(19) 대한민국특허청(KR)
(12) 등록특허공보(B1)

(45) 공고일자 2020년10월07일
(11) 등록번호 10-2162111
(24) 등록일자 2020년09월25일

(51) 국제특허분류(Int. Cl.)
C12N 15/38 (2006.01) *A61K 39/245* (2006.01)
C07K 14/03 (2006.01) *C12N 15/86* (2006.01)
(21) 출원번호 10-2013-7011527
(22) 출원일자(국제) 2011년10월11일
심사청구일자 2016년10월11일
(85) 번역문제출일자 2013년05월03일
(65) 공개번호 10-2013-0117781
(43) 공개일자 2013년10월28일
(86) 국제출원번호 PCT/US2011/055834
(87) 국제공개번호 WO 2012/051211
국제공개일자 2012년04월19일
(30) 우선권주장
61/391,960 2010년10월11일 미국(US)
(56) 선행기술조사문헌
KR1020080052509 A
KR1020090046899 A

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루미스 레베카
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전체 청구항 수 : 총 6 항 심사관 : 안규정

(54) 발명의 명칭 **항원 전달 플랫폼**

(57) 요 약

본 개시 내용은 세포에 헤르페스바이러스 단백질, 특히 생체 내에서 복합체를 형성하는 단백질의 전달에 대한 플랫폼을 제공한다. 일부 구체예에서, 그것들이 형성하는 이 단백질 및 복합체는 효능 있는 중화 항체를 유도한다. 따라서, 개시된 플랫폼을 사용하는 헤르페스바이러스 단백질의 제공은 백신 개발에 유용한 광범위하고 효능 있는 면역 반응의 발생을 허용한다.

(72) 발명자

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메이슨 피터

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명 세 서

청구범위

청구항 1

a.
MRPGLPSYLIILAVCLFSHLLSSRYGAEAVSEPLDKAFHLLLNTYGRPIRFLRENTTQCTYNSSLRNSTVVRENAISFNFFQSYNQYYVFHMPRCLFAGPLA
EQFLNQVDLTETLERYQQRLNTYALVSKDLASYRSFSQQLKAQDSLGEQPTTVPPPIDLSIPHVWMPPQTTPHGWTESHTTSGLHRPHFNQTCILFDGHDLL
FSTVTPCLHQGFYLIDELRYVKITLTEDFFVVTVSIDDDTPMLLIFGHLPRVLFKAPYQRDNFILRQTEKHELLVLVKKDQLNRHSYLKDPDFLDAALDFNY
LDLSALLRNSFHRYAVDVLKSGRCQMLDRRTVEMAFAYALALFAAARQEEAGAQVSVPRALDRQAALLQIQEFMITCLSQTPPRTTLLLYPTAVDLAKRALW
TPNQITDITSLVRLVYILSKQNQQHLIPQWALRQIADFALKLHKTHLASFLSAFARQELYLMGSLVHSMLVHTTERREIFIVETGLCSLAELSHFTQLLAHP
HHEYLSDLYTPCSSSGRRDHSLERLTRLFPDATVPATVPAALSILSTMQPSTLETFPDLFCLPLGESFSALTVSEHVSYIVTNQYLIKGISYPVSTTVVGQS
LIITQTDSQTKCELTRNMHTTHSITVALNISLENCAFCQSALLEYDDTQGVINIMYMHDSDDVLFALDPYNEVVVSSPRTHYLMLLKNGTVLEVTDVVVDAT
DSRLLMMSVYALSAIIGIYLLYRMLKTC-- 또는
MRPGLPSYLIILAVCLFSHLLSSRYGAEAVSEPLDKAFHLLLNTYGRPIRFLRENTTQCTYNSSLRNSTVVRENAISFNFFQSYNQYYVFHMPRCLFAGPLA
EQFLNQVDLTETLERYQQRLNTYALVSKDLASYRSFSQQLKAQDSLGEQPTTVPPPIDLSIPHVWMPPQTTPHGWTESHTTSGLHRPHFNQTCILFDGHDLL
FSTVTPCLHQGFYLIDELRYVKITLTEDFFVVTVSIDDDTPMLLIFGHLPRVLFKAPYQRDNFILRQTEKHELLVLVKKDQLNRHSYLKDPDFLDAALDFNY
LDLSALLRNSFHRYAVDVLKSGRCQMLDRRTVEMAFAYALALFAAARQEEAGAQVSVPRALDRQAALLQIQEFMITCLSQTPPRTTLLLYPTAVDLAKRALW
TPNQITDITSLVRLVYILSKQNQQHLIPQWALRQIADFALKLHKTHLASFLSAFARQELYLMGSLVHSMLVHTTERREIFIVETGLCSLAELSHFTQLLAHP
HHEYLSDLYTPCSSSGRRDHSLERLTRLFPDATVPATVPAALSILSTMQPSTLETFPDLFCLPLGESFSALTVSEHVSYIVTNQYLIKGISYPVSTTVVGQS
LIITQTDSQTKCELTRNMHTTHSITVALNISLENCAFCQSALLEYDDTQGVINIMYMHDSDDVLFALDPYNEVVVSSPRTHYLMLLKNGTVLEVTDVVVDAT
D--의 서열로 구성되는 CMV gH 단백질을 암호화하는 첫 번째 뉴클레오티드 서열;

b.
MCRRPDCGFSFSPGPVILLWCCLLLPIVSSAAVSVAPTAAEKVPAECPELTRRCLLGEVFEGDKYESWLRPLVNVTGRDGPLSQLIRYRPVTPEAANSVLLD
EAFLDTLALLYNNPDQLRALLTLLSSDTAPRWMTVMRGYSECGDGSPAVYTCVDDLCRGYDLTRLSYGRSIFTEHVLGFELVPPSLFNVVVAIRNEATRTNR
AVRLPVSTAAAPEGITLFYGLYNAVKEFCLRHQLDPPLLRHLDKYYAGLPPELKQTRVNLPAHSRYGPQAVDAR--의 서열로 구성되는 CMV gL 단백질을 암호화하는 두 번째 뉴클레오티드 서열;

c.
MSPKDLTPFLTTLWLLLGHSRVPRVRAEECCEFINVNHPPERCYDFKMCNRFTVALRCPDGEVCYSPEKTAEIRGIVTTMTHSLTRQVVHNKLTSCNYNPLY
LEADGRIRCGKVNDKAQYLLGAAGSVPYRWINLEYDKITRIVGLDQYLESVKKHKRLDVCRAKMGYMLQ--의 서열로 구성되는 CMV UL128 단백질을 암호화하는 세 번째 뉴클레오티드 서열;

d.
MLRLLLRHHFHCLLLCAVWATPCLASPWSTLTANQNPSPPWSKLTYSKPHDAATFYCPFLYPSPPRSPLQFSGFQRVSTGPECRNETLYLLYNREGQTLVER
SSTWVKKVIWYLSGRNQTILQRMPRTASKPSDGNVQISVEDAKIFGAHMVPKQTKLLRFVVNDGTRYQMCVMKLESWAHVFRDYSVSFQVRLTFTEANNQTY
TFCTHPNLIV--의 서열로 구성되는 CMV UL130 단백질을 암호화하는 네 번째 뉴클레오티드 서열; 및

e.
MRLCRVWLSVCLCAVVLGQCQRETAEKNDYYRVPHYWDACSRALPDQTRYKYVEQLVDLTLNYHYDASHGLDNFDVLKRINVTEVSLLISDFRRQNRRGGTN
KRTTFNAAGSLAPHARSLEFSVRLFAN--의 서열로 구성되는 CMV UL131 단백질을 암호화하는 다섯 번째 뉴클레오티드 서열

을 포함하는 폴리뉴클레오티드를 포함하며,

첫 번째, 두 번째, 세 번째, 네 번째 및 다섯 번째 뉴클레오티드 서열들은 자가 복제 RNA 분자가 세포 내로 도입될 때, CMV gH, CMV gL, CMV UL128, CMV UL130 및 CMV UL131 단백질들이 발현되고 펜타머 복합체를 형성하도록 프로모터, 바이러스 2A 부위 및 IRES로부터 선택된 조절 요소와 각각 작동 가능하게 연결되는 자가 복제 RNA 분자.

청구항 2

제 1항에 있어서, 자가 복제 RNA 분자는 알파바이러스 레플리콘인 것을 특징으로 하는 자가 복제 RNA 분자.

청구항 3

제 1항에 있어서, 자가 복제 RNA 분자는

ATAGGCGGCGCATGAGAGAAGCCCAGACCAATTACCTACCCAAAATGGAGAAAGTTCACGTTGACATCGAGGAAGACAGCCCATTCCTCAGAGCTTTGCAGC
GGAGCTTCCCGCAGTTTGAGGTAGAAGCCAAGCAGGTCACTGATAATGACCATGCTAATGCCAGAGCGTTTTCGCATCTGGCTTCAAAACTGATCGAAACGG
AGGTGGACCCATCCGACACGATCCTTGACATTGGAAGTGCGCCCGCCCGCAGAATGTATTCTAAGCACAAGTATCATTGTATCTGTCCGATGAGATGTGCGG
AAGATCCGGACAGATTGTATAAGTATGCAACTAAGCTGAAGAAAAACTGTAAGGAAATAACTGATAAGGAATTGGACAAGAAAATGAAGGAGCTCGCCGCCG
TCATGAGCGACCCTGACCTGGAAACTGAGACTATGTGCCTCCACGACGACGAGTCGTGTCGCTACGAAGGGCAAGTCGCTGTTTACCAGGATGTATACGCGG
TTGACGGACCGACAAGTCTCTATCACCAAGCCAATAAGGGAGTTAGAGTCGCCTACTGGATAGGCTTTGACACCACCCCTTTTATGTTTAAGAACTTGGCTG
GAGCATATCCATCATACTCTACCAACTGGGCCGACGAAACCGTGTTAACGGCTCGTAACATAGGCCTATGCAGCTCTGACGTTATGGAGCGGTCACGTAGAG
GGATGTCCATTCTTAGAAAGAAGTATTTGAAACCATCCAACAATGTTCTATTCTCTGTTGGCTCGACCATCTACCACGAGAAGAGGGACTTACTGAGGAGCT
GGCACCTGCCGTCTGTATTTCACTTACGTGGCAAGCAAAATTACACATGTCGGTGTGAGACTATAGTTAGTTGCGACGGGTACGTCGTTAAAAGAATAGCTA
TCAGTCCAGGCCTGTATGGGAAGCCTTCAGGCTATGCTGCTACGATGCACCGCGAGGGATTCTTGTGCTGCAAAGTGACAGACACATTGAACGGGGAGAGGG
TCTCTTTTCCCGTGTGCACGTATGTGCCAGCTACATTGTGTGACCAAATGACTGGCATACTGGCAACAGATGTCAGTGCGGACGACGCGCAAAAACTGCTGG
TTGGGCTCAACCAGCGTATAGTCGTCAACGGTCGCACCCAGAGAAACACCAATACCATGAAAAATTACCTTTTGCCCGTAGTGGCCCAGGCATTTGCTAGGT
GGGCAAAGGAATATAAGGAAGATCAAGAAGATGAAAGGCCACTAGGACTACGAGATAGACAGTTAGTCATGGGGTGTTGTTGGGCTTTTAGAAGGCACAAGA
TAACATCTATTTATAAGCGCCCGGATACCCAAACCATCATCAAAGTGAACAGCGATTTCCACTCATTCGTGCTGCCCAGGATAGGCAGTAACACATTGGAGA
TCGGGCTGAGAACAAGAATCAGGAAAATGTTAGAGGAGCACAAGGAGCCGTCACCTCTCATTACCGCCGAGGACGTACAAGAAGCTAAGTGCGCAGCCGATG
AGGCTAAGGAGGTGCGTGAAGCCGAGGAGTTGCGCGCAGCTCTACCACCTTTGGCAGCTGATGTTGAGGAGCCCACTCTGGAAGCCGATGTAGACTTGATGT
TACAAGAGGCTGGGGCCGGCTCAGTGGAGACACCTCGTGGCTTGATAAAGGTTACCAGCTACGATGGCGAGGACAAGATCGGCTCTTACGCTGTGCTTTCTC
CGCAGGCTGTACTCAAGAGTGAAAAATTATCTTGCATCCACCCTCTCGCTGAACAAGTCATAGTGATAACACACTCTGGCCGAAAAGGGCGTTATGCCGTGG
AACCATACCATGGTAAAGTAGTGGTGCCAGAGGGACATGCAATACCCGTCCAGGACTTTCAAGCTCTGAGTGAAAGTGCCACCATTGTGTACAACGAACGTG
AGTTCGTAAACAGGTACCTGCACCATATTGCCACACATGGAGGAGCGCTGAACACTGATGAAGAATATTACAAAACTGTCAAGCCCAGCGAGCACGACGGCG
AATACCTGTACGACATCGACAGGAAACAGTGCGTCAAGAAAGAACTAGTCACTGGGCTAGGGCTCACAGGCGAGCTGGTGGATCCTCCCTTCCATGAATTCG
CCTACGAGAGTCTGAGAACACGACCAGCCGCTCCTTACCAAGTACCAACCATAGGGGTGTATGGCGTGCCAGGATCAGGCAAGTCTGGCATCATTAAAAGCG
CAGTCACCAAAAAAGATCTAGTGGTGAGCGCCAAGAAAGAAAACTGTGCAGAAATTATAAGGGACGTCAAGAAAATGAAAGGGCTGGACGTCAATGCCAGAA
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CCATTATAAGACCTAAAAAGGCAGTGCTCTGCGGGGATCCCAAACAGTGCGGTTTTTTTAACATGATGTGCCTGAAAGTGCATTTTAACCACGAGATTTGCA
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AAGAGACTAAGATTGTGATTGACACTACCGGCAGTACCAAACCTAAGCAGGACGATCTCATTCTCACTTGTTTCAGAGGGTGGGTGAAGCAGTTGCAAATAG
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CACCCACCTCAGAACATGTGAACGTCCTACTGACCCGCACGGAGGACCGCATCGTGTGGAAAACACTAGCCGGCGACCCATGGATAAAAACACTGACTGCCA
AGTACCCTGGGAATTTCACTGCCACGATAGAGGAGTGGCAAGCAGAGCATGATGCCATCATGAGGCACATCTTGGAGAGACCGGACCCTACCGACGTCTTCC
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CGTTATCCATTAGGAATAATCACTGGGATAACTCCCCGTCGCCTAACATGTACGGGCTGAATAAAGAAGTGGTCCGTCAGCTCTCTCGCAGGTACCCACAAC
TGCCTCGGGCAGTTGCCACTGGAAGAGTCTATGACATGAACACTGGTACACTGCGCAATTATGATCCGCGCATAAACCTAGTACCTGTAAACAGAAGACTGC
CTCATGCTTTAGTCCTCCACCATAATGAACACCCACAGAGTGACTTTTCTTCATTCGTCAGCAAATTGAAGGGCAGAACTGTCCTGGTGGTCGGGGAAAAGT
TGTCCGTCCCAGGCAAAATGGTTGACTGGTTGTCAGACCGGCCTGAGGCTACCTTCAGAGCTCGGCTGGATTTAGGCATCCCAGGTGATGTGCCCAAATATG
ACATAATATTTGTTAATGTGAGGACCCCATATAAATACCATCACTATCAGCAGTGTGAAGACCATGCCATTAAGCTTAGCATGTTGACCAAGAAAGCTTGTC
TGCATCTGAATCCCGGCGGAACCTGTGTCAGCATAGGTTATGGTTACGCTGACAGGGCCAGCGAAAGCATCATTGGTGCTATAGCGCGGCAGTTCAAGTTTT
CCCGGGTATGCAAACCGAAATCCTCACTTGAAGAGACGGAAGTTCTGTTTGTATTCATTGGGTACGATCGCAAGGCCCGTACGCACAATCCTTACAAGCTTT
CATCAACCTTGACCAACATTTATACAGGTTCCAGACTCCACGAAGCCGGATGTGCACCCTCATATCATGTGGTGCGAGGGGATATTGCCACGGCCACCGAAG
GAGTGATTATAAATGCTGCTAACAGCAAAGGACAACCTGGCGGAGGGGTGTGCGGAGCGCTGTATAAGAAATTCCCGGAAAGCTTCGATTTACAGCCGATCG
AAGTAGGAAAAGCGCGACTGGTCAAAGGTGCAGCTAAACATATCATTCATGCCGTAGGACCAAACTTCAACAAAGTTTCGGAGGTTGAAGGTGACAAACAGT
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AGTCGGAAGCCTCCACACCACCTAGCACGCTGCCTTGCTTGTGCATCCATGCCATGACTCCAGAAAGAGTACAGCGCCTAAAAGCCTCACGTCCAGAACAAA

TTACTGTGTGCTCATCCTTTCCATTGCCGAAGTATAGAATCACTGGTGTGCAGAAGATCCAATGCTCCCAGCCTATATTGTTCTCACCGAAAGTGCCTGCGT
ATATTCATCCAAGGAAGTATCTCGTGGAAACACCACCGGTAGACGAGACTCCGGAGCCATCGGCAGAGAACCAATCCACAGAGGGGACACCTGAACAACCAC
CACTTATAACCGAGGATGAGACCAGGACTAGAACGCCTGAGCCGATCATCATCGAAGAGGAAGAAGAGGATAGCATAAGTTTGCTGTCAGATGGCCCGACCC
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CCTCCGACACCGGTCAAGGGCATTTACAACAAAAATCAGTAAGGCAAACGGTGCTATCCGAAGTGGTGTTGGAGAGGACCGAATTGGAGATTTCGTATGCCC
CGCGCCTCGACCAAGAAAAAGAAGAATTACTACGCAAGAAATTACAGTTAAATCCCACACCTGCTAACAGAAGCAGATACCAGTCCAGGAAGGTGGAGAACA
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TGTTTGATATGTCGGCTGAAGACTTTGACGCTATTATAGCCGAGCACTTCCAGCCTGGGGATTGTGTTCTGGAAACTGACATCGCGTCGTTTGATAAAAGTG
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CAATACATTTGCCCACTAAAACTAAATTTAAATTCGGAGCCATGATGAAATCTGGAATGTTCCTCACACTGTTTGTGAACACAGTCATTAACATTGTAATCG
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ACAGGTGCGCCACCTGGTTGAATATGGAAGTCAAGATTATAGATGCTGTGGTGGGCGAGAAAGCGCCTTATTTCTGTGGAGGGTTTATTTTGTGTGACTCCG
TGACCGGCACAGCGTGCCGTGTGGCAGACCCCCTAAAAAGGCTGTTTAAGCTTGGCAAACCTCTGGCAGCAGACGATGAACATGATGATGACAGGAGAAGGG
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GAGCGAGCCCCTGGACAAGGCTTTCCACCTGCTGCTGAACACCTACGGCAGACCCATCCGGTTTCTGCGGGAGAACACCACCCAGTGCACCTACAACAGCAG
CCTGCGGAACAGCACCGTCGTGAGAGAGAACGCCATCAGCTTCAACTTTTTCCAGAGCTACAACCAGTACTACGTGTTCCACATGCCCAGATGCCTGTTTGC
CGGCCCTCTGGCCGAGCAGTTCCTGAACCAGGTGGACCTGACCGAGACACTGGAAAGATACCAGCAGCGGCTGAATACCTACGCCCTGGTGTCCAAGGACCT
GGCCAGCTACCGGTCCTTTAGCCAGCAGCTCAAGGCTCAGGATAGCCTCGGCGAGCAGCCTACCACCGTGCCCCCTCCCATCGACCTGAGCATCCCCCACGT
GTGGATGCCTCCCCAGACCACCCCTCACGGCTGGACCGAGAGCCACACCACCTCCGGCCTGCACAGACCCCACTTCAACCAGACCTGCATCCTGTTCGACGG
CCACGACCTGCTGTTTAGCACCGTGACCCCCTGCCTGCACCAGGGCTTCTACCTGATCGACGAGCTGAGATACGTGAAGATCACCCTGACCGAGGATTTCTT
CGTGGTCACCGTGTCCATCGACGACGACACCCCCATGCTGCTGATCTTCGGCCACCTGCCCAGAGTGCTGTTCAAGGCCCCCTACCAGCGGGACAACTTCAT
CCTGCGGCAGACCGAGAAGCACGAGCTGCTGGTGCTGGTCAAGAAGGACCAGCTGAACCGGCACTCCTACCTGAAGGACCCCGACTTCCTGGACGCCGCCT
GGACTTCAACTACCTGGACCTGAGCGCCCTGCTGAGAAACAGCTTCCACAGATACGCCGTGGACGTGCTGAAGTCCGGACGGTGCCAGATGCTCGATCGGCG
GACCGTGGAGATGGCCTTCGCCTATGCCCTCGCCCTGTTCGCCGCTGCCAGACAGGAAGAGGCTGGCGCCCAGGTGTCAGTGCCCAGAGCCCTGGATAGACA
GGCCGCCCTGCTGCAGATCCAGGAATTCATGATCACCTGCCTGAGCCAGACCCCCCCTAGAACCACCCTGCTGCTGTACCCCACAGCCGTGGATCTGGCCAA
GAGGGCCCTGTGGACCCCCAACCAGATCACCGACATCACAAGCCTCGTGCGGCTCGTGTACATCCTGAGCAAGCAGAACCAGCAGCACCTGATCCCCCAGTG
GGCCCTGAGACAGATCGCCGACTTCGCCCTGAAGCTGCACAAGACCCATCTGGCCAGCTTTCTGAGCGCCTTCGCCAGGCAGGAACTGTACCTGATGGGCAG
CCTGGTCCACAGCATGCTGGTGCATACCACCGAGCGGCGGGAGATCTTCATCGTGGAGACAGGCCTGTGTAGCCTGGCCGAGCTGTCCCACTTTACCCAGCT
GCTGGCCCACCCTCACCACGAGTACCTGAGCGACCTGTACACCCCCTGCAGCAGCAGCGGCAGACGGGACCACAGCCTGGAACGGCTGACCAGACTGTTCCC
CGATGCCACCGTGCCTGCTACAGTGCCTGCCGCCCTGTCCATCCTGTCCACCATGCAGCCCAGCACCCTGGAAACCTTCCCCGACCTGTTCTGCCTGCCCCT
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ATAG; 및

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TGCGCCGGTTAAGGCTAAACTGAAAGGACAAGTTTTGGTGACTGCGCTCCTCCAAGCCAGTTACCTCGGTTCAAAGAGTTGGTAGCTCAGAGAACCTTCGAA
AAACCGCCCTGCAAGGCGGTTTTTTCGTTTTCAGAGCAAGAGATTACGCGCAGACCAAAACGATCTCAAGAAGATCATCTTATTAAGGGGTCTGACGCTCAG
TGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAA
AGTATATATGAGTAAACTTGGTCTGACAGTTATTAGAAAAATTCATCCAGCAGACGATAAAACGCAATACGCTGGCTATCCGGTGCCGCAATGCCATACAGC
ACCAGAAAACGATCCGCCCATTCGCCGCCCAGTTCTTCCGCAATATCACGGGTGGCCAGCGCAATATCCTGATAACGATCCGCCACGCCCAGACGGCCGCAA
TCAATAAAGCCGCTAAAACGGCCATTTTCCACCATAATGTTCGGCAGGCACGCATCACCATGGGTCACCACCAGATCTTCGCCATCCGGCATGCTCGCTTTC
AGACGCGCAAACAGCTCTGCCGGTGCCAGGCCCTGATGTTCTTCATCCAGATCATCCTGATCCACCAGGCCCGCTTCCATACGGGTACGCGCACGTTCAATA
CGATGTTTCGCCTGATGATCAAACGGACAGGTCGCCGGGTCCAGGGTATGCAGACGACGCATGGCATCCGCCATAATGCTCACTTTTTCTGCCGGCGCCAGA
TGGCTAGACAGCAGATCCTGACCCGGCACTTCGCCCAGCAGCAGCCAATCACGGCCCGCTTCGGTCACCACATCCAGCACCGCCGCACACGGAACACCGGTG
GTGGCCAGCCAGCTCAGACGCGCCGCTTCATCCTGCAGCTCGTTCAGCGCACCGCTCAGATCGGTTTTCACAAACAGCACCGGACGACCCTGCGCGCTCAGA
CGAAACACCGCCGCATCAGAGCAGCCAATGGTCTGCTGCGCCCAATCATAGCCAAACAGACGTTCCACCCACGCTGCCGGGCTACCCGCATGCAGGCCATCC
TGTTCAATCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAA
ATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTAAATTGTAAGCGTTAATATTTTGTTAAAATTCGCGTTAAATTTTTGTTAAATCAGCTCATTTT
TTAACCAATAGGCCGAAATCGGCAAAATCCCTTATAAATCAAAAGAATAGACCGAGATAGGGTTGAGTGGCCGCTACAGGGCGCTCCCATTCGCCATTCAGG
CTGCGCAACTGTTGGGAAGGGCGTTTCGGTGCGGGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAGTTGGGTAACGCC
AGGGTTTTCCCAGTCACACGCGTAATACGACTCACTATAG 으로 구성된 그룹으로부터 선택된 폴리뉴클레오티드 서열에 의해 암호화된 것을 특징으로 하는 자가 복제 RNA 분자.

청구항 4

제 1항 내지 제 3항 중 어느 한 항의 자가 복제 RNA 분자와, 리포솜, 폴리머 나노입자 또는 수중유 양이온성 나노에멀젼으로부터 선택된 전달 시스템을 포함하는 면역원성 조성물.

청구항 5

제 4항에 있어서, 전달 시스템은 수중유 양이온성 나노에멀젼인 것을 특징으로 하는 면역원성 조성물.

청구항 6

제 4항에 있어서, 전달 시스템은 리포솜인 것을 특징으로 하는 면역원성 조성물.

청구항 7

삭제

청구항 8

삭제

청구항 9

삭제

청구항 10

삭제

청구항 11

삭제

청구항 12

삭제

청구항 13

삭제

청구항 14

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청구항 15

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청구항 16

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청구항 46

삭제

발명의 설명

기 술 분 야

[0001] **관련 출원**

[0002] 이 출원은 2010년 10월 11일 출원된, 미국 가특허 출원 번호 61/391, 960의 이익을 주장하며, 이것의 전체 교시 내용은 본원에 참고로 포함된다.

배 경 기 술

[0003] **배경기술**

[0004] 헤르페스바이러스는 널리 퍼져있고 최악의 경우에, 주로 면역력이 약화된 개인 (예를 들어, 이식 수령체 및 HIV-감염된 개인)에서, 실질적인 발병률 및 사망률로 이어질 수 있는 사람에서 다양한 질환을 유발한다. 사람은 적어도 8 가지의 헤르페스바이러스에 의한 감염에 민감하다. 단순 헤르페스바이러스-1 (Herpes simplex virus-1; HSV-1, HHV-1), 단순 헤르페스바이러스-2 (Herpes simplex virus-2; HSV-2, HHV-2) 및 수두 대상 포진 바이러스 (Varicella zoster virus; VZV, HHV-3)는 알파-서브패밀리 바이러스이고, 시토메갈로바이러스 (cytomegalovirus; CMV, HHV-5) 및 로세올로바이러스 (Roseolovirus; HHV-6 및 HHV-7)는 베타-서브패밀리 바이러스이고, 엡스타인-바 바이러스 (Epstein-Barr virus; EBV, HHV-4) 및 카포시 육종-관련 헤르페스바이러스 (Kaposi's sarcoma-associated herpes virus; KSHV, HHV-8)는 사람을 감염시키는 감마-서브패밀리 바이러스이다.

[0005] CMV 감염은 면역력이 약화된 개인 (예를 들어, 이식 수령체 및 HIV-감염된 개인)에서 실질적인 발병률 및 사망률로 이어지고 선천적 감염은 신생아의 신경 발달에 치명적 결함을 발생시킬 수 있다. CMV 외피 당단백질 gB, gH, gL, gM 및 gN은 그것들이 바이러스 표면 상에 발현되고 보호 바이러스-중화 체액성 면역 반응을 유도할 수 있기 때문에 매력적인 백신 후보물질을 나타낸다. 일부 CMV 백신 전략은 주요 표면 당단백질 B (gB)를 표적화하였으며, 이것은 우성 항체 반응을 유발할 수 있다 (Go and Pollard, JID 197: 1631-1633 (2008)). CMV 당단백질 gB는 중화 항체 반응을 유발할 수 있고, CMV-양성 환자의 혈청에서 섬유아세포의 감염을 중화시키는 항체의 큰 분획은 gB로 향한다 (Britt 1990). 유사하게, gH 및 gM/gN은 자연 감염에 대한 면역 반응의 표적이다 (Urban et al (1996) J. Gen. Virol. 77 (Pt. 7): 1537-47; Mach et al (2000) J. Virol. 74(24): 11881-92).

[0006] CMV 단백질의 복합체는 또한 그것들이 바이러스의 생활 주기에서 중요한 과정에 수반되는 것으로 보이기 때문에 매력적인 백신 후보물질이다. 예를 들어, gH/gL/gO 복합체는 섬유아세포 및 상피/내피 세포 유입에 중요한 역할을 갖는 것으로 보인다. 일반적인 모델은 gH/gL/gO 복합체가 섬유아세포의 감염을 매개한다는 것을 제안한다. hCMV gO-눌 (null) 돌연변이는 섬유아세포 상에 작은 플라크 및 아주 낮은 역가의 바이러스를 생성하며, 유입시 역할을 나타낸다 (Dunn (2003), Proc. Natl. Acad. Sci. USA 100:14223-28; Hobom (2000) J. Virol. 74:7720-29). 최근 연구는 gO가 gH/gL을 갖는 비리온에 포함되지 않지만, 분자 샤페론 (chaperone)으로 작용할 수도 있으며, ER에서 골지체로의 gH/gL 유출 및 비리온에 포함을 증가시킨다는 것을 제안한다 (Ryckman (2009) J. Virol 82:60-70). 파동 추적 실험 (pulse-chase experiment)을 통해, 소량의 gO가 장기간 동안 gH/gL에 결합된 것을 유지하지만 그것이 세포 외 비리온에서 발견되지 않거나 세포 내로부터 분비되지 않기 때문에, 대부분의 gO는 gH/gL/gO 복합체와 분리되고 및/또는 이로부터 분해된다는 것으로 나타났다. gO가 CMV의 임상적 균주 (TR)로부터 삭제되었을 때 그들 바이러스 입자들은 비리온에 포함된 gH/gL의 양을 크게 감소시켰다. 추가적으로,

TR 바이러스로부터 삭제된 gO는 또한 상피 및 내피 세포 내로의 유입을 억제하였으며, gH/gL이 또한 상피/내피 세포 유입에 필요하다는 것을 제안한다 (Wille (2010) J. Virol. 84(5):2585-96).

[0007] CMV gH/gL은 또한 UL128, UL130, 및 UL131A (여기에서 UL131로 나타남)와 연관될 수 있고 상피 세포, 내피 세포, 수지상세포를 포함하는, 다수의 세포 타입으로의 유입에 필요한 펜타머 복합체를 형성한다 (Hahn et al (2004) J. Virol. 78(18): 10023-33; Wang and Shenk (2005) Proc. Natl. Acad. Sci USA 102(50): 18153-8; Gerna et al (2005). J. Gen. Virol. 84(Pt 6): 1431-6; Ryckman et al (2008) J. Virol. 82:60-70). 반대로, 이 복합체는 섬유아세포의 감염에 필요하지 않다. 연구실 hCMV 분리체는 UL128-UL131 자리에 돌연변이를 갖고 있고, 돌연변이는 배양된 섬유아세포의 단지 몇 번의 계대 후 임상 분리체에서 발생한다 (Akter et al (2003) J. Gen. Virol. 84(Pt 5): 1117-22). 자연 감염 동안, 펜타머 복합체는 매우 높은 효능으로 상피 세포, 내피 세포 (및 펜타머 복합체가 바이러스의 유입을 매개하는 일부 다른 세포 타입)의 감염을 중화시키는 항체를 유도한다 (Macagno et al (2010) J. Virol. 84(2): 1005-13). 또한 이 복합체에 대한 항체는 사람 혈청의 상피 세포의 감염을 중화시키는 능력에 크게 기여하는 것으로 보인다 (Genini et al (2011) J. Clin. Virol. 52(2): 113-8).

[0008] US 5,767,250은 gH 및 gL을 함유하는 특정 CMV 단백질 복합체를 만드는 방법을 개시한다. 복합체는 gH 및 gL이 동시발현되도록 gH를 암호화하는 DNA 구조 및 gL을 암호화하는 DNA 구조물을 세포 내로 도입함으로써 생성된다.

[0009] WO 2004/076645는 CMV 단백질을 암호화하는 재조합 DNA 분자를 설명한다. 이 문서에 따라, 다른 CMV 단백질을 암호화하는 별개의 DNA 분자의 조합이 암호화된 CMV 단백질의 동시발현을 유발하도록 세포 내로 도입될 수 있다. gM 및 gN이 이 방법으로 동시발현되었을 때, 그것들은 이황화 결합 복합체를 형성하였다. gM/gN 복합체를 생산하는 DNA 구조물 또는 gB를 암호화하는 DNA 구조물로 면역화된 토끼는 등량의 중화 항체 반응을 생산하였다.

[0010] 둘 이상의 헤르페스바이러스 단백질을 암호화하는 핵산에 대한, 같은 세포에서 둘 이상의 헤르페스바이러스 단백질을 발현하는 방법에 대한, 및 더 양호한 면역 반응을 생산하는 면역화 방법에 대한 필요가 존재한다.

발명의 내용

해결하려는 과제

[0011] 본 발명은 세포에 둘 이상의 헤르페스 단백질, 특히 생체 내에서 복합체를 형성하는 단백질, 예를 들어, 시토메갈로바이러스 (CMV) 단백질의 동시전달을 위한 플랫폼과 관련된다. 한 양태에서, 본 발명은 첫 번째 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편을 암호화하는 첫 번째 서열, 및 두 번째 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편을 암호화하는 두 번째 서열을 함유하는 재조합 폴리시스트론성 핵산 분자이다.

[0012] 예를 들어, 본 발명은 a) 헤르페스바이러스의 첫 번째 단백질 또는 이들의 단편을 암호화하는 첫 번째 뉴클레오티드 서열; 및 b) 헤르페스바이러스로부터 두 번째 단백질 또는 이들의 단편을 암호화하는 두 번째 뉴클레오티드 서열을 포함하는 폴리뉴클레오티드를 포함하는 자가 복제 RNA 분자를 제공한다. 첫 번째 뉴클레오티드 서열 및 두 번째 뉴클레오티드 서열은 자가 복제 RNA 분자가 적합한 세포 내로 도입될 때, 첫 번째 및 두 번째 헤르페스바이러스 단백질 또는 이들의 단편이 첫 번째 및 두 번째 단백질 또는 단편을 함유하는 세포에서 복합체의 형성에 충분한 양으로 생산되도록 하나 이상의 조절 요소와 작동 가능하게 연결된다. 바람직하게, 첫 번째 단백질 및 두 번째 단백질은 같은 단백질 또는 같은 단백질의 단편이 아니고, 첫 번째 단백질은 두 번째 단백질의 단편이 아니고 두 번째 단백질은 첫 번째 단백질의 단편이 아니다. 첫 번째 뉴클레오티드 서열은 첫 번째 조절 요소와 작동 가능하게 연결될 수 있고 두 번째 뉴클레오티드 서열은 두 번째 조절 요소와 작동 가능하게 연결될 수 있다.

[0013] 자가 복제 RNA 분자는 상기 헤르페스바이러스의 세 번째 단백질 또는 이들의 단편을 암호화하는 세 번째 뉴클레오티드 서열, 임의로 상기 헤르페스바이러스의 네 번째 단백질 또는 이들의 단편을 암호화하는 네 번째 뉴클레오티드 서열; 및 임의로 상기 헤르페스바이러스의 다섯 번째 단백질 또는 이들의 단편을 암호화하는 다섯 번째 뉴클레오티드 서열을 추가로 포함할 수 있다. 헤르페스바이러스의 추가적 단백질 또는 단편을 암호화하는 서열 (즉, 세 번째, 네 번째 및 다섯 번째 뉴클레오티드 서열)이 존재할 때, 그것들은 하나 이상의 조절 요소와 작동 가능하게 연결된다. 폔타시스트론성 구조물의 한 예에서, 첫 번째 뉴클레오티드 서열은 첫 번째 조절 요소와 작동 가능하게 연결되고, 두 번째 뉴클레오티드 서열은 두 번째 조절 요소와 작동 가능하게 연결되고, 세 번째 뉴

클레오티드 서열은 세 번째 조절 요소와 작동 가능하게 연결되고, 네 번째 뉴클레오티드 서열은 네 번째 조절 요소와 작동 가능하게 연결되고, 다섯 번째 뉴클레오티드 서열은 다섯 번째 조절 요소와 작동 가능하게 연결된다. 구조물에 존재하는 조절 요소 (예를 들어, 첫 번째, 두 번째, 세 번째, 네 번째 및 다섯 번째 조절 요소)는 서브게놈 프로모터, IRES, 및 바이러스 (예를 들어, FMDV) 2A 부위로 구성된 그룹으로부터 독립적으로 선택될 수 있다.

[0014] 헤르페스바이러스는 HSV-1, 1, HSV-2, VZV, EBV 타입 1, EBV 타입 2, CMV, HHV-6 타입 A, HHV-6 타입 B, HHV-7 및 HHV-8일 수 있다. 일부 구체예에서, 재조합 폴리시스트론성 핵산 분자 (예를 들어, 자가 복제 RNA)는 이 헤르페스바이러스 중 어느 하나의 gH 또는 이들의 단편 및 gL 또는 이들의 단편을 암호화한다. 더 특정 구체예에서, 헤르페스바이러스는 CMV 또는 VZV이다.

[0015] 재조합 폴리시스트론성 핵산 분자 (예를 들어, 자가 복제 RNA)가 둘 이상의 VZV 단백질을 암호화할 때, 단백질은 gB, gE, gH, gI, gL 및 이들의 단편 (예를 들어, 적어도 10개의 아미노산 중)으로 구성된 그룹으로부터 선택될 수 있다. 일부 구체예에서, 재조합 폴리시스트론성 핵산 분자 (예를 들어, 자가 복제 RNA)는 VZV gH 또는 이들의 단편 및 VZV gL 또는 이들의 단편을 암호화한다.

[0016] 특정 예에서, 본 발명은 a) 첫 번째 시토메갈로바이러스 (CMV) 단백질 또는 이들의 단편을 암호화하는 첫 번째 서열; 및 b) 두 번째 CMV 단백질 또는 이들의 단편을 암호화하는 두 번째 서열을 포함하는 폴리뉴클레오티드를 포함하는 자가 복제 RNA 분자를 제공한다. 첫 번째 서열 및 두 번째 서열은 자가 복제 RNA 분자가 적합한 세포 내로 도입될 때, 첫 번째 및 두 번째 CMV 단백질이 첫 번째 및 두 번째 CMV 단백질 또는 단편을 함유하는 세포에서 복합체의 형성에 충분한 양으로 생산되도록 하나 이상의 조절 요소와 작동 가능하게 연결된다.

[0017] 첫 번째 CMV 단백질 및 두 번째 CMV 단백질은 gB, gH, gL; gO; gM, gN; UL128, UL130, UL131, 및 전술된 것들 중 어느 하나의 단편으로 구성된 그룹으로부터 독립적으로 선택된다. 바람직하게는, 첫 번째 CMV 단백질 및 두 번째 CMV 단백질은 같은 단백질 또는 같은 단백질의 단편이 아니며, 첫 번째, CMV 단백질은 두 번째 CMV 단백질의 단편이 아니고, 두 번째 CMV 단백질은 첫 번째 CMV 단백질의 단편이 아니다. 원하는 경우, 자가 복제 RNA 분자는 세 번째 CMV 단백질을 암호화하는 세 번째 서열을 추가로 포함할 수 있으며, 세 번째 서열은 조절 요소와 작동 가능하게 연결된다. 유사하게, 추가적 CMV 단백질을 암호화하는 추가적 서열 (예를 들어, 네 번째 CMV 단백질을 암호화하는 네 번째 서열, 다섯 번째 CMV 단백질을 암호화하는 다섯 번째 서열)이 포함될 수 있다. 조절 요소는 서브게놈 프로모터, 및 IRES, 및 바이러스 2A 부위로 구성된 그룹으로부터 독립적으로 선택될 수 있다.

[0018] 일부 구체예에서, 자가 복제 핵산 분자는 CMV 단백질 gH 및 gL을 암호화한다. 다른 구체예에서, 자가 복제 RNA 분자는 CMV 단백질 gH, gL, 및 gO를 암호화한다. 다른 구체예에서, 자가 복제 RNA 분자는 CMV 단백질 gH, gL, UL128, UL130 및 UL131을 암호화한다.

[0019] 자가 복제 RNA 분자는 알파바이러스 레플리콘일 수 있다. 이러한 예에서, 알파바이러스 레플리콘은 알파바이러스 레플리콘 입자 (VRP)의 형태로 전달될 수 있다. 자가 복제 RNA 분자는 또한 "노출 (naked)" RNA 분자의 형태일 수 있다.

[0020] 본 발명은 여기에 설명된 바와 같dl 자가 복제 RNA 분자를 암호화하는 재조합 DNA 분자와 관련된다. 일부 구체예에서, 재조합 DNA 분자는 플라스미드이다. 일부 구체예에서, 재조합 DNA 분자는 암호화된 자가 복제 RNA 분자의 전사를 구동하는 포유동물 프로모터를 포함한다.

[0021] 본 발명은 또한 여기에 설명된 바와 같dl 자가 복제 RNA 분자 및 약학적으로 허용 가능한 비히클을 포함하는 조성물과 관련된다. 자가 복제 RNA 분자는 "노출"될 수 있다. 일부 구체예에서, 조성물은 CMV 단백질 gH 및 gL을 암호화하는 자가 복제 RNA 분자를 포함한다. 다른 구체예에서, 조성물은 CMV 단백질 gB를 암호화하는 자가 복제 RNA 분자를 더 포함한다. 조성물은 또한 리포솜, 폴리머 나노파티클, 수중유 양이온성 나노에멀젼 또는 이들의 조합과 같은 RNA 전달 시스템을 함유할 수 있다. 예를 들어, 자가 복제 RNA 분자는 리포솜에서 캡슐화될 수 있다.

[0022] 특정 구체예에서, 조성물은 둘 이상의 CMV 단백질을 암호화하는 알파 바이러스 레플리콘을 함유하는 VRP를 포함한다. 일부 구체예에서, VRP는 CMV gH 및 gL을 암호화하는 레플리콘을 포함한다. 원하는 경우, 조성물은 CMV gB를 암호화하는 레플리콘을 함유하는 두 번째 VRP를 추가로 포함할 수 있다. 조성물은 또한 보조제를 포함할 수 있다.

[0023] 본 발명은 또한 CMV 단백질 복합체를 형성하는 방법과 관련된다. 일부 구체예에서, 둘 이상의 단백질을 암호화하는 자가 복제 RNA가 세포에 전달되고, 세포는 CMV 단백질의 발현에 적합한 조건 하에 유지되며, CMV 단백질

복합체가 형성된다. 다른 구체예에서, 둘 이상의 CMV 단백질을 암호화하는 자가 복제 RNA를 함유하는 VRP가 세포에 전달되고, 세포는 CMV 단백질의 발현에 적합한 조건 하에 유지되며, CMV 단백질 복합체가 형성된다. 방법은 생체 내 세포에서 CMV 단백질 복합체를 형성하기 위해 이용될 수 있다.

[0024] 본 발명은 또한 개인의 면역 반응을 유발하는 방법과 관련된다. 일부 구체예에서, 둘 이상의 CMV 단백질을 암호화하는 자가 복제 RNA가 개인에게 투여된다. 자가 복제 RNA 분자는 리포솜과 같이, RNA 전달 시스템을 함유하는 조성물로서 투여될 수 있다. 다른 구체예에서, 둘 이상의 CMV 단백질을 암호화하는 자가 복제 RNA를 함유하는 VRP가 개인에게 투여된다. 바람직한 구체예에서, 자가 복제 RNA 분자는 CMV 단백질 gH 및 gL을 암호화한다. 바람직하게, 유발된 면역 반응은 중화 항-CMV 항체의 생산을 포함한다. 더 바람직하게는, 중화 항체는 보체-독립적이다.

[0025] 본 발명은 또한 세포를 gH 및 gL과 같은 둘 이상의 CMV 단백질을 암호화하는 자가 복제 RNA 분자와 접촉시키는 단계를 포함하는, 세포 내로 CMV 유입을 억제하는 방법과 관련된다. 세포는 상피 세포, 내피 세포, 섬유아세포 및 이들의 조합으로 구성된 그룹으로부터 선택될 수 있다. 일부 구체예에서, 세포는 둘 이상의 CMV 단백질을 암호화하는 자가 복제 RNA를 함유하는 VRP와 접촉된다.

[0026] 본 발명은 또한 면역 반응을 유발하기 위해 또는 세포 내로 CMV 유입을 억제하기 위해, 세포의 CMV 단백질 복합체를 형성하는 둘 이상의 CMV 단백질을 암호화하는 자가 복제 RNA 분자 (예를 들어, VRP, 자가 복제 RNA 분자 및 리포솜을 포함하는 조성물)의 이용과 관련된다.

도면의 간단한 설명

[0027] 도 1은 표적 세포 내로의 CMV 유입에 수반되는 알려진 당단백질 복합체를 확인하는 CMV의 개략도이다. 외피 당단백질은 그것들이 바이러스 표면 상에 발현되고 보호 및 지속성 바이러스-중화 체액 면역 반응을 유발할 수 있기 때문에 매력적인 백신 후보물질을 대표한다. 이 과정을 매개하는 구조 당단백질은 두 개의 클래스로 분류될 수 있다; 헤르페스바이러스 패밀리를 통해 보존되는 것들 및 그렇지 않은 것들. 보존되는 것들 중에는 gB, gH, gL, gM 및 gN이 있다. 이 당단백질 중 대부분은 바이러스 표면에 국부화을 용이하게 하고 바이러스의 부착, 유입 및 세포 융합시 그것들의 기능을 수행하기 위해 서로 복합체를 형성한다 (gH/gL/±gO; gH/gL/UL128/UL130/UL131; gM/gN).

도 2a-2f는 CMV 구조의 개략도이다. 도 2a, 실시예 1에서 설명된 gB 구조 ("gB FL", 전체 길이 gB; 가용성 gB "gB sol 750" 및 "gB sol 692")의 개략도. 두 개의 다른 가용성 버전의 gB가 구성되었다; gB sol 750은 막통과 스패닝 (spanning) 도메인 및 세포질 도메인이 없고, gB sol 692는 또한 소수성 영역이 없고 Reap et al. (2007) Clin. Vacc. Immunol. 14:748-55에 설명된 gB sol과 유사하다. 도 2b, 바이러스 복제 입자 (VRP)를 생산하기 위해 이용된 gB 레플리콘 벡터의 개략도. 도 2c, 실시예 1에서 설명된 gH 구조 ("gH FL", 전체 길이 gH; 가용성 gH "gH sol")의 개략도. 단일 가용성 버전의 gH가 구성되었으며 이것은 막통과 스패닝 도메인이 없다. 도 2d, VRP를 생산하기 위해 이용된 gH 레플리콘 벡터의 개략도. 도 2e, 실시예 1에서 설명된 gL 구조의 개략도. 도 2f, VRP를 생산하기 위해 이용된 gL 레플리콘 벡터의 개략도. 도 2b, 2d 및 2f에서, "NSP1", "NSP2", "NSP3", 및 "NSP4"는 각각 바이러스의 복제에 필요한 알파바이러스 비구조 단백질 1-4이다.

도 3a 및 3b는 gB (FL, sol 750, sol 692) 또는 gH (FL, sol) VRP로 면역화된 마우스가 기니피그 보체의 존재시 중화시키는 항체 반응을 유발하였다는 것을 나타낸다. ARPE-19 상피 세포의 감염 전에 마우스 혈청 및 기니피그 보체와 함께 CMV 바이러스 균주 TB40UL32E-GFP (이것은 향상된 녹색 형광 단백질-GFP를 암호화한다, Sampaio et al (2005) J. Virol. 79(5):2754-67)를 사전 배양함으로써 중화 검정을 수행하였다. 감염 5일 후, GFP 양성 세포의 수를 결정하였다. 도 3a, 보체의 존재시 ARPE-19 세포에서 분석된 모든 혈청에 대한 혈청 희석 곡선. 도 3b, 혈청 샘플에 대한 50% 중화 역가. 사전 면역 혈청과 함께 배양된 바이러스는 낮은 희석배수에서 낮은 중화를 수득하였다 (1:40-1:80). gB (FL, sol 750, sol 692) 혈청은 1:1800-1:2100에서 50% 중화 역가로 아주 강한 중화 활성을 갖고 있었다. 모든 gB 면역화된 마우스는 유사한 중화 프로파일을 수득하였다. gH (FL, sol) 혈청은 약 1:160에서 50% 중화 역가로 중화 활성을 가졌다. 실시예 1 참조.

도 4a는 녹색 형광 단백질 (GFP) 또는 적색 형광 단백질 (mCherry)를 암호화하는 모노시스트론성 레플리콘 및 GFP 및 mCherry를 암호화하는 바이시스트론성 레플리콘의 개략도이다. "NSP1", "NSP2", "NSP3", 및 "NSP4"는 각각 알파바이러스 비구조 단백질 1-4이다. 폴리시스트론성 알파바이러스 레플리콘 시스템은 원하는 유전자를 구동하는 다수의 서브게놈 프로모터를 수용하도록 기존 알파바이러스 레플리콘 시스템을 수정함으로써 설계되었다.

도 4b는 모노-및 바이시스트론성 RNA를 함유하는 VRP로 감염된 BHKV 세포의 FACS 분석을 나타내는 형광 발광 플롯이다. 폴리시스트론성 알파바이러스 VRP는 GFP VRP + mCherry VRP (26.30%)의 동시감염보다, 거의 같은 양으로 원하는 유전자 둘 다를 발현하는 더 많은 (GFP 및 mCherry; 72.48%) 세포를 수득한다. 실시예 2 참조.

도 5a는 gH/gL 및 gH/gL/gO를 암호화하는 폴리시스트론성 알파바이러스 레플리콘 구조의 개략도이다.

도 5b는 gH/gL가 시험관 내에서 복합체를 형성한다는 것을 나타낸다. gH, gL, gO, gH/gL 또는 gH/gL/gO를 암호화하는 레플리콘을 함유하는 VRP가 BHKV 세포에서 생산되었다. 결과의 VRP는 시험관 내에서 복합체 형성을 입증하기 위해 ARPE-19 세포를 감염시키는데 이용되었다. 알파바이러스 감염된 ARPE-19 세포는 gH 및 gL이 존재하는 동안 수확되었고 분석되었다. gH/gL을 암호화하는 VRP로 감염된 ARPE-19 세포는 gH/gL의 이황화 결합된 복합체를 생산하였다 (DTT의 부재시, 열 참조). gO는 gH/gL 결합을 검출 가능하게 변화시키지 않았다. 왼쪽 블롯은 gH 단백질의 발현을 나타낸다. 오른쪽 블롯은 gL 단백질의 발현을 나타낸다. 분자량 마커는 블롯들 사이에 표시된다. ● = 모노머 gH, ●● = 모노머 gL, < = 헤테로다이머 (gH + gL), * = 헤테로다이머의 다이머

도 5c는 VRP로 감염된 BHKV 세포의 gH 및 gH/gL 복합체의 면역 침강을 나타낸다. 면역 침강은 대조군 (레인 2, 4, 7, 및 10)으로 마우스 IgG 항체 또는 gH를 면역 침강하기 위해서 (레인 3, 5, 8, 및 11) 마우스 항-gH 항체 (Genway)를 이용하여 수행되었다. 웨스턴 블롯은 풀 (pool) 토끼 항-gL 항체 및 토끼 항-gH 항체를 이용하여 수행되었다. 레인 1, 6, 및 9는 참고로 gH 단백질 (75 kDa 정도의 높은 밴드) 및 gL 단백질 (30 kDa 정도의 낮은 밴드)를 나타낸다. 레인 2 및 3은 gH-VRP로 감염된 용해물이다. 레인 2는 대조군 항체가 gH를 면역 침강하지 않았다는 것을 나타낸다. 레인 3은 항-gH 항체가 gH를 면역 침강했다는 것을 나타낸다. 레인 4 및 5는 gL-VRP만으로 감염된 용해물이다. gH 단백질은 면역 침강되지 않았다. 레인 7 및 8은 바이시스트론성 gH/gL-VRP로 감염된 용해물이다. 레인 8은 gL이 gH 항체를 이용하여 면역 침강 되었다는 것을 나타낸다. (별표 참조). 레인 10 및 11은 트리시스트론성 gH/gL/gO-VRP로 감염된 용해물이다. 레인 11은 gL이 gH 항체를 이용하여 면역 침강 되었다는 것을 나타낸다. (별표 참조). 분자량 마커가 또한 나타난다 (MW). 실시예 3 참조.

도 6은 시험관 내에서 gH/gL 복합체 형성에 영향을 미치는 VRP가 gB VRP에 대한 반응보다 질적으로 및 양적으로 우수한 CMV에 대한 효능 있는 면역 반응을 유발한다는 것을 나타낸다. 도 6a 및 도 6b는 보체의 존재시 (도 6a) 또는 부재시 (도 6b) ARPE-19 세포의 TB40-UL32-EGFP 감염의 중화시 gH, gL, gO, gH + gL, gH + gL + gO, gH/gL 및 gH/gL/gO VRP-면역화된 마우스에 대한 혈청 희석 곡석을 나타낸다. 기니피그 보체의 존재시 또는 부재시 다양한 희석의 혈청은 TB40UL32E-GFP와 함께 사전 배양되었고 ARPE-19 상피 세포에 추가되었다. 바이러스로 감염 5일 후, GFP-양성 세포를 계산하였다. 도 6c는 보체의 존재시 또는 부재시 얻은 50% 중화 역가를 나타내는 그래프이다. "3wp3", 세 번째 면역화 3주 후. 단일 CMV 단백질을 발현하는 VRP (gH, gL, gO VRP 또는 동시투여된 gH, gL 및 gO VRP)는 gH 단독의 그것 너머로 중화 활성을 향상시키지 않았다. 반대로, 바이시스트론성 gH/gL 또는 트리시스트론성 gH/gL/gO VRP로 면역화된 마우스의 혈청은 효능 있는 중화 반응을 입증하였다. 게다가, 효능 있는 중화 반응은 기니피그 보체의 존재시 및 부재시 유사하였고, 폴리시스트론성 VRP는 성공적으로 보체-독립적인 면역 반응을 유발하였다는 것을 나타낸다. 실시예 4 참조.

도 7은 시험관 내에서 gH/gL 복합체 형성에 영향을 미치는 VRP가 MRC-5 섬유아세포의 감염을 효능있게 중화시키는 항체를 유발하였다는 것을 나타낸다. 도 7a는 보체의 부재시 MRC-5 세포의 gH, gL, gO, gH + gL, gH + gL + gO, gH/gL 및 gH/gL/gO VRP-면역화된 마우스에 대한 혈청 희석 곡선을 나타낸다. 다양한 희석의 혈청은 기니피그 보체의 존재시 또는 부재시 TB40GFP로 사전 배양되었고 MRC-5 섬유아세포에 추가되었다. 바이러스로 감염 5일 후, GFP-양성 세포를 계산하였다. 도 7b는 보체의 부재시 MRC-5 섬유아세포 모델에서 얻은 50% 중화 역가를 나타내는 그래프이다. "3wp3", 세 번째 면역화 3주 후. 단일 CMV 단백질을 발현하는 VRP (gH, gL, gO VRP 또는 동시투여된 gH, gL 및 gO VRP)는 gH 단독의 그것 이상으로 중화 활성을 향상시키지 않았다. 반대로 바이시스트론성 gH/gL 또는 트리시스트론성 gH/gL/gO VRP로 면역화된 마우스의 혈청은 매우 효능 있는 중화 반응을 입증하였다. 실시예 4 참조.

도 8a 및 8b는 폴리시스트론성 VRP의 전달에 의해 유발된 중화 항체가 항체를 교차-중화하였다는 것을 나타내는 그래프이다. gH/gL 및 gH/gL/gO VRP로 면역화된 마우스의 혈청은 IE-1 중화 검정시 기니피그 보체의 부재시 ARPE-19 상피 세포 (도 8a) 및 MRC-5 섬유아세포 (도 8b) 둘 다에서 CMV의 TB40UL32E-GFP 및 VR1814 임상적 균주를 중화할 수 있었다.

도 9는 gH FL/gL에 대하여 유도된 중화 항체가 보체-독립적이고 역가에서 자연 면역력과 유사하다는 것을 나타내는 그래프이다. 마우스는 1 x 10^6 IU의 gB FL 또는 gH FL/gL VRP로, 최종 채혈 전 3주 간격으로 3번 면역화되

었다. 혈청은 중화 검정에서 기니피그 보체의 존재시 및 부재시 ARPE-19 세포의 TB40UL32E-EGFP CMV 감염을 중화하는 능력에 대하여 분석되었다. gB에 의해 유도된 항체와 달리, gH FL/gL에 의해 유도된 항체는 보체-독립적이다. 게다가, 이 백신 접종된 마우스에서 gH FL/gL 항체는 자연 감염된 사람 대상체에서 발견된 것들에 대한 역가와 비슷했다.

도 10은 pVCR 변형된 gH-SGPgL-SGPgO에 대한 플라스미드 지도를 나타낸다.

도 11은 pVCR 변형된 gH-SGPgL에 대한 플라스미드 지도를 나타낸다.

도 12는 pVCR 변형된 gH sol-SGPgL에 대한 플라스미드 지도를 나타낸다.

도 13은 pVCR 변형된 gH sol-SGPgL-SGPgO에 대한 플라스미드 지도를 나타낸다.

도 14a-14g는 CMV 표면 당단백질 H (gH) 및 CMV 표면 당단백질 L (gL)을 암호화하는 A160 자가 복제 RNA 분자를 암호화하는 플라스미드의 뉴클레오티드 서열 (SEQ ID NO:83)을 나타낸다. gH 및 gL을 암호화하는 뉴클레오티드 서열은 밑줄쳐져 있다.

도 15a-15h는 CMV 표면 당단백질 H (gHsol) 및 CMV 표면 당단백질 L (gL)의 가용성 형태를 암호화하는 A322 자가 복제 RNA 분자를 암호화하는 플라스미드의 뉴클레오티드 서열 (SEQ ID NO:84)을 나타낸다. gHsol 및 gL을 암호화하는 뉴클레오티드 서열은 밑줄쳐져 있다.

도 16a-16h는 CMV 표면 당단백질 B (gB)를 암호화하는 A323 자가 복제 RNA 분자를 암호화하는 플라스미드의 뉴클레오티드 서열 (SEQ ID NO:85)을 나타낸다. gB를 암호화하는 뉴클레오티드 서열은 밑줄쳐져 있다.

도 17a 및 도 17b는 VRP 또는 자가 복제 RNA로 면역화된 마우스의 혈청의 50% 중화 역가를 나타내는 막대그래프이다. 도 17a는 ARPE-19 세포에서 사람 CMV 균주 TB40UL32E-EGFP ("TB40)에 대하여 50% 중화 역가를 나타내고, 도 17b는 ARPE-19 세포에서 사람 CMV 균주 8819에 대하여 50% 중화 역가를 나타낸다.

도 18은 다섯 개의 CMV 단백질을 암호화하는, 페타시스트론성 RNA 레플리콘, A526(SEQ ID NO:56), A527(SEQ ID NO:57), A554(SEQ ID NO:65), A555(SEQ ID NO:66) 및 A556(SEQ ID NO:67)의 개략도이다. 서브게놈 프로모터는 화살표로 나타나고, 다른 대조군 요소가 표시된다.

도 19는 A527 RNA 레플리콘으로 트랜스펙션된 BHKV 세포가 gH/gL/UL128/UL130/UL131 펜타머 복합체를 발현한다는 것을 나타내는 형광 발광 막대 그래프이다. 펜타머 복합체 상에 존재하는 구조 에피토프와 결합하는 항체를 이용하여 세포 염색을 수행하였다 (Macagno (2010) J. Virol. 84(2): 1005-13).

도 20은 개략도 및 그래프이다. 개략도는 CMV gH 및 gL을 암호화하는, 바이시스트론성 RNA 레플리콘, A160 및 A531-A537을 나타낸다. 그래프는 레플리콘을 함유한 VRP로 면역화된 마우스의 면역 혈청의 중화 활성을 나타낸다.

도 21은 VZV 단백질을 암호화하는 모노시스트론성 RNA 레플리콘 또는 VZV gE 및 gI, 또는 gH 및 gL을 암호화하는 바이시스트론성 RNA 레플리콘으로 면역화된 마우스의 면역 혈청에서 항-VZV 단백질 항체 반응을 나타낸다. 마우스는 CNE로 조제된 7 μg RNA로 면역화되었다 (실시예 7 참조).

도 22는 VZV 단백질을 암호화하는 모노시스트론성 RNA 레플리콘 또는 VZV gE 및 gI, 또는 gH 및 gL을 암호화하는 바이시스트론성 RNA 레플리콘으로 면역화된 마우스의 면역 혈청에서 항-VZV 단백질 항체 반응을 나타낸다. 마우스는 CNE로 조제된 1 μg RNA로 면역화되었다 (실시예 7 참조).

발명을 실시하기 위한 구체적인 내용

[0028] 본 발명은 세포에 시토메갈로 바이러스 (CMV) 단백질과 같이, 헤르페스바이러스 단백질, 특히 생체 내에서 복합체를 형성하는 단백질의 동시전달을 위한 플랫폼을 제공한다. 일부 구체예에서, 이 단백질 및 그것들이 형성하는 복합체는 효능 있는 중화 항체를 유도한다. 헤르페스바이러스 (예를 들어, CMV) 단백질, 특히 생체 내에서 복합체를 형성하는 것들 (예를 들어, gH/gL)의 동시전달에 의해 생산된 면역 반응은 다른 접근법을 이용하여 생산된 면역 반응보다 더 뛰어날 수 있다. 예를 들어, CMV의 gH 및 gL을 암호화하는 RNA 분자 (예를 들어, 레플리콘)는 gB를 암호화하는 RNA 분자, gH를 암호화하는 RNA 분자, gL을 암호화하는 RNA 분자 또는 개별적으로 gH 또는 gL을 암호화하는 RNA 분자의 혼합물과 비교하여 더 양호한 중화 역가 및/또는 보호 면역력을 유발할 수 있다. 게다가, gH/gL/UL128/UL130/UL131을 암호화하는 레플리콘은 gH/gL만을 암호화하는 것들보다 더 뛰어난 반응을 제공할 수 있다.

[0029] 일반적인 양태에서, 본 발명은 세포에 둘 이상의 헤르페스바이러스 (예를 들어, CMV) 단백질의 전달을 위한 플랫폼과 관련된다. 플랫폼은 첫 번째 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편을 암호화하는 첫 번째 서열, 및 두 번째 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편을 암호화하는 두 번째 서열을 함유하는 재조합 폴리시스트론성 핵산 분자를 포함한다. 원하는 경우, 추가적 단백질, 예를 들어, 세 번째 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편, 네 번째 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편, 다섯 번째 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편 등을 암호화하는 하나 이상의 추가적인 서열은 재조합 폴리시스트론성 핵산 분자에 존재할 수 있다. 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 단편이 재조합 폴리시스트론성 핵산을 함유하는 세포에 의해 생산되도록 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편을 암호화하는 서열은 하나 이상의 적합한 대조군 요소와 작동 가능하게 연결되었다.

[0030] 여기에 설명된 폴리시스트론성 핵산에서, 암호화된 첫 번째 및 두 번째 헤르페스바이러스 단백질 또는 단편, 및 암호화된 세 번째, 네 번째, 및 다섯 번째 헤르페스바이러스 단백질 또는 단편은, 존재하면, 일반적으로 및 바람직하게 같은 헤르페스바이러스의 것이다. 특정 예에서, 폴리시스트론성 벡터에 의해 암호화된 모든 헤르페스바이러스 단백질 또는 단편은 CMV 단백질 또는 VZV 단백질이다.

[0031] 여기에 설명된 재조합 폴리시스트론성 핵산 분자는 세포에 둘 이상의 헤르페스바이러스 (예를 들어, CMV) 단백질을 암호화하는 서열의 전달, 및 생체 내에서 둘 이상의 헤르페스바이러스 (예를 들어, CMV) 단백질을 함유하는 단백질 복합체의 형성을 일으키기 위해 충분한 수준으로 헤르페스바이러스 (예를 들어, CMV) 단백질의 발현의 구동의 이점을 제공한다. 이 접근법을 이용하여, 둘 이상의 암호화된 헤르페스바이러스 (예를 들어, CMV) 단백질은 헤르페스바이러스 (예를 들어, CMV) 단백질 복합체 (예를 들어, gH/gL)의 형성에 충분한 세포 내 수준으로 발현될 수 있다. 예를 들어, 암호화된 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편은 실질적으로 같은 수준으로, 또는 원하는 경우, 적절한 발현 조절 서열 (예를 들어, 프로모터, IRES, 2A 부위 등)을 선택함으로써 다른 수준으로 발현될 수 있다. 이것은 비효율적이고 매우 가변적일 수 있는, 같은 세포에 다른 헤르페스바이러스 (예를 들어, CMV)를 암호화하는 둘 이상의 개개의 DNA 분자를 동시전달하는 것보다 생체 내에서 단백질 복합체를 생산하기 위해 훨씬 더 효율적인 방법이다. 예를 들어, WO 2004/076645 참조.

[0032] 재조합 폴리시스트론성 핵산 분자는 DNA (예를 들어, 플라스미드 또는 바이러스 DNA) 또는 RNA와 같이 어떤 원하는 핵산에도 기초할 수 있다. 어떤 적합한 DNA 또는 RNA는 헤르페스바이러스 (예를 들어, CMV) 단백질 또는 이들의 단편을 암호화하는 오픈 리딩 프레임을 갖고 있는 핵산 벡터로서 이용될 수 있다. 적합한 핵산 벡터는 하나 이상의 단백질 유전자를 운반하고 이의 발현을 구동하는 능력을 갖는다. 이러한 핵산 벡터는 업계에 알려져 있고, 예를 들어, 플라스미드, 우두 바이러스 (vaccinia virus) 벡터 (예를 들어, NYVAC, 미국 5,494,807 참조), 수두 바이러스 (poxvirus) 벡터 (예를 들어, ALVAC 카나리폭스 벡터, Sanofi Pasteur)와 같이, DNA 바이러스로부터 얻어진 DNA, 및 알파바이러스와 같이 적합한 RNA 바이러스로부터 얻어진 RNA를 포함한다. 원하는 경우, 재조합 폴리시스트론성 핵산 분자는 변형될 수 있다, 예를 들어, 추가로 여기에 설명된 바와 같이 변형된 핵염기 및/또는 결합을 함유할 수 있다. 바람직하게는, 폴리시스트론성 핵산 분자는 RNA 분자이다.

[0033] 일부 양태에서, 재조합 폴리시스트론성 핵산 분자는 플라스미드 DNA와 같은 DNA 분자이다. 이러한 DNA 분자는, 예를 들어, 폴리시스트론성 레플리콘을 암호화하고 레플리콘의 전사를 구동하는 포유동물 프로모터를 함유할 수 있다. 재조합 폴리시스트론성 핵산 분자 또는 이 타입은 포유동물에 투여될 수 있고 이후 헤르페스바이러스 단백질을 발현하는 폴리시스트론성 레플리콘을 생산하기 위해 제자리에서 전사될 수 있다.

[0034] 일부 양태에서, 본 발명은 헤르페스바이러스 gH 또는 이들의 단편, 및 헤르페스바이러스 gL 또는 이들의 단편을 암호화하는 서열을 함유하는 폴리시스트론성 핵산 분자이다. gH 및 gL 단백질, 또는 이들의 단편은 어떤 원하는 헤르페스바이러스, 예를 들어, HSV-1, HSV-2, VZV, EBV 타입 1, EBV 타입 2, CMV, HHV-6 타입 A, HHV-6 타입 B, HHV-7, KSHV, 등의 것일 수도 있다. 바람직하게는, 헤르페스바이러스는 VZV, HSV-2, HSV-1, EBV (타입 1 또는 타입 2) 또는 CMV이다. 더 바람직하게는, 헤르페스바이러스는 VZV, HSV-2 또는 CMV이다. 더 바람직하게, 헤르페스바이러스는 CMV이다. gH 및 gL 단백질의 서열 및 이 바이러스로부터 단백질을 암호화하는 핵산의 서열은 업계에 잘 알려져 있다. 전형적인 서열은 표 1에서 확인된다. 폴리시스트론성 핵산 분자는 표 1에 개시된 gH 단백질을 암호화하는 첫 번째 서열, 또는 이들의 단편, 또는 그것과 적어도 약 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 또는 99% 동일한 서열을 함유할 수 있다. 폴리시스트론성 핵산 분자는 또한 표 1에 개시된 gL 단백질을 암호화하는 두 번째 서열, 또는 이들의 단편, 또는 그것과 적어도 약 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 또는 99% 동일한 서열을 함유할 수 있다.

표 1		
바이러스	gH 수납 번호	gL 수납 번호
HSV-1 (HHV-1)	NP_044623.1	NP_044602.1
HSV-2 (HHV-2)	NP_044491.1	NP_044470.1
VZV (HHV-3)	NP_040160.1	NP_040182.1
EBV 타입 1 (HHV-4)	YP_401700.1	YP_401678.1
EBV 타입 2 (HHV-4)	YP_001129496.1	YP_001129472.1
CMV (HHV-5)	YP_081523.1	YP_081555.1
HHV-6 타입 A	NP_042941.1	NP_042975.1
HHV-6 타입 B	NP_050229.1	NP_050261.1
HHV-7	YP_073788.1	YP_073820.1
KSHV (HHV-8)	YP_001129375.1	YP_001129399.1

[0035]

[0036] 본 발명의 이 설명에서, 핵산의 뚜렷한 설명을 용이하게 하기 위해서, 특정 서열 성분은 "첫 번째 서열", "두 번째 서열" 등으로 나타난다. 첫 번째 및 두 번째 서열은 어떤 원하는 순서 또는 방향으로도 나타날 수 있고, 특정 순서 또는 방향은 단어 "첫 번째", "두 번째 등에 의해 의도되지 않는 것으로 이해될 것이다. 유사하게, 단백질 복합체는 복합체, 예를 들어, gH/gL에 존재하는 단백질을 나열함으로써 나타난다. 이것은 복합체에 존재하는 단백질에 의해 복합체를 설명하기 위한 것이고 단백질의 상대적인 양 또는 재조합 핵산에서 단백질을 암호화하는 서열의 순서 또는 방향을 나타내기 위한 것이 아니다.

[0037] 알파바이러스 VRP 및 CMV 단백질을 암호화하는 서열을 함유하는 자가 복제 RNA와 같이, 특정 바람직한 구체예는 여기에 추가로 설명된다. 이러한 바람직한 구체예에서, CMV 단백질을 암호화하는 서열은 다른 헤르페스바이러스의 gH 및 gL과 같이, 단백질을 암호화할 수 있는 서열로 대체될 수 있는 것으로 생각된다.

[0038] **알파바이러스 VRP 플랫폼**

[0039] 일부 구체예에서, CMV 단백질은 하기 설명된 바와 같이 폴리시스트론성 레플리콘 (또는 벡터)을 이용하는 알파바이러스 레플리콘 입자 (VRP)를 이용하여 세포에 전달된다. 여기에 이용된 바와 같이, "폴리시스트론성"은 바이시스트론성 벡터 뿐만 아니라 셋 이상의 시스트론을 포함하는 벡터를 포함한다. 폴리시스트론성 벡터의 시스트론은 같은 CMV 균주로부터 또는 다른 CMV 균주로부터 CMV 단백질을 암호화할 수 있다. 시스트론은 어떤 5'-3' 순서의 방향도 될 수 있다. CMV 단백질을 암호화하는 어떤 뉴클레오티드 서열은 단백질을 생산하기 위해 이용될 수 있다. 둘 이상의 CMV 단백질 또는 이들의 단편을 암호화하는 폴리시스트론성 핵산의 제조에 유용한 전형적인 서열이 여기에 설명된다.

[0040] 여기에 이용된 바와 같이, 용어 "알파바이러스"는 업계에서 그것의 통상적인 의미를 갖고 다양한 종, 예를 들어, 베네수엘라 말 뇌염 바이러스 (Venezuelan equine encephalitis virus; VEE; 예를 들어, 트리니다드 당나귀, TC83CR, 등), 셈리키 포레스트 바이러스 (Semliki Forest virus; SFV), 신드비스 바이러스 (Sindbis virus), 로스 리버 바이러스 (Ross River virus), 웨스턴 말 뇌염 바이러스 (Western equine encephalitis virus), 이스턴 말 뇌염 바이러스 (Eastern equine encephalitis virus), 치쿤군야 바이러스 (Chikungunya virus), S.A. AR86 바이러스, 에버글레이드 바이러스 (Everglades virus), 무캄보 바이러스 (Mucambo virus), 바마 포레스트 바이러스 (Barmah Forest virus), 미델부르크 바이러스 (Middelburg virus), 픽수나 바이러스 (Pixuna virus), 오뇽뇽 바이러스 (O'nyong-nyong virus), 게타 바이러스 (Getah virus), 사기야마 바이러스 (Sagiyama virus), 베바루 바이러스 (Bebaru virus), 마야로 바이러스 (Mayaro virus), 우나 바이러스 (Una virus), 아우라 바이러스 (Aura virus), 화타로아 바이러스 (Whataroa virus), 반반키 바이러스 (Banbanki virus), 키질라가크 바이러스 (Kyzylagach virus), 하이랜드 제이 바이러스 (highlands J virus), 포트 모건 바이러스 (Fort Morgan virus), 은두무 바이러스 (Ndumu virus), 및 버기 크릭 바이러스 (Buggy Creek virus)를 포함한다. 용어 알파바이러스는 또한 하나 이상의 알파바이러스의 게놈 서열을 함유하는 키메라 알파바이러스 (예를 들어, Perri et al, (2003) J. Virol. 77(19): 10394-403에 의해 설명된 바와 같은)를 포함할 수도 있다.

[0041] "알파바이러스 레플리콘 입자" (VRP) 또는 "레플리콘 입자"는 알파바이러스 구조 단백질로 둘러싸인 알파바이러스 레플리콘이다.

[0042] "알파바이러스 레플리콘" (또는 "레플리콘")은 표적 세포의 생체 내에서 자체의 증폭을 지시할 수 있는 RNA 분자이다. 레플리콘은 RNA 증폭을 촉진하는 폴리머라제(들) (nsP1, nsP2, nsP3, nsP4)을 암호화하고 암호화된 폴리머라제에 의해 인식되고 이용되는, 복제에 필요한 씨스 RNA 서열을 함유한다. 알파바이러스 레플리콘은 전형적으로 다음 순서의 요소를 함유한다: 씨스에서 복제에 필요한 5' 바이러스 서열, 생물학적 활성 알파바이러스 비구조 단백질 (nsP1, nsP2, nsP3, nsP4)을 암호화하는 서열, 씨스에서 복제에 필요한 3' 바이러스 서열, 및 폴리아데닐레이트 구역. 알파바이러스 레플리콘은 또한 이종 기원 뉴클레오티드 서열의 발현을 지시하는, 하나 이상의 바이러스 서브게놈 "접합 영역" 프로모터를 함유할 수도 있으며, 특정 구체예에서, 이것은 발현되는 서브게놈 단편 및 이종 기원 서열(들)의 바이러스 전사를 증가시키거나 감소시키기 위해 변형될 수도 있다. 하기 설명된 바와 같이, 다른 조절 요소들이 이용될 수 있다.

[0043] CMV 단백질을 암호화시키는 알파바이러스 레플리콘은 VRP를 생산하기 위해 이용된다. 이러한 알파바이러스 레플리콘은 적어도 두 개의 CMV 단백질 또는 이들의 단편을 암호화하는 서열을 포함한다. 이 서열은 서브게놈 프로모터, IRES (예를 들어, EMCV, EV71), 및 바이러스 2A 부위와 같은, 하나 이상의 적합한 조절 요소와 작동 가능하게 연결되며, 이것은 같거나 다를 수 있다. 여기에 설명된 폴리시스트론성 벡터를 이용하여 이 복합체의 성분의 전달은 원하는 상대적인 양으로 둘 이상의 CMV 단백질을 암호화하는 핵산 서열을 제공하는 효율적인 방법이다; 반면에 다수의 알파바이러스 구조물이 복합체 형성을 위해 개개의 CMV 단백질을 전달하는데 이용되는 경우, VRP의 효율적인 동시전달이 필요할 것이다.

[0044] 적합한 조절 요소의 어떤 조합은 어떤 순서로도 이용될 수 있다. 한 예에서, 단일 서브게놈 프로모터는 두 개의 다른 CMV 단백질을 암호화하는 두 개의 서열과 작동 가능하게 연결되고, IRES는 두 개의 암호화 서열 사이에 위치한다. 또 다른 예에서, 두 개의 다른 CMV 단백질을 암호화하는 두 개의 서열은 별도의 프로모터와 작동 가능하게 연결된다. 또 다른 예에서, 두 개의 다른 CMV 단백질을 암호화하는 두 개의 서열은 단일 프로모터와 작동 가능하게 연결된다. 두 개의 다른 CMV 단백질을 암호화하는 두 개의 서열은 바이러스 2A 부위를 암호화하는 뉴클레오티드 서열을 통해 서로 연결되고, 따라서 CMV 단백질 둘 다의 아미노산 서열을 함유하는 단일 아미노산 사슬을 암호화한다. 이 맥락에서 바이러스 2A 부위는 암호화된 다단백질로부터 두 개의 CMV 단백질을 발생시키는데 이용된다.

[0045] **서브게놈 프로모터**

[0046] 접합 영역 프로모터로도 알려진 서브게놈 프로모터는 단백질 발현을 조절하는데 이용될 수 있다. 알파바이러스 서브게놈 프로모터는 알파바이러스 구조 단백질의 발현을 조절한다. Strauss and Strauss, "The alphaviruses: gene expression, replication, and evolution", Microbiol Rev. 1994 Sep;58(3):491-562 참조. 폴리시스트론성 폴리뉴클레오티드는 어떤 알파바이러스의 서브게놈 프로모터도 포함할 수 있다. 둘 이상의 서브게놈 프로모터는 폴리시스트론성 폴리뉴클레오티드에 존재하고, 프로모터는 같거나 다를 수 있다. 예를 들어, 서브게놈 프로모터는 서열 CTCTCTACGGCTAACCTGAATGGA (SEQ ID NO:1)을 갖는다. 특정 구체예에서, 서브게놈 프로모터는 단백질의 바이러스 전사를 증가시키거나 감소시키기 위해 변형될 수 있다. 미국 특허 번호 6,592,874 참조.

[0047] **내부 리보솜 유입점 (Internal Ribosomal Entry Site; IRES)**

[0048] 일부 구체예에서, 하나 이상의 조절 요소는 내부 리보솜 유입점 (IRES)이다. 리보솜이 각각의 IRES에 결합하고 정상적으로 진핵세포의 단백질의 번역을 개시하는데 필요한 5'-캡의 부재시 다수의 단백질이 번역을 개시하기 때문에, IRES는 단일 mRNA 전사로부터 만들어지는 것을 허용한다. 예를 들어, IRES는 EV71 또는 EMCV일 수 있다.

[0049] **바이러스 2A 부위**

[0050] FMDV 2A 단백질은 비구조 단백질로부터 FMDV의 구조 단백질을 분리하기 위해 제공하는 짧은 펩티드이다 (FMDV 2B). 이 펩티드에 대한 초기 연구는 그것이 자가 촉매 프로테아제로서 작용하는 것을 제안하였지만, 다른 작업 (예를 들어, Donnelly et al, (2001), J.Gen.Virol. 82, 1013-1025)은 이 짧은 서열 및 FMDV 2B (Gly)의 다음 단일 아미노산이 번역 중단-시작으로서 작용하는 것을 제안한다. 정확한 작용의 방식에 관계없이, 서열은 두 개의 폴리펩티드 사이에 삽입될 수 있고, 단일 오픈 리딩 프레임으로부터 다수의 개개의 폴리펩티드의 생산에 영향을 미칠 수 있다. 본 발명의 맥락에서, FMDV 2A 서열은 적어도 두 개의 CMV 단백질을 암호화하는 서열들 사이에 삽입될 수 있고, 단일 오픈 리딩 프레임의 일부로서 그것들의 합성이 생각된다. 예를 들어, 오픈 리딩 프레임은 바이러스 2A 부위를 암호화하는 서열에 의해 분리된 gH 단백질 및 gL 단백질을 암호화할 수도 있다. 어떤 적합한 바이러스 2A 서열도 이용될 수 있다. 종종, 바이러스 2A 부위는 공통 서열 Asp-Val/Ile-Glu-X-Asn-Pro-

Gly-Pro을 포함하며, 여기에서 X는 어떤 아미노산 (SEQ ID NO:2)일 수도 있다. 예를 들어, 구제역 (Foot and Mouth Disease) 바이러스 2A 펩티드 서열은 DVESNPGP (SEQ ID NO:3)이다. Trichas et al, "Use of the viral 2A peptide for bicistronic expression in transgenic mice", BMC Biol. 2008 Sep 15;6:40, 및 Halpin et al, "Self-processing 2A-polyproteins--a system for co-ordinate expression of multiple proteins in transgenic plants", Plant J. 1999 Feb;17(4):453-9 참조.

[0051] 일부 구체예에서, 알파바이러스 레플리콘은 VEE-신드비스 키메라 레플리콘 (VCR) 또는 VEE 균주 TC83 레플리콘 (TC83R) 또는 TC83-신드비스 키메라 레플리콘 (TC83CR)과 같은, 키메라 레플리콘이다. 일부 구체예에서, VCR은 nsP3의 서열의 위치에서 및 VEE 레플리콘의 3' 말단에서 패키징 시그날 및 신드비스 레플리콘의 3' UTR을 함유한다; Perri et al, J. Virol. 77, 10394-403, 2003 참조. 일부 구체예에서, TC83CR은 패키징 시그날 및 nsP3의 서열의 위치에서 및 VEE 균주 TC83레플리콘의 3' 말단에서 신드비스 레플리콘의 3' UTR을 함유한다.

[0052] **VRP 생산**

[0053] VRP를 제조하는 방법은 업계에 잘 알려져 있다. 일부 구체예에서, 알파바이러스는 패키징 세포를 이용하여 VRP로 조립된다. "알파바이러스 패키징 세포" (또는 "패키징 세포")는 하나 이상의 알파바이러스 구조 단백질 발현 카세트를 함유하고 알파바이러스 레플리콘, 진핵세포층 벡터 개시 시스템 (예를 들어, 미국 특허 5,814,482), 또는 재조합 알파바이러스 입자의 도입 후 재조합 알파바이러스 입자를 생산하는 세포이다. 하나 이상의 다른 알파바이러스 구조 단백질 카세트는 알파바이러스 구조 단백질을 제공함으로써 "헬퍼"의 역할을 한다. "알파바이러스 구조 단백질 카세트"는 하나 이상의 알파바이러스 구조 단백질을 암호화하는 발현 카세트이고 알파바이러스 레플리카제 인식 서열의 적어도 하나 및 최대 다섯 개의 카피 (즉, 1, 2, 3, 4, 또는 5)를 포함한다. 구조 단백질 발현 카세트는 전형적으로, 5'에서 3'으로, 알파바이러스 RNA의 전사를 개시하는 5' 서열, 임의의 알파바이러스 서브게놈 영역 프로모터, 알파바이러스 구조 단백질을 암호화하는 뉴클레오티드 서열, 3' 번역되지 않은 영역 (이것은 또한 RNA 전사를 지시한다), 폴리A 구역을 포함한다. 예를 들어, WO 2010/019437 참조.

[0054] 바람직한 구체예에서, 두 개의 다른 알파바이러스 구조 단백질 카세트 ("분할" 결핍 헬퍼)는 복제-성분 바이러스를 생산할 수 있는 재조합 이벤트를 최소화하기 위해 패키징 세포에서 이용된다. 일부 구체예에서, 알파바이러스 구조 단백질 카세트는 캡시드 단백질 (C)을 암호화하지만 당단백질 (E2 및 E1) 중 어느 것도 암호화하지 않는다. 일부 구체예에서, 알파바이러스 구조 단백질 카세트는 캡시드 단백질 및 E1 또는 E2 당단백질 (하지만 둘 다는 아님)을 암호화한다. 일부 구체예에서 알파바이러스 구조 단백질 카세트는 E2 및 E1 당단백질을 암호화하지만 캡시드 단백질은 아니다. 일부 구체예에서, 알파바이러스 구조 단백질 카세트는 E1 또는 E2 당단백질 (하지만 둘 다는 아님)을 암호화하지만 캡시드 단백질은 아니다.

[0055] 일부 구체예에서, VRP는 레플리콘 및 헬퍼 RNA의 다양한 근원의 세포 내로 동시의 도입에 의해 생산된다. 예를 들어, 이 조건 하에 BHKV 세포 (1×10^7)는, 예를 들어, 220 볼트, 1000 μF, 10 μg 레플리콘 RNA:6 μg 결핍된 헬퍼 Cap RNA:10 μg 결핍된 헬퍼 Gly RNA로 2번 수동 펄스로 전기 천공되고, 알파바이러스를 함유하는 상층액은 약 24 시간 후 수거된다. 레플리콘 및/또는 헬퍼는 또한 트랜스펙션된 세포 내에 적합한 RNA를 론치 (launch)하는 DNA 형태로 도입될 수 있다.

[0056] 패키징 세포는 포유동물 세포 또는 곤충 (예를 들어, SF9) 또는 조류 세포 (1차 병아리 또는 오리 섬유아세포 또는 섬유아세포 세포주)와 같은 비포유동물 세포일 수도 있다. 미국 특허 7,445,924 참조. 조류 근원의 세포는 EB66® (VIVALIS)와 같은 조류 배아 줄기 세포; EBx® 세포와 같은 닭 배아 줄기 세포를 포함하는 닭 세포, 닭 배아 섬유아세포 및 닭 배아 생식 세포; 예를 들어, Vaccine 27:4975-4982 (2009) 및 WO2005/042728에 설명된 AGE1.CR 및 AGE1.CR.pIX 세포주 (ProBioGen)과 같은 오리 세포; 및 거위 세포를 포함하지만, 이에 제한되지 않는다. 일부 구체예에서, 패키징 세포는 1차 오리 섬유아세포 또는 AGE.CR (PROBIOGEN)과 같은 오리 망막 세포주이다.

[0057] 동시 핵산 도입에 대한 포유동물 근원의 세포 및/또는 패키징 세포는 WO 01/38362 및 WO 02/40665에 설명되는 PerC6 (PER.C6) 세포 (CRUCELL N.V.) 뿐만 아니라 ECACC 수탁 번호 96022940 하에 기탁된 것들; MRC-5 (ATCC CCL-171); WI-38 (ATCC CCL-75); 태아 붉은털원숭이 폐 세포 (ATCC CL-160); 사람 배아 신장 세포 (예를 들어, 293 cells, 전형적으로 전단된 아데노바이러스 타입 5 DNA로 트랜스펙션됨); 원숭이 신장의 VERO 세포; 말, 소, (예를 들어, MDBK 세포), 양, 개 (예를 들어, 개 신장의 MDCK 세포, ATCC CCL34 MDCK (NBL2) 또는 MDCK 33016, WO 97/37001에 설명된 바와 같은 수탁 번호 DSM ACC 2219)의 세포; 고양이, 쥐 (예를 들어, BHK21-F, 및 HKCC 세포와 같은 햄스터 세포, 또는 중국 햄스터 난소 (CHO) 세포)의 세포를 포함하는, 사람 또는 비-사람 영장류 세포를 포함하지만, 이에 제한되지 않고, 예를 들어, 성인, 신생아, 태아, 및 배아를 포함하는 다양한 발달 단

계로부터 얻어질 수도 있다.

[0058] 일부 구체예에서, 패키징 세포는 하나 이상의 구조 단백질 발현 카세트(들)로 안정하게 트랜스펙션된다. 구조 단백질 발현 카세트는 트랜스페린-다가 양이온-매개 DNA 전이, 노출된 또는 캡슐화된 핵산으로 트랜스펙션, 리포솜-매개 세포 융합, 바이러스 감염, 전기 천공, "유전자 총 (gene gun)" 방법, 및 DEAE-또는 인산 칼슘-매개 트랜스펙션을 포함하는, 표준 재조합 DNA 기술을 이용하여 세포 내로 도입될 수 있다. 구조 단백질 발현 카세트는 전형적으로 DNA 분자로서 숙주 세포 내로 도입되지만, 또한 시험관 내-전사된 RNA로서 도입될 수 있다. 각각의 발현 카세트는 별도로 또는 실질적으로 동시에 도입될 수 있다.

[0059] 일부 구체예에서, 안정한 알파바이러스 패키징 세포주는 재조합 알파바이러스 입자를 생산하는데 이용된다. 이것들은 게놈에 안정하게 포함되는 결핍된 헬퍼 RNA를 발현하는 DNA 카세트를 포함하는 알파바이러스-허용 세포이다. Polo et al, Proc. Natl. Acad. Sci. USA 96, 4598-603, 1999 참조. 헬퍼 RNA는 본질적으로 발현되지만 알파바이러스 구조 단백질은 아닌데, 유전자가 알파바이러스 서브게놈 프로모터의 조절 하에 있기 때문이다 (Polo et al., 1999). 알파바이러스 레플리콘의 트랜스펙션 또는 VRP 감염에 의한 패키징 세포의 게놈 내 도입 시, 레플리카제 효소가 생산되고 헬퍼 RNA에서 캡시드 및 당단백질 유전자의 발현을 유발하고 결과 VRP가 생산된다. 레플리콘의 도입은 알파바이러스 레플리콘 입자의 종자로 트랜스펙션 및 감염을 포함하는, 다양한 방법으로 달성될 수 있다. 패키징 세포는 배양 상층액에서 포장된 알파바이러스 레플리콘 입자를 생산하는데 충분한 조건 하에 및 시간 동안 배양된다.

[0060] 따라서, 패키징 세포는 VRP가 자가-번식 바이러스로서 작용하게 한다. 이 기술은 VRP가 아데노바이러스 E1A 및 E1B 유전자를 발현하는 세포에서 성장한 복제-불가능 아데노바이러스 벡터와 같이, 살아있는 감쇠 백신 또는 이용 가능한 생산자 세포주를 갖는 다른 바이러스 벡터에 이용된 것들과 거의 같은 방식으로, 및 같은 장비를 이용하여 생산되게 한다.

[0061] 일부 구체예에서, 2-단계 공정이 이용된다: 제 1단계는 패키징 세포를 레플리콘 RNA 또는 플라스미드 DNA-기반 레플리콘으로 트랜스펙션함으로써 알파바이러스 레플리콘 입자의 종자를 생산하는 단계를 포함한다. 이 감염은 MOI=0.00001, 0.00005, 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, 3, 5, 10 또는 20을 포함하는, 다양한 감염 다중도 (multiplicities of infection; MOI)를 이용하여 수행될 수 있다. 일부 구체예에서, 감염은 낮은 MOI (예를 들어, 1 미만)로 수행된다. 시간이 지남에 따라, 레플리콘 입자는 종자로 감염된 패키징 세포 내로부터 수확될 수 있다. 일부 구체예에서, 레플리콘 입자는 반복되는 낮은 감염 다중도에 의해 나이브 (naive) 패키징 세포의 더 큰 배양으로 계대 배양될 수 있으며, 같은 높은 역가를 갖는 상업적 규모의 조제물을 발생시킨다.

[0062] **자가 복제 RNA 플랫폼**

[0063] 둘 이상의 CMV 단백질은 대상체의 세포의 단백질을 암호화하는 재조합 핵산의 발현에 의해 생산될 수 있다. 바람직하게는, 재조합 핵산 분자는 둘 이상의 CMV 단백질을 암호화하는데, 예를 들어, 폴리시스트론성인 것들이다. 상기 정의된 바와 같이, "폴리시스트론성"은 바이시스트론성을 포함한다. CMV 단백질의 생산을 유발하기 위해 대상체에 투여될 수 있는 바람직한 핵산은 자가 복제 RNA 분자이다. 본 발명의 자가 복제 RNA 분자는 RNA 바이러스의 게놈 RNA에 기초하지만, 하나 이상의 구조 단백질을 암호화하는 유전자가 결핍된다. 자가 복제 RNA 분자는 RNA 바이러스의 비-구조 단백질 및 자가 복제 RNA에 의해 암호화된 CMV 단백질을 생산하기 위해 번역될 수 있다.

[0064] 자가 복제 RNA는 일반적으로 바이러스 레플리카제, 바이러스 프로테아제, 바이러스 헬리카제 및 다른 비구조 바이러스 단백질로 구성된 그룹으로부터 선택되는 적어도 하나 이상의 유전자를 함유하고, 또한 5'-및 3'-말단 씨스-활성 복제 서열, 및 둘 이상의 원하는 CMV 단백질을 암호화하는 이종 기원 서열을 포함한다. 이종 기원 서열(들)의 발현을 지시하는 서브게놈 프로모터는 자가 복제 RNA에 포함될 수 있다. 원하는 경우, 이종 기원 서열은 자가 복제 RNA의 다른 암호화 지역에 대한 프레임에 융합될 수도 있고 및/또는 내부 리보솜 유입점 (IRES)의 조절하에 있을 수도 있다.

[0065] 본 발명의 자가 복제 RNA 분자는 감염성 바이러스 입자의 생산을 유발할 수 없도록 설계될 수 있다. 이것은, 예를 들어, 자가 복제 RNA에서 바이러스 입자의 생산에 필요한 구조 단백질을 암호화하는 하나 이상의 바이러스 유전자를 생략함으로써 달성될 수 있다. 예를 들어, 자가 복제 RNA 분자가 신드비스 바이러스 (SIN), 셈리키 포레스트 바이러스 및 베네수엘라 말 뇌염 바이러스 (VEE)와 같은 알파바이러스에 기초할 때, 캡시드 및/또는 외피 당단백질과 같은 바이러스 구조 단백질을 암호화하는 하나 이상의 유전자는 생략될 수 있다. 원하는 경우,

본 발명의 자가 복제 RNA 분자는 약화되거나 악성인 감염성 바이러스 입자의 생산을 유발하도록, 또는 다음 단일 라운드의 감염이 가능한 바이러스 입자를 생산하도록 설계될 수 있다.

[0066] 자가 복제 RNA 분자는, 어떤 단백질도 없이 척추동물 세포에 전달될 때, 자체의 (또는 자체의 안티센스 카피의) 전사에 의해 다수의 딸 RNA의 생산으로 이어질 수 있다. 자가 복제 RNA는 세포에 전달 후 바로 번역될 수 있고, 이 번역은 전달된 RNA의 전사물을 생산하는 RNA-의존 RNA 폴리머라제를 제공한다. 따라서 전달된 RNA는 다수의 딸 RNA의 생산으로 이어진다. 이 전사물들은 전달된 RNA에 관하여 안티센스이고 암호화된 CMV 단백질의 제자리 발현을 제공하기 위해 스스로 번역될 수도 있거나, 암호화된 CMV 단백질(들)의 제자리 발현을 제공하도록 번역된 전달된 RNA와 같은 센스를 갖는 전사물을 추가로 생산하기 위해 전사될 수도 있다.

[0067] 자가 복제를 달성하기 위한 한 적합한 시스템은 알파바이러스-기반 RNA 레플리콘, 예를 들어, 여기에 설명된 바와 같이 알파바이러스 레플리콘을 이용하는 것이다. 이 + 나선 레플리콘은 레플리카제 (또는 레플리카제-트랜스크립타제)를 생산하기 위해 세포에 전달 후 번역된다. 레플리카제는 + 나선 전달된 RNA의 게놈-나선 카피를 생성하는 복제 복합체를 제공하기 위해 자동 분할되는 다단백질로서 번역된다. 이들-나선 전사물은 + 나선 모체 RNA의 추가의 카피를 제공하기 위해 및 또한 둘 이상의 CMV 단백질을 암호화하는 하나 이상의 서브게놈 전사물을 유발하기 위해 스스로 전사될 수 있다. 서브게놈 전사물의 번역은 감염된 세포에 의해 CMV 단백질(들)의 제자리 발현으로 이어진다. 적합한 알파바이러스 레플리콘은 신드비스 바이러스, 셈리키 포레스트 바이러스, 이스턴 말 뇌염 바이러스, 베네수엘라 말 뇌염 바이러스, 등의 레플리카제를 이용할 수 있다.

[0068] 바람직한 자가 복제 RNA 분자는 (i) 자가 복제 RNA 분자로부터 RNA를 전사할 수 있는 RNA-의존 RNA 폴리머라제 및 (ii) 둘 이상의 CMV 단백질 또는 이들의 단편을 암호화한다. 폴리머라제는, 예를 들어, 알파바이러스 단백질 nsP4를 포함하는 알파바이러스 레플리카제일 수 있다. 단백질 nsP4는 레플리카제의 주요 촉매 성분이다.

[0069] 자연 알파바이러스 게놈은 비구조 레플리카제 다단백질에 더하여 구조 비리온 단백질을 암호화하는 한편, 본 발명의 자가 복제 RNA 분자 기반 알파바이러스나 모든 알파바이러스 구조 단백질을 암호화하지 않는 것이 바람직하다. 따라서 자가 복제 RNA는 세포에서 자체의 게놈 RNA 카피의 생산으로 이어질 수 있지만, RNA-함유 알파바이러스 비리온의 생산은 아니다. 이 비리온을 생산할 수 없는 것은, 야생형 알파바이러스와 달리, 자가 복제 RNA 분자가 자체를 감염성 형태로 영구화할 수 없다는 것을 의미한다. 야생형 바이러스의 영구화에 필요한 알파바이러스 구조 단백질은 본 발명의 자가 복제 RNA에 없고 그것들의 위치는 원하는 유전자 생성물 (CMV 단백질 또는 이들의 단편)을 암호화하는 유전자(들)에 의해 취해지고, 서브게놈 전사물은 구조 알파바이러스 비리온 단백질 대신에 원하는 유전자 생성물을 암호화한다.

[0070] 따라서 본 발명에 유용한 자가 복제 RNA 분자는 다른 CMV 단백질 또는 이들의 단편을 암호화하는 두 개의 서열을 갖는다. CMV 단백질 또는 단편을 암호화하는 서열은 어떤 원하는 방향일 수도 있고, 같은 또는 별도의 프로모터에 작동 가능하게 연결될 수 있다. 원하는 경우, CMV 단백질 또는 단편을 암호화하는 서열은 단일 오픈 리딩 프레임의 일부일 수 있다. 일부 구체예에서, RNA는 하나 이상의 추가적인 (다운스트림) 서열 또는, 예를 들어, 다른 추가적인 CMV 단백질 또는 이들의 단편을 암호화하는 오픈 리딩 프레임을 가질 수도 있다. 자가 복제 RNA 분자는 암호화된 레플리카제와 호환되는 5' 서열을 가질 수 있다.

[0071] 한 양태에서, 자가 복제 RNA 분자는 여기에 정의된 바와 같이 알파바이러스 레플리콘과 같은, 알파바이러스로부터 유도되거나 이에 기초한다. 다른 양태에서, 자가 복제 RNA 분자는 알파바이러스 이외의 바이러스, 바람직하게는, 양성-가닥 RNA 바이러스, 및 더 바람직하게는 피코르나바이러스 (picornavirus), 플라비바이러스 (flavivirus), 루비바이러스 (rubivirus), 페스티바이러스 (pestivirus), 헤파시바이러스 (hepacivirus), 칼리시바이러스 (calicivirus), 또는 코로나바이러스 (coronavirus)로부터 유도되거나 이에 기초한다. 적합한 야생형 알파바이러스 서열은 잘 알려져 있고 American Type Culture Collection, Rockville, Md와 같은, 서열 수탁소로부터 이용 가능하다. 적합한 알파바이러스의 적합한 예는 아우라 (ATCC VR-368), 베바루 바이러스 (Bebaru virus; ATCC VR-600, ATCC VR-1240), 카바쏘우 (Cabassou; ATCC VR-922), 치쿤군야 바이러스 (ATCC VR-64, ATCC VR-1241), 이스턴 말 뇌염 바이러스 (ATCC VR-65, ATCC VR-1242), 포트 모건 (ATCC VR-924), 게타 바이러스 (ATCC VR-369, ATCC VR-1243), 키질라가크 (ATCC VR-927), 마야로 바이러스 (ATCC VR-66; ATCC VR-1277), 미들부르크 (ATCC VR-370), 무캄보 바이러스 (ATCC VR-580, ATCC VR-1244), 은두무 (ATCC VR-371), 픽수나 바이러스 (ATCC VR-372, ATCC VR-1245), 로스 리버 바이러스 (ATCC VR-373, ATCC VR-1246), 셈리키 포레스트 (ATCC VR-67, ATCC VR-1247), 신드비스 바이러스 (ATCC VR-68, ATCC VR-1248), 토나테 (Tonate; ATCC VR-925), 트리니티 (Triniti; ATCC VR-469), 우나 (ATCC VR-374), 베네수엘라 말 뇌염 (ATCC VR-69, ATCC VR-923, ATCC VR-1250 ATCC VR-1249, ATCC VR-532), 웨스턴 말 뇌염 (ATCC VR-70, ATCC VR-1251, ATCC VR-622, ATCC VR-

1252), 화타로아 (ATCC VR-926), 및 Y-62-33 (ATCC VR-375)을 포함한다.

[0072] 본 발명의 자가 복제 RNA 분자는 하나 이상의 변형된 뉴클레오티드를 함유할 수 있고 그러므로 개선된 안정성을 갖고 생체 내에서 분해 및 제거에 대하여 저항성이고, 다른 이점을 갖는다. 어떤 특정 이론에 결부되지 않고, 자가 복제 RNA가 세포 내로 전달될 때 변형된 뉴클레오티드를 함유하는 자가 복제 RNA 분자는 엔도솜 및 세포질 면역 수용체의 자극을 방지하거나 감소시키는 것으로 생각된다. 이것은 단백질의 자가 복제, 증폭 및 발현이 발생하는 것을 허용한다. 이것은 또한 변형된 뉴클레오티드를 함유하지 않는 자가 복제 RNA에 관하여 안전 의식을 감소시키는데, 변형된 뉴클레오티드를 함유하는 자가 복제 RNA가 선천적인 면역 시스템의 활성화 및 이후의 원하지 않는 결과 (예를 들어, 주사 부위의 염증, 주사 부위의 자극, 통증, 등)를 감소시키기 때문이다. 또한 자가 복제의 결과로서 생산된 RNA 분자는 세포질 면역 수용체에 의해 외부 핵산으로 인식되는 것으로 생각된다. 따라서, 변형된 뉴클레오티드를 함유하는 자가 복제 RNA 분자는 숙주 세포에서 RNA의 효율적인 증폭 및 CMV 단백질의 발현, 뿐만 아니라 보조 효과를 제공한다.

[0073] RNA 서열은, 예를 들어, 번역 효과 및 RNA의 반감기를 증가시키기 위해 그것의 코돈 이용에 대하여 변형될 수 있다. 폴리 A 꼬리 (예를 들어, 약 30개 이상의 아데노신 잔기의)는 그것의 반감기를 증가시키기 위해 RNA의 3' 말단에 부착될 수도 있다. RNA의 5' 말단은 구조 m7G (5') ppp (5') N (캡 0 구조) 또는 이들의 유도체를 갖는 변형된 리보뉴클레오티드로 캐핑 (capped)될 수도 있으며, 이것은 RNA 합성 중에 포함될 수 있거나 RNA 전사 후 효소로 설계될 수 있다 (예를 들어, 이것은 N7-모노메틸화된 캡 0 구조의 구성을 촉진하는, mRNA 트리포스파타제, 구아닐일-트랜스퍼라제 및 구아닌-7-메티트랜스퍼라제로 구성된 우두 바이러스 캐핑 효소 (VCE)를 이용하여). 캡 0 구조는 RNA 분자에 대한 안정성 및 번역 효과를 제공할 수 있다. RNA 분자의 5' 캡은 캡 1 구조 (m7Gppp [m2'-O]N)의 발생을 일으키는 2'-O-메틸트랜스퍼라제에 의해 추가로 변형될 수도 있으며, 이것은 번역 효과를 추가로 증가시킬 수도 있다. 캡 1 구조는 또한 생체 내 효능을 증가시킬 수도 있다.

[0074] 여기에 이용된 바와 같이, "변형된 뉴클레오티드"는 뉴클레오시드 (예를 들어, 시토신 (C), 티민 (T) 또는 유라실 (U), 아데닌 (A) 또는 구아닌 (G))의 질소 염기에서 또는 위에 하나 이상의 화학적 변형 (예를 들어, 치환)을 함유하는 뉴클레오티드를 나타낸다. 원하는 경우, 자가 복제 RNA 분자는 뉴클레오시드의 당 모이어티 (예를 들어, 리보스, 데옥시리보스, 변형된 리보스, 변형된 데옥시리보스, 6-멤버의 당 유사체, 또는 오픈-사슬 당 유사체), 또는 포스페이트에서 또는 위에 화학적 변형을 함유할 수 있다.

[0075] 자가 복제 RNA 분자는 적어도 하나의 변형된 뉴클레오티드를 함유할 수 있고, 이것은 바람직하게 5' 캡의 일부가 아니다 (예를 들어, 5'' 캡의 일부인 변형에 더하여). 따라서, 자가 복제 RNA 분자는 단일 위치에서 변형된 뉴클레오티드를 함유할 수 있고, 둘 이상의 위치에서 특정 변형된 뉴클레오티드 (예를 들어, 슈도유리딘, N6-메틸아데노신, 5-메틸시티딘, 5-메틸유리딘)을 함유할 수 있거나, 둘, 셋, 넷, 다섯, 여섯, 일곱, 여덟, 아홉, 열 개 이상의 변형된 뉴클레오티드 (예를 들어, 하나 이상의 위치에서 각각)를 함유할 수 있다. 바람직하게는, 자가 복제 RNA 분자는 질소 염기 상에 또는 질소 염기에 변형을 함유하는 변형된 뉴클레오티드를 포함하지만, 변형된 당 또는 포스페이트 모이어티를 함유하지 않는다.

[0076] 일부 예에서, 자가 복제 RNA 분자의 뉴클레오티드 중 0.001% 내지 99%는 변형된 뉴클레오티드이다. 예를 들어, 자가 복제 RNA 분자의 뉴클레오티드중 0.001%-25%, 0.01%-25%, 0.1%-25%, 또는 1%-25%는 변형된 뉴클레오티드이다.

[0077] 다른 예에서, 자가 복제 RNA 분자의 특정 변형되지 않은 뉴클레오티드 중 0.001% 내지 99% 또는 100%는 변형된 뉴클레오티드로 대체된다. 예를 들어, 유리딘을 함유하는 자가 복제 RNA 분자 중 약 1%는, 예를 들어, 유리딘의 슈도유리딘으로의 대체에 의해 변형될 수 있다. 다른 예에서, 자가 복제 RNA 분자에서 둘, 셋, 또는 네 개의 특정 뉴클레오티드 (유리딘, 시티딘, 구아노신, 또는 아데닌을 함유하는 뉴클레오티드)의 원하는 양 (퍼센트)은 변형된 뉴클레오티드이다. 예를 들어, 자가 복제 RNA 분자의 특정 뉴클레오티드 중 0.001%-25%, 0.01%-25%, 0.1%-25, 또는 1%-25%는 변형된 뉴클레오티드이다. 다른 예에서, 자가 복제 RNA 분자의 특정 뉴클레오티드 중 0.001%-20%, 0.001%-15%, 0.001%-10%, 0.01%-20%, 0.01%-15%, 0.1%-25, 0.01%-10%, 1%-20%, 1%-15%, 1%-10%, 또는 약 5%, 약 10%, 약 15%, 약 20%는 변형된 뉴클레오티드이다.

[0078] 자가 복제 RNA 분자의 뉴클레오티드 중 100% 미만이 변형된 뉴클레오티드인 것이 바람직하다. 또한 자가 복제 RNA 분자 중 특정 뉴클레오티드의 100% 미만이 변형된 뉴클레오티드인 것이 바람직하다. 따라서, 바람직한 자가 복제 RNA 분자는 적어도 일부 변형되지 않은 뉴클레오티드를 포함한다.

[0079] 포유동물 RNA에서 발견된 96개 이상의 자연 발생 뉴클레오시드 변형이 있다. 예를 들어, Limbach et al.,

Nucleic acids Research, 22(12):2183-2196 (1994) 참조. 예를 들어, 미국 특허 번호 4373071, 4458066, 4500707, 4668777, 4973679, 5047524, 5132418, 5153319, 5262530, 5700642의 뉴클레오티드 및 변형된 뉴클레오티드 및 뉴클레오시드의 제조는 업계에 잘 알려져 있으며, 이것들 모두는 전문이 본원에 참고로 포함되고, 많이 변형된 뉴클레오시드 및 변형된 뉴클레오티드는 상업적으로 이용 가능하다.

[0080] 변형된 뉴클레오시드 및 뉴클레오티드에 포함될 수 있고 RNA 분자에 존재할 수 있는 변형된 핵염기는 m5C (5-메틸시티딘), m5U (5-메틸유리딘), m6A (N6-메틸아데노신), s2U (2-티오유리딘), Um (2'-O-메틸유리딘), m1A (1-메틸아데노신); m2A (2-메틸아데노신); Am (2-1-O-메틸아데노신); ms2m6A (2-메틸티오-N6-메틸아데노신); i6A (N6-이소펜테닐아데노신); ms2i6A (2-메틸티오-N6이소펜테닐아데노신); io6A (N6-(씨스-히드록시이소펜테닐)아데노신); ms2hn6A (2-메틸티오-N6-(씨스-히드록시이소펜테닐)아데노신); g6A (N6-글리시닐카르바모일아데노신); t6A (N6-트레오닐 카르바모일아데노신); ms2t6A (2-메틸티오-N6-트레오닐 카르바모일아데노신); m6t6A (N6-메틸-N6-트레오닐카르바모일아데노신); hn6A(N6-히드록시노르발일카르바모일 아데노신); ms2hn6A (2-메틸티오-N6-히드록시노르발일 카르바모일아데노신); Ar(p) (2'-O-리보실아데노신 (포스페이트)); I (이노신); m1I (1-메틸이노신); m'Im (1, 2'-O-디메틸이노신); m3C (3-메틸시티딘); Cm (2T-O-메틸시티딘); s2C (2-티오시티딘); ac4C (N4-아세틸시티딘); f5C (5-포닐시티딘); m5Cm (5, 2-O-디메틸시티딘); ac4Cm (N4아세틸2TO메틸시티딘); k2C (리시딘); m1G (1-메틸구아노신); m2G (N2-메틸구아노신); m7G (7-메틸구아노신); Gm (2'-O-메틸구아노신); m22G (N2, N2-디메틸구아노신); m2Gm (N2, 2'-O-디메틸구아노신); m22Gm (N2, N2, 2'-O-트리메틸구아노신); Gr(p) (2'-O-리보실구아노신 (포스페이트)); yW (위부토신); o2yW (퍼옥시위부토신); OHyW (히드록시위부토신); OHyW* (변형되지 않은 히드록시위부토신); imG (위오신); mimG (메틸구아노신); Q (퀘오신); oQ (에폭시퀘오신); galQ (갈탁토실-퀘오신); manQ (만노실-퀘오신); preQo (7-시아노-7-데아자구아노신); preQi (7-아미노메틸-7-데아자구아노신); G* (아케오신); D (디히드로유리딘); m5Um (5, 2'-O-디메틸유리딘); s4U (4-티오유리딘); m5s2U (5-메틸-2-티오유리딘); s2Um (2-티오-2'-O-메틸유리딘); acp3U (3-(3-아미노-3-카르복시프로필)유리딘); ho5U (5-히드록시유리딘); mo5U (5-메톡시유리딘); cmo5U (유리딘 5-옥시아세트산); mcmo5U (유리딘 5-옥시아세트산 메틸 에스테르); chm5U (5-(카르복시히드록시메틸)유리딘)); mchm5U (5-(카르복시히드록시메틸)유리딘 메틸 에스테르); mcm5U (5-메톡시카르보닐 메틸유리딘); mcm5Um (S-메톡시카르보닐메틸-2-O-메틸유리딘); mcm5s2U (5-메톡시카르보닐메틸-2-티오유리딘); nm5s2U (5-아미노메틸-2-티오유리딘); mnm5U (5-메틸아미노메틸유리딘); mnm5s2U (5-메틸아미노메틸-2-티오유리딘); mnm5se2U (5-메틸아미노메틸-2-셀레노유리딘); ncm5U (5-카르바모일메틸 유리딘); ncm5Um (5-카르바모일메틸-2'-O-메틸유리딘); cmnm5U (5-카르복시메틸아미노메틸유리딘); cnmm5Um (5-카르복시메틸아미노메틸-2-L-O메틸유리딘); cmnm5s2U (5-카르복시메틸아미노메틸-2-티오유리딘); m62A (N6, N6-디메틸아데노신); Tm (2'-O-메틸이노신); m4C (N4-메틸시티딘); m4Cm (N4, 2-O-디메틸시티딘); hm5C (5-히드록시메틸시티딘); m3U (3-메틸유리딘); cm5U (5-카르복시메틸유리딘); m6Am (N6, T-O-디메틸아데노신); rn62Am (N6, N6, O-2-트리메틸아데노신); m2'7G (N2, 7-디메틸구아노신); m2'2'7G (N2, N2, 7-트리메틸구아노신); m3Um (3, 2T-O-디메틸유리딘); m5D (5-메틸디히드로유리딘); f5Cm (5-포밀-2'-O-메틸시티딘); m1Gm (1, 2'-O-디메틸구아노신); m'Am (1, 2-O-디메틸 아데노신) 이리노메틸유리딘); tm5s2U (S-타우리노메틸-2-티오유리딘)); imG-14 (4-데메틸 구아노신); imG2 (이소구아노신); ac6A (N6-아세틸아데노신), 히폭산틴, 이노신, 8-옥소-아데닌, 7-치환된 이들의 유도체, 디히드로유라실, 슈도유라실, 2-티오유라실, 4-티오유라실, 5-아미노유라실, 5-(C_1-C_6)-알킬유라실, 5-메틸유라실, 5-(C_2-C_6)-알케닐유라실, 5-(C_2-C_6)-알키닐유라실, 5-(히드록시메틸)유라실, 5-클로로유라실, 5-플루오로유라실, 5-브로모유라실, 5-히드록시시토신, 5-(C_1-C_6)-알킬시토신, 5-메틸시토신, 5-(C_2-C_6)-알케닐시토신, 5-(C_2-C_6)-알키닐시토신, 5-클로로시토신, 5-플루오로시토신, 5-브로모시토신, N2-디메틸구아닌, 7-데아자구아닌, 8-아자구아닌, 7-데아자-7-치환된 구아닌, 7-데아자-7-(C_2-C_6)알키닐구아닌, 7-데아자-8-치환된 구아닌, 8-히드록시구아닌, 6-티오구아닌, 8-옥소구아닌, 2-아미노퓨린, 2-아미노-6 클로로퓨린, 2, 4-디아미노퓨린, 2, 6-디아미노퓨린, 8-아자퓨린, 치환된 7-데아자퓨린, 7-데아자-7-치환된 퓨린, 7-데아자-8-치환된 퓨린, 수소 (무염기 잔기), m5C, m5U, m6A, s2U, W, 또는 2'-O-메틸-U를 포함한다. 이 변형된 핵염기 중 어느 하나 또는 어느 조합도 본 발명의 자가 복제 RNA에 포함될 수 있다. 이 변형된 핵염기 및 그것들의 해당 리보뉴클레오시드의 대부분은 상업적 공급자로부터 이용 가능하다. 원하는 경우, 자가 복제 RNA 분자는 포스포르아미데이트, 포스포로티오에이트, 및/또는 메틸포스포네이트 연결을 함유할 수 있다.

[0081] 적어도 하나의 변형된 뉴클레오티드를 포함하는 자가 복제 RNA 분자는 어떤 적합한 방법을 이용하여 제조될 수 있다. 변형된 뉴클레오티드를 함유하는 RNA 분자를 생산하는 다수의 적합한 방법은 업계에 알려져 있다. 예를 들어, 변형된 뉴클레오티드를 함유하는 RNA 분자는 적합한 DNA-의존 RNA 폴리머라제, 예를 들어, T7 파지 RNA

폴리머라제, SP6 파지 RNA 폴리머라제, T3 파지 RNA 폴리머라제, 등, 또는 변형된 뉴클레오티드의 RNA 분자에 효율적인 포함을 허용하는 이 폴리머라제의 돌연변이를 이용하여 자가 복제 RNA 분자를 암호화하는 DNA를 전사(예를 들어, 시험관 내 전사)함으로써 제조될 수 있다. 전사 반응은 뉴클레오티드 및 변형된 뉴클레오티드, 및 적합한 완충액, 및 적합한 염과 같은, 선택된 폴리머라제의 활성을 지원하는 다른 요소를 함유할 것이다. 뉴클레오티드 유사체의 자가 복제 RNA에 포함은, 예를 들어, 이러한 RNA 분자의 안정성을 변화시키기 위해, RN아제에 대한 저항성을 증가시키기 위해, 적절한 숙주 세포 내로 도입 후 복제 (RNA의 "감염성")를 확립하기 위해, 및/또는 선천적 및 후천적 면역 반응을 유발하거나 감소시키기 위해, 설계될 수도 있다.

[0082] 하나 이상의 변형된 뉴클레오티드를 함유하는 자가 복제 RNA 분자를 생산하기 위하여, 적합한 합성 방법은 단독으로, 또는 하나 이상의 다른 방법 (예를 들어, 재조합 DNA 및 RNA 기술)과 조합하여 이용될 수 있다. 데 노보 (de novo) 합성에 적합한 방법은 업계에 잘 알려져 있고 특정 용도로 적용될 수 있다. 전형적인 방법은, 예를 들어, CEM과 같은 적합한 보호기를 이용하는 화학적 합성 (Masuda et al., (2007) Nucleic Acids Symposium Series 57:3-4), β-시아노에틸 포스포르아미디트 방법 (Beaucage S L et al. (1981) Tetrahedron Lett 22: 1859); 뉴클레오시드 H-포스포네이트 방법 (Garegg P et al. (1986) Tetrahedron Lett 27:4051-4; Froehler B C et al. (1986) Nucl Acid Res 14:5399-407; Garegg P et al. (1986) Tetrahedron Lett 27:4055-8; Gaffney B L et al. (1988) Tetrahedron Lett 29:2619-22). 이 화학법들은 상업적으로 이용 가능한 자동화된 핵산 합성기를 이용하여 수행되거나 적용될 수 있다. 추가적인 적합한 합성 방법은 Uhlmann et al. (1990) Chem Rev 90:544-84, 및 Goodchild J (1990) Bioconjugate Chem 1: 165에 개시된다. 핵산 합성은 또한 폴리뉴클레오티드 및 이러한 폴리뉴클레오티드에 의해 암호화된 유전자 생성물의 클로닝, 가공, 및/또는 발현을 포함하는, 업계에 잘 알려져 있고 통상적인 적합한 재조합 방법을 이용하여 수행될 수 있다. 유전자 단편 및 합성 폴리뉴클레오티드의 무작위 단편화 및 PCR 재결합에 의한 DNA 셔플링은 폴리뉴클레오티드 서열을 디자인 및 설계하기 위해 이용될 수 있다.

[0083] 부위-방향 돌연변이 발생은, 예를 들어, 새로운 제한 부위를 삽입하고, 글리코실화 패턴을 변화시키고, 코돈 선호도를 바꾸고, 스플라이스 변이체를 생산하고, 돌연변이를 도입하기 위해 핵산 및 암호화된 단백질을 변화시키기 위해 이용될 수 있다. 핵산 서열의 전사, 번역 및 발현을 위한 적합한 방법은 업계에 알려져 있고 통상적이다. (일반적으로, Current Protocols in Molecular Biology, Vol. 2, Ed. Ausubel, et al., Greene Publish. Assoc. & Wiley Interscience, Ch. 13, 1988; Glover, DNA Cloning, Vol. II, IRL Press, Wash., D.C., Ch. 3, 1986; Bitter, et al., in Methods in Enzymology 153:516-544 (1987); The Molecular Biology of the Yeast Saccharomyces, Eds. Strathern et al., Cold Spring Harbor Press, Vols. I and II, 1982; 및 Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, 1989. 참조)

[0084] 자가 복제 RNA 분자에서 하나 이상의 변형된 뉴클레오티드의 존재 및/또는 양은 어떤 적합한 방법을 이용하여 결정될 수 있다. 예를 들어, 자가 복제 RNA는 모노포스페이트에 분해되고 (예를 들어, 뉴클레아제 PI) 탈인산화될 수 있고 (예를 들어, CIAP와 같은 적합한 포스파타제를 이용하여), 결과의 뉴클레오시드는 역상 (reversed phase) HPLC (예를 들어, YMC Pack ODS-AQ 컬럼 (5 미크론, 4.6 X 250 mm)을 이용하여) 및 구배, 0% B (0-5 분) 내지 100% B (5-13 분) 및 100 % B (13-40 분), 유속 (0.7 ml/ 분), UV 검출 (파장: 260 nm), 컬럼 온도 (30 ℃)를 이용하여 용출에 의해 분석된다. 완충액 A (20mM 아세트산-암모늄 아세테이트 pH 3.5), 완충액 B (20mM 아세트산-암모늄 아세테이트 pH 3.5/메탄올 [90/10])).

[0085] 자가 복제 RNA는 전달 시스템과 연관될 수도 있다. 자가 복제 RNA는 보조제와 함께 또는 없이 투여될 수도 있다.

[0086] **RNA 전달 시스템**

[0087] 여기에 설명된 자가 복제 RNA는 노출 RNA 전달과 같이, 다양한 양상으로 또는 지질, 폴리머 또는 세포 내로 유입을 용이하게 하는 다른 화합물과 조합하여 전달에 적합하다. 자가 복제 RNA 분자는 어떤 적합한 기술을 이용하여, 예를 들어, 직접적인 주사, 미크로주사, 전기 천공, 리포펙션, 생물 분해, 등에 의해 표적 세포 또는 대상체 내로 도입될 수 있다. 자가 복제 RNA 분자는 또한 수용체-매개 세포 이물 흡수의 방법에 의해 세포 내로 도입될 수도 있다. 예를 들어, 미국 특허 번호 6,090,619; Wu and Wu, J. Biol. Chem., 263: 14621 (1988); 및 Curiel et al, Proc. Natl. Acad. Sci. USA, 88:8850 (1991) 참조. 예를 들어, 미국 특허 번호 6, 083, 741는 핵산을 다가 양이온 모이어티 (예를 들어, 3-100개의 리신 잔기(SEQ ID NO:4)를 갖는 폴리-L-리신)에 연관시킴으로써 포유동물 세포 내로 외인성 핵산을 도입하는 것을 개시하며, 그것은 스스로 인테그린 수용체-결합 모이어티 (예를 들어, 서열 Arg-Gly-Asp (SEQ ID NO:5)를 갖는 고리형 펩티드)에 결합된다

[0088] 자가 복제 RNA 분자는 양친매성 물질 (amphiphile)을 통해 세포 내로 전달될 수 있다. 예를 들어, 미국 특허 번호 6, 071, 890 참조. 전형적으로, 핵산 분자는 양이온성 양친매성 물질과 함께 복합체를 형성할 수도 있다. 복합체에 접촉된 포유동물 세포는 쉽게 그것을 수용할 수 있다.

[0089] 자가 복제 RNA는 노출 RNA로서 (예를 들어, 단지 RNA의 수용액으로서) 전달될 수 있지만, 세포 내로 유입 및 또한 이후의 세포 내 효과를 향상시키기 위해, 자가 복제 RNA는 바람직하게 미립자 또는 에멀젼 전달 시스템과 같은, 전달 시스템과 조합하여 투여된다. 다수의 전달 시스템이 당업자에게 잘 알려져 있다. 이러한 전달 시스템은, 예를 들어, 리포솜-기반 전달 (DebsVRPZhu (1993) WO 93/24640; Mannino and Gould-Fogerite (1988) BioTechniques 6(7): 682-691; Rose 미국 특허 번호 5,279,833; Brigham (1991) WO 91/06309; 및 Feigner et al. (1987) Proc. Natl. Acad. Sci. USA 84: 7413-7414), 뿐만 아니라 바이러스 벡터 (예를 들어, 아데노바이러스 (재검토를 위해, 예를 들어, Berns et al. (1995) Ann. NY Acad. Sci. 772: 95-104; Ali et al. (1994) Gene Ther. 1: 367-384; 및 Haddada et al. (1995) Curr. Top. Microbiol. Immunol. 199 (Pt 3): 297-306 참조), 파필로마바이러스 (papillomavirus), 레트로바이러스 (예를 들어, 상기 Buchscher et al. (1992) J. Virol. 66(5) 2731-2739; Johann et al. (1992) J. Virol. 66 (5): 1635-1640 (1992); Sommerfelt et al, (1990) Virol. 176:58-59; Wilson et al. (1989) J. Virol. 63:2374-2378; Miller et al, J. Virol. 65:2220-2224 (1991); Wong-Staal et al, PCT/US94/05700, 및 Rosenburg and Fauci (1993) in Fundamental Immunology, Third Edition Paul (ed) Raven Press, Ltd., New York 및 그것들의 참고문헌, 및 Yu et al, Gene Therapy (1994) 참조), 및 아데노-연관된 바이러스 벡터 (West et al. (1987) Virology 160:38-47; Carter et al. (1989) 미국 특허 번호 4,797,368; Carter et al. WO 93/24641 (1993); Kotin (1994) Human Gene Therapy 5:793-801; Muzyczka (1994) J. Clin. Invst. 94: 1351 및 AAV 벡터의 개요를 위해 Samulski (상기); 또한, Lebkowski, 미국 특허 번호 5,173,414; Tratschin et al. (1985) Mol. Cell. Biol. 5(11):3251-3260; Tratschin, et al. (1984) Mol. Cell. Biol, 4:2072-2081; Hermonat and Muzyczka (1984) Proc. Natl. Acad. Sci. USA, 81:6466-6470; McLaughlin et al. (1988) 및 Samulski et al. (1989) J. Virol, 63:03822-3828 참조), 등의 이용을 포함한다.

[0090] 세 개의 특히 유용한 전달 시스템은 (i) 리포솜, (ii) 비독성 및 생 분해성 폴리머 미세입자, 및 (iii) 양이온성 서브미크론 수중유 에멀젼이다.

[0091] **리포솜**

[0092] 다양한 양친매성 지질은 리포솜과 같은 RNA-함유 수성 코어를 캡슐화하기 위하여 수성 환경에서 이중층을 형성할 수 있다. 이 지질들은 음이온성, 양이온성 또는 쌍성이온성 친수성 머리 그룹을 가질 수 있다. 음이온성 인지질로부터 리포솜의 형성은 1960년대 부터이고, 양이온성 리포솜-형성 지질은 1990년대 이후에 연구되었다. 일부 인지질은 음이온성인 한편, 다른 것들은 쌍성이온성이다. 적합한 인지질의 종류는 포스파티딜에탄올아민, 포스파티딜콜린, 포스파티딜세린, 및 포스파티딜글리세롤을 포함하지만, 이에 제한되지 않고, 일부 유용한 인지질은 표 2에 나열된다. 유용한 양이온성 지질은 디올레오일 트리메틸 암모늄 프로판 (DOTAP), 1, 2-디스테아릴옥시-N, N-디메틸-3-아미노프로판 (DSDMA), 1, 2-디올레일옥시-N, N디메틸-3-아미노프로판 (DODMA), 1, 2-디리놀레일옥시-N, N-디메틸-3-아미노프로판 (DLinDMA), 1, 2-디리놀레닐옥시-N, N-디메틸-3-아미노프로판 (DLenDMA)을 포함하지만, 이에 제한되지 않는다. 쌍성이온성 지질은 아실 쌍성이온성 지질 및 에테르 쌍성이온성 지질을 포함하지만, 이에 제한되지 않는다. 유용한 쌍성이온성 지질의 예는 DPPC, DOPC, 및 도데실포스포콜린이다. 지질은 포화되거나 불포화될 수 있다.

[0093] 리포솜은 단일 지질로부터 또는 지질의 혼합물로부터 형성될 수 있다. 혼합물은 (i) 음이온성 지질의 혼합물, (ii) 양이온성 지질의 혼합물, (iii) 쌍성이온성 지질의 혼합물, (iv) 음이온성 지질 및 양이온성 지질의 혼합물, (v) 음이온성 지질 및 쌍성이온성 지질의 혼합물, (vi) 쌍성이온성 지질 및 양이온성 지질의 혼합물 또는 (vii) 음이온성 지질, 양이온성 지질 및 쌍성이온성 지질의 혼합물을 포함할 수도 있다. 유사하게, 혼합물은 포화된 및 불포화된 지질 둘 다를 포함할 수도 있다. 예를 들어, 혼합물은 DSPC (쌍성이온성, 포화), DlinDMA (양이온성, 불포화), 및/또는 DMPG (음이온성, 포화)를 포함할 수도 있다. 지질의 혼합물이 이용되는 경우, 혼합물의 성분 지질 모두가 양친매성 물질일 필요는 없다, 예를 들어, 하나 이상의 양친매성 지질이 콜레스테롤과 혼합될 수 있다.

[0094] 지질의 친수성 부 분은 PEG와 반응될 수 있다 (즉, 폴리에틸렌 글리콜의 공유 부착에 의해 변형된다). 이 변형은 안정성을 증가시킬 수 있고 리포솜의 비-특이적 흡착을 방지한다. 예를 들어, 리피드는 Heyes et al. (2005) J Controlled Release 107:276-87에 개시된 것들과 같은 기술을 이용하여 PEG와 접합될 수 있다.

[0095] DSPC, DlinDMA, PEG-DMPG 및 콜레스테롤의 혼합물은 리포솜을 형성하기 위해 이용될 수 있다. 본 발명의 별도의 양태는 DSPC, DlinDMA, PEG-DMG 및 콜레스테롤을 포함하는 리포솜이다. 이 리포솜은 바람직하게는, 예를 들어, 면역원을 암호화하는 자가 복제 RNA와 같은 RNA를 캡슐화한다.

[0096] 리포솜은 보통 세 그룹으로 분류된다: 중층 소낭 (MLV); 작은 단층 소낭 (SUV); 및 큰 단층 소낭 (LUV). MLV는 각각의 소낭에 다수의 이중층을 갖고, 여러 별도의 수성 구획을 형성한다. SUB 및 LUV는 수성 코어를 캡슐화하는 단일 이중층을 갖는다; SUV는 전형적으로 50 nm보다 작은 직경을 갖고, LUV는 50 nm보다 큰 직경을 갖는다. 본 발명에 유용한 리포솜은 이상적으로 50-220 nm의 범위의 직경을 갖는 LUV이다. 다른 직경을 갖는 LUV의 개체군을 포함하는 조성물에 대하여: (i) 숫자로 적어도 80%는 20-220 nm의 범위의 직경을 갖고, (ii) 개체군의 평균 직경 (Zav, 강도로)은 이상적으로 40-200 nm의 범위에 있고, 및/또는 (iii) 직경은 0.2보다 작은 다 분산 지수 (polydispersity index)를 가져야 한다.

[0097] 적합한 리포솜을 제조하는 기술은 업계에 잘 알려져 있다, 예를 들어, Liposomes: Methods and Protocols, Volume 1: Pharmaceutical Nanocarriers: Methods and Protocols, (ed. Weissig). Humana Press, 2009. ISBN 160327359X; Liposome Technology, volumes I, II & III. (ed. Gregoriadis). Informa Healthcare, 2006; 및 Functional Polymer Colloids and Microparticles volume 4 (Microspheres, microcapsules & liposomes), (eds. Arshady & Guyot). Citus Books, 2002 참조. 한 유용한 방법은 (i) 지질의 에탄올성 용액, (ii) 핵산의 수용액 및 (iii) 완충액을 혼합한 후 이어서 혼합, 평형, 희석 및 정제하는 단계를 수반한다 (Heyes et al. (2005) J Controlled Release 107:276-87.).

[0098] RNA는 바람직하게는 리포솜 내에 캡슐화되고, 그래서 리포솜은 수성 RNA-함유 코어 주위에 외층을 형성한다. 이 캡슐화는 RN아제 분해로부터 RNA를 보호하는 것으로 발견되었다. 리포솜은 일부 외부 RNA를 포함할 수 있지만 (예를 들어, 리포솜의 표면 상에), 바람직하게는, 적어도 절반의 RNA (및 이상적으로는 그것의 실질적으로 모든 것)는 캡슐화된다.

[0099] **폴리머 미세입자**

[0100] 다양한 폴리머는 RNA를 캡슐화하거나 흡착하기 위해 미세입자를 형성할 수 있다. 실질적으로 비-독성 폴리머의 이용은 수령체가 안전하게 입자를 받을 수 있다는 것을 의미하고, 생 분해성 폴리머의 이용은 입자가 장기간 지속을 방지하기 위해 전달 후 대사될 수 있다는 것을 의미한다. 유용한 폴리머는 또한 약학적 등급의 제형의 제조를 돕기 위해, 멸균 가능하다.

[0101] 적합한 비-독성 및 생 분해성 폴리머는 폴리(α-히드록시산), 폴리히드록시 부티르산, 폴리락톤 (폴리카프로락톤을 포함), 폴리디옥사논, 폴리발레로락톤, 폴리오르토에스테르, 폴리무수물, 폴리시아노아크릴레이트, 티로신-유도된 폴리카르보네이트, 폴리비닐피롤리디논 또는 폴리에스테르-아미드, 및 이들의 조합을 포함하지만, 이에 제한되지 않는다.

[0102] 일부 구체예에서, 미세입자는 폴리(락티드) ("PLA")와 같은 폴리(α-히드록시산), 폴리(D, L-락티드-코-글리콜리드) ("PLG")와 같은 락티드 및 글리콜리드의 코폴리머, 및 D, L-락티드 및 카프로락톤의 코폴리머로부터 형성된다. 유용한 PLG 폴리머는, 예를 들어, 20:80 내지 80:20, 예를 들어, 25:75, 40:60, 45:55, 55:45, 60:40, 75:25의 범위의 락티드/글리콜리드 분자비를 갖는 것들을 포함한다. 유용한 PLG 폴리머는, 예를 들어, 5, 000-200, 000 Da, 예를 들어, 10, 000-100, 000, 20, 000-70, 000, 40, 000-50, 000 Da의 분자량을 갖는 것들을 포함한다.

[0103] 미세입자는 이상적으로 0.02 μm 내지 8 μm의 범위의 직경을 갖는다. 숫자로 적어도 80%에서 다른 직경을 갖는 미세입자의 개체군을 포함하는 조성물은 0.03 μm-7 μm의 범위의 직경을 갖는다.

[0104] 적합한 미세입자를 제조하는 기술은 업계에 잘 알려져 있고, 예를 들어, Functional Polymer Colloids Microparticles volume 4 (Microspheres, microcapsules & liposomes), (eds. Arshady & Guyot). Citus Books, 2002; Polymers in Drug Delivery, (eds. Uchegbu & Schatzlein). CRC Press, 2006. (특히 7장에) 및 Microparticulate Systems for the Delivery of Proteins and Vaccines. (eds. Cohen & Bernstein). CRC Press, 1996 참조. RNA의 흡착을 용이하게 하기 위해서, 미세입자는, 예를 들어, O'Hagan et al. (2001) J Virology 75: 9037-9043; 및 Singh et al. (2003) Pharmaceutical Research 20: 247-251에 개시된 바와 같은, 양이온성 계면활성제 및/또는 지질을 포함할 수도 있다. 폴리머 미세입자를 만드는 대체 방법은, 예를 들어, WO2009/132206에 개시된 바와 같이 성형 및 경화에 의한 것이다.

[0105] 본 발명의 미세입자는 40-100 mV의 제타 전위를 가질 수 있다.

[0106] RNA는 미세입자에 흡착될 수 있고, 흡착은 미세입자에 양이온성 물질 (예를 들어, 양이온성 지질)을 포함함으로써 촉진된다.

[0107] **수중유 양이온성 에멀젼**

[0108] 수중유 에멀젼은 보조 인플루엔자 백신, 예를 들어, FLUAD™ 제품의 MF59™, 및 PREPANDRIX™ 제품의 AS03 보조제에 대하여 알려져 있다.RNA 전달은 수중유 에멀젼의 이용으로 달성될 수 있으며, 에멀젼이 하나 이상의 양이온성 분자를 함유한다는 것이 제공된다. 예를 들어, 양이온성 지질은 음전하를 띈 RNA가 부착할 수 있는 양전하를 띈 방울 표면을 제공하기 위해 에멀젼에 포함될 수 있다.

[0109] 에멀젼은 하나 이상의 오일을 포함한다. 적합한 오일(들)은, 예를 들어, 동물 (물고기와 같은) 또는 식물성 근원의 것들을 포함한다. 오일은 이상적으로 생 분해성 (대사 가능) 및 생체적합성이다. 식물성 오일에 대한 근원은 견과류, 씨앗 및 곡물을 포함한다. 가장 일반적으로 이용 가능한, 땅콩 오일, 대두 오일, 코코넛 오일, 및 올리브 오일은 견과류 오일의 예이다. 예를 들어, 호호바 (jojoba) 콩에서 얻어진 호호바 오일이 이용될 수 있다. 씨앗 오일은 잇꽃 오일, 목화씨 오일, 해바라기 씨 오일, 참기름 등을 포함한다. 곡물 그룹에서, 옥수수 오일은 가장 쉽게 이용 가능하지만, 밀, 귀리, 호밀, 쌀, 테프 (teff), 라이밀 (triticale) 등과 같은 다른 곡물의 오일이 또한 이용될 수도 있다. 글리세롤 및 1, 2-프로판디올의 6-10개의 탄소 지방산 에스테르는 씨앗 오일에서 자연 발생하지 않는 반면, 견과류 및 씨앗 오일에서 적절한 물질의 가수 분해, 분리 및 에스테르화에 의해 제조될 수도 있다. 포유동물의 우유의 지방 및 오일은 대사 가능하고 그래서 이용될 수도 있다. 분리, 정제, 비누화에 대한 공정 및 동물 근원의 순수한 오일을 얻는데 필요한 다른 방법들은 업계에 잘 알려져 있다.

[0110] 대부분의 물고기는 쉽게 회수될 수도 있는 대사 가능한 오일을 함유한다. 예를 들어, 대구 간 오일, 상어 간 오일, 및 경뇌유 (spermaceti)와 같은 고래 오일은 여기에 이용될 수도 있는 다양한 물고기 오일의 예이다. 다수의 분지형 사슬 오일이 생화학적으로 5-탄소 이소프렌 단위로 합성되고 일반적으로 테르페노이드로서 나타난다. 스쿠알렌, 스쿠알렌에 대한 포화 유사체가 또한 이용될 수 있다. 스쿠알렌 및 스쿠알란을 포함하는 물고기 오일은 상업적 근원으로부터 쉽게 이용 가능하거나 업계에 알려진 방법에 의해 얻어질 수도 있다.

[0111] 다른 유용한 오일은, 특히 스쿠알렌과 조합된, 토코페롤이다. 에멀젼의 유상이 토코페롤을 포함하는 경우, α, β, γ, δ, ε 또는 ξ 토코페롤 중 어느 것도 이용될 수 있지만, α-토코페롤이 바람직하다. D-α-토코페롤 및 DL-α-토코페롤은 둘 다 이용될 수 있다. 바람직한 α-토코페롤은 DL-α-토코페롤이다. 스쿠알렌 및 토코페롤 (예를 들어, DL-α-토코페롤)을 포함하는 오일 조합이 이용될 수 있다.

[0112] 바람직한 에멀젼은 분지형, 불포화 테르페노이드 ($C_{30}H_{50}$; $[(CH_3)_2C[=CHCH_2CH_2C(CH_3)]_2=CHCH_2-]_2$; 2, 6, 10, 15, 19, 23-헥사메틸-2, 6, 10, 14, 18, 22-테트라코사헥사엔; CAS R 7683-64-9)인, 스쿠알렌, 상어 간 오일을 포함한다.

[0113] 에멀젼 중의 오일은 오일의 조합, 예를 들어, 스쿠알렌 및 적어도 하나의 추가 오일을 포함할 수도 있다.

[0114] 에멀젼의 수성 성분은 담수 (예를 들어, w.f.i.)일 수 있거나 추가 성분, 예를 들어, 용질을 포함할 수 있다. 예를 들어, 그것은 완충액을 형성하기 위해 염, 예를 들어, 시트레이트 또는 포스페이트 염, 예를 들어, 나트륨 염을 포함할 수도 있다. 전형적인 완충액은 포스페이트 완충액; 트리스 완충액; 붕산염 완충액; 숙신산염 완충액; 히스티딘 완충액; 또는 시트레이트 완충액을 포함한다. 완충된 수상이 바람직하고, 완충액은 전형적으로 5-20 mM 범위에 포함될 것이다.

[0115] 에멀젼은 또한 양이온성 지질을 포함한다. 바람직하게는 이 지질은 에멀젼의 형성 및 안정화를 용이하게 할 수 있는 계면활성제이다. 예를 들어, 3차 또는 4차 아민과 같이 유용한 양이온성 지질은 일반적으로 생리학적 조건하에 양전하를 띈 질소 원자를 함유한다. 이 질소는 양친매성 계면활성제의 친수성 머리 그룹에 있을 수 있다. 유용한 양이온성 지질은 1, 2-디올레오일옥시-3-(트리메틸암모니오)프로판 (DOTAP), 3'-[N-(N', N'-디메틸아미노에탄)-카르바모일]콜레스테롤 (DC 콜레스테롤), 디메틸디옥타데실암모늄 (DDA, 예를 들어, 브로마이드), 1, 2-디미리스토일-3-트리메틸-암모늄프로판 (DMTAP), 디팔미토일(C16:0)트리메틸 암모늄 프로판 (DPTAP), 디스테아로일트리메틸암모늄 프로판 (DSTAP)을 포함하지만, 이에 제한되지 않는다. 다른 유용한 양이온성 지질은 벤잘코늄 클로라이드 (BAK), 벤제토늄 클로라이드, 세트라미드 (이것은 테트라데실트리메틸암모늄 브로마이드 및 경우에 따라 소량의 데데실트리메틸암모늄 브로마이드 및 헥사데실트리메틸 암모늄 브로마이드를 포함한다), 세틸프리디늄 클로라이드 (CPC), 세틸 트리메틸암모늄 클로라이드 (CTAC), N, N', N'-폴리옥시에틸렌 (10)-N-수

지-1, 3-디아미노프로판, 도데실트리메틸암모늄 브로마이드, 헥사데실트리메틸-암모늄 브로마이드, 혼합된 알킬-트리메틸-암모늄 브로마이드, 벤질디메틸도데실암모늄 클로라이드, 벤질디메틸헥사데실-암모늄 클로라이드, 벤질트리메틸암모늄 메톡시드, 세틸디메틸에틸암모늄 브로마이드, 디메틸디옥타데실 암모늄 브로마이드 (DDAB), 메틸벤제토늄 클로라이드, 데카메토늄 클로라이드, 메틸 혼합된 트리알킬 암모늄 클로라이드, 메틸 트리옥틸암모늄 클로라이드), N, N-디메틸-N-[2(2-메틸-4-(1, 1, 3, 3테트라메틸부틸)-페녹시]-에톡시)에틸]-벤젠메타-나미늄 클로라이드 (DEBDA), 디알킬디메틸암모늄 염, [1-(2, 3-디올레일옥시)-프로필]-N, N, N, 트리메틸암모늄 클로라이드, 1, 2-디아실-3-(트리메틸암모니오) 프로판 (아실기=디미리스토일, 디팔미토일, 디스테아로일, 디올레오일), 1, 2-디아실-3 (디메틸암모니오)프로판 (아실기=디미리스토일, 디팔미토일, 디스테아로일, 디올레오일), 1, 2-디올레오일-3-(4'-트리메틸-암모니오)부타노일-sn-글리세롤, 1, 2-디올레오일 3-숙시닐-sn-글리세롤 콜린 에스테르, 콜레스테릴 (4'-트리메틸암모니오) 부타노에이트), N-알킬 피리디늄 염 (예를 들어, 세틸프리디늄 브로마이드 및 세틸프리디늄 클로라이드), N-알킬피페리디늄 염, 이중양이온성 볼라폼 전해질 (C12Me6; C12BU6), 디알킬글리세틸포스포릴콜린, 리소레시틴, L-α디올레오일포스파티딜에탄올아민, 콜레스테롤 헤미숙시네이트 콜린 에스테르, 디옥타데실아미도글리실스페르민 (DOGS), 디팔미토일 포스파티딜에탄올-아미도스페르민 (DPPES), 리포폴리-L (또는 D)-리신 (LPLL, LPDL), N-글루타릴포스파티딜에탄올아민에 접합된 폴리 (L (또는 D)-리신을 포함하지만, 이에 제한되지 않는, 리포폴리아민, 펜던트 아미노기를 갖는 디도데실 글루타메이트 에스테르 (C^GluPhCnN), 펜던트 아미노기를 갖는 디테트라데실 글루타메이트 에스테르 (C14GIuCnN+), 콜레스테릴-3 β-옥시숙신아미도에틸렌트리메틸암모늄 염, 콜레스테릴-3 β-옥시숙신아미도에틸렌-디메틸아민, 콜레스테릴-3 β-카르복시아미도에틸렌트리메틸암모늄 염, 및 콜레스테릴-3 β-카르복시아미도에틸렌디메틸아민을 포함하지만, 이에 제한되지 않는, 콜레스테롤의 양이온성 유도체이다. 다른 유용한 양이온성 지질은 US 2008/0085870 및 US 2008/0057080에 설명되며, 이것은 본원에 참고로 포함된다. 양이온성 지질은 바람직하게는 생 분해성 (대사 가능) 및 생체적합성이다.

[0116] 오일 및 양이온성 지질에 더하여, 에멀젼은 비이온성 계면활성제 및/또는 쌍성이온성 계면활성제를 포함한다. 이러한 계면활성제는 폴리옥시에틸렌 소르비탄 에스테르 계면활성제 (일반적으로 Tween으로 나타냄), 특히 폴리소르베이트 20 및 폴리소르베이트 80; DOWFAX™ 상표명 하에 판매되는 에틸렌 옥시드 (EO), 프로필렌 옥시드 (PO), 및/또는 부틸렌 옥시드 (BO)의 코폴리머, 예를 들어, 선형 EO/PO 블록 코폴리머; 옥톡시놀-9 (Triton X-100, 또는 t-옥틸페녹시폴리에톡시에탄올)가 특히 흥미있는, 반복되는 에톡시 (옥시-1, 2-에탄디일) 기의 수에 따라 달라질 수 있는 옥톡시놀; (옥틸페녹시)폴리에톡시에탄올 (IGEPAL CA-630/NP-40); 포스파티딜콜린 (레시틴)과 같은 포스포리피드; 라우릴, 세틸, 스테아릴 및 올레일 알콜로부터 유도된 폴리옥시에틸렌 지방 에테르 (Brij 계면활성제로서 알려짐), 예를 들어, 트리에틸렌글리콜 모노라우릴 에테르 (Brij 30); 폴리옥시에틸렌-9-라우릴 에테르; 및 소르비탄 에스테르 (일반적으로 Span으로 알려짐), 예를 들어, 소르비탄 트리올레에이트 (Span 85) 및 소르비탄 모노라우레이트를 포함하지만, 이에 제한되지 않는다. 에멀젼에 포함하기 위한 바람직한 계면활성제는 폴리소르베이트 80 (Tween 80; 폴리옥시에틸렌 소르비탄 모노올레에이트), Span 85 (소르비탄 트리올레에이트), 레시틴 및 Triton X-100이다.

[0117] 이 계면활성제의 혼합물, 예를 들어, Tween 80/Span 85 혼합물, 또는 Tween 80/Triton-X100 혼합물은 에멀젼에 포함될 수 있다. 폴리옥시에틸렌 소르비탄 모노올레에이트 (Tween 80)와 같은 폴리옥시에틸렌 소르비탄 에스테르 및 t-옥틸페녹시-폴리에톡시에탄올 (Triton X-100)과 같은 옥톡시놀의 조합이 또한 적합하다. 또 다른 유용한 조합은 라우레쓰 9 플로스 폴리옥시에틸렌 소르비탄 에스테르 및/또는 옥톡시놀을 포함한다. 유용한 혼합물은 10-20의 범위의 HLB 값을 갖는 계면활성제 (예를 들어, 15.0의 HLB를 갖는 폴리소르베이트 80) 및 1-10의 범위의 HLB 값을 갖는 계면활성제 (예를 들어, 1.8의 HLB를 갖는 소르비탄 트리올레에이트)를 포함할 수 있다.

[0118] 최종 에멀젼에서 바람직한 오일의 양 (부피%)은 2-20%, 예를 들어, 5-15%, 6-14%, 7-13%, 8-12%이다. 약 4-6% 또는 약 9-11%의 스쿠알렌 함량이 특히 유용하다.

[0119] 최종 에멀젼에서 바람직한 계면활성제의 양 (중량%)은 0.001% 내지 8%이다. 예를 들어, 폴리옥시에틸렌 소르비탄 에스테르 (폴리소르베이트 80와 같은)는 0.2 내지 4%, 특히 0.4-0.6%, 0.45-0.55%, 약 0.5% 또는 1.5-2%, 1.8-2.2%, 1.9-2.1%, 약 2%, 또는 0.85-0.95%, 또는 약 1%; 또는 소르비탄 에스테르 (소르비탄 트리올레에이트와 같은)는 0.02 내지 2%, 특히 약 0.5% 또는 약 1%; 옥틸-또는 노닐페녹시 폴리옥시에탄올 (Triton X-100와 같은)은 0.001 내지 0.1%, 특히 0.005 내지 0.02%; 폴리옥시에틸렌 에테르 (라우레쓰 9)는 0.1 내지 8%, 바람직하게 0.1 내지 10% 및 특히 0.1 내지 1% 또는 약 0.5%이다.

[0120] 오일 및 계면활성제의 절대적인 양, 및 그것들의 비율은 에멀젼을 형성하는 동안 넓은 한도 내에서 달라질 수 있다. 숙련자는 원하는 에멀젼을 얻기 위해서 성분의 상대적 비율을 쉽게 바꿀 수 있지만, 오일 및 계면활성제

에 대하여 4:1 내지 5:1의 중량비가 전형적이다 (오일 과다).

[0121] 특히 큰 동물에서, 에멀젼의 면역자극 활성을 보장하는 중요한 파라미터는 오일 방울 크기 (직경)이다. 가장 효율적인 에멀젼은 서브미크론 범위의 방울 크기를 갖는다. 적합하게 방울 크기는 범위 50-750 nm에 있을 것이다. 가장 유용하게는, 평균 방울 크기는 250 nm 미만, 예를 들어, 200 nm 미만, 150 nm 미만이다. 평균 방울 크기는 유용하게도 80-180 nm의 범위에 있다. 이상적으로, 에멀젼의 오일 방울 중 적어도 80% (숫자로)는 직경이 250 nm보다 작다, 예를 들어, 200 nm보다 작고, 150보다 작다. 평균 방울 크기는 유용하게도 80-180 nm의 범위에서 유용하다. 이상적으로, 에멀젼 오일 방울 중 적어도 80% (숫자로)는 직경이 250 nmq보다 작고, 바람직하게 적어도 90%도 그러하다. 에멀젼의 평균 방울 크기, 및 크기 분포를 결정하는 기구는 상업적으로 이용 가능하다. 이것들은 전형적으로 동적 광산란 (dynamic light scattering) 및/또는 단일-입자 광학 판독 (single-particle optical sensing)의 기술, 예를 들어, Particle Sizing Systems (Santa Barbara, USA)에서 이용 가능한 기기의 Accusizer™ 및 Nicomp™ 시리즈, 또는 Malvern Instruments (UK)에서 이용 가능한 Zetasizer™ 기기, 또는 Horiba (Kyoto, Japan)의 Particle Size Distribution Analyzer 기기를 이용한다.

[0122] 이상적으로, 방울 크기 (숫자로)의 분포는 두 개의 최대값 대신에, 단 하나의 최대값을 갖는다, 즉, 평균 (방식) 주위에 분포된 방울의 단일 개체군이 있다. 바람직한 에멀젼은 0.4보다 작은, 예를 들어, 0.3, 0.2보다 작은 다 분산성을 갖는다.

[0123] 서브미크론 방울 및 좁은 크기 분포을 갖는 적합한 에멀젼은 미세유동화의 이용에 의해 얻어질 수 있다. 이 기술은 높은 온도 및 높은 속도에서 기하학적으로 고정된 채널을 통해 투입 성분의 스트림을 추진함으로써 평균 오일 방울 크기를 감소시킨다. 이 스트림들은 채널 벽, 챔버 벽 및 서로와 접촉한다. 결과 전단, 영향 및 캐비테이션 (cavitation) 힘은 방울 크기의 감소를 유발한다. 반복된 미세유동화 단계는 원하는 방울 크기 평균 및 분포를 갖는 에멀젼이 달성될 때까지 수행될 수 있다.

[0124] 미세유동화에 대한 대안으로서, 열법 (thermal method)은 상전환 (phase inversion)을 유발하기 위해 이용될 수 있다. 이 방법들은 또한 좁은 입자 크기 분포를 갖는 서브미크론 에멀젼을 제공할 수 있다.

[0125] 바람직한 에멀젼은 여과 멸균될 수 있다, 즉, 그것들의 방울은 220 nm 필터를 통과할 수 있다. 멸균을 제공할 뿐만 아니라, 이 공정은 또한 에멀젼의 어떤 큰 방울도 제거한다.

[0126] 특정 구체예에서, 에멀젼의 양이온성 지질은 DOTAP이다. 양이온성 수중유 에멀젼은 약 0.5 mg/ml 내지 약 25 mg/ml DOTAP를 포함할 수도 있다. 예를 들어, 양이온성 수중유 에멀젼은 DOTAP를 약 0.5 mg/ml 내지 약 25 mg/ml, 약 0.6 mg/ml 내지 약 25 mg/ml, 약 0.7 mg/ml 내지 약 25 mg/ml, 약 0.8 mg/ml 내지 약 25 mg/ml, 약 0.9 mg/ml 내지 약 25 mg/ml, 약 1.0 mg/ml 내지 약 25 mg/ml, 약 1.1 mg/ml 내지 약 25 mg/ml, 약 1.2 mg/ml 내지 약 25 mg/ml, 약 1.3 mg/ml 내지 약 25 mg/ml, 약 1.4 mg/ml 내지 약 25 mg/ml, 약 1.5 mg/ml 내지 약 25 mg/ml, 약 1.6 mg/ml 내지 약 25 mg/ml, 약 1.7 mg/ml 내지 약 25 mg/ml, 약 0.5 mg/ml 내지 약 24 mg/ml, 약 0.5 mg/ml 내지 약 22 mg/ml, 약 0.5 mg/ml 내지 약 20 mg/ml, 약 0.5 mg/ml 내지 약 18 mg/ml, 약 0.5 mg/ml 내지 약 15 mg/ml, 약 0.5 mg/ml 내지 약 12 mg/ml, 약 0.5 mg/ml 내지 약 10 mg/ml, 약 0.5 mg/ml 내지 약 5 mg/ml, 약 0.5 mg/ml 내지 약 2 mg/ml, 약 0.5 mg/ml 내지 약 1.9 mg/ml, 약 0.5 mg/ml 내지 약 1.8 mg/ml, 약 0.5 mg/ml 내지 약 1.7 mg/ml, 약 0.5 mg/ml 내지 약 1.6 mg/ml, 약 0.6 mg/ml 내지 약 1.6 mg/ml, 약 0.7 mg/ml 내지 약 1.6 mg/ml, 약 0.8 mg/ml 내지 약 1.6 mg/ml, 약 0.5 mg/ml, 약 0.6 mg/ml, 약 0.7 mg/ml, 약 0.8 mg/ml, 약 0.9 mg/ml, 약 1.0 mg/ml, 약 1.1 mg/ml, 약 1.2 mg/ml, 약 1.3 mg/ml, 약 1.4 mg/ml, 약 1.5 mg/ml, 약 1.6 mg/ml, 약 12 mg/ml, 약 18 mg/ml, 약 20 mg/ml, 약 21.8 mg/ml, 약 24 mg/ml, 등으로 포함할 수도 있다. 전형적인 구체예에서, 양이온성 수중유 에멀젼은 약 0.8 mg/ml 내지 약 1.6 mg/ml DOTAP, 예를 들어, 0.8 mg/ml, 1.2 mg/ml, 1.4 mg/ml 또는 1.6 mg/ml를 포함한다.

[0127] 특정 구체예에서, 양이온성 지질은 DC 콜레스테롤이다. 양이온성 수중유 에멀젼은 DC 콜레스테롤을 약 0.1 mg/ml 내지 약 5 mg/ml DC 콜레스테롤로 포함할 수도 있다. 예를 들어, 양이온성 수중유 에멀젼은 DC 콜레스테롤을 약 0.1 mg/ml 내지 약 5 mg/ml, 약 0.2 mg/ml 내지 약 5 mg/ml, 약 0.3 mg/ml 내지 약 5 mg/ml, 약 0.4 mg/ml 내지 약 5 mg/ml, 약 0.5 mg/ml 내지 약 5 mg/ml, 약 0.62 mg/ml 내지 약 5 mg/ml, 약 1 mg/ml 내지 약 5 mg/ml, 약 1.5 mg/ml 내지 약 5 mg/ml, 약 2 mg/ml 내지 약 5 mg/ml, 약 2.46 mg/ml 내지 약 5 mg/ml, 약 3 mg/ml 내지 약 5 mg/ml, 약 3.5 mg/ml 내지 약 5 mg/ml, 약 4 mg/ml 내지 약 5 mg/ml, 약 4.5 mg/ml 내지 약 5 mg/ml, 약 0.1 mg/ml 내지 약 4.92 mg/ml, 약 0.1 mg/ml 내지 약 4.5 mg/ml, 약 0.1 mg/ml 내지 약 4 mg/ml, 약 0.1 mg/ml 내지 약 3.5 mg/ml, 약 0.1 mg/ml 내지 약 3 mg/ml, 약 0.1 mg/ml 내지 약 2.46 mg/ml, 약 0.1 mg/ml 내지 약 2 mg/ml, 약 0.1 mg/ml 내지 약 1.5 mg/ml, 약 0.1 mg/ml 내지 약 1 mg/ml, 약 0.1 mg/ml 내지

약 0.62 mg/ml, 약 0.15 mg/ml, 약 0.3 mg/ml, 약 0.6 mg/ml, 약 0.62 mg/ml, 약 0.9 mg/ml, 약 1.2 mg/ml, 약 2.46 mg/ml, 약 4.92 mg/ml, 등으로 포함할 수도 있다. 전형적인 구체예에서, 양이온성 수중유 에멀젼은 약 0.62 mg/ml 내지 약 4.92 mg/ml, 예를 들어, 2.46 mg/ml DC 콜레스테롤을 포함한다.

[0128] 특정 구체예에서, 양이온성 지질은 DDA이다. 양이온성 수중유 에멀젼은 약 0.1 mg/ml 내지 약 5 mg/ml DDA이다. 예를 들어, 양이온성 수중유 에멀젼은 DDA를 약 0.1 mg/ml 내지 약 5 mg/ml, 약 0.1 mg/ml 내지 약 4.5 mg/ml, 약 0.1 mg/ml 내지 약 4 mg/ml, 약 0.1 mg/ml 내지 약 3.5 mg/ml, 약 0.1 mg/ml 내지 약 3 mg/ml, 약 0.1 mg/ml 내지 약 2.5 mg/ml, 약 0.1 mg/ml 내지 약 2 mg/ml, 약 0.1 mg/ml 내지 약 1.5 mg/ml, 약 0.1 mg/ml 내지 약 1.45 mg/ml, 약 0.2 mg/ml 내지 약 5 mg/ml, 약 0.3 mg/ml 내지 약 5 mg/ml, 약 0.4 mg/ml 내지 약 5 mg/ml, 약 0.5 mg/ml 내지 약 5 mg/ml, 약 0.6 mg/ml 내지 약 5 mg/ml, 약 0.73 mg/ml 내지 약 5 mg/ml, 약 0.8 mg/ml 내지 약 5 mg/ml, 약 0.9 mg/ml 내지 약 5 mg/ml, 약 1.0 mg/ml 내지 약 5 mg/ml, 약 1.2 mg/ml 내지 약 5 mg/ml, 약 1.45 mg/ml 내지 약 5 mg/ml, 약 2 mg/ml 내지 약 5 mg/ml, 약 2.5 mg/ml 내지 약 5 mg/ml, 약 3 mg/ml 내지 약 5 mg/ml, 약 3.5 mg/ml 내지 약 5 mg/ml, 약 4 mg/ml 내지 약 5 mg/ml, 약 4.5 mg/ml 내지 약 5 mg/ml, 약 1.2 mg/ml, 약 1.45 mg/ml, 등으로 포함할 수도 있다. 대안으로서, 양이온성 수중유 에멀젼은 DDA를 약 20 mg/ml, 약 21 mg/ml, 약 21.5 mg/ml, 약 21.6 mg/ml, 약 25 mg/ml으로 포함할 수도 있다. 전형적이 구체예에서, 양이온성 수중유 에멀젼은 약 0.73 mg/ml 내지 약 1.45 mg/ml, 예를 들어, 1.45 mg/ml DDA를 포함한다.

[0129] 카테터 또는 유사한 장치는 본 발명의 자가 복제 RNA 분자를, 노출 RNA로서 또는 전달 시스템과 조합하여, 표적 장기 또는 조직으로 전달하기 위해 이용될 수도 있다. 적합한 카테터는, 예를 들어, 미국 특허 번호 4, 186, 745; 5, 397, 307; 5, 547, 472; 5, 674, 192; 및 6, 129, 705에 개시되며, 이것들 모두는 본원에 참고로 포함된다.

[0130] 본 발명은, 예를 들어, 단독으로, 또는 또 다른 고 분자와 조합하여 면역 반응을 유도하기 위해, 둘 이상의 CMV 단백질을 암호화하는 자가 복제 RNA 분자를 전달하도록 캡슐화된 또는 흡착된 자가 복제 RNA를 갖는 리포솜, 폴리머 미세입자 또는 서브미크론 에멀젼 미세입자와 같은, 적합한 전달 시스템의 이용을 포함한다. 본 발명은 흡착된 및/또는 캡슐화된 자가 복제 RNA 분자, 및 이들의 조합을 갖는 리포솜, 미세입자 및 서브미크론 에멀젼을 포함한다.

[0131] 리포솜 및 서브미크론 에멀젼 미세입자와 연관된 자가 복제 RNA 분자는 숙주 세포에 효율적으로 전달될 수 있고 자가 복제 RNA에 의해 암호화된 단백질에 대한 면역 반응을 유발할 수 있다.

[0132] CMV 단백질을 암호화하는 폴리시스트론성 자가 복제 RNA 분자, 폴리시스트론성 알파바이러스 레플리콘을 이용하여 생산된 VRP는 세포에서 CMV 단백질 복합체를 형성하기 위해 이용될 수 있다. 복합체는 gB/gH/gL; gH/gL; gH/gL/gO; gM/gN; gH/gL/UL128/UL130/UL131; 및 UL128/UL130/UL131을 포함하지만, 이에 제한되지 않는다.

[0133] 일부 구체예에서, VRP의 조합은 세포에 전달된다. 조합은 다음을 포함하지만, 이에 제한되지 않는다:

[0134] 1. gH/gL VRP 및 또 다른 VRP;

[0135] 2. gH/gL VRP 및 gB VRP;

[0136] 3. gH/gL/gO VRP 및 gB VRP;

[0137] 4. gB VRP 및 gH/gL/UL128/UL130/UL131 VRP;

[0138] 5. gB VRP 및 UL128/UL130/UL131 VRP;

[0139] 6. gB VRP 및 gM/gN VRP;

[0140] 7. gB VRP, gH/gL VRP, 및 UL128/UL130/UL131 VRP;

[0141] 8. gB VRP, gH/gLgO VRP, 및 UL128/UL130/UL131 VRP;

[0142] 9. gB VRP, gM/gN VRP, gH/gL VRP, 및 UL128/UL130/UL131 VRP;

[0143] 10. gB VRP, gM/gN VRP, gH/gL/O VRP, 및 UL128/UL130/UL131 VRP;

[0144] 11. gH/gL VRP 및 UL128/UL130/UL131 VRP; 및

[0145] 일부 구체예에서, 자가 복제 RNA 분자의 조합은 세포에 전달된다. 조합은 다음을 포함하지만, 이에 제한되지 않

는다:

[0146] 1. gH/gL을 암호화하는 자가 복제 RNA 분자 및 또 다른 단백질을 암호화하는 자가 복제 RNA 분자;

[0147] 2. gH 및 gL을 암호화하는 자가 복제 RNA 분자 및 gB를 암호화하는 자가 복제 RNA 분자;

[0148] 3. gH, gL 및 gO를 암호화하는 자가 복제 RNA 분자 및 gB를 암호화하는 자가 복제 RNA 분자 ;

[0149] 4. gB를 암호화하는 자가 복제 RNA 분자 및 gH, gL, UL128, UL130 및 UL131을 암호화하는 자가 복제 RNA 분자 ;

[0150] 5. gB를 암호화하는 자가 복제 RNA 분자 및 UL128, UL130 및 UL131을 암호화하는 자가 복제 RNA 분자;

[0151] 6. gB를 암호화하는 자가 복제 RNA 분자 및 gM 및 gN을 암호화하는 자가 복제 RNA 분자 ;

[0152] 7. gB를 암호화하는 자가 복제 RNA 분자, gH 및 gL을 암호화하는 자가 복제 RNA 분자, 및 UL128, UL130 및 UL131을 암호화하는 자가 복제 RNA 분자;

[0153] 8. gB를 암호화하는 자가 복제 RNA 분자, gH, gL, 및 gO를 암호화하는 자가 복제 RNA 분자, 및 UL128, UL130 및 UL131를 암호화하는 자가 복제 RNA 분자;

[0154] 9. gB를 암호화하는 자가 복제 RNA 분자, gM 및 gN을 암호화하는 자가 복제 RNA 분자, gH 및 gL을 암호화하는 자가 복제 RNA 분자, 및 UL128, UL130 및 UL131을 암호화하는 자가 복제 RNA 분자;

[0155] 10. gB를 암호화하는 자가 복제 RNA 분자, gM 및 gN을 암호화하는 자가 복제 RNA 분자, gH, gL 및 gO를 암호화하는 자가 복제 RNA 분자, 및 UL128, UL130 및 UL131를 암호화하는 자가 복제 RNA 분자;

[0156] 11. gH 및 gL을 암호화하는 자가 복제 RNA 분자, 및 UL128, UL130 및 UL131을 암호화하는 자가 복제 RNA 분자; 및

[0157] **CMV 단백질**

[0158] 적합한 CMV 단백질은 gB, gH, gL, gO를 포함하고, 어떤 CMV 균주의 것일 수 있다. 다른 적합한 CMV 단백질은 UL128, UL130 및 UL131을 포함하고, 어떤 CMV 균주의 것일 수 있다. 예를 들어, CMV 단백질은 CMV 단백질의 Merlin, AD 169, VR1814, Towne, Toledo, TR, PH, TB40, 또는 Fix 균주의 것일 수 있다. 전형적인 CMV 단백질 및 단편이 여기에 설명된다. 이 단백질 및 단편은 사람 세포와 같은, 원하는 숙주에서 발현을 위해 최적화 또는 탈최적화된 코돈인 서열을 포함하는, 어떤 적합한 뉴클레오티드 서열에 의해서도 암호화될 수 있다. CMV 단백질의 전형적인 서열 및 단백질을 암호화하는 핵산은 표 2에 제공된다.

[0159] 표 2

전체 길이 gH 폴리뉴클레오티드	(CMV gH FL) SEQ ID NO: 31
전체 길이 gH 폴리펩티드	(CMV gH FL) SEQ ID NO: 32
전체 길이 gL 폴리뉴클레오티드	(CMV gL FL) SEQ ID NO: 35
전체 길이 gL 폴리펩티드	(CMV gL FL) SEQ ID NO: 36
전체 길이 gO 폴리뉴클레오티드	(CMV gO FL) SEQ ID NO: 41
전체 길이 gO 폴리펩티드	(CMV gO FL) SEQ ID NO: 42
gH sol 폴리뉴클레오티드	(CMV gH sol) SEQ ID NO: 33
gH sol 폴리펩티드	(CMV gH sol) SEQ ID NO: 34
전체 길이 UL128 폴리뉴클레오티드	(CMV UL128 FL) SEQ ID NO: 43
전체 길이 UL128 폴리펩티드	(CMV UL128 FL) SEQ ID NO: 44
전체 길이 UL130 폴리뉴클레오티드	(CMV UL130 FL) SEQ ID NO: 45
전체 길이 UL130 폴리펩티드	(CMV UL130 FL) SEQ ID NO: 46
전체 길이 UL131 폴리뉴클레오티드	(CMV UL131 FL) SEQ ID NO: 47
전체 길이 UL131 폴리펩티드	(CMV UL131 FL) SEQ ID NO: 48
전체 길이 gB 폴리뉴클레오티드	(CMV gB FL) SEQ ID NO: 25
전체 길이 gB 폴리펩티드	(CMV gB FL) SEQ ID NO: 26
gB sol 750 폴리뉴클레오티드	(CMV gB 750) SEQ ID NO: 27
gB sol 750 폴리펩티드	(CMV gB 750) SEQ ID NO: 28
gB sol 692 폴리뉴클레오티드	(CMV gB 692) SEQ ID NO: 29
gB sol 692 폴리펩티드	(CMV gB 692) SEQ ID NO: 30
Full length gM 폴리뉴클레오티드	(CMV gM FL) SEQ ID NO: 37
Full length gM 폴리펩티드	(CMV gM FL) SEQ ID NO: 38
Full length gN 폴리뉴클레오티드	(CMV gN FL) SEQ ID NO: 39
Full length gN 폴리뉴클레오티드	(CMV gN FL) SEQ ID NO: 40

[0160]

[0161] **CMV gB 단백질**

[0162] gB 단백질은 전체 길이일 수 있거나 단백질의 하나 이상의 지역을 생략할 수 있다. 대안으로는, gB 단백질의 단편이 이용될 수 있다. gB 아미노산은 SEQ ID NO:26로 나타나는 전체 길이 gB 아미노산 서열 (CMV gB FL)에 따라 번호가 매겨지며, 이것은 907 아미노산 길이이다. gB 단백질의 적합한 영역은 전체 길이 단백질로부터 제외될 수 있거나 단편으로서 포함될 수 있으며, 다음을 포함한다: 신호 서열 (아미노산 1-24), gB-DLD 디스인테그린-유사 도메인 (아미노산 57-146), 퓨린 분할 부위 (아미노산 459-460), 7가 반복 영역 (679-693), 막 스패닝 도메인 (아미노산 751-771), 및 아미노산 771-906의 세포질 도메인. 일부 구체예에서, gB 단백질은 아미노산 67-

86 (중화 에피토프 AD2) 및/또는 아미노산 532-635 (면역 우성 에피토프 AD1)를 포함한다. gB 단편의 특정 예는 gB의 첫 번째 692 아미노산을 포함하는 "gB sol 692" 및 gB의 첫 번째 750 아미노산을 포함하는 "gB sol 750"을 포함한다. 신호 서열, 아미노산 1-24는 원하는 바와 같이 gB sol 692 및 gB sol 750으로부터 존재하거나 없을 수 있다. 임의로, gB 단백질은 10개 이상의 아미노산의 gB 단편일 수 있다. 예를 들어, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800, 825, 850, 또는 875개의 아미노산을 포함할 수 있다. gB 단편은 잔기 번호 중 어느 것에서도 시작할 수 있다: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 또는 897.

[0163] 임의로, gB 단편은 단편의 시작 잔기로부터 N-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다. 임의로, gB 단편은 단편의 마지막 잔기로부터 C-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다.

[0164] **CMV gH 단백질**

[0165] 일부 구체예에서, gH 단백질은 전체 길이 gH 단백질이다 (CMV gH FL, SEQ ID NO:32, 예를 들어, 이것은 742개의 아미노산 단백질이다). gH는 위치 716에서 743까지 시작하는 막 스패닝 도메인 및 세포질 도메인을 갖는다. 717 내지 743의 아미노산의 제거는 가용성 gH를 제공한다 (예를 들어, CMV gH sol, SEQ ID NO:34). 일부 구체예에서, gH 단백질은 10개 이상의 아미노산의 gH 단편일 수 있고, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 또는 725개의 아미노산을 포함할 수 있다. 임의로, gH 단백질은 10개 이상의 아미노산의 gH 단편일 수 있다. 예를 들어, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 또는 725개의 아미노산을 포함할 수 있다. gH 단편은 잔기 번호 중 어느 것에서도 시작할 수 있다: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 또는 732.

[0166] gH 잔기는 SEQ ID NO:32로 나타나는 전체 길이 gH 아미노산 서열 (CMV gH FL)에 따라 번호가 매겨진다. 임의로, gH 단편은 단편의 시작 잔기로부터 N-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다. 임의로, gH 단편은 단편의 마지막 잔기로부터 C-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다.

[0167] **CMV gL 단백질**

[0168] 일부 구체예에서, gL 단백질은 전체 길이 gL 단백질이다 (CMV gL FL, SEQ ID NO:36, 예를 들어, 이것은 278개의 아미노산 단백질이다). 일부 구체예에서, gL 단편이 이용될 수 있다. 예를 들어, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 또는 250개의 아미노산을 포함할 수 있다. gL 단편은 잔기 번호 중 어느 것에서도 시작할 수 있다: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 또는 268.

[0169] gL 잔기는 SEQ ID NO:36로 나타나는 전체 길이 gL 아미노산 서열 (CMV gL FL)에 따라 번호가 매겨진다. 임의로, gL 단편은 단편의 시작 잔기로부터 N-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다. 임의로, gL 단편은 단편의 마지막 잔기로부터 C-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다.

[0170] **CMV gO 단백질**

[0171] 일부 구체예에서, gO 단백질은 전체 길이 gO 단백질 (CMV gO FL, SEQ ID NO:42, 예를 들어, 이것은 472개의 아미노산 단백질이다). 일부 구체예에서, gO 단백질은 10개 이상의 아미노산의 gO 단편일 수 있다. 예를 들어, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 또는 450개의 아미노산을 포함할 수 있다. gO 단편은 잔기 번호 중 어느 것에서도 시작할 수 있다: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398,

399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 또는 462.

[0172] gO 잔기는 SEQ ID NO:42로 나타나는 전체 길이 gO 아미노산 서열 (CMV gO FL)에 따라 번호가 매겨진다. 임의로, gO 단편은 단편의 시작 잔기로부터 N-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다. 임의로, gO 단편은 단편의 마지막 잔기로부터 C-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다.

[0173] **CMV gM 단백질**

[0174] 일부 구체예에서, gM 단백질은 전체 길이 gM 단백질이다 (CMV gM FL, SEQ ID NO:38, 예를 들어, 이것은 371개의 아미노산 단백질이다). 일부 구체예에서, gM 단백질은 10개 이상의 아미노산의 gM 단편일 수 있다. 예를 들어, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 또는 350개의 아미노산을 포함할 수 있다. gM 단편은 잔기 번호 중 어느 것에서도 시작할 수 있다: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 또는 361.

[0175] gM 잔기는 SEQ ID NO:38로 나타나는 전체 길이 gM 아미노산 서열 (CMV gM FL)에 따라 번호가 매겨진다. 임의로, gM 단편은 단편의 시작 잔기로부터 N-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다. 임의로, gM 단편은 단편의 마지막 잔기로부터 C-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다.

[0176] **CMV gN 단백질**

[0177] 일부 구체예에서, gN 단백질은 전체 길이 gN 단백질이다 (CMV gN FL, SEQ ID NO:40, 예를 들어, 이것은 135개의 아미노산 단백질이다). 구체예에서, gN 단백질은 10개 이상의 아미노산의 gN 단편일 수 있다. 예를 들어, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 또는 125개의 아미노산을 포함할 수 있다. gN 단편은 잔기 번호 중 어느 것에서도 시작할 수 있다: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 또는 125.

[0178] gN 잔기는 SEQ ID NO:40로 나타나는 전체 길이 gN 아미노산 서열 (CMV gN FL)에 따라 번호가 매겨진다. 임의로, gN 단편은 단편의 시작 잔기로부터 N-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다. 임의로, gN 단편은 단편의 마지막 잔기로부터 C-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다.

[0179] **CMV UL128 단백질**

[0180] 일부 구체예에서, UL128 단백질은 전체 길이 UL128 단백질이다 (CMV UL128 FL, SEQ ID NO:44, 예를 들어, 이것은 171개의 아미노산 단백질이다). 일부 구체예에서, UL128 단백질은 10개 이상의 아미노산의 UL128 단편일 수 있다. 예를 들어, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 또는 150개의 아미노산을 포함할 수 있다. UL128 단편은 잔기 번호 중 어느 것에서도 시작할 수 있다: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 또는 161.

[0181] UL128 잔기는 SEQ ID NO:44로 나타나는 전체 길이 UL128 아미노산 서열 (CMV UL128 FL)에 따라 번호가 매겨진다. 임의로, UL128 단편은 단편의 시작 잔기로부터 N-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다. 임의로, UL128 단편은 단편의 마지막 잔기로부터 C-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다.

[0182] **CMV UL130 단백질**

[0183] 일부 구체예에서, UL130 단백질은 전체 길이 UL130 단백질이다 (CMV UL130 FL, SEQ ID NO:46, 예를 들어, 이것은 214개의 아미노산 단백질이다). 일부 구체예에서, UL130 단백질은 10개 이상의 아미노산의 UL130 단편일 수 있다. 예를 들어, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 또는 200개의 아미노산을 포함할 수 있다. UL130 단편은 잔기 번호 중 어느 것에서도 시작할 수 있다: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 또는 204.

[0184] UL130 잔기는 SEQ ID NO:46로 나타나는 전체 길이 UL130 아미노산 서열 (CMV UL130 FL)에 따라 번호가 매겨진다. 임의로, UL130 단편은 단편의 시작 잔기로부터 N-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다. 임의로, UL130 단편은 단편의 마지막 잔기로부터 C-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다.

[0185] **CMV UL131 단백질**

[0186] 일부 구체예에서, UL131 단백질은 전체 길이 UL131 단백질이다 (CMV UL131 FL, SEQ ID NO:48, 예를 들어, 이것은 129개의 아미노산 단백질이다). 일부 구체예에서, UL131 단백질은 10개 이상의 아미노산의 UL131 단편일 수 있다. 예를 들어, 단편의 아미노산의 수는 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 또는 200개의 아미노산을 포함할 수 있다. UL131 단편은 잔기 번호 중 어느 것에서도 시작할 수 있다: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119.

[0187] UL131 잔기는 SEQ ID NO:48로 나타나는 전체 길이 UL131 아미노산 서열 (CMV UL131 FL)에 따라 번호가 매겨진다. 임의로, UL131 단편은 단편의 시작 잔기로부터 N-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연

장될 수 있다. 임의로, UL131 단편은 단편의 마지막 잔기로부터 C-말단으로 5, 10, 20, 또는 30개의 아미노산으로 추가로 연장될 수 있다.

[0188] 상기 진술된 바와 같이, 본 발명은 첫 번째 헤르페스바이러스 단백질 또는 이들의 단편을 암호화하는 첫 번째 서열, 및 두 번째 헤르페스바이러스 단백질 또는 이들의 단편을 암호화하는 두 번째 서열을 함유하는 재조합 폴리시스트론성 핵산 분자와 관련된다. 따라서, 알파바이러스 VRP 및 둘 이상의 CMV 단백질 또는 이들의 단편을 암호화하는 서열을 함유하는 자가 복제 RNA와 같은, 특정 바람직한 구체예의 전술된 설명은 본 발명의 예시이지만 본 발명의 범위를 제한하지 않는다. 이러한 바람직한 구체예에서 CMV 단백질을 암호화하는 서열은 gH 및 gL, 또는 10개 이상의 아미노산 길이인 이들의 단편과 같이, 다른 헤르페스바이러스, 예를 들어, HHV-1, HHV-2, HHV-3, HHV-4, HHV-6, HHV-7 및 HHV-8의 단백질을 암호화하는 서열로 대체될 수 있는 것으로 이해될 것이다. 예를 들어, 적합한 VZV (HHV-3) 단백질은 gB, gE, gH, gI, 및 gL, 및 10개 이상의 아미노산 길이인 이들의 단편을 포함하고, 어떤 VZV 균주의 것일 수도 있다. 예를 들어, VZV 단백질 또는 이들의 단편은 VZV의 pOka, Dumas, HJO, CA123, 또는 DR 균주일 수 있다. 이 전형적인 VZV 단백질 및 이들의 단편은 사람 세포와 같이, 원하는 숙주에서 발현에 최적화된 또는 탈최적화된 코돈인 서열을 포함하는 어떤 적합한 뉴클레오티드 서열에 의해서도 암호화될 수 있다. VZV 단백질의 전형적인 서열은 여기에 제공된다.

[0189] 예를 들어, 한 구체예에서, 폴리시스트론성 핵산 분자는 VZV gH 단백질 또는 이들의 단편을 암호화하는 첫 번째 서열, 및 VZV gL 단백질 또는 이들의 단편을 암호화하는 두 번째 서열을 함유한다.

[0190] 일부 구체예에서, 폴리시스트론성 핵산 분자에 존재하는 헤르페스바이러스 단백질 또는 단편을 암호화하는 각각의 서열은 그것의 자체 조절 요소와 작동 가능하게 연결된다. 예를 들어, 헤르페스바이러스 단백질 또는 단편을 암호화하는 각각의 서열은 그것의 자체 서브게놈 프로모터와 작동 가능하게 연결된다. 따라서 알파바이러스 레플리콘과 같은, 폴리시스트론성 핵산 분자는 둘, 셋, 넷 또는 다섯 개의 서브게놈 프로모터를 함유할 수 있으며, 이것들 각각은 헤르페스바이러스 단백질 또는 단편의 발현을 조절한다. 이 타입의 폴리시스트론성 핵산 분자가 알파바이러스 레플리콘과 같은, 자가 복제 RNA일 때, 그것은 VRP로서 포장될 수 있거나, RNA 전달 시스템과 관련되거나 이로 조제될 수 있다.

[0191] **방법 및 이용**

[0192] 일부 구체예에서, 자가 복제 RNA 분자 또는 VRP는 면역 반응을 자극하기 위해 개인에게 투여된다. 이러한 구체예에서, 자가 복제 RNA 분자 또는 VRP는 전형적으로 약학적으로 허용 가능한 담체 및, 임의로, 보조제를 포함할 수도 있는 조성물에 존재한다. 예를 들어, U.S. 6,299,884; U.S. 7,641,911; U.S. 7,306,805; 및 US 2007/0207090 참조.

[0193] 면역 반응은 체액 면역 반응, 세포-매개 면역 반응, 또는 둘 다를 포함할 수 있다. 일부 구체예에서, 면역 반응은 각각 전달된 CMV 단백질에 대하여 유발된다. 세포-매개 면역 반응은 헬퍼 T-세포 (T_h) 반응, CD8+ 세포 독성 T-세포 (CTL) 반응, 또는 둘 다를 포함할 수 있다. 일부 구체예에서, 면역 반응은 체액 면역 반응이고, 항체는 중화 항체이다. 중화 항체는 세포의 바이러스 감염을 차단한다. CMV는 상피 세포 및 또한 섬유아세포를 감염시킨다. 일부 구체예에서, 면역 반응은 두 세포 타입의 감염을 감소시키거나 방지한다. 중화 항체 반응은 보체-의존적 또는 보체-독립적일 수 있다. 일부 구체예에서, 중화 항체 반응은 보체-독립적이다. 일부 구체예에서, 중화 항체 반응은 교차-중화이다; 즉, 투여된 조성물에 대하여 발생한 항체는 조성물에 이용된 균주 이외의 균주의 CMV 바이러스를 중화시킨다.

[0194] 업계에서 항체 효능의 유용한 측정값은 "50% 중화 역가"이다. 50% 중화 역가를 결정하기 위해, 면역화된 동물의 혈청은 얼마나 희석된 혈청이 세포 내로 바이러스의 50%의 유입을 차단하는 능력을 유지할 수 있는지 평가하기 위해 희석된다. 예를 들어, 700의 역가는 혈청이 700배 희석된 후 바이러스의 50%를 중화시키는 능력을 유지하였다는 것을 의미한다. 따라서, 더 높은 역가는 더 효능 있는 중화 항체 반응을 나타낸다. 일부 구체예에서, 이 역가는 약 200, 약 400, 약 600, 약 800, 약 1000, 약 1500, 약 2000, 약 2500, 약 3000, 약 3500, 약 4000, 약 4500, 약 5000, 약 5500, 약 6000, 약 6500, 또는 약 7000의 하한을 갖는 범위에 있다. 50% 중화 역가 범위는 약 400, 약 600, 약 800, 약 1000, 약 1500, 약 200, 약 2500, 약 3000, 약 3500, 약 4000, 약 4500, 약 5000, 약 5500, 약 6000, 약 6500, 약 7000, 약 8000, 약 9000, 약 10000, 약 11000, 약 12000, 약 13000, 약 14000, 약 15000, 약 16000, 약 17000, 약 18000, 약 19000, 약 20000, 약 21000, 약 22000, 약 23000, 약 24000, 약 25000, 약 26000, 약 27000, 약 28000, 약 29000, 또는 약 30000의 상한을 가질 수 있다. 예를 들어, 50% 중화 역가는 약 3000 내지 약 6500일 수 있다. "약"은 나열된 값의 플러스 또는 마이너스 10%를 의미

한다. 중화 역가는 하기, 특정 예에서 설명된 바와 같이 측정될 수 있다.

[0195] 면역 반응은 VRP 또는 자가 복제 RNA를 개인, 전형적으로 사람을 포함하는, 포유동물에게 투여함으로써 자극될 수 있다. 일부 구체예에서, 유발된 면역 반응은 보호 면역 반응이다, 즉, 반응은 CMV 감염의 위험 또는 심각도를 감소시킨다. 보호 면역 자극을 자극하는 것은 특히 CMV 감염 및 질환의 위험에 있는 일부 개체군에서 특히 바람직하다. 예를 들어, 위험에 있는 개체군은 고체 장기 이식 (SOT) 환자, 골수 이식 환자, 및 조혈모세포 이식 (HSCT) 환자를 포함한다. VRP는 이식 전 이식 기증자, 또는 이식 전 및/또는 후 이식 수령체에게 투여될 수 있다. 모체로부터 아이에게 수직 전달은 유아를 감염시키는 일반적인 근원이기 때문에, 임신할 수 있는 여성에게 VRP 또는 자가 복제 RNA를 투여하는 것은 특히 유용하다.

[0196] 투여의 어떤 적합한 루트도 이용될 수 있다. 예를 들어, 조성물은 근육 내로, 복강 내로, 피하로, 또는 경피성으로 투여될 수 있다. 일부 구체예는 점막 내 루트를 통해, 예를 들어, 구강 내로, 비강내로, 질 내로, 및 직장내로 투여될 것이다. 조성물은 어떤 적합한 계획에 따라서도 투여될 수 있다.

[0197] 수탁 번호로 나타나는 뉴클레오티드 및 아미노산 서열을 포함하는, 이 개시에 인용된 모든 특허, 특허 출원, 및 참고는 표현적으로 본원에 참고로 포함된다. 상기 개시된 내용은 일반적인 설명이다. 더 완벽한 이해는 다음 특정 실시예에 대한 참고에 의해 얻어질 수 있으며, 이것은 예시의 목적으로만 제공된다.

[0198] **실시예 1**

[0199] *VRP 플랫폼을 이용하여 개개의 CMV 항원의 전달*

[0200] 각각의 CMV 당단백질 gB 및 gH는 중화 반응을 유발하고, gB는 섬유아세포의 감염을 중화시키는 사람 혈청의 항체 사이에서 우성 항원이다 (Britt et al. (1990) J. Virol. 64(3): 1079-85). 다음 실험은 마우스에서 vRP 플랫폼을 이용하여 전달된 이 항원들에 대한 중화 반응을 입증한다.

[0201] 각각의 CMV 항원을 pcDNA-6His 벡터 (Invitrogen) 내로 클로닝하였고 알파바이러스 레플리콘 벡터, 도 2에 나타난 구조물을 생산하는, Perri et al. (J. Virol 77(19)10394-10403 (2003))에 의해 설명된 플라스미드로부터 유도된 pVCR 2.1 SalI/XbaI 내로 클로닝하기 전 단백질 발현에 대하여 테스트하였다. pVCR 2.1 SalI/XbaI는 자가 복제 RNA 벡터이며, 이것은 결함 헬퍼 캡시드 및 당단백질 RNA로 전기 천공될 때, 감염성 알파바이러스 입자를 형성한다. pVCR 벡터를 베네수엘라 말 뇌염 바이러스 (VEE)로부터 유도된 결함 헬퍼 캡시드 및 당단백질 RNA의 존재시 아기 햄스터 신장 (BHKV) 세포 내로 전기 천공되는 RNA를 만들기 위해 이용하였다. 전기 천공 후, 분비된 알파바이러스 벡터 입자 (VRP)를 함유하는 상층액을 마우스 면역화 연구를 위해 수거, 정제, 적정, 및 이용하였다. 마우스는 3주 간격으로, 연속적인 두 번의 면역화에서 1 x 10^6 감염 유닛 (IU)/마우스로 면역화되었다. 2차 면역화 3주 후에 마지막 채혈을 하였다.

[0202] 모노시스트론성 gB, gH 및 gL VRP

[0203] 두 개의 다른 버젼의 가용성 gB를 구성하였다: "gB sol 750"은 막 통과 스패닝 도메인 및 세포질 도메인이 없고; "gB sol 692"는 또한 소수성 영역이 없고 (도 2a) Reap et al. 구조와 유사하다. 막 통과 스패닝 도메인 및 세포질 도메인이 없는 가용성 gH ("gH sol 716")을 또한 제조하였다 (도 2c). 면역화된 마우스의 혈청을 다수의 검정으로 선별하였다. 면역블롯 (데이터 미도시) 및 면역형광 검정을 항원에 대한 특정 항체 반응을 확인하기 위해 이용하였다. 유도된 항체 반응이 CMV 감염을 중화시킬 수 있다는 것을 입증하기 위해 중화 검정을 이용하였다.

[0204] 면역화된 마우스의 혈청을 gB-6His를 발현하는 구조물로 트랜스펙션된 293T 세포에서 gB의 인식을 위해 면역형광법으로 조사하였다. 세포를 항-His 항체 ("항-6His"), 단클론성 gB 항체 ("항-gB 27-156"), 또는 수거된 풀 마우스 항체로 탐침하였다. 사전 면역화된 혈청은 모든 경우에 음성이었다. gB FL-6His를 발현하는 구조물로 트랜스펙션되고, 고정되고, 통과된 세포에서, 항-6His 염색은 엔도사이트/엑소사이트 트래피킹 경로 (endocytic/exocytic trafficking pathway)에 대부분 해당하는 반점 세포질 패턴으로 표면 발현의 발현 패턴을 나타내었다. 항-gB 27-156 및 풀 마우스 혈청은 유사한 발현 패턴을 나타내었다. gB FL VRP, gB sol 750 VRP, 및 gB sol 692 VRP 각각으로 면역화된 마우스의 혈청은 같은 발현 패턴을 나타내었다.

[0205] gH FL VRP 및 gH sol 716 VRP로 면역화된 마우스는 gH에 특이적인 항체를 생산하였다. gH FL-6His를 발현하는 구조물로 트랜스펙션된 293T 세포의 면역형광 분석은 항-6His, 항-gH, 및 풀 마우스 혈청에 의해 gH의 강한 인식을 검출하였다. gL VRP로 면역화된 마우스로부터 수거한 혈청은 면역블롯 분석 및 면역형광법으로 결정된 바와 같은 특이적 항체 반응을 생산하였다. gL VRP는 중화 반응을 유도하는데 실패하였다.

[0206] gB VRP 또는 gH VRP로 면역화된 마우스의 혈청을 중화 항체의 존재에 대하여 CMV 중화 검정을 이용하여 분석하였다. 다양하게 희석된 혈청을 CMV 바이러스 TB40UL32EGFP ("TB40-GFP," GFP를 발현하도록 설계된 임상 분리체)와 함께 사전 배양하였고 ARPE-19 상피 세포에 추가하였고 5일 동안 배양하였다. 감염 5일 후에, GFP-양성 세포를 계산하였다. 이 검정에서, 중화 항체를 함유하는 혈청과 함께 배양된 세포는 바이러스 단독과 함께 또는 사전 면역 혈청과 함께 배양된 바이러스와 함께 배양된 세포에 비해 더 적은 GFP-양성 세포를 갖는다. gB VRP, gB FL VRP, gB sol 750 VRP, 또는 gB sol 692 VRP로 면역화된 마우스의 혈청은 기니피그 보체의 존재시 강한 중화 활성이 있었다 (1:1280-1:2560의 혈청 희석시 50% 중화 역가; 도 3). gH FL VRP 또는 gH sol VRP로 면역화된 마우스의 혈청은 기니피그 보체에 독립적인, 일부 중화 활성이 있었다 (도 3).

[0207] **실시예 2**

[0208] *폴리시스트론성 알파바이러스 벡터의 구조*

[0209] CMV는 감염 중에 다수의 다단백질 복합체를 생산한다. 대상체에서 CMV 복합체를 생산하기 위해 원하는 복합체의 모든 성분을 발현하는 단일 레플리콘이 이용될 수 있는지, 또는 복합체의 성분이 다수의 레플리콘 벡터로부터 동시전달될 수 있는지 결정하기 위하여, 우리는 다수의 CMV 단백질의 제어된 발현을 허용하는 플랫폼을 디자인하였다.

[0210] 알파바이러스 벡터 (pVCR 2.1 SalI/XbaI)를 다수의 서브게놈 프로모터 (SGP) 및 원하는 유전자 (GOI)의 조립체를 허용하도록 변형하였다. 11026-31 bp의 pVCR 2.1SalI/XbaI ApaI 부위를 GGGCCC (SEQ ID NO:7)에서 GGCGCC (SEQ ID NO:8)로 바꿨다. ClaI 및 PmlI 제한 부위는 첫 번째 서브게놈 프로모터 및 SalI-XbaI 삽입 부위의 다운스트림 근처 영역에 추가된다. 7727-7754 bp의 서열을 ctcgatgtacttccgaggaactgatgtg (SEQ ID NO:9)에서 ATCGATGTACTTCCGAGGAACTCACGTG (SEQ ID NO:10)로 바꿨다.

[0211] 셔틀 (shuttling) 벡터 시스템을 SalI-XbaI 부위를 이용하여 SGP의 다운스트림에 직접 GOI의 삽입을 허용하기 위해 디자인하였다. pcDNA 3.1 (-) C를 다음과 같이 변형시켰다. 세 개의 SalI 부위, 위치 1046-1051 bp, 3332-3337 bp 및 5519-21, 1-3 bp가 GTCGAC (SEQ ID NO:11)에서 GTCTAC (SEQ ID NO:12)로 삭제되었다.

[0212] 위치 916-921 bp에 XbaI 부위의 돌연변이를 일으키기 위해 TCTAGA (SEQ ID NO:13)에서 pcDNA 3.1 (-) C를 TCAAGA (SEQ ID NO:14)로 변형하였다. 위치 942-947 (ClaI) 및 950-955 (SacII) bp에 ClaI 부위 및 SacII 부위를 추가하기 위해 pcDNA 3.1 (-) C를 ctggatatctgcag (SEQ ID NO:15)에서 ATCGATATCCGCGG (SEQ ID NO:16)로 변형시켰다.

[0213] 제한 부위가 추가되었고 결과 서열이 입증되었고, bp 7611-7689 (ctataactctctacggctaacctgaatggactacgacatagtctagtcgaccaagcctctagacggc gcgcccaccca) (SEQ ID NO:17)의 영역은 다음 프라이머를 이용하여 변형된 pVCR 2.1 알파바이러스 벡터로부터 증폭되었다

[0214] 정방향 SGP S-X Not F:

[0215] 5'ATAAGAAT**GCGGCCGC**CTATAACTCTCTACGGCTAACC3' (SEQ ID NO:18) 및

[0216] 역방향 SGP S-X Cla R:

[0217] 5'CC**ATCGAT**TGGGTGGGCGCGCCGTCTAG3' (SEQ ID NO:19) 또는

[0218] 정방향 SGP S-X Cla F:

[0219] 5'CC**ATCGAT**CTATAACTCTCTACGGCTAACC3' (SEQ ID NO:20) 및

[0220] 역방향 SGP S-X Sac R:

[0221] 5'TCC**CCGCGG**TGGGTGGGCGCGCCGTCTAG3' (SEQ ID NO:21).

[0222] 적절한 부위의 사이에 (NotI-ClaI 또는 ClaI-SacII) 셔틀 벡터 (pcDNA SV)를 만들기 위해 증폭된 영역을 변형된 pcDNA 3.1 (-) C 벡터 내로 추가하였다. NotI-SGP Sal-Xba-ClaI의 삽입은 pcDNA SV 카세트 2를 형성하고, ClaI-SGP Sal-Xba-SacII의 삽입은 pcDNA SV 카세트 3을 형성한다. 이 SV 카세트를 배열하였다. pcDNA SV 카세트 2는 ClaI 부위가 pcDNA SV 카세트 2 벡터에서 절단되지 않았기 때문에 XbaI 부위 및 ClaI 부위 사이에 추가적인 12 bp (CCACTGTGATCG) (SEQ ID NO:22)를 함유한다. 그러므로 PmlI 부위를 추가하였다. pcDNA SV 카세트 2에 대하여, PmlI 부위를 bp 1012 (CACGTG) (SEQ ID NO:23)에 삽입하였다. 카세트 3에 대하여, PmlI 부위를 bp 935-940 (ACTGTG (SEQ ID NO:24)에 추가하였고 CACGTG (SEQ ID NO:23)로 바꾸었다.

[0223] 각각의 폴리시스트론성 벡터에 대하여, 첫 번째 유전자를 SalI-XbaI 부위를 이용하여 pVCR 2.1 변형된 벡터 내로 직접 삽입하였다. 두 번째 유전자를 SalI-XbaI를 이용하여 pcDNA SV 카세트 2로 결찰하였고 NotI-PmlI, NotI-SacII를 이용하여 잘라내거나 NotI-ClaI에 대한 프라이머를 이용하여 PCR하였고 NotI 및 ClaI를 이용하여 촉진하였다. 결과 삽입물 SGP-SalI-GOI-Xba을 NotI-PmlI, NotI-SacII, 또는 NotI-ClaI 부위를 이용하여 변형된 pVCR 2.1 벡터에 결찰하였다. NotI-ClaI 삽입물은 구조물에서 원하는 유전자가 PmlI 부위를 함유할 때만 이용되었다.

[0224] 일부 경우에서, 세 번째 유전자를 SalI-XbaI를 이용하여 pcDNA SV 카세트 3에 결찰하였고 PmlI-SacII를 이용하여 잘라내거나 ClaI-SacII에 대한 프라이머를 이용하여 PCR하였고 ClaI 및 SacII를 이용하여 촉진하였다. 결과 삽입물 SGP-SalI-GOI-XbaI을 PmlI-SacII 또는 ClaI-SacII를 이용하여 변형된 pVCR 2.1로 결찰하였다.

[0225] SalI-XbaI 촉진을 폴리시스트론성 벡터 DNA의 구조물을 입증하기 위해 이용하였다. SalI-XbaI으로 촉진 후, GOI의 존재를 확인하기 위해 아가로스 겔 전기영동을 수행하였다. 폴리시스틀노성 벡터 DNA를 PmeI로 하룻밤 동안 선형화하였고, Qiagen의 PCR 정제 키트를 사용하여 정제하였고, Ambion mMessage mMachine 키트를 사용하여 RNA를 만들기 위해 주형으로 사용하였다. RNA 질을 RNA 아가로스 겔 상에 샘플 앨리쿼트를 실행함으로써 체크하였다.

[0226] **폴리시시트론성 벡터로부터 발현**

[0227] 폴리시스트론성 벡터의 두 개의 단백질을 발현하는 능력을 평가하기 위하여 형광 발광 단백질 GFP (녹색 형광 단백질) 및 mCherry (적색 형광 단백질)을 이용하였다. 우리는 첫 번째 서브게놈 프로모터를 사용하여 GFP가 발현되고 두 번째 서브게놈 프로모터를 사용하여 mCherry가 발현되는 바이시스트론성 벡터를 제조하였다 (도 4a). 이 단백질에 대한 암호화 서열을 함유하는 폴리뉴클레오티드를 SalI-XbaI 부위를 사용하여 삽입하였다. 첫 번째 폴리뉴클레오티드 (GFP)를 변형된 알파바이러스 레플리콘 벡터로 직접 삽입하였다. 두 번째 폴리뉴클레오티드 (mCherry)를 암호화 서열의 직접적으로 업스트림인 서브게놈 프로모터를 함유하는 tu틀 벡터로 먼저 삽입하였다. 두 번째 서브게놈 프로모터 및 두 번째 폴리뉴클레오티드 둘 다를 함유하는 단편을 분리하였고 첫 번째 폴리뉴클레오티드를 함유하는 변형된 알파바이러스 레플리콘 벡터에 결찰하였으며, 다수의 서브게놈 프로모터를 갖는 알파바이러스 레플리콘을 제공한다.

[0228] Cap 및 Gly에 대하여 결함 헬퍼 RNA와 함께 레플리콘 RNA를 전기 천공함으로써 BHKV 세포에서 VRP를 생산하였다. VRP를 전기 천공 24 시간 후 수확하였고 세포 당 20개의 감염 유닛 (IU)의 감염 다중도 (MOI)로 BHKV 세포를 감염시키기 위해 이용하였다.

[0229] 실험은 네 개의 세트의 VRP를 테스트하였다: GFP만을 발현하는 한 VRP; mCherry를 발현하는 한 VRP; 둘 다 20 IU/세포의 MOI에서, GFP만을 발현하는 한 VRP 및 mCherry만을 발현하는 한 VRP; 및 바이시스트론성 벡터 GFP(1)-SGPmCherry(2)를 함유하는 한 VRP. VRP-감염된 BHKV 세포를 공존의 퍼센트를 결정하기 위해 감염 24 시간 후 조사하였다. 거의 모든 세포는 개별적으로 감염될 때 GFP 또는 mCherry에 대해 양성이었다. 두 개의 별도으이 VRP로 감염된 세포는 녹색 또는 적색을 나타냈다. 극소수의 세포는 황색이었고, 소수의 세포가 동등한 수준으로 GFP 및 mCherry를 나타내고 동시-감염의 수준이 낮다는 것을 나타낸다. 이 데이터를 FACS 분석법을 사용하여 확인하였다 (도 4b).

[0230] 반대로, 바이시스트론성 벡터 GFP(1)-SGPmCherry(2)를 함유하는 알파바이러스로 감염된 세포는 모두 황색이었으며, 이것은 GFP 및 mCherry의 거의 동일한 발현을 나타낸다. 이 연구는 다수의 단백질이 단일 폴리시스트론성 알파바이러스 레플리콘 벡터로부터 성공적으로 발현될 수 있다는 것을 입증한다.

[0231] **실시예 3**

[0232] *CMV 복합체의 생산*

[0233] 이 실시예는 폴리시스트론성 알파바이러스 레플리콘 벡터의 복합체 성분의 전달 후 세포에서 CMV 단백질 복합체가 형성될 수 있다는 것을 입증한다.

[0234] gH/gL 및 gH/gL/gO 복합체

[0235] 폴리시스트론성 gH/gL 및 gH/gL/gO 알파바이러스 레플리콘을 상기 설명된 바와 같이 구성하였다 (도 5a에 도면으로 나타남). 레플리콘을 암호화하는 gH, gL, gO, gH/gL 및 gH/gL/gO를 함유하는 VRP를 상기 설명된 바와 같이 BHKV tph에서 생산하였고 시험관 내에서 복합체 형성을 입증하기 위해 BHKV 세포를 감염시키는데 사용하였다. VRP 감염된 ARPE-19 세포들은 gH/gL의 이황화 결합된 복합체를 생성하였다. gO는 gH/gL 결합을 검출 가능하게

변화시키지 않았다 (도 5b).

[0236] 단독으로 전달된 gH 및 gL의 국부화를 평가하기 위해 및 동시발현될 때 단백질의 재국부화를 관찰하기 위해 폴리시스트론성 알파바이러스를 사용하여 전달될 때 면역형광 연구를 수행하였다. gH 국부화는 gL, 또는 gL/gO의 존재시 또는 부재시 바뀌지 않는 것으로 보였다. gL 국부화는 gH 및 gH/gO의 존재시 바뀌지 않았다.

[0237] 최종적으로, gH/gL 결합을 면역침강법을 통해 검사하였다. 상업적인 gH 항체 (Genway)를 gH 및 gL의 결합을 조사하기 위해 사용하였다. 모든 경우에서, gH 항체는 gH를 효율적으로 면역침강하였다 (도 5c). gH가 존재하지 않을 때, gL은 면역침강되지 않았다. gH 또는 gH/gO의 존재시 gL이 발현될 때, gL과 gH의 결합이 있었다 (도 5c).

[0238] gH의 존재시 gL의 재국부화 및 gH/gL의 결합은 (gO의 유무에 상관없이) 폴리시스트론성 알파바이러스 레플리콘의 모든 성분이 발현되고 복합체를 형성하기 위해 결합된다는 것을 나타낸다.

[0239] **실시예 4**

[0240] 시험관 내에서 gH/gL 복합체 형성에 영향을 미치는 VRP는 gB VRP에 대하여 유도된 면역 반응에 비해 질적으로 및 양적으로 뛰어난 효능 있는 면역 반응을 유발한다.

[0241] 이 실시예는 폴리시스트론성 gH/gL VRP 또는 gH/gL/gO VRP를 전달함으로써 형성되는 강한 면역 반응의 유발이 조합으로 투여된 단일 성분들을 전달하는 VRP 및 단일 성분 VRP를 사용하여 얻어진 면역 반응 또는 gB VRP에 의해 유도된 반응과 비교된다는 것을 입증한다.

[0242] 마우스를 3주 간격으로 투여된 VRP로 세 번 감염시켰다 (마우스 당 106 IU; 5 마리 BalbC 마우스/그룹). 단일 및 폴리시스트론성 VRP로 면역화로부터 수거된 혈청을 상기 설명된 바와 같이 CMV 중화 검정을 사용하여 중화 항체에 대하여 선별하였다. 중화 역가를 다음과 같이 측정하였다. 다양한 희석의 혈청을 기니피그 보체의 존재시 또는 부재시 TB40-UL32-EGFP와 함께 사전 배양하였고 ARPE-19 상피 세포 또는 MRC-5 섬유아세포에 추가하였고 5일 동안 배양하였다. 바이러스로 감염 5일 후, GFP-양성 세포를 계산하였다. ARPE-19 세포에 대한 결과는 도 6a, 도 6b, 및 도 6c에 나타난다. MRC-5 세포에 대한 결과는 도 7a 및 도 7b에 나타난다.

[0243] gH FL VRP로 면역화된 마우스의 혈청은 낮은 보체-독립적 중화 활성이 있었다 (도 6a 및 도 6b). 기니피그 보체의 존재시 또는 부재시 gL 또는 gO만으로 면역화된 마우스의 혈청을 사용하여 중화 활성이 관찰되지 않았다 (도 6c). 다수의 CMV gB 단백질 (gB FL, gB sol 750, 및 gB sol 692)로 면역화된 풀 혈청은 기니피그 보체의 존재시 1:1280 혈청 희석시 50% 중화 역가를 갖는, 강한 중화 활성을 입증하였다. 하지만, 풀 gB 혈청에 대하여 ARPE-19 세포에서 기니피그 보체의 부재시 중화 활성이 없었다. 단일 CMV 단백질을 발현하는 VRP (106 IU/마우스/VRP로 gH-또는 gL-VRP 또는 동시투여 gH-, gL-, 및 gO-VRP)는 gH 단독의 그것 이상으로 중화 활성을 향상시키지 않았다.

[0244] 반대로, 바이시스트론성 gH/gL 또는 트리시스트론성 gH/gL/gO VRP로 면역화된 마우스의 혈청 (1x106 IU/마우스)은 강한 중화 반응을 입증하였다. 게다가, 반응은 기니피그 보체의 존재시 및 부재시 유사하였으며, 폴리시스트론성 VRP가 보체-독립적 면역 반응을 성공적으로 유발하였다는 것을 나타낸다 (도 6c). 50% 중화 역가는 TB40-GFP CM 바이러스를 갖는 ARPE-19 세포에서 1:3500-6400+ 혈청 희석이었다. 이 역가는 gB 풀 혈청에 대하여 50% 보체-의존적 중화 역가보다 대략 3-4배 더 높은 역가이다.

[0245] MRC-5 섬유아세포에서 결과는 ARPE-19 세포의 그것과 유사하였다 (도 7a 및 도 7b). 바이시스트론성 gH/gL 또는 트리시스트론성 gH/gL/gO VRP로 면역화된 마우스의 혈청은 gH 단독, gL 단독, 또는 gO 단독을 암호화하는 VRP로 면역화된 마우스의 혈청 및 gH VRP 및 gL VRP의 동시투여, 또는 gH VRP, gL VRP, 및 gO VRP의 동시투여에 의해 면역화된 마우스의 혈청에 비해 강한 중화 활성을 입증하였다. 이 결과들은 폴리시스트론성 VRP의 투여가 섬유아세포의 CMV 감염의 양호한 보체-독립적 중화를 제공하는 면역 반응을 유발한다는 것을 입증한다. CMV의 다른 균주에 대한 gH/gL 면역 혈청의 범위 및 효능을 평가하기 위해, 우리는 혈청의 섬유아세포 및 상피 세포의 감염을 차단하는 능력과 CMV의 6개의 다른 균주를 비교하였다. 도 8은 gH/gL 혈청이 광범위한 균주로 세포 타입 둘 다의 감염을 효능 있게 중화시킨다는 것을 나타낸다.

[0246] 이 데이터는 또한 폴리시스트론성 VRP로 면역화되지만 단지 하나의 단백질을 발현하는 VRP의 혼합된 풀이 아닌 마우스의 혈청에 대한 강한 중화 활성을 입증한다. 이는 단일 레플리콘에서 단백질 복합체의 성분을 암호화하는 폴리시스트론성 레플리콘이 제자리에서 복합체의 효율적인 생산을 일으킨다는 것을 나타낸다. 게다가, Merlin 균주 CMV 단백질을 이 반응들을 자극하기 위해 사용하였고, TB40 균주 CMV 바이러스를 사용하여 얻어진 시험관

내 데이터는 폴리시스트론성 VRP의 전달에 의해 유발된 중화 항체가 교차-중화 항체인 것을 입증한다.

[0247] **실시예 5**

[0248] RNA 합성

[0249] 알파바이러스 레플리콘을 암호화하는 플라스미드 DNA (도 14-16 참조)는 시험관 내에서 RNA의 합성을 위한 주형의 역할을 하였다. 알파바이러스 레플리콘은 RNA 복제에 필요한 유전적 요소를 함유하지만 입자성 조립체에 필요한 유전자 생성물을 암호화하는 것이 없다; 알파바이러스 게놈의 구조 유전자는 이종 기원 단백질을 암호화하는 서열에 의해 대체된다. 진핵세포에 레플리콘의 전달시, 양성-가닥 RNA는 네 개의 비구조 단백질을 생산하기 위해 번역되며, 이것은 함께 게놈 RNA를 복제하고 이종 기원 유전자 생성물 또는 원하는 유전자 (GOI)를 암호화하는 풍부한 서브게놈 mRNA를 전사한다. 알파바이러스 구조 단백질의 발현의 결핍으로 인해, 레플리콘은 감염성 입자의 발생을 유발할 수 없다. 알파바이러스 cDNA의 박테리오파지 (T7 또는 SP6) 프로모터 업스트림은 시험관 내에서 레플리콘 RNA의 합성을 용이하게 하고 폴리(A)-꼬리의, 델타 간염 바이러스 (hepatitis delta virus; HDV) 다운스트림은 그것의 자체-분할 활성을 통해 정확한 3'-말단을 발생시킨다.

[0250] 항원성 단백질 복합체의 형성을 허용하기 위해, 같은 세포에서 상기 복합체의 개개의 성분의 발현이 가장 중요하다. 이론상으로, 이것은 개개의 성분을 암호화하는 유전자를 갖는 세포를 동시트랜스펙션함으로써 이루어질 수 있다. 하지만, 비-바이러스성 또는 VRP 전달 알파바이러스 레플리콘 RNA의 경우에, 이 계획은 불다수의 RNA의 같은 세포에 충분한 동시전달에 의해 또는, 대안으로서, 개개의 세포에서 다수의 자가 복제 RNA의 불충분한 론치에 의해 방해된다. 단백질 복합체의 성분의 동시발현을 용이하게 하는 잠재적으로 더 효율적인 방법은 같은 자가 복제 RNA 분자의 일부로서 각각의 유전자를 전달하는 것이다. 이를 위해, 우리는 원하는 다수의 유전자를 암호화하는 알파바이러스 레플리콘 구조물을 설계하였다. 모든 GOI는 알파바이러스 전사 장치에 의해 인식되는 그것 자체의 서브게놈 프로모터에 의해 진행된다. 그 때문에, 다수의 서브게놈 메신저 RNA 종은 다성분 단백질 복합체의 조립체를 허용하는 개개의 세포에서 합성된다.

[0251] 적합한 제한 엔도뉴클레아제를 갖는 HDV 리보자임의 플라스미드 DNA 다운스트림의 선형화에 따라, 유출 전사물 (run-off transcript)을 T7 박테리오파지 유도 DNA-의존적 RNA 폴리머라제를 사용하여 시험관 내에서 합성하였다. 전사를 제조사 (Ambion, Austin, TX)에 의해 제공된 지시에 따라 각각 7.5 mM의 뉴클레오시드 트리포스페이트 (ATP, CTP, GTP 및 UTP)의 존재시 37 ℃에서 2 시간 동안 수행하였다. 전사 후, 주형 DNA를 TURBO DN아제로 소화시켰다. 레플리콘 RNA를 LiCl로 침전시켰고 뉴클레아제 없는 물로 재구성하였다. 캐핑되지 않은 RNA를 사용자 매뉴얼에 설명된 바와 같이 ScriptCap m7G Capping System (Epicentre Biotechnologies, Madison, WI)을 사용하여 Vaccinia Capping Enzyme (VCE)로 전사 후 캐핑하였다. 전사 후 캐핑된 RNA를 LiCl로 침전시켰고 뉴클레아제 없는 물로 재구성하였다. RNA 샘플의 농도를 250 nm에서 흡광도를 측정함으로써 결정하였다. 시험관 내 전사의 무결성을 아가로스 겔 전기 영동을 변성시킴으로써 확인하였다.

[0252] 지질 나노입자 (LNP) 조제

[0253] 1,2-디리놀레일옥시-N,N-디메틸-3-아미노프로판 (DlinDMA)을 이전에 출판된 공정 [Heyes, J., Palmer, L., Bremner, K., MacLachlan, I. Cationic lipid saturation influences intracellular delivery of encapsulated nucleic acids. Journal of Controlled Release, 107: 276-287 (2005)]을 사용하여 합성하였다. 1,2-디아스테아로일-sn-글리세로-3-포스포콜린 (DSPC)을 Genzyme에서 구입하였다. 콜레스테롤을 Sigma-Aldrich (St. Lois, MO)에서 얻었다. 1,2-디미리스토일-sn-글리세로-3-포스포에탄올아민-N-[메톡시(폴리에틸렌 글리콜)-2000] (암모늄 염) (PEG DMG 2000)을 Avanti Polar Lipids에서 얻었다.

[0254] LNP (RV01(14))를 다음 방법을 사용하여 조제하였다. 150 μg 배치, (PES 유공 섬유 및 무스탕 없음): 에탄올 중에 신선한 지질 스톡 (stock) 용액을 제조하였다. 37 mg DlinDMA, 11.8 mg DSPC, 27.8 mg 콜레스테롤 및 8.07 mg PEG DMG 2000을 계량하였고 7.55 mL 에탄올에 용해시켰다. 신선하게 제조된 지질 스톡 용액을 균질한 혼합물을 형성하기 위해 37 ℃에서 약 15 분 동안 부드럽게 흔들었다. 이후에, 2 mL의 작용 지질 스톡 용액을 만들기 위해 453 μL의 스톡을 1.547 mL 에탄올에 추가하였다. 이 지질의 양을 8:1 N:P (질소 대 인)에서 150 μg RNA로 LNP를 형성하기 위해 사용하였다. 이 계산을 위해 DlinDMA 상에 양성자성 질소 (양이온성 지질) 및 RNA 상에 인산이 사용된다. 자가 복제 RNA 분자의 각각의 μg이 음이온성 인의 3 nmole을 함유하는 것으로 가정하였고, DlinDMA의 각각의 μg은 양이온성 질소의 1.6 nmole을 함유하는 것으로 가정하였다. 2 mL의 RNA 작용 용액을 또한 100 mM 시트레이트 완충액 (pH 6) (Teknova)중의 1 μg/μL 이하의 스톡 용액으로부터 제조하였다. 세 개의 20 mL 유리 바이알 (스터 바 (stir bar)와 함께)을 RNase Away 용액 (Molecular BioProducts)으로 행

구고 RN아제로 바이알을 정화하기 위해 사용 전 충분한 MilliQ 물로 세척하였다. 바이알 중 하나를 RNA 작용 용액을 위해 사용하였고 다른 것을 지질 및 RNA 혼합물을 수거하기 위해 사용하였다 (하기 설명된 바와 같음). 작용 지질 및 RNA 용액을 3 cc 루어록 (luer-lok) 주사기 (BD Medical)에 로딩하기 전에 37 ℃에서 10 분 동안 가열하였다. 2 mL의 시트레이트 완충액 (pH 6)을 또 다른 3 cc 주사기에 로딩하였다. RNA 및 지질을 함유하는 주사기를 FEP 튜빙 ([불소화 에틸렌-프로필렌] 2mm ID x 3mm OD, Idex Health Science, Oak Harbor, WA)을 사용하여 T 믹서 (PEEK™ 500 μm ID 접합)에 연결하였다. T 믹서의 배출구는 또한 FEP 튜빙 (2mm ID x 3mm)이었다. 세트레이트 완충액을 함유하는 세 번째 주사기를 별도의 조각의 튜빙 (2mm ID x 3mm OD)에 연결하였다. 모든 주사기를 주사기 펌프 (kdScientific의 것, 모델 번호 KDS-220)를 사용하여 7 mL/ 분의 유속으로 구동하였다. 혼합물을 수거하기 위해 튜브 배출구를 20 mL 유리 바이알에 배치하였다 (교반하면서). 스터 바를 꺼내고 에탄올/수용액을 1 시간 동안 상온과 평형을 허용하였다. 혼합물을 5 cc 주사기 (BD Medical)에 로딩하였으며, 이것은 FEP 튜빙 (2mm ID x 3mm OD)의 조각에 맞춰졌고 같은 길이의 FEP 튜빙을 갖는 또 다른 5 cc 주사기에서, 같은 양의 100 mM 시트레이트 완충액 (pH 6)을 로딩하였다. 두 개의 주사기를 주사기 펌프를 사용하여 7 mL/ 분의 유속으로 구동하였고 최종 혼합물을 20 mL 유리 바이알에 수거하였다 (교반하면서). 그 다음, LNP를 2 mL로 농축하였고 최종 생성물을 회수하기 전에 접선 유동 여과 (Tangential Flow Filtration; TFF) 시스템을 사용하여 10-15배의 1X PBS (Teknova의 것)에 대하여 투석하였다. TFF 시스템 및 유공 섬유 여과막을 Spectrum Labs에서 구입하였고 제조사의 가이드라인에 따라 사용하였다. 100 kD 기공 크기 컷오프 및 20 cm^2 표면적을 갖는 폴리에테르술폰 (PES) 유공 섬유 여과막 (부품 번호 P-C1-100E-100-01N)을 사용하였다. 시험관 내 및 생체 내 실험에 대하여, 제형을 1X PBS (Teknova의 것)를 가지고 필요한 RNA 농도로 희석하였다.

[0255] 입자 크기

[0256] 입자 크기를 제조사의 지시에 따라 Zetasizer Nano ZS (Malvern Instruments, Worcestershire, UK)를 사용하여 측정하였다. 입자 크기는 다 분산 지수 (pdi)와 함께 Z 평균으로 보고된다. 측정 전 리포솜을 1X PBS로 희석하였다.

[0257] 캡슐화 효능 및 RNA 농도

[0258] 캡슐화된 RNA의 퍼센트 및 RNA 농도를 Quant-iT RiboGreen RNA 시약 키트 (Invitrogen)으로 결정하였다. 검정 시 제조사의 지시를 따랐다. 키트에 제공된 리보솜 RNA 표준을 표준 곡선을 발생시키기 위해 사용하였다. 염료의 추가 전에, 방법 1 또는 방법 2-5로부터 얻어진 LNP를 1X TE 완충액 (키트의 것)으로 각각 10배 또는 100배 희석하였다. 별도로, 염료의 추가 전에, LNP를 0.5% Triton X (Sigma-Aldrich)를 함유하는 1X TE 완충액으로 10배 또는 100배 희석하였다. 그 후에 같은 양의 염료를 각각의 용액에 추가하였고 염료 추가 후에 180 μL 이하의 각 용액을 96 웰 조직 배양 플레이트에 두 번 로딩하였다 (VWR에서 얻어짐, 카탈로그 # 353072). 형광발광 (Ex 485 nm, Em 528 nm)을 미크로플레이트 리더 (BioTek Instruments, Inc.의 것)에서 측정하였다.

[0259] LNP를 방해하기 위해 Triton X를 사용하였으며, 총 RNA 양에 해당하는 형광발광 측정값을 제공하고 Triton X가 없는 샘플은 캡슐화되지 않은 RNA에 해당하는 형광발광을 제공한다. % RNA 캡슐화를 다음과 같이 결정하였다: LNP RNA 캡슐화 (%) = $[(F_t-F_i)/F_t]$ X 100, 여기에서 F_t는 Triton X가 추가된 LNP의 형광 강도이고 F_i는 세제 추가 없는 LNP의 형광 강도이다. 이 값들 (F_t 및 F_i)은 블랭크 (blank) (1X TE 완충액) 형광 강도에서 뺀 후에 얻어진다. 캡슐화된 RNA의 농도를 F_t-F_i를 발생된 표준 곡선과 비교함으로써 얻어졌다. 모든 LNP 제형을 캡슐화된 용량에 기초하여 생체 내에 투여하였다.

[0260] 바이러스 레플리콘 입자 (VRP)

[0261] RNA 백신을 리포터 유전자 또는 항원의 생체 내 발현을 달성하기 위한 전통적인 RNA-벡터 접근법과 비교하기 위하여, 우리는 Perri et al. (J. Virol 77(19): 10394-10403 (2003))에 의해 설명된 방법으로 BHK 세포에서 생산되고, 해당하는 RNA 구조물과 같은 항원의 발현을 위해 암호화하는 바이러스 레플리콘 입자 (VRP)를 활용하였다. 이 시스템에서, 항원은 신드비스 바이러스의 3' 말단 서열 (3' UTR) 및 신드비스 바이러스 패키징 신호 (PS)를 함유하도록 설계된 베네수엘라 말 뇌염 바이러스 (VEEV)의 게놈으로부터 유도된 알파바이러스 키메라 레플리콘 (VCR)로 구성되었다 (Perri et al의 도 2 참조). 그것들을 신드비스 바이러스 캡시드 및 당단백질 유전자를 암호화하는 결함 헬퍼 RNA로 아기 햄스터 신장 (BHK) 세포에 동시전기천공함으로써 레플리콘을 VRP 내로 포장하였다 (Perri et al의 도 2 참조). 이후 VRP를 수거하였고 수크로스 쿠션에서 초원심 분리에 의해 부 분적으로 정제하였고 Amicon 농축기에서 농축하였다. 결과 VRP 스톡을 표준 방법에 의해 적정하였고 배양 유동체 또는 다른 등장성 완충액의 동물에 접종하였다. 베네수엘라 말 뇌염 및 신드비스 바이러스로부터 유도된 알파바이

러스 레플리콘 입자 키메라는 효능 있는 유전자-기반 백신 전달 벡터이다. J. Virol 77, 10394-10403.

[0262] 쥐 면역원성 연구

[0263] 10마리의 8-10주령 및 약 20 g 중량의 BALB/c 마우스 그룹을 제 0일, 제 21일 및 제 42일에 $1x10^6$ IU (VRP) 또는 1.0 μg (RNA)로 면역화하였으며, 두 번째 백신 접종 3주 후에 및 세 번째 백신 접종 3주 후에 채혈하였다. 모든 동물은 두 개의 뒷다리의 사두근에 주사되었고 각각 동등한 양 (부위 당 50 μl)을 얻었다.

[0264] 미크로 중화 검정

[0265] 혈청 샘플을 중화 항체에 대하여 감염 감소 중화 테스트로 테스트하였다. 두 배의 단계 희석된 HI-혈청 (10% HI FBS가 첨가된 DMEM으로)을 약 200 IU/50 μl를 제공하도록 이전에 적정된 동량의 CMV (균주 TB40 또는 임상 분리체 8819)에 추가하였다. VR1814, Towne, AD 169 균주 및 임상 분리체 8822를 또한 사용하였다. 바이러스 중화가 발생하는 것을 허용하기 위해 혈청/바이러스 혼합물을 37 ℃ 및 5% CO_2에서 2 시간 동안 배양하였고, 이후 이 혼합물의 50 μl (약 200 IU 함유)를 96 하프 웰 플레이트의 ARPE-19 세포의 웰에 두 번 접종하였다. 플레이트를 40-44 시간 동안 배양하였다. 달리 지시되지 않으면, 양성 감염된 병소의 수를 AlexaFluor 488 접합 IE1 CMV 단클론성 항체로 면역염색 후 이어서 자동화 계산에 의해 결정하였다. 중화 역가는 대조군 (혈청 없음)에 비해, 웰 당 양성 바이러스 병소의 수의 50% 감소를 생산하는 혈청 희석의 역수로서 정의된다.

[0266] gH/gL VRP의 면역원성 및 LNP 조제 RNA

[0267] CMV의 표면 당단백질 B (gB)를 발현하는 A323 레플리콘, 전체 길이 당단백질 H 및 L (gH/gL)의 막 복합체를 발현하는 A160 레플리콘 및 가용성 형태의 당단백질 H 및 L (gHsol/gL)의 막 복합체를 발현하는 A322 레플리콘을 이 실험에 사용하였다. BALB/c 마우스, 그룹 당 10마리의 동물에 제 0일, 제 21일 및 제 42일에 gB를 발현하는 VRP ($1x10^6$ IU), gH/gL을 발현하는 VRP ($1x10^6$ IU), gHsol/gL을 발현하는 VRP ($1x10^6$ IU) 및 대조군으로서 PBS로 양측 근육 내 백신 접종 (다리 당 50 μl)을 제공하였다. 세 개의 테스트 그룹 (A160, A322 또는 A323)은 LNP (RV01(14))에서 조제된 자가 복제 RNA를 받았다. 제 39일 (3wp2) 및 제 63일 (3wp3)에 면역학적 분석을 위해 혈청을 수거하였다.

[0268] 결과

[0269] 실험을 위해 만들어진 RV01(14) 조제시 캡슐화된 RNA의 시브 (sive) 및 퍼센트는 표 3에 나타난다.

표 3.

RV#	지질 조성물(전체 중의 % 몰)	RNA	양이온성 지질의 pKa	입자 크기 Zav (nm)	pdI	퍼센트 RNA 캡슐화
RV01 (14)	DlinDMA 40%, DSPC-10%, Chol- 48%, PEG DMG 2k-2%	gB FL	5.8	170	0.098	88.3
RV01 (14)	DlinDMA 40%, DSPC-10%, Chol- 48%, PEG DMG 2k-2%	gH FL/gL	5.8	168.8	0.144	87.4
RV01 (14)	DlinDMA 40%, DSPC-10%, Chol- 48%, PEG DMG 2k-2%	gHsol/gL	5.8	162	0.131	90

[0270]

[0271] 마지막 혈청 (제 63일, 최종 백신 접종 3주 후)에 대한 50% 중화 역가는 표 4에 나타난다.

표 4.

		ARPE-19, HCMV TB40			ARPE-19, HCMV 8819		
		풀 #1	풀 #2	평균	풀 #1	풀 #2	평균
사전 면역 혈청	-	126	212	169	50	50	50
gB FL VRP	10^6 IU	1332	295	814	5085	1031	3058
gB FL RNA-RV01(14)	1μg	686	179	433	1261	557	909
gH FL/gL VRP	10^6 IU	1425	1624	1525	2496	1374	1935
gH FL/gL RNA-RV01(14)	1 μg	6196	6390	6293	5800	10267	8034
gH sol/gL VRP	10^6 IU	2375	2254	2315	1733	1924	1829
gH sol/gL RNA-RV01(14)	1 μg	4600	2062	3331	2912	1533	2223

[0272]

[0273] 두 개의 다른 HCMV 균주를 사용하여 상피 세포에서 검정된 바와 같이, HCMV gH/gL 복합체의 전체 길이 또는 추정 가용성 형태를 발현하는 RNA는 중화 항체의 높은 역가를 유도한다. gH/gL RNA에 의해 유도된 평균 역가는 적

어도 해당하는 gH/gL VRP에 대한 평균 역가만큼 높다 (도 17 참조)

[0274] **실시예 6 CMV 단백질을 암호화하는 바이시스트론성 및 펜타시스트론성 핵산**

[0275] 사람 시토메갈로바이러스 (HCMV)의 당단백질 복합체를 발현하는 추가적인 바이시스트론성 및 펜타시스트론성 알파바이러스 레플리콘을 제조하였고, 도 18 및 20에 개략적으로 나타난다. 알파바이러스 레플리콘은 베네수엘라 말 뇌염 바이러스 (VEE)에 기초하였다. 레플리콘은 바이러스 레플리콘 입자 (VRP) 내로 포장되었고, 지질 입자 (LNP)로 캡슐화되거나 양이온성 나노에멀젼 (CNE)을 가지고 조제되었다. 각각의 레플리콘의 암호화된 HCMV 단백질 및 단백질 복합체의 발현을 면역블롯, 동시면역침강법, 및 유동 세포 분석법으로 확인하였다. 펜타머 복합체에 존재하는 구조 에피토프에 특이적인 사람 단클론성 항체를 사용하여, 복합체의 단백질 성분을 암호화하는 펜타머 레플리콘의 펜타머 gH/gL/UL128/UL130/UL131 복합체의 발현을 입증하기 위해 유동 세포 분석법을 사용하였다 (Macagno et al (2010), J. Virol. 84(2): 1005-13). 도 19는 이 항체들이 HCMV gH/gL/UL128/UL130/UL131 펜타머 복합체 (A527)를 발현하는 레플리콘 RNA로 트랜스펙션된 BHKV 세포에 결합한다는 것을 나타낸다. 세포가 같은 레플리콘 구조물로 만들어진 VRP로 감염되었을 때 유사한 결과를 얻었다. 이는 펜타머 복합체를 발현하도록 설계된 레플리콘이 원하는 항원을 정말로 발현하지만 잠재적 부산물 gH/gL은 아니라는 것을 나타낸다.

[0276] LNP에 캡슐화된 RNA인, 및 CNE로 조제된 RNA인, VRP는 후방 사두근의 근육 내 주사로 Balb/c 마우스를 면역화하기 위해 사용하였다. 마우스를 세 번, 3주 간격으로 면역화하였고, 혈청 샘플을 면역화 이전에 뿐만 아니라 세 번째 및 최종 면역화 3주 후에 각각 수거하였다. 혈청을 평가하였다. 혈청을 백신 접종에 의해 유도된 중화 항체 반응의 효능을 측정하기 위해 미크로중화 검정으로 평가하였다. 역가는 50% 중화 역가로서 발현된다.

[0277] 가용성 HCMV gH/gL 복합체에 대한 바이시스트론성 발현 카세트의 많은 다른 배열의 면역원성을 평가하였다. 도 20은 막-고정된, 전체 길이 gH/gL 복합체를 발현하는 VRP가 효능 있는 중화 항체를 유사한 바이시스트론성 발현 카세트에서 발현되는 가용성 복합체 (gHsol/gL)보다 약간 더 높은 역가로 발현하였다는 것을 나타낸다. gHsol 및 gL을 암호화하는 유전자의 순서를 바꾸거나 서브게놈 프로모터 중 하나를 IRES 또는 FMDV 2A 부위로 대체하는 것은 실질적으로 면역원성을 개선하지 않았다.

[0278] gH/gL을 발현하는 VEE/SIN VRP로 면역화된 마우스의 혈청의 HCMV 중화 활성의 범위 및 효능을 다른 균주의 HCMV로 섬유아세포 및 상피 세포의 감염을 차단하기 위해 혈청을 사용함으로써 평가하였다. 표 5는 보체의 부재시 두 가지 세포 타입에서 gH/gL 면역 혈청이 여섯 가지의 다른 균주의 HCMV에 대하여 광범위하고 유효하게 중화하였다는 것을 나타낸다. 보체의 추가는 혈청의 중화 효능에 대하여 약간 부정적인 효과가 있었다.

[0279]

표 5. gH/gL 을 발현하는 pVCR-유도된 VRP 로 면역화된 마우스의 혈청에서 중화 항체 적정 농도

	gH/gL 을 발현하는 pVCR-유도된 VRP 로 면역화된 마우스의 혈청		
HCMV 균주	세포	보체 없음	보체 있음
Towne	섬유아세포 (MRC-5)	5244	4081
AD169		2126	2208
TB40-UL32-EGFP		678	505
VR1814		4764	2126
TB40-UL32-EGFP	상피 세포 (ARPE-19)	5602	3247
VR1814		6510	2420
8819 (임상 분리체)		8706	5242
8822 (임상 분리체)		3427	2684

[0280] LNP-캡슐화된 RNA (A160)에 비해 펜타머 복합체 (A526 및 A527)를 암호화하는 LNP-캡슐화된 RNA 및 VRP (pVCR 변형된 gH-SGPgL)의 면역원성을 평가하였다. 표 6은 펜타머 복합체를 발현하는 레플리콘이 gH/gL을 발현하는 레플리콘 보다 더 많은 효능 있는 중화 항체를 유도하였다는 것을 나타낸다.

[0281]

표 6. 중화 항체 적정 농도.

레플리콘	첫 번째 후 적정 농도	두 번째 후 적정 농도	세 번째 후 적정 농도
C313 pVCR 변형된 gH-SGP-gL VRP 10^6 IU	126	6,296	26,525
A160 gH FL/gL 1 μg LNP	347	9,848	42,319
A526 펜타머 2A 1 μg LNP	179	12,210	80,000
A527 펜타머 IRES 1 μg LNP	1,510	51,200	130,000

[0282] 가장 높은 역가의 중화 항체 (A527)를 유도하는 펜타시스트론성 VEE-기반 RNA 레플리콘을 VRP로 포장하였고 VRP의 면역원성을 gH/gL-발현 VRP 및 gH/gL 및 펜타머 복합체를 발현하는 LNP-캡슐화된 레플리콘에 비교하였다. 표 7은 펜타머 복합체를 발현하는 VRP가 gH/gL을 발현하는 VRP보다 더 높은 역가의 중화 항체를 유도하였다는 것을

나타낸다. 게다가, VRP의 106개의 감염성 유닛은 VRP 및 RNA가 같은 단백질 복합체를 암호화할 때 적어도 1 μg의 LNP-캡슐화된 RNA만큼 효과가 있다.

표 7. 중화 항체 적정 농도. 혈청을 두 번째 면역화 3주 후 수거하였다.

레플리콘	50% 중화 적정 농도
A160 gH FL/gL VRP 10^6 IU	14,833
A527 펜타머 IRES VRP 10^6 IU	51,200
A160 gH FL/gL LNP 0.01 μg	4,570
A160 gH FL/gL LNP 0.1 μg	9,415
A160 gH FL/gL LNP 1 μg	14,427
A527 펜타머 IRES 0.01 μg LNP	12,693
A527 펜타머 IRES 0.1 μg LNP	10,309
A527 펜타머 IRES 1 μg LNP	43,157

[0283]

[0284] 펜타머 복합체 (A527)을 암호화하는 VEE-기반 RNA로 면역화된 마우스 혈청의 HCMV 중화 활성의 범위 및 효능을 HCMV의 다른 균주로 섬유아세포 및 상피 세포의 감염을 차단하기 위해 혈청을 사용함으로써 평가하였다. 표 8은 항-gH/gL/UL128/UL130/UL131 면역 혈청이 광범위하고 상피 세포의 감염을 효능있게 중화하였다는 것을 나타낸다. 이 노력은 보체 독립적이었다. 반대로, 혈청은 섬유아세포의 감염에 대하여 감소된 또는 검출 불가능한 효과가 있었다. 펜타머 복합체는 섬유아세포의 감염이 필요하지 않기 때문에, 이 결과들은 주로 gH/gL/UL128/UL130/UL131 펜타머 복합체에 대해 특이적인 항체를 함유하는 면역 혈청에 대하여 예상된 것이고, 그 결과로서, UL128, UL130, 및 UL131에 대한 항체는 섬유아세포의 감염을 차단하지 않는다 (Adler et al (2006), J. Gen. Virol. 87(Pt.9):2451-60; Wang and Shenk (2005), Proc. Natl. Acad. Sci. USA 102(50): 18153-8). 따라서, 이 데이터는 gH/gL/UL128/UL130/UL131 펜타머 복합체를 암호화하는 펜타머 레플리콘은 특이적으로 생체 내에서 복합체에 대한 항체를 유도한다.

표 8. LNP 에서 캡슐화된 A527 RNA 레플리콘으로 면역화된 마우스의 혈청에서 중화 항체 적정 농도. 레플리콘은 서브게놈 프로모터 및 IRES 를 사용하여 HCMV 펜타머 복합체를 발현한다.

		LNP 의 A527 펜타머 IRES RNA 로 면역화된 마우스의 혈청	
HCMV 균주	Cell	보체 없음	보체 있음
Towne	섬유아세포 (MRC-5)	3433	1574
AD169		2292	<1000
TB40-UL32-EGFP		<1000	<1000
VR1814		4683	1324
TB40-UL32-EGFP	상피 세포 (ARPE-19)	86991	59778
VR1814		82714	37293
8819 (임상 분리체)		94418	43269
8822 (임상 분리체)		85219	49742

[0285]

[0286] gH/gL 및 펜타머 복합체를 발현하는 바이시스트론성 및 펜타시스트론성 레플리콘이 다른 제형에서 중화 항체를 유도할 것인지 알기 위해서, 코튼 래트 (cotton rat)를 양이온성 나노에멀젼 (CNE)과 혼합된 바이시스트론성 또는 펜타시스트론성 레플리콘으로 면역화하였다. 표 9는 CNE 중의 레플리콘이 LNP에서 캡슐화된 같은 레플리콘에 비교 가능한 중화 항체 역가를 유도하였다는 것을 나타낸다.

표 9. 중화 항체 적정 농도. 혈청을 두 번째 면역화 3주 후 수거하였다.

레플리콘	50% 중화 적정 농도
A160 gH FL/gL VRP 10^6 IU	594
A160 gH FL/gL 1 μg LNP	141
A527 펜타머 IRES 1 μg LNP	4,416
A160 gH FL/gL 1 μg CNE	413
A527 펜타머 IRES 1 μg CNE	4,411

[0287]

[0288] **실시예 7. VZV 단백질을 암호화하는 레플리콘**

[0289] gB, gH, gL, gE, 및 gI를 암호화하는 모노시스트론성 레플리콘을 생산하기 위해 및 gH/gL 또는 gE/gI를 암호화하는 바이시스트론성 레플리콘을 생산하기 위해 VZV 단백질을 암호화하는 핵산을 VEE 레플리콘 벡터에 클로닝하였다. 바이시스트론성 레플리콘에서, 각각의 VZV 오픈 리딩 프레임의 발현은 별도의 서브게놈 프로모터에 의해 구동되었다.

[0290] 레플리콘 RNA를 제조하기 위해, 레플리콘을 암호화하는 플라스미드를 PmeI로 소화에 의해 선형화하였고, 선형화

된 플라스미드를 페놀/클로로포름/이소아밀알콜로 추출하였고, 나트륨 아세테이트/에탄올에서 침전시켰고 20μl의 RN아제 없는 물에 재현탁시켰다.

[0291] MEGAscript T7 키트 (AMBION# AM1333)를 사용하여 1 μg의 선형화된 DNA의 시험관 내 전사에 의해 RNA를 제조하였다. 20 μl 반응물을 캡 유사체 없이 제조사의 지시에 따라 셋업하였고 32 ℃에서 2 시간 동안 배양하였다. TURBO DN아제 (1 μl)을 추가하였고 혼합물을 32 ℃에서 30 분 동안 배양하였다. RN아제 없는 물 (30 μl) 및 암모늄 아세테이트 (30 μl)를 추가하였다. 용액을 혼합하였고-20 ℃에서 적어도 30 분 동안 냉각하였다. 이후 용액을 4 ℃에서 25 분 동안 최대 속도로 원심 분리하였다. 상층액을 제거하였고, 펠렛을 70% 에탄올로 헹궜고, 다시 4 ℃에서 10 분 동안 최대 속도로 원심 분리 하였다. 펠렛을 공기 건조하였고 50 μl의 RN아제-없는 물로 재현탁하였다. RNA의 농도를 측정하였고 품질을 변성 겔 상에서 체크하였다.

[0292] ScriptCap m7G Capping System (Epicentre #SCCE0625)을 사용하여 RNA를 캐핑하였다. 반응물은 RNA 및 RN아제-없는 물을 결합시킴으로써 양을 조정하였다. 이후 RNA를 65 ℃에서 5-10 분 동안 변성시켰다. 변성된 RNA를 신속하게 얼음으로 옮겼고 다음 시약을 다음 순서로 추가하였다: ScriptCap Capping Buffer, 10 mM GTP, 새로 제조된 2 mM SAM, ScriptGuard RN아제 억제제, 및 ScriptCap Capping Enzyme. 반응은 RN아제-없는 물 및 7.5 M LiCl을 추가하고, 잘 혼합하고-20 ℃에서 적어도 30 분 동안 혼합물을 저장함으로써 중단되었다. 이후, 혼합물을 4 ℃에서 25 분 동안 최대 속도로 원심 분리하였고, 펠렛을 70% 에탄올로 헹궜고, 다시 4 ℃에서 10 분 동안 최대 속도로 원심 분리하였고 펠렛을 공기 건조하였다. 펠렛을 RN아제-아제 없는 물로 재현탁하였다. RNA의 농도를 측정하였고 품질을 변성 겔 상에서 체크하였다.

[0293] RNA 트랜스펙션

[0294] 세포 (BHK-V 세포)를 트랜스펙션 시점에 90-95% 포화되도록 6-웰 플레이트에 분주하였다. 각각의 트랜스펙션을 위해 3 g의 RNA를 첫 번째 튜브의 50 mL OPTIMEM 배지에 희석하였다. Lipofectamine 2000을 50 mL OPTIMEM 배지가 함유된 두 번째 튜브에 추가하였다. 첫 번째 및 두 번째 튜브를 결합하였고 상온에서 20 분 동안 유지하였다. 6-웰 플레이트의 배양 배지를 새로운 배지로 교체하였고, RNA-리포펙타민 복합체를 세포에 배치하였고, 부드럽게 흔들어서 혼합시켰다. 플레이트를 CO2 배양기에서 37 ℃에서 24 시간 동안 배양하였다.

[0295] 트랜스펙션된 세포에서 VZV 단백질의 발현을 웨스턴 블롯 및 면역형광법에 의해 평가하였다. 웨스턴 블롯을 위해, 트랜스펙션된 세포의 용해물을 전기영동법에 의해 분류하였고 (5 μg 총 단백질/레인) 블롯하였다. OKA/Merck 백신 균주로부터 유도된 온전한 바이러스 현탁액 (7 μg 총 단백질/레인)을 양성 대조군으로서 사용하였다. VZV 단백질과 결합하는 상업적으로 이용 가능한 항체 (1:1000 희석)를 사용하여 블롯을 프로빙하였다.

[0296] 면역형광법을 위해, 트랜스펙션된 세포를 수확하였고 96 웰 플레이트에 분주하였고, 상업적으로 이용 가능한 마우스 mAb (희석 범위 1:100 1:400)를 사용하여 세포 내 염색을 수행하였다. 세포 펠렛을 고정하였고 Citofix-Citoperm 용액으로 통과시켰다. 두 번째 시약, 염소 항-마우스 F(ab')2 표지된 Alexa488 (1:400 최종 희석)을 사용하였다.

[0297] 상업적으로 이용 가능한 마우스 항체, gE에 대하여 13B1 및 gI에 대하여 8C4를 사용하여 VZV 단백질 gE 및 gI의 발현은 모노시스트론성 구조물 (gE 또는 gI)로 트랜스펙션된 세포에서 검출되었고, gE 및 gI 둘 다의 발현은 바이시스트론성 gE/gI 구조물로 트랜스펙션된 세포에서 검출되었다. 상업적으로 이용 가능한 항체 10G6을 사용하는 면역형광법에 의해, VZV 단백질 gB의 발현은 gB를 암호화하는 모노시스트론성 구조물로 트랜스펙션된 세포에서 검출되었다. VZV 단백질 복합체 gH/gL의 발현은 모노시스트론성 gH 및 모노시스트론성 gL, 또는 바이시스트론성 gH/gL 구조물로 트랜스펙션된 세포에서 면역형광법에 의해 검출되었다. gH/gL 복합체는 상업적으로 이용 가능한 항체 SG3을 사용하여 검출되었다.

[0298] **쥐 면역원성 연구**

[0299] 8마리의 6-8주령 및 약 20 g 중량의 암컷 BALB/c 마우스의 그룹을 제 0일, 제 21일 및 제 42일에 CNE 또는 LNP (RV01)로 조제된, 7.0 또는 1.0 μg의 레플리콘 RNA로 근육 내 면역화하였다. 혈액 샘플을 면역화된 동물로부터 두 번째 면역화 3주 후 및 세 번째 면역화 3주 후 채취하였다. 그룹은 표 10에 나타난다.

표 10			
그룹	항원	용량 (미크로그램)	제형
연구 1			
1	YFP	7	CNE
2	YFP	1	CNE
3	gB	7	CNE
4	gB	1	CNE
5	gE	7	CNE
6	gE	1	CNE
7	gH	7	CNE
8	gH	1	CNE
9	gI	7	CNE
10	gI	1	CNE
11	gL	7	CNE
12	gL	1	CNE
13	gE/gI	7	CNE
14	gE/gI	1	CNE
15	gH/gL	7	CNE
16	gH/gL	1	CNE
연구 2			
1	gB	1	RV01
2	gE	1	RV01
3	gH	1	RV01
4	gI	1	RV01
5	gL	1	RV01
6	gE/gI	1	RV01
7	gH/gL	1	RV01

[0300]

[0301] VZV 항원에 대한 면역 반응

[0302] 혈청 샘플을 VZV-레플리콘 트랜스펙션된 MRC-5 세포의 세포 내 염색으로 gB에 대한 항체의 존재에 대하여 테스트하였다. MRC-5 세포를 10% 태아 소 혈청이 들어있는 Dulbeco Modified Eagle's Medium에서 유지하였다. VZV Oka 균주 접종원 (ATCC로부터 얻어짐)을 MRC-5 세포 배양액을 감염시키기 위해 사용하였고 감염된 전체 세포를 바이러스의 서브계대 (subpassage)에 사용하였다. 감염된 및 감염되지 않은 세포 사이의 비율은 1:10이었다. 감염 30 시간 후 면역화 후 얻어진 마우스 혈청 (희석 범위 1:200 내지 1:800)의 풀로 세포 내 염색을 수행하기 위해 96 웰 플레이트에 분주를 위해 세포를 트립신-분산시켰다. 상업적인 mAb를 감염 수준을 정량하기 위한 대조군으로서 사용하였다. 세포 펠렛을 고정하였고 Citofix-Citoperm 용액으로 통과시켰다. 두 번째 시약, 염소 항-마우스 F(ab')2 표지된 Alexa488 (1:400 최종 희석)을 사용하였다.

[0303] gB (10G6), gH (SG3), 및 gE (13B1 (SBA) 및 8612 (Millipore))에 대한 상업적인 항체를 양성 대조군으로서 사용하였고, 각각 감염된 MRC-5 세포를 세포 내 염색하였다. CNE 또는 LNP로 조제된 1 또는 7 μg의 RNA로 세 번째 면역화 3주 후 얻어진 면역 혈청을 1/200, 1/400 및 1/800로 희석하였고 감염된 MRC-5 세포를 세포 내 염색하기 위해 사용하였다. 결과는 도 21 (연구 1, 그룹 1, 5, 7, 9, 11, 13 및 15, CNE 제형) 및 도 22 (연구 2, 그룹 1-7, LNP 제형)에 나타난다.

[0304] 중화 검정

[0305] 각각의 면역화된 마우스 혈청을 표준 배양 배지에서 1:20에서 시작하여 2배 증가로 단계적으로 희석하였고, 기니피그 보체의 존재시 동량의 VZV 현탁액에 추가하였다. 37 ℃에서 1시간 동안 배양 후, 사람 상피 세포주 A549를 추가하였다. 감염된 세포를 배양의 일주일 후 현미경 하에 배양액에서 형성된 플라크를 계산함으로써 측정할 수 있다. 플라크 수로부터, 각각의 혈청 희석시 % 억제를 계산하였다. 로그 눈금, 희석 인자에 대하여 % 억제의 값을 플로팅함으로써 각각의 혈청 샘플의 차트를 만들었다. 그 결과 희석 인자 및 % 억제 사이의 관계의 근사한 선이 그려졌다. 이후 선이 50% 억제의 값에서 교차되는 경우 희석 인자로서 50% 중화 역가를 결정하였다.

[0306] 표 11은 모노시스트론성 gE, 바이시스트론성 gE/gI, 및 바이시스트론성 gH/gL로 면역화된 마우스로부터 얻어진 혈청이 강한 중화 항체 역가를 함유하였다는 것을 나타낸다.

표 11 7 μg RNA 로 면역화된 마우스의 풀 혈청의 중화 적정 농도

대조군 (YFP)	gB	gE	gI	gE/gI	gH	gL	gH/gL
<20	<20	1111	<20	440	<20	<20	1070
<20	<20	413	51	>2560	<20	<20	>2560
<20	<20	>2560	<20	1031	<20	<20	>2560
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* 사전 면역 풀 혈청

[0307]

[0308] 참고문헌

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[0337] 서열

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ggcaccgtgctggaagtgaccgacgtggtggtggacgccaccgacagcagactgctgatgatgagcgtgtacgcc
ctgagcgccatcatcggcatctacctgctgtaccggatgctgaaaacctgctgataa - 2232

Cmv gH FL;
MRPGLPSYLIILAVCLFSHLLSSRYGAEAVSEPLDKAFHLLLNTYGRPIRFLRENTTQCTYN
SSLRNSTVVRENAISFNFFQSYNQYYVFHMPRCLFAGPLAEQFLNQVDLTETLERYQQRLNT
YALVSKDLASYRSFSQQLKAQDSLGEQPTTVPPPIDLSIPHVWMPPQTTPHGWTESHTTSGL
HRPHFNQTCILFDGHDLLFSTVTPCLHQGFYLIDELRYVKITLTEDFFVVTVSIDDDTPMLL
IFGHLPRVLFKAPYQRDNFILRQTEKHELLVLVKKDQLNRHSYLKDPDFLDAALDFNYLDLS

[0341]

ALLRNSFHRYAVDVLKSGRCQMLDRRTVEMAFAYALALFAAARQEEAGAQVSVPRALDRQAA
LLQIQEFMITCLSQTPPRTTLLLYPTAVDLAKRALWTPNQITDITSLVRLVYILSKQNQQHL
IPQWALRQIADFALKLHKTHLASFLSAFARQELYLMGSLVHSMLVHTTERREIFIVETGLCS
LAELSHFTQLLAHPHHEYLSDLYTPCSSSGRRDHSLERLTRLFPDATVPATVPAALSILSTM
QPSTLETFPDLFCLPLGESFSALTVSEHVSYIVTNQYLIKGISYPVSTTVVGQSLIITQTDS
QTKCELTRNMHTTHSITVALNISLENCAFCQSALLEYDDTQGVINIMYMHDSDDVLFALDPY
NEVVVSSPRTHYLMLLKNGTVLEVTDVVVDATDSRLLMMSVYALSAIIGIYLLYRMLKTC--

CMV gH sol :

1-

atgaggcctggcctgccctcctacctgatcatcctggccgtgtgcctgttcagccacctgct
gtccagcagatacggcgccgaggccgtgagcgagcccctggacaaggctttccacctgctgc
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gcggcagaccgagaagcacgagctgctggtgctggtcaagaaggaccagctgaaccggcact
cctacctgaaggaccccgacttcctggacgccgccctggacttcaactacctggacctgagc
gccctgctgagaaacagcttccacagatacgccgtggacgtgctgaagtccggacggtgcca
gatgctcgatcggcggaccgtggagatggccttcgcctatgccctcgccctgttcgccgctg
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cgccctgaccgtgtccgagcacgtgtcctacatcgtgaccaatcagtacctgatcaagggca
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aacgaggtggtggtgtccagcccccggacccactacctgatgctgctgaagaacggcaccgt
gctggaagtgaccgacgtggtggtggacgccaccgactgataa - 2151

CMV gH sol;

MRPGLPSYLIILAVCLFSHLLSSRYGAEAVSEPLDKAFHLLLNTYGRPIRFLRENTTQCTYN
SSLRNSTVVRENAISFNFFQSYNQYYVFHMPRCLFAGPLAEQFLNQVDLTETLERYQQRLNT
YALVSKDLASYRSFSQQLKAQDSLGEQPTTVPPPIDLSIPHVWMPPQTTPHGWTESHTTSGL
HRPHFNQTCILFDGHDLLFSTVTPCLHQGFYLIDELRYVKITLTEDFFVVTVSIDDDTPMLL

[0342]

IFGHLPRVLFKAPYQRDNFILRQTEKHELLVLVKKDQLNRHSYLKDPDFLDAALDFNYLDLS
ALLRNSFHRYAVDVLKSGRCQMLDRRTVEMAFAYALALFAAARQEEAGAQVSVPRALDRQAA
LLQIQEFMITCLSQTPPRTTLLLYPTAVDLAKRALWTPNQITDITSLVRLVYILSKQNQQHL
IPQWALRQIADFALKLHKTHLASFLSAFARQELYLMGSLVHSMLVHTTERREIFIVETGLCS
LAELSHFTQLLAHPHHEYLSDLYTPCSSSGRRDHSLERLTRLFPDATVPATVPAALSILSTM
QPSTLETFPDLFCLPLGESFSALTVSEHVSYIVTNQYLIKGISYPVSTTVVGQSLIITQTDS
QTKCELTRNMHTTHSITVALNISLENCAFCQSALLEYDDTQGVINIMYMHDSDDVLFALDPY
NEVVVSSPRTHYLMLLKNGTVLEVTDVVVDATD--

CMV gL fl:

1-

atgtgcagaaggcccgactgcggcttcagcttcagccctggacccgtgatcctgctgtggtg
ctgcctgctgctgcctatcgtgtcctctgccgccgtgtctgtggcccctacagccgccgaga
aggtgccagccgagtgccccgagctgaccagaagatgcctgctgggcgaggtgttcgagggc
gacaagtacgagagctggctgcggcccctggtcaacgtgaccggcagagatggcccctgag
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tactacgccggcctgcccccagagctgaagcagaccagagtgaacctgcccgcccacagcag
atatggccctcaggccgtggacgccagatgataa - 840

CMV gL FL;

MCRRPDCGFSFSPGPVILLWCCLLLPIVSSAAVSVAPTAAEKVPAECPELTRRCLLGEVFEG
DKYESWLRPLVNVTGRDGPLSQLIRYRPVTPEAANSVLLDEAFLDTLALLYNNPDQLRALLT
LLSSDTAPRWMTVMRGYSECGDGSPAVYTCVDDLCRGYDLTRLSYGRSIFTEHVLGFELVPP
SLFNVVVAIRNEATRTNRAVRLPVSTAAAPEGITLFYGLYNAVKEFCLRHQLDPPLLRHLDK
YYAGLPPELKQTRVNLPAHSRYGPQAVDAR--

CMV gM FL:

1-

atggcccccagccacgtggacaaagtgaacacccggacttggagcgccagcatcgtgttcat
ggtgctgaccttcgtgaacgtgtccgtgcacctggtgctgtccaacttcccccacctgggct
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[0343]

gtaccaggccctggccacagcctctggcgaagaggtggccgccctgagccaccacgacagcc
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taa - 1119

CMV gM FL;

MAPSHVDKVNTRTWSASIVFMVLTFVNVSVHLVLSNFPHLGYPCVYYHVVDFERLNMSAYNV
MHLHTPMLFLDSVQLVCYAVFMQLVFLAVTIYYLVCWIKISMRKDKGMSLNQSTRDISYMGD
SLTAFLFILSMDTFQLFTLTMSFRLPSMIAFMAAVHFFCLTIFNVSMVTQYRSYKRSLFFFS
RLHPKLKGTVQFRTLIVNLVEVALGFNTTVVAMALCYGFGNNFFVRTGHMVLAVFVVYAIIS
IIYFLLIEAVFFQYVKVQFGYHLGAFFGLCGLIYPIVQYDTFLSNEYRTGISWSFGMLFFIW
AMFTTCRAVRYFRGRGSGSVKYQALATASGEEVAALSHHDSLESRRLREEEDDDDEDFEDA-
-

CMV gN FL:

1-
atggaatggaacaccctggtcctgggcctgctggtgctgtctgtcgtggccagcagcaacaa
cacatccacagccagcacccctagacctagcagcagcacccacgccagcactaccgtgaagg
ctaccaccgtggccaccacaagcaccaccactgctaccagcaccagctccaccacctctgcc
aagcctggctctaccacacacgaccccaacgtgatgaggccccacgcccacaacgacttcta
caacgctcactgcaccagccacatgtacgagctgtccctgagcagctttgccgcctggtgga
ccatgctgaacgccctgatcctgatgggcgccttctgcatcgtgctgcggcactgctgcttc
cagaacttcaccgccaccaccaccaagggctactgataa - 411

CMV gN FL;

MEWNTLVLGLLVLSVVASSNNTSTASTPRPSSSTHASTTVKATTVATTSTTTATSTSSTTSA
KPGSTTHDPNVMRPHAHNDFYNAHCTSHMYELSLSSFAAWWTMLNALILMGAFCIVLRHCCF
QNFTATTTKGY--

CMV gO FL:

1-
atgggcaagaaagaaatgatcatggtcaagggcatccccaagatcatgctgctgattagcat
caccttttctgctgctgtccctgatcaactgcaacgtgctggtcaacagccggggcaccagaa
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[0344]

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1422

CMV gO FL;
MGKKEMIMVKGIPKIMLLISITFLLLSLINCNVLVNSRGTRRSWPYTVLSYRGKEILKKQKE
DILKRLMSTSSDGYRFLMYPSQQKFHAIVISMDKFPQDYILAGPIRNDSITHMWFDFYSTQL
RKPAKYVYSEYNHTAHKITLRPPPCGTVPSMNCLSEMLNVSKRNDTGEKGCGNFTTFNPMFF
NVPRWNTKLYIGSNKVNVDSQTIYFLGLTALLLRYAQRNCTRSFYLVNAMSRNLFRVPKYIN
GTKLKNTMRKLKRKQALVKEQPQKKNKKSQSTTTPYLSYTTSTAFNVTTNVTYSATAAVTRV
ATSTTGYRPDSNFMKSIMATQLRDLATWVYTTLRYRNEPFCKPDRNRTAVSEFMKNTHVLIR
NETPYTIYGTLDMSSLYYNETMSVENETASDNNETTPTSPSTRFQRTFIDPLWDYLDSLLFL
DKIRNFSLQLPAYGNLTPPEHRRAANLSTLNSLWWWSQ--

CMV UL128 FL :
1-
atgagccccaaggacctgacccccttcctgacaaccctgtggctgctcctgggccatagcag
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cctgacccggcaggtggtgcacaacaagctgaccagctgcaactacaaccccctgtacctgg
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cctggaccagtacctggaaagcgtgaagaagcacaagcggctggacgtgtgcagagccaaga
tgggctacatgctgcagtgataa - 519

CMV UL128 FL;
MSPKDLTPFLTTLWLLLGHSRVPRVRAEECCEFINVNHPPERCYDFKMCNRFTVALRCPDGE
VCYSPEKTAEIRGIVTTMTHSLTRQVVHNKLTSCNYNPLYLEADGRIRCGKVNDKAQYLLGA
AGSVPYRWINLEYDKITRIVGLDQYLESVKKHKRLDVCRAKMGYMLQ--

CMV UL130 FL:
1-
atgctgcggctgctgctgagacaccacttccactgcctgctgctgtgtgccgtgtgggccac
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cacccaccccaacctgatcgtgtgataa - 648

CMV UL130 FL;
MLRLLLRHHFHCLLLCAVWATPCLASPWSTLTANQNPSPPWSKLTYSKPHDAATFYCPFLYP
SPPRSPLQFSGFQRVSTGPECRNETLYLLYNREGQTLVERSSTWVKKVIWYLSGRNQTILQR
MPRTASKPSDGNVQISVEDAKIFGAHMVPKQTKLLRFVVNDGTRYQMCVMKLESWAHVFRDY
SVSFQVRLTFTEANNQTYTFCTHPNLIV--

[0345]

CMV UL131 FL:
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atgcggctgtgcagagtgtggctgtccgtgtgcctgtgtgccgtggtgctgggccagtgcca
gagagagacagccgagaagaacgactactaccgggtgccccactactgggatgcctgcagca
gagccctgcccgaccagacccggtacaaatacgtggagcagctcgtggacctgaccctgaac
taccactacgacgccagccacggcctggacaacttcgacgtgctgaagcggatcaacgtgac
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cggctgttcgccaactgataa - 393

CMV UL131 FL;
MRLCRVWLSVCLCAVVLGQCQRETAEKNDYYRVPHYWDACSRALPDQTRYKYVEQLVDLTLN
YHYDASHGLDNFDVLKRINVTEVSLLISDFRRQNRRGGTNKRTTFNAAGSLAPHARSLEFSV
RLFAN--

EMCV IRES 뉴클레오티드 서열
aacgttactggccgaagccgcttggaataaggccggtgtgcgtttgtctatatgttattttc
caccatattgccgtcttttggcaatgtgagggcccggaaacctggccctgtcttcttgacga
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EV71 IRES 뉴클레오티드 서열
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g

VEE 서브게놈 프로모터
5′-CTCTCTACGGCTAACCTGAATGGA-3′

pVCR 변형된 벡터 **gH sol-SGP gL**
cgcgtcggctacaattaatacataaccttatgtatcatacacatacgatttaggtgacacta
tagatgggcggcgcatgagagaagcccagaccaattacctacccaaaatggagaaagttcac

[0346]

[0347]

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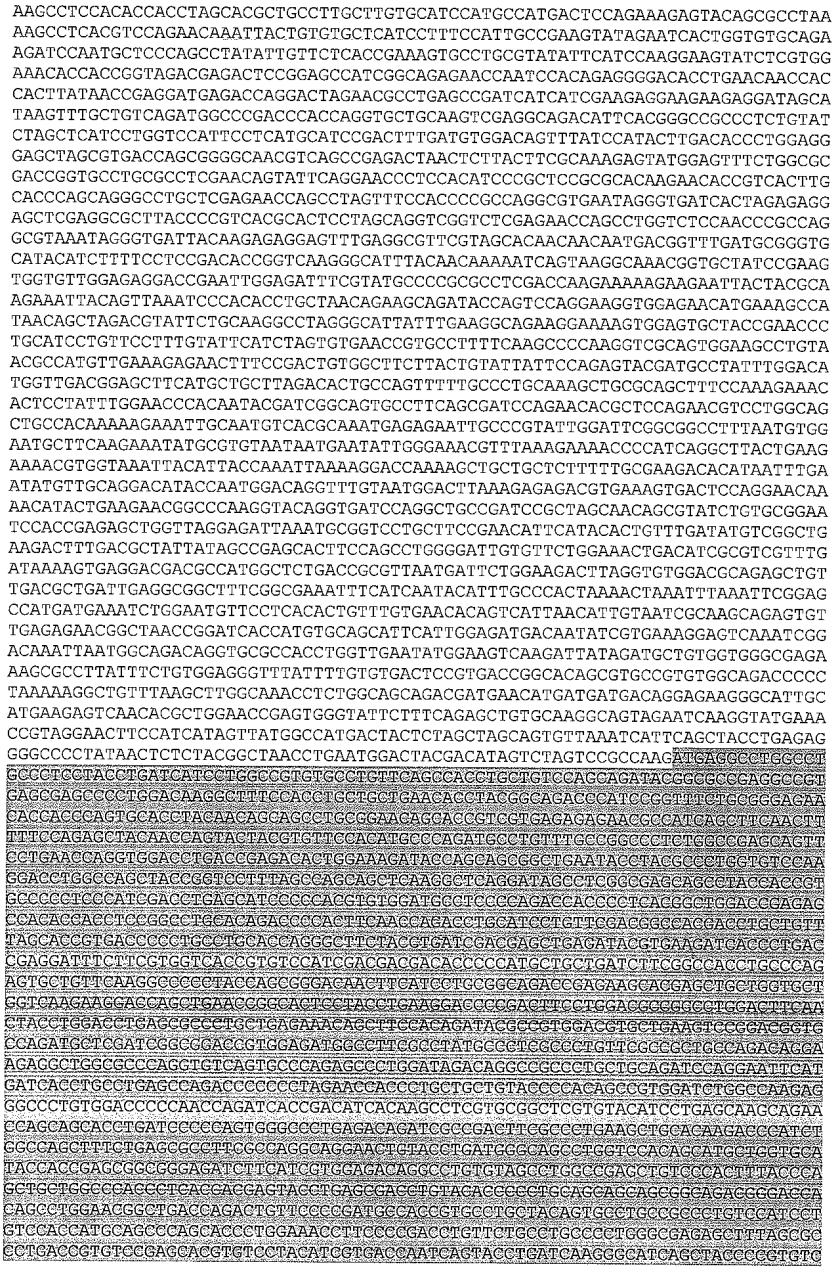
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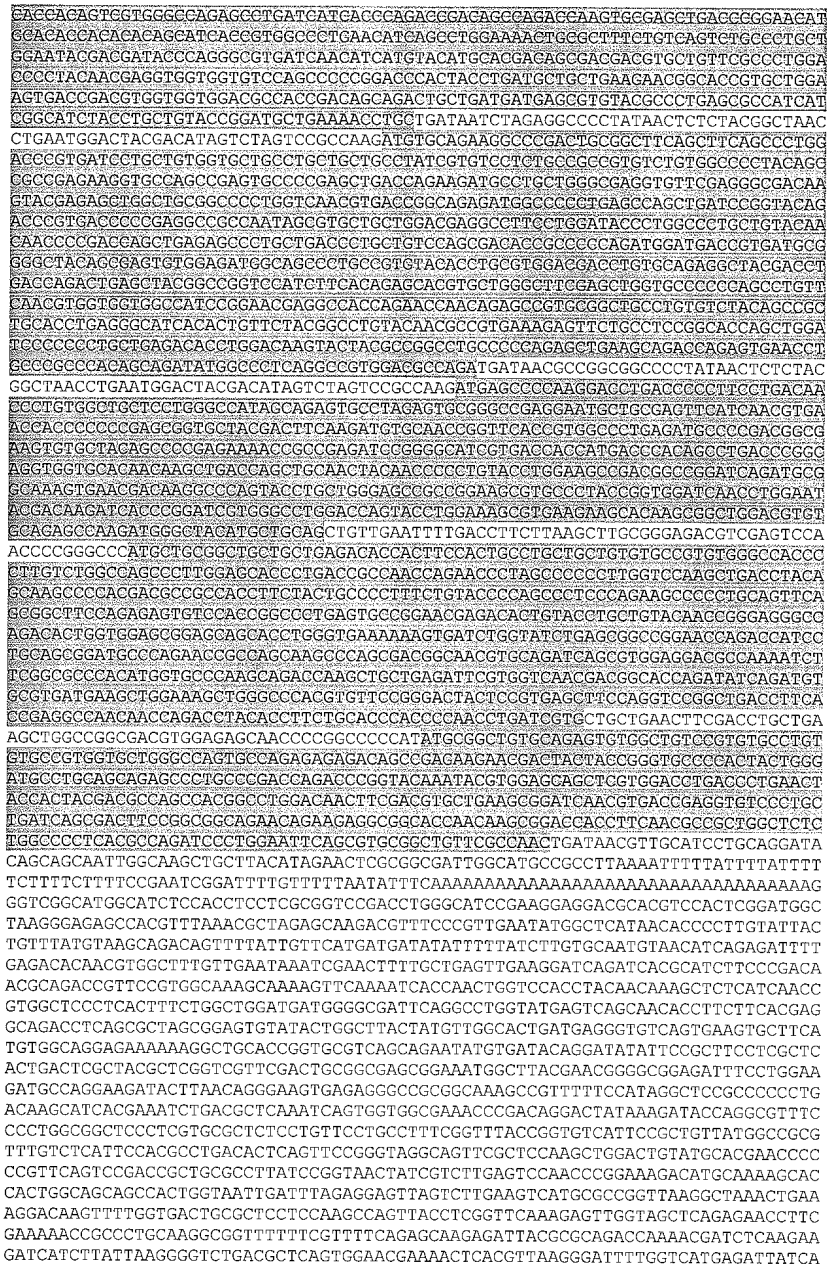

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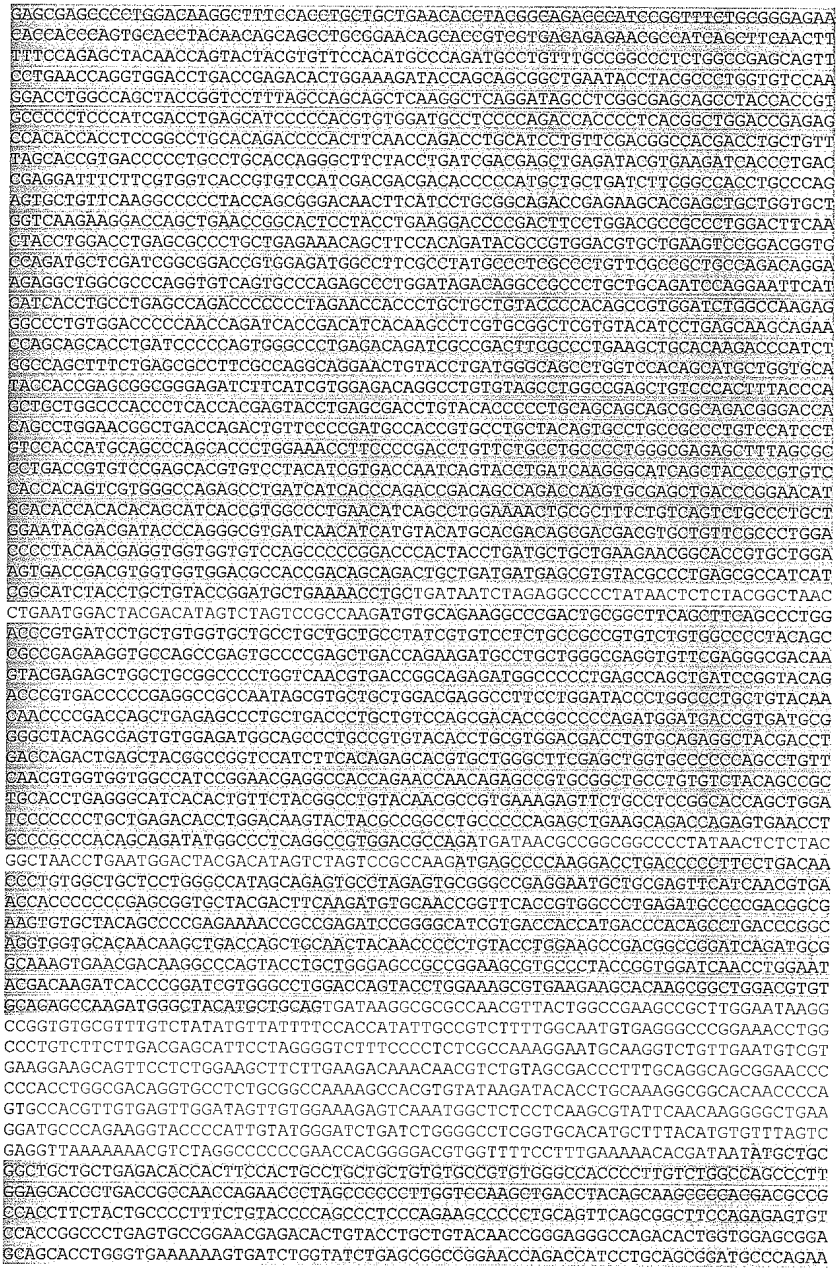

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A531 벡터 : SGP-gHsol-SGP-gL

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[0372]

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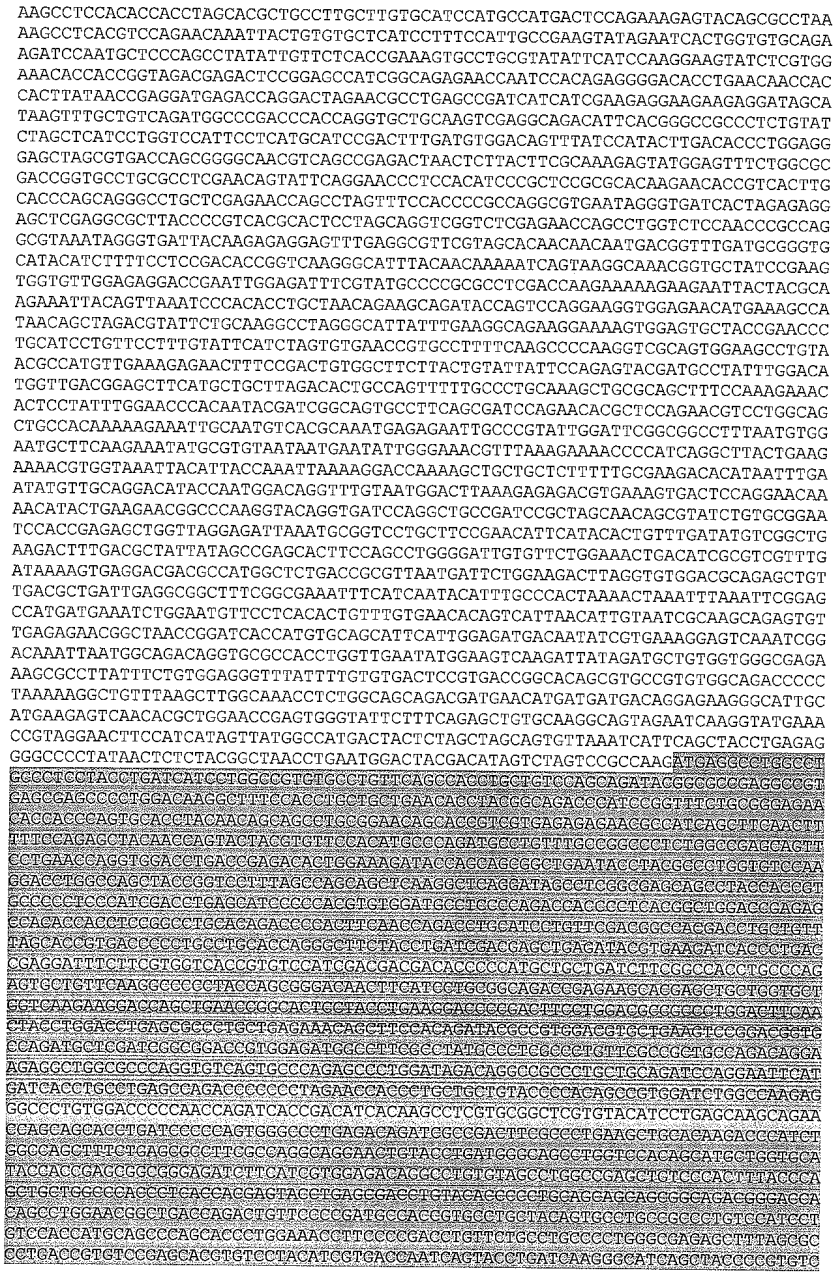
[0373]



[0374]

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A532 벡터 : SGP-gHsol-2A-gL

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[0375]

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A533 벡터 : SGP-gHsol-EV71-gL

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A535 벡터 : SGP-342-EV71-gHsol-2A-gL

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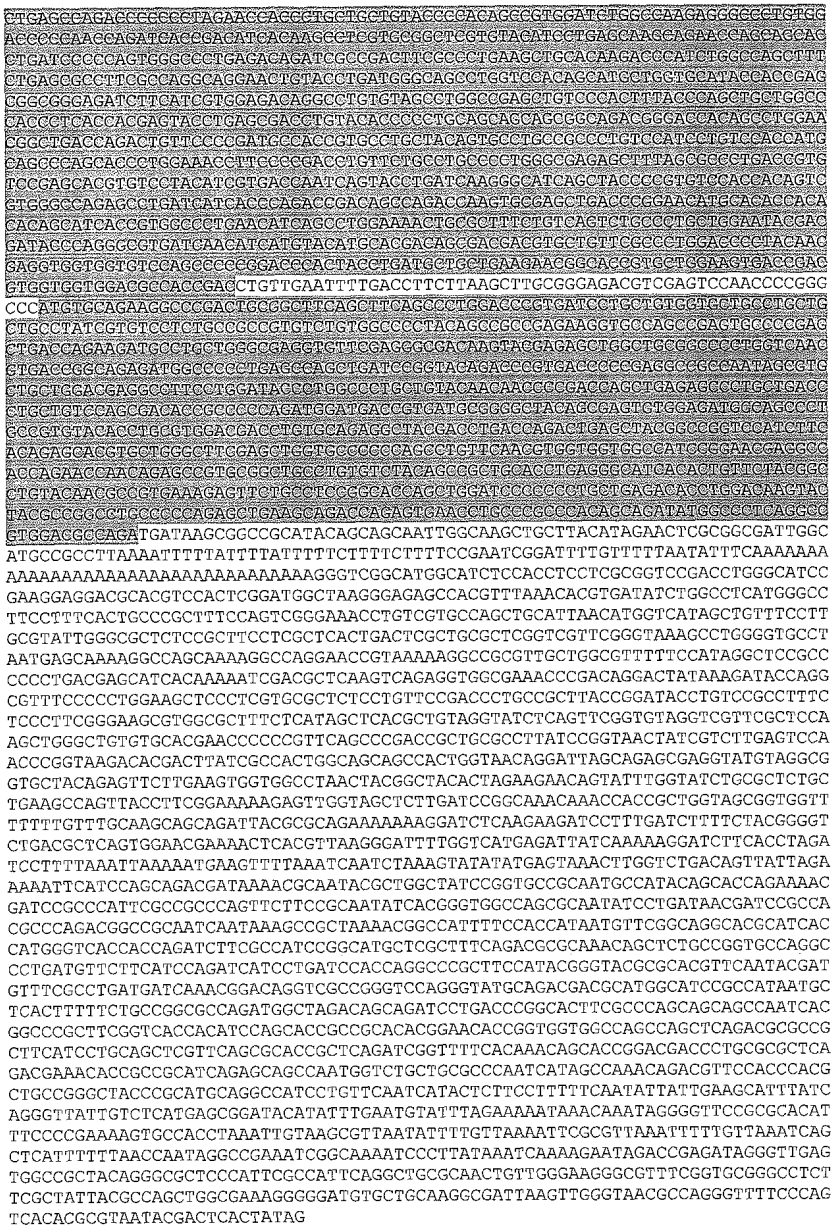

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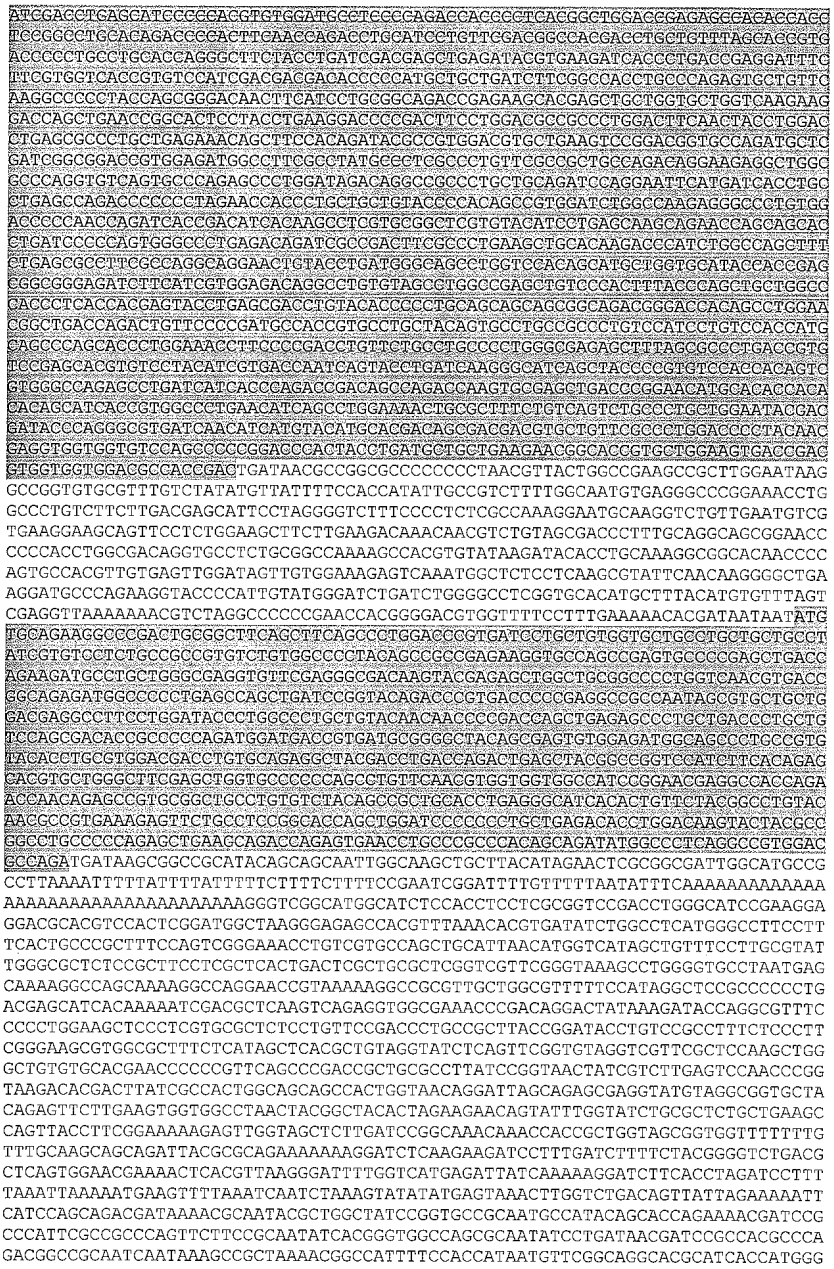

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[0392]

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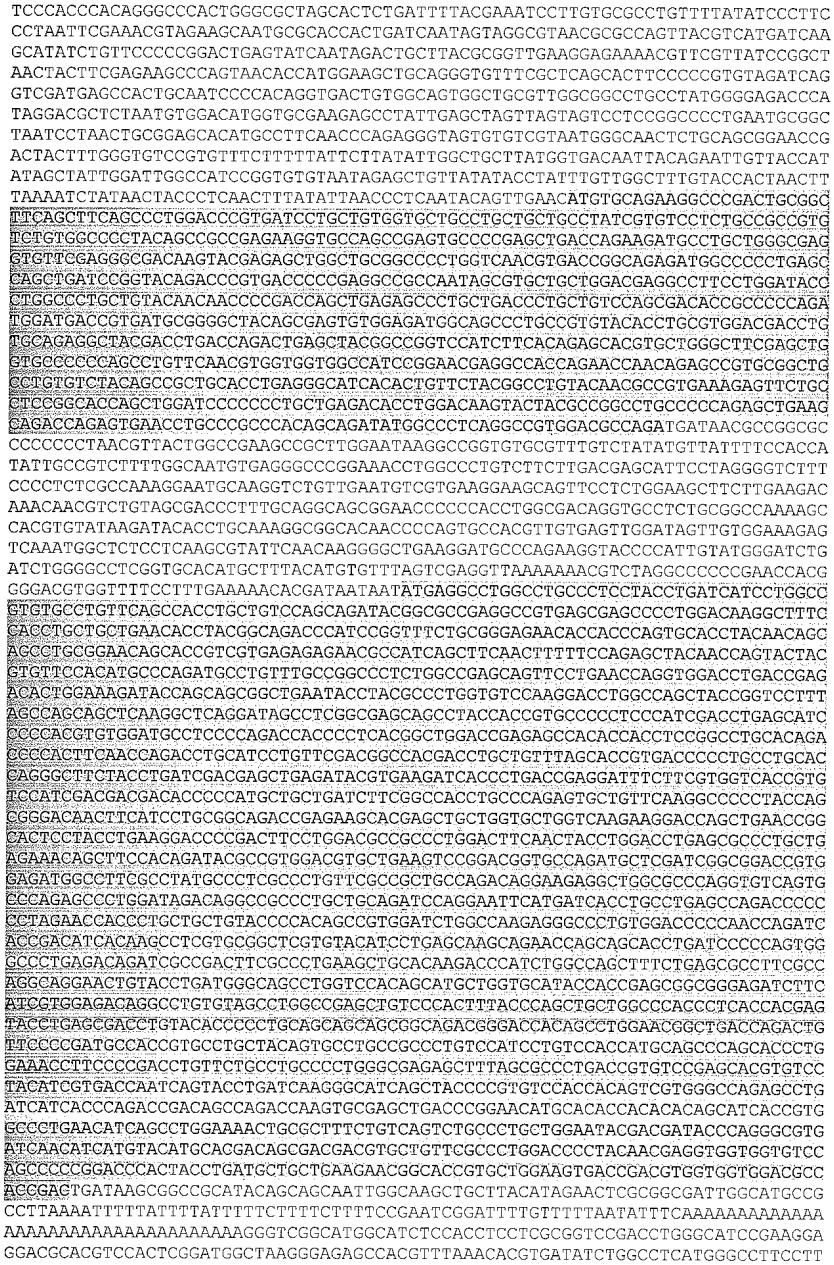

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A554 벡터 : SGP-gH-SGP-gL-SGP-UL128-SGP-UL130-SGP-UL131

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[0394]

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[0395]

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A555 벡터 : SGP-gHsol-SGP-gL-SGP-UL128-SGP-UL130-SGP-UL131

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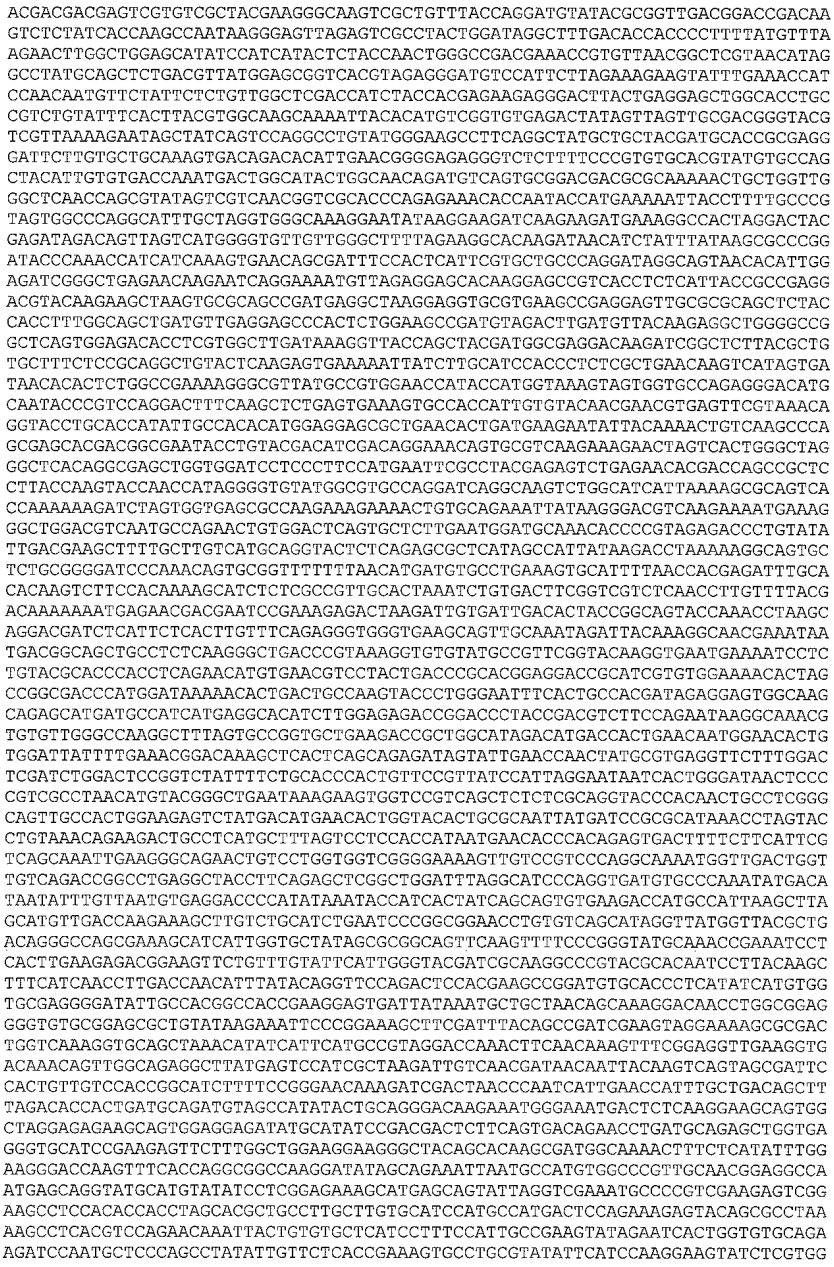
[0398]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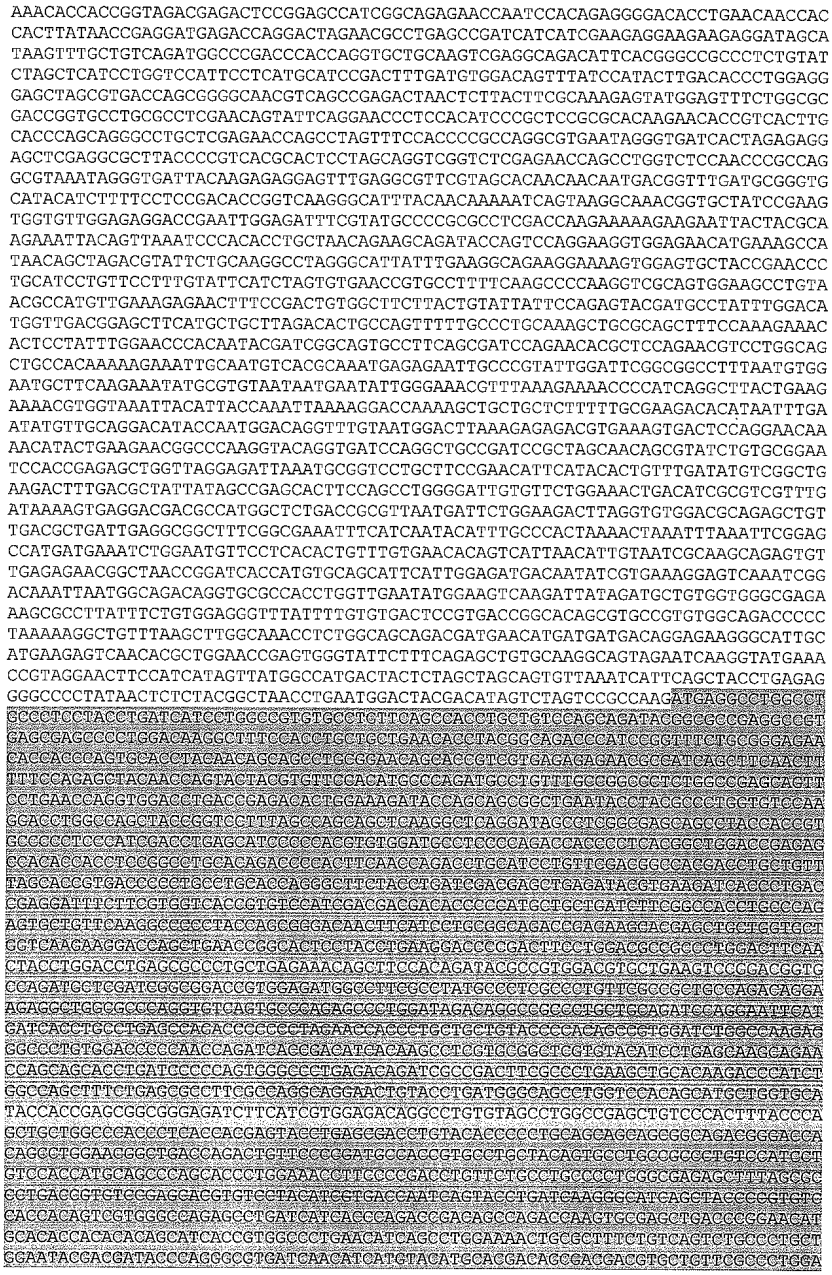

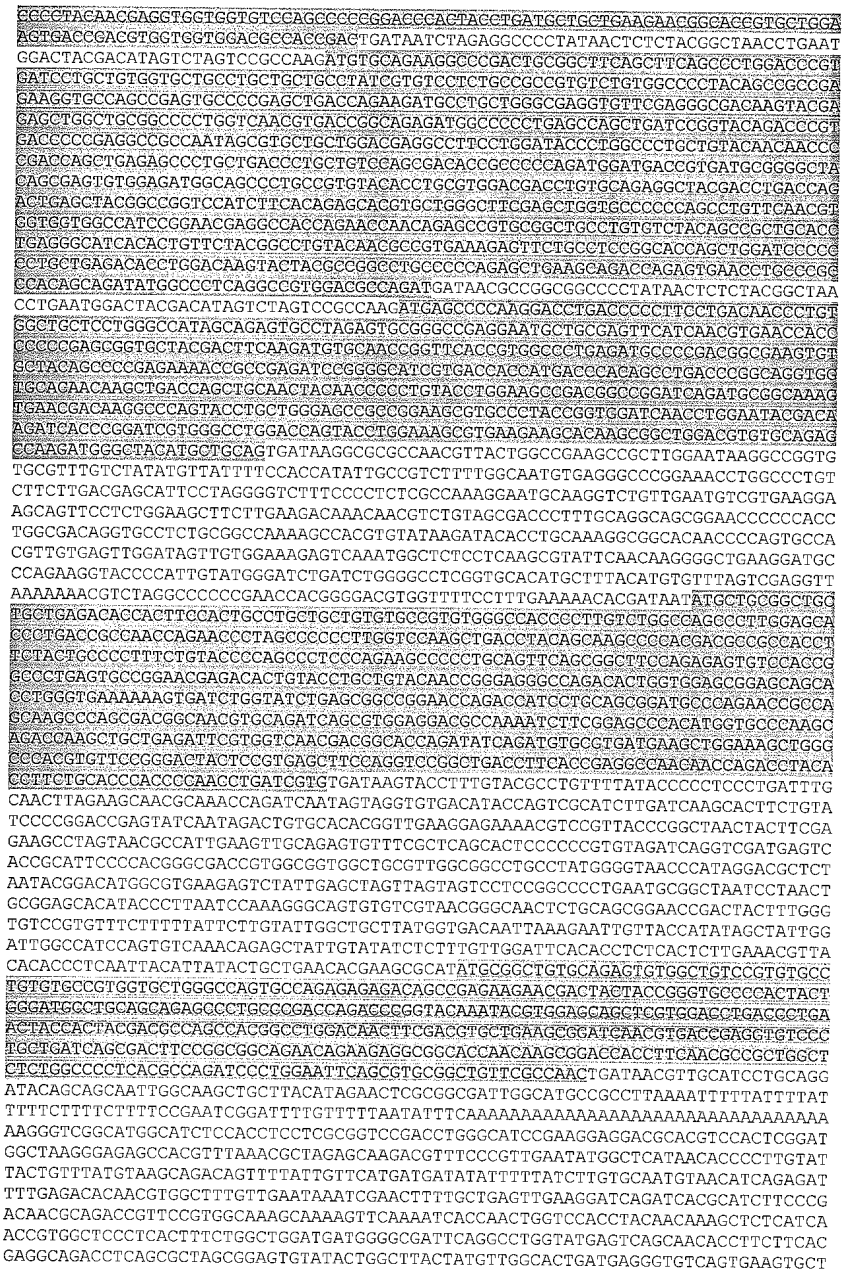

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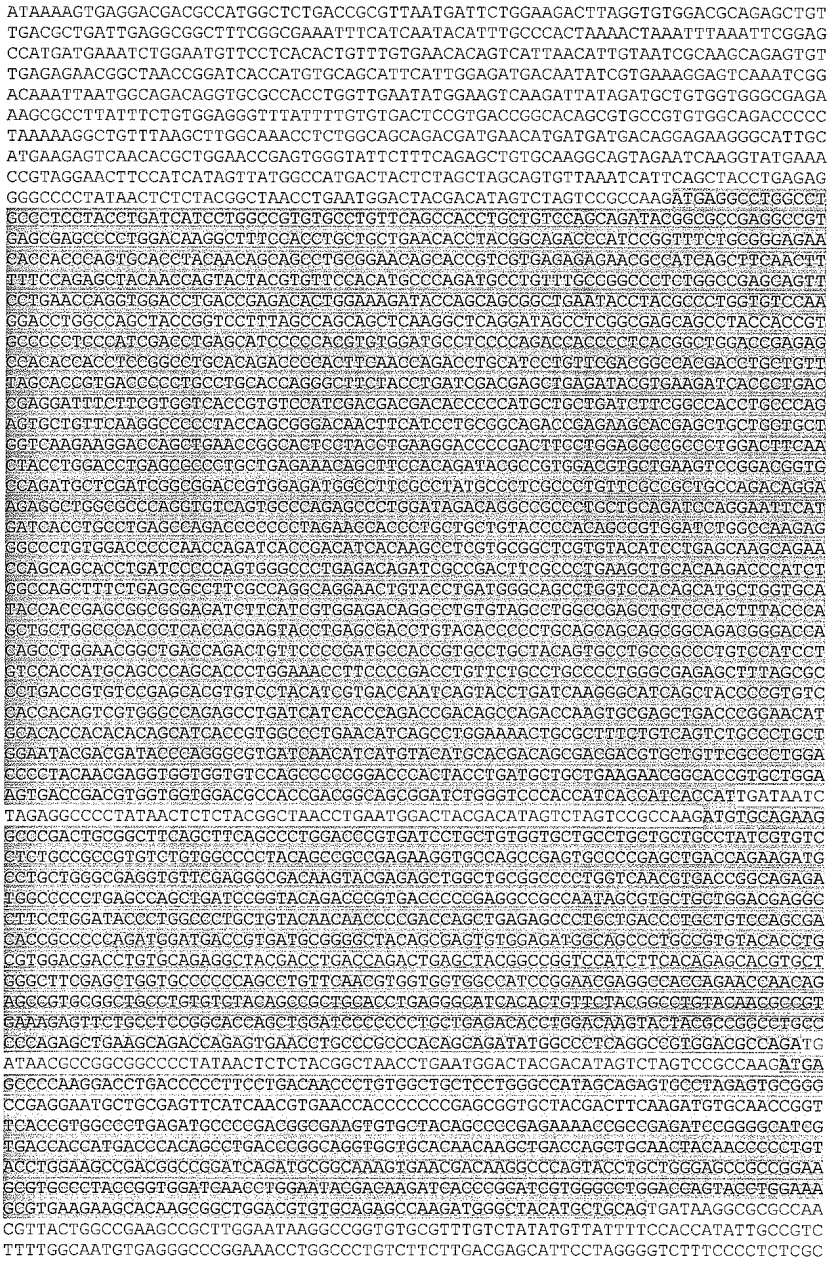

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[0429]

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eGFP를 암호화하는 VEE-기반 레플리콘

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[0430]

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241 GTGCGCCCGC CCGCAGAATG TATTCTAAGC ACAAGTATCA TTGTATCTGT CCGATGAGAT
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901 TCGTTAAAAG AATAGCTATC AGTCCAGGCC TGTATGGGAA GCCTTCAGGC TATGCTGCTA
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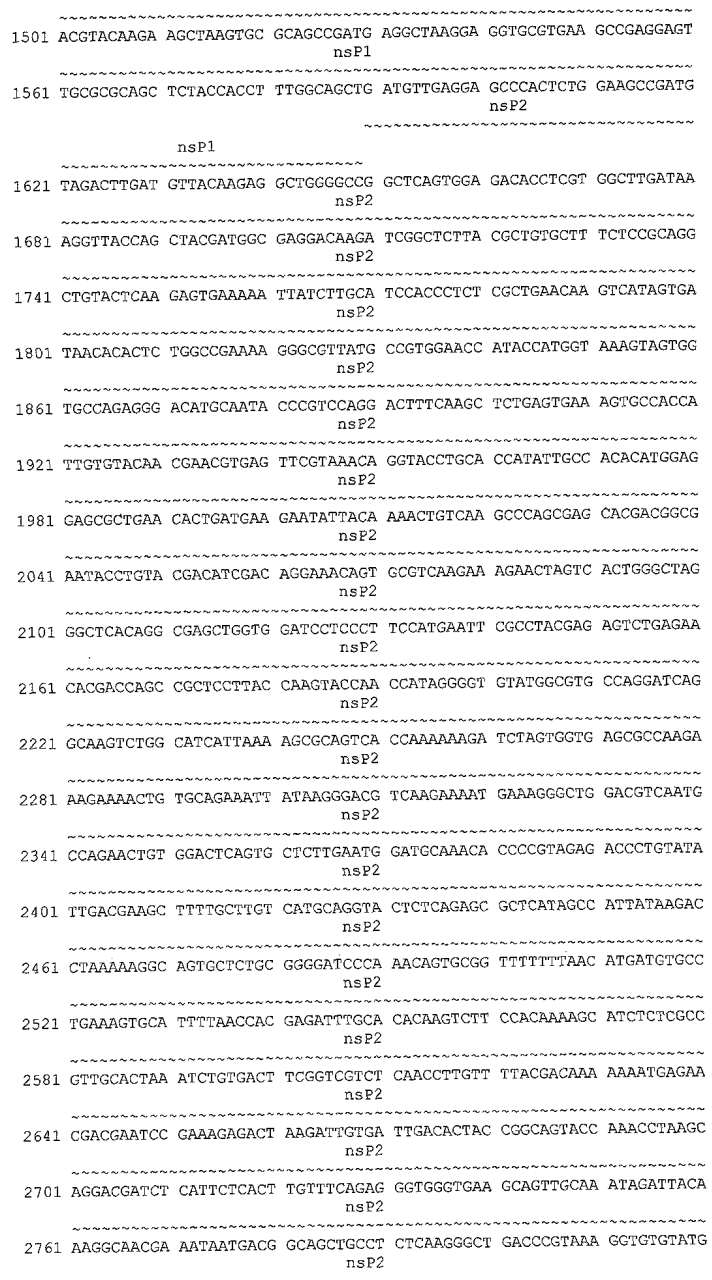
[0431]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nsP1
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1681 AGGTTACCAG CTACGATGGC GAGGACAAGA TCGGCTCTTA CGCTGTGCTT TCTCCGCAGG
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1741 CTGTACTCAA GAGTGAAAAA TTATCTTGCA TCCACCCTCT CGCTGAACAA GTCATAGTGA
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1801 TAACACACTC TGGCCGAAAA GGGCGTTATG CCGTGGAACC ATACCATGGT AAAGTAGTGG
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nsP2
2101 GGCTCACAGG CGAGCTGGTG GATCCTCCCT TCCATGAATT CGCCTACGAG AGTCTGAGAA
nsP2
2161 CACGACCAGC CGCTCCTTAC CAAGTACCAA CCATAGGGGT GTATGGCGTG CCAGGATCAG
nsP2
2221 GCAAGTCTGG CATCATTAAA AGCGCAGTCA CCAAAAAAGA TCTAGTGGTG AGCGCCAAGA
nsP2
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nsP2
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nsP2
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nsP2
2581 GTTGCACTAA ATCTGTGACT TCGGTCGTCT CAACCTTGTT TTACGACAAA AAAATGAGAA
nsP2
2641 CGACGAATCC GAAAGAGACT AAGATTGTGA TTGACACTAC CGGCAGTACC AAACCTAAGC
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2701 AGGACGATCT CATTCTCACT TGTTTCAGAG GGTGGGTGAA GCAGTTGCAA ATAGATTACA
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nsP2

[0432]

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3001 CAGAGCATGA TGCCATCATG AGGCACATCT TGGAGAGACC GGACCCTACC GACGTCTTCC
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3061 AGAATAAGGC AAACGTGTGT TGGGCCAAGG CTTTAGTGCC GGTGCTGAAG ACCGCTGGCA
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3121 TAGACATGAC CACTGAACAA TGGAACACTG TGGATTATTT TGAAACGGAC AAAGCTCACT
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3181 CAGCAGAGAT AGTATTGAAC CAACTATGCG TGAGGTTCTT TGGACTCGAT CTGGACTCCG
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3481 TCCTCCACCA TAATGAACAC CCACAGAGTG ACTTTTCTTC ATTCGTCAGC AAATTGAAGG
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3721 AGCAGTGTGA AGACCATGCC ATTAAGCTTA GCATGTTGAC CAAGAAAGCT TGTCTGCATC
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3841 GCATCATTGG TGCTATAGCG CGGCAGTTCA AGTTTTCCCG GGTATGCAAA CCGAAATCCT
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3901 CACTTGAAGA GACGGAAGTT CTGTTTGTAT TCATTGGGTA CGATCGCAAG GCCCGTACGC
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3961 ACAATCCTTA CAAGCTTTCA TCAACCTTGA CCAACATTTA TACAGGTTCC AGACTCCACG
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        nsP2
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4021 AAGCCGGATG TGCACCCTCA TATCATGTGG TGCGAGGGGA TATTGCCACG GCCACCGAAG
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4081 GAGTGATTAT AAATGCTGCT AACAGCAAAG GACAACCTGG CGGAGGGGTG TGCGGAGCGC
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[0433]

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4321 ACGATAACAA TTACAAGTCA GTAGCGATTC CACTGTTGTC CACCGGCATC TTTTCCGGGA
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4381 ACAAAGATCG ACTAACCCAA TCATTGAACC ATTTGCTGAC AGCTTTAGAC ACCACTGATG
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4441 CAGATGTAGC CATATACTGC AGGGACAAGA AATGGGAAAT GACTCTCAAG GAAGCAGTGG
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4501 CTAGGAGAGA AGCAGTGGAG GAGATATGCA TATCCGACGA CTCTTCAGTG ACAGAACCTG
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4561 ATGCAGAGCT GGTGAGGGTG CATCCGAAGA GTTCTTTGGC TGGAAGGAAG GGCTACAGCA
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4741 TGTATATCCT CGGAGAAAGC ATGAGCAGTA TTAGGTCGAA ATGCCCCGTC GAAGAGTCGG
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5401 GACCGGTGCC TGCGCCTCGA ACAGTATTCA GGAACCCTCC ACATCCCGCT CCGCGCACAA
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[0434]

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5581  CTAGCAGGTC GGTCTCGAGA ACCAGCCTGG TCTCCAACCC GCCAGGCGTA AATAGGGTGA
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                        nsP3
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5641  TTACAAGAGA GGAGTTTGAG GCGTTCGTAG CACAACAACA ATGACGGTTT GATGCGGGTG
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5761  CGGTGCTATC CGAAGTGGTG TTGGAGAGGA CCGAATTGGA GATTTCGTAT GCCCCGCGCC
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5821  TCGACCAAGA AAAAGAAGAA TTACTACGCA AGAAATTACA GTTAAATCCC ACACCTGCTA
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5881  ACAGAAGCAG ATACCAGTCC AGGAAGGTGG AGAACATGAA AGCCATAACA GCTAGACGTA
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5941  TTCTGCAAGG CCTAGGGCAT TATTTGAAGG CAGAAGGAAA AGTGGAGTGC TACCGAACCC
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6001  TGCATCCTGT TCCTTTGTAT TCATCTAGTG TGAACCGTGC CTTTTCAAGC CCCAAGGTCG
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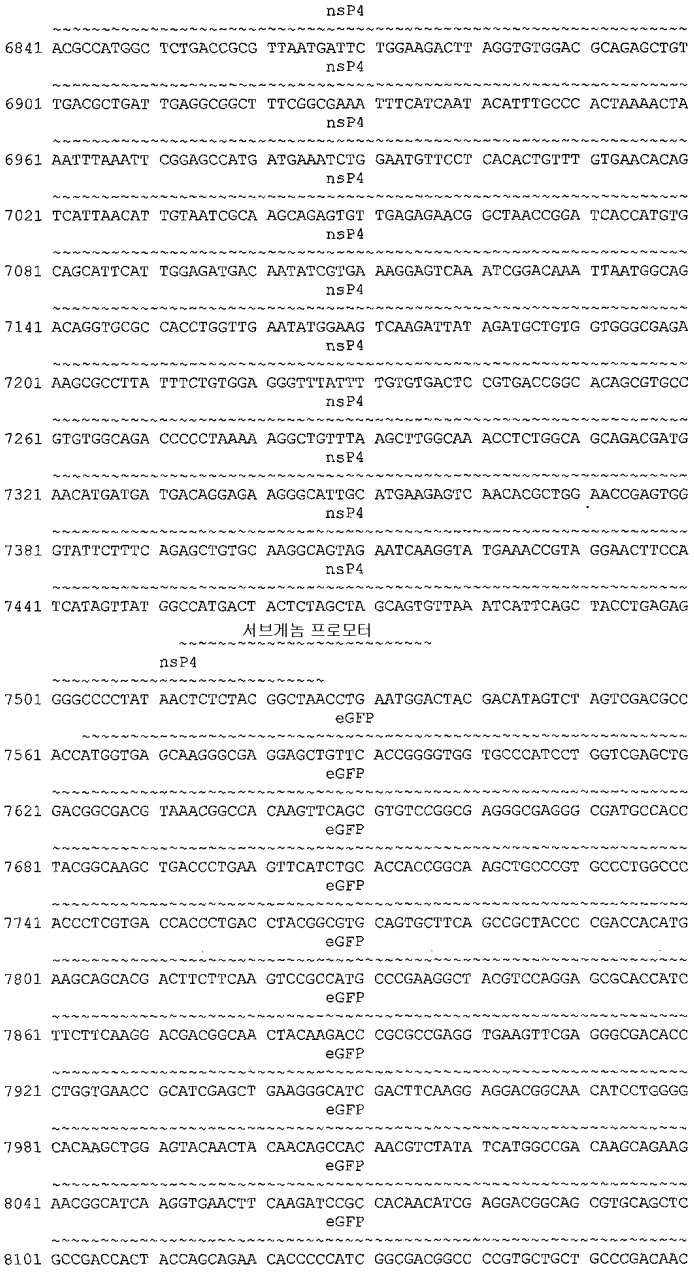
[0435]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7261 GTGTGGCAGA CCCCCTAAAA AGGCTGTTTA AGCTTGGCAA ACCTCTGGCA GCAGACGATG
nsP4
7321 AACATGATGA TGACAGGAGA AGGGCATTGC ATGAAGAGTC AACACGCTGG AACCGAGTGG
nsP4
7381 GTATTCTTTC AGAGCTGTGC AAGGCAGTAG AATCAAGGTA TGAAACCGTA GGAACTTCCA
nsP4
7441 TCATAGTTAT GGCCATGACT ACTCTAGCTA GCAGTGTTAA ATCATTCAGC TACCTGAGAG
서브게놈 프로모터
nsP4
7501 GGGCCCCTAT AACTCTCTAC GGCTAACCTG AATGGACTAC GACATAGTCT AGTCGACGCC
eGFP
7561 ACCATGGTGA GCAAGGGCGA GGAGCTGTTC ACCGGGGTGG TGCCCATCCT GGTCGAGCTG
eGFP
7621 GACGGCGACG TAAACGGCCA CAAGTTCAGC GTGTCCGGCG AGGGCGAGGG CGATGCCACC
eGFP
7681 TACGGCAAGC TGACCCTGAA GTTCATCTGC ACCACCGGCA AGCTGCCCGT GCCCTGGCCC
eGFP
7741 ACCCTCGTGA CCACCCTGAC CTACGGCGTG CAGTGCTTCA GCCGCTACCC CGACCACATG
eGFP
7801 AAGCAGCACG ACTTCTTCAA GTCCGCCATG CCCGAAGGCT ACGTCCAGGA GCGCACCATC
eGFP
7861 TTCTTCAAGG ACGACGGCAA CTACAAGACC CGCGCCGAGG TGAAGTTCGA GGGCGACACC
eGFP
7921 CTGGTGAACC GCATCGAGCT GAAGGGCATC GACTTCAAGG AGGACGGCAA CATCCTGGGG
eGFP
7981 CACAAGCTGG AGTACAACTA CAACAGCCAC AACGTCTATA TCATGGCCGA CAAGCAGAAG
eGFP
8041 AACGGCATCA AGGTGAACTT CAAGATCCGC CACAACATCG AGGACGGCAG CGTGCAGCTC
eGFP
8101 GCCGACCACT ACCAGCAGAA CACCCCCATC GGCGACGGCC CCGTGCTGCT GCCCGACAAC

[0436]

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                                    eGFP
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8161  CACTACCTGA GCACCCAGTC CGCCCTGAGC AAAGACCCCA ACGAGAAGCG CGATCACATG
                                    eGFP
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8221  GTCCTGCTGG AGTTCGTGAC CGCCGCCGGG ATCACTCTCG GCATGGACGA GCTGTACAAG
       eGFP                                                    3'UTR
      ~~~~~~                                    ~~~~~~~~~~~~~~~~~~~~~~~~~~~
8281  TGATAATCTA GACGGCGCGC CCACCCAGCG GCCGCATACA GCAGCAATTG GCAAGCTGCT
                                    3'UTR
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8341  TACATAGAAC TCGCGGCGAT TGGCATGCCG CCTTAAAATT TTTATTTTAT TTTTCTTTTC
                  3'UTR
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8401  TTTTCCGAAT CGGATTTTGT TTTTAATATT TCAAAAAAAA AAAAAAAAAA AAAAAAAAAA
                                    HDV 리보자임
            ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8461  AAAAAAAGGG TCGGCATGGC ATCTCCACCT CCTCGCGGTC CGACCTGGGC ATCCGAAGGA
                   HDV 리보자임
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
8521  GGACGCACGT CCACTCGGAT GGCTAAGGGA GAGCCACGTT TAAACCAGCT CCAATTCGCC
8581  CTATAGTGAG TCGTATTACG CGCGCTCACT GGCCGTCGTT TTACAACGTC GTGACTGGGA
8641  AAACCCTGGC GTTACCCAAC TTAATCGCCT TGCAGCACAT CCCCCTTTCG CCAGCTGGCG
8701  TAATAGCGAA GAGGCCCGCA CCGATCGCCC TTCCCAACAG TTGCGCAGCC TGAATGGCGA
8761  ATGGGACGCG CCCTGTAGCG GCGCATTAAG CGCGGCGGGT GTGGTGGTTA CGCGCAGCGT
8821  GACCGCTACA CTTGCCAGCG CCCTAGCGCC CGCTCCTTTC GCTTTCTTCC CTTCCTTTCT
8881  CGCCACGTTC GCCGGCTTTC CCCGTCAAGC TCTAAATCGG GGGCTCCCTT TAGGGTTCCG
8941  ATTTAGTGCT TTACGGCACC TCGACCCCAA AAAACTTGAT TAGGGTGATG GTTCACGTAG
9001  TGGGCCATCG CCCTGATAGA CGGTTTTTCG CCCTTTGACG TTGGAGTCCA CGTTCTTTAA
9061  TAGTGGACTC TTGTTCCAAA CTGGAACAAC ACTCAACCCT ATCTCGGTCT ATTCTTTTGA
9121  TTTATAAGGG ATTTTGCCGA TTTCGGCCTA TTGGTTAAAA AATGAGCTGA TTTAACAAAA
9181  ATTTAACGCG AATTTTAACA AAATATTAAC GCTTACAATT TAGGTGGCAC TTTTCGGGGA
9241  AATGTGCGCG GAACCCCTAT TTGTTTATTT TTCTAAATAC ATTCAAATAT GTATCCGCTC
                                                                  bla
                                                                  ~~~~~~~~~
9301  ATGAGACAAT AACCCTGATA AATGCTTCAA TAATATTGAA AAAGGAAGAG TATGAGTATT
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9361  CAACATTTCC GTGTCGCCCT TATTCCCTTT TTTGCGGCAT TTTGCCTTCC TGTTTTTGCT
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9421  CACCCAGAAA CGCTGGTGAA AGTAAAAGAT GCTGAAGATC AGTTGGGTGC ACGAGTGGGT
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9481  TACATCGAAC TGGATCTCAA CAGCGGTAAG ATCCTTGAGA GTTTTCGCCC CGAAGAACGT
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9541  TTTCCAATGA TGAGCACTTT TAAAGTTCTG CTATGTGGCG CGGTATTATC CCGTATTGAC
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9601  GCCGGGCAAG AGCAACTCGG TCGCCGCATA CACTATTCTC AGAATGACTT GGTTGAGTAC
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9661  TCACCAGTCA CAGAAAAGCA TCTTACGGAT GGCATGACAG TAAGAGAATT ATGCAGTGCT
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9721  GCCATAACCA TGAGTGATAA CACTGCGGCC AACTTACTTC TGACAACGAT CGGAGGACCG
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9781  AAGGAGCTAA CCGCTTTTTT GCACAACATG GGGGATCATG TAACTCGCCT TGATCGTTGG
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9841  GAACCGGAGC TGAATGAAGC CATACCAAAC GACGAGCGTG ACACCACGAT GCCTGTAGCA
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
9901  ATGGCAACAA CGTTGCGCAA ACTATTAACT GGCGAACTAC TTACTCTAGC TTCCCGGCAA
                                    bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
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[0437]

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 9961 CAATTAATAG ACTGGATGGA GGCGGATAAA GTTGCAGGAC CACTTCTGCG CTCGGCCCTT
                                  bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
10021 CCGGCTGGCT GGTTTATTGC TGATAAATCT GGAGCCGGTG AGCGTGGGTC TCGCGGTATC
                                  bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
10081 ATTGCAGCAC TGGGGCCAGA TGGTAAGCCC TCCCGTATCG TAGTTATCTA CACGACGGGG
                                  bla
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
10141 AGTCAGGCAA CTATGGATGA ACGAAATAGA CAGATCGCTG AGATAGGTGC CTCACTGATT
         bla
      ~~~~~~~~~
10201 AAGCATTGGT AACTGTCAGA CCAAGTTTAC TCATATATAC TTTAGATTGA TTTAAAACTT
10261 CATTTTTAAT TTAAAAGGAT CTAGGTGAAG ATCCTTTTTG ATAATCTCAT GACCAAAATC
10321 CCTTAACGTG AGTTTTCGTT CCACTGAGCG TCAGACCCCG TAGAAAAGAT CAAAGGATCT
10381 TCTTGAGATC CTTTTTTTCT GCGCGTAATC TGCTGCTTGC AAACAAAAAA ACCACCGCTA
10441 CCAGCGGTGG TTTGTTTGCC GGATCAAGAG CTACCAACTC TTTTTCCGAA GGTAACTGGC
10501 TTCAGCAGAG CGCAGATACC AAATACTGTT CTTCTAGTGT AGCCGTAGTT AGGCCACCAC
10561 TTCAAGAACT CTGTAGCACC GCCTACATAC CTCGCTCTGC TAATCCTGTT ACCAGTGGCT
10621 GCTGCCAGTG GCGATAAGTC GTGTCTTACC GGGTTGGACT CAAGACGATA GTTACCGGAT
10681 AAGGCGCAGC GGTCGGGCTG AACGGGGGGT TCGTGCACAC AGCCCAGCTT GGAGCGAACG
10741 ACCTACACCG AACTGAGATA CCTACAGCGT GAGCTATGAG AAAGCGCCAC GCTTCCCGAA
10801 GGGAGAAAGG CGGACAGGTA TCCGGTAAGC GGCAGGGTCG GAACAGGAGA GCGCACGAGG
10861 GAGCTTCCAG GGGGAAACGC CTGGTATCTT TATAGTCCTG TCGGGTTTCG CCACCTCTGA
10921 CTTGAGCGTC GATTTTTGTG ATGCTCGTCA GGGGGGCGGA GCCTATGGAA AAACGCCAGC
10981 AACGCGGCCT TTTTACGGTT CCTGGCCTTT TGCTGGCCTT TTGCTCACAT GTTCTTTCCT
11041 GCGTTATCCC CTGATTCTGT GGATAACCGT ATTACCGCCT TTGAGTGAGC TGATACCGCT
11101 CGCCGCAGCC GAACGACCGA GCGCAGCGAG TCAGTGAGCG AGGAAGCGGA AGAGCGCCCA
11161 ATACGCAAAC CGCCTCTCCC CGCGCGTTGG CCGATTCATT AATGCAGCTG GCACGACAGG
11221 TTTCCCGACT GGAAAGCGGG CAGTGAGCGC AACGCAATTA ATGTGAGTTA GCTCACTCAT
11281 TAGGCACCCC AGGCTTTACA CTTTATGCTC CCGGCTCGTA TGTTGTGTGG AATTGTGAGC
11341 GGATAACAAT TTCACACAGG AAACAGCTAT GACCATGATT ACGCCAAGCG CGCAATTAAC
11401 CCTCACTAAA GGGAACAAAA GCTGGGTACC GGGCCCACGC GTAATACGAC TCACTATAG
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VEE 캡 헬퍼

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                        5'UTR
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                                              nsP1
                                                            ~~~~~~~~~~~~~~~~~~
    1 ATAGGCGGCG CATGAGAGAA GCCCAGACCA ATTACCTACC CAAATAGGAG AAAGTTCACG
                                  nsP1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   61 TTGACATCGA GGAAGACAGC CCATTCCTCA GAGCTTTGCA GCGGAGCTTC CCGCAGTTTG
                                  nsP1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  121 AGGTAGAAGC CAAGCAGGTC ACTGATAATG ACCATGCTAA TGCCAGAGCG TTTTCGCATC
                                  nsP1
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  181 TGGCTTCAAA ACTGATCGAA ACGGAGGTGG ACCCATCCGA CACGATCCTT GACATTGGAC
                                    VEECAP
               ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  241 GGACCGACCA TGTTCCCGTT CCAGCCAATG TATCCGATGC AGCCAATGCC CTATCGCAAC
                                  VEECAP
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  301 CCGTTCGCGG CCCCGCGCAG GCCCTGGTTC CCCAGAACCG ACCCTTTTCT GGCGATGCAG
                                  VEECAP
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  361 GTGCAGGAAT TAACCCGCTC GATGGCTAAC CTGACGTTCA AGCAACGCCG GGACGCGCCA
                                  VEECAP
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  421 CCTGAGGGGC CATCCGCTAA GAAACCGAAG AAGGAGGCCT CGCAAAAACA GAAAGGGGGA
                                  VEECAP
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  481 GGCCAAGGGA AGAAGAAGAA GAACCAAGGG AAGAAGAAGG CTAAGACAGG GCCGCCTAAT
                                  VEECAP
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  541 CCGAAGGCAC AGAATGGAAA CAAGAAGAAG ACCAACAAGA AACCAGGCAA GAGACAGCGC
                                  VEECAP
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[0438]

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     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 601 ATGGTCATGA AATTGGAATC TGACAAGACG TTCCCAATCA TGTTGGAAGG GAAGATAAAC
                                 VEECAP
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                                        H152G
                                                        ~~~
 661 GGCTACGCTT GTGTGGTCGG AGGGAAGTTA TTCAGGCCGA TGGGTGTGGA AGGCAAGATC
                                 VEECAP
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 721 GACAACGACG TTCTGGCCGC GCTTAAGACG AAGAAAGCAT CCAAATACGA TCTTGAGTAT
                                 VEECAP
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 781 GCAGATGTGC CACAGAACAT GCGGGCCGAT ACATTCAAAT ACACCCATGA GAAACCCCAA
                                 VEECAP
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 841 GGCTATTACA GCTGGCATCA TGGAGCAGTC CAATATGAAA ATGGGCGTTT CACGGTGCCG
                                 VEECAP
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 901 AAAGGAGTTG GGGCCAAGGG AGACAGCGGA CGACCCATTC TGGATAACCA GGGACGGGTG
                                 VEECAP
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 961 GTCGCTATTG TGCTGGGAGG TGTGAATGAA GGATCTAGGA CAGCCCTTTC AGTCGTCATG
                                 VEECAP
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1021 TGGAACGAGA AGGGAGTTAC CGTGAAGTAT ACTCCGGAGA ACTGCGAGCA ATGGTAATAG
     VEECAP                          3'UTR
     ~~~          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1081 TAAGCGGCCG CATACAGCAG CAATTGGCAA GCTGCTTACA TAGAACTCGC GGCGATTGGC
                                 3'UTR
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1141 ATGCCGCCTT AAAATTTTTA TTTTATTTTT CTTTTCTTTT CCGAATCGGA TTTTGTTTTT
      3'UTR                                                HDV 리보자임
     ~~~~~~~~                                             ~~~~~~~~~~~~~~~~~~~
1201 AATATTTCAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAGGGTCGG CATGGCATCT
                           HDV 리보자임
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1261 CCACCTCCTC GCGGTCCGAC CTGGGCATCC GAAGGAGGAC GCACGTCCAC TCGGATGGCT
     HDV 리보자임
     ~~~~~~~~~~~~~~~
1321 AAGGGAGAGC CACGTTTAAA CACGTGATAT CTGGCCTCAT GGGCCTTCCT TTCACTGCCC
1381 GCTTTCCAGT CGGGAAACCT GTCGTGCCAG CTGCATTAAC ATGGTCATAG CTGTTTCCTT
1441 GCGTATTGGG CGCTCTCCGC TTCCTCGCTC ACTGACTCGC TGCGCTCGGT CGTTCGGGTA
                                        colE1
                        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1501 AAGCCTGGGG TGCCTAATGA GCAAAAGGCC AGCAAAAGGC CAGGAACCGT AAAAAGGCCG
                                 colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1561 CGTTGCTGGC GTTTTTCCAT AGGCTCCGCC CCCCTGACGA GCATCACAAA AATCGACGCT
                                 colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1621 CAAGTCAGAG GTGGCGAAAC CCGACAGGAC TATAAAGATA CCAGGCGTTT CCCCCTGGAA
                                 colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1681 GCTCCCTCGT GCGCTCTCCT GTTCCGACCC TGCCGCTTAC CGGATACCTG TCCGCCTTTC
                                 colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1741 TCCCTTCGGG AAGCGTGGCG CTTTCTCATA GCTCACGCTG TAGGTATCTC AGTTCGGTGT
                                 colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1801 AGGTCGTTCG CTCCAAGCTG GGCTGTGTGC ACGAACCCCC CGTTCAGCCC GACCGCTGCG
                                 colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1861 CCTTATCCGG TAACTATCGT CTTGAGTCCA ACCCGGTAAG ACACGACTTA TCGCCACTGG
                                 colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1921 CAGCAGCCAC TGGTAACAGG ATTAGCAGAG CGAGGTATGT AGGCGGTGCT ACAGAGTTCT
                                 colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
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[0439]

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1981 TGAAGTGGTG GCCTAACTAC GGCTACACTA GAAGAACAGT ATTTGGTATC TGCGCTCTGC
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2041 TGAAGCCAGT TACCTTCGGA AAAAGAGTTG GTAGCTCTTG ATCCGGCAAA CAAACCACCG
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2101 CTGGTAGCGG TGGTTTTTTT GTTTGCAAGC AGCAGATTAC GCGCAGAAAA AAAGGATCTC
               colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2161 AAGAAGATCC TTTGATCTTT TCTACGGGGT CTGACGCTCA GTGGAACGAA AACTCACGTT
2221 AAGGGATTTT GGTCATGAGA TTATCAAAAA GGATCTTCAC CTAGATCCTT TTAAATTAAA
2281 AATGAAGTTT TAAATCAATC TAAACTATAT ATGAGTAAAC TTGGTCTGAC AGTTATTAGA
                                                          ~~~
                                                           KanR
2341 AAAATTCATC CAGCAGACGA TAAAACGCAA TACGCTGGCT ATCCGGTGCC GCAATGCCAT
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2401 ACAGCACCAG AAAACGATCC GCCCATTCGC CGCCCAGTTC TTCCGCAATA TCACGGGTGG
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2461 CCAGCGCAAT ATCCTGATAA CGATCCGCCA CGCCCAGACG GCCGCAATCA ATAAAGCCGC
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2521 TAAAACGGCC ATTTTCCACC ATAATGTTCG GCAGGCACGC ATCACCATGG GTCACCACCA
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2581 GATCTTCGCC ATCCGGCATG CTCGCTTTCA GACGCGCAAA CAGCTCTGCC GGTGCCAGGC
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2641 CCTGATGTTC TTCATCCAGA TCATCCTGAT CCACCAGGCC CGCTTCCATA CGGGTACGCG
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2701 CACGTTCAAT ACGATGTTTC GCCTGATGAT CAAACGGACA GGTCGCCGGG TCCAGGGTAT
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2761 GCAGACGACG CATGGCATCC GCCATAATGC TCACTTTTTC TGCCGGCGCC AGATGGCTAG
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2821 ACAGCAGATC CTGACCCGGC ACTTCGCCCA GCAGCAGCCA ATCACGGCCC GCTTCGGTCA
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2881 CCACATCCAG CACCGCCGCA CACGGAACAC CGGTGGTGGC CAGCCAGCTC AGACGCGCCG
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
2941 CTTCATCCTG CAGCTCGTTC AGCGCACCGC TCAGATCGGT TTTCACAAAC AGCACCGGAC
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
3001 GACCCTGCGC GCTCAGACGA AACACCGCCG CATCAGAGCA GCCAATGGTC TGCTGCGCCC
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
3061 AATCATAGCC AAACAGACGT TCCACCCACG CTGCCGGGCT ACCCGCATGC AGGCCATCCT
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                  KanR
3121 GTTCAATCAT ACTCTTCCTT TTTCAATATT ATTGAAGCAT TTATCAGGGT TATTGTCTCA
     ~~~~~~~~~~~
        KanR
3181 TGAGCGGATA CATATTTGAA TGTATTTAGA AAAATAAACA AATAGGGGTT CCGCGCACAT
3241 TTCCCCGAAA AGTGCCACCT AAATTGTAAG CGTTAATATT TTGTTAAAAT TCGCGTTAAA
3301 TTTTTGTTAA ATCAGCTCAT TTTTTAACCA ATAGGCCGAA ATCGGCAAAA TCCCTTATAA
3361 ATCAAAAGAA TAGACCGAGA TAGGGTTGAG TGGCCGCTAC AGGGCGCTCC CATTCGCCAT
3421 TCAGGCTGCG CAACTGTTGG GAAGGGCGTT TCGGTGCGGG CCTCTTCGCT ATTACGCCAG
3481 CTGGCGAAAG GGGGATGTGC TGCAAGGCGA TTAAGTTGGG TAACGCCAGG GTTTTCCCAG
               T7 프로모터
             ~~~~~~~~~~~~~~~~~~~~
3541 TCACACGCGT AATACGACTC ACTATAG
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VEE gly 헬퍼

[0440]

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                    5'UTR
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                                                              nsP1
                                                      ~~~~~~~~~~~~~~~~~~
   1 ATAGGCGGCG CATGAGAGAA GCCCAGACCA ATTACCTACC CAAATAGGAG AAAGTTCACG
                              nsP1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  61 TTGACATCGA GGAAGACAGC CCATTCCTCA GAGCTTTGCA GCGGAGCTTC CCGCAGTTTG
                              nsP1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 121 AGGTAGAAGC CAAGCAGGTC ACTGATAATG ACCATGCTAA TGCCAGAGCG TTTTCGCATC
                             nsP1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 181 TGGCTTCAAA ACTGATCGAA ACGGAGGTGG ACCCATCCGA CACGATCCTT GACATTGGAC
                                 VEE GLY
             ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 241 GGACCGACCA TGTCACTAGT GACCACCATG TGTCTGCTCG CCAATGTGAC GTTCCCATGT
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 301 GCTCAACCAC CAATTTGCTA CGACAGAAAA CCAGCAGAGA CTTTGGCCAT GCTCAGCGTT
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 361 AACGTTGACA ACCCGGGCTA CGATGAGCTG CTGGAAGCAG CTGTTAAGTG CCCCGGAAGG
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 421 AAAAGGAGAT CCACCGAGGA GCTGTTTAAT GAGTATAAGC TAACGCGCCC TTACATGGCC
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 481 AGATGCATCA GATGTGCAGT TGGGAGCTGC CATAGTCCAA TAGCAATCGA GGCAGTAAAG
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 541 AGCGACGGGC ACGACGGTTA TGTTAGACTT CAGACTTCCT CGCAGTATGG CCTGGATTCC
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 601 TCCGGCAACT TAAAGGGCAG GACCATGCGG TATGACATGC ACGGGACCAT TAAAGAGATA
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 661 CCACTACATC AAGTGTCACT CTATACATCT CGCCCGTGTC ACATTGTGGA TGGGCACGGT
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 721 TATTTCCTGC TTGCCAGGTG CCCGGCAGGG GACTCCATCA CCATGGAATT TAAGAAAGAT
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 781 TCCGTCAGAC ACTCCTGCTC GGTGCCGTAT GAAGTGAAAT TTAATCCTGT AGGCAGAGAA
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 841 CTCTATACTC ATCCCCCAGA ACACGGAGTA GAGCAAGCGT GCCAAGTCTA CGCACATGAT
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 901 GCACAGAACA GAGGAGCTTA TGTCGAGATG CACCTCCCGG GCTCAGAAGT GGACAGCAGT
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 961 TTGGTTTCCT TGAGCGGCAG TTCAGTCACC GTGACACCTC CTGATGGGAC TAGCGCCCTG
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1021 GTGGAATGCG AGTGTGGCGG CACAAAGATC TCCGAGACCA TCAACAAGAC AAAACAGTTC
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1081 AGCCAGTGCA CAAAGAAGGA GCAGTGCAGA GCATATCGGC TGCAGAACGA TAAGTGGGTG
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1141 TATAATTCTG ACAAACTGCC CAAAGCAGCG GGAGCCACCT TAAAAGGAAA ACTGCATGTC
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1201 CCATTCTTGC TGGCAGACGG CAAATGCACC GTGCCTCTAG CACCAGAACC TATGATAACC
                            VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1261 TTCGGTTTCA GATCAGTGTC ACTGAAACTG CACCCTAAGA ATCCCACATA TCTAATCACC
                            VEE GLY
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[0441]

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     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1321 CGCCAACTTG CTGATGAGCC TCACTACACG CACGAGCTCA TATCTGAACC AGCTGTTAGG
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1381 AATTTTACCG TCACCGAAAA AGGGTGGGAG TTTGTATGGG GAAACCACCC GCCGAAAAGG
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1441 TTTTGGGCAC AGGAAACAGC ACCCGGAAAT CCACATGGGC TACCGCACGA GGTGATAACT
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1501 CATTATTACC ACAGATACCC TATGTCCACC ATCCTGGGTT TGTCAATTTG TGCCGCCATT
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1561 GCAACCGTTT CCGTTGCAGC GTCTACCTGG CTGTTTTGCA GATCTAGAGT TGCGTGCCTA
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1621 ACTCCTTACC GGCTAACACC TAACGCTAGG ATACCATTTT GTCTGGCTGT GCTTTGCTGC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1681 GCCCGCACTG CCCGGGCCGA GACCACCTGG GAGTCCTTGG ATCACCTATG GAACAATAAC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1741 CAACAGATGT TCTGGATTCA ATTGCTGATC CCTCTGGCCG CCTTGATCGT AGTGACTCGC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1801 CTGCTCAGGT GCGTGTGCTG TGTCGTGCCT TTTTTAGTCA TGGCCGGCGC CGCAGGCGCC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1861 GGCGCCTACG AGCACGCGAC CACGATGCCG AGCCAAGCGG GAATCTCGTA TAACACTATA
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1921 GTCAACAGAG CAGGCTACGC ACCACTCCCT ATCAGCATAA CACCAACAAA GATCAAGCTG
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
1981 ATACCTACAG TGAACTTGGA GTACGTCACC TGCCACTACA AAACAGGAAT GGATTCACCA
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2041 GCCATCAAAT GCTGCGGATC TCAGGAATGC ACTCCAACTT ACAGGCCTGA TGAACAGTGC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2101 AAAGTCTTCA CAGGGGTTTA CCCGTTCATG TGGGGTGGTG CATATTGCTT TTGCGACACT
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2161 GAGAACACCC AAGTCAGCAA GGCCTACGTA ATGAAATCTG ACGACTGCCT TGCGGATCAT
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2221 GCTGAAGCAT ATAAAGCGCA CACAGCCTCA GTGCAGGCGT TCCTCAACAT CACAGTGGGA
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2281 GAACACTCTA TTGTGACTAC CGTGTATGTG AATGGAGAAA CTCCTGTGAA TTTCAATGGG
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2341 GTCAAAATAA CTGCAGGTCC GCTTTCCACA GCTTGGACAC CCTTTGATCG CAAAATCGTG
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2401 CAGTATGCCG GGGAGATCTA TAATTATGAT TTTCCTGAGT ATGGGGCAGG ACAACCAGGA
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2461 GCATTTGGAG ATATACAATC CAGAACAGTC TCAAGCTCTG ATCTGTATGC CAATACCAAC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2521 CTAGTGCTGC AGAGACCCAA AGCAGGAGCG ATCCACGTGC CATACACTCA GGCACCTTCG
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2581 GGTTTTGAGC AATGGAAGAA AGATAAAGCT CCATCATTGA AATTTACCGC CCCTTTCGGA
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2641 TGCGAAATAT ATACAAACCC CATTCGCGCC GAAAACTGTG CTGTAGGGTC AATTCCATTA
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[0442]

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                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2701 GCCTTTGACA TTCCCGACGC CTTGTTCACC AGGGTGTCAG AAACACCGAC ACTTTCAGCG
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2761 GCCGAATGCA CTCTTAACGA GTGCGTGTAT TCTTCCGACT TTGGTGGGAT CGCCACGGTC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2821 AAGTACTCGG CCAGCAAGTC AGGCAAGTGC GCAGTCCATG TGCCATCAGG GACTGCTACC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2881 CTAAAAGAAG CAGCAGTCGA GCTAACCGAG CAAGGGTCGG CGACTATCCA TTTCTCGACC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
2941 GCAAATATCC ACCCGGAGTT CAGGCTCCAA ATATGCACAT CATATGTTAC GTGCAAAGGT
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3001 GATTGTCACC CCCCGAAAGA CCATATTGTG ACACACCCTC AGTATCACGC CCAAACATTT
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3061 ACAGCCGCGG TGTCAAAAAC CGCGTGGACG TGGTTAACAT CCCTGCTGGG AGGATCAGCC
                                  VEE GLY
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3121 GTAATTATTA TAATTGGCTT GGTGCTGGCT ACTATTGTGG CCATGTACGT GCTGACCAAC
         VEE GLY                                3'UTR
     ~~~~~~~~~~~~~~~~~~~~~~~~~        ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3181 CAGAAACATA ATTAATAGTA AGCGGCCGCA TACAGCAGCA ATTGGCAAGC TGCTTACATA
                                   3'UTR
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3241 GAACTCGCGG CGATTGGCAT GCCGCCTTAA AATTTTTATT TTATTTTTCT TTTCTTTTCC
            3'UTR
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3301 GAATCGGATT TTGTTTTTAA TATTTCAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
                                HDV 리보자임
      ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3361 AGGGTCGGCA TGGCATCTCC ACCTCCTCGC GGTCCGACCT GGGCATCCGA AGGAGGACGC
           HDV 리보자임
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3421 ACGTCCACTC GGATGGCTAA GGGAGAGCCA CGTTTAAACA CGTGATATCT GGCCTCATGG
3481 GCCTTCCTTT CACTGCCCGC TTTCCAGTCG GGAAACCTGT CGTGCCAGCT GCATTAACAT
3541 GGTCATAGCT GTTTCCTTGC GTATTGGGCG CTCTCCGCTT CCTCGCTCAC TGACTCGCTG
                                                    colE1
                                          ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3601 CGCTCGGTCG TTCGGGTAAA GCCTGGGGTG CCTAATGAGC AAAAGGCCAG CAAAAGGCCA
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3661 GGAACCGTAA AAAGGCCGCG TTGCTGGCGT TTTTCCATAG GCTCCGCCCC CCTGACGAGC
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3721 ATCACAAAAA TCGACGCTCA AGTCAGAGGT GGCGAAACCC GACAGGACTA TAAAGATACC
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3781 AGGCGTTTCC CCCTGGAAGC TCCCTCGTGC GCTCTCCTGT TCCGACCCTG CCGCTTACCG
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3841 GATACCTGTC CGCCTTTCTC CCTTCGGGAA GCGTGGCGCT TTCTCATAGC TCACGCTGTA
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3901 GGTATCTCAG TTCGGTGTAG GTCGTTCGCT CCAAGCTGGG CTGTGTGCAC GAACCCCCCG
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
3961 TTCAGCCCGA CCGCTGCGCC TTATCCGGTA ACTATCGTCT TGAGTCCAAC CCGGTAAGAC
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4021 ACGACTTATC GCCACTGGCA GCAGCCACTG GTAACAGGAT TAGCAGAGCG AGGTATGTAG
                                  colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4081 GCGGTGCTAC AGAGTTCTTG AAGTGGTGGC CTAACTACGG CTACACTAGA AGAACAGTAT
```

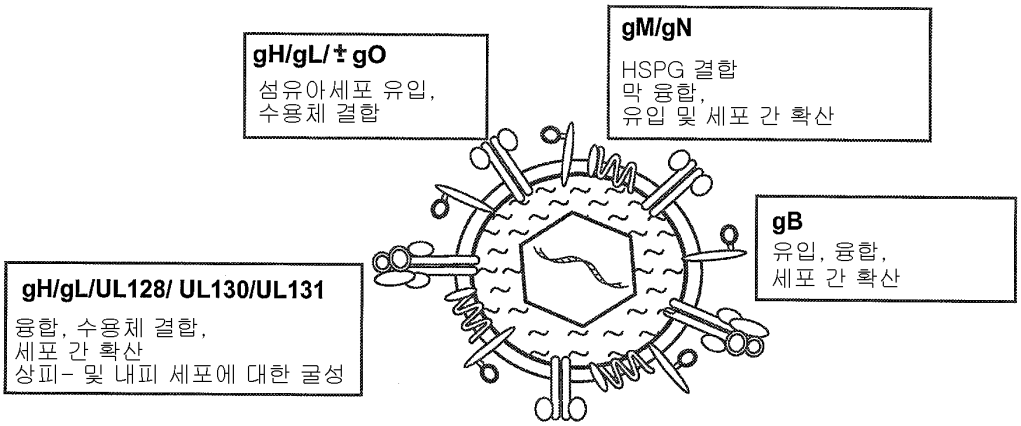
[0443]

```
                                    colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4141 TTGGTATCTG CGCTCTGCTG AAGCCAGTTA CCTTCGGAAA AAGAGTTGGT AGCTCTTGAT
                                    colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4201 CCGGCAAACA AACCACCGCT GGTAGCGGTG GTTTTTTTGT TTGCAAGCAG CAGATTACGC
                          colE1
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
4261 GCAGAAAAAA AGGATCTCAA GAAGATCCTT TGATCTTTTC TACGGGGTCT GACGCTCAGT
4321 GGAACGAAAA CTCACGTTAA GGGATTTTGG TCATGAGATT ATCAAAAAGG ATCTTCACCT
4381 AGATCCTTTT AAATTAAAAA TGAAGTTTTA AATCAATCTA AAGTATATAT GAGTAAACTT
4441 GGTCTGACAG TTATTAGAAA AATTCATCCA GCAGACGATA AAACGCAATA CGCTGGCTAT
                ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                       KanR
4501 CCGGTGCCGC AATGCCATAC AGCACCAGAA AACGATCCGC CCATTCGCCG CCCAGTTCTT
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
4561 CCGCAATATC ACGGGTGGCC AGCGCAATAT CCTGATAACG ATCCGCCACG CCCAGACGGC
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
4621 CGCAATCAAT AAAGCCGCTA AAACGGCCAT TTTCCACCAT AATGTTCGGC AGGCACGCAT
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
4681 CACCATGGGT CACCACCAGA TCTTCGCCAT CCGGCATGCT CGCTTTCAGA CGCGCAAACA
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
4741 GCTCTGCCGG TGCCAGGCCC TGATGTTCTT CATCCAGATC ATCCTGATCC ACCAGGCCCG
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
4801 CTTCCATACG GGTACGCGCA CGTTCAATAC GATGTTTCGC CTGATGATCA AACGGACAGG
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
4861 TCGCCGGGTC CAGGGTATGC AGACGACGCA TGGCATCCGC CATAATGCTC ACTTTTTCTG
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
4921 CCGGCGCCAG ATGGCTAGAC AGCAGATCCT GACCCGGCAC TTCGCCCAGC AGCAGCCAAT
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
4981 CACGGCCCGC TTCGGTCACC ACATCCAGCA CCGCCGCACA CGGAACACCG GTGGTGGCCA
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
5041 GCCAGCTCAG ACGCGCCGCT TCATCCTGCA GCTCGTTCAG CGCACCGCTC AGATCGGTTT
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
5101 TCACAAACAG CACCGGACGA CCCTGCGCGC TCAGACGAAA CACCGCCGCA TCAGAGCAGC
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
5161 CAATGGTCTG CTGCGCCCAA TCATAGCCAA ACAGACGTTC CACCCACGCT GCCGGGCTAC
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                                    KanR
5221 CCGCATGCAG GCCATCCTGT TCAATCATAC TCTTCCTTTT TCAATATTAT TGAAGCATTT
     ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
                  KanR
5281 ATCAGGGTTA TTGTCTCATG AGCGGATACA TATTTGAATG TATTTAGAAA AATAAACAAA
5341 TAGGGGTTCC GCGCACATTT CCCCGAAAAG TGCCACCTAA ATTGTAAGCG TTAATATTTT
5401 GTTAAAATTC GCGTTAAATT TTTGTTAAAT CAGCTCATTT TTTAACCAAT AGGCCGAAAT
5461 CGGCAAAATC CCTTATAAAT CAAAAGAATA GACCGAGATA GGGTTGAGTG GCCGCTACAG
5521 GGCGCTCCCA TTCGCCATTC AGGCTGCGCA ACTGTTGGGA AGGGCGTTTC GGTGCGGGCC
5581 TCTTCGCTAT TACGCCAGCT GGCGAAAGGG GGATGTGCTG CAAGGCGATT AAGTTGGGTA
                                       T7 프로모터
                                     ~~~~~~~~~~~~~~~~~~~~
5641 ACGCCAGGGT TTTCCCAGTC ACACGCGTAA TACGACTCAC TATAG
```

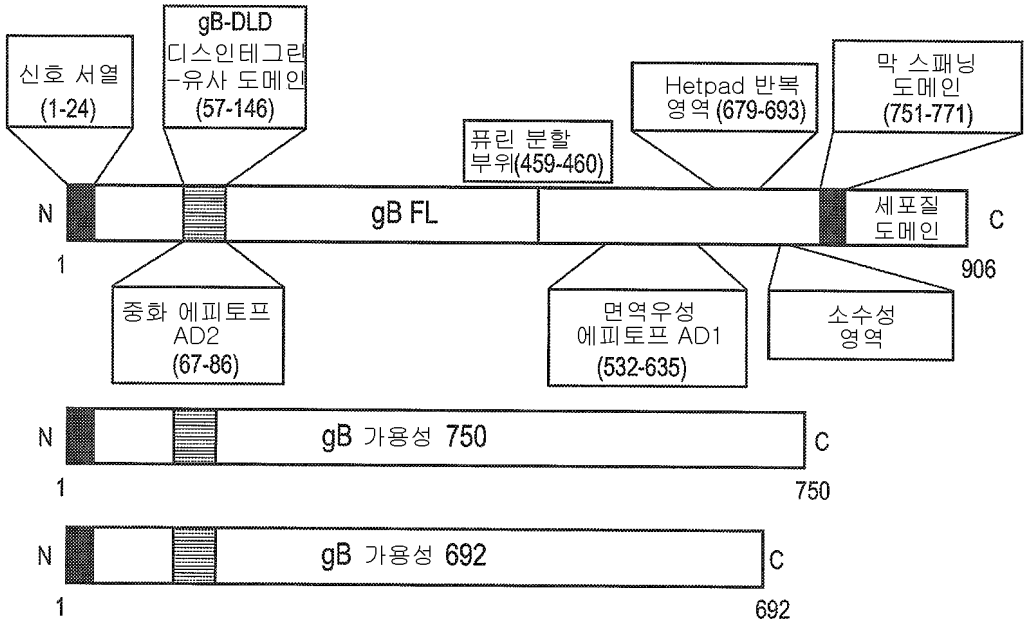
[0444]

도면

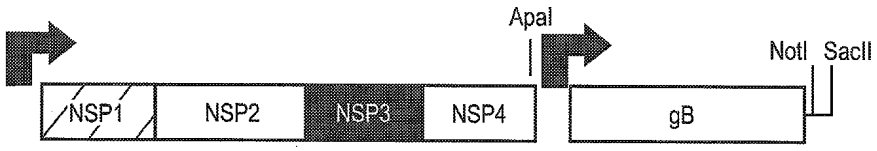
도면1



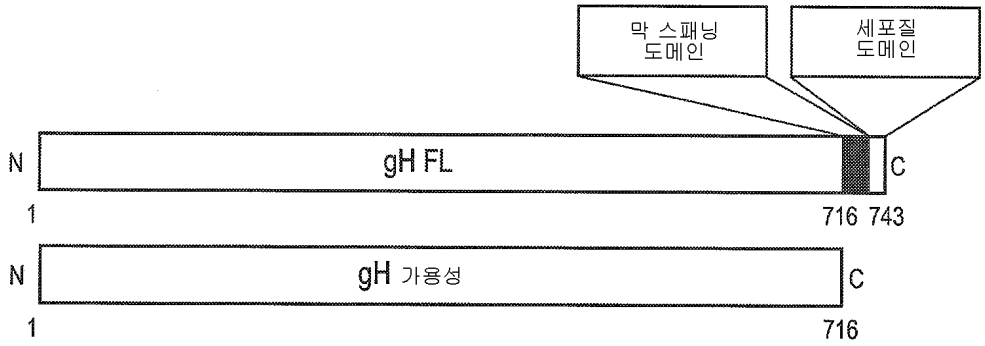
도면2a



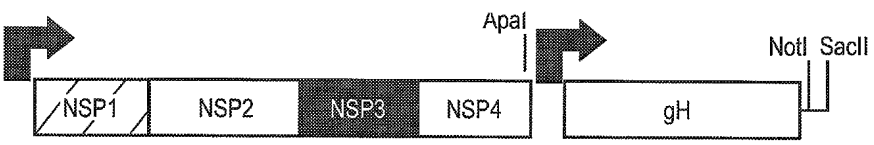
도면2b



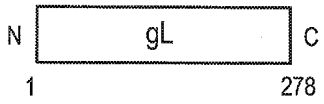
도면2c



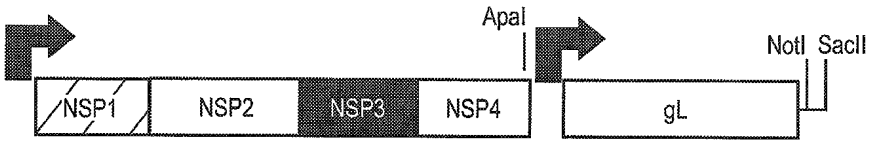
도면2d



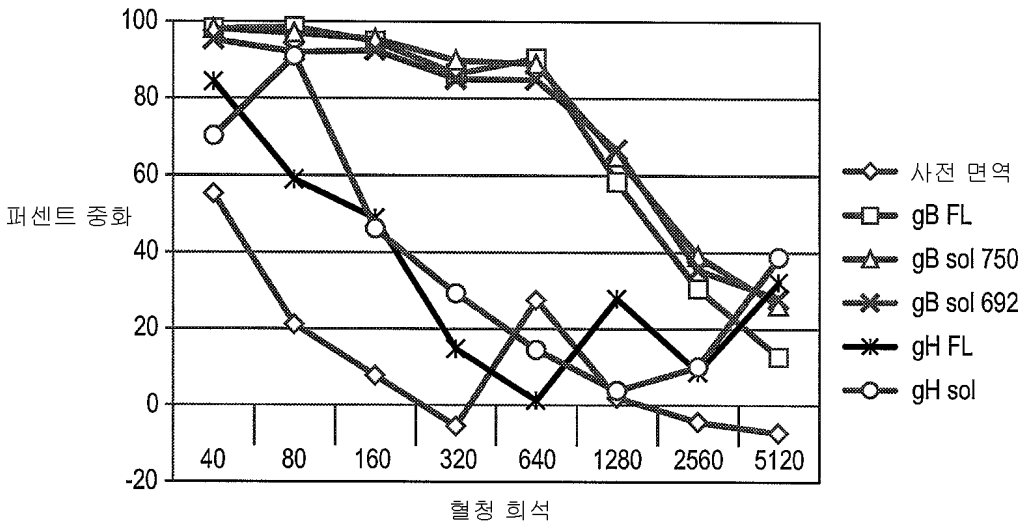
도면2e



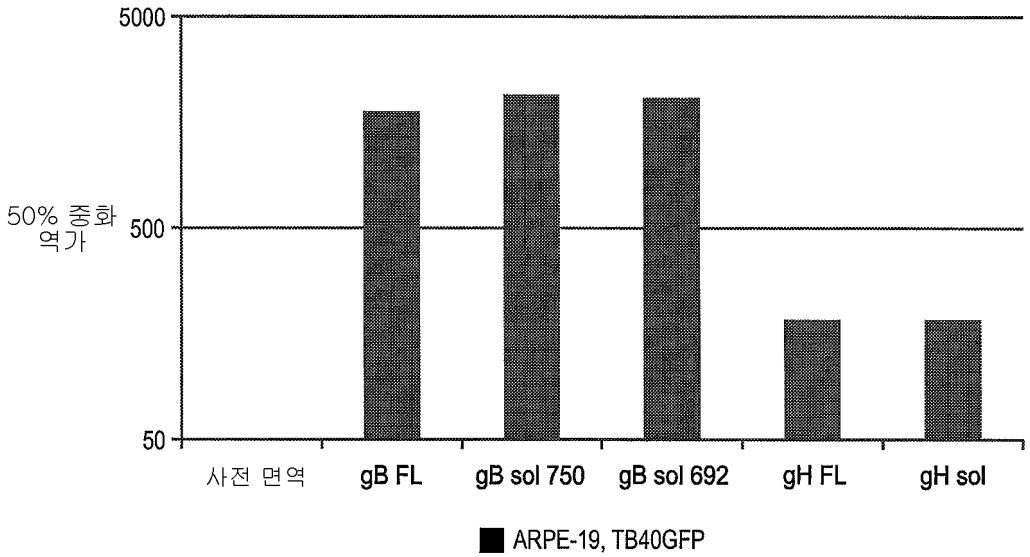
도면2f



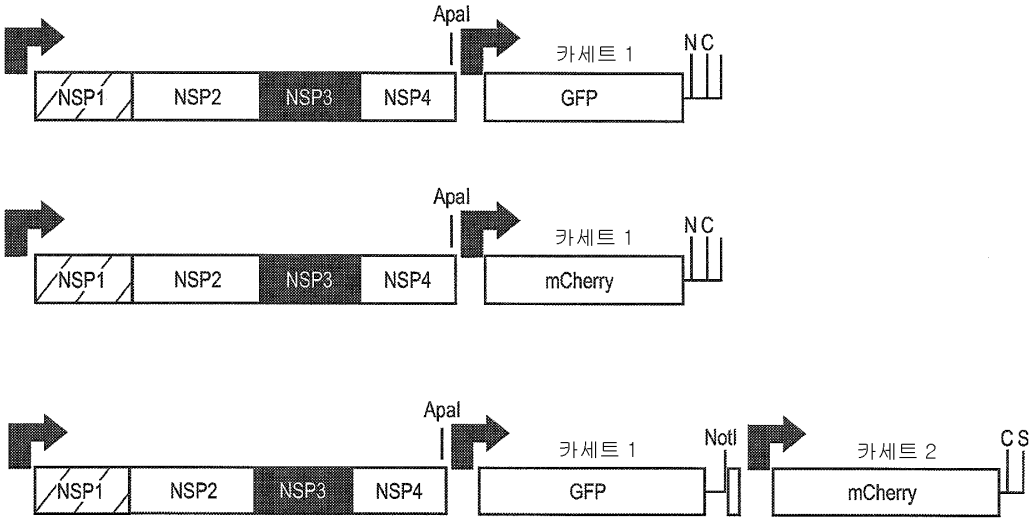
도면3a



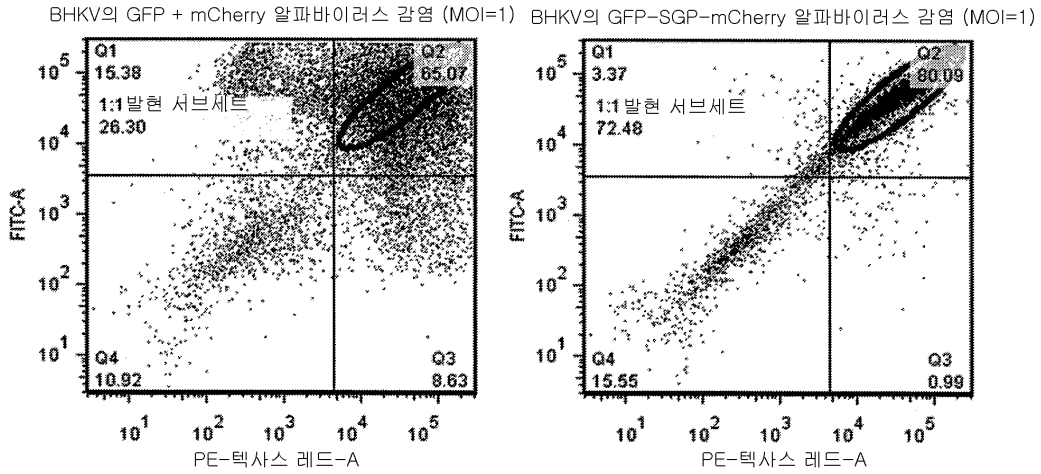
도면3b


5000
500
50
50% 중화 역가
사전 면역
gB FL
gB sol 750
gB sol 692
gH FL
gH sol
ARPE-19, TB40GFP

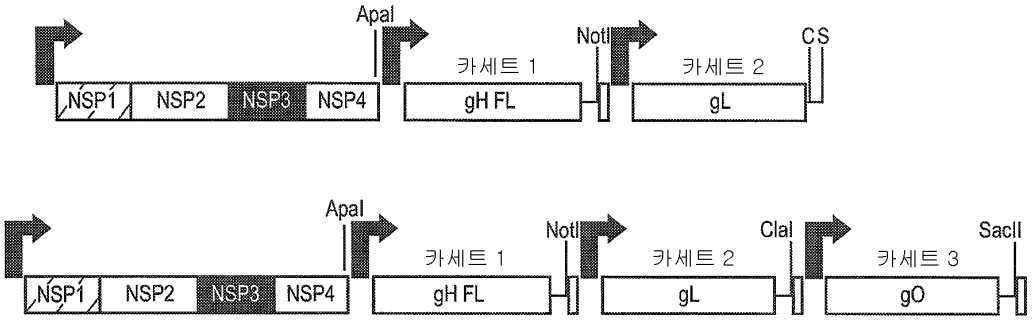
도면4a


ApaI
카세트 1
N C
NSP1
NSP2
NSP3
NSP4
GFP
ApaI
카세트 1
N C
NSP1
NSP2
NSP3
NSP4
mCherry
ApaI
카세트 1
NotI
카세트 2
C S
NSP1
NSP2
NSP3
NSP4
GFP
mCherry

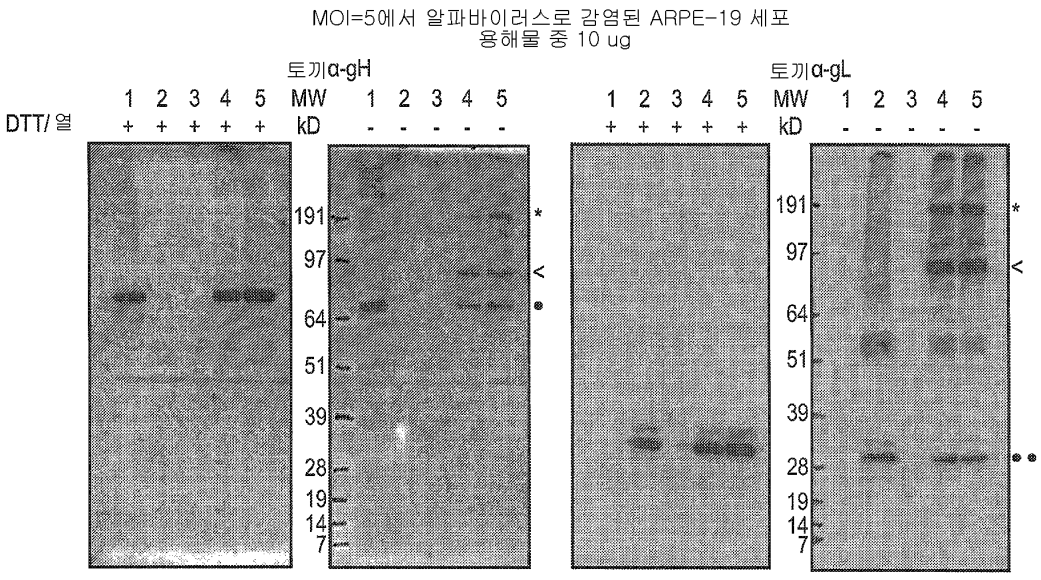
도면4b



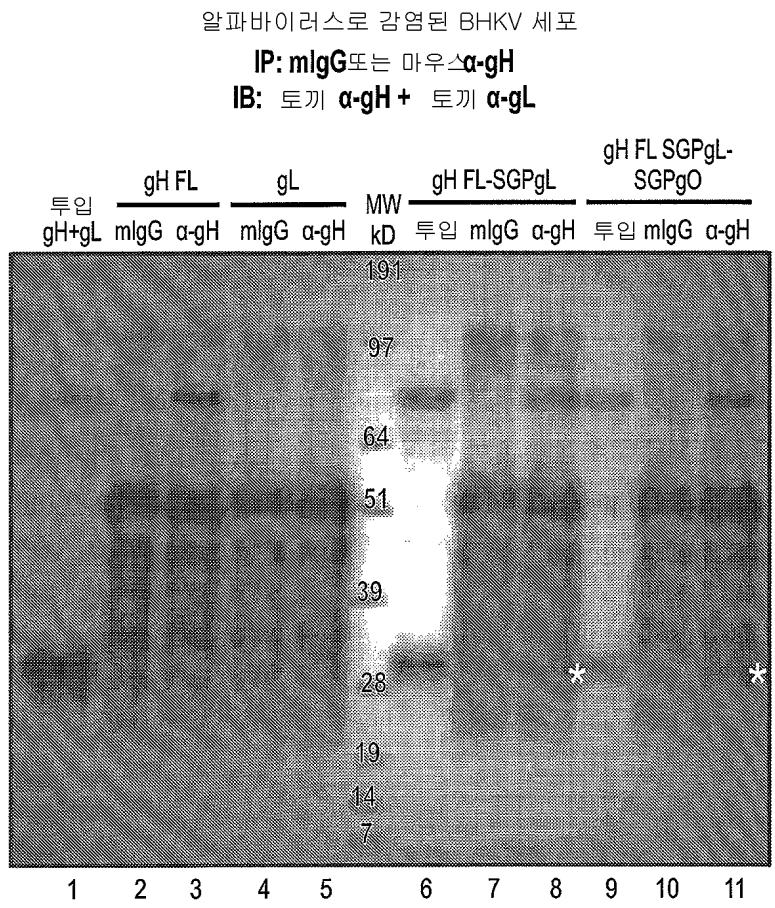
도면5a



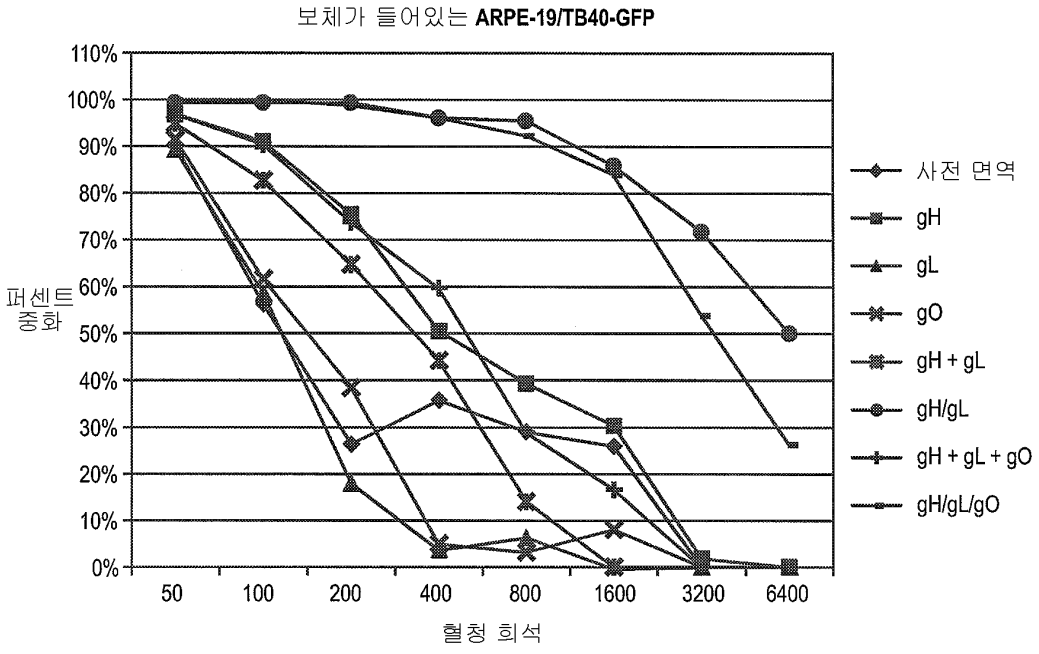
도면5b



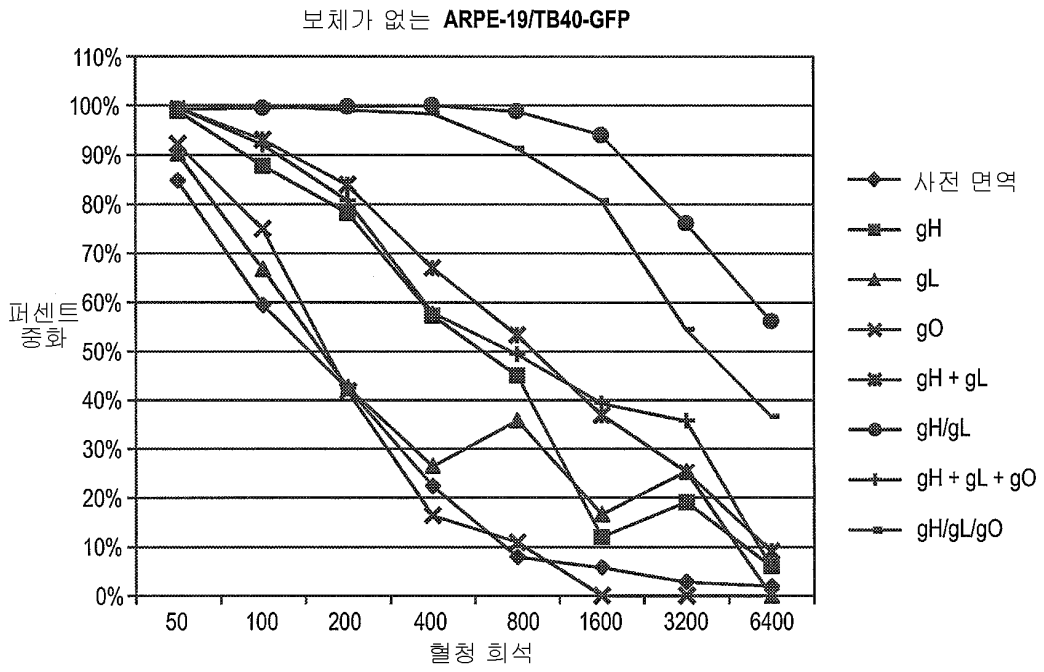
도면5c


알파바이러스로 감염된 BHKV 세포
IP: mIgG또는 마우스α-gH
IB: 토끼 α-gH + 토끼 α-gL
gH FL
gL
gH FL-SGPgL
gH FL SGPgL-SGPgO
투입
gH+gL
mIgG
α-gH
mIgG
α-gH
MW kD
투입
mIgG
α-gH
투입
mIgG
α-gH
191
97
64
51
39
28
19
14
7
1
2
3
4
5
6
7
8
9
10
11

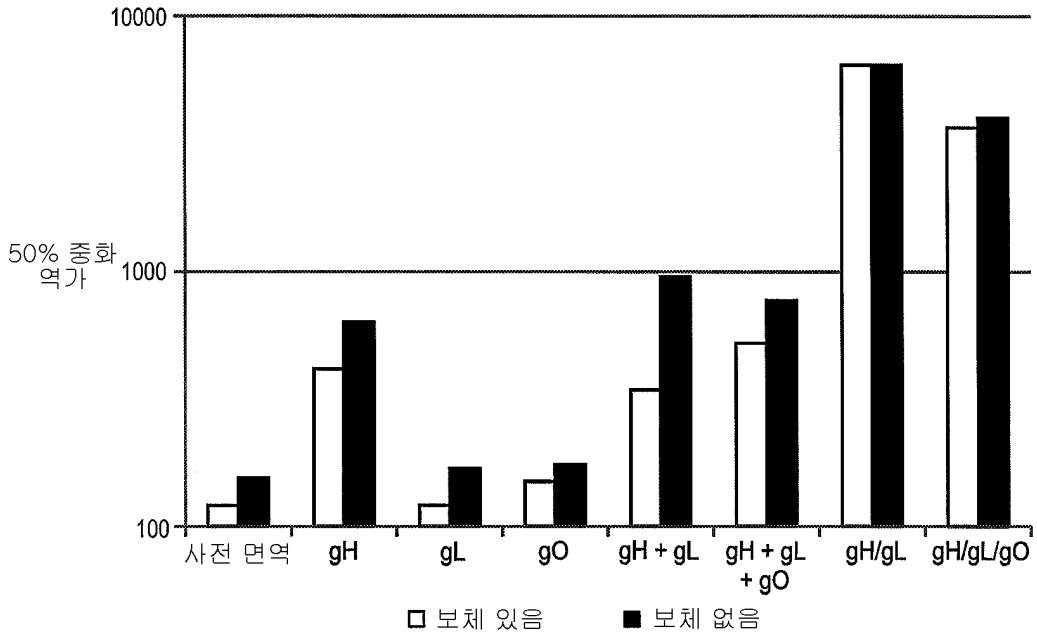
도면6a


보체가 들어있는 ARPE-19/TB40-GFP
퍼센트 중화
110%
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
50
100
200
400
800
1600
3200
6400
혈청 희석
사전 면역
gH
gL
gO
gH + gL
gH/gL
gH + gL + gO
gH/gL/gO

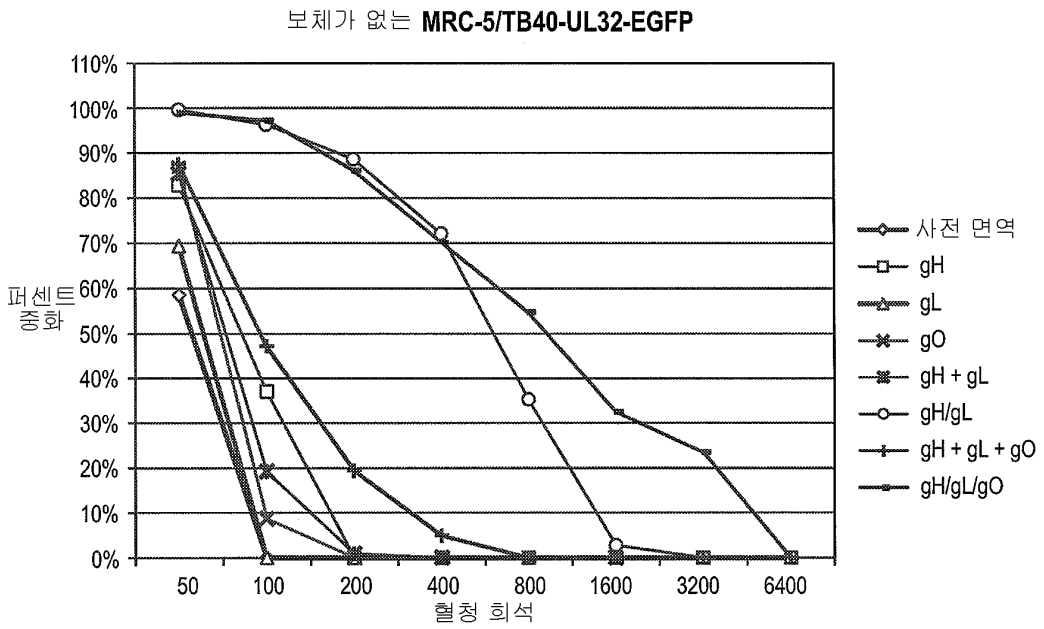
도면6b


보체가 없는 ARPE-19/TB40-GFP
퍼센트 중화
110%
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
50
100
200
400
800
1600
3200
6400
혈청 희석
사전 면역
gH
gL
gO
gH + gL
gH/gL
gH + gL + gO
gH/gL/gO

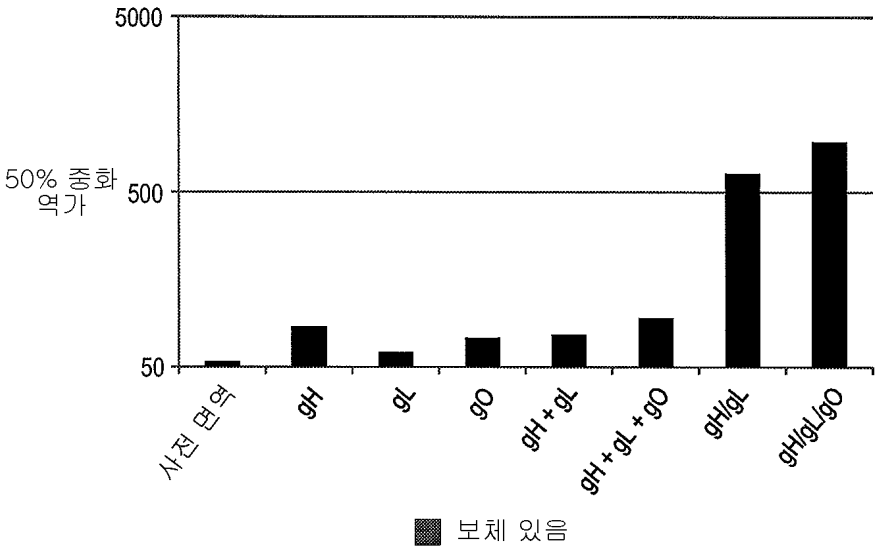
도면6c


50% 중화 역가
10000
1000
100
사전 면역
gH
gL
gO
gH + gL
gH + gL + gO
gH/gL
gH/gL/gO
보체 있음
보체 없음

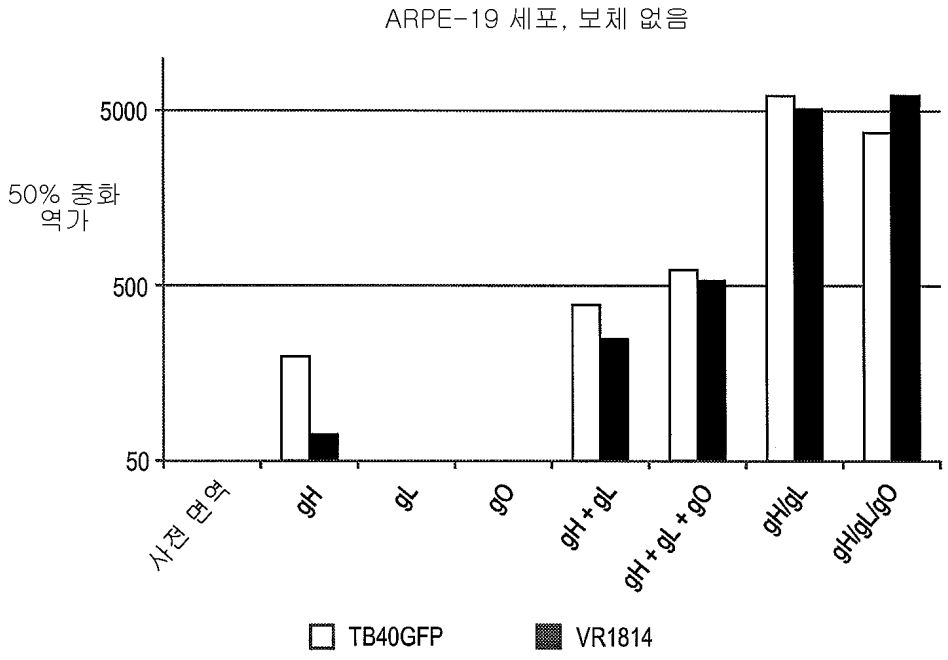
도면7a


보체가 없는 MRC-5/TB40-UL32-EGFP
110%
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
퍼센트 중화
50
100
200
400
800
1600
3200
6400
혈청 희석
사전 면역
gH
gL
gO
gH + gL
gH/gL
gH + gL + gO
gH/gL/gO

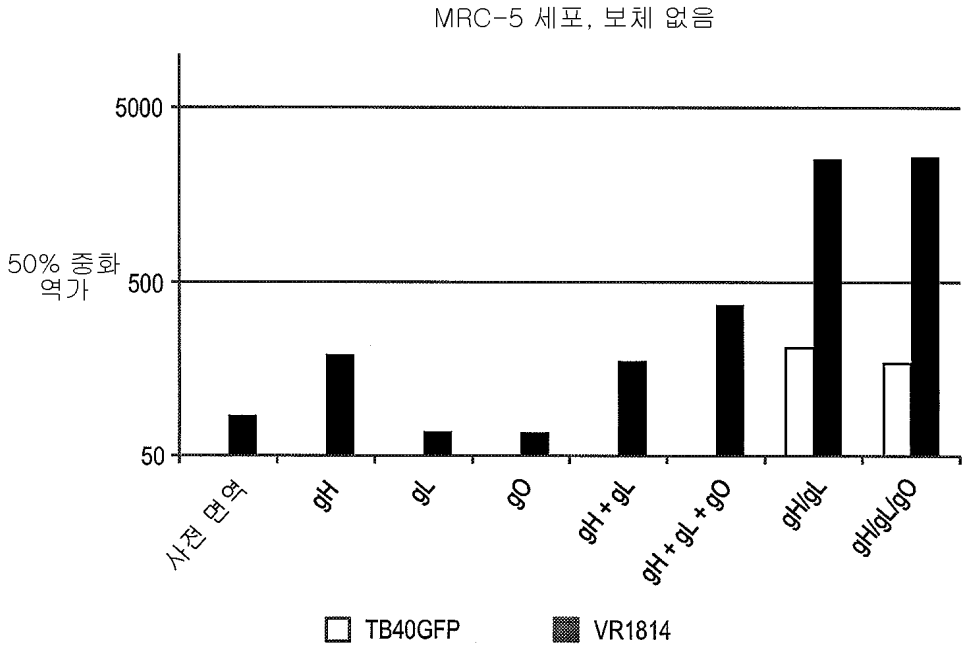
도면7b


5000
500
50
50% 중화 역가
사전 면역
gH
gL
gO
gH + gL
gH + gL + gO
gH/gL
gH/gL/gO
보체 있음

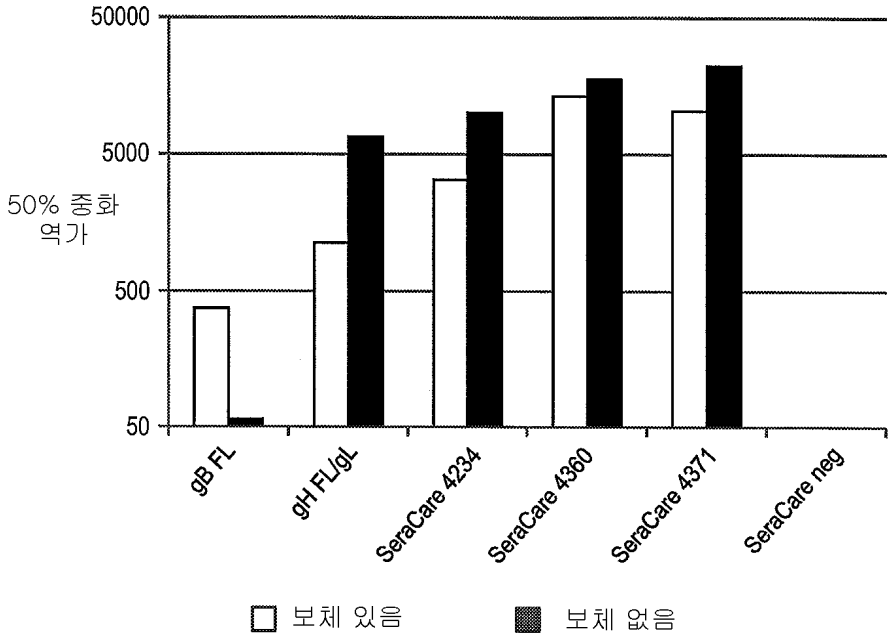
도면8a


ARPE-19 세포, 보체 없음
50% 중화 역가
5000
500
50
사전 면역
gH
gL
gO
gH+gL
gH+gL+gO
gHlgL
gHlgL/gO
TB40GFP
VR1814

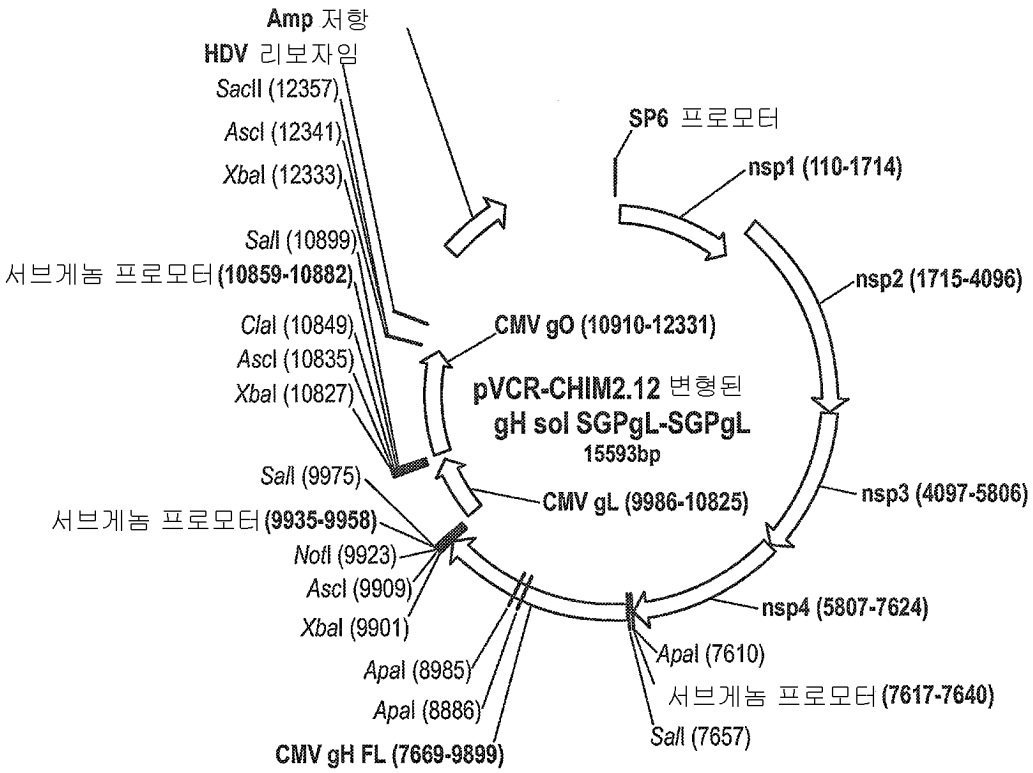
도면8b


MRC-5 세포, 보체 없음
50% 중화 역가
5000
500
50
사전 면역
gH
gL
gO
gH+gL
gH+gL+gO
gHlgL
gHlgL/gO
TB40GFP
VR1814

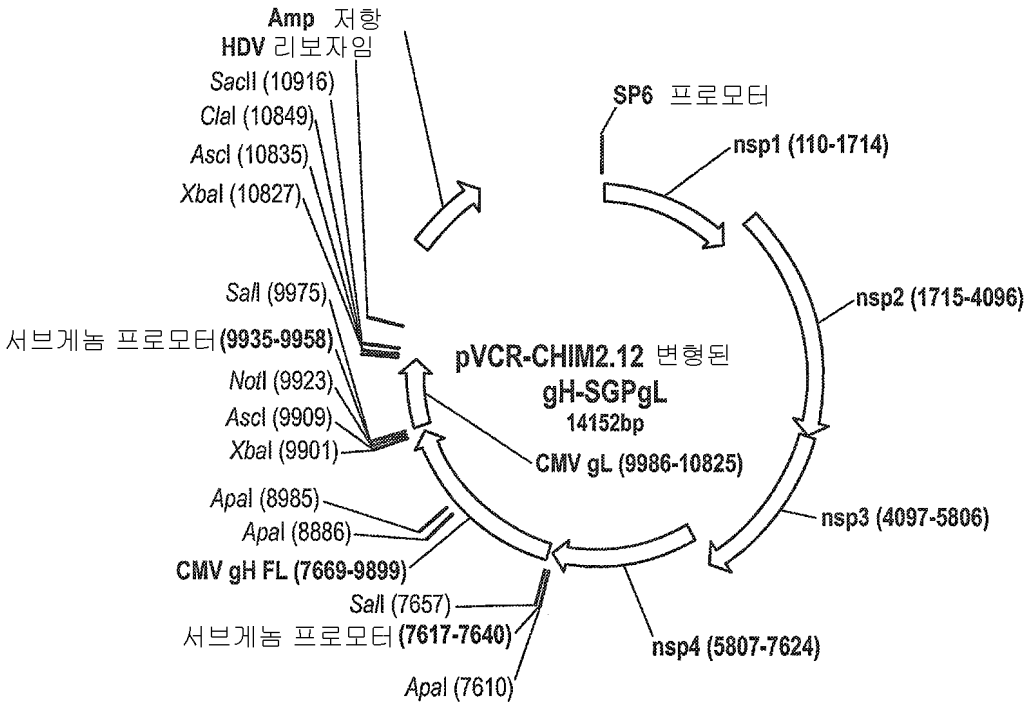
도면9


50000
5000
500
50
50% 중화
역가
gB FL
gH FL/gL
SeraCare 4234
SeraCare 4360
SeraCare 4371
SeraCare neg
보체 있음
보체 없음

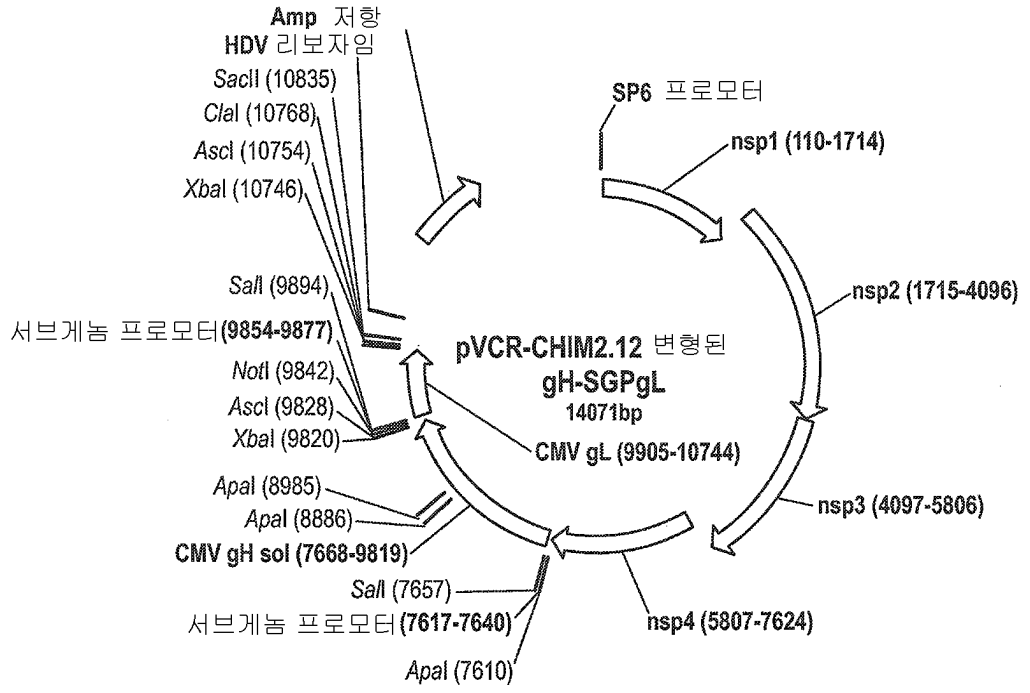
도면10


Amp 저항
HDV 리보자임
SacII (12357)
AscI (12341)
XbaI (12333)
SalI (10899)
서브게놈 프로모터 (10859-10882)
ClaI (10849)
AscI (10835)
XbaI (10827)
SalI (9975)
서브게놈 프로모터 (9935-9958)
NotI (9923)
AscI (9909)
XbaI (9901)
ApaI (8985)
ApaI (8886)
CMV gH FL (7669-9899)
SP6 프로모터
nsp1 (110-1714)
nsp2 (1715-4096)
nsp3 (4097-5806)
nsp4 (5807-7624)
ApaI (7610)
서브게놈 프로모터 (7617-7640)
SalI (7657)
CMV gO (10910-12331)
pVCR-CHIM2.12 변형된
gH sol SGPgL-SGPgL
15593bp
CMV gL (9986-10825)

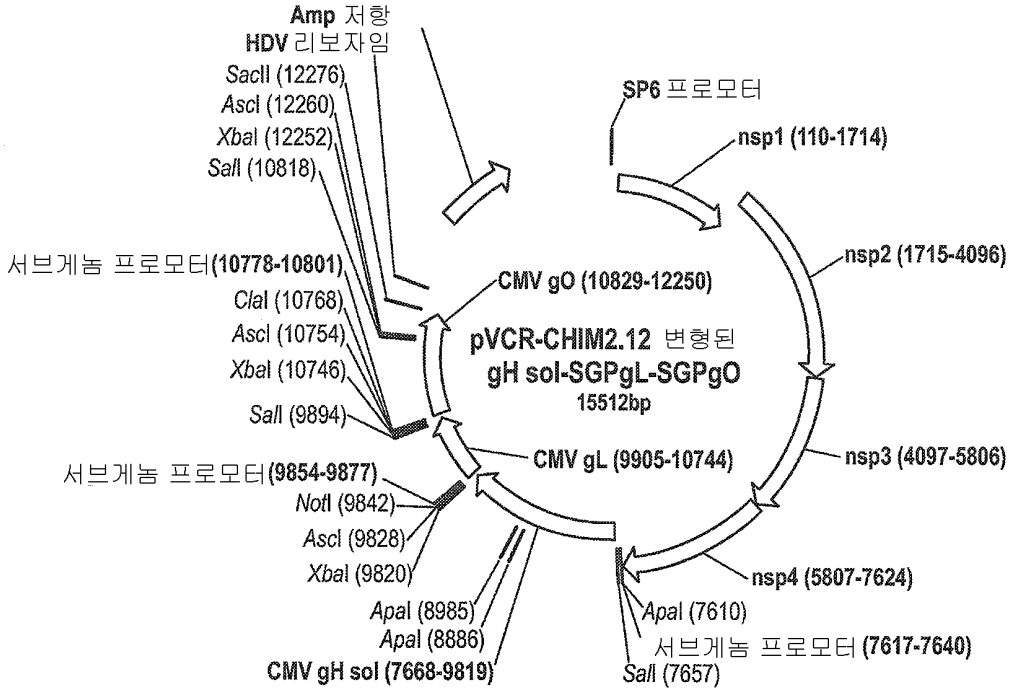
도면11


Amp 저항
HDV 리보자임
SacII (10916)
ClaI (10849)
AscI (10835)
XbaI (10827)
SalI (9975)
서브게놈 프로모터(9935-9958)
NotI (9923)
AscI (9909)
XbaI (9901)
ApaI (8985)
ApaI (8886)
CMV gH FL (7669-9899)
SalI (7657)
서브게놈 프로모터 (7617-7640)
ApaI (7610)
SP6 프로모터
nsp1 (110-1714)
nsp2 (1715-4096)
nsp3 (4097-5806)
nsp4 (5807-7624)
pVCR-CHIM2.12 변형된
gH-SGPgL
14152bp
CMV gL (9986-10825)

도면12


Amp 저항
HDV 리보자임
SacII (10835)
ClaI (10768)
AscI (10754)
XbaI (10746)
SalI (9894)
서브게놈 프로모터(9854-9877)
NotI (9842)
AscI (9828)
XbaI (9820)
ApaI (8985)
ApaI (8886)
CMV gH sol (7668-9819)
SalI (7657)
서브게놈 프로모터(7617-7640)
ApaI (7610)
SP6 프로모터
nsp1 (110-1714)
nsp2 (1715-4096)
nsp3 (4097-5806)
nsp4 (5807-7624)
pVCR-CHIM2.12 변형된
gH-SGPgL
14071bp
CMV gL (9905-10744)

도면13


Amp 저항
HDV 리보자임
SacII (12276)
AscI (12260)
XbaI (12252)
SalI (10818)
서브게놈 프로모터(10778-10801)
ClaI (10768)
AscI (10754)
XbaI (10746)
SalI (9894)
서브게놈 프로모터(9854-9877)
NotI (9842)
AscI (9828)
XbaI (9820)
ApaI (8985)
ApaI (8886)
CMV gH sol (7668-9819)
SP6 프로모터
nsp1 (110-1714)
nsp2 (1715-4096)
nsp3 (4097-5806)
nsp4 (5807-7624)
ApaI (7610)
서브게놈 프로모터 (7617-7640)
SalI (7657)
CMV gO (10829-12250)
pVCR-CHIM2.12 변형된
gH sol-SGPgL-SGPgO
15512bp
CMV gL (9905-10744)

도면14a

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도면14b

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도면14c

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도면14d

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도면14e

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도면14f

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도면14g

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도면14h

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p15-T7G-TC83R-벌린 CMV-gH-sg.gL (A160)를 암호화하는 플라스미드

도면15a

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도면15b

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도면15c

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도면15d

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도면15e

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도면15f

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도면15g

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도면15h

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p15-T7G-TC83R- 벌린 CMV-gHsol-sg.gL (A322)을 암호화하는 플라스미드

도면16a

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도면16b

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도면16c

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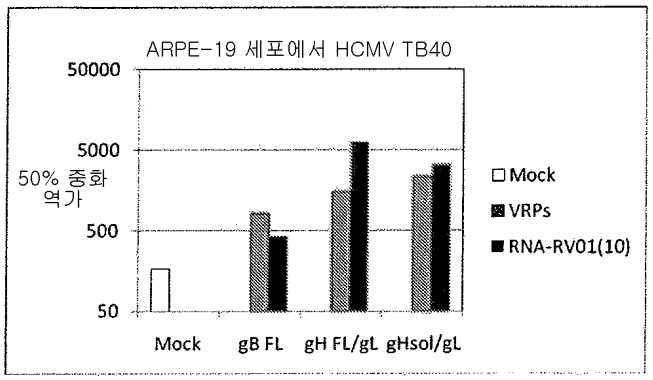

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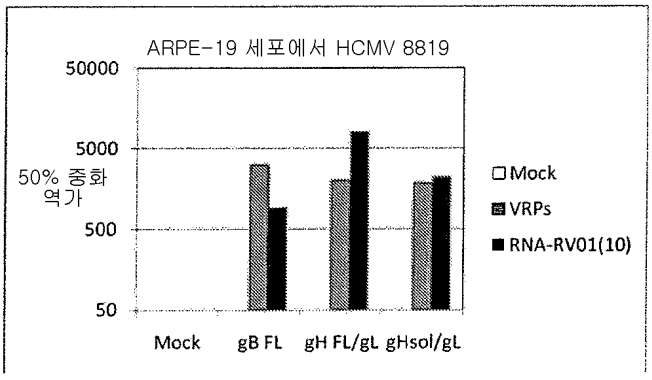

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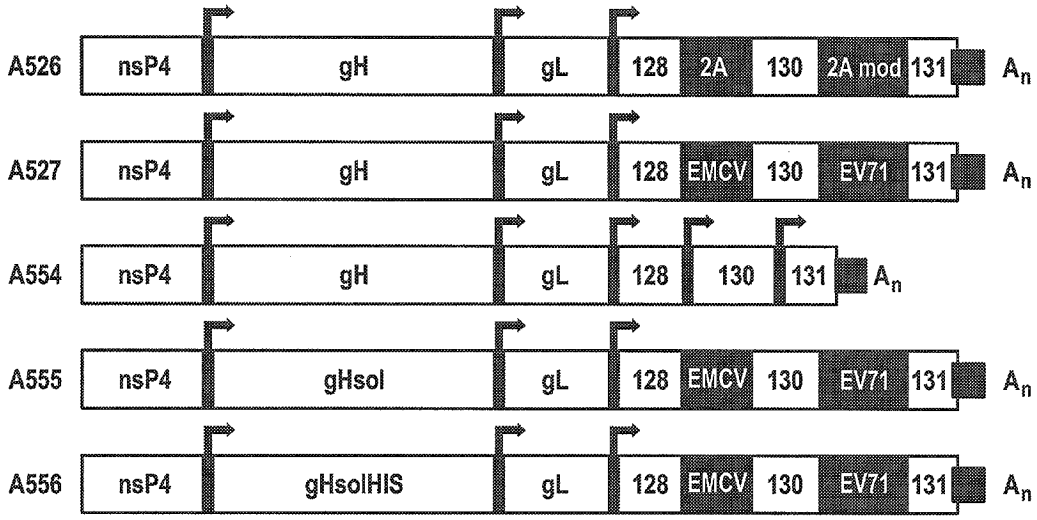
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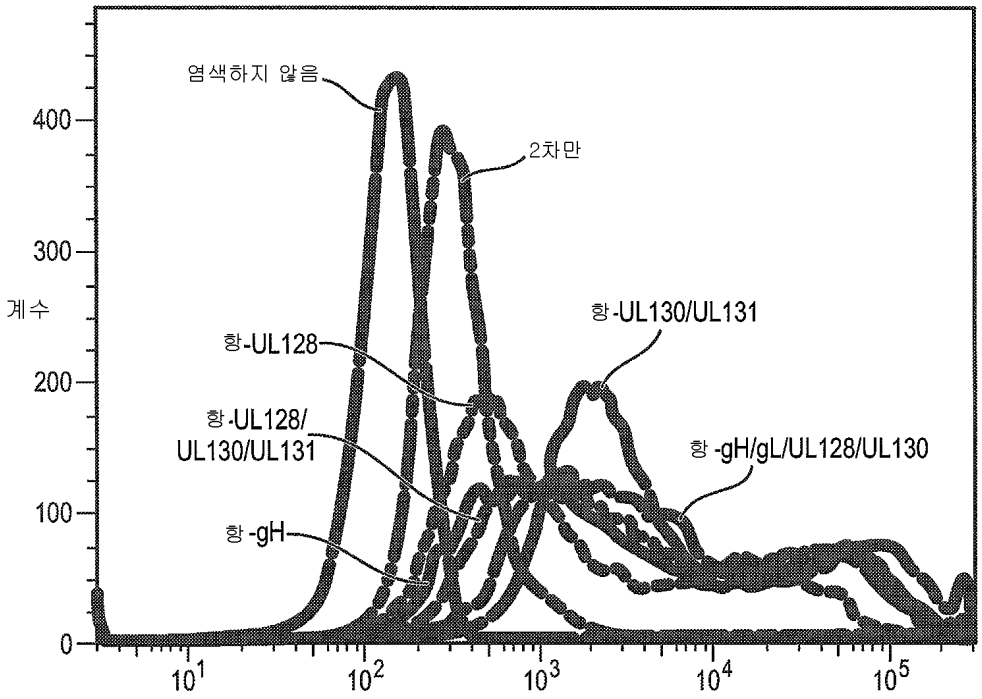
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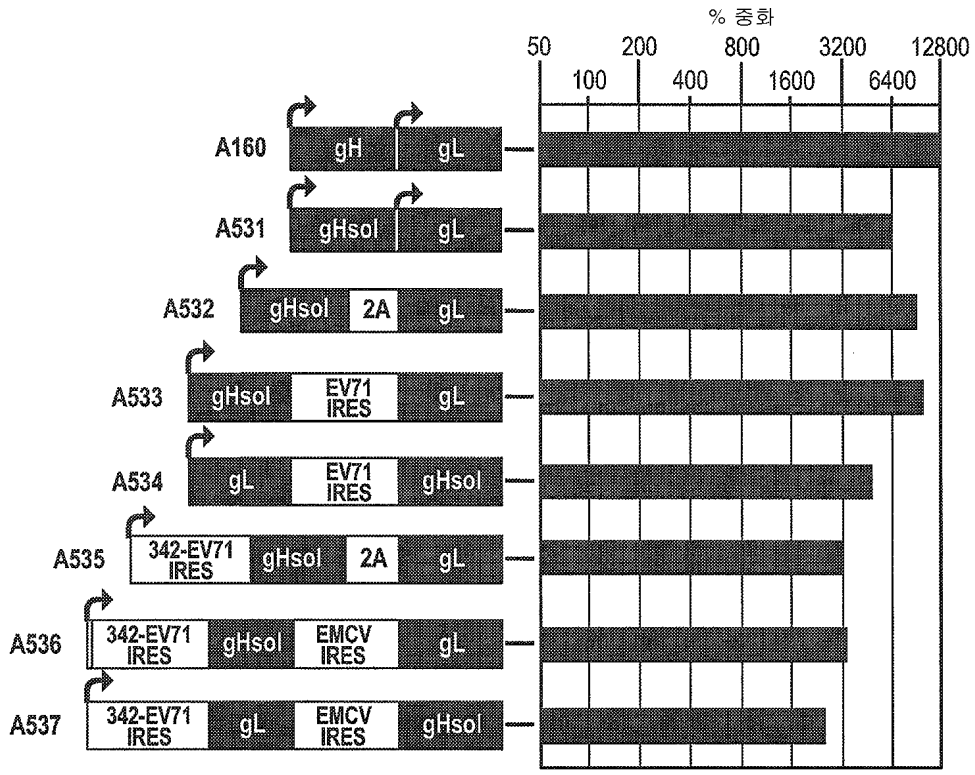
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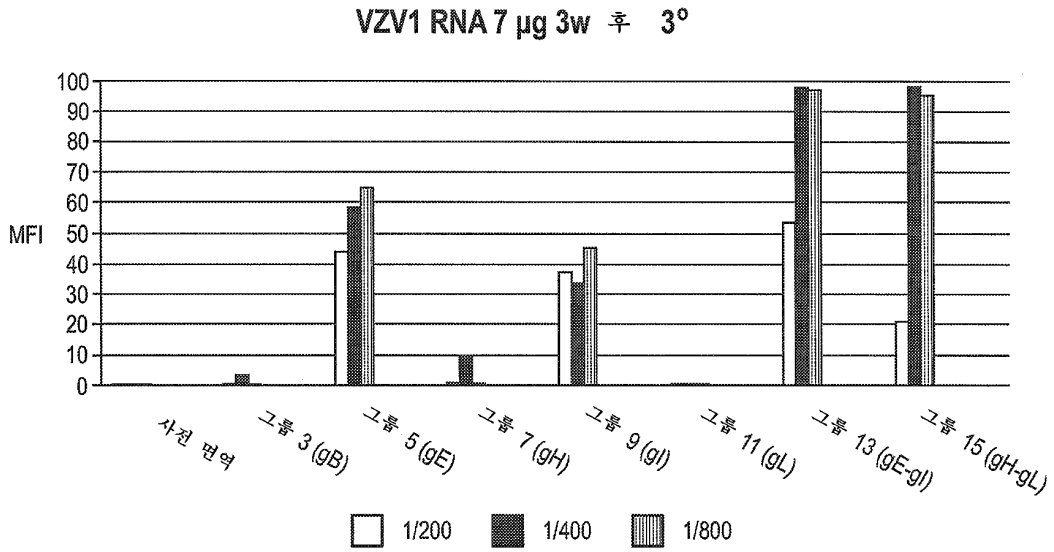
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그룹 5 (gE)
그룹 7 (gH)
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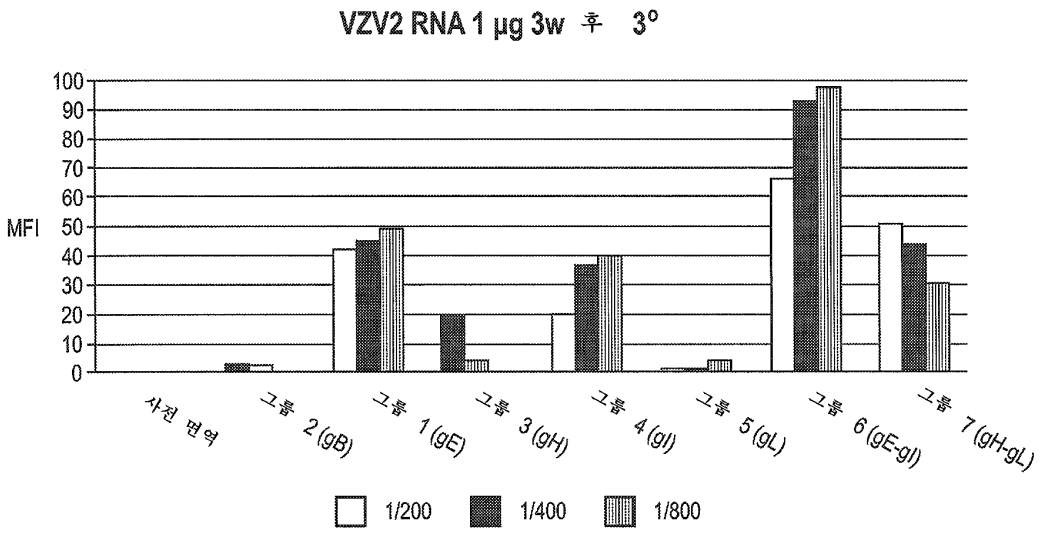

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Kelly, Marcus

Ma, Dangshe

Olson, William

Tavare, Richard

Thurston, Gavin

<120> ANTIGEN DELIVERY PLATFORMS

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<141> 2013-10-11

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