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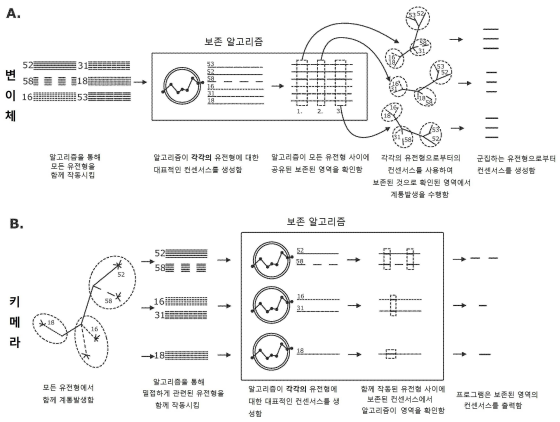
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(54) 발명의 명칭 **HPV 백신**

(57) 요 약

본 발명은 다수의 보존된 펩타이드 서열, 또는 이의 변이체를 포함하는 폴리펩타이드를 암호화하는 핵산으로서, 여기서 보존된 서열이 하나 이상의 HPV 유전형 16, 18, 31, 52, 53, 및 58에 걸쳐 보존되어 있고 여기서 폴리펩타이드는 각각의 HPV 단백질 E1, E2, E4, E5, E6, 및 E7의 보존된 펩타이드 서열을 포함하는 핵산; 및 관련된 백신, 바이러스 벡터, 치료 및 예방에 관한 것이다.

대 표 도



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명 세 서

청구범위

청구항 1

다수의 보존된 펩타이드 서열을 포함하는 폴리펩타이드를 암호화하는 핵산으로서, 상기 폴리펩타이드가 서열 번호: 61 또는 66의 서열을 포함하는, 핵산.

청구항 2

제1항에 있어서,

상기 핵산이 서열 번호: 60, 65, 또는 62의 서열을 포함하는, 핵산.

청구항 3

제1항 또는 제2항에 있어서,

핵산이 예방접종을 위한 플라스미드 벡터이거나;

핵산이 바이러스 벡터 서열을 포함하는, 핵산.

청구항 4

제1항에 따른 핵산을 포함하는 백신.

청구항 5

제4항에 있어서, 다른 치료학적으로 또는 예방학적으로 활성인 성분을 추가로 포함하거나; 보조제를 추가로 포함하는, 백신.

청구항 6

제1항에 따른 핵산에 의해 암호화된 폴리펩타이드.

청구항 7

제1항에 따른 핵산을 포함하는 바이러스 벡터로서, 임의로 여기서 바이러스 벡터가 아데노바이러스 벡터인, 바이러스 벡터.

청구항 8

- 제1항에 따른 핵산;
- 제6항에 따른 폴리펩타이드; 및
- 제7항에 따른 바이러스 벡터

중 하나 이상을 포함하는 조성물로서, 임의로, 상기 조성물이 포유동물 내에서 면역원성이거나, 임의로, 상기 조성물이 약제학적으로 허용되는 담체를 추가로 포함하는, 조성물.

청구항 9

제1항에 따른 핵산으로서, HPV 감염의 예방 또는 치료에 사용하기 위한, 핵산.

청구항 10

삭제

청구항 11

삭제

청구항 12

삭제

청구항 13

삭제

청구항 14

삭제

청구항 15

삭제

청구항 16

삭제

청구항 17

삭제

청구항 18

삭제

청구항 19

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청구항 37

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청구항 38

삭제

청구항 39

삭제

청구항 40

삭제

발명의 설명

기 술 분 야

[0001] 본 발명은 HPV 감염에 대한 백신화(vaccination)에서 사용하기 위한 바이러스-벡터화된 백신(virus-vectored vaccine)에 관한 것이다.

배 경 기 술

[0002] 사람 파필로마바이러스 감염은 사람 파필로마바이러스(human papillomavirus: HPV)에 의한 감염이다. 대부분의

HPV 감염은 증상없이 유발되며 자발적으로 분해된다. 그러나, 일부 경우에, 이들은 지속되며 이는 무사마귀 또는 전암성 병변의 발달을 야기할 수 있다. 전암성 병변은 자궁경관, 음문, 질, 음경, 항문, 입, 또는 목의 암 위험을 증가시킨다.

[0003] 대략 50만개의 사례의 HPV에 기인하는 자궁경부암이 전세계적으로 매년 발생하고 있으며, 이들 중 거의 1/2이 치명적이다. 사례들의 약 85%가 후진국/중진국에서 발생하며 이러한 국가에서는 이용가능한 치료가 제한되거나 이용가능한 치료가 없다. 예방 백신을 제공받지 않은 여성은 자궁경부 상피내 종양형성(intra-epithelial neoplasia: CIN)을 확인하고 치료하기 위해 3년의 스크리닝(screening)을 필요로 한다. 영국 국민건강보험공단에서 스크리닝 비용은 매년 대략 1억 7천 5백만 유로(£175 million)이다.

[0004] CIN에 대한 현재의 치료요법은 전기소작법(electrocautery) 또는 수술에 의한 비정상적인 자궁경부 조직의 절제이다. HPV 바이러스 감염을 제거하는데 이용가능한 치료요법은 현재 존재하지 않다. 여성은 치료 후 재발이 없음을 보증하기 위하여 치료 후 다수의 후속 방문을 필요로 한다. 치료요법은 또한 조산의 증가된 위험과 관련이 있다.

발명의 내용

해결하려는 과제

[0005] 존재하는 HPV 감염의 치료요법을 위해 개발되어온 HPV 백신은 이노비오(Inovio) - VGX-3100(E6, E7을 암호화하는 DNA) 유사하게 게넥신(Genexine)(GX-188E); E2, E6, E7 융합 단백질을 암호화하는 얀쎈(Janssen) -Ad26/Ad35 +/-MVA; 합성의 긴 펩타이드(E6, E7) 및 유사한 eg. PepCan, GTL001; 애드박시스(Advaxis) - ADXS-HPV; 및 E7을 암호화하는 엘. 모노사이토게네스(L. Monocytogenes)를 포함한다. 그러나, 이러한 개발된 백신은 HPV16 및 18 만을 표적하였으며, 안전성 우려가 있고/있거나 효율이 낮다. 예를 들면, VGX-3100의 순(net) 효율은 제IIb 상의 무작위처리된 조절된 시험에서 18%이었다(백신 아암(vaccine arm)에서 48% 대 위약 아암(placebo arm)에서 30%).

[0006] 요구되는 것은 지금까지 시험된 치료학적 백신 후보물보다 안전하고, 전달하기 용이하며 보다 큰 효율을 갖는 백신이다. 따라서, 본 발명의 목표는 HPV 감염을 위한 개선된 백신을 제공하는 것이다.

과제의 해결 수단

[0007] 본 발명의 제1 양태에 따라서, 다수의 보존된 펩타이드 서열, 또는 이의 변이체을 포함하는 폴리펩타이드를 암호화하는 핵산으로서,

[0008] 여기서 보존된 서열은 하나 이상의 HPV 유전형 16, 18, 31, 52, 53, 및 58에 걸쳐 보존되어 있고;

[0009] 여기서 폴리펩타이드는 각각의 HPV 단백질 E1, E2, E4, E5, E6, 및 E7의 보존된 펩타이드 서열을 포함하는 핵산이 제공된다.

[0010] 본 발명은 유리하게는 예방접종에 대해 신규의 대안적이고 보다 안전한 접근법을 제공하며 이에 의해 T 세포는 비리온(virion)의 비교적 보존된 항원에 대해 유도될 수 있다. 비-구조 단백질로부터의 특이적으로 설계된 보존된 바이러스 분절(segment)의 사용은 다수의 중요한 유전형에 대한 보호를 제공할 수 있다.

[0011] 일 구현예에서, 폴리펩타이드는 융합 폴리펩타이드이다. 폴리펩타이드는 야생형 폴리펩타이드가 아닐 수 있다. 폴리펩타이드는 합성/인공일 수 있으며, 예를 들면, 폴리펩타이드는 천연에 존재하지 않을 수 있다. 일 구현예에서, 폴리펩타이드는 완전한 유전자 서열을 포함하지 않을 수 있다. 폴리펩타이드는 보존된 펩타이드 서열로 필수적으로 이루어질 수 있다. 다른 구현예에서, 폴리펩타이드는 보존된 펩타이드 서열 및 펩타이드 보조제(adjuvant) 서열로 필수적으로 이루어질 수 있다. 다른 구현예에서, 폴리펩타이드는 보존된 펩타이드 서열 및 이들 사이의 하나 이상의 링커(linker)로 필수적으로 이루어질 수 있다. 다른 구현예에서, 폴리펩타이드는 보존된 펩타이드 서열, 펩타이드 보조제 서열 및 이들 사이의 하나 이상의 링커로 필수적으로 이루어질 수 있다. 일 구현예에서, 폴리펩타이드는 재조합 폴리펩타이드, 예컨대, 재조합 융합 폴리펩타이드이다.

[0012] 본원에 사용된 용어 "융합 폴리펩타이드"는 상이한 유전자 생성물(예를 들면 상이한 HPV 단백질)로부터 유래된 서열의 조합 또는 동일한 유전자 생성물(예를 들면, 단일 HPV 단백질)로부터의 서열의 조합을 포함하는 폴리펩타이드를 의미하는 것으로 이해되며, 여기서 서열은 야생형 유전자 생성물의 명백한/별도의 영역으로부터 유래된다. 예를 들면, 융합 폴리펩타이드는 야생형인 다른 서열 분절에 의해 일반적으로 분리된 서열의 조합을 포함

할 수 있으며, 분리되는 서열(들)은 제거되었다.

[0013] 본원에 사용된 용어 "보존된 펩타이드 서열" 또는 "보존된 분절"은 하기 정의된 바와 같이, 하나 이상의 유전형으로 보존된 서열로 정의된다. 보존의 평가 전에 유전형 16, 18, 31, 52, 53 및 58로부터 HPV 단백질 E1, E2, E4, E5, E6 및 E7에 대한 모든 이용가능한 전체 길이의 서열을 NCBI 단백질 데이타베이스(2014년에 입수됨)로부터 수집하고 본 발명의 접근법을 위한 입력으로 사용하였다. 모든 이용가능한 서열을 사용하여 선택된 보존된 펩타이드 서열이 전체 환경적 집단을 균등하게 나타낼 수 있도록 보증하였다(참고: 표 1). 보존된 펩타이드 서열은 '변이체' 접근법을 사용하여 확인하였으며(도 1a); 모든 유전형을 정렬하고 각각의 유전형 내의 서열을 보존 평가 전에 가중(weighting)시켜서 유전형 다양성의 균등한 표시를 보증함으로써 백신 후보물이 전체 환경적 집단을 대표하도록 보증하였다. 이후에 유전형 내의 보존(유전형-내 보존(intra-genotype conservation))을 15개 아미노산 슬라이딩 윈도우(sliding window)를 사용하여 평가함으로써 각각의 윈도우에 대해 보존 값을 윈도우내 아미노산 만연(prevalence)을 조합하고 각각의 유전형 내에 보존된 단편을 확인하기 위한 각각의 서열의 값을 가중시키는 것을 기반으로 하여 측정하고, 표준화된 유전형-내 컨센서스를 각각의 윈도우에 대해 생성시켰다. '표준화된 컨센서스'는 각각의 위치에서 가장 일반적인 아미노산이 아니라, 유전형 서열의 가중된 세트를 나타낸 아미노산 서열을 의미한다. 보존된 것으로 분류하기 위하여 윈도우는 단백질에 대한 모든 윈도우 보존값의 첫번째 사분위수(first quartile) 내에서 보존 값을 가져야만 한다. 후속적으로, 모든 유전형에 걸쳐 동일한 위치에서 보존된 유전형-내부 윈도우는 유전형 사이에 공유된 유전형-내 표준화된 컨센서스의 확인 퍼센트(percentage identity)와는 독립적으로 확인되었다(유전형-간(inter-genotype) 보존). 이후에, 수득되는 영역의 계통발생을 생성시키고 트리 그룹내 서열(tree ingroup sequence)을 조합하여 고 수준의 공유된 컨센서스 동일성을 지닌 유전형-간 컨센서스를 생성시켰다. 이러한 경우에, '유전형-간 컨센서스(inter-genotype consensus)'는 각각의 유전형으로부터 생성된 표준화된 컨센서스를 사용하여 생생된 컨센서스를 지칭한다. 일부 시나리오에서, '변형된 변이체'가 생성되었으며 여기서 유전형 사이에 60% 초과로 공유된 유전형-내 표준화된 컨센서스 퍼센트 동일성을 공유한 모든 단백질에 걸쳐 동일한 위치에서 보존된 유전형-내 윈도우가 확인되었다.

[0014] 트리 그룹내로부터의 확인된 혈청형-간 단편이 60% 미만의 퍼센트 동일성을 갖는 경우, 서열은 변이체 접근법에 사용된 "덜 다른(less divergent)" 서열과 대조적으로, "매우 다른(highly divergent)" 것으로 분류되었다. 유전형 사이에서 매우 다른 단백질의 경우 '키메라' 접근법을 사용하여 보존된 펩타이드 서열을 확인하였고(도 1b); 계통발생을 생성시키고 그룹내 유전형 만을 함께 정렬하고 유전형-내 보존을 평가하였다. 따라서, 유전형-간 보존 만을 그룹내(ingroup)와 선택된 유전형에 걸쳐 60% 초과의 공유된 컨센서스 동일성을 지닌 혈청형-내 보존된 윈도우 사이에서 평가하였다. 일부 경우에 유전형은 '키메라(chimerics)'로서 실시되었지만 유전형-간 보존은 평가되지 않았다('키메라성-변이체').

[0015] 다수의 보존된 펩타이드 서열은 10개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 다른 구현예에서, 다수의 보존된 펩타이드 서열은 15개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 다른 구현예에서, 다수의 보존된 펩타이드 서열은 20개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 다른 구현예에서, 다수의 보존된 펩타이드 서열은 25개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 다른 구현예에서, 다수의 보존된 펩타이드 서열은 30개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 다수의 보존된 서열은 35개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 다른 구현예에서, 다수의 보존된 펩타이드 서열은 40개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 다수의 보존된 펩타이드 서열은 45개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 다른 구현예에서, 다수의 보존된 펩타이드 서열은 50개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 다른 구현예에서, 다수의 보존된 펩타이드 서열은 55개 이상의 보존된 펩타이드 서열을 포함할 수 있다. 일 구현예에서, 다수의 보존된 펩타이드 서열은 약 56개 이상의 보존된 펩타이드 서열로 이루어진다. 일 구현예에서, 다수의 보존된 펩타이드 서열은 약 57개 이상의 보존된 펩타이드 서열로 이루어진다. 일 구현예에서, 다수의 보존된 펩타이드 서열은 약 58개 이상의 보존된 펩타이드 서열로 이루어진다. 일 구현예에서, 다수의 보존된 펩타이드 서열은 약 59개 이상의 보존된 펩타이드 서열로 이루어진다. 일 구현예에서, 다수의 보존된 펩타이드 서열은 약 59개의 보존된 펩타이드 서열로 이루어진다.

[0016] 암호화된 폴리펩타이드는 각각의 HPV 단백질 E1, E2, E4, E5, E6, 및 E7의 적어도 3개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E1의 적어도 3개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 3개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E4의 적어도 3개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E5의 적어도 3개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E6의 적어도 3개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

암호화된 폴리펩타이드는 HPV 단백질 E7의 적어도 3개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0017] 암호화된 폴리펩타이드는 HPV 단백질 E1의 적어도 4개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 4개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E4의 적어도 4개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E6의 적어도 4개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E7의 적어도 4개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0018] 암호화된 폴리펩타이드는 HPV 단백질 E1의 적어도 5개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 5개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E4의 적어도 5개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E6의 적어도 5개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0019] 암호화된 폴리펩타이드는 HPV 단백질 E1의 적어도 6개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 6개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E4의 적어도 6개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E6의 적어도 6개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0020] 암호화된 폴리펩타이드는 HPV 단백질 E1의 적어도 7개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 7개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는HPV 단백질 E4의 적어도 7개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E6의 적어도 7개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0021] 암호화된 폴리펩타이드는 HPV 단백질 E1의 적어도 8개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 8개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E4의 적어도 8개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E6의 적어도 8개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0022] 암호화된 폴리펩타이드는 HPV 단백질 E1의 적어도 9개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 9개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E4의 적어도 9개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0023] 암호화된 폴리펩타이드는 HPV 단백질 E1의 적어도 10개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 10개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0024] 암호화된 폴리펩타이드는 HPV 단백질 E1의 적어도 11개의 상이한 보존된 펩타이드 서열을 포함할 수 있다. 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 11개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0025] 암호화된 폴리펩타이드는 HPV 단백질 E2의 적어도 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 또는 24개의 상이한 보존된 펩타이드 서열을 포함할 수 있다.

[0026] 암호화된 폴리펩타이드는 HPV 단백질 E1의 11개 이상의 상이한 보존된 펩타이드 서열, HPV 단백질 E2의 24개 이상의 상이한 보존된 펩타이드 서열, HPV 단백질 E4의 9개 이상의 상이한 보존된 펩타이드 서열, HPV 단백질 E5의 3개 이상의 상이한 보존된 펩타이드 서열, HPV 단백질 E6의 8개 이상의 상이한 보존된 펩타이드 서열, 및 HPV 단백질 E7의 4개 이상의 보존된 펩타이드 서열을 포함할 수 있다.

[0027] 다수의 보존된 펩타이드 서열은 서로에 관하여 서열의 상이한 영역으로부터 유래될 수 있다(즉, 비-천연적으로 공존함). 예를 들면, "상이한 보존된 펩타이드 서열"에 대한 언급은 서로에 관하여 야생형 서열의 별개의 영역으로부터 유래된 서열을 포함할 수 있다(즉, 천연적으로 공존함). 예를 들면, 야생형 유전형에서 보존된 서열은 가변성/비-보존된 서열에 의해 야생형 유전형내에서 분리될 수 있다. 다수의 보존된 펩타이드 서열은 서로 중합되지 않을 수 있거나 서로 유의적으로 중첩되지 않을 수 있다. 2개 이상, 또는 모든 다수의 보존된 펩타이드 서열은 예를 들면, 이들 사이에 임의의 비-보존된/가변성 잔기를 포함하지 않는, 폴리펩타이드내에서 함께 직접 결합될 수 있다. 폴리펩타이드 서열은 천연적으로 발견되지 않을 수 있다. 폴리펩타이드는 비-보존된 서열 또는 잔기를 포함하지 않을 수 있다. 보존된 펩타이드 서열은 예를 들면, 보존된 펩타이드 서열 사이에 링커/연결 잔기가 존재하는 구현예에서, 폴리펩타이드 서열내에 1, 2, 3, 4, 또는 5개 잔기 이상 떨어지지 않을 수 있다. 대안적으로, 보존된 펩타이드 서열은 예를 들면, 보존된 펩타이드 서열 사이에 링커/결합 잔기가 존재하는 구현예에서, 폴리펩타이드 서열내에 6, 7, 8, 9, 또는 10개 잔기 이상 떨어지지 않을 수 있다. 폴리펩타이드는 2, 3,

4, 5, 6, 7, 8, 9, 또는 10개 이상의 아미노산의 비-보존된 서열을 포함하지 않을 수 있다.

[0028] 일 구현예에서, 링커 잔기는 1개 이상, 또는 모든 보존된 펩타이드 서열(예컨대, 폴리펩타이드내 보존된 펩타이드 서열 사이에 연결부를 제공) 사이에 제공될 수 있다. 링커 잔기는 무작위 아미노산 서열, 또는 동물 모델에서의 에피토프 예측 컴퓨터 프로그램 또는 실험을 기반으로 비-면역원성이 되도록 선택된 아미노산 서열을 포함할 수 있다. 예를 들면, 링커는 에피토프인 것으로 예측되거나 공지된 경우(즉, HPV에서 발견되지 않는 에피토프, 예컨대, 인공 에피토프에 대한 면역 반응을 피하기 위하여) 고려되지 않을 수 있다. 링커는 가요성일 수 있다. 링커는 K, G, P, A 또는 S 아미노산 잔기, 또는 이의 조합을 포함할 수 있거나 이로 이루어질 수 있다. 일 구현예에서, 링커는 G 및/또는 P 아미노산 잔기를 포함할 수 있거나 이로 이루어질 수 있다. 일 구현예에서, 링커는 하나 이상의 알라닌(A) 아미노산 잔기를 포함할 수 있거나 이로 이루어질 수 있다. 링커 잔기는 길이가 1 내지 10개 아미노산일 수 있다. 다른 구현예에서, 링커 잔기는 길이가 2 내지 8개 잔기일 수 있다. 다른 구현예에서, 링커 잔기는 길이가 1 내지 6개 잔기일 수 있다. 보존된 펩타이드 서열은, 예를 들면 보존된 펩타이드 서열 사이에 링커/연결부가 존재하는 구현예에서, 폴리펩타이드 서열내에서 1 내지 10개 잔기 사이에서 떨어질 수 있다.

[0029] 일 구현예에서, 폴리펩타이드는 보존된 펩타이드 서열 및 하나 이상의 링커로 필수적으로 이루어질 수 있으며, 임의로 여기서 하나 이상의 링커는 인접한 보존된 펩타이드 서열 사이에 배치된다.

[0030] 보존된 펩타이드 서열은 서열 번호: 1 내지 59를 포함하는 그룹 중 어느 하나; 이의 변이체 또는 이의 조합물로부터 선택될 수 있다. 다른 구현예에서, 보존된 펩타이드 서열은 서열 번호: 1 내지 59를 포함하는 그룹 중 어느 하나; 이의 변이체 또는 어느 순서이든 이의 조합물로부터 선택될 수 있다. 일 구현예에서, 보존된 펩타이드 서열은 서열 번호: 1 내지 59를 포함하는 그룹으로 이루어질 수 있다.

[0031] 폴리펩타이드는 서열 번호: 1 내지 11 중 어느 하나로부터 선택된 하나 이상의 보존된 E1 서열(들); 서열 번호: 12 내지 35 중 어느 하나로부터 선택된 하나 이상의 보존된 E2 서열(들); 서열 번호: 36 내지 44 중 어느 하나로부터 선택된 하나 이상의 보존된 E4 서열(들); 서열 번호: 45 내지 47 중 어느 하나로부터 선택된 하나 이상의 보존된 E5 서열(들); 서열 번호: 48 내지 55 중 어느 하나로부터 선택된 하나 이상의 보존된 E6 서열(들); 및 서열 번호: 56 내지 59 중 어느 하나로부터 선택된 하나 이상의 보존된 E7 서열(들)을 포함할 수 있다.

[0032] 폴리펩타이드는 임의의 서열 번호: 1 내지 11로부터 선택된 2개 이상의 보존된 E1 서열(들); 임의의 서열 번호: 12 내지 352로부터 선택된 2개 이상의 보존된 E2 서열(들); 임의의 서열 번호: 36 내지 44로부터 선택된 2개 이상의 보존된 E4 서열(들); 임의의 서열 번호: 45 내지 47로부터 선택된 2개 이상의 보존된 E5 서열(들); 임의의 서열 번호: 48 내지 55로부터 선택된 2개 이상의 보존된 E6 서열(들); 및 임의의 서열 번호: 56 내지 59로부터 선택된 2개 이상의 보존된 E7 서열(들)을 포함할 수 있다.

[0033] 폴리펩타이드는 서열 번호: 1 내지 11 중 어느 하나로부터 선택된 3개 이상의 보존된 E1 서열(들); 서열 번호: 12 내지 353 중 어느 하나로부터 선택된 3개 이상의 보존된 E2 서열(들); 서열 번호: 36 내지 44 중 어느 하나로부터 선택된 3개 이상의 보존된 E4 서열(들); 서열 번호: 45내지 47 중 어느 하나로부터 선택된 3개 이상의 보존된 E5 서열(들); 서열 번호: 48 내지 55 중 어느 하나로부터 선택된 3개 이상의 보존된 E6 서열(들); 및 서열 번호: 56 내지 59 중 어느 하나로부터 선택된 3개 이상의 보존된 E7 서열(들)을 포함할 수 있다.

[0034] 보존된 서열은 HPV 유전형 16, 18, 31, 52, 및 58 중 하나 이상에 걸쳐 보존된다. 보존된 서열은 HPV 유전형 16, 18, 31, 52, 및 58 중 모두에 걸쳐 보존된다.

[0035] 폴리펩타이드는 다음을 포함할 수 있다:

[0036] 서열 번호: 1 내지 11 중 어느 하나로부터 선택된 하나 이상의 보존된 E1 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 적어도 하나의 보존된 E1 서열에 의해 나타낸다;

[0037] 서열 번호: 12 내지 35 중 어느 하나로부터 선택된 하나 이상의 보존된 E2 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 적어도 하나의 보존된 E2 서열에 의해 나타낸다;

[0038] 서열 번호: 36 내지 44 중 어느 하나로부터 선택된 하나 이상의 보존된 E4 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 적어도 하나의 보존된 E4 서열에 의해 나타낸다;

[0039] 서열 번호: 45 내지 47 중 어느 하나로부터 선택된 하나 이상의 보존된 E5 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 적어도 하나의 보존된 E5 서열에 의해 나타낸다;

[0040] 서열 번호: 48 내지 55 중 어느 하나로부터 선택된 하나 이상의 보존된 E6 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 적어도 하나의 보존된 E6 서열에 의해 나타낸다; 및

[0041] 서열 번호: 56 내지 59 중 어느 하나로부터 선택된 하나 이상의 보존된 E7 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 적어도 하나의 보존된 E7 서열에 의해 나타낸다.

[0042] 폴리펩타이드는 다음을 포함할 수 있다:

[0043] 서열 번호: 1 내지 11 중 어느 하나로부터 선택된 하나 이상의 보존된 E1 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 적어도 하나의 보존된 E1 서열에 의해 나타낸다;

[0044] 서열 번호: 12 내지 35 중 어느 하나로부터 선택된 하나 이상의 보존된 E2 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 적어도 하나의 보존된 E2 서열에 의해 나타낸다;

[0045] 서열 번호: 36 내지 44 중 어느 하나로부터 선택된 하나 이상의 보존된 E4 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 적어도 하나의 보존된 E4 서열에 의해 나타낸다;

[0046] 서열 번호: 45 내지 47 중 어느 하나로부터 선택된 하나 이상의 보존된 E5 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 적어도 하나의 보존된 E5 서열에 의해 나타낸다;

[0047] 서열 번호: 48 내지 55 중 어느 하나로부터 선택된 하나 이상의 보존된 E6 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 적어도 하나의 보존된 E6 서열에 의해 나타낸다; 및

[0048] 서열 번호: 56 내지 59 중 어느 하나로부터 선택된 하나 이상의 보존된 E7 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 적어도 하나의 보존된 E7 서열에 의해 나타낸다.

[0049] 폴리펩타이드는 다음을 포함할 수 있다:

[0050] 서열 번호: 1 내지 11 중 어느 하나로부터 선택된 2개 이상의 보존된 E1 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E1 서열의 그룹내에 나타나 있다;

[0051] 서열 번호: 12 내지 35 중 어느 하나로부터 선택된 2개 이상의 보존된 E2 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E2 서열의 그룹으로 나타낸다;

[0052] 서열 번호: 36 내지 44 중 어느 하나로부터 선택된 2개 이상의 보존된 E4 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E4 서열의 그룹으로 나타낸다;

[0053] 서열 번호: 45 내지 47 중 어느 하나로부터 선택된 2개 이상의 보존된 E5 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E5 서열의 그룹으로 나타낸다;

[0054] 서열 번호: 48 내지 55 중 어느 하나로부터 선택된 2개 이상의 보존된 E6 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E6 서열의 그룹으로 나타낸다; 및

[0055] 서열 번호: 56 내지 59 중 어느 하나로부터 선택된 2개 이상의 보존된 E7 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E7 서열의 그룹으로 나타낸다.

[0056] 폴리펩타이드는 다음을 포함할 수 있다:

[0057] 서열 번호: 1 내지 11 중 어느 하나로부터 선택된 2개 이상의 보존된 E1 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E1 서열의 그룹으로 나타낸다;

[0058] 서열 번호: 12 내지 35 중 어느 하나로부터 선택된 2개 이상의 보존된 E2 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E2 서열의 그룹으로 나타낸다;

[0059] 서열 번호: 36 내지 44 중 어느 하나로부터 선택된 2개 이상의 보존된 E4 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E4 서열의 그룹으로 나타낸다;

[0060] 서열 번호: 45 내지 47 중 어느 하나로부터 선택된 2개 이상의 보존된 E5 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E5 서열의 그룹으로 나타낸다;

[0061] 서열 번호: 48 내지 55 중 어느 하나로부터 선택된 2개 이상의 보존된 E6 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E6 서열의 그룹으로 나타낸다; 및

[0062] 서열 번호: 56 내지 59 중 어느 하나로부터 선택된 2개 이상의 보존된 E7 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E7 서열의 그룹으로 나타나 있다.

[0063] 폴리펩타이드는 다음을 포함할 수 있다:

[0064] 서열 번호: 1 내지 11 중 어느 하나로부터 선택된 3개 이상의 보존된 E1 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E1 서열의 그룹으로 나타낸다;

[0065] 서열 번호: 12 내지 35 중 어느 하나로부터 선택된 3개 이상의 보존된 E2 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E2 서열의 그룹으로 나타낸다;

[0066] 서열 번호: 36 내지 44 중 어느 하나로부터 선택된 3개 이상의 보존된 E4 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E4 서열의 그룹으로 나타낸다;

[0067] 서열 번호: 45 내지 47로부터 선택된 3개의 보존된 E5 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E5 서열의 그룹으로 나타낸다;

[0068] 서열 번호: 48 내지 55 중 어느 하나로부터 선택된 3개 이상의 보존된 E6 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E6 서열의 그룹으로 나타낸다; 및

[0069] 서열 번호: 56 내지 59 중 어느 하나로부터 선택된 3개 이상의 보존된 E7 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 53, 및 58은 보존된 E7 서열의 그룹으로 나타낸다.

[0070] 폴리펩타이드는 다음을 포함할 수 있다:

[0071] 서열 번호: 1 내지 11 중 어느 하나로부터 선택된 3개 이상의 보존된 E1 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E1 서열의 그룹으로 나타낸다;

[0072] 서열 번호: 12 내지 35 중 어느 하나로부터 선택된 3개 이상의 보존된 E2 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E2 서열의 그룹으로 나타낸다;

[0073] 서열 번호: 36 내지 44 중 어느 하나로부터 선택된 3개 이상의 보존된 E4 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E4 서열의 그룹으로 나타낸다;

[0074] 서열 번호: 45 내지 47로부터 선택된 3개의 보존된 E5 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E5 서열의 그룹으로 나타낸다;

[0075] 서열 번호: 48 내지 55 중 어느 하나로부터 선택된 3개 이상의 보존된 E6 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E6 서열의 그룹으로 나타낸다; 및

[0076] 서열 번호: 56 내지 59 중 어느 하나로부터 선택된 3개 이상의 보존된 E7 서열(들)로서, 여기서 각각의 유전형 16, 18, 31, 52, 및 58은 보존된 E7 서열의 그룹으로 나타낸다.

[0077] "각각의 유전형 16, 18, 31, 52, 53, 및 58은 나타낸다" 또는 "각각의 유전형 16, 18, 31, 52, 및 58은 나타낸다"는 각각의 확인된 유전형이 보존된 펩타이드 서열의 적어도 하나의 컨센서스 서열을 정의하기 위해 사용되었음을 의미하는 것으로 의도된다. 따라서, 주어진 그룹은 각각의 유전형으로부터의 보존된 펩타이드를 포함할 수 있거나, 보존된 펩타이드는 2개 이상의 유전형의 컨센서스로부터 유래될 수 있다. 서열 동일성이 충분히 유사한 경우, 모든 유전형 16, 18, 31, 52, 53, 및 58 또는 16, 18, 31, 52, 및 58은 단일의 보존된 펩타이드 서열로 나타날 수 있으며, 이는 모든 유전형 16, 18, 31, 52, 53, 및 58 또는 16, 18, 31, 52, 및 58 각각의 컨센서스일 수 있다. 그러나, 서열 동일성에 있어서의 차이로 인하여, 단일의 보존된 펩타이드는 모든 유전형 16, 18, 31, 52, 53, 및 58 또는 16, 18, 31, 52, 및 58로부터의 컨센서스 서열을 나타낼 수 없으며 대신에 2개 이상의 보존된 펩타이드 서열이 모든 유전형 16, 18, 31, 52, 53, 및 58 또는 16, 18, 31, 52, 및 58를 포함/나타내기 위해 필요하다. 예를 들면(단지 설명 목적), 하나의 보존된 E6 펩타이드 서열은 E6 유전형 16 및 18을 나타낼 수 있으며, 다른 것은 E6 유전형 52를 나타낼 수 있고, 세번째는 E6 유전형 53 및 58을 나타낼 수 있으므로, 그룹내 모든 3개의 보존된 E6 펩타이드 서열은 모든 E6 유전형 16, 18, 31, 52, 53, 및 58 또는 16, 18, 31, 52, 및 58을 나타낸다.

[0078] 핵산은 서열 번호: 60, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 다른 구현예에서, 핵산은 서열 번호: 60의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있으며 TPA 리드 서열(lead sequence)을 암호화하지 않는다. 다른 구현예에서, 핵산은 서열 번호: 60의 서열, 또는 이의 변이체를 포함하거나 이로 이루어

질 수 있으며, TPA 리드 서열 이외에 암호화된 상이한/대안적 펩타이드 보조제(adjuvant)를 지닌다. 다른 구현예에서, 핵산은 서열 번호: 65의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다.

[0079] 핵산의 변이체는 서열 번호: 60 또는 65와 적어도 80% 동일성을 가진 서열을 포함하거나 이로 이루어질 수 있다. 대안적으로, 핵산의 변이체는 서열 번호: 60 또는 65와 적어도 85% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 60 또는 65와 적어도 90% 동일성을 가진 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 60 또는 65와 적어도 95% 동일성을 가진 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 60 또는 65와 적어도 98% 동일성을 가진 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 60 또는 65와 적어도 99% 동일성을 가진 서열을 포함하거나 이로 이루어질 수 있다. 기술자는 핵산의 변이체가 서열 번호: 60 또는 65와 동일한 펩타이드를 암호화하는 풍부한 코돈 변이체를 포함할수 있음을 이해할 것이다.

[0080] 핵산은 서열은 서열 번호: 62의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 다른 구현예에서, 핵산은 서열 번호: 62의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있고, TPA 리드 서열을 암호화하지 않는다. 다른 구현예에서, 핵산은 서열 번호: 62의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있고, TPA 리드 서열외에 암호화된 상이한/대안적 펩타이드 보조제를 포함한다.

[0081] 핵산의 변이체는 서열 번호: 62와 적어도 80% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 대안적으로, 핵산의 변이체는 서열 번호: 62와 적어도 85% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 62와 적어도 90% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 62와 적어도 95% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 62와 적어도 98% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 62와 적어도 99% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 62와 적어도 99.5% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 62와 적어도 99.9% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 기술자는 핵산의 변이체가 서열 번호: 62와 동일한 바이러스 벡터 및/또는 펩타이드를 암호화하는 풍부한 코돈 변이체를 포함할 수 있음을 이해할 것이다.

[0082] 핵산은 서열 번호: 71, 73 또는 75의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 다른 구현예에서, 핵산은 서열 번호: 71, 73 또는 75의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있으며, TPA 리드 서열을 암호화하지 않는다. 다른 구현예에서, 핵산은 서열 번호: 71, 73 또는 75의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있으며, TPA 리드 서열 이외에 암호화된 상이한/대안적 펩타이드 보조제를 지닌다.

[0083] 핵산의 변이체는 서열 번호: 71, 73 또는 75와 적어도 80% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 대안적으로, 핵산의 변이체는 서열 번호: 71, 73 또는 75와 적어도 85% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 71, 73 또는 75와 적어도 90% 동일성을 갖는 서열을 포함하거나 이로 이루어진다. 핵산의 변이체는 서열 번호: 71, 73 또는 75와 적어도 95% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 71, 73 또는 75와 적어도 98% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 71, 73 또는 75와 적어도 99% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 71, 73 또는 75와 적어도 99.5% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 핵산의 변이체는 서열 번호: 71, 73 또는 75와 적어도 99.9% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 기술자는 핵산의 변이체가 서열 번호: 71, 73 또는 75와 동일한 바이러스 벡터 및/또는 펩타이드를 암호화하는 풍부한 코돈 변이체를 포함할 수 있음을 이해할 것이다.

[0084] 폴리펩타이드는 서열 번호: 61의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 다른 구현예에서, 폴리펩타이드는 서열 번호: 61의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있고, TPA 리드 서열을 지니지 않는다. 다른 구현예에서, 폴리펩타이드는 서열 번호: 61의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있으며, TPA 리드 서열 이외에 상이한/대안적 펩타이드 보조제를 지닌다. 다른 구현예에서, 폴리펩타이드는 서열 번호: 66의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다.

[0085] 폴리펩타이드는 서열 번호: 72, 74 또는 76의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다. 다른 구현예에서, 폴리펩타이드는 서열 번호: 72, 74 또는 76의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있으며, TPA 리드 서열을 지니지 않는다. 다른 구현예에서, 폴리펩타이드는 서열 번호: 72, 74 또는 76

의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있고 TPA 리드 서열 이외에 상이한/대안적 펩타이드 보조제를 지닌다. 다른 구현예에서, 폴리펩타이드는 서열 번호: 72, 74 또는 76의 서열, 또는 이의 변이체를 포함하거나 이로 이루어질 수 있다.

[0086] 일 구현예에서, 폴리펩타이드는 보존된 펩타이드 서열 및 펩타이드 보조제로 필수적으로 이루어질 수 있다. 일 구현예에서, 폴리펩타이드는 보존된 펩타이드 서열, 하나 이상의 링커, 및 펩타이드 보조제로 필수적으로 이루어질 수 있다. 하나 이상의 링커는 인접한 보존된 펩타이드 서열 사이에 배치될 수 있다. 펩타이드 보조제는 N-말단일 수 있다.

[0087] 폴리펩타이드의 변이체는 서열 번호: 61, 66, 72, 74 또는 76과 적어도 80% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 대안적으로, 폴리펩타이드의 변이체는 서열 번호: 61, 66, 72, 74 또는 76과 적어도 85% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 폴리펩타이드의 변이체는 서열 번호: 61, 66, 72, 74 또는 76과 적어도 90% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 폴리펩타이드의 변이체는 서열 번호: 61, 66, 72, 74 또는 76과 적어도 95% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 폴리펩타이드의 변이체는 서열 번호: 61, 66, 72, 74 또는 76과 적어도 98% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다. 폴리펩타이드의 변이체는 서열 번호: 61, 66, 72, 74 또는 76과 적어도 99% 동일성을 갖는 서열을 포함하거나 이로 이루어질 수 있다.

[0088] 보존된 펩타이드 서열의 변이체는 보존된 펩타이드 서열의 절단된(truncated) 서열을 포함하거나 이로 이루어질 수 있다. 예를 들면, 본원의 서열 번호: 1 내지 59의 서열 중 어느 하나 이상은 절단될 수 있거나 폴리펩타이드 내에서 면역원성을 여전히 제공할 수 있다. 절단된 서열은 충부한 수의 아미노산을 포함함으로써 서열 번호: 1 내지 59의 서열 중 임의의 하나 내에서의 서열로부터 인식가능한 에피토프(예컨대, 특이적인 T 세포 인식을 위한 잔기의 적어도 최소의 수)를 형성할 수 있다. 절단된 서열은 서열 번호: 1 내지 59의 서열의 적어도 7개의 아미노산을 포함할 수 있다. 대안적으로, 절단된 서열은 서열 번호: 1 내지 59의 서열 중 적어도 8개의 아미노산을 포함할 수 있다. 대안적으로, 절단된 서열은 서열 번호: 1 내지 59의 서열 중 적어도 9, 10, 11 또는 12개의 아미노산을 포함할 수 있다. 다수의 절단된 서열은 서열 번호: 1 내지 59의 보존된 펩타이드 서열 중 하나 내에서 제공될 수 있다.

[0089] 일 구현예에서, 서열 번호: 1 내지 59의 보존된 펩타이드 서열 중 임의의 하나는 예를 들면, 잔기 치환, 첨가 또는 결실에 의해 변할 수 있다. 다른 구현예에서, 서열 번호: 1 내지 59의 보존된 펩타이드 서열 중 일부 또는 모두는 예를 들면, 잔기 치환, 첨가 또는 결실에 의해 변할 수 있다. 변이체 보존된 펩타이드 서열은 인식가능한 HPV 에피토프를 제공하기 위해 여전히 작용할 수 있다. 기술자는 천연의 변이가 임의의 주어진 집단에서 존재하며 이러한 변이체는 컨센서스 서열을 지닌 일부 서열 변이체, 또는 서열 번호: 1 내지 59에 제공된 예시적인 환자 서열을 가질 수 있음을 이해할 것이다. 따라서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 70% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 74% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 75% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 79% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 80% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 82% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 83% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 85% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 88% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 90% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 92% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 95% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 98% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 99% 서열 동일성을 가질 수 있다. 다른 구현예에서, 변이체 보존된 펩타이드 서열은 서열 번호: 1 내지 59 중 임의의 하나와 적어도 99.5% 서열 동일성을 가질 수 있다.

[0090] 본원에 사용된 서열 "동일성"에 대한 언급은 표준 NCBI BLASTp 매개변수(http://blast.ncbi.nlm.nih.gov)를 사

용한 2개의 정렬된 서열 사이의 동일성 퍼센트를 지칭할 수 있다.

[0091] 보존된 펩타이드 서열은 길이가 다양할 수 있으며, 최소 길이는 인식가능한 에피토프를 형성하는데 요구되는 잔기의 최소의 수로서 정의된다. 따라서, 보존된 펩타이드 서열은 길이가 약 7 내지 250개 이상의 아미노산일 수 있다. 예를 들면, 적어도 하나의 보존된 펩타이드 서열은 길이가 적어도 약 7개의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 적어도 약 8개의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 적어도 약 10개의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 적어도 약 15개의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 적어도 약 20개의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 적어도 약 30개의 아미노산일 수 있다. 일 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 약 20개 내지 약 220개 아미노산일 수 있다. 일 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 약 300개 이하의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 약 250개 이하의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 약 200개 이하의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 약 150개 이하의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 약 100개 이하의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 약 55개 이하의 아미노산일 수 있다. 다른 구현예에서, 적어도 하나의 보존된 펩타이드 서열은 길이가 약 54개 이하의 아미노산일 수 있다.

[0092] 보존된 펩타이드 서열은 보존된 펩타이드 서열의 집단 내에서 평균 길이가 약 15 및 약 50개의 아미노산일 수 있다.

[0093] 본 발명의 일부 구현예에서, 폴리펩타이드는 펩타이드 보조제, 예컨대, TPA(조직 플라스미노겐 활성인자) 서열, 또는 이의 기능성 변이체를 추가로 포함할 수 있다. TPA는 서열: MDAMKRGLCCVLLLCGAVFVSPSQEIHARFRR(서열번호: 63), 또는 이의 기능성 변이체를 포함하거나 이로 이루어질 수 있다. 일 구현예에서, 펩타이드 보조제는 예를 들면, 서열 SLLWGGVTVLAAMLIAGQVASSVVFLV(서열 번호: 64), 또는 이의 기능성 변이체의 예에 대한 상어 불변 쇄(Shark invariant chain)를 포함할 수 있다. 펩타이드 보조제는 본 발명의 폴리펩타이드 상에서 N-말단일 수 있다. 펩타이드 보조제의 기능성 변이체는 절단되거나 돌연변이된 펩타이드 변이체일 수 있으며, 이는 보조제로서 여전히 기능할 수 있는 절단되거나 돌연변이된 펩타이드 변이체, 예를 들면, 보조제로서 여전히 기능하는 TPA 또는 상어 불변 쇄의 절단되거나 돌연변이된 변이체일 수 있다. 기술자는 1, 2, 3, 4, 5개 이상의 아미노산 잔기가 기능에 영향을 미치지 않고 치환되거나, 첨가되거나 제거될 수 있음을 인지할 것이다. 예를 들면, 보존적 치환이 고려될 수 있다. 펩타이드 보조제가 제공되는(또는 적절하게 암호화되는) 구현예에서, 펩타이드 보조제와 제1의 보존된 펩타이드 서열 사이에 제공된(또는 암호화된) 링커 서열이 추가로 제공될 수 있다. 펩타이드 보조제의 부재하에서의 구현예에서, 제1의 링커 서열은 제공되지 않을 수 있다.

[0094] 본 발명에 따른 상이한 폴리펩타이드를 암호화할 수 있는 핵산의 조합은 백신으로서 제공될 수 있다. 예를 들면, 프라임(prime) 및/또는 부스트(boost) 백신 제형은 본 발명의 2개 이상의 폴리펩타이드를 암호화하는 핵산 또는 바이러스 벡터를 포함할 수 있으며, 이는 서로에 대해 상이할 수 있다.

[0095] 핵산은 다른 치료학적으로 또는 예방학적으로 활성인 성분과 함께 백신에서 사용될 수 있다. 핵산은 보조제와 함께 백신에서 사용될 수 있다.

[0096] 본 발명의 다른 양태에 따라서, 본 발명에 따른 다수의 상이한 핵산을 포함하는 조성물이 제공되며, 임의로 여기서 조성물은 약제학적으로 허용되는 조성물이다.

[0097] 본 발명의 다른 양태에 따라서 본원의 발명에 따른 핵산에 의해 암호화된 폴리펩타이드가 제공된다.

[0098] 일 구현예에서 폴리펩타이드는 단리된 폴리펩타이드이다. 폴리펩타이드, 폴리펩타이드를 암호화하는 핵산, 또는 관련된 바이러스 입자는 약제학적으로 허용되는 담체속에 제공될 수 있다.

[0099] 핵산은 예방접종을 위한 플라스미드 벡터일 수 있다. 핵산은 바이러스 벡터 서열을 포함할 수 있다.

[0100] 본 발명의 다른 양태에 따라서, 본원의 본 발명에 따른 핵산을 포함하는 바이러스 벡터가 제공된다.

[0101] 바이러스 벡터는 바이러스를 포함할 수 있다. 바이러스 벡터는 아데노바이러스, 예컨대, 사람 또는 시미안(simian) 아데노바이러스를 포함할 수 있다. 바이러스 벡터는 프라임 부스트 요법(prime boost regime)의 프라임 백신에서 사용된 경우 아데노바이러스를 포함할 수 있다. 바이러스 벡터는 ChAdOx1(말라리아 시험에서 안전

하게 사용된 AdCh63 벡터와 같은, 그룹 E 시미안 아데노바이러스) 또는 ChAdOx2(Morris et al 2016. Future Virol 11(9), pp. 649-659에 기술된 바와 같음)를 포함할 수 있다. ChAdOx2 서열은 본원에 기술된 서열(예컨대, 서열 번호: 67+68)을 포함하거나 이로 이루어질 수 있다. 바이러스 벡터는 AdCh63을 포함할 수 있다. 바이러스 벡터는 AdC3 또는 AdH6을 포함할 수 있다. 바이러스 벡터는 사람 혈청형일 수 있다. 바이러스 벡터는 변형된 박시니아 안카라(Modified Vaccinia Ankara: MVA)를 포함할 수 있다. 바이러스 벡터는 F11 MVA(예컨대, F11 유전자자리(locus)에서 핵산 작제물 삽입체를 지닌 MVA)를 포함할 수 있다. 본 발명의 핵산(HPV 백신 작제물 삽입체(construct insert))은 p7.5 프로모터의 제어하에서, 예를 들면, p7.5 MVA 셔틀(shuttle) 플라스미드(서열 번호: 158)와의 재조합을 통해 모 MVA 바이러스의 TK 유전자자리에서 삽입될 수 있다. 핵산은 서열 번호: 158에 제공된 핵산 백신 작제물 삽입체(밑줄쳐짐)를 지니거나, 본원의 본 발명에 따른 대안적 핵산 백신 작제물을 지닌 서열 번호: 158의 서열을 포함할 수 있다. 다른 구현예에서, 본 발명의 핵산(HPV 백신 작제물 삽입체)는 F11 프로모터의 제어하에서, 예를 들면, F11 셔틀 플라스미드(서열 번호: 159)와의 재조합을 통해 모 MVA 바이러스의 F11 유전자자리에 삽입될 수 있다. 핵산은 서열 번호: 159내에 제공된 핵산 백신 작제물 삽입체(밑줄쳐짐)과 함께, 또는 본원의 본 발명에 따른 대안적 핵산 백신 작제물과 함께 서열 번호: 159의 서열을 포함할 수 있다. MVA 서열은 본원에 기술된 서열(예컨대, 서열 번호: 69+70)을 포함하거나 이로 이루어질 수 있다. 바이러스 벡터는 프라임 부스트 요법에서 백신 부스트로서 사용되는 경우 MVA를 포함할 수 있다. 바이러스 벡터는 아데노-관련 바이러스(AAV) 또는 렌티바이러스를 포함할 수 있다. 바이러스 벡터는 약화된(attenuated) 바이러스 벡터일 수 있다. 본 발명의 폴리펩타이드 서열은 양호한 면역 반응을 유발하는 것으로 공지된 임의의 적합한 바이러스 벡터내로 클로닝(cloning)될 수 있다. 적합한 바이러스 벡터는 문헌: Dicks et al (Vaccine. 2015 Feb 25;33(9):1121-8. doi: 10.1016/j.vaccine.2015.01.042. Epub 2015 Jan 25), Antrobus et al (Mol Ther. 2014 Mar;22(3):668-74. doi: 10.1038/mt.2013.284. Epub 2013 Dec 30.), 및 (Warimwe et al. (Virol J. 2013 Dec 5;10:349. doi: 10.1186/1743-422X-10-349)에 기술되어 있으며, 이는 본원에 참고로 포함된다.

[0102] 본 발명의 다른 양태에 따라서, 다음 중 하나 이상을 포함하는 조성물이 제공된다:

[0103] - 본 발명에 따른 폴리펩타이드;

[0104] - 본 발명에 따른 핵산; 및

[0105] - 본 발명에 따른 바이러스 벡터.

[0106] 조성물은 예를 들면, 포유동물, 예컨대, 사람에서 면역원일 수 있다. 조성물은 약제학적으로 허용되는 담체를 포함할 수 있다. 조성물은 약제학적으로 허용되는 담체를 포함하는 약제학적 조성물일 수 있다. 조성물은 HPV 감염의 예방 또는 치료시 사용될 수 있다.

[0107] 본 발명의 다른 양태에 따라서, 다음을 투여함을 포함하는 HPV 감염의 치료 또는 예방 방법이 제공된다:

[0108] - 본 발명에 따른 폴리펩타이드;

[0109] - 본 발명에 따른 핵산;

[0110] - 본 발명에 따른 조성물 또는

[0111] - 본 발명에 따른 바이러스 벡터.

[0112] HPV 감염의 치료 또는 예방 방법은 예방접종의 방법일 수 있다.

[0113] 본 발명의 다른 양태에 따라서 HPV 감염의 예방 또는 치료시 사용하기 위한 제제가 제공되며, 이러한 제제는 다음을 포함하거나 이로 이루어진다:

[0114] - 본 발명에 따른 폴리펩타이드;

[0115] - 본 발명에 따른 조성물;

[0116] - 본 발명에 따른 핵산; 또는

[0117] - 본 발명에 따른 바이러스 벡터.

[0118] 일 구현예에서, HPV 감염의 치료 또는 예방은 항문성기 HPV-유래된 병변, 예컨대, 항문, 외음, 질, 또는 음경 상피내 종양의 치료 또는 예방을 포함한다. 추가로 또는 대안적으로, HPV 감염의 치료 또는 예방은 HPV에 의해

유발된 구강인두 병변의 치료 또는 예방을 포함한다.

[0119] 본 발명의 다른 양태에 따라서, 백신에서, 또는 백신으로서 사용하기 위한, 본 발명에 따른 폴리펩타이드; 본 발명에 따른 조성물; 본 발명에 따른 핵산; 또는 본 발명에 따른 바이러스 벡터가 제공된다.

[0120] 본 발명의 다른 양태에 따라서, 본 발명의 핵산, 본 발명에 따른 폴리펩타이드; 본 발명에 따른 조성물; 또는 본 발명에 따른 바이러스 벡터를 포함하는 백신이 제공된다.

[0121] 백신은 프라임 백신일 수 있다. 백신은 부스트 백신일 수 있다. 부스트 백신에 이어서 프라임 백신이 제공되는 경우, 폴리펩타이드는 상이할 수 있다. 예를 들면, 폴리펩타이드는 보존된 펩타이드 서열의 재-정렬된 서열을 포함할 수 있다. 보존된 펩타이드 서열은 동일할 수 있지만, 이들이 폴리펩타이드내에서 제공된 순서는 변할 수 있다. 따라서, 본원의 발명은 본 발명의 임의의 서열/양태를 제공하며, 여기서 보존된 펩타이드 서열이 제공된 순서는 변할 수 있다. 이러한 구현예는 또한 재-정렬되거나 상이한 링커/연결 서열을 포함할 수 있다.

[0122] 유리하게는, 프라임 백신과 부스트 백신 사이의 폴리펩타이드의 보존된 펩타이드 서열의 재-정렬화는 하나의 보존된 펩타이드 서열과 다른 보존된 펩타이드 서열의 연결부에 걸쳐 형성된 "거짓(false)" 에피토프의 제공을 피할 수 있는데, 즉, 동일한 연결부는 재-정렬된 폴리펩타이드내에서 발생하지 않을 수 있다.

[0123] 본 발명의 다른 양태에 따라서, 백신에서, 또는 백신으로서 사용하기 위한, 본 발명에 따른 핵산 또는 폴리펩타이드가 제공된다.

[0124] 본 발명의 다른 양태에 따라서, 다음을 포함하는 프라임 부스트 예방접종 키트(kit)가 제공된다:

[0125] - 본 발명에 따른 프라임 예방접종;

[0126] - 본 발명에 따른 부스트 백신접종.

[0127] 프라임 및 부스트 예방접종은 상이할 수 있다. 프라임 및 부스트 예방접종은 폴리펩타이드 서열에 있어서 상이할 수 있다. 프라임 및 부스트 예방접종은 상이한 바이러스 벡터(즉, 상이한 바이러스 과(family), 예컨대, MVA 대 아데노바이러스)를 포함할 수 있다.

[0128] 본 발명의 다른 양태에 따라서, 본원의 본 발명에 따른 핵산, 및 약제학적으로 허용되는 담체를 포함하는 조성물이 제공된다.

[0129] 조성물은 야생형 HPV를 포함하지 않을 수 있다. 조성물은 전체 길이(full length)의 HPV 단백질 서열을 포함하지 않을 수 있다. 바이러스 벡터 또는 핵산은 HPV의 비-보존된 단백질/펩타이드 서열을 암호화하지 않을 수 있다.

[0130] 약제학적으로 허용되는 담체와 함께 사용될 수 있다. 추가로 또는 대안적으로, 보조제와 함께 사용할 수 있다.

[0131] 용어 "면역원성"은 본 발명의 핵산, 폴리펩타이드 또는 조성물에 적용되는 경우, 사람 또는 동물 체내에서 면역반응을 유발할 수 있음을 의미한다. 면역 반응은 보호성일 수 있다.

[0132] 용어 "보호성"은 질환의 예방, 질환 감염, 전파 및/또는 진행의 감소된 위험, 질환의 감소된 중증도, 상태 또는 질환의 치유(cure), 증상의 완화, 또는 질환 또는 질환 증상의 중증도에 있어서의 감소를 의미한다.

[0133] 용어 "예방(prophylaxis)"은 질환에 대한 보호성 치료의 방지(prevention)를 의미한다. 예방은 질환 감염, 전파 및/또는 진행의 감소된 위험, 또는 질환의 감소된 중증도를 포함할 수 있다.

[0134] 용어 "치료"는 상태 또는 질환의 치유, 증상의 완화, 또는 질환 또는 질환 증상의 중증도에 있어서의 감소를 의미한다.

[0135] 기술자는 본 발명의 하나의 구현예 또는 양태의 임의의 특징이 적절하게는, 본 발명의 다른 구현예 또는 양태에 적용가능할 수 있음을 이해할 것이다.

[0136] 본 발명의 구현예를 이제 첨부된 도면을 참고로, 단지 예로써, 보다 상세히 설명할 것이다.

도면의 간단한 설명

[0137] **도 1 - HPV 후보물을 생성하는데 사용된 키메라(chimeric) 및 변형 방법.**

도 2 - 하기 생성된 변이체를 지닌 보존된 영역.

도 3 - A) 키메라를 형성하는데 사용된 2개의 유전형 내에 보존된 것으로 확인된 영역. B) 변형된 변이체의 보존 플롯(plot).

도 4 - A) 키메라를 형성하는데 사용된 2개의 유전형에서 보존된 것으로 확인된 영역. B) 변이체의 보존 플롯.

도 5 - 키메라를 형성하는데 사용된 2개의 유전형내에 보존된 것으로 확인된 영역.

도 6 - 키메라-변이체를 형성하는데 사용된 2개의 유전형내에 보존된 것으로 확인된 영역.

도 7 - 키메라를 형성하는데 사용된 2개의 유전형내에 보존된 것으로 확인된 영역.

도 8 - 백신-특이적인 T 세포의 고 빈도는 프라임 부스트 예방접종 후 유도된다. IFNɣ 엘리스포트(Elispot)는 DNA-HPV, MVA-HPV 또는 ChAdOx1-5GHPV3으로 근육내 프라임된 다음 2주 후 이종 또는 동종 백신으로 근육내 부스트시킨 C57BL/6 마우스(6마리/그룹)로부터의 PBMC에서 수행하였다. PBMC를 프라임 후 2주째 및 부스트 후 1 및 2주째에 꼬리 정맥을 방혈시켜 수집하였다.

도 9 - 프라임 부스트 예방접종은 면역원내에 암호화된 모든 항원에 대해 반응을 유도할 수 있다. PBMC를 부스트 2주째에 수집하고 전체 면역원 서열에 걸쳐 펩타이드와 함께 IFNɣ 엘리스포트(Elispot)에서 사용하고, 단백질 공급원에 따라 혼주(pooling)시켰다. 거대한 수의 펩타이드로 인하여 면역원의 E2 영역에 걸친 펩타이드를 2개의 혼주물로 분할하고 E4 및 E5에 걸친 영역에 대한 펩타이드를 하나의 혼주물내로 합하였다.

도 10 - 백신-특이적인 CD8+ T 세포는 ChAdOx1-5GHPV3 프라임 MVA-5GHPV3 부스트 후 6주째에 고 빈도로 검출될 수 있다. 10a 부스트 후 2, 3, 4 및 6주째에 꼬리 정맥 방혈에 의해 수집한 PBMC를 사용한 IFNɣ 엘리스포트(DM; DNA-5GHPV3 프라임 MVA-5GHPV3 부스트, CM; ChAdOx1-5GHPV3 프라임 MVA-5GHPV3 부스트). 10b ChAdOx1-5GHPV3 프라임, MVA-5GHPV3 부스트 후 1주 및 6주째에 수득된 PBMC에서 수행된 ICS. PBMC는 E6 및 E7 펩타이드 혼주물로 자극시켰다. 측정된 IFN-ɣ, CD107, TNF-α 및 IL2.

도 11 - HPV E6- 및 E7-특이적인 CD8+ T 세포 반응은 다기능성이며 세포독성 잠재능을 갖는다. ChAdOx1-5GHPV3 프라임 MVA-5GHPV3 부스트 후 1주째에 수집한 꼬리 정맥 방혈로부터의 PBMC를 면역우세 펩타이드 혼주물 E6 및 E7 및 E6내에 우세한 서브 혼주물(sub pool)인 서브 혼주물 22로 자극시켰다. 반응하는 CD8+ T 세포는 3개의 기능(CD107, IFNɣ 및 TNFα)을 우세하게 발현한다.

도 12 - ChAdOx1-5GHPV3 프라임 MVA-5GHPV3 부스트는 부스트 후 6주째에 여전히 검출가능한 HPV E6- 및 E7-특이적인 CD4+ T 세포 반응을 또한 프라임한다. ICS를 ChAdOx1-5GHPV3 프라임, MVA-5GHPV3 부스트 후 1주 및 6주째에 수득한 PBMC에서 수행하였다. PBMC는 E6 및 E7 펩타이드 혼주물로 자극시켰다. 측정된 IFN-ɣ, CD107, TNF-α 및 IL2.

도 13 - 대부분의 E6 및 E7-특이적인 CD4+ T 세포는 2개의 기능을 발현한다. ChAdOx1-5GHPV3 프라임 MVA-5GHPV3 부스트 후 1주째에 수집한 꼬리 정맥 방혈로부터의 PBMC를 면역우세한 펩타이드 혼주물 E6 및 E7 및, E6 내의 우세한 서브 혼주물인 서브 혼주물 22로 자극시켰다. 반응하는 CD4+ T 세포는 2개의 기능을 우세하게 발현한다(감소된(Discounting) CD107+ 일기능성 세포).

도 14 - HPV E6- 및 E7-특이적인 CD8+ T 세포를 자궁경부에서 검출할 수 있다. ICS를 ChAdOx1-5GHPV3 프라임 MVA-5GHPV3 부스트 후 2주째에 마우스로부터 단리한 자궁경질(cervicovaginal) 림프구에서 수행하고 면역우세한 펩타이드 혼주물 E6 및 E7 및 서브 혼주물 22로 자극시켰다. 측정된 IFN-ɣ, CD107, TNF-a 및 IL2.

도 15 - 자궁경질 HPV E6- 및 E7-특이적인 CD8+ T 세포 반응은 다기능성이다. ChAdOx1-5GHPV3 프라임 MVA-5GHPV3 부스트 후 1주째에 수집한 자궁경질 림프구를 면역우세한 펩타이드 혼주물 E6 및 E7 및, E6 내의 우세한 서브 혼주물인 서브 혼주물 22로 자극시켰다. 반응하는 CD8+ T 세포는 3개의 기능(CD107, IFNɣ 및 TNFα)을 우세하게 발현한다.

도 16 - 자궁경부내에서 백신-유도된 E6 및 E7-특이적인 CD8+ 및 CD4+ T 세포는 거의 오로지 효과기 표현형이다. 나이브(Naive): CD44-CD62L+. 항원-경험 있음: 중심 기억 - CD62L+, CD127+; 효과기 기억 - CD62L-, CD127+; 효과기 - CD62L-, CD127-. 6마리의 마우스로부터의 자궁경부 림프구를 낮은 림프구 수로 인하여, 3개의 쌍으로 혼주시켰다.

도 17 - 자궁경부와는 대조적으로, 비장내에서 백신-유도된 E6 및 E7-특이적인 CD8+ 및 CD4+ T 세포는 효과기 및 효과기 기억 집단을 포함한다.

도 18 - ChAdOx1-5GHPV3 프라임, MVA-5GHPV3 부스트로 예방접종받은 마우스는 대조군 마우스보다 증가된 생존을 나타낸다. 마우스에게 0일째에 5x10^{4}개의 TC-1 세포를 접종한 다음 3일째에 프라임하고 17일째에 부스트하였다. 종양을 2일마다 디지탈 캘리퍼스(digital callipers)로 측정하고 종양이 어느 하나의 방향으로도 10mm에 이르는 경우 마우스를 도태시켰다.

도 19 - 이계교배된(outbred) CD1 마우스의 예방접종은 고 빈도 T 세포 반응을 유도한다. IFNɣ 엘리포트를 DNA-5GHPV3, MVA-5GHPV3 또는 ChAdOx1-5GHPV3로 근육내 프라임한 CD1 마우스(10마리/그룹)로부터의 PBMC에서 수행한 다음 2주 후 이종 또는 동종 백신으로 근육내 부스트하였다. PBMC를 프라임 후 2주째에 및 부스트 후 3주째에 꼬리 정맥 방혈에 의해 수집하였다.

도 20 - 예방접종된 CD1 마우스에서 T 세포 반응을 전체 면역원에 걸쳐 지시한다. PBMC를 2주 부스트에서 수집하고 전체 면역원 서열에 걸친 펩타이드로 IFNɣ 엘리스포트내에서 사용하고, 단백질 공급원에 따라 혼주시켰다. 다수의 펩타이드 및 E4 및 E5에 걸친 영역에 대한 펩타이드를 하나의 혼주물로 합하였으므로, 면역원의 E2 영역에 걸친 펩타이드를 2개 혼주물로 분할하였다.

도 21 - 상부 패널: 16 내지 24명의 76세 여성으로부터의 말초 혈액 단핵 세포(PBMC)를 생체외(ex vivo) IFN-ɣ 엘리스포트 검정에서 고 위험 HPV(hrHPV)로부터 조기 단백질(early protein)을 기반으로 한 펩타이드의 인식에 대해 시험하였다. '삽입체'는 hrHPV 이식유전자에 걸쳐 11개 아미노산에 의해 중첩된 15-머(mer) 펩타이드의 혼주물이다. '참고' 펩타이드는 HPV16 및 HPV52로부터의 조기 단백질을 기반으로 한 펩타이드의 혼주물이었으며, 이는 다음과 같이 조합되었다: E1/E2, E4/E5 및 E6/E7. 'FEC'(flu, EBV 및 CMV) 펩타이드 및 PHA(파이토헤마글루티닌(phytohaemaglutinnin))을 양성 대조군으로서 사용하였다. 나타낸 데이타는 음성 대조군 값(모의(mock)-자극된 세포)을 감한 후 펩타이드-자극된 웰로부터 수득된 스폿-형성 단위(spot-forming unit: SFU)이다. 양성 반응에 대한 컷-오프(cut-off)는 25 SFU/백만개의 PBMC(모든 공여체로부터의 모의-자극된 값의 평균 + 2개의 표준 편차로부터 유도됨)에서 설정하였다. 여성을 질 샘플링(vaginal sampling)에서 hrHPV DNA에 대해 동시에 시험하였다: 26%가 양성으로 시험되었다. 데이타는 현재 hrHPV 감염되었거나 또는 노출 전인 76명의 여성 중 9명의 여성이 전이유전자내에서 암호화된 HPV 서열을 인식하였다. 하부 패널: 삽입체 혼주물에 대한 반응은 삽입체 혼주물의 서브-혼주물을 사용하여 PBMC를 시험(좌측, 백만개의 PBMC당 SFU)한 다음 혼주물 내에서 개개 펩타이드를 시험(우측, 웰당 SFU)함으로써 하나의 반응하는 공여체내에서 추가로 정보를 얻어서, 실제 HPV-특이적인 반응의 존재를 확인하였다. SFU - 200,000개의 PBMC 또는 백만개의 PBMC당 함유하는, 웰당 보고된 스폿-형성 단위).

도 22 - ChAdOX1-5G-HPV3 프라임 MVA-5GHPV3 부스트 후 C57BL/6 마우스(상부 패널) 및 CD1 마우스(하부 패널)에서 서브혼주물(subpool) 맵핑. 마우스를 부스트 후 2주째에 도태시키고 비장세포를 단리하였다. 면역원 서열을 포함하는 서브혼주물을 사용하는 IFNɣ 엘리스포트 검정에서 비장세포를 사용하였다. 서브혼주물 21, 25 및 26(예를 들면)은 HPV53 서열을 함유하지 않으며 여전히 큰 규모의 반응을 수득할 수 있으므로, HPV53 분절이 없는 서열이 여전히 면역원일 수 있다는 증거를 제공한다.

발명을 실시하기 위한 구체적인 내용

[0138] **HPV 면역원 설계**

[0139] HPV 면역원은 보존된 아미노산 단편으로 구성되고 단백질 수준에서 전반적인 HPV 집단을 지리적으로 나타낸다. 각각의 단편을 키메라 또는 변이체 기반 단편을 생성하기 위해 활용된 보존 알고리즘을 사용하여 생성시킨다. 각각의 HPV 단백질의 특성에 따른 선택을 사용하였다.

[0140] 코어 보존 알고리즘(core conservation algorithm)은 유전형 내에서(유전형-내) 및 유전형 사이(유전형-간) 둘 다에서 보존된 윈도우를 확인하기 위해 수집 편향(collection bias)을 고려한 표준화 방법과 조합된 슬라이딩 윈도우 접근법(sliding window approach)을 사용한다. 유전형-내 보존된 윈도우를 전체 서열에 대해 모든 윈도우 보존 값의 합의 1 사분위수(one quartile) 미만의 보존 값을 지닌 윈도우로서 분류한다. 표준화된 대표적인 컨센서스 서열을 이러한 공정 동안 각각의 유전형에 대해 생성시킨다. 후속적으로 유전형-간 윈도우는, 보존되고 > 60%의 공유된 컨센서스 동일성을 갖는 각각의 유전형내 동일한 위치에서 윈도우로서 확인된다.

[0141] 각각의 단백질의 영역에 대해 모든 선택된 유전형을 나타내는 서열을 생성하는데 있어서 주요 과제는 많은 유전형이 유일한 계통발생적 집단화(clustering)를 나타내었다는 것이었다. 유전형에 걸쳐 보존된 영역의 확인과 이러한 영역들 사이에 공유된 컨센서스 동일성% 수준 사이에 중요한 균형이 존재하였다. 많은 경우에 유전형-간

다양성은 공유된 컨센서스 동일성%를 희생시킬 정도로 극심했다. 일부 유전형을 의미하는 것은 서로 매우 명백하므로 대표적인 서열을 생성하는 것은 불가능하였다. 이를 해결하기 위하여, 미가공(raw) 서열을 2개의 방법 중 하나로 코어(core) 알고리즘 내로 투입하였다(도 1). (i) 변이체; 모든 유전형에 대한 서열을 알고리즘내로 투입하고 유전형-간 보존 영역을 공유된 컨센서스 동일성%와는 독립적으로 확인한다. 계통발생을 수득되는 영역으로부터 생성시키고 그룹내 서열을 조합하여 높은 수준의 공유된 컨센서스 동일성을 지닌 컨센서스를 생성시켰다(도 1b), (ii) 키메라; 일부 예에서 유전형 사이의 거리는 매우 유의적이어서 유전형은 적합하게 정렬되지 않는다. 따라서, 그룹내 사이의 유전형만을 알고리즘내로 함께 투입하고, > 60%의 공유된 컨센서스 동일성을 지닌 그룹내 사이에 보존된 영역을 확인한다(도 1a).

[0142] **HPV 후보물**

[0143] 후보물 서열을 NCBI 단백질 데이타베이스로부터 수집된 투입 서열을 사용하여 6개의 HPV 단백질(E1-2, E4-7)에 대해 생성시키고, 정렬하고 수동으로 검사하여 불완전하고 불량한 품질의 서열을 제거하였다(표 1).

[0144] [표 1]

검사 후 투입물로서 사용된 서열의 번호

	유전형					
단백질	*16*	*18*	*31*	*52*	*53*	*58*
E1	126	49	24	27	15	53
E2	195	56	26	32	18	54
E4	161	48	24	24	14	52
E5	197	48	24	24	—	60
E6	1205	78	90	218	131	185
E7	566	70	85	193	114	199

[0145]

[0146] **E1 후보물**

접근법:	변이체	
단편:	1	E1_V1_52+58: DEDETAYDSGTDLIDFIDDS (서열 번호: 1) E1_V1_31+16+18: DENENDSDTGEDMVDFIDN (서열 번호: 2) E1_V1_53: DETDEESTESDLDGFIDNS (서열 번호: 3)
	2	배제됨
	3	E1_V3_31+53: AQLADSDSNACAFLK (서열 번호: 4) E1_V3_52+58+18+16: AQLADVNSNAAAFLK (서열 번호: 5)
	4	E1_V4_16+31: NCILLYGAANTGKSLFGMSL (서열 번호: 6) E1_V4_18+52+58: NCLVLCGPANTGKSYFGMSL (서열 번호: 7) E1_V4_53: NCLVIYGPPNTGKSCFAMSL (서열 번호: 8)
	5	E1_V5_16+31+52: WPYLHSRLVVFTFPNPF (서열 번호: 9) E1_V5_18+58: WPYLESRITVFEFPNAF (서열 번호: 10) E1_V5_53: LRYLHSRIHVLQFLNPF (서열 번호: 11)

[0147]

[0148] 윈도우를 지닌 E1 단백질내에서 확인된 5개의 단편은 이들 각각의 유전형 내에서 동일한 위치에 보존되었다. 분기학은 고 수준의 공유된 컨센서스 동일성을 제공하는 가장 적합한 유전형 조합을 확인하였다(도 2).

[0149] **E2 후보물**

접근법:	키메라		
단편:	1 *(16+31)*	E2_C1-1_16+31	NVCQDKILEHYENDSKD (서열 번호: 12)
		E2_C1-2_16+31	ILEHYENDSKDLCDHI (서열 번호: 13)
		E2_C1-3_16+31	CDHIDYWKHIRLECAIMYKAR (서열 번호: 14)
		E2_C1-4_16+31	IRLECAIMYKAREMGFH (서열 번호: 15)
		E2_C1-5_16+31	QFDGDICNTMHYTNW (서열 번호: 16)
		E2_C1-6_16+31	IYICEDAQCTVVEGQVD (서열 번호: 17)
		E2_C1-7_16+31	KKWEVHAGGQVILCPES (서열 번호: 18)
		E2_C1-8_16+31	GQRRIKRPRSE (서열 번호: 19)
		E2_C1-9_16+31	NCHPNKLL (서열 번호: 20)
		E2_C1-10_16+31	ILKCLRYRFKKHCKL (서열 번호: 21)
		E2_C1-11_16+31	SSTWHWTCHDGKHK (서열 번호: 22)
		E2_C1-12_16+31	WHWTCHDGKHKNAIVTLTY (서열 번호: 23)
	2 *(52+58)*	E2_C1-1_52+58 YEADKNDLNAQIEHWKLIRMECAIFYKAKELGIS (서열 번호: 24)	
		E2_C1-2_52+58 ICHQVVPPLAASKAKACQAIELQLALEALNASPY (서열 번호: 25)	
		E2_C1-3_52+58	DEWTLQQTSLEMWLAEPQ (서열 번호: 26)

[0150]

		E2_C1-4_52+58 FKKHGITITVQYDNDKANTMDYTNWKEIY (서열 번호: 27) E2_C1-5_52+58 VIVCPASIPSDEISTEEA (서열 번호: 28)
	3 *(53+18)*	E2_C1-1_53+18 DHIDYWKAIRQENAIFFAAR (서열 번호: 29) E2_C1-2_53+18 HQVVPALNICKAKACKAIE (서열 번호: 30) E2_C1-3_53+18 WNTEPKHCFKKGGQHIEVWFD (서열 번호: 31) E2_C1-4_53+18 YVAWDSVYYCGDDGWCKT (서열 번호: 32) E2_C1-5_53+18 EAEKYGCKGTWEVHFG (서열 번호: 33) E2_C1-6_53+18 NSIDCNDSMCSTFDDNVSATELVK (서열 번호: 34)
접근법:	변형된 변이체	
단편:	1	E2_FC1_모두 DHIDYWKLIRLECAIFYKAR (서열 번호: 35)

[0151]

[0152] 정렬 불일치로 인하여 3개의 키메라를 계통발생을 기반으로 생성시켰다(16 & 31, 52 & 58, 52 & 18)(도 3a). 추가로, 모든 유전형을 유사한 방식으로 알고리즘내에 투입하여 변이체를 생성시켰으나 60% 이상의 공유된 컨센서스 동일성%를 지닌 각각의 유전형으로부터 보존된 윈도우를 단지 선택하기 위한 프로그램 필터(program filter)는 손상되지 않았다. 이는 '변형된 변이체'로 지칭된 하나의 단편을 확인하였다(도 3b).

[0153] **E4 후보물**

접근법:	키메라	
단편:	1 *(16+31)*	E4_C1-1_16+31 RRLSSDQDQSQ (서열 번호: 36)
	2 *(52+58)*	E4_C1-1_52+58 LVTKYPLLKLLS (서열 번호: 37)
	3 *(53)*	E4_C1-1_53 RPPNMGVKAHGKCIWENKVFIVPTLCPVPLDPTYPLLKLLT (서열 번호: 38) E4_C1-2_53 TQTTTPENTSLVELRVTTPKSTVVIRLHL (서열 번호: 39)
	4 *(18)*	E4_C1-1_18 TTRYPLLSLLNSYSTPPHRIPAPCPWAPQRP (서열 번호: 40)
접근법:	변이체	
단편:	1	E4_V1_16+31 PIPKPSPWAP (서열 번호: 41) E4_V1_18 RIPAPCPWAP (서열 번호: 42) E4_V1_52 PRPPHCPWVP (서열 번호: 43) E4_V1_53 PPPPPRPWAP (서열 번호: 44) E4_V1_58 배제됨

[0154]

[0155] 4개의 키메라를 생성시켰으며, 단편 중 2개는 유전형 특이적이다(도 4a). 또한, 변이체 분석은 하나의 영역을 확인하였다(도 4b).

[0156] **E5 후보물**

접근법:	키메라	
단편:	1 *(16+31)*	E5_C1_16_31 CFLLCFCVLLCVCLLIRPLLLSVSTY (서열 번호: 45)
	2 *(52+58)*	E5_C1_52+58 LRPLLLSISVYAQVLVLVLLLWVSIGS (서열 번호: 46)
	3 *(18)*	E5_C1_18 LLPSVCMCAYAWVLVFVYIVVITSPATA (서열 번호: 47)

[0157]

[0158] 3개의 키메라를 생성시켰다(도 5).

[0159] **E6 후보물**

접근법:	키메라-변이체	
단편:	1 *(16+18)*	E6_CV1_16 IVYRDGNPYAVCDKCLKFYSKISEYRHYCYSLYGTTLEQQYN KPLCDLLIRCIN (서열 번호: 48) E6_CV1_18 VVYRDSIPHAACHKCIDFYSRIRELRHYSDSVYGDTLEKLTN TGLYNLLIRCLR (서열 번호: 49)
	2 *(53+31)*	E6_CV2-1_53 VFCKKALTASEVYNFAYTDLRVVYRD (서열 번호: 50) E6_CV2-2_53 SKVRKLRYYNCSVYGASL (서열 번호: 51) E6_CV2-1_31 VYCKGQLTETEVLDFAFTDLTIVYRD (서열 번호: 52) E6_CV2-2_31 SKVSEFRWYRYSVYGTTL (서열 번호: 53)
	3 *(52_58)*	E6_CV3-1_52+58 CVECKKTLQRSEVYD (서열 번호: 54) E6_CV3-2_52+58 CQRPLCPQEKKRHVDLNKRFH (서열 번호: 55)

[0160]

[0161] E6 단백질은 유전형에 걸쳐 매우 제한된 보존을 나타내었다. 대신에, 그룹내를 가공하여 공유된 컨센서스 동일성 필터 %가 없는 키메라를 생성하였지만, 보존된 윈도우는 유전형 52 및 58을 제외하고는, 컨센서스를 생성하기 위해 조합되지 않았다(도 6).

[0162] **E7 후보물**

접근법:	키메라	
단편:	1 *(16+31)*	E7_C1_16+31 TLHEYMLDLQPETTDLYCYEQ (서열 번호: 56)
	2 *(52+58)*	E7_C1_58_52 PETTDLHCYEQLGDSSDEEDTGGLDG (서열 번호: 57)
	3 *(53+18)*	배제됨
접근법:	키메라-변이체	
단편:	1	E7_V1_53 DEDEDEVDHLQEQPQQARRDEQHPCYLIETQCCRCESLV (서열 번호: 58) E7_V1_18 EENDEIDGVNHQHLPARRAEPQRHTMLCMCCKCEARI (서열 번호: 59)

[0163]

[0164] 키메라를 유전형 16 & 31 및 52 & 58에 대해 생성시켰다(도 7). 유전형 53 및 18은 키메라 변이체이다.

[0165] 서열 번호를 지닌 백신 단편의 요약

서열 번호 :	단백질	단편
1	E1_V1_52+58	DEDETAYDSGTDLIDFIDDS
2	E1_V1_31+16+18	DENENDSDTGEDMVDFIDN
3	E1_V1_53	DETDEESTESDLDGFIDNS
4	E1_V3_31+53	AQLADSDSNACAFLK
5	E1_V3_52+58+18 +16	AQLADVNSNAAAFLK
6	E1_V4_16+31	NCILLYGAANTGKSLFGMSL
7	E1_V4_18+52+58	NCLVLCGPANTGKSYFGMSL
8	E1_V4_53	NCLVIYGPPNTGKSCFAMSL
9	E1_V5_16+31+52	WPYLHSRLVVFTFPNPF
10	E1_V5_18+58	WPYLESRITVFEFPNAF
11	E1_V5_53	LRYLHSRIHVLQFLNPF
12	E2_C1-1_16+31	NVCQDKILEHYENDSKD
13	E2_C1-2_16+31	ILEHYENDSKDLCDHI
14	E2_C1-3_16+31	CDHIDYWKHIRLECAIMYKAR
15	E2_C1-4_16+31	IRLECAIMYKAREMGFH
16	E2_C1-5_16+31	QFDGDICNTMHYTNW
17	E2_C1-6_16+31	IYICEDAQCTVVEGQVD
18	E2_C1-7_16+31	KKWEVHAGGQVILCPES
19	E2_C1-8_16+31	GQRRIKRPRSE
20	E2_C1-9_16+31	NCHPNKLL

[0166]

21	E2_C1-10_16+31	ILKCLRYRFKKHCKL
22	E2_C1-11_16+31	SSTWHWTCHDGKHK
23	E2_C1-12_16+31	WHWTCHDGKHKNAIVTLTY
24	E2_C1-1_52+58	YEADKNDLNAQIEHWKLIRMECAIFYKAKELGIS
25	E2_C1-2_52+58	ICHQVVPPLAASKAKACQAIELQLALEALNASPY
26	E2_C1-3_52+58	DEWTLQQTSLEMWLAEPQ
27	E2_C1-4_52+58	FKKHGITITVQYDNDKANTMDYTNWKEIY
28	E2_C1-5_52+58	VIVCPASIPSDEISTEEA
29	E2_C1-1_53+18	DHIDYWKAIRQENAIFFAAR
30	E2_C1-2_53+18	HQVVPALNICKAKACKAIE
31	E2_C1-3_53+18	WNTEPKHCFKKGGQHIEVWFD
32	E2_C1-4_53+18	YVAWDSVYYCGDDGWCKT
33	E2_C1-5_53+18	EAEKYGCKGTWEVHFG
34	E2_C1-6_53+18	NSIDCNDSMCSTFDDNVSATELVK
35	E2_FC1_All	DHIDYWKLIRLECAIFYKAR
36	E4_C1-1_16+31	RRLSSDQDQSQ
37	E4_C1-1_52+58	LVTKYPLLKLLS
38	E4_C1-1_53	RPPNMGVKAHGKCIWENKVFIVPTLCPVPLDPTYPLLKLLT
39	E4_C1-2_53	TQTTTPENTSLVELRVTTPKSTVVIRLHL
40	E4_C1-1_18	TTRYPLLSLLNSYSTPPHRIPAPCPWAPQRP
41	E4_V1_16+31	PIPKPSPWAP
42	E4_V1_18	RIPAPCPWAP
43	E4_V1_52	PRPPHCPWVP

[0167]

44	E4_V1_53	PPPPPRPWAP
45	E5_C1_16_31	CFLLCFCVLLCVCLLIRPLLLSVSTY
46	E5_C1_52+58	LRPLLLSISVYAQVLVLVLLLWVSIGS
47	E5_C1_18	LLPSVCMCAYAWVLVFVYIVVITSPATA
48	E6_CV1_16	IVYRDGNPYAVCDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIR CIN
49	E6_CV1_18	VVYRDSIPHAACHKCIDFYSRIRELRHYSDSVYGDTLEKLTNTGLYNLLIR CLR
50	E6_CV2-1_53	VFCKKALTASEVYNFAYTDLRVVYRD
51	E6_CV2-2_53	SKVRKLRYYNCSVYGASL
52	E6_CV2-1_31	VYCKGQLTETEVLDFAFTDLTIVYRD
53	E6_CV2-2_31	SKVSEFRWYRYSVYGTTL
54	E6_CV3-1_52+58	CVECKKTLQRSEVYD
55	E6_CV3-2_52+58	CQRPLCPQEKKRHVDLNKRFH
56	E7_C1_16+31	TLHEYMLDLQPETTDLYCYEQ
57	E7_C1_58_52	PETTDLHCYEQLGDSSDEEDTGGLDG
58	E7_V1_53	DEDEDEVDHLQEQPQQARRDEQHPCYLIETQCCRCESLV
59	E7_V1_18	EENDEIDGVNHQHLPARRAEPQRHTMLCMCCKCEARI

[0168]

[0169] **HPV3 뉴클레오타이드 서열(서열 번호: 60)**

[0170] 출발 코돈으로부터, 추가의 링커로 암호화된 TPA 리딩 서열로부터 출발함(TPA 및 링커는 굵은 글자체로 밑줄쳐

져 있다)

[0171]

ATGGATGCTATGAAGAGGGGCCTGTGCTGCGTGCTGCTGCTGTGTGGCGC
CGTGTTTGTGTCCCCCAGCCAGGAAATCCACGCCCGGTTCAGAAGAGGCA
GCAAGCTGGCCGACGAGGACGAGACAGCCTACGACAGCGGCACCGACCTG
ATCGACTTCATCGACGACAGCGACGAGAATGAGAACGACTCCGACACCGG
CGAGGACATGGTGGATTTCATCGACAACGACGAAACCGACGAAGAGAGCA
CCGAGAGCGACCTGGACGGCTTTATCGACAACTCCGCCCAGCTGGCTGAC
AGCGACAGCAATGCCTGCGCCTTCCTGAAGGCTCAGCTGGCAGACGTGAA
CAGCAACGCCGCTGCTTTTCTGAAGAACTGCATCCTGCTGTACGGCGCTG
CCAACACCGGCAAGAGCCTGTTCGGCATGAGCCTGAACTGCCTGGTGCTG
TGCGGCCCAGCCAATACCGGAAAGTCCTACTTCGGCATGTCCCTGAATTG
TCTCGTGATCTACGGCCCACCTAACACAGGCAAGTCCTGCTTTGCCATGT
CTCTGTGGCCCTACCTGCACAGCAGACTGGTGGTGTTTACCTTCCCCAAC
CCCTTCTGGCCTTACCTGGAAAGCCGGATCACCGTGTTCGAGTTCCCCAA
TGCCTTTCTGAGATACCTGCACTCCCGGATCCACGTGCTGCAGTTTCTGA
ACCCCTTCAACGTGTGCCAGGACAAGATCCTGGAACACTACGAGAACGAC
AGCAAGGACATTCTGGAACATTATGAGAATGATTCCAAGGACCTGTGCGA
CCACATCTGCGATCACATCGACTACTGGAAGCACATCCGGCTGGAATGCG
CCATCATGTACAAGGCCCGGATCAGACTGGAATGTGCTATTATGTATAAG
GCTCGCGAGATGGGCTTCCACCAGTTCGACGGCGACATCTGCAACACCAT
GCACTACACCAACTGGATCTATATCTGCGAGGACGCCCAGTGCACCGTGG
TGGAAGGCCAGGTGGACAAGAAATGGGAGGTGCACGCTGGCGGCCAAGTG
ATCCTGTGTCCTGAGAGCGGCCAGCGGCGGATCAAGAGGCCCAGAAGCGA
GAACTGCCACCCCAACAAGCTGCTGATCCTGAAGTGCCTGCGGTACAGAT
TCAAGAAGCACTGCAAGCTGAGCAGCACCTGGCACTGGACCTGCCACGAC
GGCAAGCACAAGTGGCATTGGACATGTCACGATGGGAAACACAAGAACGC
CATTGTGACCCTGACCTACTACGAGGCCGACAAGAACGACCTGAACGCCC
AGATCGAGCACTGGAAACTGATCCGGATGGAATGTGCAATCTTCTATAAG
GCCAAAGAGCTGGGCATCAGCATCTGCCACCAGGTGGTGCCTCCACTGGC
CGCCTCTAAAGCCAAAGCCTGCCAGGCCATCGAACTGCAGCTGGCCCTGG
AAGCCCTGAATGCCAGCCCCTACGATGAGTGGACCCTGCAGCAGACCAGC
CTGGAAATGTGGCTGGCCGAGCCCCAGTTTAAGAAGCACGGCATCACCAT
CACCGTGCAGTACGACAATGACAAGGCCAATACCATGGATTACACAAATT
GGAAAGAAATCTACGTGATCGTGTGCCCCGCCAGCATCCCCTCCGATGAG
ATCAGCACCGAGGAAGCCGACCACATTGATTATTGGAAAGCCATCAGGCA
GGAAAACGCCATCTTCTTCGCCGCCAGACACCAGGTGGTGCCCGCCCTGA
ATATCTGCAAGGCCAAGGCCTGTAAAGCCATCGAGTGGAACACCGAGCCC
AAGCACTGCTTCAAGAAGGGCGGCCAGCACATCGAAGTGTGGTTCGACTA
CGTGGCCTGGGACAGCGTGTACTACTGCGGCGACGATGGCTGGTGCAAGA
CCGAGGCCGAGAAGTACGGCTGCAAGGGCACCTGGGAAGTGCATTTCGGC

[0172]

AACAGCATCGACTGCAACGACTCCATGTGCAGCACCTTCGACGACAACGT
GTCCGCCACCGAGCTCGTGAAGGACCATATCGACTATTGGAAGCTGATTC
GCCTGGAATGTGCCATTTTTTACAAGGCCAGACGGCGGCTGTCCAGCGAC
CAGGATCAGTCTCAGCTCGTGACCAAGTACCCCCTGCTGAAGCTGCTGTC
CAGACCCCCCAACATGGGCGTGAAGGCCCACGGCAAGTGCATCTGGGAGA
ACAAGGTGTTCATCGTGCCCACCCTGTGCCCCGTGCCTCTGGATCCAACA
TATCCTCTGCTGAAACTGCTGACCACCCAGACCACCACCCCCGAGAATAC
CTCCCTGGTGGAACTGAGAGTGACCACCCCCAAGAGCACAGTCGTGATCA
GGCTGCACCTGACCACCAGATACCCACTGCTGTCACTGCTGAACAGCTAC
AGCACCCCCCCCTCACCGGATCCCTGCTCCATGTCCTTGGGCTCCTCAGAG
GCCCCCCATCCCTAAGCCTTCTCCATGGGCCCCTAGAATCCCTGCCCCTT
GCCCCTGGGCACCTCCTAGACCTCCACACTGTCCATGGGTGCCCCCTCCA
CCTCCTCCAAGACCTTGGGCCCCTTGCTTCCTGCTGTGCTTTTGTGTGCT
GCTGTGCGTGTGCCTGCTGATCAGACCCCTGCTGCTGAGTGTGTCCACCT
ACCTGAGGCCTCTGCTGCTGTCTATCAGCGTGTACGCTCAGGTGCTGGTG
CTGGTGCTGCTGCTGTGGGTGTCCATCGGAAGCCTGCTGCCCAGCGTGTG
CATGTGTGCCTATGCCTGGGTGCTGGTGTTCGTGTACATCGTCGTGATTA
CCAGCCCCGCCACCGCCATCGTGTACCGGGATGGCAATCCTTACGCCGTG
TGCGACAAGTGCCTGAAGTTCTACAGCAAGATCAGCGAGTACCGGCACTA
CTGCTACAGCCTGTACGGCACCACCCTGGAACAGCAGTACAACAAGCCCC
TGTGCGATCTGCTGATTCGGTGCATCAACGTGGTGTACAGAGACTCCATC
CCCCACGCCGCCTGCCACAAGTGTATCGACTTCTACTCCAGAATCAGAGA
GCTGCGGCACTACAGCGACTCCGTGTACGGCGATACCCTGGAAAAGCTGA
CCAACACTGGCCTGTACAACCTGCTGATTAGATGCCTGCGGGTGTTCTGC
AAGAAGGCCCTGACAGCCAGCGAGGTGTACAACTTCGCCTACACCGATCT
GCGGGTGGTGTATCGGGACAGCAAAGTGCGGAAGCTGAGGTACTACAACT
GCTCTGTGTATGGCGCCAGCCTGGTGTATTGCAAGGGACAGCTGACCGAG
ACAGAGGTGCTGGATTTCGCCTTCACAGACCTGACAATCGTGTATCGCGA
CTCCAAGGTGTCCGAGTTCCGGTGGTACAGATATTCCGTGTATGGCACCA
CACTGTGCGTGGAATGCAAGAAAACCCTGCAGAGATCTGAGGTGTACGAC
TGCCAGCGGCCACTGTGTCCGCAGGAAAAGAAAAGACACGTGGACCTGAA
CAAGCGGTTCCACACCCTGCACGAGTACATGCTGGATCTGCAGCCCGAGA
CAACCGACCTGTACTGCTACGAGCAGCCTGAAACCACTGATCTGCACTGT
TATGAGCAGCTGGGAGACAGCTCCGATGAAGAGGACACTGGCGGCCTGGA
TGGGGACGAGGATGAGGACGAAGTGGACCATCTGCAGGAACAGCCCCAGC
AGGCTAGACGGGACGAACAGCACCCTTGCTATCTGATCGAGACACAGTGC
TGCAGATGCGAATCTCTGGTGGAAGAGAACGACGAGATCGACGGCGTGAA
CCACCAGCATCTGCCCGCTAGAAGGGCCGAGCCTCAGAGACACACCATGC
TGTGTATGTGCTGCAAGTGCGAGGCCAGAATCGCCGGCTCTGGACCTGGC
GCCTCTGGCAAGCCTATCCCCAATCCACTGCTGGGCCTGGACTCCACCCG
GACCTGATAA

[0173] 펩타이드 보조제/TPA를 암호화하지 않는 HPV3 뉴클레오타이드 서열(서열 번호: 65)

GACGAGGACGAGACAGCCTACGACAGCGGCACCGACCTG
ATCGACTTCATCGACGACAGCGACGAGAATGAGAACGACTCCGACACCGG
CGAGGACATGGTGGATTTCATCGACAACGACGAAACCGACGAAGAGAGCA
CCGAGAGCGACCTGGACGGCTTTATCGACAACTCCGCCCAGCTGGCTGAC
AGCGACAGCAATGCCTGCGCCTTCCTGAAGGCTCAGCTGGCAGACGTGAA
CAGCAACGCCGCTGCTTTTCTGAAGAACTGCATCCTGCTGTACGGCGCTG
CCAACACCGGCAAGAGCCTGTTCGGCATGAGCCTGAACTGCCTGGTGCTG
TGCGGCCCAGCCAATACCGGAAAGTCCTACTTCGGCATGTCCCTGAATTG
TCTCGTGATCTACGGCCCACCTAACACAGGCAAGTCCTGCTTTGCCATGT
CTCTGTGGCCCTACCTGCACAGCAGACTGGTGGTGTTTACCTTCCCCAAC
CCCTTCTGGCCTTACCTGGAAAGCCGGATCACCGTGTTCGAGTTCCCCAA
TGCCTTTCTGAGATACCTGCACTCCCGGATCCACGTGCTGCAGTTTCTGA
ACCCCTTCAACGTGTGCCAGGACAAGATCCTGGAACACTACGAGAACGAC
AGCAAGGACATTCTGGAACATTATGAGAATGATTCCAAGGACCTGTGCGA
CCACATCTGCGATCACATCGACTACTGGAAGCACATCCGGCTGGAATGCG
CCATCATGTACAAGGCCCGGATCAGACTGGAATGTGCTATTATGTATAAG
GCTCGCGAGATGGGCTTCCACCAGTTCGACGGCGACATCTGCAACACCAT
GCACTACACCAACTGGATCTATATCTGCGAGGACGCCCAGTGCACCGTGG
TGGAAGGCCAGGTGGACAAGAAATGGGAGGTGCACGCTGGCGGCCAAGTG
ATCCTGTGTCCTGAGAGCGGCCAGCGGCGGATCAAGAGGCCCAGAAGCGA
GAACTGCCACCCCAACAAGCTGCTGATCCTGAAGTGCCTGCGGTACAGAT
TCAAGAAGCACTGCAAGCTGAGCAGCACCTGGCACTGGACCTGCCACGAC
GGCAAGCACAAGTGGCATTGGACATGTCACGATGGGAAACACAAGAACGC
CATTGTGACCCTGACCTACTACGAGGCCGACAAGAACGACCTGAACGCCC
AGATCGAGCACTGGAAACTGATCCGGATGGAATGTGCAATCTTCTATAAG
GCCAAAGAGCTGGGCATCAGCATCTGCCACCAGGTGGTGCCTCCACTGGC
CGCCTCTAAAGCCAAAGCCTGCCAGGCCATCGAACTGCAGCTGGCCCTGG
AAGCCCTGAATGCCAGCCCCTACGATGAGTGGACCCTGCAGCAGACCAGC
CTGGAAATGTGGCTGGCCGAGCCCCAGTTTAAGAAGCACGGCATCACCAT
CACCGTGCAGTACGACAATGACAAGGCCAATACCATGGATTACACAAATT
GGAAAGAAATCTACGTGATCGTGTGCCCCGCCAGCATCCCCTCCGATGAG
ATCAGCACCGAGGAAGCCGACCACATTGATTATTGGAAAGCCATCAGGCA
GGAAAACGCCATCTTCTTCGCCGCCAGACACCAGGTGGTGCCCGCCCTGA
ATATCTGCAAGGCCAAGGCCTGTAAAGCCATCGAGTGGAACACCGAGCCC
AAGCACTGCTTCAAGAAGGGCGGCCAGCACATCGAAGTGTGGTTCGACTA
CGTGGCCTGGGACAGCGTGTACTACTGCGGCGACGATGGCTGGTGCAAGA
CCGAGGCCGAGAAGTACGGCTGCAAGGGCACCTGGGAAGTGCATTTCGGC
AACAGCATCGACTGCAACGACTCCATGTGCAGCACCTTCGACGACAACGT
GTCCGCCACCGAGCTCGTGAAGGACCATATCGACTATTGGAAGCTGATTC
GCCTGGAATGTGCCATTTTTTACAAGGCCAGACGGCGGCTGTCCAGCGAC
CAGGATCAGTCTCAGCTCGTGACCAAGTACCCCCTGCTGAAGCTGCTGTC
CAGACCCCCCAACATGGGCGTGAAGGCCCACGGCAAGTGCATCTGGGAGA
ACAAGGTGTTCATCGTGCCCACCCTGTGCCCCGTGCCTCTGGATCCAACA

[0174]

TATCCTCTGCTGAAACTGCTGACCACCCAGACCACCACCCCCGAGAATAC
CTCCCTGGTGGAACTGAGAGTGACCACCCCCAAGAGCACAGTCGTGATCA
GGCTGCACCTGACCACCAGATACCCACTGCTGTCACTGCTGAACAGCTAC
AGCACCCCCCCTCACCGGATCCCTGCTCCATGTCCTTGGGCTCCTCAGAG
GCCCCCCATCCCTAAGCCTTCTCCATGGGCCCCTAGAATCCCTGCCCCTT
GCCCCTGGGCACCTCCTAGACCTCCACACTGTCCATGGGTGCCCCCTCCA
CCTCCTCCAAGACCTTGGGCCCCTTGCTTCCTGCTGTGCTTTTGTGTGCT
GCTGTGCGTGTGCCTGCTGATCAGACCCCTGCTGCTGAGTGTGTCCACCT
ACCTGAGGCCTCTGCTGCTGTCTATCAGCGTGTACGCTCAGGTGCTGGTG
CTGGTGCTGCTGCTGTGGGTGTCCATCGGAAGCCTGCTGCCCAGCGTGTG
CATGTGTGCCTATGCCTGGGTGCTGGTGTTCGTGTACATCGTCGTGATTA
CCAGCCCCGCCACCGCCATCGTGTACCGGGATGGCAATCCTTACGCCGTG
TGCGACAAGTGCCTGAAGTTCTACAGCAAGATCAGCGAGTACCGGCACTA
CTGCTACAGCCTGTACGGCACCACCCTGGAACAGCAGTACAACAAGCCCC
TGTGCGATCTGCTGATTCGGTGCATCAACGTGGTGTACAGAGACTCCATC
CCCCACGCCGCCTGCCACAAGTGTATCGACTTCTACTCCAGAATCAGAGA
GCTGCGGCACTACAGCGACTCCGTGTACGGCGATACCCTGGAAAAGCTGA
CCAACACTGGCCTGTACAACCTGCTGATTAGATGCCTGCGGGTGTTCTGC
AAGAAGGCCCTGACAGCCAGCGAGGTGTACAACTTCGCCTACACCGATCT
GCGGGTGGTGTATCGGGACAGCAAAGTGCGGAAGCTGAGGTACTACAACT
GCTCTGTGTATGGCGCCAGCCTGGTGTATTGCAAGGGACAGCTGACCGAG
ACAGAGGTGCTGGATTTCGCCTTCACAGACCTGACAATCGTGTATCGCGA
CTCCAAGGTGTCCGAGTTCCGGTGGTACAGATATTCCGTGTATGGCACCA
CACTGTGCGTGGAATGCAAGAAAACCCTGCAGAGATCTGAGGTGTACGAC
TGCCAGCGGCCACTGTGTCCGCAGGAAAAGAAAAGACACGTGGACCTGAA
CAAGCGGTTCCACACCCTGCACGAGTACATGCTGGATCTGCAGCCCGAGA
CAACCGACCTGTACTGCTACGAGCAGCCTGAAACCACTGATCTGCACTGT
TATGAGCAGCTGGGAGACAGCTCCGATGAAGAGGACACTGGCGGCCTGGA
TGGGGACGAGGATGAGGACGAAGTGGACCATCTGCAGGAACAGCCCCAGC
AGGCTAGACGGGACGAACAGCACCCTTGCTATCTGATCGAGACACAGTGC
TGCAGATGCGAATCTCTGGTGGAAGAGAACGACGAGATCGACGGCGTGAA
CCACCAGCATCTGCCCGCTAGAAGGGCCGAGCCTCAGAGACACACCATGC
TGTGTATGTGCTGCAAGTGCGAGGCCAGAATCGCCGGCTCTGGACCTGGC
GCCTCTGGCAAGCCTATCCCCAATCCACTGCTGGGCCTGGACTCCACCCG
GACCTGATAA

[0175]

[0176] **HPV3 폴리펩타이드 서열(서열 번호: 61)**

[0177] 출발 코돈으로부터 시작하여, TPA 리딩 서열로 출발함.

MDAMKRGLCCVLLLCGAVFVSPSQEIHARFRRGSKLADEDETAYDSGTDL
IDFIDDSDENENDSDTGEDMVDFIDNDETDEESTESDLDGFIDNSAQLAD
SDSNACAFLKAQLADVNSNAAAFLKNCILLYGAANTGKSLFGMSLNCLVL
CGPANTGKSYFGMSLNCLVIYGPPNTGKSCFAMSLWPYLHSRLVVFTFPN
PFWPYLESRITVFEFPNAFLRYLHSRIHVLQFLNPFNVCQDKILEHYEND
SKDILEHYENDSKDLCDHICDHIDYWKHIRLECAIMYKARIRLECAIMYK
AREMGFHQFDGDICNTMHYTNWIYICEDAQCTVVEGQVDKKWEVHAGGQV
ILCPESGQRRIKRPRSENCHPNKLLILKCLRYRFKKHCKLSSTWHWTCHD
GKHKWHWTCHDGKHKNAIVTLTYYEADKNDLNAQIEHWKLIRMECAIFYK
AKELGISICHQVVPPLAASKAKACQAIELQLALEALNASPYDEWTLQQTS
LEMWLAEPQFKKHGITITVQYDNDKANTMDYTNWKEIYVIVCPASIPSDE
ISTEEADHIDYWKAIRQENAIFFAARHQVVPALNICKAKACKAIEWNTEP
KHCFKKGGQHIEVWFDYVAWDSVYYCGDDGWCKTEAEKYGCKGTWEVHFG
NSIDCNDSMCSTFDDNVSATELVKDHIDYWKLIRLECAIFYKARRRLSSD
QDQSQLVTKYPLLKLLSRPPNMGVKAHGKCIWENKVFIVPTLCPVPLDPT
YPLLKLLTTQTTTPENTSLVELRVTTPKSTVVIRLHLTTRYPLLSLLNSY
STPPHRIPAPCPWAPQRPPIPKPSPWAPRIPAPCPWAPPRPPHCPWVPPP
PPPRPWAPCFLLCFCVLLCVCLLIRPLLLSVSTYLRPLLLSISVYAQVLV
LVLLLWVSIGSLLPSVCMCAYAWVLVFVYIVVITSPATAIVYRDGNPYAV
CDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCINVVYRDSI
PHAACHKCIDFYSRIRELRHYSDSVYGDTLEKLTNTGLYNLLIRCLRVFC
KKALTASEVYNFAYTDLRVVYRDSKVRKLRYYNCSVYGASLVYCKGQLTE
TEVLDFAFTDLTIVYRDSKVSEFRWYRYSVYGTTLCVECKKTLQRSEVYD
CQRPLCPQEKKRHVDLNKRFHTLHEYMLDLQPETTDLYCYEQPETTDLHC
YEQLGDSSDEEDTGGLDGDEDEDEVDHLQEQPQQARRDEQHPCYLIETQC
CRCESLVEENDEIDGVNHQHLPARRAEPQRHTMLCMCCKCEARIAGSGPG
ASGKPIPNPLLGLDSTRT**

[0178]

[0179] **TPA/펩타이드 보조제 서열이 없는 HPV3 폴리펩타이드 서열(서열 번호: 66)**

DEDETAYDSGTDL
IDFIDDSDENENDSDTGEDMVDFIDNDETDEESTESDLDGFIDNSAQLAD
SDSNACAFLKAQLADVNSNAAAFLKNCILLYGAANTGKSLFGMSLNCLVL
CGPANTGKSYFGMSLNCLVIYGPPNTGKSCFAMSLWPYLHSRLVVFTFPN
PFWPYLESRITVFEFPNAFLRYLHSRIHVLQFLNPFNVCQDKILEHYEND
SKDILEHYENDSKDLCDHICDHIDYWKHIRLECAIMYKARIRLECAIMYK
AREMGFHQFDGDICNTMHYTNWIYICEDAQCTVVEGQVDKKWEVHAGGQV
ILCPESGQRRIKRPRSENCHPNKLLILKCLRYRFKKHCKLSSTWHWTCHD
GKHKWHWTCHDGKHKNAIVTLTYYEADKNDLNAQIEHWKLIRMECAIFYK
AKELGISICHQVVPPLAASKAKACQAIELQLALEALNASPYDEWTLQQTS
LEMWLAEPQFKKHGITITVQYDNDKANTMDYTNWKEIYVIVCPASIPSDE
ISTEEADHIDYWKAIRQENAIFFAARHQVVPALNICKAKACKAIEWNTEP
KHCFKKGGQHIEVWFDYVAWDSVYYCGDDGWCKTEAEKYGCKGTWEVHFG
NSIDCNDSMCSTFDDNVSATELVKDHIDYWKLIRLECAIFYKARRRLSSD
QDQSQLVTKYPLLKLLSRPPNMGVKAHGKCIWENKVFIVPTLCPVPLDPT
YPLLKLLTTQTTTPENTSLVELRVTTPKSTVVIRLHLTTRYPLLSLLNSY
STPPHRIPAPCPWAPQRPPIPKPSPWAPRIPAPCPWAPPRPPHCPWVPPP
PPPRPWAPCFLLCFCVLLCVCLLIRPLLLSVSTYLRPLLLSISVYAQVLV
LVLLLWVSIGSLLPSVCMCAYAWVLVFVYIVVITSPATAIVYRDGNPYAV
CDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCINVVYRDSI
PHAACHKCIDFYSRIRELRHYSDSVYGDTLEKLTNTGLYNLLIRCLRVFC
KKALTASEVYNFAYTDLRVVYRDSKVRKLRYYNCSVYGASLVYCKGQLTE
TEVLDFAFTDLTIVYRDSKVSEFRWYRYSVYGTTLCVECKKTLQRSEVYD
CQRPLCPQEKKRHVDLNKRFHTLHEYMLDLQPETTDLYCYEQPETTDLHC
YEQLGDSSDEEDTGGLDGDEDEDEVDHLQEQPQQARRDEQHPCYLIETQC
CRCESLVEENDEIDGVNHQHLPARRAEPQRHTMLCMCCKCEARIAGSGPG
ASGKPIPNPLLGLDSTRT**

[0180]

[0181] **면역원 암호화 서열 삽입체를 지닌 바이러스 벡터 서열 ChAdOx1**

[0182] 면역원 암호화 서열 삽입체의 출발 및 종결 코돈이 밑줄쳐져 있다. 리드 TPA 서열 및 링커는 굵은 글씨체이다.

[0183] **(서열 번호: 62)**

GTTTAAACGCGGCCGCCAGGCCTACCCACTAGTCAATTCGGGAGGATCGAAACGGCAGATCGCAA
AAAACAGTACATACAGAAGGAGACATGAACATGAACATCAAAAAAATTGTAAAACAAGCCACAGT
TCTGACTTTTACGACTGCACTTCTGGCAGGAGGAGCGACTCAAGCCTTCGCGAAAGAAAATAACC
AAAAAGCATACAAAGAAACGTACGGCGTCTCTCATATTACACGCCATGATATGCTGCAGATCCCT
AAACAGCAGCAAAACGaAAAATACCAAGTGCCTCAATTCGATCAATCAACGATTAAAAATATTGA
GTCTGCAAAAGGACTTGATGTGTGGGACAGCTGGCCGCTGCAAAACGCTGACGGAACAGTAGCTG
AATACAACGGCTATCACGTTGTGTTTGCTCTTGCGGGAAGCCCGAAAGACGCTGATGACACATCA
ATCTACATGTTTTATCAAAAGGTCGGCGACAACTCAATCGACAGCTGGAAAAACGCGGGCCGTGT
CTTTAAAGACAGCGATAAGTTCGACGCCAACGATCCGATCCTGAAAGATCAGACGCAAGAATGGT
CCGGTTCTGCAACCTTTACATCTGACGGAAAAATCCGTTTATTCTACACTGACTATTCCGGTAAA
CATTACGGCAAACAAAGCCTGACAACAGCGCAGGTAAATGTGTCAAAATCTGATGACACACTCAA
AATCAACGGAGTGGAAGATCACAAAACGATTTTTGACGGAGACGGAAAAACATATCAGAACGTTC
AGCAGTTTATCGATGAAGGCAATTATACATCCGGCGACAACCATACGCTGAGAGACCCTCACTAC
GTTGAAGACAAAGGCCATAAATACCTTGTATTCGAAGCCAACACGGGAACAGAAAACGGATACCA
AGGCGAAGAATCTTTATTTAACAAAGCGTACTACGGCGGCGGCACGAACTTCTTCCGTAAAGAAA
GCCAGAAGCTTCAGCAGAGCGCTAAAAAACGCGATGCTGAGTTAGCGAACGGCGCCCTCGGTATC
ATAGAGTTAAATAATGATTACACATTGAAAAAAGTAATGAAGCCGCTGATCACTTCAAACACGGT
AACTGATGAAATCGAGCGCGCGAATGTTTTCAAAATGAACGGCAAATGGTACTTGTTCACTGATT
CACGCGGTTCAAAAATGACGATCGATGGTATTAACTCAAACGATATTTACATGCTTGGTTATGTA
TCAAACTCTTTAACCGGCCCTTACAAGCCGCTGAACAAAACAGGGCTTGTGCTGCAAATGGGTCT
TGATCCAAACGATGTGACATTCACTTACTCTCACTTCGCAGTGCCGCAAGCCAAAGGCAACAATG
TGGTTATCACAAGCTACATGACAAACAGAGGCTTCTTCGAGGATAAAAAGGCAACATTTGCGCCA

[0184]

AGCTTCTTAATGAACATCAAAGGCAATAAAACATCCGTTGTCAAAAACAGCATCCTGGAGCAAGG
ACAGCTGACAGTCAACTAATAACAGCAAAAAGaAAATGCCGATACTTCATTGGCATTTTCTTtTA
TTTCTCAACAAGATGGTGAATTGACTAGTGGGTAGATCCACAGGACGGGTGTGGTCGCCATGATC
GCGTAGTCGATAGTGGCTCCAAGTAGCGAAGCGAGCAGGACTGGGCGGCGGCCAAAGCGGTCGGA
CAGTGCTCCGAGAACGGGTGCGCATAGAAATTGCATCAACGCATATAGCGCTAGCAGCACGCCAT
AGTGACTGGCGATGCTGTCGGAATGGACGATATCCCGCAAGAGGCCCGGCAGTACCGGCATAACC
AAGCCTATGCCTACAGCATCCAGGGTGACGGTGCCGAGGATGACGATGAGCGCATTGTTAGATTT
CATACACGGTGCCTGACTGCGTTAGCAATTTAACTGTGATAAACTACCGCATTAAAGCTTATCGA
TGATAAGCTGTCAAACATGAGAATTGATCCGGAACCCTTAATATAACTTCGTATAATGTATGCTA
TACGAAGTTATTAGGTCCCTCGACTATAGGGTCACCGTCGACAGCGACACACTTGCATCGGATGC
AGCCCGGTTAACGTGCCGGCACGGCCTGGGTAACCAGGTATTTTGTCCACATAACCGTGCGCAAA
ATGTTGTGGATAAGCAGGACACAGCAGCAATCCACAGCAGGCATACAACCGCACACCGAGGTTAC
TCCGTTCTACAGGTTACGACGACATGTCAATACTTGCCCTTGACAGGCATTGATGGAATCGTAGT
CTCACGCTGATAGTCTGATCGACAATACAAGTGGGACCGTGGTCCCAGACCGATAATCAGACCGA
CRAYACGAGTGGGAYCGTGGTCCCAGACTAATAATCAGACCGACGATACGAGTGGGACCGTGGTC
CCAGACTAATAATCAGACCGACGATACGAGTGGGACCGTGGTYCCAGWCTRATWATCAGACCGAC
GATACRAGTGGRACMGTGGKCCCAGASAKAATAWTCAGRCCgAGWTAYGcWKTCKGGCCTGTAAC
AAAGGACATTAAGTAAAGACAGATAMRMGTgRGACtaaaaCGTGGTCCCAGTCTGATTATCAGAC
CGACGATACGAGTGGGACCGTGGTCCCAGACTAATAATCAGACCGACGATACGAGTGGGACCGTG
GTCCCAGACTAATAATCAGACCGACGATACGAGTGGGACCGTGGTCCCAGTCTGATTATCAGACC
GACGATACAAGTGGAACAGTGGGCCCAGAGAGAATATTCAGGCCAGTTATGCTTTCTGGCCTGTA
ACAAAGGACATTAAGTAAAGACAGATAAACGTAGACTAAAACGTGGTCGCATCAGGGTGCTGGCT
TTTCAAGTTCCTTAAGAATGGCCTCAATTTTCTCTATACACTCAGTTGGAACACGAGACCTGTCC
AGGTTAAGCACCATTTTATCGCCCTTATACAATACTGTCGCTCCAGGAGCAAACTGATGTCGTGA
GCTTAAACTAGTTCTTGATGCAGATGACGTTTTAAGCACAGAAGTTAAAAGAGTGATAACTTCTT
CAGCTTCAAATATCACCCCAGCTTTTTTCTGCTCATGAAGGTTAGATGCCTGCTGCTTAAGTAAT
TCCTCTTTATCTGTAAAGGCTTTTTGAAGTGCATCACCTGACCGGGCAGATAGTTCACCGGGGTG
AGAAAAAAGAGCAACAACTGATTTAGGCAATTTGGCGGTGTTGATACAGCGGGTAATAATCTTAC
GTGAAATATTTTCCGCATCAGCCAGCGCAGAAATATTTCCAGCAAATTCATTCTGCAATCGGCTT
GCATAACGCTGACCACGTTCATAAGCACTTGTTGGGCGATAATCGTTACCCAATCTGGATAATGC
AGCCATCTGCTCATCATCCAGCTCGCCAACCAGAACACGATAATCACTTTCGGTAAGTGCAGCAG
CTTTACGACGGCGACTCCCATCGGCAATTTCTATGACACCAGATACTCTTCGACCGAACGCCGGT
GTCTGTTGACCAGTCAGTAGAAAAGAAGGGATGAGATCATCCAGTGCGTCCTCAGTAAGCAGCTC
CTGGTCACGTTCATTACCTGACCATACCCGAGAGGTCTTCTCAACACTATCACCCCGGAGCACTT
CAAGAGTAAACTTCACATCCCGACCACATACAGGCAAAGTAATGGCATTACCGCGAGCCATTACT
CCTACGCGCGCAATTAACGAATCCACCATCGGGGCAGCTGGTGTCGATAACGAAGTATCTTCAAC
CGGTTGAGTATTGAGCGTATGTTTTGGAATAACAGGCGCACGCTTCATTATCTAATCTCCCAGCG
TGGTTTAATCAGACGATCGAAAATTTCATTGCAGACAGGTTCCCAAATAGAAAGAGCATTTCTCC

[0185] AGGCACCAGTTGAAGAGCGTTGATCAATGGCCTGTTCAAAAACAGTTCTCATCCGGATCTGACCT

TTACCAACTTCATCCGTTTCACGTACAACATTTTTTAGAACCATGCTTCCCCAGGCATCCCGAAT
TTGCTCCTCCATCCACGGGGACTGAGAGCCATTACTATTGCTGTATTTGGTAAGCAAAATACGTA
CATCAGGCTCGAACCCTTTAAGATCAACGTTCTTGAGCAGATCACGAAGCATATCGAAAAACTGC
AGTGCGGAGGTGTAGTCAAACAACTCAGCAGGCGTGGGAACAATCAGCACATCAGCAGCACATAC
GACATTAATCGTGCCGATACCCAGGTTAGGCGCGCTGTCAATAACTATGACATCATAGTCATGAG
CAACAGTTTCAATGGCCAGTCGGAGCATCAGGTGTGGATCGGTGGGCAGTTTACCTTCATCAAAT
TTGCCCATTAACTCAGTTTCAATACGGTGCAGAGCCAGACAGGAAGGAATAATGTCAAGCCCCGG
CCAGCAAGTGGGCTTTATTGCATAAGTGACATCGTCCTTTTCCCCAAGATAGAAAGGCAGGAGAG
TGTCTTCTGCATGAATATGAAGATCTGGTACCCATCCGTGATACATTGAGGCTGTTCCCTGGGGG
TCGTTACCTTCCACGAGCAAAACACGTAGCCCCTTCAGAGCCAGATCCTGAGCAAGATGAACAGA
AACTGAGGTTTTGTAAACGCCACCTTTATGGGCAGCAACCCCGATCACCGGTGGAAATACGTCTT
CAGCACGTCGCAATCGCGTACCAAACACATCACGCATATGATTAATTTGTTCAATTGTATAACCA
ACACGTTGCTCAACCCGTCCTCGAATTTCCATATCCGGGTGCGGTAGTCGCCCTGCTTTCTCGGC
ATCTCTGATAGCCTGAGAAGAAACCCCAACTAAATCCGCTGCTTCACCTATTCTCCAGCGCCGGG
TTATTTTCCTCGCTTCCGGGCTGTCATCATTAAACTGTGCAATGGCGATAGCCTTCGTCATTTCA
TGACCAGCGTTTATGCACTGGTTAAGTGTTTCCATGAGTTTCATTCTGAACATCCTTTAATCATT
GCTTTGCGTTTTTTTATTAAATCTTGCAATTTACTGCAAAGCAACAACAAAATCGCAAAGTCATC
AAAAAACCGCAAAGTTGTTTAAAATAAGAGCAACACTACAAAAGGAGATAAGAAGAGCACATACC
TCAGTCACTTATTATCACTAGCGCTCGCCGCAGCCGTGTAACCGAGCATAGCGAGCGAACTGGCG
AGGAAGCAAAGAAGAACTGTTCTGTCAGATAGCTCTTACGCTCAGCGCAAGAAGAAATATCCACC
GTGGGAAAAACTCCAGGTAGAGGTACACACGCGGATAGCCAATTCAGAGTAATAAACTGTGATAA
TCAACCCTCATCAATGATGACGAACTAACCCCCGATATCAGGTCACATGACGAAGGGAAAGAGAA
GGAAATCAACTGTGACAAACTGCCCTCAAATTTGGCTTCCTTAAAAATTACAGTTCAAAAAGTAT
GAGAAAATCCATGCAGGCTGAAGGAAACAGCAAAACTGTGACAAATTACCCTCAGTAGGTCAGAA
CAAATGTGACGAACCACCCTCAAATCTGTGACAGATAACCCTCAGACTATCCTGTCGTCATGGAA
GTGATATCGCGGAAGGAAAATACGATATGAGTCGTCTGGCGGCCTTTCTTTTTCTCAATGTATGA
GAGGCGCATTGGAGTTCTGCTGTTGATCTCATTAACACAGACCTGCAGGAAGCGGCGGCGGAAGT
CAGGCATACGCTGGTAACTTTGAGGCAGCTGGTAACGCTCTATGATCCAGTCGATTTTCAGAGAG
ACGATGCCTGAGCCATCCGGCTTACGATACTGACACAGGGATTCGTATAAACGCATGGCATACGG
ATTGGTGATTTCTTTTGTTTCACTAAGCCGAAACTGCGTAAACCGGTTCTGTAACCCGATAAAGA
AGGGAATGAGATATGGGTTGATATGTACACTGTAAAGCCCTCTGGATGGACTGTGCGCACGTTTG
ATAAACCAAGGAAAAGATTCATAGCCTTTTTCATCGCCGGCATCCTCTTCAGGGCGATaAAAAAC
CACTTCCTTCCCCGCGAAACTCTTCAATGCCTGCCGTATATCCTTACTGGCTTCCGCAGAGGTCA
ATCCGAATATTTCAGCATATTTAGCAACATGGATCTCGCAGATACCGTCATGTTCCTGTAGGGTG
CCATCAGATTTTCTGATCTGGTCAACGAACAGATACAGCATACGTTTTTGATCCCGGGAGAGACT
ATATGCCGCCTCAGTGAGGTCGTTTGACTGGACGATTCGCGGGCTATTTTTACGTTTCTTGTGAT
TGATAACCGCTGTTTCCGCCATGACAGATCCATGTGAAGTGTGACAAGTTTTTAGATTGTCACAC
TAAATAAAAAAGAGTCAATAAGCAGGGATAACTTTGTGAAAAAACAGCTTCTTCTGAGGGCAATT
[0186] TGTCACAGGGTTAAGGGCAATTTGTCACAGACAGGACTGTCATTTGAGGGTGATTTGTCACACTG

AAAGGGCAATTTGTCACAACACCTTCTCTAGAACCAGCATGGATAAAGGCCTACAAGGCGCTCTA
AAAAAGAAGATCTAAAAACTATaAAAAAAATAATTATAAAAATATCCCCGTGGATAAGTGGATAA
CCCCAAGGGAAGTTTTTtCAGGCATCGTGTGTAAGCAGAATATATAAGTGCTGTTCCCTGGTGCT
TCCTCGCTCACTCGAGGGCTTCGCCCTGTCGCTCAACTGCGGCGAGCACTACTGGCTGTAAAAGG
ACAGACCACATCATGGTTCTGTGTTCATTAGGTTGTTCTGTCCATTGCTGACATAATCCGCTCCA
CTTCAACGTAACACCGCACGAAGATTTCTATTGTTCCTGAAGGCATATTCAAATCGTTTTCGTTA
CCGCTTGCAGGCATCATGACAGAACACTACTTCCTATAAACGCTACACAGGCTCCTGAGATTAAT
AATGCGGATCTCTACGATAATGGGAGATTTTCCCGACTGTTTCGTTCGCTTCTCAGTGGATAACA
GCCAGCTTCTCTGTTTAACAGACAAAAACAGCATATCCACTCAGTTCCACATTTCCATATAAAGG
CCAAGGCATTTATTCTCAGGATAATTGTTTCAGCATCGCAACCGCATCAGACTCCGGCATCGCAA
ACTGCACCCGGTGCCGGGCAGCCACATCCAGCGCAAAAACCTTCGTGTAGACTTCCGTTGAACTG
ATGGACTTATGTCCCATCAGGCTTTGCAGAACTTTCAGCGGTATACCGGCATACAGCATGTGCAT
CGCATAGGAATGGCGGAACGTATGTGGTGTGACCGGAACAGAGAACGTCACACCGTCAGCAGCAG
CGGCGGCAACCGCCTCCCCAATCCAGGTCCTGACCGTTCTGTCCGTCACTTCCCAGATCCGCGCT
TTCTCTGTCCTTCCTGTGCGACGGTTACGCCGCTCCATGAGCTTATCGCGAATAAATACCTGTGA
CGGAAGATCACTTCGCAGAATAAATAAATCCTGGTGTCCCTGTTGATACCGGGAAGCCCTGGGCC
AACTTTTGGCGAAAATGAGACGTTGATCGGCACGTAAGAGGTTCCAACTTTCACCATAATGAAAT
AAGATCACTACCGGGCGTATTTTTTGAGTTATCGAGATTTTCAGGAGCTAAGGAAGCTAAAATGG
AGAAAAAAATCACTGGATATACCACCGTTGATATATCCCAATGGCATCGTAAAGAACATTTTGAG
GCATTTCAGTCAGTTGCTCAATGTACCTATAACCAGACCGTTCAGCTGGATATTACGGCCTTTTT
AAAGACCGTAAAGAAAAATAAGCACAAGTTTTATCCGGCCTTTATTCACATTCTTGCCCGCCTGA
TGAATGCTCATCCGGAGTTCCGTATGGCAATGAAAGACGGTGAGCTGGTGATATGGGATAGTGTT
CACCCTTGTTACACCGTTTTCCATGAGCAAACTGAAACGTTTTCATCGCTCTGGAGTGAATACCA
CGACGATTTCCGGCAGTTTCTACACATATATTCGCAAGATGTGGCGTGTTACGGTGAAAACCTGG
CCTATTTCCCTAAAGGGTTTATTGAGAATATGTTTTTCGTCTCAGCCAATCCCTGGGTGAGTTTC
ACCAGTTTTGATTTAAACGTGGCCAATATGGACAACTTCTTCGCCCCCGTTTTCACCATGGGCAA
ATATTATACGCAAGGCGACAAGGTGCTGATGCCGCTGGCGATTCAGGTTCATCATGCCGTTTGTG
ATGGCTTCCATGTCGGCAGAATGCTTAATGAATTACAACAGTACTGCGATGAGTGGCAGGGCGGG
GCGTAAtTTTTTTAAGGCAGTTATTGGTGCCCTTAAACGCCTGGTTGCTACGCCTGAATAAGTGA
TAATAAGCGGATGAATGGCAGAAATTCGATGATAAGCTGTCAAACATGAGAATTGGTCGACGGCG
CGCCAAAGCTTGCATGCCTGCAGCCGCGTAACCTGGCAAAATCGGTTACGGTTGAGTAATAAATG
GATGCCCTGCGTAAGCGGGGCACATTTCATTACCTCTTTCTCCGCACCCGACATAGATAATAACT
TCGTATAGTATACATTATACGAAGTTATCTAGTAGACTTAATCGCGTTTAAACCCATCATCAATA
ATATACCTCAAACTTTTTGTGCGCGTTAATATGCAAATGAGGCGTTTGAATTTGGGAAGGGAGGA
AGGTGATTGGCCGAGAGAAGGGCGACCGTTAGGGGCGGGGCGAGTGACGTTTTGATGACGTGACC
GCGAGGAGGAGCCAGTTTGCAAGTTCTCGTGGGAAAAGTGACGTCAAACGAGGTGTGGTTTGAAC
ACGGAAATACTCAATTTTCCCGCGCTCTCTGACAGGAAATGAGGTGTTTCTAGGCGGATGCAAGT
GAAAACGGGCCATTTTCGCGCGAAAACTGAATGAGGAAGTGAAAATCTGAGTAATTTCGCGTTTA
[0187] TGACAGGGAGGAGTATTTGCCGAGGGCCGAGTAGACTTTGACCGATTACGTGGGGGTTTCGATTA

CCGTGTTTTTCACCTAAATTTCCGCGTACGGTGTCAAAGTCCGGTGTTTTTACGTAGGTGTCAGC
TGATCGCCAGGGTATTTAAACCTGCGCTCTCCAGTCAAGAGGCCACTCTTGAGTGCCAGCGAGAA
GAGTTTTCTCCTCCGCGCGCGAGTCAGATCTACACTTTGAAAGGCGATCGCTAGCGACATCGATC
ACAAGTTTGTACAAAAAAGCAGGCTCCACCATGGGAACCAATTCAgTCGAGCCTTTCACTCATTA
GATGCATGTCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCC
CATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAA
TGGGTGGAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTAC
GCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTAT
GGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTT
TGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCAT
TGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAACAACT
CCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCTC
CCTATCAGTGATAGAGATCTCCCTATCAGTGATAGAGATCGTCGACGAGCTCGTTTAGTGAACCG
TCAGATCGCCTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCA
GCCTCCGGTTAAGCTcGgtacCGCTAGCCGCGCCGCCACC**ATGGATGCTATGAAGAGGGGCCTGT**
GCTGCGTGCTGCTGCTGTGTGGCGCCGTGTTTGTGTCCCCCAGCCAGGAAATCCACGCCCGGTTC
AGAAGAGGCAGCAAGCTGGCCGACGAGGACGAGACAGCCTACGACAGCGGCACCGACCTGATCGA
CTTCATCGACGACAGCGACGAGAATGAGAACGACTCCGACACCGGCGAGGACATGGTGGATTTCA
TCGACAACGACGAAACCGACGAAGAGAGCACCGAGAGCGACCTGGACGGCTTTATCGACAACTCC
GCCCAGCTGGCTGACAGCGACAGCAATGCCTGCGCCTTCCTGAAGGCTCAGCTGGCAGACGTGAA
CAGCAACGCCGCTGCTTTTCTGAAGAACTGCATCCTGCTGTACGGCGCTGCCAACACCGGCAAGA
GCCTGTTCGGCATGAGCCTGAACTGCCTGGTGCTGTGCGGCCCAGCCAATACCGGAAAGTCCTAC
TTCGGCATGTCCCTGAATTGTCTCGTGATCTACGGCCCACCTAACACAGGCAAGTCCTGCTTTGC
CATGTCTCTGTGGCCCTACCTGCACAGCAGACTGGTGGTGTTTACCTTCCCCAACCCCTTCTGGC
CTTACCTGGAAAGCCGGATCACCGTGTTCGAGTTCCCCAATGCCTTTCTGAGATACCTGCACTCC
CGGATCCACGTGCTGCAGTTTCTGAACCCCTTCAACGTGTGCCAGGACAAGATCCTGGAACACTA
CGAGAACGACAGCAAGGACATTCTGGAACATTATGAGAATGATTCCAAGGACCTGTGCGACCACA
TCTGCGATCACATCGACTACTGGAAGCACATCCGGCTGGAATGCGCCATCATGTACAAGGCCCGG
ATCAGACTGGAATGTGCTATTATGTATAAGGCTCGCGAGATGGGCTTCCACCAGTTCGACGGCGA
CATCTGCAACACCATGCACTACACCAACTGGATCTATATCTGCGAGGACGCCCAGTGCACCGTGG
TGGAAGGCCAGGTGGACAAGAAATGGGAGGTGCACGCTGGCGGCCAAGTGATCCTGTGTCCTGAG
AGCGGCCAGCGGCGGATCAAGAGGCCCAGAAGCGAGAACTGCCACCCCAACAAGCTGCTGATCCT
GAAGTGCCTGCGGTACAGATTCAAGAAGCACTGCAAGCTGAGCAGCACCTGGCACTGGACCTGCC
ACGACGGCAAGCACAAGTGGCATTGGACATGTCACGATGGGAAACACAAGAACGCCATTGTGACC
CTGACCTACTACGAGGCCGACAAGAACGACCTGAACGCCCAGATCGAGCACTGGAAACTGATCCG
GATGGAATGTGCAATCTTCTATAAGGCCAAAGAGCTGGGCATCAGCATCTGCCACCAGGTGGTGC
CTCCACTGGCCGCCTCTAAAGCCAAAGCCTGCCAGGCCATCGAACTGCAGCTGGCCCTGGAAGCC
CTGAATGCCAGCCCCTACGATGAGTGGACCCTGCAGCAGACCAGCCTGGAAATGTGGCTGGCCGA
[0188] GCCCCAGTTTAAGAAGCACGGCATCACCATCACCGTGCAGTACGACAATGACAAGGCCAATACCA

TGGATTACACAAATTGGAAAGAAATCTACGTGATCGTGTGCCCCGCCAGCATCCCCTCCGATGAG
ATCAGCACCGAGGAAGCCGACCACATTGATTATTGGAAAGCCATCAGGCAGGAAAACGCCATCTT
CTTCGCCGCCAGACACCAGGTGGTGCCCGCCCTGAATATCTGCAAGGCCAAGGCCTGTAAAGCCA
TCGAGTGGAACACCGAGCCCAAGCACTGCTTCAAGAAGGGCGGCCAGCACATCGAAGTGTGGTTC
GACTACGTGGCCTGGGACAGCGTGTACTACTGCGGCGACGATGGCTGGTGCAAGACCGAGGCCGA
GAAGTACGGCTGCAAGGGCACCTGGGAAGTGCATTTCGGCAACAGCATCGACTGCAACGACTCCA
TGTGCAGCACCTTCGACGACAACGTGTCCGCCACCGAGCTCGTGAAGGACCATATCGACTATTGG
AAGCTGATTCGCCTGGAATGTGCCATTTTTTACAAGGCCAGACGGCGGCTGTCCAGCGACCAGGA
TCAGTCTCAGCTCGTGACCAAGTACCCCCTGCTGAAGCTGCTGTCCAGACCCCCCAACATGGGCG
TGAAGGCCCACGGCAAGTGCATCTGGGAGAACAAGGTGTTCATCGTGCCCACCCTGTGCCCCGTG
CCTCTGGATCCAACATATCCTCTGCTGAAACTGCTGACCACCCAGACCACCACCCCCGAGAATAC
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[0195]

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[0200]

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TATTTGAATGATG

[0201]

[0202] **ChAdOx2 서열(서열 번호: 67+68)**

[0203] 면역원 카세트에 대한 ChAdOx2 서열 5'는 서열 번호: 67로서 제공되며 면역원 카세트에 대한 ChAdOx2 서열 3'는

서열 번호: 68로서 제공된다.

[0204] **MVA 서열(서열 번호: 69 + 70)**

[0205] 면역원 카세트에 대한 MVA 서열 5'는 서열 번호: 69로서 제공되고 면역원 카세트에 대한 MVA 서열 3'는 서열 번호: 70으로 제공된다.

[0206] MVA 백신은 2개의 상이한 셔틀 플라스미드(shuttle plasmid)를 사용하여 제조하였다:

[0207] 1. P7.5 셔틀 플라스미드. 모 MVA 바이러스내 TK 유전자자리의 영역에 대해 상동성인 상류 및 하류 플랭크(upstream and downstream flank)를 지닌 HPV 삽입체. p7.5 프로모터의 제어 하에서의 삽입체.

[0208] 2. F11 셔틀 플라스미드. 모 MVA 바이러스내 F11 유전자자리의 영역에 대해 상동성인 상류 및 하류 플랭크를 지닌 HPV 삽입체. F11 프로모터의 제어하의 삽입체.

[0209] 이후에 닭 배아 섬유아세포를 MVA 모 바이러스로 감염시키고 p7.5 또는 F11 MVA 셔틀 플라스미드로 형질감염시켜 MVA 게놈과의 동종 재조합을 허용한다. 따라서, TK 유전자자리(p7.5 셔틀 플라스미드) 또는 F11 유전자자리(F11 셔틀 플라스미드)에서 MVA 게놈내로 삽입된 목적한 유전자를 지닌 모 MVA가 수득된다. MVA 백신의 2개 버전이 수득된다.

[0210] **P7.5 셔틀 플라스미드(서열 번호: 158)(삽입체는 밑줄쳐져 있다)**

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[0211]

[0212]

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[0213]

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[0214]

[0215]

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[0216] F11-HPV 셔틀 플라스미드(서열 번호: 159)(백신 작제물 삽입체는 밑줄쳐져 있다)

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[0218]

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CGATGCCCTTCAGCTCGATGCGGTTCACCAGGGTaTCGCCCTCGAACTTCACCTCGGCGCGGGTC
TTGTAGTTGCCGTCGTCCTTGAAGAAGATGGTGCGCTCCTGGACGTAGCCTTCGGGCATGGCGGA
CTTGAAGAAGTCGTGCTGCTTCATGTGGTCGGGGTAGCGGCTGAAGCACTGCACGCCGTAGGTCA
GGGTGGTCACGAGGGTcGGCCAGGGCACGGGCAGCTTGCCGGTGGTGCAGATGAACTTCAGGGTC
AGCTTGCCGTAGGTGGCATCGCCCTCGCCCTCGCCGGACACGCTGAACTTGTGGCCGTTTACGTC
GCCGTCCAGCTCGACCAGGATGGGCACCACCCCGGTaAACAGCTCCTCGCCCTTGCTCACCATgt
ttaaacTTTATATTCCAAAAAAAAAAAAATAAAATTTCAATTTTTgtttaaacgttGTACGGCAGT
TTAAGGTTTACACCTATAAAAGAGAGAGCCGTTATCGTCTGTTTGTGGATGTACAGAGTGATATT
ATTGACACGCCGGGGCGACGGATGGTGATCCCCCTGGCCAGTGCACGTCTGCTGTCAGATAAAGT

[0219]

CTCCCGTGAACTTTACCCGGTGGTGCATATCGGGGATGAAAGCTGGCGCATGATGACCACCGATA
TGGCCAGTGTGCCGGTCTCCGTTATCGGGGAAGAAGTGGCTGATCTCAGCCACCGCGAAAATGAC
ATCAAAAACGCCATTAACCTGATGTTCTGGGGAATATAAATGTCAGGCATGAGATTATCAAAAAG
GATCTTCACCTAGATCCTTTTCACGTAGAAAGCCAGTCCGCAGAAACGGTGCTGACCCCGGATGA
ATGTCAGCTACTGGGCTATCTGGACAAGGGAAAACGCAAGCGCAAAGAGAAAGCAGGTAGCTTGC
AGTGGGCTTACATGGCGATAGCTAGACTGGGCGGTTTTATGGACAGCAAGCGAACCGGAATTGCC
AGCTGGGGCGCCCTCTGGTAAGGTTGGGAAGCCCTGCAAAGTAAACTGGATGGCTTTCTCGCCGC
CAAGGATCTGATGGCGCAGGGGATCAAGCTCTGATCAAGAGACAGGATGAGGATCGTTTCGCATG
ATTGAACAAGATGGATTGCACGCAGGTTCTCCGGCCGCTTGGGTGGAGAGGCTATTCGGCTATGA
CTGGGCACAACAGACAATCGGCTGCTCTGATGCCGCCGTGTTCCGGCTGTCAGCGCAGGGGCGCC
CGGTTCTTTTTGTCAAGACCGACCTGTCCGGTGCCCTGAATGAACTGCAAGACGAGGCAGCGCGG
CTATCGTGGCTGGCCACGACGGGCGTTCCTTGCGCAGCTGTGCTCGACGTTGTCACTGAAGCGGG
AAGGGACTGGCTGCTATTGGGCGAAGTGCCGGGGCAGGATCTCCTGTCATCTCACCTTGCTCCTG
CCGAGAAAGTATCCATCATGGCTGATGCAATGCGGCGGCTGCATACGCTTGATCCGGCTACCTGC
CCATTCGACCACCAAGCGAAACATCGCATCGAGCGAGCACGTACTCGGATGGAAGCCGGTCTTGT
CGATCAGGATGATCTGGACGAAGAGCATCAGGGGCTCGCGCCAGCCGAACTGTTCGCCAGGCTCA
AGGCGAGCATGCCCGACGGCGAGGATCTCGTCGTGACCCATGGCGATGCCTGCTTGCCGAATATC
ATGGTGGAAAATGGCCGCTTTTCTGGATTCATCGACTGTGGCCGGCTGGGTGTGGCGGACCGCTA
TCAGGACATAGCGTTGGCTACCCGTGATATTGCTGAAGAGCTTGGCGGCGAATGGGCTGACCGCT
TCCTCGTGCTTTACGGTATCGCCGCTCCCGATTCGCAGCGCATCGCCTTCTATCGCCTTCTTGAC
GAGTTCTTCTGAATTATTAACGCTTACAATTTCCTGATGCGGTATTTTCTCCTTACGCATCTGTG
CGGTATTTCACACCGCATACAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTT
ATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAAT
AATAGCACGTGAGGAGGGCCACCATGGCCAAGTTGACCAGTGCCGTTCCGGTGCTCACCGCGCGC
GACGTCGCCGGAGCGGTCGAGTTCTGGACCGACCGGCTCGGGTTCTCCCGGGACTTCGTGGAGGA
CGACTTCGCCGGTGTGGTCCGGGACGACGTGACCCTGTTCATCAGCGCGGTCCAGGACCAGGTGG
TGCCGGACAACACCCTGGCCTGGGTGTGGGTGCGCGGCCTGGACGAGCTGTACGCCGAGTGGTCG
GAGGTCGTGTCCACGAACTTCCGGGACGCCTCCGGGCCGGCCATGACCGAGATCGGCGAGCAGCC
GTGGGGGCGGGAGTTCGCCCTGCGCGACCCGGCCGGCAACTGCGTGCACTTCGTGGCCGAGGAGC
AGGACTGACACGTGCTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGAT
AATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAA
GATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAAC
CACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACT
GGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTT
CAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCA
GTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGG
TCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAG
ATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATC
[0220] CGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTAT

CTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGG
GGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGGCTTTTGCTGGC
CTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTT
GAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGC
[0221] GGAAG

[0222] **HPV2-무작위 뉴클레오타이드 서열(분절은 무작위 순서로 존재한다)(밑줄쳐진, tPA 리딩 서열 및 HindIII 클로닝 링커 포함함)(서열 번호: 71).**

[0223]

ATGGATGCTATGAAGAGGGGCCTGTGCTGCGTGCTGCTGCTGTGTGGCGCCGTGTTTGTGTCCCC
CAGCCAGGAAATCCACGCCCGGTTCAGAAGAGGCAGCAAGCTGGCTGCTCAGCTGGCCGACAGCG
ACAGCAATGCCTGCGCCTTCCTGAAGCTGAGATACCTGCACAGCCGGATCCACGTGCTGCAGTTT
CTGAACCCCTTCACCCTGCACGAGTACATGCTGGACCTGCAGCCCGAGACAACCGACCTGTACTG
CTACGAGCAGGACGAGGATGAGGACGAGGTGGACCATCTGCAGGAACAGCCCCAGCAGGCCAGAA
GGGATGAGCAGCACCCCTGCTACCTGATCGAGACACAGTGCTGCAGATGCGAGAGCCTGGTGGCC
CAGCTGGCTGACGTGAACTCTAACGCCGCAGCCTTTCTGAAGAACAGCATCGACTGCAACGACAG
CATGTGCAGCACCTTCGACGACAACGTGTCCGCCACCGAGCTCGTGAAGAGAATCCCTGCCCCTT
GCCCCTGGGCCCCTGAGGAAAATGACGAGATCGACGGCGTGAACCACCAGCATCTGCCCGCTAGA
AGGGCCGAGCCTCAGAGACACACCATGCTGTGCATGTGCTGCAAGTGCGAGGCCCGGATCTGCTT
CCTGCTGTGCTTTTGTGTGCTGCTGTGCGTGTGCCTGCTGATCAGACCCCTGCTGCTGAGTGTGT
CCACCTACTGCCAGCGGCCGCTGTGTCCTCAGGAAAAGAAACGGCACGTGGACCTGAACAAGCGG
TTCCACATCTACATCTGCGAGGACGCCCAGTGCACCGTGGTGGAAGGCCAGGTGGACAGCAAGGT
GTCCGAGTTCCGGTGGTACAGATACAGCGTGTACGGCACCACCCTGGGCCAGCGGAGAATCAAGA
GGCCCAGATCCGAGGTGTACTGCAAGGGACAGCTGACCGAGACAGAGGTGCTGGACTTCGCCTTC
ACCGACCTGACCATCGTGTACCGGGACATCCGGCTGGAATGCGCCATCATGTACAAGGCCAGAGA
GATGGGCTTCCACGACCACATCGACTACTGGAAGCTGATTAGACTGGAATGTGCTATCTTCTACA
AAGCCCGGATCCTGAAGTGCCTGCGGTACAGATTCAAGAAGCACTGCAAGCTGTACGTGGCCTGG
GACTCCGTGTACTACTGCGGCGACGATGGCTGGTGCAAGACCAGCTCTACCTGGCACTGGACATG
CCACGACGGCAAGCACAAGAACGTGTGCCAGGACAAGATCCTGGAACACTACGAGAACGACTCCA
AGGACGACGAGGACGAGACAGCCTACGACAGCGGCACCGATCTGATCGACTTCATCGACGATAGC
AACTGCCACCCCAACAAGCTGCTGCGGAGACTGAGCAGCGACCAGGACCAGTCTCAGAGGCCCCC
CAACATGGGAGTGAAGGCCCACGGCAAGTGCATCTGGGAGAACAAGGTGTTCATCGTGCCCACCC
TGTGCCCCGTGCCTCTGGATCCAACATACCCCCTGCTGAAGCTGCTGACCCCCGAAACCACAGAT
CTGCACTGTTATGAGCAGCTGGGCGACTCCTCCGACGAAGAGGATACAGGCGGCCTGGATGGCTA
CGAGGCCGACAAGAACGACCTGAACGCCCAGATCGAGCACTGGAAACTGATCCGGATGGAATGTG
CAATTTTCTATAAGGCCAAAGAGCTGGGGATCAGCGACGAGAATGAGAACGACAGCGATACCGGC
GAGGACATGGTGGATTTCATCGACAATGAGGCCGAGAAGTACGGCTGCAAGGGCACCTGGGAGGT

GCACTTCGGCTTTAAGAAGCACGGCATCACCATCACCGTGCAGTACGACAACGACAAGGCCAACA
CCATGGACTACACCAACTGGAAAGAGATCTACCCCCCTCCCCCCCCACGGCCTTGGGCTCCTCCA
ATTCCTAAGCCCTCTCCATGGGCCCCTCAGTTCGACGGCGACATCTGCAATACCATGCACTATAC
CAATTGGGTGGTGTACAGAGACAGCATCCCCCACGCCGCCTGCCACAAGTGTATCGACTTCTACA
GCAGAATCAGAGAGCTGCGGCACTACAGCGACTCTGTGTACGGCGATACCCTGGAAAAGCTGACC
AACACCGGCCTGTACAATCTGCTGATCCGGTGCCTGAGGCTCGTGACCAAGTATCCTCTGCTGAA
ACTGCTGTCCAACTGCATCCTGTACGGCGCTGCCAATACCGGCAAGAGCCTGTTCGGCATGAGCC
TGAGCAAAGTGCGGAAGCTGAGGTACTACAACTGCTCCGTGTATGGGGCCAGCCTGTGCGTGGAA
TGCAAGAAAACCCTGCAGCGGAGCGAAGTGTACGACGACGAAACCGACGAGGAAAGCACCGAGAG
CGACCTGGACGGCTTCATCGATAACAGCGTGATCGTGTGCCCCGCCTCCATCCCCTCCGATGAGA
TCTCTACCGAGGAAGCCCCCAGACCCCCTCACTGTCCTTGGGTGCCAGTGTTCTGCAAGAAGGCC
CTGACCGCCTCTGAGGTGTACAATTTTGCCTATACCGACCTGCGCGTGGTGTATAGGGACATTCT
GGAACATTATGAGAATGATAGCAAGGACCTGTGCGATCACATCAACTGCCTCGTGATCTACGGCC
CTCCTAACACCGGCAAGTCCTGCTTCGCCATGTCCCTGTGGAACACCGAGCCCAAGCACTGCTTC
AAGAAGGGCGGCCAGCACATCGAAGTGTGGTTCGATATTGTGTACAGGGACGGCAACCCTTACGC
CGTGTGCGACAAGTGCCTGAAGTTCTACTCCAAGATCAGCGAGTACCGCCACTACTGCTACTCCC
TGTATGGCACAACACTGGAACAGCAGTACAACAAGCCCCTGTGCGACCTGCTGATTCGCTGCATC
AACACCACCAGATACCCTCTGCTGTCCCTGCTGAACAGCTACAGCACCCCCCCTCATCGGATTCC
CGCCCCATGTCCATGGGCTCCACAGAGGCCTACCCAGACCACCACCCCCGAGAATACCTCCCTGG
TGGAACTGAGAGTGACCACCCCCAAGAGCACAGTCGTGATCAGGCTGCACCTGTGGCCCTACCTG
CACTCCAGACTGGTGGTGTTCACCTTCCCCAACCCCTTTCACCAGGTGGTGCCCGCCCTGAATAT
CTGCAAGGCCAAGGCCTGCAAAGCCATCGAGAAGAAATGGGAAGTGCACGCTGGCGGCCAAGTGA
TCCTGTGTCCTGAGAGCCTGCGGCCTCTGCTGCTGTCCATTAGCGTGTACGCCCAGGTGCTGGTG
CTGGTGCTGCTGCTGTGGGTGTCCATCGGCAGCAACTGTCTGGTGCTGTGCGGCCCTGCCAACAC
AGGGAAGAGTTACTTCGGCATGTCTCTGATCTGCCATCAGGTGGTGCCTCCACTGGCCGCCTCTA
AGGCTAAAGCCTGTCAGGCCATCGAACTGCAGCTGGCCCTGGAAGCCCTGAATGCCAGCCCCTAT
GATCACATTGATTACTGGAAAGCCATCCGGCAGGAAAATGCCATCTTCTTCGCCGCCAGATGGCA
TTGGACCTGTCACGATGGAAAACACAAGAATGCCATTGTGACCCTGACCTACCTGCTGCCCAGCG
TGTGTATGTGCGCCTACGCTTGGGTGCTGGTGTTCGTGTACATCGTCGTGATTACCAGCCCCGCC
ACCGCCGATGAGTGGACACTGCAGCAGACAAGCCTGGAAATGTGGCTGGCCGAGCCCCAGTGTGA
CCATATCGATTATTGGAAACACATCCGCCTGGAATGTGCTATTATGTATAAGGCCCGGTGGCCTT
ACCTGGAAAGCAGAACCGTGTTCGAGTTCCCCAATGCCTTCGCCGGCTCTGGACCTGGCGCCTCT

[0224] GGAAAACCCATCCCCAATCCACTGCTGGGCCTGGACTCCACCCGGACC

[0225] **HPV2-무작위화된 서열 폴리펩타이드(밑줄쳐진 tPA 리딩 서열 및 HindIII 클로닝 링커를 포함함)(서열 번호: 72)**

MDAMKRGLCCVLLLCGAVFVSPSQEIHARFRRGSKLAAQLADSDSNACAFLKLRYLHSRIHVLQF
LNPFTLHEYMLDLQPETTDLYCYEQDEDEDEVDHLQEQPQQARRDEQHPCYLIETQCCRCESLVA
QLADVNSNAAAFLKNSIDCNDSMCSTFDDNVSATELVKRIPAPCPWAPEENDEIDGVNHQHLPAR
RAEPQRHTMLCMCCKCEARICFLLCFCVLLCVCLLIRPLLLSVSTYCQRPLCPQEKKRHVDLNKR
FHIYICEDAQCTVVEGQVDSKVSEFRWYRYSVYGTTLGQRRIKRPRSEVYCKGQLTETEVLDFAF
TDLTIVYRDIRLECAIMYKAREMGFHDHIDYWKLIRLECAIFYKARILKCLRYRFKKHCKLYVAW
DSVYYCGDDGWCKTSSTWHWTCHDGKHKNVCQDKILEHYENDSKDDEDETAYDSGTDLIDFIDDS
NCHPNKLLRRLSSDQDQSQRPPNMGVKAHGKCIWENKVFIVPTLCPVPLDPTYPLLKLLTPETTD
LHCYEQLGDSSDEEDTGGLDGYEADKNDLNAQIEHWKLIRMECAIFYKAKELGISDENENDSDTG
EDMVDFIDNEAEKYGCKGTWEVHFGFKKHGITITVQYDNDKANTMDYTNWKEIYPPPPPRPWAPP
IPKPSPWAPQFDGDICNTMHYTNWVVYRDSIPHAACHKCIDFYSRIRELRHYSDSVYGDTLEKLT
NTGLYNLLIRCLRLVTKYPLLKLLSNCILYGAANTGKSLFGMSLSKVRKLRYYNCSVYGASLCVE
CKKTLQRSEVYDDETDEESTESDLDGFIDNSVIVCPASIPSDEISTEEAPRPPHCPWVPVFCKKA
LTASEVYNFAYTDLRVVYRDILEHYENDSKDLCDHINCLVIYGPPNTGKSCFAMSLWNTEPKHCF
KKGGQHIEVWFDIVYRDGNPYAVCDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCI
NTTRYPLLSLLNSYSTPPHRIPAPCPWAPQRPTQTTTPENTSLVELRVTTPKSTVVIRLHLWPYL
HSRLVVFTFPNPFHQVVPALNICKAKACKAIEKKWEVHAGGQVILCPESLRPLLLSISVYAQVLV
LVLLLWVSIGSNCLVLCGPANTGKSYFGMSLICHQVVPPLAASKAKACQAIELQLALEALNASPY
DHIDYWKAIRQENAIFFAARWHWTCHDGKHKNAIVTLTYLLPSVCMCAYAWVLVFVYIVVITSPA
TADEWTLQQTSLEMWLAEPQCDHIDYWKHIRLECAIMYKARWPYLESRTVFEFPNAFAGSGPGAS

[0226] GKPIPNPLLGLDSTRT**

[0227] HPV53del 뉴클레오타이드 서열(HPV53으로부터의 분절은 제거되었다)(밑줄쳐진 tPA 리딩 서열 및 HindIII 클로닝 링커를 포함함)(서열 번호: 73)

ATGGATGCTATGAAGCGAGGACTGTGCTGCGTGCTGCTGCTGTGTGGCGCTGTGTTTGTGTCCCCTAGCC
AAGAGATCCACGCCAGATTCAGACGGGGCAGCAAACTGGCCGACGAGGATGAGACAGCCTACGACTCTGG
CACCGACCTGATCGACTTCATCGACGACAGCGACGAGAACGAGAATGACAGCGACACCGGCGAGGACATG
GTGGATTTCATCGACAATGCCCAGCTGGCCGACTCCGACTCTAATGCCTGTGCCTTTCTGAAGGCTCAGC
TGGCTGACGTGAACAGCAATGCCGCCGCTTTCCTGAAGAACTGCATCCTGCTGTACGGCGCTGCCAACAC
AGGCAAGAGCCTGTTTGGCATGAGCCTGAACTGCCTGGTGCTGTGCGGACCTGCCAATACCGGCAAAAGC
TACTTCGGCATGTCCCTGTGGCCTTACCTGCACAGCAGACTGGTGGTGTTTACATTCCCCAATCCTTTCT
GGCCCTACCTGGAAAGCCGGATCACCGTGTTCGAGTTCCCCAACGCCTTCAACGTGTGCCAGGACAAGAT
CCTGGAACACTATGAGAACGACAGCAAGGACATCCTTGAGCACTACGAAAACGACTCCAAGGACCTGTGC
GACCACATCTGCGATCACATCGACTACTGGAAGCACATCCGGCTGGAATGCGCCATCATGTACAAGGCCC
GGATCAGACTGGAATGTGCTATTATGTATAAGGCTCGCGAGATGGGCTTCCACCAGTTCGACGGCGACAT
CTGCAACACCATGCACTACACCAACTGGATCTATATCTGCGAGGACGCCCAGTGCACCGTGGTGGAAGGA
CAGGTGGACAAGAAATGGGAAGTGCACGCTGGCGGCCAAGTGATTCTGTGTCCTGAGAGCGGCCAGCGGA
GAATCAAGAGGCCCAGATCCGAGAACTGTCACCCCAACAAGCTGCTGATCCTGAAGTGCCTGCGGTACAG
ATTCAAGAAGCACTGCAAGCTGAGCAGCACCTGGCACTGGACATGCCACGATGGCAAGCACAAGTGGCAT
TGGACCTGTCACGACGGGAAACACAAGAACGCCATCGTGACCCTGACCTACTACGAGGCCGACAAGAACG
ACCTGAACGCCCAGATTGAGCACTGGAAACTGATCCGGATGGAATGTGCAATCTTCTATAAGGCCAAAGA
GCTGGGGATCAGCATCTGCCACCAGGTGGTGCCTCCACTGGCTGCCTCTAAAGCCAAAGCCTGTCAGGCC
ATCGAACTGCAGCTGGCCCTGGAAGCCCTGAACGCTAGCCCTTACGATGAGTGGACCCTGCAGCAGACCA
GCCTGGAAATGTGGCTGGCCGAGCCTCAGTTTAAGAAGCACGGCATCACCATCACCGTGCAGTACGACAA
CGACAAGGCCAATACCATGGATTACACGAATTGGAAAGAAATCTACGTGATCGTGTGCCCCGCCAGCATT

[0228]

CCCTCCGATGAGATCTCTACCGAGGAAGCCGACCACATTGATTATTGGAAGGCCATCCGGCAAGAGAATG
CCATCTTCTTCGCCGCCAGACATCAGGTGGTCCCCGCTCTGAATATCTGCAAGGCCAAGGCCTGCAAAGC
CATCGAGTGGAACACCGAGCCTAAGCACTGCTTCAAGAAAGGCGGCCAGCACATCGAAGTTTGGTTCGAC
TACGTGGCCTGGGACAGCGTGTACTACTGCGGAGATGATGGCTGGTGCAAGACCGAGGCCGAGAAGTACG
GCTGTAAAGGCACCTGGGAAGTCCACTTCGGCAACAGCATCGACTGCAACGATAGCATGTGCAGCACCTT
CGACGACAACGTGTCCGCCACAGAGCTGGTCAAGGACCATATAGACTATTGGAAGCTGATCAGGCTTGAG
TGCGCCATTTTCTACAAGGCCAGACGGCGGCTGTCCAGCGACCAGGATCAATCTCAGCTCGTGACCAAGT
ATCCCCTGCTGAAGCTGCTGTCTACCCAGACCACCACACCTGAGAACACAAGCCTGGTGGAACTGAGAGT
GACCACACCTAAGAGCACCGTCGTGATTCGGCTGCACCTGACCACAAGATACCCTCTGCTGAGCCTGCTG
AACAGCTACAGCACCCCTCCACACAGGATCCCCGCTCCATGTCCTTGGGCTCCTCAGAGGCCTCCTATTC
CTAAGCCTTCTCCATGGGCTCCTAGAATCCCCGCACCTTGTCCATGGGCACCACCAAGACCTCCACATTG
CCCTTGGGTGCCCTGTTTCCTGCTGTGCTTTTGCGTGCTCCTGTGCGTGTGCCTGCTGATCAGACCTCTG
CTGCTGAGCGTGTCCACCTACCTTAGACCACTGCTCCTGTCCATCTCCGTGTACGCACAGGTGCTGGTGC
TGGTCCTGCTTCTGTGGGTGTCCATCGGAAGCCTGCTGCCTAGCGTGTGCATGTGTGCCTATGCTTGGGT
GCTCGTGTTCGTGTACATCGTGGTCATCACAAGCCCCGCCACAGCCATCGTGTACAGAGATGGCAATCCC
TACGCCGTGTGCGACAAGTGCCTGAAGTTCTACAGCAAGATCAGCGAGTACCGGCACTACTGCTACAGCC
TGTACGGCACCACACTGGAACAGCAGTACAACAAGCCCCTGTGCGATCTGCTGATTCGGTGCATCAACGT
GGTGTACCGGGACAGCATTCCTCACGCCGCCTGCCACAAGTGCATCGACTTCTACTCCAGAATCAGAGAG
CTGCGGCACTACAGCGACTCTGTGTACGGCGACACCCTGGAAAAGCTGACCAACACCGGCCTGTACAACC
TGCTGATTAGATGCCTGCGGGTGTACTGCAAGGGACAGCTGACAGAGACAGAGGTGCTGGACTTCGCCTT
CACCGATCTGACAATCGTGTATCGGGATAGCAAGGTGTCCGAGTTCCGGTGGTACAGATATAGCGTGTAC
GGAACAACCCTGTGCGTCGAGTGCAAGAAAACCCTGCAGAGAAGCGAGGTGTACGACTGCCAGAGGCCAC
TGTGCCCTCAAGAGAAGAAACGGCACGTGGACCTGAACAAGCGGTTTCACACCCTGCACGAGTACATGCT
GGACCTGCAGCCTGAGACAACCGACCTGTACTGCTACGAGCAGCCCGAAACCACAGATCTGCACTGTTAT
GAGCAGCTGGGCGACAGCAGCGACGAAGAGGATACAGGCGGACTGGACGGCGAGGAAAACGACGAAATTG
ACGGCGTGAACCACCAGCATCTCCCCGCCAGAAGGGCTGAACCTCAGAGACACACCATGCTGTGTATGTG
CTGCAAGTGCGAGGCCAGAATCGCCTGATGA

[0229]

[0230] HPV53del 폴리펩타이드 서열(밑줄쳐진 tPA 리딩 서열 및 HindIII 클로닝 링커를 포함함)(서열 번호: 74)

MDAMKRGLCCVLLLCGAVFVSPSQEIHARFRRGSKLADEDETAYDSGTDLIDFIDDSDENENDSDTGEDM
VDFIDNAQLADSDSNACAFLKAQLADVNSNAAAFLKNCILLYGAANTGKSLFGMSLNCLVLCGPANTGKS
YFGMSLWPYLHSRLVVFTFPNPFWPYLESRITVFEFPNAFNVCQDKILEHYENDSKDILEHYENDSKDLC
DHICDHIDYWKHIRLECAIMYKARIRLECAIMYKAREMGFHQFDGDICNTMHYTNWIYICEDAQCTVVEG
QVDKKWEVHAGGQVILCPESGQRRIKRPRSENCHPNKLLILKCLRYRFKKHCKLSSTWHWTCHDGKHKWH
WTCHDGKHKNAIVTLTYYEADKNDLNAQIEHWKLIRMECAIFYKAKELGISICHQVVPPLAASKAKACQA
IELQLALEALNASPYDEWTLQQTSLEMWLAEPQFKKHGITITVQYDNDKANTMDYTNWKEIYVIVCPASI
PSDEISTEEADHIDYWKAIRQENAIFFAARHQVVPALNICKAKACKAIEWNTEPKHCFKKGGQHIEVWFD
YVAWDSVYYCGDDGWCKTEAEKYGCKGTWEVHFGNSIDCNDSMCSTFDDNVSATELVKDHIDYWKLIRLE
CAIFYKARRRLSSDQDQSQLVTKYPLLKLLSTQTTTPENTSLVELRVTTPKSTVVIRLHLTTRYPLLSLL
NSYSTPPHRIPAPCPWAPQRPPIPKPSPWAPRIPAPCPWAPPRPPHCPWVPCFLLCFCVLLCVCLLIRPL
LLSVSTYLRPLLLSISVYAQVLVLVLLLWVSIGSLLPSVCMCAYAWVLVFVYIVVITSPATAIVYRDGNP
YAVCDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKPLCDLLIRCINVVYRDSIPHAACHKCIDFYSRIRE
LRHYSDSVYGDTLEKLTNTGLYNLLIRCLRVYCKGQLTETEVLDFAFTDLTIVYRDSKVSEFRWYRYSVY
GTTLCVECKKTLQRSEVYDCQRPLCPQEKKRHVDLNKRFHTLHEYMLDLQPETTDLYCYEQPETTDLHCY
EQLGDSSDEEDTGGLDGEENDEIDGVNHQHLPARRAEPQRHTMLCMCCKCEARIA**

[0231]

[0232] HPV3-링커 뉴클레오타이드 서열(밑줄쳐진 tPA 리딩 서열 및 HindIII 클로닝 링커를 포함함)(서열 번호: 75)

ATGGATGCTATGAAGAGGGGCCTGTGCTGCGTGCTGCTGCTGTGTGGCGCCGTGTTTGTGTCCCCCAGCC
AGGAAATCCACGCCCGGTTCAGAAGAGGCAGCAAGCTGGCCGACGAGGACGAGACAGCCTACGACAGCGG
CACCGACCTGATCGACTTCATCGACGATAGCGCCGCTGCCGACGAGAATGAGAACGACAGCGATACCGGC
GAGGACATGGTGGATTTCATCGACAACGCTGCCGCCGACGAAACCGACGAAGAGAGCACCGAGAGCGACC
TGGACGGCTTTATCGACAACAGCGCAGCCGCCCAGCTGGCTGACAGCGACTCTAATGCCTGCGCCTTCCT
GAAGGCCGCTGCTCAGCTGGCAGACGTGAACAGCAATGCCGCCGCTTTTCTGAAGGCTGCCGCCAACTGC
ATCCTGCTGTACGGCGCTGCCAACACCGGCAAGAGCCTGTTCGGCATGTCTCTGGCCGCAGCCAACTGCC
TGGTGCTGTGCGGACCTGCCAATACTGGCAAAAGCTACTTCGGCATGAGCCTGGCAGCCGCCAATTGTCT
CGTGATCTACGGCCCTCCTAATACCGGCAAGTCCTGCTTTGCCATGAGTCTGGCCGCTGCCTGGCCCTAC
CTGCACTCTAGACTGGTGGTGTTCACCTTCCCCAACCCCTTCGCTGCCGCTTGGCCTTACCTGGAAAGCC
GGATCACCGTGTTCGAGTTCCCCAATGCCTTCGCCGCAGCCCTGAGATACCTGCACAGCAGAATCCACGT
GCTGCAGTTTCTGAACCCCTTTGCCGCCGCAAACGTGTGCCAGGACAAGATCCTGGAACACTACGAGAAC
GACTCCAAGGATGCCGCTGCCATTCTGGAACATTATGAGAATGATAGCAAGGACCTGTGCGACCACATTG
CTGCCGCCTGCGATCACATCGACTACTGGAAGCACATCCGGCTGGAATGCGCCATCATGTACAAGGCCAG
AGCCGCCGCTATCAGACTGGAATGTGCTATTATGTATAAGGCTCGCGAGATGGGCTTCCACGCTGCTGCC
CAGTTCGACGGCGACATCTGCAACACCATGCACTACACCAACTGGGCTGCCGCTATCTACATCTGCGAGG
ACGCCCAGTGCACCGTGGTGGAAGGACAGGTGGACGCCGCTGCTAAGAAATGGGAGGTGCACGCTGGCGG
CCAAGTGATCCTGTGTCCAGAGTCTGCTGCCGCAGGCCAGCGGAGAATCAAGAGGCCTAGAAGCGAGGCA
GCCGCTAACTGCCACCCCAACAAACTGCTGGCTGCTGCCATCCTGAAGTGCCTGCGGTACAGATTCAAGA
AGCACTGCAAACTGGCTGCAGCTAGCAGCACCTGGCACTGGACCTGTCACGACGGCAAGCACAAAGCCGC
CGCATGGCATTGGACATGCCACGATGGAAAACACAAGAACGCCATCGTGACCCTGACCTATGCAGCCGCC
TACGAGGCCGACAAGAACGACCTGAACGCCCAGATCGAGCACTGGAAGCTGATCAGGATGGAATGTGCAA
TCTTCTATAAGGCCAAAGAGCTGGGCATCAGCGCTGCCGCAATCTGCCACCAGGTGGTGCCTCCACTGGC
CGCCTCTAAAGCCAAAGCCTGCCAGGCCATCGAACTGCAGCTGGCCCTGGAAGCCCTGAATGCCAGCCCT
TATGCCGCAGCCGATGAGTGGACCCTGCAGCAGACCAGCCTGGAAATGTGGCTGGCCGAACCTCAGGCCG
CAGCTTTTAAGAAGCACGGCATCACCATCACCGTGCAGTACGACAACGACAAGGCCAATACCATGGATTA
CACCAATTGGAAAGAGATCTACGCCGCAGCTGTGATCGTGTGCCCCGCCAGCATCCCTAGCGACGAGATC
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CCGCCGCTGCAGAGGCCGAGAAGTATGGCTGCAAGGGCACCTGGGAAGTGCATTTCGGCGCAGCTGCCAA
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GCTGCCGCTGACCATATTGATTACTGGAAACTGATTCGCCTGGAATGCGCTATTTTCTACAAAGCCAGGG
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GCTGAAGCTGCTGAGCGCCGCAGCAAGACCCCCCAACATGGGAGTGAAGGCCCACGGCAAGTGCATCTGG
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TGCTGACCGCTGCCGCCACCCAGACCACCACACCTGAGAATACCTCCCTGGTGGAACTGAGAGTGACCAC
CCCCAAGAGCACAGTCGTGATCAGGCTGCACCTGGCTGCCGCAACCACCAGATACCCTCTGCTGTCCCTG
CTGAACAGCTACAGCACCCCCCCTCATCGGATCCCTGCCCCTTGTCCTTGGGCTCCTCAGAGGCCTGCCG
CTGCACCTATCCCTAAGCCTTCTCCATGGGCCCCTGCCGCAGCTAGAATCCCAGCTCCATGTCCATGGGC
ACCAGCTGCTGCTCCCAGACCTCCTCATTGCCCTTGGGTGCCAGCAGCCGCTCCTCCACCTCCTCCTAGA
CCTTGGGCCCCAGCCGCCGCTTGTTTCCTGCTGTGCTTCTGTGTGCTGCTGTGCGTGTGCCTGCTGATCA
GACCCCTGCTGCTGAGTGTGTCCACCTACGCAGCTGCTCTGCGGCCACTGCTGCTGTCCATCTCTGTGTA
CGCACAGGTGCTGGTGCTGGTGCTGCTGCTGTGGGTGTCCATCGGATCTGCCGCAGCACTGCTGCCCTCC
GTGTGCATGTGTGCCTATGCCTGGGTGCTGGTGTTCGTGTACATCGTCGTGATTACCAGCCCCGCCACCG
CAGCCGCAATCGTGTACAGGGACGGCAACCCTTACGCCGTGTGCGACAAGTGCCTGAAGTTCTACAGCAA
GATCAGCGAGTACCGCCACTACTGCTACAGCCTGTACGGCACCACCCTGGAACAGCAGTACAACAAGCCC

[0233]

CTGTGCGATCTGCTGATCCGGTGCATCAACGCAGCCGCTGTGGTGTACAGAGACAGCATCCCACACGCCG
CCTGCCACAAGTGTATCGACTTCTACTCCCGGATCAGAGAGCTGAGACACTACTCCGACTCCGTGTACGG
CGATACCCTGGAAAAGCTGACCAATACCGGCCTGTACAACCTGCTGATTAGATGCCTGCGGGCAGCCGCA
GTGTTCTGCAAGAAAGCCCTGACCGCCAGCGAGGTGTACAACTTCGCCTACACCGATCTGCGGGTGGTGT
ACCGGGATGCTGCTGCCTCCAAAGTGCGGAAGCTGCGGTACTACAACTGCTCTGTGTATGGCGCCTCCCT
GGCAGCTGCCGTGTATTGCAAGGGACAGCTGACCGAGACAGAGGTGCTGGATTTCGCCTTCACAGACCTG
ACCATCGTGTATAGAGATGCAGCTGCTAGCAAGGTGTCCGAGTTCCGGTGGTACAGATATAGCGTGTACG
GAACAACACTGGCAGCAGCTTGCGTGGAATGCAAGAAAACACTGCAGCGGAGCGAAGTGTACGATGCTGC
AGCTTGCCAGAGGCCGCTGTGTCCTCAGGAAAAGAAAAGACACGTGGACCTGAACAAGCGGTTCCACGCA
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CAGCTGCACCCGAAACCACAGATCTGCACTGTTATGAGCAGCTGGGAGACAGCTCCGATGAAGAGGACAC
CGGCGGACTGGATGCTGCCGCTGGGGATGAGGACGAGGATGAGGTGGACCATCTGCAGGAACAGCCCCAG
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[0234] GCTAGCGGAAAGCCCATCCCCAATCCACTGCTGGGCCTGGACTCCACCCGGACCTGATAA

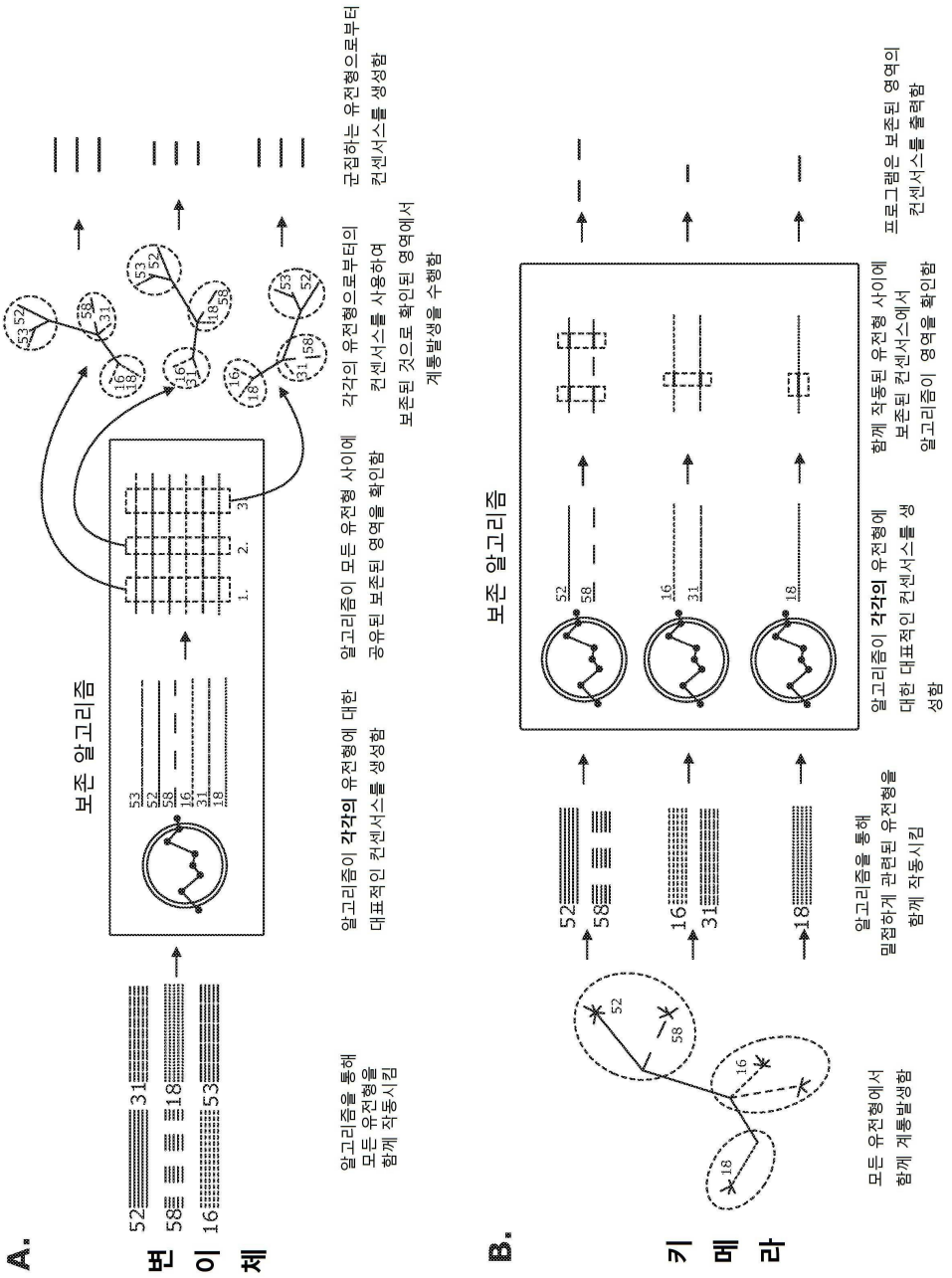
[0235] HPV3-링커 폴리펩타이드 서열(밑줄쳐진 tPA 리딩 서열 및 HindIII 클로닝 링커를 포함함)(서열 번호: 76)

MDAMKRGLCCVLLLCGAVFVSPSQEIHARFRRGSKLADEDETAYDSGTDLIDFIDDSAAADENENDSDTG
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ILLYGAANTGKSLFGMSLAAANCLVLCGPANTGKSYFGMSLAAANCLVIYGPPNTGKSCFAMSLAAAWPY
LHSRLVVFTFPNPFAAAWPYLESRITVFEFPNAFAAALRYLHSRIHVLQFLNPFAAANVCQDKILEHYEN
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VCMCAYAWVLVFVYIVVITSPATAAAIVYRDGNPYAVCDKCLKFYSKISEYRHYCYSLYGTTLEQQYNKP
LCDLLIRCINAAAVVYRDSIPHAACHKCIDFYSRIRELRHYSDSVYGDTLEKLTNTGLYNLLIRCLRAAA
VFCKKALTASEVYNFAYTDLRVVYRDAAASKVRKLRYYNCSVYGASLAAAVYCKGQLTETEVLDFAFTDL
TIVYRDAAASKVSEFRWYRYSVYGTTLAAACVECKKTLQRSEVYDAAACQRPLCPQEKKRHVDLNKRFHA
AATLHEYMLDLQPETTDLYCYEQAAAPETTDLHCYEQLGDSSDEEDTGGLDAAAGDEDEDEVDHLQEQPQ
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ASGKPIPNPLLGLDSTRT**

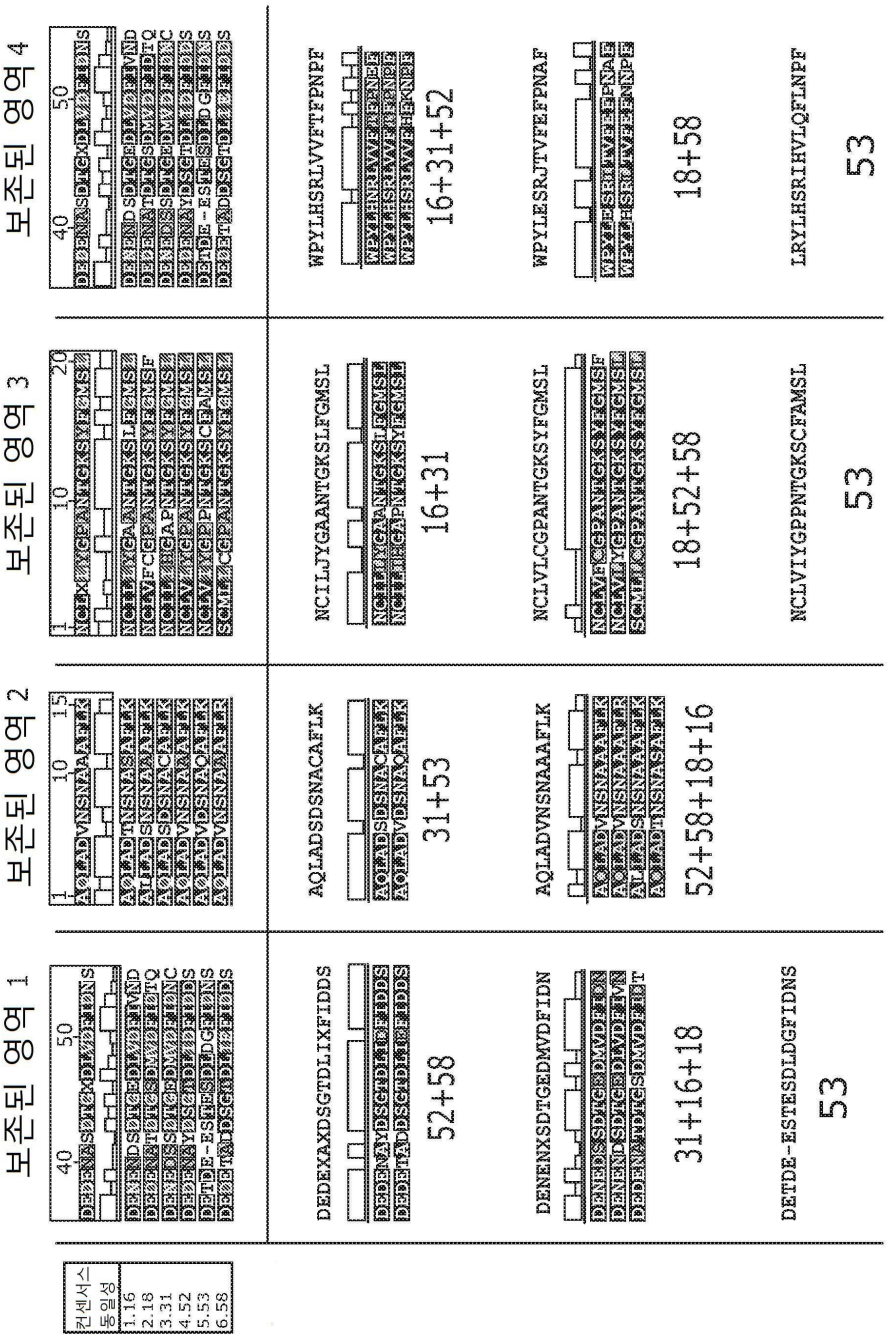
[0236]

도면

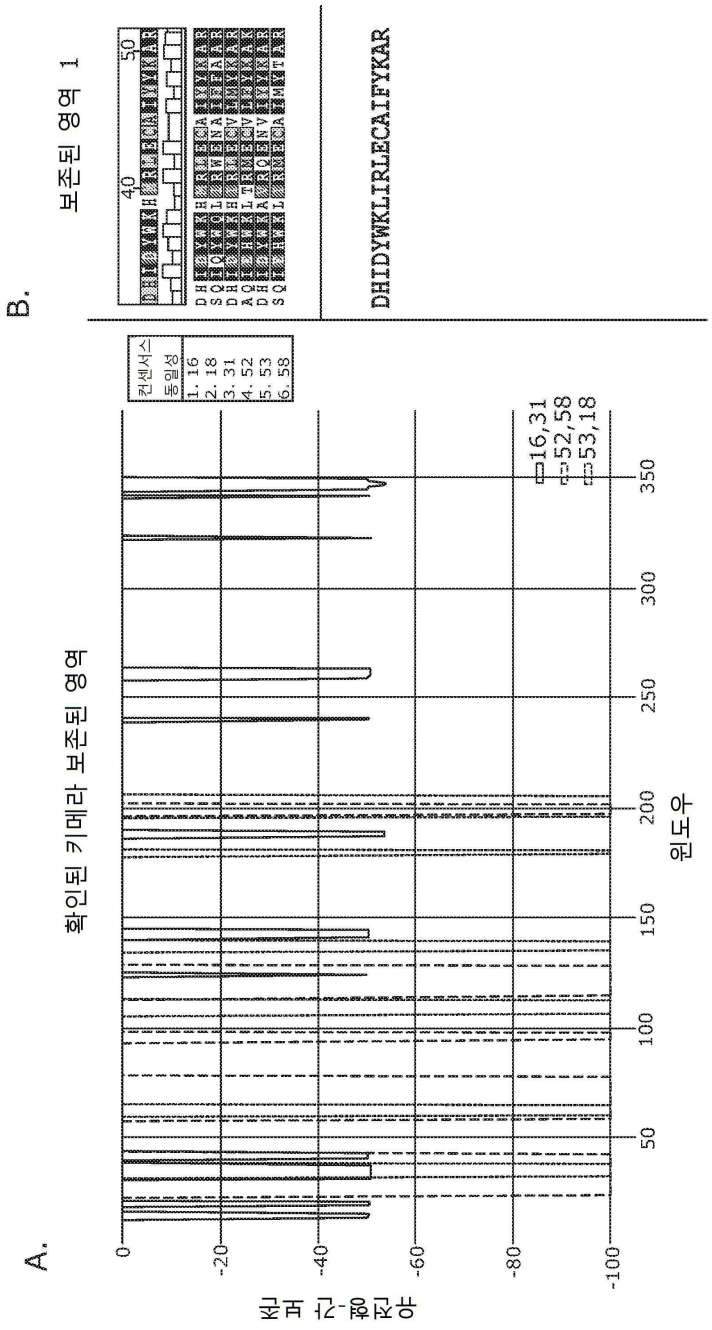
도면1


A.
번 이 체
52 58 16 31 18 53
보존 알고리즘
1. 2. 3.
알고리즘을 통해
모든 유전형을
함께 작동시킴
알고리즘이 각각의 유전형에 대한
대표적인 컨센서스를 생성함
알고리즘이 모든 유전형 사이에
공유된 보존된 영역을 확인함
각각의 유전형으로부터의
컨센서스를 사용하여
보존된 것으로 확인된 영역에서
계통발생을 수행함
군집하는 유전형으로부터
컨센서스를 생성함
B.
키 메 라
52 58 16 31 18
보존 알고리즘
모든 유전형에서
함께 계통발생함
알고리즘을 통해
밀접하게 관련된 유전형을
함께 작동시킴
알고리즘이 각각의 유전형에
대한 대표적인 컨센서스를 생
성함
함께 작동된 유전형 사이에
보존된 컨센서스에서
알고리즘이 영역을 확인함
프로그램은 보존된 영역의
컨센서스를 출력함

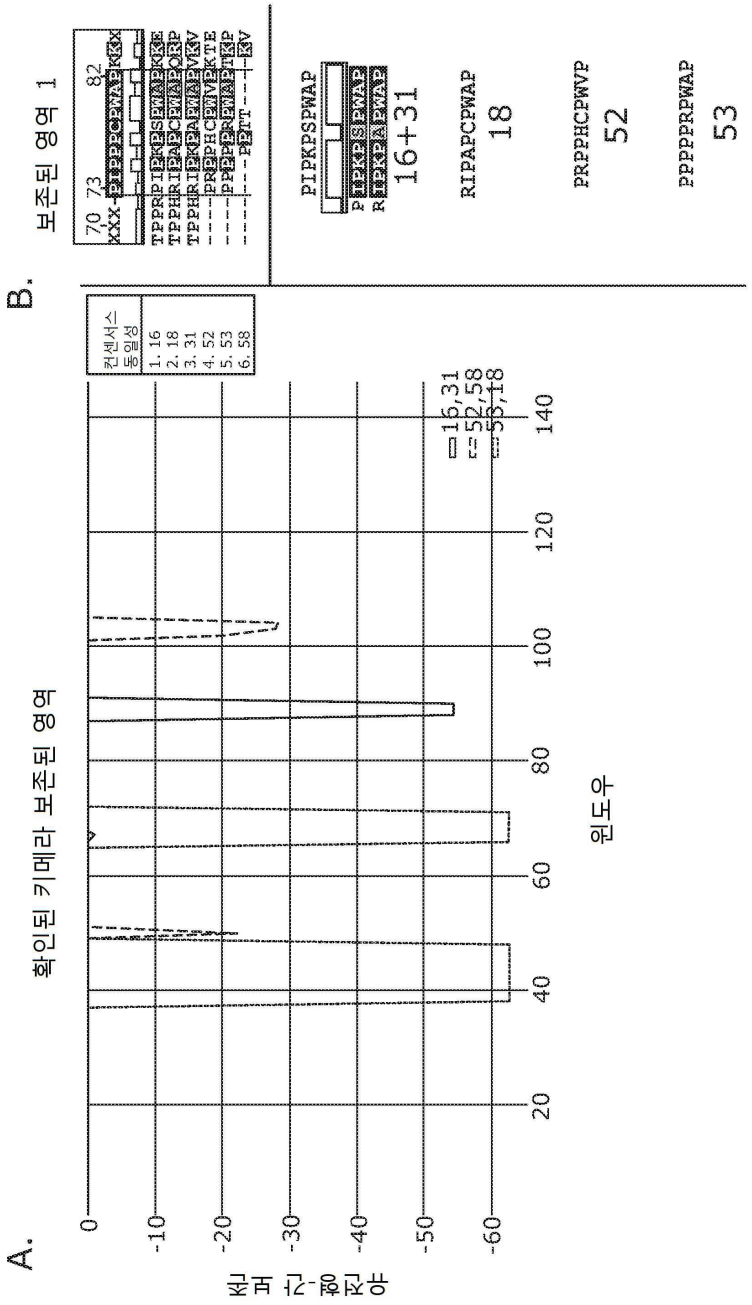
도면2


보존된 영역 1
보존된 영역 2
보존된 영역 3
보존된 영역 4
컨센서스 동일성
1.16
2.18
3.31
4.52
5.53
6.58
52+58
31+53
16+31
16+31+52
31+16+18
52+58+18+16
18+52+58
18+58
53
53
53

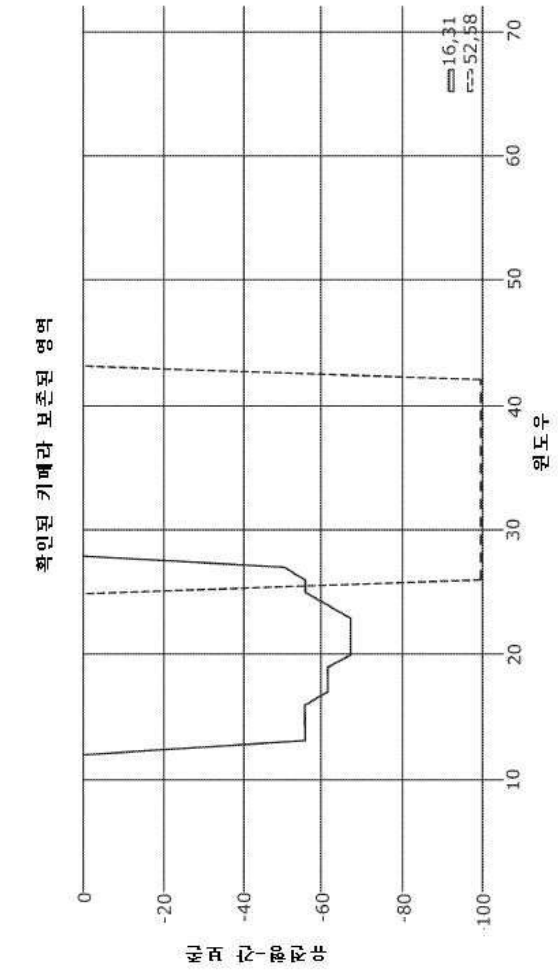
도면3


A.
확인된 키메라 보존된 영역
컨센서스
동일성
1. 16
2. 18
3. 31
4. 52
5. 53
6. 58
16,31
52,58
53,18
상관영-간 보존
윈도우
B.
보존된 영역 1
DHIDYWKLIRLECAIFYKAR

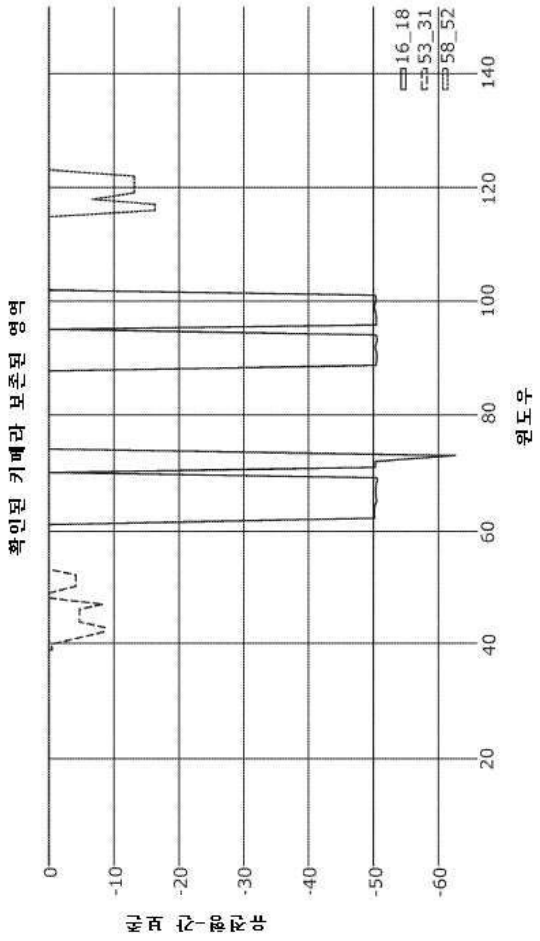
도면4


A.
확인된 키메라 보존된 영역
상관계수-간 분산
윈도우
16,31
52,58
55,18
컨센서스 동일성
1. 16
2. 18
3. 31
4. 52
5. 53
6. 58
B.
보존된 영역 1
16+31
RIPAPCPWAP
18
PRPPHCPWVP
52
PPPPPRPWAP
53

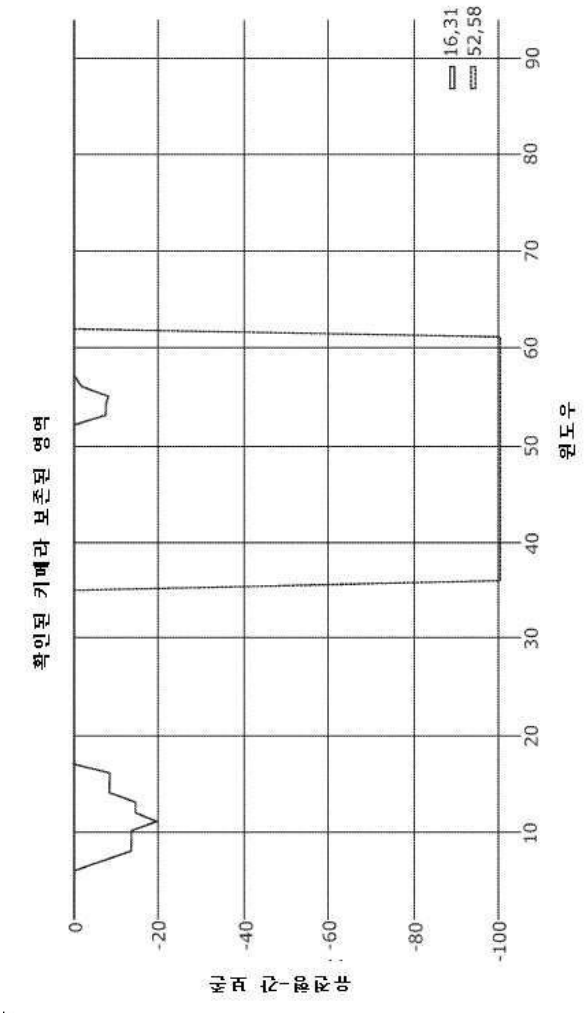
도면5


확인된 키메라 보존된 영역
유전형-간 보존
원도우
16,31
52,58
0
-20
-40
-60
-80
-100
10
20
30
40
50
60
70

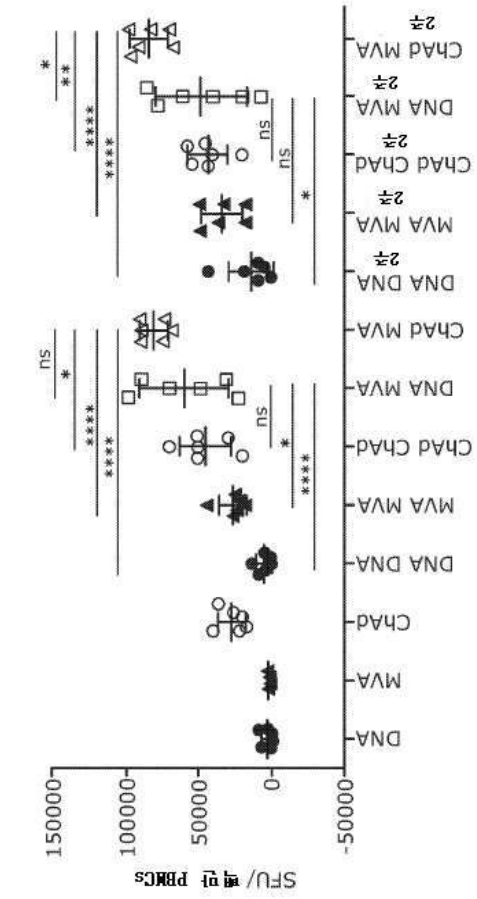
도면6


확인된 키메라 보존된 영역
유전형-간 보존
원도우
16_18
53_31
58_52
0
-10
-20
-30
-40
-50
-60
20
40
60
80
100
120
140

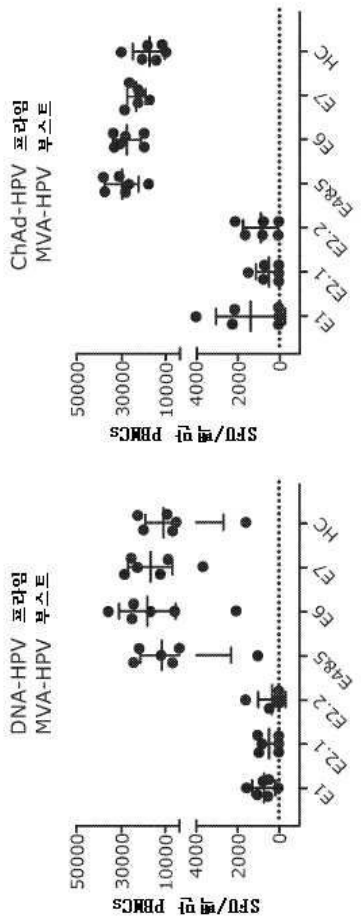
도면7


16,31
52,58
0
-20
-40
-60
-80
-100
10
20
30
40
50
60
70
80
90
유전형-간 보존
확인된 카메라 보존된 영역
원도우

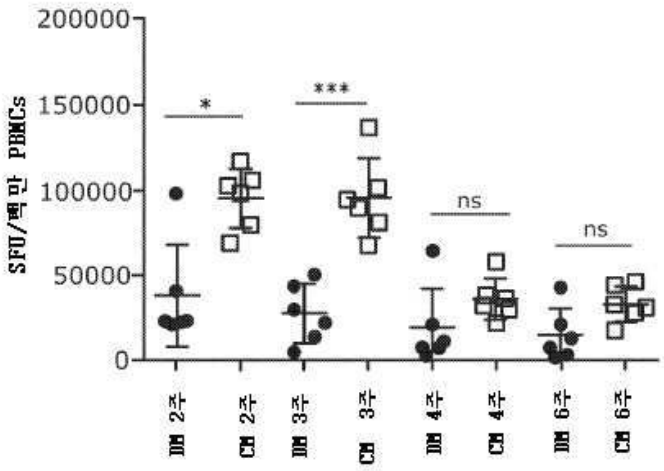
도면8


SFU/ 백만 PBMCs
150000
100000
50000
0
-50000
DNA
MVA
ChAd
DNA DNA
MVA MVA
ChAd ChAd
DNA MVA
ChAd MVA
2주
ns
*
**
****

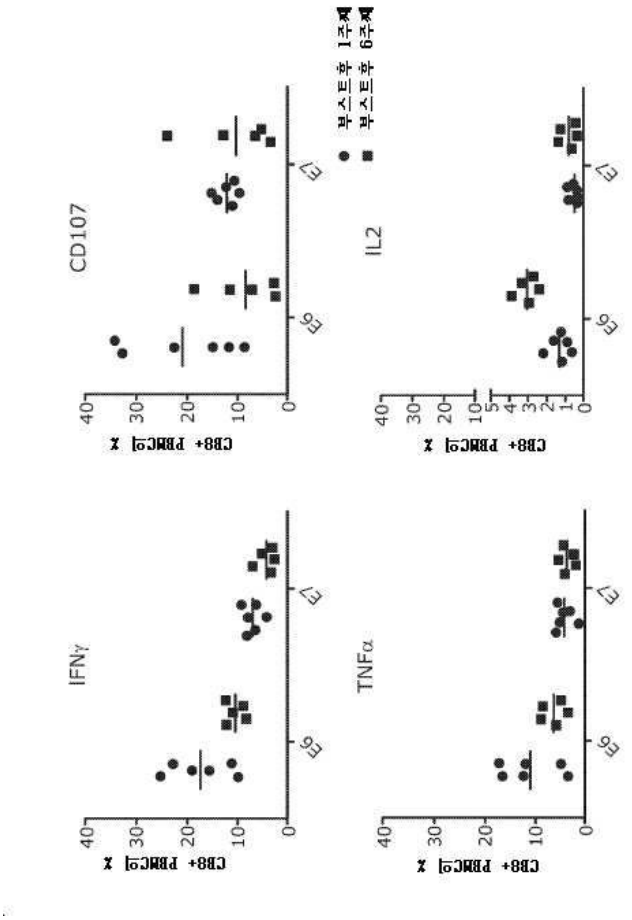
도면9


ChAd-HPV 프라임
MVA-HPV 부스트
DNA-HPV 프라임
MVA-HPV 부스트
SFU/백만 PBMCs
50000
30000
10000
4000
2000
0
E1
E2.1
E2.2
E4&5
E6
E7
HC

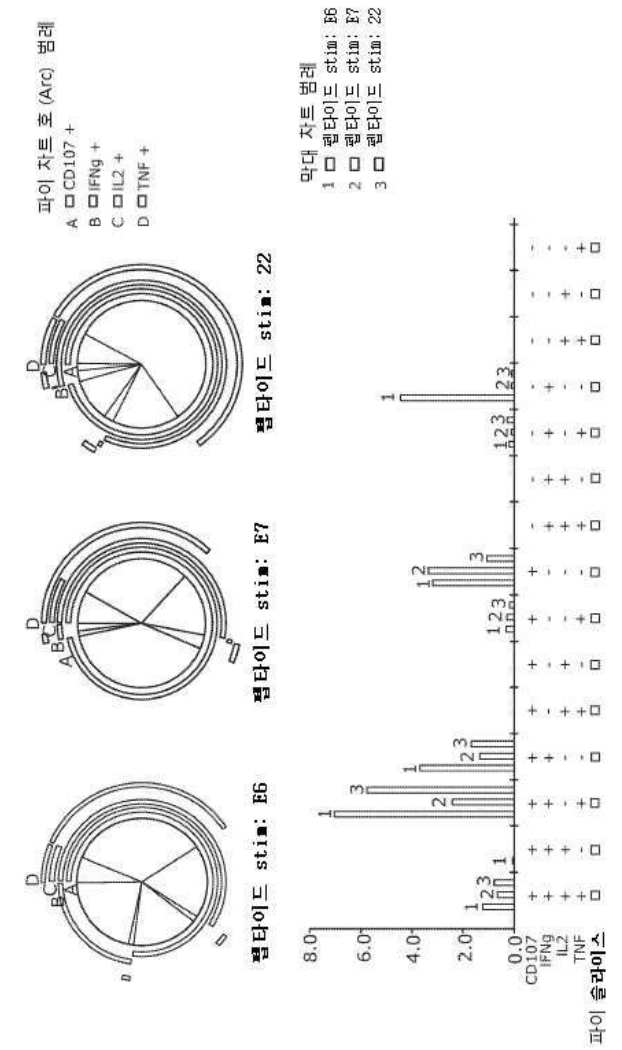
도면10a


SFU/백만 PBMCs
200000
150000
100000
50000
0
*
***
ns
ns
DM 2주
CM 2주
DM 3주
CM 3주
DM 4주
CM 4주
DM 6주
CM 6주

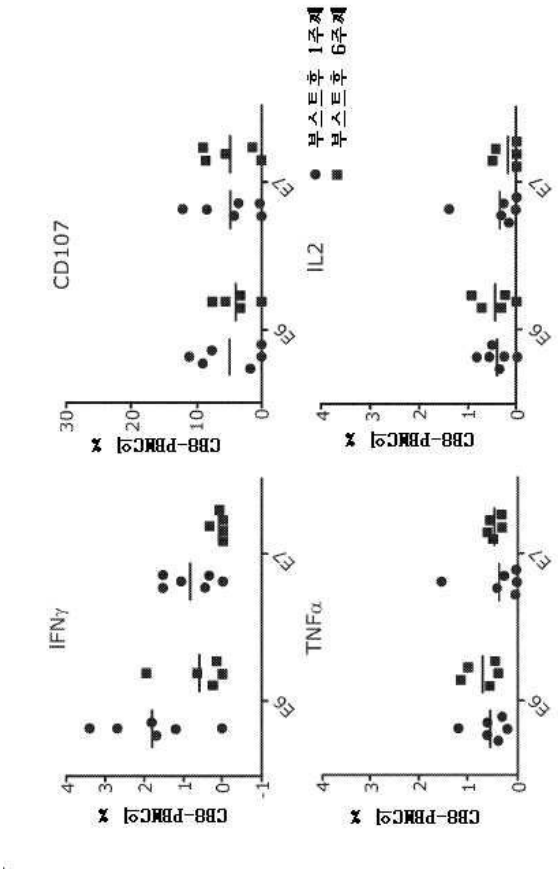
도면10b



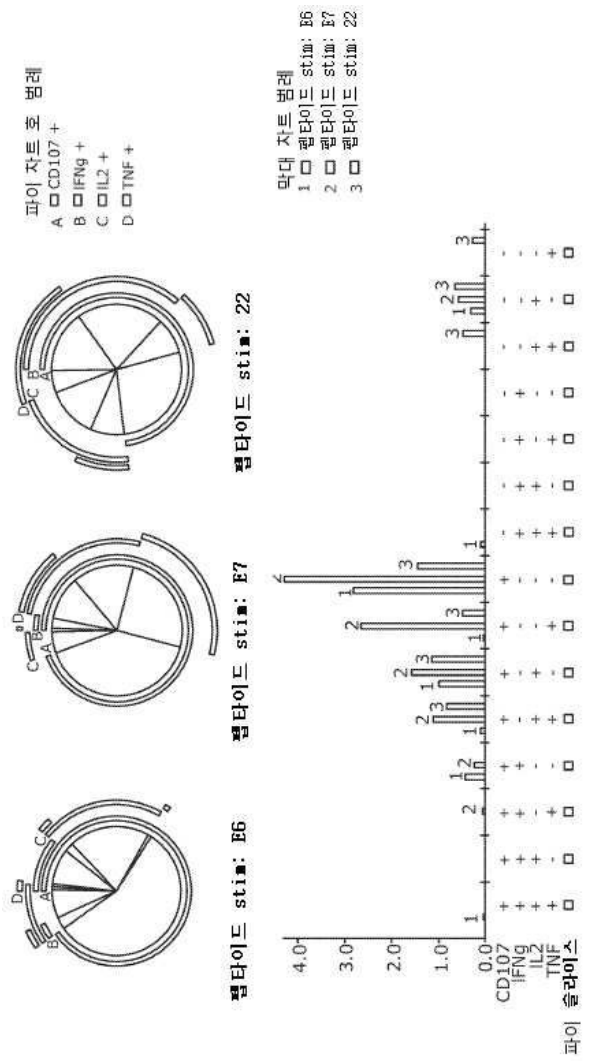
도면11


파이 차트 호 (Arc) 범례
A CD107 +
B IFNg +
C IL2 +
D TNF +
펩타이드 stim: E6
펩타이드 stim: E7
펩타이드 stim: 22
막대 차트 범례
1 펩타이드 stim: E6
2 펩타이드 stim: E7
3 펩타이드 stim: 22
8.0
6.0
4.0
2.0
0.0
CD107
IFNg
IL2
TNF
파이 슬라이스

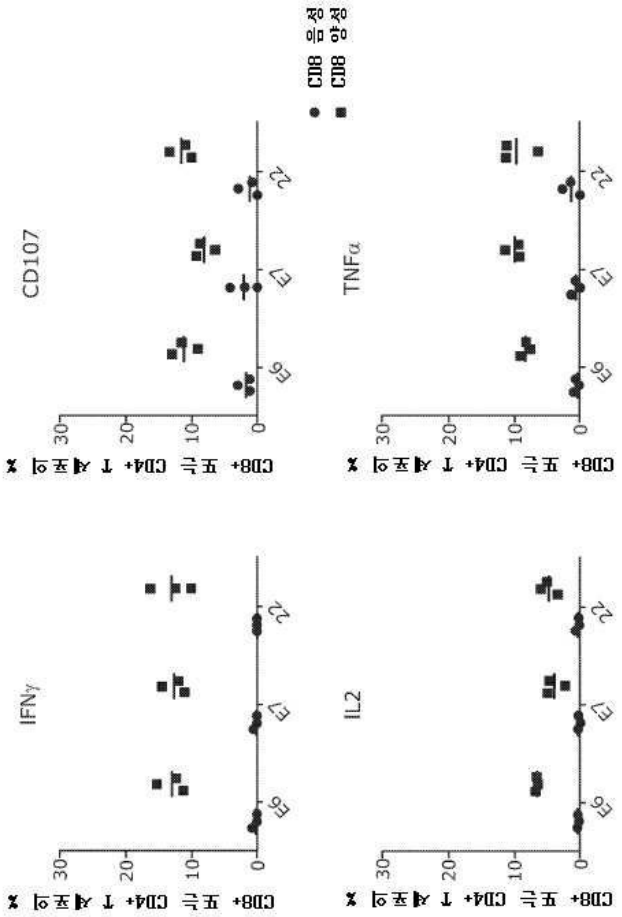
도면12



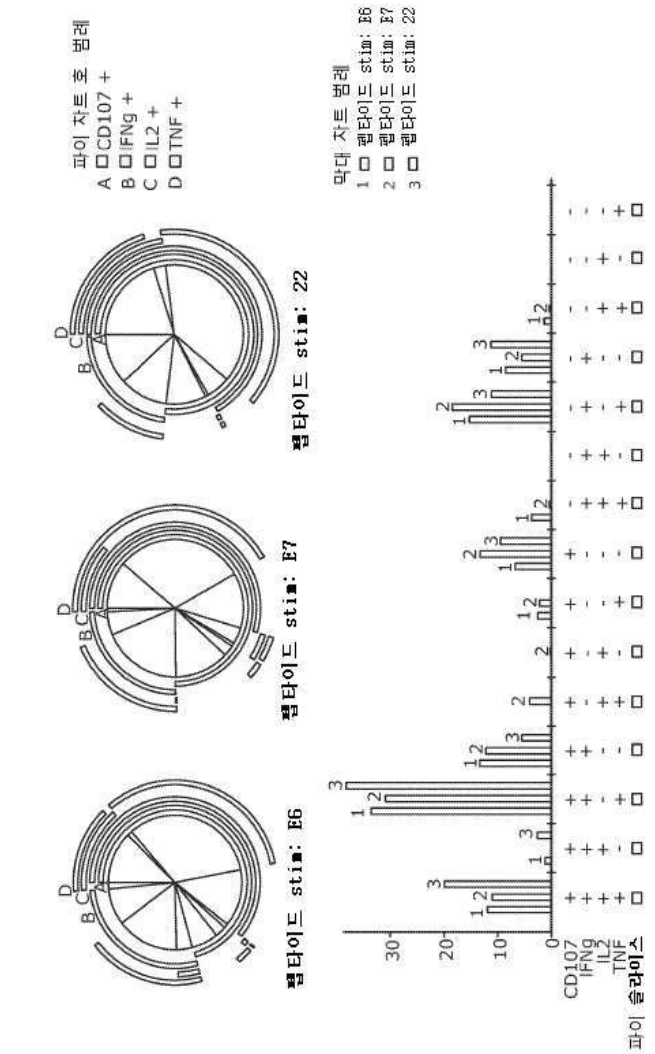
도면13


파이 차트 범례
A CD107 +
B IFNg +
C IL2 +
D TNF +
펩타이드 stim: B6
펩타이드 stim: E7
펩타이드 stim: 22
막대 차트 범례
1 펩타이드 stim: B6
2 펩타이드 stim: E7
3 펩타이드 stim: 22
4.0
3.0
2.0
1.0
0.0
CD107
IFNg
IL2
TNF
파이 슬라이스

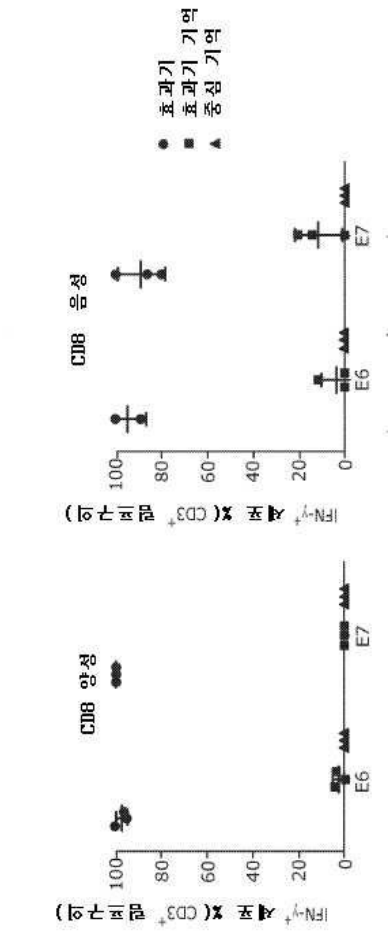
도면14


CD8 음성
CD8 양성
CD107
TNFα
IFNγ
IL2
CD8+ 또는 CD4+ T 세포의 %
0
10
20
30
6
11
22

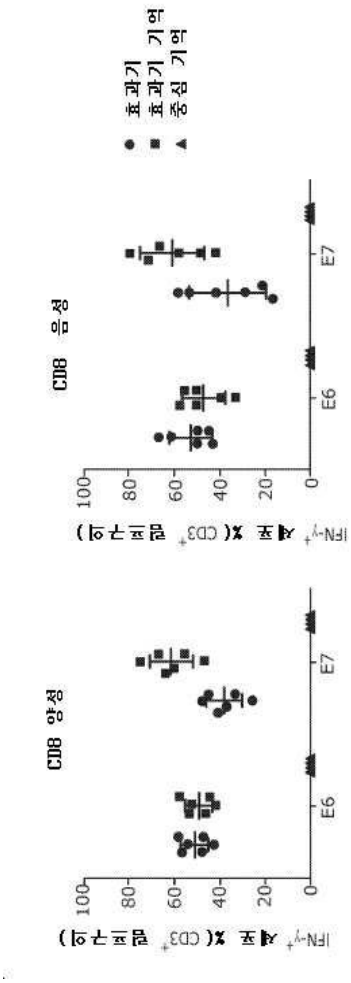
도면15


파이 차트 호 범례
A CD107 +
B IFNg +
C IL2 +
D TNF +
막대 차트 범례
1 펩타이드 stim: E6
2 펩타이드 stim: E7
3 펩타이드 stim: 22
펩타이드 stim: E6
펩타이드 stim: E7
펩타이드 stim: 22
CD107
IFNg
IL2
TNF
파이 슬라이스

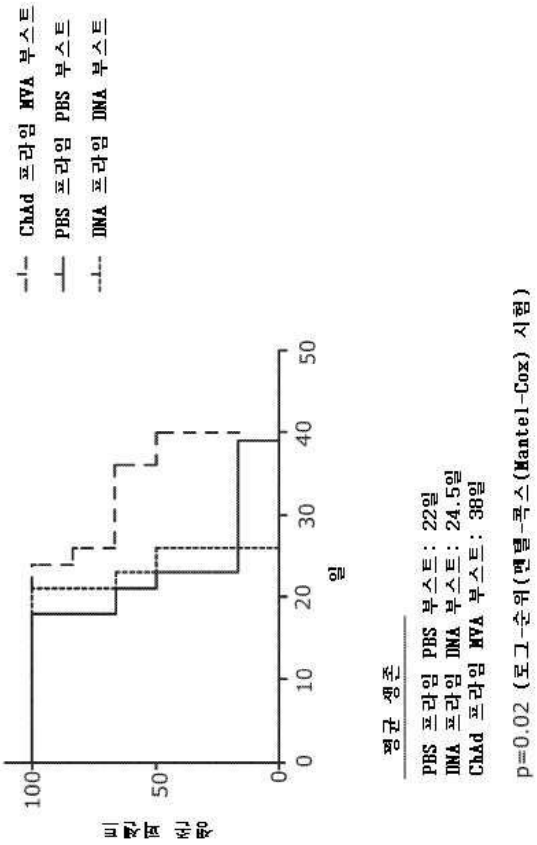
도면16



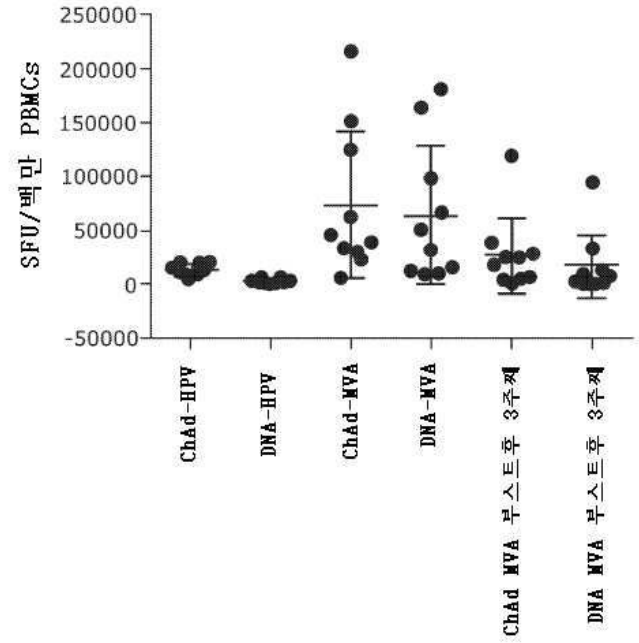
도면17



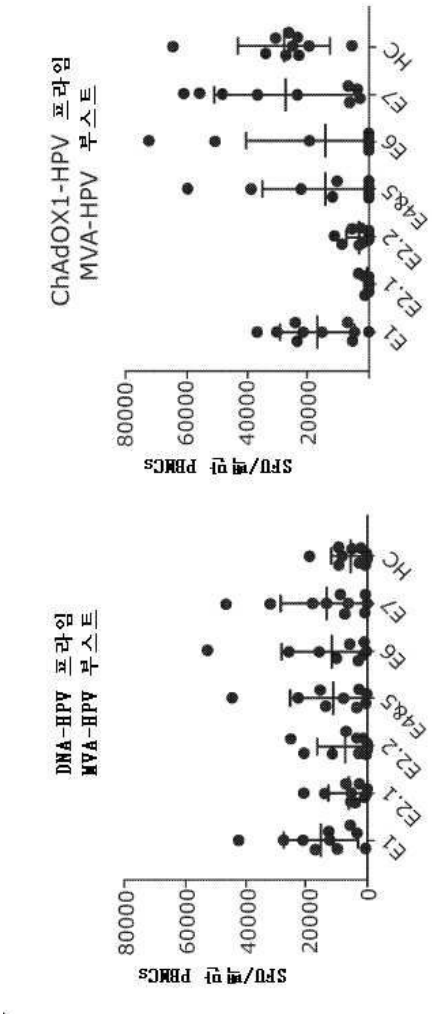
도면18


ChAd 프라임 MVA 부스트
PBS 프라임 PBS 부스트
DNA 프라임 DNA 부스트
생존 퍼센트
100
50
0
0
10
20
30
40
50
일
평균 생존
PBS 프라임 PBS 부스트: 22일
DNA 프라임 DNA 부스트: 24.5일
ChAd 프라임 MVA 부스트: 38일
p=0.02 (로그-순위(맨텔-콕스(Mantel-Cox) 시험)

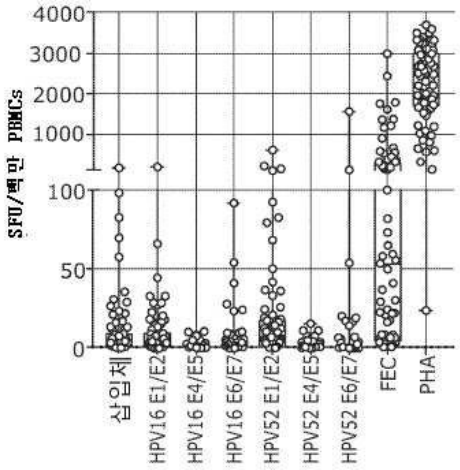
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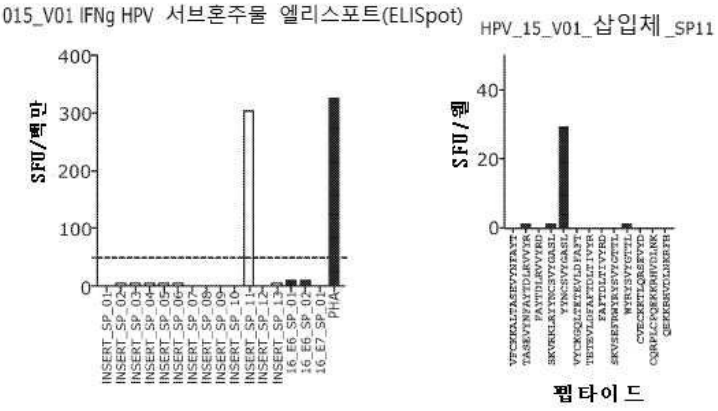

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250000
200000
150000
100000
50000
0
-50000
ChAd-HPV
DNA-HPV
ChAd-MVA
DNA-MVA
ChAd MVA 부스트후 3주째
DNA MVA 부스트후 3주째

도면20

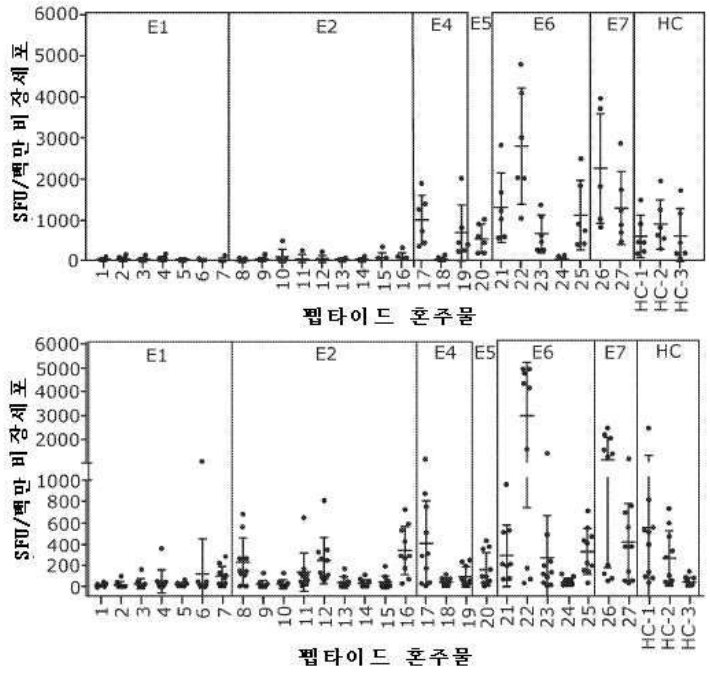

ChAdOX1-HPV 프라임
MVA-HPV 부스트
SFU/백만 PBMCs
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60000
40000
20000
E1
E2.1
E2.2
E4&5
E6
E7
HC
DNA-HPV 프라임
MVA-HPV 부스트
SFU/백만 PBMCs
80000
60000
40000
20000
0
E1
E2.1
E2.2
E4&5
E6
E7
HC

도면21


SFU/백만 PBMCs
4000
3000
2000
1000
100
50
0
삽입체
HPV16 E1/E2
HPV16 E4/E5
HPV16 E6/E7
HPV52 E1/E2
HPV52 E4/E5
HPV52 E6/E7
FEC
PHA


015_V01 IFNg HPV 서브혼주물 엘리스포트(ELISpot)
SFU/백만
400
300
200
100
0
HPV_15_V01_삽입체 _SP11
SFU/웰
40
20
0
펩타이드

도면22


SFU/백만 비정제 표
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5000
4000
3000
2000
1000
0
E1
E2
E4
E5
E6
E7
HC
HC-1
HC-2
HC-3
펩타이드 혼주물
SFU/백만 비정제 표
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5000
4000
3000
2000
1000
800
600
400
200
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E1
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서 열 목 록

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<151> 2017-08-16

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<170> PatentIn version 3.5

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Ile Asp Asn

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<211> 15

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Gly Met Ser Leu

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Ala Met Ser Leu

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Trp Pro Tyr Leu His Ser Arg Leu Val Val Phe Thr Phe Pro Asn Pro

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Phe

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Met Tyr Lys Ala Arg

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Ile Arg Leu Glu Cys Ala Ile Met Tyr Lys Ala Arg Glu Met Gly Phe

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His

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Ile Arg Leu Glu Cys Ala Ile Met Tyr Lys Ala Arg Glu Met Gly Phe

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His

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Asp

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Lys Lys Trp Glu Val His Ala Gly Gly Gln Val Ile Leu Cys Pro Glu

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Ser

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Gly Gln Arg Arg Ile Lys Arg Pro Arg Ser Glu

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Ile Leu Lys Cys Leu Arg Tyr Arg Phe Lys Lys His Cys Lys Leu

1 5 10 15

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Ser Ser Thr Trp His Trp Thr Cys His Asp Gly Lys His Lys

1 5 10

<210> 23

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Trp His Trp Thr Cys His Asp Gly Lys His Lys Asn Ala Ile Val Thr

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Leu Thr Tyr

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Tyr Glu Ala Asp Lys Asn Asp Leu Asn Ala Gln Ile Glu His Trp Lys

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Ile Ser

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Pro Tyr

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Pro Gln

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Phe Lys Lys His Gly Ile Thr Ile Thr Val Gln Tyr Asp Asn Asp Lys

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Ala Asn Thr Met Asp Tyr Thr Asn Trp Lys Glu Ile Tyr

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Glu Ala

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Asp His Ile Asp Tyr Trp Lys Ala Ile Arg Gln Glu Asn Ala Ile Phe

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Phe Ala Ala Arg

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Ala Ile Glu

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1 5 10 15

Glu Val Trp Phe Asp

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Tyr Val Ala Trp Asp Ser Val Tyr Tyr Cys Gly Asp Asp Gly Trp Cys

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Lys Thr

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Val Ser Ala Thr Glu Leu Val Lys

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Asp His Ile Asp Tyr Trp Lys Leu Ile Arg Leu Glu Cys Ala Ile Phe

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Tyr Lys Ala Arg

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Arg Arg Leu Ser Ser Asp Gln Asp Gln Ser Gln

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Leu Val Thr Lys Tyr Pro Leu Leu Lys Leu Leu Ser

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Arg Pro Pro Asn Met Gly Val Lys Ala His Gly Lys Cys Ile Trp Glu
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Thr Thr Pro Lys Ser Thr Val Val Ile Arg Leu His Leu
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Thr Thr Arg Tyr Pro Leu Leu Ser Leu Leu Asn Ser Tyr Ser Thr Pro
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Pro His Arg Ile Pro Ala Pro Cys Pro Trp Ala Pro Gln Arg Pro
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Pro Ile Pro Lys Pro Ser Pro Trp Ala Pro

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Pro Pro Pro Pro Pro Arg Pro Trp Ala Pro

1 5 10

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

1 5 10 15

Arg Pro Leu Leu Leu Ser Val Ser Thr Tyr

20 25

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Leu Val Leu Leu Leu Trp Val Ser Ile Gly Ser

20 25

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Leu Leu Pro Ser Val Cys Met Cys Ala Tyr Ala Trp Val Leu Val Phe

1 5 10 15

Val Tyr Ile Val Val Ile Thr Ser Pro Ala Thr Ala

20 25

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Ile Val Tyr Arg Asp Gly Asn Pro Tyr Ala Val Cys Asp Lys Cys Leu

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Lys Phe Tyr Ser Lys Ile Ser Glu Tyr Arg His Tyr Cys Tyr Ser Leu
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Tyr Gly Thr Thr Leu Glu Gln Gln Tyr Asn Lys Pro Leu Cys Asp Leu
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Leu Ile Arg Cys Ile Asn
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Val Val Tyr Arg Asp Ser Ile Pro His Ala Ala Cys His Lys Cys Ile
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Tyr Thr Asp Leu Arg Val Val Tyr Arg Asp
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Ser Lys Val Arg Lys Leu Arg Tyr Tyr Asn Cys Ser Val Tyr Gly Ala

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Ser Leu

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Tyr Cys Tyr Glu Gln
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Asp Glu Glu Asp Thr Gly Gly Leu Asp Gly

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Ala Arg Arg Asp Glu Gln His Pro Cys Tyr Leu Ile Glu Thr Gln Cys

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His Gln Val Val Pro Ala Leu Asn Ile Cys Lys Ala Lys Ala Cys Lys

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tattggaaac acatccgcct ggaatgtgct attatgtata aggcccggtg gccttacctg 3840

gaaagcagaa ccgtgttcga gttccccaat gccttcgccg gctctggacc tggcgcctct 3900

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<210> 72

<211> 1316

<212> PRT

<213> Artificial Sequence

<220><223> vaccine construct

<400> 72

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
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Ala Val Phe Val Ser Pro Ser Gln Glu Ile His Ala Arg Phe Arg Arg
20 25 30

Gly Ser Lys Leu Ala Ala Gln Leu Ala Asp Ser Asp Ser Asn Ala Cys
35 40 45

Ala Phe Leu Lys Leu Arg Tyr Leu His Ser Arg Ile His Val Leu Gln
50 55 60

Phe Leu Asn Pro Phe Thr Leu His Glu Tyr Met Leu Asp Leu Gln Pro
65 70 75 80

Glu Thr Thr Asp Leu Tyr Cys Tyr Glu Gln Asp Glu Asp Glu Asp Glu
85 90 95

Val Asp His Leu Gln Glu Gln Pro Gln Gln Ala Arg Arg Asp Glu Gln
100 105 110

His Pro Cys Tyr Leu Ile Glu Thr Gln Cys Cys Arg Cys Glu Ser Leu
115 120 125

Val Ala Gln Leu Ala Asp Val Asn Ser Asn Ala Ala Ala Phe Leu Lys
130 135 140

Asn Ser Ile Asp Cys Asn Asp Ser Met Cys Ser Thr Phe Asp Asp Asn
145 150 155 160

Val Ser Ala Thr Glu Leu Val Lys Arg Ile Pro Ala Pro Cys Pro Trp
165 170 175

Ala Pro Glu Glu Asn Asp Glu Ile Asp Gly Val Asn His Gln His Leu
180 185 190

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

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

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

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

435 440 445

Ile Asp Phe Ile Asp Asp Ser Asn Cys His Pro Asn Lys Leu Leu Arg

450 455 460

Arg Leu Ser Ser Asp Gln Asp Gln Ser Gln Arg Pro Pro Asn Met Gly

465 470 475 480

Val Lys Ala His Gly Lys Cys Ile Trp Glu Asn Lys Val Phe Ile Val

485 490 495

Pro Thr Leu Cys Pro Val Pro Leu Asp Pro Thr Tyr Pro Leu Leu Lys

500 505 510

Leu Leu Thr Pro Glu Thr Thr Asp Leu His Cys Tyr Glu Gln Leu Gly

515 520 525

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

530 535 540

Asp Lys Asn Asp Leu Asn Ala Gln Ile Glu His Trp Lys Leu Ile Arg

545 550 555 560

Met Glu Cys Ala Ile Phe Tyr Lys Ala Lys Glu Leu Gly Ile Ser Asp

565 570 575

Glu Asn Glu Asn Asp Ser Asp Thr Gly Glu Asp Met Val Asp Phe Ile

580 585 590

Asp Asn Glu Ala Glu Lys Tyr Gly Cys Lys Gly Thr Trp Glu Val His

595 600 605

Phe Gly Phe Lys Lys His Gly Ile Thr Ile Thr Val Gln Tyr Asp Asn

610 615 620

Asp Lys Ala Asn Thr Met Asp Tyr Thr Asn Trp Lys Glu Ile Tyr Pro

625 630 635 640

Pro Pro Pro Pro Arg Pro Trp Ala Pro Pro Ile Pro Lys Pro Ser Pro

645 650 655

Trp Ala Pro Gln Phe Asp Gly Asp Ile Cys Asn Thr Met His Tyr Thr

660 665 670

Asn Trp Val Val Tyr Arg Asp Ser Ile Pro His Ala Ala Cys His Lys

675 680 685

Cys Ile Asp Phe Tyr Ser Arg Ile Arg Glu Leu Arg His Tyr Ser Asp

690 695 700

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

755 760 765

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

820 825 830

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

885 890 895

Phe Ala Met Ser Leu Trp Asn Thr Glu Pro Lys His Cys Phe Lys Lys
900 905 910
Gly Gly Gln His Ile Glu Val Trp Phe Asp Ile Val Tyr Arg Asp Gly
915 920 925
Asn Pro Tyr Ala Val Cys Asp Lys Cys Leu Lys Phe Tyr Ser Lys Ile

930 935 940

Ser Glu Tyr Arg His Tyr Cys Tyr Ser Leu Tyr Gly Thr Thr Leu Glu

945 950 955 960

Gln Gln Tyr Asn Lys Pro Leu Cys Asp Leu Leu Ile Arg Cys Ile Asn

965 970 975

Thr Thr Arg Tyr Pro Leu Leu Ser Leu Leu Asn Ser Tyr Ser Thr Pro

980 985 990

Pro His Arg Ile Pro Ala Pro Cys Pro Trp Ala Pro Gln Arg Pro Thr

995 1000 1005

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

1010 1015 1020

Thr Thr Pro Lys Ser Thr Val Val Ile Arg Leu His Leu Trp Pro

1025 1030 1035

Tyr Leu His Ser Arg Leu Val Val Phe Thr Phe Pro Asn Pro Phe

1040 1045 1050

His Gln Val Val Pro Ala Leu Asn Ile Cys Lys Ala Lys Ala Cys

1055 1060 1065

Lys Ala Ile Glu Lys Lys Trp Glu Val His Ala Gly Gly Gln Val

1070 1075 1080

Ile Leu Cys Pro Glu Ser Leu Arg Pro Leu Leu Leu Ser Ile Ser

1085 1090 1095

Val Tyr Ala Gln Val Leu Val Leu Val Leu Leu Leu Trp Val Ser

1100 1105 1110

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

1115 1120 1125

Lys Ser Tyr Phe Gly Met Ser Leu Ile Cys His Gln Val Val Pro

1130 1135 1140

Pro Leu Ala Ala Ser Lys Ala Lys Ala Cys Gln Ala Ile Glu Leu

1145 1150 1155

Gln Leu Ala Leu Glu Ala Leu Asn Ala Ser Pro Tyr Asp His Ile

1160 1165 1170

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

1175 1180 1185

Ala Arg Trp His Trp Thr Cys His Asp Gly Lys His Lys Asn Ala

1190 1195 1200

Ile Val Thr Leu Thr Tyr Leu Leu Pro Ser Val Cys Met Cys Ala

1205 1210 1215

Tyr Ala Trp Val Leu Val Phe Val Tyr Ile Val Val Ile Thr Ser

1220 1225 1230

Pro Ala Thr Ala Asp Glu Trp Thr Leu Gln Gln Thr Ser Leu Glu

1235 1240 1245

Met Trp Leu Ala Glu Pro Gln Cys Asp His Ile Asp Tyr Trp Lys

1250 1255 1260

His Ile Arg Leu Glu Cys Ala Ile Met Tyr Lys Ala Arg Trp Pro

1265 1270 1275

Tyr Leu Glu Ser Arg Thr Val Phe Glu Phe Pro Asn Ala Phe Ala

1280 1285 1290

Gly Ser Gly Pro Gly Ala Ser Gly Lys Pro Ile Pro Asn Pro Leu

1295 1300 1305

Leu Gly Leu Asp Ser Thr Arg Thr

1310 1315

<210> 73

<211> 3321

<212> DNA

<213> Artificial Sequence

<220><223> vaccine construct

<400> 73

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tcccctagcc aagagatcca cgccagattc agacggggca gcaaactggc cgacgaggat 120

gagacagcct acgactctgg caccgacctg atcgacttca tcgacgacag cgacgagaac 180

gagaatgaca gcgacaccgg cgaggacatg gtggatttca tcgacaatgc ccagctggcc 240

gactccgact ctaatgcctg tgcctttctg aaggctcagc tggctgacgt gaacagcaat 300

gccgccgctt tcctgaagaa ctgcatcctg ctgtacggcg ctgccaacac aggcaagagc 360

ctgtttggca tgagcctgaa ctgcctggtg ctgtgcggac ctgccaatac cggcaaaagc 420

tacttcggca tgtccctgtg gccttacctg cacagcagac tggtggtgtt tacattcccc 480

aatcctttct ggccctacct ggaaagccgg atcaccgtgt tcgagttccc caacgccttc 540

aacgtgtgcc aggacaagat cctggaacac tatgagaacg acagcaagga catccttgag 600

cactacgaaa acgactccaa ggacctgtgc gaccacatct gcgatcacat cgactactgg 660

aagcacatcc ggctggaatg cgccatcatg tacaaggccc ggatcagact ggaatgtgct 720

attatgtata aggctcgcga gatgggcttc caccagttcg acggcgacat ctgcaacacc 780

atgcactaca ccaactggat ctatatctgc gaggacgccc agtgcaccgt ggtggaagga 840

caggtggaca agaaatggga agtgcacgct ggcggccaag tgattctgtg tcctgagagc 900

ggccagcgga gaatcaagag gcccagatcc gagaactgtc accccaacaa gctgctgatc 960

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agcatctgcc accaggtggt gcctccactg gctgcctcta aagccaaagc ctgtcaggcc 1260

atcgaactgc agctggccct ggaagccctg aacgctagcc cttacgatga gtggaccctg 1320

cagcagacca gcctggaaat gtggctggcc gagcctcagt ttaagaagca cggcatcacc 1380

atcaccgtgc agtacgacaa cgacaaggcc aataccatgg attacacgaa ttggaaagaa 1440

atctacgtga tcgtgtgccc cgccagcatt ccctccgatg agatctctac cgaggaagcc 1500

gaccacattg attattggaa ggccatccgg caagagaatg ccatcttctt cgccgccaga 1560

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gatacaggcg gactggacgg cgaggaaaac gacgaaattg acggcgtgaa ccaccagcat 3240

ctccccgcca gaagggctga acctcagaga cacaccatgc tgtgtatgtg ctgcaagtgc 3300

gaggccagaa tcgcctgatg a 3321

<210> 74

<211> 1105

<212> PRT

<213> Artificial Sequence

<220><223> vaccine construct

<400> 74

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly

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20 25 30

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

35 40 45

Asp Leu Ile Asp Phe Ile Asp Asp Ser Asp Glu Asn Glu Asn Asp Ser

50 55 60

Asp Thr Gly Glu Asp Met Val Asp Phe Ile Asp Asn Ala Gln Leu Ala

65 70 75 80

Asp Ser Asp Ser Asn Ala Cys Ala Phe Leu Lys Ala Gln Leu Ala Asp

85 90 95

Val Asn Ser Asn Ala Ala Ala Phe Leu Lys Asn Cys Ile Leu Leu Tyr

100 105 110

Gly Ala Ala Asn Thr Gly Lys Ser Leu Phe Gly Met Ser Leu Asn Cys

115 120 125

Leu Val Leu Cys Gly Pro Ala Asn Thr Gly Lys Ser Tyr Phe Gly Met

130 135 140

Ser Leu Trp Pro Tyr Leu His Ser Arg Leu Val Val Phe Thr Phe Pro

145 150 155 160

Asn Pro Phe Trp Pro Tyr Leu Glu Ser Arg Ile Thr Val Phe Glu Phe

165 170 175

Pro Asn Ala Phe Asn Val Cys Gln Asp Lys Ile Leu Glu His Tyr Glu

180 185 190

Asn Asp Ser Lys Asp Ile Leu Glu His Tyr Glu Asn Asp Ser Lys Asp

195 200 205

Leu Cys Asp His Ile Cys Asp His Ile Asp Tyr Trp Lys His Ile Arg

210 215 220

Leu Glu Cys Ala Ile Met Tyr Lys Ala Arg Ile Arg Leu Glu Cys Ala

225 230 235 240

Ile Met Tyr Lys Ala Arg Glu Met Gly Phe His Gln Phe Asp Gly Asp

245 250 255

Ile Cys Asn Thr Met His Tyr Thr Asn Trp Ile Tyr Ile Cys Glu Asp

260 265 270

Ala Gln Cys Thr Val Val Glu Gly Gln Val Asp Lys Lys Trp Glu Val

275 280 285

His Ala Gly Gly Gln Val Ile Leu Cys Pro Glu Ser Gly Gln Arg Arg

290 295 300

Ile Lys Arg Pro Arg Ser Glu Asn Cys His Pro Asn Lys Leu Leu Ile

305 310 315 320

Leu Lys Cys Leu Arg Tyr Arg Phe Lys Lys His Cys Lys Leu Ser Ser

325 330 335

Thr Trp His Trp Thr Cys His Asp Gly Lys His Lys Trp His Trp Thr

340 345 350

Cys His Asp Gly Lys His Lys Asn Ala Ile Val Thr Leu Thr Tyr Tyr

355 360 365

Glu Ala Asp Lys Asn Asp Leu Asn Ala Gln Ile Glu His Trp Lys Leu

370 375 380

Ile Arg Met Glu Cys Ala Ile Phe Tyr Lys Ala Lys Glu Leu Gly Ile

385 390 395 400

Ser Ile Cys His Gln Val Val Pro Pro Leu Ala Ala Ser Lys Ala Lys

405 410 415

Ala Cys Gln Ala Ile Glu Leu Gln Leu Ala Leu Glu Ala Leu Asn Ala

420 425 430

Ser Pro Tyr Asp Glu Trp Thr Leu Gln Gln Thr Ser Leu Glu Met Trp

435 440 445

Leu Ala Glu Pro Gln Phe Lys Lys His Gly Ile Thr Ile Thr Val Gln

450 455 460

Tyr Asp Asn Asp Lys Ala Asn Thr Met Asp Tyr Thr Asn Trp Lys Glu

465 470 475 480

Ile Tyr Val Ile Val Cys Pro Ala Ser Ile Pro Ser Asp Glu Ile Ser

485 490 495

Thr Glu Glu Ala Asp His Ile Asp Tyr Trp Lys Ala Ile Arg Gln Glu

500 505 510

Asn Ala Ile Phe Phe Ala Ala Arg His Gln Val Val Pro Ala Leu Asn

515 520 525

Ile Cys Lys Ala Lys Ala Cys Lys Ala Ile Glu Trp Asn Thr Glu Pro
530 535 540
Lys His Cys Phe Lys Lys Gly Gly Gln His Ile Glu Val Trp Phe Asp

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

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

675 680 685
His Leu Thr Thr Arg Tyr Pro Leu Leu Ser Leu Leu Asn Ser Tyr Ser
690 695 700
Thr Pro Pro His Arg Ile Pro Ala Pro Cys Pro Trp Ala Pro Gln Arg
705 710 715 720
Pro Pro Ile Pro Lys Pro Ser Pro Trp Ala Pro Arg Ile Pro Ala Pro
725 730 735
Cys Pro Trp Ala Pro Pro Arg Pro Pro His Cys Pro Trp Val Pro Cys

740 745 750
Phe Leu Leu Cys Phe Cys Val Leu Leu Cys Val Cys Leu Leu Ile Arg
755 760 765
Pro Leu Leu Leu Ser Val Ser Thr Tyr Leu Arg Pro Leu Leu Leu Ser

770 775 780

Ile Ser Val Tyr Ala Gln Val Leu Val Leu Val Leu Leu Leu Trp Val

785 790 795 800

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

805 810 815

Val Leu Val Phe Val Tyr Ile Val Val Ile Thr Ser Pro Ala Thr Ala

820 825 830

Ile Val Tyr Arg Asp Gly Asn Pro Tyr Ala Val Cys Asp Lys Cys Leu

835 840 845

Lys Phe Tyr Ser Lys Ile Ser Glu Tyr Arg His Tyr Cys Tyr Ser Leu

850 855 860

Tyr Gly Thr Thr Leu Glu Gln Gln Tyr Asn Lys Pro Leu Cys Asp Leu

865 870 875 880

Leu Ile Arg Cys Ile Asn Val Val Tyr Arg Asp Ser Ile Pro His Ala

885 890 895

Ala Cys His Lys Cys Ile Asp Phe Tyr Ser Arg Ile Arg Glu Leu Arg

900 905 910

His Tyr Ser Asp Ser Val Tyr Gly Asp Thr Leu Glu Lys Leu Thr Asn

915 920 925

Thr Gly Leu Tyr Asn Leu Leu Ile Arg Cys Leu Arg Val Tyr Cys Lys

930 935 940

Gly Gln Leu Thr Glu Thr Glu Val Leu Asp Phe Ala Phe Thr Asp Leu

945 950 955 960

Thr Ile Val Tyr Arg Asp Ser Lys Val Ser Glu Phe Arg Trp Tyr Arg

965 970 975

Tyr Ser Val Tyr Gly Thr Thr Leu Cys Val Glu Cys Lys Lys Thr Leu

980 985 990

Gln Arg Ser Glu Val Tyr Asp Cys Gln Arg Pro Leu Cys Pro Gln Glu

995 1000 1005

Lys Lys Arg His Val Asp Leu Asn Lys Arg Phe His Thr Leu His

1010 1015 1020

Glu Tyr Met Leu Asp Leu Gln Pro Glu Thr Thr Asp Leu Tyr Cys

1025 1030 1035

Tyr Glu Gln Pro Glu Thr Thr Asp Leu His Cys Tyr Glu Gln Leu

1040 1045 1050

Gly Asp Ser Ser Asp Glu Glu Asp Thr Gly Gly Leu Asp Gly Glu

1055 1060 1065

Glu Asn Asp Glu Ile Asp Gly Val Asn His Gln His Leu Pro Ala

1070 1075 1080

Arg Arg Ala Glu Pro Gln Arg His Thr Met Leu Cys Met Cys Cys

1085 1090 1095

Lys Cys Glu Ala Arg Ile Ala

1100 1105

<210> 75

<211> 4470

<212> DNA

<213> Artificial Sequence

<220><223> vaccine construct

<400> 75

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gagacagcct acgacagcgg caccgacctg atcgacttca tcgacgatag cgccgctgcc 180

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gctcagctgg cagacgtgaa cagcaatgcc gccgcttttc tgaaggctgc cgccaactgc 420

atcctgctgt acggcgctgc caacaccggc aagagcctgt tcggcatgtc tctggccgca 480

gccaactgcc tggtgctgtg cggacctgcc aatactggca aaagctactt cggcatgagc 540

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Gly Ser Lys Leu Ala Asp Glu Asp Glu Thr Ala Tyr Asp Ser Gly Thr
35 40 45

Asp Leu Ile Asp Phe Ile Asp Asp Ser Ala Ala Ala Asp Glu Asn Glu
50 55 60

Asn Asp Ser Asp Thr Gly Glu Asp Met Val Asp Phe Ile Asp Asn Ala
65 70 75 80

Ala Ala Asp Glu Thr Asp Glu Glu Ser Thr Glu Ser Asp Leu Asp Gly
85 90 95

Phe Ile Asp Asn Ser Ala Ala Ala Gln Leu Ala Asp Ser Asp Ser Asn
100 105 110

Ala Cys Ala Phe Leu Lys Ala Ala Ala Gln Leu Ala Asp Val Asn Ser
115 120 125

Asn Ala Ala Ala Phe Leu Lys Ala Ala Ala Asn Cys Ile Leu Leu Tyr
130 135 140

Gly Ala Ala Asn Thr Gly Lys Ser Leu Phe Gly Met Ser Leu Ala Ala
145 150 155 160

Ala Asn Cys Leu Val Leu Cys Gly Pro Ala Asn Thr Gly Lys Ser Tyr
165 170 175

Phe Gly Met Ser Leu Ala Ala Ala Asn Cys Leu Val Ile Tyr Gly Pro
180 185 190

Pro Asn Thr Gly Lys Ser Cys Phe Ala Met Ser Leu Ala Ala Ala Trp

195 200 205

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

Lys Ile Leu Glu His Tyr Glu Asn Asp Ser Lys Asp Ala Ala Ala Ile
275 280 285
Leu Glu His Tyr Glu Asn Asp Ser Lys Asp Leu Cys Asp His Ile Ala
290 295 300
Ala Ala Cys Asp His Ile Asp Tyr Trp Lys His Ile Arg Leu Glu Cys
305 310 315 320
Ala Ile Met Tyr Lys Ala Arg Ala Ala Ala Ile Arg Leu Glu Cys Ala
325 330 335

Ile Met Tyr Lys Ala Arg Glu Met Gly Phe His Ala Ala Ala Gln Phe
340 345 350
Asp Gly Asp Ile Cys Asn Thr Met His Tyr Thr Asn Trp Ala Ala Ala
355 360 365
Ile Tyr Ile Cys Glu Asp Ala Gln Cys Thr Val Val Glu Gly Gln Val
370 375 380
Asp Ala Ala Ala Lys Lys Trp Glu Val His Ala Gly Gly Gln Val Ile
385 390 395 400

Leu Cys Pro Glu Ser Ala Ala Ala Gly Gln Arg Arg Ile Lys Arg Pro
405 410 415
Arg Ser Glu Ala Ala Ala Asn Cys His Pro Asn Lys Leu Leu Ala Ala
420 425 430
Ala Ile Leu Lys Cys Leu Arg Tyr Arg Phe Lys Lys His Cys Lys Leu
435 440 445

Ala Ala Ala Ser Ser Thr Trp His Trp Thr Cys His Asp Gly Lys His
450 455 460

Lys Ala Ala Ala Trp His Trp Thr Cys His Asp Gly Lys His Lys Asn
465 470 475 480
Ala Ile Val Thr Leu Thr Tyr Ala Ala Ala Tyr Glu Ala Asp Lys Asn
485 490 495
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Ala Ile Phe Tyr Lys Ala Lys Glu Leu Gly Ile Ser Ala Ala Ala Ile
515 520 525

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

Ile Thr Val Gln Tyr Asp Asn Asp Lys Ala Asn Thr Met Asp Tyr Thr
595 600 605
Asn Trp Lys Glu Ile Tyr Ala Ala Ala Val Ile Val Cys Pro Ala Ser
610 615 620
Ile Pro Ser Asp Glu Ile Ser Thr Glu Glu Ala Ala Ala Asp His Ile
625 630 635 640
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Arg Ala Ala Ala His Gln Val Val Pro Ala Leu Asn Ile Cys Lys Ala
660 665 670
Lys Ala Cys Lys Ala Ile Glu Ala Ala Ala Trp Asn Thr Glu Pro Lys
675 680 685
His Cys Phe Lys Lys Gly Gly Gln His Ile Glu Val Trp Phe Asp Ala

690 695 700

Ala Ala Tyr Val Ala Trp Asp Ser Val Tyr Tyr Cys Gly Asp Asp Gly

705 710 715 720

Trp Cys Lys Thr Ala Ala Ala Glu Ala Glu Lys Tyr Gly Cys Lys Gly

725 730 735

Thr Trp Glu Val His Phe Gly Ala Ala Ala Asn Ser Ile Asp Cys Asn

740 745 750

Asp Ser Met Cys Ser Thr Phe Asp Asp Asn Val Ser Ala Thr Glu Leu

755 760 765

Val Lys Ala Ala Ala Asp His Ile Asp Tyr Trp Lys Leu Ile Arg Leu

770 775 780

Glu Cys Ala Ile Phe Tyr Lys Ala Arg Ala Ala Ala Arg Arg Leu Ser

785 790 795 800

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

805 810 815

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820 825 830

Lys Ala His Gly Lys Cys Ile Trp Glu Asn Lys Val Phe Ile Val Pro

835 840 845

Thr Leu Cys Pro Val Pro Leu Asp Pro Thr Tyr Pro Leu Leu Lys Leu

850 855 860

Leu Thr Ala Ala Ala Thr Gln Thr Thr Thr Pro Glu Asn Thr Ser Leu

865 870 875 880

Val Glu Leu Arg Val Thr Thr Pro Lys Ser Thr Val Val Ile Arg Leu

885 890 895

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

900 905 910

Ser Tyr Ser Thr Pro Pro His Arg Ile Pro Ala Pro Cys Pro Trp Ala

915 920 925

Pro Gln Arg Pro Ala Ala Ala Pro Ile Pro Lys Pro Ser Pro Trp Ala

930 935 940

Pro Ala Ala Ala Arg Ile Pro Ala Pro Cys Pro Trp Ala Pro Ala Ala
945 950 955 960
Ala Pro Arg Pro Pro His Cys Pro Trp Val Pro Ala Ala Ala Pro Pro
965 970 975

Pro Pro Pro Arg Pro Trp Ala Pro Ala Ala Ala Cys Phe Leu Leu Cys
980 985 990
Phe Cys Val Leu Leu Cys Val Cys Leu Leu Ile Arg Pro Leu Leu Leu
995 1000 1005
Ser Val Ser Thr Tyr Ala Ala Ala Leu Arg Pro Leu Leu Leu Ser
1010 1015 1020
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Val Ser Ile Gly Ser Ala Ala Ala Leu Leu Pro Ser Val Cys Met
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Thr Ser Pro Ala Thr Ala Ala Ala Ile Val Tyr Arg Asp Gly Asn
1070 1075 1080
Pro Tyr Ala Val Cys Asp Lys Cys Leu Lys Phe Tyr Ser Lys Ile
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Ser Glu Tyr Arg His Tyr Cys Tyr Ser Leu Tyr Gly Thr Thr Leu
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Glu Gln Gln Tyr Asn Lys Pro Leu Cys Asp Leu Leu Ile Arg Cys
1115 1120 1125
Ile Asn Ala Ala Ala Val Val Tyr Arg Asp Ser Ile Pro His Ala
1130 1135 1140
Ala Cys His Lys Cys Ile Asp Phe Tyr Ser Arg Ile Arg Glu Leu
1145 1150 1155

Arg His Tyr Ser Asp Ser Val Tyr Gly Asp Thr Leu Glu Lys Leu
1160 1165 1170
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1175 1180 1185

Ala Ala Val Phe Cys Lys Lys Ala Leu Thr Ala Ser Glu Val Tyr

1190 1195 1200

Asn Phe Ala Tyr Thr Asp Leu Arg Val Val Tyr Arg Asp Ala Ala

1205 1210 1215

Ala Ser Lys Val Arg Lys Leu Arg Tyr Tyr Asn Cys Ser Val Tyr

1220 1225 1230

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

1235 1240 1245

Glu Thr Glu Val Leu Asp Phe Ala Phe Thr Asp Leu Thr Ile Val

1250 1255 1260

Tyr Arg Asp Ala Ala Ala Ser Lys Val Ser Glu Phe Arg Trp Tyr

1265 1270 1275

Arg Tyr Ser Val Tyr Gly Thr Thr Leu Ala Ala Ala Cys Val Glu

1280 1285 1290

Cys Lys Lys Thr Leu Gln Arg Ser Glu Val Tyr Asp Ala Ala Ala

1295 1300 1305

Cys Gln Arg Pro Leu Cys Pro Gln Glu Lys Lys Arg His Val Asp

1310 1315 1320

Leu Asn Lys Arg Phe His Ala Ala Ala Thr Leu His Glu Tyr Met

1325 1330 1335

Leu Asp Leu Gln Pro Glu Thr Thr Asp Leu Tyr Cys Tyr Glu Gln

1340 1345 1350

Ala Ala Ala Pro Glu Thr Thr Asp Leu His Cys Tyr Glu Gln Leu

1355 1360 1365

Gly Asp Ser Ser Asp Glu Glu Asp Thr Gly Gly Leu Asp Ala Ala

1370 1375 1380

Ala Gly Asp Glu Asp Glu Asp Glu Val Asp His Leu Gln Glu Gln

1385 1390 1395

Pro Gln Gln Ala Arg Arg Asp Glu Gln His Pro Cys Tyr Leu Ile

1400 1405 1410

Glu Thr Gln Cys Cys Arg Cys Glu Ser Leu Val Ala Ala Ala Glu

1415 1420 1425

Glu Asn Asp Glu Ile Asp Gly Val Asn His Gln His Leu Pro Ala

1430 1435 1440

Arg Arg Ala Glu Pro Gln Arg His Thr Met Leu Cys Met Cys Cys

1445 1450 1455

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<212> PRT

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1 5 10 15

Val Asn Asp

<210> 79

<211> 20

<212> PRT

<213> Human papillomavirus type 18

<400> 79

Asp Glu Asp Glu Asn Ala Thr Asp Thr Gly Ser Asp Met Val Asp Phe
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Ile Asp Thr Gln
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<210> 80

<211> 20

<212> PRT

<213> Human papillomavirus type 31

<400> 80

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Ile Asp Asn Cys
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<211> 20

<212> PRT

<213> Human papillomavirus type 52

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1 5 10 15

Ile Asp Asp Ser
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<210> 82

<211> 19

<212> PRT

<213> Human papillomavirus type 53

<400> 82

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

<210> 83

<211> 20

<212> PRT

<213> Human papillomavirus type 58

<400> 83

Asp Glu Asp Glu Thr Ala Asp Asp Ser Gly Thr Asp Leu Ile Glu Phe

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Ile Asp Asp Ser

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<210> 84

<211> 15

<212> PRT

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Ala Gln Leu Ala Asp Thr Asn Ser Asn Ala Ser Ala Phe Leu Lys

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<212> PRT

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Ala Leu Leu Ala Asp Ser Asn Ser Asn Ala Ala Ala Phe Leu Lys

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<211> 15

<212> PRT

<213> Human papillomavirus type 31

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Ala Gln Leu Ala Asp Ser Asp Ser Asn Ala Cys Ala Phe Leu Lys

1 5 10 15

<210> 88

<211> 15

<212> PRT

<213> Human papillomavirus type 52

<400> 88

Ala Gln Leu Ala Asp Val Asn Ser Asn Ala Ala Ala Phe Leu Lys

1 5 10 15

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<211> 15

<212> PRT

<213> Human papillomavirus type 53

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Ala Gln Leu Ala Asp Val Asp Ser Asn Ala Gln Ala Phe Leu Lys

1 5 10 15

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Ala Gln Leu Ala Asp Val Asn Ser Asn Ala Ala Ala Phe Leu Arg

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<210> 91

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<210> 92

<211> 20

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1 5 10 15

Gly Met Ser Phe

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<210> 94

<211> 20

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<213> Human papillomavirus type 31

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Asn Cys Ile Leu Ile His Gly Ala Pro Asn Thr Gly Lys Ser Tyr Phe

1 5 10 15

Gly Met Ser Leu

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<210> 95

<211> 20

<212> PRT

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<213> Human papillomavirus type 53

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Ala Met Ser Leu

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<213> Human papillomavirus type 58

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Gly Met Ser Leu

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<211> 20

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Ile Asp Thr Gln

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<211> 20

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<213> Human papillomavirus type 31

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<210> 102

<211> 20

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Ile Asp Asp Ser

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<210> 103

<211> 19

<212> PRT

<213> Human papillomavirus type 53

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

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Asp Asn Ser

<210> 104

<211> 20

<212> PRT

<213> Human papillomavirus type 58

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<220><221> misc_feature

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<223> Xaa can be any naturally occurring amino acid

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<222> (7)..(7)

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<222> (15)..(15)

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<400> 105

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Ile Asp Asp Ser

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<210> 106

<211> 20

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<211> 20

<212> PRT

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<211> 15

<212> PRT

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<220><223> consensus sequence

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1 5 10 15

<210> 109

<211> 15

<212> PRT

<213> Human papillomavirus type 31

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Ala Gln Leu Ala Asp Ser Asp Ser Asn Ala Cys Ala Phe Leu Lys

1 5 10 15

<210> 110

<211> 15

<212> PRT

<213> Human papillomavirus type 53

<400> 110

Ala Gln Leu Ala Asp Val Asp Ser Asn Ala Gln Ala Phe Leu Lys

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Gly Met Ser Leu

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Gly Met Ser Leu

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<210> 113

<211> 20

<212> PRT

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1 5 10 15

Gly Met Ser Leu

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<210> 114

<211> 17

<212> PRT

<213> Artificial Sequence

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Trp Pro Tyr Leu His Ser Arg Leu Val Val Phe Thr Phe Pro Asn Pro

1 5 10 15

Phe

<210> 115

<211> 17

<212> PRT

<213> Human papillomavirus type 16

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Trp Pro Tyr Leu His Asn Arg Leu Val Val Phe Thr Phe Pro Asn Glu

1 5 10 15

Phe

<210> 116

<211> 17

<212> PRT

<213> Human papillomavirus type 31

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1 5 10 15

Phe

<210> 117

<211> 17

<212> PRT

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Phe

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