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(54) 발명의 명칭 레트로바이러스의 계내 생성을 위한 생산자 바이러스

(57) 요약

본 개시내용은 바이러스 계놈 내의 변형 및 단백질을 코딩하는 외인성 핵산을 함유할 수 있는 변형된 종양용해 바이러스를 포함하는 조성물을 제공한다. 본원에 제공된 바이러스 조성물 및 방법은 암의 치료에 이용될 수 있다. 한 실시양태는 그의 계놈으로부터 비-복제 레트로바이러스를 생산하는 바이러스를 제공하며, 여기서 바이러스는 종양용해 바이러스이다.

대표도 - 도8

T7 폴리머라제 구축물



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명세서

청구범위

청구항 1

바이러스의 게놈으로부터 비-복제 레트로바이러스를 생산하는 바이러스이며, 여기서 바이러스는 종양용해 바이러스인 바이러스.

청구항 2

제1항에 있어서, 비-복제 레트로바이러스가 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하는 것인 바이러스.

청구항 3

바이러스의 게놈으로부터 비-복제 레트로바이러스를 생산하는 바이러스이며, 여기서 바이러스는 종양용해 바이러스이고, 비-복제 레트로바이러스는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하고, 비-복제 레트로바이러스는 종양 미세환경 내 종양용해 바이러스에 의해 감염된 세포에서 및 종양용해 바이러스에 의해 감염되지 않은 세포에서 비-레트로바이러스 단백질을 발현할 수 있는 것인 바이러스.

청구항 4

바이러스의 게놈으로부터 비-복제 레트로바이러스를 생산하는 종양용해 바이러스이며, 여기서 비-복제 레트로바이러스는 비-렌티바이러스 단백질을 코딩하는 트랜스진을 포함하고, 비-복제 레트로바이러스는 포유동물 세포의 표적 집단에서 분열 및 비-분열 세포 둘 다를 감염시키고 형질도입할 수 있는 것인 종양용해 바이러스.

청구항 5

비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하는 바이러스이며, 여기서 트랜스진은 비-복제 레트로바이러스의 단백질을 코딩하는 유전자를 추가로 포함하는 외인성 핵산 구축물 내에 있고, 여기서 바이러스는 종양용해성인 바이러스.

청구항 6

레트로바이러스 외피 구축물, 레트로바이러스 패키징 구축물 및 레트로바이러스 전달 구축물을 포함하는 바이러스이며, 여기서 외피 구축물, 패키징 구축물 또는 전달 구축물 중 적어도 하나는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하고, 바이러스는 종양용해 바이러스인 바이러스.

청구항 7

제6항에 있어서, 외피 구축물, 패키징 구축물, 및 전달 구축물이 종양용해 바이러스의 게놈 내의 상이한 위치에 삽입된 것인 바이러스.

청구항 8

제6항 또는 제7항에 있어서, 외피 구축물이 레트로바이러스 외피 단백질을 코딩하는 유전자를 포함하며, 패키징 구축물이 레트로바이러스 구조 단백질을 코딩하는 유전자를 포함하는 것인 바이러스.

청구항 9

제8항에 있어서, 레트로바이러스 외피 단백질을 코딩하는 유전자가 제1 초기 바이러스 프로모터의 제어 하에 있고, 레트로바이러스 구조 단백질을 코딩하는 유전자가 제2 초기 바이러스 프로모터의 제어 하에 있는 것인 바이러스.

청구항 10

제8항에 있어서, 레트로바이러스 외피 단백질을 코딩하는 유전자가 제1 초기 바이러스 프로모터, 제1 초기/후기

바이러스 프로모터 또는 제1 후기 바이러스 프로모터의 제어 하에 있고; 레트로바이러스 구조 단백질을 코딩하는 유전자가 제2 초기 바이러스 프로모터, 제2 초기/후기 바이러스 프로모터, 또는 제2 후기 바이러스 프로모터의 제어 하에 있는 것은 것인 바이러스.

청구항 11

제6항 내지 제10항 중 어느 한 항에 있어서, 외피 구축물이 그의 5'-말단 영역에 종결 서열을 추가로 포함하는 것인 바이러스.

청구항 12

제6항 내지 제11항 중 어느 한 항에 있어서, 패키징 구축물이 그의 3'-말단 영역에 종결 서열을 추가로 포함하는 것인 바이러스.

청구항 13

제6항 내지 제12항 중 어느 한 항에 있어서, 전달 구축물이 3'-긴 말단 반복 영역을 포함하는 것인 바이러스.

청구항 14

제6항 내지 제13항 중 어느 한 항에 있어서, 전달 구축물이 하이브리드 5'-긴 말단 반복 영역을 포함하는 것인 바이러스.

청구항 15

제14항에 있어서, 하이브리드 5'-긴 말단 반복 영역이 제3 초기 바이러스 프로모터 및 HIV-1 단백질 5'-긴 말단 반복 영역을 포함하는 것인 바이러스.

청구항 16

제14항에 있어서, 하이브리드 5'-긴 말단 반복 영역이 HIV-1 단백질 5'-긴 말단 반복 영역 및 바이러스 프로모터를 포함하며, 여기서 바이러스 프로모터는 제3 초기 바이러스 프로모터, 제3 초기/후기 바이러스 프로모터 또는 제3 후기 바이러스 프로모터인 바이러스.

청구항 17

제6항 내지 제16항 중 어느 한 항에 있어서, 전달 구축물이 자기-절단 RNA 리보자임을 코딩하는 유전자를 추가로 포함하는 것인 바이러스.

청구항 18

제17항에 있어서, 자기-절단 RNA 리보자임을 코딩하는 유전자가 전달 구축물의 3'-긴 말단 반복 영역의 하류에 위치하는 것인 바이러스.

청구항 19

제18항에 있어서, 자기-절단 리보자임이 델타 바이러스 리보자임 또는 망치머리형 리보자임을 포함하는 것인 바이러스.

청구항 20

제9항 내지 제19항 중 어느 한 항에 있어서, 패키징 구축물이 5'-긴 말단 반복 영역을 포함하고, 제2 초기 바이러스 프로모터가 5'-긴 말단 반복 영역에 융합된 것인 바이러스.

청구항 21

제6항 내지 제20항 중 어느 한 항에 있어서, 외피 구축물이 그의 5'-말단 영역에 종결 서열을 포함하는 것인 바이러스.

청구항 22

제6항 내지 제21항 중 어느 한 항에 있어서, 패키징 구축물이 그의 3'-말단 영역에 종결 서열을 포함하는 것인 바이러스.

청구항 23

제6항 내지 제22항 중 어느 한 항에 있어서, 전달 구축물이 그의 3'-말단 영역에 종결 서열을 포함하는 것인 바이러스.

청구항 24

제11항 내지 제23항 중 어느 한 항에 있어서, 종결 서열이 서열식별번호: 7에 제시된 뉴클레오티드 서열을 포함하는 것인 바이러스.

청구항 25

제8항 내지 제24항 중 어느 한 항에 있어서, 레트로바이러스 구조 단백질이 성숙 gag-pol 단백질을 포함하는 것인 바이러스.

청구항 26

제25항에 있어서, 성숙 gag-pol 단백질이 p55, p41 및 p24를 포함하는 것인 바이러스.

청구항 27

제8항 내지 제26항 중 어느 한 항에 있어서, 레트로바이러스 외피 단백질이 VSV-G 단백질을 포함하는 것인 바이러스.

청구항 28

제1항 내지 제3항 및 제5항 내지 제27항 중 어느 한 항에 있어서, 핵산 폴리머라제를 코딩하는 외인성 핵산 서열을 포함하는 바이러스.

청구항 29

제28항에 있어서, 핵산 폴리머라제가 T7 RNA 폴리머라제, T3 RNA 폴리머라제 및 SP6 RNA 폴리머라제, RNA 폴리머라제 변이체, 및 DNA 폴리머라제 돌연변이체로 이루어진 군으로부터 선택되는 것인 바이러스.

청구항 30

제1항 내지 제3항 및 제5항 내지 제27항 중 어느 한 항에 있어서, 박테리오파지 폴리머라제를 코딩하는 외인성 핵산 서열을 포함하는 바이러스.

청구항 31

제30항에 있어서, 박테리오파지가 T3 박테리오파지, T7 박테리오파지 및 SP6 박테리오파지로 이루어진 군으로부터 선택되는 것인 바이러스.

청구항 32

제31항에 있어서, T3 박테리오파지 폴리머라제가 T3 박테리오파지 프로모터로 발현되고, T7 박테리오파지 폴리머라제가 T7 박테리오파지 프로모터로 발현되고, SP6 박테리오파지 폴리머라제가 SP6 박테리오파지 프로모터로 발현되는 것인 바이러스.

청구항 33

제4항에 있어서, 핵산 폴리머라제를 코딩하는 외인성 핵산 서열을 포함하는 종양용해 바이러스.

청구항 34

제33항에 있어서, 핵산 폴리머라제가 T7 RNA 폴리머라제, T3 RNA 폴리머라제 및 SP6 RNA 폴리머라제, RNA 폴리머라제 변이체, 및 DNA 폴리머라제 돌연변이체로 이루어진 군으로부터 선택되는 것인 종양용해 바이러스.

청구항 35

제4항에 있어서, 박테리오파지 폴리머라제를 코딩하는 외인성 핵산 서열을 포함하는 종양용해 바이러스.

청구항 36

제35항에 있어서, 박테리오파지가 T3 박테리오파지, T7 박테리오파지 및 SP6 박테리오파지로 이루어진 군으로부터 선택되는 것인 종양용해 바이러스.

청구항 37

제36항에 있어서, T3 박테리오파지 폴리머라제가 T3 박테리오파지 프로모터로 발현되고, T7 박테리오파지 폴리머라제가 T7 박테리오파지 프로모터로 발현되고, SP6 박테리오파지 폴리머라제가 SP6 박테리오파지 프로모터로 발현되는 것인 종양용해 바이러스.

청구항 38

(i) 바이러스의 게놈 내의 제1 위치에 삽입된 레트로바이러스 외피 구축물; 및 (ii) 바이러스의 게놈 내의 제2 위치에 삽입된 레트로바이러스 패키징 구축물을 포함하는 바이러스이며, 여기서 제1 위치 및 제2 위치는 인접하지 않고, 외피 구축물은 레트로바이러스 외피 단백질을 코딩하는 핵산을 포함하고, 패키징 구축물은 레트로바이러스 구조 단백질을 코딩하는 핵산을 포함하고, 바이러스는 종양용해 바이러스인 바이러스.

청구항 39

제38항에 있어서, (iii) 종양용해 바이러스의 게놈 내의 제3 위치에 삽입된 전달 구축물을 추가로 포함하는 바이러스.

청구항 40

제39항에 있어서, 전달 구축물이 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하는 것인 바이러스.

청구항 41

제39항 또는 제40항에 있어서, 전달 구축물이 종양용해 바이러스의 게놈의 3' 말단 근처에 삽입된 것인 바이러스.

청구항 42

제38항 내지 제41항 중 어느 한 항에 있어서, 레트로바이러스 외피 단백질을 코딩하는 유전자가 제1 초기 바이러스 프로모터의 제어 하에 있고, 레트로바이러스 구조 단백질을 코딩하는 유전자가 제2 초기 바이러스 프로모터의 제어 하에 있는 것인 바이러스.

청구항 43

제38항 내지 제41항 중 어느 한 항에 있어서, 레트로바이러스 외피 단백질을 코딩하는 유전자가 제1 초기 바이러스 프로모터, 제1 초기/후기 바이러스 프로모터 또는 제1 후기 바이러스 프로모터의 제어 하에 있고; 레트로바이러스 구조 단백질을 코딩하는 유전자가 제2 초기 바이러스 프로모터, 제2 초기/후기 바이러스 프로모터 또는 제2 후기 바이러스 프로모터의 제어 하에 있는 것인 바이러스.

청구항 44

제38항 내지 제42항 중 어느 한 항에 있어서, 전달 구축물이 하이브리드 5'-긴 말단 반복 영역을 포함하는 것인 바이러스.

청구항 45

제44항에 있어서, 하이브리드 5'-긴 말단 반복 영역이 제3 초기 바이러스 프로모터 및 HIV-1 단백질 5'-긴 말단 반복 영역을 포함하는 것인 바이러스.

청구항 46

제44항에 있어서, 하이브리드 5'-긴 말단 반복 영역이 HIV-1 단백질 5'-긴 말단 반복 영역 및 바이러스 프로모터를 포함하고, 여기서 바이러스 프로모터가 제3 초기 바이러스 프로모터, 제3 초기/후기 바이러스 프로모터 또는 제3 후기 바이러스 프로모터인 바이러스.

청구항 47

제39항 내지 제46항 중 어느 한 항에 있어서, 전달 구축물이 자기-절단 RNA 리보자임을 코딩하는 유전자를 추가로 포함하는 것인 바이러스.

청구항 48

제47항에 있어서, 자기-절단 RNA 리보자임을 코딩하는 유전자가 전달 구축물의 3'-긴 말단 반복 영역의 하류에 위치하는 것인 바이러스.

청구항 49

제48항에 있어서, 자기-절단 리보자임이 델타 바이러스 리보자임 또는 망치머리형 리보자임을 포함하는 것인 바이러스.

청구항 50

제42항 내지 제49항 중 어느 한 항에 있어서, 패키징 구축물이 5'-긴 말단 반복 영역을 포함하고, 제2 초기 바이러스 프로모터가 5'-긴 말단 반복 영역에 융합된 것인 바이러스.

청구항 51

제38항 내지 제50항 중 어느 한 항에 있어서, 레트로바이러스 외피 단백질을 코딩하는 핵산이 서열식별번호: 1에 제시된 뉴클레오타이드 서열, 또는 서열식별번호: 1에 제시된 서열에 대해 적어도 약 70% 내지 적어도 약 99% 동일한 뉴클레오타이드 서열을 포함하는 것인 바이러스.

청구항 52

제38항 내지 제51항 중 어느 한 항에 있어서, 레트로바이러스 구조 단백질을 코딩하는 핵산이 서열식별번호: 2에 제시된 뉴클레오타이드 서열, 또는 서열식별번호: 2에 제시된 서열에 대해 적어도 약 70% 내지 적어도 약 99% 동일한 뉴클레오타이드 서열을 포함하는 것인 바이러스.

청구항 53

제38항 내지 제52항 중 어느 한 항에 있어서, 전달 구축물이 3'-긴 말단 반복 영역을 포함하는 것인 바이러스.

청구항 54

제38항 내지 제53항 중 어느 한 항에 있어서, 외피 구축물이 그의 5'-말단 영역에 종결 서열을 포함하는 것인 바이러스.

청구항 55

제38항 내지 제54항 중 어느 한 항에 있어서, 패키징 구축물이 그의 3'-말단 영역에 종결 서열을 포함하는 것인 바이러스.

청구항 56

제39항 내지 제55항 중 어느 한 항에 있어서, 전달 구축물이 그의 3'-말단 영역에 종결 서열을 포함하는 것인 바이러스.

청구항 57

제53항 내지 제56항 중 어느 한 항에 있어서, 종결 서열이 서열식별번호: 5에 제시된 뉴클레오타이드 서열을 포함하는 것인 바이러스.

청구항 58

제38항 내지 제57항 중 어느 한 항에 있어서, 제1 위치 및 제2 위치가 적어도 약 10,000개 염기만큼 분리되어 있는 것인 바이러스.

청구항 59

제39항 내지 제58항 중 어느 한 항에 있어서, 제1 위치 및 제3 위치가 적어도 약 10,000개 염기만큼 분리되어 있는 것인 바이러스.

청구항 60

제39항 내지 제59항 중 어느 한 항에 있어서, 제2 위치 및 제3 위치가 적어도 약 10,000개 염기만큼 분리되어 있는 것인 바이러스.

청구항 61

제38항 내지 제60항 중 어느 한 항에 있어서, 구조 단백질이 성숙 gag-pol 단백질을 포함하는 것인 바이러스.

청구항 62

제61항에 있어서, 성숙 gag-pol 단백질이 p55, p41 및 p24를 포함하는 것인 바이러스.

청구항 63

제38항 내지 제62항 중 어느 한 항에 있어서, 외피 단백질이 VSV-G 단백질을 포함하는 것인 바이러스.

청구항 64

제1항 내지 제63항 중 어느 한 항에 있어서, 종양용해 바이러스가 복제에서 종양 선택적인 것인 바이러스.

청구항 65

제64항에 있어서, 비-복제 레트로바이러스가 종양 미세환경 내에서 선택적으로 생산되는 것인 바이러스.

청구항 66

제1항 내지 제65항 중 어느 한 항에 있어서, 종양용해 바이러스가 종양용해 백시니아 바이러스인 바이러스.

청구항 67

제66항에 있어서, 제1, 제2 및 제3 초기 바이러스 프로모터를 포함하며, 여기서 제1 초기 바이러스 프로모터는 제1 백시니아 바이러스 초기 프로모터이고, 제2 초기 바이러스 프로모터는 제2 백시니아 바이러스 초기 프로모터이고, 제3 초기 바이러스 프로모터는 제3 백시니아 바이러스 초기 프로모터인 바이러스.

청구항 68

제67항에 있어서, 제1 백시니아 바이러스 초기 프로모터가 서열식별번호: 9에 제시된 서열을 포함하는 것인 바이러스.

청구항 69

제67항 또는 제68항에 있어서, 제2 백시니아 바이러스 초기 프로모터가 서열식별번호: 10에 제시된 서열을 포함하는 것인 바이러스.

청구항 70

제67항 내지 제69항 중 어느 한 항에 있어서, 제3 백시니아 바이러스 초기 프로모터가 서열식별번호: 11로서 제시된 서열을 포함하는 것인 바이러스.

청구항 71

제6항 내지 제37항 및 제39항 내지 제70항 중 어느 한 항에 있어서, 전달 구축물이 인간 PGK 프로모터 (서열식 별번호: 12)를 포함하는 것인 바이러스.

청구항 72

제66항 내지 제71항 중 어느 한 항에 있어서, 외피 구축물이 종양용해 백시니아 바이러스의 유전자 vacwr032와 vacwr033 사이에 삽입된 것인 바이러스.

청구항 73

제66항 내지 제72항 중 어느 한 항에 있어서, 패키징 구축물이 종양용해 백시니아 바이러스의 유전자 vacwr093과 vacwr095 사이에 삽입된 것인 바이러스.

청구항 74

제6항 내지 제73항 중 어느 한 항에 있어서, 종양용해 백시니아 바이러스의 게놈이 vacwr094 유전자의 결실을 포함하고, 패키징 구축물이 vacwr094 유전자의 위치로 삽입된 것인 바이러스.

청구항 75

제66항 내지 제74항 중 어느 한 항에 있어서, 전달 구축물이 종양용해 백시니아 바이러스의 유전자 vacwr205와 vacwr206 사이에 삽입된 것인 바이러스.

청구항 76

제1항 내지 제75항 중 어느 한 항에 있어서, 비-레트로바이러스 단백질이 치료 단백질 또는 진단 단백질을 포함하는 것인 바이러스.

청구항 77

제76항에 있어서, 비-레트로바이러스 단백질이 치료 단백질을 포함하고, 여기서 치료 단백질은 면역 체크포인트 조정제, 항체 또는 그의 부분, Fc 융합 단백질, 항응고제, 혈액 인자, 골 형태발생 단백질, 면역억제제, 면역자극제, 효소, 성장 인자, 호르몬, 인터페론, 인터류킨, 혈전용해제, 항혈관신생제, 화학요법제, 항생제, 항진균제, 항바이러스제, 및 그의 임의의 조합을 포함하는 것인 바이러스.

청구항 78

제1항 내지 제77항 중 어느 한 항에 있어서, 레트로바이러스가 알파레트로바이러스, 베타레트로바이러스, 델타레트로바이러스, 엡실론레트로바이러스, 감마 레트로바이러스 또는 렌티바이러스인 바이러스.

청구항 79

제78항에 있어서, 레트로바이러스가 렌티바이러스인 바이러스.

청구항 80

제79항에 있어서, 렌티바이러스가 HIV인 바이러스.

청구항 81

제78항에 있어서, 레트로바이러스가 감마 레트로바이러스인 바이러스.

청구항 82

제81항에 있어서, 감마 레트로바이러스가 몰로니 뮤린 백혈병 바이러스인 바이러스.

청구항 83

제78항 내지 제80항 중 어느 한 항에 있어서, 핵산 폴리머라제를 코딩하는 외인성 핵산 서열을 포함하는 바이러스.

청구항 84

제83항에 있어서, 핵산 폴리머라제가 T7 RNA 폴리머라제, T3 RNA 폴리머라제 및 SP6 RNA 폴리머라제, RNA 폴리머라제 변이체, 및 DNA 폴리머라제 돌연변이체로 이루어진 군으로부터 선택되는 것인 바이러스.

청구항 85

제78항 내지 제80항 중 어느 한 항에 있어서, 박테리오파지 폴리머라제를 코딩하는 외인성 핵산 서열을 포함하는 바이러스.

청구항 86

제85항에 있어서, 박테리오파지가 T3 박테리오파지, T7 박테리오파지 및 SP6 박테리오파지로 이루어진 군으로부터 선택되는 것인 바이러스.

청구항 87

제86항에 있어서, T3 박테리오파지 폴리머라제가 T3 박테리오파지 프로모터로 발현되고, T7 박테리오파지 폴리머라제가 T7 박테리오파지 프로모터로 발현되고, SP6 박테리오파지 폴리머라제가 SP6 박테리오파지 프로모터로 발현되는 것인 바이러스.

청구항 88

대상체에게 제1항 내지 제87항 중 어느 한 항에 따른 종양용해 바이러스를 투여하는 것을 포함하며, 여기서 종양용해 바이러스로부터 생성된 비-복제 레트로바이러스는 종양 조직에 선택적으로 표적화된 것인, 암을 치료하는 방법.

청구항 89

제88항에 있어서, 종양 조직이 악성 신생물성 조직을 포함하는 것인 방법.

청구항 90

바이러스의 게놈으로부터 비-복제 레트로바이러스를 생성하는 조작된 생산자 바이러스이며, 여기서 조작된 생산자 바이러스는 하기 변형 중 적어도 하나를 포함하는 것인 조작된 생산자 바이러스:

- i. 적어도 하나의 바이러스 유전자의 돌연변이 또는 결실;
- ii. 적어도 하나의 외인성 핵산의 삽입;
- iii. 변경된 향성; 또는
- iv. 그의 임의의 조합.

청구항 91

제90항에 있어서, 비-복제 레트로바이러스가 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하는 것인 조작된 생산자 바이러스.

청구항 92

제90항 또는 제91항에 있어서, 생산자 바이러스가 백시니아 바이러스이고, 적어도 하나의 바이러스 유전자가 B5R, A52R (VACWR178), F13L, A36R, A34R, A33R, B8R, B18R, SPI-1, SPI-2, B15R, VGF, E3L, K3L, A41L, K7R, N1L, C12L, TK, 및 그의 임의의 조합으로 이루어진 군으로부터 선택되는 것인 조작된 생산자 바이러스.

청구항 93

제90항 내지 제92항 중 어느 한 항에 있어서, 적어도 하나의 외인성 핵산이 CXCR4, CCR2, PH-20, HMGB1, PIAS3, IL15, IL15-R α , LIGHT, ITAC, 프랙탈카인, CCL5, 대사 조정 단백질, 시토카인, 상기의 임의의 조합을 포함하는 융합 단백질로 이루어진 군으로부터 선택되는 단백질, 및 그의 기능적 도메인 또는 단편 또는 변이체, 또는 그의 임의의 조합을 코딩하는 것인 조작된 생산자 바이러스.

청구항 94

제93항에 있어서, 적어도 하나의 외인성 핵산이 PIAS3을 코딩하는 것인 조작된 생산자 바이러스.

청구항 95

제90항 내지 제94항 중 어느 한 항에 있어서, 생산자 바이러스가 레트로바이러스 외피 구축물, 레트로바이러스 패키징 구축물 및 레트로바이러스 전달 구축물을 포함하며, 여기서 외피 구축물, 패키징 구축물 및 전달 구축물은 생산자 바이러스의 게놈 내의 상이한 위치에 삽입된 것인 조작된 생산자 바이러스.

청구항 96

제95항에 있어서, 외피 구축물이 레트로바이러스 외피 단백질을 코딩하는 유전자를 포함하고, 패키징 구축물이 레트로바이러스 구조 단백질을 코딩하는 유전자를 포함하는 것인 조작된 생산자 바이러스.

청구항 97

제96항에 있어서, 레트로바이러스 외피 단백질을 코딩하는 유전자가 제1 초기 바이러스 프로모터의 제어 하에 있고, 레트로바이러스 구조 단백질을 코딩하는 유전자가 제2 초기 바이러스 프로모터의 제어 하에 있는 것인 조작된 생산자 바이러스.

청구항 98

제95항 내지 제97항 중 어느 한 항에 있어서, 외피 구축물이 그의 5'-말단 영역에 종결 서열을 추가로 포함하는 것인 조작된 생산자 바이러스.

청구항 99

제95항 내지 제98항 중 어느 한 항에 있어서, 패키징 구축물이 그의 3'-말단 영역에 종결 서열을 추가로 포함하는 것인 조작된 생산자 바이러스.

청구항 100

제95항 내지 제99항 중 어느 한 항에 있어서, 전달 구축물이 종결 서열을 포함하는 것인 조작된 생산자 바이러스.

청구항 101

제95항 내지 제100항 중 어느 한 항에 있어서, 전달 구축물이 하이브리드 5'-긴 말단 반복 영역을 포함하는 것인 조작된 생산자 바이러스.

청구항 102

제101항에 있어서, 하이브리드 5'-긴 말단 반복 영역이 제3 초기 바이러스 프로모터 및 HIV-1 단백질 5'-긴 말단 반복 영역을 포함하는 것인 조작된 생산자 바이러스.

청구항 103

제95항 내지 제102항 중 어느 한 항에 있어서, 패키징 구축물이 5'-긴 말단 반복 영역을 포함하고, 제2 초기 바이러스 프로모터가 5'-긴 말단 반복 영역에 융합된 것인 조작된 생산자 바이러스.

청구항 104

제95항 내지 제103항 중 어느 한 항에 있어서, 외피 구축물이 그의 5'-말단 영역에 종결 서열을 포함하는 것인 조작된 생산자 바이러스.

청구항 105

제95항 내지 제104항 중 어느 한 항에 있어서, 패키징 구축물이 그의 3'-말단 영역에 종결 서열을 포함하는 것인 조작된 생산자 바이러스.

청구항 106

제95항 내지 제105항 중 어느 한 항에 있어서, 전달 구축물이 종결 서열을 포함하는 것인 조작된 생산자 바이러스.

청구항 107

제104항 내지 제106항 중 어느 한 항에 있어서, 종결 서열이 서열식별번호: 7에 제시된 뉴클레오타이드 서열을 포함하는 것인 조작된 생산자 바이러스.

청구항 108

제96항 내지 제107항 중 어느 한 항에 있어서, 레트로바이러스 구조 단백질이 성숙 gag-pol 단백질을 포함하는 것인 조작된 생산자 바이러스.

청구항 109

제108항에 있어서, 성숙 gag-pol 단백질이 p55, p41 및 p24를 포함하는 것인 조작된 생산자 바이러스.

청구항 110

제96항 내지 제109항 중 어느 한 항에 있어서, 레트로바이러스 외피 단백질이 VSV-G 단백질을 포함하는 것인 조작된 생산자 바이러스.

청구항 111

제95항 내지 제110항 중 어느 한 항에 있어서, 생산자 바이러스가 종양용해 백시니아 바이러스인 조작된 생산자 바이러스.

청구항 112

제111항에 있어서, 외피 구축물이 제1 초기 백시니아 프로모터를 포함하고, 패키징 구축물이 제2 초기 백시니아 프로모터를 포함하고, 전달 구축물이 제3 초기 백시니아 프로모터를 포함하는 것인 조작된 생산자 바이러스.

청구항 113

제112항에 있어서, 제1 백시니아 바이러스 초기 프로모터가 서열식별번호: 9에 제시된 서열을 포함하는 것인 조작된 생산자 바이러스.

청구항 114

제112항 또는 제113항에 있어서, 제2 백시니아 바이러스 초기 프로모터가 서열식별번호: 10에 제시된 서열을 포함하는 것인 조작된 생산자 바이러스.

청구항 115

제112항 내지 제114항 중 어느 한 항에 있어서, 제3 백시니아 바이러스 초기 프로모터가 서열식별번호: 11로서 제시된 서열을 포함하는 것인 조작된 생산자 바이러스.

청구항 116

제95항 내지 제115항 중 어느 한 항에 있어서, 전달 구축물이 인간 PGK 프로모터 (서열식별번호: 12)를 포함하는 것인 조작된 생산자 바이러스.

청구항 117

제95항 내지 제116항 중 어느 한 항에 있어서, 외피 구축물이 종양용해 백시니아 바이러스의 유전자 vacwr032와 vacwr033 사이에 삽입된 것인 조작된 생산자 바이러스.

청구항 118

제95항 내지 제116항 중 어느 한 항에 있어서, 패키징 구축물이 종양용해 백시니아 바이러스의 유전자 vacwr093과 vacwr095 사이에 삽입된 것인 조작된 생산자 바이러스.

청구항 119

제95항 내지 제118항 중 어느 한 항에 있어서, 종양용해 백시니아 바이러스의 게놈이 vacwr094 유전자의 결실을 포함하고, 패키징 구축물이 vacwr094 유전자의 위치로 삽입된 것인 조작된 생산자 바이러스.

청구항 120

제95항 내지 제119항 중 어느 한 항에 있어서, 전달 구축물이 종양용해 백시니아 바이러스의 유전자 vacwr205와 vacwr206 사이에 삽입된 것인 조작된 생산자 바이러스.

청구항 121

제90항 내지 제120항 중 어느 한 항에 있어서, 비-레트로바이러스 단백질이 치료 단백질 또는 진단 단백질을 포함하는 것인 조작된 생산자 바이러스.

청구항 122

제121항에 있어서, 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하며, 여기서 비-레트로바이러스 단백질은 치료 단백질을 포함하고, 치료 단백질은 면역 체크포인트 조절제, 항체 또는 그의 부분, Fc 융합 단백질, 항응고제, 혈액 인자, 골 형태발생 단백질, 면역억제제, 면역자극제, 효소, 성장 인자, 호르몬, 인터페론, 인터류킨, 혈전용해제, 항혈관신생제, 화학요법제, 항생제, 항진균제, 항바이러스제, 및 그의 임의의 조합을 포함하는 것인 조작된 생산자 바이러스.

청구항 123

제90항 내지 제122항 중 어느 한 항에 있어서, 레트로바이러스가 알파레트로바이러스, 베타레트로바이러스, 델타레트로바이러스, 엡실론레트로바이러스, 감마 레트로바이러스 또는 렌티바이러스인 조작된 생산자 바이러스.

청구항 124

제123항에 있어서, 레트로바이러스가 렌티바이러스인 조작된 생산자 바이러스.

청구항 125

제124항에 있어서, 렌티바이러스가 HIV인 조작된 생산자 바이러스.

청구항 126

제123항에 있어서, 레트로바이러스가 감마 레트로바이러스인 조작된 생산자 바이러스.

청구항 127

제126항에 있어서, 감마 레트로바이러스가 몰로니 류린 백혈병 바이러스 (MMLV)인 조작된 생산자 바이러스.

청구항 128

대상체에게 제90항 내지 제127항 중 어느 한 항에 따른 조작된 생산자 바이러스를 투여하는 것을 포함하며, 여기서 조작된 생산자 바이러스로부터 생성된 비-복제 레트로바이러스는 종양 조직에 선택적으로 표적화된 것인, 암을 치료하는 방법.

청구항 129

제128항에 있어서, 종양 조직이 악성 신생물성 조직을 포함하는 것인 방법.

청구항 130

포유동물 세포에서 종양용해 바이러스의 집단을 성장시킨 후, 레트로바이러스 외피 구축물, 레트로바이러스 패키징 구축물 및 레트로바이러스 전달 구축물을 순차적으로 부가하고 선택하는 것을 포함하며, 여기서 외피 구축

물, 패키징 구축물 또는 전달 구축물 중 적어도 하나는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하는 것인, 비-복제 레트로바이러스를 생산하는 종양용해 바이러스를 생성하는 방법.

청구항 131

제130항에 있어서, 레트로바이러스가 알파레트로바이러스, 베타레트로바이러스, 델타레트로바이러스, 엡실론레트로바이러스, 감마 레트로바이러스 또는 렌티바이러스인 방법.

청구항 132

제131항에 있어서, 레트로바이러스가 렌티바이러스인 방법.

청구항 133

제132항에 있어서, 렌티바이러스가 HIV인 방법.

청구항 134

제131항에 있어서, 레트로바이러스가 감마 레트로바이러스인 방법.

청구항 135

제134항에 있어서, 감마 레트로바이러스가 몰로니 류틴 백혈병 바이러스인 방법.

발명의 설명

기술 분야

- [0001] 상호 참조
- [0002] 본 출원은 2019년 10월 16일에 출원된 미국 가출원 번호 62/916,095를 우선권 주장하며, 그 전문은 본원에 참조로 포함된다.
- [0003] 참조로 포함
- [0004] 본 명세서에서 언급된 모든 간행물, 특허, 특허 출원 및 NCBI 등록 번호는 각각의 개별 간행물, 특허 또는 특허 출원이 참조로 포함되는 것으로 구체적으로 및 개별적으로 지시되고 그 전문이 제시된 것과 동일한 정도로 본원에 참조로 포함된다. 본원에 사용된 용어와 포함된 참고문헌에 정의된 용어가 상충하는 경우에, 본 개시내용의 정의가 우선한다.

발명의 내용

- [0005] 한 실시양태는 그의 게놈으로부터 비-복제 레트로바이러스를 생산하는 바이러스를 제공하며, 여기서 바이러스는 종양용해 바이러스이다. 일부 실시양태에서, 비-복제 레트로바이러스는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함한다. 한 실시양태는 그의 게놈으로부터 비-복제 레트로바이러스를 생산하는 바이러스를 제공하며, 여기서 바이러스는 종양용해 바이러스이고, 비-복제 레트로바이러스는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하고, 비-복제 레트로바이러스는 종양 미세환경 내 종양용해 바이러스에 의해 감염된 세포에서 및 종양용해 바이러스에 의해 감염되지 않은 세포에서 비-레트로바이러스 단백질을 발현할 수 있다.
- [0006] 한 실시양태는, 그의 게놈으로부터 비-복제 레트로바이러스는 종양용해 바이러스를 제공하며, 여기서 비-복제 레트로바이러스는 비-렌티바이러스 단백질을 코딩하는 트랜스진을 포함하고, 비-복제 레트로바이러스는 포유동물 세포의 표적 집단에서 분열 및 비-분열 세포 둘 다를 감염시키고 형질도입할 수 있다. 한 실시양태는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하는 바이러스를 제공하며, 여기서 트랜스진은 비-복제 레트로바이러스의 단백질을 코딩하는 유전자를 추가로 포함하는 외인성 핵산 구축물 내에 있고, 바이러스는 종양용해성이다. 한 실시양태는 레트로바이러스 외피 구축물, 레트로바이러스 패키징 구축물 및 레트로바이러스 전달 구축물을 포함하는 바이러스를 제공하며, 여기서 외피 구축물, 패키징 구축물 또는 전달 구축물 중 적어도 하나는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하고, 바이러스는 종양용해 바이러스이다.
- [0007] 일부 실시양태에서, 외피 구축물, 패키징 구축물, 및 전달 구축물은 종양용해 바이러스의 게놈 내의 상이한 위치에 삽입된다. 일부 실시양태에서, 외피 구축물은 레트로바이러스 외피 단백질을 코딩하는 유전자를

포함하며, 패키징 구축물은 레트로바이러스 구조 단백질을 코딩하는 유전자를 포함한다. 일부 실시양태에서, 레트로바이러스 외피 단백질을 코딩하는 유전자는 제1 초기 바이러스 프로모터의 제어 하에 있고, 레트로바이러스 구조 단백질을 코딩하는 유전자는 제2 초기 바이러스 프로모터의 제어 하에 있다. 일부 실시양태에서, 레트로바이러스 외피 단백질을 코딩하는 유전자는 제1 초기 바이러스 프로모터, 제1 초기/후기 바이러스 프로모터 또는 제1 후기 바이러스 프로모터의 제어 하에 있고; 레트로바이러스 구조 단백질을 코딩하는 유전자는 제2 초기 바이러스 프로모터, 제2 초기/후기 바이러스 프로모터 또는 제2 후기 바이러스 프로모터의 제어 하에 있다. 일부 실시양태에서, 외피 구축물은 그의 5'-말단 영역에 종결 서열을 추가로 포함한다. 일부 실시양태에서, 패키징 구축물은 그의 3'-말단 영역에 종결 서열을 추가로 포함한다. 일부 실시양태에서, 전달 구축물은 3'-긴 말단 반복 영역을 포함한다. 일부 실시양태에서, 전달 구축물은 하이브리드 5'-긴 말단 반복 영역을 포함한다. 일부 실시양태에서, 하이브리드 5'-긴 말단 반복 영역은 제3 초기 바이러스 프로모터 및 HIV-1 단백질 5'-긴 말단 반복 영역을 포함한다. 일부 실시양태에서, 하이브리드 5'-긴 말단 반복 영역은 HIV-1 단백질 5'-긴 말단 반복 영역 및 바이러스 프로모터를 포함하며, 여기서 바이러스 프로모터는 제3 초기 바이러스 프로모터, 제3 초기/후기 바이러스 프로모터 또는 제3 후기 바이러스 프로모터이다. 일부 실시양태에서, 전달 구축물은 자기-절단 RNA 리보자임을 코딩하는 유전자를 추가로 포함한다. 일부 실시양태에서, 자기-절단 RNA 리보자임을 코딩하는 유전자는 전달 구축물의 3'-긴 말단 반복 영역의 하류에 위치한다. 일부 실시양태에서, 자기-절단 리보자임은 델타 바이러스 리보자임 또는 망치머리형 리보자임을 포함한다. 일부 실시양태에서, 패키징 구축물은 5'-긴 말단 반복 영역을 포함하고, 여기서 제2 초기 바이러스 프로모터는 5'-긴 말단 반복 영역에 융합된다.

[0008] 일부 실시양태에서, 외피 구축물은 그의 5'-말단 영역에 종결 서열을 포함한다. 일부 실시양태에서, 패키징 구축물은 그의 3'-말단 영역에 종결 서열을 포함한다. 일부 실시양태에서, 전달 구축물은 그의 3'-말단 영역에 종결 서열을 포함한다. 일부 실시양태에서, 종결 서열은 서열식별번호: 7에 제시된 뉴클레오티드 서열을 포함한다. 일부 실시양태에서, 레트로바이러스 구조 단백질은 성숙 gag-pol 단백질을 포함한다. 일부 실시양태에서, 성숙 gag-pol 단백질은 p55, p41 및 p24를 포함한다. 일부 실시양태에서, 레트로바이러스 외피 단백질은 VSV-G 단백질을 포함한다. 일부 실시양태에서, 바이러스는 핵산 폴리머라제를 코딩하는 외인성 핵산 서열을 포함한다. 일부 실시양태에서, 핵산 폴리머라제는 T7 RNA 폴리머라제, T3 RNA 폴리머라제 및 SP6 RNA 폴리머라제, RNA 폴리머라제 변이체, 및 DNA 폴리머라제 돌연변이체로 이루어진 군으로부터 선택된다. 일부 실시양태에서, 바이러스는 박테리오파지 폴리머라제를 코딩하는 외인성 핵산 서열을 포함한다. 일부 실시양태에서, 박테리오파지는 T3 박테리오파지, T7 박테리오파지 및 SP6 박테리오파지로 이루어진 군으로부터 선택된다. 일부 실시양태에서, T3 박테리오파지 폴리머라제는 T3 박테리오파지 프로모터로 발현되고, T7 박테리오파지 폴리머라제는 T7 박테리오파지 프로모터로 발현되고, SP6 박테리오파지 폴리머라제는 SP6 박테리오파지 프로모터로 발현된다. 일부 실시양태에서, 바이러스는 핵산 폴리머라제를 코딩하는 외인성 핵산 서열을 포함한다. 일부 실시양태에서, 핵산 폴리머라제는 T7 RNA 폴리머라제, T3 RNA 폴리머라제 및 SP6 RNA 폴리머라제, RNA 폴리머라제 변이체, 및 DNA 폴리머라제 돌연변이체로 이루어진 군으로부터 선택된다. 일부 실시양태에서, 바이러스는 박테리오파지 폴리머라제를 코딩하는 외인성 핵산 서열을 포함한다. 일부 실시양태에서, 박테리오파지는 T3 박테리오파지, T7 박테리오파지 및 SP6 박테리오파지로 이루어진 군으로부터 선택된다. 일부 실시양태에서, T3 박테리오파지 폴리머라제는 T3 박테리오파지 프로모터로 발현되고, T7 박테리오파지 폴리머라제는 T7 박테리오파지 프로모터로 발현되고, SP6 박테리오파지 폴리머라제는 SP6 박테리오파지 프로모터로 발현된다.

[0009] 한 실시양태는 (i) 바이러스의 게놈 내의 제1 위치에 삽입된 레트로바이러스 외피 구축물; 및 (ii) 바이러스의 게놈 내의 제2 위치에 삽입된 레트로바이러스 패키징 구축물을 포함하는 바이러스를 제공하며, 여기서 제1 위치 및 제2 위치는 인접하지 않고, 외피 구축물은 레트로바이러스 외피 단백질을 코딩하는 핵산을 포함하고, 패키징 구축물은 레트로바이러스 구조 단백질을 코딩하는 핵산을 포함하고, 바이러스는 종양용해 바이러스이다. 일부 실시양태에서, 바이러스는 (iii) 종양용해 바이러스의 게놈 내의 제3 위치에 삽입된 전달 구축물을 포함한다. 일부 실시양태에서, 전달 구축물은 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함한다. 일부 실시양태에서, 전달 구축물은 종양용해 바이러스의 게놈의 3' 말단 근처에 삽입된다. 일부 실시양태에서, 레트로바이러스 외피 단백질을 코딩하는 유전자는 제1 초기 바이러스 프로모터의 제어 하에 있고, 레트로바이러스 구조 단백질을 코딩하는 유전자는 제2 초기 바이러스 프로모터의 제어 하에 있다. 일부 실시양태에서, 레트로바이러스 외피 단백질을 코딩하는 유전자는 제1 초기 바이러스 프로모터, 제1 초기/후기 바이러스 프로모터 또는 제1 후기 바이러스 프로모터의 제어 하에 있고; 레트로바이러스 구조 단백질을 코딩하는 유전자는 제2 초기 바이러스 프로모터, 제2 초기/후기 바이러스 프로모터 또는 제2 후기 바이러스 프로모터의 제어 하에 있다. 일부 실시양태에서, 전달 구축물은 하이브리드 5'-긴 말단 반복 영역을 포함한다. 일부 실시양태에서, 하이브리드 5'-긴 말단 반복 영역은 제3 초기 바이러스 프로모터 및 HIV-1 단백질 5'-긴 말단 반복 영역을 포함한다. 일부 실시

양태에서, 하이브리드 5'-긴 말단 반복 영역은 HIV-1 단백질 5'-긴 말단 반복 영역 및 바이러스 프로모터를 포함하며, 여기서 바이러스 프로모터는 제3 초기 바이러스 프로모터, 제3 초기/후기 바이러스 프로모터 또는 제3 후기 바이러스 프로모터이다. 일부 실시양태에서, 전달 구축물은 자기-절단 RNA 리보자임을 코딩하는 유전자를 추가로 포함한다. 일부 실시양태에서, 자기-절단 RNA 리보자임을 코딩하는 유전자는 전달 구축물의 3'-긴 말단 반복 영역의 하류에 위치한다. 일부 실시양태에서, 자기-절단 리보자임은 델타 바이러스 리보자임 또는 망치머리형 리보자임을 포함한다. 일부 실시양태에서, 패키징 구축물은 5'-긴 말단 반복 영역을 포함하고, 여기서 제2 초기 바이러스 프로모터는 5'-긴 말단 반복 영역에 융합된다. 일부 실시양태에서, 레트로바이러스 외피 단백질을 코딩하는 핵산은 서열식별번호: 1에 제시된 뉴클레오타이드 서열, 또는 서열식별번호: 1에 제시된 서열에 대해 적어도 약 70% 내지 적어도 약 99% 동일한 뉴클레오타이드 서열을 포함한다.

[0010] 일부 실시양태에서, 레트로바이러스 구조 단백질을 코딩하는 핵산은 서열식별번호: 2에 제시된 뉴클레오타이드 서열, 또는 서열식별번호: 2에 제시된 서열에 대해 적어도 약 70% 내지 적어도 약 99% 동일한 뉴클레오타이드 서열을 포함한다. 일부 실시양태에서, 전달 구축물은 3'-긴 말단 반복 영역을 포함한다. 일부 실시양태에서, 외피 구축물은 그의 5'-말단 영역에 종결 서열을 포함한다. 일부 실시양태에서, 패키징 구축물은 그의 3'-말단 영역에 종결 서열을 포함한다. 일부 실시양태에서, 전달 구축물은 그의 3'-말단 영역에 종결 서열을 포함한다. 일부 실시양태에서, 종결 서열은 서열식별번호: 5에 제시된 뉴클레오타이드 서열을 포함한다. 일부 실시양태에서, 제1 위치 및 제2 위치는 적어도 약 10,000개 염기만큼 분리되어 있다. 일부 실시양태에서, 제1 위치 및 제3 위치는 적어도 약 10,000개 염기만큼 분리되어 있다. 일부 실시양태에서, 제2 위치 및 제3 위치는 적어도 약 10,000개 염기만큼 분리되어 있다. 일부 실시양태에서, 구조 단백질은 성숙 gag-pol 단백질을 포함한다. 일부 실시양태에서, 성숙 gag-pol 단백질은 p55, p41 및 p24를 포함한다. 일부 실시양태에서, 외피 단백질은 VSV-G 단백질을 포함한다. 일부 실시양태에서, 종양용해 바이러스는 복제에서 종양 선택적이다. 일부 실시양태에서, 비-복제 레트로바이러스는 종양 미세환경 내에서 선택적으로 생산된다. 일부 실시양태에서, 종양용해 바이러스는 종양용해 백시니아 바이러스이다. 일부 실시양태에서, 제1, 제2 및 제3 초기 바이러스 프로모터이고, 여기서 제1 초기 바이러스 프로모터는 제1 백시니아 바이러스 초기 프로모터이고, 제2 초기 바이러스 프로모터는 제2 백시니아 바이러스 초기 프로모터이고, 제3 초기 바이러스 프로모터는 제3 백시니아 바이러스 초기 프로모터이다. 일부 실시양태에서, 제1 백시니아 바이러스 초기 프로모터는 서열식별번호: 9에 제시된 서열을 포함한다. 일부 실시양태에서, 제2 백시니아 바이러스 초기 프로모터는 서열식별번호: 10에 제시된 서열을 포함한다. 일부 실시양태에서, 제3 백시니아 바이러스 초기 프로모터는 서열식별번호: 11에 제시된 서열을 포함한다. 일부 실시양태에서, 전달 구축물은 인간 PGK 프로모터 (서열식별번호: 12)를 포함한다. 일부 실시양태에서, 외피 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr032와 vacwr033 사이에 삽입된다. 일부 실시양태에서, 패키징 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr093과 vacwr095 사이에 삽입된다. 일부 실시양태에서, 종양용해 백시니아 바이러스의 게놈은 vacwr094 유전자의 결실을 포함하고, 여기서 패키징 구축물은 vacwr094 유전자의 위치로 삽입된다. 일부 실시양태에서, 전달 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr205와 vacwr206 사이에 삽입된다. 일부 실시양태에서, 비-레트로바이러스 단백질은 치료 단백질 또는 진단 단백질을 포함한다. 일부 실시양태에서, 비-레트로바이러스 단백질은 치료 단백질을 포함하고, 여기서 치료 단백질은 면역 체크포인트 조절제, 항체 또는 그의 부분, Fc 융합 단백질, 항응고제, 혈액 인자, 골 형태발생 단백질, 면역억제제, 면역자극제, 효소, 성장 인자, 호르몬, 인터페론, 인터류킨, 혈전용해제, 항혈관신생제, 화학요법제, 항생제, 항진균제, 항바이러스제, 및 그의 임의의 조합을 포함한다.

[0011] 일부 실시양태에서, 레트로바이러스는 알파레트로바이러스, 베타레트로바이러스, 델타레트로바이러스, 엡실론레트로바이러스, 감마 레트로바이러스 또는 렌티바이러스이다. 일부 실시양태에서, 레트로바이러스는 렌티바이러스이다. 일부 실시양태에서, 렌티바이러스는 HIV이다. 일부 실시양태에서, 레트로바이러스는 감마 레트로바이러스이다. 일부 실시양태에서, 감마 레트로바이러스는 몰로니 뮤린 백혈병 바이러스이다. 일부 실시양태에서, 바이러스는 핵산 폴리머라제를 코딩하는 외인성 핵산 서열을 포함한다. 일부 실시양태에서, 핵산 폴리머라제는 T7 RNA 폴리머라제, T3 RNA 폴리머라제 및 SP6 RNA 폴리머라제, RNA 폴리머라제 변이체, 및 DNA 폴리머라제 돌연변이체로 이루어진 군으로부터 선택된다. 일부 실시양태에서, 바이러스는 박테리오파지 폴리머라제를 코딩하는 외인성 핵산 서열을 포함한다. 일부 실시양태에서, 박테리오파지는 T3 박테리오파지, T7 박테리오파지 및 SP6 박테리오파지로 이루어진 군으로부터 선택된다. 일부 실시양태에서, T3 박테리오파지 폴리머라제는 T3 박테리오파지 프로모터로 발현되고, T7 박테리오파지 폴리머라제는 T7 박테리오파지 프로모터로 발현되고, SP6 박테리오파지 폴리머라제는 SP6 박테리오파지 프로모터로 발현된다.

[0012] 한 실시양태는, 대상체에게 본 개시내용에 따른 종양용해 바이러스를 투여하는 것을 포함하며, 여기서 종양용해 바이러스로부터 생성된 비-복제 레트로바이러스는 종양 조직에 선택적으로 표적화된 것인, 암을 치료하는 방법

을 포함한다. 일부 실시양태에서, 종양 조직은 악성 신생물성 조직을 포함한다. 한 실시양태는 그의 게놈으로부터 비-복제 레트로바이러스를 생성하는 조작된 생산자 바이러스를 제공하며, 여기서 조작된 생산자 바이러스는 하기 변형 중 적어도 하나를 포함하고:

i. 적어도 하나의 바이러스 유전자의 돌연변이 또는 결실;

ii. 적어도 하나의 외인성 핵산의 삽입;

iii. 변경된 항성; 또는

iv. 그의 임의의 조합,

여기서 비-복제 레트로바이러스는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함한다. 일부 실시양태에서, 비-복제 레트로바이러스는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함한다. 일부 실시양태에서, 생산자 바이러스는 백시니아 바이러스이고, 적어도 하나의 바이러스 유전자는 B5R, A52R (VACWR178), F13L, A36R, A34R, A33R, B8R, B18R, SPI-1, SPI-2, B15R, VGF, E3L, K3L, A41L, K7R, N1L, C12L, TK, 및 그의 임의의 조합으로 이루어진 군으로부터 선택된다. 일부 실시양태에서, 적어도 하나의 외인성 핵산은 CXCR4, CCR2, PH-20, HMGB1, PIAS3, IL15, IL15-R α , LIGHT, ITAC, 프랙탈카인, CCL5, 대사 조정 단백질, 시토키인, 상기의 임의의 조합을 포함하는 융합 단백질로 이루어진 군으로부터 선택되는 단백질, 및 그의 기능적 도메인 또는 단편 또는 변이체, 또는 그의 임의의 조합을 코딩한다. 일부 실시양태에서, 적어도 하나의 외인성 핵산은 PIAS3을 코딩한다.

일부 실시양태에서, 생산자 바이러스는 레트로바이러스 외피 구축물, 레트로바이러스 패키징 구축물 및 레트로바이러스 전달 구축물을 포함하며, 여기서 외피 구축물, 패키징 구축물 및 전달 구축물은 생산자 바이러스의 게놈 내의 상이한 위치에 삽입된다. 일부 실시양태에서, 외피 구축물은 레트로바이러스 외피 단백질을 코딩하는 유전자를 포함하며, 패키징 구축물은 레트로바이러스 구조 단백질을 코딩하는 유전자를 포함한다. 일부 실시양태에서, 레트로바이러스 외피 단백질을 코딩하는 유전자는 제1 초기 바이러스 프로모터의 제어 하에 있고, 레트로바이러스 구조 단백질을 코딩하는 유전자는 제2 초기 바이러스 프로모터의 제어 하에 있다. 일부 실시양태에서, 외피 구축물은 그의 5'-말단 영역에 종결 서열을 추가로 포함한다.

일부 실시양태에서, 패키징 구축물은 그의 3'-말단 영역에 종결 서열을 추가로 포함한다. 일부 실시양태에서, 전달 구축물은 종결 서열을 포함한다. 일부 실시양태에서, 전달 구축물은 하이브리드 5'-긴 말단 반복 영역을 포함한다. 일부 실시양태에서, 하이브리드 5'-긴 말단 반복 영역은 제3 초기 바이러스 프로모터 및 HIV-1 단백질 5'-긴 말단 반복 영역을 포함한다. 일부 실시양태에서, 패키징 구축물은 5'-긴 말단 반복 영역을 포함하고, 여기서 제2 초기 바이러스 프로모터는 5'-긴 말단 반복 영역에 융합된다. 일부 실시양태에서, 외피 구축물은 그의 5'-말단 영역에 종결 서열을 포함한다. 일부 실시양태에서, 패키징 구축물은 그의 3'-말단 영역에 종결 서열을 포함한다. 일부 실시양태에서, 전달 구축물은 종결 서열을 포함한다. 일부 실시양태에서, 종결 서열은 서열식별번호: 7에 제시된 뉴클레오타이드 서열을 포함한다. 일부 실시양태에서, 레트로바이러스 구조 단백질은 성숙 gag-pol 단백질을 포함한다. 일부 실시양태에서, 성숙 gag-pol 단백질은 p55, p41 및 p24를 포함한다. 일부 실시양태에서, 레트로바이러스 외피 단백질은 VSV-G 단백질을 포함한다. 일부 실시양태에서, 생산자 바이러스는 종양용해 백시니아 바이러스이다.

일부 실시양태에서, 외피 구축물은 제1 초기 백시니아 프로모터를 포함하고, 포장 구축물은 제2 초기 백시니아 프로모터를 포함하고, 전달 구축물은 제3 초기 백시니아 프로모터를 포함한다. 일부 실시양태에서, 제1 백시니아 바이러스 초기 프로모터는 서열식별번호: 9에 제시된 서열을 포함한다. 일부 실시양태에서, 제2 백시니아 바이러스 초기 프로모터는 서열식별번호: 10에 제시된 서열을 포함한다. 일부 실시양태에서, 제3 백시니아 바이러스 초기 프로모터는 서열식별번호: 11에 제시된 서열을 포함한다. 일부 실시양태에서, 전달 구축물은 인간 PGK 프로모터 (서열식별번호: 12)를 포함한다. 일부 실시양태에서, 외피 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr032와 vacwr033 사이에 삽입된다. 일부 실시양태에서, 패키징 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr093과 vacwr095 사이에 삽입된다. 일부 실시양태에서, 종양용해 백시니아 바이러스의 게놈은 vacwr094 유전자의 결실을 포함하고, 여기서 패키징 구축물은 vacwr094 유전자의 위치로 삽입된다. 일부 실시양태에서, 전달 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr205와 vacwr206 사이에 삽입된다. 일부 실시양태에서, 비-레트로바이러스 단백질은 치료 단백질 또는 진단 단백질을 포함한다. 일부 실시양태에서, 바이러스는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하며, 여기서 비-레트로바이러스 단백질은 치료 단백질을 포함하고, 여기서 치료 단백질은 면역 체크포인트 조절제, 항체 또는 그의 부분, Fc 융합 단백질,

항응고제, 혈액 인자, 골 형태발생 단백질, 면역억제제, 면역자극제, 효소, 성장 인자, 호르몬, 인터페론, 인터류킨, 혈전용해제, 항혈관신생제, 화학요법제, 항생제, 항진균제, 항바이러스제, 및 그의 임의의 조합을 포함한다. 일부 실시양태에서, 레트로바이러스는 알파레트로바이러스, 베타레트로바이러스, 델타레트로바이러스, 엡실론레트로바이러스, 감마 레트로바이러스 또는 렌티바이러스이다. 일부 실시양태에서, 레트로바이러스는 렌티바이러스이다. 일부 실시양태에서, 렌티바이러스는 HIV이다. 일부 실시양태에서, 레트로바이러스는 감마 레트로바이러스이다. 일부 실시양태에서, 감마 레트로바이러스는 몰로니 뮤린 백혈병 바이러스 (MMLV)이다.

[0021] 한 실시양태는, 대상체에게 본 개시내용에 따른 조작된 생산자 바이러스를 투여하는 것을 포함하며, 여기서 조작된 생산자 바이러스로부터 생성된 비-복제 레트로바이러스는 종양 조직에 선택적으로 표적화된 것인, 암을 치료하는 방법을 제공한다. 일부 실시양태에서, 종양 조직은 악성 신생물성 조직을 포함한다.

[0022] 한 실시양태는, 포유동물 세포에서 종양용해 바이러스의 집단을 성장시킨 후, 레트로바이러스 외피 구축물, 레트로바이러스 패키징 구축물 및 레트로바이러스 전달 구축물을 순차적으로 첨가하고 선택하는 것을 포함하며, 여기서 외피 구축물, 패키징 구축물 또는 전달 구축물 중 적어도 하나는 비-레트로바이러스 단백질을 코딩하는 트랜스진을 포함하는 것인, 비-복제 레트로바이러스를 생산하는 종양용해 바이러스를 생성하는 방법을 제공한다. 일부 실시양태에서, 레트로바이러스는 알파레트로바이러스, 베타레트로바이러스, 델타레트로바이러스, 엡실론레트로바이러스, 감마 레트로바이러스 또는 렌티바이러스이다. 일부 실시양태에서, 레트로바이러스는 감마 레트로바이러스이다. 일부 실시양태에서, 감마 레트로바이러스는 몰로니 뮤린 백혈병 바이러스이다. 일부 실시양태에서, 레트로바이러스는 렌티바이러스이다. 일부 실시양태에서, 렌티바이러스는 HIV이다.

도면의 간단한 설명

[0023] 본 개시내용의 신규 특색은 첨부된 청구범위에 구체적으로 제시되어 있다. 본 개시내용의 원리가 이용된 예시적인 실시양태를 제시하는 하기 상세한 설명 및 그의 첨부 도면을 참조로 본 개시내용의 특색 및 이점의 보다 양호한 이해가 얻어질 것이다.

도 1은 백시니아 바이러스 게놈 내의 각각의 렌티바이러스 구축물의 삽입 또는 삽입/결실의 위치를 도시한다.

도 2는 렌티바이러스 env 구축물의 맵을 도시한다.

도 3은 렌티바이러스 패키징 구축물의 맵을 도시한다.

도 4는 렌티바이러스 전달 구축물의 맵을 도시한다.

도 5는 웨스턴 블롯에 의한 GAG 발현의 검출을 도시한다.

도 6은 웨스턴 블롯에 의한 VSV-G 발현의 검출을 도시한다.

도 7은 세포 상에서 TagRFP-T 및 sfGFP의 존재에 의해 나타난 바와 같은, 감염성 렌티바이러스를 생성하는 렌티-Vac 바이러스로 감염된 HEK293 세포의 형광 현미경검사 영상을 도시하며; 이는 각각 백시니아 바이러스 감염 및 렌티바이러스 형질도입을 나타낸다.

도 8은 T7 RNA 폴리머라제 서열을 함유하는 예시적인 구축물을 도시한다.

발명을 실시하기 위한 구체적인 내용

[0024] 본 개시내용의 바람직한 실시양태가 본원에서 제시되고 기재되었지만, 이러한 실시양태가 단지 예로서만 제공된다는 것이 관련 기술분야의 통상의 기술자에게 명백할 것이다. 본 개시내용을 벗어나지 않으면서 이제 다수의 변경, 변화 및 치환이 관련 기술분야의 통상의 기술자에게 발생할 것이다. 본원에 기재된 본 개시내용의 실시양태에 대한 다양한 대안이 본 개시내용을 실시하는데 사용될 수 있음을 이해하여야 한다. 하기 청구범위는 본 개시내용의 범주를 규정하고 이들 청구범위의 범주 내의 방법 및 구조물 및 그의 등가물이 이에 의해 포함되는 것으로 의도된다.

[0025] 특정 정의

[0026] 본원에 사용된 용어는 특정한 사례를 기재하기 위한 목적일 뿐이고, 제한적인 것으로 의도되지 않는다. 본원에서 사용된 단수 형태는 문맥이 달리 명백하게 나타내지 않는 한 복수 형태를 또한 포함할 수 있다. 추가로, 용어 "함유하다", "함유하는", "포함한", "포함하다", "갖는", "갖는다", "있는" 또는 그의 변형이 상세한 설명 및/또는 청구범위에서 사용되는 한, 이러한 용어는 용어 "포함하는"과 유사한 방식으로 포괄적인 것으로 의도된

다.

- [0027] 용어 "약" 또는 "대략적으로"는 관련 기술분야의 통상의 기술자에 의해 결정된 바와 같은 특정한 값에 대한 허용가능한 오차 범위 내에 있는 것을 의미할 수 있고, 이는 부분적으로 어떻게 값이 측정 또는 결정되는지에, 예를 들어 측정 시스템의 한계에 좌우될 것이다. 예를 들어, "약"은 소정의 값의 실시당 1 또는 1 초과의 표준편차 이내인 것을 의미할 수 있다. 특정한 값이 본 출원 및 청구범위에 기재되는 경우에, 달리 언급되지 않는 한 용어 "약"은 특정한 값에 대한 허용가능한 오차 범위, 예컨대 용어 "약"이 수식하는 값의 $\pm 10\%$ 를 의미하는 것으로 가정되어야 한다.
- [0028] 용어 "개체", "환자" 또는 "대상체"는 상호교환가능하게 사용된다. 이러한 용어 중 어떤 것도 건강 관리 종사자 (예를 들어 의사, 공인 간호사, 간호사, 의사 보조자, 간호조무사, 또는 호스피스 종사자)의 감독 (예를 들어, 일정한 또는 간헐적)을 특징으로 하는 상황을 필요로 하거나 또는 이에 제한되지 않는다. 일부 실시양태에서, 환자, 대상체 또는 개체는 건강 관리 종사자의 감독 하에 있을 수 있다.
- [0029] 특정 바이러스와 관련하여 본원에 사용된 용어 "이종 핵산 서열" 또는 "외인성 핵산 서열" 또는 "트랜스진"은 명시된 바이러스 이외의 공급원으로부터 기원하는 핵산 서열을 지칭할 수 있다.
- [0030] 본원에 사용된 용어 "돌연변이"는 결실, 이종 핵산의 삽입, 역전 또는 치환, 예컨대 관련 기술분야에서 통상적으로 이해되는 바와 같은 오픈 리딩 프레임 제거 돌연변이를 지칭할 수 있다.
- [0031] 본원에 사용된 용어 "암" 및 그의 문법적 등가물은 그의 고유한 형질-정상 제어의 상실-이 비조절된 성장, 분화의 결여, 국부 조직 침습 및 전이를 유발하는 세포의 과다증식을 지칭할 수 있다. 본 발명의 방법과 관련하여, 암은 임의의 급성 림프구성 암, 급성 골수성 백혈병, 폐포 횡문근육종, 방광암, 골암, 뇌암, 유방암, 항문암, 항문관암, 직장암, 안암, 간내 담관암, 관절암, 경부, 담낭 또는 흉막의 암, 코, 비강 또는 중이의 암, 구강암, 외음부암, 만성 림프구성 백혈병, 만성 골수성암, 결장암, 식도암, 자궁경부암, 섬유육종, 위장 카르시노이드 종양, 호지킨 림프종, 하인두암, 신장암, 후두암, 백혈병, 액상 종양, 간암, 폐암, 림프종, 악성 중피종, 비만 세포종, 흑색종, 다발성 골수종, 비인두암, 비-호지킨 림프종, 난소암, 췌장암, 복막암, 망 및 장간막암, 인두암, 전립선암, 직장암, 신암, 피부암, 소장암, 연부조직암, 고형 종양, 위암, 고환암, 갑상선암, 요관암 및/또는 방광암을 포함한 임의의 암일 수 있다. 본원에 사용된 용어 "종양"은, 예를 들어 악성 유형 또는 양성 유형의 세포 또는 조직의 비정상적 성장을 지칭한다.
- [0032] 본원에 사용된 용어 "유전자"는, 임의로 코딩 서열의 상류 또는 하류에 위치할 수 있는 연관된 조절 영역, 예컨대 프로모터, 오퍼레이터, 종결인자 등과 함께, 개별 단백질 또는 RNA를 코딩하는 핵산의 절편 ("코딩 서열" 또는 "코딩 영역"으로도 지칭됨)을 지칭할 수 있다.
- [0033] 본원에서 상호교환가능하게 사용된 용어 "돌연변이체 바이러스" 및 "변형된 바이러스"는 그의 게놈 내에 결실, 이종 핵산의 삽입, 역전, 치환, 또는 그의 조합을 포함하나 이에 제한되지 않는 1개 이상의 돌연변이를 포함하는 바이러스를 지칭할 수 있다.
- [0034] 바이러스에 관하여 본원에 사용된 용어 "자연 발생"은 바이러스가 자연에서 발견될 수 있다는 것, 즉 자연의 공급원으로부터 단리될 수 있고 의도적으로 변형되지 않았다는 것을 나타낼 수 있다.
- [0035] 본원에 언급된 용어 "억제하는", "감소시키는" 또는 "방지", 또는 이들 용어의 임의의 변형은 목적하는 결과를 달성하기 위한 임의의 측정가능한 감소 또는 완전한 억제를 포함할 수 있다.
- [0036] 본원에 사용된 "프로모터"는 전사의 개시 및 속도가 제어되는 핵산 서열의 영역인 제어 서열일 수 있다. 특정 실시양태에서, 프로모터는 조절 단백질 및 분자, 예컨대 RNA 폴리머라제 및 다른 전사 인자가 결합할 수 있는 유전자 요소를 함유할 수 있다. 용어 "작동적으로 위치한", "작동적으로 연결된", "제어 하의" 및 "전사 제어 하의"는 프로모터가 핵산 서열의 전사 개시 및/또는 발현을 제어하기 위해 핵산 서열과 관련하여 정확한 기능적 위치 및/또는 배향으로 존재하는 것을 의미할 수 있다. 특정 실시양태에서, 프로모터는 "인핸서"와 함께 사용될 수 있거나 또는 그렇지 않을 수 있고, 이는 핵산 서열의 전사 활성화에 수반되는 시스-작용 조절 서열을 지칭한다.
- [0037] 본원에 사용된 용어 "상동성"은 최적의 비교 목적을 위해 서열들을 정렬함으로써 (예를 들어, 제1 서열의 서열에 갭을 도입할 수 있음) 결정될 수 있는 2개 이상의 뉴클레오타이드 또는 아미노산 서열 사이의 "상동성" 또는 "퍼센트 상동성"의 계산일 수 있다. 이어서, 상응하는 위치의 뉴클레오타이드들을 비교할 수 있고, 2개의 서열 사이의 퍼센트 동일성은 서열들이 공유하는 동일한 위치의 개수의 함수일 수 있다 (즉, % 상동성 = 동일한 위치

의 # / 위치의 총 # x 100). 예를 들어, 제1 서열 내의 위치를 제2 서열 내의 상응하는 위치와 동일한 뉴클레오타이드가 차지할 수 있고, 그러면 분자들이 그 위치에서 동일하다. 2개의 서열 사이의 퍼센트 상동성은 2개의 서열의 최적의 정렬을 위해 도입될 필요가 있는 갭의 개수 및 각각의 갭의 길이를 고려하여, 서열들이 공유하는 동일한 위치의 개수의 함수일 수 있다. 일부 실시양태에서, 비교 목적을 위해 정렬된 서열의 길이는 참조 서열의 길이의 적어도 약 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% 또는 95%일 수 있다. BLAST® 검색은 2개의 서열 사이의 상동성을 결정할 수 있다. 상동성은 2개의 서열의 전체 길이 사이 또는 2개의 서열의 전체 길이의 분획 사이의 것일 수 있다. 2개의 서열은 유전자, 뉴클레오타이드 서열, 단백질 서열, 펩티드 서열, 아미노산 서열 또는 그의 단편일 수 있다. 2개의 서열의 실제 비교는 널리 공지된 방법, 예를 들어 수학적 알고리즘을 사용하여 달성될 수 있다. 이러한 수학적 알고리즘의 비제한적 예가 문헌 [Karlin, S. and Altschul, S., Proc. Natl. Acad. Sci. USA, 90- 5873-5877 (1993)]에 기재되어 있을 수 있다. 이러한 알고리즘이 문헌 [Altschul, S. et al., Nucleic Acids Res., 25:3389-3402 (1997)]에 기재된 바와 같은 NBLAST 및 XBLAST 프로그램 (버전 2.0) 내로 혼입될 수 있다. BLAST 및 갭도입 BLAST 프로그램을 이용하는 경우에, 각각의 프로그램 (예를 들어, NBLAST)의 임의의 관련 파라미터가 사용될 수 있다. 예를 들어, 서열 비교를 위한 파라미터가 점수= 100, 워드 길이= 12로 설정될 수 있거나, 또는 달라질 수 있다 (예를 들어, W=5 또는 W=20). 다른 예는 문헌 [Myers and Miller, CABIOS (1989)]의 알고리즘, ADVANCE, ADAM, BLAT 및 FASTA를 포함한다. 또 다른 실시양태에서, 예를 들어, GCG 소프트웨어 패키지 (엑셀리스(Accelrys), 영국 캠브리지) 내의 GAP 프로그램을 사용하여 2개의 아미노산 서열 사이의 퍼센트 동일성이 달성될 수 있다.

[0038] 용어 "대상체"는 영장류 (예를 들어, 인간), 소, 양, 염소, 말, 개, 고양이, 토끼, 래트 또는 마우스를 포함하나 이에 제한되지는 않는 동물을 지칭할 수 있다. 용어 "대상체" 및 "환자"는, 예를 들어 포유동물 대상체, 예컨대 인간 대상체와 관련하여 본원에서 상호교환가능하게 사용된다.

[0039] 용어 "치료하다", "치료하는" 및 "치료"는 장애, 질환 또는 상태, 또는 장애, 질환 또는 상태와 연관된 증상 중 1종 이상을 완화시키거나 제거하는 것; 또는 장애, 질환 또는 상태 자체의 원인(들)을 완화시키거나 근절시키는 것을 포함하는 것으로 의도될 수 있다. 치료의 바람직한 효과는 질환의 발생 또는 재발을 방지하는 것, 증상 완화, 질환의 임의의 직접적 또는 간접적 병리학적 결과를 감소시키는 것, 전이를 방지하는 것, 질환 진행 속도를 감소시키는 것, 질환 상태의 호전 또는 완화, 및 완화 또는 개선된 예후를 포함할 수 있으나 이에 제한되지는 않는다.

[0040] 용어 "치료 유효량"은 투여되었을 때, 치료될 질환, 장애 또는 상태의 증상 중 1종 이상의 발생을 방지하거나 또는 이를 어느 정도 완화시키는데 충분할 수 있는 화합물의 양을 지칭할 수 있다. 또한 용어 "치료 유효량"은 연구원, 의사, 의사 또는 임상가가 추구하고 있는 세포, 조직, 계, 동물 또는 인간의 생물학적 또는 의학적인 반응을 도출하는데 충분한 화합물의 양을 지칭할 수 있다.

[0041] 용어 "제약상 허용되는 담체", "제약상 허용되는 부형제", "생리학상 허용되는 담체" 또는 "생리학상 허용되는 부형제"는 제약상 허용되는 물질, 조성물 또는 비히클, 예컨대 액체 또는 고체 충전제, 희석제, 부형제, 용매 또는 캡슐화 물질을 지칭할 수 있다. 성분은 제약 제제의 다른 성분과 상용성이라는 의미에서 "제약상 허용되는" 것일 수 있다. 이는 또한 합리적인 이익/위험 비에 부합하여, 과도한 독성, 자극, 알레르기 반응, 면역원성 또는 다른 문제 또는 합병증 없이 인간 및 동물의 조직 또는 기관과 접촉하여 사용하는데 적합할 수 있다. 예를 들어, 문헌 [Remington: The Science and Practice of Pharmacy, 21st Edition; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; Handbook of Pharmaceutical Excipients, 5th Edition; Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association: 2005; 및 Handbook of Pharmaceutical Additives, 3rd Edition; Ash and Ash Eds., Gower Publishing Company: 2007; Pharmaceutical Preformulation and Formulation, Gibson Ed., CRC Press LLC: Boca Raton, FL, 2004)]을 참조한다.

[0042] 용어 "제약 조성물"은 본원에 개시된 화합물과 다른 화학적 성분, 예컨대 희석제 또는 담체의 혼합물을 지칭할 수 있다. 제약 조성물은 화합물을 유기체에 투여하는 것을 용이하게 할 수 있다. 경구, 주사, 에어로졸, 비경구 및 국소 투여를 포함하나 이에 제한되지는 않는, 화합물을 투여하는 다수의 기술이 관련 기술분야에 존재한다. 제약 조성물은 화합물을 무기 또는 유기 산, 예컨대 염산, 브로민화수소산, 황산, 질산, 인산, 메탄술포산, 에탄술포산, p-톨루엔술포산, 살리실산 등과 반응시킴으로써 또한 획득될 수 있다.

[0043] 본원에 사용된 "항암제"는, 예를 들어 암 세포를 사멸시키거나, 암 세포의 아포토시스를 유도하거나, 암 세포의

성장 속도를 감소시키거나, 전이의 발생 또는 개수를 감소시키거나, 종양 크기를 감소시키거나, 종양 성장을 억제하거나, 종양 또는 암 세포로의 혈액 공급을 감소시키거나, 암 세포 또는 종양에 대한 면역 반응을 촉진하거나, 암의 진행을 방지 또는 억제하거나, 또는 암을 갖는 대상체의 수명을 증가시킴으로써, 대상체 내의 암에 음성적으로 영향을 미칠 수 있는 작용제 또는 요법을 지칭할 수 있다. 항암제의 비제한적 예는 생물학적 작용제(생물요법), 화학요법제 및 방사선요법제를 포함할 수 있다.

[0044] 본원에 사용된 용어 "종양용해"는 암 또는 종양 세포를, 예를 들어 상기 세포의 직접적인 용해, 상기 세포에 대한 면역 반응의 자극, 아포토시스, 독성 단백질의 발현, 자가포식 및 단백질 합성 중단, 항종양 면역의 유도, 또는 그의 임의의 조합에 의해, 작용제, 예컨대 종양용해 폭스바이러스, 예컨대 종양용해 백시니아 바이러스에 의해 사멸시키는 것을 지칭할 수 있다. 작용제, 예컨대 종양용해 백시니아 바이러스에 의해 감염된 암 또는 종양 세포의 직접적인 용해는 상기 세포 내에서의 바이러스 복제의 결과일 수 있다. 특정 예에서, 용어 "종양용해"는 암 또는 종양 세포를 상기 세포의 용해 없이 사멸시키는 것을 지칭할 수 있다.

[0045] 본원에 사용된 용어 "종양용해 바이러스"는 종양 세포를 우선적으로 감염시키고 사멸시키는 바이러스를 지칭할 수 있다. 특정 비제한적 상황 하에서, 종양용해 바이러스는 종양 세포의 선택적 사멸 뿐만 아니라 숙주 항종양 면역 반응의 자극에 의존적인 이중 메커니즘을 통해 항종양 반응을 촉진할 수 있는 것으로 이해된다.

[0046] 일부 실시양태에서, 종양용해 바이러스는 (i) 암 세포에서 우선적으로 자연 복제되고 인간에서 종종 선천성 항바이러스 신호전달에 대한 상승된 감수성 또는 종양원성 신호전달 경로에 대한 의존성으로 인해 비-병원성인 바이러스; 및 (ii) 사용을 위해 유전자 조작된 바이러스를 포함할 수 있으나 이에 제한되지는 않는다. 일부 실시양태에서, 종양용해 바이러스는 홍역 바이러스, 폴리오바이러스, 폭스바이러스, 백시니아 바이러스, 아데노바이러스, 아데노 연관 바이러스, 단순 포진 바이러스, 수포성 구내염 바이러스, 레오바이러스, 뉴캐슬병 바이러스, 세네카바이러스, 렌티바이러스, 멩고바이러스 또는 점액종바이러스일 수 있다. 특정 실시양태에서, 종양용해 바이러스는 폭스 바이러스일 수 있다. 특정 실시양태에서, 종양용해 바이러스는 백시니아 바이러스일 수 있다.

[0047] 본원에 사용된 용어 "변형된 종양용해 바이러스"는 그의 구성성분에 대한 변형, 예컨대 비제한적으로, 바이러스의 천연 게놈 ("백본")에서의 변형, 예컨대 바이러스 유전자의 돌연변이 또는 결실, 외인성 핵산의 도입, 바이러스 핵산 또는 바이러스 단백질의 화학적 변형, 및 외인성 단백질 또는 변형된 바이러스 단백질의 바이러스성 캡시드에의 도입을 포함하는 종양용해 바이러스를 지칭할 수 있다. 일반적으로, 종양 세포에 대한 개선된 치료 효과를 얻기 위해 종양용해 바이러스가 변형 (또한 "조작"으로 공지됨)될 수 있다. 특정 실시양태에서, 변형된 종양용해 바이러스는 변형된 폭스 바이러스일 수 있다. 특정 실시양태에서, 변형된 종양용해 바이러스는 변형된 폭스 바이러스일 수 있다.

[0048] 본원에서 상호교환가능하게 사용되는 용어 "전신 전달" 및 "전신 투여"는 일부 경우에 의약, 종양용해 바이러스 또는 다른 물질을 순환계 내로 투여하는 경로를 지칭할 수 있다. 전신 투여는 경구 투여, 비경구 투여, 비강내 투여, 설하 투여, 직장 투여, 경피 투여, 또는 그의 임의의 조합을 포함할 수 있다.

[0049] 본원에 사용된 용어 "복제 결핍 바이러스" 또는 "비-복제 바이러스" 또는 "복제 부적격 바이러스"는 그의 게놈에 대한 변형의 결과로서 전파 부적격인 바이러스와 같은 그의 통상적인 의미를 갖는다. 따라서, 이러한 재조합 바이러스가 세포를 감염시키면, 이에 따를 수 있는 유일한 과정은 그의 게놈에 함유된 임의의 바이러스 및 이중 단백질을 발현하는 것이다. 구체적 실시양태에서, 본원에 제공된 복제 결손 벡터는 비구조 단백질을 코딩하는 유전자를 함유할 수 있고, RNA 전사 및 유전자 발현에 스스로 충분하다. 그러나, 이들 벡터는 구조 단백질을 코딩하는 유전자가 결여되어 있어, 감염성 입자 내로 이들을 패키징되도록 하기 위해 헬퍼 게놈이 필요하다. 치료적으로 안전한 벡터를 제공하는 것에 추가로, 구조 단백질의 제거는 6 kb 초과 이종 서열을 혼입하는 이들 벡터의 능력을 증가시킨다. 또 다른 실시양태에서, 본 발명의 아데노바이러스 벡터의 전파 부적격은 예를 들어 구조 단백질이 패키징 세포주로부터 방출되는 비리온 내에 패키징되도록 하는 패키징 신호를 제거함으로써 간접적으로 달성된다.

[0050] 한 측면에서, 복제 결손 바이러스, 예를 들어 생산자 바이러스와 상이한 패밀리의 복제 결손 바이러스를 포함하는 적재물을 전달할 수 있는 생산자 바이러스가 본원에 제공된다. 한 측면에서, 생산자 바이러스는 종양용해 바이러스, 예를 들어 그의 게놈으로부터 비-복제 바이러스, 예컨대 비-복제 렌티바이러스를 생산하는 백시니아 바이러스일 수 있다. 일부 경우에, 적재물은 비-복제 렌티바이러스 (LV)의 적어도 일부일 수 있다. 일부 경우에, 비-복제 렌티바이러스는 트랜스진, 예컨대 비-렌티바이러스 단백질을 포함할 수 있다. 비-렌티바이러스 단백질은 치료 단백질 또는 그의 기능적 단편 및/또는 진단 단백질일 수 있다. 일부 경우에, 비-복제 렌티바이러스는 종양용해 바이러스에 의해 감염된 세포에서 비-렌티바이러스 단백질을 발현하여 감염된 세포, 예컨대 암

세포의 용해를 유발할 수 있다. 일부 경우에, 비-복제 바이러스는 계내에서, 예컨대 종양 세포 내에서 또는 종양 미세환경에서 생산자 바이러스에 의해 생산될 수 있다. 예를 들어, 비-복제 바이러스는 종양용해 생산자 바이러스에 의해 감염된 종양 세포에서 생산될 수 있고, 비-복제 바이러스는 치료 또는 진단 단백질을 계내에서 발현할 수 있다.

[0051] 일부 측면에서, 생산자 종양용해 바이러스를 포함하는 벡터 시스템이 본원에 제공될 수 있다. 일부 측면에서, 벡터 시스템은 파괴된 바이러스 게놈을 포함할 수 있다. 일부 측면에서, 단일 벡터는 적어도 2개의 바이러스 게놈을 포함할 수 있다. 일부 측면에서, 단일 벡터는 적어도 3개의 바이러스 게놈을 포함할 수 있다. 한 측면에서, 생산자 종양용해 백시니아 바이러스 게놈은 외래 바이러스, 예컨대 HIV 바이러스로부터의 서열을 포함할 수 있다. 일부 측면에서, 바이러스의 env, 패키징 및 전달 기능이 3개의 상이한 플라스미드 상에 있을 수 있는 3-플라스미드 시스템이 본원에 제공될 수 있다. 일부 측면에서, env, 패키징 및 전달은 적어도 1개의 바이러스 게놈을 포함하는 단일 벡터 상에 있을 수 있다.

[0052] 일부 예에서, 생산자 바이러스는 미오비리다에, 포도비리다에, 시포비리다에, 알로헤르페스비리다에, 헤르페스비리다에, 말라코헤르페스비리다에, 리포트락스비리다에, 루디비리다에, 아테노비리다에, 암폴라비리다에, 아스코비리다에, 바쿨로비리다에, 비카우다비리다에, 클라바비리다에, 코르티코비리다에, 푸셀로비리다에, 글로불로비리다에, 구타비리다에, 히트로사비리다에, 이리도비리다에, 마르세일레비리다에, 미미비리다에, 니마비리다에, 판도라비리다에, 파필로마비리다에, 피코드나비리다에, 플라스마비리다에, 폴리드나바이러스, 폴리오마비리다에, 폭스비리다에, 스파에로리포비리다에 또는 텍티비리다에 중 어느 하나의 패밀리로부터의 것일 수 있다. 한 측면에서, 생산자 종양용해 바이러스는 폭스비리다에 바이러스, 예컨대 백시니아 바이러스일 수 있다. 한 측면에서, 백시니아 바이러스는 상이한 패밀리로부터의 바이러스를 코딩할 수 있다. 예를 들어, 백시니아 바이러스 게놈은 하기 패밀리 중 임의의 것의 바이러스로부터 선택되는 바이러스에 대한 제2 게놈을 포함할 수 있다: 미오비리다에, 포도비리다에, 레트로비리다에, 시포비리다에, 알로헤르페스비리다에, 헤르페스비리다에, 말라코헤르페스비리다에, 리포트락스비리다에, 루디비리다에, 아테노비리다에, 암폴라비리다에, 아스코비리다에, 아스파비리다에, 바쿨로비리다에, 비카우다비리다에, 클라바비리다에, 코르티코비리다에, 푸셀로비리다에, 글로불로비리다에, 구타비리다에, 히트로사비리다에, 이리도비리다에, 마르세일레비리다에, 미미비리다에, 니마비리다에, 판도라비리다에, 파필로마비리다에, 피코드나비리다에, 플라스마비리다에, 폴리드나바이러스, 폴리오마비리다에, 스파에로리포비리다에, 또는 텍티비리다에.

[0053] 일부 실시양태에서, 계내 생산된 바이러스는 레트로바이러스 (렌티바이러스 포함), 헤르페스 바이러스, 알파바이러스, 아테노-연관 바이러스, 백시니아 바이러스, 유두종바이러스 또는 엡스타인 바르 바이러스 (EBV)일 수 있다. 본 개시내용에 따르면, 관련 기술분야의 기술 내의 통상적인 분자 생물학, 미생물학, 및 재조합 DNA 기술이 사용될 수 있다. 특정 실시양태에서, 본 개시내용의 생산자 바이러스에 의해 생산된 바이러스는 복제 결손이고, 즉 표적 세포에서 자율적으로 복제할 수 없을 수 있다. 바람직하게는, 복제 결손 바이러스는 바이러스 게놈의 표적 세포 인식 및 캡시드화에 필요한 그의 게놈의 서열만을 보유하도록 하는 최소 바이러스이다. 복제 결손 바이러스는 세포 내로의 도입 후에 감염성이 아닐 수 있다. 복제 결손 바이러스 벡터의 사용은 벡터가 다른 세포를 감염시킬 수 있다는 우려 없이 특정 국소 영역 내의 세포에 대한 투여를 허용할 수 있다. 따라서, 특정 조직, 예를 들어 암 세포에 특이적으로 표적화될 수 있다.

[0054] 한 측면에서, 본원에 제공된 생산자 바이러스로부터 생산된 바이러스는 레트로비리다에 패밀리로부터의 것일 수 있다. 한 측면에서, 레트로비리다에 바이러스는 알파레트로바이러스, 베타레트로바이러스, 델타레트로바이러스, 엡실론레트로바이러스, 감마 레트로바이러스 (예를 들어, 몰로니 뮤린 백혈병 바이러스), 또는 렌티바이러스 중 어느 하나일 수 있다. 일부 실시양태에서, 레트로바이러스의 추가의 구체적 예는 HIV-1, HIV-2, HTLV-1, HTLV-2, HTLV-3, HTLV-4, 말 감염성 빈혈 바이러스 (EIAV) 렌티바이러스 또는 그의 조합 중 어느 하나일 수 있다.

[0055] 본원에 개시된 생산자 바이러스에 의해 생산된 레트로바이러스는 일부 실시양태에서 분열 세포 뿐만 아니라 비-분열 세포를 감염시킬 수 있는 통합 바이러스이다. 레트로바이러스 게놈은 2개의 LTR, 캡시드화 서열 및 3개의 코딩 영역 (gag, pol 및 env)을 가질 수 있다. 복제 결손 비-감염성 레트로바이러스 벡터는 바이러스 패키징 신호를 파괴하도록 조작될 수 있지만, 이중 유전자 및 패키징 신호를 함유하도록 조작된 공동-도입된 바이러스를 패키징하는데 요구되는 구조 유전자를 보유할 수 있다. 따라서, 재조합 복제 결손 레트로바이러스 벡터에서, gag, pol 및 env 유전자는 일반적으로 전체적으로 또는 부분적으로 결실되고, 관심 이중 핵산 서열로 대체될 수 있다. 이들 벡터는 다양한 유형의 레트로바이러스, 예컨대 HIV (인간 면역결핍 바이러스), MoMuLV (뮤린 몰로니 백혈병 바이러스), MSV (뮤린 몰로니 육종 바이러스), HaSV (하비 육종 바이러스), SNV (비장 괴

사 바이러스), RSV (라우스 육종 바이러스) 및 프렌드 바이러스로부터 구축될 수 있다.

[0056] 본 개시내용의 구체적 실시양태에서, 종양용해 생산자 바이러스로부터 생산된 복제 결손 렌티바이러스는 뇌, 망막, 근육, 간, 및 혈액을 포함한 여러 조직 유형에서 트랜스진의 직접 전달 및 지속 발현을 위한 작용제로서 사용될 수 있다. 레트로바이러스 벡터의 이러한 하위유형은 이들 조직에서 분열 및 비분열 세포를 효율적으로 형질도입하고, 관심 유전자의 장기간 발현을 유지할 수 있다 (검토를 위해, 문헌 [Naldini, Curr. Opin. Biotechnol. 1998, 9:457-63; Zufferey, et al., J. Virol. 1998, 72:9873-80] 참조). 렌티바이러스 패키징 세포주는 이용가능하고, 관련 기술분야에 일반적으로 공지되어 있다 (예를 들어, 문헌 [Kafri, et al., J. Virol., 1999, 73: 576-584] 참조).

[0057] 한 측면에서, 생산자 바이러스 또는 계내 생산된 바이러스는 또한 아데노바이러스일 수 있다. 아데노바이러스는 본 개시내용의 핵산을 다양한 세포 유형에 효율적으로 전달하도록 변형될 수 있는 진핵 DNA 바이러스이다. 아데노바이러스의 다양한 혈청형, 예컨대 유형 2 또는 유형 5 인간 아데노바이러스 (Ad 2 또는 Ad 5) 또는 동물 기원의 아데노바이러스가 존재한다 (PCT 공개 번호 W094/26914 참조). 동물 기원의 아데노바이러스는 개, 소, 뿔 (예를 들어, Mav1 [Beard et al., Virology, 1990, 75:81]), 양, 돼지, 조류 및 원숭이 (예를 들어, SAV) 기원의 아데노바이러스를 포함할 수 있다. 바람직하게는, 동물 기원의 아데노바이러스는 개 아데노바이러스, 보다 바람직하게는 CAV2 아데노바이러스 (예를 들어, 만하탄 또는 A26/61 균주 [ATCC 수탁 번호 VR-800])이다. 다양한 복제 결손 아데노바이러스 및 최소 아데노바이러스 벡터가 기재되어 있다 (PCT 공개 번호 W094/26914, W095/02697, W094/28938, W094/28152, W094/12649, W095/02697, W096/22378). 본 개시내용에 따른 복제 결손 재조합 아데노바이러스는 관련 기술분야의 통상의 기술자에게 공지된 임의의 기술에 의해 제조될 수 있다 (문헌 [Levrero et al., Gene, 1991, 101:195]; EP 공개 번호 185 573; 문헌 [Graham, EMBO J., 1984, 3:2917; Graham et al., J. Gen. Virol., 1977, 36:59]). 재조합 아데노바이러스는 관련 기술분야의 통상의 기술자에게 널리 공지된 표준 분자 생물학적 기술을 사용하여 회수 및 정제된다. 아데노-연관 바이러스-기반 벡터. 아데노-연관 바이러스 (AAV)는 안정하고 부위-특이적 방식으로 이들이 감염시키는 세포의 게놈 내로 통합될 수 있는 비교적 작은 크기의 DNA 바이러스이다. 이들은 세포 성장, 형태 또는 분화에 대한 임의의 효과를 유도하지 않으면서 광범위한 세포를 감염시킬 수 있고, 인간 병리상태에 관여하는 것으로 보이지 않는다. AAV 게놈은 클로닝, 서열분석 및 특징화되었다. 시험관내 및 생체내에서 유전자를 전달하기 위한 AAV로부터 유래된 벡터의 용도가 기재되어 있다 (PCT 공개 번호 WO 91/18088 및 WO 93/09239; 미국 특허 번호 4,797,368 및 5,139,941; EP 공개 번호 488 528 참조). 본 개시내용에 따른 복제 결손 재조합 AAV는 2개의 AAV 역전된 말단 반복 (ITR) 영역에 의해 플랭킹된 관심 핵산 서열을 함유하는 플라스미드, 및 AAV 캡시드화 유전자 (rep 및 cap 유전자)를 보유하는 플라스미드를 생산자 바이러스 (예를 들어, 종양용해 백시니아 바이러스)로 감염된 세포주 내로 공동형질감염시킴으로써 제조될 수 있다. 이어서, 생산된 AAV 재조합체는 표준 기술에 의해 정제될 수 있다.

[0058] 종양용해 바이러스

[0059] 본원은 종양용해 생산자 바이러스 또는 그의 부분을 제공할 수 있다. 종양용해 바이러스는 암 세포를 감염시키고 용해시킬 수 있는 바이러스일 수 있다. 한 측면에서, 종양용해 바이러스는 암 요법에서 다음 기능 중 적어도 하나를 가질 수 있다: (1) 바이러스 용해에 의한 종양 세포의 직접 파괴, (2) 종양 부위에서 이중 단백질을 발현하기 위한 벡터로서의 역할, 및 (3) 면역계를 프라임/활성화시키기 위한 자가 종양 항원의 제시. 암 세포에 대한 종양용해 바이러스 선택성은 감염 동안 또는 복제 동안 발생할 수 있다. 종양-선택적 바이러스는 특이적 세포 수용체를 인식하는 바이러스 표면 단백질을 변형시킴으로써 조작하여, 바이러스가 특이적으로 암 세포에 진입하도록 할 수 있다. 복제 선택성은, 바이러스가 정상 항상성 경로에서의 파괴, 예컨대 종양-억제 결합 또는 종양원성 경로의 활성화를 갖는 세포에서만 복제될 수 있도록 효율적인 복제에 필요한 바이러스 유전자를 변형시킴으로써 달성될 수 있다.

[0060] 한 측면에서, 종양용해 바이러스는 수포성 구내염 바이러스 (VSV), 뉴캐슬병 바이러스 (NDV), 레트로바이러스, 레오바이러스, 홍역 바이러스, 신비스 바이러스, 인플루엔자 바이러스, 단순 포진 바이러스, 백시니아 바이러스, 및 아데노바이러스 중 어느 하나일 수 있다. 일부 경우에, 종양용해 바이러스는 폭스바이러스를 포함할 수 있다. 일부 경우에, 폭스바이러스는 홍역 바이러스, 폴리오바이러스, 폭스바이러스, 백시니아 바이러스, 아데노바이러스, 아데노 연관 바이러스, 단순 포진 바이러스, 수포성 구내염 바이러스, 레오바이러스, 뉴캐슬병 바이러스, 세네카바이러스, 렌티바이러스, 멧고바이러스, 점액종바이러스, 베타엔토모폭스바이러스, 야타 폭스바이러스, 세르비드폭스바이러스, 감마엔토모폭스바이러스, 레포리폭스바이러스, 수이폭스바이러스, 몰루시 폭스바이러스, 크로코딜리드폭스바이러스, 알파엔토모폭스바이러스, 카프리폭스바이러스, 아비폭스바이러스 또는

[0062]

[0063]

[0064]

TCAGACACACGCTTTGAGITTTGTGAATCGATGAGTGAAGTATCATCGGTTGCACCTTCAGATGCCGAT CCGTCGACATACCTTAAATCCATCCTTGACCTCAAGTTCAGATGATTCCTTGACATGTCTCCGATACGAA CGCTAAACTCTAGATTCCTTGACACATTTGTATCGACGATCGTTGAACCGATGATATCTTCGTAACCTCAC TTCTCTTATGAGAGATGTTAGACCCGAGTACTGGATGGGTCTTGATGTCGCTGTCTTTCTCTCTTCGTA CATCTGATGTCGATAGACACCTCACAGTCTTTGATCATAGCCAGAGCTTCTCATGAGTGATCGCGGGAG AGTCTCTACCTTGTCTCGGGACACGCTGGACAATCTAGCATTCACATGTGTTTCCATCAGCGGATCTGA GATGGATTTAATCTGAGGACATTTGGTGAATCCAAAGTTCATCTCAGACCTCCACCGATGATGGAGTAA TAAGTGGTAGGAGGATCTACATCCTCGACTGATGTGGAATCATCTTCTGATTCCACCTCGGGATCTGGAT CTGACTCGGACTCTGTAATTTCCGTTACGGATGGCAAATCTTATCATTTGGTCCGTGTTTGGTCTTGCTT TGTGACTTTGATAAATACATCGATTTCCCATATGATGTTTGTCTTCTTCTTCCGTACACGAGGAGGAGGAT GAGGATGATTGCTGAAGACTGGCAGGCACATGCATGCCAGGACGATATATTGTTTCATGATTGCTATTGA TTGAGTACTGTCTTATGATTCTACTTCTTACCGTGCAATAAATAGAAATATATTTTCTACTTTTACG AGAAATTAATTATTTGATTTATTTATTTATGGGTGAAAACTTACTATAAAAAAGCGGGTGGGTTTGGAAAT AGTGATCAGTTTATGTATATCGCAACTACCGGCATATGGCTATCGACATCGAGAACATTACCCACATGA TAAGAGATTTGATCAGTTTCTGATGCTTGGATTTGGTATTTACTATATAGTATATAGATGTCGACGCTAG ATAGACAGTCTCCGAATGGGCATGATACCGTCATCATCTTTGCTTTCGTTAACTGGATACAGATTAAATTTCC TTTTTGTATTGCAATTTAATCTCGAAATTCAGAGTGCACACCTTTCTCTGTAAAGAAACCTGAAGTTGC TACCTTATTAAGGACGGAGAAGTATTTCTCACGAAATACGGGATACAGTCTTTATGATTATAGTAAATA GTATGTTCCGACGTTGAGATGGATTCGCTGAGACCGGTAGTGGTCTTAAGTGGATACAGATTAAATTTCC ACATCGATATAGTTAAAGTATTACTGGGTACGGGTTGCGATTTATCTGCGGAAGAGACGGTGTGAGAAT ATGTTCCGAGACCAACGAGAACAGATGACGTCCTCGGATACCTCGATCCTATTCCACATTTTGTTTG GGAAACACATGCTTCGATTCGGATGATCCTTTGAGAAACAAATATATCCGGGAGAGCATTCACAGATT CTATTGTGAGTCTGTTACACGGTCGCGTCTTCCGTTACAACCTTAGACAAGCGGGTAAATGATTATTGCG AGATGTGAAGGTACCCGAACACACGGCTACATTTGTGTTAGTCTTGTCTATCGCATATCGGAAGCG TATGTTCCCGGACACAAATTTAGCGGTTTGTATTGCTTGTCTTACACTTTCATCGGATGGTGCATGCG GTGCTATATCTCTTCCGTTTATTTATATACATGAGAGAAACAATATATACGAGTATAATACGGACTTCAT GATTTAATAATGATGATATCTGCTCTTGTCTCTTCTACTTCTCCAATCATATAGATATTTCTTT CTATCATGGATAATATTTGTAATGGTCTTTTCTGTAACAACATCTGTTTAGATGATATTGCGCATAAATTT CCGGAGGCAATACGATAGTCTAGATTGACCGATGGTAGACTCTAATTTATTGAGTCTTTGTGACGAG TTTACTTTTACGCTCCATCGATAGATGGCACTGTTCTATGAGATCGTCGATACATGGGAAATGAAATGTGA CTGTCGTAATGTTTACGTAGTAACTGCTGATACCGTATACAGGTCGGTGTGCGAGATTCGAATCTCT TTAAGGCGACTTATGTCACGATGATGGAATCTATCTTATCGAATGATATATTTTTCATAAATACACTTTT ATAGTCTTCTGTTTAAACAGAAATTTACTATGATTTCCGCGAAATGACTCGTCCCTTAATAGGCAGTAGGCT ATTATCTCTTTACGTAGTAACTGCTGATAGGAGAGACATCTGTAGAACAAACGATTAAATCATAGGTAG AGATACTTTTCACTGTTGGTGGATGATGTCATTCACAACATCCGCCCTTGTATATGATGTTTCTGTTTCA AACCAAGTCAATACCGCTCTTGTAGTCGGAAGGTTGATGTCGATCCGATGATGAGGCAACATTTGTTG TTACAAATTTGAAAGCGGTTATATAGTATTCGTCTTTCTGAATGTGCAACCTATCTAGTAGATACCGTA GTATATTGAGAGTGTATCCTTGATTATGTTTATGAATAGATAAAGTAGATGTTGCTCTTCTCTCTTTG TTCTGCGCAATTTGATTAACATTTATGAAATATGACCTGTTGCACAATCGTTCATGATGGGTGTACAATC AAGATTTATACGTATCCTCGTATCGGCTCCTCGAGATAAAGAGCATACACCACACGAGGACTATGTTTG GTATACTGTTGAAGTAAAGTGTGTAACCGGCTTAATGTTTGTCTCCATAATCTATTATCGGCTAGATGAAT CGCTTCTCGGCTCGCATCTTAGTGTGACTTAACTTGAATAAATGCTTTTGTAGAAGCTGGATATGTGTT TACAGTAGTAATGAAGAGAAGTGAATTCATCCTCGTCGGATCCTTTGTACAGAACGTAATAGTTTAAGCT CCCATTTGAATTTATATCTAAGATAACACAGCAATAGATCGGATGATTTACTAAAGTCATCAATGGTGCTC GTTAGTATATCAAGATCTTGTATCGATTGATAGTGGTCTCTTTTCTCATCTTGTCTATCAAGTTACG CATGCCGTGGTGAACAATATCTTTAATACAGATGGATTAAATCGTGTATTCATCGTATAGCAATGTAAT GGAGAGTTACCTCGTTTATTCAGATCGCAGTGTTTAATAACTAGCTTAAACAGATGAGACGATGATCCA CATCAAGAAGCTGAAATACATATGACAGACATTTGTGACAGAAACGTGACCTTCATTCTTACCGTCGTC CATAAATACGTTAGGTATGTACCACATACTGTGCGGAACGATGCGTACAATCTCGTCCATCTCATAATGA TTTACTTTTTCATAATTAAGATGTGAAAGAAAAACAGAACAAATATATTTTTTTAGTAATGTTTATGCGA GACATATAAAATAAACTCCGTGTTTATGATCATTTTTTAACAGCAACACATTCATAATTTGATTGTTATTT TTATATTTTACACAATTAACAATATATTTAGTTTATATTAAGTAAATTAATAATAAAATTTCCCAA TCTTGTCTATAACACACACTGAGAAACAGCATAAACACAAAATCCATCAAAAATGTCGATGAAATATCTG ATGTTGTTGTTGCTGCTATGATAATCAGATCATTCGCGGATAGTGGTAACGCTATCGAAACGACATCGC CAGAAATTAACAACGCTACAACAGATATTCAGCTATCAGATTATGCGGTCCAGAGGGAGATGGATATTG TTTACACGGTGACTGTATCCACGCTAGAGATATTTGACGGTATGATTGTAGATGCTCTCATGGTTATACA GGCATTAGATGTCAGCATGATGATTAGTAGACTATCAACGTTTCAAAAACCCAAACACTACAACGTCAT ATATCCCATCTCCGGAATTTGCTTGTATTAGTAGGCATTTATTTATTACGTTGTTGCTATTATCTGT TTATAGGTTCACTCGACGAACTAAACTACCTATACAAGATATGGTTGTGCCATAATTTTTATAAAATTTT TTATGAGTATTTTACAAAAAAATGTATAAAGTGTATGTTTATGTATATTTATAAAATGCTAAGTAT GCGATGTATCTATGTTATTTGATTTATCTAAACAATACCTCTACCTCTAGATATTATACAAAATTTTT

[0065]

TATTTCGGCATATTAAAGTAAATCTAGTTACCTTGAAAATGAATACAGTGGTGGTTCGGTATCACCAG
TAAGAACATAATAGTCGAATACAGTATCCGATTGAGATTTTGCATACAATACTAGTCTAGAAAGAAATTT
GTAATCATCTTCTGTGACGGGAGTCCATATATCTGTATCATCGTCTAGTTTATCAGTGTCCCATGCTATA
TTCCGTGTTATCATCATTAATGAAATAAATCTCTCGTCTCAGAAAAGTCAAATATTGTATCCATAC
ATACATCTCCAAATATCGCTTATACGTTTATCTTTAACGATACCTATACCTAGATGGTTATTTACTAA
CAGACATTTTCAGATCTATTGACTATAACTCCTATAGTTTCCACATCAACCAAGTAATGATCATCTATT
GTTATATAACAAATAACATAACTCTTTTCCATTTTATACAGTATGTATATCTATATCAACGTCTGTGT
AGTGAATAGTAGTCATTGATCTATTATATGAAACGGATATGTCTAGAACGGCAATTGTTTTACGTCCAGT
TAACACTTTCTTTGATTTAAAGTCTAGAGTCTTTGCAACATAATATCCTTATCCGACTTTATATTTCT
GTAGGGTGGTATTAATTTTATTTTCCCTCCACATATCGGTGTTTCCAAATATATTACTAGACAATATCCCA
TATAGTTATTAGTTAAGGGTACCCAATTAGAACACGTACGCTTATTATCATCATTTGGATCGTATTTCA
AAAAATTATGTACTATCGATGTCAACACATTTACATTTTAAATCGTCTATATAGTATTTTCTGATA
TTTTCTATAATATCAGAATTGCTTCCATCGGAAGTTGTATACTATCGGAATCAGTTACATGTTTAAATA
ATTTCTCTGATGTCTTCTTATACAATCAAATTCATTATTTAAACAGTTTAAATAGTCTGTAGACCTTTATC
GTCTGTAATTCATTTGTCTTATAGTTACGCTTATTTTATGTGTTTACGTTGCTTTATATATTTTAA
TAAGAAATGATTTGTTTACGAATCACGAGAATCTATTAAGACACATTTATAGGTATATATTATAAAAAAGTT
TTTGATTACGATGTTTATAAGAGGAAAGAGGACATTAACATCATACATCAATTAACATACATTTTATAA
CATCTGTAATCAAAGAAATGCAATTTTGTATGTATAACAATGTCAATGGGTATGGAATGTATATTACA
TATTATACGGTATGTTGGTAACGACAAATACCGATCGGTAAATGCTGCGCGGTGAATAGAATTATATAT
ATCTATCTATTACACCGGCTGAGTATGCATAATAAAGTTGTGGTAGTATGATCTCCATATTTATAATT
TAGGACTTTGTATTCAGTATTTTGGAAATCATAAAAATAAAAAAAGTTTACTAATTTAAAAATTTAAA
AAGTATTTACATTTTTTCTACTGTTTAGTCGCGGATATGGAATTCGATCCTGCCAAAATCAATACATCAT
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[0067]

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[0068]

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[0070]

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[0071]

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[0072]

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[0073]

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[0078]

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[0079]

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[0080]

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[0081]

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[0082]

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[0083]

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[0084]

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[0085]

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[0086]

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[0087]

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[0088]

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[0089]

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[0094]

[0095]

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[0096]

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[0097]

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[0098]

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[0103]

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[0104]

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[0105]

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[0106]

TACATATACAGACAAGTTTATATTTCTAAGAATATAGTTACCAAGTGTGATATGATGGTGAGCACTGAG AATAACTTGCATATGTACATATTAATGAATTATTCGGAGGATTCTCTATTATCGATATTCATACGAGG GAAACTCTAGTATGTAATTAATCTACCGGACGACATAGAAAGTATATATAACATAGAAAAAATATAAC AGATGAAAAATTTAAAAATGTTGGTATGTTATCTACTAAAAAGTATAGACTTGTATATGCCAAAGTTT AAAGTGGAAATGACAGAACCGTATAATCTGGTACCGATTAGAAAAATTTAGGACTTACTAATATATTCG GATATTATGCAGATTTTAGCAGATGTGTAATGAACTATCACTGTAGAAAAATTTCTACATACGACGTT TATAGATGTTAATGAGGAGTATACAGAAGCATCGGCCGTTACAGGAGTATTTATGACTAAGTTTCGATG GTATATCGTACGAGGTCTACATAAACCCATCCATTGATGATGATTAAGACAAACACAGGACGTATAC TTTTTATAGGGAATACTGCTATCCGCAATAATATAACAAATAGACTTTATCAGCTTTATCTATGTC TAAATATTACAATAGTAAATAGTATAAACTAAAGCTGATAATACCTTAAAAAATAAATATCATTTACA ATTAATAGTATAAACTAAAAATTAACAAATCGTTATTATAAGTAAATCAAAATGATGATATACGGATT AATAGCGTGTCTATATTCGTGACTTCATCCATCGCTAGTCCACTTTATATCCCCTTATCCACCCATT TCGGAAGATAAATCGTTCAATAGTGTAGAGGTATTAGTTTCTTGTAGAGATGACCAAAAAGACTATA CGGTAACTTCTCAGTTCAATAACATACATATCGATACCAAGACTGGACTATCGGCGTACTATCCACACC TGATGGTTTGGATATACCATGACTAATAATACTTATTTGGTACCGGTTTACTATAGGTGCTGCATTGTTT AAATCAGAGTCTGAGGATATTTCCAAAAGAAAAAGAGTATTCTAGGTGTTTCTATAGAAATGTAAGAAGT CGTCGACATTAATCTTACTTTTGGACCGTGCCTAAAAATGACTCGAGTATTAAATAAATTTCCAGATATGGC TTATTATCGAGGAGACTGTTTAAAGCCGTTTATGTAAACAATGACTTATAAAAAATCTAAACCTGGAGAG ACTGATTACAGTACCTCTCTAATGGGGGTTGCTGCATACCTATCGTAATGGGGTGCATGGTTGATTAT TGATTAGTATATCTCTTATCTTTTATTCACACAAAAAGAACATTTTATAAATCATGAACCACTGTCT AAATGTAATTATGATCTTGTATTATAGATGAAGATCAGCCTTTAGAGGATTTTAAACAGTATGTTAATA TGAAAAAATAAACATAACATATTTGAGATTAAGCGCTATTGTGCAAGATTATATTAGAATCAAAATTA CTTTTCAATACGAGAAAAATTAACGACATACGTCGTCAACAAATTAACCTTTTATTATTAGTTAACTAGC TTATAGAACTTGTCTATTGTTATGTTTCTAAACGGGTACGACATATAGGACAATTATCCGACGACCCGG TTTCTCTTCTGTTTATGCCATATATTGATGCATGTTATGCAAAATATATGAGTACACGAATCCAATAA ACCAAAGTATCTATCGTTTTGAGTAAACAACCTTCATAGCAAAATCCACATCTTTTCTTACTTACTCT ATACACGTCCTCGTATTTATCCAGTATTTTGATGATATCCAATCAGAAATGTTGTTGATTATTGGGT GTATTGGGAGTATAGGTATTTAGCTATGTACCAATTTACCAACCTCTTAATATTGATTGAACAACTCA CATCGGTTATCCAATCAATAACCACTTAATACTAAATTTAGTGTATATATAGACCATATATGTTTCT ATTTTCTTGGACAGTTACGTATAGTTTCAAGTATTTGATTGTTGATTTCTCTATCTAGATAAGTTA GTATATAGTCCCTTCCGGCGATACGTTTTTCCAAGCCGAAATGATTAGCCAAATGTGATTTATTT TTGTGATATTGATATAAATATGAATGTTATTAATATTTGCGATAATGCATACCTTTAGTCTTATATCAT TGGTTCACTATGATTTGAATATTGTTACATGATCTATAGATGATGATTTGATTTTGGCAGGATCGAAT TCCATATCCGGACTAAACAGTAAAAAATGTAATACTTTTAAATTTTAAATTAGTAAAACTTTTCT TTATTTTATGATTCCAAAAATCTGAATACAAAGTCTAAATTTATAAATATGGAGATCATACTACCAC AACTTATTATTATGCATCTCAGCCGGTGTAAATAGATAGATATATAAATCTATTACACCGGACAGCAA TTACCGATCGGTATTTGTCGTTACCAACATACCGTATAATATGTAATATACAAATCCATAACCCATTGAC AGTTGTTATACATCAAAATGCAATTTCTTTGATTACGATGTTATAAGAATGTAGTTAATGATGTATGA TGTTAATGTGTCCTCTTCTCTTATAACATCGTAATCAAAAACCTTTTATAATATATACCTAATAATG TGCTTAATAGTTCTCGTGATTCTGCAACCAATCATTTCTATAAATAATAAAGCAACGTAAACACA TAAAAATAAGCGTAACATAAAGACAATGGATATTTACGACGATAAAGGTCACAGACTATTAACTGTT TAATAATGAATTTGATTGTATAAGGAATGACATCAGAGAATTATTTAAACATGTAAGTATCCGATAGT ATACAACTTCCGATGGAAGACAATTCGTATATTATAGAAAAATATCAGAAAAATCTATATAGACGATTAA AAAAATGTAGAAATGTTGATGACATCGATAGTACAAATAACTTTTATGAAATACGATCCAAATGATGATAA GCGTACGTTCTAATTTGGGTACCTTAACTAATAACTATATGGAATATTGCTAGTAAATATTTGGAA ACCCGATATGTTGGAGGCAAAATAAATTTATACCCCTTACAGGAAATATAAGTCCGATAAGGATATTA TGTTTGCAGAGCTCTAGACTTTAAATCAAAGAAAGTGTAACTGGACGTAAACAAATGCGCTTCTAGA CATATCCGTTTATATAATAGATCAATGACTACTATTTCACTACAACGACGCTGATATAGATATACAT ACTGATAAAAAATGAAAAAGATTATGTTATTGTTATATAACAATAGATGATCTTACTTGGTTGATGTTG AACTATAGGAGTTATAGTCAATAGATCTGGAAAAATGCTGTTAGTAAATAACCATCTAGGTATAGGTAT CGTTAAAGATAAAGCTATAAGCGATAGTTTGGAGATGATGTTAGGATACAAATTTGACTTTTCTGAA GCACGAGAGTTATTTCAATTAATATGATGATAACAGGAATATAGCATGGGACACTGATAAATAGACG ATGATACAGATATATGGACTCCGTCACAGAGATGATTACAAATTTCTTTCTAGACTAGTATTGTATGC AAAACTCAATCGGATACGTATTCGACTATTATGTTCTTACTGGTGATACGGAACCCACCTGTATTC ATTTTCAAGGTAACTAGATTTTACTTTAATATGCCGAAATAAAAAATTTTGTATAATATCTAGAGGTAG AGGTATTGTTTAGATAAATAACAAATAACATAGATACATCGCATACTAGCATTTTATAAATATACATAA GACATACACTTTATACATTTTCTTGTAAAAATCTCATAAAAAATTTATAAATATATGGCACAACCA TATCTTGTATAGGTAGTTTGTTCGTCGAGTGAACCTATAAACAGATAATAGACAACACGTAATAAAT AATGCCCTACTAATAACAGCATAAATACCGGGAGATGGGATATATGACGTTGTAGTGTGTTGGGTTTCTGAA CGTTGATAGTCTACTAATACTACATGCTGACATCTAATGCCTGTATAACCATGAGAGCATCTACAATACA TACCGTCAATATCTCTAGCGTGGATACAGTCACCGTGTAAACAATATCCATCTCCCTCTGGACCGCATAA
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[0107]

TCTGATAGCTGGAATATCTGTTGTAGCGTTTGTAAATTTCTGGCGATGTCGTTTCGATAGCGTTACCACTA
TCGGCGAATGATCTGATTATCATAGCAGCGAACAACACATCAGATATTTATCGACATTTTGTATGGAT
TTTGTGTTTATGCTGTTTCTCAGTGTGTGTTTATGACAAGATTGGGAATTTATATATTAAATCAGTAA
TATAAACTAATAATATTGTTAATTGTGTAATAATATAAAAAATAACAATACAATATGAATGTGTTGC
TGTAAAAATGATCATATAACACCGGAGTTTATTTATATGTCTCGCATAAACATTACTAAAAAATATATT
GTTCTGTTTCTTTTACATCTTTAATTATGAAAAAGTAAATCATTATGAGATGGACGAGATTGTACGCA
TCGTTTCGCGACATGATGTGGTACATACCTAACGTATTTATGGACGACGGTAAGAAATGAAGGTCACGTTTC
TGTCACCAATGCTGTCTATATGATTTCACGTTCTTTGATGTGGATACATCGTCTCATCTGTTTAAAGCTA
GTTATTAACACTGCGATCTGAATAAACGAGGTAACCTCTCCATTACATTTGCTATACGATGAATACACGAT
TTAATCCATCTGTATTAAAGATATTGTTACACCACGGCATGCGTAACCTTTGATAGCAAGGATGAAAAAGG
ACACCACCTTAATCGATAAAGACGATCTTTGATATACTAACGGACACCATGATGACTTTAGTAAATCAT
CCGATCTATGTGTGTTATCTTAGATATAAATCAATGGGAGCTTAACTATTACGTTCTGTACAAAGG
ATCCGACGAGGATGAACCTACTTCTCTTACTACTGTAAACACATATCCAGGTTCTACAAAAGCAAT
TATTTACAGTTAAGTACACTAAGATGCGAGCGGAGAGCGATTTCATCTACGCGATAATAGATTATGGAG
CAAACTATTACCGCGTTACACACTTACCTTCAACAGTATACCAACATAGTCTCGTGTGGTGTATGCTC
TTTTATCTCGAGGAGCGGATACGAGGATACGTAATAATCTTGATTGTACACCCATCATGGAACGATTGTG
CAACAGGTCAGTTCTCATATTTTACTCAATTGGCACGAACAAAAGGAAGGACAACTACTACTTTA
TCTATTCATAAAACATAATCAAGGATACACTCTCAATATACTACGGTATCTACTAGATAGGTTTCGACATT
CAGAAAGACGAATATATAATACCGCTTCAAAATGTAAACAACATGTTGCTCATACATCGGATACG
ACATCAACCTTCGATACGATAAAGACGATTTGACTTGGTGTGTTGAAAACAGAAACATCATATACAAGCGG
ATGTTGTGAATGACATCATCCACACAGACTGAAAGTATCTTACCTATGATTAATCGTTGTTCTACAA
GATGTCCTCTCCCTACGAGATTACTACGTAAGAAGATAATAGCCTACTGCTTATTAAGGGACGAGTCAT
TCGCGGAGAGTCAATCGATAAAGACGATTTCTGTTAAACGAGGACTATAAAAGTGTATTTATGAAAAATATATCAT
CGATAAGATAGATTCCATCATCGTGACATAAGTTCGCTTAAAGAGATTGCAATCTCCGACACCGACCTGT
ATACGGTATCACAGCTATCTTAAAGCCATACATTGACAGCTCACATTTTCCATGTACGACGATC
TCATAGAACAGTCCATCTCATATCGATGGAGCGTAAAGTAACTCGTCGACAAAGCACTCAATAAATTAGA
GTCTACCATCGGTCAATCTGACTATCGTATTTGCCCTCCGGAATATGCGCAATATCATCTAAACAGTA
TGTTGTACGAAAAGAACCATTAACAATATATCCATGATAGAAAAGAAATATCTATATGATTGGAGAAAT
AGGAAACAGGAACAGACGAGTACTACATTTAAATCATGAAGTCCGTATTTACTCGTATATATAT
GTTTCTCTCATGTATATAATAAACCGGAAGAGATATAGCACCAGCATGCACCATCCGATGGAAGTGTAAA
GACAACGAATACAAACGCCATAATTTGTGTCCGGGAACATACGCTTCAGATTATGCGATAGCAAGACTA
ACACACAATGTACCGGTGPGTTCCGGTACCTTCACATCTCGCAATAATCATTTACCGCTTGTCTAAG
TTGTAACGGAAAGACGGGACCGGTAAACACGACTCACAAATAGAACTGTGAATGCTCTCCCGATATTATT
GTCTTCTCAAAGGATCATCCGATGCAAGGCATGTGTTCCCAAACAAAATGTGGAATAGGATACGGAGT
ATCCCGAGACGTCATCTGTTCTCCGTGTGGTCTCGGAACATATCTCACACCGTCTCTCCGAGATAAA
TGCGAACCCGTCACCGTAAATACCTTTAACTATATCGATGTGGAATTAATCTGTATCCAGTTAACGACC
ACTACCGGTCTCAGCGAATCCAATCTCAACGTCGGAACTAATTTACTATGAATCATAAAGACTGTAATC
CCGTATTTCTGAGGAATACTTCTCCGTCTTAATAAGGTAGCAACTTCAGGTTCTTTTACAGGAGAAAG
GTGTGCATCTGAATTTGAGATTAATGCAATAACAAAATTTTCTCCAAACAGTTAACGAAAGCAA
AGAATGATGACGGTATCATGCGCATTCGGAGACTGTCTATCTAGCGTCGACATCTATATACTATATAGT
AATACCAATACTCAAGACTACGAACTGATACAATCTCTATCATGTGGGTAATGTTCTCGATGTCGATA
GCCATATGCCCGGTAGTTGCGATATACATAAACTGATCACTAATTCCAAACCCACCCGCTTTTTATAGTA
AGTTTTTCACCATAAATAAATAACAATAATTAATTTCTCGTAAAGTAGAAAAATATATTCTAATTTA
TTGACCGGTAAAGGAATAGAAATATAAAGAACAGTACTCAATCAATAGCAATCATGAAACAAATATATCGT
CCTGGCATGCATGTGCTGCCAGTCTTCAGCAATCATCTCTCATCTCTCTGTTACGGAAGAAAGAAA
ACAAACATCATATGGGAATCGATGTTATTATCAAAGTCACAAAGCAAGACCAACACCGACCAATGATAA
GATTTGCCAATCCGTAACGGAATTAACAGATCCGAGTCAGATCCAGATCCCGAGGTGGAATCAGAAAGAT
GATTCACATCAGTCGAGGATGTAGATCTCTTACCCTTATTACTCCATCATCGGTGGAGGCTGTGAGAA
TGAACCTTTGGATTACCAAAATGTCCTCAGATTAAATCCATCTCAGAAATCCGCTGATGGAACACAGTGAA
TGCTAGATTGTCCAGCGTGTCCAGGACAAAGGTAAGGACTCTCCGCGATCACTCATGAAGAACTCTG
GCTATGATCAAAGACTGTGAGGTGTCTATCGACATCAGATGTAGCGAAGAGAGAAAGACAGCGACATCA
AGACCCATCCAGTACTCGGCTTAACATCTCTCATAAGAAAGTGAGTTACGAAGATATCATCGGTTCAAC
GATCTGTCGATACAAAATGTGTCAAGAACTTAGAGTTTAGCGTTGATTCGGAGACATGTGCAAGGAATCA
TCTGAACCTGAGGTCAAGGATGGATTTAAGTATGTGACGGATCGGCATCTGAAGGTGCAACCGATGATA
CTTCACTCATCGATTCAACAAAACCTCAAAGCGTGTGTCTGAATCGATAACTCTATTCATCTGAAATGGA
TGAGTAGGGTTAATCGAACGATTACGGCACACCAGAAATAAAAAGGTACCGGACACTATATTCGGGT
TTGCAAAACAAAATGTTCTTAACATACATTCAAAAAAGTTACCTCTCGCGACTCTTCTTTTCTGTCT
CAATAGTGTGATACGATTATGACACTATTCTATCTCTATCTCTATTTCTTTCAGGGTATCACAAAAT
ATTAACCTCTTCTGATGGTCTCATAAAAAAGTTTACAAAAATATTTTATCTCTTTCTCTCTTTG
ATGGTCTCATAAAAAAGTTTACAAAAATATTTTATCTCTTCTCTCTTTGATGGTCTCATAAAAAA
AGTTTTACAAAAATATTTTATCTCTTCTCTCTTTGATGGTCTCATAAAAAAGTTTACAAAAATAT

[illegible]

[0109]

[0110]

일부 실시양태에서, 종양용해 바이러스 (예를 들어, 본원에 기재된 바와 같은 생산자 바이러스, 조작된 생산자 바이러스)는 다양한 외인성 핵산을 단독으로, 또는 바이러스 유전자 변형, 예컨대 돌연변이 또는 결실 (완전 또는 부분 결실) 또는 바이러스 유전자와 조합하여 포함할 수 있다. 바이러스 유전자의 비제한적 예는 B5R, A52R (VACWR178), F13L, A36R, A34R, A33R, B8R, B18R, SPI-1, SPI-2, B15R, VGF, E3L, K3L, A41L, K7R, N1L, C12L, TK, 및 그의 임의의 조합을 포함할 수 있다. 외인성 핵산의 비제한적 예는 CXCR4, CCR2, PH-20, HMGB1, PIAS3, IL15, IL15-R α , LIGHT, ITAC, 프랙탈카인, CCL5, 대사 조정 단백질, 시토카인, 상기의 임의의 조합을 포함하는 융합 단백질, 및 그의 기능적 도메인 또는 단편 또는 변이체, 또는 그의 임의의 조합을 코딩하는 핵산 서열을 포함할 수 있다.

[0111]

히알루로난 (HA)은 ECM의 중요한 구조 요소이고, 반복 디사카라이드 단위로 이루어진 고분자량 선형 글리코사미노글리칸이다. 이는 결합, 상피 및 신경 조직 전체에 걸쳐 광범위하게 분포될 수 있고, 그의 발현 수준은 많은 유형의 종양에서 유의하게 상승될 수 있다. 히알루로니다제는 HA의 분해를 촉매하는 효소의 패밀리이다. 인간에서 다음 적어도 5종의 기능적 히알루로니다제가 지금까지 확인되었다: HYAL1, HYAL2, HYAL3, HYAL4 및 HYAL5 (또한 PH-20 또는 SPAM1로 공지됨), 이 중에서 PH-20은 비교적 중성인 pH에서 기능적인 것으로 지금까지 알려진 유일한 것이다. 본 개시내용의 일부 실시양태에서, 히알루로니다제를 다른 종양-표적화 치료제 (예컨대, 트랜스젠, 또한 본원에서 외인성 핵산으로 지칭됨)와 조합하는 것은, 적어도 ECM을 감소시키고 종양 내부 및 종양 사이의 치료제의 수송을 증진시킴으로써 본원에 기재된 바와 같은 생산자 바이러스로서 사용될 수 있는 변형된 종양용해 바이러스의 치료 효과를 촉진할 수 있다.

[0112]

본원의 일부 실시양태는 히알루로난을 분해할 수 있는 막 연관 단백질, 예컨대 히알루로니다제를 코딩하는 외인성 핵산을 포함할 수 있는, 본원에 기재된 바와 같은 생산자 바이러스로서 사용될 수 있는 변형된 종양용해 바이러스를 개시한다. 본원에 사용된 용어 "히알루로니다제"는 종양에서 HA의 분해를 촉매하는 임의의 효소 또는 그의 단편, 예컨대 비제한적으로, PH-20 및 다른 종으로부터의 그의 상동체, 뿐만 아니라 유사한 효소 기능을 갖는 다른 조작된/설계 단백질을 지칭할 수 있다는 것을 주목해야 한다. 본원에 사용된 히알루로니다제는 히알

루로난 분해 효소의 부류를 지칭할 수 있다.

[0113] 일부 실시양태에서, 본원에 기재된 바와 같은 생산자 바이러스로서 사용될 수 있는 변형된 종양용해 바이러스는 키메라 단백질인 케모카인 수용체를 코딩할 수 있는 외인성 핵산을 포함할 수 있다. 그의 세포외 도메인의 적어도 일부는 바이러스의 종양-표적화 전달을 촉진하는 케모카인 수용체로부터의 것일 수 있고, 그의 세포내 도메인의 적어도 일부는 종양-특이적 복제를 촉진하거나, 면역억제 활성을 억제하거나 또는 일부 다른 유익한 효과를 전달하는 케모카인 수용체로부터의 것일 수 있거나, 또는 그 반대의 경우일 수 있다. 예를 들어, 변형된 종양용해 바이러스는 CCR5의 세포내 GTPase 도메인 및 CXCR4 또는 CCR2의 세포외 케모카인-결합 도메인을 갖는 단백질을 코딩하는 핵산을 포함할 수 있다. 일부 경우에, 상이한 기능성을 갖는 도메인들을 조합함으로써 변형된 종양용해 바이러스의 치료 성능의 추가의 개선을 달성할 수 있다. 본 개시내용의 한 실시양태는 변형된 종양용해 바이러스가 적어도 1종의 케모카인 수용체를 코딩할 수 있는 외인성 핵산을 포함할 수 있다는 것이다. 일부 경우에, 변형된 종양용해 바이러스는 2종 이상의 상이한 케모카인 수용체를 코딩할 수 있는 외인성 핵산을 포함할 수 있고, 이는 바이러스에 의해 동시에 발현될 수 있다. 본원에 기재된 변형된 종양용해 바이러스로부터 동시에 발현될 수 있는 예시적인 케모카인 수용체는 CXCR4 및 CCR2를 포함할 수 있다. 1종 초과인 케모카인 수용체를 발현하는 변형된 종양용해 바이러스에서, 종양용해 바이러스의 치료적 적용에 관하여 종양 세포에 대한 조합 또는 상승작용적 효과가 달성될 수 있다.

[0114] 특정 실시양태에서, 변형된 종양용해 바이러스는 외인성 CXCR4-발현 핵산을 포함한다. 특정 실시양태에서, 변형된 종양용해 바이러스는 외인성 CCR2-발현 핵산을 포함한다. 특정 실시양태는 CXCR4 및 CCR2 둘 다를 코딩하는 외인성 핵산을 포함하는 변형된 종양용해 바이러스를 개시하고, 두 케모카인은 동일한 바이러스로부터 발현된다. 특정 상황 하에서, 전형적으로 종양 미세환경에서 발현되는 CXCL12 및/또는 CCL2는 CXCR4 및/또는 CCR2-발현 림프구 또는 변형된 종양용해 바이러스에 의해 감염된 다른 이동 세포를 유인하여, 변형된 종양용해 바이러스의 종양-표적화 전달을 증진시킬 수 있다.

[0115] 특정 실시양태에서, 본원에 기재된 생산자 바이러스는 STAT3의 활성을 조정할 수 있고, 그 결과 STAT3에 의해 조절되는 유전자의 활성화를 또한 조정할 수 있는 작용제를 코딩하는 mRNA를 생성할 수 있는 하나 이상의 외인성 핵산 서열 (대안적으로 트랜스진으로 지칭됨)을 포함할 수 있다. 따라서, 본원에 제공된 특정 예는 STAT-3 매개 유전자-활성화를 조정할 수 있는 작용제를 코딩할 수 있는 외인성 핵산 서열을 함유하는 종양용해 백시니아 바이러스를 제공한다. 본원에 사용된 어구 "STAT3-매개 유전자 활성화를 조정한다"는 STAT3 활성이 조정되고, 그 결과 STAT3에 의해 조절되는 1종 이상의 유전자의 활성화가 또한 조정되는 과정을 지칭할 수 있다.

[0116] 특정 실시양태에서, STAT3-매개 유전자 활성화를 조정할 수 있는 작용제는 단백질 또는 그의 단편일 수 있다. 특정 실시양태에서, 단백질 또는 그의 단편은 STAT3 활성 및 STAT3-매개 유전자 활성화를 억제, 감소 또는 최소화할 수 있다. STAT3 활성 및 STAT3-매개 유전자 활성화를 억제, 감소 및/또는 최소화하는 단백질 또는 그의 단편은, 예를 들어 STAT3 반응성 유전자의 프로모터 영역 내의 DNA 결합 서열에 대한 STAT3의 결합을 차단할 수 있다. 추가의 예에서, STAT3 활성 및 STAT3-매개 유전자 활성화를 억제, 감소 또는 최소화하는 단백질 또는 그의 단편은, 예를 들어 SH2 도메인에서 STAT3 단백질에 직접 결합할 수 있다. 특정 실시양태에서, STAT3 활성을 억제, 감소 및/또는 최소화하는 단백질은 STAT3의 인산화를 차단, 방지, 감소 및/또는 최소화하고/거나 STAT3을 탈인산화시킨다. 특정한 비제한적 실시양태에서, STAT3 활성을 조정하는 단백질은 포스포타이로신 포스포타제 (PTP), 활성화된 STAT의 단백질 억제제 (PIAS, 예를 들어 PIAS3) 및 시토카인 신호전달의 억제제 (SOCS) 단백질 (예를 들어, SOC3)을 포함할 수 있다.

[0117] 예를 들어, 일부 측면에서, 백시니아 바이러스 게놈은 렌티바이러스의 외인성 env, 패키징 구축물 및 전달 구축물을 포함할 수 있다. 외인성 서열은 백시니아 바이러스 게놈의 임의의 부분에 삽입될 수 있다. 한 측면에서, 외인성 서열은 5' 또는 3' 말단에 근접하여 삽입될 수 있다. 한 측면에서, 외인성 서열은 또 다른 외인성 서열에 인접하여 삽입된다. 한 측면에서, 외인성 서열은 다음으로 가장 가까운 외인성 서열로부터 약 0.5 kb 내지 약 1000 kb 떨어져 삽입된다. 일부 경우에, 렌티바이러스 단백질을 코딩하는 외인성 서열은 초기 백시니아 바이러스 프로모터의 제어 하에 있을 수 있다. 일부 실시양태에서, 생산자 바이러스는 박테리오파지 조절 서열, 예컨대 박테리오파지 프로모터, 박테리오파지 종결 서열, 또는 그의 조합을 발현하는 종양용해 백시니아 바이러스일 수 있다. 박테리오파지 프로모터 또는 종결 서열은 T3 박테리오파지, T7 박테리오파지 및 SP6 박테리오파지로부터의 것일 수 있다. 박테리오파지 조절 서열은 클로닝 및 조작을 위한 표준 방법을 사용하여 클로닝될 수 있다. 일부 실시양태에서, 생산자 바이러스는 박테리오파지 폴리머라제를 발현하는 종양용해 백시니아 바이러스일 수 있다. 용어 "박테리오파지 폴리머라제"는 T3 박테리오파지, T7 박테리오파지 및 SP6 박테리오파지 프로모터와 상용성인 것을 비롯한 임의의 박테리오파지 폴리머라제를 지칭할 수 있다. 일부 실시양태에서, 생

산자 바이러스는 박테리오파지 폴리머라제를 발현하는 종양용해 백시니아 바이러스일 수 있고, 박테리오파지 폴리머라제는 클로닝 및 조작의 표준 방법을 사용하여 클로닝될 수 있다.

[0118] Env 요소

[0119] 일부 측면에서, 외인성 서열은 env 요소일 수 있다. 일부 측면에서, env 요소는 vsvg-함유 env 구축물로부터의 것일 수 있다. 일부 측면에서, vsvg-함유 env 구축물은 vacwr032 (k11) 및 vacwr033 (k21) 유전자 사이의 지점에서 백시니아 바이러스 게놈과 재조합할 수 있다. 한 측면에서, vsvg-함유 env 구축물은 vacwr032 (k11) 및 vacwr033 (k21) 유전자 사이의 지점에서 백시니아 바이러스 게놈과 재조합하도록 설계될 수 있다. 이러한 게놈 위치는 몇몇의 이점을 제공할 수 있다: (1) 유전자 사이의 적절한 공간을 제공하고, (2) 확인가능한 프로모터가 vacwr032에 대해 발견될 수 있고, (3) 내인성 백시니아 바이러스 게놈을 파괴할 수 있는 임의의 다른 외인성 서열로부터 가장 멀리 떨어진 게놈의 5' 말단에 구축물을 위치시킨다. 한 측면에서, vsvg 유전자 및 그의 프로모터는 인접한 VV 유전자의 방향과 매칭되도록 3'에서 5'으로 위치할 수 있다. 일부 경우에, env는 백시니아 게놈의 위치 bp 26041에 삽입된다. 한 측면에서, 외피 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr032와 vacwr033 사이에 삽입될 수 있다. 한 측면에서, 외피 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr032 또는 그의 부분과 vacwr033 또는 그의 부분 사이에 삽입될 수 있다.

[0120] 한 측면에서, env 요소는 서열식별번호: 2에 대해 적어도 약 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% 또는 100% 동일성을 갖는 서열을 포함한다. 한 측면에서, env 요소는 서열식별번호: 3에 대해 적어도 약 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% 또는 100% 동일성을 갖는 vsvg 서열을 포함한다.

[0121] 패키징 구축물

[0122] 한 측면에서, 외인성 서열은 패키징 구축물 서열일 수 있다. 한 측면에서, 패키징 구축물은 유전자, 예를 들어 vacwr093 (j1r)과 vacwr033 (j3r) 유전자 사이의 vacwr094 (j2r)에 대한 코딩 서열을 대체하기 위해 백시니아 바이러스 게놈과 재조합하도록 설계될 수 있다. 한 측면에서, 외인성 서열의 삽입으로 인한 게놈 파괴가 수행될 수 있다. 한 측면에서, 게놈 파괴는 바이러스의 기능을 약화시킬 수 있다. 예를 들어, 파괴, 예를 들어 j2r-결실이 종양 세포를 우선적으로 감염시키는 약독화 바이러스를 생성하기 때문에, 패키징 구축물은 백시니아 바이러스 게놈과 재조합하여 유전자에 대한 코딩 서열을 대체하거나 파괴하도록 설계될 수 있다. 또한, 이러한 파괴/삽입은 다른 외인성 서열, 예컨대 env로부터 비교적 먼 백시니아 바이러스 게놈의 중심 근처에 외인성 패키징 구축물을 위치시킨다. 일부 경우에, 패키징 구축물은 백시니아 바이러스 게놈의 위치 bp 80724-81257에서 삽입 또는 결실된다. 한 측면에서, 패키징 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr093과 vacwr095 사이에 삽입될 수 있다. 한 측면에서, 종양용해 백시니아 바이러스의 게놈은 vacwr094 유전자 또는 그의 부분의 결실을 포함한다. 한 측면에서, 패키징 구축물은 vacwr094 유전자 또는 그의 부분의 위치로 삽입될 수 있다. 한 측면에서, 패키징 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr093 또는 그의 부분과 vacwr095 또는 그의 부분 사이에 삽입될 수 있다. 한 측면에서, 종양용해 백시니아 바이러스의 게놈은 vacwr094 유전자 또는 그의 부분의 결실을 포함한다. 한 측면에서, 패키징 구축물은 vacwr094 유전자 또는 그의 부분의 위치로 삽입될 수 있다.

[0123] 한 측면에서, 패키징 요소는 서열식별번호: 4에 대해 적어도 약 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% 또는 100% 동일성을 갖는 서열을 포함한다. 한 측면에서, 패키징 요소는 서열식별번호: 5에 대해 적어도 약 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% 또는 100% 동일성을 갖는 gag/pol 서열을 포함한다. 한 측면에서, 렌티바이러스 구조 단백질을 코딩하는 핵산은 서열식별번호: 4에 제시된 뉴클레오타이드 서열, 또는 서열식별번호: 5에 제시된 서열에 대해 적어도 약 70% 내지 적어도 약 99% 동일한 뉴클레오타이드 서열을 포함한다.

[0124] 전달 구축물

[0125] 한 측면에서, 외인성 서열은 전달 구축물 서열일 수 있다. 한 측면에서, 백시니아 바이러스 후기 유전자는 단일 유전자-함유 mRNA로 전사되지 않을 수 있지만, 대신 종결 전에 여러 유전자만큼 떨어진 프로모터를 사용하여 개시되었을 수 있는 대형 10-20 kb mRNA로 전사될 수 있다. 한 측면에서, 파괴된 백시니아 바이러스 게놈은 VV 게놈의 먼 3' 말단 근처에 후기 유전자 전사체가 없는 영역인 vacwr205와 vacwr206 사이에 전달 구축물을 포함할 수 있다. 일부 경우에, 전달 구축물은 백시니아 바이러스 게놈의 bp 183645에 삽입된다. 한 측면에서, 전달 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr205 또는 그의 부분과 vacwr206 또는 그의 부분 사이에 삽입될 수 있다.

- [0126] 한 측면에서, 본원에 제공된 백시니아 바이러스는 적어도 1개의 프로모터를 포함할 수 있다. 한 측면에서, 본원에 제공된 백시니아 바이러스는 약 1개의 프로모터 내지 약 3개의 프로모터를 포함할 수 있다. 한 측면에서, 본원에 제공된 백시니아 바이러스는 약 1, 2, 3, 4, 5, 6, 7, 8, 9, 또는 약 10개 이하의 프로모터를 포함할 수 있다. 한 측면에서, 프로모터는 초기 프로모터일 수 있다. 한 측면에서, 프로모터는 초기/후기 프로모터 또는 후기 프로모터일 수 있다. 일부 경우에, 전달 구축물은 자기-절단 RNA 리보자임, 예컨대 델타 간염 바이러스 리보자임 또는 망치머리형 리보자임을 코딩하는 유전자를 추가로 포함할 수 있다. 임의의 특정 이론에 얽매이지 않지만, 자기-절단 RNA 서열이 전사될 때, 이들은 전사 동안 신속하게 그 자체를 절단할 수 있음이 고려된다. 따라서, 상기 시스템은 RNA를 종결시키기 위해 조기 발현에 의존할 필요가 없을 수 있는데, 이는 이들이 올바른 지점에서 그 자신을 신속하게 절단할 가능성이 있기 때문이다. 따라서, 후기 프로모터 (예를 들어, 백시니아 바이러스 후기 프로모터)를 사용하는 것이 유리할 수 있는데, 이는 이제 모든 레트로바이러스 (예를 들어, 렌티바이러스) 성분이 후기 프로모터, 예컨대 VV 후기 프로모터로 발현될 수 있으며, 이는 더 높은 규모의 발현을 갖고, 현저하게 더 많은 레트로바이러스 (예를 들어, 렌티바이러스)를 생산할 수 있기 때문이다. 자기-절단 리보자임을 코딩하는 유전자는 일부 경우에 전달 구축물의 종결 서열 (예를 들어, 도 4의 U5NU)의 3'에 위치할 수 있다.
- [0127] 한 측면에서, 전달 구축물은 종양용해 백시니아 바이러스의 유전자 vacwr205 또는 그의 부분과 vacwr206 또는 그의 부분 사이에 삽입될 수 있다. 한 측면에서, 전달 요소는 서열식별번호: 6에 대해 적어도 약 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% 또는 100% 동일성을 갖는 서열을 포함한다.
- [0128] 렌티바이러스
- [0129] 한 측면에서, 그의 계능으로부터 비-복제 렌티바이러스 또는 그의 부분을 생산하는 종양용해 바이러스, 예컨대 백시니아 바이러스가 본원에 제공될 수 있다. 일부 실시양태에서, 비-복제 렌티바이러스는 비-렌티바이러스 단백질 또는 그의 기능적 단편을 코딩하는 트랜스진을 포함한다. 한 측면에서, 비-복제 렌티바이러스는 포유동물 세포의 표적 집단에서 분열 및 비-분열 세포 둘 다를 감염시키고 형질도입할 수 있다. 한 측면에서, 포유동물 세포는 인간일 수 있다.
- [0130] 한 측면에서, 제2 세대 렌티바이러스가 본원에 제공될 수 있다. 제2 세대 렌티바이러스는 패키징을 위해 tat 요소를 이용할 수 있는 전달 플라스미드를 포함할 수 있다. 한 측면에서, 제2 세대 렌티바이러스는 단일 플라스미드 내에 패키징 요소, 예를 들어: Gag, pol, rev, 및 tat를 포함할 수 있다. 한 측면에서, 제2 세대 렌티바이러스는 VSV-G를 코딩할 수 있는 env 요소를 포함할 수 있다. 제2 세대 렌티바이러스는 3-플라스미드 시스템일 수 있다. 한 측면에서, 제2 세대 렌티바이러스는 야생형 LTR을 이용할 수 있다. 제2 세대 렌티바이러스는 복제 부적격일 수 있고, 다양한 HIV 유전자를 코딩하는 3개의 플라스미드를 이용할 수 있다.
- [0131] 한 측면에서, 제3 세대 렌티바이러스가 본원에 제공될 수 있다. 제3 세대 렌티바이러스는 전달 요소를 패키징하기 위해 제2 세대 또는 제3 세대 패키징 시스템을 이용할 수 있다. 한 측면에서, 제3 세대 렌티바이러스는 패키징을 위해 최대 2개의 플라스미드, 예를 들어 gag 및 pol을 코딩하는 제1 플라스미드 및 rev를 코딩하는 제2 플라스미드를 이용한다. 한 측면에서, 제3 세대 렌티바이러스는 VSV-G를 코딩할 수 있는 env 요소를 포함할 수 있다. 한 측면에서, 제3 세대 렌티바이러스는 4개 이하의 플라스미드를 사용하고, tat 요소의 사용을 제거할 수 있다. 한 측면에서, 제3 세대 렌티바이러스는 제2 세대 렌티바이러스보다 안전할 수 있다. 제3 세대 렌티바이러스는 하이브리드 LTR 바이러스 프로모터를 포함할 수 있고, 예를 들어 5'LTR은 결실되거나 부분적으로 결실될 수 있고, 외인성 프로모터, 예를 들어 백시니아 바이러스, CMV 또는 RSV 프로모터에 융합될 수 있다.
- [0132] 일부 경우에, 렌티바이러스 또는 그의 부분이 본원에 제공될 수 있다. 일부 경우에, 렌티바이러스는 HIV-1 바이러스로부터 유래될 수 있다. 일부 측면에서, 렌티바이러스는 비-HIV-1 바이러스, 예를 들어: HIV-2, 원숭이 면역결핍 바이러스, 고양이 면역결핍 바이러스, 소 면역결핍 바이러스, 또는 염소 관절염-뇌염 바이러스, 말 감염성 빈혈 바이러스 (EIAV), 및 그의 임의의 조합으로부터 유래될 수 있다.
- [0133] 일부 경우에, HIV-1 바이러스로부터의 렌티바이러스가 본원에 제공될 수 있다. 일부 측면에서, HIV-1 바이러스의 상이한 성분을 코딩하는 다중 플라스미드는 다중 플라스미드 상에 전달될 수 있다. 렌티바이러스 벡터 시스템은 렌티바이러스의 부분을 포함하는 적어도 2개의 플라스미드를 포함할 수 있다. 일부 측면에서, 적어도 2, 3, 4, 5, 6, 7, 또는 최대 약 8개의 플라스미드가 렌티바이러스의 부분을 포함할 수 있다. 일부 측면에서, LV 벡터는 3-플라스미드 시스템일 수 있다. 일부 경우에, 3-플라스미드 시스템은 gag-pol 및 env 기능을 코딩하는 2개의 헬퍼 플라스미드 뿐만 아니라 TV 플라스미드를 포함한다. 일부 측면에서, LV 벡터는 4-플라스미드 시스템일 수 있다. 4 플라스미드 LV 시스템은 HIV-1의 보조 유전자 (예를 들어: vif, vpr, vpu, 및 nef)를 포함할

수 있고, 단지 제1 세대의 LV에만 존재할 수 있다. 일부 측면에서, 이들은 필요하지 않을 수 있기 때문에 제거되었다. 유사하게, 제2 세대 LV에 존재하는 조절 tat 유전자는, TV에서 5' 긴 말단 반복부 (LTR)의 U3 프로모터가 구성적으로 활성인 프로모터 서열에 의해 대체되었는 바 그의 트랜스액팅 기능이 불필요하기 때문에 일부 경우에 제거되었다. 일부 측면에서, 백시니아 바이러스는 외래 바이러스로부터의 유전자, 예컨대 HIV-1 rev 유전자가 부재할 수 있다. 일부 측면에서, 본원에 제공된 벡터는 하이브리드 5' LTR 영역을 함유할 수 있다. 하이브리드 5' LTR 영역은 백시니아 바이러스로부터의 적어도 하나의 성분 및 HIV-1로부터의 적어도 하나의 성분을 함유할 수 있다. 일부 측면에서, HIV-1로부터의 성분은 5' LTR이다. 일부 측면에서, HIV-1로부터의 성분은 3' LTR이다. 하이브리드 구축물은 tat가 부재할 수 있다. 일부 측면에서, 하이브리드 구축물은 tat 대신에 백시니아 바이러스 전사 인자를 이용할 수 있다.

[0134] 일부 실시양태에서, 구성적으로 활성인 프로모터 서열은 시토메갈로바이러스 (프로모터) 또는 라우스 육종 바이러스 (프로모터) 중 어느 하나일 수 있다. 일부 경우에, 임의적인 인핸서 또는 유도성/억제성 프로모터 서열, 예컨대 7tet0가 포함될 수 있다 (pRRL (키메라 라우스 육종 바이러스 (RSV)-HIV 5' LTR을 함유하는 렌티바이러스 전달 벡터 구축물) 설계 또는 pCCL 설계 ((CMV)-HIV 5' LTR)). 이들 변형은 HIV-1 및 env로부터 유래된 gag-pol (구조 단백질 및 바이러스 효소를 코딩함) 및 rev (전사후 조절자를 코딩함)의 사용에 기초한 헬퍼 기능을 갖는 LV 벡터 시스템을 유발할 수 있다. 일부 측면에서, 본원에 제공된 벡터는 rev가 부재한다. 일부 측면에서, LV 벡터는 상이한 이중 외피 당단백질로 유사형화될 수 있다. 일부 측면에서, 수포성 구내염 바이러스 (VSV-g) 외피의 당단백질은 하류 프로세싱 동안의 개선된 안정성 뿐만 아니라 그의 큰 형질도입 스펙트럼으로 인해 이용될 수 있다. 일부 측면에서, TV 플라스미드는 표적 세포로 전달된 유전 물질이고, 캡시드화, 역전사 및 통합에 필요한 시스-작용 요소가 플랭킹된 트랜스진 발현 카세트를 함유하는 LV 백본을 포함할 수 있다. 일부 측면에서, 형질감염된 세포는 감염 후에 TV 플라스미드의 적어도 일부를 포함한다. 일부 측면에서, 자기-불활성화 (SIN)-LV 벡터가 본원에 제공될 수 있다. SIN-LV 벡터는 2'LTR의 U3 요소에서 결실을 포함한다. 일부 측면에서, SIN-LV 벡터는 표적 세포로 전달되고 나면 바이러스 LTR의 전사 능력을 상실하고; 이는 복제 적격 재조합체의 출현 위험을 최소화시킬 수 있고, 프로모터 간섭과 연관된 문제를 피할 수 있다. 일부 측면에서, tat가 시스템으로부터 제거된 제3 세대 플라스미드 시스템이 본원에 제공될 수 있다. 일부 측면에서, 제3 세대 벡터는 이중 프로모터에 융합된 키메라 5' LTR을 사용함으로써 HIV-1 단백질 TAT의 활성을 대체할 수 있다.

[0135] 일부 경우에, 백시니아 바이러스 초기 유전자 전사의 종결은, 백시니아 바이러스-특이적 인자를 유인하여 전사를 중단시키고 폴리(A) 꼬리를 생성하여 바이러스 mRNA를 보호하기 위해 종결 서열 UUUUUNU (U5NU) (서열식별번호: 7)를 이용할 수 있다. 한 측면에서, 본원에 제공된 벡터는 구축물의 목적하는 말단 영역에 인접한 ATTTTAT (서열식별번호: 8) 서열을 포함할 수 있다. 일부 실시양태에서, 종결 서열은 서열식별번호: 7에 제시된 서열에 대해 약 60%, 70%, 80%, 90%, 95%, 또는 최대 약 100%의 퍼센트 동일성을 갖는 뉴클레오타이드 서열을 포함한다.

[0136] 특정 실시양태에서, 본원에 제공된 레트로바이러스 벡터는 복제 결손일 수 있으며, 즉 이들은 표적 세포에서 자율적으로 복제할 수 없다. 일부 측면에서, 복제 결손 바이러스는 바이러스 게놈을 표적 세포 인식하고 캡시드화하는데 필요한 그의 게놈의 서열만을 보유하도록 하는 최소 바이러스이다. 일부 경우에, 복제 결손 바이러스는 세포 내로의 도입 후에 감염성이 아니다. 복제 결손 바이러스 벡터의 사용은 벡터가 다른 세포를 감염시킬 수 있다는 우려 없이 특정 국소 영역 내의 세포에 대한 투여를 허용한다. 따라서, 특정 조직은 특이적으로 표적화될 수 있다.

[0137] 한 측면에서, 생산자 종양용해 바이러스로부터의 발현을 위한 본원에 제공된 렌티바이러스 구축물은 프로모터를 포함할 수 있다. 한 측면에서, 렌티바이러스 요소의 발현은 초기에 발현될 수 있다. 한 측면에서, 렌티바이러스 요소의 발현은 강건할 수 있다. 예를 들어, 백시니아 바이러스는 감염의 초기 단계 동안, 예를 들어 감염 후 2시간 내에 폴리(A) 꼬리를 갖는 짧은 단일 유전자 mRNA를 생성할 수 있다. 상기 기간 후, 감염의 중간 및 후기 단계로부터의 바이러스 mRNA는 특이적으로 종결되거나 폴리아데닐화되지 않을 수 있다. 기능적 렌티바이러스 전달 RNA를 형성하기 위해, 전사는 렌티바이러스 긴 말단 반복부 (LTR)에 인접한 특정 부위에서 개시 및 종결될 수 있고, 따라서 렌티바이러스 요소는 백시니아 바이러스 감염 후 처음 2시간 내에 강건하게 발현될 수 있다. 따라서, 일부 경우에, 본원에 제공된 벡터는 각각의 요소에 대한 강한 초기 프로모터를 가질 수 있고, 강한 초기 프로모터를 전달 구축물의 5' LTR에 융합시킬 수 있다. 한 측면에서, 선행하는 강한 초기 프로모터를 갖는 약 1-10개의 바이러스 요소가 존재한다. 한 측면에서, 선행하는 강한 초기 프로모터를 갖는 약 1-5개의 바이러스 요소가 존재한다. 한 측면에서, 선행하는 강한 초기 프로모터를 갖는 약 1-3개의 바이러스 요소가 존재한다. 일부 경우에, 렌티바이러스 구축물의 성분은 초기/후기 또는 후기 바이러스 프로모터의 제어 하에

있을 수 있다. 예를 들어, 패키징 구축물, 전달 구축물, 및 외피 구축물은 각각 독립적으로 초기/후기 바이러스 프로모터 또는 후기 바이러스 프로모터를 포함한다.

[0138] 프로모터는 RNA 폴리머라제 및 전사 인자의 결합을 제어하는 핵산의 서열이고, 유전자가 세포에서 발현될 수 있는 유전자 전사의 효율, 및/또는 유전자가 발현될 수 있는 세포 유형에 주요 효과를 가질 수 있다. 프로모터의 비제한적 예는 백시니아 바이러스 프로모터, 시토크로마틴 바이러스 (CMV) 프로모터, 신장 인자 1 알파 (EF1 α) 프로모터, 원숭이 공포화 바이러스 (SV40) 프로모터, 포스포글리세레이트 키나제 (PGK1) 프로모터, 유비퀴틴 C (Ubc) 프로모터, 인간 베타 액틴 프로모터, CAG 프로모터, 테트라시클린 반응 요소 (TRE) 프로모터, UAS 프로모터, 액틴 5c (Ac5) 프로모터, 다면체 프로모터, Ca²⁺/칼모듈린-의존성 단백질 키나제 II (CaMKII α) 프로모터, GAL1 프로모터, GAL 10 프로모터, TEF1 프로모터, 글리세르알데히드 3-포스페이트 탈수소효소 (GDS) 프로모터, ADH1 프로모터, CaMV35S 프로모터, Ubi 프로모터, 인간 폴리머라제 III RNA(H1) 프로모터, U6 프로모터 또는 그의 조합을 포함한다.

[0139] 일부 실시양태에서, 본 개시내용은 암을 나타내거나 암이 발생할 위험이 있는 대상체에서 항종양 면역 반응을 도출하는 방법을 제공한다. 일부 측면에서, 암은 전이성일 수 있다. 한 측면에서, 종양용해 바이러스 (예를 들어, HSV, 백시니아 바이러스 또는 아데노바이러스), 종양용해 바이러스로부터 생산된 레트로바이러스, 또는 둘 다는 치료 단백질 또는 진단 단백질을 발현할 수 있다. 한 측면에서, 치료 단백질은 PD-1의 활성을 길항하는 PD-1 결합제, 예컨대 단일 체 항-PD-1 항체일 수 있다. 다른 실시양태에서, 치료 단백질은 수용체에 대한 PD-1 리간드의 결합을 길항하는 작용제, 예를 들어 항-PD-L1 및/또는 PD-L2 항체, PD-L1 및/또는 PD-L2 디코이, 또는 가용성 PD-1 수용체이다. 한 측면에서, PD-1 차단은 또한 T-세포 (CTL 및 헬퍼) 및 B-세포의 불활성화를 차단하여 증가된 암 사멸을 유도함으로써 항종양 면역 반응을 자극할 수 있다.

[0140] 패키징 세포주

[0141] 한 측면에서, 패키징 세포주가 본원에 제공될 수 있다. 복제 결손 바이러스의 생산은 패키징 세포가 감염성 입자를 생성하는데 필요한 모든 바이러스 단백질, 뿐만 아니라 전달을 위해 그 내에 패키징될 관심 핵산 서열, 예를 들어 바이러스 서열을 함께 발현하는 다중 플라스미드 (예를 들어, 약 2, 3, 4, 5개 또는 그 초과 플라스미드로부터)로 공동형질감염될 수 있는 트랜스-상보를 통해 달성될 수 있다. 많은 렌티바이러스 벡터 시스템은 2개의 헬퍼 플라스미드 (제2 세대)의 전달 플라스미드로의 형질도입을 기반으로 하지만, 일부 보다 새로운 시스템 (제3 세대)은 전달 플라스미드와 조합되고 패키징 세포주를 형질감염시키는데 이용되는 3개의 플라스미드 상에 패키징 및 외피 구축물을 갖는다. 한 측면에서, 레트로바이러스와 함께 사용하기 위한 패키징 세포주가 본원에 제공될 수 있다. 한 측면에서, 제1 세대 레트로바이러스 패키징 세포주가 이용될 수 있다. 제1 세대 레트로바이러스 패키징 세포주는 마우스 3T3 세포로부터 유래될 수 있다. 한 측면에서, 제2 세대 레트로바이러스 벡터 패키징 세포주가 이용될 수 있다. 제2 세대 레트로바이러스 벡터 패키징 세포주의 비제한적 예는 인간 세포, 예컨대 HEK293 (배아 신장), TE671 (황문근육종) 및 HT1080 (섬유육종)을 포함한다. 제3 세대 패키징 세포주는 제2 세대 패키징 플라스미드 및 또한 전달 벡터에 존재하는 불필요한 바이러스 서열이 없을 수 있고, 이를 결실시켜 안전성을 개선하였다.

[0142] 비-렌티바이러스 단백질

[0143] 치료 단백질 또는 그의 부분

[0144] 일부 실시양태에서, 비-렌티바이러스 단백질은 치료 단백질 또는 그의 부분일 수 있다. 한 측면에서, 치료 단백질 또는 그의 부분은 면역 체크포인트 조절제, 항체 또는 그의 부분, Fc 융합 단백질, 항응고제, 혈액 인자, 골 형태발생 단백질, 면역억제제, 면역자극제, 효소, 성장 인자, 호르몬, 인터페론, 인터류킨, 혈전용해제, 항혈관신생제, 화학요법제, 항생제, 항진균제, 항바이러스제, 및 그의 임의의 조합 중 어느 하나일 수 있다.

[0145] 한 측면에서, 치료 단백질 또는 그의 부분은 면역 체크포인트 조절제일 수 있다. 한 측면에서, 면역 체크포인트 조절제는 면역 체크포인트를 억제할 수 있다. 한 측면에서, 면역 체크포인트 조절제는 면역 체크포인트를 활성화시킬 수 있다. 면역 체크포인트 억제제는 일부 유형의 면역계 세포, 예컨대 T 세포, 및 일부 암 세포에 의해 제조된 단백질을 차단하는 약물일 수 있다. 이들 면역 체크포인트 단백질은 체크에서 면역 반응을 억제하는 것을 돕고, T 세포가 암 세포를 사멸시키는 것을 방지할 수 있다. 이들 단백질이 억제되면, 면역계 상의 "브레이크"가 방출되고, T 세포는 암 세포를 사멸시킬 수 있다. T 세포 또는 암 세포 상에서 발견되는 체크포인트 단백질의 예는 PD-1/PD-L1 및 CTLA-4/B7-1/B7-2를 포함하나 이에 제한되지는 않는다. 한 측면에서, 면역 체크포인트 억제제는 본원에 제공된 바이러스에 의해 전달될 수 있다.

[0146] 면역 체크포인트 조정제 및/또는 임의의 치료 단백질에 의해 표적화될 수 있는 다양한 면역 체크포인트가 표 2에 존재한다.

[0147] 표 2: 면역 체크포인트 조정제에 의해 표적화된 면역 체크포인트를 코딩하는 유전자

유전자 기호	약어	명칭	NCBI 번호 (GRCh38.p2) *AC010327.8 ** GRCh38.p7	게놈 내 위치
ADORA 2A	A2aR; RDC8; ADORA2	아데노신 A2a 수용체	135	22q11.23
CD276	B7H3; B7-H3; B7RP- 2; 4Ig-B7-H3	CD276 분자	80381	15q23-q24
VTCN1	B7X; B7H4; B7S1; B7-H4; B7h.5; VCTN1; PRO1291	T 세포 활성화 억제제 1을 함유한 V-세트 도메인	79679	1p13.1
BTLA	BTLA1; CD272	B 및 T 림프구 연관	151888	3q13.2
CTLA4	GSE; GRD4; ALPS5; CD152; CTLA-4; IDDM12; CELIAC3	세포독성 T- 림프구- 연관 단백질 4	1493	2q33
IDO1	IDO; INDO; IDO-1	인돌아민 2,3- 디옥시게나제 1	3620	8p12-p11
KIR3DL1	KIR; NKB1; NKAT3; NKB1B; NKAT-3; CD158E1; KIR3DL2; KIR3DL1/S1	킬러 세포 이뮤노글로불린- 유사 수용체, 3개 도메인, 긴 세포질 꼬리, 1	3811	19q13.4
LAG3	LAG3; CD223	림프구- 활성화 유전자 3	3902	12p13.32
PDCD1	PD1; PD-1; CD279; SLEB2; hPD-1; hPD- 1; hSLE1	프로그래밍된 세포 사멸 1	5133	2q37.3
HAVCR2	TIM3; CD366; KIM- 3; TIMD3; Tim-3; TIMD-3; HAVcr-2	A형 간염 바이러스 세포 수용체 2	84868	5q33.3
VISTA	C10orf54, ESC-1의 분화 (Dies1); 혈소판 수용체 Gi24 전구체; PD1 동족체 (PD1H) B7H5; GI24; B7-H5; SISP1; PP2135	T-세포 활성화의 V-도메인 이뮤노글로불린 억제자	64115	10q22.1
CD244	2B4; 2B4; NAIL; Nmrk; NKR2B4; SLAMF4	CD244 분자, 자연 킬러 세포 수용체 2B4	51744	1q23.3

[0148]

CISH	CIS; G18; SOCS; CIS-1; BACTS2	시토카인 유도성 SH2-함유 단백질	1154	3p21.3
HPRT1	HPRT; HGPRT	하이포크산틴 포스포리보실트랜스 퍼라제 1	3251	Xq26.1
AAV*S1	AAV	아데노-연관 바이러스 통합 부위 1	14	19q13
CCR5	CCR5; CCR-5; CD195; CKR-5; CCCKR5; CMKBR5; IDDM22; CC-CKR-5	케모카인 (C-C 모티프) 수용체 5 (유전자/위유전자)	1234	3p21.31
CD160	NK1; BY55; NK28	CD160 분자	11126	1q21.1
TIGIT	VSIG9; VSTM3; WUCAM	Ig 및 ITIM 도메인을 갖는 T- 세포 면역수용체	201633	3q13.31
CD96	TACTILE	CD96 분자	10225	3q13.13- q13.2
CRTAM	CD355	세포독성 및 조절 T-세포분자	56253	11q24.1
LAIR1	CD305; LAIR-1	백혈구 연관 이류노글로블린 유사 수용체 1	3903	19q13.4
SIGLEC 7	p75; QA79; AIRM1; CD328; CDw328; D- siglec; SIGLEC-7; SIGLECP2; SIGLEC19P; p75/AIRM1	시알산 결합Ig 유사 력틴 7	27036	19q13.3
SIGLEC 9	CD329; CDw329; FOAP-9; siglec-9; OBBP-LIKE	시알산 결합Ig 유사 력틴 9	27180	19q13.41
TNFRSF 10B	DR5; CD262; KILLER; TRICK2; TRICKB; ZTNFR9; TRAILR2; TRICK2A; TRICK2B; TRAIL- R2; KILLER/DR5	종양 괴사 인자 수용체 슈퍼패밀리 구성원 10b	8795	8p22-p21
TNFRSF 10A	DR4; APO2; CD261; TRAILR1; TRAILR-1	종양 괴사 인자 수용체 슈퍼패밀리 구성원 10a	8797	8p21
CASP8	CAP4; MACH; MCH5; FLICE; ALPS2B; Casp-8	카스파제 8	841	2q33-q34
CASP10	MCH4; ALPS2; FLICE2	카스파제 10	843	2q33-q34

[0149]

CASP3	CPP32; SCA-1; CPP32B	카스파제 3	836	4q34
CASP6	MCH2	카스파제 6	839	4q25
CASP7	MCH3; CMH-1; LICE2; CASP-7; ICE-LAP3	카스파제 7	840	10q25
FADD	GIG3; MORT1	사멸 도메인을 통해 연결된 Fas	8772	11q13.3
FAS	APT1; CD95; FAS1; APO-1; FASTM; ALPS1A; TNFRSF6	Fas 세포 표면 사멸 수용체	355	10q24.1
TGFBRII	AAT3; FAA3; LDS2; MFS2; RIIC; LDS1B; LDS2B; TAAD2; TGFR-2; TGFbeta-RII	형질전환 성장 인자 베타 수용체 II	7048	3p22
TGFR1	AAT5; ALK5; ESS1; LDS1; MSSE; SKR4; ALK-5; LDS1A; LDS2A; TGFR-1; ACVRLK4; tbetaR-I	형질전환 성장 인자 베타 수용체 I	7046	9q22
SMAD2	JV18; MADH2; MADR2; JV18-1; hMAD-2; hSMAD2	SMAD 패밀리 구성원 2	4087	18q21.1
SMAD3	LDS3; LDS1C; MADH3; JV15-2; HSPC193; HsT17436	SMAD 패밀리 구성원 3	4088	15q22.33
SMAD4	JIP; DPC4; MADH4; MYHRS	SMAD 패밀리 구성원 4	4089	18q21.1
SKI	SGS; SKV	SKI 원종양유전자	6497	1p36.33
SKIL	SNO; SnoA; SnoI; SnoN	SKI-유사 원종양유전자	6498	3q26
TGIF1	HPE4; TGIF	TGFB 유도 인자 호메오박스 1	7050	18p11.3
IL10RA	CD210; IL10R; CD210a; CDW210A; HIL-10R; IL-10R1	인터류킨 10 수용체 서브유닛 알파	3587	11q23
IL10RB	CRFB4; CRF2-4; D21S58; D21S66; CDW210B; IL-10R2	인터류킨 10 수용체 서브유닛 베타	3588	21q22.11
HMOX2	HO-2	헴 옥시게나제 2	3163	16p13.3
IL6R	IL6Q; gp80; CD126; IL6RA; IL6RQ; IL-6RA; IL-6R-1	인터류킨 6 수용체	3570	1q21
IL6ST	CD130; GP130; CDW130; IL-6RB	인터류킨 6 신호 전달자	3572	5q11.2
CSK	CSK	c-src 티로신 키나제	1445	15q24.1
PAG1	CBP; PAG	클리코스펩고지질 마이크로도메인 1을 갖는 인단백질 막 앵커	55824	8q21.13

[0150]

SIT1	SIT1	신호전달 억제 조절 막횡단 어댑터 1	27240	9p13-p12
FOXP3	JM2; AIID; IPEX; PIDX; XPID;DIETER	포크헤드 박스 P3	50943	Xp11.23
PRDM1	BLIMP1; PRDI-BF1	PR 도메인 1	639	6q21
BATF	SFA2; B-ATF; BATF1; SFA-2	염기성 류신 지퍼 전사 인자, ATF-유사	10538	14q24.3
GUCY1 A2	GC-SA2; GUC1A2	구아닐레이트 시클라제 1, 가용성, 알파 2	2977	11q21-q22
GUCY1 A3	GUCA3; MYMY6; GC-SA3; GUC1A3; GUCA3; GUCY1A1	구아닐레이트 시클라제 1, 가용성, 알파 3	2982	4q32.1
GUCY1 B2	GUCY1B2	구아닐레이트 시클라제 1, 가용성, 베타 2 (위유전자)	2974	13q14.3
GUCY1 B3	GUCB3; GC-SB3; GUC1B3; GUCSB3; GUCY1B1; GC-S- 베타-1	구아닐레이트 시클라제 1, 가용성, 베타 3	2983	4q31.3-q33
TRA	IMD7; TCRA; TCRD; TRA알파; TRAC	T-세포 수용체 알파 유전자좌	6955	14q11.2
TRB	TCRB; TRB베타	T 세포 수용체 베타 유전자좌	6957	7q34
EGLN1	HPH2; PHD2; SM20; ECYT3; HALAH; HPH-2; HIFPH2; ZMYND6; C1orf12; HIF-PH2	egl-9 패밀리 저산소증-유도성 인자 1	54583	1q42.1
EGLN2	EIT6; PHD1; HPH-1; HPH-3; HIFPH1; HIF- PH1	egl-9 패밀리 저산소증-유도성 인자 2	112398	19q13.2
EGLN3	PHD3; HIFPH3; HIFP4H3	egl-9 패밀리 저산소증-유도성 인자 3	112399	14q13.1
PPP1R12 C**	p84; p85; LENG3; MBS85	단백질 포스포타제 1 조절 서브유닛 12C	54776	19q13.42

[0151]

[0152]

일부 경우에, 치료 단백질은 인간화 항-CD20 모노클로날 항체 (예를 들어, 가지바(Gazyva)), VEGFR Fc-융합체 (예를 들어, 아일리아(Eylea)), CTLA-4 Fc-융합체 (예를 들어, 뉴로직스(Nulojix)), 글루카곤-유사 펩티드-1 수용체 효능제 Fc-융합체 (예를 들어, 트룰리티(Trulicity)), VEGFR Fc-융합체 (예를 들어, 잘트랩(Zaltrap)), 재조합 인자 IX Fc 융합체 (예를 들어, 알프롤릭스(Alprolix)), 재조합 인자 VIII Fc-융합체 (예를 들어, 엘록테이트(Eloctate)), GLP-1 수용체 효능제-알부민 융합체 (예를 들어, 탄제움(Tanzeum)), 재조합 인자 IX 알부민 융합체 (예를 들어, 이델비온(Idelvion)), PEG화 IFN β -1a (예를 들어, 플레그리디(Plegridy)), PEG화 재조합 인자 VIII (예를 들어, 아디노베이트(Adynovate)), 엠탄신에 접합된 인간화 항-HER2/neu (예를 들어, 카드실라(Kadcyla)), 마우스/인간 키메라 항-CD30 (예를 들어, 애드세트리스(Adcetris)), 항-인간 표피 성장 인자 수용체 2 (HER2) (예를 들어, 페르제타(Perjeta)), 항-IL-6 수용체 (악템라(Actemra)), 항-CD20 (예를 들어, 오비누투주맙(obinutuzumab); 가지바), 항-인테그린 α 4 β 7 (LPAM-1) (예를 들어, 엔티비오(Entyvio)), 항-PD-1 (예를 들어, 키트루다(Keytruda)), 항-다비가트란 (예를 들어, 프락스빈드(Praxbind)), 항-IL-5 (예를 들어, 누칼라(Nucala)), 항-CD319 (SLAMF7) (예를 들어, 엠플리시티(Empliciti)), 항-IL-17a (예를 들어, 탈츠(Taltz)), 항-IL-5 (예를 들어, 신케어(Cinqair)), 항-PD-L1 (예를 들어, 테센트릭(Tecentriq)), 항-CD25 (예를 들어, 진브리티(Zinbryta)), 항-CD30 (예를 들어, 애드세트리스(Adcetris)), 항-IL-6 (예를 들어, 실반트(Sylvant)), 항-GD2 (예를 들어, 유니톡신(Unituxin)), 항-바실루스 안트라시스(*Bacillus anthracis*) (예를 들어, 안탐(Anthim)), 항-TNF α (예를 들어, 인플렉트라(Inflectra)), 인간 항-B-세포 활성화 인자 (BAFF) (예를 들어, 벨리무맙(belimumab)), 인간 항-CTLA-4 (예를 들어, 이필리무맙(ipilimumab)), CTLA-4 Fc-융합체 (예를 들어, 벨라타셉트(belatacept)), 인간화 항-인간 표피 성장 인자 수용체 2 (HER2) (예를 들어, 페르투주맙), VEGFR Fc 융합체 (예를 들어, 지브-아필베르셉트(ziv-aflibercept)),

G-CSF (예를 들어, tbo-필그라스티움(filgrastim)), 인간 항-VEGFR2 (KDR) (예를 들어, 라무시루맙(ramucirumab)), 마우스/인간 키메라 항-IL-6 (예를 들어, 실투시맙), 램브롤리주맙, 마우스 이중특이적 항-CD19/항-CD3 (예를 들어, 블린투모맙(blintumomab)), 니볼루맙, 부갑상선 호르몬, 마우스/인간 키메라 항-GD2 (예를 들어, 디누특시맙), 인간 항-CD38 (예를 들어, 다라투무맙), 인간 항-표피 성장 인자 수용체 (EGFR) (예를 들어, 네시투무맙), 인간화 항-CD319 (SLAMF7) (예를 들어, 엘로투주맙), 아테졸리주맙일 수 있다.

[0153] 한 측면에서, 치료 단백질은 시토카인일 수 있다. 시토카인은 염증유발 시토카인일 수 있다. 한 측면에서, 시토카인은 IL-2, IL-7, IL-12, IL-15, IL-21, 및 그의 조합일 수 있다. 추가로, 염증유발 시토카인은 또한 본원에 제공된 바이러스와 함께 도입될 수 있다. 염증유발 시토카인의 비제한적 예는 인터류킨 6 (IL-6), 인터페론 알파 (IFN α), 인터페론 베타 (IFN β), C-C 모티프 리간드 4 (CCL4), C-C 모티프 리간드 5 (CCL5), C-X-C 모티프 리간드 10 (CXCL10), 인터류킨 1 베타 (IL-1 β), IL-18 및 IL-33을 포함한다.

[0154] 한 측면에서, 치료 단백질은 성장 인자일 수 있다. 일부 측면에서, 성장 인자는 인터류킨일 수 있다. 인터류킨의 비제한적 예는 인터류킨-2 (IL-2), 인슐린, IFN- γ , IL-4, IL-7, GM-CSF, IL-10, IL-21, IL-15, TGF 베타 및 TNF 알파 또는 세포, 예컨대 면역 세포의 성장을 위한 임의의 다른 첨가제를 포함한다.

[0155] 한 측면에서, 치료 단백질은 화학요법제일 수 있다. 화학요법제 또는 화합물은 암의 치료에 유용한 화학적 화합물일 수 있다. 개시된 바이러스와 조합하여 사용될 수 있는 화학요법 암 작용제는 유사분열 억제제 (빈카 알칼로이드)를 포함하나 이에 제한되지는 않는다. 이들은 빈크리스틴, 빈블라스틴, 빈데신 및 나벨빈(Navelbin)TM (비노렐빈, 5'-노란히드로블라스틴)을 포함한다. 또 다른 경우, 화학요법 암 작용제는 토포이소머라제 I 억제제, 예컨대 캄프토테신 화합물을 포함한다. 본원에 사용된 "캄프토테신 화합물"은 캄프토테신(Camptosar)TM (이리노테칸 HCL), 하이캄틴(Hycamtin)TM (토포테칸 HCL) 및 캄프토테신 및 그의 유사체로부터 유래된 다른 화합물을 포함한다. 본원에 개시된 방법 및 조성물에 사용될 수 있는 화학요법 암 작용제의 또 다른 카테고리는 포도필로톡신 유도체, 예컨대 에토포시드, 테니포시드 및 미토포도지드이다. 본 개시내용은 종양 세포에서 유전 물질을 알킬화하는 알킬화제로 공지된 다른 화학요법 암 작용제를 추가로 포함한다. 이들은 비제한적으로 시스플라틴, 시클로포스파미드, 질소 머스타드, 트리메틸렌 티오포스포르아미드, 카르무스틴, 부술판, 클로람부실, 벨루스틴, 우라실 머스타드, 클로마파진 및 다카르바진을 포함한다. 본 개시내용은 화학요법제로서 항대사물을 포괄한다. 이들 유형의 작용제의 예는 시토신 아라비노시드, 플루오로우라실, 메토포렉세이트, 메르캅토피린, 아자티오프라임 및 프로카르바진을 포함한다.

[0156] 한 측면에서, 치료제는 항생제일 수 있다. 일부 경우에, 항생제는 박테리아 벽 표적화제, 세포 막 표적화제, 박테리아 효소 간섭제, 살박테리아제, 단백질 합성 억제제, 또는 정박테리아제일 수 있다. 박테리아 벽 표적화제는 페니실린 유도체 (페남), 세팔로스포린 (세펄), 모노박탐 및 카르바페넴일 수 있다. β -락탐 항생제는 살균성 또는 정균성이고, 박테리아 세포벽의 펩티도글리칸 층의 합성을 억제함으로써 작용한다. 일부 경우에, 항생제는 단백질 합성 억제제일 수 있다. 단백질 합성 억제제는 박테리아에 의해 세포벽을 만드는데 필요한 효소 트랜스펩티다제의 비가역적 억제제로서 작용하는 암피실린일 수 있다. 이는 이원 분열에서 박테리아 세포벽 합성의 제3 및 최종 단계를 억제하며, 이는 궁극적으로 세포 용해로 이어지고; 따라서, 암피실린은 통상적으로 박테리아용해성이다. 일부 경우에, 살박테리아제는 세팔로스포린 또는 퀴놀론일 수 있다. 다른 경우, 정박테리아제는 트리메토프림, 술파메톡사졸 또는 펜타미딘이다. 항생제의 추가의 예는 비제한적으로 독소루비신, 블레오마이신, 닥티노마이신, 다우노루비신, 미트라마이신, 미토마이신, 미토마이신 C 및 다우노마이신을 포함한다.

[0157] 한 측면에서, 치료제는 또한 항체 또는 그의 부분일 수 있다. 항체는 폴리클로날 항체 또는 모노클로날 항체일 수 있다. 투여될 수 있는 폴리클로날 항체는 항립구 또는 항홍선세포 항원일 수 있다. 모노클로날 항체는 항-IL-2 수용체 항체, 항-CD25 항체, 또는 항-CD3 항체일 수 있다. 항-CD20 항체가 또한 사용될 수 있다. B-세포 제거 요법, 예컨대 CD20과 반응하는 작용제, 예를 들어 리툭산이 또한 면역억제제로서 사용될 수 있다. 예시적인 항암 항체는 다카르바진, 아자티딘, 암사크린, 멜팔란, 이포스파미드 및 미토산트론을 포함하나 이에 제한되지는 않는다.

[0158] 한 측면에서, 치료제는 또한 항진균제일 수 있다. 일부 경우에, 항진균제는 폴리엔, 아졸, 알릴아민 또는 에키노칸딘의 부류로부터의 것일 수 있다. 일부 실시양태에서, 폴리엔 항진균제는 암포테리신 B, 칸디시딘, 필리핀, 하마이신, 나타마이신, 니스타틴, 또는 리모시딘이다. 일부 경우에, 항진균제는 아졸 페닐리로부터의 것일 수 있다. 아졸 항진균제는 라노스테롤 14 α -테메틸라제를 억제할 수 있다. 아졸 항진균제는 이미다졸, 예컨대 비포나졸, 부토코나졸, 클로트리마졸, 에코나졸, 펜티코나졸, 이소코나졸, 케토코나졸, 물리코나졸, 미코나졸, 오모코나졸, 옥시코나졸, 세르타코나졸, 술코아졸, 또는 티오코나졸일 수 있다. 아졸 항진균제는 트리

아졸, 예컨대 알바코나졸, 에피코나졸, 에폭시코나졸, 플루코나졸, 이사부보나졸, 이트라코나졸, 포사코나졸, 프로피코나졸, 라부코나졸, 테르코나졸 또는 보리코나졸일 수 있다. 일부 경우에, 아졸은 티아졸, 예컨대 아바편진일 수 있다. 항진균제는 알릴아민, 예컨대 아모롤핀, 부테나핀, 나프티핀 또는 테르비나핀일 수 있다. 항진균제는 또한 에키노칸딘, 예컨대 아니둘라핀진, 카스포핀진 또는 미카핀진일 수 있다. 항진균제일 수 있는 추가의 작용제는 아우론, 벤조산, 시클로피록스, 플루시토신, 그리세오폴빈, 할로프로진, 톨나프테이트, 운데실렌산, 크리스탈 바이올렛 또는 페루 발삼일 수 있다.

[0159] 제약 조성물

[0160] 제약상 허용되는 바이러스 치료제가 본원에 제공된다. 한 측면에서, 또한 종양용해 바이러스를 포함하는 제약상 허용되는 바이러스 치료제를 구현하는 방법이 본원에 제공된다. 본원에 제공된 조성물 및 방법은 질환, 예컨대 암의 치료에 사용될 수 있다.

[0161] 암은 흑색종, 간세포성 암종, 유방암, 폐암, 복막암, 전립선암, 방광암, 난소암, 백혈병, 림프종, 신암종, 췌장암, 상피 암종, 위암, 결장 암종, 십이지장암, 췌장 선암종, 중피종, 다형성 교모세포종, 성상세포종, 다발성 골수종, 전립선 암종, 간세포성 암종, 담관암종, 췌장 선암종, 두경부 편평 세포 암종, 결장직장암, 장-유형 위선암종, 자궁경부 편평-세포 암종, 골육종, 상피 난소 암종, 급성 림프모구성 림프종, 골수증식성 신생물 및 육종을 포함할 수 있으나 이에 제한되지는 않는다.

[0162] 한 측면에서, 종양용해 바이러스는 암 내에서 치료제를 선택적으로 증폭시킬 수 있다. 한 측면에서, 종양용해 바이러스는 또한 치료 단백질 또는 진단 단백질을 보유하고, 암에 근접하여 단백질 또는 그의 기능적 단편을 발현할 수 있다. 한 측면에서, 치료 단백질 또는 진단 단백질은 내인성 면역 반응을 증진시킬 수 있다. 한 측면에서, 본원에 제공된 치료 단백질과 커플링된 본원에 제공된 종양용해 바이러스 및/또는 레트로바이러스는 치료제와 커플링되지 않은 동등한 바이러스와 비교하여 더 큰 항암 효과를 가질 수 있다. 한 측면에서, 본원에 제공된 치료 단백질과 커플링된 본원에 제공된 종양용해 바이러스 및/또는 레트로바이러스는 치료제와 커플링되지 않은 동등한 바이러스와 비교하여 약 1배, 2배, 3배, 4배, 5배, 6배, 7배, 8배, 9배, 또는 최대 약 10배 더 큰 항암 효과를 가질 수 있다. 한 측면에서, 본원에 제공된 치료 단백질과 커플링된 본원에 제공된 종양용해 바이러스 및/또는 레트로바이러스는 치료제와 커플링되지 않은 동등한 바이러스와 비교하여 암을 약 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 또는 최대 100% 더 감소시킬 수 있다.

[0163] 한 측면에서, 본원에 제공된 핵산, 폴리펩티드, 벡터 및 플라스미드와 접촉된 세포의 독성을 감소시키는 방법이 또한 본원에 제공될 수 있다. 예를 들어, 본원에 제공된 바이러스를 코딩하는 벡터는 폴리시스트론일 수 있고, 이에 의해 다중 요소, 예컨대 바이러스를 단일 벡터 구축물 내에 도입하고, 벡터와 연관된 독성을 감소시킨다. 한 측면에서, 본원에 제공된 종양용해 바이러스 및 본원에 제공된 치료 단백질을 코딩하는 비시스트론 벡터는 2개의 모노시스트론 벡터, 즉 본원에 제공된 종양용해 바이러스를 코딩하는 제1 벡터 및 치료제를 코딩하는 제2 벡터를 도입하는 것과 비교하여 약 1배, 2배, 3배, 4배, 5배, 6배, 7배, 8배, 9배, 또는 최대 약 10배 더 적은 독성을 가질 수 있다. 일부 경우에, 세포 독성은 각각의 요소를 단독으로 이중 벡터 시스템에 도입하는 것과 비교하여 적어도 본원에 제공된 비시스트론 벡터가 사용되는 경우에 약, 적어도 약, 또는 최대 약 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 15%, 17%, 18%, 19%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 82%, 85%, 88%, 90%, 92%, 95%, 97%, 98%, 99% 또는 100% 감소된다.

[0164] 본원에 기재된 바와 같이, 본원에 제공된 바이러스 입자는 복제 결손 바이러스의 적어도 일부를 포함하는 트랜스진을 포함하는 바이러스 벡터를 세포 내로 생체외 또는 생체내 전달하는데 사용될 수 있다. 일부 실시양태에서, 본원에 제공된 바이러스는 pfu (플라크 형성 단위)로서 측정될 수 있다. 일부 경우에, 본 개시내용의 조성물 및 방법의 바이러스 투여량의 pfu는 약 10^8 내지 약 5×10^{10} pfu일 수 있다. 일부 경우에, 본원에 제공된 바이러스의 투여량은 적어도 약 1×10^8 , 2×10^8 , 3×10^8 , 4×10^8 , 5×10^8 , 6×10^8 , 7×10^8 , 8×10^8 , 9×10^8 , 1×10^9 , 2×10^9 , 3×10^9 , 4×10^9 , 5×10^9 , 6×10^9 , 7×10^9 , 8×10^9 , 9×10^9 , 1×10^{10} , 2×10^{10} , 3×10^{10} , 4×10^{10} , 및 5×10^{10} pfu이다. 일부 경우에, 본 개시내용의 바이러스는 최대 약 1×10^8 , 2×10^8 , 3×10^8 , 4×10^8 , 5×10^8 , 6×10^8 , 7×10^8 , 8×10^8 , 9×10^8 , 1×10^9 , 2×10^9 , 3×10^9 , 4×10^9 , 5×10^9 , 6×10^9 , 7×10^9 , 8×10^9 , 9×10^9 , 1×10^{10} , 2×10^{10} , 3×10^{10} , 4×10^{10} , 5×10^{10} , 1×10^{11} , 2×10^{11} , 3×10^{11} , 4×10^{11} , 5×10^{11} , 6×10^{11} , 7×10^{11} , 8×10^{11} , 9×10^{11} , 1×10^{12} , 2×10^{12} , 3×10^{12} , 4×10^{12} , 5×10^{12} , 6×10^{12} , 7×10^{12} , 8×10^{12} , 9×10^{12} , 1×10^{13} , 2×10^{13} , 3×10^{13} , 4×10^{13} , 5×10^{13} , 6×10^{13} , 7×10^{13} , 8×10^{13} , 9×10^{13} , 1×10^{14} , 2×10^{14} ,

3×10^{14} , 4×10^{14} , 5×10^{14} , 1×10^{15} , 2×10^{15} , 3×10^{15} , 4×10^{15} , 5×10^{15} , 6×10^{15} , 7×10^{15} , 8×10^{15} , 9×10^{15} pfu이다. 일부 측면에서, 본 개시내용의 바이러스 벡터는 벡터 게놈으로서 측정될 수 있다. 일부 경우에, 본 개시내용의 바이러스는 1×10^{10} 내지 3×10^{12} 벡터 게놈, 또는 1×10^9 내지 3×10^{13} 벡터 게놈, 또는 1×10^8 내지 3×10^{14} 벡터 게놈, 또는 적어도 약 1×10^1 , 1×10^2 , 1×10^3 , 1×10^4 , 1×10^5 , 1×10^6 , 1×10^7 , 1×10^8 , 1×10^9 , 1×10^{10} , 1×10^{11} , 1×10^{12} , 1×10^{13} , 1×10^{14} , 1×10^{15} , 1×10^{16} , 1×10^{17} , 및 1×10^{18} 벡터 게놈이거나, 또는 1×10^8 내지 3×10^{14} 벡터 게놈이거나, 또는 최대 약 1×10^1 , 1×10^2 , 1×10^3 , 1×10^4 , 1×10^5 , 1×10^6 , 1×10^7 , 1×10^8 , 1×10^9 , 1×10^{10} , 1×10^{11} , 1×10^{12} , 1×10^{13} , 1×10^{14} , 1×10^{15} , 1×10^{16} , 1×10^{17} , 및 1×10^{18} 벡터 게놈이다.

[0165] 일부 경우에, 본 개시내용의 바이러스 또는 바이러스 벡터의 투여량은 감염 다중도 (MOI)를 사용하여 측정될 수 있다. 일부 경우에, MOI는 핵산이 전달될 수 있는 세포에 대한 벡터 또는 바이러스 게놈의 비 또는 배수를 지칭할 수 있다. 일부 경우에, MOI는 1×10^6 GC/mL (게놈 카피/mL)일 수 있다. 일부 경우에, MOI는 1×10^5 GC/mL 내지 1×10^7 GC/mL일 수 있다. 일부 경우에, MOI는 1×10^4 GC/mL 내지 1×10^8 GC/mL일 수 있다. 일부 경우에, 본 개시내용의 재조합 바이러스는 적어도 약 1×10^1 GC/mL, 1×10^2 GC/mL, 1×10^3 GC/mL, 1×10^4 GC/mL, 1×10^5 GC/mL, 1×10^6 GC/mL, 1×10^7 GC/mL, 1×10^8 GC/mL, 1×10^9 GC/mL, 1×10^{10} GC/mL, 1×10^{11} GC/mL, 1×10^{12} GC/mL, 1×10^{13} GC/mL, 1×10^{14} GC/mL, 1×10^{15} GC/mL, 1×10^{16} GC/mL, 1×10^{17} GC/mL, 및 1×10^{18} GC/mL MOI이다. 일부 경우에, 본 개시내용의 바이러스는 약 1×10^8 GC/mL 내지 약 3×10^{14} GC/mL MOI이거나, 또는 최대 약 1×10^1 GC/mL, 1×10^2 GC/mL, 1×10^3 GC/mL, 1×10^4 GC/mL, 1×10^5 GC/mL, 1×10^6 GC/mL, 1×10^7 GC/mL, 1×10^8 GC/mL, 1×10^9 GC/mL, 1×10^{10} GC/mL, 1×10^{11} GC/mL, 1×10^{12} GC/mL, 1×10^{13} GC/mL, 1×10^{14} GC/mL, 1×10^{15} GC/mL, 1×10^{16} GC/mL, 1×10^{17} GC/mL, 및 1×10^{18} GC/mL MOI이다.

[0166] 본원에 기재된 벡터는 형질감염, 전기천공, 리포솜 전달, 막 융합 기술, 고속 DNA-코팅된 펠릿, 바이러스 감염 및 원형질체 융합을 포함한 임의의 적합한 방법에 의해 전달될 수 있다. 예를 들어, 네온(Neon)® 형질감염 시스템 (써모피셔 사이언티픽) 또는 아막사(AMAXA)® 뉴클레오펙터 (아막사® 바이오시스템즈)를 사용하는 전기천공이 세포 내로의 핵산의 전달에 또한 사용될 수 있다.

[0167] 본원에 제공된 임의의 벡터 및 플라스미드에 의한 세포, 예컨대 생산자 세포의 형질감염 효율은 약 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, 또는 99.9% 초과일 수 있거나 또는 그일 수 있다. 일부 실시양태에서, 형질감염 효율은 대조군 전달 플랫폼 (예를 들어, 본원에 제공된 방법의 부재 하에 조작된 바이러스)을 사용한 동등한 세포의 형질감염 효율의 약 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, 또는 99.9% 초과일 수 있거나 또는 그일 수 있다. 일부 경우에, 형질감염 또는 형질도입 효율은 세포 선택, 분류 등의 부재 하에 정량화될 수 있다.

[0168] 한 측면에서, 본원에 제공된 벡터는 개별 대상체에게의 투여에 의해, 전형적으로 전신 투여 (예를 들어, 정맥내, 복강내, 근육내, 피하 또는 두개내 주입)에 의해 생체내 전달될 수 있다.

[0169] 키트

[0170] 바이러스 조성물을 포함하는 키트가 본원에 개시될 수 있다. 암, 병원체 감염 및/또는 면역 장애의 치료 또는 예방을 위한 키트가 또한 본원에 개시될 수 있다. 한 실시양태에서, 키트는 유효량의 바이러스 조성물을 단위 투여 형태로 함유하는 치료 또는 예방 조성물을 포함할 수 있다. 일부 실시양태에서, 키트는 바이러스의 치료 조성물을 함유할 수 있는 멸균 용기를 포함하고; 이러한 용기는 박스, 앰플, 병, 바이알, 튜브, 백, 파우치, 블리스터-팩, 또는 관련 기술분야에 공지된 다른 적합한 용기 형태일 수 있다. 이러한 용기는 플라스틱, 유리, 적층지, 금속 호일, 또는 의약을 보유하기에 적합한 다른 물질로 제조될 수 있다. 일부 경우에, 본원에 제공된 바이러스는 암, 병원체 감염, 면역 장애를 갖거나 또는 이것이 발병할 위험이 있거나 또는 이식을 받을 대상체에게 바이러스를 투여하는 것에 대한 지침서와 함께 제공될 수 있다. 지침서는 일반적으로 암, 병원체 감염, 면역 장애 또는 이식의 치료 또는 예방을 위한 조성물의 용도에 관한 정보를 포함할 수 있다.

[0171] <실시예>

[0172] 하기 실시예는 본 개시내용의 범주를 제한하지 않으면서 기재된 실시양태를 추가로 예시한다.

[0173] 실시예 1: 비-복제 렌티바이러스를 포함하는 바이러스 구축물의 벡터 설계 및 서열

[0174] 비-복제 렌티바이러스를 포함하는 바이러스 벡터를 하기와 같이 생성하였다. env, 패키징, 및 전달 요소를 야생형 백시니아 바이러스 (VV) 계놈, 진뱅크 수탁 번호 AY243312.1을 갖는 백시니아 바이러스 웨스턴 리저브 균주 (표 1 및 서열식별번호: 1)에 통합하였고, 이는 도 1에 도시된 바와 같이 모두 수만개의 염기만큼 분리되어 있었다. 바이러스 벡터는 백시니아 바이러스 프로모터와, 백시니아 바이러스 전사 인자를 이용함으로써 전사를 위한 TAT의 부재 하에 기능하는 HIV-1 5' LTR 사이의 융합체인 하이브리드 5' LTR 영역을 함유한다. 백시니아 바이러스 강한 초기 프로모터를 각각의 성분에 대해 부가하고, 강한 초기 프로모터를 전달 구축물의 5' LTR에 융합시켰다. 백시니아 바이러스 초기 유전자 전사의 종결은, 백시니아 바이러스-특이적 인자를 유인하여 전사를 중단시키고 폴리(A) 꼬리를 생성하여 바이러스 mRNA를 보호하기 위해 종결 서열 UUUUUNU (U5NU) (서열식별번호: 7)를 이용한다. 서열 ATTTTAT (서열식별번호: 8)를 각각의 구축물의 목적하는 말단 영역에 부가하였다.

[0175] env 구축물

[0176] vsvg-함유 env 구축물은 vacwr032 (k11) 및 vacwr033 (k21) 유전자 사이의 지점에서 백시니아 바이러스 계놈과 재조합하도록 설계되었다. 강한 백시니아 바이러스 초기 프로모터: TATTTATATTCACAAAAAATAAAATTTCAATTTTT (서열식별번호: 9)를 사용하였다.

[0177] 맵, 및 맵과 유사한 색으로 표시된 요소를 갖는 서열을 하기 도 2 및 표 2에 나타낸다.

[0178] 표 2: 렌티바이러스 env 구축물의 맵: Vacwr032 (1-790); U5NU (906-914 및 917-925); VSVG (926-2461); 백시니아 바이러스 프로모터 (2470-2509); loxP (2529-2562 및 3343-3376); GFP (2606-3322); Vacwr033 (3503-4416)

SEQ ID	ID	서열
2	렌티 바이러스 env 구축물	CACAATTGACGTACATGAGTCTGAGTTCCTTGTGTTTGTCTAATTATTTTCATCCAATTT ATTATTTCTTGACTATATCGAGATCTTTGTATAGGAGTCAGACTTGTATTCACATGCT TTTTCTATAATCATTTTAGCTATTTGGGCATCATCCAATAGTACATTTTCCAGATTAG CAGAATAGATATTAAATGTCGTATTTGAACAGAGCCTGTAACATCTCAATGTCCTTTATT ATCTATAGCCAATTTAATGTCGGGAATGAAGAGAAGGAATTTTGGTGTGTCGAC GTCATATAGTCGAGCAAGAAATCATCATATCCACGTGTCCATTTTATAGTGATGT GAATACAACCTAAGGAGAATAGCCAGATCAAAAGTAGATGGTATCTCTGAAAGAAAGTA GGAAACAAATACCTTACATCATTAAGCATGACGGCATGATAAAATGAAGTTTCCATCCA GTTTTCCCATAGAACATCAGTCTCCAATTTTCTTAACAAACAGTTTACCGTTTGCA TGTTACCACTATCAACCGCATAATACAATGCGGTGTTTCCCTTGTCTCAAAATTGTGA ATCATCCAGTCCACTGAATAGCAAAATCTTACTATTTTGGTATCTTCCAATGTGGCT GCCTGATGTAATGGAATTCATTTCTAGAAAGATTTTCAATGCTCCAGCGTTCAACA ACGTACATACTAGACGCACGTTATTATCAGCTATTTGCATAATACAAGGCATATGTCC ATGGACATCCGCCTTAAATGCATCTTTGCTAGAGAGGTCTGAAACGAGACGCTAATTA GTGTATATTTTTCATTTTATTAATTTTGTCTATTTGCACCAGAAATTAATTAATCT CTAATAGATCTGATTAGTAGATACATGGCTATCGCATAAAAATTCGATAAAAATTTTA CTTTCCAAGTCGTTTCTATCTATGTCTGTATAAATCTGTCTTTTCTTGGTGTGCTTT AATTTAATGCAAAGATGGATACCAACTCGGAGAACCAAGAATAGTCCAATGATTAACC CTATGATAAAGAAGAAAGAGGCAATAGAGCTTTTCCAACCTACTGAACCAACCTCTAC AAGCTCGATTGGATTTTGGATAGCCAGTATCACAAAGAATAAACTCTCATCATCA GGAAGTTGCGAAGCAGCGTCTTGAATGTGAGGATGTTGGAACACCTGAGCCTTTGAGC TAAGATGAAGATCGGAGTCCAACATACCATGTCCAATCATGTATAAAGGAACTTATA TCCTGAACTGGTCTCAGAACTCCATGGGTCCAATTTCCAGTCTTCATATGGTGCC CAGTCATCCCACAGTCCCTTTCTGTGGTAGTTCCACTGATCATTCGACCATTCCTG

[0179]

		AGAGGATTGGAGCAGCAATATCGACTCTGATGTATCTGGTCTCAAAGTATTTAGGGT ACCATTTGATTATGGTGAAAGCAGGACCGGTTCCCTGGGTTTTTAGGAGCAAGATAGCTG AGATCCACTGGAGAGATTGGAAGACCCGCTCTGATTTTGCTCCAGGTTCTTTGGCAGA GGGAATAATCCAAGATCCTCTCAACGTCCTGAATTAGACTTACATCCACTGAGGTCG AGATGGAGCAGAGATACTTGACCCCTCTGGGCATTGAGGGAATCTGGCTGCAGCAAAG AGATCCTTATCAGCCATCTCGAACCAGACACCTGATGGGAGTCTGACTCCCCAATGCT TGCAGTATTGCATTTTGCAGGCCTTGCTCCAGTTTCATAAGCAAAGTAGTTACTTCT GAACCTGTGCCCTCCTTTCCAGGGATGATAGCTCTCCGCTCTGAGAAGAAAGGTG ATGTCCATGGAAATGAGGTAGAATCACATAGCCCTTGACCTTATAGTCAGAATGCC TGGACAATCACTGCTTCGGCATCCGTCACAGTTGCATATCCACAACCTTTGAGGAGGGA AGCCTGGATTGAGCAAGTTCCCTGTTTGGTTCGTTTGTCAATGCTTTCCGTTGATGAA CTGTGAATCAACCCATTCTCCTGTGTATTCATCAACCAGCACATGGTGAGGAGTCACC TGGACAATCACTGCTTCGGCATCCGTCACAGTTGCATATCCACAACCTTTGAGGAGGGA AGCCTGGATTGAGCAAGTTCCCTGTTTGGTTCGTTTGTCAATGCTTTCCGTTGATGAA TACAGATGGATGAAGGATCGGATGGACTGTGTATATACCTTCGGTCCATACCAAGCGG AAATCACAAGTAGTGACCCATTTGGAAGCATGACACATCAACCGCTCTGCTTGAATAG CCTTTGTGACTTTTGGGCATTTGACTTGTATGGCTGTGCCCTATTAAGTCAATTATGCCA ATTTAAATCTGAGCTTGACGGCAATAATGGTAATTAGAAGGAACATTTTCCAGTTT CCTTTTGTGTGTGGGAAACATATGGTGAACCTTGAATTCACCCCAATGAATAAGA AGCTTAAGTACAAAAGGCATTCATTAGAAGCTTATTTATATCCAAAAAATAAAT AAAATTTCAATTTTGTGCTAGCGGGCCCTAAGGCCATAACTTCGTATAGCATACATTAT ACGAAGTTATAATCTGCAGATGAATTCATTTGTTTCTATGCTATAAATGCG TAAGGCGAAGAGCTGTTCACTGGTGTCTGCCCTATTCGGTGAACCTGGATGGTGAT GTCAACGGTCAATAAGTTTTCCGTGCTGGCGAGGGTGAAGGTGACGCAACTAATGGTA AACTGACGCTGAAGTTCATCTGTACTACTGGTAACTGCCGGTACCTTGGCCGACTCT GGTAACGACGCTGACTTATGGTGTTCAGTGCTTTGCTCGTTATCCGGACCATATGAAG CAGCATGACTTCTTCAAGTCCGCCATGCCGGAAGGCTATGTGAGGAACGCACGATTT CCTTTAAGGATGACGGCACGTACAAAACGCGTGCAGGAGTGAATTTGAAGGCGATAC CCTGGTAAACCGCATGAGCTGAAAGGCATTGACTTTAAAGAAGACGGCAATATCCTG GGCCATAAGCTGGAATACAATTTTAAACGCCACAATGTTTACATCAACCGCGGATAAAC AAAAAATGGCATTAAGCGAATTTTAAATTCGCCACAACGTGGAGGATGGCAGCGT GCAGCTGGCTGATCACTACGAGCAAAACACTCCAATCGGTGATGGTCTCTGTTCTGCTG CAGACAATCACTATCTGAGCAGCAGCAAGCGTTCTGTCTAAGAGTCCGAACGAGAAAC GCCATCATATGGTCTGCTGGAGTTCTGAACCGCAGCGGGCATCACGCATGGTATGGA TGAACGTGACAAATAATTAATTAAGGCGCGCTCGAATAACTTCGTATAGCATACATT ATACGAAGTTATGCTAGCAGCATGCTCTTAGAATAACAACATATACACATTTAATAAA AATAATATTTATTAAGAAAATTCAGATTTACGTAACCATCAATATAAATAAATAAT GATTCCTTACACCGTACCCATATTAAGGAGATTCCACCTTACCCATAAACAATATAAA TCCAGTAATATCATGTCTGATGATGAACACAAATGGTGTATTAATTCAGTTTTTCA GGAGATGATCTCGCCGTAGCTACCATATAGTAGATGCTCTGTACAGTTCTTGTGT CGTCGACATCTATCTTGCATTCTGAAACATTTTATAAATATATAATGGTCCCTAGT CATATGTTTAAACGACGCATTTATCTGGATTAAACATACTAGGAGCCATCATTTCCGCT ATCGACTTAATATCCCTCTTATTTTGCATAGAAAATTTAGGGAGTTTAAAGATTGTACA CTTTATTTCCCTAATTGAAACGACCAATAGTCTAATTTTGCAGCGTAAATAGAATCTGT GAAATGGGTCAATATATCACTATTTGCCAGGTACATACTAATATAGCATCTTATAC GGAAGGCGTACCATATCATATTTCTGTCATCGATTGTGATTGTATTTCCTTGCAATT TAGTAACCTACGTTTCATCATGGGAACCGTTTTCTGACCGTACTTATAGTAAACCTAGC ATTGCGGTGTTTTAGTGATATCAACCGGATATTTGCCATATACCTTTAAATATATAGTA TTAATGATTGCCCATAGAGTATTATTTGTCGAGCATATTAGAATCTACTACATTAGACA TACCGGATCTACGTTCTACTATAGAATTAATTTTATTAACCGCATCTCGCTAAAGTT TAATCTATATAGGCGAATCTATGATATTGTTGATAATACGACGGTTTAAAGGCAACA GTATTATCTACGAAACCTTTGATAAGTTAGATCAGTGTACGTATATTTAGATGTTTTCA GCTTAGCTAATCCTGATATTAATCTGTAAATGCTGGACCAGATCTCTTTTCTCAA ATCCATAG
3	vsvg	TTACTTTCGAAGTCGGTTCATCTCTATGTCTGTATAAATCTGTCTTTTCTTGGTGTGC TTTAATTTAATGCAAGATGGATACCAACTCGGAGAACCAAGAATAGTCCAATGATTA ACCTTATGATTAAGAGAAAGAGGCAATAGAGCTTTTCCAACCTACTGAACCAACCTTC TACAAGCTCGATTGGATTTTGGATAGCCAGTATCACCAGGAATAAATCTCATCA TCAGGAAGTTGCGAAGCAGCGTCTTGAATGTGAGGATGTTGCAACACCTGAGCCTTTG AGCTAAGATGAAGATCGGAGTCCAACATACCATGTCCAATCATGTATAAAGGAACTT ATATCCTGAAGTGGTCTCAGAACTCCATTGGGTCCAATTTCCACGTCTTCATATGGT GCCAGTCATCCACAGATTCCCTTCTGTGGTAGTTCACCTGATCATTCGACCATTC

[0180]

		TTGAGAGGATTGGAGCAGCAATATCGACTCTGATGTATCTGGTCTCAAAGTATTTAG GGTACCATTTGATTATGGTGAAAGCAGGACCGGTTCCCTGGGTTTTTAGGAGCAAGATAG CTGAGATCCACTGGAGAGATTGGAAGACCCGCTCTGATTTTGCTCCAGGTTCTTTGGC AGAGGGAAATAATCCAAGATCCTCTCAACGTCCTGAATTAGACTTACATCCACTGAGGT CTGAGATGGAGCAGAGATACTTGACCCCTCTGGGCATTGAGGGAATCTGGCTGCAGCA AAGAGATCCTTATCAGCCATCTCGAACCAGACACCTGATGGGAGTCTGACTCCCCAAT GCTTGCAATATTGCATTTTGCAGGCCTTGCTCCAGTTTCATAAGCAAAGTAGTTACT TCTGAACCTGTGCCCTCCTTTCCAGGGATGATAGCTCTCCGCTCTCTGAGAAGAAAG GTGATGTCCATGGAAATGAGGTTAGAATCACATAGCCCTTGACCTTATAGTCAGAAT GCCAGGTTGTAGAGTTATGGACAGTGGGGCATATGTAATTGCTGCATTTTCCGTTGAT GAACTGTGAATCAACCCATTCTCCTGTGTATTCATCAACCAGCACATGGTGAGGAGTC ACCTGGACAACACTGCTTCGGCATCCGTCACAGTTGCATATCCACAACCTTTGAGGAG GGAAGCCTGGATTGAGCAAGTTCTTGTGTTTGTGTTTCAATGCTTTCTTGCATTG TTCTACAGATGGAGTGAAGGATCGGATGGAGTGTGTTATATACTTCGGTCCATACCCAG CGGAATCACAAGTAGTGACCCATTTGGAAGCATGACACATCCAAACCGTCTGCTTGAA TAGCCTTGTGACTCTTGGGCATTTGACTTGTATGGCTGTGCCTATTAAAGTCATTATG CCAATTTAAATCTGAGCTTGACGGGCAATAATGGTAATTAGAAGGAACATTTTCCAG TTTCTTTTGGTTGTGGGAAACATATGGTGAACCTGCAATTCACCCCAATGAATA AGAAGGCTAAGTACAAAAGGCATTTCAAT
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[0181]

[0182]

패키징 구축물

[0183]

패키징 구축물은 백시니아 바이러스 계놈과 재조합하여 vacwr093 (j1r) 및 vacwr033 (j3r) 유전자 사이의

vacwr094 (j2r)에 대한 코딩 서열을 대체하도록 설계되었다. 이러한 결실은, j2r-결실이 종양 세포를 우선적으로 감염시키는 약독화된 바이러스를 생성하기 때문에 선택되었다. 또한, 이러한 삽입은 다른 구축물로부터 상대적으로 먼 백시니아 바이러스 계통의 중심 근처에 구축물을 위치시킨다. 맵, 및 맵과 유사한 색으로 표시된 요소를 갖는 주석이 달린 서열을 도 3 및 표 3에 나타낸다. 패키징 구축물은 강한 백시니아 바이러스 초기 프로모터: AAAAATTGAAATTTATTTTTTTTTTTTGAATATAAATA (서열식별번호: 10)를 이용한다.

[0184] 표 3: 렌티바이러스 패키징 구축물의 맵: vacwr093 (524-985); 백시니아 바이러스 프로모터 (1000-1039); gapol (1040-5346); U5NU (5750-5757 및 5773-5780); loxP (5869-5902 및 6699-6732); GFP (5979-6698); vacwr095 (6798-7729)

SEQ ID	ID	서열
4	렌티 바이러스 패키징 구축물	CACAATTGACGTACATGAGTCTGAGTTCCTTGTTTTTGCTAATTATTTTCATCCAATTTAT TATTTCTTGACTATATCGAGATCTTTTGTAATAGGAGTCAGACTTGATTTCAACATGCTTTT CTATAATCATTTTAGCTATTTTCGGCATCATCCAATAGTACATTTTCCAGATTAGCAGAAT AGATATTAATGTCGTATTTGAACAGAGCCTGTAACATCTCAATGTCTTTATTATCTATAG CCAAATTTAATGTCGGGAATGAAGAGAAGGGAATTATTGGTGTTCGACGTCATATAGT CGAGCAAGAGAATCATCATATCCACGTGTCCATTTTTTATAGTGATGTGAATACAACATA GGAGAATAGCCAGATCAAAAGTAGATGGTATCTCTGAAAGAAAGTAGGAAACAATACCTTA CATCATTAAGCATGACGGCATGATAAAATGAAGTTTCCATCCAGTTTCCCATAGAACAT TCAGTCTCCAATTTTTCTTAACAAACAGTTTACCGTTTGCATGTTACCACTATCAACCG CATAATACAATGCGGTGTTTCCCTTGTCATCAAATTTGGAATCATCCAGTCCACTGAATA GCAAAATCTTTACTATTTTGGTATCTTCCAATGTGGCTGCCTGATGTAATGGAAATTCAT TCTCTAGAAGATTTTTCAATGCTCCAGCGTTCAACAACGTACATACTAGACGCACGTTAT TATCAGCTATTGCATAATACAAGGCACTATGTCCATGGACATCCGCCTTAAATGCATCTT TGCTAGAGAGGTCTGAAACGAGACGCTAATAGTGTATATTTTTCATTTTTTATAATTT TGTCATATTGCACCAGAATTAAATAATCTCTAATAGATCTGATTAGTAGATACATGGCT ATCGCATAAAAATTGCATAAAAAATTTACTTTCCAAGTCGGTTCATCTCTATGTCTGTAT

[0185]

		AAATCTGTCTTTTCTTGGTGTGCTTTAATTTAATGCAAAGATGGATACCAACTCGGAGAA CCAAGAATAGTCCAATGATTAAACCCTATGATAAGAAGAAAGAGGCAATAGAGCTTTTCC AACTACTGAACCAACCTTCTACAAGCTCGATTGGATTTTGGATAGCCAGTATCACCAA AGAATAAATCTCATCATCAGGAAGTTGCGAAGCAGCGTCTTGAATGTGAGGATGTTTGA ACACCTGAGCCTTTGAGCTAAGATGAAGATCGGAGTCCAACATACCATGTCCAATCATGT ATAAAGGAAACTTATATCCTGAACTGGTCTCAGAACTCCATTGGGTCCAATTTCCACGT CTTCATATGGTGCCAGTCATCCACAGTTCCCTTTCTGTGGTAGTTCCACTGATCATTC CGACCATTCTTGAGAGGATTGGAGCAGCAATATCGACTCTGATGTATCTGGTCTCAAAGT ATTTTAGGGTACCATTGATTATGGTGAAAGCAGGACCGGTTCCTGGGTTTTAGGAGCAA GATAGCTGAGATCCACTGGAGAGATTGGAAGACCCGCTCTGATTTGCTCCAGGTTTCTT GGCAGAGGGAATAATCCAAGATCCTCTCAACGTCCTGAATTAGACTTACATCCACTGAGG TCTGAGATGGAGCAGAGATACTTGACCTTCTGGGCATTGAGGGAATCTGGCTGCAGCAA AGAGATCCTTATCAGCCATCTCGAACGAGACCTGATGGGAGTCTGACTCCCAATGCT TGCAGTATTGCATTTTGCAGGCCTTGCTCCAGTTTCTAAGCAAAGTAGTTACTTCTGA ACCTGTGCCCTCCTTTCCAGGGATGATAGCTCTCCGTCTCTGAGAAGAAGGTGATGT CCATGGAAATGAGGTAGAAATCACATAGCCCTTTGACCTTATAGTCAGAAATGCCAGGTTG TAGAGATTATGGACAGTGGGCATATGTAATTGCTGCATTTCCGTTGATGAACTGTGAAT CAACCCATTCTCCTGTGTATTCATCAACCAGCACATGGTGAGGAGTCACCTGGACAATCA TGTGCTCGGCATCCGTCACAGTTGCATATCCACAACCTTGAGGAGGGAAGCCTGGATTCA GGCAAGTTCCCTGTTTCTGCTTTCATGCTTTCCCTTGCAATGTTCTACAGATGGAGTGA AGGATCGGATGGAAGTGTGTATATATCTCGGTCCATACAGCGGAAATCACAAGTAGTGA CCCATTTGGAAGCATGACACATCCAACCGTCTGCTTGAATAGCCTTGACTCTTGGGCA TTTGTACTTGTATGGCTGTGCTTATTAAGTCATTATGCCAATTTAAATCTGAGCTTGACG GGCAATAATGGTAATTAGAAGGAACATTTTCCAGTTTCTTTTGGTTGTGTGGGAAAA CTATGGTGAACCTGCAATTCACCCCAATGAATAAGAAGGCTAAGTACAAAAGGCATTCA TTAGAAGCTTATTTATATTTCAAAAAAATAAAATTTCAATTTTGGTACGGGGCC CTAAGGCCATAACTTCGTATAGCATACATTATACGAAGTTATAATTCGTCAGATGAATTT CATTTTGTTTTTCTATGCTATAAATGCGTAAAGGCGAAGAGCTGTTCACTGGTGTGCT CCCTATCTGCTGGAACCTGGATGGTGATGTCACGGTCATAAGTTTCCGTGCGTGGCGA GGGTGAAGGTGACGCAACTAATGGTAACTGACGCTGAAGTTTCACTGTACTACTGGTAA ACTGCCGTGACTTGGCCGACTCTGTTAAGCAGCTGACTTATGGTGTTCAGTGCTTTGC TCGTTATCCGGACCATATGAAGCAGCATGACTTCTTCAAGTCCGCCATGCCGGAAGGCTA TGTGACGGAACGCACGATTTCCTTAAAGGATGACGGCAGTACAAAACGCGTGGCGAAGT GAAATTTGAAGGCGATACCTTGGTAAACCGCATTGAGCTGAAAGGCATTTGACTTTAAAGA AGACGGCAATATCCTGGGCCATAAGCTGGAATACAAATTTAAGCAGCCACAATGTTTACAT CACCCCGCATAAACAAAAAATGGCATTAAGCGAATTTTAAATTCGCCACAACGTGGA GGATGGCAGCGTGCAGCTGGCTGATCACTACCAGCAAAACACTCCAATCGGTGATGGTCC TGTCTGCTGCCAGACAATCACTATCTGAGCAGCAAGCGTTCTGTCTAAAGATCCGAA CGAGAAACGCGATCATATGGTCTGCTGGAGTTCGTAAACGCGAGCGGCATCACGCATGG TATGGATGAATGTACAAATAATTAATTAAGGCCGCTCGAATAACTTCGTATAGCATA CATTATACGAAGTTATGCTAGCACGATGCTCTTAGAATAACAACATATACCATTTAATA AAAAATAATTTATTAAGAAAAATTCAGATTTACGCTACCCATCAATATAAATAAATAAT GATTCCTTACACCGTACCCATATTAAGGAGATTCACCTTACCCATAAACAAATAAATC CAGTAATATCATGTCTGATGATGAACACAAATGGTGATTAATTCAGTTTTTTCAGGAG ATGATCTCGCCGTAGCTACCATATAGTAGATGCCTCTGCTACAGTTCTTGTTCGTGCA CATCTATCTTTGCATTCTGAAACATTTTATAAATATATAATGGGTCCCTAGTCATATGTT TAAACGACGCAATATCTGGATTAAACATACTAGGAGCCATCATTTTCGGCTATCGACTTAA TATCCCTCTTATTTTCGATAGAAAATTTAGGGAGTTTAAAGATTGTACACTTTATTCCTA ATTGAAACGACCAATAGTCTAATTTTCGAGCCGTAATAGAACTGTGAAATGGGTGATAT TATCACCTATTGCCAGGTACATACTAATATTAGCATCCTTATACGGAAGGCGTACCATAT CATATTTCTTCGTATCGATTGTGATTGTATTTCTTGCAATTTAGTAACCTACGTTTATCA TGGGAACCGTTTTCTGTAACGTAATTTATAGTAAACATGACATTGCGTGTTTTAGTGATAT CAAACGATATTGCCATATACCTTTAAAAATATATAGTATTAATGATTGCCCATAGAGTAT TATTTGTCGAGCATATTAGAATCTACTACATTAGACATACCGGATCTACGTTCTACTATAG AATTAATTTTATTAACCGCATCTCGTCTAAAGTTTAAATCTATATAGGCCGAATCTATGAT ATTGTTGATAATACGACGGTTTAAATGCACACAGTATTATCTACGAACTTTGATAAGTTA GATCAGTGTACGTATATTTAGATGTTTTCAGCTTAGCTAATCCTGATTTAATTTCTGTAA ATGCTGGACCCAGATCTCTTTTCTCAATCCATAG
5	Gagpo 1	ATGGGTGCGAGAGCGTCAGTATTAAGCGGGGAGAAATAGATCGATGGGAAAAATTCGG TTAAGGCCAGGGGAAAGAAAAAATAAAATTAACATATAGTATGGGCAAGCAGGGAG CTAGAACGATTCGAGTTAATCCTGGCCTGTTAGAAACATCAGAAGGCTGTAGACAAATA

[0186]

	CTGGGACAGCTACAACCATCCCTTCAGACAGGATCAGAAGAACTTAGATCATTATATAAT ACAGTAGCAACCTCTATTGTGTGCATCAAAGGATAGAGATAAAGACACCAAGGAAGCT TTAGACCAAGATAGAGGAAGAGCAAAACAAAGTAAGAAAAAGCACAGCAAGCAGCAGCT GACACAGGACACAGCAATCAGGTCAGCCAAAATTACCTATAGTGCAGAACATCCAGGGG CAAAATGGTACATCAGGCCATATCACCTAGAACTTTAAATGCATGGGTAAAGTAGTAGAA GAGAAGGCTTTAGCCCAAGAGTGATACCCATGTTTTCAGCATTTATCAGAAAGGAGCCACC CCACAAGATTTAAACACCATGCTAAACACAGTGGGGGACATCAAGCAGCCATGCAATG TTAAAGAGAGACCATCAATGAGGAAGCTGCAGAATGGGATAGAGTGCATCCAGTGCATGCA GGGCTTATGCAACAGGCCAGATGAGAGAACCAAGGGGAAGTGACATAGCAGGAACCTACT AGTACCCCTTCAGGAACAAATAGGATGGATGACACATAATCCACCTATCCAGTAGGAGAA ATCTATAAAAGATGGATAATCTGGGATTAAATAAAATAGTAAGAAATGTATAGCCCTACC AGCATTTCTGGACATAAGACAAGGACCAAGGAACCCCTTTAGAGACTATGTAGACCGATTC TATAAACTCTAAGAGCCGAGCAAGCTTCACAAGAGGTAAAAAATGGATGACAGAAACC TTGTTGGTCCGAAATGCGAACCCAGATTGTAAGACTATTTTAAAGCAATGGGACCGGA GGGACACTAGAAGAAATGATGACAGCATGTGAGGGAGTGGGGGACCCGGCCATAAGGCA AGAGTTTGGCTGAAGCAATGAGCCAAGTAACAAATCCAGCTACCATATGATACAGAAA GGCAATTTTAGGAACCAAGAAAGACTGTTAAGTGTTCATTTGTGGCAAGAAAGGGCAC ATAGCCCAAAATTTGCAAGGCCCTTAGGAAAAAGGGCTGTTGGAATGTGGAAGGAAGGA CACCAATGAAGATTGTACTGAGAGACAGGCTAATTTCTTAGGGAAGATCTGGCCCTCC CACAAGGGGAAGGCCAGGGAATTTCTTCAGAGCAGACAGGCCAACAGCCCAACAGAA GAGAGCTTCAGTTTGGGGAAGAGACAACACTCCCTCTCAGAGCAGGAGCCGATAGAC AAGGAACTGTATCCCTTAGCTTCCCTCAGATCACTCTTTGGCAGCGACCCCTCGTCACAA TAAAGATAGGGGGCAATTAAGGAAGCTCTATTAGATACAGGAGCAGATGATACAGTAT TAGAAGAAATGAATTTGCCAGGAAGATGGAACCAAAATGATAGGGGGAATGGAGGTT TTATCAAAGTAAGACAGTATGATCAGATACTCATAGAAATCTGCGGACATAAGCTATAG GTACAGTATTTAGGACCTACACCTGTCAACATAATTTGGAAGAAATCTGTGTACTCAGA TTGGCTGCACTTTAAATTTTCCATTAGTCTTATGAGACTGTACCAGTAAATTAAGC CAGGAATGGATGGCCCAAAAGTTAAACAATGGCCATTGACAGAAGAAAAATAAAGCAT TAGTAGAATTTGTACAGAAATGGAAAAGGAAGGAAAAATTTCAAAATTTGGGCTGAAA ATCCATACAACTACTCCAGTATTTGCCATAAAGAAAAAGACAGTACTAAATGGAGAAAT TAGTAGATTTTCAGAGAATTAATAAGAGAACTCAAGATTCTGGGAAGTTCAATTAGGAA TACCACATCTCCAGGTTTAAACAGAAAAATCAGTAACAGTACTGGATGTGGGCGAT CATATTTCTCAGTCCCTTAGATAAAGACTTCAGGAAGTATCTGCAATTTACCATACCTA GTATAAACAATGAGACACCAGGATTAGATATCAGTACAATGTGCTTCCACAGGGATGGA AAGGATCACCAGCAATATTCAGTGTAGCATGACAAAAATCTTAGAGCCTTTTAGAAAAAC AAAAATCCAGACATAGTCATCTATCAATACATGGATGATTTGTATGTAGGATCTGACTTAG AAATAGGGCAGCATAGAACAAAAATAGAGGAACAGACAAACATCTGTTGAGGTGGGGAT TTACCACACCAGACAAAAACATCAGAAAGAACCTCCATTCCTTTGGATGGGTTATGAAC TCCATCCTGATAAATGGACAGTACAGCCTATAGTGCTGCCAGAAAAGGACAGCTGGACTG TCAATGACATACAGAAATTAGTGGGAAAAATGAATTTGGCAAGTCAGATTTATGCAGGGA TTAAAGTAAGGCAATTTATGTAACCTCTTAGGGGAAACCAAGCACTAACAGAAAGTAGTAC CACTAACAGAAAGCAGAGCTAGAACTGGCAGAAAACAGGGAGATTCTAAAGAACCCGG TACATGGAGTGTATTATGACCCATCAAAAGACTTAATAGCAGAAATACAGAAGCAGGGGC AAGGCCAATGGGCAATCAAAATTTATCAAGAGCCATTTAAAAATCTGAAACAGGAAAGT ATGCAAGAAATGAAGGGTGGCCACACTAATGATGTGAACAAATTAACAGAGGCAGTACAAA AAATAGCCACAGAAAGCATAGTAATATGGGAAAGACTCCTAAATTTAAATTTACCCATAC AAAAGGAACATGGGAAGCATGGTGGACAGAGTATTGGCAAGCCACCTGGATTCTGAGT GGGAGTTTGTCAATACCCCTCCCTTAGTGAAGTTATGGTACCAGTTAGAGAAAGAACCCA TAATAGGAGCAGAACTTTCTATGTAGATGGGGCAGCCAATAGGGAACCTAAATTAGGAA AAGCAGGATATGTAATGACAGAGGAAGACAAAAAGTTGTCCTCCCTAACCGGACACAAAC ATCAGAAGACTGAGTTACAAGCAATTCATCTAGCTTGCAGGATTCGGGATTAGAAGTAA ACATAGTGACAGACTCACAATATGCATTGGGAATCATTCAGCACAACCATAGATAGAGT AATCAGAGTTAGTCACTCAAAATTAATAGAGCAGTTAATAAAAAAGGAAAAAGTCTACCTGG CATGGGTACCAGCACACAAGGAATTTGGAGGAATGAACAGTAGATAAATTTGGTCAGTG CTGGAATCAGGAAAGTACTATTCTTAGATGGAATAGATAAGGCCAAGAAGAACATGAGA AATATCAGATTAATTTGGAGAGCAATGGCTAGTGATTTAACCTACCACCTGTAGTAGCAA AAGAAATAGTAGCCAGCTGTGATAAATGTGAGCTAAAGGGGAGCCATGCATGGACAAG TAGACTGTAGCCAGGAATATGGCAGCTAGATTGTACACATTTAGAAGGAAAAGTTATCT TGGTAGCAGTTTATGTAGCCAGTGGATATATAGAAGCAGAAAGTAATTCAGCAGAGACAG GGCAAGAAACAGCATACTTCCCTCTTAAATTTAGCAGGAAGATGGCCAGTAAAAACAGTAC ATACAGACAAATGGCAGCAATTTACCAGTACTACAGTTAAGGCCGCTGTTGGTGGGCGG
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[0187]

	GGATCAAGCAGGAATTTGGCATTCCTTACAATCCCAAGTCAAGGAGTAATAGAATCTA TGAATAAGAAATTAAGAAAAATATAGGACAGGTAAGAGATCAGGCTGAACATCTTAAGA CAGCAGTACAAATGGCAGTATTCATCCACAATTTTAAAGAAAAAGGGGGGATTTGGGGGT ACAGTGCAGGGGAAAGAAATAGTAGACATAATAGCAACAGACATACAACTAAAGAAATTAC AAAAACAAATTAACAAAAATCAAAATTTTCGGGTTTATTTACAGGGACAGCAGAGATCCAG TTTGGAAAGGACAGCAAGCTCCTCTGGAAGGTGAAGGGGCGATAGTAATACAAGATA ATAGTGACATAAAGTAGTGCCAAGAAAGCAAGATCATCAGGGATTATGGAAGAAC AGATGGCAGGTGATGATTGTGGCAAGTAGACAGGATGAGGATTAA
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[0188]

[0189]

전달 구축물

[0190]

전달 요소를 백시니아 바이러스 계놈 (표 1)의 먼 3' 말단 근처에 후기 유전자 전사체가 없는 영역인 vacwr205와 vacwr206 사이에 삽입하였다. 맵, 및 맵과 유사한 색으로 표시된 요소를 갖는 서열을 도 4 및 표 4에 나타낸다. 전달 구축물은 강한 백시니아 바이러스 초기 프로모터:

GTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGG
GATTTCCAAGTCTCCACCCCATTTGACGTCAATGGGAGTTTGTGTTTGGCACCAAAA
TCAACGGGACTTTCCAAAATGTGCGTAACAACCTCCGCCCCATTGACGCAAATGGGC
GGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCT (서열식별번호: 11)

[0191]

및

[0192]

인간 PGK 프로모터:

GGGGTTGGGGTTGCGCCTTTTCCAAGGCAGCCCTGGGTTTGCAGAGGACGCGGC
TGCTCTGGGCGTGGTTCCGGGAAACGCAGCGCGCCGACCCTGGGTCTCGACA
TTCTTCACGTCCGTTTCGACGCGTCACCCGGATCTTCGCCGCTACCCTTGTGGGCCC
CCCGGCGACGCTTCCTGCTCCGCCCTAAGTCGGGAAGGTTCTTGCGGTTCGCG
GCGTGCCGGACGTGACAAACGGAAGCCGCACGTCTCACTAGTACCCTCGCAGAC
GGACAGCGCCAGGGAGCAATGGCAGCGCGCCGACCGCGATGGGCTGTGGCCAAT
AGCGGCTGCTCAGCAGGGCGCGCCGAGAGCAGCGGCCGGAAGGGGCGGTGCG
GGAGGCGGGGTGTGGGGCGGTAGTGTGGGCCCTGTTCTGCCCCGCGGGTGTTC
GCATTCTGCAAGCCTCCGGAGCGCACGTCGGCAGTCGGCTCCCTCGTTGACCGAA
TCACCGACCTCTCTCCCCAG (서열식별번호: 12)

[0193]

[0194]

를 이용한다.

[0195]

표 4: 렌티바이러스 전달 구축물의 맵: vacwr205 (1-905); 5'LTR (1012-1192); Ψ (1239-1364); RRE (1857-2090); CMV 프로모터 (2926-3129); GFP (3174-3890); cPPT/CTS (4584-4701); hPGK 프로모터 (4750-5260); PAC (5282-5881); 3'LTR (6009-6242); U5NU (6243-6251); SV40폴리(a) (6323-6331); LoxP (6469-6502 및 7332-7369); rfp (6579-7313); vacwr206 (7455-8158)

[0196]

SEQ ID	ID	서열
6	LV 전달	CACCCGATGACAATAATGACATGGACGTAGATATTCGGTATTGTGCGACACTAGCTACCG CAAAATAAAATATACGGTAGCGATAGTATCGAGTTCACGCCTCCTTCCTACAAAAAATAA AAGACGATTTTCAAACGTAAACTTTAATAATGCTAACCAACAAAGGAACATAATCAACG

	AATGGGTAAAGACAATGACAAATGGTAAAATTAATTCTTATTGACTAGTCCGCTATCCA TTAATACTCGTATGACAGTTGTTAGCGCCGTCATTTTAAAGCAATGTGGAAATATCCAT TTTCTTAAACATCTTACATATACAGACAAGTTTATATTTCTAAGAAATATAGTTACCAGTG TTGATATGATGGTGGACACTGAGAATAACTTGCAATATGTACATATTAATGAATTATTCG GAGGATCTCTTATTCGATATTCATACGAGGGAACTCTAGTATGGTAATTATACTAC CGGACGACATAGAAAGGTATATATAACATAGAAAAAATATAACAGATGAAAAATTTAAAA AATGGTGTGGTATGTTATCTACTAAAAGTATAGACTTGTATATGCCAAAGTTTAAAGTGG AAATGACAGAACCGTATAATCTGGTACCGATTTTAGAAAAATTTAGGACTTACTAATATAT TCGGATATTATGCGAGATTTTAGCAAGATGTGAATGAACTATCACTGTAGAAAAATTC TACATACGACGTTTATAGATGTTAATGAGGAGTATACAGAAGCATCGGCCGTTACAGGAG TATTTATGCACTAATTTTCGATGGTATATCGTACGAAGGTCTACATAAACCATCCATTCA TGATACATGATTAAAGACAACACAGGACGTATACCTTTTATAGGGAAATACTGCTATCCGC AATAAATATAACAAATAGACTTTTTATCACGTTTATCTATGCTAAATATTACAAATAG TAATAATATAAATAAGCCTAGGAAAAATGAAACATATATTAATCAGCGGGTCTCTC TGGTTAGACCAGATCTGAGCCTGGGAGCTCTCTGGCTAACAGGAAACCCACTGCTTAAG CCTCAATAAAGCTTGCCCTTGAGTGCTTCAAGTAGTGTGTGCCGCTCTGTTGTGTGACTCT GTAAGCATAGAGTCCCTCAGACCTTTTATGTCAGTGTTGGAAAACTCTAGCAGTGGCGCC CGAACAGGGAAGTTGAAAGCGAAAGGGAAACAGAGGAGCTCTCTCGACGCGAGGACTCGGC TTGCTGAAGCGCGCACGGCAAGAGGCGAGGGGCGGCGACTGGTGAGTACGCCAAAAATTT TGACTAGCGGAGGCTAGAAAGGAGAGAGATGGGTGCGAGAGCGTCAGTATTAAGCGGGGA GAATTAGATCGCGATGGGAAAAATTCGGTTAAGGCCAGGGGGAAGAAAAATATAAAT TAAAAATATAGTATGGGCAAGCAGGAGCTAGAACGATTGCGAGTTAATCCTGGCCTGT TAGAAACATCAGAAAGCTGTAGACAAATCTGGGACAGCTACAAACCATCCCTTACAGCAG GATCAGAAAGAACTTAGATCATATATATAACAGTAGCAACCCCTCTATTTGTGTGCATCAAA GGATAGAGATAAAAGACACCAAGGAAGCTTTAGACAAGATAGAGGAAGAGCAAAACAAAA GTAAGACCAACCGCACAGCAAGCGGCCGCTGATCTTCAGACCTGGAGGAGGAGATATGAGG GACAAATGGAGAAAGTGAATTATATAAATATAAAGTAGTAAAAATGAACCATTAGGAGTA GCACCCCAAGGCAAGAGAGAGTGGTGACAGAGAAAAAGAGCAGTGGGAATAGGA GGTTTCTTCTGGGTTCTTGGGAGCAGCAGGAAGCACTATGGGCGCAGCGTCAATGACG CTGACGGTACAGGCCAGACAATATTGTCTGGTATAGTGACGAGCAGAACAATTTGCTG AGGGCTATTGAGGCGCAACAGCATCTGTTGCAACTCACAGTCTGGGCGATCAAGCAGCTC CAGGCAAGAAATCCTGGCTGTGGAAGATACCTAAAGGATCAACAGCTCCTGGGGATTTGG GGTTGCTCTGGAAGAACTCATTTGCACCACTGCTGTGCTTGGAAATGCTAGTTGGAGTAAT AAATCTCTGGAACAGATTTGGAATCACACGACCTGGATGGAGTGGGACAGAGAAATTAAC AATTACACAAGCTTAATACACTCCTTAATTGAAGAAATCGCAAAACAGCAAGAAAAAGAA GAACAAGAAATATTGGAATTAGATAAATGGGCAAGTTTGTGGAATTGGTTTAAACATAACA AATTGGCTGTGGTATATAAAATTAATCATAATGATAGTAGGAGGCTTGGTAGGTTTAAAG ATAGTTCTTGGCTGACTTTCTATAGTGAATAGAGTTAGGCAGGGATATTCCACATTATCG TTTCAGACCCACCTCCCAACCCGAGGGGACCCGACAGGCCCGAAGGAATAGAAGAGAA GGTGGAGAGAGAGACAGAGACAGATCCATTGATTAGTGAACCGATCTCGACGGTATCGA TCACGAGACTAGCCTCGAGCGGCCGCCCTTCACCGAGGGCTATTTCCCATGATTCCT TCATATTTGCATATACGATACAAGGCTGTTAGAGAGATTAATTGGAATTAATTTGACTGTA AACACAAAGATATTAGTACAAATACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTT GCAGTTTAAAAATTAATGTTTAAAAATGGACTATCATATGCCAAGTACGCCCCCTATTGAC GTCAATGACGGTAAATGGCCCGCTGGCATTATGCCAGTACATGACCTTATGGGACTTT CCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTGG CAGTACATCAATGGCGGTGGATAGCGGTTTGGACTCACGGGGATTTCGAAGTCTCCACCCC ATTGACGTCAATGGGAGTTTGTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCTGT AACAACTCCGCCCATTTGACGCAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATA AGCAGAGCTGGTTTGTGAAACCGTCAGATCCGCTAGCGCTACCGGTGCGCCACCATGCGTA AAGGGCAAGAGCTGTTTCACTGGTGTCTGTCCTATTTCTGGTGGAACTGGATGGTGATGTA ACGGTCATAAGTTTTCCTGCGGTGGCGAGGGTGAAGGTGACGCAACTAATGGTAAACTGA CGCTGAAGTTTCACTGTACTACTGTTAACTGCGGTCCTTTGGCCGACTCTGGTAAACGA CGCTGACTTATGGTGTTCAGTGCTTTGCTCGTTATCCGGACCATATGAAGCAGCATGACT TCTTCAAGTCCGCCATGCGGGAAGGCTATGTGCAGGAACGCACGATTTCTTTAAGGATG ACGGCACGTACAAAACCGGTGCGGAAAGTGAATTTGAAGCGGATACCTGGTAAACCGCA TTGAGCTGAAAGGCATGACTTTAAAGAGACGGCAATATCCTGGGCCATAGCTGGAAT ACAATTTTAAACAGCCACAATGTTTACATCACCGCCGATAAACAAAAAATGGCATTAAG CGAATTTTAAAAATTCGCCACAACGTGGAGGATGGCAGCGTGCAGCTGGCTGATCACTACC AGCAAAACACTCCAACTCGGTGATGGTCTGTTCTGCTGCCAGACAATCACTATCTGAGCA CGCAAGCGTTCTGTCTAAAGATCCGAACGAGAAACCGCATCATATGGTTCTGTGGAGT
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[0197]

	TCGTAACCCGAGCGGGCATCACGCATGGTATGGATGAACGTACAAATAAGAATTCGATA TCAAGCTTATCGATAATCAACCTCTGGATTACAAAAATTTGTGAAAGATTGACTGGTATTC TTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTAAATGCCTTTGTATCATG CTATTGCTTCCGCTATGGCTTTTCAATTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTC TTTATTGAGGAGTTGTGGCCGTTGTGACGGCAACGTGGCGTGGTGTGCACTGTGTTGCTG ACGCAACCCCACTGGTGGGGCATTTGCCACCACCTGTGAGCTCCTTTCCGGGACTTTCCG CTTTCCCTCCCTATTTGCCACGGCGGAATCATCGCCGCTGCTTTGCCGCTGCTGGA CAGGGGCTCGGCTTTGGGCACTGACAATTCCTGGTGTGTCGGGGAAATCATGCTCCT TTCTTTGGCTGCTGCGCTGTGTTGCCACCTGGATTCTGCGCGGGACGCTCCTTTCTGCTACG TCCCTTCGGCCCTCAATCCAGCGGACCTTCTTCCCGCGGCTGCTGCCGGCTCTGCGGC CTCTTCCGCTGCTTCCCTTCCGCTCAGACGAGTCCGATCTCCTTTTGGGCGGCTCCC CGCATCGATACCTCGGACTCAGATCTCGAGCTCAAGCTTCAAGTTCTCGACCTCGAGA CAAAATGGCAGTATTCATCCACAATTTTAAAGAAAAGGGGGATTGGGGGTACAGTGCA GGGGAAGAATAAGTACATAAATAGCAACAGACATACAACTAAAGAAATACAAAAACAA ATTACAAAATTTCAAATTTTCGGGTTTATTACAGGGACAGCAGAGATCCACTTTGGCCG CGGCTCGAGGGGTTGGGGTTGCGCCTTTTCCAAGCGAGCCTGGGTTTGGCAGGGACG CGGCTGCTCTGGCGCTGGTTCCGGGAACGACGCGGCGGACCTGGGTCTCGCAGATT CTTCAGCTCCGTTGCGAGCTCACCCGATCTTCCGCGCTACCTTTGTGGGCCCCCGGC GACGCTTCTGCTCCGCCCTAAGTCGGGAAGGTTCTTGGGTTCCGCGCTGCCGAC GTGACAAACCGGAAGCCGACGCTCTCACTAGTACCTCGCAGACGGAAGCGCCAGGGAGC AATGGCAGCGCGCCGACCGCATGGGCTGTGGCCAATAGCGGCTGCTCAGCAGGGCGCGC CGAGAGCAGCGCGCGGAAGGGCGGTGCGGGAGGCGGGGTGTGGGGCGGTAGTGTGGG CCTGTTCCGTGCCCGCGCGTGTTCGCGATTCTGCAAGCTTCCGAGCGCAGCTCGGCACT CGGCTCCTCGTTGACCGAATCACCGACTCTCTCCCCAGGGGGATCCACCGAGCTTAC CATGACCGAGTACAAGCCACGGTGCCTTCGCCACCCGCGACGAGCTCCCAGGGCCGT ACGCACTCTCGCGCGCGGTTCCGCGACTACCCCGCCACGCGCCACACCGCTCGATCCGA CCGCCACATCGAGCGGGTCAACGAGCTGCAAGAACTCTTCTCAGCGCGCTCGGGCTCGA CATCGGCAAGGTGTGGGTGCGCGGACGAGCGCGCGGTTGGCGGTCTGGACCAGCCGGA GAGGCTCGAAGCGGGGGCGGTGTTCGCGAGATCGGCGCGCATGCGCGAGTTGAGCGG TTCCCGGTGGCGCGCAGCAACAGATGGAAGGCTCTTGGCGCGCACCGGCGCAAGGA GCCCGCGTGGTTCTGGCCACCGTGGCGCTCTCGCCGACCCAGGCAAGGGTCTGGG CAGCGCCCTCGCTCCTCCCGAGTGGAGCGGCGGAGCGCGCGGGGTGCCCGCTCTCT GGAGACTCCGCGCCCCGCAACCTCCCTTCTACGAGCGGCTCGGCTTCAACGCTCACCGC CGAGCTCGAGGTGCCGAAGGACCGCGACCTGGTGCATGACCCGCAAGCCCGGTGCTG TGGGCTCTCTGTTAGTGTAGTGTCTGAGCCTGGGAGCTCTTGGCTAACTAGGGAACCC ACTGCTTAAGCCTCAATAAAGCTTGCCTTGAGTGCTTCAAGTAGTGTGTGCCGCTCTGTT GTGTGACTCTGGTAAGTAGATCCCTCAGACCTTTTAGTCAGTGTGGAATCTCTAG CAAAATTTTATGTAGTGTCTGATGCTATTTATTTAGTATTTATAACTTGCAAGAA ATGAATATCAGAGAGTGAAGGAATTTTATAACTTGTATTGCGAGCTTATAATGGTTA CAAAATAAGCAATAGCATCAAAATTTCAAAATAAAGCATTTTTTCACTGCATTCTAG TTGTGGTTTGTCCAACTCATCAATGTATCTTAGGTATAGCTCTAGAATAACTTCGTAT AGCATACATTATACGAAGTTATAATTCTGCAGATGGATCATAAAATATAGTAGAATTTC ATTTTGTTTTTTCTATGCTATAAATAGCTTCTCGAGCATGGTGTCTAAGGGCGAAGGC TGATTAAAGGAACATGCACATGAAGCTGTACATGGAGGGCACCTGAACACACCCACT TCAAGTGCACATCCGAGGGCGAAGGCAAGCCCTACGAGGGCACCCAGACCATGAGAATCA AGGTGGTCGAGGGCGGCTCTCCCTTCGCTTCGACATCCTGGCTACAGCTTCATGT ACGGCAGCAGAACCTTCATCAACACACCCAGGGCATCCCGATTCTTTAAGCAGTCTCT TCCCTGAGGGCTTCACATGGGAGAGAGTCAACACATACGAAGAGGGGGCGTGTGACCG CTACCCAGGACACCGCTCCAGGACGGCTGCTCATCTACAACGTCAAGATCAGAGGGG TGAACTTCCCATCAACGGCCCTGTGATGCAGAAGAAACACTCGGCTGGGAGGCAACA CCGAGATGTGTACCCGCTGACGGCGGCTGGAAGGCAGAACCACATGGCCCTGAAGC TCGTGGGGGGGGCCACCTGATCTGCAACTTCAAGACCACATACAGATCCAGAAACCCG CTAAGACTCAAGATGCCGGCGCTACTATGTGGACACAGACTGGAAAGAAATCAAGG AGGCGCAGAAAGAGACTACGTGAGCAGCAGAGGTGGCTGTGGCCAGATACTGCGACC TCCCTAGCAAACTGGGGCACAACCTTAATGGCATGGACGAGCTGTACAAGTAATTAATTA AGGCGCTCGAATAACTTCGTATAGCATACATTATACGAAGTTATCTGATAATACTTAAA AAAATAATAATATCATTTACAATTAATAGTATAAATTAATAAATAAACAATCGTTATTA TAAGTAATATCAAAATGATGATATACGGATTAAAGCGTGTCTTATATTCGTGACTTCAT
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[0198]

	CCATCGCTAGTCCACTTTATATTTCCGTTATTCACCCATTTTCGGAAGATAAATCGTTCA ATAGTGTAGAGGTATTAGTTTCTTGTATTAGAGATGACCAAAAGACTATACGGTAACCT CTCAGTTCAATAACTACACTATCGATACCAAGACTGGACTATCGGCTACTATCCACAC CTGATGGTTTGGATATACCATGACTAATATACTTATTGGTCACGGTTTACTATAGGTC GTGCATGTTCAAATCAGAGTCTGAGGATATTTCCAAAAGAAAATGAGTATTTAGGTG TTTCTATAGAATGTAAAGAGTGTGACATTACTTACTTTTGGACCTGCGTAAAATGA CTCGAGTATTTAATAAATTTCCAGATATGGCTTATTATCGAGGAGCTGTTTAAAGCCG TTTATGTAACAATGACTTATAAAATACTAAACTGGAGAGACTGATTACACGTACCTCT CTAATGGGGGGTTCCTGCATACTATCGTAATGGGGTCGATGGTTGATTATGATTAGTA TATTCCTTATTCTTTTATTACACAAAAAGAACATTTTATAAACATGAACCACTGTC TAAATGTAATTATGATCTTGATTATAGATGAAGATCAGCCTTTAGAGGATTTTAACC
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[0199]

[0200]

[0201]

실시예 2: 비-복제 렌티바이러스를 포함하는 바이러스 구축물의 생성

바이러스 구축물은 인테그레이티드 DNA 테크놀로지스(Integrated DNA Technologies)에 의해 합성된 짧은 DNA 단편 "gBlock", 프라이머 연장물을 조합하고/거나 젠스크립트(GenScript)로부터의 전체 플라스미드 합성 생성물에 의해 생성하였다. BS-C-1 세포를 완성된 플라스미드로 형질감염시킨 후, ATCC로부터 얻은 웨스턴 리저브 균주의 야생형 백시니아 바이러스로 감염시켰다. 구축물을 env 구축물로 시작하여, 이어서 패키징 구축물, 및 최종적으로 전달 구축물로 순차적으로 부가하고 선택하였다. 각각의 부가 사이에, 백시니아 바이러스 리포터를

Cre+ 세포 상에서 성장시켜 제거하여 sfGFP 또는 TagRFP-T를 제거한 다음, 리포터-음성 바이러스 플라크를 선택하였다.

[0202] Gag/Pol의 발현

[0203] GAG 발현의 검출은 웨스턴 블롯에 의해 수행하였다. BS-C-1 세포를 명시된 바이러스로 5 감염 다중도 (MOI)로 감염시켰다. 24시간 후, 세포를 웨스턴 블롯을 위해 처리하고, Gag를 비로랩으로부터의 HRP-접합된 항-HIV-1 Gag 항체 (Cat# HIVGAG-HRP, Lot# 0516P4)를 사용하여 가시화하였다. 레트로-Vac로부터의 gagpol의 발현은 도 5에 도시된 바와 같이 p55, p41 및 p24를 포함하는 완전히 성숙하고 프로세싱된 Gag 단백질을 생성하였다. 이는 pol 서열의 시작 근처에서 HIV-1 리보솜 프레임시프트 신호에 의해 유도된 성공적인 -1 프레임시프트로 인해 HIV 프로테아제 (pol의 N-말단)가 발현되고 활성임을 나타냈다. 이러한 프레임시프트를 보조하는 숙주 인자, 예컨대 진핵생물 방출 인자 1 (eRF1)이 세포질 및 핵시니아 바이러스 공장에 존재할 수 있는 것이 가능하다. 프레임시프트는 전체 전사 사건의 5%에서 HIV-1에서 발생하는 것으로 여겨지며, 이 비는 적격 바이러스를 생성하기 위해 거의 5%에 머무르는 것이 중요하다.

[0204] VSV-G의 발현

[0205] 레트로-Vac로부터의 VSV-G의 성공적인 발현이 웨스턴 블롯 상에서 검출되었다. BS-C-1 세포를 명시된 바이러스로 5 MOI로 감염시켰다. 24시간 후, 세포를 웨스턴 블롯을 위해 프로세싱하고, VSV-G를 도 6에 도시된 바와 같이 바이오 레전드로부터의 항-VSV-G 항체 (클론 폴리29039) (Cat# 903901, Lot# B232548)를 사용하여 가시화하였다. VSV-G는 57.4 kDa인 것으로 예측된다.

[0206] 리포터 유전자는 성공적인 레트로바이러스 생산을 나타낸다.

[0207] 모든 렌티바이러스 구축물이 동일한 핵시니아 바이러스 계통에 포함되면, 최종 생성물을 공통 렌티바이러스 성장 세포주 HEK293 상에서 성장시켰다. 감염 24시간 후, 핵시니아 바이러스로부터의 TagRFP-T 리포터를 도 7에 도시된 바와 같이 형광 현미경검사를 사용하여 바이러스 플라크 내에서 가시화하였다. 또한, 레트로바이러스 전달 구축물 내의 sfGFP 리포터는 바이러스 플라크 내에 산란된 세포 상에서 검출되었다. 이는 레트로바이러스가 핵시니아 바이러스-감염된 세포로부터 생성되고 있고, 이웃 세포를 형질도입하였음을 나타냈다.

[0208] 실시예 3: 바이러스 입자의 수집

[0209] 바이러스 입자를 분리하기 위해, 약 12×10^6 개의 293T 세포를 형질감염 24시간 전에 15 cm² 플레이트 상에 20 ml로 플레이팅하였다. 일반적으로, 2개의 15cm 플레이트가 사용된다. 세포는 잘 유지되어야 하고, 계대수가 비교적 낮아야 한다. 하기 단계를 한번에 1개의 플레이트로 수행하였다. 2 ml의 2X HBS를 파스퇴르 피펫으로 버블링하면서 DNA 혼합물에 적가하였다. 완결 시, 혼합물을 12-15초 동안 버블링되도록 하였다. 인큐베이터로부터 293T의 플레이트를 꺼내고 (플레이트는 가능한 한 오랫동안 인큐베이터에서 유지됨), 형질감염 혼합물을 플레이트 전체에 걸쳐 적가하였다. 플레이트를 앞에서 뒤로 부드럽게 와류시키고, 즉시 인큐베이터로 복귀시켰다. 3.5 내지 4시간 후에 배지를 제거하고, 10 ml의 따뜻한 PBS로 2x 세척하고, 20 ml의 따뜻한 D10을 플레이트 상에 첨가하고, 인큐베이터에 두었다. 형질감염 36-48시간 후에 바이러스 상청액을 수거하고, 50 ml 튜브에서 4℃에서 7분 동안 2000 rpm으로 회전시켰다. 바이러스 SN을 0.45 μ m 필터를 통해 여과하였다. 여과된 상청액 35 ml를 초원심분리 튜브에 첨가하였다. 추가의 배지로 튜브의 균형을 이루었다. 작은 파라필름 조각으로 튜브를 덮었다. (잔류 상청액의 일부를 적정하여 농축 동안 바이러스의 손실이 있는지를 측정하는 것이 유용하다.) 튜브를 SW-28 로터를 사용하여 25,000 rpm, 90분, 4℃에서 회전시켰다. 액체를 경사분리하고, 튜브를 10분 동안 김wipe(Kimwipe) 상에 뒤집어 두었다. 나머지 배지를 튜브의 바닥에 접촉하지 않도록 조심스럽게 흡인하였다. 15 μ l의 차가운 PBS (배아 감염을 위해, 또는 원하는 임의의 부피)를 첨가하고, 튜브를 진탕하지 않으면서 4℃에서 밤새 두었다. 재현탁시키기 위해, 튜브를 비스듬히 유지하고, 펠렛이 팁과 접촉하지 않도록 주의하면서 유체를 펠렛에 대해 20회 피펫팅하였다. 이것이 완료된 후 펠렛은 재현탁되지 않을 것으로 예상된다. 이 펠렛은 바이러스를 함유하지 않으며 폐기될 수 있다. 바이러스를 분취하거나 사용한다. 바이러스는 분취되고, 액체 질소에서 급속-동결되고, -80에서 저장되어야 한다. 동결 농축된 바이러스의 경우에는 역가에 변화가 없어야 한다. 다회 동결-해동을 피한다.

[0210] 또 다른 실험에서, 세포를 본원에 기재된 벡터로부터 생성된 바이러스로 감염시켰다. 생산-증진 돌연변이체를 우선적으로 선택하기 위해, 바이러스 풀로 감염된 플라스크로부터의 배지를 비-감염 플라스크에 첨가하였다. 클로날 플라크를 여러 라운드의 연속 감염 후에 분리하였다.

- [0211] 실시예 4: 세포 생존율 검정
- [0212] 한 실험에서, HeLa 세포를 6-웰 플레이트에서 전면생장물로 성장시키고, 1 MOI의 레트로-Vac로 감염시켰다. 24 시간 후, 1 mL의 상청액을 제거하고, 800 g에서 원심분리한 다음, 500 uL의 상청액을 제거하고, 바이러스 플라크 검정에 사용하였다. 연속 희석 동안, 샘플을 항-L1 NR-45114 항체 또는 VIG로 처리한 다음, 37°C에서 1시간 동안 인큐베이션하였다. 이어서, 희석물을 플라크 검정을 위해 BS-C-40 세포의 전면생장 6 웰 플레이트에 첨가하였다. 1.5시간 후, 배지를 3% CMC를 함유한 CM10으로 대체하였다. 48시간 후에, 세포를 크리스탈 바이올렛으로 염색하여 바이러스 플라크를 계수함으로써 HeLa 세포 상청액 중 바이러스의 역가 및 중화 항체의 차단 능력을 측정하였다.
- [0213] 또 다른 실험에서, HCT116 또는 MC38 세포주를 96-웰 플레이트에 시딩하고, 90% 전면생장물까지 성장시켰다. 이어서, 세포를, 예를 들어 본원에 제공된 서열을 포함하는, 본원에 제공된 바이러스 벡터로부터 생성된 바이러스 1 MOI로 감염시켰다. 24시간 간격으로 매일, 세포 생존율을 프로메가로부터의 셀타이터 96 수정 비-방사성 세포 증식 키트로 시험하였다. 모든 웰로부터 블랭크 값 평균을 제거하고, 비감염된 대조군의 평균 값을 계산한 다음, 각각의 감염된 웰의 상대 값 (A490/비감염된 웰의 평균)을 계산함으로써 상대 생존율을 계산하였다.
- [0214] 실시예 5: 마우스에서 바이러스 벡터의 종양용해 잠재력의 시험
- [0215] 본 연구의 목적은 다른 벡터, 예컨대 대조군 벡터와 비교하여 암의 무인 마우스 모델에서 제공된 바이러스 벡터의 효과를 조사하는 것이다.
- [0216] 한 실험에서, 비-복제 렌티바이러스를 생산하는 바이러스 벡터를 비히클 (완충 염수) 대조군, 및 렌티바이러스 벡터를 생성하지 않는 또 다른 변형된 백시니아 바이러스와 비교하였다. 2종의 바이러스 중 1종 (1×10^7 PFU) 또는 염수 대조군의 단일 용량을 투여하여, 사전-확립된 RENCA 종양을 피하로 이식한 BALB/c 마우스를 치료하였다. 종양 부피를 캘리퍼 측정에 의해 모니터링하였다.
- [0217] 또 다른 실험에서, 상이한 마우스 종양 모델인 피하 B16 종양을 보유하는 C57/BL6 마우스를 사용하여 레트로-Vac 바이러스의 효과를 시험하였다. 종양 이식 96시간 후에 어느 하나의 바이러스의 단일 정맥내 주사를 마우스에 제공한 후 (1×10^8 PFU/마우스, 군 당 $n = 5$ /시점), 주사 1일 또는 2일 후에 마우스를 희생시켰다. 종양을 수집하여 qPCR에 의한 종양 그램당 바이러스 게놈의 수를 정량화하였다.
- [0218] 한 실험에서, 레트로-Vac 벡터를 동소 (유방 지방 패드) 4T1 종양을 피하 보유하는 마우스에서 시험하였다. 각각의 마우스를 1×10^8 PFU의 용량으로 레트로-Vac 벡터의 단일 주사로 치료하였다. 종양 내의 바이러스의 수를 주사 후 3일 동안 매일 생물발광 영상화 및 생체내 루시페라제 활성의 측정에 의해 정량화하였다. 바이러스의 치료 효과를 또한 검사하였다. 종양 부피를 마우스 생존 백분율과 함께 모니터링하였다.
- [0219] 또 다른 실험에서, 동일한 바이러스를 상이한 종양 모델인 B16 종양을 피하 보유하는 C57/BL6 마우스에서 시험하였다.
- [0220] 또 다른 실험에서, 시험관내 상이한 암 세포주에서 비-복제 렌티바이러스를 포함하는 바이러스에 대한 바이러스 복제 능력을 플라크 검정으로 검사하였다. 바이러스를 세포주에 첨가한 후 24시간마다 플라크-형성을 정량화하였다. 생체내 증진된 효과가 검출될 수 있는지 여부를 결정하기 위해 결과를 모니터링할 것이다.
- [0221] CXCR4 발현에 의해 부여되는 증진된 치료 효과의 기초가 되는 메커니즘을 이해하기 시작하기 위한 노력으로, B-세포가 고갈된 트랜스제닉 마우스 (본원에서 JH로 지칭됨)를 사용하여 실험을 수행하였다. 상기 기재된 바와 같은 바이러스를 B-세포를 갖는 Balb/C 마우스 및 B-세포가 없는 JH 마우스에 투여하였고, 이는 둘 다 사전-확립된 4T1 종양을 피하 이식하였다. 생물발광 영상화 방사휘도를 사용하여 레트로-Vac 바이러스가 종양에서 증가된 축적을 나타내는지 여부를 결정하였다. 4T1 종양을 피하 보유하는 BALB/c 마우스에서 종양 내로의 B 세포의 진입이 존재하지만, 다른 기관, 예컨대 비장 또는 림프절 (LN)은 존재하지 않는지 여부를 결정하기 위해 유동 세포측정법 실험을 또한 수행하였다.
- [0222] 또 다른 실험에서, 4T1 종양을 피하 이식한 마우스로부터 T 세포를 수집하고, 후속적으로 상기 기재된 바와 같이 처리하고, 상이한 면역원에 반응하여 그의 인터페론- γ (IFN γ) 방출을 시험하는 ELISpot 검정에 의해 그의 면역 활성을 검사하였다. 바이러스 주사 14일 후에 시험된 T 세포를 비장으로부터 회수하였다.
- [0223] 한 실험에서, RENCA 종양을 피하 보유하는 BALB/c 마우스를 레트로-Vac의 단일 정맥내 주사 (1×10^7 PFU)로 치

료하였다. 종양을 24시간 후에 수거하고, 조직 밀리그램당 바이러스 계놈의 수를 qPCR에 의해 정량화하였다.

[0224] 또 다른 실험에서, RENCA 종양을 피하 보유하는 BALB/c 마우스를 제1일 및 제4일에 동일한 4종의 변형된 바이러스 중 1종의 정맥내 주사 (1×10^7 PFU)에 의해 치료하고, 종양 부피를 상기 기재된 바와 같이 모니터링하였다.

[0225] 또 다른 실험에서, 렌티바이러스 발현을 상기 기재된 바와 같이 바이러스 주사 후 14일 동안 종양 샘플에서 검정하였다. PD1 체크포인트 억제제의 장기 발현이 이 시스템을 사용하여 조정될 것으로 예상된다.

[0226] 실시예 6: 감마레트로바이러스 성분을 갖는 레트로-Vac

[0227] 패키징 및 전달 구축물의 렌티바이러스 성분이 감마 레트로바이러스 (예를 들어, 몰로니 뮤린 백혈병 바이러스 (MMLV))의 것으로 대체된 본 개시내용의 예시적인 레트로-Vac를 설계하였다. 렌티바이러스 시스템에 비해, MMLV와 같은 감마레트로바이러스는 활발하게 분열하는 세포에만 선택적 감염 및 통합을 갖는다. 따라서, 이러한 접근법은 감염을 활발하게 분열하는 신생물성 세포로만 제한함으로써 레트로바이러스 표적화의 안전성 프로파일 및 특이성을 증가시킬 것으로 예상될 수 있다.

[0228] 실시예 7: T7 폴리머라제 발현 시스템을 사용한 레트로-Vac

[0229] 폭스바이러스 시스템에서, 초기 유전자 전사는 낮은 카피, 더 짧은 수명, 및 덜 안정한 바이러스 mRNA를 생산할 수 있는 반면에, 중간 및 후기 유전자 전사는 가장 풍부하고, 높은 카피, 및 안정한 바이러스 mRNA를 생산할 수 있다. 초기 유전자로부터의 mRNA는 깨끗한 전사 개시 부위 (TSS)를 갖고, 특정 바이러스 종결 부위에서 종결된다. 그러나, 중간체 및 후기 유전자는 5 폴리(A) 캡을 포함하도록 변형되고, 조절되지 않고 매우 가변적인 종결을 가질 수 있다. 따라서, 렌티바이러스 전달 구축물로부터 레트로바이러스 gRNA로서 적합한 RNA를 크래프팅하기 위해서는, 정확한 TSS를 고려하여 단지 초기 유전자 전사에만 통상적으로 의존할 수 있고, 종결은 레트로바이러스 RNA 패키징에 필수적이다. 이는 전달 구축물의 전사를 낮은 카피, 낮은 안정성 시스템으로 제한한다. 이들 제한을 피하기 위해, 백시니아 바이러스를 T7 박테리오파지로부터의 DNA-의존성 RNA 폴리머라제에 기초한 발현 시스템으로 생성하였다. 이러한 버전의 레트로-Vac 시스템은 또한, 렌티바이러스 전달 구축물의 상류 18 bp 프로모터와 높은 특이성으로 결합하는 T7 폴리머라제 (서열식별번호: 8은 T7 RNA 폴리머라제 유전자의 서열을 제공함)를 발현할 수 있다. 전사는 고도로 효율적인 종결 부위에서 중단될 때까지 계속될 수 있다. 이 시스템은 초기-단독 VV 전사에 비해 훨씬 더 높은 RNA 카피를 생성하고, 또한 RNA 말단의 보다 큰 제어를 가능하게 할 수 있다. 전달 구축물의 전사는 렌티바이러스 생산에서 속도-제한 단계일 수 있기 때문에, 레트로-Vac에 대한 이러한 T7 폴리머라제 시스템의 첨가는 렌티바이러스 역가를 유의하게 증가시키는 것으로 고려된다. 이러한 구축물의 예는 도 8에 제공된다. T7 RNA 폴리머라제 함유 구축물에 대한 예시적인 서열은 서열식별번호: 7로서 제공된다.

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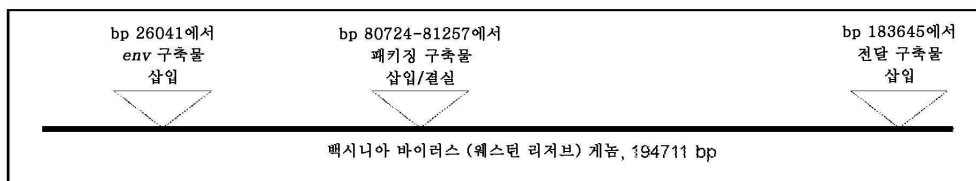
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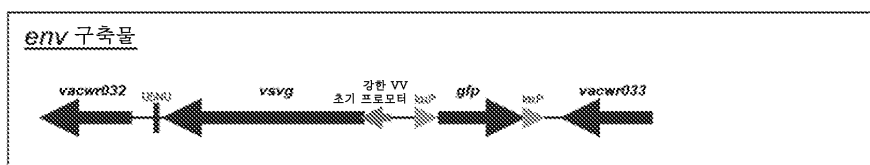
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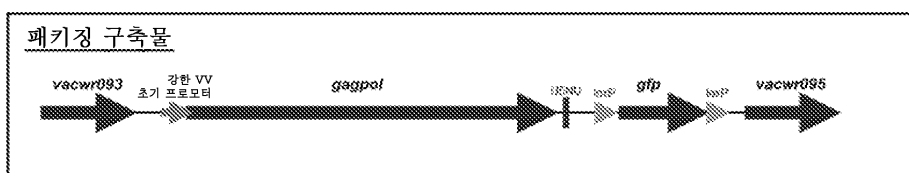
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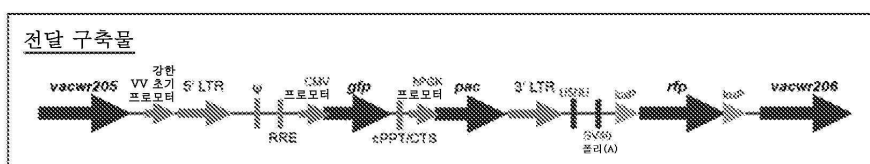
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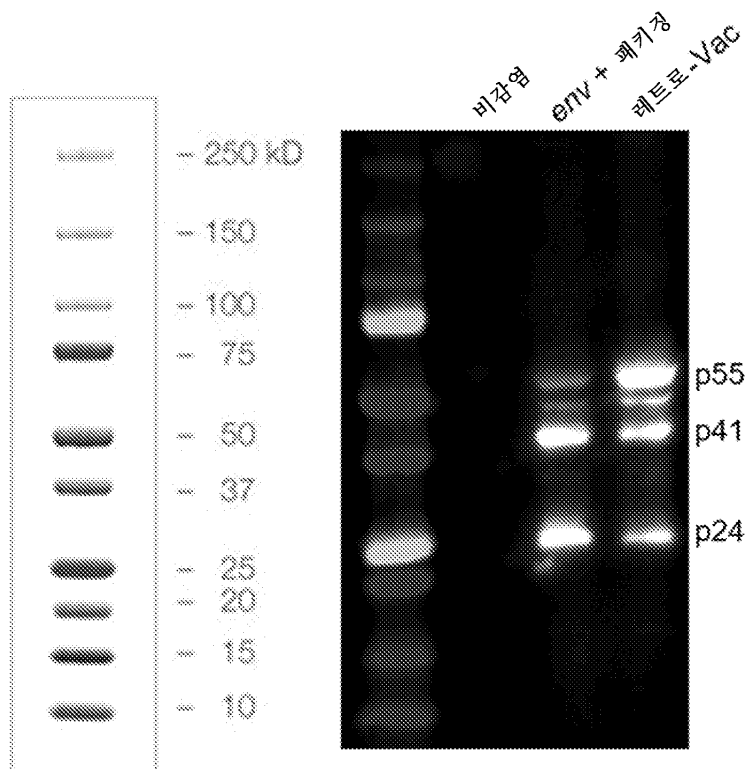
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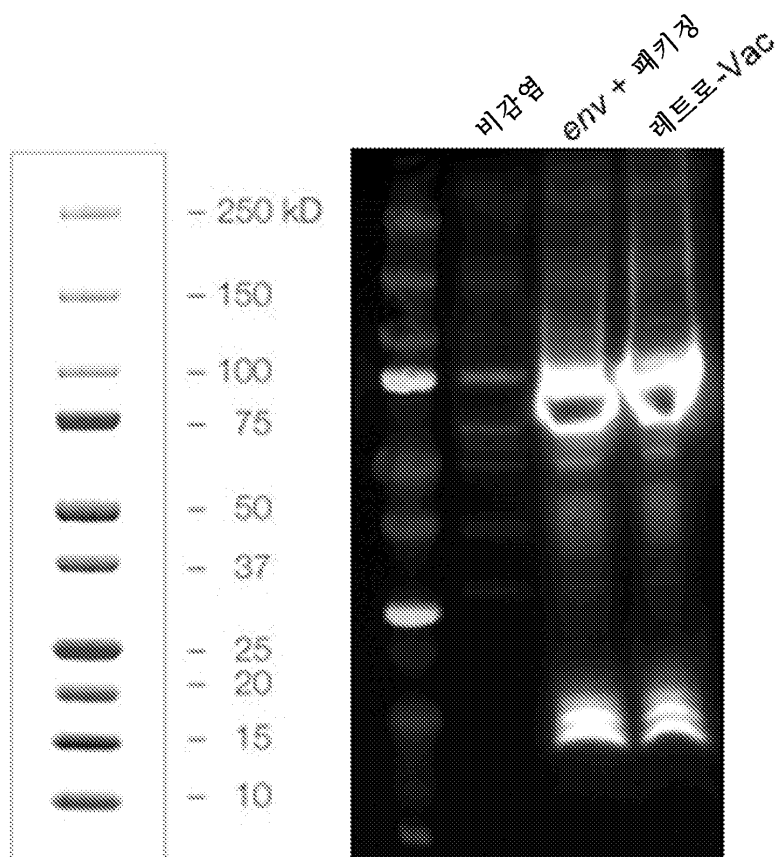
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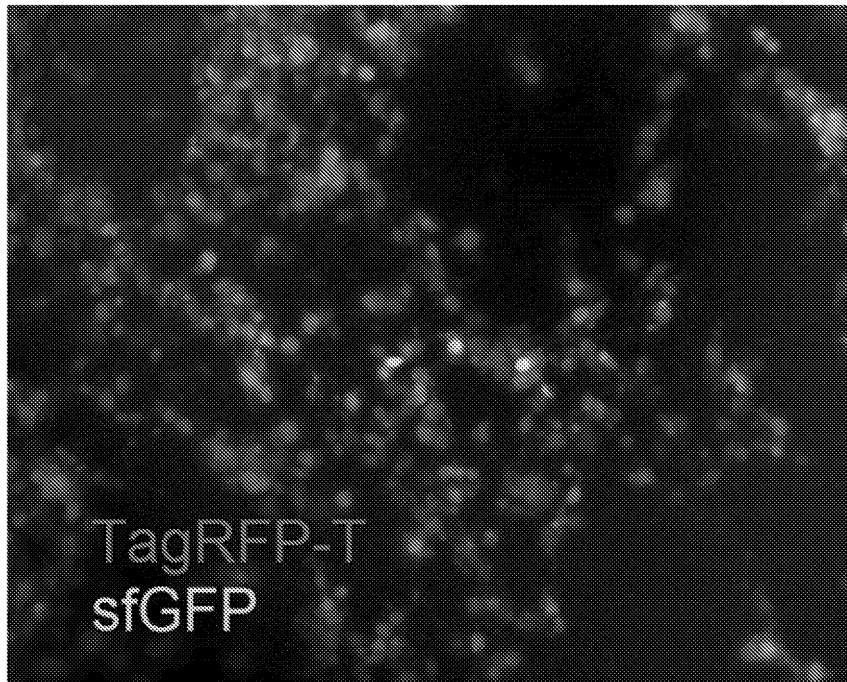
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도면6



도면7



도면8

T7 폴리머라제 구축물



서열 목록

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<141> 2020-10-16

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catttttttc tagacactaa ataaaattag taaaattaaa ttaattataa aattatatat 194640

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<210> 2

<211> 4416

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 2

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tattcttgac tatatcgaga tcttttgtat aggagtcaga cttgtattca acatgctttt 120

ctataatcat tttagctatt tcggcatcat ccaatagtag atttccaga ttagcagaat 180

agatattaat gtcgtatttg aacagagcct gtaacatctc aatgtcttta ttatctatag 240

ccaatttaat gtccggaatg aagagaaggg aattattggg gtttgtcgac gtcatatagt 300

cgagcaagag aatcatcata tccacgtgtc cattttttat agtgatgtga atacaactaa 360

ggagaatagc cagatcaaaa gtagatggta tctctgaaag aaagtaggaa acaatactta 420

catcattaag catgacggca tgataaaatg aagttttcca tccagttttc ccatagaaca 480

tcagtctcca atttttctta acaaacagtt ttaccgtttg catgttacca ctatcaaccg 540

cataatacaa tgcggtgttt cccttgtcat caaattgtga atcatccagt ccactgaata 600

gcaaaatctt tactattttg gtatcttcca atgtggctgc ctgatgtaat ggaaattcat 660

tctctagaag atttttcaat gtcaccagct tcaacaacgt acatactaga cgcacgttat 720

tatcagctat tgataatac aaggcactat gtccatggac atccgcctta aatgcatctt 780

tgctagagag gtctgaaacg agacgctaat tagtgtatat ttttcatctt ttataattt 840

tgtcatattg caccagaatt aataatatct ctaatagatc tgattagtag atacatggct 900

atcgcataaa aattgcataa aaattttact ttccaagtcg gttcatctct atgtctgtat 960

aaatctgtct tttcttgggtg tgctttaatt taatgcaaag atggatacca actcggagaa 1020

ccaagaatag tccaatgatt aaccctatga taaagaagaa agaggcaata gagcttttcc 1080

aactactgaa ccaaccttct acaagctcga ttggattttt ggatagccca gtatcaccaa 1140

agaataaact ctcatcatca ggaagtgtcg aagcagcgtc ttgaatgtga ggatgttcga 1200

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gaaatttgaa ggcgataccc tggtaaaccg cattgagctg aaaggcattg actttaaaga	3000
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caccgccgat aaacaaaaaa atggcattaa agcgaatfff aaaattcgcc acaacgtgga 3120

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tgttctgctg ccagacaatc actatctgag cagcaaaagc gttctgtcta aagatccgaa 3240

cgagaaacgc gatcatatgg ttctgctgga gtccgtaacc gcagcgggca tcacgcatgg 3300

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cattatagc agttatgcta gcacgatgct cttagaataa caacatatat acatttaata 3420

aaaaataat ttattaagaa aattcagatt tcacgtaccc atcaatataa ataaaataat 3480

gattccttac accgtaccca tattaaggag attccacctt acccataaac aatataaatc 3540

cagtaatatc atgtctgatg atgaacacaa atgggtgtatt aaattccagt ttttcaggag 3600

atgatctcgc cgtagctacc ataatagtag atgcctctgc tacagttcct tgttcgtcga 3660

catctatctt tgcattctga aacattttat aaatatataa tgggtcccta gtcatatgtt 3720

taaacgacgc attatctgga ttaaacatac taggagccat catttcggct atcgacttaa 3780

tatccctctt attttcgata gaaaatttag ggagttaaag attgtacact ttattcccta 3840

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catattcttc gtcacgatt gtgattgtat ttctttgcaa tttagtaact acgttcatca 4020

tgggaaccgt ttctgtaccg tacttattag taaaactagc attgcgtgtt ttagtgatat 4080

caaacggata ttgcatata cttttaaaat atatagtatt aatgattgcc catagagtat 4140

tattgtcgag catattagaa tctactacat tagacatacc ggatctacgt tctactatag 4200

aattaatttt attaaccgca tctctgtctaa agtttaactt atataggccg aatctatgat 4260

attgttgata atacgacggt ttaatgcaca cagtattatc tacgaaactt tgataagtta 4320

gatcagtgtg cgtatattta gatgttttca gcttagctaa tctgatatt aattctgtaa 4380

atgctggacc cagatctctt ttctcaaat ccatag 4416

<210> 3

<211> 1536

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 3

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tatgataaag aagaaagagg caatagagct ttccaacta ctgaaccaac cttctacaag 180
ctcgattgga tttttggata gcccagtatc accaaagaat aaactctcat catcaggaag 240

ttgcgaagca gcgtcttgaa tgtgaggatg ttcgaacacc tgagcctttg agctaagatg 300
aagatcggag tccaacatac catgtccaat catgtataaa ggaaacttat atcctgaact 360
ggtcctcaga actccattgg gtccaatttc cacgtcttca tatggtgccc agtcaccca 420
cagttccctt tctgtggtag ttccactgat cattccgacc attcttgaga ggattggagc 480
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gaaagcagga ccggttcttg ggttttttagg agcaagatag ctgagatcca ctggagagat 600
tggaagaccc gctctgattt tgctccaggt ttcttggcag agggaataat ccaagatcct 660

ctcaacgtcc tgaattagac ttacatccac tgaggtctga gatggagcag agatacttga 720
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ccagacacct gatgggagtc tgactccca atgcttgacag tattgcattt tgcaggcctt 840
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gtaattgctg cattttccgt tgatgaactg tgaatcaacc cattctcctg tgtattcatc 1080

aaccagcaca tggtagaggag tcacctggac aatcactgct tcggcatccg tcacagtgc 1140
atatccacaa ctttagaggag ggaagcctgg attcagccaa gttccttggt tcgtttgttc 1200
aatgctttcc ttgcattggt ctacagatgg agtgaaggat cggatggact gtgttatata 1260
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taagtcatta tgccaattta aatctgagct tgacgggcaa taatggtaat tagaaggaac 1440
atctttccag tttccttttt ggttgtgtgg gaaaactatg gtgaacttgc aattcacccc 1500

aatgaataag aaggctaagt acaaaaggca cttcat 1536

<210> 4

<211> 4416

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 4

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tattcttgac tatatcgaga tcttttgtat aggagtcaga cttgtattca acatgctttt	120
ctataatcat ttiagctatt tgggcatcat ccaatagtag attttccaga ttagcagaat	180
agatattaat gtcgtatttg aacagagcct gtaacatctc aatgtcttta ttatctatag	240
ccaatttaat gtccggaatg aagagaaggg aattattggg gtttgcgac gtcatatagt	300
cgagcaagag aatcatcata tccacgtgtc catTTTTtTat agtgatgtga atacaactaa	360
ggagaatagc cagatcaaaa gtagatggta tctctgaaag aaagtaggaa acaatactta	420
catcattaag catgacggca tgataaaatg aagttttcca tccagttttc ccatagaaca	480
tcagtctcca atttttctta acaaacagtt ttaccgtttg catgttacca ctatcaaccg	540
cataatacaa tgcggtgttt cccctgtcat caaattgtga atcatccagt ccaactgaata	600
gcaaaatctt tactattttg gtatcttcca atgtggctgc ctgatgtaat ggaaattcat	660
tctctagaag atttttcaat gtcccagcgt tcaacaacgt acatactaga cgcacgttat	720
tatcagctat tgcataatac aaggcactat gtccatggac atccgcctta aatgcatctt	780
tgctagagag gtctgaaacg agacgctaat tagtgtatat ttttcatTTt ttataattt	840
tgatcatattg caccagaatt aataatatct ctaatagatc tgattagtag atacatggct	900
atgcataaa aattgcataa aaattttact ttccaagtgc gttcatctct atgtctgtat	960
aaatctgtct tttcttggtg tgctttaatt taatgcaaag atggatacca actcggagaa	1020
ccaagaatag tccaatgatt aacctatga taaagaagaa agaggcaata gagcttttcc	1080
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agaataaact ctcatcatca ggaagtgtcg aagcagcgtc ttgaatgtga ggatgttcga	1200
acacctgagc ctttgagcta agatgaagat cggagtcgaa cataccatgt ccaatcatgt	1260
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cgaccattct tgagaggatt ggagcagcaa tatcgactct gatgtatctg gtctcaaagt	1440
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accctgtgcc ctcccttccc agggatgata gctctccgtc ctctgagaag aaggtgatgt	1860
ccatggaaat gaggttagaa tcacatagcc ctttgacctt atagtcagaa tgccaggttg	1920
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caaccattc tctgtgtat tcatcaacca gcacatgggtg aggagtcacc tggacaatca	2040
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gattccttac accgtaccca tattaaggag attccacctt acccataaac aatataaatc	3540

cagtaatatc atgtctgatg atgaacacaa atgggtgtatt aaattccagt ttttcaggag 3600

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catattcttc gtcacgatt gtgattgtat ttccttgcaa tttagtaact acgttcatca 4020

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caaacggata ttgcatata cctttaaaat atatagtatt aatgattgcc catagagtat 4140

tattgtcgag catattagaa tctactacat tagacatacc ggatctacgt tctactatag 4200

aattaatatt attaacgca tctcgtctaa agtttaactt atataggccg aatctatgat 4260

attgttgata atacgacggt ttaatgcaca cagtattatc tacgaaactt tgataagtta 4320

gatcagtgtg cgtatattta gatgttttca gcttagctaa tcttgatatt aattctgtaa 4380

atgctggacc cagatctctt tttctcaaat ccatag 4416

<210> 5

<211> 4307

<212> DNA

<213> Artificial Sequence

<220><223> Description of Artificial Sequence: Synthetic
polynucleotide

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ctagaacgat tcgcagttaa tcttggcctg ttagaaacat cagaaggctg tagacaaata 180

ctgggacagc tacaaccatc ccttcagaca ggatcagaag aacttagatc attatataat 240

acagtagcaa cctctatttg tgtgcatcaa aggatagaga taaaagacac caaggaagct 300

ttagacaaga tagaggaaga gcaaaacaaa agtaagaaaa aagcacagca agcagcagct 360

gacacaggac acagcaatca ggtcagccaa aattacccta tagtcagaa catccagggg 420

caaatggtac atcaggccat atcacctaga actttaaatg catgggtaaa agtagtagaa 480

gagaaggctt tcagcccaga agtgataccc atgttttcag cattatcaga aggagccacc 540

ccacaagatt taaacaccat gctaaacaca gtggggggac atcaagcagc catgcaaattg	600
ttaaaagaga ccatcaatga ggaagctgca gaattgggata gattgcatcc agtgcattgca	660
gggcctattg caccaggcca gatgagagaa ccaaggggaa gtgacatagc aggaactact	720
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tataaaactc taagagccga gcaagcttca caagaggtaa aaaattggat gacagaaacc	960
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caggaatgga tgcccaaaa gttaacaat ggccattgac agaagaaaaa ataaaagcat	1860
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atccatacaa tactccagta ttgtccataa agaaaaaaga cagtactaaa tggagaaaat	1980
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