKRSYNLLKDSTNTAYRSWYLAYNYGDPSTGVRSWTLLCTPDVTCGSEQVYWSL
 PDMMQDPVTFRSTRQVSNFPVVGAE LLPVHSKSFYNDQAVYSQLIRQFTSLTHVFNRFENQILARPP
 APTITTVSENVPALTDHGTLP LRSIGGVQRVTVDARRRTC PYVYKALGIVSPRVLSSRTF

[0370]

[0371] SEQ ID NO: 4 - ChAd155 펜톤을 인코딩하는 폴리뉴클레오타이드 서열

ATGCGGCGCGCGCGATGTACCAGGAGGGACCTCCTCCCTTTACGAGAGCGTGGTGGGCGCGG
CGGCGGCGGCGCCCTCTTCTCCCTTTGCGTTCGACAGCTGCTGGAGCCGCGTACGTGCCTCCGCGC
TACCTGCGGCCTACGGGGGGGAGAAACAGCATCCGTTACTCGAGAGCTGGCGCCCTGTTTCGACA
CCACCCGGGTGTACCTGGTGGACAACAAGTCGGCGGACGTGGCCTCCCTGAACTACCAGAACGA
CCACAGCAATTTTTGACCACGGTTCATCCAGAACAAATGACTACAGCCCGAGCGAGGCCAGCACC
CAGACCATCAATCTGGATGACCGGTGCGACTGGGGCGGCGACCTGAAAACCATCCTGCACACCA
ACATGCCCCAACGTGAACGAGTTCATGTTACCAATAAGTTCAAGGCGCGGTGATGTTGTCGCG
CTCGCACACCAAGGAAGACCGGGTGGAGCTGAAGTACGAGTGGGTGGAGTTCGAGCTGCCAGA
GGGCAACTACTCCGAGACCATGACCATTGACCTGATGAACAACGCGATCGTGGAGCACTATCTG
AAAGTGGGCGAGCAGAACCGGGTCTGGAGAGCGACATCGGGGTCAAGTTCGACACCAGGAAC
TTCCGCTGGGGCTGGACCCCGTGACCGGGCTGGTTATGCCCGGGGTGTACACCAACGAGGCCT
TCCATCCCGACATCATCTGCTGCCCGGTGCGGGGTGGACTTCACTTACAGCCGCTGAGCAAC
CTCTGGGCATCCGCAAGCGGACGCCCTCCAGGAGGGCTTCAGGATCACCTACGAGGACCTGG
AGGGGGGCAACATCCCCGCGTCTCGATGTGGAGGCCTACCAGGATAGCTTGAAGGAAAATG
AGGCGGGACAGGAGGATACCGCCCCGCGCTCCGCCGCGCGAGCAGGGCGAGGATGCTG
CTGACACCGCGCGCGGACGGGCAGAGGCGGACCCCGCTATGGTGGTGGAGGCTCCCGAGC
AGGAGGAGGACATGAATGACAGTGGCGTGCGCGGAGACACCTTCGTACACCGGGGGAGGAAA
AGCAAGCGGAGGCGAGGCCGCGGCCGAGGAAAAGCAACTGGCGGCAGCAGCGGCGGCGCG
GCGTTGGCGCGCGGAGGCTGAGTCTGAGGGGACCAAGCCCGCAAGGAGCCCGTGATTAAG
CCCCTGACCGAAGATAGCAAGAAGCGCAGTTACAACCTGCTCAAGGACAGCACCAACACCGCG
TACCGCAGCTGGTACCTGGCCTACAACCTACGGCGACCCGTCGACGGGGGTGCGCTCCTGGACCC
TGCTGTGCACGCCGACGTGACCTGCGGCTCGGAGCAGGTGTAAGTGGTGGTGGCGGACATGAT
GCAAGACCCCGTGACCTTCCGCTCCACGCGGCAGGTCAGCAACTTCCCGGTGGTGGGCGCGGAG
CTGCTGCCCGTGCACTCCAAGAGCTTCTACAACGACAGGCCGCTACTCCCAGCTCATCCGCCA
GTTCACCTCTCTGACCCACGTGTTCAATCGCTTCTCTGAGAACCAGATTCTGGCGCGCCCGCCG
CCCCACCATCACCACCGTCAGTGAAAACGTTCTGCTCTCACAGATCACGGGACGCTACCGCT
GCGCAACAGCATCGGAGGAGTCCAGCGAGTGACCGTTACTGACGCCAGACGCGCCACCTGCCCC
TACGTTTACAAGGCCTTGGGCATAGTCTCGCCGCGCGTCTTTCCAGCCGCACTTTT

[0372]

[0373] SEQ ID NO: 5 - ChAd155 핵손의 폴리펩티드 서열

MATPSMMPQWSYMHISGQDASEYLSPLVQFARATDSYFSLSNKFRNPVAPTHDVTDRSQRLTL
RFIPVDREDTAYSYKARFTLAVGDNRVLDMASTYFDIRGVLDRGPTFKPYSGTAYNSLAPKGAPNSC
EWEQEETQTAEAAQDEEEDAEAEEMPQEEQAPVKKTHVYAQAPLSGEKITKDGLQIGTDATATE
QKPIYADPTFQPEPQIGESQWNEADASVAGGRVLKKTTPMKPCYGSYARPTNANGGQGVLEKDDG
KMESQVDMQFFSTSENARNEANNIQPKLVLYSEDVHMETPDTHISYKPAKSDDNSKVMLGQQSMPN
RPNYIGFRDNFIGLMYNSTGNMGVLAGQASQLNAVVDLQDRNTELSYQLLLDSMGDRTRYFSMW
NQAVDSYDPDVRIENHGTDELPNYCFPLGGIGVTDITYQAIKTNGNGNGGGNTTWTKDETFAERN
EIGVGNNFAMEINLSANLWRNFLYSNVALYLPDKLKYNPSNVEISDNPNITYDYMNRVVPGLVDC
YINLGARWSDYMDNVNPFNHHRNAGLRYRSMMLGNGRYVPFHIQVPQKFFAIKNLLLLPGSYTYE
WNFRKDVNMVLQSSLGNDLRVDGASIKFESICLYATFFPMAHNTASTLEAMLRNDTNDQSFNDYLS
AANMLYPIPANATNPISIPSRNWAARFWAFTRLKTKETPSLGSFDPYYTYSGSIPYLDGTFYLNH
TFKKVSVTFDSSVSWPGNDRLLTPNEFEIKRSVDGEGYNVAQCNMTKDWFLIQMLANYNIGYQGFY
IPESYKDRMYSFFRNFPMSRQVVDETKYKDYQVGHQHNSGFGYLAPTMREGQAYPANFPY
PLIGKTAVDSVTQKKFLCDRTLWRIPFSSNFMMSGALTDLGQNLLYANSAHALDMTFEVDPMDEPT
LLYVLFVFDVVRVHQPHRGVIETVYLRTPFSAAGNATT

[0374]

[0375] SEQ ID NO: 6 - ChAd155 핵손을 인코딩하는 폴리뉴클레오티드 서열

ATGGCGACCCCATCGATGATGCCGCGAGTGGTCGTACATGCACATCTCGGGCCAGGACGCCTCGG
AGTACCTGAGCCCCGGGCTGGTGACAGTTCCGCCGCGCCACCGAGAGCTACTTCAGCCTGAGTAA
CAAGTTTAGGAACCCACGGGTGGCGCCACGCACGATGTGACCACCGACCGGTCTCAGCGCCTG
ACGCTGCGGTTTATCCCGTGGACCGCGAGGACACCGCGTACTCGTACAAGGCGCGGTTACCC
TGGCCGTGGGCGACAACCGCGTGCTGGACATGGCCTCCACCTACTTTGACATCCGCGGGGTGCT
GGACCGGGTCCCCTTTCAAGCCCTACTCTGGCACCGCCTACAACCTCCCTGGCCCCAAGGGC
GCTCCCAACTCCTGCGAGTGGGAGCAAGAGGAACTCAGGCAGTTGAAGAAGCAGCAGAAAGAG
GAAGAAGAAGATGCTGACGGTCAAGCTGAGGAAGAGCAAGCAGCTACCAAAAAGACTCATGTA
TATGCTCAGGCTCCCCCTTTCTGGCGAAAAAATTAGTAAAGATGGTCTGCAATAGGAACGGACG
CTACAGCTACAGAACAAAAACCTATTTATGCAGACCTACATTCCAGCCCGAACCCCAATCGG
GGAGTCCCAGTGAATGAGGCAGATGCTACAGTCGCCGGCGGTAGAGTGCTAAAGAAATCTACT
CCCATGAAACCATGCTATGGTTCTATGCAAGACCCACAAATGCTAATGAGGTCAGGGTGTAC
TAACGGCAAATGCCAGGGACAGCTAGAATCTCAGGTTGAAATGCAATTCTTTCACTTCTGA
AAACGCCGTAAACGAGGCTAACAACATTCAGCCCAAAATTGGTGCTGTATAGTGAGGATGTGCAC
ATGGAGACCCCGGATACGCACCTTTCTTACAAGCCCGCAAAAAGCGATGACAATTCAAAAATCA
TGCTGGGTGAGCAGTCCATGCCCCAACAGACCTAATTACATCGGCTTCAGAGACAACCTTATCGG
CCTCATGTATTACAATAGCACTGGCAACATGGGAGTGCTTGCAGGTCAGGCCTCTCAGTTGAAT
GCAGTGGTGGACTTGCAAGACAGAAACACAGAACTGTCTACCAGCTCTTGCTTGATTCCATGG
GTGACAGAACCAGATACTTTTCCATGTGAATCAGGCAGTGGACAGTTATGACCCAGATGTTAG
AATTATTGAAAATCATGGAAGTGAAGACGAGCTCCCCAACTATTGTTTCCCTCTGGGTGGCATAG
GGGTAAGTACACTTACCAGGCTGTAAAACCAACAATGGCAATAACGGGGGCCAGGTGACTTG
GACAAAAGATGAACTTTTGACAGATCGCAATGAAATAGGGGTGGGAAACAATTCGCTATGGA
GATCAACCTCAGTGCCAACCTGTGGAGAACTTCCTGTACTCCAACGTGGCGCTGTACCTACCA
GACAAGCTTAAGTACAACCCCTCCAATGTGGACATCTCTGACAACCCCAACACCTACGATTACA
TGAACAAGCGAGTGGTGGCCCCGGGGCTGGTGGACTGCTACATCAACCTGGGCGCGCGTGGTC
GCTGGACTACAGTGACACGTCAACCCCTTCAACCAACCGCAATGCGGGCCTGCGCTACCGC
TCCATGCTCCTGGGCAACGGGGCCTACGTGCCCTTCCACATCCAGGTGCCCGAGAAAGTTCTTGC
CATCAAGAACCTCCTCCTGCGGGCTCCTACCTACGAGTGGAACCTCAGGAAGGATGTC
AACATGGTCTCCAGAGCTCTCTGGGTAAACGATCTCAGGGTGGACGGGGCCAGCATCAAGTTG
AGAGCATCTGCCTCTACGCCACCTTTTCCCCATGGCCCAACAACAGCGCTCCACGCTCGAGGCC
ATGCTCAGGAACGACACCAACGACAGTCTTCAATGACTACCTCTCCGCGCCAACATGCTCT
ACCCCATACCCGCCAACGCCACCAACGTCCCATCTCCATCCCTCGCGCAACTGGGCGGCCCTC
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CCTACTACACCTACTCGGGCTCCATTCCTACCTGGACGGCACCTTCTACCTCAACCACACTTTC
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CCAACGAGTTCGAGATCAAGCGCTCGGTGACGGGAGGGCTACAACGTGGCCAGTGCAACA
TGACCAAGGACTGGTTCCTGGTCCAGATGCTGGCCAACTACAACATCGGCTACCAGGGCTTCTA
CATCCAGAGAGCTACAAGGACAGGATGTACTCTTCTCAGGAACCTCCAGCCCATGAGCCGG
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TCCCTATCCGCTCATAGGCAAGACCGCGTTCGACAGCATACCCAGAAAAAGTTCTCTGCGA
CCGCAACCTCTGGCGCATCCCTTCTCCAGCAACTTCATGTCCATGGGTGCGCTCTCGGACCTGG
GCCAGAACTTGCTCTACGCAACTCCGCCACGCCCTCGACATGACCTTCGAGGTGACCCCATG
GACGAGCCACCTTCTATGTCTGTTCGAAGTCTTTGACGTGGTCCGGGTCCACCAGCCGCA
CCGCGGCGTCATCGAGACCGTGTACCTGCGTACGCCCTTCTCGGCCGGCAACGCCACCACC

[0376]

[0377] SEQ ID NO: 7 - ChAd155#1434 백본 작제물을 인코딩하는 폴리뉴클레오티드 서열

CATCATCAATAATACCTTATTTTGGATTGAAGCCAATATGATAATGAGATGGGCGGCGCGGG
GCGGGGCGGGGGGGGAGCGGGTTTGGGGGCGGGCGGCGGGCGGGCGGTGTGGCGGAA
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CGTGCGGACAACGCCCCGGGAAGTGACATTTTTCCCGCGGTTTTTACCGGATGTTGTAGTGAA
TTTGGGCGTAACCAAGTAAGATTTGGCCATTTTCGCGGGAAGTGAACGCGGGAAGTGAATC
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CGTGAGGAGTCTGCCCCAGGTGTTTTTGAAGGTGAATTTCCGCGTTCGGGTCAAAGTCTGCGTTT
TATTATTATAGGATATCCATTGCATACGTTGTATCCATATCATAATATGTACATTTATTTGGCT
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[0378]

GGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCC
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[0379]

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[0380]

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[0381]

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[0382]

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[0383]

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[0384]

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[0385]

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[0386]

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[0387]

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[0388]

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[0389]

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[0391]

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[0392]

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TTCGTTTAAAC

[0393]

[0394] SEQ ID NO: 8 - ChAd155#1390 백본 작제물을 인코딩하는 폴리뉴클레오티드 서열

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[0395]

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[0396]

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[0397]

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[0398]

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[0399]

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[0400]

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[0401]

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[0402]

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[0403]

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[0404]

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[0405]

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[0406]

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[0407]

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[0408]

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[0409]

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[0410]

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[0411]

[0412] SEQ ID NO: 9 - ChAd155#1375 백본 작제물을 인코딩하는 폴리뉴클레오티드 서열

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[0413]

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[0414]

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[0415]

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[0416]

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[0417]

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[0418]

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[0419]

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[0420]

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[0421]

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[0422]

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[0423]

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[0424]

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[0425]

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[0426]

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[0427]

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[0428]

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[0429]

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[0432] SEQ ID NO: 10 - 야생형 ChAd155를 인코딩하는 폴리뉴클레오티드 서열

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[0433]

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[0434]

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 CCTAGCATGTAGAACTGGTTGACGGCCTGGTAGGCGCAGCAGCCCTTCTCCACGGGGAGGGCGT
 AGGCCTGCGCGGCTTGCGGAGCGAGGTGGGTGAGGGCGAAGGTGTCCCTGACCATGACTTT
 GAGGTACTGGTGTGTAAGTCGAGTCGTGCGAGCCGCCCGCTCCAGAGCGAGAAGTCGGTG
 CGCTTCTTGAGCGGGGGTTGGGCAGAGCGAAGGTGACATCGTTGAAGAGGATTTGCCCGCGC

[0435]

GGGGCATGAAGTTGCGGGTGATGCGGAAGGGCCCCGGCACTTCAGAGCGGTTGTTGATGACCTG
GGCGGCGAGCACGATCTCGTCGAAGCCGTTGATGTTGTGGCCACGATGTAGAGTTCCAGGAAG
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GAGGCCGTGCTCGGCCAGGGCCAGTCCGCGAGGTGCGGGTTGTCTCTGAGGAAGGACTTCCAG
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TTGTAGTAGTCTTGATGAGCCTTCCACCGGCACCTCTTCTCCTCCTCTCTGCTTCTTCCATGT
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[0436]

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GCTGGCCGAGAACAGGGCCATCCGCCCGACGAGGCCGGGTGGTGTACGACGCGCTGTGCA
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[0437]

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[0438]

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[0439]

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[0440]

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[0441]

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[0442]

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[0443]

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[0444]

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[0445]

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[0446]

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 ATGATG

[0447]

[0448] SEQ ID NO: 11 - ChAd155/RSV를 인코딩하는 폴리뉴클레오티드 서열

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[0449]

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[0450]

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[0451]

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[0452]

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[0453]

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[0454]

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[0455]

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[0456]

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[0457]

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[0458]

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[0459]

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[0460]

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[0461]

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[0462]

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CTTAGATCTCTAACGCAGCACCAGCACCAACACTTCGCAGTGTAAAAGGCCAAGTGCCGAGAG
AGTATATATAGGAATAAAAAGTGACGTAAACGGGCAAAGTCCAAAAACGCCAGAAAAACCG
CACGCGAACCTACGCCCCGAAACGAAAGCCAAAAAACAAGTACACTCCCTTCCGGCGTCAACT
TCCGCTTTCCACGCTACGTCACTTCCCCAGTCAAACAACTACATATCCCGAACTTCCAAGTC
GCCACGCCCCAAACACCGCTACACCTCCCCGCGCGCGCGCGCCCCAAACCCGCCTCCCGC
CCCGCGCCCCGCGCGCGCCCATCTCATTATCATATTGGCTTCAATCCAAAATAAGGTATAT
TATTGATGATG

[0463]

[0464] SEQ ID NO: 12 - CASI 프로모터를 인코딩하는 폴리뉴클레오티드 서열

GGAGTTCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCGC
CCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGAAGTTCATTGACGTCA
ATGGGTGGAGTATTACGGTAAACTGCCCACTTGCGAGTACATCAAGTGATCATATGCCAAGT
ACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCAGTACATGACCTT
ATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGTATTACCATGGTCGAGGTGA
GCCCCACGTTCTGCTTCACTCTCCCCATCTCCCCCCCCCTCCCCACCCCAATTTGTATTTATTTAT
TTTTAATTATTTGTGCAGCGATGGGGGCGGGGGGGGGGGGGCGCGCCAGGCGGGGCG
GGGCGGGGCGAGGGGCGGGGCGGGGCGAGGCGGAGAGGTGCGGCGCAGCCAATCAGAGCGG
CGGCTCCGAAAGTTTCTTTATGGCGAGGCGGCGGCGGCGGCGGCGGCTATAAAAAGCGAAGC
GCTCCCTATCAGTGATAGAGATCTCCCTATCAGTGATAGAGATCGTCGACGAGCTCGCGGCGGG
CGGGAGTCGCTGCGCGTGCCTTCCGCCCTGCCCCGCTCCGCCGCGCCTCGCGCGCGCGGCC
CGGCTCTGACTGACCGGTTACTAAACAGGTAAGTCCGGCTCCGCGCGGGTTTGGCGCCTC
CCGCGGGCGCCCCCTCTCAGGGGAGCGCTGCCACGTACAGCGAAGGCGCGCAGCGAGCGTCC
TGATCCTTCCGCCCGACGCTCAGGACAGCGGCCGCTGCTCATAAGACTCGGCCTTAGAACCC
CAGTATCAGCAGAAGGACATTTAGGACGGGACTTGGGTGACTCTAGGGCACTGGTTTTCTTTCC
AGAGAGCGGAACAGGCGAGGAAAAGTAGTCCCTTCTCGGCGATTCTCGGAGGGATCTCCGTG
GGGCGGTGAACGCCGATGATGCCTCTACTAACCATGTTATGTTTTCTTTTTTCTACAGGTCC
TGGGTGACGAACAG

[0465]

[0466] SEQ ID NO: 13 - Ad5orf6 프라이머 1 폴리뉴클레오티드 서열

ATACGGACTAGTGGAGAAGTACTCGCCTACATG

[0467]

[0468] SEQ ID NO: 14 - Ad5orf6 프라이머 2 폴리뉴클레오티드 서열

[0469] ATACGGAAGATCTAAGACTTCAGGAAATATGACTAC

[0470] SEQ ID NO: 15 - BAC/CHAd155 ΔE1_Tet0 hCMV RpsL-Kana 프라이머 1 폴리뉴클레오티드 서열

[0471] ATTCAGTGTACAGGCGCGCCAAAGCATGACGCTGTTGATTTGATTC

[0472] SEQ ID NO: 16 - BAC/CHAd155 ΔE1_Tet0 hCMV RpsL-Kana (#1375) 프라이머 2 폴리뉴클레오티드 서열

[0473] ACTAGGACTAGTTATAAGCTAGAAATGGGGCTTTGC

[0474] SEQ ID NO: 17 - 1021-FW E4 Del Step1 프라이머 폴리뉴클레오티드 서열

[0475] TTAATAGACACAGTAGCTTAATAGACCCAGTAGTGCAAAGCCCCATTCTAGCTTATAACCCCTAT
TTGTTATTTTCT

[0476] SEQ ID NO: 18 - 1022-RW E4 Del Step1 프라이머 폴리뉴클레오티드 서열

[0477] ATATATACTCTCTCGGCACTTGGCCTTTTACACTGCGAAGTGTGGTGCTGGTGCTGCGTTGAGA
GATCTTTATTTGTAACTGTAAATTGTC

[0478] SEQ ID NO: 19 - 1025-FW E4 Del Step2 프라이머 폴리뉴클레오티드 서열

[0479] TTAATAGACACAGTAGCTTAATA

[0480] SEQ ID NO: 20 - 1026-RW E4 Del Step2 프라이머 폴리뉴클레오티드 서열

[0481] GGAAGGGAGTGTCTAGTGTT

[0482] SEQ ID NO: 21 - 91-SubMonte FW 프라이머 폴리뉴클레오티드 서열

[0483] CAATGGGCGTGGATAGCGGTTTGAC

[0484] SEQ ID NO: 22 - 90-BghPolyA RW 프라이머 폴리뉴클레오티드 서열

[0485] CAGCATGCCTGCTATTGTC

[0486] SEQ ID NO: 23 - CMVfor 프라이머 폴리뉴클레오티드 서열

[0487] CATCTACGTATTAGTCATCGCTATTACCA

[0488] SEQ ID NO: 24 - CMVrev 프라이머 폴리뉴클레오티드 서열

[0489] GACTTGGAATCCCCGTGAGT

[0490] SEQ ID NO: 25 - CMVFAM-TAMRA qPCR 프로브 폴리뉴클레오티드 서열

[0491] ACATCAATGGGCGTGGATAGCGGTT

[0492] SEQ ID NO: 26 - 우드척 간염 바이러스 전사후 조절 요소(WPRE) 폴리뉴클레오티드 서열

[0493] TAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAAGTATGTTGCTCCTTT
TACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCAT
TTTCTCCTCCTGTATAAATCCTGGTTGCTGTCTTTATGAGGAGTTGTGGCCCGTTGTCAGGCA
ACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCACTGGTTGGGGCATTGCCACCACT
GTCAGCTCCTTTCCGGGACTTTTCGCTTTCCCTCCCTATTGCCACGGCGGAATCATCGCCGCCT
GCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCTGGTGTGTGCGGG
GAAATCATCGTCCTTTCTTGCTGCTCGCTGTGTTGCCACCTGGATTCTGCGCGGGACGTCCTT
CTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGC
GGCCTCTCCGCGTCTTCGCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCGCCTCCCG
CCT

[0494] SEQ ID NO: 27 - ChAd3 섬유 아미노산 서열

MKRTKTSDESFNPVYPYDTESGPPSVFPLTPPFVSPDGFQESPPGVLSLNLAEPVLTSHGMLALKMGS
 GLSLDDAGNLTSDITTASPLKKTKTNLSLETSSPLTVSTSGALTVAAAAPLAVAGTSLTMQSEAPL
 TVQDAKLTATKGPLTVSEGLKALQTSAPLTAADSSTLTVSATPPINVSSGSLGLDMEDPMYTHDGK
 LGIRIGGPLRVVDSLHTLTVVTGNGLTVDNNALQTRVTGALGYDTSGNLQLRAAGGMRIDANGQLI
 LNVAYPFDAQNLSRLRGQGPLYINTDHNLDLNCNRGLTTTTNNTKKLETKISSGLDYDTNGAVIHK
 LGTGLSFDNTGALTGVNTGDDKLTWTTDPDSPNCRIHSDKDCKFTLVLTCKGSQILASVAALAVSG
 NLASITGTVASVTIFLRFQNGVLMENSSLDKQYWNFRNGNSTNAAPYTNAVGFMPNLAAAYPKTQS
 QTAKNNIVSQVYLNGDKSKPMTLTITLNGTNESETSQVSHYMSFTWAWESGQYATETFATNSFTF
 SYIAEQ

[0495]

[0496] SEQ ID NO: 28- PanAd3 섬유 아미노산 서열

MKRAKTSDETFNPVYPYDTENGPPSVFPLTPPFVSPDGFQESPPGVLSRLSEPLVTSHGMLALKMGN
 GLSLDDAGNLTSDVTTVPPLKKTKTNLSLQTSAPLTVSSGSLTVAAAAPLAVAGTSLTMQSQA
 TVQDAKLGATQGPLTVSEGLKALQTSAPLTAADSSTLTVGTTPIVSSGSLGLDMEDPMYTHDGK
 LGIRIGGPLRVVDSLHTLTVVTGNGITVANNALQTKVAGALGYDSSGNLELRAAGGMRINTGGQLIL
 DVAYPFDAQNLSRLRGQGPLYVNTNHNLDLNCNRGLTTTTSSNTKKLETKIDSGLDYNANGAIIAK
 LGTGLTFDNTGALTGVNTGDDKLTWTTDPDSPNCRIHADKDKFTLVLTCKGSQILASVAALAVSGN
 LSSMTGTVSSVTIFLRFQNGVLMENSSLDKEYWNFRNGNSTNATPYTNAVGFMPNLSAYPKTQS
 TAKNNIVSEVYLHGDKSKPMTLTITLNGTNESETSQVSHYMSFTWWSGKYATETFATNSFTFSY
 IAEQ

[0497]

[0498] SEQ ID NO: 29 - ChAd17 섬유 아미노산 서열

MKRTKTSDESFNPVYPYDTESGPPSVFPLTPPFVSPDGFQESPPGVLSLNLAEPVLTSHGMLALKMGS
 GLSLDDAGNLTSDITSTTTPPLKKTKTNLSLETSSPLTVSTSGALTVAAAAPLAVAGTSLTMQSEAPL
 AVQDAKLTATKGPLTVSEGLKALQTSAPLTAADSSTLTVSSTPIVSSGSLGLDMEDPMYTHDGK
 LGIRIGGPLRVVDSLHTLTVVTGNGLTVDNNALQTRVTGALGYDTSGNLQLRAAGGMRIDANGQLI
 LDVAYPFDAQNLSRLRGQGPLYVNTDHNLDLNCNRGLTTTTNNTKKLETKISSGLDYDTNGAVII
 KLGTGLSFDNTGALTGVNTGDDKLTWTTDPDSPNCRIHSDKDCKFTLVLTCKGSQILASVAALAVS
 GNLASITGTVASVTIFLRFQNGVLMENSSLDKQYWNFRNGNSTNAPYTNAVGFMPNLAAAYPKTQ
 SQTAKNNIVSQVYLNGDKSKPMTLTITLNGTNESETSQVSHYMSFTWAWESGQYATETFATNSFT
 FSYIAEQ

[0499]

[0500] SEQ ID NO: 30 - ChAd19 섬유 아미노산 서열

MKRTKTSKSFNPVYPYDTENGPPSVFPLTPPFVSPDGFQESPPGVLSLNLAEPVLTSHGMLALKMGS
 GLSLDDAGNLTSDVTTTTTTPPLKKTKTNLSLETSAPLTVSTSGALTLAAAAPLAVAGTSLTMQSEAPL
 TVQDAKLTATKGPLTVSEGLKALQTSAPLTAADSSTLTVSATPPISVSSGSLGLDMEDPMYTHDGK
 LGIRIGGPLRVVDSLHTLTVVTGNGIADVNNALQTRVTGALGYDTSGNLQLRAAGGMRIDANGQLIL
 DVAYPFDAQNLSRLRGQGPLYVNTDHNLDLNCNRGLTTTTNNTKKLETKIGSGLDYDTNGAVIHK
 LGTGVSFDTGALSVDNTGDDKLTWTTDPDSPNCRIHSDKDCKFTLVLTCKGSQILASVAALAVSG
 NLASITGTVSSVTIFLRFQNGVLMENSSLDKQYWNFRNGNSTNATPYTNAVGFMPNLAAAYPKTQS
 QTAKNNIVSQVYLNGDKSKPMTLTITLNGTNESETSQVSHYMSFTWAWESGQYATETFATNSFTF
 SYIAEQ

[0501]

[0502] SEQ ID NO: 31 - ChAd24 섬유 아미노산 서열

MKRTKTSDESFNPVYPYDTENGPPSVFPLTPPFVSPDGFQESPPGVLSLNLAEPVLTSHGMLALKMGS
 GLSLDDAGNLTSDVTTTTTTPPLKKTKTNLSLETSAPLTVSTSGALTLAAAAPLAVAGTSLTMQSEAPL
 TVQDAKLTATKGPLTVSEGLKALQTSAPLTAADSSTLTVSATPPINVSSGSLGLDMENPMYTHDGK
 LGIRIGGPLRVVDSLHTLTVVTGNGIADVNNALQTRVTGALGYDTSGNLQLRAAGGMRIDANGQLIL
 DVAYPFDAQNLSRLRGQGPLYVNTDHNLDLNCNRGLTTTTNNTKKLETKIGSGLDYDTNGAVIHK
 LGTGVSFDTGALSVDNTGDDKLTWTTDPDSPNCRIHSDKDCKFTLVLTCKGSQILASVAALAVSG
 NLASITGTVSSVTIFLRFQNGVLMENSSLDKQYWNFRNGNSTNATPYTNAVGFMPNLAAAYPKTQS
 QTAKNNIVSQVYLNGDKSKPMTLTITLNGTNESETSQVSHYMSFTWAWESGQYATETFATNSFTFS
 YIAEQ

[0503]

[0504] SEQ ID NO: 32 - ChAd11 섬유 아미노산 서열

MKRTKTSDESFNPVYPYDTENGPPSPFLTPPFVSPDGFQESPPGVLSLNLAEPVLTSHGMLALKMGS
 GLSLDDAGNLTSDQVTTTTPPLKKTKTNLSLETSAPLTVSTSGALTLAAAVPLAVAGTSLTMQSEAPL
 TVQDAKLTATKGPLTVSEGKALQTSAPLTAADSSSTLTISATPPLSTSNGLGIDMQAPIYTTNGKLG
 LNFGAPLHVVDLSNALTVVTGQGLTINGTALQTRVSGALNYDSSGNLELRAAGGMRVDANGKLILD
 VAYPFDAQNLSRLRGQGPLFVNSAHNLDVNYNRGLYLFTSGNTKKLEVNIKTAKGLIYDDTAIAIN
 PGDGLFEGSGSDTNPLKTKLGLGLEYPDSSRAIIAKLGTGLSFDNTGAITVGNKNDDKLTWTTTPDPSP
 NCRIYSEKDAKFTLVLTCKGSQLASVSVLSVKGSLAPISGTVTSAQIILRFDENGVLLSNSSLDQPQY
 NYRKGDLTGEGTAYTNAVGFMPNLTAYPKTQSQTAASNIVSQVYLNNGDKSKPMTLTITLNGTNETGD
 ATVSTYSMSFSWNWNGSNYINETFQTNSTFTFSYIAQE

[0505]

[0506] SEQ ID NO: 33 - ChAd20 섬유 아미노산 서열

MKRTKTSDESFNPVYPYDTESGPPSPFLTPPFVSPDGFQESPPGVLSLNLAEPVLTSHGMLALKMGS
 GLSLDDAGNLTSDITASPLKKTKTNLSLETSSPLTVSTSGALTVAAPLAVAGTSLTMQSEAPL
 TVQDAKLTATKGPLTVSEGKALQTSAPLTAADSSSTLTVSATPPLSTSNGLGIDMQAPIYTTNGKL
 GLNFGAPLHVVDLSNALTVVTGQGLTINGTALQTRVSGALNYDTSGNLELRAAGGMRVDANGQLIL
 DVAYPFDAQNLSRLRGQGPLFVNSAHNLDVNYNRGLYLFTSGNTKKLEVNIKTAKGLIYDDTAIAI
 NAGDGLQFDSGSDTNPLKTKLGLGLDYDSSRAIIAKLGTGLSFDNTGAITVGNKNDDKLTWTTTPDP
 SPNCRIYSEKDAKFTLVLTCKGSQLASVSVLSVKGSLAPISGTVTSAQIVLRFDENGVLLSNSSLDQPQ
 YWNYRKGDLTGEGTAYTNAVGFMPNLTAYPKTQSQTAASNIVSQVYLNNGDKSKPMTLTITLNGTNET
 GDATVSTYSMSFSWNWNGSNYINETFQTNSTFTFSYIAQE

[0507]

[0508] SEQ ID NO: 34 - ChAd31 섬유 아미노산 서열

MKRTKTSDESFNPVYPYDTESGPPSPFLTPPFVSPDGFQESPPGVLSLNLAEPVLTSHGMLALKMGS
 GLSLDDAGNLTSDITASPLKKTKTNLSLETSSPLTVSTSGALTVAAPLAVAGTSLTMQSEAPL
 TVQDAKLTATKGPLTVSEGKALQTSAPLTAADSSSTLTVSATPPLSTSNGLGIDMQAPIYTTNGKL
 GLNFGAPLHVVDLSNALTVVTGQGLTINGTALQTRVSGALNYDTSGNLELRAAGGMRVDANGQLIL
 DVAYPFDAQNLSRLRGQGPLFVNSAHNLDVNYNRGLYLFTSGNTKKLEVNIKTAKGLIYDDTAIAI
 NAGDGLQFDSGSDTNPLKTKLGLGLDYDSSRAIIAKLGTGLSFDNTGAITVGNKNDDKLTWTTTPDP
 SPNCRIYSEKDAKFTLVLTCKGSQLASVSVLSVKGSLAPISGTVTSAQIVLRFDENGVLLSNSSLDQPQ
 YWNYRKGDLTGEGTAYTNAVGFMPNLTAYPKTQSQTAASNIVSQVYLNNGDKSKPMTLTITLNGTNET
 GDATVSTYSMSFSWNWNGSNYINETFQTNSTFTFSYIAQE

[0509]

[0510] SEQ ID NO: 35 - PanAd1 섬유 아미노산 서열

MKRAKTSDETFNPVYPYDTENGPPSPFLTPPFVSPDGFQESPPGVLSLRLSEPLVTSHGMLALKMGN
 GLSLDDAGNLTSDQVTTTTPPLKKTKTNLSLQTSAPLTVSSGSLTVAAAPLAVAGTSLTMQSQAPL
 TVQDAKLGLATQGPLTVSEGKLTQTSAPLTAADSSSTLTVSATPPLSTSNGLSIDMQAPIYTTNGKL
 ALNIGAPLHVVDLTNALTVVTGQGLTINGRALQTRVTGALSVDTEGNIQLQAGGMRIDNNGQLILN
 VAYPFDAQNLSRLRGQGPLIVNSAHNLDLNLNRGLYLFTSGNTKKLEVNIKTAKGLFYDGTIAIN
 AGDGLQFGSGSDTNPLQTKLGLGLEYDSNKAIITKLTGLSFDNTGAITVGNKNDDKLTWTTTPDP
 PNCRIYSEKDAKLTVLTKCGSQLASVSVLSVKGSLAPISGTVTSAQIVLRFDENGVLLSNSSLDQPQY
 WNYRKGDSTEGTAYTNAVGFMPNLTAYPKTQSQTAASNIVSQVYLNNGDKTKPMTLTITLNGTNETG
 DATVSTYSMSFSWNWNGSNYINDTFQTNSTFTFSYIAQE

[0511]

[0512] SEQ ID NO: 36 - PanAd2 섬유 아미노산 서열

MKRAKTSDETFNPVYPYDTENGPPSPFLTPPFVSPDGFQESPPGVLSLRLSEPLVTSHGMLALKMGN
 GLSLDDAGNLTSDQVTTTTPPLKKTKTNLSLQTSAPLTVSSGSLTVAAAPLAVAGTSLTMQSQAPL
 TVQDAKLGLATQGPLTVSEGKLTQTSAPLTAADSSSTLTVSATPPLSTSNGLSIDMQAPIYTTNGKL
 ALNIGAPLHVVDLTNALTVVTGQGLTINGRALQTRVTGALSVDTEGNIQLQAGGMRIDNNGQLILN
 VAYPFDAQNLSRLRGQGPLIVNSAHNLDLNLNRGLYLFTSGNTKKLEVNIKTAKGLFYDGTIAIN
 AGDGLQFGSGSDTNPLQTKLGLGLEYDSNKAIITKLTGLSFDNTGAITVGNKNDDKLTWTTTPDP
 PNCRIYSEKDAKLTVLTKCGSQLASVSVLSVKGSLAPISGTVTSAQIVLRFDENGVLLSNSSLDQPQY
 WNYRKGDSTEGTAYTNAVGFMPNLTAYPKTQSQTAASNIVSQVYLNNGDKTKPMTLTITLNGTNETG
 DATVSTYSMSFSWNWNGSNYINDTFQTNSTFTFSYIAQE

[0513]

[0514]

SEQ ID NO: 37 - RSV F ΔTM 아미노산 서열

MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSKGYLSALRTGWYTSVITIELSNIKENKCN
GTDAKVKLIKQELDKYKNAVTELQLLMQSTPATNNRRELPRFMNYTLNNAKKTNTVLSKKRRR
RFLGFLLGVGSAIASGVAVSKVLHLEGEVNIKSALLSTNKAVVSLNGVSVLTSKVLDLKNYIDKQ
LLPIVKNQSCSISNIETVIEFQQKNNRLLLEITREFSVNAGVTTTPVSTYMLTNSELLSLNDMPITNDQKKL
MSNNVQIVRQQSYSIMSIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSLNCLTRTDRGW
YCDNAGSVSFFPQAECKVQSNRVFCDTMNSLTLPSEVNLCNVDFINPKYDCKIMTSKTDVSSSVITS
LGAIVSCYGKTKCTASNKNRGIKTFNSGCDYVSNKGVDTVSVGNTLYYVKNQEGKSLYVKGEPIIN
FYDPLVFPDEFDASISQVNEKINQSLAFIRKSDELLHNVNAGKSTTNRRRAPVKQTLNFDLLKLAG
DVESNPGMALSKVKLNDTLNKDQLLSKYTIQRSTGDSIDTPNYDVQKHINKLCGMILLITEDANH
KFTGLIGMLYAMSRLGREDTIKILRDAGYHVKANGVDVTTHRQDINGKEMKFEVLTLASLTTEIQINI
EIESRKSYYKMLKEMGEVAPEYRHSDPCGMILCIAALVITKLAAGDRSGLTAVIRRANNVLKNEM
KRYKGLLPKDIANS
FYEVEKEYPHFIDVFVHFQIAQSSTRGGSRVGEIFAGLFMNAYGAGQVMLRWGVLAHSVKNIMLGH
ASVQAEMEQQVEVVEYYAQKLGEAGFYHILNPNKASLLSLTQPHFSSVVLGNAAGLGIMGEYRGT
PRNQDLYDAAKAYAEQLKENGVINYSVLDLTAELEAIKHQLNPKDNDVELGGGGSGGGGMSRRN
PCKFEIRGHCLNGKRCFHSHNYFEWPPHALLVRQNFMLNRILKSMDSIDTLSEISGAELDRTEEYA
LGVVGVLESYIGSINNITKQSACVAMSKLLTELNSDDIKLRDNEELNSPKIRVYNTVISYIESNRKNN
KQTIHLLKRLPADVLKKTIKNTLDIHKISITINNPKESTVSDTNHAKNNDTT

[0515]

[0516]

SEQ ID NO: 38 - HIV Gag 폴리뉴클레오티드 서열

ATGGGTGCTAGGGCTTCTGTGCTGTCTGGTGGTGAGCTGGACAAGTGGGAGAAGATCAGGCTGA
GGCCTGGTGGCAAGAAGAAGTACAAGCTAAAGCACATTGTGTGGGCCTCCAGGGAGCTGGAGA
GGTTTGCTGTGAACCTGGCCTGCTGGAGACCTCTGAGGGGTGCAGGCAGATCCTGGGCCAGCT
CCAGCCCTCCCTGCAAAACAGGCTCTGAGGAGCTGAGGTCCCTGTACAACACAGTGGCTACCCCTG
TACTGTGTGCACCAGAAGATTGATGTGAAGGACACCAAGGAGGCCCTGGAGAAGATTGAGGAG
GAGCAGAACAAGTCCAAGAAGAAGGCCAGCAGGCTGCTGCTGGCACAGGCAACTCCAGCCAG
GTGTCCCAGAACTACCCCATTTGTGCAGAACCTCCAGGGCCAGATGGTGACACAGGCCATCTCCC
CCCGGACCCTGAATGCCTGGGTGAAGGTGGTGGAGGAGAGGCCCTTCTCCCTGAGGTGATCCCC
ATGTTCTCTGCCCTGTCTGAGGGTGCCACCCCCAGGACCTGAACACCATGCTGAACACAGTGG
GGGGCCATCAGGCTGCCATGCAGATGCTGAAGGAGACCATCAATGAGGAGGCTGCTGAGTGGG
ACAGGCTGCATCCTGTGCACGCTGGCCCCATTGCCCCCGGCCAGATGAGGGAGCCAGGGGCTC
TGACATTGCTGGCACCACTCCACCCTCCAGGAGCAGATTGGCTGGATGACCAACAACCCCCC
ATCCCTGTGGGGGAAATCTACAAGAGGTGGATCATCCTGGGCCTGAACAAGATTGTGAGGATGT
ACTCCCCACCTCCATCCTGGACATCAGGCAGGGCCCCAAGGAGCCCTTCAGGGACTATGTGGA
CAGGTTCTACAAGACCCTGAGGGCTGAGCAGGCCTCCCAGGAGGTGAAGAACTGGATGACAGA
GACCCTGTGGTGCAGAATGCCAACCTGACTGCAAGACCATCCTGAAGGCCCTGGGCCCTGCT
GCCACCCTGGAGGAGATGATGACAGCCTGCCAGGGGGTGGGGGGCCCTGGTCAACAAGGCCAGG
GTGCTGGCTGAGGCCATGTCCCAGGTGACCAACTCCGCCACCATCATGATGCAGAGGGGCAACT
TCAGGAACCAAGAGGAAGACAGTGAAGTGCTTCAACTGTGGCAAGGTGGGCCACATTGCCAAGA
ACTGTAGGGCCCCAGGAAGAAGGGCTGCTGGAAGTGTGGCAAGGAGGGCCACCAGATGAAGG
ACTGCAATGAGAGGCAGGCCAAGCTTCTGGGCAAAATCTGGCCCTCCACAAAGGCAGGCCTGG
CAACTTCTCCAGTCCAGGCCTGAGCCACAGCCCTCCCGAGGAGTCCTTCAGGTTTGGGGAG
GAGAAGACCACCCAGCCAGAAGCAGGAGCCATTGACAAGGAGCTGTACCCCTGGCCTCCC
TGAGGTCCCTGTTTGGCAACGACCCCTCCTCCAGTAA

[0517]

도면

도면 1a

[illegible]

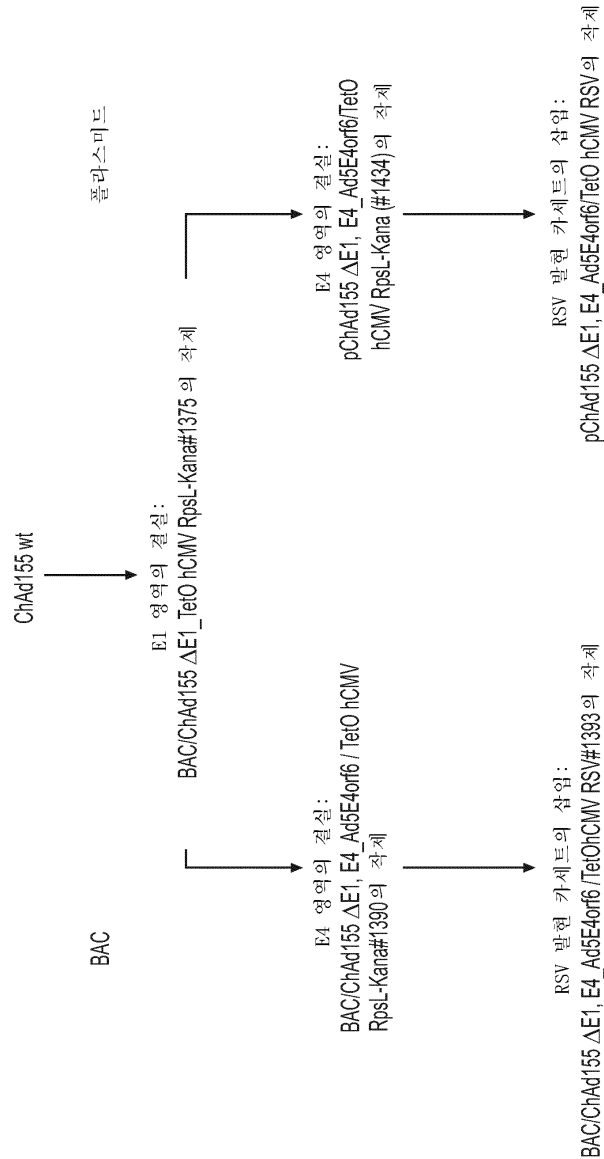
도면1b

ChAd3 (201)	DGGEH QCEEPWVWISH HIAWVWEN LUDNNVLOKRECAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
PanAd3 (200)	DGGEH QCEEPWVWISH HIAWVWEN LUDNNVLOKRECAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
ChAd17 (201)	DGGEH QCEEPWVWISH HIAWVWEN LUDNNVLOKRECAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
ChAd19 (201)	DGGEH QCEEPWVWISH HIAWVWEN LUDNNVLOKRECAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
ChAd24 (201)	DGGEH QCEEPWVWISH HIAWVWEN LUDNNVLOKRECAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
ChAd155 (201)	QSGGNNPREEVEVSI NIAVAVGCGE LUNG HIOKRSAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
ChAd11 (201)	QSGGNNPREEVEVSI NIAVAVGCGE LUNG HIOKRSAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
ChAd20 (201)	QSGGNNPREEVEVSI NIAVAVGCGE LUNG HIOKRSAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
ChAd31 (201)	QSGGNNPREEVEVSI NIAVAVGCGE LUNG HIOKRSAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
PanAd 1 (200)	QSGGNNPREEVEVSI NIAVAVGCGE LUNG HIOKRSAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
PanAd2 (200)	QSGGNNPREEVEVSI NIAVAVGCGE LUNG HIOKRSAPVHSG IOIRAGGORDANUJINVAYFDONUSRI GGGPIV N QINB
ChAd3 (301)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
PanAd3 (300)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
ChAd17 (301)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
ChAd19 (301)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
ChAd24 (301)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
ChAd155 (301)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
ChAd11 (301)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
ChAd20 (301)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
ChAd31 (301)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
PanAd1 (300)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH
PanAd2 (300)	QNNRGH VHT DNWKKKEJ ----- KISSGIDIN FAL KICG EISENTG E LUNG QDQKPAH

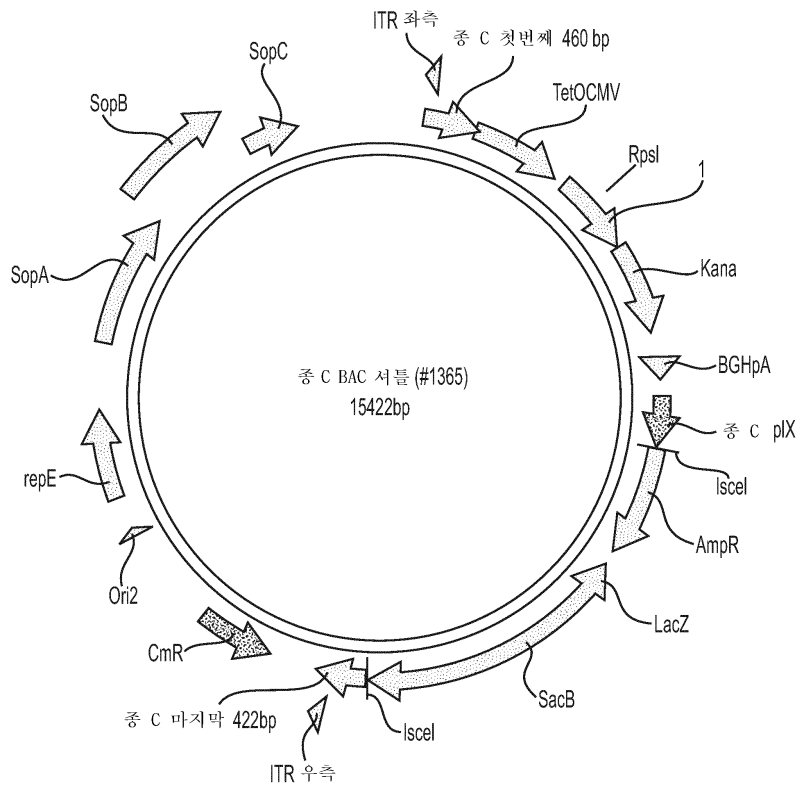
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PanAd3 (364)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
ChAd17 (365)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
ChAd19 (365)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
ChAd24 (365)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
ChAd155 (401)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
ChAd11 (401)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
ChAd20 (401)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
ChAd31 (401)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
PanAd1 (400)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
PanAd2 (400)	PPESPPCEPISDZPPEUUVKGGSCDASDAPVNSHSTITWASWTHREHGGVNNSSPQVNNHNSGAPDAVAGVNNPP
ChAd3 (465)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
PanAd3 (464)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
ChAd17 (465)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
ChAd19 (465)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
ChAd24 (465)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
ChAd155 (501)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
ChAd11 (501)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
ChAd20 (501)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
ChAd31 (501)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
PanAd1 (500)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ
PanAd2 (500)	NPZTOSQANNUVOWINGDKKPPQIPQINGNNSPISOWSTSGHAWSCGAQDTHNSPFSYHQ

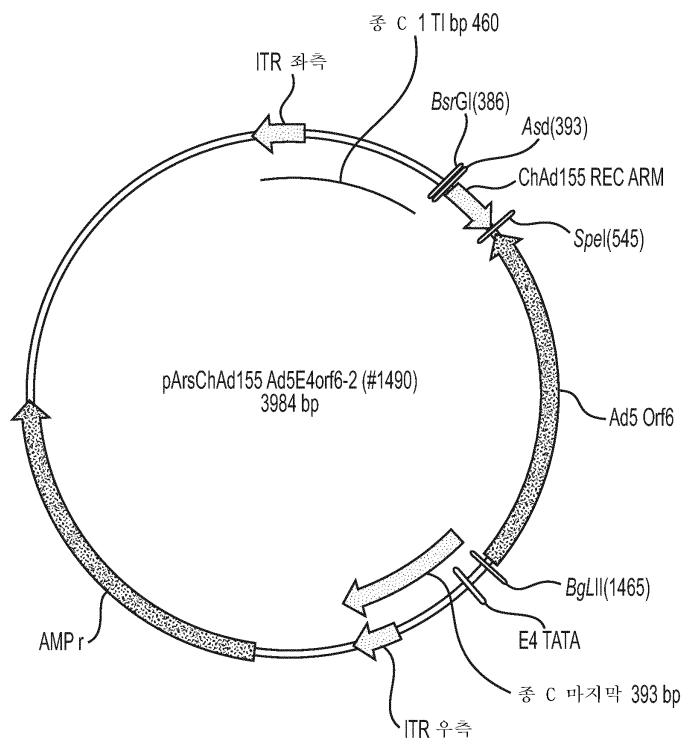
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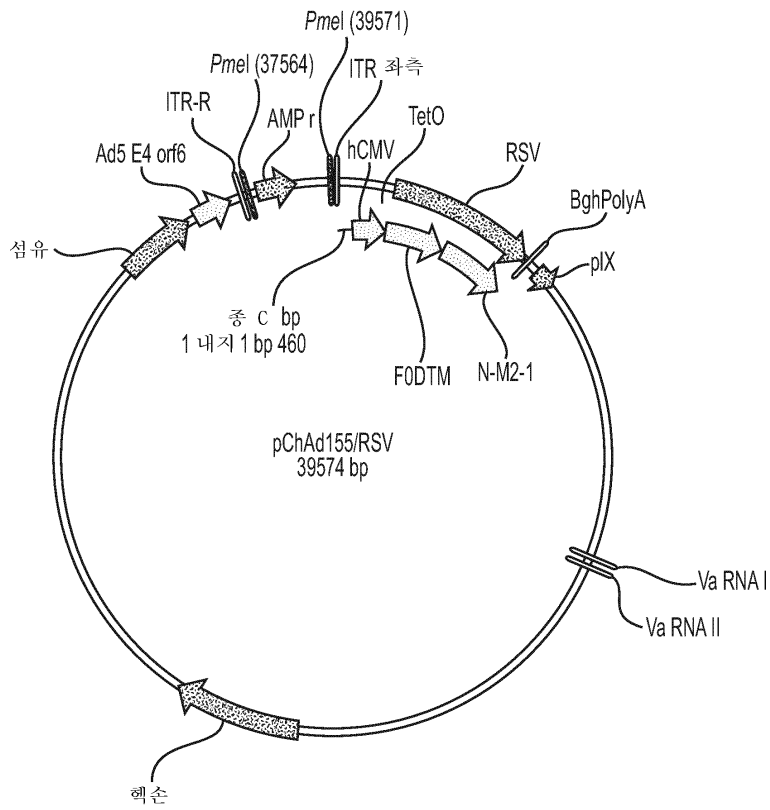
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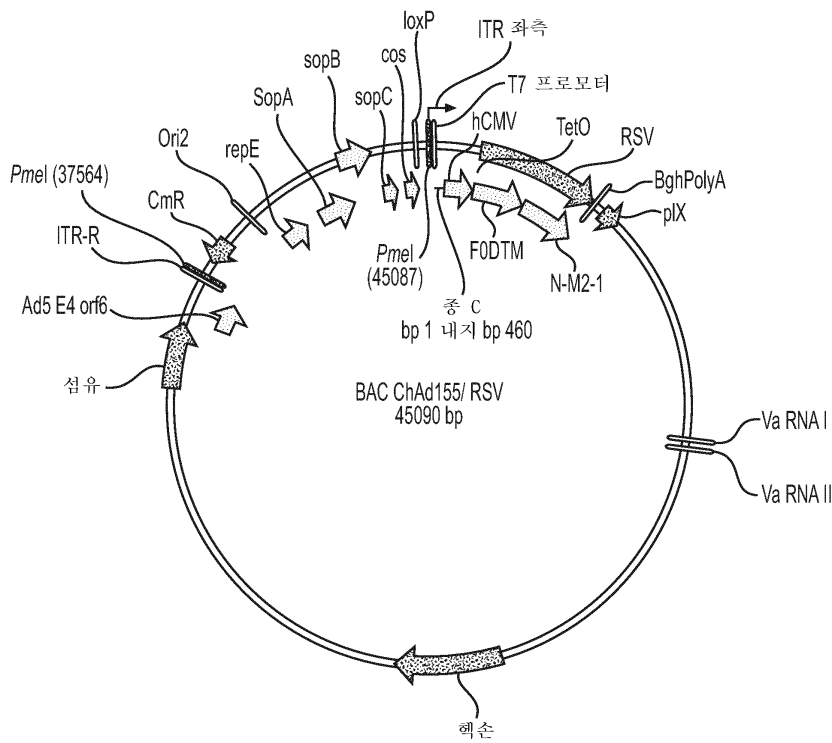
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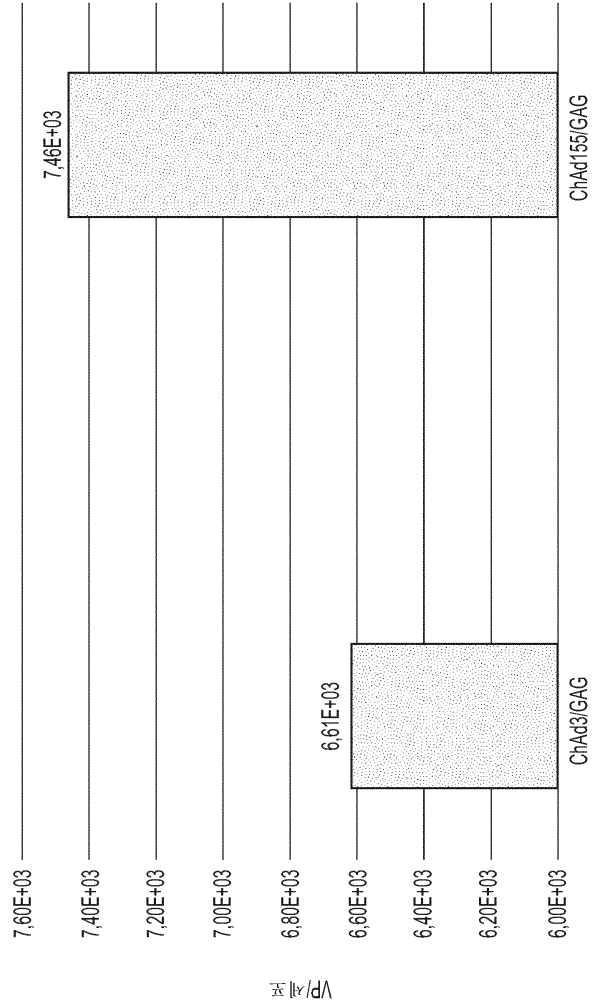
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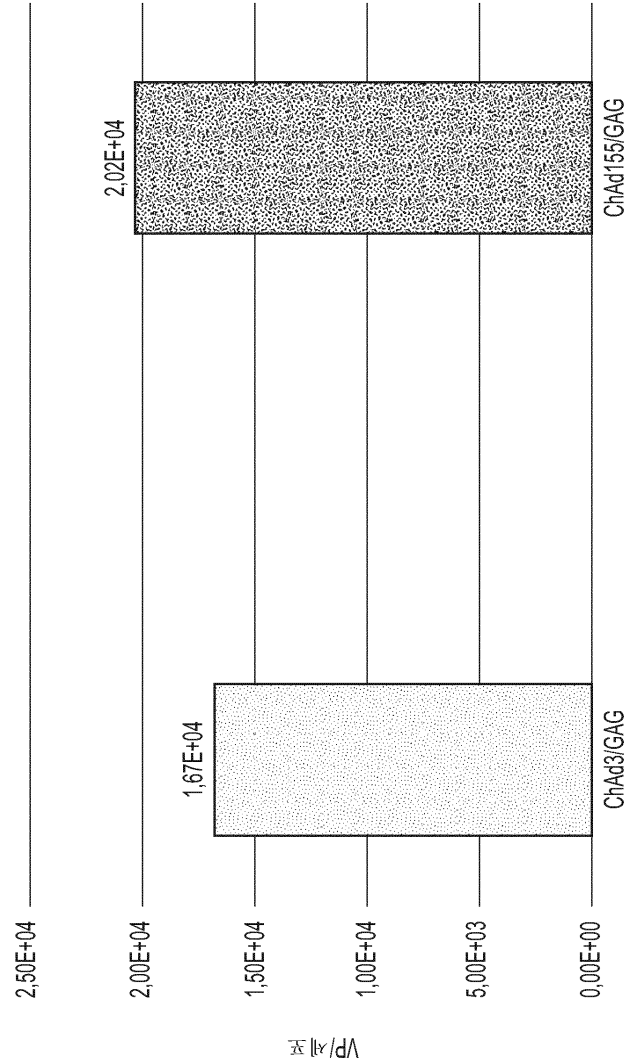
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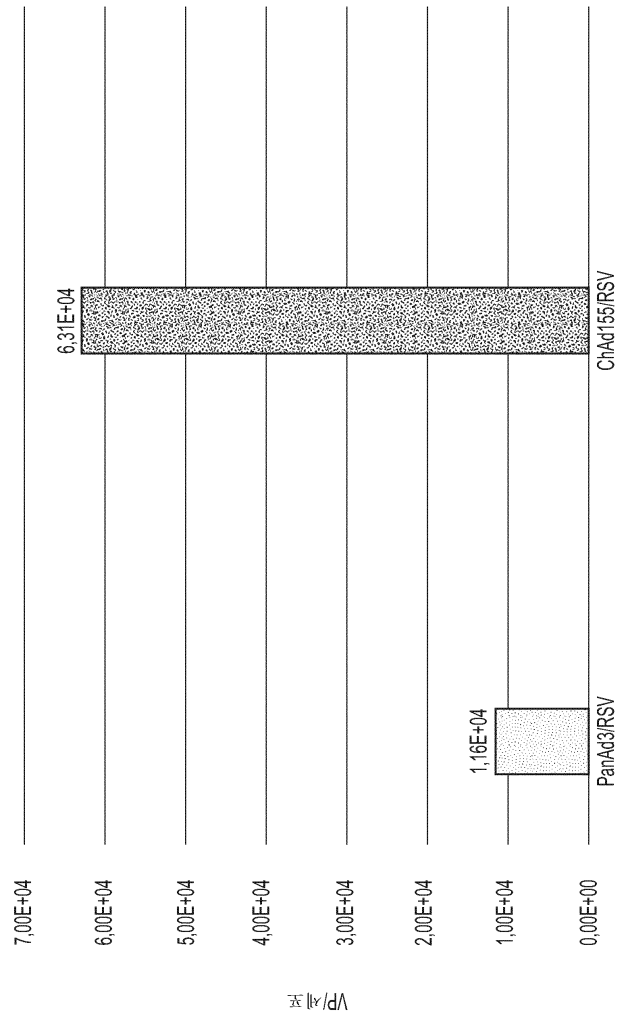
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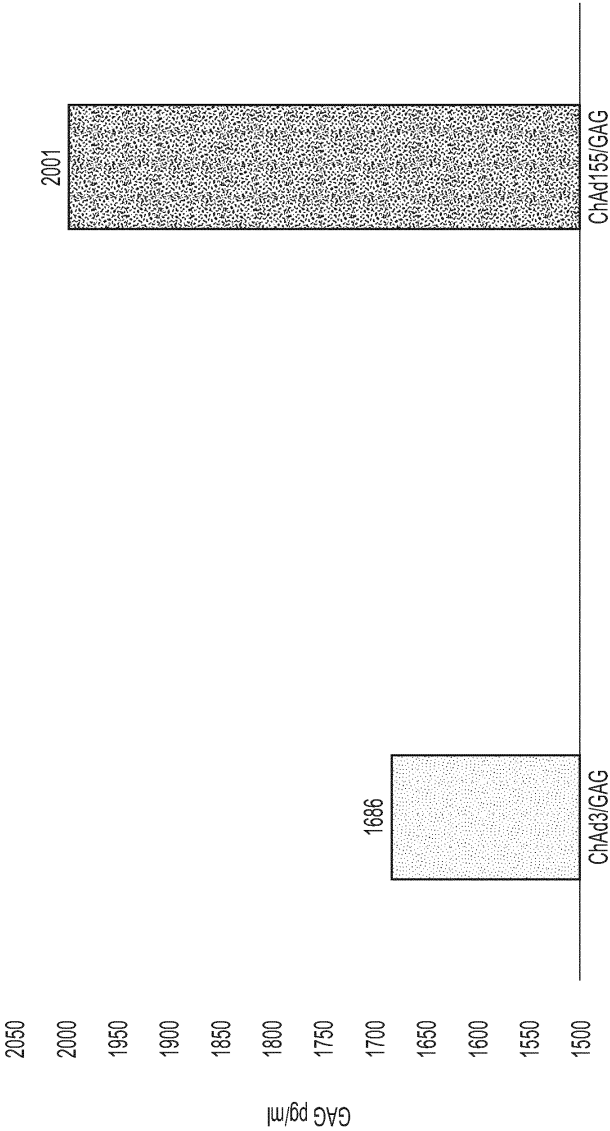
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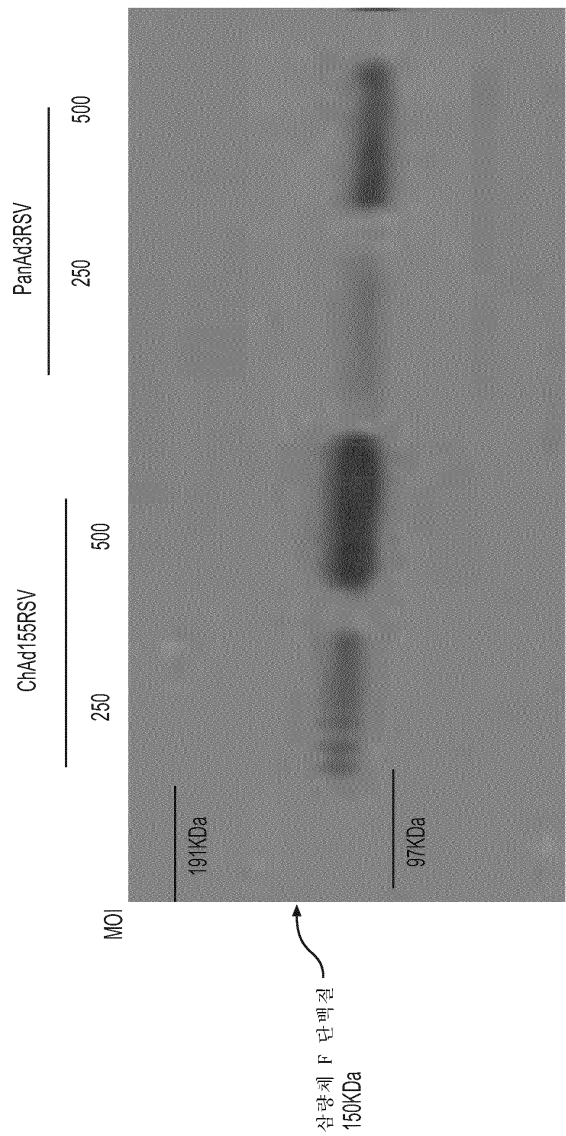
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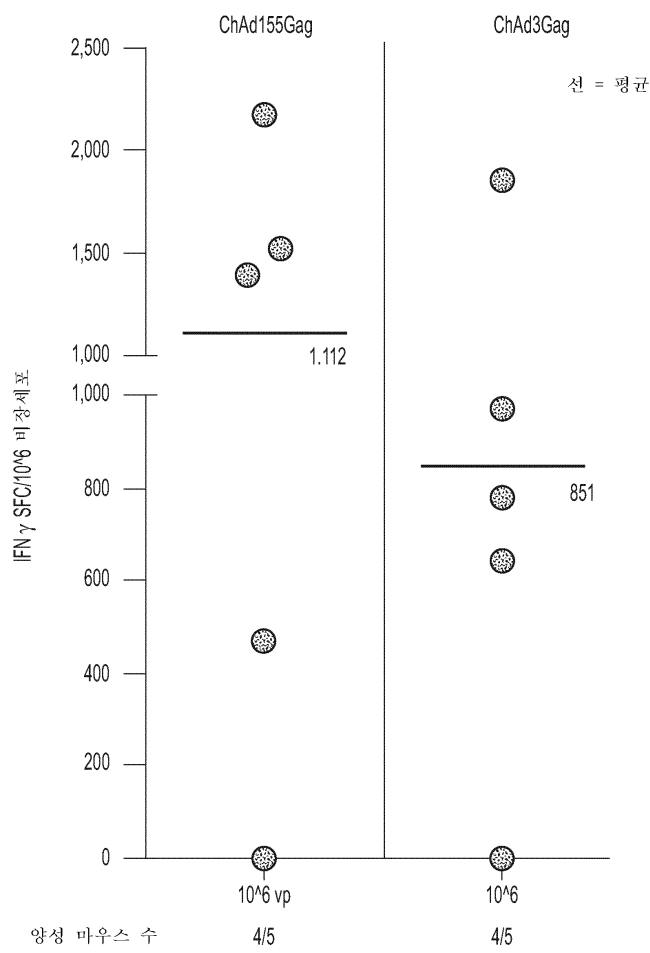
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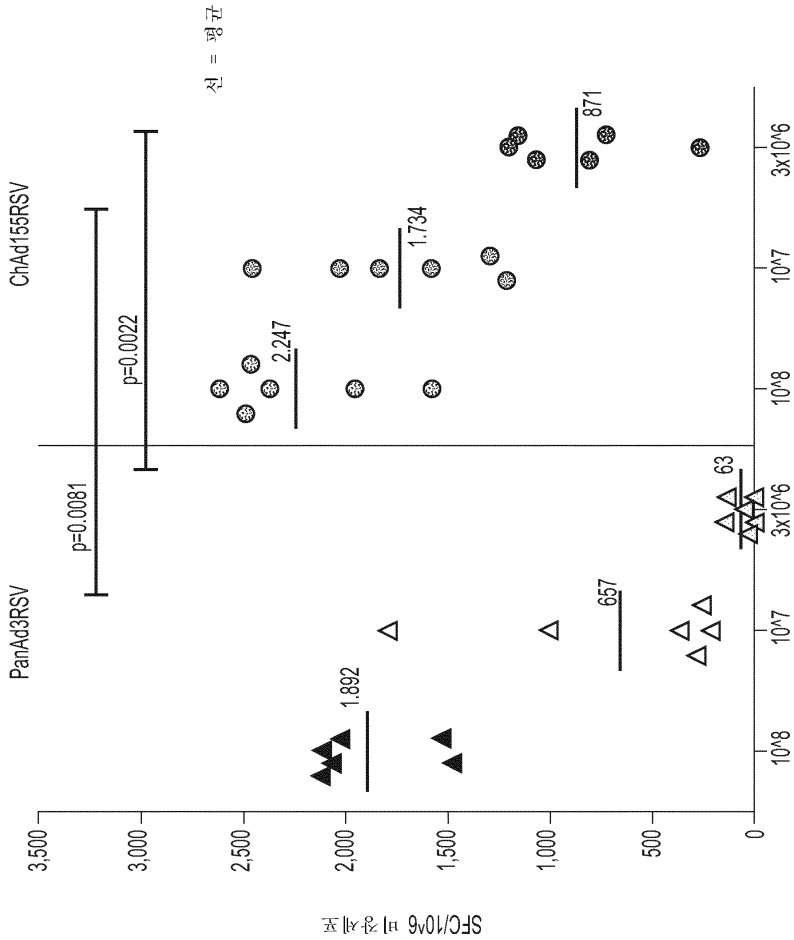
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도면12



도면13



서열목록

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- <140><141><150> UK 1514772.1
- <151> 2015-08-19
- <150> UK 1510357.5
- <151> 2015-06-12
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- <213> Simian adenovirus

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Lys Met Gly Ser Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser

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Gln Asp Ile Thr Thr Ala Ser Pro Pro Leu Lys Lys Thr Lys Thr Asn

85 90 95

Leu Ser Leu Glu Thr Ser Ser Pro Leu Thr Val Ser Thr Ser Gly Ala

100 105 110

Leu Thr Val Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu

115 120 125

Thr Met Gln Ser Glu Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Thr

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Leu Ala Thr Lys Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Ala Leu

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Gln Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val

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

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Met Gln Ala Pro Ile Tyr Thr Thr Asn Gly Lys Leu Gly Leu Asn Phe

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Gly Ala Pro Leu His Val Val Asp Ser Leu Asn Ala Leu Thr Val Val

210 215 220

Thr Gly Gln Gly Leu Thr Ile Asn Gly Thr Ala Leu Gln Thr Arg Val

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Ser Gly Ala Leu Asn Tyr Asp Thr Ser Gly Asn Leu Glu Leu Arg Ala
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 260 265 270
 Ala Tyr Pro Phe Asp Ala Gln Asn Asn Leu Ser Leu Arg Leu Gly Gln
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 Arg Gly Leu Tyr Leu Phe Thr Ser Gly Asn Thr Lys Lys Leu Glu Val
 305 310 315 320
 Asn Ile Lys Thr Ala Lys Gly Leu Ile Tyr Asp Asp Thr Ala Ile Ala
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 Ile Asn Ala Gly Asp Gly Leu Gln Phe Asp Ser Gly Ser Asp Thr Asn
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 Pro Leu Lys Thr Lys Leu Gly Leu Gly Leu Asp Tyr Asp Ser Ser Arg
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 385 390 395 400
 Thr Pro Asp Pro Ser Pro Asn Cys Arg Ile Tyr Ser Glu Lys Asp Ala
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 Lys Phe Thr Leu Val Leu Thr Lys Cys Gly Ser Gln Val Leu Ala Ser
 420 425 430
 Val Ser Val Leu Ser Val Lys Gly Ser Leu Ala Pro Ile Ser Gly Thr
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 Asp Leu Thr Glu Gly Thr Ala Tyr Thr Asn Ala Val Gly Phe Met Pro

485 490 495
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<212> DNA

<213> Simian adenovirus

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<212> PRT

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Gln Leu Leu Glu Pro Pro Tyr Val Pro Pro Arg Tyr Leu Arg Pro Thr

35 40 45

Gly Gly Arg Asn Ser Ile Arg Tyr Ser Glu Leu Ala Pro Leu Phe Asp

50 55 60

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

65 70 75 80

Leu Asn Tyr Gln Asn Asp His Ser Asn Phe Leu Thr Thr Val Ile Gln

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Asp Asp Arg Ser His Trp Gly Gly Asp Leu Lys Thr Ile Leu His Thr		
115	120	125
Asn Met Pro Asn Val Asn Glu Phe Met Phe Thr Asn Lys Phe Lys Ala		
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Arg Val Met Val Ser Arg Ser His Thr Lys Glu Asp Arg Val Glu Leu		
145	150	155
Lys Tyr Glu Trp Val Glu Phe Glu Leu Pro Glu Gly Asn Tyr Ser Glu		
165	170	175
Thr Met Thr Ile Asp Leu Met Asn Asn Ala Ile Val Glu His Tyr Leu		
180	185	190
Lys Val Gly Arg Gln Asn Gly Val Leu Glu Ser Asp Ile Gly Val Lys		
195	200	205
Phe Asp Thr Arg Asn Phe Arg Leu Gly Leu Asp Pro Val Thr Gly Leu		
210	215	220
Val Met Pro Gly Val Tyr Thr Asn Glu Ala Phe His Pro Asp Ile Ile		
225	230	235
Leu Leu Pro Gly Cys Gly Val Asp Phe Thr Tyr Ser Arg Leu Ser Asn		
245	250	255
Leu Leu Gly Ile Arg Lys Arg Gln Pro Phe Gln Glu Gly Phe Arg Ile		
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Asp Thr Ala Ala Ala Asp Gly Ala Glu Ala Asp Pro Ala Met Val Val		
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Glu Ala Pro Glu Gln Glu Glu Asp Met Asn Asp Ser Ala Val Arg Gly
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 Thr Pro Asp Val Thr Cys Gly Ser Glu Gln Val Tyr Trp Ser Leu Pro
 450 455 460
 Asp Met Met Gln Asp Pro Val Thr Phe Arg Ser Thr Arg Gln Val Ser
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 Asn Phe Pro Val Val Gly Ala Glu Leu Leu Pro Val His Ser Lys Ser
 485 490 495
 Phe Tyr Asn Asp Gln Ala Val Tyr Ser Gln Leu Ile Arg Gln Phe Thr
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 Ser Leu Thr His Val Phe Asn Arg Phe Pro Glu Asn Gln Ile Leu Ala
 515 520 525
 Arg Pro Pro Ala Pro Thr Ile Thr Thr Val Ser Glu Asn Val Pro Ala
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 Leu Thr Asp His Gly Thr Leu Pro Leu Arg Asn Ser Ile Gly Gly Val
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580

585

590

Phe

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Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu

50 55 60

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

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Lys Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met

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

100 105 110

Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ser Leu Ala Pro Lys Gly

115 120 125

Ala Pro Asn Ser Cys Glu Trp Glu Gln Glu Glu Thr Gln Thr Ala Glu

130 135 140

Glu Ala Gln Asp Glu Glu Glu Asp Glu Ala Glu Ala Glu Glu Glu Met

145 150 155 160

Pro Gln Glu Glu Gln Ala Pro Val Lys Lys Thr His Val Tyr Ala Gln
165 170 175

Ala Pro Leu Ser Gly Glu Lys Ile Thr Lys Asp Gly Leu Gln Ile Gly
180 185 190

Thr Asp Ala Thr Ala Thr Glu Gln Lys Pro Ile Tyr Ala Asp Pro Thr
195 200 205

Phe Gln Pro Glu Pro Gln Ile Gly Glu Ser Gln Trp Asn Glu Ala Asp
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Pro Cys Tyr Gly Ser Tyr Ala Arg Pro Thr Asn Ala Asn Gly Gly Gln
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260 265 270

Met Gln Phe Phe Ser Thr Ser Glu Asn Ala Arg Asn Glu Ala Asn Asn
275 280 285

Ile Gln Pro Lys Leu Val Leu Tyr Ser Glu Asp Val His Met Glu Thr
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Pro Asp Thr His Ile Ser Tyr Lys Pro Ala Lys Ser Asp Asp Asn Ser
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Asp Leu Gln Asp Arg Asn Thr Glu Leu Ser Tyr Gln Leu Leu Leu Asp
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Ser Met Gly Asp Arg Thr Arg Tyr Phe Ser Met Trp Asn Gln Ala Val
385 390 395 400

Asp Ser Tyr Asp Pro Asp Val Arg Ile Ile Glu Asn His Gly Thr Glu

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 Asp Thr Tyr Gln Ala Ile Lys Thr Asn Gly Asn Gly Asn Gly Gly Gly
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 Asn Thr Thr Trp Thr Lys Asp Glu Thr Phe Ala Asp Arg Asn Glu Ile

 450 455 460
 Gly Val Gly Asn Asn Phe Ala Met Glu Ile Asn Leu Ser Ala Asn Leu
 465 470 475 480
 Trp Arg Asn Phe Leu Tyr Ser Asn Val Ala Leu Tyr Leu Pro Asp Lys
 485 490 495
 Leu Lys Tyr Asn Pro Ser Asn Val Glu Ile Ser Asp Asn Pro Asn Thr
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 Tyr Asp Tyr Met Asn Lys Arg Val Val Ala Pro Gly Leu Val Asp Cys

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 Tyr Ile Asn Leu Gly Ala Arg Trp Ser Leu Asp Tyr Met Asp Asn Val
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 Asn Pro Phe Asn His His Arg Asn Ala Gly Leu Arg Tyr Arg Ser Met
 545 550 555 560
 Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe His Ile Gln Val Pro Gln
 565 570 575
 Lys Phe Phe Ala Ile Lys Asn Leu Leu Leu Leu Pro Gly Ser Tyr Thr

 580 585 590
 Tyr Glu Trp Asn Phe Arg Lys Asp Val Asn Met Val Leu Gln Ser Ser
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<213> Woodchuck hepatitis virus

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<211> 543

<212> PRT

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<400> 27

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Phe Val Ser Pro Asp Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser

35 40 45

Leu Asn Leu Ala Glu Pro Leu Val Thr Ser His Gly Met Leu Ala Leu

50 55 60

Lys Met Gly Ser Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser

65 70 75 80

Gln Asp Ile Thr Thr Ala Ser Pro Pro Leu Lys Lys Thr Lys Thr Asn

85 90 95

Leu Ser Leu Glu Thr Ser Ser Pro Leu Thr Val Ser Thr Ser Gly Ala

100 105 110

Leu Thr Val Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu

115 120 125

Thr Met Gln Ser Glu Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Thr

130 135 140

Leu Ala Thr Lys Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Ala Leu

145 150 155 160

Gln Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val

165 170 175

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

180 185 190

Met Glu Asp Pro Met Tyr Thr His Asp Gly Lys Leu Gly Ile Arg Ile

195 200 205

Gly Gly Pro Leu Arg Val Val Asp Ser Leu His Thr Leu Thr Val Val

210 215 220

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 Gly Pro Leu Tyr Ile Asn Thr Asp His Asn Leu Asp Leu Asn Cys Asn
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 Arg Gly Leu Thr Thr Thr Thr Thr Asn Asn Thr Lys Lys Leu Glu Thr
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Val Tyr Leu Asn Gly Asp Lys Ser Lys Pro Met Thr Leu Thr Ile Thr
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<211> 541
<212> PRT
<213> Simian adenovirus
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35 40 45
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Lys Met Gly Asn Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser
65 70 75 80
Gln Asp Val Thr Thr Val Thr Pro Pro Leu Lys Lys Thr Lys Thr Asn
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Thr Val Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu Thr
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Met Gln Ser Gln Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Gly Leu
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Ala Thr Gln Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Thr Leu Gln

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Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val Gly

165 170 175

Thr Thr Pro Pro Ile Ser Val Ser Ser Gly Ser Leu Gly Leu Asp Met

180 185 190

Glu Asp Pro Met Tyr Thr His Asp Gly Lys Leu Gly Ile Arg Ile Gly

195 200 205

Gly Pro Leu Gln Val Val Asp Ser Leu His Thr Leu Thr Val Val Thr

210 215 220

Gly Asn Gly Ile Thr Val Ala Asn Asn Ala Leu Gln Thr Lys Val Ala

225 230 235 240

Gly Ala Leu Gly Tyr Asp Ser Ser Gly Asn Leu Glu Leu Arg Ala Ala

245 250 255

Gly Gly Met Arg Ile Asn Thr Gly Gly Gln Leu Ile Leu Asp Val Ala

260 265 270

Tyr Pro Phe Asp Ala Gln Asn Asn Leu Ser Leu Arg Leu Gly Gln Gly

275 280 285

Pro Leu Tyr Val Asn Thr Asn His Asn Leu Asp Leu Asn Cys Asn Arg

290 295 300

Gly Leu Thr Thr Thr Thr Ser Ser Asn Thr Thr Lys Leu Glu Thr Lys

305 310 315 320

Ile Asp Ser Gly Leu Asp Tyr Asn Ala Asn Gly Ala Ile Ile Ala Lys

325 330 335

Leu Gly Thr Gly Leu Thr Phe Asp Asn Thr Gly Ala Ile Thr Val Gly

340 345 350

Asn Thr Gly Asp Asp Lys Leu Thr Leu Trp Thr Thr Pro Asp Pro Ser

355 360 365

Pro Asn Cys Arg Ile His Ala Asp Lys Asp Lys Phe Thr Leu Val Leu

370 375 380

Thr Lys Cys Gly Ser Gln Ile Leu Ala Ser Val Ala Ala Leu Ala Val

385 390 395 400
Ser Gly Asn Leu Ser Ser Met Thr Gly Thr Val Ser Ser Val Thr Ile

 405 410 415
Phe Leu Arg Phe Asp Gln Asn Gly Val Leu Met Glu Asn Ser Ser Leu

 420 425 430
Asp Lys Glu Tyr Trp Asn Phe Arg Asn Gly Asn Ser Thr Asn Ala Thr

 435 440 445
Pro Tyr Thr Asn Ala Val Gly Phe Met Pro Asn Leu Ser Ala Tyr Pro

 450 455 460
Lys Thr Gln Ser Gln Thr Ala Lys Asn Asn Ile Val Ser Glu Val Tyr

465 470 475 480
Leu His Gly Asp Lys Ser Lys Pro Met Ile Leu Thr Ile Thr Leu Asn

 485 490 495
Gly Thr Asn Glu Ser Ser Glu Thr Ser Gln Val Ser His Tyr Ser Met

 500 505 510
Ser Phe Thr Trp Ser Trp Asp Ser Gly Lys Tyr Ala Thr Glu Thr Phe

 515 520 525
Ala Thr Asn Ser Phe Thr Phe Ser Tyr Ile Ala Glu Gln

 530 535 540

<210> 29

<211> 543

<212> PRT

<213> Simian adenovirus

<400> 29

Met Lys Arg Thr Lys Thr Ser Asp Glu Ser Phe Asn Pro Val Tyr Pro

1 5 10 15

Tyr Asp Thr Glu Ser Gly Pro Pro Ser Val Pro Phe Leu Thr Pro Pro

20 25 30

Phe Val Ser Pro Asp Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser

35 40 45

Leu Asn Leu Ala Glu Pro Leu Val Thr Ser His Gly Met Leu Ala Leu

50	55	60	
Lys Met Gly Ser Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser			
65	70	75	80
Gln Asp Ile Thr Ser Thr Thr Pro Pro Leu Lys Lys Thr Lys Thr Asn			
	85	90	95
Leu Ser Leu Glu Thr Ser Ser Pro Leu Thr Val Ser Thr Ser Gly Ala			
	100	105	110
Leu Thr Val Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu			
	115	120	125
Thr Met Gln Ser Glu Ala Pro Leu Ala Val Gln Asp Ala Lys Leu Thr			
	130	135	140
Leu Ala Thr Lys Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Ala Leu			
145	150	155	160
Gln Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val			
	165	170	175
Ser Ser Thr Pro Pro Ile Ser Val Ser Ser Gly Ser Leu Gly Leu Asp			
	180	185	190
Met Glu Asp Pro Met Tyr Thr His Asp Gly Lys Leu Gly Ile Arg Ile			
	195	200	205
Gly Gly Pro Leu Arg Val Val Asp Ser Leu His Thr Leu Thr Val Val			
	210	215	220
Thr Gly Asn Gly Leu Thr Val Asp Asn Asn Ala Leu Gln Thr Arg Val			
225	230	235	240
Thr Gly Ala Leu Gly Tyr Asp Thr Ser Gly Asn Leu Gln Leu Arg Ala			
	245	250	255
Ala Gly Gly Met Arg Ile Asp Ala Asn Gly Gln Leu Ile Leu Asp Val			
	260	265	270
Ala Tyr Pro Phe Asp Ala Gln Asn Asn Leu Ser Leu Arg Leu Gly Gln			
	275	280	285
Gly Pro Leu Tyr Val Asn Thr Asp His Asn Leu Asp Leu Asn Cys Asn			
	290	295	300

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

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

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

Leu Asn Gly Thr Asn Glu Ser Ser Glu Thr Ser Gln Val Ser His Tyr
 500 505 510
 Ser Met Ser Phe Thr Trp Ala Trp Glu Ser Gly Gln Tyr Ala Thr Glu
 515 520 525
 Thr Phe Ala Thr Asn Ser Phe Thr Phe Ser Tyr Ile Ala Glu Gln
 530 535 540

<210> 30

<211> 543

<212> PRT

<213> Simian adenovirus

<400> 30

Met Lys Arg Thr Lys Thr Ser Asp Lys Ser Phe Asn Pro Val Tyr Pro

1 5 10 15
Tyr Asp Thr Glu Asn Gly Pro Pro Ser Val Pro Phe Leu Thr Pro Pro

20 25 30
Phe Val Ser Pro Asp Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser

35 40 45
Leu Asn Leu Ala Glu Pro Leu Val Thr Ser His Gly Met Leu Ala Leu

50 55 60
Lys Met Gly Ser Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser

65 70 75 80
Gln Asp Val Thr Thr Thr Thr Pro Pro Leu Lys Lys Thr Lys Thr Asn

85 90 95
Leu Ser Leu Glu Thr Ser Ala Pro Leu Thr Val Ser Thr Ser Gly Ala

100 105 110
Leu Thr Leu Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu

115 120 125
Thr Met Gln Ser Glu Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Thr

130 135 140
Leu Ala Thr Lys Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Ala Leu

145 150 155 160
Gln Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val

165 170 175
Ser Ala Thr Pro Pro Ile Ser Val Ser Ser Gly Ser Leu Gly Leu Asp

180 185 190
Met Glu Asp Pro Met Tyr Thr His Asp Gly Lys Leu Gly Ile Arg Ile

195 200 205
Gly Gly Pro Leu Arg Val Val Asp Ser Leu His Thr Leu Thr Val Val

210 215 220

Thr Gly Asn Gly Ile Ala Val Asp Asn Asn Ala Leu Gln Thr Arg Val
 225 230 235 240
 Thr Gly Ala Leu Gly Tyr Asp Thr Ser Gly Asn Leu Gln Leu Arg Ala
 245 250 255
 Ala Gly Gly Met Arg Ile Asp Ala Asn Gly Gln Leu Ile Leu Asp Val
 260 265 270
 Ala Tyr Pro Phe Asp Ala Gln Asn Asn Leu Ser Leu Arg Leu Gly Gln
 275 280 285
 Gly Pro Leu Tyr Val Asn Thr Asp His Asn Leu Asp Leu Asn Cys Asn
 290 295 300
 Arg Gly Leu Thr Thr Thr Thr Thr Asn Asn Thr Lys Lys Leu Glu Thr
 305 310 315 320
 Lys Ile Gly Ser Gly Leu Asp Tyr Asp Thr Asn Gly Ala Val Ile Ile
 325 330 335
 Lys Leu Gly Thr Gly Val Ser Phe Asp Ser Thr Gly Ala Leu Ser Val
 340 345 350
 Gly Asn Thr Gly Asp Asp Lys Leu Thr Leu Trp Thr Thr Pro Asp Pro
 355 360 365
 Ser Pro Asn Cys Arg Ile His Ser Asp Lys Asp Cys Lys Phe Thr Leu
 370 375 380
 Val Leu Thr Lys Cys Gly Ser Gln Ile Leu Ala Ser Val Ala Ala Leu
 385 390 395 400
 Ala Val Ser Gly Asn Leu Ala Ser Ile Thr Gly Thr Val Ser Ser Val
 405 410 415
 Thr Ile Phe Leu Arg Phe Asp Gln Asn Gly Val Leu Met Glu Asn Ser
 420 425 430
 Ser Leu Asp Lys Gln Tyr Trp Asn Phe Arg Asn Gly Asn Ser Thr Asn
 435 440 445
 Ala Thr Pro Tyr Thr Asn Ala Val Gly Phe Met Pro Asn Leu Ala Ala
 450 455 460
 Tyr Pro Lys Thr Gln Ser Gln Thr Ala Lys Asn Asn Ile Val Ser Gln

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

 515 520 525
 Thr Phe Ala Thr Asn Ser Phe Thr Phe Ser Tyr Ile Ala Glu Gln
 530 535 540
 <210> 31
 <211> 543
 <212> PRT
 <213> Simian adenovirus
 <400> 31
 Met Lys Arg Thr Lys Thr Ser Asp Glu Ser Phe Asn Pro Val Tyr Pro
 1 5 10 15
 Tyr Asp Thr Glu Asn Gly Pro Pro Ser Val Pro Phe Leu Thr Pro Pro
 20 25 30

 Phe Val Ser Pro Asp Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser
 35 40 45
 Leu Asn Leu Ala Glu Pro Leu Val Thr Ser His Gly Met Leu Ala Leu
 50 55 60
 Lys Met Gly Ser Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser
 65 70 75 80
 Gln Asp Val Thr Thr Thr Pro Pro Leu Lys Lys Thr Lys Thr Asn
 85 90 95

 Leu Ser Leu Glu Thr Ser Ala Pro Leu Thr Val Ser Thr Ser Gly Ala
 100 105 110
 Leu Thr Leu Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu
 115 120 125
 Thr Met Gln Ser Glu Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Thr
 130 135 140

Leu Ala Thr Lys Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Ala Leu
145 150 155 160

Gln Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val
165 170 175

Ser Ala Thr Pro Pro Ile Asn Val Ser Ser Gly Ser Leu Gly Leu Asp
180 185 190

Met Glu Asn Pro Met Tyr Thr His Asp Gly Lys Leu Gly Ile Arg Ile
195 200 205

Gly Gly Pro Leu Arg Val Val Asp Ser Leu His Thr Leu Thr Val Val
210 215 220

Thr Gly Asn Gly Ile Ala Val Asp Asn Asn Ala Leu Gln Thr Arg Val
225 230 235 240

Thr Gly Ala Leu Gly Tyr Asp Thr Ser Gly Asn Leu Gln Leu Arg Ala
245 250 255

Ala Gly Gly Met Arg Ile Asp Ala Asn Gly Gln Leu Ile Leu Asp Val
260 265 270

Ala Tyr Pro Phe Asp Ala Gln Asn Asn Leu Ser Leu Arg Leu Gly Gln
275 280 285

Gly Pro Leu Tyr Val Asn Thr Asp His Asn Leu Asp Leu Asn Cys Asn
290 295 300

Arg Gly Leu Thr Thr Thr Thr Thr Asn Asn Thr Lys Lys Leu Glu Thr
305 310 315 320

Lys Ile Gly Ser Gly Leu Asp Tyr Asp Thr Asn Gly Ala Val Ile Ile
325 330 335

Lys Leu Gly Thr Gly Val Ser Phe Asp Ser Thr Gly Ala Leu Ser Val
340 345 350

Gly Asn Thr Gly Asp Asp Lys Leu Thr Leu Trp Thr Thr Pro Asp Pro
355 360 365

Ser Pro Asn Cys Arg Ile His Ser Asp Lys Asp Cys Lys Phe Thr Leu
370 375 380

Val Leu Thr Lys Cys Gly Ser Gln Ile Leu Ala Ser Val Ala Ala Leu

385 390 395 400
Ala Val Ser Gly Asn Leu Ala Ser Ile Thr Gly Thr Val Ser Ser Val
 405 410 415

Thr Ile Phe Leu Arg Phe Asp Gln Asn Gly Val Leu Met Glu Asn Ser
 420 425 430
Ser Leu Asp Lys Gln Tyr Trp Asn Phe Arg Asn Gly Asn Ser Thr Asn
 435 440 445
Ala Thr Pro Tyr Thr Asn Ala Val Gly Phe Met Pro Asn Leu Ala Ala
 450 455 460
Tyr Pro Lys Thr Gln Ser Gln Thr Ala Lys Asn Asn Ile Val Ser Gln
465 470 475 480

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

<210> 32

<211> 578

<212> PRT

<213> Simian adenovirus

<400> 32

Met Lys Arg Thr Lys Thr Ser Asp Glu Ser Phe Asn Pro Val Tyr Pro
1 5 10 15
Tyr Asp Thr Glu Asn Gly Pro Pro Ser Val Pro Phe Leu Thr Pro Pro
 20 25 30
Phe Val Ser Pro Asp Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser
 35 40 45
Leu Asn Leu Ala Glu Pro Leu Val Thr Ser His Gly Met Leu Ala Leu

50 55 60
 Lys Met Gly Ser Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser
 65 70 75 80
 Gln Asp Val Thr Thr Thr Thr Pro Pro Leu Lys Lys Thr Lys Thr Asn
 85 90 95
 Leu Ser Leu Glu Thr Ser Ala Pro Leu Thr Val Ser Thr Ser Gly Ala
 100 105 110
 Leu Thr Leu Ala Ala Ala Val Pro Leu Ala Val Ala Gly Thr Ser Leu

 115 120 125
 Thr Met Gln Ser Glu Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Thr
 130 135 140
 Leu Ala Thr Lys Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Ala Leu
 145 150 155 160
 Gln Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Ile
 165 170 175
 Ser Ala Thr Pro Pro Leu Ser Thr Ser Asn Gly Ser Leu Gly Ile Asp

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

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

Arg Gly Leu Tyr Leu Phe Thr Ser Gly Asn Thr Lys Lys Leu Glu Val

305 310 315 320

Asn Ile Lys Thr Ala Lys Gly Leu Ile Tyr Asp Asp Thr Ala Ile Ala

325 330 335

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

340 345 350

Pro Leu Lys Thr Lys Leu Gly Leu Gly Leu Glu Tyr Asp Ser Ser Arg

355 360 365

Ala Ile Ile Ala Lys Leu Gly Thr Gly Leu Ser Phe Asp Asn Thr Gly

370 375 380

Ala Ile Thr Val Gly Asn Lys Asn Asp Asp Lys Leu Thr Leu Trp Thr

385 390 395 400

Thr Pro Asp Pro Ser Pro Asn Cys Arg Ile Tyr Ser Glu Lys Asp Ala

405 410 415

Lys Phe Thr Leu Val Leu Thr Lys Cys Gly Ser Gln Val Leu Ala Ser

420 425 430

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

435 440 445

Val Thr Ser Ala Gln Ile Ile Leu Arg Phe Asp Glu Asn Gly Val Leu

450 455 460

Leu Ser Asn Ser Ser Leu Asp Pro Gln Tyr Trp Asn Tyr Arg Lys Gly

465 470 475 480

Asp Leu Thr Glu Gly Thr Ala Tyr Thr Asn Ala Val Gly Phe Met Pro

485 490 495

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

500 505 510

Ile Val Ser Gln Val Tyr Leu Asn Gly Asp Lys Ser Lys Pro Met Ile

515 520 525

Leu Thr Ile Thr Leu Asn Gly Thr Asn Glu Thr Gly Asp Ala Thr Val

530 535 540

Ser Thr Tyr Ser Met Ser Phe Ser Trp Asn Trp Asn Gly Ser Asn Tyr

545 550 555 560
 Ile Asn Glu Thr Phe Gln Thr Asn Ser Phe Thr Phe Ser Tyr Ile Ala

 565 570 575
 Gln Glu

 <210> 33
 <211> 578
 <212> PRT
 <213> Simian adenovirus
 <400> 33
 Met Lys Arg Thr Lys Thr Ser Asp Glu Ser Phe Asn Pro Val Tyr Pro
 1 5 10 15
 Tyr Asp Thr Glu Ser Gly Pro Pro Ser Val Pro Phe Leu Thr Pro Pro
 20 25 30
 Phe Val Ser Pro Asp Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser
 35 40 45

 Leu Asn Leu Ala Glu Pro Leu Val Thr Ser His Gly Met Leu Ala Leu
 50 55 60
 Lys Met Gly Ser Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser
 65 70 75 80
 Gln Asp Ile Thr Thr Ala Ser Pro Pro Leu Lys Lys Thr Lys Thr Asn
 85 90 95
 Leu Ser Leu Glu Thr Ser Ser Pro Leu Thr Val Ser Thr Ser Gly Ala
 100 105 110

 Leu Thr Val Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu
 115 120 125
 Thr Met Gln Ser Glu Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Thr
 130 135 140
 Leu Ala Thr Lys Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Ala Leu
 145 150 155 160
 Gln Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val

	165	170	175
Ser Ala Thr Pro Pro Leu Ser Thr Ser Asn Gly Ser Leu Gly Ile Asp			
	180	185	190
Met Gln Ala Pro Ile Tyr Thr Thr Asn Gly Lys Leu Gly Leu Asn Phe			
	195	200	205
Gly Ala Pro Leu His Val Val Asp Ser Leu Asn Ala Leu Thr Val Val			
	210	215	220
Thr Gly Gln Gly Leu Thr Ile Asn Gly Thr Ala Leu Gln Thr Arg Val			
225	230	235	240
Ser Gly Ala Leu Asn Tyr Asp Thr Ser Gly Asn Leu Glu Leu Arg Ala			
	245	250	255
Ala Gly Gly Met Arg Val Asp Ala Asn Gly Gln Leu Ile Leu Asp Val			
	260	265	270
Ala Tyr Pro Phe Asp Ala Gln Asn Asn Leu Ser Leu Arg Leu Gly Gln			
	275	280	285
Gly Pro Leu Phe Val Asn Ser Ala His Asn Leu Asp Val Asn Tyr Asn			
	290	295	300
Arg Gly Leu Tyr Leu Phe Thr Ser Gly Asn Thr Lys Lys Leu Glu Val			
305	310	315	320
Asn Ile Lys Thr Ala Lys Gly Leu Ile Tyr Asp Asp Thr Ala Ile Ala			
	325	330	335
Ile Asn Ala Gly Asp Gly Leu Gln Phe Asp Ser Gly Ser Asp Thr Asn			
	340	345	350
Pro Leu Lys Thr Lys Leu Gly Leu Gly Leu Asp Tyr Asp Ser Ser Arg			
	355	360	365
Ala Ile Ile Ala Lys Leu Gly Thr Gly Leu Ser Phe Asp Asn Thr Gly			
	370	375	380
Ala Ile Thr Val Gly Asn Lys Asn Asp Asp Lys Leu Thr Leu Trp Thr			
385	390	395	400
Thr Pro Asp Pro Ser Pro Asn Cys Arg Ile Tyr Ser Glu Lys Asp Ala			
	405	410	415

Lys Phe Thr Leu Val Leu Thr Lys Cys Gly Ser Gln Val Leu Ala Ser
420 425 430

Val Ser Val Leu Ser Val Lys Gly Ser Leu Ala Pro Ile Ser Gly Thr
435 440 445

Val Thr Ser Ala Gln Ile Val Leu Arg Phe Asp Glu Asn Gly Val Leu
450 455 460

Leu Ser Asn Ser Ser Leu Asp Pro Gln Tyr Trp Asn Tyr Arg Lys Gly
465 470 475 480

Asp Leu Thr Glu Gly Thr Ala Tyr Thr Asn Ala Val Gly Phe Met Pro
485 490 495

Asn Leu Thr Ala Tyr Pro Lys Thr Gln Ser Gln Thr Ala Lys Ser Asn
500 505 510

Ile Val Ser Gln Val Tyr Leu Asn Gly Asp Lys Ser Lys Pro Met Thr
515 520 525

Leu Thr Ile Thr Leu Asn Gly Thr Asn Glu Thr Gly Asp Ala Thr Val
530 535 540

Ser Thr Tyr Ser Met Ser Phe Ser Trp Asn Trp Asn Gly Ser Asn Tyr
545 550 555 560

Ile Asn Glu Thr Phe Gln Thr Asn Ser Phe Thr Phe Ser Tyr Ile Ala
565 570 575

Gln Glu

<210> 34

<211> 578

<212> PRT

<213> Simian adenovirus

<400> 34

Met Lys Arg Thr Lys Thr Ser Asp Glu Ser Phe Asn Pro Val Tyr Pro
1 5 10 15
Tyr Asp Thr Glu Ser Gly Pro Pro Ser Val Pro Phe Leu Thr Pro Pro
20 25 30

Phe Val Ser Pro Asp Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser

35 40 45

Leu Asn Leu Ala Glu Pro Leu Val Thr Ser His Gly Met Leu Ala Leu

50 55 60

Lys Met Gly Ser Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser

65 70 75 80

Gln Asp Ile Thr Thr Ala Ser Pro Pro Leu Lys Lys Thr Lys Thr Asn

85 90 95

Leu Ser Leu Glu Thr Ser Ser Pro Leu Thr Val Ser Thr Ser Gly Ala

100 105 110

Leu Thr Val Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu

115 120 125

Thr Met Gln Ser Glu Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Thr

130 135 140

Leu Ala Thr Lys Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Ala Leu

145 150 155 160

Gln Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val

165 170 175

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

180 185 190

Met Gln Ala Pro Ile Tyr Thr Thr Asn Gly Lys Leu Gly Leu Asn Phe

195 200 205

Gly Ala Pro Leu His Val Val Asp Ser Leu Asn Ala Leu Thr Val Val

210 215 220

Thr Gly Gln Gly Leu Thr Ile Asn Gly Thr Ala Leu Gln Thr Arg Val

225 230 235 240

Ser Gly Ala Leu Asn Tyr Asp Thr Ser Gly Asn Leu Glu Leu Arg Ala

245 250 255

Ala Gly Gly Met Arg Val Asp Ala Asn Gly Gln Leu Ile Leu Asp Val

260 265 270

Ala Tyr Pro Phe Asp Ala Gln Asn Asn Leu Ser Leu Arg Leu Gly Gln

275 280 285
Gly Pro Leu Phe Val Asn Ser Ala His Asn Leu Asp Val Asn Tyr Asn

290 295 300
Arg Gly Leu Tyr Leu Phe Thr Ser Gly Asn Thr Lys Lys Leu Glu Val
305 310 315 320
Asn Ile Lys Thr Ala Lys Gly Leu Ile Tyr Asp Asp Thr Ala Ile Ala
325 330 335
Ile Asn Ala Gly Asp Gly Leu Gln Phe Asp Ser Gly Ser Asp Thr Asn
340 345 350
Pro Leu Lys Thr Lys Leu Gly Leu Gly Leu Asp Tyr Asp Ser Ser Arg

355 360 365
Ala Ile Ile Ala Lys Leu Gly Thr Gly Leu Ser Phe Asp Asn Thr Gly
370 375 380
Ala Ile Thr Val Gly Asn Lys Asn Asp Asp Lys Leu Thr Leu Trp Thr
385 390 395 400
Thr Pro Asp Pro Ser Pro Asn Cys Arg Ile Tyr Ser Glu Lys Asp Ala
405 410 415
Lys Phe Thr Leu Val Leu Thr Lys Cys Gly Ser Gln Val Leu Ala Ser

420 425 430
Val Ser Val Leu Ser Val Lys Gly Ser Leu Ala Pro Ile Ser Gly Thr
435 440 445
Val Thr Ser Ala Gln Ile Val Leu Arg Phe Asp Glu Asn Gly Val Leu
450 455 460
Leu Ser Asn Ser Ser Leu Asp Pro Gln Tyr Trp Asn Tyr Arg Lys Gly
465 470 475 480
Asp Leu Thr Glu Gly Thr Ala Tyr Thr Asn Ala Val Gly Phe Met Pro

485 490 495
Asn Leu Thr Ala Tyr Pro Lys Thr Gln Ser Gln Thr Ala Lys Ser Asn
500 505 510
Ile Val Ser Gln Val Tyr Leu Asn Gly Asp Lys Ser Lys Pro Met Thr
515 520 525

Leu Thr Ile Thr Leu Asn Gly Thr Asn Glu Thr Gly Asp Ala Thr Val
530 535 540

Ser Thr Tyr Ser Met Ser Phe Ser Trp Asn Trp Asn Gly Ser Asn Tyr

545 550 555 560

Ile Asn Glu Thr Phe Gln Thr Asn Ser Phe Thr Phe Ser Tyr Ile Ala

565 570 575

Gln Glu

<210> 35

<211> 577

<212> PRT

<213> Simian adenovirus

<400> 35

Met Lys Arg Ala Lys Thr Ser Asp Glu Thr Phe Asn Pro Val Tyr Pro

1 5 10 15

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

20 25 30

Phe Val Ser Pro Asp Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser

35 40 45

Leu Arg Leu Ser Glu Pro Leu Val Thr Ser His Gly Met Leu Ala Leu

50 55 60

Lys Met Gly Asn Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser

65 70 75 80

Gln Asp Val Thr Thr Val Thr Pro Pro Leu Lys Lys Thr Lys Thr Asn

85 90 95

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

100 105 110

Thr Val Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu Thr

115 120 125

Met Gln Ser Gln Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Gly Leu

130 135 140

Ala Thr Gln Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Thr Leu Gln

145	150	155	160
Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val Ser			
	165	170	175
Ala Thr Pro Pro Leu Ser Thr Ser Asn Gly Ser Leu Ser Ile Asp Met			
	180	185	190
Gln Ala Pro Ile Tyr Thr Thr Asn Gly Lys Leu Ala Leu Asn Ile Gly			
	195	200	205
Ala Pro Leu His Val Val Asp Thr Leu Asn Ala Leu Thr Val Val Thr			
	210	215	220
Gly Gln Gly Leu Thr Ile Asn Gly Arg Ala Leu Gln Thr Arg Val Thr			
225	230	235	240
Gly Ala Leu Ser Tyr Asp Thr Glu Gly Asn Ile Gln Leu Gln Ala Gly			
	245	250	255
Gly Gly Met Arg Ile Asp Asn Asn Gly Gln Leu Ile Leu Asn Val Ala			
	260	265	270
Tyr Pro Phe Asp Ala Gln Asn Asn Leu Ser Leu Arg Leu Gly Gln Gly			
	275	280	285
Pro Leu Ile Val Asn Ser Ala His Asn Leu Asp Leu Asn Leu Asn Arg			
	290	295	300
Gly Leu Tyr Leu Phe Thr Ser Gly Asn Thr Lys Lys Leu Glu Val Asn			
305	310	315	320
Ile Lys Thr Ala Lys Gly Leu Phe Tyr Asp Gly Thr Ala Ile Ala Ile			
	325	330	335
Asn Ala Gly Asp Gly Leu Gln Phe Gly Ser Gly Ser Asp Thr Asn Pro			
	340	345	350
Leu Gln Thr Lys Leu Gly Leu Gly Leu Glu Tyr Asp Ser Asn Lys Ala			
	355	360	365
Ile Ile Thr Lys Leu Gly Thr Gly Leu Ser Phe Asp Asn Thr Gly Ala			
	370	375	380
Ile Thr Val Gly Asn Lys Asn Asp Asp Lys Leu Thr Leu Trp Thr Thr			
385	390	395	400

Pro Asp Pro Ser Pro Asn Cys Arg Ile Asn Ser Glu Lys Asp Ala Lys
405 410 415

Leu Thr Leu Val Leu Thr Lys Cys Gly Ser Gln Val Leu Ala Ser Val
420 425 430

Ser Val Leu Ser Val Lys Gly Ser Leu Ala Pro Ile Ser Gly Thr Val
435 440 445

Thr Ser Ala Gln Ile Val Leu Arg Phe Asp Glu Asn Gly Val Leu Leu
450 455 460

Ser Asn Ser Ser Leu Asp Pro Gln Tyr Trp Asn Tyr Arg Lys Gly Asp
465 470 475 480

Ser Thr Glu Gly Thr Ala Tyr Thr Asn Ala Val Gly Phe Met Pro Asn
485 490 495

Leu Thr Ala Tyr Pro Lys Thr Gln Ser Gln Thr Ala Lys Ser Asn Ile
500 505 510

Val Ser Gln Val Tyr Leu Asn Gly Asp Lys Thr Lys Pro Met Thr Leu
515 520 525

Thr Ile Thr Leu Asn Gly Thr Asn Glu Thr Gly Asp Ala Thr Val Ser
530 535 540

Thr Tyr Ser Met Ser Phe Ser Trp Asn Trp Asn Gly Ser Asn Tyr Ile
545 550 555 560

Asn Asp Thr Phe Gln Thr Asn Ser Phe Thr Phe Ser Tyr Ile Ala Gln
565 570 575

Glu

<210> 36

<211> 577

<212> PRT

<213> Simian adenovirus

<400> 36

Met Lys Arg Ala Lys Thr Ser Asp Glu Thr Phe Asn Pro Val Tyr Pro
1 5 10 15

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

20 25 30

Phe Val Ser Pro Asp Gly Phe Gln Glu Ser Pro Pro Gly Val Leu Ser

35 40 45

Leu Arg Leu Ser Glu Pro Leu Val Thr Ser His Gly Met Leu Ala Leu

50 55 60

Lys Met Gly Asn Gly Leu Ser Leu Asp Asp Ala Gly Asn Leu Thr Ser

65 70 75 80

Gln Asp Val Thr Thr Val Thr Pro Pro Leu Lys Lys Thr Lys Thr Asn

85 90 95

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

100 105 110

Thr Val Ala Ala Ala Ala Pro Leu Ala Val Ala Gly Thr Ser Leu Thr

115 120 125

Met Gln Ser Gln Ala Pro Leu Thr Val Gln Asp Ala Lys Leu Gly Leu

130 135 140

Ala Thr Gln Gly Pro Leu Thr Val Ser Glu Gly Lys Leu Thr Leu Gln

145 150 155 160

Thr Ser Ala Pro Leu Thr Ala Ala Asp Ser Ser Thr Leu Thr Val Ser

165 170 175

Ala Thr Pro Pro Leu Ser Thr Ser Asn Gly Ser Leu Ser Ile Asp Met

180 185 190

Gln Ala Pro Ile Tyr Thr Thr Asn Gly Lys Leu Ala Leu Asn Ile Gly

195 200 205

Ala Pro Leu His Val Val Asp Thr Leu Asn Ala Leu Thr Val Val Thr

210 215 220

Gly Gln Gly Leu Thr Ile Asn Gly Arg Ala Leu Gln Thr Arg Val Thr

225 230 235 240

Gly Ala Leu Ser Tyr Asp Thr Glu Gly Asn Ile Gln Leu Gln Ala Gly

245 250 255

Gly Gly Met Arg Ile Asp Asn Asn Gly Gln Leu Ile Leu Asn Val Ala

260 265 270
Tyr Pro Phe Asp Ala Gln Asn Asn Leu Ser Leu Arg Leu Gly Gln Gly

275 280 285
Pro Leu Ile Val Asn Ser Ala His Asn Leu Asp Leu Asn Leu Asn Arg

290 295 300

Gly Leu Tyr Leu Phe Thr Ser Gly Asn Thr Lys Lys Leu Glu Val Asn

305 310 315 320

Ile Lys Thr Ala Lys Gly Leu Phe Tyr Asp Gly Thr Ala Ile Ala Ile

325 330 335

Asn Ala Gly Asp Gly Leu Gln Phe Gly Ser Gly Ser Asp Thr Asn Pro

340 345 350

Leu Gln Thr Lys Leu Gly Leu Gly Leu Glu Tyr Asp Ser Asn Lys Ala

355 360 365

Ile Ile Thr Lys Leu Gly Thr Gly Leu Ser Phe Asp Asn Thr Gly Ala

370 375 380

Ile Thr Val Gly Asn Lys Asn Asp Asp Lys Leu Thr Leu Trp Thr Thr

385 390 395 400

Pro Asp Pro Ser Pro Asn Cys Arg Ile Asn Ser Glu Lys Asp Ala Lys

405 410 415

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

420 425 430

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

435 440 445

Thr Ser Ala Gln Ile Val Leu Arg Phe Asp Glu Asn Gly Val Leu Leu

450 455 460

Ser Asn Ser Ser Leu Asp Pro Gln Tyr Trp Asn Tyr Arg Lys Gly Asp

465 470 475 480

Ser Thr Glu Gly Thr Ala Tyr Thr Asn Ala Val Gly Phe Met Pro Asn

485 490 495

Leu Thr Ala Tyr Pro Lys Thr Gln Ser Gln Thr Ala Lys Ser Asn Ile

500 505 510

Val Ser Gln Val Tyr Leu Asn Gly Asp Lys Thr Lys Pro Met Thr Leu
515 520 525
Thr Ile Thr Leu Asn Gly Thr Asn Glu Thr Gly Asp Ala Thr Val Ser
530 535 540
Thr Tyr Ser Met Ser Phe Ser Trp Asn Trp Asn Gly Ser Asn Tyr Ile
545 550 555 560
Asn Asp Thr Phe Gln Thr Asn Ser Phe Thr Phe Ser Tyr Ile Ala Gln
565 570 575
Glu
<210> 37
<211> 1145
<212> PRT
<213> Respiratory syncytial virus
<400> 37
Met Glu Leu Leu Ile Leu Lys Ala Asn Ala Ile Thr Thr Ile Leu Thr
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Ala Val Thr Phe Cys Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe
20 25 30
Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
35 40 45
Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
50 55 60
Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65 70 75 80
Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
85 90 95
Met Gln Ser Thr Pro Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro
100 105 110
Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
115 120 125
Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val

130	135	140	
Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu			
145	150	155	160
Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys			
	165	170	175
Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val			
	180	185	190
Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn			
195	200	205	
Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln			
210	215	220	
Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn			
225	230	235	240
Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu			
	245	250	255
Leu Leu Ser Leu Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys Leu			
260	265	270	
Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile Met			
275	280	285	
Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro Leu			
290	295	300	
Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro Leu			
305	310	315	320
Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg Thr			
	325	330	335
Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe Pro			
340	345	350	
Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp Thr			
355	360	365	
Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val Asp			
370	375	380	

Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr Asp
385 390 395 400

Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys Tyr
405 410 415

Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile Lys
420 425 430

Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp Thr
435 440 445

Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly Lys
450 455 460

Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro Leu
465 470 475 480

Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu
485 490 495

Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu Leu
500 505 510

His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Arg Lys Arg Arg Ala
515 520 525

Pro Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala Gly Asp
530 535 540

Val Glu Ser Asn Pro Gly Pro Met Ala Leu Ser Lys Val Lys Leu Asn
545 550 555 560

Asp Thr Leu Asn Lys Asp Gln Leu Leu Ser Ser Ser Lys Tyr Thr Ile
565 570 575

Gln Arg Ser Thr Gly Asp Ser Ile Asp Thr Pro Asn Tyr Asp Val Gln
580 585 590

Lys His Ile Asn Lys Leu Cys Gly Met Leu Leu Ile Thr Glu Asp Ala
595 600 605

Asn His Lys Phe Thr Gly Leu Ile Gly Met Leu Tyr Ala Met Ser Arg
610 615 620

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

625 630 635 640
 Val Lys Ala Asn Gly Val Asp Val Thr Thr His Arg Gln Asp Ile Asn
 645 650 655

 Gly Lys Glu Met Lys Phe Glu Val Leu Thr Leu Ala Ser Leu Thr Thr
 660 665 670
 Glu Ile Gln Ile Asn Ile Glu Ile Glu Ser Arg Lys Ser Tyr Lys Lys
 675 680 685
 Met Leu Lys Glu Met Gly Glu Val Ala Pro Glu Tyr Arg His Asp Ser
 690 695 700
 Pro Asp Cys Gly Met Ile Ile Leu Cys Ile Ala Ala Leu Val Ile Thr
 705 710 715 720

 Lys Leu Ala Ala Gly Asp Arg Ser Gly Leu Thr Ala Val Ile Arg Arg
 725 730 735
 Ala Asn Asn Val Leu Lys Asn Glu Met Lys Arg Tyr Lys Gly Leu Leu
 740 745 750
 Pro Lys Asp Ile Ala Asn Ser Phe Tyr Glu Val Phe Glu Lys Tyr Pro
 755 760 765
 His Phe Ile Asp Val Phe Val His Phe Gly Ile Ala Gln Ser Ser Thr
 770 775 780

 Arg Gly Gly Ser Arg Val Glu Gly Ile Phe Ala Gly Leu Phe Met Asn
 785 790 795 800
 Ala Tyr Gly Ala Gly Gln Val Met Leu Arg Trp Gly Val Leu Ala Lys
 805 810 815
 Ser Val Lys Asn Ile Met Leu Gly His Ala Ser Val Gln Ala Glu Met
 820 825 830
 Glu Gln Val Val Glu Val Tyr Glu Tyr Ala Gln Lys Leu Gly Gly Glu
 835 840 845

 Ala Gly Phe Tyr His Ile Leu Asn Asn Pro Lys Ala Ser Leu Leu Ser
 850 855 860
 Leu Thr Gln Phe Pro His Phe Ser Ser Val Val Leu Gly Asn Ala Ala
 865 870 875 880

Gly Leu Gly Ile Met Gly Glu Tyr Arg Gly Thr Pro Arg Asn Gln Asp
885 890 895
Leu Tyr Asp Ala Ala Lys Ala Tyr Ala Glu Gln Leu Lys Glu Asn Gly
900 905 910

Val Ile Asn Tyr Ser Val Leu Asp Leu Thr Ala Glu Glu Leu Glu Ala
915 920 925
Ile Lys His Gln Leu Asn Pro Lys Asp Asn Asp Val Glu Leu Gly Gly
930 935 940
Gly Gly Ser Gly Gly Gly Gly Met Ser Arg Arg Asn Pro Cys Lys Phe
945 950 955 960
Glu Ile Arg Gly His Cys Leu Asn Gly Lys Arg Cys His Phe Ser His
965 970 975

Asn Tyr Phe Glu Trp Pro Pro His Ala Leu Leu Val Arg Gln Asn Phe
980 985 990
Met Leu Asn Arg Ile Leu Lys Ser Met Asp Lys Ser Ile Asp Thr Leu
995 1000 1005
Ser Glu Ile Ser Gly Ala Ala Glu Leu Asp Arg Thr Glu Glu Tyr
1010 1015 1020
Ala Leu Gly Val Val Gly Val Leu Glu Ser Tyr Ile Gly Ser Ile
1025 1030 1035

Asn Asn Ile Thr Lys Gln Ser Ala Cys Val Ala Met Ser Lys Leu
1040 1045 1050
Leu Thr Glu Leu Asn Ser Asp Asp Ile Lys Lys Leu Arg Asp Asn
1055 1060 1065
Glu Glu Leu Asn Ser Pro Lys Ile Arg Val Tyr Asn Thr Val Ile
1070 1075 1080
Ser Tyr Ile Glu Ser Asn Arg Lys Asn Asn Lys Gln Thr Ile His
1085 1090 1095

Leu Leu Lys Arg Leu Pro Ala Asp Val Leu Lys Lys Thr Ile Lys
1100 1105 1110
Asn Thr Leu Asp Ile His Lys Ser Ile Thr Ile Asn Asn Pro Lys

1115	1120	1125
Glu Ser Thr Val Ser Asp Thr	Asn Asp His Ala Lys	Asn Asn Asp
1130	1135	1140
Thr Thr		
1145		
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<213> Human immunodeficiency virus		
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aa	1502